Hartmann's procedure versus sigmoidectomy with primary anastomosis for perforated diverticulitis with purulent or faecal peritonitis (LADIES): a multicentre, parallel-group, randomised, open-label, superiority trial

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Summary

Background Previous studies have suggested that sigmoidectomy with primary anastomosis is superior to Hartmann's procedure. The likelihood of stoma reversal after primary anastomosis has been reported to be higher and reversal seems to be associated with lower morbidity and mortality. Although promising, results from these previous studies remain uncertain because of potential selection bias. Therefore, this study aimed to assess outcomes after Hartmann's procedure versus sigmoidectomy with primary anastomosis, with or without defunctioning ileostomy, for perforated diverticulitis with purulent or faecal peritonitis (Hinchey III or IV disease) in a randomised trial.

Methods A multicentre, randomised, open-label, superiority trial was done in eight academic hospitals and 34 teaching hospitals in Belgium, Italy, and the Netherlands. Patients aged between 18 and 85 years who presented with clinical signs of general peritonitis and suspected perforated diverticulitis were eligible for inclusion if plain abdominal radiography or CT scan showed diffuse free air or fluid. Patients with Hinchey I or II diverticulitis were not eligible for inclusion. Patients were allocated (1:1) to Hartmann's procedure or sigmoidectomy with primary anastomosis, with or without defunctioning ileostomy. Patients were enrolled by the surgeon or surgical resident involved, and secure online randomisation software was used in the operating room or by the trial coordinator on the phone. Random and concealed block sizes of two, four, or six were used, and randomisation was stratified by age (<60 and ≥60 years). The primary endpoint was 12-month stoma-free survival. Patients were analysed according to a modified intention-to-treat principle. The trial is registered with the Netherlands Trial Register, number NTR2037, and ClinicalTrials.gov, number NCT01317485.

Findings Between July 1, 2010, and Feb 22, 2013, and June 9, 2013, and trial termination on June 3, 2016, 133 patients (93 with Hinchey III disease and 40 with Hinchey IV disease) were randomly assigned to Hartmann's procedure (68 patients) or primary anastomosis (65 patients). Two patients in the Hartmann's group were excluded, as was one in the primary anastomosis group; the modified intention-to-treat population therefore consisted of 66 patients in the Hartmann's procedure group (46 with Hinchey III disease, 20 with Hinchey IV disease) and 64 in the primary anastomosis group (46 with Hinchey III disease, 18 with Hinchey IV disease). In 17 (27%) of 64 patients assigned to primary anastomosis, no stoma was constructed. 12-month stoma-free survival was significantly better for patients undergoing primary anastomosis compared with Hartmann's procedure (94·6% [95% CI 88·7–100] *vs* 71·7% [95% CI 60·1–83·3], hazard ratio 2·79 [95% CI 1·86–4·18]; log-rank p<0·0001). There were no significant differences in short-term morbidity and mortality after the index procedure for Hartmann's procedure compared with primary anastomosis (morbidity: 29 [44%] of 66 patients *vs* 25 [39%] of 64, p=0·60; mortality: two [3%] *vs* four [6%], p=0·44).

Interpretation In haemodynamically stable, immunocompetent patients younger than 85 years, primary anastomosis is preferable to Hartmann's procedure as a treatment for perforated diverticulitis (Hinchey III or Hinchey IV disease).

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Introduction

Diverticular disease is the third most costly gastrointestinal disorder in developed countries, making it an important condition in terms of health-care utilisation.[1] An estimated 8–35% of patients with acute diverticulitis present with complicated disease, including abscess formation (Hinchey classification Ib and II) or perforation with purulent or faecal peritonitis (Hinchey III or IV).[2,3]

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See Online for appendix

Research in context

Evidence before this study

We did a systematic literature search in PubMed for articles published from inception to Jan 17, 2019, with the keywords "diverticulitis", "peritonitis", "Hartmann*", "primary", and "anastomosis", without language restrictions. We specifically included randomised controlled trials that compared Hartmann's procedure with sigmoidectomy with primary anastomosis for perforated diverticulitis with purulent or faecal peritonitis (Hinchey III or Hinchey IV); three of 127 articles identified by our search met this criterion. Quality assessment of these studies is given in the appendix (p 6). Overall, these trials randomly allocated 116 patients to primary anastomosis and 138 patients to Hartmann's procedure, of whom 204 (80%) had Hinchey III diverticulitis. All three studies were prematurely terminated, either because of slow patient accrual (two studies) or for safety reasons (one study). No significant differences in mortality or overall morbidity were reported after the index procedure or reversal procedure. Two studies found a significant difference in stoma reversal rates in favour of primary anastomosis.

Added value of this study

To our knowledge, the LADIES trial is the largest study to date on primary anastomosis in Hinchey III and Hinchey IV diverticulitis and has several methodological differences compared with previous randomised trials. First, to our knowledge, this is the first trial to report on stoma-free survival as a primary endpoint and to incorporate patient-reported outcomes. Second, the decision to construct a defunctioning ileostomy was left to the discretion of the surgeon, whereas in previous studies, by design, a defunctioning ileostomy had to be constructed in all patients undergoing sigmoidectomy with primary anastomosis. However, in one previous trial, a third of patients underwent primary anastomosis without construction of an ileostomy, thereby deviating from the study protocol. Furthermore, patients in the present study were randomly assigned after diagnostic laparoscopy, allowing for a more accurate distinction between Hinchey III and Hinchey IV diverticulitis and, consequently, this is the first study to report on outcomes in Hinchey III and IV disease separately. Finally, although not all non-included patients could be registered during the trial period, baseline demographics and preoperative disease severity data for 235 eligible non-included patients were available to compare with included patients. This comparison improves the external generalisability of our study.

Implications of all the available evidence

The LADIES trial provides strong support in favour of sigmoidectomy with primary anastomosis as the most appropriate surgical treatment for diverticulitis with purulent or faecal peritonitis in patients who are haemodynamically stable and immunocompetent. This finding is important because, in combination with existing evidence, it has the potential to fundamentally change current practice and reduce both patient and socioeconomic burden.

In cases of perforated diverticulitis with purulent or faecal peritonitis, emergency operative treatment is standard practice.[4–7] Hartmann's procedure—resection with end colostomy construction—remains the favoured option for most surgeons and avoids the risk of anastomotic leakage.[3,8] However, several studies have suggested that sigmoidectomy with primary anastomosis is equal to Hartmann's procedure in terms of post-operative mortality and morbidity.[5,7,9] Additionally, the likelihood of reversal of end colostomies after Hartmann's procedure has been reported to be lower (50–60%) than that of closure of defunctioning ileostomies after sigmoidectomy with primary anastomosis (85%), thereby increasing associated health-care costs and negatively affecting quality of life.[10–12] Moreover, Hartmann's procedure reversal is associated with high mortality and morbidity,[13,14] whereas primary anastomosis allows for a safer, less challenging closure procedure.[12,13,15] In selected cases of sigmoidectomy with primary anastomosis, a defunctioning ileostomy might even be avoided.[8,16]

Despite increased interest in sigmoidectomy with primary anastomosis and its potential advantages, high-quality evidence from randomised studies comparing this procedure with Hartmann's procedure is scarce, particularly with regard to stoma-free survival, which, as a single outcome measure, reflects both the risk of mortality and the likelihood of stoma reversal. Therefore, the aim of the DIVA arm of the international, multicentre, randomised controlled LADIES trial[17] was to compare Hartmann's procedure with primary anastomosis (with or without defunctioning ileostomy) to determine the optimal strategy for perforated diverticulitis with purulent or faecal peritonitis.

Methods

Study design and participants

The LADIES trial[17] was a multicentre, randomised, open-label, superiority trial done at 34 teaching hospitals and eight academic hospitals in Belgium, Italy, and the Netherlands. Initially, the trial had a combined design to compare laparoscopic peritoneal lavage with sigmoidectomy for purulent perforated diverticulitis (LOLA arm) and Hartmann's procedure with sigmoidectomy with primary anastomosis in both purulent and faecal perforated diverticulitis (DIVA arm; appendix p 3).[17] After preliminary termination of the LOLA arm, patients with purulent peritonitis were no longer randomly assigned to laparoscopic lavage and enrolment of patients with both purulent or faecal peritonitis continued in the DIVA arm.[18]

Patients aged between 18 and 85 years, who presented with clinical signs of general peritonitis and suspected perforated diverticulitis were eligible for inclusion if

plain abdominal radiography or CT scan showed diffuse free air or fluid. Patients with Hinchey I and II diverticulitis were not eligible for inclusion. Details of the Hinchey classification are provided in the appendix (p 7).[19] Exclusion criteria were dementia, previous sigmoidectomy, previous pelvic radiotherapy, chronic steroid treatment (≥20 mg daily), and preoperative shock requiring inotropic support. Before the study procedure, written informed consent was obtained from patients by the surgeon or surgical resident involved.

The study was designed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, and received ethics approval from the institutional review board (IRB) of the University Medical Centre Amsterdam and local approval was provided in the participating hospitals.

Randomisation and masking

Patients underwent diagnostic laparoscopy to confirm their diagnosis, exclude other causes of peritonitis, and distinguish between types of peritonitis. After confirmation of diagnosis, patients with purulent peritonitis (Hinchey III) were randomly assigned (2:1:1) within the LOLA arm between laparoscopic lavage, Hartmann's procedure, or sigmoidectomy with primary anastomosis with or without defunctioning ileostomy. Patients with faecal peritonitis or an overt perforation (Hinchey IV) were randomly assigned within the DIVA arm. In the DIVA arm, patients were allocated (1:1) to Hartmann's procedure or primary anastomosis, with or without defunctioning ileostomy. After termination of the LOLA arm, random assignment to Hartmann's procedure and sigmoidectomy with primary anastomosis (1:1) continued to allow further comparison between these strategies. Patients with purulent peritonitis who underwent Hartmann's procedure or sigmoidectomy with primary anastomosis in the LOLA arm before its termination were included in the present analyses.

Patients were enrolled by the surgeon or surgical resident involved. Secure online randomisation software (ALEA version 2.2) was used in the operating room or by the trial coordinator on the phone. Random concealed block sizes of two, four, or six were generated by the randomisation software and used for randomisation. Randomisation was stratified by age (<60 years *vs* ≥60 years). Patients, physicians, and researchers were not masked to the allocated treatment during the complete study period after randomisation.

Procedures

The surgical procedures have previously been described in detail.[17] When allocated to Hartmann's procedure, resection of the diseased segment was done without the explicit requirement of the distal transection line to be on the proximal rectum. Construction of an end colostomy and closure of the rectal stump were done according to the preference of the operating surgeon. For sigmoidectomy with primary anastomosis, the distal transection margin was on the proximal rectum and the proximal margin was determined by the absence of wall thickening due to diverticulitis. Anastomotic construction and configuration were done according to the surgeon's preference. Decisions on type of anastomosis, minimally invasive surgery, construction of defunctioning ileostomy, and drain placement were left at the surgeon's discretion. Stoma reversal was offered to patients if they were willing to undergo surgery and if they were considered operable by the surgeon and anaesthesiologist.

After the index procedure, patients were followed up at least once in an outpatient setting and follow-up after stoma reversal was done according to local protocols. Patients who were not in active follow-up at 12 months were contacted to verify remaining follow-up.

We measured health-related quality of life with EuroQol-5D-3-level, Short Form-36 v2, and gastrointestinal quality-of-life index,[20] at weeks 2 and 4, and months 3, 6, and 12 of follow-up.

An electronic case report form was used to collect data on patient demographics, including sex, age, body-mass index, medical history, medication, American Society of Anesthesiologists (ASA) score, physiological and operative severity score for the enumeration of mortality and morbidity (POSSUM), acute physiology and chronic health evaluation (APACHE) II score, Mannheim peritonitis index (MPI), and operative and postoperative characteristics, such as surgical approach, type of anastomosis, operating time, intra-operative blood loss, and duration of hospital stay. Moreover, during 12-month follow-up, outcomes such as major and minor morbidity, mortality, surgical reinterventions, readmissions to hospital, stoma reversal procedures, incisional hernia occurrence, and the number of days alive and outside of hospital were recorded. Questionnaires were sent by mail and the trial coordinator contacted patients who did not return or fill out questionnaires. During the study period until July 31, 2014, a chart review was done in 28 Dutch participating centres that included at least one patient in the trial to assess baseline characteristics of eligible non-included patients.[18]

Outcomes

The primary endpoint was 12-month stoma-free survival. Secondary endpoints were short-term mortality and morbidity, regarded as separate endpoints, after index and reversal procedures, operative (presence of gastrointestinal surgeon, laparoscopic procedure, operating time, drain placement, and anastomotic construction and configuration) and postoperative (type of postoperative admission, length of postoperative stay, intensive care unit stay, and days until normal intake) care characteristics, and health-related quality of life. We defined short-term as within 30 days after surgery or until discharge, if the patient remained in hospital at that time. Predefined major morbidity included any of the following events or

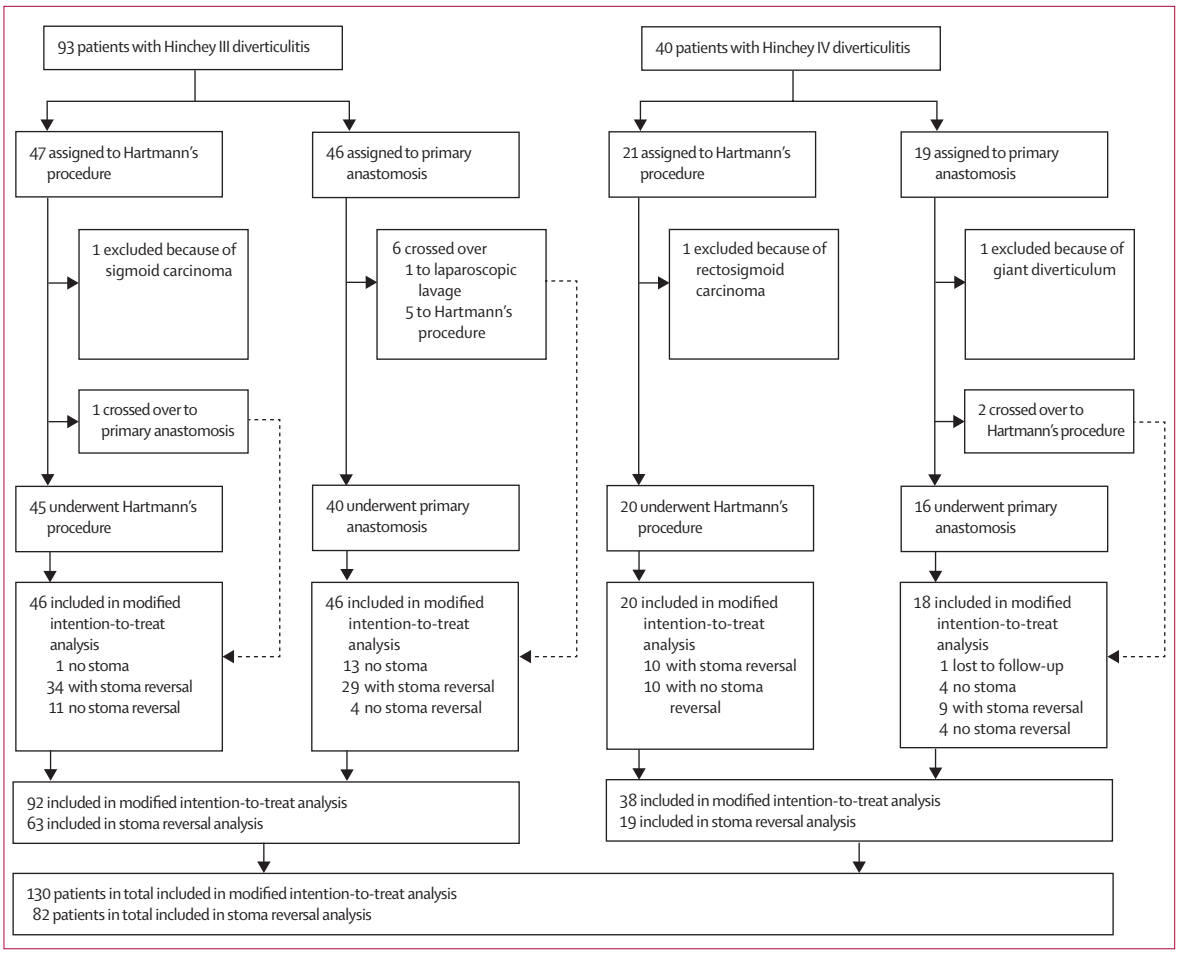

Figure 1: **Trial profile**

conditions: surgical reintervention, percutaneous abscess drainage, fascial dehiscence, urosepsis, myocardial infarction, renal failure, and respiratory insufficiency. Other prespecified secondary outcomes were duration of hospital stay, incisional hernia occurrence, and the number of days alive and outside of the hospital.

Separately, complications were scored according to the Clavien-Dindo classification[21] over a 90-day period. Elective stoma reversal was not defined as morbidity or reintervention in either treatment group. Although prespecified as a secondary endpoint, an economic evaluation of health-care use and associated costs was not included in the present study, but will be reported separately.

Statistical analysis

We suspected postoperative mortality to be 15% for both treatment strategies.[7] Around 60% of patients in the Hartmann's procedure group and 85% of patients in the sigmoidectomy with primary anastomosis group were estimated to undergo stoma reversal.[13,14] When corrected for expected mortality, reversal rates were calculated to be 50% and 72%, respectively. Before termination of the LOLA arm, a sample size of 264 was needed, which was based on an expected difference of 15% (10% *vs* 25%) in combined mortality and major morbidity between laparoscopic lavage and sigmoidectomy, respectively (90% power; 5% two-sided α). After termination of the LOLA arm, a sample size calculation was done based on the primary endpoint of the DIVA arm. We calculated a sample size of 212 patients would be needed to show a significant difference in 12-month stoma-free survival with log-rank statistics with 90% power and a two-sided α of 5%, based on an estimated difference of 22% (50% *vs* 72% for Hartmann's procedure and primary anastomosis, respectively). When corrected for potential loss to follow-up (10%), the sample size was 236 patients.

Patients were analysed according to a modified intention-to-treat principle, as three patients were excluded shortly after randomisation because of the following alternate diagnoses: wedge excision of giant diverticulum in the absence of other diverticula (one patient in the primary anastomosis group with Hinchey IV disease), subtotal colectomy with end ileostomy for colonic metastases of a

	Hartmann's procedure group (n=66)	Primary anastomosis group (n=64)
Patient characteristics		
Age (years)	61·7 (11·4)	62·4 (13·1)
Sex		
Female	25 (38%)	23 (36%)
Male	41 (62%)	41 (64%)
Body-mass index (kg/m²)	28 (4·7)	26·3 (4·8)
American Society of Anesthesiologists score*		
I–II	37 (63%)	45 (76%)
III–IV	22 (37%)	14 (24%)
Previous diverticulitis	12 (18%)	12 (19%)
Previous laparotomy†	3 (5%)	1 (2%)
CT diagnosis	61 (92%)	60 (94%)
Hinchey grade IV	20 (30%)	18 (28%)
Preoperative disease severity		
Acute Physiology and Chronic Health Evaluation II score	8 (5–12)	7·5 (5–11)
POSSUM physiological score	20 (18–24)	20 (17–23)
POSSUM operative score	19 (19–20)	19 (19–20)
Portsmouth-POSSUM predicted mortality (%)	6 (4·4–15·0)	6·5 (3·8–11·2)
POSSUM predicted morbidity (%)	71·7 (64·1–86·6)	73 (61·1–82·1)
Mannheim peritonitis index	23 (17–27)	21 (17–26)
Interval from presentation to surgery (h)	8·0 (4·4–22·9)	9·4 (6·0–30·2)
C-reactive protein (mg/L)		
≤10	4 (6%)	6 (9%)
11–100	15 (23%)	13 (20%)
101–200	13 (20%)	15 (23%)
201–300	19 (29%)	10 (16%)
301–400	8 (12%)	9 (14%)
401–500	4 (6%)	6 (9%)
>500	2 (3%)	3 (5%)
Missing	1 (2%)	2 (3%)
White blood cell count (cells per µL)	14 600 (10 200–20 600)	14 200 (9000–16 900)
(Table 1 continues in next column)		

	Hartmann's procedure group (n=66)	Primary anastomosis group (n=64)
(Continued from previous column)		
Operative characteristics		
Gastrointestinal surgeon present	57 (86%)	58 (91%)
Laparoscopic procedure	20 (30%)	17 (27%)
Operating time (min)	118·0 (95·5–135·3)	125·0 (110·0–154·0)
Drain placement‡	21 (32%)	27 (44%)
Anastomotic construction		
Manual	1 (2%)	11 (17%)
Stapler	0	43 (67%)
Missing	0	2 (3%)
Anastomotic configuration		
End-to-end	0	18 (28%)
End-to-side	0	3 (5%)
Side-to-side	1 (2%)	9 (14%)
Side-to-end	0	20 (31%)
Missing	0	6 (9%)
Blood loss (mL)		
≤100	30 (45%)	31 (48%)
101–500	24 (36%)	20 (31%)
501–1000	3 (5%)	4 (6%)
>1000	0	1 (2%)
Missing	9 (14%)	8 (13%)

Data are mean (SD), n (%), or median (IQR). POSSUM=Physiological and operative severity score for the enumeration of mortality and morbidity. *Missing in seven patients in the Hartmann's procedure group and five patients in the primary anastomosis group. †One patient missing (Hinchey III). ‡One patient missing in Hinchey III group and one patient in Hinchey IV group.

Table 1: **Baseline patient and perioperative characteristics in the modified intention-to-treat population**

previously unknown pancreatic carcinoma (one patient in the Hartmann's procedure group with Hinchey III disease), and rectosigmoid cancer in the absence of diverticula (one patient in the Hartmann's procedure group with Hinchey IV disease). We estimated 12-month stoma-free survival with the Kaplan-Meier method and analysed differences in survival with the Mantel-Cox log-rank test, without adjustment for other covariates. We used a post-hoc Cox regression analysis, with treatment and age stratification groups as covariates, to adjust for age stratification. We compared categorical data with Fisher's exact test and reported the results as numbers with percentages. Depending on normality, we tested continuous variables with Student's *t* test or Mann-Whitney *U* test and presented the results as means with SD or medians with IQR. We analysed questionnaires according to the relevant guidelines and presented results as subscales and summarised scores. For questionnaires, we imputed missing data with a regression model with predictive mean matching, creating ten imputed data sets by taking treatment group, Hinchey grade, and questionnaire values of other time points into account. We calculated pooled means if at least one questionnaire was returned and corrected p values for multiple testing with the Benjamini-Hochberg method.

A data safety monitoring board, comprising independent clinical, epidemiological, and statistical experts, was established to assess trial progress and safety. The IRB approved a formal charter, allowing the data safety monitoring board to stop the study for safety reasons or early treatment superiority outside any prespecified definitions. After inclusion of every 25 patients, safety variables were supplied to the data safety monitoring board by the trial coordinator. In cases of patients with study-related severe morbidity or

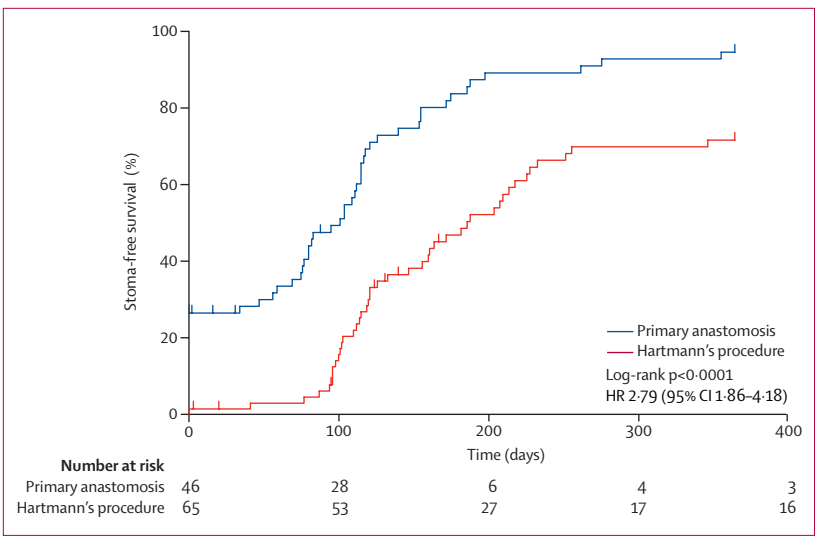

Figure 2: **Kaplan-Meier graph of 12-month stoma-free survival**
HR=hazard ratio.

mortality, the data safety monitoring board was granted access to these individual data.

Statistical analyses were done with SPSS version 24.0 and R version 3.4.1. The trial is registered with the Netherlands Trial Register, number NTR2037, and ClinicalTrials.gov, number NCT01317485.

Role of the funding source

The LADIES trial was investigator-initiated and supported by a grant from the Netherlands Organisation for Health Research and Development. The funder of the study critically reviewed and adjusted the study design, but had no role in data collection, data analysis, data interpretation, writing of the report, or the submission process. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 1, 2010, and Feb 22, 2013, 90 patients (47 assigned to laparoscopic lavage and 43 to sigmoidectomy) were recruited and enrolled in the trial, after which recruitment was temporarily stopped, as advised by the data safety monitoring board, because of safety concerns in the LOLA arm at the third interim analysis. After IRB approval, randomisation (1:1) between Hartmann's procedure and sigmoidectomy with primary anastomosis continued in the DIVA arm, as safety concerns were limited to the laparoscopic lavage group.[18] Continuation of the study commenced on June 9, 2013, and lasted until June 3, 2016, after which the DIVA arm was prematurely terminated because of slow patient accrual, leading to substantial delays in trial progression. After both the data safety monitoring board and IRB approved early termination, 12-month follow-up was continued and finished for all 130 included patients. Included patients were from one Belgian hospital, two Italian hospitals, and 25 Dutch hospitals (19 teaching and six academic hospitals).

133 patients (93 with Hinchey III disease and 40 with Hinchey IV disease) were randomly assigned to Hartmann's procedure or sigmoidectomy with primary anastomosis (Hinchey III: 47 patients to Hartmann's procedure and 46 patients to primary anastomosis; Hinchey IV: 21 patients to Hartmann's procedure and 19 patients to primary anastomosis; figure 1). Of the patients with Hinchey III disease, one patient in the primary anastomosis group crossed over to laparoscopic lavage and five patients crossed over to Hartmann's procedure. One patient assigned to Hartmann's procedure was excluded because of sigmoid carcinoma (metastases of previously undiagnosed pancreatic carcinoma; this patient underwent subtotal colectomy with end ileostomy for colonic metastases) and one patient crossed over to primary anastomosis. Of the patients with Hinchey IV disease, one patient assigned to Hartmann's procedure was excluded because of rectosigmoid carcinoma (figure 1). Two patients assigned to primary anastomosis crossed over to Hartmann's procedure and one was excluded because of a giant sigmoid diverticulum requiring wedge excision. Reasons for crossover are listed in the appendix (p 8).

Thus, 130 patients were included in the modified intention-to-treat population: 66 patients in the Hartmann's procedure group and 64 in the primary anastomosis group; 92 patients had Hinchey III disease and 38 had Hinchey IV disease (figure 1). 82 patients were included in the analysis of stoma reversal, and in the remaining patients no stoma was constructed (18 patients) or no reversal was done during follow-up (29 patients). One patient was lost to follow-up after short-term follow-up and could therefore only be included in analyses of short-term outcomes after the index procedure. The number of patients included per centre is provided in the appendix (p 9).

We observed no major differences between randomised groups in terms of baseline characteristics in the modified intention-to-treat population (table 1). In the Hartmann's procedure group, 20 (30%) of 66 patients had Hinchey grade IV diverticulitis and in the primary anastomosis group, 18 (28%) of 64 patients had Hinchey grade IV diverticulitis. A gastrointestinal surgeon was present during the procedure for 57 (86%) of 66 patients in the Hartmann's procedure group and 58 (91%) of 64 patients in the primary anastomosis group. Procedures were done laparoscopically in 20 (30%) of 66 patients in the Hartmann's procedure group and 17 (27%) of 64 patients in the primary anastomosis group. None of these surgeries were converted to an open procedure. A comparison between baseline characteristics of patients with Hinchey III and Hinchey IV disease and data for separate Hinchey grades are provided in the appendix (pp 10–11). We also compared baseline patient and perioperative

characteristics and outcomes between eligible non-included patients (235 patients) and included patients (appendix p 12). We observed significantly lower preoperative disease severity scores in non-included patients compared with included patients (eg, median Portsmouth-POSSUM predicted mortality 4·4% [IQR 2·8–11·6] *vs* 6·1% [4·3–11·3]; p=0·011; and median POSSUM predicted morbidity scores 64·8% [IQR 52·5–82·4] *vs* 71·7% [61·2–82·3]; p=0·0028), whereas ASA, APACHE II, and MPI scores were not significantly different between non-included and included patients. 20 (9%) of 235 eligible non-included patients died, compared with six (5%) of 130 patients in the study population (p=0·21). In the non-included patients, the presence of a gastrointestinal surgeon was significantly less likely compared with the included patients (68·7% *vs* 88·5%; p<0·0001).

Patients in the primary anastomosis group had significantly better 12-month stoma-free survival compared with patients in the Hartmann's procedure group (94·6% [95% CI 88·7–100] *vs* 71·7% [95% CI 60·1–83·3], hazard ratio [HR] 2·79 [95% CI 1·86–4·18]; log-rank p<0·0001; figure 2). Median time to being stoma-free was 101·0 days (95% CI 71·5–130·5) for patients in the primary anastomosis group and 186·0 days (138·0–234·0) for patients in the Hartmann's procedure group. A post-hoc subgroup analysis found a HR for stoma-free survival of 2·35 (95% CI 1·33–4·15; log-rank p=0·0032) for patients younger than 60 years versus 3·41 (1·88–6·20; log-rank p<0·0001) for patients aged 60 years and older. Moreover, when adjusted for age (<60 years or ≥60 years), the HR for stoma-free survival was 2·72 (95% CI 1·81–4·08). Survival curves for the primary outcome in both separate Hinchey groups are given in the appendix (pp 4–5). In both Hinchey groups, patients in the primary anastomosis group had significantly better 12-month stoma-free survival (Hinchey III: primary anastomosis 95·3% [95% CI 89·7–100·0] *vs* Hartmann's procedure 79·8% [67·5–92·2], HR 2·35 [95% CI 1·49–3·71]; log-rank p=0·00025; Hinchey IV: primary anastomosis 92·2% [CI 77·7–100] *vs* Hartmann's procedure 51·9% [28·2–75·6], HR 4·15 [1·71–10·1]; log-rank p=0·0016).

We found no significant differences in short-term postoperative outcomes of the index procedures (tables 2, 3). 29 (44%) of 66 patients in the Hartmann's procedure group and 25 (39%) of 64 patients in the primary anastomosis group had major or minor morbidity; major morbidity was noted in eight (12%) of 66 patients in the Hartmann's procedure group and nine (14%) of 64 patients in the primary anastomosis group (table 2). In the Hartmann's procedure group, two (3%) patients with Hinchey IV disease died from ongoing sepsis with multiorgan failure. In the primary anastomosis group, four (6%) patients died: three patients with Hinchey IV disease because of ongoing sepsis and one patient with Hinchey III disease, with known cardiovascular comorbidities, of sepsis further complicated by an occlusion of the right common iliac artery. One of these four patients assigned to primary anastomosis crossed over to the Hartmann's procedure group. Mortality was not significantly different between patients assigned to Hartmann's procedure versus primary anastomosis (p=0·44). Surgical reinterventions in the Hartmann's procedure group consisted of revision of necrotic stoma (two patients), closure after open abdomen treatment (one patient), and relaparotomy for ongoing sepsis (one patient). In the primary anastomosis group, surgical reinterventions were repair of fascial dehiscence (one patient), surgical abscess drainage (one patient), and relaparotomy for ongoing sepsis (two patients). One of the patients who underwent relaparotomy for ongoing sepsis required a second relaparotomy.

	Hartmann's procedure group (n=66)		Primary anastomosis group (n=64)		p value
	Patients	Events	Patients	Events	
Major morbidity	8 (12%)	16	9 (14%)	12	0·80
Surgical reintervention	4 (6%)	4	4 (6%)	5	..
Abscess with drainage	2 (3%)	5	2 (3%)	2	..
Fascial dehiscence	0	0	3 (5%)	3	..
Myocardial infarction	1 (2%)	1	0	0	..
Respiratory failure	4 (6%)	4	1 (2%)	1	..
Renal failure	3 (5%)	3	1 (2%)	1	..
Minor morbidity	26 (39%)	36	19 (30%)	21	0·27
Surgical site infection	8 (12%)	8	7 (11%)	7	..
Postoperative ileus	6 (9%)	6	7 (11%)	7	..
Pneumonia	5 (8%)	5	0	0	..
Delirium	5 (8%)	5	3 (5%)	3	..
Urinary tract infection or urine retention	2 (3%)	2	2 (3%)	2	..
Abscess without drainage	5 (8%)	5	0	0	..
Thrombosis	1 (2%)	1	0	0	..
Cardiac complications	4 (6%)	4	2 (3%)	2	..
Overall morbidity	29 (44%)	52	25 (39%)	33	0·60

Data are n (%). P values are for numbers of patients, not event numbers. Overall morbidity is major morbidity plus minor morbidity.

Table 2: **Morbidity outcomes after the index procedure**

	Hartmann's procedure group (n=66)	Primary anastomosis group (n=64)	p value
Postoperative admission to	..	..	0·53
Surgical ward	44 (67%)	40 (63%)	..
Post-anaesthesia care unit or medium care unit	4 (6%)	2 (3%)	..
ICU	18 (27%)	22 (34%)	..
Postoperative stay (days)	9·0 (7–15)	9·5 (7–13)	0·75
ICU stay (days)	2·0 (1–11)	1·5 (1–3)	0·18
Time until normal intake (days)	4·0 (1–6)	4·0 (2–6·8)	0·46

Data are n (%) or median (IQR). ICU=intensive care unit.

Table 3: **Short-term postoperative outcomes of the index procedure**

	Hartmann's procedure group (n=66)	Primary anastomosis group (n=63)	p value
Presence of stoma			
Without stoma	1 (2%)	17 (27%)	<0·0001
With stoma	65 (98%)	46 (73%)	..
Stoma reversal*	44 (68%)	38 (83%)	0·085
Ileostomy reversal	0	34 (89%)	..
Colostomy reversal (open)	24 (55%)	3 (8%)	..
Colostomy reversal (laparoscopic)	20 (45%)	1 (3%)	..

Data are n (%). *One Hinchey III patient in the Hartmann's procedure group had an anastomotic leakage after Hartmann's reversal for which an end colostomy was constructed, which was not reversed before the end of the 12-month follow-up period. One Hinchey IV patient in the Hartmann's procedure group underwent open end colostomy reversal, during which it was decided to construct a protective loop ileostomy, which was reversed outside the 12-month follow-up period.

Table 4: **Stoma outcomes**

	Hartmann's procedure group (n=44)		Primary anastomosis group (n=38)		p value
	Patients	Events	Patients	Events	
Major morbidity	7 (16%)	9	1 (3%)	1	0·063
Surgical reintervention	4 (9%)	4	1 (3%)	1	..
Abscess with drainage	3 (7%)	3	0	0	..
Fascial dehiscence	1 (2%)	1	0	0	..
Myocardial infarction	1 (2%)	1	0	0	..
Respiratory failure	0	0	0	0	..
Renal failure	0	0	0	0	..
Minor morbidity	6 (14%)	6	2 (5%)	2	0·28
Surgical site infection	5 (11%)	5	1 (3%)	1	..
Postoperative ileus	0	0	1 (3%)	1	..
Pneumonia	0	0	0	0	..
Delirium	0	0	0	0	..
Urinary tract infection or urine retention	1 (2%)	1	0	0	..
Abscess without drainage	0	0	0	0	..
Thrombosis	0	0	0	0	..
Cardiac complications	0	0	0	0	..
Overall morbidity	13 (30%)	15	3 (8%)	3	0·023

Data are n (%). Morbidity was scored in the first 30 days after reversal, or during admission for stoma reversal if still in hospital after 30 days.

Table 5: **Morbidity outcomes of the stoma reversal procedure**

90-day Clavien-Dindo scores showed no significant differences between the groups, with grade IIIb or worse complications in 12 (18%) of 66 patients in the Hartmann's procedure group and nine (14%) of 63 patients in the primary anastomosis group (appendix p 13). Overall morbidity was not significantly different for Hartmann's procedure and primary anastomosis in patients with Hinchey III (17 [37%] of 46 patients in the Hartmann's procedure group *vs* 17 [37%] of 46 patients in the primary anastomosis group, p=1·0) and Hinchey IV (12 [60%] of 20 patients in the Hartmann's procedure *vs* eight [44%] of 18 patients in the primary anastomosis group; p=0·52) disease (appendix p 14).

In the Hartmann's procedure group, a stoma was constructed in 65 (98%) of 66 patients, whereas only 46 (73%) of 64 patients in the primary anastomosis group had a stoma constructed (table 4). In the patients in the primary anastomosis group without a stoma, major and minor morbidity were both 12% (two of 17 patients), overall morbidity was 24% (four of 17 patients), and there were no deaths related to the index procedure. A comparison between patients in the primary anastomosis group with and without an ileostomy is given in the appendix (p 15). In all but two patients, postoperative histopathology details were available, which showed a sigmoid carcinoma in two patients (one patient with Hinchey III diverticulitis and one with Hinchey IV diverticulitis).

44 (68%) of 65 patients with a stoma in the Hartmann's procedure group underwent stoma reversal, compared with 38 (83%) of 46 patients with a stoma in the primary anastomosis group (p=0·085; table 4). Hartmann's procedure reversal was done laparoscopically in 20 (45%) of 44 patients. In 16 (25%) of 66 patients allocated to Hartmann's procedure and one crossover patient from the primary anastomosis group, both the index procedure and Hartmann's reversal procedure were done laparoscopically and without conversion.

For postoperative outcomes of stoma reversal, overall morbidity was significantly lower in the primary anastomosis group compared with the Hartmann's procedure group (13 [30%] of 66 patients *vs* three [8%] of 38 patients; p=0·023; table 5). Furthermore, the median interval to reversal (113·5 days [IQR 80·0–155·0] *vs* 133·0 days [102·0–208·0]; p=0·021) and median postoperative stay (4·0 days [IQR 2·8–5·0] *vs* 5·0 days [4·0–6·0]; p=0·011) were significantly shorter for the primary anastomosis group. There were no deaths related to stoma reversal. One patient in the Hartmann's procedure group had an anastomotic leakage after stoma reversal, for which an end colostomy was constructed. For patients with Hinchey IV diverticulitis, there was no overall morbidity related to stoma reversal in the primary anastomosis group, compared with 30% (three of ten patients) in the Hartmann's procedure group (p=0·21; appendix p 16). Overall, no stoma reversal was done in 29 patients (appendix p 17). 19 patients were alive with a stoma at 12-month follow-up, of whom six patients (all in the Hartmann's procedure group) eventually underwent stoma reversal outside the follow-up period after a median total duration of 13·2 months (IQR 12·7–23·3).

Although not significantly different, overall morbidity for both the index procedure and any subsequent reversal was lower for primary anastomosis than for Hartmann's procedure (25 [40%] of 63 patients *vs* 37 [56%] of 66 patients; p=0·078; table 6). Furthermore, although not

significantly different, the overall median postoperative stay was shorter for primary anastomosis than for Hartmann's procedure (12·5 days [IQR 9·0–16·8] *vs* 14·0 days [10·8–19·0]; p=0·054). Overall, two (3%) of 66 patients in the Hartmann's group and four (6%) of 63 patients in the primary anastomosis group died. Overall, no postoperative urosepsis occurred. The median number of days alive and outside of the hospital was 348·0 (IQR 335·5–354·0) for Hartmann's procedure and 351·0 (342·3–358·0) for primary anastomosis (p=0·21). A midline incisional hernia was diagnosed in eight patients (five in the Hartmann's procedure group and three in the primary anastomosis group), of which four were treated conservatively, whereas the remaining four underwent open repair (two patients), laparoscopic repair (one patient), or repair during Hartmann's reversal (one patient). In two of these patients no stoma was constructed, in three the stoma was reversed before hernia occurrence, and in the remaining three the stoma was reversed after hernia occurrence. One patient with a midline incisional hernia also had a parastomal hernia without undergoing stoma reversal during follow-up. Ten patients in the Hartmann's procedure group developed a parastomal hernia during follow-up, of which three were treated conservatively, and the remaining seven underwent Hartmann's procedure reversal. After stoma reversal, stoma site incisional hernia was diagnosed in three patients (two in the Hartmann's procedure group and one in the primary anastomosis group). Moreover, one patient in the primary anastomosis group developed a trocar site hernia.

Quality-of-life results and questionnaire response rates are given in the appendix (pp 18–19). After correction for multiple testing, no significant differences between the groups were found in any of the subscales and summarised scores.

	Hartmann's procedure group (n=66)		Primary anastomosis group (n=63*)		p value
	Patients	Events	Patients	Events	
Major morbidity	15 (23%)	25	9 (14%)	13	0·26
Surgical reintervention	8 (12%)	10	5 (8%)	6	..
Abscess with drainage	5 (8%)	5	2 (3%)	2	..
Fascial dehiscence	1 (2%)	1	3 (5%)	3	..
Myocardial infarction	2 (3%)	2	0	0	..
Respiratory failure	4 (6%)	4	1 (2%)	1	..
Renal failure	3 (5%)	3	1 (2%)	1	..
Minor morbidity	30 (45%)	42	19 (30%)	23	0·10
Surgical site infection	12 (18%)	13	7 (11%)	8	..
Postoperative ileus	6 (9%)	6	8 (13%)	8	..
Pneumonia	5 (8%)	5	0	0	..
Delirium	5 (8%)	5	3 (5%)	3	..
Urinary tract infection or urine retention	3 (5%)	3	2 (3%)	2	..
Abscess without drainage	5 (8%)	5	0	0	..
Thrombosis	1 (2%)	1	0	0	..
Cardiac complications	4 (6%)	4	2 (3%)	2	..
Overall morbidity	37 (56%)	67	25 (40%)	36	0·078

Data are n (%). P values are from statistical comparison of numbers of patients, not event numbers. Overall morbidity is major morbidity plus minor morbidity. *One patient lost to follow-up after providing data for short-term outcomes for the index procedure only

Table 6: **Short-term postoperative outcomes of the index procedure and (if applicable) reversal procedure combined**

Discussion

This randomised trial, comparing Hartmann's procedure to sigmoidectomy with primary anastomosis in patients with perforated diverticulitis and purulent or faecal peritonitis, showed significantly better 12-month stoma-free survival for patients in the primary anastomosis group, without significant differences in short-term morbidity and mortality. Furthermore, we found significantly lower short-term overall morbidity after stoma reversal for primary anastomosis, and a significantly shorter median time to reversal and postoperative stay after reversal.

Other randomised clinical trials comparing Hartmann's procedure with primary anastomosis have shown similar outcomes regarding the difference in morbidity after the index and reversal procedures. In a study by Oberkofler and colleagues,[22] which compared 30 patients who underwent Hartmann's procedure with 32 patients who underwent primary anastomosis (with defunctioning ileostomy), no difference was found in the number of overall complications. Similarly, a trial by Binda and colleagues[23] did not find a difference in morbidity between Hartmann's procedure and primary anastomosis. Bridoux and colleagues[24] also reported similar overall morbidity rates for Hartmann's procedure and primary anastomosis. With the exception of a significant difference in overall morbidity after the stoma reversal procedure in favour of primary anastomosis, short-term outcomes after the index procedure were also similar in our study. Exact morbidity figures differ between studies, which might be due to a difference in definitions of morbidity. Although no significant differences were found in morbidity rates after the index procedure and both procedures combined in the present trial, the absolute number of events in each group was higher in the Hartmann's procedure group than in the primary anastomosis group. Furthermore, mortality was twice as high after primary anastomosis than with Hartmann's procedure, although the absolute difference was low (four patients in the primary anastomosis group *vs* two patients in the Hartmann's procedure group). One of the four deceased patients in the primary anastomosis group crossed over to Hartmann's procedure. When interpreting these results, it should be noted that the study was not powered to detect clinically significant differences in these secondary outcomes.

To our knowledge, this is the first trial to report on 12-month stoma-free survival. Our trial showed significantly better stoma-free survival for patients

undergoing primary anastomosis compared with patients undergoing Hartmann's procedure. This difference might be explained by the higher percentage of stoma reversals and the higher number of patients without a stoma in the primary anastomosis group, since the decision to construct a defunctioning ileotomy was left to the discretion of the surgeon. These results reflect the important benefit of potentially avoiding stoma construction in patients undergoing primary anastomosis, which is not possible in patients undergoing Hartmann's procedure. Moreover, the significantly lower percentage of post-reversal overall morbidity associated with primary anastomosis, as well as the shorter interval until stoma reversal and postoperative stay after stoma reversal, further advocate the benefits of primary anastomosis. Results from a recent meta-analysis of experimental and observational studies[25] indicate decreased morbidity rates after stoma reversal for primary anastomosis, whereas in a meta-analysis of three randomised studies,[26] Hartmann's procedure and primary anastomosis were not found to be different in terms of mortality or overall morbidity. Additionally, no difference in the number of permanent stoma was reported between the groups, despite the fact that two of three studies reported more stoma reversals after primary anastomosis than after Hartmann's procedure.[22,24,26]

Overall, baseline patient characteristics did not differ significantly between patients with Hinchey III and Hinchey IV diverticulitis. Additionally, the primary endpoint was found to be significantly better for patients undergoing primary anastomosis in both of these Hinchey grades. Moreover, from these analyses, morbidity and mortality in those with Hinchey IV disease appeared to be higher than for those with Hinchey III disease. Nevertheless, differences in secondary outcomes between Hartmann's procedure and primary anastomosis in patients with Hinchey IV diverticulitis were not clearly shown in our study, although these results should be interpreted with caution because of the relatively small group size.

An important limitation of this trial is its premature termination and consequent non-achievement of the planned sample size because of low accrual rates. Trials done in an emergency care setting are vulnerable to premature discontinuation because of slow patient recruitment.[27] Moreover, surgical trials with invasive interventions tend to be more frequently discontinued because of slow recruitment.[28] In patients with suspected perforated diverticulitis, the narrow time window in which decisions regarding trial participation had to be made by both patients and surgeons might have been an important limitation. Moreover, because of the emergency setting of our trial and the large number of participating hospitals, awareness among clinicians of the trial might not always have been optimal, despite efforts to increase this. Furthermore, treatment preferences of involved surgeons and subsequent refusal to randomly assign patients might have affected patient inclusion. Similar difficulties with slow patient recruitment and underlying reasons for these difficulties have been reported in three previously published trials.[22–24] Early termination of trials for reasons of benefit potentially leads to overestimation of treatment effects.[29] However, in the case of our study, termination was because of slow accrual, in which case the main concern is loss of study power. However, our primary endpoint was still statistically significant, which could partly be explained by the fact that the sample size calculation was based on 90% power.[30]

Selection bias might have been introduced before randomisation due to surgeon or patient preferences. As a complete account of patients excluded before study enrolment could not be obtained in this trial, we cannot completely rule out the influence of selection bias. However, data on 235 non-included patients were available through an extensive medical chart review in many participating hospitals. Therefore, by contrast with previous trials, an important strength of the present study was the possibility to compare baseline characteristics of eligible non-included patients with included patients to assess potential selection bias and increase external validity.[31] These results showed that included patients had slightly worse preoperative disease severity, although absolute differences were small. The proportion of procedures for which a gastrointestinal surgeon was present was significantly lower in non-included patients than in included patients. Although speculative, this fact could be explained by increased trial awareness of the involved gastrointestinal surgeons and more willingness to enroll patients, leading to a higher percentage of patients operated on by gastrointestinal surgeons. A population-based cohort study[32] found 24·3% mortality in a cohort with a mean age of 72 years (range 30–95), both of which are higher values than in our study. Additionally, Gawlick and Nirula[33] reported mortality rates of 6·2% and 7·9% and mean ages of 63·4 years (SD 15·8) and 63·0 years (15·0) for primary anastomosis and Hartmann's procedure, respectively. These figures are more in line with the present study, as well as with the cumulative mortality in previously published trials (six [5·2%] of 116 patients for primary anastomosis) and 12 [8·7%] of 138 patients for Hartmann's procedure).[26] Importantly, we did not find large differences in the mortality of included and non-included patients in the present study. Additionally, another strength of our trial is the multicentre setting, which increases the generalisability of the results and has made it possible to analyse, to our knowledge, the largest cohort of patients randomly assigned to Hartmann's procedure or primary anastomosis to date. To our knowledge, the present study also included the largest subgroup of patients with Hinchey IV diverticulitis to date. Second, with regard to Hinchey III and Hinchey IV subgroups and preoperative disease

classification, prediction of Hinchey classification by preoperative CT scanning is not very accurate.[34] Previous trials have randomly assigned patients before the start of surgery, whereas in the present study, patients were randomised after diagnostic laparoscopy, thereby leading to a more accurate distinction between Hinchey grades. Hence, subgroup analyses for both Hinchey grades could also be done. We assumed centre-specific effects due to the multicentre setting to be small because of the low accrual rate per centre and the large number of hospitals. Finally, although we found no significant differences in quality-of-life scores between Hartmann's procedure and primary anastomosis, to our knowledge, this is the first randomised study to evaluate and compare these patient-reported outcomes for both treatment strategies, which have previously be shown to be important in survivors of perforated diverticulitis, particularly with regard to the presence of a stoma.[35]

In conclusion, to our knowledge, this is the largest randomised trial comparing Hartmann's procedure with primary anastomosis in patients with perforated diverticulitis with purulent and faecal peritonitis. We found that primary anastomosis was superior to Hartmann's procedure with regard to 12-month stoma-free survival and overall morbidity after stoma reversal, with no significant differences in short-term morbidity and mortality after the index procedure. Therefore, in haemodynamically stable, immunocompetent patients, primary anastomosis is preferable to Hartmann's procedure for the treatment of perforated diverticulitis.

Contributors

DPVL, SV, GDM, IMM, HAS, JV, WAB, and JFL contributed to study design or coordination. DPVL, SV, GDM, IMM, HAS, AGMH, EHJB, HBACS, QAJE, MFG, BAvW, AAWvG, RMPHC, SWN, MJPMG, SdS, AJLD, ECJC, WMUvG, REGJMP, PMK, JABvdH, WHS, FC, JLMK, WAB, and JFL contributed to data acquisition. DPVL and SvD contributed to data analysis. DPVL, SV, GDM, IMM, HAS, JV, SvD, WAB, and JFL contributed to data interpretation. DPVL, WAB, and JFL drafted the report. All authors critically revised the content and approved the final manuscript.

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Declaration of interests

We declare no competing interests.

Data sharing

If requested, deidentified data collected for the LADIES trial, the study protocol, and informed consent form can be made available. Please contact WAB (w.a.bemelman@amsterdamumc.nl) or JFL (j.lange@erasmusmc.nl), who will review all requests with the members of the Dutch Diverticular Disease (3D) Collaborative Study Group and the LADIES trial investigators. Requests should fulfil the following access criteria: research can only be conducted in collaboration with and after approval of the members of the 3D Collaborative Study Group and the LADIES trial investigators, and with a signed data access and sharing agreement. The members of the 3D Collaborative Study Group and the LADIES trial investigators must approve all research done with the shared data.

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