Gastrointestinal and Cardiovascular Risk of Non-selective NSAIDs and Cox-2 Inhibitors in Elderly Patients with Knee Osteoarthritis

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Objective: *To evaluate the incidence and risk profiles for gastrointestinal (GI) events and cardiovascular (CV) events in elderly patients (aged ≥ 60 years) with knee osteoarthritis using tNSAIDs (traditional non-steroidal anti-inflammatory drugs) or coxibs users in patients with knee osteoarthritis aged ≥ 60 years.*

Material and Method: *A hospital-based retrospective cohort study was applied. Data on prescription drug (NSAIDs, celecoxib, etoricoxib) was obtained from hospital database. Data on CV events and GI adverse events was obtained from the registry of the Cardiology Unit and Gastroesophagoscope Diagnosis Center, GI Center, Department of Internal medicine, Police General Hospital. Patients visiting the hospitals' outpatient clinics from June 2004 to June 2007 were included if they were aged ≥ 60 years and received at least one follow-up visit on the prescription of a tNSAIDNSAID or coxibs (etoricoxib or celecoxib). Patients with a history of gastrointestinal disease or heart disease were excluded. All patients were followed-up from their first visit to the date of their earliest event or to the end of the study period. The interested event was assumed to be attributed to the last prescription shown in the study period.*

Results: *A total 12,591 prescriptions from 1,030 patients, an average of 4 prescriptions/patient/year, were screened -3,982 (31.6%) prescriptions were for NSAIDs, 4,426 (35.2%) were for celecoxib, and 4,183 (33.2%) were for etoricoxib. The most common traditional NSAID prescribed was meloxicam (24%), followed by nimesulide (21.4%) and naproxen (13.1%). The mean age of cohort was 69.6 years, with the majority being female (74%). We found a comparable dose of celecoxib (200 mg OD) and etoricoxib (90 mg OD) prescribed in the respective patients. A total of 78 gastrointestinal events occurred and Esophagogastroscopy indicated that 37 (47.4%) were dyspepsia, 22 (28.2%) were anemia (28.2%), 17 (21.7%) were upper GI bleeding, and 2 (2.6%) were others. Forty (40) of these events were attributed to NSAIDs, 21 to celecoxib and 17 to etoricoxib. Observed GI events included gastritis (50, 64.1%), gastric ulcer (14, 17.9%), duodenal ulcer (3, 3.8%), and normal (11, 14.1%). Patients receiving traditional NSAIDs, celecoxib and etoricoxib had 20, 18, and 11 CV events respectively. Of these 49 CV events, the most common was heart failure (20), followed by chronic heart failure (9), angina pectoris (9), unstable angina (6), and myocardial infarction (5). Comparing celecoxib with NSAID use in logistic regression analysis, patients who received celecoxib were significantly less likely to suffer GI events than those who received NSAIDs; OR = 0.36 (95% CI 0.21-0.63, p = 0.00.). Similarly, etoricoxib was less likely to cause GI events than NSAIDs; OR = 0.52 (95% CI 0.28-0.98, p = 0.04). Comparing to patients aged under 60 years, patients aged >70 years had a significantly higher chance of developing GI events, OR = 1.79 (95% CI 1.13-2.4) for patients aged 70-80 years and 3.36 (95% CI 1.78-5.81) for those aged > 80 years. Drug exposure time, which was defined as the number of days of medication supplied, significantly increased the GI risks. For CV event, there were only 3 significantly associated with CV events - female (OR = 0.29, 95% CI 0.16-0.59, p =0.00), age >80 years (OR =2.98, 95% CI 1.57-4.23, p = 0.00), and drug exposure time (OR = 1.05, 95% CI 1.02-1.54, p = 0.00).*

Conclusion: *Incidence of GI and CV events was lower for coxibs than for NSAIDs and celecoxib had a lower incidence than etoricoxib. Patients with advanced age and higher drug exposure time had a significantly increased risk of GI; the use of gastroprotective agents significantly decreased GI risks. Being female, advanced age, and drug exposure time significantly affected CV events.*

Keywords: *OA, Gastrointestinal, Cardiovascular, Coxibs, NSIADs*

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Selective COX-2 inhibitors (coxibs) are approved for the relief of acute and chronic pain and symptoms of chronic inflammatory conditions, such as osteoarthritis (OA). They have a better gastrointestinal (GI) safety profile compared with traditional nonsteroidal anti-inflammatory drugs (tNSAIDs). However, long-term use of coxibs has been associated with an increased risk of cardiovascular (CV) adverse events (AEs), especially in elderly patients and those patients with multiple co-prescibed medications and/or multiple co-morbidities. The appropriate approach to minimize these possible risks from both tNSAIDs and coxibs has still been widely discussed nowadays. One well-accepted approach for GI event included using low-dose regimen and co-prescribing of GI protective agent. Data on risk profile of using coxibs in Thai patients at possible high risk of developing GI and

CV event in real-life is limited. The objective of this study is to evaluate the gastrointestinal and cardiovascular risk of coxibs compared with tNSAIDs in elderly Thai patients with common chronic pain indication of knee osteoarthritis in real-life practice.

Objective

The primary objective was to examine the incidence of gastrointestinal and cardiovascular events associated with cyclooxygenase-2 inhibitors (coxibs) and nonsteroidal anti-inflammatory drugs (NSAIDs). The secondary objective was to determine the adjusted odds ratio of exposing two different coxibs (celecoxib, etoricoxib) comparing to tNSAIds.

Material and Method

Study design

We conducted a hospital-based retrospective cohort study by using the hospitalization records and dispensing database in Police General Hospital from July 2004 through to June 2007. This study was approved by the Ethics Review Board of Police General Hospital. Eligible patients to be included in the study were limited to those have been diagnosed with osteoarthritis (OA), aged $\geq$ 60 years, received at least two successive prescriptions of study drugs during study period. All patients were followed-up from their first prescription shown in the study period to the date of their earliest event or to the end of the study. Osteoarthritis was diagnosed based on the assessment criteria given by the American College of Rheumatology. Exclusion criteria were (1) patients who received more than one study drugs in the same prescription and (2) patients with a prior history of any of gastrointestinal events and cardiovascular attacks; myocardial infarction (MI) and congestive heart failure.

Study drugs

Study drugs included all tNSAIDs (diclofenac, diflunisal, sulindac, piroxicam, indomethacin, loxoprofen, meloxicam, nimesulide, and naproxen) available on the hospital formula listing and two coxibs (celecoxib and etoricoxib). We assumed all tNSAIDs used in varied doses are comparably efficacious then they were grouped to compare with coxibs. The prescriptions of celecoxib and etoricoxib were separately grouped regardless the daily dose prescribed. Exposure time to a study drug was defined as the number of days of medication supplied. All patients can possibly be users of more than one drug as their physicians might switch drug at any visit. Patients who switched from one study drug to another were then categorized as a new user for the second study drug. Co-medications prescribed were also recorded for each prescription.

Outcomes assessment

Gastrointestinal events included in the study range from gastric ulcer (GU), peptic ulcer (PU), gastritis, dyspepsia, and duodenitis. These events have to be clinically confirmed by esophago-gastroscopy. Similarly, the data on hospitalized cardiovascular events based on ICD-10 which included MI (all subtypes) and CHF were obtained from the patient registry at the Cardiology Unit and Gastroesophagoscope Diagnosis Center, GI Center, Department of Internal medicine, Police General Hospital. Only the outcome which was associated with an in-hospital prescribed drug was included in the analysis. Determination of association between the prescribed tNSAIDs or coxibs and ocurr were with the events entirely relied on the considered opinion of the treating physician and their team. Events that might be related to a study drug that the patients may be given from another source, *e.g.*, drugstore, another hospital, were excluded. For additional demographic data, co-morbidities we collected from the outpatient record charts

Since there might be more than one time of any types of GI or CV suffered by a patient, we included only the first occurrence of each outcome category into the analysis in order to focus on the number of patients who had at least one event and then quantify the risk incidence of these events.

Statistical analyses

Descriptive analysis was used to report all demographic and drug utilization data. Incidence rate of each event of interest was also calculated. The logistic regression analysis was applied to obtain the adjusted odds ratios of developing the GI and CV event comparing between tNSAIDs and two coxibs. At the p-value, a < 0.05 or 5% significance level was considered statistically significant.

Results

Demographic data

1,030 patients with a total of 12,591 prescriptions enrolled in this study, resulting in an average of 4 prescriptions/patient/year, with 27 days of average drug exposure time per prescription. Of the 12,591 prescriptions, 3,982 (31.6%) were for tNSAIDs, 4,426 (35.2%) were for celecoxib, and 4,183 (33.2%) were for etoricoxib. The three most common tNSAIDs prescribed was meloxicam (24%), followed by nimesulide (21.4%) and naproxen (13.1%) respectively. The mean age of patients was 69.6 years, the majority of which being female (74%). Table 1 shows the prescription-based patients' characteristic data.

Incidence of GI and CV events

A total of 78 gastrointestinal events occurred in the studied patients. These were verified by esophagogastroscope as dyspepsia (37), anemia (22), upper GI bleeding (17), and others (2). The greatest number of events were attributed to tNSAIDs (40), followed by celecoxib (21) and etoricoxib (17). Observed GI events included gastritis (50), gastric ulcer (14), duodenal ulcer (3), normal (11). In the tNSAIDs group, 20 patients had CV events whereas 18 celecoxib and etoricoxib users had 18 and 11 CV events respectively. Of these 49 CV events, the most frequently observed event was heart failure (20 events). Other CV events were chronic heart failure (9), angina pectoris (9), unstable angina (6), and myocardial infarction (5).

Table 2 presents the incidence rates per person-year. For both GI and CV events, the lowest rate was found in the celecoxib group. On the other hand, the highest rate was found in patients who received tNSAIDs.

Adjusted risks for coxibs comparing to tNSAIDs

Comparing celecoxib with NSAIDs, patients who received celecoxib were significantly less likely to have GI event; OR = 0.36 (95% CI 0.21-0.63, p = 0.00.). Similarly, using etoricoxib associated with a lower risk of GI events than tNSAIDs; OR = 0.52 (95% CI 0.28-0.98, p = 0.04). Female patients were at higher GI risk comparing to male. Similarly, those patients with advance age had a significantly highest risk of developing GI events comparing to patients aged < 70

Table 1. Patient's characteristics (prescription-based data)

Variable	Drug exposure group		
	tNSAIDs (3,982 prescriptions)	Celecoxib (4,426 prescriptions)	Etoricoxib (4,183 prescriptions)
Age			
< 70 years	2,211	2,120	2,307
71-80 years	1,536	1,934	1,687
> 80 years	235	372	189
Gender			
Female	3,139	3,417	3,048
Male	843	1,009	1,135
Co-morbidities			
Dyslipidemia	1,724	2,201	2,067
Diabetes	1,424	2,307	1,824
Hypertension	1,797	2,120	1,852
PPI* use	3,431	3,289	3,000
Low dose ASA use	962	1,161	1,107

* Proton pump inhibitor

Table 2. Incidence of gastrointestinal and cardiovascular events associated with tNSAIDs, celecoxib, and etoricoxib

Drug exposure category	No. of patients	Person-year	Gastrointestinal events		Cardiovascular events	
			No. of GI events	Event rate/ 100 person-year	No. of CV events	Event rate/ 100 person-year
tNSAIDs	353	104	40	3.85	20	1.93
Celecoxib	401	112	21	1.79	18	1.53
Etoricoxib	331	67	17	2.54	11	1.64

Table 3. Adjusted odds ratio of GI and CV events

Variable	GI event		CV event	
	Adjusted OR	Sig.	Adjusted OR	Sig.
tNSAIDs	Reference		Reference	
Celecoxib	0.36	0.00*	0.37	0.40
Etoricoxib	0.52	0.04*	0.55	0.65
Female	0.63	0.06	0.29	0.00*
Age				
< 70 years	Reference		Reference	
70-80 years	1.79	0.02*	1.72	0.10
> 80 years	3.36	0.00*	2.98	0.00*
Co-morbidities				
Dyslipidemia	-	-	0.61	0.15
Diabetes	-	-	2.81	0.07
Hypertension	-	-	1.78	0.05
Drug exposure time (days)	1.03	0.00*	1.05	0.00*
Gastro-protective use	0.49	0.00*	-	-
Low dose ASA use	0.81	0.94	-	-

* Significant at $p < 0.05$ level

years; OR = 3.36 (p = 0.00) and OR = 1.79 (p = 0.02) in patients aged 70-80 years and > 80 years respectively. Using gastro-protective agents could reduce the GI risk associated with all drug groups by approximately 51% (OR = 0.49, p = 0.00). Drug exposure time, which was defined as the number of days of medication supplied also significantly increased the developing of GI events.

Celecoxib and etoricoxib associated with the lower OR of CV event comparing to tNSAIDs but not significant at $p < 0.05$. However, there were 3 factors significantly increase the risk of CV events. These included female (OR = 0.29, p = 0.00), age > 80 years (HR = 2.98, p = 0.00) comparing to male and reference age group (< 70 years) respectively, and drug exposure time (OR = 1.05, p = 0.00).

Discussions

It is well documented that the long-term use of traditional NSAIDs and selective COX-2 inhibitors may cause GI and CV adverse events, including some co-morbidities and co-medication used[1-3]. In the intermediate to high-risk group defined by many risk factors, such as age, co-morbidities, co-medications use, co-prescribing of the gastro-protective agents has been recommended for tNSAIDs[4-6]. However there is still debate about whether or not the co-prescribing of PPI to tNSAIDs is associated with a reduction of GI risk comparing to coxibs alone[7]. Risk factors are prior complicated/non complicated ulcer, use of multiple tNSAIDs, high dose of tNSAIDs, use of anti-coagualants, age > 65, H pylori, use of steroids. The severity of a GI adverse event is rated according to a

risk stratification of 0.8%, 2%, 8%, and 18% from no risk to more than 4 risks respectively[8]. Prevention of GI events is recommended in asymptomatic patients aged more than 70 years, with a history of GI events, or with a co-medication such as anti-platelet or anti-coagulant therapy[9-11].

From this study, we found that coxibs were significantly associated with fewer risk of GI comparing to tNSAIDs. Most of patients were co-given PPI to both of tNSAIDs and coxibs. We also found that the use of PPI significantly decreased the risk of GI events. Comparing to tNSAIDs, the greatest reduction of GI risk was observed in celecoxib group following by etoricoxib. However, it should be noted that the patients' baseline risk might be different among these two drug groups even there might be some of them were the same, then the greater reduction of GI risk in celecoxib may not reflect its superior GI safety profile than etoricoxib. This may be due to the treating physicians varying views of their patients' baseline risks of GI, hence affecting choice of drug prescribed.

It has been well known that the using tNSAIDs and coxibs increases the risk of cardiac failure and acute thrombosis in coronary artery diseases[12,13]. The mechanism of this event associated with the imbalances of Thrombroxene A2 and Prostacyclines[14,15]. Recent studies of CHF risk are relatively limited[16,17]. Different drugs may have different risks but, overall, tNSAIDs and COXIBs caused similar CV risks. Then there has been a recommendation on tNSAIDs and coxibs that they should be used with caution in patients at high risk of developing cardiac failure, such as those with diabetes mellitus, renal disease or receiving treatment for hypertension, as well as patients known to have had cardiac failure and coronary artery diseases[18]. Multiple factors, such as specific heart diseases (MI, any state of CHF) within 6 months of percutaneous cardiac intervention, chest pain, should rule out the use of not only selective cox-2 inhibitors but all tNSAIDs as well[19-22]. Minimizing the dose and duration of anti-inflammation medications are also recommended[23].

In addition, we found two major factors positively affecting the odds ratio of GI and CV events: aged > 70 years and drug exposure time. These results supported what was discovered in previous research[24-26]. OA frequently found in aging population, and age is an inevitable factor to consider while the drug exposure time can be easily managed to be clinically rational by individual patient basis. The main implication from this finding is how the physician can select the appropriate drug and how long it should be used in individual patient. ASA use in our patients did not significantly increase the odds ratio of GI which was similar to previous works[27-29]. This could be a result of intensive precaution among physician in selection of drug use, co-medication prescribed in particularly GI protective agents in this patient group.

Two studied coxibs were not significantly different from tNSAIDs in their association with CV events based on the adjusted odds ratio, and even the CV incidence rate found in tNSAIDs was higher than coxibs. There were only three factors: female, ages > 80 years, and drug exposure time, that significantly increased CV risks. Selective cox-2 inhibitors should be used with caution due to risks of CHF and ischemic heart[30]. In our study, there is no significant increase in odds ratio between tNSAIDs and coxibs although the increase is less for in celecoxib than etoricoxib, as previously reported in many studies. The reason for the difference in odds ratio between tNSAids and coxibs could be the appropriate selection of patients and drug use; choice and duration of use, to minimize the possible CV risks and physician awareness on the association of coxibs and tNSAIDs with CV adverse events. The physicians' compliance on the recommendation of tNSAIDs and coxibs use is vital.

Regarding the utilization pattern of tNSAIDs and coxibs use in our patients, it possibly signified that they were sporadic users, as their average number of prescription per person per year was just only 4 prescriptions, with 27 days of average drug exposure time per prescription. As a result, our patients were given pain-relieving agents about 3 months per year. This evidence may support the rationale of how the appropriate approach for pain management in knee OA should be in the elderly patients with multiple co-morbidities. However, to ensure the effective and rationale use of these two drug groups, the actual drug utilization should be further studied.

It is worth noting that there were some study limitations. There was some unavailable data of confounders, such as smoking data, the use of pain-relieving OTC products affecting both GI and CV events Availability of such information would make the individual covariate analysis less confounded. However, this is quite a general limitation of a retrospective database research. Choice of drug use may vary among the treating physicians. In particularly, in this elderly patient group, bias in drug use selection appeared to be towards patients who are at high risk of

GI and CV events. They commonly were given the coxibs rather than tNSAIDs. Thus the baseline risk of GI and CV events in this drug exposure group was more advanced than in tNSAIDs users. This study did not control confounders because matching the high number of them with each physician was not practical. The risks reported here are mostly hospital-based, not community-based.

Conclusion

Incidence of GI and CV events was lower in coxibs than tNSAIDs and celecoxib was observed to have the lowest incidence. Patients with advanced age and increased drug exposure time significantly increased their GI risk and using gastro-protective agents significantly decreased GI risk. Being female, of advanced age, and drug exposure time significantly affect CV events. Further studies should be conducted to determine the actual drug utilization pattern along with the patients' factors that affect the different incidence rates of GI and CV event.

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การศึกษาระบาดวิทยาของภาวะแทรกซ้อนทางระบบทางเดินอาหารและระบบหลอดหัวใจและเลือดจากการใช้ยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์กลุ่มดั้งเดิม และ ยากลุ่มยับยั้งคอกซ์ทูแบบจำเพาะในผู้สูงอายุที่เป็นโรคข้อเสื่อม

ธนา ธุระเจน, รังสี วงศ์บุญหนัก, ธนิสา พัชรตระกูล, เกษม รัตนสุมาวงศ์, ยุทธนา พลอยแกมเพชร, ทวี ทรงพัฒนาศิลป์

วัตถุประสงค์: *เพื่อประเมินอุบัติการณ์และอัตราเสี่ยงเกี่ยวกับระบบทางเดินอาหาร และระบบหลอดเลือดหัวใจในผู้ป่วยข้อเข่าเสื่อมที่อายุมากกว่า 60 ปีในกลุ่มที่ใช้ ยากลุ่มต้านการอักเสบและยากลุ่มต้านการอักเสบเฉพาะคอกซ์ทู ได้แก่ ซีรีค็อกซิปและอีโทริค็อกซิป*

วัสดุและวิธีการ: *การศึกษานี้เป็นการใช้ข้อมูลการใช้ยากลุ่มต้านการอักเสบย้อนหลัง โดยข้อมูลภาวะแทรกซ้อนทางระบบทางเดินอาหารจากหน่วยทางเดินอาหาร และข้อมูลภาวะแทรกซ้อนทางระบบหลอดเลือดหัวใจจากหน่วยโรคหัวใจ แผนกอายุรกรรม โรงพยาบาลตำรวจ ตั้งแต่ เดือนมิถุนายน พศ.2547 ถึงพศ. 2550*

ผลการศึกษา: *ข้อมูลใบสั่งยาจำนวน 12591 ใบ ผู้ป่วยจำนวน 1030 คน โดยค่าเฉลี่ย 4 ใบสั่งยาต่อคนต่อปี โดย 3,982 (31.6%) ใบสั่งยาใช้ยาต้านการอักเสบ, 4,426 (35.2%) ใบสั่งยาสำหรับยาซีริคอกซิป, และ 4,183 (33.2%) ใบสั่งยาสำหรับอีโทริคอกซิป ยาต้านการอักเสบที่ใช้มากที่สุดได้แก่ เมลอกซิแคม(24%), นามิซูลาย (21.4%) และ นาโปรซิน (13.1%) อายุเฉลี่ย 69.6 ปี, ผู้หญิง (74%) อายุเฉลี่ยส่วนใหญ่อยู่ช่วง 60-70 ปี โดยการใช้ส่วนใหญ่ ของยากลุ่มต้านการอักเสบเฉพาะค็อกทูได้แก่ ยาซีรีค็อกซิป (200mg OD) และอีโทริค็อกซิป (90 mg OD) ภาวะแทรกซ้อนทางระบบทางเดินอาหารโดยการวินิจฉัยผ่านกล้องพบ 78 ราย ได้แก่ 37 (47.4%) อาการดีสเป็ปเซีย, 22 (28.2%) อาการโลหิตจาง (28.2%), 17 (21.7%) อาการเลือดออกในกระเพาะส่วนต้น, and 2 (2.6%) จากอาการอื่น ๆ ผู้ป่วยจำนวน 40 ราย ได้รับยาต้านการอักเสบ, 21 ราย ได้รับยา ซีรีค็อกซิป และ 17 ได้รับอีโทริค็อกซิป ภาวะแทรกซ้อนระบบทางเดินอาหารได้แก่ กระเพาะอักเสบ (50, 64.1%), แผลในกระเพาะ (14, 17.9%), แผลลำไส้ส่วนต้น (3, 3.8%), และปกติ (11, 14.1%) ผู้ป่วยที่มีภาวะแทรกซ้อน ทางระบบหลอดเลือดหัวใจ ได้รับยาต้านการอักเสบ ยาซีรีค็อกซิป ยาอีโทริค็อกซิป จำนวน 20, 18 และ 11 ราย ตามลำดับผู้ป่วยจำนวนรวม 49 ราย, ภาวะที่พบได้แก่ หัวใจล้มเหลว (29), หัวใจขาดเลือด angina (9), หัวใจขาดเลือด unstable angina (6), และกล้ามเนื้อหัวใจตาย (5) โดยวิธีวิเคราะห์ logistic regression analysis, พบว่าผู้ที่ได้รับ ซีริค็อกซิปมีการลดลง อย่างมีนัยสำคัญของภาวะแทรกซ้อนทางระบบอาหาร เมื่อเทียบกับยาต้านการอักเสบทั่วไป; OR = 0.36 (95% CI 0.21-0.63, p = 0.00) และเมื่อเทียบกับอีโทริค็อกซิปกับยาต้านการอักเสบทั่วไป OR = 0.52 (95% CI 0.28-0.98, p = 0.04) เปรียบเทียบกับผู้ป่วยที่อายุ 60 ปี ผู้ป่วยที่มีอายุ มากกว่า 70 ปี มีความเสี่ยงภาวะแทรกซ้อนทางเดินอาหารอย่างมีนัยสำคัญ, OR = 1.79 สำหรับอายุระหว่าง 70-80 ปี และ 3.36 สำหรับอายุมากกว่า 80 ปี ระยะเวลาการทานยา เพิ่มอุบัตการณ์การเกิดภาวะแทรกซ้อนทางเดินอาหารอย่างมีนัยสำคัญ ปัจจัยสามอย่างที่มีผลต่อภาวะแทรกซ้อนทางระบบหลอดเลือดหัวใจอย่างมีนัยสำคัญได้แก่ ผู้หญิง (OR = 0.29, p = 0.00), อายุมากกว่า 80 ปี (OR = 2.98, p = 0.00), ระยะเวลาการใช้ยา (OR = 1.05, p = 0.00)*

สรุป: *อุบัติการณ์การเกิดภาวะแทรกซ้อนในระบบทางเดินอาหารและหลอดเลือดหัวใจ พบว่าเกิดขึ้นน้อยกว่าจากยาต้านการอักเสบเฉพาะค็อกซ์ทูเมื่อเทียบกับยาต้านการอักเสบทั่วไป และซีรีค็อกซิปน้อยกว่าอีโทริคอกซิป การใช้ยาป้องกันการระคายเคืองกระเพาะอาหาร สามารถลดภาวะแทรกซ้อนทางเดินอาหารได้อย่างมีนัยสำคัญ เพศหญิง, ผู้ป่วยสูงอายุ ระยะเวลาการใช้ยามีผลต่อการเกิดภาวะแทรกซ้อนทางระบบหลอดเลือดและหัวใจ*