Over-the-scope-clips versus standard treatment in high-risk patients with acute non-variceal upper gastrointestinal bleeding: a randomised controlled trial (STING-2)

Benjamin Meier ,[1] Andreas Wannhoff,[1] Ulrike Denzer,[2] Petros Stathopoulos,[2] Brigitte Schumacher,[3] David Albers,[3] Albrecht Hoffmeister,[4] Jürgen Feisthammel,[4] Benjamin Walter ,[5] Alexander Meining,[5,6] Edris Wedi,[7,8] Markus Zachäus,[9] Tilman Pickartz,[10] Armin Küllmer,[11] Arthur Schmidt,[11] Karel Caca[1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2021-325300).

For numbered affiliations see end of article.

Correspondence to
Professor Karel Caca, Gastroenterology, Klinikum Ludwigsburg, 71640 Ludwigsburg, Baden-Württemberg, Germany; karel.caca@rkh-kliniken.de

Received 1 June 2021
Accepted 26 February 2022
Published Online First 23 March 2022

To cite: Meier B, Wannhoff A, Denzer U, *et al*. *Gut* 2022;**71**:1251–1258.

ABSTRACT

Objective Acute non-variceal upper gastrointestinal bleeding (NVUGIB) is managed by standard endoscopic combination therapy, but a few cases remain difficult and carry a high risk of persistent or recurrent bleeding. The aim of our study was to compare first-line over-the-scope-clips (OTSC) therapy with standard endoscopic treatment in these selected patients.

Design We conducted a prospective, randomised, controlled, multicentre study (NCT03331224). Patients with endoscopic evidence of acute NVUGIB and high risk of rebleeding (defined as complete Rockall Score ≥7) were included. Primary endpoint was clinical success defined as successful endoscopic haemostasis without evidence of recurrent bleeding.

Results 246 patients were screened and 100 patients were finally randomised (mean of 5 cases/centre and year; 70% male, 30% female, mean age 78 years; OTSC group n=48, standard group n=52). All but one case in the standard group were treated with conventional clips. Clinical success was 91.7% (n=44) in the OTSC group compared with 73.1% (n=38) in the ST group (p=0.019), with persistent bleeding occurring in 0 vs 6 in the OTSC versus standard group (p=0.027), all of the latter being successfully managed by rescue therapy with OTSC. Recurrent bleeding was observed in four patients (8.3%) in the OTSC group and in eight patients (15.4%) in the standard group (p=0.362).

Conclusion OTSC therapy appears to be superior to standard treatment with clips when used by trained physicians for selected cases of primary therapy of NVUGIB with high risk of rebleeding. Further studies are necessary with regards to patient selection to identify subgroups benefiting most from OTSC haemostasis.

Trial registration number NCT03331224.

Significance of this study

What is already known on this subject?

⇒ Over-the-scope-clips (OTSCs) are increasingly used for treatment of severe upper gastrointestinal bleeding. OTSC therapy has shown to be superior to endoscopic standard treatment for recurrent peptic ulcer bleeding.

What this study adds?

⇒ In experienced hands, primary OTSC therapy appears to be superior to endoscopic standard treatment with clips for selected cases of non-variceal upper gastrointestinal bleeding (NVUGIB) with high risk of rebleeding.

How might it impact on clinical practice in the foreseeable future?

⇒ OTSC therapy should be considered for primary therapy in selected cases of NVUGIB with high risk of rebleeding. Further studies are necessary to identify subgroups benefiting most from OTSC haemostasis.

INTRODUCTION

Acute non-variceal upper gastrointestinal bleeding (NVUGIB) is a common clinical challenge with an estimated annual incidence of 40–150 cases per 100 000 in Europe and the USA.[1] NVUGIB is associated with mortality rates up to 10%, especially in the elderly and patients with comorbidities.[2] Endoscopic haemostasis is highly effective with success rates of ≥90%.[3] Combination of haemoclips or thermal therapy (coagulation) with submucosal injection (diluted epinephrine or fibrin) is considered to be the standard endoscopic approach for first-line treatment. However, insufficient haemostasis results in lower chance (75%) for successful endoscopic retreatment[4] and rebleeding is associated with increased mortality.[2] When angiographic or surgical salvage therapy is needed mortality increases to 10%–29%.[5 6]

Over-the-scope-clips (OTSC, Ovesco Endoscopy AG, Tübingen, Germany) were initially developed for closure of gastrointestinal (GI) perforations or fistulas[7 8] but are increasingly used for treatment of GI bleeding. Several retrospective studies have shown high efficacy of haemostasis with OTSC in patients with severe (Forrest Ia/Ib/IIa/IIb; haemoglobine <70 g/L) or high-risk (Rockall Score >7) NVUGIB.[9–14] For recurrent peptic ulcer bleeding, OTSC application has shown to be superior to standard endoscopic treatment in a prospective randomised controlled trial (RCT).[15] These studies

suggest that OTSC may also be effective as first-line therapy in high-risk patients. However, data on first-line OTSC treatment is scarce and the exact indications have not yet been defined.[16–21]

The aim of our study was to compare first-line OTSC therapy to standard endoscopic treatment in patients with acute NVUGIB and high risk of rebleeding.

METHODS

Trial design

We conducted a prospective, randomised, controlled, multicentre study ('stop bleeding-2', STING-2). Study was not blinded (patients, all participating study members, data recording and analysis).

Study sites

The study was conducted at 13 academic referral centres in Germany starting in september 2017 with different starting points at each centre (online supplemental table 4). Endoscopic procedures were performed by 1–2 endoscopists per centre and all were highly experienced in management of GI bleeding and OTSC application (>20 OTSC applications per year).

Participants

All patients hospitalised with suspected acute NVUGIB were to be screened for study enrolment. Written informed consent was obtained prior to oesophagogastroduodenoscopy (EGD). Intubated patients were included only when informed consent could be obtained from a legal surrogate. Inclusion criteria were: endoscopic evidence of acute NVUGIB (definition see below) with high risk of rebleeding (defined as complete Rockall Score ≥7), patient age ≥18 years, signed consent. Exclusion criteria were: variceal bleeding, tumour bleeding, endoscopic pretreatment of NVUGIB within last 4 weeks, obvious requirement of surgical therapy (eg, perforated ulcer), pregnancy or breast feeding, patient age <18 years, lack of written and informed consent.

Patient involvement

Patients were not involved in study design, study conduction, setting the research question/outcome measures or dissemination of study results. Patients were able to report their study experiences in a telephone interview on day 30 (not systematically assessed).

Randomisation

The random allocation sequence was generated in the coordinating centre (Ludwigsburg) by means of computer-generated random numerical series with odd numbers encoding for OTSC and even numbers for standard therapy (ST). Randomisation was done in blocks by 4 and stratified per centre. Sealed envelopes were created by trained study nurses and distributed to the participating centres. Patients meeting the inclusion criteria were randomised in a 1:1 ratio during endoscopy by opening the sealed envelopes. Randomisation was performed by the treating endoscopist.

Interventions and definitions

After obtaining written informed consent, patients with clinically suspected acute NVUGIB underwent EGD. Endoscopy was performed under deep sedation (propofol and/or midazolam) or after endotracheal intubation when indicated by treating physicians. Procedure time was recorded from first insertion until final extraction of the endoscope. Endoscopic definition of acute NVUGIB was evidence of active bleeding from peptic ulcers (Forrest Ia: spurting, Forrest Ib: oozing, Forrest IIa: visible vessel and presence of fresh blood/clots in the upper GI-tract), Dieulafoy's lesions or other lesions. Rebleeding risk was assessed using complete Rockall Score[22] (online supplemental table 1) and high risk of rebleeding was defined as complete Rockall Score ≥7.

If acute NVUGIB with high risk of rebleeding was confirmed, patients were enrolled and underwent randomisation during endoscopy. Treatment in the ST group consisted of application of at least two haemoclips or haemostasis with a thermal method. Choice of clip type or thermal treatment modality was left to the discretion of the endoscopist. Haemoclips or thermal therapy were combined with injection of diluted epinephrine (1:10 000–1: 50 000). Choice of volume and timing (injection before or after clip application) was left to the discretion of the endoscopist. In the OTSC group, the endoscope was extracted and equipped with the OTSC system. Choice of OTSC size (11 mm or 12 mm) and type (traumatic or atraumatic) was left to the discretion of the endoscopist. Before OTSC application the lesion was mobilised into the applicator cap using suction or tissue retraction. Injection of diluted epinephrine was allowed before clip application when indicated by the endoscopist (not mandatory). Successful endoscopic haemostasis was defined as absence of persistent bleeding after the assigned endoscopic therapy. Persistent bleeding was defined as present bleeding at the conclusion of index endoscopy.[23] This may occur when active bleeding does not stop despite study intervention (sufficient endoscopic attempt in ST group: injection therapy +application of at least two haemoclips or coagulation therapy; sufficient endoscopic attempt in OTSC group: application of an OTSC +injection therapy) or when a nonbleeding lesion develops active bleeding during the index endoscopy (eg, induced by endoscopic therapy) and is not controlled with the study therapy.

After successful haemostasis patients were scheduled for second-look endoscopy within 3 days (mandatory by study protocol). Further endoscopy was unscheduled and performed when indicated by treating physicians) and following criteria were met: haematemesis, melena or haematochezia after normalisation of stool colour, new evidence of tachycardia (>110 /min) or hypotension (systolic blood pressure <90 mm Hg) without alternative explanation, tachycardia or hypotension not resolving after endoscopy despite appropriate haemostasis and volume resuscitation associated with persistent melena or haematochezia, drop in haemoglobin ≥20 g/L or increase <10 g/L per transfused blood unit. Recurrent bleeding was defined as endoscopic evidence of active bleeding (Forrest Ia or Ib) or new evidence of fresh blood/clots within 7 days after primary successful endoscopic haemostasis/randomisation. Late rebleeding was defined as recurrent bleeding at day 8–30. Further bleeding was defined as cumulative 30-day rate of persistent and recurrent bleeding and late rebleeding. In case of further bleeding, secondary endoscopic attempt was performed. Choice of technique was left to the discretion of the endoscopist (OTSC rescue therapy was allowed, after removal of all haemoclips). In case of insufficient endoscopic control of bleeding, patients were referred for angiographic or surgical salvage therapy.

Peri-interventional management and follow-up

Peri-interventional management was determined by the responsible medical teams and according to international guidelines (eg, management of anticoagulants). Patients received 80 mg pantoprazole intravenously before endoscopy. Pantoprazole was continued intravenously for at least 72 hours. Choice of bolus regime (40 mg, two times a day) or continuous high-dose

administration (8 mg/hour) was left to the decision of the treating physicians. Pantoprazole was continued for at least 7 days (40 mg by mouth, two times a day) after endoscopic haemostasis. In case of evidence of Helicobacter pylori, eradication was performed according to current guidelines. A telephone follow-up was scheduled 30 days after endoscopy and performed by a trained study nurse. Patients were interviewed regarding clinical signs of upper GI bleeding, hospital readmisson or re-endoscopy since discharge.

Outcomes, study endpoints

Primary endpoint was clinical success defined as successful endoscopic haemostasis without evidence of recurrent bleeding. Secondary endpoints were: mortality, necessity of surgical or angiographic salvage therapy, duration of hospital stay, admission to intensive care unit (ICU) and duration of stay, number of blood units transfused.

Sample size calculation

The study hypothesis was: 'First-line therapy with OTSC is superior to standard treatment regarding clinical success in patients with acute NVUGIB and high risk of rebleeding'. We estimated clinical success rate to be 90% in the OTSC group based on several case series and retrospective studies discussed previously.[15] Few data are available comparing complete Rockall Score with endoscopic standard treatment. Rockall *et al* and two retrospective studies described clinical success rates between 56.2% and 80% for endoscopic standard treatment and complete Rockall Score 6–8.[22 24 25] In consequence, we estimated clinical success rate to be 70% in the standard group. Estimating a difference of ≥20% (clinical success, in favour of first-line OTSC application) with a power of 80%, $\alpha=0.05$, $\beta=0.10$ and a significance level of 0.05, 46.5 patients per treatment arm were required. Sample size calculation was performed by an independent statistical institute (York Hilger Statistical Consulting, Freiburg, Germany).

Data management and statistical analysis

Study data were documented on case report forms by the participating physicians or trained study nurses. Data were collected and reviewed in the coordinating study centre (Ludwigsburg). Data were transferred to an electronic database (Microsoft Excel) by trained study nurses. Data entry was validated by the coordinating physician of the coordinating study centre (BM). Data were analysed in an intention-to-treat analysis. Continuous variables were expressed as median with its range, whereas categorial variables were reported as frequencies and percentages unless stated otherwise. For continuous variables, differences were determined using Mann-Whitney and Kruskal-Wallis tests, as there was no Gaussian distribution of the data as confirmed by Kolmogorov-Smirnov test. χ^2s or Fisher's exact tests were used for categorial variables. For subanalyses of statistically significant tests, Bonferroni correction was applied. Statistical analysis was performed with SPSS (V.27, IBM). P values <0.05 were considered significant.

Protocol amendment

The protocol was amended in March 2018. The initial version of the protocol included a wrong version of complete Rockall Score (missing category). Consecutively, an amendment was submitted without consequence for enrolled patients. Rockall Score was higher for all patients after amendment. No patients had to be excluded because of the amendment.

RESULTS

Enrolment and patient characteristics

From September 2017 to February 2021, 246 patients from 9 different German centres (detailed information in online supplemental table 4) with suspected acute NVUGIB were screened for eligibility. Of those, 100 were enrolled in the trial and randomised. Three cases were excluded because of protocol violation (sealed envelopes were opened prior endoscopy). In all three cases the bleeding source could not be reached with a diagnostic (9.2 mm) endoscope because of high-grade oesophageal (n=2) or pyloric (n=1) stenosis. All three patients were primarily referred for angiographic or surgical therapy. Finally, 52 patients in the ST group and 48 patients in the OTSC group were analysed. Patient recruitment and reasons for non-enrolment are shown in figure 1. Patient and lesion characteristics are shown in table 1.

Endoscopic treatment

In the ST group, median procedure time was 28 min compared with 27 min in the OTSC group (p=0.593). In the ST group, endoscopic haemostasis was performed with haemoclips in 51 patients and 1 patient received thermal therapy using a Gold Probe (Boston Scientific, Natick, Massachusetts, USA). Additionally, all patients received injection therapy (diluted epinephrine). A median number of 2 clips (range 2–6) was used. The median volume of epinephrine solution was 10 mL (range 1–30 mL). In the OTSC group, haemostasis was performed with application of one clip in all cases. Twenty-four patients (50%) received additional injection therapy with diluted epinephrine before clip application and median volume was 5 mL (range 1–10 mL). All patients received second-look endoscopy within 3 days. Procedural characteristics are shown in table 2.

Primary endpoint

Primary endpoint of the study (clinical success) was reached in 44 patients (91.7%) in the OTSC group and in 38 patients (73.1%) in the ST group (p=0.019).

In the ST group, persistent bleeding occurred in six patients (11.5%) vs 0 patients in the OTSC group (p=0.027). In all cases, persistent bleeding occurred in spurting or oozing bleeding and was successfully managed by immediate OTSC application (OTSC rescue therapy). Characteristics of persistent bleedings are shown in online supplemental table 3.

In the ST group, recurrent bleeding was observed in eight patients (15.4%) compared with four patients (8.3%) in the OTSC group (p=0.362). Median time to recurrent bleeding in the ST group was 1 day (range 1–7 days). In four patients recurrent bleeding was detected during scheduled second look endoscopy, the other four cases were detected during unscheduled endoscopies. All recurrent bleedings in the ST group received successful endoscopic treatment: OTSC application (n=5, 62.5%), haemoclip/injection therapy (n=1, 12.5%), haemoclip (n=1, 12.5%), injection therapy (n=1, 12.5%).

In the OTSC group, all cases of recurrent bleeding were detected during unscheduled endoscopies. Recurrent bleedings in the OTSC group received successful endoscopic treatment: haemoclip/injection therapy (n=2, 50%), thermal therapy (n=1, 25%), topical agent (n=1, 25%). However, one patient (recurrent bleeding on day 3, successful secondary haemoclip/injection therapy) again developed recurrent bleeding on day 7 and was referred for surgical salvage therapy.

No recurrent bleeding was observed in the patient after thermal/injection therapy. Seven-day outcomes are shown in

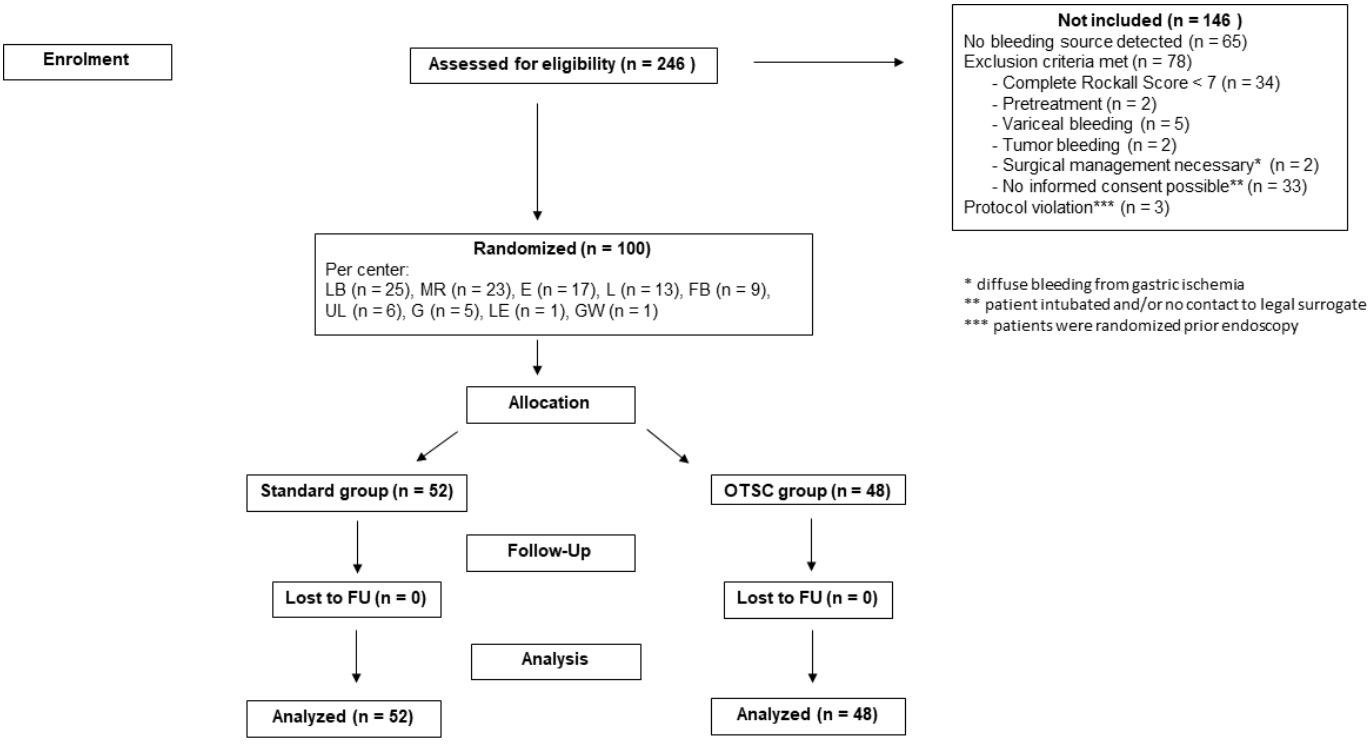

Figure 1 CONSORT flow diagram showing enrolment and analysis. CONSORT, Consolidated Standards of Reporting Trials; OTSC, over-the-scope-clips.

table 2. Management of further bleeding is shown in online supplemental table 2).

Secondary outcomes and follow-up

All patients completed 30-day follow-up. Late rebleeding was observed in the OTSC group only (n=2, 4.2%, p=0.228). In one patient, late rebleeding occurred 14 days after primary haemostasis (anastomotic ulcer) and secondary haemostasis was achieved endoscopically (haemoclip). Another patient experienced late rebleeding 10 days after primary haemostasis (gastric ulcer) and secondary haemostasis was also achieved endoscopically (thermal therapy). Further bleeding was 26.9% (n=14) in the ST group vs 12.5% (n=6) in the OTSC group (p=0.084). Median time to recurrent bleeding/late rebleeding was 4 days in the OTSC group (range 2–14 days) and detected later when compared with ST (4 days vs 1 day, p=0.043).

Median number of transfused blood units was three in both groups. Median number of ICU stay/hospital stay was 2 days/10 days in the ST group vs 3 days/9 days in the OTSC group. 30d mortality was 7.7% (n=4) in the ST group and 6.3% (n=3) in the OTSC group. Overall 30d mortality was 7.0%. Causes of death were not related to bleeding in all cases (sepsis n=5, liver failure n=1, hypoxia/pulseless electric activity n=1) and all events occurred during hospital stay. One patient in the ST group was readmitted to hospital because of deep vein thrombosis after discontinuation of apixaban on day 27. In the ST group, two patients (3.8%) required surgical therapy. In one patient, biopsies unexpectedly revealed gastric cancer and oncologic surgical resection was performed on day 28. Another patient was readmitted on day 16 with abdominal pain after successful treatment of a Dieulafoy's lesion in the stomach. Endoscopy unexpectedly showed a perforated duodenal ulcer (not described during index EGD or second look endoscopy) and patient received surgical therapy. In the OTSC group, two patients (4.2%) required surgical therapy. One patient (history of numerous anastomotic ulcer bleedings) was re-admitted on day 13 because of decreasing haemoglobin level without clinical bleeding signs. Endoscopy showed the OTSC in situ without bleeding signs. Patient was scheduled for surgical revision of gastric anastomosis (interdisciplinary and patients decision). Another patient received surgical salvage therapy after recurrent bleedings on day 3 and 7 (case described above). Cumulative (30 day) rate of surgical therapy was 4%. Secondary outcomes are shown in table 3.

DISCUSSION

OTSC therapy has shown to be more effective than standard treatment in patients with recurrent peptic ulcer bleeding in our previously STING-1 trial.[15] Furthermore, it is associated with high success rates for severe bleeding and was therefore suggested as primary therapy for high-risk patients. However, apart from one recent smaller RCT,[17] data are mainly limited to retrospective studies with heterogeneous study populations and inconsistent definitions of high-risk lesions.[16 18–21] We, therefore, aimed to investigate first-line OTSC treatment vs ST in patients with NVUGIB and high risk for rebleeding in a larger multicentre RCT. In contrast to other studies, we used complete Rockall Score (≥7) to define patients at high risk of rebleeding.

In our study, clinical success (primary endpoint, successful endoscopic haemostasis without evidence of recurrent bleeding) was significantly higher in the OTSC group compared with the ST group (91.7% vs 73.1%, p=0.019). We chose this combined endpoint, as immediate and durable haemostasis is the most important outcome for the patients. This is also in accordance with international recommendations for studies on upper GI

Table 1 Patient and lesion characteristics

Patient characteristics	Standard (n=52)	OTSC (n=48)	P value
Age, years, median (range)	79 (51–96)	78 (42–92)	0.981
Sex, n (%)			0.830
Male	37 (71.2)	33 (68.8)	
Female	15 (28.8)	15 (31.2)	
History of peptic ulcer, n (%)	12 (23.1)	7 (14.6)	0.317
History of upper GI surgery, n (%)	4 (7.7)	5 (10.4)	0.734
NSAID monotherapy, n (%)	20 (38.5)	19 (39.6)	1.000
Anticoagulation or platelet inhibition, n (%)	22 (42.3)	19 (39.6)	0.840
New oral anticoagulants (paused periprocedurally), n	10 (5)	8 (4)	
Phenprocoumon (paused periprocedurally), n	7 (3)	8 (4)	
Dual platelet inhibition (paused periprocedurally), n	5 (1)	2 (2)	
Triple therapy (paused periprocedurally), n	0 (-)	1 (0)	
Glucocorticoid use, n (%)	4 (7.7)	8 (16.7)	0.223
Presence of cirrhosis, n (%)	5 (9.6)	4 (8.3)	1.000
Presence of renal insufficiency, n (%)	7 (13.5)	7 (14.6)	1.000
Haemodynamic instability at randomisation, n (%)	29 (55.8)	29 (60.4)	0.839
Initial treatment on ICU, n (%)	31 (59.6)	31 (64.6)	
Haemoglobin level at randomisation, g/L, median (range)	74 (42–120)	6.8 (3.5–12.8)	0.234
Complete Rockall Score, median (range)	8 (7–10)	8 (7–10)	0.417
Complete Rockall Score, n (%)			0.873
7 points	24 (46.2)	18 (37.5)	
8 points	17 (32.7)	18 (37.5)	
9 points	9 (17.3)	10 (20.8)	
10 points	2 (3.8)	2 (4.2)	
Location of lesion, n (%)			0.395
Oesophagus	4 (7.7)	1 (2.1)	
Stomach	21 (40.4)	15 (31.3)	
Duodenum	24 (46.1)	29 (60.4)	
Posterior wall of bulbus, n	3	4	
Postbulbar, n	5	4	
Anastomosis	3 (5.8)	3 (6.2)	
Type of lesion, n (%)			1.000
Peptic ulcer	42 (80.7)	42 (87.5)	
Anastomotic ulcer	3 (5.8)	3 (6.2)	
Dieulafoy's lesion	3 (5.8)	2 (4.2)	
Associated with reflux esophagitis	3 (5.8)	1 (2.1)	
Oozing bleeding, n	2	1	
Spurting bleeding, n	1	–	
Mallory-Weiss-Tear (oozing bleeding)	1 (1.9)	–	
Forrest classification, n (%)			0.660
Ia (spurting)	9 (17.3)	6 (12.5)	
Ib (oozing)	23 (44.2)	24 (50.0)	
IIa (visible vessel)+evidence of bleeding	16 (30.8)	17 (35.4)	
Lesion size			0.204
≤20 mm, n (%)	44 (84.6)	45 (93.8)	
>20 mm, n (%)	8 (15.4)	3 (6.2)	
>30 mm, n	5	1	

GI, gastrointestinal; ICU, intensive care unit; NSAID, nonsteroidal antiinflammatory drugs; OTSC, over-the-scope-clips.

bleeding.[23] A trend towards OTSC superiority was also observed at day 30. However, due to two late rebleedings in the OTSC group (day 10 and 14) difference did not reach statistical significance (p=0.084). This may be due to the small sample size of the study.

Successful immediate endoscopic haemostasis could be achieved in all cases in the OTSC group. This is in line with previous published study results on haemostasis with OTSC.[9 10 12 13 17] Twenty-seven per centof lesions included into our study can be considered as 'difficult' (table 1) because of size (>20 mm) or location (fundus, postbulbar or posterior wall of the bulbus). Bleeding from large fibrotic ulcers might be treated more effectively with OTSC compared with haemoclips due to their ability to grasp more tissue and their significantly higher compression force.[26 27] Additionally, the 'bear claw' design allows anchoring in fibrotic ulcer base. Haemoclip application can be hampered by limited space in the duodenal bulb. In this situation, OTSC application might be easier because the tip of the cap allows better visualisation and clip application does not require as much distance from the duodenal wall as haemoclips.[15] In our study, all patients with persistent (n=6) or recurrent (n=5/8) bleeding after ST were successfully treated with OTSC. In line with the STING-1 study, these results underline the efficacy of OTSC for difficult bleeding sources and endoscopic rescue strategy after fuilure of standard methods.

Recurrent bleeding was observed more frequently in the ST group (15.4% vs 8.3%). However, this difference did not reach statistical significance (p=0.362). Furthermore, we did not observe a significant difference in other secondary endpoints such as need for angiographic or surgical therapy. This may be due to the sample size as the study was not designed to prove a difference in those outcomes and may therefore be underpowered to address this topic. Another reason could be the design of the study which allowed OTSC rescue therapy (with more durable haemostatic effect) in cases of persistent bleeding after treatment with standard methods.

A recent randomised controlled single-centre study by Jensen *et al* (n=53 patients) also compared OTSC first-line treatment with standard treatment.[17] Rebleeding rate was significantly lower after OTSC application compared with ST (4.0% vs 28.6%, p=0.017). Additionally, rate of severe complications was significantly lower after OTSC application (0.0% vs 14.3%, p=0.049). Although both studies indicate superiority of OTSC treamtent, comparability between the study of Jensen *et al* and our study is limited. As stated above, our study was designed to address a combined endpoint (clinical success) and allowed OTSC rescue therapy. The strength of our study is a consistent and objective definition for high-risk lesions (complete Rockall Score ≥7). The Rockall score is well evaluated and was shown to accurately predict risk of rebleeding. Compared with other criteria it is more objective and reproducible. Moreover, we included nearly double amount of patients (n=100 vs n=53) compared with study by Jensen *et al*.

In our study, clinical success rate after endoscopic standard treatment (73.1%) was lower when compared with other studies. This may have several reasons. In contrast to other studies but similar to the study of Jensen *et al*, we included patients only considered to be at high risk for rebleeding and over 40% of patients in the ST group were on anticoagulants or platelet inhibition. Furthermore, therapy in the ST group was almost exclusively haemoclip application as opposed to coagulation plus injection of diluted epinephrine (n=1), both of which are considered to be the standard approach.[1] A possible explanation for the clip preference could be, that in Europe coagulation therapy is not as popular as in the USA or some other countries. Therefore, our study results do not allow direct comparison of OTSC vs thermal therapy, and are strictly speaking a comparative therapy of two clip options. In the above mentioned RCT by Jensen *et al*, large (≥15 mm) firm-based fibrotic ulcers were primarily treated with coagulation (n=11/28) in the ST group, with similar efficacy compared with our study as far as can be told from limited case numbers. On the other hand, a study by Toka *et al* indicated lower risk of rebleeding for monopolar coagulation versus haemoclip application.[28] We, therefore, cannot fully

Table 2 Endoscopic therapy and 7 days outcome

Endoscopic therapy	Standard (n=52)*	OTSC (n=48)†	P value	Absolute difference (%)
Clinical success‡, n (%)	38 (73.1)	44 (91.7)	0.019	18.6
Endoscopic therapy				
No of OTSC, n (range)	–	1 (1–1)	–	–
No of haemoclips, median (range)	2 (2–6)	–	–	–
Use of thermal therapy, n (%)	1 (1.9)	–	–	–
Volume of injection (diluted epinephrine), ml, median (range)	10 (1–30)	5 (1–10)	<0.001	–
Procedure time, min, median (range)	28 (15–95)	27 (15–75)	0.593	–
Persistent bleeding, n (%)	6 (11.5)	0 (0)	0.027	–11.5
Recurrent bleeding, n (%)	8 (15.4)	4 (8.3)	0.362	–7.1

*Application of at least two haemoclips (or haemostasis with a thermal method) plus injection of of diluted epinephrine.
†Injection of diluted epinephrine was allowed before OTSC application but not mandatory.
‡Successful endoscopic haemostasis without evidence of recurrent bleeding.
OTSC, over-the-scope-clips.

exclude that for some ulcers in our study, suboptimal standard treatment might have been used. Furthermore, our study results may not be directly transferable to countries in which thermal therapy is used more frequently as clinical standard. Another reason for the relatively low success rate of ST in our study may be that additional treatment modalities like injection of fibrin glue or use of haemostatic powders were not allowed. When defining endoscopic treatment, we aimed to adhere to international guidelines but as well tried to mimic 'real-world' clinical practice in German tertiary referral centres. In consequence, we defined standard treatment according to current guidelines but also allowed procedural and peri-interventional management according to local standards. Management of anticoagulants for example was not defined in the protocol and determined by the treating physicians according to international guidelines. However, type of anticoagulants and peri-interventional pausing of medication was similar in both groups.

Our study may have other limitations. The most relevant may be a possible case selection, due to several facts: Only endoscopists experienced with OTSC application did participate, usually 1–2 per centre. This limited the number of team members on call for emergency endoscopy confronted with upper GI bleeding. It also could mean that these physicians may have selected cases which are especially useful for OTSC. Our study was unblinded and randomisation by the treating endoscopist during endoscopy might have resulted in a selection bias. All endoscopists were instructed to document patients not undergoing randomisation on the screening lists and we provided reasons for non-enrolment in figure 1. However, we cannot exclude that some patients were not randomised

Table 3 Thirty-day outcome/secondary endpoints

	Standard (n=52)*	OTSC (n=48)†	P vlaue	Absolute difference (%)
Further bleeding‡, n (%)	14 (26.9)	6 (12.5)	0.084	–14.4
Persistent bleeding, n (%)	6 (11.5)	0 (0)	0.027	
Recurrent bleeding, n (%)	8 (15.4)	4 (8.3)	0.777	
Late rebleeding, n (%)	0 (0)	2 (4.2)		
Time to recurrent bleeding/late rebleeding, days (range)	1 (1–7)	4 (2–14)	0.043	
Blood units transfused, median (range)	3 (0–10)	3 (0–13)	0.484	
Duration of ICU stay, days, median (range)	2 (0–18)	3 (1–36)	0.058	
Duration of hospital stay, days, median (range)	10 (3–71)	9 (3–67)	0.836	
Deep vein thrombosis, n (%)	1 (1.9)	–		
Mortality, n (%)	4 (7.7)	3 (6.3)	1.000	–1.4
Sepsis, n (%)	2 (50.0)	3 (100.0)		
Liver failure, n (%)	1 (25.0)	–		
Hypoxia/PEA, n (%)	1 (25.0)	–		
Surgical therapy, n (%)	2 (3.8)	2 (4.2)	1.000	–0.4
Salvage therapy, n (%)	–	1 (50.0)	–	–
Oncological resection, n (%)	1 (50.0)	–	–	–
Perforation, n (%)	1 (50.0)	–	–	–
Revision of gastric anastomosis, n (%)	–	1 (50.0)		

*Application of at least two haemoclips (or haemostasis with a thermal method) plus injection of diluted epinephrine.
†Injection of diluted epinephrine was allowed before OTSC application but not mandatory.
‡Cumulative 30 days rate of persistent and recurrent bleeding and late rebleeding.
§Recurrent bleeding at day 8–30.
ICU, intensive care unit; OTSC, over-the-scope-clips; PEA, pulseless electrical activity.

(because of personal decision of the endoscopist, for example, based on lesion type or location) and not documented. Additionally, data recording and documentation by treating endoscopists might also have biased study results. In general, this may explain the low number of screened and included cases per centre and year, namely five per centre on year on average (online supplemental table 4). In the prior study of Jensen *et al*,[17] this rate was much higher in two centres (about 50 screened cases/year).

For ethical reasons, OTSC rescue therapy was allowed. The study design allowed an immediate switch to OTSC therapy when ST was unsuccessful (personal decision in case of persistent bleeding). Some endoscopists might have had a low threshold to declare persistent bleeding and switch to OTSC treatment. As all endoscopists were experienced OTSC users, they might have switched early to OTSC therapy (or might have preferred OTSC rescue therapy in case of recurrent bleeding after ST) based on personal experience, especially in large firm-based fibrotic ulcers. Furthermore, we did not define a minimum time to spend for haemostasis. However, study protocol demanded application of at least two haemoclips in the ST group to assure sufficient effort for primary haemostasis. Only expert centres participated in the study, so we assume that efforts made for haemostasis were sufficient in the ST group. However, we cannot exclude a potential bias towards OTSC due to rescue therapy and unblinded study design. Moreover, as all endoscopists in our study were highly experienced in OTSC application, our data may not be generalisable. In our clinical experience, there certainly is a learning curve for OTSC application and associated accessories, especially for large lesions or lesions located at difficult positions. Gölder *et al* showed no differences in bleeding control rates between unexperienced (<5 OTSC applications), medium experienced (5–20 OTSC applications) and highly experienced (>20 OTSC applications) OTSC users.[29] Those results indicate that OTSC haemostasis can be learnt relatively fast. However, due to the expanding role of OTSC haemostasis, structured training should be offered in more centres worldwide. Further studies may address the learning curve of OTSC haemostasis in more detail. Another potential limitation of the study is the inhomogeneous enrolment of patients between the participating centres. Patient recruitment was more difficult than expected and additional study sites were included after initiation of the study. Only four centres (4–8 endoscopists) participated actively and included 78% of patients. Centres evaluated few patients per month, probably because of study design. High possibility for inclusion (complete Rockall Score ≥7) was only given for very old patients (≥80 years) and/or patients with haemodynamic instability which in not represented in a majority of cases in NVUGIB. Additionally, obtaining informed consent from this subgroup can be challenging, especially in emergency situations or at night. There is a high possibility, that haemodynamic stable and younger patients (complete Rockall Score <7) were screened but not documented on the screening lists. However, low inclusion numbers per month and centre may also indicate case selection bias.

In conclusion, this is the second RCT comparing first-line OTSC therapy vs ST (mostly conventional clipping) in patients with NVUGIB and high risk of rebleeding. Our study results indicate superiority of OTSC first-line therapy compared with standard endoscopic treatment in difficult patients and under certain conditions such as specially trained endoscopists. It also highlighted the efficacy of OTSC salvage therapy after unsuccessful initial haemostasis. However, further trials are necessary to study the possibility of a broader use of this more complex and expensive haemostatic therapy as well as to identify subgroups benefiting most from OTSC haemostasis.

Author affiliations
[1]Gastroenterology, Klinikum Ludwigsburg, Ludwigsburg, Germany
[2]Gastroenterology, University of Marburg, Marburg, Germany
[3]Gastroenterology, Elisabeth-Krankenhaus-Essen, Essen, Germany
[4]Gastroenterology, University of Leipzig, Leipzig, Germany
[5]Gastroenterology, University of Ulm, Ulm, Germany
[6]Gastroenterology, University of Würzburg, Würzburg, Germany
[7]Gastroenterology, Sana Klinikum Offenbach, Offenbach, Germany
[8]Gastroenterology, University of Göttingen, Göttingen, Germany
[9]Gastroenterology, Helios Park-Klinikum Leipzig, Leipzig, Germany
[10]Gastroenterology, University of Greifswald, Greifswald, Germany
[11]Gastroenterology, University of Freiburg, Freiburg im Breisgau, Germany

Acknowledgements Professor Dr. Ellenrieder from University of Göttingen for patient recruitment and treatment. All other members of the participating centres for patient recruitment and treatment. Juliane Behn and Katja Hahmann-Dolle (study nurses at study centre) for coordination and data management.

Contributors KC, AS and BM designed the study and wrote the protocol. BM was the coordinating physician at the study centre and wrote the manuscript according to CONSORT guidelines. AS and KC reviewed the manuscript extensively. All authors had access to the study data and reviewed and approved the final manuscript. Ovesco Endoscopy provided a financial allowance for participating centres and was involved in planning and designing the trial but did not participate in data collection, analysis or manuscript drafting. Guarantor of work: BM.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests BM received fees for research activities and lecture fees from Ovesco Endoscopy AG. AM is a consultant for Ovesco Endoscopy AG and received lecture fees from Ovesco Endoscopy AG. AS received lecture fees and study grants from Ovesco Endoscopy AG. EW and KC received lecture fees from Ovesco Endoscopy AG. AW, UD, PS, BS, DA, AH, JF, BMW, MZ, TP and AK have no disclosures to report.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This study involves human participants and was approved by Ludwigsburg ID: S-445/2017. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

All data relevant to this study are included in the article or uploaded as supplementary information.

ORCID iDs
Benjamin Meier http://orcid.org/0000-0003-3625-7062
Benjamin Walter http://orcid.org/0000-0002-7356-024X

REFERENCES

1 Gralnek IM, Dumonceau J-M, Kuipers EJ, *et al*. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of gastrointestinal endoscopy (ESGE) guideline. *Endoscopy* 2015;47:a1–46.
2 Lau JYW, Barkun A, Fan D-ming, *et al*. Challenges in the management of acute peptic ulcer bleeding. *Lancet* 2013;381:2033–43.
3 Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol* 2012;107:345–60.
4 Elmunzer BJ, Young SD, Inadomi JM, *et al*. Systematic review of the predictors of recurrent hemorrhage after endoscopic hemostatic therapy for bleeding peptic ulcers. *Am J Gastroenterol* 2008;103:2625–32.

5 Jairath V, Kahan BC, Logan RFA, *et al*. National audit of the use of surgery and radiological embolization after failed endoscopic haemostasis for non-variceal upper gastrointestinal bleeding. *Br J Surg* 2012;99:1672–80.
6 Nykänen T, Peltola E, Kylänpää L, *et al*. Bleeding gastric and duodenal ulcers: case-control study comparing angioembolization and surgery. *Scand J Gastroenterol* 2017;52:523–30.
7 Arezzo A, Verra M, Reddavid R, *et al*. Efficacy of the over-the-scope clip (OTSC) for treatment of colorectal postsurgical leaks and fistulas. *Surg Endosc* 2012;26:3330–3.
8 Weiland T, Fehlker M, Gottwald T, *et al*. Performance of the OTSC system in the endoscopic closure of iatrogenic gastrointestinal perforations: a systematic review. *Surg Endosc* 2013;27:2258–74.
9 Chandrasekar VT, Desai M, Aziz M, *et al*. Efficacy and safety of over-the-scope clips for gastrointestinal bleeding: a systematic review and meta-analysis. *Endoscopy* 2019;51:941–9.
10 Kirschniak A, Kratt T, Stüker D, *et al*. A new endoscopic over-the-scope clip system for treatment of lesions and bleeding in the Gi tract: first clinical experiences. *Gastrointest Endosc* 2007;66:162–7.
11 Richter-Schrag H-J, Glatz T, Walker C, *et al*. First-Line endoscopic treatment with over-the-scope clips significantly improves the primary failure and rebleeding rates in high-risk gastrointestinal bleeding: a single-center experience with 100 cases. *World J Gastroenterol* 2016;22:9162–71.
12 Wedi E, Gonzalez S, Menke D. One hundred and one over-the-scope-clip applications for severe gastrointestinal bleeding, leaks and fistulas. *World J Gastroenterol* 2016;22:1844–53.
13 Wedi E, von Renteln D, Gonzalez S, *et al*. Use of the over-the-scope-clip (OTSC) in non-variceal upper gastrointestinal bleeding in patients with severe cardiovascular comorbidities: a retrospective study. *Endosc Int Open* 2017;05:E875–82.
14 Weiland T, Rohrer S, Schmidt A, *et al*. Efficacy of the OTSC system in the treatment of Gi bleeding and wall defects: a PMCF meta-analysis. *Minim Invasive Ther Allied Technol* 2020;29:121–39.
15 Schmidt A, Gölder S, Goetz M, *et al*. Over-the-Scope clips are more effective than standard endoscopic therapy for patients with recurrent bleeding of peptic ulcers. *Gastroenterology* 2018;155:674–86.
16 Brandler J, Baruah A, Zeb M, *et al*. Efficacy of Over-the-Scope clips in management of high-risk gastrointestinal bleeding. *Clin Gastroenterol Hepatol* 2018;16:690–6.
17 Jensen DM, Kovacs T, Ghassemi KA, *et al*. Randomized controlled trial of Over-the-Scope clip as initial treatment of severe Nonvariceal upper gastrointestinal bleeding. *Clin Gastroenterol Hepatol* 2021;19:2315-2323.e2.
18 Mangiafico S, Pigò F, Bertani H, *et al*. Over-the-scope clip vs epinephrine with clip for first-line hemostasis in non-variceal upper gastrointestinal bleeding: a propensity score match analysis. *Endosc Int Open* 2020;08:E50–8.
19 Manta R, Mangiafico S, Zullo A, *et al*. First-Line endoscopic treatment with over-the-scope clips in patients with either upper or lower gastrointestinal bleeding: a multicenter study. *Endosc Int Open* 2018;06:E1317–21.
20 Robles-Medranda C, Oleas R, Alcívar-Vásquez J, *et al*. Over-The-Scope clip system as a first-line therapy for high-risk bleeding peptic ulcers: a retrospective study. *Surg Endosc* 2021;35:2198-2205.
21 Wedi E, Fischer A, Hochberger J, *et al*. Multicenter evaluation of first-line endoscopic treatment with the OTSC in acute non-variceal upper gastrointestinal bleeding and comparison with the Rockall cohort: the FLETRock study. *Surg Endosc* 2018;32:307–14.
22 Rockall TA, Logan RF, Devlin HB, *et al*. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut* 1996;38:316–21.
23 Laine L, Spiegel B, Rostom A, *et al*. Methodology for randomized trials of patients with nonvariceal upper gastrointestinal bleeding: recommendations from an international consensus conference. *Am J Gastroenterol* 2010;105:540–50.
24 Bessa X, O'Callaghan E, Ballesté B, *et al*. Applicability of the Rockall score in patients undergoing endoscopic therapy for upper gastrointestinal bleeding. *Dig Liver Dis* 2006;38:12–17.
25 Lip HT, Heah HT, Huei TJ, *et al*. Rockall risk score in predicting 30 days non-variceal upper gastrointestinal rebleeding in a Malaysian population. *Med J Malaysia* 2016;71:225–30.
26 Kato M, Jung Y, Gromski MA, *et al*. Prospective, randomized comparison of 3 different hemoclips for the treatment of acute upper Gi hemorrhage in an established experimental setting. *Gastrointest Endosc* 2012;75:3–10.
27 Naegel A, Bolz J, Zopf Y, *et al*. Hemodynamic efficacy of the over-the-scope clip in an established porcine cadaveric model for spurting bleeding. *Gastrointest Endosc* 2012;75:152–9.
28 Toka B, Eminler AT, Karacaer C, *et al*. Comparison of monopolar hemostatic forceps with soft coagulation versus hemoclip for peptic ulcer bleeding: a randomized trial (with video). *Gastrointest Endosc* 2019;89:792–802.
29 Gölder S, Neuhas L, Freuer D, *et al*. Over-the-scope clip in peptic ulcer bleeding: clinical success in primary and secondary treatment and factors associated with treatment failure. *Endosc Int Open* 2019;7:E846–54.

Clinic	Score
Age	
< 60	0
60 - 79	1
≥ 80	2
Shock	
No shock	0
Heart rate > 100/min	1
Systolic blood pressure < 100 mmHg	2
Comorbidities	
None	0
Any EXEPT renal failure, liver failure, disseminated malignancy	2
Renal failure, liver failure, disseminated malignancy	3
Endoscopy	
Diagnosis	
Mallory-Weiss-tear	0
No lesion identified and no stigmata of recent hemorrhage	0
All other diagnosis	1
Malignany of upper GI-tract	2
Major stigmata of recent hemorrhage	
None or dark spot only	0
Visible or spurting vessel or blood in upper GI-tract or adherent clot	2

Supplementary Table 1: Complete Rockall Score

	Standard (n = 52)	OTSC (n = 48)
Persistent bleeding, n (%)	6 (11.5)	0 (0)
OTSC therapy, n (%)	6 (100)	-
Recurrent bleeding/Late rebleeding until d30, n (%)	0 (0)	-
Recurrent bleeding, n (%)	8 (15.4)	4 (8.3)
OTSC therapy, n (%)	5 (62.5)	0 (0)
Recurrent bleeding/Late rebleeding until d30, n	0	-
Hemoclip therapy, n (%)	1 (12.5)	0 (0)
Hemoclip + injection therapy, n (%)	1 (12.5)	2 (50)
Injection therapy, n (%)	1 (12.5)	0 (0)
Thermal therapy, n (%)	0 (0)	1 (25)
Topical agent, n (%)	0 (0)	1 (25)
Surgical therapy, n	0	1*
Late rebleeding, n (%)	0 (0)	2 (4.2)
Hemoclip therapy, n (%)	-	1 (50)
Thermal therapy, n (%)	-	1 (50)

Supplementary Table 2: Management of further bleeding. * after recurrent bleeding on day 3 and day 7

Sex	Age	cRS	Anticoagulants	Schock	Hb (g/dl)	Bleeding sign	Lesion type	Lesion location	Lesion size (mm)	Center
m	82	9	Phenprocoumon	no	9.7	Hematemesis	FIb	Duodenal bulb	20	G
w	84	7	Phenprocoumon	no	7.8	Melena	FIb	Gastric antrum	20	MR
w	83	8	Apixaban	yes	4.8	Melena	FIa	Gastric antrum	50	MR
m	72	7	ASS + Glucocorticiod	no	6.6	Melena	FIa	Gastric ventricle	15	LB
w	86	9	Apixaban	no	10.3	Hematemesis	FIb	Gastric antrum	30	LB
m	67	7	ASS + Glucocorticiod	no	10.3	Melena	FIb	Gastric antrum	15	LB

Supplementary Table 3: Characteristics of persistent bleedings after standard treatment

Study center	Recruitment	Enrolled (n)	Screened, not enrolled (n)
Ludwigsburg	09/2017-02/2021	25	23
Marburg	12/2018-02/2021	23	17
Essen	11/2017-02/2021	17	data not available
Leipzig (University)	12/2018-02/2021	13	49
Freiburg	11/2018-02/2021	9	17
Ulm	07/2018-02/2021*	6	34
Göttingen	10/2018-02/2021*	5	2
Greifswald	12/2020-02/2021	1	4
Leipzig (Helios Park-Klinikum)	12/2019-02/2021	1	0

Supplementary Table 4: Study participation stratified per center *recruiting stopped earlier when major coordinating physician left the institute