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Malignant distal biliary obstruction – palliative treatment-modality of endoscopic stent: metal stent × plastic stent

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field to standardize how to conduct and to assist in the reasoning and decision-making of doctors. The information provided by this project must be critically evaluated by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical condition of each patient.

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Societies: Sociedade Brasileira de Endoscopia Digestiva.

Group AMB: Wanderley Marques Bernardo

INTRODUCTION

Although malignant bile duct tumors are uncommon and estimated to have an incidence of 8000 new intrahepatic and extrahepatic cases per year according to the American Cancer Society[1], these neoplasms are associated with a very poor overall prognosis. In many cases, these lesions have no curative perspective by the time of diagnosis. Thus, palliative treatment methods to achieve bile duct clearance play a major role, providing a longer life expectancy and improved quality of life[2].

Endoscopic stenting, percutaneous transhepatic bile duct drainage (PTBD), and surgical bile derivation (i.e., surgical bypass) are established methods to achieve bile duct drainage. Endoscopic biliary stenting was first described by Soehendra[3] in 1979, and is currently considered the treatment of choice in the palliative care of unresectable or inoperable malignant distal biliary obstruction (MDBO). Additionally, endoscopic biliary drainage may be considered an alternative or as a combined approach method to PTBD[4]. Endoscopic drainage has been shown to be associated with a decreased mortality and lower complication rate, as well as a higher clinical success rate, compared to a traditional surgical approach; however, there does appear to be a higher rate of recurrent biliary obstruction[4,5].

Two types of stents may be utilized to achieve successful endoscopic biliary drainage: plastic stent (PS) and self-expanding metal stent (SEMS) placement. Each of these stent types possess different characteristics regarding stent patency, need for reintervention, potential for stent dysfunction, and other adverse events.

METHODS

A systematic review and meta-analysis of the literature (Medline, Central Cochrane, Embase, LILACS/VHL, and grey search) was carried out according to the recommendations of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) using the PICO system, including more patients aged 18 years with indication of palliative drainage of the biliary duct. The intervention and control were SEMS and PS, respectively, and the SEMS group was divided into subgroups, uncovered metal stent (uSEMS), partially and fully covered metal stent (pcSEMS/cSEMS), and third subgroup, SEMS that do not specify (SEMS not specified).

We screened all studies comparing PS versus SEMS placement among patients with inoperable MDBO, due to unresectability or poor patient status (after evaluation by the surgeon or anesthesiologist). The outcomes were assessed as follows: stent dysfunction rate, reintervention rate, duration of stent patency, median survival, complications (e.g., cholecystitis, bleeding, pancreatitis, perforation, and liver abscess), and clinical success.

Risk of bias was evaluated through the individual randomized controlled trials (RCTs) by Cochrane's risk assessment tool for randomized trials, available as ROB-II[18]. The quality of the evidence was analyzed using the Recommendation Classification, Development, and Evaluation (GRADE) working group[19]. The data from the selected works were analyzed through the software Review Manager version 5.4 (RevMan 5.4). The results were exposed as Forest plot and are available as Appendix.

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RESULTS

The search strategy identified 4378 articles. After excluding the duplicates, retrospective studies, and applying the eligibility criteria, 12 RCTs were selected, with a total of 1005 patients[6-17] (Figure A1).

The risk of bias analysis for each individualized study is shown in Table A1.

Results exposed by comparison were obtained as follows:

CLINICAL SUCCESS

→ Clinical success was evaluated in eight studies[6,8,9,11-13,16,17], evaluating a total of 765 patients.

There was no difference between the two groups (RD=0.03, 95%CI -0.01, 0.07). There was also no difference in the uncovered SEMS (RD=0.04, 95%CI -0.05, 0.13). Partially/fully covered SEMS (RD=0.03, 95%CI -0.03, 0.10), and SEMS not specified subgroups (RD=0.01, 95%CI -0.04, 0.06) (Figure A2).

The quality of evidence was moderate.

Mean survival

→ The mean survival analysis was performed in days and documented in six studies[7-9,11,14,16], evaluating a total of 610 patients.

There was no difference between the two groups (MD=0.63, 95%CI -18.07, 19.33). Regarding the subgroups, uSEMS (MD=65 days, 95%CI -18.44, 148.44) and SEMS not specified (MD=14.10 days, 95%CI -22.43, 50.63) were not different from PS placement. However, pcSEMS/cSEMS revealed an increase in mean survival (MD=-17.45 days, 95%CI -32.68, -2.21) (Figure A3).

The quality of evidence was low.

Complications

Analysis of 10 studies[6,8,9,11-17], totaling 1005 patients.

There was no difference between the two groups (RD=-0.03, 95%CI -0.10, 0.03). Subgroup analyses revealed no differences by specific SEMS type (uSEMS: RD=-0.09, 95%CI -0.21, 0.03; pcSEMS/cSEMS: RD=-0.00, 95%CI -0.09, 0.09; and SEMS not specified: RD=-0.06, 95%CI -0.21, 0.08) (Figure A4).

The quality of evidence was very low.

Stent dysfunction

→ Analysis of 11 studies[7-17], totaling 465 patients in the PS group and 542 patients in the SEMS group.

The rate of stent dysfunction was 24% lower in the SEMS group (RD=-0.24, 95%CI -0.33, -0.15) (Figure A5). Performing a subgroup analysis by type of SEMS revealed no difference in stent dysfunction rate between uSEMS and PS placement (RD=-0.08, 95%CI -0.56, 0.39). In the other two subgroups, there was a statistically significant difference: in the pcSEMS/cSEMS subgroup, the stent dysfunction rate was 21% lower than in the PS group (RD=-0.21, 95%CI -0.32, -0.1), and in the SEMS not specified subgroup, there was 29% less dysfunction than in the PS group (Figure A5).

The quality of evidence was very low.

Stent patency

→ Data from seven studies[7-9,11,12,14,16] were evaluated in a total of 720 patients.

The duration of patency was longer in the SEMS group (MD=125.77, 95%CI 77.5, 174.01).

In all subgroups, there was a longer time for stent dysfunction compared to PS (Figure A6).

The quality of evidence was very low.

Reintervention

→ The reintervention analysis was divided into two analyses, one evaluating studies in which the result was expressed in dichotomous variables and the other in continuous variables.

Dichotomous variables

It was possible to evaluate four studies[11,12,14,15], totaling 443 patients. The reintervention rate was 34% lower in the SEMS group, with statistical difference (RD=-0.34, 95%CI -0.46, -0.22).

In both the pcSEMS/cSEMS subgroup and the SEMS not specified subgroup, there was a lower reintervention rate than in the PS group. In the first subgroup, the intervention rate was 29% lower (RD=-0.29, 95%CI -0.41, -0.17), and in the second group, it was 39% lower than PS group (RD=-0.39, 95%CI -0.63, -0.15) (Figure A7).

The quality of evidence was very low.

Continuous variables

Three studies[10,16,17] were evaluated, with 176 patients.

The reintervention rate was 67% lower in the SEMS group (MD=-0.67, 95%CI -0.85, -0.50).

The uSEMS subgroup revealed no difference versus the PS group (RD=-0.76 95%CI -1.53, 0.01); however, the SEMS not specified subgroup had a reintervention rate 67% lower than in the PS group (RD=-0.67, 95%CI -0.85, -0.49) (Figure A8).

The quality of evidence was low.

DISCUSSION

Despite promising therapies that are the subject of studies and clinical trials, most of the time, at the time of diagnosis, these tumors are unresectable and present obstruction of the bile duct. Thus, endoscopic drainage using stents plays an important role in this condition.

In the comparisons between SEMS and PS, SEMS was associated with a longer duration of patency, lower rate of stent dysfunction, and decreased need for reintervention. This may be explained by two factors. First, SEMS is self-expanding and reaches a larger diameter when compared to PS placement, allowing for a greater flow and consequently better drainage of the bile duct. Furthermore, SEMS possess less surface for bacterial multiplication and fixation, which may lead to the formation of biofilm and deposition of bile sludge, responsible for earlier obstruction of the PS[10,16,17].

In the subgroup of uncovered metal stents, the main cause of obstruction was internal tumor growth ("ingrowth"), making replacement extremely challenging in cases of obstruction. In the subgroups of partially covered or covered metal stents, due to their covering, the main complication is migration. This is due to the fact that this type of stent applies a greater expandable force that, associated with tumor growth, leads to its migration. However, partially or fully covered SEMS allows for a greater possibility of stent removal or replacement in case of failure/clogging compared to uSEMS[10,16].

Regarding survival, there was no difference between SEMS and PS. However, when analyzing the subgroups, the pcSEMS/cSEMS placement outperformed PS.

This guideline presents as limitation the heterogeneity present in the RCTs analyzed, such as the presence of metastatic and non-metastatic patients, the use of different metal stents (i.e., fully cSEMS, pcSEMS, or uSEMS), the difference in diameters and subjective definitions for inoperable patients or for dysfunction. However, to minimize these limitations, we divided the SEMS groups into subgroups, in addition to evaluating a large number of studies, standardizing the location and approach method, maintaining relative homogeneity between the compared groups.

The limitations of this guideline and the difficulty of availability of the recommended resources are factors that can hinder the dissemination of the exposed recommendations. In contrast, the high level of evidence facilitates the dissemination of the content covered.

RECOMMENDATIONS

For MDBOs, the use of SEMS has a longer time for stent dysfunction (showing a longer patency time), a lower rate of reintervention, and a lower rate of dysfunction when compared to the use of PS in patients with MDBO. In the analysis of survival, there is no statistical difference between two groups; however when assessing the subgroups, pcSEMS / cSEMS showed higher survival compared to the PS. Regarding clinical success and rate of complications, there was no difference between the methods.

Thus, the SEMS presented favorable results in relation to the PS. However, the patient's survival time should always be taken into account, since those with an average survival of less than 4–6 months, the use of PS is more indicated, due to its lower initial cost.

The level of evidence varies from very low to low depending on the outcome analyzed.

AUTHORS' CONTRIBUTIONS

MVCVS: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, and Writing – review & editing. **VMTS**: Conceptualization, Data curation, Formal Analysis, Investigation, Visualization, Writing – original draft, and Writing – review & editing. **MPF**: Data curation, Investigation, and Visualization. **EM**: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Supervision, Validation, and Visualization. **WB**: Data curation, Methodology, Software, Supervision, and Visualization.

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APPENDIX

Protocol and registration

This study was performed in conformity with the PRISMA guidelines and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under file number CRD42020191234.

Eligibility Criteria

We analyzed all RCTs that compared the placement of PS versus SEMS, only through endoscopy in patients with inoperable/unresectable MDBO or poor condition of the patient (after evaluation by the surgeon or anesthesiologist). No restrictions were set for the publication date or language.

Literature search strategy, study selection, and data extraction

A comprehensive search was performed in MEDLINE, Cochrane, Embase, LILACS, and grey literature, from their inception to December 2020.

Search

We used this search strategy: ((Neoplasia OR Neoplasias OR Neoplasm OR Neoplasms OR Tumors OR Tumor OR Cancer OR Cancers OR Malignancy OR Malignancies) AND (Biliary Tract OR Biliary Tree OR Biliary System OR Bile Duct OR Bile Ducts)) OR (Bile Duct Neoplasms OR Bile Duct Neoplasm OR Bile Duct Cancer OR Bile Duct Cancers OR Biliary Tract Neoplasm OR Biliary Tract Neoplasm OR Biliary Tract Cancer OR Biliary Tract Cancers)) AND ((Prostheses and Implants) OR Prosthetic OR Implants OR Implant OR Prostheses OR Prosthesis OR Endoprosthesis OR Endoprostheses OR Stent OR Stents).

Statistical analysis

The data from the selected works were analyzed through the software Review Manager version 5.4 (RevMan 5.4).

For dichotomous end points, the difference was calculated by the risk difference, using the Cochran-Mantel-Haenszel test, with 95% confidence interval (CI). For continuous variables, the inverse variance test was applied. Statistically, we considered the 95%CI and $p<0.05$. The results were exposed in the form of a forest plot.

The inconsistency index was evaluated through I^2, in which it is possible to observe the presence of heterogeneity. The I^2 varies from 0% to 100%, and when it presents heterogeneity, >50% is considered high and >75% is considered very high. The sensitivity test (Egger) was performed whenever the heterogeneity was high in the search for publication bias (outlier)[20].

Risk of bias

Risk of bias was evaluated through the individual RCTs study by Cochrane's risk assessment tool for randomized trials, available as ROB-II[18].

The quality of the evidence was analyzed using the Recommendation Classification, Development, and Evaluation (GRADE) working group[19] (Table A2).

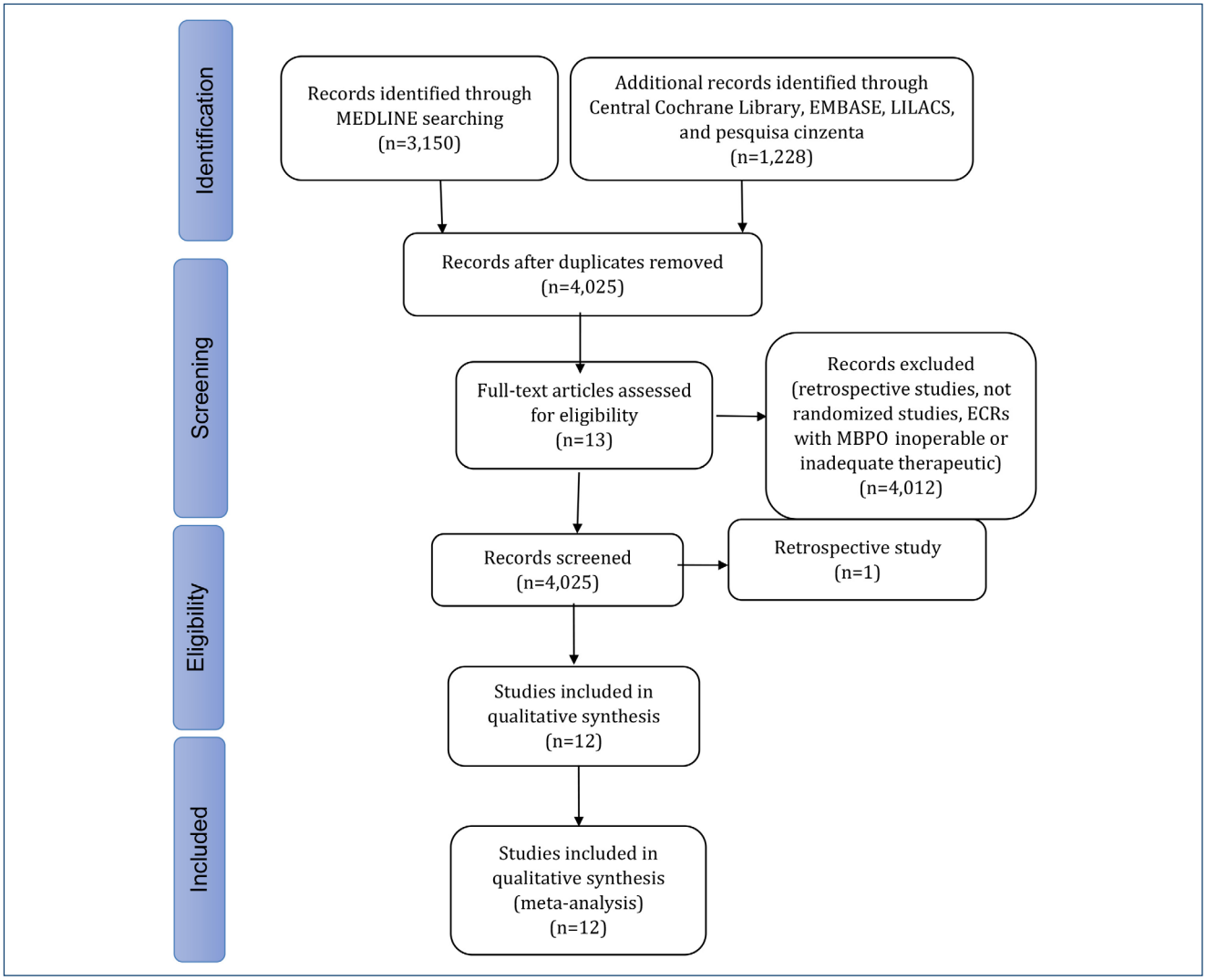

Figure A1. Flow diagram showing the article selection process.

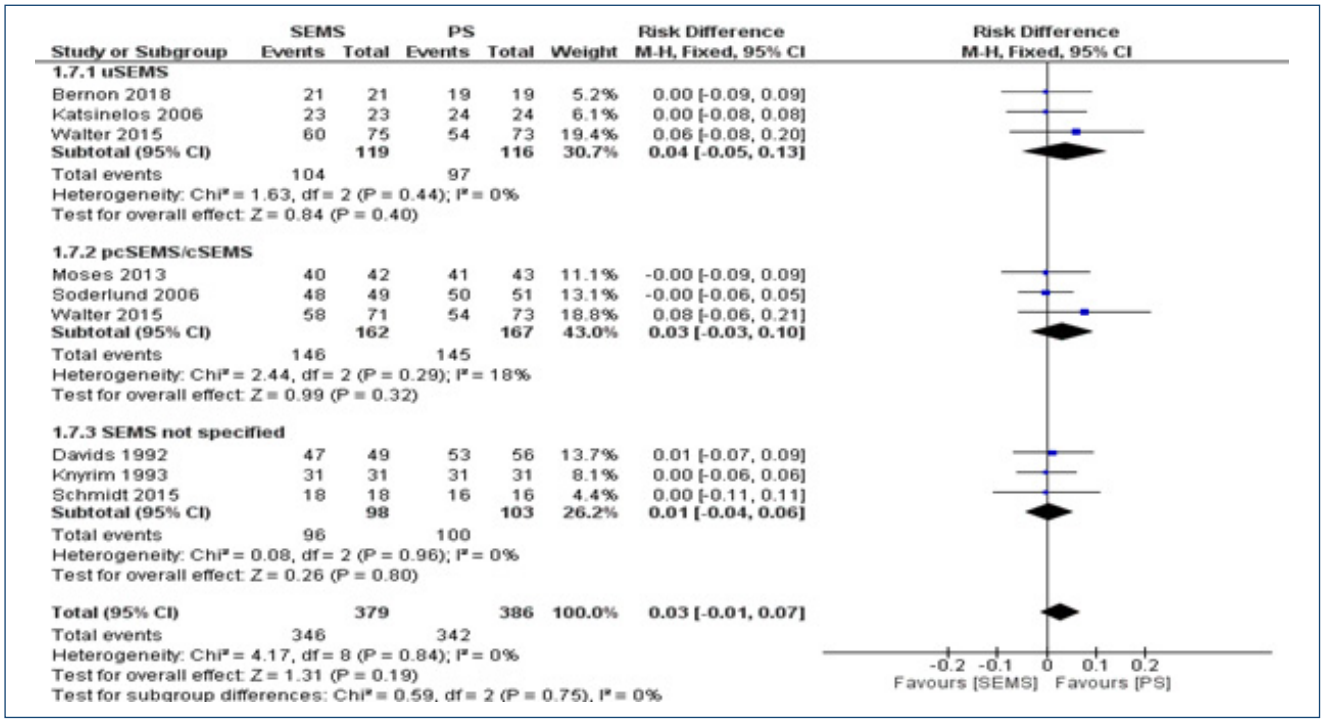

Figure A2. Clinical success – forest plot.

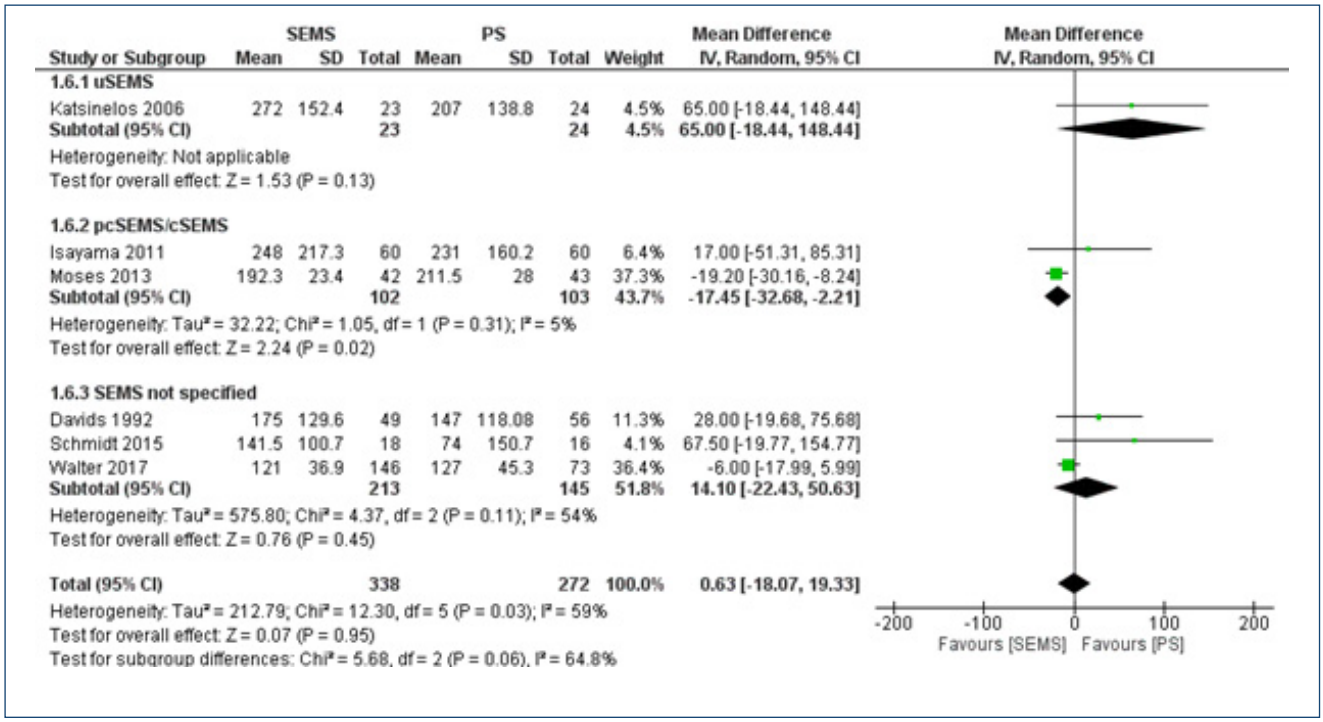

Figure A3. Mean survival (days) – forest plot.

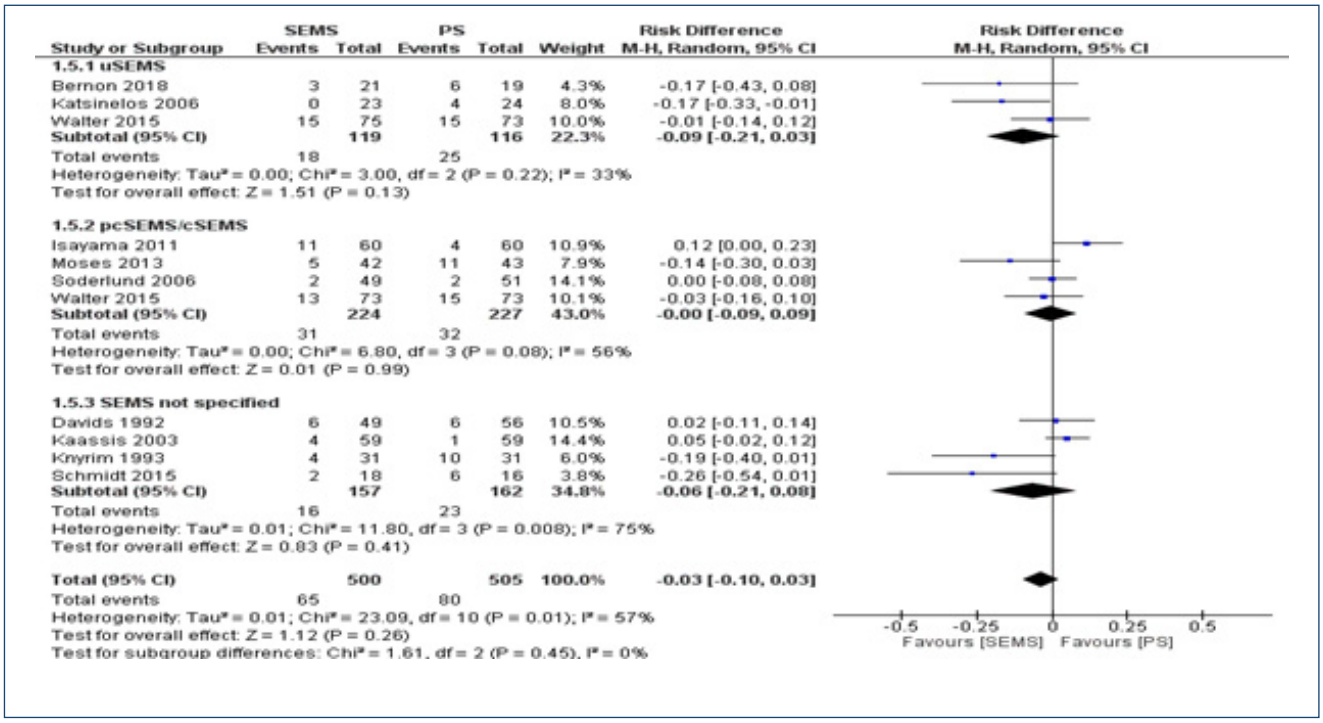

Figure A4. Complications – forest plot.

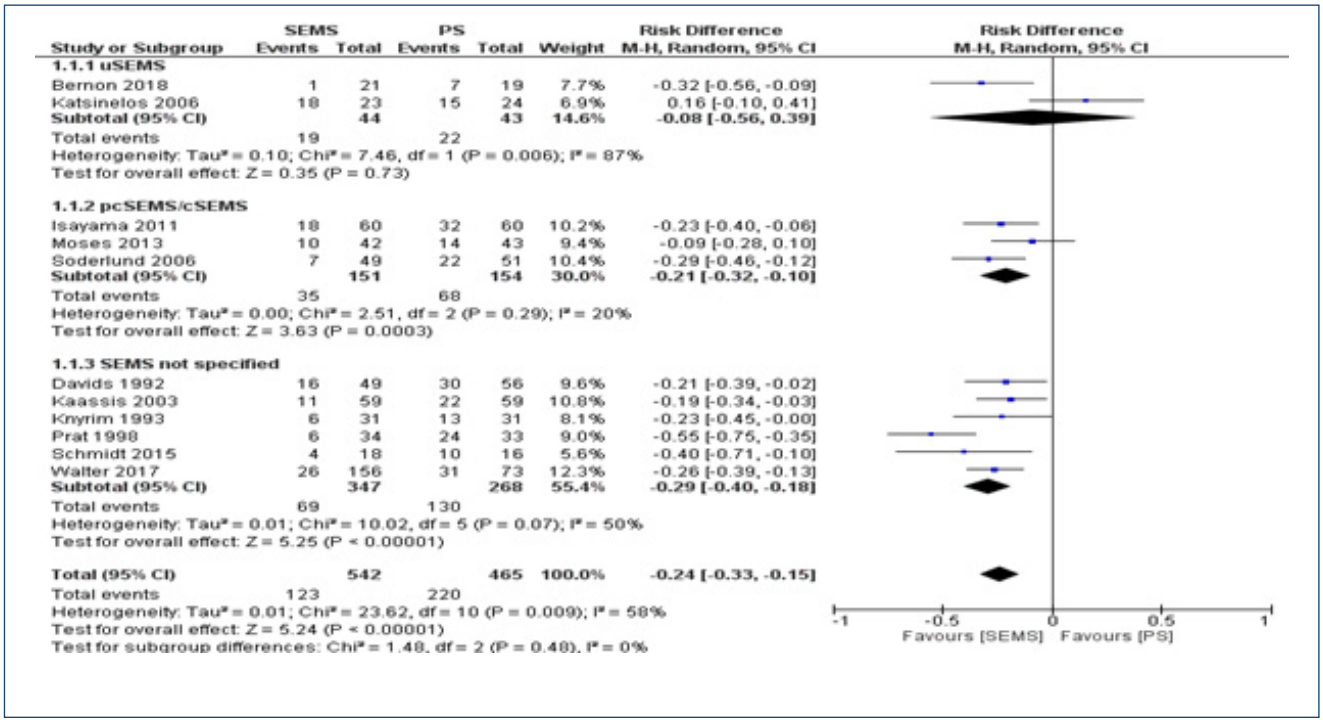

Figure A5. Stent dysfunction – forest plot.

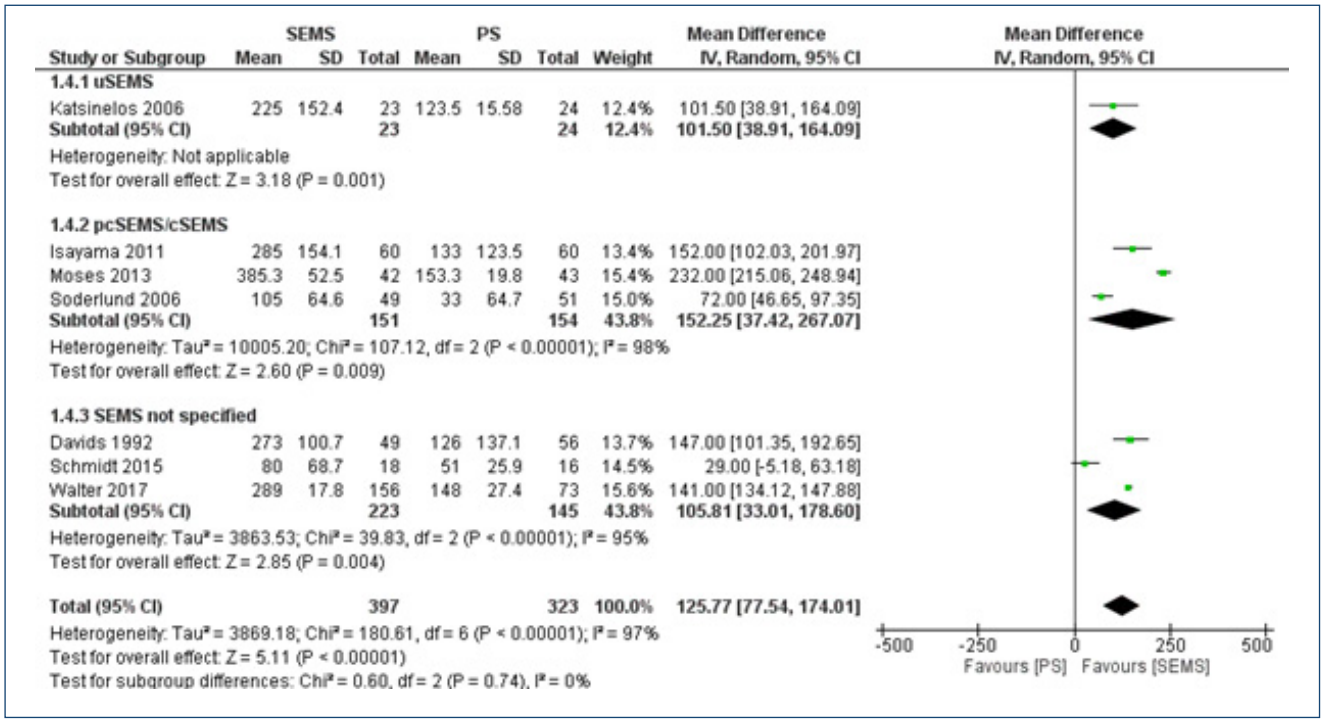

Figure A6. Stent patency (days) – forest plot.

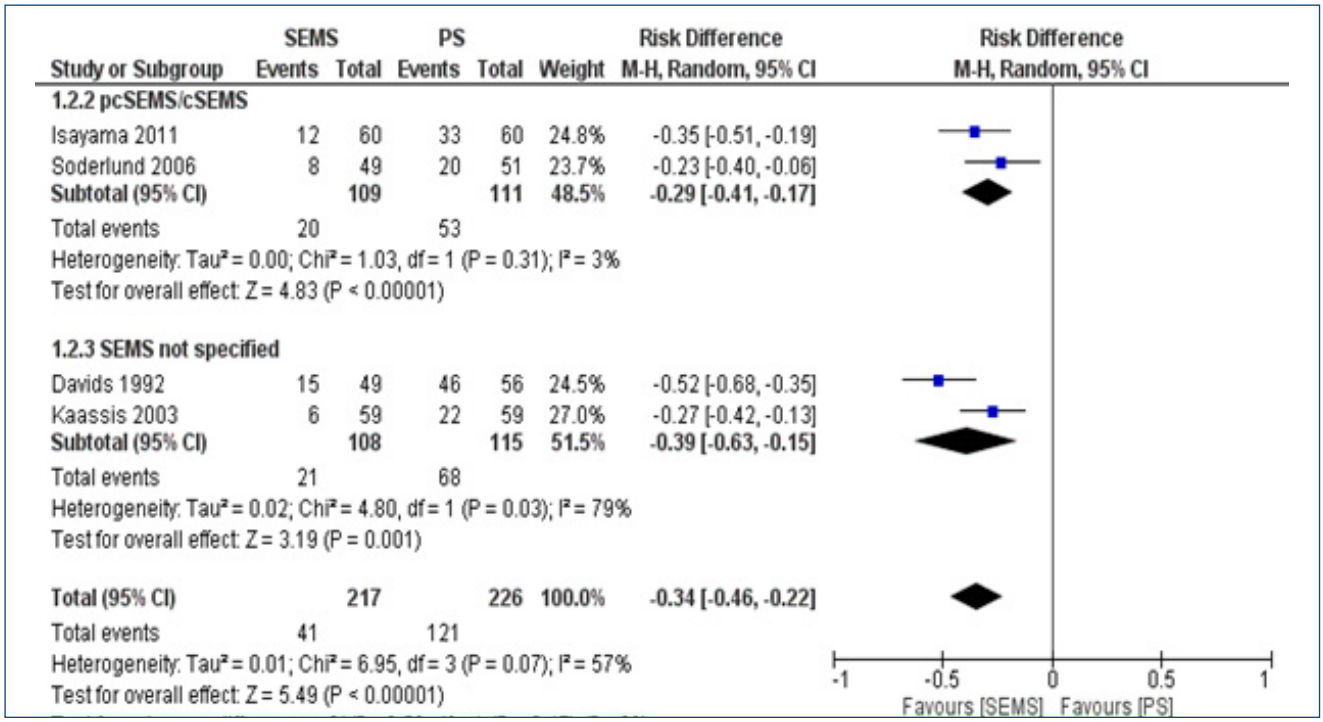

Figure A7. Reinterventions (dichotomic) – forest plot.

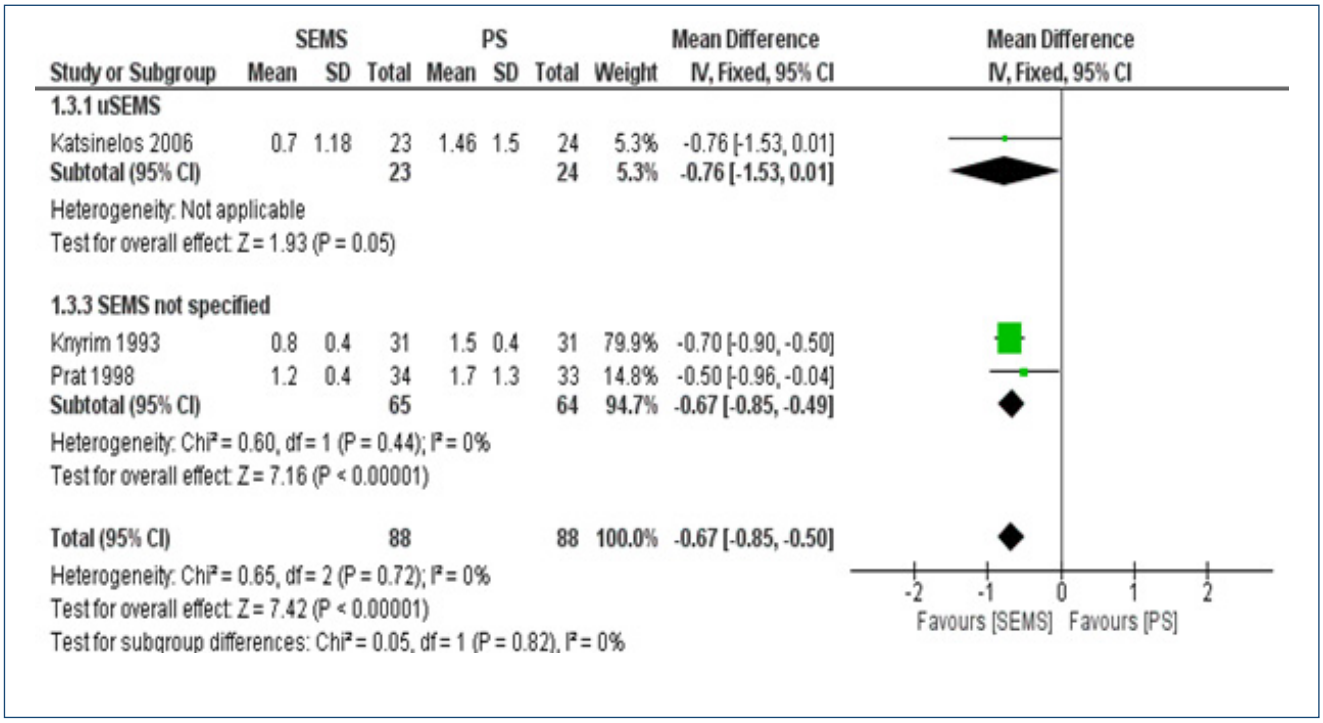

Figure A8. Reinterventions (continuous) – forest plot.

Table A1. Description of risk of biases in therapeutic study (ROB-II).

RCT	APPROPRIATE RANDOMIZATION	BLINDFOLDED ALLOCATION	DOUBLE-BLIND	BLIND AND BLINDED EVALUATOR	LOSS >20%	PROGNOSTIC CHARACTERISTICS	ANALYSIS BY INTENTION OF TREATMENT	SAMPLE CALCULATION	EARLY INTERRUPTION
Davis et al. (1992)	🟢	🟡	🔴	🟡	🟢	🟢	🟢	🟢	🟢
Knyrim et al. (1993)	🟢	🟡	🔴	🟡	🟢	🟢	🔴	🟢	🟢
Prat et al. (1998)	🔴	🟡	🔴	🟡	🟢	🟢	🟢	🟢	🟢
Kaassis et al. (2003)	🔴	🟡	🔴	🟡	🟢	🟢	🟢	🟢	🟢
Katsinelos et al. (2006)	🟢	🟢	🔴	🟡	🟢	🟢	🟢	🟢	🟢
Soderlund et al. (2006)	🔴	🟢	🔴	🔴	🟢	🟢	🟢	🟢	🟢
Isayama et al. (2011)	🟢	🟡	🔴	🔴	🟢	🟢	🟢	🟢	🟢
Moses et al. (2013)	🔴	🟢	🔴	🔴	🟢	🟢	🟢	🟢	🟢
Schmidt et al. (2015)	🟢	🟡	🔴	🔴	🟢	🟢	🟢	🟢	🟢
Walter et al. (2015)	🟢	🟡	🔴	🔴	🟢	🟢	🟢	🟢	🟢
Walter et al. (2017)	🟢	🟡	🔴	🔴	🔴	🟢	🟢	🟢	🟢
Bernon et al. (2018)	🟢	🟢	🔴	🟡	🟢	🟢	🟢	🟢	🟢

🟢 Appropriatea

🟡 Not available

🔴 Improper

Table A2. Quality of evidence was evaluated by Recommendation Classification, Development, and Evaluation criteria.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95%CI)	Anticipated absolute effects	
							With metal stent	With plastic stent		Risk with metal stent	Risk difference with plastic stent
COMPLICATIONS											
930 (10 RCTs)	Very serious[a,b]	Serious[c]	Not serious	Not serious	None	⊕◯◯◯ Very low	65/432 (15.0%)	65/498 (13.1%)	RR 0.80 (0.58–1.10)	150/1,000	30 fewer per 1,000 (from 63 fewer to 15 more)
STENT DYSFUNCTION											
1007 (11 RCTs)	Very serious[a,b,d]	Serious[c]	Not serious	Not serious	None	⊕◯◯◯ Very low	220/465 (47.3%)	123/542 (22.7%)	RR 0.50 (0.42–0.60)	473/1,000	237 fewer per 1,000 (from 274 fewer to 189 fewer)
SURVIVAL											
610 (6 RCTs)	Serious[a,d]	Serious[c]	Not serious	Not serious	None	⊕⊕◯◯ Low	272	338	–	The mean SURVIVAL was 0	MD 10.33 lower (18.18 lower to 2.47 lower)
DRAINAGE SUCCESS											
692 (8 RCTs)	Serious[a]	Not serious	Not serious	Not serious	None	⊕⊕⊕◯ Moderate	288/313 (92.0%)	346/379 (91.3%)	RR 1.02 (0.98 to 1.07)	920/1,000	18 more per 1,000 (from 18 fewer to 64 more)
REINTERVENTIONS											
443 (4 RCTs)	Very serious[a]	Serious[c]	Not serious	Not serious	None	⊕◯◯◯ Very low	121/226 (53.5%)	41/217 (18.9%)	RR 0.36 (0.27–0.48)	535/1,000	343 fewer per 1,000 (from 391 fewer to 278 fewer)
REINTERVENTIONS											
176 (3 RCTs)	Very serious[a,b]	Not serious	Not serious	Not serious	None	⊕⊕◯◯ Low	88	88	–	The mean REINTERVENTIONS was 0	MD 0.67 lower (0.85 lower to 0.5 lower)
TIME FOR STENT DYSFUNCTION											
710 (7 RCTs)	Very serious[a,d]	Very serious[e]	Not serious	Not serious	None	⊕◯◯◯ Very low	323	387	–	The mean TIME FOR STENT DYSFUNCTION was 0	MD 144.97 higher (138.99 higher to 150.95 higher)

CI: confidence interval; RR: risk ratio; MD: mean difference. [a]Inappropriate randomization; [b]Intention to treat analysis; [c]Heterogeneity >50%; [d]Lost to follow-up >20%; [e]Heterogeneity >75%.