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Anti-reflux versus conventional self-expanding metal stents in the palliation of esophageal cancer: A systematic review and meta-analysis

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Conflict of Interest: Dr. Diogo Turiani Hourneaux De Moura: BariaTek - Advisory Board Member (Consulting fees)

Dr. Sergio A. Sanchéz-Luna: Recipient of the 2021 American Society for Gastrointestinal Endoscopy (ASGE) Endoscopic Training Award by the ASGE and Fujifilm. This was not relevant to this study.

Dr. Eduardo Guimaraes Hourneaux De Moura: Olympus - Consultant (Consulting fees), Boston Scientific - Consultant (Consulting fees). They were not relevant to this study.

Abstract:

BACKGROUND AND AIMS: Self-expanding metal stents (SEMS) are an effective palliative endoscopic therapy to reduce dysphagia in esophageal cancer. Gastroesophageal reflux disease (GERD) is a relatively common complaint after non-valved conventional self-expanding metal stent placement. Therefore, valved self-expanding metal stents (SEMS-V) were designed to reduce the rate of GERD symptoms. We aim to perform a systematic review and meta-analysis comparing the two stents.

MATERIAL AND METHODS: This is a systematic review and meta-analysis including only randomized clinical trials (RCT) comparing the outcomes between SEMS-V and non-valved self-expanding metal stents (SEMS-NV) following the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. The risk of bias was assessed using the Cochrane Risk of Bias 2 tool. Data were analyzed with the Review Manager Software. Quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation guidelines.

RESULTS: Ten randomized clinical trials including a total of 467 patients, 234 in the SEMS-V group and 233 in the SEMS-NV group, were included. There were no statistically significant differences regarding GERD qualitative analysis (RD -0.17; 95% CI -0.67, 0.33; p = 0.5) and quantitative analysis (SMD -0.22; 95% CI -0.53, 0.08; p = 0.15) technical success (RD -0.03; 95% CI -0.07, 0.01; p = 0.16), dysphagia improvement (RD -0.07; 95% CI -0.19, 0.06; p = 0.30), and adverse events (RD 0.07; 95% CI -0.07, 0.20; p = 0.32).

CONCLUSION: Both SEMS-V and SEMS-NV are safe and effective in the palliation of esophageal cancer with similar rates of GERD, dysphagia relief, technical success, adverse events, stent migration, stent obstruction, bleeding, and improvement of the quality of life.

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Anti-reflux versus conventional self-expanding metal stents in the palliation of esophageal cancer: A systematic review and meta-analysis

Running head: Management of esophageal cancer using SEMS

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None.

Ethical statement:

The study was approved by the Research Ethics Committee of the Hospital das Clínicas - University of São Paulo School of Medicine.

ABSTRACT

BACKGROUND AND AIMS: Self-expanding metal stents (SEMS) are an effective palliative endoscopic therapy to reduce dysphagia in esophageal cancer. Gastroesophageal reflux disease (GERD) is a relatively common complaint after non-valved conventional self-expanding metal stent placement. Therefore, valved self-expanding metal stents (SEMS-V) were designed to reduce the rate of GERD symptoms. We aim to perform a systematic review and meta-analysis comparing the two stents.

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CONCLUSION: Both SEMS-V and SEMS-NV are safe and effective in the palliation of esophageal cancer with similar rates of GERD, dysphagia relief, technical success, adverse events, stent migration, stent obstruction, bleeding, and improvement of the quality of life.

Keywords: Esophagus cancer; endoscopy; dysphagia; reflux; stent

Abbreviations:

1. Cancer: **CA**
2. Gastroesophageal junction: **GEJ**
3. Gastroesophageal reflux disease: **GERD**
4. Quality of life: **QoL**
5. Self-expanding metal stents: **SEMS**
6. Adverse events: **AE**
7. Valved self-expanding metal stents: **SEMS-V**
8. Non-valved self-expanding metal stents: **SEMS-NV**
9. Randomized clinical trials: **RCTs**
10. International Prospective Register of Systematic Reviews: **PROSPERO**
11. Preferred Reporting Items for Systematic Reviews and Meta-analysis: **PRISMA**
12. Version 2 of the Cochrane Risk-of-Bias tool for Randomized Trials: **RoB2**
13. Grading of Recommendations Assessment, Development, and Evaluation: **GRADE**
14. I-125 seed-loaded stent: **ISS**
15. Proton pump inhibitor: **PPI**
16. Health-related Quality of life: **HRQL**

INTRODUCTION

The incidence of esophageal cancer (CA) was estimated to be more than 600,000 cases worldwide in 2020, associated with a 5-year survival rate of 19.9%, making it one of the most deadly malignancies[1,2]. There has been an increase in the incidence of gastroesophageal junction (GEJ) cancer in young patients with Barrett's esophagus, which raises annually due to an increase in the incidence of obesity, which subsequently increases the risk of gastroesophageal reflux disease (GERD), a well-known risk factor for adenocarcinoma of the distal esophagus[3–5].

The cornerstone of treatment is complete resection; however, patients unfortunately present symptoms once they are at an advanced stage of their disease. For that reason, resection is not feasible in most cases, and thus therapeutic approaches to improve the patients' quality of life (QoL) are needed[6]. Self-expanding metal stents (SEMS) are widely indicated to improve dysphagia and increase calorie intake, both of which are independent causes of poor prognosis, and thus are considered the standard of care for the palliation of symptoms in this population of patients, especially in the presence of a tracheoesophageal or bronchoesophageal fistula[7,8].

The main adverse events (Aes) that impact the QoL of patients using SEMS are post-procedural pain, dysphagia recurrence, migration, and gastroesophageal reflux disease (GERD)[9,10]. Unfortunately, GERD can occur in about 7% of patients, due to obliteration of the lower esophageal sphincter due to the inherent mechanism of the SEMS, and thus can also be associated with bronchoaspiration, a life-threatening complication, especially for these patients[10,11]. Therefore, it has been proposed that valved SEMS (SEMS-V) could theoretically improve patients' QoL, reducing GERD symptoms with the same clinical efficacy and safety as the non-valved SEMS (SEMS-NV).

To evaluate the best evidence available in the literature regarding the efficacy and safety of SEMS-V compared to the SEMS-NV, we aim to perform this systematic review and meta-analysis based only on randomized clinical trials (RCT) to deliver the highest grade of evidence and recommendation.

MATERIAL AND METHODS

Protocol registration

This study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the file number CRD42021258196 and was approved by the Ethics Committee of Hospital das Clínicas, Faculty of Medicine at The University of São Paulo. This systematic review and meta-analysis was performed in conformity with the recommendations from the Cochrane Handbook of Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[12].

Eligibility criteria

All relevant published abstracts and full-text manuscripts, regardless of language and year of publication, were included. The eligibility criteria included RCTs comparing SEMS-V versus SEMS-NV in the palliative treatment of esophageal cancer in patients over 18 years of age. The exclusion criteria were studies that were not RCTs or RCTs in which it was not possible to retrieve the required data.

Information Sources

We performed individualized searches in multiple electronic databases including MEDLINE, Embase, Cochrane, LILACS, clinicaltrials.gov, and a cross-reference search, from their inception until February 2022. The search strategy was: (Esophageal Neoplasms OR Esophageal Neoplasm OR Esophagus Neoplasm OR Esophagus Neoplasms OR Cancer of Esophagus OR Esophagus Cancers OR Esophageal Cancers) AND (Prostheses and Implants OR Prosthetic Implants OR Prosthetic Implant OR Artificial Implant OR Artificial Implants OR Prostheses OR Prosthesis OR Endoprosthesis OR Endoprostheses OR Stents OR Stent).

Study selection and data collection process

Two independent researchers reviewed the title and abstract of each article after the removal of duplicated articles. Articles that were found to be relevant were selected for full-text evaluation. The final decision on choosing the studies was based on predetermined inclusion and exclusion criteria. Any disagreement on selecting the studies was resolved by consensus with a third experienced researcher.

Evaluation of bias and quality of studies

The risks of bias was assessed by the version 2 of the Cochrane Risk-of-Bias tool for Randomized Trials (RoB2)[13]. The quality of evidence, expressed in high, moderate, low, and very low, was assessed utilizing the objective criteria from the GRADE (Grading Recommendations Assessment, Development, and Evaluation) guidelines for each of the pre-specified results, and the outcomes were evaluated using the GRADEpro – Guideline Development Tool software (McMaster University, 2015; Evidence Prime, Inc., Ontario, Canada).

Data items

The following data were extracted: name of the first author, year of publication, country, study design, population (number of patients), SEMS type (valved vs non-valved), and outcomes. The evaluated primary outcome was GERD qualitative and quantitative analyses. The quantitative analysis of GERD was displayed as the variation of the different reflux scores one to three months after SEMS placement. On the other hand, the secondary outcomes included technical success, dysphagia improvement, adverse events, stent migration, stent obstruction, bleeding, and QoL improvement. Clinical success was defined as an improvement in the patient's GERD symptoms and dysphagia.

Data analysis

The data of interest extracted from the selected studies were meta-analyzed using the Review Manager (RevMan) software (Review Manager Software version 5.4 – Cochrane Collaboration Copyright © 2020), also, the interval prediction was calculated by the Comprehensive Meta-Analysis (CMA version 3) software.

For dichotomous variables, the risk difference was determined by calculating the number of events and the sample size using the Mantel Haenszel test with a 95% confidence interval[14]. For continuous variables, the mean or median with standard deviation and the total number of patients were used, employing the inverse variance test with a 95% confidence interval.

A fixed-effect was used when the heterogeneity was <50% and a random effect when it was >50%. Heterogeneity was calculated using the Higgins test (I^2), ranging from 0% to 100%. I^2 values higher than 50% were considered substantial

heterogeneity[14,15]. Additionally, the prediction interval was calculated as true effects [16], and a P value of <0.05 was considered statistically significant.

Due to the low number of identified randomized clinical trials and the low heterogeneity between them, funnel plots were not useful to assess the presence of publication bias, and therefore, were not used.

RESULTS

Literature search results and characteristics of included studies

The initial search strategy identified 7612 records, resulting in ten studies[17–26] (Figure 1).

The ten RCTs evaluated a total of 467 patients, 234 in the SEMS-V group, and 233 in the SEMS-NV group. The characteristics of the included studies are summarized in Table 1.

Evaluation of biases and quality of studies

The studies[17–25] included in the meta-analysis presented a low risk of bias, except for the study realized by Kaduthodil et al, which had a high risk of bias (Figure 2). The evidence quality of the evaluated outcomes was different as exposed by the GRADE illustrated in figure 3. In accordance with the GRADE, we exposed a maximum of seven outcomes evidence quality.

META-ANALYSIS

Gastroesophageal reflux disease (GERD) – qualitative evaluation

Three RCTs[20,24,25] with a total of 122 patients (59 in the SEMS-V group and 63 in the SEMS-NV group), were included in this meta-analysis showing no statistically significant difference (RD -0.17; 95% CI -0.67, 0.33; p = 0.5; I^2=93%) between the groups (Figure 4), with a prediction interval ranging from -6.46 to 6.12 (Figure 5). This outcome presented a very low quality of evidence (Figure 3).

Gastroesophageal reflux disease (GERD) – quantitative evaluation

Five RCTs[17, 19, 22, 23, 26] with a total of 172 patients (81 in the SEMS-V group and 91 in the SEMS-NV group), were included in this meta-analysis showing no statistically significant difference (SMD -0.22; 95% CI -0.53, 0.08; p = 0.15; I^2=48%) between the groups (Figure 6). This outcome presented a very low quality of evidence (Figure 3).

Dysphagia Improvement

The meta-analysis included three RCTs[17, 20, 25] with a total of 150 patients (74 in the SEMS-V group and 76 in the SEMS-NV group) and showed no statistically significant difference (RD -0.07; 95% CI -0.19, 0.06; p = 0.30; I^2=0%) between SEMS-V and SEMS-NV groups for this outcome (Figure 7). This outcome presented a moderate quality of evidence (Figure 3).

Technical success

Eight RCTs[17–21,23–25], with a total of 364 patients (176 in the SEMS-V group and 188 in the SEMS-NV group), were included in the meta-analysis showing no statistically significant difference (RD -0.03; 95% CI -0.07, 0.01; p = 0.16; I^2=0%) between groups (Figure 8). This outcome presented a moderate quality of evidence (Figure 3).

Adverse events (Aes)

Seven RCTs[17–19,21,22,24,25] analysis with 335 patients (160 in the SEMS-V group and 175 in the SEMS-NV group) were included in this analysis. Our meta-analysis showed no statistically significant difference (RD 0.07; 95% CI -0.07, 0.20; p = 0.32; I^2=59%) between SEMS-V and SEMS-NV groups (Figure 9). With a prediction interval ranging from -0.33 to 0.47 (Figure 10). This outcome presented a low quality of evidence (Figure 3).

Stent migration

A total of 364 patients (158 in the SEMS-V group and 188 in the SEMS-NV group) from seven RCTs[17–19,21,22,24,25] were included in this meta-analysis, showing no statistically significant difference (RD 0.07; 95% CI -0.02, 0.15; p = 0.11; I^2=0%) between SEMS-V and SEMS-NV groups (Figure 11). This outcome presented a moderate quality of evidence (Figure 3).

Stent obstruction

Six RCTs[18–22,25], with 291 patients (138 in the SEMS-V group and 153 in the SEMS-NV group), were included in this analysis. The meta-analysis showed no statistically significant difference (RD -0.01; 95% CI -0.08, 0.05; p = 0.26; I^2=23%) between the groups (Figure 12). This outcome presented a moderate quality of evidence (Figure 3).

Bleeding

A total of 281 patients (133 in the SEMS-V group and 148 in the SEMS-NV group) from six RCTs[17–20,22,24] were included in this meta-analysis showing no statistically significant difference (RD 0.01; 95% CI -0.05, 0.06; p = 0.91; I^2=0%) between the two types of SEMS (Figure 10). This outcome presented a moderate quality of evidence. (Figure 13).

Quality of Life (QoL)

Two RCTs[19,22], with a total of 56 patients (25 in the SEMS-V group and 31 in the SEMS-NV group) were included in this meta-analysis showing no statistically significant difference (MD -1.00; 95% CI -14.98, 12.98; p = 0.89; I^2=0%) between the groups (Figure 14). This outcome presented a low quality of evidence.

DISCUSSION

Self-expanding metal stents (SEMS) are one of the most efficient treatments for the palliation of advanced esophageal cancer[27,28], but when placed across the cardia, they have the potential of causing gastroesophageal reflux disease (GERD) symptoms due to the obliteration of the lower esophageal sphincter. This systematic review and meta-analysis of only on randomized clinical trials (RCTs) represent the most updated evidence-based data regarding the use of SEMS-NV and SEMS-V in the endoscopic palliation of esophageal cancer. Unlike the last evidence data published in 2019[29], we attempted to use dichotomous outcomes as well for the evaluation of GERD, so that our meta-analysis could be more robust and reliable. We also included two more RCTs, a recent multicenter study[17], and a single-center study published in 2002[25].

The incidence of post-procedure GERD was theoretically expected to be lower in the SEMS-V group. However, no statistically significant difference was found between both groups, as exposed in both analyses that included a total of eight studies, 294 patients, 140 in the SEMS-V group, and 154 in the SEMS-NV group, in contrast to the last meta-analysis that included four studies and performed a quantitative analysis only. Unfortunately, we could not include two studies, particularly, Coron et al [18], which performed a highly refined radiological evaluation, finding superior results on the SEMS-V group, however, the data exposed in the article is insufficient to calculate the SMD, and thus be included in the meta-analysis.

The use of proton pump inhibitors (PPIs) in the SEMS-NV group was not reported in all studies, and this factor could have influenced the heterogeneity of the results. Additionally, the qualitative analysis included a minor number of studies, but is more reliable, as the quantitative analysis has some limitations because of the combination of different scales mixed and evaluated together. Some observational studies have reported the superiority of the SEMS-V regarding GERD incidence, although they are conflicting too[30,31].

In this systematic review and meta-analysis, both valved and non-valved SEMS showed similar technical and clinical success rates. There was no difference in dysphagia improvement between the SEMS-V and SEMS-NV. However, only data from three RCTs were included due to the different patterns used to report their results, such as different dysphagia scores and, also, due to a lack of description of the total number of patients with dysphagia improvement. Although both types of SEMS are associated with high rates of dysphagia improvement, recently, a novel radioactive SEMS such as the I-125 seed-loaded stent (ISS) have been developed to potentially improve the benefits. As described in two recent meta-analyses, this novel radioactive ISS provided better dysphagia improvement than conventional SEMS and other therapies[32,33].

In the total adverse events analyses, there was no difference between both groups. Furthermore, individualized analyses were performed to evaluate stent migration, obstruction, and bleeding rates, which did not show a statistical difference between SEMS-V and SEMS-NV.

The risk of migration is considerably higher when the SEMS is placed across the gastroesophageal junction (GEJ) as it loses its natural sphincter function.

Additionally, the peristalsis of the stomach may elevate the risk of migration, especially with SEMS-V. Furthermore, some patients need dilation of the malignant stricture before SEMS-V placement due to the larger diameter of its delivery system when compared to the SEMS-NV. Although our meta-analysis did not evaluate SEMS fixation/anchoring techniques, such as suturing, clipping, and external fixation through the nares, it is essential to know that stent fixation could potentially reduce SEMS migration[34,35]. Only Dua et al.[17], reported that SEMS fixation was not performed, and thus if some of the other studies used these fixation/anchoring approaches in just one of the groups, then the results may have been potentially affected.

Furthermore, is important to evaluate the possibility of tumoral bleeding or bleeding caused by the procedure itself after SEMS placement. Regarding the diameter of the release mechanism, the two SEMS models are not similar. Although, SEMS-V could have had a bigger impact on bleeding after SEMS placement we found no statistically significant differences between the groups.

In terms of SEMS obstruction, it was expected the valved model to be more associated with obstruction because the valve of the SEMS-V could serve as an obstacle to the free passage of food. However, both SEMS presented similar rates of obstruction in this meta-analysis. At least all the studies described that the SEMS utilized were similar in the two groups regarding being covered, partially covered, or uncovered SEMS, even, nitinol or stainless metal, as it can affect migration or obstruction[36–38].

Another important adverse event (AE) related to SEMS use is aspiration pneumonia, as these patients generally have an additional risk of reflux by narcotic use or involvement of periesophageal nerves by the tumor. In theory, the SEMS-V may protect from aspiration, but the low incidence of this AE did not allow us to evaluate for this outcome. On the other hand, as the GERD results were similar between groups, it is theoretically expected to have similar aspiration rates in both groups.

Endoscopic palliation therapies must prioritize the evaluation of the Health-Related Quality of Life (HRQL)[39,40]. Three studies evaluated QoL[17,19,22]. However, our qualitative analysis regarding QoL could only include two studies that utilized the same score (QLQ-C30)[19,22]. The most recent RCT included the GERD-HRQL scale[17]; although it is reliable, it is a different score and thus we

could not include it in the meta-analysis due to other methods applied to measure it. Furthermore, it is important to note that after the SEMS deployment, there was an almost immediate increase in the QoL of the patients. However, the difference between both groups was not statistically significant.

Despite this being a systematic review and meta-analysis including only RCTs (level of evidence 1 A) and carefully following the PRISMA guidelines, our study has some limitations. First, there is significant variability in the parameters and measurement scales utilized for some of the outcomes, including some essential outcomes such as dysphagia improvement, GERD, and QoL. As an example, for GERD some studies utilized simple clinical scores, while others used other diagnostic tools, such as an upper endoscopy or Ph study, to confirm or quantify GERD. However, to overcome this limitation, we used dichotomous variables to elevate its reliability, thus reducing bias,. Particularly on GERD, we presented a quantitative analysis with regards, but with similar results as the qualitative analysis. Second, there is a limited number of patients (minimum of 36 and a maximum of 65 patients) per included RCT, which may potentially reduce the power of our analysis thus, the results of our analysis may represent an insufficient sample size, as exposed by the width of the confidence intervals of the outcomes, particularly, on the primary outcomes. However, advanced esophageal cancer in the distal esophagus with adequate criteria to utilize SEMS-V is not common, thus making it challenging to perform a large RCT. Third, the different models of SEMS used in each study could have affected the outcomes since there is a wide variety of anti-reflux mechanisms, delivery systems, and models. Furthermore, included in the RCTs, there were differences between the groups' SEMS length and diameter. Finally, the size and extension of the tumor were not correlated to the outcomes in our analysis, as they were not described in the included studies.

In summary, SEMS is an cornerstone treatment in the endoscopic palliation of advanced esophageal cancer. Regarding SEMS-V, they have similar technical and clinical success rates when compared to the SEMS-NV, although there is a lack of statistical significance, thus, the demand for more RCTs is warranted. Therefore, we cannot acknowledge the best approach, then, the decision on the type of SEMS to be utilized should be individualized, considering the anatomy, local expertise, resources availability, and patients' preference.

CONCLUSION

The use of SEMS-V and SEMS-NV for the endoscopic palliation of advanced esophageal cancer is similar in terms of technical success, dysphagia relief, post stent GERD, AEs, stent migration, stent obstruction, bleeding, and QoL.

DISCLOSURES

Drs. João Guilherme Ribeiro Jordão Sasso, Igor Mendonça Proença, Epifanio Silvino do Monte Junior, Igor Braga Ribeiro, Alexandre Moraes Bestetti, Angelo So Taa Kum and Wanderley Marques Bernardo have no relevant conflicts of interest or financial ties to disclose.

Dr. Diogo Turiani Hourneaux De Moura: BariaTek - Advisory Board Member (Consulting fees)

Dr. Sergio A. Sanchéz-Luna: Recipient of the 2021 American Society for Gastrointestinal Endoscopy (ASGE) Endoscopic Training Award by the ASGE and Fujifilm. This was not relevant to this study.

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FIGURES AND TABLES LEGENDS

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5-6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8-9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

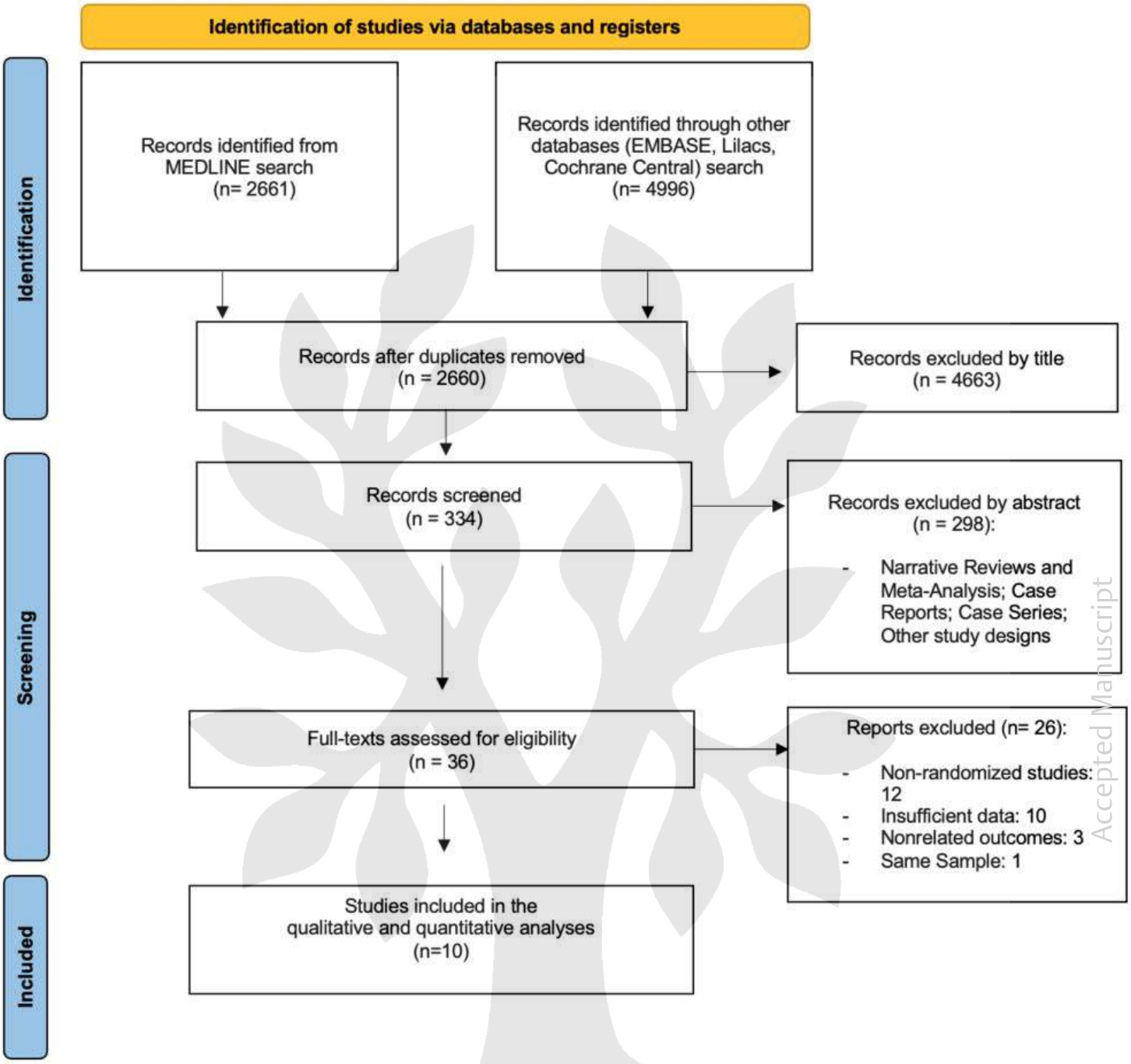
PRISMA 2009 Checklist

Author	Year of publication	Country	Study design	Patients (n) SEMS-V SEMS-NV	Type of Stent	Outcomes utilized
Dua KS et al. [17]	2019	United States	RCT, multicenter	V: 30 NV: 30	FDA: G130155 EndoMAXX-ES	GERD, TS, DI, AEs, SM, BL
Coron E et al. [18]	2016	France	RCT, multicenter	V: 20 NV: 18	Dostent Choostent	TS, AEs, SM, SO, BL
Kaduthodil M et al.[26]	2011	United Kingdom	RCT, single-center	V: 27 NV: 23	NA NA	GERD
Blomberg J et al.[19]	2010	Sweden	RCT, multicenter	V: 28 NV: 37	Z-stent Dua-valve	GERD, TS, AEs, SM, SO, BL, QoL
Sabharwal T et al.[20]	2008	United Kingdom	RCT, single-center	V: 22 NV: 26	FerX-Ella-valve Ultraflex	GERD, TS, DI, SM, SO, BL
Power C et al. [21]	2007	Ireland	RCT, single-center	V: 24 NV: 25	Hanarostent-valve Ultraflex	TS, AEs, SO
Wenger U et	2006	Sweden	RCT, multicenter	V: 19	Z-stent-dua	GERD. AEs, SM,

al. [22]				NV: 22	Z-stent	SO, BL, QoL
Shim CS et al. [23]	2005	South Korea	RCT, single-center	V1: 12 V2: 12 NV: 12	Hanarostent-valve Dostent Covered metal	GERD. TS
Homs MY et al. [24]	2004	Netherlands	RCT, single-center	V: 15 NV: 15	FerX-Ella-valve FerX-Ella	GERD, TS, AEs, SM, BL
Laasch HU et al. [25]	2002	United Kingdom	RCT, single-center	V: 25 NV: 25	Dua-Z Flamingo Stent	GERD, TS, DI, AEs, SM, SO

Table 1: Characteristics of the included studies.

RCT: Randomized clinical trial; **TS**: Technical success; **DI:** Dysphagia improvement; **GERD**: gastroesophageal reflux disease; **AEs**: adverse events; **SM**, Stent Migration; **SO:** Stent obstruction; **BL:** Bleeding; **QoL:** Quality of life; **NA**: not available.



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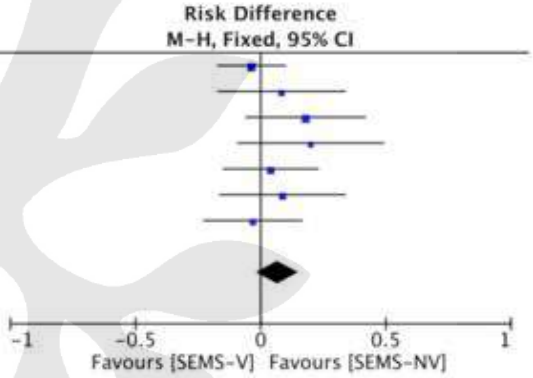
Study or Subgroup	SEMS-NV Events	SEMS-NV Total	SEMS-V Events	SEMS-V Total	Weight	Risk Difference M-H, Fixed, 95% CI
BLOMBERG J 2010	2	28	4	37	19.2%	-0.04 [-0.17, 0.10]
CORON E 2016	5	20	3	18	11.4%	0.08 [-0.17, 0.34]
DUA KS 2019	14	29	10	33	18.6%	0.18 [-0.06, 0.42]
HOMS MYV 2004	5	15	2	15	9.0%	0.20 [-0.09, 0.49]
LAASCH HU 2002	4	25	3	25	15.1%	0.04 [-0.15, 0.23]
SABHARWAL T 2008	7	22	6	26	14.4%	0.09 [-0.17, 0.34]
WENGER U 2006	2	19	3	22	12.3%	-0.03 [-0.23, 0.17]
Total (95% CI)		**158**		**176**	**100.0%**	**0.07 [-0.02, 0.15]**
Total events	39		31			

Heterogeneity: $Chi^2 = 4.91$, df = 6 (P = 0.56); $I^2 = 0\%$

Test for overall effect: Z = 1.61 (P = 0.11)



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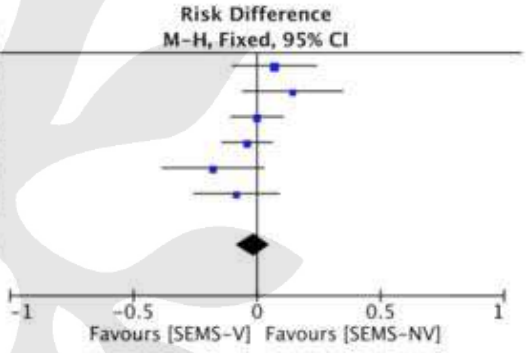
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
BLOMBERG J 2010	5	28	4	37	22.1%	0.07 [-0.10, 0.24]
CORON E 2016	4	20	1	18	13.1%	0.14 [-0.06, 0.35]
LAASCH HU 2002	1	25	1	25	17.3%	0.00 [-0.11, 0.11]
POWER C 2007	0	24	1	25	16.9%	-0.04 [-0.15, 0.07]
SABHARWAL T 2008	2	22	7	26	16.5%	-0.18 [-0.39, 0.03]
WENGER U 2006	1	19	3	22	14.1%	-0.08 [-0.26, 0.09]
Total (95% CI)		**138**		**153**	**100.0%**	**-0.01 [-0.08, 0.05]**
Total events	13		17			

Heterogeneity: $Chi^2 = 6.51$, df = 5 (P = 0.26); $I^2 = 23\%$

Test for overall effect: Z = 0.39 (P = 0.70)

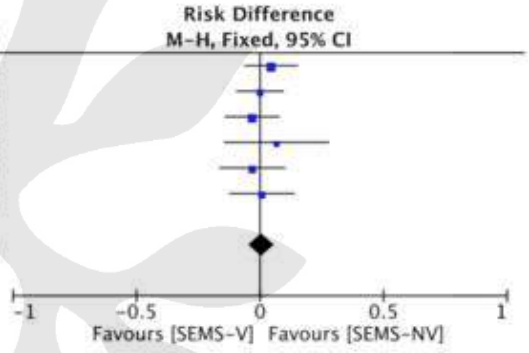


Kommentare

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference M-H, Fixed, 95% CI
BLOMBERG J 2010	2	28	1	37	22.8%	0.04 [-0.06, 0.15]
CORON E 2016	0	20	0	18	13.6%	0.00 [-0.10, 0.10]
DUA KS 2019	1	29	2	30	21.1%	-0.03 [-0.14, 0.08]
HOMS MYV 2004	2	15	1	15	10.7%	0.07 [-0.15, 0.28]
SABHARWAL T 2008	1	22	2	26	17.1%	-0.03 [-0.17, 0.10]
WENGER U 2006	1	19	1	22	14.6%	0.01 [-0.13, 0.14]
Total (95% CI)		**133**		**148**	**100.0%**	**0.01 [-0.05, 0.06]**
Total events	7		7			

Heterogeneity: $Chi^2 = 1.56$, $df = 5$ ($P = 0.91$); $I^2 = 0\%$

Test for overall effect: $Z = 0.23$ ($P = 0.82$)



Kommentare

Kommentare

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Author	D1	D2	D3	D4	D5	Overall
Dua KS	+	+	+	+	+	+
Coron E	+	+	+	+	+	+
Blomberg J	+	+	+	+	+	+
Sabharwal T	+	+	+	+	+	+
Power C	+	+	+	+	+	+
Wenger U	+	+	+	+	+	+
Shim CS	+	+	+	+	+	+
Homs MYV	+	+	+	+	+	+
Laasch HU	+	+	+	+	+	+
Kaduthodil M	+	+	-	!	!	-

	Interpretation
+	Low risk
!	Some concerns
-	High risk
D1	Randomisation process
D2	Deviations from the intended interventions
D3	Missing outcome data
D4	Measurement of the outcome
D5	Selection of the reported result

Kommentare

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Author(s):
Question: SEMS-V compared to SEMS-NV for Advanced oesophageal cancer
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SEMS-V	SEMS-NV	Relative (95% CI)	Absolute (95% CI)		
GERD - Qualitative analysis												
3	randomised trials	not serious	serious[a]	not serious	very serious	none	9/59 (15.3%)	23/63 (36.5%)	**RR 0.68** (0.12 to 3.76)	**117 fewer per 1.000** (from 321 fewer to 1.000 more)	⨁◯◯◯ Very low	
GERD - Quantitative analysis												
5	randomised trials	serious	serious	serious	serious	none	81	91	-	SMD **0.22 lower** (0.53 lower to 0.08 higher)	⨁◯◯◯ Very low	
Dysphagia improvement												
3	randomised trials	not serious	not serious	not serious	serious	none	57/74 (77.0%)	64/76 (84.2%)	**RR 0.92** (0.79 to 1.08)	**67 fewer per 1.000** (from 177 fewer to 67 more)	⨁⨁⨁◯ Moderate	
Technical Success												
8	randomised trials	not serious	not serious	not serious	serious	none	170/176 (96.6%)	187/188 (99.5%)	**RR 0.97** (0.93 to 1.01)	**30 fewer per 1.000** (from 70 fewer to 10 more)	⨁⨁⨁◯ Moderate	
Adverse Events												
7	randomised trials	not serious	serious	not serious	serious	none	53/160 (33.1%)	45/175 (25.7%)	**RR 1.32** (0.86 to 2.02)	**82 more per 1.000** (from 36 fewer to 262 more)	⨁⨁◯◯ Low	
Stent Migration												
7	randomised trials	not serious	not serious	not serious	serious	none	39/158 (24.7%)	31/176 (17.6%)	**RR 1.39** (0.92 to 2.10)	**69 more per 1.000** (from 14 fewer to 194 more)	⨁⨁⨁◯ Moderate	
Obstruction												
6	randomised trials	not serious	not serious	not serious	serious	none	13/138 (9.4%)	17/153 (11.1%)	**RR 0.88** (0.45 to 1.73)	**13 fewer per 1.000** (from 61 fewer to 81 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardised mean difference

Explanations

a. elevated Heterogenity

Kommentare

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Exifcleaner ausgeführt. 26 Merkmale entfernt. vorher: 57 nachher: 31;
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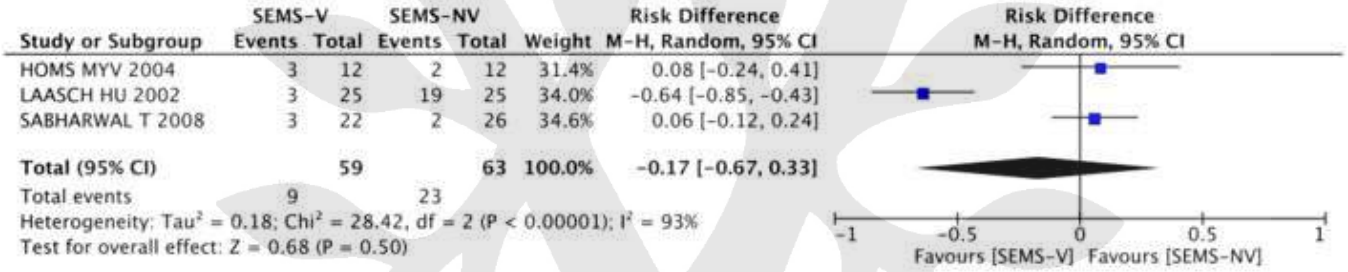
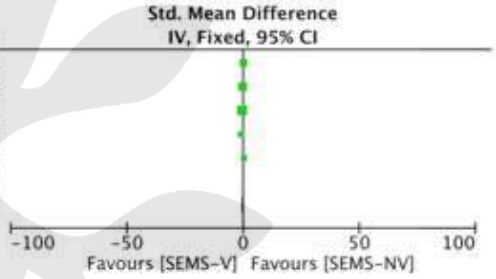


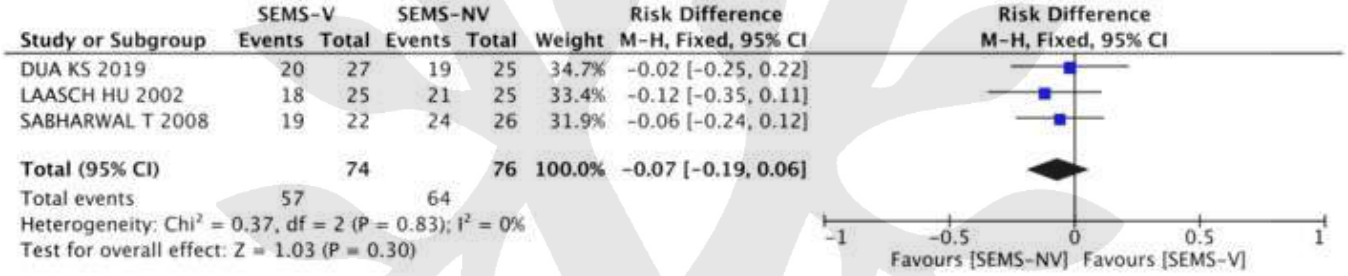
Kommentare

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
BLOMBERG J 2010	17	44.8	15	7	42	19	20.3%	0.23 [-0.45, 0.91]
DUA KS 2019	-7.4	10.2	17	-5.2	8.3	25	24.5%	-0.24 [-0.86, 0.38]
KADUTHODIL 2011	0.8	0.8	27	1.2	1.1	23	29.6%	-0.41 [-0.98, 0.15]
SHIM CS 2005	-2.92	4.2	12	1.83	4.3	12	12.5%	-1.08 [-1.95, -0.21]
WENGER U 2006	15	49.2	10	0	33.6	12	13.1%	0.35 [-0.50, 1.20]
Total (95% CI)			**81**			**91**	**100.0%**	**-0.22 [-0.53, 0.08]**

Heterogeneity: $Chi^2 = 7.62$, df = 4 (P = 0.11); $I^2 = 48\%$
Test for overall effect: Z = 1.43 (P = 0.15)



Kommentare

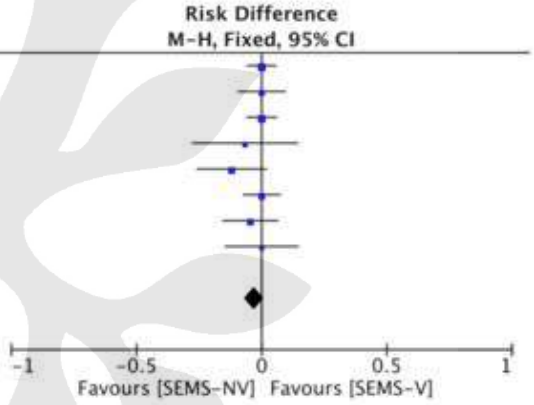


Kommentare

Study or Subgroup	SEMS-V Events	SEMS-V Total	SEMS-NV Events	SEMS-NV Total	Weight	Risk Difference M-H, Fixed, 95% CI
BLOMBERG J 2010	28	28	37	37	17.6%	0.00 [-0.06, 0.06]
CORON E 2016	20	20	18	18	10.5%	0.00 [-0.10, 0.10]
DUA KS 2019	30	30	30	30	16.6%	0.00 [-0.06, 0.06]
HOMS MYV 2004	13	15	14	15	8.3%	-0.07 [-0.28, 0.15]
LAASCH HU 2002	22	25	25	25	13.8%	-0.12 [-0.26, 0.02]
POWER C 2007	24	24	25	25	13.5%	0.00 [-0.08, 0.08]
SABHARWAL T 2008	21	22	26	26	13.2%	-0.05 [-0.16, 0.07]
SHIM CS 2005	12	12	12	12	6.6%	0.00 [-0.15, 0.15]
Total (95% CI)		**176**		**188**	**100.0%**	**-0.03 [-0.07, 0.01]**
Total events	170		187			

Heterogeneity: $Chi^2 = 4.44$, df = 7 (P = 0.73); $I^2 = 0\%$

Test for overall effect: Z = 1.40 (P = 0.16)

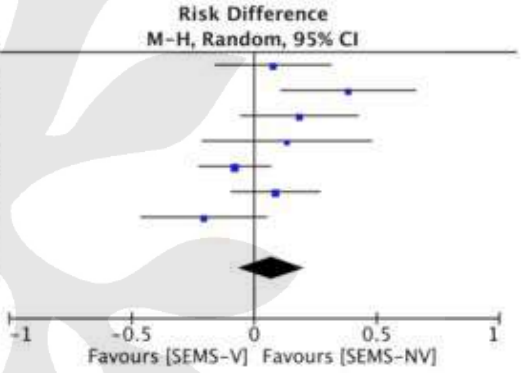


Kommentare

Study or Subgroup	SEMS-V Events	SEMS-V Total	SEMS-NV Events	SEMS-NV Total	Weight	Risk Difference M-H, Random, 95% CI
BLOMBERG J 2010	12	28	13	37	14.2%	0.08 [-0.16, 0.32]
CORON E 2016	11	20	3	18	12.3%	0.38 [0.11, 0.66]
DUA KS 2019	15	29	11	33	14.0%	0.18 [-0.06, 0.43]
HOMS MYV 2004	7	15	5	15	9.5%	0.13 [-0.21, 0.48]
LAASCH HU 2002	1	25	3	25	19.5%	-0.08 [-0.23, 0.07]
POWER C 2007	4	24	2	25	17.4%	0.09 [-0.10, 0.27]
WENGER U 2006	3	19	8	22	13.2%	-0.21 [-0.47, 0.05]
Total (95% CI)		**160**		**175**	**100.0%**	**0.07 [-0.07, 0.20]**
Total events	53		45			

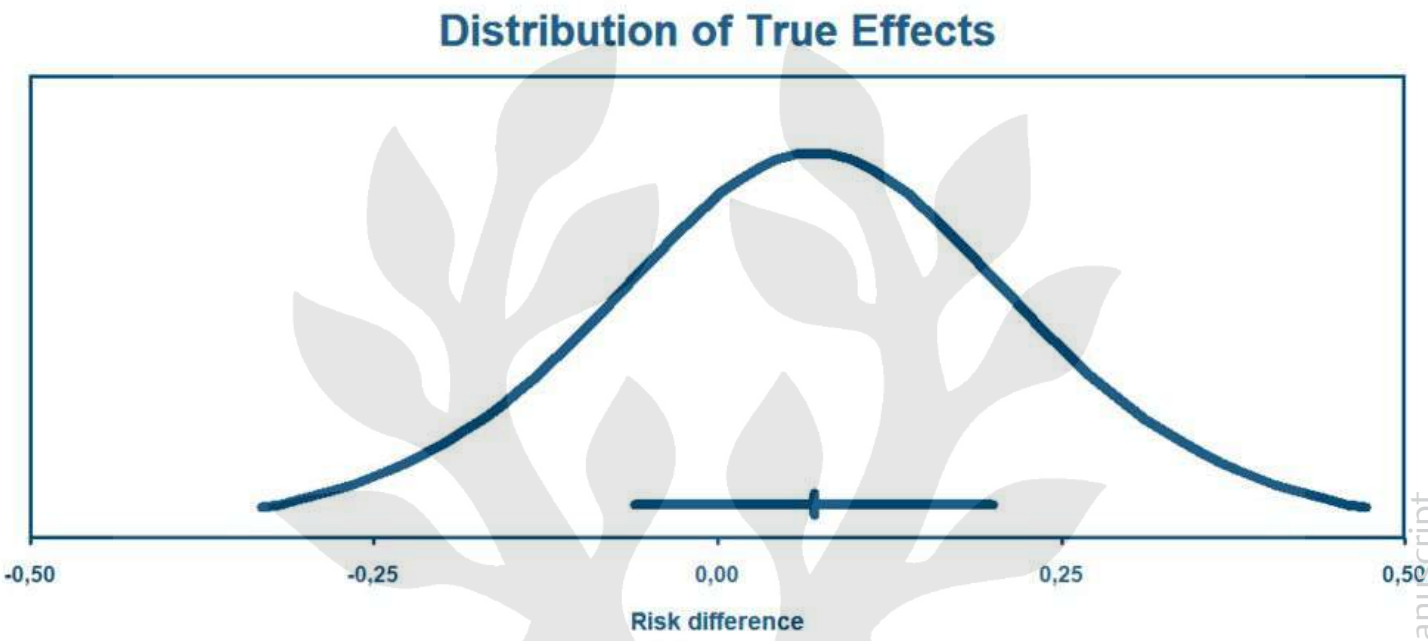
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 14.49$, df = 6 (P = 0.02); $I^2 = 59\%$

Test for overall effect: Z = 1.00 (P = 0.32)



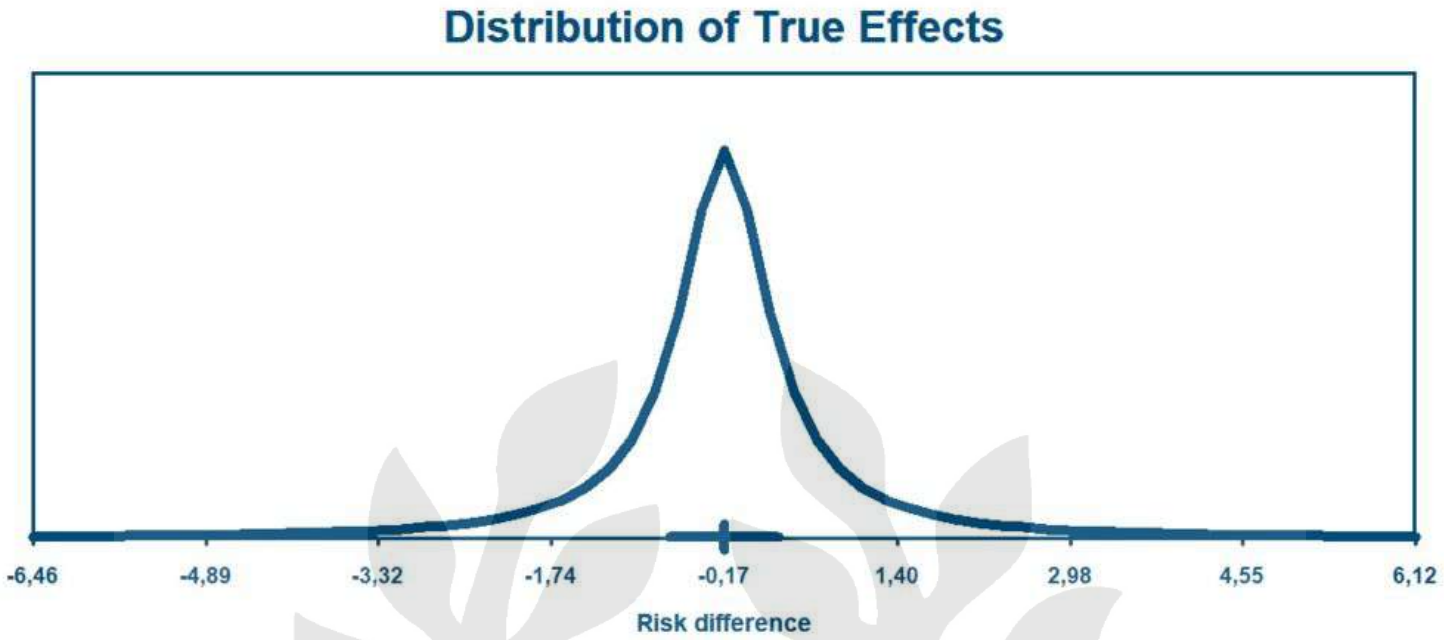
Kommentare

System user am 07.07.2022 13:02:05
Exifcleaner ausgeführt. 26 Merkmale entfernt. vorher: 57 nachher: 31;
verbleibende Merkmale: ExifTool:ExifToolVersion=12.30, System:FileName=tmp11836909621987494244, System:Directory=/tmp, System:FileSize=7.4 MiB, System:FileModifyDate=2022:07:07 13:02:05+02:00, System:FileAccessDate=2022:07:07 13:02:05+02:00, System:FileInodeChangeDate=2022:07:07 13:02:05+02:00, System:FilePermissions=-rw-r--r--, File:FileType=TIFF, File:FileTypeExtension=tif, File:MIMEType=image/tiff, File:ExifByteOrder=Big-endian (Motorola, MM), IFD0:ImageWidth=1224, IFD0:ImageHeight=1584, IFD0:BitsPerSample=8 8 8 8, IFD0:Compression=Uncompressed, IFD0:PhotometricInterpretation=RGB, IFD0:FillOrder=Normal, IFD0:StripOffsets=(Binary data 476 bytes, use -b option to extract), IFD0:Orientation=Horizontal (normal), IFD0:SamplesPerPixel=4, IFD0:RowsPerStrip=26, IFD0:StripByteCounts=(Binary data 426 bytes, use -b option to extract), IFD0:XResolution=1000, IFD0:YResolution=1000, IFD0:PlanarConfiguration=Chunky, IFD0:Resolu



Kommentare

System user am 07.07.2022 13:02:06
Exifcleaner ausgeführt. 39 Merkmale entfernt. vorher: 70 nachher: 31;
verbleibende Merkmale: ExifTool:ExifToolVersion=12.30, System:FileName=tmp4103094203231869181, System:Directory=/tmp, System:FileSize=2.3 MiB, System:FileModifyDate=2022:07:07 13:02:06+02:00, System:FileAccessDate=2022:07:07 13:02:06+02:00, System:FileInodeChangeDate=2022:07:07 13:02:06+02:00, System:FilePermissions=-rw-r--r--, File:FileType=TIFF, File:FileTypeExtension=tif, File:MIMEType=image/tiff, File:ExifByteOrder=Big-endian (Motorola, MM), IFD0:ImageWidth=1175, IFD0:ImageHeight=523, IFD0:BitsPerSample=8 8 8 8, IFD0:Compression=Uncompressed, IFD0:PhotometricInterpretation=RGB, IFD0:FillOrder=Normal, IFD0:StripOffsets=(Binary data 148 bytes, use -b option to extract), IFD0:Orientation=Horizontal (normal), IFD0:SamplesPerPixel=4, IFD0:RowsPerStrip=27, IFD0:StripByteCounts=(Binary data 138 bytes, use -b option to extract), IFD0:XResolution=1000, IFD0:YResolution=1000, IFD0:PlanarConfiguration=Chunky, IFD0:Resoluti



Kommentare

System user am 07.07.2022 13:02:00

Exifcleaner ausgeführt. 39 Merkmale entfernt. vorher: 70 nachher: 31;
verbleibende Merkmale: ExifTool:ExifToolVersion=12.30, System:FileName=tmp11968535691722887870, System:Directory=/tmp, System:FileSize=2.3 MiB, System:FileModifyDate=2022:07:07 13:02:00+02:00, System:FileAccessDate=2022:07:07 13:02:00+02:00, System:FileInodeChangeDate=2022:07:07 13:02:00+02:00, System:FilePermissions=-rw-r--r--, File:FileType=TIFF, File:FileTypeExtension=tif, File:MIMEType=image/tiff, File:ExifByteOrder=Big-endian (Motorola, MM), IFD0:ImageWidth=1168, IFD0:ImageHeight=524, IFD0:BitsPerSample=8 8 8 8, IFD0:Compression=Uncompressed, IFD0:PhotometricInterpretation=RGB, IFD0:FillOrder=Normal, IFD0:StripOffsets=(Binary data 140 bytes, use -b option to extract), IFD0:Orientation=Horizontal (normal), IFD0:SamplesPerPixel=4, IFD0:RowsPerStrip=28, IFD0:StripByteCounts=(Binary data 131 bytes, use -b option to extract), IFD0:XResolution=1000, IFD0:YResolution=1000, IFD0:PlanarConfiguration=Chunky, IFD0:Resolut