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Original Article

Antireflux covered metal stent for nonresectable distal malignant biliary obstruction: Multicenter randomized controlled trial

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Background and Aim: An antireflux metal stent (ARMS) for nonresectable distal malignant biliary obstruction (MBO) may prevent recurrent biliary obstruction (RBO) as a result of duodenobiliary reflux and prolong time to RBO (TRBO). Superiority of ARMS over conventional covered self-expandable metal stents (SEMS) has not been fully examined.

Methods: We conducted a multicenter randomized controlled trial to examine whether TRBO of an ARMS with a funnel-shaped valve was longer than that of a covered SEMS in SEMS-naïve patients. We enrolled 104 patients (52 patients per arm) at 11 hospitals in Japan. Secondary outcomes included causes of RBO, adverse events, and patient survival.

Results: TRBO did not differ significantly between the ARMS and covered SEMS groups (median, 251 *vs* 351 days, respectively; $P = 0.11$). RBO as a result of biliary sludge or food impaction was observed in 13% and 9.8% of patients who received an ARMS and covered SEMS, respectively ($P = 0.83$). ARMS was associated with a higher rate of stent migration compared with the covered SEMS (31% *vs* 12%, $P = 0.038$). Overall rates of adverse events were 20% and 18% in the ARMS and covered SEMS groups, respectively ($P = 0.97$). No significant between-group difference in patient survival was observed ($P = 0.26$).

Conclusions: The current ARMS was not associated with longer TRBO compared with the covered SEMS. Modifications including addition of an anti-migration system are required to use the current ARMS as first-line palliative treatment of distal MBO (UMIN-CTR clinical trial registration number: UMIN000014784).

Key words: common bile duct, endoscopic retrograde cholangiopancreatography, extrahepatic cholestasis, pancreatic neoplasm, stent

INTRODUCTION

ENDOSCOPIC PLACEMENT OF a self-expandable metal stent (SEMS) has been first-line palliative treatment of nonresectable distal malignant biliary obstruction (MBO) because of longer duration of patency compared to plastic stents.[1–5] Covered SEMS have emerged as an alternative to uncovered SEMS with the expectation of further prolonged patency through preventing tumor tissue and reactive epithelial hyperplasia from invading through

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the mesh wall.[6–11] Furthermore, improvements in conformability of SEMS in the bile duct have reduced the risk of recurrent biliary obstruction (RBO) as a result of stent migration.[10] In this setting, biliary sludge and food impaction serve as major causes of covered SEMS occlusion.[12] Reflux of duodenal contents into the biliary system (i.e. duodenobiliary reflux), as well as formation of bacterial biofilms,[13] contributes to these phenomena,[14–16] because a SEMS is positioned across the ampulla in most cases with distal MBO, resulting in loss of sphincter function.

An antireflux metal stent (ARMS) with a valve against duodenobiliary reflux was developed to mitigate the risk of SEMS dysfunction as a result of duodenobiliary reflux.[17–22] Despite different designs of antireflux valves in prior studies,[23] ARMS have generally been associated with lower risks of stent occlusion and non-occlusion cholangitis compared with conventional SEMS. We have evaluated the effectiveness of an ARMS with a funnel-shaped antireflux valve[24] in patients who underwent covered SEMS occlusion as a result of duodenobiliary reflux and, thus, were considered to be at higher risk of recurrent occlusion after a reintervention.[25–27] Our previous pilot study showed the feasibility and safety of the new ARMS as a first-line SEMS for nonresectable distal MBO.[28]

Therefore, we conducted a randomized controlled trial comparing stent patency times between ARMS and a conventional covered SEMS.

METHODS

Study design

THIS IS A randomized controlled trial conducted at 11 referral centers in Japan. The aim of this study was to evaluate the superiority of ARMS over a conventional covered SEMS for SEMS-naïve patients with nonresectable distal MBO. To evaluate the effect of the antireflux valve on stent patency, we used a covered SEMS harboring the same body design as a control. Primary endpoint was time to RBO (TRBO). Secondary endpoints included causes of RBO, adverse events, and patient survival. This study was approved by the institutional review board of each institution and was conducted in accordance with the Helsinki Declaration (clinical trial registration number: UMIN000014784). Written informed consent was obtained from all patients at enrolment.

Study population

Between September 2014 and June 2016, we enrolled patients who were diagnosed with obstructive jaundice as a result of nonresectable distal MBO and did not have a history of biliary SEMS placement. Distal MBO was defined as a malignant biliary stricture ≥2 cm from the communication of the bilateral hepatic ducts. Patients were randomly allocated in a 1:1 ratio to receive an ARMS or a conventional covered SEMS using centralized web-based randomization stratified by institution. Patients were excluded: (i) if hilar biliary stricture or duodenal obstruction distal to the ampulla was concomitantly present; (ii) if the gastrointestinal anatomy had been surgically altered (e.g. Billroth-II and Roux-en-Y reconstructions, gastrojejunostomy); or (iii) if the World Health Organization performance status was four. The patients were followed every 2–4 weeks on an outpatient basis and through telephone interview by study physicians until death or until 31 January 2017, whichever came first. When adverse events were suspected based on clinical symptoms (fever, abdominal pain, and/or jaundice) and blood tests, abdominal radiograph, ultrasound, and/or computed tomography were carried out. Patients were hospitalized when further examination and management were indicated.

Antireflux metal stent and conventional covered self-expandable metal stent

The ARMS used in this study was a fully covered SEMS with an antireflux valve attached to the duodenal end (Taewoong Medical Inc., Gimpo, Korea).[24,28] We used a fully covered SEMS with the same body structure (Niti-S COMVI biliary stent; Taewoong Medical Inc.)[29,30] as a control. The stent body was made with an expanded polytetrafluoroethylene (PTFE) membrane sandwiched by two nitinol mesh layers. The ARMS had a 7-mm-long funnel-shaped valve made of expanded PTFE, including four 5-mm-long longitudinal nitinol wires to maintain its shape (Fig. 1). This valve was designed to shrink in the duodenal lumen to prevent duodenobiliary reflux while ensuring antegrade bile flow. Diameter of the stent was 10 mm, and the length (60 and 80 mm available for the ARMS; and 60, 70, and 80 mm available for the covered SEMS) was determined according to the location and length of the biliary stricture. Both SEMS were commercially available in Japan during the study period.

Self-expandable metal stents were deployed during endoscopic retrograde cholangiopancreatography (ERCP) in the usual method.[31] Cholangiography along with intraductal ultrasonography was carried out to examine biliary stricture and confirm the absence of accessary bile ducts. Sphincterotomy was carried out at the discretion of the endoscopist.[32] Stents were placed with the distal end of the metal part being 5–10 mm in the duodenum.

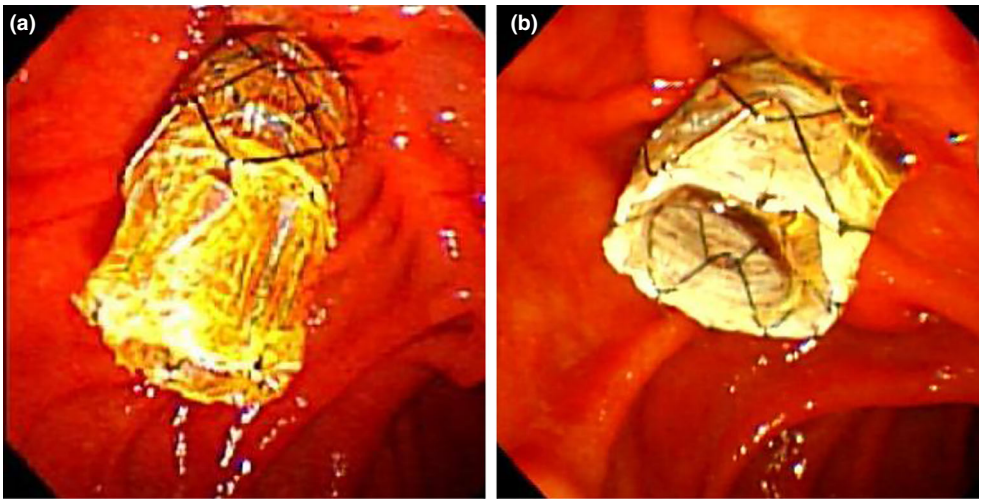

Figure 1 Endoscopic images of an antireflux metal stent (ARMS) and a conventional covered self-expandable metal stent (SEMS). (a) ARMS. (b) Covered SEMS.

Study endpoints

Study endpoints were defined according to our consensus, which was later published as the TOKYO criteria.[33,34] TRBO was defined as the period from SEMS placement to RBO. RBO was defined as a composite endpoint of either occlusion or migration of a stent, whichever came first. Stent occlusion was considered to be present if elevated liver enzymes compared with baseline values were observed along with biliary dilation on imaging studies or endoscopic findings that suggested stent occlusion. Stent migration was diagnosed when a completely or partially migrated stent was observed at the time of a reintervention for RBO. Patients who were lost to follow up or died without RBO were treated as censored cases at the time of last follow up or death, respectively. Adverse events were graded according to the American Society of Gastrointestinal Endoscopy (ASGE) lexicon guidelines.[35]

Statistical analyses

Primary hypothesis testing was assessment of the superiority of ARMS over conventional covered SEMS in terms of TRBO based on Kaplan–Meier analysis. TRBO cannot be evaluated for cases where biliary drainage is not feasible, and characteristics of RBO and adverse events are substantially different for cases where endoscopic ultrasound-guided, percutaneous, or surgical biliary drainage is carried out; therefore, we analyzed per-protocol populations.[34] When we assumed a 20% difference in rates of non-recurrence of biliary obstruction at 6 months of SEMS placement (65% *vs* 45% for ARMS and covered SEMS, respectively) and planned 36 months for patient accrual and 12 months for follow up, 98 patients were required with a two-sided α level of 0.05 and a power of 0.80. Taking dropout into account, we planned a sample size of 104 patients (52 patients per arm).

Categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate, and continuous variables were compared using the Wilcoxon rank-sum test. TRBO and survival time were estimated using the Kaplan–Meier product-limit method. Survival time was assessed on an intention-to-treat basis.[34] Kaplan–Meier curves were compared using the log–rank test. Cox proportional hazards regression model was used to estimate a hazard ratio for RBO comparing the ARMS group to the covered SEMS group. Assumption of proportionality of hazards was verified by assessing the Schoenfeld residual plot ($P = 0.48$).

A two-sided P-value <0.05 was considered statistically significant. All analyses were carried out using R software version 3.3.1 and the Survival package.

RESULTS

WE ENROLLED A total of 104 patients (52 patients for each arm) during 1.8 years (Table 1 and Fig. 2). Pancreatic cancer was the predominant cause of MBO. Compared with patients who received a covered SEMS, patients who received an ARMS were more likely to be younger and have higher levels of total bilirubin.

These findings were also observed in per-protocol populations (Table S1). In the per-protocol populations, the rate of patients receiving chemotherapy was higher in the ARMS group than in the covered SEMS group. After excluding patients with unsuccessful SEMS placement, we analyzed 45 and 51 patients in the ARMS and covered SEMS groups, respectively (Fig. 2). No patients were lost to follow up during the study period.

SEMS was deployed successfully in 45 (87%) and 51 (98%) patients enrolled in the ARMS and covered SEMS groups, respectively ($P = 0.060$). Sphincterectomy was carried out in 34 (76%) and 41 (80%) patients who received ARMS and covered SEMS, respectively. Lengths of stents were 60 and 80 mm for 17 (38%) and 28 (62%) patients, respectively, with ARMS placement, and 60, 70, and 80 mm for 13 (25%), five (9.8%), and 33 (65%) patients, respectively, with covered SEMS placement.

Table 1 Baseline characteristics of patients who received an antireflux metal stent or conventional covered SEMS for nonresectable distal malignant biliary obstruction (intention-to-treat populations)

Characteristic[†]	Type of SEMS		*P*-value
	Antireflux ($n = 52$)	Covered ($n = 52$)	
Gender			
Male	30 (58%)	30 (58%)	0.99
Female	22 (42%)	22 (42%)	
Age, years	72.5 (66.8–81.5)	76.5 (69.8–82.0)	<0.001
Performance status[‡]			
1	11 (21%)	17 (33%)	0.41
2	27 (52%)	23 (44%)	
3	14 (27%)	12 (23%)	
Primary cancer			
Pancreatic cancer	40 (77%)	37 (71%)	0.62
Bile duct cancer	3 (5.8%)	7 (13%)	
Gallbladder cancer	0	1 (1.9%)	
Lymph node metastasis	6 (12%)	5 (9.6%)	
Other	3 (5.8%)	2 (3.8%)	
Liver metastasis	11 (21%)	10 (19%)	0.99
Duodenal tumor invasion	7 (13%)	10 (19%)	0.60
Ascites	5 (9.6%)	9 (17%)	0.39
Total bilirubin on admission, mg/dL	5.6 (1.8–11.4)	5.0 (2.4–9.6)	<0.001
Prior drainage[§]	31 (60%)	36 (69%)	0.41
Chemotherapy after SEMS placement	36 (69%)	26 (50%)	0.072

[†]Data are expressed as number of patients (percentage) or median (interquartile range). Percentage indicates the proportion of patients with a specific characteristic in each group.
[‡]Determined according to the World Health Organization classification.
[§]Includes a plastic stent and a nasobiliary catheter.
SEMS, self-expandable metal stent.

ARMS was not associated with longer TRBO compared with covered SEMS ($P = 0.11$, Fig. 3). Median TRBO was 251 days (interquartile range [IQR], 127–450 days) in the ARMS group and 351 days (IQR, 187 days to not available) in the covered SEMS group. Rates of non-RBO at 3, 6, and 12 months of stent placement were 90%, 67%, and 25%, respectively, for ARMS; and 87%, 76%, and 47%, respectively, for covered SEMS. Hazard ratio for RBO comparing ARMS to covered SEMS was 1.71 (95% confidence interval, 0.88–3.32). Overall rate of RBO did not differ by stent type with 47% in the ARMS group and 29% in the covered SEMS group (Table 2). RBO as a result of biliary sludge or food impaction was observed in 13% and 9.8% of patients who received ARMS and covered SEMS, respectively ($P = 0.83$). At the time of reinterventions for occluded ARMS, we often observed antireflux valves that were collapsed and accompanied by biliary sludge (Fig. 4). ARMS was associated with a higher rate of stent migration compared with covered SEMS (31% *vs* 12%, respectively; $P = 0.038$). Among 14 patients who underwent ARMS migration, the stent migrated distally in 10 patients (71%) and proximally in four patients (29%). Among patients receiving chemotherapy (33 and 26 patients in the ARMS and covered SEMS groups, respectively), rate of stent migration was higher in the ARMS group than in the covered SEMS group (39% *vs* 12%, $P = 0.036$). Among patients receiving no chemotherapy (12 and 25 patients in the ARMS and covered SEMS groups, respectively), rates of stent migration did not differ between the groups (8.3% *vs* 12%, $P = 0.99$), but statistical power was limited. In 19 out of 21 patients with occlusion or migration of ARMS, reinterventions were carried out endoscopically with a technical success rate of 100%. Procedures for reinterventions included covered SEMS placement in 13 patients, plastic stent placement in three patients, endoscopic ultrasound-guided hepaticogastrostomy in one patient, and no additional stent placement in two patients (as a result of stricture resolution). The remaining two patients did not receive a reintervention because of the absence of symptoms. The dysfunctional ARMS were successfully removed in all nine cases with attempted removal. During a median follow-up time of 231 days after SEMS placement, 58 (56%) patients died. Median survival times were 429 days

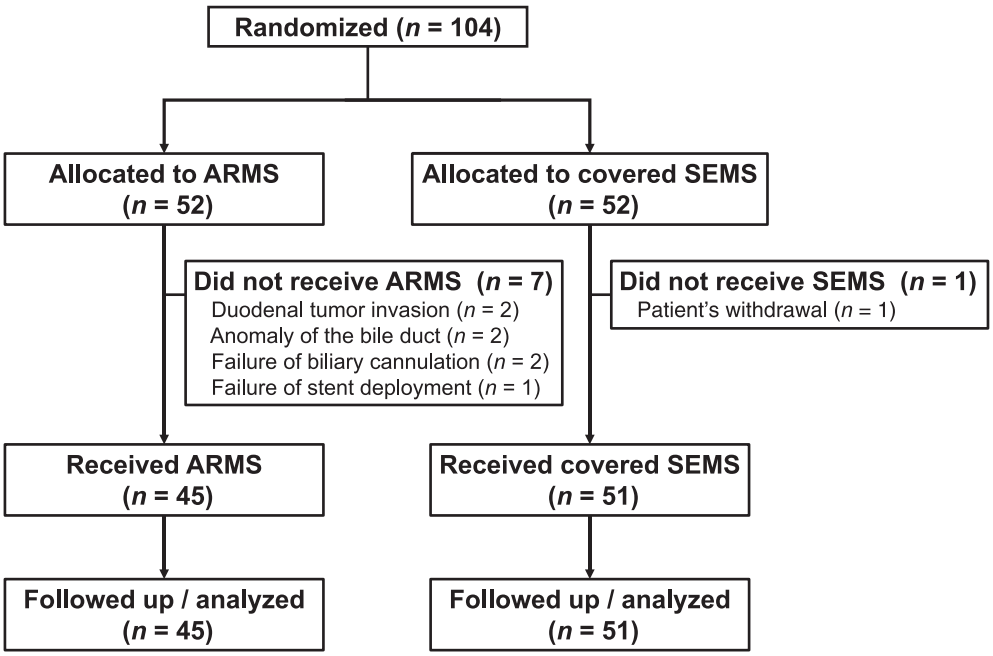

Figure 2 Flowchart of randomization and follow up of the patients. ARMS, antireflux metal stent; SEMS, self-expandable metal stent.

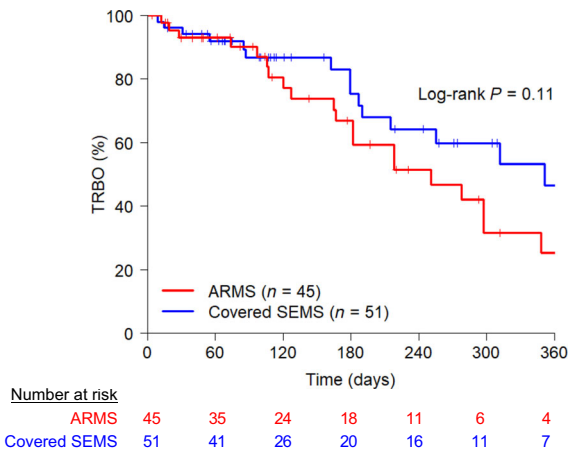

Figure 3 Kaplan–Meier curves of time to recurrent biliary obstruction of ARMS and conventional covered SEMS. ARMS, antireflux metal stent; SEMS, self-expandable metal stent.

Table 2 Recurrent biliary obstruction (RBO) among patients who received an antireflux metal stent or conventional covered SEMS

Cause of RBO†	Type of SEMS		*P*-value
	Antireflux (*n* = 45)	Covered (*n* = 51)	
Occlusion	7 (16%)	9 (18%)	0.99
Biliary sludge	6 (13%)	4 (7.8%)	
Food	0	1 (2.0%)	
Tumor ingrowth	1 (2.2%)	0	
Tumor overgrowth	0	2 (3.9%)	
Others	0	2 (3.9%)	
Migration	14 (31%)	6 (12%)	0.038
Total	21 (47%)	15 (29%)	0.13

†Percentage indicates the proportion of patients with a specific cause of RBO in each group.
SEMS, self-expandable metal stent.

(IQR, 143–621 days) in the ARMS group and 265 days (IQR, 109–549 days) in the covered SEMS group (P = 0.26).

Overall rates of adverse events after stent placement were 20% and 18% in the ARMS and covered SEMS groups, respectively (P = 0.97, Table 3, detailed in Table S2). The rate or severity of acute pancreatitis did not differ by stent type, and all patients with pancreatitis were managed conservatively.

DISCUSSION

IN THIS MULTICENTER randomized clinical trial, ARMS with a funnel-type valve was not associated with

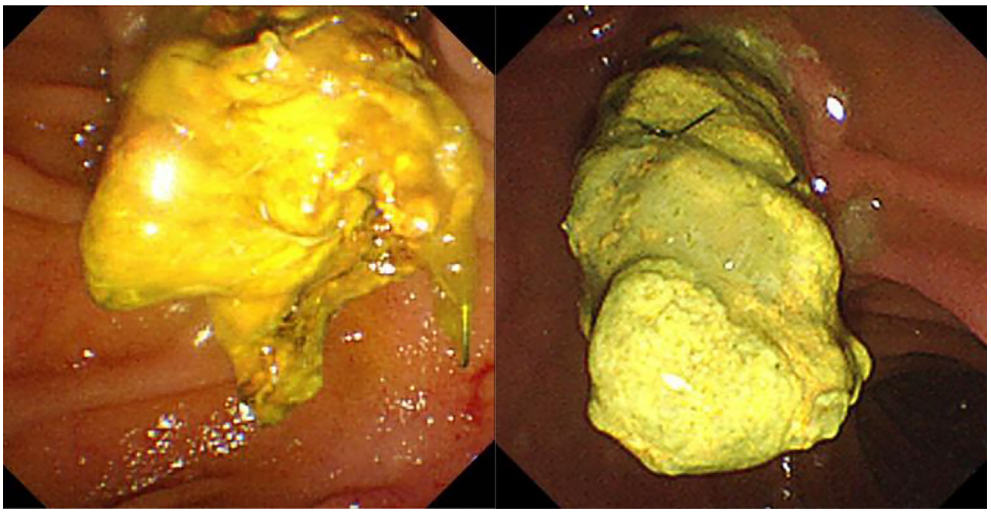

Figure 4 Endoscopic images of occluded antireflux metal stents with a collapsed valve.

Table 3 Stent-related adverse events among patients who received an antireflux metal stent or conventional covered SEMS

Adverse event[†]	Type of SEMS		*P*-value
	Antireflux (*n* = 45)	Covered (*n* = 51)	
Pancreatitis	2 (4.4%)	5 (9.8%)	0.44
Cholecystitis	4 (8.9%)	3 (5.9%)	0.70
Liver abscess	2 (4.4%)	1 (2.0%)	0.60
Hemobilia	0	1 (2.0%)	0.99
Abscess around the bile duct	1 (2.2%)	0	0.47
Total[‡]	9 (20%)	9 (18%)	0.97

[†]Percentage indicates the proportion of patients with a specific adverse event in each group.
[‡]One patient in the covered SEMS group underwent both pancreatitis and cholecystitis.
SEMS, self-expandable metal stent.

longer TRBO compared to conventional covered SEMS in patients with nonresectable distal MBO. We found no evidence of prevention of RBO by the antireflux valve and observed a higher migration rate of the ARMS compared with the covered SEMS. The current study highlights the necessity for improvements in the antireflux valve and development of an effective antimigration system to introduce this ARMS as a first-line covered SEMS for nonresectable distal MBO.

Accumulating evidence suggests that ARMS, compared with covered SEMS, may provide longer TRBO through prevention of duodenobiliary reflux after SEMS placement.[20,22] A randomized clinical trial of 112 patients showed that an ARMS with a nipple-shaped valve was associated with not only a lower rate of cholangitis but also significantly longer patency time compared with a conventional uncovered SEMS (13 *vs* 10 months).[20] However, this study was limited by the use of uncovered SEMS as a comparative group because tumor ingrowth was reported to be a predominant cause of RBO in this group. In a more recent randomized trial of 77 patients, ARMS was first compared with a covered SEMS in terms of patency duration.[22] ARMS with a windsock-shaped valve provided significantly longer patency time compared with the covered SEMS (14 *vs* 7 months). Using a dedicated delivery system, ARMS with a 20-mm-long antireflux valve were successfully deployed. Notably, the researchers conducted a proof-of-concept evaluation using barium meal examination and demonstrated a significantly lower rate of duodenobiliary reflux in the ARMS group. Given considerably heterogeneous designs of ARMS and different commercial availability of ARMS across countries,[23] a well-powered prospective study is required to evaluate a specific type of ARMS.

Our study failed to show the superiority of the current ARMS over the covered SEMS in terms of TRBO. The antireflux valve did not appear to be durable enough to prevent duodenobiliary reflux during a long follow-up period. A retrospective study involving 59 patients with nonresectable distal MBO reported a null association of SEMS types (the current type of ARMS *vs* Niti-S SUPREMO [a fully covered SEMS; Taewoong Medical Inc.]) with TRBO,[36] which was consistent with our findings.

The ARMS that were shown to provide longer stent patency compared with conventional SEMS were characterized by a closed valve structure or quite a long antireflux valve.[20,22] Compared with the current ARMS, the ARMS with these features might contribute to a higher likelihood of successful prevention of duodenobiliary reflux. In contrast, stent migration was a major cause of RBO associated with the current ARMS. Increased outflow pressure of bile at the antireflux valve might have led to an elevated risk of stent migration. However, the current ARMS migrated proximally in some cases; therefore, we speculate that attachment of the antireflux valve at the duodenal end of the SEMS might prevent full expansion of this end. Chemotherapy may increase the risk of SEMS migration through reducing tumor burden.[37] Between-group difference in migration rates was observed only in patients receiving chemotherapy, suggesting the potential effect of chemotherapy on ARMS migration. Given the limited statistical power in these subgroup analyses, further investigation is warranted. Antimigration properties (e.g. flared ends, low axial force[38–40]), which have been introduced to covered SEMS, may be useful to overcome this disadvantage. Despite the disappointing results of the current ARMS as a first-line SEMS for nonresectable MBO, further investigation is warranted to evaluate this ARMS for a specific subset of patients at higher risk of RBO as a result of duodenobiliary reflux (e.g. patients who have tumor invasion to the duodenum and those who experience early SEMS dysfunction as a result of reflux).[41–43]

The current study has notable strengths including a randomized controlled prospective study design. The endoscopic procedures were carried out by a number of endoscopists with various expertise at more than 10 hospitals, which might ensure the generalizability of our findings. As opposed to previous studies that have compared ARMS and SEMS with a different body design, in the present study, we unified the body designs of the ARMS and covered SEMS. Therefore, we successfully evaluated the impact of the current antireflux valve on prevention of duodenobiliary reflux in the context of stent patency. Almost complete follow up of patients allowed us to evaluate long-term adverse events.

We also acknowledge several limitations in our study. Our study lacked preclinical and clinical functional studies for evaluation of the effectiveness of the antireflux valve.[19,22,23] As a result of the nature of the procedures, the physicians involved in the procedures and collection of follow-up data were not blinded to the types of SEMS.

In conclusion, the current multicenter randomized controlled trial indicates that attachment of a funnel-shaped valve might not prolong TRBO of covered SEMS for nonresectable distal MBO. Further modifications of the current ARMS, particularly development of an antimigration system, are required to justify use of this ARMS as a first-line palliative therapeutic modality for nonresectable distal MBO.

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CONFLICTS OF INTEREST

AUTHORS DECLARE NO conflicts of interest for this article.

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SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found in the online version of this article at the publisher's web site.

Table S1 Baseline characteristics of patients who received an antireflux metal stent or conventional covered self-expandable metal stent (SEMS) for nonresectable distal malignant biliary obstruction (per-protocol populations)

Table S2 Severities and times to occurrence of stent-related adverse events among patients who received an antireflux metal stent or conventional covered self-expandable metal stent (SEMS)