

## **The Efficacy of Proton-pump Inhibitors in Acute Ulcer Bleeding: A Qualitative Review**

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Bustamante, Manuel M.D.; Stollman, Neil M.D., F.A.C.P.,  
F.A.C.G.

From the Department of Medicine (M.B.), University of Miami School of Medicine, Miami, Florida; and the Division of Gastroenterology (N.S.), University of Miami School of Medicine and Miami VA Medical Center, Miami, Florida.

Address correspondence and reprint requests to Dr. Neil H. Stollman, Division of Gastroenterology (D-1007), Miami VA Medical Center, 1201 NW 16th Street, Miami, FL 33125.

### **Abstract**

Despite remarkable progress in the treatment of chronic peptic ulcer disease, acute gastroduodenal ulcer hemorrhage remains a therapeutic challenge. Numerous trials of H-2 receptor antagonists have not consistently shown a significant benefit in such patients. Proton-pump inhibitors, which more profoundly suppress gastric acid, are being increasingly evaluated. We have performed a qualitative systematic review to analyze the results of these trials to determine if a reasonable consensus can be reached. We searched for all published, randomized, controlled studies that evaluated proton-pump inhibitors in patients with acute peptic ulcer hemorrhage. The primary outcomes evaluated were: (A) persistent or recurrent bleeding; (B) need for surgery; and (C) mortality. Sixteen trials were evaluated, enrolling 3154 patients. Four of the sixteen studies showed a statistically significant decrease in overall rebleeding rate, and two described specific benefit in patients with Type IIa and IIb endoscopic stigmata. Four studies also showed a significantly decreased surgery rate, but none demonstrated a significant mortality reduction. Proton-pump inhibitors may improve outcome in acute peptic ulcer bleeding, but the available clinical data remain inconsistent. Further study is necessary to define the optimal dosage, route of administration, duration of therapy, and subsets of patients most likely to benefit.

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Bleeding in the upper gastrointestinal (UGI) tract causes significant morbidity and mortality, with an overall incidence of approximately 150 hospital admissions per 100,000 population per year.<sup>1</sup> Mortality from acute UGI bleeding has remained at 6-10% despite improved medical and surgical treatments, the development of diagnostic and therapeutic endoscopy, and the use of intensive care units.<sup>2</sup> One contributing factor might be that patients with acute UGI bleeding tend to be older, with more co-morbid illnesses.<sup>1</sup> Furthermore, the widespread use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) has also substantially increased the risk of bleeding and its potential morbidity.<sup>3</sup>

Fortunately, bleeding stops spontaneously in the majority of patients with UGI bleeding. However, patients with continued or recurrent bleeding pose the greatest challenge. For these patients, endoscopic techniques (injection therapy, thermal, and laser treatment) are widely

used.<sup>4-7</sup> Despite the fact that these techniques may halve the rebleeding rate<sup>8,9</sup> and constitute the cornerstone of modern therapy, severe hemorrhage from peptic ulcer disease continues to expose patients to substantial risk. The rebleeding rate after initial hemostatic control with endoscopic treatment may still remain as high as 10-30%.<sup>10</sup> Therefore, there remains a clinical need for additional therapeutic options (e.g., acid suppressive therapy) in the care of these patients. The rationale for the use of agents that inhibit acid secretion in peptic ulcer bleeding is based on in vitro data showing that hemostatic mechanisms are highly pH dependent. At a pH of < 6.0, platelet disaggregation takes place. Below a pH of 5.4, platelet aggregation and plasma coagulation are virtually abolished, and below a pH of 4.0 fibrin clots are dissolved by the proteolytic activity of pepsin in the gastric juice.<sup>11</sup> Consequently, a profound reduction of gastric acidity, such that the pH approaches neutrality, could theoretically stabilize a clot overlying an ulcer and either help diminish bleeding or its recurrence.<sup>12-14</sup> Numerous trials of H<sub>2</sub> receptor antagonists (H<sub>2</sub>RAs) in patients with bleeding peptic ulcers have not consistently demonstrated a significant therapeutic benefit, either individually or by meta-analysis.<sup>15-18</sup>

In contrast to H<sub>2</sub>RAs, proton-pump inhibitors (PPIs) such as omeprazole, lansoprazole, rabeprazole, and pantoprazole more profoundly suppress acid secretion. Omeprazole has been the agent most frequently studied. These agents belong to the substituted benzimidazole group, and block H<sup>+</sup>/K<sup>+</sup> adenosinetriphosphatase (ATPase) in the parietal cells, markedly inhibiting gastric acid secretion and more consistently raising the intragastric pH.<sup>19,20</sup>

A number of studies have been performed using various methodologies to assess the clinical effect of PPIs in UGI bleeding. Overall, the individual trials using PPIs in acute UGI bleeding have yielded conflicting results, likely due to the various sample sizes, differing dosages or routes of administration, duration of treatment, and inconsistent use of adjunct endoscopic therapy. We have, therefore, performed a qualitative systematic review to appraise the characteristics of these trials, summarized the data where possible, and attempted to interpret the results. The aim of the project was to perform a qualitative systematic review of all randomized controlled trials performed between 1990 and 1998 evaluating PPIs in acute UGI bleeding.

## **MATERIALS AND METHODS**

We searched for all published and unpublished randomized, controlled trials evaluating the effect of a proton-pump inhibitor on acute UGI bleeding in patients with endoscopically documented bleeding peptic ulcers. These studies were identified by conducting manual and computer-assisted (MEDLINE) literature searches, and by reviewing the reference lists in relevant papers. We also contacted and queried the manufacturers of omeprazole (Astra-Zeneca, Wayne, PA), lansoprazole (TAP Pharmaceutical, Deerfield, IL) and Pantoprazole (Wyeth-Ayerst, Philadelphia, PA) about any unpublished data in this area. None reported having any such data. Reports published solely in abstract form were not included.

We included only those randomized controlled studies with diagnostic endoscopy at entry which showed acute peptic ulcer hemorrhage with or without initial endoscopic therapy. Studies in which patients were treated in a randomized fashion with proton-pump inhibitors and compared to treatment with either placebo (i.e., mannitol as placebo), somatostatin, or H<sub>2</sub>RAs were accepted. The primary outcomes considered as criteria for success or failure in all studies were: (A) persistent

or recurrent bleeding; (B) need for surgery; and (C) mortality.

We excluded unrandomized trials, comparisons solely between medical and endoscopic treatments, and those trials evaluating only intragastric pH while not reporting the primary clinical outcomes of rebleeding, surgery, and death.

## RESULTS

After a thorough review of all randomized controlled trials that investigated the use of proton-pump inhibitors in acute peptic ulcer bleeding, we identified 16 trials that satisfied the stated inclusion criteria. Three thousand one hundred and fifty-four patients were enrolled in these 16 trials. The characteristics of these studies are summarized in [Table 1](#), which shows the number of patients included in each study and the specific type and route of treatment and control. Eleven of the 16 studies did not use initial endoscopic hemostatic treatment and evaluated the effect of proton-pump inhibitors alone. Five studies assessed PPIs in conjunction with endoscopic therapy. In those using endoscopic therapies, the ulcers were treated initially with injection therapy in two studies,[30,31](#) with heater-probe or multi-polar electrocoagulation in one study,[10](#) and with a combination of injection therapy, heater probe, or multi-polar coagulation in two studies.[34,35](#) Only five of the sixteen studies were double blinded.[22,29,33-35](#) Two studies used a placebo (not defined specifically) as the control regimen,[29,33](#) three used mannitol,[22,34,35](#) eight used ranitidine,[21,23,26-28,30-32](#) two used cimetidine,[10,24](#) and one study used somatostatin plus ranitidine as the control regimen.[25](#) The results of the primary outcomes of rebleeding, surgery, and death are presented in [Table 2](#).

Trial	Double blinded	No. of patients evaluated			Active treatment	Control treatment	Endpoints evaluated		
		Randomized	Excluded after random	Endosc. therapy			Bleeding	Surgery	Death
Brunner <sup>21</sup>	No	39	-	-	Om IV 80 mg bolus + 40 IV q 12 h x 5 d	Ranit IV 50 mg bolus + 400 IV qd	+	+	+
Daneshmend <sup>22</sup>	Yes	1147	98	-	Om IV 80 mg bolus + 40 IV q8h x 3 doses + 40 PO q12h x 5 d	IV Mannitol + PO placebo	+	+	+
Perez Flores <sup>23</sup>	No	81	-	-	Om IV 80 mg bolus + 40 IV q8h x 72 h + 20 PO qd	Ranit IV 50 mg bolus + 100 IV q6h x 72 h + 150 PO q12h	+	+	+
Uribarrena <sup>24</sup>	No	282	-	-	Om IV 80 mg bolus + 40 IV q12h + 20 PO q12h until DC	Cimetidine IV 1200 mg qd + 400 IV q12h until DC	-	+	+
Goletti <sup>25</sup>	No	30	10	-	Om IV 80 mg bolus + 8 mg/h x 12 h + 4 mg/h until stable + 40 PO until endosc. heal	Somatostatin IV 250 µg bolus + 250 µg/h + Ranit 50 mg IV q4h until stable	+	+	+
Michel <sup>26</sup>	No	75	-	-	Lansop PO 60 mg/d x 6	Ranit PO 600 mg/d x 6 d	+	+	+
Ortiz <sup>27</sup>	No	519	-	-	Om IV 80 mg bolus + 40 IV q8h x 48 h + 40 IV q 12 h until DC	Ranit IV 50 mg bolus + 50 IV q6h until DC	+	+	+
Lanas <sup>28</sup>	No	51	-	-	Om IV 80 mg bolus + 40 IV q12h	Ranit IV 50 mg q4h	+	+	+
Lind <sup>29</sup>	Yes	333	11	-	Om IV 80 mg bolus + 8 mg/h x 72 h + 20 PO until day 21	Placebo	-	+	-
Prassler <sup>30</sup>	No	232	-	+	Om IV 80 mg bolus + 40 IV q8h	Ranit 3 mg/kg IV	+	+	+
Villanueva <sup>31</sup>	No	86	5	+	Om IV 80 mg bolus + 40 IV q8h x 4 d + PO	Ranit IV 50 mg q6h x 12-24 h + PO	+	+	+
Cardi <sup>32</sup>	No	63	18	-	Om IV 40 mg bolus + 80 IV/d x 3 d	Ranit IV 50 mg bolus + 400 + 80 IV/d x 3 d	+	+	+
Khuroo <sup>33</sup>	Yes	220	-	-	Om PO 40 mg BID x 5 d	Placebo	+	+	+
Schaffalitzky <sup>34</sup>	Yes	274	9	+	Om IV 80 mg bolus + 8 mg/h x 72 h + 20 PO qd until day 21	Mannitol 40 mg x 3 d + 20 PO qd until day 21	-	+	+
Hasselgren <sup>35</sup>	Yes	333	11	+	Om IV 80 mg bolus + 8 mg/h x 72 h + 20 PO qd until day 21	Mannitol IV 40 mg bolus + inf. x 72 h + Om PO 20 mg qd until day 21	+	+	+
Lin <sup>36</sup>	No	100	-	+	Om IV 40 mg bolus + 160 mg/d x 72 h + 20 PO qd x 2 months	Cimetidine IV 300 mg bolus + 1200/d x 72 h + 400 PO BID x 2 mo	+	+	+

Om, omeprazole; Lansop, lansoprazole; Ranit, ranitidine; IV, intravenous; PO, oral.

TABLE 1. Characteristics of evaluated trials

Trial	Bleeding			Surgery			Death		
	PPIs (%)	Control (%)	p value	PPIs (%)	Control (%)	p value	PPIs (%)	Control (%)	p value
Brunner <sup>21</sup>	3/19 (16)	17/20 (85)	NR	1/19 (5)	3/20 (15)	NS	1/19 (5)	1/20 (5)	NS
Daneshmend <sup>22</sup>	58/246 (24)	70/257 (27)	NS	45/246 (18)	50/257 (19)	NS	23/246 (9)	13/257 (5)	NS
Perez Flores <sup>23</sup>	1/38 (2.6)	4/43 (9)	NS	1/38 (2.6)	1/43 (2)	NS	0/38	0/43	NS
Uribarrena <sup>24</sup>	NA	NA	NA	6/131 (4.5)	6/151 (3.9)	NS	2/131 (1.5)	5/151 (3)	NS
Goletti <sup>25</sup>	0/10	1/10 (10)	NS	0/10	1/10 (10)	NS	0/10	0/10	NS
Michel <sup>26</sup>	8/38 (21)	11/37 (29)	NS	5/38 (13)	9/37 (24)	NS	1/38 (2.5)	2/37 (5)	NS
Orti <sup>27</sup>	2/267 (0.7)	4/252 (1.5)	NS	9/267 (3)	11/252 (4)	NS	2/267 (0.7)	2/252 (0.7)	NS
Lanas <sup>28</sup>	6/28 (21)	9/23 (39)	NS	1/28 (3.5)	5/23 (21)	NS	2/28 (7)	2/23 (8.6)	NS
Lind <sup>29</sup>	NA	NA	NA	4/159 (2.5)	16/163 (9.8)	p < 0.05	1/159 (0.6)	1/163 (0.6)	NS
Cardi <sup>32</sup>	1/21 (4.7)	7/24 (29)	p < 0.05	1/21 (4.7)	2/24 (8)	NS	0/21	0/24	NS
Khuroo <sup>33</sup>	10/108 (9)	37/107 (35)	p < 0.001	8/108 (7)	26/107 (24)	p < 0.001	2/108 (1.8)	6/107 (5.6)	NS
Prassier <sup>30</sup>	21/106 (20)	22/126 (17)	NS	9/106 (8)	11/126 (8.7)	NS	6/106 (5.6)	5/126 (3.9)	NS
Villanueva <sup>31</sup>	11/43 (26)	9/38 (24)	NS	8/43 (18)	8/38 (21)	NS	3/43 (6.9)	1/38 (2.6)	NS
Schaffalitzky <sup>34</sup>	NA	NA	NA	6/130 (4.6)	15/135 (11)	NR	2/130 (1.5)	0/135	NS
Hasselgren <sup>35</sup>	NA	NA	NA	4/159 (2.5)	16/163 (9)	p = 0.003	1/159 (0.6)	1/163 (0.6)	NS
Lin <sup>10</sup>	2/50 (4)	12/50 (24)	p < 0.05	0/50	0/50	NS	0/50	2/50 (4)	NS

NA, not available; NS, not significant; NR, not reported (results reported as 'significant'; p value not reported); PPIs, proton pump inhibitors.

TABLE 2. Outcomes of evaluated trials

### Rebleeding Rate

For the 11 studies in which endoscopic therapy was not administered, the rebleeding rate in the control groups had a very wide range, from 1.5%<sup>27</sup> to 85%.<sup>21</sup> Omeprazole, however, was associated with generally lower rates of rebleeding, ranging from 0%<sup>25</sup> to 24%.<sup>22</sup> This attained statistical significance in three of the studies, those of Brunner <sup>21</sup>: 16% vs. 85%; Khuroo <sup>33</sup>: 9% vs. 35%, and Cardi <sup>32</sup>: 4% vs. 29%.

In the five studies that used concomitant initial endoscopic therapy in both arms, rebleeding rates in the control groups ranged from 17%<sup>30</sup> to 24%.<sup>10,31</sup> The active therapy groups again showed a generally lower rebleeding rate, ranging from 4%<sup>10</sup> to 26%<sup>31</sup>; in only one study, however, did this result attain statistical significance.<sup>10</sup>

### Endoscopic Stigmata

Endoscopic features of the ulcer (e.g., clean-based, visible vessel, etc.) have been shown to be important independent predictors of recurrent ulcer bleeding. Table 3 shows the results in the only three studies that described the incidence of recurrent bleeding based on endoscopic criteria (e.g., stigmata of recent hemorrhage).<sup>10,28,33</sup> Two of these three studies, those of Khuroo <sup>33</sup> and Lin,<sup>10</sup> reported statistically significant results in terms of a decreased rebleeding rate (p < 0.001 and p < 0.05, respectively), particularly with ulcers type IIa and IIb from the Forrest Classification

(non-bleeding visible vessels or clots).

Trial	Arterial spurting			Active oozing			NBVV			Adherent clot			All categories		
	PPIs, (%)	Control, (%)	p value	PPIs, (%)	Control, (%)	p value	PPIs, (%)	Control, (%)	p value	PPIs, (%)	Control, (%)	p value	PPIs, (%)	Control, (%)	p value
Khuroo <sup>33</sup>	6/9 (67)	11/12 (92)	NS	2/18 (11)	3/16 (19)	NS	2/17 (12)	10/18 (56)	p < 0.05	0/64 (0)	13/61 (21)	p < 0.001	10/108 (9)	37/107 (35)	p < 0.001
Lanas <sup>28</sup>	Lesion not included			1/5 (20)	2/4 (50)	NS	1/3 (33)	2/4 (50)	NS	4/20 (20)	5/15 (33)	NS	6/28 (21)	9/23 (39)	NS
Lin <sup>10</sup>	0/9 (0)	2/12 (17)	NS	1/4 (25)	1/9 (11)	NS	1/37 (3)	9/29 (31)	NR	Lesion not included			2/50 (4)	12/50 (24)	p < 0.05

NBVV, non-bleeding visible vessel; NR, not reported; NS, not significant.

TABLE 3. Rebleeding rates in trials stratifying results by endoscopic findings

### Surgical Rate

The incidence of continued bleeding requiring surgical intervention was similar in the studies with and without endoscopic therapy. In the eleven trials that did not use endoscopic therapy, two [29,33](#) demonstrated statistically significant reductions compared to placebo while three studies [21,26,28](#) described a trend toward lower surgical rates, but these did not attain statistical significance. The other six trials did not reveal any statistically significant results pertaining to this outcome.

Among the five trials that used adjunct endoscopic treatment, two reported statistically significant lower surgical rates compared to placebo.[34,35](#)

### Mortality Rate

None of the studies, either with or without adjunct endoscopic therapy, demonstrated a significant benefit of active treatment in terms of reduction of mortality rate.

## DISCUSSION

Despite remarkable progress in the treatment of chronic peptic ulcer disease in the past decades, gastroduodenal ulcer hemorrhage remains a therapeutic challenge. H-2 receptor antagonists are quite effective in healing peptic ulcers, but they do not reduce the transfusion requirement, episodes of further bleeding, or the need for surgery in patients with acute peptic ulcer bleeding.[2](#) This may be due to incomplete suppression of gastric acid secretion or to the observation that these agents only reduce basal acid secretion but not food or pentagastrin-stimulated secretion.[34](#) Furthermore, patients may develop a tolerance of the acid suppressive effects of these agents.[36,37](#)

Proton pump (H<sup>+</sup>/K<sup>+</sup> ATPase) inhibitors more profoundly suppress gastric acid production and secretion, and have been used since 1985 for the treatment of acid peptic disease. However, IV preparations are not available in the United States at this time. There is a theoretical basis for believing that these agents may be more effective than H-2 blockers in the treatment of acute bleeding in that a more effective suppression of acid secretion may minimize the deleterious effects of an acidic environment on hemostasis. Their role, however, remains controversial, with conflicting results in the clinical trials reported to date. Due to the significant heterogeneity in the reported trials (e.g., differences in sample size, route of administration, adjunct endoscopic therapy, and

dosage/duration of therapy), combining their statistical results by formal meta-analyses is likely inappropriate. Alternatively, we have prepared a qualitative systematic review to analyze the results of the 16 reported trials in an attempt to assess whether a reasonable consensus may be reached.

Overall, only 7 of these 16 trials [10,21,29,32-35](#) demonstrated a statistically significant reduction in the endpoints of rebleeding (4 of 16) or need for emergent surgical intervention (4 of 16, one showed benefit for both endpoints). None showed a reduction in mortality. In 5 of these 7 trials, continuous IV infusions of omeprazole were used.[10,29,32,34,35](#) One used intermittent IV omeprazole [21](#) and one used oral omeprazole.[33](#) One negative trial [26](#) used oral lansoprazole, but theoretically this agent, as well as other proton-pump inhibitors, would be equally effective if adequately studied.

Over half (9 of 16) of the trials evaluated did not show a significant reduction in any of the primary outcomes: rebleeding, surgery, or mortality rate. A number of factors may have made demonstrating such a benefit difficult, however (e.g., a type II error). Some studies included limited numbers of patients, in one case as few as 30.[25](#) Others included larger study populations, for example the UK study [22](#) in which 1147 patients were enrolled. The UK study also included patients with bleeding from malignancies and esophageal varices, two situations in which a benefit from PPIs might not be expected. In fact, no overall benefit of omeprazole was demonstrated in this study. Furthermore, 11 of the studies compared proton pump inhibitors to H-2 blockers rather than to placebos, which might also have obscured a benefit. Both therapies decrease gastric acidity, differing mainly in degree. If H-2 blockers have a modest beneficial effect, this could have partially masked an additional benefit of proton-pump blockers, most notably in the smaller studies.

Numerous design flaws are apparent in the majority of these studies, such as a relatively low dosage of omeprazole used (< 8mg/h for at least 72 hours or < 40 mg PO QD),[21-24,27,28,30-32](#) a small number of patients,[10,21,23,25,26,28,31,32](#) and inhomogenous patient characteristics with multiple bleeding etiologies.[22](#) Only five of the sixteen were double-blinded,[22,29,33-35](#) but of these, four of five [29,33-35](#) demonstrated a favorable clinical outcome in rebleeding and/or surgery. [Table 4](#) characterizes the the design attributes and flaws for the studies reported, specifically for blinding, number of patients studied, drug dosage, duration of therapy, ancillary endoscopic therapy, and stratification by stigmata of recent hemorrhage.

Trial	Double blinded	Size*	Dosage†	Duration‡	Concomitant endosc. therapy	Stratification by endosc. stigmata
Brunner <sup>21</sup>	-	-	-	+	-	-
Daneshmend <sup>22</sup>	+	+	-	+	-	-
Perez Flores <sup>23</sup>	-	-	-	+	-	-
Uribarrena <sup>24</sup>	-	+	-	+	-	-
Goletti <sup>25</sup>	-	-	+	+	-	-
Michel <sup>26</sup>	-	-	-	+	-	-
Orti <sup>27</sup>	-	+	-	+	-	-
Lanas <sup>28</sup>	-	-	-	+	-	+
Lind <sup>29</sup>	+	+	+	+	-	-
Prassler <sup>30</sup>	-	+	-	-	+	-
Villanueva <sup>31</sup>	-	-	-	+	+	-
Card <sup>32</sup>	-	-	-	+	-	-
Khuroo <sup>33</sup>	+	+	+	+	-	+
Schaffalitzky <sup>34</sup>	+	+	+	+	+	-
Hasselgren <sup>35</sup>	+	+	+	+	+	-
Lin <sup>10</sup>	-	-	+	+	+	+

\*Size of the sample, ≥200.  
†Dosage, continuous infusion for at least 72 hours (8 mg/h) or ≥40 mg PO q day.  
‡Duration; ≥72 hours.  
Endosc, endoscopic.

TABLE 4. Quality of trials

We identified three studies that demonstrated a statistically significant benefit in the omeprazole treated group but that did not incorporate initial adjunct endoscopic therapy, which would be standard practice in this country for ulcers with such stigmata.<sup>21,32,33</sup> The results of these studies, although favorable, might be of limited applicability to clinicians in countries where endoscopic therapy is available and considered standard-of-care for ulcers with endoscopic stigmata. Two of these studies used IV omeprazole <sup>21,32</sup> and one used a high dose of oral omeprazole.<sup>33</sup> This latter study,<sup>33</sup> performed in India, reported a significant reduction in further bleeding and a need for surgery in patients with visible vessels or adherent clots (IIa and IIb from Forrest Classification). It is noteworthy, however, that the dose of omeprazole (40 mg PO BID × 5 days) was relatively high. Furthermore, these patients had fewer coexistent medical illnesses than typical patients in the United States. In addition, it has been suggested that patients in India may have different patterns of peptic ulcer disease than individuals in Western countries,<sup>2</sup> which might further limit the ability to extrapolate this result. The positive results of the IV studies <sup>21,32</sup> suggests that faster and more potent acid suppression may be more effective, but again, the failure to use therapeutic endoscopy hinders a more expansive generalization of these results.

Initial endoscopic therapy was performed in five studies,<sup>10,30,31,34,35</sup> which more accurately reflects current management strategies, but could also serve to obscure an added beneficial effect of proton-pump inhibitors in acute management of peptic ulcer bleeding. Only one of these five trials with prior endoscopic therapy <sup>10</sup> demonstrated a significant decrease in rebleeding rates (4 vs. 24%). This trial used a continuous infusion of IV omeprazole during the first three days of treatment and demonstrated the ability to maintain an intragastric pH > 6.0 for >80% of the time. Additionally, two trials <sup>34,35</sup> demonstrated a significant reduction in surgical rates after initial endoscopic therapy and continuous infusion of omeprazole for 72 hours. In both, endoscopic therapy was given to all patients with evidence of arterial spurting. In one study,<sup>34</sup> endoscopic therapy was also given to patients with arterial oozing or visible vessel. However, in both trials all patients received oral omeprazole after the third day for a total of three weeks that might explain the lack of significant differences in outcomes at day 21.

Only three studies included results stratified by endoscopic stigmata.<sup>10,28,33</sup> Of these, Khuroo and Lin<sup>10,33</sup> showed that rebleeding from ulcers with non-bleeding visible vessels and adherent clots (IIa and IIb, respectively) occurred less often following omeprazole treatment, even when endoscopic therapy had also been administered.<sup>10</sup> The presence of Ia and Ib stigmata (arterial spurting and oozing) required initial endoscopic therapy to stop bleeding; however, the associated use of proton-pump inhibitors to prevent rebleeding did not show significant results in any study reported.

In summary, several studies reported to date have suggested that using the optimal dosage of a proton-pump inhibitor, most likely a continuous infusion for at least 72 hours, can reduce rebleeding episodes as well as the need for surgical procedures in patients with acute peptic ulcer bleeding. Conversely, of the two studies of the highest apparent quality (e.g., were double-blind, had large sample size, optimal dosing, and used concomitant endoscopic therapy),<sup>34,35</sup> neither reported decreased rebleeding rates. Further, neither stratified patients by endoscopic criteria, which is likely to help identify those patients at highest risk and thus who are most likely to benefit from therapy. We conclude, therefore, that the available data suggests, but does not definitively prove, that use of proton-pump inhibitors may improve outcomes in some patients with acute peptic ulcer bleeding. Further study is clearly necessary to define the optimal dose, route of administration, duration of therapy, and the subsets of patients most likely to benefit from such therapy. We suggest that well designed double-blinded randomized controlled trials using initial endoscopic treatment where appropriate, with stratification by stigmata of recent hemorrhage be undertaken. Continuous infusion may be more efficacious than intermittent dosing, but this too requires confirmation.

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