TIPS versus drug therapy in preventing variceal rebleeding in advanced cirrhosis: a randomized controlled trial

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The health technology of interest was transjugular, intrahepatic, portosystemic shunt (TIPS). Wallstent endo-prostheses were used (10mm nominal expanded diameter Wallstent; Boston Scientific, Schneider, Bulach, Switzerland). This was compared to propranolol (a beta-blocker) combined with isosorbide-5-mononitrate (ISMN). Propranolol was administered at the maximal tolerated dose, established through a process of stepwise increases or decreases from a starting dose of 20mg twice daily. ISMN was added at increasing doses, up to 40mg twice daily.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The population consisted of Child-Pugh class B and C cirrhotic patients. Patients of Child-Pugh class A were excluded as they are considered to be good surgical candidates. The reader can infer that including such patients may have created a bias towards TIPS. Patients had to have biopsy-proven, or clinical and imaging findings compatible with cirrhosis, and had to have been admitted because of their first episode of variceal bleeding. There were extensive inclusion and exclusion criteria.

Inclusion criteria included: being aged between 18 and 75; endoscopy-proven variceal bleed within two weeks; and haemodynamic stability without signs of bleeding for at least 3 days.

Exclusion criteria included: known hepatocellular carcinoma; chronic renal failure; contraindications to pharmacologic therapy; and previous treatment with portosystemic shunt.

Setting
The setting was secondary care. The economic study was carried out in two hospitals in Spain.

Dates to which data relate
The effectiveness data were collected between March 1994 and September 1997. A price year for costs was not reported.

Source of effectiveness data
Effectiveness data were derived from a single study.
Link between effectiveness and cost data
Although not stated explicitly, the use of the term ‘identified costs’ suggests that costs were collected prospectively on the same patient sample as that used in the effectiveness study.

Study sample
Two power calculations were used to determine the number of patients required in each arm of the study. These were based on the rate of rebleeding for each treatment and the incidence of encephalopathy.

The sample was selected using eligible patients who were admitted to the participating hospitals because of their first variceal rebleeding, over the time period for enrolment. This study sample was relevant for the study question, which concerned patients with advanced cirrhosis suffering rebleeding. 122 Child-Pugh class B and C cirrhotic patients were admitted.

Thirty-one patients were not included in the study due to: death from uncontrolled variceal bleeding before randomisation (n=6); need for emergency shunt or TIPS before randomisation (n=7); previously known hepatocellular carcinoma (n=5); portal vein thrombosis (n=2); concomitant life-threatening diseases (n=3); concomitant acute alcohol-induced hepatitis demonstrated by transjugular liver biopsy (n=2); or refusal to give consent (n=6).

Of 91 patients included in the study, 44 patients received drug therapy and 47 received TIPS.

Study design
The study was based on a randomised controlled trial. The randomisation sequence was carried out by a computer for each participating centre. No further details of the method of randomisation were reported. The treatment code was kept at the coordinating centre in sealed consecutively numbered, opaque envelopes.

Two centres took part in the study. 66 patients were treated at the Hospital Clinic, Barcelona, and 25 patients were treated at the Hospital Gregorio Maranon, Madrid.

Follow-up was carried out monthly during the first three months, then every three months thereafter. It is not clear what the authors anticipated the total length of follow-up would be. However, the authors reported that ultrasonography would be included during the visits in months 6, 12, 24 and 30. From this the reader can infer that follow-up could be expected to last around 30 months.

Blinding was only reported for the independent interviewer responsible for obtaining quality of life (QOL) scores perceived by the relatives and the patients themselves. One patient in each arm died before receiving the allocated treatment. On average patients in the pharmacological therapy arm were followed for 15.4 months (SD = 10.3) and patients in the TIPS arm were followed for 14.4 moths (SD = 9.6). The reasons for ending follow-up are not clear.

Analysis of effectiveness
Analysis was based on intention to treat. The primary health outcomes were incidence of variceal bleeding, rebleeding from any source (excluding peptic ulcers), and incidence of new encephalopathy. The secondary health outcomes were incidence of clinically significant variceal rebleeding, incidence of death from any cause, death caused by rebleeding, encephalopathy requiring hospitalisation, incidence of TIPS dysfunction, QOL profile, and cost. The patients in the two groups were compared at baseline for factors including age, sex, etiology, Child-Pugh class, origin of bleeding, and QOL. The authors found no significant difference between the patients in the two groups.

Effectiveness results
The incidence of rebleeding in the TIPS group was 8 from any cause, 6 from varices rebleeding, 5 from clinically significant variceal rebleeding and 2 from non-variceal bleeding.

The incidence of rebleeding in the pharmacological therapy group was 22 from any cause, 17 from variceal rebleeding, 14 from clinically significant variceal rebleeding and 5 from non-variceal bleeding.
A multivariate analysis identified the treatment (TIPS) (OR = 2.2; 95% CI: 1.21 - 4.1) and the transfusional requirements (OR = 1.2; 95% CI: 1.02 - 1.53) as independent predictors of rebleeding.

The incidence of encephalopathy overall was 18 for the TIPS group and 6 for the pharmacological therapy group.

The incidence of new encephalopathy was 15 for the TIPS group and 2 for the pharmacological therapy group.

The probability of remaining free from new encephalopathy after 2 years of follow-up was 68% for patients undergoing TIPS and 96% for patients undergoing drug therapy (P=0.0009).

A multivariate analysis identified the allocated treatment as the only independent predictor of developing new encephalopathy on follow-up (OR = 3; 95% CI: 1.4 - 6.7, P=0.0008).

Under drug therapy 17 patients suffered rebleeding and received further treatment.

10 out of 12 patients receiving pharmacologic and/or endoscopic therapy as a rescue treatment were successful.

5 patients required a portosystemic shunt.

Under TIPS, 33 of 47 patients had reintervention with balloon dilation or restenting.

Under TIPS 6 patient required treatment for rebleeding.

3 patients required surgical stunts.

1 required angioplasty.

2 patients required 5 sessions of endoscopic therapy (both these patients died).

The survival probability was reported to be identical between the two groups, 72% at two years.

No difference was reported in the quality of life between the patients in the two groups.

**Clinical conclusions**

The authors concluded that, whilst medical therapy is less effective than TIPS in terms of preventing variceal bleeding, it is as good as TIPS in terms of survival, days of hospital stay, and quality of life. In addition they concluded that medical therapy is preferable in terms of incidence of encephalopathy, and impact on liver function.

**Measure of benefits used in the economic analysis**

The authors carried out a cost-consequences analysis. The effects from the study were not combined with the cost analysis to create a summary measure of benefit.

**Direct costs**

The authors focussed on the cost per patient. A perspective was not explicitly stated although hospital tariffs were used, suggesting that the perspective was that of the hospital. The following sources of cost were accounted for: overall days in hospital (per patient); hospital admissions; TIPS procedures; angioplasty or additional stent; endoscopic therapeutic procedures; surgical shunts. Volumes were not reported separately from prices and a price year was not stated. The authors did not report discounting. However, as the average follow-up was 14.4 months in the TIPS group and 15.4 months in the drug therapy group, the time horizon was less than 2 years and discounting was not necessary for patients who received the average length of follow-up. The quantity of resources used seems to have been measured between 1994 and September 1997, as the trial progressed, although this was not explicitly stated.
Statistical analysis of costs
No statistical analysis of cost was reported.

Indirect Costs
The authors reported that they excluded "out-of-work days of the patient (most of them unfit for work)". In other words, assuming indirect costs were based on productivity, then indirect costs were, appropriately, not measured.

Currency
Euros. A conversion rate of 1 Euro = 0.85 US dollars was reported for reference.

Sensitivity analysis
No sensitivity analysis of costs was reported.

Estimated benefits used in the economic analysis
As the authors carried out a cost-consequences analysis, please refer to the effectiveness results reported earlier.

Cost results
The following costs were reported:

The cost per day of hospital stay was Euro 229. TIPS (Wallstent), including the cost of the devices used and the radiology room use time, was Euro 4,470.

Angioplasty or an additional stent (Wallstent), including the cost of the devices used and the radiology room use time, was Euro 3,159.

Endoscopic therapy cost Euro 331.

Pharmacologic therapy/d (drug prices were reported to be drug market prices for propranolol and ISMN adjusted for mean dosage used) cost Euro 0.5. The authors did not clarify what '/d' stands for; for instance, it may refer to per day or per dose.

Surgical shunt cost Euro 1,773.

Laboratory tests per admission in hospital (including haematology and hemostasia parameters, serum and urine biochemistry) cost Euro 47.

The cost of TIPS per patient was Euro 21,603.

The cost of drug therapy per patient was Euro 10,692.

As the costs were reported to be "identified costs" per patient it is implicit that the total cost per patient accounts for adverse effects incurred over the period of follow-up.

Synthesis of costs and benefits
This was a cost-consequences analysis and therefore costs and effects were not combined.

Authors' conclusions
The authors concluded that, whilst TIPS does reduce the incidence of rebleeding, drug therapy is as good as TIPS on many other grounds including survival and length of hospital stay. In addition they concluded that drug therapy is
preferable when the alternatives are compared by incidence of encephalopathy, and impact on the liver. TIPS was reported to be the more expensive treatment.

**CRD COMMENTARY - Selection of comparators**
The comparators were appropriate for the stated study question and were reported explicitly at the outset. They were justified with reference to previous studies that showed the various advantages and disadvantages of the two treatment alternatives.

**Validity of estimate of measure of effectiveness**
The analysis was based on a randomised controlled trial, which was appropriate for the study question. No systematic differences between the patients in the two groups were identified so no analysis for confounding variables was required. The study has good internal validity.

The study sample was taken from patients admitted to hospital with their first variceal bleeding making the sample representative of the study population, patients in whom variceal bleeding might be prevented. Extensive inclusion and exclusion criteria were reported, which might reduce the representativeness of the population; 31 of 122 patients admitted to the participating centres were not included in the study.

**Validity of estimate of measure of benefit**
The authors did not derive a summary measure of health benefit. The analysis was therefore categorised as a cost-consequences analysis.

**Validity of estimate of costs**
As the perspective of the cost analysis was not stated explicitly it is not possible to assess whether all cost categories were considered. Costs were taken from the "hospital's tariff". No further details are given of this source. The breakdown of costs by type reassures the reader that, whatever the true perspective, appropriate sources of cost were considered. Appropriately, the authors neither included indirect costs, nor discounted the costs analysed. Volumes were not reported separately from costs. The costs of various resources used were reported, but no volumes were reported. This means that the reader cannot verify the total costs per patient reported by the authors. No price year was given. This prevents the reader from reflating the estimates for comparison with other studies. No sensitivity analysis was conducted to assess the robustness of the results to changes in cost. However, given the relative difference in the estimated total cost per patient for each treatment, small omissions in the cost analysis are unlikely to affect the overall conclusion that the authors drew with respect to the cost of the alternatives.

**Other issues**
The authors made appropriate comparisons of their results with those from previous studies. For instance, the current results are said to confirm previous studies showing the value of haemodynamic targets in the treatment of portal hypertension. The issue of generalisability was not addressed by the authors although some comparison to the USA was drawn with the suggestion that "the difference (in cost) may have been less using American fees, rather than those in Spain, where health care is provided free of charges for the patients". This comment is not substantiated, and is not appropriate as no perspective for the economic study was explicitly stated; the cost within the USA would depend on the perspective adopted. The authors did not report their results selectively. They provided a balanced analysis demonstrating the relative efficacy of the two alternatives. The authors' conclusions accurately reflected the results presented. However, the study had extensive inclusion and exclusion criteria, and in particular excluded Child-Pugh class A patients. These criteria were not reflected in the conclusions.

**Implications of the study**
The authors recommended that TIPS should not be used as first-line treatment to prevent variceal rebleeding in patients with advanced cirrhosis. Instead they suggested TIPS should be used to rescue patients who are treated with medical
therapy but who, nevertheless, develop severe or recurrent variceal bleeding. Although the authors did not explicitly discuss the need for further work, they mentioned that technological developments may reduce the reintervention requirements following TIPS thus reducing its cost. By implication the authors appeared to be suggesting that reanalysis at a later date, following technological development, would be a worthwhile area for further study.

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