Title: Efficacy and Tolerability of High- vs Low-Volume Split-Dose Bowel Cleansing Regimens for Colonoscopy: a Systematic Review and Meta-analysis

Short title: Low vs High-Volume Split dose for Bowel Prep

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Abbreviations:

- colorectal cancer (CRC)
- Polyethylene Glycol (PEG)
- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
- International Prospective Register of Systematic Reviews (PROSPERO)
- randomized controlled trials (RCTs)
- Boston Bowel Preparation Scale (BBPS)
- Ottawa Bowel Preparation Score (OBPS)
- intention-to-treat (ITT)
- per-protocol (PP)
- risk ratio (RR)
- confidence interval (CI)
- 2L-PEG with citrate and simethicone (PEG-C)
- sodium picosulfate with magnesium citrate (SPMC)
- oral sulfate solution (OSS)

Abstract:

Background & Aims: Efficacy of bowel preparation is an important determinant of outcomes of colonoscopy. It is not clear whether approved low-volume polyethylene glycol (PEG) and non-PEG regimens are as effective as high-volume PEG regimens when taken in a split dose.

Methods: In a systematic review of multiple electronic databases through January 31, 2019 with a registered protocol (PROSPERO: CRD42019128067), we identified randomized controlled trials that compared low- vs high-volume bowel cleansing regimens, administered in a split dose, for colonoscopy. The primary efficacy outcome was rate of adequate bowel cleansing, and the secondary efficacy outcome was adenoma detection rate. Primary tolerability outcomes were compliance, tolerability, and willingness to repeat. We calculated relative risk (RR) and 95% CI values and assessed heterogeneity among studies by using the I^2 statistic. The overall quality of evidence was assessed using the GRADE framework.

Results: In an analysis of data from 17 randomized controlled trials, comprising 7528 patients, we found no significant differences in adequacy of bowel cleansing between the low- vs high-volume split-dose regimens (86.1% vs 87.4%; RR, 1.00; 95% CI, 0.98–1.02) and there was minimal heterogeneity (I^2=17%). There was no significant difference in adenoma detection rate (RR, 0.96; 95% CI, 0.87–1.08) among 4 randomized controlled trials. Compared with high-volume, split-dose regimens, low-volume split-dose regimens had higher odds for compliance or completion (RR, 1.06; 95% CI, 1.02–1.10), tolerability (RR, 1.39; 95% CI, 1.12–1.74), and willingness to repeat bowel preparation (RR, 1.41; 95% CI, 1.20–1.66). The overall quality of evidence was moderate.

Conclusions: Based on a systematic review of 17 randomized controlled trials, low-volume, split-dose regimens appear to be as effective as high-volume, split-dose regimens in bowel cleansing and are better tolerated, with superior compliance.

KEY WORDS: endoscopy, comparative, adherence, screening

Need to Know

Background: It is not clear whether approved low-volume polyethylene glycol (PEG) and non-PEG regimens are as effective as high-volume PEG regimens when either are taken in a split dose.

Findings: In a systematic review of 17 studies, we found split-dose, approved, low-volume regimens to be effective in bowel cleansing and more acceptable than high-volume regimens.

Implications for patient care: Patients can effectively prepare for colonoscopy with split-dose, low-volume cleansing regimens.

BACKGROUND

Adequate bowel cleansing is critical for detection of colorectal neoplasia and to minimize the risk of missed lesions and post-colonoscopy colorectal cancer (CRC) [1–3]. In addition, it improves colonoscopy efficiency, as inadequate cleansing has been associated with shorter surveillance intervals [4,5], longer procedure time [6] and need for early repetition of colonoscopy [7].

Based on a favorable combination of high efficacy and high safety [8–10], a split regimen of high-volume (3-4 liters, L) Polyethylene Glycol (PEG) regimen has become the reference standard for bowel preparation [11,12]. Suboptimal patient compliance and acceptability have been attributed to the large volume of bowel preparation to be administered, affecting patient experience and willingness to repeat the procedure [8,13]. Bowel preparation has been consistently rated as the worst phase of colonoscopy experience.

When considering patient experience as a relevant outcome of bowel preparation, low-volume PEG and non-PEG split regimens appear to be an attractive alternative, due to a substantial reduction in the volume to be administered, i.e. $\leq$2 L. Despite their hyper-osmolarity, these low-volume regimens appear to be safe after exclusion of high-risk patients, i.e. those with renal or cardiovascular comorbidities [8,11–13].

Thus, it is clinically relevant to assess whether low-volume split preparations are equally effective as high-volume split PEG regimens in order to implement their use in clinical practice. Most of the previous meta-analyses did not show difference between split and non-split regimens, only partially addressing such an issue [13,14]. In addition, the only systematic review focusing on split-administration included non-approved low-volume PEG regimens (i.e., Miralax-Gatorade) [8]. There is currently a paucity of data comparing high-volume PEG and most of the low-volume, non-PEG regimens. [8].

The primary aim of this systematic review and meta-analysis is to assess whether low-volume PEG and non-PEG regimens are equally efficacious as high-volume PEG regimens, when administered in a split dose.

METHODS

The methods of our analysis and inclusion criteria were based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [15]. Our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, www.crd.york.ac.uk/prospero/) on March 2019 (CRD42019128067).

Data sources and search strategy

A comprehensive electronic literature search was conducted in PubMed/MEDLINE, EMBASE and Scopus (up to January 31st 2019) to identify eligible studies comparing low and high volume bowel preparation before colonoscopy. PROSPERO was searched for ongoing or recently completed systematic reviews.References of the studies which were included were also manually searched for eligible articles. . Literature search was performed and verified by two authors (MS; GV).

The search for studies of relevance was performed using the following text words and corresponding Medical Subject Heading/entrée (MeSH) terms when possible: “bowel preparation”, “low volume”, “split dose”, “split regimen”. The Medline search strategy was: “(((((low[All Fields] OR (low[All Fields] AND volume[All Fields])) OR (low[All Fields] AND dose[All Fields])) AND split[All Fields]) OR (split[All Fields] AND dose[All Fields])) OR (split[All Fields] AND ("clinical protocols"[MeSH Terms] OR ("clinical"[All Fields] AND "protocols"[All Fields]) OR "clinical protocols"[All Fields] OR "regimen"[All Fields]))) AND (("intestines"[MeSH Terms] OR "intestines"[All Fields] OR "bowel"[All Fields]) AND preparation[All Fields])”.

Inclusion and exclusion criteria

For the purpose of our meta-analysis, we screened all clinical studies published as full text paper or presented as an abstract at international meetings, for the following inclusion criteria:

(I) Population: all adults undergoing elective colonoscopy, irrespective of the indication.

(II) Intervention: all low-volume bowel preparation regimens administered in split dose.

(III) Comparison: all high-volume PEG-based bowel preparation regimens administered in split dose.

(IV) Outcome: bowel preparation efficacy was recorded as the primary outcome. Secondary outcomes included compliance with the regimen, willingness to repeat the same bowel solution, palatability of the regimen, side effects.

(V) Study design: only randomized controlled trials (RCTs) were considered.

Exclusion criteria were as follows:

(I) Essential information not available;

(II) Studies investigating bowel preparation regimen in special patients, such as pediatric patients, patients with a history of colorectal resection, inflammatory bowel disease patients or patients with a previous poor bowel preparation.

(III) Studies investigating bowel preparation regimens not approved and/or discouraged by European Guidelines (i.e., sodium phosphate).

(IV) Studies investigating bowel preparation regimens obtained by a non-approved combination of two products (e.g. Miralax-Gatorade).

(V) Studies not reporting colon cleansing as a categorical parameter.

Outcome assessment

In our systematic review and meta-analysis, the primary outcome was the rate of patients with a successful bowel preparation in the 1) overall colon and 2) right colon. Considering the expected variation in outcomes nomenclature among the studies, we pre-defined a successful bowel preparation as a Boston Bowel Preparation Scale (BBPS)[16] score of ≥6, an Ottawa Bowel Preparation Score (OBPS)[17] of <5, an excellent or good bowel preparation reported by the endoscopists using the Aronchik Scale [18], or other non-validated 3-, 4- or 5-point scales. A successful right colon preparation was defined as BBPS ≥2 or an OBPS ≤2 in the right colon. Data on tolerability and side effects were extracted from the results of non-standardized questionnaires administered to the patients before colonoscopy: compliance with bowel preparation was defined as consumption of 75-100% of the prescribed solution, according to the cut-off adopted in the different series. Further, secondary outcomes were the proportion of patients willing to repeat the same bowel preparation and the rate of patients who reported a good/neutral palatability (tolerability) of the prescribed solution. Side effects such as abdominal bloating, nausea, vomiting, and abdominal pain/cramping were also reported. Other secondary outcomes were the rate of patients in whom at least an adenomatous lesion was detected (Adenoma Detection Rate, ADR), and the rate of patients with an excellent level of cleansing, when reported. We

included withdrawals in the intention-to-treat (ITT) analysis. When both were presented, values from ITT were preferred to per-protocol (PP).

Selection process

Two review authors (MS; GV) independently screened the titles and abstracts. Full reports were obtained for all titles that appeared to meet the inclusion criteria or where there was any uncertainty and they were screened based on the selection criteria. Any disagreement was resolved by consensus with the senior author (CH). The reasons for excluding trials were recorded. Neither of the review authors were blinded to the journal titles or to the study authors or institutions. When there were multiple articles from a single institute, we used the latest publication from that institute.

Data extraction

Using standardized forms, two reviewers (MS, GV) extracted data independently. Any disagreements were resolved by discussion with two senior authors (CH and AR). The following data were extracted for each study: first author, year of publication, study design, number of endoscopy centers, country, number of patients, withdrawals, patients with an adequate level of cleansing, patients with an excellent level of cleansing, compliance, willingness to repeat, palatability, side effects (abdominal pain, bloating, nausea, vomiting, sleep disturbance), and ADR.

Statistical Analysis

As the outcomes were dichotomous events, the measure of effect of interest were pooled proportions and risk ratios (RR) along with 95% confidence interval (95% CI). P-value < 0.05 was considered statistically significant. A random effects model described by DerSimion and Laird was used for calculating pooled rates. Heterogeneity among studies was assessed by calculating the I^2 measure of inconsistency. An I^2-value of 0-30%, 30-60%, 50-90% and 75-100% was indicated as low, moderate, substantial and considerable heterogeneity, respectively. Publication bias was assessed by funnel plot with trim-and-fill methodology and by Egger's regression test. Sensitivity analysis was performed for the most clinically relevant variables. Statistical analyses were conducted with *metafor* package for R [19,20]. Heterogeneity was investigated through subgroup analyses according to country, type of study (i.e. single or multicenter) and type of bowel preparation, along with meta-

regression including the following variables: country, publication year, type of bowel preparation, type of study, mean age and sex.

Quality assessment

Study quality was assessed by the Cochrane risk bias tool for randomized studies. Two reviewers (MS, GV) assessed quality measures for included studies and discrepancies were adjudicated by collegial discussion. We appraised the overall quality of evidence by applying GRADE methodology for the primary outcome[21].

RESULTS

Study characteristics and quality

The literature search resulted in 727 articles **(Figure 1).** After reviewing the title and abstract, 24 articles were retrieved as full text. Of these, 17 articles fulfilled the inclusion criteria and were finally included in the systematic review [22–39].

Studies characteristics are briefly reported in **Table 1.** All studies were published between 2008 and 2019. Six studies were performed in Italy (4,928 patients), 5 studies (1,015 patients) in Korea, 4 studies(767 patients) in Netherlands, and the remaining studies in Czech Republic (259 patients), Germany (359 patients) and Lebanon (200 patients), respectively. Eleven studies involved multiple centers, while 7 studies were single-center experiences.

Regarding bowel preparation scales, the Aronchick scale was used in 5 studies, the Ottawa bowel preparation scale in 4 studies, the Boston bowel preparation scale in 4 studies, and non-validated scales were used in 8 studies.

Altogether, the 17 studies included 7,528 patients in the intention-to-treat analysis, 3,749 being in the low-volume split group and 3,779 in the high-volume split group. Baseline characteristics in terms of age and gender were comparable between the two groups. Risk of bias was low for all except for allocation concealment (i.e. blinding of endoscopists at randomization) and incomplete outcome data (i.e., for excluded patients) (**Appendix 1**). Reasons to remain included at PP analysis are explainedin **Appendix 2.**

Regarding the type of low-volume regimen, 2L-PEG with ascorbic acid as adjuvant (PEG-A) was the low-volume preparation adopted in 9 studies, a combination of 2L-PEG with citrate and simethicone (PEG-C) in 4 studies (with the addition of bysacodil in 2), sodium picosulfate with magnesium citrate (SPMC) in 3 studies, and oral sulfate solution (OSS) in 2 studies.

Primary outcome: Efficacy (overall and right colon)

Low-volume PEG and non-PEG regimens vs. high-volume regimen in split dose

Based on the data reported by all the 17 studies (7,528 patients, 36 arms of treatment), low-volume split bowel regimens had an equivalent proportion of patients with an adequate bowel preparation compared with split-dose high-volume PEG [**86.1%** (95%CI 82.6-90%) vs. **87.4%** (95%CI 84.1-90.7%)]. The pooled RR was 1.00 (95% CI 0.98-1.02; I^2= 17%; p= 0.2) showing no statistically significant difference with low heterogeneity (**Figure 2**) (Table 2).

In the studies reporting data on right colon (10 studies, 5,288 patients), there was no difference in efficacy between low-(PEG and non-PEG) volume and high-volume PEG regimens [**91.2**% (95%CI 89.1-93.3%) vs. **89.6%** (95%CI 87.3-92%)] with a RR of 1.01(95% CI 0.99-1.03; I^2= 18%; p=0.22) (Figure 3) (**Table 2**).

Publication bias was assessed using Funnel plots and Egger's test (p=0.13 and p=0.06) for both the primary outcomes (**Appendix 3**). According to trim-and-fill, no significant difference between the included studies, with or without trimmed studies, was found for primary outcome.

Low-volume PEG

Split-dose 2L-PEG with the adjuvant of ascorbic or citric acid had a comparable proportion of patients with an adequate bowel preparation compared with high-volume split PEG [13 studies: 6,593 patients; **84.9%** (95%CI 80.8-89%) vs. **86.3%** (95%CI 82-90.5%)] with a RR of 1.00(95% CI: 0.96-1.02; I^2= 38%; p=0.09) **Table 2**]. For those studies reporting data on right colon cleansing (7 studies: 4,805), no difference in efficacy between low- and high-volume PEG was found [**90.5%** (95%CI 87.3-93.6%) vs. **88.4%** (95%CI 85-91.9%)] with a RR of 1.01(95% CI: 0.98-1.04; I^2= 48%; p=0.07) (**Table 2**). There was no significant publication bias (Egger's test: p=0.18 and p=0.32) for the two end-points.

Separate analysis for PEG-A and PEG-C is reported in **Table 2 and Appendix 4.**

Low-volume non-PEG

As shown in **Table 2,** split-dose non-PEG regimens had a comparable proportion of patients with an adequate bowel preparation compared with high-volume split PEG [5 studies: 935 patients; **89.5%** (95%CI 83.6-95.4%) vs. **91%** (95%CI 87.8-94.2%)] with a RR of 1.00 (95%CI: 0.96-1.04; I^2= 0%; p=0.72).

For those studies reporting data on right colon cleansing, no difference in efficacy between low-volume non-PEG and high-volume PEG regimens was found [3 studies: 483 patients; **92.2%** (95%CI 88.8-95.6%) vs**91.4%** (95%CI 87.9-94.9%)] with an RR of 1.01(95% CI: 0.96-1.06; I^2= 0%; p=0.99) (**Table 2**). No significant publication bias was seen (Egger's test: p=0.32 and p=0.90) for the two end-points.

Separate analysis for SPMC and OSS is reported in **Table 2 and Appendix 4.**

Secondary outcomes: Patient experience (Table 3)

Compliance

In 13 studies (6,570 patients) assessing compliance to bowel preparation, patients receiving low-volume PEG and non-PEG regimens were more likely to complete the preparation than those receiving high-volume volume preparation [**92.8%** (95%CI 89.6-96.1%) vs. **86.8%** (95%CI 82.1-91.4%)] with a RR of 1.06(95% CI: 1.02-1.10; I^2= 85%; p<0.01). Separate analysis for PEG and non-PEG low-volume regimens are provided in **Table 3 (Forest Plot in Appendix 5)**.

Tolerability

In 9 studies (5,364 patients) assessing tolerability (i.e. palatability/acceptability) of bowel preparation, the low-volume PEG and non-PEG group demonstrated statistically significantly higher tolerability as compared with the high-volume group [**72.5%** (95%CI 56.4-88.7%) vs. **49.6%** (95%CI 28.8-70.5%)] with a RR of 1.39[95% CI: 1.12-1.74; I^2= 98%; p<0.001)]. Separate analysis for PEG and non-PEG low-volume regimens are provided in **Table 3 (Forest Plot in Appendix 6).**

Willingness to repeat the same preparation

In the 4 studies (815 patients) assessing the willingness to repeat the same bowel preparation regimen, there was a significant difference in favour of low-dose PEG and non-PEG regimens as compared to high-volume PEG [**89.5%** (95%CI 80.3-98.7%) vs. **61.9%** (95%CI 47.8-76.1%)] with a RR of 1.41[95% CI: 1.20-1.66; I^2= 71%; p<0.001)]. Separate

analysis for PEG and non-PEG low-volume regimens are provided in **Table 3 (Forest Plot in Appendix 7).**

Adverse events, adenoma detection rate and sensitivity analysis

Data on adverse events for each study, ADR, and sensitivity analysis (per protocol analysis, validated scales, exclusion of BBPS, year of publication) are summarized in **Appendix 8 and 9**, respectively. There was no significant difference in adenoma detection rate between low- and high-volume regimens (RR: 0.96; 95% CI 0.87, 1.08).

No variable was found to significantly influence the pooled estimates for the primary outcome in the meta-regression analysis (**Appendix 10**). Compliance to low-volume bowel preparation was significantly worse in multicenter studies (p = 0.013) (**Appendix 11**). Tolerability to low-volume bowel preparation was significantly increased among studies using SPMC (p=0.004), whereas it was inversely related to the percentage of CRC screening patients (**Appendix 12**). Willingness to repeat low-volume bowel preparation was significantly increased in studies using PEG-A than in PEG-CS ones (p=0.003), and among older patients (**Appendix 13**). Subgroup analyses according to country, type of study (i.e. mono or multicenter) and type of preparation according to adjuvants were consistent with main analyses for both primary and secondary outcomes (**Appendix 14 and 15**, respectively).

GRADE

The quality of evidence was assessed by applying GRADE methodology. Overall, moderate quality of evidence shows that split-dose low-volume bowel preparations are equally effective as high-volume regimens. The level of evidence for RCTs was downgraded due to inconsistency owing to heterogeneity among patients (i.e. different indications to colonoscopy) and scales for bowel cleansing evaluation. Details can be found in **Appendix 16**.

DISCUSSION

According to our meta-analysis, both low- and high-volume preparations used in split dose are equally effective in cleansing the overall colon and the right colon. The equivalence in efficacy was independent of the type of preparations – i.e. PEG or non-PEGlow-volume regimens, as all the individual preparations analyzed showed a similar pattern of efficacy. In addition, our analysis confirms a better patient experience, especially in terms of willingness to repeat the same preparation, with a low-volume regimen.

Our analysis shows that the low-volume PEG and non-PEG regimens are comparative to high-volume PEG regimen which is different whencompared to the previous meta-analysis showing superiority in efficacy of a high-volume PEG over a low-volume PEG regimen used in a split dose [8]. First, by including 7 more low-volume PEG and 3 additional non-PEG RCTs compared to the previous meta-analysis,we increased the number of patients by 7-fold and 2-fold respectively. This also allowed us to make statistically meaningful comparison between each individual non-PEG regimen and a high-volume regimen, as only one RCT for each regimen was available in the previous review [8]. Secondly, we excluded non-approved regimens of low-volume PEG preparations, such as those based on the combination between PEG and Gatorade, as well as those preparations which are discouraged, such as sodium phosphate. Both of these factors attenuated thesuperiority shown for high-volume PEG split regimens. Although similar results have been shown in a previous meta-analysis [13], the equivalence we showed between low- and high-volume regimens was restricted to studies adopting a split regimen which makes it different from the previous meta-analysis by Xie et al. As non-split dose series represent a mere confounder [11,12], our analysis with only split dose regimens is more clinically meaningful setting for decision-making process. Third, we did not limit the efficacy of cleansing in the overall colon [8,13], but we also showed the equivalence between low- and high-volume regimens in the right colon. This is clinically relevant, as both adenomatous and serrated lesions tend to be more frequently flat and subtle in the proximal colon, requiring good preparation of the right colon.

The better patient experience achieved by low-volume regimens is also clinically relevant. Low-volume regimens were superior in each individual end-point we selected for patient experience, with a similar trend for most of the adverse events related with bowel preparation. When coupling the equivalent efficacy with a better experience, there is

compelling evidence to recommend a low-volume split regimen as alternative to the high-volume regimen, unless additional factors, such as cost or patient preferences, supports a different choice. Of note, the advantage of the low-volume group in terms of willingness to repeat bowel preparation was significantly increased when considering PEG-A vs. PEG-CS studies, suggesting a possible role of the adjuvants. The consistency of the study results across regimens with different mechanism of action – such as PEG and non-PEG agents, is unclear. This may be related tothe timing of administration – i.e. split vs. non-split, rather than just theaction of the hyperosmolar product. Thus the efficacy of the split-dose regimens could be related to both the timing of administration and also the laxative properties of the different regimens. Of note, we also excluded that the main mechanism of efficacy of low-volume regimens is a higher compliance to low- versus high-volume for two reasons. First, the equivalence between low- and high-volume was nearly the same when passing from ITT to PP analysis, despite the main difference between ITT and PP is represented by the cut-off in the amount of product actually taken; secondly, the difference between low- and high-volume regimens in terms of compliance was limited to 6%.

The strength of our analysis is not only because of the large number of patients , but also thelow heterogeneity found in most of the comparisons on primary outcomes, as well as by its robustness in any of the sensitivity analysis applied. This is to be related to the fact that the operators in such studies are fully blinded to the product used, while the fact that patients were not blinded may have affected the secondary rather than primary outcomes.

The main limitation of our analysis is that an intrinsic selection bias in high-quality randomized trials – i.e. the exclusion of patients with major comorbidities, which limits the assessment of safety of the hyperosmolar low-volume regimens. Thus, caution is required when prescribing these agents to frail or severely-ill patients, whereas the isotonic high-volume regimens may be a safer choice. The same selection bias may apply to inpatients, patients with prior failed preps, those with prior resections, severe constipation or treated with opiates. We included studies using the Boston Bowel Preparation Scale that is somewhat suboptimal for assessing the efficacy of products as it is influenced by washing the colon during the procedure. However, only 4 studies actually used this scale, and the results were unchanged when these studies were excluded in sensitivity analysis. Adjuvants to bowel preparation may play a role in the efficacy of colon cleansing therefore acting as confounders [40]. However, subgroup analyses on PEG-A and PEG-C confirmed similar

efficacy rates. A concern regarding all the meta-analyses, including ours,on bowel preparation, is about the primary outcome being not homogeneously reported across the included studies because of the different scales used. However, we corroborated our findings through subgroup analysis pooling data of studies which used comparable definitions for bowel preparation and cleanliness.

In conclusion, our analysis shows the equivalence between low- and high-volume regimens, when a split dose administration is adopted. The better patient experience associated with such low-volume regimens indicates their potential as first-choice agents.

Table 1: Studies characteristics.

Study	Country	Centers (n)	Low-volume regimen	Patients (ITT)		Mean / Median age (range / SD)	Sex (Male, %)	Indication for the exam	Other factors influencing the preparation				Bowel Cleansing scale	Adeguate preparation (ITT)	
				Low-volume	4L				I/O status	Comorbidities	Antidepressants	Constipation		Low-Volume	4L
Ell 2008 [23]	Germany	14	PEG-A	180	179	59 (18–88)[1]	48.7%[1]	Various; Screening: 9.4%; Diarrhea: 15.6%	Inpatients: 100%	$	NA	9.4%	NV	136 (75.5%)	147 (82.1%)
Marmo 2010 [27]	Italy	3	PEG-A	217	218	58.3 (14.8)	62.5%	Various; Screening: 11.5%	Outpatients: 77.9%	$, Diabetes: 5.5%	NA	18.6%	OBPS	167 (76.9%)	160 (73.4%)
Corporaal 2010 [39]	The Netherlands	1	PEG-A	62	73	NA[2]	NA[2]	Various[2]	Outpatients: 100%	NA	NA	NA	NV	58 (93.5%)	72 (98.6%)
Jansen 2011 [24]	The Netherlands	1	PEG-A	188	182	57.7 (14.9)	41.9%	NA	Outpatients: 100%	NA	NA	NA	NV	149 (79.3%)	141 (77.5%)
Valiante 2013 [31]	Italy	1	PEG-C	140	140	63.6 (7.1) & 61.3 (7.7)[1,3]	59.4% & 64.3%[1,3]	Screening: 100%	Outpatients: 100%	NA	NA	NA	NV	128 (91.4%)	116 (82.9%)
Mathus-Vliengen 2013 [22]	The Netherlands	1	PEG-A	43	46	NA[2]	NA[2]	Various; Screening: 0%	Outpatients: 100%	$	NA	NA	OBPS	38 (88.4%)	44 (95.6%)
Moon 2014	Korea	3	PEG-A	181	180	52.3	50.2%[1]	Various;	Outpatien	$	NA	NA	NV	159	162

[28]						(11.8) & 54.0 (11.6)[1,3]		Screening: 35%	ts: 100%					(87.8%)	(90%)
Munsterman 2014 [36]	The Netherlands	1	SPMC	85	88	55.26 (13.7) & 57.39 (12.2)[3]	49.7%	Various; Screening: < 2.3%; Diarrhea: 9.8%	Outpatients: 100%	$	NA	8.1%	BBPS	79 (92.9%)	81 (92%)
Kojecky 2014 [37]	Czech Republic	3	SPMC	125	134	56.8 (16.1) & 65.0 (14.7)[3]	49.4%	Various; Diarrhea: 6.2%	Outpatients: 100%	$, Diabetes: 21.2%	NA	NA	AS	102 (81.6%)	117 (87.3%)
Kim 2014 [33]	Korea	1	SPMC	50	50	NA[2]	NA[2]	Various; Screening: 48%	Outpatients: 100%	$	NA	NA	AS	40 (80%)	42 (84%)
Parente 2015 [30]	Italy	5	PEG-C	193	189	60 (13) & 59 (14)[3]	42.9%	Various	Outpatients: 100%	$, Hypertension: 28.7%, Cirrhosis: 0.7%	NA	100%	OBPS	154 (79.8%)	153 (80.9%)
Zorzi 2015 [29]	Italy	14	PEG-A	924	938	59 (6)	55.8%	Screening: 100%	Outpatients: 100%	$	NA	16.9%	AS	872 (94.4%)	868 (92.5%)
			PEG-C	940	938									862 (91.7%)	868 (92.5%)
Sharara 2015 [38]	Lebanon	1	PEG-A	100	100	54 (13.7) & 55 (13.8)[3]	52%	Various; Screening: 44.5%	Outpatients: 100%	$	NA	0%	AS	74 (74%)	85 (85%)
Jung 2016 [25]	Korea	3	PEG-A	74	77	71.3 (5.0) & 71.2 (4.4)[1,3]	43.9%[1]	Various; Screening: 33%	Outpatients: 100%	$, Elderly (> 65 aa): 100%, Dabetes: 19.2%,	5.4%	NA	BBPS	58 (78.4%)	63 (81.8%)

										Hypertension: 40.8%, Stroke: 3.8%; Dementia: 1.5%					
Yang 2016 [35]	Korea	3	OSS	105	105	51.2 (9.3) & 53.4 (8.5)[1,3]	58.3%[1]	Various; Screening: 56.8%	Outpatients: 100%	$	NA	NA	BBPS	97 (92.4%)	96 (91.4%)
Spada 2017 [32]	Italy	6	PEG-C	45	46	NA[2]	NA[2]	NA[2]	Outpatients: 100%	$	NA[2]	NA[2]	OBPS	39 (86.7%)	38 (82.6%)
Kwak 2019 [34]	Korea	9	OSS	97	96	68.6 ± 2.9 & 69.3 ± 2.9[3]	46.1%	Various; Screening: 44%	Outpatients: 100%	$, Elderly (> 65 aa): 100%, Diabetes: 4.1%, Hypertension: 29.5%	NA	0%	BBPS	93 (95.9%)	91 (94.8%)

[1]available for Per-Protocol population, [2]available for the main cohort, [3]separately available for the 2 arms
$: Severe systemic comorbidities excluded, consistent with contraindications of bowel preparations.
NA: Not Available
AS: Aronchick Scale, BBPS: Boston Bowel Preparation Scale, I/O: Inpatient/Outpatient, ITT: intention-to-treat, NV: Non-validated scale, OBPS: Ottawa Bowel Preparation Score, OSS: Oral Sulfate Solution, PEG-A: Polyethylene Glycol plus Ascorbic Acid, PEG-C: Polyethylene Glycol-citrate, SPMC: Sodium picosulfate with magnesium citrate,

Table 2. Primary outcome in terms of efficacy of cleansing for the overall colon and right colon according to low-volume PEG and non-PEG split regimens as compared with high-volume split regimens at ITT. RR: Relative Risk; CI: Confidence Interval.

Low-volume regimens	**N° of trials**	**Patients (ITT, n)**	**Relative Risk (95% CI) All colon**	**I^2**	**N° of trials**	**Patients (ITT, n)**	**Relative Risk (95% CI) Right colon**	**I^2**
	Efficacy *all colon*				**Efficacy *right-colon***			
PEG & non-PEG	**18**	**7,528**	**1.00 [0.98, 1.02]**	**17%**	**10**	**5,288**	**1.01 [0.99-1.03]**	**18%**
- PEG	**13**	**6,593**	**1.00 [0.96, 1.02]**	**38%**	**7**	**4,805**	**1.01 [0.98-1.04]**	**48%**
-PEG-A	9	3,962	0.98 [0.94, 1.02]	40%	5	2,647	1.02 [0.99, 1.04]	1%
-PEG-C	4	2,631	1.02 [0.96, 1.08]	48%	2	2,158	1.04 [0.93-1.15]	80%
- non-PEG	**5**	**935**	**1.00 [0.96-1.04]**	**0%**	**3**	**483**	**1.01 [0.96-1.06]**	**0%**
-SPMC	3	532	0.98 [0.92-1.04]	0%	2	273	1.01 [0.94-1.08]	0%
-OSS	2	403	1.01 [0.96-1.06]	0%	1	210	1.01 [0.93-1.09]	NA

Table 3. Secondary outcomes in terms of patient experience. CI: Confidence Interval.

Secondary end-point	**Number of trials**	**Patients (ITT, n)**	**Relative Risk (95% CI)**	**I^2**
Compliance				
-PEG & non-PEG	**13**	**6,570**	**1.06 [1.02-1.10]**	**85%**
-PEG	9	5,808	1.08 [1.03-1.14]	86%
-non-PEG	4	762	1.01 [0.98-1.04]	16%
Tolerability				
-PEG & non-PEG	**9**	**5,364**	**1.39 [1.12-1.74]**	**98%**
-PEG	5	4,566	0.92 [0.85, 0.99]	84%
-non-PEG	4	742	0.51 [0.27, 0.95]	96%
Willingness to repeat				
-PEG & non-PEG	**4**	**815**	**1.41 [1.20-1.66]**	**71%**
-PEG	3	622	1.46 [1.15-1.86]	74%
-non-PEG	1	193	1.37 [1.18-1.59]	NA

Figure 1. Study flow-chart.

Figure 2. Forest plot for the primary outcome (rate of adequate level of bowel preparation in the overall colon) according to the low-volume PEG and non-PEG regimen adopted in the included studies.

Figure 3. Forest plot for the primary outcome (rate of adequate level of bowel preparation in the right colon) according to the low-volume PEG and non-PEG regimen adopted in the included studies.

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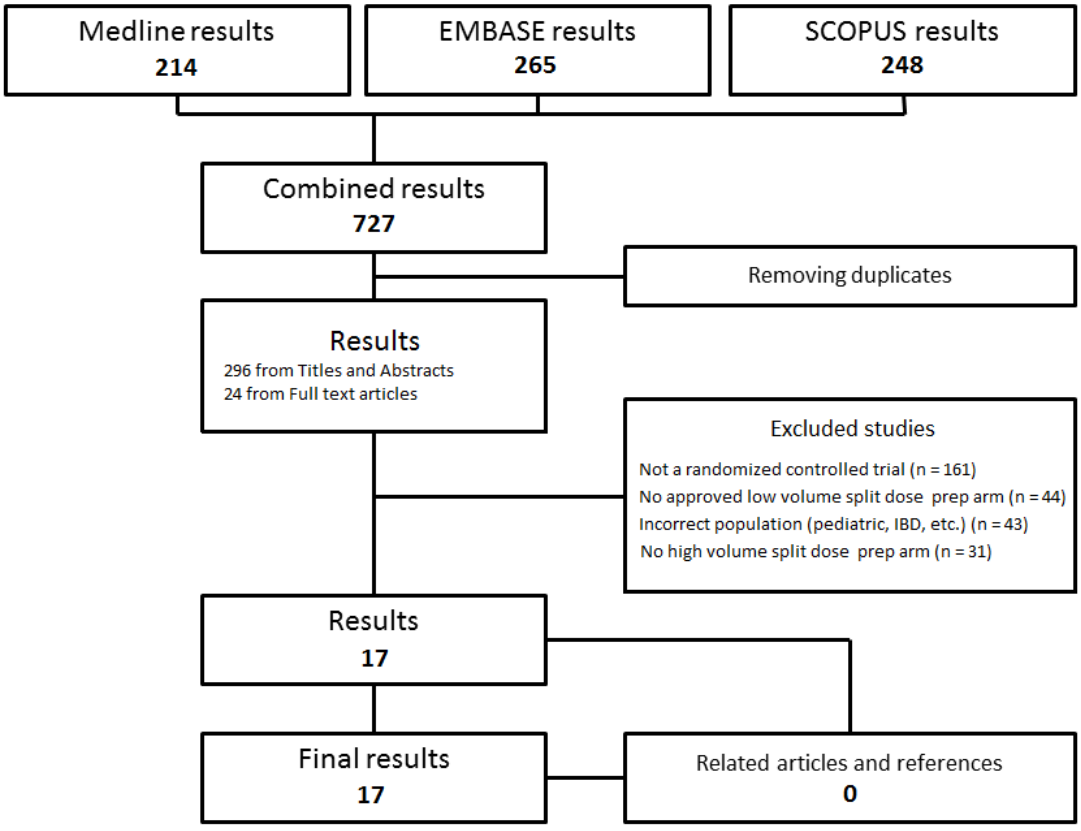
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EMBASE results
265
SCOPUS results
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Combined results
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No approved low volume split dose prep arm (n = 44)
Incorrect population (pediatric, IBD, etc.) (n = 43)
No high volume split dose prep arm (n = 31)
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17
Final results
17
Related articles and references
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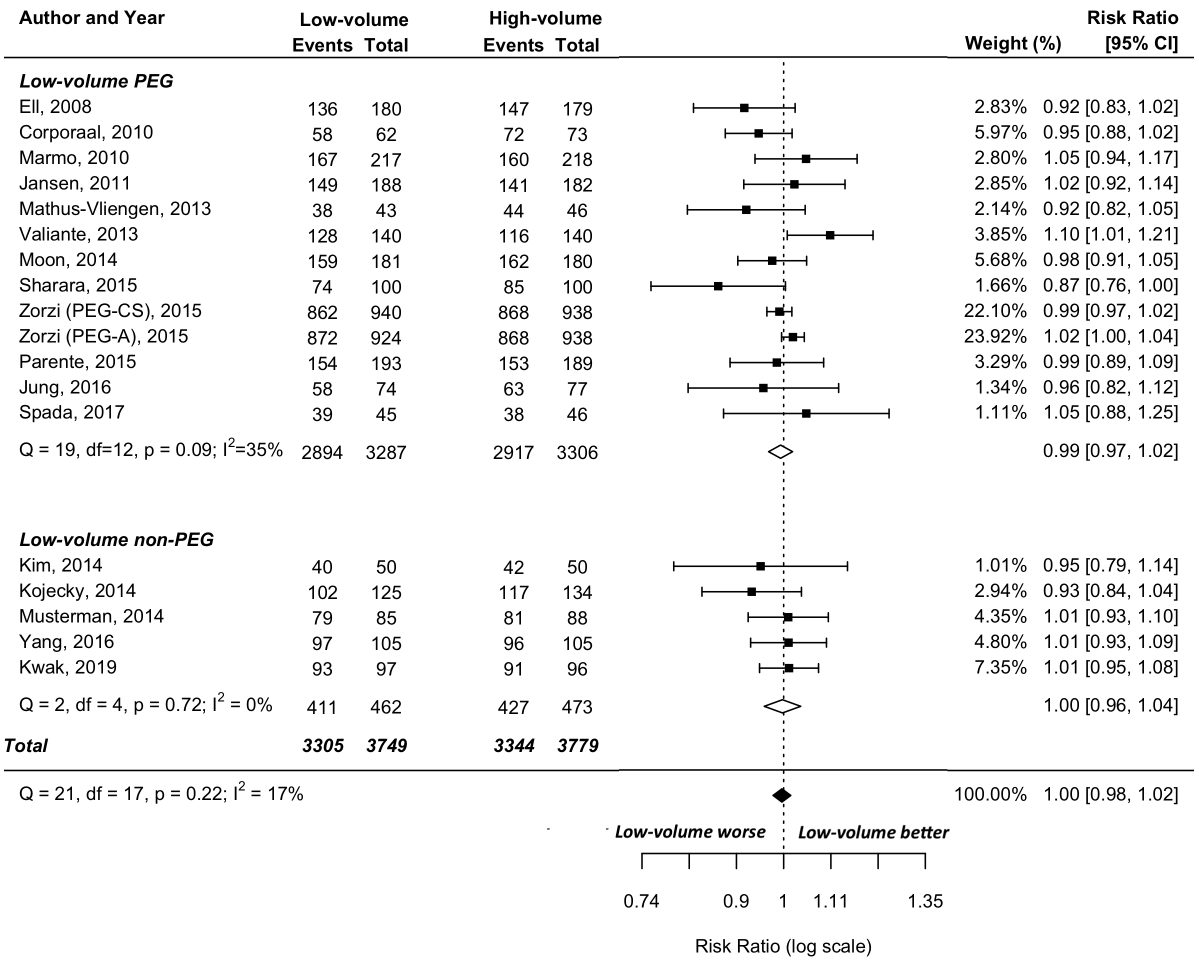
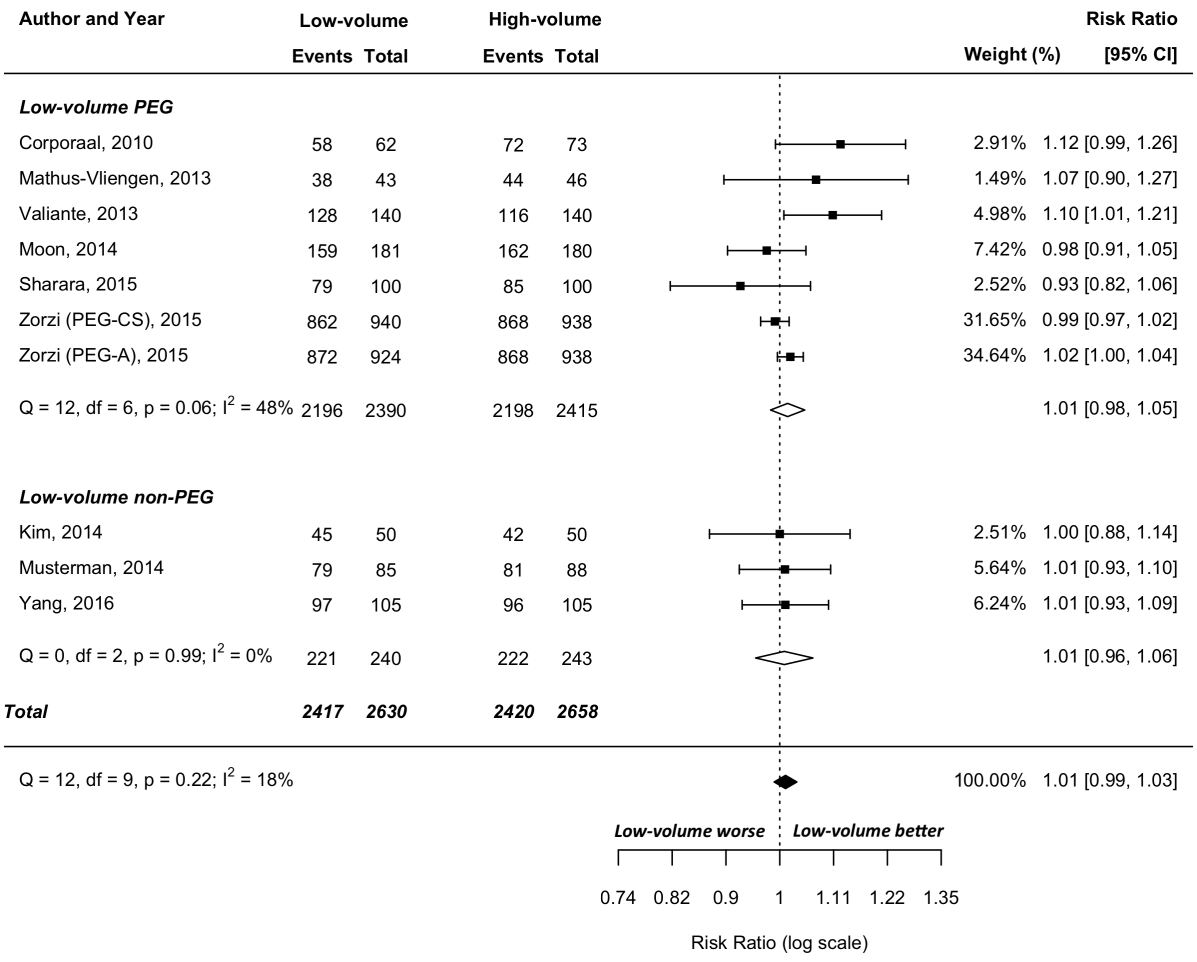
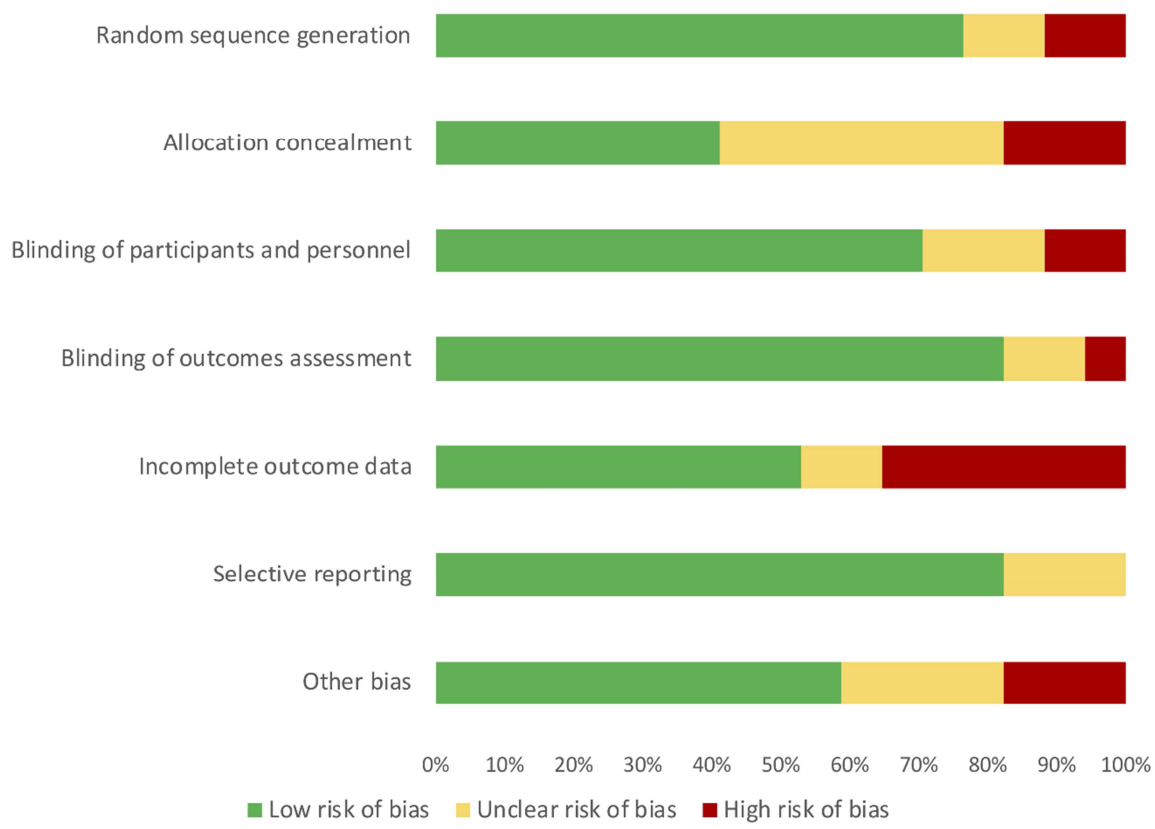

Author and Year
Low-volume Events Total
High-volume Events Total
Weight (%)
Risk Ratio [95% CI]
Low-volume PEG
Ell, 2008 136 180 147 179 2.83% 0.92 [0.83, 1.02]
Corporaal, 2010 58 62 72 73 5.97% 0.95 [0.88, 1.02]
Marmo, 2010 167 217 160 218 2.80% 1.05 [0.94, 1.17]
Jansen, 2011 149 188 141 182 2.85% 1.02 [0.92, 1.14]
Mathus-Vliengen, 2013 38 43 44 46 2.14% 0.92 [0.82, 1.05]
Valiante, 2013 128 140 116 140 3.85% 1.10 [1.01, 1.21]
Moon, 2014 159 181 162 180 5.68% 0.98 [0.91, 1.05]
Sharara, 2015 74 100 85 100 1.66% 0.87 [0.76, 1.00]
Zorzi (PEG-CS), 2015 862 940 868 938 22.10% 0.99 [0.97, 1.02]
Zorzi (PEG-A), 2015 872 924 868 938 23.92% 1.02 [1.00, 1.04]
Parente, 2015 154 193 153 189 3.29% 0.99 [0.89, 1.09]
Jung, 2016 58 74 63 77 1.34% 0.96 [0.82, 1.12]
Spada, 2017 39 45 38 46 1.11% 1.05 [0.88, 1.25]
Q = 19, df=12, p = 0.09; I2=35% 2894 3287 2917 3306 0.99 [0.97, 1.02]
Low-volume non-PEG
Kim, 2014 40 50 42 50 1.01% 0.95 [0.79, 1.14]
Kojecky, 2014 102 125 117 134 2.94% 0.93 [0.84, 1.04]
Musterman, 2014 79 85 81 88 4.35% 1.01 [0.93, 1.10]
Yang, 2016 97 105 96 105 4.80% 1.01 [0.93, 1.09]
Kwak, 2019 93 97 91 96 7.35% 1.01 [0.95, 1.08]
Q = 2, df = 4, p = 0.72; I2 = 0% 411 462 427 473 1.00 [0.96, 1.04]
Total 3305 3749 3344 3779
Q = 21, df = 17, p = 0.22; I2 = 17% 100.00% 1.00 [0.98, 1.02]
Low-volume worse
Low-volume better
0.74
0.9
1
1.11
1.35
Risk Ratio (log scale)


Author and Year
Low-volume
Events Total
High-volume
Events Total
Risk Ratio
Weight (%) [95% CI]
Low-volume PEG
Corporaal, 2010 58 62 72 73 2.91% 1.12 [0.99, 1.26]
Mathus-Vliengen, 2013 38 43 44 46 1.49% 1.07 [0.90, 1.27]
Valiante, 2013 128 140 116 140 4.98% 1.10 [1.01, 1.21]
Moon, 2014 159 181 162 180 7.42% 0.98 [0.91, 1.05]
Sharara, 2015 79 100 85 100 2.52% 0.93 [0.82, 1.06]
Zorzi (PEG-CS), 2015 862 940 868 938 31.65% 0.99 [0.97, 1.02]
Zorzi (PEG-A), 2015 872 924 868 938 34.64% 1.02 [1.00, 1.04]
Q = 12, df = 6, p = 0.06; I² = 48% 2196 2390 2198 2415 1.01 [0.98, 1.05]
Low-volume non-PEG
Kim, 2014 45 50 42 50 2.51% 1.00 [0.88, 1.14]
Musterman, 2014 79 85 81 88 5.64% 1.01 [0.93, 1.10]
Yang, 2016 97 105 96 105 6.24% 1.01 [0.93, 1.09]
Q = 0, df = 2, p = 0.99; I² = 0% 221 240 222 243 1.01 [0.96, 1.06]
Total 2417 2630 2420 2658
Q = 12, df = 9, p = 0.22; I² = 18% 100.00% 1.01 [0.99, 1.03]
Low-volume worse
Low-volume better
0.74 0.82 0.9 1 1.11 1.22 1.35
Risk Ratio (log scale)

Appendix 1 Risk of bias across the included studies (a. Figure; b. Table)



Study	***Random sequence generation***	***Allocation concealment***	***Blinding of participants and personnel***	***Blinding of outcome assessment***	***Incomplete outcome data***	***Selective reporting***	***Other bias (demographic imbalance, indication…)***
Parente	*low*	*Unclear*	*low*	*low*	*low*	*low*	*Low*
Zorzi	*low*	*Unclear*	*low*	*low*	*low*	*low*	*low*
Valiante	*low*	*High*	*low*	*low*	*high*	*low*	*high*
Moon	*low*	*Unclear*	*low*	*unclear*	*high*	*low*	*low*
Sharara	*low*	*Unclear*	*low*	*low*	*unclear*	*low*	*low*
Marmo	*low*	*Low*	*low*	*low*	*low*	*low*	*high*
Jansen	*low*	*Unclear*	*low*	*low*	*low*	*low*	*low*
Jung	*low*	*Unclear*	*low*	*low*	*low*	*low*	*low*
Mathus-Vliengen	*high*	*High*	*high*	*low*	*low*	*unclear*	*Unclear (comorbidities not reported)*
Ell	*low*	*Low*	*unclear*	*low*	*high*	*low*	*Low*
Musterman	*low*	*Low*	*high*	*low*	*low*	*low*	*Unclear (comorbidities not reported)*
Kojecky	*unclear*	*Low*	*unclear*	*low*	*high*	*unclear*	*High (imbalance in diabetes prevalence)*
Kim	*unclear*	*Unclear*	*low*	*low*	*unclear*	*unclear*	*Unclear (demographics not reported)*
Corporaal	*high*	*High*	*low*	*high*	*high*	*low*	*Unclear (demographics not reported)*
Spada	*low*	*Low*	*low*	*low*	*low*	*low*	*low*
Kwak	*low*	*Low*	*unclear*	*unclear*	*high*	*low*	*low*
Yang	*low*	*Low*	*low*	*low*	*low*	*low*	*low*

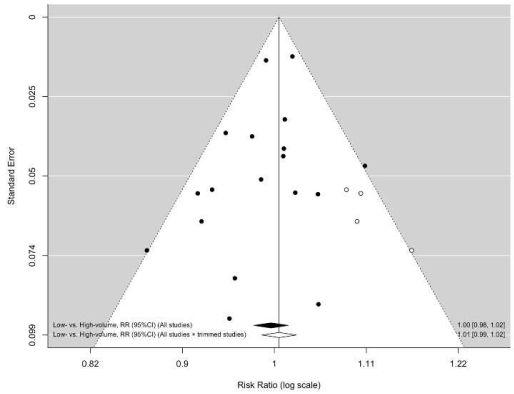
Other bias included: demographic imbalance, imbalanced indication to colonoscopy, imbalanced presence of comorbidities which might impact on bowel cleansing between the study arms.

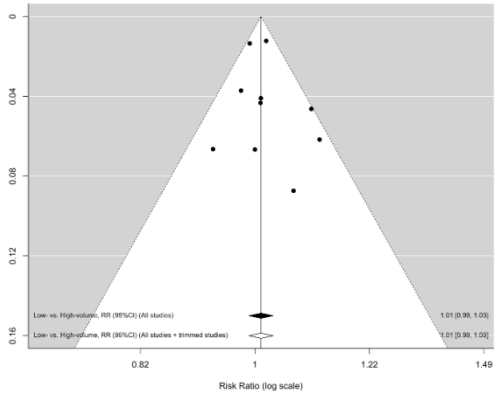
Appendix 2. Reasons to pass from ITT to PP analysis.

Reference	**Criteria to exclude from the PP analysis**
Ell 2008	Participants ingesting < 75% of study medication; Colonoscopy not taken; assessment by expert panel
Marmo 2010	\
Corporaal 2010	\
Jansen 2011	\
Valiante 2013	Colonoscopy not taken; patients not reporting the bowel preparation taken.
Mathus-Vliengen 2013	\
Moon 2014	\
Musterman 2014	Patients taking different bowel preparation.
Kojecky 2014	\
Kim 2014	\
Parente 2015	\
Zorzi 2015	Patients taking different bowel preparation; not reporting the bowel preparation taken.
Zorzi 2015	Patients taking different bowel preparation; not reporting the bowel preparation taken.
Sharara 2015	\
Jung 2016	Withdrawal of consent; Colonoscopy not taken; Failure of cecal intubatioin; prior colorectal surgery
Yang 2016	Participants ingesting < 75% of study medication or not completing colonoscopy
Spada 2017	\
Kwak 2019	\

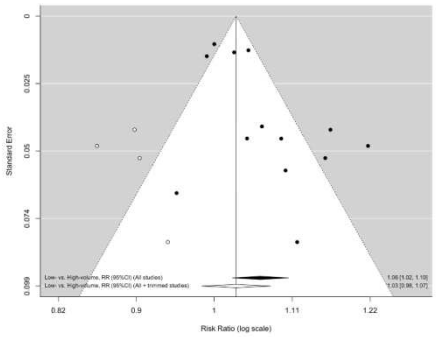
Appendix 3. Funnel plots for assessing publication bias.

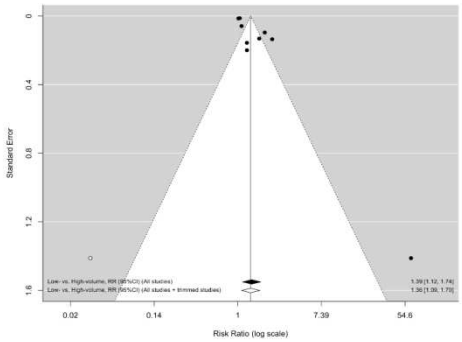
1) Primary outcome: overall colon (left) and right colon (right).

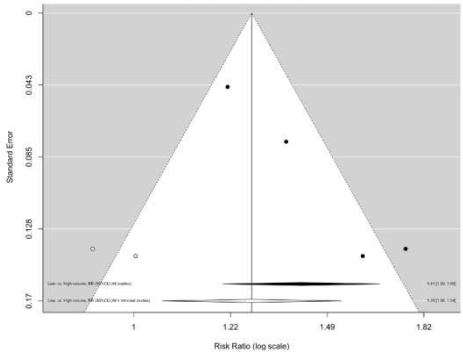




2) Secondary outcome: compliance (left), tolerability (centre), willingness to repeat (right)







Appendix 4. Further details on primary outcomes for specific low-volume PEG and non-PEG products.

2 L-PEG + Ascorbic Acid (PEG-A)

Split-dose 2L-PEG with the adjuvant of ascorbic acid had a comparable proportion of patients with an adequate bowel preparation compared with high-volume split PEG (9 studies: 3,962 patients; 1,711/1,969, 83.5% (95%CI 78.1-88.8%) vs. 1,742/1,993, 86.6% (95%CI 81-92.3%); RR: 1.00; 95% CI, 0.97, 1.02; I^2= 48%; p= 0.74). The moderate heterogeneity was purely attributed to one series weighting for 26% of the overall population. For the right colon cleansing level (5 studies: 2,647 patients; 1,030/1,310, 89.3% (95%CI 84.1-94.6%) vs. 1,046/1,337, 88.4% (95%CI 84.3-92.4%); RR: 1.00; 95% CI: 0.97-1.05; I^2= 44%; p= 0.89). When excluding one series, [27] no residual heterogeneity was found (I^2= 0%).

2L-PEG -citrate (PEG-C)

No statistically significant difference was shown between split-dose low volume PEG-C and split-dose high-volume PEG. The pooled RR was 0.99 (4 studies: 2,631 patients; 1,183/1,318, 87.8% (95%CI 82-93.6%) vs. 1,175/1,313, 85.5% (95%CI 79.3-91.7%); RR: 0.99; 95% CI: 0.96-1.02; I^2= 38%; p= 0.48). When excluding one series, [29] no residual heterogeneity was found (I^2= 0%). For the right colon cleansing level (2 studies: 2,158 patients; 859/1,080, 82.1% (95%CI 74.3-89.8%) vs. 838/1,078, 77.8% (95%CI 75.3-80.3%); RR: 1.02; 95% CI: 0.98-1.07; I^2= 0%; p= 0.23).

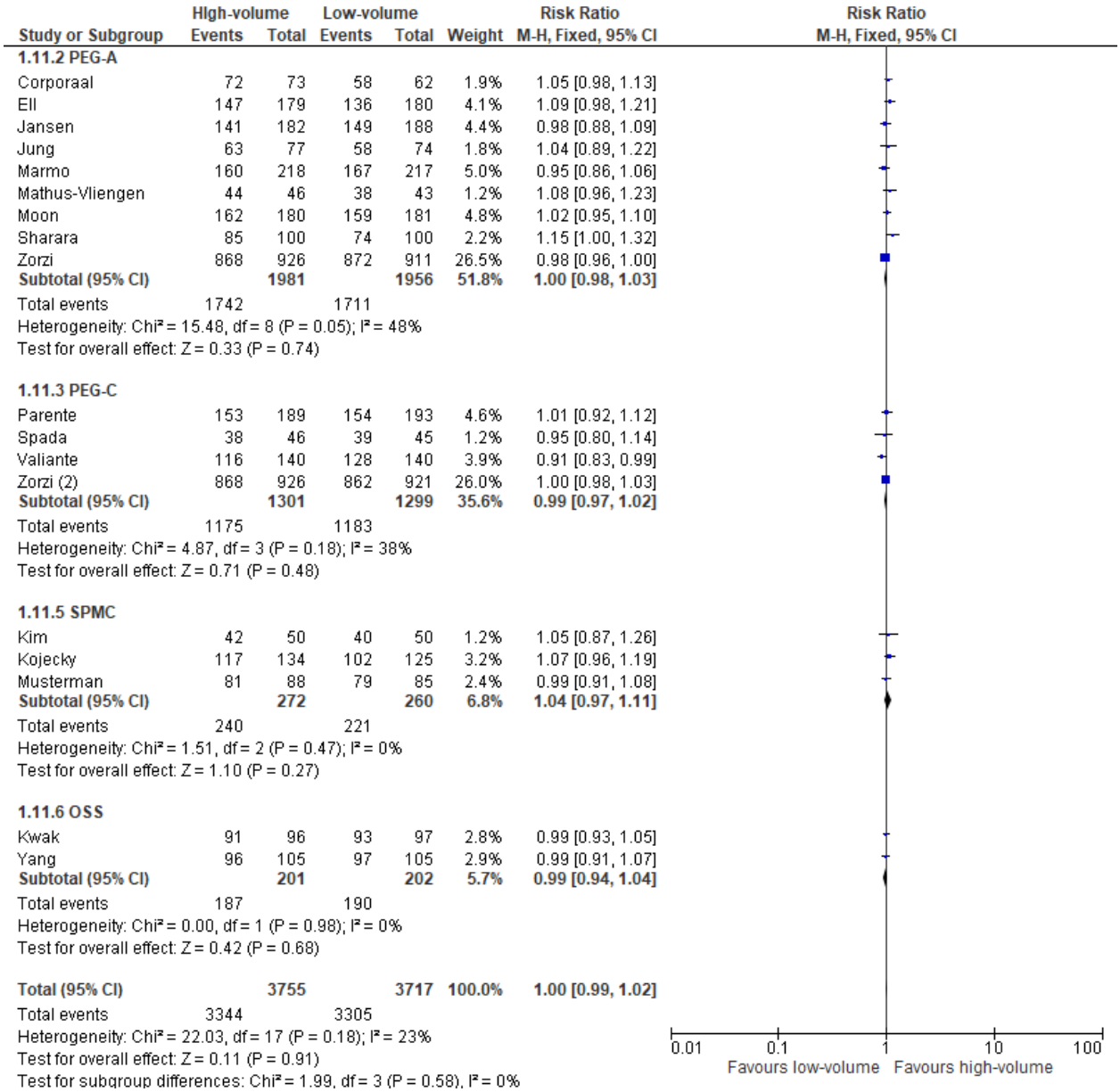
Sodium picosulfate with magnesium citrate (SPMC)

In the 3 trials (532 patients) reporting data on SPMC, the proportion of patients with adequate cleansing was similar between SPMC and high-volume PEG (221/260, 85.6% (95%CI 77.1-94%) vs. 240/272, 88.8% (95%CI 84.6-92.3%); RR: 0.96; 95% CI 0.90-1.03; I^2= 0%; p=0.30).

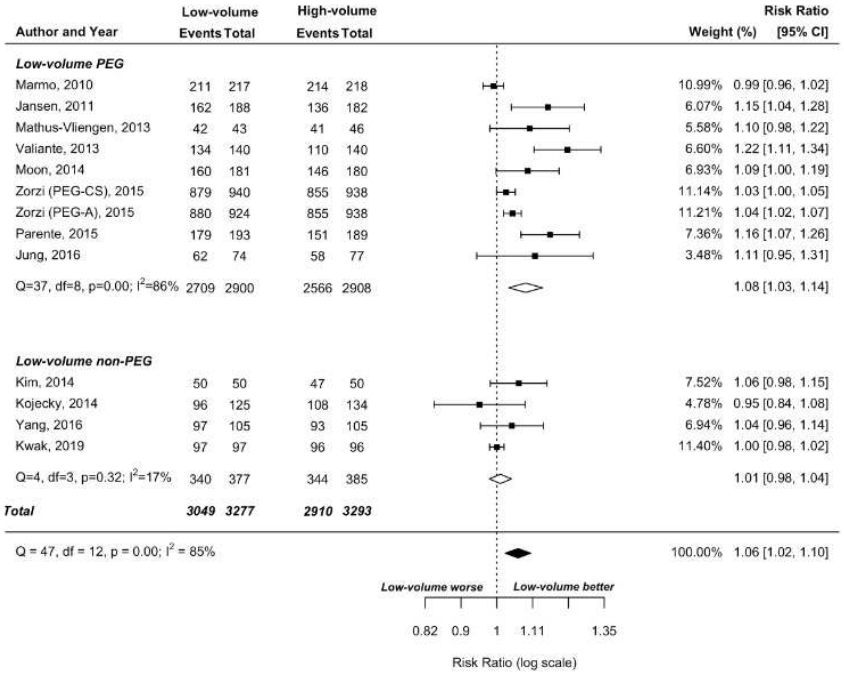
Oral Sulfate Solution (OSS)

In the 2 trials (403 patients) reporting data on OSS, the proportion of patients with adequate cleansing was similar between OSS and high-volume PEG (190/202, 94.5% (95%CI 91.2-97.9%) vs. 187/201, 93.4% (95%CI 90-96.8%); RR: 1.01; 95% CI 0.93-1.09; I^2= 0%; p=0.68).

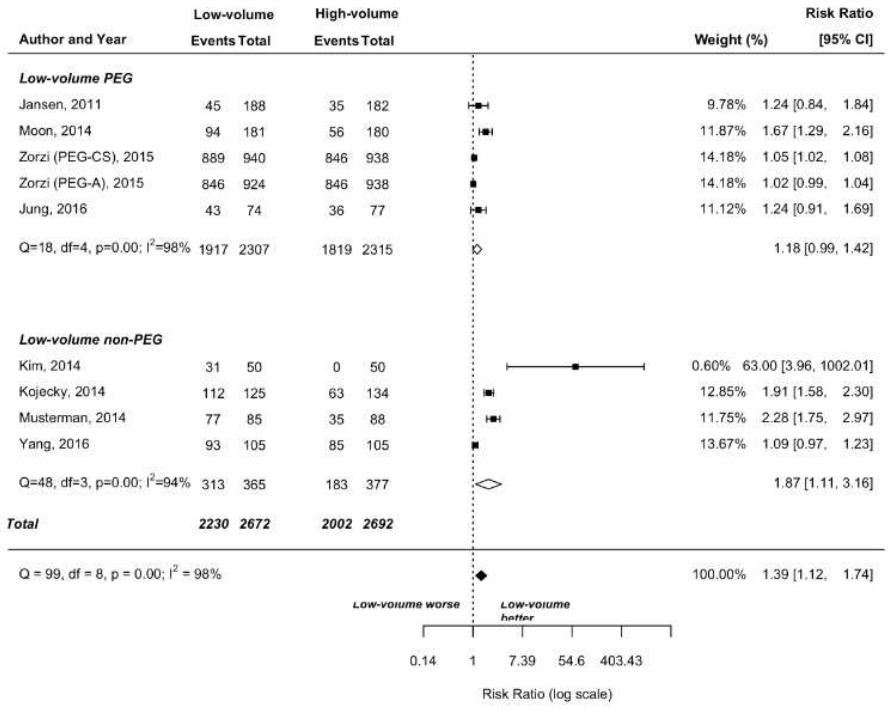
Figure. Forest plot according to the individual low-volume PEG and non-PEG regimen.



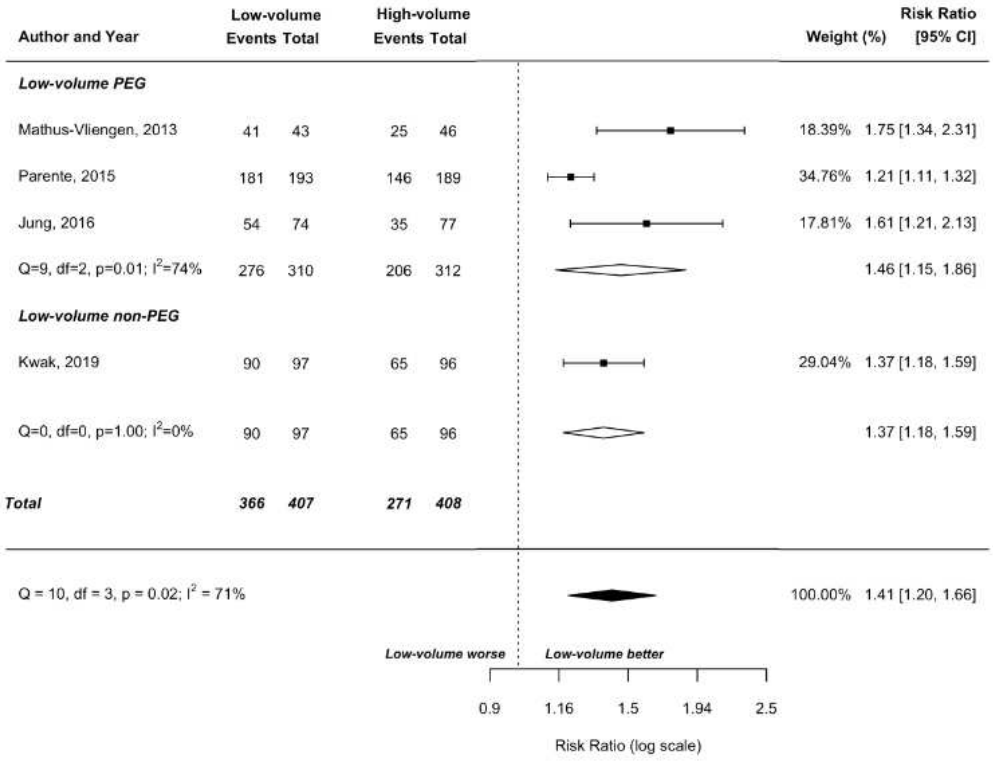
Appendix 5. Forest plot for the secondary outcome: Compliance.



Appendix 6. Forest plot for the secondary outcome: Tolerability.



Appendix 7. Forest plot for the secondary outcome: Willingness to repeat the same preparation).



Appendix 8. Adverse events, adenoma detection rate and rate of excellent cleansing in the low- and high-volume split regimens. For adverse events, RR <1 indicates lower risk in the low-volume group. For adenoma detection and excellent level of cleansing RR ≥1 favours low-volume regimens.

Adverse event	**Number of trials**	**Patients (ITT, n)**	**Relative Risk (95% CI) All colon**	**I^2**
Abdominal pain	8	1820	1.22 [0.73-2.03]	54%
Bloating	6	918	0.66 [0.48-0.92]	48%
Nausea	8	1198	0.86 [0.72-1.02]	50%
Vomiting	7	1529	0.68 [0.46-1.00]	4%
Sleep disorders	4	822	0.67 [0.39-1.15]	0%
Adenoma detection rate	4	5,399	0.96 [0.87, 1.08]	0%

Rate of excellent level of cleansing	7	6,281	0.94 [0.86, 1.02]	21%

Appendix 9. Sensitivity analysis for the primary outcome (rate of adequate bowel preparation for overall colon).

Sensitivity analysis	**Number of trials**	**Patients**	**Relative Risk (95% CI) All colon**	**I^2**
EFFICACY Per Protocol				
Low-volume PEG & non-PEG	18	7,399	0.99 [0.98, 1.01]	22%
-Low-volume PEG	13	6476	0.99 [0.97, 1.01]	38%
-PEG-A	9	3861	0.98 [0.94, 1.01]	59%
-PEG-C	4	2615	1.00 [0.98, 1.02]	0%
-Low-volume non-PEG	5	923	1.00 [0.97, 1.04]	0%
-SPMC	3	531	0.97 [0.91, 1.04]	0%
-OSS	2	392	1.02 [0.98, 1.06]	0%
EFFICACY only validated scales				
Low-volume PEG & non-PEG	13	6,023	1.00 [0.98, 1.02]	10%
-Low-volume PEG	8	5,088	1.00 [0.97, 1.02]	23%
-PEG-A	5	2,737	0.98 [0.92, 1.04]	50%
-PEG-C	3	2,351	0.99 [0.97, 1.02]	0%
-Low-volume non-PEG	5	935	1.00 [0.96, 1.04]	0%
-SPMC	3	532	0.98 [0.92-1.04]	0%
-OSS	2	403	1.01 [0.96-1.06]	0%
EFFICACY (studies ≥2014)				
Low-volume PEG & non-PEG	12	5,794	1.00 [0.98, 1.02]	10%
-Low-volume PEG	7	4,859	1.00 [0.97, 1.02]	25%
-PEG-A	4	2,549	0.98 [0.92-1.04]	52%
-PEG-C	3	2,320	0.99 [0.97-1.03]	0%
-Low-volume non-PEG	5	935	1.00 [0.96-1.04]	0%
-SPMC	3	532	0.98 [0.92-1.04]	0%
-OSS	2	403	1.01 [0.96-1.06]	0%

Appendix 10. Metaregression analysis for bowel cleansing efficacy.

	Coefficient	Standard Error	P value	R^2
Publication year	0.005	0.004	0.253	27%
Country (Europe vs. Asia)	0.015	0.024	0.516	0%
Multicenter study (vs. monocenter)	0.012	0.023	0.620	0%
Bowel preparation scale				0%
Not validated (reference)	-	-	-	
Aronchick	-0.001	0.030	0.968	
BBPS	0.016	0.034	0.633	
OBPS	0.007	0.041	0.856	
Type of preparation				0%
PEG-A (reference)	-	-	-	
PEG-CS	0.069	0.096	0.475	
OSS	0.032	0.038	0.405	
SPMC	-0.006	0.041	0.884	
Type of preparation (PEG vs. non-PEG)	-0.001	0.025	0.976	0%
Indication to colonoscopy (% of CRC screening patients)	0.001	0.001	0.151	0%
Constipation %	-0.001	0.001	0.834	0%
Mean age in low-volume group	0.003	0.002	0.261	0%
Mean age in high-volume group	0.001	0.002	0.793	0%
Male sex % in low-volume group	-0.032	0.086	0.713	0%
Male sex % in high-volume group	0.050	0.124	0.686	0%

Appendix 11. Metaregression analysis for compliance to the bowel preparation.

	Coefficient	Standard Error	P value	R^2
Publication year	-0.005	0.008	0.548	0%
Country (Europe vs. Asia)	0.019	0.040	0.637	0%
Multicenter study (vs. monocenter)	-0.087	0.035	0.013	50%
Type of preparation				0%
PEG-A (reference)	-	-	-	
PEG-CS	0.046	0.048	0.345	
OSS	-0.047	0.054	0.389	
SPMC	-0.045	0.062	0.465	
Type of preparation (PEG vs. non-PEG)	0.061	0.040	0.125	3%
Indication to colonoscopy (% of CRC screening patients)	0.001	0.001	0.440	0%
Constipation %	-0.001	0.001	0.834	0%
Mean age in low-volume group	0.001	0.004	0.851	0%
Mean age in high-volume group	-0.002	0.005	0.635	0%
Male sex % in low-volume group	-0.005	0.116	0.968	0%
Male sex % in high-volume group	0.027	0.193	0.890	0%

Appendix 12. Metaregression analysis for tolerability of the bowel preparation.

	Coefficient	Standard Error	P value	R^2
Publication year	-0.075	0.080	0.345	4%
Country (Europe vs. Asia)	-0.002	0.251	0.993	0%
Multicenter study (vs. monocenter)	-0.399	0.255	0.117	14%
Type of preparation				62%
PEG-A (reference)	-	-	-	
PEG-CS	-0.168	0.216	0.575	
OSS	-0.126	0.224	0.437	
SPMC	0.550	0.190	0.004	
Type of preparation (PEG vs. non-PEG)	-0.361	0.213	0.090	16%
Indication to colonoscopy (% of CRC screening patients)	-0.007	0.002	0.001	82%
Constipation %	-0.001	0.001	0.215	0%
Mean age in low-volume group	-0.001	0.022	0.658	0%

Mean age in high-volume group	-0.004	0.022	0.850	0%
Male sex % in low-volume group	-0.942	1.529	0.538	0%
Male sex % in high-volume group	-2.046	1.744	0.241	12%

Appendix 13. Metaregression analysis for willingness to repeat the bowel preparation.

	Coefficient	Standard Error	P value	R^2
Publication year	-0.023	0.046	0.614	0%
Country (Europe vs. Asia)	-0.042	0.201	0.834	0%
Multicenter study (vs. monocenter)	-0.279	0.180	0.123	54%
Type of preparation				99%
PEG-A (reference)	-	-	-	
PEG-CS	-0.325	0.109	0.003	
OSS	-0.204	0.126	0.104	
Type of preparation (PEG vs. non-PEG)	0.063	0.232	0.785	0%
Indication to colonoscopy (% of CRC screening patients)	-0.006	0.004	0.116	99%
Constipation %	-0.001	0.001	0.834	0%
Mean age in low-volume group	0.017	0.008	0.042	99%
Mean age in high-volume group	0.016	0.008	0.040	99%
Male sex % in low-volume group	0.303	0.258	0.240	29%
Male sex % in high-volume group	0.691	0.363	0.057	76%

Appendix 14. Subgroup analyses for bowel cleansing efficacy.

Subgroup analysis	Number of trials	Patients	RR (95%CI)	I^2
EFFICACY all colon				
Country				
Europe	12	6,313	1.00 (0.98-1.02)	29%
Asia	6	1,215	0.99 (0.95-1.02)	0%
Type of study				
Monocenter	7	1,347	0.98 (0.93-1.04)	51%
Multicenter	11	6,181	1.00 (0.98-1.02)	11%
Scale for bowel cleansing evaluation				
Aronchick	5	4,299	0.98 (0.94-1.03)	64%
BBPS	4	727	1.01 (0.97-1.05)	0%
OBPS	4	997	1.00 (0.94-1.06)	0%
Not validated	5	1,505	0.99 (0.93-1.05)	57%
EFFICACY right colon				
Country				
Europe	6	4,417	1.00 (0.97-1.03)	51%
Asia	4	871	0.97 (0.93-1.02)	0%
Type of study				
Monocenter	6	977	0.98 (0.91-1.04)	58%
Multicenter	4	4,311	1.00 (0.98-1.03)	27%
Scale for bowel cleansing evaluation				
Aronchick	4	4,040	1.00 (0.96-1.03)	53%
BBPS	2	383	1.01 (0.95-1.07)	0%
OBPS	1	89	0.92 (0.82-1.05)	NA
Not validated	3	776	1.00 (0.92-1.09)	73%

NA, not applicable.

Appendix 15. Subgroup analyses for secondary outcomes.

Subgroup analysis	Number of trials	Patients	RR (95%CI)	I^2
COMPLIANCE				
Country				
Europe	8	5,555	1.07 (1.01-1.13)	90%
Asia	5	1,015	1.04 (0.99-1.09)	46%
Type of study				
Monocenter	4	839	1.13 (1.06-1.20)	43%
Multicenter	9	5,731	1.03 (1.00-1.07)	79%
Type of preparation				
PEG-A	6	3,268	1.06 (1.01-1.11)	75%
PEG-CS	3	2,540	1.12 (1.01-1.25)	87%
OSS	2	403	1.00 (0.98-1.02)	0%
SPMC	2	359	1.02 (0.92-1.13)	51%
TOLERABILITY				
Country				
Europe	5	4,542	1.40 (1.01-1.90)	99%
Asia	4	822	1.35 (1.02-1.77)	71%
Type of study				
Monocenter	3	643	3.62 (0.57-22.9)	97%
Multicenter	6	4,721	1.27 (1.03-1.57)	99%
Type of preparation				
PEG-A	4	2,744	1.25 (0.99-1.57)	76%
PEG-CS	1	1,878	1.05 (1.02-1.08)	NA
OSS	1	210	1.09 (0.97-1.23)	0%
SPMC	3	532	3.59 (0.88-14.60)	93%
WILLINGNESS TO REPEAT BOWEL PREPARATION				
Country				
Europe	2	471	1.43 (1.00-2.04)	84%
Asia	2	344	1.42 (1.24-1.62)	0%
Type of study				
Monocenter	1	89	1.75 (1.34-2.31)	NA
Multicenter	3	726	1.33 (1.16-1.52	58%
Type of preparation				
PEG-A	2	240	1.68 (1.38-2.04)	0%
PEG-CS	1	382	1.21 (1.11-1.32	NA
OSS	1	193	1.37 (1.18-1.59)	NA
SPMC	0	0	NA	NA

NA, not applicable.

Appendix 16. GRADE evidence profile for efficacy of split-dose low- vs. high-volume bowel preparations for colonoscopy.

	Quality assessment					Summary of findings			Quality
Outcome, No. of studies, design (no. of patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Low-volume	High-volume	Relative Risk (95%CI)	
Overall, 17 RCTs (7,528)	Not serious	Serious*	Not serious	Not serious	Not serious	3,305/3,749 (88.2%)	3,344/3,779 (88.5%)	1.00 (0.98-1.01)	⊕⊕⊕O Moderate
Right colon, 10 RCTs (5,288)	Not serious	Serious*	Not serious	Not serious	Serious**	2,417/2,630 (91.9%)	2,420/2,658 (91%)	1.01 (0.99-1.03)	⊕⊕OO Low
Low-volume PEG overall, 13 RCTs (6,593)	Not serious	Serious*	Not serious	Not serious	Not serious	2,894/3,287 (88%)	2,917/3,306 (88.2%)	1.00 (0.98-1.02)	⊕⊕⊕O Moderate
Low-volume PEG right colon, 7 RCTs (4,805)	Not serious	Serious*	Not serious	Not serious	Serious**	1,889/2,390 (79%)	1,884/2,415 (78%)	1.01 (0.99-1.04)	⊕⊕OO Low
Low-volume non-PEG overall, 5 RCTs (935)	Not serious	Serious*	Not serious	Not serious	Serious**	411/462 (89%)	427/473 (90.3%)	0.98 (0.94-1.03)	⊕⊕OO Low
Low-volume non-PEG overall, 3 RCTs (483)	Not serious	Serious*	Not serious	Not serious	Serious**	218/240 (90.1%)	216/243 (88.9%)	1.02 (0.96-1.08)	⊕⊕OO Low

* Inconsistency risk was judged as serious due to heterogeneity among patients (i.e. different indications to colonoscopy) and scales for bowel cleansing evaluation.

** Funnel plot visual inspection revealed asymmetry even though Egger's test was not significant.

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