NSAIDS, ENDOSCOPES, AND THE ELDERLY:
CURRENT THOUGHTS ON BLEEDING PEPTIC ULCER

MEDICAL GRAND ROUNDS

UT SOUTHWESTERN MEDICAL SCHOOL

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EPIDEMIOLOGY OF PEPTIC ULCER TODAY

Although statistics dealing with peptic ulcer disease (PUD) are subject to many problems (1), it can be estimated that the annual incidence is about 2-3/1000, the 1-year prevalence about 17/1000, and the lifetime prevalence approximately 5-10% (1). As shown in Figures 1 and 2, overall hospitalization, operations, and deaths from PUD have declined (2,3). On the other hand, hospitalizations for bleeding remain relatively stable at about 30-40/100,000 (ie., about 90,000/year in the U.S.) (Figure 3) and operations for bleeding are unchanged (Figure 2) (2,3).

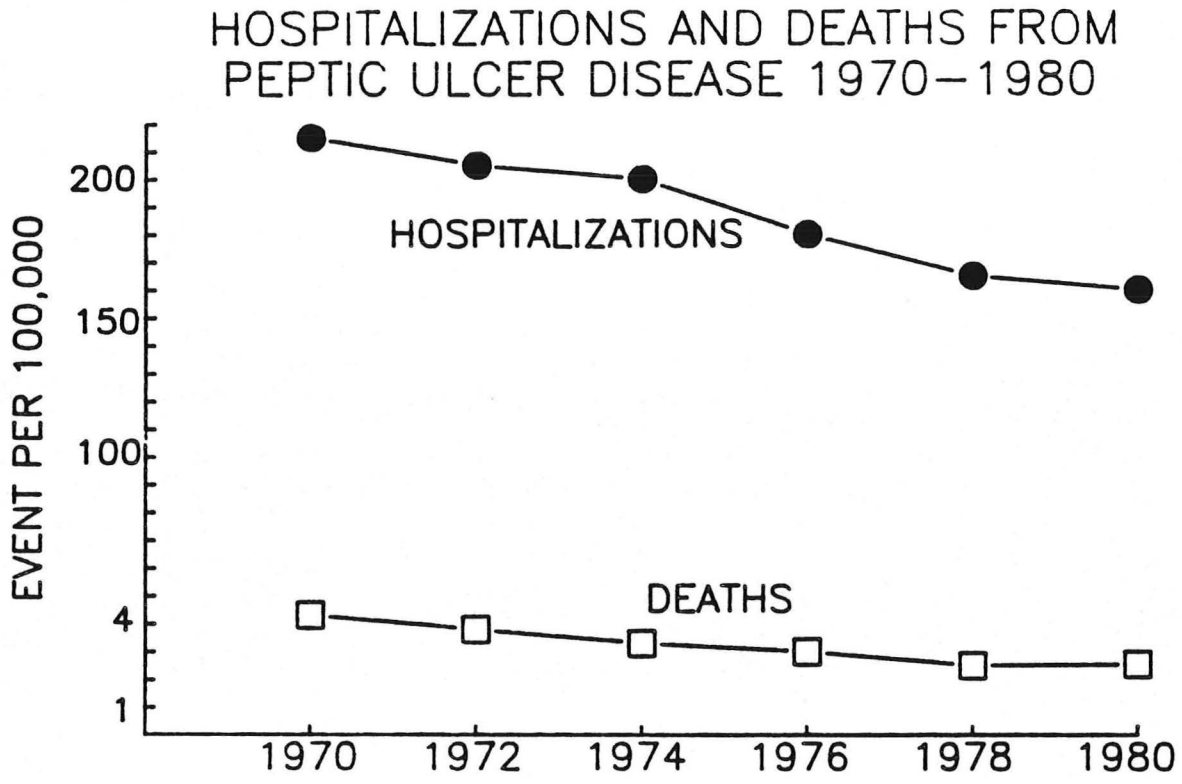

Figure 1. Hospitalization and death from peptic ulcer disease 1970-1980 (From reference 2).

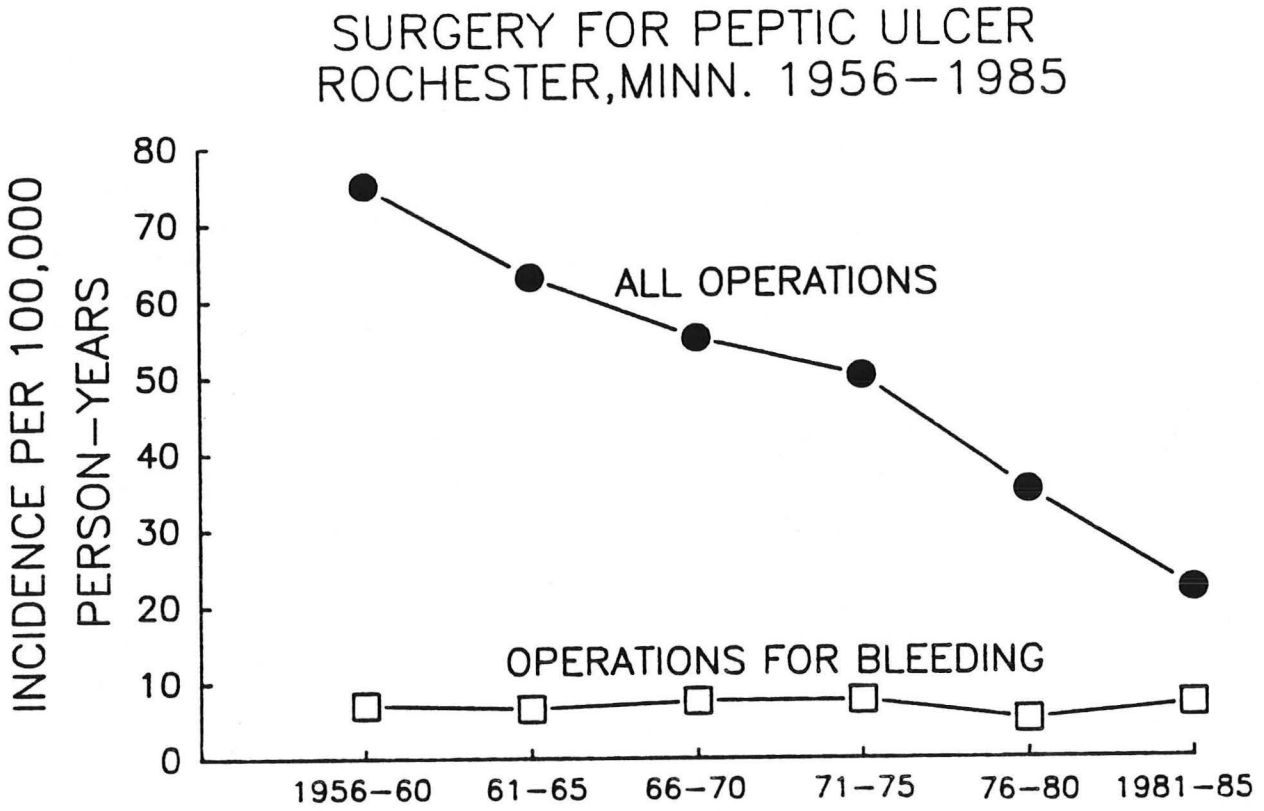

Figure 2. Surgery for peptic ulcer in Rochester, Minnesota from 1956-1985 (From reference 3).

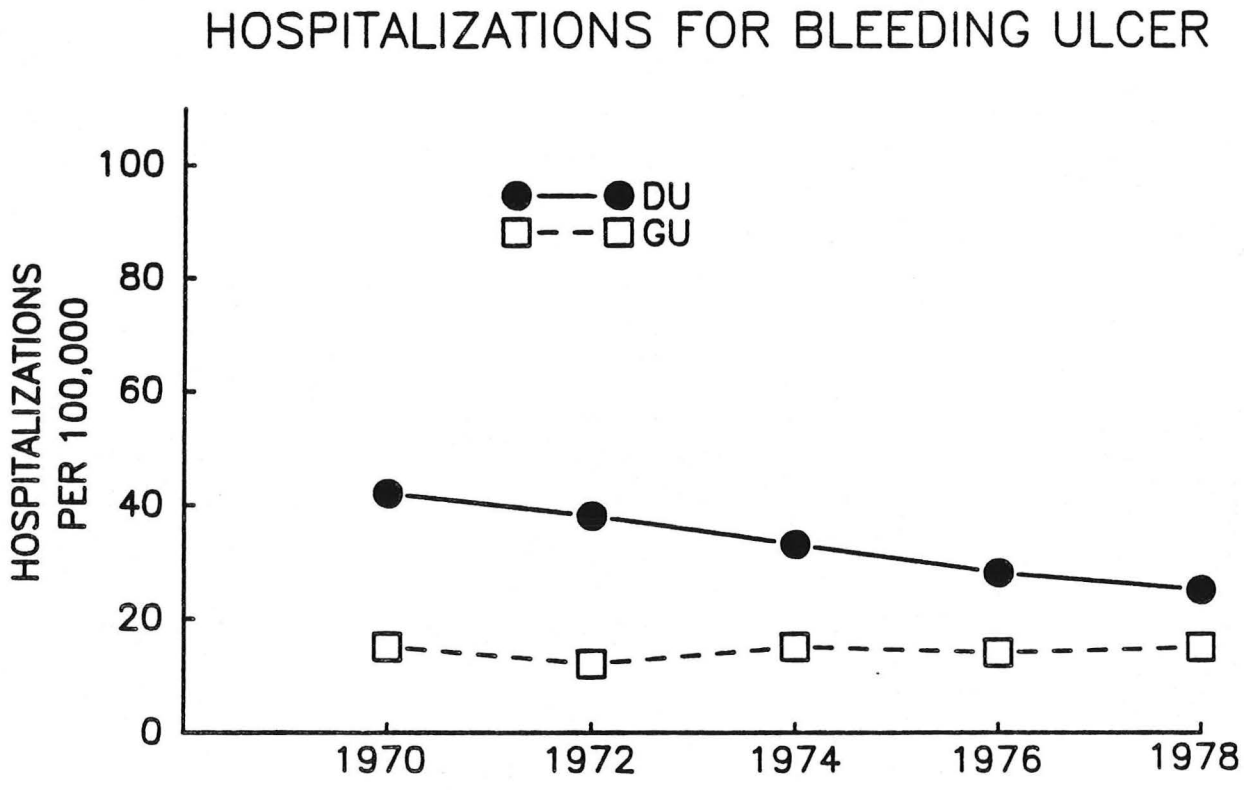

Figure 3. Hospitalization for bleeding gastric (GU) and duodenal ulcer (DU) from 1970 to 1978 (From reference 2).

Peptic ulcer continues to be a problem of the elderly. The incidence of PUD is directly proportional to advancing age (Figure 4) (4), about 70% of patients hospitalized for PUD complications are >60 years old (5-7), and mortality remains high in the elderly (Figure 5) (8-11). It has been reported that 80% of ulcer deaths occur in patients over 65 years old (11), the average mortality from complicated PUD in the elderly is about 30% (8), and the average age at death from PUD has increased to 65-70 years old (10). Mortality from gastric ulcer (GU) remains higher than that for duodenal ulcer (DU).

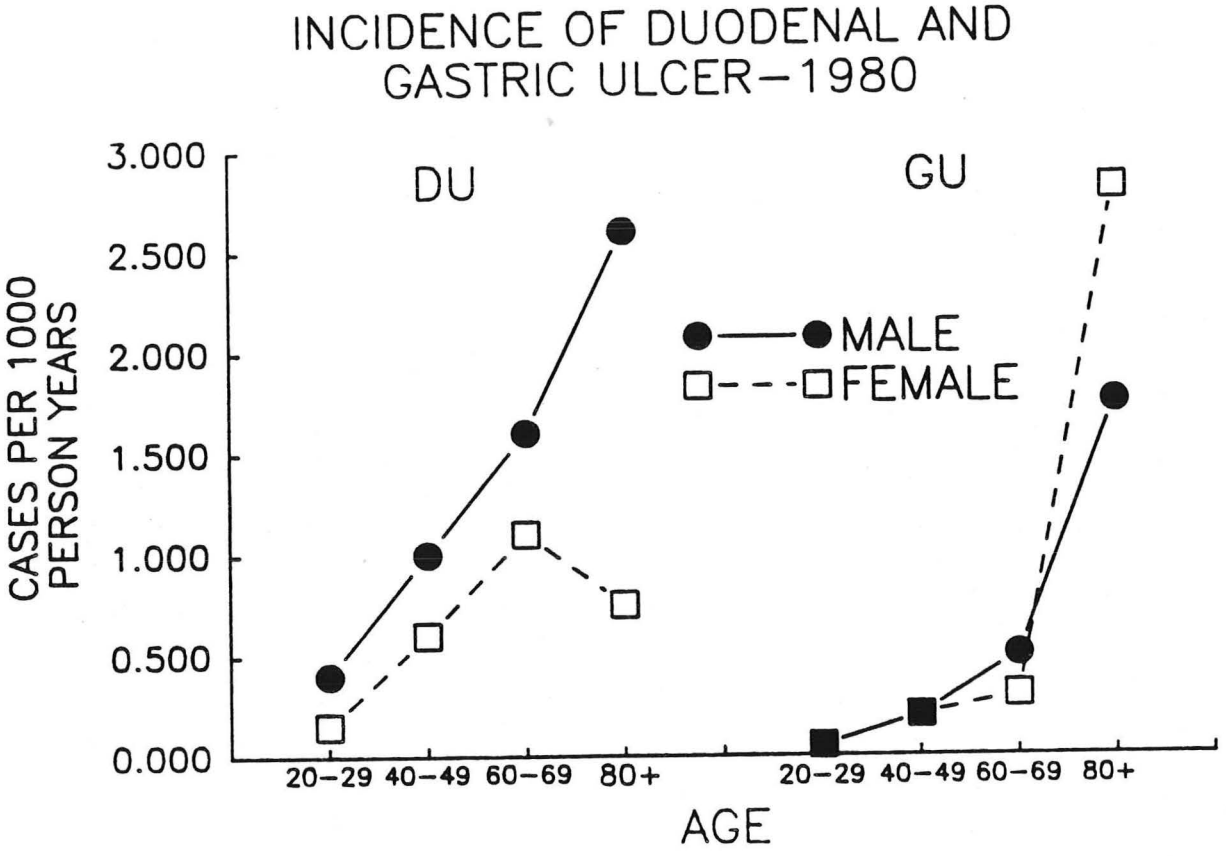

Figure 4. Incidence of duodenal and gastric ulcer by age in 1980 (From reference 4).

ROLE OF NSAIDs IN BLEEDING ULCER

Accompanying the phenomenon of the aging ulcer bleeder has been a steady increase in the use of NSAIDs in the elderly (12) (Figure 6). Although the point prevalence of GU in patients taking NSAIDs is about 10-15% (13,14), the relative risk of bleeding is only about two-fold (15-17). However, the number of prescriptions written for NSAIDS, especially to the elderly, make them an important factor in bleeding ulcer. For example, up to one-half of all NSAIDs are taken by individuals over 60, 15% of all individuals over 60 take NSAIDs, and NSAIDs account for 9% of prescription sales to patients over 65 years of age

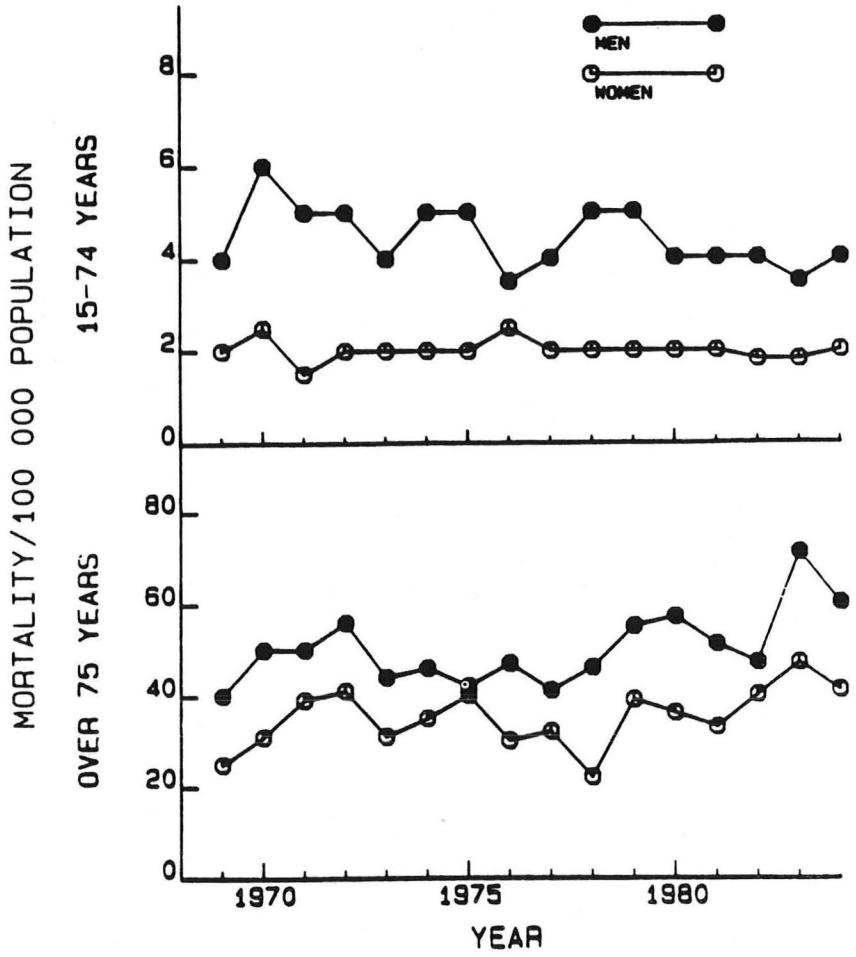

Figure 5. Annual age-specific mortality from peptic ulcer disease in Finland from 1969 to 1984.

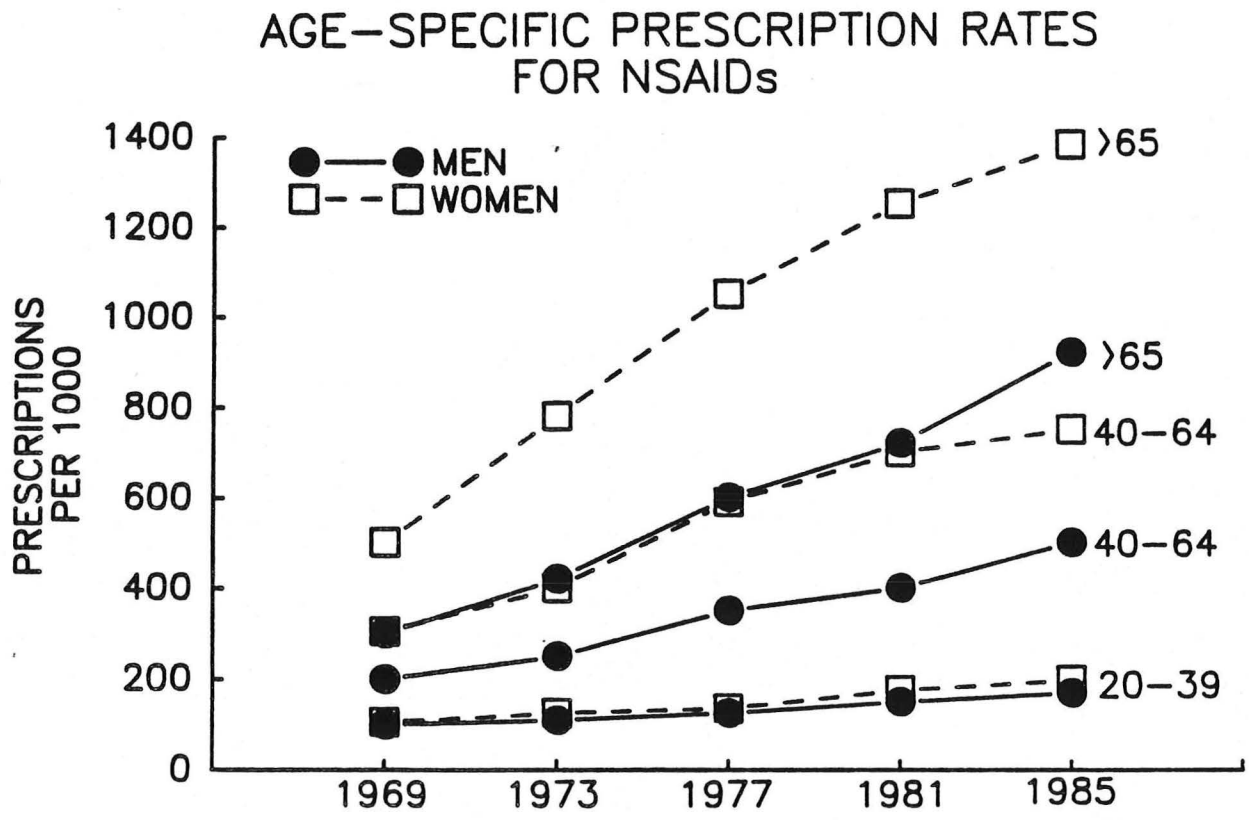

Figure 6. Age-specific prescription rates for NSAIDs (From reference 12).

(8). The prevalence of NSAID use is clearly higher in the elderly bleeder. (Figure 7, Tables 1 and 2) (5-7,18). Several series have also noted a substantial proportion of painless bleeds in patients taking NSAIDs (Table 3) (5,6,19,20). The likely reasons for this phenomenon are that those who develop NSAID-induced symptoms stop the drug before bleeding or, as suggested by Matthewson and Skander, the observation is related to age rather than NSAIDs (Table 4) (6,20).

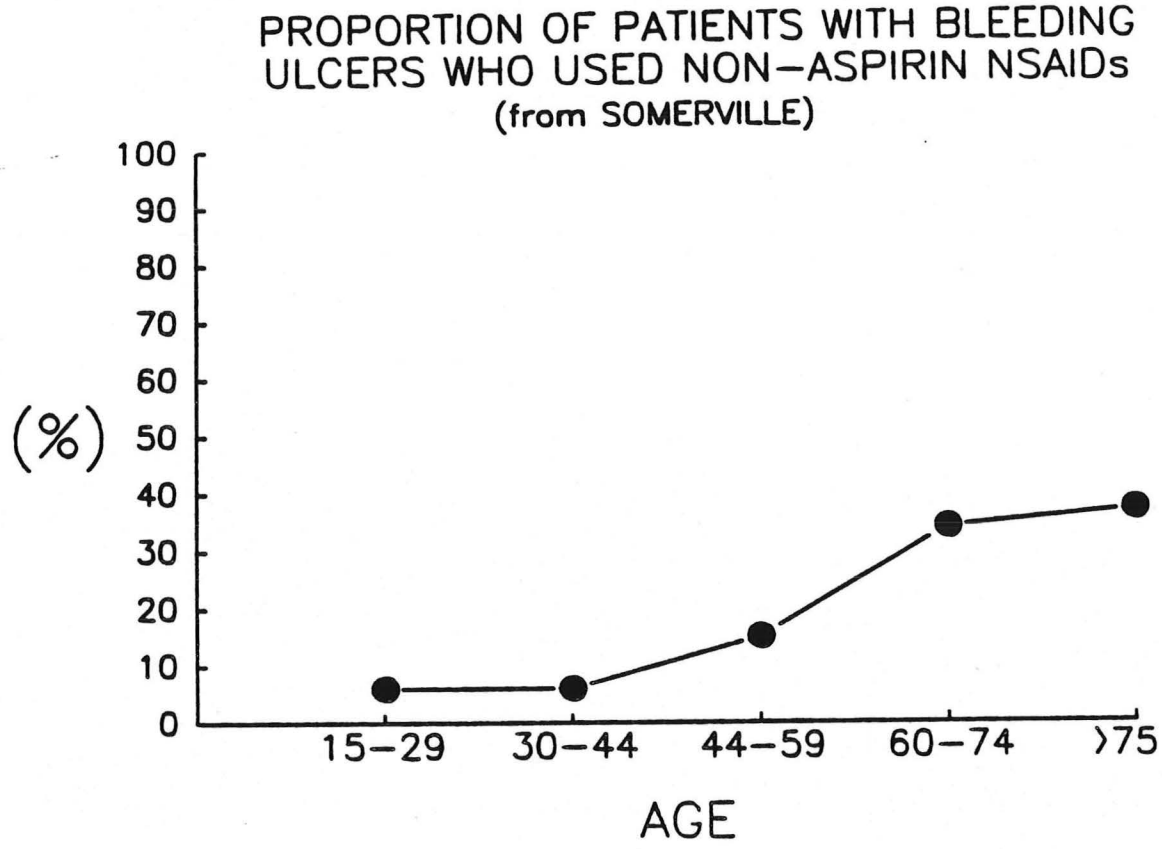

Figure 7. Proportion of patients with bleeding ulcers who used non-aspirin NSAIDs (From reference 7).

Table 1. NSAID use in patients with complicated PUD compared to control subjects.

Investigator	Type of NSAID	Proportion Using NSAIDs Patients <60	Patients >60	Controls
Griffin	Non ASA	-	34%	11%
Somerville	Non ASA	10%	35%	15%
Armstrong	All	21%	72%	10%
Matthewson	All	48%	64%	18%

Table 2. NSAID use in hospitalized patients with "bleeding" or "painful" peptic ulcer (From reference 6).

	Proportion Using NSAIDs			
	<60 years old		>60 years old	
Type of NSAID	Bleeding	Painful	Bleeding	Painful
ASA	44%	11%	13%	19%
NANSAID	4%	0%	51%	10%
	48%	11%	64%	29%

Table 3. Proportion of patients who are (+) or are not (-) taking NSAIDs whose bleed is painless.

	Proportion with Painless Bleed	
Investigator	NSAID+	NSAID-
Armstrong	58%	24%
Mellem	26%	3%
Skander	69%	31%
Matthewson	49%	48%

Table 4. Role of age in painless bleeding ulcer.

	Proportion With Painless Bleed	
Investigator	<70 y/o	>70 y/o
Matthewson	37%	62%
Skander	38%	66%

The attributable risk of NSAIDs to bleeding in the elderly has been estimated by Langman (Table 5) (21).

Table 5. Attributable risk of NSAIDs to bleeding in elderly (From reference 21).

- NSAIDs account for 22% of ulcer bleeds in patients over 60 years
- In the U.S., approximately 13,000 elderly patients per year would have NSAID-induced bleeding
- Risk of a bleed if taking NSAIDs:
  <60 1/20,000
  >60 1/3,000

THE CLINICAL PROBLEM OF BLEEDING ULCER

The average mortality from bleeding PUD is 4-8% (22-24). However, these figures include patients at one end of the spectrum whose bleeding settles quickly, with no need for blood transfusion or surgery, to patients with continued or recurrent bleeding who have a large transfusion requirement and the need for urgent surgery at the other end of the spectrum. The correlation of transfusion requirements with the need for surgery and, ultimately, mortality are shown in Tables 6 and 7 (25,26).

Table 6. Correlation of transfusion requirements with need for surgery in patients with bleeding ulcer (From reference 25).

Transfusion Requirement (Units)	Proportion Undergoing Surgery
0	0/60 (0%)
1-3	5/85 (6%)
4-7	25/68 (37%)
>7	53/60 (88%)

Table 7. Correlation of transfusion requirements with mortality in patients with bleeding ulcer (From reference 26).

Transfusion Requirement (Units)	Mortality
0	2/50 (4%)
1-3	16/90 (18%)
>3	15/53 (29%)

Clinical Risk Factors

There are several clinical factors which have been suggested as predictive of an adverse outcome from bleeding peptic ulcer. These can be grouped broadly into those factors which are a reflection of a large initial bleed and those factors unassociated with the size of the index bleed (27).

Hematemesis

Several large series report that bleeding which presents as hematemesis predicts a worse outcome (22,28-30). In one study, presentation as red hematemesis (with or without melena) or black hematemesis plus melena connoted a more severe course than if the bleed presented as black hematemesis or melena alone (30).

Nasogastric Aspirate

The color and clearance of the nasogastric aspirate has been reported to predict outcome (22,31). Results from one such study are shown in Table 8 (31).

Table 8. Nasogastric aspirate as a predictive factor in UGI bleeding (From reference 31).

N/G Aspirate	No.	Proportion of Patients: Needing Transfusion	Undergoing Surgery	Dying
Clear	15	40%	0	0
Coffee Ground	47	47%	11%	0
Red-Clear <1L of fluid	13	54%	8%	8%
Clear 1-6L of fluid	16	81%	25%	25%
No Clearing	10	100%	50%	50%

Vital Signs

Perhaps the most important predictive clinical factors are the patient's vital signs upon presentation to the hospital. For example, recurrent bleeding in one study occurred in only 2% of patients with normal vital signs, 18% of patients with tachycardia, and 48% of patients in clinical shock (32).

Age

In study after study, patients over 60 years of age are reported to have higher mortality than younger patients (5,22,26,28,29,33-37). Table 9 displays results from four such studies (5,26,29,33). Reasons for higher mortality in the elderly include a higher probability of associated diseases (see below) and a greater likelihood of having a large, deep gastric ulcer located high in the gastric body.

Table 9. Age as a factor in mortality from complicated ulcer.

Investigator	Mortality: <60 y/o	>60 y/o
Armstrong	4/45 (9%)	74/190 (39%)
Pimpl	8/99 (8%)	27/94 (29%)
Duggan	33/546 (6%)	67/284 (24%)
Schiller	47/1129 (4%)	145/1020 (14%)

Associated Diseases

Several studies have documented increasing mortality with an increasing number of associated illnesses. As an example, in one study, mortality in patients with no accompanying illnesses was 1.2% compared to 71% in those with 4 or more associated illnesses (26).

NSAIDs

Mortality has been reported in one study to be two-fold higher in patients taking NSAIDs (5). On the other hand, another study finds no significant difference in mortality between NSAID users and non-users (38). Further studies are indicated.

Conclusion

Clinical factors can be very helpful in stratifying patients into low and high risk groups. Such factors are probably more powerful when coordinated with endoscopic risk factors.

Endoscopic Risk Factors

Endoscopic factors predictive of a bad outcome include ulcer location (high gastric ulcer, posterior duodenal ulcer) (39-42), large ulcers (43), and ulcers with stigmata of hemorrhage (Figure 8). Patients in whom an ulcer has breached a major, large artery (eg., gastroduodenal artery) are at imminent risk of

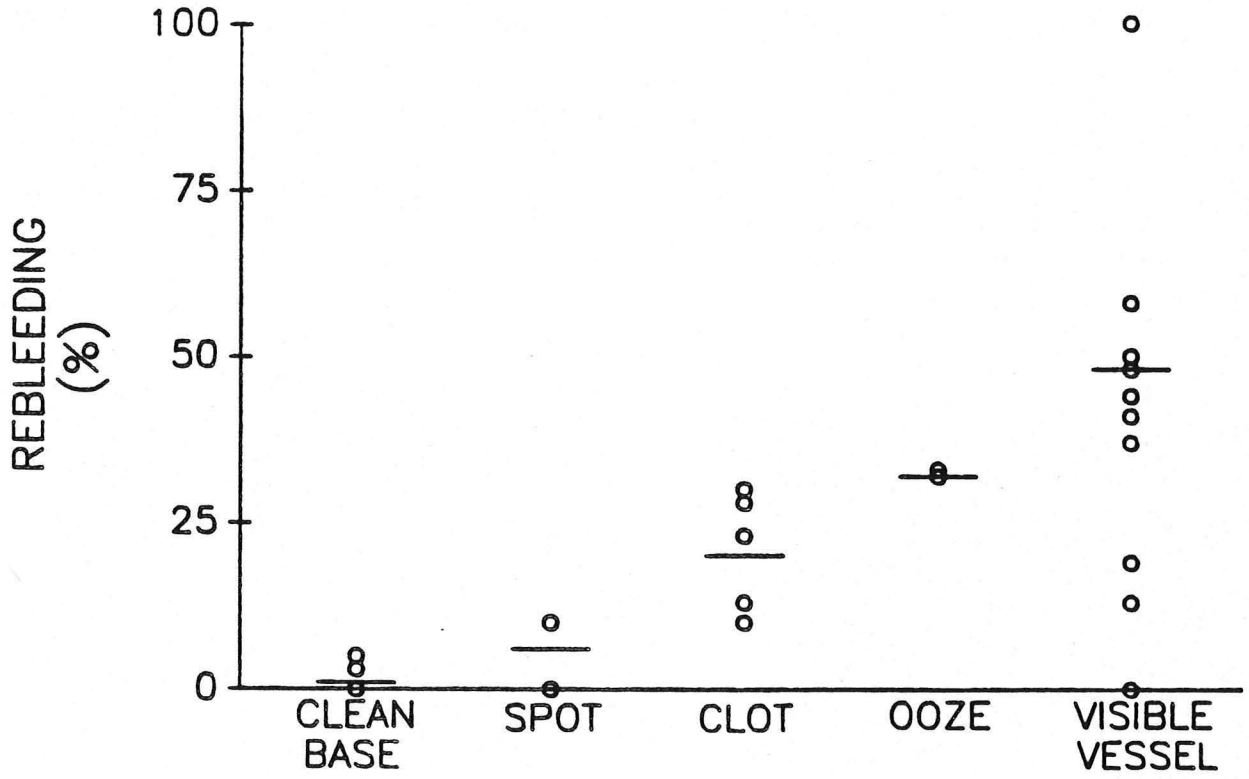

Figure 8. Incidence of major rebleeding as a function of endoscopic ulcer appearance. Open circles represent individual studies; horizontal lines represent mean values.

exsanguination and must be dealt with immediately. However, for those whose bleeding has slowed or ceased, the risk of further bleeding is correlated with the appearance of the ulcer. If there is a clean ulcer base, the chance of further bleeding is very low, less than 5% (44-49). If a flat stain, or spot, is present, the chance of further bleeding is only moderately increased (32,44,45,49,50). Presence of an adherent clot or oozing blood, however, predicts an incidence of major rebleeding of about 20% and 30%, respectively (32,44,51-54).

The ulcer with the greatest likelihood of rebleeding is one with a "visible vessel" (32,44-46,49-56) (Figure 9). This lesion represents only a portion, if any, of the actual arterial wall, but is rather a plug of clot and fibrin overlying the point where an ulcer crater has eroded one wall of a large vessel (46,57). Thus the term "sentinel clot" may be more accurate. The integrity and

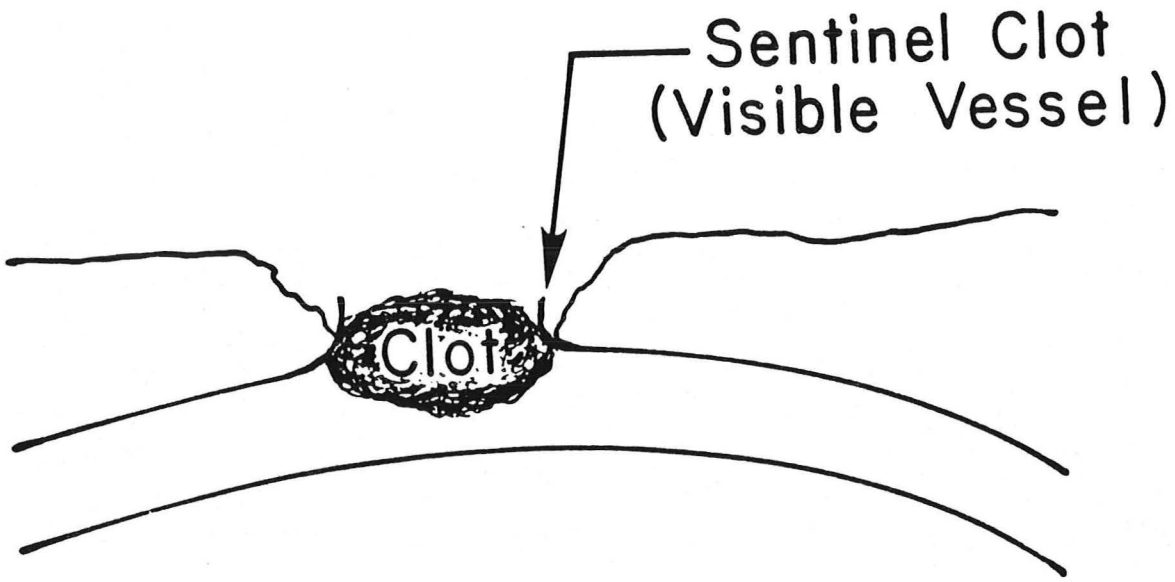

Figure 9. Diagramatic representation of ulcer with "visible vessel".

extent of this plug determines the likelihood of recurrent bleeding, which in many, but not all studies, is 40% or higher. The reason for the wide variation in rebleeding rates from study to study is unknown, but may reflect differences in definition of a "visible vessel", differences in the clinical severity of bleeding, differences in delay between presentation and endoscopy (ie., stigmata may change over time), and the difficulty in categorizing a lesion with both visible vessel and either a clot or oozing. For example, the results of one

careful, prospective study are shown in Table 10, from which several points can be made (44). First, an ulcer with a visible vessel that has no associated oozing or clot will rebleed less than 20% of the time, compared to over twice that figure if a clot or oozing is present. Second, the investigator admitted that in many instances it was impossible because of bleeding, clot, or anatomic location to document clearly the presence or absence of a visible vessel. Third, a well-visualized ulcer with no visible vessel, no clot, and no oozing rebled less than 10% of the time.

Table 10. Proportion of ulcers rebleeding as a function of stigmata of hemorrhage. Ulcers with a completely clean base were excluded (From reference 44).

	Visible Vessel Present	No Visible Vessel		Totals
		Good Exam	Inadequate Exam	
Oozing	5/14 (36%)	8/38 (21%)	11/24 (46%)	24/76 (32%)
Clot	8/17 (47%)	8/24 (33%)	11/55 (20%)	27/96 (28%)
Other stigma of recent hemorrhage	4/22 (18%)	5/55 (9%)	0/1 (0%)	9/78 (12%)
Totals	17/53 (32%)	21/117 (18%)	22/80 (28%)	60/250 (24%)

Another cause for variable results may be the location of the ulcer (ie, gastric, prepyloric, or duodenal). Table 11 displays the results from the study discussed above (44).

Table 11. Proportion of ulcers rebleeding based on location and presence or absence of visible vessel (From reference 44)

	Gastric Ulcer	Prepyloric Ulcer	Duodenal Ulcer
Visible Vessel Present	6/13 (46%)	2/17 (12%)	9/22 (41%)
No Visible Vessel	5/39 (13%)	4/34 (12%)	12/40 (30%)

Recently, it has been reported that the use of endoscopic Doppler may predict which ulcers with clot or visible vessel will rebleed (50). If the test detects no audible pulse through the eroded artery (implying a more extensive clot/plug), the chance of rebleeding is much lower than if an audible pulse is present. Further studies are needed to confirm these data.

It is important to know the prevalence of the various stigmata of recent hemorrhage, since the number of patients at risk for rebleeding from a particular lesion is directly proportional to the prevalence of that lesion. The prevalences of the various stigmata of recent hemorrhage in patients who have bled from a peptic ulcer, as taken from recent reports, are shown in Figure 10 (32,44-47,51,52,58,59). Approximately 75% of patients have at least one stigma of recent hemorrhage, although there is substantial variation from study to study.

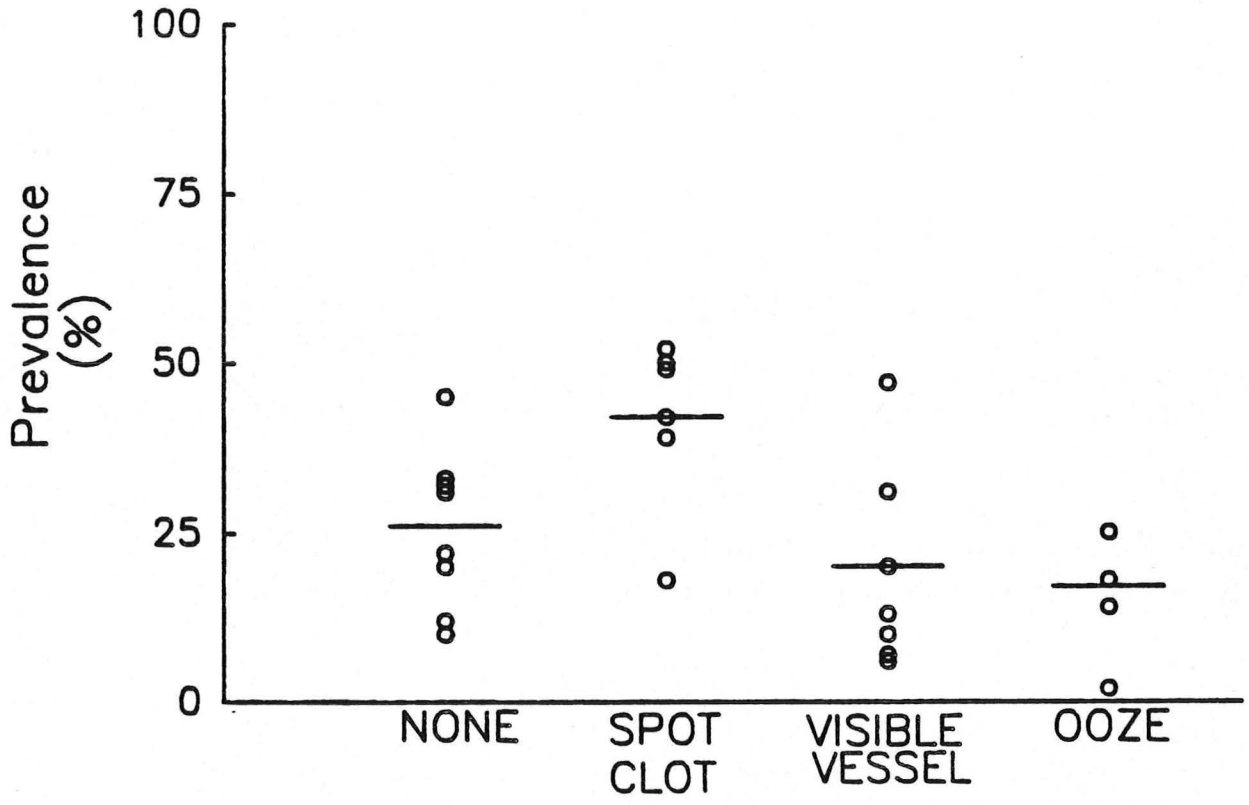

Figure 10. Prevalence of stigmata of recent hemorrhage in bleeding peptic ulcers. Open circles represent individual studies; horizontal lines are mean values.

PHARMACOLOGIC AND ENDOSCOPIC THERAPY OF BLEEDING PEPTIC ULCERS

Pharmacologic Therapy

A number of pharmacologic agents including intravenous vasopressin, secretin, H_2-receptor antagonists, and somatostatin, have been tried as means of stopping active ulcer bleeding (60-66). None has been clearly shown to be effective. It is not surprising that these agents, which act to reduce gastric acidity and/or constrict the bleeding vessel, are ineffective when one remembers that the cause of bleeding is an eccentric breach in the wall of a large vessel. Results with prostaglandins (67,68) and tranexamic acid (69-71) an antifibrinolytic agent, have also not been impressive in terms of cessation of bleeding, although there is some evidence that surgical intervention may be required less often in patients treated with tranexamic acid than those treated with placebo.

Since bleeding ceases at least initially in about 90% of patients, the goal of most pharmacologic regimens is to prevent recurrent bleeding. Most regimens that have been designed to prevent recurrent ulcer bleeding have used as a mechanism the reduction of gastric acidity. This makes some sense in that *in vitro* data suggest that coagulation and platelet function are inhibited at low pH levels (72). However, dissolution of a clot is not strictly an acid phenomenon. If a clot is placed in a solution of 0.1 N hydrochloric acid alone, no dissolution will occur (73). On the other hand, if the clot is placed in gastric juice at the same pH, rapid and progressive dissolution occurs (73). This is most likely due to the fact that gastric juice possesses pepsin, a fibrinolytic agent. It is well known that the activity of pepsin is pH-dependent, with reduced activity at higher pH levels (74,75). As pH is raised, the ability of gastric juice to dissolve a clot is markedly retarded (76).

Analysis of clinical trials assessing the effect of H_2-receptor antagonists on recurrent ulcer bleeding suggests that the incidence of recurrent bleeding from gastric ulcers may be reduced (albeit only slightly) with such drugs, whereas there is no benefit in duodenal ulcers (48), even if antacid is added (61). There are two possible reasons why reduction of gastric acidity has not been shown to have an important impact on the incidence of recurrent bleeding. First, it may well be that *in vitro* data regarding clot function are not relevant to the human model. Secondly, it is possible that previously tested regimens have failed to reduce gastric acidity to low enough levels. Indeed, it is possible that prevention of recurrent bleeding via reduction of gastric acidity requires reduction to levels near achlorhydria. This may be achieved with a constant intravenous infusion of an H_2-receptor antagonist with supplemental nasogastric administration of antacids (77). It is also possible that administration of omeprazole, a hydrogen-potassium ATPase inhibitor, may raise gastric pH to levels near achlorhydria. Whether such regimens will actually result in reduction of recurrent ulcer bleeding must be proved by controlled clinical trials.

Recent studies have also evaluated the effect of somatostatin, prostaglandins, and tranexamic acid as means of preventing recurrent ulcer bleeding (68,78,79). None of these agents has been proved effective at preventing recurrent bleeding, although tranexamic acid may lower transfusion requirement, the need for urgent surgery, and mortality.

Endoscopic Therapy

Non-surgical therapy for bleeding ulcers can be divided into three forms: pharmacologic, endoscopic, and arteriographic. Since pharmacologic approaches to stop active bleeding or prevent recurrent bleeding have not been convincingly proven effective, and since arteriographic therapy requires great expertise and has important complications, the only readily available and practical potential forms of therapy today are endoscopic. Thermal therapy (laser photocoagulation, bipolar electrocoagulation, and the heater probe) and injection therapy are discussed below. While cessation of active bleeding or prevention of further bleeding are in themselves worthy goals, it is important that there be accompanying reductions in the need for urgent surgery, transfusion requirements, and, hopefully, mortality. Of course, the modalities must be safe.

Efficacy of Laser Photocoagulation

Argon or Neodymium: Yttrium-Aluminum-Garnet (Nd:YAG) lasers have been subjected to double-blinded, controlled clinical trials in patients with bleeding ulcer (45,51,80-82). Results in patients with spurting or oozing lesions are shown in Table 12. With spurting lesions, spontaneous cessation occurs less than 20% of the time. Results with laser are numerically superior in each of three studies, although statistical significance is achieved in only one due to the small sample sizes. Laser is more successful with oozing lesions, achieving permanent hemostasis almost 90% of the time. However, spontaneous cessation also occurs frequently (about 70% of patients), and statistical significance was achieved in only one study.

Table 12. Proportion of patients in whom permanent hemostasis of active ulcer bleeding was achieved with laser or control therapy.

Investigator (ref.)	Laser Used	Spurting		Oozing	
		Control	Laser	Control	Laser
Vallon (45)	Argon	2/13	8/15	-	-
Swain (80)	Argon	0/4	3/7	5/5	3/3
Swain (81)	Nd:YAG	2/10	8/10*	8/10	7/7
Rutgeerts (82)	Nd:YAG	-	-	20/32	36/38*
Krejs (51)	Nd:YAG	-	-	10/15	12/17

*$p<0.05$ compared to control

Interpretable data concerning the prophylactic treatment of non-bleeding lesions are available from 5 studies (Figure 11) (45,51,80,81,83). With stigmata other than visible vessels there is agreement that laser provides no significant reduction in the incidence of rebleeding (45,51,80,81). With visible vessels, the studies of Krejs and Vallon (45,51) showed no significant benefit with laser while those of Swain disclosed remarkable benefit using either Argon (80) or Nd:YAG (81) laser. Buset found Nd:YAG laser to be of no effect in duodenal ulcers, but as effective as in Swain's study for bleeding gastric ulcer (83). From Figure 11, two questions concerning laser treatment of bleeding ulcers with visible vessels come to mind:

1) Why did Krejs's (51) control subjects with visible vessel have such a low incidence of rebleeding compared to those in the other studies? The answer is unknown but may reflect a more severely ill patient population in the other studies or, as Krejs points out, other investigators may be more vigorous in washing off clots and exposing visible vessels. While such vessels would then be more amenable to laser treatment, patients randomly assigned to the control group might be at greater risk for rebleeding after vigorous washing-away of clots from the ulcer base.

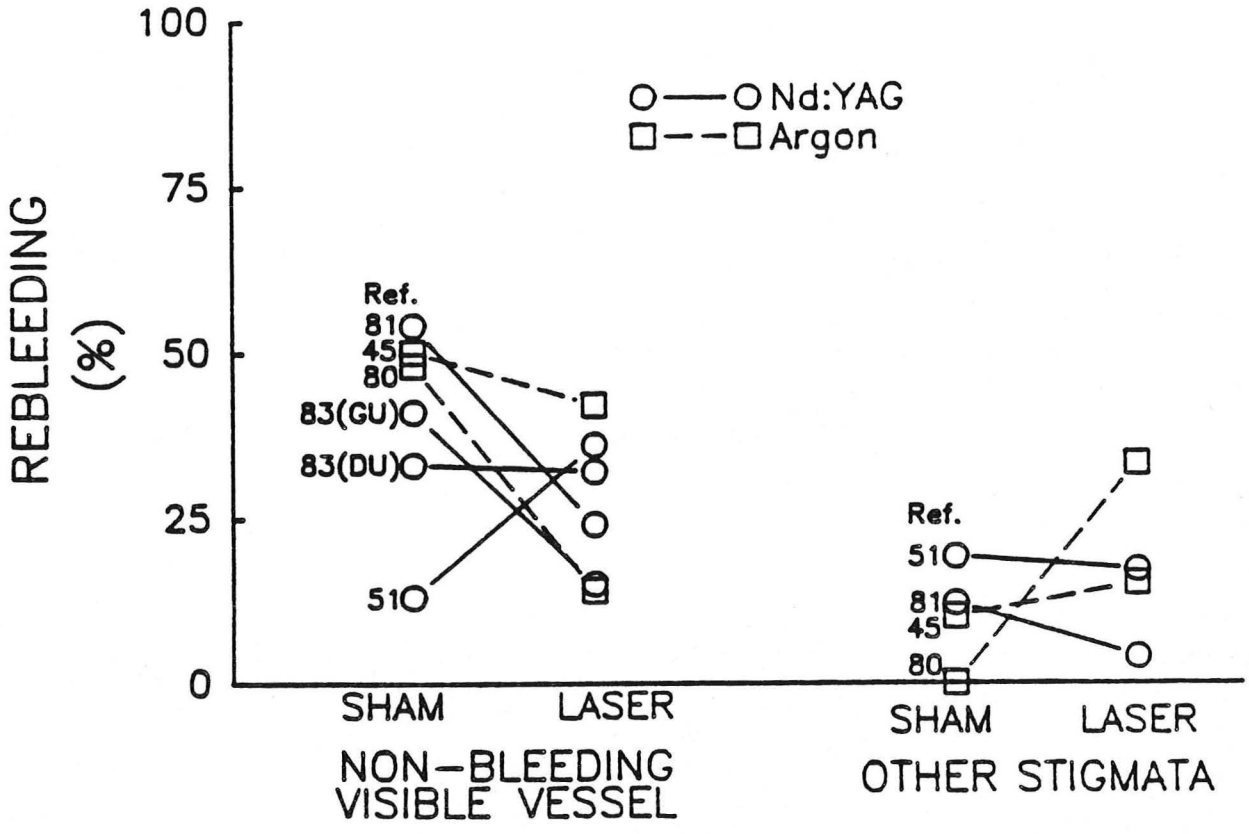

Figure 11. Rebleeding after sham or laser therapy in patients whose ulcer has a visible vessel or other stigma of hemorrhage. Solid lines are studies with Nd:YAG laser and dashed lines, Argon laser. Lines connect results from the same study. Studies include those of Vallon (45), Krejs (51), Swain (80,81), and Buset (83).

2) Why was laser so much more effective with visible vessels in Swain's studies (80,81) than in Vallon's and Krejs'? It is possible that Swain's group of investigators was more experienced. Another possibility is that Swain's treatment group was weighted toward patients with easily accessible gastric ulcers which, as suggested by the Buset study (83), may respond to laser therapy better than duodenal ulcers.

There are several problems in assessing the impact of laser therapy on the need for urgent surgery, transfusion requirements, and mortality. First, sample sizes tend to be small, so that there may be large Type II errors in concluding that differences are not statistically significant. Second, not every paper reports results for each outcome for each type of lesion. Third, transfusion requirements are reported only in the Krejs study and the Swain Nd:YAG study. With these provisions in mind, what do the studies suggest? Not surprisingly, Krejs (81) found not even a trend in favor of laser. Neither did Buset, although in this study (83) all rebleeders were treated with laser. Vallon (51) reported a trend toward less surgery and lower mortality in patients with spurting ulcer bleeding, while Rutgeerts (82) found a similar trend toward less surgery for oozers treated with laser, but not even a trend toward improved survival. Swain's studies stand out since he reported a significant reduction in mortality when patients with spurting lesions or nonbleeding visible vessels were treated with either Argon (80) or Nd:YAG (81) laser. He also reported a trend toward less urgent surgery (80) and a signficant difference in the number of laser-treated patients requiring transfusions from 24 hours after admission on (81).

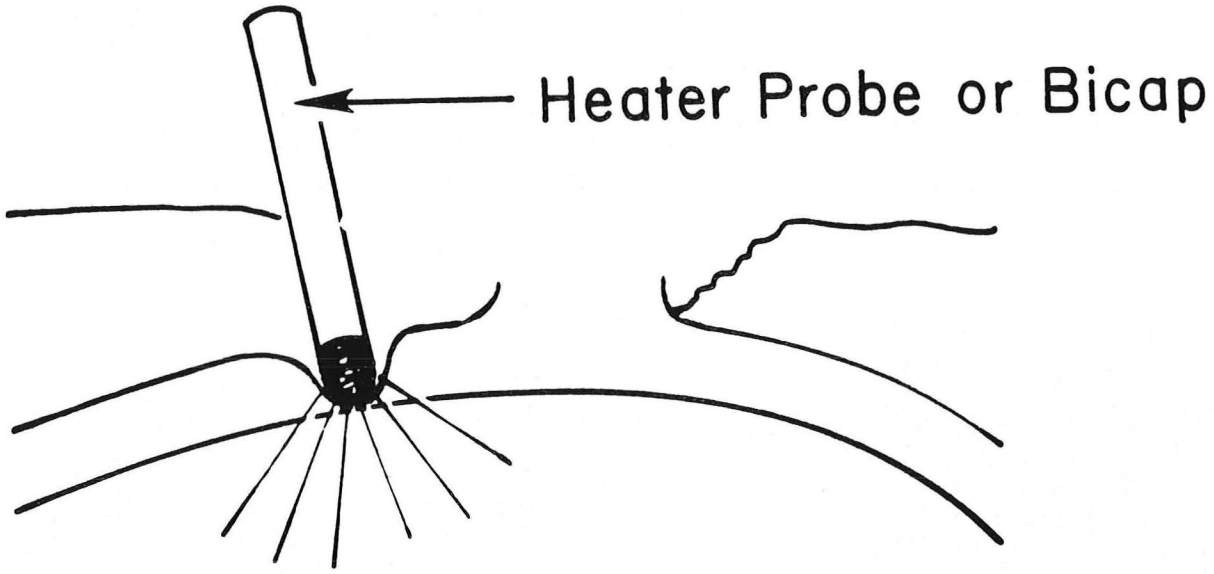

Figure 12. Contact probes to treat bleeding ulcer.

Two things have occurred to limit most endoscopist's use of laser therapy of bleeding ulcers. First, results of controlled clinical trials with laser were not as impressive as first hoped. Second, development of contact probes (ie., bipolar electrocoagulation unit [BICAP] and the heater probe) (Figure 12) offered far less expensive, more convenient, and potentially more effective means of treating bleeding ulcers (84,85).

Efficacy of Contact Probes

BICAP

Two early reports suggested that the BICAP was ineffective in the treatment of bleeding ulcer (86,87). Unfortunately, lesions were not stratified for the various stigmata of recent hemorrhage. For active bleeding, O'Brien reported 85% permanent cessation of bleeding with the BICAP compared to 38% with sham therapy ($p<0.05$) (53). However, the type of active bleeding was not specified. Jensen and his Hemostasis Research Group noted primary cessation of active bleeding (mostly "spurters") in 91% of the patients treated with the BICAP compared to only 14% of those sham-treated (88 and personal communication). The incidence of permanent hemostasis, while numerically greater (36% vs 7%), was not significantly different. Results of four studies using BICAP for non-bleeding lesions are shown in Table 13 (53,56,58,88).

Table 13. Proportion of patients experiencing rebleeding after BICAP or sham therapy of non-bleeding visible vessel.

Investigator (ref.)	Rebleeding		Urgent Surgery		Transfusion($\bar{X}$U)		Mortality	
	Sham	Bicap	Sham	Bicap	Sham	Bicap	Sham	Bicap
O'Brien (53)	16/43 (37%)	7/43* (16%)	---		---		---	
Laine (56)	15/37 (41%)	7/37* (19%)	11/37 (30%)	3/37* (8%)	3.0	1.6	0/37 (0%)	1/37 (3%)
Brearley (58)	8/21 (38%)	6/20 (30%)	4/21 (19%)	5/20 (25%)	2	4	0/21 (0%)	0/20 (0%)
Jensen (88)	12/22 (55%)	8/25 (32%)	7/22 (32%)	7/25 (28%)	3.0	2.6	1/22 (5%)	0/25 (0%)

*$p<0.05$ compared to sham

Table 14. BICAP (BC) or Heater Probe (HP) Versus Medical Therapy of Spurting Ulcer or Non-Bleeding Visible Vessel (NBVV). (From Jensen)

Spurting Ulcer	Medical	BICAP	Heater Probe
Cessation of Active Bleeding	2/14 (14%)	10/11* (91%)	15/16* (94%)
Permanent Hemostasis	1/14 (7%)	4/11 (36%)	13/16* (81%)
Urgent Surgery	8/14 (57%)	4/11 (36%)	1/16* (6%)
Blood transfusions (Mean Units)	4.6 ±1.3	3.5 ±1.2	1.7* ±1.2
Mortality	3/14 (21%)	1/11 (9%)	1/16 (6%)
NBVV			
Rebleed	12/22 (55%)	8/25 (32%)	4/19* (21%)
Urgent Surgery	7/22 (32%)	7/25 (28%)	0/19* (0%)
Blood Transfusions (Mean Units)	3.0 ±0.8	2.6 ±1.0	0.8* ±0.5
Mortality	1/22 (5%)	0/25 (0%)	0/25 (0%)

*$p<0.05$ compared to medical therapy

When considering outcome (ie., surgery, transfusion, mortality) Jensen found a trend toward fewer operations, fewer tranfusions, and lower mortality in BICAP-treated patients with spurting bleeding, but sample sizes were too small to achieve statistical significance (88). BICAP therapy in his study resulted in barely even a trend toward benefit in patients with nonbleeding visible vessels. O'Brien reported a reduction (again, not statistically significant) in mean numbers of post-endoscopy transfusions (if required) from 7.3U to 4.6U in BICAP-treated patients with active bleeding or nonbleeding visible vessel. Finally, Laine noted a significant reduction in the need for urgent surgery and a trend toward fewer transfusion in BICAP-treated patients with nonbleeding visible vessels.

Heater Probe

Only three abstracted reports are available to assess the effectiveness of the heater probe in bleeding peptic ulcer (88-90). Swain does not present data for each of the stigmata of hemorrhage, but when all lesions were combined, the incidence of rebleeding after heater probe therapy was 28% compared to 42% with control (p=N.S.) (89). Mortality was about 10% in each group. Fullarton enrolled 43 patients with active bleeding or "major stigmata of hemorrhage" and found an incidence of rebleeding in 0/20 heater probe treated patients compared to 5/23 (22%) sham treated patients ($p<0.05$) (88). The need for urgent surgery was no different in the two groups and there were no deaths in either group. The results of Jensen's (30 and personal communication) study provide the best support for the effectiveness of the heater probe and also suggest that the heater probe may be superior to BICAP, although sample sizes are inadequate to achieve statistical significance between the two treatment modalities (Table 14). It should be noted that the patients in Jensen's study tended to be quite ill which may account for the high incidence of rebleeding with sham therapy.

Safety of Endoscopic Means of Thermal Coagulation

Not all reports specifically comment on the complications noted with thermal coagulation of bleeding ulcers, but several have noted perforation or induction of massive bleeding unable to be stopped with thermal therapy. Krejs noted 1 perforation and induction of 2 "unstoppable" bleeds in 85 Nd:YAG laser-treated patients (51), while Swain had 2 such bleeds in 40 patients treated with argon laser (80). With BICAP, Brearly reported one perforation in 20 treated patients, Goudie noted 1 massive bleed in 21 patients, and Laine described 7 induced bleeds, in 37 patients, one of whom required surgery. Jensen noted no complication with BICAP or heater probe. Thus, with the exception of Jensen's study, a major complication has occurred occurs in 3 to 5% of patients.

Injection Therapy

The latest innovation in the endoscopic therapy of bleeding ulcers, and clearly the most convenient and inexpensive one, is injection of a vasoconstrictor/sclerosing agent into and around a bleeding ulcer. A randomized, controlled trial by Chung reported permanent cessation of active bleeding in 26/34 (76%) of ulcers injected with 1:10,000 epinephrine (91). The incidence of permanent hemostasis in the control group cannot be determined from the paper, although there was a significant reduction in the need for urgent surgery in the treated group (5/34 vs 14/34, $p<0.02$). Unfortunately, one of the surgeons making the decision regarding surgery was aware of the group to which the patient had been randomly assigned. Mortality was about 10% in each group. Results from a second study are shown in Table 15 (54). In this study, patients

Table 15. Proportion of patients with major rebleed with or without injection therapy of bleeding ulcer (From reference 54).

Lesion	Control	Injection	
Bleeding Visible Vessel	7/13 (54%)	1/15 (7%)	$p<0.01$
Non-Bleeding Vessel	10/21 (48%)	2/18 (11%)	$p<0.05$
Oozing or Clot	8/24 (33%)	0/22 (0%)	$p<0.01$

received injections of both 1:10,000 epinephrine and 1:100 polidocanal. Rebleeding was reduced in each category with injection therapy, surgery was required less often in the injection group (3/55 vs 20/58 $p<0.001$) and the number of units of blood transfused was lower. Mortality was not significantly affected (2/55 injection vs 4/58 control).

Lin and colleagues compared the heater probe against injection therapy with pure alcohol (92), although the study appears to be unblinded. They concluded that for spurting lesions the heater probe is significantly more successful than injection therapy, but for oozing or non-bleeding visible vessel the two modalities are equally effective.

Summary: Panes' study (54) supports the effectiveness of injection therapy in bleeding ulcers. However, before this modality is accepted, more data regarding efficacy and safety must be provided through properly blinded, controlled trials, especially in comparison to the contact probes.

Conclusions

1. Is endoscopic thermal therapy effective? Variation in results among studies, inadequate detail regarding lesions treated, and small sample sizes in individual studies limit the confidence with which one can assess the efficacy of laser, BICAP, and the heater probe. However, using the data at hand, I would conclude the following:

   a. Active Bleeding - With laser and BICAP, there is a strong trend toward efficacy in stopping active arterial hemorrhage. In Jensen's study, the heater probe produced a statistically significant, and clinically important improvement in permanent hemostasis compared to routine medical therapy.

b. Non-Bleeding Visible Vessel - Most studies (Krejs' excepted) suggest at least a trend toward reduction in rebleeding from ulcers with visible vessels. Swain and Buset with laser, O'Brien and Laine with the BICAP, and Jensen with the heater probe report statistically significant results.

c. Other Stigma of Hemorrhage - There is reasonable consensus that thermal therapy of oozing lesions, clots or spots is ineffective.

2. Does the patient benefit from the use of endoscopic thermal therapy? Results here are even more difficult to interpret. With active bleeding, only use of the heater probe in Jensen's study resulted in significantly less surgery and transfusion requirements. With visible vessels, use of BICAP in Laine's study and the heater probe in Jensen's study resulted in significantly fewer operations, but only in Jensen's series was there a significant reduction in transfusions. A reduction in mortality has been the most difficult outcome with which to demonstrate statistical significance. When considered separately, thermal therapy of active arterial bleeding has produced only trends toward improved survival, while treatment of nonbleeding visible vessels has not shown even a trend. Swain combined patients with active bleeding and nonbleeding visible vessels and was able to show significantly fewer operations, late transfusions, and mortality with laser therapy.

3. Are results with endoscopic thermal therapy good enough to warrant the performance of routine endoscopy in all patients with UGI bleeding to look for ulcers amenable to such therapy? While the incidence of further bleeding can be reduced by endoscopic thermal therapy of active arterial bleeding or nonbleeding visible vessels, I am reluctant to recommend endoscopy in every patient to look for these lesions for five reasons:

a. It has been difficult to show statistically significant benefit in terms of patient outcome, especially regarding transfusion requirements and mortality, with thermal therapy.

b. Most patients who undergo endoscopy will not have a lesion amenable to thermal therapy.

c. Cost-effectiveness of routine endoscopy in all patients to treat a few has not been proven.

d. Thermal therapy may result in complications in 3 to 5% of patients.

e. Buset (83) suggests that one can wait until patients rebleed and then treat, with good results.

Having stated these reservations, I am nevertheless impressed with Jensen's data and those of Bornman (32) and would suggest the following:

a. Patients with hemodynamically important bleeding episodes or patients with obvious, rapid, ongoing hemorrhage are a high risk sub-group and should be endoscoped as soon as possible.

b. If active arterial bleeding or a nonbleeding visible vessel is seen, it should be treated. Other lesions should be left alone.

c. Endoscopy and treatment of other patients can await a rebleeding episode.

d. Selection of elective endoscopy or air contrast UGI series as a diagnostic tool should be made in all other patients on a case by case basis.

CONCLUSIONS

Bleeding ulcer remains, in 1989, a major clinical problem, especially in the elderly. The increased prescription of NSAIDs in anti-inflammatory doses, when perhaps only analgesia is needed, is believed by many to be a contributing factor to the problem. While endoscopic therapy appears capable of aiding in the management of such patients in the hospital, a more important concern is the prevention of bleeding ulcer. Long-term maintenance therapy with H_2-receptor antagonists has not been proven to prevent recurrent bleeding. Neither have synthetic prostaglandin analogues given concommitantly with NSAIDs been proven effective at preventing ulcer complications, much less in a cost-effective manner. Well-designed, long-term, prospective studies of H_2 blockers and prostaglandin analogues, given to patients taking NSAIDs, using ulcer complications as the end point, are urgently needed before unproven and expensive regimens become "standard of practice".

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