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ADVANCES IN THE SURGICAL TREATMENT OF REFLUX DISEASE

ONTWIKKELINGEN IN DE CHIRUGISCHE BEHANDELING VAN REFLUXZIEKTE

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
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CONTENTS

1

Introduction

Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease (GORD) is one of the most prevalent benign disorders of the upper gastrointestinal tract[1] and involves a wide spectrum of disorders in which the reflux of gastric content leads to troublesome symptoms and/or lesions to the oesophageal mucosa. Defined by the Montreal definition as "a condition which develops when the reflux of the stomach content causes troublesome symptoms and/or complications".[2] Key symptoms of gastro-oesophageal reflux disease are heartburn and regurgitation. Uncommon symptoms are dysphagia and extra-oesophageal symptoms (chronic cough and dental erosions). Gastro-oesophageal reflux disease is a common upper gastrointestinal disorder and severely impairs the quality of life of patients compared with control populations[3,4] and patients with other chronic diseases.[5–7] Between 9 and 26 per cent of Europe's adult population suffers weekly from heartburn or acid regurgitation.[2,3,8]

The gastro-oesophageal junction

Reflux disease is a multifactorial disorder caused by failure of the anti-reflux mechanisms,[1] resulting in retrograde flow of gastric content into the oesophagus.[9] The gastro-oesophageal junction is a valve that separates the intrathoracic oesophageal and intra-abdominal gastric cavities. This junction consists of an intrinsic and an extrinsic sphincter.[10] The intrinsic sphincter is formed by the lower oesophageal sphincter (LOS). The crural diaphragm is attached to the distal oesophagus via the phreno-oesophageal membrane and forms the extrinsic sphincter. These intrinsic and extrinsic sphincters have an anatomical overlay at the level of the gastro-oesophageal junction which results in combined strength and a valve that divides the intrathoracic oesophagus and intra-adbominal stomach. This valve has 3 functions. The first function is to create a barrier to prevent retrograde flow of acid gastric content into the oesophagus pressed by the positive abdomen-to-thorax pressure and therefore preventing gastro-oesophageal reflux disease. The squamous mucosa of the oesophagus is vulnerable to reflux of gastric content into the oesophagus, which causes both reflux symptoms and oesophagitis. The second function is to allow passage of food and other content from the oesophagus to the stomach during swallowing. The final function of this valve is to allow excessive gas to ventilate from the stomach to the mouth by belching. This happens during transient lower oesophageal sphincter relaxations. These three functions are normally perfectly balanced to make swallowing and belching possible, while protecting the oesophagus from harmful gastric content. An ineffective valve can result in excessive gastro-oesophageal reflux, causing gastro-oesophageal reflux disease or, on the other side of the spectrum, difficulty in swallowing or belching.[1,11]

Diagnosis of GORD

Gastro-oesophageal reflux disease is diagnosed based on the presence and combination of typical symptoms such as heartburn and regurgitation with a favourable response to pharmacological therapy. The most important diagnostic test to prove the presence of GORD are 24-h pH monitoring and upper gastrointestinal endoscopy, and can be a part of the preoperative work-up for anti-reflux surgery.[2,12] Ambulatory 24-h oesophageal pH monitoring enables physicians to diagnose reflux disease by quantifying total oesophageal acid exposure time and symptom-reflux correlation.[1,13] A pH sensor is used to record reflux of acid gastric content above the gastro-oesophageal junction. Based on the percentage of time the oesophageal pH is below 4, patients can be classified as having pathological or physiological acid exposure time.[13] In addition, this investigation provides the opportunity to evaluate the temporal relationship between symptoms and acid reflux episodes. In absence of oesophagitis, the gold standard objective test to investigate whether a patient's symptoms are caused by gastro-oesophageal reflux is ambulatory 24-hour pH monitoring with symptom association analysis.[14,15] Endoscopy is an important investigation to document gastro-oesophageal reflux disease when there is mucosal damage as a sign of reflux oesophagitis.[16] Manometry is not used to diagnose reflux disease in patients with gastro-oesophageal reflux disease symptoms and candidates for anti-reflux surgery.[1] Conventional manometry enables physicians to evaluate oesophageal peristalsis and lower oesophageal sphincter pressure. It is performed prior to antireflux surgery to exclude oesophageal motility disorders such as achalasia and oesophageal spasm as alternative causes for the patient's symptoms.[1,8]

Anti-reflux surgery

Pharmacological treatment with proton pump inhibitors (PPIs) is the standard initial therapy for gastro-oesophageal reflux disease.[8] PPI therapy provides long-term control of gastro-oesophageal reflux disease in up to 95 per cent of the patients.[17,18] The remaining 5 per cent of gastro-oesophageal reflux disease patients have an incomplete response to PPIs. These patients suffer from PPI-refractory gastro-oesophageal reflux disease and are candidates for anti-reflux surgery, together with patients who are unwilling to take lifelong medication and patients with extra-oesophageal manifestations.[18–20] Laparoscopic fundoplication is the current surgical treatment of choice for gastro-oesophageal reflux disease.[8,21–23]

Nissen fundoplication

Nissen performed the first fundoplication for gastro-oesophageal reflux disease in 1956.[24] After some modifications, total fundoplication according to Nissen has become the most frequently performed operation for GORD. The procedure includes mobilisation of the distal oesophagus, division of the short gastric vessels, posterior repair of the crural diaphragm and wrapping the fundus of the stomach posteriorly around the oesophagus with a 360° circumference.[25] (Figure 1)

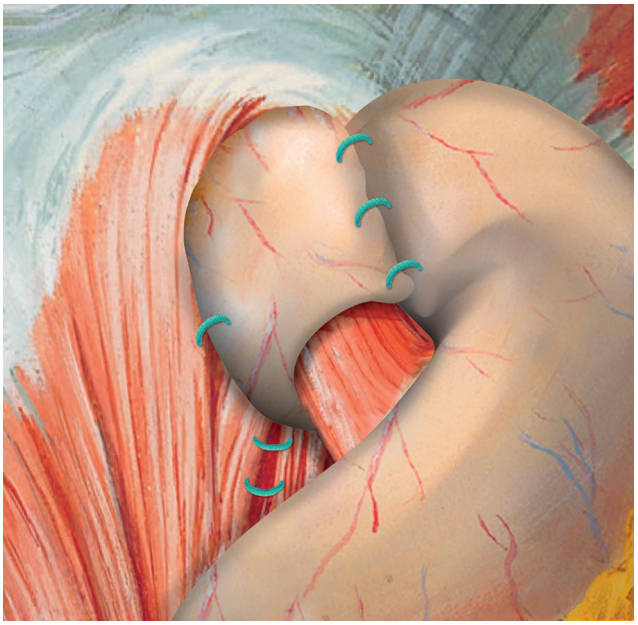

Figure 1. Nissen fundoplication

Laparoscopic Nissen fundoplication rapidly replaced conventional Nissen fundoplication after its initial report in the nineties.[26] The aim was a reduction of morbidity with similar long-term effectiveness. Results of up to 10 years have been published.[23,27] These studies demonstrate that laparoscopic Nissen fundoplication restores the anti-reflux barrier with excellent control up to 10 years of follow-up compared to its conventional counterpart.[23,27] In **chapter 2** long-term results are investigated to ensure durability of both procedures based on the 17-year outcome of a randomised clinical trial (RCT) comparing laparoscopic Nissen and conventional Nissen fundoplication.
In order to identify which patient would have a higher risk of recurrent reflux disease after Nissen fundoplication, a predictive study was carried out. The results are reported in **chapter 3**.

Partial fundoplications
Despite the good results on reflux control after Nissen fundoplication, the procedure can result in a gastro-oesphageal valve that delivers good reflux control, but might impair the two other functions. This results in post-fundoplication symptoms like difficulty in swallowing (dysphagia) and gas-related symptoms.[28–30] As many as 12 per cent of Nissen fundoplication patients develop post-fundoplication dysphagia[31,32] and up to 18 per cent develop gas-related symptoms.[31,33–35] Therefore, partial fundoplications have been developed to reduce postfundoplication symptoms like gas-related symptoms, dysphagia and belching, while maintaining reflux control.

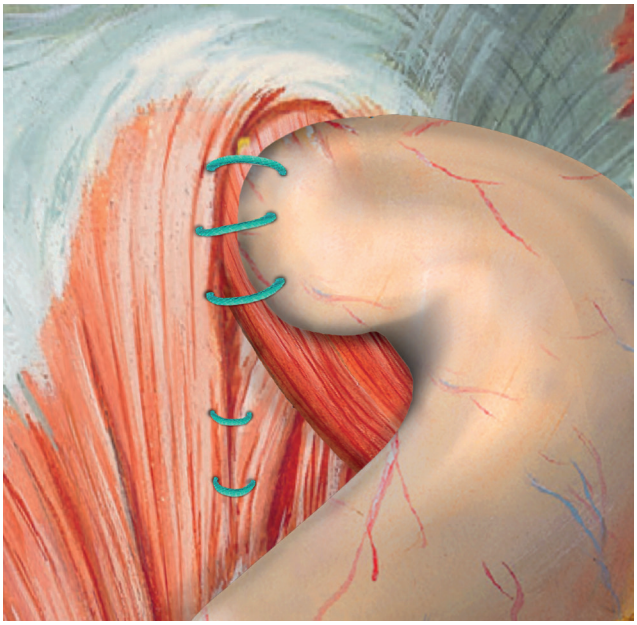

Figure 2. 180° anterior fundoplication

Laparoscopic anterior fundoplication

Jacques Dor introduced the anterior partial fundoplication.[28] (Figure 2) This anti-reflux procedure includes wrapping the fundus of the stomach anteriorly around the oesophagus. The technique was designed to reduce post-operative dysphagia and gas-related symptoms, while preserving reflux control. The modifications of this procedure that are currently used in clinical practice are laparoscopic 90°[29,30] and 180°[31] anterior fundoplication. The modified Dor fundoplication includes mobilisation of the oesophagus and posterior crural repair without division of the short gastric vessels.[32] An anterior partial wrap with a circumference of either 90° or 180° is then created.

Laparoscopic Toupet fundoplication

André Toupet introduced partial posterior fundoplication as an alternative operation for Nissen fundoplication in 1963[33] aiming to reduce dysphagia and gas-related symptoms after surgery.[34–36] The only mayor difference between a modified laparoscopic Toupet fundoplication and a Nissen fundoplication is the creation of a partial posterior wrap with a circumference of 270° instead of 360°.[37] All other steps of the fundoplication are similar. (Figure 3)

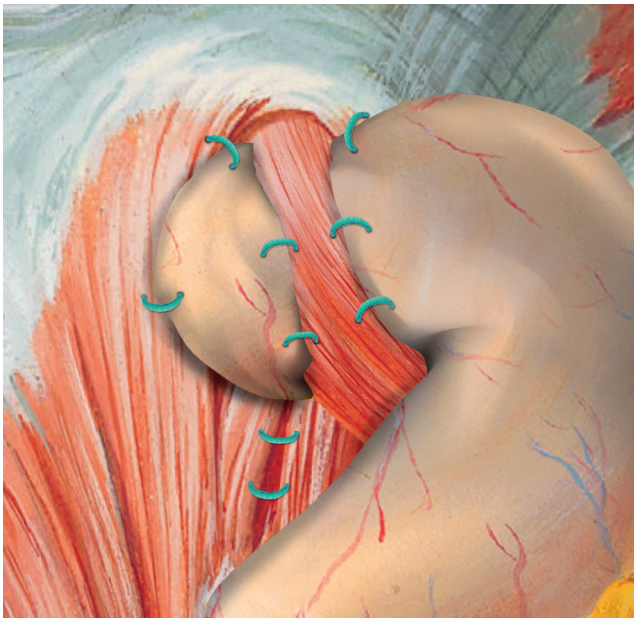

Figure 3. Toupet fundoplication

Level 1 evidence

Seven randomised clinical trials have been conducted comparing laparoscopic Nissen versus Toupet fundoplication for gastro-oesophageal reflux disease and are summarized in a systematic review and meta-analysis of these trials.[38] This meta-analysis concluded that laparoscopic Toupet fundoplication achieves similar reflux control, with a reduction of post-operative dysphagia and dilatation for dysphagia, compared to Nissen fundoplication.[38] Furthermore, reoperation rates and the presence of gas-related symptoms were lower after Toupet fundoplication, providing level 1 support for the use of Toupet fundoplication compared to Nissen.[38] Another systematic review and meta-analysis was conducted to compare all posterior fundoplications (Nissen and Toupet) with all anterior fundoplications. The results of this systematic review and meta-analysis comparing laparoscopic anterior and posterior fundoplication are given in **chapter 4**.
Chapter 5 reports the 5-year combined results of four RCTs [30,31,39,40] comparing laparoscopic 90° and 180° anterior versus Nissen fundoplication. In addition, **chapter 6** reports the results of a systematic review and meta-analysis comparing only laparoscopic 180° anterior fundoplication with Nissen fundoplication. **Chapter 7** describes the long term symptomatic outcome 12 years after a randomised clinical trial comparing Nissen and laparoscopic 180° anterior fundoplication.[40]

The results of **chapter 4, 5 and 6** raised the question which partial fundoplication achieves the best reflux control with minimal post-fundoplication symptoms. In order to find the answer a multi-centre trial was initiated and conducted in the St. Antonius Hospital in Nieuwegein and the Isala Clinics in Zwolle, the Netherlands. The results of this randomised

clinical trial, comparing laparoscopic 180° partial anterior fundoplication versus laparoscopic Toupet fundoplication are discussed in **chapter 8**.

Thesis Outline

The aim of this research was to evaluate advances in the surgical treatment of reflux disease. The following questions were addressed.

- Is laparoscopic fundoplication superior to conventional fundoplication at 17 years of follow-up?
- Does laparoscopic anterior fundoplication ensure durable reflux control with a reduction of postfundoplication symptoms compared to laparoscopic Nissen fundoplication at long term follow-up?
- Is there a difference in outcome between the laparoscopic 90° anterior and 180° anterior fundoplication?
- Which partial fundoplication (180° anterior fundoplication versus laparoscopic Toupet fundoplication) achieves the best reflux control with minimal postfundoplication symptoms when compared in a randomised clinical trial?

REFERENCES

1. Fuchs KH, Babic B, Breithaupt W, et al. EAES recommendations for the management of gastroesophageal reflux disease. Surg Endosc Other Interv Tech. 2014;28(6):1753-1773.

2. Vakil N, Van Zanten S V., Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: A global evidence-based consensus. Am J Gastroenterol. 2006;101(8).

3. Dent J, El-Serag HB, Wallander M-A, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2005;54(5):710-717.

4. McDougall NI, Johnston BT, Kee F, Collins JS, McFarland RJ, Love a H. Natural history of reflux oesophagitis: a 10 year follow up of its effect on patient symptomatology and quality of life. Gut. 1996;38(4):481-486.

5. Dimenas E. Methodological aspects of evaluation of quality of life in upper gastrointestinal diseases. Scandanavia J Gastroenterol. 1993;28(Suppl 199):18.

6. Revicki DA, Wood M, Maton PN, Sorensen S. The Impact of Gastroesophageal Reflux Disease on Health-related Quality of Life. 9343(17).

7. Stewart AL, Greenfield S, Hays RD, et al. Functional status and well-being of patients with chronic conditions. Results from the Medical Outcomes Study. J Am Med Assoc. 1989;262:907-913.

8. Scheffer R, Bredenoord A, Smout A. Richtlijn gastro-oesofageale refluxziekte. Ned Ver Maag-Darm-Leverartsen. 2010.

9. Dent J, Armstrong D, Delaney B, Moayyedi P, Talley NJ, Vakil N. Symptom evaluation in reflux disease: workshop background, processes, terminology, recommendations, and discussion outputs. Gut. 2004;53 Suppl 4:iv1-24.

10. R.K. M, D.H. B. The esophagogastric junction. N Engl J Med. 1997;336(13):924-932.

11. Zaninotto G, DeMeester TR, Schwizer W, Johansson K-E, Cheng S-C. The lower esophageal sphincter in health and disease. Am J Surg. 1988;155(1).

12. Stefanidis D, Hope W, Kohn G, Reardon P, Richardson W FR. SAGES Guideline committee (2010) SAGES guidelines for surgical treatment of GERD. Surg Endosc. 2010;24(11):2647-2669.

13. Johnson LF, Demeester TR. Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. Am J Gastroenterol. 1974;62(4):325-332.

14. Wiener GJ, Richter JE, Copper JB, Wu WC, Castell DO. The Symptom Index: A Clinically Important Parameter of Ambulatory 24 Hour Esophageal pH Monitoring. Am J Gastroenterol. 1988;83(4):358-361.

15. Weusten BL, Roelofs JM, Akkermans LM, Van Berge-Henegouwen GP, Smout a J. The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. Gastroenterology. 1994;107(6):1741-1745.

16. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut. 1999;45(2):172-180.

17. Klinkenberg-Knol EC, Nelis F, Dent J, et al. Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety, and influence on gastric mucosa. Gastroenterology. 2000;118(4):661-669.

18. Bredenoord AJ, Dent J. Proton pump inhibitor-therapy refractory gastro-oesophageal reflux disease patients, who are they? Gut. 2007;56(4):593-594.

19. Spechler SJ, Lee E, Ahnen D, et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease - Follow-up of a randomized controlled trial. Jama-Journal Am Med Assoc. 2001;285(18):2331-2338.

20. Vakil V. Review article: The role of surgery in gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2007;25(12):1365-1372.

21. Schijven MP, Gisbertz SS, Van Berge Henegouwen MI. Laparoscopic surgery for gastro-esophageal acid reflux disease. Best Pract Res Clin Gastroenterol. 2014;28(1):97-109.

22. Draaisma WA, Rijnhart-de Jong HG, Broeders IAMJ, Smout AJPM, Furnee EJB, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. Ann Surg. 2006;244(1):34-41.

23. Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. Ann Surg. 2009;250(5):698-706.

24. NISSEN R. [A simple operation for control of reflux esophagitis]. Schweiz Med Wochenschr. 1956;86(Suppl 20):590-592.

25. Jamieson GG, Duranceau A. What is a nissen fundoplication? Surg Gynecol Obstet. 1984;159(6):591-593.

26. Dallemagne B, Weerts JM, Jehaes C, Markiewicz S LR. Laparoscopic Nissen fundoplication: preliminary report. Surg Laparosc Endosc. 1991;1:138-143.

27. Draaisma WA, Rijnhart-de Jong HG, Broeders IAMJ, Smout AJPM, Furnee EJB, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. Ann Surg. 2006;244(1):34-41.

28. Dor J, Humbert P, Paoli JM, Miorclerc M AJ. Treatment of reflux by the so-called modified Heller-Nissen technic. Press Med. 1967;75(50):2563-2565.

29. Krysztopik RJ, Jamieson GG, Devitt PG, Watson DI. A further modification of fundoplication: 90 degree Anterior fundoplication. Surg Endosc Other Interv Tech. 2002;16(10):1446-1451.

30. Watson DI, Jamieson GG, Lally C, et al. Multicenter, prospective, double-blind, randomized trial of laparoscopic nissen vs anterior 90 degrees partial fundoplication. Arch Surg. 2004;139(11):1160-1167.

31. Watson DI, Jamieson GG, Pike GK, Davies N, Richardson M, Devitt PG. Prospective randomized double-blind trial between laparoscopic Nissen fundoplication and anterior partial fundoplication. Br J Surg. 1999;86(1):123-130.

32. Gatenby PAC, Bright T, Watson DI. Anterior 180 degree Partial Fundoplication-How I Do It. J Gastrointest Surg. 2012;16(12):2297-2303.

33. Toupet A. Technic of esophago-gastroplasty with phrenogastropexy used in radical treatment of hiatal hernias as a supplement to Heller's operation in cardiospasms. Mem Acad Chir (Paris). 1963;89:384-389.

34. Lundell L, Abrahamsson H, Ruth M, Rydberg L, Lönroth H, Olbe L. Long-term results of a prospective randomized comparison of total fundic wrap (Nissen-Rossetti) or semifundoplication (Toupet) for gastro-oesophageal reflux. Br J Surg. 1996;83(6):830-835.

35. Thor KB, Silander T. A long-term randomized prospective trial of the Nissen procedure versus a modified Toupet technique. Ann Surg. 1989;210(6):719-724.

36. Granderath FA, Kamolz T, Granderath UM, Pointner R. Gas-related symptoms after laparoscopic 360 Nissen or 270 Toupet fundoplication in gastrooesophageal reflux disease patients with aerophagia as comorbidity. Dig Liver Dis. 2007.

37. Katkhouda N, Khalil MR, Manhas S, et al. Andre Toupet: surgeon technician par excellence. Ann Surg. 2002;235(4):591-599.

38. Broeders JAJL, Mauritz FA, Ali UA, et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. Br J Surg. 2010;97(9):1318-1330.

39. Spence GM, Watson DI, Jamiesion GG, Lally CJ, Devitt PG. Single center prospective randomized trial of laparoscopic Nissen versus anterior 90 degrees fundoplication. J Gastrointest Surg. 2006;10(5):698-705.

40. Baigrie RJ, Cullis SNR, Ndhluni a J, Cariem A. Randomized double-blind trial of laparoscopic Nissen fundoplication versus anterior partial fundoplication. Br J Surg. 2005;92(7):819-823.

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2

Seventeen-year outcome of a randomized clinical trial comparing laparoscopic and conventional Nissen fundoplication: a plea for patient counselling and clarification

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ABSTRACT

Objective
To analyze long-term outcome of a randomized clinical trial comparing laparoscopic (LNF) and conventional Nissen fundoplication (CNF) for the treatment of gastroesophageal reflux disease (GERD).

Summary Background Data
LNF has replaced CNF, based on positive short- and mid-term outcome. Studies with a follow-up of over 15 years are scarce, but desperately needed for patient counselling.

Methods
Between 1997 and 1999, 177 patients with proton pump inhibitor (PPI)-refractory GERD were randomized to CNF or LNF. Data regarding the presence of reflux symptoms, dysphagia, general health, PPI use and need for surgical reintervention at 17 years are reported.

Results
A total of 111 patients (60 LNF, 51 CNF) were included. Seventeen years after LNF and CNF, 90% and 95% of the patients reported symptom relief, with no differences in GERD symptoms or dysphagia. Forty-three and 49% of the patients used PPI's (NS). Both groups demonstrated significant improvement in general health (77% vs. 71%, NS) and quality of life (75.3 vs. 74.7, NS). Surgical reinterventions were more frequent after CNF (18% vs. 45%, *P*=0.002), mainly due to incisional hernia corrections (3% vs. 14%, *P*=0.047).

Conclusions
The effects of LNF and CNF on symptomatic outcome and general state of health remain for up to 17 years after surgery, with no differences between the two procedures. CNF carries a higher risk of surgical reintervention, mainly due to incisional hernia corrections. Patients should be informed that 17 years after Nissen fundoplication, 60% of the patients are off PPI's, and 16% require reoperation for recurrent GERD and/or dysphagia.

INTRODUCTION

Fundoplication is considered the standard surgical procedure for patients diagnosed with objectified proton pump inhibitor (PPI)-refractory gastroesophageal reflux disease (GERD). Since its introduction in 1991,[1] laparoscopic 360° total (Nissen) fundoplication (LNF) demonstrated excellent short-term results, with a significant reduction in perioperative morbidity and recovery time compared to conventional Nissen fundoplication (CNF).[2] However, since the introduction of Nissen fundoplication for the surgical treatment of GERD, concerns have been raised about long-term sustainability of the beneficial effect, both in terms of subjective and objective outcome. This has induced reluctance to refer patients for surgery by general practitioners, internists and gastroenterologists.[3, 4]
Previously, our group reported the three-months,[5] five-[6] and 10-year[7] subjective and objective outcome of a multicenter randomized clinical trial (RCT) performed between 1997 and 1999 in the Netherlands. In this clinical trial, 177 patients were included and randomized to either laparoscopic (LNF) or conventional Nissen fundoplication (CNF). At five years, no significant differences in subjective and objective outcome after LNF and CNF were found, and 15% and 12% of the patients respectively underwent surgical reintervention.[6] At 10-years, twice as many patients underwent reoperation after CNF than after LNF (15% versus 35%, *P*=0.006), with no differences in reoperation for recurrent GERD and/or dysphagia, and comparable outcome in terms of GERD symptoms, PPI use, quality of life and objective reflux control.[7] These findings have been confirmed by Salminen et al, who published the 11-year outcome of their RCT comparing LNF and CNF (n=110), with no differences in subjective outcome between the two groups, despite a higher incidence of incisional hernia and endoscopically diagnosed insufficient wraps after CNF compared to LNF.[8] Recently, Salminen et al. published the results of 15-year follow-up of this RCT (n=86), which were in line with the outcome at 11 years.[9] The present study is the largest RCT comparing LNF and CNF and provides the longest follow-up duration, with special emphasis on control of reflux symptoms, general health, need for medical treatment and reoperation rate at 17 years.

METHODS

Study Design and Participants

Between 1997 and 1999, 177 patients were included in a multicenter RCT and underwent either LNF or CNF for PPI-refractory GERD in one of the participating tertiary centers (n=98, LNF; n=79, CNF).[5] After three months follow-up was available in 103 patients (n=57, LNF; n=46, CNF), an interim analysis demonstrated a significantly higher incidence of dysphagia requiring endoscopic dilatation or surgical reintervention after LNF compared to CNF, and the trial was therefore prematurely terminated.[5] In the period between the interim analysis and the termination of the trial, another 64 patients had been randomized and were subsequently operated, bringing the total number of included patients to 167

(n=93, LNF; n=74, CNF). All 167 patients underwent symptomatic and objective evaluation, including esophageal manometry and 24-hr pH-monitoring, at three-months follow-up. At five years, 151 patients were eligible for evaluation of symptomatic outcome using validated questionnaires, and esophageal manometry and 24-hr pH-monitoring (n=8 lost to follow-up, n=4 died, n=4 emigrated).[6] Of these 151 eligible patients, three refused further follow-up. Therefore, at five years, clinical outcome was available in 148 patients (n=79, LNF; n=69, CNF). At 10 years, two patients had died within the CNF-group, consequently clinical 10-year outcome was available for 146 patients (n=79, LNF; n=67, CNF).[7] All patients were identified 17 years after surgery and have been included in the present study. The CONSORT analysis of five- and 10-year follow-up and 17-year follow-up are described in detail in Figure 1A and 1B respectively.

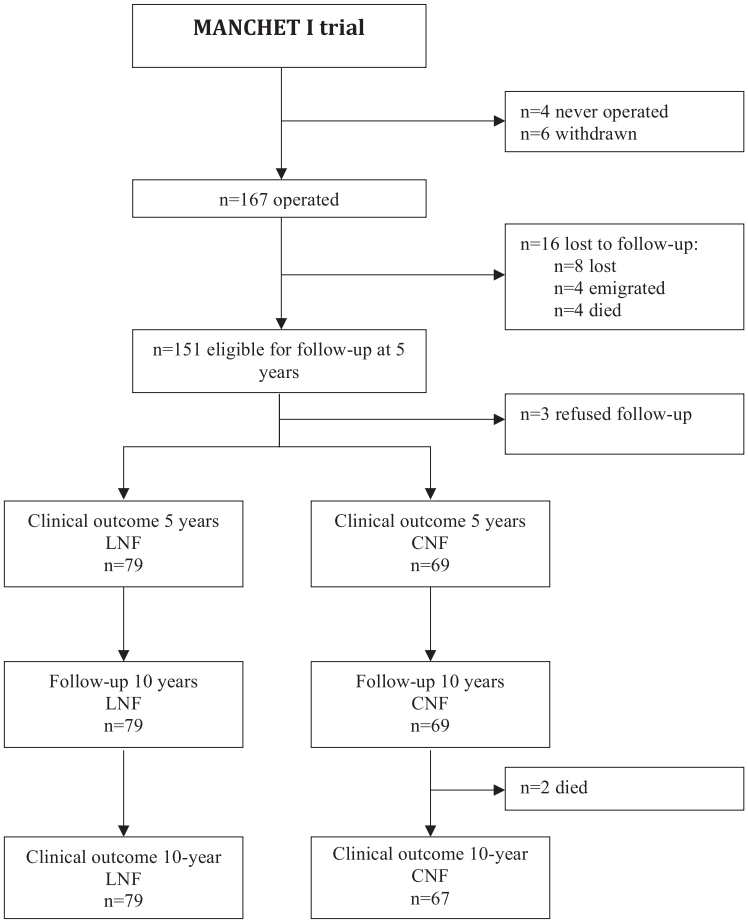

Figure 1A. Study Profile: CONSORT Analysis 5- and 10-Year Follow-Up.

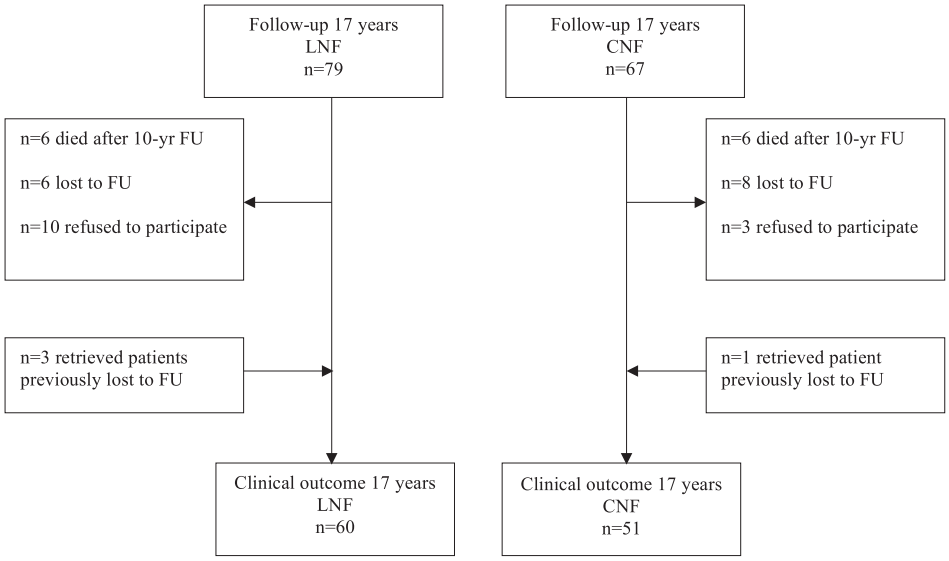

Figure 1B. Study Profile: CONSORT Analysis 17-Year Follow-Up

All patients were contacted by mail and asked to complete questionnaires on reflux symptoms, general state of health, quality of life (QoL), patient satisfaction, use of acid suppressing drugs, and the need for surgical reintervention.

Surgical Procedures

All primary fundoplications were performed between January 1997 and August 1999 in the participating tertiary centers.[5] After division of the short gastric vessels, full esophageal mobilization, and posterior crural repair using non-absorbable sutures, a floppy 360° total fundoplication of 2.5 to 3.0 cm was constructed in both the LNF- and CNF-group. Open surgery was performed using a standard upper midline incision.

Clinical Outcome

Clinical outcome, including the use of acid suppressing drugs, the need for surgical reintervention, the interval between primary fundoplication and reintervention, the indication for and type of reintervention, and the Visick scores, were registered at 17 years of follow-up.

To enable direct comparison of subjective outcomes at the different follow-up periods, the same questionnaires were used preoperatively, at three months, five years, 10 years and 17 years after surgery. The Visick score was used for analyzing the subjective effect of surgery, since it has been demonstrated to correlate well with a validated questionnaire for reflux symptoms and provides valuable insight in the overall appreciation of antireflux surgery by patients.[10-12] Patients were asked to rate the effect of surgery on reflux

symptoms using the modified Visick grading as follows: complete resolution (Visick I), improvement (Visick II), no effect of surgery (Visick III), and deterioration (Visick IV) compared to their preoperative symptoms. Using a combined frequency and severity grading system, resulting in grades ranging from 0 (no symptom) to 3 (frequent and severe), the presence of heartburn, regurgitation and dysphagia was assessed.[13] Furthermore, the presence and frequency of nausea, vomiting and increased flatulence were monitored.

A visual analogue scale (VAS) validated for the QoL assessment following esophageal surgery,[14] was used to assess the impact of surgery on the QoL. The scale ranged from 0 to 100, with 0 representing worst possible health and 100 representing perfect health.[15] The effect of surgery on self-rated change in general health was measured using a 3-point scale ranging from "improved" to "worsened". Finally, patients were asked if they would opt for surgery again in retrospect.

Statistics

All data were entered in a computerized database and analyzed using the statistical software package SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA). All data were analyzed based on the intention-to-treat principle. Per-protocol analysis was also performed in order to examine possible changes between the two groups based upon the surgical procedure patients had undergone. Data were expressed as mean ± standard deviation (SD) or total number of patients (%), unless stated otherwise. The Chi square test was used for comparing binary variables between groups, and the Mann-Whitney U test for continues variables. Kaplan-Meier analysis was used to evaluate the surgical reintervention rate during the 17-year follow-up period. Statistical significance was defined as $P<0.05$.

RESULTS

Overall Responses and Completeness of Follow-Up

Baseline characteristics of included patients were available and comparable for both groups (Table 1). Six patients (7.6%) required conversion to an open procedure and were maintained in the LNF-group based on the intention-to-treat principle. The mean time to follow-up was 17.8 (0.9) years after LNF and 17.7 (0.9) years after CNF.

Of the patients in the LNF group with 10-year clinical outcome (n=79), six patients died and six were lost to follow-up. In the CNF-group (n=69), also six patients died and seven were lost to follow-up (Figure 1B). Additionally, four patients who had been lost to follow-up at 10 years were contacted at 17 years and included in the present study (n=3, LNF; n=1, CNF). Therefore, a total of 124 patients were available for evaluation 17 years after surgery (n=70, LNF; n=54, CNF). Of these 124 patients, data on clinical outcome could be retrieved for 111 patients (90%; n=60, LNF; n=51, CNF), of whom 105 completed the questionnaires. (n=58, LNF; n=47, CNF). Thirteen patients refused to participate in the present study.

Table 1. Baseline Characteristics According to Treatment Allocation.

	LNF	CNF
Patients (n)	60	51
Sex (male / female)	35/25	33/18
Age (yr.)	41.0 (12.6)	41.8 (11.3)
BMI (kg/m2)	26.0 (4.5)	27.1 (3.7)
Conversion rate	6 (7.6%)	-
Follow-up interval (yr.)	17.8 (0.9)	17.7 (0.9)

All data are expressed as mean (SD) or n (%)

Symptomatic Outcome

There was no difference in improvement of reflux symptoms after surgery between the two groups, with 57 of 60 patients (95%) reporting their reflux symptoms to be either resolved or improved (Visick I + II resp.) after LNF, and 46 of 51 (90%) patients after CNF (*P*=0.24; Table 2). After LNF, 54 of the 58 patients (93%) who completed the questionnaires reported no or mild symptoms of heartburn, which did not differ between the two groups (39/47 [83%], CNF, *P*=0.41). No or mild regurgitation was reported in 97% after LNF and 90% after CNF (*P*=0.28). There was no difference in the incidence of troublesome dysphagia 17 years after LNF and CNF, with no or mild dysphagia reported in 84% and 85% of the patients respectively (*P*=0.79). The incidence of troublesome nausea, vomiting and increased flatulence also did not differ between the two groups (17% vs. 15%, *P*=0.78; 7% vs. 15%, *P*=0.31; and 41% vs. 45%, *P*=0.98 respectively). Per-protocol analysis did not change these results.

Both groups demonstrated a similar general state of health at 17 years, with 77% and 71% of the patients reporting that their general state of health had improved compared to the preoperative state after LNF and CNF respectively, with similar mean QoL VAS scores (Table 3, 75.3 [13] vs. 72.4 [20], *P*=0.75). Both LNF and CNF resulted in a significant increase in QoL at 17 years compared to the preoperative state (both *P*<0.001, Figure 2). Seventeen years after LNF and CNF, 82% and 69% of the patients answered that they would opt for surgery again in retrospect (*P*=0.41), and there was no difference between the two groups in the use of acid suppressing drugs (42% vs. 49%, *P*=0.44). In the LNF group, 25 patients (42%) were dependent on daily use of acid suppressing drugs, of whom two reported typical reflux symptoms with no relief compared to the preoperative state (Visick grade III), and 23 reported their reflux symptoms to be either completely resolved or improved (Visick grades I and II). Within the CNF group, 25 patients (49%) were dependent on daily acid suppressing medication, of whom one reported no relief of reflux symptoms compared to the preoperative state (Visick III) and three reported worsening of the symptoms (Visick IV). Despite the fact that in both groups the usage of acid suppressing medication increased at 17 years compared to the use three months after surgery (3 months vs. 17 years postoperative *P*<0.001 for both groups), the usage at 17 years was significantly lower compared to the preoperative state (Figure 4, *P*<0.001 and

P=0.001). Changes in the use of acid suppressing medication during 17-year follow-up are described in Figure 3. Per-protocol analysis did not change these results.

Surgical Reintervention

Within the group of patients in whom clinical outcome was available at 17 years, 11 of the 60 patients (18%) and 23 of the 51 patients (45%) had undergone one or more surgical reinterventions after LNF and CNF respectively (*P*=0.002). The specification of surgical reinterventions reported by the included patients at 17 years is provided in table 4. Overall, 18 of the 111 patients (16%) underwent surgical reintervention for recurrent GERD and/or persistent dysphagia, with no significant differences between the groups (7/60 [12%] vs. 11/51 [22%], *P*=0.16). Based on the available clinical outcome at 17 years, there was a higher rate of surgical reintervention for incisional hernia after CNF compared to LNF (7/51 [14%] vs. 2/60 [3%], *P*=0.047). In the per-protocol analysis, this difference was significant as well (1/54 [2%] vs. 8/57 [14%], *P*=0.032).

Table 2. Self-Rated Change in Reflux Symptoms Compared to Preoperative State and Grades of Heartburn, Regurgitation, and Dysphagia at 17 Years.

	LNF (n=60)	**CNF** (n=51)
Self-rated change in reflux symptoms, n (%)		
Visick I: resolved	30 (50%)	27 (53%)
Visick II: improved	27 (45%)	19 (37%)
Visick III: unchanged	2 (3%)	1 (2%)
Visick IV: worsened	-	4 (8%)
Heartburn, n (%)		
Grade 0	30 (52%)	22 (47)
Grade 1	24 (41%)	18 (38%)
Grade 2	1 (1.7%)	3 (6%)
Grade 3	-	1 (2%)
Regurgitation, n (%)		
Grade 0	43 (74%)	34 (72%)
Grade 1	13 (22%)	9 (19%)
Grade 2	2 (3%)	2 (4%)
Grade 3	-	3 (6%)
Dysphagia, n (%)		
Grade 0	26 (45%)	26 (55%)
Grade	23 (40%)	15 (32%)
Grade2	4 (7%)	4 (8%)
Grad 3	1 (2%)	1 (2%)

No or mild symptoms = grade 0 and 1

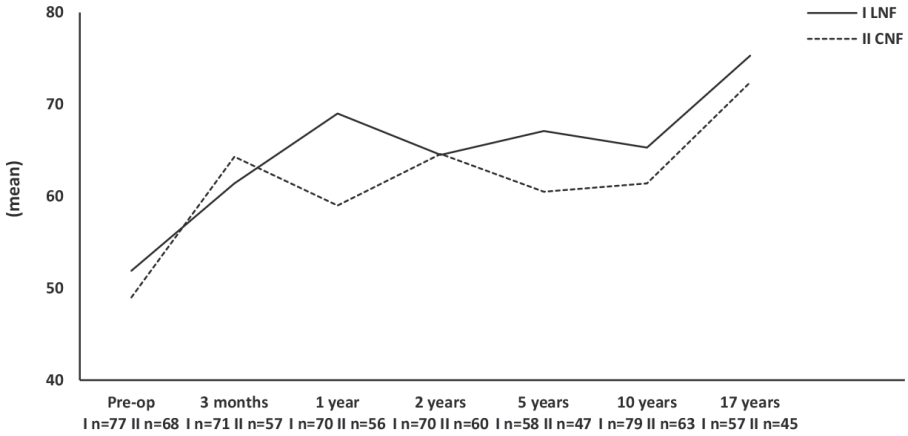

Figure 2. Mean Quality of Life (VAS 0-100) During 17-Year Follow-Up After LNF and CNF.

Nine patients (n=3, LNF; n=6, CNF) who had been included in the 10-year study and undergone surgical reintervention within 10 years after surgery, were lost to follow-up (n=7) or had died (n=2) in the period between 10 and 17-year follow-up. Reinterventions and their indications included re-Nissen for recurrent GERD and/or persistent dysphagia (n=1 LNF; n=2 CNF), Belsey-Mark IV for recurrent reflux and/or persistent dysphagia (n=1, LNF; n=1, CNF), and correction of incisional hernia (n=1, LNF; n=3, CNF). When these patients were added to the present analysis, a total of 43 surgical reinterventions had been performed in 120 patients (14/63 [22%], LNF; 29/57 [51%], CNF, *P*=0.001) during the entire 17-year follow-up period, with correction of incisional hernia in 10 patients after CNF, compared to three after LNF (*P*=0.028; see Figure 4, Supplemental Digital Content 1, demonstrating the percentage of patients undergoing surgical reintervention after LNF and CNF during 17 year follow-up (Kaplan-Meier analysis, one-minus-survival). Of the patients who used acid suppressing drugs 17 years after surgery, more had undergone surgical reintervention compared to those not using acid suppressing medication (24/50 [48%] vs. 10/51 [20%], *P*<0.001). Surgical reintervention for GERD and/or dysphagia was more frequently performed in this group compared to patients not using acid suppressing drugs (16/50 vs. 2/51, *P*=0.013). Per-protocol analysis did not significantly alter these results.

In order to analyze the risk for selection bias, baseline characteristics were compared between patients who responded to the questionnaires and those who did not. Patients who did not respond to the questionnaires were more often male than female (83% vs. 17%, *P*=0.024), had a lower mean age (53 [8] vs. 60 [12] years, *P*=0.016) and did not undergo more surgical reinterventions up to 10 years of follow-up. These findings suggest that the risk for selection bias in the present study is low.

Table 3. General State of Health, Quality of Life, and Patient Satisfaction at 17 Years.

	LNF (n=60)	**CNF** (n=51)
General state of health, n (%)		
Improved	44 (77%)	34 (72%)
Unchanged	6 (11%)	6 (13%)
Worsened	7 (12%)	8 (17%)
General QoL (VAS-score 0-100)*	75.3 (13)	72.4 (20)
Opt for surgery again in retrospect, n (%)		
Yes	49 (85%)	35 (74%)
No	6 (10%)	7 (15%)
Unsure	3 (5%)	5 (11%)
Use of daily acid-suppressing medication, n (%)	25 (42%)‡	25 (49%)§

* Data are expressed as mean (SD). † P=0.045. ‡ P<0.001 versus preoperative use. §P=0.001 versus preoperative use

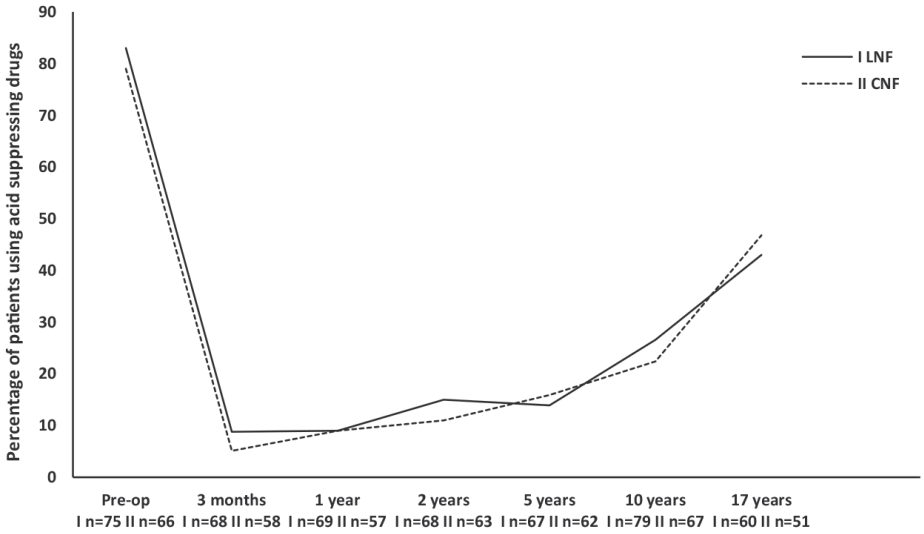

Figure 3. Changes in Use of Acid-Suppressing Medication (Percentage of Patients) During 17-Year Follow-Up.

Table 4. Surgical Reinterventions Performed During 17-Year Follow-Up

	LNF (n=60)	**CNF** (n=51)
Surgical reintervention, n (%)	11 (19%)	23 (45%)*
Mean time to reintervention (months)	51 (69)	74 (60)
Indication for reintervention (n)		
Recurrent GERD	3	5
Persistent dysphagia	3	2
Recurrent GERD and persistent dysphagia	1	4
Incisional hernia	2	7†
Abdominal pain	1	2
Paraesophageal hernia	0	2
Gastric perforation	1	0
Barrett's esophagus	0	1
Type of reoperation (n)		
Re-Nissen	5	8
Belsey-Mark IV	2	2
Conversion to partial fundoplication	0	1
Correction incisional hernia	2	7†
Adhesiolysis	1	1
Paraesophageal hernia repair	0	2
Esophagectomy	0	1
Other	1	1

All data are expressed as mean (SD) or n (%). * P=0.002 versus LNF. † P=0.047 versus LNF

DISCUSSION

As occurred with other abdominal surgical procedures after the introduction of laparoscopy, the conventional Nissen fundoplication was rapidly replaced by its laparoscopic counterpart. This occurred despite the fact that the previously mentioned interim analysis of this trial demonstrated a higher risk for troublesome dysphagia requiring endoscopic dilatation or surgical reintervention after LNF compared to CNF,[5] and one-year outcome of another RCT comparing LNF and CNF was not yet available.[16] The most important reason for this transition was the reduced short-term morbidity rate associated with laparoscopy and number of days till return to normal activity compared to the conventional approach, which has been confirmed by recent meta-analyses.[17, 18] Currently, laparoscopic Nissen fundoplication is the most frequently performed type of fundoplication worldwide.

In the present study, 17-year symptomatic outcome and the need for surgical reintervention of patients included in the largest RCT comparing LNF and CNF are reported.

We demonstrated no differences between the two procedures in improvement of reflux symptoms at 17 years after LNF and CNF, with 90 to 95% of the patients reporting their reflux symptoms to be either completely resolved or significantly improved compared to the preoperative state. Additionally, the symptoms heartburn and regurgitation were either totally absent or only present in a mild form in 83 to 93% and 90 to 97% of the patients respectively, with no differences between the two procedures. In 2012, Salminen et al published the 15-year outcome of their Finnish RCT comparing laparoscopic with conventional Nissen fundoplication, including 86 patients in whom symptomatic outcome was available.[9] Since preoperative symptom-scores were not available in their study, the effect of fundoplication on reflux symptoms could not be determined. Our findings regarding the prevalence and grading of reflux symptoms at 17 years following surgery compare favorably with those reported in their 15-year outcome study, in which approximately 77% of the patients reported to be either asymptomatic or only experiencing mild symptoms of heartburn or regurgitation.

This significant improvement in reflux symptoms 17 years after surgery is supported by the reported decrease in use of acid suppressing drugs after LNF and CNF compared to the preoperative state. However, 17 years after primary fundoplication, 42 to 49% of the patients reported to use acid suppressing drugs. Compared to the use three months after surgery, the number of patients using daily acid suppressing medication at 10 and 17 years after surgery is significantly higher, indicating a progressive increase in use of acid suppressing drugs with extension of follow-up.[5, 7] This is supported by the study of Salminen et al, reporting that 46.5% of the included patients had reinstated PPI use 15 years after surgery.[9] Therefore, if primary indication for Nissen fundoplication is unwillingness of patients to take life-long acid suppressing medication, the success rate is around 60%.

However, these findings should be interpreted with caution, since it is has been demonstrated that only a small portion of the patients using acid suppressing medication after antireflux surgery is diagnosed with abnormal esophageal acid exposure on 24-hr pH-monitoring.[6, 19, 20] Indeed, in the current RCT, 65% of the patients using PPIs on a daily basis had no objectified pathological esophageal acid exposure at 10 years.[7] Possible explanations for the increase in use of acid suppressing drugs include continues use by patients despite absence of typical reflux symptoms, and prescription of acid suppressing drugs to provide gastric protection for concurrent medication, such as nonsteroidal anti-inflammatory drugs (NSAIDS) and platelet inhibitors.[21]

Three-months results of the present trial demonstrated a higher incidence of dysphagia requiring endoscopic dilatation or surgical reintervention after LNF,[5] most likely caused by a relative lack of experience with laparoscopic fundoplication by the participating surgeons at the start of this trial. Symptomatic outcome at 5- and 10-years demonstrated no difference in reported dysphagia between LNF and CNF,[6, 7] and our present 17-year findings demonstrate these results are maintained during long-term follow-up, with approximately 85% of the included patients reporting absence or the presence of only mild dysphagia with no differences between the two procedures. The initial higher

incidence of dysphagia in the early postoperative period after LNF compared to CNF,[22-24] and the decrease in incidence of dysphagia with extension of follow-up, has also been described by other RCTs comparing outcome of LNF with CNF.[23, 25, 26]

At 17 years, surgical reintervention was more frequently performed after CNF compared to LNF. The main reason for this difference (18% vs. 45%) is the higher incidence of symptomatic incisional hernia following CNF. Whilst at five-years follow-up of the present trial no significant difference in the need for surgical reintervention between the two groups was found,[6] significantly more patients required surgery for symptomatic incisional hernia after CNF at 10- and 17-year follow-up.[7] The current study is the first RCT to demonstrate that laparoscopic antireflux surgery reduces the number of incisional hernia corrections compared with upper midline incision in non-obese patients. This is an important finding, again underlining the long-term benefit of laparoscopic surgery compared to the conventional approach.

Eighteen patients (16%) underwent surgical reintervention for recurrent GERD and/or persistent dysphagia, with no significant difference between the two groups at 17 years. This finding indicates that approximately one in eight patients needs a second operation for recurrent GERD and/or dysphagia. This is an important finding that should be addressed when discussing the possibility of Nissen fundoplication for the treatment of GERD. Salminen et al. found lower rates of surgical reintervention in both groups at both 11- and 15-year follow-up.[8, 9] At 15 years, seven (25%) incisional hernias were detected in the CNF-group, which were all asymptomatic and did not require surgical repair, and none after LNF. The overall reoperation rate 15 years after fundoplication was 5.5% (n=3) and 7.3% (n=4) after LNF and CNF respectively (*P*=1.000), which is low compared to our results.[9] Selection-bias and referral-bias pose an important problem with long-term follow-up studies and could explain differences between trials. Two meta-analyses performed by Catarci et al and Peters et al demonstrated a reoperation rate of 9.6% and 8.2% respectively, with follow-up periods of 2.5 years (mean) and 3.6 years (average) after LNF and CNF.[17, 18] These studies only included reoperation for recurrent GERD, and taking the extended length of follow-up of our trial into account, our findings are largely in line with these two meta-analyses.

The present study is based on the largest RCT comparing LNF with CNF and provides the longest follow-up for both procedures currently available. A possible limitation of this study is the fact that no objective outcome is provided for the patients. This has been performed at five and 10 years after surgery for this cohort of patients however, demonstrating no significant differences in esophageal acid exposure between the two procedures.[6, 7] Since 17-year symptomatic outcome did not demonstrate any differences between the two groups, one may assume objective follow-up will be in line with these results. In the present study, 17-year clinical outcome is provided for 111 (66%) of the initially included and operated 167 patients. Additionally, validated questionnaires were completed by 105 (63%) of the initially included patients, and by using the same questionnaires at all postoperative intervals as those used preoperatively, direct comparison between the preoperative phase and the different follow-up periods could

be performed, providing valuable insight in the symptomatic outcome throughout 17 years follow-up. The response rate of 63% in this study was as is to be expected with these type of surveys, especially given the fact that 18 patients died during 17-year follow-up.[27] A potential risk of long-term follow-up studies through questionnaires is selection bias. However, as previously stated, the risk for selection bias in the present study is low.
In summary, this study demonstrates that the previously described effects of both LNF and CNF on symptomatic outcome and general state of health at five and 10 years are sustained for up to 17 years after surgery, with no significant differences between the two procedures. CNF carries a higher risk for surgical reintervention compared to LNF, mainly due to incisional hernia corrections, supporting the use of LNF as the surgical procedure of choice for GERD. Despite the fact that 40% of the patients are back on medical treatment after 15 years and a substantial proportion needs reoperation, when regurgitation is the dominating symptom, surgery is the only option for adequate control of this incapacitating symptom. If a patient is reluctant to take life-long medication, surgery should be proposed, while informing patients that for this indication, their chances of sustained success are approximately 60%, with a 16% chance of needing a second operation for control of recurrent reflux symptoms and/or dysphagia.

REFERENCES

1. Dallemagne B, Weerts JM, Jehaes C, et al. Laparoscopic Nissen fundoplication: preliminary report. Surg Laparosc Endosc 1991;1:138-143.

2. Nissen R. A simple operation for control of reflux esophagitis. Schweiz Med Wochenschr 1956;86:590-592.

3. Sandbu R, Khamis H, Gustavsson S, et al. Long-term results of antireflux surgery indicate the need for a randomized clinical trial. Br J Surg 2002;89:225-230.

4. Franzen T, Anderberg B, Wiren M, et al. Long-term outcome is worse after laparoscopic than after conventional Nissen fundoplication. Scand J Gastroenterol 2005;40:1261-1268.

5. Bais JE, Bartelsman JF, Bonjer HJ, et al. Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. Lancet 2000;355:170-174.

6. Draaisma WA, Rijnhart-de Jong HG, Broeders IA, et al. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. Ann Surg 2006;244:34-41.

7. Broeders JA, Rijnhart-de Jong HG, Draaisma WA, et al. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. Ann Surg 2009;250:698-706.

8. Salminen PT, Hiekkanen HI, Rantala AP, et al. Comparison of long-term outcome of laparoscopic and conventional nissen fundoplication: a prospective randomized study with an 11-year follow-up. Ann Surg 2007;246:201-206.

9. Salminen P, Hurme S, Ovaska J. Fifteen-year outcome of laparoscopic and open Nissen fundoplication: a randomized clinical trial. Ann Thorac Surg 2012;93:228-233.

10. Rijnhart-De Jong HG, Draaisma WA, Smout AJ, et al. The Visick score: a good measure for the overall effect of antireflux surgery? Scand J Gastroenterol 2008;43:787-793.

11. Zeman Z, Rozsa S, Tihanyi T, et al. Psychometric documentation of a quality-of-life questionnaire for patients undergoing antireflux surgery (QOLARS). Surg Endosc 2005;19:257-261.

12. Velanovich V, Karmy-Jones R. Measuring gastroesophageal reflux disease: relationship between the Health-Related Quality of Life score and physiologic parameters. Am Surg 1998;64:649-653.

13. Horbach JM, Masclee AA, Lamers CB, et al. Prospective evaluation of 24 hour ambulatory pH metry in Belsey Mark IV antireflux surgery. Gut 1994;35:1529-1535.

14. de Boer AG, van Lanschot JJ, Stalmeier PF, et al. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? Qual Life Res 2004;13:311-320.

15. Nord E. The validity of a visual analogue scale in determining social utility weights for health states. Int J Health Plann Manage 1991;6:234-242.

16. Laine S, Rantala A, Gullichsen R, et al. Laparoscopic vs conventional Nissen fundoplication. A prospective randomized study. Surg Endosc 1997;11:441-444.

17. Peters MJ, Mukhtar A, Yunus RM, et al. Meta-analysis of randomized clinical trials comparing open and laparoscopic anti-reflux surgery. Am J Gastroenterol 2009;104:1548-61; quiz 1547, 1562.

18. Catarci M, Gentileschi P, Papi C, et al. Evidence-based appraisal of antireflux fundoplication. Ann Surg 2004;239:325-337.

19. Lord RV, Kaminski A, Oberg S, et al. Absence of gastroesophageal reflux disease in a majority of patients taking acid suppression medications after Nissen fundoplication. J Gastrointest Surg 2002;6:3-9; discussion 10.

20. Jenkinson AD, Kadirkamanathan SS, Scott SM, et al. Relationship between symptom response and oesophageal acid exposure after medical and surgical treatment for gastro-oesophageal reflux disease. Br J Surg 2004;91:1460-1465.

21. Drepper MD, Spahr L, Frossard JL. Clopidogrel and proton pump inhibitors--where do we stand in 2012? World J Gastroenterol 2012;18:2161-2171.

22. Heikkinen TJ, Haukipuro K, Koivukangas P, et al. Comparison of costs between laparoscopic and open Nissen fundoplication: a prospective randomized study with a 3-month followup. J Am Coll Surg 1999;188:368-376.

23. Luostarinen M, Virtanen J, Koskinen M, et al. Dysphagia and oesophageal clearance after laparoscopic versus open Nissen fundoplication. A randomized, prospective trial. Scand J Gastroenterol 2001;36:565-571.

24. Wenner J, Nilsson G, Oberg S, et al. Short-term outcome after laparoscopic and open 360 degrees fundoplication. A prospective randomized trial. Surg Endosc 2001;15:1124-1128.

25. Heikkinen TJ, Haukipuro K, Bringman S, et al. Comparison of laparoscopic and open Nissen fundoplication 2 years after operation. A prospective randomized trial. Surg Endosc 2000;14:1019-1023.

26. Nilsson G, Wenner J, Larsson S, et al. Randomized clinical trial of laparoscopic versus open fundoplication for gastro-oesophageal reflux. Br J Surg 2004;91:552-559.

27. Cummings SM, Savitz LA, Konrad TR. Reported response rates to mailed physician questionnaires. Health Serv Res 2001;35:1347-1355.

SUPPLEMENTAL

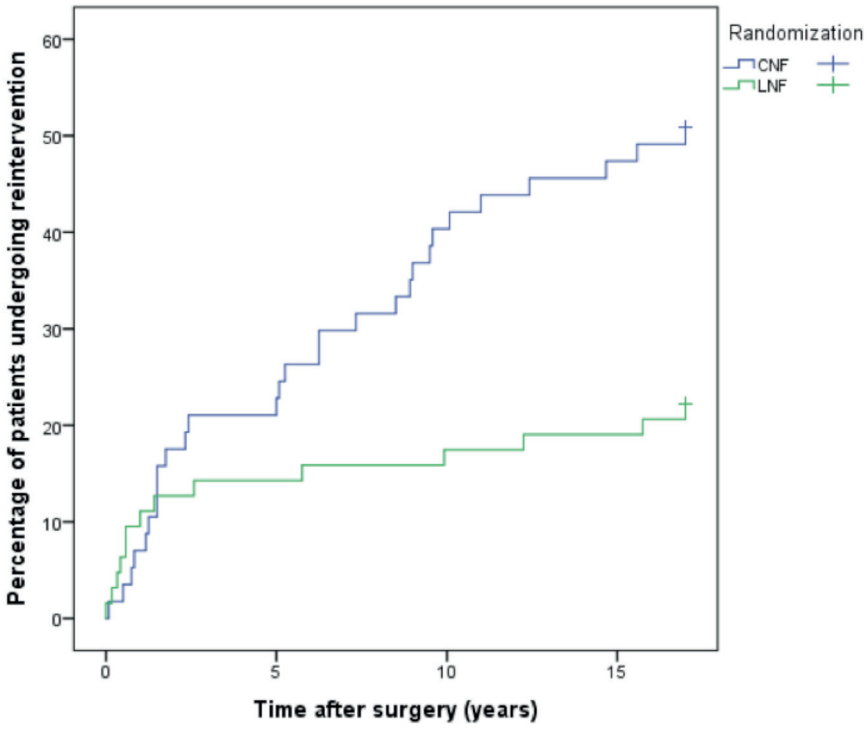

Figure 4. Percentage of Patients Undergoing Surgical Reintervention After Laparoscopic (LNF) and Conventional Nissen Fundoplication (CNF) During 17-Year Follow-Up (Kaplan-Meier Analysis, One-Minus-Survival)

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3

Predictors of objectively identified recurrent reflux after primary Nissen fundoplication

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ABSTRACT

Background

Laparoscopic Nissen fundoplication is the most frequently performed operation for gastro-oesophageal reflux disease (GORD). Studies on predictors of subjective outcome of fundoplication have yielded inconsistent results. This study identified predictors of objective reflux control after Nissen fundoplication.

Methods

This was a retrospective analysis of prospectively collected data from patients who underwent Nissen fundoplication for proton pump inhibitor refractory GORD with pathological acid exposure in a single centre between 1997 and 2005. The predictive value of demographics, endoscopic hiatal hernia size, oesophagitis, lower oesophageal sphincter pressure, distal oesophageal contraction amplitude, percentage of peristaltic contractions and acid exposure was determined. Endpoints were recurrent pathological acid exposure on 24-h pH monitoring at 6 months and surgical reintervention for recurrent GORD up to 6 years.

Results

Of 177 patients, 22 had recurrent pathological acid exposure at 6 months for which 11 had surgery within 6 years. Only low percentage of peristaltic contractions (odds ratio (OR) 0.97, 95 per cent confidence interval 0.95 to 0.99; $P = 0.004$) and high supine acid exposure (OR 1.03, 1.00 to 1.07; $P = 0.025$) were independent predictors of recurrent pathological acid exposure. The absolute risk of recurrent exposure was 45.5 per cent in patients with both predictors. High supine acid exposure was also an independent predictor of surgical reintervention (OR 1.05, 1.01 to 1.08; $P = 0.006$).

Conclusion

Nissen fundoplication should not necessarily be withheld from patients with poor oesophageal peristalsis or excessive supine acid exposure. As about half of patients with both variables experience recurrent pathological acid exposure after primary Nissen fundoplication, surgery should be restricted in this group.

INTRODUCTION

Gastro-oesophageal reflux disease (GORD) is the most common upper gastrointestinal tract disorder in the Western world[1]. GORD that is refractory to proton pump inhibitor (PPI) therapy in patients with pathological acid exposure on 24-h pH monitoring is a well accepted indication for antireflux surgery. Laparoscopic Nissen fundoplication is the most frequently performed surgical procedure for GORD[2]. Several studies have attempted to identify predictors of outcome after fundoplication. In 2009 a systematic review found that the quality and consistency of data are mixed, and as a result studies report no or disparate predictive values[3]. The authors concluded that the strength of the associations remains uncertain and that their role in guiding treatment decisions in individual patients requires further clarification[3].

The studies included in the review[3] and subsequently published studies[4–10] that investigated the association between patient characteristics and outcome of primary antireflux surgery all used subjective outcome as endpoint. A predictive model based on objective outcome is expected to yield more consistent results. A prognostic model for the assessment of objective outcome after redo antireflux surgery has been pubished[11].

The aim of the present study was to evaluate preoperative predictors of objective reflux control after primary Nissen fundoplication by analysing the predictive value of pathophysiological parameters for recurrent pathological acid exposure and long-term surgical reintervention for recurrent GORD. The present study design followed the methodological recommendations made in the review: a larger sample size, consistent definitions of preoperative patient characteristics, standardized preoperative investigations and surgical techniques ,and full reporting of clinically important outcomes using validated instruments[3].

METHODS

This study was a retrospective analysis of the data from three prospective cohorts of patients who underwent primary Nissen fundoplication for GORD refractory to PPI therapy with pathological acid exposure at a single centre. These patients completed preoperative and postoperative investigations as part of a multicentre randomized controlled trial (RCT)[12], a single-centre RCT[13] and a prospective multicentre cohort study[14] carried out between 1997 and 2005. PPI refractory GORD was defined as heartburn and regurgitation persisting over 6 months despite double-dose PPI use (more than 40 mg omeprazole in 24 h or comparable therapy), with pathological oesophageal acid exposure time registered during 24-h pH monitoring. Demographics (age, sex and body mass index) were recorded before surgery and collected prospectively in consecutive patients. All patients, both symptomatic and asymptomatic, were asked to undergo upper gastrointestinal endoscopy, oesophageal manometry and 24-h pH-metry before and 6 months after surgery. Patients were followed prospectively for 6 years.

Surgical procedures

All operations were performed between January 1997 and October 2005. Surgical techniques were standardized, and included ligation and division of the short gastric vessels, mobilization of the distal oesophagus, posterior crural repair and construction of a floppy 360° Nissen fundoplication of 2.5–3.0 cm. All surgeons had gone through the learning curve for laparoscopic Nissen fundoplication , as defined by Watson and colleagues[15]: more than five fundoplications by an experienced laparoscopic surgeon and over 20 procedures by a less experienced laparoscopic surgeon.

Upper gastrointestinal endoscopy

The presence of oesophagitis and hiatal hernia size were determined endoscopically. Oesophagitis grading was initially performed according to the Savary–Miller classification[16]. From 1999 onwards, oesophagitis was graded according to the Los Angeles classification[17].

Oesophageal manometry

Manometric studies were undertaken before and 6 months after operation. Patients ceased taking any medication that could affect oesophageal motility 7 days beforehand. A water-perfused system with a multiple-lumen catheter and an incorporated sleeve sensor was used (Dentsleeve Pty, Adelaide, Australia). After transnasal introduction, the catheter was retracted to determine the distal border of the lower oesophageal sphincter (LOS). The sleeve sensor was positioned at the level of the LOS, and intraluminal oesophageal pressures were recorded at 5, 10 and 15 cm above the proximal margin. Thereafter, the manometric response to ten standardized wet swallows was studied (5-ml water bolus). The gastric baseline pressure was registered 2 cm below the distal margin of the sleeve sensor and served as the zero reference point. Mean end-expiratory LOS pressure, mean peak contraction amplitude in the distal part of the oesophagus and the percentage of peristaltic wave contractions in the body of the oesophagus were measured. The distal amplitude was defined as the average amplitude of two recording sites positioned at 3 and 8 cm above the LOS[18,19]. A peristaltic contraction was defined as a wet swallow followed by a peristaltic wave that was transmitted to the distal oesophagus and resulted in a distal amplitude higher than 30 mmHg[18,19]. A simultaneous contraction was defined as a wet swallow that was followed by a pressure with an upstroke that occurred simultaneously at 3 and 8 cm above the LOS. The upstroke was considered to be simultaneous if the calculated propagation velocity exceeded 8 cm/s.

Ambulatory 24-h pH monitoring

Ambulatory pH monitoring studies were performed before and 6 months after fundoplication.. Medication that could affect the results was stopped 7 days before testing. A catheter with a pH glass electrode (model LOT440; Medical Instruments Corporation, Solothurn, Switzerland) was positioned 5 cm above the manometrically determined upper border of the LOS after transnasal introduction. A digital data logger (Medical Measurements Systems (MMS), Enschede, The Netherlands) stored the 24-h pH

recordings, and patients registered body position and reflux symptoms in a diary. Patients were instructed to press a button on the digital data logger when they experienced a symptom. The recordings were analysed automatically using dedicated software (MMS). Classification into pathological or physiological oesophageal acid exposure was based on the percentage of time with pH below 4. The upper limit for physiological oesophageal acid exposure in upright and supine body position was two standard deviations above the mean value obtained in healthy volunteers during ambulatory 24-h pH monitoring[20,21]. Pathological acid exposure time was defined as an acid exposure time of at least 8.2 per cent in the upright body position, or an acid exposure time of at least 3.5 per cent in the supine position, or a total time with pH below 4 of at least 5.8 per cent.

Surgical reintervention

Surgical reinterventions, time to reoperation and indication for reintervention were registered for up to 6 years after primary surgery.

Study endpoints

The primary endpoint was recurrent pathological acid exposure on 24-h pH monitoring. The secondary endpoint was surgical reintervention for recurrent GORD in the first 6 years after primary surgery. The value of the following variables in predicting these outcomes was determined: demographics, endoscopic hiatal hernia size, oesophagitis, manometric LOS pressure, distal oesophageal contraction amplitude, percentage of peristaltic contractions and acid exposure.

Statistical analysis

Statistical analysis was performed separately for the primary and secondary endpoints. Continuous variables were expressed as median (interquartile range). For univariable analysis, the significance of all continuous and categorical variables was tested separately by binary logistic regression analysis. Variables with $P < 0.200$ in univariable analysis were entered into a multivariable binary logistic regression model, using backward stepwise selection of variables. Variables with $P < 0.100$ were considered to be significant predictors of outcome. Odds ratios (ORs) were presented with 95 per cent confidence intervals. ORs per unit were reported for continuous variables. In an additional analysis independent predictors were dichotomized at clinically relevant cut-off values. SPSS® version 15.0 was used for statistical analysis (SPSS, Chicago, Illinois, USA).

RESULTS

In the study period 177 patients underwent Nissen fundoplication and met the inclusion criteria of pathological oesophageal acid exposure before surgery and ambulatory 24-hour pH monitoring at 6 months' follow-up.

Recurrent pathological acid exposure

Pathological oesophageal acid exposure persisted or recurred in 22 patients, whereas oesophageal acid exposure normalized to physiological values in the remaining 155. Patient characteristics, hiatal hernia size, presence of oesophagitis and LOS pressure were similar in the two groups, and had no predictive value in univariable analysis (*Table 1*). Patients who developed recurrent pathological oesophageal acid exposure after Nissen fundoplication had significantly reduced oesophageal peristalsis before surgery compared with those who did not. They also had greater supine acid exposure before surgery. There were no significant differences in oesophagitis grade and upright and total acid exposure between the two groups.

Four preoperative variables were entered into the multivariable model: percentage of peristaltic contractions, distal oesophageal contraction amplitude, supine acid exposure and total acid exposure. Multivariable regression analysis demonstrated that the percentage of peristaltic contractions (OR per cent 0.97, 0.95 to 0.99; P = 0.004; regression coefficient = –0.030) and supine acid exposure (OR per cent 1.03, 1.00 to 1.07); P = 0.025; regression coefficient = 0.034) were independent predictors of recurrent reflux.

Table 1. Univariable analysis of recurrent pathological acid exposure

	Reflux (*n* = 22)*	**No reflux** (*n* = 155)*	**Odds ratio†**
Demographics			
Age (years)‡	45.8 (36.0–54.6)	42.9 (33.1–52.8)	1.01 (0.98, 1.04)
Sex (M)	15 (68)	95 (61.3)	1.35 (0.52, 3.51)
Body mass index (kg/m^2)‡	26.3 (23.4–28.0)	26.1 (24.0–29.7)	0.92 (0.81, 1.04)
Upper gastrointestinal endoscopy			
Hiatal hernia size (cm)‡	3.5 (2.5–5.3)	3.0 (2.0–4.0)	1.19 (0.92, 1.55)
Oesophagitis	12 of 22 (55)	82 of 142 (57.7)	1.14 (0.46, 2.81)
Mean LOS pressure (kPa)‡	0.7 (0.4–1.3)	1.0 (0.6–1.7)	0.76 (0.45, 1.29)
Oesophageal peristalsis‡			
Peristaltic contractions (%)	90 (58–100)	100 (90–100)	0.97 (0.95, 0.99)
Distal contraction amplitude (kPa) Oesophageal acid	6.0 (3.6–7.6)	8.1 (5.8–12.2)	0.83 (0.72, 0.96)
exposure (% time)‡			
Upright	11.3 (9.1–20.6)	12.9 (8.9–19.4)	1.01 (0.96, 1.06)
Supine	17.3 (8.0–23.9)	4.8 (0.9–14.9)	1.04 (1.01, 1.07)
Total	15.2 (9.6–23.3)	11.1 (7.5–16.1)	1.05 (1.00, 1.10)

Values in parentheses are *percentages and †95 per cent confidence intervals unless indicated otherwise; ‡group values are median (interquartile range), with odds ratios per unit. LOS, lower oesophageal sphincter.

The independent predictors from the multivariable model were dichotomized using clinically relevant cut-off values. Normal oesophageal peristalsis was defined as at least 70 per cent peristaltic contractions, according to the most widely used classification for oesophageal motility[18,19]. Excessive supine acid exposure was defined as at least 8 per cent of the time, as this cut-off resulted in superior prediction of endpoints. Based on this cut-off value, 79 (44.6 per cent) of 177 patients were classified as having excessive supine acid exposure before surgery. Multivariable regression analysis demonstrated that poor oesophageal peristalsis (OR 3.77, 1.12 to 11.96; *P* = 0.024; regression coefficient = 1.327) and excessive supine acid exposure (OR 4.56, 1.57 to 13.30; *P* = 0.005; regression coefficient = 1.518) were independent predictors of recurrent reflux.

The absolute risk of recurrent pathological acid exposure was 4.5 per cent in patients with no excessive supine acid exposure and with normal oesophageal peristalsis. This risk increased to 12.5 per cent in patients with poor oesophageal peristalsis and to 16.9 per cent in patients with excessive supine acid exposure. This risk was as high as 45.5 per cent in patients with both poor oesophageal peristalsis and excessive supine acid exposure.

Long-term surgical reintervention for recurrent gastro-oesophageal reflux disease

The reflux symptoms of 11 of the 22 patients with recurrent pathological acid exposure were well controlled with PPI therapy. The remaining 11 patients underwent reoperation for recurrent PPI refractory reflux symptoms, with pathological acid exposure on 24-h pH monitoring. Another eight surgical reinterventions were performed for persisting dysphagia, two for intrathoracic herniation of the wrap and one for an incisional hernia. Median follow-up was 72 (72–72) months and median time to reintervention 15 (6–22) months.

The 11 patients who underwent surgical reintervention for recurrent GORD were compared with 166 who did not (*Table 2*). Patients who underwent reoperation for recurrent reflux disease alone had significantly greater postoperative supine acid exposure than those who did not require further surgery, but were comparable with respect to all other variables evaluated. Supine acid exposure was also the only independent predictor in multivariable regression analysis (OR per cent 1.05; 1.01 to 1.08; *P* = 0.006).

Supine acid exposure was dichotomized at an 8 per cent cut-off for this endpoint as well. Univariable regression analysis demonstrated that excessive supine acid exposure was non-significantly associated with surgical reintervention for recurrent GORD (OR 3.57; 0.91 to 13.93; *P* = 0.067, regression coefficient 1.272). The absolute risk of reoperation for recurrent GORD was 10.1 per cent in patients with excessive supine acid exposure compared with 3.1 per cent in patients without.

Table 2. Univariable analysis of long-term surgical reintervention for recurrent gastro-oesophageal reflux disease

	Surgical reintervention (*n* = 11)*	**No surgical reintervention** (*n* =166)*	**Odds ratio†**
Demographics			
Age (years)‡	44.4 (33.6–56.0)	43.0 (33.1–53.0)	1.01 (0.96,1.06)
Sex (M)	8 (73)	102 (61.4)	1.67 (0.43, 6.54)
Body mass index (kg/m^2)‡	26.0 (25.0–28.0)	26.1 (23.9–29.4)	0.96 (0.81,1.13)
Upper gastrointestinal endoscopy			
Hiatal hernia size (cm)‡	3.5 (1.8–5.0)	3.0 (2.0–5.0)	0.96 (0.69, 1.32)
Oesophagitis	6 of 11 (55)	88 of 153 (57.5)	1.13 (0.33, 3.86)
Mean LOS pressure (kPa)‡	0.6 (0.4–1.4)	1.0 (0.6–1.7)	0.58 (0.24,1.39)
Oesophageal peristalsis‡			
Peristaltic contractions (%)	90 (80–100)	100 (90–100)	0.99 (0.96, 1.02)
Distal contraction amplitude (kPa)	7.1 (5.3–10.6)	7.6 (5.6–12.0)	0.99 (0.85,1.14)
Oesophageal acid exposure (% time)‡			
Upright	13.7 (8.6–20.7)	12.8 (8.9–19.4)	0.99 (0.92, 1.06)
Supine	22.2 (3.2–46.1)	5.7 (1.1–15.3)	1.05 (1.01,1.08)
Total	19.7 (7.3–24.0)	11.4 (7.6–16.1)	1.05 (0.99,1.10)

Values in parentheses are *percentages and †95 per cent confidence intervals unless indicated otherwise; ‡group values are median (interquartile range), with odds ratios per unit. LOS, lower oesophageal sphincter.

DISCUSSION

The search for predictors of objective outcome is legitimate as more than 8 per cent of patients suffer from objectively identified recurrent pathological acid exposure at 5 years after Nissen fundoplication[22]. In the present study, the rate of recurrent pathological acid exposure after Nissen fundoplication was 12.4 per cent, with a surgical reintervention rate of 11.8 per cent up to 6 years after operation. Considering the extended length of follow-up, these results are largely in line with a recent meta-analysis of RCTs in which 16.5 per cent of the patients developed recurrent reflux disease and 9.6 per cent needed surgical reintervention at a mean follow-up of 2.5 years after fundoplication[23].

The present study evaluated predictors of objective reflux control after primary Nissen fundoplication and long-term reoperation for recurrent GORD. Poor preoperative oesophageal peristalsis and excessive supine acid exposure predicted objective reflux control after primary Nissen fundoplication. The presence of both variables before surgery was highly predictive of treatment failure with respect to recurrent pathological acid exposure. Patients with both factors present had a ten times higher risk of recurrence than those without. Demographics, hiatal hernia size, presence of oesophagitis and LOS pressure did not predict outcome after antireflux surgery. The majority of studies in a recently published systematic review confirmed that age, sex and body mass index do

not predict outcome after fundoplication[3]. One subsequent study reported age as a weak predictor[8], whereas four studies did not[4–7]. A relationship between sex and outcome was reported by two studies[4,8], but not by two others[6,7]. In contrast to a previous report[24], hiatal hernia size had no predictive value in the present study. The systematic review[3] did not address the impact of hiatal hernia size, but more recent studies did not find a relationship with outcome[6, 8,10]. The presence of oesophagitis had no predictive value in the present series, in line with 11 of 12 reviewed studies[3] and a later report[8].

Confirming the findings of eight of nine reviewed studies[3] as well as three other articles[6,10,19], no significant impact of LOS characteristics on outcome after fundoplication was found here. In contrast, oesophageal peristalsis predicted outcome after Nissen fundoplication; both the percentage of peristaltic contractions and the distal contraction amplitude were negative predictors of recurrent pathological reflux. The first was also an independent predictor of recurrent pathological acid exposure. Previous studies have demonstrated that poor oesophageal peristalsis leads to greater, particularly supine, oesophageal exposure as a result of poorer oesophageal clearance[25–31]. Reduced oesophageal clearance of gastric contents owing to poor oesophageal peristalsis probably explains the higher rate of recurrent pathological acid exposure. In contrast, the majority of reviewed articles[3] and a recent study[9] found that oesophageal dysmotility had no impact on outcome after fundoplication. However, most of these studies used dysphagia as endpoint, whereas the present study focused on recurrent reflux. Several RCTs have demonstrated that the construction of a total fundoplication is not associated with a higher dysphagia rate in patients with oesophageal motility disorders[32–34]. Other recent studies that focused on predictors of recurrent GORD support the present findings, also reporting that poor oesophageal peristalsis increased the risk of recurrent reflux symptoms[7,8].

In the present series, supine and total oesophageal acid exposure times during 24-h pH monitoring were positive predictors of recurrent pathological acid exposure. Previous studies have evaluated only differences in the outcome of fundoplication in patients with pathological acid exposure *versus* those with physiological acid exposure before surgery. Their findings remain inconclusive as three studies reported better, two studies worse and four studies similar outcomes after fundoplication in the patients with pathological acid exposure[3]. In contrast, the present study included only patients with pathological acid exposure before surgery and evaluated acid exposure as a continuous variable. Three studies have previously evaluated the predictive value of excessive acid exposure. Two confirmed the present results, reporting that a DeMeester score of at least 50 increased the risk of recurrence of symptoms[7,35], whereas one study did not[8]. In the present study acid exposure time in the upright body position had no predictive value. In contrast, excessive supine acid exposure was an independent predictor of recurrent pathological reflux and repeat antireflux surgery for GORD. However, these patients should not be denied antireflux surgery as they are likely to gain the most from it.

The present results support the view that objective reflux control after primary Nissen fundoplication is not predicted by preoperative patient characteristics, hiatal hernia size,

presence of oesophagitis and LOS pressure. Patients with good oesophageal peristalsis or low supine acid exposure before antireflux surgery have a lower risk of recurrent pathological acid exposure. Nissen fundoplication should not not necessarily be withheld from patients with poor oesophageal peristalsis or excessive supine acid exposure. As about one in every two patients with both these variables will experience recurrent pathological acid exposure after primary Nissen fundoplication, surgery in this group should be restricted. Careful counselling is necessary and can be optimized based on the present results, by providing patients with differentiated information on individual risk of recurrence and reoperation for reflux.

REFERENCES

1 Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005; **54**: 710–717.

2 Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. Ten-year outcome of laparoscopic and conventional Nissen fundoplication: Randomized clinical trial. *Ann Surg* 2009; **250**: 698–706.

3 Ip S, Tatsioni A, Conant A, Karagozian R, Fu L, Chew P *et al*. Predictors of clinical outcomes following fundoplication for gastroesophageal reflux disease remain insufficiently defined: a systematic review. *Am J Gastroenterol* 2009; **104**: 752–758.

4 Beck PE, Watson DI, Devitt PG, Game PA, Jamieson GG. Impact of gender and age on the long-term outcome of laparoscopic fundoplication. *World J Surg* 2009; **33**: 2620–2626.

5 Pizza F, Rossetti G, Limongelli P, Del Genio G, Maffettone V, Napolitano V *et al*. Influence of age on outcome of total laparoscopic fundoplication for gastroesophageal reflux disease. *World J Gastroenterol* 2007; **13**: 740–747.

6 Morgenthal CB, Lin E, Shane MD, Hunter JG, Smith CD. Who will fail laparoscopic Nissen fundoplication? Preoperative prediction of long-term outcomes. *Surg Endosc* 2007; **21**: 1978–1984.

7 Hafez J, Wrba F, Lenglinger J, Miholic J Fundoplication for gastroesophageal reflux and factors associated with the outcome 6 to 10 years after the operation: multivariate analysis of prognostic factors using the propensity score. *Surg Endosc* 2008; **22**: 1763–1768.

8 Oelschlager BK, Quiroga E, Parra JD, Cahill M, Polissar N, Pellegrini CA. Long-term outcomes after laparoscopic antireflux surgery. *Am J Gastroenterol* 2008; **103**: 280–287.

9 Pizza F, Rossetti G, Del Genio G, Maffettone V, Brusciano L, Del Genio A. Influence of esophageal motility on the outcome of laparoscopic total fundoplication. *Dis Esophagus* 2008; **21**: 78–85.

10 Riedl O, Gadenstätter M, Lechner W, Schwab G, Marker M, Ciovica R. Preoperative lower esophageal sphincter manometry data neither impact manifestations of GERD nor outcome after laparoscopic Nissen fundoplication. *J Gastrointest Surg* 2009; **13**: 1189–1197.

11 Furnée EJ, Draaisma WA, Broeders IA, Smout AJ, Vlek AL, Gooszen HG. Predictors of symptomatic and objective outcomes after surgical reintervention for failed antireflux surgery. *Br J Surg* 2008; **95**: 1369–1374.

12 Bais JE, Bartelsman JF, Bonjer HJ, Cuesta MA, Go PM, Klinkenberg-Knol EC *et al*. Laparoscopic or conventional Nissen fundoplication for gastro-oesophageal reflux disease: randomised clinical trial. The Netherlands Antireflux Surgery Study Group. *Lancet* 2000; **355**: 170–174.

13 Draaisma WA, Ruurda JP, Scheffer RC, Simmermacher RK, Gooszen HG, Rijnhart-de Jong HG *et al*. Randomized clinical trial of standard laparoscopic *versus* robot-assisted laparoscopic Nissen fundoplication for gastro-oesophageal reflux disease. *Br J Surg* 2006; **93**: 1351–1359.

14 Draaisma WA, Buskens E, Bais JE, Simmermacher RK, Rijnhart-de Jong HG, Broeders IA *et al*. Randomized clinical trial and follow-up study of cost-effectiveness of laparoscopic *versus* conventional Nissen fundoplication. *Br J Surg* 2006; **93**: 690–697.

15 Watson DI, Baigrie RJ, Jamieson GG. A learning curve for laparoscopic fundoplication. Definable, avoidable, or a waste of time? *Ann Surg* 1996; **224**: 198–203.

16 <B>Savary M, Miller G (eds.) *The Esophagus: Handbook and Atlas of Endoscopy.* Gassmann: Solothurn, 1978.

17 Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP *et al*. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999; **45**: 172–180.

18 Richter JE. Oesophageal motility disorders. *Lancet* 2001; **358**: 823–828.

19 Spechler SJ, Castell DO. Classification of oesophageal motility abnormalities. *Gut* 2001; **49**: 145–151.

20 Richter JE, Bradley LA, DeMeester TR, Wu WC. Normal 24-hr ambulatory esophageal pH values. influence of study center, pH electrode, age, and gender. *Dig Dis Sci* 1992; **37**: 849–856.

21 Jamieson JR, Stein HJ, DeMeester TR, Bonavina L, Schwizer W, Hinder RA *et al*. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. *Am J Gastroenterol* 1992; **87**: 1102–1111.

22 Draaisma WA, Rijnhart-de Jong HG, Broeders IA, Smout AJ, Furnee EJ, Gooszen HG Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. *Ann Surg* 2006; **244**: 34–41.

23 Catarci M, Gentileschi P, Papi C, Carrara A, Marrese R, Gaspari AL *et al*. Evidence-based appraisal of antireflux fundoplication. *Ann Surg* 2004; **239**: 325–337.

24 Power C, Maguire D, McAnena O. Factors contributing to failure of laparoscopic Nissen fundoplication and the predictive value of preoperative assessment. *Am J Surg* 2004; **187**: 457–463.

25 Achem AC, Achem SR, Stark ME, DeVault KR. Failure of esophageal peristalsis in older patients: association with esophageal acid exposure. *Am J Gastroenterol*. 2003; **98**: 35–39.

26 Lee J, Anggiansah A, Anggiansah R, Young A, Wong T, Fox M. Effects of age on the gastroesophageal junction, esophageal motility, and reflux disease. *Clin Gastroenterol Hepatol* 2007; **5**: 1392–1398.

27 Fornari F, Blondeau K, Durand L, Rey E, Diaz-Rubio M, De Meyer A *et al*. Relevance of mild ineffective oesophageal motility (IOM) and potential pharmacological reversibility of severe IOM in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2007; **26**: 1345–1354.

28 Bremner RM, DeMeester TR, Crookes PF, Costantini M, Hoeft SF, Peters JH *et al*. The effect of symptoms and nonspecific motility abnormalities on outcomes of surgical therapy for gastroesophageal reflux disease. *J Thorac Cardiovasc Surg* 1994; **107**: 1244–1249.

29 Diener U, Patti MG, Molena D, Fisichella PM, Way LW Esophageal dysmotility and gastroesophageal reflux disease. *J Gastrointest Surg* 2001; **5**: 260–265.

30 Leite LP, Johnston BT, Barrett J *et al*. Ineffective esophageal motility (IEM): the primary finding in patients with nonspecific esophageal motility disorder. *Dig Dis Sci* 1997; **42**: 1859–1865.

31 Ho SC, Chang CS, Wu CY, Chen GH. Ineffective esophageal motility is a primary motility disorder in gastroesophageal reflux disease. *Dig Dis Sci* 2002; **47**: 652–656.

32 Fibbe C, Layer P, Keller J, Strate U, Emmermann A, Zornig C. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized, clinical, and manometric study. *Gastroenterology* 2001; **121**: 5–14.

33 Booth MI, Stratford J, Jones L, Dehn TC. Randomized clinical trial of laparoscopic total (Nissen) *versus* posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. *Br J Surg* 2008; **95**: 57–63.

34 Chrysos E, Tsiaoussis J, Zoras OJ, Athanasakis E, Mantides A, Katsamouris A *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.

35 Horvath KD, Jobe BA, Herron DM, Swanstrom LL. Laparoscopic Toupet fundoplication is an inadequate procedure for patients with severe reflux disease. *J Gastrointest Surg* 1999; **3**: 583–591.

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Laparoscopic anterior *versus* posterior fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Objective

To compare short and long-term outcome after laparoscopic anterior fundoplication (LAF) *versus* posterior fundoplication (LPF) through a systematic review and meta-analysis of randomized clinical trials (RCTs).

Summary of background data

LPF is currently considered the surgical therapy of choice for GERD. Alternatively, LAF has been alleged to reduce troublesome dysphagia and gas-related symptoms.

Methods

Four electronic databases (MEDLINE, EMBASE, Cochrane Library and ISI web of Knowledge CPCI-S) were searched for RCTs comparing primary LAF *versus* LPF for GERD. The methodological quality was evaluated to assess bias risk. Primary outcomes were esophageal acid exposure time, heartburn, Dakkak dysphagia score [0-45] and reoperation rate. Short and long-term results were pooled separately in meta-analyses as relative risk (RRs) and weighted mean differences (WMDs).

Results

Eleven reports on 7 eligible RCTs (anterior *vs* posterior total[n=5];anterior *vs* posterior partial[n=2]) comparing LAF (n=345) *versus* LPF (n=338) were identified. Short-term (6-12months) esophageal acid exposure time (3.3 *vs* 0.8%: WMD2.04;95%CI [0.84,3.24];P<0.001), heartburn (21 *vs* 8%; RR2.71;95%CI[1.72,4.26];*P*<0.001) and reoperation rate (8 *vs* 4%; RR1.94;95%CI[0.97,3.87];*P*=0.06) were higher after LAF. In contrast, the Dakkak dysphagia score was lower after LAF (2.5 vs 5.7; WMD-2.87;95%CI[-3.88,-1.87];P<0.001). There were no short-term differences in prevalence of esophagitis, regurgitation and perioperative outcomes. The higher rate of heartburn after LAF persisted during long-term (2-10 years) follow-up (31 *vs* 14%; RR 2.15;95%CI[1.49,3.09];*P*<0.001) with more PPI use (25 *vs* 10%; RR2.53;95%CI[1.40,4.45];*P*=0.002). The long-term reoperation rate was twice as high after LAF (10 *vs* 5%; RR 2.12;95%CI[1.07,4.21];*P*=0.03). Long-term Dakkak dysphagia scores, inability to belch, gas bloating and satisfaction were not different.

Conclusions

Esophageal acid exposure time and the prevalence of heartburn are higher after LAF compared with LPF. In the short-term this is counterbalanced by less severe dysphagia. However, dysphagia scores become similar in the long-term, with a persistent substantial increase in prevalence of heartburn and PPI use after LAF. The reoperation rate is twice as high after LAF as well, mainly due to reinterventions for recurrent GERD. The prevalence of gas-related symptoms is similar. These results lend level 1a support for the use of LPF as the surgical treatment of choice for GERD.

INTRODUCTION

Laparoscopic fundoplication is the surgical approach of choice for gastroesophageal reflux disease (GERD). Three randomized clinical trials (RCTs) have recently demonstrated that the laparoscopic approach offers similar 5-year[1] and 10-year rates for disease control[2] compared with open fundoplication, with fewer incisional hernias[2,3].

A fundoplication is created by wrapping the fundus of the stomach anteriorly or posteriorly around the esophagus. Currently, laparoscopic posterior fundoplication (LPF) is widely considered the surgical therapy of choice for GERD[1-3]. In North America total posterior fundoplication is considered the gold standard[4-6], whereas partial posterior fundoplication is more common in Europe[7]. Generally, the aim of antireflux surgery is to control reflux symptoms with minimal postoperative dysphagia and gas-related symptoms. A recently published systematic review comparing posterior total to posterior partial fundoplication demonstrated that posterior fundoplication ensures excellent reflux control, although this is traded off against a high prevalence of postfundoplication symptoms[7]. Eleven percent of the patients develop dysphagia and 5 per cent require dilation for dysphagia after LPF[7]. In addition, 12 percent of the patients suffer from the inability to belch and 29 percent report gas bloating after posterior fundoplication[7]. Therefore, the development of dysphagia and gas-related symptoms seem to be clinically important drawbacks associated with LPF.

Laparoscopic anterior fundoplication (LAF) has been proposed as an alternative operation aiming to reduce postfundoplication symptoms. Several RCTs have demonstrated that LAF reduces dysphagia[8-13] and gas-related symptoms[10,11,13], when compared with LPF. Some RCTs suggest that this is offset by a higher reflux recurrence rate[8,10-12,14-16], though other RCTs report similar reflux control[9,13,17]. As a result, these individual RTCs comparing LAF to LPF have not provided a definitive answer.

Up to date, no systematic review of literature exists to address this question. The current study aims, therefore, to systematically review all RCTs comparing LAF to LPF for GERD. Short and long-term outcomes are analyzed separately, in order to generate the highest level of evidence to determine which procedure should be regarded as the surgical therapy of choice.

METHODS

Study selection

A systematic literature search with predefined search terms (Figure 1) was carried out in MEDLINE (from 1960)[18], EMBASE (from 1980)[19], Cochrane Library (issue 1, 2010) and the ISI Web of Knowledge Conference Proceedings Citation Index - Science (CPCI-S; from 1990) databases for articles published to June 1st, 2010 (Figure 1). All identified articles were screened for cross-references. Language restrictions were not applied.

Inclusion criteria

Title and abstract of all identified articles were screened and selected according to the following inclusion criteria: study population - adult patients with established GERD undergoing primary antireflux surgery; intervention - clearly documented surgical technique of laparoscopic anterior fundoplication and laparoscopic posterior fundoplication, irrespective of division of the short gastric vessels[20]; study outcomes - at least one of the outcome measures reported below; study design - patients assigned to either LAF or LPF by random allocation; publication - published as a full article in a peer-reviewed journal.

Exclusion criteria

Studies were excluded from analysis if they did not meet the inclusion criteria, or if the corresponding author was not able to provide data requested and it was impossible to extract or calculate appropriate data from the published results. Abstracts of RCTs were excluded as the methodological quality and the risk of bias of these studies could not be assessed.

Outcomes of interest and definitions

Primary outcomes were: esophageal acid exposure time on pH monitoring, heartburn, the validated Dakkak dysphagia score (0, no dysphagia; 45, severe dysphagia)[21] and reoperation rate. Secondary outcomes included endoscopic esophagitis, regurgitation, PPI use, inability to belch, gas bloating, ability to relieve bloating, satisfaction with intervention, willingness to undergo surgery again, lower esophageal sphincter (LES) pressure and LES relaxation nadir pressure on manometry, operating time, conversion rate, in-hospital complications and length of hospital stay. Short (6-12 months) and long-term (2-10 years) results were pooled separately in meta-analysis. Subgroup analysis was performed after exclusion of RCTs with 90 degree anterior fundoplication, since short[10,11] and long-term[14] reflux control after this procedure is poor compared to short[9] and long-term[17] effectiveness of 180 degree fundoplication.

Data extraction

Titles and abstracts of all retrieved records, and subsequently full-text articles, were examined independently by two authors (JAB, DJR) according to the Quality of Reporting of Meta-analyses (QUOROM) guidelines[22-24]. The following data were extracted separately by the same two authors (JAB, DJR) for all studies meeting the inclusion criteria: reference of study, study population characteristics, study design, inclusion and exclusion criteria and number of participating subjects for each endpoint. For dichotomous outcomes, the number of events was recorded and for continuous outcomes means and standard deviations (SDs) were registered. In case of discrepancies, a third author (UAA) was consulted and agreement was reached by consensus.

Authors of all the original RCTs were contacted to provide missing data. When authors could not provide missing data, the following methods of handling missing data were

applied. If the number of patients per arm was missing for an outcome, an equal distribution between both arms was assumed. Missing standard deviations (SDs) were either imputed based on ranges when available[25] or based on the average SDs reported by other RCTs for the same outcome[18]. If both means and SDs were missing, they were imputed based on the medians and ranges[25] or based on medians and interquartile ranges[18], according to availability.

Risk of bias assessment

Risk of bias was assessed of all articles using both the Cochrane Collaboration's tool for assessing risk of bias[18] and the Jadad scoring system[26].

Statistical analysis

Statistical analyses were performed following the recommendations of the Cochrane Collaboration and QUOROM guidelines[22-24]. Outcomes reported by three or more studies were pooled in meta-analyses. Short and long-term results were analyzed separately. Dichotomous and continuous outcomes were presented as risk ratios (RRs) and weighted mean differences (WMDs), respectively. Data were pooled using the Mantel-Haenszel and the inverse-variance method for dichotomous outcomes and for continuous outcomes, respectively. Trials with zero events in both arms were excluded from meta-analysis. Trials with zero events in one arm were included in the analysis by adding a continuity correction of 0.5 to all cells in the 2x2 table of that study. As a robustness assessment, meta-analyses with RCTs with zero events in one arm were also performed using risk differences in a sensitivity analyses. For all analyses the 95% confidence interval (CI) was calculated.

Heterogeneity was calculated using Higgins χ^2 test[27], and inconsistency in study effects was quantified by I^2 values[18,28]. The fixed-effects model was used if no heterogeneity was present (χ^2 P value > 0.100 and I^2 < 50%). If excessive heterogeneity was present, data were first re-checked and the DerSimonian random-effects model was used when heterogeneity persisted[29]. Funnel plots were used to help identify the presence of publication or other types of bias[30-32]. Review Manager software (RevMan© v. 5.0.16) provided by The Cochrane Collaboration was used for data management and statistical analyses.

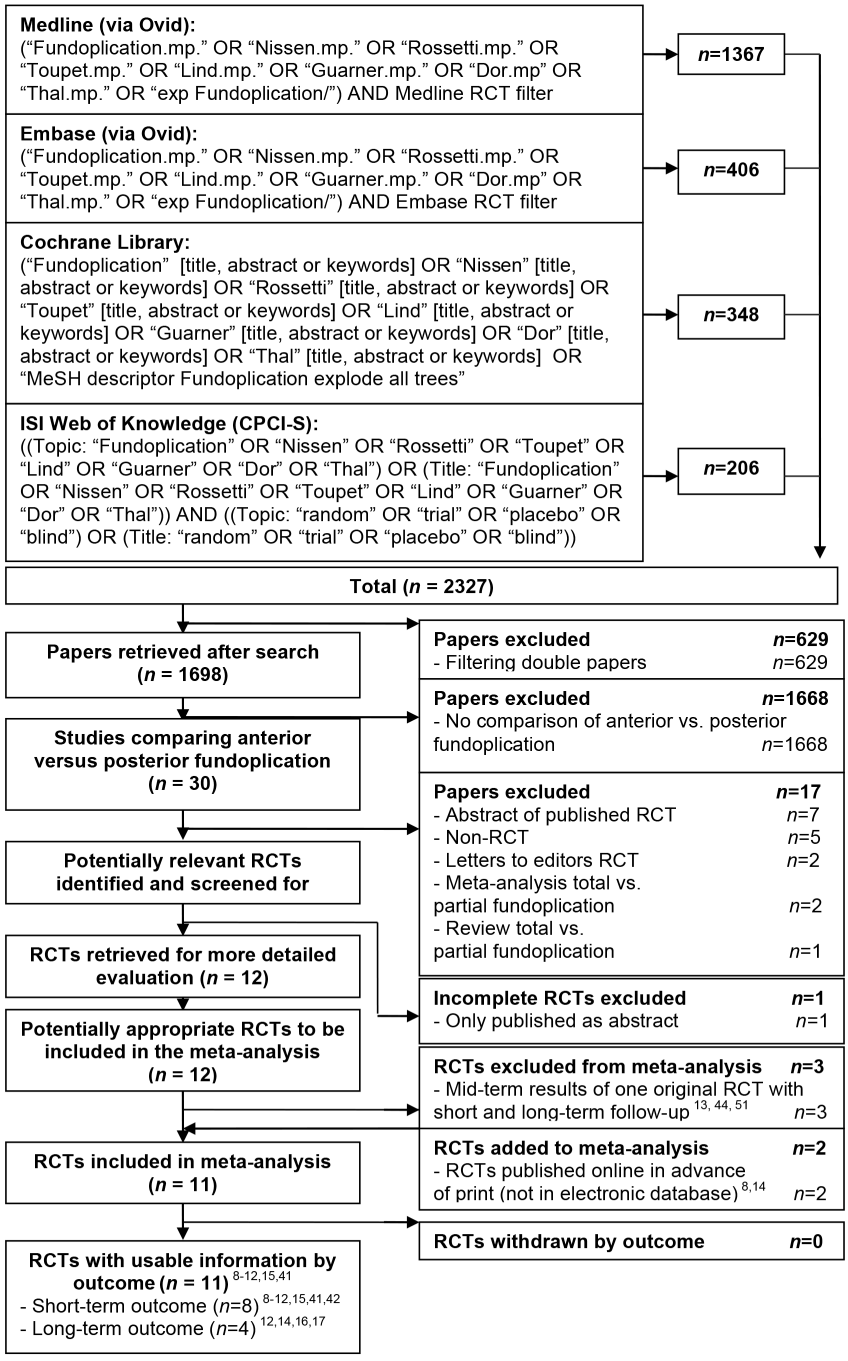

Figure 1. Flow-chart illustrating the details of the search strategy and study selection process according to the QUOROM-statement.[22–24] RTC indicates randomized clinical trial; MesH, medical subject heading; CPCI-S, conference proceedings citation index—science.

RESULTS

Description of studies

A total of 2327 potential relevant publications were identified (Figure 1). Thirty papers comparing anterior versus posterior fundoplication were identified. Five studies did not randomly allocate patients[33-37]. Two meta-analyses[20,38], one review[39] and one German publication that was published as an abstract only without a peer-reviewed publication[40] were excluded. Two RCTs were added that had been published online in advance of print and were not listed in the electronic database[8,14]. Finally, 11 publications on seven original RCTs[8-12,15,41] comparing laparoscopic anterior *versus* posterior fundoplication were identified. Eight publications[8-12,15,41,42] reported short-term results and four publications evaluated long-term outcome[12,14,16,17] (Figure 1).

Table 1. Details of included RCTs comparing LAF *versus* LPF

	Year	Period	Method	n	°	Crural repair	DSGV	Bougie	Fixation to esophagus†	Short term FU	Long term FU
Baigrie[12]	'05	'99-'01	Anterior	79	180°	Yes	No	NR	No	12 [12]	24 [12]
			Posterior	84	360°	Yes	No	56 Fr	No		
Chrysos[41]	'04	NR	Anterior	12	180°	Yes	No	None	Yes	6 [41]	
		NR	Posterior	12	360°	Yes	No	None	No		
Khan[8]	'10	NR	Anterior	53	180°	Yes	No	None	Yes	12 [8]	
		NR	Posterior	50	180°	Yes	No	None	Yes		
Lundell[15,16,42]	'03/'07	NR	Anterior	47	120°	Yes	No	None	Yes	12 [15,42]	65 [16]
			Posterior	48	180-200°	Yes	Yes	None	Yes		
Spence[11]	'06	'99-'03	Anterior	40	90°	Yes	No	None	Yes	12 [11]	
			Posterior	39	360°	Yes	No	52 Fr	No		
Watson '99[9,17]	'99/'04/'08	'95-'97	Anterior	54	180°	Yes	No	None	Yes	6 [9]	120 [17]
			Posterior	53	360°	Yes	No	52 Fr	No		
Watson '04[10,14]	'04/''10	'00-'03	Anterior	60	90°	Yes	No	None	Yes	6 [10]	60 [14]
			Posterior	52	360°	Yes	Yes	52-60 Fr	No		

°, Circumference of the wrap; DSGV, Division of the short gastric vessels; †Fixation of the fundoplication to the esophagus; FU, Follow-up (months); NR, Not reported; Fr, French

The seven included trials were published between 1999 and 2010, all with at least 6 months of follow-up. A total of 683 fundoplications (345 LAF; 338 LPF) were performed. In all patients, a standardized LAF with a circumferential range of 90-180° or a standardized LPF with a circumference of 180-360° was created after crural repair (Table 1). Two trials divided the short gastric vessels in the LPF group[10,14-16,42]. One trial enrolled patients with esophageal dysmotility and included 11 patients of this subgroup in both arms[9,17]. Patient characteristics and indications for surgical treatment are listed in Table 2.

Table 2. Patient characteristics

	Method	Age (yr)	Male / female sex	Esophageal dysmotility / total	Indication for surgical treatment
Baigrie[12]	Anterior	NR	45/34	NR	pH or endoscopically proven GERD
	Posterior	NR	49/34	NR	
Chrysos[41]	Anterior	58	4/8	0/12	pH or endoscopically proven GERD
	Posterior	52	9/3	0/12	
Khan[8]	Anterior	43	36/17	0/53	pH or endoscopically proven GERD
	Posterior	43	38/12	0/50	
Lundell[5,16,42]	Anterior	47	34/13	NR	chronic GERD
	Posterior	46	38/18	NR	
Spence[11]	Anterior	46	24/16	0/40	pH or endoscopically proven GERD
	Posterior	47	19/20	0/39	
Watson 1999[9,17]	Anterior	NR	NR	11/54	pH or endoscopically proven GERD
	Posterior	NR	NR	11/53	
Watson 2004[10,14]	Anterior	47	35/25	0/60	pH or endoscopically proven GERD
	Posterior	49	33/19	0/52	

GERD, gastroesophageal reflux disease; pH or endoscopically proven GERD, GERD proven on endoscopy or 24h pH-metry

Table 3 . Risk of bias summary

	Baigrie[12]	Chrysos[41]	Khan[8]	Lundell[15,16,42]	Spence[11]	Watson 1999[9,17]	Watson 2004[10,14]
Adequate sequence generation	Yes	Yes	Yes	No	Yes	Yes	Yes
Allocation concealment	Yes	No	Yes	No	Yes	Yes	Yes
Blinding (observer)	Yes	No	No	No	Yes	Yes	Yes
Blinding (patient)	Yes	No	NR	No	Yes	Yes	Yes
Adequate report on loss to follow-up	Yes	No	Yes	Yes	Yes	Yes	Yes
Free of other sources of bias	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jadad score	5	2	3	1	5	5	5

NR, Not reported

Methodological quality of included studies

The trials had good methodological quality, with a mean Jadad score of 4 (range 1-5) (Table 3). Three trials lacked double blinding[8,15,16,41,42] and two trials did not conceal allocation[15,16,41,42]. One trial did not report the method of sequence generation[15,16,42] and another study did not report loss to follow-up[41]. Four trials reported a sample size calculation[8-11,14,17].

Short-term outcomes

PPI use was the only short-term outcome that was not reported by three or more studies. Mean esophageal acid exposure time on 24-h pH monitoring was higher after LAF (3.3% *vs* 0.8%; WMD 2.04%; 95% CI [0.84, 3.24]; P<0.001; Figure 2). The percentage of patients with heartburn was higher after LAF as well (21% *vs* 8%; RR 2.71; 95% CI [1.72, 4.26]; *P*<0.001; Figure 3). In contrast, the mean Dakkak dysphagia score was lower after LAF (2.5 *vs* 5.7; WMD -2.87; 95% CI [-3.88, -1.87]; P<0.001; Figure 4) and this was accompanied by a lower LES relaxation nadir pressure (4.3 *vs* 8.0 mm Hg; WMD -3.12 mm Hg; 95% CI [-6.04, -0.21]; *P*=0.04; Figure 5). The number of surgical reinterventions was twice as high after LAF compared with LPF, although this difference did not reach statistical significance (8% *vs* 4%; RR 1.94; 95% CI [0.97, 3.87]; *P*=0.06; Figure 6). In the LAF group, 18 out of 22 reoperations were performed for recurrent GERD and 1 for dysphagia. In contrast, 2 out of 11 surgical reinterventions after LPF were for recurrent GERD and 8 for dypshagia. There were no differences in the prevalence of esophagitis and regurgitation (Table 4). The prevalence of inability to belch and gas bloating were similar as well (Table 4). The ability to relieve bloating was higher after LAF (77% *vs* 60%; RR 1.30; 95% CI [1.12, 1.50]; *P*<0.001; Figure 7).

Satisfaction with intervention, willingness to undergo surgery again and LES pressure were not different (Table 4). Operating time, conversion rate, in-hospital complications and length of hospital stay were similar for both groups (Table 4). The included trials reported no mortality. Sensitivity analysis of outcomes with zero events in one arm (heartburn, gas bloating and conversion) yielded similar results. Funnel plots did not demonstrate evidence of publication bias (Figure 8).

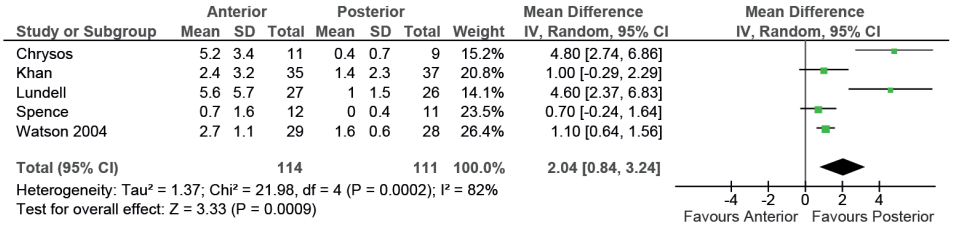

Figure 2. Short-term acid exposure

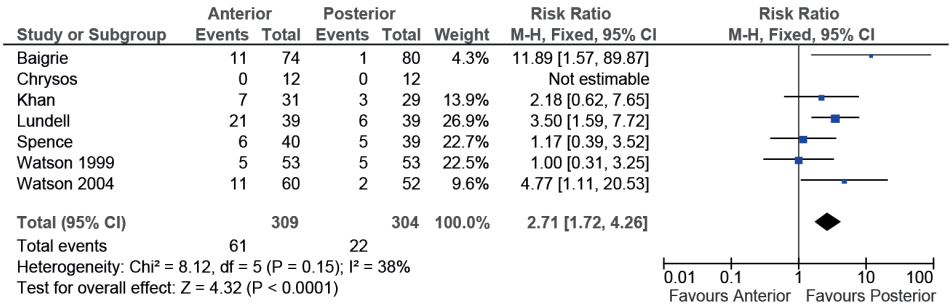

Figure 3. Short-term heartburn

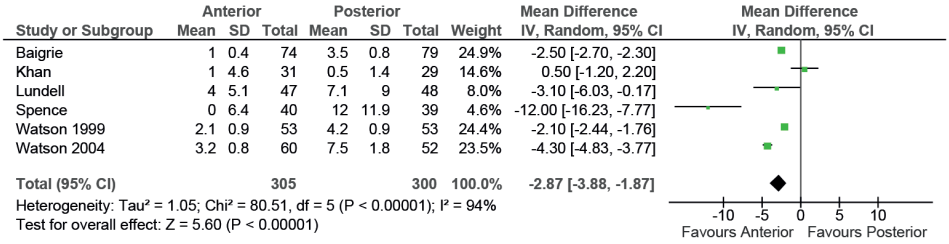

Figure 4. Short-term Dakkak dysphagia score

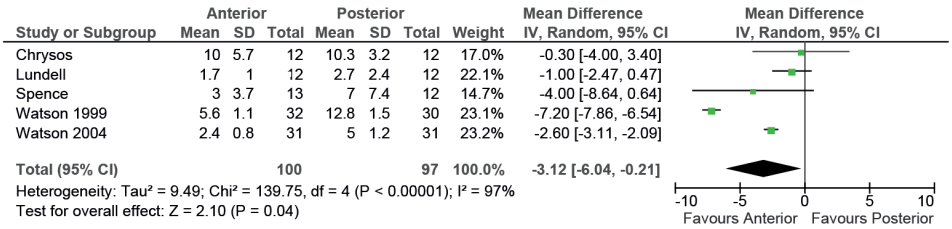

Figure 5. Short-term LES relaxation nadir pressure (mm Hg)

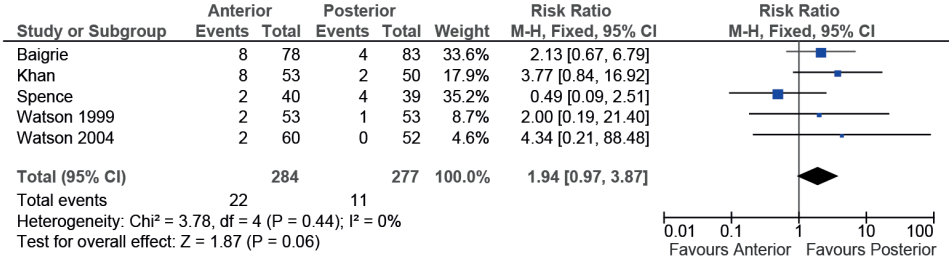

Figure 6. Short-term reoperation rate

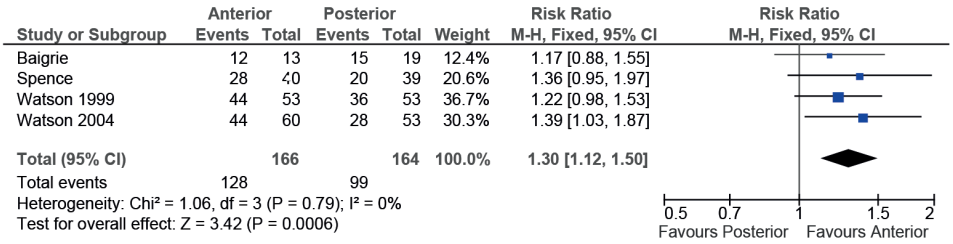

Figure 7. Short-term ability to relieve bloating

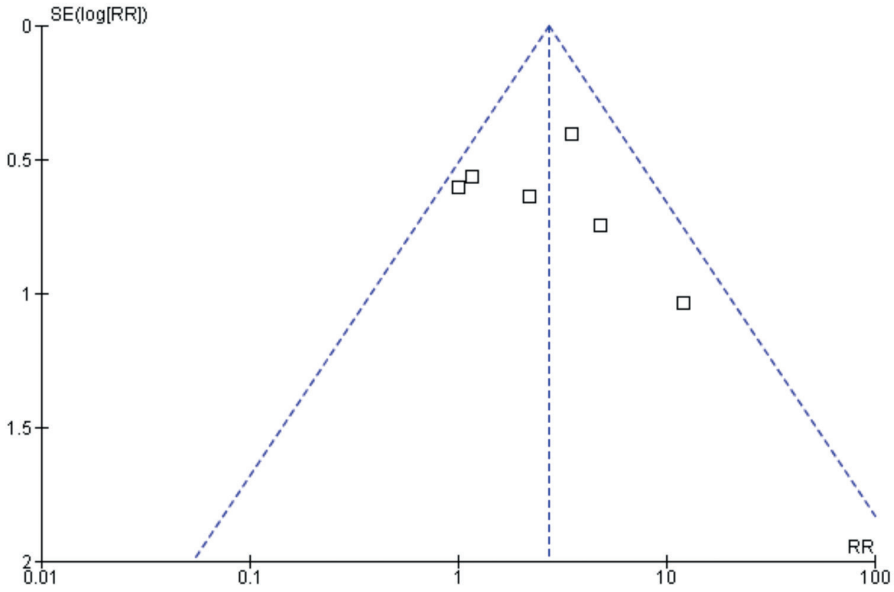

Figure 8. Funnel plot short-term heartburn

Subgroup analysis after exclusion of two RCTs[10,11] that performed 90 degree LAF yielded similar results: mean esophageal acid exposure time (4.0% *vs* 1.1%; WMD 3.36%; 95% CI [0.61, 6.10]; *P*=0.02), heartburn (21% *vs* 7%; RR 2.93; 95% CI [1.72, 5.02]; *P*<0.001), Dakkak dysphagia score (2.0 *vs* 4.1; WMD -2.03; 95% CI [-2.68, -1.39]; *P*<0.001) and ability to relieve bloating (85% *vs* 71%; RR 1.21; 95%CI [1.01, 1.45]; *P*=0.04). The only discrepancies compared with the main analysis were that the difference in surgical reintervention (9.8% *vs* 3.8%; RR 2.60; 95%CI [1.11, 6.08]; *P*=0.03), regurgitation (13% *vs 7%*; RR 3.61; 95% CI [1.79, 7.25]; *P*<0.001) and LES pressure (18.7 *vs* 25.5 mm Hg; WMD -5.65 mmHg; 95% CI [-10.74, -0.56]; *P*=0.03) were significant and the difference in LES relaxation nadir pressure was not significant in the subgroup (5.7 *vs* 10 mm Hg; WMD
-2.99 mm Hg; 95% CI [-8.05, 2.08]; *P*=0.25).

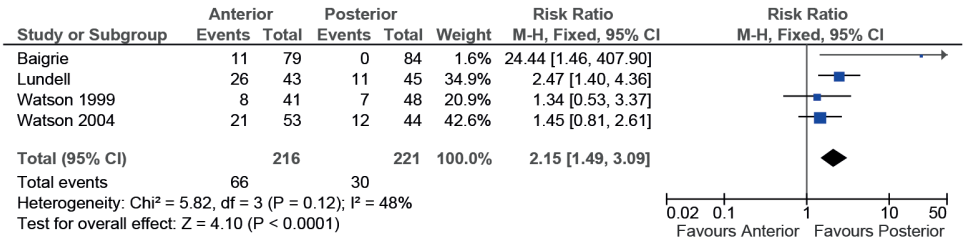

Figure 9. Long-term heartburn

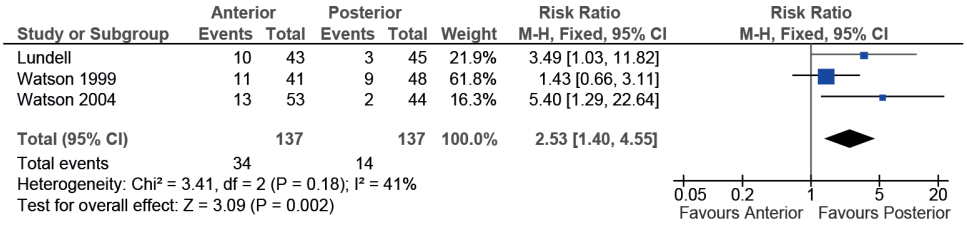

Figure 10. Long-term PPI use

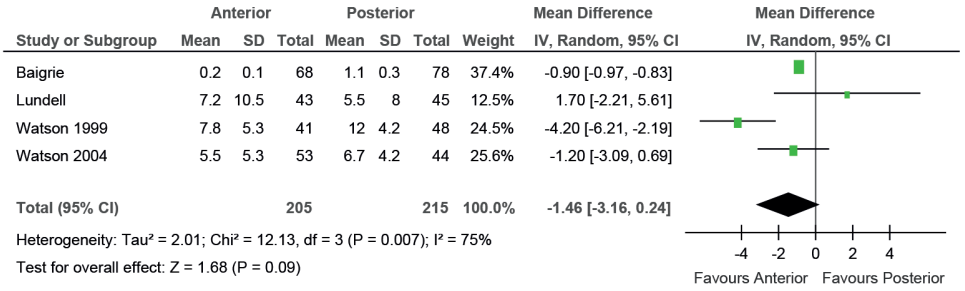

Figure 11. Long-term Dakkak dysphagia score

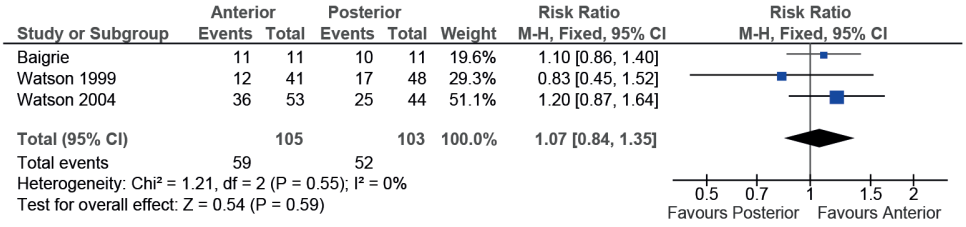

Figure 12. Long-term ability to relieve bloating

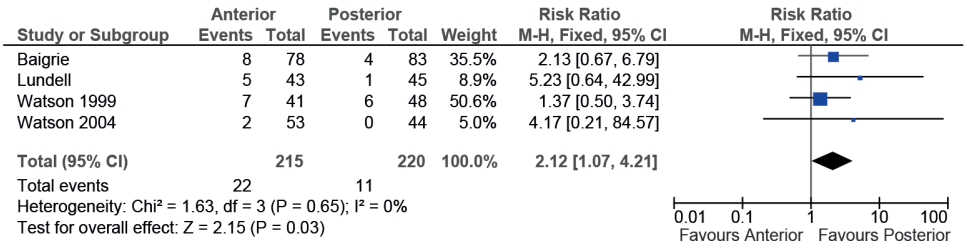

Figure 13. Long-term reoperation rate

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Table 4. Short-term outcome

Short-term outcom	RCTs (n)	LAF	LPF	RR	WMD	CI	P-value
Esophagitis	3	8/67 [12%]	4/72 [6%]	2.17		0.67, 7.02	0.19
Regurgitation	5	36/225 [16%]	25/214 [12%]	1.09		0.28, 4.24	0.90
Inability to belch	5	21/201 [10%]	44/188 [23%]	0.52		0.21, 1.25	0.14
Gas boating	6	50/245 [20%]	63/245 [26%]	0.76		0.56, 1.03	0.07
Satisfaction with intervention	5	213/258 [83%]	214/253 [85%]	0.98		0.91, 1.05	0.55
Willing to repeat surgery	5	257/276 [93%]	241/270 [89%]	1.04		0.96, 1.14	0.35
LES pressure (mm Hg)	6	17.7 (*n*=135)	16.6 (*n*=133)		-3.87	-10.56, 2.82	0.26
Conversion rate	6	7/298 [2%]	4/290 [1%]	1.57		0.50, 4.91	0.44
Operating time (min)	5	67 (*n*=280)	68 (*n*=272)		-1.60	-8.79, 5.58	0.66
In-hospital complications	5	17/286 [6%]	15/278 [5%]	1.06		0.54, 2.08	0.86
Length of hospital stay (days)	4	2.5 (*n*=208)	2.4 (*n*=199)		0.09	-0.05, 0.24	0.21

Long-term outcomes

In the long-term, 3 out of 4 primary outcomes and 6 out of 10 secondary outcomes were reported by three or more studies. LAF resulted in a persistent two-fold higher rate of heartburn compared with LPF at long-term follow-up (31% *vs* 14%; RR 2.15; 95% CI [1.49, 3.09]; *P*<0.001; Figure 9). This was associated with more PPI use in the LAF group (25% *vs* 10%; RR 2.53; 95% CI [1.40, 4.45]; *P*=0.002; Figure 10). Dakkak dysphagia scores (4.6 *vs* 5.6; WMD -1.46; 95% CI [-3.16, 0.24]; *P*=0.09; Figure 11) and the ability to relieve bloating (56% *vs* 50%; RR 1.07; 95% CI [0.84, 1.35]; *P*=0.59; Figure 12) became similar in the LAF and LPF group with extension of follow-up. The reoperation rate remained twice as high after LAF in the long-term (10% *vs* 5%; RR 2.12; 95% CI [1.07, 4.21]; *P*=0.03; Figure 13). In the LAF group, 18 out of 22 reoperations were performed for recurrent GERD and 1 for dysphagia. In contrast, 2 out of 11 surgical reinterventions after LPF were for recurrent GERD and 8 for dysphagia.

In line with the short-term outcome, there were no differences in inability to belch, gas bloating, satisfaction with intervention and willingness to undergo surgery again (Table 5). Sensitivity analysis of outcomes with zero events in one arm (heartburn and reoperation rate) yielded similar results. Funnel plots did not demonstrated evidence of publication bias.
Subgroup analysis after exclusion of an RCT that performed 90 degree LAF[14] yielded similar results: PPI use (25% *vs* 13%; RR 1.97; 95% CI [1.03, 3.76]; *P*=0.04), Dakkak dysphagia score (4.2 *vs* 5.3; WMD -1.46; 95% CI [-4.10, 1.17]; *P*=0.28) and ability to relieve bloating (44% *vs* 46%; RR 0.93; 95% CI [0.65, 1.34]; *P*=0.71). The differences in heartburn (28% *vs* 10%; RR 2.41; 95% CI [0.95, 6.11]; *P*=0.06) and reoperation rate (12% *vs* 6%; RR 2.01; 95% CI [1.00, 4.07]; *P*=0.05) were similar as well and the only discrepancy compared with the main analysis was that the differences of the subgroup were at the limit of statistical significance.

Table 5. Long-term outcome

Long-term outcome	RCTs (n)	LAF	LPF	RR	CI	P-value
Inability to belch	4	24/155 [15%]	49/158 [31%]	0.53	0.25, 1.11	0.09
Gas bloating	3	53/131 [40%]	46/140 [33%]	1.12	0.84, 1.49	0.45
Satisfaction with intervention	4	167/204 [82%]	195/214 [91%]	0.89	0.74, 1.08	0.23
Willing to repeat surgery	3	121/132 [92%]	126/135 [93%]	0.99	0.90, 1.09	0.84

RCT, Randomized clinical trial; LAF, Laparoscopic anterior fundoplication; LPF, Laparoscopic posterior fundoplication; RR, Risk ratio; WMD, Weighted mean difference; CI, Confidence interval

DISCUSSION

Between 2004 and 2010, seven RCTs were published comparing LAF and LPF for GERD[8,11,12,14,16,17,41]. These individual trials are inconclusive and are too small to identify significant differences regarding the most important determinants of successful antireflux surgery: objective reflux control and the need for surgical reintervention. Previous meta-analysis on antireflux surgery[7,20,38,43] have not reviewed 9 recent publications on 6 out of 7 original RCTs comparing LAF to LPF[8,13-17,41,42,44]. More importantly, 4 recent papers[13,14,16,17] on 5- and 10-year outcome have not yet been pooled in meta-analysis. Long-term follow-up is critical to evaluate differences in reflux control and reoperation rate. Previous systematic reviews on antireflux surgery lack meta-analysis of long-term outcome and definite conclusions regarding the surgical procedure of choice[7,20,38,43]. This meta-analysis aims to provide this evidence by pooling short and long-term outcomes separately.
The methodological quality of the 7 RCTs included in the current meta-analysis was good, with a mean Jadad score of 4. Surgical techniques of the included trials were standardized and similar: in all patients a 90-180° anterior or 180-360° posterior fundoplication was

created after crural repair. Two trials divided the short gastric vessels in the LPF group[10,14-16,42]. This is not likely to introduce any bias since it has previously been demonstrated that division of the short gastric vessels does not influence outcome[20]. One trial enrolled a small number of patients with esophageal dysmotility[9]. The current study analyzed patients with and without esophageal dysmotility together as 4 RCTs have shown that outcome of fundoplication is similar in patients with normal and abnormal esophageal motility[45-48]. There were no other potential sources of bias.

The current short-term results demonstrate that esophageal acid exposure time, as measured with 24-hr pH monitoring, is higher after LAF. The clinical impact of this higher acid exposure is illustrated by a 2-fold higher rate of recurrent heartburn compared with LPF. The short-term reoperation rate is twice as high after LAF with the notable fact that 80% of these reinterventions are performed for recurrent GERD. In the short-term this is counterbalanced by a lower LES relaxation nadir pressure, resulting in a lower Dakkak dysphagia score and less difficulty to relieve bloating in the LAF group. Physiological studies have previously demonstrated that LES relaxation nadir pressure is the only standard manometry parameter correlated with postfundoplication dysphagia[49,50].

The present long-term results demonstrate that Dakkak dysphagia scores and ability to relieve bloating become similar with extension of follow-up. The individual results of the 4 RCTs underline that dysphagia decreases during long-term follow-up[12,14,16,17]. The current results demonstrate that differences in these postfundoplication symptoms between LAF and LPF are most prominent in the early postoperative period and gradually fade with time. In contrast, the higher rate of heartburn after LAF persists during long-term follow-up. Twice as many patients have recurrent GERD after LAF, with more PPI use compared with LPF. The long-term reoperation rate is twice as high after LAF as well and recurrent GERD is the indication for surgical reintervention in more than 80% of the patients. There are no differences in the ability to belch and gas bloating in both the short and the long-term. The high PPI use after LAF probably explains why patient satisfaction was similar in both groups, despite the higher rate of recurrent GERD compared with LPF. The short and long-term results of subgroup analysis after exclusion of two RCTs[10,11] that performed 90 degree LAF were similar.

On the basis of the current results LPF should be regarded as the fundoplication of choice for GERD. LPF comprises both posterior total (Nissen) and posterior partial fundoplication. A modified Toupet fundoplication, including crural repair and division of the short gastric vessels, is by far the most commonly performed posterior partial fundoplication[7]. The current study does not include separate analysis of posterior total and posterior partial fundoplication, because the individual results of 10 RCTs and two meta-analyses of these studies have demonstrated that reflux control is similar[7,20]. A subgroup analysis of the first meta-analysis demonstrated no differences in reflux recurrence detected by either endoscopy and/or pH-metry or symptoms between posterior partial (Toupet) fundoplication and posterior total fundoplication (Nissen) at 30 [6-60] months[20]. The second meta-analysis showed that Toupet fundoplication has a similar rate of recurrent pathological acid exposure, esophagitis and reflux symptoms compared with Nissen

fundoplication at 23 months [12-60], with homogeneity of 1-, 2- and 5-year outcome[7].
A recent systematic review that included 10-year follow-up studies confirmed that there are no differences in esophagitis, heartburn and reflux recurrence[43]. The second meta-analysis also found that posterior partial fundoplication reduces dysphagia, gas-related symptoms and reoperation rate compared with posterior total fundoplication[7]. On the basis of the level 1a evidence provided by our previous meta-analysis[7] and this study, it could be argued that laparoscopic posterior partial fundoplication offers effective reflux control with minimal postfundoplication symptoms, and can be considered the surgical procedure of choice for GERD.
In conclusion, LAF is associated with higher esophageal acid exposure time and prevalence of heartburn compared with LPF. In the short-term this is counterbalanced by less severe dysphagia compared with LPF. However, dysphagia scores become similar in the long-term, with a persistent higher rate of recurrent heartburn and PPI use after LAF. The reoperation rate is twice as high after LAF as well, mainly due to reinterventions for recurrent GERD. Perioperative outcomes, patient satisfaction and the prevalence of gas-related symptoms are similar. These results lend level 1a support for the use of LPF as the surgical treatment of choice for GERD.

REFERENCES

1 Draaisma WA, Rijnhart-de Jong HG, Broeders IA et al. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. Ann Surg 2006; 244:34-41.

2 Broeders JA, Rijnhart-de Jong HG, Draaisma WA et al. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. Ann Surg 2009; 250:698-706.

3 Salminen PT, Hiekkanen HI, Rantala AP et al. Comparison of long-term outcome of laparoscopic and conventional nissen fundoplication: a prospective randomized study with an 11-year follow-up. Ann Surg 2007; 246:201-206.

4 Horvath KD, Jobe BA, Herron DM et al. Laparoscopic Toupet fundoplication is an inadequate procedure for patients with severe reflux disease. J Gastrointest Surg 1999; 3:583-591.

5 Patti MG, Robinson T, Galvani C et al. Total fundoplication is superior to partial fundoplication even when esophageal peristalsis is weak. J Am Coll Surg 2004; 198:863-869.

6 Eubanks TR, Omelanczuk P, Richards C et al. Outcomes of laparoscopic antireflux procedures. Am J Surg 2000; 179:391-395.

7 Broeders JA, Mauritz FA, Ahmed AU et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. Br J Surg 2010; 97:1318-1330.

8 Khan M, Smythe A, Globe J et al. Randomized controlled trial of laparoscopic anterior versus posterior fundoplication for gastro-oesophageal reflux disease. in press Aust NZ J Surg 2010.

9 Watson DI, Jamieson GG, Pike GK et al. Prospective randomized double-blind trial between laparoscopic Nissen fundoplication and anterior partial fundoplication. Br J Surg 1999; 86:123-130.

10 Watson DI, Jamieson GG, Lally C et al. Multicenter, prospective, double-blind, randomized trial of laparoscopic nissen vs anterior 90 degrees partial fundoplication. Arch Surg 2004; 139:1160-1167.

11 Spence GM, Watson DI, Jamiesion GG et al. Single center prospective randomized trial of laparoscopic Nissen versus anterior 90 degrees fundoplication. J Gastrointest Surg 2006; 10:698-705.

12 Baigrie RJ, Cullis SN, Ndhluni AJ et al. Randomized double-blind trial of laparoscopic Nissen fundoplication versus anterior partial fundoplication. Br J Surg 2005; 92:819-823.

13 Ludemann R, Watson DI, Jamieson GG et al. Five-year follow-up of a randomized clinical trial of laparoscopic total versus anterior 180 degrees fundoplication. Br J Surg 2005; 92:240-243.

14 Nijjar R, Watson D, Jamieson G et al. Five-year follow-up of a multicenter, double-blind randomized clinical trial of laparoscopic Nissen vs anterior 90 degrees partial fundoplication. Arch Surg 2010; 145:552-557.

15 Hagedorn C, Jonson C, Lonroth H et al. Efficacy of an anterior as compared with a posterior laparoscopic partial fundoplication: results of a randomized, controlled clinical trial. Ann Surg 2003; 238:189-196.

16 Engström C, Lönroth H, Mardani J et al. An anterior or posterior approach to partial fundoplication? Long-term results of a randomized trial. World J Surg 2007; 31:1221-1225.

17 Cai W, Watson DI, Lally CJ et al. Ten-year clinical outcome of a prospective randomized clinical trial of laparoscopic Nissen versus anterior 180(degrees) partial fundoplication. Br J Surg 2008; 95:1501-1505.

18 Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Chichester: John Wiley & Sons; 2008.

19 BMJ Clinical Evidence website. Search Filters. http://clinicalevidence.bmj.com/ceweb/about/search_filters.jsp [accessed 1 June 2010].

20 Catarci M, Gentileschi P, Papi C et al. Evidence-based appraisal of antireflux fundoplication. Ann Surg 2004; 239:325-337.

21 Dakkak M, Bennett JR. A new dysphagia score with objective validation. J Clin Gastroenterol 1992; 14:99-100.

22 Moher D, Cook DJ, Eastwood S et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999; 354:1896-1900.

23 Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283:2008-2012.

24 Clarke M, Horton R. Bringing it all together: Lancet-Cochrane collaborate on systematic reviews. Lancet 2001; 357:1728.

25 Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5:13.

26 Jadad AR, Moore RA, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17:1-12.

27 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21:1539-1558.

28 Higgins JP, Thompson SG, Deeks JJ et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327:557-560.

29 DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7:177-188.

30 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50:1088-1101.

31 Egger M, Davey SG, Schneider M et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315:629-634.

32 Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. Stat Med 2001; 20:641-654.

33 Fein M, Bueter M, Thalheimer A et al. Ten-year outcome of laparoscopic antireflux surgery. J Gastrointest Surg 2008; 12:1893-1899.

34 Polfo N, Borgonovo G, Puglisi M et al. Partial fundoplication (DOR) versus fundoplication (Nissen-Rossetti) in the therapy of the reflux gastric esophageal disease. Ann Gastroenterol Hepatol (Paris) 1983; 19:191.

35 Stewart GD, Watson AJ, Lamb PJ et al. Comparison of three different procedures for antireflux surgery. Br J Surg 2004; 91:724-729.

36 Watson A. Update: total versus partial laparoscopic fundoplication. Dig Surg 1998; 15:172-180.

37 Wong AS, Myers JC, Jamieson GG. Esophageal pH profile following laparoscopic total fundoplication compared to anterior fundoplication. J Gastrointest Surg 2008; 12:1341-1345.

38 Varin O, Velstra B, De SS et al. Total vs partial fundoplication in the treatment of gastroesophageal reflux disease: a meta-analysis. Arch Surg 2009; 144:273-278.

39 Fein M, Seyfried F. Is there a role for anything other than a Nissen's operation? J Gastrointest Surg 2010; 14 Suppl 1:S67-74.

40 Terzic A, Muller M, Hermeneit S et al. The laparoscopic therapy of GERD - semifundoplication according to Dor or Toupet? A prospective, randomised study. Z Gastroenterol 2007; 45:803.

41 Chrysos E, Athanasakis E, Pechlivanides G et al. The effect of total and anterior partial fundoplication on antireflux mechanisms of the gastroesophageal junction. Am J Surg 2004; 188:39-44.

42 Engström C, Ruth M, Lönroth H et al. Manometric characteristics of the gastroesophageal junction after anterior versus posterior partial fundoplication. Dis Esophagus 2005; 18:31-36.

43 Shan CX, Zhang W, Zheng XM et al. Evidence-based appraisal in laparoscopic Nissen and Toupet fundoplications for gastroesophageal reflux disease. World J Gastroenterol 2010; 16:3063-3071.

44 Woodcock SA, Watson DI, Lally C et al. Quality of life following laparoscopic anterior 90 degrees versus Nissen fundoplication: results from a multicenter randomized trial. World J Surg 2006; 30:1856-1863.

45 Rydberg L, Ruth M, Lundell L. Mechanism of action of antireflux procedures. Br J Surg 1999; 86:405-410.

46 Fibbe C, Layer P, Keller J et al. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized, clinical, and manometric study. Gastroenterology 2001; 121:5-14.

47 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.

48 Booth MI, Stratford J, Jones L et al. Randomized clinical trial of laparoscopic total (Nissen) versus posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. Br J Surg 2008; 95:57-63.

49 Scheffer RC, Samsom M, Frakking TG et al. Long-term effect of fundoplication on motility of the oesophagus and oesophagogastric junction. Br J Surg 2004; 91:1466-1472.

50 Mathew G, Watson DI, Myers JC et al. Oesophageal motility before and after laparoscopic Nissen fundoplication. Br J Surg 1997; 84:1465-1469.

51 Anderson JA, Myers JC, Watson DI et al. Concurrent fluoroscopy and manometry reveal differences in laparoscopic Nissen and anterior fundoplication. Dig Dis Sci 1998; 43:847-853.

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5

Five-year outcome of laparoscopic anterior partial versus Nissen fundoplication: four randomized trials

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ABSTRACT

Objective

To compare longer term (5-year) outcomes for reflux control and post-surgery side effects following laparoscopic anterior (90° and 180°) partial vs. Nissen fundoplication for gastroesophageal reflux.

Summary Background Data

Laparoscopic Nissen fundoplication is the most frequently performed surgical procedure for gastroesophageal reflux. It achieves excellent control of reflux, but in some patients is followed by troublesome side effects. To reduce the risk of side effects laparoscopic anterior partial fundoplication variants have been advocated, although some studies suggest poorer reflux control.

Methods

From 1995 to 2003, 461 patients with gastroesophageal reflux were enrolled in 4 randomized controlled trials comparing anterior partial vs. Nissen fundoplication. Two trials evaluated anterior 180°, and 2 anterior 90° partial fundoplication. The original trial data were combined and a re-analysis from original data was undertaken to determine outcomes at 5-years follow-up. Reflux symptom control and side effects were evaluated in a blinded fashion using standardized questionnaires, including 0-10 analog scores (0=no symptoms, 10=severe symptoms).

Results

At 5 years, patients who underwent an anterior 90° or 180° partial fundoplication had less side effects compared with Nissen fundoplication and were equally satisfied with the overall outcome. Reflux control, measured by heartburn scores and antisecretory medication use, was similar for anterior 180° partial vs. Nissen fundoplication, but inferior after anterior 90° partial vs. Nissen fundoplication.

Conclusions

Anterior 180° partial fundoplication achieves durable control of reflux symptoms and less side effects compared with Nissen fundoplication. Although reflux control following anterior 90° partial fundoplication appears less effective than after Nissen fundoplication. This data supports the use of anterior 180° partial fundoplication for the surgical treatment of gastroesophageal reflux.

INTRODUCTION

Laparoscopic fundoplication is the surgical approach of choice for the treatment of gastroesophageal reflux disease. It achieves similar long-term reflux control, with less short and long-term problems, compared to open fundoplication.[1] Laparoscopic Nissen fundoplication is the most frequently performed antireflux operation and alters the anatomy of the gastroesophageal junction. The gastroesophageal junction serves three functions. The first is to allow swallowed solids and liquids to pass from esophagus to the stomach. The second is to allow venting of gas from the stomach to the mouth (i.e. belching), and the third function is to prevent the backward flow of gastric contents into the esophagus (i.e. gastroesophageal reflux). Nissen fundoplication restores the third function and provides excellent reflux control.[1-3] However, it delivers a supracompetent valve which can impair the first two functions. Three meta-analyses have demonstrated that Nissen fundoplication is followed by a significant incidence of troublesome postfundoplication side effects, including troublesome postoperative dysphagia and gas related problems.[4-6]

Laparoscopic partial fundoplication procedures have been proposed as alternatives and aim to reduce the incidence of post-fundoplication side effects. Recently published American guidelines for antireflux surgery state that partial fundoplication provides similar 5-year reflux control, but with less postoperative dysphagia and fewer reoperations compared with Nissen fundoplication.[7] The guidelines suggested that laparoscopic anterior partial fundoplication may be less effective in the long-term. However, there may be important differences between different anterior partial fundoplication variants (e.g. 90° vs. 120° vs. 180°), and therefore generalizing all anterior partial fundoplication procedures into a single category might not be appropriate. Further, specific differences between different anterior partial fundoplication variants are not well understood. A recent meta-analysis also pooled anterior 90°, 120° and 180° partial fundoplications, and compared this group to pooled results of posterior 180°, 200° and Nissen fundoplication.[8] This analysis also suggested that reflux control for the pooled anterior fundoplication types was inferior to the pooled results of the posterior and Nissen fundoplication procedures.[8] However, this analysis failed to recognize and consider important differences between the fundoplication subtypes, and that technical differences might be important for achieving good clinical outcomes. Further, this meta-analysis did not access raw data from the original trials. Hence, it is not appropriate to extrapolate its conclusions to specific fundoplication procedures.

To overcome the problems inherent in previous studies, we combined raw data sets from 4 randomized controlled trials of laparoscopic anterior partial vs. laparoscopic Nissen fundoplication, and used the original data to determine the clinical outcomes at 5-years follow-up. Two of the trials compared anterior 90° partial with Nissen fundoplication,[9;10] and 2 compared anterior 180° with Nissen fundoplication.[11;12] These combined data sets allowed randomized comparisons of both anterior partial fundoplication variants with Nissen fundoplication.

METHODS

Study design and participants

Data sets from 4 previously reported randomized controlled trials of anterior 180° [11;12] or anterior 90° [9;10] partial fundoplication vs. Nissen fundoplication were combined and reanalyzed (Figure 1). Patients presenting for primary antireflux surgery from 1995 to 2003 were recruited into these trials. Two trials compared anterior 90° partial vs. Nissen fundoplication[9;10] and 2 compared anterior 180° partial vs. Nissen fundoplication.[11;12] Five-year outcome data for 2 of the trials has been reported previously.[13;14]

All trials used a common methodology. Procedures were standardized across all centers, follow-up was undertaken in a blinded fashion, and common standardized symptom and outcome scores were used in all studies. All enrolled patients had objective evidence of gastroesophageal reflux disease at either 24-hour pH monitoring (pH <4 for more than 7% of time) or upper endoscopy (ulcerative esophagitis).[9-12] 393 patients underwent laparoscopic fundoplication in either Adelaide, South Australia[9-11] or in Cape Town, South Africa.[12] Sixty eight patients underwent surgery elsewhere in Australia or New Zealand within a multicentre trial of anterior 90° vs. Nissen fundoplication which was coordinated from Adelaide.[9] The lead clinician in the South African study worked in Adelaide in 1995, and participated in the development of the first anterior 180° partial vs. Nissen fundoplication trial undertaken in Adelaide.[11] He applied the same surgical techniques, clinical outcome scores and follow-up methodology in the South African trial.

Exclusion criteria were: age under 18 yrs or over 75 yrs, esophageal motility disorders which precluded Nissen fundoplication, contemporaneous abdominal procedures, and previous gastric or esophago-gastric junction surgery. Data for preoperative work-up, perioperative care and follow-up was collected prospectively and entered into computerized databases. Follow-up was undertaken yearly by "blinded" research nurses.

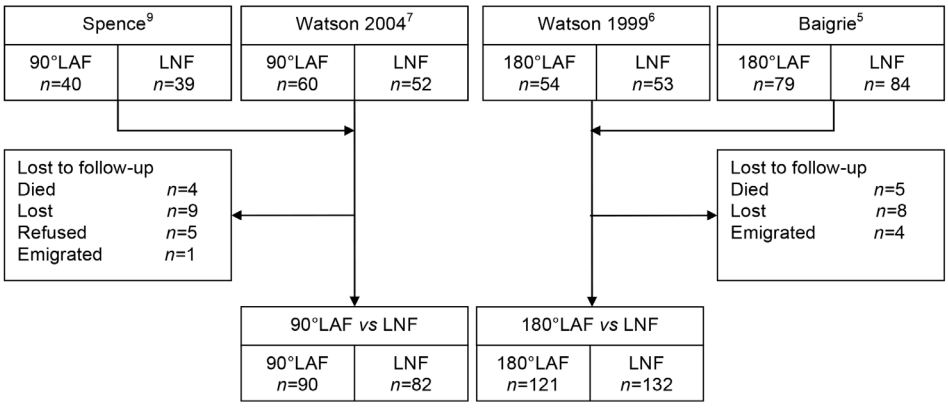

Figure 1. Study profile: CONSORT analysis 5-year follow-up for the anterior 90° partial (90°LAF), anterior 180° partial (180°LAF) and Nissen fundoplication (LNF) groups

The human research ethics committees of the hospitals in which surgery was undertaken approved the protocols of all trials.

Surgical procedures

In each trial, patients were randomized 1:1 to undergo either anterior (90° or 180°) partial or Nissen fundoplication. All procedures were commenced laparoscopically. The surgical techniques have been described in detail elsewhere.[9-12] The initial steps for all three types of fundoplication were identical: hiatal dissection with minimal use of diathermy, preservation of the hepatic branch of the vagus nerve, mobilization of the distal esophagus and routine posterior hiatal repair. Short gastric blood vessels were not routinely divided, except in patients undergoing Nissen fundoplication in one of the 4 trials.[9]

Laparoscopic anterior 90° partial fundoplication was fashioned by first stabilizing the intra-abdominal esophagus with a posterior esophagopexy suture. The angle of His was then accentuated by placing two sutures between the left side of the esophagus and the adjacent gastric fundus – the upper suture also incorporating the hiatal rim. Next, the gastric fundus was sutured loosely over the left side and the front of the esophagus using an apical suture that anchored the fundus to the anterior esophagus and the apex of the hiatal rim in the midline. The inferior edge of the fundal fold was also sutured to the anterior esophagus in the midline.[9;10] Laparoscopic anterior 180° partial fundoplication was constructed by suturing the anterior fundal wall to the right and left hiatal pillars and the apex of the hiatal rim using five to six sutures.[11;12] The key difference between the 2 anterior partial fundoplication techniques was that the fundus was anchored to the right hiatal pillar during anterior 180° fundoplication, but not during anterior 90° fundoplication. Laparoscopic Nissen fundoplication entailed construction of a loose 1 and 2 cm long 360° fundoplication with a 52 to 60 Fr intra-esophageal bougie present to help ensure a tension-free wrap .[9-12;15] Three sutures were used to secure the wrap.[9-12;15]

Clinical outcomes

Preoperative, perioperative and follow-up data were collected prospectively. Follow-up entailed the application of a standardized set of questions, administered each year by either postal questionnaire or telephone interview, 5-year follow-up data was analyzed. Other events during the follow-up period, such as endoscopic dilatation for dysphagia or surgical reoperation, were also identified prospectively and recorded. Visual analog scores were used to assess symptoms. Heartburn was evaluated using an analog score (0=no heartburn; 10=severe heartburn) and by determining the use of antisecretory medications. The presence of dysphagia (yes/no question) and analog scores for solids and liquids (0=no dysphagia; 10=severe dysphagia) were recorded. A validated 0-45 dysphagia score[16] was used to quantify the ability to swallow nine types of liquids and solids (0=no dysphagia; 45=severe dysphagia).[17] Patients were also asked if they were able to eat a normal diet. Gas-related symptoms were assessed by yes/no questions which determined the ability to belch, presence of abdominal bloating symptoms, ability to relieve bloating by belching, and increased flatulence. Patient satisfaction was scored using a analog score

(0=dissatisfied; 10=satisfied), and a Visick score (1= no symptoms; 2= mild symptoms; 3= moderate symptoms; 4= moderate symptoms interfering with life; 5= symptoms as bad or worse after surgery).[17] Patients were also asked whether they still regarded their initial decision to undergo surgery to be correct.

Statistical Analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS inc., Chicago, IL). Data were analyzed according to the intention-to-treat principle. Continuous variables were expressed as mean ± standard deviation [SD] and groups were compared using the Mann-Whitney U test. Ordinal variables were expressed as percentages and differences between groups were analyzed using the χ^2 test. Differences in the number of patients undergoing endoscopic dilatation for dysphagia or reoperation were determined using Kaplan-Meier survival curves with log-rank tests.

RESULTS

461 patients were enrolled in the 4 randomized controlled trials and underwent either laparoscopic anterior partial fundoplication (n=233) or laparoscopic Nissen fundoplication (n=228) for gastroesophageal reflux. A 5-year outcome was available for 434 (94.1%). Nine (2.0%) patients died during follow-up, and clinical outcome scores were available for 425 (92.2%) patients 5 years after surgery; anterior partial (n=211), Nissen fundoplication (n=214). Full details of patient follow-up are summarized in Figure 1. Data was available from a subset of 172 patients for comparison of anterior 90° partial (n=90) vs. Nissen fundoplication (n=82), and from 253 patients for comparison of anterior 180° partial (n=121) vs. Nissen fundoplication (n=132). Baseline patient characteristics were similar for the anterior partial and Nissen groups (Table 1).

Table 1. Baseline characteristics of patients according to treatment group

	Anterior 90° vs. Nissen fundoplication		**Anterior 180° vs Nissen fundoplication**	
	Anterior 90°	Nissen	Anterior 180°	Nissen
Patients (*n*)	90	82	121	132
Age (yr)	46.5 (22-76)	47.7 (22-72)	44.9 (20-74)	44.7 (16-71)
Male / female sex	52 / 38	48 / 34	72 / 49	82 / 50
Body mass index (kg/m^2)*	29.5 [5.1]	30.0 [5.7]	27.7 [4.3]	30.0 [6.6]
Follow-up interval (months)*	64.7 [9.6]	63.2 [8.2]	67.7 [10.1]	67.4 [9.6]

* values are gives as mean [SD]

Anterior 90° partial vs. Nissen fundoplication

Outcomes at 5 years for anterior 90° partial vs. Nissen fundoplication are summarized in Table 2. Heartburn scores were higher following anterior 90° partial fundoplication and the use of antisecretory medication was more common. However, dysphagia was less common, more patients were able to eat a normal diet, the mean analog score for dysphagia for solid food was lower, and the mean 0-45 dysphagia score was lower following anterior 90° partial fundoplication. Gas-related symptoms were less common after anterior 90° partial fundoplication, with better preserved ability to belch, and less flatulence. All measures of overall satisfaction with the outcome of surgery were similar for the 2 procedures.

Table 2. Symptomatic outcome at 5 years after anterior 90° and Nissen fundoplication

	Anterior 90°	Nissen	P-value
Reflux symptoms			
Analog heartburn score*	2.2 [2.5] (*n*=78)	1.6 [2.5] (*n*=73)	0.043
Use of antisecretory drugs	29/84 [34.5%]	9/76 [11.8%]	0.001
Dysphagia			
Dysphagia	26/84 [30.9%]	38/76 [50.0%]	0.014
Analog score for dysphagia for liquids*	0.7 [1.6] (*n*=90)	1.2 [2.5] (*n*=82)	0.399
Analog score for dysphagia for solids*	1.6 [2.4] (*n*=89)	2.9 [3.0] (*n*=81)	0.001
0-45 Dysphagia score*	6.4 [8.3] (*n*=90)	10.8 [11.0] (*n*=82)	0.007
Normal diet	83/87 [95.4%]	68/82 [82.9%]	0.009
Dilatation for dysphagia	2/90 [2.2%]	5/82 [6.1%]	0.202
Gas-related symptoms			
Inability to belch	3/87 [3.4%]	29/82 [35.4%]	<0.001
Gas bloating	48/89 [53.9%]	47/82 [57.3%]	0.656
Inability to relieve bloating	32/64 [50.0%]	26/61 [42.6%]	0.408
Increased flatulence	36/88 [40.9%]	55/82 [67.1%]	0.001
Patient satisfaction			
Analog score for satisfaction*	7.3 [3.3] (*n*=90)	7.5 [3.0] (*n*=82)	0.975
Correct decision for surgery?	72/87 [82.8%]	68/81 [84.0%]	0.836
Visick score			0.404
1 (no symptoms)	24 [27.6%]	17 [20.7%]	
2 (mild symptoms)	36 [41.4%]	37 [45.1%]	
3 (moderate symptoms)	7 [8.0%]	7 [8.5%]	
4 (symptoms interfering with life)	8 [9.2%]	14 [17.1%]	
5 (symptoms not improved)	12 [13.8%]	7 [8.5%]	
Visick 1 and 2 (no or mild symptoms)	60/87 [69.0%]	54/82 [65.9%]	0.666

* values are gives as mean [SD]

There were no significant differences in the number of endoscopic dilatations performed for dysphagia (2.0% *vs.* 6.0%; *P*=0.202) or the overall number of reoperations (10.0% *vs.* 4.9%; *P*=0.212) undertaken within the 5 yr follow-up period (Figure 2). In the group which underwent anterior 90° partial fundoplication most reoperations were performed for recurrent reflux (6.7%), whereas in the Nissen fundoplication group most reoperations were for dysphagia (3.7%).

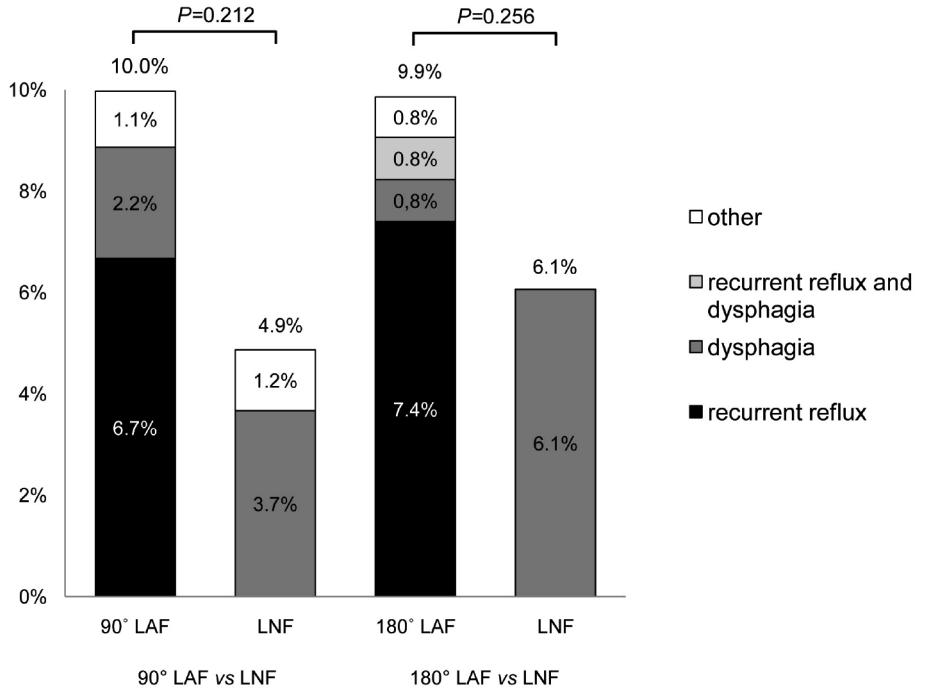

Figure 2. Reoperation rate and indications for reoperation at 5 years after anterior 90° partial (90°LAF) *versus* Nissen fundoplication (LNF), and anterior 180° partial (180°LAF) *versus* Nissen fundoplication (LNF)

Anterior 180° partial vs. Nissen fundoplication

The outcomes at 5 years for anterior 180° partial vs. Nissen fundoplication are summarized in Table 3. Heartburn scores and the use of antisecretory medication were similar for the 2 procedures. Dysphagia was less common following anterior 180° partial fundoplication, the mean analog scores for dysphagia for solids and liquids was lower, and the mean 0-45 dysphagia score was lower following anterior 180° partial fundoplication. Gas-related symptoms were also less common after anterior 180° partial fundoplication, belching ability and the ability to relieve bloating were better preserved, and flatulence was less troublesome. All measures of overall satisfaction with the outcome of surgery were similar. There were no significant differences in the number of endoscopic dilatations performed

for dysphagia (2.0% *vs.* 5.0%; *P*=0.191) or the overall number of reoperations (9.9% *vs.* 6.1%; *P*=0.256) undertaken (Figure 2). In the group which underwent anterior 180° partial fundoplication most reoperations were performed for recurrent reflux (7.4%), whereas in the Nissen fundoplication group most reoperations were for dysphagia (6.1%).

Table 3. Symptomatic outcome at 5 years after anterior 180° and Nissen fundoplication

	Anterior 180°	**Nissen**	***P*-value**
Reflux symptoms			
Analog heartburn score*	1.8 [2.7] (*n*=120)	1.6 [2.7] (*n*=132)	0.316
Use of antisecretory drugs	2/51 [3.9%]	4/52 [7.7%]	0.414
Dysphagia			
Dysphagia	8/38 [21.1%]	19/33 [57.6%]	0.002
Analog score for dysphagia for liquids*	0.5 [1.4] (*n*=121)	1.2 [1.8] (*n*=132)	<0.001
Analog score for dysphagia for solids*	1.3 [2.1] (*n*=121)	2.5 [2.8] (*n*=131)	<0.001
0-45 Dysphagia score*	5.3 [7.3] (*n*=120)	8.8 [9.5] (*n*=132)	0.003
Normal diet	106/119 [89.1%]	114/131 [87.0%]	0.618
Dilatation for dysphagia	2/121 [1.7%]	6/132 [4.5%]	0.191
Gas-related symptoms			
Inability to belch	19/120 [15.8%]	46/132 [34.8%]	0.001
Gas bloating	63/120 [52.5%]	77/132 [58.3%]	0.352
Inability to relieve bloating	30/100 [30.0%]	55/123 [44.7%]	0.024
Increased flatulence	57/110 [51.8%]	79/119 [66.4%]	0.025
Patient satisfaction			
Analog score for satisfaction*	8.5 [2.2] (*n*=119)	8.2 [2.8] (*n*=130)	0.643
Correct decision for surgery?	107/116 [92.2%]	111/124 [89.5%]	0.465
Visick score			0.254
1 (no symptoms)	55 [47.4%]	51 [39.5%]	
2 (mild symptoms)	41 [35.3%]	54 [41.9%]	
3 (moderate symptoms)	13 [11.2%]	10 [7.8%]	
4 (symptoms interfering with life)	5 [4.3%]	6 [4.7%]	
5 (symptoms not improved)	2 [1.7%]	8 [6.2%]	
Visick 1 and 2 (no or mild symptoms)	96/116 [82.8%]	105/129 [81.4%]	0.781

* values are gives as mean [SD]

DISCUSSION

Antireflux surgery aims to provide durable reflux control with minimal postfundoplication side effects. In general, for most patients this is achieved, although some are troubled by side effects. To minimize the risk of side effects, routine use of a partial fundoplication has been proposed. However, the perception that there is a paucity of long-term follow-up data for antireflux surgery, has recently led to published American guidelines for the surgical treatment of reflux recommending "controlled studies with long-term follow-up" to determine the surgical therapy of choice.[7] Long-term follow-up data is available in many relevant randomized trials,[13;14;18;19] and excellent outcomes have been demonstrated for anterior partial fundoplication variants in randomized trials at 5 and 10 years follow-up.[13;14;18] In contrast, the 5-year outcomes of another trial has suggested inferior reflux control after anterior partial fundoplication.[19] In our current study we provide further analysis of long-term outcome data from 4 randomized trials, and by combining the 5-year outcome data sets for further analysis of the original data we have accessed the largest randomized data set which evaluates anterior partial vs. Nissen fundoplication. The American guidelines for antireflux surgery correctly conclude that differences in outcome between anterior 90° and 180° partial fundoplication have not been investigated.[7] To identify potential differences in outcome between the anterior fundoplication sub-types we have stratified and compared these subtypes separately with Nissen fundoplication in a randomized fashion.

At 5 years follow-up, control of heartburn symptoms were similar for anterior 180° partial vs. Nissen fundoplication, but inferior for anterior 90° fundoplication vs. Nissen fundoplication. The use of antisecretory medication after anterior 180° partial fundoplication was similar to Nissen fundoplication, but more common after anterior 90° partial fundoplication vs. Nissen fundoplication. This supports the contention that anterior 90° partial fundoplication creates a less effective antireflux barrier than the Nissen fundoplication. It should be noted, however, that use of antisecretory medication does not imply that all patients using these medications have recurrent reflux. Earlier studies have demonstrated that only a small proportion of these patients have abnormal esophageal acid exposure on pH monitoring[1;2;20] or endoscopic evidence of fundoplication disruption.[3] Others have demonstrated that approximately two thirds of patients who take these medications after fundoplication, use them for atypical abdominal symptoms, unrelated to the original symptoms, or use medication in combination with non-steroidal anti-inflammatory agents for gastric mucosal protection.[1;20] The use of antisecretory medications should therefore only be interpreted as an "relative" indicator of recurrent reflux.[1;20] Both anterior 90° and 180° partial fundoplications were associated with less dysphagia and gas-related symptoms compared with Nissen fundoplication, and the extent of the reduction in this problem was similar for both anterior partial fundoplication procedures. Consistent with these outcomes was a higher incidence of reoperation for recurrent reflux after anterior partial fundoplication, a higher incidence of reoperation for dysphagia after Nissen fundoplication, even though the overall number of operative

revision procedures were not significantly different for all procedures. Measures of overall patient satisfaction were not significantly different for both types of anterior partial fundoplication and Nissen fundoplication. Overall, this suggests that the best clinical outcome at 5 years follow-up was achieved following anterior 180° partial fundoplication. The long-term differences in postfundoplication symptoms between anterior and Nissen fundoplication are supported by studies that have evaluated physiological effects of fundoplication. Impaired lower esophageal sphincter relaxation correlates with post-fundoplication dysphagia.[21;22] A recent meta-analysis suggested that lower esophageal sphincter relaxation is more likely to be incomplete after Nissen than anterior partial fundoplication.[8] This is probably a consequence of placement of the stomach behind the intra-abdominal esophagus, and this mechanism probably contributes to the higher incidence of dysphagia after Nissen fundoplication. Furthermore, it is commonly assumed that impairment of the ventilation of swallowed air from the stomach (i.e. inability to belch) causes gas bloating and flatulence after fundoplication.[23] A recent study by our group suggests that air venting from the stomach is easier after partial than Nissen fundoplication, and this could explain a reduced risk of gas bloat and flatulence.

A previous randomized controlled trial reported by Hagedorn et al demonstrated poorer reflux control 5 years after an anterior 120° partial fundoplication, compared with posterior partial fundoplication.[19;24] Might different types of anterior partial fundoplication have different outcomes? The key difference between the anterior 180° and the 90° and 120° variants is extent of anchorage of the fundoplication to the hiatal rim on the right side of the esophagus. In the anterior 180° partial fundoplication the gastric fundus is sutured securely to the right hiatal pillar and to the esophageal wall with 3 to 4 sutures, whereas the stomach is not sutured to the right hiatal pillar in the 90° and 120° variants. When undertaking revision surgery for recurrent reflux, we have noted that an anterior 180° fundoplication always remains securely attached to the right hiatal pillar, whereas with the lesser anterior 90° and 120° partial fundoplications lack of anchorage on the right side can allow the fundoplication to unravel to some extent in some patients. This might account for differences in the rates of recurrent reflux. In general posterior partial fundoplications are also anchored to the hiatal rim, and the Nissen fundoplication is constructed in a manner that does not allow it to "unwind". Variation in construction probably accounts for different clinical outcomes between different wrap types at late follow-up, and we now believe that secure anchorage of a partial fundoplication to a rigid structure such as the hiatal rim during construction is a key step for achieving effective long-term control of reflux.

Strengths of our current study are the randomized design, common protocols across all trials, and the large sample size (*n*=461). Surgical techniques for construction of the fundoplication were identical, except that in one trial short gastric vessels were routinely divided in the Nissen fundoplication arm.[9] However, multiple randomized trials have shown that division of the short gastric blood vessels during Nissen fundoplication provides no advantage.[5] Bias associated with incomplete follow-up[25] was limited by the high level of complete follow-up at 5 years across our combined data set.

A potential limitation of our study is that 3 of the 4 trials were performed in Australia,[9-11] and 1 in South Africa.[12] However, the principal investigator of the South African trial worked with the Australian research group during the first trial, and then applied identical surgical techniques and questionnaires in the South African patient population.[12] The only difference in data collection was that the use of antisecretory medication was not assessed in the South African trial.[12] Another limitation is that we relied on clinical follow-up using validated questionnaires and we did not repeat pH monitoring or esophageal manometry at 5 years. Objective studies were undertaken at early follow-up in each trial, and the results have been reported previously.[9-11] Our previous experience with trying to obtain compliance with objective follow-up in otherwise well patients has shown that a high rate of compliance with studies such as manometry and pH monitoring at multiple points during clinical trails is not feasible in our communities.[11;25] Despite this, the clinical outcomes we have reported are still informative, and these clinical outcomes are arguably more relevant to day-to-day clinical practice, in which patients determine the success of antireflux surgery by the resolution of clinical symptoms, rather than the results of objective investigations. Even though our data has demonstrated equivalence for reflux control, and less side effects for anterior 180° partial versus Nissen fundoplication, it remains possible that subgroups of patients might have different outcomes. For example, equivalence of reflux control might not be true for individuals with more severe gastroesophageal reflux, and a tailored approach to fundoplication might have some merit. Unfortunately, however, it is difficult to undertake meaningful subgroup analyses on smaller groups of patients without compromis- ing the statistical validity of our current data analysis. Further appro- priately designed studies are needed to specifically explore whether some clinical subgroups might do better after one or other type of fundoplication. Recently published meta-analyses comparing posterior partial (Toupet) with Nissen fundoplication, have also concluded that posterior partial fundoplication offers similar reflux control, but with fewer troublesome postfundoplication side effects compared with the Nissen procedure.[4;26] Our study demonstrates that anterior 180° partial fundoplication has the same advantages over Nissen fundoplication. Two randomized controlled trials of an anterior vs. posterior partial fundoplication have been reported and both suggest better reflux control following posterior fundoplication, less side effects after anterior partial fundoplication, and equivalent overall satisfaction with the outcome of surgery.[19;27] However, as discussed above, Hagedorn et al evaluated an anterior 120° not a 180° partial fundoplication.[19;24] The trial reported by Khan et al did evaluate an anterior 180° partial fundoplication, but only reported 12 months follow-up, and this follow-up was incomplete, being available for only 57% of the enrolled patients at this early time point.[27] Hence, more trials are needed to address the relative advantages, if any, of anterior 180° vs. posterior partial fundoplication for the surgical treatment for gastroesophageal reflux.

In conclusion, in this comparison of anterior 90° and anterior 180° vs. Nissen fundoplication at 5-years follow-up, anterior 180° partial fundoplication achieved the best overall outcome, with equivalent reflux symptom control but less side effects compared with Nissen fundoplication. Reflux control after anterior 90° partial fundoplication appears less

effective than after Nissen fundoplication, and overall this suggests that an anterior 180° partial fundoplication is an appropriate operation for the treatment of uncomplicated gastroesophageal reflux disease, and in our centers this is now the most commonly performed antireflux procedure.

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REFERENCES

1 Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. Ann Surg 2009; 250(5):698-706.

2 Draaisma WA, Rijnhart-de Jong HG, Broeders IA, Smout AJ, Furnee EJ, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. Ann Surg 2006; 244(1):34-41.

3 Salminen PT, Hiekkanen HI, Rantala AP, Ovaska JT. Comparison of long-term outcome of laparoscopic and conventional nissen fundoplication: a prospective randomized study with an 11-year follow-up. Ann Surg 2007; 246(2):201-206.

4 Broeders JA, Mauritz FA, Ahmed AU, Draaisma WA, Ruurda JP, Gooszen HG et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. Br J Surg 2010; 97(9):1318-1330.

5 Catarci M, Gentileschi P, Papi C, Carrara A, Marrese R, Gaspari AL et al. Evidence-based appraisal of antireflux fundoplication. Ann Surg 2004; 239(3):325-337.

6 Varin O, Velstra B, De SS, Ceelen W. Total vs partial fundoplication in the treatment of gastroesophageal reflux disease: a meta-analysis. Arch Surg 2009; 144(3):273-278.

7 Stefanidis D, Hope WW, Kohn GP, Reardon PR, Richardson WS, Fanelli RD. Guidelines for surgical treatment of gastroesophageal reflux disease. Surg Endosc 2010; 24(11):2647-2669.

8 Broeders JA, Roks DJ, Ali U.A., Draaisma WA. Laparoscopic anterior versus posterior fundoplication for gastroesphageal reflux disease; systematic review and meta-analysis of randomized clinical trials. In press Ann Surg 2011.

9 Watson DI, Jamieson GG, Lally C, Archer S, Bessell JR, Booth M et al. Multicenter, prospective, double-blind, randomized trial of laparoscopic nissen vs anterior 90 degrees partial fundoplication. Arch Surg 2004; 139(11):1160-1167.

10 Spence GM, Watson DI, Jamiesion GG, Lally CJ, Devitt PG. Single center prospective randomized trial of laparoscopic Nissen versus anterior 90 degrees fundoplication. J Gastrointest Surg 2006; 10(5):698-705.

11 Watson DI, Jamieson GG, Pike GK, Davies N, Richardson M, Devitt PG. Prospective randomized double-blind trial between laparoscopic Nissen fundoplication and anterior partial fundoplication. Br J Surg 1999; 86(1):123-130.

12 Baigrie RJ, Cullis SN, Ndhluni AJ, Cariem A. Randomized double-blind trial of laparoscopic Nissen fundoplication versus anterior partial fundoplication. Br J Surg 2005; 92(7):819-823.

13 Ludemann R, Watson DI, Jamieson GG, Game PA, Devitt PG. Five-year follow-up of a randomized clinical trial of laparoscopic total versus anterior 180 degrees fundoplication. Br J Surg 2005; 92(2):240-243.

14 Nijjar R, Watson D, Jamieson G, Archer S. Five-year follow-up of a multicenter, double-blind randomized clinical trial of laparoscopic Nissen vs anterior 90 degrees partial fundoplication. Arch Surg 2010; 145(6):552-557.

15 Jamieson GG, Watson DI, Britten-Jones R, Mitchell PC, Anvari M. Laparoscopic Nissen fundoplication. Ann Surg 1994; 220(2):137-145.

16 Dakkak M, Bennett JR. A new dysphagia score with objective validation. J Clin Gastroenterol 1992; 14(2):99-100.

17 Watson DI, Pike GK, Baigrie RJ, Mathew G, Devitt PG, Britten-Jones R et al. Prospective double-blind randomized trial of laparoscopic Nissen fundoplication with division and without division of short gastric vessels. Ann Surg 1997; 226(5):642-652.

18 Cai W, Watson DI, Lally CJ, Devitt PG, Game PA, Jamieson GG. Ten-year clinical outcome of a prospective randomized clinical trial of laparoscopic Nissen versus anterior 180(degrees) partial fundoplication. Br J Surg 2008; 95(12):1501-1505.

19 Engström C, Lönroth H, Mardani J, Lundell L. An anterior or posterior approach to partial fundoplication? Long-term results of a randomized trial. World J Surg 2007; 31(6):1221-1225.

20 Wijnhoven BP, Lally CJ, Kelly JJ, Myers JC, Watson DI. Use of antireflux medication after antireflux surgery. J Gastrointest Surg 2008; 12(3):510-517.

21 Scheffer RC, Samsom M, Frakking TG, Smout AJ, Gooszen HG. Long-term effect of fundoplication on motility of the oesophagus and oesophagogastric junction. Br J Surg 2004; 91(11):1466-1472.

22 Mathew G, Watson DI, Myers JC, Holloway RH, Jamieson GG. Oesophageal motility before and after laparoscopic Nissen fundoplication. Br J Surg 1997; 84(10):1465-1469.

23 Woodward ER, Thomas HF, McAlhany JC. Comparison of crural repair and Nissen fundoplication in the treatment of esophageal hiatus hernia with peptic esophagitis. Ann Surg 1971; 173(5):782-792.

24 Hagedorn C, Jonson C, Lonroth H, Ruth M, Thune A, Lundell L. Efficacy of an anterior as compared with a posterior laparoscopic partial fundoplication: results of a randomized, controlled clinical trial. Ann Surg 2003; 238(2):189-196.

25 Ludemann R, Watson DI, Jamieson GG. Influence of follow-up methodology and completeness on apparent clinical outcome of fundoplication. Am J Surg 2003; 186(2):143-147.

26 Shan CX, Zhang W, Zheng XM, Jiang DZ, Liu S, Qiu M. Evidence-based appraisal in laparoscopic Nissen and Toupet fundoplications for gastroesophageal reflux disease. World J Gastroenterol 2010; 16(24):3063-3071.

27 Khan M, Smythe A, Globe J, Stoddard CJ, Ackroyd R. Randomized controlled trial of laparoscopic anterior versus posterior fundoplication for gastro-oesophageal reflux disease. ANZ J Surg 2010; 80(7-8):500-505.

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6

Laparoscopic anterior 180-degree versus Nissen fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Objective

To compare short- and long-term outcome after 180-degree laparoscopic anterior fundoplication (180-degree LAF) *versus* laparoscopic Nissen fundoplication (LNF).

Summary of background data

LNF is currently the most frequently performed surgical therapy for gastroesophageal reflux disease. Alternatively, 180-degree LAF has been alleged to reduce troublesome dysphagia and gas-related symptoms, with similar reflux control.

Methods

MEDLINE, EMBASE, Cochrane Library and ISI web of Knowledge CPCI-S were searched for randomized clinical trials (RCTs) comparing primary 180-degree LAF *versus* LNF. The methodological quality was evaluated to assess bias risk. Primary outcomes were esophageal acid exposure, esophagitis, heartburn score, dilatation for dysphagia, modified Dakkak dysphagia score [0-45] and reoperation rate. Meta-analysis was conducted at 1 and 5 years.

Results

Five distinct randomized clinical trials comparing 180-degree LAF (n = 227) with LNF (n = 231) were identified. At 1 year, the Dakkak dysphagia score [2.8 vs 4.8; weighted mean difference: −2.25; 95% confidence interval (CI): −2.66 to −1.83; $P < 0.001$], gas bloating [11% vs 18%; relative risk (RR) 0.59; 95% CI: 0.36–0.97; $P = 0.04$], flatulence (14% vs 25%; RR: 0.57; 95% CI: 0.35–0.91; $P = 0.02$), inability to belch (19% vs 31%; RR: 0.63; 95% CI: 0.40–0.99; $P = 0.05$), and inability to relieve bloating (34% vs 44%; RR: 0.74; 95% CI: 0.55–0.99; $P = 0.04$) were lower after 180-degree LAF. Esophageal acid exposure (standardized mean difference: 0.19; 95% CI: −0.07 to 0.46; $P = 0.15$), esophagitis (19% vs 13%; RR: 1.42; 95% CI: 0.69– 2.91; $P = 0.34$), heartburn score (standardized mean difference: 1.27; 95% CI:−0.36 to 2.90; $P = 0.13$), dilatation rate (1.4% vs 2.8%; RR: 0.60; 95% CI: 0.19–1.91; $P = 0.39$), reoperation rate (5.7% vs 2.8%; RR: 2.08; 95% CI: 0.80– 5.41; $P = 0.13$), perioperative outcome, regurgitation, proton pump inhibitor (PPI) use, lower esophageal sphincter pressure, and patient satisfaction were similar after 180-degree LAF and LNF. At 5 years, the Dakkak dysphagia score, flatulence, inability to belch, and inability to relieve bloating remained lower after 180-degree LAF. The 5-year heartburn score, dilatation rate, reoperation rate, PPI use, and patient satisfaction were similar.

Conclusions

At 1 and 5 years, dysphagia and gas-related symptoms are lower after 180-degree LAF than after LNF, and esophageal acid exposure and esophagitis are similar, with no differences in heartburn scores, patient satis- faction, dilatations, and reoperation rate. These results lend level 1a support for the use of 180-degree LAF for the surgical treatment of gastroesophageal reflux disease.

INTRODUCTION

Laparoscopic fundoplication is the surgical approach of choice for gastroesophageal reflux disease (GERD). Total fundoplication according to Nissen provides excellent reflux control and is the most frequently performed operation for GERD.[1-3] However, laparoscopic Nissen fundoplication (LNF) is followed by a significant incidence of troublesome dysphagia and gas-related symptoms.[4-6] Partial fundoplications have been developed as alternatives and aim to reduce the incidence of these postfundoplication symptoms.

A fundoplication is created by wrapping the fundus of the stomach anteriorly or posteriorly around the esophagus. Total fundoplication according to Nissen is an example of a posterior fundoplication. Commonly used partial fundoplications are posterior 270-degree fundoplication, anterior 90-degree fundoplication and anterior 180-degree fundoplication.[7] Several randomized clinical trials (RCTs) have evaluated whether partial wraps reduce postfundoplication symptoms and whether this is associated with inferior reflux control compared to LNF.[7] Systematic reviews have been performed to combine the results of these RCTs. Two meta-analyses have compared LNF to the pooled results of various types of partial fundoplications[5,6] and another review combined a mixture of posterior fundoplications and compared them to the pooled results of anterior fundoplications.[8] However, this year the long-term results of randomized trials demonstrated that 180-degree laparoscopic anterior fundoplication (LAF) offers similar reflux control compared to LNF, whereas reflux control after 90-degree LAF is less effective than after LNF.[9] Therefore, generalizing these 2 fundoplication types into 1 category in the setting of a meta-analysis is probably not appropriate. Comparing 1 partial fundoplication type head-to-head to LNF increases the validity of the analysis and facilitates application of the results in clinical practice. This study aims, therefore, to systematically review all RCTs comparing 180-degree LAF and LNF for GERD and to generate the highest level of evidence.

METHODS

Study selection

A systematic literature search with predefined search terms (Figure 1) was carried out in MEDLINE (from 1960),[10] EMBASE (from 1980)[11], Cochrane Library (issue 1, 2012) and the ISI Web of Knowledge Conference Proceedings Citation Index - Science (CPCI-S; from 1990) databases on April 14th, 2012 (Figure 1). All identified articles were screened for cross-references. Language restrictions were not applied.

Inclusion criteria

Title and abstract of all identified articles were screened and selected according to the following inclusion criteria: study population - adult patients with established GERD undergoing primary antireflux surgery; intervention - clearly documented surgical technique of 180-degree LAF[12] and LNF[13], irrespective of division of the short gastric

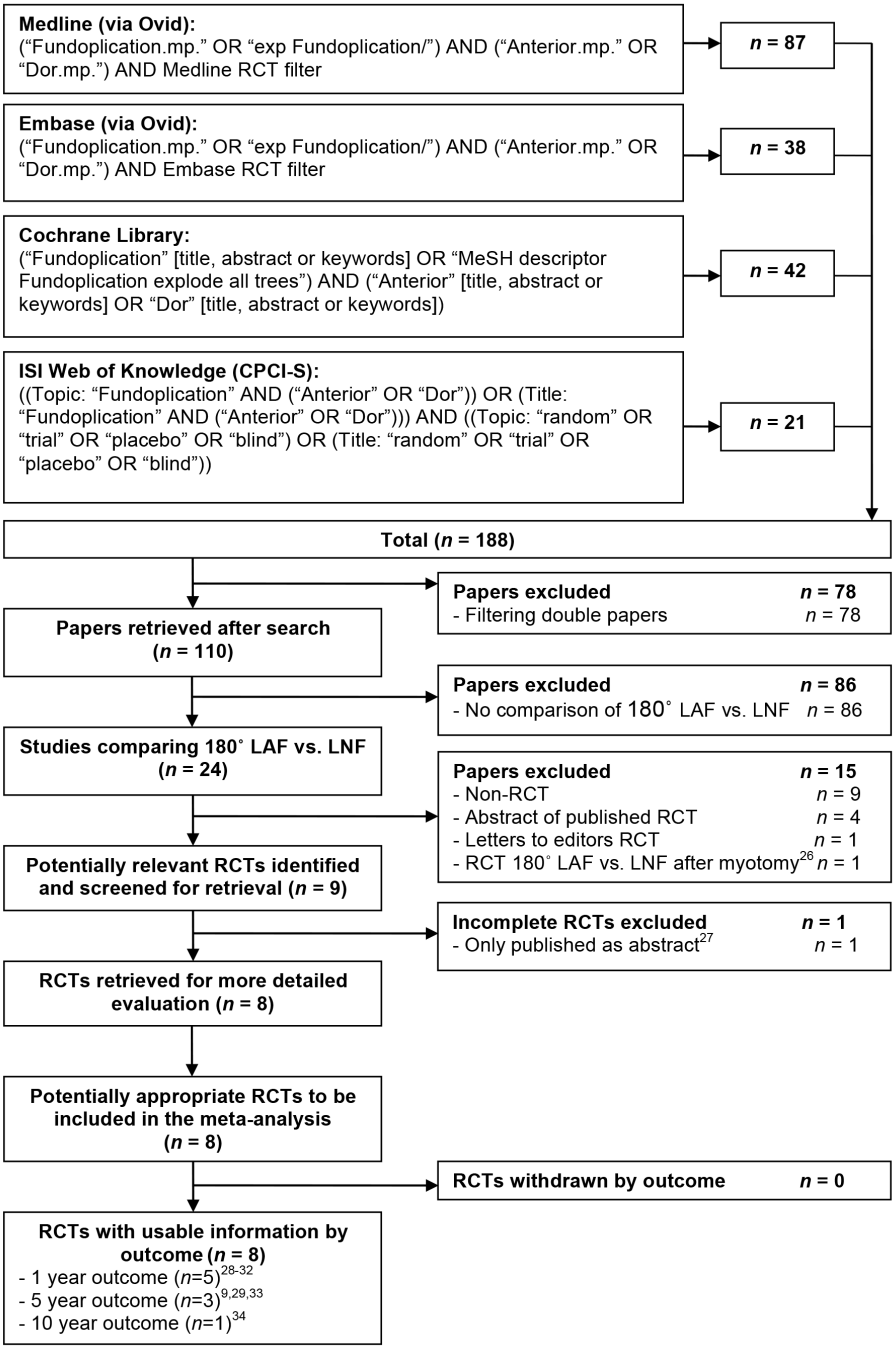

Figure 1. Flow-chart illustrating the details of the search strategy and study selection process according to the QUOROM-statement[17-19]

vessels;[5] study outcomes - at least one of the outcome measures reported below; study design - patients assigned to either 180-degree LAF or LNF by random allocation; publication - published as a full article in a peer-reviewed journal.

Exclusion criteria

Studies were excluded from analysis if they did not meet the inclusion criteria, or if the corresponding author was not able to provide data requested and it was impossible to extract or calculate appropriate data from the published results. Abstracts of RCTs were excluded as the fundoplication circumference, surgical technique, methodological quality and the risk of bias of these studies could not be assessed.

Outcomes of interest and definitions

Primary outcomes were esophageal acid exposure on pH monitoring (total esophageal acid exposure time or DeMeester score[14]), endoscopic esophagitis, presence of heartburn, severity of heartburn (an analog score (0=no heartburn; 10=severe heartburn), dilatation for dysphagia, presence of dysphagia, severity of dysphagia (validated modified Dakkak dysphagia score: 0, no dysphagia; 45, severe dysphagia)[15] and reoperation rate. Secondary outcomes included operating time, conversion rate, in-hospital complications, length of hospital stay, regurgitation, proton pump inhibitor (PPI) use, inability to belch, gas bloating, ability to relieve bloating and increased flatulence. Patient satisfaction was scored using an analog score (0=dissatisfied; 10=satisfied), the percentage of patients that was satisfied with outcome, a Visick score (1= no symptoms; 2= mild symptoms; 3= moderate symptoms; 4= moderate symptoms interfering with life; 5= symptoms as bad or worse after surgery)[16] and willingness to undergo surgery again. One-year results (6-18 months), 5-year outcome and results at 5 years and beyond were pooled separately in meta-analysis.

Data extraction

Titles and abstracts of all retrieved records, and subsequently full-text articles, were examined independently by two authors (JAB, DJR) according to the Quality of Reporting of Meta-analyses (QUOROM) guidelines.[17-19] The following data were extracted separately by the same two authors (JAB, DJR) for all studies meeting the inclusion criteria: reference of study, study population characteristics, study design, inclusion and exclusion criteria and number of participating subjects for each endpoint. For dichotomous outcomes, the number of events was recorded and for continuous outcomes means and standard deviations (SDs) were registered. In case of discrepancies, a third author (UAA) was consulted and agreement was reached by consensus.

Authors of all the original RCTs were contacted and agreed to provide missing data. When authors could not provide missing data, the following methods of handling missing data were applied. If the number of patients per arm was missing for an outcome, an equal distribution between both arms was assumed. Missing standard deviations (SDs) were either imputed based on ranges when available[20] or based on the average SDs reported by other RCTs for the same outcome.[10] If both means and SDs were missing, they were imputed based on the medians and ranges[20] or based on medians and interquartile ranges[10], according to availability.

Risk of bias assessment

Risk of bias was assessed of all articles using both the Cochrane Collaboration's tool for assessing risk of bias[10] and the Jadad scoring system.[21]

Statistical analysis

Statistical analyses were performed following the recommendations of the Cochrane Collaboration and QUOROM guidelines.[17-19] Outcomes reported by 2 or more studies were pooled in meta-analyses. Short -and long-term results were analyzed separately. Dichotomous and continuous outcomes were presented as risk ratios (RRs) and weighted mean differences (WMDs), respectively. Results were pooled using standardized mean differences (SMDs) if trials reported different scales for a continuous outcome measure. Data were pooled using the Mantel-Haenszel and the inverse-variance method for dichotomous outcomes and for continuous outcomes, respectively. Trials with zero events in both arms were excluded from meta-analysis. Trials with zero events in 1 arm were included in the analysis by adding a continuity correction of 0.5 to all cells in the 2x2 table of that study. As a robustness assessment, meta-analyses with RCTs with zero events in 1 arm were also performed using risk differences in a sensitivity analysis. For all analyses the 95% confidence interval (CI) was calculated.

Heterogeneity was calculated using Higgins χ^2 test,[22] and inconsistency in study effects was quantified by I^2 values.[10,23] The fixed-effects model was used if no heterogeneity was present (χ^2 *P* value > 0.100 and I^2 < 50%). If excessive heterogeneity was present, data were first re-checked and the DerSimonian random-effects model was used when heterogeneity persisted.[24] Funnel plots were used to help identify the presence of publication or other types of bias.[25-27] Review Manager software (RevMan© v. 5.0.16) provided by The Cochrane Collaboration was used for data management and statistical analyses.

RESULTS

Description of studies

A total of 188 potential relevant publications were identified (Figure 1). Twenty-four articles comparing 180-degree LAF with LNF were identified. Nine studies did not randomly allocate patients. An Italian trial randomly allocated patients with achalasia to Heller myotomy followed by either 180-degree LAF or LNF.[28] This trial was excluded because the indication for surgery was not primary fundoplication for established GERD. One potentially relevant RCT that had been published as an abstract only without a peer-reviewed publication was excluded.[29] Finally, 8 publications from five original RCTs[30-34] comparing laparoscopic anterior *versus* posterior fundoplication were identified. Five publications reported 1-year results,[30-34] 3 articles evaluated 5-year outcome[9,31,35] and there was 1 trial[36] with 10-year follow-up (Figure 1).

The five included trials were published between 1999 and 2012, all with at least 6 months of follow-up. A total of 458 fundoplications (180-degree LAF n=227; LNF n=231) were performed. In all patients hiatal repair was performed, followed by either a standardized LAF with a circumferential range of 180 degrees and fixation to right crus or a standardized LNF with a circumference of 360º. One trial divided the short gastric vessels in the LNF group (Table 1).[33] Patient characteristics are listed in Table 2. All patients had proof of GERD on upper endoscopy and/or 24h pH-monitoring. Two trials enrolled some patients with esophageal dysmotility and these patients were divided equally between both arms.[31,34]

Table 1. Details of included RCTs comparing 180˚ LAF *versus* LNF

Author	Year	Period	Method	n	Hiatal repair	DSGV	Bougie	Fixation to right crus/ esophagus†	1-year FU	5-year FU
Baigrie[9,30]	'05	'99-'01	180˚ LAF	79	Yes	No	None	Yes/No	12 [30]	60 [9]
			LNF	84	Yes	No	56 Fr	No/No		
Cao[31]	'12	'02-'07	180˚ LAF	50	Yes	No	52 Fr	Yes/Yes	12 [31]	60 [31]
			LNF	50	Yes	No	52 Fr	No/No		
Chrysos[32]	'04	'99-'02	180˚ LAF	12	Yes	No	None	Yes/Yes	6 [32]	
			LNF	12	Yes	No	None	No/Yes		
Raue[33]	'11	'05-'07	180˚ LAF	32	Yes	No	42 Fr	Yes/Yes	18 [33]	
			LNF	32	Yes	Yes	42 Fr	No/Yes		
Watson[34-36]	'99/'04/'08	'95-'97	180˚ LAF	54	Yes	No	None	Yes/Yes	6 [34]	60 [35]
			LNF	53	Yes	No	52 Fr	No/Yes		120 [36]

°, Circumference of the wrap; DSGV, Division of the short gastric vessels; †Fixation of the fundoplication to the right crus/esophagus; FU, Follow-up (months); NR, Not reported; Fr, French

Table 2. Patient characteristics

Author	Method	Age (yr)	Male / female sex	Esophageal dysmotility / total	Indication for surgical treatment
Baigrie[9,30]	180˚ LAF	45	45/34	NR	pH or endoscopically proven GERD
	LNF	43	49/34	NR	
Cao[31]	180˚ LAF	57	16/34	8/50	pH or endoscopically proven GERD
	LNF	59	21/29	6/50	
Chrysos[32]	180˚ LAF	58	4/8	0/12	pH or endoscopically proven GERD
	LNF	52	9/3	0/12	
Raue[33]	180˚ LAF	53	14/16	0/30	pH or endoscopically proven GERD
	LNF	50	16/11	0/27	
Watson[34-36]	180˚ LAF	45	34/30	11/54	pH or endoscopically proven GERD
	LNF	47	36/17	11/53	

GERD, gastroesophageal reflux disease; NR, Not reported; pH or endoscopically proven GERD, GERD proven on upper endoscopy or 24h pH-monitoring

Methodological quality of included studies

The trials had good methodological quality, with a mean Jadad score of 4 (range 2-5) (Table 3). All trials had adequate sequence generation. Two trials[31,32] did not report double blinding and allocation concealment and one of these did not report loss to follow-up[32]. Two trials reported a sample size calculation.[33,34]

Table 3. Risk of bias summary

	Baigrie[9,30]	Cao[31]	Chrysos[32]	Raue[33]	Watson[34-36]
Adequate sequence generation	Yes	Yes	Yes	Yes	Yes
Allocation concealment	Yes	No	No	Yes	Yes
Blinding (observer)	Yes	Yes	No	Yes	Yes
Blinding (patient)	Yes	No	No	Yes	Yes
Adequate report on loss to follow-up	Yes	Yes	No	Yes	Yes
Free of other sources of bias	Yes	Yes	Yes	Yes	Yes
Jadad score	5	3	2	5	5

Table 4. 1-year outcome

	RCT	180˚ LAF	LNF	RR	WMD	95% CI	P-value
Operating time (min)	4	79.7 (n=205)	78.8 (n=206)		-1.07	-12.8,10.7	0.86
In-hospital complications	4	8/213 [3.8%]	3/214 [1.4%]	2.18		0.69,6.93	0.19
Length of hospital stay (days)	4	3.1 (n=181)	3.0 (n=182)		0.02	-0.10,0.13	0.76
Regurgitation	3	9/145 [6.2%]	7/142 [4.9%]	1.25		0.48,3.23	0.65
PPI use	3	7/127 [5.5%]	9/121 [7.4%]	0.74		0.29,1.91	0.54
Gas bloating	5	21/196 [11%]	36/201 [18%]	0.59		0.36,0.97	0.04
Increased flatulence	3	19/133 [14%]	33/130 [25%]	0.57		0.35,0.91	0.02
Inability to belch	3	24/124 [19%]	37/120 [31%]	0.63		0.40,0.99	0.05
Inability to relieve bloating	3	39/116 [34%]	54/122[44%]	0.74		0.55,0.99	0.04
LES resting pressure (mm Hg)	4	16.7 (n=123)	20.1 (n=116)		-3.58	-9.93,2.77	0.27
LES relaxation pressure (mm Hg)	3	5.6 (n=94)	7.9 (n=92)		-2.48	-8.48,3.51	0.42
Satisfied with outcome	3	159/177 [90%]	163/183 [89%]	1.01		0.94,1.08	0.84
Satisfaction score	3	9.1 (n=177)	8.9 (n=183)		0.27	-0.52,1.05	0.50
Willingness repeat surgery	3	162/173 [94%]	160/179 [89%]	1.05		0.99,1.12	0.13
Resolved or mild symptoms	4	181/209 [87%]	188/213 [88%]	0.99		0.92,1.06	0.68

RCT, Randomized clinical trial; RR, Risk ratio; WMD, Weighted mean difference; CI, Confidence interval

One-year outcome

One-year outcome was available for 448 of 458 (97.8%) of the patients. All primary and secondary outcome measures were reported by 3 or more trials. Operating time, in-hospital complications, and length of hospital stay were similar for both groups (Table 4). The included trials reported no mortality. The prevalence (15% vs 27%; RR: 0.56; 95% CI: 0.38–0.81; *P* = 0.002; Figure 2A) and severity (2.8 vs 4.8; WMD: −2.25; 95% CI: −2.66 to −1.83; *P* < 0.001; Figure 2B) of dysphagia were lower after 180-degree LAF than after LNF. Esophageal acid exposure on 24-hour pH monitoring (SMD: 0.19; 95% CI: −0.07 to 0.46; *P* = 0.15; Figure 3A) and prevalence of esophagitis (19% vs 13%; RR: 1.42; 95% CI: 0.69–2.91; *P* = 0.34; Figure 3B) were similar after both procedures. This was accompanied by a comparable prevalence (10% vs 6%; RR: 1.39; 95% CI: 0.43–4.46; *P* = 0.58; Figure 4A) and severity of heartburn (SMD: 1.27; 95% CI: −0.36 to 2.90; *P* = 0.13; Figure 4B) and prevalence of regurgitation and PPI use (Table 4). Dilatation (1.4% vs 2.8%; RR: 0.60; 95% CI: 0.19–1.91; *P* = 0.39; Figure 5A) and reoperation rates were similar (5.7% vs 2.8%; RR: 2.08; 95% CI: 0.80–5.41; *P* = 0.13; Figure 5B).

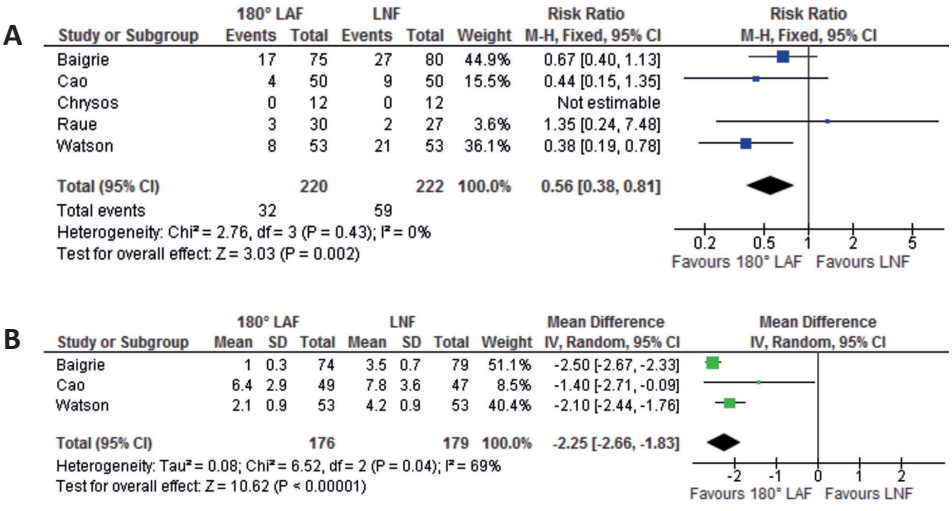

Figure 2. One-year prevalence (A) and severity dysphagia (B)

Gas bloating (11% vs 18%; RR: 0.59; 95% CI: 0.36–0.97; *P* = 0.04), flatulence (14% vs 25%; RR: 0.57; 95% CI: 0.35–0.91; *P* = 0.02), inability to belch (19% vs 31%; RR: 0.63; 95% CI: 0.40–0.99; *P* = 0.05), and inability to relieve bloating (34% vs 44%; RR: 0.74; 95% CI: 0.55–0.99; *P* = 0.04) were lower after 180-degree LAF (Table 4). Mean lower esophageal sphincter (LES) resting and relaxation pressure were similar (Table 4).

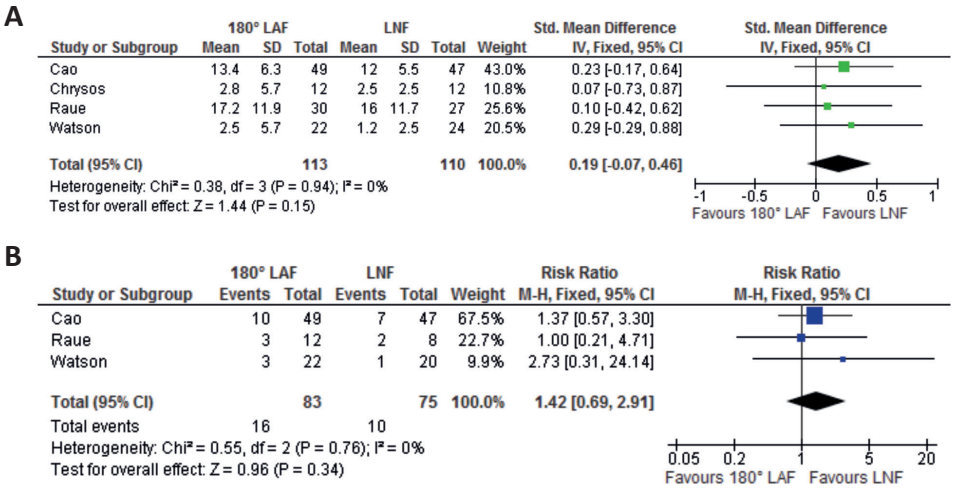

Figure 3. One-year esophageal acid exposure (A) and esophagitis (B)

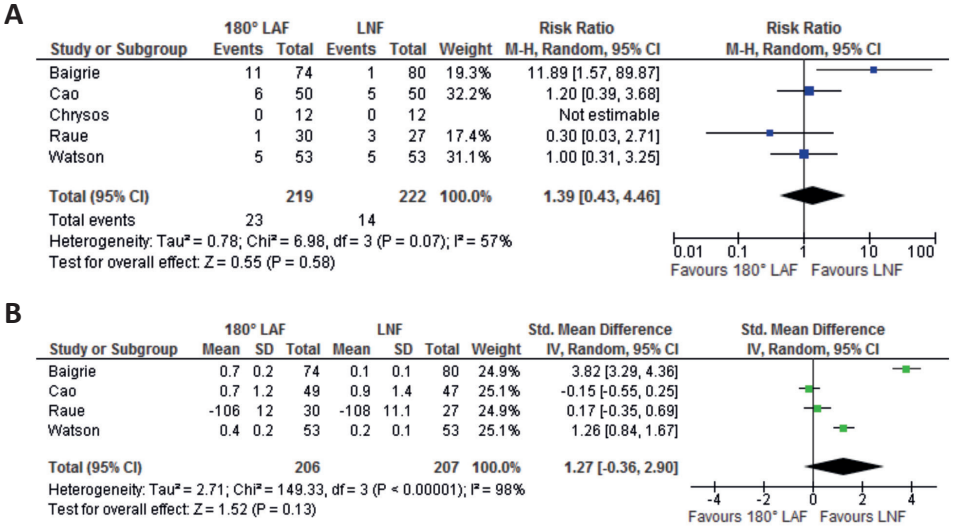

Figure 4. One-year prevalence (A) and severity heartburn (B)

There were no differences in the number of patients who were satisfied with outcome, satisfaction scores, willingness to undergo surgery again, and the percentage of patients with resolved or mild symptoms (Table 4). Sensitivity analysis of outcomes with zero events in 1 arm (dilatation, in-hospital complications) yielded similar results. Funnel plots did not demonstrate evidence of publication bias (Figure 6).

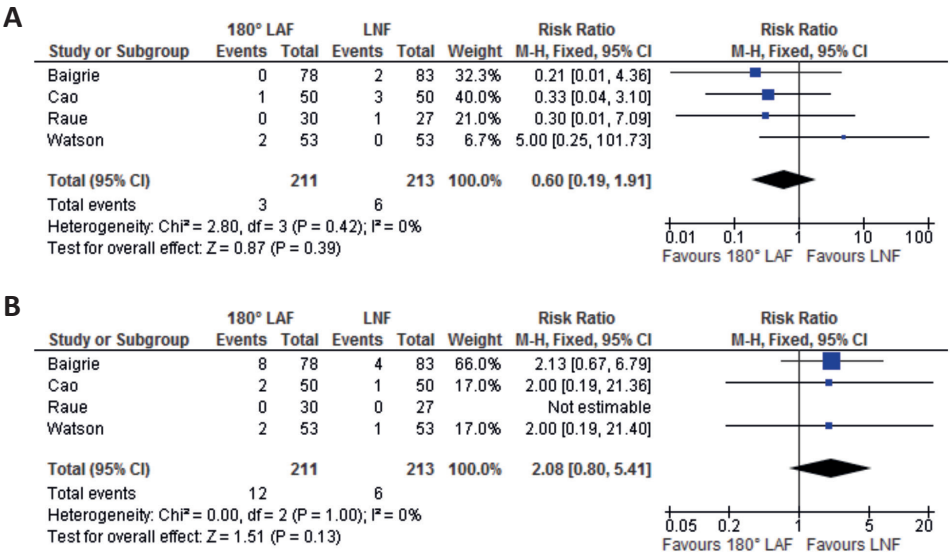

Figure 5. One-year dilatation (A) and reoperation rate (B)

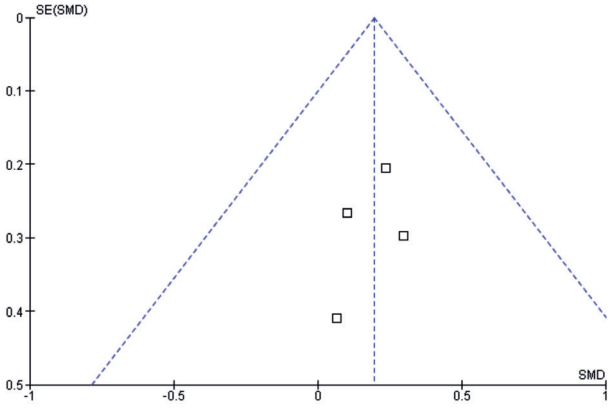

Figure 6. Funnel plot 1 year esophageal acid exposure

Five-year outcome

Five-year outcome was available for 347 of 370 (93.8%) patients. At 5 years, PPI use and the number of patients who was satisfied with intervention were reported by 2 trials. All the remaining primary and secondary outcome measures were reported by 3 or more trials. In line with the 1-year results, the prevalence (21% vs 33%; RR: 0.67; 95% CI: 0.47–0.94; Figure 7A) and severity (5.0 vs 8.3; WMD: −2.33; 95% CI: −3.32 to −1.34; *P* < 0.00; Figure 7B) of dysphagia remained lower after 180-degree LAF than after LNF. The prevalence (17% vs 12%; RR: 1.40; 95% CI: 0.83–2.36; Figure 8A) and severity (1.7 vs 1.5; WMD: 0.13; 95% CI: −0.19 to 0.46; *P* = 0.43; Figure 8B) of heartburn and PPI use were comparable. Dilatation (2.4% vs 5.6%; RR: 0.44; 95% CI: 0.15–1.30; *P* = 0.14; Figure 9A) and reoperation rates (9.5% vs 6.2%; RR: 1.53; 95% CI: 0.73–3.19; *P* = 0.26; Figure 9B) were similar.

Flatulence (37% vs 50%; RR: 0.75; 95% CI: 0.60–0.94; *P* = 0.01), inability to belch (16% vs 34%; RR: 0.47; 95% CI: 0.32–0.70; *P* < 0.001), and inability to relieve bloating (31% vs 44%; RR: 0.69; 95% CI: 0.53–0.92; *P* = 0.01) remained lower after 180-degree LAF. The difference in gas bloating that was identified at 1 year was no longer present at 5 years (Table 5). Again, there were no differences in the number of patients who were satisfied with outcome, satisfaction scores, willingness to undergo surgery again, and the percentage of patients with resolved or mild symptoms (Table 5). Sensitivity analysis of outcomes with zero events in 1 arm (dilatation) yielded similar results.

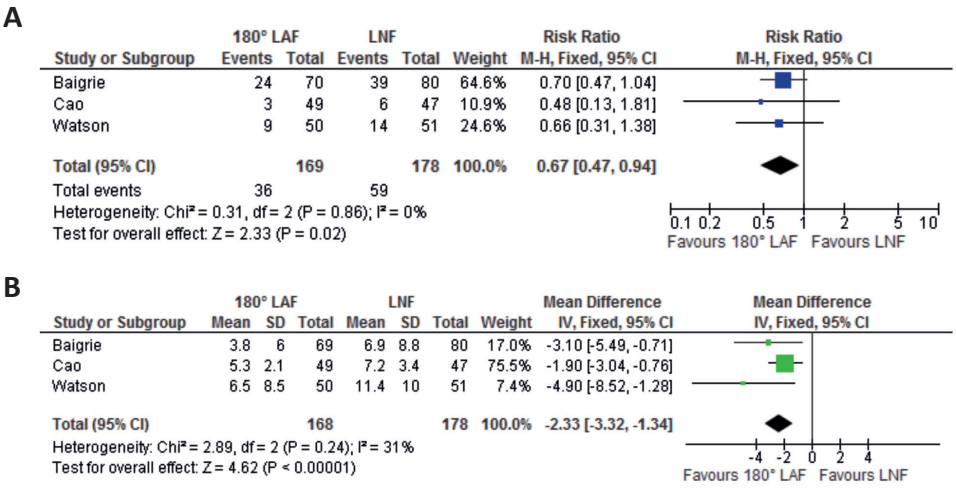

Figure 7. Five-year prevalence (A) and severity dysphagia (B)

Outcome at five years and beyond

One trial reported both 5- and 10-year results.[35,36] An additional analysis was performed on the basis of the latest follow-up of the 3 trials that reported outcome at 5 years and beyond. Outcome at 5 years and beyond was available for 335 of 370 (90.5%) patients. This analysis yielded similar results compared with the 5-year analysis. The only discrepancy was that the difference in inability to relieve bloating that was identified by the 5-year analysis was no longer present in the analysis that included 10-year data (Table 6). Sensitivity analysis of outcomes with zero events in 1 arm (dilatation) yielded similar results.

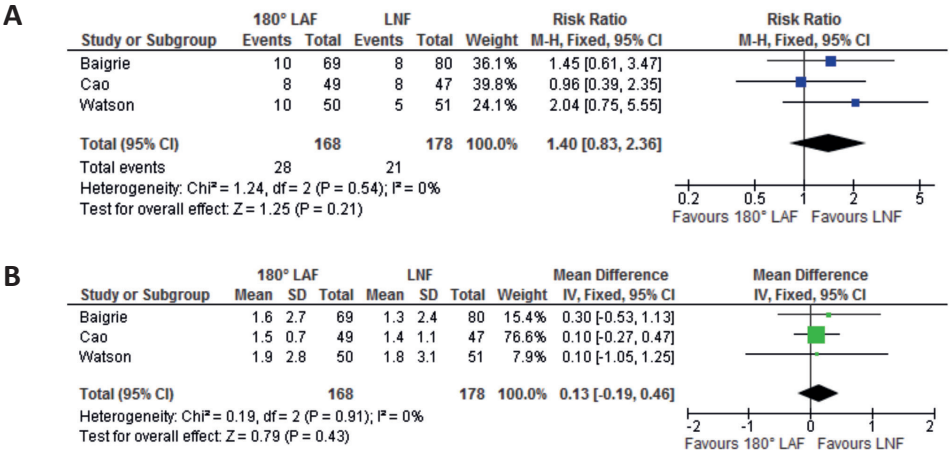

Figure 8. Five-year prevalence (A) and severity heartburn (B)

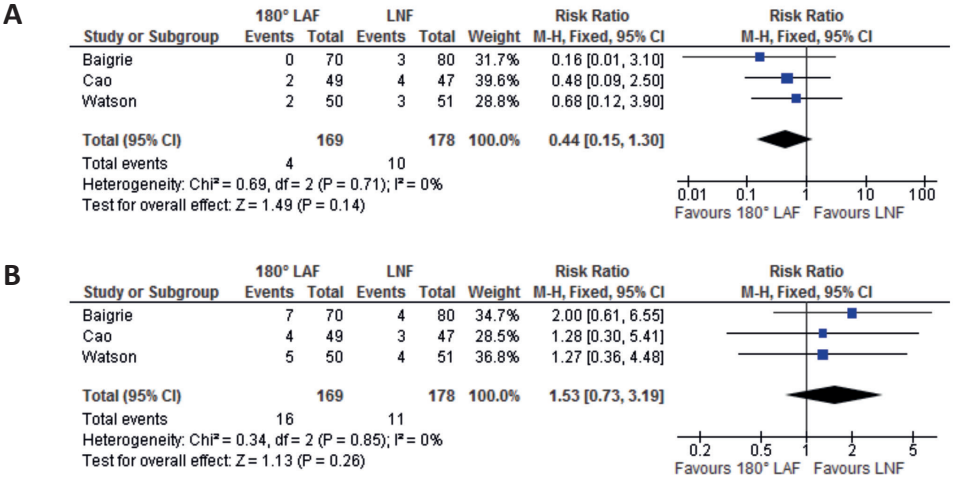

Figure 9. Five-year dilatation (A) and reoperation rate (B)

Table 5. 5-year outcome

	RCT	180˚ LAF	LNF	RR	WMD	95% CI	P-value
PPI use	2	7/99 [7.1%]	10/98 [10%]	0.69		0.27,1.75	0.44
Gas bloating	3	61/168 [36%]	86/178 [48%]	0.71		0.41,1.12	0.20
Increased flatulence	3	58/158 [37%]	82/165 [50%]	0.75		0.60,0.94	0.01
Inability to belch	3	27/168 [16%]	61/178 [34%]	0.47		0.32,0.70	<0.001
Inability to relieve bloating	3	52/168 [31%]	78/178 [44%]	0.69		0.53,0.92	0.01
Satisfied with outcome	2	89/99 [90%]	86/98 [88%]	1.01		0.86,1.19	0.91
Satisfaction score	3	8.4 (n=167)	8.3 (n=178)		-0.08	-0.46,0.30	0.69
Willingness repeat surgery	3	151/164 [92%]	154/174 [89%]	1.04		0.97,1.12	0.27
Resolved or mild symptoms	3	138/165 [84%]	144/177 [81%]	1.03		0.93,1.13	0.57

RCT, Randomized clinical trial; RR, Risk ratio; WMD, Weighted mean difference; CI, Confidence interval

Table 6. Outcome at 5 years and beyond

	RCT	180˚ LAF	LNF	RR	WMD	95% CI	P-value
Presence dysphagia	3	41/160 [26%]	70/175 [40%]	0.67		0.49,0.90	0.009
Severity dysphagia	3	5.3 (n=159)	8.4 (n=175)		-2.23	-3.23,-1.23	<0.001
Prevalence heartburn	3	26/159 [16%]	23/175 [13%]	1.23		0.74,2.07	0.42
Severity heartburn	3	1.7 (n=159)	1.4 (n=175)		0.17	-0.16,0.49	0.31
Dilatation rate	3	4/160 [2.5%]	10/175 [5.7%]	0.46		0.16,1.35	0.16
Reoperation rate	3	18/160 [11%]	13/175 [7.4%]	1.54		0.78,3.02	0.21
PPI use	2	16/90 [18%]	13/95 [14%]	1.35		0.70,2.62	0.37
Gas bloating	3	58/159 [36%]	62/175 [35%]	1.03		0.59,1.79	0.92
Increased flatulence	3	58/158 [37%]	82/165 [50%]	0.75		0.60,0.94	0.01
Inability to belch	3	31/159 [19%]	63/175 [36%]	0.55		0.38,0.79	0.001
Inability to relieve bloating	3	68/159 [43%]	87/175 [50%]	0.86		0.69,1.07	0.17
Satisfied with outcome	2	84/90 [93%]	91/95 [96%]	0.97		0.91,1.04	0.44
Satisfaction score	3	8.3 (n=158)	8.4 (n=175)		-0.18	-0.56,0.21	0.37
Willingness repeat surgery	3	144/155 [93%]	153/171 [89%]	1.04		0.97,1.11	0.27
Resolved or mild symptoms	3	138/165 [84%]	144/177 [81%]	1.03		0.93,1.13	0.57

RCT, Randomized clinical trial; RR, Risk ratio; WMD, Weighted mean difference; CI, Confidence interval

DISCUSSION

Antireflux surgery aims to provide durable reflux control with minimal postoperative dysphagia and gas-related symptoms. Partial fundoplications have been proposed to reduce the risk of side effects that are associated with LNF. In 2010, American guidelines for surgical treatment of GERD have evaluated partial and Nissen fundoplication. These guidelines concluded that there is "paucity of long-term follow-up data" and recommended "controlled studies with long-term follow-up".[7] Posterior 270-degree, anterior 90-degree and anterior 180-degree fundoplication have all been described.[7] Last year the long-term results of randomized trials demonstrated that 180-degree LAF offers similar reflux control compared to LNF, whereas reflux control after 90-degree LAF is less effective than after LNF.[9] A systematic review that directly compared posterior 270-degree fundoplication to LNF concluded that it reduces dysphagia and gas-related symptoms compared LNF, with similar reflux control up to 5 years.[4] A similar meta-analysis comparing outcome after 180-degree LAF and LNF has not been reported previously.

In the past year, 2 RCTs[31,33] have been published comparing 180-degree LAF to LNF in addition to the 3 trials[30,32,34] that had been reported earlier, with 5-year results of 2 of these trials reported as well.[9,31] Some of these individual trials were inconclusive as they were underpowered, and hence too small to identify significant differences regarding the most important determinants of successful antireflux surgery: objective reflux control, dilatations for dysphagia and the need for surgical reintervention. The results from all of these trials, however, have not been previously pooled in meta-analysis comparing 180-degree LAF to LNF. The current meta-analysis aims to provide this evidence.

The methodological quality of the 5 RCTs included in the current meta-analysis was good, with a mean Jadad score of 4. Surgical techniques of the included trials were standardized and similar. In all patients hiatal repair was performed, followed by either 180-degree LAF with fixation to right hiatal pillar or LNF. One trial divided the short gastric vessels in the LNF group.[33] This is not likely to introduce any bias since it has previously been demonstrated that division of the short gastric vessels does not influence outcome.[5] Two trials enrolled an equal number of patients with esophageal dysmotility in both arms.[31,34] This study analyzed patients with and without esophageal dysmotility together, as 4 RCTs have shown that outcome of fundoplication is similar in patients with normal and abnormal esophageal motility[37-40]. Study population and surgical interventions were similar between trials in all other aspects.

There are no significant differences in perioperative outcome measures. The 1-year outcomes demonstrate that 180-degree LAF is followed by less dysphagia and gas-related symptoms compared to LNF. Both procedures similarly increased LES pressure, which was accompanied by comparable subjective and objective reflux control. Patient satisfaction, endoscopic dilatation and reoperation rates are similar in the short-term as well. The 5-year outcomes show that the differences in dysphagia and gas-related symptoms persist at longer-term follow-up. Extension of follow-up to 5 years does not demonstrate differences in reflux symptoms, PPI use, patient satisfaction, dilatation or reoperation rates.

The reduction in gas-related symptoms after 180-degree LAF, with similar reflux control at up to 5 years compared with LNF, is supported by a study that has evaluated the physiological effects of fundoplication. It is commonly assumed that impairment of ventilation of swallowed air from the stomach causes gas bloating and flatulence after fundoplication.[41] The first author recently reported that air venting is easier after partial than Nissen fundoplication.[42] In addition, partial and Nissen fundoplication were found to reduce acid and weakly acidic reflux to a similar extent.[42] These results are in line with the current observation that reflux control is similar after 180-degree LAF and LNF at 1 and 5 years. This is in contrast with findings of RCTs that report that 90-degree LAF and 120-degree LAF are associated with inferior reflux control in both the short term[43-45] and the long-term.[9,46] The 2 main differences between 90-degree LAF and 120-degree LAF *versus* 180-degree LAF are the reduced circumference of the wrap and the lack of fixation of the wrap to the right hiatal pillar. Fixation to the right hiatal pillar is probably the main factor that accounts for differences in the risk of recurrent reflux between various anterior fundoplications and probably accounts for the good results following 180-degree LAF demonstrated by this meta-analysis. Supporting this is the experience of some of us when undertaking revision surgery for recurrent reflux. During revision for recurrent reflux an anterior 180-degree fundoplication always remains securely attached to the right hiatal pillar and failure is due to proximal migration of the gastroesophageal junction, whereas lesser degrees of anterior partial fundoplications such as 90 degrees and 120 degrees the fundoplication seem to unravel and loosen in some patients. Hence, it seems reasonable to speculate that this is due to the lack of anchorage of the fundus to the right hiatal pillar. The 5-year reoperation rates of the current study were 9.5% for 180-degree anterior fundoplication and 6.2% for Nissen fundoplication. Reoperation rates in case series with less than complete follow-up can differ considerably from the randomized controlled trials with high follow-up rates that have been included this review. Publication bias and selection bias probably help to explain the difference in these results. A benchmark meta-analysis of randomized controlled trials demonstrated that 9.6% of patients who had a Nissen fundoplication underwent surgical reintervention at mean follow-up of 2 ½ years.[5] The reoperation rate in the present study is consistent with these results, especially considering the extended length of follow-up.

The internal validity of the current study is high because the analysis was based on high-quality RCTs, with high follow-up rates and low risk of bias. The fact that the trials were performed across 4 continents increases the external validity of this meta-analysis. It is notable that the senior authors of every trial agreed to provide both short- and long-term missing data. The principal investigators of the South African and Chinese RCT worked with the Australian research group during the first trial[34] and subsequently applied identical surgical techniques and questionnaires for their trials.[30,31] Consequently, a complete set of identical outcome measures and scales could be pooled. These 3 trials comprise 81% of the included patients and reported both 1- and 5-year results. This analysis is limited by the fact that 5-year follow-up was not yet available for the 2 remaining trials. However, these 2 trials were the smallest and of limited size, contributing only 19%

of the included patients. Another flaws is that physiological studies were performed in only 50% of patients.

A recent meta-analysis concluded that posterior 270-degree fundoplication offers similar reflux control up to 5 years but fewer dysphagia and gas-related compared to LNF.[4] The present study has similar methodology and demonstrates that 180-degree LAF has similar advantages over Nissen fundoplication up to 5 years. There is 1 RCT that has compared 180-degree LAF to posterior 180-degree fundoplication for the surgical treatment of GERD, but in this study follow-up was incomplete (57%) and short term.[47] Two parallel RCTs are currently being conducted in Australia and The Netherlands to evaluate differences between 180-degree LAF and posterior 270-degree fundoplication, and it is hoped they will address this question better.

In conclusion, dysphagia and gas-related symptoms are lower after 180-degree LAF compared with LNF at 1 and 5 years. Esophageal acid exposure and prevalence of esophagitis are similar after both procedures. Control of reflux symptoms, PPI use, patient satisfaction, dilatations, and reoperation rate are similar in both the short term and the long term. These results lend level 1a support for the use of 180-degree LAF for the surgical treatment of GERD.

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REFERENCES

1. Broeders JA, Rijnhart-de Jong HG, Draaisma WA et al. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. Ann Surg 2009; 250:698-706.

2. Salminen PT, Hiekkanen HI, Rantala AP et al. Comparison of long-term outcome of laparoscopic and conventional nissen fundoplication: a prospective randomized study with an 11-year follow-up. Ann Surg 2007; 246:201-206.

3. Draaisma WA, Rijnhart-de Jong HG, Broeders IA et al. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. Ann Surg 2006; 244:34-41.

4. Broeders JA, Mauritz FA, Ahmed AU et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. Br J Surg 2010; 97:1318-1330.

5. Catarci M, Gentileschi P, Papi C et al. Evidence-based appraisal of antireflux fundoplication. Ann Surg 2004; 239:325-337.

6. Varin O, Velstra B, De SS et al. Total vs partial fundoplication in the treatment of gastroesophageal reflux disease: a meta-analysis. Arch Surg 2009; 144:273-278.

7. Stefanidis D, Hope WW, Kohn GP et al. Guidelines for surgical treatment of gastroesophageal reflux disease. Surg Endosc 2010; 24:2647-2669.

8. Broeders JA, Roks DJ, Ahmed AU et al. Laparoscopic anterior versus posterior fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials. Ann Surg 2011; 254:39-47.

9. Broeders JA, Roks DJ, Jamieson GG et al. Five-year outcome after laparoscopic anterior partial versus nissen fundoplication: four randomized trials. Annals of Surgery 2012; 255:637-642.

10. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Chichester: John Wiley & Sons; 2008.

11. BMJ Clinical Evidence website. Search Filter. http://clinicalevidence.bmj. com/x/set/static/ebm/learn/665076.html. Accessed 14 April 2012.

12. Gatenby PA, Bright T, Watson DI. Anterior 180 degrees Partial Fundoplication-How I Do It. J Gastrointest Surg 2012;in press.

13. Jamieson GG, Watson DI, Britten-Jones R et al. Laparoscopic Nissen fundoplication. Ann Surg 1994; 220:137-145.

14. Johnson LF, Demeester TR. Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. Am J Gastroenterol 1974; 62:325-332.

15. Dakkak M, Bennett JR. A new dysphagia score with objective validation. J Clin Gastroenterol 1992; 14:99-100.

16. Watson DI, Pike GK, Baigrie RJ et al. Prospective double-blind randomized trial of laparoscopic Nissen fundoplication with division and without division of short gastric vessels. Ann Surg 1997; 226:642-652.

17. Moher D, Cook DJ, Eastwood S et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999; 354:1896-1900.

18. Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283:2008-2012.

19. Clarke M, Horton R. Bringing it all together: Lancet-Cochrane collaborate on systematic reviews. Lancet 2001; 357:1728.

20. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5:13.

21. Jadad AR, Moore RA, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17:1-12.

22. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21:1539-1558.

23. Higgins JP, Thompson SG, Deeks JJ et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327:557-560.

24. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7:177-188.

25. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50:1088-1101.

26. Egger M, Davey SG, Schneider M et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315:629-634.

27. Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. Stat Med 2001; 20:641-654.

28. Rebecchi F, Giaccone C, Farinella E et al. Randomized controlled trial of laparoscopic Heller myotomy plus Dor fundoplication versus Nissen fundoplication for achalasia: long-term results. Annals of Surgery 2008; 248:1023-1030.

29. Boutelier P. A double-blind, randomized prospective trial of Nissen fundoplication and anterior partial fundoplication using laparoscopy. Chirurgie 124(4):459-61 1999.

30. Baigrie RJ, Cullis SN, Ndhluni AJ et al. Randomized double-blind trial of laparoscopic Nissen fundoplication versus anterior partial fundoplication. Br J Surg 2005; 92:819-823.

31. Cao Z, Cai W, Qin M et al. Randomized clinical trial of laparoscopic anterior 180degrees partial versus 360degrees Nissen fundoplication: 5-year results. Diseases of the Esophagus 2012; 25:114-120.

32. Chrysos E, Athanasakis E, Pechlivanides G et al. The effect of total and anterior partial fundoplication on antireflux mechanisms of the gastroesophageal junction. Am J Surg 2004; 188:39-44.

33. Raue W, Ordemann J, Jacobi CA et al. Nissen versus Dor fundoplication for treatment of gastroesophageal reflux disease: a blinded randomized clinical trial. Digestive Surgery 2011; 28:80-86.

34. Watson DI, Jamieson GG, Pike GK et al. Prospective randomized double-blind trial between laparoscopic Nissen fundoplication and anterior partial fundoplication. Br J Surg 1999; 86:123-130.

35. Ludemann R, Watson DI, Jamieson GG et al. Five-year follow-up of a randomized clinical trial of laparoscopic total versus anterior 180 degrees fundoplication. Br J Surg 2005; 92:240-243.

36. Cai W, Watson DI, Lally CJ et al. Ten-year clinical outcome of a prospective randomized clinical trial of laparoscopic Nissen versus anterior 180(degrees) partial fundoplication. Br J Surg 2008; 95:1501-1505.

37. Rydberg L, Ruth M, Lundell L. Mechanism of action of antireflux procedures. Br J Surg 1999; 86:405-410.

38. Fibbe C, Layer P, Keller J et al. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized, clinical, and manometric study. Gastroenterology 2001; 121:5-14.

39. 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.

40. Booth MI, Stratford J, Jones L et al. Randomized clinical trial of laparoscopic total (Nissen) versus posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. Br J Surg 2008; 95:57-63.

41. Woodward ER, Thomas HF, McAlhany JC. Comparison of crural repair and Nissen fundoplication in the treatment of esophageal hiatus hernia with peptic esophagitis. Ann Surg 1971; 173:782-792.

42. Broeders JA, Bredenoord AJ, Hazebroek EJ et al. Reflux and belching after 270 degree versus 360 degree laparoscopic posterior fundoplication. Ann Surg 2012; 255:59-65.

43. Hagedorn C, Jonson C, Lonroth H et al. Efficacy of an anterior as compared with a posterior laparoscopic partial fundoplication: results of a randomized, controlled clinical trial. Ann Surg 2003; 238:189-196.

44. Spence GM, Watson DI, Jamiesion GG et al. Single center prospective randomized trial of laparoscopic Nissen versus anterior 90 degrees fundoplication. J Gastrointest Surg 2006; 10:698-705.

45. Watson DI, Jamieson GG, Lally C et al. Multicenter, prospective, double-blind, randomized trial of laparoscopic nissen vs anterior 90 degrees partial fundoplication. Arch Surg 2004; 139:1160-1167.

46. Engström C, Lönroth H, Mardani J et al. An anterior or posterior approach to partial fundoplication? Long-term results of a randomized trial. World J Surg 2007; 31:1221-1225.

47. Khan M, Smythe A, Globe J et al. Randomized controlled trial of laparoscopic anterior versus posterior fundoplication for gastro-oesophageal reflux disease. ANZ J Surg 2010; 80:500-505.

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Long-term symptom control of gastro-oesophageal reflux disease 12 years after laparoscopic Nissen or 180˚ anterior partial fundoplication in a randomized clinical trial

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ABSTRACT

Background

Laparoscopic 180° anterior fundoplication has been shown to achieve similar reflux control to Nissen fundoplication, with fewer side-effects, up to 5 years. However, there is a paucity of long-term follow-up data on this technique and antireflux surgery in general. This study reports 12-year outcomes of a double-blind RCT comparing laparoscopic Nissen *versus* 180° laparoscopic anterior fundoplication for gastro-oesophageal reflux disease (GORD).

Methods

Patients with proven GORD were randomized to laparoscopic Nissen or 180° anterior fundoplication. The 12-year outcome measures included reflux control, dysphagia, gas-related symptoms and patient satisfaction. Measures included scores on a visual analogue scale, a validated Dakkak score for dysphagia and Visick scores.

Results

Of the initial 163 patients randomized (Nissen 84, anterior 79), 90 (55.2 per cent) completed 12-year follow-up (Nissen 52, anterior 38). There were no differences in heartburn, dysphagia, gas-related symptoms, patient satisfaction and surgical reintervention rate. Use of acid-suppressing drugs was less common after Nissen than after 180° anterior fundoplication: four of 52 (8 per cent) and 11 of 38 (29 per cent) respectively ($P = 0.008$). The proportion of patients with absent or only mild symptoms was slightly higher after Nissen fundoplication: 45 of 50 (90 per cent) *versus* 28 of 38 (74 per cent) ($P = 0.044$).

Conclusion

The two surgical procedures provided similar control of heartburn and postfundoplication symptoms, with similar patient satisfaction and reoperation rates on long-term follow-up.

INTRODUCTION

Laparoscopic fundoplication is the surgical approach of choice for gastro-oesophageal reflux disease (GORD)[1]. Total fundoplication according to Nissen provides excellent reflux control and is the most frequently performed operation for GORD[2–4]. However, laparoscopic Nissen fundoplication causes troublesome dysphagia and gas-related symptoms in a significant number of patients[5–9]. Partial fundoplications have been developed as alternatives to total fundoplication and aim to reduce the incidence of adverse postfundoplication symptoms[5,7–9]. The 180° laparoscopic anterior fundoplication is the most commonly used anterior wrap[5,7–9].

Several trials[10–12] have been performed to determine whether anterior fundoplication is able to reduce postfundoplication symptoms, without compromising reflux control. Short-term (2 years) and mid-term (5 years) analyses of current trials have been published[6,12]. A meta-analysis[7] of trials comparing laparoscopic Nissen with 180° anterior fundoplication concluded that the latter achieves similar reflux control to Nissen, with fewer side-effects up to 5 years. However, recent guidelines[13] for antireflux surgery concluded that there is a paucity of long-term follow-up data on this topic.

This study report the 12-year results of a randomized double-blinded trial comparing laparoscopic Nissen with 180° anterior fundoplication to evaluate whether differences in efficacy, side-effects, patient satisfaction and reoperation rate develop with extension of follow-up beyond 5 years.

METHODS

The short-term[12] and mid-term[6] results of this double-blind RCT have been described previously. Patients with proven GORD undergoing primary laparoscopic antireflux surgery were enrolled between June 1999 and August 2001. GORD was defined as unequivocal reflux disease during endoscopy associated with retrosternal burning discomfort and/or acid regurgitation. All patients underwent preoperative endoscopy. In patients who did not satisfy the endoscopic criteria, 24-h pH monitoring and manometry were performed to diagnose GORD objectively. In addition, all patients had an unequivocal response to proton pump inhibitor therapy. Patients who had undergone antireflux surgery previously or were younger than 18 years of age were excluded. All procedures were performed in a single centre by a single surgeon with extensive experience (more than 120 laparoscopic fundoplications before commencement of the study).

The trial was conducted in a double-blinded fashion. The type of fundoplication was concealed from all patients unless revisional surgery was required. Although patients underwent routine postoperative review by the surgeon, these data were not included in the trial database. Patients were interviewed in the years following surgery using a structured postal questionnaire administered by an independent investigator, who remained unaware of the operation each patient had undergone. The final analysis of

these double-blinded data was performed jointly by the surgeon and the investigator. After informed consent had been obtained, randomization took place using sealed envelopes.

Operative technique and postoperative care

Procedures in both groups commenced with blunt dissection of the oesophageal hiatus with minimal use of diathermy and preservation of the hepatic branch of the vagus nerve, if possible. The short gastric vessels were left intact. Laparoscopic Nissen fundoplication was followed by routine posterior hiatal repair and the creation of a short loose 360° wrap over a 56-Fr bougie using 2/0 polypropylene sutures[12,14]. A 180° anterior fundoplication was created by suturing the anterior wall of the fundus to the right hiatal pillar and the posterior hiatal repair[15]. The angle of His was accentuated by a suture to the apex of the left hiatal pillar. Four to six 2/0 polypropylene sutures were used to create the wrap[12].

Follow-up

Outcome was assessed using a standardized set of questions, administered at 3 months and after each year, by either postal questionnaire or telephone interview. The questionnaires were analysed by an independent investigator, who was unaware of treatment allocation. Other events during follow-up were identified and recorded. Thorough efforts were made to track missing patients by reference to general practitioner records, next of kin, previous employers and the internet. Follow-up was abandoned at 12 years as these efforts became less successful and the number of patients lost to follow-up rose.

Heartburn was scored using a visual analogue scale (VAS; 0, no heartburn; 10, severe heartburn) and by determining the use of antisecretory drugs. Dysphagia was scored in two ways: using VAS scores for solids and liquids (0, no dysphagia; 10, total dysphagia) and a validated Dakkak dysphagia score (0, no dysphagia; 45, severe dysphagia)[16]. Patients were asked whether they were able to eat a normal diet. Gas-related symptoms were assessed by the presence or absence of gas bloating, flatulence and ability to relieve bloating and belch. Patient satisfaction was scored using a VAS and a Visick score (1, no symptoms; 2, mild symptoms; 3, moderate symptoms; 4, moderate symptoms interfering with life; 5, symptoms as bad or worse after surgery)[17]. In addition, patients were asked whether they would choose to undergo the same procedure again under similar circumstances.

Statistical analysis

Data were analysed according to the intention-to-treat principle and non-normal distribution was assumed. Ordinal variables were expressed as percentages, and differences between groups were analysed using the _^{2} test. For continuous variables data were expressed as median (range) and groups were compared using the Mann–Whitney *U* test. All tests were two-tailed and $P < 0.050$ was considered statistically significant. Statistical analyses were performed using SPSS® version 22.0 (IBM, Armonk, New York, USA).

RESULTS

A total of 163 patients were enrolled in the randomized trial, and underwent laparoscopic Nissen fundoplication (84) or 180° anterior fundoplication (79). The initial trial results and study design were published in 2005[12] and the 5-year results in 2012[6]. Fifty-five patients were untraceable, 14 declined to participate and four died during follow-up from causes unrelated to antireflux surgery. Ninety patients completed long-term follow-up (*Figure 1*). Baseline patient characteristics after 12 years of follow-up were similar in the two groups (*Table 1*). Characteristics of patients lost to follow-up were similar to those of patients who completed follow-up. Median age at time of surgery was 43 years in the Nissen group and 46 years in the 180° anterior fundoplication group. Median duration of follow-up was 144.5 months (Nissen 143.5 months, anterior 145.5 months).

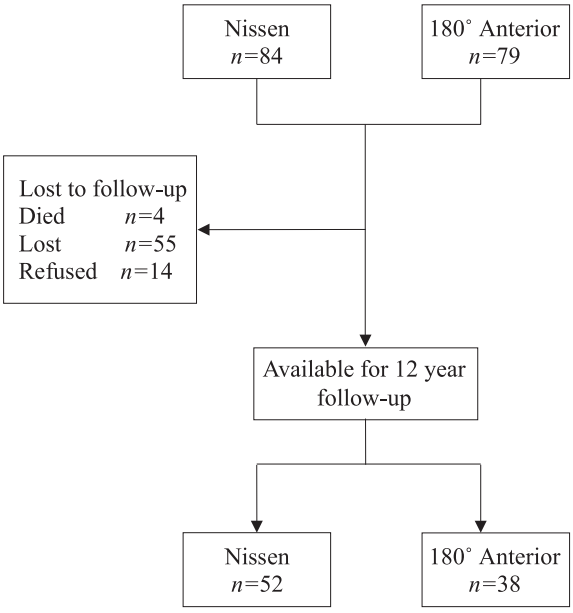

Figure 1. Flow diagram for the long-term follow-up study

Clinical outcomes are summarized in *Table 2.* Heartburn scores were similar for both procedures. The use of antisecretory drugs was significantly more common after anterior fundoplication: 11 of 38 (29 per cent) *versus* four of 52 (8 per cent) after Nissen fundoplication (*P*=0.008). There were no clinical or statistical differences in dysphagia, with similar VAS and Dakkak scores in both groups and proportion of patients on a normal diet. Gas-related symptoms, including ability to belch, gas bloating, ability to relieve bloating and flatulence, were comparable in the two groups (*Table 2*).

Table 1. Baseline characteristics of patients according to treatment group

	With long-term follow-up		
	Nissen fundoplication (*n* = 52)	**180° anterior fundoplication** (*n* = 38)	**Lost to follow-up** (*n* = 73)
Age (years)*	43 (16–69)	46 (27–66)	39 (22-70)
Sex ratio (M : F)	29 : 23	19 : 19	46 : 26
Follow-up interval (months)*	143.5 (130–158)	145.5 (132–183)	–

Values in parentheses are percentages unless indicated otherwise; *values are median (range). Thirty-two patients (38 per cent) in the initial Nissen fundoplication group and 41 (52 per cent) in the original 180° anterior fundoplication group were lost to follow-up.

Table 2. Symptomatic outcome at long-term follow-up

	Nissen fundoplication (*n* = 52)	**180° anterior fundoplication** (*n* = 38)	*P*†
Reflux symptoms			
Heartburn (VAS)*	0.0(0-4)	1.0 (0-9)	0.107‡
Acid-suppressing drugs	4 (8)	11 (29)	0.008
Dysphagia			
Dysphagia for liquids (VAS)*	0.0(0-10)	0.0(0-9)	0.428‡
Dysphagia for solids (VAS)*	1.5(0-10)	0.0(0-9)	0.128‡
Dakkak dysphagia score*	4.0(0-40) (*n* = 50)	2.5(0-37.5) (*n* = 35)	0.762‡
Normal diet	45 (87)	32 (84)	0.756
Gas-related symptoms			
Ability to belch	41 (79)	30 (79)	0.991
Gas bloating	21 (40)	20 (53)	0.249
Ability to relieve bloating	35 (67)	25 (66)	0.880
Flatulence	30 (58)	18 (47)	0.332

Values in parentheses are percentages unless indicated otherwise; *values are median(range). VAS, visual analogue scale. c^2 test, except ‡Mann–Whitney *U* test.

The median score for overall satisfaction was similar and the vast majority of patients would undergo surgery again in the Nissen and 180° anterior fundoplication groups: 47 of 52 (90 per cent) *versus* 31 of 38 (82 per cent) respectively (*P* = 0.225) (*Table 3*). Overall, Visick scores were lower after Nissen procedures (*P*=0.039), with more patients with absent or mild symptoms after Nissen compared with 180°anterior fundoplication: 45 of 50 (90 per cent) *versus* 28 of 38 (74 per cent) (*P*=0.044) (*Table 3*).

There was a higher surgical reintervention rate after 180° anterior fundoplication but this did not reach statistical significance: four of 52 (8 per cent) after Nissen and six of 38 (16 per cent) after partial fundoplication (*P* = 0.227). In the Nissen group two of four reoperations were for dysphagia, whereas in the 180° anterior group four of six reoperations were for recurrent reflux (*Table 4*).

Table 3. Patient satisfaction at long-term-follow-up

	Nissen fundoplication (*n* = 52)	**180° anterior fundoplication** (*n* = 38)	*P*†
Satisfaction (VAS)*	10 (2-10)	10 (0-10)	0.852‡
Patient would opt for surgery again	47 (90)	31 (82)	0.225
Visick score			0.039
1 (no symptoms)	16 (32)	15 (39)	
2 (mild symptoms)	29 (58)	13 (34)	
3 (moderate symptoms)	1 (2)	7 (18)	
4 (symptoms interfering with life)	3 (6)	3 (8)	
5 (symptoms not improved)	1 (2)	0 (0)	
Visick 1 and 2 (symptoms absent or mild)	45 of 50 (90)	28 (74)	0.044

Values in parentheses are percentages unless indicated otherwise; *values are median(range). VAS, visual analogue scale. c^2 test, except ‡Mann–Whitney *U* test.

Table 4. Surgical reintervention

	Nissen fundoplication (*n* = 52)	**180° anterior fundoplication** (*n* = 38)	*P**
Surgical reintervention	4 (8)	6 (16)	0.227
Recurrent reflux	2 of 4	4 of 6	
Dysphagia	2 of 4	2 of 6	

Values in parentheses are percentages. *c^2 test.

DISCUSSION

In patients available for long-term follow-up in an RCT comparing two techniques of fundoplication for GORD, the effect on symptom control after 12 years was similar in both groups. Patients undergoing Nissen fundoplication had slightly better rates of absent or only mild symptoms than those having partial fundoplication.

The main goal of antireflux surgery is to establish durable reflux control with minimal side-effects. Several trials and a meta-analysis[6,7,10,18,19] have compared laparoscopic Nissen and 180° anterior fundoplication, demonstrating that the latter provides similar reflux control with fewer side-effects up to 5 years. There is, however, a paucity of long-term results[13], so it is not clear whether Nissen and 180° anterior fundoplication provide similar reflux control with minimal side-effects in the long run[20,21]. The 10-year results of one trial[21] did not demonstrate differences in efficacy between the two procedures. The present study was designed to compare the long-term differences between Nissen and 180° anterior fundoplication in a head-to-head comparison in an attempt to strengthen the evidence base. The results demonstrate similar heartburn scores for both groups, consistent with the comparable reflux control demonstrated at short- and mid-term

follow-up of this trial[6,12]. These findings are in line with the 10-year results reported by Cai and colleagues[21]. With extension of follow-up, a higher rate of acid-suppressing drug use developed in the 180° anterior compared with the Nissen group. The percentage of patients using acid-suppressing drugs after 180° anterior was high at 29 per cent in the present study, but similar to the rates in other trials (27 per cent)[20]. However, it has been demonstrated previously that only a small proportion of patients who have restarted acid-suppressing therapy suffer from objective recurrent reflux disease[22–24].

The reduced rate of dysphagia and gas-related symptoms after 180° anterior compared with Nissen fundoplication that was present at 2 years[12] and 5 years[6] disappeared with extension of follow-up to 12 years. This trend is consistent with the findings of other long-term studies[20,21]. The two procedures had similar patient satisfaction rates, with the majority in both groups willing to undergo surgery again in a similar situation. In general, patient satisfaction scores were similar at 5 years (8.2 *versus* 8.5[6]) and after 12 years (mean 8.6 *versus* 8.1). Satisfaction rates were in line with the 10-year results of Cai *et al.*[21], who reported that 90 per cent of the patients who had a Nissen procedure and 98 per cent of those who underwent 180° anterior fundoplication would be willing to undergo surgery again. Patients in the Nissen group had lower Visick scores and a higher percentage had no or only mild symptoms. Reoperation rates were not significantly different between the interventions. The total reoperation rate of 11 per cent was slightly higher than in other long-term studies, which reported surgical reintervention in up to 9.3 per cent of patients[21].

Strengths of the present study are the double-blind randomized design and the duration of follow-up beyond 12 years (average 145 months). The present methodology has been consistently described and accepted as a valid form of double-blinding in all previous publications from the authors' group and the Adelaide group who first described this method of blinding[2,6,10,12].

One of the limitations of this trial is that it relied on clinical follow-up using validated questionnaires and did not use objective data to support the subjective findings. It would, for example, have been useful to perform 24-h pH monitoring in all patients who recommenced acid-suppressing drugs. However, these investigations can be invasive and it has been well documented that a significant percentage of patients refuse invasive follow-up[21,25]. In addition, the present study had substantial loss to follow-up owing to failure to return the questionnaires or inability to contact patients by post or telephone despite multiple attempts. This loss to follow-up limits the validity of the study and might have increased the potential bias associated with incomplete follow-up[25]. South Africa's geography, high migration rates and infrastructure might have contributed to the loss to follow-up. However, the follow-up rate here is in line with that in comparable trials which considered the duration of follow-up of 12 years[26]. A study by the authors' group that also compared the long-term results of laparoscopic Nissen and 180° anterior fundoplication demonstrated no differences in outcome between patients who refused part of the study protocol and those who completed the entire long-term outcome assessment. The authors, therefore, feel that the results for the participants in the present study are representative of those who originally enrolled in the trial.

REFERENCES

1 Schijven MP, Gisbertz SS, van Berge Henegouwen MI. Laparoscopic surgery for gastro-esophageal acid reflux disease. *Best Pract Res Clin Gastroenterol* 2014; **28**: 97–109.

2 Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. *Ann Surg* 2009; **250**: 698–706.

3 Salminen PT, Hiekkanen HI, Rantala AP, Ovaska JT. Comparison of long-term outcome of laparoscopic and conventional nissen fundoplication: a prospective randomized study with an 11-year follow-up. *Ann Surg* 2007; **246**: 201–206.

4 Draaisma WA, Rijnhart-de Jong HG, Broeders IA, Smout AJ, Furnee EJ, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. *Ann Surg* 2006; **244**: 34–41.

5 Broeders JA, Roks DJ, Ahmed AU, Draaisma WA, Smout AJ, Hazebroek EJ. Laparoscopic anterior *versus* posterior fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials. *Ann Surg* 2011; **254**: 39–47.

6 Broeders JA, Roks DJ, Jamieson GG, Devitt PG, Baigrie RJ, Watson DI. Five-year outcome after laparoscopic anterior partial *versus* Nissen fundoplication: four randomized trials. *Ann Surg* 2012; **255**: 637–642.

7 Broeders JA, Roks DJ, Ahmed AU, Watson DI, Baigrie RJ, Cao Z *et al.* Laparoscopic anterior 180-degree *versus* nissen fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials. *Ann Surg* 2013; **257**: 850–859.

8 Catarci M, Gentileschi P, Papi C, Carrara A, Marrese R, Gaspari AL *et al.* Evidence-based appraisal of antireflux fundoplication. *Ann Surg* 2004; **239**: 325–337.

9 Varin O, Velstra B, De SS, Ceelen W. Total *vs* partial fundoplication in the treatment of gastroesophageal reflux disease: a meta-analysis. *Arch Surg* 2009; **144**: 273–278.

10 Watson DI, Jamieson GG, Pike GK, Davies N, Richardson M, Devitt PG. Prospective randomized double-blind trial between laparoscopic Nissen fundoplication and anterior partial fundoplication. *Br J Surg* 1999; **86**: 123–130.

11 Chrysos E, Tsiaoussis J, Zoras OJ, Athanasakis E, Mantides A, Katsamouris A *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.

12 Baigrie RJ, Cullis SN, Ndhluni AJ, Cariem A. Randomized double-blind trial of laparoscopic Nissen fundoplication *versus* anterior partial fundoplication. *Br J Surg* 2005; **92**: 819–823.

13 Stefanidis D, Hope WW, Kohn GP, Reardon PR, Richardson WS, Fanelli RD *et al.* Guidelines for surgical treatment of gastroesophageal reflux disease. *Surg Endosc* 2010; **24**: 2647–2669.

14 Nissen R. [A simple operation for control of reflux esophagitis.] *Schweiz Med Wochenschr* 1956; **86**: 590–592.

15 Gatenby PA, Bright T, Watson DI. Anterior 180 degrees partial fundoplication – how I do it. *J Gastrointest Surg* 2012; **16**: 2297–2303.

16 Dakkak M, Bennett JR. A new dysphagia score with objective validation. *J Clin Gastroenterol* 1992; **14**: 99–100.

17 Watson DI, Pike GK, Baigrie RJ, Mathew G, Devitt PG, Britten-Jones R *et al.* Prospective double-blind randomized trial of laparoscopic Nissen fundoplication with division and without division of short gastric vessels. *Ann Surg* 1997; **226**: 642–652.

18 Chrysos E, Athanasakis E, Pechlivanides G, Tzortzinis A, Mantides A, Xynos E. The effect of total and anterior partial fundoplication on antireflux mechanisms of the gastroesophageal junction. *Am J Surg* 2004; **188**: 39–44.

19 Ludemann R, Watson DI, Jamieson GG, Game PA, Devitt PG. Five-year follow-up of a randomized clinical trial of laparoscopic total *versus* anterior 180 degrees fundoplication. *Br J Surg* 2005; **92**: 240–243.

20 Broeders JA, Broeders EA, Watson DI, Devitt PG, Holloway RH, Jamieson GG. Objective outcomes 14 years after laparoscopic anterior 180-degree partial *versus* nissen fundoplication: results from a randomized trial. *Ann Surg* 2013; **258**: 233–239.

21 Cai W, Watson DI, Lally CJ, Devitt PG, Game PA, Jamieson GG. Ten-year clinical outcome of a prospective randomized clinical trial of laparoscopic Nissen *versus* anterior 180° partial fundoplication. *Br J Surg* 2008; **95**: 1501–1505.

22 Draaisma WA, Rijnhart-de Jong HG, Broeders IA Smout AJ, Furnee EJ, Gooszen HG Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. *Ann Surg* 2006; **244**: 34–41.

23 Jenkinson AD, Kadirkamanathan SS, Scott SM, Yazaki E, Evans DF. Relationship between symptom response and oesophageal acid exposure after medical and surgical treatment for gastro-oesophageal reflux disease. *Br J Surg* 2004; **91**: 1460–1465.

24 Lord RV, Kaminski A, Oberg S, Bowrey DJ, Hagen JA, DeMeester SR *et al.* Absence of gastroesophageal reflux disease in a majority of patients taking acid suppression medications after Nissen fundoplication. *J Gastrointest Surg* 2002; **6**: 3–9.

25 Ludemann R, Watson DI, Jamieson GG. Influence of follow-up methodology and completeness on apparent clinical outcome of fundoplication. *Am J Surg* 2003; **186**: 143–147.

26 Sgromo B, Irvine LA, Cuschieri A, Shimi SM. Long-term comparative outcome between laparoscopic total Nissen and Toupet fundoplication: symptomatic relief, patient satisfaction and quality of life. *Surg Endosc* 2008; **22**: 1048–1053.

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Randomized clinical trial of 270° posterior versus 180° anterior partial laparoscopic fundoplication for gastro-oesophageal reflux disease

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ABSTRACT

Background

Partial fundoplications provide similar reflux control with fewer postfundoplication symptoms compared with Nissen fundoplication for gastro-oesophageal reflux disease (GORD). The best choice of procedure for partial fundoplication remains unclear. The aim of this study was to compare the outcome of two different types of partial fundoplication for GORD.

Methods

A double-blind RCT was conducted between 2012 and 2015 in two hospitals specializing in antireflux surgery. Patients were randomized to undergo either a laparoscopic 270° posterior fundoplication (Toupet) or a laparoscopic 180° anterior fundoplication. The primary outcome was postoperative dysphagia at 12 months, measured by the Dakkak score. Subjective outcome was analysed at 1, 3, 6 and 12 months after surgery. Objective reflux control was assessed before and 6 months after surgery.

Results

Ninety-four patients were randomized to laparoscopic Toupet or laparoscopic 180° anterior fundoplication (47 in each group). At 12 months, 85 patients (90 per cent) were available for follow-up. Objective scores were available for 76 (81 per cent). Postoperative Dakkak dysphagia score at 12 months was similar in the two groups (mean 5.9 for Toupet *versus* 6.4 for anterior fundoplication; $P = 0.773$). Subjective outcome at 12 months demonstrated no significant differences in control of reflux or postfundoplication symptoms. Overall satisfaction and willingness to undergo surgery did not differ between the groups. Postoperative endoscopy and 24-h pH monitoring showed no significant differences in mean oesophageal acid exposure time or recurrent pathological oesophageal acid exposure.

Conclusion

Both types of partial fundoplication provided similar control of GORD at 12 months, with no difference in postfundoplication symptoms. Registration number: NTR5702 (www.trialregister.nl).

INTRODUCTION

For patients suffering from gastro-oesophageal reflux disease (GORD) who are not responding to medical treatment or not willing to take life-long medication, laparoscopic fundoplication is currently considered the treatment of choice[1,2]. Previous studies have demonstrated comparable and durable subjective and objective reflux control, with a lower risk of surgical reintervention following laparoscopic fundoplication compared with open fundoplication[1,3]. Laparoscopic Nissen fundoplication has been the most frequently performed antireflux procedure[1,4,5]. However, the 360° posterior wrap in this fundoplication is associated with a high incidence of troublesome dysphagia and gas-related symptoms, such as gas bloating, flatulence and inability to belch[6–8]. Partial fundoplications have been developed as alternatives for the Nissen fundoplication, with the aim of reducing the incidence of such postfundoplication symptoms[6,9–15]. The most commonly used partial fundoplications are either the posterior 270° fundoplication (Toupet) or the anterior 180° fundoplication[10,16].

Several RCTs[9,14,17–23] and meta-analyses[6,10,24] have evaluated whether partial wraps reduce postfundoplication symptoms and whether this is at the expense of inferior reflux control compared with laparoscopic Nissen fundoplication[16]. Both laparoscopic Toupet[6] and laparoscopic 180° anterior fundoplication[10] provide similar reflux control with a lower rate of postoperative dysphagia and gas-related symptoms compared with laparoscopic Nissen fundoplication[6]. However, it is unclear which of these two partial fundoplications yields the best reflux control with minimal postoperative side-effects. Only two trials[25,26] have previously compared laparoscopic anterior with posterior partial fundoplication. The first[26] compared 120° anterior fundoplication with laparoscopic Toupet fundoplication and reported poor results after the anterior approach. However, the technique applied in the anterior arm might be inferior to a wrap with a 180° circumference. The second trial[25] used identical surgical techniques to those in the present study, but was underpowered.

The aim of the present study was to determine whether laparoscopic Toupet or laparoscopic 180° anterior fundoplication offers the best subjective and objective reflux control, with the fewest post-fundoplication symptoms.

METHODS

This two-centre double-blind RCT compared two antireflux procedures: laparoscopic 270° posterior fundoplication (Toupet)[27] and laparoscopic 180° anterior fundoplication[28]. Differences in short-term reflux control, postoperative dysphagia and gas-related symptoms, and patient satisfaction were examined using upper gastrointestinal endoscopy, oesophageal manometry and 24-h pH monitoring, and questionnaires. The trial was designed in a similar fashion as that conducted in Australia[25]. Trial design was based partially on that protocol, with similar surgical methods, and similar questionnaires and follow-up intervals.

Ethical approval and trial registration

The protocol for this study was approved by the medical ethics committees of the St Antonius Hospital, Nieuwegein, and the Isala Clinics, Zwolle (RCT no. NL39193.100.12). To guarantee safety and quality throughout the study, an independent data safety monitoring board was established, which has monitored the quality of the trial and followed the occurrence of all patient safety-related endpoints. A safety analysis was performed by the data safety monitoring board, and reported to the medical ethics committees when 50 per cent (47) of the patients had been included.
This trial was registered in the Netherlands Trial Register (no. NTR5702).

Study design

The study was performed as a randomized two-centre trial in two large teaching hospitals in the Netherlands, with all patients operated on by one experienced gastrointestinal surgeon (60 fundoplications annually; total case load more than 400) per centre.

Patient selection

Adult patients with GORD confirmed by endoscopy and/or 24-h oesophageal pH monitoring, and with an indication for antireflux surgery, were considered eligible for inclusion. Patients who had undergone previous antireflux surgery and/or suffered from a large hiatus hernia (more than 50 per cent of the stomach in the chest), oesophageal aperistalsis, spasms or achalasia were excluded.

Randomization

After informed consent, 1 : 1 randomization to laparoscopic Toupet or laparoscopic 180° anterior fundoplication was performed using web-based randomization. Only patients who were deemed to be suitable for both procedures were randomized. Preoperative investigation was as per standard clinical practice, which included upper gastrointestinal endoscopy, oesophageal manometry and 24-h pH monitoring. Oesophagitis was graded according to Los Angeles classification[29]. The pH electrode was positioned 5 cm above the manometrically determined upper margin of the lower oesophageal sphincter (LOS). Preoperative barium swallows were performed only when clinically indicated, as barium swallows do not provide sufficient screening for GORD[30]. Patients were not informed regarding the type of fundoplication performed, and objective follow-up investigations were carried out by an observer blinded to the type of surgical procedure. Both hospitals had similar preoperative and postoperative care and investigation.

Surgical procedures

All fundoplications were performed using standardized laparoscopic techniques. Tutoring and a convention meeting between the two participating surgeons ensured similar techniques in both hospitals.
In all instances, the procedure commenced with dissection of the lower oesophagus and routine posterior hiatal repair using non-absorbable sutures. If present, the size and type

of the hiatus hernia was assessed by the surgeon and noted in the case record forms. In none of the patients was a bougie used. Laparoscopic Toupet fundoplication entailed the creation of a posterior partial fundoplication of the gastric fundus, which was anchored to the oesophagus on left and right sides, as well as to the crus posterolaterally on the right side, while leaving the anterior oesophagus uncovered. When constructing a laparoscopic 180° anterior fundoplication, the ventral wall of the gastric fundus was sutured to the anterior oesophagus and right crus[31].
If the operation had to be converted to an open procedure, the patient remained included in the study. If the fundoplication type performed was not consistent with the allocated fundoplication, the patient was not excluded and remained in the allocated group for intention-to-treat analysis.

Postoperative care
Patients were allowed oral fluids directly, and soft solid food the next day. Early discharge from the hospital was usually on postoperative day 1 or 2. Barium meal X-ray was not performed routinely before discharge.

Primary outcome
The primary outcome was the difference in Dakkak dysphagia scores between the two study groups at 12 months after surgery, as assessed by validated questionnaires[32]. Reflux control was determined by means of upper gastrointestinal endoscopy and oesophageal 24-h pH monitoring 6 months after operation. All postoperative examinations were performed by gastroenterologists with extensive expertise in antireflux surgery and the associated changes in oesophagogastric anatomy.
The presence of reflux, dysphagia and gas-related symptoms were assessed at 1, 3, 6 and 12 months after surgery using standardized questionnaires. All patients were interviewed before the operation, and received these questionnaires by post. If a patient did not return these questionnaires within 1 month, they were reminded by telephone.
The presence or absence of the following symptoms was determined: heartburn, chest pain, epigastric pain, regurgitation, dysphagia, satiety, inability to belch, gas bloating, anorexia, nausea, vomiting, nocturnal coughing, flatulence and diarrhoea. In addition, the presence and degree of heartburn and dysphagia for liquids and solids was assessed using a 0–10 visual analogue scale (VAS) (0, no symptoms; 10, severe symptoms). The presence and degree of dysphagia was further examined using the validated Dakkak dysphagia score[32], which addresses the difficulty (0, never; 1, sometimes; 2, always) of swallowing nine types of liquid and solid.
The overall outcome of surgery was ranked using an analogue satisfaction score (0, dissatisfied; 10, satisfied), a modified Visick grading score[33] (1, no symptoms; 5, worse symptoms following surgery), the question whether the patient would undergo surgery again (0, no; 1, yes) and an overall outcome score (1, perfect; 4, bad outcome).
Changes in the use of proton pump inhibitors and histamine$_2$ blockers were also determined.

Sample size calculation

Sample size calculation was based on an estimated reduction in Dakkak dysphagia scores at 6 months of follow-up. A previous study[26] found a Dakkak dysphagia score of 7.0 following Toupet fundoplication. The aim was to reduce this score by a clinically relevant 50 per cent, to 3.5, following 180° anterior fundoplication at 12 months' follow-up, based on another clinical study[34] that found a dysphagia score of 3.5 following anterior fundoplication. A two-sample *t* test power analysis, with a power of 0.8 and α of 0.05 was performed, resulting in a sample size of 47 in each arm (PASS 2008, version 8.0.8; https://www.ncss.com/software/pass).

Statistical analysis

All data were entered in a computerized database and analysed using the statistical software package SPSS® version 22.0 (IBM, Armonk, New York, USA). All included patients were analysed on an intention-to-treat basis, with a separate per-protocol analysis. No stratification analyses for centre were conducted. Data were expressed as mean (95 per cent c.i.) or total number of patients, unless indicated otherwise.

The χ^2 test, or Fisher's exact test where necessary, were used to compare binary variables between groups, and the Mann–Whitney *U* test for continuous variables. The Wilcoxon signed rank test was used for comparisons of the effects of surgery within either the laparoscopic Toupet or the laparoscopic 180° anterior fundoplication arm. Statistical significance was set at $P < 0.050$.

RESULTS

A total of 94 patients were included (*Figure 1*). Forty-seven patients were randomized to laparoscopic Toupet and 47 to laparoscopic 180° fundoplication. Eighty-five (90 per cent) of these patients, completed the questionnaires at 12 months after surgery. Objective follow-up data were available for 76 patients (81 per cent). During the 12-month follow-up, one patient withdrew from the study. Missing symptomatic or objective follow-up data were due to patients being lost to follow-up or their unwillingness to complete questionnaires or undergo postoperative investigations. Baseline characteristics of the patients are summarized in *Table 1*; there were no differences between the two groups.

Perioperative outcome

All 94 patients underwent the allocated surgical treatment and there were no conversions to open surgery. Median operating time did not significantly differ between the two procedures (50 min for Toupet *versus* 43 min for anterior fundoplication; $P = 0.091$) (*Table S1*, supporting information).

A hiatus hernia was present in 36 patients in the Toupet group and in 42 in the anterior fundoplication group ($P = 0.251$) (*Table S1*, supporting information). Cruroplasty using non-absorbable sutures was carried out in all patients, with posterior cruroplasty being

performed in 22 and 34 patients respectively, and posterior and anterior cruroplasty done more frequently after laparoscopic Toupet fundoplication (25 patients *versus* 13 in the anterior group; *P* = 0.012) (*Table S1*, supporting information). None of the hiatus hernia repairs was done using mesh.

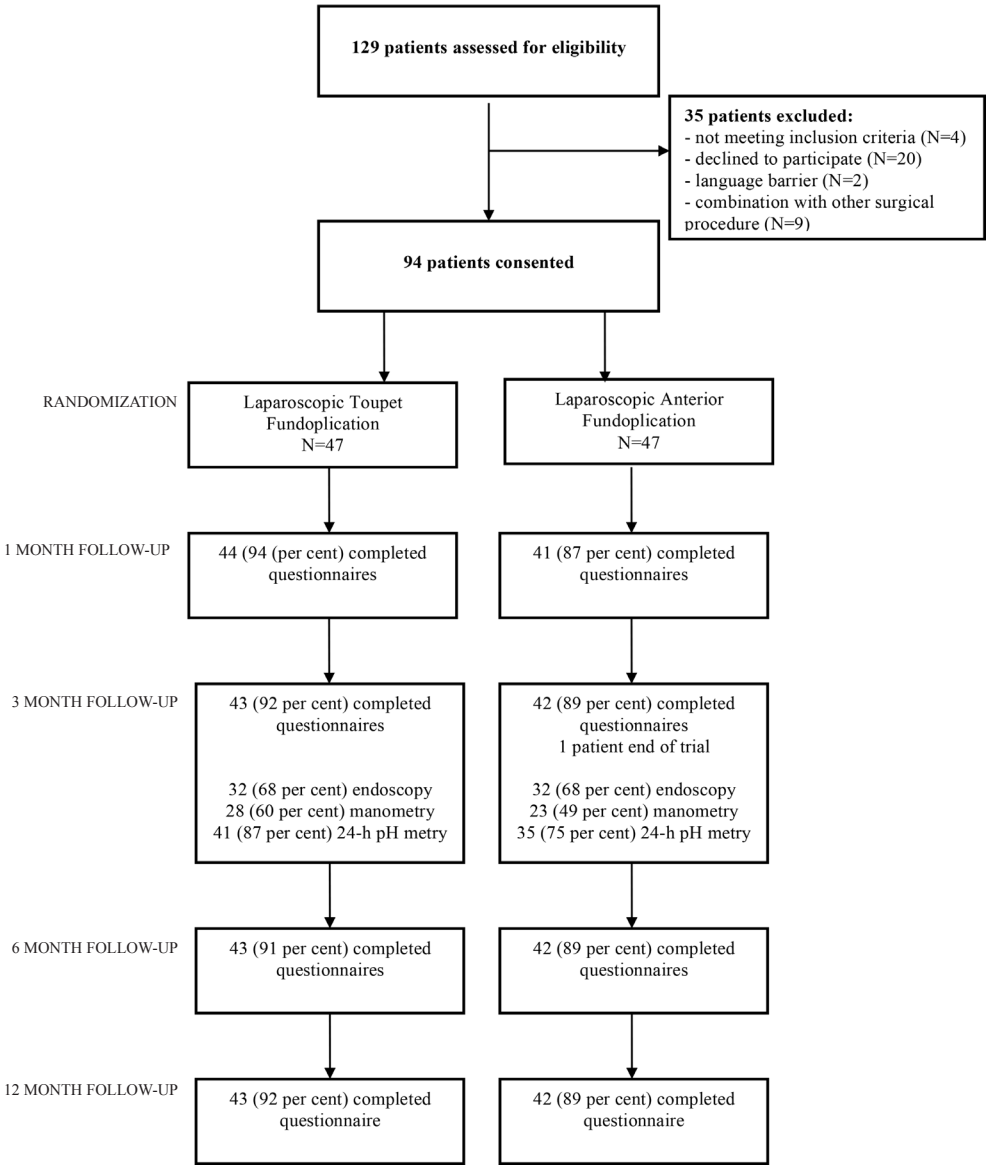


Figure 1. CONSORT flow diagram of enrolment and follow-up of patients

An intraoperative complication (a diaphragmatic bleed of 600 ml) occurred in one patient in the anterior fundoplication group. Postoperative complications within 30 days of surgery occurred in three patients in the Toupet group (acute dysphagia, 2; acute obstruction based on food stasis, 1) and in one patient in the anterior fundoplication group developed gastroenteritis. Revision fundoplication was performed in the two patients in the Toupet group who had acute dysphagia at 5 and 14 days after the primary operation. In both patients, the Toupet fundoplication was converted to a laparoscopic 180° anterior fundoplication, with no complications, and the dysphagia resolved.

Symptomatic outcome

Preoperative symptom scores for the two groups and symptomatic outcome at 12 months after surgery are summarized in *Tables 2* and *3*. Only increased flatulence (1 month: 27 *versus* 20 patients; $P = 0.034$) and chest pain (6 months: 10 *versus* 3 patients; $P = 0.039$**)** were observed significantly more often in the Toupet than in the 180° anterior fundoplication group.

In both groups there was a significant decrease in mean VAS score for heartburn at 12 months' follow-up compared with the preoperative score (Toupet: 1.3 *versus* 5.1 respectively, $P < 0.001$; anterior: 1.2 *versus* 4.6, $P < 0.001$) (*Table 3*). Mean heartburn score between the two groups was similar at 1, 3, 6 and 12 months after surgery. At 12 months, approximately 90 per cent of all included patients reported control of heartburn (39 of 43 patients in the Toupet group and 38 of 42 in the anterior group; $P = 0.944$).

At 12 months after surgery, seven patients in both the Toupet and anterior fundoplication group reported the presence of dysphagia ($P = 0.962$). The 12-month VAS score for dysphagia for liquids did not change in either group compared with the preoperative score (Toupet: 0.5 *versus* 0.8 respectively, $P = 0.471$; anterior: 1.0 *versus* 1.0, $P = 0.411$); neither did VAS dysphagia score for solids (Toupet: 1.1 *versus* 2.0, $P = 0.194$; anterior: 1.0 *versus*

Table 1. Baseline characteristics of patients undergoing laparoscopic fundoplication

	Toupet (n = 47)	**Anterior** (n = 47)
Age (years)*	54.0 (19–73)	56.0 (20–75)
Sex ratio (M : F)	24 : 23	23 : 24
BMI (kg/m2)*	27.2 (19–41)	26.8 (19–37)
Duration of symptoms (years)*	5.0 (1–30)	5.0 (1–30)
Previous surgery†	17	22
ASA fitness grade		
I	21	14
II	24	27
III	2	3
Lost to follow-up at 1 year	4	5

*Values are median (range). †History of thoracic or abdominal surgery other than antireflux surgery.

1.9, *P* = 0.107) (*Table 3*). There were no differences between the two groups for any of the four follow-up intervals, with mean scores of 0.5 and 1.0 for liquids (*P* = 0.313) and 1.1 and 1.0 for solids (*P* = 0.535) in the Toupet and anterior fundoplication groups respectively at 12 months. Neither did the Dakkak dysphagia score significantly differ between the two groups at all four follow-up intervals, with mean scores of 5.9 and 6.4 respectively at 12 months (*Table 3*).

The patient satisfaction score (8.2 in both groups; *P* = 0.679), the Visick score (*Table 4*) and overall outcome (*P* = 0.544) were similar between the two groups at 12 months' follow-up, as well as at the other three intervals. At 12 months, 39 patients in the Toupet group and 40 in the 180° anterior fundoplication group reported that they would undergo the same operation again (*P* = 0.676).

Compared with preoperative usage, the use of acid-suppressing drugs decreased in both groups at the 12-month follow-up (from 44 of 47 patients to 9 of 43 in the Toupet group; from 43 of 47 to 9 of 42 in the anterior fundoplication group), with no significant difference in medication usage between the two groups at 12 months (*P* = 0.950). Per-protocol analysis based on the type of procedure patients had undergone at the time of completing follow-up, including the two cross-over patients in whom the Toupet procedure was converted to a laparoscopic 180° anterior fundoplication, did not influence the results, except that the higher rates of flatulence at 1 month (*P* = 0.078) and chest pain at 6 months (*P* = 0.120) in the Toupet compared with the anterior group were no longer significant.

Table 2. Assessment of preoperative and postoperative symptoms between the two types of laparoscopic fundoplication

	Before surgery		12 months after surgery		
	Toupet (n = 47)	**Anterior (n = 47)**	**Toupet (n = 43)**	**Anterior (n = 42)**	**P***
Heartburn	44	41	9	6	0.422
Chest pain	31	35	7	7	0.962
Epigastric pain	23	28	7	7	0.962
Regurgitation	31	37	9	7	0.615
Pain during swallowing	3	6	3	0	0.081
Postprandial satiety	12	18	19	11	0.083
Inability to belch	0	0	6	4	0.526
Gas bloating	16	18	14	11	0.519
Anorexia	3	4	0	0	–
Nausea	18	14	6	4	0.526
Vomiting	8	15	2	0	0.157
Nocturnal coughing	17	12	7	3	0.191
Increased flatulence	–	–	26	21	0.160
Diarrhoea	0	0	5	6	0.715

*$\chi 2$ or Fisher's exact test.

Table 3. Preoperative and postoperative control of heartburn and presence of dysphagia in patients undergoing laparoscopic fundoplication

	Before surgery		12 months after surgery		
	Toupet (n = 47)	**Anterior (n = 47)**	**Toupet (n = 43)**	**Anterior (n = 42)**	**P†**
Dakkak dysphagia score (0–45)*	8.6 (5.5, 11.6)	8.4 (5.3, 11.6)	5.9 (3.5, 8.3)	6.4 (3.8, 8.9)	0.773‡
Presence of dysphagia	16	18	7	7	0.962
VAS score*					
Liquids	0.8 (0.2, 1.3)	1.0 (0.4, 1.7)	0.5 (0.2, 0.8)	1.0 (0.4, 1.6)	0.313‡
Solids	2.0 (1.1, 2.9)	1.9 (1.2, 2.7)	1.1 (0.6, 1.6)	1.0 (0.3, 1.7)	0.535‡
Control of heartburn	16	11	39	38	0.944
VAS score for heartburn*	5.1 (4.1, 6.0)	4.6 (3.7, 5.1)	1.3 (0.8, 1.8)	1.2 (0.6, 1.7)	0.759‡

*Values are mean (95 per cent c.i.). †χ^2 or Fisher's exact test, except ‡Mann–Whitney *U* test.

Table 4. Symptoms assessed by Visick score in patients under

	Before surgery		12 months after surgery		
Visick score	**Toupet (n = 43)**	**Anterior (n = 42)**	**Toupet (n = 41)**	**Anterior (n = 38)**	**P***
1	0	0	12	11	0.975
2	3	6	18	18	0.941
3	10	4	5	3	0.528
4	30	32	6	6	0.883
5	0	0	0	0	–

*χ^2 or Fisher's exact test.

Upper gastrointestinal endoscopy

Preoperative upper gastrointestinal endoscopy was performed in 90 patients (96 per cent) (*Table S2*, supporting information). Before surgery, reflux oesophagitis was present in 26 patients (29 per cent), with no differences between the two groups. Nineteen patients (21 per cent) suffered from Barrett's oesophagus. Endoscopy was used to verify reflux disease in the seven patients who did not have pH studies. In this group, no patient had grade A, three had grade B, one had grade C and none had grade D oesophagitis; a further three patients had Barrett's oesophagus.

Some 6 months after surgery, endoscopy was performed in 64 patients (68 per cent). Nine (14 per cent) showed signs of oesophagitis, and in 14 patients (22 per cent) Barrett's oesophagus was found (*Table S2*, supporting information), with no differences between the two groups (P = 1.000 for both comparisons). Per-protocol analysis did not change these results.

Oesophageal pH monitoring and manometry

A total of 76 patients (81 per cent) underwent 24-h oesophageal pH monitoring 6 months after surgery. Postoperative pH < 4 for more than 4 per cent of the time was found in four of 41 patients in the Toupet group and in four of 35 in the 180° anterior fundoplication group (*Table S2*, supporting information), with a mean percentage of time with pH < 4 of 1.9 in the Toupet group *versus* 2.6 in the anterior group ($P = 0.483$). Of these eight patients, one had normal oesophageal acid exposure before fundoplication. Only one patient reported typical reflux symptoms (regurgitation) at 3 and 6 months after surgery, and none of these eight patients reported heartburn. Per-protocol analysis did not affect these results.

Preoperative oesophageal manometry was performed in 55 (59 per cent) of the 94 included patients, and did not demonstrate abnormalities or significant differences between the two groups. Six months after surgery 51 patients (54 per cent) underwent oesophageal manometry again, which revealed a significantly lower mean residual resting pressure in the Toupet group than in the anterior group ($P = 0.008$ (*Table S2*, supporting information). Per-protocol analysis did not change these results.

DISCUSSION

This RCT found no difference between the two types of partial fundoplication in controlling the symptoms and oesophageal acid exposure associated with GORD. Few postoperative side-effects were found in either arm, and patient satisfaction rates were high. Based on the 12-month results of this trial, the authors suggest that selecting a laparoscopic 270° posterior (Toupet) or 180° anterior fundoplication should be based on surgeons' experience and preference.

The Dakkak dysphagia score was the primary outcome of this trial, and no differences between the two groups were identified at 1, 3, 6 and 12 months of follow-up. There were no differences in secondary outcomes such as reflux control, overall outcome and patient satisfaction. The only differences that were observed included a higher rate of flatulence 1 month after Toupet fundoplication and of chest pain 6 months after laparoscopic Toupet fundoplication. At 12 months these differences were no longer present. The presence of typical postfundoplication symptoms also did not differ significantly between the two groups.

An RCT[25] comparing laparoscopic Toupet with laparoscopic 180° anterior fundoplication found no significant differences in terms of dysphagia, but a trade-off between reflux *versus* inability to belch and nausea. Heartburn scores were higher after 180° anterior fundoplication, accompanied by a trend towards higher pH scores. Satisfaction after both procedures was similarly high[25]. The present study randomized twice as many patients and the results are in line with the findings of Daud and colleagues[25], with no major differences in reflux control and postfundoplication symptoms between laparoscopic Toupet and 180° anterior fundoplication.

A possible advantage of a laparoscopic 180° anterior over Toupet fundoplication could be the fact that the anterior fundoplication requires less division of short gastric vessels. However, the present authors did not find a significant difference in total duration of surgery, indicating equal technical feasibility of the two procedures.

The manometric studies are in line with those of Daud and co-workers[25], reporting a trend towards reduced LOS resting and residual pressures after Toupet compared with 180° anterior fundoplication. These manometric results are in contrast with those from a Swedish trial[35] in which a trend toward a higher LOS resting and residual pressures after Toupet fundoplication was found compared with pressures following anterior fundoplication. A possible explanation for these conflicting results may be the fact that the latter trial used a 120° anterior fundoplication technique, which may be inferior to the 180° approach used by Daud *et al*.[25] and in the present trial. This might have resulted in different lower postoperative oesophageal sphincter resting and residual pressures[35]. Despite a significantly lower LOS residual resting pressure in the Toupet group compared with that in the 180° anterior group, no difference was found in oesophageal acid exposure during 24-h oesophageal pH monitoring in the present study, indicating that the decrease in LOS residual resting pressure did not result in an increase in acidic reflux episodes. Continuing follow-up, including oesophageal function testing, will determine whether this finding has any long-term clinical implications. LOS length was not registered adequately in manometric studies, so it is not possible to determine whether the reduced LOS pressure in the Toupet fundoplication arm was due to a shortening of the LOS length.

The effectiveness on patient's well-being of both procedures is demonstrated by high patient satisfaction and Visick scores. These findings are in line with those of other trials[25,36]. At least 93 per cent (79 of 85) of all included patients would undergo surgery again under similar conditions. Furthermore, approximately 90 per cent of all patients reported control of heartburn, and a significant reduction in mean heartburn scores was seen at 12 months, demonstrating the excellent reflux-controlling potential of both procedures.

A possible weakness of the present study is the fact that not all of the included patients underwent postoperative oesophageal 24-h pH monitoring, which is considered the standard for diagnosing GORD. It remains difficult to convince patients of the necessity of invasive postoperative oesophageal function testing if they experience no postoperative symptoms. This is a common problem in prospective studies describing the outcome of antireflux surgery. However, postoperative 24-h oesophageal pH studies were obtained for approximately 81 per cent of the patients, demonstrating no significant differences between the two groups and demonstrating pH < 4 for more than 4 per cent of the total time in four of 41 patients after Toupet and four of 35 after 180° anterior fundoplication, of whom only one patient reported regurgitation and none reported heartburn. A study by the authors' group[37] comparing the results of laparoscopic Nissen and 180° anterior fundoplication demonstrated no differences in outcome between patients who had only subjective outcome assessment and those who completed both subjective and objective follow-up. Furthermore, there were no significant differences in symptomatic outcome

between laparoscopic Toupet and 180° anterior fundoplication groups, making it unlikely that a higher rate of patients undergoing postoperative pH monitoring would result in a significant difference in recurrent pathological acid exposure between the two groups.
Investigator bias is deemed unlikely as both surgeons conducted the operations in a similar fashion after training together in the two procedures and performing them on patients together, as well as discussing intraoperative videos of the two techniques before commencement of the trial. There was no learning curve, as both surgeons are experienced in reflux and upper gastrointestinal surgery[38]. In addition, a two-centre design and intention-to-treat analysis is probably the best reflection of clinical practice.
There were no differences in typical reflux symptoms such as heartburn and regurgitation, or in oesophageal acid exposure. Based on objective oesophageal studies 6 months after surgery, only LOS residual resting pressure was found to be lower for the Toupet procedure compared with 180°anterior fundoplication. These findings were not reported in other comparable trials[25,36].

Disclosure
The authors declare no conflict of interest.

REFERENCES

1 Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG *et al*. Ten-year outcome of laparoscopic and conventional Nissen fundoplication: randomized clinical trial. *Ann Surg* 2009; **250**: 698–706.

2 Schijven MP, Gisbertz SS, van Berge Henegouwen MI. Laparoscopic surgery for gastro-esophageal acid reflux disease. *Best Pract Res Clin Gastroenterol* 2014; **28**: 97–109.

3 Peters MJ, Mukhtar A, Yunus RM, Khan S, Pappalardo J, Memon B *et al*. Meta-analysis of randomized clinical trials comparing open and laparoscopic anti-reflux surgery. *Am J Gastroenterol* 2009; **104**: 1548–1561.

4 Salminen PT, Hiekkanen HI, Rantala AP, Ovaska JT. Comparison of long-term outcome of laparoscopic and conventional Nissen fundoplication: a prospective randomized study with an 11-year follow-up. *Ann Surg* 2007; **246**: 201–206.

5 Draaisma WA, Rijnhart-de Jong HG, Broeders IA, Smout AJ, Furnee EJ, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. *Ann Surg* 2006; **244**: 34–41.

6 Broeders JA, Mauritz FA, Ahmed AU, Draaisma WA, Ruurda JP, Gooszen HG *et al*. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) *versus* Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. *Br J Surg* 2010; **97**: 1318–1330.

7 Catarci M, Gentileschi P, Papi C, Carrara A, Marrese R, Gaspari AL *et al*. Evidence-based appraisal of antireflux fundoplication. *Ann Surg* 2004; **239**: 325–337.

8 Varin O, Velstra B, De Sutter S, Ceelen W. Total *vs* partial fundoplication in the treatment of gastroesophageal reflux disease: a meta-analysis. *Arch Surg* 2009; **144**: 273–278.

9 Baigrie RJ, Cullis SN, Ndhluni AJ, Cariem A. Randomized double-blind trial of laparoscopic Nissen fundoplication *versus* anterior partial fundoplication. *Br J Surg* 2005; **92**: 819–823.

10 Broeders JA, Roks DJ, Ahmed AU, Watson DI, Baigrie RJ, Cao Z *et al*. Laparoscopic anterior 180-degree *versus* Nissen fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials. *Ann Surg* 2013; **257**: 850–859.

11 Khan M, Smythe A, Globe J, Stoddard CJ, Ackroyd R. Randomized controlled trial of laparoscopic anterior *versus* posterior fundoplication for gastro-oesophageal reflux disease. *Aust NZ J Surg* 2010; **80**: 500–505.

12 Koch OO, Kaindlstorfer A, Antoniou SA, Asche KU, Granderath FA, Pointner R. Laparoscopic Nissen *versus* Toupet fundoplication: objective and subjective results of a prospective randomized trial. *Surg Endosc* 2012; **26**: 413–422.

13 Ludemann R, Watson DI, Jamieson GG, Game PA, Devitt PG. Five-year follow-up of a randomized clinical trial of laparoscopic total *versus* anterior 180 degrees fundoplication. *Br J Surg* 2005; **92**: 240–243.

14 Strate U, Emmermann A, Fibbe C, Layer P, Zornig C. Laparoscopic fundoplication: Nissen *versus* Toupet two-year outcome of a prospective randomized study of 200 patients regarding preoperative esophageal motility. *Surg Endosc* 2008; **22**: 21–30.

15 Watson DI, Jamieson GG, Pike GK, Davies N, Richardson M, Devitt PG. Prospective randomized double-blind trial between laparoscopic Nissen fundoplication and anterior partial fundoplication. *Br J Surg* 1999; **86**: 123–130.

16 Stefanidis D, Hope WW, Kohn GP, Reardon PR, Richardson WS, Fanelli RD; SAGES Guidelines Committee. Guidelines for surgical treatment of gastroesophageal reflux disease. *Surg Endosc* 2010; **24**: 2647–2669.

17 Booth MI, Stratford J, Jones L, Dehn TC. Randomized clinical trial of laparoscopic total (Nissen) *versus* posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. *Br J Surg* 2008; **95**: 57–63.

18 Cao Z, Cai W, Qin M, Zhao H, Yue P, Li Y. Randomized clinical trial of laparoscopic anterior 180 degrees partial *versus* 360 degrees Nissen fundoplication: 5-year results. *Dis Esophagus* 2012; **25**: 114–120.

19 Chrysos E, Athanasakis E, Pechlivanides G, Tzortzinis A, Mantides A, Xynos E. The effect of total and anterior partial fundoplication on antireflux mechanisms of the gastroesophageal junction. *Am J Surg* 2004; **188**: 39–44.

20 Guerin E, Bétroune K, Closset J, Mehdi A, Lefèbvre JC, Houben JJ *et al*. Nissen *versus* Toupet fundoplication: results of a randomized and multicenter trial. *Surg Endosc* 2007; **21**: 1985–1990.

21 Mickevicius A, Endzinas Z, Kiudelis M, Jonaitis L, Kupcinskas L, Maleckas A *et al*. Influence of wrap length on the effectiveness of Nissen and Toupet fundoplication: a prospective randomized study. *Surg Endosc* 2008; **22**: 2269–2276.

22 Raue W, Ordemann J, Jacobi CA, Menenakos C, Buchholz A, Hartmann J *et al*. Nissen *versus* Dor fundoplication for treatment of gastroesophageal reflux disease: a blinded randomized clinical trial. *Dig Surg* 2011; **28**: 80–86.

23 Shaw JM, Bornman PC, Callanan MD, Beckingham IJ, Metz DC. Long-term outcome of laparoscopic Nissen and laparoscopic Toupet fundoplication for gastroesophageal reflux disease: a prospective, randomized trial. *Surg Endosc* 2010; **24**: 924–932.

24 Broeders JA, Roks DJ, Ahmed AU, Draaisma WA, Smout AJ, Hazebroek EJ. Laparoscopic anterior *versus* posterior fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials. *Ann Surg* 2011; **254**: 39–47.

25 Daud WN, Thompson SK, Jamieson GG, Devitt PG, Martin IJ, Watson DI. Randomized controlled trial of laparoscopic anterior 180 degrees partial *versus* posterior 270 degrees partial fundoplication. *ANZ J Surg* 2015; **85**: 668–672.

26 Hagedorn C, Jönson C, Lönroth H, Ruth M, Thune A, Lundell L. Efficacy of an anterior as compared with a posterior laparoscopic partial fundoplication: results of a randomized, controlled clinical trial. *Ann Surg* 2003; **238**: 189–196.

27 Toupet A. [Technique of esophago-gastroplasty with phrenogastropexy used in radical treatment of hiatal hernias as a supplement to Heller's operation in cardiospasm.] *Mem Acad Chir (Paris)* 1963; **89**: 384–389.

28 Watson A, Jenkinson LR, Ball CS, Barlow AP, Norris TL. A more physiological alternative to total fundoplication for the surgical correction of resistant gastro-oesophageal reflux. *Br J Surg* 1991; **78**: 1088–1094.

29 Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP *et al*. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999; **45**: 172–180.

30 Johnsson F, Holloway RH, Ireland AC, Jamieson GG, Dent J. Effect of fundoplication on transient lower oesophageal sphincter relaxation and gas reflux. *Br J Surg* 1997; **84**: 686–689.

31 Gatenby PA, Bright T, Watson DI. Anterior 180 degrees partial fundoplication – how I do it. *J Gastrointest Surg* 2012; **16**: 2297–2303.

32 Dakkak M, Bennett JR. A new dysphagia score with objective validation. *J Clin Gastroenterol* 1992; **14**: 99–100.

33 Rijnhart-de Jong HG, Draaisma WA, Smout AJ, Broeders IA, Gooszen HG. The Visick score: a good measure for the overall effect of antireflux surgery? *Scand J Gastroenterol* 2008; **43**: 787–793.

34 Broeders JA, Roks DJ, Jamieson GG, Devitt PG, Baigrie RJ, Watson DI *et al*. Five-year outcome after laparoscopic anterior partial *versus* Nissen fundoplication: four randomized trials. *Ann Surg* 2012; **255**: 637–642.

35 Engström C, Ruth M, Lönroth H, Lundell L. Manometric characteristics of the gastroesophageal junction after anterior *versus* posterior partial fundoplication. *Dis Esophagus* 2005; **18**: 31–36.

36 Engström C, Lönroth H, Mardani J, Lundell L. An anterior or posterior approach to partial fundoplication? Long-term results of a randomized trial. *World J Surg* 2007; **31**: 1221–1225.

37 Broeders JA, Broeders EA, Watson DI, Devitt PG, Holloway RH, Jamieson GG. Objective outcomes 14 years after laparoscopic anterior 180-degree partial *versus* Nissen fundoplication: results from a randomized trial. *Ann Surg* 2013; **258**: 233–239.

38 Broeders JA, Draaisma WA, Rijnhart-de Jong HG, Smout AJ, van Lanschot JJ, Broeders IA. Impact of surgeon experience on 5-year outcome of laparoscopic Nissen fundoplication. *Arch Surg* 2011; **146**: 340–346.

SUPPLEMENTARY INFO

Table S1. Perioperative outcome

	Toupet (N=47)	**Anterior** (N=47)	***p*-value**
Hiatal hernia	0.251		
<10 per cent	26 (55.3)	28 (59.6)	0.251
10-25 per cent	10 (21.3)	11 (23.4)	
25-49 per cent	0 (0)	3 (6.4)	
50-75 per cent	0 (0)	0 (0)	
Crural closure			0.012
Posterior	22 (46.8)	34 (72.3)	
Posterior + anterior	25 (53.2)	13 (27.7)	
Procedure time (min)	50.0 (25-105)	43.0 (25-86)	0.091
Intraoperative complications	0 (0)	1 (2.1)	1.000
Postoperative complications within 30 days	3 (6.4)	1 (2.1)	0.617
Length of hospital stay	1.0 (0-7)	1.0 (0-4)	0.136
Need for surgical reintervention	2 (4.3)	0 (0)	0.495

All data are expressed as N (per cent) or median (ranges)
Toupet (Laparoscopic Toupet fundoplication); Anterior (180˚ Laparoscopic anterior fundoplication)

Table S2. Pre- and Postoperative Outcome of Objective Studies

	Pre-op		6 months post-op	
	Toupet	**Anterior**	**Toupet**	**Anterior**
Endoscopy				
Studied	45 (95.7)	45 (95.7)	32 (68.1)	32 (68.1)
Oesophagitis				
Grade A	3 (6.7)	5 (11.1)	3 (9.4)	3 (9.4)
Grade B	5 (11.1)	7 (15.6)	1 (3.1)	1 (3.1)
Grade C	2 (4.4)	3 (6.7)	0 (0.0)	1 (3.1)
Grade D	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)
Barrett's oesophagus	10 (22.2)	9 (20.0)	7 (21.9)	7 (21.9)
Hiatal hernia present	32 (71.1)	37 (82.2)	1 (3.1)	3 (9.4)
24-hr pH-study				
Studied	43 (91.5)	44 (93.6)	41 (87.2)	35 (74.5)
pH<4 for >4 per cent	36 (83.7)*	43 (97.7)*	4 (9.8)	4 (11.4)
Normalization acid exposure	37 (90.2)	31 (88.6)		
Percentage acid upright	14.5 (10.2-17.7)	13.7 (11.5-16.0)	2.0 (0.7-3.3)	2.2 (1.1-3.3)
Percentage acid supine	10.4 (4.9-15.8)	14.9 (7.6-22.1)	1.7 (0.3-3.2)	3.5 (0.2-7.6)
Percentage acid total	13.0.(9.7-16.4)	14.1 (10.6-17.5)	1.9 (0.6-3.2)	2.6 (0.8-4.3)
Manometry				
Studied	27 (57.4)	28 (59.6)	28 (59.6)	23 (48.9)
LOS resting pressure	0.8 (0.5-1.1)	0.9 (0.5-1.3)	1.3 (1.0-1.6)	2.1 (1.6-2.6)
LOS residual resting pressure	0.3 (0.1-0.4)	0.3 (0.1-0.5)	0.3 (0.2-0.5) ^	1.1 (0.5-1.7) ^

Data are presented as N (per cent) or mean (95 per cent CI); *p= 0.030; ^ p= 0.008; Toupet (Laparoscopic Toupet fundoplication); Anterior (180˚ Laparoscopic anterior fundoplication) LOS pressure in kPa.

9

Summary

The studies presented in this thesis have addressed the advances of surgical treatment of gastro-oesophageal reflux disease. Current thesis aimed to compare the long-term outcome of conventional and laparoscopic approach to anti-reflux surgery and to evaluate which laparoscopic fundoplications provides the best subjective and objective outcome, maintaining reflux control with minimal postoperative dysphagia and gas-related symptoms. The effectiveness and side effects of various fundoplication types were evaluated in systematic reviews and meta-analyses. The two best performing types of fundoplication were head-to-head compared in a randomised clinical trial. Furthermore, this thesis focused on predictive factors for failing anti-reflux surgery.

Chapter 1 offers a general introduction to the physiology of the gastro-oesophageal junction and the background of gastro-oesophageal reflux disease. Subsequently, surgical approaches and fundoplication types are introduced.

Gastro-oesophageal reflux disease is one of the most frequent benign disorders of the upper gastrointestinal tract[1] and involves a wide spectrum of disorders in which the reflux of gastric content leads to troublesome symptoms or lesions to the oesophageal mucosa.[2] Key symptoms for gastro-oesophageal reflux disease are heartburn and regurgitation. The gastro-oesophageal junction is a valve that separates the intrathoracic oesophageal from intra-abdominal gastric cavities. This junction consists of an intrinsic and an extrinsic sphincter.[3] These intrinsic and extrinsic sphincters have an anatomic overlay at the level of the gastro-oesophageal junction which augments efficacy and creates a valve that establishes the division of intrathoracic oesophagus and intra-adbominal stomach. A non-functioning valve results in excessive gastro-oesophageal reflux, causing gastro-oesophageal reflux disease. On the other side of the spectrum, a overcompetent valve results in difficulty in swallowing and belching, which lead to dysphagia and gas-related symptoms espectively.[1,4]

Gastro-oesophageal reflux disease is diagnosed based on the presence and combination of the typical symptoms of heartburn and regurgitation, with a favourable response to pharmacological therapy. The most important tests to diagnose the presence of gastro-oesophageal reflux disease are 24-h pH monitoring and upper gastrointestinal endoscopy, and are a part of the preoperative work-up for anti-reflux surgery.[2,5] Ambulatory 24-h oesophageal pH monitoring enables physicians to diagnose reflux disease by quantifying total oesophageal acid exposure time and symptom-reflux correlation.[1,6] Manometry is not used to diagnose reflux disease in patients with gastro-oesophageal reflux disease symptoms and candidates for anti-reflux surgery.[1]

Candidates for anti-reflux surgery are patients with PPI-refractory gastro-oesophageal reflux disease, patients who are unwilling to take lifelong medication and patients with extra-oesophageal manifestations.[7–9] Laparoscopic fundoplication is momentarily the surgical treatment of choice for gastro-oesophageal reflux disease, as discussed in **chapter 2**.[10–13]

Rudolph Nissen performed the first fundoplication for gastro-oesophageal reflux diseasein 1956.[14] After some modifications, total fundoplication according to Nissen has become the most frequently performed operation for gastro-oesophageal reflux disease. The procedure includes mobilisation of the distal oesophagus, division of the short gastric vessels, posterior repair of the crural diaphragm and wrapping the fundus of the stomach posteriorly around the oesophagus with a 360° circumference.[15]

Following the trend in other abdominal surgical procedures conventional Nissen fundoplication was rapidly replaced by its laparoscopic counterpart. **Chapter 2** describes the long-term results of the largest randomised clinical trial (RCT) comparing laparoscopic Nissen and conventional Nissen fundoplication with the longest follow-up duration of up to 17 years, with special focus on control of reflux symptoms, general health, need for medical treatment and reoperation rate. Previously reported are the three-months,[16] five-[12] and 10-year[13] subjective and objective outcome of this multicenter smized clinical trial performed between 1997 and 1999 in the Netherlands. In this clinical trial, 177 patients were included and randomised to either laparoscopic or conventional Nissen fundoplication. At five years, no significant differences in subjective and objective outcome after laparoscopic Nissen and conventional Nissen fundoplication were found, and 15% and 12% of the patients respectively underwent surgical reintervention.[12] At 10-years, twice as many patients underwent reoperation after conventional Nissen fundoplication than after its laparoscopic counterpart (15% versus 35%), with no differences in reoperation rate for recurrent gastro-oesophageal reflux disease or dysphagia, and comparable outcome in terms of gastro-oesophageal reflux disease symptoms, PPI use, quality of life and objective reflux control.[13]

In **chapter 2**, we demonstrated no differences between the two procedures in improvement of reflux symptoms at 17 years after laparoscopic and conventional Nissen fundoplication, with 90 to 95% of the patients reporting their reflux symptoms to be either completely resolved or significantly improved compared to the preoperative state. This significant improvement in reflux symptoms 17 years after surgery is supported by the decrease in use of acid suppressing drugs after laparoscopic and conventional Nissen fundoplication, compared to the preoperative state. However, 17 years after primary fundoplication, 42 to 49% of the patients reported to use acid suppressing drugs. Compared to the use three months after surgery, the number of patients using daily acid suppressing medication at 10 and 17 years after surgery is significantly higher, indicating a progressive increase in use of acid suppressing drugs with extension of follow-up.[12,13,16] Therefore, if primary indication for Nissen fundoplication is unwillingness of patients to take life-long acid suppressing medication, the success rate is around 60%. However, these findings should be interpreted with caution, since it is has been demonstrated that only a small portion of the patients using acid suppressing medication after antireflux surgery is diagnosed with abnormal oesophageal acid exposure on 24-hr pH-monitoring.[12,17,18] Possible explanations for the

increase in use of acid suppressing drugs include regular PPI use by patients despite absence of typical reflux symptoms, and prescription of acid suppressing drugs to provide gastric protection for concurrent medication, such as nonsteroidal anti-inflammatory drugs (NSAIDS) and platelet inhibitors.[19] Symptomatic outcome at 5 and 10 years demonstrated no difference in reported dysphagia,[13,20] and our present 17 year findings in **chapter 2** demonstrate these results are maintained during long-term follow-up. At 17 years, surgical reintervention was more frequently performed after conventional Nissen compared to laparoscopic Nissen fundoplication. The main reason for this difference (18% *versus* 45%) is the higher incidence of symptomatic incisional hernia following conventional Nissen fundoplication. Significantly more patients required surgery for symptomatic incisional hernia after conventional Nissen fundoplication at 10- and 17-year follow-up.[13] **Chapter 2** describes the first randomised clinical trial to demonstrate that laparoscopic anti-reflux surgery reduces the number of incisional hernia corrections compared with upper midline incision in non-obese patients. This is an important finding, underlining the long-term benefit of laparoscopic surgery compared to the conventional approach.

Chapter 3 describes a study aiming to identify objective predictors for recurrent reflux disease after fundoplication. Multivariate analysis demonstrated that patients with poor oesophageal peristalsis or high supine acid exposure time are independent predictors of recurrent pathological acid exposure. Considering patients with excessive supine acid exposure are likely to gain the most from fundoplication, this group should not be denied anti-reflux surgery. However, as about half of patients with both predictors experience recurrent pathological acid exposure after Nissen fundoplication, we would advise based on the results of **chapter 3** that surgery should be restricted in this group. Careful counselling is necessary and can be optimized, by providing patients with differentiated information on individual risk of recurrence.

Despite the good results on reflux control after Nissen fundoplication, the procedure can result in a gastro-oesophageal valve that delivers good reflux control, but might impair other functions, resulting in post-fundoplication symptoms such as difficulty in swallowing and troublesome gas-related symptoms.[21–23] As many as 12 per cent of Nissen fundoplication patients develop severe post-fundoplication dysphagia[24,25] and up to 18 per cent develop gas-related symptoms.[24,26–28]

Alternatively, partial fundoplications have been developed aiming to reduce these postfundoplication symptoms and maintaining reflux control. Jacques Dor introduced the anterior partial fundoplication.[29] This anti-reflux procedure includes wrapping the fundus of the stomach anteriorly around the oesophagus. The technique was designed to reduce postoperative dysphagia and gas-related symptoms, while preserving reflux control. The modifications of this procedure, that are currently used in clinical practice, are laparoscopic 90°[30,31] and 180°[32] anterior fundoplication. The modified Dor fundoplication includes

mobilisation of the oesophagus and posterior crural repair without division of the short gastric vessels.[33] An anterior partial wrap with a circumference of either 90° or 180° is then created.

Furthermore, a partially posteriorly created fundoplication was developed in 1963 by André Toupet. He introduced partial posterior fundoplication as an alternative operation for Nissen fundoplication[34] aiming to reduce dysphagia and gas-related symptoms after surgery.[35–37] The only mayor difference between a modified laparoscopic Toupet fundoplication and Nissen fundoplication is the creation of a partial posterior wrap with a circumference of 270° as opposed to a 360° wrap.[38]

Several randomised clinical trials have demonstrated that laparoscopic anterior fundoplication reduces dysphagia[31,32,39–41] and gas-related symptoms[31,39,41], when compared with posterior fundoplication. Some randomised clinical trials suggest that this is offset by a higher reflux recurrence rate[21,31,39,40,42–44], though other randomised clinical trials report similar reflux control.[32,41,45] As a result, these individual randomised clinical trials have not provided a definitive answer. **Chapter 4** aimed to systematically review all randomised clinical trials comparing laparoscopic anterior fundoplication (*n*=345) to posterior fundoplication (*n*=338) for gastro-oesophageal reflux disease. Oesophageal acid exposure time and the prevalence of heartburn were higher after laparoscopic anterior fundoplication. In the short-term this was counterbalanced by less severe dysphagia. However, dysphagia scores became similar in the long-term, with a persistent substantial increase in prevalence of heartburn and proton pump inhibitor use after laparoscopic anterior fundoplication. The reoperation rate was twice as high after laparoscopic anterior fundoplication as well, mainly due to reinterventions for recurrent gastro-oesophageal reflux disease. These results demonstrate that differences in these post-fundoplication symptoms between laparoscopic anterior fundoplication and posterior fundoplication are most prominent in the early postoperative period and gradually fade with time. In contrast, the higher rate of heartburn after laparoscopic anterior fundoplication persists during long-term follow-up.

However, there may be important differences between different anterior partial fundoplication variants (90° *versus* 120° *versus* 180°), and therefore generalizing all anterior partial fundoplication procedures into a single category might not be appropriate. Subsequently, the analysis in **chapter 4** failed to recognize and consider important differences between the fundoplication subtypes, and the fact that technical differences might be important for achieving good clinical outcomes. Therefore the study described in **chapter 5** aimed to stratify the two most common anterior fundoplication types and compare these results to the most frequently performed posterior fundoplication, in order to identify potential differences in outcome between the anterior fundoplication types.

The study in **chapter 5** stratified the 90° and 180° anterior partial fundoplication group and compared it to Nissen fundoplication only. We evaluated the original 5-year results of two randomised clinical trials comparing laparoscopic anterior 90° fundoplication *versus* laparoscopic Nissen fundoplication [31,39] and two studies that randomised laparoscopic 180° anterior fundoplication *versus* Nissen.[32,40] A randomised comparison between laparoscopic anterior 90° fundoplication (*n*=90) *versus* laparoscopic Nissen fundoplication (*n*=82*)* and laparoscopic 180° anterior fundoplication (*n*=121) *versus* laparoscopic Nissen fundoplication (*n*=132) was made.

At five-years follow-up, control of heartburn symptoms were similar for anterior 180° partial *versus* Nissen fundoplication, but inferior for anterior 90° fundoplication *versus* Nissen fundoplication. At five years, 90° and 180° anterior partial fundoplication similarly reduced dysphagia and gas-related symptoms compared with laparoscopic Nissen fundoplication. There were no significant differences in reoperation and dilatation rate between 90° and 180° laparoscopic anterior fundoplication *versus* Nissen within the follow-up period. Summarizing the results of **chapter 5**, stratification demonstrated that anterior 180° partial fundoplication ensures durable control of reflux symptoms with minimal post-fundoplication symptoms. In contrast, reflux control after 90° anterior fundoplication is inferior to laparoscopic Nissen fundoplication and Nissen is associated with more side-effects compared with anterior 180° partial fundoplication. Overall, results of chapter 5 suggest that the best clinical outcome at 5-years follow-up was achieved following anterior 180° partial fundoplication.

The meta-analysis described in **chapter 4** pooled 90°, 120° and 180° laparoscopic anterior fundoplication together and compared this group to the pooled results of 180°, 200° and 360° posterior fundoplication. Results of **chapter 5** made clear that a more specific meta-analysis of only the superior anterior fundoplication versus the most frequently performed posterior fundoplication, should be performed. This study is described in **chapter 6.**

Chapter 6 describes a meta-analysis comparing outcomes after laparoscopic 180° anterior fundoplication and laparoscopische Nissen fundoplication. The one-year outcome demonstrate that laparoscopic 180° anterior fundoplication is followed by less dysphagia and gas-related symptoms compared to laparoscopische Nissen fundoplication. Both procedures similarly increased lower oesophageal sphincter pressure, which was accompanied by comparable subjective and objective reflux control. Patient satisfaction, endoscopic dilatation and reoperation rates are similar in the short-term as well. The 5-year outcomes showed that the differences in dysphagia and gas-related symptoms persist at long-term follow-up. Extension of follow-up to 5 years did not demonstrate differences in reflux symptoms, PPI use, patient satisfaction, dilatation or reoperation rates.

In **chapter 7** we investigated the long-term outcome of laparoscopic Nissen and 180˚ anterior fundoplication in a randomised clinical trial. The study described in **chapter 7** was designed to compare the long-term differences between Nissen and 180° anterior fundoplication in a head-to-head comparison in an attempt to strengthen the evidence base by adding 12 year outcome. The results demonstrated similar heartburn scores for both groups, consistent with the comparable reflux control demonstrated at short- and mid-term follow-up of this trial.[40,46] With extension of follow-up, a higher rate of acid-suppressing drug use developed in the 180° anterior group compared with the Nissen group. The percentage of patients using acid-suppressing drugs after 180° anterior fundoplication was high at 29 per cent in the present study, but similar to the rates in other trials (27 per cent).[47] However, it has been demonstrated previously, as earlier discussed, that only a small proportion of patients who have restarted acid-suppressing therapy suffer from objective recurrent reflux disease.[12,17,18] The reduced rate of dysphagia and gas-related symptoms after 180° anterior compared with Nissen fundoplication that was present at 2 years[40] and 5 years,[46] disappeared with extension of follow-up to 12 years. The two procedures had similar patient satisfaction rates, with the majority in both groups willing to undergo surgery again in a similar situation.

Seven randomised clinical trials have been conducted comparing laparoscopic Nissen versus Toupet fundoplication for gastro-oesophageal reflux disease and a systematic review and meta-analysis of these trials[25] concluded that laparoscopic Toupet fundoplication achieves similar reflux control, with a reduction of post-operative dysphagia and dilatation for dysphagia, compared to Nissen fundoplication.[25] Furthermore reoperation rates and the presence of gas-related symptoms were lower after Toupet fundoplication, providing support for the use of Toupet fundoplication as the posterior fundoplication of choice.[25] **Chapter 5, 6 and 7** support the use of laparoscopic 180° anterior fundoplication as the anterior fundoplication of choice for gastro-oesophageal reflux disease.

Both laparoscopic Toupet[25] and laparoscopic 180˚ anterior fundoplication provide similar reflux control with a lower prevalence of postoperative dysphagia and gas-related symptoms compared to laparoscopic Nissen fundoplication. However, it is unclear which of these two partial fundoplications yields the best reflux control with minimal postoperative side effects. **Chapter 8** aimed to determine whether laparoscopic Toupet or laparoscopic 180˚ anterior fundoplication offers the best subjective and objective reflux control, with the least postfundoplication symptoms. The randomised trial presented in **chapter 8** found no difference between laparoscopic Toupet and laparoscopic 180˚ anterior fundoplication in controlling gastro-oesophageal reflux disease symptoms and oesophageal acid exposure. A low rate of postoperative side-effects was found in both groups and patient satisfaction rates were high. The Dakkak dysphagia score was the primary outcome of this trial and no differences between the two groups were identified at one-, three, six and 12 months of follow-up. There were no differences in secondary

outcomes including reflux control, overall outcome and patient satisfaction. The only differences that were observed included a higher prevalence of flatulence one month after Toupet fundoplication and chest pain six months after laparoscopic Toupet fundoplication. At 12 months these differences were no longer present. The presence of typical post-fundoplication symptoms also did not significantly differ between the two groups. The impact on patient's wellbeing of both procedures is demonstrated by high patient satisfaction and Visick scores. Approximately 90 per cent of all patients reported control of heartburn and a significant reduction in mean heartburn scores was seen after 12 months, demonstrating the excellent reflux control after both procedures.

Conclusions

The studies presented in this thesis lead to the following conclusions:

- Laparoscopic fundoplication is associated with less incisional hernia corrections compared to conventional fundoplication at 17 years of follow-up.
- Laparoscopic 180° anterior fundoplication ensures durable control of reflux symptoms with minimal postfundoplication symptoms compared to laparoscopic Nissen fundoplication, which is associated with a higher rate of transient side effects up to 12 years.
- Laparoscopic 90° anterior fundoplication is associated with inferior reflux control compared to 180° anterior fundoplication.
- In the short-term there is no difference between laparoscopic Toupet and laparoscopic 180˚ anterior fundoplication in controlling gastro-oesophageal reflux disease symptoms and oesophageal acid exposure, with a low rate of postoperative side effects and high patient satisfaction.

In conclusion, laparoscopic partial fundoplication is the current surgical therapy of choice for gastro-oesophageal reflux disease, with no differences in short-term between laparoscopic 180˚ anterior fundoplication and 270˚ posterior fundoplication (Toupet).

Future reseach of our group will focus on collecting the long-term results of this trial. The results of the current trial will also be combined with an Australian trial that has an identical design to increase statistical power to detect minor differences. Furthermore, fundoplications correct the pathophysiological mechanisms causing gastro-oesophageal reflux disease. These effects have not yet been investigated thoroughly after laparoscopic Toupet and 180° anterior fundoplication. The physiological mechanisms of both procedures are currently being compared by our group using 24-h combined impedance and pH monitoring.

REFERENCES

1. Fuchs KH, Babic B, Breithaupt W, et al. EAES recommendations for the management of gastroesophageal reflux disease. *Surg Endosc Other Interv Tech*. 2014;28(6):1753-1773.

2. Vakil N, Van Zanten S V., Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: A global evidence-based consensus. *Am J Gastroenterol*. 2006;101(8).

3. R.K. M, D.H. B. The esophagogastric junction. *N Engl J Med*. 1997;336(13):924-932.

4. Zaninotto G, DeMeester TR, Schwizer W, Johansson K-E, Cheng S-C. The lower esophageal sphincter in health and disease. *Am J Surg*. 1988;155(1).

5. Stefanidis D, Hope W, Kohn G, Reardon P, Richardson W FR. SAGES Guideline committee (2010) SAGES guidelines for surgical treatment of GERD. *Surg Endosc*. 2010;24(11):2647-2669.

6. Johnson LF, Demeester TR. Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. *Am J Gastroenterol*. 1974;62(4):325-332.

7. Bredenoord AJ, Dent J. Proton pump inhibitor-therapy refractory gastro-oesophageal reflux disease patients, who are they? *Gut*. 2007;56(4):593-594.

8. Spechler SJ, Lee E, Ahnen D, et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease - Follow-up of a randomized controlled trial. *Jama-Journal Am Med Assoc*. 2001;285(18):2331-2338.

9. Vakil V. Review article: The role of surgery in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2007;25(12):1365-1372.

10. Scheffer R, Bredenoord A, Smout A. Richtlijn gastro-oesofageale refluxziekte. *Ned Ver Maag-Darm-Leverartsen*. 2010.

11. Schijven MP, Gisbertz SS, Van Berge Henegouwen MI. Laparoscopic surgery for gastro-esophageal acid reflux disease. *Best Pract Res Clin Gastroenterol*. 2014;28(1):97-109.

12. Draaisma WA, Rijnhart-de Jong HG, Broeders IAMJ, Smout AJPM, Furnee EJB, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. *Ann Surg*. 2006;244(1):34-41.

13. Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. *Ann Surg*. 2009;250(5):698-706.

14. NISSEN R. [A simple operation for control of reflux esophagitis]. *Schweiz Med Wochenschr*. 1956;86(Suppl 20):590-592.

15. Jamieson GG, Duranceau A. What is a nissen fundoplication? *Surg Gynecol Obstet*. 1984;159(6):591-593.

16. Bais JE, Bartelsman J, Bonjer HJ, et al. Laparoscopic or conventional Nissen fundoplication for gastrooesophageal reflux disease: randomised clinical trial. *Lancet*. 2015;355(9199):170-174.

17. Lord RVN, Kaminski A, Öberg S, et al. Absence of gastroesophageal reflux disease in a majority of patients taking acid suppression medications after nissen fundoplication. *J Gastrointest Surg*. 2002;6(1):3-10.

18. Jenkinson AD, Kadirkamanathan SS, Scott SM, Yazaki E, Evans DF. Relationship between symptom response and oesophageal acid exposure after medical and surgical treatment for gastro-oesophageal reflux disease. *Br J Surg*. 2004;91(11):1460-1465.

19. Drepper MD, Spahr L, Frossard JL. Clopidogrel and proton pump inhibitors--where do we stand in 2012? *World J Gastroenterol*. 2012;18(18):2161-2171.

20. Draaisma WA, Rijnhart-de Jong HG, Broeders IAMJ, Smout AJPM, Furnee EJB, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. *Ann Surg*. 2006;244(1):34-41.

21. Hagedorn C, Jönson C, Lönroth H, Ruth M, Thune A, Lundell L. Efficacy of an anterior as compared with a posterior laparoscopic partial fundoplication: results of a randomized, controlled clinical trial. *Ann Surg*. 2003;238(2):189-196.

22. Watson DI, Pike GK, Baigrie RJ, et al. Prospective double-blind randomized trial of laparoscopic Nissen fundoplication with division and without division of short gastric vessels. *Ann Surg*. 1997;226(5):642-652.

23. Zaninotto G, Anselmino M, Costantini M, Boccu C, Ancona E. Laparoscopic treatment of gastro-esophageal reflux disease: Indications and results. *Int Surg*. 1995;80(4):380-385.

24. Catarci M, Gentileschi P, Papi C, et al. Evidence-Based Appraisal of Antireflux Fundoplication. *Ann Surg*. 2004;239(3):325-337.

25. Broeders JAJL, Mauritz FA, Ali UA, et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. *Br J Surg*. 2010;97(9):1318-1330.

26. Lundell L. Complications after anti-reflux surgery. *Best Pract Res Clin Gastroenterol*. 2004;18(5):935-945.

27. Zaninotto G, Costantini M, Anselmino M, et al. Excessive competence of the lower oesophageal sphincter after Nissen fundoplication: Evaluation by three-dimensional computerised imaging. *Eur J Surgery, Acta Chir*. 1995;161(4).

28. Klaus A, Hinder RA, DeVault KR, Achem SR. Bowel dysfunction after laparoscopic antireflux surgery: Incidence, severity, and clinical course. *Am J Med*. 2003;114(1):6-9.

29. Dor J, Humbert P, Paoli JM, Miorclerc M AJ. Treatment of reflux by the so-called modified Heller-Nissen technic. *Press Med*. 1967;75(50):2563-2565.

30. Krysztopik RJ, Jamieson GG, Devitt PG, Watson DI. A further modification of fundoplication: 90 degree Anterior fundoplication. *Surg Endosc Other Interv Tech*. 2002;16(10):1446-1451.

31. Watson DI, Jamieson GG, Lally C, et al. Multicenter, prospective, double-blind, randomized trial of laparoscopic nissen vs anterior 90 degrees partial fundoplication. *Arch Surg*. 2004;139(11):1160-1167.

32. Watson DI, Jamieson GG, Pike GK, Davies N, Richardson M, Devitt PG. Prospective randomized double-blind trial between laparoscopic Nissen fundoplication and anterior partial fundoplication. *Br J Surg*. 1999;86(1):123-130.

33. Gatenby PAC, Bright T, Watson DI. Anterior 180 degree Partial Fundoplication-How I Do It. *J Gastrointest Surg*. 2012;16(12):2297-2303.

34. Toupet A. Technic of esophago-gastroplasty with phrenogastropexy used in radical treatment of hiatal hernias as a supplement to Heller's operation in cardiospasms. *Mem Acad Chir (Paris)*. 1963;89:384-389.

35. Lundell L, Abrahamsson H, Ruth M, Rydberg L, Lönroth H, Olbe L. Long-term results of a prospective randomized comparison of total fundic wrap (Nissen-Rossetti) or semifundoplication (Toupet) for gastro-oesophageal reflux. *Br J Surg*. 1996;83(6):830-835.

36. Thor KB, Silander T. A long-term randomized prospective trial of the Nissen procedure versus a modified Toupet technique. *Ann Surg*. 1989;210(6):719-724.

37. Granderath FA, Kamolz T, Granderath UM, Pointner R. Gas-related symptoms after laparoscopic 360 Nissen or 270 Toupet fundoplication in gastrooesophageal reflux disease patients with aerophagia as comorbidity. *Dig Liver Dis*. 2007.

38. Katkhouda N, Khalil MR, Manhas S, et al. Andre Toupet: surgeon technician par excellence. *Ann Surg*. 2002;235(4):591-599.

39. Spence GM, Watson DI, Jamiesion GG, Lally CJ, Devitt PG. Single center prospective randomized trial of laparoscopic Nissen versus anterior 90 degrees fundoplication. *J Gastrointest Surg*. 2006;10(5):698-705.

40. Baigrie RJ, Cullis SNR, Ndhluni a J, Cariem A. Randomized double-blind trial of laparoscopic Nissen fundoplication versus anterior partial fundoplication. *Br J Surg*. 2005;92(7):819-823.

41. Ludemann R, Watson DI, Jamieson GG, Game P a, Devitt PG. Five-year follow-up of a randomized clinical trial of laparoscopic total versus anterior 180 degrees fundoplication. *Br J Surg*. 2005;92(2):240-243.

42. Khan M, Smythe A, Globe J, Stoddard CJ, Ackroyd R. Randomized controlled trial of laparoscopic anterior versus posterior fundoplication for gastro-oesophageal reflux disease. *ANZ J Surg*. 2010;80(7-8):500-505.

43. Nijjar RS, Watson DI, Jamieson GG, et al. Five-year follow-up of a multicenter, double-blind randomized clinical trial of laparoscopic Nissen vs anterior 90 degrees partial fundoplication. *Arch Surg*. 2010;145(6):552-557.

44. Engström C, Lönroth H, Mardani J, Lundell L. An anterior or posterior approach to partial fundoplication? Long-term results of a randomized trial. *World J Surg*. 2007;31(6):1221-5-7.

45. Cai W, Watson DI, Lally CJ, Devitt PG, Game P a, Jamieson GG. Ten-year clinical outcome of a prospective randomized clinical trial of laparoscopic Nissen versus anterior 180(degrees) partial fundoplication. *Br J Surg*. 2008;95(12):1501-1505.

46. Broeders J a., Roks DJ, Jamieson GG, Devitt PG, Baigrie RJ, Watson DI. Five-Year Outcome After Laparoscopic Anterior Partial Versus Nissen Fundoplication. *Ann Surg*. 2012;255(4):637-642.

47. Broeders JA, Broeders EA, Watson DI, Devitt PG, Holloway RH, Jamieson GG. Objective outcomes 14 years after laparoscopic anterior 180-degree partial versus nissen fundoplication: Results from a randomized trial. *Ann Surg*. 2013.

10

SUMMARY IN DUTCH

Nederlandse samenvatting

In dit proefschrift is de chirurgische vooruitgang in de behandeling van refluxziekten onderzocht. Dit proefschrift heeft als doel te onderzoeken of conventionele of laparoscopische (kijkoperatie) chirurgie voor refluxziekten de beste uitkomst geeft met behoud van refluxcontrole en met zo min mogelijk hinderlijke postoperatieve bijwerkingen, zoals slikklachten of een opgeblazen gevoel. Eveneens werden de effectiviteit en bijwerkingen van verschillende laparoscopische operaties voor de behandeling van refluxziekten onderzocht, middels systematische reviews en meta-analyses. De twee best presterende partiële operaties (fundoplicaties) werden in een gerandomiseerde klinische trial vergeleken. Als laatste bekeek dit proefschrift de langetermijn uitkomst na fundoplicatie en onderzochten we factoren met een voorspellende waarden voor het falen van de fundoplicatie.

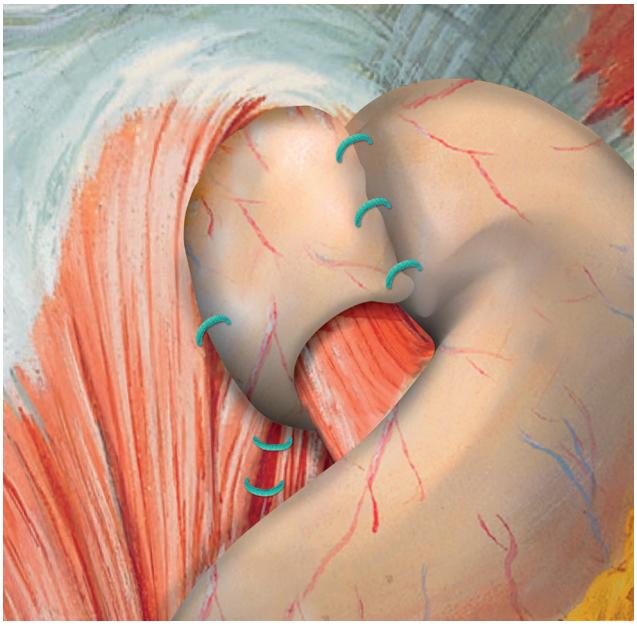
Hoofdstuk 1 geeft een algemene introductie over de fysiologie van gastro-oesofageale refluxziekten. Daarnaast geeft dit hoofdstuk achtergronden over de slokdarm-maagovergang en de verschillende chirugische behandelmethoden.

Gastro-oesofageale refluxziekten zijn een van de meest voorkomende goedaardige aandoeningen van het bovenste deel van het spijsverteringsstelsel[1] en omvatten een breed spectrum aan klachten, waarbij het terugstromen van maaginhoud hinderlijke klachten en schade aan het slokdarmslijmvlies veroorzaakt.[2] Veel voorkomende symptomen van gastro-oesofageale refluxziekten zijn zuurbranden en regurgitatie (het terugstromen van zure maaginhoud in de mond). De slokdarm-maagovergang bestaat uit een klep die de borstholte van de buikholte scheidt.[3] Als deze klep niet goed functioneert kan er zure maaginhoud vanuit de maag de borstkas instromen en gastro-oesofageale refluxziekte veroorzaken. Aan de andere kant kan een te goedwerkende klep moeilijkheden met slikken geven en dysfagie veroorzaken.[1,4]

Gastro-oesofageale refluxziekte wordt gediagnostiseerd op basis van de aanwezigheid van van kenmerkende symptomen, zoals zuurbranden en regurgitatie, met een goed resultaat van deze symptomen op medicamenteuze behandeling. De belangrijkste onderzoeken voor het aantonen van gastro-oesofageale refuxziekte zijn de 24-uurs pH-meting en het endoscopische onderzoek van de maag- en slokdarm. Deze zijn dan ook onderdeel van de pre-operatieve voorbereiding voor antirefluxchirurgie.[2,5] Een 24-uurs pH-meting zorgt ervoor dat onderzoekers de refluxziekte kunnen meten door de duur van de zuurexpositie in de slokdarm te bepalen en dit met de klachten van de patiënt te correleren.[1,6] Het meten van de drukken en peristatiek in de slokdarm (manometrie) wordt niet gebruikt voor het aantonen van refluxziekte of voor pre-operatieve voorbereiding.[1]

Patiënten met gastro-oesofageale refluxziekte die niet goed reageren op medicamenteuze behandelingen met proton-pompremmers (PPI's), niet levenslang deze PPI's willen gebruiken, of symptomen hebben die zich buiten de slokdarm manifesteren, zijn goede kandidaten voor anti-reflux-chirurgie.[7–9] Momenteel is de laparopscopische

fundoplicatie de chirurgische voorkeursbehandeling voor gastro-oesofageale refluxziekte zoals in **hoofdstuk 2** wordt besproken.[10–13]
De eerste fundoplicatie voor gastro-oesofageale refluxziekte werd in 1956 uitgevoerd door Rudolph Nissen.[14] Na enkele modificaties werd de totale fundoplicatie volgens Nissen de meest uitgevoerde ingreep voor de behandeling van gastro-oesofageale refluxziekte. De procedure hield onder andere in dat het distale deel van de slokdarm werd gemobiliseerd, de vasa brevia werd doorgenomen en het posterieurde deel van het crus werd gesloten. Hierna werd de fundus van de maag geheel rondom, achter de slokdarm langs, gepositioneerd. De fundus bedekt hierbij de slokdarm over 360°.[15] (Figuur 1.)



Figuur 1. Nissen fundoplicatie

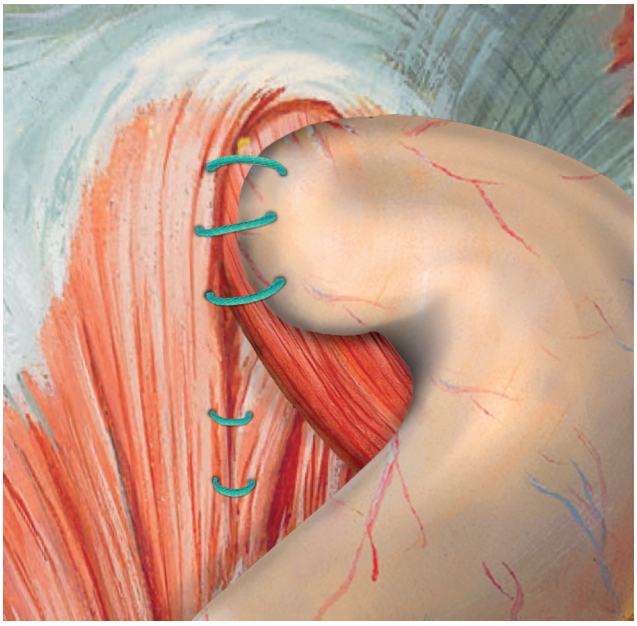
Na de introductie van de kijkoperatie (laparoscopie), werd, zoals bij bijna alle buikoperaties gebeurde, ook de Nissen fundoplicatie snel vervangen door zijn laparoscopische tegenhanger. **Hoofdstuk 2** beschrijft het grootste gerandomiseerde onderzoek (RCT) waarbij laparoscopische Nissen en conventionele Nissen fundoplicatie worden vergeleken. Dit hoofdstuk levert de langste follow-up tot 17 jaar na de initiële operatiek, waarbij speciaal wordt gekeken naar de controle van refluxklachten, algemene gezondheid en de noodzaak tot re-interventie. De 3 maanden,[16] 5-[12] en 10-jaars[13] resultaten van dit onderzoek zijn reeds gepubliceerd, welke onderzoeken tussen 1997 en 1999 in Nederand werd uitgevoerd.
In deze klinische trial werden 177 patiënten geïncludeerd en gerandomiseerd om een laparoscopische Nissen- danwel een conventionele Nissen fundoplicatie te ondergaan.

Na 5 jaar werden er geen significante verschillen gezien in subjectieve en objectieve uitkomsten tussen beide operatietechnieken.[12] 15 procent en respectievelijk 12 procent van de patiënten onderging een chirurgische re-interventie.[12] Na 10 jaar ondergingen twee keer zoveel patiënten een chirurgische re-interventie na de conventionele Nissen fundoplicatie vergeleken met de laparoscopische variant (15 procent versus 35 procent), zonder dat er verschillen zijn aangetoond voor reoperatie voor recidief refluxziekte of dysfagie.[13] Eveneens waren de uitkomsten vergelijkbaar voor refluxsymptomen, PPI-gebruik, kwaliteit van leven en objectieve refluxcontrole.[13]

In **hoofdstuk 2** tonen we aan dat er geen verschil is tussen beide procedures in refluxsymptomen 17 jaar na laparoscopische en conventionele Nissen fundoplicatie. Bij 90 tot 95 procent van de patiënten waren de refluxklachten compleet verdwenen of significant verbeterd vergeleken met de pre-operatieve klachten. Deze verbetering in refluxklachten, 17 jaar post-operatief, wordt ondersteund door een verminderd postoperatief gebruik van zuurremmende medicijnen. Desondanks gebruiken 42 to 49 procent van de patiënten dagelijks zuurremmende medicijnen 17 jaar na de fundoplicatie, waarbij we een progressie zien in het gebruik van zuurremmende medicijnen bij het verlengen van de follow-up.[12,13,16] Indien de indicatie voor een Nissen fundoplicatie het niet levenslang willen gebruiken van zuurremmende medicatie is, is het succespercentage rond de 60 procent. Desalniettemin moeten we deze bevindingen met enige voorzichtigheid interpreteren daar verscheidene studies hebben aangetoond dat maar een klein gedeelte van de patiënten na antirefluxchirurgie zuurremmende medicatie gebruiken voor aangetoonde abnormale oesofageale zuurexpositie bij 24-uurs pH-meting.[12,17,18] Mogelijke verklaringen hiervoor kunnen we mogelijk vinden in het doorgebruiken van zuurremmende medicatie bij afwezigheid van typische refluxsymptomen en het voorschrijven van zuurremmende medicatie als maagbeschermer bij medicatie zoals ontstekingsremmende pijnstillers (NSAIDS) en trombocytenaggregatieremmers.[19] Symptomatische uitkomst na 5 en 10 jaar toonde geen verschil aan in dysfagie.[13,20] Deze resultaten blijven behouden gedurende onze 17jaars follow-up in **hoofdstuk 2**. Na 17 jaar komt chirurgische reinterventie frequenter voor na conventionele Nissen fundoplicatie vergeleken met laparoscopische Nissen fundoplicatie. De belangrijkste reden voor dit verschil (18 procent *versus* 45 procent) is de hogere frequentie van sympomatische littekenbreuken na conventionele Nissen fundoplicatie. Significant meer patiënten hadden een chirurgische re-interventie nodig voor een symptomatische littekenbreuk na conventionele Nissen fundoplicatie vergeleken met de laparoscopische tegenhanger na 10 en 17 jaar.[13] **Hoofdstuk 2** is dan ook de eerste gerandomiseerde studie die beschrijft dat laparoscopische antirefluxchirurgie het aantal littekenbreukcorrecties reduceert vergeleken met een conventionele mediane laparotomie in niet-obese patiënten.

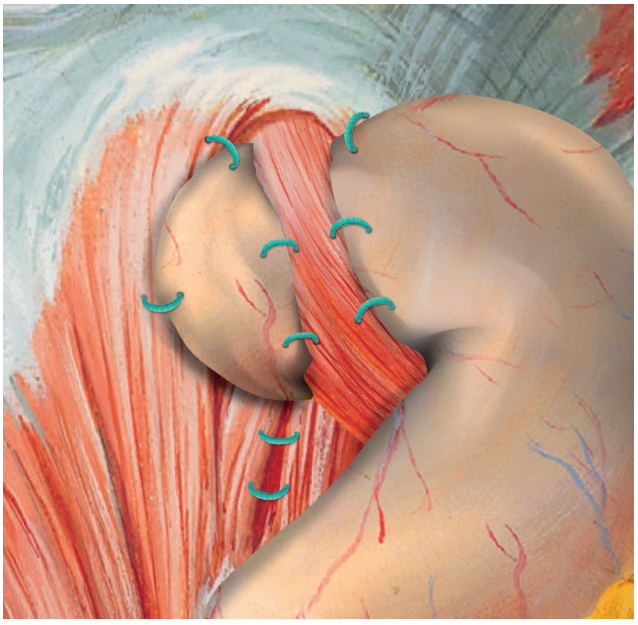
In **hoofdstuk 3** beschrijven we een studie die als doel had predictoren van recidief refluxziekte te identificeren na fundoplicatie. Multivariate analyse toonde aan dat slechte slokdarmperistaltiek en hoge liggende zuurexpositie onafhankelijke voorspellers zijn voor recidief pathologische zuurexpositie na fundoplicatie. Realiserende dat patiënten met

een hoge liggende zuurexpositie het meeste baat hebben bij een fundoplicatie, zou deze groep een fundoplicatie niet moeten worden onthouden. De helft van de patiënten met beide voorspellers heeft recidief refluxziekte na fundoplicatie, zodoende adviseren we dan ook terughoudend te zijn met fundoplicaties in deze groep.
Ondanks de goede resultaten van een Nissen fundoplicatie op refluxcontrole, kan deze procedure resulteren in een slokdarm-maagovergang die goede refluxcontrole geeft, maar de andere functies van deze overvang compromiteerd. Met als gevolg moeite met slikken en het ontstaan van gasgerelateerde symptomen.[21–23] Tot 12 procent van de patiënten na Nissen fundoplicatie ontwikkelen postoperatief ernstige dysfagie.[24,25] Tot maar liefst 18 procent ontwikkelt gasgerelateerde symptomen.[24,26–28]
Alternatieve partiële fundoplicaties zijn ontwikkeld met het doel deze postfundoplicatie-symptomen zoals dysfagie en gasgerelateerde symptomen te verminderen met behoud van refluxcontrole. De anterieure partiële fundoplicatie is ontwikkeld door Jacques Dor.[29] Deze operatie wordt uitgevoerd door de fundus van de maag over de voorzijde van de slokdarm te plaatsen. Deze techniek was ontwikkeld om de postoperatieve dysfagie en gasgerelateerde symptomen te reduceren met behoud van refluxcontrole. Aanpassingen van deze techniek die momenteel worden gebruikt zijn de laparoscopische 90°[30,31] en 180°[32] anterieure fundoplicatie. Bij deze gemodificeerde Dor fundoplicaties wordt onder andere de slokdarm gemobiliseerd, het crus aan de posterieure zijde hersteld en de vasia brevia intact gelaten.[33] Een anterieure partiële fundoplicatie die voor 90° danwel 180° de slokdarm omvat, wordt aansluitend gecreëerd. (Figuur 2.)



Figuur 2. 180° Anterieure fundoplicatie

Als aanvulling hierop werd er in 1963 ook een partiële posterieure fundoplicatie ontwikkeld door André Toupet. Hij introduceerde de partiële posterieure fundoplicatie als alternatief voor de Nissen fundoplicatie[34] met als doel de dysfagie en gasgerelateerde klachten te reduceren.[35–37] Het enige relevante verschil tussen een Toupet en Nissen fundoplicatie is dat de wikkeling van de fundus rondom de slokdarm partieel is aan de posterieure zijde voor 270°.[38] (Figuur 3.)
Meerdere gerandomiseerde klinische studies hebben aangetoond dat laparoscopische anterieure fundoplicatie dysfagie reduceert[31,32,39–41] net als gasgerelateerde symptomen[31,39,41], vergeleken met posterieure fundoplicatie (Nissen en Toupet). Sommige van deze studies hebben gesuggereerd dat dit ten kosten ging van de refluxcontrole [21,31,39,40,42–44], aan de andere kant raporteerden andere studies vergelijkbare refluxcontrole.[32,41,45] Deze individuele studies hebben het definitieve antwoord hierop niet gegeven. In **hoofdstuk 4** wordt een systematisch literatieroverzicht gegeven en meta-anayse van alle gerandomiseerde klinische trials die laparoscopische anterieure (*n*=345) met posterieure fundoplication (*n*=338) voor gastro-oesofageale refluxziekte vergeleken. Oesofageale zuurexpositie en het voorkomen van zuurbranden waren hoger na laproscopische anterieure fundoplicatie. Op korte termijn wordt dit gecompenseerd door minder ernstige dysfagie. Desondanks wordt op lange termijn dysfagie vergelijkbaar, waarbij er een aanhoudend frequenter voorkomen van zuurbranden en het gebruik van zuurremmende medicatie werd geregistreerd na laparoscopische anterieure fundoplicatie. Er werden twee keer zoveel re-operaties uitgevoerd na anterieure fundoplicatie, wat grotendeels veroorzaakt werd door re-interventies voor recidief



Figuur 3. Toupet fundoplicatie

gastro-oesofageale refluxziekte. Deze resultaten laten zien dat verschillen in post-fundoplicatie symptomen tussen laparoscopische anterior en posterior fundoplicatie het meest uitgeproken zijn in het korte postoperatieve beloop en dat deze met het verlengen van de follow-up vervagen. In tegenstelling hierop komt zuurbranden ook frequenter voor in de langetermijn follow-up.

Er zijn mogelijk belangrijke verschillen tussen de verschillende types partiële anterieure fundoplicaties (90° *versus* 120° *versus* 180°), waardoor het generaliseren van alle anterieure fundoplocaties in een enkele categorie misschien niet juist is geweest. Hierdoor faalde de analyse beschreven in **hoofdstuk 4,** om het belang van verschillen tussen deze types te herkennen, waarbij kleine technische verschillen misschien wel belangrijk zijn voor het verschil in een goede klinische uitkomst. De studie beschreven in **hoofdstuk 5** heeft het doel de resultaten van de twee meest voorkomende anterieure fundoplicaties te stratificeren en deze te vergelijken met de meest uitgevoerde posterieure fundoplicatie. Dit met het doel mogelijke verschillen tussen de subtypes anterieure fundoplicaties te identificeren.

De studie beschreven in **hoofdstuk 5** statificeerde de laparoscopische 90° en 180° partiële anterieure fundoplicatie en vergeleek dit met een laparoscopische Nissen fundoplicatie. De originele 5-jaarsresultaten van twee gerandomiseerde onderzoeken, die laparoscopische anterieure 90° fundoplicatie *versus* laparoscopische Nissen fundoplication vergeleken,[31,39] en twee studies die laparoscopische 180° anterieure fundoplicatie met Nissen vergeleken werden gecombineerd.[32,40] Een gerandomiseerde vergelijking tussen de laparoscopische anterieure 90° fundoplicatie (*n*=90) *versus* laparoscopische Nissen fundoplicatie (*n*=82*)* en laparoscopische 180° anterieure fundoplicatie (*n*=121) *versus* laparoscopische Nissen fundoplicatie (*n*=132) werd verricht.

Bij vijf jaar follow-up was er geen verschil in controle van zuurbrandsymptomen voor de 180° anterieure en Nissen fundoplicatie. De 90° anterieure fundoplicatie levert inferieure controle op. Na vijf jaar reduceerde de 90° en 180° anterieure fundoplicatie dysfagie en gasgeraleteerde klachten. Er zijn geen significante verschillen voor re-operatie en dilatatie tussen de groepen. Samengevat laat de 180° anterieure fundoplicatie duurzame refluxcontrole zien met minimale post-fundoplicatie symptomen. Daarentegen is reluxcontrole inferieur na 90° anterieure fundoplicatie. Nissen fundoplicatie is geassocieerd met meer bijwerkingen vergeleken met 180° anterieure fundoplicatie. Concluderend suggereren de resultaten van **hoofdstuk 5** dat de beste klinische uitkomst na 5 jaar follow-up werd bereikt na 180° anterieure fundoplicatie.

De meta-analyse beschreven in **hoofdstuk 4** combineerde 90°, 120° and 180° laparoscopische anterieure fundoplicatie en vergeleek deze groep met de gecombineerde data van 180°, 200° and 360° posterieure fundoplicatie. De resultaten van **hoofdstuk 5** maakte duidelijk dat een specifiekere meta-analyse, van alleen de superieure anterieure fundoplicatie, met de meest uitgevoerde posterieure fundoplicatie uitgevoerd moest worden. Deze studie is beschreven in **hoofdstuk 6.**

Hoofdstuk 6 beschrijft een meta-analyse waarbij de uitkomsten na laparoscopische 180° anterieure fundoplicatie en laparoscopische Nissen fundoplicatie worden vergeleken.

De resultaten na een jaar laten zien dat laparoscopische 180° anterieure fundoplicatie is geassocieerd met minder dysfagie en gasgerelateerde klachten vergeleken met Nissen fundoplicatie. Beide operaties verhoogden op vergelijkbare wijze de slokdarmsfincterdruk, samen met vergelijkbare subjectieve en objectieve refluxcontrole. Patiënttevredenheid, endoscopische dilataties en het aantal re-operaties was gelijk gedurende de kortetermijn follow-up. De vijfjaars-resultaten lieten zien dat de verschillen in slikklachten en gasgeralateerde klachten aanhouden. Het verlengen van de follow-up tot 5 jaar liet geen verschillen zien in refluxsymptomen, PPI-gebruik, patiënttevredenheid, dilatatie of het aantal re-operaties.

In **hoofdstuk 7** hebben we de langetermijn uitkomsten na laparoscopische Nissen en 180˚ anterieure fundoplicatie in een gerandomiseerde trial onderzocht. Deze studie beschreven in **hoofdstuk 7** was ontworpen om de langetermijn resultaten te vergelijken met als doel de bewijsvoering te verstevigen door er 12-jaars resultaten aan toe te voegen. De resultaten demonstreerden vergelijkbare zuurbrandscores voor beide groepen voor korte- en middellange follow-up van deze studie.[40,46] Met het verlengen van de follow-up termijn, demonstreerden we een hoger gebruik van zuurremmers in de 180° anterieure groep vergeleken met de Nissen groep. Het percentage van patiënten die, 12 jaar na 180° anterieure fundoplicatie, zuurremmende medicijnen gebruikte, was hoog, 29 procent, maar vergelijkbaar met andere studies (27 procent).[47] Voorheen is aangetoond dat een klein deel van de patiënten die herstarten met zuurremmende medicijnen daadwerkelijk geobjectiveerde recidief refluxziekte hebben.[12,17,18] Het minder voorkomen van dysfagie en gasgerelateerde klachten na 180° anterieure fundoplicatie vergeleken met Nissen fundoplicatie, wat aanwezig was bij 2 jaar[40] en 5 jaar,[46] verdwijnt met het verlengen van de follow-up naar 12 jaar. Beide procedures hadden vergelijkbare hoge patiënttevredenheidscijfers, waarbij de meerderheid van de patiënten de operatie wederom zou willen ondergaan in vergelijkbare omstandigheden.

Zeven gerandomiseerde klinische trials die laparoscopische Nissen met Toupet fundoplicatie vergeleken, samen met een systematische review en meta-analyse[25], concludeerden dat laparoscopische Toupet fundoplicatie vergelijkbare refluxcontrole laat zien, met een reductie van post-operatieve dysfagie en dilatatie voor dysfagie, vergeleken met Nissen fundoplicatie.[25] Verder was het aantal reoperaties en het vóórkomen van gasgerelateerde klachten lager na Toupet fundoplicatie. Deze bevindingen ondersteunen het gebruik van de Toupet fundoplicatie als posterieure fundoplicatie.[25]

Hoofdstuk 5, 6 and 7 ondersteunen het gebruik van de laparoscopische 180° anterieure fundoplicatie als anterieure fundoplicatie van keuze voor gastro-oesofageale refluxziekte. Zowel laparoscopische Toupet[25] als laparoscopische 180˚ anterieure fundoplicatie demonstreren vergelijkbare refluxcontrole met een reductie van postoperatieve dysfagie en gasgerelateerde klachten vergeleken met Nissen fundoplicatie. Het is onduidelijk welke van deze partiële fundoplicaties de beste refluxcontrole levert met minimale postoperatieve bijwerkingen. De gerandomiseerde klinische trial in **hoofdstuk 8** onderzocht of laparoscopische Toupet- danwel laparoscopische 180˚ anterieure fundoplicatie de beste subjectieve en objectieve controle van reflux leverde, met de

minste postfundoplicatie bijwerkingen. In deze studie vonden we geen verschillen tussen laparoscopische Toupet- en laparoscopische 180˚ anterieure fundoplicatie bij het controleren van gastro-oesofageale refluxsymptomen en oesofageale zuurexpositie. Beide groepen hadden weinig postoperatieve bijwerken en hoge patiënttevredenheidscijfers. De Dakkak-dysfagiescore was het primaire eindpunt en toonde geen verschil tot 12 maanden follow-up. De overige uitkomsten, zoals controle van reflux en patiënt tevredenheid, waren gelijk. Het enige verschil dat werd gezien is het frequenter vóórkomen van flatulentie na Toupet fundoplicatie na een maand en pijn op de borst-klachten na 6 maanden. Het voorkomen van typische postfundoplicatie symptomen verschilde niet tussen beide groepen. De invloed op de patiënttevredenheid was groot, met hoge patiënttevredenheid en Visickscores. Ongeveer 90 procent van alle patiënten gaf aan dat de zuurbrandklachten onder controle zijn, met een significante reductie in zuurbrandscores na 12 maanden. Dit wijst op de excellente refluxcontrole na beide procedures.

Conclusie

De studies beschreven in dit proefschrift leiden tot de volgende conclusies:

- Laparoscopische fundoplicatie is geassocieerd met het minder vóórkomen van littekenbreukcorrecties vergeleken met de conventionele fundoplicatie na 17 jaar follow-up.
- Laparoscopische 180° anterieure fundoplicatie geeft langdurige controle van refluxsymptomen met minimale postfundoplicatie bijwerkingen vergeleken met Nissen fundoplicatie, welke wordt geassocieerd met het frequenter voorkomen van voorbijgaande bijwerkingen tot 12 jaar postoperatief.
- Laparoscopische 90° anterieure fundoplicatie is geassocieerd met minder goede reflux controle.
- Op kortetermijn is er geen verschil tussen laparoscopische Toupet- en laparoscopische 180˚ anterieure fundoplicatie in het controleren van gastro-oesofageale refluxklachten en oesofageale zuurexpositie, met daarbij een lage frequentie van postoperatieve bijwerkingen en hoge patiënttevredenheid.

Concluderend is momenteel laparoscopische partiële fundoplicatie de chirurgische voorkeursbehandeling voor gastro-oesofageale refluxziekte. Er is daarbij geen verschil, op kortetermijn, tussen laparoscopische 180˚ anterieure fundoplicatie of 270˚ posterieure fundoplicatie (Toupet).

Vervolgonderzoek van onze onderzoeksgroep zal zich bezighouden met het verzamelen van langetermijn resultaten en deze combineren met de resulaten van een vergelijkbare Australische trial om zo de statistische power te vergroten en kleine verschillen tussen de beide operatietechnieken te onderzoeken. Verder corrigeert een fundoplicatie de pathofysiologische mechanisme die gastro-oesofageale refluxziekte veroorzaken. Deze effecten zijn nog niet voldoende onderzocht. Onze onderzoeksgroep is momenteel bezig deze verschillen middels 24-uurs gecombineerde pH-impendantiemetingen te onderzoeken.

REFERENTIES

1. Fuchs KH, Babic B, Breithaupt W, et al. EAES recommendations for the management of gastroesophageal reflux disease. *Surg Endosc Other Interv Tech*. 2014;28(6):1753-1773.

2. Vakil N, Van Zanten S V., Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: A global evidence-based consensus. *Am J Gastroenterol*. 2006;101(8).

3. R.K. M, D.H. B. The esophagogastric junction. *N Engl J Med*. 1997;336(13):924-932.

4. Zaninotto G, DeMeester TR, Schwizer W, Johansson K-E, Cheng S-C. The lower esophageal sphincter in health and disease. *Am J Surg*. 1988;155(1).

5. Stefanidis D, Hope W, Kohn G, Reardon P, Richardson W FR. SAGES Guideline committee (2010) SAGES guidelines for surgical treatment of GERD. *Surg Endosc*. 2010;24(11):2647-2669.

6. Johnson LF, Demeester TR. Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. *Am J Gastroenterol*. 1974;62(4):325-332.

7. Bredenoord AJ, Dent J. Proton pump inhibitor-therapy refractory gastro-oesophageal reflux disease patients, who are they? *Gut*. 2007;56(4):593-594.

8. Spechler SJ, Lee E, Ahnen D, et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease - Follow-up of a randomized controlled trial. *Jama-Journal Am Med Assoc*. 2001;285(18):2331-2338.

9. Vakil V. Review article: The role of surgery in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2007;25(12):1365-1372.

10. Scheffer R, Bredenoord A, Smout A. Richtlijn gastro-oesofageale refluxziekte. *Ned Ver Maag-Darm-Leverartsen*. 2010.

11. Schijven MP, Gisbertz SS, Van Berge Henegouwen MI. Laparoscopic surgery for gastro-esophageal acid reflux disease. *Best Pract Res Clin Gastroenterol*. 2014;28(1):97-109.

12. Draaisma WA, Rijnhart-de Jong HG, Broeders IAMJ, Smout AJPM, Furnee EJB, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. *Ann Surg*. 2006;244(1):34-41.

13. Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG. Ten-year outcome of laparoscopic and conventional nissen fundoplication: randomized clinical trial. *Ann Surg*. 2009;250(5):698-706.

14. NISSEN R. [A simple operation for control of reflux esophagitis]. *Schweiz Med Wochenschr*. 1956;86(Suppl 20):590-592.

15. Jamieson GG, Duranceau A. What is a nissen fundoplication? *Surg Gynecol Obstet*. 1984;159(6):591-593.

16. Bais JE, Bartelsman J, Bonjer HJ, et al. Laparoscopic or conventional Nissen fundoplication for gastrooesophageal reflux disease: randomised clinical trial. *Lancet*. 2015;355(9199):170-174.

17. Lord RVN, Kaminski A, Öberg S, et al. Absence of gastroesophageal reflux disease in a majority of patients taking acid suppression medications after nissen fundoplication. *J Gastrointest Surg*. 2002;6(1):3-10.

18. Jenkinson AD, Kadirkamanathan SS, Scott SM, Yazaki E, Evans DF. Relationship between symptom response and oesophageal acid exposure after medical and surgical treatment for gastro-oesophageal reflux disease. *Br J Surg*. 2004;91(11):1460-1465.

19. Drepper MD, Spahr L, Frossard JL. Clopidogrel and proton pump inhibitors--where do we stand in 2012? *World J Gastroenterol*. 2012;18(18):2161-2171. doi:10.3748/wjg.v18.i18.2161.

20. Draaisma WA, Rijnhart-de Jong HG, Broeders IAMJ, Smout AJPM, Furnee EJB, Gooszen HG. Five-year subjective and objective results of laparoscopic and conventional Nissen fundoplication: a randomized trial. *Ann Surg*. 2006;244(1):34-41.

21. Hagedorn C, Jönson C, Lönroth H, Ruth M, Thune A, Lundell L. Efficacy of an anterior as compared with a posterior laparoscopic partial fundoplication: results of a randomized, controlled clinical trial. *Ann Surg*. 2003;238(2):189-196.

22. Watson DI, Pike GK, Baigrie RJ, et al. Prospective double-blind randomized trial of laparoscopic Nissen fundoplication with division and without division of short gastric vessels. *Ann Surg*. 1997;226(5):642-652.

23. Zaninotto G, Anselmino M, Costantini M, Boccu C, Ancona E. Laparoscopic treatment of gastro-esophageal reflux disease: Indications and results. *Int Surg*. 1995;80(4):380-385.

24. Catarci M, Gentileschi P, Papi C, et al. Evidence-Based Appraisal of Antireflux Fundoplication. *Ann Surg*. 2004;239(3):325-337.

25. Broeders JAJL, Mauritz FA, Ali UA, et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. *Br J Surg*. 2010;97(9):1318-1330.

26. Lundell L. Complications after anti-reflux surgery. *Best Pract Res Clin Gastroenterol*. 2004;18(5):935-945.

27. Zaninotto G, Costantini M, Anselmino M, et al. Excessive competence of the lower oesophageal sphincter after Nissen fundoplication: Evaluation by three-dimensional computerised imaging. *Eur J Surgery, Acta Chir*. 1995;161(4).

28. Klaus A, Hinder RA, DeVault KR, Achem SR. Bowel dysfunction after laparoscopic antireflux surgery: Incidence, severity, and clinical course. *Am J Med*. 2003;114(1):6-9.

29. Dor J, Humbert P, Paoli JM, Miorclerc M AJ. Treatment of reflux by the so-called modified Heller-Nissen technic. *Press Med*. 1967;75(50):2563-2565.

30. Krysztopik RJ, Jamieson GG, Devitt PG, Watson DI. A further modification of fundoplication: 90 degree Anterior fundoplication. *Surg Endosc Other Interv Tech*. 2002;16(10):1446-1451.

31. Watson DI, Jamieson GG, Lally C, et al. Multicenter, prospective, double-blind, randomized trial of laparoscopic nissen vs anterior 90 degrees partial fundoplication. *Arch Surg*. 2004;139(11):1160-1167.

32. Watson DI, Jamieson GG, Pike GK, Davies N, Richardson M, Devitt PG. Prospective randomized double-blind trial between laparoscopic Nissen fundoplication and anterior partial fundoplication. *Br J Surg*. 1999;86(1):123-130.

33. Gatenby PAC, Bright T, Watson DI. Anterior 180 degree Partial Fundoplication-How I Do It. *J Gastrointest Surg*. 2012;16(12):2297-2303.

34. Toupet A. Technic of esophago-gastroplasty with phrenogastropexy used in radical treatment of hiatal hernias as a supplement to Heller's operation in cardiospasms. *Mem Acad Chir (Paris)*. 1963;89:384-389.

35. Lundell L, Abrahamsson H, Ruth M, Rydberg L, Lönroth H, Olbe L. Long-term results of a prospective randomized comparison of total fundic wrap (Nissen-Rossetti) or semifundoplication (Toupet) for gastro-oesophageal reflux. *Br J Surg*. 1996;83(6):830-835.

36. Thor KB, Silander T. A long-term randomized prospective trial of the Nissen procedure versus a modified Toupet technique. *Ann Surg*. 1989;210(6):719-724.

37. Granderath FA, Kamolz T, Granderath UM, Pointner R. Gas-related symptoms after laparoscopic 360 Nissen or 270 Toupet fundoplication in gastrooesophageal reflux disease patients with aerophagia as comorbidity. *Dig Liver Dis*. 2007.

38. Katkhouda N, Khalil MR, Manhas S, et al. Andre Toupet: surgeon technician par excellence. *Ann Surg*. 2002;235(4):591-599.

39. Spence GM, Watson DI, Jamiesion GG, Lally CJ, Devitt PG. Single center prospective randomized trial of laparoscopic Nissen versus anterior 90 degrees fundoplication. *J Gastrointest Surg*. 2006;10(5):698-705.

40. Baigrie RJ, Cullis SNR, Ndhluni a J, Cariem A. Randomized double-blind trial of laparoscopic Nissen fundoplication versus anterior partial fundoplication. *Br J Surg*. 2005;92(7):819-823.

41. Ludemann R, Watson DI, Jamieson GG, Game P a, Devitt PG. Five-year follow-up of a randomized clinical trial of laparoscopic total versus anterior 180 degrees fundoplication. *Br J Surg*. 2005;92(2):240-243.

42. Khan M, Smythe A, Globe J, Stoddard CJ, Ackroyd R. Randomized controlled trial of laparoscopic anterior versus posterior fundoplication for gastro-oesophageal reflux disease. *ANZ J Surg*. 2010;80(7-8):500-505.

43. Nijjar RS, Watson DI, Jamieson GG, et al. Five-year follow-up of a multicenter, double-blind randomized clinical trial of laparoscopic Nissen vs anterior 90 degrees partial fundoplication. *Arch Surg*. 2010;145(6):552-557.

44. Engström C, Lönroth H, Mardani J, Lundell L. An anterior or posterior approach to partial fundoplication? Long-term results of a randomized trial. *World J Surg*. 2007;31(6):1221-5-7.

45. Cai W, Watson DI, Lally CJ, Devitt PG, Game P a, Jamieson GG. Ten-year clinical outcome of a prospective randomized clinical trial of laparoscopic Nissen versus anterior 180(degrees) partial fundoplication. *Br J Surg*. 2008;95(12):1501-1505. doi:10.1002/bjs.6318.

46. Broeders J a., Roks DJ, Jamieson GG, Devitt PG, Baigrie RJ, Watson DI. Five-Year Outcome After Laparoscopic Anterior Partial Versus Nissen Fundoplication. *Ann Surg*. 2012;255(4):637-642.

47. Broeders JA, Broeders EA, Watson DI, Devitt PG, Holloway RH, Jamieson GG. Objective outcomes 14 years after laparoscopic anterior 180-degree partial versus nissen fundoplication: Results from a randomized trial. *Ann Surg*. 2013.

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LIST OF AUTHOR'S PUBLICATIONS

Predictors of objectively identified recurrent reflux after primary Nissen fundoplication.
Broeders JA, **Roks DJ**, Draaisma WA, Vlek AL, Hazebroek EJ, Broeders IA, Smout AJ.
British Journal of Surgery 2011;98(5):673-9.

Laparoscopic anterior *versus* posterior fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized cinical trials.
Broeders JA, **Roks DJ**, Ahmed Ali U, Draaisma WA, Smout AJ, Hazebroek EJ.
Annals of Surgery 2011; 254(1)39-47

Five-year outcome after laparoscopic anterior partial versus Nissen fundoplication: four randomized trials.
Broeders JA, **Roks DJ**, Jamieson GG, Devitt PG, Baigrie RJ, Watson DI.
Annals of Surgery 2012; 255(4):637-42

Laparoscopic anterior 180-degree versus Nissen fundoplication for gastroesophageal reflux disease: systematic review and meta-analysis of randomized clinical trials.
Broeders JA, **Roks DJ**, Ahmed Ali U, Watson DI, Baigrie RJ, Cao Z, Hartmann J, Maddern GJ.
Annals of Surgery 2013;257(5):850-9.

Laparoscopic Hiatal Hernia Repair in the Elderly Patient.
Oor JE, Koetje JH, **Roks DJ**, Nieuwenhuijs VB, Hazebroek EJ.
World Journal of Surgery 2016; 40(6):1404-11

Laparoscopic sleeve gastrectomy and gastroesophageal reflux disease: a systematic review and meta-analysis.
Oor JE, **Roks DJ**, Ünlü C, Hazebroek EJ.
The American Journal of Surgery. 2016; 211(1):250-67

Seventeen-year outcome of a randomized clinical trial comparing laparoscopic and conventional Nissen fundoplication: a plea for patient counselling and clarification.
Roks DJ*, Oor JE*, Broeders JA, Hazebroek JE, Gooszen HG.
Annals of Surgery, 2017 Epub ahead of print.

Long-term symptom control of gastro-oesophageal reflux disease 12 years after laparoscopic Nissen or 180˚ anterior partial fundoplication in a randomized clinical trial.
Roks DJ, Broeders JA, Baigrie RJ.
British Journal of Surgery 3 Feb 2017; Epub ahead of print

Randomized Clinical Trial of 270˚ posterior versus 180˚ anterior partial fundoplication for gastro-oesophageal reflux disease.
Roks DJ, Koetje JH, Oor JE, Broeders JA, Nieuwenhuijs VB, Hazebroek JE.
British Journal of Surgery 13 March 2017; Epub ahead of print

Equal patient satisfaction, quality of life and objective recurrence rate after laparoscopic hiatal hernia repair with and without mesh.
Koetje JH, Oor JE, **Roks DJ**, v Westreenen HL, Hazebroek EJ, Nieuwenhuijs VB.
Surgical Endoscopy 11 Jan 2017; Epub ahead of print.