NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation: Danis Stent for acute oesophageal variceal bleeds (MT450)

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.

   1B. EAC assessment report Addendum 1 – additional analysis

   1C. EAC assessment report Addendum 2 – micro-costing

2. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
3. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
4. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
5. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
6. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
7. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.
8. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

Document cover sheet

Assessment report: Danis Stent

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2.0	Revisions after comments from NICE	A Chalkidou J Erskine K Goddard A Clark M Pennington	26/06/2020	
2.1	Revisions after fact-check comments from company	J Erskine A Clark M Pennington	07/07/2020	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance
MT450 Danis Stent for acute oesophageal variceal bleeds
External Assessment Centre report

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Contains confidential information: No

Number of attached appendices: 6

Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

Declared interests of the authors

None.

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Responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

Abbreviations

Term	Definition
AVB	Acute Variceal Bleed
BSG	British Society of Gastroenterology
BT	Balloon Tamponade
CRD	Centre for Reviews and Dissemination
CLD	Chronic Liver Disease
CP	Child-Pugh
CI	Confidence interval
DS	Danis stent
DHSC	Department of Health and Social Care
EAC	External Assessment Centre
EBL	Endoscopic Band Ligation
GOJ	Gastro-Oesophageal Junction
HE	Hepatic Encephalopathy
HR	Hazard Ratio
ICU	Intensive Care Unit
IQR	Interquartile range
MAUDE	Manufacturer and User Facility Device Experience
MELD	Model For End-Stage Liver Disease
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
PBRC	Packed Red Blood Cell
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRS	Propensity Risk Score
PSA	Probabilistic Sensitivity Analysis
PSS	Personal and Social Services
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised controlled trial
SAE	Severe Adverse Event
SEMS	Self-expanding Metal Stent
S-B	Sengstaken-Blakemore
SD	Standard deviation

TIPS	Transjugular Intrahepatic Portosystemic Shunt
VAS	Visual analogue scale
Vs	Versus

Executive summary

The company included 9 full text studies in their clinical submission. The EAC included all 9 of these studies and after updating the company's search to include records published up to 6 May 2020, did not find any other relevant studies. Two included studies compared Danis stent to balloon tamponade (1 also included repeat endotherapy and vasoactive drugs) in people with oesophageal variceal bleeding. One study was a multicentre RCT performed in Spain (Escorsell et al. 2016). The remaining 7 studies were non-comparative studies with broadly similar populations and outcomes. One small study (Wright et al. 2010) was performed in the UK.

Escorsell et al. 2016 represents the strongest evidence available. However, the study was underpowered and there is uncertainty in the generalisability in the clinical pathway in Spain to the UK, particularly in terms of the availability of TIPS as a definitive treatment. The results of this RCT and the other comparative study (Maiwall et al. 2018) suggest that Danis stent may improve control of bleeding, survival and rate of serious adverse events at 15 days after implantation when compared to balloon tamponade. These results were not significantly different between the groups 6 weeks after implantation. The company did not carry out a meta-analysis as they did not consider that quantitative evidence synthesis was appropriate for the 2 comparative studies. The EAC agreed, however, quantitative analysis was performed on outcomes from the 7 non-comparative studies. Heterogeneity was low between the studies and immediate control of bleeding was estimated at 88% (95% CI: 0.38 to 0.9) from the 7 studies.

The company provided a cost comparison model over a 6 week time horizon using a cost calculator approach, finding Danis stent to be cost saving in the base case. The EAC amended 5 parameters in the company's model and found that Danis stent incurs a cost of £982 per patient in the base case. Two other scenarios were presented by the company. The EAC found that in a micro-costing scenario where the use of Danis stent is associated with a reduction in intensive care bed days and procedure costs, the cost incurred per patient falls to £397. Given the limited evidence available, all scenarios should be considered.

Overall, the EAC believes that further research is required before this technology can be recommended for adoption. A well-designed, UK-based RCT comparing Danis stent to Balloon Tamponade and capturing patient-related outcomes is vital to inform a robust cost-effectiveness model.

1 Decision problem

The company clarified 2 points in the scope, both of which the EAC accepts as valid (see table 1). The company state that emergency or salvage TIPS could be an appropriate comparator performed at the same stage in the pathway as Danis stent. However, as this can only be performed in select hospitals in the UK and comparative data is not available, Balloon Tamponade is the only included comparator. Several outcomes were also not present in the literature and so were not included in this assessment.

Table 1 Decision Problem from Final Scope

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	People aged 16 years and over with acute refractory oesophageal variceal bleeding in whom first line therapy, such as terlipressin, prophylactic antibiotics, variceal band ligation or sclerotherapy is unsuitable or has failed	There has been no variation from the scope	Not applicable
Intervention	Danis stent insertion	There has been no variation from the scope	Not applicable
Comparator(s)	Balloon tamponade or Early trans-jugular intrahepatic portosystemic shunt (TIPS)	Balloon tamponade only	No studies were identified comparing Danis stent to TIPS

Outcomes	Control of bleeding Re-bleeding rate Blood transfusion use Device-related adverse events, including stent migration Mortality rate Hepatic encephalopathy Patient-related quality of life Additional/further interventions including TIPS	Data included on the following outcomes: Control of bleeding Re-bleeding rate Blood transfusion use Device-related adverse events, including stent migration Mortality rate Hepatic encephalopathy Additional/further interventions including TIPS	No studies reported any data for the outcome patient-related quality of life
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed. The cost analysis should allow for the expected costs of different methods of removal of the Danis stent, including the use of Ella Extractor	There has been no variation from the scope.	Not applicable
Subgroups to be considered	None identified	None identified	Not applicable

Special considerations, including issues related to equality	Danis stent is intended for use in people aged 16 years and over with acute refractory variceal bleeding. Oesophageal variceal bleeding is a common and life-threatening complication of cirrhosis in people with chronic liver disease. 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'. Age and disability are protected characteristics under the Equality Act 2010. Danis stent may also be an advantage to people who do not accept blood transfusions due to religious beliefs, such as Jehovah's Witnesses.	There has been no variation from the scope.	Not applicable

2 Overview of the technology

The Danis stent (Ella CS), also known as the SX-Ella Stent Danis is a removable, self-expanding stent intended to stop acute and refractory bleeding from oesophageal varices. The stent is a variable weave, constructed of nitinol with a silicone membrane. It is 135mm long and 25mm in diameter at the centre, increasing to 30mm in diameter at the flared distal ends. The company claims that the stent conforms to oesophageal peristalsis, which may reduce the risk of stent migration. A balloon-style delivery system is intended to allow accurate positioning of the stent at the gastro-oesophageal junction (GOJ), to provide direct compression of oesophageal varices. Unlike balloon tamponade, this system can be used without endoscopy or x-ray imaging for guidance. The delivery system also includes a security pressure valve which may reduce the risk of oesophageal perforation due to balloon inflation in the oesophagus. Gold markers are present at both ends and the midpoint of the stent so that its position can be confirmed with post-procedure chest x-ray. The Danis Stent is intended to stay in place for up to 7 days, compared to a balloon tamponade, which must be removed after 24-36 hours. This potentially allows clinicians more time to plan definitive therapy or secondary prophylaxis prior to the removal of the stent. The lumen of the stent allows oral nutrition to be maintained and physiological drainage of saliva. Experts confirmed that this can be of particular use in patients with cirrhosis, who are often malnourished.

The gold markers allow the Danis stent to be removed with endoscopic and fluoroscopic guidance using the Ella Extractor. The Ella Extractor is a specifically designed removal device that can be purchased from Ella CS. The Ella Extractor is required for removal in patients who have not had invasive definitive treatment and may be used to address stent migration. If definitive treatment, such as TIPS, has been performed and portal hypertension is no longer a concern, the Danis Stent can be removed under endoscopic guidance using grasping forceps without fluoroscopic guidance. The Danis Stent and delivery system, along with a guide wire and syringe, are available as part of a procedure pack. All components of this procedure pack are single-use.

The device has been CE marked as a class IIb medical device since 2005. The covering of the stent was polyurethane until 2009, when it was replaced with silicone. All other changes to the device have been non-substantial. The most recent CE certification was awarded in 2017 and is valid until 28 June 2022.

3 Clinical context

Bleeding from oesophageal varices is a major complication of portal hypertension, which is most commonly caused by liver cirrhosis. The current standard of care for people with acute variceal bleeding includes basic resuscitation, vasoactive drugs, prophylactic antibiotics and endoscopic techniques (usually band ligation or, more rarely, endoscopic variceal sclerotherapy).

NICE's guideline on acute upper gastrointestinal bleeding in over 16s recommends offering terlipressin and prophylactic antibiotic therapy to people with suspected variceal bleeding at presentation. The recommended primary therapy is band ligation and where this is unsuccessful, TIPS is recommended. NICE's interventional procedures guidance on stent insertion for bleeding oesophageal varices states that this procedure has been shown to be efficacious when other methods of treatment have failed to control bleeding. The overall incidence of acute upper gastrointestinal bleeding in the UK ranges from 50-150 per 100,000 population per year. This is estimated to account for 5000 deaths per year in the UK (NICE CG141).

The British Society of Gastroenterology's (BSG) UK guidelines on the management of variceal haemorrhage in cirrhotic patients, published in 2015, recommend offering antibiotics to all patients with variceal bleeding, along with terlipressin or somatostatin. Variceal band ligation is considered to be the preferred endoscopic method and early TIPS (defined as <72 hours after index variceal bleed) can be considered in selected patients with Child's B cirrhosis and active bleeding or Child's C cirrhosis with Child's score <14 (level 1b, grade B). Experts estimate that 10-15% of those admitted with acute upper gastrointestinal bleeding will have endoscopic band ligation as definitive treatment.

Early TIPS has been shown to decrease mortality and rebleeding when compared with no TIPS (Njei et al. 2017). If bleeding is difficult to control using these techniques, a Sengstaken-Blakemore (S-B) tube should be used as a bridge treatment until further endoscopic treatment, TIPS or surgery can be performed. It is noted that the available treatments will vary depending on the local resources and expertise and that transfer to a specialist centre can be considered after the insertion of an S-B tube. If units do not offer a 24 hour TIPS service, then an alternative specialist centre should be identified, along with appropriate arrangements for the safe transfer of patients. Experts confirmed that TIPS is not available in most general hospitals and this affects the length of time that bridge treatments are required for. In a national audit including 212 UK hospitals (Jairath et al. 2014), only 4 of 526 people with acute variceal haemorrage (<1%) were referred for TIPS. The BSG guideline

also listed the utility of early TIPS (<72h hours) and the role of removable oesophageal stents to be areas requiring further study. The company suggests that the Danis Stent could replace Balloon Tamponade as a bridge treatment prior to TIPS.

The Baveno VI consensus report (Journal of Hepatology, 2015) concluded that SEMS may be as effective and safer than balloon tamponade in refractory oesophageal variceal bleeding. A recent meta-analysis (Mohan et al. 2019) comparing SEMS to TIPS in oesophageal varices found that SEMS provided immediate bleeding control. However, mortality rate and rebleeding rate were higher with SEMS than in TIPS and the authors note that they were unable to validate their results as most of the included studies were retrospective.

The company suggests that Danis stent can also be used as a palliative care measure, to allow more time without sedation for patients who cannot receive definitive treatment. This is considered to be an "off-label" use of the technology and has not been evaluated in the literature.

Special considerations, including issues related to equality

Danis stent is intended for use in people aged 16 years and over with acute refractory variceal bleeding. Oesophageal variceal bleeding is often a complication cirrhosis in people with chronic liver disease (CLD); some people with CLD may be considered disabled under the Equality Act 2010 if their condition has a 'substantial' and 'long-term' negative effect on the ability to do normal daily activities. Both age and disability are protected characteristics under the Equality Act 2010.

The company claims that Danis stent may be of particular advantage to those whose who may not accept blood transfusions, such as Jehovah's Witnesses. Religion or belief is a protected characteristic under the Equality Act 2010.

4 Clinical evidence selection

4.1 *Evidence search strategy and study selection*

The EAC considered the company's search strategy to be appropriate for the topic. The searches were thorough and the EAC agreed with the search terms, choice of databases and inclusion and exclusion criteria.

The EAC re-ran the company's searches for new date limits to capture results from the first 5 months of 2020, only. The updated searches revealed 95 records; no duplicates were present. Following a sift of the abstracts of these records, no new relevant studies were found. A meta-analysis comparing

several Self-Expanding Metal Stents (including Danis stent) to TIPS, was identified. This was briefly detailed in section 3.

The company included 9 fulltext studies in their clinical submission. No further studies were considered by the EAC.

4.2 *Included and excluded studies*

Table 2 Studies selected by the EAC as the evidence base

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Escorsell 2016 Spain in 9 teaching hospitals.	RCT comparing Danis stent with S-B tube (balloon tamponade) ● All patients followed up for 6 months, or until death. Not funded by company.	28 people with a diagnosis of cirrhosis and refractory AVB or massive variceal bleeding based on Baveno II criteria between March 2009 and January 2013. Excluded people who had previously had balloon tamponade treatment (23) Danis stent (n=13): 13 men, mean age 69 (40-81). Child-Pugh class A/BC: 3/10 S-B tube (n=15): 12 men, mean age 54 (35-79). Child-Pugh class A/BC: 2/13 Aetiology of cirrhosis: DS: Alcohol: 8, Hepatitis C: 3	Compared with the balloon tamponade group, the composite endpoint of absence of digestive bleeding, absence of SAEs and survival at 15 days was higher in the Danis stent group: 66% vs. 20%; p=0.025. Bleeding control was higher in the Danis stent group at 15 days (85% compared with 47%; p=0.037) No significant difference was seen at 6 weeks (54% compared with 47%; p=0.25).	The randomisation sequence was generated by a computer in a 1:1 ratio, stratified for the degree of liver failure (Child-Pugh class A or B/C). Patients were comparable in severity of liver failure, active bleeding at endoscopy, and initial therapy. 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

		S-B tube: Alcohol: 7, Hepatitis C: 4 	Mortality was not statistically significantly different between the 2 groups at both 15-day or 6 weeks (p>0.05). More device-related SAEs were found in the balloon tamponade-treated patients versus the Danis stent group (6 vs. 1; p = 0.049). 	which was 60% of desired sample size. Multicentre randomised controlled trial which was independent and independently funded. The study was done in Spain and may not be generalisable to the NHS. No female patients were included the Danis stent group and there was an imbalance in the groups in terms of age and gender. More patients in the balloon tamponade group had earlier TIPS which could have affected survival results. Excluded people who had previously had balloon tamponade treatment (23)

Maiwall 2018 India, 1 centre	Retrospective case-control. Danis Stent 🟢 Repeat endotherapy and vasoactive drugs or balloon tamponade or both (“control”) 🟡 At least 6 week follow up Funding not reported	88 patients who had acute on-chronic liver failure with refractory variceal bleeds from 2014 to 2016. Danis Stent (n=35): 34 men, mean age 46.4 (SD 12.7). Child-Pugh score (CP) A/B/C 0/6/29, MELD score 39 (30-47) Control (n=53): 49 men, mean age 47.91 (9.7). CP A/B/C 0/2/51. MELD score 43 (34.4-65) Propensity Risk Score (PRS)-Matched Cohort (n = 44) Across both groups, alcohol was the most common aetiology: 69 (78.4%). Not reported by treatment arm Loss to follow up: NR 🟢	Initial bleeding control 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). Significant reduction in mortality 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 overall mortality significantly reduced in Danis stent group in pre matched (p=0.004, HR 2.56, 95% CI 1.35 to 4.83) and PRS-matched cohorts (p = 0.07, HR 6.94, 95% CI 0.85 to 56.6). 6-week overall mortality was significantly reduced in PRS-matched cohort	Patients with Danis Stent were significantly different from patients in the control group with respect to disease severity scores, i.e., the MELD (p = 0.05) and the CTP scores (p = 0.003). Propensity score analysis controlled for differences in baseline characteristics. Selection bias may have occurred with endoscopists potentially choosing the therapy based on experience and preference. Study included patients with acute-on-chronic liver failure only, excluding other patients (such as those with portal vein thrombosis) who could be a key target population

			(p=0.05, HR 8.1, 95% CI 1.02 to 64.4). ●	Follow up duration unclear
Wright 2010 UK, 1 tertiary referral liver centre.	Case series Danis stent ● No comparator. ● 42 day follow up. Funding not reported	10 people (9 men, age range 18-70 years) with cirrhosis and variceal haemorrhage, with contraindications to TIPS insertion or balloon tamponade, between March 2007 to July 2008. Causes or cirrhosis: alcohol (6) alcohol and hepatitis C (2) and cryptogenic and biliary cirrhosis (both 1) ●	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. 6/9 (67%) patients survived the acute bleeding episode. Overall survival rate at 42 days was 50%. Proximal oesophageal ulceration caused by stent insertion: 1 patient. ●	UK study Study was a single-centre case series with no comparator. 2 patients had gastric varices which cannot be treated with Danis stent. No statistical analysis. The study uses a short follow-up of 42 days and does not report long-term outcomes. The median duration of Danis stent implantation was 9 days (range 6 to 14 days) which reflects clinical practice according to clinical expert opinion.

				However, this exceeds the manufacturer's recommended implantation duration of 7 days. Source of funding unclear. Included patients in whom previous balloon tamponade therapy had failed.
Zehetner 2008 Austria, 1 centre	Case series, pilot study. Danis stent No comparator. Funding not reported	39 patients (33 men), mean age = 56 years (range, 32–91 years) underwent stent implantation. 34 received Danis Stent. 34 patients with liver cirrhosis and acute oesophageal variceal bleeding not controlled with standard therapy between January 2003 to August 2007. Cause of bleeding: liver cirrhosis due to alcoholism (26), immunologic or cryptogenic cirrhosis (4), virus-induced liver cirrhosis (4).	For all 34 patients, the implantation of the esophageal stent succeeded in stopping ongoing bleeding. No bleeding recurrence during stent implantation (median: 5 days, range 1-14days). Stent migration 21%, 7/34), slight distal oesophageal ulceration	Non-UK study Study was a single-centre case series with no comparator. No statistical analysis done. There was a short follow-up period of 60 days. Patients with previous balloon tamponade treatment were included.

		Child-Pugh grade B (13), Child-Pugh grade C (21). ●	(3%, 1/34) during extraction of the stent. Mortality at 30 days: 26.5% (9/34) and at 60 days: 29.5% (10/34). ●	
Zakaria 2013 Egypt, 1 centre	Case series, pilot study Danis stent ● No comparator ● No funding received	16 people (mean age 55.6 SD 5.62, 14 men) with acute ongoing variceal bleeding between January 2008 to December 2009 Hepatitis C viral related: 16 (100) Child-Pugh score A/B/C: 2/8/6 Stent duration (n = 11) range 2-4 days. ●	Initial control of variceal bleeding in 87.5% (14/16 patients) Mortality: 25% (4/16) died during the study one case was related to a failure to control the initial bleeding episode. The remaining 3 cases were due to the worsening of the general condition of the patient despite control of the bleeding. ●	Non-UK study Study was a single-centre case series with no comparator. Small sample size Unclear time points for the outcome data.

Pfisterer 2019 Austria, 4 tertiary care centres	Retrospective multicentre observational study Danis stent 🟢 No comparator 🔴 All patients followed up for 1 year, or until death. Funding not reported	34 patients aged 18 years or over (mean age 55.5 years, SD 11.5; 28 men) with cirrhosis and refractory oesophageal variceal bleeding between January 2009 to December 2016. Child-Pugh class A/B/C: 1/10/8 (information only available in 19 patients) Median MELD was 18 (IQR 10) Alcoholic liver disease: 16 (47.1), Viral hepatitis: 8 (23.5) Combined alcoholic liver disease/viral hepatitis: 4 (11.8) Other: 3 (8.8) Cryptogenic: 3 (8.8) 🟢	Control of acute refractory bleeding (within 5 days): 79.4% (27/34). Rebleeding within 6 weeks: 17.6% (6/34) (only 1 with DS in place). Bleeding related mortality within 6-weeks: 47.1% (16/34). Median survival after DS placement: 62 days. 5-day mortality: 20.6% (7/34) Overall mortality (median follow up of 2.1 months): 64.7% (22/34) Adverse events: stent dislocations (n = 13; 38.2%), ulcers/necrosis of the oesophageal mucosa (n = 4; 11.8%) patients.	Non-UK study Multicentre study with a long follow-up (1 year). Observational case series, retrospective design with no comparator is relatively low-quality evidence. 3 patients had additional gastric varices which cannot be controlled with Danis stent. No patients had early TIPS procedures that could have affected mortality rates.

Ghidirim 2012 Moldova, 1 centre	Retrospective Case-series Danis stent No comparator 30 day follow up Funding not reported	14 adults (mean age 51.1 years SD 2.63, 8 men) with oesophageal bleeding refractory to standard therapy (EBL) Viral (hepatitis B or hepatitis C) liver cirrhosis induced portal hypertension: 14 (100) Mean Child-Pugh 9.54 SD 0.44 (range 7-12) Mean MELD 17.68 SD1.7 (range 9.2-27.8) Mean stent in situ time was 94.31 (SD 14.09, range 18-170) hours	Initial control of bleeding was 100%. Device related SAEs: 0 Partial distal stent migration in 5 patients (41.6%). The overall 30-days mortality was 35.7% (5/14)	Non-UK study Relatively small sample size All patients had hepatitis. Short follow up
Goenka 2017	Retrospective Case series	12 patients (11 men, mean age 53 ± 13.7) with either persistent variceal	All patients had immediate cessation of bleeding.	Non-UK, non-comparative study

India, 1 hospital centre	Danis stent ● No comparator ● 30 day follow up Funding not reported	bleeding or VBL-induced ulcer bleeding between April 2012 and May 2016. Mean MELD score 20.17±5.97. 10 patients (11 procedures) had DS placed in an endoscopy suite, while 2 were placed in the intensive therapeutic unit at bed site Nine procedures had both endoscopic and fluoroscopic guidance while 4 (including 2 bedside cases) had placement done only with endoscopic assistance. ●	None of the patients developed post-deployment complications. 58.3% (7/12) patients treated by DS survived at 30 days 1 patient experienced re-bleeding 10 days after stent removal and there were no cases of re-bleeding at 30 days following stent removal. ●	Relatively small sample size Short follow up. 8 patients with VBL) ulcer bleed and only 4 with persistent variceal bleed (contrast with other studies) Danis stents were also implanted for varying durations from 7 to 30 days (mean 17.5, SD:8.58 days), however the manufacturer's instructions for the device is implantation for 7 days. The procedures in the study were carried out using endoscopic/ fluoroscopic guidance although Danis can be inserted without guidance.

Muller 2015 Germany, 1 centre	Retrospective case series Danis stent No comparator Not funded by company	11 people (8 men, mean age 64.2 SD 12.4) with oesophageal variceal bleeding, refractory to standard therapy between 2011 and 2014 10/11 patients were Child-Pugh score B or C (advanced liver cirrhosis). A/B/C: 1/6/3, 1 patient was non-cirrhotic MELD score range: 8-36 Alcoholic liver disease n =9; hepatitis B n=1, cryptogenic cirrhosis n=1, portal vein thrombosis associated with a Jak2 mutation n=1). Endoscopy unit	Immediate bleeding control = 100%. Rebleeding rate within 48 hours = 9% (1/11 patients). Re-bleeding during stent removal = 9% (1/11 patients). No rebleeding while the stent was in situ (mean 12.1 days, range 5-24 days) or at stent extraction. Stent dislocation within 24 hours: 4/11 patients (2 proximal,2 distal)	Non-UK study The sample size is small, 11 patients, however, this is indicative of the small clinical population. Danis stents were reported to be in situ for 5 to 24 days. We note that the indication for the Danis stent is implantation of up to 7 days.

The EAC did not exclude any studies included by the company.

5 Clinical evidence review

5.1 *Overview of methodologies of all included studies*

The EAC included 9 studies; all studies were reported in full text. One study was an RCT (Escorsell et al. 2016), 1 study was a retrospective case-control study, 3 were prospective case-series (2 of which were pilot studies) and 4 were retrospective case-series. Two studies (Escorsell et al. 2016, Pfisterer et al. 2019) were multicentre, reporting data from 9 centres in Spain and 4 centres in Austria, respectively. The remaining studies were single-centre (Wright et al. 2010, Zakaria et al. 2013, Zehetner et al. 2008, Goenka et al. 2017, Maiwall et al. 2018, Ghidirim et al. 2012, Muller at al. 2015). One retrospective case-series was undertaken in the UK (Wright et al. 2010). This study included 10 people referred to a tertiary liver centre.

Two studies were comparative (Escorsell et al. 2016 and Maiwall et al. 2018); Escorsell et al. 2016 compared Danis stent to balloon tamponade. Maiwall et al. 2018 compared Danis stent to either repeat endotherapy and vasoactive drugs or balloon tamponade (or a combination). The exact number of patients with balloon tamponade in Maiwall et al. 2018 was not reported. The randomisation sequence used in Escorsell et al. 2016 was stratified for Child-Pugh score only and did not take age and gender into account. As a result, the Danis stent group had a greater proportion of men (100% vs 80%) and a higher mean age (69 vs 54 years) than the control. The study was also underpowered; 46 patients were required by the author's calculation while only 28 patients were included in their intention-to-treat analysis. No blinding was reported.

Two-hundred and forty-seven patients were included in total. Included populations were generally small, although this reflects the low prevalence of acute bleeding in oesophageal varices. Inclusion criteria was broadly the same for all studies; patients with refractory acute variceal bleeds due to chronic liver disease. Patients with alcoholic liver disease and hepatitis were included; experts agree that these populations are generally comparable in terms of outcomes and comorbidities. The standards used to define these patients varied. Only Ghidirim et al. 2012 had a relative balance of men and women (57% men), while the other studies varied from 73% men (Muller et al. 2015) to 94% men (Maiwall et al. 2018). Mean age varied from 47.2 years (Maiwell et al. 2018) to 64.2 years (Muller et al. 2015).

The duration of follow up varied from 30 days (Ghidirim et al. 2012, Goenka et al. 2017) to 1 year (Pfisterer et al. 2019). Experts believed that 6 week follow up was required to properly assess re-bleeding rates and that six months to 1 year follow up is likely adequate to assess long term outcomes in this population, in which long-term survival is low. Outcomes were reported at several lengths of follow up.

5.2 *Critical appraisal of studies and review of company's critical appraisal*

The company used the checklist proposed by MTEP for the critical appraisal of the RCT (the CRD criteria for assessment of risk of bias in RCTs). For the case-control and case-series studies they used the Joanna Briggs Institute (JBI) checklists.

The EAC carried out a separate quality appraisal of the 9 publications included in the assessment report. The EAC used the CASP checklists for the 2 comparatives studies and the Canada Institute of Health Economics (IHE) quality appraisal tool for case-series studies. A copy of the EAC's methodological quality appraisal checklist is included in appendix B. The EAC requested advice from the clinical experts on the significance of factors such as age and gender.

The multicentre RCT (Escorsell et al. 2016) is considered the highest quality study. Randomisation was carried out in a 1:1 ratio by computer generated sequence, stratified for the degree of liver failure (Child-Pugh class A or B/C). This was deemed partially adequate. The 2 treatment arms differed in terms of patient age and gender (no women were included in the Danis stent arm), but not for other factors in consideration. Most experts did not consider male gender to be a factor in clinical outcomes, however and felt that Child-Pugh class was more important. A retrospective study by Maimone et al. 2019 did not find that age and gender were predictive of mortality in salvage TIPS. One expert felt that both factors were significant, however, and cited Chen et al. 2012, which showed age and gender, along with comorbidities doubled mortality in patients with active oesophageal variceal bleeding.

The sample size included in Escorsell et al. (2016) was fairly small and the study was underpowered for the primary outcome - 28 patients were randomised, which was 60% of the intended sample. However, there were no patients lost to follow up and all had results analysed at conclusion. Some selective reporting may have occurred as survival, bleeding and hospital stay were all due to be assessed at 6 months but were not reported. More patients in the balloon tamponade group had earlier TIPS, which could have affected survival results. The EAC agrees with the company appraisal that this study has moderate risk of bias.

The case-control study (Maiwall et. al 2018) only included patients with acute-on-chronic liver failure only, excluding other patients that could be part of the target population. The same criteria were used for the identification of cases and controls and the exposure to the treatment was assessed for both case and control patients using hospital database records. The intervention and control groups, however, were significantly different with respect to disease severity scores. Further, the percentage of patients who had an initial control of bleed was significantly higher for the Danis stent group as compared to controls as also the percentage of patients dying of gastrointestinal bleed. Given the observed differences in the baseline characteristics

in the patients who underwent Danis stent versus those who did not, the authors also did an analysis based on PRS matching. The EAC considered the matching methodology to be reasonable. The direction of outcome was consistent with other studies and within the pre-matched and PRS matched cohorts. Control of initial bleeding, bleeding related death were both significantly lower in Danis stent versus control in both pre-match and PRS matched cohorts. Multivariate competing risk Cox regression analysis, intervention with Danis stent was significant factor associated with a reduced bleed-related mortality. The EAC agrees with the company appraisal that this study has moderate risk of bias.

The remaining 7 case series studies were deemed relatively low quality evidence. The most limiting factor was the lack of comparator. Sample sizes tended to be small, ranging from n=10 (Wright et al. 2010) to Zehetner et al. (2008) which had a slightly larger population (n=39). Five studies had sample sizes ranging from n=10 to n=16. A meta-analysis was carried out on the outcome data for immediate bleeding control, successful stent insertion, and survival after stent insertion between the 7 case series studies (see section 7).

5.3 *Results from the evidence base*

The results of the 9 included studies are summarised in table 3 below:

Table 3 Outcomes and results from included studies

Study	Therapy success (composite score)	Successful Stent Insertion	Bleeding Control/ Rebleeding	Mortality	SAEs	Blood Units Used	Stent Migration/ dislocation	Hospitalisation /ICU LOS
Escorsell 2016	Composite endpoint (absence of digestive bleeding and absence of SAEs and survival at 15 days): Danis stent: 66% (8/13) S-B tube: 20% (3/15) p=0.025	NR	Day 15 control: Danis stent 85% (11/13) S-B tube 47% (7/15) p=0.037 6 weeks control: **DS 54% (7/13)** S-B tube 47% (7/15) p=0.25	Mortality at Day 15: Danis stent 31% (4/13) S-B tube 53% (7/15) p=0.39 6 weeks: **DS 46% (6/13)** S-B tube 60% (9/15) p=0.46	Of patients with at least 1 SAE: Danis stent 15% (2/13) S-B tube 47% (7/15) p=0.077 Of patients with at least 1 device related SAE: Danis stent 8% (1/13) S-B tube 40% (6/15) p=0.049	PRBC Transfusion (Units): Danis stent: 3 ± 3.3 S-B Tube: 6 ± 4.8 p = 0.08	NR	Median days hospital stay Danis stent 14 S-B tube 14 p=0.55 Median days in ICU Danis stent 8 S-B tube 8 p=0.93

Maiwall 2018	NR	NR	Day 5 control: Danis stent 89% Control 37% p<0.001 In PRS matched cohorts Danis stent 73% Control 32% p=0.007	Mortality secondary to bleeding: Danis stent 14%, Control 64%, p=0.001 In PRS matched cohorts Danis stent 6% Control 56% p=0.001 15-day overall mortality significantly reduced in Danis stent group in pre matched (p=0.004, HR 2.56, 95% CI 1.35 to 4.83)	NR	NR	NR	NR

Study	Therapy success (composite score)	Successful Stent Insertion	Bleeding Control/ Rebleeding	Mortality	SAEs	Blood Units Used	Stent Migration/ dislocation	Hospitalisation /ICU LOS
				and PRS-matched cohorts (p = 0.07, HR 6.94, 95% CI 0.85 to 56.6). 6-week mortality was only significantly reduced in PRS-matched cohort (p=0.05, HR 8.1, 95% CI 1.02 to 64.4).				

Study	Therapy success (composite score)	Successful Stent Insertion	Bleeding Control/ Rebleeding	Mortality	SAEs	Blood Units Used	Stent Migration/ dislocation	Hospitalisation /ICU LOS
Wright 2010	NR	8/10 patients at first attempt 1 patient had successful insertion on second attempt, 1 patient had unsuccessful insertion due to gastric balloon not inflating	Immediate control: 78% Rebleeding 60 days after stent removal: 1 patient	Mortality: 33% at bleed, 50% at 42 days (reported as 67% survived bleed, 50% survived at 42 days) Failure to control acute bleeding (n=3): all 3 patients died due to multiorgan failure or severe blood loss	NR	NR	**0% of patients had distal stent migration**	NR

Study	Therapy success (composite score)	Successful Stent Insertion	Bleeding Control/ Rebleeding	Mortality	SAEs	Blood Units Used	Stent Migration/ dislocation	Hospitalisation /ICU LOS
Zakaria 2013	NR	93.75%	Initial control: 87.5%	Mortality 25% during study period (not defined)	None.	Mean 2.5 units per hospital stay	37.5% (6/16) Total/partial distal/**partial proximal**: 3/2/**1**	NR
Zehetner 2008	NR	100%	Immediate control: 100%	Mortality 30 days: 26.5% 60 days: 29.5%	NR	NR	**21% had stent migration to the stomach**	**NR**

Study	Therapy success (composite score)	Successful Stent Insertion	Bleeding Control/ Rebleeding	Mortality	SAEs	Blood Units Used	Stent Migration/ dislocation	Hospitalisation /ICU LOS
Pfisterer 2019	NR	64.7%	Rebleeding in 35% after stent removal Rebleeding in 71% at 6 weeks	5 day mortality: 20.6% Bleeding related mortality at 6 weeks: 35.3% Overall mortality: (median follow up duration 2.1 months): 64.7%	NR	NR	0% migration (38.2% stent dislocation)	NR
Ghidirim 2012	NR	NR	Initial control: 100%	Mortality at 30 days: 35.7%	0	NR	**41.6% partial distal stent migration**	NR

Study	Therapy success (composite score)	Successful Stent Insertion	Bleeding Control/ Rebleeding	Mortality	SAEs	Blood Units Used	Stent Migration/ dislocation	Hospitalisation /ICU LOS
Goenka 2017	NR	100%	Immediate control: 100%	Mortality at 30 days: 41.7% (reported as survival at 30 days: 58.3%)	NR	NR	0%	NR
Muller 2015	NR	NR	Immediate: 100% Rebleeding at 48hrs: 9%	27.3% mortality at 42 days	NR	Mean 3.1 units per patient	**Dislocation at 24 hours: 36% (4/11; 2 proximal, 2 distal)**	NR
	Acronyms: NR, Not Reported; PBRC, Packed Red Blood Cell; DS, Danis Stent; S-B Tube; Sengstaken-Blakemore Tube **Results in bold used in economic model.**							

6 Adverse events

The EAC searched the MHRA and FDA (MAUDE) databases on the 19th of May 2020, using the terms ‘Danis’, ‘Danis Stent’, ‘SX-Ella’, ‘SX Ella’ and ‘Ella Stent’. No results were found on the FDA database. The company confirmed that the device does not have FDA approval and is not used in the US.

One Field Safety Notice was found on 14th February 2017 for Ella-CS: SX ELLA Stent Danis Procedure Pack (Basic); this was also listed in the company’s submission. However, the MHRA reference: 2017/002/015/291/004 is not currently available. The company stated that a product was returned, after which it was discovered that there had been unintended movement of the safety valve fixation. This led to an update of the IFU. No clinical complications were associated with this Field Safety Notice.

In the RCT (Escorsell et al. 2016), the rates of adverse events did not differ significantly between treatments. Rates of stent dislocation were as high as 63.6% in Muller et al. 2010. Five experts suggested that the percentage of stent dislocations reported in the literature was high, although 2 experts thought that this number would be lower with experienced operators. One expert also noted that he believed that the dislocation rates were still lower than the complication rate of balloon tamponade. Appendix C summarises the adverse events reported in the literature.

7 Evidence synthesis and meta-analysis

The company did not perform quantitative evidence sythnesis as it was considered innappropriate. The EAC believed that while this was true when considering the small number of comparative studies, evidence synthesis was suitable for aggregating the results of the non-comparative studies. Figures 1 to 4 show the results of a random effects model for 4 outcomes which were reported in at least 3 of the included case-series studies. Heterogeneity was low in immediate bleeding control, successful stent insertion and survival at 30 days after stent insertion, although confidence intervals were wide.

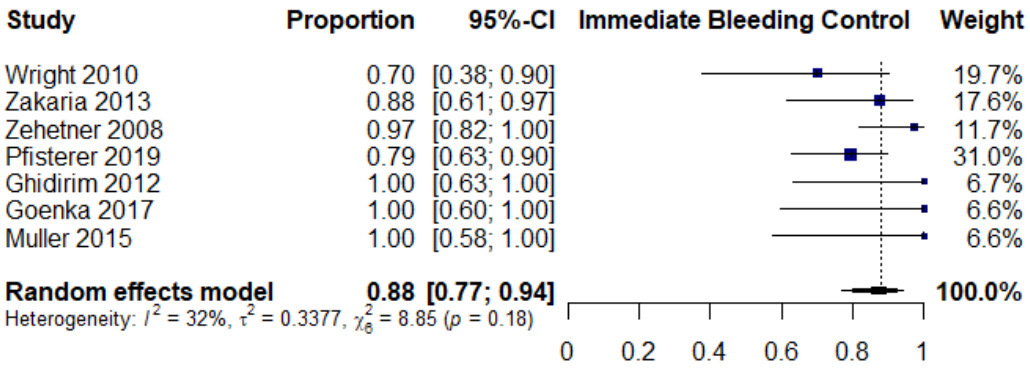


Figure 1 Immediate Bleeding Control

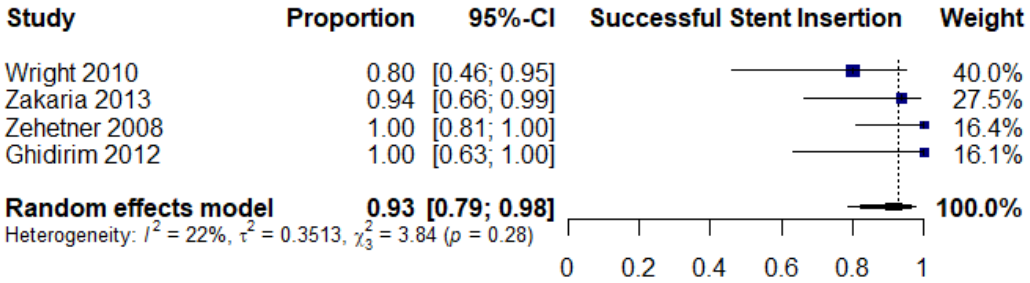


Figure 2 Successful Stent Insertion

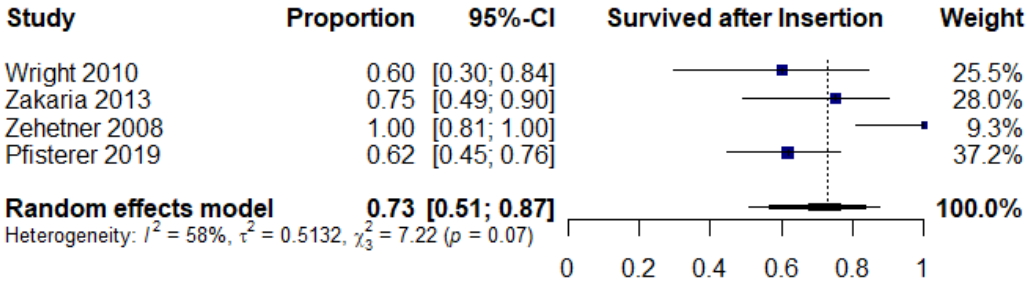


Figure 3 Survived after stent insertion

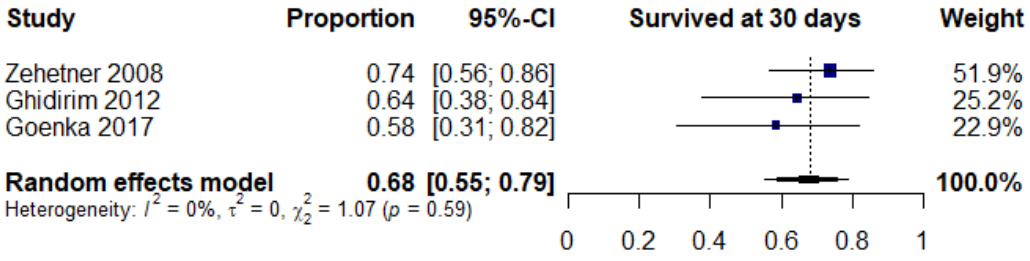


Figure 4 Survival at 30 days after stent insertion

The results of the evidence synthesis show that immediate bleeding control was achieved in 88% of patients, from 7 retrospective studies. The Danis stent was

successfully inserted in 93% of patients and 68% survived after 30 days. These results should be interpreted with caution due to the low quality of the included studies.

8 Interpretation of the clinical evidence

The evidence base is comprised of data from a variety of countries and some may not be generalisable to the NHS, particularly studies conducted outside of Europe (Goenka et al. 2017, Maiwall et al. 2018, Zakaria et al. 2013). The EAC considers Escorsell et al. 2016, which was conducted in Spain, to be the strongest evidence. Some expert advice suggests that while the patient demographics and comorbidities are transferable, the clinical pathway may differ between Spain and the UK, although there was no consensus between experts. Due to the expertise in management of portal hypertension at Spanish centres, it may be more likely that preventative action will be taken. This may mean that TIPS will be performed in patients of Child-Pugh classes B and C, which is uncommon in UK centres. Thirteen out of 14 TIPS interventions were performed within 48 hours, which experts considered much quicker than would be possible in the UK. As mentioned in section 3, rates of TIPS in the UK may be less than 1%, while 50% of patients (from both treatment arms) in Escorsell et al. 2016 received TIPS. It should also be noted that grading systems of oesophageal varices, such as the Pacquet system used in Escorsell et al. 2016, are not common in the UK, where the BSG guidelines (see section 3) are often used. Experts noted that the grading of the underlying liver disease is a better predictor of future bleeding risk than the severity of oesophageal varices. The patient groups included in this study could be considered to be high-risk, based on Child-Pugh class of B and C.

Results from the RCT suggest that the Danis stent controls bleeding better at 15 days than S-B Tube (Danis stent 85% (11/13), S-B tube 47% (7/15), p=0.037). This result was not statistically significant at 6 weeks, however (p=0.46). This is not unexpected given the generally poor survival outcomes for patients with acute variceal bleeding, and the high-risk population in this study in particular. Survival rate was also greater at day 15 in the Danis stent group than the control, although not statistically significant (p=0.39). The study was also underpowered to detect the primary outcome, which was a composite of survival at day 15 with control of bleeding and without serious adverse events. The Danis stent arm of the study included more men (100%) vs the control arm (80%) and the mean age was significantly higher (69 years vs 54 years). Some experts believed, however, that these factors are not as prognostically significant as Child-Pugh score, while 1 expert felt that these factors were important. As confirmed by the authors of Escorsell et al. 2016, the randomisation algorithm only took Child-Pugh score into consideration and did not stratify for age and gender.

The other comparative study, Maiwall et al. 2018, was a retrospective case-control study. Mortality related to bleeding was significantly lower in the Danis stent group vs the control group (14% vs 64%, p = 0.001). This result was confirmed in the PRS-matched cohort (6 vs. 56%; p = 0.001). Bleeding control at 5 days was also significantly better in the Danis group than the control (89% vs 37%, p=0.001), which was again seen in the PRS-matched cohort (73 vs. 32% p=0.007). Notably, these results were not significant at 6 weeks, similarly to the RCT, further suggesting that this result is expected. The authors of the study note that mortality was usually due other causes such as multiorgan failure or active uncontrolled sepsis, which are common complications where liver transplantation is not possible.

Seven non-comparative studies were included; all of these were case-series and included small populations. Comparing the outcomes of these studies can be difficult due to the varied lengths of follow up and poor reporting of study procedures. Where outcomes were more widely reported (see section 7), heterogeneity was generally low (insignificant in immediate bleeding control, successful stent insertion and survival at 30 days after stent insertion). Immediate bleeding control varied from 70% (Wright et al. 2010) to 100% (Ghidirim et al. 2012, Goenka et al. 2017 and Muller et al. 2015). This suggests that Danis stent is effective at achieving haemostasis after implantation. Survival after 30 days varied from 58% (Goenka et al. 2017) to 74% (Zehetner et al. 2008).The EAC's meta-analysis calculated a survival rate of 68% after 30 days, from 3 studies.

The evidence base has several weaknesses. The majority of studies are small, retrospective and non-comparative, providing a low quality of evidence. Conclusions should not be drawn from these results. The comparative studies represent a low to moderate quality of evidence and so conclusions may be drawn from these results with caution. Danis stent is likely to improve bleeding control and survival at 15 days, however, an adequately powered UK-based RCT is required to verify this result in an NHS setting.

8.1 *Integration into the NHS*

One study (Wright et al. 2010) was conducted in the UK. This retrospective case-series only included 10 patients referred to a tertiary liver centre between March 2007 and July 2008. Six patients were referred to the centre from secondary care; the remaining 4 were admitted directly. According to the company, 37 NHS trusts have purchased a Danis stent in the past 12 months.

The EAC does not foresee any major changes to the pathway. The Danis stent would replace Balloon Tamponade as a bridge treatment prior to

definitive treatment such as TIPS. This could remove the need for endoscopic guidance at insertion and increase the available time for planning and scheduling of definitive treatment.

In-person training is provided free of charge by UK Medical for consultants and nursing staff. Training sessions can last between 1 hour and 1 day depending on the centre's requirements and availability. The frequency of training sessions is also dependent on the availability of the centre. A YouTube video detailing the implantation procedure is also available as a reference tool. All Danis resources are available through the UK Medical 'Showpad' app which does not require network connectivity for functionality.

8.2 *Ongoing studies*

The EAC believes the company's understanding that there are no relevant ongoing studies is correct. No ongoing studies or unpublished studies were identified by the EAC.

9 Economic evidence

9.1 *Published economic evidence*

Search strategy and selection

The company conducted an extensive systematic literature review to retrieve economic evidence on specialised databases. The search was carried out in the Health Technology Assessment Database (HTA Database); NHS Economic Evaluation Database (NHS EED); EconLit; and Cost Effectiveness Analysis Registry (CEA Registry). Figure 5 shows the PRISMA flow diagram where the results of the global search are displayed. Following deduplication, 3,107 records were screened from the global search. From these, 11 records correspond to economic evidence (2, 5, and 4 from HTA Database, NHS EED and EconLit respectively), none of which were considered relevant by the company to inform the decision problem.

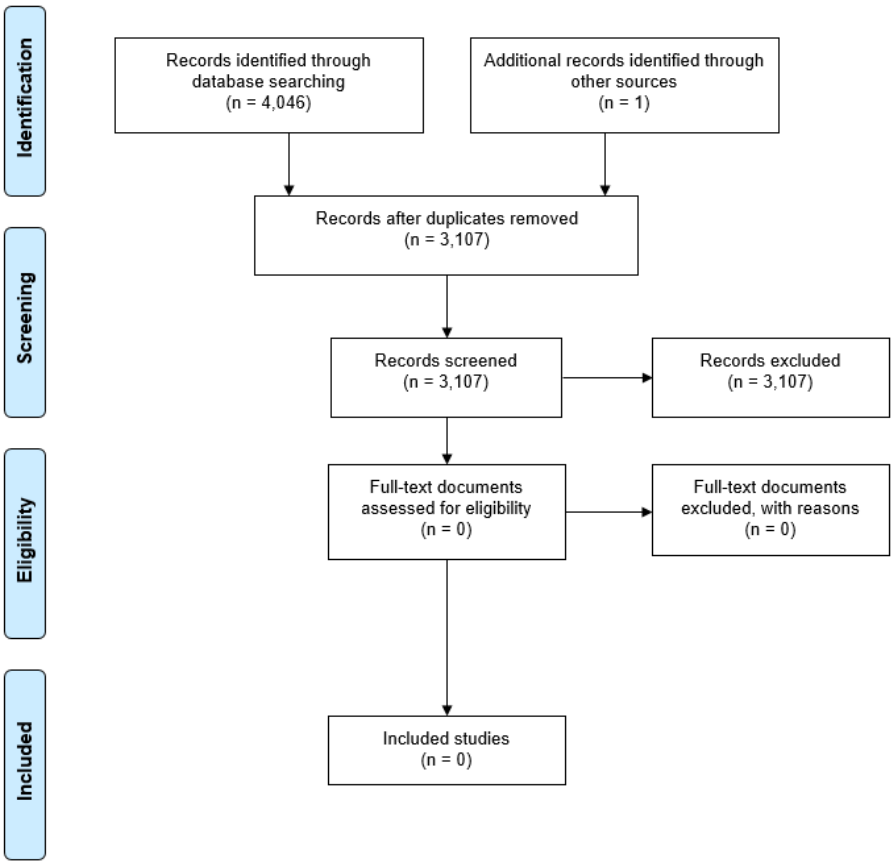


Figure 5 Company PRISMA flow diagram for global evidence.

The EAC considers that the search strategy (Appendix D) developed by the company was appropriate. For consistency with the clinical evidence review, the EAC conducted its own research considering records published after January 2020 (see Appendix D).

Published economic evidence review

The EAC did not identify any relevant economic evidence, and therefore agrees with the company submission that no applicable studies were found.

Results from the economic evidence

No applicable studies were found.

9.2 *Company de novo cost analysis*

Economic model structure

The company submitted a cost comparison over a 6-week time horizon using a 'cost calculator' approach and undertaking an NHS and Personal and Social Services (PSS) perspective. The model is largely based on data from the only RCT identified in the clinical submission (Escorsell et al. 2016). The model

estimates the cost associated with the use of Danis stent versus balloon tamponade as bridging treatment for patients aged 16 or over with acute refractory oesophageal variceal bleeding in whom first line therapy such as terlipressin, prophylactic antibiotics, variceal band ligation or sclerotherapy is unsuitable or has failed. The model captures the likelihood and costs of adverse events for both technologies. The adverse events considered were re-bleeding following initial treatment; cardiorespiratory arrest; aspiration pneumonia; esophageal bacterial peritonitis; hepatorenal syndrome; and severe hepatic encephalopathy (HE). Additionally, the model captures the rate of additional resource use: removal of both technologies, stent migration for Danis stent only, and training for Danis stent only. The proportion of patients receiving definitive treatment options - endoscopic band ligation (EBL) plus non-selective beta-blockers or TIPS - within 6 weeks were also considered. The model considers mortality rates and differences in survival are presented alongside cost comparison results. The model was validated by a health economist separate to the original development team. The company's diagram is shown in figure 6. The EAC considers the model structure to be best described as in figure 7.

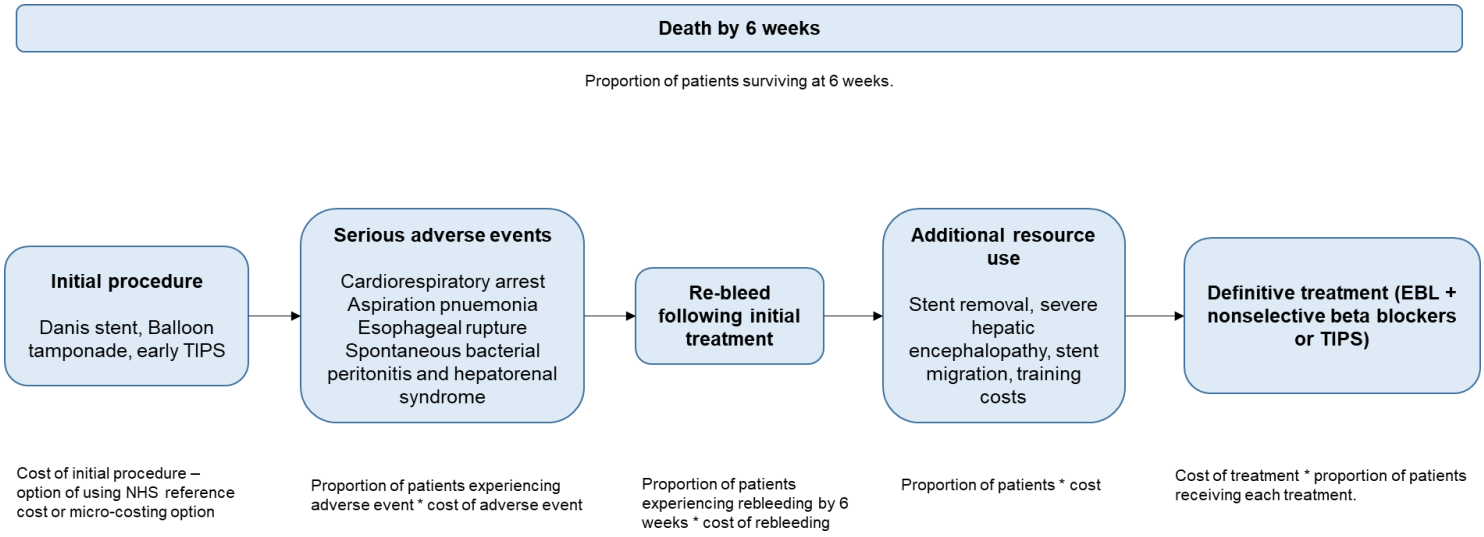


Figure 6 Company diagram showing structure of economic model

Cost calculator: $\sum(p_i * C_i) - \sum(p_x * c_x)$

where p_x is the proportion of patients experiencing a given event in the (balloon tamponade) group, and Cx is the cost of that event, and p_i is the proportion of patients experiencing an event in the intervention group (Danis Stent) and C_i is the cost of that event.

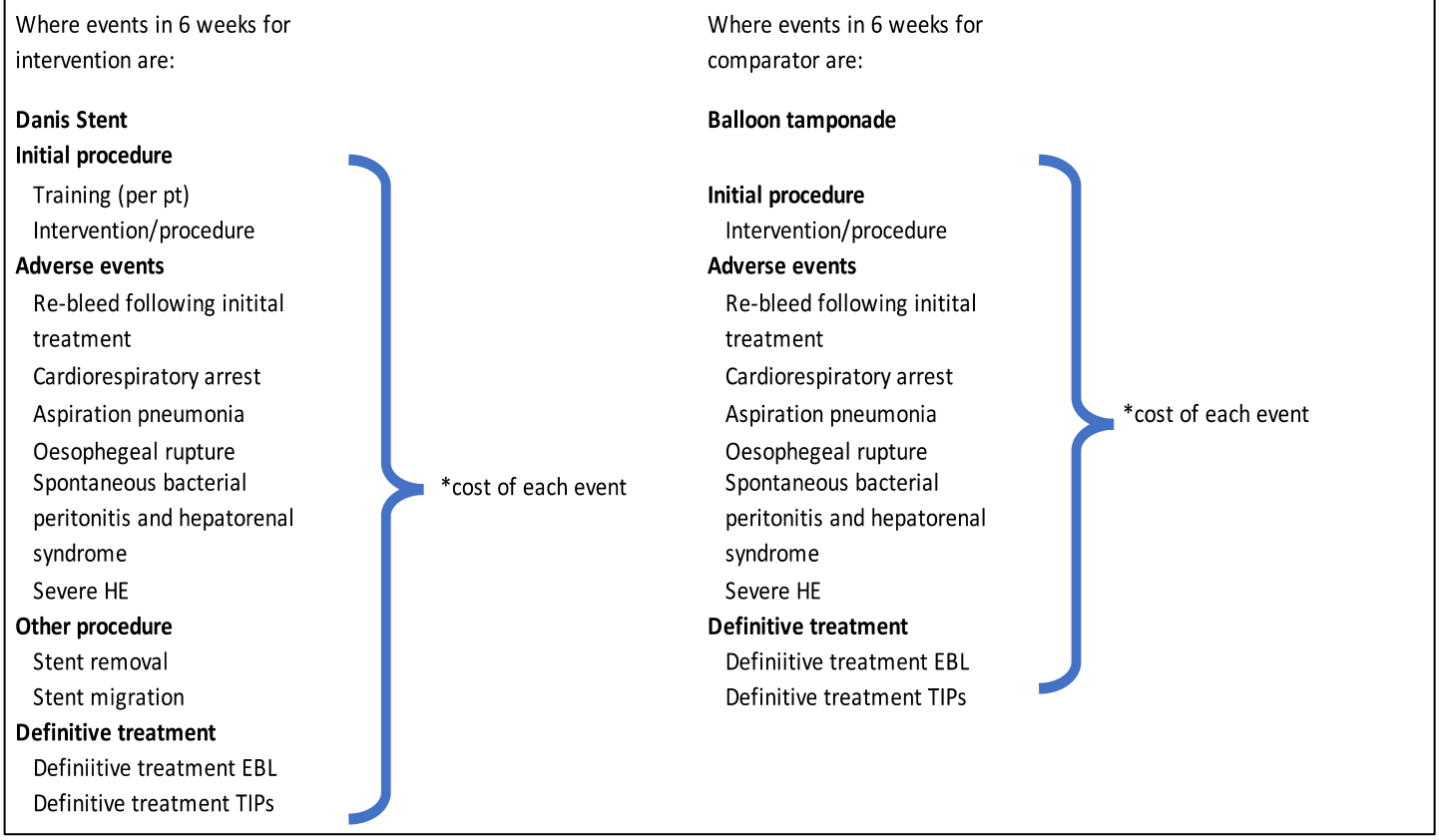


Figure 7 EAC figure showing structure of cost calculator model

The company model made the following assumptions outlined in table 4. The EAC assessment of these assumptions is included below.

Table 4 Model Assumptions

Assumption in model	Company justification	Source	EAC comments
Longer term outcomes beyond 6 weeks are not captured in the model despite patients	Clinical data did not extend beyond 6 weeks and there is a paucity of data in this population due to the small patient population with acute refractory oesophageal variceal bleeding who fail or are contraindicated to first line	Section 4 of clinical evidence submission	Acceptable given the availability of evidence and that longer-term survival is likely related to underlying disease and not

receiving differing definitive treatments between treatment arms in the RCT	therapy. This could impact on the results in either direction dependent on the outcomes of definitive treatment and the survival of patients following this 6-week period. More patients in the Danis stent arm underwent band ligation as their definitive treatment and it is unknown if this treatment was successful or whether further treatment was then required in the future such as repeat band ligation or TIPS. Similarly, it is unknown how survival was impacted by the differing treatments. However, clinical experts agreed that definitive treatment would be dependent on the patient and not necessarily impacted by whether they had received balloon tamponade or the Danis stent. All agreed both were viewed as a bridge to definitive treatment and therefore longer-term outcomes should not be impacted by choice of bridging treatment. Further, it was suggested that the life expectancy of patients in this condition was not expected to be long.		bridging treatment (this was confirmed by clinical experts).
A cost of use of the Ella extractor to remove the Danis stent was only applied to patients receiving endoscopic	Clinical expert opinion stated that if a TIPS procedure was undertaken the Ella extractor would not be required as part of the removal procedure. Additionally, use of the Ella extractor appears to vary in practice with one clinician noting that they did not typically use it.	Clinical expert opinion	This is an acceptable assumption that is explored in the company's sensitivity analysis. However, there is further uncertainty as to

band ligation as a definitive treatment.			whether Ella extractor would be needed to resolve stent migration as reported in Wright et al. 2010. This is explored in the EAC's sensitivity analysis.
It is assumed that there is no impact on efficacy of the stent from a learning curve (with exception of stent migration which is already captured within the model)	No data were reported that suggested a learning curve would impact on clinical efficacy other than occurrence of stent migration (Zehetner et al. 2008). One clinical expert suggested that inserting a stent was a common procedure and the Danis stent was easy to insert and required very little training. However, another expert noted that because the stent was a new device learning was needed to be able to insert it properly and there was a reluctance to undertake the procedure. Clinical experts reported differing rates of stent migration and it was judged this could be related to correct insertion and therefore experience with inserting the device. One case series also commented on low positioning of the stent leading to stent migration which appeared to be observed in the learning phase (Zehetner et al. 2008). Stent migration is included in the model as a risk for all procedures, not just in the learning phase. This may or may not be a conservative	Clinical expert opinion (Zehetner et al. 2008)	Clinical expert opinion indicates there would be a learning curve, however, there is a lack of evidence to incorporate the effect of this in the model. The company's assumption and accounting of stent migration are acceptable.

	assumption depending on how much more likely this would be to occur during the learning phase and whether the risk of stent migration reported in the studies was based on experienced users of the stent. Costs for training in how to insert the stent correctly are also included in the model.		
A difference in use of opiates for analgesia between treatment arms was reported in the Escorsell (2016) study. This was not included explicitly in the model.	The use of opiates for analgesia was assumed to be captured within the cost of a bed day in a general ward or in ICU or within the procedure cost. A reduction in the use of opiates with Danis stent was reported so this is a conservative assumption, however the impact on the results of the model would be expected to be very minor due to the low cost of opiates.	Assumption	Acceptable assumption.
A difference in the use of packed red blood cells and vasoactive drugs between treatment arms was reported in the Escorsell (2016) study. This was not included explicitly in the model.	Captured within sourced costs. The use of packed red blood cells was assumed to be captured within the cost of a re-bleeding event. The cost of vasoactive drugs was assumed to be captured within the procedure costs. Packed red blood cells were reported to be used in fewer patients in the Danis stent arm so this is a conservative assumption. An increase in the use of vasoactive drugs was reported with Danis stent due to fewer patients receiving TIPS as their definitive treatment in this treatment arm (which means vasoactive drugs are stopped). Therefore, if the costs of these	Assumption	Acceptable assumption

	are not captured within the procedure cost this would increase the cost of the Danis stent.		
Costs to train staff in how to insert the Danis stent are assumed to be incurred each year.	Clinical experts indicated that due to the small patient population indicated for the Danis stent or balloon tamponade, very few procedures are carried out each year. Therefore, it was judged that ongoing refresher training may be required. This is a conservative assumption. If this is not required it will reduce the cost associated with the Danis stent.	Clinical expert opinion Muller et al. (2015) notes that regular training is required	Acceptable assumption
In the base case, it is assumed the only difference in terms of resources between the procedures to insert the Danis stent and balloon tamponade are the costs of the devices. Potential differences in the cost of surgery to place the device (beyond the cost of the device) is considered in	NHS reference costs (NHS Improvement 2019) were used to cost the procedure and therefore the costs of the procedures were assumed to be the same. Clinical experts agreed the procedures would be largely similar to insert both types of device. However, one expert suggested that the Danis stent can be inserted in an endoscopy suite under conscious sedation, rather than in theatre under general anaesthetic, in around 1/3 of patients. Therefore, the cost of the procedure to insert the Danis stent could be overstated. Further, the same expert suggested that in these patients you would expect to see a reduction in ICU stay following the procedure for insertion of the Danis stent, further reducing the cost of the procedure. Another expert	Clinical expert opinion	Acceptable assumption explored in company scenario analysis.

sensitivity analysis.	agreed that the ICU stay would likely be shorter with Danis stent patients, and that use of high dependency units (HDU) would also be less for Danis stent patients due to less intensive monitoring due to the reduced risk of rebleeding. Therefore, this assumption in the model is conservative, and if Danis stent results in a reduction in ICU and HDU stay and potentially use of general anaesthetic and theatre then the cost of the Danis stent in the analysis is overstated.		
Patient transportation costs were not included in the model. Expert opinion suggests transportation costs may be incurred as surgery is limited to a few specialist centres in UK.	Clinical experts suggested that only a few centres in the UK are able to carry out a TIPS procedure and therefore patients may require transfer to a specialist centre. Costs for transportation were not included in the model because this would be required regardless of whether patients received Danis stent or balloon tamponade.	Simplifying assumption	Acceptable assumption
The model structure assumes that the choice of bridging treatment impacts the choice of definitive therapy. with The costs of these definitive	[N/A] The company reported that there is uncertainty (clinical experts and Escorsell et al. 2016) around whether bridging treatment effects the choice of definitive treatment. The company also noted there is uncertainty in the use of Ella extractor as this is related to the choice of definitive treatment.	Assumption	The EAC feels this is a very strong assumption based on weak evidence and direction of company results are reliant on this assumption. Although there is no consensus amongst expert

therapies are included in the cost comparison. Where TIPS is chosen as the definitive treatment, the Ella extractor (and associated costs) is not required.			advisors, some expert opinion indicates that TIPS is less common in the UK than is reported in the Spanish Escorsell et al. 2016 trial population, and therefore, there is uncertainty in the generalisability of results. Assumptions are explored in the company's sensitivity analysis.
Cost and likelihood of minor adverse events are not included in the model.	Minor adverse events are assumed to be captured in the procedure/initial hospital stay costs. Clinical experts noted ulceration is not commonly a problem with the Danis stent and ulceration tended to be minor and treated with anti-acids.	Assumption	Acceptable assumption

Given the paucity of available comparative evidence, the EAC considers the time horizon and cost comparison approach are appropriate and the overall model structure is acceptable. The model does vary from the scope as outlined in section 1 as no studies were identified comparing Early TIPS to Danis stent. The company state that emergency or salvage TIPS could be an appropriate comparator performed at the same stage in the pathway as Danis stent. However, as this can only be performed in select hospitals in the UK and comparative data is not available, this has not included. On consultation with clinical experts, the EAC considers these justifications to be appropriate.

The EAC note that the modelling of definitive treatment is in line with the NICE scope. However, the base case assumption that the choice of bridging treatment affects definitive treatment is a key driver of model uncertainty, relying on weak evidence and a lack of expert consensus. Escorsell et al.

2016 indicates a trend towards a lower use of TIPS as definitive treatment in Danis stent patients (31%) compared to those who had received balloon tamponade (67%), however this does not reach statistical significance (p = 0.12). Further, although there is a lack of consensus amongst clinical expert advisors, the rates at which alternative definitive treatment options are applied in Spanish settings may not be generalisable to the UK.

In the company base case, where definitive treatment costs are included in the model, Danis stent appears to be cost saving. The company explores two other scenarios in their sensitivity analysis, with scenario 2 changing the direction of results. The EAC advises that both scenario 1 (a micro-costing approach taken to include the impact on length of stay in intensive care units) and scenario 2 (no impact on definitive treatment or intensive care unit stay and HE events excluded) are also feasible models. In addition, the EAC presents a further scenario 3 (definitive treatment excluded but HE events included). The results of all scenarios should be considered alongside the base case.

The EAC accepts the company's base case model but updates 5 parameter estimates, including the parameter values assigned to the cost of definitive treatments. These parameter alterations mean the difference in rates of definitive treatments are no longer key drivers of uncertainty and there is consistency between the EAC base case and scenario 2 results.

Economic model parameters

The company model is based upon 1 RCT (Escorsell et al. 2016), 5 case series studies and NHS reference costs. Alongside the cost of procedures, the parameters that drive the overall results in the base case model are the cost of SAEs, including severe HE and the cost of the definitive treatment. The company note HE is likely to be associated with definitive treatment. However, EAC expert clinical opinion suggests HE could also occur during bridging treatment. Overall, SAEs are more frequent in the balloon tamponade group.

The EAC believes that a number of parameters, including the choice of definitive treatment, lack strong supporting evidence. The EAC reviewed all parameters in the company submission and assigned different values for five cost parameters, based on available published evidence. These changes altered the direction of results for the base case compared to the company submission.

Clinical parameters and variables

Table 5 summarises the clinical parameters used in the company's model; the EAC did not change any of these values.

Table 5 Clinical Parameters used in Company Model

Variable	Company value	Source
Proportion of patients dying at 6 weeks with Danis stent	46%	Escorsell et al. (2016)
Relative risk of patients dying at 6 weeks with Balloon tamponade compared with Danis stent	1.3	Extrapolated from Escorsell et al. (2016) Table 2, Survival at 6 weeks with balloon tamponade 6 patients out of 15
Proportion of patients experiencing re-bleed during 6 weeks with Danis stent	46%	Extrapolated from Escorsell et al. (2016) Table 2, Absence of bleeding at 6 weeks with Danis stent 7 patients out of 13
Relative risk of re-bleed during 6 weeks with Balloon tamponade compared with Danis stent	1.2	Extrapolated from Escorsell et al. (2016) Table 2, Absence of bleeding at 6 weeks with Balloon tamponade 7 patients out of 15
Incidence of cardiorespiratory arrest within 6 weeks with Danis stent	7.7%	Escorsell et al. (2016) Table 3, 1 patient out of 13
Incidence of cardiorespiratory arrest within 6 weeks with Balloon tamponade	6.7%	Escorsell et al. (2016) Table 3, 1 patient out of 15
Incidence of aspiration pneumonia within 6 weeks with Danis stent	0%	Escorsell et al. (2016) Table 3, 0 patients out of 13
Incidence of aspiration pneumonia within 6 weeks with Balloon tamponade	33.3%	Escorsell et al. (2016) Table 3, 5 patients out of 15

Incidence of oesophageal rupture within 6 weeks with Danis stent	0%	Escorsell et al. (2016) Table 3, 0 patients out of 13
Incidence of oesophageal rupture arrest within 6 weeks with Balloon tamponade	6.7%	Escorsell et al. (2016) Table 3, 1 patient out of 15
Incidence of spontaneous bacterial peritonitis and hepatorenal syndrome within 6 weeks with Danis stent	7.7%	Escorsell et al. (2016) Table 3, 1 patient out of 13
Incidence of spontaneous bacterial peritonitis and hepatorenal syndrome within 6 weeks with Balloon tamponade	0%	Escorsell et al. (2016) Table 3, 0 patients out of 15
Proportion of patients with severe hepatic encephalopathy within 6 week period with Danis stent	38%	Escorsell et al. (2016) Table 4, 5 patients out of 13
Proportion of patients with severe hepatic encephalopathy within 6 week period with Balloon tamponade	73%	Escorsell et al. (2016) Table 4, 11 patients out of 15
Proportion of patients with definitive treatment of endoscopic band ligation & nonselective beta blockers at 6 weeks with Danis stent	38%	Escorsell et al. (2016) Table 4, 5 patients out of 13
Proportion of patients with definitive treatment of endoscopic band ligation & nonselective beta blockers at 6 weeks with Balloon tamponade	0%	Escorsell et al. (2016) Table 4, 0 patients out of 15
Proportion of patients with definitive treatment of TIPs at 6 weeks with Danis stent	31%	Escorsell et al. (2016) Table 4, 4 patients out of 13

Proportion of patients with definitive treatment of TIPs at 6 weeks with Balloon tamponade	67%	Escorsell et al. (2016) Table 4, 10 patients out of 15
Proportion of patients with stent migration with Danis stent	20% 17 out of 83 patients	Average calculated based on Ghidirim et al. (2012) (5 of 12 patients) Muller et al. (2015) (4 of 11 patients) Wright et al. (2010) (0 of 10 patients) Zakaria et al. (2013) (1 of 16 patients) Zehetner et al. (2008) (7 of 34 patients) Company excluded Pfisterer et al. 2019 case series figures from average as study reports no stent migration and only stent dislocation (13 of 34 patients). The EAC accepts this exclusion as there is a lack of information on subsequent resource use associated with stent dislocation in Pfisterer et al. but notes this assumption favours Danis Stent and there is uncertainty amongst clinical experts as to the difference between stent dislocation and migration.

Resource identification, measurement and valuation

Costs for the technology

All identified resources and associated costs used in the analysis are included in table 6. The procedure costs of inserting the devices were assumed to be equivalent for both technologies and calculated using NHS reference costs to be £5,377 in the base case. The micro-costing scenario was also used to identify procedure costs in the sensitivity analysis (scenario 1). This analysis used a combination of national reference costs and clinical expert advice. The EAC view on the assumptions and values used are also presented in Table 6.

The EAC updated values for five cost parameters: cost of re-bleed, cost of severe hepatic encephalopathy, cost of stent removal, and the cost of both definitive treatments.

Table 6 Resource Costs

Parameter	Company value	Source	EAC value	EAC comments
Danis stent unit cost	£1,495.00	Company NICE MIB185 (National Institute for Health and Care Excellence 2019)	Same	-
Balloon tamponade unit cost	£300.00	Company NICE MIB185 (National Institute for Health and Care Excellence 2019)	Same	-
Cost of procedure per treatment	£5,377.81	NHS refence cost 2018/2019 FD03A Non-elective gastrointestinal bleed with multiple interventions with CC score 5+	Same	Appropriate procedural reference cost chosen. The company assumes procedural costs are equivalent in both groups.
	Procedure cost Danis = £9,194 Procedure cost balloon tamponade = £8,584	Micro costing	Same	Values and assumptions acceptable.

Training cost for Danis Stent per procedure	£65.40	PSSRU 2019. Figure for surgical consultant time. The company assumes 3 hours training per year over 5 procedures.	Same	Acceptable assumptions used. Cost assumes continued provision of free training from company and accounts for clinical time. Costs do not include training cost for removal but as training is not a key cost driver this is an acceptable simplifying assumption.
Cost of re-bleed	£3,287.00	Uplifted from NICE resource impact report for cirrhosis in over 16s [NG50] (2016) with lowest cost from range of three HRGs chosen.	£4,978.75	NICE impact report provides non-elective reference costs for HRG GB02A, GB02B, GB02C. These codes are no longer available. The company assumes that the 2016 impact report refers to 2015 prices and inflates 2018/19 prices using PSSRU HCHS/NHS inflators for all sectors. The EAC repeats this method and takes an unweighted average of all three HRGs to reflect the range given in the NICE impact report. (No weights given as 2016/17 tariff does not report activity).
Cost of stent migration	£699.00	NHS reference costs 2018/19 FE20Z Therapeutic endoscopic upper gastrointestinal tract procedure	Same	Acceptable assumption confirmed by EAC clinical experts. However, as identified in Wright et al. (2010) the Ella extractor may also be used to reposition following stent migration. This is

				explored in EAC sensitivity analysis.
Cost of severe hepatic encephalopathy (HE)	£400.52	Cost of treatment for HE used. Adapted from annual cost of Rifixamin + lactulose reported in NICE costing template TA2337 (2015). Drug costs updated based on NHS electronic drug tariff 2020. Annual cost then divided by 52 to get a weekly cost and then multiplied by 6 to get a 6-week cost to apply in the model.	£400.56	Acceptable assumption. EAC failed to replicate company value and adjusted it slightly. Marginal difference which would not impact results.
Cost of stent removal	£1,257 per of removal with Ella extractor (£757+£500) £1,066 mean cost per patient in model	Company submission: the resource associated with removal procedure (£757) for the Danis stent was based on clinical expert opinion and comprised use of endoscopy (£699) and fluoroscopy (£58) (NHS reference costs 2018/19 (NHS Improvement 2019) (FE20Z therapeutic endoscopic upper gastrointestinal tract procedures, 19 years and over; RD34Z contrast fluoroscopy, mobile or intraoperative procedures with duration of 20 to 40 minutes direct access). The use of the Ella extractor was included for those patients undergoing band ligation as their definitive treatment at a cost of £500 (cost based on discounted price when bought as	£1,452.00 per removal with Ella extractor (£757 + £695) £1,141.35 mean cost per patient in model	Assumptions on removal procedure costs acceptable (£757). However, basing the cost of an Ella extractor on discounted price when bought as a bundle with Danis Stent was not considered appropriate whilst also assuming that not all Danis Stent patients would require use of Ella extractor. EAC applies undiscounted cost of £695. Some experts suggested there could be lower rates of TIPS in the UK compared to a Spanish setting, or that Ella extractor would be used in TIPS patients, resulting in higher

		a bundle with the Danis stent, undiscounted price = £695). Clinical experts and previous experience notes that the Ella extractor may not be required for removal of the stent if TIPS was being undertaken, and therefore the cost of this was only included for the 38% of patients undergoing band ligation based on Escorsell et al. (2016). Multiplying these costs by the proportion of patients surviving and requiring each type of removal procedure gave an overall estimated cost of the stent removal procedure of £1,066 per patient.		rates of Ella extractor use. Deterministic sensitivity analysis therefore explores use of Ella extractor for all patients surviving for 7 days.
Cost for balloon removal	£4.13 cost per removal £3.03 mean cost per patient in the model	Company submission: clinical expert opinion - the cost of a foundation year 2 doctor's time (Personal Social Services Research Unit 2019b) for 7.5 minutes is calculated as £4. This is multiplied by the proportion requiring removal (74%) resulting in an average per patient cost of £3.	Same	Acceptable and conservative assumption.
Cost of definitive treatment elective TIPS	£3,928.00	Company submission: taken from NHS reference costs 2018/19 (NHS Improvement 2019) [YR16B Transjugular Intrahepatic Creation of Portosystemic	£4,965.56	The company uses the HRG reference cost with lower CC score of 0-5. However, as CC score reflects the complexity of the procedure rather than incidences of

		Shunt with CC Score 0-5]. Total HRG costs were used. Due to low numbers of full consultant episodes for elective procedures it was judged these would be less reliable. This is explored in sensitivity analysis. Costs relating to lower CC score were used by company because it was assumed that definitive procedures would be undertaken within 1 to 2 weeks after the stent or balloon procedure and complications therefore already captured in the 6 week time horizon of the model		complications, EAC uses the higher complexity score and selects elective tariff for YR16A Transjugular Intrahepatic Creation of Portosystemic Shunt with CC Score 6+. The EAC believe the higher complication score is appropriate for TIPS for bleeding in this acutely unwell population. The low complication score would be appropriate for TIPS when used electively, for management of refractory ascites in a stable patient. Although FCEs are low in elective tariff, which introduces uncertainty in estimates (as company notes), the EAC view the elective tariff to be more representative of the population. Expert clinical view was mixed which may partly be due to a lack of knowledge of CC scores. There was broad agreement however that these were complex procedures for comorbid patients which supports the EAC choice. Uncertainty in this choice is

				explored in sensitivity analysis.
Cost of definitive treatment endoscopic band ligation + nonselective beta blockers	£1,114.00	Company submission: NHS reference costs 2018/19 (NHS Improvement 2019) based on Endoscopic, Sclerotherapy or Rubber Band Ligation, of Lesion of Upper Gastrointestinal Tract, with CC Score 0-2 [FE11D].	£4,983.67	As above. EAC selected the elective tariff for FE11A - Endoscopic, Sclerotherapy or Rubber Band Ligation of lesion of Upper Gastrointestinal Tract, with CC Score 9+. Expert clinical view was mixed which may be partly due to a lack of knowledge of CC scores. There was broad agreement that these were complex procedures for comorbid patients which supports the EAC choice of the highest complexity score. Uncertainty in this choice is explored in sensitivity analysis. The two definitive treatment options are appropriate for UK (clinical expert opinion).
Adverse event parameter	**Cost**	**Source**	**EAC value**	**EAC comments**
Cardiorespiratory arrest	£2,912.68	National NHS cost collection (2018/19) (NHS Improvement 2019) Weighted average of codes EB05A-EB05C NEL; cardiac arrest with CC score 0 to 9+	Same	-
Aspiration pneumonia	£2,701.77	National NHS cost collection (2018/19)	Same	-

		(NHS Improvement 2019) Weighted average of codes DZ11K-V NEL Lobar, Atypical or viral pneumonia without interventions, with single intervention or with multiple interventions, various CC scores.		
Oesophageal rupture	£9,054.28	National NHS cost collection (2018/19) (NHS Improvement 2019) Weighted average of codes FF01A - FF02C, FF04A - FF04D NEL; very complex to major oesophageal, stomach or duodenum procedures, 19 years and over with various CC scores	Same	-
Spontaneous bacterial peritonitis and hepatorenal syndrome	£2,833.75	National NHS cost collection (2018/19) (NHS Improvement 2019) Weighted average of codes LA07H-P NEL; acute kidney injury with and without interventions, various complication scores	Same	-

Sensitivity analysis

The company undertook extensive sensitivity analysis. Deterministic one-way sensitivity analysis was undertaken to explore uncertainty in:

- use of vasoactive drugs between treatment arms; differing use would increase the procedure costs for Danis stent
- use of Ella extractor for stent removal; if used in all cases where patient survived to day 7 stent removal costs would increase
- cost of re-bleeding
- cost of definitive treatment

- whether Danis Stent may lead to a reduced length of stay in intensive care units (ICUs) in line with expert opinion
- confidence intervals for relative risk of dying and re-bleeding
- cost of aspirational pneumonia – a key adverse event with high incidence in balloon tamponade

Two-way sensitivity analysis was undertaken to explore uncertainty in training requirements for Danis stent and impact on stent migration rates.

Ranges used in the above analyses are presented in appendix E, alongside changes made by the EAC to the deterministic ranges for five parameters.

A 10,000-iteration probabilistic sensitivity analysis (PSA) was also undertaken for base case and scenario 1, using the distributions outlined in appendix E. Upon request, the company also provided a 10,000 iteration PSA for scenario 2.

Scenario analysis

Two scenarios were explored by the company as outlined in table 7. An additional scenario (scenario 3) was explored by the EAC.

Table 7 Scenarios Explored by Company (copyright belongs to UK Medical)

Scenario	Base case values	Scenario values
Scenario 1 - Microcosting of each treatment procedure allowing for variation in procedure costs. Patients undergoing Danis Stent assumed to have fewer days in Intensive Care Units.	Procedure cost Danis = £6,872 Procedure cost balloon tamponade = £5,677	Procedure cost Danis = £9,194 Procedure cost balloon tamponade = £8,584
Scenario 2 - Definitive treatments not considered relevant and HE cost removed	EBL Danis stent = 38% TIPS Danis stent = 31% EBL balloon tamponade = 0%	EBL Danis stent = 0% TIPS Danis stent = 0% EBL balloon tamponade = 0%

	TIPS balloon tamponade 67% Use of Ella extractor for removal of Danis stent = 38% Incidence severe HE Danis stent = 38% Incidence severe HE balloon tamponade = 73%	TIPS balloon tamponade 0% Use of Ella extractor for removal of Danis stent = 38% Incidence severe HE Danis stent = 0% Incidence severe HE balloon tamponade = 0%
Scenario 3 – explored by EAC: Definitive treatments not considered relevant. HE costs included and assumed that all associated with bridging treatment	EBL Danis stent = 38% TIPS Danis stent = 31% EBL balloon tamponade = 0% TIPS balloon tamponade 67% Use of Ella extractor for removal of Danis stent = 38% Incidence severe HE Danis stent = 38% Incidence severe HE balloon tamponade = 73%	EBL Danis stent = 0% TIPS Danis stent = 0% EBL balloon tamponade = 0% TIPS balloon tamponade 0% Use of Ella extractor for removal of Danis stent = 38% Incidence severe HE Danis stent = 38% Incidence severe HE balloon tamponade = 73%

The EAC agrees with the two scenarios chosen by the company, however expert opinion indicates HE may occur during the bridging treatment phase, although the trial data is unclear. The EAC have therefore considered an additional scenario which removes definitive treatments but retains HE event costs.

9.3 *Results from the economic modelling*

Table 8 Summary of base case results

	Company's results			EAC results		
	Technology: Danis stent	**Comparator: balloon tamponade**	**Cost saving per patient**	**Technology: Danis stent**	**Comparator: balloon tamponade**	**Cost saving per patient**
Device	£1,495	£300	£1,195	£1,495	£300	£1,195
Procedure (excluding device)	£5,377	£5,377	£0	£5,377	£5,377	£0
Training per procedure	£65	£0	£65	£65	£0	£65
Re-bleed	£1,517	£1,753	-£236	£2,298	£2,655	-£357
Adverse event	£442	£1,698	-£1,256	£442	£1,698	-£1,256
Stent migration	£143	£0	£143	£143	£0	£143
Severe hepatic encephalopathy	£154	£294	-£140	£154	£294	-£140
Stent/balloon removal	£1,066	£3	£1,063	£1,141	£3	£1,138
Definitive treatment: endoscopic band ligation + nonselective beta blockers	£428	£0	£428	£1,916.80	£0	£1,916.80
Definitive treatment: TIPS	£1,209	£2,619	-£1410	£1,527.86	£3,310	-£1,782.51
Total	**£11,897**	**£12.044**	**-£147**	**£14,560**	**£13,638**	**£923**

Table 9 summary of base case survival and adverse event results

	Company's results			EAC results		
	Technology: Danis stent	**Comparator: balloon tamponade**	**Difference per patient**	**Technology: Danis stent**	**Comparator: balloon tamponade**	**Difference per patient**
Number of deaths	0.46	0.60	-0.14	0.46	0.60	-0.14

per patient						
Number of serious adverse events	0.15	0.47	-0.31	0.15	0.47	-0.31
Cost per death avoided	Dominant -£1,059.59			**£6,663.72**		

Due to the revised values for five cost parameters, the EAC base case shows a cost difference of £923 per Danis stent patient (whereas the company base case shows a cost saving of £147). Similarly, the EAC base case shows a cost of £6,663.72 per death avoided, whereas the company base case shows a dominant cost saving.

As noted above, the three scenarios explored in sensitivity analysis are also plausible models and results should be considered alongside the base case.

Scenario analysis

The scenario analysis undertaken by the company reveals that a micro costing approach with a reduction in procedure costs and days in ICU within the Danis stent arm reduces the cost difference between Danis stent and balloon tamponade. The micro costing approach is detailed in appendix E. In the EAC analysis, this reduces the incremental cost per patient for use of Danis stent compared to the base case.

In scenario 2, when definitive treatments and HE costs are removed, and in scenario 3, when definitive treatments are removed but HE costs retained, the company analysis indicates the intervention is not cost saving, in line with EAC results for all scenarios. The EAC advises that all four scenarios are plausible.

Table 10 Resource Costs in Company Scenario Analysis

Results, cost per patient		**Mean cost per patient using Danis stent (£)**	**Mean cost per patient using balloon tamponade (£)**	**Difference in cost per patient (£)***
Base case	Company	£11,972	£12,044	-£72
	EAC	**£14,560**	**£13,638**	**£923**

Scenario 1 – microcosting of each treatment procedure	Company	£14,219	£14,951	-£732
	EAC	**£16,883**	**£16,545**	**£338**
Scenario 2 - Definitive treatments not considered relevant to bridging treatment, and removal of HE cost	Company	£10,181	£9,131	£1,050
	EAC	**£10,962**	**£10,034**	**£928**
Scenario 3 - Definitive treatments not considered relevant. HE costs included and assumed that all associated with bridging treatment.	EAC	**£11,116**	**£10,327**	**£788**
	* Negative values indicate a cost saving.			

Table 11 Cost per Death Avoided

Results, cost per death avoided		**Cost per death avoided**
Base case	Company	Dominant -£1,059.59
	EAC	**£6,663.72**
Scenario 1 – microcosting of each treatment procedure	Company	Dominant -£5,284.04
	EAC	**£2,439.28**
	Company	£7,038.37

Scenario 2 - Definitive treatments not considered relevant to bridging treatment, and removal of HE cost	EAC	**£6,702.84**
Scenario 3 - Definitive treatments not considered relevant. HE costs included and assumed that all associated with bridging treatment	EAC	**£5,694.03**

Deterministic sensitivity analysis

The deterministic sensitivity analysis results show the key drivers for uncertainty in estimates of the comparative cost of Danis stent and Balloon Tamponade in the base case. The parameters where deterministic ranges alter the direction of results are:

- relative risk of re-bleed by 6 weeks in balloon tamponade group
- procedure costs
- cost of band ligation (EBL)
- cost of aspiration pneumonia
- proportion of balloon tamponade patients having band ligation as definitive treatment

Deterministic sensitivity analysis results for the top drivers of uncertainty in the model are presented in in Figure 8 for the EAC base case and in Appendix F for company base case and both scenarios.

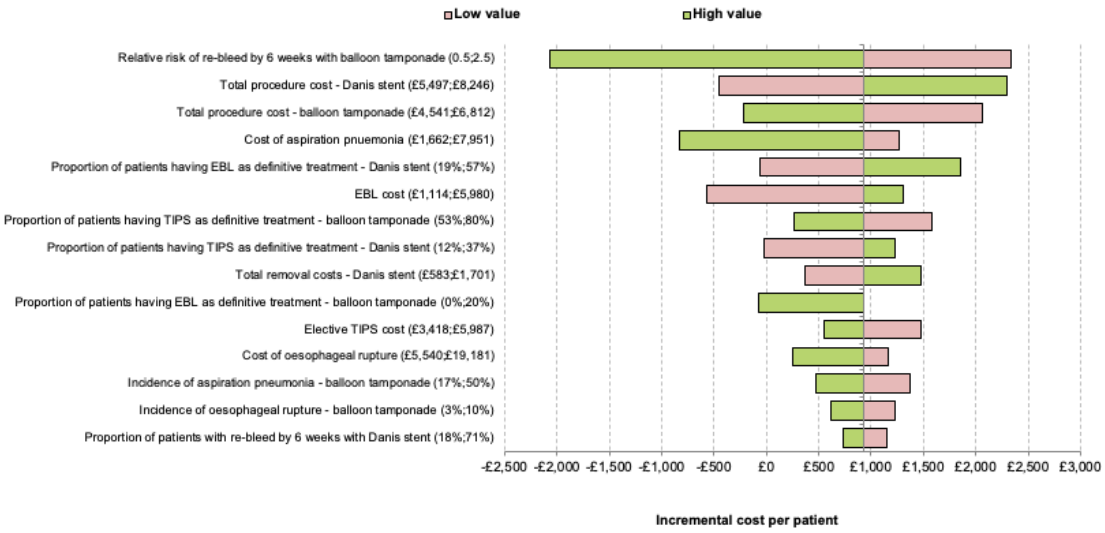


Figure 8 EAC base case

Company results for the two-way sensitivity analysis exploring the interaction between training costs per procedure for Danis stent insertion and the incidence of stent migration requiring intervention are shown in Appendix F.

In addition to the company sensitivity analysis, at NICE's request, the EAC also undertook threshold analysis on the break-even price for the technology for all scenarios. This is presented in table 12.

Table 12 Break even analysis for cost of device

Scenario	Cost of device that will result in difference in cost per patient of £0
EAC Base case	£572.33
EAC Scenario 1 – microcosting of each treatment procedure	£1,157.25
EAC Scenario 2 - Definitive treatments not considered relevant to bridging treatment, and removal of HE cost	£567.91
Scenario 3 - Definitive treatments not considered relevant. HE costs included and assumed that all associated with bridging treatment.	£707.60

Probabilistic sensitivity analysis:

The EAC base case analysis shows that 34% of iterations were cost saving, suggesting a probability of 0.34 that the intervention is cost saving. Probabilistic sensitivity analyses were not able to be performed for scenario 1 or scenario 2 due to an error in the company model.

Comparatively, the company analysis suggested that 55% of iterations were shown to be cost saving in the base case. In the micro costing scenario 1 62% of iterations were cost saving, and in scenario 2, 33% of iterations were cost saving.

Results are presented in appendix F for the incremental cost per patient. The PSA results provide further evidence of decision uncertainty.

9.4 *The EAC's interpretation of the economic evidence*

The company submission assumes a relationship between choice of bridging treatment and definitive treatment based on very limited evidence. Due to the values assigned to a number of key parameters, including the choice of definitive treatment, this results in the company estimating that Danis Stent is cost saving in the base case. The company also presents a micro-costing scenario (scenario 1), and a model where definitive treatment is not affected by choice of bridging treatment (scenario 2).

The EAC accepts the base case model given definitive treatment is within the scope, and updates five cost parameters. The changes alter the direction of results and the EAC estimates that Danis Stent incurs a cost of £982 per patient treated in the base case.

However, given the paucity of evidence in this area, the EAC recommends consideration is given to all scenario analysis results. In scenario 1, where there are reduced ICU bed days and procedure costs associated with Danis Stent, the cost per patient reduces to £397 in the EAC analysis. Across all four scenarios analysed by the EAC, use of Danis Stent incurred additional costs of between £397 to £987.

Whilst the evidence points to a cost increase associated with the use of Danis Stent, a key limitation of the cost comparison approach is that it only enables consideration of the costs associated with a technology and not its effect on patient outcomes. The EAC notes that evidence presented by the company of patient benefit in Escorsell et al. (2016) trends towards increased survival in acutely unwell patients. Evidence of health related quality of life outcomes are required to enable a cost-utility analysis.

10 Conclusions

10.1 *Conclusions from the clinical evidence*

The company submitted 9 full text studies in their submission; the EAC agreed with the inclusion of all 9 studies and did not include any further studies. Overall the EAC believes the evidence base is of moderate quality with several important weaknesses. The majority of studies were non-comparative (7 out of 9) and more than half were retrospective (5 out of 9). The highest quality evidence was a small, underpowered RCT performed in multiple Spanish teaching hospitals (Escorsell et al. 2016). The pathway in Spain may differ to the UK pathway; hospitals in the UK may have less availability to provide definitive treatment after Danis stent or Balloon Tamponade, although there was no consensus between experts on whether this is the case.

The results of the RCT suggest that Danis stent improves control of bleeding, rate of survival and reduces severe adverse events at 15 days after stent implantation, when compared to balloon tamponade, using a composite primary endpoint (Danis stent 85% (11/13), S-B tube 47% (7/15), p=0.037). The study was underpowered for this result, however, and there was no significant difference at 6 weeks post-procedure (p=0.46). This may be expected given the high risk population and the nature of Danis stent as a bridge treatment. The other comparative study (Maiwall et al. 2018) was a retrospective case-control study which showed that mortality related to bleeding was significantly lower in the Danis stent group vs the control group (14% vs 64%, p=0.001). Bleeding control at 5 days was also significantly better in the Danis group than the control (89% vs 37%, p=0.001). Again, these results were not significant at 6 weeks.

Although the company did not perform a meta-analysis, the EAC analysed the results of the 7 non-comparative studies using a random effects model. Heterogeneity was found to be low in immediate bleeding control, successful stent insertion and survival at 30 days after stent insertion. Immediate bleeding control was found to have been achieved in 88% of cases (95% CI: 0.38 to 0.9) based on the 7 case-series, one of which (Wright et al. 2010) was performed in the UK. Survival rate at 30 days was 68% from 3 studies.

10.2 *Conclusions from the economic evidence*

The company's base case model found Danis stent to be cost saving. However, the company's submission assumes that there is a relationship between the choice of bridging treatment and definitive treatment. There is very limited evidence to suggest that this is the case. The company also applied the lowest CC score for tariffs associated with procedures for both

Danis Stent and balloon tamponade. The EAC consulted clinical experts on the likely CC score in this population; there was some heterogeneity of opinion but overall support that patients would likely attract a high CC score. The EAC altered 5 cost parameters and estimated that Danis stent incurs a cost of £923 per patient in the base case.

The company also provided 2 further scenarios; a micro-costing scenario (scenario 1) and a model where definitive treatment is not affected by choice of bridging treatment and HE costs are excluded (scenario 2). The EAC presents a third scenario where definitive treatment is excluded but HE costs are retained in the model (scenario 3). Given the limited evidence, the EAC recommends that consideration is given to all four scenarios. In scenario 1, where there are reduced ICU bed days and procedure costs associated with Danis Stent, the EAC estimates that the cost per patient is £338.

The EAC analysis indicates that Danis Stent is likely to be cost incurring. However, the relative consistency of findings across the four scenarios hides considerable uncertainty regarding the costs associated with Danis Stent and balloon tamponade, and the definitive procedures received by surviving patients. Hence the EAC considers the conclusion that Danis Stent is cost incurring should be interpreted with caution.

The EAC highlights that the cost comparison approach is limited as it does not take patient outcomes into consideration. Further research should be undertaken to investigate how Danis stent affects health-related quality of life in patients with oesophageal variceal bleeding. A longer time horizon may also change results and therefore future studies should ensure that patients are followed up for longer than 6 weeks.

11 Summary of the combined clinical and economic sections

The current evidence base comparing Danis stent to Balloon Tamponade has several weaknesses. One Spanish RCT suggested that the Danis stent may improve clinical outcomes for patients at 15 days, however the study was underpowered, and the treatment arms were unbalanced. Differences between the groups were not significant at 6 weeks. It is unclear how differences in the clinical pathway between Spain and the UK may affect results, particularly due to the availability of definitive treatment, such as TIPS. A cost comparison model suggests that Danis stent will incur a cost of £923 per patient in the base case. Scenario analyses suggest that this cost may be reduced to £338 per patient if there are reduced ICU bed days and procedure costs associated with Danis stent. However, the economic model is limited and due to the number of assumptions made and the lack of strong evidence,

none of the scenarios presented should be considered alone. Further research is required to assess the utility of the Danis stent in the UK.

12 Implications for research

Firm conclusions are unable to be drawn from the results from the current evidence base. The strongest evidence, coming in the form of a small RCT, has several shortcomings. Selection bias may be present due to differences in patient characteristics between the treatment arms. The study was also underpowered, and the population and pathway may differ from current NHS practice. A UK-based RCT with well-matched patient cohorts, powered to detect the difference in long-term survival and health-related quality of life in patients with Danis stent and patients with Balloon Tamponade is required.

13 References

Chen P et al. (2012) Delayed endoscopy increases re-bleeding and mortality in patients with hematemesis and active esophageal variceal bleeding: A cohort study. Journal of Hepatology 57(6):1207-1213.

De Franchis R, Baveno VI Faculty. (2015) Expanding Consensus in Portal Hypertension: Report of the Baveno VI Consensus Workshop: Stratifying Risk and Individualizing Care for Portal Hypertension. Journal of Hepatology. 63(3):743-52

Escorsell À, Pavel O, Cárdenas A et al. (2016) Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: A multicenter randomized, controlled trial. Hepatology 63(6):1957-1967.

Ghidirim G, Mishin I, Dolghii A et al. (2012) Self-expanding Metal stent for the management of bleeding esophageal varices – single centre experience. Clinical anatomy and operative surgery. 11(4):100-103.

Goenka M, Goenka U, Tiwary I et al. (2017) Use of self-expanding metal stents for difficult variceal bleed. Indian Journal of Gastroenterology. 36(6):468-473.

Jairath V, Rehal S, Logan R et al. (2014) Acute Variceal Haemorrhage in the United Kingdom: Patient Characteristics, Management and Outcomes in a Nationwide Audit. Digestive and Liver Disease. 46(5):419-426.

Maiwall R, Jamwal K, Bhardwaj A et al. (2017) SX-Ella Stent Danis Effectively Controls Refractory Variceal Bleed in Patients with Acute-on-Chronic Liver Failure. Digestive Diseases and Sciences. 63(2):493-501.

Maimone S, Saffioti F, Filomia R et al. (2019) Predictors of Re-bleeding and Mortality Among Patients with Refractory Variceal Bleeding Undergoing Salvage Transjugular Intrahepatic Portosystemic Shunt (TIPS). Digestive Diseases and Sciences. 64:1335–1345

Mohan B, Chandan S, Khan S et al. (2019) Efficacy of Self Expanding Metal Stent (SEMS) in Refractory Bleeding Esophageal Varices, Is There a Mortality Benefit? An Indirect-Comparison Meta-Analysis to Trans-Jugular Intra-Hepatic Porto-Systemic Shunt (TIPS). American Journal of Gastroenterology. 114:S346-S347.

Müller M, Seufferlein T, Perkhofer L, Wagner M, Kleger A. Self-Expandable Metal Stents for Persisting Esophageal Variceal Bleeding after Band Ligation or Injection-Therapy: A Retrospective Study. (2015) PLOS ONE. 10(6):e0126525.

NICE. 2011 Stent insertion for bleeding oesophageal varices (IPG392). Available at https://www.nice.org.uk/guidance/ipg392 Accessed 1 June 2020

NICE. 2012 Acute upper gastrointestinal bleeding in over 16s: management (CG141). Available at https://www.nice.org.uk/guidance/cg141 Accessed 1 June 2020

NICE. 2015 Rifaximin for preventing episodes of overt hepatic encephalopathy (TA337). Available at https://www.nice.org.uk/guidance/ta337/resources Accessed 1 June 2020

NICE. 2019 Danis stent for acute oesophageal variceal bleeds (MIB 185). Available at https://www.nice.org.uk/advice/mib185 Accessed 1 June 2020

Njei B, McCarty T, Laine L. (2017) Early transjugular intrahepatic portosystemic shunt in US patients hospitalized with acute esophageal variceal bleeding. Journal of Gastroenterology and Hepatology 32(4):852-858.

Pfisterer N, Riedl F, Pachofszky T, et al. (2018) Outcomes after placement of a SX-ELLA oesophageal stent for refractory variceal bleeding-A national multicentre study. Liver International. 39(2):290-298.

Tacconelli E. (2010) Systematic reviews: CRD's guidance for undertaking reviews in health care. The Lancet Infectious Diseases. 10(4):226.

Tripathi D, Stanley A, Hayes P et al. (2015) UK guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut. 46(90003):1iii-15.

Wright G, Lewis H, Hogan B, et al. (2010) A self-expanding metal stent for complicated variceal hemorrhage: experience at a single center. Gastrointestinal Endoscopy. 71(1):71-78.

Zakaria M, Hamza I, Mohey M et al. (2013) The First Egyptian Experience Using New Self-Expandable Metal Stents in Acute Esophageal Variceal Bleeding: Pilot Study. The Saudi Journal of Gastroenterology. 19:177-81

Zehetner J, Shamiyeh A, Wayand W. (2008) Results of a new method to stop acute bleeding from esophageal varices: implantation of a self-expanding stent. Surgical Endoscopy. 22(10):2149-2152.

14 Appendices

Appendix A

Clinical evidence

Total records retrieved: 95

Database: Ovid MEDLINE(R) ALL <1946 to May 06, 2020>
Search Strategy:

1	(danis or danisc or danisr or danistm).ti,ab,kf.	118
2	(sx-ella$ or sxella$ or ella-cs$ or ellacs$ or cs-ella$ or csella$).ti,ab,kf,in.	32
3	1 or 2	140
4	"Esophageal and Gastric Varices"/	13120
5	Gastrointestinal Hemorrhage/	41567
6	((variceal$ or varices or varix$ or varicose$ or varicosis) adj5 (bleed$ or rebleed$ or ruptur$ or h?emorrhag$ or h?ematochez$ or h?ematoches$)).ti,ab,kf.	10710
7	((variceal$ or varices or varix$ or varicose$ or varicosis) adj5 (esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric)).ti,ab,kf.	11681
8	((esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric) adj5 (bleed$ or rebleed$ or h?emorrhag$ or h?ematochez$ or h?ematoches$)).ti,ab,kf.	38733

9	((esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric or refractory) adj5 VB).ti,ab,kf.	12
10	or/4-9	68247
11	stents/ or self expandable metallic stents/	67039
12	(stent or stents or stenting or stented).ti,ab,kf.	99751
13	(sem or sems).ti,ab,kf.	107955
14	or/11-13	219198
15	10 and 14	1599
16	3 or 15	1728
17	exp animals/ not humans/	4695902
18	(news or editorial or case reports).pt. or case report.ti.	2863411
19	16 not (17 or 18)	1186
20	limit 19 to yr="2020 -Current"	30
21	remove duplicates from 20	30

Database: Embase <1974 to 2020 May 06>
Search Strategy:

1	(danis or danisc or danisr or danistm).ti,ab,kw,dj,dv,my,mv.	171
2	(sx-ella$ or sxella$ or ella-cs$ or ellacs$ or cs-ella$ or csella$).ti,ab,kw,in,dj,dm,my,mv.	231
3	1 or 2	361
4	esophagus varices/ or esophagus varices bleeding/ or esophagus hemorrhage/	20275
5	((variceal$ or varices or varix$ or varicose$ or varicosis) adj5 (bleed$ or rebleed$ or ruptur$ or h?emorrhag$ or h?ematochez$ or h?ematoches$)).ti,ab,kw,dj.	16618
6	((variceal$ or varices or varix$ or varicose$ or varicosis) adj5 (esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric)).ti,ab,kw,dj.	17377
7	((esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric) adj5 (bleed$ or rebleed$ or h?emorrhag$ or h?ematochez$ or h?ematoches$)).ti,ab,kw,dj.	58318
8	((esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric or refractory) adj5 VB).ti,ab,kw,dj.	26
9	or/4-8	77921
10	self expandable metallic stent/ or self expanding stent/	7015
11	digestive stent/ or esophageal stent/ or stent/	90291
12	(stent or stents or stenting or stented).ti,ab,kw,dj.	168389

13	(sem or sems).ti,ab,kw,dj.	134328
14	or/10-13	313342
15	9 and 14	3203
16	3 or 15	3490
17	(animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/	6008500
18	editorial.pt. or case report.ti.	939106
19	16 not (17 or 18)	3286
20	limit 19 to yr="2020 -Current"	53
21	remove duplicates from 20	53
22	21 not "22".mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	48
23	21 and 22	48

Source: Pubmed
Interface / URL: https://www.ncbi.nlm.nih.gov/pubmed, Legacy interface was used
Database coverage dates: 1940s to current
Search date: 06/05/2020
Retrieved records: 0
Search strategy:

Search	Query	Items found
#24	Search #22 Filters: Publication date from 2020/01/01 to 2020/12/31	0
#23	Search #22	226
#22	Search (#20 NOT #21)	226
#21	Search medline[sb]	26775699
#20	Search (#17 NOT (#18 OR #19))	1537
#19	Search ((news[pt] OR editorial[pt] OR case reports[pt]) OR case report[ti])	2860252
#18	Search (animals[mh] NOT humans[mh:noexp])	4696922
#17	Search (#4 OR #16)	2190
#16	Search (#11 AND #15)	2068
#15	Search (#12 OR #13 OR #14)	212062
#14	Search (sem[tiab] OR sems[tiab])	101157
#13	Search (stent[tiab] OR stents[tiab] OR stenting[tiab] OR stented[tiab])	99396

#12	Search ("stents"[mesh:noexp] OR "self expandable metallic stents"[mesh:noexp])	67050
#11	Search (#5 OR #6 OR #7 OR #8 OR #9 OR #10)	80925
#10	Search ((esophag*[tiab] OR oesophag*[tiab] OR gastrointestinal[tiab] OR gastro-intestinal[tiab] OR GI[tiab] OR gastric[tiab] OR refractory[tiab]) AND VB[tiab])	76
#9	Search ((esophag*[tiab] OR oesophag*[tiab] OR gastrointestinal[tiab] OR gastro-intestinal[tiab] OR GI[tiab] OR gastric[tiab]) AND (bleed*[tiab] OR rebleed*[tiab] OR hemorrhag*[tiab] OR hematochez*[tiab] OR hematoches*[tiab] OR haemorrhag*[tiab] OR haematochez*[tiab] OR haematoches*[tiab]))	53245
#8	Search ((variceal*[tiab] OR varices[tiab] OR varix*[tiab] OR varicose*[tiab] OR varicosis[tiab]) AND (esophag*[tiab] OR oesophag*[tiab] OR gastrointestinal[tiab] OR gastro-intestinal[tiab] OR GI[tiab] OR gastric[tiab]))	12896
#7	Search ((variceal*[tiab] OR varices[tiab] OR varix*[tiab] OR varicose*[tiab] OR varicosis[tiab]) AND (bleed*[tiab] OR rebleed*[tiab] OR ruptur*[tiab] OR hemorrhag*[tiab] OR hematochez*[tiab] OR hematoches*[tiab] OR haemorrhag*[tiab] OR haematochez*[tiab] OR haematoches*[tiab]))	12646
#6	Search "Gastrointestinal Hemorrhage"[mesh:noexp]	41575
#5	Search ("Esophageal and Gastric Varices"[mesh:noexp])	13120
#4	Search (#1 OR #2 OR #3)	135
#3	Search (sx-ella*[ad] OR sxella*[ad] OR ella-cs*[ad] OR ellacs*[ad] OR cs-ella*[ad] OR csella*[ad])	3
#2	Search (sx-ella*[tiab] OR sxella*[tiab] OR ella-cs*[tiab] OR ellacs*[tiab] OR cs-ella*[tiab] OR csella*[tiab])	26
#1	Search (danis[tiab] OR danisc[tiab] OR danisr[tiab] OR danistm[tiab])	116

A.4: Source: Cochrane Database of Systematic Reviews (CDSR)

Interface / URL: Cochrane Library, Wiley
Database coverage dates: Issue 5 of 12, May 2020
Search date: 06/05/2020
Retrieved records: 0
Search strategy:

ID Search Hits
#1 (danis OR danisc OR danisr OR danistm):ti,ab,kw 4
#2 ((sx NEXT ella*) OR sxella* OR (ella NEXT cs*) OR ellacs* OR (cs NEXT ella*) OR csella*):ti,ab,kw 7

#3 #1 OR #2 8
#4 MeSH descriptor: [Esophageal and Gastric Varices] this term only 874
#5 MeSH descriptor: [Gastrointestinal Hemorrhage] this term only 1456
#6 ((variceal* OR varices OR varix* OR varicose* OR varicosis) NEAR/5 (bleed* OR rebleed* OR ruptur* OR h?emorrhag* OR h?ematochez* OR h?ematoches*)):ti,ab,kw 2150
#7 ((variceal* OR varices OR varix* OR varicose* OR varicosis) NEAR/5 (esophag* OR oesophag* OR gastrointestinal OR (gastro NEXT intestinal) OR GI OR gastric)):ti,ab,kw 2076
#8 ((esophag* OR oesophag* OR gastrointestinal OR (gastro NEXT intestinal) OR GI OR gastric) NEAR/5 (bleed* OR rebleed* OR h?emorrhag* OR h?ematochez* OR h?ematoches*)):ti,ab,kw 6306
#9 ((esophag* OR oesophag* OR gastrointestinal OR (gastro NEXT intestinal) OR GI OR gastric OR refractory) NEAR/5 VB):ti,ab,kw 3
#10 #4 OR #5 OR #6 OR #7 OR #8 OR #9 7446
#11 MeSH descriptor: [Stents] this term only 2927
#12 MeSH descriptor: [Self Expandable Metallic Stents] explode all trees 40
#13 (stent OR stents OR stenting OR stented):ti,ab,kw 15024
#14 (sem OR sems).ti,ab,kw 1414
#15 #11 OR #12 OR #13 OR #14 16425
#16 #15 AND #10 242
#17 #16 OR #3 247
#18 #17 with Cochrane Library publication date Between Jan 2020 and May 2020, in Cochrane Reviews 0

Source: Conference Proceedings Citation Index- Science (CPCI-S) --
Interface / URL: Web of Science, Clarivate Analytics
Database coverage dates: 1990-present. Last updated 2020-06-05
Search date: 05/06/2020
Retrieved records: 2
Search strategy:

#14	#13	2
	Indexes=CPCI-S Timespan=Year to date	
#13	#12 OR #3	117
	Indexes=CPCI-S Timespan=All years	
#12	#11 AND #8	112
	Indexes=CPCI-S Timespan=All years	

#11	#10 OR #9	90890
	Indexes=CPCI-S Timespan=All years	
#10	TS=("sem" OR "sems")	68443
	Indexes=CPCI-S Timespan=All years	
#9	TS=("stent" OR "stents" OR "stenting" OR "stented")	22677
	Indexes=CPCI-S Timespan=All years	
#8	#7 OR #6 OR #5 OR #4	5511
	Indexes=CPCI-S Timespan=All years	
#7	TS=((esophag* OR oesophag* OR "gastrointestinal" OR "gastro intestinal" OR "GI" OR "gastric" OR "refractory") NEAR/5 "VB")	1
	Indexes=CPCI-S Timespan=All years	
#6	TS=((esophag* OR oesophag* OR "gastrointestinal" OR "gastro intestinal" OR "GI" OR "gastric") NEAR/5 (bleed* OR rebleed* OR h$emorrhag* OR h$ematochez* OR h$ematoches*))	4236
	Indexes=CPCI-S Timespan=All years	
#5	TS=((variceal* OR "varices" OR varix* OR varicose* OR "varicosis") NEAR/5 (esophag* OR oesophag* OR "gastrointestinal" OR "gastro intestinal" OR "GI" OR "gastric"))	1302
	Indexes=CPCI-S Timespan=All years	
#4	TS=((variceal* OR "varices" OR varix* OR varicose* OR "varicosis") NEAR/5 (bleed* OR rebleed* OR ruptur* OR h$emorrhag* OR h$ematochez* OR h$ematoches*))	1291
	Indexes=CPCI-S Timespan=All years	
#3	#2 OR #1	8
	Indexes=CPCI-S Timespan=All years	
#2	TS=("sx ella*" OR sxella* OR "ella cs*" OR ellacs* OR "cs ella*" OR csella*)	4
	Indexes=CPCI-S Timespan=All years	

#1	TS=("danis" OR "danisc" OR "danisr" OR "danistm")	5
	Indexes=CPCI-S Timespan=All years	

Source: Cochrane Central Register of Controlled Trials (CENTRAL)
Interface / URL: Cochrane Library, Wiley
Database coverage dates: Issue 5 of 12, May 2020
Search date: 05/06/2020
Retrieved records: 315
Search strategy:

ID Search Hits
#1 danis OR danisc OR danisr OR danistm 139
#2 (sx NEXT ella*) OR sxella* OR (ella NEXT cs*) OR ellacs* OR (cs NEXT ella*) OR csella* 9
#3 #1 OR #2 145
#4 MeSH descriptor: [Esophageal and Gastric Varices] this term only 874
#5 MeSH descriptor: [Gastrointestinal Hemorrhage] this term only 1486
#6 (variceal* OR varices OR varix* OR varicose* OR varicosis) NEAR/5 (bleed* OR rebleed* OR ruptur* OR h?emorrhag* OR h?ematochez* OR h?ematoches*) 2326
#7 (variceal* OR varices OR varix* OR varicose* OR varicosis) NEAR/5 (esophag* OR oesophag* OR gastrointestinal OR (gastro NEXT intestinal) OR GI OR gastric) 2133
#8 (esophag* OR oesophag* OR gastrointestinal OR (gastro NEXT intestinal) OR GI OR gastric) NEAR/5 (bleed* OR rebleed* OR h?emorrhag* OR h?ematochez* OR h?ematoches*) 6873
#9 (esophag* OR oesophag* OR gastrointestinal OR (gastro NEXT intestinal) OR GI OR gastric OR refractory) NEAR/5 VB 4
#10 #4 OR #5 OR #6 OR #7 OR #8 OR #9 8000
#11 MeSH descriptor: [Stents] this term only 2927
#12 MeSH descriptor: [Self Expandable Metallic Stents] explode all trees 40
#13 stent OR stents OR stenting OR stented 15296
#14 sem OR sems 7490
#15 #11 OR #12 OR #13 OR #14 22523
#16 #15 AND #10 292
#17 #16 OR #3 433
#18 #17 with Cochrane Library publication date Between Jan 2020 and May 2020, in Trials 15

Source: ClinicalTrials.gov
Interface / URL: https://www.clinicaltrials.gov/ct2/results/refine?show_xprt=Y – Expert search interface
Database coverage dates: 01/01/2020-current
Search date: 05/06/2020
Retrieved records: 0

Search strategy:

danis OR danisc OR danisr OR danistm OR sx-ella OR sxella OR ella-cs OR ellacs OR cs-ella OR csella - 0 results

Appendix B

CASP checklist (for RCTs)

Escorcell et al. 2016	**Comment**	**Response**
Section A: Are the results of the study valid?		
1. Did the study address a clearly focused issue?	RCT comparing the success of therapy in Danis stent versus balloon tamponade in patients with cirrhosis and oesophageal variceal bleeding refractory to medical and endoscopic treatment. Success of therapy, defined as survival at day 15 with control of bleeding and without serious adverse events.	Y
2. Was the assignment of patients to treatments randomised?	Prospectively recruited cohort. Patients randomised by Child-Pugh score but not by any other patient profile information. The randomisation sequence was generated by computer in a 1:1 ratio, stratified for the degree of liver failure (Child-Pugh class A or B/C). Concealment of treatment allocation used a sealed envelope method. Patients randomised to balloon tamponade or Danis stent were similar except for a lower age in the balloon tamponade group.	Y
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	28 patients randomised. All had results analysed at conclusion. There were no dropouts or loss to follow up until after the main study time points.	Y
4. Were patients, health workers and study personnel 'blind' to treatment?	This study was open label and, therefore, patients, assessors and personnel were not blinded.	N

5. Were the groups similar at the start of the trial	2 treatment arms differed in terms of patient age and gender (no females were included in the Danis stent arm). Child-Pugh score was randomised and therefore similar.	N
6. Aside from the experimental intervention, were the groups treated equally?	Patients fulfilling inclusion criteria with no exclusion criteria were randomised to the oesophageal stent or the balloon tamponade group. Analgesia with paracetamol (1 g/8 hours, IV) or methadone (5 mg/8 hours, subcutaneous) was provided for oesophageal stenting and balloon tamponade. In addition, conscious sedation with IV propofol (20-30 mg) given as needed. All patients had a complete 6-week follow-up, but 2 of them were lost afterward. The lack of differences between groups at 6 weeks is likely to have been influenced by the more frequent use of TIPS as a rescue therapy in the tamponade group.	Y – however, unsure if this was adequate (see 6 weeks outcome).
Section B: What are the results?		
7. How large was the treatment effect?	Danis stent was significantly superior to balloon tamponade in the following outcomes: Success of therapy (66% vs. 20%; P = 0.025), control of bleeding (85% vs. 47%; P=0.037). Transfusional requirements and SAEs were lower but no significantly so (2 vs 6 PRBC; P = 0.08, 15% vs. 47%; P 5 0.077, respectively). TIPS was used more frequently in the tamponade group (4 vs. 10; P 5 0.12). There were no significant differences in 6-week survival (54% vs. 40%; P 5 0.46). Potential selective reporting as survival, bleeding and hospital stay were all due to be assessed at 6-months but were not reported in the publication	
8. How precise was the estimate of the treatment effect?	Small sample and confidence limits not reported.	

Section C: Will the results help locally?		
9. Can the results be applied to the local population, or in your context?	Study was carried out in Spain which may limit generalisability to the UK and patients who had undergone balloon tamponade as treatment for the index bleed were excluded which would not necessarily be in line with UK clinical practice.	N
10. Were all clinically important outcomes considered?		Y
11. Are the benefits worth the harms and costs?		Y

CASP checklist (for case-control studies)

Maiwall et al. 2018	**Comment**	**Response**
Section A: Are the results of the study valid?		
1. Did the study address a clearly focused issue?	Retrospective study evaluating the feasibility and success of Danis stent in patients with refractory variceal bleed in patients with acute-on-chronic liver failure. This study only included patients with acute-on- chronic liver failure only, excluding other patients that could be part of the target population	Y
2. Did the authors use an appropriate method to	The authors noted the selection bias that could affect non-randomised studies and used PRS-matched analysis which is a recognised method to minimise this form of bias and therefore provides strength to	Y

answer their question?	the observed results. Competing risk analysis according to the method of Fine and Gray was done to identify event-specific mortality.	
3. Were the cases recruited in an acceptable way?	Retrospective study. The same criteria were used for the identification of cases and controls and the exposure to the treatment was assessed for both case and control patients using hospital database records. Patients with ACLF defined according to the Asia Pacific Association for the Study of the Live (APASL) definition.	Y
4. Were the controls selected in an acceptable way?	The same criteria were used for the identification of cases and controls and the exposure to the treatment was assessed for both case and control patients using hospital database records. Patients with Danis stent (cases, n = 35) versus those without Danis stent (the controls, n = 53) were significantly different with respect to disease severity scores. Further, the percentage of patients who had an initial control of bleed was significantly higher for the DE group as compared to controls as also the percentage of patients dying of gastrointestinal bleed . Given the observed differences in the baseline characteristics in the patients who underwent Danis stent vs those who did not, a cohort of patients who underwent Danis stent (cases, n = 22) versus those who did not (controls, n = 22) for refractory variceal bleed were matched by PRS.	N – but controlled for by PRS
5. Was the exposure accurately measured to minimise bias?	The effects of treatment were assessed in the same way in both groups. The outcomes were assessed in the same way in both groups and the follow up period following treatment was 6-weeks. Full details of statistical analyses were reported.	Y
6. (a) Aside from the experimental intervention, were the groups treated equally?	The effects of treatment were assessed in the same way in both groups.	Y
6. (b) Have the authors taken account of the potential	Unclear if confounding factors were identified. None were reported.	N/Unclear

confounding factors in the design and/or in their analysis?		
Section B: What are the results?		
7. How large was the treatment effect?	Control of initial bleeding, bleeding related death were both significantly lower in Danis stent versus control in both pre-match and PRS matched cohorts. Multivariate competing risk Cox regression analysis, intervention with DE stent was significant factor associated with a reduced bleed-related mortality (hazard ratio 0.36)	NA
8. How precise was the estimate of the treatment effect?		NA
9. Do you believe the results?	Direction of outcome consistent with other studies and consistent within study (see q 7).	Y
Section C: Will the results help locally?		
10. Can the results be applied to the local population?	Study carried out in India so may have limited generalisability to NHS population.	N
11. Do the results of this study fit with other available evidence?	Direction of outcome consistent with other studies.	Y

	Ghidirim 2012	Goenka 2017	Muller 2015	Pfisterer 2019	Wright 2010	Zakaria 2013	Zehetner 2008
Study objective							
Was the hypothesis /aim/objective of the study clearly stated?	Partial - To assess DS haemostatic efficacy in severe variceal haemorrhage in patients with bleeding EV and endoscopic treatment failure	Partial - experience of using DS over the past 5 years.	Yes – DS and relation to haemostasis and mortality	Yes - to assess the safety and efficacy of SEMS in patients with refractory VB.	Yes - experience of using DS at 1 centre (safety and efficacy of DS for control of bleeding in refractory VB (TIPS and BT contraindicated)	Yes - effectiveness and safety of DS in the initial control of acute variceal bleeding.	Yes - to assess the safety and efficacy of SEMS in patients with refractory VB.
Study design							
Was the study conducted prospectively?	Unclear	No.	No	No	Unclear	Unclear (possibly yes)	Unclear
Were the cases collected in more than one centre?	No	No.	No	Yes	No	No	No

Were patients recruited consecutively?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Study population							
Were the characteristics of the patients included in the study described?	Partial Some criteria were described, but very brief so not clear how patients were selected	Yes.	Yes	Yes	Yes - description of patients, no inclusion criteria	Yes	Yes
Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Partial - Some criteria were described briefly (endoscopic treatment failure).	Partial - Some criteria were described briefly.	Yes	Yes	No	Yes Clear inclusion and exclusion criteria	No
Did patients enter the study at a similar point in the disease?	Unclear - All patients with acute variceal bleeding.	Unclear - All patients with acute variceal bleeding.	Unclear	Unclear - Most patients had a prior history of variceal bleeding (52.9%).	Unclear Unclear how patients were	Unclear -	Unclear – 34/39 patients classified as

	Selection criteria were brief.	Selection criteria were brief.		More than a half of them (55.6%) had previously been treated with a combination of NSBBs and EBL.	identified however, cirrhosis was confirmed by biopsy or a combination of typical biochemical and radiographic abnormalities		Child-Pugh grade B/C.
Intervention and co-intervention							
Was the intervention of interest clearly described?	Partial	Yes.	Yes	Partial	Yes	Yes	Partial
Were additional interventions (co-interventions) clearly described?	No	Partial - vasoactive drugs, intravenous proton-pump inhibitors mentioned.	Yes e.g. Coagulation disorders were treated with prothrombine complex concentrate or fresh frozen plasma	Yes e.g. vasoactive drugs and endoscopy	Partial	Yes - All patients were exposed to the standards of care in emergency situations like vasoactive therapy	Partial – unsure which concurrent therapy patients were given.

						(somatostatin), hemodynamic stabilisation, and antibiotic treatment.	
Outcome measures							
Were relevant outcome measures established a priori?	Partial - haemostasis	Partial - haemostasis	Yes	Yes	Yes	Yes	Yes
Were outcome assessors blinded to the intervention that patients received?	No – not mentioned	No – not mentioned	No – not mentioned	No – not mentioned	No – not mentioned	No – not mentioned	No – not mentioned
Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes - Baveno consensus IV guidance	Yes - Definition of bleeding was reported by authors	Yes - German S3 guidelines "sedation in gastrointestinal endoscopy"	Yes – Baveno consensus IV guidance	Yes - Baveno consensus IV guidance	Yes - Definition of bleeding was reported by authors	Partial - No criteria for bleeding reported, however all bleeding due to cirrhosis

Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Statistical analysis							
Were the statistical tests used to assess the relevant outcomes appropriate?	Unclear	Unclear	Yes	Yes	Unclear Not reported	Unclear Not reported	Unclear Not reported
Results and conclusions							
Was follow-up long enough for important events and outcomes to occur?	Yes- 30 day mortality	Yes- 30 day mortality	Yes – 42 days mortality	Yes – 1 year	Yes – 42 days mortality	Unclear – follow up period not given	Yes – 60 days
Were losses to follow-up reported?	Yes – no losses.	Yes.	Yes – no losses	Yes – no losses	Yes – no losses	Yes – no losses	Yes – no losses
Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Partial	No	Yes	Yes	No	No	No

Were the adverse events reported?	Yes -partial distal stent migration	Yes	Yes - stent dislocation	Yes - stent dislocation	Yes - ulceration in the oesophagus	Yes	Yes
Were the conclusions of the study supported by the results?	Yes	Yes	Yes	Yes	Partial	Yes	Yes
Competing interests and sources of support							
Were both competing interests and sources of support for the study reported?	No	No	Yes	No	No	No	No

Appendix C

Adverse events in the Literature (Copyright belongs to UK Medical)

Study	Outcome definition and measure	Time point of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
(Escorsell et al. 2016)	Patients with at least one AE	NR	Danis stent	13	4 (31)	p=0.024
			Balloon tamponade	15	11 (73)	
	Patients with at least one SAE	NR	Danis stent	13	2 (15)	p=0.077
			Balloon tamponade	15	7 (47)	
	Patients with at least one device-related SAE	NR	Danis stent	13	1 (8)	p=0.049
			Balloon tamponade	15	6 (40)	
	SAE: Cardio respiratory arrest	NR	Danis stent	13	1 (7.7*)	NR
			Balloon tamponade	15	1 (6.7*)	
	SAE: Aspiration pneumonia	NR	Danis stent	13	0	NR
			Balloon tamponade	15	5 (33.3*)	
	SAE: Oesophageal rupture	NR	Danis stent	13	0	NR
			Balloon tamponade	15	1 (6.7*)	
	SAE: Spontaneous bacterial peritonitis and hepatorenal syndrome	NR	Danis stent	13	1 (7.7*)	NR
			Balloon tamponade	15	0	
	Mild AE: Infections	NR	Danis stent	13	2 (15.4*)	NR
			Balloon tamponade	15	1 (6.7*)	
	Mild AE: Oesophageal ulcer (not bleeding)	NR	Danis stent	13	1 (7.7*)	NR
			Balloon tamponade	15	1 (6.7*)	
	Mild AE: Broncho aspiration not causing pneumonia	NR	Danis stent	13	1 (7.7*)	NR
			Balloon tamponade	15	3 (20*)	

Study	Outcome definition and measure	Time point of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
	Mild AE: Seizures	NR	Danis stent	13	0	NR
			Balloon tamponade	15	1 (6.7*)	
	Mild AE: Transitory acute stroke	NR	Danis stent	13	0	NR
			Balloon tamponade	15	1 (6.7*)	NR
(Ghidirim et al. 2012)	Major device related complications (bronchial compression or impairment of pulmonary function)	NR	Danis stent	14	0	NA
	Tanatogensis induced by hepatic failure	NR		14	3 (21.4*)	
	Bleeding oesophageal varice distally to the device distal end	NR		14	1 (7.1*)	
	Haemorrhagic stroke	NR		14	1 (7.1*)	
	Partial distal stent migration (documented on x-ray and CT scan)	NR		12	5 (41.6)	
(Muller et al. 2015)	Stent dislocation	24 hours	Danis stent	11	4 (36.4*)	NA
		At stent removal		11	3 (27.3*)	
		NR		11	7 (63.6*)	
	Dislocation to the stomach	NR		11	0	
	Pulmonary infection or pneumonia	NR		11	3 (27)	
	Acute renal failure	NR		11	3 (27)	
	Stent associated ulceration	NR		11	2 (18.2)	

Study	Outcome definition and measure	Time point of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
(Pfisterer et al. 2019)	Stent dislocation	NR	Danis stent	34	13 (38.2)	NA
	Ulcers/necrosis of the oesophageal mucosa	NR		34	4 (11.8)	
(Wright et al. 2010)	Failed deployment caused by failure of gastric balloon to inflate	At insertion	Danis stent	10	1 (10)	NA
	Stent migration	NR		10	0	
	Major complications associated with stent removal	NR		10	0	
	Ulceration in the oesophagus related to the proximal end of the stent	NR		10	1 (10*)	
(Zakaria et al. 2013)	Unsuccessful deployment	Implantation	Danis stent	16	1 (6.3*)	NA
	Technical error during stenting: bending of the guide wire	Implantation		16	1 (6.3*)	
	Technical error during stenting: slipped in the stomach immediately after deployment	Implantation		16	1 (6.3*)	
	Technical error during stenting: Malfunction of the delivery system causing rupture of the gastric balloon	Implantation		16	1 (6.3*)	

Study	Outcome definition and measure	Time point of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
	AE following stenting: Chest pain	NR		16	1 (6.25)	
	AE following stenting: Hiccups	NR		16	2 (12.5)	
	AE following stenting: Fever	NR		16	0	
	AE following stenting: Dysphagia	NR		16	1 (6.25)	
	AE following stenting: Reflux symptoms	NR		16	0	
	Deep ulcer at extraction	NR		16	1 (6.25)	
	Stent migration	NR		16	6 (37.5)	
	Stent migration: total migration	NR		16	3 (18.75)	
	Stent migration: partial migration	NR		16	2 (12.5)	
	Stent migration: partial migration proximally	NR		16	1 (6.25)	
(Zehetner et al. 2008)	Complications in stent placement	NR	Danis stent	34	0	NA
	Local complications: aggravation	NR		34	0	
	Local complications: bleeding	NR		34	0	
	Local complications: perforation	NR		34	0	

Study	Outcome definition and measure	Time point of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
	Local complications: penetration of stent into mediastinum	NR		34	0	
	Stent migration to stomach	NR		34	7 (20.6*)	
	Ulceration at the distal end of the stent location on stent extraction	NR		34	1 (2.9*)	
	Injury of varices	NR		34	0	
	Mucosal lesions	NR		34	0	
	Injury of the throat	NR		34	0	

Appendix D

EconLit (ProQuest)

Search date: 07/05/2020

Limited to year=2020

Retrieved records: 0

Search term	Results
TI(danis OR danisc OR danisr OR danistm) OR AB(danis OR danisc OR danisr OR danistm) OR TI(sx-ella* OR sxella* OR ella-cs* OR ellacs* OR cs-ella* OR csella*) OR AB(sx-ella* OR sxella* OR ella-cs OR ellacs* OR cs-ella OR csella*)	0
(variceal* OR varices OR varix* OR varicose* OR varicosis) NEAR/4 (bleed* OR rebleed* OR ruptur* OR haemorrhag* OR hemorrage* OR h?ematoches*)	0
(variceal* OR varices OR varix* OR varicose* OR varicosis) NEAR/5 (esophag* OR oesophag* OR gastrointestinal OR gastro-intestinal OR GI OR gastric)	0
(esophag* OR oesophag* OR gastrointestinal OR gastro-intestinal OR GI OR gastric OR refractory) NEAR/5 VB	0
(stent OR stents OR stenting OR stented)	0
mainsubject((sem OR sems))	0

Ovid MEDLINE(R) ALL

Search date: 07/05/2020

Retrieved records: 0

ID	Search term	Results
1	Economics/	27177
2	"costs and cost analysis"/	48459
3	Cost allocation/	2004
4	Cost-benefit analysis/	80323
5	Cost control/	21474
6	Cost savings/	11749
7	Cost of illness/	26845

8	Cost sharing/	2498
9	"deductibles and coinsurance"/	1746
10	Medical savings accounts/	534
11	Health care costs/	39072
12	Direct service costs/	1189
13	Drug costs/	15942
14	Employer health costs/	1090
15	Hospital costs/	10955
16	Health expenditures/	20041

17	Capital expenditures/	1989
18	Value of life/	5697
19	exp economics, hospital/	24407
20	exp economics, medical/	14182
21	Economics, nursing/	3997
22	Economics, pharmaceutical/	2927
23	exp "fees and charges"/	30209
24	exp budgets/	13670

25	(low adj cost).mp.	57201
26	(high adj cost).mp.	14435
27	(health?care adj cost$).mp.	11473
28	(fiscal or funding or financial or finance).tw.	144462
29	(cost adj estimate$).mp.	2256
30	(cost adj variable).mp.	45
31	(unit adj cost$).mp.	2488
32	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	296283
33	or/1-32	722353

34	(danis or danisc or danisr or danistm).ti,ab,kf.	118
35	(sx-ella$ or sxella$ or ella-cs$ or ellacs$ or cs-ella$ or csella$).ti,ab,kf,in.	32
36	34 or 35	140
37	"Esophageal and Gastric Varices"/	13120
38	Gastrointestinal Hemorrhage/	41572
39	((variceal$ or varices or varix$ or varicose$ or varicosis) adj5 (bleed$ or rebleed$ or ruptur$ or h?emorrhag$ or h?ematochez$ or h?ematoches$)).ti,ab,kf.	10708
40	((variceal$ or varices or varix$ or varicose$ or varicosis) adj5 (esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric)).ti,ab,kf.	11680
41	((esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric) adj5 (bleed$ or rebleed$ or h?emorrhag$ or h?ematochez$ or h?ematoches$)).ti,ab,kf.	38726

42	((esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric or refractory) adj5 VB).ti,ab,kf.	12
43	or/37-42	68240
44	stents/ or self expandable metallic stents/	67047
45	(stent or stents or stenting or stented).ti,ab,kf.	99716
46	(sem or sems).ti,ab,kf.	107958
47	or/44-46	219169
48	43 and 47	1598
49	36 or 48	1727

50	exp animals/ not humans/	4696506
51	(news or editorial or case reports).pt. or case report.ti.	2863295
52	49 not (50 or 51)	1185
53	33 and 52	16
54	limit 53 to yr="2020"	0

Embase

Search date: 07/05/2020

Retrieved records: 0

ID	Search strategy	Results
1	(danis or danisc or danisr or danistm).ti,ab,kw,dj,dv,my,mv.	171

2	(sx-ella$ or sxella$ or ella-cs$ or ellacs$ or cs-ella$ or csella$).ti,ab,kw,in,dj,dm,my,mv.	231
3	1 or 2	361
4	esophagus varices/ or esophagus varices bleeding/ or esophagus hemorrhage/	20275
5	((variceal$ or varices or varix$ or varicose$ or varicosis) adj5 (bleed$ or rebleed$ or ruptur$ or h?emorrhag$ or h?ematochez$ or h?ematoches$)).ti,ab,kw,dj.	16618
6	((variceal$ or varices or varix$ or varicose$ or varicosis) adj5 (esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric)).ti,ab,kw,dj.	17377
7	((esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric) adj5 (bleed$ or rebleed$ or h?emorrhag$ or h?ematochez$ or h?ematoches$)).ti,ab,kw,dj.	58318
8	((esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric or refractory) adj5 VB).ti,ab,kw,dj.	26
9	or/4-8	77921

10	self expandable metallic stent/ or self expanding stent/	7015
11	digestive stent/ or esophageal stent/ or stent/	90291
12	(stent or stents or stenting or stented).ti,ab,kw,dj.	168389
13	(sem or sems).ti,ab,kw,dj.	134328
14	or/10-13	313342
15	9 and 14	3203
16	3 or 15	3490
17	(animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/	6008500
18	editorial.pt. or case report.ti.	939106

19	16 not (17 or 18)	3286
20	Socioeconomics/	138082
21	Cost benefit analysis/	83974
22	Cost effectiveness analysis/	149836
23	Cost of illness/	19052
24	Cost control/	67786
25	Economic aspect/	111850
26	Financial management/	112396

27	Health care cost/	187660
28	Health care financing/	13232
29	Health economics/	32620
30	Hospital cost/	21232
31	(fiscal or financial or finance or funding).tw.	194254
32	Cost minimization analysis/	3478
33	(cost adj estimate$).mp.	3374
34	(cost adj variable$).mp.	260
35	(unit adj cost$).mp.	4446

36	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	913006
37	19 and 36	67
38	limit 76 to yr="2020"	0

Appendix E

Total costs for the technology in the model (Option 2: Micro costing for technology in model)

Description	Cost	Note	Source
Cost of stent	£1,495	Cost ex-VAT	NICE Medtech innovation briefing (National Institute for Health and Care Excellence 2019)
Procedure costing:			
Procedure setting cost – theatre setting	£16.73	Per minute cost. Assumed to include cost of staff and consumables	ISD Scotland (2019) theatre services – gastroenterology surgery (ISD Scotland 2019)
Procedure setting cost – non-theatre setting	£3.35	Setting cost assumed to be included within overheads from staff costs. Cost of gastroenterologist and nurse practitioner included.	Cost of hospital based consultant (medical or surgical) and band 5 hospital based nurse (per hour of patient contact) from PSSRU 2019 (Personal Social Services Research Unit 2019b)
Total procedure cost -theatre setting	£501.90	Per minute cost multiplied by 30 minutes	Clinical experts estimated procedure time to range from 5 minutes to 30
Total procedure cost – non-theatre setting	£100.50	Per minute cost multiplied by 30 minutes	Clinical experts estimated procedure time to range from 5 minutes to 30
Total cost of x-ray (applied to both settings)	£62.00	Unit cost: £31.00 Number: 2	Direct access plain film. National NHS cost collection (2018/19) (NHS Improvement 2019) Number required based on Escorsell et al. (2016)
Total cost of vasoactive drugs (applied to both settings	£1,396.08	Cost per mg: £19.39 (1mg/8.5ml solution for injection ampoules - £96,95 for pack of 5) BNF (British National Formulary) Dose per day: 12 (based on Escorsell et al. (2016) – 2mg/4hours No. of days: 6 (based on Escorsell et al. (2016))	
Total cost of general ward stay (applied to both settings)	£2,170	No. of days: 6.4 Cost per day: £341	Cost based on NHS reference costs (NHS Improvement 2019). Number based on Escorsell et al. (2016) and NHS reference costs (2017/18) (NHS Improvement 2019) – see section on ‘procedure cost’

Total cost of ICU stay – theatre setting cost	£4,883.02	No. of days: 3.6 Cost per day: £1,343	Cost based on NHS reference costs, weighted average cost by activity of surgical adult ICU bed day with 1 to 3 organs supported [XC04Z-06Z] assuming liver and kidney may require support (NHS Improvement 2019). Number based on Escorsell et al. 2016 and NHS reference costs (2017/18) (NHS Improvement 2019) – see section on 'procedure cost' (Escorsell et al. 2016)
Total cost of ICU stay – non-theatre setting	£4,427.71	No. of days: 1 Cost per day: £1,343	Cost based on NHS reference costs, weighted average cost by activity of surgical adult ICU bed day with 1 to 3 organs supported [XC04Z-06Z] assuming liver and kidney may require support (NHS Improvement 2019). Number assumed based on clinical expert opinion.
Proportion of patients undergoing procedure in a theatre setting	67%		Clinical expert opinion
Grand total cost for stent insertion procedure	**£9,194.14**		Calculation

Appendix F

Deterministic sensitivity analysis results

The tornado diagrams show the top 15 key drivers of uncertainty in the model by incremental cost per patient and by cost per death avoided. Analysis is presented for the company base case, scenario 1 and 2. The company also submitted tornado diagrams for cost per death avoided, these are not reported here. EAC analysis is presented for base case and scenario 2. The EAC was unable to run sensitivity analysis for scenario 1 with the company's model.

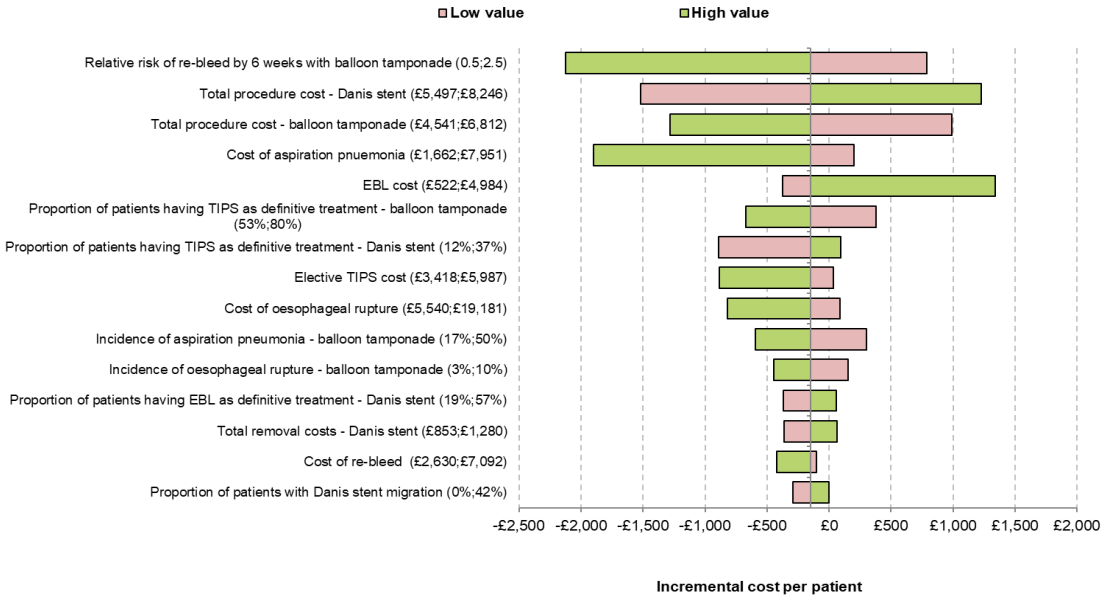


Figure 9a Tornado diagram **company** base case – incremental cost per patient outcome

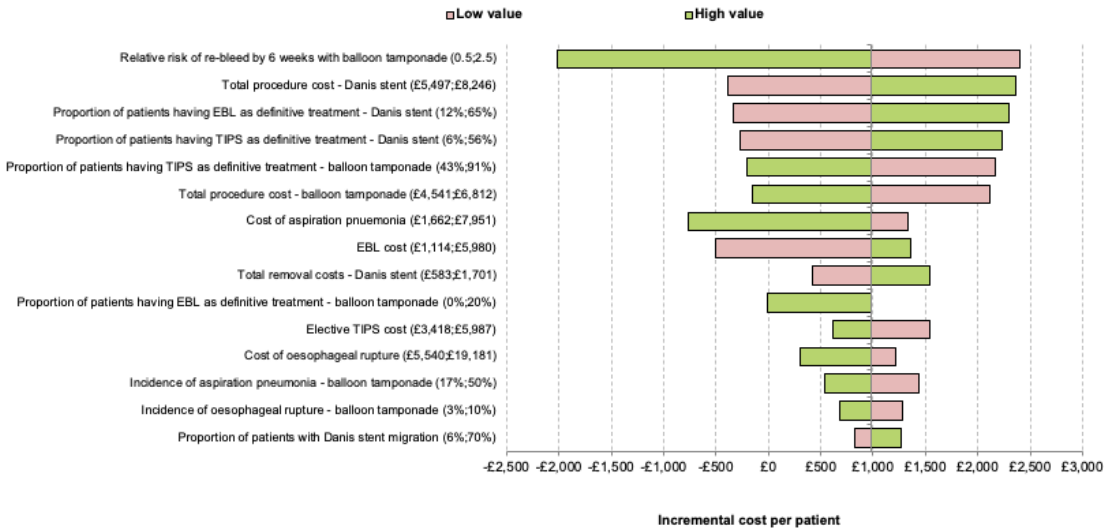


Figure 9b Tornado diagram **EAC** base case – incremental cost per patient outcome

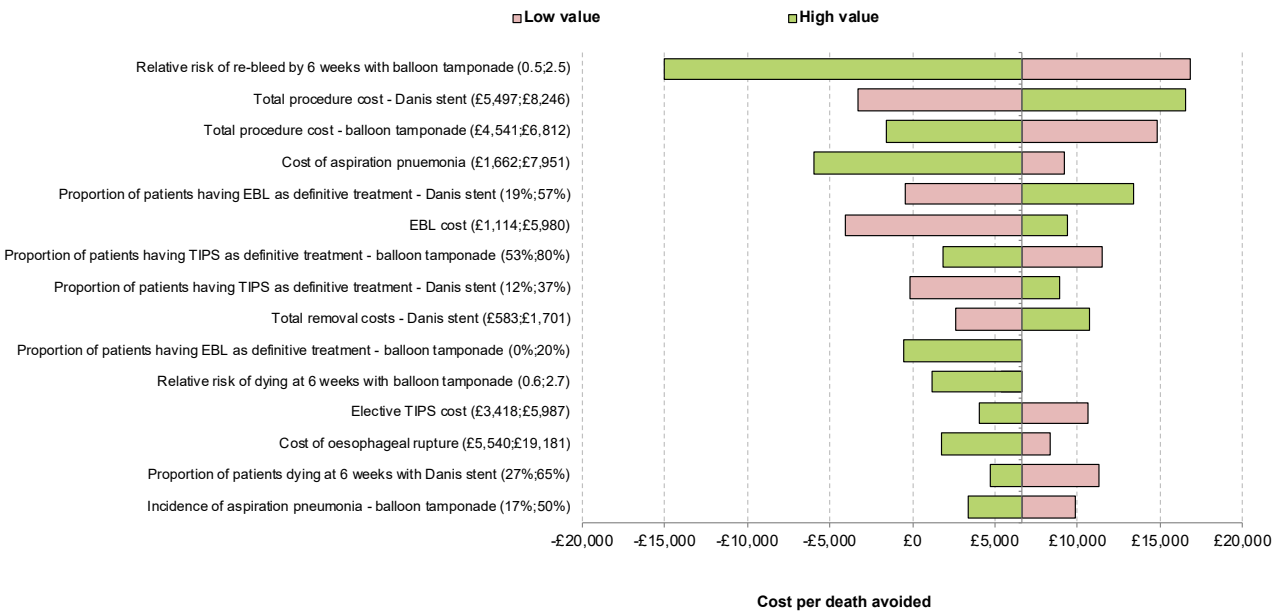


Figure 10 Tornado diagram **EAC** base case– cost per death avoided outcome

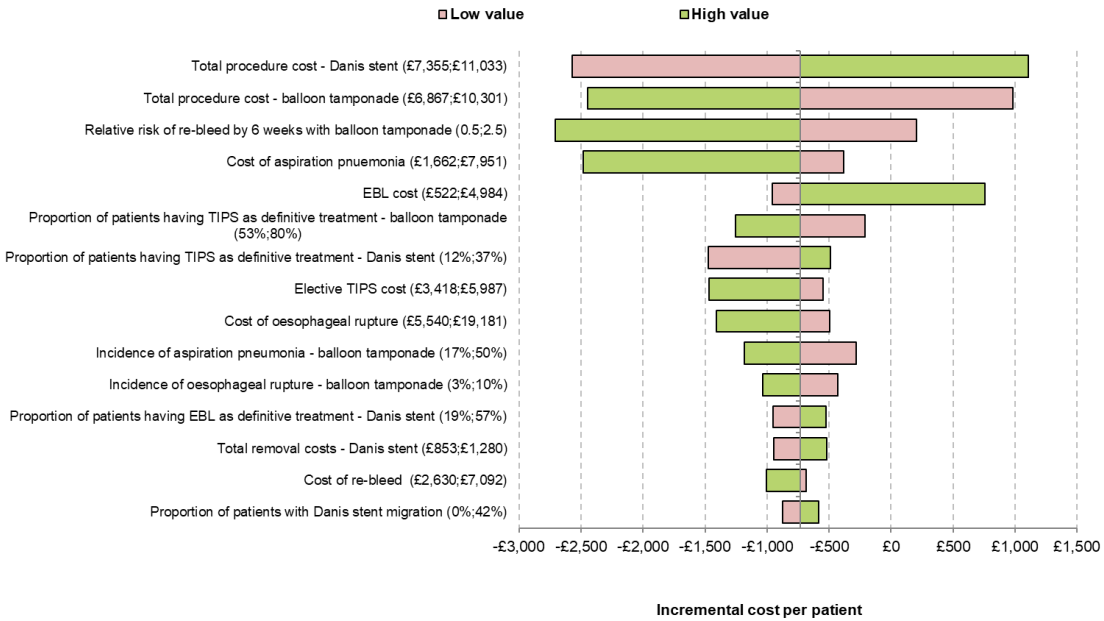


Figure 11 Tornado diagram **company** scenario 1 – incremental cost per patient

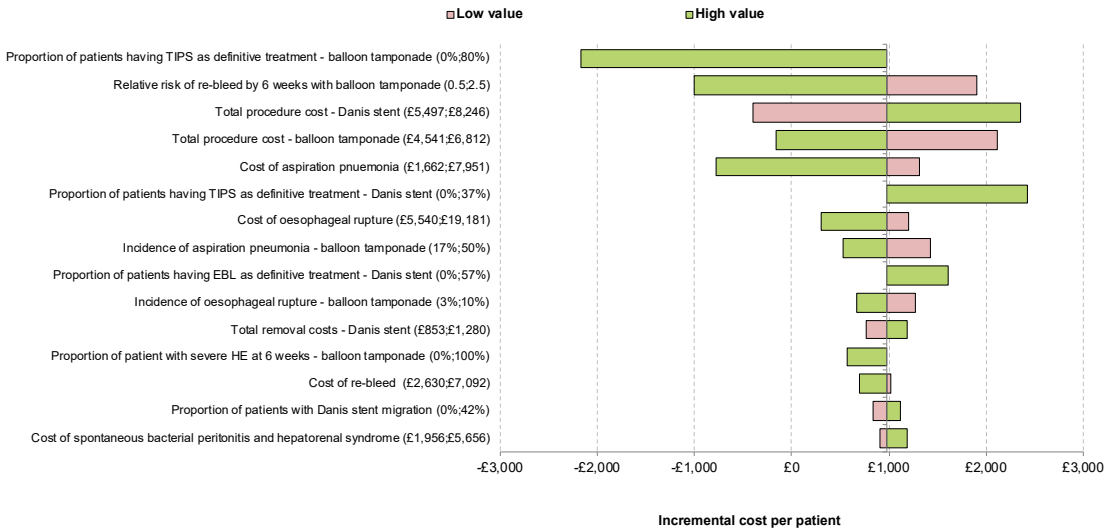


Figure 12a Tornado diagram **company** scenario 2 – incremental cost per patient

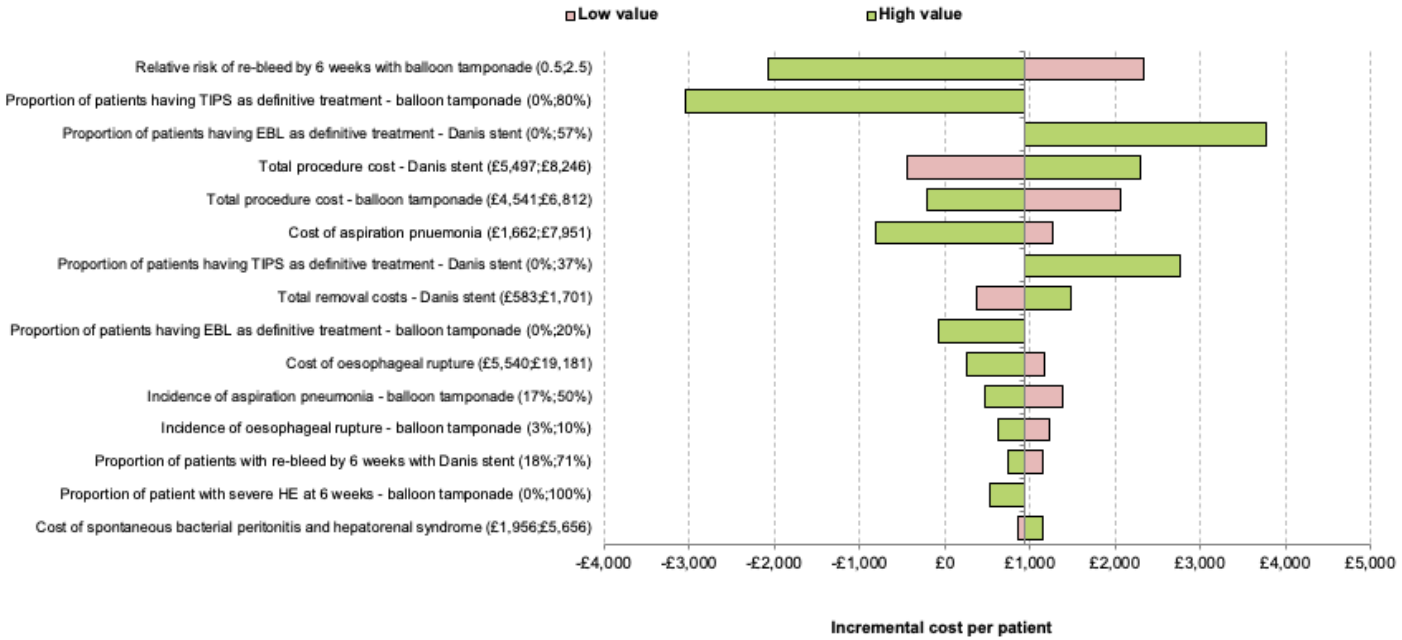


Figure 12b Tornado diagram **EAC** scenario 2 – incremental cost per patient

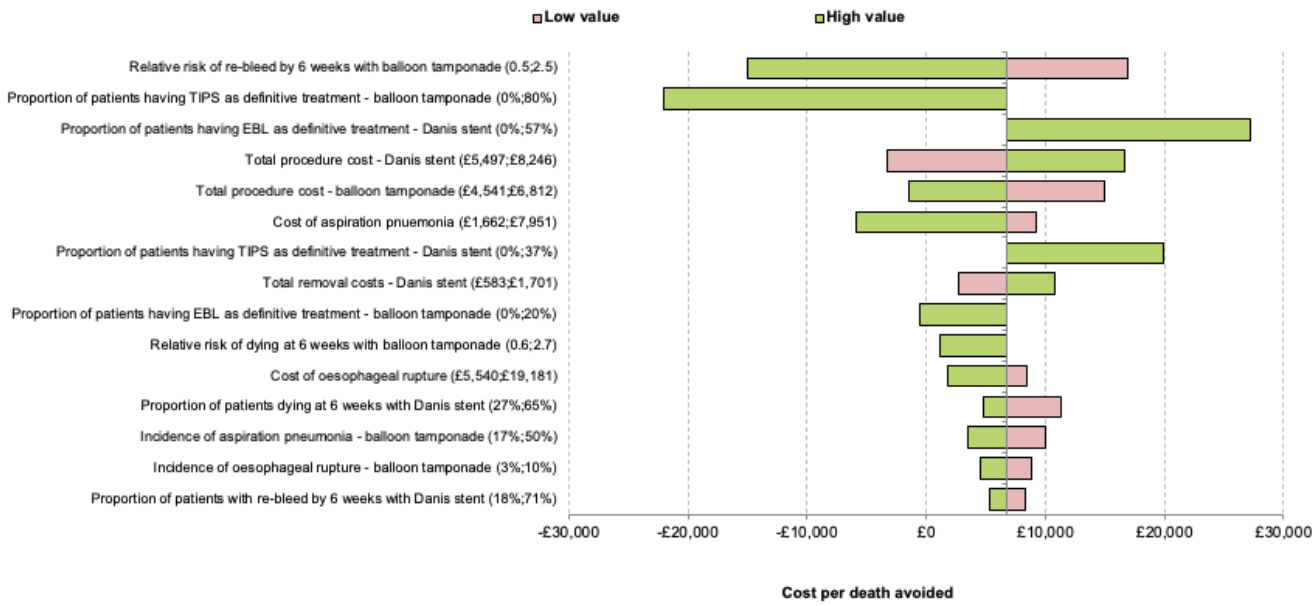


Figure 13 Tornado diagram **EAC** scenario 2 – cost per death avoided

Two-way sensitivity analysis

Company results for the two-way sensitivity analysis exploring the interaction between training costs per procedure for Danis stent insertion and the incidence of stent migration requiring intervention is shown in table 14. This indicates that in the company base case if occurrence of stent migration remains at 40% or below, where training costs are high (e.g. more training is needed), Danis stent would remain cost saving.

Table 14: two way sensitivity analysis provided by company

	Stent migration										
Training cost per procedure	-£146.71	0%	5%	10%	15%	20%	25%	30%	35%	40%	45%
	£0	-£355	-£320	-£285	-£250	-£215	-£181	-£146	-£111	-£76	-£41
	£10	-£345	-£310	-£275	-£240	-£205	-£171	-£136	-£101	-£66	-£31
	£20	-£335	-£300	-£265	-£230	-£195	-£161	-£126	-£91	-£56	-£21
	£30	-£325	-£290	-£255	-£220	-£185	-£151	-£116	-£81	-£46	-£11
	£40	-£315	-£280	-£245	-£210	-£175	-£141	-£106	-£71	-£36	-£1
	£50	-£305	-£270	-£235	-£200	-£165	-£131	-£96	-£61	-£26	£9
	£60	-£295	-£260	-£225	-£190	-£155	-£121	-£86	-£51	-£16	£19
	£70	-£285	-£250	-£215	-£180	-£145	-£111	-£76	-£41	-£6	£29
	£80	-£275	-£240	-£205	-£170	-£135	-£101	-£66	-£31	£4	£39

Probabilistic sensitivity analysis results.

The company's probabilistic sensitivity results for incremental cost per patient are shown in figure 14 for the base case, figure 15 for scenario 1 and figure 16 for scenario 2. EAC results for the base case are presented in figure 14a.

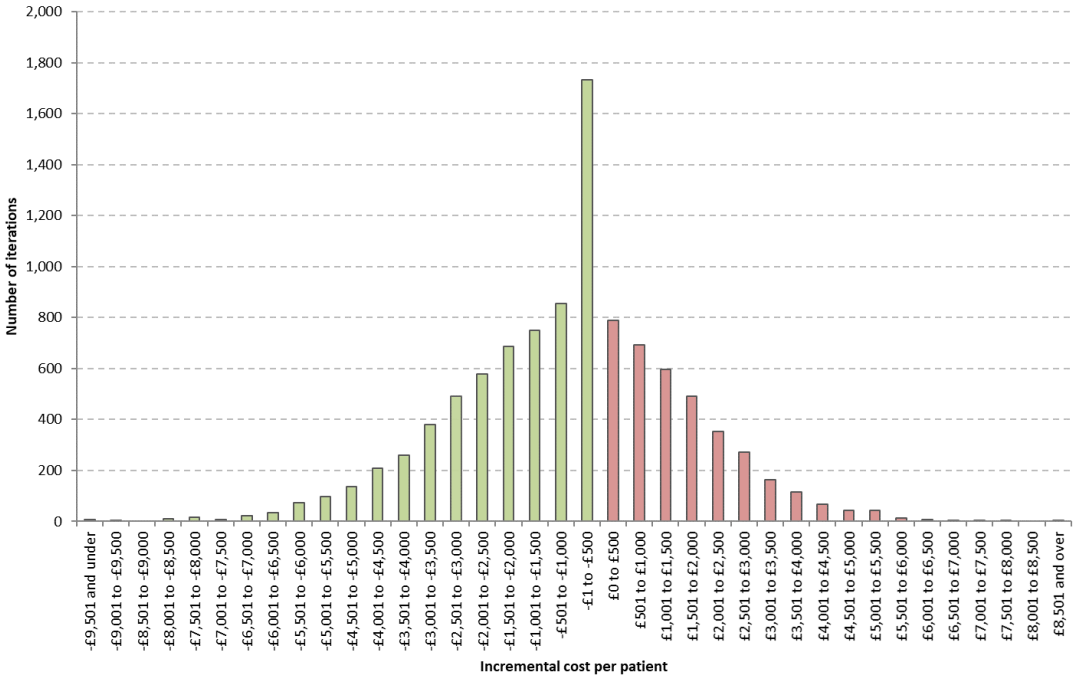


Figure 14a **company** base case

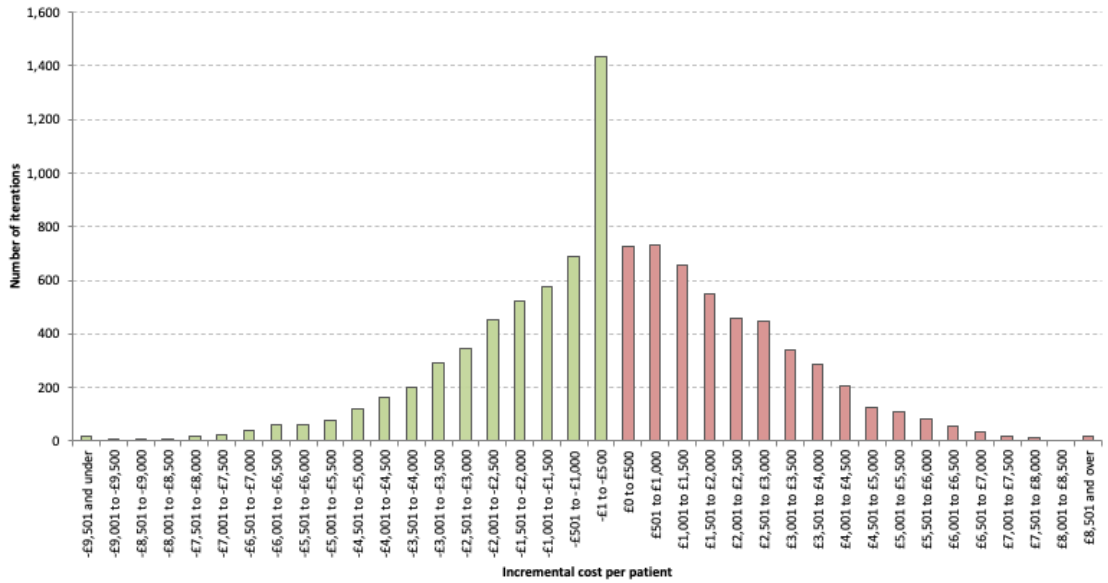


Figure 14b **EAC** base case

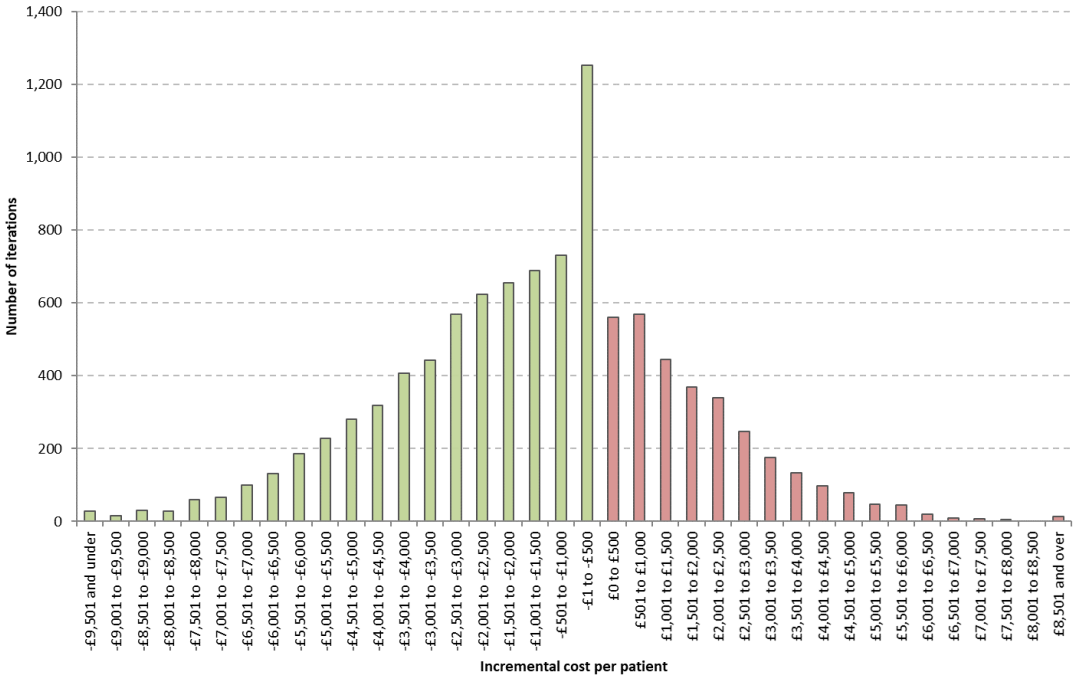


Figure 15 company scenario 1

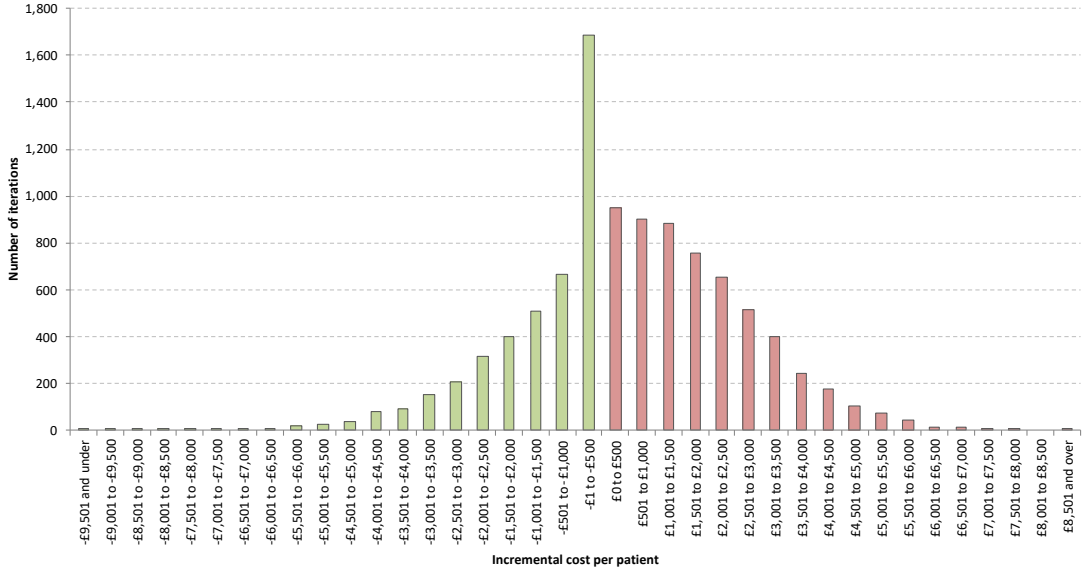


Figure 16 company scenario 2

Variables used in economic model sensitivity analyses

Table reports variables used in sensitivity analysis. Annotation highlights where EAC deterministic range and probabilistic parameter values differ to company submission.

Parameter	Base case value	Deterministic range	Probabilistic parameters
Relative risk of patients dying at 6 weeks with balloon tamponade compared with Danis stent	1.3	0.63 to 2.67 Confidence interval calculated from Escorsell et al. (2016)	0.63 to 2.67 Lognormal distribution Confidence interval calculated from Escorsell et al. (2016)
Proportion of patients dying at 6 weeks with Danis stent	46%	27% to 65% Based on range reported across studies	Alpha 6 Beta 7 Beta distribution Based on Escorsell et al. (2016)
Relative risk of re-bleeding during 6 weeks with balloon tamponade compared with Danis stent	1.2	0.54 to 2.46 Confidence interval calculated from Escorsell et al. (2016)	0.54 to 2.46 Lognormal distribution Confidence interval calculated from Escorsell et al. (2016)

Parameter	Base case value	Deterministic range	Probabilistic parameters
Proportion of patients experiencing re-bleed within 6 weeks with Danis stent	46%	18% to 71% Based on range reported across studies	Alpha 6 Beta 7 Beta distribution Based on Escorsell et al. (2016)
Proportion of patients with cardiorespiratory arrest	Danis - 7.7% Balloon Tamponade (BT) – 6.7%	Danis – 4% to 12% BT – 3% to 10% Assumed range based on +/-50%	Danis Alpha 1 Beta 12 BT Alpha 1 Beta 14 Both Beta distribution based on Escorsell et al. (2016)
Proportion of patients with aspiration pneumonia	Danis – 0.0% BT - 33.3%	BT – 17% to 50% based on +/- 50% Assumed not applicable for Danis stent so not varied	Danis Alpha 0 Beta 13

Parameter	Base case value	Deterministic range	Probabilistic parameters
			BT Alpha 5 Beta 10 Both Beta distribution based on Escorsell et al. (2016)
Proportion of patients with oesophageal rupture	Danis – 0.0% BT – 6.7%	BT – 3% to 10% based on +/- 50% Assumed not applicable for Danis stent so not varied	Danis Alpha 0 Beta 13 BT Alpha 1 Beta 14 Both Beta distribution based on Escorsell et al. (2016)
Proportion of patients with spontaneous bacterial peritonitis and	Danis – 7.7% BT – 0.0%	Danis – 4% to 12% BT – 0% to 5% Assumed range	Danis Alpha 1 Beta 12

Parameter	Base case value	Deterministic range	Probabilistic parameters
hepatorenal syndrome			BT Alpha 0 Beta 15 Both Beta distribution based on Escorsell et al. (2016)
Proportion of patients with severe hepatic encephalopathy within 6 week period	Danis – 38% BT – 73%	Danis 19% to 58% BT 37% to 100% Assumed range based on +/- 50%	Danis Alpha 5 Beta 8 BT Alpha 11 Beta 4 Both Beta distribution based on Escorsell et al. (2016)
Proportion of patients undergoing band ligation (EBL)	Danis – 38% BT – 0%	Company values: Danis 19% to 57% based on range reported across studies	Danis Alpha 5 Beta 8

Parameter	Base case value	Deterministic range	Probabilistic parameters
		BT 0% to 20% assumed range EAC values: Danis 12% to 65% based on approximate standard error of 14% derived from Escorsell et al (2016) BT accept range.	BT – adjusted to allow for variation Alpha 0.5 Beta 14.5 Both Beta distribution based on Escorsell et al. (2016)
Proportion of the patients undergoing TIPS	Danis – 31% BT – 67%	Company values: Danis 12% to 37% lowest value reported across studies, higher value +20% for Escorsell et al. (highest value reported in studies) BT 53% to 80% assumed range +/- 20% **EAC values:** **Danis 6% to 56% based on**	Danis Alpha 4 Beta 9 BT Alpha 10 Beta 5 Both Beta distribution based on Escorsell et al. (2016)

Parameter	Base case value	Deterministic range	Probabilistic parameters
		approximate standard error of 13% derived from Escorsell et al (2016) **BT 42% to 92% based on approximate standard error of 12% derived from Escorsell et al (2016)**	
Proportion of patients with stent migration with Danis stent	Company value: 20%	Company value: 0% to 42% based on range reported across studies	Company value: Alpha 17 Beta 66 Beta distribution Combination of figures reported across studies as discussed in 'stent migration' section of 'Resource use'.

Parameter	Base case value	Deterministic range	Probabilistic parameters
Total procedure cost (including costs of devices)	Danis - £6,872 BT - £5,677	Danis £5,497 to £8,246 assumed range based on +/- 20% BT £4,541 to £6,812 assumed range based on +/- 20%	Danis Standard error £1,374 BT Standard error £1,135 Both gamma distribution and assumed based on 20% of mean
Cost of re-bleeding	Company value £3,287 **EAC value:** **£4,978.75**	Company value: £2,630 to £7,092 Lower value assumed based on -20%. Upper value based on NICE resource impact report (National Institute for Health and Care Excellence 2016) **EAC value:** **£3,286.99-£7,091.86** **Based on range uplifted from NICE**	Company value: Standard error £1,644 Gamma distribution Assumed based on 50% of mean **EAC value:** **Standard error £2489.37** **Gamma distribution** **Based on 50% of the point estimate.**

Parameter	Base case value	Deterministic range	Probabilistic parameters
		resource impact report 2016	
Cost of stent migration	£699	Company value: £559 to £839 assumed range based on +/- 20% **EAC value:** **£599-£1394** **Lower value accepted company range. Upper value based on Ella extractor used for stent migration procedures**	Company value: Standard error £140 Gamma distribution Assumed based on 20% of mean **EAC value:** **Standard error £139.80 based on 20% of point estimate.**
Cost of cardiorespiratory arrest	£2,913	£1,715 to £3,527 Based on low and high value reported in NHS reference costs 2018/19 (NHS Improvement 2019).	Standard error £583 Gamma distribution Assumed based on 20% of mean

Parameter	Base case value	Deterministic range	Probabilistic parameters
		EB05A to C NEL Cardiac arrest with CC score 0-4 and 9+	
Cost of aspiration pneumonia	£2,702	£1,622 to £7,951 Based on low and high value reported in NHS reference costs 2018/19 (NHS Improvement 2019). DZ11K to V NEL Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 0-3 and 14+	Standard error £1,351 Gamma distribution Assumed based on 50% of mean
Cost of oesophageal rupture	£9,054	Company value: £5,540 to £19,181 Based on low and high value reported in NHS reference costs 2018/19 (NHS Improvement 2019). FF01A - FF02C, FF04A - FF04D NEL; very	Company value: Standard error £4,527 Gamma distribution Assumed based on 50% of mean

Parameter	Base case value	Deterministic range	Probabilistic parameters
		complex to major oesophageal, stomach or duodenum procedures, 19 years and over with various CC scores	
Cost of spontaneous bacterial peritonitis and hepatorenal syndrome	£2,834	£1,956 to £5,656 Based on low and high value reported in NHS reference costs 2018/19 (NHS Improvement 2019). LA07H to P NEL Acute Kidney Injury without Interventions, with CC Score 0-3 and 11+	Standard error £1,417 Gamma distribution Assumed based on 50% of mean
Cost of severe hepatic encephalopathy	£401	£200 to £601 Assumed range based on +/- 20%	Standard error £80 Gamma distribution Assumed based on 20% of mean
Cost of stent removal (mean	Company value:	Company value: £583 to £1,551	Company value: Standard error £213

Parameter	Base case value	Deterministic range	Probabilistic parameters
per patient in model)	£1,066 **EAC value:** **£1,141.35**	Lower and upper based on everyone using Ella extractor and no one using Ella extractor for removal **EAC value:** **£582.89-£1,700.93** **Lower and upper based on everyone surviving to day 7 (77%) using Ella extractor and no one (0%) using Ella extractor for removal. The unbundled price is applied to the upper range to provide a maximum plausible cost.**	Gamma distribution Assumed based on 20% of mean **EAC value:** **Standard error: £228.27** **Gamma distribution** **Assumed based on 20% of mean**
Cost of balloon removal	£3	£0 to £4 Assumed range	Standard error £2 Gamma distribution

Parameter	Base case value	Deterministic range	Probabilistic parameters
			Assumed based on 50% of mean
Cost of EBL	Company value: £1,114 **EAC value:** **£4,983.67**	Company value: £522 to £4,984 Lower value based on NICE resource impact report for one ligation procedure (National Institute for Health and Care Excellence 2016) Higher value based on highest value reported from NHS reference costs 2018/19 Elective (NHS Improvement 2019). FE11A Endoscopic, Sclerotherapy or Rubber Band Ligation, of Lesion of Upper Gastrointestinal Tract, with CC Score 9+ **EAC value:**	Company value: Standard error £557 Gamma distribution Assumed based on 50% of mean **EAC value: Standard error £2,491.83** **Gamma distribution** **Assumed based on 50% of mean**

Parameter	Base case value	Deterministic range	Probabilistic parameters
		£1,113.53-£5,980.40 **Based on lowest value from NHS ref costs 2018/19 across Total HRGs and Elective HRG tariffs considering all complication (CC) scores (FE11A-D). Highest value +20% of parameter estimate.**	
Cost of TIPS	Company value: £3,928 **EAC value:** **£4,965.56**	Company value: £3,418 to £5,987 Based on high and low values from NHS reference costs 2018/19 (NHS Improvement 2019). Low value elective cost for YR16B Transjugular Intrahepatic Creation of Portosystemic	Company value: Standard error £786 Gamma distribution Assumed based on 20% of mean **EAC value:** **Standard error: £993.11** **Gamma distribution**

Parameter	Base case value	Deterministic range	Probabilistic parameters
		Shunt with CC Score 0-5. High value total HRG cost for YR16A Transjugular Intrahepatic Creation of Portosystemic Shunt with CC Score 6+ **EAC value:** **£3,418-£5,987** **Based on highest and lowest value from NHS ref costs 20/18/19 for across Total HRGs and Elective HRG tariffs considering all complication (CC) scores (YR16A-B)**	**Assumed based on 20% of mean**

Parameter	Base case value	Deterministic range	Probabilistic parameters
Training costs for Danis stent per procedure	£65	Company values:£5 to £90 Low value based on assuming half an hour of training per year and 10 procedures per year – lower estimates provided by experts High value based on assuming 4 hours training per year and only 2 procedures per year – higher values provided by experts **EAC values:** **£5.45-£87.20** **Low value based on assuming half an hour of training per year and 10 procedures per year – lower estimates provided by experts**	Standard error £65 Gamma distribution Assumed based on 50% of mean **EAC value:** **Standard error £32.70** **Gamma distribution** **Assumed based on 50% of mean**

Parameter	Base case value	Deterministic range	Probabilistic parameters
		in company submission High value based on assuming 4 hours training per year and only 5 procedures per year – higher values provided by experts in company submission	

Table 10 Resource Costs in Company Scenario Analysis

Results, cost per patient		**Mean cost per patient using Danis stent (£)**	**Mean cost per patient using balloon tamponade (£)**	**Difference in cost per patient (£)***
Base case	Company	£11,897	£12,044	-£147
	EAC	**£14,560**	**£13,638**	**£923**
Scenario 1 – microcosting of each treatment procedure	Company	£14,219	£14,951	-£732
	EAC	**£16,883**	**£16,545**	**£338**
Scenario 2 - Definitive treatments not considered relevant to bridging treatment, and removal of HE cost	Company	£10,181	£9,131	£1,050
	EAC	**£10,962**	**£10,034**	**£928**
Scenario 3 - Definitive treatments not considered relevant. HE costs included and assumed that all associated with bridging treatment.	EAC	**£11,116**	**£10,327**	**£788**

Scenario 4 (*builds on scenario 2 model*) – additional endoscopy for all who require balloon tamponade removal/survive 24 hours, definitive treatments not considered relevant to bridging treatment, and removal of HE cost.**	EAC	**£10,962**	**£10,547**	**£414**
Scenario 5 *(new builds on scenario 1)* – microcosting of each treatment procedure (includes reduced ICU bed days with Danis Stent) with additional endoscopy for all who require balloon tamponade removal/survi	EAC	**£13,284**	**£13,455**	**-£171**

ve 24 hours, definitive treatments not considered relevant to bridging treatment, and removal of HE cost ***				
	* Negative values indicate a cost saving.			

Table 11 Cost per Death Avoided

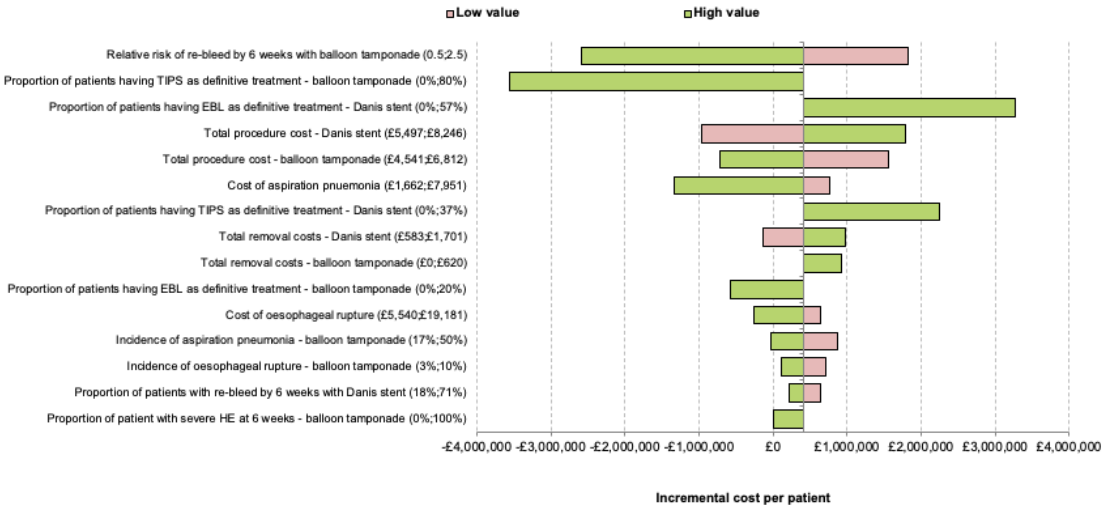
Results, cost per death avoided		**Cost per death avoided**
Base case	Company	Dominant -£1,059.59
	EAC	**£6,663.72**
Scenario 1 – microcosting of each treatment procedure	Company	Dominant -£5,284.04
	EAC	**£2,439.28**
Scenario 2 - Definitive treatments not considered relevant to bridging treatment, and removal of HE cost	Company	£7,038.37
	EAC	**£6,702.84**
Scenario 3 - Definitive treatments not considered relevant. HE costs included and assumed that all associated with bridging treatment	EAC	**£5,694.03**
Scenario 4 (*builds on scenario 2 model*) – additional endoscopy for all who require balloon tamponade removal/survive 24 hours,	EAC	**£2,991.31**

definitive treatments not considered relevant to bridging treatment, and removal of HE cost.**		
Scenario 5 *(new builds on scenario 1)* – microcosting of each treatment procedure (includes reduced ICU bed days with Danis Stent) with additional endoscopy for all who require balloon tamponade removal/survive 24 hours, definitive treatments not considered relevant to bridging treatment, and removal of HE cost ***	EAC	**Dominant** **-£1,232.13**

**scenario 4 is equivalent to scenario 2 but add an additional removal of balloon tamponade procedure cost of £699 (source: FE20Z Therapeutic endoscopic upper gastrointestinal tract procedure NHS reference costs 2018/19) is applied for all those who survive 24 hrs/receive balloon removal. Increases average per person removal cost to £517.

Deterministic ranges = £0 - £620 (no one receives endoscopy, £0 removal costs) and (all who undergo a removal, also undergo endoscopy £517+20%)

Scenario 4 tornado diagram:



The parameters where deterministic ranges alter the direction of results are: risk of rebleed, proportion receiving definitive treatments, procedure costs, cost of aspiration pneumonia, stent removal costs, cost of oesophageal rupture, incidence of aspiration pneumonia.

*** scenario 5 builds on microcosting scenario 1, adds additional endoscopy (as described in 4) and removes definitive treatment and HE costs.

EAC unable to run sensitivity analysis using the scenario 1 company model.

12.10.20 requests

Table 12 Break even analysis for cost of device

Scenario	**Cost of device that will result in difference in cost per patient of £0**
EAC Base case	£572.33
EAC Scenario 1 – microcosting of each treatment procedure	£1,157.25
EAC Scenario 2 - Definitive treatments not considered relevant to bridging treatment, and removal of HE cost	£567.91
Scenario 3 - Definitive treatments not considered relevant. HE costs included and assumed that all associated with bridging treatment.	£707.60
Scenario 4 (*builds on scenario 2 model*) – additional endoscopy for all who require balloon tamponade removal/survive 24 hours, definitive treatments not considered relevant to bridging treatment, and removal of HE cost.**	**£1,080.68**

Scenario 5: further sensitivity analysis.

The micro costing is included to allow for variation in procedure costs for each treatment. In the Danis Stent arm it assumes that for a third (33%) of patients the stent is inserted outside of a theatre setting and results in 1 day in ICU (compared to 3.6 days for those receiving insertion in a theatre setting). The balloon tamponade comparator patients are all assumed to undergo procedure in a theatre setting and stay 3.6 days in ICU.

Danis Stent becomes cost incurring (£1 per patient difference in cost compared to balloon tamponade) if the proportion of patients receiving insertion in a theatre setting increases to 71%. Thus the proportion receiving in non-theatre setting reduces from 33% to 29%.

Similarly, Danis Stent becomes cost incurring (£1 per patient difference in cost) if the number of ICU days for those having non-theatre procedure increases from 1 day per patient to 1.4 days.

If the number of ICU bed days for non-theatre procedure patients increases from 1 to 2 days, Danis Stent has an incremental per patient cost of £277.

If all patients receive Danis Stent in a theatre setting the incremental cost is £1,143 per patient.

December 2020

MT450 Danis stent assessment report addendum

Background

Following the 16 October NICE committee meeting, it was identified that no scenario presented accurately reflected the clinical pathways in England. The key limitation being that parameters were largely drawn from a small Spanish trial, limiting generalizability (Escorsell et al (2016)). Scenario 5, which built on the company's procedure micro-costing, was considered for further development. The results of scenario 5 are set out in Table 1 for reference.

Table 1 - Scenario 5 results:

Results, cost per patient		**Mean cost per patient using Danis stent (£)**	**Mean cost per patient using balloon tamponade (£)**	**Difference in cost per patient (£)***
Scenario 5	EAC	**£13,284**	**£13,455**	**-£171**
	* Negative values indicate a cost saving.			

Results, cost per death avoided		**Cost per death avoided**
Scenario 5	EAC	**Dominant -£1,232.13**

On 17 November 2020 the EAC discussed the clinical pathway with three NICE expert advisors (Dr Deepak Joshi, Dr Claire Salmon, and Dr Dhiraj Tripathi) and updated the micro-costing parameters to more closely resemble current pathways. The new scenarios A and B build on scenario 5 and retain the following features from scenario 5:

- an additional endoscopy for all who require balloon tamponade removal/survive to 24 hours
- definitive treatments not considered relevant to bridging treatment and costs excluded
- severe hepatic encephalopathy costs are removed

Limitations of scenario 5 included the procedure setting for Danis Stent insertion and the length of Intensive Care Unit (ICU) stay for both bridging treatments. These have been updated as set out below. In addition, a number

of parameters are updated based on expert advice and Hospital Episode Statistics (HES) data analysed by the Newcastle EAC.

Mortality rates

For both scenarios mortality rates are inferred from Escorsell et al. The 6 week mortality rate has no bearing on costs but is used for the 'cost per death avoided result'. The 24 hour and 7 day mortality rate for balloon tamponade and Danis Stent, respectively, affect costs; the short term survivors incur removal and/or second procedure costs.

Table 2 - Mortality rates used in model

	Proportion dying at 6 weeks	**Survivors requiring removal and/or second procedure***	**Notes**
Danis Stent	46%	77%	Newcastle EAC analysis indicates 65.2% of patients identified in HES as receiving a bridging treatment between 1/4/2019-31/3/2020 were discharged alive. Although derived from a Spanish study with insufficient power, considering the HES analysis, the values used in the model are accepted by the EAC as reasonable. The reduced mortality rate in Danis Stent has some supporting evidence as set out in the primary EAC assessment.
Balloon Tamponade	60%	74%	

*For Danis stent this is the proportion who survive 7 days as stents were removed at 7 days in Escorsell et al. For Balloon Tamponade this is the proportion who survive 24 hours and therefore require balloon deflation and follow-up procedure in line with expert advice. Both values were extracted by the company from Kaplan Meier graphs in Escorsell et al 2016.

New scenario parameters

The following tables set out the changes made to scenario 5 to produce the two new scenarios. In scenario A the micro-costing is updated as set out in Table 3. In scenario B the same changes are included as per A, and transport costs are also included as set out in Table 4.

Table 3 - Scenario A parameter changes to micro-costing.

Parameter	Value	Note
Proportion of Danis Stent procedures undertaken in theatre	80%	This is an increase from the company micro-costing value (67%) and based on expert opinion that the majority of patients would receive in theatre.
Cost of Danis Stent procedures undertaken out of theatre	£128.00	In addition to the costs used by the company, 30 minute of anesthetist time is included. Expert opinion is that Danis Stent would not be inserted under conscious sedation.
No. of x-rays for Danis Stent patients	1	Reduced from company value (2). Expert opinion is that number of x-rays would not be greater in Danis Stent compared to Balloon Tamponade. In sensitivity analysis this was reduced to 0.5 (as expert opinion is that only half of patients may require x-ray).
Length of vasoactive drug treatment	3 days	Reduced from company value (6). Expert opinion is that number of days would not be greater in Danis Stent compared to BT. In

		sensitivity analysis, 6 days assumed for Balloon Tamponade as expert opinion is that Balloon Tamponade patients may require longer.
Danis Stent ICU length of stay (those in theatre and those out of theatre)	3.6 days	Expert opinion is that those receiving Danis Stent out of theatre would require the same length of ICU stay as those in theatre (company assumed out of theatre 1 day). In sensitivity analysis, a lower length of ICU stay (1 day) was assumed following a theatre procedure as expert opinion is ICU stay more likely to be lower after theatre procedures. The length of stay values of 3.6 days and 6 days used in both treatments are taken from the company base case using the following sources: Total bed days based on average length of stay for gastrointestinal bleed (non-elective) of 10 days (NHS reference costs 2017/18). Escorsell et al report a ratio of 14:8 general ward:ICU days in both arms which is applied

		to the NHS length of stay.
Balloon Tamponade ICU length of stay	6 days	Expert opinion was that the company value (3.6 days) was very low for an English setting where patients would need to await TIPS, and 6 days is a more appropriate estimate. Reduced to 3.6 days in sensitivity analysis.
Cost of Balloon Tamponade removal	£754 Per patient average: £553.82	Removal cost increased based on expert opinion to include: 30 minutes of gastroenterologist time and endoscopy for all those who require removal/survive 24 hours. This is an increase from company value (7.5 minutes of FY2 medic time). The additional endoscopy had already been included in EAC scenario 5.
Proportion who require a second Balloon Tamponade	50%	Expert opinion is that 50% of Balloon Tamponade survivors incur a second Balloon Tamponade device.
Cost of second procedure for Balloon Tamponade	Cost of procedure: £128 Cost of device: £300	In addition to removal, expert opinion is that all those who survive to 24 hours undergo a second procedure in ICU requiring 30 minutes of

	Average per patient cost for procedure: £204.33	gastroenterologist, anesthetist and Band 5 ICU nurse practitioner time. Half of these patients will require a second BT. The average per patient cost reported here is inclusive of all surviving patients receiving procedure and 50% receiving the second Balloon Tamponade device. In sensitivity analysis procedure cost increased from £128 to £502 assuming second procedure requires 30 mins of theatre time.
Adverse events considered	Oesophageal rupture (0% Danis Stent, 6.7% BT)	Expert opinion is that incidence of cardiorespiratory arrest, aspiration pneumonia, spontaneous bacterial peritonitis and hepatorenal syndrome and HE reported in Escrosell et al are independent of choice of bridging treatment. These costs are therefore removed and only oesophageal rupture retained.
Cost of training for Danis Stent*	£65 per patient	The same value of £65 per patient is used in all scenarios and based on 3 hours training per year per consultant,

		across an average of 5 patient procedures. In all scenarios sensitivity analysis is used to vary from 30 minutes to 4 hours.
Cost of an hour of nurse practitioner time	£38	Source: Band 5 nurse from PSSRU reference costs 2018/19. This is updated from value used in previous scenarios which was £92 based on 'patient contact' reference cost. As there are no equivalent 'patient contact' values for medical professionals, for consistency, the EAC applies the lower hourly rate for all clinicians.

*this parameter and sensitivity analysis has not changed in scenario A and B compared to company model but is included here following committee member request for information.

In Scenario B the same parameter changes are used as set out in Table 3 and transport parameters are included as set out in Table 4.

Table 4 - Scenario B - additional parameter changes

Parameter	Value	Note
Proportion of patients who require a transfer	16%	HES data indicates 16.3% of bridging treatment patients have a transfer for definitive treatment (65.2% discharged alive, of which 45% have TIPS, of which 55.6% have been transferred).

		In sensitivity analysis explore 12%-33% (25% fewer require transfer, or 100% more if equivalent number of patients incur transfer for band ligation definitive treatment).
Proportion of Danis Stent patients not requiring transfer under sedation	20%	Expert opinion is that 20% of Danis Stent patients would not require sedation for transfer.
Cost of transfer	£342.34	For all transfers under sedation assume ambulance accompanied by escorting anesthetist and nurse practitioner, based on expert opinion. Sources: NHS national reference costs 2018/19 for 'see and treat and convey' conveyance PSSRU reference costs 2018/19 used to value an hour of anesthetist registrar (£47 per hour) and Band 5 nurse practitioner (£38 per hour) time. In sensitivity analysis explore 30-90 minutes.

Cost of transfer for patients not requiring sedation	£257.34	NHS national reference costs 2018/19 for 'see and treat and convey' ambulance conveyance. In sensitivity analysis explore additional cost of escorting nurse practitioner based on some expert opinion.

Results

The changes made in scenario A and B alter the direction of results compared to the base case EAC analysis and increase the cost saving compared to scenario 5. Results are set out in Table 5 and 6.

Table 5 - Results

Results, cost per patient		**Mean cost per patient using Danis stent (£)**	**Mean cost per patient using balloon tamponade (£)**	**Difference in cost per patient (£)***
Scenario A	EAC	**£13,352**	**£15,775**	**-£2,423**
Scenario B	EAC	**£13,405**	**£15,831**	**-£2,426**
	* Negative values indicate a cost saving.			

Cost breakdown (per patient)

	Danis stent	Balloon tamponade	Incremental
Procedure cost	£9,704	£11,758	-£2,054
Re-bleed costs	£2,298	£2,655	-£357
Adverse event costs	£0	£604	-£604
Stent migration cost	£143	£0	£143
Removal and/or second procedure costs	£1,141	£758	£383
Training costs	£65	£0	£65
Transport costs for scenario B	£53	£56	-£3
Total scenario A	**£13,352**	**£15,775**	**-£2,423**
Total scenario B	**£13,405**	**£15,831**	**-£2,426**

The procedure costs for Balloon Tamponade are substantially higher in Scenario A and B compared to previous analysis seen by the committee due to the change in assumed ICU bed days. This drives the direction of results compared to the original scenarios and is explored in sensitivity analysis.

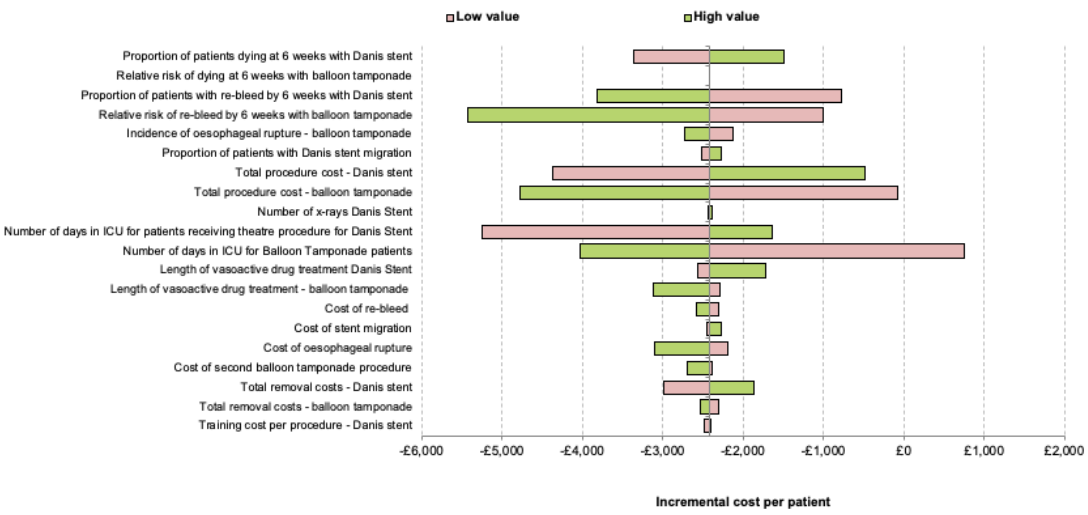
Removal of adverse event costs favours Balloon Tamponade (in scenario 5 the incremental difference was -£1,256). The transport costs included in scenario B have a marginal effect on results favouring Danis Stent.

Table 6 - Cost per Death Avoided

Results, cost per death avoided		**Cost per death avoided**
Scenario A	EAC	Dominant -£17,500.47
Scenario B	EAC	Dominant -£17,520.50

Sensitivity analysis

Figure 1 - Scenario A one way sensitivity analysis

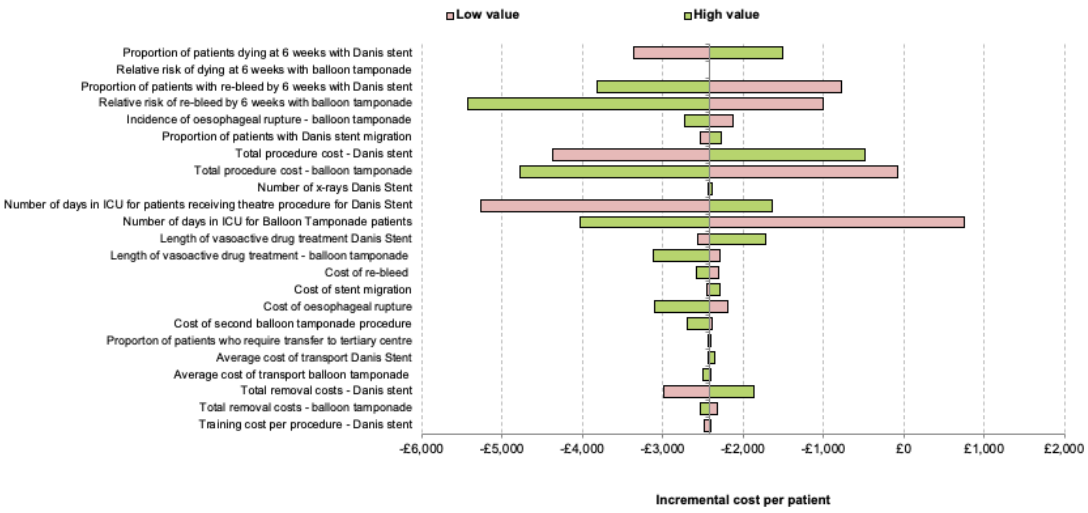


The Scenario A sensitivity analysis suggest the results are robust to uncertainty in the majority of parameters. This finding should be interpreted with caution as some parameter values are based on expert opinion only. The parameters with greatest bearing on the incremental cost per patient are: relative risk of re-bleed, total procedure costs, and number of days spent in ICU.

The number of days in ICU for Balloons Tamponade patients changes the direction of results when length of stay is reduced to 3.6 days. As such the EAC have provided break even analysis:

- If the length of stay in ICU was equivalent between Balloon Tamponade and Danis Stent patients (3.6), Danis Stent would be cost incurring at £751 per patient.
- With an equivalent length of ICU stay, the cost of the Danis Stent device that would result in a difference in cost per patient of £0 would be £744.
- If ICU length of stay for Balloon Tamponade is increased from 3.6 to 4.2 days there is a difference in cost of £0.

Figure 2 - Scenario B one way sensitivity analysis



In Scenario B, similarly the relative risk of re-bleed, total procedure costs, and number of days in ICU are the parameters that introduce the greatest uncertainty. The transport costs included in scenario B have a minimal effect on results and this is also reflected in Figure 2.

As with scenario A, if ICU days are equivalent for Danis Stent and Balloon Tamponade patients, Danis Stent is cost incurring at £748 per patient.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

Danis stent for acute oesophageal variceal bleeds

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This report contains information that has been supplied in confidence and will be redacted before publication. This information is highlighted in yellow. This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- [Appendix D: Additional analyses carried out by External Assessment Centre] [delete if no appendix D]

1 The technology

Danis stent (Ella CS), also known as the SX-Ella Stent Danis, is a self-expanding and removable stent. The stent is a variable weave, constructed of nitinol with a silicone membrane. It is 135mm long and 25mm in diameter, inflating to 30mm in diameter. It has a balloon-style delivery system which is intended to allow accurate positioning of the stent at the gastro-oesophageal junction, to provide direct compression of oesophageal varices. Unlike balloon tamponade, this delivery system can be used without endoscopy or x-ray imaging for guidance. The company claims that this allows for more rapid insertion and control of variceal bleeding in emergency situations compared with balloon tamponade. The delivery system also includes a security pressure valve which may reduce the risk of oesophageal perforation caused by balloon inflation in the oesophagus. Radiopaque markers are present at the distal end and midpoint of the stent to allow its position to be confirmed on chest X-ray after the insertion, although the company state that this confirmation is not routinely required. Danis stent has retrieval loops with gold markers at both ends which facilitate stent removal under endoscopic or fluoroscopic guidance using either grasping forceps or a specifically designed removal device, Ella Extractor. The company recommends that Danis stent should remain in place for no longer than 7 days, whether or not the patient has received definitive treatment, such as trans-jugular intrahepatic portosystemic shunts (TIPS). If TIPS has been done earlier and portal hypertension is no longer a concern, the company state that the stent can be removed using grasping forceps because of a lower risk of re-bleed.

The device has been CE marked as a class IIb medical device since 2005. The covering of the stent was polyurethane until 2009, when it was replaced with silicone. All other changes to the device have been non-substantial. The most recent CE certification was awarded in 2017 and is valid until June 2022.

2 Proposed use of the technology

2.1 Disease or condition

Bleeding from oesophageal varices is a major complication of portal hypertension, which is most commonly caused by liver cirrhosis. 70% of upper gastrointestinal bleeding cases in patients with liver cirrhosis area result of acute variceal bleeding (Rudler et al., 2012). In patients with oesophageal varices, haemorrhage is common and can lead to life-threatening bleeding and complications. 30-50% of patients with portal hypertension will have an episode of acute variceal bleeding, and for approximately 20% of these patients the first episode of bleeding is fatal (Tripathi et al., 2015).

2.2 Patient group

Danis stent is intended for use in acute refractory oesophageal variceal bleeding, after first line therapy, such as variceal band ligation, has failed. It is intended to be used as an alternative to balloon tamponade or early TIPS in people aged 16 years and over. The overall incidence of acute upper gastrointestinal bleeding in the UK ranges from 50-150 per 100,000 population per year. This is estimated to account for 5000 deaths per year in the UK (NICE CG141). HES data indicates that in 2018/19 there were 869 emergency admissions with a primary diagnosis of oesophageal varices with bleeding. The company estimate that approximately 500 to 1000 patients per year would be eligible for Danis stent.

2.3 Current management

The current standard care for people with acute variceal bleeding involves a combination of usual resuscitation, administration of vasoactive drugs and prophylactic antibiotics, and the use of endoscopic techniques. NICE's clinical guideline on the management of 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. Early TIPS (defined as <72 hours after variceal bleed) can be considered in

selected patients with Child's B cirrhosis and active bleeding or Child's C cirrhosis with Child's score <14. Experts estimate that 10-15% of those admitted with acute upper gastrointestinal bleeding will have endoscopic band ligation as definitive treatment. When bleeding is difficult to control, the guideline recommends the insertion of a temporary tamponade balloon (a Sengstaken-Blakemore tube) as a bridge to more definitive treatment such as endoscopic, TIPS, or surgical treatment. TIPS is not available in many general hospitals and patients may need to be transferred to specialist centres, this will affect the amount of time that bridge treatments are required for. In a national audit including 212 UK hospitals (Jairath et al., 2014), only 4 of 526 people with acute variceal haemorrage (<1%) were referred for TIPS.

NICE's interventional procedure guidance on stent insertion for bleeding oesophageal varices states that there is enough evidence to show that stent insertion is safe and effective for people with bleeding oesophageal varices .

2.4 Proposed management with new technology

Danis Stent would be used as an alternative to balloon tamponade or early TIPS after first line therapy, such as variceal band ligation, has failed. Danis Stent is intended to stay in place for up to 7 days, compared to a balloon tamponade, which must be removed after 24-36 hours. This potentially allows clinicians more time to plan definitive therapy or secondary prophylaxis prior to the removal of the stent. The lumen of the stent allows oral nutrition to be maintained and physiological drainage of saliva. Experts confirmed that this can be of particular use in patients with cirrhosis, who are often malnourished.

3 Company claimed benefits and the decision problem

The decision problem from the scope listed in Appendix D.

The company clarified two points from the decision problem. Firstly, they suggested that balloon tamponade should be considered as the only comparator because no studies were identified that compared Danis Stent to

TIPS. Patient-related quality of life measures were also not reported in the literature and were not included in the company. The EAC agreed with both of the company's observations.

4 The evidence

4.1 Summary of evidence of clinical benefit

The evidence submitted by the company consisted of 9 full text studies. There was 1 RCT (Escorsell et al., 2016), 1 retrospective case-control study (Maiwall et al., 2018), 3 prospective case-series (2 of which were pilot studies; Wright et al., 2010; Zehetner et al., 2008; Zakaria et al., 2013) and 4 retrospective case-series (Pfisterer et al., 2019; Ghidirim et al., 2012; Goenka et al., 2017; Muller et al., 2015). The EAC completed a literature search and included all studies submitted by the company. No further studies were identified by the EAC.

All of the included studies had a broadly similar inclusion criteria of patients with refractory acute variceal bleeds associated with chronic liver disease including those with alcoholic liver disease and hepatitis. Experts deemed that these populations are generally comparable in terms of outcomes and comorbidities. The total number of patients in all studies was 247, and this is reflective of the low prevalence of acute bleeding in oesophageal varices. Only one study was undertaken in the UK (Wright et al. 2010). This study was a retrospective case-series and included 10 people referred to a tertiary liver centre.

Two comparative studies were included in the assessment, an RCT (Escorsell et al., 2016) and a retrospective case-controlled study (Maiwall et al., 2018). Both studies compared Danis stent to balloon tamponade, and one study also compared Danis stent to repeat endotherapy and vasoactive drugs or a combination of both treatments (Maiwall et al, 2018). Both studies (Escorsell et al., 2016 and Maiwell et al., 2018) found that Danis stent controls bleeding better at 15 and 5 days respectively (85% (11/13) vs 47% (7/15), p=0.037; PRS-matched cohort 73% vs 32% p=0.007). Neither study found a significant

difference in bleeding control at 6 weeks. This is not unexpected because of generally poor survival outcomes for patients with acute variceal bleeding, especially in the high-risk population included in the studies. One study (Maiwell et al., 2018) noted that mortality was usually related to other causes such as multiorgan failure or active uncontrolled sepsis and found that mortality related to bleeding was significantly lower in the Danis stent group compared with the control group (PRS-matched cohort 6% vs. 56%; p = 0.001).

The RCT (Escorsell et al., 2016) was deemed by the EAC as the highest quality evidence for Danis Stent. However, both studies were considered to have a moderate risk of bias by the EAC. The method of randomisation in the RCT (Escorsell et al., 2016) was computer generated and stratified for the degree of liver failure (Child-Pugh score A or B/C). It didn't account for age and gender; the Danis stent had a greater proportion of men (100% vs 80%) compared to the control arm and a higher mean age (69 vs 54 years). The study was underpowered and was conducted outside of the UK, and so the findings may not be generalisable to the NHS. Experts believed that TIPS interventions were carried out faster than would be expected in the UK and performed on patients of Child-Pugh scores B and C which is uncommon in UK centres. The other comparative study (Maiwall et al., 2018) had a limited study population as only included patients with acute-on-chronic liver failure and there was a significant difference in the disease severity scores of the control group compared with the interventional group. Additional analyses were conducted based on propensity risk score (PRS) matching, the EAC deemed the matching methodology to be reasonable.

The 7 case series studies (Zehertner et al., 2008; Wright et al., 2010; Ghidrim et al., 2012; Zakaria et al., 2013; Muller et al., 2015; Goenka et al., 2017; Pfisterer et al., 2019) were deemed relatively low-quality evidence and were mostly limited by the lack of comparator and low sample sizes. The EAC carried out a meta-analysis on the outcome data for immediate bleeding control (achieved in 68% of patients), successful stent insertion (89% of stent insertions), and survival after stent insertion (68% of patients) between the 7

case series studies. Additionally, the EAC noted there were varying levels of stent migration, ranging from 0% (Wright et al., 2010) to 63.3% of cases (Muller et al., 2010).

Overall, the evidence base has several weaknesses. The majority of studies are small, retrospective and non-comparative, providing a low quality of evidence. The comparative studies represent a low to moderate quality of evidence and so the EAC believe that conclusions may be drawn from these results with caution. The EAC conclude that Danis stent is likely to improve bleeding control and survival at 15 days, however, more research is needed to verify this result in an NHS setting.

Study and design	Participants/ population	Intervention & comparator	Outcome measures and follow up	Results	Withdrawals	Funding	Comments
Escorsell 2016 RCT, Spain	28 people with a diagnosis of cirrhosis and refractory AVB or massive variceal bleeding based on Baveno II criteria. Excluded people who had previously had balloon tamponade treatment. Danis stent (n=13): 13 men, mean age 69 (40-	Danis stent vs S-B tube (balloon tamponade)	**Primary outcome:** Composite endpoint (absence of digestive bleeding and absence of SAEs and survival at 15 days): **Secondary outcomes:** Absence of bleeding at day 15 Absence of bleeding at 6 weeks Survival at day 15 Survival at 6 weeks	**Primary outcome:** Composite endpoint: DS: 66% (8/13), S-B tube: 20% (3/15), p=0.025 **Secondary outcomes:** Absence of bleeding at day 15: DS: 85% (11/13), S-B tube: 47% (7/15), p=0.037 Absence of bleeding at 6 weeks: DS: 54% (7/13), S-B tube: 47% (7/15), p=0.25 Survival at day 15:	None	Not funded by company.	Computer randomisation sequence in a 1:1 ratio, stratified for the degree of liver failure (Child-Pugh score A or B/C); Patients were comparable in severity of liver failure, active bleeding at endoscopy, and initial therapy; study used interim analysis results which was 60% of desired sample size; No female patients were included the Danis stent group; imbalance in the age between groups; More patients in the balloon tamponade group had earlier TIPS which could have affected survival results.

	81). Child-Pugh score A/BC: 3/10 S-B tube (n=15): 12 men, mean age 54 (35-79). Child-Pugh score A/BC: 2/13 Aetiology of cirrhosis: Danis Stent: Alcohol: 8, Hepatitis C: 3 S-B tube: Alcohol: 7, Hepatitis C: 4		Overall units of packed red blood cells used Patients with at least 1 device related SAE Median days hospital stay Days in ICU PBRC Transfusion (Units)	DS: 69% (9/13), S-B tube: 47% (8/15), p=0.39 Survival at 6 weeks: DS: 54% (7/13), S-B tube: 40% (6/15), p=0.46 Overall units of packed red blood cells used: DS: 2, S-B tube: 6, p=0.08 Patients with at least 1 device related SAE: DS: 15% (2/13), S-B tube: 47% (7/15), p=0.077 Median days hospital stay: DS: 14, S-B tube: 14, p=0.55 Days in ICU: DS: 8, S-B tube: 8, p=0.93			

				PBRC Transfusion (Units) DS: 3 ± 3.3, S-B Tube: 6 ± 4.8, p= 0.08			
Maiwall 2018 Retrospective case-control, India	88 patients who had acute-on-chronic liver failure with refractory variceal bleeds. Danis Stent (n=35): 34 men, mean age 46.4 (SD 12.7). Child-Pugh score A/B/C 0/6/29, MELD score 39 (30-47) Control (n=53): 49 men, mean age 47.91 (9.7). Child-	Danis Stent vs Control (repeat endotherapy, vasoactive drugs and balloon tamponade)	Control of initial bleeding (day 5) Mortality related to bleeding 15-day overall mortality 6-week overall mortality	Control of initial bleeding (day 5): DS: (89%, PRS 37%), Control (73%, PRS 32%), p<0.001, PRS p<0.007 Mortality related to bleeding DS: (14%, PRS 6%), Control: (64%, PRS 56%), p=0.001, PRS p=0.001 15-day overall mortality significantly reduced in Danis stent	Not reported	Funding not reported	Patients with Danis Stent were significantly different from patients in the control group with respect to disease severity scores (MELD score p=0.05 and Child-Pugh score p=0.003); PRS analysis controlled for differences in baseline characteristics; Selection bias may have occurred with endoscopists choosing the therapy based on experience and preference; Study only included patients with acute-on-chronic liver failure only; Follow up duration unclear.

	Pugh score A/B/C 0/2/51. MELD score 43 (34.4-65)			group in pre matched (p=0.004, HR 2.56, 95% CI 1.35 to 4.83) and PRS-matched cohorts (p = 0.07, HR 6.94, 95% CI 0.85 to 56.6). 6-week overall mortality not significantly different between Danis stent and controls in pre-match analysis (p = 0.19, HR 1.39, 95% CI 0.85–2.29), but significantly reduced in PRS-matched cohort (p=0.05, HR 8.1, 95% CI 1.02 to 64.4).			
Zehertner et al., 2008; Wright et al., 2010; Ghidrim	129 people with variceal bleeding and	No comparator	Immediate control of bleeding	Immediate bleeding control, from 7 studies,	N/A	Not funded	The studies included in the meta-analysis are low quality

et al., 2012; Zakaria et al., 2013; Muller et al., 2015; Goenka et al., 2017; Pfisterer et al., 2019 Unpublished EAC meta-analysis of 7 non-comparative retrospective studies	treated with Danis stent		Successful stent insertion, Survival after stent insertion Survival after 30 days	achieved in 88% of patients (ranging from 70% [Wright 2010] to 100% [Ghidrim 2012; Muller 2015; Goenka 2017]). Successful stent insertion, from 4 studies, was achieved in 89% of cases (ranging from 80% [Wright 2010] to 100% [Zehetner 2008 and Ghidirim 2012]) Survival after stent insertion, from 4 studies, was achieved in 73% of patients (ranging from 60% [Wright			and varied in length of follow up and reporting of study procedures was poor. Heterogeneity was low in immediate bleeding control, successful stent insertion and survival at 30 days after stent insertion, although confidence intervals were wide.

				2010] to 100% [Zehetner 2008] Survival after stent insertion after 30 days, from 3 studies, was achieved in 68% of patients (ranging from 58% [Goenka 2017] to 74% [Zehetner 2008])			
Abbreviations used: PBRC, Packed Red Blood Cell; DS, Danis Stent; S-B Tube; Sengstaken-Blakemore Tube; HR, Hazard Ratio; PRS, Propensity Risk Score; CI, Confidence Interval; SAE, Severe Adverse Event; AVB, Acute Variceal Bleed; MELD, Model For End-Stage Liver Disease; ICU, Intensive Care Unit; TIPS, Transjugular Intrahepatic Portosystemic Shunt; PBRC, Packed Red Blood Cell.							

4.2 Summary of economic evidence

The company conducted an extensive systematic literature review and identified no economic evidence relevant to the decision problem. The EAC considered the search strategy to be appropriate and agreed with the company after undertaking a review.

De novo analysis

The company submitted a cost comparison over a 6-week time horizon using a 'cost calculator' approach and undertaking an NHS and Personal and Social Services perspective. The model is based on data from the RCT identified in the clinical submission (Escorsell et al.,2016), 6 case series studies (Ghidirim et al., 2012; Muller et al., 2015; Wright et al., 2010; Zakaria et al., 2013; Zehetner et al.,2008) and NHS reference costs. The model estimates the cost associated with the use of Danis stent versus balloon tamponade as bridging treatment for patients aged 16 or over with acute refractory oesophageal variceal bleeding in whom first line therapy (such as terlipressin, prophylactic antibiotics, variceal band ligation or sclerotherapy) is unsuitable or has failed.

The model captures the cost of the initial procedure as well as the likelihood and costs of adverse events for both technologies. Adverse events considered were re-bleeding following initial treatment; cardiorespiratory arrest; aspiration pneumonia; oesophageal bacterial peritonitis; hepatorenal syndrome; and severe hepatic encephalopathy (HE). The cost and use of additional resources included the removal of both technologies as well as stent migration and training for Danis stent only. The proportion of patients receiving definitive treatment (endoscopic band ligation, non-selective beta-blockers or TIPS) within 6 weeks were also considered. The model also considers mortality rates and differences in survival. The model structure is shown in figure 1. The EAC considers the time horizon and cost comparison approach are appropriate and the overall model structure is acceptable.

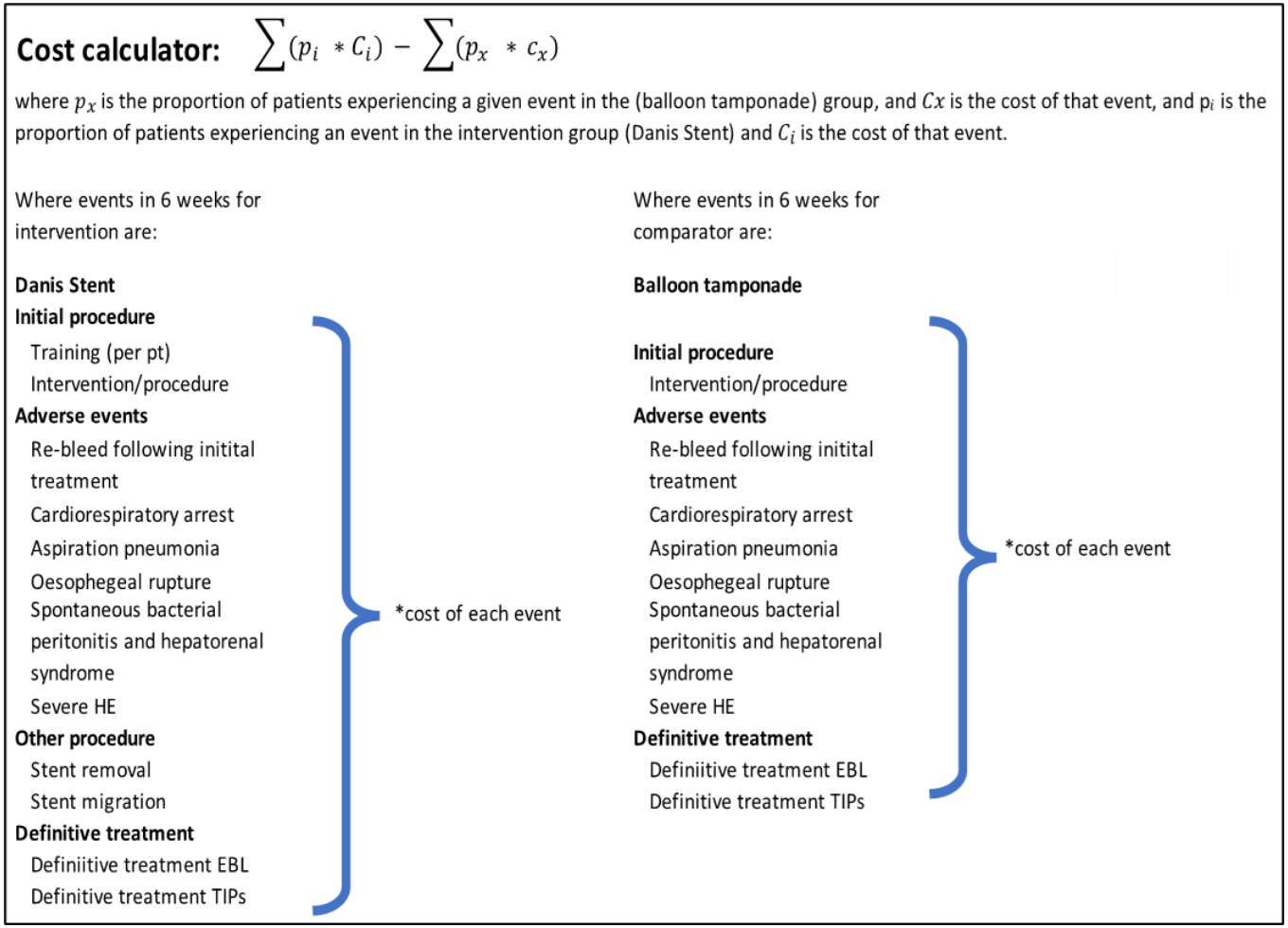


Figure 1EAC figure showing structure of cost calculator model

Model parameters

The main parameters included in the economic modelling were:

- The proportion of patients that had either Balloon tamponade or Danis stent as a bridging treatment and the proportion of patients that had either TIPS or band ligation as a definitive treatment.
- The proportion of patients that died at 6 weeks after treatment with Danis stent and the relative risk of dying at 6 weeks with balloon tamponade compared with Danis stent.
- The proportion of patients that experienced adverse events after having bridging treatment of either Balloon tamponade or Danis stent, such as rebleed, aspiration pneumonia, serve hepatic encephalopathy and stent migration.

The EAC reviewed all parameters in the company submission and agreed with the clinical parameters used and made changes to 5 cost parameters described in the cost and resource use section.

Costs and resource use

The key costs included were the technology costs, cost of SAEs and cost of definitive treatment. The EAC modified five cost parameters, the below table describes the changes and rationale for the modifications.

Parameter	Company	EAC	Comment
Cost of stent removal	£1,257 per of removal with Ella extractor (£757+£500) £1,066 mean cost per patient in model Company estimated costs based on expert opinion and NHS reference costs	£1,452.00 per removal with Ella extractor (£757 + £695) £1,141.35 mean cost per patient in model The EAC assume the full cost of the Ella Extractor.	The EAC disagreed with the company assumption that all Ella Extractors will be purchased at the discounted price as part of a bundle with Danis Stent.

	2018/2019. Average cost accounted for the use of Ella extractor in some cases and not others.		
Cost of rebleed	£3,287.00 Uplifted from NICE resource impact report for cirrhosis in over 16s [NG50] (2016) with lowest cost from range of three HRGs chosen. The company inflates 2018/2019 prices using PSSRU HCHS/NHS inflators for all sectors.	£4,978.75 The EAC repeats this method and takes an unweighted average of all 3 HRGs.	
Cost of definitive treatment elective TIPS	£3,928.00 Taken from NHS reference costs 2018/19 (NHS Improvement 2019) [YR16B Transjugular Intrahepatic Creation of Portosystemic Shunt with CC Score 0-5].	£4,965.56 EAC uses the higher complexity score and selects elective tariff for YR16A Transjugular Intrahepatic Creation of Portosystemic Shunt with CC Score 6+.	The EAC believe higher CC scores were more appropriate for procedures involving patient populations that are acutely unwell. Expert opinion was mixed due to lack of knowledge about CC scores but there was broad agreement with the EAC's assumptions.
Cost of definitive treatment band ligation and non selective blockers	£1,114.00 NHS reference costs 2018/19 (NHS Improvement 2019) based on Endoscopic, Sclerotherapy or Rubber Band Ligation, of Lesion of Upper Gastrointestinal Tract, with CC	£4,983.67 EAC selected the elective tariff for FE11A - Endoscopic, Sclerotherapy or Rubber Band Ligation of lesion of Upper Gastrointestinal Tract, with CC Score 9+.	The EAC believe higher CC scores were more appropriate for procedures involving patient populations that are acutely unwell. Expert opinion was mixed due to lack of knowledge about CC scores but there was broad agreement

	Score 0-2 [FE11D].		with the EAC's assumptions.
Cost of severe hepatic encephalopathy (HE)	£400.52	£400.56 EAC failed to replicate company value and adjusted it slightly.	Marginal difference which would not impact results.

Results

The EAC's revised base case resulted in a cost increase of £982 per patient compared with the £147 per patient cost saving calculated by the company. The EAC base case shows a cost of £7,089.65 per death avoided, whereas the company base case shows a £1,059.59 cost saving. Probabilistic sensitivity analysis by the EAC indicated there was a 33% of chance that Danis Stent is cost saving compared to balloon tamponade in the base case compared to a 55% chance calculated by the company.

Deterministic sensitivity analysis found that a number of factors were key drivers of uncertainty in the cost comparison in the base case. These were: relative risk of re-bleed by 6 weeks in balloon tamponade group; procedure costs; cost of band ligation; cost of aspiration pneumonia; and proportion of balloon tamponade patients having band ligation as definitive treatment.

	Company's results			EAC results		
	Technology: Danis stent	Comparator: balloon tamponade	Cost saving per patient	Technology: Danis stent	Comparator: balloon tamponade	Cost saving per patient
Device and procedure (including training)	£6,937	£5,677	-£1,260	£6,937	£5,677	-£1,260
Adverse events (including stent migration, severe HE and rebleed)	£2,256	£3,745	£1,489	£3,037	£4,647	£1,610
Stent/balloon removal	£1,066	£3	-£1,063	£1,141	£3	-£1,138
Definitive treatment: endoscopic band ligation + nonselective beta blockers	£428	£0	-£428	£1,916.80	£0	-£1,916.80
Definitive treatment: TIPS	£1,209	£2,619	£1,410	£1,527.86	£3,310	£1,782.14
Total	£11,897	£12,044	£147	£14,560	£13,638	-£923

Three further scenarios were explored. In the micro-costing scenario, the cost for the procedures are based on estimated cumulative costs of the hospital stay, drugs, imaging and procedure costs instead of the NHS reference costs 2018/19 used in the base case. The cost of both procedures increased using this approach: Danis stent to £9,9194 [base case £6,872] and balloon tamponade to £8,584 [base case £5,378]. The Danis stent procedure increase was smaller because it was assumed to have a shorter ICU length of stay.

The second and third scenario explore the cost of using Danis stent and balloon tamponade without assuming that the use of bridging treatment impacts the choice of definitive treatment. Based on results from an RCT (Escorsell et al.,2016), the base case assumes 67% of patients that had balloon tamponade go on to have TIPS as a definitive treatment and none have band ligation, whereas 31% of patients that had Danis stent go on to have TIPS and 38% band ligation. Scenario 2 assumes patients are equally likely to have either TIPS or band ligation as a definitive treatment irrespective of the intervention received. In scenario 2 HE costs were also removed. The EAC explored a third scenario which mirrored scenario 2 but retained all costs related to incidences of HE.

Scenario modelled	Cost impact per patient	
	Company model	EAC model
Scenario 1 – micro costed model procedure costs based on estimated resource use rather than NHS reference costs)	£732	£-338
Scenario 2 – definitive treatment is not dependent on bridging treatment and cost of HE is removed	£-1,050	£-928
Scenario 3 - definitive treatment is not dependent on bridging treatment and cost of HE included.	n/a	£-788

Given the limited evidence and uncertainties in the cost modelling , the EAC considers that all scenarios are considered alongside the base case. Tthe EAC highlight that there is considerable uncertainty regarding the costs associated with Danis Stent and balloon tamponade, as well as the definitive

procedures received by surviving patients and considers the conclusion that Danis Stent is cost incurring should be interpreted with caution.

5 Ongoing research

The company and the External Assessment Centre are not aware of any ongoing research on Danis Stent.

6 Issues for consideration by the Committee

Clinical evidence

- The evidence reports that Danis stent improves clinical outcomes after 15 days compared with Balloon tamponade. Is the evidence sufficient in quality and quantity to demonstrate the clinical effectiveness of Danis stent?

- The model does vary from the scope as no studies were identified comparing Early TIPS to Danis stent. Is early TIPS an appropriate comparator?

- Is the evidence generalisable to the UK care pathway?

- Are there any clinical or patient benefits not captured in the evidence base?

Cost evidence

- The impact of bridging treatment on choice of definitive treatment is a key driver in the economic model. The EAC believe the assumption lacks strong supporting evidence. Is the assumption that the choice of definitive treatment is impacted by the choice of bridging treatment reasonable?

- The CC score reflects the complexity of a procedure and has a significant impact on the definitive procedures costs used in the model. Are they EAC's assumed definitive procedure costs reasonable?

- Which of the scenarios, if any, best reflects clinical practise in the UK?
- Have any potential benefits not been included in the model?

7 Authors

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September, 2020

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- Erskine J, Goddard K, et al. Danis Stent for acute oesophageal variceal bleeds External Assessment Centre report , July 2020

B Submissions from the following sponsors:

- UK Medical

C Related NICE guidance

- Acute upper gastrointestinal bleeding in over 16s: management. NICE clinical guideline 141(2012; updated 2016). Available from www.nice.org.uk/guidance/CG141
- Stent insertion for bleeding oesophageal varices. NICE interventional procedure guidance 392(2011). Available from www.nice.org.uk/guidance/IPG392

D References

Chen P et al. (2012) Delayed endoscopy increases re-bleeding and mortality in patients with hematemesis and active esophageal variceal bleeding: A cohort study. Journal of Hepatology 57(6):1207-1213.

De Franchis R, Baveno VI Faculty. (2015) Expanding Consensus in Portal Hypertension: Report of the Baveno VI Consensus Workshop: Stratifying Risk and Individualizing Care for Portal Hypertension. Journal of Hepatology. 63(3):743-52

Escorsell À, Pavel O, Cárdenas A et al. (2016) Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: A multicenter randomized, controlled trial. Hepatology 63(6):1957-1967.

Ghidirim G, Mishin I, Dolghii A et al. (2012) Self-expanding Metal stent for the management of bleeding esophageal varices – single centre experience. Clinical anatomy and operative surgery. 11(4):100-103.

Goenka M, Goenka U, Tiwary I et al. (2017) Use of self-expanding metal stents for difficult variceal bleed. Indian Journal of Gastroenterology. 36(6):468-473.

Jairath V, Rehal S, Logan R et al. (2014) Acute Variceal Haemorrhage in the United Kingdom: Patient Characteristics, Management and Outcomes in a Nationwide Audit. Digestive and Liver Disease. 46(5):419-426.

Maiwall R, Jamwal K, Bhardwaj A et al. (2017) SX-Ella Stent Danis Effectively Controls Refractory Variceal Bleed in Patients with Acute-on-Chronic Liver Failure. Digestive Diseases and Sciences. 63(2):493-501.

Mohan B, Chandan S, Khan S et al. (2019) Efficacy of Self Expanding Metal Stent (SEMS) in Refractory Bleeding Esophageal Varices, Is There a Mortality Benefit? An Indirect-Comparison Meta-Analysis to Trans-Jugular Intra-Hepatic Porto-Systemic Shunt (TIPS). American Journal of Gastroenterology. 114:S346-S347.

Müller M, Seufferlein T, Perkhofer L, Wagner M, Kleger A. Self-Expandable Metal Stents for Persisting Esophageal Variceal Bleeding after Band Ligation or Injection-Therapy: A Retrospective Study. (2015) PLOS ONE. 10(6):e0126525.

NICE. 2011 Stent insertion for bleeding oesophageal varices (IPG392). Available at https://www.nice.org.uk/guidance/ipg392 Accessed 1 June 2020

NICE. 2012 Acute upper gastrointestinal bleeding in over 16s: management (CG141). Available at https://www.nice.org.uk/guidance/cg141 Accessed 1 June 2020

NICE. 2015 Rifaximin for preventing episodes of overt hepatic encephalopathy (TA337). Available at https://www.nice.org.uk/guidance/ta337/resources Accessed 1 June 2020

NICE. 2019 Danis stent for acute oesophageal variceal bleeds (MIB 185). Available at https://www.nice.org.uk/advice/mib185 Accessed 1 June 2020

Njei B, McCarty T, Laine L. (2017) Early transjugular intrahepatic portosystemic shunt in US patients hospitalized with acute esophageal variceal bleeding. Journal of Gastroenterology and Hepatology 32(4):852-858.

Pfisterer N, Riedl F, Pachofszky T, et al. (2018) Outcomes after placement of a SX-ELLA oesophageal stent for refractory variceal bleeding-A national multicentre study. Liver International. 39(2):290-298.

Tacconelli E. (2010) Systematic reviews: CRD's guidance for undertaking reviews in health care. The Lancet Infectious Diseases. 10(4):226.

Tripathi D, Stanley A, Hayes P et al. (2015) UK guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut. 46(90003):1iii-15.

Wright G, Lewis H, Hogan B, et al. (2010) A self-expanding metal stent for complicated variceal hemorrhage: experience at a single center. Gastrointestinal Endoscopy. 71(1):71-78.

Zakaria M, Hamza I, Mohey M et al. (2013) The First Egyptian Experience Using New Self-Expandable Metal Stents in Acute Esophageal Variceal Bleeding: Pilot Study. The Saudi Journal of Gastroenterology. 19:177-81

Zehetner J, Shamiyeh A, Wayand W. (2008) Results of a new method to stop acute bleeding from esophageal varices: implantation of a self-expanding stent. Surgical Endoscopy. 22(10):2149-2152.

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Dr Jason Dunn

Consultant Gasteroenterologist, Guy's and St Thomas' NHS Foundation Trust

Dr Philip Berry

Consultant Gastroenterologist & Hepatologist, Guy's and St Thomas' NHS Foundation Trust

Dr Ian Beales

Consultant in Gastroenterology & Clinical Reader in Gastroenterology and Therapeutics, Norfolk and Norwich University Hospitals NHS Foundation Trust

Dr Emmanuel Tsochatzis

Associate Professor and Honorary Consultant in Hepatology, UCL Institute for Liver and Digestive Health at the Royal Free Hospital

Dr Dhiraj Tripathi

Consultant Hepatologist and Liver Transplant Physician, University Hospitals Birmingham NHS Foundation Trust

Dr Deepak Joshi

Consultant Hepatologist, Institute of Liver Studies, King's College Hospital

Please see the clinical expert statements included in the pack for full details

Appendix C: Comments from patient organisations

The following patient organisations were contacted and no response was received.

- Barrett's Oesophagus Campaign
- Fighting Oesophageal Reflux Together (FORT)
- Guts UK
- Oesophageal Patients Association
- Tracheo Oesophageal Fistula Support (TOFS)

Appendix D: decision problem from scope

Population	People aged 16 years and over with acute refractory oesophageal variceal bleeding in whom first line therapy, such as terlipressin, prophylactic antibiotics, variceal band ligation or sclerotherapy is unsuitable or has failed
Intervention	Danis stent insertion
Comparator(s)	• Balloon tamponade • Early trans-jugular intrahepatic portosystemic shunt (TIPS)
Outcomes	The outcome measures to consider include: • Control of bleeding • Rebleeding rate • Blood transfusion use • Device-related adverse events, including stent migration • Mortality rate • Hepatic encephalopathy • Patient-related quality of life • Additional/further interventions including TIPS
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed. The cost analysis should allow for the expected costs of different methods of removal of the Danis stent, including the use of Ella Extractor.
Subgroups to be considered	None identified
Special considerations, including those related to equality	Danis stent is intended for use in people aged 16 years and over with acute refractory variceal bleeding. Oesophageal variceal bleeding is a common and life-threatening complication of cirrhosis in people with chronic liver disease. 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'. Age and disability are protected characteristics under the Equality Act 2010. Danis stent may also be an advantage to people who do not accept blood transfusions due to religious beliefs, such as Jehovah's Witnesses.

Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Not applicable	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

Danis stent for acute oesophageal variceal bleeds

1 Technology

1.1 Description of the technology

Danis stent is a self-expanding and removable silicone-covered nitinol stent. It is positioned at the gastro-oesophageal junction to compress oesophageal varices and stop acute bleeding. It comes preloaded in a balloon-style delivery system that facilitates accurate positioning without radiological or endoscopic assistance. It is claimed by the company that this allows for more rapid insertion and control of variceal bleeding in emergency situations compared with balloon tamponade. Radiopaque markers are present at the distal end and midpoint of the stent which allows its position to be confirmed on chest X-ray after the insertion, although the company state that this confirmation is not routinely required. Danis stent has retrieval loops with gold markers at both ends which facilitate stent removal under endoscopic or fluoroscopic guidance using either grasping forceps or a specifically designed removal device, Ella Extractor, which can be purchased separately from the company. The company recommends that Danis stent should remain in place for no longer than 7 days, whether or not the patient has received definitive treatment, such as trans-jugular intrahepatic portosystemic shunts (TIPS). If TIPS has been done earlier and portal hypertension is no longer a concern, the company state that the stent can be removed using grasping forceps because of a lower risk of re-bleed.

The stent is 135 mm long and 25 mm in diameter when deployed. The technology is intended to be used in secondary care by clinicians including gastroenterologists, hepatologists, endoscopy nurses, ITU or emergency

department clinicians. Endoscopy is likely to be required in the majority of cases, and so clinicians who are competent in endoscopy and with experience of managing bleeds are those most likely to insert Danis stent. Danis stent is provided in a pack which contains the stent (preloaded in the delivery system), guide wire and syringe.

Innovative aspects of this device claimed by the company are that Danis stent allows for more rapid control of bleeding because it does not need endoscopic image guidance; that it can remain in place for longer than a balloon used for tamponade (which should not be left in place for more than 24 to 36 hours); that patients' oral intake can be maintained while the stent is in place; and the stent is designed to prevent migration.

1.2 Relevant diseases and conditions

Danis stent is intended for use in acute refractory oesophageal variceal bleeding, after first line therapy, such as variceal band ligation, has failed. It is intended to be used as an alternative to balloon tamponade or early TIPS in people aged 16 years and over.

Acute variceal bleeding is a major cause of upper gastrointestinal bleeding in patients with liver cirrhosis, accounting for 70% of cases (Rudler et al. 2012). 30-50% of patients with portal hypertension will have an episode of acute variceal bleeding, and for approximately 20% of these patients the first episode of bleeding is fatal (Tripathi et al. 2015). HES data indicates that in 2018/19 there were 869 emergency admissions with a primary diagnosis of oesophageal varices with bleeding. The company estimate that approximately 500 to 1000 patients per year would be eligible for Danis stent.

1.3 Current management

The current standard care for people with acute variceal bleeding involves a combination of usual resuscitation, administration of vasoactive drugs and prophylactic antibiotics and the use of endoscopic techniques. NICE's clinical guideline on the management of 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, followed by TIPS if the bleeding is still not controlled. NICE's interventional procedure guidance on stent insertion for bleeding oesophageal varices states that there is enough evidence to show that stent insertion is safe and effective for people with bleeding oesophageal varices that it can be used with normal arrangements for clinical governance, consent and audit when other methods of treatment have failed to control the bleeding.

UK guidelines on the management of variceal haemorrhage in cirrhotic patients recommend upper gastrointestinal endoscopy as soon as the patient is haemodynamically stable to locate the bleeding site. Band ligation is recommended as the first-choice therapy to control bleeding varices. If banding is difficult because of continued bleeding or this technique is not available, endoscopic variceal sclerotherapy is recommended as an alternative. When bleeding is difficult to control, the guideline recommends the insertion of a temporary tamponade balloon (a Sengstaken-Blakemore tube) as a bridge to more definitive treatment such as endoscopic, TIPS, or surgical treatment. The guideline also states that, ideally, variceal bleeding should be treated in a unit where the staff are familiar with managing bleeds and where routine therapeutic interventions are available.

Baveno VI consensus report (Journal of Hepatology, 2015) states that the evidence supports the use of self-expanding oesophageal metal stents (SEMS) as being safer and more effective than balloon tamponade.

1.4 Regulatory status

Danis stent received a CE mark in June 2006 as a class IIb device for acute refractory oesophageal variceal bleeding.

1.5 Claimed benefits

The benefits to patients claimed by the company are:

- Faster recovery following the procedure

- Improved quality of life
- Fewer procedural complications
- The ability to maintain oral intake
- Reduced need for patient transfer
- Better patient compliance
- Eliminated/minimised high dependency hospitalisation
- Increased possibility of stabilised bilirubin and renal function to facilitate the option of TIPS, where otherwise not possible
- Eliminated need for general anaesthetic and/or heavy sedation while achieving haemostasis

The benefits to the healthcare system claimed by the company are:

- Reduced bed use in ITU/high dependency units
- Decreased strain on fluoroscopic imaging facilities
- Reduced length of hospital stay
- Reduced hospital admissions/interventions
- Helping trusts achieve government targets relating to efficiency savings, hospital stays, positive outcomes and reduced repeated procedures
- Increased time for planning of definitive treatment (7 days vs. 24/48 hours for balloon tamponade)
- Increased possibility of successful TIPS and providing definitive treatment
- Significant cost saving compared with current treatment options

2 Decision problem

Population	People aged 16 years and over with acute refractory oesophageal variceal bleeding in whom first line therapy, such as terlipressin, prophylactic antibiotics, variceal band ligation or sclerotherapy is unsuitable or has failed
Intervention	Danis stent insertion
Comparator(s)	• Balloon tamponade • Early trans-jugular intrahepatic portosystemic shunt (TIPS)
Outcomes	The outcome measures to consider include: • Control of bleeding

	• Rebleeding rate • Blood transfusion use • Device-related adverse events, including stent migration • Mortality rate • Hepatic encephalopathy • Patient-related quality of life • Additional/further interventions including TIPS	
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed. The cost analysis should allow for the expected costs of different methods of removal of the Danis stent, including the use of Ella Extractor.	
Subgroups to be considered	None identified	
Special considerations, including those related to equality	Danis stent is intended for use in people aged 16 years and over with acute refractory variceal bleeding. Oesophageal variceal bleeding is a common and life-threatening complication of cirrhosis in people with chronic liver disease. 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'. Age and disability are protected characteristics under the Equality Act 2010. Danis stent may also be an advantage to people who do not accept blood transfusions due to religious beliefs, such as Jehovah's Witnesses.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No

Any other special considerations	Not applicable

3 Related NICE guidance

Published

- Alcohol-use disorders: diagnosis and management of physical complications (2017). NICE guideline CG100.
- Acute upper gastrointestinal bleeding in over 16s: management (2016) NICE guideline CG141.
- Cirrhosis in over 16s: assessment and management (2016). NICE guideline NG50.
- Stent insertion for bleeding oesophageal varices (2011) NICE interventional procedure guidance 392.

4 External organisations

4.1 Professional

The following organisations have been asked to comment on the draft scope:

- British Association for the Study of the Liver
- British Liver Nurses' Association
- British Society of Gastroenterology
- Royal College of General Practitioners
- Royal College of Physicians

4.2 Patient

NICE's Public Involvement Programme contacted the following organisations for patient commentary and asked them to comment on the draft scope:

- Guts UK
- British Liver Trust

Adoption report: MTG Danis stent for acute oesophageal variceal bleeds

Summary – for first meeting

Adoption levers

- Reportedly stops acute oesophageal variceal bleeds
- Enables eating and drinking providing the patient is clinically stable and does not require an ITU bed
- Can stay in place for up to 14 days giving time to establish the next treatment. A Sengstaken-Blakemore tube must be removed after 24 hours.

Adoption barriers

- Low and infrequent patient numbers make it difficult to maintain staff competency.
- Device and extraction kit cost more than Sengstaken-Blakemore tube and silo budgeting can mean budget holders will not see return on investment.
- People requiring Danis stent are very unwell and may still require HDU or ITU for organ support.

1 Introduction

The NICE adoption team has collated information from 7 healthcare professionals working within NHS organisations, 6 of whom have experience of using Danis stent.

This adoption report includes some of the considerations for the routine NHS use of the technology.

2 Contributors

Details of contributing individuals are listed in the below table.

	Job title	Using Danis stent	Experience	Onsite TIPS
1	Consultant Hepatologist/Gastroenterologist	Yes.	Inserted 12-14 Danis stent adopted summer 2012. On average 1-3 inserted annually	No
2	Consultant Gastroenterologist/Hepatologist	Yes	Inserted 3 Danis stent adopted in Trust in 2017 On average 3-4 stents inserted annually	No
3	Consultant Hepatologist	Yes.	Danis stent adopted at Trust in 2010. On average 10-12 inserted annually Clinician has 5 years experience of inserting.	Yes
4	Consultant Nurse in Endoscopy & Interventional Radiology/ Surgery	Yes.	Danis stent adopted at trust spring 2018 7 inserted since adoption Clinician has inserted 5	No
5	Consultant Hepatologist (same trust as clinicians 6)	Yes.	Trust adopted Danis stent in Autumn 2017 On average 5-10 are inserted at the trust per year Clinician inserts 2-4 per year	Yes
6	Consultant Hepatologist and gastroenterologist (same trust as clinicians 5)	Yes.	Trust adopted Danis stent in Autumn 2017 On average 5-10 are inserted at the trust per year Clinician inserts 1-2 per year	Yes
7	Reader in medicine, Consultant Gastroenterologist, Clinical lead for gastroenterology	No	N/A	No

3 Current practice

The care pathways for acute oesophageal variceal bleeds described by contributors were in line with NICE and British Society of Gastroenterology guidance recognising that there are slight differences in recommendations between them. One contributor said there was variation in the management across sites due to differences in expertise and availability of endoscopy services.

Resuscitation, stabilisation and effective use of terlipressin are the key first step in ensuring the patient is safe and reducing the bleed. In patients who continue to bleed, the endoscopist will attempt band ligation which is successful most of the time. If band ligation does not work or is not technically possible endoscopic variceal sclerotherapy may be done although this is rare. Most commonly a Sengstaken-Blakemore tube is inserted to stop the bleeding. This is reported to be an easy procedure for someone who is trained and experienced in inserting them. Transjugular intrahepatic portosystemic (TIPS) procedure is done at specialist liver centres, so patient transfer may be necessary. Contributors used Danis stent instead of a Sengstaken-Blakemore tube or to replace an already inserted Sengstaken-Blakemore tube.

Contributors reported that patients with acute oesophageal variceal bleeds can present to any hospital. hospital admitted patient care activity data indicates that in 2018/19 there were 869 emergency admissions with a primary diagnosis of oesophageal varices with bleeding. Contributors reported around 20-35 cases of acute oesophageal variceal bleeds presented to their hospital per year of which between 2–12 could benefit from a Danis stent. One site, which is a tertiary referral centre for the management of advanced liver disease, estimated they had inserted 10-12 Danis stents in 1 year.

4 Reported benefits

The potential benefits of adopting Danis stent, as reported to the adoption team by the healthcare professionals using the technology when compared with a Sengstaken-Blakemore tube are that:

- Patients can be cared for on a ward and can eat and drink. Potentially no ITU bed is required.

- It causes fewer complications and can be used to replace a Sengstaken-Blakemore tube before the point complications start to arise (contributors suggested this occurred at around 12 hours) .
- It can stay in place for up to 14 days compared with 24 hours for the Sengstaken-Blakemore tube. This could allow more time:
  - for the bleed to stop (if definitive treatment is not planned) and some relative liver recovery to be achieved
  - to assess and prepare the patient for a TIPS procedure (stabilising them, conducting required tests and checks). This includes Computed Topography (CT) and cardiac scans. It is reported to be extremely difficult to do all of this within 24 hours.

5 Insights from the NHS

Clinician competency and training

Contributors reported that Danis stent was inserted by a consultant gastroenterologist or consultant hepatologist with the support of an endoscopy nurse. At one site a consultant nurse did the procedure. Most contributors thought the team inserting the device should be competent in endoscopy with experience of managing bleeds.

There were differing views about the ease of insertion. Three contributors said it was fiddly and complex whilst 3 said it was not difficult. All acknowledged that a situation where a Danis stent is required is stressful because the patient is haemorrhaging severely, and this will add to the complexity of the procedure.

Contributors reported that the company provided free training and updates to meet their requirements. This consisted of a company representative visiting the site and bringing models and kit to practice with. Additionally, prior to an insertion some contributors said, as a team, they would re-read the instructions and watch a YouTube video to refresh their memory.

Low and infrequent patient numbers and varying on-call rotas make it difficult to maintain staff competency and develop staff expertise in all settings where these

patients may present. Contributors said training updates should be every 6-9 months. Some contributors who regularly insert metal gastrointestinal stents said that although it is not exactly the same insertion technique, this helped maintained their skills.

Contributors said most hospitals should have an 'on-call GI bleed rota' which an out of hours service staffed by a consultant (most commonly a consultant gastroenterologist or hepatologist) or consultant nurse ideally who are JAG (Joint Advisory Group on GI endoscopy) accredited to manage upper GI bleeds and supported by an endoscopy nurse. They were unsure what the availability and skill mix of this service would be at different hospitals. At the sites where Danis stent had been adopted, this out of hours service was available, and some (between 3 and 6) of the gastroenterologists and hepatologists on the rota were trained to insert Danis stent.

Care pathway - insertion

Danis stent was used to stop acute oesophageal variceal bleeding and for some patients, a bridge to more definitive treatment such as a TIPS procedure. All contributors explained that for these patients all other interventions have failed and this is the very last option. In this situation there were no contraindications for use. At sites where Danis stent had been adopted, the care pathway for insertion varied for each patient and was dependent upon the admission method (patient transfer or emergency department [ED]), availability of trained staff, treatment given during index endoscopy and the patient history.

The procedure would generally take place in emergency theatres, endoscopy or ITU because these were locations with the facilities to manage unstable patients (intubation and ventilation) and where endoscopy equipment was available or could be moved to. Patients may receive Danis stent during the first (index) endoscopy if band ligation was not technically possible or failed immediately. Alternatively, patients who continued to deteriorate, often on ITU or HDU following band ligation on initial endoscopy, had Danis stent inserted during a subsequent endoscopy where it was identified the initial band ligation was not working.

Immediately prior to insertion of Danis stent, endoscopy is required to confirm the cause of bleeding and if required attempt band ligation. Following deployment most contributors would use the endoscope to confirm the Danis stent position and some use it to remove any excess blood. These patients would also commonly receive an X-ray or Computerised tomography (CT) scan (for other reasons) and those could also be used to confirm stent location.

Contributors agreed that most of the patients who had received a Danis stent could be moved to a ward but these patients are ill and there would be some with organ failure still requiring ITU. One contributor said that given the amount of blood lost, ideally these patients would spend 24 hours on a high dependency unit for closer monitoring whilst their condition stabilises. This may be important in realising any proposed cost benefits.

Where a member of staff trained to insert Danis stent is not available when required (commonly out of hours) contributors described how they overcame this. At one site, a Sengstaken-Blakemore tube was inserted first and the patient admitted to ITU. The following day a trained hepatologist would insert Danis stent. At another site some ITU and ED physicians had been trained to insert Danis stent and could be authorised to insert it (without endoscopy first) to minimise delay caused by awaiting the arrival of the on-call team (around 30 minutes). This was only done in patients in whom there was certainty it was an acute oesophageal variceal bleed.

Care pathway - removal

Sites reported leaving Danis stent in for between 7-14 days however the manufacturer recommendation is up to 7 days only. Two contributors reported when it was used in end of life care it would not be removed. There was consensus that the longer it was left in the more likely it would be to become embedded. Removal is a planned endoscopy procedure with fluoroscopy. It was reported to be more complex than insertion and required training. Two contributors said that securing the right room and staff to meet these requirements, including a radiographer, was challenging.

Contributors adhered to the manufacturer's recommendations using the Ella extractor (an additional cost on top of the insertion kit) when definitive treatment had not been given (the risk of re-bleed is higher) and some also used it after definitive treatment. One site used an 'over tube' which is placed over the end of an endoscope in people who had received definitive treatment. A contributor estimated that 50% of patients who had Danis stent would go on to have TIPS.

One site removed Danis stent without fluoroscopy and using forceps.

Cost / Resource impact

Cost was seen as a barrier to adoption compared with a Sengstaken-Blakemore tube. It was common for the Danis stent device to come from the endoscopy budget however they would not benefit from the potential savings from reduced ITU costs. One contributor said their trust wanted evidence that Danis stent reduced the length of patient stay in order to support the case for adoption but they did not have this evidence.

Storage and procurement

Contributors reported keeping 1-3 Danis stents on site at any one time. As soon as one had been used they contacted the company who delivered another one the next day. Sites purchased Danis stent from the company directly.

Clinician confidence

Contributors thought it was an innovative technology which was effective at stopping an acute oesophageal variceal bleed and would buy time to plan for the next treatment. However, one noted it had been available to the NHS for up to 10 years and the fact there had not been widescale adoption would indicate there were barriers.

Contributors said Danis stent had fewer complications compared with Sengstaken-Blakemore tube but did report on examples of some complications of its use that they had experienced:

- Stent migration was possible but rarely occurred to the extent that removal was required. When it had occurred, the bleeding had already stopped
- One contributor said a Danis stent had migrated into the patient's stomach and that was difficult to extract
- One contributor had a patient who re-bled on removal and a new Danis stent had to be applied. This caused a serious bronchoesophageal fistula.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

[MT450 Danis Stent for acute oesophageal variceal bleeds]

Company evidence submission

Part 1: Decision problem and clinical evidence

Company name	UK Medical
Submission date	09 April 2020~~28 February 2020~~
Regulatory documents attached	Instructions for use Declaration of conformity CE certificate Statement on Latex MHRA Field Safety Notice 2017/002/015/291/004
Contains confidential information	No

Contents

1 Decision problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	People aged 16 years and over with acute refractory oesophageal variceal bleeding in whom first line therapy, such as terlipressin, prophylactic antibiotics, variceal band ligation or sclerotherapy is unsuitable or has failed	There has been no variation from the scope	Not applicable
Intervention	Danis stent insertion	There has been no variation from the scope	Not applicable
Comparator(s)	Balloon tamponade or Early trans-jugular intrahepatic portosystemic shunt (TIPS)	Balloon tamponade only	No studies were identified comparing Danis stent to TIPS
Outcomes	Control of bleeding Re-bleeding rate Blood transfusion use Device-related adverse events, including stent migration Mortality rate Hepatic encephalopathy Patient-related quality of life Additional/further interventions including TIPS	Data included on the following outcomes: Control of bleeding Re-bleeding rate Blood transfusion use Device-related adverse events, including stent migration Mortality rate Hepatic encephalopathy Additional/further interventions including TIPS	No studies reported any data for the outcome patient-related quality of life
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and	There has been no variation from the scope.	Not applicable

	consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed. The cost analysis should allow for the expected costs of different methods of removal of the Danis stent, including the use of Ella Extractor		
Subgroups to be considered	None identified	None identified	Not applicable
Special considerations, including issues related to equality	Danis stent is intended for use in people aged 16 years and over with acute refractory variceal bleeding. Oesophageal variceal bleeding is a common and life-threatening complication of cirrhosis in people with chronic liver disease. 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'. Age and disability are protected characteristics under the Equality Act 2010. Danis stent may also	There has been no variation from the scope.	Not applicable

	be an advantage to people who do not accept blood transfusions due to religious beliefs, such as Jehovah's Witnesses.		

2 The technology

Give the brand name, approved name and details of any different versions of the same device (including future versions in development and due to launch). Please also provide links to (or send copies of) the instructions for use for each version of the device.

Brand name	SX-Ella Stent Danis
Approved name	SX-Ella Stent Danis
CE mark class and date of authorisation	Class IIb, 12/10/2005

Version(s)	Launched	Features
1	13/04/2016	Self-expanding, removable stent made from nitinol with a silicone membrane. Radiopaque markers and removal loops.

Throughout this document the SX-Ella Stent Danis will be referred to as Danis Stent for brevity.

What are the claimed benefits of using the technology for patients and the NHS?

The claimed benefits in the NICE scope are not aligned with the outcomes in the NICE scope and therefore, it has not been possible to assess the available evidence against all of the claimed benefits. However, a rationale for the benefits has been provided based on the recommended indication, the instructions for use for Danis Stent, clinical evidence where available, expert clinical opinion (Mr Owen Dickinson, Dr David Patch and Dr Amer Al-Joudeh)(York Health Economics Consortium 2020c, York Health Economics Consortium 2020b, York Health Economics Consortium 2020a) and anecdotal clinical feedback.

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
– Faster recovery following procedure.	Anecdotal information driven by clinical feedback and commentary.	Relative claim based on several factors listed below. Ability to intake oral nutrition and reduced need for both general anaesthetic and/or intensive care unit care means patient may be admitted directly to standard ward. Additionally and perhaps most importantly, the patient is not required to have external fixation of the device as per balloon tamponade
– Improved quality of life.	Anecdotal information driven by clinical feedback	Relative claim based on several factors listed below. Reduced/eliminated intensive care unit care under general anaesthetic allows for a fast procedure recovery and allows oral nutrition, leading to improved quality of life.
– Fewer procedural complications.	Escorsell 2015 adverse event rate	Statistically fewer (p=0.049) device related adverse events were reported for patients receiving the Danis Stent compared to patients receiving balloon tamponade.
– Ability to intake oral sustenance.	Procedural instructions for use	Balloon tamponade requires external fixation of the system to either the patients face, or localised saline pole. Patient's oesophagus is obstructed during placement and while balloon tamponade remains in-situ. Danis Stent allows the oesophagus to remain un-obstructed, thus allowing oral intake and

		can be left in place for greater length of time.
– Reduced need for patient transfer.	Dependent on hospital facilities, based on anecdotal clinical feedback.	Patients with a balloon tamponade cannot be transferred thus limiting care options. Some tertiary centres that do not have a TIPS service may still transfer patients after Danis Stent implant, although this is dependent on hospital facilities.
– Better patient compliance.	Information driven by clinical experience and device placement.	Zero risk of patient removal of Danis Stent. Balloon tamponade is often 'self-removed' by uncompliant patients. This is one contributing factor that leads to balloon tamponade patients being kept under general anaesthetic.
– Eliminated/minimized high dependency hospitalisation.	Information driven by clinical experience, however, this is hospital dependent and may vary from Trust to Trust depending on existing hospital protocols.	Eliminated/reduced need for intensive care unit /intensive therapy unit care. Very patient specific and is determined by other clinical factors that help determine if a patient is suitable for TIPS e.g. Hepatic encephalopathy, renal function, bilirubin count etc..
– Increased possibility of stabilized bilirubin and renal functions promote TIPS option, where otherwise not possible.	Anecdotal clinical feedback	Danis Stent can be left in place for (7 days), combined with oral nutrition compared to the shorter duration of implantation for patient's receiving balloon tamponade (24 hours).
– Eliminates the need for GA and/or heavy sedation during haemostasis period.	Danis Stent instructions for use	Danis Stent implantation can be conducted without general anaesthetic however, this is patient and situation specific.
System benefits		
– Increased bed availability in ITU/high dependency units.	Clinical experience confirms that many Danis Stent patients can be cared for on standard wards within the NHS.	Reduced need to for high dependency care should free up beds for other patients
– Improved statistical positive patient outcomes.	Escorsell 2015	The number of patients with an absence of continued or further bleeding was statistically higher for patients receiving a Danis stent compared to patients receiving a balloon tamponade (p =0.037) at 15 days.

		Mortality was lower for patients receiving the Danis stent at 15 days compared to patients receiving the balloon tamponade (p=0.044). Device related adverse events were fewer in the Danis Stent arm compared to the balloon tamponade arm p= 0.049.
– Decreased strain on fluoroscopic imaging facilities.	Danis Stent instructions for use	Guidelines state oesophageal stents should be placed with radiological guidance. Danis Stent can be placed without guidance.
– Reduced length of patient's hospital stay.	Patient/situation specific	Faster stabilisation and more successful definitive treatment (TIPS) should reduce overall hospitalisation.
– Reduced hospital admissions/interventions.	No current evidence to support this.	Successful early/elective TIPS should provide definitive long-lasting treatment. Heavily reliant on habitual pattern changes by the patient. Should reduce overall admissions.
– Helps trusts achieve government targets relating to efficiency savings, hospital stays, positive outcomes & reduced repeated procedures.	Escorsell 2015 and economic model (Part 2 of the company evidence submission)	Statistically positive outcomes for Danis Stent compared to balloon tamponade for controlling bleeding, decreased mortality and reduced device related adverse events. Although not statistically significant, fewer packs of red blood cells were used for patients receiving Danis Stent compared to balloon tamponade and fewer cases of hepatic encephalopathy in patients receiving Danis Stent.
– Increased time for planning of definitive treatment (7 days vs 24-36 hours with balloon tamponade).	Instructions for use Escorsell 2015 Anecdotal clinical evidence	7 days implantation duration, and up to 2 weeks implantation duration according to anecdotal evidence and clinical trial evidence, provide a period of stabilisation allowing for successful definitive treatment.
– Increased possibility of successful TIPS, providing definitive treatment, thus reducing strain on NHS.	Anecdotal clinical evidence Escorsell 2015	By controlling the bleeding the patients can be stabilised and then are suitable candidates for TIPS.
– Significant cost saving against current treatment option.	Economic model (Part 2 of the company evidence submission)	Compared to balloon tamponade Danis Stent is likely to be cost-saving.
Cost benefits		

– Reduced costs associated with hospital stay in ITU or associated high dependency units.	Economic model (Part 2 of the company evidence submission)	Due to the greater control of bleeding, fewer adverse events, and the reduced or eliminated need for general anaesthetic for Danis Stent placement the requirement for ITU or associated high dependency units are reduced.
– Reduced costs in relation to minimized hospital visits and interventions.	Economic model (Part 2 of the company evidence submission) Escorsell 2015 Expert clinical opinion	Patients in receiving Danis Stent had statistically fewer device related adverse events, therefore the need for additional interventions is minimised and thus the control of bleeding can reduce the need for additional treatment.
– Efficiency savings based on streamlined patient care pathway.	Escorsell 2015 Economic model (Part 2 of the company evidence submission)	Few complications, fewer mortalities, lower costs, better definitive treatment.
Sustainability benefits		
– Less pharmaceutical usage with reduced environmental impacts associated with sedation and/or general anaesthetic.	Danis Stent instructions for use Expert clinical opinion	Reduced need for repeat procedures, as well as sedation/anaesthesia during haemostasis.
– Reduced need for repeat surgical interventions, which carry a substantial environmental impact.	No current evidence to support this.	Definitive treatment is achieved more rapidly.
– Reduced healthcare resource use, particularly resulting from high dependency care i.e. in the ICU.	Economic model (Part 2 of the company evidence submission) Anecdotal clinical evidence	Frequency and length of hospital admissions, particularly in high dependency care, are reduced.

Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology.

Danis stent is a self-expanding nitinol stent with a silicone membrane. It is designed to stop acute and/or refractory bleeding from oesophageal varices, as an alternative to balloon tamponade and early/salvage transjugular intrahepatic portosystemic shunt (TIPS) Danis stent works by applying standardised compression to varices, thus achieving effective haemostasis.

Danis stent comes pre-loaded in a balloon-style delivery system designed to enable accurate positioning at the gastro-oesophageal junction (GOJ). The stent can be inserted into the lower oesophagus without radiological or endoscopic assistance. After insertion, radiopaque markers at the distal ends and midpoint allow the stent's position to be confirmed by chest X-ray.

The stent is 135mm long and 25mm in diameter. It is supplied as part a basic procedure pack containing the stent, delivery system, guide wire, and syringe for inflation of the gastric balloon.

Danis stent is removable and can be extracted using the retrieval loops with gold markers positioned at both ends. The stent can stay in place for up to 7 days, after which it should be removed using a specifically designed device, the Ella extractor system. Alternatively, if the patient has received definitive treatment, e.g. TIPS (described in further detail in Section 3), and portal hypertension is no longer a concern, the stent can be removed under endoscopic guidance using grasping forceps.

Innovative features:

- Readily implantable without the need for endoscopic image guidance. This allows for more rapid control of variceal bleeds in emergency situations compared with balloon tamponade.
- Delivery system has a security pressure valve that prevents the gastric balloon from being inflated in the oesophagus, minimising risk of oesophageal perforation.
- Stent lumen allows oral nutrition to be maintained and ensures physiological drainage of saliva.
- Variable stent weave conforms to oesophageal peristalsis reducing the risk of stent migration.
- Can stay in place for up to 7 days, while balloon tamponade must be removed after 24-36 hours (National Institute for Health and Care Excellence 2019b). This gives clinicians more time to plan definitive therapy or secondary prophylaxis for the patient before device removal.
- Increased indwelling time also means that there is a longer stabilisation period for improvement in liver function compared with balloon tamponade.

Briefly describe the environmental impact of the technology and any sustainability considerations (no more than 1,000 words).

The Danis stent and its accessories (e.g. the delivery system and Ella extractor) are single-use technologies, which must be discarded after removal and cannot be recycled.

Despite this, Danis stent is expected to lead to a net reduction in the environmental impact of the clinical care pathway for oesophageal bleeding. This is because the technology aims to reduce the frequency and length of stay of hospital admissions, as well as the need for high dependency care and other resource-intensive NHS processes.

Use of Danis stent increases the possibility of definitive treatment, namely successful TIPS, for variceal oesophageal bleeds that have not been controlled with band ligation. This could reduce the need for pharmaceutical treatment, repeated interventions, and the associated environmental impact. Surgical interventions, which require use of anaesthesia/sedation and single-use instruments, are known to result in substantial carbon dioxide equivalent (CO_2e) emissions (Thiel et al. 2015).

Danis stent could also reduce the need for use of general anaesthetic and/or heavy sedation during haemostasis. The drugs and carrier gases (e.g. nitrous oxide) used in anaesthesia are potent greenhouse gases with ozone depletion potential (Sherman et al. 2012).

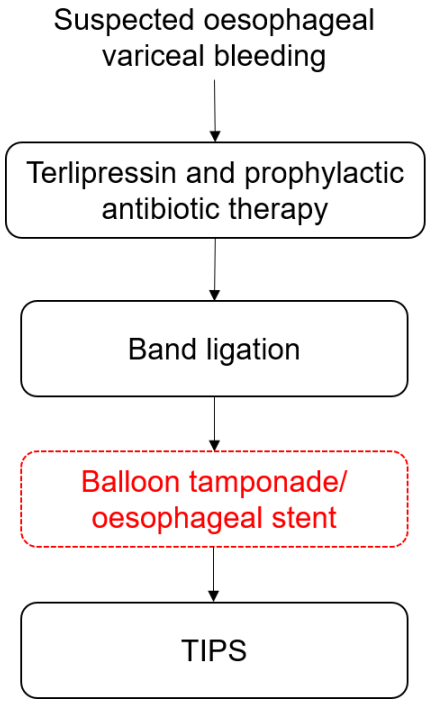
Finally, use of Danis stent could reduce the length and frequency of hospital admissions, as well as the need for high dependency care, e.g. in an ICU. This is because the technology allows effective haemostasis and definitive treatment to be achieved more rapidly. This can reduce healthcare resource use, particularly resource-intensive aspects of care such as ICU stays, thus reducing the environmental impact associated with treatment for variceal oesophageal bleeding.

One previous life cycle assessment of a medical stent technology, which analysed the environmental impact of a drug-eluting cardiological stent, found that the total CO_2e emissions were around 15kg per unit, with >90% emissions occurring in the distribution phase (Lee 2008). However, it is worth noting that this analysis could be outdated (published in 2008) and emissions may vary between technology and their distribution chains. Therefore, these results may not be generalisable to Danis stent.

3 Clinical context

Describe the clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. Provide source(s) for any relevant pathways.

3.1 Flowchart showing clinical care pathway for treatment of bleeding from oesophageal varices



The current care pathway for patients presenting with acute upper gastrointestinal bleeding involves basic resuscitation and endoscopy to determine the site of bleeding and investigate the possibility of the use of band ligation as a rescue therapy as soon as the patient is haemodynamically stable (Tripathi et al. 2015, National Institute for Health and Care Excellence 2012). If variceal bleeding is suspected, NICE's guideline on acute upper gastrointestinal bleeding in over 16s recommends offering the vasoactive drug terlipressin and prophylactic antibiotic therapy at presentation (National Institute for Health and Care Excellence 2012).

Band ligation is the first-choice therapy to stop bleeding (Tripathi et al. 2015, National Institute for Health and Care Excellence 2012). If bleeding from oesophageal varices cannot be controlled with band ligation, the NICE guideline recommends using TIPS (National Institute for Health and Care Excellence 2012). British Society for Gastroenterology UK guidelines on the management of variceal bleeding in cirrhotic patients suggest using temporary balloon tamponade (Sengstaken-Blakemore tube) as a bridge to more definitive treatment such as TIPS. There is some evidence to suggest that early TIPS (<72 hours) could be an effective option for controlling bleeding and improving patient survival; however, further evidence from multicentre RCTs is required (Tripathi et al. 2015).

Removable oesophageal stents like Danis stent can be used as a bridge to definitive treatment, or as an alternative to early TIPS. At the time the British Society for Gastroenterology guidelines were published, the authors stated that no published controlled trials had compared oesophageal stenting with balloon tamponade (Tripathi et al. 2015). However, this is no longer the case and published evidence suggests that there may be certain advantages to using a stent such as Danis stent over balloon tamponade as a bridge to definitive treatment (see Section 4).

Furthermore, NICE interventional procedures guidance on stent insertion for bleeding oesophageal varices states that there is enough evidence to demonstrate that stents are effective in people with oesophageal varices when other methods of treatment have failed to control bleeding (National Institute for Health and Care Excellence 2011). The Baveno VI consensus report, which makes recommendations for management of portal hypertension and associated complications, also states

that evidence on self-expanding metal stents suggests that they are equally effective and a safer option than balloon tamponade (de Franchis 2015).

Expert clinical expert feedback suggests that the Danis stent can be a vital palliative care measure. Allowing patients, for whom no definitive treatment is possible, additional time without being sedated. However, this is not an approved indication for the Danis Stent and therefore, the use of the Danis Stent in this way is considered off-label as it does not comply with the manufacturer's instructions for use.

Describe any training (for healthcare professionals and patients) and system changes that would be needed if the NHS were to adopt the technology.

No system changes would be required for use of Danis stent in the health and social care system. The procedure for stent insertion is similar to that used for balloon tamponade, which is already included in the current care pathway. Use of Danis stent could actually streamline the current care pathway because the technology does not require endoscopic image guidance, unlike balloon tamponade.

Training sessions are recommended to ensure that healthcare professionals are confident using the stent in an acute setting and refresh their knowledge of the technology on a regular basis. In-person training for consultants and nursing staff is provided free of charge by UK Medical at agreed intervals. These sessions can last between 1 hour and 1 day depending on the centre's needs and the frequency of repeat trainings.

A YouTube video of the implantation procedure, available from UK Medical, has been confirmed by clinicians implanting the Danis Stent to be a useful reference tool. All Danis resources are available to instant share through the UK Medical 'Showpad' app. This can be done 'off-line' and is not reliant on network connectivity, thus avoiding any potential issues of not being able to access the video tutorials.

4 Published and unpublished clinical evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		4,047
Number of studies identified as being relevant to the decision problem.		9 studies
Of the relevant studies identified:	Number of published studies (included in table 1).	9 studies
	Number of abstracts (included in table 2).	10 abstracts associated to the 9 published studies above
	Number of ongoing studies (included in table 3).	Zero studies

List of relevant studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published studies in table 1.
- Summarise details of abstracts in table 2.
- Summarise details of ongoing and unpublished studies in table 3.
- List the results of all studies (from tables 1, 2 and 3) in table 4.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1a Summary of all relevant published studies

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
(Escorsell et al. 2016)	Escorsell 2016, Spain	Multi-centre, open-label, RCT	• Cirrhosis patients with acute oesophageal variceal bleeding refractory to medical and endoscopic treatment • All patients had a complete 6-week follow-up, but 2 of them were lost afterward; it is not reported from which group	Danis stent (n = 13)	Balloon tamponade; lumen Sengstaken-Blakemore (n = 15)	• Composite endpoint of combination of absence of digestive bleeding and absence of SAEs and survival during the first 15 days after inclusion based on a modified Baveno III definition of treatment failure • Absence of bleeding at day 15 and at 6 weeks from inclusion • Survival at day 15 and at 6 weeks from inclusion • Overall transfusion requirements (units of packed red blood cells) • Device-related AEs • Length of hospital stay • Applicability of definitive haemostatic therapy • Use of additional therapeutic resources (TIPS, derivative surgery or additional endoscopic therapy)
(Ghidirim et al. 2012)	Ghidirim 2012, Moldova	Single-arm case series	• Patients with oesophageal bleeding refractory to standard therapy (EBL) • Loss to follow up NR	Danis stent (n = 14)	No comparator	• Initial haemostatic efficacy • Device related complications • 30-day mortality
(Goenka et al. 2017)	Goenka 2017, India	Single-arm case series	• Patients with persistent (after variceal band ligation) or	Danis stent (n = 12)	No comparator	• Re-bleeding • Mortality • Complications

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			complicated variceal bleeding • Loss to follow up NR			
(Maiwall et al. 2018)	Maiwall 2018, India	Retrospective case-control study	• Patients with acute-on-chronic liver failure and refractory variceal bleeds • Loss to follow up NR	Danis stent (n = 35)	Repeat endotherapy (polidocanol or cyanoacrylate glue or haemospray) with or without Sengstaken–Blakemore tube as a bridging therapy and continuation of vasoactive drugs (n = 53)	• Successful control of bleed at day 5 in the absence of SAE • 6-week bleed-related mortality • Overall mortality at day 15 and 6 weeks
(Muller et al. 2015)	Müller 2015, Germany	Retrospective, single-arm case series	• Patients with oesophageal variceal bleeding, refractory to standard therapy • Loss to follow up NR	Danis stent (n = 11)	No comparator	• Control of bleeding • Re-bleeding • Complications • Blood transfusion • Mortality
(Pfisterer et al. 2019)	Pfisterer 2018, Austria	Retrospective, single-arm case series	• Patients with cirrhosis and refractory bleeding from oesophageal varices • Of 42 relevant patients, 8 were excluded of these 7 had insufficient records and were not included in the analysis, 1 was not	Danis stent (n = 34)	No comparator	• Re-bleeding rates and mortality after self-expanding metal stent placement • Self-expanding metal stent dwell time, AE and the patients' clinical course • Rates of successful bleeding control (≤5 days), early re-bleeding (≤6

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
			eligible due to use of self-expanding mental stent with balloon tamponade			weeks) and re-bleeding rates within one year • Death within 5 days, bleeding-related mortality (≤6 weeks) and overall mortality • Successful self-expanding metal stent removal was defined as no re-bleeding or death within 1 day after stent removal
(Wright et al. 2010)	Wright 2010, UK	Single-arm case series	• Patients with refractory variceal bleeding with contraindications to TIPS and balloon-tamponade	Danis stent (n = 10)	No comparator	• Control of bleeding • Re-bleeding • Mortality • Complications
(Zakaria et al. 2013)	Zakaria 2013, Egypt	Single-arm case series	• Patients with acute oesophageal variceal bleeding exposed to standards of care in emergency situations • Reports that 4 were not included in the study as they refused to participate. 4 (25%) patients dropped out during follow up	Danis stent (n = 16)	No comparator	• Technical errors • Control of bleeding • Mortality • Hepatic encephalopathy • Blood transfusion • Treatment after stenting • Stent migration • AEs

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
(Zehetner et al. 2008)	Zehetner 2008, Austria	Single-arm case series	• Patients with oesophageal variceal bleeding that could not be managed with standard therapy • Loss to follow up NR	Danis stent (n = 34)	No comparator	• Haemorrhage stopped • Mortality • Definitive treatments • Complications

Key: AE – adverse event; EBL - endoscopic band ligation; NR – not reported; RCT – randomised controlled trial; SAE – serious adverse event; TIPS - transjugular intrahepatic portosystemic shunt

Table 1b Summary of population details

An asterisk (*) denotes a reviewer calculated value.

One study (Ghidirim 2012) reported that all patients in that study had portal hypertension, this was not reported by any of the other studies. Feedback from 3 clinical experts confirms that all patients with oesophageal variceal bleeding would have portal hypertension.

Data source	Author, year and location	Intervention	Age Mean years (SD)	Gender n (%) male	Aetiology of CLD n (%)	Active alcoholism n (%)	Previous variceal bleeding n (%)	On prophylaxis from bleeding n (%)	Cirrhotic ascites n (%)	Hepatic encephalopathy n (%)	Size of oesophageal varices n (%)
(Escorsell et al. 2016)	Escorsell 2016, Spain	Danis stent (n = 13)	Median (range): 69 (40-81)	13 (100)	Aetiology of cirrhosis: Alcohol: 8 (61.5*) Hepatitis C: 3 (23.1*) Other: 2 (15.4*)	4 (30.8*)	6 (46.2*)	6 (46.2*)	NR	NR	Small: 3 (23.1*) Large: 10 (76.9*)
		Balloon tamponade (n = 15)	Median (range): 54 (35-79)	12 (80*)	Aetiology of cirrhosis: Alcohol: 7 (46.7*) Hepatitis C: 4 (26.7*) Other: 4 (26.7*)	7 (46.7*)	9 (60*)	10 (66.7*)	NR	NR	Small: 1 (6.7*) Large: 14 (93.3*)
(Ghidirim et al. 2012)	Ghidirim 2012, Moldova	Danis stent (n = 14)	51.1 (2.63)	8 (57.1*)	Viral (hepatitis B or hepatitis C) liver cirrhosis induced portal hypertension: 14 (100)	NR	NR	NR	NR	NR	NR
(Goenka et al. 2017)	Goenka 2017, India	Danis stent (n = 12)	53 (13.7)	11 (91.7*)	Alcoholic: 4 (33.3*) Hepatitis B: 1 (8.3*) Hepatitis C: 3 (25*) Cryptogenic disease: 2 (16.7*) Non-alcoholic steatohepatitis: 1 (8.3*) Autoimmune hepatitis: 1 (8.3*)	NR	NR	All patients were initiated with resuscitative measures along with vasoactive drugs (octreotide or terlipressin)	NR	Advanced encephalopathy: 4 (33.3*)	NR

Data source	Author, year and location	Intervention	Age Mean years (SD)	Gender n (%) male	Aetiology of CLD n (%)	Active alcoholism n (%)	Previous variceal bleeding n (%)	On prophylaxis from bleeding n (%)	Cirrhotic ascites n (%)	Hepatic encephalopathy n (%)	Size of oesophageal varices n (%)
(Maiwall et al. 2018)	Maiwall 2018, India	Danis stent (unmatched cohort) (n = 35)	46.4 (12.7)	34 (97.1)	Across both groups, alcohol was the most common aetiology: 69 (78.4). Not reported by treatment arm	NR	NR	NR	NR	NR	NR
		Repeat endotherapy (unmatched cohort) (n = 53)	47.9 (9.7)	49 (92.5)		NR	NR	NR	NR	NR	NR
		Danis stent (matched cohort) (n = 22)	48.3 (13.6)	21 (95.5)	NR	NR	NR	NR	NR	NR	NR
		Repeat endotherapy (matched cohort) (n = 22)	47.5 (9.8)	21 (95.5)	NR	NR	NR	NR	NR	NR	NR
(Muller et al. 2015)	Müller 2015, Germany	Danis stent (n = 11)	64.2 (12.4)	8 (72.7*)	Cirrhosis: 10 (90) Aetiology ethanol: 9 (81) Hepatitis B or C: 1 (9) Cryptogenic: 1 (9) Jak-Mutation (with portal vein thrombosis): 1 (9) More than one aetiology possible	NR	5 (45)	11 (100)	9 (81.8)	NR	Paquet grade I: 1 (9) II: 2 (18) III: 6 (54) IV: 2 (18)
(Pfisterer et al. 2019)	Pfisterer 2018, Austria	Danis stent (n = 34)	55.5 (11.5)	28 (82.4)	Alcoholic liver disease: 16 (47.1) Viral hepatitis: 8 (23.5) Combined alcoholic liver disease/viral hepatitis: 4 (11.8) Other: 3 (8.8) Cryptogenic: 3 (8.8)	NR	18 (52.9)	NR	21 (72.4)	NR	Large: 23 (67.6)

Data source	Author, year and location	Intervention	Age Mean years (SD)	Gender n (%) male	Aetiology of CLD n (%)	Active alcoholism n (%)	Previous variceal bleeding n (%)	On prophylaxis from bleeding n (%)	Cirrhotic ascites n (%)	Hepatic encephalopathy n (%)	Size of oesophageal varices n (%)
(Wright et al. 2010)	Wright 2010, UK	Danis stent (n = 10)	Median (range): 49.5* (18 - 70)	9 (90)*	Alcohol: 6 (60*) Alcohol and hepatitis C virus infection: 2 (20*) Cryptogenic: 1 (10*) Primary biliary cirrhosis: 1 (10*)	NR	NR	NR	NR	NR	NR
(Zakaria et al. 2013)	Zakaria 2013, Egypt	Danis stent (n = 16)	55.6 (5.62)	14 (87.5)	Hepatitis C viral related: 16 (100)	NR	Mean (SD) number of past bleeding episodes: 0.75 (1.23)	NR	11 (68.75)	NR	Grade I-II: 5 (31.25) Grade III-IV: 11 (68.75)
(Zehetner et al. 2008)	Zehetner 2008, Austria	Danis stent (n = 34)	NR	NR	Alcoholism: 26 (32.4*) Immunologic or cryptogenic: 4 (11.8*) Virus-induced: 4 (11.8*)	NR	24 (70.5*)	NR	NR	NR	NR

Key: NR – not reported; SD – standard deviation
*calculated by reviewer

Table 1c Summary of population details (renal function)

Data source	Author, year and location	Intervention	Albumin levels Mean (SD)	Creatinine levels Median (range)	Child Pugh score n (%)	MELD score Median (range)	Bilirubin level Median (range)	Coagulation n (%)	Co-morbidities n (%)
(Escorsell et al. 2016)	Escorsell 2016, Spain	Danis stent (n = 13)	NR	NR	A: 3 (23.1*) B/C: 10 (76.9*)	16.5 (9-32)	NR	NR	Portal vein thrombosis: 1 (7.7*) Hepatocellular carcinoma: 2 (15.4*) Shock at index bleed: 5 (38.5*)
		Balloon tamponade (n = 15)	NR	NR	A: 2 (13.3*) B/C: 13 (86.7*)	17 (11-25)	NR	NR	Portal vein thrombosis: 2 (13.3*) Hepatocellular carcinoma: 2 (13.3*) Shock at index bleed: 10 (66.7*)
(Ghidirim et al. 2012)	Ghidirim 2012, Moldova	Danis stent (n = 14)	NR	NR	9.54 (0.44)	Mean (SD): 17.68 (1.7)	NR	NR	NR
(Goenka et al. 2017)	Goenka 2017, India	Danis stent (n = 12)	NR	NR	NR	Mean (SD): 20.17 (5.97)	NR	NR	NR
(Maiwall et al. 2018)	Maiwall 2018, India	Danis stent (unmatched cohort) (n = 35)	2.4 (0.67) g/dL	Median (NR):** 1.08 (0.72 -1.93) mg/dL	A: 0: B: 6 (17.1) C: 29 (82.9)	Median (NR): 39 (30 - 47)	Median (NR): 11.9 (3.4 - 27.7) mg/dL	Platelets mean (SD): 125 (71.5) $10^3/mm^3$ Haemoglobin mean (SD): 9.1 (2.1)g/dl International normalised ratio: Median 2.1 (1.58 - 2.5)	Hepatic encephalopathy and bacterial infections were reported by this study however, it is unclear if this was at baseline or after treatment. Study authors were contacted but no response was received.

Data source	Author, year and location	Intervention	Albumin levels Mean (SD)	Creatinine levels Median (range)	Child Pugh score n (%)	MELD score Median (range)	Bilirubin level Median (range)	Coagulation n (%)	Co-morbidities n (%)
		Repeat endotherapy (unmatched cohort) (n= 53)	1.9 (0.61) g/dL	Median (NR):** 1.38 (0.7–2.58) mg/dL	A: 0 B: 2 (3.8) C: 51 (96.2)	Median (NR): 43 (34.4–65)	Median (NR): 20.4 (10.6–27.6) mg/dL	Platelets mean (SD): 141.9 (81.5) $10^3/mm^3$ Haemoglobin mean (SD): 9.8 (2.3)g/dl International normalised ratio: Median 2.28 (1.74 - 3.32)	Hepatic encephalopathy and bacterial infections were reported by this study however, it is unclear if this was at baseline or after treatment. Study authors were contacted but no response was received.
		Danis stent (matched cohort) (n = 22)	2.4 (0.66) g/dL	Median (NR):** 1.26 (0.75–2.7) mg/dL	A: 0 B: 2 (9) C: 20 (91)	Median (NR): 39 (32–52)	Median (NR): 12.5 (3.2–30.2) mg/dL	Platelets mean (SD): 129 (77) $10^3/mm^3$ Haemoglobin mean (SD): 9.2 (2.2)g/dl International normalised ratio: Median 2.1 (1.56 - 2.6)	Hepatic encephalopathy and bacterial infections were reported by this study however, it is unclear if this was at baseline or after treatment. Study authors were contacted but no response was received.
		Repeat endotherapy (matched cohort) (n = 22)	2.2 (0.64) g/dL	Median (NR):** 1.04 (0.62–1.38) mg/dL	A: 0 B: 3 (14) C: 19 (86)	Median (NR): 37 (25–45)	Median (NR): 9.5 (4.4–24) mg/dL	Platelets mean (SD): 157 (88.5) $10^3/mm^3$ Haemoglobin mean (SD): 9.7 (2.4)g/dl International normalised ratio: Median 1.96 (1.46 - 2.4)	Hepatic encephalopathy and bacterial infections were reported by this study however, it is unclear if this was at baseline or after treatment. Study authors were contacted but no response was received.

Data source	Author, year and location	Intervention	Albumin levels Mean (SD)	Creatinine levels Median (range)	Child Pugh score n (%)	MELD score Median (range)	Bilirubin level Median (range)	Coagulation n (%)	Co-morbidities n (%)
(Muller et al. 2015)	Müller 2015, Germany	Danis stent (n = 11)	NR	119 (53-192) mcmol/L	A: 1 (9.1*) B: 6 (54.5*) C: 3 (27.2*) Non-cirrhotic patient: 1 (9.1*)	At day of admission: 15.5* (8 to 36) Non-cirrhotic patient n (%): 1 (9.1*)	23 (12-514)	Coagulation disorder: 4 (36.4*) Low platelets: 8 (72.7*)	Hepatocellular carcinoma: 3 (27) Portal vein thrombosis: 4 (36) Isolated oesophageal distribution of varicose: 8 (72) Combined oesophageal and gastric distribution of varicose: 8 (72) Hiatal hernia: 4 (36) Cardiac arrest due to hypovolemic shock: 1 (9.1*)
(Pfisterer et al. 2019)	Pfisterer 2018, Austria	Danis stent (n = 34)	Median (IQR): 28.9 (8.2)g/L	Median (IQR): 0.95 (0.75) mg/dL	A: 1 (2.9) B: 10 (29.4) C: 8 (23.5)	18 (10)	Median (IQR): 2 (3.7) mg/dL	International normalised ratio, Median (IQR): 1.5 (0.5)	Hepatocellular carcinoma: 6 (17.6) Portal vein thrombosis: 4 (11.8) Additional gastric varices: 3 (8.8)
(Wright et al. 2010)	Wright 2010, UK	Danis stent (n = 10)	24.5 (5.64)* g/dL	93.5 (29-245) mcmol/L	NR	NR	153 (27-711) mcmol/L	Platelet count Median (range): 108* (40 -153)* Giga/L	Hepatocellular carcinoma: 2 (20*)
(Zakaria et al. 2013)	Zakaria 2013, Egypt	Danis stent (n = 16)	NR	NR	A: 2 (12.5) B: 8 (50.0) C: 6 (37.5)	NR	NR	NR	Abdominal collaterals: 11 (68.75)
(Zehetner et al. 2008)	Zehetner 2008, Austria	Danis stent (n = 34)	NR	NR	A: 0 B: 13 (38.2*) C: 21 (61.8*)	NR	NR	NR	NR

Key: IQR – interquartile range; NR – not reported
*Calculated by reviewer; ** Maiwall 2018 study authors did not confirm if this was a range or interquartile range.

Table 2 Included studies list

The abstracts identified as eligible during the systematic review provide supplementary information to the 9 studies in Table 1 and, therefore, are not standalone studies hence Table 2 lists all included studies and their associated (conference abstract) publications eligible for inclusion in the systematic review.

Study	Reference (Primary publication in bold)
Escorsell, 2016	Escorsell A, Pavel O, Cardenas A, Morillas R, Llop E, Villanueva C, et al. Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: A multicenter randomized, controlled trial. Hepatology. 2016;63(6):1957-67.
Ghidirim, 2012	Ghidirim G, Mishin IV, Dolghii AN, Bunic GC, Zastavnitsky GM. Self-expanding metal stent for the management of bleeding esophageal varices - Single centre experience. Clin Anat Oper Surg. 2012;11(4):100-03.
Goenka, 2017	**Goenka MK, Goenka U, Tiwary IK, Rai V. Use of self-expanding metal stents for difficult variceal bleed. Indian J Gastroenterol. 2017;36(6):468-73.**
	Goenka M, Bera C, Rai V, Tiwar II, Goenka U. The use of self-expanding fully covered metal stent for control of refractory variceal haemorrhage. Dig Endosc. 2017;29(Suppl 1):112.
	Goenka MK, Bera C, Rai V, Tiwary IK, Goenka U. The use of self-expanding metal stent for refractory variceal haemorrhage. J Gastroenterol Hepatol (Aus). 2016;31(Suppl 3):281.
	Goenka MK, Rai VK, Bera C, Tiwary I, Goenka U. The use of self-expanding metal stent for refractory variceal haemorrhage. Gastrointest Endosc. 2017;85(5 Suppl 1):AB413.
Maiwall, 2018	**Maiwall R, Jamwal KD, Bhardwaj A, Bhadoria AS, Maras JS, Kumar G, et al. SX-Ella Stent Danis effectively controls refractory variceal bleed in patients with acute-on-chronic liver failure. Dig Dis Sci. 2018;63(2):493-501.**
	Maiwall R, Jamwal K, Sharma M, Kumar G, Chowdhury A, Jindal A, et al. Management of refractory variceal bleed with Dannis-Ella stent in in patients with acute on chronic liver failure. J Gastroenterol Hepatol (Aus). 2016;31(Suppl 3):358-59.
	Maiwall R, Jamwal K, Sharma MK, Kumar G, Bhadoria AS, Chowdhury AK*, et al.* Management of refractory variceal bleed with Dannis-ella stent in patients with acute-on-chronic liver failure. Indian J Gastroenterol. 2016;35(1 Supplement):A6.
	Maiwall R, Jamwal KD, Kumar G, Sharma M, Choudhary A, Jindal A*, et al.* Management of refractory variceal bleed with dannis-ella stent in patients with acute on chronic liver failure. Hepatology. 2016;64(1 Suppl 1):844A.
Muller, 2015	Muller M, Seufferlein T, Perkhofer L, Wagner M, Kleger A. Self-expandable metal stents for persisting esophageal variceal bleeding after band ligation or injection-therapy: A retrospective study. PLoS ONE. 2015;10(6):e0126525.
Pfisterer, 2019	**Pfisterer N, Riedl F, Pachofszky T, Gschwantler M, Konig K, Schuster B, et al. Outcomes after placement of a SX-ELLA oesophageal stent for refractory variceal bleeding-A national multicentre study. Liver Int. 2019;39(2):290-98.**
	Pfisterer N, Dolak W, Pachofszky T, Schoniger-Hekele M, Schuster B, Tribl B, et al. Outcome after the use of SX-ELLA Danis bleeding stents for refractory variceal bleeding-A Vienna multicenter experience. J Hepatol. 2018;68(Suppl 1):S729-S30.
	Pfisterer N, Dolak W, Pachofszky T, Schoniger-Hekele M, Schuster B, Tribl B, et al. Outcome after SX-ELLA Danis bleeding stent implantation for refractory variceal bleeding-A Vienna multicenter experience. Z Gastroenterol. 2017;55(5)

	Pfisterer N, Pachofszky T, Dolak W, Schoniger-Hekele M, Schuster B, Tribl B, et al. Outcome after the use of sx-ella danis bleeding stents for refractory variceal bleeding-A vienna multicenter experience. United European Gastroenterol J. 2017;5(5 Suppl 1):A256.
Wright, 2010	**Wright G, Lewis H, Hogan B, Burroughs A, Patch D, O'Beirne J. A self-expanding metal stent for complicated variceal hemorrhage: Experience at a single center. Gastrointest Endosc. 2010;71(1):71-8.**
	Hogan B, Patch D, Burroughs A, O'Beirne J. Use of the SX-Ella self-expanding mesh metal stent in the management of complex variceal haemorrhage: Initial experience in a single centre. J Hepatol. 2009;50(Suppl 1):S86-S87.
Zakaria, 2013	Zakaria MS, Hamza IM, Mohey MA, Hubamnn RG. The first Egyptian experience using new self-expandable metal stents in acute esophageal variceal bleeding: Pilot study. Saudi J Gastroenterol. 2013;19(4):177-81.
Zehetner, 2008	Zehetner J, Shamiyeh A, Wayand W, Hubmann R. Results of a new method to stop acute bleeding from esophageal varices: Implantation of a self-expanding stent. Surg Endosc. 2008;22(10):2149-52.

Table 3 Summary of all relevant ongoing or unpublished studies

It is understood that there no relevant studies are ongoing and no unpublished studies have been identified.

RESULTS

No studies reported any data regarding patient related quality of life. Results of all relevant studies are reported in Table 4a to 4f for each of the efficacy outcomes relevant to the submission scope.

Table 4a Control of bleeding

Study	Population	Outcome definition and measure	Time point of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
(Escorsell et al. 2016)	ITT	Absence of continued or further bleeding; Continuous bleeding was defined as haematemesis (or >100 mL of fresh blood by nasogastric	15 days	Danis stent	13	11 (85)	p=0.037
				Balloon tamponade	15	7 (47)	

Study	Population	Outcome definition and measure	Time point of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
		tube) 2 hours after the placement of the assigned device or a decrease in haemoglobin >3 g versus previous values (without blood transfusion)	6 weeks	Danis stent	13	7 (54)	p=0.25
				Balloon tamponade	15	7 (47)	
(Ghidirim et al. 2012)	Treated sample	Initial haemostatic efficacy	NR	Danis stent	14	14 (100)	NA
(Goenka et al. 2017)	Treated sample	Cessation of bleeding confirmed by endoscopic examination after stent placement. Haemostasis was also confirmed by repeat endoscopy 48 hours later	48 hours	Danis stent	12	12 (100)	NA
(Maiwall et al. 2018)	Unmatched cohort	Control of bleeding	5 days	Danis stent	35	31 (89)	p = <0.001
				Repeat endotherapy	53	18 (36.5)	
	Matched cohort	Control of bleeding	5 days	Danis stent	22	16 (72.7)	p = 0.007
				Repeat endotherapy	22	7 (31.8)	
(Muller et al. 2015)	Treated patients	Immediate control of bleeding (after stent deployment)	Immediately following stent deployment	Danis stent	11	11 (100)	NA
(Pfisterer et al. 2019)	Treated patients	Control of bleeding	≤5 days	Danis stent	34	27 (79.4)	NA
		Bleeding control without re-bleeding within 6 weeks	≤ 6 weeks		34	10 (29.4)	NA
(Wright et al. 2010)	Treated patients	Control of bleeding according to Baveno IV criteria	NR	Danis stent	10	7 (70*)	NA
(Zakaria et al. 2013)	Treated patients	Initial control of variceal bleeding (acute ongoing variceal bleeding defined as endoscopically proven	NR	Danis stent	16	14 (87.5)	NA

Study	Population	Outcome definition and measure	Time point of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
		ongoing (and/or spurting) active bleeding from oesophageal varices. This included also the presence of cherry red spots as stigmata of variceal bleeding and or blood in the oesophagus or stomach (verified by endoscopy)					
(Zehetner et al. 2008)	Treated patients	Haemorrhage stopped immediately	Immediately after placement	Danis stent	34	34 (100)	NA

Key: NA – not applicable; NR – not reported
*Calculated by reviewer

Table 4b Rate of re-bleeding

Study	Population	Outcome definition and measure	Time point of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)
(Goenka et al. 2017)	Treated sample	Re-bleeding after stent removal	10 days after stent removal	Danis stent	12	1 (8.33*)
	Patients surviving 30 day follow up	Re-bleeding after stent removal	30 days		7	0 (0)
(Muller et al. 2015)	Treated patients	Re-bleeding within 48 hours of stent deployment	48 hours	Danis stent	11	1 (9)
		Re-bleeding while the stent was in situ	5 to 24 days		11	0 (0)
		Re-bleeding during stent removal	NR		11	1 (9*)
(Maiwall et al. 2018)	Treated patients	Re-bleed after initial haemostasis	NR	Danis stent	35	5 (14)
				Repeat endotherapy	53	NR
(Pfisterer et al. 2019)	Treated patients	Re-bleeding at stent removal: Re-bleeding was defined according to the Baveno V guidelines; evidence of re-bleeding from portal hypertensive sources (haematemesis, melaena, aspiration of >100 mL of fresh blood in patients with a nasogastric tube and/or decrease in haemoglobin of 3 g/dL without blood transfusion	NR	Danis stent	34	3 (8.8)
		Re-bleeding after successful stent removal: Re-bleeding defined as above	NR		20	7 (35)
		Re-bleeding while stent in situ: Re-bleeding defined as above	NR		34	5 (14.7)
		Re-bleeding within 6 weeks	≤6 weeks		34	6 (17.6)
(Wright et al. 2010)	Treated patients	Re-bleeding after initial control	60 days after stent removal	Danis stent	10	1 (10*)

Key: NR – not reported *Calculated by reviewer

Table 4c Blood transfusion use

Study	Population	Outcome definition and measure	Time point of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
(Escorsell et al. 2016)	ITT	Packed red blood cell transfusion after inclusion	NR	Danis Stent	13	Median number of transfusions (range): 2 (0 to 12)	p=0.08
				Balloon tamponade	15	Median number of transfusions (range): 6 (0 to 15)	
(Muller et al. 2015)	Treated patients	Blood transfusion use	NR	Danis stent	11	8 (72)	NA
(Zakaria et al. 2013)	Treated patients	Number of blood units transfused during hospital stay	NR	Danis stent	16	NR	NA

Key: ITT – intention-to-treat; NA – not applicable; NR – not reported

Table 4d Mortality

Study	Population	Outcome definition and measure	Time point of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
(Escorsell et al. 2016)	ITT	Mortality	15 days	Danis stent	13	4* (30.8*)	0.044
				Balloon tamponade	15	7* (46.7*)	

Study	Population	Outcome definition and measure	Time point of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
			6 weeks	Danis stent	13	6* (46.2*)	p = 0.46
				Balloon tamponade	15	9* (60*)	
(Ghidirim et al. 2012)	Treated sample	30-day mortality	30 days	Danis stent	14	5 (35.7)	NA
(Goenka et al. 2017)	Treated sample	Mortality on initial self-expanding metal stent	NR	Danis stent	12	4 (33.3*)	NA
		Mortality following re-bleeding after stent removal and implantation if a second Danis stent	7 days after a 2nd stent was implanted	Danis stent	12	1 (8.3*)	NA
(Maiwall et al.)	Unmatched cohort	Died due to bleed	NR	Danis stent	35	5 (14.3)	p = 0.001
				Repeat endotherapy	53	27 (64)	
	Matched cohort	Died due to bleed	NR	Danis stent	22	1(5.6)	p = 0.001
				Repeat endotherapy	22	9 (56.3)	
	Unmatched cohort	Overall mortality	15 days	Danis stent	35	NR	HR: 2.56 (95% CI 1.35–4.83) p = 0.004**
				Repeat endotherapy	53	NR	
	Matched cohort	Overall mortality	15 days	Danis stent	22	NR	HR: 6.94 (95% CI 0.85–56.6) p = 0.07**
				Repeat endotherapy	22	NR	
	Unmatched cohort	Overall mortality	6 weeks	Danis stent	35	NR	HR: 1.39 (95% CI 0.85–2.29) p = 0.19**
				Repeat endotherapy	53	NR	
	Matched cohort	Overall mortality	6 weeks	Danis stent	22	NR	HR: 8.1 (95% CI 1.02–64.4) p = 0.05**
				Repeat endotherapy	22	NR	
(Muller et al. 2015)	Treated patients	Mortality	Day 5 after stent implantation	Danis stent	11	1 (9.1*)	NA

Study	Population	Outcome definition and measure	Time point of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
			42 days		11	3 (27.3)	
(Pfisterer et al. 2019)	Treated patients	Mortality due to uncontrolled bleeding	≤5 days	Danis stent	34	7 (20.6)	NA
		Mortality related to bleeding	≤6 weeks		34	9 (26.5)	
		Mortality with stent in situ	NR		34	13 (38.2)	
		Mortality within 5 days of stent removal due to uncontrolled bleeding	≤5 days of stent removal		34	1 (2.9)	
		Mortality within 6 weeks of stent removal related to uncontrolled bleeding	≤6 weeks of stent removal		34	4 (11.8)	
		Overall mortality	NR		34	22 (64.7)	
		Overall mortality due to bleeding	NR		34	16 (47.1)	
(Wright et al. 2010)	Treated patients	Mortality after failure to control bleeding	NR	Danis stent	10	3 (30*)	NA
		Mortality due to progressive multiple organ failure	Day 11 after stent insertion		10	1 (10*)	
			Day 17 after stent insetion		10	1 (10*)	
		Mortality at day 42	42 days		10	5 (50*)	
(Zakaria et al. 2013)	Treated patients	Mortality	NR	Danis stent	16	4 (25)	NA
(Zehetner et al. 2008)	Treated patients	30-day mortality	30 days	Danis stent	34	9 (26.5)	NA
		60-day mortality	60 days		34	10 (29.4)	

Key: CI – confidence interval; HR – hazard ratio; NA – not applicable; NR – not reported
*Calculated by reviewer; ** These data are reported inconsistently between the text and the tables of this study paper. Data from the text have been used.

Table 4e Hepatic encephalopathy

Study	Population	Outcome definition and measure	Time point of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
(Escorsell et al. 2016)	ITT	Severe hepatic encephalopathy after inclusion	NR	Danis stent	13	5 (39)	p=0.063
				Balloon tamponade	15	11 (73)	
(Zakaria et al. 2013)	Treated patients	Development of hepatic encephalopathy	NR	Danis stent	16	2 (12.5)	NA

Key: ITT – intent-to-treat; NA – not applicable; NR – not reported

Table 4f Additional interventions/further treatments

Study	Population	Outcome definition and measure	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
(Escorsell et al. 2016)	ITT	Definitive treatment oesophageal band ligation and nonselective beta blockers	Danis stent	13	5 (38*)	NR
			Balloon tamponade	15	0	
		Definitive treatment TIPS	Danis stent	13	4 (31)	p = 0.12
			Balloon tamponade	15	10 (67)	
(Ghidirim et al. 2012)	Treated sample	Definitive treatment EBL	Danis stent	14	7 (50*)	NA
		Definitive treatment Oesophageal variceal ligation		14	2 (14.3*)	
(Goenka et al. 2017)	Treated sample	Second self-expanding metal stent placed after study stent	Danis stent	12	1 (8.33*)	NA
	Patients surviving 30 day follow up	Variceal band ligation after 30-day follow up	Danis stent	7	4 (57.1*)	NA
(Muller et al. 2015)	Treated patients	Treatment after stent removal: TIPS	Danis stent	11	2 (18)	NA
		Treatment after stent removal: Liver transplantation		11	1 (9)	

Study	Population	Outcome definition and measure	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
(Pfisterer et al. 2019)	Treated patients	Early TIPS	Danis stent	34	0 (0)	NA
		Elective TIPS after stent placement		34	4 (11.8)	
		In patients with uncontrolled bleeding after 5 days: EBL		7	3 (42.9*)	
		In patients with uncontrolled bleeding after 5 days: renewed/replacement of self-expanding metal stent		7	2 (28.6*)	
		In patients with uncontrolled bleeding after 5 days: Stent removed and Linton balloon tamponade		7	1 (14.3*)	
		In patients with uncontrolled bleeding after 5 days: Additional balloon tamponade		7	1 (14.3*)	
		In patients with early re-bleeding ≤6 weeks: EBL		5	4 (80*)	
		In patients with early re-bleeding ≤6 weeks: Sengstaken balloon tamponade		5	1 (20*)	
		In patients with early re-bleeding ≤6 weeks: Stent renewed or replaced		5	1 (20*)	
		In patients who survived 6 weeks without early re-bleeding: treated with Sengstaken balloon tamponade after unsuccessful EBL		12	2 (16.7*)	
(Wright et al. 2010)	Treated patients	TIPS	Danis stent	10	3 (30)	NA
(Zakaria et al. 2013)	Treated patients	Further intervention during follow up: Band ligation	Danis stent	16	3 (18.75)	NA
		Further intervention during follow up: Sclerotherapy	Danis stent	16	7 (43.75)	NA
(Zehetner et al. 2008)	Treated patients	Total gastrectomy and azygoportal disconnection	Danis stent	34	1 (2.9*)	NA
		Endoscopic band ligations		34	11 (32.4*)	

Study	Population	Outcome definition and measure	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
		TIPS		34	8 (23.5*)	
		Laparoscopic azygoportal disconnection		34	5 (14.7*)	
		Radiologic interventional procedure (coiling)		34	2 (5.9*)	
		Liver transplant list and treated with interventional and endoscopic therapies		34	2 (5.9*)	

Key: EBL - endoscopic band ligation; ITT – intent-to-treat; NA – not applicable; NR – not reported; TIPs – transjugular intrahepatic portosystemic shunt; *Calculated by reviewer

5 Details of relevant studies

Please give details of all relevant studies (all studies in table 4). Copy and paste a new table into the document for each study. Please use 1 table per study.

The claimed benefits in the NICE scope are not aligned with the outcomes in the NICE scope. Therefore, we have summarised the evidence for the outcomes in the scope in each of the tables below. The presence of an asterisk (*) denotes a reviewer calculated value.

(Escorsell et al. 2016)	
How are the findings relevant to the decision problem?	This is the only RCT evaluating Danis stent comparing it balloon tamponade and, therefore, provides the most comprehensive assessment available of Danis stent of patients with acute refractory oesophageal bleeds.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Below is a summary of the evidence for the outcomes in the scope reported in Tables 4a, 4c, 4d, 4e and 4f. This study confirmed that: **Control of bleeding** The number of patients with an absence of continued or further bleeding was statistically higher for patients receiving a Danis stent compared to patients receiving a balloon tamponade (p =0.037) at 15 days. This difference was not statistically significant at 6-weeks. **Blood transfusion use** Blood transfusion of packed red blood cells was lower in the Danis stent arm (Median 2, range 0 to 12) when compared to patients receiving balloon tamponade (Median 6, range 0 to 15). However, this was not found to be statistically significant p=0.08. **Mortality** Mortality was lower for patients receiving the Danis stent at 15 days compared to patients receiving the balloon tamponade (p=0.044). However, although the trend continued at 6-weeks there was no statistically significant difference. **Hepatic encephalopathy** Hepatic encephalopathy occurred in fewer patients in the Danis stent arm (39%) compared to patients receiving the balloon tamponade (73%); however, this difference was not statistically significant. **Additional/further interventions** The definitive treatment of oesophageal band ligation and non-selective beta-blockers was used in 39% of patients who had undergone Danis stent implantation, whereas this treatment was not used at all in patients

(Escorsell et al. 2016)	
	receiving balloon tamponade, however, this was not statistically assessed. TIPS was used as the definitive treatment less frequently in patients who had received the Danis stent (31%) when compared to those patients who had received balloon tamponade (67%), however, this was not statistically significant. **Unreported outcomes** This study did not report data on the rate of re-bleeding nor did it assess patient related quality of life.
Will any information from this study be used in the economic model?	This is the key study informing the economic model.
What are the limitations of this evidence?	Whilst the small sample number is a limitation of this study, this is representative of the small number of patients with acute refractory oesophageal variceal bleeding. This study was not conducted in the UK but was conducted in Europe, and so is considered generalisable. However, patients who had previously undergone balloon tamponade as treatment for the index bleed where excluded from the study and this does not reflect UK clinical practice.
How was the study funded?	Supported by grants from the Fondo Sanitario de la Seguridad Social, Instituto de Salud Carlos III, Spain, and from the CIBERehd

(Ghidirim et al. 2012)	
How are the findings relevant to the decision problem?	The findings of this case series include the relevant population to the scope as all patients were refractory to standard therapy of endoscopic band ligation for oesophageal bleeding for the decision problem and the intervention assessed was the Danis stent reported data on a number of eligible outcomes.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Below is a summary of the evidence for the outcomes in the scope reported in Tables 4a, 4d and 4f. This study confirmed that: **Control of bleeding** There was initial haemostatic efficacy of the Danis stent in all 14 patients (100%) treated with the device. However, the time point at which this occurred was not reported. **Mortality** 30-day mortality occurred in 5 patients (35.7%). **Additional/further interventions**

(Ghidirim et al. 2012)	
	Definitive treatment of endoscopic band ligation was administered to 7 patients (50%*) following treatment with the Danis stent. Two patients (14.3%*) received oesophageal variceal ligation as the definitive treatment. **Unreported outcomes** This study did not report data on the rate of re-bleeding, the use of blood transfusions, the number of patients with hepatic encephalopathy or patient related quality of life.
Will any information from this study be used in the economic model?	This study will be used to inform sensitivity analyses conducted on the economic model.
What are the limitations of this evidence?	The limitations of this evidence are that the study was not comparative and the sample size was small, 14 patients only. However, due to the small number of patients with acute refractory oesophageal variceal bleeding this is not unexpected. Overall study reporting in this study was limited as and limited baseline data reported. This study was not conducted in the UK but was conducted in Europe, and so is considered generalisable.
How was the study funded?	Not reported

(Goenka et al. 2017)	
How are the findings relevant to the decision problem?	The findings of this case series include the relevant population as all patients either had persistent variceal bleeding despite variceal band ligation or experienced variceal band ligation induced ulcer bleeding. In all cases the treatment intervention was the Danis stent.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Below is a summary of the evidence for the outcomes in the scope reported in Tables 4a, 4b, 4d and 4f. This study confirmed that: **Control of bleeding** Bleeding was controlled at 48 hours following Danis stent placement in all 12 patients (100%) as was haemostasis 48 hours later. **Rate of re-bleeding** Of the 12 treated patients, 1 patient (8.33%*) experienced re-bleeding 10 days after stent removal. None of the patients surviving 30-days experienced re-bleeding. **Mortality** Mortality following initial Danis stent implantation (time point not reported) occurred in 4 patients (38.3%*). These deaths were not due to bleeding

(Goenka et al. 2017)	
	but caused by worsening encephalopathy or sepsis. The 1 patient who re-bled 10 days after stent removal, died 7 days later due to worsening sepsis a second Danis stent had been implanted to try and stop the bleeding. **Additional/further interventions** Of the 7 surviving patients 4 patients (57.1*) required further variceal band ligation. **Unreported outcomes** This study did not report data on the use of blood transfusions, the numbers of patients with hepatic encephalopathy or patient related quality of life.
Will any information from this study be used in the economic model?	This study will be used to inform sensitivity analyses conducted on the economic model.
What are the limitations of this evidence?	There was limited clinical data reported and whilst the text would suggest that some patients experienced hepatic encephalopathy the exact numbers of patients were not reported either at baseline or as an outcome. The sample size is also low with 12 patients and no comparator was used. Danis stents were also implanted for varying durations from 7 to 30 days (mean 17.5, SD:8.58 days), however the manufacturer's instructions for the device is implantation for 7 days. Expert clinical feedback would suggest though that the device is routinely implanted for up to 2-weeks. This study was conducted in India and so may have limited generalisability to the NHS. Consequently the results of the study need to be considered in light of these limitations.
How was the study funded?	Not reported

(Maiwall et al. 2018)	
How are the findings relevant to the decision problem?	This retrospective case control study is the only comparative study providing a comparison between Danis stent and repeat endotherapy (polidocanol or cyanoacrylate glue or haemospray) with or without balloon tamponade (Sengstaken–Blakemore tube) and continuation of vasoactive drugs.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Below is a summary of the evidence for the outcomes in the scope reported in Tables 4a, 4b and 4d This study confirmed that: **Control of bleeding** Bleeding was controlled at a higher rate in patients receiving the Danis stent (89%) when compared to patients receiving the endotherapy

(Maiwall et al. 2018)	
	(36.5%) in the unmatched cohort at 5 days (p= <0.001). This trend was enhanced in the matched cohort (p=0.007). **Rate of re-bleeding** 5 patients (14%) in the Danis stent group re-bled after initial haemostasis. However, we note that the time point of assessment is unclear and data on re-bleeding are not reported for the comparator arm. **Mortality** In both the unmatched and matched cohorts fewer patients in the Danis stent arm died due to a bleed than patients receiving repeat endotherapy. In both cohorts the statistical difference was p=0.001. Overall mortality at 15-days and 6-weeks was reported for both the unmatched and matched cohorts. However, there was inconsistency in the paper on how these data were reported between the texts and the figures therefore correct values are unclear. The study authors were contacted on 29 January 2020 for clarification but no response has been received. **Unreported outcomes** This study did not report data on the rate of re-bleeding, blood transfusion use, hepatic encephalopathy, the use of additional interventions or patient related quality of life.
Will any information from this study be used in the economic model?	This study will be used to inform sensitivity analyses conducted on the economic model.
What are the limitations of this evidence?	The reporting by this study is unclear in parts based on the data reported in the text and that reported in the figures. Clarification has been sought from the study authors but no reply has been received. This study included patients with acute-on –chronic liver failure only, a subgroup of the target population. This study was conducted in India and so may have limited generalisability to the NHS. The results of this study need to be considered in light of these limitations.
How was the study funded?	Not reported

(Muller et al. 2015)	
How are the findings relevant to the decision problem?	The findings of this case series are relevant as the patient population had oesophageal variceal bleeding that was refractory to standard therapy and 11 patients received the Danis stent as treatment, data was also reported for outcomes relevant to scope.

(Muller et al. 2015)	
Does this evidence support any of the claimed benefits for the technology? If so, which?	Below is a summary of the evidence for the outcomes in the scope reported in Tables 4a, 4b, 4c, 4d and 4f. This study confirmed that: **Control of bleeding** Immediate control of bleeding after stent deployment was achieved in all 11 patients (100%). **Rate of re-bleeding** Re-bleeding within 48-hours of stent deployment occurred in 1 patient (9%) this patient had bleeding at distal end of the stent and required histoacryl injection and oesophageal peri-variceal sclerotherapy. No re-bleeding occurred whilst the stent was in situ (5 to 24 days) in any of the 11 patients. One patient (9%) experienced re-bleeding at stent removal. **Blood transfusion use** Blood transfusions were used in 8 patients (72%). **Mortality** One patient (9.1%*) died 5-days after Danis stent implantation due to acute liver failure. At 42-days, 3 patients (27.3%) had died no deaths were related to uncontrolled bleeding. **Additional/ further interventions** Following stent removal 2 patients (18%) received TIPS as their definitive treatment and 1 patient (9%) underwent liver transplantation. **Unreported outcomes** This study did not report data on outcome relating to hepatic encephalopathy or patient related quality of life.
Will any information from this study be used in the economic model?	This study will be used to inform sensitivity analyses conducted on the economic model.
What are the limitations of this evidence?	Some of the reporting is unclear suggesting that more outcome data is available than has been reported. The study authors have been contacted to request this data, however, no response has been received. This study did not include a comparator treatment. The sample size is small, 11 patients, however, this is indicative of the small clinical population. Danis stents were reported to be in situ for 5 to 24 days. We note that the indication for the Danis stent is implantation of up to 7 days, however, expert clinical evidence suggests that Danis stent is often implanted for up to 15 days in routine clinical practice. This study was not conducted in the UK but was conducted in Europe, and so is considered generalisable.
How was the study funded?	Baden-Württemberg Stiftung for the financial support of this research project by the Elite programme for Postdocs. Author A.K. is also an Else-Kröner-Fresenius Memorial Fellow

(Pfisterer et al. 2019)	
How are the findings relevant to the decision problem?	The findings of this case series are relevant to the decision problem because all patients studied had cirrhosis and refractory bleeding from oesophageal varices. All 34 patients were treated with the Danis stent.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Below is a summary of the evidence for the outcomes in the scope reported in Tables 4a, 4b, 4d and 4f. This study confirmed that: **Control of bleeding** Bleeding was controlled in 5 days or less in 27 patients (79.4%) and 10 patients (29.4%) had their bleeding controlled without re-bleeding within 6-weeks. **Rate of re-bleeding** • Re-bleeding while the stent was in situ occurred in 5 patients (14.7%) • Re-bleeding at stent removal occurred in 3 patients (8.8%). • Re-bleeding after successful stent removal occurred in 7 patients (20.6%*) • Re-bleeding within 6-weeks occurred in 6 patients (17.6%*) **Mortality** • Overall study mortality was 22 patients (64.7%) • Overall mortality due to bleeding was 16 patients (47.1%) • Mortality relating to uncontrolled bleeding within 5 days or less occurred in 7 patients (20.6%) • Mortality related to bleeding in 6-weeks or less occurred in 9 patients (26.5%) • Mortality whilst the stent was in situ occurred in 13 patients (38.2%) • Mortality within 5-days of stent removal due to uncontrolled bleeding occurred in 1 patient (2.9%) • Mortality within 6-weeks of stent removal related to uncontrolled bleeding occurred in 4 patients (11.8%) **Additional/further interventions** The use of early TIPS was not used in any patient. However, elective TIPS after stent placement was reported for 4 patients (11.8%). In patients with uncontrolled bleeding after 5-days the following treatments were used: • Endoscopic band ligation in 3 patients (42.9%*) • Renewed replacement of Danis stent in 2 patients (28.6%*) • Stent removed and Linton balloon tamponade used in 1 patient (14.3%*) • Additional balloon tamponade used in 1 patient (14.3%*)

(Pfisterer et al. 2019)	
	In patients with early re-bleeding (6-weeks or less) the following treatments were used: • Endoscopic band ligation in 4 patients (80%*) • Sengstaken balloon tamponade in 1 patient (20%*) • Stent renewed or replaced in 1 patient (20%*) In patients who survived 6-weeks without early re-bleeding 2 patients (16.7%*) were treated with Sengstaken balloon tamponade after unsuccessful endoscopic band ligation. **Unreported outcomes** This study did not report data relating to blood transfusion use, hepatic encephalopathy or patient related quality of life.
Will any information from this study be used in the economic model?	This study will be used to inform sensitivity analyses conducted on the economic model.
What are the limitations of this evidence?	This is 1 of the largest case series identified, however, the observational, retrospective design with no comparator is relatively low-quality evidence and there was limited reporting overall of this study. Whilst this study was not conducted in the UK, this study was conducted in Austria and therefore, is considered generalisable.
How was the study funded?	Not reported

(Wright et al. 2010)	
How are the findings relevant to the decision problem?	This study is the only eligible study conducted in the UK and therefore is most generalisable to the NHS. 10 patients were identified with variceal haemorrhage with contraindications to TIPS or balloon tamponade, however, 2 patients were later to found to have gastric varices. These patients have still been included in the overall number assessed.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Below is a summary of the evidence for the outcomes in the scope reported in Tables 4a, 4b, 4d and 4f. This study confirmed that: **Control of bleeding** Bleeding was controlled according to Baveno IV criteria in 7 patients (70%*). **Rate of re-bleeding** Re-bleeding after initial control occurred in 1 patient (10%*) 60-days after stent removal.

(Wright et al. 2010)	
	Mortality Three patients (30%*) died after failure to control bleeding. One patient died (10%*) 11 days after Danis stent insertion and 1 patient died (10%*) 17 days after Danis stent insertion both of progressive multiple organ failure. At 42-days 5 patients (50%*) had died. **Unreported outcomes** This study did not report data relating to blood transfusion use, hepatic encephalopathy or patient related quality of life.
Will any information from this study be used in the economic model?	This study will be used to inform sensitivity analyses conducted on the economic model.
What are the limitations of this evidence?	The limitations of this study are the inability to differentiate between the patients with oesophageal varices and gastric varices and the lack of a comparator. Although the sample size is small this is indicative of the indicated clinical population. The median duration of Danis stent implantation was 9 days (range 6 to 14 days) which reflects clinical practice according to clinical expert opinion. However, this exceeds the manufacturer's recommended implantation duration of 7 days.
How was the study funded?	Not reported

(Zakaria et al. 2013)	
How are the findings relevant to the decision problem?	The findings from this case series are relevant to the decision problem because all patients had acute variceal bleeding and had been exposed to the standard care and were therefore considered refractory to treatment as all patients had ongoing variceal bleeding. All 16 patients were implanted with the Danis stent and reported data on all but one of the eligible outcomes.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Below is a summary of the evidence for the outcomes in the scope reported in Tables 4a, 4c, 4d, 4e and 4f. This study confirmed that: **Control of bleeding** There was initial control of variceal bleeding in 14 patients (87.5%) treated with the Danis stent. **Blood transfusion use** The mean number of blood units transfused during a hospital stay was 2.5 units (SD: 2.55) **Mortality** 4 patients (25%) died during the study one case was related to a failure to control the initial bleeding episode. The remaining 3 cases were due

(Zakaria et al. 2013)	
	to the worsening of the general condition of the patient despite control of the bleeding. **Hepatic encephalopathy** 2 patients (12.5%) were reported to have hepatic encephalopathy. **Additional interventions** During follow up (time point not reported) 3 patients (18.75%) underwent band ligation and 7 patients (43.75%) underwent sclerotherapy. **Unreported outcomes** This study did not report data on the rate of re-bleeding or patient related quality of life.
Will any information from this study be used in the economic model?	This study will be used to inform sensitivity analyses conducted on the economic model.
What are the limitations of this evidence?	The limitations of this evidence are that the patient population was small, included 16 patients although this is representative of the small clinical population with acute refractory oesophageal variceal bleeds, and there was no comparator treatment. In addition this study was conducted in Egypt and therefore, generalisability to the NHS may be limited.
How was the study funded?	No funding was received

(Zehetner et al. 2008)	
How are the findings relevant to the decision problem?	The findings from this case series are relevant to the decision problem because the patients assessed had oesophageal variceal bleeding that could not be managed with standard therapy. Thirty four patients were treated with the Danis stent and data was reported for some of the eligible outcomes.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Below is a summary of the evidence for the outcomes in the scope reported in Tables 4a, 4d and 4f. This study confirmed that: **Control of bleeding** Haemorrhage was stopped immediately in all 34 (100%) patients treated with the Danis stent. **Rate of re-bleeding**

(Zehetner et al. 2008)	
	The study authors reported that no patients experienced recurrence of re-bleeding. **Mortality** At 30-days 9 patients (26.5%) who had been implanted with the Danis stent had died, this increased by 1 patient to 10 patients (29.4%) at 60-days. Two patients died of hepatic failure during the first 24 hours after Danis stent implantation and 7 patients died of hepatic and multi-organ failure after stent removal. No reason is reported for the death of the tenth patient. **Unreported outcomes** This study did not report data on the rate of re-bleeding, blood transfusion use, or patient related quality of life.
Will any information from this study be used in the economic model?	This study will be used to inform sensitivity analyses conducted on the economic model and provides information relating to stent migration.
What are the limitations of this evidence?	The limitations of this study are that there was no comparator arm. The Danis stents in this study remained implanted for a mean of 5 days (range 1 to 14 days) so in some cases Danis stents were implanted longer than the manufacturer's recommended 7 days however expert clinical opinion suggests this is representative of clinical practice. This study was not conducted in the UK but was conducted in Europe and therefore, is considered generalisable.
How was the study funded?	Not reported

6 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please provide links and references.

A hand search of the MHRA database and the FDA (Maude) databases was conducted on 27 January 2020 using the terms 'Danis stent', 'SX-Ella' and 'SX Ella'
MHRA Field Safety Notice on 14 February 2017 for Ella-CS: SX ELLA Stent Danis Procedure Pack (Basic)
MHRA reference: 2017/002/015/291/004 which was based on a returned product on which it was identified that there was an unintended movement of the safety valve fixation. The corrective action was that an update was made to the Danis Stent instructions for use. No clinical complications were associated with this Field Safety Notice.

No adverse events have been reported on the FDA (MAUDE) database.

Describe any adverse events and outcomes associated with the technology in the clinical evidence.

A table of all adverse events (AE) is shown in Table 6a. For completeness and transparency, this table includes all reported AEs. All studies except Maiwall 2018 reported details of at least one AE related to the use of the Danis stent. The author of the Maiwall 2018 study has been contacted to clarify whether the bacterial infections reported occurred at baseline or following treatment. No reply has been received to date.

A summary of the AEs related to the Danis stent is reported below:

The RCT conducted by Escorsell (2015) reported that were more patients experiencing at least 1 device related serious AE in the balloon tamponade group than in the Danis stent group. This difference was found to be statistically significant (p=0.049).

The other eight studies were all single arm case series.

Ghidirim (2012) reported the partial distal stent migration in 5 patients (41.6%).

Műller (2015) reported that 4 patients (36.4%*) experienced Danis stent dislocation at 24 hours and 3 patients (27.3%*) experienced stent dislocation at stent removal. There was no dislocation to the stomach reported. Danis stent related ulceration occurred in 2 patients (18.2%).

Pfisterer (2018) reported that stent dislocation occurred in 13 patients (38.2%).

Wright (2010) reported 1 case (10%) of failed Danis stent deployment caused by failure of the gastric balloon to inflate. There were no cases of stent migration, or major complications associated with stent removal in this study. There was 1 case (10%*) of ulceration in the oesophagus related to the proximal end of the Danis stent.

Zakaria (2013) reported that there was 1 case (6.25%*) of unsuccessful deployment during implantation. There were also 3 cases of technical error on during stent implantation. These related to the bending of the guide wire, slippage of the stent in the stomach immediately following deployment and malfunction of the delivery system causing rupture of the gastric balloon. Following stenting, 1 patient (6.25%*) experienced chest pain, 2 patients (12.5%*) experienced hiccups and 1 patient (6.25%*) experienced dysphagia. A deep ulcer was present at stent extraction in 1 patient (6.25%). Overall 6 patients (37.5%). experienced stent migration, there were 3 cases of total Danis stent migration, 2 cases of partial Danis stent migration and 1 case of partial stent migration proximally.

Zehetner (2008) reported no cases of complications during Danis stent placement or local complications. There were 7 cases (20.6%*) of Danis stent migration to the stomach and 1 case (2.9%*) of ulceration at the distal end of the stent location on stent extraction.

Table 6 Adverse events

Study	Outcome definition and measure	Time point of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
(Escorsell et al. 2016)	Patients with at least one AE	NR	Danis stent	13	4 (31)	p=0.024
			Balloon tamponade	15	11 (73)	
	Patients with at least one SAE	NR	Danis stent	13	2 (15)	p=0.077
			Balloon tamponade	15	7 (47)	
	Patients with at least one device-related SAE	NR	Danis stent	13	1 (8)	p=0.049
			Balloon tamponade	15	6 (40)	
	SAE: Cardio respiratory arrest	NR	Danis stent	13	1 (7.7*)	NR
			Balloon tamponade	15	1 (6.7*)	
	SAE: Aspiration pneumonia	NR	Danis stent	13	0	NR
			Balloon tamponade	15	5 (33.3*)	
	SAE: Oesophageal rupture	NR	Danis stent	13	0	NR
			Balloon tamponade	15	1 (6.7*)	
	SAE: Spontaneous bacterial peritonitis and hepatorenal syndrome	NR	Danis stent	13	1 (7.7*)	NR
			Balloon tamponade	15	0	
	Mild AE: Infections	NR	Danis stent	13	2 (15.4*)	NR
			Balloon tamponade	15	1 (6.7*)	
	Mild AE: Oesophageal ulcer (not bleeding)	NR	Danis stent	13	1 (7.7*)	NR
			Balloon tamponade	15	1 (6.7*)	
	Mild AE: Broncho aspiration not causing pneumonia	NR	Danis stent	13	1 (7.7*)	NR
			Balloon tamponade	15	3 (20*)	
	Mild AE: Seizures	NR	Danis stent	13	0	NR
			Balloon tamponade	15	1 (6.7*)	
	Mild AE: Transitory acute stroke	NR	Danis stent	13	0	NR
			Balloon tamponade	15	1 (6.7*)	NR
(Ghidirim et al. 2012)	Major device related complications (bronchial compression or impairment of pulmonary function)	NR	Danis stent	14	0	NA

Study	Outcome definition and measure	Time point of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
	Tanatogensis induced by hepatic failure	NR		14	3 (21.4*)	
	Bleeding oesophageal varice distally to the device distal end	NR		14	1 (7.1*)	
	Haemorrhagic stroke	NR		14	1 (7.1*)	
	Partial distal stent migration (documented on x-ray and CT scan)	NR		12	5 (41.6)	
(Muller et al. 2015)	Stent dislocation	24 hours	Danis stent	11	4 (36.4*)	NA
		At stent removal		11	3 (27.3*)	
		NR		11	7 (63.6*)	
	Dislocation to the stomach	NR		11	0	
	Pulmonary infection or pneumonia	NR		11	3 (27)	
	Acute renal failure	NR		11	3 (27)	
	Stent associated ulceration	NR		11	2 (18.2)	
(Pfisterer et al. 2019)	Stent dislocation	NR	Danis stent	34	13 (38.2)	NA
	Ulcers/necrosis of the oesophageal mucosa	NR		34	4 (11.8)	
(Wright et al. 2010)	Failed deployment caused by failure of gastric balloon to inflate	At insertion	Danis stent	10	1 (10)	NA
	Stent migration	NR		10	0	
	Major complications associated with stent removal	NR		10	0	
	Ulceration in the oesophagus related to the proximal end of the stent	NR		10	1 (10*)	
(Zakaria et al. 2013)	Unsuccessful deployment	Implantation	Danis stent	16	1 (6.3*)	NA
	Technical error during stenting: bending of the guide wire	Implantation		16	1 (6.3*)	
	Technical error during stenting: slipped in the stomach immediately after deployment	Implantation		16	1 (6.3*)	
	Technical error during stenting: Malfunction of the delivery system causing rupture of the gastric balloon	Implantation		16	1 (6.3*)	

Study	Outcome definition and measure	Time point of assessment	Intervention	Number of patients analysed	Number of patients experiencing event (%)	Difference between treatments
	AE following stenting: Chest pain	NR		16	1 (6.25)	
	AE following stenting: Hiccups	NR		16	2 (12.5)	
	AE following stenting: Fever	NR		16	0	
	AE following stenting: Dysphagia	NR		16	1 (6.25)	
	AE following stenting: Reflux symptoms	NR		16	0	
	Deep ulcer at extraction	NR		16	1 (6.25)	
	Stent migration	NR		16	6 (37.5)	
	Stent migration: total migration	NR		16	3 (18.75)	
	Stent migration: partial migration	NR		16	2 (12.5)	
	Stent migration: partial migration proximally	NR		16	1 (6.25)	
(Zehetner et al. 2008)	Complications in stent placement	NR	Danis stent	34	0	NA
	Local complications: aggravation	NR		34	0	
	Local complications: bleeding	NR		34	0	
	Local complications: perforation	NR		34	0	
	Local complications: penetration of stent into mediastinum	NR		34	0	
	Stent migration to stomach	NR		34	7 (20.6*)	
	Ulceration at the distal end of the stent location on stent extraction	NR		34	1 (2.9*)	
	Injury of varices	NR		34	0	
	Mucosal lesions	NR		34	0	
	Injury of the throat	NR		34	0	

Key: AE – adverse event; NA – not applicable; NR – not reported; SAE – serious adverse event
*Calculated by reviewer

7 Evidence synthesis and meta-analysis

Although evidence synthesis and meta-analyses are not necessary for a submission, they are encouraged if data are available to support such an approach.

If an evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

Not applicable as quantitative evidence synthesis is inappropriate.

Report all relevant results, including diagrams if appropriate.

Not applicable as quantitative evidence synthesis is inappropriate.

Explain the main findings and conclusions drawn from the evidence synthesis.

Not applicable as quantitative evidence synthesis is inappropriate.

Qualitative review

Please only complete this section if a quantitative evidence synthesis is not appropriate.

Explain why a quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal.

A quantitative review is not considered to be appropriate. Two comparative studies were identified, 1 RCT and 1 comparative case-control study and both compared Danis stents to different interventions. A qualitative assessment of the data from the 9 identified studies is considered to be more appropriate. **Risk of bias assessment of the studies**

The risk of bias of each study was assessed using the tool most applicable to the study design. The detailed risk of bias assessments can be found in Tables 7a to 7c.

RCT

Escorsell (2016) was assessed using the MTEP risk of bias criteria (Table 7a). This assessment found that randomisation was carried out appropriately using a computer generated sequence, the concealment of treatment allocation was also deemed adequate as a sealed envelope method was used based on the central randomisation codes. Although the 2 treatment arms differed in terms of patient age and gender (no females were included in the Danis stent arm), they were similar for prognostic factors. This study was open label and, therefore, patients, assessors and personnel were not blinded. There were no drop outs or loss to follow up until after the main study time points. There was evidence of selective reporting as survival, bleeding and hospital stay were all due to be assessed at 6-months but were not reported in the publication. An intention to treat (ITT) analysis was at all reported time points. Overall this study was deemed to have a moderate risk of bias increased further by the small sample size of 28 patients which was 60% of the intended sample. We note that this study was carried out in Spain with limited generalisability to the UK and patients who had undergone balloon tamponade as treatment for the index bleed were excluded which would not necessarily be in line with UK clinical practice.

Case control study

Maiwall (2018) was assessed using the Joanna Briggs Institute (JBI) case control checklist (Table 7b). This assessment confirmed that the groups were comparable as the difference between the case and the control arms was based on the absence of treatment not disease and in the matched cohort patients were matched on baseline characteristics. The method of matching used has raised some concerns and therefore, this method was rated as having an unclear risk of bias. The same criteria were used for the identification of cases and controls and the exposure to the treatment was assessed for both case and control patients using hospital database records. The effects of treatment were assessed in the same way in both groups. It was unclear if confounding factors were identified as none were reported and nor were any strategies reported relating to how confounding factors were dealt with. The outcomes were assessed in a standard, valid and reliable way and the follow up period following treatment was 6-weeks. Full details of statistical analyses were reported. Overall this study was deemed to have a moderate risk of bias. Some of the data were difficult to interpret due to lack of clarity in time points. In addition, some data were reported in a way which meant that it was difficult to ascertain if they were reported at baseline or following treatment. Clarification was sought from the study authors however, no response was received. We note that this study was carried out in India so may have limited generalisability to the UK. This study also only included patients with acute-on-chronic liver failure only, excluding other patients that could be part of the target population

Case series studies

The 7 case series (Ghidirim 2012, Goenka 2017, Műller 2015, Pfisterer 2018, Wright 2010, Zakaria 2013, Zehetner 2008) were assessed using the JBI case series checklist.

Overall, the case series studies were generally found to be of low quality due to the unclear and limited reporting and small patient sample numbers. Full details can be found in Table 7c.

Qualitative synthesis

No evidence was identified comparing Danis stent and TIPS.

Control of bleeding

All 9 studies assessed control of bleeding (shown in Table 4a). However, the time point at which control of bleeding was assessed differed across the studies and was not reported by 3 studies (Ghidirim 2012, Wright 2010, Zakaria 2013). The reporting of the definition of this outcome was limited and varied across the studies (see Table 4a).

Two studies (Műller 2015, Zehetner 2008) reported that 100% of patients had control of bleeding immediately following Danis stent placement.

One study (Goenka 2017) reported that 100% of patients had control of bleeding at 48 hours.

Maiwall (2018) and Pfisterer (2018) assessed control of bleeding within 5 days. In Maiwall (2018), control of bleeding was significantly higher in the Danis stent group compared with the comparator arm in both the unmatched (89% versus 36.5%; p<0.001) and matched cohorts (72.7% versus 31.8%; p=0.007). Control of bleeding was achieved for 79.4% of patients receiving the Danis stent in the Pfisterer (2018) study, which is a similar proportion to those in the matched cohort of the Maiwall (2018) study.

In Escorsell (2016), there was higher control of bleeding in the Danis stent group compared with the comparator arm at 15 days (85% versus 47%; p=0.037), but no significant difference was seen at 6 weeks (54% versus 47%; p=0.25).

Pfisterer (2018) reported that 29.4% of patients had bleeding controlled, without re-bleeding, at 6 weeks.

Of the 3 studies that did not report a time point of assessment, the proportion of patients with a Danis stent who had their bleeding controlled ranged from 70%* (Wright 2010) to 100% (Ghidirim 2012).

These results would suggest that Danis stent has good early control of bleeding both immediately following implantation of the Danis stent and up to 15 days. According to the comparative data from Escorsell (2016) treatment with Danis stent provides increased control of bleeding compared to balloon tamponade to a statistically significant level at 15-days and is trending towards increased control at 6-weeks. It should be noted that once bleeding is controlled patient's should progress to a definitive therapy and therefore, outcomes reported at the 6-week time point will be effected by not just the definitive treatment received but also the patient's underlying condition. Maiwall (2018), has also reported statistically greater control of bleeding at 5-days for patients receiving the Danis stent when compared to the comparator arm in both the unmatched and matched cohorts.

Rate of re-bleeding

Table 4b presents the outcome data for the rate of re-bleeding, reported by 5 studies (Goenka 2017, Maiwall 2018, Műller 2015, Pfisterer 2018 and Wright 2010). Three of the studies reported data at multiple time points.

Műller (2015) reported 1 patient (9%) experienced re-bleeding within 48 hours of Danis stent deployment.

Both Műller (2015) and Pfisterer (2018) assessed re-bleeding whilst the Danis stent was in situ. In Műller (2015) this was between 5 to 24 days and no cases were reported. Pfisterer (2018) did not

report details of the specific time point but reported that there were 5 cases (14.7%) of re-bleeding whilst the stent was in situ. Pfisterer (2018) also reported that there was early re-bleeding (within 6 weeks) for 6 patients (17.6%) implanted with the Danis stent, however, it is unclear whether there is overlap in the patients considered in these two outcomes.

Re-bleeding at Danis stent removal occurred in 1 patient (9%*) in Műller (2015) and in 3 patients (8.8%) in Pfisterer (2018).

Three studies reported data on the rate of re-bleeding following Danis stent removal. Goenka (2017) reported that 1 patient (8.33%*) experienced re-bleeding 10 days after stent removal and there were no cases of re-bleeding at 30 days following stent removal. Pfisterer (2018) reported that re-bleeding occurred in 7 of 20 patients who had Danis stent successfully removed (35%) (specific time point not reported). Wright (2010) reported that 1 patient (10%*) experienced re-bleeding after initial control 60-days after stent removal in a patient who resumed alcohol following discharge.

In Maiwall (2018), 5 patients (14%) in the Danis stent group re-bled after initial haemostasis. However, we note that the time point of assessment is unclear and data on re-bleeding are not reported for the other treatment arm.

Blood transfusion use

Three studies reported data on blood transfusions (Table 4c). However all 3 studies reported different types of data for this outcome. Escorsell (2016) reported on the median number of packed red blood cell transfusions following study inclusion. Patients in the Danis stent arm received fewer packs (median: 2 packs, range: 0 to 12) compared to the balloon tamponade comparator arm (median: 6 packs, range 0 to 15), but there was no statistically significant difference (P=0.08). Műller (2015) reported that 8 patients (72%) implanted with the Danis stent received a blood transfusion. Zakaria (2013) reported that the mean number of blood units transfused during the hospital stay was 2.5 units (SD: 2.55).

Mortality

Mortality was reported by all 9 studies (Table 4d). However, the time point at which mortality was reported and the cause of mortality differed across the studies.

Three studies reported on bleeding related mortality. In Maiwall (2018), there was a statistically significant reduction in deaths due to bleeding in the Danis stent arm compared to the comparator arm (repeat endotherapy with or without Sengstaken–Blakemore tube) in both the unmatched (14.3% versus 64%; p=0.001) and matched cohorts (5.6% versus 56.3%; p=0.001). The time point at which this outcome was assessed is not reported.

Pfisterer (2018) reported that, overall, 16 patients (47.1%) died due to bleeding. 5-day mortality due to uncontrolled bleeding was 20.6% (7 patients). 9 patients (26.5%) had bleeding related mortality within 6 weeks. One patient died within 5 days of stent removal due and 4 patients (11.8%) died within 6 weeks of stent removal due to uncontrolled bleeding.

In Wright (2010), mortality caused by failure to control bleeding occurred in 3 patients (30%*).

Goenka (2017) reported that 4 patients (33.3%*) died with the Danis stent implanted but these deaths were not related to bleeding but to worsening encephalopathy or sepsis. No details of time point were

reported. One additional patient had the Danis stent implanted twice and died 7 days after the second stent placement due to sepsis. Pfisterer (2018) also reported mortality with the Danis stent in situ which occurred in 13 patients (38.2%). No details of the time point were reported by this study either. Műller (2015) reported that 1 patient (9.1%*) died 5 days after stent implantation due to acute liver failure.

15-day mortality was reported by two studies (Escorsell 2016, Maiwall 2018). Escorsell reported that 4 patients (30.8%*) died at 15-days in the Danis stent arm compared to 7 patients (46.7%*) in the balloon tamponade arm of the study and this was statistically significant (p=0.044)

Maiwall (2018) did not report the number and proportion of patients that died at 15-days but instead reported a hazard ratio. However, we note that there was inconsistency in the paper on how these data were reported between the text and the figures and the correct values are unclear. The study authors were contacted on 29 January 2020 for clarification, however no response has been received. In the unmatched cohort mortality was significantly reduced in the Danis stent arm compared to the comparator at 15-days and at 6-weeks this same statistical trend was reported for the matched cohort.

Ghidirim (2012) and Zehetner (2008) reported 30-day mortality. The 30-day mortality rate was 26.5% in Zehetner (2008) and 37.5% in Ghidirim (2012). However, we note that the sample sizes in both these studies was small. 60-day mortality rate was reported to be 29.4% in Zehetner (2008).

6-week or 42-day mortality was reported by 4 studies (Escorsell 2016, Maiwall 2018, Műller 2015 and Wright 2010). The 42-day mortality rate was 50% in Wright (2010) and 27.3% in Műller (2015).

Escorsell (2016) reported that 6 patients (46.2%*) who had received the Danis stent died at this 6-week time point compared to 9 patients (60%*) in the balloon tamponade arm, however there was no statistically significant difference. Maiwall (2018) did not report the number and proportion of patients dying at 60-days but instead reported a hazard ratio. However, we note that there was inconsistency in the paper on how these data were reported between the text and the figures and the correct values are unclear. The study authors were contacted on 29 January 2020 for clarification, however, no response has been received.

In Zakaria (2013) mortality occurred in 4 patients (25%), however, the time point of assessment is unclear.

Overall mortality across the studies for patients treated with a Danis stent ranged from 25% to 50%. However, expert clinical opinion confirms that mortality is not unexpected in patients experiencing oesophageal variceal bleeding, even if control of bleeding is achieved, due to the trauma to the body caused by the large blood loss and the underlying cause of the variceal bleeding. The comparative data from Escorsell (2016) shows that mortality was lower for patients receiving the Danis stent at 15 days compared to patients receiving the balloon tamponade (p=0.044). However, although the trend continued at 6-weeks there was no statistically significant difference. At 6-weeks however, the patients will have had the Danis Stent removed following control of bleeding and therefore outcome data reported at this time point are impacted by the definitive treatment received and the patient's underlying condition.

Hepatic encephalopathy

Two studies reported data on hepatic encephalopathy (Table 4e). However, due to the small sample numbers and differences in definition of this outcome used by the 2 studies, overall conclusions are limited. Escorsell (2016) specifically reported that the proportion of patients with severe encephalopathy was higher in the comparator treatment arm of patients' receiving a balloon tamponade (n=11, 73%) compared with patients receiving the Danis stent (n=5, 39%) but noted that the difference was not statistically significant (p=0.063). In Zakaria (2013), 2 patients (12.5%) developed hepatic encephalopathy.

Additional/further interventions (including TIPS)

Table 4f report details of the additional interventions conducted across the 9 studies. Five studies (Escorsell 2016, Műller 2015, Pfisterer 2018, Wright 2010, Zehetner 2008) reported the use of TIPS. The proportion of patients receiving TIPS following Danis stent removal ranged across the studies from 11.8% (Pfisterer 2018) to 31% (Escorsell 2016).

Endosopic band ligation, also referred to as oesophageal band ligation, band ligation and variceal band ligation, was used as definitive treatment in 6 studies (Escosell 2016, Ghidirim 2012, Goenka 2017, Pfisterer 2018, Zakaria 2013, Zehetner 2008). It should be noted that Ghidirim (2012) reported the number of patients undergoing both definitive treatment with endoscopic band ligation (n=7, 50%*) and oesophageal variceal ligation (n=2, 14.3%*) separately. Pfisterer (2018) reported the use of endoscopic band ligation in patients with uncontrolled bleeding after 5 days in 3 patients (42.9%*) and separately for those with early re-bleeding at 6-weeks or less (n=4, 80%*). The proportion of patients undergoing endoscopic band ligation in the remaining 4 studies was between 18.75% (Zakaria 2013) to 57.1% (Goenka 2017).

All other additional interventions were each reported by only 1 study and are presented in Table 4f.

None of the studies reported data on patient related quality of life and, therefore, it is not possible to consider the effect of the Danis stent on this outcome.

Table 7a Risk of bias assessment for RCTs (MTEP suggested risk of bias)

Study	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Were the care providers and participants blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)	Were the outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)	Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Additional info
(Escorsell et al. 2016)	**Yes** Sequence generated by computer in a 1:1 ratio, stratified for the degree of liver failure (Child-Pugh class A or B/C)	**Yes** Sealed envelope and central randomisation using codes	**Yes** Groups differed in terms of age and gender but not on prognostic factors	**No** Open-label	**No** Open-label	**No** No drop outs - loss to follow up occurred after the main time points of 15-days and 6-weeks	**Yes** Clinical trial record available which referred to assessment at 6-months of various outcomes which have not been reported in the publication	**Yes** ITT used no report of how missing data were dealt with. However, all patients were assessed at the main time points of 15-days and 6-weeks (no dropouts until after this point) and none of the data for binary outcomes indicated there were missing data	Small sample size and conducted in Spain

Key: ITT – intent-to-treat

Table 7b Risk of bias assessment for case control studies (JBI case control checklist)

Study	1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	2. Were cases and controls matched appropriately ?	3. Were the same criteria used for identification of cases and controls?	4. Was exposure measured in a standard, valid and reliable way?	5. Was exposure measured in the same way for cases and controls?	6. Were confounding factors identified?	7. Were strategies to deal with confounding factors stated?	8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?	9. Was the exposure period of interest long enough to be meaningful ?	10. Was appropriate statistical analysis used?	Overall appraisal
(Maiwall et al. 2018)	**Yes** Was based on presence of absence of treatment not disease, but both groups were comparable in matched cohort	**Unclear** Methods described in detail, propensity matching, some concerns over the use of this method have been published. https://gking.harvard.edu/files/gking/files/psnot.pdf	**Yes** Patients were required to have the same condition and criteria were the same	**Yes** Identified from a hospital database	**Yes** Exposure was treatment, patients were assessed in the same way for exposure to treatment	**Unclear** Not reported	**Unclear** Not reported	**Yes** The primary and secondary outcomes were stated, it was not always clear which time point was being referred to but this was true across groups	**Yes** Exposure was procedure, so in this instance not required to be meaningful, the follow up of 6-weeks was appropriate for both groups	**Yes** Full details reported and appears appropriate	Some of the data were difficult to interpret due to lack of clarity in time points.

Table 7c Risk of bias assessment for case series studies (JBI case series checklist)

Study	1. Were there clear criteria for inclusion in the case series?	2. Was the condition measured in a standard, reliable way for all participants included in the case series?	3. Were valid methods used for identification of the condition for all participants included in the case series?	4. Did the case series have consecutive inclusion of participants ?	5. Did the case series have complete inclusion of participants ?	6. Was there clear reporting of the demographics of the participants in the study?	7. Was there clear reporting of clinical information of the participants?	8. Were the outcomes or follow up results of cases clearly reported?	9. Was there clear reporting of the presenting site(s)/ clinic(s) demographic information?	10. Was statistical analysis appropriate ?	Overall appraisal
(Ghidirim et al. 2012)	**Unclear** Some criteria were described, but very brief so not clear how patients were selected	**Yes** Study authors report the use of Baveno consensus IV guidance	**Yes** Reports the diagnostic work up procedures conducted	**Unclear** Does not report if patients were consecutive	**Unclear** Not reported	**Yes** Data reported in the text	**Unclear** Very limited reporting - although does report MELD and Child Pugh scores	**No** Outcomes were not well defined or well reported	**No** Not reported	**Unclear** Not reported	Low quality study due to the limited and unclear reporting and small population size (n=14), therefore, at high risk of bias
(Goenka et al. 2017)	**Yes** Inclusion and exclusion criteria were short but adequately reported	**Yes** Definition of bleeding was reported by study authors	**Yes** All patients underwent endoscopies and standard resuscitative measures were conducted	**Unclear** Does not report if patients were consecutive	**Unclear** Not reported	**Yes** Demographic data reported for individual patients	**Unclear** Clinical data reported for individual patients, however the data is limited	**Yes** Data reported clearly	**No** Not reported	**Unclear** Not reported	Low quality study whilst study was in the most part adequately reported the patient number was very low (n=12) and therefore, this needs to be considered in the context of the outcome data. Results mainly reported in text and any events were reported for individual patients

Study	1. Were there clear criteria for inclusion in the case series?	2. Was the condition measured in a standard, reliable way for all participants included in the case series?	3. Were valid methods used for identification of the condition for all participants included in the case series?	4. Did the case series have consecutive inclusion of participants ?	5. Did the case series have complete inclusion of participants ?	6. Was there clear reporting of the demographics of the participants in the study?	7. Was there clear reporting of clinical information of the participants?	8. Were the outcomes or follow up results of cases clearly reported?	9. Was there clear reporting of the presenting site(s)/ clinic(s) demographic information?	10. Was statistical analysis appropriate ?	Overall appraisal
(Muller et al. 2015)	**Yes** Criteria for retrospectiv e selection are clearly stated	**Unclear** Study authors report that the definition of gastrointestinal bleeding was according to the diagnosis in the database but all patients with variceal bleeding were analysed	**Yes** Patients were evaluated retrospectively . Details are reported on the assessments of each patient conducted	**Yes** All patients were evaluated for inclusion in the study	**Yes** Does not report any missing cases, seems that patients were only excluded for being ineligible	**Yes** Data presented in table	**Unclear** Some data were not clear e.g. baseline hepatic encephalopathy and some data were reported as IPD and some by overall stent population	**Unclear** Very difficult to understand some of the data and some outcomes and whether some of the data was reported for the overall study population or specifically those with the Danis stent. Also the text appears to suggest that "Bleeding associated complications and re-bleeding rate within 42-days" were assessed but no data is reported	**Yes** Patients treated with conventional treatment were described, creating whole picture of the clinic	**Yes** Reported and appeared appropriate	Low quality study although the study methods and baseline data were adequately reported some of the outcome data was not clearly reported in addition the patient number was very low (n=11) and therefore, this needs to be considered in the context of the outcome data
(Pfisterer et al. 2019)	**Unclear** Limited information reported	**Unclear** Limited information reported other than confirmation that all patients were refractory	**Unclear** Not clear how patients were identified from the clinics or the requirements for stenting	**Unclear** Not reported	**Unclear** Patients were excluded for a number of reasons	**Yes** Data presented in table	**Yes** Detailed clinical data reported in a table	**Unclear** Difficult to understand calculations and N for some data which made data appear contradictory in some cases	**No** Not reported	**Yes** Reported and appeared appropriate	Low quality study due to the unclear reporting, whilst this was the largest sample size of all of the case series the issues with reporting must be considered

Study	1. Were there clear criteria for inclusion in the case series?	2. Was the condition measured in a standard, reliable way for all participants included in the case series?	3. Were valid methods used for identification of the condition for all participants included in the case series?	4. Did the case series have consecutive inclusion of participants ?	5. Did the case series have complete inclusion of participants ?	6. Was there clear reporting of the demographics of the participants in the study?	7. Was there clear reporting of clinical information of the participants?	8. Were the outcomes or follow up results of cases clearly reported?	9. Was there clear reporting of the presenting site(s)/ clinic(s) demographic information?	10. Was statistical analysis appropriate ?	Overall appraisal
(Wright et al. 2010)	**No** Not reported, only description of patients	**Yes** All patients required the Danis stent due to contraindications to other treatment and reasons provided for all patients	**Unclear** Unclear how patients were identified however, cirrhosis was confirmed by biopsy or a combination of typical biochemical and radiographic abnormalities	**Unclear** Does not report if patients were consecutive	**Unclear** Not reported	**Yes** Individual data reported allowing calculation	**Yes** Individual data reported allowing calculation	**Unclear** Some of the narrative reporting was not clear	**No** Not reported	**Unclear** Not reported	Low quality study with limited reporting and very small sample size (n=10) although only n=8 were found to have oesophageal varices
(Zakaria et al. 2013)	**Yes** Clear inclusion and exclusion criteria reported	**Yes** Clearly defined by the study authors	**Yes** Endoscopic investigation reported for confirmation of oesophageal varices	**Unclear** Does not report if patients were consecutive	**Unclear** Not reported	**Yes** Data presented in table	**Yes** Clear reporting of clinical information in a table	**Yes** Clear reporting, easy to interpret outcomes	**No** Not reported	**Unclear** Not reported	Overall a study of medium quality with good reporting of baseline and outcome data however the sample size was small (n=16) and therefore the outcome data need to be considered in light of this
(Zehetner et al. 2008)	**No** Does not describe the predefined criteria, but describes patients	**Unclear** No criteria for bleeding reported, but report that all bleeding was caused by liver cirrhosis	**Unclear** Details of how the patients were identified were not reported, however ongoing bleeding was confirmed by endoscopy	**Unclear** Does not report if patients were consecutive	**Unclear** Not reported	**No** Data only reported for overall population and not the 34 patients receiving Danis stent.	**Unclear** Clinical data was not reported apart from aetiology. Does not give clear picture of prognostic factors	**Yes** Clear reporting	**Unclear** Not reported	**Unclear** Not reported	Due to the very limited reporting a study of low quality and whilst the sample size is one of largest sample sizes the low quality of the study increases the risk of bias associated with this study

Key: MELD - model for end-stage liver disease

8 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefit and any risks relating to adverse events from the technology.

There is 1 RCT evaluating the use of the Danis stent (compared to balloon tamponade), 1 case control study (comparing Danis to repeat endotherapy) and 7 case series. No studies were identified that compared Danis stent to TIPS.

Results from the RCT suggest that Danis stent does control bleeding at 15 days when compared to balloon tamponade, suggesting it can provide control of acute variceal bleeding. Fewer adverse events were experienced in patients receiving the Danis stent compared to those receiving balloon tamponade suggesting it is potentially a safer alternative treatment. Mortality at 15-days was statistically lower for patients receiving the Danis stent compared to patients receiving balloon tamponade.That the statistical differences between Danis stent and balloon tamponade for control of bleeding do not extend to the 6-week time point is not unexpected, given that the Danis stent was implanted for a median of 5 days (range 0 to 12) after which definitive treatment was required. The lack of statistical significance between the two treatment arms regarding mortality at 6-weeks is also not surprising as clinically patients in both treatment arms are exceedingly ill due to both the effect of experiencing such high blood loss and the underlying cause of the oesophageal variceal bleed.

Although, the use of Danis stents did reduce the need for blood transfusions and reduce cases of hepatic encephalopathy compared to balloon tamponade this was not found to be statistically significant. TIPS was used as the definitive treatment less frequently in patients who had received the Danis stent when compared to those patients who had received balloon tamponade but, this was not statistically assessed.

Results of the other studies support the suggestion that Danis stents are effective for control of bleeding, within the first 5 days. Data for longer-term follow up are less consistent and are likely influenced by the subsequent interventions and procedures that patients receive in addition to their underlying condition

Briefly discuss the relevance of the evidence base to the scope. This should focus on the claimed benefits described in the scope and the quality and quantity of the included studies.

The evidence base relevant to the scope is limited as there is only 1 small RCT comparing Danis stent to 1 of the named comparators and no studies were identified comparing Danis stent to TIPS. The claimed benefits in the NICE scope are not aligned with the outcomes in the NICE scope and therefore, it has not been possible to assess the available evidence against the claimed benefits.

The quantity of the evidence available is small due to there being only 1 small RCT (13 patients receiving Danis stent and 15 patients receiving balloon tamponade). The 1 case control study and 7 case series have been found to be of low to moderate quality due to the overall poor and unclear reporting and small sample sizes. Attempts have been made to contact study authors for clarification on unclear data however, no responses have been received. The small sample numbers included in the studies however, are indicative of the small number of patients with acute refractory oesophageal variceal bleeds.

We acknowledge the need for a larger RCT in the UK NHS in order to facilitate a more robust assessment of the Danis Stent which may be possible with increased uptake of the device.

Identify any factors which might be different between the patients in the submitted studies and patients having routine care in the UK NHS.

Only 1 small study (10 patients) was conducted in the UK. Studies conducted in Europe are more likely to have similar treatment pathways to those patients in the UK and similar causes of acute oesophageal variceal bleeding and therefore can be considered generalisable. One clinical expert suggested that caution should be used in the patient population included in studies conducted in India as portal hypertension historically occurred more commonly there in non-cirrhotic patients with fewer patients there having cirrhosis induced portal hypertension.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

If the variceal bleed is considered acute i.e. bleeding to such an extent that the patient could expire from exsanguination, and band ligation either fails, or is deemed to be unlikely to work.

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

The clinical evidence comprises 1 small RCT, 1 case control study and 7 single-arm case series. The RCT (Escorsell 2016) compared Danis stent to 1 of the eligible comparators. The results from this study would suggest that the Danis stent is superior to the balloon tamponade in controlling bleeding, 15-day mortality and reducing adverse events. The small sample size is indicative of a small patient population available and, whilst the study was not conducted in the UK, it is considered generalisable to the UK setting. However, patients who had received treatment with balloon tamponade for the index bleed were excluded from this study which is not considered similar to UK clinical practice and therefore, this difference should be noted.

The other 8 studies are limited both in their size and quality. One study provides data on a UK population in a case series (n=10). However, it is acknowledged that the patient population with acute refractory oesophageal bleeds is small (500 to 1000 patients estimated in the UK (National Institute for Health and Care Excellence 2019a)) and, given the emergency nature of the treatment, conducting large randomised clinical trials is problematic. This has further been confirmed by feedback from 3 clinical experts.

The Danis stent is recommended for an implantable duration of 7 days it would appear from several of the studies (Goenka 2017, Műller 2015, Wright 2010, Zehetner 2008) and expert clinical feedback that the Danis stent is implanted for longer than this for example in Goenka (2017), Danis stents were implanted for a period of 7 to 30 days. Therefore, whilst this is not compliant with the manufacturer's instructions, the results of the studies do appear to reflect implantation durations that may occur in clinical practice. In addition, expert clinical opinion (3 clinicians) confirms that implantation of the Danis stent for over 2 weeks reflects the off-label palliative use of the device based on individual patient needs.

9 References

Please include all references below using NICE's standard referencing style.

de Franchis R (2015) Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. Journal of Hepatology 63(3)**:** 743-752

Escorsell A, Pavel O, Cardenas A, et al. (2016) Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: A multicenter randomized, controlled trial. Hepatology 63(6)**:** 1957-67

Ghidirim G, Mishin IV, Dolghii AN, et al. (2012) Self-expanding metal stent for the management of bleeding esophageal varices - Single centre experience. Clinical Anatomy and Operative Surgery 11(4)**:** 100-103

Goenka MK, Goenka U, Tiwary IK, et al. (2017) Use of self-expanding metal stents for difficult variceal bleed. Indian Journal of Gastroenterology 36(6)**:** 468-473

Lee ES (2008) Life Cycle Assessment (LCA) - Environmental impacts of a medical device product (master's project). Duke University Available from: https://hdl.handle.net/10161/816

Maiwall R, Jamwal KD, Bhardwaj A, et al. (2018) SX-Ella Stent Danis effectively controls refractory variceal bleed in patients with acute-on-chronic liver failure. Digestive Diseases and Sciences 63(2)**:** 493-501

Muller M, Seufferlein T, Perkhofer L, et al. (2015) Self-expandable metal stents for persisting esophageal variceal bleeding after band ligation or injection-therapy: A retrospective study. Plos One [Electronic Resource] 10(6)**:** e0126525

National Institute for Health and Care Excellence (2011) Stent insertion for bleeding oesophageal varices (NICE guidance IPG392). National Institute for Health and Care Excellence Available from: https://www.nice.org.uk/guidance/ipg392

National Institute for Health and Care Excellence (2012) Acute upper gastrointestinal bleeding in over 16s: Management (NICE guidance CG141). National Institute for Health and Care Excellence Available from: https://www.nice.org.uk/guidance/cg141

National Institute for Health and Care Excellence (2019a) Danis stent for acute oesophageal variceal bleeds (NICE guidance MT537). National Institute for Health and Care Excellence Available from: https://www.nice.org.uk/guidance/gid-mt537

National Institute for Health and Care Excellence (2019b) Danis stent for acute oesophageal variceal bleeds (NICE guideline MIB185). National Institute for Health and Care Excellence Available from: https://www.nice.org.uk/advice/mib185

Pfisterer N, Riedl F, Pachofszky T, et al. (2019) Outcomes after placement of a SX-ELLA oesophageal stent for refractory variceal bleeding-A national multicentre study. Liver International 39(2)**:** 290-298

Rössle M, Maruschke L, Schmidt AR, et al. (2017) Early versus rescue transjugular intrahepatic portosystemic shunt in patients with acute variceal bleeding. AME Med J 2(11)

Sherman J, Le C, Lamers V, et al. (2012) Life cycle greenhouse gas emissions of anesthetic drugs. Anesthesia & Analgesia 114(5)**:** 1086-90

Thiel CL, Eckelman M, Guido R, et al. (2015) Environmental impacts of surgical procedures: Life cycle assessment of hysterectomy in the United States. Environmental Science & Technology 49(3)**:** 1779-1786

Tripathi D, Stanley AJ, Hayes PC, et al. (2015) UK guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut 64(11)**:** 1680-1704

Wright G, Lewis H, Hogan B, et al. (2010) A self-expanding metal stent for complicated variceal hemorrhage: Experience at a single center. Gastrointestinal Endoscopy 71(1)**:** 71-8
York Health Economics Consortium (2020a) Danis stent clinician teleconference (Dr Al-Joudeh). Minutes of clinical expert teleconference meeting 12th February 2020
York Health Economics Consortium (2020b) Danis stent clinician teleconference (Dr Patch). Minutes of clinical expert teleconference meeting 17th February 2020
York Health Economics Consortium (2020c) Danis stent clinician teleconference (Mr Dickinson). Minutes of clinical expert teleconference meeting 14th February 2020
Zakaria MS, Hamza IM, Mohey MA, et al. (2013) The first Egyptian experience using new self-expandable metal stents in acute esophageal variceal bleeding: Pilot study. Saudi Journal of Gastroenterology 19(4)**:** 177-81
Zehetner J, Shamiyeh A, Wayand W, et al. (2008) Results of a new method to stop acute bleeding from esophageal varices: Implantation of a self-expanding stent. Surgical Endoscopy 22(10)**:** 2149-52

10 Appendices

Appendix A: Search strategy for clinical evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	07/01/20 - 08/01/20
Date span of search:	2005 - last available update.
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
SEARCH STRATEGY A MEDLINE (OvidSP) search strategy was designed to identify studies of Danis stent insertion for the treatment of acute oesophageal variceal bleeds. The final MEDLINE strategy is presented in A.1. The main structure of the search strategy comprised two concepts: 1) Oesophageal variceal bleeds (search lines 4 to 10). 2) Stents (search lines 11 to 14). An additional standalone, precise search line was used to capture the brand name of the device and the manufacturer's name (search lines 1 to 3). The concepts were combined as follows: (oesophageal variceal bleeds AND stents) OR danis OR ella-cs. This approach was designed to identify stent studies of any design, reporting any outcomes, and with or without a comparator. Stents were used as a generic concept were used, rather than the Danis stent specifically, due to the inconsistent description of device names in database records and the difficultly in capturing these with a search strategy. The strategy was devised using a combination of subject indexing terms and free text search terms in the title, abstract and keyword heading word fields. The search terms were identified through discussion within the research team, scanning background literature, browsing database thesauri and use of the PubMed PubReminer tool (http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi). The strategy excluded animal studies from MEDLINE using a standard algorithm (search line 17). The strategy also excluded some publication types which were unlikely to yield relevant study	

reports (editorials, news items and case reports) and records with the phrase 'case report' in the title field (search line 18).

The search strategy was date-limited from 2005 to current (search line 20); this reflects the date that Danis was granted a CE mark. The strategy was not restricted by language.

The final Ovid MEDLINE strategy was peer-reviewed by a second Information Specialist for errors in spelling, syntax and line combinations.

RESOURCES SEARCHED

We conducted the literature search in the databases and information resources shown in Table A.1.

Table A.1: Databases and information sources searched

Database or resource	Interface or URL
Ovid MEDLINE ALL	Ovid SP
PubMed	http://www.ncbi.nlm.nih.gov/pubmed
Embase	Ovid SP
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library / Wiley
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library / Wiley
Database of Abstracts of Reviews of Effects (DARE)	https://www.crd.york.ac.uk/CRDWeb/
Health Technology Assessment Database (HTA Database)	https://www.crd.york.ac.uk/CRDWeb/
NHS Economic Evaluation Database (NHS EED)	https://www.crd.york.ac.uk/CRDWeb/
Conference Proceedings Citation Index – Science (CPCI-S)	Web of Knowledge / Thomson Reuters
WHO International Clinical Trials Registry Portal (ICTRP)	http://apps.who.int/trialsearch/
ClinicalTrials.gov.	https://clinicaltrials.gov./
EconLit	OvidSP
Cost Effectiveness Analysis Registry (CEA Registry)	https://research.tufts-nemc.org/cear4/
FDA webpages	http://www.fda.gov/

The PubMed search was restricted to records not yet fully indexed for MEDLINE.

The trials register sources (ClinicalTrials.gov and ICTRP) were searched to identify information on studies in progress.

Recent research published as conference abstracts was identified by searching Embase, which indexes a significant number of conference publications, and CPCI-S, which is a conference proceedings citation index for science disciplines.

We conducted searches using each database or resource listed above, translating the agreed Ovid MEDLINE strategy appropriately. Translation included consideration of differences in database

interfaces and functionality, in addition to variation in indexing languages and thesauri. Below the full strategies for all sources searched are reported.

Search strategies

A.1: Source: Ovid MEDLINE(R) ALL
Interface / URL: OvidSP
Database coverage dates: 1946 to January 06 2020
Search date: 07/01/2020
Retrieved records: 729
Search strategy:

Database: Ovid MEDLINE(R) ALL <1946 to January 06, 2020>
Search Strategy:

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1 (danis or danisc or danisr or danistm).ti,ab,kf. (116)
2 (sx-ella$ or sxella$ or ella-cs$ or ellacs$ or cs-ella$ or csella$).ti,ab,kf,in. (31)
3 1 or 2 (137)
4 "Esophageal and Gastric Varices"/ (13018)
5 Gastrointestinal Hemorrhage/ (41215)
6 ((variceal$ or varices or varix$ or varicose$ or varicosis) adj5 (bleed$ or rebleed$ or ruptur$ or h?emorrhag$ or h?ematochez$ or h?ematoches$)).ti,ab,kf. (10569)
7 ((variceal$ or varices or varix$ or varicose$ or varicosis) adj5 (esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric)).ti,ab,kf. (11547)
8 ((esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric) adj5 (bleed$ or rebleed$ or h?emorrhag$ or h?ematochez$ or h?ematoches$)).ti,ab,kf. (38164)
9 ((esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric or refractory) adj5 VB).ti,ab,kf. (12)
10 or/4-9 (67457)
11 stents/ or self expandable metallic stents/ (65935)
12 (stent or stents or stenting or stented).ti,ab,kf. (97423)
13 (sem or sems).ti,ab,kf. (104469)
14 or/11-13 (213220)
15 10 and 14 (1557)
16 3 or 15 (1683)
17 exp animals/ not humans/ (4660757)
18 (news or editorial or case reports).pt. or case report.ti. (2820625)
19 16 not (17 or 18) (1159)
20 limit 19 to yr="2005 -Current" (731)
21 remove duplicates from 20 (729)

A.2: Source: Embase
Interface / URL: OvidSP
Database coverage dates: 1974 to 2020 January 03
Search date: 07/01/20

Retrieved records: 2494 (records indexed as conference abstracts by Embase [1210] were downloaded separately from the rest of the records [1284])
Search strategy:

Database: Embase <1974 to 2020 January 03>
Search Strategy:
---
1 (danis or danisc or danisr or danistm).ti,ab,kw,dj,dv,my,mv. (169)
2 (sx-ella$ or sxella$ or ella-cs$ or ellacs$ or cs-ella$ or csella$).ti,ab,kw,in,dj,dm,my,mv. (228)
3 1 or 2 (356)
4 esophagus varices/ or esophagus varices bleeding/ or esophagus hemorrhage/ (19941)
5 ((variceal$ or varices or varix$ or varicose$ or varicosis) adj5 (bleed$ or rebleed$ or ruptur$ or h?emorrhag$ or h?ematochez$ or h?ematoches$)).ti,ab,kw,dj. (16286)
6 ((variceal$ or varices or varix$ or varicose$ or varicosis) adj5 (esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric)).ti,ab,kw,dj. (17036)
7 ((esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric) adj5 (bleed$ or rebleed$ or h?emorrhag$ or h?ematochez$ or h?ematoches$)).ti,ab,kw,dj. (57016)
8 ((esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric or refractory) adj5 VB).ti,ab,kw,dj. (26)
9 or/4-8 (76279)
10 self expandable metallic stent/ or self expanding stent/ (6757)
11 digestive stent/ or esophageal stent/ or stent/ (89178)
12 (stent or stents or stenting or stented).ti,ab,kw,dj. (164685)
13 (sem or sems).ti,ab,kw,dj. (130145)
14 or/10-13 (305353)
15 9 and 14 (3106)
16 3 or 15 (3390)
17 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5911147)
18 editorial.pt. or case report.ti. (919749)
19 16 not (17 or 18) (3192)
20 limit 19 to yr="2005 -Current" (2541)
21 remove duplicates from 20 (2494)
22 (conference abstract or conference paper or conference proceeding or conference review).pt. (4437118)
23 21 not 22 (1284)
24 21 and 22 (1210)

The total number of records identified is shown in line 21.
The total number of conference publications is shown in line 24 – these were downloaded separately.
The total number of non-conference publications is shown in line 23 – these were downloaded separately.

A.3: Source: PubMed
Interface / URL: https://www.ncbi.nlm.nih.gov/pubmed, Legacy interface was used
Database coverage dates: 1940s to current
Search date: 08/01/2020

Retrieved records: 216
Search strategy:

Search	Query	Items found
#24	Search #22 Filters: Publication date from 2005/01/01 to 2020/12/31	216
#23	Search #22	224
#22	Search #20 NOT #21	224
#21	Search medline[sb]	26452778
#20	Search #17 NOT (#18 OR #19)	1506
#19	Search (news[pt] OR editorial[pt] OR case reports[pt]) OR case report[ti]	2816992
#18	Search animals[mh] NOT humans[mh:noexp]	4657076
#17	Search #4 OR #16	2136
#16	Search #11 AND #15	2016
#15	Search #12 OR #13 OR #14	206662
#14	Search sem[tiab] OR sems[tiab]	97990
#13	Search stent[tiab] OR stents[tiab] OR stenting[tiab] OR stented[tiab]	97326
#12	Search "stents"[mesh:noexp] OR "self expandable metallic stents"[mesh:noexp]	65924
#11	Search #5 OR #6 OR #7 OR #8 OR #9 OR #10	79906
#10	Search (esophag*[tiab] OR oesophag*[tiab] OR gastrointestinal[tiab] OR gastro-intestinal[tiab] OR GI[tiab] OR gastric[tiab] OR refractory[tiab]) AND VB[tiab]	73
#9	Search (esophag*[tiab] OR oesophag*[tiab] OR gastrointestinal[tiab] OR gastro-intestinal[tiab] OR GI[tiab] OR gastric[tiab]) AND (bleed*[tiab] OR rebleed*[tiab] OR hemorrhag*[tiab] OR hematochez*[tiab] OR hematoches*[tiab] OR haemorrhag*[tiab] OR haematochez*[tiab] OR haematoches*[tiab])	52435
#8	Search (variceal*[tiab] OR varices[tiab] OR varix*[tiab] OR varicose*[tiab] OR varicosis[tiab]) AND (esophag*[tiab] OR oesophag*[tiab] OR gastrointestinal[tiab] OR gastro-intestinal[tiab] OR GI[tiab] OR gastric[tiab])	12743
#7	Search (variceal*[tiab] OR varices[tiab] OR varix*[tiab] OR varicose*[tiab] OR varicosis[tiab]) AND (bleed*[tiab] OR rebleed*[tiab] OR ruptur*[tiab] OR hemorrhag*[tiab] OR hematochez*[tiab] OR hematoches*[tiab] OR haemorrhag*[tiab] OR haematochez*[tiab] OR haematoches*[tiab])	12471
#6	Search "Gastrointestinal Hemorrhage"[mesh:noexp]	41208
#5	Search "Esophageal and Gastric Varices"[mesh:noexp]	13016
#4	Search #1 OR #2 OR #3	133
#3	Search sx-ella*[ad] OR sxella*[ad] OR ella-cs*[ad] OR ellacs*[ad] OR cs-ella*[ad] OR csella*[ad]	3
#2	Search sx-ella*[tiab] OR sxella*[tiab] OR ella-cs*[tiab] OR ellacs*[tiab] OR cs-ella*[tiab] OR csella*[tiab]	25
#1	Search danis[tiab] OR danisc[tiab] OR danisr[tiab] OR danistm[tiab]	115

A.4: Source: Cochrane Database of Systematic Reviews (CDSR)
Interface / URL: Cochrane Library, Wiley
Database coverage dates: Issue 12 of 12, December 2019
Search date: 07/01/2020
Retrieved records: 9
Search strategy:

Search Name:
Date Run: 07/01/2020 15:04:47
Comment:

ID	Search	Hits
#1	(danis OR danisc OR danisr OR danistm):ti,ab,kw	4
#2	((sx NEXT ella*) OR sxella* OR (ella NEXT cs*) OR ellacs* OR (cs NEXT ella*) OR csella*):ti,ab,kw	5
#3	#1 OR #2	7
#4	MeSH descriptor: [Esophageal and Gastric Varices] this term only	859
#5	MeSH descriptor: [Gastrointestinal Hemorrhage] this term only	1458
#6	((variceal* OR varices OR varix* OR varicose* OR varicosis) NEAR/5 (bleed* OR rebleed* OR ruptur* OR h?emorrhag* OR h?ematochez* OR h?ematoches*)):ti,ab,kw	2171
#7	((variceal* OR varices OR varix* OR varicose* OR varicosis) NEAR/5 (esophag* OR oesophag* OR gastrointestinal OR (gastro NEXT intestinal) OR GI OR gastric)):ti,ab,kw	2105
#8	((esophag* OR oesophag* OR gastrointestinal OR (gastro NEXT intestinal) OR GI OR gastric) NEAR/5 (bleed* OR rebleed* OR h?emorrhag* OR h?ematochez* OR h?ematoches*)):ti,ab,kw	6464
#9	((esophag* OR oesophag* OR gastrointestinal OR (gastro NEXT intestinal) OR GI OR gastric OR refractory) NEAR/5 VB):ti,ab,kw	3
#10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	7610
#11	MeSH descriptor: [Stents] this term only	2926
#12	MeSH descriptor: [Self Expandable Metallic Stents] explode all trees	34
#13	(stent OR stents OR stenting OR stented):ti,ab,kw	14833
#14	(sem OR sems).ti,ab,kw	1390
#15	#11 OR #12 OR #13 OR #14	16211
#16	#15 AND #10	245
#17	#16 OR #3	249
#18	#17 with Cochrane Library publication date Between Jan 2005 and Jan 2020, in Cochrane Reviews	9

A.5: Source: Cochrane Central Register of Controlled Trials (CENTRAL)
Interface / URL: Cochrane Library, Wiley
Database coverage dates: Issue 12 of 12, December 2019
Search date: 07/01/2020
Retrieved records: 310
Search strategy:

Search Name:
Date Run: 07/01/2020 15:25:12
Comment:

ID	Search	Hits
#1	danis OR danisc OR danisr OR danistm	139
#2	(sx NEXT ella*) OR sxella* OR (ella NEXT cs*) OR ellacs* OR (cs NEXT ella*) OR csella*	7
#3	#1 OR #2	144

#4 MeSH descriptor: [Esophageal and Gastric Varices] this term only 859
#5 MeSH descriptor: [Gastrointestinal Hemorrhage] this term only 1458
#6 (variceal* OR varices OR varix* OR varicose* OR varicosis) NEAR/5 (bleed* OR rebleed* OR ruptur* OR h?emorrhag* OR h?ematochez* OR h?ematoches*) 2344
#7 (variceal* OR varices OR varix* OR varicose* OR varicosis) NEAR/5 (esophag* OR oesophag* OR gastrointestinal OR (gastro NEXT intestinal) OR GI OR gastric) 2161
#8 (esophag* OR oesophag* OR gastrointestinal OR (gastro NEXT intestinal) OR GI OR gastric) NEAR/5 (bleed* OR rebleed* OR h?emorrhag* OR h?ematochez* OR h?ematoches*) 6979
#9 (esophag* OR oesophag* OR gastrointestinal OR (gastro NEXT intestinal) OR GI OR gastric OR refractory) NEAR/5 VB 4
#10 #4 OR #5 OR #6 OR #7 OR #8 OR #9 8152
#11 MeSH descriptor: [Stents] this term only 2926
#12 MeSH descriptor: [Self Expandable Metallic Stents] explode all trees 34
#13 stent OR stents OR stenting OR stented 15086
#14 sem OR sems 7564
#15 #11 OR #12 OR #13 OR #14 22393
#16 #15 AND #10 295
#17 #16 OR #3 435
#18 #17 with Publication Year from 2005 to 2019, in Trials 310

A.6: Source: Health Technology Assessment Database (HTA Database)
Interface / URL: CRD Databases
Database coverage dates: Last updated 31st March 2018
Search date: 08/01/2020
Retrieved records: 2
Search strategy:

1 (danis OR danisc OR danisr OR danistm) 1
2 (sx ella* OR sxella* OR ella cs* OR ellacs* OR cs ella* OR csella) 1
3 #1 OR #2 2
4 MeSH DESCRIPTOR Esophageal and Gastric Varices 91
5 MeSH DESCRIPTOR Gastrointestinal Hemorrhage 206
6 ((variceal* OR varices OR varix* OR varicose* OR varicosis) NEAR5 (bleed* OR rebleed* OR rupture* OR hemorrhag* OR haemorrhag* OR hematochez* OR haematochez* OR hematoches* OR haematoches*)) 136
7 ((bleed* OR rebleed* OR rupture* OR hemorrhag* OR haemorrhag* OR hematochez* OR haematochez* OR hematoches* OR haematoches*) NEAR5 (variceal* OR varices OR varix* OR varicose* OR varicosis)) 66
8 ((variceal* OR varices OR varix* OR varicose* OR varicosis) NEAR5 (esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric)) 75
9 ((esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric) NEAR5 (variceal* OR varices OR varix* OR varicose* OR varicosis)) 124
10 ((esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric) NEAR5 (bleed* OR rebleed* OR hemorrhag* OR haemorrhag* OR hematochez* OR haematochez* OR hematoches* OR haematoches*)) 497

11 ((bleed* OR rebleed* OR hemorrhag* OR haemorrhag* OR hematochez* OR haematochez* OR hematoches* OR haematoches*) NEAR5 (esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric)) 157
12 ((esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric OR refractory) NEAR5 VB) 0
13 (VB NEAR5 (esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric OR refractory)) 0
14 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 592
15 MeSH DESCRIPTOR Stents 834
16 MeSH DESCRIPTOR Self Expandable Metallic Stents 0
17 (stent OR stents OR stenting OR stented) 1397
18 (sem OR sems) 52
19 #15 OR #16 OR #17 OR #18 1432
20 #14 AND #19 22
21 #3 OR #20 24
22 (#21) FROM 2005 TO 2020 15
23 (#22) IN HTA FROM 2005 TO 2020 2

A.7: Source: Database of Abstracts of Reviews of Effects (DARE)
Interface / URL: CRD Databases
Database coverage dates: Last update 31st March 2015, searches continued to the end of 2014.
Search date: 8/01/2020
Retrieved records: 8
Search strategy:

1 (danis OR danisc OR danisr OR danistm) 1
2 (sx ella* OR sxella* OR ella cs* OR ellacs* OR cs ella* OR csella) 1
3 #1 OR #2 2
4 MeSH DESCRIPTOR Esophageal and Gastric Varices 91
5 MeSH DESCRIPTOR Gastrointestinal Hemorrhage 206
6 ((variceal* OR varices OR varix* OR varicose* OR varicosis) NEAR5 (bleed* OR rebleed* OR rupture* OR hemorrhag* OR haemorrhag* OR hematochez* OR haematochez* OR hematoches* OR haematoches*)) 136
7 ((bleed* OR rebleed* OR rupture* OR hemorrhag* OR haemorrhag* OR hematochez* OR haematochez* OR hematoches* OR haematoches*) NEAR5 (variceal* OR varices OR varix* OR varicose* OR varicosis)) 66
8 ((variceal* OR varices OR varix* OR varicose* OR varicosis) NEAR5 (esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric)) 75
9 ((esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric) NEAR5 (variceal* OR varices OR varix* OR varicose* OR varicosis)) 124
10 ((esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric) NEAR5 (bleed* OR rebleed* OR hemorrhag* OR haemorrhag* OR hematochez* OR haematochez* OR hematoches* OR haematoches*)) 497
11 ((bleed* OR rebleed* OR hemorrhag* OR haemorrhag* OR hematochez* OR haematochez* OR hematoches* OR haematoches*) NEAR5 (esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric)) 157

12 ((esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric OR refractory) NEAR5 VB) 0
13 (VB NEAR5 (esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric OR refractory)) 0
14 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 592
15 MeSH DESCRIPTOR Stents 834
16 MeSH DESCRIPTOR Self Expandable Metallic Stents 0
17 (stent OR stents OR stenting OR stented) 1397
18 (sem OR sems) 52
19 #15 OR #16 OR #17 OR #18 1432
20 #14 AND #19 22
21 #3 OR #20 24
22 (#21) FROM 2005 TO 2020 15
23 (#22) IN DARE FROM 2005 TO 2020 8

A.8: Source: NHS Economic Evaluation Database (NHS EED)

Interface / URL: CRD Databases
Database coverage dates: Last update 31st March 2015, searches continued to the end of 2014.
Search date: 08/01/2020
Retrieved records: 5
Search strategy:

1 (danis OR danisc OR danisr OR danistm) 1
2 (sx ella* OR sxella* OR ella cs* OR ellacs* OR cs ella* OR csella) 1
3 #1 OR #2 2
4 MeSH DESCRIPTOR Esophageal and Gastric Varices 91
5 MeSH DESCRIPTOR Gastrointestinal Hemorrhage 206
6 ((variceal* OR varices OR varix* OR varicose* OR varicosis) NEAR5 (bleed* OR rebleed* OR rupture* OR hemorrhag* OR haemorrhag* OR hematochez* OR haematochez* OR hematoches* OR haematoches*)) 136
7 ((bleed* OR rebleed* OR rupture* OR hemorrhag* OR haemorrhag* OR hematochez* OR haematochez* OR hematoches* OR haematoches*) NEAR5 (variceal* OR varices OR varix* OR varicose* OR varicosis)) 66
8 ((variceal* OR varices OR varix* OR varicose* OR varicosis) NEAR5 (esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric)) 75
9 ((esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric) NEAR5 (variceal* OR varices OR varix* OR varicose* OR varicosis)) 124
10 ((esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric) NEAR5 (bleed* OR rebleed* OR hemorrhag* OR haemorrhag* OR hematochez* OR haematochez* OR hematoches* OR haematoches*)) 497
11 ((bleed* OR rebleed* OR hemorrhag* OR haemorrhag* OR hematochez* OR haematochez* OR hematoches* OR haematoches*) NEAR5 (esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric)) 157
12 ((esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric OR refractory) NEAR5 VB) 0
13 (VB NEAR5 (esophag* OR oesophag* OR gastrointestinal OR gastro intestinal OR GI OR gastric OR refractory)) 0

14	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	592
15	MeSH DESCRIPTOR Stents 834	
16	MeSH DESCRIPTOR Self Expandable Metallic Stents	0
17	(stent OR stents OR stenting OR stented)	1397
18	(sem OR sems)	52
19	#15 OR #16 OR #17 OR #18 1432	
20	#14 AND #19	22
21	#3 OR #20	24
22	(#21) FROM 2005 TO 2020	15
23	(#22) IN NHSEED FROM 2005 TO 2020	5

A.9: Source: Conference Proceedings Citation Index- Science (CPCI-S) --
Interface / URL: Web of Science, Clarivate Analytics
Database coverage dates: 1990-present. Last updated 2020-01-07
Search date: 08/01/2020
Retrieved records: 67
Search strategy:

# 14 #13 67
Indexes=CPCI-S Timespan=2005-2020
# 13 #12 OR #3 115
Indexes=CPCI-S Timespan=All years
# 12 #11 AND #8 110
Indexes=CPCI-S Timespan=All years
# 11 #10 OR #9 89,684
Indexes=CPCI-S Timespan=All years
# 10 TS=("sem" OR "sems") 67,551
Indexes=CPCI-S Timespan=All years
# 9 TS=("stent" OR "stents" OR "stenting" OR "stented") 22,360
Indexes=CPCI-S Timespan=All years
# 8 #7 OR #6 OR #5 OR #4 5,276
Indexes=CPCI-S Timespan=All years
# 7 TS=((esophag* OR oesophag* OR "gastrointestinal" OR "gastro intestinal" OR "GI" OR "gastric" OR "refractory") NEAR/5 "VB") 1
Indexes=CPCI-S Timespan=All years
# 6 TS=((esophag* OR oesophag* OR "gastrointestinal" OR "gastro intestinal" OR "GI" OR "gastric") NEAR/5 (bleed* OR rebleed* OR h$emorrhag* OR h$ematochez* OR h$ematoches*)) 4,035
Indexes=CPCI-S Timespan=All years
# 5 TS=((variceal* OR "varices" OR varix* OR varicose* OR "varicosis") NEAR/5 (esophag* OR oesophag* OR "gastrointestinal" OR "gastro intestinal" OR "GI" OR "gastric")) 1,267
Indexes=CPCI-S Timespan=All years
# 4 TS=((variceal* OR "varices" OR varix* OR varicose* OR "varicosis") NEAR/5 (bleed* OR rebleed* OR ruptur* OR h$emorrhag* OR h$ematochez* OR h$ematoches*)) 1,251
Indexes=CPCI-S Timespan=All years
# 3 #2 OR #1 8
Indexes=CPCI-S Timespan=All years

# 2	TS=("sx ella*" OR sxella* OR "ella cs*" OR ellacs* OR "cs ella*" OR csella*) Indexes=CPCI-S Timespan=All years	4
# 1	TS=("danis" OR "danisc" OR "danisr" OR "danistm") Indexes=CPCI-S Timespan=All years	5

A.10: Source: WHO International Clinical Trials Registry Portal (ICTRP)
Interface / URL: https://apps.who.int/trialsearch/
Database coverage dates: Latest updates December 2019
Search date: 08/01/2020
Retrieved records: 93
Search strategy:

Limited search functionality necessitates several individual searches. Due to the lack of functionality to combine multiple concepts, only the terms most likely to identify relevant studies were searched. Each string below was run separately via the basic interface and the results downloaded individually.

danis OR danisc OR danisr OR danistm OR sx-ella OR sxella OR ella-cs OR ellacs OR cs-ella OR csella OR sx ella OR ella cs OR cs ella - 6 records for 6 trials. 6 trial records downloaded.

stent* AND variceal OR stent* AND varix OR stent* AND varicose* OR stent* AND varices OR stent* AND varicoses 18 records for 15 trials. 15 trial records downloaded.

stent* AND esophag* OR stent* AND oesophag* 76 records for 72 trials. 72 trial records downloaded.

A.11: Source: ClinicalTrials.gov
Interface / URL: https://www.clinicaltrials.gov/ct2/results/refine?show_xprt=Y – Expert search interface
Database coverage dates: 2000-current
Search date: 08/01/2020
Retrieved records: 109
Search strategy:

Limited search functionality necessitates several individual searches. Each string below was run separately via the Expert interface and the results downloaded individually.

danis OR danisc OR danisr OR danistm OR sx-ella OR sxella OR ella-cs OR ellacs OR cs-ella OR csella - 13 results

(stent OR stents OR stenting OR stented OR SEM OR SEMS) AND (esophageal OR esophagus OR oesophageal OR oesophagus OR gastrointestinal OR gastro-intestinal OR GI OR gastric) AND (bleed OR bleeding OR bleeds OR rebleed OR rebleeding OR rebleeds OR hemorrhage OR hemorrhaged OR hemorrhages OR hemorrhaging OR haemorrhage OR haemorrhaged OR haemorrhages OR haemorrhaging OR hematochezia OR hematochesia OR haematochezia OR haematochesia OR variceal OR varices OR varix OR varicose OR varicoses OR varicosis) – 96 results

A.12: Source: EconLit
Interface / URL: OvidSP
Database coverage dates: 1886 to December 26, 2019
Search date: 07/01/20
Retrieved records: 4
Search strategy:

Database: Econlit <1886 to December 26, 2019>
Search Strategy:
---
1 (danis or danisc or danisr or danistm).ti,ab,kw. (4)
2 (sx-ella$ or sxella$ or ella-cs$ or ellacs$ or cs-ella$ or csella$).ti,ab,kw. (0)
3 1 or 2 (4)
4 ((variceal$ or varices or varix$ or varicose$ or varicosis) adj5 (bleed$ or rebleed$ or ruptur$ or h?emorrhag$ or h?ematochez$ or h?ematoches$)).ti,ab,kw. (0)
5 ((variceal$ or varices or varix$ or varicose$ or varicosis) adj5 (esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric)).ti,ab,kw. (0)
6 ((esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric) adj5 (bleed$ or rebleed$ or h?emorrhag$ or h?ematochez$ or h?ematoches$)).ti,ab,kw. (3)
7 ((esophag$ or oesophag$ or gastrointestinal or gastro-intestinal or GI or gastric or refractory) adj5 VB).ti,ab,kw. (0)
8 or/4-7 (3)
9 (stent or stents or stenting or stented).ti,ab,kw. (36)
10 (sem or sems).ti,ab,kw. (757)
11 9 or 10 (793)
12 8 and 11 (0)
13 3 or 12 (4)
14 limit 13 to yr="2005 -Current" (4)

A.13: Source: FDA webpages
Interface / URL: https://search.fda.gov/
Database coverage dates: N/A
Search date: 08/01/2020
Retrieved records: 0
Search strategy:

Site wide search option used. Results scanned by information specialist for relevance. Only potentially relevant records selected and downloaded.

Danis – 24 results, 0 relevant
SX Ella – 5 results, 0 relevant
CS Ella – 12 results, 0 relevant

A.14: Source: CEA Registry
Interface / URL: http://healtheconomicsdev.tuftsmedicalcenter.org/cear2/search/search.aspx
Database coverage dates: Information not provided
Search date: 08/01/2020

Retrieved records: 0
Search strategy:

Only access to the Basic Search function was available. This allows for single search terms only. No Boolean, truncation, or other search syntax appears to be supported. No export options, results scanned by information specialist for relevance. Only potentially relevant records selected and downloaded.

Danis – 36 results, 0 relevant
DanisR – 0 results
DanisC – 0 results
DanisTM – 0 results
SX Ella – 0 results
SXElla – 0 results
CS Ella – 0 results
CSElla – 0 results
Ella CS – 0 results
EllaCS – 0 results

Literature Search Results

The searches identified 4047 records (Table A.2). Following deduplication, 3107 records were assessed for relevance.

Table A.2: Literature search results

Resource	**Number of records identified**
Ovid MEDLINE ALL	729
PubMed	216
Embase	2494
Cochrane Database of Systematic Reviews (CDSR)	9
Cochrane Central Register of Controlled Trials (CENTRAL)	310
Database of Abstracts of Reviews of Effects (DARE)	8
Health Technology Assessment Database (HTA Database)	2
NHS Economic Evaluation Database (NHS EED)	5
Conference Proceedings Citation Index – Science (CPCI-S)	67
WHO International Clinical Trials Registry Portal (ICTRP)	93
ClinicalTrials.gov.	109
EconLit	4
Cost Effectiveness Analysis Registry (CEA Registry)	0
FDA webpages	0
Records identified by other methods (supplied by sponsor)	1
Total number of records retrieved	**4047**
Total number of records after deduplication	**3107**

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):
The protocol stated we would search the conferences webpages or relevant journal supplements for abstracts from the following two conferences if they were not indexed in Embase. • British Society of Gastroenterology (BSG) Annual Meeting 2017, 2018 and 2019 • British Association for the Study of the Liver (BASL) Annual Meeting 2017, 2018 and 2019 The British Society of Gastroenterology (BSG) Annual Meeting was indexed in Embase for the three years of interest (2017, 2018, 2019) and so was not handsearched. The abstracts of the British Association for the Study of the Liver (BASL) Annual Meeting were not indexed in Embase for the years required. We could not find the abstracts freely available online, either as a journal supplement or on the conference webpages. BASL did not respond to our email request for the abstracts within the timelines required the review. This resource was therefore not searched.
Inclusion and exclusion criteria:
POPULATION Studies assessing patients aged 16 years and over with refractory oesophageal variceal bleeding in whom first line therapy such as terlipressin, prophylactic antibiotics, variceal band ligation or sclerotherapy, is unsuitable or has failed were eligible for inclusion in the SR. **INTERVENTION** Studies assessing patients who have the Danis stent inserted were eligible for inclusion in the SR. **COMPARATORS** Studies of patients receiving either of the following comparators were eligible for inclusion in the SR: • Balloon tamponade • Early trans-jugular intrahepatic portosystemic shunt (TIPS) Early TIPS may also be described as emergency TIPS, acute TIPS or rescue TIPS. Early TIPS has been defined in the literature as placement within three days of hospitalisation for acute variceal bleeding after one session of endoscopic therapy and rescue TIPS has been defined as TIPS implantation after two endoscopic interventions for variceal bleeding .

Therefore, studies of TIPS used under either of these two conditions were eligible for inclusion in this review.

OUTCOMES

Studies reporting data for one or more of the following outcomes were eligible for inclusion in the review:

- Control of bleeding
- Rebleeding rate
- Blood transfusion use
- Device-related adverse events, including stent migration
- Mortality rate
- Hepatic encephalopathy
- Patient-related quality of life (e.g. EQ-5D or SF-36)
- Additional/further interventions, including TIPS

STUDY DESIGN

Randomised controlled trials (RCTs) of any size or duration will be considered for inclusion in the SR. Prospective and retrospective non-randomised comparative trials were also eligible.

Case series and single arm studies including 10 or more patients were eligible. This cut off has been used to increase the robustness of the evidence identified for the SR. Case series with less than 10 patients and case reports were not eligible for inclusion in this SR.

We identified systematic reviews published in the last five years and check their included studies list to ensure that all relevant articles were identified and assessed. Systematic reviews were not data extracted.

LIMITS

Only studies published from 2005 onwards were eligible for inclusion in the review since 2005 was the year that the Danis stent was granted a CE mark. Conference abstracts were only included if they provide additional information for studies published in full. Non-English studies were excluded.

Letters, editorials, news articles and comments were excluded since they are unlikely to contain enough data to extract and use in the review.

Data abstraction strategy:

The studies are summarised in tables providing data on their methods and results. We have provided a narrative summary exploring the quality of the studies, the relationship between studies and patterns that we have discerned in the data in the appropriate sections of this document.

Excluded studies

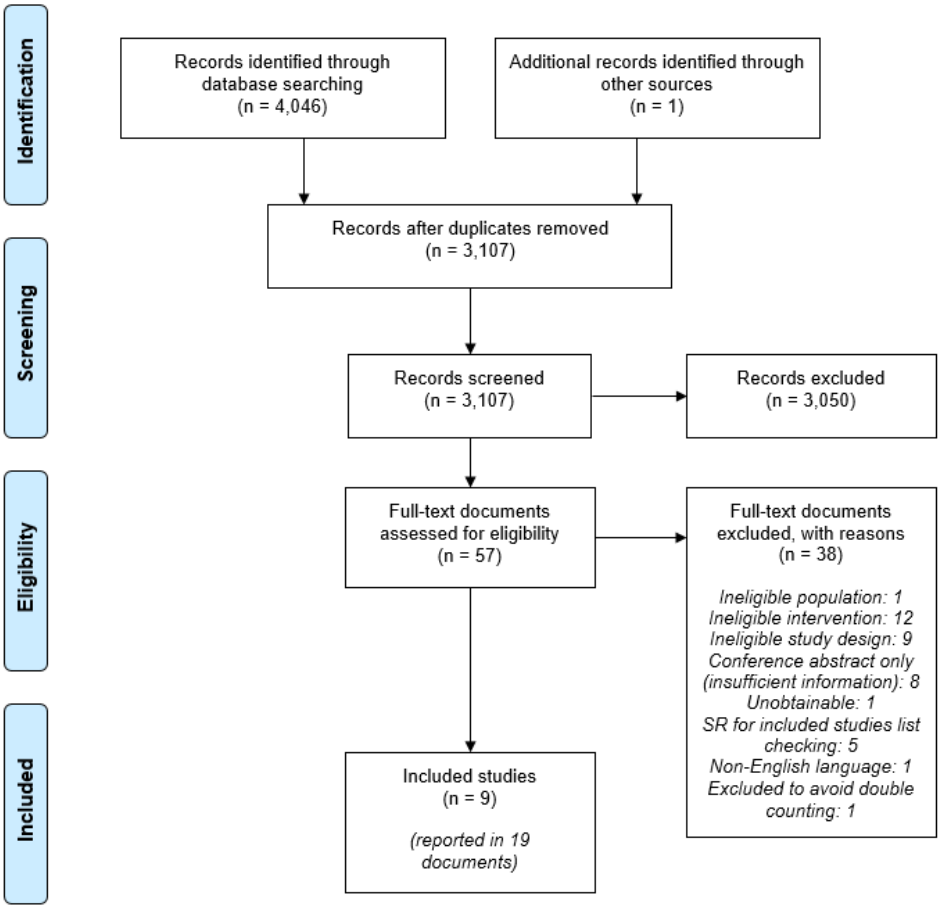
List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Excluded study	Rationale for exclusion
Aabakken L. Endoscopic haemostasis. Best Pract Res Clin Gastroenterol. 2008;22(5):899-927.	Ineligible study design
Alonso Larraga JO, Flores Carmona DY, Hernandez Guerrero A, Ramirez Solis ME, de la Mora Levy JG, Sanchez Del Monte JC. Fully covered stents versus partially covered stents for palliative treatment of esophageal cancer: Is there a difference? Rev Gastroenterol Mex. 2018;83(3):228-33.	Non-English language
Anisimov AA, Loginov AV. Danish stent is the modern way to endoscopic hemostasis in portal hypertension. Our clinical experience. Int J Rheum Dis. 2019;22(Suppl 2):37-38.	Conference abstract only insufficient information
Boyer TD, Henderson JM, Heerey AM, Arrigain S, Konig V, Connor J, et al. Cost of preventing variceal rebleeding with transjugular intrahepatic portal systemic shunt and distal splenorenal shunt. J Hepatol. 2008;48(3):407-14.	Ineligible intervention
Brunner F, Berzigotti A, Bosch J. Prevention and treatment of variceal haemorrhage in 2017. Liver Int. 2017;37(Suppl 1):104-15.	Ineligible study design
Cabrera L, Tandon P, Abraldes JG. An update on the management of acute esophageal variceal bleeding. Gastroenterol Hepatol. 2017;40(1):34-40.	Ineligible study design
The effect of different stents configuration in reducing the rate of restenosis and hepatic encephalopathy based on multi-center clinical study. Identifier: ChiCTR-ICR-15006829. In: ClinicalTrials.gov [internet]. Chengdu: Chinese University of Hong Kong: 2015. Available from http://www.chictr.org.cn/hvshowproject.aspx?id=3699.	Ineligible intervention
Drastich P, Brezina J, Sperl J, Frankova S, Benes M, Spicak J. Treatment of uncontrollable acute variceal bleeding with self-expanding metal stent: A single center experience. Gastroenterology. 2016;150(4 Suppl 1):S339.	Conference abstract only insufficient information
Ertel AE, Chang AL, Kim Y, Shah SA. Management of gastrointestinal bleeding in patients with cirrhosis. Curr Probl Surg. 2016;53(8):366-95.	Ineligible intervention
Fejfar T, Safka V, Jirkovsky V, Hulek P. Danis oesophageal stent in treatment of variceal bleeding. Gastroenterol Hepatol. 2013;67(2):98-103.	Unobtainable
Filin A, Duvanskiy V. Endoscopy in prevention and treatment of esophageal and gastric variceal bleedings. Endoscopy. 2019;51(4):S239.	Conference abstract only insufficient information
Franco MC, Nakao FS, Rodrigues R, Maluf-Filho F, de Paulo GA, Libera ED. Proposal of a clinical care pathway for the management of acute upper gastrointestinal bleeding. Arq Gastroenterol. 2015;52(4):283-92.	Ineligible intervention
Gamsjager M, Heghedus A, Resch H, Bodlaj G. Use of the Ella Danis stent in esophageal bleeding due to severe reflux esophagitis. Endoscopy. 2016;48(Suppl 01):E127.	Ineligible study design
Garbuzenko DV. Current approaches to the management of patients with liver cirrhosis who have acute esophageal variceal bleeding. Curr Med Res Opin. 2016;32(3):467-75.	Ineligible intervention

Grant C, Kemp D, Beattie M, Austin A. Trends in variceal bleeding: A single centre experience from 2006-2013. Gut. 2014;63(Suppl 1):A181.	Conference abstract only insufficient information
Grubnik YUV, Yuzvak OM, Fomenko VA. Miniinvasive procedures in the patients with liver cirrosis complicated by variceal bleeding. Surg Endosc. 2018;32(Suppl 2):S564.	Conference abstract only insufficient information
Grubnik Y, Iuzvak OM, Moskovchenko IV, Golovchenko MY. Laparascopic operations in the patients with liver cirrosis complicated by variceal bleeding. Surg Endosc. 2017;31(2 Suppl 1):S141.	Conference abstract only insufficient information
Hayman AV, Fisher MJ, Ryu RK, Bentrem DJ, Skaro AI, Omary RA. Splenic vein stent placement for refractory gastric variceal bleeding. J Surg Radiol. 2010;1(2):115-17.	Ineligible study design
Hirdes MM, Siersema PD, Houben MH, Weusten BL, Vleggaar FP. The stent-in-stent technique is effective and safe for removal of embedded esophageal stents. Gastrointest Endosc. 2010;71(5):AB315-AB16.	Ineligible intervention
Hogan BJ, O'Beirne JP. Role of self-expanding metal stents in the management of variceal haemorrhage: Hype or hope? World J Gastrointest Endosc. 2016;8(1):23-9.	Ineligible study design
Hosokawa I, Adam R, Allard MA, Pittau G, Vibert E, Cherqui D, et al. Outcomes of surgical shunts and transjugular intrahepatic portasystemic stent shunts for complicated portal hypertension. Br J Surg. 2017;104(4):443-51.	Ineligible intervention
Hubmann R, Bodlaj G, Czompo M, Benko L, Pichler P, Al-Kathib S, et al. The use of self-expanding metal stents to treat acute esophageal variceal bleeding. Endoscopy. 2006;38(9):896-901.	20 patients from this study also reported in Zehetner 2008 therefore, excluded to prevent double counting
Jain M, Balkrishanan M, Chenduran SNK, Sridhar CGS, Ramakrishnan R, Venkataraman J. SX-Ella Danis stent in massive upper gastrointestinal bleeding in cirrhosis - A case series. Clin Exp Hepato. 2018;4(2):97-99.	Ineligible study design
Kobryn K, Koziel S, Porecka M, Kobryn K, Holowko W, Patkowski W, et al. Endoscopic treatment of early biliary complications in liver transplant recipients. Ann Transplan. 2015;20:741-6.	Ineligible intervention
Luo S, Chu J, Huang H, Yao K. Direct intrahepatic portocaval shunt for sinusoidal obstruction syndrome associated with hepatotoxicity of pyrrolizidine alkaloids. Biomed Res Int. 2018;2018:9804582.	Ineligible intervention
Marot A, Trepo E, Doerig C, Moreno C, Moradpour D, Deltenre P. Systematic review with meta-analysis: Self-expanding metal stents in patients with cirrhosis and severe or refractory oesophageal variceal bleeding. Aliment Pharmacol Ther. 2015;42(11-12):1250-60.	SR for included studies list checking
McCarty TR, Njei B. Self-expanding metal stents for acute refractory esophageal variceal bleeding: A systematic review and meta-analysis. Dig Endosc. 2016;28(5):539-47.	SR for included studies list checking
Messner Z, Gschwantler M, Resch H, Bodlaj G. Use of the Ella Danis stent in severe esophageal bleeding caused by acute necrotizing esophagitis. Endoscopy. 2014;46(Suppl 1):E225-E26.	Ineligible study design
Mishin I, Zastavnitsky G, Ghidirim G, Bunic G. Self-expanding metal stents: A new hemostasis method for bleeding esophageal varices. Hepatol Int. 2013;7(Suppl 1):S540.	Conference abstract only insufficient information
SX ELLA Esophageal Degradable BD Stent System. Identifier: NCT01337206. In: ClinicalTrials.gov [internet]. Bethesda: US National	Ineligible population

Library of Medicine: 2011. Available from https://clinicaltrials.gov/ct2/show/NCT01337206.	
Ososanya A, Pick H, Kayani J, Austin A, Salmon C, Taylor N, et al. Experience in the use of self-expandable metal stents for the management of variceal haemorrhage. Gut. 2015;64(Suppl 1):A407.	Conference abstract only insufficient information
Pontone S, Giusto M, Filippini A, Cicerone C, Pironi D, Merli M. Hemostasis in uncontrolled esophageal variceal bleeding by self-expanding metal stents: A systematic review. Gastroenterol Hepatol Bed Bench. 2016;9(1):6-11.	SR for included studies list checking
Qi X, Jia J, Bai M, Guo X, Su C, Garcia-Pagan JC, et al. Transjugular intrahepatic portosystemic shunt for acute variceal bleeding: A meta-analysis. J Clin Gastroenterol. 2015;49(6):495-505.	Ineligible intervention
Roberts D, Tsochatzis E, Gurusamy KS. Treatment for bleeding oesophageal varices in people with decompensated liver cirrhosis: A network meta-analysis. Cochrane Database Syst Rev. 2018(10):CD013155.	Ineligible study design
Rodrigues SG, Cardenas A, Escorsell A, Bosch J. Balloon tamponade and esophageal stenting for esophageal variceal bleeding in cirrhosis: A systematic review and meta-analysis. Semin Liver Dis. 2019;39(2):178-94.	SR for included studies list checking
Shao X-D, Qi X-S, Guo X-Z. Esophageal stent for refractory variceal bleeding: A systemic review and meta-analysis. Biomed Res Int. 2016;2016:4054513.	SR for included studies list checking
Sharma A, Goel A, Moses V, Keshava SN, Zachariah UG, Elias E, et al. Anticoagulating Budd Chiari syndrome patients presenting with variceal bleed - A retrospective study. J Gastroenterol Hepatol. 2020	Ineligible intervention
Zhang H, Zhang H, Li H, Zhang H, Zheng D, Sun C-M, et al. TIPS versus endoscopic therapy for variceal rebleeding in cirrhosis: A meta-analysis update. J Huazhong U Sci-Med. 2017;37(4):475-85.	Ineligible intervention

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



Structured abstracts for unpublished studies

No unpublished studies have been identified.

Appendix B: Search strategy for adverse events

Date search conducted:	NA
Date span of search:	NA
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
The search for the clinical evidence, as reported in Appendix A, was designed to identify any studies of stent insertion for acute oesophageal variceal bleeds. A study design filter was not used and therefore the search would retrieve studies of any design, reporting any outcomes, and with or without a comparator. This includes studies reporting adverse events associated with the Danis stent. As a result, a separate search of bibliographic databases for this evidence was not required.	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
NA	
Inclusion and exclusion criteria:	
NA see Appendix A for the eligibility criteria used	
Data abstraction strategy:	
NA	

Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☒ If no, please proceed to declaration (below)

☐

Yes ☐ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: 

** Must be Medical Director or equivalent*

Date: 9th April 2020

Print: Ian W Aaron

Role / organisation: Managing Director, UK Medical Ltd

Contact email: ian.aaron@ukmedical.com

Formatted: Superscript

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

[MT450 Danis stent for acute oesophageal variceal bleeds]

Company evidence submission

Part 2: Economic evidence

Company name	UK Medical Ltd
Submission date	5th May 2020
Contains confidential information	No

Contents

1 Published and unpublished economic evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		4,047*
Number of studies identified as being relevant to the decision problem.		None
Of the relevant studies identified:	Number of published studies.	None
	Number of abstracts.	None
	Number of ongoing studies.	None

* Note that one search was conducted for economic and clinical evidence

List of relevant studies

In table 1, provide brief details of any published or unpublished economic studies or abstracts identified as being relevant to the decision problem.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data provided.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Not applicable – no studies were identified.

2 Details of relevant studies

Please give details of all relevant studies (all studies in table 1). Copy and paste a new table into the document for each study. Please use 1 table per study.

Not applicable – no economic studies were identified.

3 Economic model

This section refers to the de novo economic model that you have submitted.

Description

Patients

Describe which patient groups are included in the model.

The model includes people aged 16 years and over with acute refractory oesophageal variceal bleeding in whom first line therapy such as terlipressin, prophylactic antibiotics, variceal band ligation or sclerotherapy is unsuitable or has failed.

Technology and comparator(s)

State the technology and comparators used in the model. Provide a justification if the comparator used in the model is different to that in the scope.

The technology is the Danis stent. The comparator in the model is balloon tamponade in line with the NICE scope. Early trans-jugular intrahepatic portosystemic shunt (TIPS) is included in the scope, however no clinical data were identified with which to populate the model hence this comparison has not been included. Additionally, early TIPS is typically performed within 72 hours of variceal bleeding and usually after placement of a stent or balloon tamponade. Therefore, a more appropriate comparator would be emergency or salvage TIPS which would be performed at the same point in the clinical pathway (Tripathi et al. 2015). This can however only be performed in select hospitals in the UK and comparative data were not available with which to populate the model.

Model structure

Provide a diagram of the model structure you have chosen in Appendix B.

Justify the chosen structure of the model by referring to the clinical care pathway outlined in part 1, section 3 (Clinical context) of your submission.

A *de novo* economic model was developed to estimate the costs and benefits associated with use of the Danis stent compared with balloon tamponade in patients with acute oesophageal variceal bleeding from an NHS perspective over a 6-week period. A cost calculator approach was taken and a diagram of this structure is presented in Appendix B.

The Escorsell et al. (2016) study was the key clinical trial and the only randomised controlled trial identified as part of the clinical submission. The model structure is largely based on the data available from this study. Specifically, the model is designed to capture differences between treatments in the rate of re-bleeding, survival, adverse events and proportion of patients receiving definitive treatments by 6 weeks. Other clinical outcomes that were captured in the model include the proportion of patients experiencing severe hepatic encephalopathy, and stent migration with the Danis stent which was reported in six single arm case series studies (Pfisterer et al. 2019, Zehetner et al. 2008, Ghidirim et al. 2012, Muller et al. 2015, Wright et al. 2010, Zakaria et al. 2013). Costs include costs of the procedure, costs associated with re-bleeding events, adverse events, stent migration, severe hepatic encephalopathy, stent or balloon removal, and the type of definitive treatment received being either endoscopic band ligation or elective TIPS. A training cost was also included to capture the cost of time taken to learn how to use the Danis stent to the NHS. The model uses the proportion of patients experiencing each event from the Escorsell et al. (2016) trial and multiplies this by the cost of each event.

Longer term outcomes are not captured by the model because the proportion of patients surviving beyond 6 weeks from the key clinical study was considered to be low (54% with Danis stent, 40% with balloon tamponade) and both treatments are designed to be a bridge to definitive treatment with either TIPS or endoscopic band ligation. Data beyond 6 weeks was not reported by Escorsell et al. (2016), and data availability on the specific patient population modelled is very limited due to the small number of patients failing or contraindicated to first line therapy. Therefore, it was judged that any data available on survival or re-bleeding following definitive treatment would not be generalizable to the patient population in the model. Given the paucity of data and small patient numbers a simple cost calculator approach to modelling was judged to be the best way to capture the key benefits and costs associated with the Danis stent based on the key clinical data.

Table 2 Assumptions in the model

In this table, list the main assumptions in the model and justify why each has been used.

Assumption	Justification	Source
Longer term outcomes beyond 6 weeks are not captured in the model despite patients receiving differing definitive treatments between treatment arms in the RCT	Clinical data did not extend beyond 6 weeks and there is a paucity of data in this population due to the small patient population with acute refractory oesophageal variceal bleeding who fail or are contraindicated to first line therapy. This could impact on the results in either direction dependent on the outcomes of definitive treatment and the survival of patients following this 6-week period. More patients in the Danis stent arm underwent band ligation as their definitive treatment and it is unknown if this treatment was successful or whether further treatment was then required in the future such as repeat band ligation or TIPS. Similarly, it is unknown how survival was impacted by the differing treatments. However, clinical experts agreed that definitive treatment would be dependent on the patient and not necessarily impacted by whether they had received balloon tamponade or the Danis stent. All agreed both were viewed as a bridge to definitive treatment and therefore longer-term outcomes should not be impacted by choice of bridging treatment. Further, it was suggested that the life expectancy of patients in this condition was not expected to be long.	Section 4 of clinical evidence submission
A cost of use of the Ella extractor to remove the Danis stent was only applied to patients receiving endoscopic band ligation as a definitive treatment.	Clinical expert opinion stated that if a TIPS procedure was undertaken the Ella extractor would not be required as part of the removal procedure. Additionally, use of the Ella extractor appears to vary in practice with one clinician noting that they did not typically use it.	Clinical expert opinion
It is assumed that there is no impact on efficacy of the stent from a learning curve (with exception of stent migration which is already captured within the model)	No data were reported that suggested a learning curve would impact on clinical efficacy other than occurrence of stent migration (Zehetner et al. 2008). One clinical expert suggested that inserting a stent was a common procedure and the Danis stent was easy to insert and required very little training. However, another expert noted that because the stent was a new device learning was needed to be able to insert it properly and there was a reluctance to undertake the procedure. Clinical experts reported differing rates of stent migration and it was judged this could be related to correct insertion and therefore experience with inserting the device. One case series also commented on low positioning of the stent leading to stent migration which appeared to be observed in the learning phase (Zehetner et al. 2008). Stent migration is included in the model as a risk for all procedures, not just in the learning phase. This may or may not be a conservative assumption depending on how much more likely this would be to occur during the learning phase and whether the risk of stent migration reported in the studies was based on experienced users of the stent. Costs for training in how to insert the stent correctly are also included in the model.	Clinical expert opinion (Zehetner et al. 2008)

A difference in use of opiates for analgesia between treatment arms was reported in the Escorsell (2016) study. This was not included explicitly in the model.	The use of opiates for analgesia was assumed to be captured within the cost of a bed day in a general ward or in ICU or within the procedure cost. A reduction in the use of opiates with Danis stent was reported so this is a conservative assumption, however the impact on the results of the model would be expected to be very minor due to the low cost of opiates.	Assumption
A difference in the use of packed red blood cells between treatment arms was reported in the Escorsell (2016) study. This was not included explicitly in the model.	The use of packed red blood cells was assumed to be captured within the cost of a re-bleeding event. Packed red blood cells were reported to be used in fewer patients in the Danis stent arm so this is a conservative assumption.	Assumption
A difference in the use of vasoactive drugs between treatment arms was reported in the Escorsell (2016) study. This was not included explicitly in the model.	The use of vasoactive drugs was assumed to be captured within the procedure cost. An increase in the use of vasoactive drugs was reported with Danis stent due to fewer patients receiving TIPS as their definitive treatment in this treatment arm (which means vasoactive drugs are stopped). Therefore, if the costs of these are not captured within the procedure cost this would increase the cost of the Danis stent.	Assumption
Costs to train staff in how to insert the Danis stent are assumed to be incurred each year.	Clinical experts indicated that due to the small patient population indicated for the Danis stent or balloon tamponade, very few procedures are carried out each year. Therefore, it was judged that ongoing refresher training may be required. This is a conservative assumption. If this is not required it will reduce the cost associated with the Danis stent.	Clinical expert opinion Muller et al. (2015) notes that regular training is required
It is assumed the only difference in terms of resources between the procedures to insert the Danis stent and balloon tamponade are the costs of the devices.	NHS reference costs (NHS Improvement 2019) were used to cost the procedure and therefore the costs of the procedures were assumed to be the same. Clinical experts agreed the procedures would be largely similar to insert both types of device. However, one expert suggested that the Danis stent can be inserted in an endoscopy suite under conscious sedation, rather than in theatre under general anaesthetic, in around 1/3 of patients. Therefore, the cost of the procedure to insert the Danis stent could be overstated. Further, the same expert suggested that in these patients you would expect to see a reduction in ICU stay following the procedure for insertion of the Danis stent, further reducing the cost of the procedure. Another expert agreed that the ICU stay would likely be shorter with Danis stent patients, and that use of high dependency units (HDU) would also be less for Danis stent patients due to less intensive monitoring due to the reduced risk of rebleeding. Therefore, this assumption in the model is conservative, and if Danis stent results in a reduction in ICU and HDU stay and potentially use of general anaesthetic and theatre then the cost of the Danis stent in the analysis is overstated.	Clinical expert opinion
Patient transportation costs were not included in the model. Transportation costs not included for TIPs – clinicians suggest only a few centres can carry	Clinical experts suggested that only a few centres in the UK are able to carry out a TIPS procedure and therefore patients may require transfer to a specialist centre. Costs for transportation were not included in the model because this would be required regardless of whether patients received Danis stent or balloon tamponade.	Simplifying assumption

this out. But this will be common to both arms – however more are applied in the BT arm		

Table 3 Clinical parameters, patient and carer outcomes and system outcomes used in the model

In this table, describe the clinical parameters, patient and carer outcomes and system outcomes used in the model.

Parameter/outcomes	Source	Relevant results	Range or distribution	How are these values used in the model?
Proportion of patients dying at 6 weeks with Danis stent	Escorsell et al. (2016)	Table 2, Survival at 6 weeks with Danis stent 7 patients out of 13	Beta distribution Alpha; 6 Beta; 7	Value of 46% used for proportion of patients dying at 6 weeks with Danis stent Other studies reported mortality of 27.3% (Muller et al. 2015), 50% (Wright et al. 2010) at 6 weeks. The majority of case studies reported varying time frames, see Clinical submission, Table 4d.
Relative risk of patients dying at 6 weeks with Balloon tamponade compared with Danis stent	Escorsell et al. (2016)	Table 2, Survival at 6 weeks with balloon tamponade 6 patients out of 15	Lognormal distribution Confidence interval: 0.63 to 2.67 [calculated]	Used to calculate a relative risk of 1.3 for patients dying with balloon tamponade compared with Danis stent.
Proportion of patients experiencing re-bleed during 6 weeks with Danis stent	Escorsell et al. (2016)	Table 2, Absence of bleeding at 6 weeks with Danis stent 7 patients out of 13	Beta distribution Alpha 6 Beta 7	Value of 46% used for proportion of patients experiencing re-bleed events during 6 week follow up with Danis stent. It should be noted that this may understate re-bleeding because only the proportion of patients without any rebleeding is reported, rather than the rate of rebleeding. Other studies reporting proportion of patients with no rebleeding during 6 weeks include Pfisterer et al. (2019) (29.4% without rebleeding). Pfisterer et al. (2019) also reported a rate of rebleeding within 6 weeks of 17.6%. Other studies reported varying time frames, see Clinical submission Tables 4a and 4b.
Relative risk of re-bleed during 6 weeks with Balloon tamponade compared with Danis stent	Escorsell et al. (2016)	Table 2, Absence of bleeding at 6 weeks with Balloon tamponade 7 patients out of 15	Lognormal distribution Confidence interval: 0.54 to 2.46 [calculated]	Used to calculate a relative risk of 1.2 for patients experiencing rebleed with balloon tamponade compared with Danis stent. It should be noted that this may understate re-bleeding because only the proportion of patients without any rebleeding is reported, rather than the rate of rebleeding. Thus, it is assumed each patient with a re-bleed only experiences this once.

Incidence of cardiorespiratory arrest within 6 weeks with Danis stent	Escorsell et al. (2016)	Table 3, 1 patient out of 13	Beta distribution Alpha 1 Beta 12	Value of 7.7% used for proportion of patients experiencing cardiorespiratory arrest with Danis stent
Incidence of cardiorespiratory arrest within 6 weeks with Balloon tamponade	Escorsell et al. (2016)	Table 3, 1 patient out of 15	Beta distribution Alpha 1 Beta 14	Value of 6.7% used for proportion of patients experiencing cardiorespiratory arrest with balloon tamponade
Incidence of aspiration pneumonia within 6 weeks with Danis stent	Escorsell et al. (2016)	Table 3, 0 patients out of 13	Beta distribution Alpha 0.1* Beta 12.9	Value of 0% used for proportion of patients experiencing aspiration pneumonia with Danis stent
Incidence of aspiration pneumonia within 6 weeks with Balloon tamponade	Escorsell et al. (2016)	Table 3, 5 patients out of 15	Beta distribution Alpha 5 Beta 10	Value of 33.3% used for proportion of patients experiencing aspiration pneumonia with balloon tamponade
Incidence of oesophageal rupture within 6 weeks with Danis stent	Escorsell et al. (2016)	Table 3, 0 patients out of 13	Not varied because judged to be not applicable to Danis stent.	Value of 0% used for proportion of patients experiencing oesophageal rupture with Danis stent.
Incidence of oesophageal rupture arrest within 6 weeks with Balloon tamponade	Escorsell et al. (2016)	Table 3, 1 patient out of 15	Beta distribution Alpha 1 Beta 14	Value of 6.7% used for proportion of patients experiencing oesophageal rupture with balloon tamponade

Incidence of spontaneous bacterial peritonitis and hepatorenal syndrome within 6 weeks with Danis stent	Escorsell et al. (2016)	Table 3, 1 patient out of 13	Beta distribution Alpha 1 Beta 12	Value of 7.7% used for proportion of patients experiencing spontaneous bacterial peritonitis and hepatorenal syndrome with Danis stent
Incidence of spontaneous bacterial peritonitis and hepatorenal syndrome within 6 weeks with Balloon tamponade	Escorsell et al. (2016)	Table 3, 0 patients out of 15	Beta distribution Alpha 0.1 Beta 14.9	Value of 0% used for proportion of patients experiencing spontaneous bacterial peritonitis and hepatorenal syndrome with balloon tamponade
Proportion of patients with severe hepatic encephalopathy within 6 week period with Danis stent	Escorsell et al. (2016)	Table 4, 5 patients out of 13	Beta distribution Alpha 5 Beta 8	Value of 38% used for proportion of patients experiencing severe hepatic encephalopathy within 6 week period with Danis stent
Proportion of patients with severe hepatic encephalopathy within 6 week period with Balloon tamponade	Escorsell et al. (2016)	Table 4, 11 patients out of 15	Beta distribution Alpha 11 Beta 4	Value of 73% used for proportion of patients experiencing severe hepatic encephalopathy within 6 week period with balloon tamponade
Proportion of patients with definitive treatment of endoscopic band ligation & nonselective beta blockers at 6 weeks with Danis stent	Escorsell et al. (2016)	Table 4, 5 patients out of 13	Beta distribution Alpha 5 Beta 8	Value of 38% used for proportion of patients receiving definitive treatment of endoscopic band ligation & nonselective beta blockers at 6 weeks with Danis stent
Proportion of patients with definitive treatment of endoscopic band ligation & nonselective beta blockers at 6 weeks with Balloon tamponade	Escorsell et al. (2016)	Table 4, 0 patients out of 15	Beta distribution Alpha 0.1 Beta 14.9	Value of 0% used for proportion of patients receiving definitive treatment of endoscopic band ligation & nonselective beta blockers at 6 weeks with balloon tamponade

Proportion of patients with definitive treatment of TIPs at 6 weeks with Danis stent	Escorsell et al. (2016)	Table 4, 4 patients out of 13	Beta distribution Alpha 4 Beta 9	Value of 31% used for proportion of patients of receiving definitive treatment of TIPS at 6 weeks with Danis stent
Proportion of patients with definitive treatment of TIPs at 6 weeks with Balloon tamponade	Escorsell et al. (2016)	Table 4, 10 patients out of 15	Beta distribution Alpha 10 Beta 5	Value of 67% used for proportion of patients of receiving definitive treatment of TIPS at 6 weeks with balloon tamponade
Proportion of patients with stent migration with Danis stent	Average based on Ghidirim et al. (2012) Muller et al. (2015) Wright et al. (2010) Zakaria et al. (2013) Zehetner et al. (2008)	17 patients out of 83 patients Ghidirim et al. (2012) – 5 patients out of 12 Muller et al. (2015) – 4 patients out of 11 (only those that required repositioning) Wright et al. (2010) – 0 patients out of 10 Zakaria et al. (2013) – 1 patient out of 16 (only those that were not identified during extraction) Zehetner et al. (2008) – 7 patients out of 34	Beta distribution Alpha 7 Beta 76	Value of 20% used for proportion of patients experiencing stent migration with Danis stent

*Note a value of 0.1 was used so this is varied within the PSA.

If any outcomes listed in table 4 are extrapolated beyond the study follow-up periods, explain the assumptions that underpin this extrapolation.

Not applicable, no extrapolation was undertaken due to paucity of data and the time horizon of the model.

Table 4 Other parameters in the model

Describe any other parameters in the model. Examples are provided in the table. You can adapt the parameters as needed.

Parameter	Description	Justification	Source
Time horizon	6 weeks	Clinical trial data did not extend beyond 6 weeks. The population expected to receive Danis stent is very small and therefore data were not available in this population with which to extrapolate into the future. Additionally, a high mortality rate was shown during the study period and patients are not expected to live for an extended period.	See Clinical submission, Results section. Clinical expert opinion.
Discount rate	Not applicable	Time horizon of the model is less than 1 year	NA
Perspective (NHS/PSS)	NHS/PSS	In line with NICE reference case	NICE methods guide (National Institute for Health and Care Excellence (NICE) 2017)
Cycle length	Not applicable	Not applicable	Not applicable
Transition probabilities	Not applicable	Not applicable	Not applicable
Health states	Not applicable	Not applicable	Not applicable
Sources of unit costs	NHS reference costs 2018/19 (NHS Improvement 2019) Personal social services research unit 2019 (Personal Social Services Research Unit 2019b) NICE resource impact report NG50 (National Institute for Health and Care Excellence 2016) NICE costing template TA337 (National Institute for Health and Care Excellence 2015)	Standard UK sources used where possible.	Not applicable

Explain the transition matrix used in the model and the transformation of clinical outcomes, health states or other details.

Not applicable. A transition matrix was not used in the model and clinical outcomes were based on the Escorsell et al. (2016) study. Transformation of these outcomes was not required. Details on clinical outcomes used are provided in Table 3.

Resource identification, measurement and valuation

Technology costs

Provide the list price for the technology (excluding VAT).

£1,495 per use.

If the list price is not used in the model, provide the price used and a justification for the difference.

Not applicable, list price is used in the model.

NHS and unit costs

Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC). Please provide relevant codes and values (e.g. OPCS codes and ICD codes) for the operations, procedures and interventions included in the model.

The following reference costs and PbR tariffs might apply to patients with variceal bleeding:

FD03A	Gastrointestinal Bleed with Multiple Interventions, with CC Score 5+
FD03B	Gastrointestinal Bleed with Multiple Interventions, with CC Score 0-4
FD03C	Gastrointestinal Bleed with Single Intervention, with CC Score 8+
FD03D	Gastrointestinal Bleed with Single Intervention, with CC Score 5-7
FD03E	Gastrointestinal Bleed with Single Intervention, with CC Score 0-4
FD03F	Gastrointestinal Bleed without Interventions, with CC Score 9+
FD03G	Gastrointestinal Bleed without Interventions, with CC Score 5-8
FD03H	Gastrointestinal Bleed without Interventions, with CC Score 0-4

Resource use

Describe any relevant resource data for the NHS in England reported in published and unpublished studies. Provide sources and rationale if relevant. If a literature search was done to identify evidence for resource use then please provide details in appendix A.

A systematic literature search was not undertaken to inform resource use parameters in the model. Resource use parameters were informed via targeted searching of the literature for specific parameters and by clinical expert opinion.

Studies identified in the clinical evidence review reported on the following resource use:

- Blood transfusion use (Table 4c Clinical evidence submission). This was not used explicitly in the model because it was assumed this would already be captured within the cost of re-bleeding in the model
- Use of further and additional treatments following initial stent placement (Table 4f Clinical evidence submission). This is captured explicitly in the model through use of definitive treatments and is based on Escorsell et al. (2016) because this was the only comparative study identified.

Only one UK study was identified in the clinical evidence review (Wright et al. 2010). Stent insertion and removal procedures are described in this study and the following information is provided regarding resource use requirements for insertion and removal:

- Endoscopy was used to place the stent. Fluoroscopy was not required.
- Stents were removed using the Ella extractor device and endoscopy. One patient required use of fluoroscopy to remove the stent. The remainder were removed in the endoscopy suite or intensive therapy unit.
- Intensive care unit was the most common setting for stent insertion but they were also performed in the accident and emergency department and in the endoscopy unit.

Other non-UK studies provided some information on:

- the stent insertion procedure (Escorsell et al. 2016, Ghidirim et al. 2012, Trikudanathan et al. 2018, Zakaria et al. 2013, Zehetner et al. 2008)

- the stent removal procedure (Escorsell et al. 2016, Ghidirim et al. 2012, Zakaria et al. 2013)
- Stent migration (Escorsell et al. 2016, Muller et al. 2015, Pfisterer et al. 2019, Zehetner et al. 2008)
- use of vasoactive drugs (Escorsell et al. 2016, Trikudanathan et al. 2018)
- use of PRBC and/or blood transfusion (Escorsell et al. 2016, Muller et al. 2015, Zakaria et al. 2013)
- use of intubation (Escorsell et al. 2016, Muller et al. 2015)
- length of stay (Escorsell et al. 2016, Muller et al. 2015)
- time taken to insert stent (Ghidirim et al. 2012, Zakaria et al. 2013)
- requirement for further band ligation (Trikudanathan et al. 2018)
- use of endoscopy and chest X-ray following stent insertion (Muller et al. 2015, Zehetner et al. 2008)

Describe the resources needed to implement the technology in the NHS. Please provide sources and rationale.

Procedure cost

Two options were included in order to cost the procedure to insert the Danis Stent or balloon tamponade. In the base case the cost of the procedure is costed using NHS reference costs (NHS Improvement 2019). This assumes the cost of the procedure to insert each device is equal (excluding the cost of the device). This was confirmed with clinical experts to be a reasonable assumption.

A second micro costing option was included to allow for variation in the cost of the procedure being applied for each treatment. In this micro costing option, it is assumed the procedure to insert the Danis stent is undertaken outside of a theatre setting for a third of patients, based on clinical expert opinion. This third of patients are also assumed to have a reduced stay in ICU which is also based on clinical expert opinion. The cost of the procedure setting and staff are multiplied by the estimated time to undertake the procedure for both Danis stent and balloon tamponade. Other resources such as X-rays and vasoactive drugs are also included as well as an initial hospital stay. The use of vasoactive drugs and X-rays were based on Escorsell et al. (2016). In Escorsell et al. (2016) the length of stay in hospital was equal between both treatment arms. The hospital stay in the study was assumed to be inclusive of adverse events. Therefore, this initial hospital stay was reduced so that adverse events could be included separately. Information on the average length of stay for a gastrointestinal bleed from NHS reference costs was used to reduce the length of stay in a general ward and ICU keeping the same ratio between the ward types.
Further information on the procedure cost is provided in Tables 7a and 7b.

Training cost

Training would be required in order to implement the Danis stent in the NHS. Training is provided free of charge so only the cost of clinician time required for training was included in the model. The cost of clinician time was taken from PSSRU (Personal Social Services Research Unit 2019b) and the cost of a surgical consultant used (£109 per hour). It was estimated that 3 hours would be required for training based on clinical expert opinion, with clinical experts providing estimates from 30 minutes to 4 hours. It was also conservatively assumed that re-training would be required each year due to the low number of procedures being performed (clinical experts estimated between 5 and 10 procedures

would be performed per year per clinician). A cost of training per procedure was therefore estimated using the lower value of 5 procedures per surgeon per year giving an estimated training cost per procedure of £65.40.

Describe the resources needed to manage the change in patient outcomes after implementing the technology. Please provide sources and rationale.

Cost of rebleeding

A cost of rebleeding was included in order to capture the differences between treatment arms in the proportion of patients experiencing rebleeding events during the 6 weeks following their procedure. This cost was taken from a NICE resource impact report for cirrhosis in over 16s [NG50] (National Institute for Health and Care Excellence 2016). The report estimated the cost of a bleeding event may range from £3,110 to £6,710 based on non-elective tariff GB02A to C. The original source could not be identified so the cost was inflated from 2015 to 2019 prices using PSSRU inflation indices (Personal Social Services Research Unit 2019a). The lower value of £3,287 was used with higher values tested in sensitivity and scenario analyses.

Cost of stent migration

A cost for stent migration was included in the model to capture the impact of this event for patients undergoing Danis stent insertion. A value of 20% was used for the proportion of patients experiencing stent migration as shown in Table 3. The studies reporting stent migration as an adverse event (see Clinical submission Table 6) were combined with the exception of Pfisterer et al. (2019) because they stated that no stent migrations occurred and instead reported stent dislocation. There was no information provided in the paper on whether or not these required any intervention or had a clinical impact. All included studies reported that stents were repositioned. Only 1 migration was included for Zakaria et al. (2013) because the paper stated that all migrations except 1 were identified during the process of extraction. The only UK study, Wright et al. (2010), reported no stent migration. One clinical expert noted that migration was caused by hiatus hernia or misplacement of the stent on insertion and that they had only experienced one. Another expert agreed that migration of the stent would likely be caused by incorrect placement and that they had never experienced one. The third clinical expert commented that they found this to be a common problem and observed it in around half of patients having the stent; however, they have found clipping the stent in place can help to solve this problem.

The cost was estimated based on the treatment provided in Zehetner et al. (2008) and Muller et al. (2015) who reported that correct positioning could be achieved by endoscopy. Clinical experts also confirmed that the stent would likely be repositioned with endoscopy. One expert commented that there would be a risk of rebleeding with stent migration. However, this would be captured within the model by the rebleeding rate because stent migration would have occurred during the 6-week time horizon (due to stents only being in place for 7 days). Therefore, the cost of a therapeutic endoscopic upper gastrointestinal tract procedure (FE20Z) from NHS reference costs 2018/19 was used for the cost of stent migration (NHS Improvement 2019).

Cost of severe hepatic encephalopathy

A cost for severe hepatic encephalopathy was included in the model to capture the difference in treatment arms of this event occurring. It was judged that this could be related to the increased proportion of patients undergoing a TIPS procedure in the balloon tamponade arm based on clinical expert opinion. However, it is unclear whether the proportion of patients undergoing TIPS is related to the choice of bridging treatment (i.e. stent or balloon) due to the small trial sizes and small patient population. Clinical experts indicated that choice of definitive treatment would be dependent on the patient and that some patients will be contraindicated to TIPS. Therefore, the exclusion of this cost is explored in a scenario analysis.

Cost of stent and balloon removal

The cost of stent and balloon removal was based on Escorsell et al. (2016). The study states that Danis stents were scheduled for removal after 7 days and balloons were scheduled for removal after 24 hours. Therefore, the proportion of patients surviving in each treatment arm at these timepoints was estimated using Webplot digitiser to extract the survival data from the Kaplan Meier survival curves reported in the paper. It was estimated that 77% of patients in the Danis stent survived to 7 days and therefore had a stent removed, and 74% of balloon tamponade patients survived to 24 hours and required the balloon removing.

The cost of the removal procedure for the Danis stent was based on clinical expert opinion and comprised use of endoscopy (£699) and fluoroscopy (£58). Both costs were taken from NHS reference costs 2018/19 (NHS Improvement 2019) (FE20Z therapeutic endoscopic upper gastrointestinal tract procedures, 19 years and over; RD34Z contrast fluoroscopy, mobile or intraoperative procedures with duration of 20 to 40 minutes direct access). The use of the Ella extractor was included for those patients undergoing band ligation as their definitive treatment at a cost of £500 (cost based on discounted price when bought as a bundle with the Danis stent, undiscounted price = £695). Clinical experts and previous experience notes that the Ella extractor may not be required for removal of the stent if TIPS was being undertaken, and therefore the cost of this was only included for the 38% of patients undergoing band ligation based on Escorsell et al. (2016). Multiplying these costs by the proportion of patients surviving and requiring each type of removal procedure gave an overall estimated cost of the stent removal procedure of £1,066 per patient.

The cost of the removal procedure for the balloon was also costed based on clinical expert opinion. Three clinical experts agreed that the balloon would be deflated bedside with no additional equipment required and would take between 30 seconds and 10 minutes. One expert commented that this would likely be undertaken by a junior doctor. Therefore, the cost of a foundation year 2 doctor's time (Personal Social Services Research Unit 2019b) for 7.5 minutes was included. This cost multiplied by the proportion requiring removal (74%) results in a cost per patient of the balloon removal procedure of £3.

Cost of definitive treatment

Two definitive treatments were described in the Escorsell et al. (2016) study, endoscopic band ligation (EBL) plus non-selective beta-blockers, and TIPS. According to the study 38% of patients in the Danis stent arm underwent EBL, and 31% underwent a TIPS procedure following removal of the stent. In the balloon tamponade 67% of patients underwent a TIPS procedure following the removal of the balloon with no patients undergoing EBL.

The cost of EBL (£1,114) was taken from NHS reference costs 2018/19 (NHS Improvement 2019) based on endoscopic sclerotherapy or rubber band ligation of lesion of upper gastrointestinal tract [FE11D].

The cost of elective TIPS (£3,928) was also taken from NHS reference costs 2018/19 (NHS Improvement 2019). This was based on a weighted average by full consultant episode of transjugular intrahepatic creation of portosystemic shunt [YR16B].

Both costs were based on 'Total HRG' reference costs because there were very few finished consultant episodes for elective procedures so it was judged that the elective costs would be less reliable. The costs relating to fewer complications were used because it was assumed that definitive procedures would be undertaken on removal of the balloon or stent and therefore within 1 to 2 weeks after the stent or balloon procedure. Any further complications associated with the definitive procedures such as bleeding would therefore already be captured in the model because a 6-week time horizon is used.

Describe the resources needed to manage the change in system outcomes after implementing the technology. Please provide sources and rationale.

Not applicable.

Table 5 Resource use costs

In this table, summarise how the model calculates the results of these changes in resource use. Please adapt the table as necessary.

	Technology costs	Comparator 1 costs	Difference in resource use costs (technology vs comparator 1)
Cost of training per procedure	£65	£0	£65
Cost of re-bleed	£3,287		NA
Cost of stent migration	£699	NA	£699
Cost of severe hepatic encephalopathy	£401		NA
Cost of removal procedure	£1,066	£3	£1,138
Cost of endoscopic band ligation + nonselective beta blockers	£1,114		NA
Cost of elective TIPS	£3,928		NA

Adverse event costs

If costs of adverse events were included in the analysis, explain how and why the risk of each adverse event was calculated.

Adverse events were included in the model with the proportion of patients experiencing each event based on Escorsell et al. (2016). Only those events described as 'severe' were included in the model because it was judged that any minor events would be captured within the procedure cost/initial hospital stay. The proportions of patients experiencing each event in each treatment arm of the model are provided in Table 3.

Escorsell et al. (2016) was the only comparative evidence identified with which to base adverse events in the model on. Ulceration was commonly reported in other case series on the Danis stent. This was judged to be a minor event. When consulted, clinical experts commented that this was not commonly a problem with the Danis stent and ulceration tended to be minor. One expert also commented that this was also likely to be much worse with balloon tamponade. Additionally, it was noted that ulceration does not necessarily require treatment and if it does then anti-acid medication would be prescribed.

No adverse events were reported on the FDA (MAUDE) database when this was searched as part of the clinical submission. One field safety notice was identified in the MHRA database but did not result in any clinical complications (see Section 6 of clinical submission).

Table 6 Adverse events and costs in the model

In this table, summarise the costs associated with each adverse event included in the model. Include all adverse events and complication costs, both during and after long-term use of the technology. Please explain whether costs are provided per patient or per event.

Adverse event	Cost	Source
Cardiorespiratory arrest	£2,913	National NHS cost collection (2018/19) (NHS Improvement 2019) Weighted average of codes EB05A-EB05C NEL; cardiac arrest with CC score 0 to 9+
Aspiration pneumonia	£2,702	National NHS cost collection (2018/19) (NHS Improvement 2019) Weighted average of codes DZ11K-V NEL Lobar, Atypical or viral pneumonia without interventions, with single intervention or with multiple interventions, various CC scores.
Oesophageal rupture	£9,054	National NHS cost collection (2018/19) (NHS Improvement 2019) Weighted average of codes FF01A - FF02C, FF04A - FF04D NEL; very complex to major oesophageal, stomach or duodenum procedures, 19 years and over with various CC scores
Spontaneous bacterial peritonitis and hepatorenal syndrome	£2,834	National NHS cost collection (2018/19) (NHS Improvement 2019) Weighted average of codes LA07H-P NEL; acute kidney injury with and without interventions, various complication scores

Miscellaneous costs

Describe any additional costs or resource considerations that have not been included elsewhere (for example, PSS costs, and patient and carer costs). If none, please state.

All costs are included in the above descriptions and tables.

Are there any other opportunities for resource savings or redirection of resources that have not been possible to quantify?

Clinicians noted that TIPS procedures are often carried out in specialist centres or hospitals and therefore patients may need to be transported. Additionally, (Pfisterer et al. 2019) noted that 3 of the 4 centres in their study were not able to offer TIPS implantation without transferring the patient to other centres. Use of the Danis stent may allow for this transportation more easily due to the additional time the stent can remain in place. This is not captured within the model.

Total costs

In the following tables, summarise the total costs:

- Summarise total costs for the technology in table 7.
- Summarise total costs for the comparator in table 8. This can only be completed if the comparator is another technology.

Table 7a Total costs for the technology in the model (Base case: NHS reference costs)

Description	Cost	Source
Total cost of procedure per treatment	£5,377 cost of procedure not including cost of device	National NHS cost collection (NHS Improvement 2019) FD03A non-elective gastrointestinal bleed with multiple interventions with CC score 5+
Cost of Danis stent	£1,495	NICE MIB185 (National Institute for Health and Care Excellence 2019)
Total cost per treatment/patient over lifetime of device	**£6,872**	**Calculation**

Table 7b Total costs for the technology in the model (Option 2: Micro costing for technology in model)

Description	Cost	Note	Source
Cost of stent	£1,495	Cost ex-VAT	NICE Medtech innovation briefing (National Institute for Health and Care Excellence 2019)
Procedure costing:			
Procedure setting cost – theatre setting	£16.73	Per minute cost. Assumed to include cost of staff and consumables	ISD Scotland (2019) theatre services – gastroenterology surgery (ISD Scotland 2019)
Procedure setting cost – non-theatre setting	£3.35	Setting cost assumed to be included within overheads from staff costs. Cost of gastroenterologist and nurse practitioner included.	Cost of hospital based consultant (medical or surgical) and band 5 hospital based nurse (per hour of patient contact) from PSSRU 2019 (Personal Social Services Research Unit 2019b)
Total procedure cost -theatre setting	£501.90	Per minute cost multiplied by 30 minutes	Clinical experts estimated procedure time to range from 5 minutes to 30
Total procedure cost – non-theatre setting	£100.50	Per minute cost multiplied by 30 minutes	Clinical experts estimated procedure time to range from 5 minutes to 30
Total cost of x-ray (applied to both settings)	£62.00	Unit cost: £31.00 Number: 2	Direct access plain film. National NHS cost collection (2018/19) (NHS Improvement 2019) Number required based on Escorsell et al. (2016)
Total cost of vasoactive drugs (applied to both settings	£1,396.08	Cost per mg: £19.39 (1mg/8.5ml solution for injection ampoules - £96,95 for pack of 5) BNF (British National Formulary) Dose per day: 12 (based on Escorsell et al. (2016) – 2mg/4hours No. of days: 6 (based on Escorsell et al. (2016))	
Total cost of general ward stay (applied to both settings)	£2,170	No. of days: 6.4 Cost per day: £341	Cost based on NHS reference costs (NHS Improvement 2019). Number based on Escorsell et al. (2016) and NHS reference costs (2017/18) (NHS Improvement 2019) – see section on 'procedure cost'
Total cost of ICU stay – theatre setting cost	£4,883.02	No. of days: 3.6 Cost per day: £1,343	Cost based on NHS reference costs, weighted average cost by activity of surgical adult ICU bed day with 1 to 3 organs supported [XC04Z-06Z] assuming liver and kidney may require support (NHS Improvement 2019). Number based on Escorsell et al. 2016 and NHS reference costs (2017/18) (NHS Improvement 2019) – see section on 'procedure cost' (Escorsell et al. 2016)
Total cost of ICU stay – non-theatre setting	£4,427.71	No. of days: 1 Cost per day: £1,343	Cost based on NHS reference costs, weighted average cost

			by activity of surgical adult ICU bed day with 1 to 3 organs supported [XC04Z-06Z] assuming liver and kidney may require support (NHS Improvement 2019). Number assumed based on clinical expert opinion.
Proportion of patients undergoing procedure in a theatre setting	67%		Clinical expert opinion
Grand total cost for stent insertion procedure	**£9,194.14**		Calculation

Table 8a Total costs for the comparator in the model (Base case: NHS reference costs)

Description	Cost	Source
Total cost of procedure per treatment	£5,377 cost of procedure not including cost of device	National NHS cost collection (NHS Improvement 2019) FD03A non-elective gastrointestinal bleed with multiple interventions with CC score 5+
Cost of the balloon	£300	NICE Medtech innovation briefing (National Institute for Health and Care Excellence 2019)
Grand total cost per treatment	**£5,677**	**Calculation**

Table 8b Total costs for the comparator in the model (Option 2: Micro costing for balloon tamponade)

Description	Cost	Note	Source
Cost of balloon and equipment	£300		NICE Medtech innovation briefing (National Institute for Health and Care Excellence 2019)
Procedure costing:			
Procedure setting cost	£16.73	Per minute cost. Assumed to include cost of staff and consumables	Theatre services – gastroenterology surgery (ISD Scotland 2019)
Total procedure cost	£502.00	Per minute cost multiplied by 30 minutes	Clinical experts estimated procedure time to range from 5 minutes to 30
Total cost of x-ray	£31.00	Unit cost: £31.00 Number: 1	Direct access plain film. National NHS cost collection (2018/19) (NHS Improvement 2019) Number required based on Escorsell et al. (2016)
Total cost of vasoactive drugs	£698.04	Cost per mg: £19.39 (1mg/8.5ml solution for injection ampoules - £96,95 for pack of 5) BNF (British National Formulary) Dose per day: 12 (based on Escorsell et al. (2016) – 2mg/4hours No. of days: 3 (based on Escorsell et al. (2016))	

Total cost of general ward stay	£2,170	No. of days: 6.4 Cost per day: £341	NHS reference costs (2017/18). Cost of regular day or night admission (NHS Improvement 2018) Number based on Escorsell et al. (2016) and NHS reference costs (2017/18) – see section on 'procedure cost'
Total cost of ICU stay	£4,883	No. of days: 3.6 Cost per day: £1,343	Cost based on NHS reference costs, weighted average cost by activity of surgical adult ICU bed day with 1 to 3 organs supported [XC04Z-06Z] assuming liver and kidney may require support (NHS Improvement 2019). Number based on Escorsell et al. 2016 and NHS reference costs (2017/18) (NHS Improvement 2019) – see section on 'procedure cost' (Escorsell et al. 2016)
Grand total cost for balloon tamponade	**£8,584.06**		**Calculation**

Results

Table 9 Base-case results

In this table, report the results of the base-case analysis. Specify whether costs are provided per treatment or per year. Adapt the table as necessary to suit the cost model. If appropriate, describe costs by health state.

The base case results are presented below per patient over a 6-week time horizon.

	Mean discounted cost per patient using Danis stent (£)	**Mean discounted cost per patient using balloon tamponade (£)**	**Difference in mean discounted cost per patient (£): technology vs comparator 1***
Procedure cost	£6,872	£5,677	£1,195
Re-bleeding costs	£1,517	£1,753	-£236
Adverse event costs	£442	£1,698	-£1,256
Stent migration costs	£143	£0	£143
Costs of definitive treatments	£1,637	£2,619	-£982
Severe hepatic encephalopathy costs	£154	£294	-£140
Stent/balloon removal costs	£1,066	£3	£1,063
Training costs	£65	£0	£65
Total cost per patient	**£11,897**	**£12,044**	**-£147**
Number of deaths per patient	0.5	0.6	-0.14
Number of serious adverse events per patient	0.2	0.5	-0.31
Cost per death avoided	**Dominant**		

Scenario analysis

If relevant, explain how scenario analyses were identified and done. Cross-reference your response to the decision problem in part 1, section 1 of the submission.

Scenario analyses were identified by highlighting key uncertainties within the submission either due to lack of clinical evidence or variations in clinical practice noted by speaking with clinical experts.

The following scenarios were undertaken:

1. Microcosting of each treatment procedure

2. Definitive treatments not considered related to bridging treatment, and removal of HE cost

Additionally, the following were highlighted as areas of uncertainty, however, it was judged that these would be addressed by deterministic one way or two sensitivity analysis.

- Differing use of vasoactive drugs between treatment arms increasing the procedure cost for Danis stent by approximately £700
- Uncertainty and variation in clinical practice of use of Ella extractor for removal of the Danis stent and therefore the cost of removal.
- Uncertainty in the cost of re-bleeding as noted in NICE resource impact report (National Institute for Health and Care Excellence 2016)
- Uncertainty in the cost of definitive treatments as discussed in the resource use section where total HRG costs were used due to low full consultant episodes for elective procedures in NHS reference costs 2017/18 (NHS Improvement 2018)
- Uncertainty around whether there would be a reduction in length of stay in high dependency units or critical care units with Danis stent as noted by clinical experts
- Uncertainty around training requirements for Danis stent and impact of training or stent migration rates
- Uncertainty around confidence intervals for relative risks of dying and re-bleeding with balloon tamponade compared with Danis stent due to low patient numbers in the RCT (Escorsell et al. 2016)
- Uncertainty around cost of aspiration pneumonia – a key adverse event with high incidence in the balloon tamponade arm

Describe the differences between the base case and each scenario analysis.

Scenario	Base case values	Scenario values
Scenario 1 - Microcosting of each treatment procedure	Procedure cost Danis = £6,872 Procedure cost balloon tamponade = £5,677	Procedure cost Danis = £9,194 Procedure cost balloon tamponade = £8,584
Scenario 2 - Definitive treatments not considered relevant and HE cost removed	EBL Danis stent = 38% TIPS Danis stent = 31% EBL balloon tamponade = 0% TIPS balloon tamponade 67% Use of Ella extractor for removal of Danis stent = 38% Incidence severe HE Danis stent = 38% Incidence severe HE balloon tamponade = 73%	EBL Danis stent = 0% TIPS Danis stent = 0% EBL balloon tamponade = 0% TIPS balloon tamponade 0% Use of Ella extractor for removal of Danis stent = 38% Incidence severe HE Danis stent = 0% Incidence severe HE balloon tamponade = 0%

Describe how the scenario analyses were included in the cost analysis.

The microcosting scenario can be run in the model by selecting the microcosting option from the user drop down menu on the costs input sheet. For scenario 2, individual inputs were changed in order to run the scenario and it was not integrated in the model.

Describe the evidence that justifies including any scenario analyses.

Two options were used in the model to cost the procedures for Danis stent and balloon tamponade. It was judged that use of NHS reference costs may be more accurate and is also more conservative so this was used in the base case. The microcosting option whereby each element of the procedure was costed separately and the potential for cost reductions from variation in the procedure setting for the insertion of the Danis stent and potential reduction in ICU stay is explored as a scenario analysis.

The scenario where definitive treatments are considered not relevant and subsequently severe HE is also not considered in the model was run because there were very low numbers of patients in the trial so it was not possible to tell whether the increase in TIPS in the balloon tamponade arm, and therefore the likely reason for the increase in severe HE according to clinical expert input, was due to the interventions or patient characteristics. Clinical experts commented that HE is an adverse effect of TIPS which was more commonly undertaken in the balloon tamponade arm in the trial. There appeared to be disagreement between clinical experts about whether bridging treatment used (i.e. Danis or balloon tamponade) would have an impact on the definitive treatment chosen.

Table 10 Scenario analyses results

In this table, describe the results of any scenario analyse that were done. Adapt the table as necessary.

	Mean discounted cost per patient using Danis stent(£)	Mean discounted cost per patient using balloon tamponade (£)	Difference in cost per patient (£)*
Base case	£11,972	£12,044	-£72
Scenario 1 – Microcosting of each treatment procedure	£14,219	£14,951	-£732
Scenario 2 - Definitive treatments not considered relevant to bridging treatment, and removal of HE cost	£10,181	£9,131	£1,050
* Negative values indicate a cost saving.			

Sensitivity analysis

Describe what kinds of sensitivity analyses were done. If no sensitivity analyses have been done, please explain why.

Deterministic and probabilistic sensitivity analysis were both undertaken. Deterministic sensitivity analysis is presented as a tornado diagram and all key parameters in the model were varied between plausible ranges.

All key parameters in the model were also varied in probabilistic sensitivity analysis with 1,000 model iterations.

Summarise the variables used in the sensitivity analyses and provide a justification for them. This may be easier to present in a table (adapt as necessary).

Table 11: Variables used in sensitivity analyses

Parameter	Base case value	Deterministic range	Probabilistic range
Relative risk of patients dying at 6 weeks with balloon tamponade compared with Danis stent	1.3	0.63 to 2.67 Confidence interval calculated from Escorsell et al. (2016)	0.63 to 2.67 Lognormal distribution Confidence interval calculated from Escorsell et al. (2016)
Proportion of patients dying at 6 weeks with Danis stent	46%	27% to 65% Based on range reported across studies	Alpha 6 Beta 7 Beta distribution Based on Escorsell et al. (2016)
Relative risk of re-bleeding during 6 weeks with balloon tamponade compared with Danis stent	1.2	0.54 to 2.46 Confidence interval calculated from Escorsell et al. (2016)	0.54 to 2.46 Lognormal distribution Confidence interval calculated from Escorsell et al. (2016)
Proportion of patients experiencing re-bleed within 6 weeks with Danis stent	46%	18% to 71% Based on range reported across studies	Alpha 6 Beta 7 Beta distribution Based on Escorsell et al. (2016)
Proportion of patients with cardiorespiratory arrest	Danis - 7.7% BT – 6.7%	Danis – 4% to 12% BT – 3% to 10% Assumed range based on +/-50%	Danis Alpha 1 Beta 12 BT Alpha 1 Beta 14

Parameter	Base case value	Deterministic range	Probabilistic range
			Both Beta distribution based on Escorsell et al. (2016)
Proportion of patients with aspiration pneumonia	Danis – 0.0% BT - 33.3%	BT – 17% to 50% based on +/- 50% Assumed not applicable for Danis stent so not varied	Danis Alpha 0 Beta 13 BT Alpha 5 Beta 10 Both Beta distribution based on Escorsell et al. (2016)
Proportion of patients with oesophageal rupture	Danis – 0.0% BT – 6.7%	BT – 3% to 10% based on +/- 50% Assumed not applicable for Danis stent so not varied	Danis Alpha 0 Beta 13 BT Alpha 1 Beta 14 Both Beta distribution based on Escorsell et al. (2016)
Proportion of patients with spontaneous bacterial peritonitis and hepatorenal syndrome	Danis – 7.7% BT – 0.0%	Danis – 4% to 12% BT – 0% to 5% Assumed range	Danis Alpha 1 Beta 12 BT Alpha 0 Beta 15 Both Beta distribution based on Escorsell et al. (2016)
Proportion of patients with severe hepatic encephalopathy within 6 week period	Danis – 38% BT – 73%	Danis 19% to 57% BT 37% to 100% Assumed range based on +/- 50%	Danis Alpha 5 Beta 8 BT Alpha 11

Parameter	Base case value	Deterministic range	Probabilistic range
			Beta 4 Both Beta distribution based on Escorsell et al. (2016)
Proportion of patients undergoing EBL	Danis – 38% BT – 0%	Danis 19% to 57% based on range reported across studies BT 0% to 20% assumed range	Danis Alpha 5 Beta 8 BT – adjusted to allow for variation Alpha 0.5 Beta 14.5 Both Beta distribution based on Escorsell et al. (2016)
Proportion of the patients undergoing TIPS	Danis – 31% BT – 67%	Danis 12% to 37% based on range reported across studies BT 53% to 80% assumed range	Danis Alpha 4 Beta 9 BT Alpha 10 Beta 5 Both Beta distribution based on Escorsell et al. (2016)
Proportion of patients with stent migration with Danis stent	20%	0% to 42% based on range reported across studies	Alpha 17 Beta 66 Beta distribution Combination of figures reported across studies as discussed in 'stent migration' section of 'Resource use'.
Total procedure cost (including costs of devices)	Danis - £6,872 BT - £5,677	Danis £5,497 to £8,246 assumed range based on +/- 20% BT £4,541 to £6,812 assumed range based on +/- 20%	Danis Standard error £1,374 BT Standard error £1,135 Both gamma distribution and assumed based on 20% of mean
Cost of re-bleeding	£3,287	£2,630 to £7,092	Standard error £1,644

Parameter	Base case value	Deterministic range	Probabilistic range
		Lower value assumed based on -20%. Upper value based on NICE resource impact report (National Institute for Health and Care Excellence 2016)	Gamma distribution Assumed based on 50% of mean
Cost of stent migration	£699	£559 to £839 assumed range based on +/- 20%	Standard error £140 Gamma distribution Assumed based on 50% of mean
Cost of cardiorespiratory arrest	£2,913	£1,715 to £3,527 Based on low and high value reported in NHS reference costs 2018/19 (NHS Improvement 2019). EB05A to C NEL Cardiac arrest with CC score 0-4 and 9+	Standard error £583 Gamma distribution Assumed based on 20% of mean
Cost of aspiration pneumonia	£2,702	£1,622 to £7,951 Based on low and high value reported in NHS reference costs 2018/19 (NHS Improvement 2019). DZ11K to V NEL Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 0-3 and 14+	Standard error £1,351 Gamma distribution Assumed based on 50% of mean
Cost of oesophageal rupture	£9,054	£5,540 to £19,181 Based on low and high value reported in NHS reference costs 2018/19 (NHS Improvement 2019). FF04A to C NEL Major, Oesophageal, Stomach or Duodenum Procedures, 19 years and over, with CC Score 2-3 and 6+	Standard error £4,527 Gamma distribution Assumed based on 50% of mean
Cost of spontaneous bacterial peritonitis and hepatorenal syndrome	£2,834	£1,956 to £5,656 Based on low and high value reported in NHS reference costs 2018/19 (NHS Improvement 2019). LA07H to P NEL Acute Kidney Injury without	Standard error £1,417 Gamma distribution Assumed based on 50% of mean

Parameter	Base case value	Deterministic range	Probabilistic range
		Interventions, with CC Score 0-3 and 11+	
Cost of severe hepatic encephalopathy	£401	£200 to £601 Assumed range based on +/- 20%	Standard error £80 Gamma distribution Assumed based on 20% of mean
Cost of stent removal	£1,066	£583 to £1,551 Lower and upper based on everyone using Ella extractor and no one using Ella extractor for removal	Standard error £213 Gamma distribution Assumed based on 20% of mean
Cost of balloon removal	£3	£0 to £4 Assumed range	Standard error £2 Gamma distribution Assumed based on 50% of mean
Cost of EBL	£1,114	£522 to £4,984 Lower value based on NICE resource impact report for one ligation procedure (National Institute for Health and Care Excellence 2016) Higher value based on highest value reported from NHS reference costs 2018/19 Elective (NHS Improvement 2019). FE11A Endoscopic, Sclerotherapy or Rubber Band Ligation, of Lesion of Upper Gastrointestinal Tract, with CC Score 9+	Standard error £557 Gamma distribution Assumed based on 50% of mean
Cost of TIPS	£3,928	£3,418 to £5,987 Based on high and low values from NHS reference costs 2018/19 (NHS Improvement 2019). Low value elective cost for YR16B Transjugular Intrahepatic Creation of Portosystemic Shunt with CC Score 0-5. High value total HRG cost for YR16A Transjugular Intrahepatic Creation of	Standard error £786 Gamma distribution Assumed based on 20% of mean

Parameter	Base case value	Deterministic range	Probabilistic range
		Portosystemic Shunt with CC Score 6+	
Training costs for Danis stent per procedure	£65	£5 to £90 Low value based on assuming half an hour of training per year and 10 procedures per year – lower estimates provided by experts High value based on assuming 4 hours training per year and only 2 procedures per year – higher values provided by experts	Standard error £65 Gamma distribution Assumed based on 50% of mean

If any parameters or variables listed in table 3 were omitted from the sensitivity analysis, please explain why.

N/A all parameters are included.

Sensitivity analyses results

Present the results of any sensitivity analyses using tornado plots when appropriate.

Deterministic sensitivity analysis results for the base case are presented in the tornado diagram shown in Figure 1 and Figure 2 for the top 15 key drivers in the model by incremental cost per patient and by cost per death avoided. Deterministic sensitivity analysis for scenario 1 using the microcosting approach are shown in Figure 3 and Figure 4.

Figure 1: Tornado diagram base case – incremental cost per patient outcome

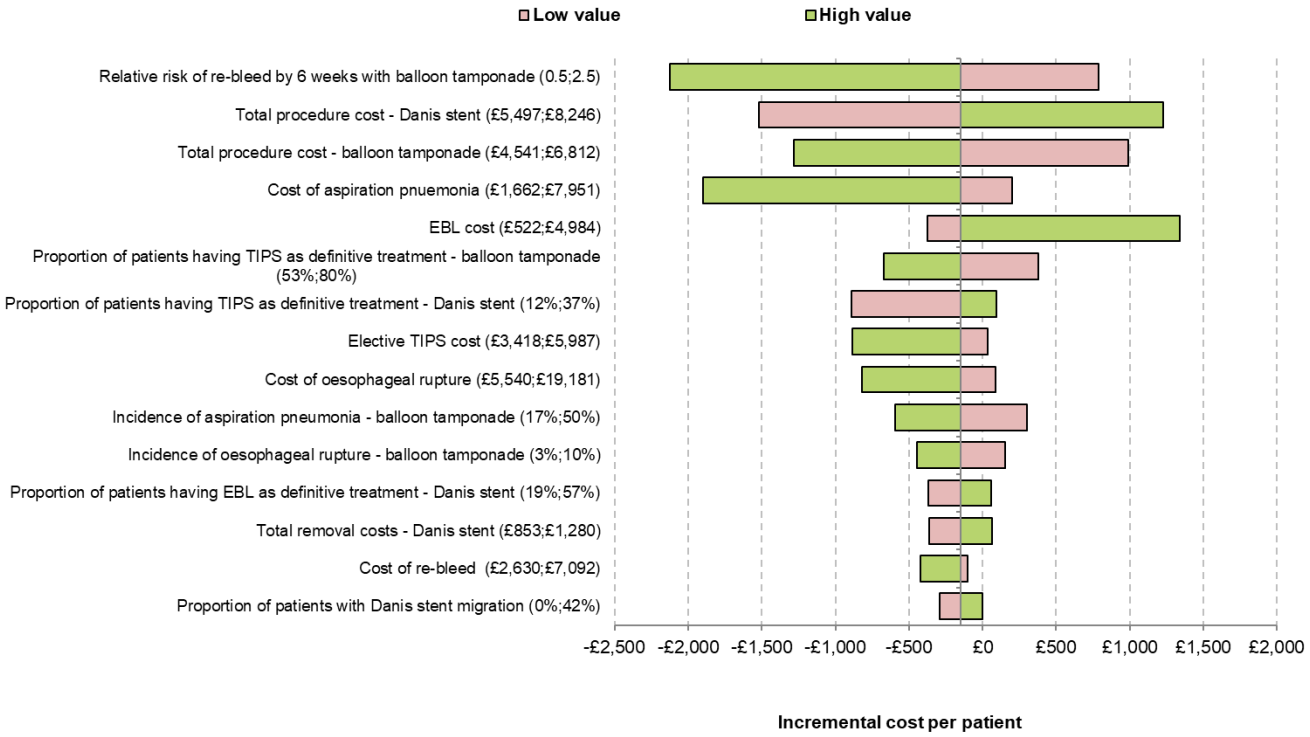


Figure 2: Tornado diagram base case– cost per death avoided outcome

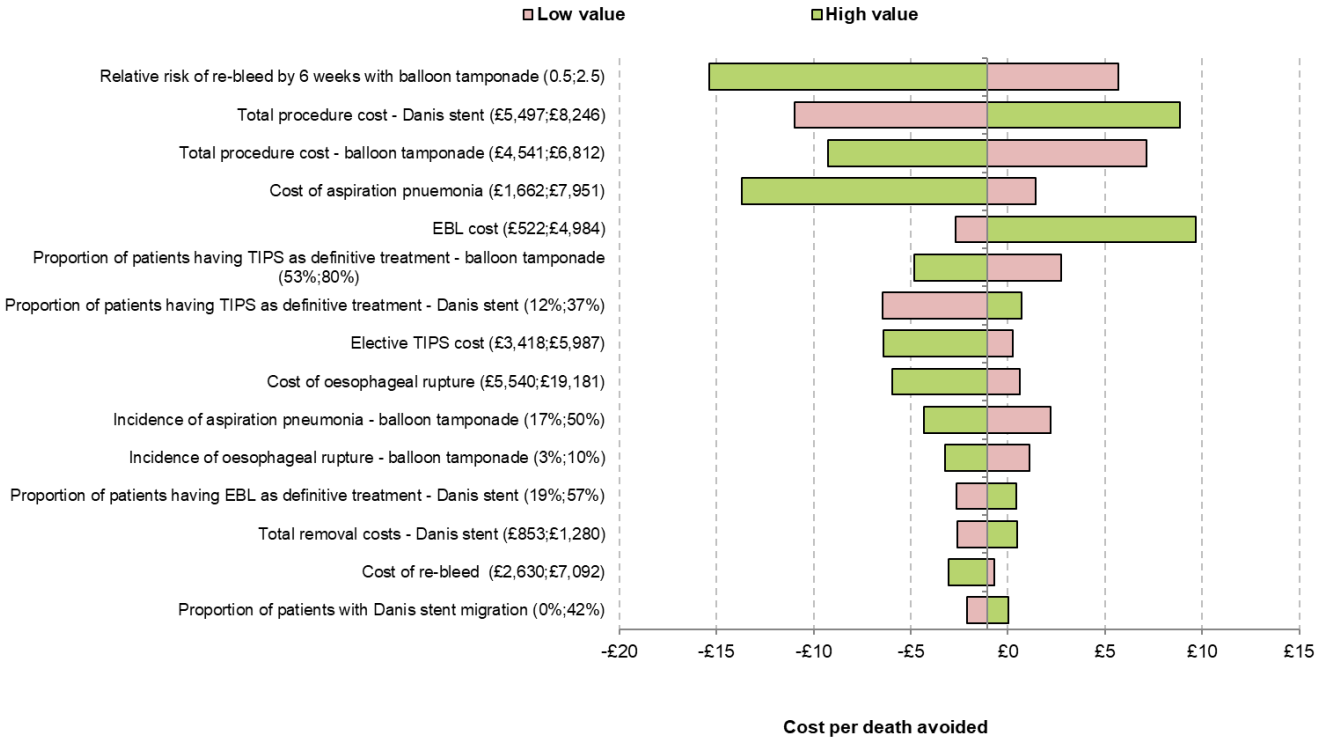


Figure 3: Tornado diagram scenario 1 – incremental cost per patient

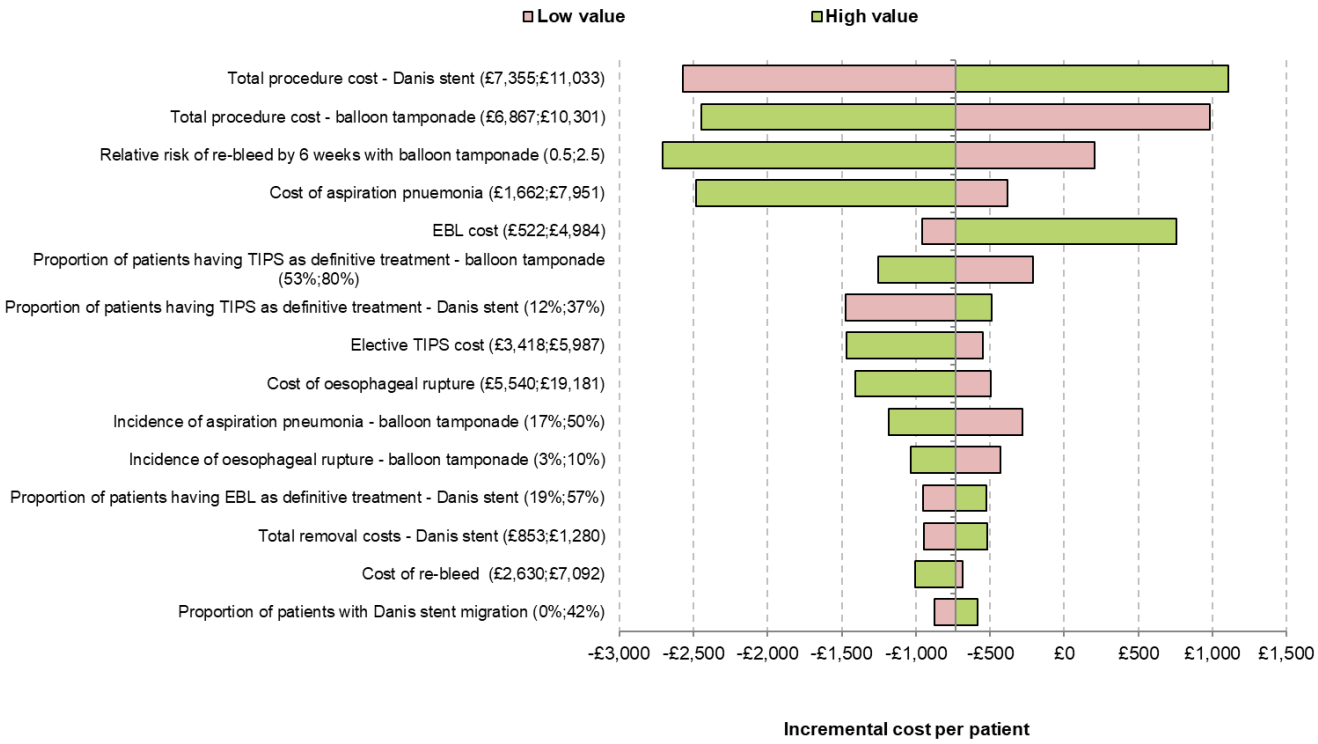
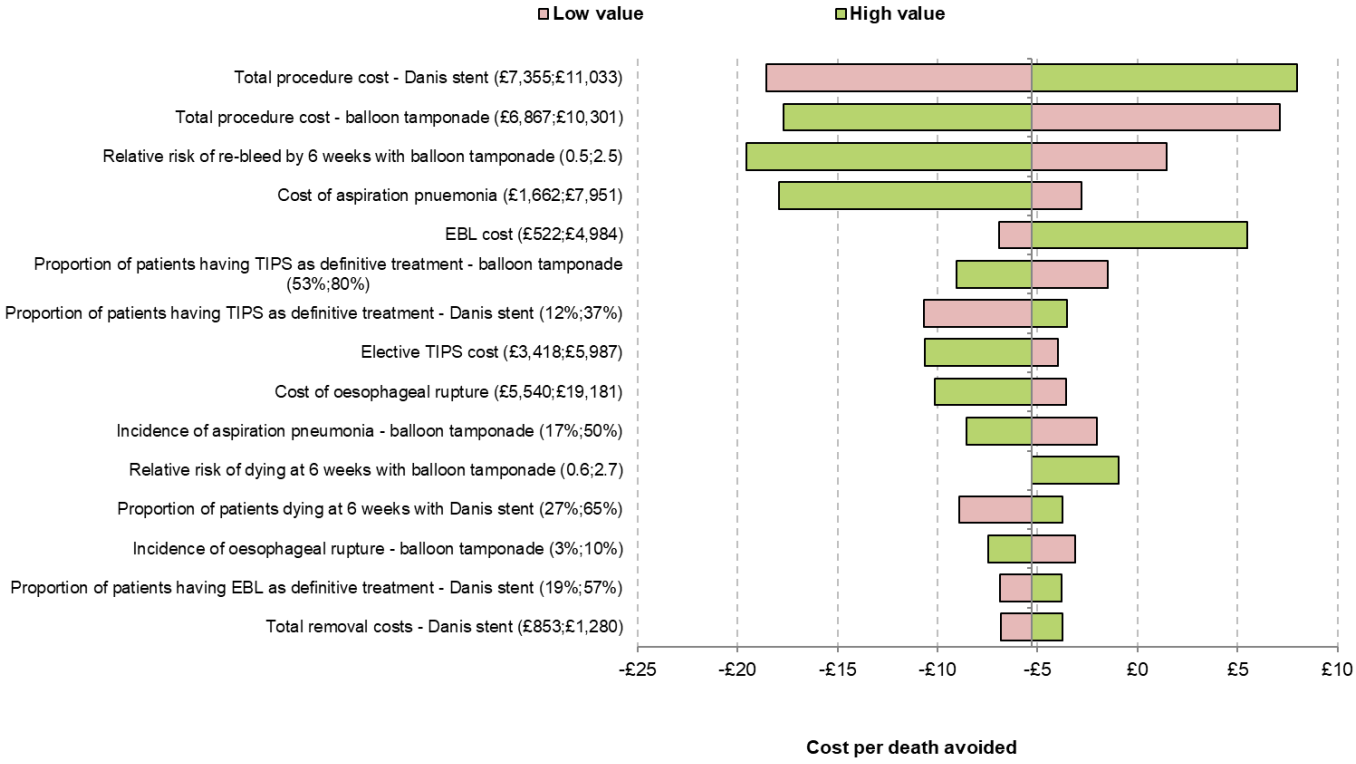


Figure 4: Tornado diagram scenario 1 – cost per death avoided



A two-way sensitivity analysis exploring the interaction between training costs per procedure for Danis stent insertion and the incidence of stent migration requiring intervention is shown in **Error! Not a valid bookmark self-reference.**.

Figure 5: Two-way sensitivity analysis – training costs and incidence stent migration

	Stent migration										
Training cost per procedure	-£146.71	0%	5%	10%	15%	20%	25%	30%	35%	40%	45%
	£0	-£355	-£320	-£285	-£250	-£215	-£181	-£146	-£111	-£76	-£41
	£10	-£345	-£310	-£275	-£240	-£205	-£171	-£136	-£101	-£66	-£31
	£20	-£335	-£300	-£265	-£230	-£195	-£161	-£126	-£91	-£56	-£21
	£30	-£325	-£290	-£255	-£220	-£185	-£151	-£116	-£81	-£46	-£11
	£40	-£315	-£280	-£245	-£210	-£175	-£141	-£106	-£71	-£36	-£1
	£50	-£305	-£270	-£235	-£200	-£165	-£131	-£96	-£61	-£26	£9
	£60	-£295	-£260	-£225	-£190	-£155	-£121	-£86	-£51	-£16	£19
	£70	-£285	-£250	-£215	-£180	-£145	-£111	-£76	-£41	-£6	£29
	£80	-£275	-£240	-£205	-£170	-£135	-£101	-£66	-£31	£4	£39

The probabilistic sensitivity analysis was run for 10,000 iterations of the model which was shown to achieve stabilisation in the probabilistic results. The spread of these results according to incremental cost is shown in

Figure ***6*** for the base case and

Figure ***7*** for scenario 1.

Figure 6: Probabilistic sensitivity analysis results – base case

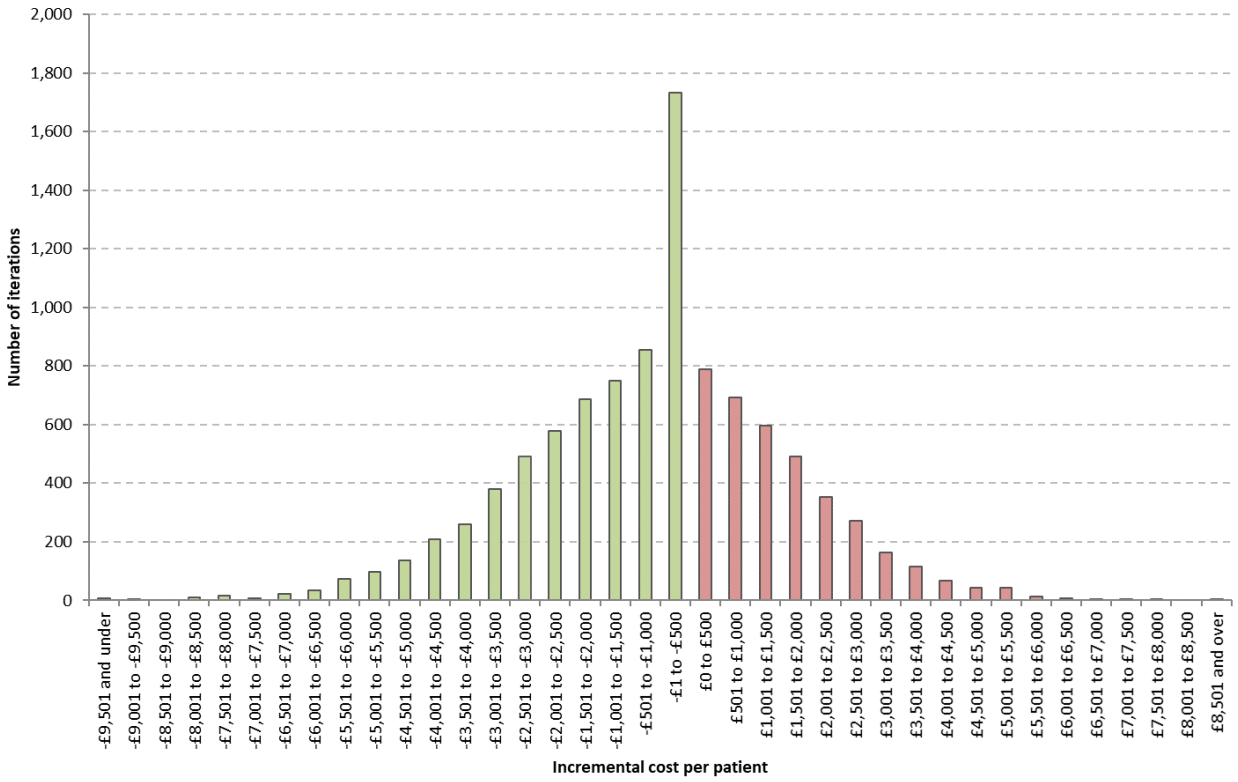
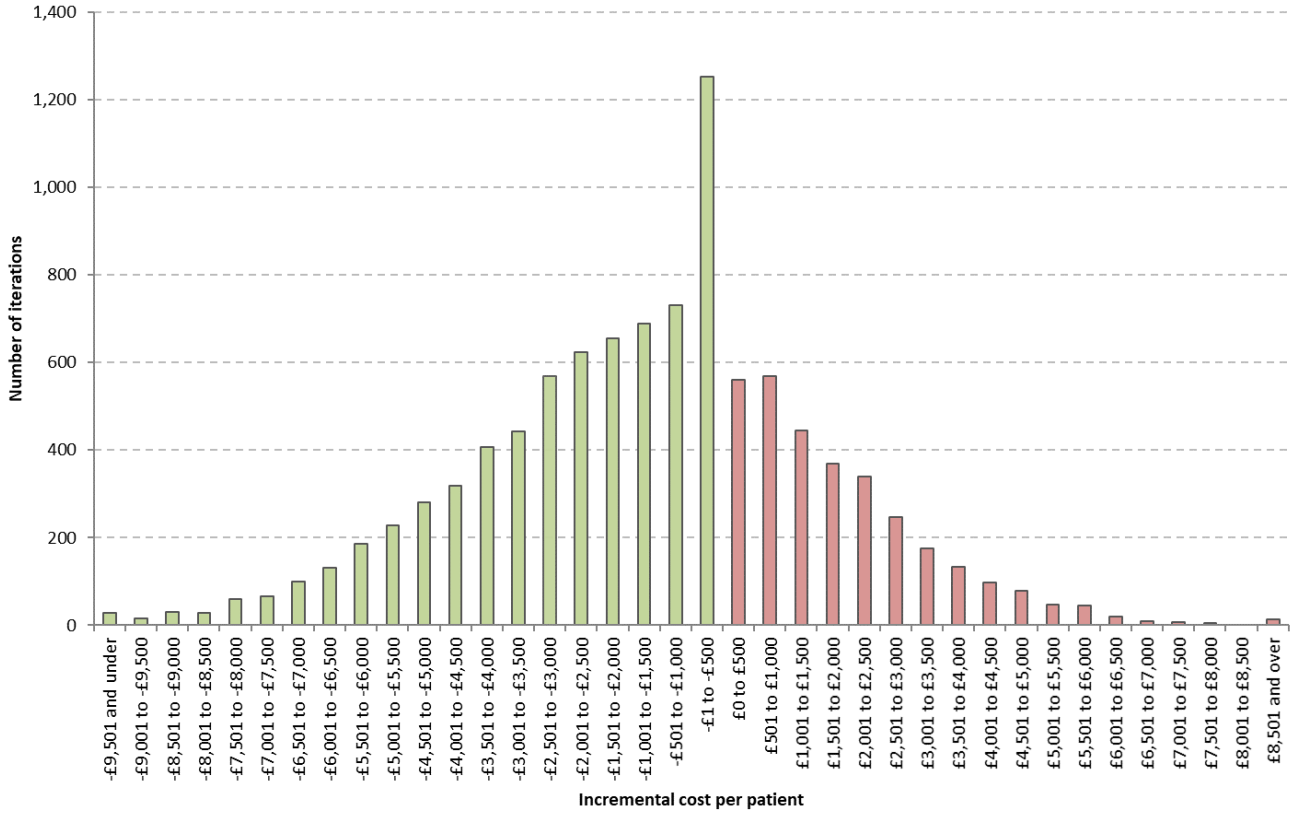


Figure 7: Probabilistic sensitivity analysis results – scenario 1



What were the main findings of each of the sensitivity analyses?

Deterministic sensitivity analysis

The results of the deterministic sensitivity analysis show that the results of the model with the base case parameters are not robust to changes in individual parameters and are sensitive to changes in the majority of input parameters. The key drivers as shown in the tornado diagram are the relative risk of re-bleeding with balloon tamponade, the total procedure costs for each intervention, the cost of aspiration pneumonia, and the cost of EBL as a definitive treatment.

There is uncertainty around many of these parameters due to the small size of the trials and rarity of patients undergoing these procedures in clinical practice. In particular there is uncertainty around the procedure cost and whether it can be considered to be equivalent to the procedure to insert the balloon tamponade. In the Escorsell et al. (2016) RCT there was a difference between treatment arms between use of vasoactive drugs due to more patients in the Danis stent undergoing EBL. This would increase the procedure cost for Danis stent and may change the direction of the results. However, it was also noted by clinical experts that there may be a reduction in the length of stay in ICU and high dependency units for patients undergoing the Danis procedure within the NHS and that these procedures may be undertaken under sedation in an endoscopy suite rather than under general anaesthetic in around a third of patients, therefore reducing the procedure cost and increasing the incremental cost difference. Variation in the cost of rebleeding was reported in the NICE resource impact report. Varying this input has less of an impact on the results of the model but a relatively low estimate has been used in the base case and increasing this cost would increase the incremental cost difference between Danis and balloon tamponade.

Similarly, the cost of aspiration pneumonia has a wide range reported in NHS reference costs (NHS Improvement 2019). A weighted average by finished consultant episode was used for the base case which gives a value at the lower end of the scale. However, if these patients are more likely to have more serious complications because of their existing health condition then this cost may be underestimated. Increasing this cost increases the incremental cost difference between the two interventions.

The costs of the definitive treatments are also uncertain. This has also been explored in a scenario analysis due to uncertainty as to whether a difference in the choice of definitive treatment between treatment arms should be expected. Additionally, the cost of EBL is uncertain because it is unclear whether patients would need additional treatments following this, for example further EBL or TIPS. The time horizon of the trial was 6 weeks so no data were available on whether patients undergoing EBL received subsequent treatments after this period. If patients required further treatments this would increase the cost of EBL and therefore likely change the direction of the results. Further, the costs of the definitive treatments were based on NHS reference costs 2018/19 (NHS Improvement 2019). The cost of total HRGs was used due to the small number of finished consultant episodes for the elective procedures meaning there was more uncertainty in the costs. The costs for the elective procedures were higher, and use of these would change the direction of the results.

The cost of training for the Danis stent and incidence of stent migration has been explored in a two-way sensitivity analysis. This is because it was judged that the two inputs may be linked based on input from clinical experts and published evidence Zehetner et al. (2008) stated that migration was observed in the learning phase). As shown in the analysis **Error! Not a valid result for table.**, where

training costs are lower and therefore stent migration incidence is expected to be higher, as long as stent migration remains below 40% the direction of the results do not change. Where training costs are high, stent migration incidence of around 30% or higher would change the direction of the results.

There appears to be variation in clinical practice in use of the Ella extractor to remove the stent with one clinical expert noting that they rarely use the extractor and instead use an overtube. Other experts noted that the extractor is not required if the patient is undergoing a TIPS procedure. This leads to uncertainty around the cost of removal of the stent. Although this is not one of the key drivers of the analysis it still has the potential to change the direction of the results if all removal procedures are undertaken using the extractor.

Scenario analysis

The microcosting scenario reflects the uncertainty around the costs of the procedure. Clinical experts agreed that carrying out insertion of the Danis stent and balloon tamponade are largely similar. However, one expert noted that they would expect to see a reduction in the length of ICU or HDU stay, and that some Danis stent procedures may be able to be undertaken in a non-theatre based setting under sedation rather than general anaesthetic. There is uncertainty around whether differences in the use of vasoactive drugs due to differing definitive treatments used should be included or whether this is patient dependent and therefore not relevant to the choice of bridging treatment. Using microcosting with a reduction in the procedure setting cost and reduction in ICU LoS increases the cost savings with the Danis stent.

The scenario where the definitive treatment choice is not linked to the initial intervention questions whether use of the Danis stent is expected to have any impact on the definitive treatment chosen or whether this is dependent on the individual patients' characteristics. There was still uncertainty regarding this after feedback from clinical experts. If it is not expected to have any impact then the costs of HE and definitive treatments may not need to be considered within the model. This changes the direction of results because EBL is the less costly of the definitive treatments and occurs more in the Danis stent treatment arm in the trial. The increase in patients receiving TIPS in the balloon tamponade treatment arm also appears to increase the incidence of severe HE so removing this cost also reduces the cost in the balloon tamponade arm further. However, if the bridging treatment does have an impact on the definitive treatment available or chosen then the basecase is more appropriate. This does raise further uncertainty, however, as to whether patients undergoing EBL would require further subsequent treatments beyond the 6-week time horizon of the trial. If they do and the cost of EBL were to increase then this could change the direction of the results as shown in the tornado diagrams.

Probabilistic sensitivity analysis

The probabilistic analysis showed a wide variation in the results reflecting the uncertainty in the parameter inputs. The average probabilistic incremental cost per patient from 10,000 model iterations was -£328 per patient. 55% of iterations were shown to be cost saving and 42% with a dominant outcome i.e. cost saving and reduction in deaths. The average probabilistic incremental deaths shown by the probabilistic analysis was -181 per 1,000 patients.

For the microcosting scenario the average probabilistic incremental cost per patient from 10,000 model iterations was -£932 per patient. 62% of iterations were shown to be cost saving and 48% with

a dominant outcome i.e. cost saving and reduction in deaths. The average probabilistic incremental deaths shown by the probabilistic analysis was -183 per 1,000 patients.

What are the main sources of uncertainty about the model's conclusions?

The key source of uncertainty is due to the limited comparative clinical evidence. The only RCT on the Danis stent is small, however, as noted in the clinical submission this is reflective of the small patient population available. This study does suggest that the Danis stent is superior to the balloon tamponade in controlling bleeding, reducing adverse events and reducing mortality at 15 days. However, again due to the small size of the study, there are wide confidence intervals around these key parameters, and therefore much uncertainty in the cost analysis.

The RCT duration was 6 weeks. This means there is uncertainty in the longer-term outcomes of patients surviving beyond this period in terms of their clinical outcomes, but also their costs and resource use. For example, for those undergoing band ligation as their definitive treatment it is unknown whether these patients would have required further subsequent treatments.

It is also unclear whether the costs of these definitive treatments should be considered in the analysis. There appears to be a difference in the RCT between treatment arms in the choice of definitive treatments. However, because of the small sample size it is unclear whether this is due to the bridging treatment used i.e. Danis stent or balloon tamponade or whether it is a coincidence. Advice from clinical experts appeared to be conflicting and so further clinical input would be useful.

Miscellaneous results

Include any other relevant results here.

No data on patient quality of life were collected in any of the clinical studies and therefore this was not included within the cost model. However, clinical experts commented on the Danis stent being much more comfortable for the patient and that it can reduce their stay in ICU and therefore their risk for further complications. Additionally, the Danis stent allows for patients to remain conscious whereas, with balloon tamponade patients are usually under sedation because the balloon is uncomfortable and this minimises the risk of the patient removing the balloon themselves according to clinical experts. Further, the Danis stent allows for oral nutrition to be administered which can increase overall health of the patient in the 24 to 48-hour period following bleeding compared with balloon tamponade. Experts also suggested that the Danis stent could be used as a palliative care measure. Allowing patients, for whom no definitive treatment is possible, additional time without being sedated. As noted in the clinical submission however, this is considered off-label use. The significant reduction in device related adverse events (p=0.049) with the Danis stent compared with balloon tamponade would also impact on quality of life.

Validation

Describe the methods used to validate, cross-validate (for example with external evidence sources) and quality assure the model. Provide sources and cross-reference to evidence when appropriate.

The model was checked for errors by a health economist separate to the original development team. No economic evidence was identified with which to cross-validate the model with.

Give details of any clinical experts who were involved in validating the model, including names and contact details. Highlight any personal information as confidential.

Three clinical experts were consulted during development of the model. Their names and contact details are:

- Dr David Patch, Royal Free London hospital, david.patch@nhs.net
- Dr Amer Al-Joudeh, Sheffield teaching hospitals, amer.al-joudeh@nhs.net
- Mr Owen Dickenson – Rotherham district general hospital, owen.dickinson@nhs.net

4 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain any potential cost savings and the reasons for them.

The model shows there is potential for the Danis stent to save £147 per patient with oesophageal variceal bleeding who fail first line therapy compared with balloon tamponade. The savings result from a reduction in re-bleeding events and adverse events with potential for further savings in the costs of definitive treatment and resulting severe HE if the Danis stent is believed to impact on the choice of definitive treatment.

Further benefits which are not reflected in the cost model include the impact on patient quality of life. Clinical experts have noted that the Danis stent is much more comfortable for the patient, and patients can remain awake following the procedure rather than under sedation as they have to be with balloon tamponade. Additionally, the Danis stent allows for oral nutrition to be administered which can further improve patient quality of life as well as their clinical condition. A significant reduction in device related complications will also have a positive impact on quality of life. Additionally, the potential to transfer and transport patients more easily is also not reflected in the cost model. Clinical experts noted that not all hospitals in the UK are able to undertake specialist procedures such as TIPS so use of the Danis stent may allow for more time for patients to be transferred to receive these procedures.

Briefly discuss the relevance of the evidence base to the scope.

The *de novo* cost model compares the Danis stent to balloon tamponade in people with acute refractory oesophageal variceal bleeding in whom first line therapy is unsuitable or has failed. No clinical evidence was identified comparing the Danis stent to TIPS. Early TIPs, as described in the scope is not thought to be a relevant comparator to the Danis stent as it would be used at a different point in the pathway, often following a stent or balloon tamponade. An alternative comparator to consider would be emergency or salvage TIPS, however, no evidence comparing the Danis stent to any form of TIPS was identified and it was therefore not included in the cost model.

The clinical evidence used for the cost model was based on 1 RCT which was the only randomised comparative evidence identified comparing Danis stent to balloon tamponade. The RCT was conducted outside of the UK but within Europe. Clinical experts judged that patients within Europe are likely to have similar treatment pathways to those patients in the UK and similar causes of acute oesophageal variceal bleeding and therefore can be considered generalisable to a UK setting. The only other comparative evidence identified in the clinical review was a retrospective case control study (Maiwall et al. 2018) which compared Danis stent with repeat endotherapy and vasoactive drugs. Repeat endotherapy was described as (polidocanol or cyanoacrylate glue or haemospray) with or without Sengstaken–Blakemore tube as a bridging therapy and continuation of vasoactive drugs. Given that the comparator in this study was less aligned with the scope and the study was not controlled, it was judged that the RCT would be more appropriate to use to inform the model. Further not all outcomes needed for the model were reported by the Maiwall study (control of bleeding only reported at 5 days and rate of rebleeding time point not reported, incidence of severe HE and choice of definitive treatment not reported) and the reporting was unclear. Additionally, the study was conducted in India which was judged to be less generalisable to a UK setting based on clinical expert opinion that portal hypertension historically

occurred more commonly there in non-cirrhotic patients and therefore the patients in this study may differ from those typically seen in a UK NHS setting.

Costs within the model were based on nationally recognised sources and as such should be representative of a UK setting.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

No published economic studies with which to compare the results of the cost model with were identified in the economic review.

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

The cost analysis is relevant to all patients with acute refractory oesophageal variceal bleeding in whom first line therapy is unsuitable or has failed in England. The Danis stent may be more suitable than balloon tamponade in particular patient groups such as those that require transport to a specialist centre to undergo a TIPS procedure. However, there is likely to be variation in the outcomes of patients with this condition which may not be fully reflected by the clinical evidence due to the small sample sizes.

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

This appears to be the first cost analysis conducted in this area and clinical data used in the model was taken from an RCT conducted in Europe (and judged to be applicable to the UK NHS). Additionally, cost data were taken from recognised UK databases where possible and a microcosting approach was included to cost the procedure so as to reflect differences in procedure settings and length of stay following the procedure. Extensive sensitivity analyses were conducted in an attempt to capture the uncertainty in the analysis, although this remains substantial.

Limitations of the analysis include the fact that the RCT is based on a very small sample size of patients due to the limited patient population available with this condition who subsequently fail first line therapies. There also appears to be some variation in clinical practice in how these patients are managed in terms of definitive treatments used and/or available (i.e. not all hospitals are able to undertake TIPS) as well as variation in other parameters such as removal of the stent, all of which adds to the uncertainty of the analysis. The cost model does not fully reflect the scope because no data could be identified for the TIPS comparator and therefore this could not be included within the model, although it is noted that this may be a less relevant comparator than the balloon tamponade.

The model has a short time horizon which reflects the short time period over which the clinical studies were conducted and the difficulties in extrapolation of any clinical outcomes in this patient population due to paucity of data. This could impact on the analysis in either direction depending on whether patients may experience longer term benefits or further costs due to differing definitive treatments. Additionally, the cost model does not capture any quality of life benefit which is likely to be improved with the Danis stent according to clinical expert opinion.

Detail any further analyses that could be done to improve the reliability of the results.

A larger comparative study, ideally with some or all patients being in an English NHS setting, would reduce the uncertainty in the data and therefore in the results of the cost model. However, it should be acknowledged that conducting a larger trial in this patient population may not be possible due to the following reasons:

- The population of patients with this condition who fail first line therapies is very small. This was confirmed by clinical experts who commented that they typically performed 5 to 10 procedures such as insertion of the Danis stent per year.
- The procedure is typically undertaken as an emergency procedure and therefore obtaining patient consent is difficult and not always possible dependent on their condition.

5 References

Please include all references below using NICE's standard referencing style.

British National Formulary Terlipressin Acetate medicinal forms. [online] Available from: https://bnf.nice.org.uk/medicinal-forms/terlipressin-acetate.html].

Escorsell A, Pavel O, Cardenas A, et al. (2016) Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: A multicenter randomized, controlled trial. *Hepatology* 63(6),pp. 1957-67.

Ghidirim G, Mishin IV, Dolghii AN, et al. (2012) Self-expanding metal stent for the management of bleeding esophageal varices - Single centre experience. *Clinical Anatomy and Operative Surgery* 11(4),pp. 100-103.

ISD Scotland (2019) *Theatre services.* [online] Available

Maiwall R, Jamwal KD, Bhardwaj A, et al. (2018) SX-Ella Stent Danis Effectively Controls Refractory Variceal Bleed in Patients with Acute-on-Chronic Liver Failure. *Dig Dis Sci* 63(2),pp. 493-501.

Muller M, Seufferlein T, Perkhofer L, et al. (2015) Self-Expandable Metal Stents for Persisting Esophageal Variceal Bleeding after Band Ligation or Injection-Therapy: A Retrospective Study. *PLoS ONE [Electronic Resource]* 10(6),pp. e0126525.

National Institute for Health and Care Excellence (2015) *Rifaximin for preventing episodes of overt hepatic encephalopathy [TA337].* [online] Available from: https://www.nice.org.uk/Guidance/TA337

National Institute for Health and Care Excellence (2016) Resource impact report: Cirrhosis in over 16s: assessment and management (NG50).

National Institute for Health and Care Excellence (2019) *Danis stent for acute oesophageal variceal bleeds: Medtech innovation briefing [MIB185].* [online]: NICE Available from: https://www.nice.org.uk/advice/MIB185

National Institute for Health and Care Excellence (NICE) (2017) *Medical Technologies Evaluation Programme: Methods Guide.* [online] London Available from: https://www.nice.org.uk/process/pmg33/chapter/introduction [Accessed: April]

NHS Improvement (2018) *NHS reference costs 2017/18.* [online]: NHS Available from: https://improvement.nhs.uk/resources/reference-costs/

NHS Improvement (2019) *National cost collection NHS 2018/19.* [online]: NHS Available from: https://improvement.nhs.uk/resources/national-cost-collection/#ncc1819

Personal Social Services Research Unit (2019a) *Sources of Information: Inflation indices.* [online] Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2018/

Personal Social Services Research Unit (2019b) *Unit costs of Health and Social Care 2019.* [online] Available from: https://www.pssru.ac.uk/project-pages/unit-costs/

Pfisterer N, Riedl F, Pachofszky T, et al. (2019) Outcomes after placement of a SX-ELLA oesophageal stent for refractory variceal bleeding-A national multicentre study. *Liver International* 39(2),pp. 290-298.

Trikudanathan G, Hoversten P, Arain MA, et al. (2018) The use of fully-covered self-expanding metallic stents for intraprocedural management of post-sphincterotomy perforations: a single-center study (with video). *Endoscopy international open* 6(01),pp. E73-E77.

Tripathi D, Stanley AJ, Hayes PC, et al. (2015) U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. *Gut* 64(11),pp. 1680-704.

Wright G, Lewis H, Hogan B, et al. (2010) A self-expanding metal stent for complicated variceal hemorrhage: experience at a single center. *Gastrointestinal Endoscopy* 71(1),pp. 71-8.

Zakaria MS, Hamza IM, Mohey MA, et al. (2013) The first Egyptian experience using new self-expandable metal stents in acute esophageal variceal bleeding: pilot study. *Saudi Journal of Gastroenterology* 19(4),pp. 177-81.

Zehetner J, Shamiyeh A, Wayand W, et al. (2008) Results of a new method to stop acute bleeding from esophageal varices: implantation of a self-expanding stent. *Surgical Endoscopy* 22(10),pp. 2149-52.

6 Appendices

Appendix A: Search strategy for economic evidence

Describe the process and methods used to identify and select the studies relevant to the technology being evaluated. See section 2 of the user guide for full details of how to complete this section.

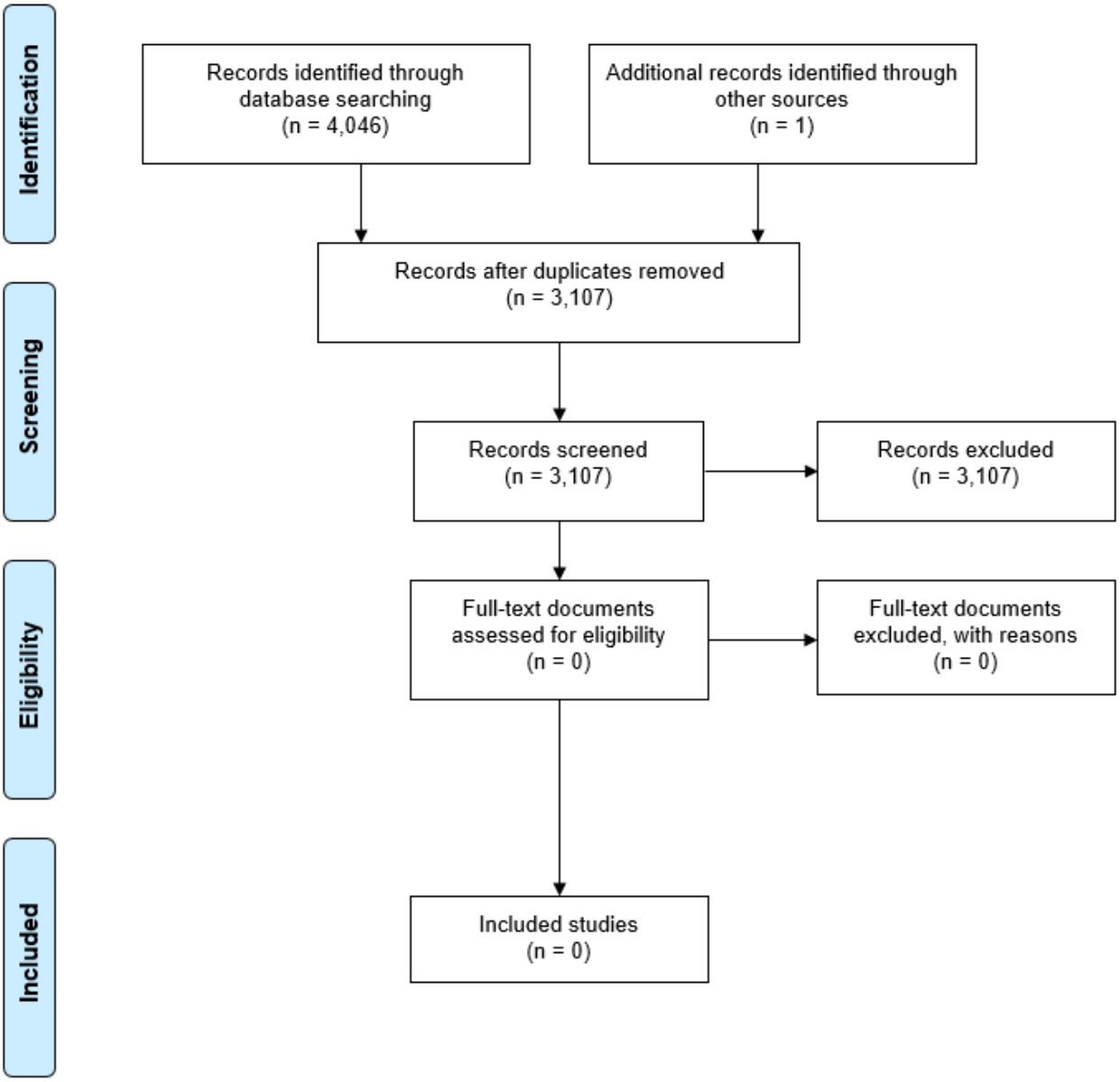
A single search was used for the clinical and economic evidence.

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

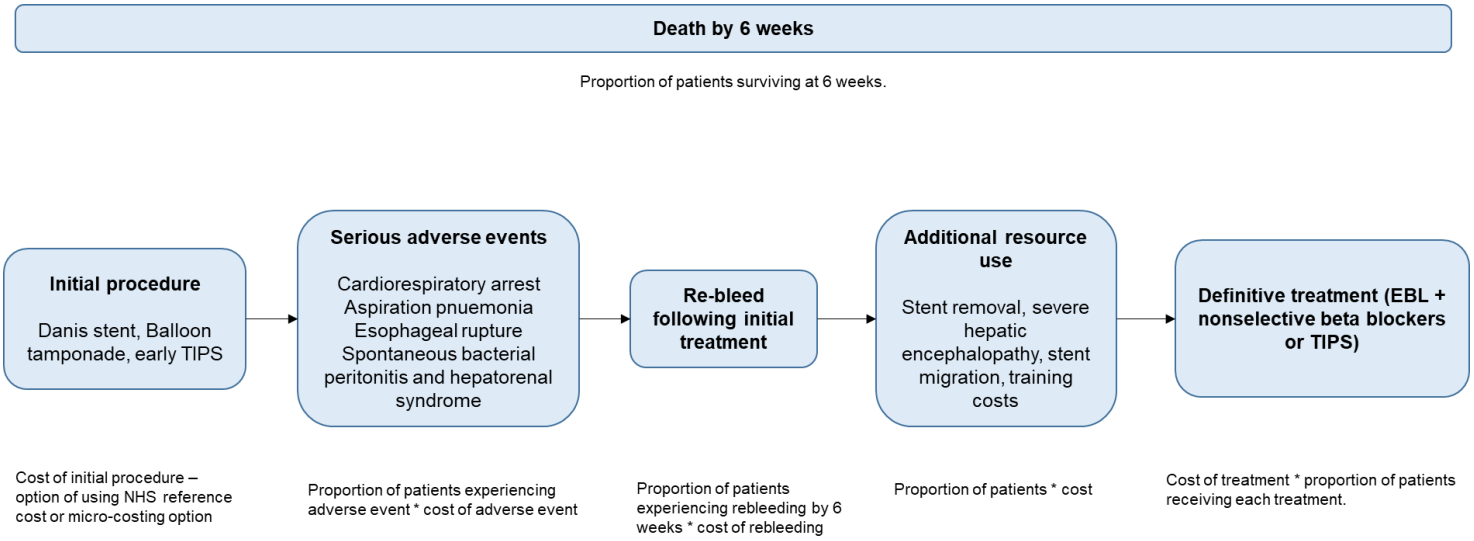
Not applicable, no studies were considered for inclusion at full text review.

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



Appendix B: Model structure

Please provide a diagram of the structure of your economic model.



Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☒ If no, please proceed to declaration (below)

Yes ☐ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	5th May 2020
Print:	Ian Aaron	**Role / organisation:**	Managing Director, UK Medical
Contact email:	ian.aaron@ukmedical.com		

NICE National Institute for Health and Care Excellence

Medical technologies guidance

Collated expert questionnaires

Technology name & indication: **Danis stent for acute oesophageal variceal bleeds**

Experts & declarations of interest (DOI)

Expert #1	Dr Deepak Joshi, Consultant Hepatologist, Institute of Liver Studies, Kings College Hospital
	DOI: None
Expert #2	Dr Sullleman Mamode Moreea, Consultant gastroenterologist, Bradford Royal Infirmary
	DOI: None
Expert #3	Dr Dhiraj Tripathi, Consultant Hepatologist, University Hospitals Birmingham NHS Trust
	DOI: Yes

Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Non-financial professional	Lead author of published guidelines on variceal bleeding for the British Society of Gastroenterology (NICE accredited)	**2015**	
Non-financial professional	Co-author of guidelines on TIPSS (transjugular intrahepatic portosystemic stent-shunt) in development for the British Society of Gastroenterology	**2018**	

Expert #4	Dr Emmanouil Tsochatzis, Associate Professor and Honorary Consultant, Inst for Liver and Digestive Hlth Div of Medicine, University College London

	DOI: None
Expert #5	Dr Ian Beales, Consultant Gastroenterologist, Norfolk & Norwich University Hospitals NHS Trust
	DOI: None
Expert#6	Dr Paul Richardson, Consultant Hepatologist, Clinical Director for Gastroenterology and Hepatology, Royal Liverpool NHS Trust
	DOI: None
Expert#7	Dr Claire Salmon, Consultant Hepatologist, Sheffield Teaching Hospitals NHS Trust
	DOI: None
Expert#8	Mr Owen Dickinson, Consultant Nurse in Endoscopy and Interventional Radiology, Rotherham NHS Foundation Trust
	DOI: None

How NICE uses this information: the advice and views given in these questionnaires are used by the NICE medical technologies advisory committee (MTAC) to assist them in making their draft guidance recommendations on a technology. It may be passed to third parties associated with NICE work in accordance with the Data Protection Act 2018 and data sharing guidance issued by the Information Commissioner's Office. Expert advice and views represent an individual's opinion and not that of their employer, professional society or a consensus view (unless indicated). Consent has been sought from each expert to publish their views on the NICE website.

For more information about how NICE processes data please see our privacy notice.

1. **Please describe your level of experience with the technology, for example: Are you familiar with the technology? Have you used it? Are you currently using it? Have you been involved in any research or development on this technology? Do you know how widely used this technology is in the NHS?**

Expert #1	I currently use the DANIS stent and have inserted approximately 15 in total. I have never been involved in any research or development of this stent. I think this technology has been used in a various centres in the UK but overall the usage has been sparse.
Expert #2	I am familiar with the use of the Danis stent. I have used it 3 times this year. If needed, I'll be using it again. I haven't been involved in any research/development of this technology. I am unsure how widely it is used in the NHS
Expert #3	Yes I am familiar with the technology having been trained in use of the Danis stent by the manufacturer. I have some experience of the technology in the past. At present our Trust is awaiting a supply of the stents. I have not been involved in research or development of the technology. The technology is established and widely used in tertiary and secondary care.
Expert #4	I am familiar with the technology through relevant publications and its use in my department in patients with recurrent variceal bleeding. We are still using it in selected patients in my department. I have not been personally involved in any research on this technology. It is not widely used in the NHS, main issues are lack of awareness/familiarity/expertise in using it by non-tertiary centre gastroenterologists.
Expert #5	I am familiar with the technology and have reviewed all the published literature. I have not personally used the technology, although I am involved in the management of acute bleeding from oesophageal varices using the other available technologies.

	I have not been involved in any research or development on this technology. The technology is currently not widely used in the NHS. This stems from lack of awareness, lack of training and the current lack of published evidenced-based guidelines supporting the use. The technology is used, mainly limited to major hepatology centres, although it is possible for it to be used much more widely.
Expert#6	I am familiar with the technology and has been used in our Department on a few occasions. I have looked after patients were it has been used but have not placed on personally. It is available for use within the Department currently I have not been involved in development or research of this device I do not know how widespread its use in the NHS is at present
Expert#7	I have used this technology in Derby Teaching Hospitals and in Sheffield Teaching Hospitals. I introduced this technology when I moved to Sheffield. We are currently using it. I have inserted or assisted in the insertion of 8-10. I have also taught other consultants within Sheffield Teaching Hospital. I have been involved in teaching on the DANIS stent practical station at the Sheffield Haemostasis course for the last 2 years.
Expert#8	1. Within the last year The Rotherham NHS Trust has placed 5 DANIS Stents 2. Yes, I have been involved in all placements 3. Yes, we are using the device over the previous medical technology = Sengstaken- Blakemore Tube. Only on balloon tamponade device has been used since the Danis stent been within the trust, this was used by a Locum Gastroenterologist not trained on the DANIS. 4. I have not been involved in the research or development.

	5. Currently in the UK from the discussions I have had I understand that this is being used in around 40-50%

2. Has the technology been superseded or replaced?

Expert #1	No
Expert #2	It is a new technology.
Expert #3	No
Expert #4	No
Expert #5	No
Expert#6	The technology as a potential niche area in the clinical management of patients with variceal bleeding that have failed SOC – endoscopic therapy / vasopressor treatment or were endoscopic therapy is not available to aid transfer to another centre or temporise until endoscopic therapy available. Currently balloon tamponade is available however I don't think stenting in this setting has been superseded / replaced.
Expert#7	No
Expert#8	The DANIS stent has taken over from the previous device, the Sengstaken-Blakemore Tube

Current management

3. How innovative is this technology, compared to the current standard of care? Is it a minor variation or a novel concept/design?

Expert #1	The stent is a novel design and data would suggest it may be safer than the traditional balloon tamponade devices.
Expert #2	Very innovative. Novel concept.

Expert #3	The technology is well established and NICE IPAC have published guidance in 2013 (IPG392) recommending it can be used under normal or standard arrangements.
Expert #4	It is a novel concept of endoscopic treatment for variceal bleeding not controlled with standard of care which is banding.
Expert #5	This is innovative technology. The management of refractory oesophageal variceal haemorrhage currently relies on using a balloon tamponade system. Although this can be effective, this essentially obstructs the oesophagus and increases the risk of aspiration pneumonitis and use of balloon tamponade requires admission to critical care (level 3). The Danis stent technology allows tamponade of the oeosphagela varices without obstructing the oeosphagal lumen and does not necessitate level 3 care. This should be regarded as a significant advance.
Expert#6	This is a novel approach though has been available for years - as previously the patients in whom this technology is mainly indicated would be treatment with balloon tamponade and emergancyTIPS
Expert#7	It is much better than the previous standard of care. It has less complications and is more effective.
Expert#8	The rebleed rate following the removal of Sengstaken-Blakemore Tube post 24hrs is 30-40%. However the rebleed rate post 24hrs of DANIS stent is approximately 10% seeing an overall reduction in around 20-30%

4. Are you aware of any other competing or alternative technologies available to the NHS which have a similar function/mode of action to the notified technology? If so, how do these products differ from the technology described in the briefing?

Expert #1	No
Expert #2	4 Are you aware of any other competing or alternative technologies available to the NHS which have a similar function/mode of action to the notified technology? If so, how do these products differ from the technology described in the briefing? Currently we see around 10-15 cases of acute variceal bleed per year (catchment population 500 000).

	Most of these cases can be controlled using variceal bands. In 3-4 cases/year where banding isn't possible (poor visibility because of severe bleeding) or isn't effective, so far we have been using balloon tamponade using a Sengstaken or Minnesota tube (https://www.youtube.com/watch?v=HVvdakyvSKc). When the tube is inserted, it comes out of the mouth and needs to be kept under traction (please have a look at the video I have produced for teaching purposes). Patients need to be kept in a HDU/ICU setting. The tube is usually removed after 24 hrs and another attempt made at banding. If this fails the tube is re-inserted and the patient considered for TIPSS (trans jugular intra hepatic porto-systemic shunt - https://www.youtube.com/watch?v=O2u4_hF3234) . Complications of balloon tamponade include perforation of the oesophagus, ulceration of the stomach, failure to control bleeding. Mortality after variceal bleed is currently around 15%. The Danis stent is an alternative to balloon tamponade. It is easier to deploy. Its role is to exert direct pressure on the bleeding point and stop the variceal bleed. It is easy to deploy and works immediately. The advantages are: 1. Easy to deploy 2. Fewer complications than the Sengstaken/Minnesota tube 3. The patient doesn't need to go to HDU/ICU following control of bleeding – even though it is best for a patient with severe bleeding to spend at least 24 hrs in a HDU setting for stabilisation. The Danis stent is meant to be kept in situ for 7 days and then removed. If kept for longer it can damage the oesophagus. There is a risk of rebleeding following removal of the stent as the bleeding point hasn't been 'treated' (as we do with a band that actually shuts down the bleeding point). So, ideally when the stent is removed, it would be best to apply variceal bands to prevent further bleeding episodes. Or the patient can be considered for TIPSS if the endoscopist thinks that banding would be difficult. Therefore the Danis stent should be considered as a bridge to the final treatment of a bleeding oesophageal varix. Disadvantages:

	1.Migration of the stent into the stomach 2. Cost 3. Needs to be removed under X-ray (fluoroscopy) using specialist equipment. 4. We have had one case of possible broncho-oesophageal fistula
Expert #3	The main alternative is balloon tamponade.
Expert #4	The alternative is for patients to have a TIPS procedure, which is much more invasive, requires an ITU bed and has more restrictive eligibility criteria for patients but provides a permanent solution. A Sengstaken tube can be used for up to 24 hours to prevent further bleeding but is a bridge to a TIPS or a Danis stent.
Expert #5	There are no directly competing technologies. Endoscopic hameostatic powders have began to be used for refractory varieal bleeding. There are limited data on their safety and efficacy but probably also fit into this role of salvage treatment for variceal bleeding. This is outside the recommended indications at present for haemostatic powders and because the mode of action is different and temporary and does not involve tamponade of the varices, it is likely that the powders are less likely to secure haemostasis in anything except the very short-term
Expert#6	I am unaware of devices similar to this technology - there are different approaches to manage the clinical condition – balloon tamponade / emergency TIPS and concomitant use of vasopressors and antibiotics but they are dramatically different approaches. There may be specific patients were TIPS may be contra-indicated ie very high MELD or cardiac dysfunction for example.
Expert#7	No
Expert#8	No Other technologies are available. It could be questioned that a normal stent could be utilised, But overall standard stents lack the radial force, stent diameter and weave of DANIS, and would not stem a large varix bleed and the

	stent would migrate due to no stricture to hold the stent inplace.

Potential patient benefits

5. What do you consider to be the potential benefits to patients from using this technology?

Expert #1	Safer than balloon tamponade devices and allows the patient to be potentially extubated.
Expert #2	Please see above
Expert #3	There is evidence from just one small RCT which demonstrates it to be more effective than balloon tamponade early control of bleeding without any impact on survival. The stents may have fewer risk of adverse events. There stents can also “buy time” while considering more definite therapies such as TIPSS. Balloon tamponade should not normally be used for more than 24 hours and does not allow any oral feeding unlike the Danis stent.
Expert #4	Control of bleeding and prevention of death.
Expert #5	Cessation of bleeding from life threatening bleeding. Reductions in mortality. Reductions in complications, principally less pneumonia. Less requirement for critical care. Increased ability to transfer patients with life threatening bleeding safely to major transplant centres for more definitive treatment such as TIPSS.
Expert#6	Stopping bleeding event effectively, avoidance of the potential harmful effects of balloon tamponade, temporising the acute event and allowing a period of time – up to 7 days to allow management plans to be developed. May have particular utility in patients in peripheral hospitals to be safely transferred to liver centres for definitive management or in centres were endoscopic services are on provided all the time.
Expert#7	It allows patients to be awake (rather than under anaesthetic). Patients spend less time in intensive care unit. Patients can be fed. It allows doctors time to assess patients fully and decide who would be suitable for a TIPS. It allows patients to be safely transferred to a tertiary liver centre for further treatment.
Expert#8	The chance of rebleed is reduced, and it allows patients a bridge to TIPPS, whereby the patient can be conservatively managed longer (>14 days) for procedural work up.

6. Are there any groups of people who would particularly benefit from this technology?

Expert #1	1. Refractpry variceal bleeding 2. Post variceal banding ulcer haemorrhoage 3. Palliative procedure in patients unsuitable for TIPS 4. A bridge to TIPS
Expert #2	Please see above
Expert #3	Patient not suitable for TIPSS for example due to complete portal vein thrombosis or severe hepatic encephalopathy. The stents can be used to stabilise a patient and allow for recovery of liver function. It may also reduce the length of stay in ITU, although the RCT did not show this.
Expert #4	Those who are not eligible/fit for TIPS or when TIPS is not available.
Expert #5	Those with refractory oesophageal variceal bleeding. This may be most apparent away from the major centres where other forms of haemostasis such as TIPPs are already available.
Expert#6	Massive variceal bleed, patients were further investigations/information required to inform clinical decision making, patients needing hospital transfers for definitive management of bleeding.
Expert#7	Patients with bleeding from gastric varices
Expert#8	Cirrotic patients who have Oesophageal varices due to portal hypertension

7. Does this technology have the potential to change the current pathway or clinical outcomes? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?

Expert #1	Yes

Expert #2	Yes Please see above
Expert #3	The patients selected for this stents are a very sick group and the stents do not appear to influence overall mortality which is determined more by the severity of underlying liver disease. I do not think they replace the need for a rescue TIPSS in selected patients (note not early TIPSS – this is not an option in refractory variceal bleeding). Judging by recent studies I can't see any signal they will reduce hospital visits.
Expert #4	It could change the current pathway and outcomes and could lead to improved outcomes and less invasive treatment in a subset of patients.
Expert #5	The major benefit would seem to be the effective cessation of bleeding in refractory cases, particularly without the need for balloon tamponade. This has the potential to significantly reduce complications and critical care bed usage. This should improve short-term outcomes for patients with bleeding oesophageal varices.
Expert#6	It has the potential to improve outcomes in patients with uncontrolled variceal bleeding. The quicker control of bleeding has the potential to reduce transfusion requirements and mitigate against development of multi-organ failure needing longer LoS and Level 3 requirements
Expert#7	As it has less complications patients should have a better morbidity and mortality rates.
Expert#8	Yes – it should reduce the usage of Sengstaken-Blakemore Tube, as it doesn't provide clinician's with an exit plan. Whereas DANIS can provide a bridge to TIPP's or a means of patient palliation

Potential system impact

8. What do you consider to be the potential benefits to the health or care system from using this technology?

Expert #1	Improved patient safety
Expert #2	Improved outcome of patients with variceal bleeding which cannot be controlled with banding

Expert #3	Improved control of variceal bleeding and potentially less complications than balloon tamponade.
Expert #4	Better outcomes for patients with difficult to treat variceal bleeding.
Expert #5	Reduction in complications from variceal bleeding. Earlier effective haemostasis should reduce the rates of complications such as sepsis and renal failure. The avoidance of classical balloon tamponade should reduce the complciations such as pneumonia but will avoid admission to critical care beds, which is always required after balloon tamponade because the airway needs protecting to prevent aspiration. This is not required with the Danis stent.
Expert#6	Improving the outcomes of patients with severe uncontrolled variceal bleeding. Reduction in the side effects that are seen in patients treated with balloon tamponade. Management of patients in centres were out of hours endoscopic services are not available
Expert#7	Patients would spend less time in the intensive care unit as patients could be woken up from general anaesthetic more quickly.
Expert#8	Overall the DANIS (£1495) device is costlier to the Sengstaken-Blakemore Tube (£150-£300), until you factor in the bed stay. A patient with Sengstaken-Blakemore Tube will require a ITU/HDU bed currently tariffed at £1500-£3000 per night, compared to a deployment of DANIS, which will cost £475 per night post insertion, leading to a potential nightly saving of £1000 - £2500 per 24hrs stay. Looking at this on an average, a patient would have an ITU post bleed of three to four days. So if the patient had a three night stay there is a potential saving of 7k per patient stay of three days.

9. Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the technology likely to cost more or less than current standard care, or about the same?

Expert #1	It will cost more

Expert #2	Likely to cost less and possibly improve mortality (fewer complications as compared to the alternative of balloon tamponade)
Expert #3	The technology is really best considered an alternative to balloon tamponade and as such offers better early control of oesophageal variceal bleeding. This advantage needs to be carefully balanced against the greater cost. Overall I think it will cost more, but in refractory variceal bleeding it is important to have options available to the clinician.
Expert #4	About the same or even less, depends on eligibility criteria for the technology.
Expert #5	Overall there seems likely to be a cost saving to the health care economy as a whole. Whilst the up front cost of the new technology is greater than available standard care. This is likely to be easily offset by ther reductions in complications, reduced level 3 care and reduced overall in patient stays. The main additional cost of the Danis stent technology is the stent itself. No special equipment or support is required to insert the system.
Expert#6	I thin this is difficult however the quicker bleeding is controlled then there would be an expectation that this will reduce future events – sepsis, renal failure, aspiration etc which would increase potentially the time on ICU and potentially the LoS as well as a direct impact on mortality. Early control of bleeding reduces transfusion requirements.
Expert#7	You would save on the cost of days in intensive care.
Expert#8	Initial outlay is currently higher with DANIS, but looking at the reduced costing at the backend the savings are clear to see. Personally I prefer to have consignment, however this product is not currently available as a consignment item due to the low volumes of usage within the UK as a whole. So trusts with initial capital spend issues may question the uplift. However the SIP savings overall are clear to be seen.

10. What do you consider to be the resource impact from adopting this technology? Could it, for example, change the number or type of staff needed, the need for other equipment, or effect a shift in the care setting such as from inpatient to outpatient, or secondary to primary care?

Expert #1	This technology may help facilitate patients to extubated and transferred from an intensive care environment to general ward.
Expert #2	Must be used in secondary care by advanced endoscopists.
Expert #3	The main resource implication is the initial cost. The technique is relatively easy to learn given many gastroenterologists are experienced in inserting oesophageal stents for other indications. It is advised that radiological guidance is used initially and this will involve the resources necessary for fluoroscopic guidance in the radiology department.
Expert #4	do not expect an increased resource impact from the technology.
Expert #5	This will not alter the place of care. This is an acute secondary care intervention only. The benefits will be of downstream reductions in complications, utilization of level 3 care and reduced in hospital stay. It would not seem that extra staffing are required. 24 hour GI bleed cover is thought to be appropriate and this could become part of the skill-set for that service. It would not need extra resources over and above training.
Expert#6	Acute Trusts will have manpower available if not withing gastroenterological / hepatology then certainly in A+E etc – there may be training issues in the practicalities of using the stent. These patients by their clinical condition are requiring potential Level 3 care (ICU) and on-going IP expert management as shown by NCEPOD report so will only be managed in the acute hospital and possibly tertiary level liver centre care.
Expert#7	None
Expert#8	No impact to be seen from uptake of the device, however the device can be implanted within the Endoscopic, radiological settings. It can also be placed blind in an Acute emergency setting (A+E). Overall the role out of this product would reduce the current resources and free up beds within the ITU and HDU setting.

11. Are any changes to facilities or infrastructure, or any specific training needed in order to use the technology?

Expert #1	Training will be needed by all centres
Expert #2	None
Expert #3	Need for fluoroscopic guidance in some cases.
Expert #4	Endoscopists need demonstration/training however pretty straightforward to use.
Expert #5	There would need to be suitable training for potential operators in Trusts that deal with acute GI Bleeding. It may be possible to network this expertise.
Expert#6	There will if adopted and guidance issued to incorporate into clinical pathways will most likely require training in use of the stent. Also there may need to be a consideration to recommending early transfer to a centre that can perform TIPS due to the early re-bleeding rate
Expert#7	Training in how to insert the stent. As we don't use it regularly we would need updates on training
Expert#8	Training would be required to staff for deployment, however this deployment method is routinely used in other clinical scenarios requiring stent insertion so it would be more readily recognised by clinicians in the UK over the adhoc usage of Sengstaken-Blakemore Tube

12. Are you aware of any safety concerns or regulatory issues surrounding this technology?

Expert #1	No
Expert #2	Migration of the stent – please see above We have had one case of possible broncho-oesophageal fistula
Expert #3	The main safety issue is stent migration and localised ulceration.
Expert #4	Not to my knowledge

Expert #5	None aware
Expert#6	The only potential issue would be familiarity in its use and potential user failure in placing stent accurately to ensure effectiveness
Expert#7	No
Expert#8	No

General advice

13. Please add any further comments on your particular experiences or knowledge of the technology, or experiences within your organisation.

Expert #1	. There is an insertion video available online which helps remind the person inserting the stent of the procedural steps
Expert #2	As above
Expert #3	A multicentre UK RCT (NCT01851564) led by Royal Free Hospital is complete but I believe the results will never be published which is unfortunate, particularly if there was any major safety issue.
Expert #4	Useful in a handful of patients we used it in my unit.
Expert #5	Nothing extra to add
Expert#6	Within my Trust colleagues in the small number of patients that this has been used have found it easy to deploy and effective in stopping bleeding and controlling the clinical situation. Have also had patients that have been transferred from other trusts with stent in situ for TIPS – the fact that the stent can be left in place for days helps in some situations were there is limited immediate access to ICU beds.
Expert#7	None of the patients that I have been involved with that have had this stent inserted have bled again. It works. It is a fiddly bit of kit until you get used to it.
Expert#8	From the deployments currently completed, it has shown far better outcomes to the other historical medical management of this Acute area of bleed. Patients who have had this device implanted it has to be questioned whether they would be alive now if this technology hadn't been utilised.

Other considerations

14. Approximately how many people each year would be eligible for intervention with this technology, either as an estimated number, or a proportion of the target population?

Expert #1	100
Expert #2	From my experience, a maximum of 5 cases/year per 500 000 catchment population
Expert #3	4-5 per year in a typical University Teaching Hospital.
Expert #4	I don't expect more than 200 patients in the UK.
Expert #5	This will be relatively uncommon. The requirement will vary considerably geographically depending on the underlying prevalence of liver disease as well as being more concentrated in the specialist liver centres. As a rough guide. The prevalence of variceal bleeding is approximately 10/100 000 per year in the UK (there is wide regional variation around this). In about 85% of these haemostasis can be secured using standard endoscopic means. In the other 15% rescue therapies such as the Danis Stent might be required. Some of these patients may receive rescue TIPSS directly and some may receive haemostatic powder This would equate to perhaps ~1/100 000 of the population per year requiring a Danis stent – or about 3-4 per year in the average sized DGH (300 000).
Expert#6	I would have thought within the Trust <10/year with potentially similar number from outside Trusts in patient needing TIPS
Expert#7	For the Sheffield population I would expect to use it 5/6 times per year. However the district General Hospitals are also using this prior to transferring patients to us.
Expert#8	Rotherham has within the last annum had 5 deployments. There are 132 Acute trusts within the UK. If we correlate our numbers to the UK population that would lead to a number of >660 patients per annum. Who's lives will be potentially saved.

15. Would this technology replace or be an addition to the current standard of care?

Expert #1	In addition to
Expert #2	As above
Expert #3	It cannot replace balloon tamponade as a Danis stent is not suitable for gastric variceal bleeding. It is also not a replacement for salvage TIPSS in those patients considered suitable for TIPSS. It can be used as a temporary measure.
Expert #4	Addition to the current standard of care. Could replace the Sengtagen tubes in some cases.
Expert #5	This would be a replacement for the traditional balloon tamponade (Minnesota tube) technique. This would be complementary to other endoscopic techniques, TIPSS and drug therapy.
Expert#6	It has the potential to replace balloon tamponade – and especially in Trusts were there isn't an out of hour endoscopy service or availability of requisite experience in endoscopic management of varices, and for stabilisation for transfer for a TIPS centre.
Expert#7	It could replace the use of the Sengstaken tube or could be used the following day.
Expert#8	This would replace Sengstaken-Blakemore Tube in Oesophageal Bleeds, and not gastric

16. Are there any issues with the usability or practical aspects of the technology?

Expert #1	The removal kit can be quite difficult to use and the recommendations is that its used under fluoroscopy. This should be reviewed.
Expert #2	As above
Expert #3	No. Oesophageal stents have been used for a long time and this is simply a minor modification.
Expert #4	No particular issues. Stent can migrate if not correctly placed.
Expert #5	The main issue would be the availability of the skills to insert the technology. These are not novel skills and therapeutic endoscopists or interventional radiologists should be able to gain these skills with appropriate training. The other important issue would be the retention of such skills and how many operators with such skills are required in any area. It is relatively rare to require insertion of a Danis stent or balloon tamponade and each network would require a plan to develop and maintain such skills. However insertion of a

	traditional balloon tamponade device is part of the skills set of those providing an acute GI bleeding service and it should be possible to develop and maintain these skills
Expert#6	Ensuring that staff that may need to use it are familiar with it and confident to use.
Expert#7	It is fiddly so you do need to know how to use it.
Expert#8	Confidence and Knowledge, however when DANIS was put in Rotherham. It was put in with company reps applying training and one to one support.

17. Are you aware of any issues which would prevent (or have prevented) this technology being adopted in your organisation or across the wider NHS?

Expert #1	No although the cost is an important factor to take into account
Expert #2	None
Expert #3	Main issue is cost
Expert #4	No
Expert #5	The main issue will be the apparent high cost, up front, of the Danis stent devices. These are individually quite expensive, much more so than balloon tamponade devices. This will seem unattractive to managers and it will be less clear how the downstream subsequent cost savings are realised by reducing complications. This is an important issue because such refractory variceal bleeding is relatively uncommon and as this is an immediate life-threatening emergency, it will be necessary to have the Danis stent device immediately available on the shelf. It cannot be ordered in as desired. This means money needs to be spent on a stent that may never be used.
Expert#6	No as it is used currently and has been through our device and technologies governance process.
Expert#7	My colleagues did not feel that we would use it often enough for them to maintain their skills. Therefore the luminal gastroenterologists have opted not to use this then the hepatologists insert it the following day if required.

Expert#8	Only kick back would be initial procurement costs. As well as a lack of robust UK clinical data

18. Are you aware of any further evidence for the technology that is not included in this briefing?

Expert #1	No
Expert #2	None
Expert #3	No
Expert #4	No
Expert #5	I am not aware of any other evidence at this time.
Expert#6	No
Expert#7	No
Expert#8	To the best or my knowledge, there are a high number of studies available, with a small patient sampling and retrospective. NICE endorsement would increase DANIS endorsement and increase research yield

19. Are you aware of any further ongoing research or locally collected data (e.g. audit) on this technology? Please indicate if you would be able/willing to share this data with NICE. Any information you provide will be considered in confidence within the NICE process and will not be shared or published.

Expert #1	No
Expert #2	None
Expert #3	Not aware

Expert #4	No
Expert #5	I am not aware of any other research or data at this time.
Expert#6	I am not aware of any such research, audit , data collection.
Expert#7	I am currently auditing our local data which I would be happy to share.
Expert#8	Non – currently from the contact I have with other centres

20. Is there any research that you feel would be needed to address uncertainties in the evidence base?

Expert #1	No
Expert #2	I think we need a national registry for the use of the Danis stent and all complications need to be recorded. I think that a randomised controlled trial comparing the Danis stent to balloon tamponade may need to be considered
Expert #3	A RCT with balloon tamponade being the comparator and larger sample size with focus on cost-effectiveness and safety would be helpful.
Expert #4	It would be useful to audit its use and obtain real world data in the UK on a large scale.
Expert #5	More data on the prevalence of the requirement for using balloon tamponade and refractory severe variceal bleeding. The effect of the Danis stent on complications, hospital stay, critical care use and overall costs.
Expert#6	I suppose given the risk and varying provision of endoscopic variceal competencies – Stent v Variceal banding in patients in whom primary TIPS is considered appropriate. Stent v banding in patients were assessment is thought to be appropriate and avoid the potential risks of endoscopy inc aspiration etc.
Expert#7	No

Expert#8	There should be a RCT in the UK between DANIS and balloon tamponade. However, the numbers are low currently leading to RCT recruitment issues, or a UK or Europe registry as in the Acute setting a RCT could be difficult.

NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log

MT450 Danis Stent

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
X.	*XX/XX/XXXX*	*Who was contacted? (if an expert, include clinical area of expertise)* *Why were they contacted? (keep this brief)*	*Insert question here. If multiple questions, please break these down and enter them as new rows*	*Only include significant correspondence and attach additional documents/graphics/tables in Appendix 1, citing question number*
	24/04/20	**Manufacturer** Initial questions	1) The IFU states that it is for the Danis Procedure Pack – Basic. The Urgent Field Safety	No difference, just an irregularity in the MHRA reporting. (This was a labelling issue)

			Notice included in the submission also mentions the Danis Procedure Pack i.e. not basic. What is the difference between the 2 packs? 2) MIB185 includes one study not included in the submission (Dechene 2012). This case series mentions the Danis Stent: Ella CS as the intervention. Is this a different technology to the SX-Ella Stent Danis? If not, why is this study not considered relevant to the decision problem?	This study did not meet the eligibility criteria for the systematic review which required studies to have included 10 or more patients. As Dechene 2012 studied 8 patients, this study was not eligible for inclusion in the systematic review.
			3) The IFU states that the Danis Stent can be used as an alternative to early TIPS although none of the studies include early TIPS as a comparator. Are we correct in assuming that the company do not consider early TIPS to	The confusion here is the definition between 'early' and 'salvage/emergency' TIPS. Danis is actually a bridge to early TIPS whereas salvage/emergency TIPS would be considered as a comparator.

			be relevant to the decision problem?	
			4) What may affect the frequency of training and re-training? What is the average frequency and average training time per session?	Hospital clinical team availability. UK Medical provide regular training in accordance with hospital specified frequencies.
			5) Are all components of the procedure pack single-use?	Yes.
			6) Can the packs/stents expire if not used? The letter to distributors regarding the Urgent Field Safety Notice mentions Unexpired Danis Stents. Do the packs require particular storage conditions?	Danis carries a standard 3 year shelf life from manufacture. It is possible for an unused stent to expire, although extremely unlikely if adequate training has been carried out. No specific storage requirements.

			7) We note that the CE mark authorisation in the submission is dated as 12/10/2005 but that the current version was launched in April 2016. The certificate submitted is dated from the 29/06/2017. Several included studies were published prior to 2016. What are the differences in the technology between the first CE mark and the current version?	The product delivery system has undergone some very minor changes in order to simplify stent deployment, but the stent has remained the same. Happy to discuss on the call.
			8) The claimed benefits table in section 2 of the submission includes several outcomes from Escorsell 2016 that are listed as system benefits, such as 'absence of continued or further bleeding' and 'Mortality'. As these are not included in the patient benefit section, is the inference that because the difference	UK Medical it is unclear which section this information is missing from as the 15 day time point data is summarised in Section 8 of the submission and a reason given for the lack of statistically significant difference at 6 weeks. Agree that this needs to be clarified on the call.

			in the groups was not statistically different at 6 weeks (rather than at 15 days) that these benefits are seen only by the system in the long run?	
			9) The maximum time the stent can stay in place is 7 days. What is the variation in the time that the stent will stay in place and what factors may affect this? a. Escorsell 2016 reports that the days with the device in place ranged from 0-12. What are the safety risks of keeping the device in place for more than 7 days?	There is some variance depending on the patient's condition at the time of presenting with an acute bleed. Some patients may require more than 7 days in order to become stable enough for successful TIPS. Happy to discuss further on the call on 28th. Minimal risk and the stent is not likely to become embedded in the mucosa for several weeks. Happy to share anecdotal evidence in the call.

			10) If the stent dislocates, what is the process for dealing with this? Is the stent removed and a new one inserted?	Studies show a high rate of haemostasis even when the stent dislocates/migrates. The stent is usually removed after TIPS has been performed, in order to minimise the risk of re-bleed during the removal process.
			11) Escorsell 2016 reported that the 2 treatment arms were different in terms of patient age and gender. Are you aware of whether the randomisation algorithm took these factors into account?	UK Medical these details are not reported in the publication. Could you ask the study authors for this information?
			12) What is the likely amount of time between the removal of the stent and performance of TIPS? a. Do all patients proceed to have TIPS following the use of Danis Stent?	The vast majority of patients will have TIPS as the only option as an exit plan/definitive treatment. Average time between Danis placement and TIPS is between 7 & 14 days, although we are aware of this TIPS taking place after 4 weeks, with subsequent Danis extraction without any difficulties.

	12/05/20	**Manufacturer** Further questions	1) The clinical submission states cost benefits include 'reduced costs associated with hospital stay in ITU or HDU' – this is not included in the economic submission – why is this?	This is covered in the micro-costings.
			2) Aside from the Escorsell (2016) trial, are the company aware of other evidence to support a decision that the definitive treatment is linked to bridging treatment?	This something we would be interested in seeing in the future, but feel NICE guidance around technology adoption is essential in order to drive numbers, thus increasing patient recruitment opportunities.
			3) Was a PSA undertaken for scenario 2? If so, can this be shared.	PSA wasn't originally run for this scenario but we have since run this. This version of the model (attached) has been updated for scenario 2 inputs and the PSA has been re-run.
	15/05/20	**Manufacturer** Further question	1) Please could you clarify the source for the following cost: Cost of severe hepatic encephalopathy: £401	The annual cost of Rifixamin + lactulose (£3,481) was taken from this NICE costing template - this cost was divided by 52 to get a weekly cost and then multiplied by 6 to get a 6-week cost to apply in the model.

	16/06/20	**Manufacturer** Further questions	1) We have noticed that there are no reported adverse events on the FDA Maude database (as is recorded in your submission). Given that there are adverse events reported in each of the included studies, we wondered if the product is not in use in the USA or may be sold under another name. Is this the case?	We are not aware of any adverse incidents in the UK. I have forwarded to Ella for further comment as we are not involved with US activity.
			2) We requested more information on the changes made to the technology over time in our initial call. Do you have that information?	Awaiting response from Ella
			3) Would you be able to provide us some information about the current usage of Danis within the NHS? The MIB states that the technology is currently being used by over 20	In the last 12 months 37 trusts have purchased Danis.

			NHS centres – is this still the case?	
	12/06/20	**Expert – Dr Deepak Joshi (Consultant Hepatologist)** Initial questions	1) The scope document of NICE guideline CG141: Acute upper gastrointestinal bleeding in over 16s: management published in 2010, states the incidence of acute upper gastrointestinal bleeding in the UK ranges from 50-150 per 100,000 population per year – is this still an accurate estimate? a. What percentage of people with acute bleeding have endoscopic band ligation	There is new guidance from the BSG (British Society of Gastroenterology) in 2015 will provide better and more up to date information. Endoscopic band ligation therapy is for oesophageal variceal bleeding only.

			as definitive treatment?	
			2) The Danis Stent is intended to stay in place for up to 7 days (although the manufacturer estimates that it remains in place for an average of 10 days in the UK). What value does this extra time (when compared to a Balloon Tamponade) give in planning treatment/prophylaxis ? a. What is the likely variation in the time that the stent will stay in place and what	A Balloon tamponade device can only be left in situ inflated for a maximum of 24 hours before the balloon starts to cause complications. A Danis stent being able to stay in for up to 7 days allows clinicians to decide on further treatment including waking up the patient (if they are intubated). I think the 7-10 days allows the clinicians to assess further treatment options.

			factors may affect this?	
			3) The manufacturer of the Danis Stent considers it to be an alternative to Balloon Tamponade or emergency TIPS and as a bridge to early TIPS. What is the difference between early and emergency TIPS, particularly in terms of clinical outcomes like mortality?	In the context of acute bleeding, early and emergency TIPS will be the same thing.
			4) What other treatments/prophylaxis may be used alongside or following TIPS?	Addition of a beta blocker (if not contra-indicated), consideration for liver transplantation.

			5) Is there a standard grading system used for categorising the severity/size of oesophageal varices? We noticed that Escorsell et al. (2016) describes the size of oesophageal varices as small or large, for example, while other papers have used the Paquet grading system.	For simplicity, the grading should be small, medium or large.
			6) Escorsell et al. (2016) reported that control of bleeding using the Danis Stent was significantly (p=0.037) better than using balloon tamponade at 15 days but this difference was non-significant at 6 weeks. Are we correct to	Yes. Overall, these patients have severe liver disease.

			assume that survival at 6 weeks for this patient group is low and that the difference at 15 days supports the use of Danis Stent as an intermediate treatment?	
			7) The same study also noted that the study and control groups were imbalanced in terms of age and gender – how significant are these factors for clinical outcomes in people with chronic liver disease/oesophageal varices?	Ideally, patients would be managed for age and gender. However, clinically there should be no difference in the management of their varices in terms of gender or age.

			8) Would you expect the choice of definitive treatment and subsequent longer term outcomes, to be related to the choice of bridging treatment? (Escorsell 2016 indicated trend towards TIPS used as the definitive treatment less frequently in patients who had received the Danis stent (31%) compared to those patients who had received balloon tamponade (67%), p value reported is 0.12).	No.
			9) Is it acceptable to generalise evidence to the UK from the Spanish study	No. The health care system will be different to Spain and potentially so will be the availability of TIPS.

			population in Escorsell 2016?	
			10) What is an acceptable length of follow-up time for studies investigating outcomes after the placement of Danis stent?	The DANIS stent is a bridging therapy. I think long of follow up should be between 4 and 6 weeks.
			11) Are there differences between populations with alcohol-related liver disease and other chronic liver diseases, in terms of the likelihood of certain comorbidities or in terms of planning treatment such as TIPS?	No.

			12) Some studies, such as Muller et al. (2015) have reported stent dislocation rates of over 60% (albeit in small populations). Is this considered to be high for a device like this? a. What are the consequences of dislocation? b. Is there a defined difference between stent dislocation and migration or are these simply different terms for the same thing?	60% is too high especially if stent migration occur very early (within 24 hours of insertion). Lack of tamponade, need to re-insert a stent, stent migration into the small bowel and subsequent obstruction. I think they are describing the same thing.

			13) What would be the procedure if a Danis Stent was to dislocate? The company suggested that this would depend on the team performing the procedure. a. The company estimates the cost of stent migration by applying the reference cost of a *therapeutic endoscopic upper gastrointestinal tract procedure*. Is this appropriate e.g. the appropriate response to	If the stent migrates, the attending team need to decide whether they need to remove it endoscopically or not.

			stent migration?	
			14) How soon do you think TIPS is likely to be performed after a Danis Stent is placed?	If a TIPS is appropriate then within 24-72 hours depending on the clinical urgency and availability of TIPS.
			15) Are there other plausible definitive treatments in the UK that should be considered beyond TIPs and band ligation (the 7 case series included in the systematic review note other treatments such as sclerotherapy or transplant)?	Sclerotherapy is no longer used for oesophageal varices in Adults. Transplant is an option for some patients but not in the context of acute bleeding. Therefore, band ligation or TIPS are required in the short term.

			16) Is it plausible that severe Hepatic Encephalopathy occurs during bridging treatment phase i.e. ahead of definitive treatment?	Yes, HE can occur.
			17) Is it likely that there would be a learning curve for this technology and would this effect the likelihood of severe adverse events beyond stent migration?	Yes. All operators would need training.
			18) Is it right to assume that Ella extractor would not be needed to remove the stent if the patient was undergoing TIPS? a. Would you expect to use	No. The stent would still need to be removed. No. Use of the ELLA extractor requires a an OGD.

			Ella extractor to reposition device where there has been stent migration? b. If so, would this be used alongside therapeutic endoscopic upper gastrointestinal tract procedure?	
			19) The 2016 NICE impact report infers that cost of re-bleeding is covered by the following HRG codes: 2016/17 HRG codes GB02A, GBO2B, GB02C for: a. Major Endoscopic or Percutaneous,	No. The 2018/19 HRG codes are for a different therapeutic procedure.

			Hepatobiliary or Pancreatic Procedures, with Major CC b. Major Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, with Intermediate CC c. Major Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, without CC These codes are now out of date. **Do the following 2018/19 HRG codes describe the same procedures/are they equivalent?** 2018/19 HRG codes GB05F, GB05G, GB05H for: a. Major Therapeutic Endoscopic	

			Retrograde Cholangiopancreatography with CC Score 5+ b. Major Therapeutic Endoscopic Retrograde Cholangiopancreatography with CC Score 2-4 c. Major Therapeutic Endoscopic Retrograde Cholangiopancreatography with CC Score 0-1	
			20) There are two reference costs available for elective TIPS: a. YR16B Transjugular Intrahepatic Creation of Portosystemic	I don't know what the CC score relates to. Does it relate to co-morbidities of the patient?

			Shunt with CC Score 0-5 b. YR16A Transjugular Intrahepatic Creation of Portosystemic Shunt with CC Score 6+ **Do you have a view on whether it is more appropriate to use the lower or higher complication (CC) score (or an average of both)?**	
	17/06/20	**Expert – Dr Deepak Joshi (Consultant Hepatologist)** Further questions	1) Do you have any more information about how the pathway in Spain differs from the pathway in the UK, i.e. a. Is bridging treatment used prior to definitive treatment? b. Are the rates of TIPS comparable?	I'm not sure of the exact pathways in Spain. However, the Danis stent is a bridging therapy. Tips availability is very different and would be different in Spain. The Barcelona group that previously published the RCT on TIPS in 2010 in the NEJM are very PRO-Tipss.

			2) You mentioned you were unsure about what the CC score referred to; this does relate to the patient comorbidities. Following up on that: there are four reference costs available for elective Band Ligation: 3) FE11A Endoscopic, Sclerotherapy or Rubber Band Ligation, of Lesion of Upper Gastrointestinal Tract, with CC Score 9+ FE11B Endoscopic, Sclerotherapy or Rubber Band Ligation, of Lesion of Upper Gastrointestinal Tract, with CC Score 6-8 FE11C Endoscopic, Sclerotherapy or Rubber Band Ligation, of Lesion of Upper Gastrointestinal Tract, with CC Score 3-5 FE11D Endoscopic, Sclerotherapy or Rubber Band Ligation, of Lesion of Upper	Regarding the CC score, I'm sure it would be 11A or 11B. I would need to see the break down between the different groups to see what differentiates the groups.

			Gastrointestinal Tract, with CC Score 0-2 **Do you have a view on which complication (CC) score is most appropriate for these patients?**	
	12/06/20	**Expert – Dr Dhirag Tripathi (Consultant Hepatologist)** Initial questions	1) The scope document of NICE guideline CG141: Acute upper gastrointestinal bleeding in over 16s: management published in 2010, states the incidence of acute upper gastrointestinal bleeding in the UK ranges from 50-150 per 100,000 population per year – is this still an accurate estimate? a. What percentage of people with acute bleeding	Yes. If it is acute oesophageal variceal bleeding then endoscopic band ligation is first line treatment. So all patients where banding is feasible will have this therapy.

			have endoscopic band ligation as definitive treatment?	
			2) The Danis Stent is intended to stay in place for up to 7 days (although the manufacturer estimates that it remains in place for an average of 10 days in the UK). What value does this extra time (when compared to a Balloon Tamponade) give in planning treatment/prophylaxis? a. What is the likely variation in the time that the stent will stay in place	The extra time (provided the Danis stent is effective in controlling bleeding) allows more time for the patient's underlying liver function to improve prior to considering definitive therapies such as TIPS in selected cases. All depends on whether a decision has been made for other therapies. An example is urgent TIPS. The stent may only be in place for 2-3 days while an urgent TIPS is arranged. However, other treatment options include endoscopic therapy and here the clinician may wish to leave the stent in a bit longer before removing it.

			and what factors may affect this?	
			3) The manufacturer of the Danis Stent considers it to be an alternative to Balloon Tamponade or emergency TIPS and as a bridge to early TIPS. What is the difference between early and emergency TIPS, particularly in terms of clinical outcomes like mortality?	Emergency TIPS (also referred to as “salvage” TIPS) is where a decision for TIPS has been made *after* treatment failure i.e. endoscopic and drug therapy has failed to control bleeding. This is the situation with a patient that has a Danis stent already in place prior to decision on TIPS. Early TIPS (sometimes referred to as pre-emptive TIPS) is where a decision for TIPS has been made *before* treatment failure i.e. there is control of bleeding and patient is haemodynamically stable. The aim of early TIPS is to prevent further bleeding with the aim of improving patient survival.
			4) What other treatments/prophylaxis may be used alongside or following TIPS?	Endoscopic and drug therapy (terlipressin or octreotide) pre and during TIPS with resuscitation. After successful TIPS the drugs are weaned off and patient should not need any more endoscopic therapy or drug therapy for preventing variceal bleeding.

			5) Is there a standard grading system used for categorising the severity/size of oesophageal varices? We noticed that Escorsell et al. (2016) describes the size of oesophageal varices as small or large, for example, while other papers have used the Paquet grading system.	In UK we use the grading system as per the UK guidelines on variceal bleeding (Grades I to III). Red signs can be present on any size of varix and imply increased risk of bleeding. See also figure 1 of: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4680175/pdf/gutjnl-2015-309262.pdf
			6) Escorsell et al. (2016) reported that control of bleeding using the Danis Stent was significantly (p=0.037) better than using balloon tamponade at 15 days but this difference was non-significant at 6 weeks. Are we correct to	These patients are in the severe spectrum of variceal bleeding and it is highly unlikely any therapy will improve survival. Bleeding control and buying time for definite therapy is the aim.

			assume that survival at 6 weeks for this patient group is low and that the difference at 15 days supports the use of Danis Stent as an intermediate treatment?	
			7) The same study also noted that the study and control groups were imbalanced in terms of age and gender – how significant are these factors for clinical outcomes in people with chronic liver disease/oesophageal varices?	Recent UK study did not show that these factors influenced clinical outcomes in salvage TIPS: https://pubmed.ncbi.nlm.nih.gov/30560334/

			8) Would you expect the choice of definitive treatment and subsequent longer term outcomes, to be related to the choice of bridging treatment? (Escorsell 2016 indicated trend towards TIPS used as the definitive treatment less frequently in patients who had received the Danis stent (31%) compared to those patients who had received balloon tamponade (67%), p value reported is 0.12).	In this patient cohort I would think that emergency TIPS is unlikely to lead to good long term outcomes and in many patients liver transplantation is the best option.
			9) Is it acceptable to generalise evidence to the UK from the Spanish study	I think so.

			population in Escorsell 2016?	
			10) What is an acceptable length of follow-up time for studies investigating outcomes after the placement of Danis stent?	Minimum of 6 weeks.
			11) Are there differences between populations with alcohol-related liver disease and other chronic liver diseases, in terms of the likelihood of certain comorbidities or in terms of planning treatment such as TIPS?	Aetiology does not seem to influence outcomes. However, TIPS is generally avoided in severe hepatic encephalopathy, severe pulmonary hypertension, and severe heart failure. See also: https://gut.bmj.com/content/gutjnl/early/2020/02/28/gutjnl-2019-320221.full.pdf

			12) Some studies, such as Muller et al. (2015) have reported stent dislocation rates of over 60% (albeit in small populations). Is this considered to be high for a device like this? a. What are the consequences of dislocation? b. Is there a defined difference between stent dislocation and migration or are these simply different terms for the same thing?	Yes, it is now normally lower now due to greater experience. Failure to control bleeding. Damage to mucosa or perforation. Obstruction. Aspiration. I think migration is a better term. Both have similar meaning.

			13) What would be the procedure if a Danis Stent was to dislocate? The company suggested that this would depend on the team performing the procedure. a. The company estimates the cost of stent migration by applying the reference cost of a *therapeutic endoscopic upper gastrointestinal tract procedure*. Is this appropriate e.g. the appropriate response to	Stent could cause obstruction and may need removal. If there is only slight migration it may still be effective or need minor repositioning. Yes mostly. But if removal was complicated and require radiological guidance then costs would increase.

			stent migration?	
			14) How soon do you think TIPS is likely to be performed after a Danis Stent is placed?	Depends on urgency. A clinical call really. Also depends on TIPS logistics, in particular if a patient needs to be transferred to another hospital for TIPS. So between 1-7 days.
			15) Are there other plausible definitive treatments in the UK that should be considered beyond TIPs and band ligation (the 7 case series included in the systematic review note other treatments such as sclerotherapy or transplant)?	See above regarding transplant which must always be considered an option is selected patients with decompensated liver disease. In some patients a surgical shunt is an option but this is normally too high risk in advanced cirrhosis. Sclerotherapy is not as effective as band ligation. If a decision was made to pursue endoscopic therapy then normally this would be combined with a non-selective beta-blocker such as propranolol or carvedilol as secondary prophylaxis.

			16) Is it plausible that severe Hepatic Encephalopathy occurs during bridging treatment phase i.e. ahead of definitive treatment?	Yes. HE can occur secondary to GI bleeding and build-up of toxins that the liver is not clearing well.
			17) Is it likely that there would be a learning curve for this technology and would this effect the likelihood of severe adverse events beyond stent migration?	Yes. With experience better placement is likely to result. The procedure may also take less time reducing the risk of aspiration.
			18) Is it right to assume that Ella extractor would not be needed to remove the stent if the patient was undergoing TIPS? a. Would you expect to use	No the stent needs to be removed after TIPS. Possibly. Do not have personal experience. May be necessary if there is bleeding.

			Ella extractor to reposition device where there has been stent migration? b. If so, would this be used alongside therapeutic endoscopic upper gastrointestinal tract procedure?	
			The 2016 NICE impact report infers that cost of re-bleeding is covered by the following HRG codes: 2016/17 HRG codes GB02A, GBO2B, GB02C for: d. Major Endoscopic or Percutaneous, Hepatobiliary or Pancreatic	No these codes refer to ERCP only.

			Procedures, with Major CC e. Major Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, with Intermediate CC f. Major Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, without CC These codes are now out of date. **Do the following 2018/19 HRG codes describe the same procedures/are they equivalent?** 2018/19 HRG codes GB05F, GB05G, GB05H for: d. Major Therapeutic Endoscopic Retrograde Cholangiopancreatog	

			raphy with CC Score 5+ e. Major Therapeutic Endoscopic Retrograde Cholangiopancreatography with CC Score 2-4 f. Major Therapeutic Endoscopic Retrograde Cholangiopancreatography with CC Score 0-1	
			19) There are two reference costs available for elective TIPS: c. YR16B Transjugular Intrahepatic Creation of Portosystemic Shunt with CC Score 0-5	Elective TIPS coding would not be appropriate for patients who have a Danis stent. It would need to be emergency TIPS.

			d. YR16A Transjugular Intrahepatic Creation of Portosystemic Shunt with CC Score 6+ **Do you have a view on whether it is more appropriate to use the lower or higher complication (CC) score (or an average of both)?**	
	17/06/20	**Expert – Dr Dhirag Tripathi (Consultant Hepatologist)** Further questions	1) Do you have any more information about how the pathway in Spain differs from the pathway in the UK, i.e. a. Is bridging treatment used prior to definitive treatment? b. Are the rates of TIPS comparable?	Yes, I would expect the same pathways. Yes.
			2) You mentioned you were unsure about what the CC score referred to; this does relate to the patient	As banding would be emergency I would rate as 6-8.

			comorbidities. Following up on that: there are four reference costs available for elective Band Ligation: FE11A Endoscopic, Sclerotherapy or Rubber Band Ligation, of Lesion of Upper Gastrointestinal Tract, with CC Score 9+ FE11B Endoscopic, Sclerotherapy or Rubber Band Ligation, of Lesion of Upper Gastrointestinal Tract, with CC Score 6-8 FE11C Endoscopic, Sclerotherapy or Rubber Band Ligation, of Lesion of Upper Gastrointestinal Tract, with CC Score 3-5 FE11D Endoscopic, Sclerotherapy or Rubber Band Ligation, of Lesion of Upper Gastrointestinal Tract, with CC Score 0-2 **Do you have a view on which complication (CC) score is**	

			most appropriate for these patients?	
	12/06/20	**Expert – Dr Emmanuel Tsochatzis (Associate Professor and Honorary Consultant in Hepatology)** Initial questions	1) The scope document of NICE guideline CG141: Acute upper gastrointestinal bleeding in over 16s: management published in 2010, states the incidence of acute upper gastrointestinal bleeding in the UK ranges from 50-150 per 100,000 population per year – is this still an accurate estimate? b. What percentage of people with acute bleeding have endoscopic band ligation	Yes. Approximately 10% of admission with acute UGI bleeding.

			as definitive treatment?	
			2) The Danis Stent is intended to stay in place for up to 7 days (although the manufacturer estimates that it remains in place for an average of 10 days in the UK). What value does this extra time (when compared to a Balloon Tamponade) give in planning treatment/prophylaxis ? a. What is the likely variation in the time that the stent will stay in place and what	Crucial – balloon tamponade can stay for 24 hours maximum, and this timeframe is not enough in certain cases to allow the transfer of patients to a centre that performs TIPPS and also the performance of TIPSS (due to ITU bed shortage or a 24 hour TIPPS service). The stent will stay most of the times until a TIPSS is performed, so it can be for up to 5 days. Rarely it will be used as a definitive treatment so might stay for the full 7-10 days.

			factors may affect this?	
			3) The manufacturer of the Danis Stent considers it to be an alternative to Balloon Tamponade or emergency TIPS and as a bridge to early TIPS. What is the difference between early and emergency TIPS, particularly in terms of clinical outcomes like mortality?	Emergency TIPSS – refractory variceal bleeding, associated with higher mortality. Early TIPPS – treatment of variceal bleeding for selected patients with Child Pugh C cirrhosis, not widely adopted practice in the UK for various reasons.
			4) What other treatments/prophylaxis may be used alongside or following TIPS?	Not much else in refractory bleeding.

			5) Is there a standard grading system used for categorising the severity/size of oesophageal varices? We noticed that Escorsell et al. (2016) describes the size of oesophageal varices as small or large, for example, while other papers have used the Paquet grading system.	Numerous debates over the years on this issue, Severity/size of varices not important however in the setting of an acute variceal bleeding.
			6) Escorsell et al. (2016) reported that control of bleeding using the Danis Stent was significantly (p=0.037) better than using balloon tamponade at 15 days but this difference was non-significant at 6 weeks. Are we correct to	Correct- the Danis stent will be used as bridge treatment and will allow the safe transfer of a patient and organization of a TIPPS procedure.

			assume that survival at 6 weeks for this patient group is low and that the difference at 15 days supports the use of Danis Stent as an intermediate treatment?	
			7) The same study also noted that the study and control groups were imbalanced in terms of age and gender – how significant are these factors for clinical outcomes in people with chronic liver disease/oesophageal varices?	Not very significant.

			8) Would you expect the choice of definitive treatment and subsequent longer term outcomes, to be related to the choice of bridging treatment? (Escorsell 2016 indicated trend towards TIPS used as the definitive treatment less frequently in patients who had received the Danis stent (31%) compared to those patients who had received balloon tamponade (67%), p value reported is 0.12).	Probably – sometime it is also a case of the patient having the chance to receive a definitive treatment.
			9) Is it acceptable to generalise evidence to the UK from the Spanish study	It is a small study – this would be the main limiting factor rather than the country of origin (still a European country with similar management standards).

			population in Escorsell 2016?	
			10) What is an acceptable length of follow-up time for studies investigating outcomes after the placement of Danis stent?	6-week re-bleeding and mortality. 1 year mortality.
			11) Are there differences between populations with alcohol-related liver disease and other chronic liver diseases, in terms of the likelihood of certain comorbidities or in terms of planning treatment such as TIPS?	Patients with NASH might have higher burden of cardiovascular comorbidities and thus anaesthetic risk.

			12) Some studies, such as Muller et al. (2015) have reported stent dislocation rates of over 60% (albeit in small populations). Is this considered to be high for a device like this? a. What are the consequences of dislocation? b. Is there a defined difference between stent dislocation and migration or are these simply different terms for the same thing?	I think this also relies on the operator expertise and would be substantially lower with experienced operators. Patients will require a new stent Different terms for same thing.

			13) What would be the procedure if a Danis Stent was to dislocate? The company suggested that this would depend on the team performing the procedure. a. The company estimates the cost of stent migration by applying the reference cost of a *therapeutic endoscopic upper gastrointestinal tract procedure*. Is this appropriate e.g. the appropriate response to	Upper GI endoscopy. Yes appropriate, but also depends if the patient will require repositioning of the stent and if yes if a new stent will be required.

			stent migration?	
			14) How soon do you think TIPS is likely to be performed after a Danis Stent is placed?	3-5 days.
			15) Are there other plausible definitive treatments in the UK that should be considered beyond TIPs and band ligation (the 7 case series included in the systematic review note other treatments such as sclerotherapy or transplant)?	No. Sclerotherapy abandoned as a procedure. Transplant very unlikely in such an acute setting without control of bleeding first.

			16) Is it plausible that severe Hepatic Encephalopathy occurs during bridging treatment phase i.e. ahead of definitive treatment?	Sometime yes but resolves with control of bleeding.
			17) Is it likely that there would be a learning curve for this technology and would this effect the likelihood of severe adverse events beyond stent migration?	Defintiely yes.
			18) Is it right to assume that Ella extractor would not be needed to remove the stent if the patient was undergoing TIPS? a. Would you expect to use	Yes. Yes. Yes.

			Ella extractor to reposition device where there has been stent migration? b. If so, would this be used alongside therapeutic endoscopic upper gastrointestinal tract procedure?	
			19) The 2016 NICE impact report infers that cost of re-bleeding is covered by the following HRG codes: 2016/17 HRG codes GB02A, GBO2B, GB02C for: g. Major Endoscopic or Percutaneous,	They seem so but I have no experience with coding.

			Hepatobiliary or Pancreatic Procedures, with Major CC h. Major Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, with Intermediate CC i. Major Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, without CC These codes are now out of date. **Do the following 2018/19 HRG codes describe the same procedures/are they equivalent?** 2018/19 HRG codes GB05F, GB05G, GB05H for: g. Major Therapeutic Endoscopic	

			Retrograde Cholangiopancreatography with CC Score 5+ h. Major Therapeutic Endoscopic Retrograde Cholangiopancreatography with CC Score 2-4 i. Major Therapeutic Endoscopic Retrograde Cholangiopancreatography with CC Score 0-1	
			20) There are two reference costs available for elective TIPS: e. YR16B Transjugular Intrahepatic Creation of Portosystemic	Not sure how the CC score is computed.

			Shunt with CC Score 0-5 f. YR16A Transjugular Intrahepatic Creation of Portosystemic Shunt with CC Score 6+ **Do you have a view on whether it is more appropriate to use the lower or higher complication (CC) score (or an average of both)?**	
	12/06/20	**Expert – Dr Ian Beales (Consultant Gastro-enterologist)** Initial questions	1) The scope document of NICE guideline CG141: Acute upper gastrointestinal bleeding in over 16s: management published in 2010, states the incidence of acute upper gastrointestinal bleeding in the UK ranges from 50-150	Yes this is still an accurate estimate overall for upper GI bleeding. Oesophageal variceal bleeding accounts for about 10-15% of all cases of acute upper GI bleeding overall. These would have oesophageal band ligation as definitive treatment. With 2 sessions of band treatment successful haemostasis can be expected in ~80-85% of cases of oesophageal variceal haemorrhage

			per 100,000 population per year – is this still an accurate estimate? c. What percentage of people with acute bleeding have endoscopic band ligation as definitive treatment?	
			2) The Danis Stent is intended to stay in place for up to 7 days (although the manufacturer estimates that it remains in place for an average of 10 days in the UK). What value does this extra time (when compared to a Balloon Tamponade) give in	The main advantage of the Danis stent over balloon tamponade is the safety issue. By not compromising swallowing, the airway is safer with the Danis stent and patients do not necessarily need critical care. However ballon tamponade can only be for a maximum of 24 hours and the extra time in situ of a Danis stent is definitely beneficial. Most, if not all of these patients with severe refractory bleeding will require transfer to a unit that can perform, or organisation of a TIPSS procedure. It is often impossible to arrange this within the 24 hours granted by balloon tamponade. The exta days granted by the Danis stent allow more time to be usefully spent is arranging TIPPS and optimising the patient. This will be determined by the response of the patient to resuscitation if further ligation is being used, but more likely by the availability of transfer to or organisation of a more definitive procedure usually TIPSS less often liver

			planning treatment/prophylaxis ? a. What is the likely variation in the time that the stent will stay in place and what factors may affect this?	transplant. I would estimate most Danis stents would be in place for 3-7 days.
			3) The manufacturer of the Danis Stent considers it to be an alternative to Balloon Tamponade or emergency TIPS and as a bridge to early TIPS. What is the difference between early and emergency TIPS, particularly in terms of clinical outcomes like mortality?	TIPSS is a very effective treatment for acute variceal bleeding. It is the most effective way of reducing potal pressure, hence it reliably stops variceal bleeding. The issue with emergency TIPSS is availability. This is only available in limited centres with the full interventional radiology support and at the time of refractory bleeding in the ward or endoscopy unit, it is almost certain that emergency TIPSS will not be available immediately as a life saving procedure, needed then and there to arrest bleeding. The Danis stent is available immediately in the endoscopy room or ward (if trained personel are available). This enables stabilisation of the patient until an early TIPSS perhaps in 48-72 hours. There are no studies looking at the outcomes of Emergency TIPSS, it is rarely performed for logistic reasons and only then in patients that are exanguinating

			4) What other treatments/prophylaxis may be used alongside or following TIPS?	No additional treatments are required with TIPSS. Because TIPSS reduces portal pressure so effectively no additional therapy directed against the varices is required.
			5) Is there a standard grading system used for categorising the severity/size of oesophageal varices? We noticed that Escorsell et al. (2016) describes the size of oesophageal varices as small or large, for example, while other papers have used the Paquet grading system.	The most functional grading system for oesophageal varices is small or large as described by the Baveno group/EASL. This differentiation is reliable and consistent amongst operators (small ones flatten out during insufflation during endoscopy, large one do not). This is the recommended grading system in Europe including the UK and that recommended b the UK endoscopy training group. Additional details can be added to the small or large including stigmata or recent haemorrhage, red-whales sign, fibrin plugs.

			6) Escorsell et al. (2016) reported that control of bleeding using the Danis Stent was significantly (p=0.037) better than using balloon tamponade at 15 days but this difference was non-significant at 6 weeks. Are we correct to assume that survival at 6 weeks for this patient group is low and that the difference at 15 days supports the use of Danis Stent as an intermediate treatment?	The mortality in this group with refractory bleeding is high ~ 50% at 6 weeks. This small study was clearly underpowered to examine mortality and it is difficult to draw conclusions about this. However early secure and safe haemostasis with a Danis stent certainly improves intermediate outcomes. Larger and longer term data are lacking in terms of mortality.
			7) The same study also noted that the study and control groups were imbalanced in terms of age and	Gender is probably not that important. Age somewhat so, old patients have higher mortality. However the overriding prognostic factor in variceal bleeding is the severity of the underlying liver disease, Whether assessed by Child Pugh score or another system.

			gender – how significant are these factors for clinical outcomes in people with chronic liver disease/oesophageal varices?	
			8) Would you expect the choice of definitive treatment and subsequent longer term outcomes, to be related to the choice of bridging treatment? (Escorsell 2016 indicated trend towards TIPS used as the definitive treatment less frequently in patients who had received the Danis stent (31%) compared to those patients who had received balloon	The definitive treatment after either balloon tamponade or Danis stent is probably TIPSS in either case. Some patients will never be candidates for TIPSS because of anatomy or underlying liver disease. In those repeated ligation may be attempted after optimisation of the patients haemodynamics and the Danis stent is advantageous here, giving longer to optimise the resuscitation before attempting ligation again. Equally some patients with very severe initial haemorrhage may have had a Danis stent inserted allowing subsequent definitive ligation, in a more stable patient without respiratory compromise. So yes there is likely to be a reduced use of TIPSS after Danis stent but this is probably not an important outcome. The use of definitive TIPSS in the UK after either procedure is more likely driven by availability and geographic location.

			tamponade (67%), p value reported is 0.12).	
			9) Is it acceptable to generalise evidence to the UK from the Spanish study population in Escorsell 2016?	Yes it would seem reasonable to generalise here. The management of variceal bleeding is very similar in Spain to the UK and underlying everity and causes of liver diease are similar. Much of the other data we use to base our decisions on both acute GI bleeding and management of decompensated liver disease comes from Spain and there seems to be no suggestion these are not generalizable.
			10) What is an acceptable length of follow-up time for studies investigating outcomes after the placement of Danis stent?	If measuring cessation of bleeding 28 days would be the minimum. However really we would be much more interested in mortality and bleeding at 12 months, as in this recent trial of TIPSS timing. Not directly relevant to Danis stent but illustrates what the duration and end points should be Aliment Pharmacol Ther . 2020 Jul;52(1):98-106. doi: 10.1111/apt.15797. Epub 2020 May 2
			11) Are there differences between populations with alcohol-related liver disease and other chronic liver diseases, in terms of the likelihood of	The underlying cause of the liver disease is not a major determinant of planning TIPSS. The overriding factors are the severity of the underlying liver disease whatever the cause (which can contraindicate TIPS) and significant heart failure, which can also be a contraindication. Usually the underlying cause of the liver disease does not influence these decisions.

			certain comorbidities or in terms of planning treatment such as TIPS?	
			12) Some studies, such as Muller et al. (2015) have reported stent dislocation rates of over 60% (albeit in small populations). Is this considered to be high for a device like this? a. What are the consequences of dislocation? b. Is there a defined difference between stent dislocation and migration or are these simply different	This seems quite high, although the number are small in the studies. This is still less than the complication rate of balloon tamponade. The Danis stent needs to be removed in any case, whether it has slipped or not. Often nothing but rebleeding may occur if the varices are no longer tamponaded I have assumed dislocation actually means migration, or the whole stent moving either proximally or distally

			terms for the same thing?	
			13) What would be the procedure if a Danis Stent was to dislocate? The company suggested that this would depend on the team performing the procedure. a. The company estimates the cost of stent migration by applying the reference cost of a *therapeutic endoscopic upper gastrointestinal tract procedure*. Is this	In the UK, this would probably be dealt with by endoscopic removal. The skills to do this should be distributed widely enough for early elective removal in all units in the UK. I doubt radiological removal with endoscopy would be necessary in the UK, I think this was stated to cover those situations where the stent insertion and removal were non-endoscopic. Yes, this would be reasonable. Removing a migrated stent would be a therapeutic upper GI endoscopy equivalent to removing or re-stenting a migrated stent inserted for cancer or other therapeutic nedoscopy such as removal of a food bolus obstruction.

			appropriate e.g. the appropriate response to stent migration?	
			14) How soon do you think TIPS is likely to be performed after a Danis Stent is placed?	Within 3-7 days. TIPSS will not be as widely available as Danis stent. Patients will need to be transferred to another centre in most cases.
			15) Are there other plausible definitive treatments in the UK that should be considered beyond TIPs and band ligation (the 7 case series included in the systematic review note other treatments such as sclerotherapy or transplant)?	No. Sclerotherapy is regarded as less effective and appropriate than band ligation and should only be regarded as a salvage procedure of last resort. Liver transplantation is rarely perfomeed or available or appropriate in the setting of acute variceal bleeding. It is an excellent definitive long term treatment and the TIPSS may be an intermediate bridge to long term treatment by transplant. This only because a plausible outcome with very large numbers followed up for a long time. Many patients will not be suitable for transplantation. There are many more contraindications to transplantation than to TIPSS and very limited donor organs

			16) Is it plausible that severe Hepatic Encephalopathy occurs during bridging treatment phase i.e. ahead of definitive treatment?	There is no logical reason that encephalopathy should be any more common with Danis stent than balloon tamponade. Haemodynmically they have the same effect. Encephaloathy might be expected to be lower with Danis stent because of more secure hameostasis and reduced incidence of respiratory infections.
			17) Is it likely that there would be a learning curve for this technology and would this effect the likelihood of severe adverse events beyond stent migration?	Yes, there will always be a learning curve for new technology. However with appropriate training and given that the operators using the technology (endoscopists or interventional radiologists) are likely to already have well developed technical skills. The learning curve will be short and can be minimised further with focused training.
			18) Is it right to assume that Ella extractor would not be needed to remove the stent if the patient was undergoing TIPS? a. Would you expect to use	If TIPSS has been done, the Ella extractor would not be used Honestly I do not know enough about this situation. If the stent has migrated, probably it would just be removed endoscopically or with the Ella device, if it did require removal I have never had to deal with this situation. The manufacturer should be able to advise here, but I am sure it can be repositioned readily.

			Ella extractor to reposition device where there has been stent migration? b. If so, would this be used alongside therapeutic endoscopic upper gastrointestinal tract procedure?	This depends on where and how the stent is positioned after migration. Probably this would be either the Ella extractor or therapeutic endoscopy but depending on the actual position of the migrated stent it might not need any repositioning at all but if in a difficult position both therapeutic endoscopy and the Ella device may be needed
			19) The 2016 NICE impact report infers that cost of re-bleeding is covered by the following HRG codes: 2016/17 HRG codes GB02A, GBO2B, GB02C for: j. Major Endoscopic or Percutaneous,	The new codes you have listed are inappropriate. The codes you have given are for endoscopic procedures in the biliary tree or pancreas. There must be codes for major oesophageal, gastric or duodenal therapeutic procedures. I would imagine the Danis stent is coded something similar to insertion of an oesophageal stent in a cancer patient, that is the nearest approximation, or else something related to major bleeding and treatment there off. I am not familiar with the latests codes so cannot tell you the exact one.

			Hepatobiliary or Pancreatic Procedures, with Major CC k. Major Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, with Intermediate CC l. Major Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, without CC These codes are now out of date. **Do the following 2018/19 HRG codes describe the same procedures/are they equivalent?** 2018/19 HRG codes GB05F, GB05G, GB05H for: j. Major Therapeutic Endoscopic	

			Retrograde Cholangiopancreatography with CC Score 5+ k. Major Therapeutic Endoscopic Retrograde Cholangiopancreatography with CC Score 2-4 l. Major Therapeutic Endoscopic Retrograde Cholangiopancreatography with CC Score 0-1	
			20) There are two reference costs available for elective TIPS: g. YR16B Transjugular Intrahepatic Creation of Portosystemic	The higher score. These are very ill patients with significant comorbidity. I am sure the higher score is more likely to be accurate

			Shunt with CC Score 0-5 h. YR16A Transjugular Intrahepatic Creation of Portosystemic Shunt with CC Score 6+ **Do you have a view on whether it is more appropriate to use the lower or higher complication (CC) score (or an average of both)?**	
	29/04/20	**Expert – Dr Jason Dunn (Consultant Gastro-enterologist)** Initial questions	1) The Danis Stent is intended to stay in place for up to 7 days (although the manufacturer estimates that it remains in place for an average of 10 days in the UK). What value does this extra time (when compared to a Balloon Tamponade) give in planning treatment/prophylaxis?	May be between 7-14 days - dependent on the Unit and whether a secondary or tertiary referral centre, as definitive treatment with TIPS is not available in most DGH. Patient may improve with medical optimisation (e.g access for Nutritional optimisation - patients with EVB 2 to cirrhosis are often malnourished, and the Danis stent allows enteral feeding either via NG/J tube or orally), hence if improving this may prolong time to stent removal.

			1.1. What is the likely variation in the time that the stent will stay in place and what factors may affect this?	
			2) The manufacturer of the Danis Stent considers it to be an alternative to Balloon Tamponade or emergency TIPS and as a bridge to early TIPS. What is the difference between early and emergency TIPS, particularly in terms of clinical outcomes like mortality?	In some studies early (preventive) TIPS has been defined by placement within 3 days of hospitalization for acute variceal bleeding after one session of endoscopic therapy, whereas emergency (rescue) TIPS was defined as TIPS implantation after two endoscopic interventions for variceal bleeding. A study by Njei *et al.* compared outcomes in patients with variceal bleeding not receiving a TIPS with those receiving rescue or early TIPS (1). On multivariate analysis adjusted for age, ethnicity, sex, comorbidities, and severity of liver disease, early TIPS showed decreased inpatient mortality (1.5%) when compared to no TIPS (5.6%, P<0.01) and rescue TIPS (8.1%, P<0.01). In addition, in-hospital rebleeding was significantly reduced by early TIPS (0.5%, P<0.01) when compared to no TIPS (15.4%, P<0.01) or rescue TIPS (2.2%, P<0.01), respectively, without a difference in the occurrence of hepatic encephalopathy.

			3) What other treatments/prophylaxis may be used alongside or following TIPS?	Patients often require a multidisciplinary, multimodal approach involving prompt diagnosis, pharmacologic therapy, and endoscopic intervention prior to or alongsideTIPS. Adjunctive embolization is carried out in 24-48% of patients, though it is not clear whether the combination of TIPS and variceal embolization is more effective than TIPS alone. Embolization of oesophageal varices is most commonly performed with the use of metallic coils, but the use of liquid agents such as opacified enbucrilate and ethanol have also been described
			4) Is there a standard grading system used for categorising the severity/size of oesophageal varices? We noticed that Escorsell et al. (2016) describes the size of oesophageal varices as small or large, for example, while other papers have used the Paquet grading system.	Different systems exist. In the UK we tend to use the BSG guidance (also known as Westaby classification) - Grade 1 (Varices appearing as slight protrusion above mucosa, which can be depressed with insufflations) Grade 2: Varices occupying <50% of the lumen Grade 3: Varices occupying >50% of the lumen and which are very close to each other with confluent appearance. The small or large grading is the Baveno system, which is also used commonly. Paquet system is seldom used.

			5) Escorsell et al. (2016) reported that control of bleeding using the Danis Stent was significantly (p=0.037) better than using balloon tamponade at 15 days but this difference was non-significant at 6 weeks. Are we correct to assume that survival at 6 weeks for this patient group is low and that the difference at 15 days supports the use of Danis Stent as an intermediate treatment?	Early mortality is defined as death within 6 weeks of intial bleeding episode, so is an important metric to assess efficacy of interventions for variceal bleeding. Although early studies reported mortality of 48% after first variceal haemorrhage (2), a more recent study demonstrate a dramatic reduction in mortality following variceal bleeding of 20% 6-week mortality, with contributions from improved endoscopic, pharmacological and radiological therapies, notably TIPS (3). Intensive care treatment has also improved, with outcomes being particularly good for those requiring minimal organ support. So the 54% 6 week mortality across both groups is high, and may support the notion that this was a very high risk cohort.
			6) The same study also noted that the study and control groups were imbalanced in terms of age and gender – how significant are these	Male gender and older age have been shown to be important risk factors for patients with acute variceal bleeding - in one US study these risk factors, plus comorbidities and not undergoing a gastroscopy within 24 hours, doubled mortality (4). It is noteworthy then that the Danis stent group had a significantly higher age and proportion of male gender than the balloon tamponade group.

			factors for clinical outcomes in people with chronic liver disease/oesophageal varices?	
			7) Are there differences between populations with alcohol-related liver disease and other chronic liver diseases, in terms of the likelihood of certain comorbidities or in terms of planning treatment such as TIPS?	Data from the RCT of early TIPS vs continuing pharmacotherapy by et al, demonstrated that 66% of patients had cirrhosis due to alcohol, 14% Hep C and 20% other causes (5). In the Escorell study 54% had cirrhosis due to alcohol, 25% Hep C, 21% others. So these studies are broadly comparable, and severity of liver disease is similar in both the ALD and Hep C cohorts.
			8) What would be the procedure if a Danis Stent was to dislocate? The company suggested that this would depend on the team performing the procedure.	Stent dislocation has been reported in 38-63.6% in studies (6-7). It can be managed by repositioning of stent endoscopically, or removal and replacement of stent if dislocated proximally and ongoing bleeding.

			9) How soon do you think TIPS is likely to be performed after a Danis Stent is placed?	Ideally within 3 days, but as the NCEPOD data showed only 1% of patients with acute variceal bleeding were referred for TIPS, and access is a problem in UK (8).
	13/05/20	**Expert – Dr Jason Dunn (Consultant Gastroenterologist)** Further questions	1) Would you expect the choice of definitive treatment and subsequent longer term outcomes, to be related to the choice of bridging treatment? (Escorsell 2016 indicated trend towards TIPS used as the definitive treatment less frequently in patients who had received the Danis stent (31%) compared to those patients who had received balloon tamponade (67%), p	It is plausible there will be a delay in definitive treatment using Danis, as patients may recover prior to needing TIPS, whereas this is much less likely with balloon tamponade given the shorter time it is in place.

			value reported is 0.12).	
			2) Is it acceptable to generalise evidence to the UK from the Spanish study population in Escorsell 2016?	Yes, similar ratios of ALD and viral hepatitis.
			3) Is it plausible that severe HE occurs during bridging treatment phase i.e. ahead of definitive treatment?	Severe HE can occur at any stage, so yes plausible
			4) The company estimates the cost of stent migration by applying the reference cost of a *therapeutic endoscopic upper gastrointestinal tract procedure*. Is this appropriate e.g. the	Yes, this would be the standard way to remove a stent

			appropriate response to stent migration?	
			5) Are there other plausible definitive treatments in the UK that should be considered beyond TIPs and band ligation (the 7 case series included in the systematic review note other treatments such as sclerotherapy or transplant)?	Transplant plausible, but likely TIPS attempted first. Sclerotherapy rarely used.
			6) Is it likely that there would be a learning curve for this technology and would this effect the likelihood of severe adverse events beyond stent migration?	Most users will be trained in advanced therapeutic endoscopy, including positioning of stents.

			7) Is it right to assume that Ella extractor would not be needed to remove the stent if the patient was undergoing TIPS?	Yes
	20/05/20	**Expert – Dr Jason Dunn (Consultant Gastroenterologist)** Further questions	1) Stent migration: The Wright et al 2010 study reports the following: *The most frequent adverse event in this study was distal migration of the stent detected on radiography in 7 patients. In none of these patients was stent migration associated with bleeding, and in all patients, the stent could be repositioned by using the PEX-Ella extractor to constrain and then reposition* **Would you expect to use Ella extractor to reposition device where there has been stent migration?**	Yes this would be appropriate, if no active bleeding. Unlikely as would be in the setting of a bleed, so would use stent grabbers at the time of therapeutic endoscopy.

<table>
<tr><td></td><td></td><td></td><td>If so, would this be used alongside therapeutic endoscopic upper gastrointestinal tract procedure?</td><td></td></tr>
<tr><td></td><td></td><td></td><td>2) Cost of re-bleed
The 2016 NICE impact report infers that cost of re-bleeding is covered by the following HRG codes: 2016/17 HRG codes GB02A, GBO2B, GB02C for:

Major Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, with Major CC
Major Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, with Intermediate CC
Major Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, without CC

These codes are now out of date. Do the following 2018/19 HRG codes describe the same</td><td>No, these are for ERCP

Would be one of the following

<table><tr><td>FD03 A</td><td>Gastrointestinal Bleed with Multiple Interventions, with CC Score 5+</td></tr><tr><td>FD03 B</td><td>Gastrointestinal Bleed with Multiple Interventions, with CC Score 0-4</td></tr><tr><td>FD03 C</td><td>Gastrointestinal Bleed with Single Intervention, with CC Score 8+</td></tr><tr><td>FD03 D</td><td>Gastrointestinal Bleed with Single Intervention, with CC Score 5-7</td></tr><tr><td>FD03 E</td><td>Gastrointestinal Bleed with Single Intervention, with CC Score 0-4</td></tr><tr><td>FD03 F</td><td>Gastrointestinal Bleed without Interventions, with CC Score 9+</td></tr><tr><td>FD03 G</td><td>Gastrointestinal Bleed without Interventions, with CC Score 5-8</td></tr><tr><td>FD03 H</td><td>Gastrointestinal Bleed without Interventions, with CC Score 0-4</td></tr></table>
Most would be A-F, more often A-C if severe rebleed than D-F</td></tr>
</table>

			procedures/are they equivalent? 2018/19 HRG codes GB05F, GB05G, GB05H for: Major Therapeutic Endoscopic Retrograde Cholangiopancreatography with CC Score 5+ Major Therapeutic Endoscopic Retrograde Cholangiopancreatography with CC Score 2-4 Major Therapeutic Endoscopic Retrograde Cholangiopancreatography with CC Score 0-1	
			3) Cost of definitive TIPS There are two reference costs available for elective TIPS: YR16B Transjugular Intrahepatic Creation of Portosystemic Shunt with CC Score 0-5 YR16A Transjugular Intrahepatic Creation of	Mostly higher CC score in bleeding setting

			Portosystemic Shunt with CC Score 6+ **Do you have a view on whether it is more appropriate to use the lower or higher complication (CC) score (or an average of both)?**	
	29/04/20	**Expert – Dr Philip Berry (Consultant Gastro-enterologist & Hepatologist)** Initial questions	1) The Danis Stent is intended to stay in place for up to 7 days (although the manufacturer estimates that it remains in place for an average of 10 days in the UK). What value does this extra time (when compared to a Balloon Tamponade) give in planning treatment/prophylaxis ? 9.1. What is the likely variation in the time that the	The extra time allows optimisation of the patient, treatment of other organ failures and sepsis, improvements in coagulation and a haemodynamic response to vasoactive drugs such as Terlipressin/Octreotide. These interventions may result in a more controlled situation when the stent is removed. A number of patients will therefore move into a less urgent phase, with the opportunity to be treated with conventional banding +/- beta blockers, rather than 'going straight to TIPSS'. Likely variation in stent dwell time, as seen in the published trial and the case series, is up to 10 days. The four-centre Austrian study (Pfisterer at al, 2019) has patients well up to 12-14 days, and even one up to 38 days (who died). Factors influencing this time are likely to be organisational. Assuming a minority undergo TIPSS after stent insertion (4 out 13 in the Escorsell trial), removal will usually be performed with fluoroscopic guidance. This stage of stent management is arguably more complex and challenging than the insertion, requiring confidence with radiological interpretation and access to radiology suite. Therefore, arrangements must be made and the correct personnel involved, or the patient should be transferred to a tertiary centre for further management.

			stent will stay in place and what factors may affect this?	
			2) The manufacturer of the Danis Stent considers it to be an alternative to Balloon Tamponade or emergency TIPS and as a bridge to early TIPS. What is the difference between early and emergency TIPS, particularly in terms of clinical outcomes like mortality?	'Emergency TIPSS' is a life saving intervention performed within 24 hours when endoscopic treatment has failed. Because haemostasis has not been successful, patients are unstable, though often a tamponade balloon will have achieve are a partial reduction in bleeding. It is a reasonable statement, based on the data about haemostasis with the Danis stent, that this technology will reduce the number of emergency TIPSS. 'Early TIPSS' (<72hours) is an approach based on good quality evidence, whereby patients with the highest risk of dying in the short term are selected for TIPSS *even if the bleeding seems to be under control.* These patients are, as stated in the trial, Child Pugh grade C (but CP score <14 – i.e. not the very sickest, who will die after TIPSS anyway) and Child Pugh B with active bleeding at first endoscopy [Garcia-Pagan JC et al NEJM (2010) & Garcia-Pagan JC et al, J Hep (2013)]. The principle of this approach is to modify the underlying pathophysiology (portal hypertension) and reduce the risk of death through sepsis, decompensation and other organ failures (ACLF) rather than purely as a means to stop bleeding [Trebicka J et al, J Hep (2020)]. Early TIPSS was associated with improved 1 year survival against conventional banding programme/beta blockers in the NEJM trial (86 vs61%). Data regarding survival after 'emergency TIPSS' are lacking.

			3) What other treatments/prophylaxis may be used alongside or following TIPS?	All patients receive prophylactic antibiotics and a vasoactive drug such as Terlipessin or Octreotide (the former in the UK).
			4) Is there a standard grading system used for categorising the severity/size of oesophageal varices? We noticed that Escorsell et al. (2016) describes the size of oesophageal varices as small or large, for example, while other papers have used the Paquet grading system.	The standard approach to grading in the UK as described below: Grade 1: varices that collapse to inflation of the oesophagus with air. Grade 2: varices between grades 1 and 3. Grade 3: varices which are large enough to occlude the lumen. The current large RCTs for varices (CALIBRE, BOPPP) use this system. Other systems are used in international publications. The 4-grade system by Paquet is rarely used here. 'Small vs large' is arguably the most pragmatic, as there is subjective variation between observers even with the standard 3 grade approach. The size of varices at the time of bleeding is slightly academic, as they can look small during major bleeding episodes, and conversely, larger ones don't always bleed badly. The degree of underlying liver disease is the more important determinant of future bleeding risk.
			5) Escorsell et al. (2016) reported that control of bleeding using the Danis Stent was significantly (p=0.037) better than using balloon tamponade at	Six week survival may not be the best measure here. Table 4 contains these lines:

			15 days but this difference was non-significant at 6 weeks. Are we correct to assume that survival at 6 weeks for this patient group is low and that the difference at 15 days supports the use of Danis Stent as an intermediate treatment?	**TABLE 4. Other Outcomes** Variable / Esophageal Stent (n = 13) / Balloon Tamponade (n = 15) / *P* Value Definitive treatment, n (%) — 0.015 EBL + nonselective beta-blockers — 5 (39) — 0 TIPS — 4 (31) — 10 (67) This shows that more balloon tamponade patients proceeded to TIPSS, and it is likely this not only equalised the re-bleeding rate at 6 weeks, but also overall survival. This is because TIPSS is probably a disease modifying intervention as mentioned above. The TIPSS insertions in the balloon tamponade group were done very quickly (13 out of 14 within 48 hours), 4 being done as 'emergency' or 'rescue'. This impressive record intervention emphasises how different the conditions are in this Spanish centre, compared to a typical UK centre. In the UK, TIPSS is offered this readily in very few centres, and the 'early TIPSS' protocol for selected patients (even when bleeding appears controlled) has not been widely adopted.
			6) The same study also noted that the study and control groups were imbalanced in terms of age and gender – how significant are these factors for clinical outcomes in people	Gender is unlikely to be have been a significant factor in the RCT. The 15 year age difference is significant, but compared to liver disease stage (by MELD etc), age is not likely to have skewed the overall outcomes independently.

			with chronic liver disease/oesophageal varices?	
			7) Are there differences between populations with alcohol-related liver disease and other chronic liver diseases, in terms of the likelihood of certain comorbidities or in terms of planning treatment such as TIPS?	Comorbidities were identified in 598 Swedish cirrhosis patient [Vaz et al. BMC Gastroenterology (2020)]. The two aetiologies most strongly related to comorbidities were NAFLD and cryptogenic; many cryptogenic cases are in fact burnt out NAFLD, so this makes sense. Alcohol related cirrhosis does not carry a significantly higher risk of comorbidities, though if there is superimposed alcoholic hepatitis at presentation, patient appear more inflammatory and at higher risk of extra-hepatic organ failure. TIPSS is relatively contraindicated in patients with heart failure, due to the increased pre-load on the circulation. Patients with alcohol-related liver disease may be at higher risk of short or long term cardiac dysfunction (cardiomyopathy), and NAFLD patients are generally older than alcohol patients (median 75 vs 65 in the Swedish study) with more ischaemic heart disease, both these factors potentially restricting access to TIPSS.

Table 1 Baseline characteristics at the time of diagnosis of cirrhosis in Halland, 2011–2018

	Alcohol	HCV	Cryptogenic	NAFLD	PBC	AIH	Other causes
Overall, n (%)	302 (50.5)	80 (13.4)	87 (14.5)	34 (5.7)	31 (5.2)	30 (5.0)	34 (5.7)
Male, n (%)	212 (70)	55 (69)	59 (68)	19 (56)	5 (16)	6 (20)	24 (71)
Female, n (%)	90 (30)	25 (31)	28 (32)	15 (44)	26 (84)	24 (80)	10 (29)
Median age (years) (10–90 percentile)	65 (52–76)	57 (46–67)	76 (63–88)	75 (62–86)	72 (58–81)	69 (46–85)	64 (30–83)
Comorbidities, n (%)							
Hypertension	96 (32)	17 (21)	32 (37)	23 (68)	12 (39)	7 (23)	9 (27)
Ischaemic heart disease	59 (20)	4 (5)	27 (31)	11 (32)	7 (23)	2 (6.7)	4 (12)
Chronic heart failure	37 (12)	2 (2.5)	35 (40)	8 (24)	1 (3.2)	0 (0)	3 (8.8)
Type 2 diabetes	78 (26)	6 (21)	37 (43)	18 (53)	9 (29)	4 (13)	8 (24)
Obesity [a]	81 (27)	18 (23)	10 (11)	24 (70)	4 (13)	5 (17)	1 (2.9)

			8) What would be the procedure if a Danis Stent was to dislocate? The company suggested that this would depend on the team performing the procedure.	In the Pfinsterer paper, 13 out 34 patients experienced 'stent dislocation', which appears high. This paper also states that 'Previous studies found stent migrations in 20% to 63.3%.' If the stent was found to have partialy migrated downwards, an individualised assessment would be made as to whether it could be safely left for a few more days (as its beneficial effect on varices at the GO junction might persist), it needed to be replaced, or removed entirely and management converted to banding or TIPSS. 'Stent dislocation', which presumably means complete separation from the oesophageal mucosa so that it drops into the stomach, would require an assessment of two risks – 1. potential of the stent to enter the bowel and cause obstruction (no reported cases) and 2. possibility of early re-bleeding. At this stage expert opinions would be sought and a case-based decision made. Stent removal from the stomach would entail a risk of bleeding due to trauma on the varices, but this does not seem to be described in the available studies.
			9) How soon do you think TIPS is likely to be performed after a Danis Stent is placed?	Currently in the UK we do not proceed to early TIPSS routinely, despite the evidence for improved survival, as access to TIPSS remains restricted. If a Danis stent is inserted, the risks and benefits of TIPSS with an indwelling stent vs trying conventional banding/pharmacotherapy after stent removal will be assessed for the individual. Often, there are good reasons not to proceed to TIPSS (organ failures, high grade encephalopathy, active sepsis). In many cases, the oesophagus will have settled sufficiently for management to continue without TIPSS. If TIPSS is performed, it would usually be done within 5 days.

	13/05/20	**Expert – Dr Philip Berry (Consultant Gastro-enterologist & Hepatologist)** Further questions	1) Would you expect the choice of definitive treatment and subsequent longer term outcomes, to be related to the choice of bridging treatment? (Escorsell 2016 indicated trend towards TIPS used as the definitive treatment less frequently in patients who had received the Danis stent (31%) compared to those patients who had received balloon tamponade (67%), p value reported is 0.12).	*Choice of definitive treatment: yes. Danis stent is more likely to settle bleeding over the next 7 days, and therefore numbers proceeding to TIPSS will be reduced. More patients with a tamponade balloon in situ will be referred for urgent TIPSS, as they cannot progress (i.e. be woken up and moved out of ICU) without some sort of definitive intervention to reduce portal pressure.* *Long term outcome: unclear. Trial data doesn't answer this question, and any answer would be speculative. However, given the Danis stent's efficacy in stopping bleeding, it might be predicted that it would improve survival in the short term (7-30 days). Longer term survival is likely to be related to underlying liver disease stage and other organ failures, and the stent does not modify those.*
			2) Is it acceptable to generalise evidence to the UK from the Spanish study population in Escorsell 2016?	*Partially – the patient demographics and comorbidities are transferable. However, the Spanish centre is expert at portal hypertension management, with a culture of 'early' (preventative rather than rescue) TIPSS in Child Pugh B/Child Pugh C patients – few UK centres adopt this approach.*

			3) Is it plausible that severe HE occurs during bridging treatment phase i.e. ahead of definitive treatment?	*Yes, HE is quite common when patients bleed and decompensate, but stent will not influence this. If there is persistent HE, TIPSS may be contraindicated.*
			4) The company estimates the cost of stent migration by applying the reference cost of a *therapeutic endoscopic upper gastrointestinal tract procedure*. Is this appropriate e.g. the appropriate response to stent migration?	*If the stent migrates with resultant early (re-)bleeding, length of stay might be extended and if a 2nd stent is inserted that cost must also be included (though reports of 2nd stent insertions are lacking). However, length of stay for this group is long anyway, and the proportional increase not likely to be great. Overall, adding the cost of an endoscopy is reasonable.*
			5) Are there other plausible definitive treatments in the UK that should be considered beyond TIPs and band ligation (the 7 case series included in the systematic review	*No. Other sclerotherapy is outdated, and surgical shunts are not done outside the paediatric population. Histoacryl glue therapy is not recommended in oesophageal varices, though it is used in some centres as a last resort. Transplantation would not be done as a treatment for bleeding, only in a stabilised patient.*

			note other treatments such as sclerotherapy or transplant)?	
			6) Is it likely that there would be a learning curve for this technology and would this effect the likelihood of severe adverse events beyond stent migration?	*Yes, there is a learning curve. A centre would need to use the stent regularly to be confident and fully competent, though the technique is not complicated. I would say it should be used every 8-12 weeks for departmental competence in insertion and removal to be maintained. There is discussion about its use first line, rather than in cases of failed endoscopic haemostasis, but that indication appears outside the current remit. The only trial data [Escorsell] relates to Danis stent use after failed first line therapy. However, if the stent was to be used first line, many centres would be using it every week.*
			7) Is it right to assume that Ella extractor would not be needed to remove the stent if the patient was undergoing TIPS?	*MIB185 states that the extractor is not required after TIPSS. I cannot locate information from the maker that states this, and my personal experience doesn't cover this question. However, assuming that the minority of patients go for TIPSS in the UK, the majority of removal would require the extractor and fluoroscopy.*
	20/05/20	**Expert – Dr Philip Berry (Consultant Gastro-enterologist & Hepatologist)**	1) Stent migration: The Wright et al 2010 study reports the following: *The most frequent adverse event in this study was distal migration of the stent*	Based on the Wright et al report, yes the Ella extractor could be used to reposition if a decision was taken to persist with use of the stent despite its early migration. Yes, endoscopy is required to use the Ella extractor. Although the extractor is deployed under fluouroscopic guidance, endoscopy is needed to identify the retrieval thread at the top of the stent, and to visualise the endoscopic

		Further questions	*detected on radiography in 7 patients. In none of these patients was stent migration associated with bleeding, and in all patients, the stent could be repositioned by using the PEX-Ella extractor to constrain and then reposition* **Would you expect to use Ella extractor to reposition device where there has been stent migration?** **If so, would this be used alongside therapeutic endoscopic upper gastrointestinal tract procedure?**	hook that attaches to the thread. The endosocope is then removed, and the rest of the extraction is done with fluoroscopy.
			2) Cost of re-bleed The 2016 NICE impact report infers that cost of re-bleeding is covered by the following HRG codes: 2016/17 HRG codes GB02A, GBO2B, GB02C for: Major Endoscopic or Percutaneous, Hepatobiliary	Therapeutic Endoscopic Retrograde Cholangiopancreatography (ERCP) is an endoscopic biliary intervention that is not related to variceal bleeding management in any way. However, its complexity and associated morbidity are in the same bracket.

			or Pancreatic Procedures, with Major CC Major Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, with Intermediate CC Major Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, without CC These codes are now out of date. **Do the following 2018/19 HRG codes describe the same procedures/are they equivalent?** 2018/19 HRG codes GB05F, GB05G, GB05H for: Major Therapeutic Endoscopic Retrograde Cholangiopancreatography with CC Score 5+ Major Therapeutic Endoscopic Retrograde Cholangiopancreatography with CC Score 2-4 Major Therapeutic Endoscopic Retrograde	

			Cholangiopancreatography with CC Score 0-1	
			3) Cost of definitive TIPS There are two reference costs available for elective TIPS: YR16B Transjugular Intrahepatic Creation of Portosystemic Shunt with CC Score 0-5 YR16A Transjugular Intrahepatic Creation of Portosystemic Shunt with CC Score 6+ **Do you have a view on whether it is more appropriate to use the lower or higher complication (CC) score (or an average of both)?**	TIPSS for bleeding should be associated with a higher complication score. TIPSS is also used electively, for management of refractory ascites, and in this scenario the patients walk in to hospital and are stable. In the post-bleeding, Danis stent scenario, they have suffered a life threatening complication and are generally being managed in the ICU with a higher mortality risk.

	19/11/20	**Expert – Dr Dhiraj Tripathi – (Consultant Hepatologist)** Further questions (forwarded via NICE)	1) We are asking one of our EACs to look at HES data for this patient population and there are a couple of queries associated with that request: (A) The ICD-10 codes we propose using are: - I85.0: Oesophageal varices with bleeding - I98.3: Oesophageal varices with bleeding in diseases classified elsewhere (Oesophageal varices with bleeding in: liver disorders (K70-K71, K74), schistosomiasis (B65)) Are both these codes I85.0 and I98.3 in any diagnosis position relevant? Will all these patients have acute oesophageal variceal bleeds?	With regards to the ICD codes both are relevant. Variceal bleeding will be acute. The codes will not differentiate between controlled bleeding and uncontrolled bleeding where a Danis stent may be needed and further definitive therapy. I would say in between 10-20% there is failure to control bleeding or early rebleeding where salvage therapy with SB tube/Danis stent may be necessary.

			(B) Should the data be restricted to those aged 16 or older? (C) Does the following total admissions data for your trust look correct for 2019/20 ? We understand this data will represent admissions across the trust. Are you able to help identify or estimate how many of these patients were admitted to the regional centre(s) (and did not need transport) and how many needed some transport?	
			2)Following our meeting earlier in the week is there any other relevant information you would like to share with us?	I came across the following abstract which is interesting. There is safety data. Of note is that some patients had a Danis stent placed electively after balloon tamponade. Presumably there patients were not fit for immediate definitive therapy or Danis stent may have been palliative. https://www.giejournal.org/article/S0016-5107(20)32113-1/fulltext

	27/11/20	**Expert – Dr Dhiraj Tripathi – (Consultant Hepatologist)** Further questions (forwarded via NICE)	1) Would people only be transferred to a tertiary hospital for a TIPS procedure or would patients that have band ligation (after bridging) also be transferred to a tertiary centre?	Yes. Two scenarios: 1. Patient is admitted to spoke site and has a stent/SBT. Transfer to hub site for consideration of TIPSS. Patient is suitable and a salvage TIPSS is done. 2. As 1 but at hub site for various reasons patient not considered a good TIPSS candidate and decision made to continue with banding/drug therapy or even palliation if there has been a significant deterioration with multiorgan failure/sepsis for example.
			2) Would a TIPS procedure ever be done for any other indications or would all TIPS procedures be to resolve oesophageal bleeding	The main indications for TIPSS are variceal bleeding and ascites. There is NICE guidance for both these indications.
			3) The data we have suggests that 116 TIPS procedures were done between April 2019 and April 2020 and only 23 of those procedures were done following a rescue therapy. We're working off the assumption that TIPS wouldn't routinely be done in people with oesophageal variceal bleeding without the use of a rescue therapy, is that accurate? Do you think	The BSG guidance on TIPSS summarises the key indications for TIPSS in variceal bleeding. There is rescue therapy (emergency), early TIPSS (emergency), and TIPSS for secondary prevention (elective). I would say around 80% of indications are emergency. The other main indication is ascites and this would be an elective indication. So for the 93 other patients, most would be ascites, but some would be elective TIPSS for prevention of further variceal bleeding (secondary prevention). There are some other niche indications but I would say these compromise less than 10% of all procedures.

			the ascites population could explain the other 93 cases (ones that were done without the use of a rescue therapy)? Alternatively, do you think there might be a salvage therapy code that we have missed on the analysis. The range of included codes is already quite broad, the codes are listed below: Admissions including a salvage procedure were identified by the presence of the following procedure (OPCS) codes appearing in any procedure field: - G44.1: Fibreoptic endoscopic insertion of prosthesis into upper gastrointestinal tract - G48.5: Insertion of gastric balloon - G15.4: Fibreoptic endoscopic insertion of tubal prosthesis into oesophagus	

			- G15.6: Fibreoptic endoscopic insertion of expanding metal stent into oesophagus NEC - G15.7: Fibreoptic endoscopic insertion of expanding covered metal stent into oesophagus - G21.5: Insertion of stent in oesophagus NEC - Any oesophagus procedure G01-G25 supplemented by Y14 Placement of stent in organ NOC - Any upper gastrointestinal tract procedure G42-G46 supplemented by (Y14 Placement of stent in organ NOC AND Z27.1 Oesophagus, in any order) Admissions including a TIPS procedure were identified by the presence of the following procedure (OPCS) codes: - J11.4: Transjugular intrahepatic creation of	

			portosystemic shunt TIPS - J06.1: Transjugular intrahepatic insertion of stent into portal vein - J06.2: Transjugular intrahepatic insertion of stent graft into portal vein	
		Expert – Dr Deepak Joshi – (Consultant Hepatologist) Further questions (forwarded via NICE)	1) Would people only be transferred to a tertiary hospital for a TIPS procedure or would patients that have band ligation (after bridging) also be transferred to a tertiary centre?	Both scenarios are a possibility.
			2) **Training** Please can you describe what training you think is needed to use of Danis stent, and then what refresher training would be needed to retain the skills (particularly in cases where there may not be many occasions for the skills to be practised regularly).	One needs to practice on the model that the company has available as well as reviewing the product video that is on YouTube. I would recommend that the first 5 cases are performed with the rep of the company. With regards to refresher courses, once a year if the individual has not deployed a stent in the previous 12 months.

			3) **Transport** We've included in the modelling that 20% of Danis stent patients would be conscious when transferred. In this situation, please can you advise what clinical staff, if any, you'd expect to make the journey with them?	If the patient is on a general ward, then I would suggest a paramedic ambulance crew and a trained nurse escort.
			4)HES data This is a little bit more complicated, so I've copied some of the results, and codes from the data analysis. Ideally, we'd like your advice about whether these results are in line with what you would expect, including, number of salvage procedures per year, is the mortality rate of those patients what you would expect and do the codes used look accurate? I've highlighted some key lines	These data seem very reasonable. I don't think the limitations dimmish the data and its a fair reflection of the pathway of some of the patients with an oesophageal variceal bleed.

			for your consideration but please feel free to comment on any aspect of the results, limitations or codes used (copied results below, please do not share this content as it is confidential).	
		Expert – Dr Claire Salmon – (Consultant Hepatologist) Further questions (forwarded via NICE)	1) Would people only be transferred to a tertiary hospital for a TIPS procedure or would patients that have band ligation (after bridging) also be transferred to a tertiary centre?	Yes I would agree. We try not to accept patients that are not suitable for TIPS but sometimes that patient deteriorates or the TIPS is not technically possible.
			2) **Training** Please can you describe what training you think is needed to use of Danis stent, and then what refresher training would be needed to retain the skills (particularly in cases where there may not be many occasions for the skills to be practised regularly).	The training should be provided by the company. It needs to be done in person using the model and a stent. It only takes about 15 mins each. I would suggest a refresher every 6-12 moths depending on how many stents are being done.

			3) **Transport** We've included in the modelling that 20% of Danis stent patients would be conscious when transferred. In this situation, please can you advise what clinical staff, if any, you'd expect to make the journey with them?	They could be transferred with paramedic or ambulance staff depending on stability of patient.
			4)HES data This is a little bit more complicated, so I've copied some of the results, and codes from the data analysis. Ideally, we'd like your advice about whether these results are in line with what you would expect, including, number of salvage procedures per year, is the mortality rate of those patients what you would expect and do the codes used look accurate? I've highlighted some key lines for your consideration but please feel free to comment on any aspect of the results, limitations or codes used (copied results below,	It took me a bit of time to get my head round the figures. I agree with most of the figures. I think the number of patients undergoing salvage procedures is correct (we only do it in the patients that we can't control endoscopically so it is admitting defeat – so should be low %). The mortality with this group is high as it is in a very sick group. However I am surprised that only 26 patients of 90 have TIPS. This seems lower than I would expect. It maybe that this is because some DGH do not refer for TIPS. You can not use the last 44.8% as not all TIPS patients survive. The 26 should be a percentage of 90 unless you can see how many TIPS patients survive?

			please do not share this content as it is confidential).	

Insert more rows as necessary

Appendix 1.

During correspondence with the company and experts, additional information is sometimes included as file attachments, graphics and tables. Any questions that included additional information of this kind is added below in relation to the relevant question/answer:

Company call 28.04.20 - minutes:

MT450 Danis Stent_Sponsor TC_r

Company call 15.05.20– minutes:

Notes from call with UK medical anc

File attachments/additional information from question X:

Insert

File attachments/additional information from question X:

Insert

MT450 Danis Stent company TC

Date: Tuesday, 28 April 2020
Time: 3-4pm
Attendees: Anastasia Chalkidou (AC), Jamie Erskine (JE), Jo Boudour (JB), Kate Goddard (KG), Rebecca Owens (RO), Richard Fearn (RF), Ian Aaron (IA), Louise Aaron (LA), Rachael McCool (RM), Katy Wilson (KW), Amy Clark (ACl)

Minutes

Introductions and roles:

KiTEC:

- Kate Goddard – Health Technology Assessor - joint project lead
- Jamie Erskine – Health Technology Assessor – joint project lead
- Mark Pennington – Health Economist (not present on call)
- Amy Clark – assisting with Health Economics
- Anastasia Chalkidou – Associate Director –project oversight
- Jo Boudour – Project Manager

NICE:

- Bernice Dillon – Technical Adviser (not present on call)
- Rebecca Owens – Technical Analyst
- Victoria Fitton – Project Manager (not present on call)

Company:

- Richard Fearn - Senior management
- Ian Aaron, UK Medical Managing Director
- Louise Aaron, UK Medical Director

YHEC:

- Rachael McCool
- Katy Wilson

Questions to sponsor:

1) The IFU states that it is for the Danis Procedure Pack – Basic. The Urgent Field Safety Notice included in the submission also mentions the Danis Procedure Pack i.e. not basic. What is the difference between the 2 packs?
    - RF - Danis Procedure Pack Basic is the only one promoted in the UK.

2) MIB185 includes one study not included in the submission (Dechene 2012). This case series mentions the Danis Stent: Ella CS as the intervention. Is this a different technology to the SX-Ella Stent Danis? If not, why is this study not considered relevant to the decision problem?
    - RF – CS is the equivalent of Ltd in the Czech Republic. Ella CS is part of the company name. It is the number of patients included (not meeting threshold) that made it ineligible.

3) The IFU states that the Danis Stent can be used as an alternative to early TIPS although none of the studies include early TIPS as a comparator. Are we correct in assuming that the company do not consider early TIPS to be relevant to the decision problem?
    - RF - The three options are Balloon Tamponade, Danis Stent or Emergency TIPS. Emergency TIPS, if performed at that stage has very low survivability (as patient tends to be very ill). Early TIPS is a bit different and occurs 2-3 days a bit further down the line, there is a stabilisation period. It usually involves Balloon Tamponade or a Danis Stent. Emergency TIPS is more likely to be the comparator.

4) What may affect the frequency of training and re-training? What is the average frequency and average training time per session?
    - RF - Theoretically, we can go in and do a training session every week. We work with the trust and they specify to us what they can realistically manage. They practice deploying stents on the models. IA –there are also other resources, quick user guides etc. to make it as straightforward as possible. Dictated by needs of trust and clinician availability.

5) Are all components of the procedure pack single-use?
    - Yes.

6) Can the packs/stents expire if not used? The letter to distributors regarding the Urgent Field Safety Notice mentions Unexpired Danis Stents. Do the packs require particular storage conditions?
    - RF – There is a choice between Balloon Tamponade or a Danis Stent, if someone is not confident using Danis in that acute setting they would use the item they are a bit more comfortable with. Therefore, if the procedural team is not using Danis due to a lack of confidence, there is a greater chance of expiry.

7) We note that the CE mark authorisation in the submission is dated as 12/10/2005 but that the current version was launched in April 2016. The certificate submitted is dated from the

29/06/2017. Several included studies were published prior to 2016. What are the differences in the technology between the first CE mark and the current version?

- RF - 2017 was just a renewal of the CE mark. Changes have been minor, for example, there are a series of steps to deploy the stent, you have to remove a series of clips in sequence. Ella added labels to the clips in order to simplify deployment. We will get all the relevant documentation over to you to confirm after we've cross-referenced with Ella.

8) The claimed benefits table in section 2 of the submission includes several outcomes from Escorsell 2016 that are listed as system benefits, such as 'absence of continued or further bleeding' and 'Mortality'. As these are not included in the patient benefit section, is the inference that because the difference in the groups was not statistically different at 6 weeks (rather than at 15 days) that these benefits are seen only by the system in the long run?
    - RF – It is clear that the patient group is in a habitual pattern. No matter what treatment you give to the patient they're effectively in a palliative state, it's the nature of the disease. Whether that is the reason for this I don't know. JE – we wanted to make sure if the difference at 15 days leads to long term benefits to the system. (Claimed benefits table in section 2). Would mortality and so on be a patient benefit not a system benefit? IA – This may be something to take into account. RF – I would agree this is probably a patient benefit, this is perhaps an oversight.

9) The maximum time the stent can stay in place is 7 days. What is the variation in the time that the stent will stay in place and what factors may affect this?
    - RF - NICE produced top-level advice on this previously, it was 14 days then. Average would probably be around 10 days. There doesn't appear to be any statistical difference removing the stent between 7 and 14 days, anecdotally. If left in place after 7 days, it's off licence so is a clinical decision. From a UK Medical point of view the guidelines are to extract the stent within 7 days.
    a. Escorsell 2016 reports that the days with the device in place ranged from 0-12. What are the safety risks of keeping the device in place for more than 7 days?

10) If the stent dislocates, what is the process for dealing with this? Is the stent removed and a new one inserted?
    - RF – This a grey area and changes from trust to trust. It's dependent on them having a TIPS service at the hospital and if the patient is stable. TIPS is carried out much earlier in the pathway. If that is the case, TIPS is performed. If the hospital doesn't have TIPS, they would extract stent prior to TIPS taking place but the preference is after TIPS.

11) Escorsell 2016 reported that the 2 treatment arms were different in terms of patient age and gender. Are you aware of whether the randomisation algorithm took these factors into account?
    - IA – We will ask Ella if they have the contact details to provide this information.

12) What is the likely amount of time between the removal of the stent and performance of TIPS?
    a. Do all patients proceed to have TIPS following the use of Danis Stent?

- RF – We want to be able to remove the stent without causing a re-bleed. Two methods for removal: atraumatic, which is essential if TIPS has not been carried out, using something like an Ella extractor. If TIPS is used and is successful, this is traumatic removal and they extract the stent. The risk of re-bleed is minimal.

Next Steps:

- RO – We are continuing with the original timeline and working towards the 24th July MTAC meeting. There are plans to attempt a virtual meeting.
- KW – we are still working towards 5th May for the economic submission.

A. Question: For the micro-costing approach, where were the ICU bed day estimated derived from?
Answer: anecdotal evidence collected by the company and discussion with experts - some felt Danis Stent would not require ICU stay but panel did not all agree.

B. Questions: The submission states there is differences in expert opinion about the link between bridging treatment and definitive treatment, can you clarify what the differing opinions were?
Answer:

- This is partly based on anecdotal information. Danis Stent has been used since c.2005 in the NHS but there isn't it a wealth of clinical data/evidence.
- In the UK there is a lot of variation between providers in terms of treatment availability and what definitive treatment a patient can access.
- Few hospitals/patients have access to emergency tips (performed at point of acute bleed, with low success rate).
- Early tips can take place from 48/72hrs-1 week, this is where bridging treatment is needed.
- Until Danis Stent, the only option was balloon tamponade which can be used for 24 hrs. 24 hrs is not a sufficient amount of time to stabilise a patient – it is designed to stop fatal patient bleeding. It would only be used for stabilisation for emergency tips unless it is used 'off label' for early tips (e.g. kept in over 24hrs)
- Danis Stent can be kept in for longer and therefore fills the gap to enable you to move to early tips (48/72hrs-1 week) or stabilise for elective tips
- There are differences between Spain and the Spanish RCT evidence and the NHS (more likely to try emergency tips in Spanish setting than in UK).

C. Question: how were the severe HE events costed?
(Answered in follow-up email from YHEC) The annual cost of Rifixamin + lactulose (£3,481) was taken from this NICE costing template - this cost was divided by 52 to get a weekly cost and then multiplied by 6 to get a 6-week cost to apply in the model.

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

MT450 Danis Stent for acute oesophageal variceal bleeds External Assessment Centre report

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from King's Technology Evaluation Centre (KiTEC) to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **01st July 2020** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

29/06/2020

NICE National Institute for Health and Care Excellence

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Part 2 highlighted in red:' inflating to 30mm in diameter'	Stent does not inflate, should read; increasing to 30mm diameter at the flared ends.	Incorrect product description	Correction accepted with apologies. This now reads "It is 135mm long and 25mm in diameter at the centre, increasing to 30mm in diameter at the flared distal ends."

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
EAC refers to 7 stent migrations in the Wright paper, which we feel is mis-interpreted data. The 7 patients are mentioned in the context of the discussion section and refer to the Zehetner study, so we believe the original assessment of 0 patients/migrations is correct and therefore our percentage of patients having stent migration in the model was correct (This has been cross referenced internally at UK Medical and with the clinical team at YHEC)	Referenced stent migration in the Wright study should be 0 with this being reflected in the context of and aligning with the cost model. The difference between 70% and 0% stent migration has a significant impact on overall costs and clinical outcomes and should be reflected accurately.	**Mis-interpreted data by the EAC**. Nowhere in the results of the wright study does it mention stent migration and in the method's it notes 'all patients underwent scans to rule out stent migration'. From the Zehetner study: - *'In the largest series of 34 patients reported by Zehetner et al,11 stents were deployed for patients with active bleeding despite previous therapy (banding, n Z 21; injection sclerotherapy, n Z 7; BT, n Z 6) and resulted in hemostasis in 33 of 34 patients. The majority of the patients in this study went on*	Correction accepted with apologies. Altered throughout.

		to have further endoscopic, radiological, and/or surgical therapy, and the survival rate at 30 days was 74%. The most frequent adverse event in this study was distal migration of the stent detected on radiography in 7 patients. In none of these patients was stent migration associated with bleeding, and in all patients, the stent could be repositioned by using the PEX-Ella extractor to constrain and then reposition the stent.'	

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The EAC argues that the cost of the extractor should not be considered as part of the overall cost saving, as 'not everyone' will use the extractor, therefore the bundle discount when purchasing Danis & extractor together should not be factored into the cost model. We have a number of hospitals that do purchase at the bundle discount price, thus taking advantage of the saving. Assuming that just because not all hospitals will use the extractor, the ones that do will pay full price, when a discount is available	Whilst this argument is based on the respective opinions UKM/YHEC vs EAC and not significantly impacting on the overall cost analysis, the cost saving bundle discount, when purchasing Danis & extractor together is very relevant and should be included as part of the cost model.	Current sales data and NHS practice of purchasing at the discounted bundle price, show a precedent of the cost saving being taken advantage of. *Sales data can be provided upon request to substantiate this.*	Justification for unbundled prices to be used: - The model assumes only 38% of cases use the Ella extractor. It is unlikely that NHS buyers would be able to predict the proportion of Stents to buy as a bundle and the proportion to buy separately. - The EAC therefore considered two options either for 100% of stents to be bought as a bundle alongside the Ella extractor or to apply the unbundled prices so that fewer extractors could be bought. - The mean cost per patient for stent and extractor is lower in

seems to be an illogical opinion and not reflective of current practice. As atraumatic extraction is inherently part of the process, we feel it is not reasonable to assume hospitals will pay more when a discount is available.			the base case if unbundled costs are used than if the bundled cost is used and an extractor purchased for each patient: ○ Per patient bundle price £1,995. ○ Danis Stent alone + Ella extractor (@£695) for 38% of patients = mean cost of £1,762.30 per patient - We also used the unbundled prices in the sensitivity analysis. This explored the maximum and minimum price for the extractor cost i.e. no one using extractor (thus no cost) and all those surviving to day 7 using extractor with the highest plausible cost