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High-Dose vs Non–High-Dose Proton Pump Inhibitors After Endoscopic Treatment in Patients With Bleeding Peptic Ulcer

A Systematic Review and Meta-analysis of Randomized Controlled Trials

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• La mortalité des hémorragies digestives sur ulcère peptiques restent encore grevée d'une mortalité qui avoisine 10%.

• Plusieurs études ont montré que les IPP sont supérieurs aux antiH2 dans le contrôle des épisodes hémorragiques. Il n'y a cependant pas de consensus sur la dose optimale des IPP en IV.

•D'après les études disponibles il y aurait une supériorité pour les doses élevées mais sans évidence. Cette problématique a justifié la présente méta-analyse.

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Background: High-dose proton pump inhibitors (PPIs) (80-mg bolus, followed by 8-mg/h continuous infusion for 72 hours) have been widely studied and used. However, to date no concrete evidence has shown that high-dose PPIs are more effective than non–high-dose PPIs.

Methods: We performed a literature search for randomized controlled trials that compared the use of high-dose PPIs vs non–high-dose PPIs in patients with bleeding peptic ulcer and determined their effects on rebleeding, surgical intervention, and mortality. Outcomes data were combined in a meta-analysis and were reported as odds ratios (ORs) with 95% confidence intervals (CIs).

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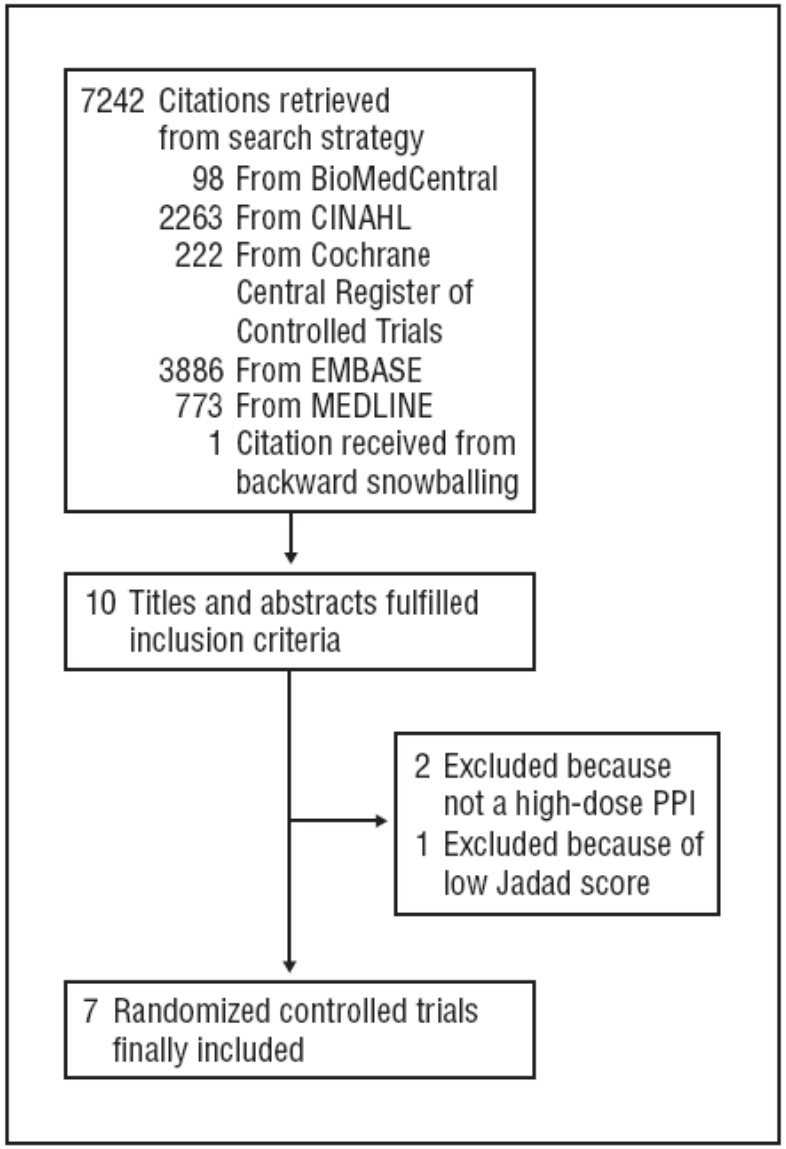

Figure 1. Literature search performed herein. PPI indicates proton pump inhibitor.

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Table 1. Study Design and Patient Characteristics

Source	Multicenter Enrollment	Double-Blind	No. of Patients	Age, Mean, y	Male Sex, No. (%)	Forrest Classification by Endoscopy, No. (%)					
						F1A	F1B	F2A	F2B	F2C	F3
Udd et al,[27] 2001[a]	Yes	Yes	142	64.7	85 (59.9)	16 (11.3)	47 (33.1)	19 (13.4)	22 (15.5)	38 (26.8)	0
Cheng et al,[22] 2005	No	No	105	64.2	67 (63.8)	98 (93.3)[b]				7 (6.7)	0
Yilmaz et al,[26] 2006	No	Yes	211	52.7	145 (68.7)	0	0	0	21 (10.0)	46 (21.8)	144 (68.2)
Bajaj et al,[28] 2007	No	No	25	63.0	16 (64.0)	7 (28.0)		7 (28.0)	0[c]	2 (8.0)	9 (36.0)
Hung et al,[23] 2007	No	No	103	60.9	67 (65.0)	11 (10.7)	52 (50.5)	26 (25.2)	13[d] (12.6)	0	0
Andriulli et al,[24] 2008[a]	Yes	Yes	474	66.5	307 (64.8)	50 (10.5)	155 (32.7)	166 (35.0)	103 (21.7)	0	0
Yüksel et al,[25] 2008	No	No	97	58.3	74 (76.3)	7 (7.2)	60 (61.9)	30 (30.9)	0	0	0

Abbreviations: F1A, spurting blood; F1B, oozing blood; F2A, nonbleeding visible vessel; F2B, adherent clot; F2C, flat pigmented spot; F3, clean ulcer base.

[a]The percentages of 2 studies[24,27] do not total 100 owing to rounding.

[b]This study used a different classification system for endoscopic findings, which were converted to corresponding Forrest classifications.

[c]There was a discrepancy between the text and table in the original article. The data in the table are given here.

[d]The original article missed 1 patient in this classification, but the correct data cannot be retrieved from the text. This mistake does not influence the outcomes nalysis.

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Table 2. Outcomes Data in the Meta-analysis

Source	No. of Patients	Analysis	High-Dose PPI	Non–High-Dose PPI	Rebleeding, No. (%)		Surgical Intervention, No. (%)		Mortality, No. (%)	
					High-Dose PPI	Non–High-Dose PPI	High-Dose PPI	Non–High-Dose PPI	High-Dose PPI	Non–High-Dose PPI
Udd et al,[27] 2001	142	PP	Omeprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)	Omeprazole (IV 20 mg/d for 3 d)	8/69 (11.6)	6/73 (8.2)	5/69 (7.2)	3/73 (4.1)	2/69 (2.9)	4/73 (5.5)
Cheng et al,[22] 2005	105	ITT	Omeprazole (IV 80-mg bolus and IF 200 mg/d for 3 d)	Omeprazole (IV 80-mg bolus and IF 80 mg/d for 3 d)	21/52 (40.4)	23/53 (43.4)	Unavailable	Unavailable	Unavailable	Unavailable
Yılmaz et al,[26] 2006	211	ITT	Omeprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)	Omeprazole (oral 40 mg every 12 h for 3 d)	7/112 (6.2)	5/99 (5.1)	3/112 (2.7)	2/99 (2.0)	3/112 (2.7)	2/99 (2.0)
Bajaj et al,[28] 2007	25	ITT	Pantoprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)	Pantoprazole (oral 80 mg every 12 h for 3 d)	2/13 (15.4)	0/12	1/13 (7.7)	0/12	0/13	0/12
Hung et al,[23] 2007	103	PP	Pantoprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)	Pantoprazole (IV 80-mg bolus and IV 40 mg every 12 h for 3 d)	2/54 (3.7)	2/49 (4.1)	0/54	1/49 (2.0)	0/54	0/49
Andriulli et al,[24] 2008	474	PP	Omeprazole or pantoprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)	Omeprazole or pantoprazole (IV 40 mg/d for 3 d)	28/238 (11.8)	19/236 (8.1)	3/238 (1.3)	1/236 (0.4)	5/238 (2.1)	5/236 (2.1)
Yüksel et al,[25] 2008	97	PP	Pantoprazole (IV 80-mg bolus and IF 8 mg/h for 3 d)	Pantoprazole (IV 40 mg every 12 h for 3 d)	4/48 (8.3)	3/49 (6.1)	2/48 (4.2)	2/49 (4.1)	0/48	0/49

Abbreviations: IF, infusion; ITT, intent to treat; IV, intravenous; PP, per protocol; PPI, proton pump inhibitor.

Effet sur la récidive hémorragie

Source	High-Dose PPI		Non–High-Dose PPI		Weight, %	OR (95% CI)
	No. of Events	No. of Patients	No. of Events	No. of Patients		
Udd et al,[27] 2001	8	69	6	73	11.3	1.46 (0.48-4.46)
Cheng et al,[22] 2005	21	52	23	53	29.7	0.88 (0.41-1.92)
Yılmaz et al,[26] 2006	7	112	5	99	10.9	1.25 (0.38-4.08)
Bajaj et al,[28] 2007	2	13	0	12	0.9	5.43 (0.24-125.59)
Hung et al,[23] 2007	2	54	2	49	4.4	0.90 (0.12-6.67)
Andriulli et al,[24] 2008	28	238	19	236	36.8	1.52 (0.83-2.81)
Yüksel et al,[25] 2008	4	48	3	49	6.0	1.39 (0.29-6.59)
Total	**72**	**586**	**58**	**571**	**100.0**	**1.30 (0.88-1.91)**

Heterogeneity: $\chi^2_6 = 2.19$, $P = .90$, $I^2 = 0\%$.
Test for overall effect: $z = 1.33$, $P = .18$

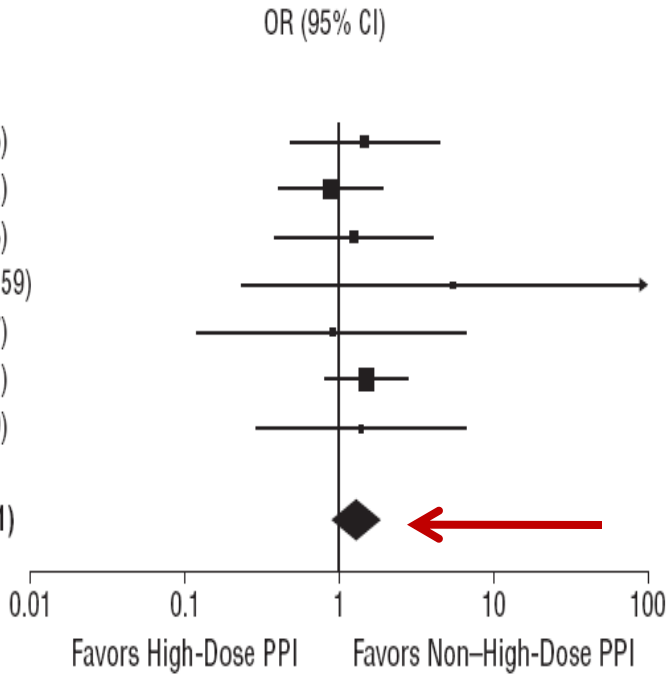

Figure 2. Effect of high-dose vs non–high-dose proton pump inhibitors (PPIs) on rebleeding. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed by the Mantel-Haenszel method.

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Effet sur le risque chirurgical

Source	High-Dose PPI		Non–High-Dose PPI		Weight, %	OR (95% CI)
	No. of Events	No. of Patients	No. of Events	No. of Patients		
Udd et al,[27] 2001	5	69	3	73	27.9	1.82 (0.42-7.94)
Yılmaz et al,[26] 2006	3	112	2	99	21.3	1.33 (0.22-8.16)
Bajaj et al,[28] 2007	1	13	0	12	4.8	3.00 (0.11-80.95)
Hung et al,[23] 2007	0	54	1	49	16.1	0.30 (0.01-7.45)
Andriulli et al,[24] 2008	3	238	1	236	10.2	3.00 (0.31-29.05)
Yüksel et al,[25] 2008	2	48	2	49	19.6	1.02 (0.14-7.56)
Total	**14**	**534**	**9**	**518**	**99.00**	**1.49 (0.66-3.37)**

Heterogeneity: $\chi^2_5=1.72$, $P=.89$, $I^2=0\%$.
Test for overall effect: $z=0.97$, $P=.33$

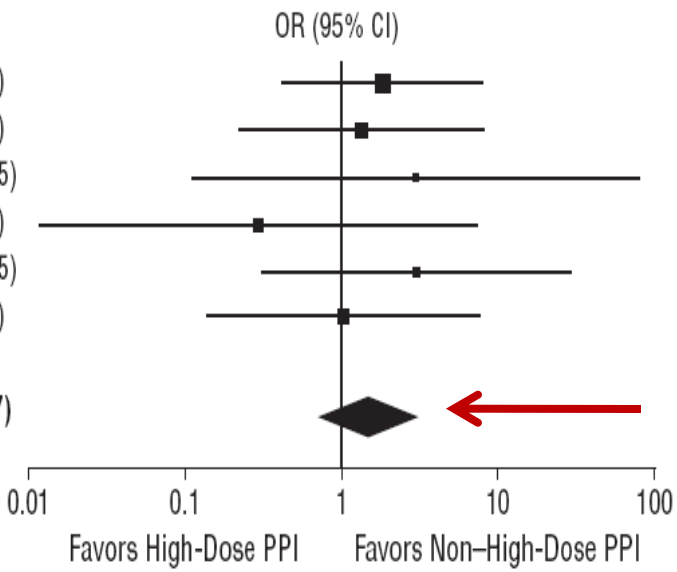

Figure 3. Effect of high-dose vs non–high-dose proton pump inhibitors (PPIs) on surgical intervention. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed by the Mantel-Haenszel method.

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Effet sur la Mortalité

Source	High-Dose PPI		Non–High-Dose PPI		Weight, %	OR (95% CI)
	No. of Events	No. of Patients	No. of Events	No. of Patients		
Udd et al,[27] 2001	2	69	4	73	35.1	0.51 (0.09-2.91)
Yılmaz et al,[26] 2006	3	112	2	99	19.2	1.33 (0.22-8.16)
Bajaj et al,[28] 2007	0	13	0	12		Not estimable
Hung et al,[23] 2007	0	54	0	49		Not estimable
Andriulli et al,[24] 2008	5	238	5	236	45.7	0.99 (0.28-3.47)
Yüksel et al,[25] 2008	0	48	0	49		Not estimable
Total	**10**	**534**	**11**	**518**	**100.0**	**0.89 (0.37-2.13)**

Heterogeneity: $\chi^2_6 = 0.61$, $P = .74$, $I^2 = 0\%$.
Test for overall effect: $z = 0.26$, $P = .79$.

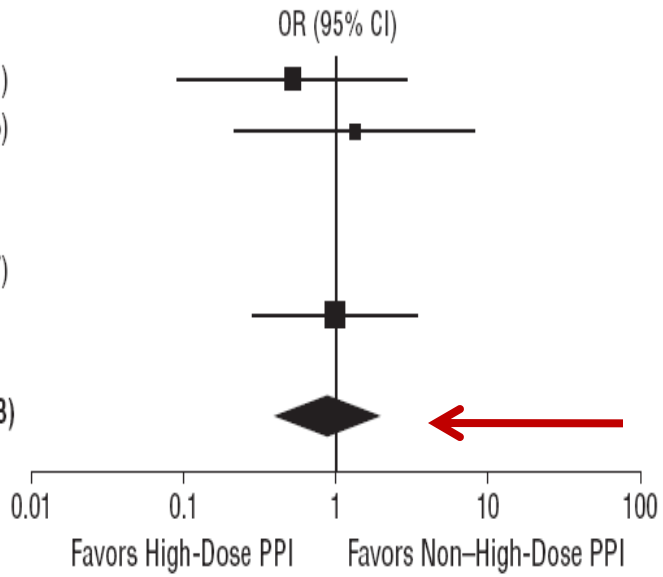

Figure 4. Effect of high-dose vs non–high-dose proton pump inhibitors (PPIs) on mortality. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed by the Mantel-Haenszel method.

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Table 3. Results of Post Hoc Subgroup Analyses of Summary Outcomes Measures

Variable	Pooled Rate, %		Heterogeneity	Odds Ratio (95% Confidence Interval)	Trials Included
	High-Dose PPI	Non–High-Dose PPI			
Severity of Signs of Recent Hemorrhage at Initial Endoscopy Among High-Risk Patients					
Rebleeding	10.2	6.9	No, *P*=.94	1.53 (0.92-2.54)	5 Studies[23-25,27,28]
Surgical intervention	1.7	1.2	No, *P*=.67	1.34 (0.42-4.32)	4 Studies[23-25,28]
Mortality	1.4	1.5	NA	0.99 (0.28-3.47)	4 Studies[23-25,28]
Route of PPI Administration					
Oral PPI as control treatment					
Rebleeding	7.2	4.5	No, *P*=.39	1.58 (0.54-4.66)	2 Studies[26,28]
Surgical intervention	3.2	1.8	No, *P*=.67	1.64 (0.34-7.87)	2 Studies[26,28]
Mortality	2.4	1.8	NA	1.33 (0.22-8.16)	2 Studies[26,28]
Intravenous PPI as control treatment					
Rebleeding	13.7	11.5	No, *P*=.85	1.26 (0.83-1.90)	5 Studies[22-25,27]
Surgical intervention	2.4	1.7	No, *P*=.67	1.44 (0.56-3.74)	4 Studies[23-25,27]
Mortality	1.7	2.2	No, *P*=.55	0.78 (0.29-2.14)	4 Studies[23-25,27]
PPI Dose					
Low-dose PPI as control treatment					
Rebleeding	11.7	8.1	No, *P*=.95	1.51 (0.88-2.58)	2 Studies[24,27]
Surgical intervention	2.6	1.3	No, *P*=.72	2.14 (0.63-7.29)	2 Studies[24,27]
Mortality	2.3	2.9	No, *P*=.55	0.78 (0.29-2.14)	2 Studies[24,27]
Intermediate-dose PPI as control treatment					
Rebleeding	12.9	12.6	No, *P*=.83	1.10 (0.63-1.92)	5 Studies[22,23,25,26,28]
Surgical intervention	2.6	2.4	No, *P*=.79	1.09 (0.36-3.32)	4 Studies[23,25,26,28]
Mortality	1.3	1.0	NA	1.33 (0.22-8.16)	4 Studies[23,25,26,28]

Abbreviations: NA, not applicable; PPI, proton pump inhibitor.

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Results: A total of 1157 patients from 7 high-quality randomized studies were included in this meta-analysis. High-dose PPIs and non–high-dose PPIs did not differ in their effects on the rates of rebleeding (7 studies and 1157 patients; OR, 1.30; 95% CI, 0.88-1.91), surgical intervention (6 studies and 1052 patients; 1.49; 0.66-3.37), or mortality (6 studies and 1052 patients; 0.89; 0.37-2.13). Post hoc subgroup analyses revealed that summary outcomes measures were unaffected by severity of signs of recent hemorrhage at initial endoscopy, route of PPI administration, or PPI dose.

Conclusion: Compared with non–high-dose PPIs, high-dose PPIs do not further reduce the rates of rebleeding, surgical intervention, or mortality after endoscopic treatment in patients with bleeding peptic ulcer.

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Commentaires

1. Ce résultat négatif peut s'expliquer par:
   a. un facteur pharmacogénétique où les asiatiques, qui représentent 2 des 7 études de la méta, seraient plus prédisposés à répondre.
   b. Les études existantes n'ont pas inclus assez de patients graves pour exclure un potentiel effet bénéfiques dans les hémorragies digestives sévères.
   c. Une erreur de type β est possible: échantillon relativement faible.
2. En d'autres termes la question n'est pas close.

Une ERC à large échelle est nécessaire.