Evidence-Based Appraisal of Antireflux Fundoplication

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Objective: To highlight the current available evidence in antireflux surgery through a systematic review of randomized controlled trials (RCTs).

Summary Background Data: Laparoscopic fundoplication is currently suggested as the gold standard for the surgical treatment of gastroesophageal reflux disease, but many controversies are still open concerning the influence of some technical details on its results.

Methods: Papers related to RCTs identified via a systematic literature search were evaluated according to standard criteria. Data regarding the patient sample, study methods, and outcomes were abstracted and summarized across studies. Defined outcomes were examined for 41 papers published from 1974 to 2002 related to 25 RCTs. A meta-analysis was performed pooling the results as odds ratios (OR), rate differences (RD), and number needed to treat (NNT). Data given as mean and/or median values were pooled as a mean ± SD (SD).

Results: No perioperative deaths were found in any of the RCTs. Immediate results showed a significantly lower operative morbidity rate (10.3% versus 26.7%, OR 0.33, RD −12%, NNT 8), shorter postoperative stay (3.1 versus 5.2 days, $P = 0.03$), and shorter sick leave (20.1 versus 35.8 days, $P = 0.03$) for laparoscopic versus open fundoplication. No significant differences were found regarding the incidence of recurrence, dysphagia, bloating, and reoperation for failure at midterm follow-up. No significant differences in operative morbidity (13.1% versus 9.4%) and in operative time (90.2 versus 84.2 minutes) were found in partial versus total fundoplication. A significantly lower incidence of reoperation for failure (1.6% versus 9.6%, OR 0.21, RD −7%, NNT 14) was found after partial fundoplication, with no significant differences regarding the incidence of recurrence and/or dysphagia. Routine division of short gastric vessels during total fundoplication showed no significant advantages regarding the incidence of postoperative dysphagia and recurrence when compared with no division. The use of ultrasonic scalpel compared with clips or bipolar cautery for the division of short gastric vessels showed no significant effect on operative time, postoperative complications, and costs.

Conclusions: Laparoscopic antireflux surgery is at least as safe and as effective as its open counterpart, with reduced morbidity, shortened postoperative stay, and sick leave. Partial fundoplication significantly reduces the risk of reoperations for failure over total fundoplication. Routine versus no division of short gastric vessels showed no significant advantages. A word of caution is needed when implementing these results derived from RCTs performed in specialized centers into everyday clinical practice, where experience and skills may be suboptimal.

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The serendipitous discovery of the antireflux effect of wrapping the gastric fundus around the distal esophagus[1] led Rudolph Nissen to perform the first fundoplication for gastroesophageal reflux disease (GERD) nearly half a century ago.[2] Since then, various technical details of total fundoplication[3–5] or partial fundoplications[6–8] have been suggested. In 1991, the so-called "Nissen fundoplication" was performed for the first time through a laparoscopic approach.[9,10] To date, various large series showed its safety, efficacy, good quality of life, short hospital stay, early return to work, and cost savings.[11–14] However, little is known about the reproducibility of such results in nonspecialized centers,[15] and about current indications and results faced by long-term acid suppression therapy.[16,17] Gastroenterologists and surgeons definitely do not share the same enthusiasm in surgical referral of patients with GERD.[18] The gastroenterological medical community appears at least skeptical about the efficacy of laparoscopic antireflux surgery,[19–21] claiming also that too many technical modifications of fundoplication are performed and complications are often blamed on 1 type of modification or another.[19,20] Furthermore, a recently introduced third party – endoscopic augmentation of lower esophageal sphincter pressure[22,23] – might potentially compete in this arena.

When one of the authors, already experienced in laparoscopic antireflux surgery, moved to his current hospital, he needed to establish a new surgical referral of patients with GERD. He was asked to provide the available evidence on

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current status of antireflux surgery, and this need prompted this review.

MATERIALS AND METHODS

The first step of evidence-based medicine is to rephrase our problems or information needs into answerable questions.[24] Therefore, we developed 4 questions:

1. Open or laparoscopic approach?
2. Partial or total wrap?
3. Division or no division of short gastric vessels?
4. Hiatoplasty and calibration of the wrap by an esophageal bougie?

We then performed a literature search of computer databases of all articles published through 2002 with no language limitation (MEDLINE 1966–2002, EMBASE 1980–2002, HealthSTAR 1975–2002, and the Cochrane Library 2/2002). A computer-assisted search was conducted using the following combination of Medical Subject Heading (MESH) terms: "Gastroesophageal reflux" and "fundoplication." We also did a manual search using references from the articles retrieved and main review articles.[11–14] For each citation, we downloaded the title, abstract, authors, institution, journal, and major and minor descriptors.

Prospective randomized controlled trials (RCTs) related to fundoplication for gastroesophageal reflux disease in adults were selected. Each study was independently reviewed by the authors, and methodological criteria and the results of each study were recorded. Studies were judged suitable for meta-analysis only if they met all the following criteria: (1) prospective randomized trial dealing with laparotomic and/or laparoscopic fundoplication for gastroesophageal reflux disease; (2) well-defined outcomes including at least 1 of the following: (a) perioperative mortality and morbidity rates, (b) details about the rates of specific postsurgical results (ie, recurrence, dysphagia, etc.). Only results fully reported in journal articles were considered. All the trials regarding already abandoned surgical techniques, such as the Angelchik device or the ligamentum teres gastroplasty, were excluded.

We found 77 papers reporting the results of RCTs; all these articles passed through a multilevel, systematic review by a team of 2 surgeons and 1 gastroenterologist, trained in epidemiology and health services research, according to the QUOROM statement.[25] Forty-one papers met all the inclusion criteria. This review is therefore based on these 41 papers, reporting the results of 25 RCTs (Fig. 1). Full papers of all these trials were reviewed blindly and independently by all authors to tabulate subject demographics, study design, definition of outcomes, and frequencies of each end point, using a standardized data abstract form. Disagreement was resolved by consensus. Independent methodological quality assessment of each article using the Jadad scale,[26] with scores ranging from 0 to 5, was also performed. Studies addressing each 1 of the 4 questions were separately analyzed.

Open Versus Laparoscopic Fundoplication

The outcomes considered were: conversion rates in the laparoscopic group, overall morbidity and mortality rates, length of the operation, length of postoperative hospital stay, length of sick leave, incidence of postoperative recurrence of GERD (detected by either endoscopy and/or pH-metry, when available, or by the recurrence of symptoms), incidence of postoperative new-onset dysphagia of any grade, incidence of postoperative bloating syndrome of any grade, incidence of reoperation for any failure, and immune status.

Partial Versus Total Wrap

The outcomes considered were: overall morbidity and mortality rates, length of the operation, incidence of postoperative new-onset dysphagia of any grade, incidence of postoperative recurrence of GERD (detected by either endoscopy and/or pH-metry, when available, or by the recurrence of symptoms), and incidence of reoperation for any failure.

Division Versus No Division of Short Gastric Vessels

The outcomes considered were: overall morbidity and mortality rates, length of the operation, incidence of postoperative new-onset dysphagia of any grade, and incidence of postoperative recurrence of GERD (detected by either endoscopy and/or pH-metry, when available, or by the recurrence of symptoms). Furthermore, different devices for laparoscopic division of short gastric vessels were compared regarding postoperative morbidity rates, length of the operation, and costs.

Hiatoplasty and Calibration

The outcomes considered were incidence of disruption of hiatal repair, incidence of postoperative new-onset dysphagia of any grade, and incidence of adverse effects (ie, esophagogastric perforation by the calibrating bougie).

Statistical Analysis

Results were analyzed by the DerSimonian-Laird (random effects) method[27] for comparing and summarizing outcomes of individual RCTs. Results were pooled as odds ratios (OR). Confidence intervals (CI) were always calculated at 95%. The alpha level was set at 0.05 for a two-tailed test. The rate difference (RD) (ie, the difference in event rates between the groups) was used as a measure of the therapeutic effect. A personally developed statistical program[28] was used for this purpose. Results were also verified using another appropriate meta-analysis software.[29] Intertrial heterogeneity in treatment effect was evaluated using the Q statistic of DerSimonian-Laird.[27] To further detect heterogeneity, a visual display was obtained, representing the results on a L'Abbè

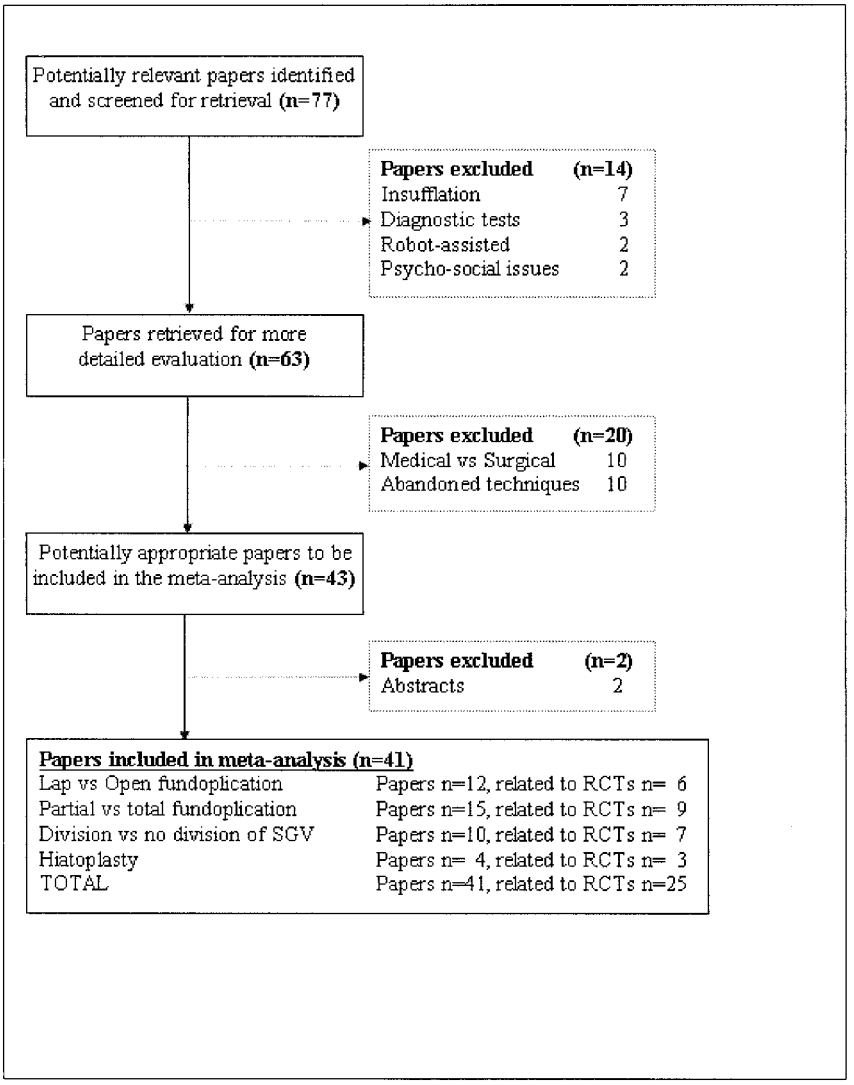

FIGURE 1. Flow diagram of papers' inclusion and exclusion according to the QUOROM statement.[25]

plot.[30] Final analyses were performed using the StatsDirect (version 1,9,8) and RevMan (version 4.2.2) statistical softwares. When significant differences were encountered, numbers needed to treat (NNT), that is the number of patients that need to be treated to obtain 1 therapeutic effect,[31] were also calculated; mathematically, NNT is equivalent to the reciprocal of RD, and the 95% CI for the NNT are the reciprocal of the 95% CI for RD. Results of continuous variables given in the trials as a mean and/or median value (length of the procedure, hospital stay, sick leave, costs) were pooled as a mean ± SD, and differences between groups were analyzed by a paired two-tail *t* test. When a specific issue was addressed by a single trial, its results where analyzed calculating absolute risk reduction (ARR), that is the difference between control event rate (CER) and experimental event rate (EER), relative risk reduction (RRR), that is the same difference divided by the CER, and number needed to treat (NNT), that is equivalent to the reciprocal of ARR.

RESULTS

Open Versus Laparoscopic Fundoplication

The results of open versus laparoscopic fundoplication were investigated in 6 RCTs: 1 from Turku, Finland,[32] 1 from Oulu, Finland,[33,34] 1 multicenter trial from the Netherlands,[35] 1 from Lund, Sweden,[36–38] another 1 from Tampere, Finland,[39] and the last 1 from Heraklion, Greece.[40] All these trials compared open versus laparoscopic Nissen fundoplication with some technical variations (Table 1). They were published between 1997 and 2002, mean (range) quality score was 3.2 (2 to 5).

TABLE 1. Details of RCTs Addressing Open Versus Laparoscopic Fundoplication

Author	Year	Period	Quality Score	Groups	No. of Patients Randomized	Hiatal Plasty	Esophageal Bougie	DSGV
Laine[32]	1997	1992–95	2	Open	55	1/55	33F	5/55
				Lap	55	4/55	33F	5/55
Heikkinen[33,34]	1999–2000	1995–96	2	Open	20	9/20	32F	17/20
				Lap	22	20/22	32F	1/22
Bais[35]	2000	1997–98	3	Open	46	Yes	no	Yes
				Lap	57	Yes	no	Yes
Nilsson[36–38]	2000–2002	1995–97	5	Open	30	Yes	36F	No
				Lap	30	Yes	36F*	No
Luostarinen[39]	2001	1994–95	3	Open	15	No	32F	No
				Lap	13	No	32F	No
Chrysos[40]	2002	1993–98	4	Open	50	Yes	60F	No
				Lap	56	Yes	60F	No

DSGV, division of the short gastric vessels; Lap, laparoscopic; NR, not reported. *Bougie used for hiatoplasty but not for wrapping.

TABLE 2. Immediate Results of RCTs Addressing Open Versus Laparoscopic Fundoplication

Author	Groups	No. of Patients Randomized	Conversion		Morbidity		Average* Length (minutes)	Average* Hospital Stay (days)	Average* Sick Leave (days)
			No.	(%)	No.	(%)			
Laine[32]	Open	55			7	(12.7)	57	6.4	37.2
	Lap	55	5	(9.1)	3	(5.5)	88	3.2	15.3
Heikkinen[33,34]	Open	20			5	(25.0)	74	5.5	44.0
	Lap	22	1	(4.5)	3	(13.6)	98	3.0	21.0
Bais[35]	Open	46			8	(17.4)	NR	NR	NR
	Lap	57	5	(8.8)	5	(8.8)	NR	NR	NR
Nilsson[36–38]	Open	30			0	(—)	109	3.0	32.0
	Lap	30	5	(16.7)	0	(—)	148	3.0	27.0
Luostarinen[39]	Open	15			0	(—)	30	5.0	30.0
	Lap	13	1	(7.7)	1	(7.7)	105	4.0	17.0
Chrysos[40]	Open	50			38	(76.0)	83	5.9	NR
	Lap	56	0	(—)	12	(21.4)	77	2.4	NR
TOTAL	Open	216			58	(26.7)	70.6	5.2	35.8
	Lap	233	17	(7.3)	24	(10.3)	103.2	3.1	20.1

*Average includes mean and median values as reported per single trial.

Considering immediate perioperative results (Table 2), no perioperative death was recorded. The need of conversion to open surgery in the laparoscopic arm arose in 17 cases (7.3%), all of which included in the original randomization arm according to an intention-to-treat analysis. Twenty-four of 233 patients submitted to laparoscopic fundoplication (10.3%) suffered at least 1 perioperative complication compared with 58 of 216 patients submitted to open fundoplication (26.7%). The pooled OR for perioperative complications in laparoscopic fundoplication was 0.33 (95% CI 0.12 to 0.90) (Fig. 2); no significant heterogeneity was found ($Q = 10.35$, $df = 5$, $P = 0.07$). The pooled RD was –12% (95% CI –30% to 6%), and pooled NNT was 8 (95% CI 3 to 16). The pooled length of the operative procedure was longer in the laparoscopic procedures (103.2 ± 27.2 minutes) than in the open ones (70.6 ± 37.5 minutes), although not significantly ($P = 0.067$). On the other hand, pooled postoperative hospital stay was significantly shorter ($P = 0.03$) in the laparoscopic

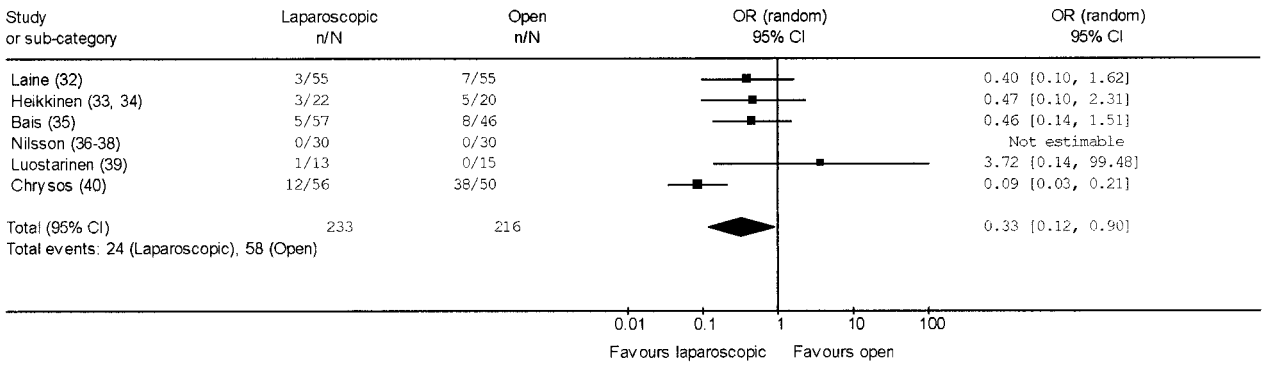

FIGURE 2. Pooled OR of operative morbidity in laparoscopic versus open Nissen fundoplication.

group (3.1 ± 0.6 days) than in the open one (5.2 ± 1.3 days), as was pooled sick leave (20.1 ± 5.2 versus 35.8 ± 6.2 days, $P = 0.03$).

Concerning postoperative results (Table 3) at the scheduled follow-up (range 3–24 months), no significant differences were found in laparoscopic versus open fundoplication regarding recurrence (pooled OR 0.80, 95% CI 0.24 to 2.68; pooled RD –0.1%, 95% CI –5% to 3%), dysphagia (pooled OR 1.16, 95% CI 0.42 to 3.20; pooled RD 1%, 95% CI –10% to 13%), bloating (pooled OR 1.21, 95% CI 0.56 to 2.63; pooled RD 1%, 95% CI –11% to 13%), and reoperation rates (pooled OR 1.74, 95% CI 0.42 to 7.25; pooled RD 1%, 95% CI –2% to 4%).

The immune system status was investigated in 3 papers related to the original trials from Turku[41] and from the Netherlands,[42,43] showing significantly reduced white blood cells counts and serum C-reactive protein levels after laparoscopic fundoplication, with no significant differences in serum cortisol levels (Table 4).

Partial Versus Total Wrap

The effects of partial versus total wrap were investigated in 9 RCTs. Six dealt with open fundoplication: 1 from Honolulu, USA;[44] 1 multicenter from France;[45] 1 from Stockolm,[46] and another from Goteborg,[47–52] Sweden; 1 from Liverpool, UK;[53] and 1 from Santiago, Chile.[54] The remaining 3 trials dealt with laparoscopic fundoplication: from Birmingham, USA;[55] from Adelaide, Australia;[56] and from Hamburg, Germany.[57,58] The details of these studies are shown in Table 5, and their results are shown in Table 6. They were published between 1974 and 2002, mean (range) quality score was 1.8 (1 to 5). Concerning the partial fundo-

TABLE 3. Postoperative Results of RCTs Addressing Open Versus Laparoscopic Fundoplication at the Scheduled Follow-Up

Author	Follow-up	Groups	Available at Scheduled Follow-up	Recurrence		Dysphagia		Bloating		Reoperations	
				No.	(%)	No.	(%)	No.	(%)	No.	(%)
Laine[32]	12 months	Open	30	3	(10.0)	4	(13.3)	2	(6.7)	0	(—)
		Lap	18	0	(—)	0	(—)	3	(16.7)	0	(—)
Heikkinen[33,34]	24 months	Open	19	2	(10.5)	11	(57.9)	10	(52.6)	0	(—)
		Lap	19	0	(—)	9	(47.4)	11	(57.9)	0	(—)
Bais[35]*	3 months	Open	46	1	(2.2)	0	(—)		NR	0	(—)
		Lap	57	2	(3.5)	7	(12.3)		NR	4	(7.0)
Nilsson[36–38]	6 months	Open	29	0	(—)	6	(20.7)	9	(31.0)	1	(3.4)
		Lap	25	0	(—)	12	(48.0)	9	(36.0)	0	(—)
Luostarinen[39]	17 months	Open	13	0	(—)	6	(46.1)		NR	0	(—)
		Lap	13	0	(—)	4	(30.8)		NR	1	(7.7)
Chrysos[40]	12 months	Open	50	1	(2.0)	2	(4.0)	3	(6.0)	0	(—)
		Lap	56	2	(3.6)	2	(3.6)	0	(—)	0	(—)
TOTAL		Open	187	7	(3.7)	29	(15.5)	24	(18.7)	1	(0.5)
		Lap	188	4	(2.1)	36	(19.1)	23	(19.5)	5	(2.6)

*Multicenter trial stopped at interim analysis because of a significantly higher incidence of dysphagia in the laparoscopic arm.

TABLE 4. Details and Results of RCTs Addressing Immune System Status in Open Versus Laparoscopic Fundoplication

		White Blood Cells		C-reactive Protein		Cortisol	
Author	**Year**	**Open**	**Lap**	**Open**	**Lap**	**Open**	**Lap**
Perttilä[41]	1999	7.2 ± 1.4	6.3 ± 1.5	89 ± 25	61 ± 41	542 ± 160	532 ± 85
Sietses[42,43]	2000–2001	7.2 ± 1.0	6.4 ± 0.3	68 ± 17	26 ± 5	465 ± 45	467 ± 42
Pooled		7.2 ± 1.1*	6.3 ± 0.9*	78.5 ± 22.3*	43.5 ± 32.4*	503.5 ± 113.2**	499.5 ± 69.7**

*P < 0.01; **$P = 0.95$.

TABLE 5. Details of RCTs Addressing Total Versus Partial Fundoplication

Author	**Year**	**Period**	**Quality Score**	**Type**	**Follow-up**	**Procedures**	**Hiatal plasty**	**Bougie**	**DSGV**	**No. of Patients**	**Esophageal Motility Disorders**
DeMeester[44]	1974	NR	1	Open	5 months	Nissen	Yes	30F	NR	15	2/15
						Hill	Yes	30F		15	6/15
Segol[45]	1989	1982–85	1	Open	2 years	Nissen	Yes	50F	NR	18	NR
						Toupet	Yes			16	
Thor[46]	1989	NR	1	Open	5 years	Nissen	No	40F	No	12	NR
						Toupet			Yes	19	
Lundell[47–52]	1991–2002	1983–91	2	Open	>3 years	Nissen	45%	no	Yes	65	10/65
						Toupet			Yes	72	17/72
Walker[53]	1992	NR	1	Open	13 months	Nissen	NR	40F	NR	26	No
						Lind				26	No
Csendes[54]	2000	1985–92	2	Open	>8 years	Nissen	Yes	30F	Yes	76	NR
						Hill	Yes	30F	Yes	88	
Laws[55]	1997	NR	1	Lap	27 months	Nissen	Yes	40F	Yes	23	Excluded
						Toupet			Yes	16	Excluded
Watson[56]	1999	1995–97	5	Lap	6 months	Nissen	Yes	52F	No	53	11/53
						Anterior	Yes		No	53	11/53
Fibbe[57,58]	2001–02	1999–2000	2	Lap	4 months	Nissen	Yes	46F	Yes	100	50/100
						Toupet			Yes	100	50/100

DSGV, division of the short gastric vessels; Lap, laparoscopic; NR, not reported.

plication arm, Toupet posterior fundoplication was evaluated in 5 of these RCTs,[45–52,55,57,58] Hill repair in 2,[44,54] Lind procedure in 1,[53] and anterior fundoplication in one.[56]

There were no perioperative deaths. No significant differences were found concerning operative morbidity in partial (40/305, 13.1%) versus total (27/288, 9.4%) fundoplication (pooled OR 1.47, 95% CI 0.84 to 2.57; pooled RD 4%, 95% CI −0.1 to 7%). The pooled length of the operative procedure was not significantly different in partial (90.2 ± 48.7 minutes) versus total fundoplication (84.2 ± 49.2 minutes). At the scheduled postoperative follow-up (range 4 months to 8 years), no significant differences were found in partial versus total fundoplication about new-onset dysphagia (9.3% versus 16.8%; pooled OR 0.56, 95%CI 0.25 to 1.22; pooled RD −5%, 95% CI −12% to 3%) and recurrence (15.1% versus 16.5%; pooled OR 0.82, 95% CI 0.53 to 1.27; pooled RD 1%, 95% CI −4% to 6%). A reoperation for failure was necessary in 4 out of 244 patients submitted to partial fundoplication (1.6%) compared with 22 out of 230 patients submitted to total fundoplication (9.6%). The pooled OR for reoperation in partial fundoplication was 0.21 (95% CI 0.06 to 0.66) (Fig. 3); no significant heterogeneity was found ($Q = 3.41$, $df = 3$, $P = 0.33$). The pooled RD was −7% (95% CI −16% to 1%) and pooled NNT was 14 (95% CI 6 to 100).

Division Versus No Division of Short Gastric Vessels

The effects of fundic mobilization by division of short gastric vessels (SGV) were investigated in 4 RCTs. One RCT related to open fundoplication was from the Tampere University

TABLE 6. Results of RCTs Addressing Total Versus Partial Fundoplication

Author	Procedures	No. of Patients	Morbidity	Average Length (minutes)	Dysphagia	Recurrence	Reoperation
DeMeester[44]	Nissen	15	2/15	NR	0/15	0/15	NR
	Hill	15	3/15	NR	0/15	1/15	NR
Segol[45]	Nissen	18	3/18	NR	1/18	0/18	NR
	Toupet	16	1/16	NR	0/16	1/16	NR
Thor[46]	Nissen	12	3/12	79	4/12	5/12	3/12
	Toupet	19	4/19	779	2/19	3/19	0/19
Lundell[47–52]	Nissen	65	0/65	NR	6/62	3/62	5/65
	Toupet	72	3/72	NR	12/71	4/71	2/72
Walker[53]	Nissen	26	8/26	NR	2/26	0/26	NR
	Lind	26	12/26	NR	4/26	0/26	NR
Csendes[54]	Nissen	76	3/76	NR	NR	29/76	NR
	Hill	88	5/88	NR	NR	33/88	NR
Laws[55]	Nissen	23	0/23	155	0/23	1/23	NR
	Toupet	16	2/16	162	0/16	0/16	NR
Watson[56]	Nissen	53	8/53	58	21/53	1/20	1/53
	Anterior	53	10/53	60	8/53	3/22	1/53
Fibbe[57,58]	Nissen	100	NR	45	18/100	18/93	13/100
	Toupet	100	NR	60	6/100	10/95	1/100
TOTAL	Nissen	388	27/288 (9.4%)	84.2	52/309 (16.8%)	57/345 (16.5%)	22/230 (9.6%)
	Partial	405	40/305 (13.1%)	90.2	32/316 (10.1%)	55/368 (14.9%)	4/244 (1.6%)

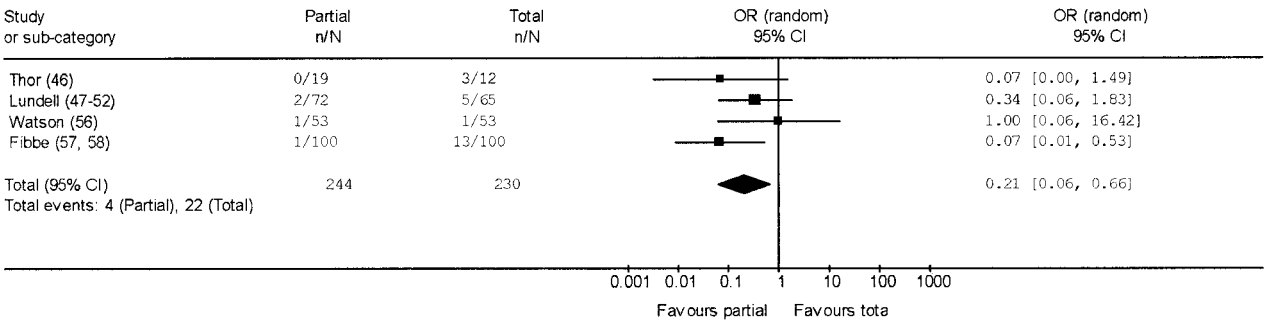

FIGURE 3. Pooled OR of reoperation for failure in partial versus total fundoplication.

in Finland,[59–61] whereas, concerning laparoscopic fundoplication, we found a trial from Adelaide, Australia;[62,63] 1 from Goteborg, Sweden;[64] and 1 from Heraklion, Greece.[65] The details of these studies are shown in Table 7, and their results are shown in Table 8.

There were no perioperative deaths. No significant differences were found in division versus no division of SGV concerning morbidity (18.7% versus 11.5%; pooled OR 1.74, 95% CI 0.76 to 3.99; pooled RD 6%, 95% CI −6% to 18%). The pooled length of the operative procedure was longer after division (105 ± 13.2 minutes) versus no division (78.3 ± 22.9 minutes) of SGV, albeit with borderline significance ($P = 0.06$). No significant differences were found in division versus no division of SGV concerning the incidence of dysphagia (24.8% versus 30.8%; pooled OR 0.72, 95% CI 0.42 to 1.21; pooled RD −6%, 95% CI −16% to 4%), and recurrence (3.9% versus 4.6%; pooled OR 0.81, 95% CI 0.27 to 2.50; pooled RD −0.2%, 95% CI −4% to 4%).

We found 3 trials comparing the use of different laparoscopic devices to divide short gastric vessels. In the first 2 trials the ultrasonic scalpel was compared with multifire clip applier,[66,67] whereas in the last trial,[68] it was compared with bipolar coagulating forceps. The details and results of these trials are shown in Table 9. No significant differences were found using the alternative device versus the ultrasonic scalpel in postoperative complications (7.0% versus 1,5%; pooled

TABLE 7. Details of RCTs Addressing Division Versus No Division of Short Gastric Vessels

Author	Year	Period	Quality Score	Type	Esophageal Bougie (French)	Esophageal Motility Disorders	Hiatal repair	No. of Patients	
								DSGV	ND
Luostarinen[59–61]	1995–96–99	1990–93	2	Open	32	Excluded	Selective	26	23
Watson[62, 63]	1997–2002	1994–95	5	Lap	52	Excluded	Routine	52	50
Blomqvist[64]	2000	NR	3	Lap	52	Excluded	Routine	52	47
Chrysos[65]	2001	NR	2	Lap	60	Excluded	Routine	24	32
TOTAL								154	152

DSGV, division of the short gastric vessels; ND, no division; Lap, laparoscopic; NR, not reported.

TABLE 8. Results of RCTs Addressing Division Versus No Division of Short Gastric Vessels

Author	Morbidity		Length (minutes)		Dysphagia		Recurrence	
	DSGV	ND	DSGV	ND	DSGV	ND	DSGV	ND
Luostarinen[59–61]	NR	NR	NR	NR	5/26	8/23	1/26	1/23
Watson[62,63]	7/52	6/50	95	71	15/52	17/50	3/52	5/50
Blomqvist[64]	15/52	5/47	120	104	11/39	15/41	1/52	1/47
Chrysos[65]	2/24	3/32	100	60	4/24	5/32	1/24	0/32
TOTAL	24/128	14/122	105	78.3	35/141	45/146	6/154	7/152
	18.7%	11.5%			24.8%	30.8%	3.9%	4.6%

DSGV, division of the short gastric vessels; ND, no division; NR, not reported.

OR 2.89, 95% CI 0.5 to 15.45; pooled RD 5%, 95% CI −2% to 12%), in length of the operation (26.6 ± 9.9 versus 19.7 ± 5.9 minutes) and in costs (552.6 ± 322.4 versus 569.7 ± 164.5 USD per single case).

Hiatoplasty and Calibration

We found no RCT comparing hiatal repair versus no repair. In one RCT from USA[69,70] the standard posterior hiatal repair was compared with a prosthetic reinforced repair in patients with large (>8 cm) hiatal hernias. In another RCT from Adelaide, Australia, the standard posterior hiatal repair was compared with an anterior repair.[71] Concerning calibration of hiatoplasty and wrapping by means of an esophageal bougie, there was 1 trial from Portland, Oregon.[72] The details and results of these trials are shown in Table 10.

DISCUSSION

The first finding of this systematic review is the complete absence of postoperative deaths in any of the RCTs, dealing either with open or laparoscopic fundoplication. Actually, both open and laparoscopic antireflux surgery entail a low but definite risk of operative mortality.[14,73,74] Actually, this rate was 0.008% (8 out of 10,489 cases) in a review of 41 laparoscopic series published between 1993 and 2000;[14] it increased to 0.09% (1 out of 1162 cases) for laparoscopic and 0.2% (9 out of 3933 cases) for open surgery in a population-based study in Finland from 1987 to 1996,[73] and to 0.8% (168 out of 20,004 cases) in a population-based study in USA from 1992 to 1997.[74] In the latter study, a volume/outcome relationship was identified, with mortality rates ranging from 1.3% among surgeons with <5 cases to 0% among surgeons with >50 cases treated during the study period. Looking at these figures, there is no doubt that postoperative mortality rates after antireflux surgery reported in case-series are affected by a publication bias. The results achieved in the RCTs analyzed in this review come from specialized centers with high caseload volumes and/or very well selected populations of patients. Whether these results are determined by a "practice makes perfect" effect or by a "selective referral" effect,[75] the possibility of postoperative mortality should be kept in mind and anticipated for the patient candidate for antireflux surgery within the everyday clinical practice of a nonspecialized surgical center.

The overall conversion rate from laparoscopic to open fundoplication in these RCTs was 7.3% and operative morbidity rate for the laparoscopic arm was 10.3%. These figures are both higher than those reported (conversion 3.1%; morbidity 6.4%) in the review of laparoscopic case-series,[74] confirming that a publication bias may be present as well.

TABLE 9. Details and Results of RCTs Addressing Division of Short Gastric Vessels by Means of Ultrasonic Scalpel Versus an Alternative Device

Author	Year	Quality Score	Alternative Device	No. of patients		Postoperative Complications		Mean Operative Time (minutes)		Cost per Single Case (USD)	
				AD	LCS	AD	LCS	AD	LCS	AD	LCS
Swanstrom[66]	1995	1	Clips	15	16	1	–	22	13	365	405
Laycock[67]	1996	1	Clips	10	10	–	–	38	24	925	734
Underwood[68]	1999	1	Bipolar	46	40	4	1	20	22	368*	570*
TOTAL			cautery	71	66	5/71	1/66	26.7	19.7	552.7	569.7

USD, United States dollars; AD, alternative device; LCS, ultrasonic scalpe. *Only the difference between the two arms was given.

TABLE 10. Details and Results of RCTs Addressing Hiatal Repair and Calibration

Author	Year	Period	Quality Score	Groups	No. of Patients	Outcome	CER	EER	ARR	RRR	NNT	95% CI
Carlson[69,70]	1999	1991–2000	2	Simple hiatoplasty	36	Recurrence	8/36	0/36	22.2%	100%	5	3 to 9
	2002			Prosthetic hiatoplasty	36							
Watson[71]	2001	1997–99	5	Posterior hiatal repair	55	Reoperation for dysphagia	6/55	0/47	10.9%	100%	10	5 to 35
				Anterior hiatal repair	47							
Patterson[72]	2000	1996–98	4	Bougie 56 F	81	Perforation	1/81	0/90	1.2%	100%	81	15 to ∞
				No bougie	90	Dysphagia	13/76	24/78	13.7%	80%	−7	−794 to −3
						Dilatation	8/81	7/90	2.1%	21%	48	9 to ∞

CER, control event rate; EER, experimental event rate; ARR, absolute risk reduction; RRR, relative risk reduction; NNT, number needed to treat; 95% CI, confidence intervals at 95%.

Open Versus Laparoscopic Fundoplication

Laparoscopic fundoplication showed a significant reduction of operative morbidity rates, hospital stay, sick-leave period (Table 1 and Fig. 1), and activation of the immune system (Table 4) when compared with its open counterpart. Only the duration of the operation seemed to be prolonged, albeit with borderline significance. It can be concluded that the immediate results of laparoscopic fundoplication are equal to or better than those of open fundoplication, confirming what was already reported in many nonrandomized comparative studies.[76–79] A short-term analysis of postoperative results at the scheduled follow-up (range 3 to 24 months) failed to show any differences concerning recurrence, dysphagia, bloating, and reoperation for failure, suggesting that, while waiting for longer follow-up, the laparoscopic approach reproduces the same results as its open counterpart. However, the only multicenter RCT[35] had to be stopped at its interim analysis due to an unacceptable rate of postoperative dysphagia in the laparoscopic arm (Table 3). The publication of this trial triggered many critiques,[80] mainly related to the low volume of cases treated per surgeon per year (about 2.7), and its authors had to admit that their results were biased by the existence of a learning curve and a maintenance curve.[80] Actually, many studies previously investigated the learning curve for the surgeon and for the institution dealing with laparoscopic fundoplication.[81–83] The issue of laparoscopic versus open fundoplication was also covered in several consensus conferences,[84–88] all reaching the conclusion that fundoplication should possibly be performed through a laparoscopic approach provided there is an expert surgeon in charge of the operation. Little or nothing is known concerning the optimal volume of cases to be treated to maintain this expert status, as no volume-outcome analysis in laparoscopic antireflux surgery is available. These considerations prompt a word of caution about the widespread application of laparoscopic antireflux surgery in nonspecialized centers.

Partial Versus Total Wrap

Before the advent of laparoscopic surgery, the Nissen procedure was considered the most successful in terms of

reflux control[4,5] and was therefore more often performed than partial fundoplications. The last decade witnessed a strong debate about partial versus total fundoplication, shifting the attention to postoperative failures due to mechanical problems (ie, dysphagia), rather than worries about the recurrence of disease. It appeared that there was a special risk for dysphagia in patients with preoperative evidence of esophageal motility disorders, and the choice between total or partial fundoplication was suggested to be tailored on the absence or presence of impaired esophageal peristalsis at the preoperative manometric assessment.[8,89,90] Surgeons began to perform partial fundoplications more frequently,[11,91] and the results of several nonrandomized trials did not confirm this hypothesis.[92–94] On the other hand, some authors still cast serious doubts regarding the effectiveness of partial fundoplication on the control of reflux,[93,95–97] and others suggest that a floppy Nissen can be effective even in patients with defective esophageal peristalsis.[98,99] In this analysis (Table 6), partial fundoplication appeared to be a better procedure than total fundoplication, showing similar operative time, morbidity and recurrence rates, but a significantly reduced rate of reoperations for failure (1.6% versus 9.6%), mainly due to postoperative dysphagia (10.1% versus 16.8%). All but 3 RCTs[45,46,54] showed an equal distribution of patients with esophageal motility disorders in this analysis (Table 5). In the most recent trial,[58] a subgroup analysis in patients with esophageal motility disorders failed to detect any difference in the occurrence of postoperative new-onset dysphagia and/or endoscopic evidence of recurrent disease. Actually, the etiology of dysphagia is multifactorial, and an abnormal preoperative manometric pattern is a poor predictor of postoperative new-onset dysphagia.[100] Should we perform more partial fundoplications based on these results? It is hard to find a final answer to this question based on current data, as several potential sources of bias are present in this analysis: first of all, many RCTs included in the analysis of this specific issue were published in the 1980s or in the early 1990s, when surgical techniques were not as well developed and standardized as they are now; second, a large body of this evidence derives from a very short follow-up period (4 to 27 months in laparoscopic RCTs); and third, it can be incorrect to pool together results of different partial repairs relying on different pathophysiologic mechanisms, such as Toupet partial fundoplication or Hill's or Lind's repairs. While there is no way to overcome the first 2 potential sources of bias, we performed a subgroup analysis including only RCTs dealing with Toupet posterior fundoplication in the partial fundoplication arm. The results (data not shown) are not different from those deriving from the entire group analysis, confirming a significantly lower rate of reoperation in the partial fundoplication arm. At the moment it seems wiser to delay the search for a final answer and wait for the results of longer follow-up.[101]

Division Versus No Division of Short Gastric Vessels

All RCTs dealing with division versus no division of short gastric vessels excluded patients with esophageal motility disorders (Table 7) to prevent any possible bias regarding the incidence of postoperative new-onset dysphagia. No significant differences were detected regarding morbidity, dysphagia, and recurrence (Table 8); routine division of short gastric vessels cannot therefore be supported anymore. As twisting deformities resulting from an unskilled attempt to wrap an immobile gastric fundus and/or a mobile gastric body around the esophagus are a major cause of failure,[102,103] it is advisable to perform complete fundal mobilization during the learning curve and in case of any doubt concerning mobility of gastric fundus.[104]

In a nonrandomized comparison, the harmonic scalpel seemed to be an extremely useful tool for the division of short gastric vessels, reducing operative time, morbidity, and costs.[105] We failed to detect any significant advantage pooling the results of 3 RCTs (Table 9), although a trend in reduction of morbidity rates was noted (1.5 versus 7.0%).

Hiatoplasty and Calibration

There are no RCTs evaluating the role of routine hiatal closure, and probably there will never be, as nonrandomized studies already show an intolerable rate of paraesophageal herniation in patients not undergoing crural repair.[106,107] Concerning the type of hiatal repair (anterior versus posterior; primary versus prosthetic) and the routine use of a bougie for calibration of the repair and of wrapping, we found only results deriving from single RCTs. Any result, therefore, should be interpreted with caution, keeping in mind that the amount of data gathered is largely insufficient to find a definitive answer to these questions, especially when faced with a large amount of data deriving from retrospective analyses and/or case-series.

Most surgeons are used to the standard posterior hiatoplasty; the group from Adelaide, Australia, described the possibility that standard posterior repair displaces the esophagus too anteriorly, therefore contributing to postoperative dysphagia.[108] The results of their RCT seem to confirm this hypothesis, with an anterior repair eliminating the risk of reoperation for dysphagia (Table 10). However, the same authors admit a potential major bias in such trial, as the incidence of reoperation in the arm treated by standard posterior repair is far too high from that previously reported in other RCTs by the same group of surgeons.[56,62]

The rates of hiatal hernia recurrence after hiatal repair during primary laparoscopic fundoplication vary between 1 and 7%, but can reach 50% when facing large and/or paraesophageal hernias. There was little doubt that any repair of large hernias should be performed with a prosthetic reinforcement,[109] and the results of one RCT[69,70] seem to confirm this

concept, with 5 patients to be treated to avoid 1 hernia recurrence (Table 10). Further research is needed to find which cut-off in hiatal hernia size mandates a prosthetic repair.[110]

The use of an esophageal bougie during hiatal closure and wrapping has long been one of the basic tenets of Nissen fundoplication[4,5] to reduce postoperative dysphagia. Moreover, we found a time-trend towards an increase in its size throughout the RCTs analyzed in this review (Tables 1, 3, and 7). However, its routine use carries the risk of iatrogenic perforation, varying around 1% of cases.[111,112] Some authors, therefore, do not recommend its routine use.[113] Looking at the only available RCT,[72] it appears that routine use of a bougie significantly reduces the rate of severe postoperative dysphagia, as defined by the authors, by 13.7%, with a 1.2% risk of iatrogenic perforation (Table 10). On the other hand, if we look at something more clinically relevant, such as the rate of postoperative dilatation, the results were higher in the group treated by routine use of the bougie. Therefore, the results of this trial have to be interpreted with caution, as they are strongly dependent upon the definition of postoperative dysphagia, and further research on this point is desirable.

CONCLUSIONS

Laparoscopic fundoplication is as effective as its open counterpart, allowing a reduced morbidity rate, shorter hospital stay, and recovery, with no significant differences in early functional results. Long-term (>5 years) follow-up, however, is needed. Partial fundoplication reduces the rate of reoperation due to mechanical failure, but longer follow-up is needed to evaluate its effectiveness in the control of reflux. There is no evidence to support routine division of short gastric vessels. Further RCTs are needed to determine the best way to perform hiatal closure (anterior versus posterior, simple versus prosthetic) and the benefit/risk ratio of routine calibration by means of an esophageal bougie. All of this evidence derives from specialized centers and from selected populations, and particular caution is therefore suggested when implementing it into everyday clinical practice.

ADDENDUM

During the review process of this manuscript, another prospective randomized trial suitable for inclusion into this meta-analysis (Chrysos E, Tsiaoussis J, Zoras OJ, et al. Laparoscopic surgery for gastroesophageal reflux disease patients with impaired esophageal peristalsis: total or partial fundoplication? J Am Coll Surg 2003;197:8-15) was published. The inclusion of data gathered from such trial into the data pooling and reanalysis did not significantly change any of the results presented in this manuscript.

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