Double Stenting for Malignant Biliary and Duodenal Obstruction: A Systematic Review and Meta-Analysis

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INTRODUCTION: Data about the efficacy of palliative double stenting for malignant duodenal and biliary obstruction are limited.

- METHODS: A systematic literature search was performed to assess the feasibility and optimal method of double stenting for malignant duodenobiliary obstruction compared with surgical double bypass in terms of technical and clinical success, adverse events, reinterventions, and survival. Event rates with 95% confidence intervals were calculated.
- RESULTS:Seventy-two retrospective and 8 prospective studies published until July 2018 were included.
Technical and clinical success rates of double stenting were 97% (95%–99%) and 92% (89%–95%),
respectively. Clinical success of endoscopic biliary stenting was higher than that of surgery (97%
[94%–99%] vs 86% [78%–92%]). Double stenting was associated with less adverse events (13%
[8%–19%] vs 28% [19%–38%]) but more frequent need for reintervention (21% [16%–27%] vs 10%
[4%–19%]) than double bypass. No significant difference was found between technical and clinical
success and reintervention rate of endoscopic retrograde cholangiopancreatography (ERCP),
percutaneous transhepatic drainage, and endoscopic ultrasound-guided biliary drainage. ERCP was
associated with the least adverse events (3% [1%–6%]), followed by percutaneous transhepatic
drainage (10% [0%–37%]) and endoscopic ultrasound-guided biliary drainage (23% [15%–33%]).
- DISCUSSION: Substantially high technical and clinical success can be achieved with double stenting. Based on the adverse event profile, ERCP can be recommended as the first choice for biliary stenting as part of double stenting, if feasible. Prospective comparative studies with well-defined outcomes and cohorts are needed.

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A243, http://links.lww.com/CTG/A244, http://links.lww.com/CTG/A245, http://links.lww.com/CTG/A246, http://links.lww.com/CTG/A247, http://links.lww.com/CTG/A248, http://links.lww.com/CTG/A249, http://links.lww.com/CTG/A250, http://links.lww.com/CTG/A251

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INTRODUCTION

Unresectable pancreatobiliary, gastroduodenal, and metastatic malignancies can lead to concomitant biliary and duodenal obstruction. Biliary obstruction may occur in 51%–72% of advanced pancreatobiliary cancers (1,2), and duodenal obstruction rate has also risen to 38% because of oncologic advances and consequently longer patient survival (3).

Historically applied double surgical bypass (gastroenterostomy with biliodigestive anastomosis) (4) is often associated with substantial perioperative mortality and morbidity (2) because of poor performance status and frequent comorbidities (5). Because duodenal obstruction usually develops after biliary obstruction and it may occur in up to 20% of those who underwent single biliary bypass, creation of prophylactic gastroenteric anastomosis (GEA) was proposed in patients with unresectable disease confirmed at surgical exploration (2,6). Prophylactic GEA use reduces the chance for developing duodenal obstruction without impairing the short-term outcomes in pancreatic and periampullary cancer (6,7). Therefore, most studies reporting double bypass involve cases where biliary bypass was combined with prophylactic GEA (8–10).

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2

Fábián et al.

Endoscopic placement of plastic or self-expandable metal stents has offered a minimal invasive palliation alternative for patients unsuitable for surgery. Currently, transpapillary stenting via endoscopic retrograde cholangiopancreatography (ERCP) is the standard treatment of malignant biliary obstruction alone (11,12). In the case of ERCP failure (reported in approximately 10% because of altered anatomy or duodenal obstruction), biliary stenting can be performed via percutaneous transhepatic drainage (PTD) or endoscopic ultrasound-guided biliary drainage (EUS-BD) (13). Recently, the first-line use of EUS-BD in malignant biliary obstruction was also proposed based on comparable technical and clinical success and favorable adverse event and reintervention rates over ERCP (14). In 2018, a Cochrane Database Systematic Review comparing stent placement and surgical palliation for malignant gastric outlet obstruction found quicker resumption of oral intake and reduced hospital stay as benefits and higher reintervention rate as a drawback of duodenal stenting over surgery (15).

Combined biliary and duodenal stent placement (double stenting) was first reported in 1994 (16). Adequate modality for double stenting should be chosen based on duodenal obstruction type (located above [type I], at the level [type II], or below the ampulla [type III]) and sequence of biliary and duodenal stenting (biliary first, duodenal first, or simultaneous). Although technically challenging, biliary stenting can also be performed through the mesh of a duodenal stent (11). Nevertheless, the efficacy data of double stenting are limited, as usually there are few such cases in a single center (17), partly because of the sequential development of biliary and duodenal obstruction, and its place in the therapeutic algorithm is not clearly specified.

AIMS

This systematic review and meta-analysis aimed to assess efficiency and safety of double stenting in malignant duodenobiliary obstruction compared with surgical double bypass in terms of technical and clinical success, survival, adverse events, and reintervention rate and determine the optimal method for double stenting: duodenal stenting combined with ERCP vs PTD vs EUS-BD.

METHODS

Protocol and registration

This work was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 Statement (18). The study protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42018103101.

Eligibility criteria

We included studies reporting the following outcome measures in patients with concomitant malignant biliary and duodenal obstruction treated either with combined duodenal and biliary stenting (via ERCP, PTD, or EUS-BD) or with double surgical bypass (gastroenterostomy with biliodigestive anastomosis): technical and clinical success, survival, adverse events, and reintervention rates. Studies reporting about temporary stenting were excluded. Studies reporting about prophylactic GEA were included; however, technical and clinical success could only be interpreted as that of biliary bypass in such cases.

Both experimental and observational studies (either prospective or retrospective) without respect to their primary objectives were included. Conference abstracts were included to minimize publication bias. Case reports and case series reporting about less than 5 patients were excluded from quantitative analysis. Eligible articles were written in English or had an English abstract (data were obtained from the abstract in such cases).

Information sources and search strategy

A systematic literature search limited to human studies without language filters was performed by 2 reviewers in the PubMed (MEDLINE), EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases with the terms "([biliary obstruction AND duodenal obstruction] OR bilio-duodenal obstruction) AND (stent OR surgery)." The final search was performed on July 17, 2018. Reference lists of included articles were also investigated to capture all relevant studies.

Study selection and data collection process

After the removal of duplicates, the following data were extracted by 2 independent authors: age, gender, type of underlying malignancy, type of duodenal obstruction, method of biliary drainage, type of biliary and duodenal stents, timing of stent placement, technical and clinical success, adverse events, reintervention rate, survival, and follow-up.

Risk of bias assessment

Risk of bias was assessed using a modified version of the Newcastle–Ottawa Scale (NOS) by 2 independent review authors. Disagreements were resolved by discussion, with involvement of a third review author, when needed.

The modified NOS contained 7 items covering 2 main domains (selection and outcome) as comparability domain was not applicable because of the lack of head-to-head comparative studies: representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, demonstration that the outcome of interest was not present at the study's start (selection domain), assessment of outcome, and length and adequacy of follow-up (outcome domain). Studies could be awarded a maximum of one star for each item. Each item was rated as "high risk" (zero stars) or "low risk" (one star).

Data synthesis and statistical methods

Pooled event rate was calculated for events, and pooled mean was calculated for continuous data with 95% confidence intervals (CIs). A random-effect model was applied in all analyses with the DerSimonian–Laird estimation. Statistical heterogeneity was analyzed using the I² and χ^2 tests to gain probability values; P < 0.10 was defined to indicate significant heterogeneity. The I² test represents the percentage of total variability across studies because of heterogeneity. I² values of 30%–60%, 50%–90%, and 75%–100% corresponded to moderate, substantial, and considerable heterogeneity, respectively, based on Cochrane's handbook (19). Statistical analyses were performed with Comprehensive Meta-Analysis Software and STATA. Forest plots displayed the results of the meta-analysis.

Outcome measures

Overall technical success was defined as adequate placement of both biliary and duodenal stents or successful performance of double bypass in the case of manifest gastric outlet and biliary obstruction (4,20,21). Clinical success of biliary stenting was usually defined as a postprocedural reduction in serum bilirubin level within 2 weeks. However, this definition varied remarkably across studies: One study required normalization of serum bilirubin level (22), whereas others considered clinical success when a 25% or 50% reduction in bilirubin was observed (17,21,23) or only stated improvement of biliary obstruction symptoms without further clarification (4,24). Clinical success of duodenal stenting, when clarified other than clinical improvement of symptoms (4,24), mainly referred to a better score on the gastric outlet obstruction scoring system (21,23). Technical and clinical success was determined for that of biliary stenting/bypass and duodenal stenting/bypass together and separately as well.

Cases of prophylactic GEA were also included in the metaanalysis because it is recommended and commonly applied in the surgical treatment of pancreatic tumors. However, when prophylactic GEA was included in the surgical group, technical and clinical success could only be interpreted as that of biliary bypass, and accordingly, this was compared with technical and clinical success of biliary stenting.

Survival was determined as the time to death from both stents' placement (or creation of double bypass). For sequential biliary and duodenal stenting, survival was calculated from placement of the later stent. The following adverse events were investigated: pancreatitis, cholangitis, cholecystitis, bleeding, bile leakage, perforation, pneumoperitoneum, abdominal pain, wound infection, pneumonia, and others (including symptomless amylasemia, atrial fibrillation, cardiac arrest, aspiration, intra-abdominal abscess, and deep vein thrombosis). Stent migration, recurrent biliary obstruction (RBO; defined mostly as per the Tokyo criteria (25)), and recurrent duodenal obstruction (RDO; reoccurrence of gastric outlet obstruction symptoms) were also investigated. Adverse event rate was given as the number of patients with one or more adverse events. Reintervention rate was defined as the number of patients who required endoscopic or surgical intervention to treat RBO or RDO.

RESULTS

Study selection and characteristics

A total of 2,765 records were identified through a database search: 833 in PubMed, 1,531 in EMBASE, 382 in Web of Science, and 19 in CENTRAL. Nine additional records were found from the reference list of relevant articles. After removing duplicates and irrelevant records, 121 studies were found eligible. From these, 41 case reports and case series were excluded from quantitative synthesis (Figure 1). Therefore, 80 studies were included in the pooled analysis: 8 prospective and 72 retrospective observational studies (Tables 1 and 2). No randomized controlled trials were available. Fifty-five studies including 5,026 patients reported about double stenting, 22 with 1,080 patients about double bypass, and only 3 about both the techniques (including 64 patients who underwent double stenting and 93 with double bypass) (8,22,26). However, insufficient outcome reporting hindered the direct comparison of outcomes.

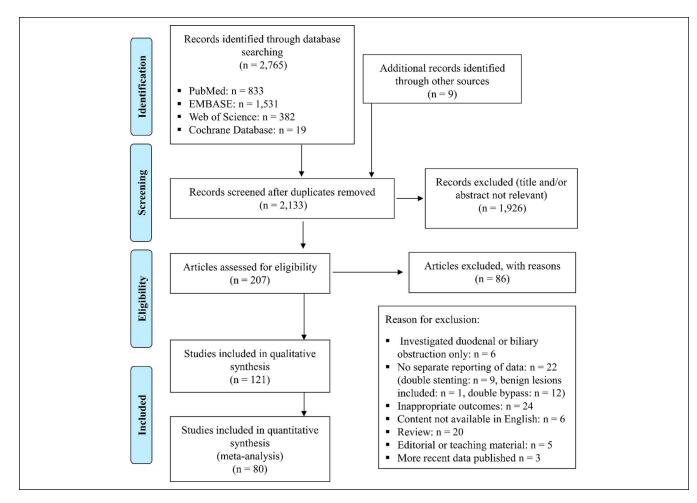


Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

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acteristics of included studies dealing with endoscopic double stenting		
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Endoscopic																									
					Age (yr)	r)			Duc	Duodenum obstruction			Bilia	Biliary stenting	ing				Timing			Follow-up (d)	(p) dn		
Study	Design C	No. Centers pa	No. patients N	Mean N	Median	SD	Range	Sex (female % of total)	Type I	Type	Type III	Type of malignancy	ERCP	EUS- BD	PTD		duodenum stent	Biliary first	Simultaneous	Duodenal first	Mean Me	Median SD	IQR		Range
Kaw et al. (30)	Retrospective	1	18	65	I	I	46-85	66		NA		Pancreatic, bile duct, metastatic, other	18	0	0	SEMS	NA		NA			NA	-		
Vanbiervliet et al. (31)	Retrospective	1	18	72	I	I	60-83	66		NA		Pancreatic	18	0	0	SEMS	NA	0	0	18		NA	-		
Choi etal. (32) (abstract)	Retrospective	1	53		NA			AN		NA		Pancreatic, ampullary, gastric, bile duct, gallbladder	11	0	12	NA	NA	17	0	9		NA	-		
Olsen et al. (33) (abstract)	Retrospective	1	8		NA			NA		NA		Pancreatic, gastric, bile duct, other	8	0	0	SEMS	NA		27	5		NA			
Maire et al. (34)	Retrospective	1	23	Ι	65	T	32-85	NA		NA		Pancreatic	23	0	0	PS, SEMS	NA	16	9	1		NA	7		
Sulieman et al. (35) (abstract)	Retrospective	NA	14		NA			NA		NA		Pancreatic, gallbladder, metastatic	14	0	0	SEMS	NA	7	4	m		NA	7		
Wang et al. (36) (abstract)	Retrospective	1	8	62		I	I	15		NA		NA	0	0	50	NA	NA	16	4	0		NA	~		
Akinci et al. (37)	Retrospective	1	6	61	I		42-80	33		AA		Pancreatic, duodenal, bile duct	0	0	б	SEMS	NA	Ð	4	0		NA	7		
Hou et al. (38) (abstract)	Retrospective	1	12		NA			NA		NA		NA	0	0	12	SEMS	NA		NA			NA	~		
Mutignani et al. (39)	Prospective	1	64	68.5	I	12.9	I	47	31	25	α	Pancreatic, gastric, metastatic, other	62	0	0	PS, SEMS	uSEMS	46	14	4		NA	~		
Moon et al. (40)	Prospective	1	00	72.8	I	I	51-85	œ	m	ш	0	Pancreatic, ampullary, gastric, bile duct, metastatic	00	0	0	SEMS	uSEMS	N	9	0		NA	~		
Katsinelos et al. (41)	Retrospective	4	32	I	11	T	52-89	8		NA		Pancreatic		NA		SEMS	NA	25	7	0		NA	~		
Keranen et al. (42) Retrospective	Retrospective	1	57	I	72	I	40-89	28		NA		Pancreatic, duodenal, gastric, bile duct, other	25	0	ы	PS, SEMS	NA	46	11	0	I	62 —	I	1	1–933
Iwamuro et al. (43) Retrospective	Retrospective	1	7	73	I	I	58-86	53		AN		Pancreatic, ampullary	0	7	0	PS	cSEMS	0	5	Q	88		I	37-	37-186
Zheng et al. (44) (abstract)	Retrospective	1	8		NA			NA		NA		NA	53	0	0	NA	NA		NA		180	I I	I		
Li et al. (45) (abstract)	Retrospective	1	18		NA			NA		AN		Pancreatic, duodenal, bile duct, metastatic		NA		SEMS	NA	14	4	0		NA	~		
Price et al. (46) (abstract)	Prospective	1	42		NA			NA		NA		Pancreatic, gastric, bile duct, gallbladder	33	0	თ	PS, SEMS	NA	40	0	0		NA	~		
Ardengh et al. (47) (abstract)	Retrospective	1	53	52	28	1	26-87	NA		AN		Pancreatic		NA		NA	NA	0	53	0		NA	-		
Hamada et al. (48)	Retrospective	Ð	33	69			62-77	40	23	Ð	വ	Pancreatic, bile duct, other	33	0	0	SEMS	cSEMS	20	11	2		NA	7		
Kanno et al. (49) (abstract)	Retrospective	1	21	72	I	I	I	62		AN		NA	13	9	0	NA	NA	12	σ	0		NA	~		
Khashab et al. (50)	Retrospective	0	თ	71.1	I	I	I	4	N	~	0	Pancreatic, duodenal, other	0	б	0	SEMS	NA	0	ω	9		NA	~		
Kim et al. (51)	Retrospective	1	24	71	T	11.6 43-89	43-89	20	4	13	7	Pancreatic, gastric, bile duct	13	0	11	PS, SEMS	NA	23	0	1		NA			

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Table 1. (Table 1. (continued)																								
Endoscopic																									
					Age (yr)	yr)			Duoc	Duodenum obstruction			Biliary	Biliary stenting		Type of			Timing			Follo	Follow-up (d)		
Study	Design	No. Centers	No. patients	Mean	Median	SD	Range	Sex (female 7 % of total)	Type Type I II		Type III	Type of malignancy	ERCP	EUS- BD	PTD		duodenum Bi stent f	Biliary first S	D Simultaneous	Duodenal first 1	Mean N	Median	SD IG	IQR	Range
Maluf-Filho et al. (52)	Retrospective	1	ы	70	72	~	46-88	99		NA		Pancreatic, other	0	ы	0	SEMS	uSEMS	0	ũ	0	37.2	17 1	16.3 -		4-90
Kushnir et al. (53) (abstract)	Retrospective	1	62	65	I	11.6	I	45		NA		Pancreatic, metastatic	62	0	15 ^a	NA	NA		NA				NA		
Pan et al. (54) (abstract)	Retrospective	1	10		NA			NA	Q	m	1 Pa	Pancreatic, ampullary, bile duct, gallbladder	9	4	0	NA	NA	m	1	9			NA		
Tonozuka et al. (55)	Retrospective	1	11	68.5	I	8.1	I	27	1	10	0	Pancreatic	m	œ	0	SEMS	NA	9	4	-			NA		
Valeshabad et al. (26) (abstract)	Retrospective	9	35	65.9	I	Ι	I	49	AN	18	AN	NA	35	12 ^a	e o	PS, SEMS	NA	0	0	35	78.4				1-500
Waidmann et al. (56)	Retrospective	1	17	70	I	11	50-85	47		NA		Pancreatic, gastric, bile duct, gallbladder, metastatic, other	17	0	0	PS, SEMS	cSEMS, uSEMS		NA		57	-	- 12	-	1–275
Carvalho et al. (57) Retrospective (abstract)	Retrospective	m	20		NA	Ŧ		NA	35	53	4	NA	42	0	00	NA	NA		NA				NA		
Canena et al. (23)	Retrospective	4	20	71.2	20	T	46-90	42	35	11	4 Pa gasi	Pancreatic, duodenal, ampullary, gastric, bile duct, gallbladder, other	42	0	00	SEMS	uSEMS	ଷ	15	9			NA		
Hamada et –al. (58)	Retrospective	m	8	66.6	65	1.1	58-76	45	6	Ð	9	Pancreatic, ampullary, gastric	13	~	۵.	PS, SEMS	cSEMS, uSEMS	0	0	20			NA		
Khashab et al. (59)	Retrospective	Q	35	64.6	I	13.5	I	45	9	19	2 Pai	Pancreatic, duodenal, metastatic, other	11 ^b	13 ^a	a a	PS, SEMS	uSEMS	0	0	35			NA		
Lee et al. (60)	Retrospective	1	45	61.3	I	11.6	38-83	47	21 1	19	5 Par	Pancreatic, duodenal, gastric, bile duct, gallbladder, other	0	0	45	SEMS	cSEMS, uSEMS	14	0	31	I	132	1	ω 	8-920
Yu et al. (61)	Retrospective	1	17	76.6	I	6.5	62-87	18	7	ω		Pancreatic, duodenal, bile duct	17	0	0	AA	NA	17	0	0			NA		
Di Mitri et al. (62) (abstract)	Retrospective	1	35	72.4	I	10.1	I	37		NA	<u>م</u>	Pancreatic, duodenal, bile duct, other	35	0	0	NA	NA	0	0	35			NA		
Kubo et al. (63) (abstract)	Retrospective	1	44	75.4	I	I	I	48		AN		NA	¥	0	10	NA	NA	œ	11	0			NA		
Manta et al. (64)	Retrospective	1	15	65.6	I	I	38-80	20	-	NA		Pancreatic	e	12	0	SEMS	uSEMS	12	0	e			NA		
Matsumoto et al. (65) (abstract)	Retrospective	1	47		NA	5		NA		AN		Pancreatic	32	15	0	NA	NA		NA				NA		
Sanchez-Ocana et al. (66) (abstract)	Retrospective	1	61	4	I	I	30-92	8	58	34		Pancreatic, gastric, other	37	24	0	AA	AN	25	σ	27			NA		
Sano et al. (67) (abstract)	Retrospective	1	21		NA	Ŧ		NA	13	9	2	Pancreatic		NA		NA	NA	17	4	0			NA		
Williamson et al. (8)	Retrospective	N	7	L	20	I	42-81	8		NA	P	Pancreatic, duodenal, ampullary, bile duct, other		AN	۵.	PS, SEMS	NA	7	0	0			NA		
Fu et al. (22)	Retrospective	1	22	64.7	T	9.3	T	30		NA		Pancreatic	0	0	22	NA	NA		NA				NA		

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					Ag	ge (yr)			ol	bstructio	on		Bilia	ry stent	ing	Type of	Type of		Timing			Fo	ollow-up	(d)	
Study	Design	No. Centers	No. patients	Mean	Media	n SD	Range	Sex (female % of total)	Туре	Type II	Type III	Type of malignancy	ERCP	EUS- BD	PTD	biliary stent	duodenum stent	Biliary first	Simultaneous	Duodenal first	Mean	Median	SD	IQR	Range
Ogura et al. (68)	Retrospective	1	39	70.3		9		46	28	11		Pancreatobiliary, other	0	39	0	SEMS	uSEMS	0	0	39	moun	moulan	NA		mange
Paik et al. (69) (abstract)	Retrospective	1	43	70.0		NA		NA	20	NA		Pancreatic, duodenal, bile duct, gallbladder, metastatic, other	11	0	32	NA	NA	0	0	43			NA		
Sato et al. (24)	Retrospective	1	43	65.4	-	9.8	-	49	12	18	13	Pancreatic, duodenal, gastric, bile duct	26	17	0	SEMS	uSEMS		NA		90	-	-	_	-
Yao et al. (70) (abstract)	Retrospective	1	42			NA		NA		NA		NA	42	0	0	NA	NA	0	0	42			NA		
Zhao et al. (71)	Retrospective	1	20	63.1	_	8.2	35–72	35		NA		Pancreatic, duodenal, bile duct, metastatic	0	0	20	NA	NA	16	1	3			NA		
Bulut et al. (72) (abstract)	Retrospective	1	21	58.7	—	15	—	38		NA		Pancreatic, duodenal, ampullary, gastric, bile duct, metastatic, other	0	0	21	NA	uSEMS	14	7	0	112.6	—	152	—	-
Fukushima et al. (73) (abstract)	Retrospective	1	15			NA		NA	7	5	3	NA		NA		NA	NA		NA				NA		
Brewer Gutierrez et al. (74)	Retrospective	3	7	64.7	—	12.5	-	57		NA		Pancreatic	0	7	0	SEMS	LAMS	0	7	0	_	106	-	66–235	-
Kim et al. (75)	Retrospective	1	58	61.1	—	12	—	38		NA		Pancreatic, duodenal, gastric, bile duct, gallbladder, metastatic	58	0	0	SEMS	cSEMS	58	0	0			NA		
Lee et al. (76)	Retrospective	1	12	67.5	—	-	38–82	50	4	3	5	Pancreatic, ampullary, bile duct, gallbladder	11	0	1	SEMS	uSEMS		6	6			NA		
Matsumoto et al. (21)	Retrospective	1	81	-	66	_	41–91	40	38	32	11	Pancreatic, ampullary, gastric, bile duct, gallbladder, metastatic	62	19	0	PS, SEMS	cSEMS, uSEMS	50	31	0			NA		
Hamada et al. (17)	Retrospective	16	110	68.8	—	11.5	-	52	45	46	19	Pancreatic, ampullary, gastric, bile duct, gallbladder, other	90	20	0	PS, SEMS	NA	67	29	14			NA		
Hori et al. (4)	Retrospective	8	109	-	70	-	39–96	44	23	74	12	Pancreatobiliary, gastric, other	101	0	8	SEMS	cSEMS, uSEMS	88	12	9			NA		
Rai et al. (77) (abstract)	Prospective	1	12			NA		67		NA		NA	7	5	0	SEMS	NA		NA				NA		
Staub et al. (20)	Retrospective	2	71	66.87	_	_	31–92	38	46	21	4	Pancreatic, duodenal, ampullary, other	71	0	0	PS, SEMS	NA			71			NA		
Yamao et al. (78)	Retrospective	5	39	68.5	_	11.3		41	11	16	12	Pancreatic	25	14	0	PS, SEMS	NA	9		30			NA		

cSEMS, covered self-expandable metallic stent; ERCP, endoscopic retrograde cholangiopancreatography; EUS-BD, endoscopic ultrasound-guided biliary drainage; IQR, interquartile range; LAMS, lumen-apposing metallic stent; NA, not available; PS, plastic stent; PTD, percutaneous transhepatic drainage; SEMS, self-expandable metallic stent; uSEMS, uncovered self-expandable metallic stent. ^aEUS-BD and/or PTD was performed in case of ERCP failure.

^bThirteen patients underwent successful biliary cannulation with ERCP, but stent was inserted only in 11 patients.

Table 2. Characteristics of included studies dealing with surgical double bypass

Surgical

		No.	No.			Age			Sex (female % of		Prophylactic		Follow-up (d	i)
Study	Design	Centers	patients	Mean	Median	SD	IQR	Range	total)	Type of malignancy	GEA	Mean	Median SD	Range
Levi et al. (79)	Retrospective	1	18			NA			NA	Pancreatic	NA		NA	
Wongsuwanporn and Basse (80) (abstract)	Retrospective	1	26			NA			NA	Pancreatic	NA		NA	
Lee (81)	Retrospective	1	65			NA			NA	Pancreatic, ampullary	NA		NA	
Parker and Postlethwaite (82)	Retrospective	1	13	59	—	11	—	—	0.5	Pancreatic	NA		NA	
La Ferla and Murray (83)	Retrospective	1	14	65	_	—	—	45–92	36	Pancreatic	14		NA	
Singh et al. (84)	Retrospective	1	70	63	—	—	—	12–88	46	Pancreatic	20		NA	
Casaccia et al. (85)	Prospective	1	2	—	64	—	—	53–72	33	Pancreatic	0	12.5		7–18
Hamade et al. (86)	Retrospective	1	8	—	70	—	_	26–81	43	Pancreatic, duodenal, bile duct	5		NA	
Hao et al. (87)	Retrospective	1	22	63	_	—	—	52–76	NA	Pancreatic, ampullary, bile duct, duodenal	22		NA	
Khan et al. (88)	Retrospective	1	2	77	—	—	_	63–90	53	Pancreatic, duodenal, gastric, bile duct	0		NA	
Mortenson et al. (89)	Retrospective	1	38	61	_	11	—	—	NA	NA	NA		NA	
Tang et al. (90) (abstract)	Retrospective	1	35	_	69	—	_	_	62	NA	NA		NA	
Ghanem et al. (91)	Prospective	1	8	_	67	—	—	26–81	59	Pancreatic	3		NA	
Lesurtel et al. (27)	Retrospective	1	83	64	_	11	_	_	46	Pancreatic	72	270	— 270	_
Mann et al. (92)	Retrospective	1	102		65	—	_	36–86	39	Pancreatic, duodenal, ampullary, bile duct, metastatic	92		NA	
Ausania et al. (93)	Prospective	1	50	—	64	—	—	39–79	34	Pancreatic, duodenal, ampullary, bile duct, other	50	—	300 —	120-99
Lyons et al. (10)	Retrospective	1	60	65	—	_	—	_	45	Pancreatic	50		NA	
Malde et al. (94) (abstract)	Retrospective	1	48	—	—	—	_	—	40	Pancreatic	NA		NA	
Valeshabad et al. (26) (abstract)	Retrospective	6	3 ^a	65.9	_	_	_	—	49	NA	0		NA	
Bartlett et al. (5)	Retrospective	315	351	66	—	—	59–75	—	45	Pancreatic	NA		NA	
Kohan et al. (9)	Prospective	1	42	64	_	_	_	38–88	56	Pancreatic	28		NA	
Kofokotsios et al. (95)	Retrospective	1	11	—	70	—	—	48–77	36	Pancreatic	11		NA	
Williamson et al. (8)	Retrospective	2	59	—	66	_	—	39–81	NA	Pancreatic, duodenal, ampullary, bile duct, other	59		NA	
Fu et al. (22)	Retrospective	1	31	61	—	9.4	—	—	NA	Pancreatic	31		NA	
Giuliani and Bonetti (96) (abstract)	Retrospective	1	12	_	67	_	_	41-83	42	Pancreatic	0	_	323 —	30-3.29

GEA, gastroenteric anastomosis; IQR, interquartile range; NA, not available. $^{\rm a}{\rm Surgery}$ was performed in case of ERCP failure.

Malignant Biliary and Duodenal Obstruction

7

REVIEW ARTICLE

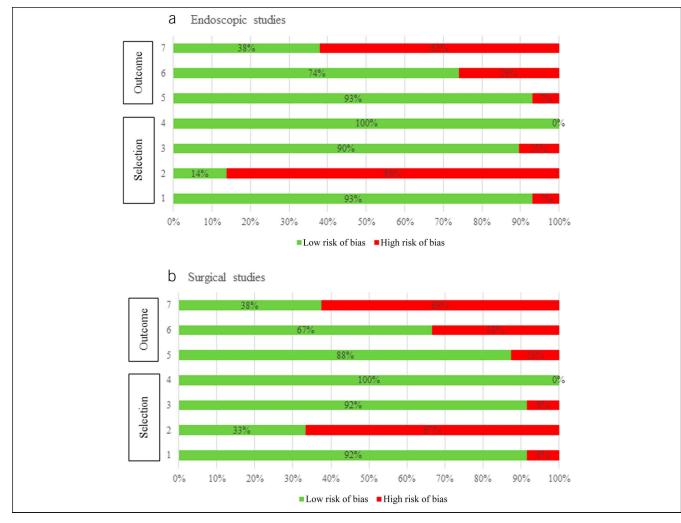


Figure 2. Risk of bias assessment of individual studies according to the modified Newcastle–Ottawa Scale. (a) Endoscopic studies and (b) surgical studies. Each item was rated as "high risk" (zero stars) or "low risk" (one star). Selection domain: (i) representativeness of the exposed cohort, (ii) selection of the nonexposed cohort, (iii) ascertainment of exposure, and (iv) demonstration that the outcome of interest was not present at the start of study. Outcome domain: (v) assessment of outcome, (vi) length of follow-up, and (vii) adequacy of follow-up.

Underlying malignancy was specified in 73% of cases: pancreatobiliary cancer in 4,149, gastroduodenal cancer in 212, metastatic cancer in 49, and other malignancies in 144 cases. Duodenal stenosis was located above and at the ampullary level in 43.7% each and below the ampulla in 12.5% of reported cases. Seventeen studies reported about prophylactic GEA, and it was applied in 69% of surgical cases. In case of double stenting, biliary stenting was performed via ERCP in 69%, PTD in 17%, and EUS-BD in 14% of patients. Biliary and duodenal stents were placed simultaneously in 25.5% of reported cases; biliary stenting preceded duodenal in 45.7% and followed it in 28.8%. The mean interval between stent placements was 114 \pm 106 days (201 \pm 173 days for biliary first and 74 \pm 75 days for duodenal first).

In *post hoc* analysis, the mean age of patients who underwent double stenting was significantly higher (67.9 years [95% CI: 67.0–68.9 years; $I^2 = 88.0\%$]) than that of those who underwent double bypass (63.7 years [95% CI: 62.3–65.0 years; $I^2 = 89.2\%$]). Gender distribution showed no difference between the groups.

Risk of bias assessment

Risk of bias of individual studies was assessed with the NOS (see Table, Supplementary Digital Content 1, http://links.lww.com/CTG/A243). Baseline characteristics were reported in almost all journal articles but were only partially available in conference abstracts (Tables 1 and 2). Clinical success rate's definition varied, and other outcome measures were defined mostly uniformly (4,17,21–24). Although assessment of different outcomes was reported reliably in more than 90% (Figure 2), outcomes were reported heterogeneously (see Tables, Supplementary Digital Content 2 and 3, http://links.lww.com/CTG/A244 and http://links.lww.com/CTG/A245). Adequate follow-up data were available in only approximately 40%, but the length of follow-up was appropriate for assessment of outcomes, when reported (Figure 2).

Meta-analytical calculations

Technical and clinical success. Overall technical and clinical success rates of double stenting were 97% (95% CI: 95%–99%) and 92% (95% CI: 89%–95%), respectively. Subgroup analysis of different biliary stenting modalities found no difference in

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Figure 3. Clinical success of biliary bypass in case of double stenting and double surgical bypass (including cases with prophylactic GEA). Cl, confidence interval; ES, effect size; GEA, gastroenteric anastomosis.

technical and clinical success (see Figures, Supplementary Digital Content 4 and 5, http://links.lww.com/CTG/A246 and http://links.lww.com/CTG/A247).

Considering frequent prophylactic GEA use during surgical double bypass, technical and clinical success in this group could only be assessed for biliary bypass. No difference was found between technical success of endoscopic stenting and surgical biliary bypass (see Figure, Supplementary Digital Content 6, http://links. lww.com/CTG/A248), whereas clinical success of endoscopic biliary stenting was higher (97% [95% CI: 94%–99%; I² = 67.3%] vs 86% [95% CI: 78%–92%; I² = 19.9%], respectively) (Figure 3). Technical and clinical success of duodenal stenting was 99% (95% CI: 97%–100%) and 97% (95% CI: 94%–99%), respectively.

Adverse event rate. Double stenting was associated with less adverse events compared with surgical double bypass (13% [95% CI: 8%-19%; $I^2 = 86.3\%$] vs 28% [95% CI: 19%-38%; $I^2 = 89.3\%$]) (Figure 4). See Table (Supplementary Digital Content 7, http://links.lww.com/CTG/A249) for details of adverse events associated with double stenting and double bypass. Adverse events occurred at 67.8 days on average (95% CI: 5.1-128.4 days) postprocedure. There was no difference between adverse events' occurrence time after double stenting and double bypass (52.8 days [95% CI: 23.7-129.3 days] vs 108.7 days [95% CI: 123.2-340.6 days], respectively).

ERCP was associated with the least adverse events (3% [95% CI: 1%-6%; I² = 42.8%]), followed by PTD (10% [95% CI: 0%-37%;

Studies		ES (95% CI)	% Weight
Endoscopic	-		
Kushnir 2013		0.00 (0.00 - 0.06)	1.68
Gutierrez 2017 Sulieman 2006		0.00 (0.00-0.35) 0.00 (0.00-0.22)	1.11 1.36
Choi 2005		0.00 (0.00 - 0.14)	1.50
Wang 2006		0.00 (0.00 - 0.16)	1.47
Vanbiervliet 2004	•	0.00 (0.00-0.18)	1.44
Zheng 2010	•	0.00 (0.00-0.15)	1.49
Di Mitri 2015		0.00 (0.00 - 0.10)	1.59
Lee 2017 Hou 2007		0.00 (0.00 - 0.24) 0.00 (0.00 - 0.24)	1.31
Maire 2006	· ·	0.00 (0.00 - 0.14)	1.50
Khashab 2014		0.03 (0.01-0.15)	1.59
Olsen 2005	•	0.03 (0.01-0.17)	1.56
Staub 2018	<u>€</u>	0.04 (0.01-0.12)	1.69
Kaw 2003		0.06 (0.01 - 0.26)	1.44
Li 2011 Matsumoto 2015		0.06 (0.01 - 0.26) 0.06 (0.02 - 0.17)	1.44
Hori 2017		0.06 (0.03 - 0.13)	1.73
Sanchez-Ocana 2015		0.07 (0.03-0.16)	1.68
Price 2011	.	0.07 (0.02-0.19)	1.63
Katsinelos 2010		0.08 (0.03-0.20)	1.61
Rai 2017 Lee 2014		0.08 (0.01 - 0.35)	1.31
Sano 2015		0.09 (0.04 - 0.21) 0.10 (0.03 - 0.29)	1.48
Hamada 2014	<u> </u>	0.10 (0.03 - 0.30)	1.47
Akinci 2007		0.11 (0.02-0.43)	1.21
Kim 2017		0.12 (0.06-0.23)	1.67
Moon 2009 Hamada 2017		0.13 (0.02 - 0.47)	1.16
Ardengh 2012	100	0.14 (0.08-0.21) 0.14 (0.05-0.33)	1.73 1.49
Kubo 2015		0.14 (0.06 - 0.27)	1.63
Kanno 2012		0.14 (0.05-0.35)	1.48
Paik 2016		0.19 (0.10-0.33)	1.63
Sato 2016	- <u>-</u> -	0.19 (0.10-0.33)	1.63
Manta 2015 Pan 2013		0.20 (0.07-0.45)	1.38
Ogura 2016		0.20 (0.06-0.51) 0.21 (0.11-0.36)	1.61
Yu 2014		0.24 (0.10-0.47)	1.42
Mutignani 2007		0.25 (0.16-0.37)	1.68
Tonozuka 2013		0.27 (0.10-0.57)	1.28
Iwamuro 2010 Khashab 2012		0.29 (0.08-0.64)	1.11
Matsumoto 2012		0.33 (0.12-0.65) 0.38 (0.28-0.49)	1.21
Maluf-Filho 2012	-	0.40 (0.12 - 0.77)	0.97
Canena 2014		0.44 (0.31-0.58)	1.65
Fu 2016		0.68 (0.47 - 0.84)	1.49
Kim 2012 Fukushima 2017		0.79 (0.60 - 0.91) 0.80 (0.55 - 0.93)	1.51
		0.95 (0.76 - 0.99)	1.35
Zhao 2016 Subtotal (I ² = 88.73%,P = 0.00)	0	0.13 (0.08 - 0.19)	72.44
Surgical			
Hao 2005 Giuliani 2016		0.00 (0.00-0.15) 0.00 (0.00-0.24)	1.49
Hamade 2005	· · · · · · · · · · · · · · · · · · ·	0.13 (0.02 - 0.47)	1.16
Ferla 1987		0.14 (0.04-0.40)	1.36
Bartlett 2014	*	0.17 (0.13-0.21)	1.78
Kofokotsios 2015		0.18 (0.05-0.48)	1.28
Malde 2012 Mortenson 2005		0.23 (0.13-0.37) 0.24 (0.13-0.39)	1.65
Ghanem 2006		0.24 (0.13 0.39)	1.16
Mann 2009	·	0.26 (0.19-0.36)	1.73
Lesurtel 2006	—	0.27 (0.18-0.37)	1.71
Wongsuwanporn 1983		0.35 (0.19-0.54)	1.53
Fu 2016		0.35 (0.21-0.53)	1.57
Lyons 2012 Kohan 2014		0.40 (0.29-0.53) 0.43 (0.29-0.58)	1.68 1.63
Tang 2005		0.43 (0.29 0.58)	1.63
Ausania 2012		0.50 (0.37-0.63)	1.65
Williamson 2015		0.81 (0.70-0.89)	1.67
Subtotal (I ² = 89.28%,P = 0.00)	\diamond	0.28 (0.19-0.38)	27.56
Heterogeneity between groups: $P = 0.008$ Overall ($I^2 = 88.88\%$, $P = 0.00$):	4	0.17 (0.12-0.22)	100.00
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Figure 4. Adverse events related to double stenting and double surgical bypass. Cl, confidence interval; ES, effect size.

EUS-BD Gutierrez 2017 Hamada 2014/2 Ogura 2016 Wamuro 2010 Khashab 2012 Hamada 2017/2 Tonozuka 2013/2 Maluf-Filho,2012 Subtotal (I ⁴ = 1.82%, p = 0.42) PTD Hou 2007 Kushnir 2013/1 Hayashi 2001/2 Choi 2005/2 Lee 2017/2 Wang 2006 Hyun 2016/2 Lee 2014 Akinci 2007 Pak 2016/2 Pak 2016/2 Pak 2016/2 Hayashi 2009 Pak 2016/2 PTD Hou 2007 Choi 2005/2 PTD Hou 2007 Choi 2005/2 Pak 2016/2 PTD Hou 2007 Pak 2016/2 PTD Hou 2007 Pak 2016/2 PTD Hou 2007 Pak 2016/2 PTD Hou 2007 Pak 2016/2 PTD Hou 2007 Pak 2016/2 PTD Hou 2007 Pak 2016/2 Pak 2016/2 PTD Hou 2007 Pak 2016/2 Pak 2016/2 P	Studies	ES (95% CI)	% Weig
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	Overan (I = 81.03%, P = 0.00);	0.07 (0.02–0.13)	100.00

Figure 5. Adverse events related to ERCP, EUS-BD, and PTD. CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; ES, effect size; EUS-BD, endoscopic ultrasound-guided biliary drainage; PTD, percutaneous transhepatic drainage.

 $I^2=90.2\%])$ and EUS-BD (23% [95% CI: 15%–33%; $I^2=1.8\%])$ (Figure 5). The difference was significant between ERCP and EUS-BD.

Reintervention rate. More reinterventions were needed after double stenting than after double bypass (21% [95% CI: 16%–27%; $I^2 = 79.4\%$] vs 10% [95% CI: 4%–19%; $I^2 = 90.2\%$]) (see Figure, Supplementary Digital Content 8, http://links.lww. com/CTG/A250). In subgroup analysis, reinterventions were least likely to be necessary after PTD (4% [95% CI: 0%–15%]), followed by ERCP and EUS-BD (16% [95% CI: 9%–24%] and 32% [95% CI: 15%–50%], respectively) (Figure 6).

Although only 2 surgical studies specified whether reintervention was necessary because of RBO or RDO (26,27), several endoscopic studies investigated RBO and RDO separately (see Table, Supplementary Digital Content 2, http://links.lww.com/CTG/ A244). RBO was reported in a total of 285 cases, whereas RDO was reported in 100 cases. The mean time until the occurrence of RBO and RDO was 167.3 days (95% CI: 93.0–241.6 days; $I^2 = 96.0\%$) and 106.0 days (95% CI: 56.7–155.3 days; $I^2 = 51.1\%$), respectively.

Survival. Cumulative mean survival of patients after double stenting was 156.4 days (95% CI: 128.3–184.5 days). Subgroup analysis of the different biliary stenting methods as part of double stenting revealed no difference in mean survival (see Figure, Supplementary Digital Content 9, http://links.lww.com/CTG/A251). A small number of surgical studies and frequent GEA use in the surgical cohort prevented comparison of survival in the endoscopic and surgical cohorts.

DISCUSSION

Although double stenting for combined malignant biliary and duodenal obstruction has been a treatment option for 25 years (16), its place in the therapeutic algorithm has not been clearly specified, and reliable efficacy data are still lacking because of the rare concomitant occurrence of these conditions (17). To the best of our knowledge,

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Gutierrez 2017 Sato 2016/2 Subtotal (l ² = .%, p = .) Heterogeneity between groups: p = 0.065		0.14 (0.03_0.51)	2.58
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Overall (I" = 67.98%, p = 0.00); U.13 (0.08-0.20) 100.00	Heterogeneity between groups: $P = 0.065$	0.40.00.00.000	100.00
	Overall $(1^{2} = 67.98\%, p = 0.00);$	0.13 (0.08–0.20)	100.00

Figure 6. Reintervention rate related to ERCP, PTD, and EUS-BD. CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; ES, effect size; EUS-BD, endoscopic ultrasound-guided biliary drainage; PTD, percutaneous transhepatic drainage.

this is the first systematic review and meta-analysis dealing with the feasibility of double endoscopic stenting in this scenario.

According to our findings, high cumulative technical and clinical success rates can be achieved with double stenting in this difficult-to-treat population. Success rates were comparable with traditionally applied surgical bypass regarding biliary bypass; moreover, clinical success rate of endoscopic biliary bypass was even higher than that of surgery. The importance of this finding lies in the fact that those underwent double stenting were significantly older compared with those with double bypass, suggesting a potential superiority of double stenting in the elderly.

The adverse event profile of double stenting was favorable over that of double bypass in terms of not only numbers but also severity (death was only reported in the surgical cohort). However, the occurrence of adverse events depends on the method of biliary stenting: ERCP was associated with significantly fewer adverse events than EUS-BD. A previous meta-analysis about EUS-BD reported a similarly high cumulative adverse event rate (23.32%) (28). The high proportion of ERCPs in the double stenting cohort may also contribute to the overall adverse event rate.

However, double stenting was associated with higher reintervention rate independently of the biliary stenting method. Duodenal stent placement alone was found to require more reinterventions than surgery (15), and a recent multicenter randomized controlled trial comparing ERCP and EUS-BD as the primary treatment modality of malignant biliary obstruction reported reintervention rates of 42.6% and 15.6%, respectively (14). These facts, and plastic biliary stents' use in numerous studies and inclusion of early studies dealing with double stenting, might also contribute to high reintervention rates (29). Considering cumulative survival and mean time until RBO or RDO, generally one reintervention will be necessary for patients undergoing double stenting. Nevertheless, PTD and EUS-BD were mostly second-line treatments after ERCP failure, and the exact number of sessions required to stent placement (especially for PTD, when stenting is often performed in a second session after temporary external biliary drainage) was generally not reported; therefore, complete burden of interventions cannot be reliably assessed.

Common prophylactic GEA use in double bypass also needs to be considered. Because it is associated with a lower risk of development of duodenal stenosis (6,7), lower rates of reinterventions for RDO are expected in the surgical cohort, which consists mostly of cases with prophylactic GEA. Therefore, cumulative overall reintervention rates might also be lower; however, details of conditions requiring reintervention in this cohort were generally not reported. Another aspect related to prophylactic GEA use is the impossibility to compare overall success rates of the cohorts because technical and clinical success of duodenal bypass is not applicable in such cases.

Limitations

The main limitation was the lack of head-to-head comparative studies assessing double stenting and double bypass; therefore, only an indirect comparison could be provided with significant heterogeneity between studies. Different timing of biliary and duodenal interventions and frequent second-line use of PTD and EUS-BD increase heterogeneity further. Numerous studies were retrospective or not available as full text, and being a relatively rare entity, a huge part of literature (particularly for EUS-BD) consists of case reports and case series.

Results of double stenting and double bypass must be compared with caution because the cohorts may not consist of the exact same population (double stenting was traditionally an alternative for patients unfit for surgery). The higher age of those underwent double stenting seems to be confirming this; however, objective measures to assess operative risk (e.g., the American Society of Anesthesiologists classification system), which might serve as a basis for such a distinction, were not reported.

Implications for practice

A crucial clinical question regarding malignant duodenobiliary obstruction is whether to refer patients to surgery or endoscopy for palliation. According to our meta-analysis, high technical and clinical success rates, especially the higher clinical success rate of endoscopic biliary stenting compared with surgical bypass, and the lower adverse event rate suggest a justification of minimally invasive techniques in this setting, but high reintervention rates should also be acknowledged. Based on the adverse event profile, when technically feasible, ERCP can be recommended as the firstchoice method for biliary stenting also in case of duodenobiliary stenosis, but high reintervention rates and frequent sequential development of duodenal stenosis do not allow to make general recommendations. Caution should be taken because of the limited and substantially heterogeneous available evidence.

Implications for research

To define the cohorts that can benefit most from double stenting, there is a pressing need for multicentric, prospective, comparative studies with well-defined outcome measures and carefully chosen cohorts. Aspects such as prophylactic GEA use, selection of patients "unfit for surgery" based on the well-defined scoring systems for risk stratification, and the possible use of EUS-BD as the primary treatment option should also be considered.

CONFLICTS OF INTEREST

Guarantor of the article: Anna Fábián, MD.

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Potential competing interests: None to report.

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