High-dose intravenous proton pump inhibition following endoscopic therapy in the acute management of patients with bleeding peptic ulcers in the USA and Canada: a cost-effectiveness analysis

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SUMMARY
Background: The efficacy of high-dose intravenous proton pump inhibition has recently been shown, yet its cost-effectiveness remains poorly studied.
Aim: To assess the cost-effectiveness of this approach separately for American and Canadian health care settings.
Methods: A validated decision model included patients with bleeding ulcers after successful endoscopic haemostasis. Probabilities were determined from the literature, and charges and lengths of stay from national databases. A third-party payer perspective was adopted over a 30-day time horizon.
Results: Re-bleeding rates were 5.9% for patients who received high-dose intravenous proton pump inhibition and 22.9% for those who did not. Hospitalization costs for patients with and without re-bleeding were US$11,802 and US$7,993, and CAN$5,220 and CAN$2,696, respectively. High-dose intravenous proton pump inhibition was more effective and less costly than the alternative of not administering it. The cost-effectiveness ratios for high-dose and no high-dose intravenous proton pump inhibition were US$9,112 and US$11,819 (CAN$3,293 and CAN$4,284 for the Canadian case), respectively. Sensitivity and threshold analyses showed that the results were robust across a wide range of clinically relevant assumptions.
Conclusion: In the USA and Canada, administering high-dose intravenous proton pump inhibition for 3 days is both more effective and less costly than not doing so for patients with bleeding ulcers after successful endoscopic haemostasis.

INTRODUCTION
Upper gastrointestinal bleeding, with ulcer haemorrhage as one of its major causes, is responsible for a considerable cost burden in the USA at an estimated 1 billion dollars annually. Based on a recent population estimate, almost 300,000 hospital admissions yearly may be attributable to acute upper gastrointestinal haemorrhage, and this significant burden is likely to continue with the ageing of the North American population.
Recent randomized controlled trials have demonstrated the efficacy of high-dose intravenous proton pump inhibition when administered to patients following endoscopic treatment, with a resultant decrease in re-bleeding. Related cost data are sparse, and we thus set out to evaluate the cost-effectiveness of administering high-dose intravenous proton pump inhibition to patients who had undergone successful primary endoscopic haemostatic therapy for the treatment of high-risk, non-variceal ulcer bleeds. Because of
the variability in practice, health resource utilization and costs, we examined the cost-effectiveness separately for the American and Canadian health care settings.

METHODS

Model structure, patient population and outcome

We constructed a decision tree model comparing two strategies in DATA 4.0 (Tree Age Software Inc., Williamstown, MA, USA): ‘high-dose intravenous proton pump inhibition’ and ‘no high-dose intravenous proton pump inhibition’ in patients with bleeding ulcers following successful endoscopic therapy for a high-risk lesion. The adopted model structure is shown in Figure 1.

The model structure is based on published trials, and its clinical validity was independently confirmed by two experienced clinician investigators (ANB and CAF). High-risk lesions were defined as ulcer beds exhibiting active bleeding (spurting/oozing), non-bleeding visible vessels or adherent clots. Patients in the ‘high-dose intravenous proton pump inhibition’ branch received an 80-mg bolus of pantoprazole within 12 h of endoscopy, followed by 8 mg/h for 3 days, and then an oral proton pump inhibitor (pantoprazole, 40 mg once daily) for the remainder of their hospital stay. Pantoprazole was chosen as the intravenous proton pump inhibitor as it is the only widely available intravenous proton pump inhibitor in both the USA and Canada. Patients in the ‘no high-dose intravenous proton pump inhibition’ branch received a 40-mg intravenous bolus for the first day, followed by oral pantoprazole, 40 mg once daily, for the remainder of their hospitalization. Patients who failed endoscopic haemostatic therapy were excluded from consideration, i.e. the outcome measure excluded the rate of primary haemostatic failure.

A 30-day time horizon was adopted, as this duration captures most clinically relevant outcomes and is a commonly reported duration of follow-up in trials of patients with ulcer bleeding. The outcome measure chosen was the 30-day re-bleeding rate.

Base-case and alternative-case scenarios

The same model structure was used for the two case scenarios, i.e. the American (base-case) and Canadian health care settings. Assumptions for each scenario with regard to hospitalization costs were thus extracted separately from documented country-specific registries and/or administrative databases using ‘real-life’ data, as described below. All probability estimates were derived from the randomized trial literature, and the same assumptions for these were used in both scenarios.

Probability assumptions

The probabilities of 30-day re-bleeding in the tree were obtained from a literature search of relevant articles, including all published randomized trials on the efficacy of high-dose intravenous proton pump inhibition (80-mg bolus followed by 8 mg/h for 3 days) following endoscopic therapy for patients with high-risk bleeding ulcer lesions. A MEDLINE search of the last 30 years up to December 2002 was performed on the terms ‘acid suppression’, ‘ulcer bleeding or haemorrhage’ and ‘proton pump’. Previously published narrative reviews on the topic were also analysed and hand searches were performed from relevant articles. Studies from which point estimates of re-bleeding rates for this patient population could not be estimated and trials using lower dosage regimens (including intermittent bolus administration) or patients without high-risk endoscopic lesions were excluded. All available study results were independently abstracted by

Figure 1. Decision model structure. IVPPI, high-dose intravenous proton pump inhibitor bolus (80 mg) followed by infusion (8 mg/h × 72 h). Patient NVU high-risk lesion, patient with a bleeding ulcer having received endoscopic therapy for a high-risk lesion (spurting, oozing, visible vessel, adherent clot).
two reviewers (KH and ANB), with discrepancies settled after discussion with a third (CAF). Robust estimates were obtained by pooling numerators and denominators, and the corresponding 95% confidence intervals (CI), when possible, were calculated using the standard approximation of the binomial distribution (Table 1).

Pharmacological costs

General considerations. As intravenous proton pump inhibition treatment is relatively new, we chose, as have others in the past,1 to adopt a conservative proton pump inhibitor cost, adding it to the average charges of hospitalization, and to subsequently perform a sensitivity analysis on this specific variable. The perspective adopted by the model was that of a third-party payer and thus indirect costs were not considered. Only hospitalization costs were entered in this analysis. All costs were adjusted for 2001.

US estimates. The specific pharmacological costs (pantoprazole 40 mg) were obtained from the manufacturer distributor in the USA (Wyeth Pharmaceuticals, Madison, NJ, USA8) and are listed in Table 1. The price range for the sensitivity analysis was arbitrarily set at US$0.01–10 for the 40-mg tablet and US$0.5–30 for the 40-mg vial.

Canadian estimates. The specific pharmacological costs (pantoprazole 40 mg) were obtained from the published list price by the Canadian distributor (Altana Pharma Canada, Oakville, Ont., Canada9) for the vial, and the governmental third-party payer, the Régie de l’Assurance-Maladie du Québec,10 for the tablet. We arbitrarily chose ranges similar to the US cost analysis.

Table 1. Point estimate and range assumptions for re-bleeding rates, lengths of stay and costs

<table>
<thead>
<tr>
<th>Source</th>
<th>Value of reference</th>
<th>Lower bound</th>
<th>Upper bound</th>
<th>Sensitivity analysis</th>
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<td>Probabilities of re-bleeding*</td>
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<td>0.16</td>
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<td></td>
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<td>US data (costs in US$)</td>
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<td>8.3</td>
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<td>3</td>
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<td>1500†</td>
<td>40 140†</td>
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<td>1500†</td>
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<td>0.01</td>
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<tr>
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<td>0.5</td>
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</table>

CHI, Canadian Institute for Health Information; IVPPI, high-dose intravenous proton pump inhibitor bolus (80 mg) followed by infusion (8 mg/h × 72 h); LOS, length of stay; NIS, Nationwide Inpatient Sample; RUGBE, Registry in Upper Gastrointestinal Bleeding and Endoscopy.

Patients who died were excluded from the calculations.

All costs are expressed in 2001 dollars (American costs in US$, Canadian costs in CAN$).

* For USA and Canada.
† Only the per diem costs were used in the model.
‡ Wyeth Pharmaceuticals (Madison, NJ, USA8).
§ Altana Pharma Canada (Oakville, Ont., Canada9).

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Determination of the lengths of stay and the costs of hospitalization

The lengths of stay were used to assist in the calculation of hospitalization costs and/or the determination of ranges for sensitivity analyses. Because of differences in available administrative data in the USA and Canada, the methodologies used varied for the determination of hospitalization costs for the two health care settings.

US estimates. The lengths of stay were obtained from the Nationwide Inpatient Sample 2000 database produced in May 2002 by the Healthcare Cost Utilization Project. We chose to use the representative 20% sample that is provided by the administrators (from the overall 7,450,992 records) to facilitate the analysis. We selected hospitalizations for patients of 18 years of age or older, who did not die, so as to focus on a homogeneous population with more representative costs. We retained only cases with Medicare as the expected first payer with registered diagnosis-related group system (DRG) codes of 174 (gastrointestinal haemorrhage with complication/co-morbidity) for cases with re-bleeding and 175 (gastrointestinal haemorrhage without complication/co-morbidity) for cases without re-bleeding. The standard deviation was used for the range of the sensitivity analysis on the length of stay (3–8.3 days if re-bleeding and 3–5.1 days if no re-bleeding). A lower limit of 3 days was chosen arbitrarily to allow for completion of the 72-h high-dose intravenous proton pump inhibitor infusion. Complication according to the DRG codes was interpreted as re-bleeding, as it is by far the most common complication amongst patients with ulcer haemorrhage.

The average charges per day were obtained from the same source as that described for the calculation of the length of stay and were computed as the sum of all the charges divided by the sum of all the lengths of stay. These included all hospital-related costs, including endoscopic procedures.

Canadian estimates. Data on medical resources were collected from the Canadian Institute for Health Information (DAD Resource Intensity Weights and Expected Length of Stay 2002; this national database includes 627,872 records). The cost per weighted case was given by the Institute of Health Economics. Within case-mix group (CMG) = 281 (gastrointestinal haemorrhage), we selected the third level of complexity defined by the Canadian Institute for Health Information. As these selection criteria were quite broad to define the ulcer bleeding diagnosis, we used the average length of stay of a national registry to more precisely determine Canadian per diem estimates. Indeed, the ascertainment of outcome into re-bleeding and no re-bleeding, and the length of stay, were provided by the Registry in Upper Gastrointestinal Bleeding and Endoscopy, a national registry of 1869 non-variceal bleeding patients included between March 1999 and January 2002. We specifically chose patients with documented bleeding ulcers. Criteria of exclusion were death during the 30 days following admission and transfer from another institution. We used the standard deviation to set the ranges for sensitivity analysis (3–20.3 days for cases with re-bleeding and 3–8.5 days if no re-bleeding occurred). Here too, a lower limit of 3 days was chosen specifically to allow for completion of the 72-h high-dose intravenous proton pump inhibitor infusion. Here too, the estimates include all hospital costs including endoscopic procedures.

US estimates. 11,474 admissions (1369 complications, i.e. re-bleeding) fulfilled the selection criteria. The mean length of stay was 3 days for cases of no re-bleeding vs. 4.7 days for patients with re-bleeding. The mean hospitalization costs varied from US$7993 for cases of no re-bleeding to US$11,802 if re-bleeding occurred (Table 1). Corresponding per diem costs were calculated. The ranges for the sensitivity analysis were based on the standard deviation of the per diem costs: US$500–12,528 for no re-bleeding and US$500–5760 for re-bleeding; for both, a minimal arbitrarily set value of $500 was chosen.

Canadian estimates. Within the Registry in Upper Gastrointestinal Bleeding and Endoscopy, 797 patients were identified with high-risk ulcer lesions, including 136 patients who re-bled. The mean length of stay was 4.7 days for patients without re-bleeding and 10.8 days in those who re-bled (Table 1). The mean hospitalization costs for a patient without and with re-bleeding were CAN$2696 and CAN$5220, respectively. Here too, the ranges for sensitivity analysis were based on the standard deviation of the per diem costs: CAN$501–671 for no re-bleeding and CAN$447–671 for re-bleeding.
Sensitivity and threshold analyses and interpretation of results

One-way and two-way sensitivity analyses were used to test the robustness of the results, and were performed on all probability assumptions, lengths of stay and cost variables across a wide range of pre-specified, clinically relevant values (Table 1). Sensitive variables were further analysed if they altered the mean cost-effectiveness estimates by at least 20%, a value that represented the smallest clinically relevant difference in the opinion of the investigators. Threshold analyses identified values of assumptions and costs for which the conclusions may change in accordance with the varying cost-effectiveness ratios.

The results of the analysis are reported as costs, effectiveness and cost-effectiveness ratios. In the context of a cost-effectiveness analysis, a strategy dominates another in the 'standard' sense if it is both less costly and more effective (i.e. cost-effective).

RESULTS

Probability estimates

Based on the literature search of randomized trials and published reviews, 4–7, 16–26 only two randomized studies fulfilled the pre-set selection criteria. 4, 7 Others either did not allow for a precise estimate of the probability of re-bleeding 5, 6 or included patients who did not have high-risk ulcer lesions. 16 The resultant re-bleeding rates following endoscopic therapy for patients with high-risk ulcer bleeding were 5.88% (95% CI, 2.9–11%) for those who received intravenous proton pump inhibition and 22.9% (95% CI, 16.3–30%) for those who did not.

Clinical scenarios

Base-case analysis. In the US setting, high-dose intravenous proton pump inhibition was also dominant, as it was both less costly (US$8576 vs. US$9112 per average patient) and more effective (5.88% vs. 22.9% re-bleeding rates) than a strategy of no high-dose intravenous proton pump inhibition; the cost-effectiveness ratios were US$9112 and US$11 819 per patient, respectively.

Alternative-case scenario. In the Canadian setting, high-dose intravenous proton pump inhibition was also dominant, as it was both less costly (CAN$3099 vs. CAN$3303) and more effective (5.88% vs. 22.9% re-bleeding rate) than a strategy of no high-dose intravenous proton pump inhibition; the cost-effectiveness ratios were CAN$3293 and CAN$4284 per patient, respectively.

Sensitivity and threshold analyses

Base-case analysis. For the US setting, the cost-effectiveness ratios varied by more than the pre-set 20% only with extreme assumptions of costs or lengths of stay for stays with and without re-bleeding. Regardless, in one-way sensitivity analysis, high-dose intravenous proton pump inhibition persistently dominated no high-dose intravenous proton pump inhibition for the range of probabilities of re-bleeding examined. In addition, the cost-effectiveness ratio was lower for high-dose intravenous proton pump inhibition for all values of cost and lengths of stay tested in the sensitivity analysis. Analogous conclusions remained in the two-way sensitivity analysis for all re-bleeding rates and for the great majority of clinically relevant assumptions of costs and lengths of stay.

Alternative-case scenario. For the Canadian setting, the one-way sensitivity analyses gave the same results as the US scenario. In contrast with the US scenario, two-way sensitivity analysis in the Canadian setting yielded some clinical circumstances in which the conclusions may alter. The result of the two-way analysis according to the re-bleeding rates is shown in Figure 2. If the re-bleeding rate in the absence of high-dose intravenous proton pump inhibitor infusion drops to 16% (lower limit of the 95% CI), the corresponding rate for high-dose intravenous proton pump inhibition will need to rise over 7% for the former to no longer be dominated. If the high-dose intravenous proton pump inhibition re-bleeding rate rises to 11% (upper limit of the 95% CI), the no high-dose intravenous proton pump inhibition alternative will cease to be dominated if its associated re-bleeding rate drops below 19.8%. With regard to the length of stay variations, decreasing the length of stay for cases without re-bleeding to 3 days (the lower limit of the selected range) would result in the no high-dose intravenous proton pump inhibition
A series of threshold analyses for both US and Canadian settings confirmed the robustness of the conclusions over all clinically plausible ranges of the variables. In particular, varying the US setting length of stay for patients undergoing re-bleeding or not across ranges of 1.1–8.3 days and 0.9–5.1 days, respectively, did not change the aforementioned conclusions.

DISCUSSION

Intravenous proton pump inhibitors are now commonly prescribed in the management of patients with acute upper gastrointestinal bleeding; although the efficacy of acute high-dose administration (80-mg bolus followed by 8 mg/h for the first 3 days) has been demonstrated in randomized trials, its cost-effectiveness remains poorly characterized in North America.

The assumptions used for the current analysis are limited by the published high-quality data on high-dose intravenous proton pump inhibition. Indeed, whereas only intravenous pantoprazole is available in North America, all of the fully published randomized controlled trials to date have studied intravenous omeprazole. The use of intravenous omeprazole estimates of efficacy is a reasonable approach as the effect of high-dose intravenous proton pump inhibitor therapy on patients with acute ulcer bleeding is thought to be a class effect, relating to profound acid suppression, and the gastric pH data using the two drugs appear to be similar.

The model excluded from consideration two initial Scandinavian studies that used a non-validated outcome measure not easily related to conventional re-bleeding rates; the most recent trial by Udd et al. was also left aside as it included a significant number of patients without high-risk endoscopic lesions.

Some differences in methodology exist between the studies by Lau et al. and Lin et al. included in the analysis. In the study by Lin et al., patients were given smaller doses of intravenous proton pump inhibitor or, in the case of controls, a cimetidine infusion. The data were nonetheless grouped, as meta-analyses support the assumption that H₂-receptor antagonist use approximates the efficacy of a placebo; moreover, the lower intravenous proton pump inhibitor dose used in the study by Lin et al. would only contribute to decrease any benefits attributable to high-dose intravenous proton pump inhibition and thus lead to more conservative results. The outcomes in the study by Lin et al. also examined 14-day and not 30-day follow-up, but it is recognized that most re-bleeding occurs early on, usually within the first 72 h. These considerations and the sensitivity analyses thus allow us to remain confident about the robustness of our conclusions.

The current decision model provides additional new support for the routine practice of acute profound acid suppression using high-dose intravenous proton pump inhibition for patients with bleeding ulcers who have undergone endoscopic treatment, this time from an economic standpoint. Indeed, high-dose intravenous proton pump inhibition is dominant for the chosen point estimates of probability assumptions and costs, being more effective at a lower cost. This conclusion is true for both American and Canadian clinical settings assessed in the base-case and alternative-case scenarios.
respectively. Furthermore, a series of one- and two-way sensitivity and one-way exploratory threshold analyses suggest that high-dose intravenous proton pump inhibition either dominates or remains more cost-effective than no high-dose intravenous proton pump inhibition across a wide range of likely and unlikely clinical scenarios.

It is unusual for a new pharmacological therapy to be both more effective and less costly, but this appears to be the case for high-dose intravenous proton pump inhibition. This observation is probably due to the high costs of an episode of re-bleeding, with its attendant prolonged hospital stay (including possible surgery), in contrast with a proportionately much more modest expense attributable to the administration of the high-dose intravenous proton pump inhibitor.

Although none of the limitations of this decision model are likely to affect the conclusions significantly, some consideration must be given to the shortcomings of some of its assumptions. The estimation of costs for patients admitted with upper gastrointestinal bleeding varies widely in the literature, and the adopted definition of complication as re-bleeding (the most prevalent complication in patients with upper gastrointestinal haemorrhage), although a workable one, could be disputed. A more uniform definition of re-bleeding in the administrative databases would also have been preferable, but we were limited by the actual elements included in these databases, where re-bleeding cases were defined using either DRG codes or clinical criteria of re-bleeding. It is more difficult to estimate the actual costs of health care in the USA than in Canada given the heterogeneous nature of the American health care system. We used the charges provided by the Nationwide Inpatient Sample for the hospitalizations mainly covered by Medicare. These do not represent the actual in-patient costs and only provide very rough estimates. Using a cost-to-charge ratio may yield better estimates. Regardless, the broad range of assumptions adopted in the sensitivity analyses suggest that none of these considerations are likely to affect the conclusions. Furthermore, the validity of our cost estimation is supported by the use of the most up-to-date large databases available for the USA and Canada; in addition, our estimates are in keeping with those previously published in the literature. The cost assumptions of the model are also based on lengths of stay that are not restricted to patients with high-risk stigmata; this could lead to an underestima-
lated based on Medicare fee schedules and DRG reimbursement. Others have examined the theoretical use of high-dose intravenous proton pump inhibition prior to endoscopy. Indeed, Enns and co-workers recently published a Canadian and later an American analysis suggesting that the administration of high-dose intravenous proton pump inhibition pre-endoscopy to all patients presenting with an upper gastrointestinal bleed, but only continued in those undergoing endoscopic haemostasis, may be cost-effective. This attractive alternative in a real-life setting, however, carries the risk of unintentionally promoting the over-utilization of high-dose intravenous proton pump inhibition. Indeed, preliminary Canadian and American data suggest that high-dose intravenous proton pump inhibitor infusions are often continued inappropriately according to current level 1 evidence following an endoscopy showing no high-risk bleeding ulcer lesion (D. Metz, 2003), a cost burden not modelled for in the analyses of Enns and co-workers. On the other hand, the Registry in Upper Gastrointestinal Bleeding and Endoscopy has raised the interesting possibility of a benefit in this lower risk group as well. Any investigation of acute acid suppression for upper gastrointestinal bleeding will also need to consider emerging data from Asia on the role of high-dose oral proton pump inhibitor use, as recently reported. The generalizability of such Asian results may be limited by differences in maximal acid output, and by genetically determined variations in the ability to metabolize proton pump inhibitors.

In conclusion, in the great majority of scenarios, the administration of high-dose intravenous proton pump inhibition to patients undergoing endoscopic haemostasis is less expensive and more effective than not providing this pharmacological treatment. This conclusion is robust over a wide range of clinically relevant assumptions in both the American and Canadian health care systems, and further supports the recommendations of a recent Consensus Conference on the management of patients with upper gastrointestinal bleeding.

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