

# Superiority of the OTSC® System in the treatment of upper GI bleeding

Symposium report • DGE-BV 2017 in Berlin



Report on the Symposium held as part of the 47th Congress of the German Society for Endoscopy and Imaging (DGE-BV) (Chair: Prof. Dr. med. Siegbert Faiss, Hamburg, PD Dr. med. Dirk Hartmann, Berlin), Berlin, 6th - 8th April 2017

The afternoon symposium supported by Ovesco Endoscopy took place on 6th April at the DGE-BV meets Endoscopy Live Congress in Berlin and was chaired by Prof. Dr. med. Karel Caca from Ludwigsburg hospital and Prof. Dr. med. Alexander Meining, from the University Hospital Ulm. This report summarizes the scientific results presented at the symposium.

## Upper gastrointestinal bleeding – Still an unsolved problem?

A. Meining, Ulm

To begin, Prof. Dr. med. A. Meining presented the current status in the treatment of upper gastrointestinal bleeding (UGIB). Peptic ulcer bleeding remains the leading cause of bleeding. The current ESGE Guideline for the procedure in non-variceal bleeding recommends the combination of two hemostasis procedures, usually conventional clips and injections. However, in the event of technical failure or recurrent bleeding, the guideline already mentions the use of the OTSC. The use of the OTSC (**Fig. 1**) is well documented in the published literature, so far primarily in the salvage treatment of upper GI bleeding otherwise unresponsive to treatment.

Prof. Meining added that he regularly uses the OTSC for cases of severe bleeding in his own clinical practice and recounted an impressive case study. In a six-year-old girl with life-threatening GI bleeding and mass transfusion who had undergone unsuccessful surgery for a suspected Meckel's diverticulum, he was called to the operating theatre where an EGD revealed a large duodenal ulcer. Despite the difficulties of anatomical access in the child, the bleeding was safely stemmed with an OTSC. The child recovered well and a follow-up after approximately three months showed that the clip had spontaneously released.

In his summary, Prof. Meining stated that standard clips are not always effective in the primary therapy of upper GI bleeding (e.g. where blood vessels are present on a fibrotic ulcer surface). The OTSC appears to be the most effective, least invasive, and probably also the most cost-effective method for treating severe and pronounced upper GI bleeding. This means that the procedure is also suitable for use in children, in consideration of anatomical limitations.



Figure 1: OTSC cap with mounted clip

## STING: Breakthrough in the treatment of recurrent bleeding in a randomized, controlled study

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For the international STING (STop bleedING; [clinicaltrials.gov: NCT1836900](https://clinicaltrials.gov/NCT1836900)) consortium, Dr. med. A. Schmidt (Ludwigsburg) presented the results of the RCT coordinated by him on the use of the OTSC in recurrent peptic ulcer bleeding. Dr. Schmidt reported that despite modern pharmacological and endoscopic treatments, the mortality rate from gastroduodenal ulcer bleeding remains at up to 8.6 %. Although endoscopy using conventional standard procedures was initially successful in 90 % of cases, recurrent bleeding occurred soon afterwards in approximately 10 % of cases, reducing the overall success rate to approximately 80 %. For rebleeding, the success rate of endoscopy is significantly reduced, and surgical intervention also has considerable morbidity and mortality. One of the reasons is that for large ulcers with fibrotic tissue, conventional clips often have a poor grip and result in ineffective vascular compression. In difficult locations (e.g. the rear wall of the duodenal bulb), standard clips are also technically difficult to apply.

As a result, there remains a clinical demand for reliable hemostasis procedures. Due to its greater compressive force, superior grip in fibrotic tissue, and ease of application particularly in tight anatomical conditions, the OTSC can offer advantages (**Fig 2**).



Figure 2: applied clip in tissue  
Source: Prof. Dr. K. Caca und Dr. A. Schmidt, Klinikum Ludwigsburg

The objectification of these benefits was the focus of the investigator-initiated STING study involving nine clinical centres from Germany, Switzerland, and Hong Kong. The test hypothesis was the superiority of the OTSC compared to standard methods (conventional clips or thermal procedures plus adrenaline injection) in recurrent ulcer bleeding, with regard to primary hemostasis and rebleeding (**Fig 3**).

The primary end point was therapeutic failure as a result of persistent bleeding despite endoscopic therapy, or recurrent bleeding following initially successful hemostasis. According to the calculation of the number of cases (power 80 %), n = 67 patients with endoscopically confirmed rebleeding from a gastroduodenal ulcer within seven days following primary successful endoscopic therapy were included in the study.

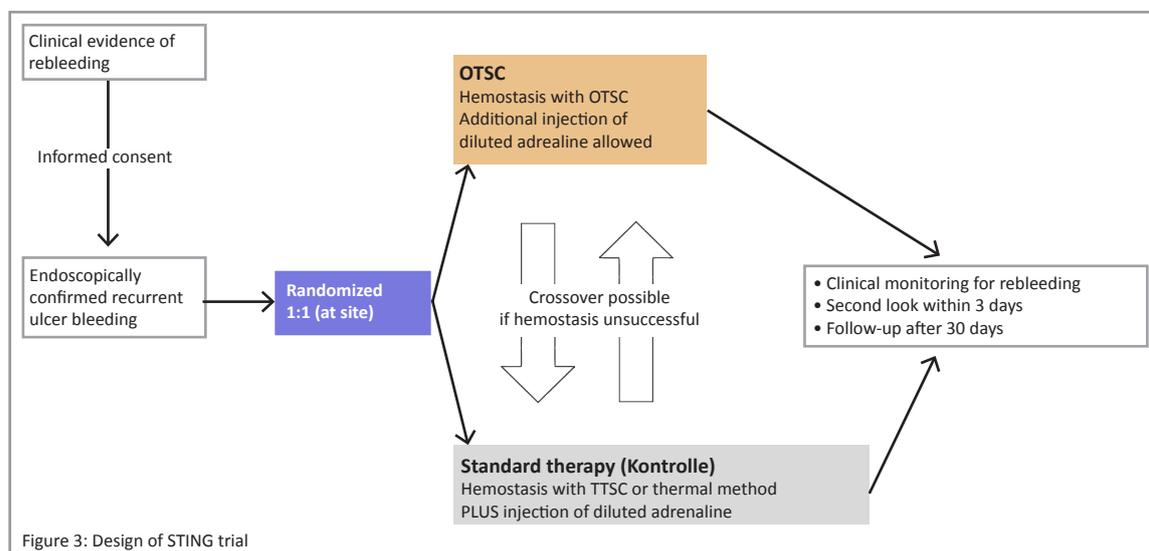


Figure 3: Design of STING trial

Table 1: Patient characteristics

	Standard therapy (n = 32)	OTSC (n = 32)
Age y, median (range)	77.5 (44 - 93)	78 (33 - 90)
Sex (m/f)	17/15	20/12
Admission due to UGIB, n (%)	22 (68.8)	26 (81.3)
Bleeding during hospital stay, n (%)	10 (30.3)	6 (18.1)
Anticoagulation and/or platelet inhibition, n (%)	12 (37.5)	15 (47.0)
NSAID use	4 (12.5)	4 (12.5)
Glucocorticoid use	3 (9.0)	4 (12.5)
Hemodynamic instability at randomization	14 (43.8)	11 (34.4)
Hemoglobin level at randomization, median, g/dl, (range)	8.4 (5.8 - 11.5)	8.6 (4.5 - 11.3)
Complete Rockall score, Median (range)	7 (1 - 10)	7 (3 - 10)
< 7, n (%)	14 (43.8)	13 (40.6)
≥ 7, n (%)	18 (56.3)	19 (59.3)
Location of ulcer		
duodenum	19 (59.4)	23 (71.9)
stomach	13 (40.6)	8 (25.0)
jejunum	0 (0)	1 (3.1)
Ulcer size, mm, median (range)	15 (5 - 35)	15 (7 - 40)
≥ 2 cm, n (%)	11 (34.4)	15 (46.9)
< 2 cm, n (%)	21 (65.6)	17 (53.1)
Forrest classification		
Ia (spurting)	5 (15.6)	5 (15.6)
Ib (oozing)	16 (50.0)	18 (56.2)
IIa (visible vessel) + evidence of bleeding	6 (18.8)	6 (18.8)
IIb (adherent clot)	5 (15.6)	3 (9.4)

Patients were randomly distributed into the two treatment arms in a 1:1 ratio (OTSC = 33 vs standard therapy = 34).

In each treatment arm, n = 32 patients with the characteristics displayed in **Table 1** were analysed. Both groups show good correspondence to the baseline. 37.5 % of patients in the standard arm and 47.0 % in the OTSC arm were undergoing anti-coagulation or antiplatelet therapy. The median Rockall score in both arms was 7, which highlights the degree of severity of the bleeding.

In the results (**Table 2**), a technical success rate (successful hemostasis) of 56.3 % was demonstrated for the standard arm, and 93.8 % for the OTSC arm.

Table 2: Study results

	Standard therapy (n = 32)	OTSC (n = 32)	p value	Odds ratio (95 % CI)
Number of clips, median (range)	2 (1-8)	1 (1-2)	0.076	
Use of thermal therapy, n (%)	2 (6.0)	0 (0)	-	
Technical success*, n (%)	18 (56.3)	30 (93.8)	< 0.001	0,085 (0,017 - 0,422)
Technical failure, n (%)	14 (43.8)	2 (6.3)	< 0.001	0,085 (0,017 - 0,422)
Crossover to OTSC after failure, n (%)	10	-	-	
Technical success after Crossover to OTSC, n (%)	10	-	-	
Rebleeding within 7 days, n (%)	5 (27.7)	3 (10.0)	0.251	0,360 (0,076 - 1,690)
Clinical success**, n (%)	13 (40.6)	27 (84.4)	< 0.001	0,15 (0,049 - 0,471)
Hospital mortality, n (%)	1 (3.1)	3 (9.4)	0.355	3,31 (0,326 - 33,629)
Total (30 day) mortality, n (%)	2 (6.25)	4 (12.5)	0.672	2,14 (0,364 - 12,629)

\* defined as successful hemostasis according to protocol

\*\* no persistent bleeding, no recurrent bleeding

The clinical success rate, taking rebleeding into account, was 40.6 % for the standard therapy and 84.4 % for OTSC. Both differences were statistically highly significant (p<0.001).

This therefore demonstrates a statistically significant and clinically relevant improvement in the outcome for patients treated with the OTSC.

As possible limitations of the study, Dr. Schmidt noted that the recruitment was a slow process (for ethical reasons), there was a possible crossover between the different arms of study, and that in the standard arm, no further procedural augmentation by additional arbitrary methods was possible.

Schmidt and co-authors derived the following conclusions from the STING study:

- This was the first randomised, controlled study on hemostasis using the OTSC
- The OTSC is superior to standard methods used in recurrent ulcer bleeding in terms of technical and clinical success
- The study was not able to demonstrate any differences in terms of mortality and the need for surgical intervention, which can presumably be attributed to the crossover design of the study

In conclusion, Dr. Schmidt reported that further studies would be desirable to analyze the role of the OTSC in first-line therapy of peptic ulcer bleeding.

## FLETRock – OTSC in first-line treatment reduces the risk of recurrence and mortality associated with upper GI bleeding: Data from the multicentre evaluation

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Dr. med. E. Wedi reported on the consistent application of the OTSC in first-line treatment of complicated upper GI bleeding on behalf of a multicentre group of authors who examined the treatment cases at three endoscopic centres in Germany and France in detail (FLETRock evaluation – First-Line Endoscopic OTSC Therapy vs Rockall prediction). The study included n = 118 patients with upper GI bleeding (all causes permitted), excluding variceal bleeding, as the OTSC System is not indicated for this. Dr. Wedi reported that both the published experience obtained in their own clinic (J. Hochberger, E. Wedi, et al.), as well as the recently published experiences from Freiburg (H.-J. Richter-Schrag), demonstrated advantages for the successful treatment of upper GI bleeding, if the OTSC System is used as primary therapy. This forms the basis for the FLETRock evaluation, which pooled the data from 118 patients in whom the OTSC was used as a first-line procedure for hemostasis. The test hypothesis was that the primary OTSC treatment reduces the rebleeding rate, the associated mortality, and the overall mortality during hospitalisation compared to the values forecast using the Rockall score. The Rockall score incorporates clinical and endoscopic findings that classify the risk of recurrence and the risk of mortality on a scale of 1 - 10, and then assigns a percentage risk to the levels on the scale. It was validated by various authors. Above a value of 6, the individual risk for the patient increases dramatically. In the FLETRock evaluation, the Rockall score was calculated for each of the 118 cases based on the clinical data, and the resulting predicted risk (quasi-control) was compared with the treatment outcome actually achieved. The end points according to the Rockall cohort were the recurrence of bleeding, the mortality associated with bleeding, and the overall hospital mortality.

The baseline demographic of the patients showed a median age of 73.5 years (29 - 93 years). 85.6 % of patients had one or more co-morbidities (of which 47.5 % were cardiac), and 65.3 % were being treated with medicinal anticoagulation or antiplatelet therapy at the time of bleeding. The median Rockall score was 7 (3 - 10), with a mean value of 7.25 (+/- 1.51).

The results presented by Dr. Wedi showed a primary clinical success of 90.8 % for hemostasis using OTSC alone. With the addition of adrenaline injections in two cases, the overall success rate was increased to 92.5 %.

The values for mortality, rebleeding, and associated mortality observed in the multicentre cohort were consistently lower than the values expected for the patients according to the validated Rockall score (Figures 4 - 6). For statistical testing of the hypothesis, the patients were divided into three clinical

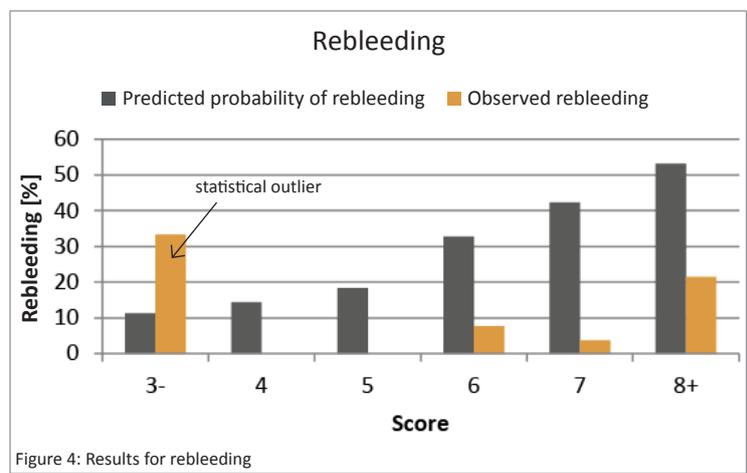


Figure 4: Results for rebleeding

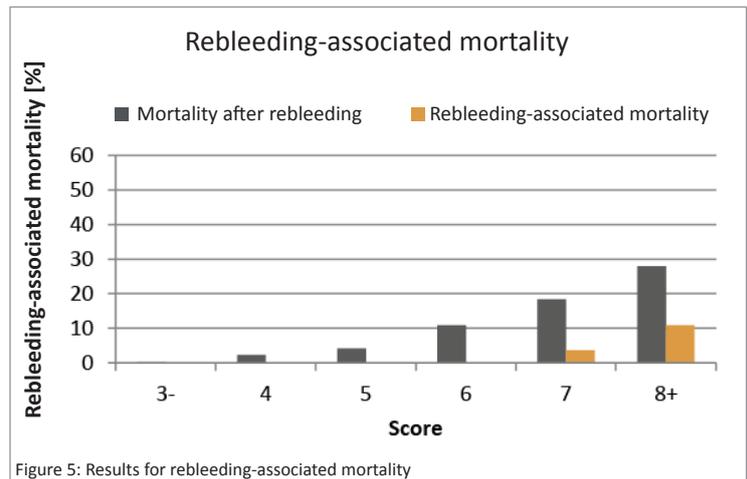


Figure 5: Results for rebleeding-associated mortality

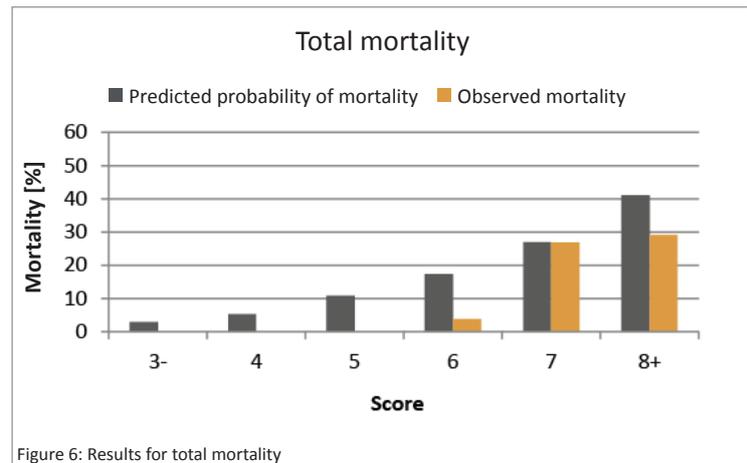


Figure 6: Results for total mortality

risk groups based on their score, low ( $\leq 3$ ), medium (4 - 7), and high ( $\geq 8$ ). The event rates per risk group were compared with the expected event rates using Fisher's exact test (Table 3). The probability of rebleeding was significantly lower in the medium and high risk groups ( $p < 0.001$ ); in the high risk group, the mortality associated with rebleeding was also substantially reduced ( $p < 0.001$ ). In the multifactorial overall hospital morbidity, there was a differing trend, although this was not significant ( $p = 0.11$ ).

Reported limitations of the study lie in the methodical approach as a quasi-controlled study with the use of the validated Rockall score. This is not comparable to a randomized controlled study in terms of informative significance. Dr. Wedi also explained it should be noted that the Rockall score and its validation date back to the 1990s, at which time the conventional hemostasis methods still in use today (injection, thermal procedures, clips) were also state of the art.

Table 3: FLETRock evaluation results

	Predicted rebleeding (Rockall)	Observed rebleeding rate		
	%	% (95 % CI)	n/N	p value
Risk-group ≤ 3	7.0	33 (0 - 71.0)	1/3	n.a.
Risk-group 4-7	24.0	4.9 (1.0 - 13.7)	3/61	< 0.001
Risk-group 8+	53.2	21.4 (11.6 - 34.4)	12/56	< 0.001
	Predicted mortality after rebleeding (Rockall)	Observed rebleeding-associated mortality		
	%	% (95 % CI)	n/N	p value
Risk-group ≤ 3	0.4	0 (0 - 70.8)	0/3	n.a.
Risk-group 4-7	7.3	1.7 (0.1 - 9.0)	1/60	0.121
Risk-group 8+	27.9	10.9 (4.1 - 22.2)	6/55	0.011
	Predicted mortality (Rockall)	Observed mortality		
	%	% (95 % CI)	n/N	p value
Risk-group ≤ 3	1.2	0 (0 - 70.8)	0/3	n.a.
Risk-group 4-7	13.0	13.3 (5.9 - 24.6)	8/60	0.847
Risk-group 8+	41.1	29.1 (17.6 - 42.9)	16/55	0.118

In his conclusion, Dr. Wedi reported that the OTSC System is superior to standard clips and conventional combination therapy, particularly for complex lesions. The FLETRock evaluation confirmed with statistical significance the practical experience obtained at many sites, that the use of the OTSC as a first-line method considerably reduces the rebleeding rates and therefore the associated mortality in upper GI bleeding.

*Following the presentations, the Ovesco scientific service was able to conduct specialist interviews with the speakers in order to find out their personal impressions of the new data and their experiences with the OTSC System for hemostasis.*

**Scientific service:** Can you remember a specific situation in which hemostasis would have been very difficult without the OTSC System?

**Prof. Meining:** Only last week, I had a patient with severe arterial bleeding from a large ulcer in the duodenal bulb, and I immediately knew that I wouldn't be able to stop this bleeding using a normal standard clip. The bleeding was then controlled within 2 minutes using the OTSC, and it worked.



**Scientific service:** Is the OTSC technically challenging to use? Are all endoscopists and their assistants in your hospital involved in the use of the OTSC?



**Dr. Schmidt:** The use and application of the OTSC are actually easier than the application of standard clips – not just in my experience, but this has also been demonstrated in experimental studies. In our clinic it is standard practice that every doctor who performs emergency endoscopies can also apply OTSCs.

**Scientific service:** What is the significance of the data from the STING study as an RCT for the standard in the treatment of upper GI bleeding?

**Prof. Caca:** I think this is really a milestone, because previously, we had no prospective randomised data. This data shows for the first time, with clear scientific significance, that the OTSC has a considerable advantage over standard upper gastrointestinal bleeding therapy.



**Scientific service:** What do you think about the cost-effectiveness of the OTSC System?

**Prof. Caca:** Well, the clip is more expensive than the standard clip, but obviously we always have to take into account that we can achieve successful hemostasis within a short period with a single clip. Overall, I consider this clip to be very economical.

**Scientific service:** Do you think the data from the multicentre FLETRock evaluation might suggest a change in the first-line treatment of upper GI bleeding?



**Dr. Wedi:** I think so. If we look at the data, the FLETRock study demonstrated that in the first-line treatment of non-variceal upper GI bleeding, the use of the Over-The-Scope clip was able to reduce the mortality rates in seriously ill patients with a high Rockall risk score. The rebleeding rate in these patients was also significantly reduced. These are actually very promising results which will definitely change the face of upper GI bleeding therapy.

## For questions, please contact us at:

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