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Summary

Background Postoperative surgical site infections are one of the most frequent complications after open abdominal surgery, and triclosan-coated sutures were developed to reduce their occurrence. The aim of the PROUD trial was to obtain reliable data for the effectiveness of triclosan-coated PDS Plus sutures for abdominal wall closure, compared with non-coated PDS II sutures, in the prevention of surgical site infections.

Methods This multicentre, randomised controlled group-sequential superiority trial was done in 24 German hospitals. Adult patients (aged ≥18 years) who underwent elective midline abdominal laparotomy for any reason were eligible for inclusion. Exclusion criteria were impaired mental state, language problems, and participation in another intervention trial that interfered with the intervention or outcome of this trial. A central web-based randomisation tool was used to randomly assign eligible participants by permuted block randomisation with a 1:1 allocation ratio and block size 4 before mass closure to either triclosan-coated sutures (PDS Plus) or uncoated sutures (PDS II) for abdominal fascia closure. The primary endpoint was the occurrence of superficial or deep surgical site infection according to the Centers for Disease Control and Prevention criteria within 30 days after the operation. Patients, surgeons, and the outcome assessors were masked to group assignment. Interim and final analyses were by modified intention to treat. This trial is registered with the German Clinical Trials Register, number DRKS00000390.

Findings Between April 7, 2010, and Oct 19, 2012, 1224 patients were randomly assigned to intervention groups (607 to PDS Plus, and 617 to PDS II), of whom 1185 (587 PDS Plus and 598 PDS II) were analysed by intention to treat. The study groups were well balanced in terms of patient and procedure characteristics. The occurrence of surgical site infections did not differ between the PDS Plus group (87 [14·8%] of 587) and the PDS II group (96 [16·1%] of 598; OR 0·91, 95% CI 0·66–1·25; p=0·64). Serious adverse events also did not differ between the groups—146 of 583 (25·0%) patients treated with PDS Plus had at least one serious adverse event, compared with 138 of 602 (22·9%) patients treated with PDS II; p=0·39).

Interpretation Triclosan-coated PDS Plus did not reduce the occurrence of surgical site infection after elective midline laparotomy. Innovative, multifactorial strategies need to be developed and assessed in future trials to reduce surgical site infections.

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Study Centre of the German Surgical Society (M K Diener MD, C Doerr-Harim MD), **Department of General, Visceral and Transplantation Surgery** (M K Diener, P Knebel MD, T Hackert MD, A Ulrich MD, Prof M W Büchler MD), **Institute of Medical Biometry and Informatics** (Prof M Kieser PhD, C Klose), **and Department of Vascular and Endovascular Surgery** (A Hyhlik-Dürr MD), **University of Heidelberg, Heidelberg, Germany; Department of General and Visceral Surgery, University Medical Center, Georg-August-Universität, Göttingen, Germany** (P Schüler MD); **Department of General, Visceral, Transplantation, Vascular and Thoracic Surgery, Ludwig-Maximilians-Universität Munich, Großhadern Campus, Munich, Germany** (T S Schiergens MD); **Visceral and Vascular Surgery, Vivantes Klinikum Neukölln, Berlin, Germany** (V Atanassov MD); **Department of General, Visceral, Vascular and Thoracic Surgery, Campus Charité Mitte, Berlin, Germany** (J Neudecker MD); **Department of General, Visceral and Trauma Surgery, St Josefs Hospital Dortmund-Hörde, Dortmund, Germany** (E Stein MD); **Clinic for General and Visceral Surgery, Unfallkrankenhaus Berlin,**

Introduction

Postoperative surgical site infections are one of the most common complications after open abdominal surgery, and represent 14% of all nosocomial infections and roughly 5% of all surgical complications.[1] The frequency of these infections after midline laparotomy varies between 12% and 16%, depending on definition, patient population, and study design.[2]

In view of the many laparotomies undertaken worldwide, the substantial occurrence of surgical site infections creates a severe burden on both patients and health-care systems. A recent trial from Japan suggested additional costs of more than US$2300 in every patient with surgical site infection after colorectal surgery.[3] Surgical site infections have a pivotal role in prolonging treatment, causing further complications, increasing health-care costs, and reducing quality of life after open abdominal surgery. The infections are believed to increase the risk of death, with 17% of the mortality after surgery attributed directly to such infections.[4–6]

Risk factors for the development of surgical site infection include patient-related and intervention-related factors, of which only some can be controlled. Known patient-related risk factors are age, baseline disease,

comorbidities such as diabetes, obesity, smoking, malnutrition, and immunosuppression.[7–9] Since patient-related factors are difficult to change after it becomes clear that an intervention is needed, further efforts by the surgeon are needed to reduce the frequency of surgical site infections. Consequently, many methods to prevent surgical site infections have been assessed in the past few decades, including antibiotic prophylaxis, hair removal at the incision site, mechanical bowel preparation, skin disinfection, hand decontamination, and the use of sterile gowns, instruments, and gloves.[1]

The use of triclosan-coated material for the sutures needed to close the abdominal fascia is a novel attempt to reduce the occurrence of surgical site infections, since any foreign material increases the risk of such an infection. Triclosan interferes with microbial lipid synthesis and consequently attenuates bacterial growth and colonisation of the suture material in a broad spectrum manner in both in-vivo and in-vitro studies.[10,11]

Several products have been introduced to the market during the past decade, including triclosan-coated polydioxanone antimicrobial suture (PDS Plus; Ethicon, Johnson & Johnson, Livingston, Scotland, UK). Several randomised trials, non-randomised studies, and two meta-analyses have assessed the effectiveness of triclosan-coated sutures for closure of the abdominal fascia after midline laparotomy.[12,13] However, the evidence remains inconclusive, potentially because of different patient groups, varying suture materials, and heterogeneity in method quality. Therefore, the effectiveness and clinical relevance of triclosan-coated sutures remains unclear and needs to be established.

The multicentre randomised controlled PROUD trial (PRevention of abdominal wOUnD infection) was designed to investigate whether a clinically relevant reduction in the occurrence of surgical site infections can be achieved with triclosan-coated PDS Plus sutures compared with non-coated PDS II sutures. The aim was to yield reliable data for the effectiveness of triclosan-coated PDS Plus sutures for abdominal fascia closure in the prevention of surgical site infections, compared with the non-coated PDS II sutures. The null hypothesis to be tested in confirmatory analysis states that the rate of superficial and deep incisional surgical site infections within 30 days after midline incision is equal in both treatment groups.

Methods

Participants

PROUD was initially designed as a single-centre randomised controlled trial, but was converted into a multicentre study when substantial funding became available from Johnson & Johnson. The trial was a randomised controlled multicentre parallel adaptive group-sequential superiority trial, in which patients, surgeons, and outcome assessors were masked to treatment assignment. The study was done in the surgical departments of 24 German secondary and tertiary care centres. People eligible for participation were adult patients (≥18 years of age) who underwent elective midline abdominal laparotomy for any reason. Patients were excluded from trial participation in cases of impaired mental state or language problems or if they were participating in another intervention trial that interfered with the intervention or outcome of this trial. Local sub-investigators asked patients whether they were prepared to participate in the trial before they were included. After being screened for the inclusion and exclusion criteria, eligible patients were enrolled in the trial after they had provided written informed consent. Patients who were screened but not enrolled (including those unable to give informed consent for any reason) were documented in the screening log and the reason for exclusion was recorded. Hospitals were allowed to participate only after they had obtained local ethics committee approval and had signed a formal agreement with the Study Centre of the German Surgical Society.

Patient recruitment started on April 7, 2010, as a single-centre trial. Multicentre recruitment began on Jan 24, 2011. The first interim analysis was done in July, 2011, when the primary outcome was available for 375 patients. The second interim analysis was completed in April, 2013, after 1224 patients had been enrolled. Both these interim analyses were prespecified.

The single-centre protocol of this trial was approved by the ethics committee of the University of Heidelberg, Germany, on March 22, 2010 (reference number S-064/2010). After acquisition of funding from Johnson & Johnson, a substantial amendment was written and approved by the ethics committee of the University of Heidelberg on Sept 29, 2010 (reference number S-064/2010), and by the ethic committees of all other participating centres between Dec 8, 2010, and Jan 11, 2011. The final study protocol was published and internationally registered.[14] The PROUD trial was designed, managed, and analysed by the Study Centre of the German Surgical Society, with the support of the Institute of Medical Biometry and Informatics of the University of Heidelberg.

Procedures

A detailed manual for the surgical procedures was developed and approved by all participating trial sites and is available in the published protocol.[14] Patients underwent routine scrub and site preparation according to the established standards of the participating centres. Antibiotic prophylaxis or therapy had to be completed and documented according to the recently updated German national guidelines from the Paul-Ehrlich-Gesellschaft für Chemotherapie e.V.[15]

The trial intervention was closure of the abdominal fascia after midline laparotomy with triclosan-coated polydioxanone sutures (PDS Plus PDP9262T; needle: CTX 48 mm 1/2 circle). In the control group, fascial

Berlin, Germany (H Thielemann MD); **Clinic for General and Visceral Surgery, St Joseph Hospital Berlin Tempelhof, Berlin, Germany** (R Kunz MD); **Department of General, Abdominal and Minimal Invasive Surgery, Krankenhaus Salem, Department of Surgery, Heidelberg, Germany** (M von Frankenberg MD); **Department of General, Visceral and Minimal Invasive Surgery, Park-Klinik Weißensee, Berlin, Germany** (U Schernikau MD); **Department of General and Visceral Surgery, Sana Klinikum Lichtenberg, Berlin, Germany** (J Bunse MD); **Clinic for General, Visceral and Transplantation Surgery, Universitätsmedizin Mainz, Mainz, Germany** (B Jansen-Winkeln MD); **Department for General, Visceral, Thoracic and Vascular Surgery, Universitätsmedizin Greifswald, Greifswald, Germany** (L I Partecke MD); **Clinic for Surgery, Kliniken des Landkreises Neumarkt i. d. Oberpfalz, Neumarkt, Germany** (G Prechtl MD); **Clinic for General, Visceral and Thoracic Surgery, Marienhospital Stuttgart, Stuttgart, Germany** (J Pochhammer MD); **Clinic for Surgery, University Clinic Schleswig-Holstein, Campus Lübeck, Lübeck, Germany** (R Bouchard MD); **Clinic for General, Visceral and Thorax Surgery, Klinikum am Steinenberg Reutlingen, Reutlingen, Germany** (R Hodina MD); **Department for General, Visceral and Trauma Surgery, Krankenhaus der Augustinerinnen, Cologne, Germany** (K T E Beckurts MD); **Clinic for General, Visceral, Thoracic, Transplantation and Pediatric Surgery Universitätsklinikum Schleswig-Holstein, Kiel, Germany** (L Leißner MD); **Department of Surgery, Gemeinschaftskrankenhaus Havelhöhe, Berlin, Germany** (H-P Lemmens MD); **Department of General and Visceral Surgery, Asklepios Klinik Harburg, Hamburg, Germany** (F Kallinowski MD); **Department of General and Visceral Surgery, Albert-Ludwig University, Freiburg, Germany** (O Thomusch MD);

Department of General, Visceral and Transplantation Surgery, Charité Campus Virchow Klinikum, Berlin, Germany (D Seehofer MD); **Department of General and Visceral Surgery, GRN Klinik Sinsheim, Sinsheim, Germany** (T Simon MD); **Department of General, Visceral and Vascular Surgery, Josephs-Hospital Warendorf, Germany** (C M Seiler MD); **Department**

closure was done with use of uncoated polydioxanone sutures (PDS II Z1950G; needle: CTX 48 mm 1/2 circle) (Johnson & Johnson Medical GmbH, Norderstedt, Germany). Fascial closure was achieved by continuous mass closure with use of two loops—one each from the cranial and the caudal end of the incision in a continuous suture technique.

No suture material or suture techniques apart from those described in the protocol were permitted. No subcutaneous drains were allowed. Skin closure was done with surgical skin staples. Patients had to receive antibiotic prophylaxis before the incision. Postoperative care was provided according to the principles and standards of the participating departments.

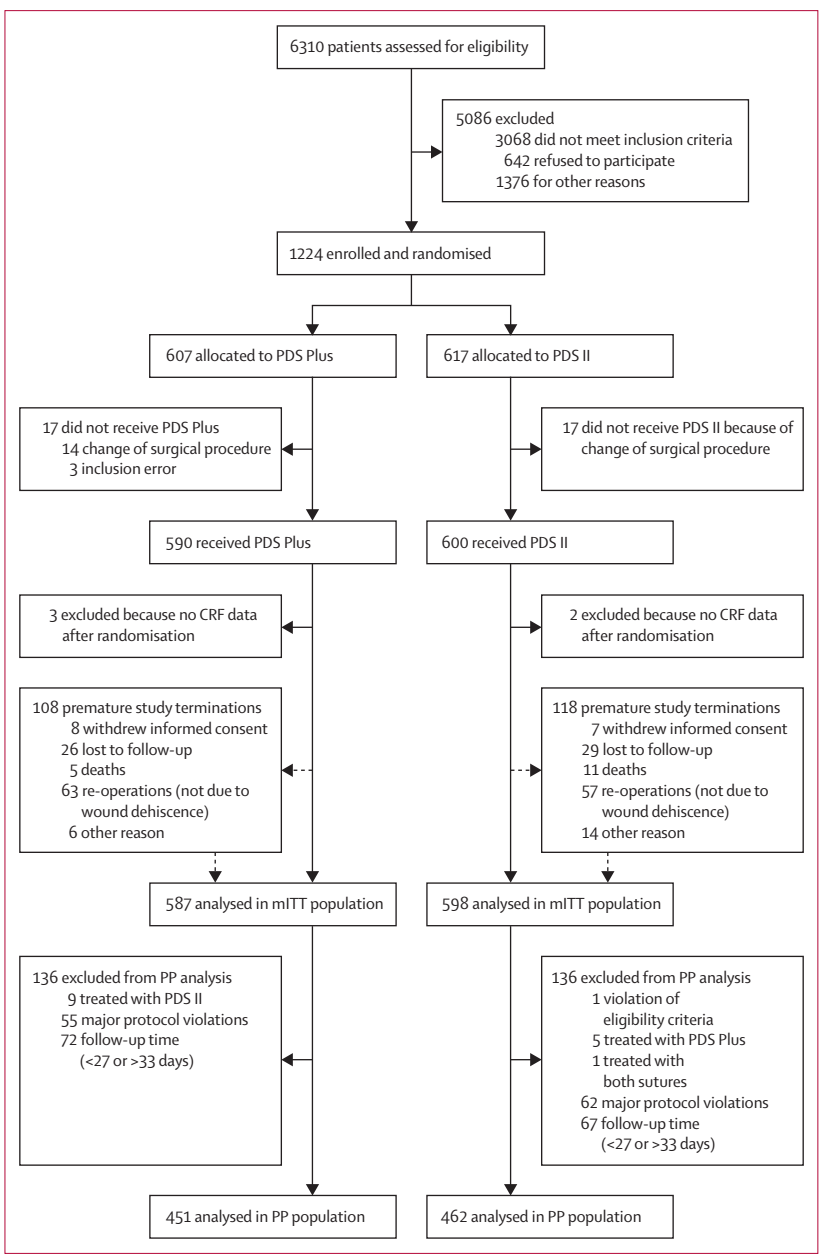

Figure 1: **Trial profile**
Screening numbers are from 21 of 24 centres (including randomisation numbers from the three centres that did not provide screening logs). CRF=case report form. mITT=modified intention to treat. PP=per protocol.

Used wrappers of the sutures were sent to the Institute of Medical Biometry and Informatics for confirmation that the study material was actually used as randomised and documented in the case report form. Photographs of the abdominal wound were assessed by an independent primary outcome validation committee consisting of three board-certified surgeons who reviewed all photographs without knowledge of the suture material used. Photographs were uploaded to a centralised database by investigators of the trial sites. Thereby, the timepoints for assessment of the primary endpoint at discharge or day 10 postoperatively (whichever occurred first) and on day 30 postoperatively were monitored and the compliance with the protocol was checked (see outcomes section). The determination of the primary endpoint was based exclusively on the clinical assessment.

Documentation of patient data was done on paper-based case report forms. Patients completed the quality-of-life questionnaires (the EQ-5D) themselves. Double data entry was done by the Institute of Medical Biometry and Informatics to ensure that the database reproduced the case report form correctly.

Central supervision of study conduct was achieved by monitoring of recruitment rates through the web-based randomisation method. Documentation of patient data, including photographs, was required 4 weeks after the final visit. Queries about missing data and implausibility were generated centrally and sent to the participating centres. Serious adverse events had to be reported to the Study Centre of the German Surgical Society within 5 days after they became known.

Randomisation and masking

We randomly assigned patients to triclosan-coated polydioxanone (PDS Plus) or standard polydioxanone suture (PDS II) just before closure of the abdominal wall. We used a centralised web-based device (Randomizer Software) for randomisation, with a specific code for each participating centre, to achieve equivalent groups. Permuted-block randomisation with an allocation ratio of 1:1 and a block size of 4 was used.

Patients, surgeons, and the outcome assessors were masked to the suture material used. Masking of the participating surgeons was possible because the two suture materials cannot be differentiated by colour, feel, or smell; furthermore, identical needles (CTX 48 mm 1/2 circle) were used and the surgeons were unable to tell whether or not the suture was coated. After randomisation, suture packages were opened and sutures were handed out by the scrub nurse in such a way that the surgeon could not see the packaging. Patients were masked to the suture material to ensure they could complete a valid assessment of their quality of life. Clinical investigators assessing wound status

were also masked, since the used suture material cannot be identified postoperatively and the randomisation sequence was concealed.

Outcomes

The primary endpoint was the occurrence of a superficial or deep surgical site infection, according to the Centers for Disease Control and Prevention criteria.[16] Superficial surgical site infection was defined as present if it occurred within 30 days after the surgical procedure and it involved only the skin or subcutaneous tissue around the incision, plus at least one of the following: purulent drainage from the incision site; organisms isolated by culture from the incision; pain or tenderness, localised swelling, redness, or heat and the incision is opened deliberately by a surgeon, unless the culture is negative; or diagnosis of superficial surgical site infection by a surgeon or attending physician. Deep surgical site infections were defined as present if they occurred within 30 days after the surgical procedure, were related to the procedure, and involved deep soft tissues, such as the fascia and muscles, plus at least one of the following: purulent drainage from the incision but not from the organ or space of the surgical site; dehiscence of a deep incision or a deep incision is opened by a surgeon because of fever, pain, or tenderness; abscess or other evidence of infection at the incision site; or diagnosis of deep surgical site infection by a surgeon or attending physician. Appendix p 1 provides a detailed overview of the primary endpoint definition.

The outcome assessors analysed the rate of surgical site infections on two occasions within 30 days after surgery during two following study visits—one on day 10 or the day of hospital discharge (whichever of these occurred first), and the other on day 30 after operation in the participating centres. Additionally, a photograph of the wound was taken at each follow-up visit and uploaded to a photo database for assessment by the primary outcome validation committee. All photographs were categorised independently as: surgical site infection present, surgical site infection not present, or wound not assessable. Secondary endpoints were frequency of wound dehiscence (cutaneous and subcutaneous layer), frequency of burst abdomen (fascial dehiscence), postoperative length of stay in intensive care unit, postoperative length of stay in hospital, 30-day mortality, and quality of life (assessed with the EQ-5D questionnaire).

Statistical analysis

Our sample size calculation was based on an assumed surgical site infection rate of 12% in the PDS II group and a reduction of this rate by 50% in the PDS Plus group, which was defined as clinically relevant.[17,18] In a fixed sample size design, a sample size of 750 randomised patients was needed to achieve a power of 80% for the χ^2 test at a two-sided significance level of 5% and to account for a 5% dropout rate. To cope with the uncertainty about the treatment effect, an adaptive group-sequential design was implemented prospectively.[19] This design allowed for early termination for efficacy or futility or recalculation of the sample size if the study was continued after the interim analysis. In the protocol, the first interim analysis was planned once the primary outcome was available for 375 patients. The trial would stop with demonstration of

of Visceral, Thoracic and Vascular Surgery, University Hospital Carl Gustav Carus, Dresden, Germany (C Reissfelder MD); **and Department of General and Visceral Surgery, Katharinenhospital,**

	PDS Plus (n=587)	PDS II (n=598)
Sex		
Male	361 (61·5%)	368 (61·5%)
Female	226 (38·5%)	230 (38·5%)
Age (years)	64·7 (11·8)	65·0 (12·1)
Body-mass index (kg/m^2)	26·1 (4·3)	26·1 (4·6)
Current or previous smoker	306 (52·1%)	308 (51·5%)
Comorbidities		
Anaemia	167 (28·4%)	166 (27·8%)
Diabetes mellitus	81 (13·8%)	96 (16·1%)
Chronic obstructive pulmonary disease	38 (6·5%)	51 (8·5%)
Chronic renal insufficiency	23 (3·9%)	20 (3·3%)
Liver cirrhosis	8 (1·4%)	9 (1·5%)
Malignant disease	407 (69·3%)	442 (73·9%)
Current immunosuppressive therapy	11 (1·9%)	11 (1·8%)
Chronic inflammatory disease*	31 (5·3%)	27 (4·5%)
Previous abdominal midline incision	122 (20·8%)	125 (20·9%)
ASA classification[23]		
I (normal healthy patient)	43 (7·3%)	43 (7·2%)
II (mild systemic disease)	296 (50·4%)	306 (51·2%)
III (severe systemic disease)	240 (40·9%)	242 (40·5%)
IV (constant threat to life)	8 (1·4%)	4 (0·7%)
Target organ for operation		
Colon	189 (32·2%)	214 (35·8%)
Rectum	145 (24·7%)	117 (19·6%)
Stomach	67 (11·4%)	73 (12·2%)
Pancreas	32 (5·5%)	37 (6·2%)
Liver	2 (0·3%)	3 (0·5%)
Combination of the above	33 (5·6%)	37 (6·2%)
Other	119 (20·3%)	117 (19·6%)
Surgical procedure		
Resection and anastomosis	422 (71·9%)	442 (73·9%)
Resection and resection plus exploration	72 (12·3%)	63 (10·5%)
Exploration	12 (2·0%)	14 (2·3%)
Resection or anastomosis and other	5 (0·9%)	3 (0·5%)
Resection and other	0	3 (0·5%)
Exploration and other	2 (0·3%)	2 (0·3%)
Resection and resection or anastomosis	0	1 (0·2%)
Antibiotic prophylaxis	578 (98·5%)	586 (98·0%)
Antibiotic therapy	126 (21·5%)	112 (18·7%)
Wound status		
Clean	144 (24·5%)	138 (23·1%)
Clean-contaminated	430 (73·3%)	450 (75·3%)
Contaminated	11 (1·9%)	9 (1·5%)
Dirty	2 (0·3%)	1 (0·2%)

(Table 1 continues on next page)

	PDS Plus (n=587)	PDS II (n=598)
(Continued from previous page)		
Stoma creation	135 (23·0%)	129 (21·6%)
Duration of surgery (min)	179·3 (87·1)	185·2 (90·9)
Blood loss (mL)	478·9 (639·6)	503·0 (666·7)
Length of incision (cm)	25·0 (5·8)	24·8 (5·6)
Surgeon's expertise		
Board certified	529 (90·1%)	523 (87·5%)
No certificate	58 (9·9%)	75 (12·5%)

Data are n (%) or mean (SD), unless otherwise indicated. *Medical disorders with chronic inflammation—eg, chronic inflammatory bowel diseases, chronic obstructive pulmonary disease, and arthritis.

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

	PDS Plus (n=587)	PDS II (n=598)	OR or MD (95% CI)	p value
Primary endpoint				
Surgical site infection	87 (14·8%)	96 (16·1%)	OR 0·91 (0·66–1·25)	0·64*
Superficial surgical site infection	53	56	..	..
Deep surgical site infection	22	25	..	..
Missing	12	15	..	..
Secondary endpoints				
Wound dehiscence	66 (13·4%)	81 (16·3%)	OR 0·80 (0·56 to 1·14)	0·21†
Missing	96	100	..	..
Burst abdomen	9 (1·9%)	22 (4·5%)	OR 0·40 (0·18 to 0·88)	0·0194†
Missing	104	109	..	..
Intensive care unit stay (days)	2·3 (3·8)	2·3 (3·6)	MD 0·01 (–0·41 to 0·43)	0·54‡
Postoperative hospital stay (days)	13·0 (7·4)	12·5 (6·3)	MD 0·47 (–0·32 to 1·25)	0·99‡
Death§	9 (1·5%)	20 (3·3%)	OR 0·46 (0·21 to 1·01)	0·48†
Quality of life (30 days after operation)				
EQ-5D visual analogue scale				
N	453	461	..	..
Mean (SD)	69·2 (20·1)	68·2 (19·6)	MD 0·96 (–1·61 to 3·54)	0·34‡
p25, p75¶	51·0, 85·0	55·0, 83·0	..	..
Median (range)	75 (0–100)	70 (3 to 100)	..	..
Quality of life (EQ-5D index)‖				
N	448	448	..	..
Mean (SD)	0·9 (0·2)	0·8 (0·2)	MD 0·01 (–0·02 to –0·04)	0·18‡
p25, p75¶	0·8, 1·0	0·8, 1·0	..	..
Median (range)	0·9 (0·0–1·0)	0·9 (–0·1 to 1·0)	..	..

Data are n (%) or mean (SD), unless otherwise indicated. For the categories with missing values, the missing patients were not included in the denominator to calculate percentages. OR=odds ratio. MD=difference of means. *p value for primary analysis (logistic regression). †χ^2 test, two-sided. ‡Wilcoxon-Mann-Whitney test, two-sided. §Analysed as treated—ie, n=583 for PDS Plus and n=602 for PDS II (because nine patients in the PDS Plus group were treated with PDS II and five in the PDS II group were treated with PDS Plus). ¶p25 and p75 denote the lower and upper quartiles of the empirical distribution as suggested by EQ-5D user guide. ‖EQ-5D index at visit 4 (all questionnaires available).

Table 2: **Primary and secondary endpoints**

superiority of PDS Plus if the one-sided p value fell below 0·0102, and would stop for futility if the one-sided p value was above 0·5; otherwise, the trial would continue to a second stage. After the second stage, superiority of PDS Plus would be shown if the product of the one-sided p values from the two stages fell below 0·0038. Use of these decision boundaries ensures control of the overall type I error rate by 2·5%, even if the sample size is recalculated with the results of the interim analysis taken into account.[19] On the basis of the results of this interim analysis, the data safety monitoring board recommended that a further interim analysis should be done after 1200 patients were enrolled. The decision rules of the adaptive group-sequential design were adjusted to ensure control of the overall one-sided type I error rate by 2·5%.[20] The study was stopped after this second interim analysis, and the results for pooled data are reported in the Results section.

The primary analysis was based on the modified intention-to-treat principle to represent clinical practice. Additionally, a per-protocol analysis of those patients without major protocol violations was done. The primary endpoint was assessed with a logistic regression model that included the covariates age, body-mass index (BMI), centre, and surgeon's expertise (board-certified *vs* no certificate). Missing values for the primary outcome variable were replaced by random imputation with probability equal to the surgical site infection rate recorded for the complete cases in the respective treatment group.[21] Multiple imputation was done as a sensitivity analysis.[22] Point estimates were expressed as odds ratios for binary variables and differences of the means for continuous variables, each with corresponding 95% CIs. We used logistic regression modelling to identify potential risk factors for the occurrence of surgical site infections. Two-sided p values are reported throughout. Calculations were done with SAS version 9.1.

This trial is registered with the German Clinical Trials Register, number DRKS00000390.

Meta-analysis

We also did a post-hoc meta-analysis that included the PROUD outcomes to analyse the existing evidence about the effectiveness of triclosan-coated versus uncoated sutures to reduce surgical site infections after closure of midline laparotomy. To identify randomised controlled trials that addressed this topic, we searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials (Central) with the search terms: "Vicryl OR polyglactin OR Monocryl", "suture OR sutures", "antimicrobial OR antibiotic OR antiseptic", "triclosan OR triclosan coated", and "randomized controlled trial". We did this meta-analysis with the Mantel-Haenszel random-effects model, and used Review Manager, version 5.1 (The Cochrane Collaboration).

Role of the funding source

Funding of project and data management, biometry and statistical analysis, case payment, material

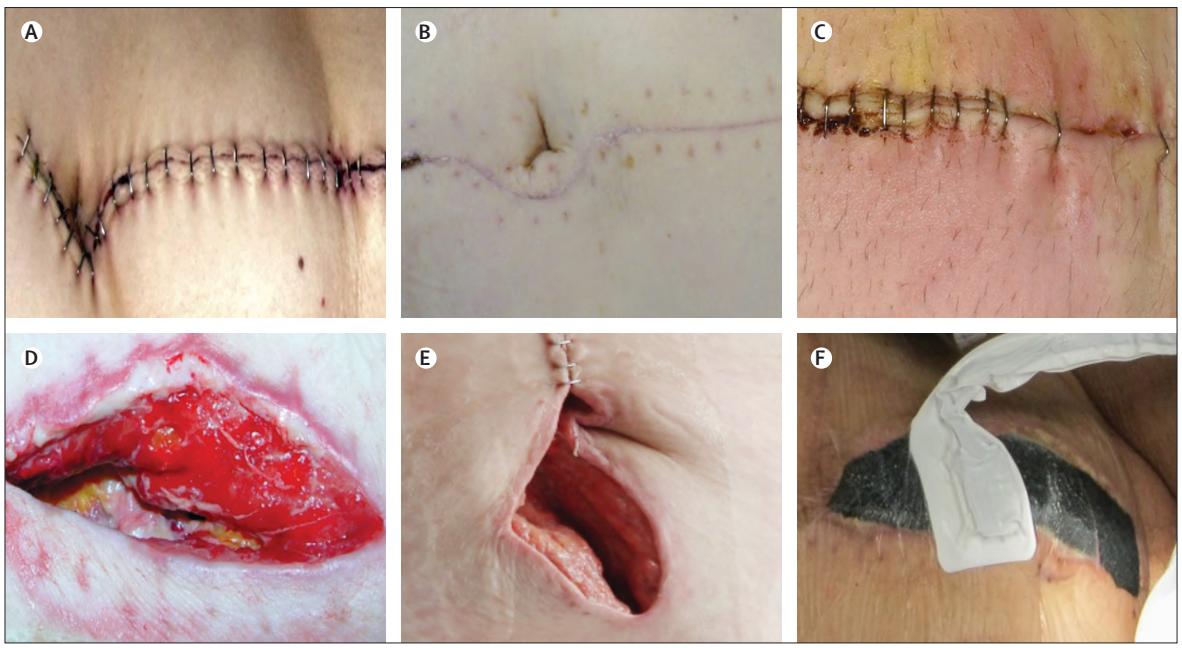

Figure 2: **Photo documentation of surgical site infection**
(A) Clean wound (discharge). (B) Healed scar (30 days after operation). (C) Superficial surgical site infection and redness of the wound (day 7 after operation). (D) Deep surgical site infection with dehiscence and local swelling (30 days after operation). (E) Wound dehiscence without local irritation (day 7 after operation). (F) Management of surgical site infection with complete wound dehiscence by VacuSeal therapy (30 days after operation).

Stuttgart, Germany
(R Hennig MD)

Correspondence to:
Prof Markus W Büchler, Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany
markus.buechler@med.uni-heidelberg.de

For the **protocol** see www.proud-studie.de/Protokoll.htm

For the **Randomizer Software** see http://www.randomizer.at

See **Online** for appendix

(sutures, case report forms, digital cameras, trial master file, and investigator site file), trial committees, investigator meetings, and internet tools was provided by Johnson & Johnson Medical Limited (Scotland, UK). Investigators received no financial incentives from the funding source. PROUD was an investigator-initiated trial and the funder had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. MKD, MK, and MWB had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 7, 2010, and Oct 19, 2012, 1224 patients were randomly assigned to triclosan-coated PDS Plus sutures (607 patients) or non-coated PDS II sutures (617 patients) (figure 1). Of these patients, 34 were excluded from the analysis because they did not receive one of the study interventions, and a further five were excluded because of missing case report form data after randomisation. Thus, the modified intention-to-treat population consisted of 1185 patients, of whom 272 were not treated according to protocol. The per-protocol population therefore consisted of 913 patients (figure 1). Dropout rates did not differ between the two study groups.

The study groups were well balanced in terms of patient and procedure characteristics (table 1). Overall, 61·5% participants were men and 38·5% were women, with a mean age of 64·8 years and a mean BMI of 26·1 kg/m². Table 1 shows the full baseline characteristics of the trial participants, including their smoking status, comorbidities, indications for surgery, and American Society of Anesthesiologists (ASA) physical status.[23]

Most of the analysed interventions were done by experienced (board-certified) surgeons (table 1). The indications for operation were well balanced between the two treatment groups and showed the expected distribution of target organs for abdominal surgery: most operations were done for treatment of diseases of the colon and rectum, whereas operations of the stomach, the pancreas, and the liver were much less frequent (table 1).

Antibiotic prophylaxis, foreseen in the protocol, was given to most (98·2%) patients in the modified intention-to-treat population (table 1). Wound status was clean in 282 (23·8%), clean-contaminated in 880 (74·3%), contaminated in 20 (1·7%), and dirty in three (0·3%) of 1185 patients (table 1). Colostomy or ileostomy formed part of the operation in nearly a quarter of all analysed patients (table 1). The mean duration of surgery was 182·3 min, with a mean blood loss of 491·1 mL and a mean length of incision of 24·9 cm.

The primary endpoint, surgical site infection within 30 days after index operation, did not differ between the two groups (table 2). The recorded rate of surgical site infection was 87 (14·8%) of 587 patients in the PDS Plus group and 96 (16·1%) of 598 in the uncoated PDS II group (OR 0·91, 95% CI 0·66–1·25; p=0·64); multiple imputation of missing values yielded a very similar result (p=0·62). Of those 156 infections, 109 (69·9%) were superficial surgical site infections, with similar

	PDS Plus (n=583)*	PDS II (n=602)*	p value
Patients with at least one SAE	146 (25·0%)	138 (22·9%)	0·39†
Number of documented SAEs	151	158	..
Maximum intensity‡			0·29§
Mild	21 (13·9%)	19 (12·0%)	..
Moderate	53 (35·1%)	48 (30·4%)	..
Severe	77 (51·0%)	91 (57·6%)	..
Causal relation to intervention			0·68§
Unrelated	130 (86·1%)	137 (87·3%)	..
Possibly related	21 (13·9%)	17 (10·8%)	..
Probably related	0	2 (1·3%)	..
Not assessable	0	1 (0·6%)	..
Missing	0	1	..
SAE specification			0·81†
Surgical site infection	7 (4·6%)	10 (6·3%)	..
Burst abdomen	8 (5·3%)	10 (6·3%)	..
Anastomotic insufficiency	39 (25·8%)	34 (21·5%)	..
Intra-abdominal fluid collection or abscess	14 (9·3%)	7 (4·4%)	..
Bleeding	12 (7·9%)	14 (8·9%)	..
Cardiovascular	9 (6·0%)	14 (8·9%)	..
Pulmonary	15 (9·9%)	13 (8·2%)	..
Renal	7 (4·6%)	8 (5·1%)	..
Other gastrointestinal problems	21 (13·9%)	24 (15·2%)	..
Other	15 (9·9%)	21 (13·3%)	..
Not assessable	4 (2·6%)	3 (1·9%)	..

For the "Causal relation" category, if patient data were missing, these patients were not included in the denominator to calculate percentages. SAE=serious adverse event. *Patients analysed as treated—ie, n=583 for PDS Plus and n=602 for PDS II (because nine patients in the PDS Plus group were treated with PDS II, and five in the PDS II group were treated with PDS Plus). †χ^2 test, two-sided. ‡Intensity of adverse events was rated by investigators and classified according to the PROUD trial protocol. §Mantel-Haenszel test, two-sided.

Table 3: **Serious adverse events reported**

frequencies in the two treatment groups (table 2), and 47 of 156 (30·1%) were deep surgical site infections, and again occurred at similar rates in the two groups (table 2).

Review of the assessment of the primary endpoint by photo documentation at visit 3 (day of discharge or at the latest day 10 after operation; 1011 patients) and visit 4 (30 days postoperatively; 838 patients) showed agreement with the clinical assessment in 970 of 1011 (95·9%) of patients for visit 3 and in 768 of 838 (91·7%) for visit 4 (data not shown) (figure 2).

The secondary endpoint of wound dehiscence occurred in 147 (14·9%) of 989 patients assessable for this endpoint, and did not differ between the two groups (table 2). The reoperation rate because of burst abdomen was lower in the PDS Plus group than in the PDS II group (table 2). Length of postoperative hospital stay and duration of stay in the intensive care unit did not differ between the groups (table 2). 29 of 1185 participants (2·4%) died during follow-up (nine of 584 [1·5%] in the PDS Plus group *vs* 20 of 602 [3·3%] in the PDS II group; analysis as treated: OR 0·46, 95% CI 0·21–1·01; p=0·0476). All deaths were classified as unrelated to the trial intervention and most of the postoperative deaths were due to septic shock, multiple organ failure, or cardiac and pulmonary decompensation (table 2).

Patient self-assessed quality of life, measured on the EQ-5D index, did not differ between the groups (table 2). The sub-items with regard to mobility, self-care, usual activities, pain and discomfort, anxiety and depression, and the observed general health status on the visual analogue scale, also did not differ between the two groups (appendix p 2). Moreover, the reported rate of serious adverse events did not differ between the groups. Overall, in 284 (24·0%) of 1185 patients, at least one serious adverse event was reported. However, no difference was detected between the groups in this respect (table 3).

To identify potential risk factors for the occurrence of surgical site infections, we undertook backwards stepwise variable selection with a critical level of 0·50 for variables to remain in the model.[24] The full model included the variables age, BMI, suture material (PDS Plus *vs* PDS II), smoking status, diabetes, chronic renal insufficiency, chronic obstructive pulmonary disease, current immunosuppressive therapy, anaemia, malignant disease, chronic inflammatory disease, previous abdominal midline incision, liver cirrhosis, ASA classification,[23] target organ for operation, surgical procedure, antibiotic prophylaxis, antibiotic treatment, surgeon's expertise, wound status, and stoma creation. The final logistic regression model showed that several variables affected the occurrence of surgical site infection: extended operative procedures with a combination of target organs (colon, rectum, liver, pancreas, and stomach [OR 6·37, 95% CI 2·71–14·98; p=0·0193]); malignant disease (OR 0·60, 95% CI 0·38–0·93; p=0·0236); missing antibiotic prophylaxis (OR 5·19, 95% CI 1·56–17·31; p=0·0074); chronic renal insufficiency (OR 2·96, 95% CI 1·36–6·46; p=0·0064); anaemia (OR 1·73, 95% CI 1·16–2·59; p=0·0071); BMI (OR 1·09, 95% CI 1·05–1·14; p<0·0001); and surgeon's expertise (OR 1·73, 95% CI 1·02–2·93; p=0·0405) (appendix p 3).

In summary, no differences were recorded in demographics or the results for the primary and secondary endpoints between the modified intention-to-treat and per-protocol analysis (data not shown).

In our meta-analysis, five trials including a total of 3020 patients proved eligible and were analysed.[3,14,25–27] In addition to the PROUD trial, four trials provided quantitative data about the occurrence of surgical site infection, two of which compared triclosan-coated polyglactin 910 braided suture material (Vicryl Plus, Ethicon, Johnson & Johnson, Sommerville, NJ, USA) versus uncoated polyglactin 910 (Vicryl; Ethicon).[3,26] The other two trials, like the PROUD trial, compared PDS Plus and PDS II.[25,27] Only one trial was done in a multicentre setting.[25] Three trials focused on colorectal

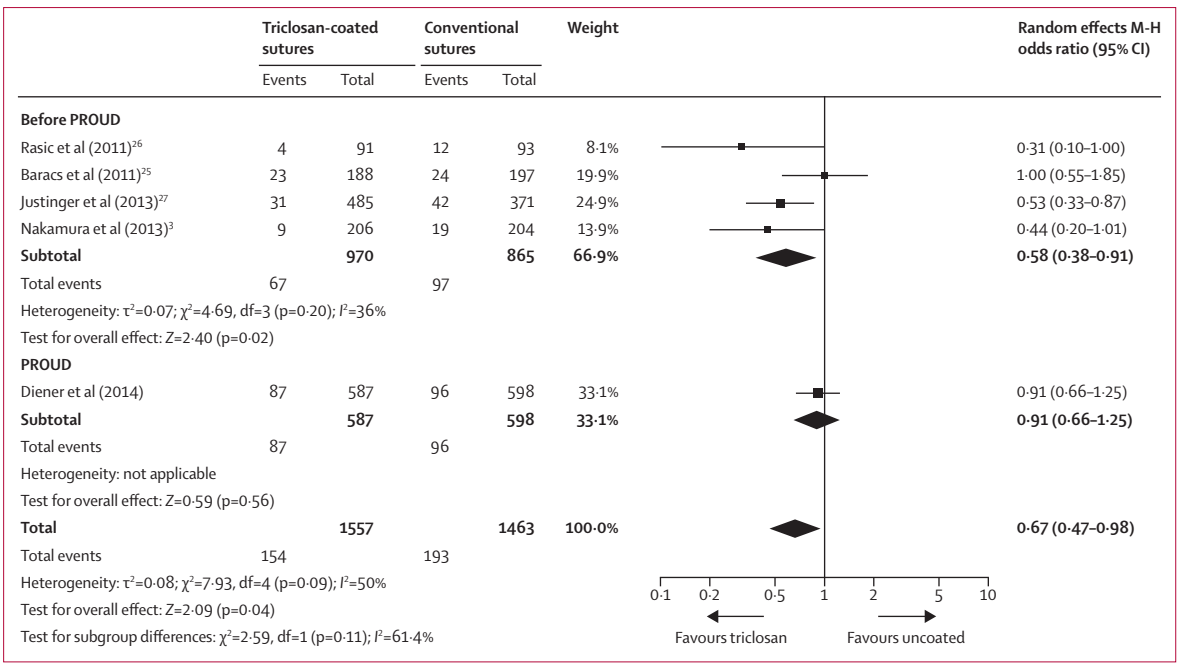

Figure 3: **Meta-analysis of randomised trials comparing triclosan-coated continuous sutures with uncoated standard continuous sutures for abdominal fascia closure after midline laparotomy**
M-H=Mantel-Haenszel. OR=odds ratio.

surgery only,[3,25,26] whereas the remaining trial included a mixed cohort of patients who underwent general and abdominal surgery.[27] Three trials applied the definition of the Centers for Disease Control and Prevention,[3,25,27] as in the PROUD trial.[14] One trial did not define surgical site infection.[26] Antibiotic prophylaxis was given in all included trials in both treatment groups,[3,25–27] as in the PROUD trial. Apart from PROUD, the funding source was specified only in one trial.[27]

Three trials showed a significant reduction of surgical site infection in the triclosan-coated group,[3,26,27] whereas one multicentre trial of 385 patients showed no significant differences between the treatment groups.[25]

The aggregated results of the trials that were done before PROUD showed a significant superiority of triclosan-coated sutures over uncoated suture material (OR 0·58, 95% CI 0·38–0·91; p=0·02) (figure 3). Since PROUD did not show any significant difference in rates of surgical site infection between triclosan-coated and uncoated sutures (OR 0·91, 95% CI 0·66–1·25; p=0·56 based on χ^2 test), the overall result of the meta-analysis was moved towards the line of no effect (ie, OR=1), but still suggested a significant reduction of surgical site infection in the triclosan-coated group (OR 0·67; 95% CI 0·47–0·98; p=0·04). Tests for subgroup differences showed no significant data heterogeneity (figure 3).

Discussion

Triclosan-coated PDS Plus sutures and uncoated PDS II sutures were associated with equal rates of surgical site infection after continuous closure of the abdominal wall. By contrast with our assumption that coated sutures would reduce the occurrence of surgical site infection from 12% to 6% before sample size calculation, the observed reduction was only 1·3%, which cannot be regarded as clinically relevant from a surgical point of view.

The overall surgical site infection rate of 15·4% shows that this complication remains a common and unsolved issue. Moreover, the multivariate analyses showed that these infections occur after both clean and contaminated surgery, which indicates that development of this complication is multifactorial and cannot be attributed to specific surgical indications alone. Additionally, BMI, chronic renal insufficiency, anaemia, missing antibiotic prophylaxis, surgical expertise (absence of board certification), oncological resection, and extended operations were shown to increase the occurrence of surgical site infection. This trial has proved that surgical site infection is related to both patient-dependent and surgery-dependent risk factors. Attempts to solve this problem by modification of one factor, such as the suture material, need to be questioned.

With regard to the secondary endpoints, burst abdomen and mortality rates were lower in the PDS Plus group. However, this finding seems to be clinically irrelevant. An association between suture material, burst abdomen, and mortality is unlikely, since the rates of deep surgical site infection, which could have been the missing link between burst abdomen and mortality, did not differ between the comparison groups. Moreover, all serious

Panel: Research in context

Systematic review

To identify randomised controlled trials comparing coated versus uncoated suture material for closure of the abdominal fascia after midline laparotomy, we searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials (Central) with the search terms: "Vicryl OR polyglactin OR Monocryl", "suture OR sutures", "antimicrobial OR antibiotic OR antiseptic", "triclosan OR triclosan coated", and "randomized controlled trial". The final search was done on July 16, 2013. The results were combined with a search of Medical Subject Headings (MeSH). We manually cross-searched the reference lists of the retrieved reports for additional publications. We did not apply any language restrictions, and no unpublished data or data from abstracts were encountered or used.

Interpretation

On the basis of our trial results and the heterogeneous findings of our meta-analysis, we conclude that the question of whether triclosan-coated sutures can reduce the occurrence of surgical site infection remains open. Further assessment will necessitate further large, multicentre randomised controlled trials in high-risk and low-risk groups after median laparotomy—for example, in contaminated versus clean surgical procedures and in obese patients. These trials should apply validated criteria for endpoint assessment, such as the Centers for Disease Control and Prevention criteria for surgical site infection.

adverse events with fatal outcome were judged to be unrelated to the trial intervention, which also refutes the theory of an association between coated suture material, burst abdomen, and mortality.

The PROUD trial investigators completed this multicentre trial within the expected timeframe—more than 1200 patients were enrolled and randomised within 31 months. In addition to sufficient sample size, the high internal validity of this trial was ensured by standardisation of the surgical technique and perioperative care, and masked assessment of predefined outcome parameters. Moreover, the multicentre approach, with the inclusion of 24 participating institutions, creates a representative trial group and supports the generalisability of the findings. The interventions in the patients included in the study were also representative for general and visceral surgery as a whole. The adaptive group-sequential design of PROUD was used because of the initial inconclusiveness of existing trials regarding the actual difference of surgical site infection rates between the two comparison groups.

Our meta-analysis of the PROUD trial in context with pre-existing randomised controlled trials assessing coated versus uncoated sutures for abdominal fascia closure showed heterogeneous results. Three single-centre trials showed superiority of coated sutures, whereas PROUD and the multicentre trial by Baracs and colleagues[25] showed no advantage for one or the other material. The potential sources of bias that could have distorted these results include small sample size, single-centre setting, clinical heterogeneity, and varying definitions of surgical site infection. The PROUD trial had the largest sample size of all the trials in the meta-analysis (1185 patients of 3020 patients overall), and shifted the results from superiority (before PROUD) towards equality (after PROUD) of coated sutures, but overall the meta-analysis still showed superiority of coated sutures (OR 0·67, 95% CI 0·47–0·98; figure 3). Since only the single-centre trials indicated superiority of coated sutures, the conclusion of the most recent systematic review and meta-analysis[13] about this topic, which showed a significant beneficial effect of triclosan-coated sutures in the prevention of surgical site infection, should be reconsidered (panel).

PROUD also shows that efficacy in laboratory circumstances does not inevitably lead to effectiveness in real-life clinical situations. Several in-vitro and in-vivo experiments have shown reduced adherence of microorganisms on the local surface of coated suture material.[28] Since a reduction of surgical site infections could not be proven in this trial, the clinical relevance of this effect could be disputed. Consequently, this finding delivers two messages to both surgeons and industry: first, the results of the PROUD trial underpin the unambiguous necessity of large and high-level clinical trials for valid assessment of surgical techniques, materials, and strategies. Second, although surgical innovation partly relies on the development of new materials, to start marketing without clear proof of effectiveness is the wrong approach.[29]

Since clinical care is heterogeneous, assessment and reduction of surgical site infection is complex. The absence of standardisation of surgical care was shown in a recent survey by Diana and colleagues.[6] Non-compliance with accepted guidelines on the one hand, and conclusions based on fragile evidence on the other, contribute to this difficult and opaque situation.[1] By contrast, the PROUD trial is distinguished by high internal validity because of standardisation of surgical and perioperative care, adequate sample size, and masked and monitored outcome assessment. Moreover, the multicentre setting assures high external validity.

In addition to clinical effectiveness, the application of triclosan-coated sutures is often discussed in the context of the costs of treatment and of health care overall.[3,4] Undoubtedly, the high rate of surgical site infection is one of the most important cost-driving factors in surgery, and all efforts to reduce the occurrence of these infections should be appreciated. However, surgical innovation and scientific evaluation need to be synchronised.[29] Huge financial investments are wasted when the anticipated effectiveness of new products cannot be confirmed in well-designed clinical trials with adequate power that focus on patient-relevant endpoints. The overall costs for the health-care system will be even higher in the situation of a keenly marketed innovative product that then fails to prove superiority. Consequently, innovative products need to be assessed for safety and effectiveness, which will clearly increase financial investment in this initial development phase. However, to put safe and effective products on the market will reduce overall health-care costs in the long term.

In conclusion, the PROUD trial showed no effect of triclosan-coated PDS Plus sutures on surgical site infection. These results contrast with those of previously published single-centre trials, which raises concerns. Additionally, enforcement of rigorous methodological standards in clinical research and reporting of surgical trials has to be improved and funding defined and displayed. Nevertheless, a surgical site infection rate of 15·4% after elective midline laparotomies discloses an unsolved problem that needs to be addressed by further surgical innovation and clinical research. Future trials on the prevention of surgical site infection should consider the multifactorial genesis of this common complication and either attempt to control the whole perioperative setting by virtue of the trial design or focus on specific high-risk constellations.

Contributors

MKD and MWB conceived and designed the study and supervised trial conduct, prepared and wrote the report, and participated in data analysis. CMS participated in study design and trial conduct. AU and CD-H were responsible for trial management and contributed to data interpretation, proof reading, and writing. PK, PS, TSS, VA, ES, HT, RK, MvF, US, JB, BJ-W, LIP, GP, JP, RB, RH, KTEB, LL, H-PL, FK, OT, DS, TS, and AH-D participated in patient recruitment. JN participated in patient recruitment and study design. TH, CR, and RH represented the primary outcome validation committee and assessed the photographs. MK and CK participated in study design, data analysis, and data interpretation.

PROUD trial coordinators

Writing committee: M K Diener and M W Büchler (Coordinating Investigator); study design: M K Diener, P Knebel, C M Seiler, U Heger, (Study Center of the German Surgical Society [SDGC]) and S Voss (SDGC), M Kieser, T Bruckner, and S Englert (Institute of Medical Biometry and Informatics [IMBI]); trial management: A Ulrich, C Dörr-Harim, and I Rossion (SDGC); serious adverse event management: M K Diener and C Dörr-Harim; data management: C Klose (IMBI); analysis: T Bruckner, M Kieser, and C Klose; steering committee: M W Büchler, M Kieser, J Neudecker, C Schuhmacher, and CM Seiler; data safety and monitoring board: G Ihorst, C Ohmann, S Sauerland; primary outcome validation committee: T Hackert, R Hennig, C Reissfelder.

Investigators

The investigators and the participating centres in this study are listed below in alphabetical order of their location, including patient recruitment numbers:
J Steinmeyer, O Haase, M Schmitt (Department of General, Visceral, Vascular and Thoracic Surgery, Campus Charité Mitte, Berlin, Germany; 66 patients); P Neuhaus, G Hunold, S Rademacher, A Köpke, S Boas-Knoop (Department of General, Visceral and Transplantation Surgery, Charité Campus Virchow Klinikum, Berlin, Germany; 10 patients); H Matthes, A Happe (Department of Surgery, Gemeinschafts-Krankenhaus Havelhöhe, Berlin, Germany; 12 patients); K Gellert, F Fritze, D Weiland, Y Atas (Department of General and Visceral Surgery, Sana Klinikum Lichtenberg, Berlin, Germany; 38 patients); B Böhm (Visceral and Vascular Surgery, Vivantes Klinikum Neukölln, Berlin, Germany; 72 patients); C Fester, L Estévez-Schwarz, U Nottrodt (Clinic for General and Visceral Surgery, St Joseph Hospital Berlin Tempelhof, Berlin, Germany; 44 patients); J Birkl, A Spranger, D Laatsch (Clinic for General and Visceral Surgery, Unfallkrankenhaus Berlin, Berlin, Germany; 45 patients); G Arlt, R Gogoll, J Haase (Department of General, Visceral and Minimal Invasive Surgery, Park-Klinik Weißensee, Berlin, Germany; 39 patients); J Stern, S Usta, J Ghafoor, A Rönsch (Department of General, Visceral and Trauma Surgery, St Josefs Hospital Dortmund-Hörde, Dortmund, Germany; 53 patients); U Hopt, M Gool, G Ruf, A Klock (Department of General and Visceral Surgery, Albert-Ludwig University, Freiburg, Germany; 10 patients); H Becker, R Talaulicar, S Klie, J Kreutzer, E Stauffer (Department of General and Visceral Surgery, University Medical Center Göttingen, Georg-August-Universität, Göttingen, Germany; 270 patients); C-D Heidecke, S Diedrich, S Peters (Department for General, Visceral, Thoracic and Vascular Surgery, Universitätsmedizin Greifswald, Greifswald, Germany; 25 patients); K Hermann, A Wahlers (Department of General and Visceral Surgery, Asklepios Klinik Harburg, Hamburg, Germany; 10 patients); M Schmid, P Conrad, B Jocher, F Winter (Department of General, Abdominal and Minimal Invasive Surgery, Krankenhaus Salem, Department of Surgery, Heidelberg, Germany; 44 patients); B Maichle, D Anders (Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany; 141 patients); A Hyhlik-Dürr (Department of Vascular and Endovascular Surgery, University of Heidelberg; 75 patients); T Becker, F Braun, K Bas (Clinic for General, Visceral, Thoracic, Transplantation and Pediatric Surgery Universitätsklinikum Schleswig-Holstein, Kiel, Germany; 16 patients); O Pfisterer, S Lilienbecker (Department for General, Visceral and Trauma Surgery, Krankenhaus der Augustinerinnen, Cologne, Germany; 17 patients); H-P Bruch, U Roblick, T Keck, H Wolken, K Larisch, U Holler (Clinic for Surgery, University Clinic Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; 20 patients); H Lang, P Kaudel, L Böttcher (Clinic for General, Visceral and Transplantation Surgery, Universitätsmedizin Mainz, Mainz, Germany; 34 patients); E Faist, KW Jauch, H Nieß, B Schreib, M Eder (Department of General, Visceral, Transplantation, Vascular and Thoracic Surgery, Ludwig-Maximilians-Universität Munich, Großhadern Campus, Munich, Germany; 108 patients); M Kästel, V Patalakh (Clinic for Surgery, Kliniken des Landkreises Neumarkt i. d. Oberpfalz, Neumarkt, Germany; 25 patients); T Zimmermann, L Kernke (Clinic for General, Visceral and Thorax Surgery, Klinikum am Steinenberg Reutlingen, Reutlingen, Germany; 21 patients); H-G Heß, M Hoffer (Department of General and Visceral Surgery, GRN Klinik Sinsheim, Sinsheim, Germany; 5 patients); M Schäffer, U Valina (Clinic for General, Visceral and Thoracic Surgery, Marienhospital Stuttgart, Stuttgart, Germany; 24 patients).

Declaration of interests

MKD has received payments for lectures given during meetings organised by Johnson & Johnson. All other authors declare that they have no competing interests.

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