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Systematic review: Temporary stent placement for benign ruptures or anastomotic leaks with special emphasis on stent type

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14 Utrecht, March 30 2011,
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16
17 Dear Jonathan Rhodes,
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19
20 Thank you for reviewing our manuscript, entitled:
21

22 APT-1037-2010: Stent placement for benign ruptures or anastomotic leaks: a pooled analysis
23 with special emphasis on stent type" .
24
25

26 The reviews were very helpful in improving the quality of our paper. Our responses to the
27 comments made by the reviewers can be summarized as follows:
28
29

30 **Your comments**

31 You cannot say "non-significantly more often" - you should say "was
32 similar" or "there was no significant difference in ...". We would
33 appreciate your sending in a revised manuscript taking into account the
34 reviewers' comments.
35
36
37

38 *This was amended as you suggested in **Abstract, p2 and Results, p8.***
39
40

41 Please do not hesitate to contact us for any further information you may require.
42
43

44 Yours sincerely,
45 on behalf of the co-authors
46
47
48

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2 **Systematic review: Temporary stent placement for benign ruptures or anastomotic leaks**
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4 **with special emphasis on stent type**
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22 Running head: Systematic review: Stent placement for benign ruptures or anastomotic leaks
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ABSTRACT

Background: Placement of self-expanding metal stents (SEMS) or plastic stents (SEPS) has emerged as a minimally invasive treatment option for benign esophageal ruptures and leaks; however, it is not clear which stent type should be preferred.

Aim & Methods: A pooled analysis was performed after searching PubMed and EMBASE databases for studies regarding placement of fully covered and partially covered SEMS (FSEMS and PSEMS) and SEPS for this indication. Data were pooled and evaluated for clinical outcome, complications and survival.

Results: Twenty-five studies, including 267 patients with complete follow-up on outcome were identified. Clinical success was achieved in 85% of patients and was not different between stent types (SEPS 84%, FSEMS 85% and PSEMS 86%, $p=0.97$). Time of stent placement was longest for SEPS (8 weeks) followed by FSEMS and PSEMS (both 6 weeks). In total 65 (34%) patients had a stent related complication. Stent migration occurred more often with SEPS ($n=47$ (31%)) and FSEMS ($n=7$ (26%)) than with PSEMS ($n=2$ (12%)), $p=<0.001$), while there was no significant difference in tissue in- and overgrowth between PSEMS (12% vs. 7% (FSEMS) and 3% (SEPS), $p=0.68$).

Conclusion: Although there is a lack of randomized controlled trials, it seems that covered stent placement for a period of 6-8 weeks is safe and effective for benign esophageal ruptures and anastomotic leaks to heal. As efficacy between different stent types is not significantly different, stent choice should depend on expected risk of stent migration (SEPS and FSEMS) and to a minor degree on expected risk of tissue in- or overgrowth (PSEMS).

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INTRODUCTION

Esophageal ruptures and leaks are rare, but may occur spontaneously, as in Boerhaave syndrome, or as a complication after an endoscopic or surgical procedure (1). Despite improvement in diagnostic procedures and (surgical) interventions, ruptures and leaks in the esophagus are still potentially life threatening injuries associated with a high morbidity and mortality if treated surgically (2-8).

Surgical treatment has long been the 'gold standard' for these emergencies (1;5;9-12).

Over the past few years, new minimally-invasive endoscopic treatment options have emerged, i.e., closure with clips or sutures, sealing with biologic glue and sealing with stent placement (13).

Endoscopic stent placement is an effective treatment for malignant dysphagia in a palliative setting (14). Recently, a good outcome with low morbidity and mortality has been reported for treating benign esophageal ruptures and leaks with temporary placement of a fully (FSEMS) or partially (PSEMS) covered self-expanding metal stent or a self-expanding plastic stent (SEPS) (15-20). Stents were found to be able to effectively seal esophageal leaks or ruptures and allow healing of the esophageal wall, particularly when concurrent adequate drainage of fluid collections in the mediastinum or pleural cavity is performed. The main drawbacks of stent placement are stent migration and tissue in- or overgrowth, which both necessitate a repeat intervention. Reactive nonmalignant tissue in- or overgrowth is mainly causing a problem when stents are inserted for a longer period and has been reported to occur more commonly with PSEMS than with FSEMS or SEPS (21-23).

Experience with temporary stent placement for benign esophageal ruptures or anastomotic leaks is until now only limited with most studies reporting small case series. In addition, studies comparing SEPS, FSEMS and PSEMS for the treatment of benign esophageal ruptures and leaks are not available.

1
2 We therefore performed a systematic review of the currently available literature to assess
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4 clinical effectiveness and safety of treating benign esophageal ruptures and anastomotic leaks
5
6 with temporary placement of a stent with special emphasis on different stent designs.
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10 **Methods**

11 **Literature search**

12 A literature search was performed in MEDLINE and EMBASE to identify all related studies
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14 on stent placement for benign esophageal ruptures or leaks. Each search was performed for
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16 studies in the English language until June 30, 2010, using the key words esophagus,
17
18 esophageal, rupture, leakage, leak, perforation, tear, Boerhaave syndrome and stent. Boolean
19
20 operators (NOT, AND, OR) were used, when appropriate, to widen or narrow the search.
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22 Then, a scan of the reference lists of each article was undertaken to identify other relevant
23
24 articles that were missed in the search. Studies that met the following inclusion criteria were
25
26 selected for our pooled analysis: (a) patients with a benign esophageal rupture or leak, (b)
27
28 endoscopic stent placement, and (c) results on a specific stent design (SEPS, FSEMS and
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30 PSEMS). Studies that were not in the English language, letters, editorials, reviews, animal
31
32 studies, case reports with fewer than four patients, and studies in patients with a malignant
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34 indication for stent placement were excluded. Patients with incomplete follow up after stent
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36 placement and patients dying from an esophageal malignancy within 1 year of follow-up were
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38 excluded from our analysis.
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43 **Date extraction**

44 Data on year of publication, country of origin, stent design, total number of patients included,
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46 number of patients with complete follow up, gender, age, etiology and size of rupture or leak,
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48 additional drainage of fluid collections in the mediastinum or pleural cavity, time between
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2 rupture or leak and stent placement, technical success of stent placement and removal, clinical
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4 success, total time of stent placement, procedure-related and stent related complications,
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6 reinterventions and mortality were extracted. All abstracts and titles of studies were screened
7
8 and data extraction from the selected studies were independently performed by two
9
10 investigators (PVB and AS) and differences in opinion were resolved by consensus opinion.
11

12 13 14 **Definitions**

15 We used the following definitions:

- 16 - Time of stent placement: time between stent placement and removal
- 17
- 18 - Successful sealing: sealing a perforation without complications
- 19
- 20 - Clinical success: healed perforation at the end of follow up without fatal complications
- 21
- 22 - Technical success: technically successful stent placement and removal
- 23
- 24 - Complication: adverse event due to the stent placement procedure (procedure-related
- 25 complication except pneumonia, for example perforation and hemorrhage) or type of stent
- 26 used (stent related complication, for example stent migration, tissue in-or overgrowth, etc.).
- 27
- 28 - Reintervention: endoscopic or surgical procedure needed to resolve complications or
- 29 because of failure of stent placement
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38 **Statistical analysis**

39 After data extraction data were pooled according to stent design. Data comparison between
40 the stent designs was performed by using the Chi-squared test. A p-value <0.05 was
41 considered statistically significant. Statistical analyses were conducted using SPSS version 15
42 (SPSS Inc, Chicago, Ill. USA).
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49 **RESULTS**

Search results

We detected 392 articles in MEDLINE and 601 articles in EMBASE. Of these, 25 articles met our inclusion criteria for the pooled analysis (Figure 1). A total of 13 studies reported results on SEPS placement(15;16;18;24-32) , 5 on FSEMS placement (13;33-36) and 7 on PSEMS placement for the treatment of benign oesophageal ruptures and leaks (19;37-42).

Descriptive analysis

All studies were published between 2001 and 2009. Sixteen studies were performed in Europe, seven in the US, one in Australia and one in China (Table 1). Twenty-five studies evaluated 267 patients with completed follow up, of whom 159 were treated with SEPS, 34 with FSEMS and 74 with PSEMS. Most of the stents used in the studies were 18-mm diameter stents. Overall, 71% of the patients were male and the mean age across studies was 60 (range 17-91) years.

The etiology of the ruptures was an anastomotic leak in 137 (51%) patients, iatrogenic (post endoscopic) in 66 (25%) patients, Boerhaave's syndrome in 46 (17%) patients, a (benign) fistula in 9 (4%) patients and other causes in the remaining 8 (3%) patients. In the PSEMS group, 4 (14%) perforations occurred during dilation, with 2 (7%) of these performed for achalasia. Two (8%) other perforations occurred during rigid esophagoscopy, 2 (2%) during ERCP and 18 (69%) following endoscopic procedures of unknown origin. In the FSEMS group, 1 (20%) perforation occurred after dilation for achalasia, 1 (20%) post EMR and 3 (60%) following endoscopic procedures of unknown origin. In the SEPS group, 7 (22%) perforations occurred during dilation, 3 (10%) during EUS, 3 (10%) during stent removal, 2 (7%) as a consequence of taking biopsies, 1 (3%) post EMR and 17 (48%) following endoscopic procedures of unknown origin.

1
2 In all but five studies (18;27;32;37;40), detailed data on size of rupture or leak was
3 missing. In these five studies, rupture or leak size varied between 10 and 30 mm and/or
4 consisted of 20-100% of the circumference. The overall mean time between occurrence of
5 rupture or leak and stent placement was 10 (range, 50 min -72 days) days.
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10 Concurrent drainage of fluid accumulations outside the esophageal lumen was performed
11 in 59% of patients (55% of patients with SEPS, 60% of patients with FSEMS and 61% of
12 patients with PSEMS) (Table 3).
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15 The mean time between rupture or leak and stent placement was shortest for PSEMS
16 placement (4 days), followed by SEPS placement (13 days) and longest for FSEMS
17 placement (16 days). Total time of stent placement was longest for SEPS (8 weeks, range 3-
18 19 weeks), followed by PSEMS and FSEMS placement (both 6 weeks, range 3-17 and 5-9
19 weeks, respectively). Results of the individual studies are summarized in Tables 2a-2c.
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26 27 28 **Outcome and survival**

29 The overall technical success rate of stent placement was 99% and was not different between
30 stent types (99% for SEPS, 100% for FSEMS and 98% for PSEMS, $p=0.65$) (Table 3).
31 Removal of SEPS and FSEMS was mostly uncomplicated (99% and 100%, respectively),
32 however removal of PSEMS was reported as complicated in 8% (92% uncomplicated)(see
33 below).
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39 Clinical success was achieved in 85% of all patients and was not significantly different
40 between SEPS (84%) FSEMS (85 %) and PSEMS (86%) ($p=0.97$) (Table 3). Mortality was
41 13% in all patients and was lowest with SEPS (11%) followed by FSEMS and PSEMS (both
42 18%). In most patients the cause of death was a septic complication due to infected fluid or an
43 abscess outside the esophageal lining.
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Complications and reinterventions

Eight (3%) patients had a procedure related complication (bleeding (n=6) or perforation due to stent misplacement (n=2)), whereas in 65 (34%) patients a stent related complication was seen (stent migration (n=56), tissue- in or overgrowth (n=9)). Stent migration occurred more often with SEPS (n=47 (31%)) and FSEMS (n=7 (26%)) than with PSEMS (n=2 (12%)) (p=<0.001), while there was no significant difference in tissue in- or overgrowth between PSEMS (n=2 (12%)) than with FSEMS (n=2(7%)) and SEPS (n=5(3%)) (p=0.68).

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An endoscopic reintervention was performed in 53 (25%) patients; however more with SEPS or FSEMS (both 26%, n= 41 and 9, respectively) than with PSEMS (13%, n=3)(p=<0.001). A surgical intervention for incomplete sealing, a procedure related or stent related complication was performed in 13% of patients and was not different between stent designs.

DISCUSSION

To our knowledge, this is the first pooled data analysis reporting the results of different stent designs in patients with a benign esophageal rupture or leak with results of 267 treated patients. There was a lack of randomized controlled trials. It is important to note that these results are only based on case series in which mainly small patient numbers were included.

Clinical success of stent placement, i.e., healing of the perforation or leak, was achieved in 85% of reported patients with no differences between PSEMS, FSEMS and SEPS. The mean time of stent placement that was needed for healing was 7 weeks and was not different between different stent types (range, 6-8 weeks). Animal studies have suggested that 4 weeks should be sufficient for tissue healing. Based on the results of this review; however, it seems advisable to remove esophageal stents after a period of approximately 7 weeks.

An absolute prerequisite for healing is adequate drainage of fluid or abscess cavities that are in continuity with the perforation or leak (43). The time between the occurrence of an

1
2 esophageal rupture or leak and the actual treatment, either surgical or endoscopic, is one of
3
4 the most critical prognostic factors (3;10;12;19). A longer delay between a rupture or leak and
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6 treatment is associated with a worsening of the prognosis due to septic complications from an
7
8 infected fluid accumulation in the mediastinum or pleural cavity. Tilanus et al. found that
9
10 extension of an esophageal rupture into the pleural cavity was an independent risk factor for
11
12 mortality (44). Most patients included in this review also died from septic complications due
13
14 to an abscess cavity outside the esophageal lining. Treatment, i.e., sealing the rupture or leak
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16 with concurrent drainage of fluid collections of abscess cavities in the pleural cavity,
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18 mediastinum and/or even peritoneal cavity should therefore be performed as early as possible.
19
20 Drainage can be performed by endoscopic, radiologic or surgical means (32).

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22 The mean time between esophageal perforation or leak and stent placement was 11 days
23
24 with significant differences between different stent types (FSEMS 16 days, SEPS 13 days,
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26 and PSEMS 4 days). Remarkably, this did not result in differences in clinical success and
27
28 mortality rates in favor of any stent type. This is probably due to the fact that the time
29
30 between perforation or leak and stent placement differed to a large extent between the
31
32 included studies, varying between 50 minutes and 50 days!

33
34 Stent migration necessitating a reintervention occurred in 25% of patients and was most
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36 commonly seen with fully covered stents, both SEPS (26%) and FSEMS (26%), compared to
37
38 PSEMS (13%) ($p < 0.001$). This is explained by the known reduced anchoring capacity of
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40 FSEMS and SEPS compared to PSEMS resulting in an increased migration rate of the former
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42 stent type (23;45). Furthermore, as the far majority of these patients have no obstructive
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44 lesion keeping the stent in place, the relatively high rate of stent migration with fully covered
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46 stent designs is not unexpected.

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48 In contrast, tissue in- and/or overgrowth was higher with PSEMS (12%) compared to
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50 SEPS (3%) and FSEMS (7%) ($p = 0.68$), although this result was not significant. The cover of
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1
2 FSEMS en SEPS that is applied along its whole length prevents tissue from growing into the
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4 stent meshes. It has been shown that this benign tissue reaction particularly occurs at the
5
6 uncovered part of FSEMS and is caused by a local fibrotic reaction and/or the proliferation of
7
8 granulation tissue. This hyperplastic tissue reaction can be clinically manifest as early as 2
9
10 weeks after stent placement but also at a later stage (46). Moreover, tissue in- and/or
11
12 overgrowth may complicate removal of PSEMS in patients, resulting in a second esophageal
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14 perforation (47). A technique to remove embedded PSEMS is to place a fully covered stent of
15
16 the same diameter inside the FSEMS. This so-called stent-in-stent method causes necrosis of
17
18 the hyperplastic tissue in- and/or overgrowth. In our experience, both these stents can be
19
20 removed uneventfully after a period of 7-14 days (48).

21
22 Although all three stent designs were found to be effective in sealing benign esophageal
23
24 ruptures or leaks, they all have their pros and cons. The main limitations of the presently used
25
26 stent types are migration and hyperplastic tissue in-and/or overgrowth..These stent types are
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28 as yet not available in a covered version. Another option could be the use of biodegradable
29
30 formulations to cover ruptures or anastomotic leaks. This material has been shown to
31
32 stimulate connective tissue and vascular ingrowth and displays only minor hyperplastic tissue
33
34 formation (49). The technique to applicate this material into an esophageal leak or rupture
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36 needs however further development.

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38 The mortality rate associated with stent placement for this indication (13%) may well
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40 compare favorably to surgical management (12%-50%) (19). There is currently no guideline
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42 which type of esophageal rupture or leak should be treated with stent placement or primary
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44 surgery. Stent placement has been proposed for ruptures or leaks less than 70% of the
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46 circumference, with surgery being reserved for larger ruptures or leaks (32). However, Doniec
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48 et al. reported a patient with a complete dehiscence that was treated with stent placement,
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50 resulting in complete closure without a complicated course (37). The only true evidence will
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2 come from a randomized trial comparing these two treatment modalities in a well defined
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4 population. Nevertheless, the limited number of patients for such a trial and the promising
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6 results of stent placement as is summarized in this review make it difficult if not impossible to
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8 perform such a trial.

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10 This review has several limitations which should be taken into account before concluding
11
12 that a particular stent type is favorable in patients with a benign esophageal rupture or leak.
13
14 First, no randomized trials have been conducted. It is important to note that these results are
15
16 only based on case series in which mainly small patient numbers were included. This is
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18 probably due to the limited number of patients in each center. Moreover, both FSEMS and
19
20 PSEMS are not approved by the Food and Drug Administration (FDA) for temporary use in
21
22 benign indications.

23
24 Second, a variety of treatment protocols have been employed in the included studies. In
25
26 some patients, stent removal or exchange was performed at shorter intervals than in others
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28 and concurrent treatment, such as drainage of fluid collections or abscesses, was also not
29
30 standard treatment in all studies. Consequently this could have affected clinical success rate,
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32 but also complication and mortality rates.

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34 Furthermore, it was not possible to analyse outcome on stent placement based on
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36 aetiology of the underlying disorder due to a lack of data in the source papers.

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38 Finally, selection bias cannot be excluded in this patient group, since it has still not been
39
40 elucidated which patients could benefit from stenting and which patients from primary
41
42 surgery.

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44 In conclusion, this review demonstrates that covered stents placed for a period of 6-8
45
46 weeks are effective and safe for benign esophageal ruptures or anastomotic leaks to heal. A
47
48 prerequisite for successful stent placement is adequate drainage of fluid collections in the
49
50 mediastinum or pleural cavity. As efficacy between PSEMS, FSEMS and SEPS was not

1
2 found to be significantly different, stent choice should depend on expected risks of stent
3
4 migration and/or tissue in- or overgrowth with a particular stent type. We are increasingly
5
6 using fully covered stents, particularly FSEMS, for this indication as these are flexible enough
7
8 and when used in large diameters (23 mm body diameter) show acceptable migration rates.
9
10 Further randomized trials are however needed to compare different stent types on the one
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12 hand and the ideal stent design that comes out of these trials with surgical treatment on the
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14 other hand; however, due to the limited number of patients this is unlikely to occur.
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For Peer Review

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Table 1: Baseline characteristics of studies on stent placement for benign esophageal leaks and ruptures

Author	Year	Country n (%)	Stent type	n	Pt. with complete FU n (%)	Males	Age mean (range)
SEPS							
Freeman et al. (25)	2009	US	Polyflex	19	19 (100)		48 (26-67)
Pennathur et al. (30)	2008	US	Polyflex	38	8 (21)		
Freeman et al. (25)	2007	US	Polyflex	17	17 (100)		54 (17-91)
Fukumoto et al. (26)	2007	US	Polyflex	4	4 (100)	0 (0)	38 (23-58)
Kiev et al. (28)	2007	US	Polyflex	14	13 (93)	8 (57)	53 (21-86)
Ott et al. (29)	2006	Germany	Polyflex	35	12 (34)	9 (75)	65 (54-95)
Freeman et al. (15)	2007	US	Polyflex	21	21 (100)		54 (14-93)
Schubert et al. (32)	2005	Germany	Polyflex	12	12 (100)	8 (67)	67 (37-84)
Radecke et al. (31)	2005	Germany	Polyflex	39	7 (18)		
Langer et al. (18)	2004	Austria	Polyflex	24	24 (100)	18 (75)	61 (37-84)
Gelbmann et al. (27)	2004	Germany	Polyflex	9	9 (100)		
Evrard et al. (23)	2004	Belgium	Polyflex	21	4 (19)	4 (100)	62 (45-78)
Hunerbrein et al. (16)	2004	Germany	Polyflex	19	9 (47)		62 (49-74)
TOTAL				272	159 (58)	47 (64)*	57 (17-91)*
FSEMS							
Amrani et al. (13)	2009	France	Niti-S/Hanaro	9	4 (44)	1 (25)	58 (34-83)
Babor et al. (33)	2009	Australia	Ella Boubella	7	7 (100)	5 (71)	66 (36-84)
Salminen et al. (36)	2009	Finland	Hanaro	10	8 (80)	6 (75)	58 (51-86)
Han et al. (34)	2006	China	Mushroom shaped	8	8 (100)	8 (100)	61 (38-71)
Roy Choudhury et al. (35)	2001	UK	Ultraflex/Telestep	14	7 (50)	6 (86)	67 (48-83)
TOTAL				48	34 (71)	26 (76)	62 (34-86)
PSEMS							
Leers et al. (39)	2009	Germany	Ultraflex	31	7 (23)		
Tuebergen et al. (41)	2008	Germany	Ultraflex	32	10 (31)	6 (60)	65 (44-81)
Fischer et al. (19)	2006	Germany	Ultraflex	15	13 (87)	11 (85)	56 (47-81)
Johnsson et al. (38)	2005	Sweden	Ultraflex	22	13 (62)		
Wadhwa et al. (42)	2003	US	Ultraflex/Wallst/Zstent	13	5 (38)		
Doniec et al. (37)	2003	Germany	Ultraflex	21	15 (71)		
Siersema et al. (40)	2003	Netherlands	FlamingoWallst/Ultraflex	11	11 (100)	8 (73)	59 (29-87)
TOTAL				145	74 (51)	25 (74)*	60 (29-87)*
OVERALL				465	267 (57)	98 (71)*	60 (17-91)*

* Computation limited to studies in which this information was provided.

Table 2a: Outcome of studies on SEPS placement for benign esophageal leaks and ruptures

Author	N	Etiology					Time before stent placement (days)	Technical success		Drainage n (%)	Sealing rate n (%)	Complications		Reintervention		Time stent in place (weeks)	Clinical success n (%)	Mortality n (%)
		Iatrogenic		Boerhaave syndrome, n (%)	Fistula, n (%)	Other, n (%)		Stent placement, n (%)	Stent removal, n (%)			Migration, n (%)	Tissue growth, n (%)	Endoscopic procedure n (%)	Surgical procedure, n (%)			
Anastomotic leak, n (%)	Post endoscopy, n (%)																	
Freeman et al. (25)	19			19 (100)			1	19 (100)	19 (100)	9 (47)	17 (89)	4 (21)	0 (0)	4 (21)	2 (11)	3	17 (89)	0 (0)
Bennathur et al. (30)	8	5 (63)	3 (37)					8 (100)		6 (75)	7 (88)			7 (88)	0 (0)		3 (38)	0 (0)
Freeman et al. (24)	17	9 (53)	8 (47)				2	17 (100)	17 (100)	6 (35)	16 (94)	3 (19)	0 (0)	3 (18)	1 (6)	7.4	16 (94)	0 (0)
Mukumoto et al. (26)	4	3 (75)			1 (25)			4 (100)	4 (100)	3 (75)	3 (75)	2 (50)	1 (25)	2 (50)	1 (25)	6	3 (75)	0 (0)
Giev et al. (28)	13	5 (38)	4 (30)	2 (16)		2 (16)		13 (100)	13 (100)	13 (100)	13 (100)	3 (23)	0 (0)	3 (23)	0 (0)		13 (100)	1 (8)
Ott et al. (29)	12	5 (42)	3 (25)	1 (8)		3 (25)		12 (100)		all infected areas	11 (92)	4 (33)	0 (0)	4 (33)	0 (0)		5 (42)	5 (42)
Freeman et al. (15)	21	12 (57)	9 (43)				12	21 (100)	20 (95)		20 (95)	5 (24)	1 (5)	5 (24)	1 (5)	7.3	20 (95)	1 (5)
Schubert et al. (32)	12	12(100)					15	12 (100)		10 (93)	12 (100)	2 (17)	0 (0)	3 (25)	0 (0)	4	11 (92)	0 (0)
Kadecke et al. (31)	7	3 (43)	4 (57)					7 (100)										
Langer et al. (18)	24	24(100)					19	22 (92)	9 (100)		22 (92)	9 (38)	0 (0)	5 (21)	9 (38)		21 (88)	6 (25)
Belbmann et al. (27)	9	5 (56)	3 (33)	1 (11)				9 (100)	6 (100)	9 (100)	3 (33)	3 (33)	1 (11)	1 (11)	0 (0)	19.2	6 (66)	3 (33)
Avrard et al. (23)	4				4 (100)		22	4 (100)	4 (100)		4 (100)	3 (75)	0 (0)	0 (0)	0 (0)	11.3	4 (100)	0 (0)
Hunerbrein et al. (16)	9	9 (100)					7.2	9 (100)	9 (100)	9 (100)	8 (89)	2 (22)	0 (0)	2 (22)	0 (0)	4.1	9 (100)	0 (0)
Total*	159	92 (58)	33 (21)	23 (14)	8 (5)	2 (1)	12.5	157 (99)	90 (99)	46 (55)	135 (89)	47 (31)	5 (3)	41 (26)	11 (14)	8	128 (84)	16 (11)

*Computation limited to studies in which this information was provided

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Table 2b: Outcome of studies on FSEMS placement for benign esophageal leaks and ruptures

Author	N	Etiology					Time before stent placem. (days)	Technical success		Drainage n (%)	Sealing rate n (%)	Complications		Reintervention		Time stent in place (weeks)	Clinical success n (%)	Mortality n (%)
		Iatrogenic		Boerhaave syndrome, n (%)	Fistula, n (%)	Other, n (%)		Stent placement, n (%)	Stent removal, n (%)			Migration, n (%)	Tissue growth, n (%)	Endoscopic procedure n (%)	Surgical procedure, n (%)			
Post anastomotic, n (%)	Post endoscopy, n (%)																	
Amrani et al. (13)	4	2 (50)	2 (50)				12	4 (100)	4 (100)		4 (100)	2 (50)	0 (0)	3 (75)	0 (0)	5	4 (100)	0 (0)
Babor et al. (33)	7			7 (100)			6	7 (100)	7 (100)	4 (57)	7 (100)	4 (57)	0 (0)	4 (57)	0 (0)	9.4	7 (100)	0 (0)
Salminen et al. (36)	8	1 (13)	3 (37)	4 (50)			12	8 (100)	4 (100)	6 (75)	6 (75)	1 (13)	1 (13)	1 (13)	3 (38)	5	4 (50)	3 (38)
Jan et al. (34)	8	8 (100)					34	8 (100)	8 (100)	8 (100)	8 (100)	0 (0)	1 (13)	0 (0)	0 (0)	4.5	8 (100)	2 (25)
Roy Choudhury (35)	7	7 (100)					12	7 (100)		3 (43)	6 (86)			1 (14)			6 (86)	1 (14)
Total*	34	18 (53)	5 (15)	11 (32)			16	34(100)	23 (100)	21 (60)	31 (91)	7 (26)	2 (7)	9 (26)	3 (11)	6	29 (85)	6 (18)

*Computation limited to those studies in which this information was provided

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Table 2c: Outcome of studies on PSEMS placement for benign esophageal leaks and ruptures

Author	N	Etiology					Time before stent placement (days)	Technical success		Drainage n (%)	Sealing rate n (%)	Complications		Reintervention		Time stent in place (weeks)	Clinical success n (%)	Mortality n (%)
		Iatrogenic		Boerhaave syndrome, n (%)	Fistula, n (%)	Other, n (%)		Stent placement, n (%)	Stent removal, n (%)			Migration, n (%)	Tissue growth, n (%)	Endoscopic procedure n (%)	Surgical procedure, n (%)			
Anastomosti laek, n (%)	Post endoscopy, n (%)																	
Beers et al. (39)	7	2 (29)	4 (57)			1 (14)		7 (100)							6		1 (14)	
Tuebergen et al.(41)	10	2 (20)	4 (40)	4 (40)				10 (100)	2 (20)	8 (80)					3.9			
Fischer et al. (19)	7	5 (71)	2 (29)				50 min	7 (100)	1 (14)	7 (100)		1 (14)	0 (0)	3.5	7 (100)	2 (29)		
	6	1 (17)	5 (83)				2.8	6 (100)	6 (100)	6 (100)			2 (33)	2.8	6 (100)	0 (0)		
Johnsson et al. (38)	13	2 (16)	5 (38)	1 (8)		5 (38)	11	12 (92)		12 (92)				2.5	9 (69)	4 (31)		
Wadhwa et al. (42)	5	3 (60)	1 (20)	1 (20)				3 (100)			1 (20)	0 (0)	1 (20)	0 (0)	17	3 (60)	2 (40)	
Doniec et al. (37)	15	11 (73)	2 (13)	1 (7)	1 (7)			5 (71)		15 (100)								
Siersema et al. (40)	11	1 (10)	5 (45)	5 (45)			1.3	11 (100)	11 (100)	10 (91)	1 (9)	2 (18)	1 (9)	2 (18)	7	10 (90)	0 (0)	
Total*	74	27 (37)	28 (38)	12 (16)	1 (1)	6 (8)	3.8	40 (98)	26 (92)	20 (61)	58 (94)	2 (12)	2 (12)	3 (13)	4 (14)	6.1	35 (85)	9 (18)

*Computation limited to those studies in which this information was provided

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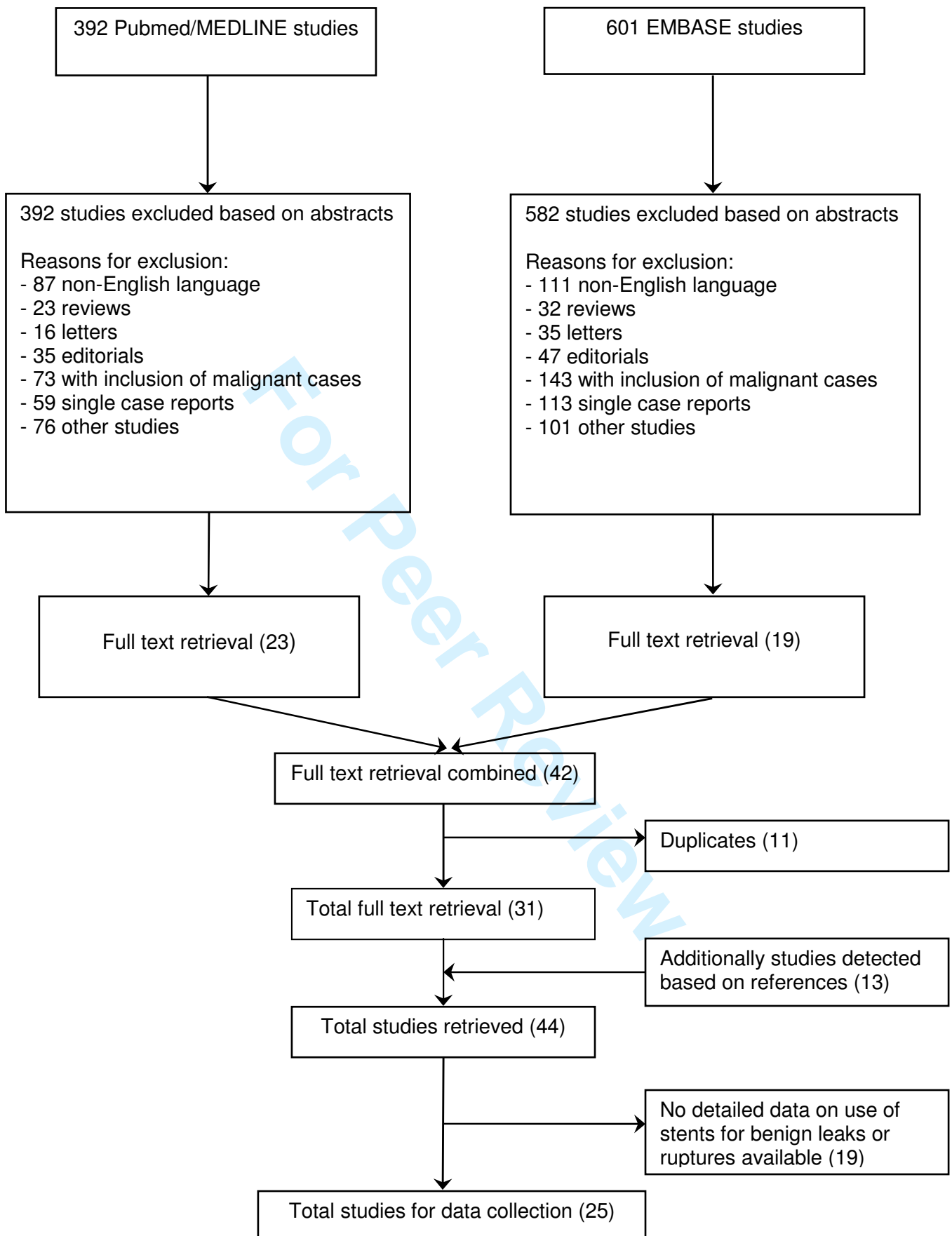
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4**Table 3: Pooled analysis of outcome of studies reporting on SEPS, FSEMS and PSEMS placement for benign esophageal leaks and ruptures**

Author	N	Etiology					Time before stent placement (days)	Technical success		Drainage n (%)	Sealing rate n (%)	Complications		Reintervention		Time stent in place (weeks)	Clinical success n (%)	Mortality n (%)
		Iatrogenic						Stent placement, n (%)	Stent removal, n (%)			Migration, n (%)	Tissue growth, n (%)	Endoscopic procedure n (%)	Surgical procedure, n (%)			
		Anastomotic leak, n (%)	Post endoscopy, n (%)	Boerhaave syndrome, n (%)	Fistula, n (%)	Other, n (%)												
SEPS	159	92 (58)	33 (21)	23 (14)	8 (5)	2 (1)	12.5	157 (99)	90 (99)	46 (55)	135 (89)	47 (31)	5 (3)	41 (26)	11 (14)	8	128 (84)	16 (11)
FSEMS	34	18 (53)	5 (15)	11 (32)			16	34 (100)	23 (100)	21 (60)	31 (91)	7 (26)	2 (7)	9 (26)	3 (11)	6	29 (85)	6 (18)
PSEMS	74	27 (37)	28 (38)	28 (38)	1 (1)	6 (8)	3.8	40 (98)	26 (92)	20 (61)	58 (94)	2 (12)	2 (12)	3 (13)	4 (14)	6.1	35 (85)	9 (18)
Total*	267	137 (51)	66 (25)	46 (17)	9 (4)	8 (3)	10.5	231 (99)	139 (98)	87 (59)	224 (88)	56 (29)	9 (5)	53 (25)	18 (13)	7.2	192 (85)	31 (13)

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*Computation limited to studies in which information was provided

Figure 1: Flowchart of search history on stents for benign esophageal leaks and ruptures





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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
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.	-
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.	4
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.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Figure 1
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).	4
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.	4-5
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
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
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
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.	4-5



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).	11
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.	Figure 1
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.	Table 1
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).	Table 2
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.	Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 3
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).	8
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).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
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.	15

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