An economic evaluation of vasoactive agents used to treat acute bleeding oesophageal varices in Belgium

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Abstract

Background and study aims : **Increasingly, cost influences all areas of healthcare, including the management of life threatening events, such as bleeding oesophageal varices (BOV). In light of the need to control costs, an economic evaluation of vasoactive agents used to treat cirrhotic patients with BOV within the emergency setting in Belgium has been assessed.**

Patients and methods : **A previously reported economic evaluation of vasoactive agents used to treat BOV was identified and adapted to the Belgium hospital setting. The economic evaluation was based on double-blind randomised controlled trials of vasoactive agents previously reported as Cochrane meta-analyses. Belgian cost data was obtained from local published sources and hospital databases. We assessed average disaggregated and aggregated treatment costs, average and incremental cost per quality adjusted life years (QALYs) and life-years gained (LYG).**

Results : **Total treatment costs at 1 year were : terlipressin € 2,734 ; somatostatine € 2,972 ; octreotide € 2,801 ; and placebo € 2,874. The average costs per QALY were : terlipressin € 4,672 ; somatostatine € 5,878 ; octreotide € 5,540 ; and placebo € 5,687. In the cost per LYG analysis terlipressin achieved the lowest cost per life-year. Results from the incremental cost per QALY and LYG analysis indicated that terlipressin was the most cost-effective agent.**

Conclusions : **One year simulations indicate somatostatine is the most expensive treatment option and terlipressin the least costly. Amongst the vasoactive products, the incremental analysis indicated terlipressin was dominant when compared with octreotide and somatostatine because of improved survival and cost-saving potential that is likely attributed to avoiding additional and more costly interventions.** (Acta gastroenterol. belg., **2008**, 71, **230-236**).

Introduction

Bleeding oesophageal varices (BOV) is an acute gastrointestinal emergency with high recurrence rates associated with mortality ranging from 17% to 57% (1,2,3,4, 5,6,7). There has been some improvement in survival from antibiotic prophylaxis and increased use of endoscopic procedures and vasoactive drugs (8,9). Guidelines have endorsed endoscopic, pharmacological and shunt therapy (10). Endoscopic and pharmacological treatments, i.e., vasoactive agents, are usually administered only after admission to hospital and following diagnostic endoscopy, despite evidence of high mortality in the first hours following the initial bleed (11,12). In this evaluation we have applied standard treatment practices in Belgium which consists of endoscopy plus therapeutic intervention (banding or sclerotherapy) in combination with vasoactive drugs as first line BOV therapy.

Recent health care reform in Belgium has delegated purchasing decisions and budget accountability to hospitals as a measure to improve effectiveness in healthcare service provision (13). Such reform strengthens the need for economic evaluations to facilitate improved hospital formulary decision-making in order to optimise outcomes with limited budgets. Furthermore, hospital budgeting reform has led to the establishment of reimbursement forfeits based on fixed hospital procedures which can be informed by economic evaluations.

There have been several economic analyses comparing the various treatment options in BOV, including primary prevention, management of acute bleeding and prevention of rebleeding, but none have compared whether vasoactive drugs are cost-effective when used in addition to the standard treatment of endotherapy (5,6,14,15,16, 17). Although terlipressin has been shown in two meta-analyses to have a significantly higher rate of haemostasis control, a significant increase in survival, with improvement in survival both alone and in combination with endoscopic treatment, there are still inconsistencies between treatment practices and the available clinical evidence for the management of BOV (18,19,20,21,22, 23).

The treatment of BOV is known to place a high demand on healthcare resources (1). In light of recent health care reform the aim of this study was to explore the combined effect of costs and effects (i.e. cost-effectiveness) in relation to vasoactive products used to treat BOV and understand how these factors could potentially influence medical decision-making and treatment practices in Belgium.

Patients, materials and methods

The economic evaluation described here is based on a recently published discrete event simulation model which accounts for relevant costs and outcomes associat-

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Table 1. — **Transition probabilities between BOV health states†**

Description	Base Value	95% uncertainty interval	References	Comments
Efficacy : **Relative risks (RR)**				
RR of failure to control bleeding on somatostatin analogues	0.65	0.47-0.89	18, 20	Cochrane review for high quality studies.
RR of failure to control bleeding on terlipressin	0.45	0.3-0.7	18, 20	Cochrane review for high quality studies.
RR of re-bleeding on somatostatin analogues	0.82	0.45-1.49	18, 20	Non-significant finding from Cochrane review. Point estimate of 1.0 applied in model.
RR of re-bleeding on terlipressin	0.93	0.46-1.87	18, 20	Non-significant finding from Cochrane review. Point estimate of 1.0 applied in model.
RR of death on somatostatin analogues	0.96	0.74-1.24	18, 20	Non-significant finding from Cochrane review. Point estimate of 1.0 applied in model.
RR of death on terlipressin	0.61	0.45-0.84	18, 20	Reported in Cochrane review for high quality studies.
Other				
Average age of cohort	60	50-70	18, 20	Based on age from trials in Cochrane review
Length of simulation time horizon in years	1	1,3	5, 26	Baseline simulations run for 1 year ; other time horizons checked for robustness.
Discount rate : Costs Benefits	 3% 1.5%	0-5%	25	KCE Guideline 12

† Reproduced from Wechowski *et al*.

ed with vasoactive products used to treat BOV (24). In light of recent Belgium hospital funding reform we have adapted this model to facilitate hospital resource allocation decisions in relation to BOV treatments. In adapting the economic model to Belgium we adhered to the pharmacoeconomic guidelines developed by the Federaal Kenniscentrum voor de gezondheidszorg (KCE) for submission to the Drug Reimbursement Committee (CRM-CTG) for obtaining Class I drug reimbursement (25). As stated in the KCE report, the Pharmacoeconomic guidelines aim to improve methodological quality, transparency and uniformity of pharmacoeconomic evaluations reviewed for reimbursement by CRM-CTG. The key probabilities and assumptions applied in the model are described in Table 1 as described in Wechowski *et al* (24).

As previously described, and as briefly outlined in this paper, the economic model consists of five health states as follows : bleeding, no bleeding, post-transjugular intrahepatic portosystemic shunt (TIPS), post-salvage surgery and death (Fig. 1). Patients transition through the health states based on the relative risk of each event, as described using high-quality Cochrane meta-analyses and previously applied in BOV modelling. The base case simulation was one year with simulations run for up to three years which is realistic in light of the natural history of BOV (KCE Guideline 9) (25). Baseline survival, control of bleeding, re-bleeding rates and health-state utility (HSU) in cirrhotic patients during bleeding and non-bleeding were sourced from observational studies with long term follow-up with adjustment made to baseline mortality as previously described (24).

Belgium cost data

Belgium inpatient and outpatient cost data was obtained from several sources as described in Table 2. BOV specific hospitalisation costs were obtained from a brief review of recent BOV hospitalisations at Ghent University Hospital conducted by the authors, and verified against cost data obtained from the IMS Belgium Hospital Disease Database. The cost obtained from the IMS Belgium Hospital Disease Database was deemed representative of institutions where the majority of BOV cases are treated. We addressed variation in hospitalization cost by sampling the cost values from 95% uncertainty intervals in probabilistic sensitivity analysis. Where published data was not available, costs were derived from local treatment practices obtained from expert opinion.

Costs of secondary prophylaxis during non-bleeding periods were also included in the calculations. These

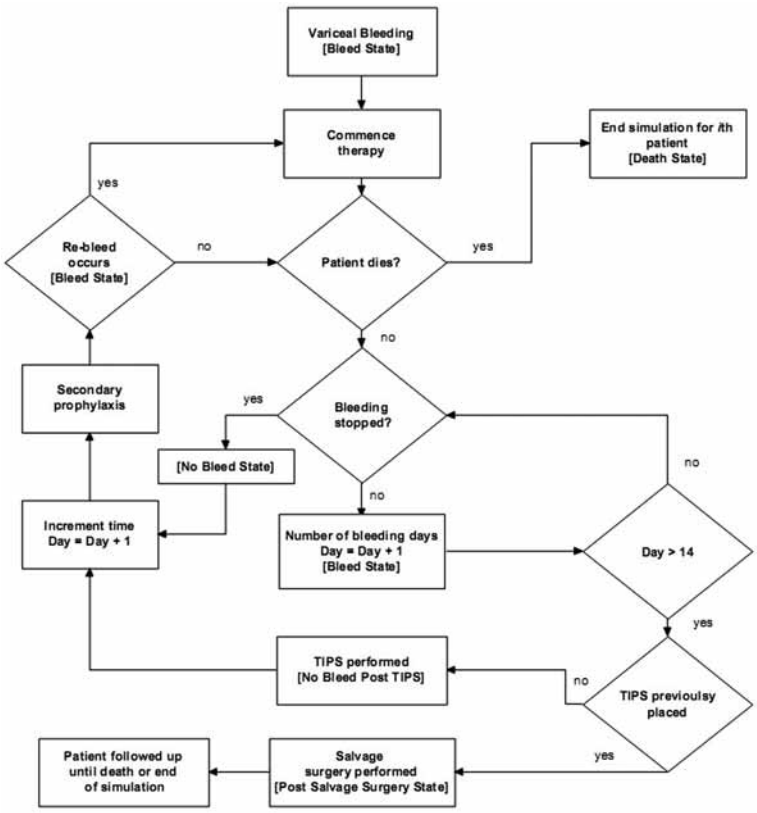

Fig. 1. — Flowchart illustrating bleeding oesophageal varices (BOV) health states used in the economic evaluation of vasoactive products (Reproduced with permission from Wechowski *et al.*).

comprised endoscopic treatment and treatment with beta-blockers (27). The following assumptions were also made when deriving costs : 5 endoscopic sessions were required following a bleeding episode with an annual chance of re-bleeding at 40% ; 120 mg daily administration of propranolol, 10 visits to a General Practitioner per year following the initial bleed for all patients. Excess cost of treatments immediately preceding death was an imputed value estimated at € 1,000. The perspective of the analysis is that of the Belgium hospital services and all costs were expressed in Euros for the year 2005 with the exception of drug costs which reflect 2007 prices.

Vasoactive treatment costs

Daily dosing for vasoactive treatments were based on Proceedings of the 4th Baveno International Consensus workshop and described in Table 3. Drug cost data were obtained from Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (RIZIV) and applied in the economic modelling.

Outcomes reported

As stated in the KCE Pharmacoeconomic guidelines the valuation of outcomes in economic evaluations should be based on final outcomes (KCE Guideline 8). In our assessment we assessed average cost per quality-adjusted life years (QALYs) and average cost per life-years gained (LYG) for each product. We also performed comparative cost-effectiveness for QALYs and LYG between the vasoactive products expressed as an incremental cost-effectiveness ratio (ICER). The ICER is a comparative metric used to represent the additional cost required to achieve an additional outcome (e.g., QALY, LYG) improvement between two different treatment options, and is instrumental in making resource allocation decisions (28).

The QALYs were determined from the time spent in each BOV health state and weighted using reported health state utility (HSU) which represent the quality of life burden associated with each BOV health stage (e.g., bleeding post-TIPS, post-salvage surgery, and death). Health state utility scores are a common metric used in economic analysis which reflect the preference that people have for different health states where score of 1.0 represents perfect health whilst a score of 0.0 corresponds to death (28). Baseline HSU for non-bleeding BOV patients of 0.75 was obtained based on previous studies (29). In the model a HSU deficit of 25% from baseline was applied for each bleeding episode, giving utility during episodes of 0.56. Utility toll post TIPS (25%) and salvage surgery (50%) was based on expert opinion, giving utility scores of 0.56 and 0.375, respectively. Uncertainty related to estimation was addressed in PSA by using confidence intervals for utility tolls of

Table 2. — **Resource utilisation items and hospital procedure costs**

Procedure / Item	**Value**	**95% uncertainty interval**	**Notes & Reference**
Band ligation	€ 290.41 (with VAT)	€ 232.33-348.49	RIZIV number 473771 (http://inami.fgov.be/)
Sclerotherapy	€ 184.32 (with VAT)	€ 176.94-265.42	RIZIV number 473270 (http://inami.fgov.be/) Includes 10 ml aethoxysclerol
Length of hospitalisation :	Average 9.9 days	5-15	Ghent University data (2005)
Daily cost hospitalisation	ICU : € 1,050 Non-ICU : € 449	ICU : 787.50-1312.50 Non-ICU : 336.75-561.25	Ghent University data (2005). Cost excludes examinations and vasoactive treatment.
Cost of TIPS	€ 2,000	€ 1,500-2,000	Expert opinion
Cost of salvage therapy	€ 3,000	€ 2,250-3,750	Expert opinion
Cost of terminal treatment (death)	€ 1,000	€ 500-2,000	Expert opinion
Propranolol (secondary prophylaxis)	In-hospital : 0.0355 € / 40 mg capsule, 120 mg average daily dose.	No uncertainty assumed	http://inami.fgov.be/
Average number of procedures following bleed	4 procedures	3-5	Expert opinion
Average follow up visits following discharge	10 visits	8-12	Expert opinion

Table 3. — **Vasoactive dosing and costs used in model**

Product	**Dosing schedule**	**Cost & Source**
Terlipressin	12 mg per day, dose was halved for first day after bleeding stopped.	€ 27.14 per 1 mg ampoule (0.2 mg/ml) Source : RIZIV
Somatostatine	Bolus of 250 micrograms (µg) and continuous infusion of 250 µg per hour.	€ 104.28 per 3 mg ampoule (3 mg/ml) ; Source : RIZIV
Octreotide	Initiate 50 µg bolus followed by 50 µg per hour up to 5 days.	€ 37.50 per ampoule (50 µg /ml) ; € 8.53 per ampoule (10 µg /ml). Source : RIZIV

18.75-31.25 and 37.5-62.5%, respectively. A similar analysis based on life years gained for each product was also performed.

Furthermore, we report average aggregated treatment costs for each vasoactive treatment at year one and three. Disaggregated treatment costs at year-1 which includes drug costs, inpatient costs, outpatient costs and salvage therapy costs were also reported to inform decision-makers where relevant costs occur within the health system.

Sensitivity Analysis

As recommended in the KCE Guidelines we performed probabilistic sensitivity analysis (PSA) and generated cost-effectiveness acceptability curves (CEAC) to address uncertainty surrounding the economic evaluation (KCE Guideline 11). All input variables were randomly sampled from reported 95% confidence intervals or intervals deemed by experts to represent this level of uncertainty. The parameter values for simulated cohort of patients were sampled 1,000 times and plotted using on the CEAC. The CEAC curves describe the probability of each treatment option being cost-effective based on a maximum willingness to pay ranging from € 0 to € 30,000 per QALY (30).

Results

Costs of treatment

Total average treatment costs after one year using terlipressin, somatostatine, octreotide and placebo were € 2,731, € 2,969, € 2,799 and € 2,871, respectively (Table 4). The simulated results indicate that average vasoactive treatment cost was highest for those treated using somatostatine when compared to terlipressin and octreotide in which vasoactive costs represented € 433, € 358, and € 262, respectively. For all other bleeding related costs, which includes inpatient treatment, sclerotherapy, band ligations and drugs for secondary prophylaxis, the costs were comparable for all vasoactive treatments, however costs were much higher for the placebo treated group. Furthermore, the costs of salvage therapy and terminal care provided were lower for terlipressin when compared with somatostatine, octreotide and placebo.

Table 4. — **Average aggregated treatment costs year-1 and 3 with disaggregated costs for year-1 only**

	Terlipressin	Somatostatine	Octreotide	Placebo
Vasoactive drug costs	€ 359	€ 433	€ 262	€ 0
Inpatient costs	€ 1,439	€ 1,556	€ 1,556	€ 1,892
Outpatient costs	€ 643	€ 554	€ 554	€ 553
Salvage/terminal	€ 294	€ 429	€ 429	€ 429
Total costs year-1†	**€ 2,734**	**€ 2,972**	**€ 2,801**	**€ 2,874**
Total costs year-3	**€ 4,065**	**€ 4,080**	**€ 3,886**	**€ 3,954**

† Numbers may not total due to rounding.

Table 5. — **Average cost-effectiveness (C/E) ratios (years 1& 3)**

Average cost-effectiveness ratios	Terlipressin	Somatostatine	Octreotide	Placebo
Cost per QALY year-1	€ 4,672	€ 5,878	€ 5,540	€ 5,687
Cost per QALY year-3	€ 2,720	€ 3,410	€ 3,348	€ 3,306
Cost per LYG year-1	€ 3,482	€ 4,383	€ 4,132	€ 4,239
Cost per LYG year-3	€ 1,999	€ 2,509	€ 2,390	€ 2,432

Abbreviations :
QALY : quality adjusted life year
LYG : life years gained.

When the simulation was extended to three years the average total costs increased for all treatments. The three year results indicate costs for somatostatine (€ 4,067) were higher than terlipressin (€ 4,050), octreotide (€ 3,873) and placebo (€ 3,942).

Economic evaluation

The average cost-effectiveness results for each product indicate that the cost to achieve one additional QALY after one year were lowest for terlipressin (€ 4,711) when compared with somatostatine (€ 5,926), octreotide (€ 5,586) and placebo (€ 5,733). At year-3 the costs required to achieve an additional QALY remained lower for terlipressin when compared with the alternatives (Table 5). Similar conclusions at year-1 were made for the cost per life-year gained analysis indicating that treatment costs required to obtain an additional life were lower for terlipressin (€ 3,478) compared with somatostatine (€ 4,379), octreotide (€ 4,128), and placebo (€ 4,235).

To establish the relative cost-effectiveness for each intervention in BOV an incremental analyses was conducted between all the available treatment options. The incremental comparison between terlipressin and somatostatine and octreotide indicated terlipressin was the dominant vasoactive treatment option (i.e. improved outcomes at a decreased cost). Similar conclusions were drawn from the cost per LYG analyses comparing all of the vasoactive products. In addition, the comparison between somatostatine and placebo and octreotide and placebo indicates that the increased costs to achieve small QALY (i.e. 0.002) improvements with these treatments are not cost-effective, with cost per QALY of € 409,000 and € 303,000, respectively. Previous randomised studies suggest somatostatine and octreotide have similar efficacy, therefore the incremental analysis was not applicable.

Probabilistic sensitivity analysis (PSA)

The robustness of critical parameters was tested using PSA and plotted using CEAC. Terlipressin was found to be 99.8% cost-effective versus octreotide (0.1%) and somatostatine (0.1%) applying a ceiling ratio of € 30,000 per QALY. This means that for 1,000 iterations of sensitivity analysis, in 998 cases terlipressin was more cost-effective than octreotide and somatostatine. Terlipressin was also more likely cost-effective than the comparators for all ceiling ratios above € 720 per QALY (Fig. 2).

Discussion

Increasingly healthcare decision-makers are required to make resource allocation decisions across a range of different disease areas, and between various products indicated for similar conditions with constrained resources. To obtain optimal outcomes with available resources, decision-makers increasingly rely on economic evaluations to establish those products which represent the best value for money. This study has compared total treatment costs and outcomes of the available vasoactive treatment options used to treat BOV to assist healthcare decision-making in Belgium.

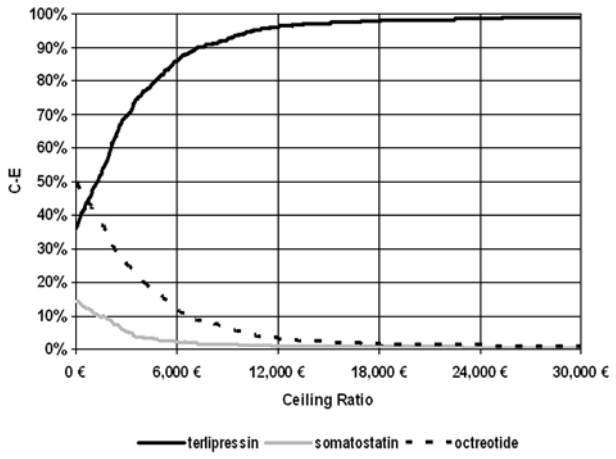

Fig. 2. — Cost-effectiveness acceptability curves for vasoactive agents in the treatment of BOV.

The results from our study highlight the importance of vasoactive treatment in the acute management of BOV. Amongst the vasoactive treatments used our results indicate drug costs at year-1 are lowest for octreotide (€ 262) when compared with terlipressin (€ 359) and somatostatine (€ 433). However, when total health care costs are considered in the management of BOV our results indicate that the lowest cost of treatment is achieved using terlipressin (€ 2,734) rather than octreotide (€ 2,801) or somatostatine (€ 2,972) suggesting that terlipressin results in additional cost savings within the healthcare system at year one. This stresses the importance for decision-makers to look beyond individual budgets when making resource allocation decisions (31).

When the costs and outcomes were extrapolated up to three years, small changes in total treatment costs amongst the vasoactive products were observed. The key findings suggest that terlipressin (€ 4,065) and somatostatine (€ 4,080) represent small but higher average treatment costs when compared to octreotide (€ 3,886) and placebo (€ 3,954) ; however this occurs for very different reasons. For terlipressin increased costs occur at year-3 because of the increased costs associated with survival which includes additional follow-up costs labelled as 'non-bleeding costs' in our model. For somatostatine, increased costs occur at year-3 because of higher vasoactive drug costs during the initial treatment phase and subsequent re-bleeds with no difference in survival compared to octreotide and placebo.

The results from the cost-effectiveness analyses indicate terlipressin is the dominant vasoactive treatment option when compared with octreotide and somatostatine both in terms of incremental cost per QALY and incremental cost per LYG (Table 6). This conclusion is based on the incremental cost-effectiveness analysis in which all of the available treatment options were compared. The incremental analysis also indicates that somatostatine and octreotide are not cost-effective treatment options when compared with placebo. The explanation for this is that improved haemostatic control alone with somatostatine and octreotide in the absence of proven survival compared to placebo provides only marginal QALY improvements. When the costs of somatostatine and octreotide are considered, it is clear that as an intervention, you are only purchasing haemostatic control without survival, hence leading to elevated incremental costs per QALY results (Table 6). Furthermore, conclusions from the economic evaluation were also supported by PSA which indicated a 99.8% of terlipressin being cost-effective based on a maximum willingness to pay of € 30,000 per QALY.

In terms of effectiveness, terlipressin controls variceal haemorrhage and improves mortality in Child-Pugh C patients and has also shown beneficial effects in combination with sclerotherapy (9). Furthermore, studies have shown earlier administration of terlipressin plus glyceryl-trinitrate is beneficial in controlling active upper gastrointestinal bleeding in cirrhotic patients (32). In contrast to terlipressin, the trials for somatostatine when used to treat BOV have come to different conclusions, in which there is no reported survival benefit (18). The use of octreotide for BOV is also controversial as no trials have shown octreotide to be superior to placebo in the absence of endotherapy, consequently it only appears beneficial when used in combination with endotherapy and yet no data shows a beneficial mortality effect (33,34). Therefore, we argue that terlipressin should be used as a first line vasoactive therapy based on efficacy, and as reported here, its ability to save costs. The usage of terlipressin in hospitals where endoscopy is not easily available or for some reason delayed or contraindicated makes terlipressin even more useful and cost-effective as a first line therapy.

Although the management of BOV has improved over the years, it still is associated with high mortality (35,36,37). This raises the question of the role of emergency sclerotherapy and band ligation in BOV and where vasoactive therapy fits with this as a haemostatic treatment for BOV ? Ligation is considered to be more preferable compared to sclerotherapy by many hepatologists and currently appears to be the preferred treatment option (38). However, it has been argued that the move from sclerotherapy to ligation is not based on randomised controlled data as shown in a recent meta-analysis (39). Equally, what is clear is that combination treatment of vasoactive agents and endoscopic therapy has a better effect on haemostasis than endoscopic therapy alone (40). Control of bleeding appears to be a major prognostic factor and first line treatment should be a combination of medical and endoscopic therapies. Vasoactive drugs have an established safety profile and can be easily administered by a wide array of care providers. They should be readily available to all patients with suspected variceal bleeding from cirrhosis. According to Baveno IV recommendations, vasoactive

therapy should be initiated as soon as possible after admission as a first line treatment (10). Medical therapy includes vasoactive agents and based on this study, terlipressin should be recommended first line over other vasoactive agents based on its cost-saving potential and effectiveness.

Conclusions

The results of this study indicate that vasoactive treatment not only saves lives but can also save health care resources. Specifically, our evaluation indicates that terlipressin offered the best opportunity to save costs over the treatment alternatives and should be considered as a first line vasoactive therapy in patients with bleeding oesophageal varices. The results presented here stress the need for decision-makers to look beyond vasoactive drug acquisition costs and consider the broader cost impact that drug formulary decisions can make on the entire healthcare system. As presented here, our results indicate that the least costly vasoactive product does not always represent the lowest total cost of treatment when a broader range of health costs are considered.

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