Prophylactic abdominal drainage after distal pancreatectomy (PANDORINA) an international, multicentre, open-label, randomised controlled, non-inferiority trial

Bodegraven, E.A. van; Balduzzi, A.; Ramshorst, T.M.E. van; Malleo, G.; Vissers, F.L.; Hilst, J. van; ... ; Dutch Pancreatic Cancer Grp

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Eduard A van Bodegraven, Alberto Balduzzi*, Tess M E van Ramshorst*, Giuseppe Malleo, Frederique L Vissers, Jony van Hilst, Sebastiaan Festen, Mohammad Abu Hilal, Horacio J Asbun, Nynke Michiels, Bas Groot Koerkamp, Olivier R C Busch, Freek Daams, Misha D P Luyer, Marco Ramera, Giovanni Marchegiani, Joost M Klaase, I Quintus Molenaar, Matteo de Pastena, Gabriella Lionetto, Pier Giuseppe Vacca, Hjalmar C van Santvoort, Martijn W J Stommel, Daan J Lips, Mariëlle M E Coolsen, J Sven D Mieog, Roberto Salvia†, Casper H J van Eijck†, Marc G Besselink†, for the Dutch Pancreatic Cancer Group*

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*Shared first author

†Shared senior author

Department of Surgery, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands (E A van Bodegraven MD, T M E van Ramshorst MD, F L Vissers MD, J van Hilst MD, Prof O R C Busch MD, F Daams MD, Prof M G Besselink MD); **Cancer Center Amsterdam, Amsterdam, Netherlands** (E A van Bodegraven, T M E van Ramshorst, F L Vissers, J van Hilst, Prof O R C Busch, F Daams, Prof M G Besselink); **Department of Surgery, Pancreas Institute, Verona University Hospital, Verona, Italy** (A Balduzzi MD, Prof G Malleo MD, G Marchegiani MD, M de Pastena MD, G Lionetto MD, P G Vacca MD, Prof R Salvia MD); **Department of Surgery, OLVG, Amsterdam, Netherlands** (J van Hilst, S Festen MD); **Department of Surgery, University Hospital Southampton NHS Foundation Trust, Southampton, UK** (Prof M Abu Hilal MD); **Department of Surgery, Poliambulanza Hospital Brescia, Brescia, Italy** (T M E van Ramshorst, Prof M Abu Hilal, M Ramera MD); **Division of Hepatobiliary and Pancreas Surgery, Miami Cancer Institute, Miami, FL, USA** (Prof H J Asbun MD);

Summary

Background Prophylactic passive abdominal drainage is standard practice after distal pancreatectomy. This approach aims to mitigate the consequences of postoperative pancreatic fistula (POPF) but its added value, especially in patients at low risk of POPF, is currently being debated. We aimed to assess the non-inferiority of a no-drain policy in patients after distal pancreatectomy.

Methods In this international, multicentre, open-label, randomised controlled, non-inferiority trial, we recruited patients aged 18 years or older undergoing open or minimally invasive elective distal pancreatectomy for all indications in 12 centres in the Netherlands and Italy. We excluded patients with an American Society of Anesthesiology (ASA) physical status of 4–5 or WHO performance status of 3–4, added by amendment following the death of a patient with ASA 4 due to a pre-existing cardiac condition. Patients were randomly assigned (1:1) intraoperatively by permuted blocks (size four to eight) to either no drain or prophylactic passive drain placement, stratified by annual centre volume (<40 or ≥40 distal pancreatectomies) and low risk or high risk of grade B or C POPF. High-risk was defined as a pancreatic duct of more than 3 mm in diameter, a pancreatic thickness at the neck of more than 19 mm, or both, based on the Distal Pancreatectomy Fistula Risk Score. Other patients were considered low-risk. The primary outcome was the rate of major morbidity (Clavien–Dindo score ≥III), and the most relevant secondary outcome was grade B or C POPF, grading per the International Study Group for Pancreatic Surgery. Outcomes were assessed up to 90 days postoperatively and analysed in the intention-to-treat population and per-protocol population, which only included patients who received the allocated treatment. A prespecified non-inferiority margin of 8% was compared with the upper limit of the two-sided 95% CI (Wald) of unadjusted risk difference to assess non-inferiority. This trial is closed and registered in the Netherlands Trial Registry, NL9116.

Findings Between Oct 3, 2020, and April 28, 2023, 376 patients were screened for eligibility and 282 patients were randomly assigned to the no-drain group (n=138; 75 [54%] women and 63 [46%] men) or the drain group (n=144; 73 [51%] women and 71 [49%] men). Seven patients in the no-drain group received a drain intraoperatively; consequently, the per-protocol population included 131 patients in the no-drain group and 144 patients in the drain group. The rate of major morbidity was non-inferior in the no-drain group compared with the drain group in the intention-to-treat analysis (21 [15%] *vs* 29 [20%]; risk difference –4·9 percentage points [95% CI –13·8 to 4·0]; $p_{non\text{-}inferiority}$=0·0022) and the per-protocol analysis (21 [16%] *vs* 29 [20%]; risk difference –4·1 percentage points [–13·2 to 5·0]; $p_{non\text{-}inferiority}$=0·0045). Grade B or C POPF was observed in 16 (12%) patients in the no-drain group and in 39 (27%) patients in the drain group (risk difference –15·5 percentage points [95% CI –24·5 to –6·5]; $p_{non\text{-}inferiority}$<0·0001) in the intention-to-treat analysis. Three patients in the no-drain group died within 90 days; the cause of death in two was not considered related to the trial. The third death was a patient with an ASA score of 4 who died after sepsis and a watershed cerebral infarction at second admission, leading to multiple organ failure. No patients in the drain group died within 90 days.

Interpretation A no-drain policy is safe in terms of major morbidity and reduced the detection of grade B or C POPF, and should be the new standard approach in eligible patients undergoing distal pancreatectomy.

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Research in context

Evidence before this study

Before the start of this trial, we performed a systematic literature review using PubMed, Embase, and the Cochrane Library database on studies published between database inception and Jan 1, 2021. The search terms included "distal pancreatectomy", "drain", "drainage", and synonyms for these terms. Inclusion criteria were randomised and non-randomised controlled trials and prospective and retrospective comparative studies on prophylactic drainage versus no drainage in patients undergoing distal pancreatectomy published in English, Dutch, Italian, and German. Our primary outcome was major morbidity (Clavien–Dindo score ≥III) and the main secondary outcomes were grade B or C postoperative pancreatic fistula (POPF) and radiological interventions. We identified five studies, of which four were retrospective studies and one was a randomised controlled trial, including a total of 2153 patients. Meta-analysis of the five studies showed a lower rate of major morbidity (risk ratio 0·55 [95% CI 0·42–0·72]) and grade B or C POPF (risk ratio 0·82 [0·68–0·99]) in the no-drain versus drain group. The rate of radiological interventions (risk ratio 0·85 [0·65–1·10]) was similar between groups.

Added value of this study

To our knowledge, our study is the first international, multicentre, randomised trial to compare a no-drain policy with prophylactic passive abdominal drainage after distal pancreatectomy in various POPF risk groups. This approach is relevant, as the value and need for drainage might differ between patients at low risk and high risk of POPF. Our study provides robust evidence for the safety of a no-drain policy in terms of major morbidity and grade B or C POPF in patients undergoing distal pancreatectomy, and explores outcomes in subgroups at low, intermediate, and high risk of POPF.

Implications of all the available evidence

On the basis of the results of this study, we expect that a no-drain policy will become the new standard approach in eligible patients undergoing distal pancreatectomy.

Introduction

Distal pancreatectomy is the standard surgical procedure for symptomatic benign, premalignant, and malignant diseases in the left part of the pancreas. For 12–25% of patients undergoing distal pancreatectomy, the post-operative course is complicated by postoperative pancreatic fistula (POPF), wherein pancreatic fluid with high amounts of amylase leaks into the abdominal cavity.[1] A POPF is considered a serious complication, as it might give rise to post-pancreatectomy haemorrhage, intra-abdominal infected collections, and sepsis. To mitigate the clinical course of POPF after distal pancreatectomy and prevent these secondary complications, prophylactic passive abdominal drainage is routine practice after distal pancreatectomy.[2,3]

Some have argued that prophylactic abdominal drainage after distal pancreatectomy can be omitted, especially in patients considered low risk, as leaks are non-infected, unlike after a pancreatoduodenectomy during which the intestinal tract is opened.[4] Moreover, a no-drain policy would free patients from the burden of a surgical drain and eliminate the risk of the drain actually facilitating infection with commensal skin flora and potentially converting a self-limiting and contained collection to a POPF.[5–8] Two systematic reviews of prophylactic abdominal drainage after distal pancreatectomy have suggested that it is safe to omit drainage, but they were mostly based on retrospective studies.[7,9] One multicentre, randomised trial found similar morbidity rates in patients after distal pancreatectomy with or without abdominal drainage.[6] However, this trial has not changed practice in many centres. No subgroup analyses for patients at low risk and high risk of POPF were conducted in this trial, and the value and need for drainage could differ between these risk categories.[10]

The scarcity of evidence in this area is illustrated by the 2023 Brescia guidelines, which concluded that no specific recommendations on prophylactic abdominal drainage after distal pancreatectomy could be made.[3] We therefore aimed to evaluate the hypotheses that a no-drain policy after distal pancreatectomy would not worsen the risk of major morbidity or POPF compared with prophylactic passive abdominal drainage.

Methods

Study design and participants

PANDORINA was an investigator-initiated, international, multicentre, open-label, randomised controlled, non-inferiority trial comparing a no-drain policy with prophylactic passive abdominal drainage in patients after distal pancreatectomy for benign, premalignant, and malignant indications. The study protocol has been published previously, describing the rationale and design of the study.[11] The study was done in ten centres of the Dutch Pancreatic Cancer Group and two centres in Italy. A list of the centres with their principal investigators and number of inclusions is provided in the appendix (p 10). Participating centres had to have performed at least ten distal pancreatectomies (any diagnosis) annually, and individual surgeons had to have performed at least 50 pancreatic resections and 20 distal pancreatectomies (any type, any diagnosis) in the past 5 years before trial enrolment. These conditions were chosen as a middle ground to recruit sufficient experience while preventing low external validity by only including very-high-volume centres. This trial complies with the principles of the

Department of Surgery, Leiden University Medical Center, Leiden, Netherlands (N Michiels MD, J S D Mieog MD); **Department of Surgery and Pulmonology, Erasmus MC Cancer Institute, Rotterdam, Netherlands** (Prof B G Koerkamp MD, Prof C H J van Eijck MD); **Department of Surgery, Catharina Hospital, Eindhoven, Netherlands** (Prof M D P Luyer MD); **Department of Surgery, University Medical Center Groningen, Groningen, Netherlands** (Prof J M Klaase MD); **Department of Surgery, Regional Academic Cancer Center Utrecht, University Medical Center Utrecht, Utrecht, Netherlands** (Prof I Q Molenaar MD); **Department of Surgery, Regional Academic Cancer Center Utrecht, St Antonius Hospital Nieuwegein, Utrecht, Netherlands** (Prof H C van Santvoort MD); **Department of Surgery, Radboud UMC, Nijmegen, Netherlands** (M W J Stommel MD); **Department of Surgery, Medisch Spectrum Twente, Enschede, Netherlands** (D J Lips MD); **Department of Surgery, Maastricht Universitair Medisch Centrum, Maastricht, Netherlands** (M M E Coolsen MD); **Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy** (M Ramera); **Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit, Department of Surgical, Oncological, and Gastroenterological Sciences, University of Padua, Padua, Italy** (G Marchegiani)

Correspondence to:
Prof Marc G Besselink, Department of Surgery, Amsterdam UMC, University of Amsterdam, Amsterdam 1081 HV, Netherlands
m.g.besselink@amsterdamUMC.nl

See **Online** for appendix

Declaration of Helsinki and the CONSORT guidelines for randomised controlled trials.[12] The institutional review boards of all participating centres approved the study protocol.

We enrolled patients aged 18 years or older who required elective, minimally invasive or open distal pancreatectomy with or without splenectomy for any indication. All patients provided written informed consent before randomisation. The exclusion criteria were pregnancy; distal pancreatectomy done as a secondary procedure during gastric or colonic resection; requirement for colonic resection due to cancer extension; requirement for additional hepatic resection; participation in another study that could have interfered with the outcomes of this study; arterial resections other than the splenic vessels; or an American Society of Anesthesiology (ASA) physical status of 4–5 or WHO performance status of 3–4. After approval by the Medical Ethical Committee of the Amsterdam University Medical Center (UMC), this last criterion was added by amendment on Feb 6, 2021, following the death of a patient with ASA 4 due to a pre-existing cardiac condition. It was thought that these patients' preoperative poor conditions could affect outcomes and acknowledged that many of the participating centres either did not operate on these patients or, if they did, initiated drainage as standard according to hospital protocols.

Randomisation and masking

All patients were centrally randomly assigned in a 1:1 ratio to drainage or no drainage by use of an online computer-controlled permuted-block randomisation module (Castor Electronic Data Capture; Ciwit, Amsterdam, the Netherlands). The block sizes were subject to random variation, varying from four to eight patients. Stratification was performed for annual centre volume (<40 or ≥40 distal pancreatectomies annually) and for patients at low risk or high risk of grade B or C POPF. High risk was defined as either a pancreatic duct diameter of more than 3 mm or a pancreatic thickness (at the neck) of more than 19 mm or both, based on the Distal Pancreatectomy Fistula Risk Score (D-FRS).[10] Other patients were considered at low risk. The entire randomisation process, including block sizes, was concealed from all local investigators except the trial coordinators. Numerical randomisation codes, to which only the principal investigator had access, were assigned to patients. The randomisation was performed intraoperatively once metastases had been excluded and the decision had been made to proceed with the resection. The operating surgeon contacted the study coordinator via telephone to randomly assign the patient. If it was decided to deviate from the assigned treatment during surgery, documentation of the reason for this choice was required. The source data were digitally stored and will be kept by the project leader for 15 years after the inclusion of the last patient. Patients, caregivers, investigators, and data analysts were not masked to treatment allocation.

Procedures

Eligible patients for the study were screened with the use of standard procedures, including multiphase CT, and were identified during an outpatient clinical visit in each individual participating centre. Baseline characteristics, including sex (male or female), were collected by the trial coordinator before randomisation. Data on race or ethnicity were not collected. Tumour size and parameters of the preoperative D-FRS (pancreatic duct diameter and pancreatic neck thickness) were assessed by a dedicated radiologist or surgeon on the last preoperative CT scan. Clinical data, including operative data and primary and secondary endpoint data, were collected postoperatively within a follow-up interval of 90 days by the principal investigator of the participating site using a web-based data management system with predefined electronic case report forms. For Dutch centres, required data were retrieved from the Dutch Pancreatic Cancer Audit and centrally checked by the study coordinator. The data were stored in a web-based data collection software (Castor Electronic Data Capture; CIWIT, Amsterdam, the Netherlands). Serious adverse events (mortality, surgical reintervention [reoperation], and ICU admission) were reported to the study coordinator from study start until the end of the study. Depending on the type of event, as defined in the protocol,[11] events were either reported to The Central Committee on Research Involving Human Subjects or the accredited Medical Ethics Committee that approved the protocol.

The surgical technique used for distal pancreatectomy has been described previously.[13,14] In short, transection of the pancreas was performed with one type of stapler (Echelon Powered stapler from Ethicon, a subsidiary of Johnson & Johnson Medical, Edinburgh, UK) by use of the progressive stepwise compression technique, as described by Asbun and colleagues.[15] Closure of the stapler was halted when resistance to closure was first felt, maintaining compression for approximately 15 s. Subsequently, the stapler compression was continued and halted when meeting resistance again. These steps were repeated until complete closure was reached, without rotating the stapler. Co-interventions for pancreatic stump closures, preoperative endoscopic injections, and the use of somatostatin analogues were not advised, and were only allowed when used already routinely in all patients undergoing distal pancreatectomy (ie, in both groups). In the drain group (control group), the abdominal drain was placed intraoperatively after randomisation. In the case of splenectomy, the drain, including the side holes, was placed beyond the former splenic bed with the tip next to the pancreatic transection margin while avoiding direct contact with the artery or vein stumps. The drain type and drain size were not standardised in the protocol, but rather according to local

clinical practice. Drain amylase concentrations were measured on days 1, 3, and 5 postoperatively (if the patient was still admitted to hospital), and the drain was removed on day 3 unless drain amylase concentrations exceeded three times the upper limit of the institution's range of serum amylase,[16] or when the fluid exceeded 200 mL in 24 h. Indications for imaging, radiological or endoscopic reintervention, start of antibiotic treatment, and removal of the abdominal drain were based on the PORSCH algorithm.[17] Postoperative care followed the enhanced recovery principles.[18]

Outcomes

The primary outcome was the rate of major morbidity, defined as complications with a Clavien–Dindo score of III or more.[19] Primary outcome data were centrally checked and analysed for all participating centres by the study coordinators EAvB and TMEvR. The most relevant secondary outcome was grade B or C POPF according to the definitions of the International Study Group for Pancreatic Surgery (ISGPS).[16] Other prespecified secondary outcomes included the occurrence of the grade B or C pancreatic-specific complications, delayed gastric emptying[20] and post-pancreatectomy haemorrhage,[21] as defined by the ISGPS; reoperation; percutaneous and endoscopic catheter drainage (hereafter combined and reported as radiological or endoscopic reintervention); wound infection; blood transfusion; length of hospital stay; in-hospital mortality; 90-day mortality; and readmission within 90 days after surgery. In the study protocol, the secondary outcome of abdominal collections was prespecified; however, this outcome was not recorded as it required standardised repeat imaging regardless of the clinical postoperative course of the patient. Definitions of outcomes are listed in the appendix (pp 2–3). All outcomes were assessed up to 90 days postoperatively. Start of adjuvant chemotherapy was mistakenly listed as a secondary outcome in the protocol when it was never intended to be collected. Post-hoc outcomes were complications (all grades), ICU admission, conversion, operative time, blood loss, staple time, stump management, C-reactive protein on day 3, time with drain in, and tumour size on pathology.

Statistical analysis

The sample size for the primary outcome of major morbidity was calculated on the basis of the following assumptions: a 2·5% one-sided significance level (α), 80% power (1–β), and a non-inferiority margin of 8% for major morbidity (proportion of patients not affected by postoperative major morbidity of 77% in the no-drain group and 70% in the drain group, based on the multicentre, randomised LEOPARD trial,[22] considering an expected majority of minimally invasive procedures). A non-inferiority margin of 8% was chosen as this margin represented the maximum allowable difference at which a no-drain policy could show non-inferiority, and was based on discussion within the study group and with a statistician. With this calculation, the minimum number of patients required was 272. Considering a potential dropout of 3% after randomisation, the total required sample size was 280 patients. The sample size for the most relevant secondary outcome of grade B or C POPF was calculated on the basis of the following assumptions: a 2·5% one-sided significance level (α), 80% power (1–β), and a non-inferiority margin of 8% for grade B or C POPF (proportion of patients not affected by grade B or C POPF of 81% in the no-drain group and 75% in the drain group, based on the trial of van Buren and colleagues[6]), resulting in a sample size of 274 patients. Allowing for a 3% dropout rate, the total required sample size was 282 patients. The larger sample size of 282 patients was used to ensure sufficient statistical power to assess non-inferiority for both the primary and most relevant secondary outcome.

All analyses were done in the intention-to-treat population (ie, comprising all randomly assigned patients). A prespecified per-protocol analysis was done for the primary outcome, which comprised only patients who received the allocated treatment. The primary and most relevant secondary outcome were expressed in proportions and presented with unadjusted risk differences between the no-drain and drain groups, with corresponding two-sided 95% CIs obtained with the Wald test. The upper limit of the 95% CI was compared with the predefined 8% non-inferiority margin for the primary and most relevant secondary outcome to test non-inferiority, with the corresponding $p_{non\text{-}inferiority}$ following Dunnett and Gent.[23] We tested for superiority post-hoc if limits of non-inferiority were exceeded (if the 95% CI did not include the non-inferiority margin of 0% to 8%). For other secondary outcomes, categorical variables were compared with the χ^2 or Fisher's exact test, as appropriate, and expressed as proportions, including risk differences with corresponding 95% CIs between the no-drain and drain groups. Normally distributed continuous variables were compared with the independent samples *t* test and values were expressed as mean (SD). Non-parametrically distributed continuous variables were compared by use of the Mann–Whitney *U* test and values were expressed as median (IQR).

Exploratory post-hoc per-protocol analyses were performed for all secondary outcomes and post-hoc outcomes. We did post-hoc subgroup analyses in low, intermediate, and high POPF risk groups (based on the D-FRS; low risk being D-FRS of <10%; intermediate risk being D-FRS of 10–25%; high risk being D-FRS of >25%)[10] and in several low-risk and high-risk clinical scenarios. These scenarios were: high-volume (performing ≥15 distal pancreatectomies annually) versus low-volume (performing <15 distal pancreatectomies annually) centres; blood loss of 500 mL or less versus more than 500 mL blood loss; ASA scores of less than 3 versus 3

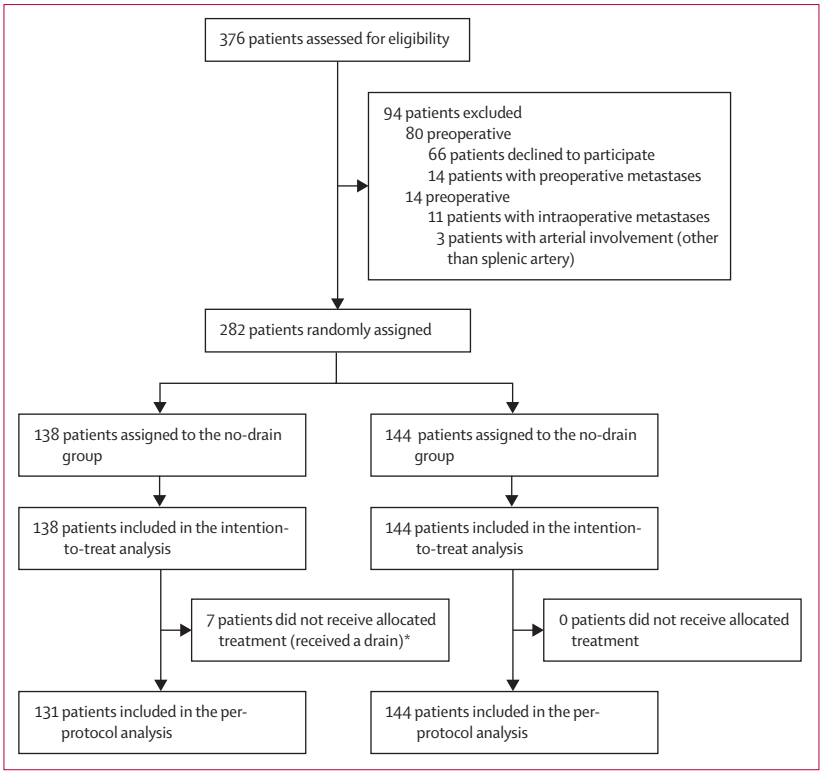

Figure 1: **Trial profile**
*Due to surgeon's intraoperative decision considering the patient at high risk for grade B or C postoperative pancreatic fistula: fractured pancreatic parenchyma; comorbidities potentially leading to postoperative sepsis; exposed vessels; or transection near the vessels.

or greater; BMI of less than 30 kg/m² versus 30 kg/m² or higher; and patients without versus with extended resection. Extended resection comprised any kind of gastric resection, colon and relevant structures of the mesocolon, small bowel, portal vein, superior mesenteric vein or mesenteric vein, hepatic artery, coeliac artery, superior mesenteric artery, inferior vena cava, left adrenal gland, left kidney, diaphragmatic crura, diaphragm, or liver.[24] In these post-hoc subgroup analyses, treatment-effect heterogeneity was assessed by use of interaction tests. Treatment effect estimates in subgroups were visualised by use of separate forest plots, with risk differences and corresponding 95% CIs, for the primary outcome of major morbidity and the most relevant secondary outcome of grade B or C POPF. Two post-hoc sensitivity analyses were conducted for the primary and most relevant secondary outcome, comparing groups with the χ^2 test: excluding patients with ASA scores of 3 or more and excluding patients with pancreatic ductal adenocarcinoma (PDAC). A post-hoc analysis was done to analyse the time to diagnosis of grade B or C POPF (all and those requiring reintervention) in both groups using the Mann–Whitney *U* test. For statistical significance, a two-tailed p value of less than 0·05 was used. Statistical analyses were done with SPSS version 26.0 and R version 4.3.1. A data safety monitoring board was initially set up for this study, but, as the safety risk was scored as negligible, the Medical Ethics Committee or Amsterdam UMC deemed it unnecessary. The study was registered in the Netherlands Trial Registry, NL9116.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Oct 3, 2020, and April 28, 2023, 376 patients with left-sided, benign, premalignant, and malignant pancreatic lesions were screened for eligibility, after which 94 patients were excluded (80 patients preoperatively and 14 patients intraoperatively; figure 1). 282 patients were randomly assigned and included in the intention-to-treat population: 138 patients in the no-drain group (75 [54%] women and 63 [46%] men) and 144 patients in the drain group (73 [51%] women and 71 [49%] men). No patients were excluded after randomisation. The per-protocol population included 144 patients in the drain group and 131 patients in the no-drain group (73 [56%] women and 58 [44%] men; appendix p 4) after exclusion of seven patients who intraoperatively received a drain. The rationale for drain placement in these patients was based on the surgeon's intraoperative decision; these patients were deemed to be high risk for a grade B or C POPF due to a fractured pancreatic parenchyma during stapling, comorbidities in combination with which a potential grade B or C POPF could lead to sepsis (which the patient would not tolerate), or exposed vessels or transection near the vessels. There were no patients with missing data for the primary outcome.

Baseline characteristics and operative details are shown in tables 1 and 2 for the intention-to-treat population and in the appendix (pp 4–5) for the per-protocol population. The three most common indications for distal pancreatectomy in both the no drain and drain groups were PDAC, pancreatic neuroendocrine tumour, and non-invasive intraductal papillary mucinous neoplasm. Baseline imbalances between the no-drain and drain groups were observed in the proportions of patients with PDAC (38% *vs* 30%) and ASA scores of 3 or more (30% *vs* 24%). 44 (32%) patients were deemed to be low risk for POPF on the basis of D-FRS, 61 (44%) patients were intermediate risk, and 33 (24%) patients were high risk. In the drain group, 37 (26%) patients were low risk, 77 (53%) patients were intermediate risk, and 30 (21%) patients were high risk. A minimally invasive distal pancreatectomy was done in 100 (72%) patients in the no-drain group and in 106 (74%) patients in the drain group (table 1). In five patients (2% of all minimally invasive procedures), a conversion was required: in two patients (one in the no-drain group and one in the

drain group) because of bleeding of the splenic artery and in three patients (one in the no-drain group and two in the drain group) because of a lack of overview.

In the intention-to-treat analysis, the primary outcome of major morbidity (Clavien–Dindo grade III or higher) occurred in 21 (15%) patients in the no-drain group and in 29 (20%) patients in the drain group (risk difference –4·9 percentage points [95% CI –13·8 to 4·0]), thus confirming non-inferiority of the no-drain approach ($p_{non\text{-}inferiority}$=0·0022; table 2). The predefined most relevant secondary outcome, grade B or C POPF, was observed in 16 (12%) patients in the no-drain group and in 39 (27%) patients in the drain group (risk difference –15·5 percentage points [95% CI –24·5 to –6·5]; $p_{non\text{-}inferiority}$<0·0001). Here, the limits of non-inferiority were exceeded and superiority of the no-drain approach was observed when testing for superiority ($p_{superiority}$=0·0010). In the per-protocol analysis (appendix p 5), major morbidity occurred in 21 (16%) of 131 patients in the no-drain group and in 29 (20%) of 144 patients in the drain group (risk difference –4·1 percentage points [–13·2 to 5·0]), again confirming the non-inferiority of the no-drain approach ($p_{non\text{-}inferiority}$=0·0045). Grade B or C POPF was observed in 15 (11%) patients in the no-drain group and in 39 (27%) patients in the drain group (risk difference –15·6 percentage points [–24·7 to –6·5]; $p_{non\text{-}inferiority}$<0·0001), per the per-protocol analysis. When tested for superiority, this was again significant ($p_{superiority}$=0.0011). Post-hoc analysis of all patients with a grade B or C POPF showed that median time to diagnosis was significantly longer in the drain group than in the no-drain group (21·0 days [IQR 6·0–21·0] *vs* 9·0 days [4·0–14·3], p=0·011; appendix p 6). However, this difference could be attributed to the fact that the diagnosis of grade B POPF was only confirmed in the drain group after 21 days of drainage. Post-hoc analysis of patients with a grade B or C POPF that required reintervention showed no significant difference between the groups in median time to diagnosis (7·5 days [3·0–22·3] in the drain group *vs* 9·0 days [4·0–14·3] in the no-drain group, p=0·89; appendix p 6).

No differences were found in the rates of delayed gastric emptying, post-pancreatectomy haemorrhage, wound infection, blood transfusion, radiological and endoscopic interventions, readmission within 90 days, and reoperations (table 2). Reasons for reoperations were the occurrence of grade B or C post-pancreatectomy haemorrhage (two patients in the no-drain group and two patients in the drain group) or were unknown (four patients in the no-drain group and two patients in the drain group). The length of hospital stay was calculated to be significantly shorter in the no-drain group, although the medians were the same (6 days [IQR 4–7] *vs* 6 days [5–8]; p=0·026). Post-hoc, no difference was found between groups in admission to intensive care, although the rate of overall complications (combining minor and major morbidity) was

	No-drain group (n=138)	Drain group (n=144)
Sex		
Female	75 (54%)	73 (51%)
Male	63 (46%)	71 (49%)
Age, years	62·9 (12·5)	61·9 (15·5)
BMI, kg/m²	26·6 (4·5)	26·3 (4·4)
BMI <30 kg/m²	107 (78%)	117 (81%)
BMI ≥30 kg/m²	31 (22%)	27 (19%)
ASA score <3	96 (70%)	110 (76%)
ASA score ≥3	42 (30%)	34 (24%)
History of diabetes	32 (23%)	28 (19%)
History of abdominal surgery	56 (41%)	53 (37%)
Neoadjuvant treatment		
Chemotherapy	12 (9%)	13 (9%)
Chemoradiation	2 (1%)	3 (2%)
Other	2 (1%)	3 (2%)
Preoperative working diagnosis		
PDAC	52 (38%)	43 (30%)
pNET	31 (22%)	34 (24%)
IPMN	27 (20%)	32 (22%)
MCN	13 (9%)	17 (12%)
SPN	2 (1%)	6 (4%)
SCN	2 (1%)	2 (1%)
Pancreatitis	6 (4%)	3 (2%)
Other or unknown	5 (4%)	7 (5%)
Tumour size, mm	28 (20–40)	28 (20–40)
Pancreatic duct diameter, mm	1 (1–3)	1 (1–2)
Pancreatic neck thickness, mm	12 (11–16)	12 (11–16)
Use of somatostatin analogues	0	0
POPF risk groups		
Low-risk POPF (D-FRS <10%)	44 (32%)	37 (26%)
Intermediate-risk POPF (D-FRS 10–25%)	61 (44%)	77 (53%)
High-risk POPF (D-FRS >25%)	33 (24%)	30 (21%)
Annual centre volume		
<40 distal pancreatectomies	88 (64%)	92 (64%)
≥40 distal pancreatectomies	50 (36%)	52 (36%)
Low-volume centre (<15 distal pancreatectomies annually)	43 (31%)	51 (35%)
High-volume centre (≥15 distal pancreatectomies annually)	95 (69%)	93 (65%)
Type of approach		
Robot-assisted	49 (36%)	54 (38%)
Laparoscopic	51 (37%)	52 (36%)
Open	38 (28%)	38 (26%)
Splenectomy	87 (63%)	93 (65%)

Data are n (%), mean (SD), or median (IQR). ASA=American Society of Anesthesiology. PDAC=pancreatic ductal adenocarcinoma. pNET=pancreatic neuroendocrine tumour. IPMN=intraductal papillary mucinous neoplasm. MCN=mucinous cystic neoplasm. SPN=solid pseudopapillary neoplasm. SCN=serous cystic neoplasm. POPF=postoperative pancreatic fistula. D-FRS=Distal Pancreatectomy Fistula Risk Score.

Table 1: **Baseline characteristics in the intention-to-treat population**

	No-drain group (n=138)	Drain group (n=144)	Risk difference, percentage points (95% CI)	p value
Primary outcome				
Complications of Clavien–Dindo grade ≥III	21 (15%)	29 (20%)	−4·9 (−13·8 to 4·0)	0·0022 ($p_{non\text{-}inferiority}$)
Secondary outcomes				
Postoperative pancreatic fistula of grades B and C	16 (12%)	39 (27%)	−15·5 (−24·5 to −6·5)	<0·0001 ($p_{non\text{-}inferiority}$); 0·0010 ($p_{superiority}$)
Grade B	14 (10%)	39 (27%)	−17·0 (−25·8 to −8·2)	..
Grade C	2 (1%)	0	1·5 (−0·5 to 3·5)	..
Delayed gastric emptying of grades B and C	2 (1%)	5 (3%)	−2·0 (−5·6 to 1·6)	0·45
Grade B	1 (1%)	5 (3%)	−2·8 (−6·1 to 0·5)	..
Grade C	1 (1%)	0	0·7 (−0·7 to 2·1)	..
Post-pancreatectomy haemorrhage of grades B and C	5 (4%)	7 (5%)	−1·3 (−6·0 to 3·4)	0·61
Grade B	4 (3%)	5 (3%)	−0·6 (−4·7 to 3·5)	..
Grade C	1 (1%)	2 (1%)	−0·7 (−3·1 to 1·7)	..
Wound infection	3 (2%)	10 (7%)	−4·7 (−9·5 to 0·1)	0·056
Intraoperative blood transfusion	1 (1%)	1 (1%)	0·0 (−2·0 to 2·0)	0·74
Radiological or endoscopic reintervention	14 (10%)	24 (17%)	−6·6 (−14·5 to 1·3)	0·11
Reoperation	6 (4%)	4 (3%)	1·5 (−2·8 to 5·8)	0·48
Length of hospital stay, days	6 (4 to 7)	6 (5 to 8)	..	0·026
Readmission within 90 days	21 (15%)	25 (17%)	−2·2 (−10·8 to 6·4)	0·63
In-hospital mortality	0	0	0·0 (0·0 to 0·0)	NA
90-day mortality	3 (2%)	0	2·2 (−0·3 to 4·7)	0·12
Additional post-hoc outcomes				
Complications, all grades	46 (33%)	73 (51%)	−17·4 (−28·7 to −6·1)	0·0032
ICU admission	8 (6%)	4 (3%)	3·0 (−1·7 to 7·7)	0·21
Conversion*	2/100 (2%)	3/106 (3%)	−0·8 (−4·4 to 2·8)	0·53
Operative time, min	194 (168 to 251)	215 (180 to 269)	..	0·054
Blood loss, mL	100 (50 to 250)	100 (50 to 300)	..	0·47
Staple time, s	240 (180 to 240)	240 (180 to 240)	..	0·30
Stump management†				
Sutures	2 (1%)	0	1·4 (0·6 to 3·4)	0·24
CRP on day 3, mg/L	184 (131 to 244)	188 (138 to 258)	..	0·57
Time with drain in, days	4 (3 to 5)	4 (3 to 15)	..	0·17
Tumour size on pathology, mm	28 (20 to 43)	30 (19 to 48)	..	0·59

Data are n (%), n/N (%), or median (IQR), unless otherwise specified. Risk difference is unadjusted. ICU=intensive care unit. CRP=C-reactive protein. *Conversion percentages were calculated by use of the number of minimally invasive procedures as the denominator. †Additional sutures were placed after stapling of the pancreas. Both patients had an uneventful postoperative course.

Table 2: **Postoperative outcomes up to 90 days in the intention-to-treat population**

lower in the no-drain group compared with the drain group (46 [33%] patients *vs* 73 [51%] patients; p=0·0032; table 2).

There was no in-hospital mortality in either group. 90-day mortality did not significantly differ between the no-drain and drain groups (three [2%] patients *vs* zero patients; p=0·12). Reasons for death in the no-drain group were sepsis and a watershed cerebral infarction at a second admission, leading to multiple organ failure and death in a patient with an ASA score of 4 on day 23 due to a pre-existing cardiac condition; euthanasia for metastasised disease, which was unknown both preoperatively and intraoperatively, on day 72; and respiratory insufficiency due to a pneumonia after aspiration at a second admission on day 65. Additional details about these deaths are provided in the appendix (p 9). In the latter two patients, the cause of death was not suspected to be related to the trial: while the patient with an ASA score of 4 had no initial suspicious indications linking death to the trial we could not definitively exclude the possibility that the patient's complications were unrelated to the omission of the drain, and we therefore amended our exclusion criteria to avoid further such events.

In the post-hoc subgroup analysis of patients at low risk of POPF, the risk of major morbidity was significantly lower in the no-drain group than in the drain group (risk difference −14·4 percentage points

[95% CI –28·4 to –0·4]; figure 2). The risk of major morbidity did not differ significantly between no drain and drain in the intermediate-risk and high-risk POPF groups. There was no evidence for an overall interaction of preoperative POPF risk with treatment assignment on the rate of major morbidity ($p_{interaction}$=0·57). In the low-risk and intermediate-risk POPF groups, the no-drain group had a significantly lower risk of grade B or C POPF than the drain group (–17·9 percentage points [95% CI –30·9 to –5·0] and –14·8 percentage points [–27·1 to –2·7]; figure 3). There was no evidence for an overall interaction of preoperative POPF risk group with treatment allocation on the rate of grade B or C POPF ($p_{interaction}$=0·42).

In post-hoc analyses of high-risk and low-risk clinical scenarios, a lower risk of grade B or C POPF was observed in the no-drain group compared with the drain group in low-volume centres (risk difference –21·7 percentage points [95% CI –37·8 to –5·6]). In all other high-risk subgroups, no significant differences were observed in the rate of major morbidity or grade B or C POPF between the no-drain and drain groups (figures 2, 3). There was no treatment-effect heterogeneity of high-risk versus low-risk clinical scenarios. Post-hoc sensitivity analyses excluding patients with ASA scores of 3 or more or excluding patients with PDAC showed concordant results to analyses in the total cohort (appendix pp 7–8).

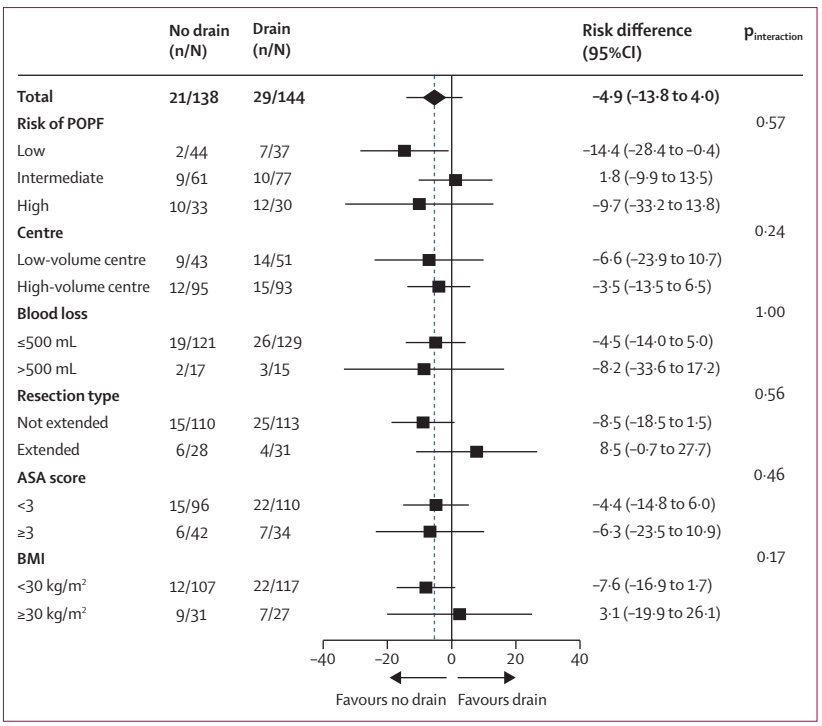

Figure 2: **Forest plot of the effect of no drain placement versus drain placement on major morbidity**
Total and post-hoc subgroup analyses are shown. Risk differences with corresponding 95% CIs are presented in percentage points. Note: axis is log scale. ASA=American Society of Anesthesiology. POPF=postoperative pancreatic fistula.

Discussion

This international, multicentre, open-label, randomised controlled, non-inferiority trial showed the non-inferiority of a no-drain policy versus prophylactic passive abdominal drainage in patients after distal pancreatectomy in terms of major morbidity and grade B and C POPF. Outcomes differed in the three risk groups for POPF. A no-drain policy reduced the risk of major morbidity and POPF in patients who were at low risk, the risk of POPF alone in patients who were at intermediate risk, and was no different to a drain policy in patients at high risk.

One previous multicentre randomised trial performed in the USA and Canada found no differences in the rate of grade 3 or higher complications (26% *vs* 29%; p=0·48) or grade B or C POPF (12% *vs* 18%; p=0·11) between a no-drain policy and routine drainage after distal pancreatectomy.[6] Although this trial provided high-quality evidence to omit drainage, in most centres and countries, this trial did not change clinical practice, and routine drainage has remained standard practice. This lack of change might be explained by the fact that no patient benefit was shown from omitting drainage. This is confirmed by the 2023 Brescia guidelines giving no clear recommendations on drainage, despite the available evidence.[3] A 2022 meta-analysis, which included the previous randomised trial alongside four retrospective studies, observed significantly lower rates of major morbidity, POPF, and readmission to hospital with no

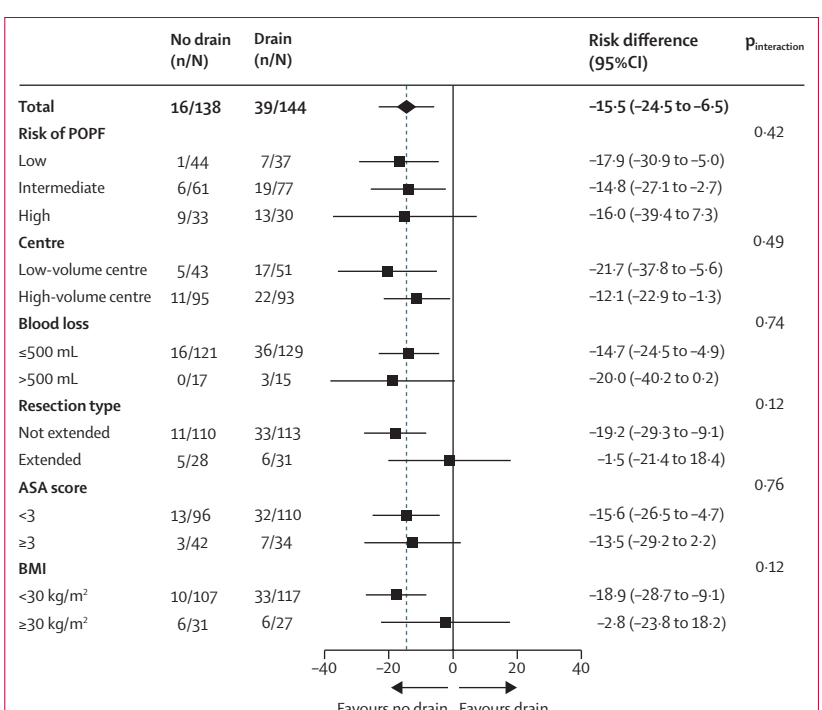

Figure 3: **Forest plot of the effect of no drain placement versus drain placement on grade B or C POPF**
Total and post-hoc subgroup analyses are shown. Risk differences with corresponding 95% CIs are presented in percentage points. Note: axis is log scale. ASA=American Society of Anesthesiology. POPF=postoperative pancreatic fistula.

drainage versus drainage.[9] The authors concluded that prophylactic drain placement should be reconsidered, and that a future randomised trial with POPF risk-adjusted analyses was indicated.[9] Subsequently, our group developed the D-FRS, aiming to differentiate between patients at high risk and low risk of POPF.[10] In the current trial, the preoperative D-FRS was used to stratify patients according to their risk of POPF, aiming to ensure balanced groups and facilitate reliable subgroup analyses. Nevertheless, a confounding effect of the division line of the pancreas at the neck, body, or tail might still exist and is an acknowledged limitation of the D-FRS.

Our trial provides highly robust evidence that a no-drain policy after distal pancreatectomy is safe in terms of major morbidity. Although the no-drain group had a higher, but not significant, 90-day mortality rate compared with the drain group, the deaths of two of the three patients in the no-drain group were not suspected to be related to the trial. Consequently, the mortality rates remained within the generally accepted range for distal pancreatectomy in the literature.[25,26] Moreover, a no-drain policy was non-inferior to a drain policy with regards to POPF rate and significantly shortened hospital stay, although the clinical relevance of the result for hospital stay is difficult to interpret due to the equal median values of both groups.

A fluid collection at the transection site is common after distal pancreatectomy, probably because of some extent of leakage of pancreatic fluids. This fluid collection is not necessarily problematic, much like a peripancreatic sterile collection in pancreatic trauma and pancreatitis, as long as it remains non-infected and asymptomatic. Typically, such collections are self-limiting. We hypothesise that introduction of a drain (as in prophylactic abdominal drainage) could actually facilitate the development of a POPF by, for example, facilitating infection with commensal skin flora. The results of this trial provide supporting evidence for this hypothesis. However, in patients with a drain in situ a POPF might be detected earlier or more frequently than in patients without a drain, due to the prolonged drainage or high amylase drain concentrations. For this reason, major morbidity was chosen as the primary outcome.

This study has several limitations that should be considered. First, specific drain-related patient symptoms or complications were not documented, which could have provided valuable insights into patient satisfaction. Second, standardised imaging was not conducted in patients in the no-drain group, which could have quantified the extent to which asymptomatic collections occur. Imaging was not done as this was a pragmatic trial and asymptomatic collections are treated conservatively in clinical practice. Third, this study does not provide a clear answer as to in which patients drainage should be recommended. In patients with a high risk of postoperative bleeding (coagulation disorders or use of anticoagulation), it cannot be ruled out that drainage prevents major morbidity. Additionally, patients with an ASA score of 4–5 or WHO scores of 3–4 were excluded, so the trial's findings do not apply to this category of patients. To gain more insight into high-risk clinical scenarios, several post-hoc subgroup analyses were done in which no additional risk for a no-drain policy could be identified. However, these subgroup analyses were suboptimally powered to detect treatment-effect heterogeneity and therefore do not provide definitive conclusions for these groups. Fourth, drain type and drain size were not standardised across centres. All centres used passive drainage rather than suction drainage or routine drain irrigation or rinsing; therefore, the findings do not apply to other drain strategies. Fifth, all staplers and part of the salary required for this investigator-initiated study were provided by a corporate sponsor, who had no role in the study.[27] In contrast to previously published studies, a standardised stump-closing technique was applied using the same surgical stapler in all participating centres.[15] Although one type of stapler was used to minimise heterogeneity, this approach might have potentially resulted in diminished external validity. However, a 2021 randomised trial reported no differences in POPF rates after distal pancreatectomy using different types of staplers.[28] Furthermore, there are currently no data available that suggest differences in outcomes with different staplers. Sixth, there was a difference of 7–8 percentage points in two baseline variables between the groups (ASA score ≥3 and PDAC). The implications of these differences are expected to be marginal on the outcomes. Both variables were higher (indicating more severe disease) in the no-drain group versus the drain group, but non-inferiority was still shown. Two post-hoc sensitivity analyses excluding patients with ASA scores of 3 or more or patients with PDAC showed concordant results with the main analysis. Finally, we did not adjust our primary analyses by stratification variables.

Major strengths of the study were the stratification based on POPF risk and the standardised technique for pancreatic transection, with the progressive stepwise compression technique used in all patients.[13,15] This technique aims to reduce the risk of POPF by preventing damage to the pancreatic parenchyma through stapling.[15] Furthermore, due to the intraoperative randomisation, the number of dropouts was minimised.

To conclude, this randomised controlled, non-inferiority trial provides strong evidence for the safety of a no-drain policy after distal pancreatectomy in terms of major morbidity. The no-drain policy was also non-inferior to drainage with regards to the rate of grade B or C POPF. In patients at low risk of POPF, a no-drain policy reduced the rates of major morbidity and POPF in post-hoc analyses. No safety risk of a no-drain policy was found in various subgroups at clinical high risk. We expect these results to be practice-changing and encourage the implementation of a no-drain policy as the

new standard approach in eligible patients undergoing distal pancreatectomy.

Contributors

EAvB, AB, FLV, CHJvE, and MGB were involved in study conceptualisation and design. All authors were involved in data acquisition. EAvB and TMEvR had full access to all the data and verified the data. EAvB, AB, TMEvR, and MGB did the analyses and interpretation of data. RS, CHJvE, and MGB provided supervision during conceptualisation, design, data acquisition, data analyses, data interpretation, drafting of the manuscript, and final approval. EAvB, TMEvR, and MGB wrote the original manuscript draft. All authors revised the manuscript critically for important intellectual content and provided final approval of the version to be published. All authors had full access to the data of their centre, and had final responsibility for the decision to submit for publication.

Declaration of interests

MAH received grants for investigator-initiated studies from Ethicon, Medtronic, and Intuitive Surgical. MGB received grants for investigator-initiated studies from Ethicon, Medtronic, OncoSil, and Intuitive Surgical. DJL received a proctoring grant from Intuitive Surgical. GM received personal consulting fees for clinical trial design from OncoSil Medical and participates in the advisory board of OncoSil Medical. CHJvE received a consultancy grant from AIM ImmunoTech. All other authors declare no competing interests.

Data sharing

De-identified individual participant data collected in the PANDORINA trial can be made available upon request by contacting the principal investigators (RS, CHJvE, and MGB), who will review all requests. There are no date restrictions on the availability of data. The PANDORINA investigators will be allowed to approve all research performed with the shared data.

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References

1 Diener MK, Seiler CM, Rossion I, et al. Efficacy of stapler versus hand-sewn closure after distal pancreatectomy (DISPACT): a randomised, controlled multicentre trial. *Lancet* 2011; **377:** 1514–22.

2 Asbun HJ, Moekotte AL, Vissers FL, et al. The Miami international evidence-based guidelines on minimally invasive pancreas resection. *Ann Surg* 2020; **271:** 1–14.

3 Abu Hilal M, van Ramshorst TME, Boggi U, et al. The Brescia internationally validated European guidelines on minimally invasive pancreatic surgery (EGUMIPS). *Ann Surg* 2024; **279:** 45–57.

4 Demir E, Abdelhai K, Demir IE, et al. Association of bacteria in pancreatic fistula fluid with complications after pancreatic surgery. *BJS Open* 2020; **4:** 432–37.

5 Fisher WE. Intraperitoneal drainage and pancreatic resection. *Adv Surg* 2018; **52:** 205–22.

6 Van Buren G II, Bloomston M, Schmidt CR, et al. A prospective randomized multicenter trial of distal pancreatectomy with and without routine intraperitoneal drainage. *Ann Surg* 2017; **266:** 421–31.

7 Lyu Y, Cheng Y, Wang B, Zhao S, Chen L. Peritoneal drainage or no drainage after pancreaticoduodenectomy and/or distal pancreatectomy: a meta-analysis and systematic review. *Surg Endosc* 2020; **34:** 4991–5005.

8 Conlon KC, Labow D, Leung D, et al. Prospective randomized clinical trial of the value of intraperitoneal drainage after pancreatic resection. *Ann Surg* 2001; **234:** 487–93.

9 van Bodegraven EA, van Ramshorst TME, Balduzzi A, et al. Routine abdominal drainage after distal pancreatectomy: meta-analysis. *Br J Surg* 2022; **109:** 486–88.

10 De Pastena M, van Bodegraven EA, Mungroop TH, et al. Distal Pancreatectomy Fistula Risk Score (D-FRS): development and international validation. *Ann Surg* 2022; **277:** e1099–105.

11 Vissers FL, Balduzzi A, van Bodegraven EA, et al. Prophylactic abdominal drainage or no drainage after distal pancreatectomy (PANDORINA): a binational multicenter randomized controlled trial. *Trials* 2022; **23:** 809.

12 Rennie D. CONSORT revised–improving the reporting of randomized trials. *JAMA* 2001; **285:** 2006–07.

13 Asbun HJ, Stauffer JA. Laparoscopic approach to distal and subtotal pancreatectomy: a clockwise technique. *Surg Endosc* 2011; **25:** 2643–49.

14 Abu Hilal M, Takhar AS. Laparoscopic left pancreatectomy: current concepts. *Pancreatology* 2013; **13:** 443–48.

15 Asbun HJ, Van Hilst J, Tsamalaidze L, et al. Technique and audited outcomes of laparoscopic distal pancreatectomy combining the clockwise approach, progressive stepwise compression technique, and staple line reinforcement. *Surg Endosc* 2020; **34:** 231–39.

16 Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. *Surgery* 2017; **161:** 584–91.

17 Smits FJ, Henry AC, Besselink MG, et al. Algorithm-based care versus usual care for the early recognition and management of complications after pancreatic resection in the Netherlands: an open-label, nationwide, stepped-wedge cluster-randomised trial. *Lancet* 2022; **399:** 1867–75.

18 Wilmore DW, Kehlet H. Management of patients in fast track surgery. *BMJ* 2001; **322:** 473–76.

19 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240:** 205–13.

20 Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2007; **142:** 761–68.

21 Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery* 2007; **142:** 20–25.

22 de Rooij T, van Hilst J, van Santvoort H, et al. Minimally invasive versus open distal pancreatectomy (LEOPARD): a multicenter patient-blinded randomized controlled trial. *Ann Surg* 2019; **269:** 2–9.

23 Dunnett CW, Gent M. Significance testing to establish equivalence between treatments, with special reference to data in the form of 2X2 tables. *Biometrics* 1977; **33:** 593–602.

24 Hartwig W, Vollmer CM, Fingerhut A, et al. Extended pancreatectomy in pancreatic ductal adenocarcinoma: definition and consensus of the International Study Group for Pancreatic Surgery (ISGPS). *Surgery* 2014; **156:** 1–14.

25 Giani A, van Ramshorst T, Mazzola M, et al. Benchmarking of minimally invasive distal pancreatectomy with splenectomy: European multicentre study. *Br J Surg* 2022; **109:** 1124–30.

26 van Ramshorst TME, Giani A, Mazzola M, et al. Benchmarking of robotic and laparoscopic spleen-preserving distal pancreatectomy by using two different methods. *Br J Surg* 2022; **110:** 76–83.

27 Probst P, Knebel P, Grummich K, et al. Industry bias in randomized controlled trials in general and abdominal surgery: an empirical study. *Ann Surg* 2016; **264:** 87–92.

28 Wennerblom J, Ateeb Z, Jönsson C, et al. Reinforced versus standard stapler transection on postoperative pancreatic fistula in distal pancreatectomy: multicentre randomized clinical trial. *Br J Surg* 2021; **108:** 265–70.