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Prevention of incisional hernias by prophylactic mesh-augmented reinforcement of midline laparotomies for abdominal aortic aneurysm treatment 5-year follow-up of a randomized controlled trial

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MINI-ABSTRACT

Long-term results of a randomized controlled trial comparing prophylactic mesh reinforcement with primary closure after open AAA repair illustrate that a prophylactic mesh in the retrorectus plane safely and effectively decreases the rate of incisional hernias. The cumulative incidence of incisional hernias continues to increase during the first 5 years after surgery when no mesh is used, which leads to a substantial rate of hernia repairs.

ABSTRACT

Introduction. The incidence of incisional hernias (IHs) after open repair of an abdominal aortic aneurysm (AAA) is high. Several randomized controlled trials have reported favorable results with the use of prophylactic mesh to prevent IHs, without increasing complications. In this analysis we report on the results of the 60-month follow-up of the PRIMAAT trial (Ann Surg 2016; 263(4): 638-45).

Methods. In a prospective, multicenter, open label, randomized design, patients were randomized between prophylactic retrorectus mesh reinforcement (MESH group), and primary closure of their midline laparotomy after open AAA repair (NOMESH group). This article reports on the results of clinical follow-up after 60 months. If performed, ultrasonography or computed tomography were used for the diagnosis of IHs.

Results. Of the 120 randomized patients, 114 were included in the intention-to-treat analysis. Thirty-three patients in the NOMESH group (33/58 - 56.9%) and 34 patients in the MESH group (34/56 - 60.7%) were evaluated after 5 years. In each treatment arm, 10 patients died between the 24-month and 60-month follow-up. The cumulative incidence of IHs in the NOMESH group was 32.9% after 24 months and 49.2% after 60 months. No incisional hernias were diagnosed in the MESH group. In the NOMESH group, 21.7% (5/23) underwent reoperation within 5 years due to an IH.

Conclusion. Prophylactic retrorectus mesh reinforcement after midline laparotomy for the treatment of AAAs safely and effectively decreases the rate of IHs. The cumulative incidence of IHs after open AAA repair, when no mesh is used, continues to increase during the first 5 years after surgery, which leads to a substantial rate of hernia repairs.

Keywords. Incisional hernia - Prophylactic mesh - Abdominal aortic aneurysm - Randomized controlled trial

INTRODUCTION

The incidence of incisional hernias (IHs) after open surgery for an abdominal aortic aneurysm (AAA) is high[1-6]. Observational studies have reported on an incidence of up to 69.1% of IHs within 5 years after surgery[2,3]. In a randomized controlled trial (RCT) comparing open to endovascular treatment of AAAs with 6 years of follow-up, IH was the main reason for reintervention in the group that underwent open surgery[4]. Several studies have been able to identify AAA as an independent risk factor for the development of an IH[2,3,5]. Despite the lack of a well-identified mechanism in the majority of cases, authors currently acknowledge the association of AAA and abdominal wall hernias as part of a connective tissue disorder[6].

Several preventive measures have been proposed to decrease the risk of an IH after open abdominal surgery. For the primary closure of laparotomies, current guidelines advise the use of a slowly absorbable running suture, 'small bites' technique, and adherence to a 4 to 1 suture to wound length ratio (4:1 SL/WL)[7,8]. Furthermore, there is increasing evidence that the use of a prophylactic mesh diminishes the rate of IHs after laparotomy in high-risk patients, including those with AAAs[1,9-13]. To date, 5 RCTs have investigated the use of prophylactic mesh reinforcement (PMR) in patients undergoing open AAA repair[9-13]. Four of these have reported a significant decrease in IHs during a mid-term follow-up of 2 to 3 years, without an increase in overall or mesh-related complications[9-12]. One randomized trial, the AIDA-trial (abdominal incision defect following AAA-surgery), failed to demonstrate this benefit, and reported similar rates of IHs when comparing primary closure and the use of an onlay PMR[13,14]. However, inclusion numbers in this study were not met, and a significant lack of power limits the interpretation of these results. A recent pooled analysis confirmed the significant decrease in the incidence of IHs when PMR was used in patients undergoing open AAA repair. Surprisingly, this did not result in a significant reduction in the reoperation rates for IHs[1,15]. Whether this is because these IHs do not pose a clinically relevant problem, or because surgeons are reluctant to operate on patients with significant comorbidities remains grossly unknown and underreported[1,9-13,15].

The most recent guidelines issued by the European Hernia Society (EHS) on the closure of midline laparotomies (2015) state that the use of prophylactic mesh in high-risk patients (including patients with an AAA) is suggested in elective cases[7]. At that point in time, evidence on this topic was considered weak, as only a single RCT in AAA patients had been published[11]. The European Society of Vascular and Endovascular Surgery (ESVS) guidelines, published in 2019, state that prophylactic mesh augmentation of the midline may be considered after open AAA repair in patients at high-risk of IHs[16]. In 2019 a survey among hernia surgeons was conducted on the use of PMR in a general population of high-risk patients, illustrating that its use remains controversial, even among abdominal wall surgeons[17].

Objectives. This article reports on the long-term results of the PRIMAAT trial (Prevention of incisional hernias by prophylactic mesh augmented reinforcement of midline laparotomies for abdominal aortic aneurysm treatment), a randomized controlled trial comparing primary closure and PMR of the abdominal wall after midline laparotomy for open AAA repair[9]. By publishing the 5-year follow-up results, we aim to monitor if the protective effect of a prophylactic mesh regarding IHs continues beyond 2 years of follow-up, and report on the number of IH repairs in this patient group.

METHODS

The study was designed as a prospective, multicenter, open label, randomized trial. The study protocol was approved by the central Ethics Committee of the Ghent University Hospital on November 6th, 2008 with the Belgian Trial Registration number B67080084346. Approval was obtained from the local ethics committees of each participating center prior to patient inclusions. No adjustments to the study protocol were made after the start of inclusions. Eight Belgian hospitals participated in the study. All patients who had a planned elective treatment of an AAA through a midline laparotomy were considered eligible for inclusion. Details on inclusion and exclusion criteria, and sample size calculation can be found in the publication reporting on the 24-month follow-up of the PRIMAAT trial[9]. The study was registered online on September 18th, 2008, with the Clinicaltrials.gov identifier NCT00757133. A signed informed consent was obtained from each included patient before randomization. Computer-generated block randomization per 6 patients was performed in a 1:1 allocation ratio.

Patients were randomized either to a conventional laparotomy closure (NOMESH group) or a closure of the abdominal wall with PMR (MESH group). After completion of the AAA repair, closure of the midline laparotomy was performed by an abdominal wall surgeon. In the NOMESH group, the abdominal wall was closed with a slowly absorbable running suture (polydioxanone) with a SL/WL ratio of 4 to 1. In patients randomized to the MESH group, the midline laparotomy was closed using a prophylactic large pore, partially absorbable and lightweight polypropylene mesh of 7.5 cm in width (Ultrapro, Ethicon Inc; Johnson & Johnson, Somerville, NJ). The mesh was placed in the retrorectus position, and both anterior and posterior rectus fascia were closed using a slowly absorbable running suture (polydioxanone). Additional details on the surgical technique can be found in the original publication of the PRIMAAT trial[9].

A clinical follow-up by the abdominal wall surgeon was scheduled at 1 month, 12 months, 24 months and 60 months after surgery. A radiological evaluation of the abdominal wall was not routinely performed. Ultrasonography (US) or computed tomography (CT), performed in case of dubious clinical evaluation or for other indications (e.g. follow-up) was used for the diagnosis of IHs. Patients and vascular surgeons were blinded for the allocated treatment arm.

The primary endpoint of the study was the incidence of IHs 24 months after surgery. IH was defined as 'any abdominal wall gap, with or without bulge, in the area of the midline scar perceptible or palpable by clinical examination or imaging'. For this long-term evaluation 60 months after surgery, the same follow-up methods and definitions were used. All data regarding the 60-month follow-up was gathered by the study secretariat of Maria Middelares Hospital, Ghent, and double-checked by the first author (MD). The database was closed at the end of November 2021 and sent for analysis by an independent statistician.

Data analysis. Descriptive statistics used were mean, standard deviation (SD), median, interquartile range (P25-P75) and % (n). Baseline characteristics of patients in the mesh and non-mesh study arms were compared according to the Mann-Whitney U test for continuous variables and Fisher's exact test for proportions. The cumulative incidences of IHs across the 5-year follow-up were computed using the Kaplan-Meier product limit estimator method. Since death or loss to follow-up were unrelated to

the allocated treatment (Figure 1), competing risks are independent and Kaplan-Meier estimates of cumulative incidences can hence be assumed to be unbiased. The Log-rank test was used to compare the estimated cumulative incidence functions across study arms. Hazard ratios were not estimated as no IHs were observed in the MESH arm. Likewise, the rule-of-three method was used to obtain the 95% confidence interval for the zero cumulative incidence in this MESH arm. An alpha value of 0.05 was chosen to indicate statistical significance. All reported P values are 2-tailed.

RESULTS

Patients. A CONSORT flow diagram of the study is shown in Figure 1. Of the 120 included patients, 114 received the allocated treatment and were included in the intention-to-treat analysis. Eventually, 33 patients in the NOMESH group and 34 patients in the MESH group were evaluated 60 months after the index surgery. In both study arms, 10 patients deceased between 24 and 60 months after surgery. Patients were enrolled in the study between February 2009 and January 2013. Follow-up visits for the 60-month follow-up were performed between February 2014 and October 2018.

Relevant patient characteristics at baseline and intraoperative details are listed in Table 1. A more detailed description of patient demographics and comorbidities, intraoperative details and short-term outcomes can be found in the paper reporting on the 24-month follow-up[9]. Regarding patient demographics, no statistically significant differences between groups were seen. Although not significant, there were more women in the NOMESH group. In 30.9% of the patients in the NOMESH group a SL/WL ratio ≥4 was measured, compared to 28.3% in the MESH group ($p>0.05$). Both skin-to-skin operative time (189.7 vs. 211.5 min; $p<0.05$) and time to close the abdominal wall (29.6 vs. 46.2 min; $p<0.001$) were significantly longer in the MESH group. In 4 patients in the MESH group, a seroma or hematoma was diagnosed 30 days after surgery. No other mesh-related complications were seen.

Outcome data. Outcome data of the 60-month follow-up is summarized in Table 2. Follow-up time in patients free of IH was comparable between groups, with a mean of 3.8 years in the NOMESH group, and 3.5 years in the MESH group. By the end of the studied period, 23 patients had been diagnosed with an incisional hernia in the NOMESH group, compared to 0 patients in the MESH group. The IH

incidence rate per 100 person-years, indicating the number of IHs that would occur during a 1-year follow-up of 100 patients, was 14.5 in the NOMESH group, and 0.0 in the MESH group (Log-rank test: $p<0.0001$). The use of diagnostic imaging 5 years after surgery was equally distributed between the patient groups. A CT scan was performed in 39.4% of the patients in the NOMESH group and 41.2% in the MESH group. No radiological evaluation was performed in 39.4% of patients in the NOMESH group and 35.3% of patients in the MESH group. Of the hernias that were diagnosed, 26.1% (6/23) were identified upon clinical evaluation, 8.7% (2/23) by ultrasound, and 65.2% (15/23) by CT-scan. The estimated cumulative incidence of IHs during the first 60 months after surgery is depicted in Figure 2. Although less prominent than during the first 2 years, a further increase in the cumulative incidence of IHs was seen in the period between 2 and 5 years post-surgery. The cumulative incidence of patients developing an IH in the NOMESH group during the first 24 months following the index surgery was 32.9%. During the first 60 months, this was 49.2%.

In this study, 17.4% (4/23) of patients with an IH reported symptoms related to this hernia, and 21.7% (5/23) underwent IH surgical repair. Only 1 patient had a symptomatic IH that was not surgically treated. In both groups, 2 patients underwent abdominal surgery for other reasons than hernia repair. Indications were prostatectomy (n=2), cystectomy (n=1) and right hemicolectomy with en bloc nephrectomy (n=1). No specific mesh-related complications were reported in these patients.

DISCUSSION

Results. The long-term results of this randomized trial confirm that the use of PMR after open AAA repair significantly decreases the IH incidence during the first 5 years after surgery. This is in concordance with currently available evidence that supports prophylactic mesh placement in patients undergoing AAA repair. Two meta-analyses have been published on PMR after open AAA repair, which evaluate the same 4 RCTs comparing primary fascial closure with PMR, including the 24-month follow-up of this trial[1,9-12,15]. Both the meta-analysis of Indrakusuma et al.[1] and the pooled analysis by Nicolajsen et al.[15] concluded that PMR significantly reduces the risk of IH after midline laparotomy for open AAA repair during a follow-up period of up to 3 years. This present trial is the first to report on long-term results. More recently, results of a fifth study, the AIDA-trial, have been

published[13]. In this study, authors were not able to confirm a significant reduction in the rate of IHs with the use of PMR after open AAA repair, when compared to a suture closure using a 4:1 SL/WL with a slowly absorbable running suture. However, major methodological flaws and statistical limitations (e.g. insufficient power and the use of a large bites technique in the primary closure group) limit the interpretation of these findings[14].

Reported studies on IH prevention vary regarding type of mesh and mesh position. Four of the published RCTs used a synthetic polypropylene mesh[9-11], and one reported using a bovine pericardium mesh[12]. Both onlay and retrorectus mesh positions have been proposed and investigated, with no clear benefit shown for either of these approaches[9-13]. When an onlay mesh was used an increase in seroma formation was seen, although this did not lead to an increase in reinterventions, and generally did not pose a clinically relevant problem[10,12,13]. However, in a recent publication reporting on infectious complications during a 2-year follow-up of the PRIMA trial, a greater number of infectious complications were seen in the group that had an onlay mesh position, when compared to a rectrorectus mesh position[18]. In the PRIMAAT trial, a retrorectus mesh placement was used. This is considered technically more challenging when compared to onlay mesh reinforcement. This fact may pose an additional threshold in performing PMR, especially in a population of vascular surgeons that have not been trained to perform IH repair.

During a 5-year follow-up period, 21.7% (5/23) of the patients in the NOMESH group underwent reoperation due to IHs. Even though surgeons may be reluctant to operate on IHs in AAA patients (who generally have significant comorbidities), reported reoperation rates for IH in the literature after open AAA repair vary between 9.3% and 10.4% during a follow-up period of between 2 and 6 years[1,15,19,20]. Despite the fact that only 17.4% of patients with an IH reported hernia-related symptoms, these long-term results confirm the substantial rates of reoperation due to IHs when no PMR was performed. Several authors have shown that IHs do pose a clinically relevant problem, and are associated with a major economic burden on healthcare systems[19-21].

Currently, the surgical treatment of an AAA is increasingly being performed using endovascular techniques. Several RCTs have shown a significant decrease in short-term complications after endovascular treatment, when compared to open surgery[22,23]. This could limit the impact of this study.

However, as this decrease in complications is no longer seen on the longer term, there is still a clear indication for an open AAA repair in young patients that do not have significant comorbidity. There is increasing evidence that the use of a prophylactic mesh in the prevention of incisional hernias could be considered after laparotomy in all high-risk patients, including patients that were not treated for an AAA. This study adds evidence on the effectiveness of a prophylactic mesh in the prevention of incisional hernias, which could be extrapolated to a broader patient group. Furthermore, this study illustrates the safety and feasibility of the use of a prophylactic mesh in the retrorectus plane.

Limitations. This study is subject to several limitations that complicate the interpretation of these long-term results.

Firstly, closure of the abdominal wall was carried out by dedicated abdominal wall surgeons. As illustrated by the delay in inclusions and high levels of non-included eligible patients, this poses significant logistical problems[9]. Outside the study setting it is usually vascular surgeons who perform the closure of the abdominal wall. This may lead to other outcomes regarding adherence to a 4:1 SL/WL, incidence of IHs after primary closure of the abdominal wall, and possibly higher reluctance in using PMR after open AAA repair.

Secondly, only elective cases were included in this study. This limits the extrapolation of these results to all cases of open AAA repair, which are often performed as emergency surgery. Besides the fact that this study is underpowered to detect complications with low incidence rates (like mesh-related complications) it is uncertain if these beneficial outcomes are equally applicable to a population of patients that undergo emergency surgery. Increased operative times that were seen in the MESH group may add an additional threshold in case of emergency surgery.

Thirdly, no routine imaging was performed during follow-up. Current evidence and guidelines support the use of radiological evaluation to detect IHs within the setting of clinical studies[7,13,24]. Probably this has led to an underestimation of the incidence of IHs in the MESH group, which is illustrated by the absence of any IHs within this study arm. However, given the highly significant difference between groups regarding the primary endpoint, it is unlikely that routine imaging would have changed the overall conclusion of this paper.

To conclude, in only 30.9% of patients in the NOMESH group a SL/WL of more than 4 was achieved, despite the study protocol. Furthermore, this study did not report on the use of the small bites technique, which has proven to be superior to the use of larger bites in the suture closure of laparotomies[8]. A state-of-the-art closure of the abdominal wall, using a SL/WL of more than 4 in a small bites technique would probably have led to a lower incidence of IHs in the NOMESH group.

Future recommendations. These long-term results illustrate that extending the follow-up period to a minimum of 5 years in studies that have IHs as a primary outcome adds highly relevant information. Traditionally, studies report on a follow-up period of 24 to 36 months, as recommended by the latest EHS guidelines[7]. However, observational studies in AAA patients have reported an increasing cumulative incidence of IHs after AAA repair up to 7 years after surgery, which is consistent with our findings[25]. Future studies with IHs as an endpoint should extend their follow-up period to a minimum of 5 years, and should use routine medical imaging by CT or dynamic US to detect abdominal wall hernias.

All currently available randomized trials comparing primary fascial closure with PMR in AAA patients aim for a 4:1 SL/WL in their study protocol. However, not a single one of them has reported on the small bites technique, and some have explicitly used a large bites technique in the primary fascial closure of the abdominal wall[13]. Future studies comparing primary fascial closure to PMR of the abdominal wall should use a small bites technique and a 4:1 SL/WL.

Current guidelines strongly advise the use of a 4:1 SL/WL following open AAA repair, but lack a strong recommendation for the use of PMR. The latest guidelines of the EHS (2015) require an update, as evidence on PMR has accumulated[7,9,10,12,13]. The 2019 ESVS AAA guidelines state that PMR 'may be considered' in high-risk patients, and that long-term results are awaited[16]. A clear recommendation in future guidelines - supported by this data with a longer follow-up period - could lead to a more widespread adoption of PMR among surgeons.

Conclusion. Long-term results illustrate that a prophylactic retrorectus mesh reinforcement of the abdominal wall after midline laparotomy for the treatment of an AAAs safely and effectively decreases the rate of IHs. The cumulative incidence of IHs after open AAA repair, when no mesh is

used, continues to increase during the first 5 years after surgery, which leads to a substantial rate of hernia repairs.

COMPLIANCE WITH ETHICAL STANDARDS

Funding. This trial was funded by research grants from Johnson & Johnson and the Belgian Section for Abdominal Wall Surgery. Surgeons received a fee for the administration related to the study per included patient. All meshes used in the study were provided by a material grant from Ethicon, Johnson & Johnson. The company was not involved in the design, conduct, follow-up or analysis of the trial.

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	NOMESH N=58	MESH N=56
Patient characteristics at baseline		
Age at the time of surgery (years)	71.9 (8.5)	72.3 (7.4)
Women	12.1% (7/58)	3.6% (2/56)
Body Mass Index (kg/m²)	26.5 (3.7)	25.5 (3.6)
ASA score: I - Normal health	8.8% (5/57)	9.1% (5/55)
II - Mild to moderate systemic disease	61.4% (35/57)	61.8% (34/55)
III - Serious systemic disease	29.8% (17/57)	29.1% (16/55)
IV - Life threatening systemic disease	0.0% (0/57)	0.0% (0/55)
Intraoperative characteristics		
SL/WL ratio	3.93 (1.61)	3.50 (0.98)
SL/WL ratio ≥ 4	30.9% (17/55)	28.3% (13/46)
Length of the mesh used (cm)	--	32.3 (3.7)
Mesh overlap beyond the incision (cm)	--	3.26 (0.81)
Skin-to-skin operative time (min)	189.7 (83.1)	211.5 (61.9)*
Time to close the abdominal wall (min)	29.6 (18.5)	46.2 (18.6)**

Table 1 - Demographics and intraoperative characteristics at baseline of the PRIMAAT trial: a randomized controlled trial on the prevention of incisional hernias by prophylactic mesh-augmented reinforcement of midline laparotomies for the treatment of abdominal aortic aneurysms
Data are reported as mean (standard deviation) or percentages (n/N), *P<0.05; **P<0.001; ASA=American Society of Anesthesiology, SL/WL ratio = Suture length to wound length ratio

	NOMESH N=58	MESH N=56
Follow-up time in patients free of IH (years)		
Mean (SD)	3.8 (1.7)	3.5 (2.1)
Median (P25-P75)	5.0 (1.4-5.0)	5.0 (2.0-5.0)
Number of IHs at 60-month follow-up	23	0
Diagnostic imaging at 60-month follow-up, % (n/N)		
CT	39.4% (13/33)	41.2% (14/34)
Ultrasound	21.2% (7/33)	23.5% (8/34)
None	39.4% (13/33)	35.3% (12/34)
IH incidence rate (per 100 person-years)	14.5	0.0*
Cumulative incidence of IHs, % (95% CI)		
at 1 year	16.4% (6.6%-26.1%)	0.0% (0.0%-5.6%)
at 2 years	32.9% (20.0%-45.8%)	0.0% (0.0%-6.4%)
at 5 years	49.2% (34.1%-64.2%)	0.0% (0.0%-10.3%)
Characteristics of IH, % (n/N)		
Symptomatic	17.4% (4/23)	--
Surgical repair during 60-month follow-up	21.7% (5/23)	--
Symptomatic patients that did not have hernia repair	4.3% (1/23)	--
Asymptomatic patients that underwent hernia repair	8.7% (2/23)	--
Diagnosis of IH, % (n/N)		
Clinical evaluation	26.1% (6/23)	--
Ultrasound	8.7% (2/23)	--
CT	65.2% (15/23)	--

Table 2 - Outcome data of 60-month follow-up in the PRIMAAT trial: a randomized controlled trial on the prevention of incisional hernias by prophylactic mesh-augmented reinforcement of midline laparotomies for the treatment of abdominal aortic aneurysms
*Log-rank test: $\chi 2=18.93$, $P<0.0001$; SD=Standard deviation; IH=Incisional hernia; CT=Computed tomography; CI=Confidence interval

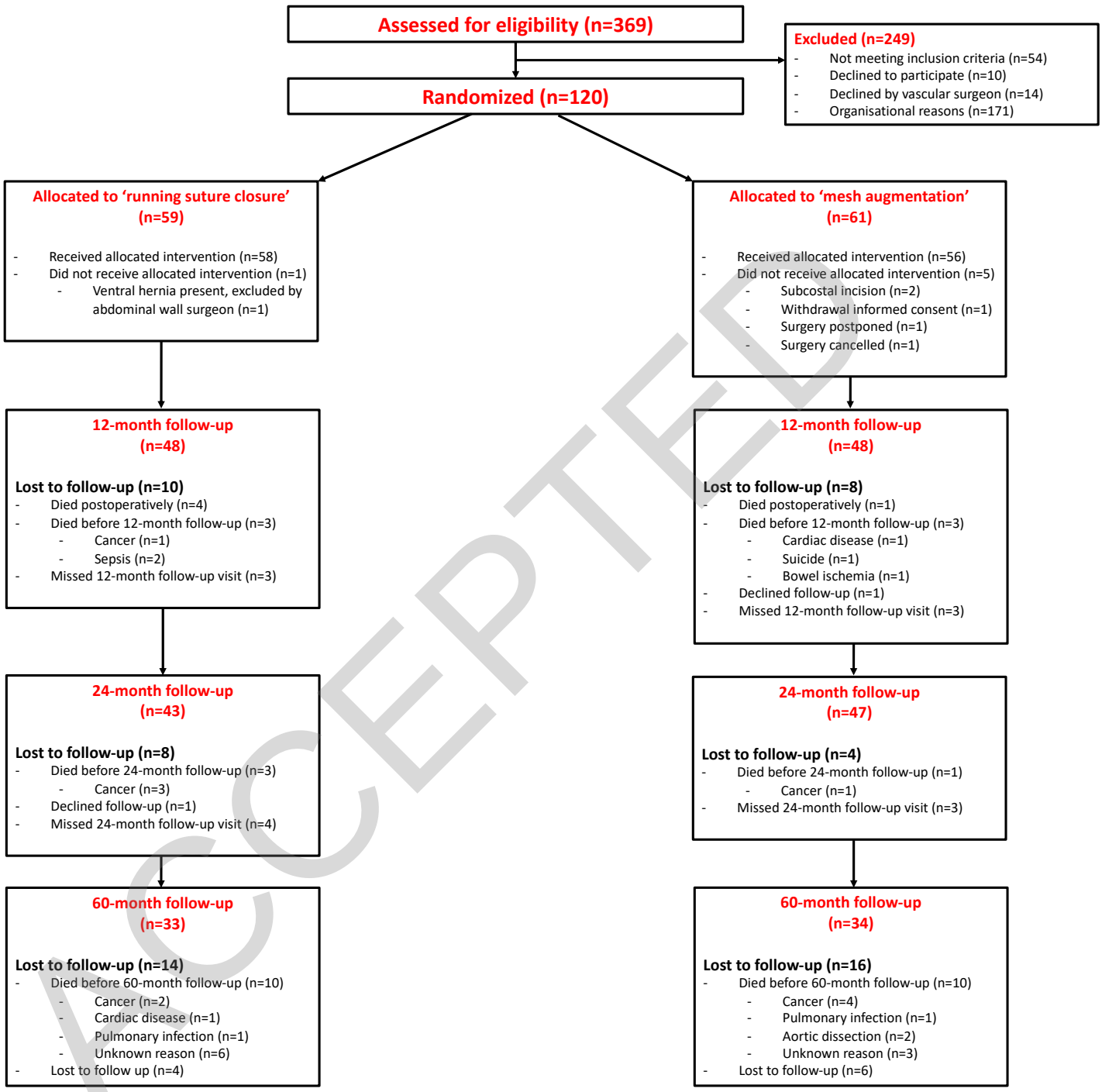

Figure 1 - CONSORT flow diagram of 60-month follow-up in the PRIMAAT trial: a randomized controlled trial on the prevention of incisional hernias by prophylactic mesh-augmented reinforcement of midline laparotomies for the treatment of abdominal aortic aneurysms

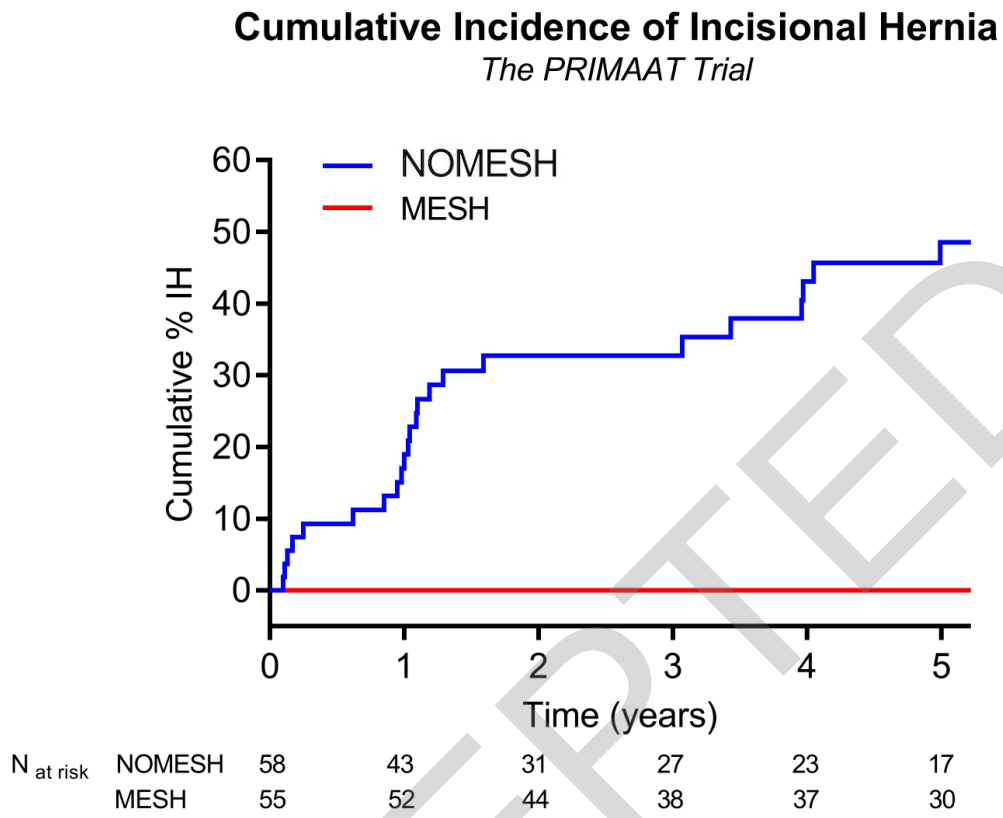

Figure 2 - Estimated cumulative incidence of incisional hernia during 60-month follow-up in a randomized controlled trial on the prevention of incisional hernias by prophylactic mesh-augmented reinforcement of midline laparotomies for the treatment of abdominal aortic aneurysms (PRIMAAT trial)