Prevention of incisional hernia with prophylactic onlay and sublay mesh reinforcement versus primary suture only in midline laparotomies (PRIMA): 2-year follow-up of a multicentre, double-blind, randomised controlled trial

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Summary

Background Incisional hernia is a frequent long-term complication after abdominal surgery, with a prevalence greater than 30% in high-risk groups. The aim of the PRIMA trial was to evaluate the effectiveness of mesh reinforcement in high-risk patients, to prevent incisional hernia.

Methods We did a multicentre, double-blind, randomised controlled trial at 11 hospitals in Austria, Germany, and the Netherlands. We included patients aged 18 years or older who were undergoing elective midline laparotomy and had either an abdominal aortic aneurysm or a body-mass index (BMI) of 27 kg/m² or higher. We randomly assigned participants using a computer-generated randomisation sequence to one of three treatment groups: primary suture; onlay mesh reinforcement; or sublay mesh reinforcement. The primary endpoint was incidence of incisional hernia during 2 years of follow-up, analysed by intention to treat. Adjusted odds ratios (ORs) were estimated by logistic regression. This trial is registered at ClinicalTrials.gov, number NCT00761475.

Findings Between March, 2009, and December, 2012, 498 patients were enrolled to the study, of whom 18 were excluded before randomisation. Therefore, we included 480 patients in the primary analysis: 107 were assigned primary suture only, 188 were allocated onlay mesh reinforcement, and 185 were assigned sublay mesh reinforcement. 92 patients were identified with an incisional hernia, 33 (30%) who were allocated primary suture only, 25 (13%) who were assigned onlay mesh reinforcement, and 34 (18%) who were assigned sublay mesh reinforcement (onlay mesh reinforcement *vs* primary suture, OR 0·37, 95% CI 0·20–0·69; p=0·0016; sublay mesh reinforcement *vs* primary suture, 0·55, 0·30–1·00; p=0·05). Seromas were more frequent in patients allocated onlay mesh reinforcement (34 of 188) than in those assigned primary suture (five of 107; p=0·002) or sublay mesh reinforcement (13 of 185; p=0·002). The incidence of wound infection did not differ between treatment groups (14 of 107 primary suture; 25 of 188 onlay mesh reinforcement; and 19 of 185 sublay mesh reinforcement).

Interpretation A significant reduction in incidence of incisional hernia was achieved with onlay mesh reinforcement compared with sublay mesh reinforcement and primary suture only. Onlay mesh reinforcement has the potential to become the standard treatment for high-risk patients undergoing midline laparotomy.

Funding Baxter; B Braun Surgical SA.

Introduction

Incisional hernia is one of the most frequent long-term complications after abdominal surgery, with an incidence of 5–20% in the general patient population. However, in high-risk patients, the incidence of incisional hernia can increase to more than 30%.[1–3] Obese individuals (ie, those with a body-mass index [BMI] ≥30 kg/m²) and people with abdominal aortic aneurysm are especially high-risk groups. Patients with abdominal aortic aneurysm are at risk because of an underlying connective tissue disorder, caused partly by dysregulation of collagen type 1 and 3; this impairment probably has an important role in the pathogenesis of distension of the aorta and in formation of incisional hernia in patients after median laparotomy.[4] Individuals with obesity or a BMI equal to or higher than 27 kg/m² have a more than 30% chance of developing incisional hernia after median laparotomy.[5] This group of patients are believed to have a higher intra-abdominal pressure, which can cause higher tension on abdominal wall sutures. However, this pressure might not be the only contributing factor: obesity is also associated with wound-healing complications due to decreased vascularity of adipose tissue, leading to local hypoxia. In hypoxic wounds, the synthesis of mature collagen is impaired, resulting in weaker tissue and a deficiency in the overall healing process. In wound healing, other known risk factors play an important part—eg, malignant disease, parastomal hernia, wound infection, and smoking.[6–10]

Incisional hernia can cause morbidity (eg, pain) and can have a negative effect on patients' quality of life and

Lancet 2017; 390: 567–76

Published Online June 19, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31332-6

This online publication has been corrected. The corrected version first appeared at thelancet.com on June 30, 2017

See Comment page 535

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Research in context

Evidence before this study

The European Hernia Society has developed guidelines on closure of abdominal wall incisions. Although prophylactic mesh reinforcement is suggested for an elective midline laparotomy in high-risk patients (ie, those with an aneurysm of the abdominal aorta or who are obese [body-mass index ≥30 kg/m²), to reduce incisional hernias, evidence for this approach is weak. The Guidelines Development Group has suggested larger trials are needed to make a strong recommendation for this strategy. However, it is unclear which mesh position (onlay or sublay) leads to a lower occurrence of incisional hernias. We did a systematic literature search up to July, 2016, with the keywords "incisional hernia", "prophylactic", "prevention", "onlay", "sublay", and "mesh". We did not restrict our search by language. Three researchers reviewed all records independently. We included prospective randomised controlled trials that enrolled patients aged 18 years or older undergoing midline laparotomy for all indications, with any type of mesh and mesh position. We evaluated 12 randomised controlled trials, with high heterogeneity among studies. Incisional hernia arose less frequently when a prophylactic mesh was placed during midline laparotomy. Occurrence of seromas was highest in patients who underwent mesh reinforcement. Individuals in whom a mesh was placed during laparotomy seemed to have a higher risk of developing a surgical-site infection compared with those without a mesh.

Added value of this study

Compared with previous studies, the PRIMA randomised controlled trial had three arms to compare onlay mesh reinforcement, sublay mesh reinforcement, and primary suture. Onlay mesh reinforcement had a stronger and more significant effect on prevention of incisional hernia than did sublay mesh reinforcement. Moreover, the frequency of surgical-site infections was not increased with onlay mesh reinforcement.

Implications of all the available evidence

The PRIMA trial provides strong evidence in favour of onlay mesh reinforcement for prevention of incisional hernia in high-risk patients undergoing midline laparotomy. This finding is important because onlay placement of a mesh is an easier surgical technique than is sublay mesh reinforcement. Therefore, this approach could be adapted readily, not only by surgeons but also by urologists and gynaecologists, who also perform midline laparotomies. Closure of laparotomy with onlay mesh reinforcement has the potential to become the standard treatment in high-risk groups.

body image.[11–13] Furthermore, there is a risk of obstruction and strangulation of the bowel with perforation and possible mortality as a result. For these reasons, repair of incisional hernia is a surgical procedure that is done frequently. However, even though repair with mesh reinforcement has lower risk of recurrence compared with primary suture, the cumulative 10-year incidence is 32%, which is still too high.[14,15] Use of laparoscopic techniques has not yielded better results with respect to recurrence of incisional hernia.[16–18] Incisional hernia not only has a large effect in medicine but also has a great socioeconomic effect. Therefore, prevention of incisional hernia is of paramount importance: it will lead to reduction of disease and is, thus, cost-effective.

Many studies have evaluated different types of incision, suture materials, and closure techniques to reduce the incidence of incisional hernia.[19–21] Horizontal incisions and laparoscopy, or endovascular aneurysm repair (EVAR), in patients with abdominal aortic aneurysm are well-known surgical techniques that minimise the risk of incisional hernia. In each patient undergoing surgery, the best available technique should be considered. However, for several individuals, conventional laparotomy is unavoidable. Until now, no adequate method or gold standard to prevent incisional hernia has been reported for people undergoing midline laparotomy. Patients at particular high risk of incisional hernia, including those with abdominal aortic aneurysm and high BMI, might benefit most from prevention.[22–25] In 1995, Pans and colleagues[26] did a prospective study to compare patients undergoing surgery for morbid obesity with or without intraperitoneal polyglactin mesh. No difference in incidence of incisional hernia was noted between the two groups.[26] Several randomised and non-randomised prospective studies have been done to investigate how incisional hernia can be prevented. Currently, no level 1 evidence is available. The quality of published randomised studies is low and there is no consensus about the mesh position in the abdominal wall that should be used.[27,28]

We initiated the PRIMA trial (PRImary Mesh closure of Abdominal midline wounds) in 2009 with the aim to investigate prophylactic mesh reinforcement in high-risk groups (ie, patients with abdominal aortic aneurysm or a BMI ≥27 kg/m²).[29,30] We also aimed to assess which mesh position in the abdominal wall should be used to prevent incisional hernia. The primary aim of the PRIMA trial was to study the effectiveness of prophylactic mesh reinforcement to prevent incisional hernia.

Methods

Study design and patients

The PRIMA trial is an international, multicentre, double-blind, randomised controlled trial. The study methods and initial (short-term) results of the PRIMA trial have been described previously,[29] and the trial protocol has been published elsewhere.[30] The medical ethics committee of the Erasmus University Medical Centre in Rotterdam approved the trial; we also obtained approval from the local ethics committees of the participating hospitals.

We selected patients from 11 hospitals in Austria, Germany, and the Netherlands. We included adults aged 18 years or older who underwent elective midline laparotomy and had either an abdominal aortic aneurysm or a BMI equal to or higher than 27 kg/m². We excluded individuals who underwent an emergency procedure, had incisional hernia in the medical history, were included in other trials, or had a life expectancy less than 24 months. Furthermore, we excluded pregnant women, those who received immune suppression therapy within 2 weeks before surgery, and people with bovine allergy. All participants gave written informed consent.

Initially, we included patients with a BMI of 30 kg/m² or greater. However, 9 months after the start of the study, Seiler and colleagues[5] on the INSECT trial showed that patients with a BMI of 27 kg/m² or greater have a 20% chance of developing an incisional hernia within 1 year after the initial operation. Therefore, we reduced the BMI threshold of 30 kg/m² to 27 kg/m². The medical ethics committee of the Erasmus University Medical Centre approved this amendment.

Randomisation and masking

After obtaining informed consent we registered patients via the trial's online process system, in which data were stored securely, and every patient received a unique trial code. We randomly allocated participants at the end of the elective midline laparotomy procedure, before closing the abdomen, securing optimum allocation concealment. We used a computer-generated randomisation sequence to allocate patients to one of three groups: closure of the abdomen with primary sutures; closure with onlay mesh reinforcement; or closure with sublay mesh reinforcement. We stratified randomisation by centre and operation indication.

Trial researchers who followed up participants were unaware of the procedure until the endpoint of the trial. To avoid bias, the surgeons who did the laparotomy and closure did not follow-up patients. The safety monitoring board had access to all data.

Procedures

The trial researcher attended the first operation of each surgeon, urologist, or gynaecologist to give instructions if needed. The operating (vascular or gastrointestinal) surgeon, urologist, or gynaecologist closed the abdomen, not a specialised abdominal wall surgeon. We assessed whether a learning curve occurred by comparing early versus later procedures per surgeon.

For the primary suture procedure, the midline fascia was closed with running, slowly absorbable sutures (MonoPlus, suture size USP 1, needle HRT 48, 150 cm loop; B Braun Surgical SA, Rubi, Spain), preferably with a loop technique. We advised a suture length-to-wound length ratio of 4:1 in all centres, which we did not measure. Subcutaneous tissue and skin were closed with sutures preferred by the surgeon.

For onlay mesh reinforcement, the midline fascia was closed with running, slowly absorbable sutures (MonoPlus), with a recommended suture length-to-wound length ratio of 4:1. An anterior plane with a width of about 8 cm was created between the anterior rectus fascia and the subcutis. A lightweight polypropylene mesh (Optilene mesh LP, 6×35 cm; B Braun Surgical SA) was used and placed on the anterior rectus fascia with an overlap of 3 cm. The mesh size was made particularly for the PRIMA trial by cutting an Optilene mesh LP to size. In case of an incision longer than 35 cm, two meshes were tied to each other to obtain an overlap of 3 cm. After the mesh was fitted in the dissected space it was fixed with 4·0 mL of fibrin sealant (Tisseel; Baxter Healthcare, Deerfield, IL, USA), which was done by glueing the edges and the centre of the mesh to the tissue and fixing it with the back of a pair of forceps on the entire surface. The subcutaneous tissue and skin were closed with sutures preferred by the surgeon.

For sublay mesh reinforcement, a posterior plane was created between both the posterior rectus sheath and the rectus muscle, and caudally to the arcuate line between the peritoneum and rectus muscle. The posterior plane (fascia and peritoneum) was closed with running, slowly absorbable sutures (MonoPlus), with a recommended suture length-to-wound length ratio of 4:1. A lightweight polypropylene mesh (Optilene) was used and placed on the posterior rectus fascia, with an overlap of 3 cm. Mesh adjustments were made as described for onlay placement, and the mesh was fixed as described for onlay mesh reinforcement. The subcutaneous tissue and skin were closed with sutures preferred by the surgeon.

Outcomes

The primary endpoint of the PRIMA study was the presence of incisional hernia during 2 years of follow-up. We defined incisional hernia as any abdominal wall gap with or without bulge in the area of a postoperative scar perceptible or palpable by clinical examination or imaging, as determined by the European Hernia Society.[28] We measured this outcome variable by inviting patients for follow-up at the outpatient clinic of the 11 hospitals 1 year and 2 years after the operation. During the visit at the outpatient clinic, we undertook a physical examination of the abdomen. Furthermore, a radiological examination (ultrasound or CT) was done by an independent radiologist, 6 months and 2 years after surgery; the radiologist was not aware of the specific closure procedure. If disagreement was noted between the observations of the doctor who did the clinical examination and the radiologist who undertook the radiological examination, we deemed the outcome of the radiological examination decisive.

Secondary endpoints were postoperative complications (assessed clinically), quality of life (self-reported), and postoperative pain (self-reported). Short-term postoperative complications (up to 1 month) have been described

elsewhere.[29] Here, we report long-term postoperative complications (up to 2 years). The surgeon and trial researcher gathered data for postoperative complications—ie, intensive-care admission, ventilation, blood transfusion, admission days, surgical-site infection, seroma, haematoma, fascial dehiscence, mesh removal, ileus, re-interventions, re-admissions, and death. We obtained data for short-term and long-term outcomes at outpatient clinic visits at 1 month, 1 year, and 2 years after surgery. We defined surgical-site infection according to guidelines proposed by Mangram.[31] The trial researcher and surgeon also obtained preoperative data for sex, age, height, weight, BMI, current smoking status, diabetes mellitus, chronic obstructive pulmonary disease (COPD), American Society of Anaesthesiologists (ASA) score, previous midline incision, and other hernia; and intraoperative data for type of operation, use of antibiotics, length of incision, subcutis suture, wound drain, operation time, blood loss, intestinal lesion, bleeding, and whether mesh placement was not possible. Intraoperative outcomes have been reported elsewhere.[29] We sent questionnaires to patients at fixed timepoints (preoperatively, 1 month after surgery, and at 3 months, 6 months, 1 year, and 2 years after surgery) to gather data for quality of life (measured with the 36-item short form health survey [SF-36] and EuroQol five dimensions [EQ-5D]) and postoperative pain (measured on a visual analogue scale).

Statistical analysis

We made three comparisons, leading to a pairwise comparison at an alpha of 0·017 (0·05/3) according to Bonferroni's correction for multiple testing. We based the sample size calculation on the results of the INSECT trial,[5] which suggested that patients with a BMI of 27 kg/m² or higher have a 20% risk of developing incisional hernia within the first year after initial surgery. After taking into account that only 50% of patients with incisional hernia will be detectable in the first year after surgery, the total risk will be more than 30% after 2 years. Patients with abdominal aortic aneurysm were included also, since they have a high risk of developing incisional hernia.

We assumed the risk of incisional hernia after 2 years was 30% for primary suture and 10% for both onlay and sublay mesh reinforcement. Primary suture versus onlay or sublay mesh reinforcement was a superiority comparison with a power of 90%, whereas onlay versus sublay mesh reinforcement was an equivalence comparison with a power of 80%. We accounted for 10% dropouts. In total, we needed 100 patients in the primary suture group and 180 patients each in the primary mesh reinforcement groups; thus, 460 patients were needed to detect a significant difference in incidence of incisional hernia. However, during the trial, more dropouts occurred than initially expected and, therefore, we aimed to recruit an additional 20 patients.

For the comparison of both experimental groups (onlay and sublay mesh reinforcement) with the control group (primary suture), we analysed incisional hernia as a binary outcome. We used mixed-effects logistic regression with two group levels to account for clustering of patients in hospitals and according to operation type. We did not apply a time-to-event analysis as stated in the protocol, since patients were seen at the outpatient clinic at specific timepoints (1 year and 2 years after surgery) and, therefore, the exact time to event (incisional hernia) was unclear. However, as a sensitivity analysis, we checked if a mixed-effects Cox regression analysis led to different results. We adjusted outcomes for the following covariates: age, sex, smoking, BMI, abdominal aortic aneurysm, COPD, cardiovascular diseases, ASA classification, and steroids. We analysed data according to the intention-to-treat principle. In addition to intention-to-treat analyses, we also did a per-protocol analysis of the primary outcome for the comparison of onlay versus sublay mesh reinforcement.[30] We assessed quality of life and pain by the intention-to-treat principle.

For the comparison of the two experimental groups (onlay and sublay mesh reinforcement), we calculated a two-sided 98·3% CI for the difference in the probability of incisional hernia. Thus, we used an equivalence test for the comparison of onlay versus sublay mesh reinforcement instead of a non-inferiority test of onlay versus sublay mesh reinforcement (which was incorrectly suggested in the protocol), since we postulated that both techniques would have a similar risk of incisional hernia. We defined equivalence between the two experimental groups as the absolute difference in the probability of incisional hernia being below an equivalence margin of 10%. A rejection of the null hypothesis of non-equivalence—ie, the 98·3% CI of the absolute difference in the probability of incisional hernia is fully between –10% and 10%, is evidence in favour of equivalence. If the evidence in favour of equivalence is not strong enough, non-equivalence cannot be ruled out.

We did not account for dropouts in our analyses: we calculated numbers and percentages for all included patients (in that specific treatment group). Therefore, we assessed not only the baseline characteristics of all participants but also those of remaining participants, since differential loss to follow-up could bias comparisons between treatment groups.[32] To analyse the effect of potential differences in baseline characteristics on the comparisons between treatment groups, we repeated the mixed-effect regression analysis with adjustment for baseline characteristics.

We analysed quality of life with multilevel regression models. We judged incisional hernia a time-varying covariate, indicating whether the incisional hernia had taken place in the period preceding follow-up. We determined the covariance structures with the deviance test on the restricted maximum likelihood function. For the difference in quality-of-life measurements between treatment groups, we entered dummy variables indicating onlay or sublay mesh reinforcement as

covariates, with primary suture as the reference group. We estimated contrasts at 24 months. We analysed postoperative pain with linear logistic regression. We used mixed modelling for the quality-of-life analysis to handle data efficiently with missing and unbalanced timepoints.[33]

We did the statistical analysis with IBM SPSS version 20.0 and *R* version 3.1.0.

This trial is registered at ClinicalTrials.gov, number NCT00761475.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. 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 March, 2009, and December, 2012, 498 patients were enrolled to the study (figure). 18 individuals were excluded because they either withdrew informed consent (n=3), did not have midline incision (n=8), had already presented with incisional hernia (n=3), or for other reasons (n=4). Of the 480 included patients, 150 (31%) patients had an abdominal aortic aneurysm and 330 (69%) individuals had a BMI of 27 kg/m² or greater. At randomisation, 107 patients were assigned closure by primary suture, 188 were allocated closure by onlay mesh reinforcement, and 185 were assigned closure by sublay mesh reinforcement. Primary mesh reinforcement was not done in 18 (10%) patients assigned onlay mesh reinforcement and in 27 (15%) allocated sublay mesh reinforcement (figure). Baseline characteristics were similar between groups (table 1).

Median follow-up was 23 months (IQR 12–25), and 376 (78%) of 480 patients completed follow-up. 104 patients were lost to follow-up during the study, 21 who were assigned closure by primary suture, 45 allocated onlay mesh reinforcement, and 38 assigned sublay mesh reinforcement. The main reasons for loss to follow-up were death and patient's decision to withdraw from the study. Baseline characteristics of remaining participants are shown in the appendix.

Besides the physical examinations at 1 year and 2 years, 283 (59%) of 480 patients also underwent radiological examinations at 6 months and 2 years, 60 in the primary suture group, 115 in the onlay mesh reinforcement group, and 108 in the sublay mesh reinforcement group. Of the 376 patients who completed follow-up, 265 (70%) underwent radiological examination, 58 in the primary suture group, 105 in the onlay mesh reinforcement group, and 102 in the sublay mesh reinforcement group.

92 (19%) of 480 patients developed incisional hernia during the 2 years of follow-up, 33 (31%) of 107 in the primary suture group, 25 (13%) of 188 in the onlay mesh reinforcement group, and 34 (18%) of 185 in the sublay mesh reinforcement group. The incidence of incisional hernia differed significantly between onlay mesh reinforcement and primary suture (OR 0·37, 95% CI 0·20–0·69; p=0·0016), but did not differ for the

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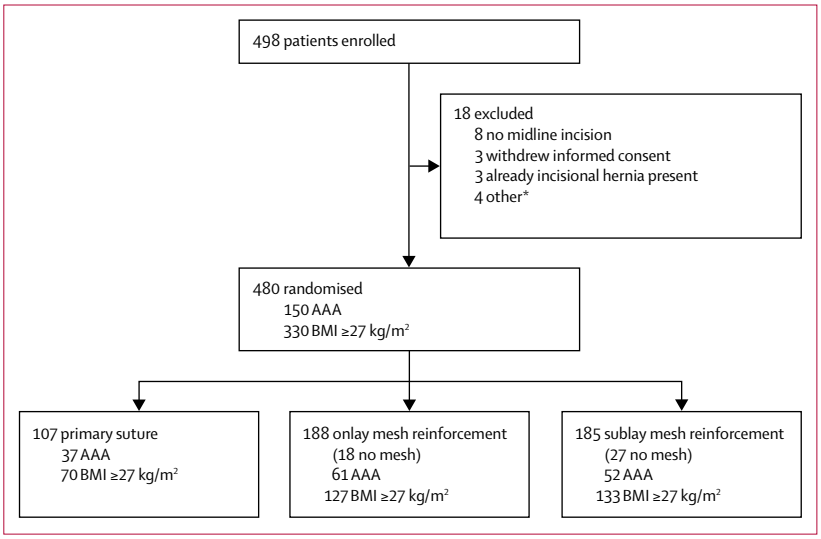

Figure: **Trial profile**
AAA=abdominal aortic aneurysm. BMI=body-mass index. *Surgeon's decision (n=1), laparoscopy done rather than laparotomy (n=1), and no operation done (n=2).

	Total (n=480)	Primary suture (n=107)	Onlay mesh reinforcement (n=188)	Sublay mesh reinforcement (n=185)
Men	292 (61%)	68 (64%)	116 (62%)	108 (58%)
Women	188 (39%)	39 (36%)	72 (38%)	77 (42%)
Age (years)	64·5 (11·2)	65·2 (10·5)	64·2 (12·3)	64·4 (10·4)
BMI (kg/m²)	30·6 (5·3)	29·8 (4·4)	30·8 (5·9)	30·8 (5·2)
Smoking	102 (21%)	17 (16%)	41 (22%)	44 (24%)
Diabetes mellitus	94 (20%)	19 (18%)	36 (19%)	39 (21%)
COPD	52 (11%)	9 (8%)	24 (13%)	19 (10%)
ASA				
I	44 (9%)	10 (9%)	21 (11%)	13 (7%)
II	234 (49%)	55 (51%)	90 (48%)	89 (48%)
III	150 (31%)	35 (33%)	54 (29%)	61 (33%)
IV	6 (1%)	1 (1%)	3 (2%)	2 (1%)
Unspecified	46 (10%)	6 (6%)	20 (11%)	20 (11%)
Previous midline incision	21 (4%)	3 (3%)	10 (5%)	8 (4%)
Other hernia	50 (10%)	13 (12%)	19 (10%)	18 (10%)
Type of operation				
Vascular	159 (33%)	39 (36%)	64 (34%)	56 (30%)
Upper gastrointestinal	65 (14%)	18 (17%)	22 (12%)	25 (14%)
Lower gastrointestinal	162 (34%)	29 (27%)	67 (36%)	66 (36%)
Hepatobiliary and pancreatic	21 (4%)	3 (3%)	8 (4%)	10 (5%)
Gynaecological	66 (14%)	15 (14%)	24 (13%)	27 (15%)
Urological	7 (1%)	3 (3%)	3 (2%)	1 (<1%)

Data are number of patients (%) or mean (SD). BMI=body-mass index. COPD=chronic obstructive pulmonary disease. ASA=American Society of Anesthesiologists.

Table 1: **Baseline characteristics**

comparisons of sublay mesh reinforcement versus primary suture (0·55, 0·30–1·00; p=0·05) or onlay versus sublay mesh reinforcement (1·39, 0·73–2·65; p=0·31; table 2). The 98·3% CI for the difference in probability of incisional hernia between sublay and onlay mesh reinforcement was –6·8 to 15·2. This confidence interval included the equivalence margin of 10%; therefore, non-equivalence of the experimental treatments cannot be ruled out. The sensitivity analysis using mixed-effects Cox regression led to very similar results, and adjustment for covariates did not had any effect on these findings either.

Among the subgroup of 150 patients with abdominal aortic aneurysm, incisional hernia occurred in 36 (24%), 16 who were assigned closure by primary suture, ten allocated onlay mesh reinforcement, and ten assigned sublay mesh reinforcement. Among the subgroup of 330 patients with a BMI of 27 kg/m² or higher, incisional hernia occurred in 54 (16%), 16 who were allocated closure by primary suture, 15 assigned onlay mesh reinforcement, and 23 allocated sublay mesh reinforcement. Subgroup analysis showed that treatment effects were consistent in both subgroups (table 2).

	Incidence (%)	Odds ratio (95% CI)	p value
All patients with follow-up to 2 years (n=480)			
Primary mesh reinforcement *vs* primary suture*	59/373 (16%) *vs* 33/107 (30%)	0·45 (0·27–0·77)	0·003
Onlay mesh reinforcement *vs* primary suture*	25/188 (13%) *vs* 33/107 (30%)	0·37 (0·20–0·69)	0·0016
Sublay mesh reinforcement *vs* primary suture*	34/185(18%) *vs* 33/107 (30%)	0·55 (0·30–1·00)	0·05
Onlay mesh reinforcement *vs* sublay mesh reinforcement†	25/188 (13%) *vs* 34/185 (18%)	1·39 (0·73–2·65)	0·31
Abdominal aortic aneurysm (n=150)			
Primary mesh reinforcement *vs* primary suture*	20/113 (17%) *vs* 16/37 (43%)	0·29 (0·12–0·67)	0·004
Onlay mesh reinforcement *vs* primary suture*	10/61 (16%) *vs* 16/37 (43%)	0·27 (0·10–0·71)	0·008
Sublay mesh reinforcement *vs* primary suture*	10/52 (19%) *vs* 16/37 (43%)	0·36 (0·13–0·93)	0·03
Onlay mesh reinforcement *vs* sublay mesh reinforcement†	10/61 (16%) *vs* 10/52 (19%)	1·04 (0·32–3·39)	0·95
BMI ≥27 kg/m² (n=330)			
Primary mesh reinforcement *vs* primary suture*	38/260 (15%) *vs* 16/70 (23%)	0·58 (0·29–1·19)	0·14
Onlay mesh reinforcement *vs* primary suture*	15/127 (12%) *vs* 16/70 (23%)	0·47 (0·21–1·06)	0·07
Sublay mesh reinforcement *vs* primary suture*	23/133 (17%) *vs* 16/70 (23%)	0·72 (0·32–1·60)	0·42
Onlay mesh reinforcement *vs* sublay mesh reinforcement†	15/127 (12%) *vs* 23/133 (17%)	1·62 (0·73–3·63)	0·24

Primary mesh reinforcement comprises both onlay and sublay mesh reinforcement. *Intention-to-treat analysis. †Per-protocol analysis.

Table 2: **Incidence of incisional hernia in all patients with 2-year follow-up and by subgroups**

	Primary suture (n=107)		Onlay mesh reinforcement (n=188)			Sublay mesh reinforcement (n=185)		
	Baseline	24 months	Baseline	24 months	p value*	Baseline	24 months	p value†
SF-36 domain								
Pain	69·03 (3·12)	80·38 (3·43)	69·16 (2·31)	78·90 (2·60)	0·73	68·95 (2·18)	78·90 (2·53)	0·73
Physical functioning	69·55 (3·25)	66·61 (3·63)	60·74 (2·43)	64·00 (2·69)	0·56	60·40 (2·29)	64·78 (2·65)	0·68
Physical health	52·42 (5·19)	65·79 (5·75)	47·66 (3·82)	65·13 (4·36)	0·93	36·31 (3·60)	61·81 (4·29)	0·58
Emotional problems	74·36 (4·84)	83·92 (5·36)	72·82 (3·59)	77·34 (4·11)	0·33	63·30 (3·39)	69·97 (4·00)	0·04
Energy or fatigue	62·30 (2·64)	61·10 (2·90)	58·20 (1·98)	62·60 (2·20)	0·68	51·70 (1·86)	60·40 (2·14)	0·85
Emotional wellbeing	74·90 (2·16)	79·60 (2·34)	74·00 (1·63)	76·30 (1·79)	0·26	69·00 (1·53)	74·80 (1·74)	0·10
Social functioning	79·00 (3·02)	82·10 (3·40)	70·70 (2·28)	79·20 (2·54)	0·50	65·30 (2·13)	78·40 (2·49)	0·38
General health	62·90 (2·40)	58·10 (2·61)	57·60 (1·81)	57·50 (1·99)	0·84	57·50 (1·71)	57·20 (1·94)	0·77
Mental component	49·20 (1·32)	52·20 (1·42)	48·80 (0·97)	50·20 (1·09)	0·27	45·10 (0·91)	48·90 (1·08)	0·06
Physical component	43·80 (1·31)	44·90 (1·42)	42·00 (0·97)	45·40 (1·08)	0·76	41·70 (0·91)	45·10 (1·07)	0·90
EQ-5D	0·81 (0·02)	0·93 (0·02)	0·82 (0·019)	0·90 (0·01)	0·33	0·77 (0·02)	0·91 (0·02)	0·63
Postoperative pain‡	1·12 (0·25)	1·27 (0·31)	1·16 (0·19)	0·71 (0·25)	0·17	1·04 (0·20)	1·06 (0·26)	0·61

Data are mean (SE). SF-36 scores range from 0 to 100. EQ-5D scores range from –0·329 to 1·000. EQ-5D=EuroQol five dimensions. SF-36=36-item short form health survey. *Difference at 24 months between primary suture and onlay mesh reinforcement. †Difference at 24 months between primary suture and sublay mesh reinforcement. ‡Measured on a visual analogue scale (range 0–10).

Table 3: **Quality-of-life scores**

Almost a quarter of patients had a postoperative complication after 2 years of follow-up. Seromas were seen most frequently in individuals assigned onlay mesh reinforcement at 1-month follow-up; however, this outcome had no further adverse outcomes for the patient—ie, the frequency of surgical-site infections, re-interventions, or re-admissions with onlay mesh reinforcement was not different when compared with primary suture or sublay mesh reinforcement. With respect to long-term complications at 2-year follow-up, there were three pulmonary infections (two with onlay mesh reinforcement, one with sublay mesh reinforcement), one urinary infection (with primary suture), one seroma (with sublay mesh reinforcement), one deep surgical-site infection with an abscess (with primary suture), seven re-interventions (four with onlay mesh reinforcement, three with sublay mesh reinforcement), and six re-admissions (two with primary suture, one with onlay mesh reinforcement, three with sublay mesh reinforcement). The risk of re-intervention (p=0·343) and re-admission (p=0·508) did not differ between groups. None of the re-interventions or re-admissions was related to the mesh used or the fibrin sealant.

73 (15%) of 480 patients died, 15 (14%) of 107 assigned primary suture, 34 (18%) of 188 allocated onlay mesh reinforcement, and 24 (13%) of 185 assigned sublay mesh reinforcement. The most common cause of death was malignant disease or tumour progression. None of the deaths was related to development of an (incarcerated) incisional hernia, the mesh used, or the fibrin sealant.

At baseline, 245 (51%) of 480 patients completed SF-36 and 342 (71%) of 480 submitted the EQ-5D questionnaire. After 2 years of follow-up, 188 and 333 patients, respectively, completed these questionnaires. No differences were recorded between the three treatment groups in SF-36 domains or the mental component summary score and physical component summary score (table 3). Moreover, no differences were noted between treatment groups with respect to EQ-5D scores and postoperative pain (measured with the visual analogue scale). Further analysis of the quality-of-life measures for patients with and without an incisional hernia showed no differences in scores on the SF-36 or EQ-5D questionnaires (table 4). However, patients with an incisional hernia had a higher score on the visual analogue scale for postoperative pain (mean estimate 1·94 [SE 0·39]) compared with patients who did not develop an incisional hernia (0·96 [0·15]; p=0·01).

	No incisional hernia (n=388)	Incisional hernia (n=92)	p value
SF-36 domain			
Pain	79·49 (1·68)	77·79 (3·15)	0·60
Physical functioning	65·89 (1·72)	58·98 (3·14)	0·03
Physical health	64·84 (2·85)	58·34 (5·57)	0·26
Emotional problems	75·93 (2·67)	75·35 (5·25)	0·92
Energy or fatigue	61·97 (1·42)	58·17 (2·57)	0·14
Emotional wellbeing	76·24 (1·15)	77·08 (2·03)	0·67
Social functioning	79·70 (1·67)	78·23 (3·18)	0·65
General health	57·54 (1·27)	57·07 (2·23)	0·83
Mental component score	49·96 (0·71)	51·04 (1·34)	0·42
Physical component score	45·44 (0·70)	43·47 (1·35)	0·14
EQ-5D	0·91 (0·01)	0·91 (0·02)	..
Postoperative pain*	0·96 (0·15)	1·94 (0·39)	0·01

Data are mean (SE). SF-36 scores range from 0 to 100. EQ-5D scores range from −0·329 to 1·000. EQ-5D=EuroQol five dimensions. SF-36=36-item short form health survey. *Measured on a visual analogue scale (range 0–10).

Table 4: **Quality-of-life scores for patients with and without incisional hernia**

Discussion

The findings of the PRIMA trial show that onlay mesh reinforcement significantly reduced the incidence of incisional hernia after midline laparotomy in patients at high risk for incisional hernia (ie, those with abdominal aortic aneurysm or a BMI ≥27 kg/m²). Sublay mesh reinforcement did not have a significant effect on the incidence of incisional hernia compared with primary suture. Although the absolute difference in incidence of incisional hernia between onlay and sublay mesh reinforcement was less than the equivalence margin of 10%, the 98·3% CI for the difference did not provide strong evidence in favour of equivalence.

Postoperative complications were analysed after 1 month (short-term)[29] and after 2 years. With respect to the short-term complications, only seromas were more frequently seen in patients allocated onlay mesh reinforcement, compared with those assigned primary suture and sublay mesh reinforcement. However, this increased incidence did not have any adverse outcomes for the patient, because the frequency of surgical-site infections, mesh infections, re-interventions, or re-admissions did not differ between treatment groups. No other differences in short-term postoperative complications were seen between the groups and no further postoperative complications were recorded after follow-up of 2 years. Furthermore, 15% of the included population died. Most deaths were due to malignant disease and no death was associated with either the fibrin sealant or the mesh used. Therefore, use of primary mesh reinforcement to reduce the incidence of incisional hernia is a safe procedure.

Incisional hernia is one of the most common complications after abdominal wall surgery. In high-risk groups, the frequency of incisional hernia is 30–40%. Incisional hernia can create a social burden for the patient and a financial burden for public health. Furthermore, it can lead to worse quality of life. In the PRIMA trial, we noted that patients with incisional hernia had a higher pain score compared with those without an incisional hernia. Thus, prevention is of paramount importance. Until now, several trials have

been done to investigate whether primary mesh reinforcement can reduce the incidence of incisional hernia. Most study findings showed that use of prophylactic mesh in patients with abdominal aortic aneurysm reduced the risk of incisional hernia to almost zero. For example, in a study by Muysoms and colleagues (PRIMAAT trial),[34] in which patients with abdominal aortic aneurysm were included, the cumulative incidence of incisional hernia was 28% in the non-mesh group compared with 0% in the mesh group, after follow-up of 2 years. Our data also provide strong evidence that use of prophylactic mesh in patients with abdominal aortic aneurysm—and in those with a high BMI (≥27 kg/m²)—significantly reduces the incidence of incisional hernia (30% incidence with primary suture *vs* 13% with onlay mesh reinforcement and 18% with sublay mesh reinforcement).

The reasons for the discrepancy in incidence between our study and other studies, including the PRIMAAT trial, could be explained by several factors. First, radiological examination was done in 59% of patients in our study, which is a more accurate procedure to diagnose hernia. In most other studies, radiological examination was not done,[1,34,35] and incisional hernia was diagnosed clinically in the PRIMAAT trial.[34]

Second, follow-up of patients in our trial was for 2 years, whereas follow-up in other studies[1,36,37] was usually shorter. A higher incidence of incisional hernia is typically seen with a longer duration of follow-up.[2,35] In a study by Fink and colleagues,[2] the incidence of incisional hernia was 12·6% in the first year, which increased significantly to 22·4% at 3 years after midline laparotomy, representing a relative increase of 60%. Thus, length of follow-up seems to affect the incidence of incisional hernia after midline laparotomy.

Third, different clinician specialties played a part in our study, not solely an abdominal closing team, as was the case in the PRIMAAT trial.[34] In the PRIMA trial, we included not only surgical patients but also those from the departments of urology and gynaecology. Thus, general surgeons and those from these different specialties operated on patients. This difference is exceptional because—as far as we know—no other study has included this variety of surgical specialties, patients, and surgical indications. Even though several specialists participated in the PRIMA trial, it is unlikely that this variety might have affected the results, considering the few gynaecological and urological patients.

Finally, we included different groups of high-risk patients in our trial, not only those with abdominal aortic aneurysm but also individuals with a BMI of 27 kg/m² or higher. Published work is contradictory with respect to primary mesh reinforcement in obese patients. For example, findings of a randomised controlled trial in obese individuals (BMI ≥40 kg/m²) did not show significant results;[35] however, this trial used an absorbable mesh. Findings of several other trials of a non-absorbable mesh did show a significant effect of prophylactic mesh placement in patients with morbid obesity (BMI ≥45 kg/m²).[23,24] In another trial,[25] a non-crosslinked biological mesh was placed in patients with a BMI greater than 40 kg/m² (or BMI >35 kg/m² with weight-related comorbidity), which did not reduce the incidence of incisional hernia substantially.

Participation of surgeons from different specialties might have led to a learning curve in our trial, but this possibility is also a strong advantage of the PRIMA trial: the results of our study are applicable to every patient undergoing midline laparotomy, operated on by different types of specialists. It is remarkable that placement of a mesh in an onlay position led to our significant results, because the sublay technique has always been assumed superior.[38] Placement of a mesh in an onlay position is a less complex surgical technique, which might have contributed to our results. The participation of different specialties might also have been a contributing factor to our findings: urologists and gynaecologists were not familiar with both onlay and sublay mesh reinforcement. However, sublay mesh reinforcement in particular is a complex technique. This factor makes onlay placement of a mesh with glue even more interesting, particularly because the onlay position did not lead to complications that had any adverse outcomes for patients.

In the PRIMA trial, we included patients not only with abdominal aortic aneurysm but also with a BMI of 27 kg/m² or higher. The possibility exists that these different risk factors affect each other in a synergistic way, which might lead to biased results. Therefore, we analysed mean BMI in both subgroups; this variable was similar among the three treatment groups of both subgroups, and the distribution was not skewed. Median BMI in the abdominal aortic aneurysm subgroup was lower than 27 kg/m² (26·6, IQR 24·3–29·3), whereas in the high BMI subgroup it was higher than this value (median 30·9, IQR 28·7–34·1). Thus, abdominal aortic aneurysm and BMI act as independent risk factors, and our results are not biased.

Findings of previous studies have shown that the combination of mesh and sealant we used in our study is effective.[39,40] As noted by us previously,[29] use of fibrin sealant in clinical practice, in combination with prophylactic mesh reinforcement, has not been investigated before. In our trial, no great complications or adverse events can be attributed with certainty to the sealant or the mesh. Application of the sealant aimed to reduce the anterior subcutaneous dissected space during onlay mesh reinforcement, which is prone to formation of seromas. Our results for postoperative complications did not confirm this expectation. This outcome can be explained by the timing of the application of the sealant, which is essential. There will be no reduction of the dissected space if polymerisation occurs before the ventral layer is closed.[41] Furthermore, other techniques that could diminish seroma formation were not applied,

such as placement of a wound drain and suturing of the subcutaneous tissue plane. Even though the expectation of fewer seromas could not be confirmed during this trial, the incidence of seroma without glue is unknown in these particular groups of patients.

We applied Bonferroni correction for multiple testing (α=0·017) in our analysis. Opinions on multiple-testing correction for multiarm trials are conflicting,[42] because controlling the overall probability of a false-positive treatment effect comes at the price of rejecting prematurely potentially effective treatments. In our study, the Bonferroni correction affected the interpretation of the difference between sublay mesh reinforcement versus primary suture (borderline significance *vs* non-significant).

We did not take into account the dropout rate in our statistical analysis. If the frequency of dropouts is equal in each arm of a trial, odds ratios should not be affected, assuming that the treatment effect in patients with complete follow-up and in those who dropped out is equal. In our trial, this assumption was plausible: the frequency of dropouts was very similar in the three treatment groups, so dropout of patients probably does not bias the odds ratios. Furthermore, we assessed whether differences in baseline characteristics between treatment groups were similar in remaining participants (appendix), which was the case. To correct for imbalance between the three treatment groups, an adjusted analysis for covariates was done, which led to a similar treatment effect.

One of the main limitations of the PRIMA study is the fact that not all included patients underwent radiological examination: 59% had radiological examination, and 70% of all individuals who completed follow-up underwent imaging. This procedure might have led to underestimation of the number of patients with incisional hernia, because radiological examination is more sensitive than physical examination alone. Therefore, we assessed incidence of incisional hernia in two subgroups: in individuals who underwent radiological examination (additional to physical examination); and in patients who did not receive radiological examination (data available on request). This analysis showed consistent treatment effects in both subgroups. Even though our study was not powered on these (small) subgroups, we believe our results are generalisable in daily practice. The fact that only 59% of participants had radiological assessment makes our study more comparable with daily practice but limits confidence of the study to some extent.

The PRIMA trial provides level one evidence for the prevention of incisional hernia after midline laparotomy in patients at risk for incisional hernia. Closure of laparotomy with onlay mesh reinforcement has the potential to become the standard treatment in high-risk groups, which will reduce the socioeconomic burden of incisional hernia. The results of the PRIMA trial also offer future perspectives. The next step will be a trial in which onlay mesh reinforcement is combined with the small bites suture technique to lower the incidence of incisional hernia even further, because the small bite technique has been shown to be superior in closing midline laparotomy.

Contributors

APJ and LT contributed to data collection, data interpretation, data analysis, and writing of the report. JFL and HJJ contributed to study design, data collection, data interpretation, and writing of the report. DvK, EWS, and RT contributed to data analysis, data interpretation, and writing of the report. G-JK contributed to data interpretation and writing of the report. HHE contributed to study design and reviewed the report. REGJMP, ACvdH, ID, JAC, CS, AM, JRI, PF, PK, and RHF contributed to data collection and reviewed the report.

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Declaration of interests

We declare no competing interests.

Acknowledgments

The PRIMA trial was funded by Baxter and B Braun Surgical SA. We thank the other members of the PRIMA Trialist Group for their contribution; Anneke van Duuren for her work as data manager; C Delin and M Bagot d'Arc (Baxter); and P Baumann (B Braun Surgical SA).

References

1 Bevis PM, Windhaber RAJ, Lear PA, Poskitt KR, Earnshaw JJ, Mitchell DC. Randomized clinical trial of mesh versus sutured wound closure after open abdominal aortic aneurysm surgery. *Br J Surg* 2010; **97:** 1497–502.

2 Fink C, Baumann P, Wente MN, et al. Incisional hernia rate 3 years after midline laparotomy. *Br J Surg* 2014; **101:** 51–54.

3 Bloemen A, van Dooren P, Huizinga BF, Hoofwijk AGM. Comparison of ultrasonography and physical examination in the diagnosis of incisional hernia in a prospective study. *Hernia* 2012; **16:** 53–57.

4 Antoniou GA, Georgiadis GS, Antoniou SA, Granderath FA, Giannoukas AD, Lazarides MK. Abdominal aortic aneurysm and abdominal wall hernia as manifestations of a connective tissue disorder. *J Vasc Surg* 2011; **54:** 1175–81.

5 Seiler CM, Bruckner T, Diener MK, et al. Interrupted or continuous slowly absorbable sutures for closure of primary elective midline abdominal incisions: a multicenter randomized trial (INSECT: ISRCTN24023541). *Ann Surg* 2009; **249:** 576–82.

6 Sorensen LT, Hemmingsen UB, Kirkeby LT, Kallehave F, Jorgensen LN. Smoking is a risk factor for incisional hernia. *Arch Surg* 2005; **140:** 119–23.

7 Franchi M, Ghezzi F, Buttarelli M, Tateo S, Balestreri D, Bolis P. Incisional hernia in gynecologic oncology patients: a 10-year study. *Obstet Gynecol* 2001; **97:** 696–700.

8 Murray BW, Cipher DJ, Pham T, Anthony T. The impact of surgical site infection on the development of incisional hernia and small bowel obstruction in colorectal surgery. *Am J Surg* 2011; **202:** 558–60.

9 Togo S, Nagano Y, Masumoto C, et al. Outcome of and risk factors for incisional hernia after partial hepatectomy. *J Gastrointest Surg* 2008; **12:** 1115–20.

10 Timmermans L, Deerenberg EB, Lamme B, Jeekel J, Lange JF. Parastomal hernia is an independent risk factor for incisional hernia in patients with end colostomy. *Surgery* 2014; **155:** 178–83.

11 van Ramshorst GH, Eker HH, Hop WCJ, Jeekel J, Lange JF. Impact of incisional hernia on health-related quality of life and body image: a prospective cohort study. *Am J Surg* 2012; **204:** 144–50.

12 van Dijk SM, Timmermans L, Deerenberg EB, et al. Parastomal hernia: impact on quality of life? *World J Surg* 2015; **39:** 2595–601.

13 Rogmark P, Petersson U, Bringman S, Ezra E, Österberg J, Montgomery A. Quality-of-life and surgical outcome 1 year after open and laparoscopic incisional hernia repair: PROLOVE—a randomized controlled trial. *Ann Surg* 2016; **263:** 244–50.

14 Burger JW, Luijendijk RW, Hop WC, Halm JA, Verdaasdonk EG, Jeekel J. Long-term follow-up of a randomized controlled trial of suture versus mesh repair of incisional hernia. *Ann Surg* 2004; **240:** 578–83.

15 Luijendijk RW, Hop WCJ, van den Tol P, et al. A comparison of suture repair with mesh repair for incisional hernia. *N Engl J Med* 2000; **343:** 392–98.

16 Al Chalabi H, Larkin J, Mehigan B, McCormick P. A systematic review of laparoscopic versus open abdominal incisional hernia repair, with meta-analysis of randomized controlled trials. *Int J Surg* 2015; **20:** 65–74.

17 Sauerland S, Walgenbach M, Habermalz B, Seiler CM, Miserez M. Laparoscopic versus open surgical techniques for ventral or incisional hernia repair. *Cochrane Database Syst Rev* 2011; **3:** CD007781.

18 Awaiz A, Rahman F, Hossain MB, et al. Meta-analysis and systematic review of laparoscopic versus open mesh repair for elective incisional hernia. *Hernia* 2015; **19:** 449–63.

19 Deerenberg EB, Harlaar JJ, Steyerberg EW, et al. Small bites versus large bites for closure of abdominal midline incisions (STITCH): a double-blind, multicentre, randomised controlled trial. *Lancet* 2015; **386:** 1254–60.

20 van 't Riet M, Steyerberg EW, Nellensteyn J, Bonjer HJ, Jeekel J. Meta-analysis of techniques for closure of midline abdominal incisions. *Br J Surg* 2002; **89:** 1350–56.

21 Diener MK, Voss S, Jensen K, Buchler MW, Seiler CM. Elective midline laparotomy closure: the INLINE systematic review and meta-analysis. *Ann Surg* 2010; **251:** 843–56.

22 Henriksen NA, Helgstrand F, Vogt KC, Jorgensen LN, Bisgaard T. Risk factors for incisional hernia repair after aortic reconstructive surgery in a nationwide study. *J Vasc Surg* 2013; **57:** 1524–30.

23 Abo-Ryia MH, El-Khadrawy OH, Abd-Allah HS. Prophylactic preperitoneal mesh placement in open bariatric surgery: a guard against incisional hernia development. *Obes Surg* 2013; **23:** 1571–74.

24 Strzelczyk JM, Szymanski D, Nowicki ME, Wilczynski W, Gaszynski T, Czupryniak L. Randomized clinical trial of postoperative hernia prophylaxis in open bariatric surgery. *Br J Surg* 2006; **93:** 1347–50.

25 Sarr MG, Hutcher NE, Snyder S, Hodde J, Carmody B. A prospective, randomized, multicenter trial of Surgisis Gold, a biologic prosthetic, as a sublay reinforcement of the fascial closure after open bariatric surgery. *Surgery* 2014; **156:** 902–09.

26 Pans A, Desaive C. Use of an absorbable polyglactin mesh for the prevention of incisional hernias. *Acta Chir Belg* 1995; **95:** 265–68.

27 Timmermans L, de Goede B, Eker HH, van Kempen BJH, Jeekel J, Lange JF. Meta-analysis of primary mesh augmentation as prophylactic measure to prevent incisional hernia. *Digest Surg* 2013; **30:** 401–09.

28 Muysoms FE, Antoniou SA, Bury K, et al. European Hernia Society guidelines on the closure of abdominal wall incisions. *Hernia* 2015; **19:** 1–24.

29 Timmermans L, Eker HH, Steyerberg EW, et al. Short-term results of a randomized controlled trial comparing primary suture with primary glued mesh augmentation to prevent incisional hernia. *Ann Surg* 2015; **261:** 276–81.

30 Nieuwenhuizen J, Eker HH, Timmermans L, et al, and PRIMA Trialist Group. A double blind randomized controlled trial comparing primary suture closure with mesh augmented closure to reduce incisional hernia incidence. *BMC Surg* 2013; **13:** 48.

31 Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999: Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 1999; **20:** 250–78.

32 Dumville JC, Torgerson DJ, Hewitt CE. Reporting attrition in randomised controlled trials. *BMJ* 2006; **332:** 969–71.

33 Little RJA, Rubin DB. Statistical analysis with missing data. New York: John Wiley and Sons, 1987.

34 Muysoms FE, Detry O, Vierendeels T, et al. Prevention of incisional hernias by prophylactic mesh-augmented reinforcement of midline laparotomies for abdominal aortic aneurysm treatment: a randomized controlled trial. *Ann Surg* 2016; **263:** 638–45.

35 Pans A, Elen P, Dewe W, Desaive C. Long-term results of polyglactin mesh for the prevention of incisional hernias in obese patients. *World J Surg* 1998; **22:** 479–83.

36 Caro-Tarrago A, Olona Casas C, Jimenez Salido A, Duque Guilera E, Moreno Fernandez F, Vicente Guillen V. Prevention of incisional hernia in midline laparotomy with an onlay mesh: a randomized controlled trial. *World J Surg* 2014; **38:** 2223–30.

37 Currò G, Centorrino T, Musolino C, Sarra G, Navarra G. Incisional hernia prophylaxis in morbidly obese patients undergoing biliopancreatic diversion. *Obes Surg* 2011; **21:** 1559–63.

38 Holihan JL, Nguyen DH, Nguyen MT, Mo J, Kao LS, Liang MK. Mesh location in open ventral hernia repair: a systematic review and network meta-analysis. *World J Surg* 2016; **40:** 89–99.

39 Fortelny RH, Petter-Puchner AH, Glaser KS, Redl H. Use of fibrin sealant (Tisseel/Tissucol) in hernia repair: a systematic review. *Surg Endosc* 2012; **26:** 1803–12.

40 Schug-Pass C, Jacob DA, Lippert H, Kockerling F. Differences in biomechanical stability using various fibrin glue compositions for mesh fixation in endoscopic inguinal hernia repair. *Surg Endosc* 2012; **26:** 3282–86.

41 Lau H. Fibrin sealant versus mechanical stapling for mesh fixation during endoscopic extraperitoneal inguinal hernioplasty: a randomized prospective trial. *Ann Surg* 2005; **242:** 670–75.

42 Wason JM, Stecher L, Mander AP. Correcting for multiple-testing in multi-arm trials: is it necessary and is it done? *Trials* 2014; **15:** 364.