A Novel Composite Endpoint to Evaluate the Gastrointestinal (GI) Effects of Nonsteroidal Antiinflammatory Drugs Through the Entire GI Tract

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ABSTRACT. ***Objective.*** Nonsteroidal antiinflammatory drugs (NSAID) not only cause damage to the upper gastrointestinal (GI) tract but also affect the lower GI tract. To date, there is no endpoint that evaluates serious GI events in the entire GI tract. The objective of this report is to introduce a novel composite endpoint that measures damage to the entire GI tract — clinically significant upper and lower GI events (CSULGIE) — in patients with NSAID-induced GI damage.

Methods. We reviewed the data from largescale, multicenter, randomized, clinical trials on lower GI toxicity associated with NSAID use. The rationale for using CSULGIE as a primary endpoint in 2 ongoing trials — the Celecoxib vs Omeprazole and Diclofenac for At-risk Osteoarthritis (OA) and Rheumatoid Arthritis (RA) Patients (CONDOR) trial and the Gastrointestinal Randomized Events and Safety Open-Label NSAID Study (GI-REASONS) — is also discussed.

Results. Previous randomized trials focused primarily on damage to the upper GI tract and often neglected the lower GI tract. The CSULGIE endpoint extends the traditional "perforation, obstruction, and bleeding" assessment of upper GI complications by including events in the lower GI tract (small/large bowel) such as perforation, bleeding, and clinically significant anemia.

Conclusion. By providing clinicians with a new, descriptive language for adverse events through the entire GI tract, the CSULGIE endpoint has the potential to become a standard tool for evaluating the GI effects of a range of therapies. (J Rheumatol First Release Nov 1 2009; doi:10.3899/jrheum.090168)

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Drug-induced gastrointestinal (GI) toxicity remains a major clinical problem; in the United States, 20%–40% of all drug-induced side effects are associated with the GI tract[1]. Nonsteroidal antiinflammatory drugs (NSAID) are well known to cause potentially serious adverse GI events such as ulcers, perforation, hemorrhage, and death[2]. Due to their antiinflammatory, antipyretic, and analgesic properties, NSAID are among the most widely prescribed medications worldwide. However, the GI side effects associated with their use are a significant cause of hospital admissions, mortality, and healthcare expenditure[3-5].

Although NSAID-induced upper GI toxicity has been well characterized[6-8], the risk of lower GI tract events is less well recognized. Traditional "perforation, obstruction, and bleeding" (POB) assessments are often used to characterize upper GI tract events; however, it should be noted that these assessments are often dominated by bleeding events. Bjarnason, *et al* were among the first group to report that nonselective NSAID could damage the lower GI tract. They showed an abnormal effect of NSAID on the permeability of

both the proximal and the distal intestine[9]. In a postmortem examination, Allison, *et al*[10] found there was a significant increase in small bowel ulcerations among patients taking NSAID compared with nonusers; further, in this study, 3 patients were reported to have died from perforation of the small bowel. In the same year, Lanas, *et al* also reported an association between NSAID use and an increased risk for lower GI bleeding[11].

There has been an increasing body of evidence to suggest that NSAID-induced GI toxicity does extend to the lower GI tract[12-19]. A number of case-control studies have consistently shown that NSAID use increases the risk of lower GI bleeding and perforation[20-22], while data derived from secondary analyses of randomized NSAID trials[13,23] suggest that 33%–50% of serious GI events reported occur in the lower GI tract. In a systematic review of published studies to identify possible adverse effects of NSAID on the small intestine[24], it was found that NSAID caused a variety of small intestinal damage such as ulcers, perforation, strictures, anemia, and hypoalbuminemia. However, assessment of NSAID damage to the small intestine has proven to be extremely difficult and many physicians were skeptical regarding the concept that NSAID could cause such damage.

Among various small intestinal events associated with NSAID use, the diagnosis of significant occult bleeding (with or without anemia) is most difficult and has often been overlooked by physicians. Although more advanced diagnostic technologies such as capsule endoscopy or double-balloon enteroscopy have provided physicians with a means of visualizing the lower GI tract, they are currently not widely adopted by the medical community due to their limitations. For example, both procedures are time-consuming, costly, and are only available in specialized centers. There are also reports that significant lesions have been missed with capsule endoscopy[25,26] and, due to the invasive nature of the procedure, serious complications such as pancreatitis and perforation have been reported with double-balloon enteroscopy[27]. On the other hand, the clinical significance of finding asymptomatic mucosal breaks among patients taking NSAID remains uncertain. Thus, while these new technologies may serve as adjuvant diagnostic tools, NSAID-induced occult bleeding from the small bowel remains largely a clinical diagnosis that is often established by excluding other causes of a drop in hemoglobin.

Recent data suggest that hospitalizations for lower GI complications are increasing. In a study in Spain, Lanas, *et al* demonstrated that, while hospitalizations due to upper GI complications fell in the decade 1996–2005 (from 87 to 47/100,000), lower GI complications increased from 20 to 33/100,000[28]; in the same study, lower GI events were also associated with higher mortality rates, longer hospitalization, and higher resource utilization than upper GI events. These data are further supported by the findings from a recent study in the US looking at the number of hospitalizations between 1998 and 2006[29]. During this period, hospitalizations for lower GI bleeding increased by 8% (per 100,000 people), while the number of upper GI bleeding events fell (14% decrease per 100,000).

We aimed to evaluate the outcomes of several pivotal trials and introduce a novel composite endpoint that measures damage to the entire GI tract — clinically significant upper and lower GI events (CSULGIE) — in patients with NSAID-induced GI damage.

MATERIALS AND METHODS

We reviewed the study design, duration of followup, endpoint definitions, and GI adverse event (AE) rates of several pivotal trials, including MUCOSA (Misoprostol Ulcer Complications Outcomes Safety Assessment)[30], CLASS (Celecoxib Long-term Arthritis Safety Study)[6], VIGOR (Vioxx Gastrointestinal Outcomes Research)[31], TARGET (Therapeutic Arthritis Research and Gastrointestinal Event Trial)[32], SUCCESS-I (Successive Celecoxib Efficacy and Safety Study I)[33], and MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term)[34] (Table 1).

In addition, 2 ongoing double-blind, randomized, multicenter trials, the Celecoxib vs Omeprazole and Diclofenac for At-risk Osteoarthritis (OA) and Rheumatoid Arthritis (RA) Patients (CONDOR) trial (NCT00141102), and the Gastrointestinal Randomized Events and Safety Open-label NSAID Study (GI-REASONS) (NCT00373685), were also included for comparison (Table 2). Both trials will include > 12,000 OA and RA subjects with moderate to high GI risk (including patients with recognized GI risk factors such as a history of upper/lower GI event, old age, and/or comorbid disease) and will use a new composite measure of GI safety — CSULGIE (Table 3).

The CONDOR trial is a double-blind, triple-dummy, randomized, parallel-group, multicenter, international study comparing treatment with celecoxib versus slow release (SR) diclofenac plus omeprazole in 4402 subjects with OA and/or RA at high risk of GI AE (Table 2; Figure 1). The primary objective of the CONDOR study is to determine whether celecoxib is superior to the combination of diclofenac plus omeprazole in the incidence of CSULGIE, as adjudicated by an independent, blinded GI events committee. The GI-REASONS trial is a prospective, randomized, open-label, blinded endpoint (PROBE) design study conducted in the US. Approximately 8000 subjects with moderate GI risk (aged ≥ 55 yrs) will be randomly assigned in a 1:1 fashion to either celecoxib or any nonselective NSAID (not aspirin) for 6 months (Table 2; Figure 1). Similar to CONDOR, aspirin users (including low-dose aspirin for cardiovascular prophylaxis) are excluded from the GI-REASONS study. The primary objective of GI-REASONS is to determine whether celecoxib use in OA subjects at moderate GI risk is associated with a lower incidence of adjudicated CSULGIE than treatment with nonselective NSAID, with or without concomitant proton-pump inhibitors.

RESULTS

To date, published clinical trials have focused primarily on damage to the upper GI tract and generally included low-risk populations; however, differences in trial designs, patient populations, and treatment comparators, as well as the use of different terminology for defining an event, have made cross-study comparisons difficult (Table 1). In addition, the use of aspirin and gastroprotective agents, and the lack of a standardized time period between first identification of an event and endoscopy, has further hindered accurate treatment comparisons. Conventional methods of GI

Table 1. Comparison of published studies.

	MUCOSA[30]	CLASS[6]	SUCCESS-I[33]	VIGOR[31]	MEDAL[34]	TARGET[32]
Study duration	6 mo	12 mo	12 wks	12 mos	18 mo (average from pooled analysis)	52 wks
Study population	RA subjects at moderate GI risk, age ≥ 52 yrs	OA or RA subjects, age ≥ 18 yrs	OA subjects, age ≥ 18 yrs	RA subjects at moderate GI risk Age ≥ 50 yrs (or ≥ 40 yrs and requiring longterm glucocorticoid therapy)	OA or RA subjects, age ≥ 50 yrs	OA subjects at moderate GI risk, age ≥ 50 yrs
Population size	8,843	8,059	13,274	8,076	34,701	18,325
Treatment arms	Misoprostol 200 μg or placebo qid	Celecoxib 400 mg bid Ibuprofen 800 mg tid Diclofenac 75 mg bid	Celecoxib 100/ 200 mg bid Diclofenac 50 mg bid or naproxen 500 mg bid	Rofecoxib 50 mg qd Naproxen 500 mg bid	Etoricoxib 60 mg or 90 mg qd Diclofenac 150 mg qd	Lumiracoxib 400 mg qd Naproxen 500 mg bid Ibuprofen 800 mg tid
GI endpoint definition	Confirmed serious upper GI events (perforation, obstruction, bleeding)	Confirmed upper GI ulcer complications (GD perforation, obstruction, upper GI bleeding)	Confirmed serious upper GI events (GD perforation, obstruction, upper GI bleeding)	Confirmed upper GI events [GD perforation, obstruction, upper GI bleeding, symptomatic GD ulcers, bleeding (≥ 2 g/dl drop in hemoglobin with visible upper GI lesion)]	Confirmed upper GI events [GD perforation, obstruction, upper GI bleeding, symptomatic GD ulcers, bleeding (≥ 2 g/dl drop in hemoglobin with visible upper GI lesion)]	Difference in time-to-event distribution of definite or probable upper GI ulcer complications [clinically significant bleeding, perforation, obstruction, bleeding (≥ 2 g/dl drop in hemoglobin and ≥ 6 point fall in hematocrit with visible lesion)]
ASA usage	Yes (7%)	Yes (21%)	Yes (7%)	Excluded	Yes (35%)	Yes (24%)
PPI usage	Excluded	Excluded	Excluded	Yes (9%)	Yes (40%)	Excluded

RA: rheumatoid arthritis; OA: osteoarthritis; GI: gastrointestinal; qid: 4 times a day; bid: twice a day; tid: 3 times a day; qd: once a day; GD: gastroduodenal; ASA: aspirin; PPI: proton-pump inhibitor.

evaluation also omit potentially important information regarding damage to the small and large bowel and thus, significant gaps remain in our understanding of the drug-induced toxicity through the entire GI tract. Given the high prevalence of NSAID use, this gap in knowledge has significant potential for suboptimal treatment.

A more comprehensive and patient-focused evaluation of therapeutic toxicity through the entire GI tract is needed. We propose a new composite measure of GI safety — CSULGIE. The CSULGIE endpoint has been developed based on lessons from previous GI outcomes studies. Extending the POB assessment of upper GI complications by including events in the lower GI tract, and thus identifying damage to the entire GI tract, we hope that the CSULGIE endpoint (Table 3), which is currently being used as a primary endpoint in the CONDOR and GI-REASONS clinical trials, will provide a more clinically relevant evaluation of drug-induced damage in the upper and lower GI tracts for these trials.

Separate adjudication committees for GI events are established for CONDOR and GI-REASONS. The GI events adjudication committees comprise a team of gastroenterologists recognized for their expertise in this area. All members of the adjudication committees are blinded to treatment (Figure 2). As discussed, the primary endpoint in these trials is the incidence of CSULGIE, a composite of clinical or laboratory changes that could lead to further investigations for GI blood loss and/or modification of current therapies (Table 3). All suspected GI events are referred to the adjudication committees for consideration; an event was confirmed when consensus could be reached by all members of the committee. Adjudication was reached if all committee members agreed on the event in the first round of review or, if a second round of review was needed, then consensus was reached following a discussion of the case among committee members. Suspected GI events include hematemesis, melena, perforation, obstruction, a reduction of hemoglobin ≥ 2 g/dl and/or hematocrit ≥ 10 percentage points from baseline, or other significant signs or symptoms that the investigator considers may represent a possible GI event. Only events confirmed by the GI events adjudication committee are included in the primary analysis.

Table 2. CONDOR and GI-REASONS study comparisons.

	CONDOR	GI-REASONS
Study duration	6 mo	6 mo
Study population	OA or RA subjects at high GI risk • Age ≥ 60 yrs, with/without history of GD ulceration; or • Any age ≥ 18 yrs with history of GD ulceration	OA subjects of moderate GI risk • Age ≥ 55 yrs
Population size	4402 subjects	8000 subjects
Treatment arms	• Celecoxib 200 mg bid • Diclofenac 75 mg bid + omeprazole 20 mg qd	• Celecoxib: any dose within the US PI recommended range; or • Prescription nonselective NSAID at the discretion of the investigator, as per US PI recommendations
Primary endpoint (adjudicated by GI events committee)	CSULGIE	CSULGIE including symptomatic ulcers
Secondary endpoints	• Incidence of CSULGIE plus symptomatic ulcers • Patient's global assessment of arthritis • Change in Hgb and Hct from baseline to final visit • Incidence of subjects with clinically significant decrease in Hct (≥ 10% points) and/or Hgb (≥ 2 g/dl) • Hepatic AE • Change in hepatic measures from baseline to final visit • Incidence of CSULGIE; symptomatic ulcers; moderate to severe abdominal symptoms; withdrawal due to GI AE • Change in iron parameters and C-reactive protein from baseline to final visit	• Patient satisfaction with celecoxib vs nonselective NSAID therapy • Patient Treatment Satisfaction Scale • Drug switching behavior, PPI utilization, non-study drug utilization • Overall safety and tolerability of celecoxib vs nonselective NSAID therapy • Incidence of moderate to severe abdominal symptoms and withdrawal due to AE • Change in Hgb and Hct from baseline to study termination visit • Incidence of fecal occult blood test positivity at study termination
Aspirin usage	No	No
PPI usage	Yes: double-blind nonselective NSAID treatment arm prescribed concomitant omeprazole, as study medication	Yes: at discretion of investigator (open-label)
Helicobacter pylori	Excluded	Included (stratified at baseline)

OA: osteoarthritis; RA: rheumatoid arthritis; GI: gastrointestinal; GD: gastroduodenal; US PI: US prescribing information; NSAID: nonsteroidal antiinflammatory drug; CSULGIE: clinically significant upper and lower gastrointestinal events; Hgb: hemoglobin; Hct: hematocrit; AE: adverse event; PPI: proton-pump inhibitor.

DISCUSSION

Previous GI outcomes studies have provided valuable data on drug-induced toxicity in the upper GI tract; however, appropriate risk reduction strategies and future patient management require a better understanding of GI risk throughout the entire GI tract. Although the effect of NSAID-induced enteropathy is becoming increasingly recognized following the emergence of technologies such as wireless capsule endoscopy, there are limitations associated with the latter; these include missing significant lesions as well as detecting trivial mucosal breaks of uncertain clinical significance.

Addressing the need for a more comprehensive and patient-focused evaluation of toxicity through the entire GI tract, the CSULGIE endpoint represents an important step in the evaluation of GI safety. The CSULGIE endpoint will not only reveal damage to the upper GI tract but, it is hoped, will also help raise awareness of damage to the lower GI tract. In addition, the CSULGIE endpoint has the potential to improve our understanding of GI risk. By enabling healthcare providers to assess patient risk and the GI effects of various therapies, both in and outside of clinical trials, CSULGIE may facilitate more effective and informed decision-making.

Further, consistent adjudication of events by expert GI committees will help investigators collect more complete and clinically relevant GI safety data from a range of therapies, across clinical trials, thus helping to create a more statistically robust measure of GI safety. CONDOR and GI-REASONS will be the first trials to evaluate the GI burden of NSAID therapies using the CSULGIE endpoint.

When interpreting the results of clinical studies it is

Table 3. CSULGIE composite endpoint.

With Lesion	Without Lesion
GD hemorrhage • Endoscopic evidence of GD ulceration or erosion or other likely causative lesion, and clinical evidence of recent hemorrhage Gastric outlet obstruction • Clinical, surgical, endoscopic, or radiographic evidence with symptoms consistent with obstruction GD, small bowel, or large bowel perforation • Clinical, surgical, or radiographic confirmation associated with symptoms consistent with perforation Large bowel hemorrhage • Frank melena or PR blood loss with no evidence of source on EGD and likely causative lesion on colonoscopy. Hemorrhoidal hemorrhage is included if associated with a clinically significant drop in Hct ≥ 10% points and/or Hgb ≥ 2 g/dl from baseline Small bowel hemorrhage • Frank melena or PR blood loss with likely causative lesion on small bowel investigation Small bowel obstruction* • Nausea and vomiting ≥ 24 h with evidence of narrowing occurring in the duodenum, jejunum, or ileum (confirmed by endoscopy, radiography, or surgery). Obstruction caused by sources in the lower GI tract such as colon cancer, diverticulitis, or adhesions from prior surgery not included Clinically significant anemia of defined GI origin • No clinical evidence of acute GI hemorrhage but with fall in Hct ≥ 10% points and/or Hgb ≥ 2 g/dl from baseline, with likely causative lesion on colonoscopy or EGD (or small bowel investigation) with • no non-GI source of anemia, and • in RA patients, disease activity should be stable Symptomatic ulcers† • Cases that do not meet the definition of an ulcer complication but do have endoscopic evidence of a gastric and/or duodenal ulcer, as adjudicated by the GI events committee	Acute GI hemorrhage of unknown origin, including presumed small bowel hemorrhage • Frank hematemesis, melena, or PR blood loss, with no evidence of likely causative lesion on EGD or colonoscopy (or small bowel investigation) Clinically significant anemia of presumed occult GI origin, including possible small bowel blood loss • No overt clinical evidence of acute GI hemorrhage but with fall in Hct ≥ 10% points and/or Hgb ≥ 2 g/dl from baseline, with no evidence of likely causative lesion on EGD or colonoscopy (or small bowel investigation) with: • no non-GI source of anemia identified, and • in RA patients, disease activity should by stable

* Primary endpoint in GI-REASONS only; † primary endpoint in GI-REASONS and a secondary endpoint in CONDOR. CSULGIE: clinically significant upper and lower gastrointestinal events; GD: gastroduodenal; GI: gastrointestinal; PR: post-rectal; EGD: esophagogastroduodenoscopy; Hgb: hemoglobin; Hct; hematocrit; RA: rheumatoid arthritis.

important to consider the study limitations. Although the CSULGIE endpoint aims to identify AE of the entire GI tract, the adjudication of "clinically significant anemia of presumed occult GI origin, including possible small bowel blood loss" remains a continuing challenge to members of the GI events adjudication committees. In the CONDOR and GI-REASONS studies, "clinically significant anemia of presumed occult GI origin, including possible small bowel blood loss" is defined as a fall in hemoglobin of ≥ 2 g/dl and/or fall in hematocrit ≥ 10 percentage points from baseline (Table 2). We found that most patients with a significant fall in hemoglobin did not undergo extensive small bowel investigation such as capsule endoscopy or double-blind balloon enteroscopy; this may be due to the availability of diagnostic procedures in different centers or compliance with local practice guidelines. However, as previously discussed, these new technologies only serve as adjuvant, rather than mandatory diagnostic tools. The diagnosis for a fall in hemoglobin is largely based on clinical judgment and exclusion of other non-GI causes such as dilutional anemia, anemia of chronic illness, or flare of RA. Nevertheless, there remains a possibility that some patients who were adjudicated to have "clinically significant anemia of presumed occult GI origin" actually had a fall in hemoglobin due to a multitude of factors. This limitation is particularly relevant to patients who had a drop in hemoglobin of ≥ 2 g/dl but did not become truly anemic (e.g., hemoglobin level fell from 14 g/dl to 12 g/dl). To overcome this limitation, members of the CONDOR and GI-REASONS adjudication committees met to ensure that there was consistency in adjudicating lower GI events, such that any uncertainty in the diagnosis would be equally reflected in the 2 treatment arms.

It is hoped that CSULGIE will become the gold standard for evaluating the gastrointestinal effects of a range of therapies, providing clinicians with a new descriptive language for adverse events through the entire GI tract. By providing a more complete measure of GI risk, the use of CSULGIE

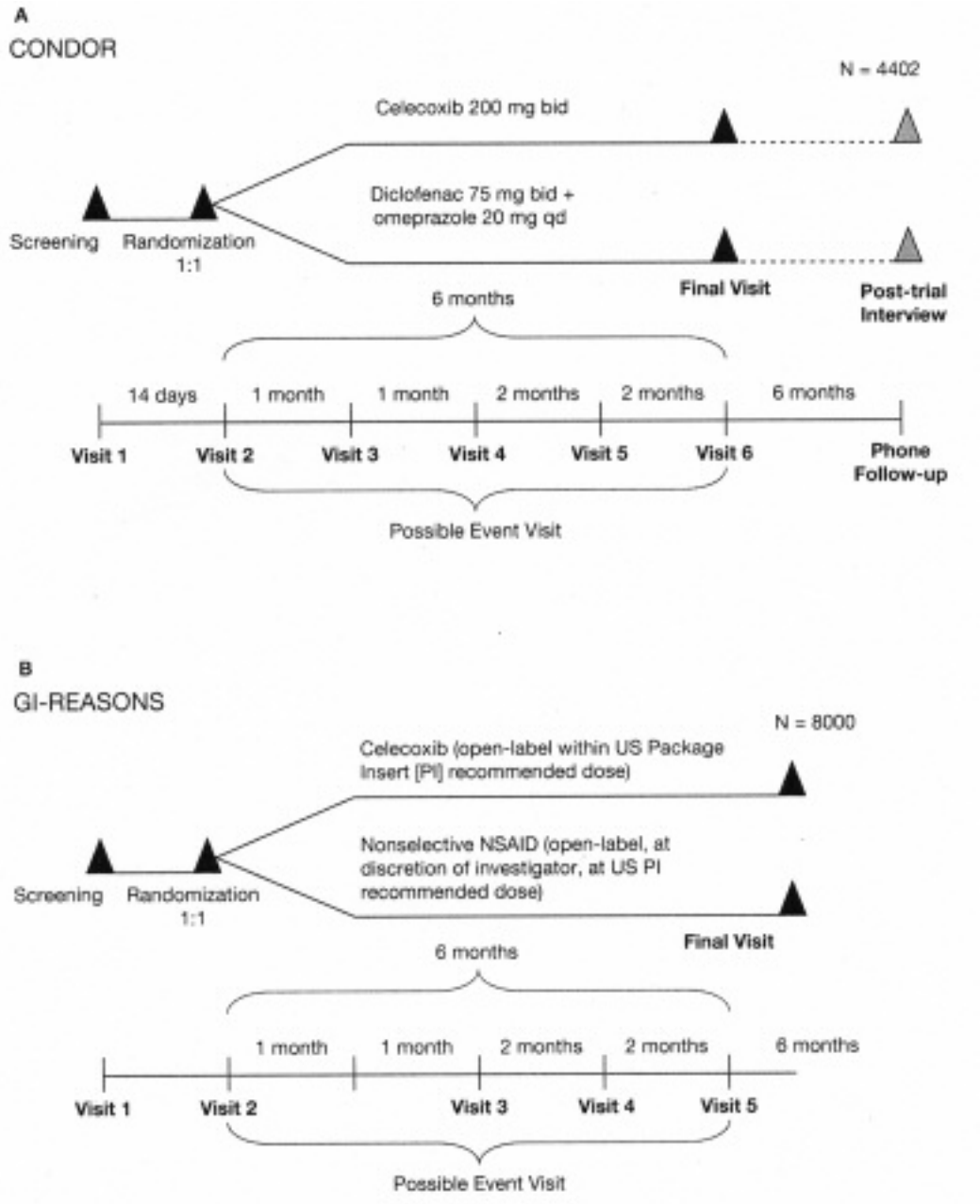

Figure 1. A. CONDOR study design; B. GI-REASONS study design.

may help physicians to identify risk reduction strategies and encourage them to make more effective treatment decisions and ultimately help improve patient care.

REFERENCES

1. Hadjibabaie M, Rastkari N, Rezaie A, Abdollahi M. The adverse drug reaction in the gastrointestinal tract: an overview. Int J Pharmacol 2005;1:1-8.
2. Peura D, Goldkind L. Balancing the gastrointestinal benefits and risks of nonselective NSAIDs. Arthritis Res Ther 2005;7 Suppl:S7-13.
3. Lanas A, Perez-Aisa MA, Feu F, Ponce J, Saperas E, Santolaria S, et al. A nationwide study of mortality associated with hospital admission due to severe gastrointestinal events and those associated with nonsteroidal antiinflammatory drug use. Am J Gastroenterol 2005;100:1685-93.
4. Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. J Rheumatol 1999;26 Suppl 56:18-24.
5. Vonkeman HE, Klok RM, Postma MJ, Brouwers JR, van de Laar MA. Direct medical costs of serious gastrointestinal ulcers among users of NSAIDs. Drugs Aging 2007;24:681-90.
6. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T,

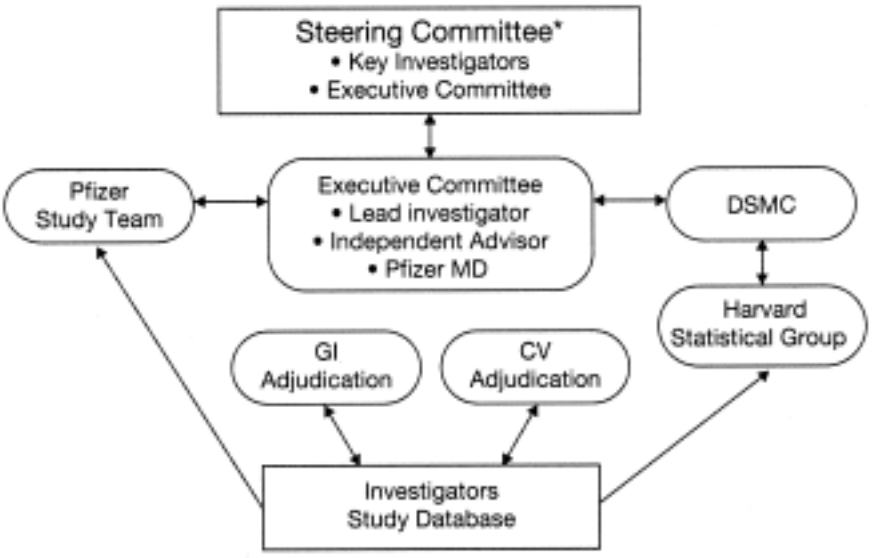

Figure 2. The structure of the study. The GI events adjudication committees consisted of gastroenterologists recognized for their expertise. *CONDOR study only. DSMC: Data Safety Monitoring Committee; GI: gastrointestinal; CV: cardiovascular.

Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. JAMA 2000;284:1247-55.

7. Garcia Rodriguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual nonsteroidal anti-inflammatory drugs. Lancet 1994;343:769-72.
8. Laine L. Proton pump inhibitor co-therapy with nonsteroidal anti-inflammatory drugs — nice or necessary? Rev Gastroenterol Disord 2004;4 Suppl:S33-41.
9. Bjarnason I, Williams P, So A, Zanelli G, Levi A, Gumpel J, et al. Intestinal permeability and inflammation in rheumatoid arthritis: effects of non-steroidal anti-inflammatory drugs. Lancet 1984;24:1171-4.
10. Allison MC, Howatson AG, Torrance CJ, Lee FD, Russell RI. Gastrointestinal damage associated with the use of nonsteroidal anti-inflammatory drugs. N Engl J Med 1992;327:749-54.
11. Lanas A, Sekar MC, Hirschowitz BI. Objective evidence of aspirin use in both ulcer and nonulcer upper and lower gastrointestinal bleeding. Gastroenterology 1992;103:862-9.
12. Wilcox CM, Alexander LN, Cotsonis GA, Clark WS. Nonsteroidal antiinflammatory drugs are associated with both upper and lower gastrointestinal bleeding. Dig Dis Sci 1997;42:990-7.
13. Laine L, Connors LG, Reicin A, Hawkey CJ, Burgos-Vargas R, Schnitzer TJ, et al. Serious lower gastrointestinal clinical events with nonselective NSAID or coxib use. Gastroenterology 2003;124:288-92.
14. Laine L, Smith R, Min K, Chen C, Dubois RW. Systematic review: the lower gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther 2006;24:751-67.
15. Lanas A, Panes J, Pique JM. Clinical implications of COX-1 and/or COX-2 inhibition for the distal gastrointestinal tract. Curr Pharm Des 2003;9:2253-66.
16. Adebayo D, Bjarnason I. Is non-steroidal anti-inflammatory drug (NSAID) enteropathy clinically more important than NSAID gastropathy? Postgrad Med J 2006;82:186-91.
17. Fortun PJ, Hawkey CJ. Nonsteroidal antiinflammatory drugs and the small intestine. Curr Opin Gastroenterol 2005;21:169-75.
18. Maiden L, Thjodleifsson B, Theodors A, Gonzalez J, Bjarnason I. A quantitative analysis of NSAID-induced small bowel pathology by capsule enteroscopy. Gastroenterology 2005;128:1172-8.
19. Lanas A, Sopena F. Nonsteroidal anti-inflammatory drugs and lower gastrointestinal complications. Gastroenterol Clin North Am 2009;38:333-52.
20. Langman MJ, Morgan L, Worral A. Use of anti-inflammatory drugs by patients admitted with small or large bowel perforations and haemorrhage. Br Med J (Clin Res Ed) 1985;290:347-9.
21. Holt S, Rigoglioso V, Sidhu M, Irshad M, Howden CW, Mainero M. Nonsteroidal antiinflammatory drugs and lower gastrointestinal bleeding. Dig Dis Sci 1993;38:1619-23.
22. Lanas A, Serrano P, Bajador E, Esteva F, Benito R, Sainz R. Evidence of aspirin use in both upper and lower gastrointestinal perforation. Gastroenterology 1997;112:683-9.
23. Chan FK, Hung LC, Suen BY, Wu JC, Lee KC, Leung VK, et al. Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis. N Engl J Med 2002;347:2104-10.
24. Bjarnason I, Hayllar J, MacPherson AJ, Russell AS. Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. Gastroenterology 1993;104:1832-47.
25. Chong AK, Chin BW, Meredith CG. Clinically significant small-bowel pathology identified by double-balloon enteroscopy but missed by capsule endoscopy. Gastrointest Endosc 2006;64:445-9.
26. Viazis N, Papaxoinis K, Vlachogiannakos J, Efthymiou A, Theodoropoulos I, Karamanolis DG. Is there a role for second-look capsule endoscopy in patients with obscure GI bleeding after a nondiagnostic first test? Gastrointest Endosc 2009;69:850-6.
27. Tanaka S, Mitsui K, Tatsuguchi A, Kobayashi T, Ehara A, Gudis K, et al. Current status of double balloon endoscopy — indications, insertion route, sedation, complications, technical matters. Gastrointest Endosc 2007;66 Suppl:S30-3.
28. Lanas A, García-Rodríguez LA, Polo-Tomás M, Ponce M, Alonso-Abreu I, Perez-Aisa MA, et al. Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. Am J Gastroenterol 2009;104:1633-41.
29. Zhao Y, Encinosa W. Hospitalizations for gastrointestinal bleeding

in 1998 and 2006. Healthcare Cost and Utilization Project (HCUP) Statistical Brief #65 [report on the Internet]. Agency for Healthcare Research and Quality, Rockville, MD. [Internet. Accessed Sept 11, 2009.] Available from: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb65.pdf
30. Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, 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 1995;123:241-9.
31. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000;343:1520-8.
32. Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehrsam E, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. Lancet 2004;364:665-74.
33. Singh G, Fort JG, Goldstein JL, Levy RA, Hanrahan PS, Bello AE, et al. Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I Study. Am J Med 2006;119:255-66.
34. Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet 2006;368:1771-81.