การทำนายโอกาสเกิดเลือดออกในทางเดินอาหารส่วนต้น
ในผู้ใช้ยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์

นางสาวมยุรี ตั้งเกียรติกำจาย

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THE PREDICTION OF UPPER GASTROINTESTINAL BLEEDING IN NONSTEROIDAL ANTI-INFLAMMATORY DRUG USERS

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ที่มาของปัญหา

การใช้ยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ (Nonsteroidal anti-inflammatory drugs; NSAIDs) เป็นสาเหตุหนึ่งของการเกิดเลือดออกในทางเดินอาหารส่วนต้น (Upper gastrointestinal bleeding; UGIB) โดยมีปัจจัยเสี่ยงที่ทำให้ ผู้ใช้ NSAIDs มีโอกาสเกิด UGIB เพิ่มขึ้น ได้แก่ ผู้สูงอายุ ผู้ที่เคยมีประวัติภาวะอาหารไม่ย่อย (Dyspepsia) ผู้ที่เคยมีประวัติแผลในทางเดินอาหาร ผู้ที่เคยมีประวัติ UGIB ผู้ใช้ NSAIDs หลายชนิดร่วมกัน หรือใช้ NSAIDs ร่วมกับยาสเตียรอยด์หรือยาวาร์ฟาริน ผู้ใช้ NSAIDs ในขนาดสูง และผู้ที่ติดเชื้อ *H. pylori* เป็นต้น ดังนั้นผู้วิจัยจึงสนใจที่จะศึกษาการทำนายโอกาสเกิด UGIB ของผู้ใช้ NSAIDs

ผู้ป่วยและวิธีวิจัย

การศึกษานี้เป็นการศึกษาวิจัยเชิงวิเคราะห์แบบย้อนหลัง (Case-control study) โดยมีเกณฑ์การคัดเลือกผู้ป่วยเข้าการศึกษาคือ เป็นผู้ใช้ NSAIDs มาเป็นเวลาอย่างน้อย 3 วัน และได้รับการส่องตรวจด้วยกล้อง ณ โรงพยาบาลจุฬาลงกรณ์ ผู้ป่วยที่มีประวัติเส้นเลือดขอดในทางเดินอาหาร มะเร็งในทางเดินอาหาร โรคไตวายเรื้อรัง และโรคเลือด จะถูกคัดออกจากการศึกษา ผู้วิจัยเก็บข้อมูลตั้งแต่ กรกฎาคม 2544 ถึง มกราคม 2545 โดยการสัมภาษณ์ผู้ป่วย และเก็บข้อมูลจากเวชระเบียน มีผู้ป่วยที่ใช้ NSAIDs ทั้งหมด 154 คน ในจำนวนนี้มีผู้ป่วยที่เกิด UGIB จำนวน 89 คน และผู้ป่วยที่ไม่เกิด UGIB จำนวน 65 คน การวินิจฉัยการติดเชื้อ *H. pylori* ตรวจโดยใช้ rapid urease test หรือ serology test ในการสร้างสมการทำนายโอกาสในการเกิด UGIB ใช้การวิเคราะห์ความถดถอยโลจิสติควิธี enter

ผลการวิจัย

ผู้ป่วยส่วนใหญ่ที่ใช้ NSAIDs ในการศึกษานี้เป็นผู้สูงอายุ มีอายุเฉลี่ย (อายุ$\pm$SD) 60.9$\pm$12.6 ปี เป็นเพศชายร้อยละ 46.1 เพศหญิงร้อยละ 63.9 พบว่าผู้ป่วยที่เกิด UGIB มีอายุและมีการใช้ NSAIDs ในปัจจุบัน (Current NSAID use) มากกว่าผู้ป่วยที่ไม่เกิด UGIB อย่างมีนัยสำคัญทางสถิติ ($p < 0.05$, $p < 0.01$ ตามลำดับ) ผู้ป่วยที่ไม่เกิด UGIB มีการใช้ยารักษาแผลในทางเดินอาหาร (Antiulceration drugs) มากกว่าผู้ป่วยที่เกิด UGIB อย่างมีนัยสำคัญทางสถิติ ($p < 0.01$)

สมการทำนายที่ดีที่สุดคือ logit (UGIB) = 0.334-0.000048อายุ-8.53เพศ+0.118(อายุXเพศ)+0.344การใช้ NSAIDs ในปัจจุบัน+2.087การใช้ NSAIDs หลายชนิดร่วมกัน+1.429การติดเชื้อ *H. pylori*-2.406การใช้ยารักษาแผลในทางเดินอาหาร สมการมีค่า –2 log likelihood= 99.9 และค่าการทำนายถูกต้องเป็นร้อยละ 80.2 การทำนายโอกาสเกิด UGIB = $e^{logit(UGIB)}/1+e^{logit(UGIB)}$ ค่าโอกาสเกิด UGIB มากกว่า 0.5 แสดงว่าผู้ใช้ NSAIDs มีโอกาสเกิด UGIB

สรุปผลการวิจัย

ปัจจัยเสี่ยงที่เพิ่มโอกาสเกิด UGIB ในผู้ใช้ NSAIDs มากที่สุดคือ การใช้ NSAIDs ร่วมกันหลายชนิด รองลงมาคือการติดเชื้อ *H. pylori* ส่วนยารักษาแผลในทางเดินอาหารจะลดโอกาสเกิด UGIB จากสมการนำมาสร้างตารางแสดงโอกาสเกิด UGIB ในผู้ป่วยกลุ่มต่างๆ เพื่อให้บุคลากรที่ปฏิบัติงานทางคลินิก สามารถนำไปใช้เป็นแนวทางประกอบการวางแผนการรักษาผู้ป่วยด้วยยาต่อไป

ภาควิชา เภสัชกรรม ลายมือชื่อนิสิต……

สาขาวิชา เภสัชกรรมคลินิก ลายมือชื่ออาจารย์ที่ปรึกษา……..

ปีการศึกษา 2544 ลายมือชื่ออาจารย์ที่ปรึกษาร่วม……

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KEY WORD: NONSTEROIDAL ANTI-INFLAMMATORY DRUGS/ NSAIDs / UPPER GASTROINTESTINAL BLEEDING/RISK FACTORS

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Background

Nonsteroidal anti-inflammatory drugs (NSAIDs) use is known as a cause of upper gastrointestinal bleeding (UGIB). Risk factors of UGIB in NSAID users are age, a history of dyspepsia, peptic ulcer, and UGIB, multiple NSAID use, concomitant corticosteroids or warfarin therapy, high dose of NSAID use, and *H. pylori* infection. The purpose of this study was to predict the risk of GI bleeding in NSAID users.

Patients and Methods

The patients of this case-control study were NSAID users who use NSAIDs for at least 3 days and were gastroscoped at King Chulalongkorn Memorial Hospital. The patients with history of gastrointestinal varices, gastrointestinal cancer, chronic renal failure, and coagulopathy were excluded from this study. The data was collected from July 2001 to January 2002 by patient interviewing and charts reviewing. *H. pylori* status was assessed by rapid urease test or serology test. One hundred fifty four NSAID users were identified (89 were in UGIB group, 65 were in non-bleeding group). An equation for prediction of the probability of UGIB in NSAID users was generated by using enter logistic regression.

Results

Most of the patients were elderly (Mean age$\pm$SD: 60.9$\pm$12.6 years). 46.1% were men, and 53.9% were women. Age and the number of current NSAID users were statistically significant higher in patients with UGIB than non-bleeding patients ($p < 0.05$, $p < 0.01$, respectively). The number of antiulceration drug users were statistically significant higher in non-bleeding patients than patients with UGIB ($p < 0.01$).

The best model of predicted the risk of UGIB event in NSAID users was logit (UGIB) = 0.334-0.000048Age-8.53Sex+0.118(AgexSex)+0.344Current NSAID use+2.087Multiple NSAID use+1.429*H. pylori* infection-2.406Antiulceration drugs. The model had 99.9 of –2 log likelihood and 80.2% of the overall rate of correct classification. The probability of UGIB = $e^{logit(UGIB)}$ /1+$e^{logit(UGIB)}$. If the value of the probability of UGIB is more than 0.5, the patients have a high risk of UGIB.

Conclusion

Multiple NSAID use is the strongest factor that impacted on the probability of UGIB in NSAID users following by *H. pylori* infection. Antiulceration drugs usage reduced the risk of UGIB in NSAID users. A table demonstrated probability of UGIB in various groups of patients was developed. This table can be use as a guide for pharmacotherapy planning in clinical practices.

Department Pharmacy Student's signature……

Field of study Clinical Pharmacy Advisor's signature……

Academic year 2001 Co-advisor's signature……

Acknowledgment

First of all, I would like to express my sincere gratitude to my thesis advisor, Dr Somratai Ratisoontorn of the Department of Pharmacy, Faculty of pharmaceutical Sciences, Chulalongkorn University, for her valuable advices, suggestions, keen interests, and encouragment throughout the course of the study.

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Abbreviations

CI	=	Confidence interval
cm	=	Centimeters
Coeff	=	Coefficient
COX-2	=	Cyclooxygenase-2
F	=	Female
GI	=	Gastrointestinal
H_2-blockers	=	Histamine$_2$-blockers
HP	=	*Helicobacter pylori*
-2LL	=	-2 Log likelihood
M	=	Male
mg/d	=	Milligram per day
NSAIDs	=	Nonsteroidal anti-inflammatory drugs
OA	=	Osteoarthritis
OR	=	Odd ratio
PPIs	=	Proton pump inhibitors
PUD	=	Peptic ulcer disease
RA	=	Rheumatoid arthritis
RR	=	Relative risk
SE	=	Standard error
UGIB	=	Upper Gastrointestinal bleeding
wk	=	Week

CHAPTER I

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used medications in many countries.[1] These medications provide antipyretic, analgesic, and anti-inflammatory effects. They are used mostly for the treatment of musculoskeletal and arthritic syndromes. Therefore, NSAIDs are among the most frequently used drugs particularly in elderly populations.[2] In Thailand, all NSAIDs are available for both prescription orders and over the counter selling.

Although NSAIDs are generally well tolerated, their well known adverse effects are gastrointestinal (GI) toxicity including peptic ulcer and upper gastrointestinal bleeding (UGIB). Many studies have shown that NSAIDs increase the risk of peptic ulcer complication by 3-5 folds.[3-5] A study revealed that NSAIDs (including aspirin) were used by 388 patients with UGIB (41%).[6] In various groups of population, it has been estimated that 15-35% of all peptic ulcer complications are due to NSAIDs.[7-10]

In Thailand, many investigators studied problems of NSAID-induced GI effects. Sriussadaporn, Tanphiphat and Vilairat (1988) found that almost half (45.5%) of the patients with peptic ulcer bleeding used NSAIDs.[11] Two-third of NSAID users in the study received the medicine regularly. Orprayoon (1991) reported that 63.1% of UGIB patients had a history of NSAID usage.[12] Similarly, Kittikun (1998) showed that the most common risk factor of peptic ulcer bleeding was NSAID use.[13] Thirty percent of the UGIB patients used NSAIDs was found in King Chulalongkorn Memorial Hospital during January 1 to December 31, 2000.[14] Upper gastrointestinal bleeding from the treatment with NSAIDs is a major cause of morbidity and mortality. Mortality rate of peptic ulcer bleeding in Thailand is 6-7%, as same as in many countries.[11,15-17]

Dyspeptic symptoms are unreliable predictors of ulcers and gastroduodenal complications in patients receiving NSAIDs.[18] Amstrong and Blower (1987) found no antecedent symptoms in 58% of NSAID-treated patients with hemorrhage, comparing with 25% of non NSAID-related hemorrhage.[18] A second study, by Wolfe, Lichtenstein and Singh (1999), showed that 40% of individuals with endoscopic evidence of erosive gastritis were asymptomatic and conversely, as many as 50% of patients with dyspepsia had normal-appearing mucosa.[17] Thus, it is important to identify factors that increase the risk of serious GI complication. Several studies revealed the risk factors for NSAID-induced UGIB. Reported risk factors include older age; history of dyspepsia, peptic ulcer disease (PUD) and GI complications; high-dose of NSAID use; multiple NSAID use and concomitant corticosteroids and/or anticoagulant therapy. Other potential, but unproven, risk factors include smoking, alcohol and *Helicobacter pylori* (*H. pylori*) infection.[19-24]

In order to reduce the number of UGIB problems in NSAID users, it is important to weigh each risk factor for NSAID-associated UGIB and their interrelationship provides a tool for identification of the patient at high risk. Rational decisions on the choice of a NSAID or antiulceration drugs can then be made. As Fries et al. (1991) reported that GI-event risk per year on NSAIDs in rheumatoid arthritis (RA) was predicted GI incidence rates of hospitalization or death over the next 12 months.[25] Singh et al. (1998) showed that the GI score was anticipated incidence rates of serious NSAID-related GI events in rheumatoid arthritis (RA) and osteoarthritis (OA).[26] These tools are proven that they are reliable and accurate predictors.

However, only a few studies have provided a tool for prediction of UGIB in NSAID users. Therefore, it is beneficial to generate the predictor of UGIB event in Thai patients receiving NSAIDs.

Objective

To provide the predictor of the probability of upper gastrointestinal bleeding in NSAID users

The significance of the study

1. This study will provide the information about risk factors of NSAID-induced GI bleeding.
2. The generated equation will be beneficial for clinical practitioners in predicting the chance of NSAID-induced UGIB an determining pharmacotherapy plan for individual patient.

CHAPTER II

NSAID-INDUCED GASTROPATHY

Treatment with NSAIDs is associated with liability to peptic ulcer complications. Two studies in normal volunteers have examined the effects of NSAIDs compared with placebo, after one week or longer.[27,28] The studies found that NSAIDs can produce significant changes in the gastroduodenal mucosa following only seven days of therapy. These changes varied from scattered submucosal hemorrhage to ulceration. Later, these patients are more likely to develop a GI complication. The increased rates of complication associated with use of NSAIDs are similar for gastric and duodenal ulcers.[20,29,30] Several studies have revealed that patients taking NSAIDs have three to four times the risk of UGIB of a non-user.[18,20,29]

Regarding other causes of UGIB, many diseases are related to peptic ulcer bleeding, such as esophageal and/or gastric varices, portal hypertensive gastropathy, Mallory-Weiss tears, gastric cancer, polyp, pancreatic pseudocyst, and arteriovenous malformations.[31,32] In addition, patients with serious trauma, burns, and severe medical problems (coagulopathy, ventilator dependency) are associated with a predisposition for peptic ulcer bleeding.[33,34]

The Mechanism of NSAID-Induced Gastropathy

According to the dual-injury hypothesis of Schoen and Vender, NSAID-induced gastric damage is mediated by two components: (1) The direct effects of the acidic drug on membrane permeability and (2) drug-related effects on prostaglandin production. (Figure 2.1) Aspirin and most NSAIDs are weak organic acids.[35] These agents damage the gastric mucosal barrier by altering cell membrane permeability, allowing “Back diffusion” of hydrogen ion.

In the strong acid environment of normal gastric juice, NSAIDs are mostly non-ionized. An undissociated acid freely diffuse into the mucosal cell. Weak organic acids are concentrated in the mucosal cell as a result of “Ion trapping”. Once inside the cell, the much higher pH of the intracellular environment favors acid dissociation. In this ionized state, aspirin and other NSAIDs are water soluble and “Trapped” inside the cell.

The rapid absorption of aspirin is associated with abnormal ion fluxes across the mucosa. Sodium and potassium enter the luminal fluid, and hydrogen ion disappears from the lumen into the mucosa. Back diffusion of hydrogen ion leads to mucosal damage, including erosion and bleeding. (Figure 2.2)

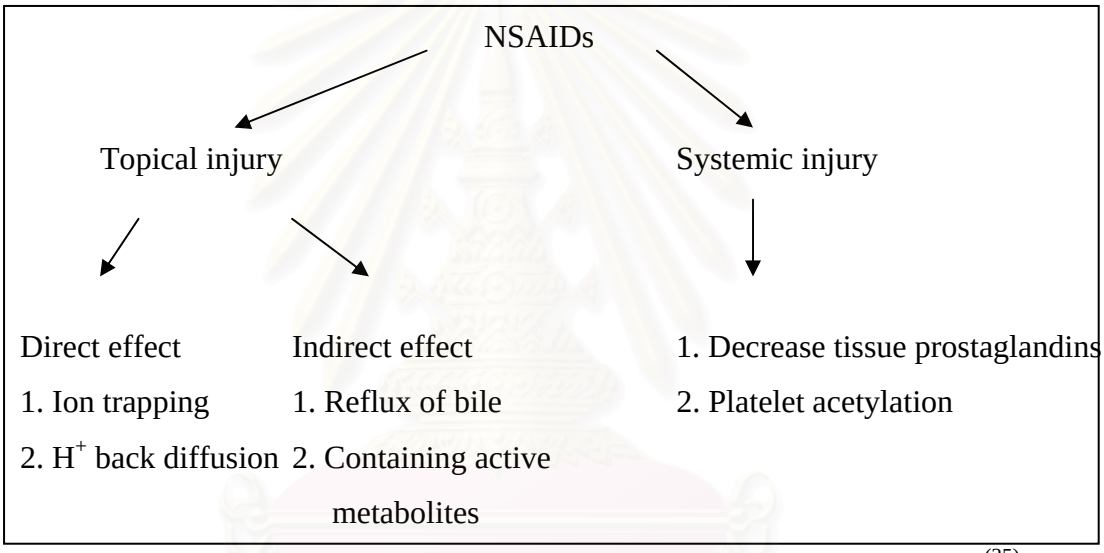

Figure 2.1 Mechanisms of NSAID-induced gastroduodenal mucosal damage[35]

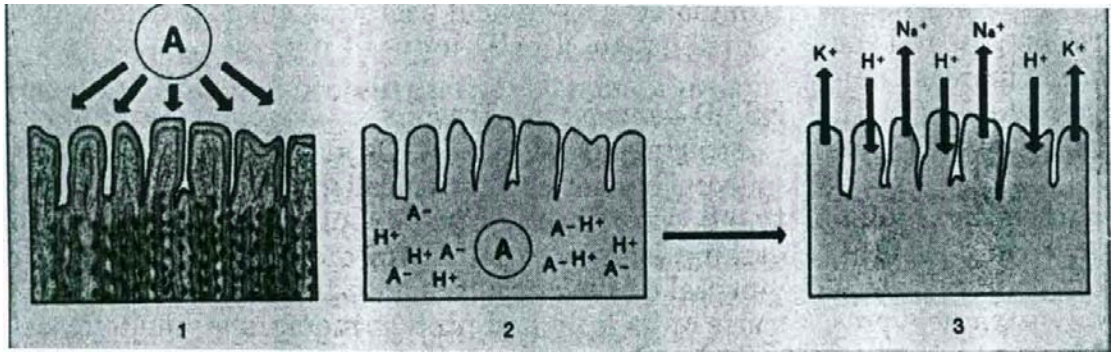

Figure 2.2 Aspirin-induced back diffusion. (1) Absorption of weak organic acids followed by ionization and entrapment (2) of aspirin is associated with abnormal ion flux across the gastric mucosa (3) Back diffusion of hydrogen ion from the lumen leads to gastric erosion and bleeding[35]

The systemic effects of NSAIDs have been shown to involve decreased mucosal synthesis of various prostaglandins through the inhibition of the enzyme cyclooxygenase.[17] (Figure 2.3) Prostaglandin inhibition leads to decrease in epithelial mucus, secretion of bicarbonate, mucosal bleed flow and gastric secretion.[17]

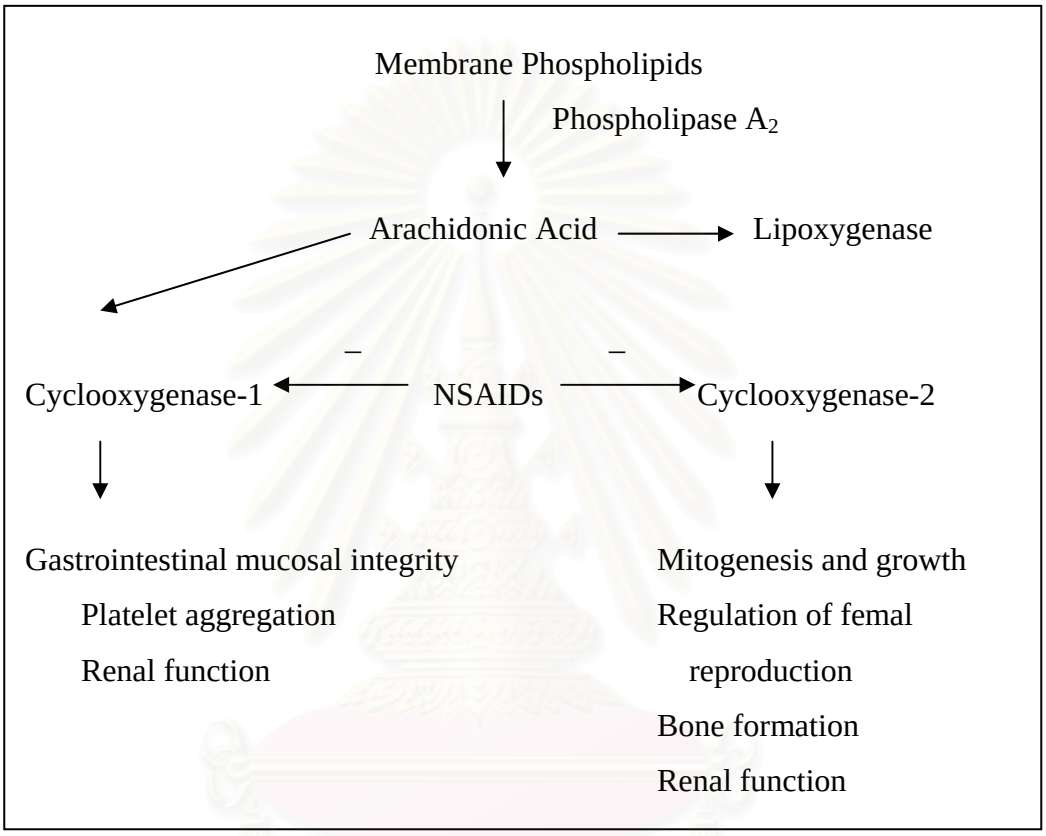

Figure 2.3 Biosynthesis of prostaglandins through the cyclooxygenase pathways[17]

CHAPTER III

RISK FACTORS FOR NSAID-ASSOCIATED UGIB

Many studies have established the association between use of NSAIDs and risk factors of increased peptic ulcer bleeding.[21,23,29,36,37] (Table 3.1)

Table 3.1 Risk factors for the development of NSAID-induced UGIB[21,23,29,36,37]

Established risk factors
Advanced age (Linear increase in risk)
History of dyspepsia, ulcer, and peptic ulcer bleeding
Higher dose of NSAIDs , including the use of more than one NSAID
Concomitant use of corticosteroids and anticoagulants
Possible risk factors
Concomitant infection with *Helicobacter pylori*
Cigarette smoking
Consumption of alcohol

Age and Gender

There are epidemiological data suggesting that advancing age and gender are an independent risk factor for NSAID complication.[29] Gender is weak the risk of UGIB. The studies are inconsistent about whether gender related with the risk of UGIB. Hernandez-Diaz and Garcia-Rodriguez (2000) and Garcia-Rodriguez et al. (1998) reported that male and female ratio of bleeding risk were 2.1:1 and 2.6:1, respectively.[19,21] However, the impact of NSAIDs on the risk of UGIB was greater in women (RR=5.1;95%CI:4.6-5.7) than in men (RR=3.5;95%CI:3.1-4.0).[19] Some studies found that both male and female did not increase risk of UGIB (M:F=1:0.9,1:0.5, respectively).[23,29]

Age is strong the risk of UGIB. Advanced age has been consistently found to be a primary risk factor for adverse gastrointestinal events. Several studies have shown that the risk of UGIB increases linearly with age.[21,23,29] Thus, the older

patients are the greater the risk of a GI complication is. Nonsteroidal anti-inflammatory drug use was associated with an increased risk across all age groups with a slight elevation in relative risk (RR) with age.[19] (Table 3.2)

Table 3.2 Relative risks of age for UGIB related to NSAID users and nonusers[19]

Age (years)	NSAID users RR (95%CI)	Age (years)	Nonusers RR (95%CI)
25-49	-	25-49	Reference
50-59	-	50-59	1.8(1.5-2.1)
<65	3.8(3.3-4.3)	60-69	2.4(2.2-2.7)
65-74	3.9(3.6-4.3)	70-80	4.5(4.0-4.9)
75-84	4.5(3.8-5.3)	>80	9.2(7.6-11.1)
>84	4.8(4.0-5.7)	-	-

History of Peptic Ulcer Disease

The second most important independent risk factor for a NSAID-induced GI complication is a history of prior peptic ulcer disease. A history of peptic ulcer disease increases the risk of an ulcer complication in the patients not taking NSAIDs.[20,28,35] (Table 3.3) Therefore, NSAID use in patients with history of peptic ulceration, hemorrhage, or dyspepsia has been associated with a higher risk of UGIB, than in patients without such a history.[22] Because the patients are high baseline risk. In two studies, the patients who both used NSAIDs and had a history of PUD had a risk of peptic ulcer complication that was 2 to 3 times greater than that in patients who had neither of these factors.[21,29] (Table 3.4)

Table 3.3 Relative risks of UGIB associated with ulcer history

Ulcer history	RR(95%CI)		
	Hernandez-Diaz and Garcia-Rodriguez (2001)	Garcia-Rodriguez et al. (1998)	Garcia-Rodriguez and Jick (1994)
No	Reference	Reference	Reference
Dyspepsia	1.9(1.6-2.2)	3.7(3.2-4.2)	2.9(2.4-3.6)
Gastritis	2.6(2.0-3.3)	-	-
Uncomplicated ulcer	5.6(4.7-6.7)	5.3(4.2-6.7)	6.1(5.1-7.3)
Complicated ulcer	9.8(7.7-12.4)	19.7(13.9-18.1)	13.5(10.3-17.7)

Table 3.4 Relative risks of prior ulcer for UGIB associated with NSAIDs

Prior ulcer	RR(95%CI)	
	Garcia-Rodriguez et al. (1998)	Garcia-Rodriguez and Jick (1994)
No history of ulcer	6.1(5.0-7.5)	5.4(4.4-6.8)
History of ulcer	12.5(9.5-16.4)	17.2(10.0-29.6)

Dose and Type of NSAIDs

The relative risk associated with NSAIDs current single use was significantly higher among patient taking high dose than among those taking low dose. Many case-control studies have shown that as the dose of NSAIDs increases, the risk of a complication increases proportionally from two- to three-folds for patients using lower or medium dose to greater than six-folds for patients on high-dose NSAIDs.[10,19,21,29] (Table 3.5)

Table 3.5 NSAID users taking high daily doses had a risk greater than that in persons using low through medium dose

Daily doses	RR(95%CI)			OR(95%CI)
	Hernandez-Diaz and Garcia-Rodriguez (2000)	Garcia-Rodriguez et al. (1998)	Garcia-Rodriguez and Jick (1994)	Langman et al. (1994)
Nonuse	-	Reference	Reference	-
Low	3.0(2.6-3.4)	3.9(3.0-5.1)*	2.6(1.8-3.8)**	2.5(1.7-3.8)
Medium	4.1(3.6-4.5)	-	-	4.5(3.6-6.0)
High	6.9(5.8-8.1)	9.8(6.4-14.9)	7.0(5.2-9.6)	8.6(5.8-12.6)

* Diclofenac ≤ 75 mg/d, Naproxen ≤ 500 mg/d, Tenoxicam ≤ 20 mg/d, Nimesulide ≤100 mg/d, Piroxicam ≤ 20 mg/d

** Ibuprofen ≤ 1500 mg/d, Diclofenac ≤ 100 mg/d, Naproxen ≤ 750 mg/d, Indomethacin ≤ 75 mg/d

The risk of UGIB among individual NSAIDs showed marked differences. In a comparison of individual NSAIDs, ibuprofen was associated with the lowest risk of bleeding peptic ulcer, where as piroxicam were found to be the most GI complication.[3,5,10,19,21,29] (Table 3.6) The concomitant use of more than one NSAID more than doubled the risk of a complication.[21,29]

Table 3.6 Relative risks of UGIB related to individual NSAIDs

NSAIDs	RR(95%CI)		
	Hernandez-Diaz and Garcia-Rodriguez (2000)	Garcia-Rodriguez et al. (1998)	Garcia-Rodriguez and Jick (1994)
Nonuse	Reference	Reference	Reference
Ibuprofen	1.9(1.6-2.2)	2.1(0.6-7.1)	2.9(1.7-5.0)
Diclofenac	3.3(2.8-3.9)	2.7(1.5-4.8)	3.9(2.3-6.5)
Sulindac	3.6(2.8-4.7)	-	-
Naproxen	4.0(3.5-4.6)	4.3(1.6-11.2)	3.1(1.7-5.9)
Ketoprofen	4.6(3.3-6.4)	3.2(0.9-11.9)	5.4(2.6-11.3)
Indomethacin	4.6(3.8-5.5)	5.5(1.6-18.9)	6.3(3.3-12.2)
Piroxicam	6.3(5.5-7.2)	9.5(6.5-13.8)	18.0(8.2-39.6)
Tenoxicam	-	4.3(1.9-9.7)	-
Nimesulide	-	4.4(2.5-7.7)	-

Table 3.7 Relative risks of UGIB associated with individual NSAIDs by daily dose

Dose of NSAIDs (mg/d)	RR(95%CI)		
	Garcia-Rodriguez et al. (1998)*	Hernandez-Diaz and Garcia-Rodriguez (2000)**	Garcia-Rodriguez and Jick (1994)
Ibuprofen	-		
≤ 1500		2.1(1.6-2.7)	2.1(1.1-4.1)
>1500		5.5(3.0-10.0)	6.5(2.6-16.4)
Diclofenac			
≤ 75	1.6(0.6-4.5)	3.1(2.0-4.7)	4.1(2.2-7.6)[a]
>75	4.0(2.0-8.1)	3.6(2.3-5.6)	3.4(1.4-8.5)[b]
Naproxen			
≤ 500	3.2(0.9-10.9)	3.5(2.8-4.3)	4.0(1.3-11.8)[c]
>500	8.3(1.6-42.4)	5.1(3.8-6.9)	3.1(1.4-6.6)[d]
Indomethacin	-		
≤ 75		3.0(2.2-4.2)	1.4(0.3-5.8)
>75		6.5(4.8-8.6)	14.4(5.7-36.4)
Piroxicam			-
≤ 20	8.8(5.9-12.9)	5.6(4.7-6.7)	
>20	90.5(10.3-794)	6.2(4.4-8.7)	
Tenoxicam		-	-
≤ 20	3.4(1.4-8.3)		
> 20	45.1(3.5-582)		
Nimesulide		-	-
≤ 100	2.9(1.5-5.7)		
> 100	58.1(10.6-318)		

* Daily dose among individual NSAIDs with 5 or more cases exposed over all

** Ibuprofen ≤ 1500 mg/d or 2400 mg/d, Diclofenac ≤ 75 mg/d or 100 mg/d, Naproxen ≤ 500 mg/d or 750 mg/d or 1000 mg/d, Indomethacin ≤ 75 mg/d or 100 mg/d

(a) Diclofenac ≤ 100 mg/d (b) Diclofenac > 100 mg/d

(c) Naproxen ≤ 750 mg/d (d) Naproxen > 750 mg/d

Duration of NSAID Use

NSAID use increased the risk of UGIB among new users and among those already on therapy for several months, at least during the first year of treatment. The

earlier studies suggested that the risk of UGIB was higher among persons who had just started treatment.[3] Gabriel, Jaakkimainen and Bombardier (1991) found that patients using NSAIDs between 1 and 30 days increased the risk of GI bleeding by 8 folds.[3]

More recent studies have shown that the risk of UGIB associated with current NSAID use is maintained relatively constant even after many months of continuous treatment.[19,21] Garcia-Rodriguez et al. (1998) and Hernandez-Diaz and Garcia-Rodriguez (2000) revealed that relative risk of UGIB was 4-6 times for patients taking NSAIDs between 3 months to 1 year, compared with nonusers.[19,21] Duration of NSAID use within 1 month is highest risk of UGIB.[3,19,21] (Table 3.8)

Table 3.8 The risks of UGIB related with duration of current NSAID use

Duration (days)	RR(95%CI)		OR(95%CI)
	Hernandez-Diaz and Garcia-Rodriguez (2000)	Garcia-Rodriguez et al. (1998)	Gabriel, Taakkimainen and Bombardier (1991)
None	Reference	Reference	Reference
1-30	5.7(4.9-6.6)	6.9(5.3-9.1)	8.00(6.37-10.06)
31-90	3.7(3.2-4.2)	5.3(3.8-7.6)	3.31(2.27-4.82)
91-180	4.1(3.5-4.7)		1.92(1.19-3.13)
181-365	5.1(3.9-6.5)	6.9(4.3-11.0)	
>365	-	3.5(2.0-6.0)	

Concomitant Medications

1. **Oral Corticosteroids**

Many studies have reported that the patients taking corticosteroids alone and patients receiving the combination use of NSAIDs and corticosteroids are inconsistent the risk of UGIB. Corticosteroids alone have not been demonstrated to increase the risk of ulcer development or bleeding.[21,24,36] (Table 3.9)

Table 3.9 Relative risks for UGIB and peptic ulcer disease among users of oral corticosteroids

Corticosteroids	RR(95%CI)		
	UGIB		PUD
	Hernandez-Diaz and Garcia-Rodriguez (2001)*	Garcia-Rodriguez et al. (1998)	Piper et al. (1991)**
None	Reference	Reference	Reference
Current	1.6(1.2-2.2)	1.4(0.7-2.8)	1.1(0.5-2.1)
Recent	1.4(1.0-2.0)	-	1.9(1.0-3.4)
Past	0.8(0.7-1.0)	-	1.2(0.7-2.0)

* None: No corticosteroids use in the 180 days before the index date
Current: Corticosteroids use between 0 and 30 days before the index date
Recent: Corticosteroids use between 31 and 90 days before the index date
Past: Corticosteroids use between 91 and 180 days before the index date

** None: No corticosteroids use in the 365 days before the index date
Current: Corticosteroids use between 1 and 90 days before the index date
Recent: Corticosteroids use between 91 and 150 days before the index date
Past: Corticosteroids use between 151 and 364 days before the index date

However, Weil et al. (2000) reported that the risk of UGIB was 9 times for NSAID users taking corticosteroids, compared with nonusers.[37] The meta-analysis study by Gabriel, Taakkimainen and Bombardier (1991) have shown that the combination use of NSAIDs and corticosteroids is an approximately two-folds increase in the relative risk of GI complication.[3] Piper et al. (1991) found that odds ratio of ulcer hemorrhage for NSAID users receiving concomitant corticosteroids was 10.6.[24]

2. **Aspirin**

Users of low-dose aspirin (325 mg daily or less) are at two-folds increased risk of UGIB.[38,39] (Table 3.10) As Cullen et al. (1997) found that odds ratio of peptic ulcer bleeding was 2.6 (95%CI: 1.2-5.7) for current users of aspirin, compared with

nonusers.[40] This is consistent with previous studies by Holvoet et al. (1991) and Gabriel et al. (1991).[3,30] (Table 3.11) In the combination use of low-dose aspirin and NSAIDs, Henry, Dobson and Turner (1993) reported that odds ratio of GI bleeding was 6.7 (95%CI:4.3-10.4).[38]

Table 3.10 Relative risks of UGIB event in patients taking aspirin

Aspirin use	RR(95%CI)	
	Hernandez-Diaz and Garcia-Rodriguez (2001)*	Garcia-Rodriguez et al. (1998)
None	Reference	Reference
Current	1.9(1.0-2.3)	2.3(1.7-3.2)
Recent	1.8(1.2-2.7)	-
Past	1.2(0.9-1.5)	-

* None: No aspirin use more than 180 days before the index date
Current: Aspirin use between 0 and 30 days before the index date
Recent: Aspirin use between 31 and 90 days before the index date
Past: Aspirin use between 91 and 180 days before the index date

Table 3.11 The risks of UGIB associated with aspirin

Aspirin	RR(95%CI)	OR(95%CI)			
	Kaufman et al.(1993)**	Cullen et al.(1997)	Henry, Dobson and Turner (1993)*	Gabriel et al.(1991)	Holvoet et al.(1991)
Nonuse	Reference	Reference	Reference	Reference	Reference
Use	3.1(1.4-7.0)	2.6(1.2-5.7)	3.0(2.2-4.0)	3.38(2.26-2.01)	2.2(1.3-4.0)

* Dose ≤ 150 mg/d

** Dose ≤ 325 mg/d

3. **Anticoagulants**

Concomitant anticoagulants use increases the risk of peptic ulcer bleeding in the setting of NSAID therapy. The increase in risk ranges from 2- to 6-folds, depending upon the patient population studied.[21,29,36,41] (Table 3.12) Shorr et al.

(1993) found that relative risk of UGIB was 12.7 (95%CI:6.3-25.7) when NSAID users receiving concomitant anticoagulants were compared with nonusers.[41]

Table 3.12 Relative risks of UGIB related to anticoagulants

Anticoagulants	RR(95%CI)			
	Hernandez-Diaz and Garcia-Rodriguez (2001)*	Garcia-Rodriguez et al. (1998)	Garcia-Rodriguez and Jick (1994)	Shorr et al.(1993)**
None	Reference	Reference	Reference	Reference
Current	2.9(2.1-4.1)	2.2(1.4-3.4)	6.4(2.8-14.6)	4.3(2.6-7.2)
Recent	1.7(0.7-4.4)	-	-	-
Past	1.2(0.7-2.0)	-	-	-

* None: No anticoagulants use more than 180 days before the index date
Current: anticoagulants use between 0 and 30 days before the index date
Recent: anticoagulants use between 31 and 90 days before the index date
Past: anticoagulants use between 91 and 180 days before the index date

** Current: anticoagulants use between 1 and 60 days before the index date

Helicobacter pylori

The studies are inconsistent about whether *H. pylori* increase the risk of NSAID ulcer complication. Several studies have revealed that both *H. pylori* infection and NSAIDs independently increase the risk of peptic ulcer bleeding.[40,42-45] The risk for UGIB associated with *H. pylori* infection was three-folds. However, two studies showed that NSAID intake led to an increased risk of bleeding in patients with *H. pylori*-related peptic ulcer diseases.[42,46] In contrast, other studies have shown that both *H. pylori* infection and NSAIDs do not additive the risk of peptic ulcer bleeding.[22,40,45] (Table 3.13)

Table 3.13 The risks of UGIB related to H. pylori infection

H. pylori	RR(95%CI)	OR(95%CI)			
	Hawkey et al.(1997)	Cullen et al.(1997)	Labenz et al.(1997)	Hsu et al.(2000)	Aalykke et al.(1999)
None	Reference	Reference	Reference	Reference	Reference
Alone	3.3(1.7-6.4)	2.8(1.1-7.2)	3.4(1.4-8.7)	-	-
HP*+NSAIDs	13.3(4.4-40.0)	2.0(0.9-4.4)	2.4(0.9-6.4)	5.4(1.4-20.9)	1.8(1.0-3.2)

* HP = *H. pylori*

CLO® test has false negative of *H. pylori* infection in bleeding patients. Recently, rapid urease test (CLO® test) is commonly used in many hospitals. This test gives a relatively quick diagnosis, and is less expensive than other invasive diagnostic techniques (histology and culture). However, the sensitivity and negative predictive value of the CLO® test are lower in patients presenting with bleeding.[47,48] Lee et al. (2000) showed that false-negative rate of CLO® test was 25% in these patients.[48] In addition, false-negative result is found in patients taking acid-suppression drugs, antibiotics, and bismuth-containing compound within 7-14 days before test.

H. pylori diagnosis should be used at least 2 tests in bleeding patients. Thus the combination use of CLO® test and serology test, urea breath test, histology test, or culture should be selected in bleeding patients. Because serology test has sensitivity values more than 90% in bleeding patients.[47] Similarly, the urea breath test was recently reported by Tu et al. (1999) to have a sensitivity value of 95.4% for *H. pylori* test in patient with bleeding peptic ulcer disease.[47] Histology is recommended to use particularly in negative results of rapid urease test.[50]

Cigarette smoking and alcohol consumption

Reported from different studies are inconsistent about whether alcohol increases the risk of NSAID ulcer complications. Alcohol has been shown to be a moderate risk factor for complicated peptic ulcer disease, with up to two-folds increases in relative risk for heavy drinkers (greater than 35 units/week or 21

units/week).[51,52] (Table 3.14) Case-control study suggested that alcohol consumption (more than 5 units/week) increased peptic ulcer bleeding (OR=2.8;95%CI:1.9-4.0).[38] In contrast, Weil et al. (2000) found that drinker consumed more than 7 units per week did not increased risk of UGIB (OR=1.20;95%CI:0.88-1.79).[37] NSAID users with alcohol consumption are associated with higher odds ratio (alcohol was consumed more than 5 units/wk).[22,38] (Table 3.15)

Table 3.14 The relative risks of GI complication associated with alcohol consumption

Alcohol (Units/wk*)	RR(95%CI)	
	Kaufman et al.(1999)	Kelly et al.(1995)
<1	Reference	Reference
1-6	0.9(0.8-1.2)	0.8(0.7-1.0)
7-13	1.3(1.0-1.7)	1.4(1.0-1.8)
14-20	1.4(1.0-2.0)	1.2(0.8-1.7)
>20	2.8(2.0-3.9)	1.4(0.9-2.2)
28-34**	-	2.8(1.4-5.8)
≥35	-	6.3(3.5-11.0)
Ex-drinker**	1.3(1.0-1.7)	1.6(1.1-2.2)

* 1 unit = 1.5 ounces of liquor or 4 ounces of wine or 12 ounces of beer

** Stopped drinking ≥ 1 month ago

Table 3.15 Odds ratio of NSAID-induced UGIB related with alcohol consumption

Alcohol (>5 units/wk)	OR(95%CI)	
	Aalykke et al.(1999)	Henry, Dobson and Turner (1993)
None	Reference	Reference
Alcohol plus NSAIDs	6.0(3.3-11.0)	2.39(1.16-4.89)

The relationship between NSAID users with cigarette smoking and UGIB has been found to be inconsistent.[22,37] Two studies have shown that smoking is a weak

risk factor for peptic ulcer bleeding.[36,37] (Table 3.16) As Weil et al. (2000) reported that odds ratio of UGIB was 4.0 (95%CI:2.9-5.5) in NSAID users with smoking.[37] In contrast, Aalykke et al. (1999) showed an odds ratio of 0.91 (95%CI:0.48-1.71).[22]

Table 3.16 The risks of peptic ulcer bleeding in smoker

Smoking	Hernandez-Diaz and Garcia-Rodriguez (2001)*	Weil et al.(2000)
	RR(95%CI)	OR(95%CI)
None	Reference	Reference
Current*	1.6(1.4-1.8)	1.6(1.2-2.0)
Ex-smoker**	1.3(1.1-1.5)	-

* Defined by at least one cigarette a day

** Stopped smoking ≥ 1 month ago

Other Risk Factors

History of Heart Disease

A large prospective study suggested that a history of heart disease increased the risk of gastrointestinal bleeding (OR=1.84;95%CI:1.07-3.15).[53]

Indications

There was no statistically significant differences in the relative risk of UGIB among patients with OA, RA, or pain when they were taking NSAIDs.[36] (Table 3.17) Therefore, the risk of peptic ulcer bleeding related with NSAIDs was independent of treatment indications.

Table 3.17 The risks of UGIB associated with NSAID indications

Indications	RR(95%CI)
Osteoarthritis	Reference
Rheumatoid arthritis	1.1(0.7-1.8)
Pain-related indication	1.0(0.7-1.3)

Antiulceration Drugs

In NSAID cohort study the risk of UGIB in patients receiving antiulceration drugs was higher than in nonusers.[23] MacDonald et al. (1997) found that relative risk of bleeding patients who used an antiulceration drug was 1.54 (95%CI:1.24-1.90).[23] Similarly, Garcia-Rodriguez et al. (1998) showed that NSAID users who received acid-suppressing drug and/or hospitalization for ulcer disease were 2.3 (95%CI:1.7-3.1) of relative risk of bleeding peptic ulcer.[21]

CHAPTER IV

PATIENTS & METHODS

Patients

Study Population

This case-control study was conducted in King Chulalongkorn Memorial Hospital, between July 1, 2001, and January 31, 2002. Inpatients and outpatients were enrolled in this study.

Inclusion Criteria

The patients who had all of these characteristics were enrolled in this study.

1. NSAID use (including aspirin), defined as at least three days use[54] before the day of endoscopic examination
2. Endoscopy-verified peptic ulcer or hemorrhagic gastritis
3. Age more than eighteen years old

The enrolled patients were separated into 2 groups: case and control. Case patients are defined as patients with signs of UGIB. Signs of UGIB are defined as melena, hematemesis, anemia (decreased in the hematocrit level of 5% or more compared with one month before peptic ulcer bleeding) or positive of stool occult blood. Control patients are defined as patients without signs of UGIB.

Case and control patients were matched at least two of the following criteria[21,23,29,36,37]

1. Pattern of NSAID use (defined as current NSAID use, single NSAID use, regular NSAID use, low dose of NSAID use, and duration of NSAID use)
2. Sex
3. Underlying diseases

4. Antiulceration drugs

Exclusion Criteria

The patients who had either one of these characteristics were excluded from this study.[31,32]

1. Gastric or duodenal cancer
2. Coagulopathy
3. Esophageal or gastric varices
4. Mallory-Weiss syndrome
5. Chronic renal failure

In addition, patients were excluded for reasons related to a predisposition for UGIB, including mechanical ventilation, burns, and major operation.[33,34] The patients of 184 were recruited for this study.

Methods

The Data Collections of The Risk Factors of UGIB

The risk factors of UGIB were collected from interview and patient charts. (Appendix A, B) The risk factors of UGIB are defined as age, a history of peptic ulcer, a history of GI complication, history of dyspeptic symptoms, pattern of NSAID use, smoking habits, alcohol consumption, the combination use of NSAIDs and/or oral corticosteroids and/or anticoagulants, *H. pylori*, and antiulceration drugs.

The case and control patients were interviewed by the same researcher using a structured questionnaire. The questionnaire covered the risk factors of UGIB and demographic data. Medication samples were used for identification of patients taking NSAIDs. (Appendix C) According to *H. pylori* status, a patient was considered infection of *H. pylori* by using the CLO® test or serological test. Informed consent to study participation was obtained before study enrollment.

The Process of Model Building

The dependence variables in the study that were dichotomous variables include bleeding events and non-bleeding events. The independence variables were continuous variables of age and dummy variables of history of dyspeptic symptoms (0= no history, 1= had a history), current NSAID use (0= past NSAID use, 1= current NSAID use), multiple NSAID use (0= single NSAID use, 1= multiple NSAID use), regular NSAID use (0= occasional NSAID use, 1= regular NSAID use), dose of NSAID use (0= low dose, 1= high dose), duration of NSAID use within 1 month (0= NSAID were used more than 1 month, 1= NSAID were used within 1 month), combination use of NSAIDs and corticosteroids (0= no combination use, 1= combination use), cigarette smoking (0= nonsmoker, 1= smoker), *H. pylori* infection (0= no *H. pylori* infection, 1= *H. pylori* infection), and antiulceration drug use (0= nonuser, 1= user).

In order to generate an equation for prediction of the probability of UGIB in NSAID users, the process of model building had several steps as followed[55]

1. Select risk factors for univariable analysis. Some risk factor whose univariable test has a *p*-value < 0.05 is a main effects of the model.
2. Check confounding factors between two risk factors. The risk factors are confounding factors, when the value of ORs of main effects are changed and the value of –2 log likelihood (-2LL) decreases compared with univariable analysis (difference significant by χ^2-test). All confounding factors are included in the model.
3. Check interactions between two risk factors. Interactions are defined as the effect of one of the variables is not constant over levels of the other. The two risk factors have interaction, when the interaction of two risk factors decreases the value of –2LL of the model (difference significant by χ^2-test) and has a *p*-value < 0.05. All the interactions of risk factors are included in the model.
4. Then, each risk factor is selected in the model and the risk factors which decreased the value of –2LL of the model (difference significant by χ^2-test), are included in the model.

5. Finally, select all risk factors from 1 to 4 steps for multivariable analysis by using enters logistic regression.

Definitions of data collection

Index Date

The index date was defined as the day of endoscopic examination.

Pattern of NSAID Use

NSAID use was defined as three categories of use as followed[3,21]

1. Current use was defined that the patients took NSAIDs between 1 and 30 days before the index date.
2. Past use was defined that the patients took NSAIDs between 31 and 90 days before the index date.
3. Nonuse was defined that the patients took NSAIDs more than 90 days before the index date or no NSAID use.

Single NSAID user was defined as a person taking one NSAID. Multiple NSAID user was defined as a person taking more than one NSAID.

Duration of NSAID use was defined as the number of consecutive days of NSAID use among current use.

Regular NSAID use was defined as the patients took NSAIDs every day. Occasional NSAID use was defined as the patients took NSAIDs less than 3 days/wk.

Concomitant Medications

Concomitant medications were defined as the combination use of NSAIDs and oral corticosteroids and/or anticoagulants or other medications involved UGIB.[24,37,41]

Concomitant medications were defined as three categories of use as followed[30,37]

1. Current use was defined that the patients took concomitant medications between 1 and 7 days before the index date.
2. Past use was defined that the patients took concomitant medications between 8 and 90 days before the index date.
3. Nonuse was defined that there was no combination use of NSAIDs and concomitant medication use more than 90 days before the index date.

Ulcer History

Ulcer history was defined as three categories as followed[56]

1. The patient having history of dyspeptic symptoms was defined as the patients reported dyspeptic symptoms or physician recorded dyspeptic symptoms within 6 months before the index date.
2. The patient having a history of peptic ulcer disease was defined that were confirmed by endoscopic examination within 6 months before the index date.
3. Gastrointestinal complications were defined as UGIB and perforation. The patient having a history of ulcer bleeding was defined as patient with hematemesis, melena, or both associated with peptic ulcer within 6 months before the index date. The patient having perforation was defined as the patients reported perforation or physician recorded perforation within 6 months before the index date.

Antiulceration Drugs

Antiulceration drugs were defined as histamine$_2$-blockers (H_2-blockers) and proton pump inhibitors (PPIs). Antiulceration drug use was defined as the patients received these medications within 7 days before the index date.

Alcohol Consumption

Alcohol-drinking habits were examined according to level of consumption, measured in unit per week. Alcohol consumption was defined as alcohol drinking at least one unit per week. One unit was defined as equivalent to 45ml of liquor, 120 ml of wine, or 360 ml of beer.[51]

Alcohol consumption was defined as three categories of use as followed[51,52]

1. Current consumption was defined that the patients drank alcohol within the previous month before the index date.
2. Past consumption was defined that the patients drank alcohol more than one month before the index date.
3. Non-consumption was defined that the patients did not consume alcohol before the index date.

Level of alcohol consumption was defined as three categories as followed[51,52]

1. Mild alcohol consumption was defined as 1 to 6 units/week of alcohol drinking.
2. Moderate alcohol consumption was defined that the patients consumed alcohol more than 6 to 20 units/week.
3. Heavy alcohol consumption was defined that the patients consumed alcohol more than 20 units/week.

Cigarette Smoking

Smoking was defined as smoke at least one cigarette per day.[37]

Cigarette smoking was defined as three categories as followed[37]

1. Current smoking was defined as smoking within one month before index date.
2. Past smoking was defined that the patients smoked cigarette more than one month before the index date.
3. Non-smoking was defined that the patients did not smoke cigarette before the index date.

Statistical Analysis

The demographic data were analyzed by independence *t*-test and χ^2-test. The building model of the prediction of UGIB in NSAID users was used enter logistic regression in SPSS for Windows version 9.0 and χ^2-test.

CHAPTER V

RESULTS

Of 184 patients considered for inclusion in the study, 30 patients were excluded because they had a history of GI cancer (7), GI varices (14), chronic renal failure (6), and diverticulum (3). Of the remaining 154 NSAID users, 71 (46.1%) were men and 83 (53.9%) were women. Mean age (SD) of this group of patients was 60.9 (12.6) years (range: 25-87). There were 89 (57.8%) patients with UGIB and 65 (42.2%) patients who had dyspepsia without bleeding. Reasons for hospital admission are various among UGIB patients, 8 patients (9.0%) presented with hematemesis, 41 patients (46.1%) with melena, 29 patients (32.6%) with both hematemesis and melena, 10 patients (11.2%) with anemia and 1 patient (1.1%) with positive of stool occult blood test. Regarding antecedent symptoms, 44.9% of the UGIB patients experienced the symptom at least 2 days before the bleeding. Most of past medical illness in the study population were cardiovascular diseases (42.9%) following by history of dyspeptic symptoms (25.3%) and bone and joint diseases (18.2%).

The number of patients who were current use (88.3%), single use (79.3%) and regular use (68.8%) was higher than past use (11.7%), multiple use (20.7%) and occasion use (32.5%), respectively. Individual NSAID uses are summarised in table 4.1. Most of the patients used low dose of NSAIDs (90.2%). Low dose is defined that aspirin dose ≤ 325 mg/d, ibuprofen dose ≤ 1200 mg/d, diclofenac dose ≤ 75 mg/d, indomethacin dose ≤ 100 mg/d, naproxen dose ≤ 750 mg/d, ketoprofen dose ≤ 100 mg/d, piroxicam dose ≤ 20 mg/d, mefenamic acid dose ≤ 1000 mg/d, sulindac dose ≤ 200 mg/d, and nabumetone dose ≤ 1000 mg/d.[10,19,21,29] Diclofenac was the most common drug usage (33.3%) followed by aspirin (30.9%) and indomethacin (18.2%).

One half of the patients used NSAIDs for more than 3 months. Thirty five percent of the patients had duration of NSAID use less than 1 month. Most of NSAID users did not receive concomitant corticosteroids and/or warfarin (72.7%). Among

NSAID users taking concomitant therapy, 39 (92.8%) of the patients used NSAIDs concomitantly with corticosteroids and 5 (11.9%) of the patients used NSAIDs with warfarin.

*Table 4.1 Individual NSAID use in the patients**

Type of NSAID use	Persons (%)
Diclofenac	42 (33.3%)
Aspirin	39 (30.9%)
Indomethacin	23 (18.2%)
Ibuprofen	18 (14.3%)
Piroxicam	17 (13.5%)
Mefenamic acid	6 (4.8%)
Ketoprofen	3 (2.4%)
Naproxen	3 (2.4%)
Sulindac	1 (0.8%)
Meloxicam	1 (0.8%)
Nimesulide	1 (0.8%)

*There is a patient who used more than one NSAID

Of 154 patients, 78 (56.5%) had *H. pylori* infection. Sixteen patients (less than 10.0%) drank alcohol. And 22 patients (less than 15.0%) smoked cigarette. Seventy four percent (114 patients) did not receive antiulceration drugs at the study time. Eighty percent (32 patients) of the patients who received antiulceration drugs used H_2-blockers (cimetidine and ranitidine) and the others took PPIs (omeprazole). The demographic characteristics of UGIB patients and control group patients ones with dyspeptic symptoms are shown in table 4.2.

Table 4.2 The demographic data of bleeding and non-bleeding patients

Characteristic data	Bleeding group	Non-bleeding group	*p*
Age*	62.7±13.3	58.6±11.1	**<0.05**
Sex**			0.051
Male	47 (52.8%)	24 (36.9%)	
Female	42 (47.2%)	41 (63.1%)	
Underlying diseases**			
Cardiovascular diseases	15 (16.9%)	23 (35.4%)	0.109
Bone and joint diseases	15 (16.9%)	13 (20.2%)	0.617
Diabetes Mellitus	14 (15.7%)	10 (15.4%)	0.953
Dyspeptic symptoms**	24 (27.0%)	15 (23.1%)	0.584
Pattern of NSAID use**			
- Current use	84 (94.4%)	52 (80.0%)	**<0.01**
Past use	5 (5.6%)	13 (20.0%)	
- Single NSAID use	49 (75.4%)	43 (84.3%)	0.239
Multiple NSAID use	16 (24.6%)	8 (15.7%)	
- Regular use	65 (73.0%)	41 (63.1%)	0.188
Occasional use	24 (27.0%)	24 (36.9%)	
Concomitant corticosteroids therapy**	27 (93.1%)	13 (20.0%)	0.094
*H. pylori***			0.120
Positive	53 (61.6%)	25 (48.1%)	
Negative	33 (38.4%)	27 (51.9%)	
Antiulceration drugs**	12 (13.5%)	28 (43.1%)	**<0.01**
H_2-blocker	12 (100.0%)	20 (71.4%)	
Proton pump inhibitors	0 (0.0%)	8 (28.6%)	

* = indepence *t*-test ** = χ^2-test

Bleeding patients were older than non-bleeding patients (difference significant by independence *t*- test). The sex distributions were similar in both groups (no difference by χ^2 test). However, the number of women in this study was higher in non-bleeding group. There was no significant difference of underlying diseases between case and control groups. The number of patients with history of dyspeptic symptoms was higher in UGIB group than in non-bleeding group. The incidence of UGIB was higher in group of patients with UGIB (6 patients, 6.7%) when compared with the group of non-bleeding (3 patients, 4.6%). Three patients

with non-bleeding group had a history of ulcer. None of patients with UGIB had a history of ulcer.

Regarding pattern of NSAID use, the number of current NSAID users was statistically significant differences between two groups. Type of NSAID use in both groups is presented in table 4.3.

*Table 4.3 Individual NSAID use in two groups**

Types of NSAID use	Bleeding group	Non-bleeding group
Aspirin	26 (36.1%)	13 (24.0%)
Diclofenac	23 (31.9%)	19 (35.2%)
Piroxicam	15 (20.8%	2 (3.7%)
Indomethacin	13 (18.1%)	10 (18.5%)
Ibuprofen	10 (13.9%)	8 (14.8%)

*There is a patient who used more than one NSAID

The number of combination use of NSAIDs and warfarin was lower in non-bleeding patients (one patient, 7.7%) than in patients with UGIB (4 patients, 13.8%). The incidence of *H. pylori* infection in UGIB patients was higher than in non-bleeding patients (no significant difference by χ^2-test). In this study, it was found that the number of patients with cigarette smoking was not different between two groups (p= 0.126). The number of patients with alcohol consumption (consumed ≥ 5U/wk) was higher in patients with UGIB (10 patients, 83.3%) than in non-bleeding patients (3 patients, 75.0%). The number of patients received antiulceration drugs was higher in non-bleeding patients (p< 0.01).

The incidence of gastric ulcer was higher than those of duodenal ulcer among NSAID users (46.8%, 22.1%, respectively). Approximately 65 percent of patients with ulcers had single ulcer. Most of gastric ulcer was found at antrum (83.1%). 81.1% of ulcer were small through large (gastric ulcer less than 3 cm., duodanal ulcer less than 2 cm.). Most of them (83.7% of ulcers) were at low risk of bleeding (defined as clean base, flat pigmented spot, and adherent clot).

Most of patients with GI bleeding had ulcers (89.9%), while patients in non-bleeding group had erosions, gastritis, and duodenitis (32.3%). (Table 4.4) 27.7% of non-bleeding patients had normal endoscopic finding. The incidence of multiple ulcers were higher in bleeding patients than in non-bleeding group (34.5% and 26.3%, respectively). Proportion of small through large and giant size of ulcers were the same in two groups. Ulcers of UGIB patients had higher risk of bleeding than ulcers of patients in non-bleeding group.

*Table 4.4 Endoscopic results in two groups**

Endoscopic results	Bleeding group	Non-bleeding group
Gastric ulcer	56 (62.9%)	16 (24.6%)
Number of ulcer		
Single ulcer	35 (62.5%)	12 (75.0%)
Multiple ulcer	21 (37.5%)	4 (25.0%)
Size of ulcer		
Not giant size	45 (80.4%)	14 (87.5%)
Giant size	11 (19.6%)	2 (12.55)
Citation of gastric ulcer		
Fundus	1 (1.8%)	2 (12.5%)
Body	9 (16.4%)	0 (0.0%)
Antrum	45 (81.8%)	14 (87.5%)
Duodenal ulcer	31 (34.8%)	3 (4.6%)
Number of ulcer		
Single ulcer	22 (71.0%)	2 (66.7%)
Multiple ulcer	9 (29.0%)	1 (33.3%)
Size of ulcer		
Not giant size	25 (80.6%)	2 (66.7%)
Giant size	6 (19.4%)	1 (33.3%)
Gastric erosion	21 (23.6%)	14 (21.5%)
Duodenal erosion	4 (4.5%)	0 (0.0%)
Gastritis/Duodenitis	18 (20.2%)	25 (38.5%)

*One patient had more than 1 results

Table 4.5 Univariable logistic regression models for prediction of UGIB event

Risk factors	Coeff.	SE.	OR	95%CI	*P*
Age	0.027	0.013	1.027	1.001-1.054	**<0.05**
Sex	0.648	0.333	1.912	0.995-3.674	0.052
History of dyspepsia	0.208	0.379	1.231	0.585-2.587	0.584
Current NSAID use	1.434	0.555	4.196	1.414-12.451	**0.01**
Multiple NSAID use	0.562	0.481	1.755	0.684-4.503	0.242
Regular NSAID use	0.461	0.351	1.585	0.797-3.153	0.189
Dose of NSAID use	0.474	0.642	1.606	0.457-5.650	0.460
Duration of NSAID use (within 1 month)	0.088	0.392	1.092	0.507-2.353	0.821
Duration of NSAID use (more than 3 months)	0.458	0.361	1.582	0.779-3.209	0.204
Concomitant corticosteroids therapy	0.654	0.394	1.923	0.888-4.163	0.097
Cigarette smoking	0.768	0.510	2.155	0.794-5.853	0.132
H. pylori infection	0.551	0.355	1.735	0.865-3.480	0.121
Antiulceration drugs	-1.580	0.399	0.206	0.094-0.450	**<0.01**

After data analysis by univariable logistic regression, main effects of the model were identified. Age, current NSAID use, and antiulceration drugs had *p* value less than 0.05. This finding implies that these 3 variables are main effects of the model for the prediction of the risk of UGIB in NSAID users. The next step is to examine multivariable relationships, enter logistic regression was obtained with the risk factors age, sex, current NSAID use, *H. pylori* infection, multiple NSAID use, and antiulceration drugs. Table 4.6 summarizes the results of enter logistic regression analysis using most of the risk factors. Both age and sex were confounding factors and they also had interaction of effects in the model. *H. pylori* infection and multiple NSAID usage were confounding factors. Thus age, sex, *H. pylori* infection, and multiple NSAID use were the next four variables stepped into the model. The results also cigarette smoking, a history of dyspepsia, and concomitant corticosteroids therapy were not confounding factors. So they were not included in the model.

Table 4.6 Results of fitting a multivariable model

Risk factors	Coeff.	SE.	OR	95%CI	*P*
Age	-0.000048	0.029	1.000	0.944-1.059	0.999
Sex	-8.533	2.909	0.0002	0.000-0.059	<0.01
Current NSAID use	0.344	0.888	1.411	0.248-8.040	0.698
Multiple NSAID use	2.087	0.747	8.058	1.863-34.864	<0.01
H. pylori infection	1.429	0.538	4.177	1.454-11.999	<0.01
Antiulceration drugs	-2.406	0.598	0.090	0.028-0.291	<0.01
Age x sex	0.118	0.045	1.125	1.030-1.229	<0.01
Constant	0.334	1.972	-	-	0.866

-2 log likelihood = 99.901 Overall percent correct = 80.19%

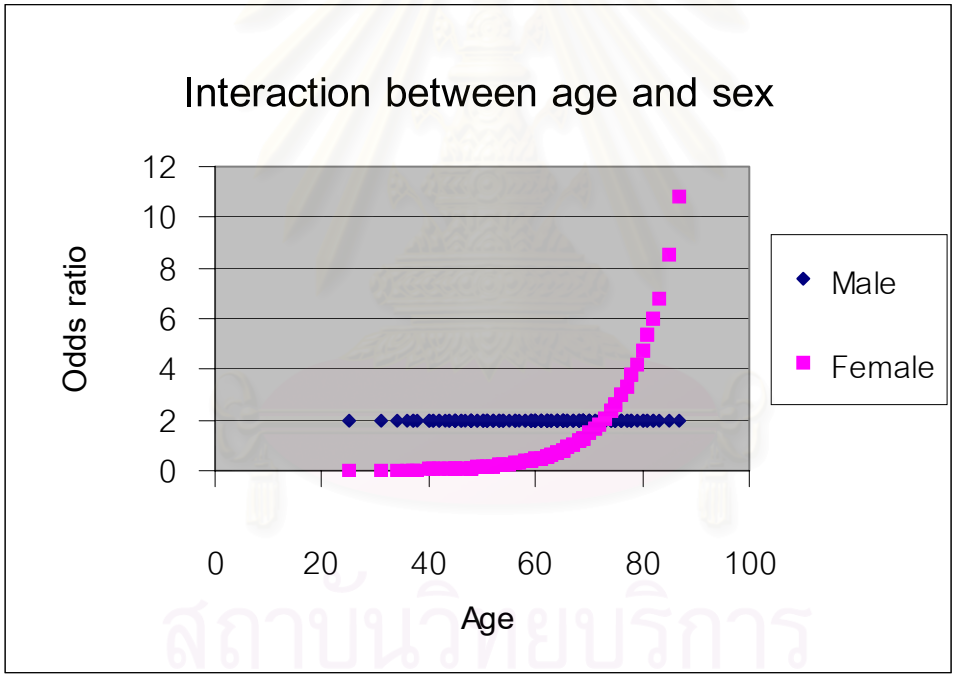

Figure 4.1 Odds ratio of the risk of UGIB event in NSAID users

To test the fitness of the various risk factors for prediction of probability of UGIB event in NSAID users, it was revealed that 99.901 of –2 log likelihood (-2LL), 80.19% of the overall rate of correct classification, 0.335 of R^2 of Cox and Snell, 0.452 of R^2 of Nagelkerke, and 4.583 of χ^2 of Hosmer and Lemeshow test (p= 0.801) were optimum fit of the model. The model of prediction for the risk of GI bleeding is shown in the equation.

Logit (UGIB) = 0.334-0.000048Age-8.533Sex+0.118(Age x Sex)
+0.344Current NSAID use+2.087Multiple NSAID use
+1.429*H. pylori* infection–2.406Antiulceration drugs ——(1)

Probability (UGIB) = $e^{\text{Logit (UGIB)}} / 1+e^{\text{Logit (UGIB)}}$ ——————————(2)

In order to use the equations, value of parameters in the equations were defined as followed. For sex, male is 0 and female is 1. For pattern of NSAID use, current NSAID use is 1, past NSAID use is 0, multiple NSAID use is 1, and single NSAID use is 0. For *H. pylori* infection, infection of *H. pylori* is 1 and non-*H. pylori* infection is 0. For antiulceration drug use, antilceration drug use is 1 and no antiulceration drug use is 0.

If the probability calculated by using equation (2) is more than 0.5, the patient is at a high risk of UGIB. How to use the equations for prediction of UGIB in NSAID users is shown in example (1). For ease of practical use, table 4.7 was developed by using the generated equations. And how to use of table 4.7 is shown in example (2).

Example (1) A 55 years old women who is taking diclofenac every day with no antiulceration drugs. She also had *H. pylori* infection. Her probability of UGIB is calculated as followed.

Logit (UGIB) = 0.334-0.000048Age-8.533Sex+0.118(Age x Sex)
+0.344CurrentNSAID use+2.087Multiple NSAID use
+1.429*H. pylori* infection–2.406Antiulceration drug

= 0.334-0.000048(55)-8.533(1) +0.118(55x1)+0.344(1)
+2.087(0)+1.429(1)-2.406(0)

= 0.061

Probability (UGIB) = $e^{\text{Logit (UGIB)}} / 1+e^{\text{Logit (UGIB)}}$

= $e^{(0.061)} / 1+e^{(0.061)}$

= 0.51

∴ The UGIB event may occur in this patient.

Table 4.7 The predictor of the probability of UGIB event in NSAID users.

Risk factors	Male	Female, Age y			
		< 50	50-59	60-69	>70
No all factors	0.58	<0.09	0.09-0.22	0.48	>0.51
Current NSAID use only (1)	0.66	<0.11	0.12-0.29	0.31-0.56(67)*	>0.59
Multiple NSAID use only (2)	0.92	<0.41	0.44-0.69(53)*	0.72-0.88	>0.89
H. pylori infection only (3)	0.85	<0.27	0.29-0.54(58)*	0.57-0.79	>0.81
Ranitidine/Omeprazole use only(4)	0.11	<0.01	0.01-0.02	0.03-0.08	0.08-<0.5
(1)+(2)	0.94	<0.49	0.53-0.76	0.78-0.91	>0.92
(1)+(3)	0.89	<0.34	0.37-0.63(55)*	0.65-0.84	>0.86
(1)+(4)	0.15	<0.01	0.01-0.03	0.04-0.10	>0.10(88)*
(2)+(3)	0.98	<0.74(40)*	0.77-0.90	0.91-0.97	>0.97
(2)+(4)	0.5	<0.05	0.06-0.17	0.18-0.40	>0.43(73)*
(3)+(4)	0.34	<0.03	0.03-0.09	0.11-0.26	>0.28(79)*
(1)+(2)+(3)	0.98	<0.47-0.82(37)*	0.82-0.93	0.94-0.98	>0.98
(1)+(2)+(4)	0.58	<0.08	0.09-0.22	0.25-0.48	>0.51
(1)+(3)+(4)	0.81	<0.04	0.05-0.13	0.14-0.33	>0.35(76)*
(2)+(3)+(4)	0.81	<0.21	0.23-0.46	0.49-0.74(61)*	>0.76
Having all factors	0.86	<0.27	0.29-0.55(58)*	0.58-0.79	>0.82

* The probability had more than 0.5 of value at the age

Example (2) A 68 years old women who is taking diclofenac every day with no antiulceration drugs. She also had *H. pylori* infection. Her probability of UGIB can be estimated by using table 4.7 as followed.

The risk factors of UGIB in this patient were current NSAID use and *H. pylori* infection. Current NSAID use is defined as (1), in the first column of the left side of the table and *H. pylori* infection is defined as (3) in the first column of the left of table

4.7 . Therefore, the probability of UGIB in this patient was 0.65-0.84 can be found in the fifth columns and the seventh rows of table 4.7 .

H. pylori infection and multiple NSAID use are 2 factors that most closely predicted the probability of UGIB event. Antiulceration drugs most closely reduced the probability of UGIB event. Current NSAID use was poorly associated with the risk of GI bleeding event in the model.

A positive logistic regression coefficient indicated that the risk of UGIB event in NSAID users increased as the value of the risk factors increased. Thus, the results were suggested that the probability of UGIB event increased with having in the infection of *H. pylori* and taking multiple NSAIDs. (Table 4.6) The patients using multiple NSAIDs were highest risk of GI bleeding (coeff.= 2.087). Ulcer bleeding was four times greater in patients infected *H. pylori* than NSAID alone (OR: 4.2, 95%CI: 1.454-11.999).

A negative logistic regression coefficient revealed that the risk of UGIB event decreased as the patients received antiulceration drugs. Taking antiulceration drugs reduced the risk of GI bleeding in NSAID users (OR: 0.090, 95%CI: 0.028-0.291).

By interpreting interaction between age and sex, the investigator also found that the increased risk of UGIB event was significant for women 70 years and older. The men patients of all age groups were estimated to have a risk of GI bleeding that was about two-folds. (Figure 4.1)

CHAPTER VI

DISCUSSION

The purpose of this study was to construct the predictor for UGIB event in NSAID users. Our studied population was NSAID users with GI symptoms. NSAID users without GI problem were not included in this study. 44.9% of the patients with UGIB in this study had dyspeptic symptoms before UGIB event. This confirmed that dyspeptic symptoms are unreliable predictors of GI complications in NSAID users.[18] 27.7% of non-bleeding patients had normal endoscopic finding. This result was lower incidence of normal appearing mucosa than other research.[17]

Most of our patients were elderly (mean age$\pm$SD = 60.9$\pm$12.6 years) and more women than men (F:M = 1.2:1). This finding is expected because study that NSAID use is more commonly seen in the elderly and women patients.[2] Diclofenac was the most common drug usage followed by aspirin and indomethacin. (Table 4.1) Type of NSAID use in this patients was not different the risk of UGIB.[3,5,10,19,21,29] Most of NSAID use had duration within 1 month and more than 3 months. This confirms that NSAID use increases the risk of UGIB among new users and among patients taking NSAIDs between 3 months to 1 year.[3,19,21]

Most of the studied patient did not consume alcohol or smoke cigarette. Most common causes of UGIB were gastric ulcer (62.9%) following by duodenal ulcer (34.8%) and erosive gastritis (8.9%). Most of gastric ulcer was found at antrum. This agrees with previous study that the incidence of gastric ulcer is higher than those of duodenal ulcer in NSAID users.[17] Most characteristic of ulcers in NSAID users was low risk of bleeding.

Eighty-nine patients were included into case group (UGIB group) and 65 patients into control group (non-bleeding group). Case and control patients were generally well matched for pattern of NSAID use, sex, and underlying diseases. (Table 4.2) However, current NSAID use and antiulceration drugs were statistically

significant differences between two groups. These risk factors were main effects from univariable analysis. Therefore, these two risk factors were included in the model.

Demographic data showed that many risk factors in this study were associated with UGIB. (Table 4.2) Patients with GI bleeding were older than patients in non-bleeding group. Our data confirms that the older patients are the greater the risk of UGIB.[21,23,24] The sex distribution was not difference between the two groups. The number of women was higher than men in the non-bleeding group. In this study, there is an interaction between age and sex when these parameters were the predictor of the risk of UGIB. Risk of UGIB event was significantly increased in women who are 70 years old or older. Men who were taking NSAIDs had the similar of the risk of GI bleeding among all age groups. Men who received NSAIDs and had no other risk factors of UGIB had more than 0.5 of probability of UGIB in all age groups. (Table 4.7) It is possible that men in our studied population consumed alcohol and cigarette more than women. These factors were confounding factors in the prediction of UGIB event for men.

The result of this study agrees with previous reports that the incidence of UGIB in NSAID users having a history of dyspepsia and GI bleeding was high.[21,29] However, a history of ulcer was higher in non-bleeding patients than in patients with bleeding. This may be because that the patients did not know a history of ulcer (confirmed by endoscopic). The number of current and multiple NSAID users in bleeding patients was higher than in non-bleeding patients. This is consistent with previous researches that the current NSAID users increase the risk of GI bleeding by 2-4 folds.[19,21] Past NSAID use was lower the risk of UGIB than current NSAID use. The multiple NSAID use resulted in bleeding more than single NSAID use. The concomitant use of more than one NSAID more than doubled the risk of UGIB.[21,29]

The NSAID users taking antiulceration drugs (including H_2-blocker and PPIs) had low incidence of UGIB event in this study. Antiulceration drugs in the study reduced the risk of UGIB in NSAID users. This result was related to effect of antiulceration drugs. However, some Thai patients received antiulceration drugs occasionally (≤ 1-2 weeks/month). Thus, data of this factor may be inaccurately

collected. The result disagrees with previous researches that the risk of UGIB patients taking antiulceration drugs in NSAID users is higher compared with nonusers.[21,23] However, antiulceration drugs are not the risk factors of UGIB in many studies.[29,36,42,46] The combination use of NSAIDs and corticosteroids and/or warfarin was higher in bleeding patients than non-bleeding patients. This result is consistent with previous studies that NSAID users taking concomitant corticosteroids or warfarin therapy increase the risk of bleeding.[3,21,24,29,36,41]

The incidence of *H. pylori* infection in patients with UGIB was higher than in non-bleeding patients. This finding agrees with previous researches that NSAID user with *H. pylori* infection increase the risk of bleeding.[42,46] In contrast, several reports have shown that both *H. pylori* infection and NSAID use do not additive the risk of bleeding.[32,40,45] The number of patients with alcohol consumption and cigarette smoking was higher in bleeding patients than in non-bleeding patients. This is consistent with previous reports that NSAID users with alcohol consumption and cigarette smoking are higher the risk of UGIB than in nonusers.[22,37,38] However, many researches showed that alcohol consumption and cigarette smoking did not increase the risk of UGIB.[22,37]

The risk factors in the model are age, current NSAID use, multiple NSAID use, and *H. pylori* infection. These factors have been reported also in previous researches that associated with the risk of ulcer bleeding in NSAID users.[21,23,29,36,42,46] Current NSAID use and age was no statistically significant in the complete model (p= 0.698, p= 0.999, respectively) because multivariable analysis showed that multiple NSAID usage was a confounding factor of current NSAID use and had stronger effect than current NSAID use for prediction of the risk of UGIB. Sex was a confounding factor and had interaction of age. A history of ulcer and bleeding, alcohol consumption, and concomitant warfarin therapy were not included in the model because small only numbers of the patients had these factors. In addition, dose and duration of NSAID usage were not included in the model because the data collection was not complete. Concomitant corticosteroids therapy, history of dyspeptic symptoms and cigarette smoking were not included in the model because these risk factors were not confounding factors in the model and did not improve the fitness of the model. The number of patients with dyspeptic symptoms could be

underestimated because the elderly patients can not remember their symptoms very well.

Several limitations of generalized use of the model should as well be considered as followed

1. The NSAID users in our study were at higher risk of peptic ulcer than in general populations. Therefore, the NSAID users with low risk of peptic ulcer may decrease the probability of bleeding less than in table 4.7.
2. The risk of GI bleeding could be lower in men who did not take alcohol and cigarette than in those who consume alcohol or cigarette.
3. The number of patients who had some factors such as (history of dyspeptic symptoms, a history of ulcer, a history of UGIB, concomitant corticosteoids therapy, concomitant warfarin therapy, alcohol consumption, and cigarette smoking) is small in our studied population. This can be a reason why these factors were not seen in the equation. Therefore, the probability of UGIB can be less accurate when this table is used to predict a chance of UGIB in a patient who also had one or more of these factors.

The model was best fit to predict of UGIB episode (overall percent correct = 80.19%). There is practical implication of the finding. The NSAID users with high risk of bleeding should give alternative therapy for avoided UGIB event. (Figure 6.1)

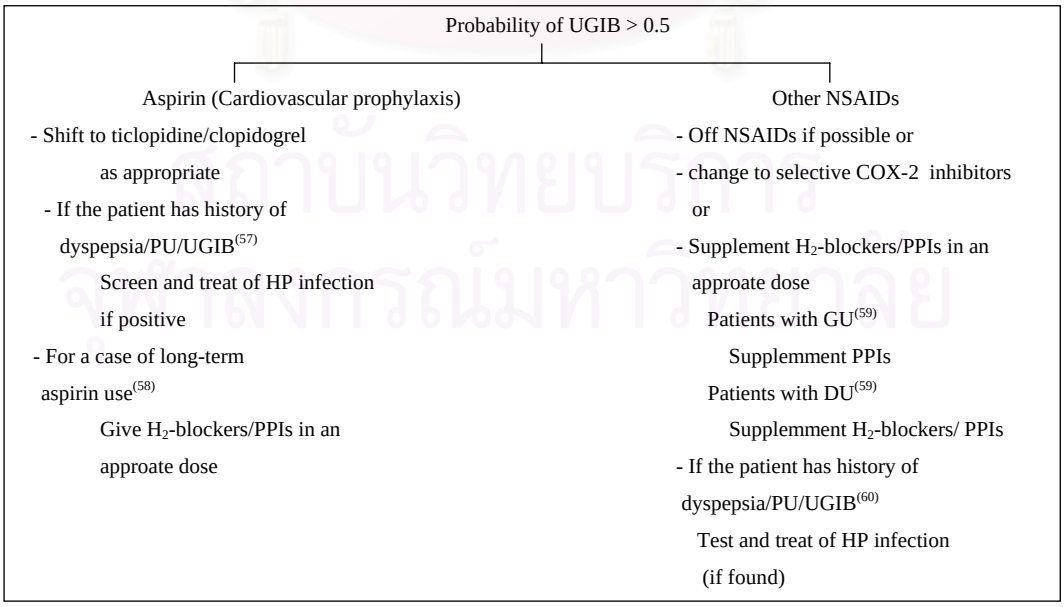

Figure 6.1 A guideline for the prevention of NSAID-induced UGIB

Note: PPIs such as[33] dose of omeprazole = 20-40mg/d for GU and 20 mg/d for DU
dose of lansoprazole = 15-30 mg/d for GU and 15 mg/d for DU
H_2-blockers such as[33] dose of cimetidine = 400 mg/d, dose of ranitidine = 150 mg/d,
dose of nizatidine = 150 mg/d, dose of famotidine = 20 mg/d

Chan et al. (2001) suggested that for the patients with *H. pylori* infection and these who were taking low-dose aspirin, the eradication of *H. pylori* was equivalent to treatment with omeprazole in preventing recurrent UGIB.[57] In long-term NSAID use, the high risk of bleeding patients should receive H_2-blockers or PPIs to prevent the GI bleeding because the eradication of *H. pylori* alone is not sufficient to prevent UGIB event.[58] Treatment for *H. pylori* is recommended for patients taking NSAIDs who have dyspepsia or ulcers and are infected with this organism.[58]

Several other limitations should as well be considered. First, negative result of *H. pylori* in the patients with bleeding can be false-negative results by using CLO® test. In addition, false-negative result is found in patients taking acid-suppression drugs, antibiotics, and bismuth-containing compound within 7-14 days before *H. pylori* test. Second, diet of these patients was confounding factor and did not control in our study.

For future study, a much larger sample size would be required to study the prediction of the risk of UGIB event. *H. pylori* status should be assessed by at least 2 tests such as CLO® test and serology test, CLO® test and histology test, or CLO® test and culture test.[47,49,50] Further research is necessary to validate the model in prospective studies.

CHAPTER VII

CONCLUSION

The populations consisted of 154 patients taking NSAIDs. Male and female ratio was 1:1.2. Most patients were elderly (mean age$\pm$SD = 60.9$\pm$12.6 years). 57.8% of patients with UGIB and 42.2% of non-bleeding patients were included in this study. Diclofenac was the most common drug usage followed by aspirin and indomathacin. Most patients did not consume alcohol and cigarette and did not have history of dyspeptic symptoms, peptic ulcer, or UGIB.

The patients with bleeding were older than non-bleeding patients ($p < 0.05$). The number of current NSAID use in UGIB patients was higher than in patients with non-bleeding ($p < 0.01$). The NSAID users receiving antiulceration drugs had low incidence of UGIB event.

Many studies have shown that the risk factors of bleeding in NSAID users are age, a history of dyspepsia, a history of peptic ulcer, a history of UGIB, more than one NSAID use, high dose of NSAID use, the combination use of NSAIDs and corticosteroids or warfarin, concomitant infection with *H. pylori*, alcohol consumption, and cigarette smoking.[21,23,29,36,37]

The main factors related with GI bleeding in the model of predicted UGIB in NSAID users were age, current NSAID use, and antiulceration drug use. Confounding factors in the model were sex, multiple NSAID use, and *H. pylori* infection. The interaction of effect in the model was age and sex. Therefore, the model of prediction of UGIB in NSAID users is shown in the equation (1) and (2).

$$\text{Logit (UGIB)} = 0.334 - 0.000048\text{Age} - 8.533\text{Sex} + 0.118(\text{Age} \times \text{Sex}) + 0.344\text{Current NSAID use} + 2.087\text{Multiple NSAID use} + 1.429\textit{H. pylori} \text{ infection} - 2.406\text{Antiulceration drugs} \quad (1)$$

$$\text{Probability (UGIB)} = e^{\text{Logit (UGIB)}} / 1 + e^{\text{Logit (UGIB)}} \quad (2)$$

A history of ulcer and bleeding, alcohol consumption, and concomitant warfarin therapy were not included in the model because small numbers of the patients had these factors. In addition, dose and duration of NSAID usage were not included in the model because the data collection was not complete. Concomitant corticosteroids therapy, history of dyspeptic symptoms and cigarette smoking were not included in the model because these risk factors were not confounding factors and did not improve the fitness of the model.

The predictor of the probability of UGIB event in NSAID users (Table 4.7) was derived from the equation (1) and (2). This table create for ease of use in clinical practice.

REFERENCES

1. Jones, R. Nonsteroidal Anti-inflammatory Drug Prescribing: Past, Present, and Future. Am J Med 110 (January 2001): 4S-7S.
2. Larkai, E. N., Smith, J. L., Lidsky, M. D., and Graham, D. Y. Gastroduodenal Mucosal and Dyspepsia Symptoms in Arthritic Patients during Chronic Nonsteroidal Anti-inflammatory Drug Use. AJG 82, 11 (November 1987): 1153-1158.
3. Gabriel, S. E., Jaakkimainem, L., and Bombardier, C. Risk for Serious Gastrointestinal Complications Related to Use of Nonsteroidal Anti-inflammatory Drugs: A meta-analysis. Ann Intern Med 115, 10 (November 1991): 787-796.
4. Bollini, P., Garcia-Rodriguez, L. A., Gutthann, S. P., and Walker, A. M. The Impact of Research Quality and Study Design on Epidemiologic Estimates of the Effect of Nonsteroidal Anti-inflammatory Drugs on Upper Gastrointestinal Tract Disease. Arch Intern Med 152 (June 1992): 1289-1295.
5. Henry, D., Lim, L. L. Y., Garcia-Rodriguez, L. A., Gutthann, S. P., Carson, J. L., Griffin, M., et al. Variability in Risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. BMJ 312 (June 1996): 1563-1566.
6. Vreeburg, E. M., Snel, P., de Bruijne, J. W., Bartelsman, J. F. W., Rauws, E. A. J., and Tytgat, G. N. J. Acute Upper Gastrointestinal Bleeding in the Amsterdam Area: Incidence, Diagnosis, and Clinical outcome. AJG 92, 2 (February 1997): 236-243.
7. Somerville, K., Faulkner, G., and Langman, M. Non-steroidal anti-inflammatory drugs and bleeding peptic ulcer. Lancet 1 (March 1986): 462-464.
8. Griffin, M. R., Ray, W. A., Schaffner, W. Nonsteroidal anti-inflammatory drug use and death from peptic ulcer in elderly persons. Ann Intern Med 109 (September 1988): 359-363.

9. Griffin, M. R., Piper, J. M., Daugherty, J. R., Snowden, M., and Ray, W. A. Nonsteroidal Anti-inflammatory Drug Use and Increased Risk for Peptic Ulcer Disease in Elderly Persons. Ann Intern Med 114, 4 (February 1991): 257-263.

10. Langman, M. J. S., Weil, J., Wain Wright, P., Lawson, D. H., Rawlins, M. D., Lagan, R. F. A., et al. Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. Lancet 343 (April 1994): 1075-1078.

11. Sriussadaporn, S., Tanphiphat, C., and Vilairat, S. Acute upper gastrointestinal bleeding a review of 1,338 patients. Chula Med J 32, 2 (February 1988): 165-174.

12. Orprayoon, P. Upper Gastrointestinal Hemorrhage in Prapokklao Hospital. J Prapokklao Hosp Clin Med Educat Center 8, 4 (October-December 1991): 29-225.

13. Kittikun, P. Bleeding Peptic Ulcer in Cholburi Hospital. Cholburi Hosp J 23, 2 (May-August 1998): 37-40.

14. Tangkiatkumjai, M., and Ratisoontorn, S. Upper Gastrointestinal Bleeding in NSAID Users. Bangkok: Chulalongkorn University, 2001. (Unpublished Manuscript)

15. Meensook, C. Upper Gastrointestinal Bleeding. J Med Ass Thailand 63, 11 (November 1980): 598-602.

16. Laine, L., and Peterson, W. L. Bleeding Peptic Ulcer. N Engl J Med 331, 11 (September 1994): 717-727.

17. Wolfe, M. M., Lichtenstein, D. R., and Singh, G. Gastrointestinal Toxicity of Nonteroidal Antiinflammatory Drugs. N Engl J Med 340, 24 (June 1999): 1888-1899.

18. Armstrong, C. P., and Blower, A. L. Nonsteroidal anti-inflammatory drugs and life threatening complications of peptic ulceration. Gut 28 (1987): 527-532.

19. Hernandez-Diaz, S., and Garcia-Rodriguez, L. A. Association Between Nonsteroidal Anti-inflammatory Drugs and Upper Gastrointestinal Tract Bleeding/Perforation. Arch Intern Med 160 (July 2000): 2093-2099.

20. Hawkey, C. J. Nonsteroidal Anti-inflammatory Drug Gastropathy. Gastroenterology 119, 2 (August 2000): 521-535.

21. Garcia-Rodriguez, L. A., Cattaruzzi, C., Grazia Troncon, M., and Agostinis, L. Risk of Hospitalization For Upper Gastrointestinal Tract Bleeding Associated With ketorolac, other Antihypertensive Drugs. Arch Intern Med 158 (January 1998): 33-39.

22. Aalykke, C., Lanritsen, J. M., Hallas, O., Reinholdt, S., Krogfelt, K., and Lauritsen, K. *Helicobacter pylori* and Risk of Ulcer Bleeding Among Users of Nonsteroidal Anti-inflammatory Drugs: A case-control study. Gastroenterology 116, 6 (June 1999): 1305-1309.

23. MacDonald, T. M., Morant, S. V., Robinson, G. C., Shield, M. J., McGilchrist, M. M., Murray, F. E., et al. Association of upper gastrointestinal Toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study. BMJ 315 (November 1997): 1333-1337.

24. Piper, J. M., Ray, W. A., Daugherty, J. R., and Griffin, M. R. Corticosteroidal Use and Peptic Ulcer Disease: Role of Nonsteroidal Anti-inflammatory Drugs. Ann Intern Med 114, 9 (May 1991): 735-740.

25. Fries, J. F., Williams, C. A., Bloch, D. A., and Michel, B. A. Nonsteroidal Anti-Inflammatory Drug-Associated Gastropathy: Incidence and Risk factor Models. Am J Med 91, 9 (September 1991): 213-222.

26. Singh, G., Ramey, D. R., Triadafilopoulus, G., Brown, B. W., and Balise, R. R. GI score: A simple Self-Assessment Instrument to Quantify The Risk of Serious NSAID-Related GI Complications in RA and OA. Arthritis Rheum 41 (1998): 57S.

27. Lanza, F. L., Royer, G. L., Nelson, R. S., Chen, T. T., Seckman, C. E., and Rack, M. F. The Effects of Ibuprofen, Indomethacin, Aspirin, Naproxen, and Placebo on the Gastric Mucosa of Normal Volunteers: A Gastroscopic and Photographic Study. Dig Dis Sci 24, 11 (November 1979): 823-828.

28. Lanza, F. L., Royer, G. L., Nelson, R. S., Chen, T. T., Seckman, C. E., and Rack, M. F. A Comparative Endoscopic Evaluation of the Damaging Effects of Nonsteroidal Anti-inflammatory Agents on the Gastric and Duodenal Mucosa. AJG 75, 1 (January 1981): 17-21.

29. Garcia-Rodrigeuz, L. A., and Jick, H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. Lancet 343 (March 1994): 769-772.

30. Holvoet, J., Terriere, L., Van Hee, W., Verbist, L., Fierens, E., and Hautekeete, M. L. Relation of upper gastrointestinal bleeding to non-steroidal anti-inflammatory drugs and aspirin: a case-control study. Gut 32 (1991): 730-734.

31. Goldman, L., and Bennett, J. C., eds. Cecil Textbook of Medicine. 21st ed. Philadelphia (PA): W.B. Saunders company, 2000.

32. Fauci, A. S., Braunwald, E., Isselbacher, K. J., Wilson, J. D., Martin, J. B., Kasper, D. L., eds. Harrison's Principles of Internal Medicine. 14th ed. New York: McGraw-Hill, 1998.

33. Dipiro, J. T., Talbert, R. L., Yee, G. C., Matzke, G. R., Wells, B. G., and Posey, L. M., eds. Pharmacotherapy A Pathophysiologic Approach. 4th ed. Stamford (CT): Appleton & Lange, 1999.

34. Terdiman, J. P., and Ostroff, T. W. Gastrointestinal Bleeding in the Hospitalized Patient: A Case-Control Study to Assess Risk Factors, Causes, and Outcome. Am J Med 104 (April 1998): 349-354.

35. Schoen, R. T., and Vender, R. J. Mechanisms of Nonsteroidal Anti-inflammatory Drug-Induced Gastric Damage. Am J Med 86 (April 1989): 449-458.

36. Hernandez-Diaz, S., and Garcia-Rodriguez, L. A. Epidemiologic Assessment of the Safety of Conventional Nonsteroidal Anti-inflammatory Drugs. Am J Med 110 (February 2001): 20S-27S.

37. Weil, J., Langman, M. J. S., Wainwright, P., Lawson, D. H., Rawlins, M., Logem, R. F. A., et al. Peptic ulcer bleeding: accessory risk factors and interactions with non-steroidal anti-inflammatory drugs. Gut 46 (2000): 27-31.

38. Henry, D., Dobson, A., and Turner, C. Variability in the Risk of Major Gastrointestinal Complications From Nonaspirin Nonsteroidal Antiinflammatory Drugs. Gastroenterology 105, 4 (October 1993): 1078-1088.

39. Kaufman, D. W., Kelly, J. P., Sheehan, J. E., Laszlo, A., Wiholm, B. E., Alfredson, L., et al. Nonsteroidal anti-inflammatory drug use in relation to major upper gastrointestinal bleeding. Clin pharmacol ther 53, 4 (April 1993): 485-494.

40. Cullen, D. J. E., Hawkey, G. M., Greenwood, D. C., Humphreys, H., Shepherd, V., Logan, R. F. A., et al. Peptic ulcer bleeding in the elderly: relative roles of *Helicobacter pylori* and non-steroidal anti-inflammatory drugs. Gut 41 (1997): 459-462.

41. Shorr, R. I., Ray, W. A., Daugherty, J. M., and Griffin, M. R. Concurrent Use of Nonsteroidal Anti-inflammatory Drugs and Oral Anticoagylants Places Elderly Persons at High Risk for Hemorrhagic Peptic Ulcer Disease. Arch Intern Med 153 (July 1993): 1661-1670.

42. Hsu, P. I., Lai, K. H., Tseng, H. H., Lin, C. K., Lo, G. H., Cheng, J. S., et al. Risk Factors for Presentation with Bleeding in Patients with *Helicobacter pylori*-related Peptic Ulcer Diseases. J Clin Gastroenterol 30, 4 (2000): 386-391.

43. Pilotto, A., Leandro, G., Mario, F. D., Franceschi, M., Bozzola, L., and Valerio, G. Role of *Helicobacter pylori* Infection Upper Gastrointestinal Bleeding in the Elderly: A Case-Control Study. Dig Dis Sci 42, 3 (March 1997): 586-591.

44. Kohl, H., Leverkus, F., and Labenz, J. *Helicobacter pylori* Infection Increases the Risk of Peptic Ulcer Bleeding-A Case-Control Study. Gut 34 (1996): A231.

45. Labenz, J., Kohl, H., Wolters, S., Modjtahedi, B., Tillenburg, B., Peitz, U., et al. *Helicobacter pylori*, NSAIDs and the risk of peptic ulcer bleeding-A Prospective case-control study with matched pairs. Gastroenterology 110, 4 (April 1996): A165.

46. Hawkey, G. M., Stack, W. A., Pearson, G., Everitt, S., Logan, R. F. A., and Hawkey, C. J. Non steroidal anti inflammatory drugs, aspirin and *Helicobacter pylori* as risk factors for bleeding peptic ulcers. Gut 41 (1997): A5.

47. Tu, T. C., Lee, C. L., Wu, C. H., Chen, T. K., Chan, C. C., Huang, S. H., et al. Comparison of invasive and noninvasive tests for detecting *Helicobacter pylori* infection in bleeding peptic ulcers. Gastrointest Endosc 49, 3 (1999): 302-306.

48. Lee, J. M., Bresline, N. P., Fallon, C., and O'Morain, C. A. Rapid Urease Tests Lack Sensitivity in *Helicobacter pylori* Diagnosis When Peptic ulcer Disease Presents With Bleeding. AJG 95, 5 (May 2000): 1166-1170.

49. Leung, W. K., Sung, J. Y., Sin, L. K., Chan, K. L., Ling, K. W., and Cheng, F. B. False-Negative Biopsy Urease Test in Bleeding Ulcers Caused by the Buffering Effects of Blood. AJG 93, 10 (October 1998): 1914-1918.

50. Cutler, A. F. Testing for *Helicobacter pylori* in Clinical Practice. Am J Med 100 (May 1996): 35S-41S.

51. Kaufman, D. W., Kelly, J. R., Wiholm, B. E., Laszlo, A., Sheehan, J. E., Koff, R. S., et al. The Risk of Acute Major Upper Gastrointestinal Bleeding Among Users of Aspirin and Ibuprofen at Various levels of Alcohol Consumption. AJG 94, 11 (November 1999): 3189-3196.

52. Kelly, J. P., Kaufman, D. W., Koff, R. S., Laszlo, A., Wiholm, B. E., and Shapiro, S. Alcohol Consumption and the Risk of Major Upper Gastrointestinal Bleeding. AJG 90, 7 (July 1995): 1058-1064.

53. Silverstein, F. E., Graham, D. Y., Senior, J. K., Davies, H. W., Struthers, B. J., Bittman, R. M., et al. Misoprostol Reduces Serious Gastrointestinal Complications in Patients with Rheumatoid Arthritis Receiving Nonsteroidal Anti-inflammatory Drugs: A Randomized, Double-Blind, Placebo-Controlled Trial. Ann Intern Med 123, 4 (August 1995): 241-249.

54. O'Laughlin, S. C., Hoftiezer, S. W., and Ivey, K. J. Effect of Aspirin on the Human Stomach in Normals: Endoscopic Comparison of Damage Produced One Hour, 24 Hours, and 2 Weeks after Administration. Scan J Gastroent 16 (1981): 211-214.

55. Hosmer, D. W., and Lemeshow, S., eds. Applied Logistic Regression. 2nd ed. New York: A Wiley-Interscience Publication, 2000.

56. Schmassmann, A. Mechanisms of Ulcer Healing and Effects of Nonsteroidal Anti-inflammatory Drugs. Am J Med 104 (March 1998): 43S-51S.

57. Chan, F. K. L., Sydney Chung, S. C., Suen, B. Y., Lee, Y. T., Leung, W. K., Leung, V. K. S., et al. Preventing Recurrent Upper Gastrointestinal Bleeding in Patients with *Helicobacter pylori* who are taking Low-dose Aspirin or Naproxen. N Engl J Med 344, 13 (March 2001): 967-973.

58. Chan, F. K. L., To, K. F., Wu, J. C. Y., Yung, M. Y., Leung, W. K., Kwok, T., et al. Eradication of *Helicobacter pylori* and risk of peptic ulcers in patients starting long-term treatment with non-steroidal anti-inflammatory drugs: a randomized trial. Lancet 359 (January 2002): 9-13.

59. Lanza, F. L. A Guideline for the Treatment and Prevention of NSAID-Induced Ulcers. AJG 93, 11 (November 1998): 2037-2046.

60. Chan, F. K. L., Sung, J. J. Y., Chung, S. C. S., To, K. F., Yung, M. Y., Leung, V. K., et al. Randomized Trial of eradication of *Helicobacter pylori* before non-steroidal anti-inflammatory drug therapy to prevent peptic ulcers. Lancet 350 (October 1997): 975-979.

APPENDICES

Appendix A

Interview Form

Name_____ **No.**_____

HN _____ **Tel** _____

Age _____ **Sex** □ Male □ Female

Past Medical Illness □ No □ Yes □ Unknown

□ GU □ DU □ EU □ Dyapepsia □ Gastritis □ Duodenitis □ esophagitis

Onset___mo./y before index date

□ UGIB □ Perforation Onset___mo./y before index date

□ EV/GV □ Chronic liver disease □ Chronic renal dissease

□ Mallory-Weiss syndrome □ GI Cancer □ Coagulopathy

□ OA □ RA □ Gout □ SLE

□ HTN □ IHD □ MI □ DM

□ Dyslipidemia □ CVA □ Others_____

Chief Complains

□ Melena □ Hematemesis □ Both □ Others_____

Prior Symptom □ No □ Yes

□ Abdominal pain □ Bloating □ N/V □ Epigastric pain

□ Heart burn □ Others _____

Past Medical History

Pattern of NSAID Use

□ Current (1-30 d) □ Past (31-90 d) □ No use (>90 d) □ Unknown

□ Regular □ Occasion □ Single NSAID □ Multiple NSAID

Individual NSAIDs □ Unknown □ Ibuprofen

□ Diclofenac □ Indomethacin □ Ketoprofen □ Naproxen

□ Piroxicam □ Sulindac □ Mefenamic acid □ Nabumetone

□ Aspirin □ Others_____

Indication □ Bone and joint diseases □ CVS □ Others _____

Dose of NSAID Use □ Unknown □ _____mg/d

Duration of NSAID use □ ≤ 1 Mo. □ > 1 - 3 Mo. □ > 3 Mo.

Appendix A (Continuing)

Concomitant Corticosteroids Therapy

□ Current (≤1 Wk.) □ Past (>1 Wk.-3 Mo.) □ No use (> 3 Mo.) □ Unknown

Concomitant Heparin Therapy

□ Current (≤1 Wk.) □ Past (>1 Wk.-3 Mo.) □ No use (> 3 Mo.) □ Unknown

Concomitant Warfarin Therapy

□ Current (≤1 Wk.) □ Past (>1 Wk.-3 Mo.) □ No use (> 3 Mo.) □ Unknown

Antiulceration Drugs

□ Sucralfate □ H_2-blocker_____□ PPIs_____□ Misoprostol □ Unknown

Duration of use_____ d./mo./y. before index date

□ Current (≤1 Wk.) □ Past (>1 Wk.-3 Mo.) □ No use (> 3 Mo.) □ Unknown

Other medications

□ Ticlopidine □ Clopidogrel □ Others _____

Alcohol Habit _____glass or bottle/wk

□ Current (1-30 d.) □ Past (> 30 d.) □ No drinking □ Unknown

Cigarette Smoking _____ cigarette or pack/d.

□ Current (1-30 d.) □ Past (> 30 d.) □ No smoking □ Unknown

Appendix B

Data collection form

Name_____ HN_____

Past Medical Illness □ No □ Yes □ Unknown

□ GU □ DU □ EU □ Dyapepsia □ Gastritis □ Duodenitis □ esophagitis

Onset___mo./y before index date

□ UGIB □ Perforation Onset___mo./y before index date

□ EV/GV □ Chronic liver disease □ Chronic renal dissease

□ Mallory-Weiss syndrome □ GI Cancer □ Coagulopathy

□ OA □ RA □ Gout □ SLE

□ HTN □ IHD □ MI □ DM

□ Dyslipidemia □ CVA □ Others_____

Diagnosis

Endoscopic finding

□ GU □ DU □ EU Size____cm. No. of ulcer_____

□ Clean base □ Pigment spot □ Adherent clot □ Visible vss □ Active bleed

□ Gastritis □ Duodenitis □ esophagitis

□ EV/GV □ Mallory-Weiss syndrome □ GI cancer □ Others____

***H.pylori* status** □ No test □ Test

□ CLO® □ Serology □ Positive □ Negative

Laboratory results □ No examination □ Examination

□ No test □ Hct/Hgb_____ □ No test □ PTT_____ □ INR____

□ Occult blood □ No test □ Positive □ Negative

Past Medical History

Pattern of NSAID Use

□ Current (1-30 d) □ Past (31-90 d) □ No use (>90 d) □ Unknown

□ Regular □ Occasion □ Single NSAID □ Multiple NSAID

Individual NSAIDs □ Unknown □ Ibuprofen

□ Diclofenac □ Indomethacin □ Ketoprofen □ Naproxen

□ Piroxicam □ Sulindac □ Mefenamic acid □ Nabumetone

□ Aspirin □ Others_____

Appendix B (Continuing)

Indication □ Bone and joint diseases □ CVS □ Others _____

Dose of NSAID Use □ Unknown □ _____mg/d

Duration of NSAID use □ ≤ 1 Mo. □ > 1 - 3 Mo. □ > 3 Mo.

Concomitant Corticosteroids Therapy

□ Current (≤1 Wk.) □ Past (>1 Wk.-3 Mo.) □ No use (> 3 Mo.) □ Unknown

Concomitant Heparin Therapy

□ Current (≤1 Wk.) □ Past (>1 Wk.-3 Mo.) □ No use (> 3 Mo.) □ Unknown

Concomitant Warfarin Therapy

□ Current (≤1 Wk.) □ Past (>1 Wk.-3 Mo.) □ No use (> 3 Mo.) □ Unknown

Antiulceration Drugs

□ Sucralfate □ H_2-blocker_____□ PPIs_____□ Misoprostol □ Unknown

Duration of use_____ d./mo./y. before index date

□ Current (≤1 Wk.) □ Past (>1 Wk.-3 Mo.) □ No use (> 3 Mo.) □ Unknown

Other medications

□ Ticlopidine □ Clopidogrel □ Others _____

Appendix C

Medication samples

Appendix D

Data base of the process of model building

1. Univariable Analysis for Identification the Main Effects of Predicted UGIB in NSAID Users

Table D1 Univariable logistic regression models for prediction of UGIB event

Risk factors	Coeff.	SE.	OR	95%CI	*P*	-2LL
Age	0.027	0.013	1.027	1.001-1.054	**<0.05**	205.606
Sex	0.648	0.333	1.912	0.995-3.674	0.052	205.890
History of dyspepsia	0.208	0.379	1.231	0.585-2.587	0.584	199.450
Current NSAID use	1.434	0.555	4.196	1.414-12.451	**0.01**	202.206
Multiple NSAID use	0.562	0.481	1.755	0.684-4.503	0.242	157.700
Regular NSAID use	0.461	0.351	1.585	0.797-3.153	0.189	208.008
Dose of NSAID use	0.474	0.642	1.606	0.457-5.650	0.460	166.457
Duration of NSAID use (within 1 month)	0.088	0.392	1.092	0.507-2.353	0.821	200.529
Duration of NSAID use (more than 3 months)	0.458	0.361	1.582	0.779-3.209	0.204	198.938
Concomitant corticosteroids therapy	0.654	0.394	1.923	0.888-4.163	0.097	206.864
Cigarette smoking	0.768	0.510	2.155	0.794-5.853	0.132	207.285
H. pylori *infection*	0.551	0.355	1.735	0.865-3.480	0.121	180.429
Antiulceration drugs	-1.580	0.399	0.206	0.094-0.450	**<0.01**	192.568

2. Multivariable Analysis for Confounding Factor Identification

Table D2 Confounding factors between age and antiulceration drugs

Risk factors	Coeff.	SE	OR	95%CI
Age	0.034	0.015	1.035	1.006-1.065
Antiulceration drugs	-1.706	0.414	0.182	0.081-0.409

-2LL = 186.682

Table D3 Confounding factors between sex and antiulceration drugs

Risk factors	Coeff.	SE	OR	95%CI
Sex	0.712	0.356	2.038	1.014-4.096
Antiulceration drugs	-1.617	0.406	0.198	0.090-0.440

-2LL = 188.473

Table D4 Confounding factors between H. pylori infection and current NSAID use

Risk factors	Coeff.	SE	OR	95%CI
H. pylori infection	0.535	0.361	1.708	0.841-3.467
Current NSAID use	1.203	0.594	3.330	1.040-10.659

-2LL = 176.110

Table D5 Confounding factors between H. pylori infection and antiulceration drugs

Risk factors	Coeff.	SE	OR	95%CI
H. pylori infection	0.612	0.382	1.845	0.873-3.901
Antiulceration drugs	-1.693	0.423	0.184	0.080-0.422

-2LL = 163.119

Table D6 Confounding factors between current NSAID use and multiple NSAID use

Risk factors	Coeff.	SE	OR	95%CI
Current NSAID use	1.479	0.699	4.390	1.115-17.288
Multiple NSAID use	0.550	0.492	1.733	0.661-4.541

-2LL = 152.507

Table D7 Confounding factors between multiple NSAID use and antiulceration drugs

Risk factors	Coeff.	SE	OR	95%CI
Multiple NSAID use	0.980	0.546	2.664	0.914-7.769
Antiulceration drugs	-1.772	0.473	0.170	0.067-0.430

-2LL = 141.629

3. Multivariable Analysis for Interaction Identification

Table D8 Interaction between age and sex

Model	-2LL
1. Age+Sex+Antiulcerationdrugs+Current NSAID use	176.335
2. Age+Sex+Antiulcerationdrugs+Current NSAID use+(Age X Sex)	171.988

Table D9 Multivariable analysis of interaction between age and sex

Risk factors	Coeff.	SE.	OR	95%CI	*P*
Age	0.002	0.022	1.002	0.959-1.046	0.92
Sex	-4.691	1.960	0.009	0.0002-0.428	0.01
Current NSAID use	1.227	0.607	3.412	1.039-11.209	<0.05
Antiulceration drugs	-1.762	0.431	0.172	0.074-0.399	<0.01
Age X Sex	0.064	0.031	1.066	1.002-1.134	**<0.05**

4. Multivariable Analysis for the Best Model of the Prediction of UGIB

Table D10 Multvariable analysis of the model of the predicted the probability of UGIB

Model	-2LL
1. Age+Current NSAID use+Antiulceration drugs	181.104
2. Age+Current NSAID use+Antiulceration drugs+Sex	176.335
3. Age+Current NSAID use+Antiulceration drugs+Sex+(Age X Sex)	171.988
4. Age+Sex+Antiulcerationdrugs+Current NSAID use+ (Age X Sex)+*H. pylori* infection	147.457
4. Age+Sex+Antiulcerationdrugs+Current NSAID use+ (Age X Sex)+*H. pylori* infection+Multiple NSAID use	99.901

Vita

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