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Novel telemetric sensor capsule for EGD urgency triage: a feasibility study

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ABSTRACT

Background and study aims Upper gastrointestinal bleeding (UGIB) is a frequent cause of hospitalization. Because of the lack of reliable noninvasive diagnostic tools, the decision to proceed with emergency endoscopy in these cases is made based on clinical parameters. A novel non-imaging telemetric real-time sensor capsule (HemoPill Acute, Ovesco Endoscopy AG) has shown promising results for noninvasive detection of UGIB in preclinical studies.

Patients and methods We conducted a prospective non-randomized, single center, open-label study to investigate feasibility and safety of the novel sensor capsule in patients with symptoms of UGIB. The primary aim of the first clinical study was to investigate feasibility and safety of the device in a clinical setting. All patients underwent endoscopy within 12 hours after capsule ingestion. Sensor data from the capsule within 10 minutes after ingestion were compared with endoscopic findings.

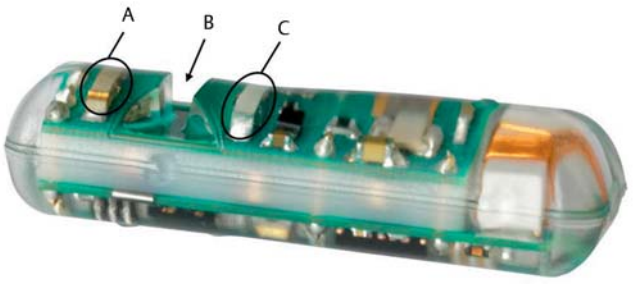
Results From April 2015 to February 2016, 30 consecutive patients with symptoms of acute UGIB were included; 27 were eligible for analysis. Capsule ingestion was well tolerated in all patients and there were no device-related adverse events. Endoscopy showed blood or hematin in the upper gastrointestinal tract of 10 of 27 patients; in 2 of 10 patients it was estimated to be more than 20 mL; in 4 of 8 patients it was between 5 and 20 mL and in 4 of 8 it was estimated to <5 mL. The sensor capsule was positive in 2 of 2 patients (100 %) with >20 mL of blood or hematin and in 1 of 8 patients (12.5 %) between 5 and 20 mL. All patients (17/17; 100 %) were correctly identified as non-bleeders.

Conclusion Both device and procedure proved to be safe and feasible. Larger studies will be necessary to evaluate the role of the sensor capsule in risk stratification of patients with acute UGIB.

Clinical.Trials.gov
NCT03176407
TRIAL REGISTRATION: Prospective, non-randomized, single center, open-label study NCT03176407 at clinicaltrials.gov

Introduction

Acute upper gastrointestinal bleeding (UGIB) is a common condition with an estimated worldwide incidence of 40 to 50/100 000 [1, 2]. It frequently leads to hospital admission and is associated with significant mortality and morbidity, especially in elderly patients [2]. Non-variceal bleeding is the most common cause of UGIB, with peptic gastroduodenal ulcers and mucosal erosions comprising the majority of bleeding sources. Esophagogastroduodenoscopy (EGD) is the gold standard for diagnosis (and treatment) of acute UGIB [1]. Given the lack of reliable noninvasive diagnostic tools, the indication for emergency endoscopy is generally based on clinical parameters [2–4]. Novel tools that can determine presence or absence of severe bleeding may aid urgent triage and also save resources by avoiding unnecessary emergency endoscopies [5]. We present a prospective pilot trial, which aimed to evaluate feasibility and



▶ **Fig. 1** Sensor capsule. Dimension of the capsule: 7.0 × 26.3 mm. **A** LED. **B** Measuring slot. **C** Phototransistor. (Source: Ovesco Endoscopy AG)

safety of detection of acute UGIB using a novel telemetric sensor capsule.

Patients and methods

Description of the device and procedure

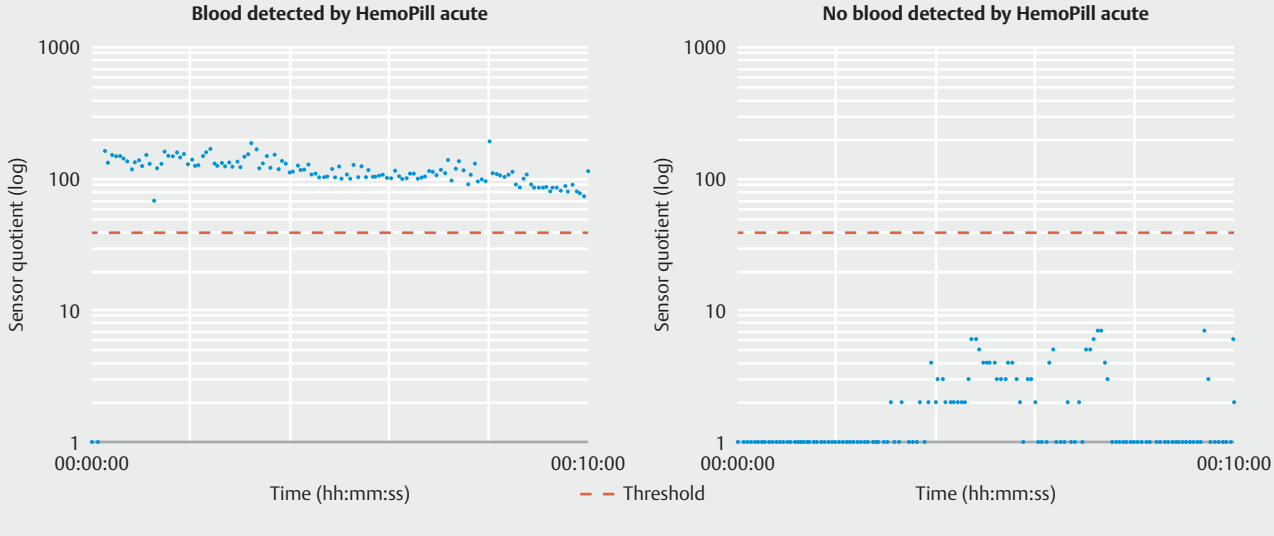
The sensor capsule (HemoPill acute, Ovesco Endoscopy AG, Tuebingen, Germany; ▶ **Fig. 1**) is a diagnostic capsule equipped with a sensor for in vivo detection of liquid blood or hematin. The device is composed of a sensor capsule to be orally administered and a wireless handheld receiver for real-time display of sensor data. The capsule contains a measuring slot for blood entry (▶ **Fig. 1b**). When the capsule is activated, red (720 nm) and violet light (415 nm) is emitted by LEDs (▶ **Fig. 1a**) on one slot side and intensity is detected on the other slot end (▶ **Fig. 1c**). Blood has distinct optical properties, which are used for the sensor to calculate an extinction ratio: high absorption of violet light at 415 nm, while red light is comparatively well transmitted; resulting in a high quotient [6]. This quotient serves as the single indicator value to predict presence of blood in the measuring slot. Thus, the quotient increases with decreasing violet intensity indicating a higher concentration of blood (▶ **Fig. 2**).

Different blood types have similar characteristic absorption of the red and violet light utilized in the sensor; the sensor is therefore not able to differentiate between fresh blood and hematin [6]. The capsule's signal can respond to a special kind of food (e. g. instant coffee or beetroot); however, the signal does not reach the defined threshold for positive detection of blood [7]. After activation, the sensor continuously emits data for 4 hours. After 4 hours, the sensor switches into a "passage mode" that lass for 3 weeks, in which no measurements are taken but every 12 seconds a data packet is sent to monitor capsule presence in the gastrointestinal tract. Thus, presence of the capsule can be checked by the wireless handheld receiver within 3 weeks after its ingestion.

The sensor capsule is used for diagnosis in patients with suspected acute bleeding in the upper digestive tract. The sensor capsule previously was investigated in an extensive preclinical assessment on a porcine bleeding model [8]. Here, basic performance and proof of principle of blood sensor performance were evaluated. Furthermore, a volunteer case series on a healthy subject was performed with different food scenarios in the test [7].

Study design and patients

We conducted a prospective, non-randomized explorative clinical trial at a tertiary referral center. The primary aim of this first clinical pilot study was to evaluate safety and feasibility of capsule ingestion and excretion. Secondary aim was to gain first clinical data comparing the sensor signals to endoscopic findings in a clinical "real-life" setting. The study protocol was approved by the institutional review board. The study was registered at clinicaltrials.gov (NCT03176407).



▶ **Fig. 2** A typical sensor capsule signal (one dot in a graph) in two patients within the first 10 minutes after capsule ingestion. Red line shows the threshold for blood detection. Left: quotient rises above the threshold (> 100), indicating presence of blood. Right: quotient is < 10, indicating the absence of blood. Axis are double logarithmic scaled on the x-axis (time) and y-axis (sensor capsule quotient).

Patients presenting to the emergency department with acute UGIB were screened for eligibility. Inclusion criteria were symptoms suggestive of UGIB defined as hematemesis, coffee ground emesis or melena (at least one of three).

Main exclusion criteria were hemodynamic instability requiring urgent endoscopy, known or suspected stenosis of the gastrointestinal tract, variceal bleeding, swallowing disorders, pregnancy, age younger than 18 years and inability to sign informed consent. In addition, the institutional review board required exclusion of patients aged older than 80 years for safety reasons, as this was a first clinical study and the device was not approved for clinical use at the time of the study.

After signing informed consent, patients were equipped with the receiver and swallowed a capsule with a sip of water (max. 100 mL). Patients did not need to fast before swallowing the capsule and were asked to report their last food intake. Independent of capsule measurements, each patient received EGD within 12 hours after capsule ingestion. It was performed by three experienced endoscopists who were all thoroughly trained in the study protocol. Endoscopic findings were categorized according to presence or absence of blood or hematin in the esophagus, stomach, and duodenum. The amount of blood or hematin was estimated by the endoscopist according to the endoscopic finding and was categorized as < 5 mL, between 5 and 20 mL, or > 20 mL. The endoscopist was blinded to the sensor signal results.

After endoscopy, patients were monitored for clinical signs of capsule retention during daily clinical visits. In addition, presence or absence of the capsule was measured using the wireless receiver. No detection of capsule signal was defined as successful capsule excretion. In case of no excretion within 4 days, a follow-up examination was conducted after 10 days.

Data recorded by the receiver were analyzed after discharge of patients and compared to the endoscopic findings. A positive sensor signal was defined according to a present threshold within the first 10 minutes after ingestion. The threshold was set to a quotient ≥ 40. If the sensor signal did not reach the threshold within the first 10 minutes after ingestion, the signal was defined as negative.

Results

From April 2015 to February 2016, 104 consecutive patients who presented with symptoms of UGIB were screened. Thirty patients were included in the study and reasons for non-enrollment are shown in ▶ **Fig. 3**. During the study, three patients were excluded due to protocol violation. In one case, the period between capsule ingestion and EGD exceeded 12 hours. In another patient, endoscopy unexpectedly showed acute bleeding from esophageal varices, which is an exclusion criterion. In the third case, the capsule signals could not be recorded due to human failure. Hence, data from 27 patients (10 female, 17 male) was available for further analysis (▶ **Fig. 4**). Mean patient age was 66 (range 28 – 80 years). Detailed patient characteristics are in ▶ **Supplementary Table 1**.

Capsule ingestion was possible and tolerated well in all cases. Mean time between capsule ingestion and EGD was 152 minutes (range 12 – 566 min). No cases of capsule retention were observed and there were no device-associated adverse events (AEs). Complete data transmission to the extracorporeal receiver was achieved in all 27 cases. Capsule excretion could be documented in 17 of 27 patients during hospital stay. Ten patients were scheduled for follow-up examination, three of whom were lost to follow-up. In the remaining seven patients, capsule excretion was documented successfully during an outpatient visit. Mean time for confirmed capsule excretion was 4.33 days (range 1 – 16).

Endoscopy showed signs of former UGIB in 10 of 27 cases (37 %). Bleeding sources included gastric ulcers (n = 3), duodenal ulcers (n = 2), gastric Dieulafoy's lesions (n = 2), duodenal angiodysplasia (n = 1), erosive gastritis (n = 1) and one case without detection of a bleeding source despite presence of blood in the stomach. A positive sensor signal was recorded in three cases; negative sensor signals were recorded in 24 cases. We detected a positive sensor signal in all cases with more than 20 mL of blood or hematin (2/2, 100 %) and in 1/8 cases with less than 20 mL of blood or hematin (12.5 %) (▶ **Fig. 4**). Details of endoscopic findings including estimated amounts of blood or hematin are shown in ▶ **Table 1**.

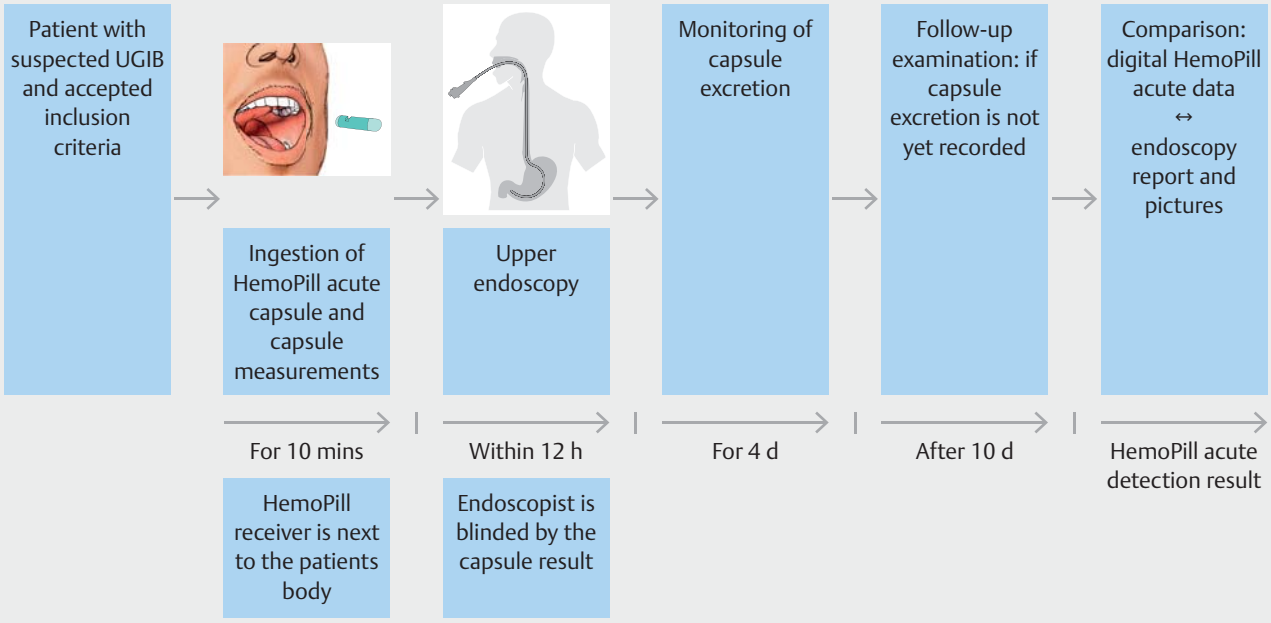
In 17/27 cases (63 %), endoscopy did not show any blood or hematin in the upper gastrointestinal tract. This included one patient with a Forrest II a duodenal ulcer. In 17/17 cases (100 %), the capsule signal was negative.

Discussion

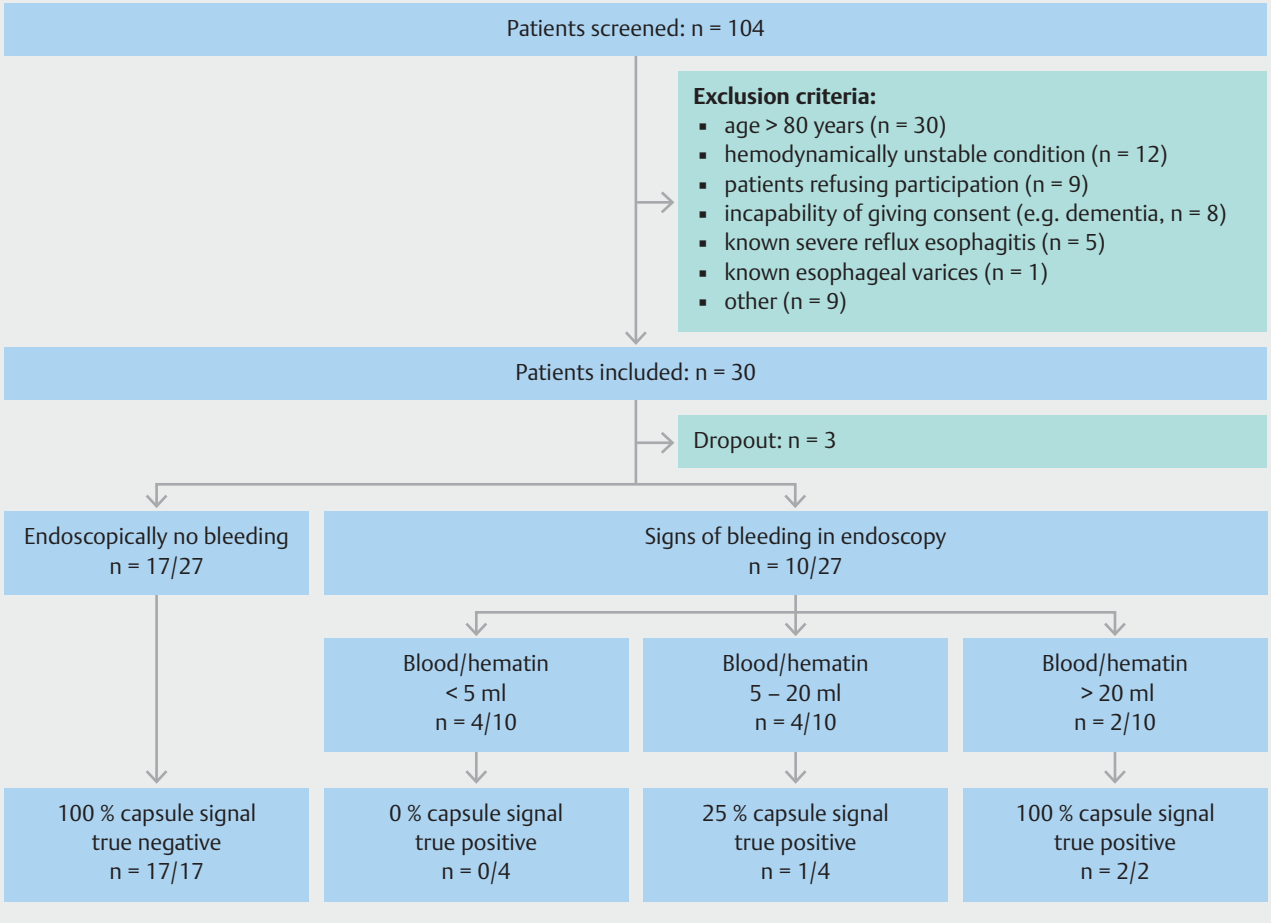
In this first clinical pilot trial, use of the novel sensor capsule for detection of UGIB was feasible and safe. The capsule is significantly smaller than common video capsules, making ingestion very tolerable. Also, there were no cases of capsule retention or other device-related AEs.

The secondary aim of our study was to gain first data on the correlation of capsule signals with presence or absence of UGIB in a clinical setting. Two preclinical studies have shown the ability of the capsule to detect blood in a porcine model as well as in a human volunteer [6 – 8]. As described above, presence of blood is detected by measuring the characteristic absorption of red and violet light. In preclinical studies, the maximum quotient of red and violet light intensities measured within 10 minutes after capsule ingestion showed a good correlation (correlation coefficient = 0.9016) with blood concentration in the stomach. Because intralumenal concentrations of blood cannot be measured in the clinical setting, we categorized endoscopically estimated amounts of blood to compare the findings with the sensor signals. In a study by Hawkey and colleagues, the amount of blood in the stomach was found to correlate with severity of bleeding and to predict unfavorable outcomes [9].

Therefore, we considered patients with an intraluminal amount of blood more than 20 mL likely to have severe or ongoing hemorrhage. In our study, the sensor capsule was able to detect all bleeding with an endoscopically estimated amount of more than 20 mL blood or hematin (100 %). In patients with less than 5 mL or between 5 and 20 mL, the sensor capsule signal was positive in 12.5 % of cases. Preclinical experimental



▶ **Fig. 3** Illustration showing sequence of procedures during the study. (Source: Ovesco Endoscopy AG)

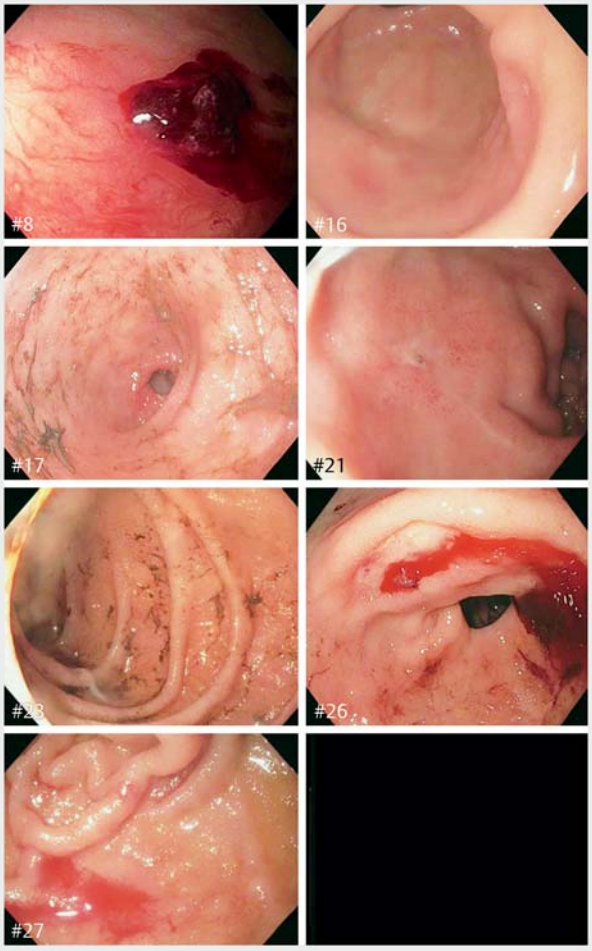


▶ **Fig. 4** Flowchart showing recruitment of patients and correlation of sensor signals with endoscopic findings.

▶ **Table 1** Overview of 10/27 patients with endoscopic bleeding signs.

Patient no	Time to endoscopy [hh:mm]	Endoscopic findings					Sensor signal within the first 10 min after ingestion (pos./neg.)
		Bleeding signs (Yes/No) and (active/not active)	Amount of blood or hematin (mL)	Bleeding source	Bleeding stigmata	Endoscopic therapy (Yes/No)	
6	01:00	Yes, active	>5 mL <20 mL	Duodenum	Duodenal ulcer; fresh blood, diffusely distributed; no residual food	Yes	pos.
8*	01:35	Yes, not active	<5 mL	Stomach	Ulcus Dieulafoy, local coagulated clot in the stomach adherent to the wall; no residual food	Yes	neg.
11	08:27	Yes, not active	>20 mL	Stomach	Ulcus Dieulafoy; fresh blood in the stomach plus >20 mL of local coagulated clot on the wall, partly diffusely distributed; low amount of residual liquid in the stomach	Yes	pos.
15	01:57	Yes, not active	>20 mL	Stomach	Source unknown; >20 mL hematin diffusely distributed in the stomach plus >20 mL local coagulated clot on the wall; low amount of residual liquid in the stomach	No	pos.
16*	01:57	Yes, not active	<5 mL	Stomach	Erosive gastritis; very low amount of local hematin, adherent to the wall; no residual food	No	neg.
17*	00:12	Yes, not active	>5 mL <20 mL	Stomach, duodenum	Ulcus duodeni and ulcus ventriculi; locally situated hematin in the stomach and duodenum, adherent to the wall; considerable amount of residual liquid and food in the stomach	Yes	neg.
21*	02:33	Yes, not active	<5 mL	Duodenum	Ulcus duodeni and erosions in the antrum; hematin in the duodenum, locally situated and adherent to the wall; no residual food in the stomach	No	neg.
23*	05:01	Yes, not active	>5 mL <20 mL	Stomach	Ulcus ventriculi; hematin locally situated and adherent to the wall; no residual food in the stomach	No	neg.
26*	01:10	Yes, not active	>5 mL <20 mL	Stomach	Ulcus ventriculi. initially between 5 – 20 mL of coagulated clot on the stomach wall, in the course of the EGD low amount of fresh blood caused by ulcus cleaning; considerable amount of residual liquid and food in the stomach	Yes	neg.
27*	00:42	Yes, active	<5 mL	Stomach, duodenum	Duodenal angiodysplasia; hematin widely spread over and fresh blood locally situated in the stomach and adherent to the wall in the duodenum; no residual food in the stomach	Yes	neg.

Right column shows sensor capsule results within the first 10 minutes after ingestion. The capsule detected 2/2 patients with more than 20 mL of blood or hematin and 2/8 patients with less than 20 mL. Endoscopic pictures of highlighted patients (*) in this table can be seen in ▶ **Fig. 5**.



▶ **Fig. 5** Endoscopic findings of patients with bleeding signs and estimated amount of intraluminal blood < 20 mL resulting in a negative capsule signal. Further patient details are reported in ▶ **Table 1**.

studies have shown that the capsule is able to detect blood in concentrations as low as 1 % [7, 10]. However, a signal can only be obtained when blood is captured by the measuring slot in the capsule (▶ **Fig. 1**). In the 87.5 % of cases less than 20 mL that did not lead to a positive sensor signal, intraluminal hematin or blood was locally situated or adherent to the wall (▶ **Fig. 5**). Thus, the blood may not have been captured in the capsule's measuring slot, leading to a negative signal. However, the primary aim of the sensor capsule is to support decision-making on urgency of endoscopy. Patients with low amounts of intraluminal blood are unlikely to have severe or ongoing hemorrhage [9]. Hence, a negative signal in those cases is to be considered true negative in terms of bleeding requiring endoscopic hemostasis. On the other hand, 17 of 17 patients (100 %) with suspected UGIB were correctly identified as non-bleeders by the sensor capsule. This indicates a high negative predictive value, which is mandatory to identify patients who do not require urgent endoscopic diagnosis and therapy. However, those findings should be still interpreted with care. Patients with signs of UGIB and negative capsule result may still undergo elective, but not urgent EGD. Another limitation is the heterogeneous interval between capsule ingestion and EGD (152 min, range 12 – 566 min). Due to physiologic gastric emptying, gastric content during sensor capsule measurement may not be the same as at the time of the actual EGD (according to the study protocol within 12 hours). Hence, both results may be difficult to compare directly. Moreover, intraluminal blood amounts were not exactly measured but rather endoscopically estimated by the physicians.

We would like to emphasize that this first clinical study was an explorative pilot trial which was not designed to determine sensitivity or specificity for detection, neither negative or positive predictive value, or any clinical outcome of acute UGIB. The number of patients and bleeding events was too low to reliably address this question. The primary aim of this study was to show feasibility and safety of this novel device and procedure in a clinical setting. We also cannot draw conclusions on the role of the capsule in other indications, such as obscure bleeding.

After this first clinical trial, it appears that the sensor capsule may have the potential to become a valuable diagnostic tool for noninvasive and real-time detection of acute UGIB and may accelerate emergency triage of these patients. In contrast to video capsule endoscopy, a result can be interpreted without special training by means of a numerical value and is rapidly available. Therefore, the capsule may facilitate decision-making on emergency referrals, such as in institutions without a 24-hour emergency endoscopy service. The device also may be helpful in tertiary centers for decision-making about where to allocate resources. Even outpatient use by family doctors or physicians may be feasible in the future.

Conclusion

In conclusion, detection of acute UGIB with the novel sensor capsule proved to be feasible and safe. The swallowable sensor capsule directly responds to presence of blood in the lumen of the upper digestive tract and provides data in real -time. Larger studies are necessary to further determine the negative predicate value to identify patients not requiring urgent endoscopic diagnosis and therapy and the clinical impact of the device on management of those patients.

Acknowledgements

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Competing interests

Klinikum Ludwigsburg received study grants from Ovesco Endoscopy. Dr. Schmidt and Prof. Caca received lecture fees from Ovesco Endoscopy.

Ms. Zimmermann is working as Project Manager at Ovesco Endoscopy AG and is a PhD candidate at the Eberhard-Karls-University of Tuebingen focusing on the technical and clinical development of the novel innovative sensor capsule.

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▶ **Supplementary Table 1** Laboratory and clinical characteristics of patients.

Patient No.	Sex [f/m]	Hemoglobin (g/dl)	Blood urea nitrogen (mmol/L)	Systolic blood pressure (mm Hg)	Heart rate (beats/min)	Melena present (Yes/No)	Recent syncope (Yes/No)	Hepatic disease history (Yes/No)	Cardiac failure present (Yes/No)	Glasgow-Blatchford-Score
1	F	7.6	108	130	71	Yes	No	No	No	13
2	F	5.9	31	95	85	Yes	No	No	No	15
3	M	9.3	33	130	106	Yes	No	No	No	14
4	F	9.3	7	130	92	Yes	No	No	No	9
5	M	6.0	55	120	84	Yes	No	No	No	13
6	M	11.2	27	140	104	Yes	No	No	No	14
7	M	15.4	12	130	76	No	No	No	No	10
8	M	6.8	28	130	80	Yes	No	No	No	13
9	M	13.8	9	140	64	Yes	No	No	No	10
10	M	14.9	12	90	56	Yes	No	No	No	13
11	M	6.0	54	140	69	Yes	No	No	Yes	15
12	F	10.7	22	120	82	Yes	No	No	Yes	13
13	Excluded									
14	F	5	21	120	90	Yes	No	No	No	11
15	M	7.8	123	110	62	Yes	No	No	No	13
16	W	8.0	15	110	99	Yes	No	No	No	11
17	M	11.9	42	120	71	Yes	No	No	No	13
18	M	5.9	22	123	120	Yes	No	No	No	12
19	W	5.0	12	120	93	Yes	No	No	No	11
20	M	10.7	18	120	80	Yes	No	No	Yes	13
21	W	8.0	29	130	130	Yes	No	No	No	14
22	Excluded									
23	M	8.9	76	121	94	Yes	No	No	Yes	15
24	W	12.5	33	140	103	Yes	No	No	No	14
25	M	11.8	43	117	93	No	No	No	No	12
26	W	13.9	47	100	80	Yes	No	No	No	14
27	M	5.6	131	100	61	Yes	No	No	No	14
28	M	6.1	14	160	99	Yes	No	No	No	11
29	M	8.9	15	150	93	Yes	No	No	No	11
30	Excluded									