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Optimal timing of rectal diclofenac in preventing post-endoscopic retrograde cholangiopancreatography pancreatitis

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ABSTRACT

Background and study aims Rectal nonsteroidal anti-inflammatory drug (NSAID) prophylaxis reduces incidence of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. Direct comparisons to the optimal timing of administration, before or after ERCP, are lacking. Therefore, we aimed to assess whether timing of rectal NSAID prophylaxis affects the incidence of post-ERCP pancreatitis.

Patients and methods We conducted an analysis of prospectively collected data from a randomized clinical trial. We included patients with a moderate to high risk of developing post-ERCP pancreatitis, all of whom received rectal diclofenac monotherapy 100-mg prophylaxis. Administration was within 30 minutes before or after the ERCP at the discretion of the endoscopist. The primary endpoint was post-ERCP pancreatitis. Secondary endpoints included severity of pancreatitis, length of hospitalization, and Intensive Care Unit (ICU) admittance.

Results We included 346 patients who received the rectal NSAID before ERCP and 63 patients who received it after ERCP. No differences in baseline characteristics were ob-

served. Post-ERCP pancreatitis incidence was lower in the group that received pre-procedure rectal NSAIDs (8 %), compared to post-procedure (18 %) (relative risk: 2.32; 95% confidence interval: 1.21 to 4.46, $P = 0.02$). Hospital stays were significantly longer with post-procedure prophylaxis (1 day; interquartile range [IQR] 1–2 days vs. 1 day; IQR 1–4 days; $P = 0.02$). Patients from the post-procedure group were more likely to be admitted to the ICU (1 patient [0.3 %] vs. 4 patients [6 %]; $P = 0.002$).

Conclusions Pre-procedure administration of rectal diclofenac is associated with a significant reduction in post-ERCP pancreatitis incidence compared to post-procedure use.

Introduction

Pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP) with an incidence rate of 3.2 % to 15 % [1]. Post-ERCP pancreatitis progresses to severe pancreatitis in 4.7 % of cases and carries a mortality rate of up to 0.7 % [1, 2].

A 2012 landmark trial positioned prophylactic rectal nonsteroidal anti-inflammatory drugs (NSAIDs) as the cornerstone in prevention of post-ERCP pancreatitis. Since then, rectal NSAIDs have been considered the standard of care in Europe, the United States, and Japan [3–5].

Prevention of post-ERCP pancreatitis potentially can be improved by exploring and combining new prophylactic strategies, as well as optimizing current care [6]. Rectal NSAIDs are one of the most effective, cheap, and easy-to-use agents for preventing post-ERCP pancreatitis [7]. Although it is clear that prophylactic administration of rectal NSAIDs is beneficial, a direct head-to-head comparison about the most optimal time point in relation to the ERCP procedure (pharmacokinetic properties) has not been performed.

The European Society of Gastrointestinal Endoscopy (ESGE) advocates the use of rectal NSAIDs immediately before ERCP. In contrast, the American Society of Gastrointestinal Endoscopy and the Japanese Society of Gastrointestinal Endoscopy do not provide recommendations regarding the timing of administration [3–5]. To date, 100 mg has been considered the optimal rectal NSAID dose (indomethacin or diclofenac) [8–11]. The optimal timing of rectal NSAIDs in relation to ERCP has not been addressed in most studies and meta-analyses [12–18].

We performed a randomized clinical trial (RCT) in which we compared aggressive periprocedural hydration in combination with rectal NSAID, compared with rectal NSAID monotherapy, for the prevention of post-ERCP pancreatitis in patients with a moderate to high risk [19]. For this trial, we prospectively identified whether the rectal NSAID was administered before or after the ERCP procedure. In this post-hoc analysis, we aimed to determine whether the timing of rectal NSAID administration affects the incidence of post-ERCP pancreatitis.

Patients and methods

Study design and setting

For this study, we selected patients from the FLUYT trial, a RCT conducted from June 2015 to June 2019 and coordinated by the Dutch Pancreatitis Study Group [19]. In this RCT, 826 patients were enrolled in 22 large teaching hospitals and university medical centers in the Netherlands. Patients were randomly assigned (1:1) to receive either the combination of aggressive periprocedural hydration and rectal NSAID 100 mg (hydration group) or rectal NSAID 100-mg monotherapy (control group). All patients received a rectal NSAID within 30 minutes before or after the ERCP procedure. The timing of administration was not dictated by the study design but was left to the discretion of the treating clinician, as guidelines did not define on preferred timing at that moment. Because concomitant use of a pancreatic duct stent and rectal NSAID is under discussion and merits further investigation, the decision to place a pancreatic duct stent was also left to the discretion of the treating clinician in the original trial. The study was performed in accordance with the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice. The Medical Research Ethics Committees United approved the protocol (NL52341.100.15). Patient demographics, patient- and procedure-related risk factors for post-ERCP pancreatitis, and follow-up data were collected prospectively using standardized digital case record forms. The study coordinator verified the data through a patient chart review of all hospital contacts between randomization and the end of follow-up (180 days post randomization). We adhered to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guideline [20].

Participants

All patients were between 18 and 85 years, had an indication for ERCP, and provided written informed consent. Exclusion criteria were patients with a low risk of post-ERCP pancreatitis, for which they had to fulfill at least one of the following criteria: chronic pancreatitis (according to the MANNHEIM criteria) [21], previous sphincterotomy, pancreatic head mass, or routine biliary stent exchange. Other exclusion criteria were: active pancreatitis prior to ERCP and contraindications to intensive hydration (e. g. cardiac/pulmonary/liver insufficiency, preexisting pitting edema, hyponatremia or hypernatremia) or rectal NSAIDs (e. g. renal insufficiency, allergy, active gastrointestinal bleeding, ulcer disease, and NSAID use for other indications [other than cardioprotective aspirin]). Because there is no international definition for classifying patients into low, moderate, or high risk of post-ERCP pancreatitis, risk stratification was estimated by adopting low-risk definitions used in the current literature [22, 23]. By excluding low-risk patients, we only included moderate- to high-risk patients.

For the current study, we excluded patients who did not undergo an ERCP, because they were unable to develop the primary endpoint of post-ERCP pancreatitis. Also, we excluded pa-

▶ **Table 1** Interaction effect of randomization group on timing of rectal NSAIDs in participants of the FLUYT trial.

	Rectal NSAID before ERCP (n PEP/n total)	Rectal NSAID after ERCP (n PEP/n total)	Relative risk (95 % CI)	Interaction term
Overall	53/653	13/128		
Group				0.017
▪ Hydration group	27/307	2/65	0.35 (0.06–1.13)	
▪ Control group	26/346	11/63	2.32 (1.15–4.33)	

ERCP – endoscopic retrograde cholangiopancreatography; PEP – post-ERCP pancreatitis; NSAIDs – nonsteroidal anti-inflammatory drugs; CI – confidence interval.

tients for whom the timing of rectal NSAID administration was not available. We decided to use only patients in the control group (rectal NSAID monotherapy), because the randomization groups in the original RCT (aggressive periprocedural hydration plus rectal NSAID vs. rectal NSAID monotherapy) showed an interaction effect with the timing of rectal NSAID administration (▶ **Table 1**). In this way, we could avoid any potential influence of additional prophylaxis (aggressive periprocedural hydration) on the analyses.

Outcomes and definitions

The primary outcome of this study was the proportion of patients that developed post-ERCP pancreatitis according to the Cotton criteria [24]. Briefly, these criteria included new onset of upper abdomen pain and elevation of pancreatic enzymes (amylase/lipase) of at least three times the upper limit of normal range at 24 hours after the procedure and hospitalization for at least two nights. Secondary outcomes included the severity of post-ERCP pancreatitis, defined according to Cotton and revised Atlanta criteria [24, 25], ERCP-related complications according to Cotton [24], length of hospitalization, stay on the Intensive Care Unit, and mortality.

Statistical analysis

Because the current study is a non-randomized comparison, known prognostic factors (age, sex, body mass index [BMI], history of pancreatitis, trainee involvement, and pancreatic duct stent placement) for the primary outcome (post-ERCP pancreatitis) were tested for differences between the two groups. The variables that were deemed statistically ($P<0.05$) or with relevant differences were entered in a log-binominal regression model with post-ERCP pancreatitis as outcome and grouping variable as independent variable of main interest, thereby correcting the outcome for the potential confounders. Second, we performed predefined subgroup analyses for the same prognostic factors by entering interaction terms in the log-binominal regression analysis.

Continuous variables are presented as means with standard deviation (SDs) or medians with interquartile ranges (IQRs) and categorical variables as frequencies with percentages. Primary and secondary outcomes were assessed using the Mann-Whitney U test, Pearson X^2 test, or Fisher exact test as appropriate. The primary endpoint is presented as relative risk (RR) with corresponding 95 % confidence intervals. All analyses were performed by using R, version 3.6.2. A two-tailed $P<0.05$ was regarded as statistically significance.

Results

Cohort identification and characteristics

The data used for our analyses originated from 826 patients. We excluded seven patients because they did not undergo an ERCP, six patients withdrew informed consent before the ERCP, 11 patients did not receive rectal NSAIDs, and in 21 patients, the exact timing of rectal NSAID administration was unknown (▶ **Fig. 1**). Of the remaining 781 patients, 372 were randomized to the aggressive hydration group, and therefore, excluded as well. Finally, 409 patients were included for the primary and secondary analyses.

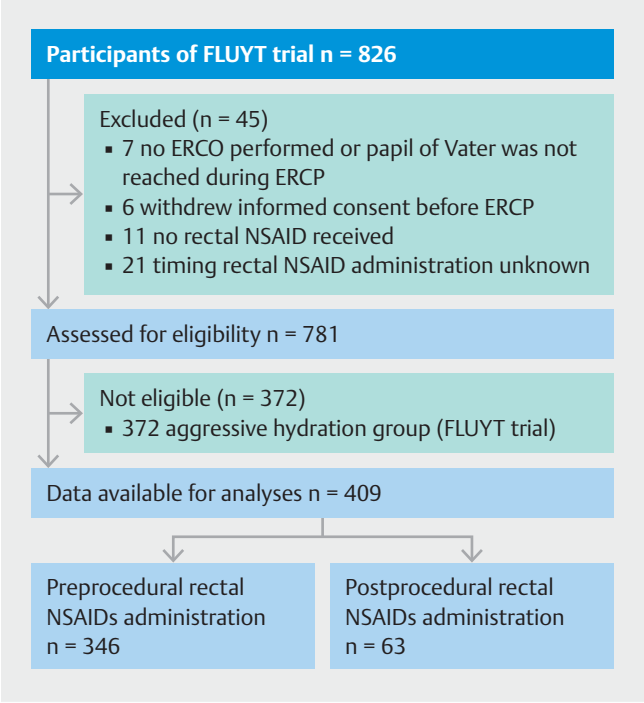
In 346 patients, the rectal NSAID was administered within 30 minutes before the start of the ERCP procedure (preprocedural group) and in 63 patients within 30 minutes after the end of the ERCP procedure (postprocedural group). Timing of rectal NSAID administration was equally distributed between hospitals and clinicians, and was often influenced by logistics around the ERCP procedure and independent of the ERCP indication. All rectal NSAIDs administered were diclofenac 100 mg.

Baseline and ERCP characteristics

Baseline and ERCP characteristics are summarized in ▶ **Table 2** and **Supplementary Table S1**. The median age was 59 years (IQR 49–71) and 237 patients (58 %) were women. The overall mean BMI was 27.45 kg/m^2 (±4.95). Choledocholithiasis was the most frequent indication for ERCP (80 %). No statistically significant differences at baseline were observed between the two groups, although BMI showed a potential clinically relevant difference ($P=0.07$).

Effectiveness and safety

Post-ERCP pancreatitis occurred in 37 of 409 patients (9 %, 95 % CI: 6.6–12.2) (▶ **Table 3**). Twenty-six of the 346 patients in the pre-procedure group had pancreatitis, compared with 11 of 63 patients in the post-procedure group (RR: 2.32; 95 % CI: 1.21 to 4.46, $P=0.020$). When adjusted for BMI, a relative risk of 2.36; 95 % CI: 1.12 to 4.55 ($P=0.015$) was found. We found fewer patients with mild pancreatitis in the pre-procedure group according to Cotton ($P=0.007$) or Atlanta ($P=0.011$) criteria. No differences between the groups were observed in development



▶ **Fig. 1** Patient recruitment flow diagram. ERCP – endoscopic retrograde cholangiopancreatography; NSAIDs – nonsteroidal anti-inflammatory drugs.

of moderate or severe pancreatitis according to Cotton (P = 0.16) or Atlanta criteria (P = 0.49), and other ERCP-related complications (P = 1.00). However, the median length of hospital stay of all patients in the post-procedure group was longer: 1.0 (IQR 1–4) vs. 1.0 (IQR 1–2), respectively (P = 0.022). Also, patients in the post-procedure group were more frequently admitted to the ICU (1 vs. 4; P = 0.002). A significant interaction was absent for all predefined subgroups (▶ **Fig. 2**). All subgroups appeared to benefit from administering rectal NSAIDs pre-procedure, although a statistically significant result was lacking. This may be explained by a type II error because we did find a statistically significant benefit for preprocedural NSAIDs in the total cohort.

Discussion

In this multicenter, prospective study, we observed that pre-procedure rectal diclofenac administration is associated with a lower risk of post-ERCP pancreatitis, a shorter hospital stay, and a lower risk of being admitted to the ICU in patients with presumed moderate to high risk compared to post-procedure use. The severity of the pancreatitis was not associated with administration timing.

A direct head-to-head comparison to assess optimal timing of rectal NSAID administration has not been performed. Several meta-analyses have evaluated the optimal timing of rectal NSAID administration by indirect comparisons. Four studies suggest that administering rectal NSAIDs before ERCP might achieve a greater reduction in post-ERCP pancreatitis incidence when comparing pre-ERCP and post-ERCP administration separately to placebo [16–18, 26]. Others, however, did not confirm this preference for pre-procedure administration [12–15]. The result of our study is in line with the only indirect, risk-stratified, RCT (n = 2600) on the timing of administering rectal NSAIDs to date [27]. This trial demonstrated that universal pre-procedure administration of rectal NSAIDs, rather than risk-stratified post-procedure administration, provides better protection against post-ERCP pancreatitis (relative risk [RR] 0.47; 95 % CI: 0.36–0.66, P < 0.0001). In high-risk patients, there was a RR of 0.47 (95 % CI: 0.27–0.82, P = 0.006) that favored preprocedural administration. This study, which provides the most robust evidence with respect to timing of rectal NSAIDs thus far, prompted the ESGE to recommend the preprocedural administration of rectal NSAID [3]. The revised ESGE guideline was published at the end of 2019, and therefore, not influence endoscopists in the original trial in their decision to administer the rectal NSAID pre-procedure or post-procedure. Our results are in line with this prospective study and confirm the revised ESGE guidelines.

The peak plasma concentration of NSAIDs occurs within 30 minutes from rectal administration [28, 29]. Furthermore, pancreatic injury starts early after induction of pancreatitis [30]. For this reason, it is logical to expect a more optimal peak serum concentration attained in the early phase of pancreatic injury to prevent pancreatic inflammation. In this regard, it is important to consider that the therapeutic window for prevention of post-ERCP pancreatitis may be narrow once the inflammatory cascade becomes activated.

A strength of this study is that the endpoints of the analysis (e. g. post-ERCP pancreatitis, severity, ERCP-related complications) were those used in the original RCT. As such, data on them were all collected prospectively on case record forms and there is no retrospective interpretation and judgment involved, which limits bias. In addition, a blinded adjudication committee evaluated all primary and secondary outcomes. Second, baseline characteristics did not differ between the two groups, and therefore, we assume only a minor risk of confounding by indication regarding the timing of administration of the rectal NSAID. Nevertheless, BMI showed a potentially clinically relevant difference, and for that reason, we decided to correct for BMI. Moreover, as we had specific data on patient- and procedure-related risk factors for post-ERCP pancreatitis, we were able to consider confounding factors and identify subgroups. This gave us an advantage over the meta-analyses that addressed the subject of rectal NSAID timing. Last, we included patients with moderate to high risk for post-ERCP pancreatitis in a multicenter setting, which increased the generalizability of our findings.

Several limitations must be acknowledged. First, we performed a non-randomized comparison. The ideal design to attain the highest level of evidence would be a randomized controlled trial. However, subjecting patients to such a trial may be deemed unethical, considering the current evidence favoring pre-procedure NSAIDs in our study, concomitant with the trial of Luo et al [27]. Second, we included a relatively small group of patients who received a rectal NSAID after the ERCP,

▶ **Table 2** Baseline and ERCP characteristics.

	Total (N = 409)	Pre-ERCP (N = 346)	Post- ERCP (N = 63)	*P* value
Age (yr) – median (IQR)	59 (49–71)	59.5 (49–71)	56.0 (47.5–70)	0.72
Female sex	237 (58 %)	203 (59 %)	34 (54 %)	0.58
Body mass index (kg/m²) – mean (SD)[1]	27.5 (4.95)	27.3 (4.98)	28.5 (4.66)	0.07
Previous cholecystectomy	112 (27 %)	96 (28 %)	16 (25 %)	0.82
ASA class on admission				0.52
▪ I: healthy status	101 (25 %)	89 (26 %)	12 (19 %)	
▪ II: mild systemic disease	245 (60 %)	204 (59 %)	41 (65 %)	
▪ III: severe systemic disease	63 (15 %)	53 (15 %)	10 (16 %)	
Smoker[2]				0.22
▪ Current	187 (46 %)	162 (47 %)	25 (40 %)	
▪ Past	92 (22 %)	76 (22 %)	16 (25 %)	
▪ Never	84 (21 %)	77 (22 %)	7 (11 %)	
Alcohol abuse[3,4]	64 (16 %)	52 (15 %)	12 (19 %)	0.19
ERCP indication				
(Suspicion of) common bile duct stones	329 (80 %)	279 (81 %)	50 (79 %)	0.95
▪ Cholangitis	46 (11 %)	36 (10 %)	10 (16 %)	0.30
▪ Postoperative bile leak	8 (2 %)	6 (2 %)	2 (3 %)	0.79
▪ Metastatic cancer	5 (1 %)	4 (1 %)	1 (2 %)	1.00
▪ Cholangiocarcinoma	7 (1 %)	7 (2 %)	0	0.54
▪ (Suspicion of) sphincter of Oddi dysfunction	5 (1 %)	4 (1 %)	1 (2 %)	1.00
▪ Other	13 (3 %)	12 (3 %)	1 (2 %)	
Complexity of ERCP [35]				0.50
▪ 1	29	23	6	
▪ 2	341	287	54	
▪ 3	37	34	3	
▪ 4	2	2	0	
Common bile duct cannulation achieved	380 (93 %)	322 (93 %)	58 (92 %)	0.79
Difficult cannulation[5,6]	117 (29 %)	98 (29 %)	19 (31 %)	0.83
(unintentional) pancreatic duct cannulation	153 (38 %)	127 (37 %)	26 (41 %)	0.58
Pancreatic duct stent placement	24 (6 %)	20 (6 %)	4 (6 %)	0.77

Data are expressed as n (%). IQR interquartile range. ASA American Society of Anesthesiologists. ERCP Endoscopic retrograde cholangiopancreatography.
[1] Eight missing: six in the preprocedural group and two in the postprocedural group.
[2] Forty-six missing: 31 in the preprocedural group and 15 in the postprocedural group.
[3] According to National Institute on Alcohol Abuse and Alcoholism (Women: more than three drinks on any single day and more than seven drinks per week. Men: more than four drinks on any single day and more than 14 drinks per week).
[4] Fifty-five missing: 38 in the preprocedural group and 17 in the postprocedural group.
[5] Difficult cannulation was defined as > 5 attempts.
[6] Eight missing. 6 missing in the preprocedural group and 2 missing in the postprocedural group.

▶ **Table 3** Primary and secondary outcomes for timing of rectal NSAID administration.

	Pre-ERCP (N = 346)	Post ERCP (N = 63)	*P* value
Primary outcome			
Post-ERCP pancreatitis	26 (7.5 %)	11 (17.5 %)	0.020
Adjusted for BMI			0.015
Secondary outcomes			
Post-ERCP pancreatitis severity Cotton			
▪ Mild	3 (< 1 %)	4 (6 %)	0.007
▪ Moderate + severe	23 (7 %)	7 (11 %)	0.16
Post-ERCP pancreatitis severity Atlanta			
▪ Mild	19 (5 %)	9 (14 %)	0.011
▪ Moderate + severe	7 (2 %)	2 (3 %)	0.49
ERCP-related complications	16 (5 %)	3 (5 %)	1
▪ Cholangitis	5 (1 %)	0	0.53
▪ Bleeding	9 (3 %)	2 (3 %)	1
▪ Perforation	3 (< 1)	1 (2 %)	0.53
Length of hospital stay (days) – median (IQR)	1 (1–2)	1 (1–4)	0.022
ICU admission	1 (< 1 %)	4 (6 %)	0.002
Length of ICU stay (days) – median (IQR)	33	2 (1.75–2.5)	0.59
30 day mortality	3 (< 1 %)	2 (3 %)	0.17
Mortality during 180 days of follow-up	6 (1 %)	2 (3 %)	0.36

Data are n (%) or median (IQR). BMI – body mass index; IQR – interquartile range; ERCP – endoscopic retrograde cholangiopancreatography.

which may potentially contribute to a type two error. Nevertheless, we deemed it justifiable to perform the analysis solely in the control group to rule out (possible) interactions of the aggressive hydration in the prevention of post-ERCP pancreatitis and rectal NSAID pharmacokinetics. Because international guidelines recommend using prophylactic rectal NSAID monotherapy, this seems even more appropriate.

Despite the use of rectal NSAIDs, the risk of post-ERCP pancreatitis remains relevant. Furthermore, the effect of rectal NSAIDs is mostly limited to prevention of mild pancreatitis [15, 19, 31–33]. Based on the results of the current study, we recommend administering a rectal NSAID before the start of ERCP to reach an optimal prophylactic effect. For future post-ERCP pancreatitis studies, we need to consider other strategies for optimizing current preventive care. A previous study established that there is an association between body weight and the effect of diclofenac [34]. Two other studies showed that a dose escalation to rectal indomethacin 200 mg administered after ERCP did not confer any advantage compared with the standard regime of 100 mg [8, 10]. It will be interesting to investigate whether the incidence of post-ERCP pancreatitis decreases when people with high body weight receive a higher dose of rectal NSAID administered before ERCP, as compared to the standard dose (100 mg). Perhaps it must also be taken into account that the pharmacodynamics of rectal NSAIDs may differ between individuals.

Conclusions

In conclusion, this study demonstrates that pre-procedure administration of prophylactic rectal NSAIDs in moderate- to high-risk patients is associated with a lower risk of post-ERCP pancreatitis, shorter hospital stay, and lower chance of ICU admittance compared to post-procedure administration. In all probability, it is a highly cost-effective intervention. These findings confirm the ESGE 2019 guideline's recommendation and guide clinicians in optimizing prophylactic care for ERCP procedures.

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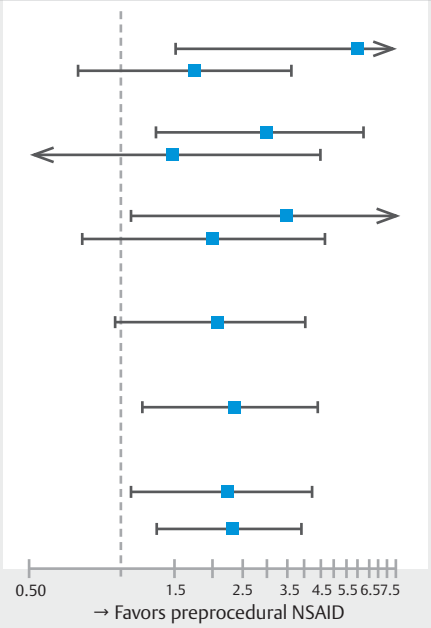
Subgroup	Preprocedural group n/N	Postprocedural group n/N	*P* value
Age			0.26
<40 years	3/54	4/12	
>40 years	23/292	7/51	
Sex			0.34
Female	16/203	8/34	
Male	10/143	3/29	
BMI			0.38
<25	10/122	4/14	
> 25	14/218	6/47	
Previous pancreatitis			0.49
Yes	1/9	2/4	
No	25/337	9/59	
Trainee involvement			0.99
Yes	1/30	0/4	
No	25/316	11/59	
Pancreatic duct stent placement			0.99
Yes	1/20	0/4	
No	25/324	10/58	
Overall	26/346	11/63	



▶ **Fig. 2** Forest plot of subgroup data. The position of the square indicates the relative risk of developing post-ERCP pancreatitis in each subgroup; the horizontal lines indicate 95 % confidence intervals. In three patients pancreatic duct stent placements technically failed: two in the preprocedural group and one in the postprocedural group. BMI – body mass index.

cess to all the data in the study and bears final responsibility for the decision to submit for publication.

Conflicts of interest

Dr. van Hooft has received research funding from Cook Medical anderved as a consultant for Medtronic, Cook Medical and Boston Scientific,outside the submitted work. Dr. Besselink has received researchfunding form Intuitive, Ethicon Endo-Surgery, and Medtronic, outsidethe submitted work. Dr. Bruno has received research funding fromBoston Scientific, Cook Medical, Pentax Medical, InterScope, ChiRho-Clin, and 3M and served as a consultant for Boston Scientific, CookMedical, and Pentax Medical, outside the submitted work. Dr. Fockenshas received consultancy fees from Cook Medical and Olympus,outside the submitted work. Dr. Drenth has received research fundingfrom Gilead to support Hepatitis C elimination in the Netherlands,outside the submitted work. Dr. van Geenen has received researchfunding from Mylan, Boston Scientific, and Olympus and served as aconsultant for MTW-Endoskopie, outside the submitted work.Christina J. Sperna Weiland, Xavier J.N.M. Smeets, Robert C. Verdonk, Alexander C. Poen, Abha Bhalla, Niels G. Venneman Wietske Kievit, Hester C. Timmerhuis, Devica S. Umans, and Hjalmar C. van Santvoort do not have potential conflicts of interest or disclosures to report.

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