

## Endoscopic hemostasis in peptic ulcer bleeding for patients with high-risk lesions: a series of meta-analyses

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**Background and Objective:** Optimal endoscopic hemostasis remains undetermined. This was a systematic review of contemporary methods of endoscopic hemostasis for patients with bleeding ulcers that exhibited high-risk stigmata.

**Setting:** Randomized trials that evaluated injection, thermocoagulation, clips, or combinations of these were evaluated from MEDLINE, EMBASE, and CENTRAL (1990-2006).

**Patients:** A total of 4261 patients were evaluated.

**Outcomes:** Outcomes were rebleeding (primary), surgery, and mortality (secondary). Summary statistics were determined; publication bias and heterogeneity were sought by using funnel plots or by subgroup analyses and meta-regression.

**Results:** Forty-one trials assessed 4261 patients. All endoscopic therapies decreased rebleeding versus pharmacotherapy alone, including sole intravenous (IV) proton pump inhibition (PPI) (OR 0.56 [95% CI, 0.34-0.92]); only one trial assessed high-dose IV PPI. Injection alone was inferior compared with other methods, except for thermal hemostasis (OR 1.02 [95% CI, 0.74-1.40]), with a strong trend of increased rebleeding if 1 injectate is used rather than 2 (OR 1.40 [95% CI, 0.95-2.05]). Injection followed by thermal therapy did not decrease rebleeding compared with clips (OR 0.82 [95% CI, 0.28-2.38]) or thermal therapy alone (OR 0.79 [95% CI, 0.24-2.62]). Subgroup analysis, however, suggested that injection followed by thermal therapy was superior to thermal therapy alone. Clips were superior to thermal therapy (OR 0.24 [95% CI, 0.06-0.95]) but, when followed by injection, were not superior to clips alone (OR 1.30 [95% CI, 0.36-4.76]). Surgery or mortality was not altered in most comparisons.

**Conclusions:** All endoscopic treatments are superior to pharmacotherapy alone; only 1 study assessed high-dose IV PPI. Optimal endoscopic therapies include thermal therapy or clips, either alone or in combination with other methods. Additional data are needed that compare injection followed by thermal therapy to clips alone or clips combined with another method. (Gastrointest Endosc 2009;69:786-99.)

The presentation of patients who are older and sicker coupled with technologic evolution have led to currently outdated conclusions arrived at by earlier meta-analyses on endoscopic hemostasis in high-risk patients with pep-

tic ulcer bleeding (PUB).<sup>1,2</sup> Calvet et al<sup>3</sup> more recently demonstrated the superiority of epinephrine injection followed by many possible additional endoscopic hemostatic methods grouped together, many of which are not relevant to North American practices that shun injection of sclerosants.<sup>4,5</sup> More recent meta-analyses have had their methodologies<sup>6</sup> or resulting interpretations challenged.<sup>7,8</sup> We, therefore, performed a series of meta-analyses to better characterize the efficacy of current endoscopic therapies.

### PATIENTS AND METHODS

#### Search strategy

Ovid (MEDLINE) was used to search CENTRAL 3rd quarter 2006, EMBASE (1998 to Week 41 2006), and

*Abbreviations:* APC, argon plasma coagulator; ARD, absolute risk difference; H2RA, H2 receptor antagonists; HPT, heat probe; IV, intravenous; MPEC, multipolar electrocoagulation; NNT, number needed to treat; OR, odds ratio; PPI, proton pump inhibitor; PUB, peptic ulcer bleeding; RR, risk ratio.

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MEDLINE (1986 to October Week 1, 2006) spanning 1990 to 2006. A highly sensitive search strategy identified randomized controlled trials.<sup>9</sup> We included all human studies fully published in French or English. Authors were contacted if a potentially eligible article was missing critical information. Sole abstracts were excluded because of the exhaustive nature of the information required.

### Clinically derived objectives

Predetermined analyses addressed a set of clinical queries that had been identified, at an international consensus meeting, as important areas of needed research.<sup>4</sup>

### Trial selection and patient population

We only included randomized controlled trials that assessed contemporary hemostatic techniques<sup>4</sup>: endoscopic injection (all injectates, single or multiple), thermal treatment (heat probe [HPT], monopolar and bipolar electrocoagulation, microwave and argon plasma coagulation [APC]), clips (alone or in combination), and combination treatment (injection followed by thermal therapy). Trials had to evaluate a method of endoscopic hemostasis (sole placebo controlled studies were disallowed because of current practice standards). Trials had to include patients with PUB who exhibited high-risk stigmata (Forrest Ia or spurting, Ib or oozing, IIa or visible vessel, and IIb or adherent clot).<sup>10,11</sup> We excluded trials that assessed postoperative or stress ulcer bleeding prophylaxis, or lesions other than ulcers. Trials had to provide adequate information concerning the number of patients randomized in each group, treatment procedures, and rates of rebleeding, surgery, and mortality. Trials that compared different accessories of a same hemostatic method or varying volumes of similar injectates were excluded. The latter was decided upon because, currently, most investigators believe that tamponade is the primary method of action of injection endoscopic therapy; the true prognosticator of outcome is thus probably the total volume injected and not the compound that is injected. Therefore, to truly study the efficacy of different injectates without confounding outcome by volume, we decided to leave out the 3 high-volume injection studies that could otherwise have significantly affected the results: it is a different clinical question.

### Choice of outcomes

The primary outcome measure was peptic ulcer rebleeding; secondary outcomes included the proportion of patients undergoing surgery for ulcer rebleeding and overall mortality. Rebleeding was the primary outcome measure, because it most accurately reflects the efficacy of endoscopic hemostasis<sup>12,13</sup> and is most consistently defined across studies.<sup>14</sup> Criteria for surgery are poorly described and not standardized. Attributable mortality is a subjective outcome that is often a source of debatable adjudication and is in fact often lacking<sup>13</sup> and may reflect, in part, poorly reported associated comorbidities, espe-

### Capsule Summary

#### What is already known on this topic

- Technologic improvements and the presentation of patients who are older and sicker may have invalidated the conclusions of early meta-analyses of endoscopic hemostasis in high-risk patients with peptic ulcer bleeding.

#### What this study adds to our knowledge

- In a systematic review of contemporary methods of endoscopic hemostasis in patients with bleeding ulcers who exhibit high-risk stigmata, all endoscopic therapies decreased rebleeding compared with pharmacotherapy alone.
- Optimal endoscopic therapies included thermal therapy or clips, either as single therapies or in combination with other methods.

cially in a contemporary setting of improved supportive measures. We adopted a standardized definition of rebleeding (after successful initial hemostasis)<sup>14</sup> and identified studies in which this outcome differed as a possible source of clinical heterogeneity.

### Validity assessment

The eligibility and quality of the studies were assessed independently by 2 investigators (M.M., M.B.; a third investigator [A.N.B.] resolved discrepancies). Studies were graded by using a previously published 10-quality criteria scoring system modified from Cook et al<sup>2</sup> and Bardou et al.<sup>14</sup>

### Sources of possible heterogeneity: both statistical and clinical

Statistical heterogeneity was handled by considering both fixed-effects and random-effects models (see below). “Clinical” sources of between-study heterogeneity included differences in experimental designs (differing methods of hemostasis), handled through sensitivity testing<sup>7</sup> and variations in patient characteristics, that were dealt with as follows: The mean age of patients, the percentage of patients in shock at inclusion (both of these stratified as in the Rockall score<sup>15</sup>), the severity of bleeding (as determined by the proportions of the different Forrest classes in each trial), and the time period of the study (defined a priori as before versus “after” 1996 to control for quality of supportive care) were recorded as potential sources of heterogeneity and interstudy variance. These and the aforementioned quality scores were considered as possible confounders of outcomes and were adjusted for using meta-regression as discussed in the statistical section. Although comorbid conditions are known to influence outcomes,<sup>15</sup> such information was not available in the majority of included trials.

## Statistical methods

**Determination of effect size.** For each outcome of rebleeding, surgery, and mortality, and in every comparison, effect size was calculated as an odds ratio (OR), a risk ratio (RR), and an absolute risk difference (ARD). The OR and the RR were analyzed on a logarithmic scale. For studies with a zero incidence in one of the treatment arms, 0.5 was added to each cell of the  $2 \times 2$  table defined by the allocated group and outcome. In cases in which a study contained multiple experimental treatment or control groups, each pairwise comparison between treatment and control was treated as a separate study in the analysis. However, if the same intervention or control group was involved in more than one comparison within the same trial, then the patients were allocated to the comparison in such a way that the data for each patient were represented only once. Moreover, every endoscopic treatment subgroup was compared with all possible other hemostatic alternatives while conserving the actual head-to-head comparisons carried out in the studies, as previously reported.<sup>14</sup> Fixed-effects models were applied to all comparisons to determine corresponding overall effect sizes and their CIs,<sup>16</sup> unless heterogeneity was noted, in which case a random-effects model was used. The corresponding standard errors of the 3 effects measures (OR, RR, and ARD) were estimated. For each effects measure estimate, the between-study variation was approximated by using the restricted maximum likelihood estimation procedure.<sup>17</sup> The pooled effects measure was then calculated by using a weighted average of the observed study effect. The weight for each study is equal to the inverse of the sum of the within-study variance and the between-study variance. The pooled standard error was calculated as the square root of the inverse of the sum of weights.<sup>18</sup> The 95% CI was then computed based on these estimates. For significant RR, the corresponding number needed to treat (NNT) was also calculated.<sup>19</sup>

**Identification of heterogeneity.** The Higgins  $I^2$  statistic was calculated to quantify the proportion of variation in treatment effects attributable to between-study heterogeneity.<sup>20</sup> Values of  $I^2$  equal to 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively. The presence of heterogeneity across studies was defined by using a  $\chi^2$  test of homogeneity, with a .10 significance level. To characterize possible sources of statistical heterogeneity, sensitivity analyses were carried out by excluding studies one by one; in addition, if noted in a comparison made up of more than 10 studies,<sup>21</sup> we also performed a meta-regression by using a mixed-effects model that included quality scores, year of publication, severity of bleeding, and mean age, as detailed above.

**Identification of publication bias.** We performed funnel plot regressions<sup>22</sup> for all comparisons to assess the possibility of publication bias, with treatment effect as the dependent variable and study size as the independent variable (in the absence of publication bias, the

regression slope has an expected value of zero). All statistical analyses were done by using the SAS software version 9.1.3 Service Pack 4 (SAS Institute, Cary, NC).

## RESULTS

### Included studies

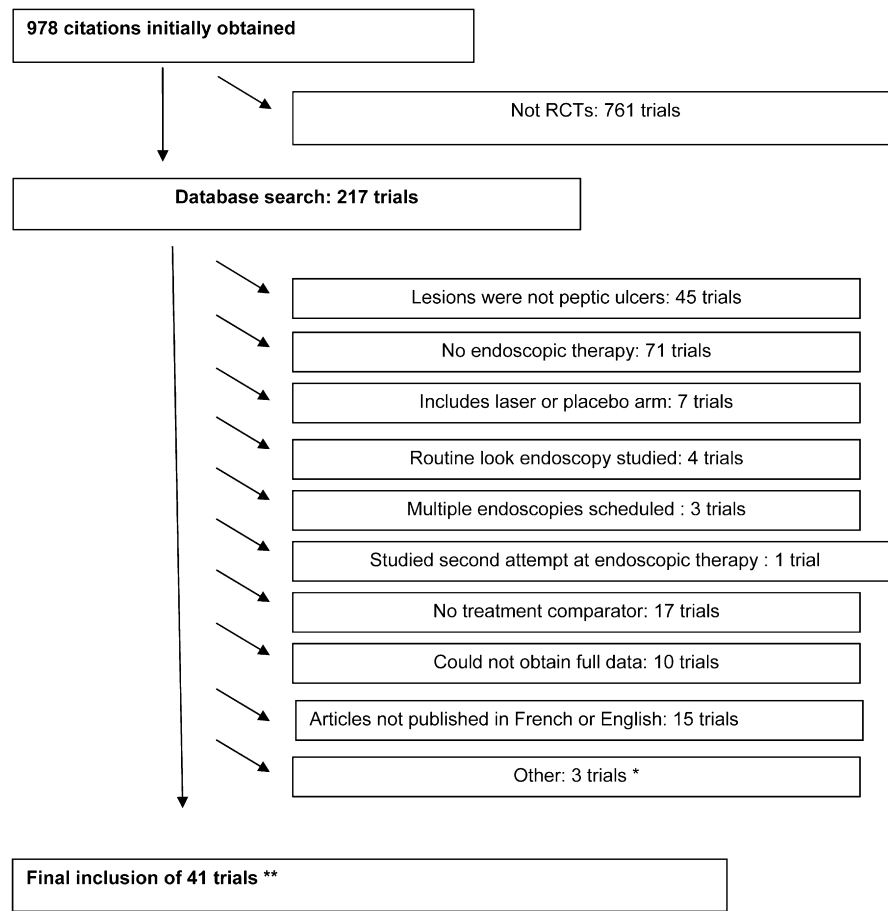
From a total of 978 studies identified through the systematic search, 761 articles were excluded because they were not randomized controlled trials. Abstracts of 217 trials were identified as pertinent to the search. Reasons for exclusion are listed in the QUORUM diagram,<sup>23</sup> which yielded 41 trials and a total of 4261 patients that were included in the analyses (Fig. 1). Forty-five trials were excluded because they reported on a mix of bleeding etiologies, with varying proportions of ulcer bleeds that were, in most cases, not clear from the publication.

### Study quality, heterogeneity, and publication bias

The quality scores attributed to each trial are reported in Table 1. These scores ranged from 3 to 10, with a mean ( $\pm$ SD) of  $7.0 \pm 1.6$ . Of all comparisons discussed below, significant heterogeneity was only noted in 3 comparisons: endoscopy versus proton pump inhibitors (PPIs) for rebleeding ( $I^2 = 49.10\%$ ,  $P = .06$ ), injection versus pharmacotherapy ( $I^2 = 51.26\%$ ,  $P = .03$ ), and injection followed by thermal therapy versus thermal therapy alone ( $I^2 = 63.46\%$ ,  $P = .04$ ), all for the outcome of rebleeding. Random-effects models were thus adopted in all 3 comparisons. With regard to the first comparison, the significant heterogeneity disappeared when the study of Sung et al<sup>24</sup> or that of Bleau et al<sup>25</sup> was removed. The significant statistical heterogeneity noted for rebleeding in the injection versus pharmacotherapy comparison remained, despite the removal of any one study in the comparison. The significant heterogeneity for the outcome of rebleeding disappeared when removing the study by Lin et al<sup>26</sup> or the one by Soon et al<sup>27</sup> for the comparison of injection followed by thermal therapy versus thermal therapy alone. Meta-regression showed that heterogeneity for the comparison of injection versus pharmacotherapy originated at least in part from between-study differences in the bleeding severity of included patients (OR 3.89 [95% CI, 1.33-11.37]) and did not identify significant predictors in the latter comparison. Funnel plot regression showed a potential publication bias for mortality in the comparison of injection followed by thermal endotherapy versus pharmacotherapy (slope -0.01 [95% CI, -0.01 to -0.00]), as well as for injection versus injection and clips for both rebleeding (slope 0.06 [95% CI, 0.04-0.08]) and mortality (slope -0.05 [95% CI, -0.06 to -0.05]).

### Presentation of results

The studies that were included in the analyses and their characteristics are listed in Table 2, whereas the results of



\* Other reasons for exclusion were: no evaluation of endoscopic technique (deMuckadell et al.<sup>89</sup>), two different mechanical methods of endoscopic therapy combined in the intervention group (Park et al.<sup>90</sup>). \*\*The publication by Gralnek et al. was considered as two studies, CURE I and CURE II but has one reference.<sup>32</sup>

**Figure 1.** QUORUM diagram of trial selection.

the different comparisons expressed as OR, RR, ARD, and, where applicable, NNT are reported in Table 3. They are detailed in the clinically relevant subheadings below. The comparisons are organized empirically according to experimental method studied (eg, the comparison of injection vs clips is detailed in the subsection “The role of endoscopic clips,” because injection was considered the control arm in those particular studies). From this point on in the text, the term combination therapy refers to injection followed by thermal therapy unless otherwise specified.

### Endoscopic therapy versus pharmacotherapy

All forms of endoscopic therapy were assessed in 18 studies (1506 patients, 1446 patients for surgery)<sup>24,25,28-42</sup> versus pharmacotherapy, and, more specifically, in 7 studies (479 patients, 439 for surgery)<sup>24,25,29,30,32,34,35</sup> versus PPI therapy and 11 studies (1697 patients, 1637 for surgery)<sup>30,31,33,36-42</sup> versus H2 receptor antagonists (H2RA). It is to be noted that, in almost all studies, the patients treated by a method

of endoscopy received a single standard daily dose of an acid suppression drug thereafter.

Endoscopic therapy was superior to pharmacotherapy with regard to rebleeding (OR 0.35 [95% CI, 0.27-0.46]), surgery (OR 0.57 [95% CI, 0.41-0.81]), and mortality (OR 0.57 [95% CI, 0.37-0.89]). Endoscopic therapy was also superior to sole PPI use with regard to rebleeding (OR 0.56 [95% CI, 0.34-0.92]) but not surgery (OR 0.94 [95% CI, 0.37-2.40]) or mortality (OR 0.85 [95% CI, 0.37-1.96]). Only 1 study<sup>24</sup> used high-dose IV PPI. Endoscopic therapy was superior to H2RA with regard to rebleeding (OR 0.30 [95% CI, 0.22-0.41]), surgery (OR 0.55 [95% CI, 0.32-0.95]), and mortality (OR 0.53 [95% CI, 0.37-0.78]).

### The role of injection therapy

Injection therapy was assessed in 27 studies (2603 patients)<sup>12,26,28,29,31,32,35,38-41,43-58</sup> and was compared with pharmacotherapy, thermal therapy, combination therapy, and endoscopic clips.

**TABLE 1. Methodologic quality assessment of the treatment for upper-GI bleeding\***

Population	
Patients selection	
1	Consecutive eligible consenting patients
0	Selected patients/not described
Patients characteristics	
1	Comparable with respect to all the characteristics
0	Noncomparable with respect with at least 2 characteristics
Intervention	
Randomization	
1	Randomization process clearly stated
0	No randomization or randomization process not described
Blinding	
1	Assessment of outcome blinded to evaluation treatment
0	Unblinded or cannot tell
Endoscopic treatment	
Injection	
1	Volume, concentration of injectate and number of applications stated
0	At least one of the above not stated
Other endoscopic treatments (laser, heat probe, BICAP, clips, microwave, APC)	
1	Technique fully stated according to the endoscopic procedure
0	Technique poorly stated, not well enough described to be reproduced
Pharmacologic treatment	
1	Dose, duration, and route stated, even for GI drugs not randomized
0	At least one of the above not stated
Outcome	
Rebleeding definition	
1	Objective direct or indirect evidence of upper-GI bleeding
0	Subjective evidence or criteria not explicitly stated
Indication for surgery	
1	Criteria stated explicitly
0	Criteria not explicitly stated
Cause of death	
1	Cause clearly stated with no need to obvious relation to bleeding
0	Cause of death not clearly stated

\*Adapted from reference 2.

**Injection versus pharmacotherapy.** Nine studies (614 patients: 306 cases, 308 controls) compared injection versus pharmacotherapy. Injection alone included the use of alcohol<sup>28,35,41</sup> or epinephrine<sup>29,31</sup> (with saline solution to dilute it), whereas combinations of injectates were

epinephrine with polidocanol,<sup>32,41</sup> epinephrine with ethanol,<sup>39,59</sup> and alcohol with thrombin.<sup>38</sup> The medications used were PPIs in 3 trials (only 1 included high-dose oral PPI, none included high-dose intravenous [IV] PPI),<sup>29,32,35</sup> H2RA in 4,<sup>31,38,40,41</sup> PPI or H2RA in 1 trial,<sup>39</sup> and antacids

**TABLE 2. List of studies included in the analyses and their characteristics.**

Study	Total no. patients per study	No. patients per study arm	Quality score of the study	No. study arms	Nature of the treatment per study arm
Acalovschi et al, <sup>28</sup> 1990	28	14/14	5	2	Epi + Eth vs H2RA
Bianco et al, <sup>68</sup> 2004	114	58/56	8	2	Epi + BICAP vs BICAP
Bleau et al, <sup>25</sup> 2002	56	21/35	6	2	Epi + HPT vs H2RA or PPI
Bour et al, <sup>29</sup> 1993	52	21/31	6	2	Epi + Polido vs PPI
Chou et al, <sup>43</sup> 2003	79	40/39	10	2	Clips vs distilled water
Choudari et al, <sup>44</sup> 1992	120	60/60	6	2	Epi vs HPT
Chua et al, <sup>30</sup> 1996	40	10/10/10/10	5	4	H2RA vs HPT vs PPI vs PPI
Chung et al, <sup>45</sup> 1991	132	68/64	6	2	Epi vs HPT
Chung et al, <sup>46</sup> 1997	276	136/140	8	2	Epi + HPT vs Epi
Chung et al, <sup>47</sup> 1999	124	41/41/42	9	3	Clips vs Epi vs clips + Epi
Church et al, <sup>69</sup> 2003	247	127/120	8	2	HPT + Thromb vs HPT
Cipolletta et al, <sup>70</sup> 2001	113	57/56	9	2	Clips vs HPT
Gralnek et al, <sup>31</sup> 1998 (cure I)	79	23/29/27	7	3	HPT vs BICAP vs H2RA
Gralnek et al, <sup>31</sup> 1998 (cure II)	76	26/24/26	7	3	HPT vs Epi vs PPI
Grosso et al, <sup>32</sup> 1995	42	21/21	5	2	Epi + Polido vs PPI
Jaramillo et al, <sup>33</sup> 1993	101	51/50	7	2	HPT vs H2RA
Jensen et al, <sup>34</sup> 2002	32	15/17	8	2	Epi + BICAP vs PPI
Jung et al, <sup>35</sup> 2002	101	53/48	7	2	Eth vs PPI
Laine, <sup>48</sup> 1990	60	31/29	7	2	Injection vs MEC
Laine and Estrada, <sup>49</sup> 2002	100	52/48	6	2	Eth vs thermal
Lin et al, <sup>50</sup> 1990	137	46/45/46	7	3	Eth vs HPT vs placebo
Lin et al, <sup>72</sup> 1995	54	20/19/15	7	3	HPT vs Oct vs H2RA
Lin et al, <sup>26</sup> 1999	96	32/32/32	8	3	Epi vs BICAP vs Epi + BICAP
Lin et al, <sup>73</sup> 2003	87	41/46	6	2	Clips vs HPT + Epi
Lin et al, <sup>36</sup> 1995	80	40/40	6	2	Clips vs HPT
Ljubicic et al, <sup>58</sup> 2004	61	30/31	6	2	Clips vs Polido
Llach et al, <sup>52</sup> 1996	104	51/53	10	1	Epi + Polido vs HPT
Lo et al, <sup>12</sup> 2006	105	53/52	10	1	Epi vs Epi + clips
Matthewson et al, <sup>37</sup> 1990	143	57/44/42	6	2	HPT vs laser vs H2RA
Moreto et al, <sup>38</sup> 1992	38	19/19	7	2	Eth + Thromb vs H2RA
Oxner et al, <sup>39</sup> 1992	93	48/45	6	2	Epi + Eth vs H2RA or PPI
Panes et al, <sup>53</sup> 1991	127	62/65	9	2	Epi + Polido vs Mw
Rajgopal and Palmer, <sup>40</sup> 1991	109	56/53	6	2	Epi + Eth vs H2RA
Rutgeerts et al, <sup>41</sup> 1993	75	25/25/25	5	3	Eth vs Epi + Polido vs H2RA
Saltzman et al, <sup>74</sup> 2005	47	21/26	7	1	Clips vs combination
Shimoda et al, <sup>54</sup> 2003	126	42/42/42	7	3	Eth vs clips vs Eth + clips

*(continued on next page)*

TABLE 2 (continued)

Study	Total no. patients per study	No. patients per study arm	Quality score of the study	No. study arms	Nature of the treatment per study arm
Skok et al, <sup>55</sup> 2004	100	50/50	7	1	Epi + Polido vs APC
Sofia et al, <sup>56</sup> 2000	208	44/42/40/42/40	8	5	Eth vs BICAP vs laser vs Epi + Oct vs Epi + PPI
Soon et al, <sup>27</sup> 2003	148	74/74	10	2	MEC vs PPI
Sung et al, <sup>24</sup> 2003	156	78/78	10	2	Epi + HPT vs PPI
Tekant et al, <sup>42</sup> 1995	155	76/79	5	2	Epi + HPT vs H2RA
Waring et al, <sup>57</sup> 1991	40	31/29	3	2	ETH vs BICAP

Epi, Epinephrine injection; Eth, absolute alcohol injection; Polido, polidocanol injection; Thromb, thrombin injection; MEC, multipolar thermal electrocoagulation; Oct, octreotide administration; Mw, microwave therapy.

in another trial.<sup>28</sup> Injection significantly reduced rebleeding compared with pharmacotherapy (OR 0.43 [95% CI, 0.24-0.78], random-effects model) but not surgery (OR 0.64 [95% CI, 0.37-1.11]) or mortality (OR 0.60 [95% CI, 0.32-1.12]).

In planned subanalysis, 8 studies (929 patients)<sup>60-67</sup> compared a single injectate with 2 injectates. Use of 1 injectate exhibited a trend toward worsening for all 3 outcomes (OR 1.40 [95% CI, 0.95-2.05], OR 1.19 [95% CI, 0.78-1.82], and OR 1.53 [95% CI, 0.82-2.83] for rebleeding, surgery, and mortality, respectively).

### The role of thermal therapy

Thermal therapy alone (multipolar electrocoagulation [MPEC] [in 7 studies], HPT [12 studies, with an additional study that compared MPEC with HPT], APC [1 study], or microwave [1 study]) were assessed in 22 studies (2400 patients, with 2113 for assessment of surgical outcome) and compared with pharmacotherapy, injection, combination, and endoscopic clips.<sup>26,27,30,31,33,36,37,44,45,48-50,52,53,55-57,68-71</sup>

**Thermal versus pharmacotherapy.** A total of 493 patients (256 thermal, 237 controls, with a total of only 433 for assessment of surgery) were included in 6 studies. Control arms were H2RA in 6 studies reported in 5 publications,<sup>30,31,33,36,37</sup> whereas 1 study also had a control PPI arm<sup>30</sup> and another had an octreotide comparator.<sup>72</sup> Rebleeding and surgery were significantly reduced with thermal therapy compared with pharmacotherapy, respectively (OR 0.41 [95% CI, 0.26-0.65] and OR 0.51 [95% CI, 0.28-0.94]) but not mortality (OR 0.64 [95% CI, 0.25-1.65]).

**Thermal versus injection therapy.** Thermal hemostasis was compared with injection therapy in 12 studies (634 thermal, 627 controls), including epinephrine injection in 4 studies,<sup>26,31,44,45</sup> alcohol injection in 4,<sup>48,50,56,57</sup> injection of epinephrine combined with polidocanol in 3,<sup>52,53,55</sup> and distilled water injection in 1 study.<sup>49</sup> The study by Sofia et al<sup>56</sup> contained 5 arms (Table 2). No significant differences were found for rebleeding, surgery, or mortality (OR 1.02 [95% CI, 0.74-1.40], OR 1.13

[95% CI, 0.74-1.72]), and OR 1.13 [95% CI, 0.64-2.00], respectively). No differences in results were noted when, in subgroup analysis, studies that used a single injectate versus 2 injectates were analyzed separately.

### The role of combined injection and thermal therapy

Combinations of some form of injection with some method of thermal therapy were used in 11 trials (1414 patients, 1167 for assessment of surgery). Epinephrine injection was combined with thermal therapy using multipolar electrocoagulation in 2 studies<sup>26,68</sup> and with HPT in 8,<sup>24,25,27,34,42,46,73,74</sup> whereas thrombin was combined with HPT in 1 study.<sup>69</sup>

**Combination versus pharmacotherapy.** Four studies compared combination therapy versus pharmacotherapy (190 treated with combination therapy and 209 controls).<sup>24,25,34,42</sup> Rebleeding was significantly decreased with combination therapy compared with pharmacotherapy (OR 0.18 [95% CI, 0.08-0.41]), but this was not so for surgery (OR 0.49 [95% CI, 0.16-1.46]) or mortality (OR 0.59 [95% CI, 0.20-1.72]). When removing 1 of the 4 studies that had included patients with a very heterogeneous group of bleeding ulcer stigmata,<sup>42</sup> combination therapy still improved rebleeding more significantly than PPI alone (OR 0.09 [95% CI, 0.02-0.33]); it should be noted that one of the included studies used IV famotidine or oral PPI when feasible in the acute phase.<sup>25</sup>

**Combination versus injection therapy.** Two studies compared combination therapy hemostasis versus injection therapy. Epinephrine alone was injected in a total of 340 patients (172 as part of combined endoscopic hemostasis and 168 as sole endoscopic therapy).<sup>26,46</sup> Combination therapy significantly decreased rebleeding (OR 0.27 [95% CI, 0.11-0.66]) (Fig. 2) but not surgery or mortality (OR 0.45 [95% CI, 0.20-1.04] and OR 0.90 [95% CI, 0.35-2.33], respectively) compared with injection.

**Combination versus thermal therapy.** Four studies compared combination with thermal therapy.<sup>26,27,68,69</sup>

TABLE 3. Results of the different comparisons analyzed\*

Treatment	Outcome	No. studies	No. patients	No. arms	Fixed effect			NNT to prevent 1 patient from experiencing a negative outcome (95% CI)
					Odds ratio (95% CI)	Risk ratio (95% CI)	Risk difference (95% CI)	
Injection vs pharmacotherapy								
	Rebleeding	9	614	10	<b>0.43</b> (0.24, 0.78)†	<b>0.57</b> (0.43, 0.76)	<b>-17.33</b> (-28.44, -10.65)	<b>6 (4-9)</b>
	Surgery	9	614	10	0.64 (0.37, 1.11)	0.74 (0.48, 1.13)	-2.95, (-6.91, 1.00)	
	Mortality	9	614	10	0.60 (0.32, 1.12)	0.63 (0.36, 1.11)	-0.83 (-4.42, 2.75)	
Thermal vs pharmacotherapy								
	Rebleeding	6	493	10	<b>0.41</b> (0.26, 0.65)	<b>0.55</b> (0.40, 0.76)	<b>-17.60</b> (-25.96, -9.23)	<b>6 (4-11)</b>
	Surgery	5	433	7	<b>0.51</b> (0.28, 0.94)	<b>0.62</b> (0.39, 1.00)	<b>-9.93</b> (-16.82, -3.05)	<b>10 (6-33)</b>
	Mortality	6	493	10	0.64 (0.25, 1.65)	0.68 (0.28, 1.64)	-2.58 (-6.24, 1.08)	
Thermal vs injection								
	Rebleeding	12	1261	14	1.02 (0.74, 1.40)	1.01 (0.78, 1.31)	0.70 (-3.53, 4.93)	
	Surgery	12	1261	14	1.13 (0.74, 1.72)	1.11 (0.77, 1.61)	0.36 (-2.44, 3.16)	
	Mortality	12	1261	14	1.13 (0.64, 2.00)	1.12 (0.65, 1.92)	0.40 (-1.89, 2.70)	
Combination vs pharmacotherapy								
	Rebleeding	4	399	4	<b>0.18</b> (0.08, 0.41)	<b>0.22</b> (0.10, 0.48)	<b>-14.30</b> (-19.93, -8.67)	<b>7 (5-11)</b>
	Surgery	4	399	4	0.49 (0.16, 1.46)	0.51 (0.18, 1.44)	-0.45 (-3.46, 2.56)	
	Mortality	4	399	4	0.59 (0.20, 1.72)	0.62 (0.23, 1.69)	-2.35 (-5.68, 0.97)	
Combination vs injection								
	Rebleeding	2	340	2	<b>0.27</b> (0.11, 0.66)	<b>0.31</b> (0.14, 0.71)	<b>-7.22</b> (-12.65, -1.80)	<b>14 (8-55)</b>
	Surgery	2	340	2	0.45 (0.20, 1.04)	0.48 (0.22, 1.05)	<b>-5.95</b> (-11.77, -0.14)	
	Mortality	2	340	2	0.90 (0.35, 2.33)	0.91 (0.37, 2.24)	-0.60 (-5.47, 4.27)	
Combination vs thermal								
	Rebleeding	4	573	4	0.79 (0.24, 2.62)†	0.85 (0.52, 1.38)	1.71 (-2.96, 6.38)	
	Surgery	3	326	3	0.38 (0.08, 1.73)	0.39 (0.09, 1.72)	-0.72 (-3.11, 1.68)	
	Mortality	4	573	4	0.52 (0.24, 1.15)	0.55 (0.26, 1.14)	-0.91 (-3.13, 1.31)	

(continued on next page)

TABLE 3 (continued)

Treatment	Outcome	No. studies	No. patients	No. arms	Fixed effect			NNT to prevent 1 patient from experiencing a negative outcome (95% CI)
					Odds ratio (95% CI)	Risk ratio (95% CI)	Risk difference (95% CI)	
Clips vs injection								
	Rebleeding	4	306	4	<b>0.36 (0.17, 0.76)</b>	<b>0.42 (0.21, 0.81)</b>	<b>-10.38 (-17.39, -3.36)</b>	<b>10 (6-30)</b>
	Surgery	4	306	4	0.42 (0.15, 1.21)	0.45 (0.17, 1.20)	-1.49 (-5.17, 2.19)	
	Mortality	4	306	4	1.42 (0.38, 5.31)	1.40 (0.39, 5.03)	1.03 (-2.98, 5.05)	
Clips vs thermal								
	Rebleeding	2	193	2	<b>0.24 (0.06, 0.95)</b>	0.28 (0.07, 1.03)	<b>-10.46 (-18.14, -2.79)</b>	<b>10 (6-36)</b>
	Surgery	2	193	2	0.49 (0.12, 2.02)	0.51 (0.13, 1.96)	-2.98 (-8.82, 2.87)	
	Mortality	2	193	2	0.76 (0.16, 3.55)	0.77 (0.17, 3.41)	-0.97 (-6.24, 4.30)	
Clips vs combination								
	Rebleeding	2	134	2	0.82 (0.28, 2.38)	0.83 (0.33, 2.06)	-0.57 (-10.77, 9.63)	
	Surgery	2	134	2	0.95 (0.15, 6.13)	0.98 (0.17, 5.77)	-2.47 (-9.43, 4.50)	
	Mortality	2	134	2	0.69 (0.10, 4.71)	0.71 (0.11, 4.52)	-0.52 (-7.22, 6.18)	
Clips + injection vs injection								
	Rebleeding	3	272	3	<b>0.38 (0.16, 0.86)</b>	<b>0.43 (0.20, 0.90)</b>	<b>-10.32 (-17.83, 2.81)</b>	<b>10 (6-36)</b>
	Surgery	3	272	3	<b>0.17 (0.03, 0.82)</b>	<b>0.18 (0.04, 0.86)</b>	-3.09 (-6.88, 0.70)	
	Mortality	3	272	3	1.35 (0.25, 7.14)	1.33 (0.26, 7.14)	0.83 (-4.29, 2.63)	
Clips + injection vs clips								
	Rebleeding	2	167	2	1.30 (0.36, 4.76)	1.25 (0.38, 4.17)	3.11 (-4.55, 10.76)	
	Surgery	2	167	2	0.58 (0.07, 4.76)	0.59 (0.08, 4.54)	-0.60 (-4.55, 3.35)	
	Mortality	2	167	2	0.50 (0.08, 2.94)	0.51 (0.09, 2.85)	-1.69 (-7.02, 3.64)	

\*Numbers in bold represent significant value.

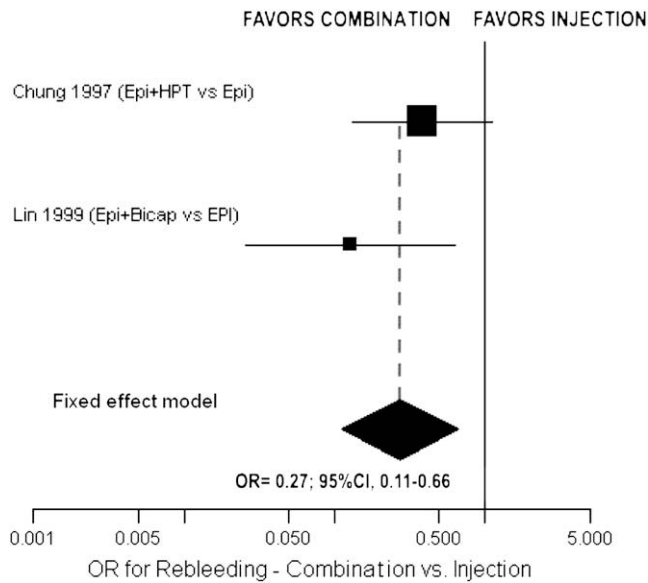
†Random-effects model.

They included 573 patients (291 cases and 282 controls, with a total of 326 patients for assessment of surgery). Rebleeding was not significantly reduced with a combination treatment compared with a sole thermal modality, although a trend was noted (rebleeding OR 0.79 [95% CI, 0.24-2.62]). Similarly, secondary outcomes were not significantly improved (surgery, OR 0.38 [95% CI, 0.08-1.73]) and mortality (OR 0.52 [95% CI, 0.24-1.15]). Soon et al<sup>27</sup> assessed a unipolar thermal modality, not commonly used. The trial by Church et al<sup>69</sup> compared combi-

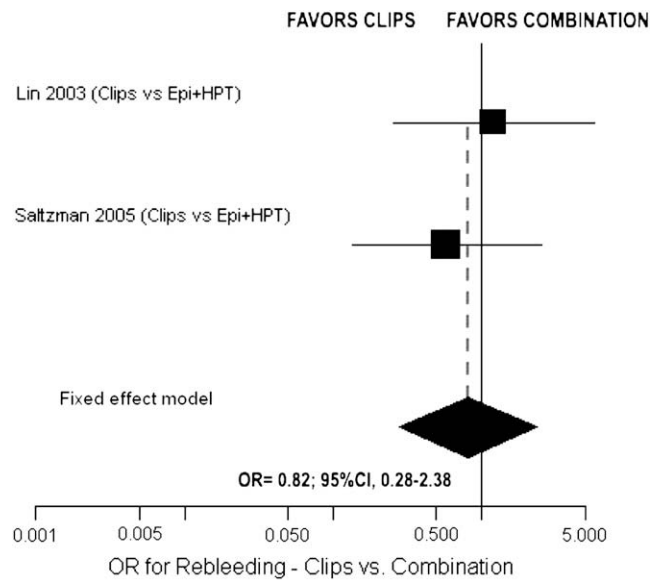
nation therapy to thermal combined to injection of a placebo solution, thus arguably providing some active injection therapy in the control group as well. Removing both the Soon and Church studies yielded a significant improvement in rebleeding (OR 0.37 [95% CI, 0.14-0.97]), in the absence of statistical heterogeneity.

### The role of endoscopic clips

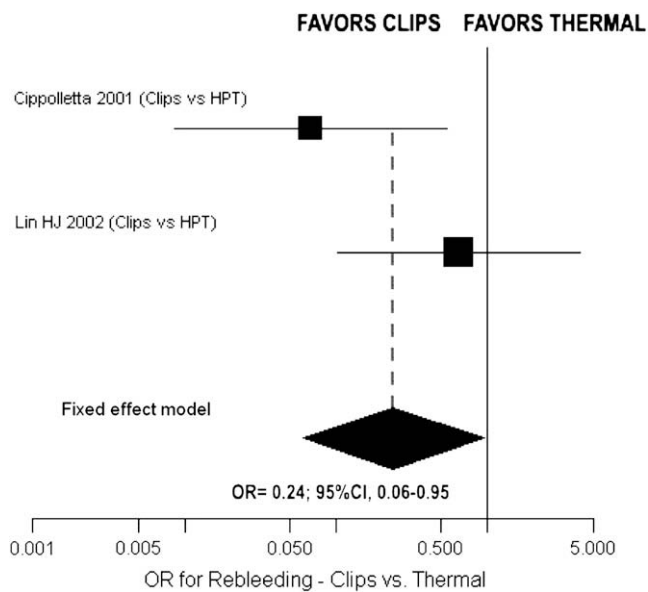
Endoscopic clips alone or in combination were assessed in 9 trials,<sup>12,43,47,54,58,70,71,73,74</sup> including a total of 723 patients.



**Figure 2.** Comparison of combination (injection followed by thermal) therapy versus injection alone for the outcome of rebleeding.



**Figure 4.** Comparison of clips application versus combination (injection followed by thermal) therapy for the outcome of rebleeding.



**Figure 3.** Comparison of clips application versus thermal for the outcome of rebleeding.

**Endoscopic clips versus injection therapy.** Endoscopic clips were compared with injection in 4 trials (153 treated with clips, 153 controls), specifically, alcohol,<sup>54</sup> distilled water,<sup>43</sup> epinephrine,<sup>47</sup> and polidocanol.<sup>58</sup> Rebleeding alone was reduced significantly more by the use of clips (OR 0.36 [95% CI, 0.17-0.76]). Surgery and mortality were not different between groups (OR 0.42 [95% CI, 0.15-1.21], and OR 1.42 [95% CI, 0.38-5.31]).

**Endoscopic clips versus thermal therapy.** Two trials compared clips with thermal therapy (HPT in both),<sup>70,71</sup> including a total of 193 patients (96 cases and

97 controls). A significant decrease in rebleeding attributable to clips compared with thermal therapy was noted (OR 0.24 [95% CI, 0.06-0.95]) (Fig. 3), whereas no differences were seen for surgery (OR 0.49 [95% CI, 0.12-2.02]) or mortality (OR 0.76 [95% CI, 0.16-3.55]).

**Endoscopic clips versus combination therapy.** Clips were compared with a combination of epinephrine and HPT in 2 studies,<sup>73,74</sup> which included a total of 134 patients (72 cases and 62 controls). No significant differences in rebleeding (Fig. 4), surgery, or mortality were noted (OR 0.82 [95% CI, 0.28-2.38], OR 0.95 [95% CI, 0.15-6.13], and OR 0.69 [95% CI, 0.10-4.71], respectively).

**Endoscopic clips plus injection versus injection alone.** Three studies were included (136 treated with clips and injection, and 136 controls) that compared injection of hypertonic saline solution and epinephrine,<sup>47</sup> epinephrine,<sup>12</sup> or absolute alcohol<sup>54</sup> versus the combination of clip applications followed by injection of these same agents, respectively.<sup>12,47,54</sup> (In the latter,<sup>54</sup> injection was performed first if the size of the visible vessel was more than 2 mm.) Rebleeding and surgery were significantly reduced by clips and injection compared with injection alone (OR 0.38 [95% CI, 0.16-0.86] and OR 0.17 [95% CI, 0.03-0.82], respectively). Mortality was not significantly altered (OR 1.35 [95% CI, 0.25-7.14]).

**Endoscopic clips plus injection versus clips alone.** Two studies included 167 patients (84 cases, 83 controls). One study compared the combination of ethanol and clips with clips alone,<sup>54</sup> whereas the second compared the combination of epinephrine and clips with clips alone.<sup>47</sup> (The same procedural order in the dual modality intervention as described above for clips and injection vs injection alone.) No significant differences in rebleeding, surgery, or mortality were noted (OR 1.30 [95% CI, 0.36-4.76],

OR 0.58 [95% CI, 0.07-4.76], and OR 0.50 [95% CI, 0.08-2.94], respectively).

## DISCUSSION

In the current meta-analysis, unpublished negative results may have been missed; we excluded gray literature<sup>75</sup> because of the completeness of data required. However, this is unlikely when considering the number of studies assessed and the nature of the trials that assess devices.<sup>75</sup> Furthermore, although no single test for publication bias performs consistently well,<sup>22</sup> funnel plots did not suggest publication bias except for combination versus pharmacotherapy (mortality) and for injection versus injection and clips (rebleeding and mortality). In the first case, the lack of improvement in mortality across most evaluations and consistent conclusions across comparisons that discourage injection alone make it unlikely that a possible publication bias would affect results. In the latter case, the use of clips and injection was studied in only 3 trials to date, 2 of which fulfilled our selection criteria.

Exclusion of 45 studies that assessed mixed etiologies of nonvariceal bleeding reflected that the same tendency of results would likely not influence our conclusions, because rebleeding is less common among the most prevalent nonulcer causes.<sup>76</sup>

To address issues of quality and study validity, we used a score derived from Cook et al<sup>2</sup> that we previously adapted for assessing the pharmacotherapy of PUB<sup>14</sup> and which also approximates that used by Kahi et al.<sup>6</sup> Only 2 comparisons of the primary analysis (assessment of patients treated with 2 injectates was a subgroup analysis) revealed statistical heterogeneity<sup>77</sup>; subgroup analyses allowed us to identify its sources in both cases and led to an important interpretation in the case of thermal therapy versus combination therapy.

Despite the inclusion of 41 trials, the numbers of studies and patients included in each comparison are relatively small (on average 4.5 studies and mean [ $\pm$ SD] 101  $\pm$  53 patients). Indeed, we stratified comparisons into biologically pertinent subgroups, based on the pathophysiology of PUB and mechanisms of action of the different endoscopic therapies. Although this clinically driven approach decreases statistical power, it enhances the validity and interpretability of results and complements information provided by previous, more general meta-analyses.<sup>3,78,84</sup> This realization must be kept in mind when interpreting the absence of significant between-modality differences for a given outcome,<sup>7,8</sup> especially when considering the rarer outcomes of surgery and mortality, further justifying our choice of rebleeding as the main outcome. In addition, the trials, for some treatment modalities, emanate from only a few groups who performed many studies, and, as for any randomized trials or meta-analyses thereof, issues

of generalizability and selection bias need to be considered.

Perhaps the most important finding of this series of meta-analyses is the finding that injection, thermal therapy, and combination (injection followed by thermal therapy) all decreased rebleeding significantly compared with sole pharmacotherapy (principally non-high-dose PPI), when considering all high-risk lesions, which confirm consensus recommendations.<sup>4,79,80</sup> The findings are robust and contradict other published summary results that, however, grouped together preendoscopy and postendoscopy use of PPI, and a large number of patients bleeding from non-ulcer causes.<sup>81</sup> Disparities in Forrest class inclusions across studies (especially adherent clots vs other high-risk lesions) limit interpretation when comparing endoscopic therapies, individually or as a group, versus sole pharmacotherapy, even more so for the comparison to PPI alone, in which only 1 study used a high-dose IV regimen.<sup>24</sup> A recent meta-analysis of patients with adherent clots<sup>6</sup> suggested the superiority of endoscopic hemostasis yet exhibited methodologic limitations.<sup>82</sup> Definitive conclusions on endoscopic versus high-dose PPI therapy require additional studies that use contemporary acid-suppressive doses and will depend on what are, to date, disparate published rebleeding estimates attributable to adherent clots.<sup>82</sup> The superiority of endoscopic therapy over H2RA we noted is in keeping with current recommendations.<sup>4</sup>

Our timely and relevant<sup>5</sup> comparison of injection to thermal methods of hemostasis showed no significant differences, yet many different injectates and volumes were used. We noted a trend that favored dual-injection versus single-injection therapy. Interestingly, Calvet et al<sup>3</sup> included 2 non-English language studies we did not include, which account for differences in noted levels of significance for this comparison. Calvet et al<sup>3</sup> also concluded, more broadly, that the use of any additional endoscopic treatment after epinephrine injection significantly improved all outcomes. The added efficacy of a second injectate may relate to its chemical nature or to the resultant increase in volume and enhanced mechanical tamponade effect.<sup>83</sup>

Injection followed by thermal therapy decreased rebleeding more than injection alone (OR 0.27 [95% CI, 0.11-0.66]), as Marmo et al<sup>84</sup> showed. This group also reported no difference between injection followed by thermal therapy versus sole thermal therapy hemostasis, concluding on their equivalence, a challenged finding in light of a calculated statistical power for their analysis that approximated only 0.4.<sup>8</sup> We included one additional trial for this important comparison, noting a similar result in the presence of significant heterogeneity. However, the heterogeneity disappeared when removing the trial by Lin et al<sup>26</sup> or Soon et al.<sup>27</sup> A further assessment of possible sources of clinical heterogeneity showed that removing the trial by Soon et al<sup>27</sup> (which studied an almost never used monopolar thermal modality) increased the trend in effect size favoring combination therapy. When also

removing the study by Church et al,<sup>69</sup> which compared active combination therapy with injection of a placebo followed by thermal therapy (thus also delivering, in effect, a form of combination therapy in the control arm), a significant improvement in rebleeding attributable to combination therapy was noted. This subgroup analysis thus suggests that contemporary combination therapy may indeed be superior to single-modality thermal therapy, as interpreted by existing consensus recommendations.<sup>4</sup> However, when considering the exploratory nature of these results, future trials are needed to more completely address this important comparison.

Sung et al<sup>78</sup> reported in a recent meta-analysis that endoscopic clips were superior to injection alone but were similar to thermocoagulation in decreasing rebleeding. The inclusion of both PUB and Dieulafoy's lesions, and the grouping of both thermal therapy alone and combination injection followed by thermal therapy under the term thermocoagulation limit interpretation of the results. No studies allowed us or others to assess clips versus pharmacotherapy, but our results show less bleeding with clips compared with injection or thermal hemostasis alone. The comparison of clips to injection followed by thermal therapy showed a trend in decreased rebleeding that favored clips (OR 0.82 [95% CI, 0.28-2.38], stemming from 134 patients in 2 trials).

As also reported by both Marmo et al<sup>84</sup> and Sung et al,<sup>78</sup> we found the combination of clips followed by injection therapy to be superior to injection alone for both rebleeding and surgery (OR 0.38 [95% CI, 0.16-0.86], and OR 0.17 [95% CI, 0.03-0.82], respectively). Interestingly, most studies assessed an approach of clipping followed by injection, presumably because clips may subsequently fall off as tissue swelling from the injection recedes.<sup>85</sup> We found no differences when comparing clips and injection versus clips alone but could only rely on 2 trials, which totaled 167 patients. Marmo et al<sup>84</sup> reached similar findings with inclusion of an additional trial by Gevers et al<sup>85</sup> that did not fulfill our inclusion criteria (because of incomplete information). Even their conclusion of equivalence remains limited by insufficient statistical power (approximately 0.2).<sup>8</sup> Taken as a whole, these results suggest that the use of clips alone is now justified, certainly when compared with other single treatment modalities, and consensus recommendations will need to be updated accordingly<sup>4,80</sup>; the exact role of clips in combination with other modalities requires further assessment.

A number of additional issues require further study: the possible tailored choice of hemostatic method based on lesion appearance and location, the comparative efficacies of different injectates, of their varying volumes, of the use of different thermal probes, or of different clip technologies, as well as the safety of endoscopic methods, and the efficacy of a second-look strategy in the era of profound acid suppression.

In conclusion, all endoscopic treatment modalities appear superior to pharmacotherapy alone; injection, if performed alone, should probably include 2 injectates. Endoscopic therapy in nonbleeding lesions appears to be more effective than sole pharmacotherapy, with, however, only one comparison to sole use of PPI at the currently recommended IV high dose. Ideally, injection should not be practiced alone, and endoscopists should familiarize themselves with other methods of hemostasis. The optimal contemporary methods appear to use thermal therapy or clips, either alone or with another modality. Further data are needed to better delineate the comparative efficacy of sole thermal therapy versus combination therapy and dual modality approaches that use clips compared with clips alone or other dual-modality therapies.

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