Table 3.1.1 *Question 1: Can treatment with acid-suppressing drugs prior to endoscopic examination (EGD) and possible endoscopic treatment of bleeding ulcers reduce the risk for recurrent bleeding, death or need for surgery?*

Meta-analyses and systematic reviews

First author Year Reference Country	Overall aim Purpose (incl study population and setting)	Number and type of studies	Outcome domains	Results	Study quality Comments
Sreedharan et al 2010 [4] United Kingdom	Systematic review The Cochrane Collaboration PPI treatment before endoscopy	6 RCTs comprising 2 223 participants PPI treatment (oral or IV) Control treatment with either placebo, H_2RA or no treatment	Recurrent bleeding Need for surgery Mortality Outcomes assessed at 30 days	*Recurrent bleeding (5 studies)* PPI 11% vs control 13.1% (OR 0.81; 95% CI 0.62–1.06) *Need for surgery (5 studies)* PPI 7.2% vs control 7.9% (OR 0.90; 95% CI 0.65–1.25) *Mortality (6 studies)* PPI 4.9% vs control 4.3% (OR 1.12; 95% CI 0.75–1.68)	High Reduced endoscopic therapy at index endoscopy; unweighted pooled rates 8.6% and 11.7% respectively (OR 0.68; 95% CI 0.50–0.93)
Leontiadis et al 2007 [3] United Kingdom	Systematic review Health Technology Assessment Investigate the efficacy of acute PPI treatment before endoscopy	5 RCTs (4 full papers) The 4 RCTs in full papers are included in the systematic review by Sreedharan 2010 [4] 1 512 patients randomised PPI (omeprazole IV and lansoprazole): n=760 Controls: n=752	Recurrent bleeding Need for surgery Mortality	*Recurrent bleeding (3 studies)* PPI 13.9% vs control 16.6% (OR 0.81; 95% CI 0.61–1.09) *Need for surgery (3 studies)* PPI 9.9% vs control 10.2% (OR 0.96; 95% CI 0.68–1.35) *Mortality (4 studies)* PPI 6.1% vs control 5.5% (OR 1.12; 95% CI 0.72–1.73)	High

CI = Confidence interval; H_2RA = Histamine-2 receptor antagonist; IV = Intravenous;
OR = Odds ratio; PPI = Proton pump inhibitor; RCT = Randomised controlled trial

Table 3.1.2a *Question 2: Can treatment with acid-suppressing drugs after EGD and endoscopic treatment of bleeding ulcers reduce the risk for recurrent bleeding, death or need for surgery?*

Meta-analyses and systematic reviews

First author Year Reference Country	Overall aim Purpose (incl study population and setting)	Number and type of studies	Outcome domains	Results	Study quality Comments
Wang et al 2010 [12] Taiwan	Systematic review Compare high dose PPI with non high dose after endoscopic treatment of peptic ulcer bleeding	7 RCTs with a total of 1 157 patients 80 mg bolus followed by 8 mg/hour continuous intravenous infusion compared to non high dose administration	Recurrent bleeding Need for surgery Mortality	*Recurrent bleeding* (7 studies and 1 157 patient) OR 1.30 (95% CI 0.88–1.91) *Need for surgery* (6 studies and 1 052 patients) OR 1.49 (95% CI 0.66–3.37) *Mortality* (6 studies and 1 052 patients) OR 0.89 (95% CI 0.37–2.13)	High Only 3 of 7 studies were double blinded. Much clinical heterogeneity across trials regarding inclusions, endoscopic treatment, route and dose of PPI in control group
Wang et al 2009 [7] China	Systematic review Evaluate the efficacy of IV pantoprazole compared to different pharmacological therapies after endoscopic treatment for bleeding peptic ulcer	5 RCTs (all full papers) 821 patients	Recurrent bleeding Need for surgery Mortality	*Recurrent bleeding (722 patients)* Pantoprazole 4.7% vs control 15.0% (RR 0.31; 95% CI 0.18–0.53) *Need for surgery (409 patients)* Pantoprazole 1.4% vs control 6.5% (RR 0.28; 95% CI 0.09–0.83) *Mortality (722 patients)* Pantoprazole 1.9% vs control 2.8% (RR 0.72; 95% CI 0.29–1.81)	Moderate
Leontiadis et al 2007 [3] 2006 [5] United Kingdom	Systematic review Evaluate the efficacy of PPIs in acute bleeding from peptic ulcer using evidence from RCTs Health Technology Assessment [3] The Cochrane Collaboration [5]	24 RCTs (19 full papers) 4 373 patients randomised to PPI treatment or placebo or H_2RA treatment	Recurrent bleeding Need for surgery Mortality	*Recurrent bleeding* PPI 10.6% vs control 17.3% (OR 0.49; 95% CI 0.37–0.65) *Need for surgery* PPI 6.1% vs control 9.3% (OR 0.61; 95% CI 0.48–0.78) *Mortality* PPI 3.9% vs control 3.8% (OR 1.01; 95% CI 0.74–1.40)	High No evidence for differences with route of administration of PPI. When active bleeding PPI reduced mortality by OR 0.53 (95% CI 0.31–0.91)

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Table 3.1.2a *continued*

Meta-analyses and systematic reviews					
First author Year Reference Country	**Overall aim Purpose (incl study population and setting)**	**Number and type of studies**	**Outcome domains**	**Results**	**Study quality Comments**
Andriulli et al 2005 [8] Italy	Systematic review Outcome of bleeding ulcers with different PPI treatment regimens compared to placebo and or H_2RA	35 RCTs (30 full papers) 4 843 patients with high risk of bleeding Endoscopic therapy + PPI vs placebo 18 RCTs (16 full papers) are included in Leontiadis 2007 [3]	Recurrent bleeding Need for surgery Mortality	*Recurrent bleeding* Risk difference: –13.7% (95% CI 0.9–27) (OR 0.50; 95% CI 0.26–0.96) *Need for surgery* Risk difference: –19% (95% CI 7–31) (OR 0.37; 95% CI 0.14–0.96) *Mortality* No difference Oral 20–40 mg/day or bolus PPI 80 mg IV + infusion or oral better than placebo or H_2RA	Moderate Multitude of PPI doses Pooling of data showed no difference between high dose PPI infusion or regular dose as intermittent bolus
Bardou et al 2005 [9] Canada	Systematic review To characterise the role of different pharmacological therapies in peptic ulcer bleeding	18 RCTs (all full papers) 1 855 patients PPI 40–80 mg IV and at least 6 mg/hour PPI 40–80 mg oral or non high dose PPI or placebo 11 RCTs in full papers are included in Leontiadis 2007 [3]	Recurrent bleeding Need for surgery Mortality	*High-dose PPI vs placebo* Recurrent bleeding: –14.6% (95% CI –16.2 to –12.9) Need for surgery: –5.4% (95% CI –8.4 to –2.4) Mortality: –2.7% (95% CI –9.2 to 3.8) *High-dose PPI vs H_2RA* Recurrent bleeding: –20.66% (95% CI –24.7 to –16.6) High-dose oral PPI (twice standard dosage) reduced recurrent bleeding by 15.3% compared with placebo	High

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Table 3.1.2a *continued*

Meta-analyses and systematic reviews					
First author Year Reference Country	**Overall aim Purpose (incl study population and setting)**	**Number and type of studies**	**Outcome domains**	**Results**	**Study quality Comments**
Khuroo et al 2005 [11] India	Systematic review Assess treatment effects of PPI in acute non-variceal upper gastrointestinal bleeding	26 RCTs (22 full papers) 4 670 subjects PPI (omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole) (n=2 317) Placebo/H_2RA (n=2 353) 17 RCTs (15 full papers) are included in Leontiadis 2007 [3]	Recurrent bleeding Need for surgery Mortality (ulcer deaths, non-ulcer deaths, all-cause mortality)	*Recurrent bleeding* OR 0.48 (95% CI 0.40–0.57) *Need for surgery* OR 0.61 (95% CI 0.48–0.76) *Mortality (ulcer death)* OR 0.58 (95% CI 0.35–0.96) All-cause mortality unaffected	High
Gisbert et al 2001 [10] Spain	Systematic review Evaluate PPIs against H_2RA for treatment of bleeding peptic ulcer	11 RCTs comprising 1 239 patients PPI 80 mg + 8 mg/hour or 40 mg/8 hour in 618 patients H_2RA in 621 patients; dosage unclear 9 RCTs in full papers are included in Leontiadis 2007 (2 spanish RCTs are included in Andriulli 2005 [8])	Persistent or recurrent bleeding Need for surgery Mortality	*Persistent or recurrent bleeding* PPI: 6.7% (95% CI 4.9–8.6) H_2RA: 13.4% (95% CI 10.8–16) (OR 0.4; 95% CI 0.27–0.59) *Need for surgery* PPI: 5.2% (95% CI 3.4–6.9) H_2RA: 6.9% (95% CI 4.9–8.9) *Mortality* PPI: 1.6% (95% CI 0.9–2.9) H_2RA: 2.2% (95% CI 1.3–3.7)	High

CI = Confidence interval; H_2RA = Histamine-2 receptor antagonist; IV = Intravenous; OR = Odds ratio; PPI = Proton pump inhibitor; RCT = Randomised controlled trial; RR = Relative risk

Table 3.1.2b *Question 2: Can treatment with acid-suppressing drugs after EGD and endoscopic treatment of bleeding ulcers reduce the risk for recurrent bleeding, death or need for surgery?*

Randomised controlled trials

First author **Year** **Reference** **Country**	**Study design** **Setting**	**Population** **Number at baseline** **Male/female** **Age** **Drop out rate**	**Intervention (I)** **Follow-up time**	**Control (C)** **Follow-up time**	**Results**	**Study quality** **Comments**
Sung et al 2009 [2] China	RCT Multicentre European-Asian hospital	n=767 I: n=376 C: n=391 Male/female: 522/242 *Mean age* I: 62.1±17.5 years C: 60.2±17.6 years 3 drop outs	Esomeprazole 80 mg IV + 8 mg/hour for 72 hours, esomeprazole 40 mg/day for 27 days 30 days	Placebo, then esomeprazole 40 mg/day for 27 days 30 days	*Recurrent bleeding* I: 5.9% C: 10.3% Difference 4.4% (95% CI 0.6–8.3), p=0.026 *Repeated endoscopic treatment within 30 days* I: 24 (6.4%) C: 45 (11.6%), p=0.012 *Surgery within 30 days* I: 10 (2.7%) C: 21 (5.4%), p=0.059 *Mortality within 30 days* I: 3 (0.8%) C: 8 (2.1%), p=0.22	High Study power 90%
Andriulli et al 2008 [13] Italy	RCT Multicentre 11 Italian hospitals	n=474 I: n=238 C: n=236 Male/female: 307/167 *Mean age:* I: 66.3±15.6 C: 66.8±16.7 8 drop outs	Omeprazole or pantoprazole 80 mg IV + 8 mg/hour for 72 hours, oral PPI 20 mg x 2 until discharge In hospital period	Omeprazole or pantoprazole 40 mg IV x 1 + continuous infusion of saline for 72 hours, oral PPI 20 mg x 2 until discharge In hospital period	*Recurrent bleeding* I: 28/238 (11.8%) C: 19/236 (8.1%) p=0.18	High Study power 80%

C = Control; I = Intervention; IV = Intravenous; NSAID = Non-steroid anti-inflammatory drugs; PPI = Proton pump inhibitor; RCT = Randomised controlled trial

Table 3.1.3a *Question 3: Can treatment of bleeding ulcers with tranexamic acid or somatostatin reduce the risk for recurrent bleeding, death or need for surgery?*

Meta-analyses and systematic reviews

First author Year Reference Country	Overall aim Purpose (incl study population and setting)	Number and type of studies	Outcome domains	Results	Study quality Comments
Gluud et al 2008 [14] Denmark	Systematic review Review randomised trials on tranexamic acid for upper gastrointestinal bleeding	7 RCTs (all full papers) 1 306 patients	Treatment given before endoscopy Recurrent bleeding Need for surgery Mortality	*Recurrent bleeding* 3% vs 6% (RR 0.66; 95% CI 0.40–1.10) *Need for surgery* 10% vs 14% (RR 0.62; 95% CI 0.35–1.09) *Mortality* 5% vs 8% (RR 0.61; 95% CI 0.42–0.89)	Moderate Endoscopic therapy in only one of seven studies
Imperiale et al 1997 [15] USA	Systematic review Determine efficacy of somatostatin/octreotide, compared to placebo or H_2RA, for treatment of acute non-variceal upper gastrointestinal haemorrhage	14 RCTs (all full papers) 1 829 patients Somatostatin 250 µg/hour with or without bolus in 12 trials. Octreotide used in 2 trials Compared to placebo (7 trials), cimetidine (7 trials), ranitidine (5 trials)	Continued or recurrent bleeding Need for surgery	*Continued or recurrent bleeding* RR 0.53 (95% CI 0.43–0.63) (In investigator blinded trials RR 0.73 (95% CI 0.64–0.81)) *Need for surgery* RR 0.71 (95% CI 0.61–0.81) (In investigator blinded trials RR 0.94 (95% CI 0.87–1.001))	Moderate Only 7 trials with adequate investigator blinding. Poor definition of bleeding source in some studies. No endoscopic therapy applied

CI = Confidence interval; H_2RA = Histamine-2 receptor antagonist; RCT = Randomised controlled trial; RR = Relative risk

Table 3.1.3b *Question 3: Can treatment of bleeding ulcers with tranexamic acid or somatostatin reduce the risk for recurrent bleeding, death or need for surgery?*

Randomised controlled trials

First author Year Reference Country	Study design Setting	Population Number at baseline Male/female Age Drop out rate	Intervention (I) Follow-up time	Control (C) Follow-up time	Results	Study quality Comments
Tsibouris et al 2007 [16] Greece	RCT Single centre Hospital	n=164 I: n=82 C: n=82 *Male/female* I: 60/22 C: 60/22 *Mean age* I: 67.8±13.1 years C: 66.4±13 years Helicobacter in every 2 patients	Pantoprazole 40 mg bolus + 8 mg/hour IV for 48 hours	Somatostatin 250 µg bolus + 250 µg/hour for 48 hours	*Recurrent bleeding* I: 4 (5%) C: 14 (17%), p=0.046 No difference in need for surgery or mortality	High Power calculation 90%. NSAID use considered

C = Control; I = Intervention; IV = Intravenous; RCT = Randomised controlled trial

Table 3.1.4 *Question 4: Can medical treatment of bleeding ulcers prevent recurrent bleeding during the first month after care for bleeding ulcers?*

Meta-analyses and systematic reviews

First author Year Reference Country	Overall aim Purpose (incl study population and setting)	Number and type of studies	Outcome domains	Results	Study quality Comments
Gisbert et al 2004 [17] Spain	Systematic review Compare the efficacy of *H. pylori* eradication (I) vs antisecretory non-eradication therapy (with or without long-term maintenance therapy) for prevention of recurrent bleeding from peptic ulcer The Cochrane Database	Controlled clinical trials Two meta-analyses performed: 1. 7 studies of 578 patients (without long-term maintenance therapy) 2. 3 studies of 470 patients (with long-term maintenance therapy) Subanalysis excludes patients on NSAIDs	Recurrent bleeding after *H. pylori* eradication *Treatments* PPI/H_2RA + 2 antibiotics + bismuth during 10–28 days Omeprazole + clarithromycin + amoxicillin for 10 days *Control* Antisecretory (*H. pylori*, H_2RA) non-eradication treatment with or without long-term maintenance antisecretory therapy	*1. Recurrent bleeding (7 studies)* I: 2.9% (95% CI 1.6–5.2) C: 20% (95% CI 14–25) (OR 0.17; 95% CI 0.10–0.32) NNT=7 *2. Recurrent bleeding (3 studies)* I: 1.6% (95% CI 0.6–3.9) C: 5.6% (95% CI 2.5–8.7) (OR 0.25; 95% CI 0.08–0.76) NNT=20 *Subanalysis showed rate of recurrent bleeding* 1. 2.7% (95% CI 1.5–5) 2. 0.78% (95% CI 0.22–2.8) Follow-up: 2 179 patient-years	High

C = Control; CI = Confidence interval; H_2RA = Histamine-2 receptor antagonist; NNT = Number needed to treat; NSAID = Non-steroidal anti-inflammatory drugs; OR = Odds ratio

Table 3.2.4 *Question 1: Is there evidence for endoscopic treatment of bleeding ulcers based on endoscopic signs according to the Forrest classification?*

Meta-analyses and systematic reviews

First author Year Reference Country	Overall aim Purpose (incl study population and setting)	Number and type of studies	Outcome domains	Results	Study quality Comments
Laine et al 2009 [6] USA	Systematic review To compare different endoscopic therapies in the treatment of bleeding peptic ulcer Forrest grade I–IIa	75 RCTs (all full papers)	Recurrent bleeding (primary endpoint) Need for surgery Mortality	*Recurrent bleeding* • Other monotherapies better than epinephrine RR 0.58 (95% CI 0.36–0.93) • Epinephrine + other therapies better than epinephrine alone RR 0.34 (95% CI 0.23–0.50) • Thermal contact RR 0.44 (95% CI 0.36–0.54) and sclerotherapy RR 0.56 (95% CI 0.38–0.83) better than no endoscopic treatment • Clips better than epinephrine RR 0.22 (95% CI 0.09–0.55) • All endoscopic therapies pooled effective for active bleeding RR 0.29 (95% CI 0.20–0.43) and visible vessel RR 0.49 (95% CI 0.40–0.59) but not for clot *Need for surgery* • Other monotherapies better than epinephrine RR 0.44 (95% CI 0.20–0.98) • Epinephrine + other therapies better than epinephrine alone RR 0.33 (95% CI 0.17–0.66) • Thermal contact RR 0.39 (95% CI 0.27–0.55) and sclerotherapy RR 0.24 (95% CI 0.09–0.64) better than no endoscopic treatment • Clips better than epinephrine RR 0.22 (95% CI 0.06–0.83) • All endoscopic therapies pooled effective for active bleeding RR 0.25 (95% CI 0.13–0.50) and visible vessel RR 0.41 (95% CI 0.24–0.71) but not for clot *Mortality* • Thermal contact RR 0.39 (95% CI 0.27–0.55) and sclerotherapy RR 0.58 (95% CI 0.34–0.98) better than no endoscopic treatment	High

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Table 3.2.4 *continued*

Meta-analyses and systematic reviews					
First author Year Reference Country	**Overall aim Purpose (incl study population and setting)**	**Number and type of studies**	**Outcome domains**	**Results**	**Study quality Comments**
Kahi et al 2005 [7] USA	Systematic review To compare endoscopic and medical therapy in patients with bleeding peptic ulcer with adherent clot Forrest grade IIb	6 RCTs (4 full papers) 4 RCTs in full papers are included in Laine 2009 [6]	Recurrent bleeding Need for surgery Mortality Hospital stay Blood transfusion	*Recurrent bleeding* Less recurrent bleeding in endoscopic therapy RR 0.35 (95% CI 0.14–0.83) No difference in other outcomes	High
Cook et al 1992 [5] USA	Systematic review To examine the effect of endoscopic therapy in non-variceal upper GI bleeding Forrest grade I–IIa	30 RCTs (20 full papers) 10 RCTs in full papers are included in Laine 2009 [6]	Recurrent bleeding Need for surgery Mortality	All endoscopic therapies reduced; *Recurrent bleeding* OR 0.38 (95% CI 0.32–0.45) *Need for surgery* OR 0.36 (95% CI 0.28–0.45) *Mortality* OR 0.55 (95% CI 0.40–0.76) Subgroup analysis showed that the effect was seen in patients with active bleeding and visible vessel only	Moderate

CI = Confidence interval; GI = Gastrointestinal; RR = Relative risk;
OR = Odds ratio; RCT = Randomised controlled trial

Table 3.2.5 *Question 2: Is there evidence that endoscopic treatment of bleeding ulcers should be delivered within a certain time frame after admission to hospital?*

Randomised controlled trials

First author **Year** **Reference** **Country**	**Study design** **Setting**	**Population** **Number at baseline** **Male/female** **Age** **Drop out rate**	**Intervention (I)** **Follow-up time**	**Control (C)** **Follow-up time**	**Results**	**Study quality** **Comments**
Björkman et al 2004 [8] USA	RCT Multicenter University hospital	n=93 Male/female: 62/31 *Mean age* I: 57 (52–62) years C: 52 (47–57) years No drop outs	Early endoscopy <6 hours 30 days	Elective endoscopy 30 days	No difference in hospital stay or ICU. Physicians did not follow endoscopists' recommendation	Moderate
Lee et al 1999 [9] USA	RCT University hospital	n=110 Male/female: 79/31 *Mean age* I: 47±15 years C: 51±18 years No drop outs	Early endoscopy 1–2 hours 30 days	Elective endoscopy 1–2 days 30 days	Shorter hospital stay: p=0.0001 (I) Lower cost: p=0.00006 (I)	High

C = Control, I=Intervention; CI = Confidence interval; ICU = Intensive care unit;
RCT = Randomised controlled trial

Table 3.2.6 *Question 3: Is there evidence of differences in effects between different endoscopic treatments? Is there evidence of differences in effects in combining different endoscopic treatments?*

Meta-analyses and systematic reviews

First author Year Reference Country	Overall aim Purpose (incl study population and setting)	Number and type of studies	Outcome domains	Results	Study quality Comments
Laine et al 2009 [6] USA	See table 3.2.4				High
Barkun et al 2009 [10] Canada	Systematic review To compare different endoscopic techniques for bleeding peptic ulcer	41 RCTs (all full papers) 30 RCTs are included in Laine 2009 [6]	Recurrent bleeding Need for surgery Mortality	*Recurrent bleeding* • Less recurrent bleeding with endoscopic therapy vs pharmacotherapy OR 0.35 (95% CI 0.27–0.46) • Less recurrent bleeding with combination therapy vs injection OR 0.27 (95% CI 0.11–0.66) • Less recurrent bleeding with clips vs injection OR 0.36 (95% CI 0.17–0.76) • Less recurrent bleeding with clips vs thermal OR 0.24 (95% CI 0.06–0.95) *Need for surgery* • Less with endoscopic therapy vs pharmacotherapy OR 0.57 (95% CI 0.41–0.81) *Mortality* • Less with endoscopic therapy vs pharmacotherapy OR 0.57 (95% CI 0.37–0.89)	High
Yuan et al 2008 [13] Canada	Systematic review To compare endoscopic clipping with other endoscopic techniques for non-variceal upper GI bleeding	12 RCTs (all full papers) 7 RCTs are included in Laine 2009 [6]	Initial homeostasis Recurrent bleeding Need for surgery Mortality	No significant differences were found	High

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Table 3.2.6 *continued*

Meta-analyses and systematic reviews					
First author Year Reference Country	**Overall aim Purpose (incl study population and setting)**	**Number and type of studies**	**Outcome domains**	**Results**	**Study quality Comments**
Marmo et al 2007 [11] Italy	Systematic review To compare endoscopic monotherapy with dual therapy in peptic ulcer bleeding	20 RCTs (all full papers) 17 RCTs are included in Laine 2009 [6]	Recurrent bleeding Need for surgery Mortality	Dual therapy reduced; *Recurrent bleeding* OR 0.59 (95% CI 0.44–0.80) *Need for surgery* OR 0.66 (95% CI 0.49–0.89) Subcategory analysis showed that dual therapy was significantly superior to injection but not to mechanical or thermal therapy *Mortality* No effect	High
Sung et al 2007 [12] China	Systematic review To compare the efficacy of hemoclips vs injection or thermocoagulation in bleeding peptic ulcers	15 RCTs (13 full papers) 8 RCTs are included in Laine 2009 [6]	Initial haemostasis Definite haemostasis Recurrent bleeding Need for surgery Mortality	*Definite haemostasis* • Higher with clips than injection RR 1.14 (95% CI 1.00–1.30) • Clips + injection vs injection alone RR 1.13 (95% CI 1.03–1.23) with less need for surgery No difference between clips and thermocoagulation *Recurrent bleeding* • Clips vs injection RR 0.49 (95% CI 0.30–0.79) • Clips+injection vs injection RR 0.47 (95% CI 0.28–0.76) *Need for surgery* • Clips vs injection RR 0.37 (95% CI 0.15–0.9) • Clips + injection vs injection RR 0.23 (95% CI 0.08–0.7) *Mortality* No differences	High

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Table 3.2.6 *continued*

Meta-analyses and systematic reviews					
First author Year Reference Country	**Overall aim Purpose (incl study population and setting)**	**Number and type of studies**	**Outcome domains**	**Results**	**Study quality Comments**
Vergara et al 2007 [16] Spain	Systematic review To compare the efficacy of epinephrine alone with epinephrine combined with a second procedure in bleeding peptic ulcers	17 RCTs (15 full papers) 13 RCTs in full papers are included in Laine 2009 [6]	Further bleeding Need for surgery Mortality	Combination reduced; *Recurrent bleeding* OR 0.51 (95% CI 0.39–0.66) *Need for surgery* OR 0.63 (95% CI 0.45–0.89) *Mortality* OR 0.50 (95% CI 0.30–0.82) No difference in complication rates	Moderate
Calvet et al 2004 [15] Spain	Systematic review To compare the efficacy of epinephrine alone with epinephrine combined with a second procedure in bleeding peptic ulcers	16 RCTs (14 full papers) 13 RCTs in full papers are included in Laine 2009 [6]	Further bleeding Need for surgery Mortality	Combination reduced; *Recurrent bleeding* OR 0.53 (95% CI 0.40–0.69) *Need for surgery* OR 0.64 (95% CI 0.46–0.90) *Mortality* OR 0.51 (95% CI 0.31–0.84)	High
Cook et al 1992 [5] USA	See table 3.2.4				Moderate

CI = Confidence interval; GI = Gastrointestinal; OR = Odds ratio;
RCT = Randomised controlled trial; RR = Relative risk

Table 3.2.7a *Question 4: Is there evidence that scheduled second look endoscopy is effective after initial endoscopic treatment of bleeding ulcers?*

Meta-analyses and systematic reviews					
First author Year Reference Country	**Overall aim Purpose (incl study population and setting)**	**Number and type of studies**	**Outcome domains**	**Results**	**Study quality Comments**
Marmo et al [17] 2003 Italy	Systematic review To evaluate the effect of a scheduled second look endoscopy with treatment in peptic ulcer bleeding	4 RCTs (all full papers) 3 with H_2RA 1 with PPI	Recurrent bleeding Need for surgery Mortality	Second look reduced the risk for; *Recurrent bleeding* OR 0.64 (95% CI 0.44–0.95) *Need for surgery* No difference *Mortality* No difference	High

CI = Confidence interval; H_2RA = Histamine-2 receptor antagonist; OR = Odds ratio;
PPI = Proton pump inhibitor; RCT = Randomised controlled trial

Table 3.2.7b *Question 4: Is there evidence that scheduled second look endoscopy is effective after initial endoscopic treatment of bleeding ulcers?*

Randomised controlled trials						
First author Year Reference Country	**Study design Setting**	**Population Number at baseline Male/female Age Drop out rate**	**Intervention (I) Follow-up time**	**Control (C) Follow-up time**	**Results**	**Study quality Comments**
Chiu et al 2003 [18] China	RCT Regional hospital	n=194 Male/female: 132/62 *Mean age* I: 68.7 years C: 67.5 years No drop outs	Second look endoscopy IV omeprazol 40 mg twice daily for 3 days 30 days	Observation IV omeprazol 40 mg twice daily for 3 days 30 days	*Recurrent bleeding* RR 0.33 (95% CI 0.1–0.96)	High

C = Control; CI = Confidence interval; I = Intervention; IV = Intravenous;
RCT = Randomised controlled trial; RR = Relative risk

Table 3.2.8 *Question 5: Is there evidence that repeating endoscopic treatment is effective in patients with recurrent bleeding ulcer after endoscopic treatment of bleeding ulcers?*

Randomised controlled trials

First author **Year** **Reference** **Country**	**Study design** **Setting**	**Population** **Number at baseline** **Male/female** **Age** **Drop out rate**	**Intervention (I)** **Follow-up time**	**Control (C)** **Follow-up time**	**Results**	**Study quality** **Comments**
Lau et al 1999 [19] China	RCT University hospital	n=92 Male/female: 70/22 *Mean age* I: 65±17 years C: 65±15 years No drop outs	Endoscopic retreatment 111 days	Surgery 111 days	Fewer complications (I). No difference in mortality	High

C = Control; I = Intervention; RCT = Randomised controlled trial

Table 3.2.9 *Question 6: Is there evidence that medical pretreatment can facilitate acute upper endoscopy (EGD) for bleeding ulcers?*

Randomised controlled trials

First author **Year** **Reference** **Country**	**Study design** **Setting**	**Population** **Number at baseline** **Male/female** **Age** **Drop out rate**	**Intervention (I)** **Follow-up time**	**Control (C)** **Follow-up time**	**Results**	**Study quality** **Comments**
Carbonell et al 2006 [22] France	RCT University hospital	n=100 Male/female: 78/21 *Mean age* I: 59.3±14.6 years C: 57.0±13.4 years 1 drop out	Erythromycin 250 mg intravenously x 1 48 hours	Placebo 48 hours	Endoscopic visibility better p<0.05 (I)	High
Coffin et al 2002 [20] France	RCT University hospital	n=41 Male/female: 25/16 *Mean age* I: 56±19 years C: 58±20 years No drop outs	Erythromycin 3 mg/kg intravenously x 1 8 days	No treatment 8 days	Endoscopic visibility better p=0.02 (I). Second look ns	Moderate
Frossard et al 2002 [21] Switzerland	RCT University hospital	n=105 Male/female: 84/21 *Mean age* I: 59.2±15 years C: 64.5±16 years No drop outs	Erythromycin 250 mg intravenously x 1 24 hours	Placebo 24 hours	Endoscopic visibility better p<0.001 (I). Shorter endoscopy p=0.036 (I). Less second look p=0.018 (I)	High

C=Control, I=Intervention; RCT = Randomised controlled trial

Table 3.3.1a *Question 1: Is there evidence to show which patients with bleeding ulcers have a high risk for an unsuccessful endoscopic treatment so that other methods (surgery or endovascular treatment) should be used instead?*

Randomised controlled trials

First author **Year** **Reference** **Country**	**Study design** **Setting**	**Population** **Number at baseline** **Male/female** **Age** **Drop out rate**	**Intervention (I)** **Follow-up time**	**Control (C)** **Follow-up time**	**Results**	**Study quality** **Comments**
Imhof et al 2003 [4] Germany	RCT multicenter Period: 1991–1995	n=61 Male/female: 40/21 55 patients included; Surgical group: 23 Endoscopic group: 32 (120 was projected). No differences between groups	Different kinds (most BI and BII; some oversewing and different kinds of vagotomy) of surgery. Outcome criteria recurrent bleeding and death during hospital stay	Endoscopic treatment with fibrin glue	*Recurrent bleeding* Endoscopic group: 48% (50% per protocol analysis) Surgical group: 11% (4%) *Emergency surgery* Endoscopic group: 21% *Mortality* Endoscopic group: 6% (6%) Surgical group: 7% (9%)	Moderate Early elective surgery effective in patients at high risk for recurrent bleeding. Fibrin glue injection carries a risk for recurrent bleeding, most can be controlled by re-endoscopic treatment. A subgroup will need emergency operations with fatal outcome in individual patients. After interim analysis the study was stopped

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Table 3.3.1a *continued*

Randomised controlled trials						
First author Year Reference Country	**Study design Setting**	**Population Number at baseline Male/female Age Drop out rate**	**Intervention (I) Follow-up time**	**Control (C) Follow-up time**	**Results**	**Study quality Comments**
Lau et al 1999 [5] Hong Kong	RCT Period: 1994–1998 Actively bleeding ulcers or non bleeding visible vessel were treated with injection of epinephrine and thermocoagulation. After recurrent bleeding randomisation to endoscopic treatment (the same as previously) or surgery (choice of operation was left to the surgeon). All patients were treated with 40 mg omeprazol (in surgery group to patients that underwent simple ulcer plication or excision). Endpoint mortality	1 169 underwent endoscopy to re-establish hemostasis. Hemostasis was not achieved in 17 patients, direct to surgery. 94 patients were randomised (2 drop outs), leaving 92 patients. Male/female: 70/22 *Endoscopic retreatment* n=48 Mean age: 68±17 years *Surgery* n=44 Mean age: 68±15 years	Endoscopic treatment with epinephrine and thermocoagulation after recurrent bleeding 30 days	Surgery after recurrent bleeding	Duration of hospital stay, need for intensive care, transfusion requirements similar in both groups. More complications in the surgery group, no difference in 30 days mortality (10% in endoscopic group, 4 of those 5 patients underwent salvage surgery). Predicting factors for unsuccessful endoscopic treatment were hypotension at randomisation, larger ulcers (>2 cm), other illnesses	High Endoscopic retreatment reduces the need for surgery without increasing the risk of death and is associated with fewer complications than surgery

BI = Billroth 1; BI I= Billroth 2; C = Control; I = Intervention;
RCT = Randomised controlled trial

Table 3.3.1b *Question 1: Is there evidence to show which patients with bleeding ulcers have a high risk for an unsuccessful endoscopic treatment so that other methods (surgery or endovascular treatment) should be used instead?*

Observational studies

First author Year Reference Country	Study design Setting	Population Number at baseline Male/female Age Drop out rate	Intervention (I) Follow-up time	Control (C) Follow-up time	Results	Study quality Comments
Choudari et al 1994 [6] United Kingdom	Prospective observational study Period: 1989–1992 To define factors associated with failed endoscopic therapy; trying to identify the group of patients that should be offered early definitive surgery Recurrent bleeding, surgical operation, 30-day mortality and endoscopic treatment success or failure was recorded	326 patients with active bleeding or visible vessel. 18 technical failure <u>*Mean age*</u> Successful therapy: 68 (17–95) years Failed therapy: 70 (41–90) years	Endoscopy with injection or thermo-coagulation in 308 patients. All patients received H_2 receptor antagonists		Endoscopic therapy was possible in 308 patients (94%). Permanent hemostasis was achieved in 269 patients (82.5%) 57 patients (17.5%) continued to bleed or showed recurrent bleeding	Low Active hemorrhage, shock on admission, and the lowest haemoglobin concentration did less well, as well as a posterior duodenal ulcer was significantly more often associated with failed endoscopic therapy

Table 3.3.2a *Question 2: Is there evidence for differences in the effects between different surgical methods for the treatment of bleeding ulcers?*

Randomised controlled trials

First author Year Reference Country	**Study design Setting**	**Population Number at baseline Male/female Age Drop out rate**	**Intervention (I) Follow-up time**	**Control (C) Follow-up time**	**Results**	**Study quality Comments**
Millat et al 1993 [7] France	RCT Period: 1978–1988 Comparing treatment of bleeding bulbar peptic ulcer with O+V or gastric resection with ulcer excision	n=202 Male/female: 136/66 Mean age: 62.4 (18–96) years 120 patients were randomised, 2 were withdrawn	n=59 O+V 1 month after discharge from hospital	n=61 GR with ulcer excision 1 month after discharge from hospital	*Recurrent bleeding* O+V: 17% GR: 3% *Duodenal leak* O+V: 3% GR: 13% *Postoperative morbidity* O+V: 13% GR: 12% *Mortality* O+V: 22% GR: 23%	Moderate GR is the procedure of choice for the emergency surgical treatment of bleeding duodenal ulcer, the bleeding recurrence is lower than O+V, the postoperative morbidity and mortality are the same

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Table 3.3.2a *continued*

Randomised controlled trials						
First author **Year** **Reference** **Country**	**Study design** **Setting**	**Population** **Number at baseline** **Male/female** **Age** **Drop out rate**	**Intervention (I)** **Follow-up time**	**Control (C)** **Follow-up time**	**Results**	**Study quality** **Comments**
Poxon et al 1991 [8] United Kingdom	RCT 14 hospitals To compare minimal surgery (underrunning the vessel or ulcer excision and adjuvant ranitidine) with conventional ulcer surgery (vagotomy and pyloroplasty or partial gastrectomy) for the treatment of bleeding peptic ulcer in patients. 18–60 years, need for ≥8 units of blood or colloid or two rebleeding in hospital. 61–90 years, need for ≥4 units of blood or colloid or one rebleeding in hospital	n=137 111 were randomised, 13 underwent an alternative surgical option for anatomical reasons, 5 cases of protocol violation =129 patients	n=62 Conservative surgery 30 days after operation	n=67 Conventional surgery 30 days after operation	Complications similar except recurrent bleeding. 7 patients after conservative surgery (6 had a fatal rebleeding), 4 after conventional. No difference in overall mortality	Low After interim analysis the study was stopped because of the high rates of fatal bleeding after conservative surgery

C = Control; GR = Gastric resection; I = Intervention; O+V = Oversewing plus vagotomy; RCT = Randomised controlled trial

Table 3.3.2b *Question 2: Is there evidence for differences in the effects between different surgical methods for the treatment of bleeding ulcers?*

Observational studies

First author Year Reference Country	**Study design Setting**	**Population Number at baseline Male/female Age Drop out rate**	**Intervention (I) Follow-up time**	**Control (C) Follow-up time**	**Results**	**Study quality Comments**
Brehant et al 2008 [9] France	Prospective observational study Period: 1995–2006 Bleeding duodenal ulcer. For patients <60 years; 2 bleeding recurrences or >8 units of blood. For patients >60 years; first bleeding recurrence or >4 units of blood. Ulcer suture and underrunning bleeding GDA with (from 2002: most patients) or without (1995–2001: most patients) double ligation of GDA	n=22 Male/female:18/4 Mean age: 63±18 (18–88) years No drop outs	Conservative surgery, in hospital		*Recurrent bleeding* 2 patients (1995–2001) none later period *Mortality* 5 patients *Morbidity* 6 patients Standard use of vagotomy-antrectomy questioned	Low Surgical conservative treatment with continuous PPI is effective with a low rate of recurrent bleeding standard use of vagotomy-antrectomy is questionable
Kubba et al 1996 [11] United Kingdom	Retrospective observational study Period: 1990–1995	67/492 patients (13.6%) with significant peptic ulcer bleeding had emergency surgery, 9 endoscopy impossible due to continuous bleeding, 5 uncontrolled continuous bleeding, 53 recurrent bleeding. Male/female: 29/38 *Mean age* Conservative group: 70 (41–86) years Aggressive group: 68 (41–88) years	Conservative surgery underrunning or excision of ulcer n=31 30 days	Aggressive surgery n=36 24 had underrunning with vagotomy and pyloroplasty, 3 had excision and vagotomy and pyloroplasty, 9 had partial gastrectomy/ antrectomy	*Recurrent bleeding* I: 23% C: 2.7% *Mortality* I: 23% C: 14%	Low Effective emergency surgery must be tailored to the individual patient but the findings suggest that a conservative surgical operation is a less effective option than a more radical approach

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Table 3.3.2b *continued*

Observational studies						
First author Year Reference Country	**Study design Setting**	**Population No at baseline Male/female Age Drop out rate**	**Intervention (I) Follow-up time**	**Control (C) Follow-up time**	**Results**	**Study quality Comments**
Kuttila et al 1991 [12] Finland	Retrospective observational study Period: 1973–1985	n=145 Male/female: 120/25 Mean age: 59 (23–87) years Preoperative endoscopy performed in 99 patients	GU-bleeding was mainly treated by partial gastrectomy. DU-bleeding was treated by partial gastrectomy with or without vagotomy in 42 patients	27 patients with DU were treated by transfixation, truncal vagotomy and pyloroplasty	*Recurrent bleeding* 5% of GU 7% in DU operated with truncal vagotomy 0% in DU with partial gastrectomy *Mortality* Overall 12%, for those with recurrent bleeding 44% Partial gastrectomy: GU 2% DU 12% Vagotomy + pyloroplasty: DU 22%	Low Recurrent bleeding was the most important cause of mortality, partial gastrectomy in bleeding gastric as well as duodenal ulcer may be preferable
Rogers et al 1988 [13] United Kingdom	Retrospective observational study Period: 1977–1985 Comparing partial gastrectomy, undersewing of the ulcer plus VD, undersewing alone	n=61 19 partial gastrectomy 22 undersewing of the ulcer plus VD 20 undersewing alone	Partial gastrectomy, undersewing of the ulcer plus VD, undersewing alone Mean follow-up: 37 months		*Mortality in hospital* Partial gastrectomy: 26% Undersewing of the ulcer plus VD: 45% Undersewing alone: 10%	Low Undersewing alone is effective
de la Fuente et al 2006 [10] USA	Retrospective observational study Period: 1991–2001 To determine postoperative outcomes and risk factors for morbidity and mortality in patients requiring surgery	n=907 VD: n=518 VR: n=389	VD 30 days	VR 30 days	*Recurrent bleeding* VD: 11.00% VR: 11.83% *Mortality* VD: 17.95% VR: 17.22% *Morbidity* VD: 52.51% VR: 50.39%	Low No difference in 30-day mortality, morbidity or recurrent bleeding rates

C = Control; DU = Duodenal ulcer; GDA = Gastroduodenal artery; GU = Gastric ulcer;
I = Intervention; PPI = Proton pump inhibitor; VD = Vagotomy and drainage;
VR = Vagotomy and resection

Table 3.3.3 *Question 3: Is there evidence for that endovascular treatment is an effective method for the treatment of bleeding ulcers?*

Observational studies

First author Year Reference Country	**Study design Setting**	**Population Number at baseline Male/female Age Drop out rate**	**Intervention (I) Follow-up time**	**Control (C) Follow-up time**	**Results**	**Study quality Comments**
Loffroy et al 2009 [17] France	Retrospective observational study Period: 1999–2008 Evaluate arterial embolisation for the treatment of severe, refractory, acute hemorrhage from gastroduodenal ulcers after failed endoscopic treatment, and identify factors associated with embolisation outcomes and with recurrent bleeding within 30 days	n=60 63 procedures Male/female: 41/19 Mean age: 69.4 (29–95) years	Embolotherapy 30 days		Procedural success: 95% Primary clinical success: 71.9% Secondary clinical success: 77.2% 16 patients needed further treatment, 8 endoscopic treatment, 3 repeated embolisation and 5 surgery 28.1% mortality within 30 days	Low Two factors independent predictors of embolisation failure, coagulation disorders and use of coils as the only embolic agent The patient material is partly published by Loffroy 2008 [16]
van Vugt et al 2009 [18] The Netherlands	Retrospective observational study Period: 2004–2007 Embolisation after failure of endoscopic treatment, as an alternative treatment for surgery Primary endpoint: Primary technical and clinical success Secondary endpoint: 30-day mortality	n=16 Male/female: 11/5 Mean age: 71 (42–89) years High-risk patients in case of surgery	Embolisation of branches of the gastroduodenal or superior mesenteric artery		Successful embolisation in 13 patients (81%), 3 had recurrent bleeding, 1 was re-embolised and 2 went to surgery 6 patients died	Low Embolisation was a successful minimal invasive alternative for surgical intervention in high-risk patients after failure of endoscopic treatment
Larssen et al 2008 [14] Norway	Retrospective observational study bleeding DU Period: 2000–2005	n=278 Male/female: 152/126 Mean age: 73 (29–98) years	TAE was attempted in 36 patients, 9 after unsuccessful endoscopic treatment, 27 after recurrent bleeding 30 days		Technical success: 92% Clinical success: 72% Mortality: 19%	Low TAE appears to be a treatment alternative to surgery

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Table 3.3.3 *continued*

Observational studies						
First author Year Reference Country	**Study design Setting**	**Population No at baseline Male/female Age Drop out rate**	**Intervention (I) Follow-up time**	**Control (C) Follow-up time**	**Results**	**Study quality Comments**
Loffroy et al 2008 [16] France	Retrospective observational study Period: 1999–2006 In haemodynamically unstable patients after failed endoscopic treatment	n=35 Male/female: 24/11 Mean age: 71 (29–95) years	Arterial embolisation Mean follow-up 27 months		33 patients could be treated, 2 patients had surgery, 6 patients required further treatment within the first 72 hours for recurrent bleeding (2 patients had endoscopic treatment, 3 patients underwent surgery, 1 underwent embolisation) 21.2% died within 1 month after the procedure not because of recurrent bleeding or ischemic complications	Low Selective angiographic embolisation is safe and effective
Langner et al 2008 [19] Germany	Retrospective observational study Period: 2001–2006 Failed endoscopic treatment. Depending on the patients, surgical risk factors, surgical or endovascular intervention was performed	n=23 18 had DU Male/female: 15/8 Mean age: 69 (43–93) years	Endovascular intervention with embolisation 8 patients had DU	Duodenotomy with purse-string ligature at the bottom of the ulcer and ligation of the gastroduodenal, the superior pancreaticoduodenal and the right gastroepiploic arteries 10 patients had DU	*Recurrent bleeding* Surgical group: 2 patients (1 treated by endoscopy 1 arterial embolisation successfully) Intervention group: 3 patients (2 emergency surgery, 1 endoscopy) *Mortality* Surgical group: 2 patients (17%) Intervention group: 3 patients (27%)	Low

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Table 3.3.3 *continued*

Observational studies

First author Year Reference Country	Study design Setting	Population No at baseline Male/female Age Drop out rate	Intervention (I) Follow-up time	Control (C) Follow-up time	Results	Study quality Comments
Ripoll et al 2004 [20] Spain	Retrospective observational study Period: 1986–2001 To compare the outcomes of embolotherapy and surgery as salvage therapy after therapeutic endoscopy failure in the treatment of upper gastrointestinal peptic ulcer bleeding	*Embolotherapy* n=31 Male/female: 19/12 Mean age: 75.2±10.9 years *Surgery* n=39 Male/female: 28/11 Mean age: 63.3±14.5 years	Embolotherapy Follow-up in hospital	Surgery Truncal vagotomy with pyloroplasty and oversewing or truncal vagotomy with distal gastrectomy	2 patients could not be selectively catheterised. No differences between groups in mean transfusion requirements, recurrent bleeding (29% vs 23.1%), mean days of hospitalisation or mortality (25.8% vs 20.5%). 5 patients in embolotherapy (recurrent bleeding) and 12 patients in surgery group needed surgery (recurrent bleeding and complications)	Low No difference between groups although more advanced age and greater prevalence of heart disease in the embolotherapy group
Ljungdahl et al 2002 [15] Sweden	Retrospective observational study Period: 1998–2001 To present experience of selective embolisation and assess its therapeutic usefulness. Success rate of haemostasis and overall outcome	n=18 Male/female: 7/11 13 patients had endoscopic failure to stop bleeding or recurrent bleeding after initial arrest (mean age 79, 68–94 years) 5 patients had recurrent bleeding after an emergency operation for bleeding ulcer (mean age 78, 53–86 years)	Embolisation was as superselective as possible		Permanent haemostasis was achieved in all but 1 patient, 2 patients needed a second embolisation because of recurrent bleeding, 1 patient had the bleeding controlled at an emergency operation, but died of respiratory complications. No serious complications of embolisation	Low Angiographic embolisation may be an effective way to stop massive bleeding from gastroduodenal ulcers. Emergency operations in poor surgical candidates can therefore be avoided

C = Control; DU = Duodenal ulcer; I = Intervention;
TAE = Transcatheter arterial embolisation

Table 3.4.1 *Question 1: How should recurrent bleeding be prevented following care of bleeding ulcers (including H. pylori eradication) when periodic or continuous analgesic treatment with NSAID is warranted?*

Randomised controlled trials

First author **Year** **Reference** **Country**	**Study design** **Setting**	**Population** **Number at baseline** **Male/female** **Age** **Drop out rate**	**Intervention (I)** **Follow-up time**	**Control (C)** **Follow-up time**	**Results**	**Study quality** **Comments**
Chan et al 2007 [11] China	RCT Single centre 2002–2004 Endpoint recurrent bleeding ulcer according to endoscopy upon clinical/laboratory signs of bleeding	Consecutive patients with bleeding ulcer while receiving non-selective NSAID for arthritis. *H. pylori* was eradicated. Only healed ulcer included n=273 I: n=137 C: n=136 *Male/female* I: 65/72 C: 67/69 *Mean age* I: 70±12 years C: 72±11 years *Drop out rate* I: 8 C: 10	Celecoxib 200 mg x 2 + esomeprazole 20 mg 12 months	Celecoxib 200 mg x 2 + placebo 12 months	*Endoscopically verified recurrent bleeding* I: 0 (0%) (95% CI 0–0) C: 12 (8.9%) (95% CI 4.1–13.7) Difference 8.9% p = 0.0004 Difference also significant when patients taking ASA were excluded. 10 of 12 recurrent ulcers at same location as previously	High Partly financed with consulting and lecture fees to author from industry
Lai et al 2005 [9] China	RCT Single centre Endpoint recurrence of ulcer complications	376 patients with PUB taking NSAID screened 134 excluded 242 randomised I: n=120 C: n=122 *H. pylori* eradicated if present *Male/female* I: 47/73 C: 55/67 *Mean age* I: 56.3 years C: 57.9 years 38 (15.7%) dropped out	Celecoxib 200 mg x 2 daily 24 weeks	Naproxen 750 mg daily and lansoprazole 30 mg daily 24 weeks	*Recurrence of ulcer complications* I: 4 (3.7%) (95% CI 0.0–7.3) C: 7 (6.3%) (95% CI 1.6–11.1) Difference –2.6% (95% CI –9.1 to 3.7)	High

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Table 3.4.1 *continued*

Randomised controlled trials						
First author Year Reference Country	**Study design Setting**	**Population No at baseline Male/female Age Drop out rate**	**Intervention (I) Follow-up time**	**Control (C) Follow-up time**	**Results**	**Study quality Comments**
Chan et al 2002 [8] China	RCT Single centre 2000–2001 Endpoint recurrent ulcer bleeding according to endoscopy on clinical/ laboratory signs of bleeding	Consecutive patients with RA, osteoarthritis or other forms of arthritis presenting with ulcer bleeding. Inclusion criteria documented ulcer healing and negative *H. pylori* status (eradicated or not) n=287 I: n=144 C: n=143 *Male/female* I: 61/83 C: 65/78 *Mean age* I: 66.5±14.2 years C: 68.8±13.2 years *Drop out rate* I: 2 C: 1	Celecoxib 200 mg x 2 + placebo 6 months post healing of ulcer	Diclofenac 75 mg + omeprazol 20 mg 6 months post healing of ulcer	*Endoscopically verified recurrent bleeding* I: 7 (4.9%) (95% CI 3.1–6.7) C: 9 (6.4%) (95% CI 4.3–8.4) Difference –1.5% (95% CI –6.8 to 3.8)	High Partly financed with consulting fee to author from industry
Chan et al 2001 [10] China	RCT Single centre PUB endoscopically verified <24 hours and NSAID intake <7 days	n=100 90 with healed PUB 4 failed to fulfil enrolment criteria and 6 patients dropped out after randomisation I: n=45 C: n=45 *Male/female (%)* I: 38/62 C: 33/67 *Median age* I: 75 (43–92) years C: 74 (42–89) years *H. pylori* negative	Naproxen 500–1 000 mg/day + misoprostol (200 µg twice daily) 24 weeks	Nabumetone (1 000–1 500 mg/ day) and placebo misoprostol 24 weeks	*Recurrent bleeding* I: 10 (22.2%) (95% CI 11.2–37.1) C: 3 (6.7%) (95% CI 1.4–18.3) RR 3.33 (95% CI 0.98–11.32, p=0.069)	Moderate

ASA = Acetylsalicylic acid; C = Control; CI = Confidence interval; I = Intervention; PUB = Peptic ulcer bleeding; RA = Rheumatoid arthritis; RCT = Randomised controlled trial; RR = Relative risk; NSAID = Non-steroidal anti-inflammatory drugs

Table 3.4.2 *Question 2: How should recurrent bleeding be prevented following care of bleeding ulcers (including H. pylori eradication) when periodic or continuous treatment with low-dose ASA is warranted?*

Randomised controlled trials

First author **Year** **Reference** **Country**	**Study design** **Setting**	**Population** **Number at baseline** **Male/female** **Age** **Drop out rate**	**Intervention (I)** **Follow-up time**	**Control (C)** **Follow-up time**	**Results**	**Study quality** **Comments**
Lai et al 2006 [12] China	RCT 2 centres 2002–2005 Endpoint recurrent ulcer bleeding according to endoscopy on clinical/laboratory signs of bleeding	Consecutive patients with bleeding ulcer while receiving low-dose ASA. Eradication treatment to *H. pylori* infected patients. Only healed ulcers included n=170 I: n=86 C: n=84 *Male/female* I: 51/35 C: 51/33 *Mean age* I: 75.5±7.8 years C: 75.8±7.8 years *Drop out rate* I: 3 C: 2	ASA 100 mg/day + esomeprazole 20 mg/day 52 weeks	Clopidogrel 75 mg/day + placebo 52 weeks	*Endoscopically verified recurrent bleeding* I: 0 (0%) C: 9 (13.6%) Difference 13.6 (95% CI 6.3–20.9) 8 of 9 ulcers occurred in the same site as previously	High However, the study was stopped due to significant difference when 170 of 250 planned patients had been randomised Esomeprazole provided by industry

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Table 3.4.2 *continued*

Randomised controlled trials						
First author Year Reference Country	**Study design Setting**	**Population Number at baseline Male/female Age Drop out rate**	**Intervention (I) Follow-up time**	**Control (C) Follow-up time**	**Results**	**Study quality Comments**
Chan et al 2005 [13] China	RCT Single centre Hospital	320 patients randomised males and females. 12 died I: n=161 C: n=159 *Male/female* I: 108/53 C: 103/56 *Mean age* I: 72.1±10.2 years C: 72.9±9.5 years *H. pylori* negative No drop outs	Clopidogrel 75 mg daily + placebo twice daily 12 months	ASA 80 mg daily + esomeprazole 20 mg x 2 12 months	*Endoscopically verified recurrent bleeding* I: 13 (8.6%) (95% CI 4.1–13.1) C: 1 (0.7%) (95% CI 0–2.0) Difference 7.9% (95% CI 3.4–12.4, p=0.001) No difference for lower GI bleeding	High Partly financed with consulting fees to authors from industry
Lai et al 2002 [14] China	RCT Single centre 1999–2001 Endpoint recurrent ulcer complication (all bleeding) according to endoscopy on clinical/laboratory signs of bleeding or obstruction (none)	Consecutive patients with bleeding or obstructing ulcer while receiving low dose ASA (min 1 month) and in need of ASA. *H. pylori* eradication. Only healed ulcer included. n=123 I: n=62 C: n=61 *Male/female* I: 46/16 C: 42/19 *Mean age* 71.5±8.0 years 69.1±7.6 years *Drop out rate* I: 4 C: 6	ASA 100 mg/day + lansoprazole 30 mg/day 12 months	ASA 100 mg/day + placebo 12 months	*Endoscopically verified recurrent bleeding* I: 1 (1.6%) (95% CI 0–9%) C: 9 (14.8%) (95% CI 7–26%) Difference 13.2 (95% CI 3.4–24.2)	High However, the study was stopped due to significant difference when 123 of 180 planned patients had been randomised

ASA = Acetylsalicylic acid; C = Control; CI = Confidence interval; GI = Gastrointestinal;
I = Intervention; RCT = Randomised controlled trial

Table 3.5.1a *Question 2: Is there evidence that proton pump inhibitors, histamine-2 receptor antagonists, or misoprostol can reduce the risk for bleeding ulcers in people with elevated risk?*

Randomised controlled trials

First author Year Reference Country	Study design Setting	Population Number at baseline Male/female Age Drop out rate	Intervention (I) Follow-up time	Control (C) Follow-up time	Results	Study quality Comments
Silverstein et al 1995 [26] USA	RCT, double-blind Evaluation of the efficacy of misoprostol prophylaxis against NSAID-induced ulcer complications Outcome: Serious ulcer complications (perforated ulcer, gastric outlet obstruction, bleeding from ulcer or erosion, active or recent visualised bleeding, melena)	Patients, at least 52 years old, with RA, expected to be taking 1 of 10 specified NSAIDs at predefined miminum doses n=8 843 I: n=4 404 C: n=4 439 Male/female: 29%/71% Mean age: 68 years *Premature withdrawals* I: 42% C: 36%	I: Misoprostol 200 µg four times daily 28% tolerated only 50% of the assigned dose 6 months	C: Placebo four times daily 16% tolerated only 50% of the assigned dose 6 months	*Serious ulcer complications* 40% risk reduction OR 0.6 (95% CI 0.36–0.98) (p=0.049), representing a risk difference of 0.38% (reduced from 0.95%–0.57%) *Ulcer bleedings with proved ulcer or erosion* OR 0.66 (95% CI 0.34–1.26), ns. The study was not powered to detect a difference in this endpoint	Moderate The effect of using lower doses of misoprostol on ulcer complications is unknown and may be associated with a significant clinical trade-off

C = Control; CI = Confidence interval; I = Intervention; NSAID = Non-steroidal anti-inflammatory drug; OR = Odds ratio; RA = Rheumatoid arthritis; RCT = Randomised controlled trial

Table 3.5.1b *Question 2: Is there evidence that proton pump inhibitors, histamine 2 receptor antagonists, or misoprostol can reduce the risk for bleeding ulcers in people with elevated risk?*

Observational studies

First author Year Reference Country	**Study design Setting**	**Population Number at baseline Male/female Age Drop out rate**	**Intervention (I)/ Cases Follow-up time**	**Controls (C) Follow-up time**	**Results**	**Study quality Comments**
Lanas et al 2007 [27] Spain	Case-control study Prospective case ascertainment and retrospective data collection Period: 2001–2004 The study is presented in Lanas 2006 [28]	*Cases* n=2 777 Male/female: 2 010/767 Patients hospitalised because of GI bleeding confirmed by an endoscopic diagnosis of a peptic ulcer lesion as the cause of bleeding. Peptic ulcer lesions included either gastroduodenal peptic ulcers or acute mucosal lesions *Controls* n=5 532 Male/female: 2 897/2 635 Matched by age, hospital, and month of admission Mean age: 61 years *H.pylori* status not mandatory, but performed in 81% of cases and 42% of controls	*Use of* NSAID: 23.7% ASA: 26.9% Clopidogrel/ Ticlopidine: 3.9% Dicumarinics: 6.4% *Use of* PPI: 8.6% H_2RA: 4.5% Nitrates: 3.7%	*Use of* NSAID: 9.2% ASA: 9.5% Clopidogrel/ Ticlopidine: 1.5% Dicumarinics: 3.7% *Use of* PPI: 13.2% H_2RA: 3.5% Nitrates: 3.1%	*Risk of UGIB* NSAID or ASA (all doses): RR 5.6 (95% CI 5.0–6.3) In users of NSAIDs or ASA PPI: RR 0.18 (95% CI 0.14–0.24) H_2RA: RR 0.39 (95% CI 0.26–0.57) Nitrates: RR 0.51 (95% CI 0.35–0.74) In users of clopidogrel/ ticlopidine PPI: RR 0.19 (95% CI 0.07–0.49) H_2RA: RR 0.83 (95% CI 0.20–3.51), ns Nitrates: RR 0.88 (95% CI 0.34–2.28), ns In users of dicumarinics PPI: RR 0.67 (95% CI 0.37–1.21) H_2RA: RR 0.88 (95% CI 0.32–2.45) Nitrates: RR 0.67 (95% CI 0.33–1.34) Results adjusted for confounders	Moderate

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Table 3.5.1b continued

Observational studies						
First author Year Reference Country	**Study design Setting**	**Population Number at baseline Male/female Age Drop out rate**	**Intervention (I) / Cases Follow-up time**	**Control (C) Follow-up time**	**Results**	**Study quality Comments**
Ng et al 2008 [29] China	Retrospective cohort study All hospitalised patients with acute coronary syndrome that received aspirin, clopidogrel, and enoxaparin simultaneously Period: 2002–2006	n=697 I: n=336 C: n=290 Patients were identified if there was a prescription of the triple therapy at hospital admission. Patients with thrombolytics or glycoprotein IIb/IIIa receptor antagonists were excluded. Excluded: 31 patients + 40 for the evaluation of the effect of PPIs There were no guidelines for primary prevention of peptic ulcer disease Male/female: 241/425	Use of PPI	No use of PPI	*GI bleeding during triple therapy or within 7 days of stopping enoxaparin* Incidence 2.7% PPI: OR 0.077 (95% CI 0.015–0.26), adjusted for predictive factors *Significant risk factors* Previous peptic ulcer disease: OR 5.1 Cardiogenic shock: OR 21.4 Lack of coprescription with PPIs: OR 14.8	Moderate
Ibanez et al 2006 [30] Spain, Italy	Case-control study Multicentre 4 309 cases of UGIB (from a duodenal or gastric ulcer, acute lesions of the gastric mucosa, erosive duodenitis, or mixed lesions) were identified, 2 813 were included Overall incidence 401.4 per million per year Period: September 1998 to 2001	*Cases* n=2 813 Patients admitted with a primary diagnosis of acute UGIB *Controls* n=7 192 Patients admitted with non-alcohol related trauma, elective surgery for non-painful disorders, or acute clinical conditions thought to be unrelated to the intake of the drugs of interest. Controls matched to cases by centre, date of admission, gender and age Follow-up of 10 734 897 person-years	*Use of* Antiplatelet drugs: 20.3% PPI: 4.8% H_2RA: 8.7% Antacids: 20.3% Misoprostol: 2.1%	*Use of* Antiplatelet drugs: 11.4% PPI : 6.1% H_2RA: 7.2% Antacids: 11.8% Misoprostol: 1.0%	*Risk of UGIB* Antiplatelet agents: OR 3.4 (95% CI 2.9–4.1) Antiplatelet and gastroprotective agent PPI: OR 1.0 (95% CI 0.5–2.0) H_2RA: OR 2.4 (95% CI 1.5–4.1) Antacids: OR 5.9 (95% CI 4.1–8.5) Misoprostol: OR 4.1 (95% CI 1.4–12.4)	Moderate

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Table 3.5.1b *continued*

Observational studies						
First author Year Reference Country	**Study design Setting**	**Population Number at baseline Male/female Age Drop out rate**	**Intervention (I) / Cases Follow-up time**	**Control (C) Follow-up time**	**Results**	**Study quality Comments**
Serrano et al 2002 [31] Spain	Prospective cohort study (nested case-control) Consecutive patients discharged from cardiology clinic with low-dose ASA. Data collected by structured telephone interview Period: Nov 1992 to June 1996 Planned follow-up 5 years following discharge	<u>*Cases*</u> n=1 224 Patients diagnosed with cardiovascular disease and discharged on low-dose ASA (75–325 mg/day), 903 analysed HP status determined in 341 patients, positive in 70% Male/female: 74%/26% Mean age: 65 years Mean time follow-up: 45±22 months	NSAIDs 2.1%/ Acid-suppressing drugs 22% Nitrates 55% – oral 26% – transdermal 29% 85% of transdermal nitrates used 10 mg/day Most common doses of oral nitrates were 40 and 60 mg/day	No use of acid-suppressing drugs or nitrates	<u>*UGIB (melena and/or haematemesis) requiring hospital admission*</u> 41 (4.5%), incidence 1.2 per 100 patient-years <u>*Multivariate relative risk of UGIB*</u> History of peptic ulcer or UGIB: RR 3.1 (95% CI 1.5–6.5) ASA dose (per 100 mg/day): RR 1.8 (95% CI 1.5–2.9) Antisecretory therapy: RR 0.22 (95% CI 0.07–0.75) Nitrates: RR 0.73 (95% CI 0.55–0.96)	Moderate

ASA = Acetylsalicylic acid; C = Control; CI = Confidence GI = Gastrointestinal; H_2RA = Histamine-2 receptor antagonist; I = Intervention; NSAID = Non-steroidal anti-inflammatory drugs; OR = Odds ratio; PPI = Proton pump inhibitor; RR = Relative risk; tNSAID = Traditional NSAID; UGIB = Upper gastrointestinal bleeding

Table 3.5.2a *Question 3: Is there evidence that coxibs carry less risk for bleeding ulcers than traditional NSAIDs in people with elevated risk?*

Meta-analyses and systematic reviews

First author Year Reference Country	Overall aim Purpose (incl study population and setting)	Number and type of studies	Outcome domains	Results	Study quality Comments
Chen et al 2008 [33] United Kingdom	1. Systematic review of clinical effec-tive-ness and cost-effectiveness of COX-2 and selective NSAIDs, including etodolac, meloxicam, celecoxib, rofecoxib, etori-coxib, valdecoxib, and lumiracoxib, for osteoarthritis and RA 2. Cost-effectiveness of COX-2 and selec-tive NSAIDs from NHS perspective 3. Potential impact of concomitant gastroprotective agents, with either COX-2 selective NSAIDs, or other non-selective NSAIDs, on the incid-ence of symptomatic GI ulcers and complications such as bleeding, per-foration, or gastric outlet obstruction 4. Impact of low-dose ASA (≤325 mg/day) used in conjunction with COX-2 selec-tive NSAIDs on the incidence of CV adverse events and symptomatic UGI ulcers and their complications	RCT: Published and unpublished reports, not separated according to prophylaxis or preven-tion or recurrent bleeding Search in databases up to Oct/Nov 2003. Invited pharmaceutical company submissions to NICE (2000 and 2004) *Number of RCTs included in meta-analyses* Celecoxib: 8 Etoricoxib: 2 Valdecoxib: 5 Lumiracoxib: 2 Etodolac: 6 Meloxicam: 6 Rofecoxib: 4	POBs	*RR for POBs, COX-2 to tNSAIDs* Celecoxib, all trials, all doses: RR 0.57 (95% CI 0.35–0.95) Etoricoxib, both trials, 90 and 120 mg/day: RR 0.46 (95% CI 0.07–3.10) Valdecoxib, all trials, all doses: RR 0.43 (95% CI 0.19–0.97)	High
Rostom et al 2007 [32] Canada	To systematically review the upper GI toxicity of COX-2s compared to that of nonselective NSAIDs and with placebo in chronic arthritis sufferers Assessment of safety by using the clinically important endpoint of ulcer complication POB	69 RCTs of COX-2s (celecoxib, rofecoxib, etoricoxib, valdecoxib, lumiracoxib, and meloxi-cam), including 4 unique studies obtained from the new drug submission docu-ments on the FDA website	Endoscopic ulcers, clinical gastrointest-inal events (PUBs and POBs)	*Assessment of safety by using the endpoint POB* 8 studies with a total 73 449 patients RR for COX-2s relative nonselective NSAIDs 0.39 (95% CI 0.31–0.50). Inclusion of the FDA 12-month CLASS study data did not essentially alter the result, RR 0.42 (95% CI 0.33–0.54) *Effects of co-administration of ASA and COX-2 on POBs* 4 trials allowed assessment of the pooled subgroup analysis of nearly 7 000 patients RR 0.89 (95% CI 0.52–1.53)	Moderate

ASA = Acetylsalicylic acid; CI = Confidence interval; COX-2 = Cyclooxygenase-2; CV = Cardiovascular; FDA = US Food and Drug Administration; GI = Gastrointestinal; NHS = National Health Service; NSAID = Non-steroidal anti-inflammatory drugs; POB = Perforation, obstruction or bleeding; PUB = Perforation, ulcer or bleeding; RA = Rheumatoid arthritis; RCT = Randomised controlled trial; RR = Relative risk; tNSAID = Traditional NSAID; UGI = Upper gastrointestinal

Table 3.5.2b *Question 3: Is there evidence that coxibs carry less risk for bleeding ulcers than traditional NSAIDs in people with elevated risk?*

Randomised controlled trials

First author **Year** **Reference** **Country**	**Study design** **Setting**	**Population** **Number at baseline** **Male/female** **Age** **Drop out rate**	**Intervention (I)** **Follow-up time**	**Control (C)** **Follow-up time**	**Results**	**Study quality** **Comments**
Laine et al 2007 [36] Multinational	Prespecified pooled analysis of three RCTs Primary endpoint: Thrombotic CV events during long-term treatment of patients with OA or RA Prespecified endpoints: Rates of clinical UGI events, complicated UGI events, and lower GI clinical events	Patients with OA or RA aged 50 years or older, and would need treatment with NSAID. n=39 984 screened I: n=17 412 C: n=17 289 Use of low-dose ASA (≤100 mg) and PPI: 39% (I and C) Low-dose ASA: 35% (I and C) *H. pylori* status: No data Male/female: 26%/74% Mean age: 63.2 years	I: Etoricoxib 60 and 90 mg daily Mean duration: 18.2 months *Complicated UGI events (per 100 patient-years)* All patients: 0.30 PPI: 0.20 Low-dose ASA: 0.57 PPI and low-dose ASA: 0.53	C: Diclofenac 150 mg daily Mean duration of exposure 17.7 months *Complicated UGI events (per 100 patient-years)* All patients: 0.32 PPI: 0.27 Low-dose ASA: 0.61 PPI and low-dose ASA: 0.88	*Complicated UGI events* All patients: HR 0.91 (95% CI 0.67–1.24) Use of PPI: HR 0.72 (95% CI 0.42–1.22) Use of low-dose ASA: HR 0.93 (95% CI 0.63–1.36) Use of PPI and low-dose ASA: HR 0.61 (95% CI 0.38–0.97)	High

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Table 3.5.2b *continued*

Randomised controlled trials						
First author Year Reference Country	**Study design Setting**	**Population Number at baseline Male/female Age Drop out rate**	**Intervention (I) Follow-up time**	**Control (C) Follow-up time**	**Results**	**Study quality Comments**
Silverstein et al 2000 [34] USA, Canada	RCT Primary endpoint: GI ulcer complications (POB) Secondary endpoint: UGI ulcer complications + symptomatic ulcers	Patients with OA or RA. Individuals with various contraindications for NSAIDs were excluded. Antiulcer drugs, antibiotics for treatment of *H. pylori*, antineoplastics, were prohibited. Low-dose aspirin use (≤325 mg/day): 21%/20% *H. pylori* positive: 39%/38% n=3 987+3 981 started treatment Male/female: 31%/69% Mean age: 61/60 years Withdrawals: celecoxib 31%, NSAIDs 35%	I: Celecoxib 400 mg twice daily Follow-up: 6 month in publication, but 52 weeks in FDA report	C: Ibuprofen 800 mg three times daily or diclofenac 75 mg twice daily	*POB at 6 months* All patients I: 0.76% C: 1.45% RR 0.53 (95% CI 0.26–1.11) No ASA use I: 0.44% C: 1.27% RR 0.35 (95% CI 0.14–0.98) Use of low-dose ASA I: About 2% C: About 2% At 52 weeks: No significant difference between celecoxib and pooled controls [35]	High Publication criticised for manipulation of data [3]. Designed as two separate studies. Study duration was 52 weeks [35]

ASA = Acetylsalicylic acid; C = Control; CI = Confidence interval; FDA = US Food and Drug Administration; GI = Gastrointestinal; HR = Hazard ratio; I = Intervention; NSAID = Non-steroidal anti-inflammatory drugs; OA = Osteoarthritis; POB = Perforation, obstruction or bleeding; PPI = Proton pump inhibitor; PUB = Perforation, ulcer or bleeding; RA = Rheumatoid arthritis; RCT = Randomised controlled trial; RR = Relative risk; UGI = Upper gastrointestinal

Table 3.5.2c *Question 3: Is there evidence that coxibs carry less risk for bleeding ulcers than traditional NSAIDs in people with elevated risk?*

Observational studies

First author **Year** **Reference** **Country**	**Study design** **Setting**	**Population** **Number at baseline** **Male/female** **Age** **Drop out rate**	**Intervention (I)/** **Cases** **Follow-up time**	**Control (C)** **Follow-up time**	**Results**	**Study quality** **Comments**
Garcia Rodriguez et al 2007 [14] United Kingdom	Nested case-control study Register for GPs, The Health Improvement Network Database in the UK Period: 2000–2005	*Cases* n=1 561 Age: 40–85 years Patients with upper gastrointestinal complications (UGIC) *Controls* n=10 000 A random selection matched by age, gender, and calender year Focused on the group with UGIC and prescription of NSAIDs (incl coxibs), but not ASA	Prescription of NSAID (incl coxibs), but not ASA Use of acid-suppressing drugs (PPI, H_2RA) or nitrates	No prescription of NSAID (incl coxibs), but not ASA No use of acid-suppressing drugs or nitrates	*UGIC* tNSAIDs: RR 3.5 (95% CI 2.9–4.2) Coxibs: RR 2.4 (95% CI 1.7–3.5) PPI: RR 1.2 (95% CI 1.0–1.4) H_2RA: RR 1.4 (95% CI 1.1–1.9) Use of coxibs and acid-suppressing drugs compared to tNSAID and acid-suppressing drugs RR 0.4 (95% CI 0.1–0.9) Results adjusted for various confounders	Moderate RR for PPI and H_2RA was duration-dependent

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Table 3.5.2c *continued*

Observational studies						
First author Year Reference Country	**Study design Setting**	**Population Number at baseline Male/female Age Drop out rate**	**Intervention (I)/ Cases Follow-up time**	**Control (C) Follow-up time**	**Results**	**Study quality Comments**
Lanas et al 2006 [28] Spain	Case-control study. See table 3.5.1b Lanas 2007 [27]		*Use of* Current tNSAID: 23.7% Current coxib: 1.2% Current ASA: 26.9%	*Use of* Current tNSAID: 9.2% Current coxib: 1.2% Current ASA: 9.5%	*Risk of UGIB* In users of tNSAIDs Current tNSAID: RR 5.3 (95% CI 4.5–6.2) tNSAID and low-dose ASA: RR 12.7 (95% CI 7.0–23.0) tNSAID and clopidogrel/ticlopidine: RR 15.2 (95% CI 4.1–56.5) In users of coxibs Current coxibs: RR 1.5 (95% CI 0.9–2.4) Celecoxib: RR 1.0 (95% CI 0.4–2.1) Coxibs and low-dose ASA: RR 14.5 (95% CI 3.3–63.9) *Other findings* Low-dose ASA and clopidogrel/ticlopidine: RR 16.4 (95% CI 5.4–49.7) Paracetamol: RR 0.9 (95% CI 0.7–1.1)	High
Battistella et al 2005 [38] Canada	Nested case-control Multiple linked health-care databases Outcome: UGIB	Patients 65 years and older with a period of uninterrupted warfarin use *Cases* Patients admitted to hospital with any diagnosis of UGIB between April 2000, and March 2001 *Controls* From the same cohort, 4 controls for each case (matched for age and gender) No information on HP status Male/female: 48%/52% Mean age: 78 years	Exposure to non-selective NSAIDs or COX-2 inhibitors (or ocular antibiotics)	No exposure	*Hospital admission for UGIB* tNSAID: OR 1.9 (95% CI 1.4–3.7) Celecoxib: OR 1.7 (95% CI 1.2–3.6) Ocular antibiotics: OR 0.9 (95% CI 0.7–1.3)	Moderate

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Table 3.5.2c *continued*

Observational studies

First author Year Reference Country	Study design Setting	Population Number at baseline Male/female Age Drop out rate	Intervention (I)/ Cases Follow-up time	Control (C) Follow-up time	Results	Study quality Comments
Nørgård et al 2004 [39] Denmark	Case-control study, population-based Period: 2000–2002 Outcome: Hospital admission for UGIB episode	*Cases* n=780 First incident cases of UGIB (specified ICD-10 diagnoses). Subjects aged 18–90 years. Four high risk groups: 1: Patients with a discharge history of non-bleeding ulcer before case status 2: Patients with a discharge history of oesophagitis, gastritis, duodenitis or Mallory-weiss lesions 3: Users of PPI or H_2RA within 2 years before case status 4: Mixed group of alcoholism, chronic liver diseases, oesophageal varices before case status Male/female: 57%/43% Mean age: 67 years *Controls* Randomly selected controls with the same four high risk profiles as above. n=2 906 Male/female: 53%/47% Mean age: 73 years	Prescriptions of celecoxib or tNSAIDs	No prescriptions	*Hospital admission for UGIB* 1. Celecoxib: OR 0.9 (95% CI 0.2–3.5) tNSAIDs: OR 3.6 (95% CI 1.8–7.3) 2. Celecoxib: OR 2.1 (95% CI 0.7–6.7) tNSAIDs: OR 4.7 (95% CI 2.6–8.6) 3. Celecoxib: OR 1.3 (95% CI 0.6–2.9) tNSAIDs: OR 3.1 (95% CI 2.2–4.4) 4. Celecoxib: No data tNSAIDs: OR 2.5 (95% CI 1.1–5.9)	Moderate

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Table 3.5.2c *continued*

Observational studies						
First author Year Reference Country	**Study design Setting**	**Population No at baseline Male/female Age Drop out rate**	**Intervention (I)/ Cases Follow-up time**	**Control (C) Follow-up time**	**Results**	**Study quality Comments**
Mamdani et al 2002 [37] Canada	Retrospective cohort study, population-based. 2000 to 2001 Outcome: Admission to hospital for UGIB	*Cases* n=364 686 Patients ≥66 years that got a prescription of any NSAID Female/Male: 70%/30% in celecoxib group 59%/41% in tNSAIDs 62%/38% in diclofenac and misoprostol group *Controls* n=100 000 Community controls. Not prescribed NSAIDs. Female/Male: 55%/45% No information on *H. pylori* status Mean age: 75–76 years	Prescriptions of 1. Celecoxib 2. tNSAIDs 3. Diclofenac and misoprostol	No prescription of NSAIDs	*Hospital admission for UGIB* 1. RR 1.0 (95% CI 0.7–1.6) 2. RR 4.0 (95% CI 2.3–6.9) 3. RR 3.0 (95% CI 1.7–5.5)	Moderate

ASA = Acetylsalicylic acid; C = Control; CI = Confidence interval; COX-2 = Cyclooxygenase-2; GP = General practitioner; H_2RA = Histamine-2 receptor antagonist; I = Intervention; NSAID = Non-steroidal anti-inflammatory drugs; OR = Odds ratio; PPI = Proton pump inhibitor; RA = Rheumatoid arthritis; RR = Relative risk; tNSAID = Traditional NSAID; UGIB = Upper gastrointestinal bleeding; UGIC = Upper gastrointestinal complications

Table 3.5.3a *Question 4: Is there evidence that nabumetone or meloxicam carry less risk for bleeding ulcers than traditional NSAIDs in people with elevated risk?*

Meta-analyses and systematic reviews

First author Year Reference Country	Overall aim Purpose (incl study population and setting)	Number and type of studies	Outcome domains	Results	Study quality Comments
Chen et al 2008 [33] United Kingdom	See table 3.5.2a 6 studies of meloxicam included data on POBs (but not as primary outcome)	Two studies with about 9 000 patients on meloxicam 7.5 mg, and 9 000 patients on active comparators Four studies with about 1 000 patients on meloxicam 7.5–22.5 mg, and about 600 patient on active comparator I: Meloxicam 7.5 or 15 mg, but in one study 7.5–22.5 mg daily C: NSAIDs (diclofenac 100–150 mg and piroxicam 20 mg)	Primary outcome: Treatment effects of meloxicam	*POBs* Meloxicam vs NSAIDs All patients: RR 0.56 (95% CI 0.27–1.15), ns	High POB not primary outcome

CI = Confidence interval; NSAID = Non-steroidal anti-inflammatory drugs;
POB = Perforation, obstruction or bleeding; RR = Relative risk

Table 3.5.4 *Question 6: Is there evidence that other drugs can reduce the risk for bleeding ulcers in people with elevated risk?*

Observational studies

First author **Year** **Reference** **Country**	**Study design** **Setting**	**Population** **Number at baseline** **Male/female** **Age** **Drop out rate**	**Intervention (I)** **Follow-up time**	**Control (C)** **Follow-up time**	**Results**	**Study quality** **Comments**
Garcia Rodriguez et al 2007 [14] United Kingdom	See table 3.5.2c				*Current use of nitrates* RR for NA-NSAID users: 0.7 (95% CI 0.4–1.2) RR for NA-NSAID non-users: 1.1 (95% CI 0.8–1.4)	Moderate
Serrano et al 2002 [31] Spain	See table 3.5.1b					Moderate

CI = Confidence interval; NA-NSAID = Non-aspirin non-steroidal anti-inflammatory drugs; NSAID = Non-steroidal anti-inflammatory drugs; RR = Relative risk

Table 5.1 *Economical aspects – empirical intervention studies.*

First author Year Reference Country	**Study design Setting**	**Population Number at baseline Male/female Age Drop out rate**	**Intervention (I) Follow-up time**	**Control (C) Follow-up time**	**Results**	**Study quality Comments**
Brullet et al 2004 [2] Spain	RCT University clinic	n=82 Male/female: 63/19 <u>Age</u> Male: 59.2 years Female: 60.3 years Drop out: no data	Outpatient group (n=40) Omeprazole 80 mg IV bolus + 8 mg/hour for minimum 6 hours before discharge. Omeprazole 20 mg every 12 hours orally for 4 weeks (DU) or 8 weeks (GU)	Inpatient group (n=42) Omeprazole 80 mg IV bolus + 8 mg/hour during 2 days. Omeprazole 20 mg every 12 hours orally for 4 weeks (DU) or 8 weeks (GU)	<u>*Mean costs of care*</u> US$970 vs US$1 595 (p<0.001) Recurrent bleeding 4.8% vs 5.0% ns	Low Limited to a hospital perspective
Lee et al 2003 [7] China	RCT (piggy back) University clinic	n=232 Male/female: No data Age: No data Drop outs: 5+3	Omeprazole 80 mg IV bolus + 8 mg/hour for 72 hours after endo- scopic treatment (n=115). Hospital length of stay	Placebo IV after endoscopic treatment (n=117) Hospital length of stay	<u>*Median direct costs*</u> HK$27 010 vs HK$28 780 (p=0.017)	Low Limited to a hospital perspective
Sitter et al 2003 [1] Germany	Cohort, random retrospective University clinics	n=319 Male/female: 220/99 Age: No data	Single polidocanol injection (n=154)	Repeated fibrin glue injection (n=165)	<u>*Costs*</u> €4 253 vs €5 271 Recurrent bleeding I: 39/154 vs C: 24/165 (p=0.02) ICER: €14 316 (the incre- mental cost of preventing one additional recurrent bleeding)	Low Limited to a hospital perspective

C = Control; DU = Duodenal ulcer, GU = Gastric ulcer, I = Intervention;
ICER = Incremental cost-effectiveness ratio; IV = Intravenously;
RCT = Randomised controlled trial

Table 5.2 *Economical aspects – model studies.*

First author Year Reference Country	**Study design Setting**	**Population Number at baseline Male/female Age Drop out rate**	**Intervention (I) Follow-up time**	**Control (C) Follow-up time**	**Results**	**Study quality Comments**
Leontiadis et al 2007 [3] United Kingdom	Model Decision analysis	*Model 1* Patients having had an acute UGI haemorrhage, but haemodynamically stable, waiting for endoscopy *Model 2* Patients using NSAID	*Model 1* Oral PPI before and after endoscopy until follow-up at 28 days. Estimated lifetime survival *Model 2* Omeprazole 20 mg orally once daily on an ongoing basis or *H. pylori* eradication or *H. pylori* eradication followed by omeprazole 20 mg orally once daily Lifetime	*Model 1* No treatment before or after endoscopy. Follow-up at 28 days. Estimated lifetime survival *Model 2* No treatment Lifetime	*Costs* Model 1: Oral PPI most effective. Cost per QALY £24 300 for 28 days and £140 for lifetime survival, compared with no treatment Model 2: *H. pylori* eradication followed by PPI most effective. Cost per QALY £13 900, compared with *H. pylori* eradication only	Moderate Limited to a health-care perspective. Some data is missing in model 2
Barkun et al 2010 [4] Sweden	Model Decision analysis	Patients with peptic ulcer bleeding	80 mg IV esomeprazole bolus over 30 minutes + 8 mg/hour for 71.5 hours. Oral esomeprazole 40 mg daily for 27 days 30 days	IV placebo for 72 hours. Oral esomeprazole 40 mg daily for 27 days 30 days	*Costs* Per patient: SEK67 862 vs SEK67 807 Per avoided recurrent bleeding: SEK938	Moderate Limited to a third-party payer

IV = Intravenously; NSAID = Non-Steroidal anti-inflammatory drugs;
PPI = Proton pump inhibitor; QALY = Quality-adjusted life year;
SEK = Swedish krona; UGI = Upper gastrointestinal