

## ORIGINAL ARTICLE

# Total intravenous anaesthesia versus single-drug pharmacological antiemetic prophylaxis in adults

## *A systematic review and meta-analysis*

Maximilian S. Schaefer\*, Peter Kranke\*, Stephanie Weibel, Robert Kreysing and Peter Kienbaum

**BACKGROUND** Postoperative nausea and vomiting (PONV) are among the most unfavourable anaesthetic outcomes attributed to the administration of inhaled anaesthetics. Accordingly, inhaled anaesthetics are frequently substituted by propofol when patients are at risk of PONV. As, on some occasions, inhalational anaesthesia may be favourable, the relative impact of propofol anaesthesia needs to be established based on robust data.

**OBJECTIVE** To compare the effectiveness of a single-drug pharmacological prophylaxis with total intravenous anaesthesia (TIVA) for prevention of PONV.

**DESIGN** Systematic review of randomised controlled trials with meta-analyses.

**DATA SOURCES** All available studies until 29 April 2015 were retrieved from MEDLINE, CENTRAL and EMBASE.

**ELIGIBILITY CRITERIA** Randomised controlled trials on adult patients undergoing general anaesthesia with at least one group receiving propofol-based intravenous anaesthesia without further antiemetic prophylaxis, and one group receiving inhalational anaesthesia with single-drug antiemetic prophylaxis.

**RESULTS** Fourteen studies involving 2051 patients were included. Compared with TIVA, after inhalational

anaesthesia and single-drug antiemetic prophylaxis, there was no difference in the overall risk of PONV [relative risk (RR) 1.06, 95% confidence interval (CI) 0.85; 1.32, GRADE rating moderate], nor was there any difference in the risk of postoperative vomiting (RR 1.17, 95% CI 0.78; 1.76), need for rescue medication (RR 1.16, 95% CI 0.68; 1.99) or early PONV (RR 1.06, 95% CI 0.88; 1.27). However, TIVA was associated with an increased risk of late PONV (RR 1.41, 95% CI 1.10; 1.79,  $P=0.006$ ). Six studies investigated other side-effects associated with anaesthesia and found no differences between the two groups. Finally, there was evidence of a publication bias that included smaller studies favouring TIVA.

**CONCLUSION** This meta-analysis confirms the results from indirect comparisons in individual studies: instead of substituting inhalational anaesthesia with propofol-based TIVA, a similar antiemetic effect can be achieved by adding single-drug pharmacological prophylaxis to the inhalational anaesthetic.

**STUDY REGISTRATION** This systematic review with meta-analysis was registered at PROSPERO ([www.crd.york.ac.uk/PROSPERO](http://www.crd.york.ac.uk/PROSPERO)), study number CRD42015019571.

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## Introduction

Postoperative nausea and vomiting (PONV) are frequent after general anaesthesia.<sup>1</sup> Without antiemetic prophylaxis, several million patients undergoing general anaesthesia every year will develop PONV.<sup>2–4</sup> Together with pain, PONV is ranked as the most undesirable event after surgery<sup>5</sup> and significantly increases healthcare costs.<sup>6</sup>

Therefore, international consensus guidelines were recently published<sup>7</sup> recommending the identification of patients at high risk of PONV<sup>8</sup> and administration of a risk-adapted prophylaxis including, when general anaesthesia cannot be avoided, the patient's risk for PONV should be reduced by substitution of inhalational anaesthetics with

From the Department of Anaesthesiology, University Hospital Düsseldorf, Düsseldorf (MSS, RK, PKIE) and Department of Anaesthesiology and Critical Care, University Hospital Würzburg, Würzburg, Germany (PKRA, SW)

Correspondence to Maximilian S. Schaefer, Department of Anaesthesiology, University Hospital Düsseldorf, Moorenstr 5, D-40225, Düsseldorf, Germany  
Tel: +49 211 81 17491; e-mail: Maximilian.schaefer@med.uni-duesseldorf.de

\* Maximilian S. Schaefer and Peter Kranke contributed equally to the writing of the article.

propofol-based total intravenous anaesthesia (TIVA).<sup>7</sup> However, in several situations, modern inhalational anaesthetics may be preferable to propofol. With inhalational anaesthetics, end-tidal anaesthetic concentrations can be used to guide anaesthetic depth<sup>9</sup> and decrease the incidence of intraoperative awareness,<sup>10</sup> as well as allowing the precise control of weaning (irrespective of a patient's weight)<sup>11</sup> and they have favourable effects on the cardiovascular system. Thus, if inhalational anaesthetics are not to be substituted by TIVA, the question is raised as to whether the reduction in the patient's risk of PONV associated with TIVA can be compensated sufficiently with pharmacological prophylaxis. Interestingly, a large international multicentre trial (IMPACT) even suggested an inferior prophylactic effect of TIVA as compared with using one single antiemetic drug as prophylaxis; however, the published analyses did not include a direct comparison of these two strategies.<sup>1</sup> Furthermore, TIVA and pharmacological prophylaxis might show differential effects on PONV in the early and late postoperative phase. Therefore, the relative potency of TIVA, as compared with pharmacological prophylaxis, needs to be established based on a direct comparison. Because recent guidelines recommend TIVA as an equivalent intervention to one single antiemetic drug for prevention of PONV,<sup>7</sup> we restricted our analysis to studies comparing TIVA with single-drug pharmacological prophylaxis.

Thus, to compare the effectiveness of antiemetic prophylaxis with propofol-based TIVA with that of single-drug prophylaxis in association with inhalational anaesthetics, we conducted a systematic literature search and subsequent meta-analysis of all the available randomised controlled trials.

## Materials and methods

### Search strategy and selection criteria

We performed this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.<sup>12</sup> The study protocol, including the full written search strategy, was registered and published online at the publicly available internet database PROSPERO ([www.crd.york.ac.uk/PROSPERO](http://www.crd.york.ac.uk/PROSPERO), registration number CRD42015019571) before the search was conducted. All deviations from that protocol are specified in the Supplemental Digital Content, <http://links.lww.com/EJA/A101> 'Deviations from the PROSPERO protocol'. Our search combined a three-part strategy, including updated syntax for identification of studies including prophylactic drugs for PONV,<sup>13</sup> with identification of studies investigating TIVA and the modified Robinson's highly sensitive search for controlled clinical trials.<sup>14</sup> Searched databases included MEDLINE (via Pubmed), EMBASE (via Ovid) and the Cochrane Central Register of Controlled Trials (CENTRAL, via Wiley) without any restrictions on language or publication year.

We included all randomised, controlled trials with at least one study group receiving propofol-based anaesthesia (TIVA group) without further antiemetic prophylaxis, and at least one study group receiving inhalational anaesthesia with additional single-drug antiemetic prophylaxis. Our definition of TIVA implied the use of propofol as the primary hypnotic but no preconditions were applied regarding the use of nitrous oxide (N<sub>2</sub>O). Studies were required to report the incidences of PONV, postoperative nausea (PON) or postoperative vomiting (POV). Studies and study groups which included multiple antiemetic prophylactics [i.e. TIVA with pharmacological antiemetic prophylaxis or inhalational anaesthesia with pharmacological antiemetic prophylaxis (IA + AE) with more than one prophylactic drug] were excluded, as well as studies involving patients less than 18 years of age. Studies were independently screened for inclusion and exclusion criteria by two investigators (M.S.S., R.K.).

### Data extraction and preparation

Our primary outcome variable was the incidence of PONV within 24 h after surgery ('overall PONV'). Additionally, the following data were independently extracted by two investigators (M.S.S., R.K.): type of inhalational anaesthetics and type of intraoperative opioid; use and dose of N<sub>2</sub>O; timing, dose and type of pharmacological antiemetic prophylaxis; type of surgery and duration of anaesthesia; PON, POV and the need for rescue medication; incidences of early and late PONV, as defined by the authors; incidences of any reported adverse events with focus on but not limited to dizziness, drowsiness, shivering, headache, gastrointestinal symptoms, extrapyramidal symptoms, awareness, prolongation of the cardiac QT interval perioperative arrhythmia and quality of recovery. If available, supplemental material and appendices were also screened for the aforementioned data. Because POV without PON is extremely rare in adults, PON was taken as a surrogate for PONV, when only PON was reported.

### Risk of bias assessment

Studies were scored for risk of bias using The Cochrane Collaboration 'Risk Of Bias' Assessment Tool, which judges risk of bias in six domains: random sequence generation and allocation concealment (selection bias), blinding of participants and study personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). Additionally, we estimated the overall risk of bias for each study. Assessments were made by two investigators (M.S.S. and S.W.) who were blind to each other's assessments. Upon disagreement, judgement by a third investigator (R.K.) was used as a referee's decision. A sensitivity analysis was performed for overall PONV, excluding studies with a high risk of overall bias. For outcomes that were reported by 10 or more included studies, publication bias was assessed

using funnel plots. After visual inspection, funnel plot asymmetry was tested with the Arcsine test and a conventionally used alpha of 0.1.<sup>15,16</sup>

### Statistical analysis

All references were imported into Endnote X7.1 (Thomson Reuters, New York, USA). Extracted data were entered into Review Manager 5.3.5 (The Cochrane Collaboration, Copenhagen, Denmark), which was used for all analyses except for funnel plots. The latter were created and tested for asymmetry using the R software (version 3.2.2, The R Project) with the meta-package. Heterogeneity was assessed using the  $I^2$  statistic with  $\chi^2$  test for significance.<sup>17,18</sup> Subsequently, pooled estimates were calculated using inverse variance weighting with random-effects modelling and alpha set to 0.05. Because the funnel plot for the primary outcome overall PONV showed significant asymmetry with different results between smaller and larger studies, we conducted an additional explorative analysis; to reduce the influence of smaller studies in the model, fixed-effect modelling instead of random-effects modelling for calculation of risk ratios for the risk for overall PONV was used.

To explore heterogeneity, a subgroup analysis was performed on the main outcome (overall PONV) with stratification according to total sample size (number of included patients  $\leq 50$ ,  $\leq 100$ ,  $\leq 200$ ,  $> 200$ ). To avoid a type 1 error because of repetitive testing, we adjusted alpha for subgroup analyses using the Bonferroni approach: as we created a total of four strata, alpha was corrected to 0.013 ( $0.05 \div 4$ ).<sup>16</sup> Furthermore, because no preconditions had been specified regarding the use of  $N_2O$ , we conducted an additional sensitivity analysis which excluded all studies with an uneven distribution of  $N_2O$  administration between the two groups (i.e. where  $N_2O$  was used with inhalational anaesthetics but not with TIVA, or vice versa). All results are reported as relative risks (RRs) with corresponding 95% confidence interval, with a RR less than 1 favouring TIVA and a RR greater than 1 favouring IA + AE. Overall, quality of evidence was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach<sup>19</sup> and incorporated in a Summary of Findings Table,<sup>20</sup> which was created for the primary outcome.

### Results

Our database search was carried out on 29 April 2015 and yielded 3106 articles, 690 from *MEDLINE*, 511 from *CENTRAL* and 1905 from *EMBASE*. After elimination of duplicates, 2206 articles were screened for inclusion and exclusion criteria. Our search results included 21 publications from two authors who have been discredited,<sup>21–24</sup> and even though not all of these articles have been retracted, we decided to exclude all 21 before further screening. Figure 1 summarises reasons for

the exclusion of the remaining 2171 articles. At the end of the screening process, 14 randomised controlled trials with a total of 2051 patients were included for final analysis.<sup>1,25–37</sup> Study characteristics and anaesthesia details including specifics of antiemetic prophylaxis are summarised in Table 1.

### Primary analysis

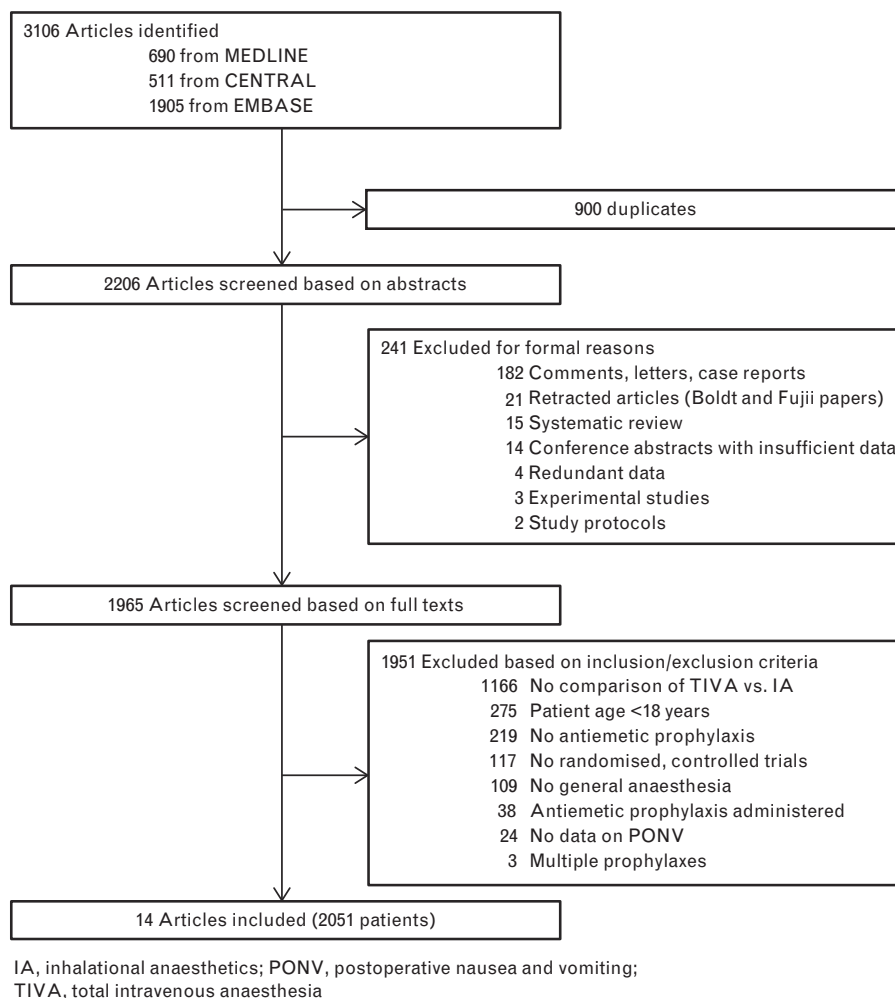
Overall PONV was reported by 12 out of 14 studies. The remaining two studies<sup>31,34</sup> only reported PONV separately for early and late periods. Despite an effort to contact the corresponding authors, data on overall PONV were not available. Thus, data from these two studies were only included in analyses of early and late PONV. In most studies, the distinction between early and late PONV was made at 2 h after awakening from anaesthesia (Table 2).

There was no difference in the risk of PONV between the groups that received TIVA or IA + AE when analysed using a random-effects model (Fig. 2). Similarly, there was no difference between the groups for the risk of POV, the need for rescue medication, or early PONV (Fig. 3). However, patients receiving TIVA had a significantly higher risk of experiencing PONV in the late postoperative phase [1.41 (1.10 to 1.79),  $P = 0.006$ , Fig. 3]. There was significant heterogeneity among studies in the analyses of overall PONV ( $I^2 = 54\%$ ), need for rescue medication ( $I^2 = 58\%$ ) and POV ( $I^2 = 60\%$ ) (Figs. 2 and 3). When a fixed effect model was applied, TIVA was inferior to IA + AE in preventing overall PONV [1.16 (1.04 to 1.30),  $P = 0.01$ , Fig. 2]. GRADE rating for quality of evidence was 'moderate' for the main outcome of overall PONV (Table 1, <http://links.lww.com/EJA/A102> Supplemental Digital Content shows the GRADE Table, <http://links.lww.com/EJA/A101>).

### Adverse events and quality of recovery

Postoperative adverse events were investigated by six studies but only four of these studies reported analysable data.<sup>25,30,31,35</sup> Frequencies of postoperative shivering, dizziness and headache were investigated by two studies, whereas postoperative myalgia and drowsiness were each reported by only one study. No differences were observed between the two groups except for a tendency towards a decreased risk of postoperative shivering after TIVA [0.46 (0.19 to 1.11),  $P = 0.08$ , Supplemental Digital Content Figure 1, <http://links.lww.com/EJA/A101>]. Two other studies provided only descriptive information with no incidence data: 'the side-effect profile did not differ' between the anaesthetic techniques<sup>29</sup> and 'there were no differences between the groups' in drowsiness and adverse events.<sup>36</sup> None of these six studies assessed intraoperative awareness, prolongation of the cardiac QT interval postoperative arrhythmias or gastrointestinal symptoms. Only one study reported on the quality of recovery,<sup>31</sup> and it found no difference in the 'Quality of

Fig. 1



Flow chart indicating screening process with details of study exclusion.

Recovery Score 40', median 155, interquartile range (149 to 159) versus 152 (150 to 156) for TIVA and IA + AE, respectively ( $P=0.114$ ).

### Sensitivity and subgroup analyses

In three studies, the use of nitrous oxide was not evenly distributed between the two groups.<sup>33,35,36</sup> After excluding these studies from the different analyses, the overall risks were basically unchanged: PONV, 1.13 (0.86 to 1.47),  $P=0.39$ ,  $I^2=52\%$ ; POV, 1.26 (0.73 to 2.20),  $P=0.41$ ,  $I^2=61\%$ ; early PONV, 1.07 (0.88 to 1.30),  $P=0.48$ ,  $I^2=0\%$ ; the need for rescue medication, 1.17 (0.52 to 2.65),  $P=0.71$ ,  $I^2=73\%$ . However, the risk of late PONV was even more pronounced in patients who received TIVA [1.51 (1.17 to 1.94),  $P=0.002$ ,  $I^2=31\%$ ].

Subgroup analyses by sample size revealed a significantly higher risk of PONV with TIVA in studies involving 101 to 200, and greater than 200 patients: 1.44 (1.11 to 1.87),

$P=0.006$  and 1.24 (1.07 to 1.44),  $P=0.005$ , respectively, (a Forest plot is provided in Supplemental Digital Content Figure 2, <http://links.lww.com/EJA/A101>). There was no statistically significant difference between groups in smaller studies involving 100 patients or less.

### Risk of bias

An overview of the risk of bias assessment is presented in Table 3. Low risk of bias was present in four, moderate risk in seven and high risk in three studies. Excluding high risk of bias studies did not change the result for the main analysis on overall PONV [1.11 (0.89 to 1.37),  $P=0.35$ ], but it reduced heterogeneity ( $I^2$  40%,  $P=0.10$ ). Data from at least 10 studies were only available for overall PONV and early PONV. Therefore, funnel plot analysis was only performed for these two outcomes. Visual inspection of the funnel plot for overall PONV suggested asymmetry favouring TIVA, which was confirmed by Arcsine analysis for funnel plot asymmetry

Table 1 Overview and characteristics of included studies

Study	Language	Design	Patients TIVA/IA + AE (n)	Type of surgery	Maintenance TIVA	Maintenance IA	Duration of anaes- thesia (TIVA/IA, min) <sup>a</sup>	Type of antiemetic	Timing of anti- emetic
Apfel 2004 <sup>1</sup>	English	Factorial RCT	345/512	Variety of operative procedures	Propofol with fentanyl or remifentanyl and N <sub>2</sub> O in 1/3 (50%) patients	Isflurane, desflurane or sevoflurane with fentanyl or remifentanyl and N <sub>2</sub> O in 254 (50%) patients	115/105 (no SD mentioned)	Ondansetron (4 mg), dexamethasone (4 mg) or droperidol (1.25 mg) i.v.	20 min after start of anaesthesia (droperidol/dexamethasone) during last 20 min (ondansetron)
Eberhart 2002 <sup>25</sup>	German	RCT	75/75	Gynaecologic surgery	Propofol with alfentanil	Desflurane with alfentanil	'Estimated duration 60 to 120 min'	Tropisetron 2 mg i.v.	10 min before end of operation
Gan 1996 <sup>26</sup>	English	RCT	21/21	Major breast surgery	Propofol with 66% N <sub>2</sub> O	Isoflurane with 66% N <sub>2</sub> O	144 ± 78/156 ± 70	Ondansetron 4 mg i.v.	Before induction
Heinke 1996 <sup>27</sup>	German	RCT	43/38	Pars plana vitrectomy	Propofol with alfentanil	Isoflurane with alfentanil	131 ± 37/130 ± 38	Droperidol 2.5 mg i.v.	At start of surgery
Jellish 1995 <sup>28</sup>	English	RCT	34/34	Middle ear surgery	Propofol with fentanyl	Isoflurane with fentanyl	161 ± 10/163 ± 8	Droperidol 25 µg kg <sup>-1</sup> i.v.	After induction
Jokela 2000 <sup>29</sup>	English	RCT	60/60	Breast surgery	Propofol with fentanyl	Sevoflurane with fentanyl	109 ± 59/117 ± 78	Ondansetron 8 mg i.v.	At end of surgery
Khan 2005 <sup>30</sup>	English	RCT	20/40	Diagnostic gynaecologic laparoscopy	Propofol with 60% N <sub>2</sub> O	Isoflurane with 60% N <sub>2</sub> O	35 ± 3/35 ± 7	Granisetron 40 µg kg <sup>-1</sup> or ondansetron 40 to 60 µg kg <sup>-1</sup> i.v.	3 min before induction
Mei 2014 <sup>31</sup>	English	Factorial RCT	74/74	Gynaecologic laparoscopy	Propofol with remifentanyl, titrated BIS 45 to 55	Sevoflurane with remifentanyl titrated BIS 45 to 55	n.a.; duration of surgery 73 (55 to 102)/78 (57 to 99)	Tropisetron 2 mg i.v.	After induction
Özünlü 2005 <sup>32</sup>	Turkish	RCT	20/20	Gynaecologic laparoscopy	Propofol with remifentanyl and 60% N <sub>2</sub> O	Desflurane with remifentanyl and 60% N <sub>2</sub> O	58 ± 27/56 ± 25	Ondansetron 4 mg i.v.	1 min before induction
Paech 2002 <sup>33</sup>	English	RCT	47/47	Day-case gynaecologic laparoscopy	Propofol with alfentanil or morphine	Sevoflurane with N <sub>2</sub> O and alfentanil or morphine	n.a.; duration of surgery 30 [20 to 45]/30 [20 to 45]	Dolasetron 12.5 mg i.v.	At induction
Park 2014 <sup>34</sup>	English	RCT	32/32	Total thyroidectomy	Propofol with remifentanyl	Sevoflurane with remifentanyl	105 ± 23/99 ± 21	Ramosecton 0.3 mg i.v.	Before end of surgery
Park 2011 <sup>35</sup>	English	RCT	50/50	Gynaecologic laparoscopy	Propofol with remifentanyl	Sevoflurane with 50% N <sub>2</sub> O	131 ± 36/140 ± 37	Palonosetron 0.075 mg i.v.	Before induction
Purhonen 2006 <sup>36</sup>	English	RCT	50/51	Gynaecologic laparoscopy	Propofol with fentanyl	Isoflurane with fentanyl and 67% N <sub>2</sub> O	65 ± 39/65 ± 40	Ondansetron 8 mg p.o.	1 h before operation
White 2007 <sup>37</sup>	English	RCT	58/68	Day-case gynaecologic surgery	Propofol with fentanyl	Sevoflurane with fentanyl	39 (26 to 59)/32 (24 to 50)	Dolasetron 12.5 mg i.v.	Before end of surgery

AE, antiemetic; BIS, Bispectral Index; i.v., intravenously; IA, inhaled anaesthetic; p.o., orally; RCT, randomised controlled trial; TIVA, total intravenous anaesthesia.

<sup>a</sup>Values are either mean ± SD or median (interquartile range).



**Table 2** Definitions of early and late postoperative nausea and vomiting, as defined by the respective authors

Study	Early PONV	Late PONV
Apfel 2004 <sup>1</sup>	0 to 2 h	2 to 24 h
Eberhart 2002 <sup>25</sup>	ND	ND
Gan 1996 <sup>26</sup>	0 to 6 h	ND
Heinke 1996 <sup>27</sup>	0 to 2 h	2 to 24 h
Jellish 1995 <sup>28</sup>	In recovery room <sup>a</sup>	ND
Jokela 2000 <sup>29</sup>	0 to 2 h	2 to 24 h
Khan 2005 <sup>30</sup>	0 to 2 h	ND
Mei 2014 <sup>31</sup>	0 to 2 h	2 to 24 h
Özünlü 2005 <sup>32</sup>	ND	ND
Paech 2002 <sup>33</sup>	ND	ND
Park 2014 <sup>34</sup>	0 to 1 h	6 to 24 h
Park 2011 <sup>35</sup>	0 to 2 h	6 to 24 h
Purhonen 2006 <sup>36</sup>	0 to 2 h	2 to 24 h
White 2007 <sup>37</sup>	Before discharge <sup>b</sup>	After discharge <sup>b</sup>

IA + AE, inhalational anaesthesia with pharmacological antiemetic prophylaxis; ND, no data; PONV, postoperative nausea and vomiting; TIVA, total intravenous anaesthesia. <sup>a</sup>Duration of stay in the recovery room in this study was not reported. <sup>b</sup>Patients were ready to be discharged at median 242 (TIVA) and 216 (IA + AE) min.

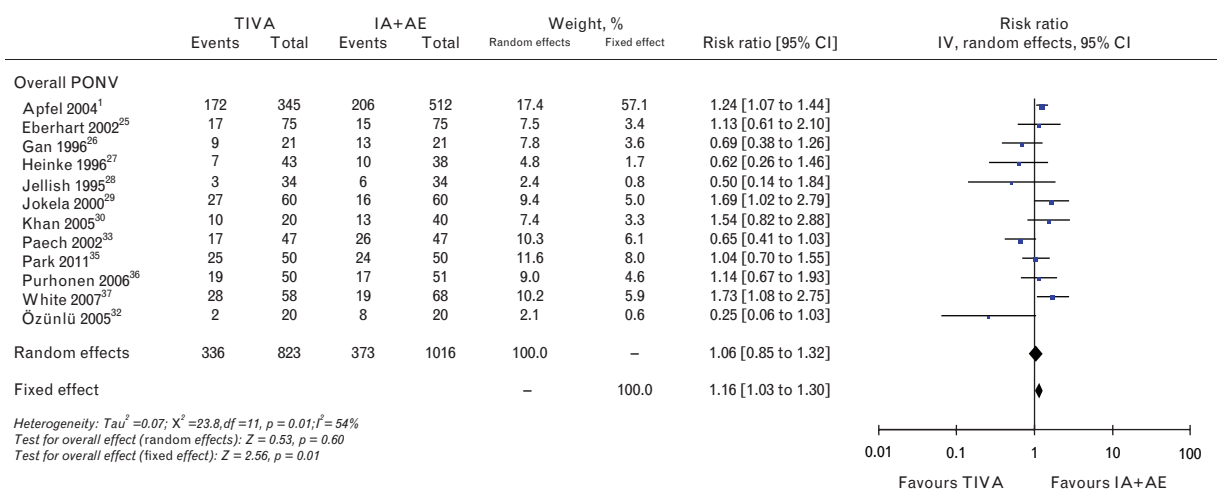
( $P=0.073$ , Fig. 4). No funnel plot asymmetry was detected for early PONV ( $P=0.27$ , Supplemental Digital Content Figure 3, <http://links.lww.com/EJA/A101>).

## Discussion

The meta-analysis summarises data from 14 prospective randomised trials and a total of more than 2000 patients. In our primary analysis, there was no difference in the overall risk of PONV, POV, need for rescue medication and early PONV in patients receiving TIVA compared with patients receiving IA + AE. However, patients receiving TIVA were more likely to suffer from PONV in the late postoperative phase than patients receiving

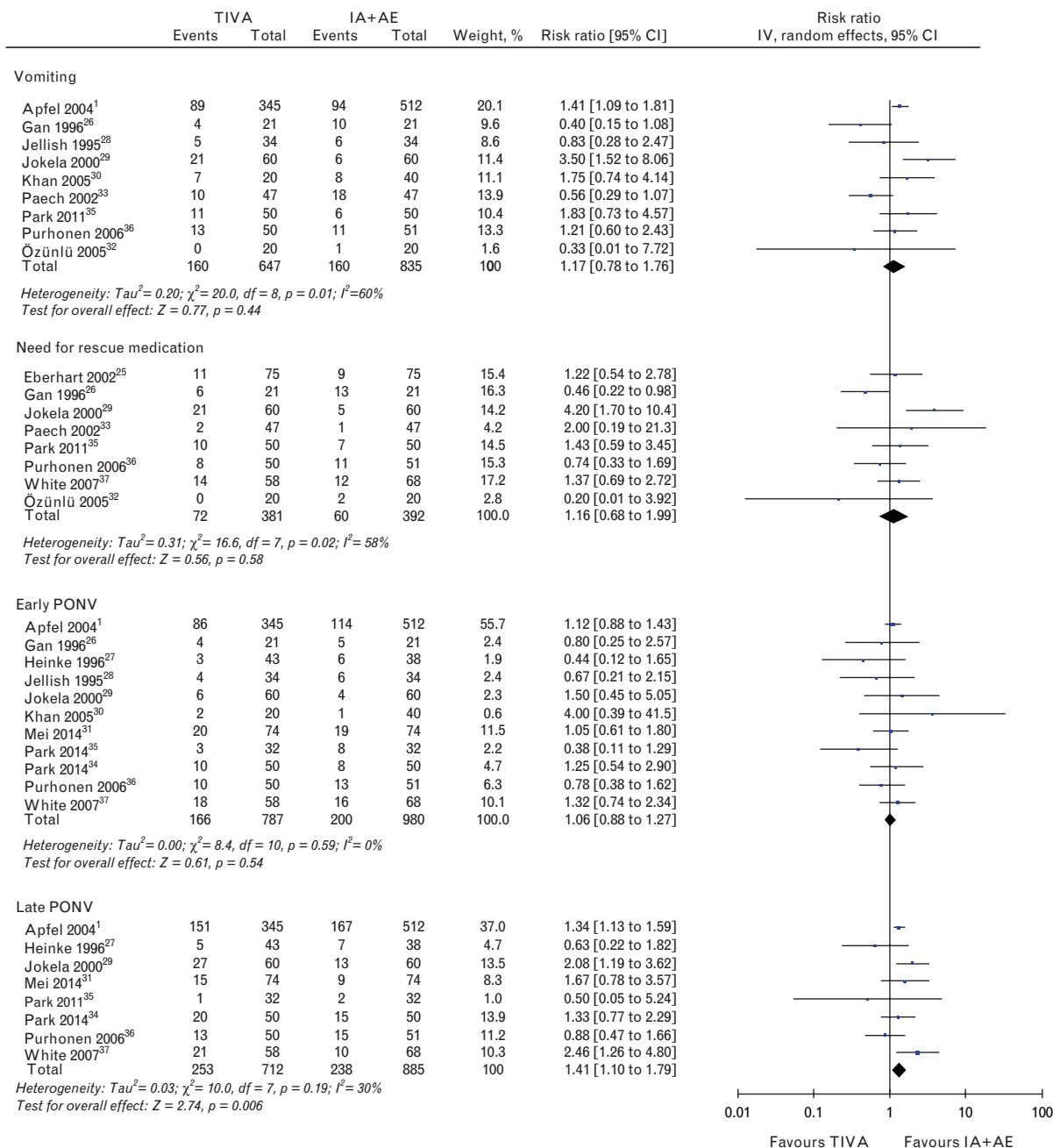
IA + AE. Also, we found evidence of a publication bias with smaller trials favouring TIVA.

As PONV has generally been attributed to inhalational anaesthetics,<sup>1</sup> recommendations to reduce the patient's risk include substituting TIVA for the inhalational anaesthetics. This strategy is supported by the notion that propofol itself provides antiemetic properties.<sup>38</sup> As, in different clinical settings, some advantages (or disadvantages) of a type of anaesthetic are judged to be less (or more) relevant than others, factors apart from the risk of PONV may guide a physician's choice of anaesthetic.<sup>9</sup> In obese patients, time to awakening from anaesthesia is more precise after desflurane compared with propofol.<sup>10</sup> Furthermore, propofol depresses sympathetic outflow and causes arterial hypotension particularly in patients at risk of experiencing adverse cardiovascular events.<sup>39</sup> In contrast, sympathetic reflexes and arterial pressure are better maintained with inhalational anaesthetics.<sup>39</sup> Moreover, in animal models and highly selected clinical situations, potent organ protective effects have been demonstrated for all inhalational anaesthetics.<sup>40,41</sup> On the other hand, as well as decreasing PONV,<sup>1</sup> propofol significantly reduces the incidence of postoperative shivering<sup>42</sup> and is associated with a decreased incidence of emergence agitation.<sup>43</sup> In this context, our analysis shows that, if a physician chooses not to substitute TIVA for an inhalational anaesthetic, then the administration of single-drug antiemetic prophylaxis is sufficient to compensate for the missing reduction in a patient's risk of PONV. Because inhalational anaesthetics increase the incidence of PONV, particularly in the early postoperative phase,<sup>44</sup> to investigate differential effects on early and late PONV, we also evaluated PONV by the time of

**Fig. 2**

Forest plot of the primary outcome overall PONV. Additional results using a fixed effect model are reported because of significant funnel plot asymmetry with smaller studies favouring TIVA. IA + AE, inhalational anaesthesia with pharmacological antiemetic prophylaxis; IV, inverse variance; PONV, postoperative nausea and vomiting; TIVA, total intravenous anaesthesia.

Fig. 3



Forest plots for POV, postoperative need for antiemetic rescue medication, PONV in the early and PONV in the late phase. IA + AE, inhalational anaesthesia with pharmacological antiemetic prophylaxis; IV, inverse variance; PONV, postoperative nausea and vomiting; POV, postoperative vomiting; TIVA, total intravenous anaesthesia.

its occurrence. We did not find any difference between the two groups with respect to early PONV. In contrast, our analysis shows that patients receiving TIVA had a higher risk of experiencing PONV in the late postoperative phase, starting 2 to 6 h after surgery. As propofol has antiemetic properties,<sup>38</sup> it may be assumed that early protection is caused by residual propofol at the effect sites after cessation of its administration. However, when

propofol has been eliminated from the body, patients will be unprotected if additional pharmacological prophylaxis has not been initiated. These findings are of particular relevance for ambulatory surgery when antiemetic rescue medication to treat PONV beginning 2 to 6 h after surgery may not be available.<sup>45</sup> The clinical relevance of late PONV following TIVA is supported by the observation that insufficient control of PONV is the leading cause of

Table 3 Risk of bias assessment for each trial

	Random sequence generation	Allocation concealment	Blinding of participants/personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall bias estimation
Apfel 2004 <sup>1</sup>	+	+	+	+	+	?	+	Low
Eberhart 2002 <sup>25</sup>	?	?	?	?	?	?	+	Moderate
Gan 1996 <sup>26</sup>	+	+	?	+	?	?	+	Low
Heinke 1996 <sup>27</sup>	?	?	?	+	?	?	+	Moderate
Jellish 1995 <sup>28</sup>	?	?	—	+	?	?	+	High
Jokela 2000 <sup>29</sup>	?	?	?	+	?	?	+	Moderate
Khan 2005 <sup>30</sup>	?	?	?	?	?	?	+	Moderate
Mei 2014 <sup>31</sup>	?	?	+	+	+	?	+	Low
Özünü 2005 <sup>32</sup>	+	?	+	+	?	?	+	Low
Paech 2002 <sup>33</sup>	+	?	?	—	+	?	+	High
Park 2014 <sup>34</sup>	+	?	?	+	?	?	+	Moderate
Park 2011 <sup>35</sup>	+	?	?	?	+	?	+	Moderate
Purhonen 2006 <sup>36</sup>	?	+	+	?	?	?	+	Moderate
White 2007 <sup>37</sup>	+	+	+	—	?	?	+	High

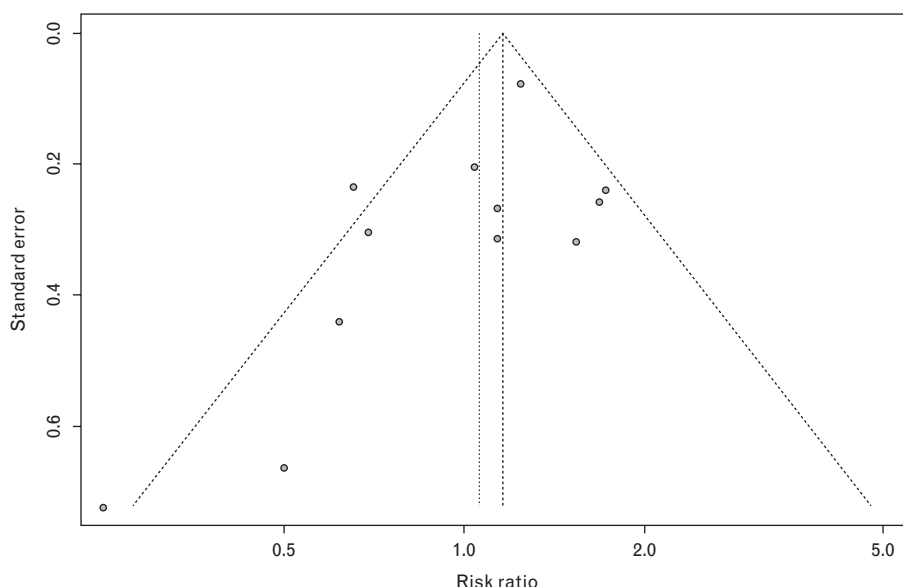
+, low risk of bias; ?, unclear risk of bias; —, high risk of bias.

unexpected hospital admission after ambulatory surgery.<sup>46</sup> Thus, the risk of late PONV and postdischarge nausea and vomiting<sup>45</sup> needs to be recognised and administration of sufficient prophylaxis initiated.

When considering PONV prophylaxis with antiemetics, potential side-effects warrant discussion: high dosages of most available antiemetics prolong cardiac QT interval.<sup>47</sup> For these reasons, the antiemetic droperidol was labelled with a black box warning by the American Food and Drug

Administration in 2001. This was followed by an intense debate, with the result that now the dose administered for prophylaxis and treatment of PONV is considered to be well tolerated as it is some 10-fold lower than the doses given historically for neurolept anaesthesia.<sup>48–50</sup> Other side-effects are characteristic of specific drugs,<sup>7</sup> e.g. headache after 5-hydroxytryptamine (5-HT<sub>3</sub>) antagonists or sedation after droperidol or dimenhydrinate.<sup>51</sup> Although slight increases in blood glucose concentration may be observed after dexamethasone administration in

Fig. 4



Funnel plot for the primary outcome, overall postoperative nausea and vomiting with weighted regression. The filled circles represent estimated treatment effects (RR) and its precision (standard error) for each individual study. Also, the random-effects estimate (vertical dotted line) as well as the fixed-effect estimate (vertical dashed line) with 95% confidence interval limits (diagonal dashed lines) are shown in the figure. In the absence of small-study effects, the treatment effects (filled circles) would scatter symmetrically around a common average treatment effect resulting in a symmetrical triangle. However, the figure depicts three studies with high standard errors clustering asymmetrically to the left (favouring TIVA) with no corresponding studies on the right side of the figure (favouring IA + AE). IA + AE, inhalational anaesthesia with pharmacological antiemetic prophylaxis; RR, relative risk; TIVA, total intravenous anaesthesia.



nondiabetic patients,<sup>52</sup> low doses of dexamethasone are proven not to increase the risk of surgical site infection.<sup>53,54</sup> To add to this discussion, we identified six studies which investigated perioperative adverse events, including dizziness, headache, myalgia, drowsiness and shivering. Except for a trend towards increased postoperative shivering following IA + AE, which has been known for decades to be associated with inhalational anaesthetics,<sup>42</sup> we did not find any difference between the two groups. We acknowledge that for the individual side-effects, the data came from only one or two studies and we could not include two of the six studies in the analysis as no data on adverse events were given. Nevertheless, despite the small number of studies, we feel that our findings do not contradict the general notion that the use of low-dose antiemetics for PONV prophylaxis is well tolerated.

Our funnel plot analysis showed significant asymmetry, suggesting a publication bias favouring TIVA. This observation is supported by our subgroup analysis stratifying studies by study size: studies involving more than 100 patients favoured IA + AE, whereas smaller studies tended to favour TIVA. Although other reasons for funnel plot asymmetry exist,<sup>16</sup> we decided to extend our analysis to assess the implications for our findings: when heterogeneity is high and random-effects modelling is applied then smaller studies are weighted disproportionately higher than larger studies, so we re-examined our primary analysis using a fixed effect model.<sup>16</sup> With fixed effect modelling, TIVA was actually inferior to IA + AE in preventing overall PONV (Fig. 2). We would like to emphasise that this analysis was conducted *a posteriori*, and its results are merely explorative. To exclude any further bias because of poor study quality, individual risk of bias for each study was assessed, revealing an overall moderate risk. Excluding studies with high risk of bias did not change the results of our primary analysis. Finally, in the face of significant heterogeneity in our primary analysis, we estimated the overall quality of evidence<sup>19</sup> to be 'moderate'.

### Limitations

Even with antiemetic prophylaxis, PONV still occurred in a high proportion (39%) of patients across all studies. Thus, irrespective of their relative effectiveness, neither strategy in isolation reduced patients' risk of PONV sufficiently. Accordingly, we would emphasise that only a multimodal approach, including administration of multiple prophylaxes, reduces the incidence of PONV satisfactorily in high-risk patients undergoing general anaesthesia. Thus, adding one or more additional antiemetic- to both strategies will further decrease the incidence of PONV. However, the aim of our analysis was to establish the relative effect of single pharmacological prophylaxis compared with TIVA, which is why we excluded studies investigating multiple prophylaxes.

Secondly, it has been shown that titration of inhalational anaesthesia to higher levels of bispectral index (BIS) with avoidance of unnecessary deep anaesthesia reduces the incidence of postoperative vomiting.<sup>55</sup> Unfortunately, only one study controlled for anaesthesia depth,<sup>31</sup> making a sensitivity analysis impossible. In the IMPACT trial, the BIS level was one of the randomised factors,<sup>56</sup> but these data were not published.<sup>1</sup> Therefore, it is possible that the relative effectiveness of pharmacological prophylaxis might be even more pronounced when anaesthetic depth is controlled; however, our data do not allow us to make any assumption about this effect.

Third, we pooled groups with different antiemetic classes and subclasses in our main analysis. Therefore, our primary findings are limited to the comparison of TIVA versus 'uncontrolled' pharmacological antiemetic prophylaxis and the results might differ between antiemetic classes. As most of the included studies investigated 5-HT<sub>3</sub> antagonists, it might be concluded that our findings are more or less restricted to that class. However, as has been shown in the IMPACT trial,<sup>1</sup> as well as many others, the prophylactic effect of antiemetics from different classes is comparable when adequate doses are used.<sup>7</sup>

Finally, although N<sub>2</sub>O is known to trigger PONV,<sup>57</sup> we did not make any preconditions regarding its use. Consequently, administration of N<sub>2</sub>O varies among studies and has also been administered to 'TIVA' groups in four trials. In each of these, the corresponding IA + AE groups received the same dose of N<sub>2</sub>O. Because there is no specific interaction between N<sub>2</sub>O and propofol or pharmacological antiemetic prophylaxis,<sup>1</sup> we tend to assume that N<sub>2</sub>O independently increased the risk for PONV in both groups to the same amount. In contrast, N<sub>2</sub>O was administered only in the IA + AE groups in three studies. Accordingly, we performed a sensitivity analysis excluding these studies which did not change any of our main findings. However, without these studies, patients receiving TIVA were even more likely to suffer from late PONV (risk ratio 1.51, as compared with 1.41).

In summary, our meta-analysis shows that when substitution of TIVA for inhalational anaesthetics to reduce a patient's risk of PONV is not an option, then the PONV risk can be compensated to an equivalent degree by the use of a single-drug pharmacological prophylaxis. Finally, as neither strategy alone decreases PONV sufficiently in high-risk patients, the use of multiple prophylactic methods should be instituted to minimise the incidence of PONV and improve surgical outcome.

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