



# Over-the-scope clip versus transcatheter arterial embolization for refractory peptic ulcer bleeding—A propensity score matched analysis

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## Abstract

**Background:** Transcatheter arterial embolization (TAE) or surgery are standard treatment of peptic ulcer bleeding (PUB) refractory to endoscopic hemostasis. Over-the-scope clips (OTSC) have shown superiority to standard endoscopic treatment.

**Objective:** To compare OTSC treatment to TAE in refractory peptic ulcer bleeding.

**Patients and Methods:** In this retrospective, multicenter study, 128 patients treated with OTSC ( $n = 66$ ) or TAE ( $n = 62$ ) for refractory PUB between 2009 and 2019 in four academic centers were analyzed. Primary endpoint was clinical success (hemostasis + no rebleeding within 7 days). Secondary endpoints were adverse events, length of ICU stay, and mortality. Propensity score matching was performed to adjust for differences in baseline characteristics.

**Results:** Patients characteristics were similar in both groups but ulcers in the TAE group were larger, more often located in the duodenal bulb (85.5% vs. 65.2%;  $p = 0.014$ ), and that the proportion of Forrest Ia bleedings was higher (38.7% vs. 19.7%;  $p = 0.018$ ). Clinical success was comparable in both groups (74.2% vs. 59.7%;  $p = 0.092$ ). Stay on the intensive care unit (ICU) was significantly longer in the TAE group (mean 8.0 vs. 4.7 days;  $p = 0.002$ ). Serious adverse events after re-therapy (12.9% vs. 1.5%;  $p = 0.042$ ) and in-hospital mortality were significantly higher in the TAE group (9.1 vs. 22.6%, OR 2.92 [95% CI 1.04–8.16];  $p = 0.05$ ). After propensity score matching, the differences found regarding ICU stay ( $4.9 \pm 5.9$  and  $9.2 \pm 11.2$ ;  $p = 0.009$ ) and in-hospital mortality (5% vs. 22.5%; OR 5.52 [95% CI: 1.11–27.43];  $p = 0.048$ ) stayed significant.

**Conclusions:** OTSC treatment for refractory PUB was superior to TAE in terms of ICU stay and in-hospital mortality.

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**KEYWORDS**

over-the-scope clips, peptic ulcer hemorrhage, refractory upper gastrointestinal hemorrhage, transcatheter arterial embolization

## INTRODUCTION

Peptic ulcers are the most common cause of non-variceal upper gastrointestinal bleeding. Standard endoscopic first-line therapy is highly effective in the majority of cases, but rebleeding occurs in about 10%.<sup>1</sup> In this situation, the chances of achieving durable hemostasis decline significantly and mortality rises. Guidelines recommend a second endoscopic hemostasis attempt,<sup>2–4</sup> but when standard endoscopic therapy fails, patients are usually referred to other therapeutic modalities such as transcatheter angiographic embolization (TAE) or surgical treatment. Meta-analyses comparing these two modalities exist. Although inferior to surgery in terms of rebleeding, TAE is a less invasive procedure with lower rates of adverse events; some studies also indicate lower mortality.<sup>5–7</sup> As a consequence, TAE is the first choice after failure of standard endoscopic therapy in most institutions. Over-the scope clips (OTSC®; Ovesco Endoscopy) have also been used increasingly in recent years. Several retrospective studies (and ex vivo studies) indicate high effectivity for severe peptic ulcer bleeding (PUB) and one randomized study also demonstrated superiority over standard endoscopic treatment for recurrent bleeding.<sup>8–12</sup> Although these results are very encouraging, OTSC therapy has not been compared with other salvage treatments so far. The purpose of this study was to compare OTSC therapy to TAE in refractory PUB of the upper gastrointestinal tract.

## MATERIALS AND METHODS

### Study design and patients

In this retrospective study, data of 1331 patients with ulcer bleeding in the upper gastrointestinal tract at four hospital sites in Germany (University Hospital Freiburg, Ludwigsburg Hospital, University Medical Center Göttingen, Carl-Thiem Hospital Cottbus) were screened for eligibility.

Inclusion criteria were the following: (a) PUB in the upper gastrointestinal tract and (b) patients undergoing OTSC or TAE after failure of initial endoscopic therapy (persistent or recurrent bleeding).

Exclusion criteria were the following: (a) bleeding of other source than peptic ulcer and (b) execution of TAE or OTSC therapy without at least one prior endoscopic hemostasis attempt. The number of endoscopic hemostasis attempts before TAE or OTSC was not limited.

For patient identification, specific codes for PUB (ICD-10; International Statistical Classification of Diseases and Related Health

### Key summary

#### Established knowledge on this subject

- Transcatheter arterial embolization (TAE) is considered standard treatment of peptic ulcer bleeding refractory to standard endoscopic therapy
- Over-the-scope clips (OTSC) have shown superiority to standard endoscopic therapy

#### Significant new findings of this study

- OTSC show a similar clinical success rate compared to TAE
- In-hospital mortality is significantly higher and length of stay on intensive care unit is significantly longer in patients treated with TAE
- These findings stay significant after correction for baseline differences via propensity score matching

Problems) and procedure codes of TAE or OTSC (“OPS—Operationen-und Prozedurenschlüssel”) of the German DRG-system were used (see Table S1). At each investigational site, a list of patients fulfilling both criteria of ICD-10 and OPS codes within a timeframe of 2009–2019 was created by searching in the hospital information system. Data acquisition and analysis for the study was approved by our institutional review board and the study was performed in accordance with the Declaration of Helsinki.

### Endpoints and definitions

The primary endpoint of the study was clinical success which was defined as a combination of successful hemostasis and absence of rebleeding within 7 days after the index intervention.

Secondary endpoints of our study were need for additional therapeutic intervention (“re-therapy”), adverse events, need for red blood cell transfusion, length of hospital stay, length of stay on intensive care unit (ICU) or intermediate care, and in-hospital mortality.

Failure in the OTSC group was defined as inability to stop the bleeding after placement of the OTSC, but also if an OTSC could not be placed (after the endoscope was loaded with the clip) due to anatomical reasons (e.g., esophageal stenosis). In analogy, failure of TAE was defined as the inability to stop bleeding via embolization, but also if the target vessel was not reached due to anatomical reasons (e.g., bleeding vessel too small for catheterization).

Rebleeding was defined using criteria as recommended<sup>13</sup> and/or if an intervention (endoscopic, radiographic, surgical) had to be performed for treatment.

Comorbidities were assessed using the Charlson comorbidity index.<sup>14</sup>

## Data management and statistical analysis

Patients were recruited at their participating center and were integrated in local databases and summarized in a central database located at the University Medical Center Freiburg. The documentation of the patients from each center was within the responsibility of the local investigators. Baseline characteristics of the patients were analyzed at the time of recurrent PUB. Continuous variables are expressed as mean with standard deviation, whereas categorical variables are reported as frequencies and percentages unless stated otherwise. For continuous variables, differences were determined using Wilcoxon–Mann–Whitney and Kruskal–Wallis tests as there was no Gaussian distribution of the data confirmed by the Kolmogorov–Smirnov test.  $\chi^2$  tests or Fisher's exact tests were used for categorical variables. *p* values 0.05 were considered significant. Propensity score matching was performed to reduce selection bias for the allocation to the OTSC group or the TAE group. Multivariable logistic regression model was performed to generate the propensity score. The following factors were included in this model: Location of the ulcer in the antrum, in the duodenum, size of the ulcer (<2 or  $\geq$ 2 cm), Forrest Ia bleeding, Forrest Ib bleeding and shock (see Table S2). After establishing the propensity score, 1:1 matching using the nearest-neighbor matching was performed with a caliper of 0.01 without replacement. Post hoc balance diagnostic was performed using mean standardized differences.<sup>15</sup>

Data collection was performed with Microsoft © Excel 2016 for Mac Os (Version 15.21;Microsoft). Statistical analyses were performed with SPSS (version 27.0; IBM).

## RESULTS

### Baseline characteristics—Total cohort

After screening of 1331 patients, 128 patients were eligible for further analysis (Figure 1). Of these, 66 patients received OTSC therapy and 62 received TAE. Patient and bleeding characteristics were similar in both groups. Table 1 summarizes the baseline characteristics of the included patients.

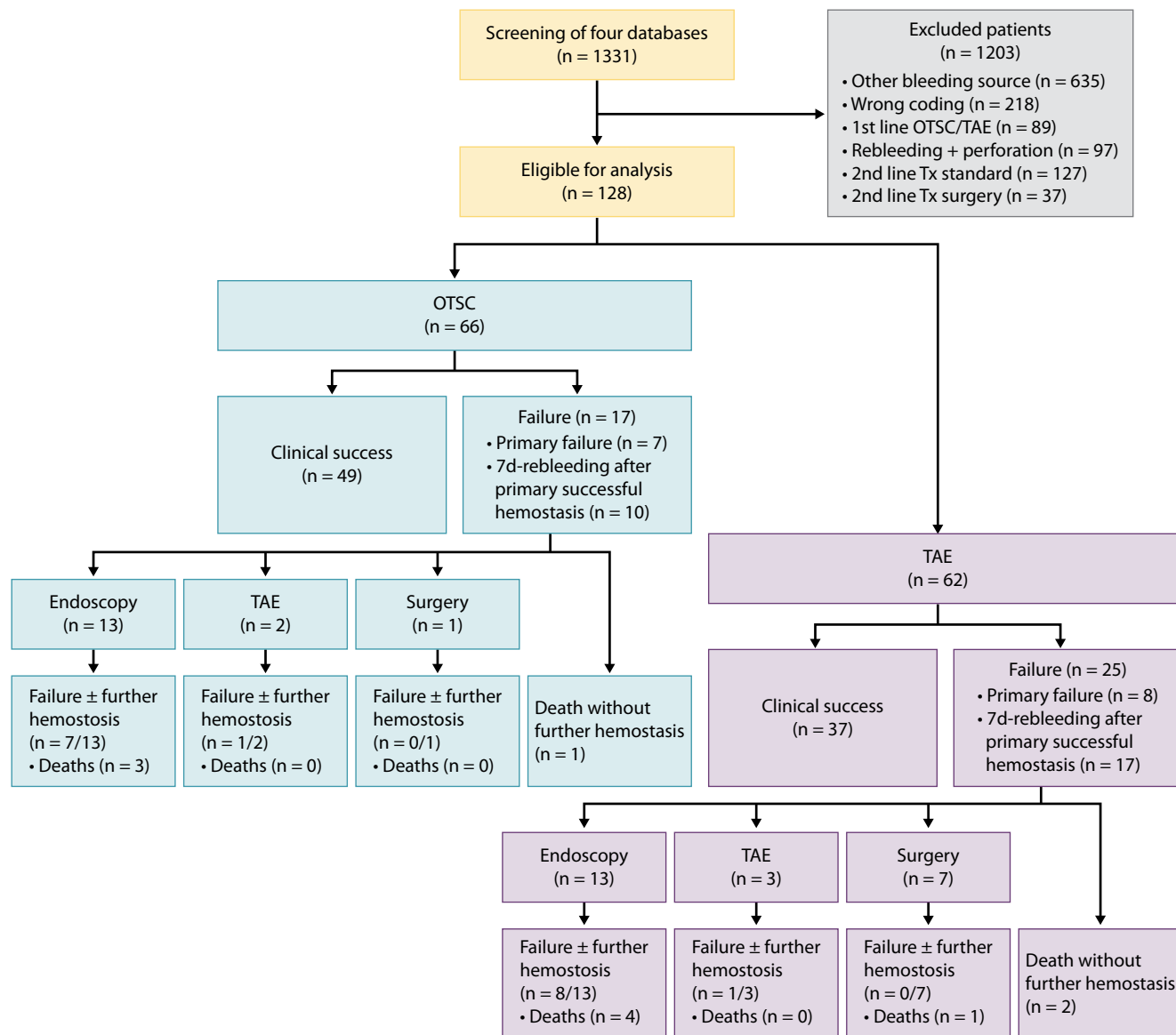
Regarding ulcer characteristics, there was no significant difference in ulcers >20 mm in both groups (27.3% vs. 33.9%; *p* = 0.447). In the majority of cases of both groups, the bleeding source was located in the duodenal bulb. The TAE group contained significantly more patients with ulcer location in the duodenal bulb compared to the OTSC group (85.5% vs. 65.2%; *p* = 0.014). Active bleedings (Fla and

Flb) were present in 83.3% (OTSC) versus 82.2% (TAE) of cases. Forrest Ia bleedings were observed in 13/66 of ulcers (19.7%) in the OTSC group in contrast to 24/62 of ulcers (38.7%) in the TAE group (*p* = 0.018), whereas Flb bleedings were significantly more frequent in the OTSC group (42/66 of patients [63.6%] vs. 27/62 of patients [43.5%]; *p* = 0.033). The mean Rockall score in both groups was  $6.91 \pm 1.8$  in the OTSC group and  $6.9 \pm 2.2$  in the TAE group (*p* = 0.689).

### Outcome in the unmatched cohort

Clinical success was achieved in 49/66 patients (74.2%) in the OTSC group in comparison to 37/62 patients (59.7%) in the TAE group (*p* = 0.092; OR 0.51 [95% CI: 0.24–1.09]). Primary success rate was 89.4% (59/66 patients) in the OTSC group and 87.1% (54/62 patients) in the TAE group (*p* = 0.786). In one patient, an OTSC placement was not possible due to a stenosis of the GI-tract. This was counted as a primary failure of OTSC therapy. Re-therapy was necessary in 20/66 patients (30.3%) in the OTSC group compared to 25/62 patients (40.3%) in the TAE group (*p* = 0.269). The total number of procedures counting as re-therapy was 38 in the OTSC group and 40 in the TAE group (*p* = 0.351). In the OTSC group, re-therapy consisted of endoscopic therapy in 27/38 procedures (70.1%), TAE was performed in 6/38 times (15.7%), and surgery in 5/38 procedures (13.1%). In the TAE group, endoscopic therapy accounted for 17/40 procedures (42.5%), re-TAE for 6/40 procedures (15%), and surgery in 17/40 procedures (42.5%). The difference in the need for surgical therapy was significantly higher in the TAE group (*p* = 0.044). Table 2 summarizes the outcome of the unmatched cohort.

Severe adverse events (SAEs) occurred in three patients of the OTSC group and in 12 patients of the TAE group (4.5% vs. 19.4%; *p* = 0.082). Of these, procedure-related SAE were present in two patients of the OTSC group (3%) and four patients in the TAE group (6.5%) (*p* = 0.362). These consisted of tissue irritation of the clip leading to hemorrhage in two patients of the OTSC group. In the TAE group, treatment-related SAE were ischemia (two patients), perforation of the bleeding vessel in angiography (one patient) and dissection of the feeding vessel (one patient). There were also SAEs that resulted from a re-therapy in case of failure of TAE or OTSC as described above. SAEs were significantly more frequent in the TAE group (12.9% vs. 1.5%; *p* = 0.042). In detail, anastomotic insufficiency occurred in one patient of the OTSC group and in four patients of the TAE group after surgical re-therapy, other SAEs in the TAE group were ischemia and wound dehiscence (two patients each). Mean number of red blood cell transfusions was comparable in both groups (4.8 vs. 3.7; *p* = 0.676). The length of the hospital stay was  $15.2 \pm 12.4$  days in the OTSC group and  $14.7 \pm 10.7$  days in the TAE group (*p* = 0.727). The length of stay on the ICU was 4.7 days  $\pm$  6.6 in the OTSC group compared to 8.0 days  $\pm$  10.3 in the TAE group (*p* = 0.002). The in-hospital mortality in the OTSC group was



**FIGURE 1** A flowchart of the study cohort is shown. Clinical success: successful hemostasis (no primary failure) AND the absence of a rebleeding within 7 days after intervention. Failure in the OTSC group: inability to stop the bleeding after placement of the OTSC, and/or if an OTSC could not be placed (after the endoscope was loaded with the clip). Failure of TAE: inability to stop a bleeding via embolization, and/or if a vessel could not be treated in angiography due to anatomical reasons (e.g., bleeding vessel too small for intubation). OTSC, over-the-scope clips; TAE, transcatheteral angiographic embolization

significantly lower than in the TAE group (9.1% vs. 22.6%;  $p = 0.05$ ; OR: 2.92 [95% CI 1.04–8.16]).

### Outcome in the matched patient cohort

As there may be a selection bias for the allocation to the OTSC group or the TAE group, we performed propensity score matching. We performed multivariable logistic regression model for development of the propensity score (Table S2). After 1:1 matching using the nearest-neighbor method, we identified 80 patients (40 patients in the OTSC group and 40 patients in the TAE group) with comparable patient and

treatment characteristics (Table 3). Covariates which were used for development of the propensity score showed mean standardized differences  $\leq 0.01$  indicating adequate balance of the matched variables.

In the matched cohort, clinical success was still similar in the OTSC group (72.5% vs. 62.5%;  $p = 0.474$ ), and the seven-day rebleeding rate remained lower (17.5% vs. 32.5%;  $p = 0.196$ ). Furthermore, the differences found in terms of length of stay on ICU (4.9 days  $\pm$  5.9 and 9.2 days  $\pm$  11.8;  $p = 0.009$ ), and regarding in-hospital mortality (5% vs. 22.5%;  $p = 0.048$ ; OR: 5.52 [95% CI 1.11–22.43]) were still significant in both groups. Table 4 shows the outcome of the matched cohort.

**TABLE 1** Baseline characteristics—Total cohort

	OTSC (n = 66)	TAE (n = 62)	SMD	p
Patient characteristics				
Age (years), mean $\pm$ SD	70.9 $\pm$ 13.4	68.5 $\pm$ 13.8	0.183	0.322
Charlson Comorbidity Index, mean $\pm$ SD	4.0 $\pm$ 2.7	4.0 $\pm$ 2.5	0.039	0.895
Anticoagulation or platelet inhibition, n (%)	34 (51.5)	26 (41.9)	0.193	0.293
Bleeding characteristics				
Number of endoscopic pretreatments, mean $\pm$ SD	1.6 $\pm$ 0.7	1.63 $\pm$ 0.9	0.124	0.866
Hemoglobin before salvage treatment (mg/), mean $\pm$ SD	8 $\pm$ 1.6	8 $\pm$ 1.8	0.117	0.355
Shock at rebleeding, n (%)	29.0 (43.9)	36.0 (58.1)	0.287	0.116
Ulcer characteristics				
Size >20 mm, n (%)	18 (27.3)	21 (33.9)	0.144	0.447
Localization				
Duodenal bulb n (%)	43 (65.2)	53 (85.5)	0.493	0.014
other, n (%)	23 (34.8)	9 (14.5)	-	0.014
Forrest				
Forrest Ia	13 (19.7)	24 (38.7)	0.427	0.018
Forrest Ib	42 (63.6)	27 (43.5)	0.414	0.033
Forrest IIa, IIb, n (%)	11 (16.7)	11 (17.7)	-	0.999
Rockall score, mean $\pm$ SD	6.91 $\pm$ 1.8	6.9 $\pm$ 2.2	0.099	0.689

Note: Baseline characteristics of the total cohort are shown. Statistical analysis was performed with Mann–Whitney U-Test (continuous variables), and  $\chi^2$  tests or Fisher's Exact tests (categorical variables). *p* values < 0.05 were considered being significant.

Abbreviations: n, number; OTSC, over-the-scope clips; SD, standard deviation; SMD, standardized mean difference; TAE, transcatheteral angiographic embolization.

**TABLE 2** Outcome—Total cohort

	OTSC (n = 66)	TAE (n = 62)	p	OR	95% CI
Clinical success, n (%)	49 (74.2)	37 (59.7)	0.092	0.51	[0.24–1.09]
Primary success, n (%)	59 (89.4)	54 (87.1)	0.786	0.8	[0.27–2.36]
7-day rebleeding, n (%)	10 (15.2)	17 (27.4)	0.128	2.12	[0.88–5.07]
Need for re-therapy, n (%)	20 (30.3)	25 (40.3)	0.269		
Number of re-therapy, n (%)	38 (0.58)	40 (0.65)	0.351		
Re-Endo, n, /patient	27 (0.41)	17 (0.27)	0.429		
Re-TAE, n, /patient	6 (0.09)	6 (0.10)	0.695		
Surgery, n, /patient	5 (0.08)	17 (0.27)	<b>0.044</b>		
Severe adverse events, TAE/OTSC related; n (%)	2 (3.0)	4 (6.5)	0.362		
Severe adverse events, re-therapy-related; n (%)	1 (1.5)	8 (12.9)	<b>0.042</b>		
Severe adverse events, TAE/OTSC and Re-therapy-related; n (%)	3 (4.5)	12 (19.4)	<b>0.082</b>		
Red blood cell transfusions, mean $\pm$ SD	3.7 $\pm$ 6.5	4.8 $\pm$ 10.0	0.676		
Length of hospital stay (days), mean $\pm$ SD	15.2 $\pm$ 12.4	14.7 $\pm$ 10.7	0.727		
Length of ICU or IMC (days), mean $\pm$ SD	4.7 $\pm$ 6.6	8.0 $\pm$ 10.3	<b>0.002</b>		
In-hospital mortality, n (%)	6 (9.1)	14 (22.6)	<b>0.05</b>	2.92	[1.04–8.16]

Note: Outcome parameters of the total cohort are shown. Statistical analysis was performed with Mann–Whitney U-Test (continuous variables), and  $\chi^2$  tests or Fisher's Exact tests (categorical variables). *p* values < 0.05 were considered being significant. OR was calculated using Mantel–Haenszel statistic.

Abbreviations: CI, confidence interval; ICU, intensive care unit; n, number; OR, odds ratio; OTSC, over-the-scope clips; SD, standard deviation; TAE, transcatheteral angiographic embolization.

**TABLE 3** Baseline characteristics—Matched cohort

	OTSC (n = 40)	TAE (n = 40)	SMD	p
Patient characteristics				
Age (years), mean ± SD	72.5 ± 12.8	68.7 ± 15.2	0.264	0.314
Charlson Comorbidity Index, mean ± SD	3.3 ± 2.4	4.1 ± 2.7	0.313	0.134
Anticoagulation or platelet inhibition, n (%)	16 (40.0)	18 (45.0)	0.1	0.821
Bleeding characteristics				
Number of endoscopic pretreatments, mean ± SD	1.7 ± 0.8	1.78 ± 0.9	0.117	0.591
Hemoglobin before salvage treatment (mg/l), mean ± SD	8 ± 1.8	8 ± 1.7	0.129	0.784
Shock at rebleeding, n (%)	22.0 (55.0)	21.0 (52.5)	0.05	0.999
Ulcer characteristics				
Size >20 mm, n (%)	11.0 (27.5)	12.0 (30)	-	0.999
Localization				
Duodenal bulb n (%)	32 (80.0)	32 (80.0)	0	0.999
other, n (%)	8 (20.0)	8 (20.0)	-	0.999
Forrest				
Forrest Ia	10 (25.0)	11 (27.5)	0.05	0.999
Forrest Ib	24 (60.0)	24 (60.0)	0	0.999
Forrest IIa, IIb, n (%)	6 (15.0)	5 (12.5)	-	0.999
Rockall score, mean ± SD	6.93 ± 2.0	6.9 ± 2.4	0.045	0.808

Note: Baseline characteristics of cohort after propensity score matching are shown. Statistical analysis was performed with Mann-Whitney U-Test (continuous variables), and  $\chi^2$  tests or Fisher's Exact tests (categorical variables). *p* values < 0.05 were considered being significant.

Abbreviations: n, number; OTSC, over-the-scope clips; SD, standard deviation; SMD, standardized mean difference; TAE, transcatheteral angiographic embolization.

## DISCUSSION

PUB refractory to standard endoscopic treatment is still a major challenge with significant morbidity and mortality. The results from our study indicate that OTSC therapy has at least comparable technical and clinical success but is associated with shorter ICU stay and lower in-hospital mortality compared to TAE. To our knowledge, this is the first study directly comparing OTSC and TAE for refractory PUB.

Our study cohort comprised 128 patients, 66 received OTSC therapy and 62 TAE. The primary endpoint of the study was clinical success, defined as a composite of primary success and absence of rebleeding.<sup>13</sup> Clinical success was 74.2% in the OTSC group compared to 59.7% in the TAE group (*p* = 0.092). Primary success and rebleeding rate in the OTSC group were 89.4% and 15.2% and are grossly in line with most other studies investigating OTSC therapy for severe upper GI-bleeding.<sup>11,12</sup> While OTSC therapy is highly effective as first-line therapy, success rates drop to 75%–84.8% when used as a second-line or salvage therapy.<sup>9–12,16</sup> In addition, Richter-Schrag et al. found that second-line OTSC therapy in comparison to first-line OTSC is an independent risk factor for rebleeding in multivariable analysis after OTSC placement.<sup>10</sup> In comparison to other studies, patients in our cohort had more

comorbidities. As known risk factors consist of both, ulcer-related and clinical parameters such as shock and comorbidities, irrespective of the treatment modalities, the failure rate in our study seems appropriate.<sup>2,17,18</sup>

Clinical success in the TAE group was more difficult to assess, as the rate of primary success can only be determined in case of an active bleeding in angiography that stopped after embolization. As a consequence, the rebleeding rate mainly accounts for clinical success. In our cohort, contrast extravasation was seen only in 46.8% of cases and blind embolization was performed in 50% of cases (see Table S3). Studies have shown that blind embolization is not inferior to standard embolization and it is therefore regularly performed.<sup>19–21</sup> Reported rebleeding rates are heterogenous and range from 4.5% to 56%.<sup>21,22</sup> In two large meta-analysis the rates were 25% and 28%, which is in line with the rebleeding rate in our study (27.4%). The fact that our clinical success rate of 59.7% seems relatively low is most attributable to our strict definition of primary failure by counting every TAE attempt (vice versa with OTSC) without embolization as a failure. Other authors only used the success rate of attempted embolizations;<sup>23</sup> however, we do believe that the respective treatment modality can be evaluated best if the whole procedure is counted.

The patient characteristics in our cohort were similar in both groups. However, the mean Charlson Comorbidity Index in our study



**TABLE 4** Outcome—Matched cohort

	OTSC (n = 40)	TAE (n = 40)	p	OR	CI
Clinical success, n (%)	29 (72.5)	25 (62.5)	0.474	0.63	[0.25–1.63]
Primary success, n (%)	36 (90.0)	38 (95.0)	0.675	2.11	[0.36–12.24]
7-day rebleeding, n (%)	7 (17.5)	13 (32.5)	0.196	2.27	[0.79–6.49]
Need for re-therapy, n (%)	13 (32.5)	16 (40.0)	0.642		
Number of re-therapy, n (%)	18 (0.45)	29 (0.73)	0.409		
Re-Endo, n, /patient	13 (0.33)	15 (0.38)	0.808		
Re-TAE, n, /patient	2 (0.05)	4 (0.10)	0.399		
Surgery, n, /patient	3 (0.08)	10 (0.25)	0.269		
Severe adverse events, TAE/OTSC related; n (%)	1 (2.5)	3 (7.5)	0.308		
Severe adverse events, re-salvage-related; n (%)	0	5 (12.5)	0.041		
Severe adverse events, TAE/OTSC and re-salvage-related; n (%)	1 (2.5)	8 (20.0)	0.086		
Red blood cell transfusions, n, mean	2.7 (3.2)	6.1 (11.9)	0.570		
Length of hospital stay (days), mean $\pm$ SD	15.2 $\pm$ 12.3	15.6 $\pm$ 11.5	0.525		
Length of ICU or IMC (days), mean $\pm$ SD	4.9 $\pm$ 5.9	9.2 $\pm$ 11.8	<b>0.009</b>		
In-hospital mortality, n (%)	2 (5.0)	9 (22.5)	<b>0.048</b>	5.52	[1.11–22.43]

Note: Outcome parameters of the total cohort are shown. Statistical analysis was performed with Mann–Whitney U-Test (continuous variables), and  $\chi^2$  tests or Fisher's Exact tests (categorical variables). *p* values <0.05 were considered being significant. OR was calculated using Mantel–Haenszel statistic. Abbreviations: CI, confidence interval; ICU, intensive care unit; n, number; OR, odds ratio; OTSC, over-the-scope clips; SD, standard deviation; TAE, transcatheteral angiographic embolization.

is higher compared to other studies<sup>7,24–26</sup> highlighting the fact that the majority of patients without durable hemostasis have at least two chronic comorbidities.<sup>27–29</sup> The bleeding characteristics such as mean number of endoscopic pretreatments of 1.6 and the proportion of patients with hemodynamic instability are in line with the reported literature.<sup>9,25</sup> With regard to ulcer characteristics, there were significant differences in both groups. The TAE group had larger ulcers (mean 18.6  $\pm$  7.5 mm vs. 22.5  $\pm$  9.7 mm; *p* = 0.03), they were more likely to be located in the duodenal bulb (65.2% vs. 85.5%; *p* = 0.014), and there were significantly more Forrest Ia bleedings (19.7% vs. 38.7%; *p* = 0.018). On the other hand, Forrest Ib bleedings were more frequently in the OTSC group (63.6% vs. 43.5%; *p* = 0.033).

Ulcer sizes are difficult to compare as size is usually estimated by the endoscopist. In the STING study, 48.5% of ulcers were  $\geq 20$  mm in size in the OTSC group. Moreover, in a recently published series of TAE of 282 patients, 50% of patients had ulcer sizes above 2 cm.<sup>7,9</sup> In our cohort, the proportion of ulcers  $\geq 20$  mm is around 30% in both groups and therefore lower. Given the fact that ulcer size is estimated and that the proportion in both groups is similar, we think that a comparison is possible. The vast majority of lesions were located in the duodenum in both groups. This confirms the finding that usually salvage therapy in PUB is necessary in this anatomic location. TAE studies report this location as bleeding source in around 80% of cases.<sup>7,17,21</sup> Besides the differences found, the mean Rockall Score in both groups was equal and with 6.9 also in the category with the highest risk of rebleeding.<sup>30</sup> However, in a systematic review,

Elmunzer et al. showed that comorbidities, hemodynamic instability, active bleeding at endoscopy (Fla and Flb), ulcer size >2 cm, location at the posterior duodenal wall are most important predictors of rebleeding.<sup>2</sup>

Therefore, a propensity score matching was performed to adjust for differences in baseline characteristics. A propensity score matching can get to the nearest of a randomization as possible in a retrospective study. After matching, the differences in ulcer size, location, and Forrest classification were no longer significantly different. However, the differences in the endpoints remained, underlining the validity of the results.

The in-hospital mortality rate in the total cohort (9.1% vs. 22.6%; *p* = 0.05) as well as the matched cohort (5.0% vs. 22.5%; *p* = 0.048) was significantly lower in the OTSC compared to the TAE group (see also Tables 2 and 4). Data on mortality rates of OTSC treatment is scarce and has only been reported in two studies using OTSC as second-line or salvage therapy. It ranges from 9.1% up to 27%, but it has to be noted that the latter is hardly comparable to our study as it included various indications of OTSC therapy (e.g., bleeding gastric metastasis or bleeding anastomotic ulcers).<sup>9,10</sup> For TAE, our rate of around 22% is in line with reported rates in two meta-analyses.<sup>5,6</sup> The reasons for the difference in mortality is not entirely clear but it has to be noted that sample sizes for mortality was low in both groups, and the study may not have been sufficiently powered to show differences in mortality. In our analysis, procedure-related SAEs (e.g., ischemic complications after TAE) were not responsible for this difference. This matches with the

finding of Wong and Spiliopoulos et al., both comparing TAE and surgery, showing that the main driver for the high mortality of these patients lies in the reduced health status due to old age and comorbidities.<sup>17,21</sup> This underlines the importance of avoiding highly invasive procedures for these frail individuals. Especially re-therapy is a huge burden for these old and multimorbid patients and is likely responsible for the significantly longer stay on ICU in our total as well as the matched cohort. In both groups, re-therapy consisted mainly in endoscopic re-therapy, which might be due to the rapid availability of an EGD in the emergency setting. But whereas 27 of 38 (71%) re-procedures in the OTSC group could be performed endoscopically as opposed to 17/40 (42.5%) in the TAE group (Table 2), a significantly higher proportion of re-therapy was surgical treatment (42.5% vs. 13.1%) in the TAE group. As a consequence, SAEs arising from the re-therapy were significantly (1.5% vs. 12.9%) more frequent in the TAE group.

Our study has several limitations: the main weakness is the retrospective design of the study. Due to the lack of a specific study protocol, patients were not randomly assigned to OTSC or TAE but decision on therapy was rather based on decision of the endoscopist. Moreover, differences in local resources regarding emergency endoscopy as well as interventional endoscopy may also have influenced individual patient management. Although we performed a propensity score matching to adjust for differences, a selection bias cannot be excluded. A second limitation is the relatively small sample size, making subgroup analysis of complications and mortality difficult.

## CONCLUSION

In conclusion, endoscopic hemostasis with OTSC shows comparable efficacy to TAE for refractory PUB. However, it is associated with shorter ICU stay and lower in-hospital mortality. OTSC treatment may therefore be attempted first in PUB refractory to standard therapy. Randomized controlled trials are needed to confirm the findings of our study.

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## CONFLICT OF INTEREST

Armin Kuellmer, Tobias Mangold, Dominik Bettinger, Lars Maruschke, Dominik Bettinger, Andreas Wannhoff, Ali Seif Amir Hosseini, Tobias Kleemann, Thomas Schulz, Carlo Jung, and Robert Thimme declare no conflict of interests. Karel Caca, Edris Wedi, and Arthur Schmidt have received lecture fees and study grants from Ovesco Endoscopy.

## ETHICS APPROVAL

This study was approved by our institutional review board on December 5<sup>th</sup>, 2019 (No 534/19).

## AUTHOR CONTRIBUTIONS

Arthur Schmidt invented the present study and was accompanying the process of data acquisition and analysis and revised the manuscript. Armin Kuellmer concipated the analysis and accompanied data acquisition, analysis, and wrote the manuscript. Tobias Mangold was responsible for data acquisition and analysis, created tables and flowchart, and revised the manuscript. Dominik Bettinger was responsible for data analysis, interpretation, and revised the manuscript. Lars Maruschke, Andreas Wannhoff, Edris Wedi, Ali Seif Amir Hosseini, Carlo Jung, and Tobias Kleemann accompanied the process of data acquisition at the respective sites and revised the manuscript. Karel Caca, Thomas Schulz, and Robert Thimme carefully revised the manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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