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Impact of Risk Assessments on Prophylactic Antiemetic Prescription and the Incidence of Postoperative Nausea and Vomiting: Adding Therapeutic Recommendations

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Summary

Background: In a previous cluster-randomized trial, presenting a calculated risk of postoperative nausea and vomiting (PONV) on-screen in the anaesthesia information management system (assistive approach) increased the administration of risk-dependent PONV prophylaxis by anaesthetists. However, this change in behaviour did not decrease the PONV incidence. The present study aimed to quantify the effects of adding a specific therapeutic recommendation to the patient's predicted risk (directive approach) on PONV prophylaxis management and the incidence of PONV.

Methods: A prospective before-after study was conducted in 1,483 elective surgical inpatients. The before-period included care-as-usual and the after-period the directive risk-based (intervention) strategy. Risk-dependent effects on the administered number of prophylactic antiemetics and incidence of PONV were analysed by mixed-effects regression analysis.

Results: During the intervention period anaesthetists administered 0.5 (95%CI 0.4 - 0.6) antiemetics more per antiemetic advised. This increased administration in PONV prophylaxis also resulted in a reduction in PONV incidence (OR 0.60, 95%CI 0.43 - 0.83), with an even greater reduction in PONV incidence in high-risk patients (OR 0.45, 95%CI 0.28 - 0.72).

Conclusions: Anaesthetists administered more risk-dependent prophylactic antiemetics when a directive approach was used for risk-tailored intervention compared to care-as-usual. In contrast to the previously studied assistive approach, the increase in PONV prophylaxis now resulted in a lower PONV incidence, particularly in high risk patients.

Keywords

Antiemetics

Clinical Decision Support Systems

Clinical Prediction Rule

Postoperative Nausea and Vomiting

Therapy, Computer-Assisted

Introduction

Current guidelines on prevention of postoperative nausea and vomiting (PONV) recommend using risk-dependent strategies, where administration of antiemetic prophylaxis is based on individual risks predicted by a prediction model.[1] Although several prediction models have been developed,[2-5] their effect on clinical practice remains minimal – mainly because of poor implementation.[6, 7] These disappointing results of risk-dependent PONV prophylaxis have resulted in an ongoing debate whether or not to shift to routinely administering multiple antiemetics to all patients, irrespective of their predicted risks.[8-10] Before switching to such a new, as yet unproven strategy of administering multiple antiemetics to every patient, the impact of risk-dependent strategies for PONV should be critically evaluated. However, comparative studies assessing the actual impact of risk-dependent prophylaxis on the incidence of PONV are rare.[11]

In a large cluster-randomized study we previously showed that assisting anaesthetists by presenting a patient's calculated risk of PONV on-screen in the anaesthesia information management system, but without further therapeutic directives per predicted risk, increased the number of prophylactic antiemetics administered by anaesthetists.[12] However, this change in physician behaviour did not decrease the incidence of PONV. We hypothesized that a greater impact would probably be achieved when being more directive by simply adding actionable recommendations to the presented risks.[13-18]

As a sequel to the previous cluster-randomized trial, the present before-after study aimed to quantify the effects of combining a specific therapeutic recommendation with the patient's predicted risk on again both the incidence of PONV and the actual administered prophylaxis.

Methods

Design and participants

The present study was a prospective before-after cohort study, conducted at the Anaesthesiology Department of a Dutch university hospital (UMC Utrecht) in 2010. The study aimed to quantify the effects of a directive PONV prediction model approach – i.e. presenting predicted risks accompanied with non-obligatory, therapeutic recommendations – on both the incidence of PONV and the administration of antiemetic prophylaxis. Care-as-usual (see below) was studied during the before-period (January-March 2010), followed by an intervention period (April-May 2010), during which all physicians were provided with a recommendation on how many prophylactic antiemetics would be required to sufficiently lower their individual patients' PONV risks (see below).

According to Dutch law, research protocols that do not subject patients to a particular treatment or that require them to behave in a particular way, do not apply to the Medical Research Involving Human Subjects Act. As the decision support tools in our study protocol only provided evidence-based information to physicians, the institutional ethical review board waived the need for individual informed consent and approved the study protocol (Medical Ethics Review Board, UMC Utrecht, 11-553).

All adult patients undergoing general anaesthesia for elective, non-ambulatory surgery who had visited the outpatient preanaesthesia evaluation clinic were considered eligible for inclusion. Exclusion criteria were pregnancy, postoperative admission to the intensive care unit, overnight ventilation at the postanaesthesia care unit, and inability to communicate in Dutch or English. All eligible patients from the time of study initiation were automatically included using the anaesthesia information management system.

The prediction model

The implemented prediction model was originally developed in a population of a different university hospital in the Netherlands and had already been externally validated.[19, 20] The model was subsequently updated for implementation at the UMC Utrecht.[21] The model consisted of seven predictor variables: age; gender; current smoking; type of surgery; inhalational anaesthesia; ambulatory surgery; and history of motion sickness or PONV (Table 1).

Intervention

Care-as-usual group

During the care-as-usual period, anaesthetists were not exposed to any automated prognostic information by a prediction model. Prophylactic management of PONV was not standardized in any way, which was according to care-as-usual in our hospital. At that time, the existing, local protocol for administration of PONV prophylaxis only included a preferable order for antiemetic drugs, their dosage and timing of administration: 1) ondansetron 4 mg IV, 30 minutes before emergence of anaesthesia; 2) droperidol 1.25 mg IV, 30 minutes before emergence of anaesthesia; 3) dexamethasone 4 mg IV, after induction of anaesthesia.

Intervention group

The prediction model was implemented as a directive decision support tool in the anaesthesia information management system (Vierkleurenpen®), a custom-made system written by one of the authors (LvW). The model presented a patient's predicted PONV risk accompanied with an advice on the number of prophylactic antiemetics to administer based on that individual's risk, i.e. a directive risk-based approach. The anaesthesia information management system automatically presented this risk and the recommendation to the responsible anaesthetist on the computer screen during the anaesthetic case. The on-screen

presentation was designed as a 'traffic light' with four colours (from green, through yellow and orange, to red). The initial colour of the traffic light depended on the patients predicted PONV risk and corresponded to the number of prophylactic antiemetics advised: from zero antiemetics (green) to three antiemetics (red). Anaesthetists then decided whether to follow the advice and administer prophylactic antiemetics accordingly. The colour – and hence the advice – would change after each antiemetic drug that was administered. The software 'adjusted' the predicted risk by a 26% relative risk reduction per antiemetic.[22] When the adjusted risk fell below a threshold of 26% plus 4% for each antiemetic that already had been administered, the traffic light would turn 'green' and no further prophylactic antiemetics were advised. The 4% addition per antiemetic was aimed to ease the achievement of a 'green light' in high risk patients, as very high risk patients otherwise would never get a 'green light' even when treated with all available antiemetics. Based on the calculations by the software tool, the predicted PONV risk was classified into one of four recommendation categories with an initial traffic light colour: no antiemetics (green) below 26% predicted risk; one antiemetic below 41% predicted risk (yellow); two antiemetics below 62% predicted risk (orange); and three antiemetics for 62% or greater predicted risk (red). The recommendations did not specify which prophylactic antiemetics to give, but it was advised to follow the order of the existing, local protocol (see paragraph 'care-as-usual group').

Outcome and Follow-up

The incidence of PONV was defined as the occurrence of at least one of the following events within the first 24 hours after surgery: an episode of nausea, an episode of vomiting, or the administration of any rescue antiemetic. For nausea, the patient was asked to rate their feeling of nausea on a three-point verbal rating scale (no / yes, a bit / yes, definitely) and for the analysis the variable was dichotomized to any nausea (no /yes). Vomiting was defined as the expulsion of gastric contents and was recorded as a binary outcome (no / yes). Research nurses and trained medical students collected data on the occurrence of

postoperative nausea using a validated questionnaire.[5, 23] Data were collected at the postanaesthesia care unit (30 minutes and 60 minutes after arrival, and when leaving the unit), and 24 hours after surgery at the ward. The outcome variable for PONV was coded as missing when any of the follow-up measurements had not been completed.

The administration of risk-dependent PONV prophylaxis (physician behaviour) was defined as the number of prophylactic antiemetics administered per patient and was recorded in the anaesthesia information management system. The use of total intravenous anaesthesia was not counted as a prophylactic intervention regarding the primary outcome, as it was unlikely to change during the anaesthetic case. However, as inhalational anaesthesia was a predictor within the prediction model, the presented recommendation did depend on the type of anaesthesia used.

Statistical Analysis

Analysis was performed under the intention-to-treat principle. All statistical analyses were performed in R software (version 2.15.0[1]). Statistical significance was defined as a two-sided alpha of 0.05. Continuous variables were visually assessed for a normal distribution using histograms and QQ-plots. Parametric variables were expressed as means with standard deviations, nonparametric variables were expressed as medians with interquartile ranges, and discrete variables were expressed as numbers with percentages.

The crude data on the administration and the incidence of PONV are shown in 4 risk categories according to the predictions and recommendations made by the decision support tool. Mixed effects regression analyses were used for both outcomes: logistic regression for the incidence of PONV and linear regression for the number of prophylactic antiemetics per patient (glmer, lme4 package, R software). A random intercept was included in the models, as the study was clustered by anaesthetists. For both outcomes, allocation group, predicted PONV risks, and interaction between allocation group and predicted PONV risk were

[1] http://www.r-project.org; last accessed August 29, 2013

included as independent variables in the model. The interaction term was included to quantify to what extent the difference in treatment effect (between intervention and care-as-usual) differed across predicted risks; e.g. an odds ratio below one would signify that a reduction in PONV due to the directive approach was greater in patients with higher risks. For the PONV incidence analysis predicted PONV risks were included as a continuous variable. For the analysis of physician behaviour, we expected a linear association between the outcome (actual number of administered prophylactic antiemetics, ranging from 0 to 3) and intervention (recommended number of antiemetics per predicted PONV risk category). Therefore, not the continuous predicted risk variable but rather the advised number of antiemetics and its interaction with allocation group were used as independent variables in a linear regression model with the administered number of antiemetics as the dependent variable.

As this was a non-randomized study we had to adjust for potential differences between the care-as-usual and intervention group. Although inclusion of the predicted risk variable and its interaction term with allocation groups would probably adjust for most of the confounding, we a priori hypothesized to additionally adjust for all variables from Table 2 which are either risk factors for PONV or may influence the decision on PONV prophylaxis (e.g. ASA class).[24]

Before multivariable modelling, all continuous variables were tested for nonlinearity using restricted cubic splines.[25] Missing data were multiply imputed (n=10) using a regression approach in R (aregImpute, Hmisc package). Imputation of missing variables was based on predictors, outcome variables, and other perioperative data.[26-28] As PONV was coded missing when any of the follow-up measurements was incomplete, non-missing follow-up measurements of PONV were added to the imputation process to serve as auxiliary variables to impute missing values for PONV. Subsequently, the imputed values for PONV were included into the mixed effects regression models, instead of deleted. The anaesthetists were added as an extra variable to the imputation model to take into account clustering in the data.

Results

A total of 1,483 patients were included in the study and analysed: 1,022 during the care-as-usual period and 461 during the intervention period. The mean predicted PONV risks were comparable between allocation periods. However, small differences in the distribution of predicted PONV risk categories existed between allocation periods. Differences in baseline of several predictor variables are likely to be related to the small differences in the distribution of the predicted PONV risk (Table 2).

In total, 81% of all follow-up measurements on PONV were completed (intervention group 75%; care-as-usual group 83%), with 92% of all patients having at least one follow-up measurement completed (intervention period 87%; care-as-usual period 94%). The incidence of PONV was 42% during the intervention period, compared to 50% during the care-as-usual period. Table 3 (left panel) shows the crude, risk-dependent effect of the intervention on the incidence of PONV. Confirmed by the regression analysis, there was a significant reduction in the incidence of PONV during the intervention period in comparison to the care-as-usual period (OR 0.60, 95% CI 0.43 - 0.83), with a greater reduction in high-risk patients (OR interaction term 0.45, 95% CI 0.28 - 0.72). The statistical significance of the risk-dependent reduction in PONV is reflected by Figure 1, Panel A. Results of the adjusted and unadjusted regression analyses can be found in Table 4. Differences in odds ratios for the variable predicted risk between complete case analysis and after multiple imputations can be explained by the confounder correction using all predictors from the prediction model.

The number and type of prophylactic antiemetics were documented for all patients. During the intervention period anaesthetists complied with the recommendation of the clinical decision support tool and administered the recommended number of prophylactic antiemetics in 66% of patients. Although no actual recommendations were given during the care-as-usual period, the fictional compliance (i.e. the prescription behaviour that would be recommended,

if the decision rule had been active) was 20%, resulting in an absolute increase of compliance of 46%. The crude, risk-dependent effect of the intervention on administration of prophylactic antiemetics is shown in Table 3, right panel. The increase in administration of prophylactic antiemetics was confirmed in the results of the linear regression analysis after multiple imputation and confounder adjustment. Anaesthetists administered more antiemetic prophylaxis in a risk-dependent manner during the intervention period. In this period, for each additional antiemetic advised the anaesthetists actually administered 0.49 (95% 0.41 - 0.58) additional antiemetics (Table 5, regression coefficient for the interaction term, far right column). The statistical significance of the increased administration of risk-dependent PONV prophylaxis is reflected by Figure 1, Panel B. These results were not different from the models without adjustment for confounding, as is shown in Table 5.

Discussion

We studied the effects of the implementation of risk-dependent PONV prophylaxis based on the calculations of a prediction model. The model provided automated decision support by presenting predicted risks directly accompanied with treatment recommendations to anaesthetists in the operating room, i.e. a directive approach was used.[15-18] This directive approach increased administration of risk-dependent antiemetic prophylaxis to patients and reduced the incidence of PONV within 24 hours after surgery, particularly in patients with higher risks.

The results of the present study are in contrast with the results of our previous study. The previous study – a large cluster-randomized trial – tested an assistive approach for model implementation, i.e. presenting only the risk of PONV without a therapeutic recommendation. This assistive strategy had little effect on the PONV incidence, whereas the directive strategy of the present study significantly reduced (OR 0.60, 95% CI 0.43 - 0.83) the incidence of PONV within 24 hours after surgery.[12] The difference in results between the two studies suggests that the impact on clinical practice may be larger when a prediction model is accompanied with an actionable recommendation to aid physicians in their decision making.

The impact on physician behaviour in the present study is similar to other impact studies of PONV decision support.[6, 7] Kooij et al. implemented a directive decision support tool with an absolute increase in compliance of 40%, which is comparable to the results of our present (directive) study (46%). Using an assistive approach Frenzel et al. achieved an absolute increase in compliance of 5%, with a single feedback report, which is similar to our previous (assistive) study.[12] Effects on the incidence of PONV (absolute risk reduction of 8%) for our directive approach were within the lower range of results from other studies that reported overall absolute risk reductions ranging from 8-35%.[11, 29-33] Unfortunately, the merit of such a

comparison is limited, due to differences in actual administration of PONV prophylaxis, study design and study analysis. Most of the other studies did not randomize, did not adjust for confounding, or did not have a proper control group, which makes it challenging to compare their results to our study.

Regardless of a significant decrease in PONV incidence, the actual impact of the directive approach on PONV occurrence seems at best moderate and does not come close to its desired potential impact – a 'PONV-free hospital'.[34] However, differences between actual and potential impact do not imply that we should discard risk-dependent strategies for administration of PONV prophylaxis. Several interactions between clinicians and the decision support tool need to be considered for our study, before coming to a conclusion.[16]

First, risk thresholds and treatment recommendations might have been suboptimal for our population. Recommendations were developed from clinical considerations, as literature on specific treatment recommendations for our prediction model was not available.[1] With lower recommendation thresholds, more PONV prophylaxis might have been administered, resulting in a larger decrease in PONV incidence. Second, the predictive performance of the prediction model may have been insufficient to improve clinical decision making. The predictive performance of our prediction model was comparable with other PONV prediction models (c-statistic around 0.70).[3, 5, 21] With a moderate predictive performance, decisions based on the model may not have been superior to care-as-usual, i.e. clinical judgment.

Third, despite a large increase in risk-dependent PONV prophylaxis, physicians did not fully adhere to the presented risks and therapeutic recommendations. For example, patients in the highest risk category where three prophylactic antiemetics advised, received on average two prophylactic antiemetics. Several barriers to use prediction models and decision support have been identified in the literature and may account for the incomplete compliance by the anaesthetists.[35-38]

In recent literature there is an ongoing debate whether more liberal use of prophylactic antiemetics should be achieved by either a risk-dependent strategy or routine administration of several prophylactic antiemetics to every patient (a routine multimodal approach).[8-10, 32] At this moment, neither points of view have a substantive evidence base. On one hand there is a debate on the clinical utility of prediction models, as their implementation rate remains very low. On the other hand there is a debate on the side-effects of antiemetics and a reluctance to administer polypharmacy with several potentially unnecessary drugs. This study adds some support for both points of view. It is one of the first, prospective comparative studies that demonstrate that risk-dependent prophylaxis actually decreases the incidence of PONV. At the same time, anaesthetists were only partially compliant with the presented recommendations and the absolute decrease in PONV incidence was limited. As long as both points of view coexist, it will be necessary to keep searching for optimal strategies to implement PONV prophylaxis and study their effects on both physician behaviour and patient outcome.

We conclude that risk-dependent PONV prophylaxis is not only efficacious in clinical trials, but also effective in clinical practice when a real-time, computer-based decision model provides an actionable recommendation on PONV prophylaxis.

Declaration of interests

Dr Kappen declares to have no conflict of interest.

Dr Vergouwe declares to have no conflict of interest.

Dr Van Wolfswinkel declares to have no conflict of interest.

Prof Kalkman declares to have no conflict of interest.

Prof Moons declares to have no conflict of interest.

Dr Van Klei declares to have no conflict of interest.

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Role of the Sponsors: The funding agreement ensured the authors' independence in design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review, or approval of the manuscript.

Author Contributions

THK	*Study concept and design; Acquisition of data; Statistical analysis; Interpretation of data; Drafting of the manuscript; Critical revision of the manuscript for important intellectual content.*
YV	*Study concept and design; Statistical analysis; Interpretation of data; Drafting of the manuscript; Critical revision of the manuscript for important intellectual content.*
LvW	*Study concept and design; Acquisition of data; Interpretation of data; Critical revision of the manuscript for important intellectual content.*

CJK	*Study concept and design; Interpretation of data; Critical revision of the manuscript for important intellectual content.*
KGMM	*Study concept and design; Statistical analysis; Interpretation of data; Critical revision of the manuscript for important intellectual content.*
WAvK	*Study concept and design; Interpretation of data; Drafting of the manuscript; Critical revision of the manuscript for important intellectual content.*

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Figure legends

Figure 1 – Graphical representation of the mixed effects regression analysis on the incidence of postoperative nausea and vomiting (Panel A) and on administration of prophylactic antiemetics by anaesthetists (Panel B). The solid lines and their 95% confidence intervals (CI) represent the fixed effects of the mixed effects regression analyses. The dotted vertical line shows the intersection point of both groups. The mixed effects models included fixed effects for the variables allocation group, predicted risk of PONV, interaction between allocation group and predicted risk, and time. Random effects were included for the intercept, predicted risk, interaction between allocation group and predicted risk, and time. The lines were calculated using the average for the variable time. The 95% CIs were calculated from the covariance matrix for the variables allocation group and its interaction term with predicted risk. The results are considered statistically significant when the 95% CIs of one study group do not overlap with the solid line of the other study group.

Panel A may be interpreted as the occurrence of postoperative nausea and vomiting (PONV) after receiving prophylaxis, in patients with a particular predicted risk within each group. The differences between the blue and red areas represent the effect of implementation of the prediction model on the occurrence of PONV in patients with a particular predicted risk. Panel B may be interpreted as the number of prophylactic antiemetics a patient with a particular predicted risk of PONV would receive from any anaesthetist within each group. The differences between the blue and red areas therefore represent the changes in physician behaviour concerning prescription of antiemetic prophylaxis, caused by implementation of the prediction model.

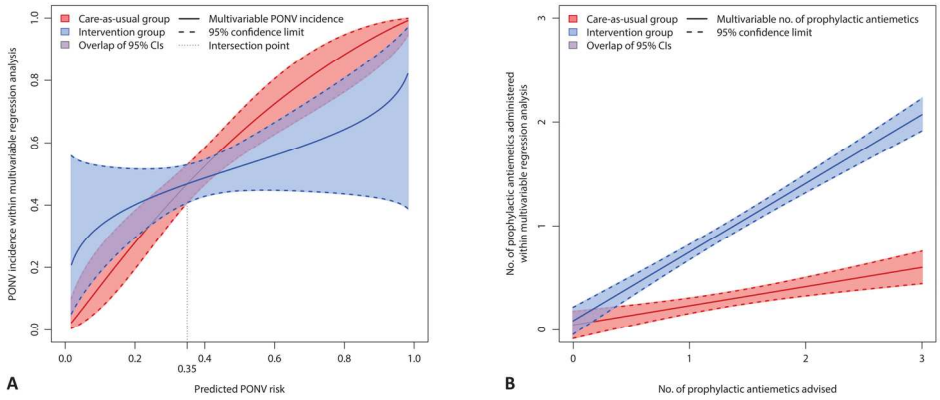

Figure 1 - Graphical representation of the mixed effects regression analyses
86x38mm (600 x 600 DPI)

Table 1 – Regression coefficients of the prediction model for postoperative nausea and vomiting

Probability of PONV as estimated by the model = 1 / (1 + exp (- (0.12 – 0.017*age + 0.36 *female gender – 0.50*current smoking + 0.60*history of PONV or motion sickness + 0.48*surgery with a high PONV risk + 0.35*inhalational anaesthesia – 1.16*outpatient surgery))). PONV = postoperative nausea and vomiting. * Definition of this predictor was 'abdominal or middle ear surgery'. † As compared to intravenous anaesthesia using propofol.

Predictor	Updated model
Age (years)	-0.017
Female gender	0.36
Current smoking	-0.50
History of PONV / motion sickness	0.60
Surgery with a high PONV risk*	0.48
Inhalational anaesthesia†	0.35
Outpatient surgery	-1.16
Intercept	0.12

Table 2 – Patient characteristics

Age, Predicted risk of PONV are presented as mean (SD), Operation duration as median (1st quartile, 3rd quartile). Other values are absolute frequencies (percentages). * N represents the total number of non-missing observations for that characteristic. PONV = Postoperative Nausea and Vomiting.

		Care-as-Usual Group	**Intervention Group**
		(*n* = 1022)	(*n* = 461)
	N*	mean (SD)	
Age, years	1483	52 (18)	54 (18)
Female gender	1483	496 (49)	195 (42)
ASA class	1480		
1		337 (33)	121 (26)
2		561 (55)	274 (60)
3		116 (11)	62 (14)
4		8 (1)	1 (0)
Current smoking	1456	288 (29)	111 (25)
Surgery with a high PONV risk	1106	82 (12)	53 (13)
History of PONV / Motion sickness	1398	212 (22)	66 (15)
Inhalational anaesthesia	1483	472 (46)	226 (49)
Predicted risk of PONV	1483	0.40 (0.13)	0.39 (0.12)
Predicted PONV risk in categories	1483		
<26% (0 antiemetics advised)		127 (12)	61 (13)
26-41% (1 antiemetic advised)		443 (43)	218 (47)
41-62% (2 antiemetics advised)		384 (38)	162 (35)
>62% (3 antiemetics advised)		68 (7)	20 (4)
Operation duration, minutes	1483	128 (85, 188)	133 (86, 206)

Table 3 – Primary and secondary outcomes per category of predicted risk of postoperative nausea and vomiting

Data represent absolute numbers of PONV (%) or the mean number of prophylactic antiemetics (SD). * N represents the total number of non-missing observations for that characteristic; † The sum of the prophylactic use of ondansetron, droperidol, dexamethasone, and/or total intravenous anaesthesia. PONV = postoperative nausea and vomiting.

	Incidence of PONV*			No. of prophylactic antiemetics†		
		Care-as-Usual Group	Intervention Group		Care-as-Usual Group	Intervention Group
Predicted PONV risk in categories	N*	(*n* = 1022)	(*n* = 461)	N*	(*n* = 1022)	(*n* = 461)
<26% (0 antiemetics advised)	116	19 (23)	10 (29)	188	0.08 (0.3)	0.1 (0.3)
26-41% (1 antiemetic advised)	432	123 (41)	50 (38)	661	0.2 (0.5)	0.7 (0.5)
41-62% (2 antiemetics advised)	354	167 (64)	48 (52)	546	0.4 (0.7)	1.5 (0.9)
>62% (3 antiemetics advised)	60	41 (82)	5 (50)	88	0.7 (0.7)	1.9 (1.1)

Table 4 – Logistic regression analysis on the risk-dependent incidence of postoperative nausea and vomiting

Numbers represent odds ratios with 95% confidence intervals. Bold numbers are statistically significant odds ratios. * Cases with missing variables were discarded; † Adjusted for possible confounders: age (continuous, restricted cubic splines, 5 knots), gender, ASA class, current smoking, middle ear of abdominal surgery, history of PONV / motion sickness, use of inhalational anaesthesia, procedure duration (continuous, restricted cubic splines, 5 knots); ‡ Using 10 imputation datasets; § Odds ratios represent predicted risks of 100% (a probability of 1). PONV = Postoperative Nausea and Vomiting; pred. = predicted.

	Complete case*		**Multiple imputation‡**	
	unadjusted	confounder adjusted†	unadjusted	confounder adjusted†
Intervention period	**0.52 (0.35 - 0.78)**	**0.43 (0.27 - 0.69)**	**0.64 (0.47 - 0.89)**	**0.60 (0.43 - 0.83)**
Predicted risk§	**3.9 (2.9 - 5.4)**	0.12 (0.0 - 7.4)	**2.9 (2.2 - 3.8)**	0.73 (0.13 - 4.2)
Interaction: Intervention period * pred. risk§	**0.43 (0.24 - 0.77)**	1.0 (0.44 - 2.4)	**0.49 (0.31 - 0.77)**	**0.45 (0.28 - 0.72)**

Table 5 – Linear regression analysis on physicians' administration of risk-dependent antiemetic prophylaxis

Numbers represent regression coefficients with 95% confidence intervals. Bold numbers are statistically significant regression coefficients. No unadjusted model is presented for multiple imputation as variables within the models were not missing. * Cases with missing variables were discarded; † Adjusted for possible confounders: age (continuous, restricted cubic splines, 5 knots), gender, ASA class, current smoking, middle ear of abdominal surgery, history of PONV / motion sickness, use of inhalational anaesthesia, procedure duration (continuous, restricted cubic splines, 5 knots); ‡ Using 10 imputation datasets; § Regression coefficients represent an increase in the number of administered prophylactic antiemetics per advised prophylactic antiemetics – i.e. per risk category. PONV = Postoperative Nausea and Vomiting; pred. = predicted.

	Complete case*		**Multiple imputation‡**
	unadjusted	confounder adjusted†	confounder adjusted†
Intervention period	0.04 (-0.09 - 0.17)	0.06 (-0.10 - 0.22)	0.04 (-0.09 - 0.17)
Recommendation categories§	**0.18 (0.14 - 0.23)**	0.07 (-0.05 - 0.20)	0.04 (-0.05 - 0.14)
Interaction: Intervention period * categories§	**0.48 (0.39 - 0.56)**	**0.49 (0.39 - 0.58)**	**0.50 (0.41 - 0.58)**