

Danis stent for acute oesophageal variceal bleeds

Medtech innovation briefing

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Summary

- The **technology** described in this briefing is Danis stent. It is used to stop acute bleeding from oesophageal varices, which are a major complication of portal hypertension and mainly happen in people with underlying liver disease.
- The **innovative aspects** are that it has a safety indicator balloon which prevents the gastric balloon from inflating in the oesophagus and aims to reduce the risk of balloon-related perforation. The company states that the stent can be inserted without image guidance, allowing rapid tamponade in acute scenarios.
- The intended **place in therapy** would be as an alternative method to balloon tamponade or early transjugular intrahepatic portosystemic shunt in people with refractory oesophageal variceal bleeding, in accordance with existing clinical guidelines.
- The **main points from the evidence** summarised in this briefing are from 6 studies including a total of 202 people with refractory variceal bleeding. They show that Danis stent is effective at controlling acute refractory bleeds as a bridging therapy to further treatment. Data from 1 randomised controlled study suggest it may be a more effective and safer method than balloon tamponade.
- **Key uncertainties** around the evidence include the lack of extensive UK evidence which may limit generalisability to the NHS. Only 1 study was done in the UK and this was a case series study involving a small number of patients.
- The **cost** of Danis stent is £1,495 per unit (basic procedure pack; excluding VAT). The company claims the technology has the potential to be resource releasing by reducing the need for high

- dependency hospitalisation. There is no published evidence to support these claims.

The technology

Danis stent (Ella CS) is a medical device intended to stop acute bleeding from oesophageal varices. It is a removable and self-expandable, silicone-covered nitinol stent which controls bleeding by direct compression of oesophageal varices. The stent is 135 mm long and 25 mm in diameter (30 mm when inflated). It comes preloaded in a balloon-style delivery system that is designed to allow accurate positioning at the gastro-oesophageal junction. The delivery system allows insertion of the stent into the lower oesophagus without radiological or endoscopic assistance. Radiopaque markers at the distal ends and midpoint of the stent allows its position to be confirmed by chest X-ray after the procedure. The Danis stent has retrieval loops with gold markers at both ends which allow the stent to be removed under endoscopic and fluoroscopic guidance using a specifically designed removal device (Ella Extractor). This can be purchased by the company. The stent will need to be removed whether or not the patient has definitive treatment, such as a transjugular intrahepatic portosystemic shunt (TIPS). If TIPS has been done (and portal hypertension is no longer a concern), the company states that the stent can be removed under endoscopic guidance using grasping forceps without fluoroscopic guidance. The Ella Extractor would only be needed to remove the stent in patients who have not had definitive treatment. Danis stent is currently available as part of a basic procedure pack which contains the stent (preloaded in the delivery system), guide wire and syringe.

Current care pathway

In patients with oesophageal varices, haemorrhage is common and can lead to life-threatening bleeding and complications. Bleeding from oesophageal varices are a major complication caused by portal hypertension and mainly happen in people with underlying liver disease. Current standard care for people with acute variceal bleeding involves a combination of basic resuscitation, vasoactive drugs, prophylactic antibiotics and endoscopic techniques. NICE's guideline on [acute upper gastrointestinal bleeding in over 16s](#) recommends offering terlipressin to people with suspected variceal bleeding at presentation. Band ligation is the recommended primary therapy for people with upper gastrointestinal bleeding from oesophageal varices, and TIPS is recommended if bleeding from oesophageal varices is not controlled by band ligation. NICE's interventional procedures guidance on [stent insertion for bleeding oesophageal varices](#) states that there is enough evidence to show that stent insertion is effective for people with oesophageal varices in whom other methods of treatment have failed to control bleeding.

The British Society of Gastroenterology's [UK guidelines on the management of variceal haemorrhage in cirrhotic patients](#) recommend doing upper gastrointestinal endoscopy as soon as

the patient is haemodynamically stable to locate the site bleeding. Variceal band ligation is recommended as the first-choice therapy to control bleeding. If banding is difficult because of continued bleeding or this technique is not available, endoscopic variceal sclerotherapy should be done. In case of bleeding that is difficult to control, the guidelines recommend inserting a temporary balloon tamponade (a Sengstaken-Blakemore tube) as a bridge to more definitive treatment such as further endoscopic treatment, TIPS, or surgical treatment. The guidelines state that, ideally, variceal bleeding should be treated in a unit where the staff are familiar with managing bleeds and where routine therapeutic interventions can be done.

The [Baveno VI consensus report](#) (Journal of Hepatology, 2015) states that evidence on self-expanding oesophageal metal stents (SEMS) suggests that they are as effective and a safer option than balloon tamponade.

Innovations

The company states that Danis stent can be used without endoscopic image guidance, which may allow for more rapid control of variceal bleeds in emergency situations compared with balloon tamponade. The delivery system has a security pressure valve that prevents the gastric balloon from being inflated in the oesophagus, which may help minimise the risk of oesophageal perforation. It can stay in place for up to a week (compared with balloon tamponade, which should not be left in place for more than 24 to 36 hours). This may allow more time to plan definitive therapy or secondary prophylaxis before removal, as well as increasing the stabilisation period for improvement in liver function. The Danis stent lumen allows oral nutrition to be maintained, which is an important element in recovery, and its variable weave stent body is designed to conform to oesophageal peristalsis, with the aim of preventing stent migration.

Population, setting and intended user

Danis stent is intended to be used as an alternative to balloon tamponade and early TIPS in people aged 16 years and over with acute refractory variceal bleeding. The technology is intended to be used in secondary care by gastroenterologists, hepatologists, emergency care practitioners, paramedics or nurse practitioners. The company highlights that training and education would be needed to make sure healthcare professionals were confident using the technology in an acute setting. Training for consultants and nursing staff is provided by the company free of charge at agreed intervals. Training sessions are in-person and can last between 1 hour and a full day depending on centre needs and frequency.

Costs

Technology costs

Danis stent procedure pack basic (containing stent, preloaded in the delivery system; guide wire and syringe) costs £1,495 (excluding VAT). The procedure cost for inserting the stent is £6,443, according to the 2019/20 national tariff payment system (HRG FD03A Gastrointestinal Bleed with Multiple Interventions, with CC Score 5+). HRG FD03A covers all care costs associated with the procedure and includes more than the cost of the device. The cost of the Ella Extractor, for atraumatic removal of the stent, is £695 (excluding VAT); this would only be used in people who have not had definitive treatment, such as TIPS.

Costs of standard care

The company states that the typical cost of standard care (Sengstaken-Blakemore/Minnesota tube 4 lumen) is £300. The cost of the procedure would be the same as that for Danis stent; £6,443 (HRG FD03A Gastrointestinal Bleed with Multiple Interventions, with CC Score 5+). HRG FD03A covers all care costs associated with the procedure and includes more than the cost of the device.

Resource consequences

According to the company, the technology is currently being used by over 20 NHS centres. The company claims Danis stent is likely to lead to cost savings because it can remove or minimise high dependency hospitalisation as well as reduce the demand on fluoroscopic imaging facilities. However, there is no relevant published evidence to support this. The technology has been associated with a substantially lower incidence of device-related serious adverse events compared with balloon tamponade ([Escorsell et al. 2016](#)). This could potentially lead to fewer repeat hospital visits and interventions needed for procedural complications, although this has not yet been proven.

Regulatory information

Danis stent is CE marked as a class IIb medical device.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Oesophageal variceal bleeding is a common and life-threatening complication of cirrhosis in people with chronic liver disease. Cirrhosis is more common among men than women. Some people with chronic liver disease may be considered disabled under the Equality Act if their condition 'has a substantial and long-term adverse effect on their ability to carry out normal day-to-day activities'.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the [interim process and methods statement](#). This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

Six studies (1 randomised controlled trial, 1 case-control and 4 case series) involving a total of 202 people with refractory variceal bleeding are summarised in this briefing. Out of a total of 202 patients, 134 were allocated to have Danis stent.

Clinically relevant outcomes that were reported include: acute bleeding control, absence of rebleeding, absence of serious adverse events and survival rates.

[Table 1](#) summarises the clinical evidence as well as its strengths and limitations.

Overall assessment of the evidence

Overall, the evidence suggests that Danis stent is effective at controlling acute refractory oesophageal bleeding, as a bridging therapy to further treatment. Results from a randomised controlled study ([Escorsell et al. 2016](#)) suggest that, compared with balloon tamponade, Danis stent provides more frequent therapy success, a higher control of bleeding and is associated with a lower incidence of device-related severe adverse events.

Most of the studies evaluating Danis stent were case series, which lacked a comparator and included a relatively small number of patients, making it difficult to draw conclusions about the efficacy of Danis stent compared with standard care. In the 2 studies including comparators ([Escorsell et al. 2016](#) and [Maiwall et al. 2018](#)), the therapies used are not recommended by NICE's guideline on [acute upper gastrointestinal bleeding in over 16s](#). Although most of the studies were done in Europe (except 1 study in India), there is a lack of robust UK evidence with only 1 small case series done in an NHS centre. The use of endoscopy for stent deployment appeared inconsistent

between studies. Although the company claims that in emergency situations, the device can be inserted without endoscopic image guidance, further research may be needed to support these claims. There was also notable variability between studies in the duration of stent implantation. In some of the studies, the stent stayed in place for up to 14 days (Dechêne et al. 2012; Wright et al. 2010; Zehetner et al. 2008), which is considerably longer than is recommended in the instructions for use (remove within 7 days of implantation). Evidence on the use of Danis stent in non-specialist centres may help to understand whether the technology is suitable for wider adoption by endoscopy units outside of larger specialist centres.

Table 1 Summary of selected studies

<u>Escorsell et al. (2016)</u>	
Study size, design and location	A randomised controlled trial involving 28 people admitted to hospital with a diagnosis of cirrhosis and refractory AVB or massive variceal bleeding between March 2009 and January 2013. Spain in 9 teaching hospitals.
Intervention and comparator(s)	Danis stent (n=13). Sengstaken-Blakemore Tube (n=15).
Key outcomes	Compared with the balloon tamponade group, the Danis stent group had a more frequent success of therapy (66% compared with 20%; p=0.025), defined by absence of digestive bleeding, absence of SAEs and 15-day survival. There was higher control of bleeding in the Danis stent group at 15 days (85% compared with 47%; p=0.037), but no significant difference was seen at 6 weeks (54% compared with 47%; p=0.25). There were no significant differences between the 2 groups in both 15-day (69% compared with 47%; p=0.39) and 6-week survival (54% compared with 40%; p=0.46). Fewer SAEs happened in the Danis stent group, however this was not statistically significant (15% versus 47%; p=0.077). There was no reduction in duration of ICU stay (8 days versus 8 days; p=0.93) or hospital stay (14 days versus 14 days; p=0.55) between the 2 groups.

Strengths and limitations	A multicentre randomised controlled trial which was independent and independently funded. Use of intention-to-treat analysis. A power calculation was used to determine minimal sample size needed (n=46), however the study used interim analysis results which was 60% of desired sample size. The study was done in Spain and may not be generalisable to the NHS. No female patients were included the Danis stent group. People who had previously had balloon tamponade treatment (n=23) were excluded, however they could be a key target population for the Danis stent. More patients in the balloon tamponade group had earlier TIPS which could have affected survival results.
<u>Wright et al. (2010)</u>	
Study size, design and location	A single-centre case series involving 10 people with cirrhosis and variceal haemorrhage, with contraindications to TIPS insertion or balloon tamponade, between March 2007 to July 2008. UK, tertiary referral liver centre.
Intervention and comparator(s)	Danis Stent. No comparator.
Key outcomes	Stent insertion was successful on first attempt in 8 out of 10 patients. 1 patient had successful insertion on second attempt, 1 patient had unsuccessful insertion because of the gastric balloon not inflating. Out of 9 patients actively bleeding at time of stent insertion, immediate control of bleeding was achieved in 7 patients (78%), with the remaining 2 patients discovered to have gastric varices. 6 of 9 stented patients (67%) survived the acute bleed, with stent removal at a median of 9 days (range 6 to 14 days). Failure to control the acute bleed was seen in 3 patients, and all 3 patients died because of either multi-organ failure or severe blood loss. Rebleeding 60 days after stent removal was seen in 1 patient. Overall survival rate at 42 days was 50%. Proximal oesophageal ulceration caused by stent insertion was seen in 1 patient.
Strengths and limitations	UK study generalisable to the NHS. Included patients in whom previous balloon tamponade therapy had failed. Study included 3 different care settings (ICU, A&E and endoscopy unit). A relatively small sample size in a single centre with no comparator group. 2 patients had gastric varices which cannot be treated with Danis stent. No statistical analysis done. A short follow-up of 42 days with no long-term outcomes reported. Source of funding was not clear.
<u>Zehetner et al. (2008)</u>	

Study size, design and location	A single-centre case series involving 34 patients with acute oesophageal variceal bleeding not controlled with standard therapy between January 2003 to August 2007. Austria.
Intervention and comparator(s)	Danis stent (n=34). No comparator.
Key outcomes	Stent placement was successful and uncomplicated for all 34 patients. 33 patients had variceal bleeding only (1 patient had a non-variceal bleeding source), and immediate bleeding control was achieved in these patients. No bleeding recurrence was seen during stent implantation (median: 5 days; range 1 to 14 days). Complications included stent migration in 7 patients (21%) and slight distal oesophageal ulceration in 1 patient (3%) during extraction of the stent. Mortality rates at 30 and 60 days were 26.5% (9 patients) and 29.5% (10 patients), respectively. 2 patients died of liver failure within 24 hours of Danis stent insertion. 7 patients died of liver failure or multi-organ failure after stent removal.
Strengths and limitations	Patients with previous balloon tamponade treatment were included. Study was a single-centre case series with no comparator. No statistical analysis done. There was a short follow-up period of 60 days. Not done in UK so may have limited generalisability to NHS.
<u>Maiwall et al. (2018)</u>	
Study size, design and location	A retrospective case-control single-centre study of 88 patients who had acute-on-chronic liver failure with refractory variceal bleeds from 2014 to 2016. India.
Intervention and comparator(s)	Danis stent (n=35). Continued treatment with repeat endotherapy and vasoactive drugs or balloon tamponade or both (n=53).

Key outcomes	Control of initial bleeding was significantly greater in Danis stent group compared with controls in pre-match (89% versus 37%; $p < 0.001$) and PRS-matched cohorts (73% versus 32%; $p = 0.007$). 5 patients (14%) in Danis stent group re-bled after initial haemostasis. There was a statistically significant reduction in deaths secondary to bleeding in Danis stent group in pre-match (14% versus 64%; $p = 0.001$) and PRS-matched cohorts (6% versus 56%; $p = 0.001$). 15-day mortality was significantly reduced in the Danis stent group in pre-match ($p = 0.004$, HR 2.56, 95% CI 1.35 to 4.83) and PRS-matched cohorts ($p = 0.017$, HR 8.1, 95% CI 1.02 to 64.4). However, 6-week mortality was only significantly reduced in PRS-matched cohort ($p = 0.05$, HR 8.1, 95% CI 1.02 to 64.4).
Strengths and limitations	An independent study with a good sample size and comparator group. Done in India so may have limited generalisability to the NHS. Statistically significant differences in patients' baseline characteristics (for example, Child-Turcotte-Pugh score, albumin and AST levels) were seen, however this was controlled using PRS. Selection bias may have happened from endoscopists choosing the therapy based on experience and preference. Study included patients with acute-on-chronic liver failure only, excluding other patients who could be a key target population.
<u>Pfisterer et al. (2019)</u>	
Study size, design and location	A retrospective multicentre observational study involving 34 patients with cirrhosis and refractory oesophageal variceal bleeding between January 2009 to December 2016. Austria 4 tertiary care centres.
Intervention and comparator(s)	Danis stent: Ella CS (n=34). No comparator.

Key outcomes	Danis stent controlled acute refractory variceal bleeding in 27 patients (79.4%). In the remaining 7 (20.6%) patients, other treatments were applied (EBL, n=3; SEMS renewed, n=2; Linton BT, n=2). Among these patients, only 1 achieved successful long-term bleeding control. Early rebleeding within 6 weeks happened in 6 out of 34 patients (17.6%). 5-day mortality was 20.6% (7 patients). 13 patients (38.2%) died with Danis stent in place. In the 20 patients who had Danis stent successfully removed, (overall median dwell time of 3 days), 7 patients (35%) experienced rebleeding and 5 patients (14.7%) died. Overall 16 patients died because of bleeding (47.1%). Median survival after Danis stent placement was 2.1 months. Complications of Danis stent included stent dislocations in 13 patients (38.2%) and oesophageal ulcers in 4 patients (11.8%).
Strengths and limitations	A multicentre study with a long follow-up (1 year) for observations of adverse events and patient outcomes. Observational, retrospective design with no comparator is relatively low-quality evidence. Not done in UK so may not be generalisable to NHS. 3 patients had additional gastric varices which cannot be controlled with Danis stent. No patients had early TIPS procedures which could have affected mortality rates.
<u>Dechêne et al. (2012)</u>	
Study size, design and location	A single-centre case series of 8 patients with cirrhosis and oesophageal variceal bleeding refractory to standard therapy between August 2007 to March 2011. Germany.
Intervention and comparator(s)	Danis stent: Ella CS (n=8). No comparator.
Key outcomes	In a total of 8 cirrhotic patients, 9 bleeding episodes were seen (1 patient treated twice in 7-month period). In all patients, immediate bleeding control with Danis stent was achieved. In the 3 patients who progressed to TIPS or liver transplant after stabilisation, all survived without any rebleeding 60 days after stent removal. The remaining 6 patients who only progressed to pharmacological treatment all died, with 3 patients experiencing rebleeding.

Strengths and limitations	An independent study. Reasonably similar baseline characteristics between patients helps to limit potential confounders. Single-centre case series with small sample size limits reliability. No comparison to standard care. Done in Germany and so may not be generalisable to the NHS. A short follow-up period of 60 days.
Abbreviations: AST, aspartate aminotransferase; AVB, acute bleeding from oesophageal varices; CI, confidence interval; EBL, endoscopic band ligation; HR, hazard ratio; ICU, intensive care unit; PRS, propensity risk score; SAE, serious adverse events; SEMS, self-expanding oesophageal metal stents; TIPS, transjugular intrahepatic portosystemic shunt.	

Recent and ongoing studies

- [Effective haemostasis using self-expandable covered mesh-metal oesophageal stents versus standard endoscopic therapy in the treatment of oesophageal variceal haemorrhage: a multicentre, open, prospective, randomised, controlled study](#). ClinicalTrials.gov identifier: NCT01851564. Status: the study has been discontinued; no published results are available. Indication: acute bleeding oesophageal varices. Intervention(s): self-expanding mesh-metal oesophageal stent (SEMS; SX-Ella Danis stent); standard endoscopic therapy. The company states that this trial is now discontinued.

Specialist commentator comments

Comments on this technology were invited from clinical specialists working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

All the commentators were familiar with the technology, and 2 out of 4 had used Danis stent before.

Level of innovation

Three of the commentators considered Danis stent novel in its concept or application. However, 1 commentator highlighted that it is not a new technology and the insertion technique compared with standard care (balloon tamponade) is similar. The innovative aspects identified were that Danis stent allows oral intake and can be left in place for a longer period than a balloon tamponade, potentially allowing stabilisation for definitive treatment. One commentator noted that Danis stent does not cause complete oesophageal obstruction, which reduces the risk of oropharyngeal aspiration and patients do not need intubation in an intensive care unit (ICU) for airway protection

(which they would need for balloon tamponade). Danis stent was identified as having a novel delivery system, with accurate stent placement, reducing risk of stent misplacement and oesophageal balloon inflation with subsequent possible oesophageal rupture. This has been a recognised complication of balloon tamponade. The use of a removal stent was identified as a novel design but has been available for some years for clinical use. Hemospray foam and histoacryl glue were identified as competing technologies by 1 commentator. None of the other commentators were aware of any competing technologies.

Potential patient impact

Potential patient benefits identified by commentators included quickly stopping bleeding, increased time to stabilise the patient before more definitive treatment and the ability to maintain oral nutrition. One commentator noted that the technology is associated with improved bleeding control and fewer adverse events compared with the Sengstaken-Blakemore tube, but that the mortality and length of ICU or hospital stay was similar. One commentator also said that the stent avoids the need for compulsory tracheal intubation and reduces the risk of oropharyngeal aspiration and pneumonia. A lower risk of oesophageal perforation compared with balloon tamponade was also mentioned by commentators. Patients with severe and refractory oesophageal variceal bleeding, including those with rebleeding from banding-induced ulcers, were identified by commentators as people who would benefit from Danis stent. Patients presenting to non-specialist centres or small district hospitals that may not have access to definitive treatment (such as transjugular intrahepatic portosystemic shunt [TIPS]) or specialist liver services were also identified by some of the commentators. One of the commentators noted that the stent would allow emergency haemostasis and allow the patient to be transferred to a specialist unit. The same commentator noted, however, that these non-specialist centres are likely to have the lowest access to Danis stent and the skills needed to do the procedure.

Potential system impact

Potential system benefits identified by commentators included: faster time to haemostasis, a reduction in number of endoscopies, less ICU beds and fewer infective complications, such as pneumonia. Identification of patients for whom more definitive treatment would be suitable was another benefit highlighted. Another commentator noted that the longer stability period for patients would allow clinicians to optimise resuscitation and plan next steps. One commentator concluded that Danis stent could cost more than current standard of care, including the need for both fluoroscopy-guided removal and a specific removal device. Other commentators specified that the upfront cost of Danis stent would be greater, but 2 of them agreed that overall costs could be reduced because of a reduction in ventilator-dependent ICU care and complications. The

remaining commentator said that it was difficult to clarify the costs because these patients are very ill and will often still need intensive care and subsequent interventions. Three commentators suggested that Danis stent would replace the current treatment option of balloon tamponade. Another commentator suggested both techniques would co-exist to be used depending on clinical context, but Danis stent could replace radiological treatments such as TIPS when its use is contraindicated.

General comments

Commentators agreed that regular product-specific training on how to use the device would be needed for healthcare professionals. Operators of the device are likely to be gastroenterologists, but radiologists could also be trained. One commentator said that inserting Danis stent is more complicated than inserting a Sengstaken-Blakemore tube, and that screening is usually needed to remove the stent. The only safety concerns raised related to inadequate training which could increase complications with use. The eligible population was estimated to be 100 patients per year in the UK by 1 commentator, with another commentator suggesting an average UK unit may have 4 refractory cases needing Danis stent per year. Based on experience from their trusts or hospitals, 1 commentator said that 3 people have treatment with Sengstaken-Blakemore tube each year, while the remaining commentator said that 10 people out of a local population of 700,000 people would be eligible for Danis stent. Adoption issues identified included cost of device and removal system and need of repeated training for gastroenterologists. One commentator highlighted that randomised controlled trials would be helpful to understand the rate of stent migration and ulceration with Danis stent as well as mortality but noted that this is a very challenging area in which to undertake clinical studies.

Specialist commentators

The following clinicians contributed to this briefing:

- Dr Deepak Joshi, consultant hepatologist, Institute of Liver Studies at King's College Hospital. Did not declare any interests.
- Dr Ian Beales, consultant in gastroenterology and general medicine, Norfolk and Norwich University Hospitals NHS Foundation Trust. Did not declare any interests.
- Dr Claire Salmon, consultant hepatologist, Sheffield Teaching Hospitals NHS Foundation Trust. Did not declare any interests.
- Professor Adrian Stanley, consultant gastroenterologist, Glasgow Royal Infirmary. Spoke at a

- 'meet the expert' session during British Society of Gastroenterology Endoscopy Live 2019 on 8 March 2019. The session was sponsored by Cantel Limited (a manufacturer of the Sengstaken-Blakemore tube), he did not receive payment for speaking at this event.

Development of this briefing

This briefing was developed by NICE. The [interim process and methods statement](#) sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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