

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2019 April 16; 11(4): 262-321





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AIMS AND SCOPE

World Journal of Gastrointestinal Endoscopy (*World J Gastrointest Endosc*, *WJGE*, online ISSN 1948-5190, DOI: 10.4253) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The *WJGE* covers topics concerning gastroscopy, intestinal endoscopy, colonoscopy, capsule endoscopy, laparoscopy, interventional diagnosis and therapy, as well as advances in technology. Emphasis is placed on the clinical practice of treating gastrointestinal diseases with or under endoscopy.

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INDEXING/ABSTRACTING

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**RESPONSIBLE EDITORS
FOR THIS ISSUE**

Responsible Electronic Editor: Yun-Xiaojuan Wu Proofing Editorial Office Director: Jin-Lei Wang

NAME OF JOURNAL

World Journal of Gastrointestinal Endoscopy

ISSN

ISSN 1948-5190 (online)

LAUNCH DATE

October 15, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Bing Hu, Anastasios Koulaouzidis, Sang Chul Lee

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5190/editorialboard.htm>

EDITORIAL OFFICE

Jin-Lei Wang, Director

PUBLICATION DATE

April 16, 2019

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ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

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ONLINE SUBMISSION

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Efficacy and safety of standard and anti-reflux self-expanding metal stent: A systematic review and meta-analysis of randomized controlled trials

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Author contributions: Pandit S and Samant H contributed equally to prepare this manuscript. Pandit S and Samant H designed study, performed data acquisition, analyzed data, drafted manuscript, final approval; Morris J analyzed data, edited manuscript; Alexander S edited manuscript, final approval.

Conflict-of-interest statement: The authors have no conflicting financial interests to disclose.

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Manuscript source: Unsolicited manuscript

Received: February 18, 2019

Peer-review started: February 18,

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Abstract

BACKGROUND

Self-expanding metal stents are the main palliative treatment modality for unresectable esophageal cancer. Gastroesophageal reflux is a common adverse outcome after placement of esophageal stent for cancer involving the gastroesophageal junction and the gastric cardia. Anti-reflux stents with valve have been designed to prevent the acid reflux. The superiority of anti-reflux stent over standard stent in preventing gastroesophageal reflux has not been established well. This study compares the anti-reflux stent and the standard stent in terms of their efficacy to prevent acid reflux.

AIM

To compare the standard and the anti-reflux stents in terms of their efficacy, safety, and complications.

METHODS

The meta-analysis included 8 randomized clinical trials (RCTs) to compare pooled outcomes of total 395 patients. Primary outcomes include improvement in reflux symptoms and dysphagia score. Secondary outcomes include complications of stent migration, occlusion, and bleeding.

RESULTS

A total of eight RCTs were included in the meta-analysis. Compared to the standard stent, the anti-reflux stent showed a trend towards reduction in the dysphagia score without reaching a statistical significance [Standardized mean

2019

First decision: February 26, 2019

Revised: March 11, 2019

Accepted: April 8, 2019

Article in press: April 9, 2019

Published online: April 16, 2019

P-Reviewer: de Moura DTH,
Richardson WS

S-Editor: Wang JL

L-Editor: A

E-Editor: Wu YXJ



difference (SMD): -0.33 (-0.71, 0.05); $P = 0.09$, I^2 : 37%]. There was no statistical difference in the gastrointestinal reflux (GER) scores between the two types of stents [SMD: -0.17 (-0.78, 0.45); $P = 0.008$, I^2 : 74%]. Compared to standard stent, anti-reflux stent showed no difference in the risk of stent migration [OR: 1.37 (0.66, 2.83); $P = 0.40$, I^2 : 0 %], bleeding [OR: 1.43 (0.40, 5.13); $P = 0.59$, I^2 : 0 %], and obstruction [OR: 1.66 (0.60, 4.60); $P = 0.33$, I^2 : 0 %].

CONCLUSION

Traditional self-expanding standard esophageal stent and anti-reflux stent with valve are similar in terms of outcomes and complications.

Key words: Self expanding metal stent; Anti-reflux stent; Randomized controlled trial; Esophageal stent; Meta-analysis

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Core tip: In this meta-analysis, we studied and compared the traditional standard self-expanding metal stent and anti-reflux stent in terms of their efficacy and safety. We included 8 randomized controlled trials in our meta-analysis from 3 different databases. We expected anti-reflux stent with valves, as its name suggests, to show improvement in reflux symptom score, however, this was not observed in our study. This review study shows that there is no difference between standard stent and anti-reflux stent in terms of improving reflux symptom and dysphagia score. This study also confirms that there is no difference in terms of complications including stent migration, bleeding, and obstruction between standard stent and anti-reflux stent.

Citation: Pandit S, Samant H, Morris J, Alexander SJ. Efficacy and safety of standard and anti-reflux self-expanding metal stent: A systematic review and meta-analysis of randomized controlled trials. *World J Gastrointest Endosc* 2019; 11(4): 271-280

URL: <https://www.wjgnet.com/1948-5190/full/v11/i4/271.htm>

DOI: <https://dx.doi.org/10.4253/wjge.v11.i4.271>

INTRODUCTION

The incidence of esophageal cancer, adenocarcinoma in particular, is rising rapidly in the western countries including the United States^[1]. Involvement of the esophagogastric junction (EGJ) and gastric cardia is common for esophageal adenocarcinoma^[2]. In 2015, a total of 17281 new cases of esophageal cancer were reported in the United States with 15211 deaths due to cancer^[3]. About 50 to 80 percent of esophageal cancer patients present with metastasis and/or locally invasive disease which is surgically unresectable^[4]. Palliative chemotherapy, radiation therapy, brachytherapy, and endoscopic management are the available treatment modalities for patients with surgically unresectable cancer^[5].

Dysphagia and food bolus impaction are the two most common presentations of esophageal cancer. Placing a stent across the tumor is one of the palliative options to relieve dysphagia, and to improve the quality of life. Nonetheless, placement of esophageal stent is associated with various complications such as stent migration, bleeding, perforation, and stent occlusion. Severe acid reflux is one of the most common symptomatic complaints in patients who undergo standard metal stent placement at tumors involving EGJ or cardia, as the lower esophageal sphincter remains wide open after stent placement^[6]. Recently, a study by Włodarczyk *et al*^[7] showed that among patients who undergo esophageal stent placement for dysphagia from unresectable esophageal cancer, 45 percent complain of severe acid reflux. To reduce these post stent placement sequels, various modification of traditional standard stent (SS) are in progress, one of them is the development of anti-reflux esophageal stent (ARS).

Many randomized and prospective studies have been reported in literature comparing the efficacy and safety of SS and ARS. Intuitively, ARS with valve is supposed to decrease the gastroesophageal reflux (GER), but multiple studies have shown mixed results. We performed a systematic review and meta-analysis of these studies to ascertain the efficacy and safety of SS and ARS.

MATERIALS AND METHODS

We conducted this systematic review and meta-analysis according to the guidelines provided by the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0^[8] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement was adopted in the preparation of this manuscript.

Literature search

All randomized controlled trials (RCTs) including anti reflux stents were identified. A literature search of PubMed, CINAHL, and Cochrane Library for RCTs was performed from inception to 2018. Search terms included self-expanding metal stent, anti-reflux esophageal stent, and RCTs. Additional articles were manually searched from bibliographies of selected articles and pertinent review articles. The title, abstracts, and full text of the articles were reviewed by two independent reviewers (S.P. and H.S.). Abstracts from national and international meetings were also included.

Our inclusion criteria were: (1) RCTs; (2) Age > 18 years old; (3) Esophageal cancer with stent crossing the EGJ and cardia; (4) Comparison between SS and ARS; and (5) Reported improvement in clinical outcome and complications. Exclusion criteria were: (1) Foreign language without English version; (2) Study that included stents for benign esophageal stricture; (3) Stents placed by radiologists; and (4) Prior history of stent placement.

If multiple publications for the same study population were identified, the most recent publication was used. All disagreements were resolved by joint decision between the two authors (S.P. and H.S.), and a senior author (J.M.).

Data extraction and quality assessment

Two authors (S.P. and H.S.) independently extracted data from each study including characteristics of study, characteristics of study population, and results of study. Characteristics of study included first author, year, study design, country, type of stents used, number of patients in each arm, preemptive dilation of stents, and types of procedural sedation. Characteristics of study population included mean age, gender, indications for stent placement, and types of histopathology. Results of study included standard mean difference for GER symptoms, and dysphagia score. Odds ratio (OR) was calculated for comparison of complications which included risk of bleeding, stent migration, and stent occlusion.

Quality assessment was independently performed according to QUADAS-2 by 2 authors (S.P. and H.S.)^[9]. The discrepancies between the two authors were resolved by joint decision between the two authors and the senior author (J.M.).

Statistical analysis

Randomized effects model was used to perform meta-analysis according to the heterogeneity. Pooled estimate of major outcomes studied were the improvement in dysphagia, GER scores, which were reported as standardized mean difference (SMD) with 95%CI. The risk of stent migration, bleeding, and obstruction were reported as OR with 95%CI.

Revman review manager version 5.3 was used for data analysis. Results were considered significant if $P < 0.05$.

RESULTS

Characteristics of studies and study population

After initial search using key words (esophageal stent, anti-reflux esophageal stent, self-expanding metal stent) fifty-three potential studies were identified. After excluding duplicate studies, twenty-two studies were screened for title and abstracts. After excluding non-RCTs, only eight studies were included for detailed review for this meta-analysis^[6,10-16] (Figure 1).

A total of 395 patients were included in the study, ARS (192 patients) and SS (203 patients), comparing their efficacy and outcome (Table 1). Among them 249 were men with mean age of 70.1 years. The studies were published between 2004 and 2016, and all the studies were conducted in the developed countries in the resource rich settings. Out of the eight studies, three studies were multicenter and five were single center studies. The indication for stent was dysphagia secondary to distal esophageal cancer and gastric cardia cancer. Histologically, 189 patients had adenocarcinoma of esophagus, 90 patients had squamous cell carcinoma of esophagus, and 14 had undifferentiated type (Table 2).

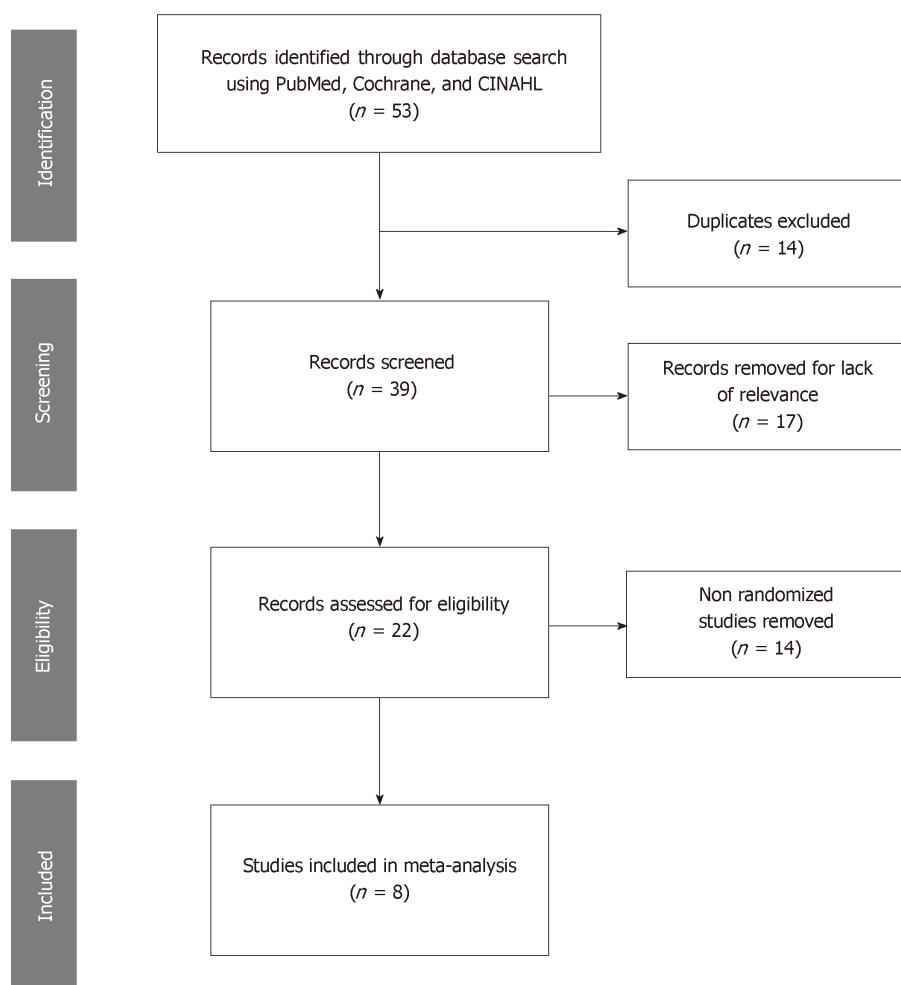


Figure 1 Flow chart of articles selected for this meta-analysis study.

Primary outcomes

Eight studies were included in the meta-analysis, however, only four studies reported primary outcome as GER and dysphagia, before and after stent placement. Among other four studies, Coron *et al*^[10], Sabharwal *et al*^[13], and Homs *et al*^[6] did not report adequate information to calculate SMD. Three studies fail to report necessary statistical information to calculate SMD, and one study provided partial statistical value that could not be used in the study^[14]. Compared to the SS, the ARS showed a trend towards reduction in the dysphagia score but it did not reach a statistical significance [SMD: -0.33 (-0.71, 0.05); $P = 0.09$, $I^2: 37\%$]. And, there was no statistical difference in the GER scores between the two types of stents [SMD: -0.17 (-0.78, 0.45); $P = 0.008$, $I^2: 74\%$] (Figure 2).

Secondary outcomes

Five studies reported data on stent migration and bleeding related to stent insertion (Figure 3). Out of five studies which reported stent migration, three studies showed stent migration is more likely with SS. However, pooled results showed there was no significant statistical difference between SS and ARS in terms of risk of stent migration (OR = 1.37, 95%CI: 0.66-2.83) (Figure 3).

Five studies reported stent related bleeding but one of them did not provide adequate statistical data to calculate OR. Pooled results from four studies showed no statistical difference in bleeding risk using either SS or ARS (OR = 1.43, 95%CI: 0.40-5.13) (Figure 2).

Four studies reported data on stent occlusion. SS had more cases of stent occlusion; however, pooled data suggested no statistical difference between SS and ARS (OR = 1.66, 95%CI: 0.60-4.60) (Figure 3).

Quality assessment and publication bias

Quality assessment of each study according to the guideline by QUADAS-2 is shown in supplementary Figure 1. Concern for biases regarding patient selection,

Table 1 Patient characteristics

	Anti-reflux stent	Standard stent
Patients, total (<i>n</i>)	192	203
Female (<i>n</i>)	47	49
Male (<i>n</i>)	118	131
mean age (yr)	70	70.24
Histology (<i>n</i>)	SCC = 39; Adenocarcinoma = 76; Undifferentiated = 1	SCC = 51; Adenocarcinoma = 113; Undifferentiated = 13

SCC: Squamous cell carcinoma.

randomization, index test, reference standard was overall low except for flow of patients through the study and timing of index tests, and reference standard. By utilizing Revman Manager funnel, plots were created for outcome gastroesophageal reflux disease (Figure 4A) and outcome dysphagia (Figure 4B). No significant publication bias was found among studies evaluated.

DISCUSSION

In this systematic meta-analysis, we compared conventional standard stent with anti-reflux stents in terms of their efficacy and safety. Both types of stents were used as palliative modality to treat dysphagia in unresectable malignant esophageal and gastroesophageal junction cancer. We showed that both types of stents were equivalent in terms of primary outcome including improving GER symptoms, and reducing dysphagia score. The results are similar to the review done by Sgourakis *et al*^[17] in 2010. Sgourakis's study compared multiple different types of SEMS with locoregional therapy whereas our study compared SS and ARS only.

Our study showed that there was no difference between the SS and ARS considering secondary endpoints that included stent migration, bleeding related to stent placement, and occlusion of stent from tumor in growth. In a meta-analysis done by Yang *et al*^[18] comparing bare metal esophageal stents with fully covered self-expanding metal stents, stent occlusion occurred more in bare metal stents, whereas, stent migration occurred more in the covered stents. In our study, all stents were covered stents, and there was no difference in stent migration or stent occlusion. Two previous studies have shown that stainless steel stents tend to migrate more than nitinol stents^[19,20]. In our study, four studies used nitinol stent^[6,13,14,16] and one study by Wenger *et al*^[15] used combination of nitinol and stainless-steel stents. We found no difference in stent migration with regards to the stent material used. Although more studies showed increased risk of bleeding, stent occlusion, and stent migration with SS; pooled data did not reach statistical significance^[6,10,12,13,15].

We anticipated anti-reflux stent to have favorable outcome in improving GER symptom, as it is marketed now, but this was not seen in this study. Even though a favorable trend was seen towards ARS^[11,12,15] in improving gastroesophageal reflux and dysphagia score, pooled statistical analysis did not show significant difference between those two stents. Three out of four studies that were included to calculate SMD for improvement of GER symptoms favored ARS, which could be attributed to the variation in the length of stents. Improvement in GER symptoms was seen with 140 mm stent compared to 70 mm stent^[11,12,15]. A study by Coron *et al*^[10] showed improvement in GER symptoms in ARS group, which included 20 patients, when proton pump inhibitors was used after the stent placement, however due to lack of sufficient data, this study was not included in the primary outcome.

Treatment related deaths are not included in this study, however, one previous network meta-analysis showed that treatment related deaths were reported more in the open stent group compared to anti-reflux stent group^[21]. In this network meta-analysis, open stent and ultraflex stent omeprazole was compared with anti-reflux stent. The relative risk (RR) for treatment related deaths were higher in open stent and ultraflex plus omeprazole (RR = 3.00, 95%CI: 0.13-70.23) and (RR = 2.55, 95%CI: 0.11-59.49), respectively^[21].

The major limitation of this meta-analysis is, it's underpowered. We included studies with reproducible data and studies which explained our research question. The power could have been improved by including the foreign language studies. Additionally, not all studies provided data on each primary or secondary outcome. Therefore, all eight studies could not be included for both primary and secondary

Table 2 Study characteristics

Study	Country	Design	Brand of stents	n (ARS, SS)	Age (ARS, SS)	Male / Female; ARS / SS	Pre-Dysphagia score (ARS / SS)	Follow-up (mo)	Use of PPI (ARS / SS)	Preemptive dilation of stent (ARS/ SS)
Coron <i>et al</i> ^[10] , 2016	France	RCT, multicenter	Dostent	20	68.9	16/4	2.75 (0-4)	6	NO	YES
			Choostent	18	74	15/3	2.65 (0-4)	6	YES	YES
Kaduthodil <i>et al</i> ^[11] , 2011	United Kingdom	RCT, single center	NR	27	NR	NR	NR	NR	NR	NR
			NR	23	NR	NR	NR	NR	NR	NR
Blomberg <i>et al</i> ^[12] , 2010	Sweden	RCT, multicenter	Z stent- Dua- valve	28	74	21/7	62 (0-100)	3	NR	YES
			Z-stent	37	74	23/14	61 (0-100)	3	NR	YES
Sabharwal <i>et al</i> ^[13] , 2008	United Kingdom	RCT, single center	FerX- Ella - valve /	24	71.3	15/7	2.73 (0-5)	3	NO	NR
			Ultraflex	26	66.3	21/5	2.54 (0-5)	3	YES	NR
Power <i>et al</i> ^[14] , 2007	Ireland	RCT, single center	Hanaro stent- valve	24	68.4	14/10	NR	2	NR	NR
			Ultraflex	25	73.9	17/8	NR	2	NR	NR
Wenger <i>et al</i> ^[15] , 2006	Sweden	RCT, multicenter	Z stent-Dua	19	75	13/6	63 ± 28	6	NR	NR
			Z-stent	25	73	13/9	56 ± 31	6	NR	NR
Shim <i>et al</i> ^[16] , 2005	South Korea	RCT, single center	Dostent	12	65.3	12/0	2.83 ± 0.85	1	NO	YES
			Covered metal	12	62.7	11/1	3.25 ± 0.4	1	NO	YES
Homs <i>et al</i> ^[6] , 2004	the Netherlands	RCT, single center	FerX-Ella -valve /	15	69	12/3	3 (0-5)	6	NR	NR
			Fer x -Ella	15	69	12/3	3 (0-5)		NR	NR

RCT: Randomized controlled trials; SS: Standard stent; ARS: Anti-reflux esophageal stent; PPT: Proton pump inhibitors.

outcome. Hence, there is a need for larger randomized controlled studies. Although there was significant heterogeneity in reporting primary and secondary end points across studies, all studies passed the heterogeneity test.

In conclusion, both traditional standard open stent and anti-reflux stent with valve are comparable in terms of their efficacy and safety for the palliative treatment of obstructive esophageal and gastroesophageal junction malignancies. Authors believe both SS and ARS could be used in clinical practice as per the availability of clinical expertise, cost, and patient preference with informed decision.

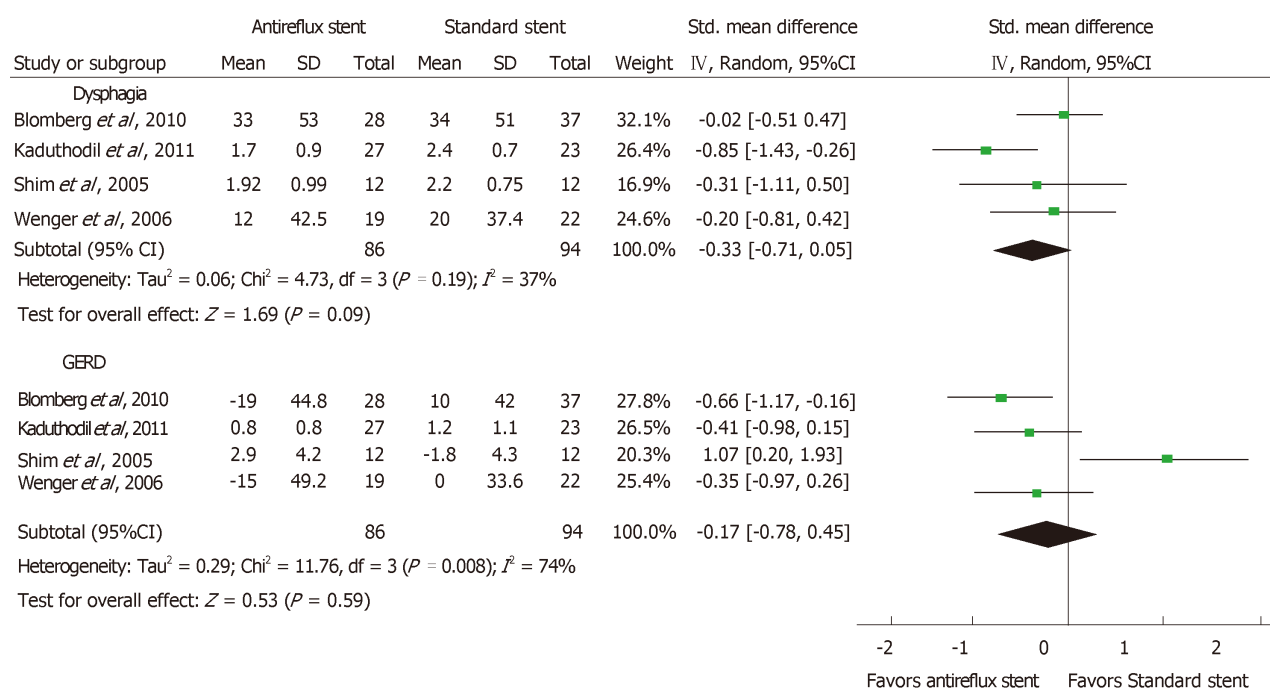


Figure 2 Forest plot comparing standardized mean difference in dysphagia and gastroesophageal reflux disease between anti-reflux stent and standard stent. GERD: Gastroesophageal reflux disease.

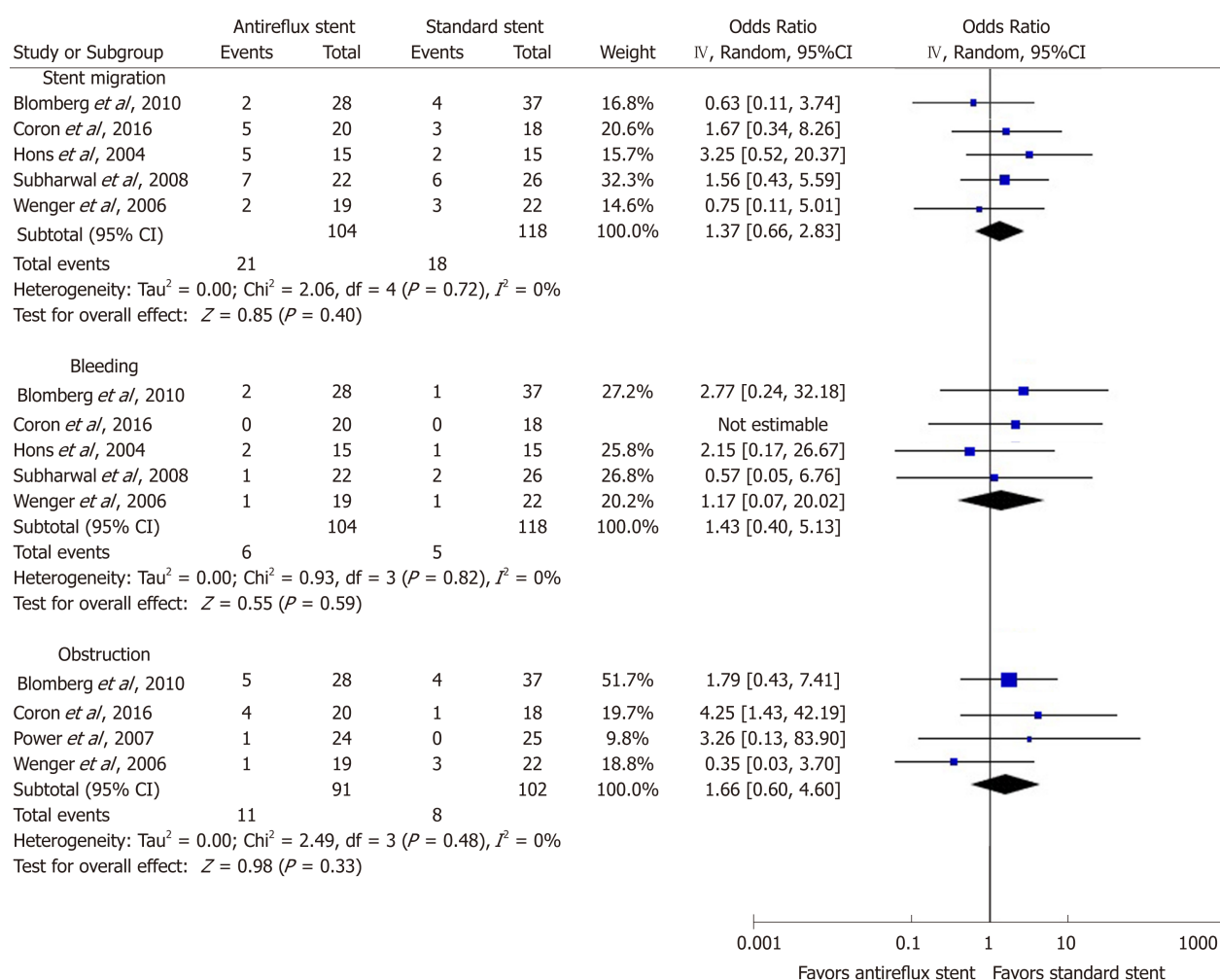


Figure 3 Forest plot comparing complications of stent migration, bleeding and obstruction between anti-reflux and standard stent.

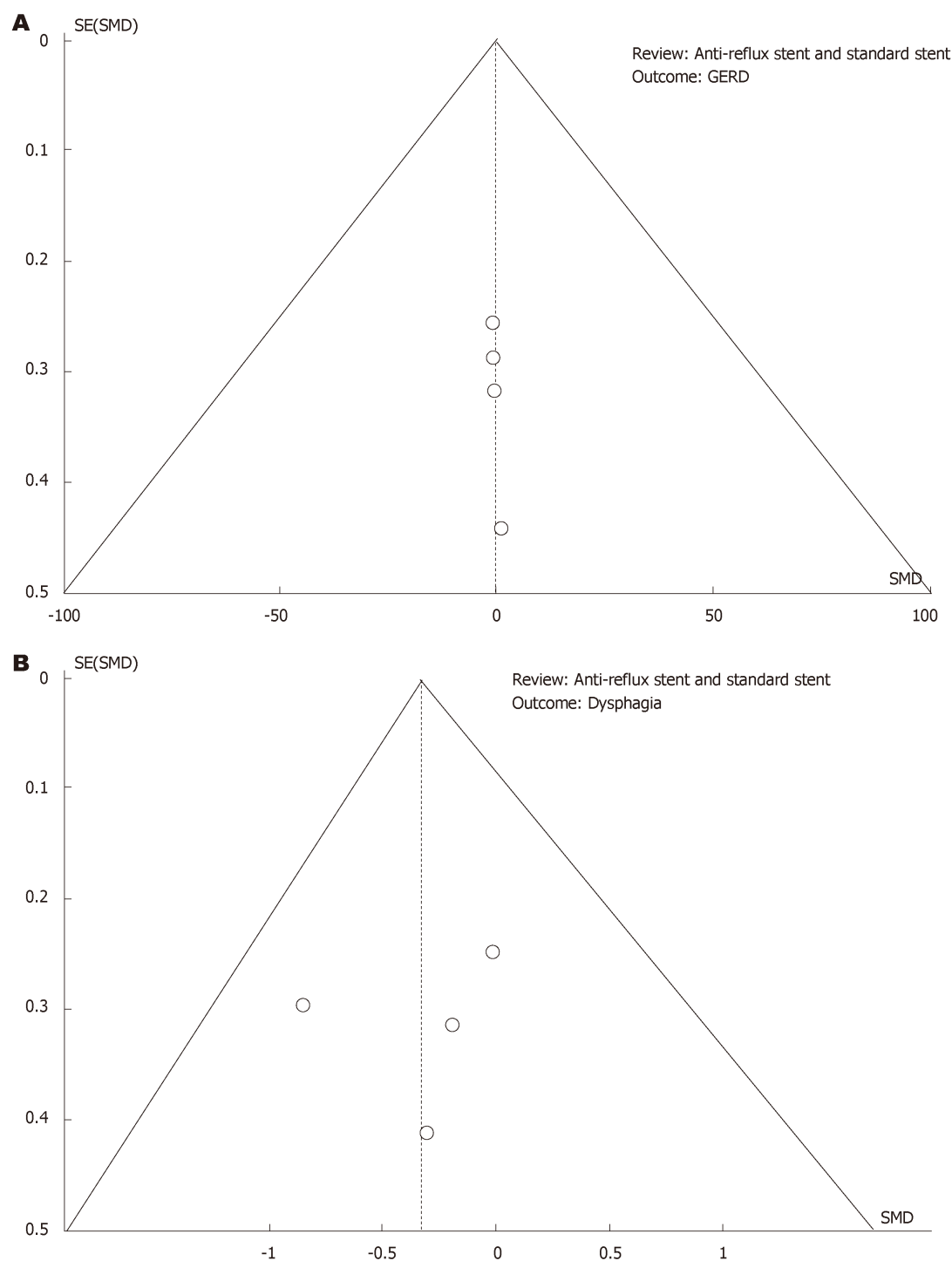


Figure 4 Funnel plot for publication bias. A: Outcome gastroesophageal reflux disease; B: Outcome dysphagia. SMD: Standard mean difference; GERD: Gastroesophageal reflux disease.

ARTICLE HIGHLIGHTS

Research background

Self-expanding metal stents are one of the palliative treatment modalities to relieve dysphagia and to improve quality of life in patients with unresectable esophageal cancer involving the gastroesophageal junction and gastric cardia. Although the quality of life improves after stent placement, it is severely limited by gastroesophageal reflux disease (GERD) especially when stent is placed across the gastroesophageal junction. To improve GERD, anti-reflux stents with valve have been designed and studied in many randomized controlled trials. However, the results from these studies are mixed. The main purpose of this study is to identify how effective is anti-reflux stent in improving gastroesophageal reflux and dysphagia when compared to standard stent.

Research motivation

Gastroesophageal reflux is one of the most common adverse outcomes after placement of esophageal stent in esophageal cancer involving the gastroesophageal junction and gastric cardia. Effective anti-reflux stents need to be designed to overcome the problem of gastroesophageal reflux.

Research objectives

The main objective of this meta-analysis was to assess the efficacy of anti-reflux stents in improving GERD. During data gathering and analysis, authors realized that many randomized controlled trials which compared anti reflux stent and standard stents were under powered. So, more randomized controlled trials with larger number of patients are needed.

Research methods

Literature search was done using electronic database to gather data for this meta-analysis where we analyzed the efficacy and safety of anti-reflux stent and standard stent. We collected data focusing on the indication for stents, material and type of stent used, demographics of patient, endoscopic technique, type of sedation used. Gastroesophageal reflux and dysphagia improvement score were our primary outcomes. Bleeding risk, stent migration risk, and stent occlusion were our secondary outcome.

Research results

There was no difference in terms of GERD score and dysphagia score between anti reflux stent and standard stent. The complications such as bleeding, stent migration, and stent occlusion were also similar between anti reflux and standard stent. Our study showed a favorable trend for anti-reflux stent to improve GERD score, though it was not statistically significant. We believe that further randomized controlled trials with larger number of patients might be helpful to ascertain if anti reflux stent indeed improves GERD score compared to standard stent.

Research conclusions

Anti-reflux stent is not superior to standard stent in preventing GERD related to stent placement. The risk of adverse outcomes of bleeding related to stent, stent migration and stent occlusion was also comparable between anti reflux and standard stent. Both anti reflux stent and standard stent are similar in efficacy and safety. Either stent could be selected as a palliative treatment modality to relieve dysphagia in unresectable esophageal cancer. There is no difference between anti reflux stent and standard stent to prevent GERD due to stent placement across the gastroesophageal junction. Few randomized controlled trials at present suggest that anti reflux stent improve GERD related to stent placement across the gastroesophageal junction. The result from this meta-analysis did not show significant statistical difference between anti reflux stent and standard stent in terms of improving GERD score. Clinicians can choose either stent to treat dysphagia related to esophageal cancer.

Research perspectives

This meta-analysis showed that there are no difference in terms of safety and efficacy between anti reflux stent and standard stent. We should focus towards betterment of safety and efficacy of newer esophageal stents. More randomized clinical trials comparing the standard and anti-reflux stents are needed to further characterize their safety and efficacy.

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