NSAIDs for high-risk patients: none, celecoxib, or naproxen?

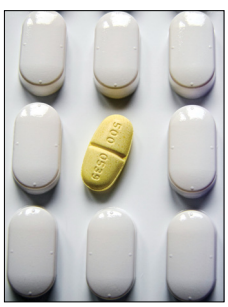
Godot-like, the all-round safe and effective oral anti-inflammatory drug is awaited. Meantime, substantial effort is devoted to discovering how the existing imperfect non-steroidal anti-inflammatory drugs (NSAIDs) might be best used—balancing the need for effective analgesia with their multiple risks. The randomised controlled trial by Francis Chan and colleagues[1] reported in *The Lancet* investigated two of these NSAIDs that have been seen as the best (or least worst) in the cardiovascular safety stakes, celecoxib and naproxen. Combining each drug with a proton-pump inhibitor for gastroprotection, the risk of upper gastrointestinal bleeding is assessed in a small but particularly high-risk population: people who have already suffered upper gastrointestinal bleeding while taking NSAIDs plus cardioprotective aspirin and who need to continue both drugs afterwards.

In view of the 30 years' worth of clinical research on gastrointestinal risk associated with individual NSAIDs plus the elucidation of their cyclo-oxygenase (COX) 1 and 2 selectivities and potencies, the trial's findings are largely predictable.[2,3] After 18 months of study in 514 patients with upper gastrointestinal bleeding recruited over 10 years at a single centre in Hong Kong, celecoxib 100 mg twice per day plus esomeprazole 20 mg once per day was shown to be superior to naproxen 500 mg twice per day plus esomeprazole 20 mg once per day. However, the superiority is relative. Neither option was safe because the cumulative incidence of recurrent upper gastrointestinal bleeding was 5·6% (95% CI 3·3–9·2) in celecoxib users and 12·3% (8·8–17·1) in naproxen users. No upper gastrointestinal bleeding-associated deaths occurred during the study. Although the incidence of upper gastrointestinal bleeding overall seems to be decreasing, case fatality has not followed, remaining around 6% in Hong Kong and elsewhere.[4,5] For a patient to choose to continue a NSAID along with aspirin after having upper gastrointestinal bleeding is thus a hugely consequential decision.

Chan and colleagues suggest the trial addresses an unmet need in present NSAID-use guidelines. These guidelines have to balance gastrointestinal and cardiac risk considerations. From a gastrointestinal perspective, naproxen is known to be riskier than celecoxib—a consequence of naproxen's COX-1 inhibitory potency.[2,3] The long awaited PRECISION trial[6] provided limited clarification on the relative cardiac risks of naproxen and celecoxib, but did not assess gastrointestinal complications according to aspirin use. Low-dose aspirin augments NSAID-associated upper gastrointestinal bleeding risks, but altering the relative upper gastrointestinal bleeding risks of celecoxib and naproxen would require a substantially larger effect on celecoxib's risk than on naproxen's, and a plausible mechanism for this is not evident. The trial findings show that risk difference is preserved, but missing is the risk estimate for aspirin use without a NSAID.

The trial's lost opportunity to fully inform guidelines is its failure to include a non-NSAID treatment group composed of the 334 patients needing aspirin whose pain was adequately managed with simple analgesia. Inclusion would have permitted judgment on the excess risk associated with aspirin plus a NSAID compared with aspirin plus simple analgesia and thereby put celecoxib versus naproxen treatment decisions for this high-risk population into an applicable clinical context. This trial amendment would potentially also have clarified indirectly the unanswered question of whether concomitant aspirin diminishes celecoxib's gastrointestinal risk advantage.

763 (66%) of 1158 patients with upper gastrointestinal bleeding screened in the trial were deemed to need continued regular use of NSAID. This number seems very high but cannot be examined because the factors that defined need for NSAID are not detailed. The dose and treatment protocol for the fixed-dose combination of paracetamol and phenyltoloxamine is omitted, as is information on NSAID-sparing non-drug treatments. In total, 514 patients consented to be included in the trial and were randomly assigned to continuous daily aspirin, proton-pump inhibitor, and celecoxib or naproxen. This protocol ensured that fewer than 20% of patients discontinued NSAID treatment, but continuous NSAID use at a non-variable high dose, especially of naproxen, possibly exposed some patients unnecessarily in view of the upper gastrointestinal bleeding risks that transpired. The protocol also limits the trial's generalisability because patients commonly use NSAIDs as needed. Risks of upper gastrointestinal bleeding in specific patient groups remain to be described, especially groups with characteristics compounding the risk; for example,



Ian Gowland/Science Photo Library

Published Online
April 11, 2017
http://dx.doi.org/10.1016/S0140-6736(17)30980-7

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prescription of a second anti-platelet drug, which would have been indicated in patients who had myocardial infarction during the study; or aspirin to clopidogrel switches in the patients with non-fatal stroke; or concomitant selective serotonin-reuptake inhibitor use. Other co-medications that are relevant for clinical applicability are also unreported in this study, which was too small to take account of any of these factors. From a public health perspective, the trial adds modestly to the body of knowledge on the benefit–risk balance of NSAID use, albeit for a very select population of patients. Because the trial provides no way of knowing if the proportion of patients with upper gastrointestinal bleeding exceeded what would happen with non-use of NSAIDs, patients, clinicians, and guideline writers are left to make a lesser of two evils recommendation as opposed to knowing the excess risk of either NSAID over simple analgesia. Until this is known and in the absence of explicit criteria defining NSAID need, the substantial proportion of patients with rebleeding reported in the Article should reinforce NSAID avoidance in people with previous upper gastrointestinal bleeding.

*Patricia McGettigan, Anne-Marie Schjerning Olsen
William Harvey Research Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London EC1M 6BQ, UK (PM); and Department of Cardiology, Copenhagen University Hospital Herlev and Gentofte, Copenhagen, Denmark (A-MSO)
p.mcgettigan@qmul.ac.uk

PM reports support from the European Medicines Agency, outside the area of work discussed here. A-MSO declares no competing interests.

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Bioprosthetic surgical and transcatheter heart valve thrombosis


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Published Online March 19, 2017 http://dx.doi.org/10.1016/S0140-6736(17)30764-X

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Excellent outcomes of transcatheter aortic valve replacement (TAVR) have been experienced by patients with aortic stenosis at high and intermediate risk of surgery.[1] Findings from large randomised trials[1,2] have shown survival with TAVR that is similar to or improved compared with bioprosthetic surgical aortic valve replacement (SAVR), and very low stroke rates have been observed with new-generation devices. Investigators of echocardiographic follow-up studies[3] have consistently reported low transvalvular gradients up to 5 years after TAVR and SAVR, with slightly greater aortic valve areas after TAVR than after SAVR. Against this background, the occurrence of subclinical valve leaflet thrombosis in patients, detected with CT after TAVR or SAVR, has been described.[4]

In *The Lancet*, Tarun Chakravarty and colleagues[5] report data from two large registries (SAVORY and RESOLVE) of 890 patients undergoing TAVR or SAVR with follow-up CT (626 [70%] in the RESOLVE registry and 264 [30%] in the SAVORY registry). Masked analyses of all CT scans, echocardiograms, and neurological events were done. Subclinical leaflet thrombosis, defined as moderate or severe restriction of leaflet motion with corresponding CT-derived hypoattenuating lesions, was detected in 106 (12%) patients, including five (4%) of 138 who had SAVR and 101 (13%) of 752 who had TAVR (p=0·001). A greater proportion of patients with subclinical leaflet thrombosis had aortic valve gradients of more than 20 mm Hg and increases in aortic valve gradients of more than 10 mm Hg (12 [14%] of 88) than did those with normal leaflet motion (seven [1%] of 632; p<0·0001). Leaflet thrombosis was less frequently observed in patients using warfarin or novel oral anticoagulants (NOACs; eight [4%] of 224) than in those using dual antiplatelet or monoantiplatelet therapy (98 [15%] of 666; p<0·0001). Subclinical leaflet thrombosis was associated with development of non-procedural stroke or transient ischaemic attack

Gastrointestinal safety of celecoxib versus naproxen in patients with cardiothrombotic diseases and arthritis after upper gastrointestinal bleeding (CONCERN): an industry-independent, double-blind, double-dummy, randomised trial

Francis K L Chan, Jessica Y L Ching, Yee Kit Tse, Kelvin Lam, Grace L H Wong, Siew C Ng, Vivian Lee, Kim W L Au, Pui Kuan Cheong, Bing Y Suen, Heyson Chan, Ka Man Kee, Angeline Lo, Vincent W S Wong, Justin C Y Wu, Moe H Kyaw

Summary

Background **Present guidelines are conflicting for patients at high risk of both cardiovascular and gastrointestinal events who continue to require non-steroidal anti-inflammatory drugs (NSAIDs). We hypothesised that a cyclooxygenase-2-selective NSAID plus proton-pump inhibitor is superior to a non-selective NSAID plus proton-pump inhibitor for prevention of recurrent ulcer bleeding in concomitant users of aspirin with previous ulcer bleeding.**

Methods **For this industry-independent, double-blind, double-dummy, randomised trial done in one academic hospital in Hong Kong, we screened patients with arthritis and cardiothrombotic diseases who were presenting with upper gastrointestinal bleeding, were on NSAIDs, and require concomitant aspirin. After ulcer healing, an independent staff member randomly assigned (1:1) patients who were negative for *Helicobacter pylori* with a computer-generated list of random numbers to receive oral administrations of either celecoxib 100 mg twice per day plus esomeprazole 20 mg once per day or naproxen 500 mg twice per day plus esomeprazole 20 mg once per day for 18 months. All patients resumed aspirin 80 mg once per day. Both patients and investigators were masked to their treatments. The primary endpoint was recurrent upper gastrointestinal bleeding within 18 months. The primary endpoint and secondary safety endpoints were analysed in the modified intention-to-treat population. This study was registered with ClinicalTrials.gov, number NCT00153660.**

Findings **Between May 24, 2005, and Nov 28, 2012, we enrolled 514 patients, assigning 257 patients to each study group, all of whom were included in the intention-to-treat population. Recurrent upper gastrointestinal bleeding occurred in 14 patients in the celecoxib group (nine gastric ulcers and five duodenal ulcers) and 31 patients in the naproxen group (25 gastric ulcers, three duodenal ulcers, one gastric ulcer and duodenal ulcer, and two bleeding erosions). The cumulative incidence of recurrent bleeding in 18 months was 5·6% (95% CI 3·3–9·2) in the celecoxib group and 12·3% (8·8–17·1) in the naproxen group (p=0·008; crude hazard ratio 0·44, 95% CI 0·23–0·82; p=0·010). Excluding patients who reached study endpoints, 21 (8%) patients in the celecoxib group and 17 (7%) patients in the naproxen group had adverse events leading to discontinuation of treatment. No treatment-related deaths occurred during the study.**

Interpretation **In patients at high risk of both cardiovascular and gastrointestinal events who require concomitant aspirin and NSAID, celecoxib plus proton-pump inhibitor is the preferred treatment to reduce the risk of recurrent upper gastrointestinal bleeding. Naproxen should be avoided despite its perceived cardiovascular safety.**

Funding **The Research Grant Council of Hong Kong.**

Published **Online**
April 11, 2017
http://dx.doi.org/10.1016/S0140-6736(17)30981-9

See **Online/Comment**
http://dx.doi.org/10.1016/S0140-6736(17)30980-7

Department of Medicine & Therapeutics, Institute of Digestive Disease (Prof F K L Chan MD, J Y L Ching MPH, Y K Tse MPhil, K Lam MBChB, G L H Wong MD, S C Ng PhD, P K Cheong MPH, H Chan MBChB, K M Kee MPH, A Lo MBChB, V W S Wong MD, J C Y Wu MD, M H Kyaw MBBS), **School of Pharmacy** (V Lee PharmD), **and Department of Surgery, Institute of Digestive Disease** (K W L Au MPH, B Y Suen BHSc), **The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China**

Correspondence to:
Prof Francis K L Chan, Department of Medicine & Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China
fklchan@cuhk.edu.hk

Introduction

Upper gastrointestinal bleeding associated with non-steroidal anti-inflammatory drug (NSAID) use has important global health-care implications in view of the vast consumption of NSAIDs, with more than 30 billion doses of NSAIDs being consumed annually in the USA.[1] Gastrointestinal bleeding is the most common cause of hospital admission due to gastrointestinal disease in the USA. It accounts for more than 507 000 hospital admissions and $4·85 billion in costs annually.[2] The problem will be more pronounced in China where the population is more than 1·3 billion people. An estimated 3·6% of Chinese adults use NSAIDs regularly.[3] Concomitant use of aspirin and NSAIDs substantially increases the risk of upper gastrointestinal bleeding.[4] Furthermore, the consumption of aspirin will be enormous with the estimated increase of 21·3 million cardiovascular events during the next 20 years in China.[5] The prevalence of upper gastrointestinal bleeding in China, currently between 3·9% and 5·5%, is anticipated to remain high.[6]

Ageing, cardiovascular comorbidities, and concomitant use of aspirin substantially increase the risks of recurrent upper gastrointestinal bleeding and mortality with NSAID use.[7] We previously reported that almost 19% of patients with a history of ulcer bleeding developed recurrent bleeding with NSAID use in 6 months.[8]

Research in context

Evidence before this study

Non-steroidal anti-inflammatory drugs (NSAIDs) are a major cause of gastrointestinal bleeding worldwide. Ageing, cardiovascular comorbidity, and use of concomitant aspirin substantially increase the risks of recurrent upper gastrointestinal bleeding and mortality with NSAID use. Present guidelines have provided conflicting recommendations for patients at high risk of both cardiovascular and gastrointestinal events who continue to require NSAIDs. We searched PubMed on Jan 31, 2017, for publications without language or date restrictions using the terms "Anti-Inflammatory Agents, Non-Steroidal", "Gastrointestinal Hemorrhage", "Cyclooxygenase 2 Inhibitors," and "Aspirin". Our search indicated there are no randomised trials designed to address the choice of NSAIDs in these high-risk patients who require both aspirin and NSAIDs for cardiovascular and anti-inflammatory therapies.

Added value of this study

We showed that celecoxib plus proton-pump inhibitor is superior to naproxen plus proton-pump inhibitor for prevention of recurrent upper gastrointestinal bleeding in patients with cardiothrombotic diseases and a history of upper gastrointestinal bleeding. Contrary to present guidelines, we found that naproxen cannot be recommended to these high-risk patients despite its perceived cardiovascular benefit.

Implications of all the available evidence

Our study has provided novel data to national and international guidelines committees on NSAID choice in patients at high risk of both cardiovascular and gastrointestinal events who require concomitant aspirin and anti-inflammatory analgesics.

Although these patients should avoid using NSAIDs, many of them continue to require anti-inflammatory analgesics. In a National UK Audit, the mortality associated with further bleeding was 13% and with surgery for recurrent bleeding was 29%, despite advances in endoscopic and pharmacological therapies.[9]

Cyclooxygenase (COX)-2-selective NSAIDs were introduced more than a decade ago as gastric-sparing anti-inflammatory analgesics. Their COX-2 selectivity was intended to reduce gastrointestinal complications related to NSAIDS.[10] However, two major concerns exist about the safety of COX-2-selective NSAIDs. First, evidence suggests that COX-2-selective NSAIDs might increase the risk of myocardial infarction.[11,12] Second, the superior gastric safety of COX-2-selective NSAIDs over non-selective NSAIDs might disappear with the concomitant use of aspirin.[13–15] A large-scale randomised trial[16] published in 2016 showed that celecoxib and naproxen have similar cardiovascular safety profiles. Additionally, celecoxib was found to induce less clinical gastrointestinal events than naproxen on secondary analysis. However, whether the finding of decreased clinical gastrointestinal events can be extrapolated to high-risk patients is uncertain because the patients recruited were relatively young (mean age 63 years) compared with a typical high-risk population and the proportion of patients with a history of gastrointestinal bleeding or who used concomitant aspirin was not reported.[16]

To date, a major unmet need remains for patients at high risk of both cardiovascular and gastrointestinal events who continue to require concomitant aspirin and anti-inflammatory analgesics. At least seven national and international guidelines exist on the use of NSAIDs. For patients at high risk of both cardiovascular and gastrointestinal events requiring concomitant aspirin and NSAIDs, the guidelines are conflicting. They either offer no advice,[17] suggest avoidance of all NSAIDs,[7,18] or advocate naproxen as the preferred NSAID.[19] Available large-scale, industry-sponsored trials were not designed to address the need of these largely neglected, high-risk patients. We aimed to test the hypothesis that a COX-2-selective NSAID plus proton-pump inhibitor is superior to a non-selective NSAID plus proton-pump inhibitor for prevention of recurrent upper gastrointestinal bleeding in concomitant users of aspirin with a history of upper gastrointestinal bleeding.

Methods

Study design and population

This industry-independent, double-blind, double-dummy, randomised trial was done at Prince of Wales Hospital of The Chinese University of Hong Kong between May 24, 2005, and Nov 9, 2015. The study was done in compliance with the principles of Good Clinical Practice and the Declaration of Helsinki. The local ethics committee approved the study protocol. A protocol amendment was made on June 14, 2006, to extend our study from 12 months to 18 months to capture any delayed serious cardiovascular events associated with NSAIDs that might occur after 12 months of therapy. The sample size was also recalculated and increased on the basis of a proportionate increase in the estimated cumulative incidence rates of recurrent ulcer bleeding in 18 months. All patients gave written informed consent.

We screened patients presenting with upper gastrointestinal bleeding who were on NSAIDs and requiring concomitant low-dose aspirin. The patients underwent endoscopy to identify the site of bleeding and *Helicobacter pylori* status. Follow-up endoscopy was done to confirm ulcer healing for all patients. Patients were offered simple analgesics (fixed combination of paracetamol and phenyltoloxamine) for pain relief. Patients were eligible if they had endoscopically confirmed ulcer healing and

negative results for *H pylori* or successful eradication of *H pylori;* required low-dose aspirin for cardiothrombotic diseases or multiple coronary risk factors; and had chronic arthritis pain that could not be relieved by simple analgesics and were anticipated to require regular use of NSAIDs for the duration of the trial. The exclusion criteria were a history of gastric or duodenal surgery other than patch repair; erosive oesophagitis; gastric outlet obstruction; renal failure (defined by a serum creatinine concentration of more than 200 μmol/L); pregnancy; and terminal illness or active malignancies.

Randomisation and masking

Eligible patients were randomly assigned (1:1) with a computer-generated list of random numbers to one of the two treatment groups: celecoxib plus esomeprazole or naproxen plus esomeprazole. An independent staff member assigned the treatments according to consecutive numbers that were kept in sealed opaque envelopes.

Both patients and investigators were masked to their treatments. Treatment allocation was masked by preparation of double dummies of celecoxib and naproxen by the School of Pharmacy at The Chinese University of Hong Kong according to International Good-Manufacturing Practice Guidelines for Pharmaceuticals.

Procedures

Before enrolment, all patients had a physical examination, laboratory testing, and an assessment of arthritis, and cardiovascular risk. Enrolled patients received oral administrations of either celecoxib 100 mg twice per day plus esomeprazole 20 mg once per day or naproxen 500 mg twice per day plus esomeprazole 20 mg once per day for 18 months. All patients were advised to resume dissolvable aspirin 80 mg per day for the duration of the trial. We had chosen doses of celecoxib 100 mg twice per day and naproxen 500 mg twice per day on the basis of scientific literature on cardiovascular safety and therapeutic efficacy of these drugs at the time of trial design. First, we previously showed in a randomised trial[8] that naproxen 500 mg twice per day effectively reduce pain in patients with arthritis. Another randomised trial[20] showed that celecoxib 100 mg twice per day had analgesic efficacy similar to naproxen 500 mg twice per day.[20] Second, celecoxib 200 mg per day and naproxen 1000 mg per day were not associated with increased risk of serious cardiovascular events.[21,22] By contrast, there were concerns about the cardiovascular safety of higher doses of celecoxib and naproxen at lower doses.[22–24]

Patients were contacted 1 month after randomisation by telephone and returned to the study centre every 3 months until the end of the study. At each visit, haemoglobin concentrations, serum biochemical values, drug compliance, efficacy, and safety were assessed. Drug compliance was assessed by pill counts. Assessment of treatment efficacy included the patient's global assessment of disease activity, graded on a scale of 1 (no limitation of normal activities) to 5 (inability to do all normal activities).[25,26] Assessment of safety was based on the physical examination, laboratory tests, and observed or reported adverse events. A direct telephone line was provided so that the patients could report any adverse events between the scheduled visits. Patients were permitted to take antacids to relieve dyspepsia and simple analgesics (fixed combination of paracetamol and phenyltoloxamine) for breakthrough pain if needed. Disease-modifying antirheumatic drugs, stable doses of corticosteroids (up to prednisolone 10 mg once per day), and standard doses of histamine H_2-receptor antagonists were permitted. Drugs prohibited during the study include non-study NSAIDs and anticoagulants. We followed up patients who withdrew early until the end of the study.

Outcomes

The primary endpoint was a safety endpoint of recurrent upper gastrointestinal bleeding within 18 months according to prespecified criteria—namely, haematemesis or melena documented by the admitting physician, with ulcers or bleeding erosions confirmed by endoscopy, or a decrease in haemoglobin of at least 2 g/dL in the presence of endoscopically proven ulcers or bleeding erosions. An ulcer was defined as a circumscribed mucosal break at least 0·5 cm in diameter and with a perceptible depth. Bleeding erosions were defined as flat mucosal breaks of any size in the presence of blood in the stomach. Members of an independent, masked adjudication committee determined whether recurrent upper gastrointestinal bleeding had occurred according to the prespecified criteria. Only events that were confirmed by the adjudication committee and that occurred during treatment were regarded as endpoint reached.

Secondary endpoints were a safety endpoint of serious cardiovascular events as defined by Anti-Platelet Trialists Collaboration criteria (non-fatal myocardial infarction, non-fatal stroke, or death from a vascular cause)[27] and an efficacy endpoint of patients' global assessment of disease activity.[25,26] The adjudication committee confirmed all suspected cardiovascular events.

Statistical analysis

We have previously shown that about 5% of patients on a non-selective NSAID plus a proton-pump inhibitor had recurrent ulcer bleeding in 6 months,[25] whereas no patient on celecoxib plus a proton-pump inhibitor had recurrent ulcer bleeding in 12 months.[26] Assuming that 13% of patients in the naproxen group and 5% in the celecoxib group will develop recurrent ulcer bleeding in 18 months, a 2-sided log-rank test with 5% significance level required 410 patients to achieve 80% power. Accordingly, we finalised the target sample size at 512 patients in total and included overages of 20% to account for patients who would be lost to follow-up.

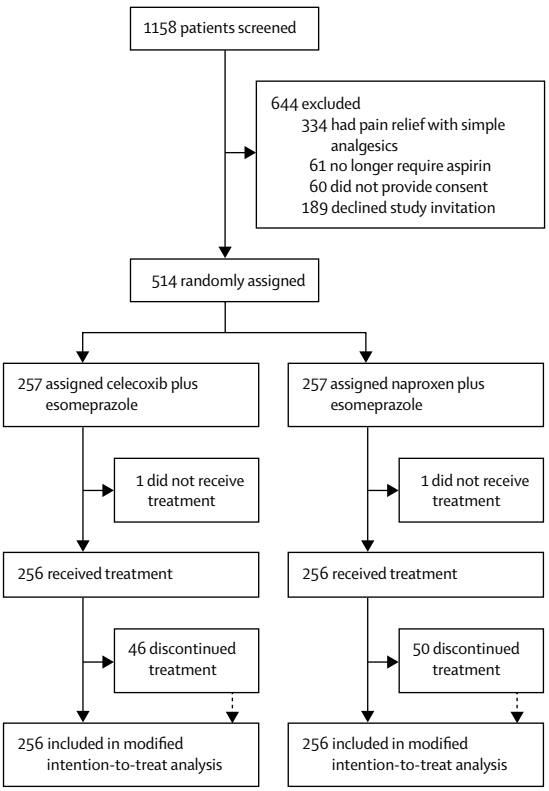

Figure 1: **Trial profile**

	Celecoxib plus esomeprazole (n=256)	Naproxen plus esomeprazole (n=256)
Sex		
Male	138 (54%)	139 (54%)
Female	118 (46%)	117 (46%)
Age (years)	72·4 (10·6)	72·7 (9·9)
Age stratified (years)		
≤60	36 (14%)	35 (14%)
61–80	158 (62%)	170 (66%)
>80	62 (24%)	51 (20%)
ASA grade*		
1	0	0
2	215 (84%)	208 (81%)
3	41 (16%)	48 (19%)
4	0	0
Current smoker	43 (17%)	30 (12%)
Current drinker†	30 (12%)	26 (10%)
Indications for NSAIDs		
Osteoarthritis	178 (70%)	188 (73%)
Rheumatoid arthritis	8 (3%)	5 (2%)
Other	70 (27%)	63 (25%)
Source of bleeding		
Gastric ulcer	142 (55%)	143 (56%)
Duodenal ulcer	85 (33%)	82 (32%)
Both	29 (11%)	31 (12%)
Previous *Helicobacter pylori* infection	109 (43%)	110 (43%)
Patients requiring of blood transfusion at baseline	141 (55%)	133 (52%)
Patients requiring of endoscopic therapy at baseline	85 (33%)	71 (28%)
Creatinine (μmol/L)	98·4 (26·0)	101·1 (31·6)

Data are n (%) or mean (SD). ASA=American Society of Anesthesiology. NSAID=non-steroidal anti-inflammatory drug. *Severity of comorbidity was classified according to the American Society of Anesthesiology: grade 1 is normal healthy patients; grade 2 is mild systemic illness; grade 3 is severe systemic disease that is not incapacitating; and grade 4 is life-threatening illness. †Current drinkers were defined as intaking alcohol at least three times per week.

Table 1: **Baseline characteristics**

Continuous variables were expressed as the mean (SD) or median (IQR) where appropriate. Categorical variables were presented as n (%). We used the Kaplan-Meier method to estimate the likelihood of reaching the endpoint of recurrent upper gastrointestinal bleeding and serious cardiovascular events within 18 months in the modified intention-to-treat population, which was defined as all patients who had received at least one dose of the study drugs. We compared time-to-event curves between the two groups with the log-rank test. We estimated hazard ratios (HRs) and 95% CIs for recurrent upper gastrointestinal bleeding using Cox proportional hazards regression. Concomitant use of aspirin (continued use *vs* discontinued use) was also adjusted in multivariable analysis. We did Schoenfeld's global test to test the proportional hazards assumption, which did not detect any significant violations. We analysed patients' global assessment of disease activity by repeated-measures ANOVA, with time as the within-participant factor, and treatment as the between-participant factor, to test for any difference in time or group. The term for the interaction between group and time was also inspected to assess whether changes over time were the same in the two treatment groups. The analysis was repeated, with missing values imputed by a last-observation-carried-forward approach. We used Mauchly's test to verify the assumption of sphericity, and the Huynh-Feldt test to measure the change in patients' global assessment of arthritis if the assumption of sphericity was violated.[26] Statistical tests were done using IBM SPSS Statistics Version 22 (IBM, Armonk, NY, USA). All statistical tests were two-sided. Statistical significance was taken as $p<0·05$. A Data Safety Monitoring Committee, consisting of two physicians and one biostatistician who were not involved in this study, monitored the progress of the trial and the safety and welfare of participants.

This study was registered with ClinicalTrials.gov, number NCT00153660.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of

the report. FKLC, JYLC, YKT, and MHK had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Between May 24, 2005, and Nov 28, 2012, we screened 1158 consecutive patients presenting with haematemesis, melena, or both, who were on NSAIDs and requiring concomitant low-dose aspirin. We enrolled 514 of these patients on the basis of the increased sample size estimation for an extended study period of 18 months (257 were randomly assigned to receive celecoxib plus esomeprazole, and 257 to receive naproxen plus esomeprazole; figure 1). Baseline characteristics were similar between groups (table 1). The median follow-up was 18 months in both groups (range 0·53–18·0; IQR 18·0–18·0).

All patients were asked to take concomitant aspirin 80 mg per day. Among them, 185 (72%) of 256 patients in the celecoxib group and 183 (71%) of 256 in the naproxen group continued to use aspirin daily throughout the study period. 229 (89%) patients in the celecoxib group and 233 (91%) in the naproxen group took at least 70% of the assigned study drugs. The proportion of patients who discontinued treatment, excluding patients who reached study endpoints, were similar in the two groups: 46 (18%) of 256 in the celecoxib group (21 [8%] because of adverse event, 19 [7%] withdrew consent, and six [2%] for other reasons) and 50 (20%) of 256 in naproxen group (17 [7%] because of adverse event, 26 [10%] withdrew consent, and seven [3%] for other reasons). The adverse events leading to discontinuation of treatment in the celecoxib group and naproxen group were congestive heart failure (two *vs* two), epigastric pain (two *vs* seven), renal failure (five *vs* four), and other causes (12 *vs* four). No patients who discontinued medication early had recurrent upper gastrointestinal bleeding within the study period. 12 patients in the celecoxib group and nine patients in the naproxen group used non-study NSAIDs.

A total of 67 cases with suspected gastrointestinal bleeding were assessed by the adjudication committee. The committee identified 45 cases of recurrent upper gastrointestinal bleeding: 14 in the celecoxib group (nine gastric ulcers and five duodenal ulcers) and 31 in the naproxen group (25 gastric ulcers, three duodenal ulcers, one gastric ulcer and duodenal ulcer, and two bleeding erosions). All the patients with recurrent upper gastrointestinal bleeding had presented with recurrent melena, haematemesis, or a haemoglobin drop of more than 2 g/dL requiring hospital treatment. Two of these patients required endoscopic control of active bleeding and 16 needed blood transfusions. The median diameter of recurrent ulcers was 0·7 cm (IQR 0·5–1·5). None of the patients with recurrent upper gastrointestinal bleeding had recurrence of *H pylori* infection. Two of the patients with recurrent upper gastrointestinal bleeding used non-study NSAIDs (one in each group). The cumulative incidence of recurrent upper gastrointestinal bleeding during the 18 month study in the modified intention-to-treat population was 5·6% (95% CI 3·3–9·2) in the celecoxib group and 12·3% (8·8–17·1) in the naproxen group (log-rank test p=0·008; crude HR 0·44, 95% CI 0·23–0·82; p=0·010; figure 2, table 2). After adjustment for concomitant aspirin use, the adjusted HR was identical to the crude HR.

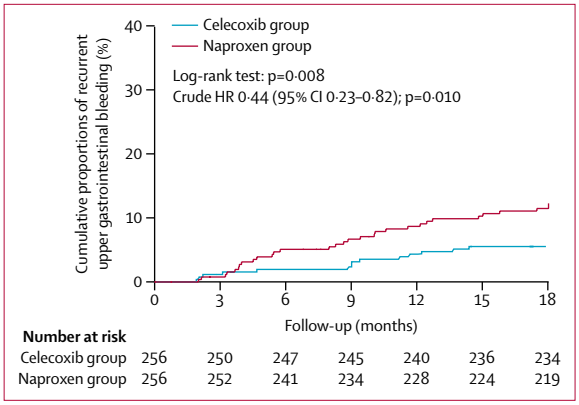

Figure 2: **Time-to-outcome analysis of recurrent upper gastrointestinal bleeding**
All patients received esomeprazole. 185 (72%) of 256 patients in the celecoxib group and 183 (71%) of 256 patients in the naproxen group continued aspirin. HR=hazard ratio.

	Celecoxib plus esomeprazole	Naproxen plus esomeprazole	p value*
Recurrent upper gastrointestinal bleeding	5·6% (3·3–9·2)	12·3% (8·8–17·1)	0·008
Serious cardiovascular events	4·4% (2·4–7·7)	5·5% (3·3–9·2)	0·543

Data are % (95% CI). *Calculated with the log-rank test.

Table 2: **Kaplan-Meier estimates of the likelihood of recurrent upper gastrointestinal bleeding and serious cardiovascular events at 18 months**

Of the 22 patients who were found on adjudication not to have recurrent upper gastrointestinal bleeding, ten were in the celecoxib group (seven had lower gastrointestinal bleeding and three had anaemia not due to gastrointestinal blood loss) and 12 were in the naproxen group (seven had lower gastrointestinal bleeding and five had anaemia not due to gastrointestinal blood loss). The causes of lower gastrointestinal bleeding in the celecoxib group were colonic angiodysplasia (n=1), colonic ulcers (n=1), overt gastrointestinal bleeding of obscure origin (n=2), and anaemia due to obscure occult gastrointestinal bleeding (n=3), and in the naproxen group were colonic diverticula (n=1), overt gastrointestinal bleeding of obscure origin (n=3), and anaemia due to obscure occult gastrointestinal bleeding (n=3). The causes of anaemia not due to gastrointestinal blood loss in the celecoxib group were non-gastrointestinal cancer (n=1) and chronic renal failure (n=2), and in the naproxen group were non-gastrointestinal cancers (n=2) and chronic renal failure (n=3).

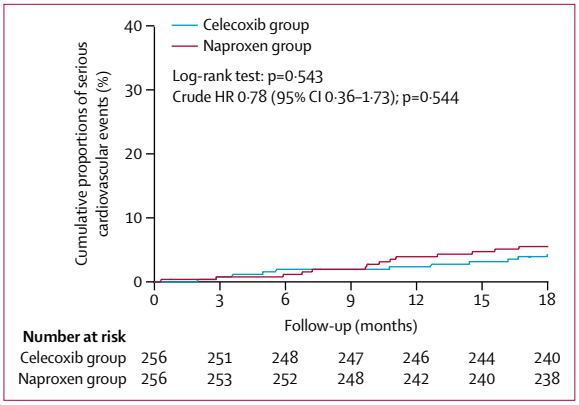

Figure 3: **Time-to-outcome analysis for serious cardiovascular event**
HR=hazard ratio.

	Celecoxib plus esomeprazole	Naproxen plus esomeprazole
Baseline	3·0 (0·7)	3·0 (0·6)
Month 3	2·6 (0·8)	2·7 (0·7)
Month 6	2·4 (0·7)	2·5 (0·8)
Month 9	2·3 (0·8)	2·5 (0·8)
Month 12	2·3 (0·8)	2·4 (0·8)
Month 15	2·2 (0·8)	2·4 (0·9)
Month 18	2·1 (0·8)*	2·3 (0·9)*

Data are mean (SD). Patient's global assessment of disease activity was scored on a scale from 1 (no limitation of normal activities) to 5 (inability to carry out all normal activities). *Significant improvement in patient's global assessment of disease activity from baseline to end of study period (p<0·0001).

Table 3: **Disease-activity score of celecoxib and naproxen for arthritis**

A total of 48 patients with suspected serious cardiovascular events were assessed by the adjudication committee. The committee identified 25 cases of serious cardiovascular events, 11 in the celecoxib group (six myocardial infarctions, three non-fatal strokes, and two deaths from a vascular cause) and 14 in the naproxen group (seven myocardial infarctions, six non-fatal strokes, and one death from a vascular cause). The cumulative incidence of cardiovascular events was 4·4% (95% CI 2·4–7·7) in the celecoxib group and 5·5% (3·3–9·2) in the naproxen group (p=0·543; crude HR 0·78, 95% CI 0·36–1·73; p=0·544; figure 3, table 2). A total of 11 patients died from other causes: six were in the celecoxib group (five patients died from sepsis and one from uncertain causes) and five were in the naproxen group (one patient died from heart failure, two from gastrointestinal cancer, and two from uncertain causes). No gastrointestinal bleeding-related deaths occurred.

We found a significant improvement in patients' global assessment of disease activity from baseline to end of the study period in both groups (p<0·0001). The improvement in patients' global assessment of disease activity did not differ between the two groups over time (p=0·386; table 3).

Discussion

We set out to test the hypothesis that COX-2-selective NSAID plus proton-pump inhibitor is superior to non-selective NSAID plus proton-pump inhibitor for prevention of recurrent upper gastrointestinal bleeding in patients with arthritis and cardiothrombotic diseases who required concomitant aspirin. In this study, our patients were susceptible to develop recurrent bleeding with NSAIDs due to a history of ulcer bleeding and use of concomitant aspirin. As shown in a UK National Audit,[9] recurrent bleeding was associated with high mortality, probably due to old age and comorbidities. We have shown that the proportion of patients with recurrent upper gastrointestinal bleeding was significantly lower in the celecoxib group (5·6%) than in the naproxen group (12·2%; p=0·008). Importantly, these high-risk patients should avoid using naproxen because even co-therapy with proton-pump inhibitor does not adequately prevent recurrent bleeding. Our findings address the major unmet need in the present guidelines[7,17–19] on the management of patients at high risk of both cardiovascular and gastrointestinal events who continue to require anti-inflammatory analgesics. These patients have been largely neglected because none of the published studies sought to identify treatments to reduce the risk of life-threatening complications in these patients.

Despite the additional risk with aspirin use, celecoxib was superior to naproxen in terms of the risk of recurrent upper gastrointestinal bleeding. Subgroup analyses of previous randomised trials indicated that the gastric-sparing effect of celecoxib disappeared with concomitant use of aspirin,[13–15] leading to the belief that COX-2-selective NSAIDs are not justified in concomitant aspirin users. We previously showed in a 12 month randomised trial[26] that among patients with a history of ulcer bleeding who did not use concomitant aspirin, none of the patients receiving celecoxib and a proton-pump inhibitor developed recurrent bleeding. In the present study, although a combination of celecoxib, aspirin, and a proton-pump inhibitor could not completely eliminate the risk of recurrent upper gastrointestinal bleeding, this treatment strategy still probably offers the best upper gastrointestinal protection for patients with arthritis and cardiothrombotic diseases who are at high risk of upper gastrointestinal bleeding. Avoidance of all NSAIDs will be the safest approach in these high-risk patients, but in patients who continue to require concomitant NSAIDs and aspirin, celecoxib plus a proton-pump inhibitor encompass the least risk of recurrent upper gastrointestinal bleeding.

Development of an optimum management strategy for patients with arthritis and at high risk of both cardiovascular and gastrointestinal events is crucial in our ageing global population. Although the PRECISION trial[16] was primarily designed to compare the cardiovascular safety of celecoxib with two non-selective NSAIDs, the gastrointestinal benefit of celecoxib over non-selective NSAIDs is difficult to conclude in patients at high risk

of gastrointestinal events on the basis of their secondary analysis. The PRECISION trial reported superior gastrointestinal safety with celecoxib than with non-selective NSAIDs on the basis of a composite endpoint of clinically significant gastrointestinal events and iron-deficiency anaemia of gastrointestinal origin. The study might be limited by a high proportion of patients discontinuing medication (68·8%) and lost to follow-up (27·4%). More importantly, the study's results cannot be extrapolated to patients at high risk of gastrointestinal events because the proportion of patients with a previous ulcer or ulcer bleeding was unknown and less than half of the patients were using aspirin before enrolment.

Unlike the PRECISION trial,[16] our study was specifically designed to assess the gastrointestinal safety of two commonly recommended strategies for patients with cardiothrombotic diseases who are at risk of ulcer bleeding. To our knowledge, this is the first randomised study using the clinical outcome of ulcer bleeding to assess the gastrointestinal safety of NSAIDs in aspirin users. We have selected patients at high risk of gastrointestinal events, knowing that they will have the highest risk of upper gastrointestinal bleeding and that the choice of NSAID will be the most important aspect of the regimen. Our study population, unintentionally being an older age group (mean age around 73 years), is more representative of patients with arthritis and cardiothrombotic diseases and at high risk of gastrointestinal events. A longer follow-up of 18 months compared with existing studies has greatly strengthened our evidence. Contrary to present guidelines,[7,12] our findings suggest that in patients with arthritis, cardiothrombotic diseases, and a history of upper gastrointestinal bleeding who continue to require NSAID therapy, a combination of naproxen and proton-pump inhibitor does not offer adequate gastrointestinal protection.

Our finding of a similar incidence of cardiovascular events in the celecoxib group and naproxen group is similar to the findings of previous reports.[28] The PRECISION trial[16] concluded that, at moderate doses, celecoxib was found to be non-inferior to naproxen with regard to cardiovascular safety. Whether the perceived cardiovascular safety of naproxen is true in patients prescribed aspirin is unclear in view of published reports[29] suggesting that naproxen might interfere with the antiplatelet effect of aspirin. Although our study was not powered to assess the cardiovascular safety of NSAIDs, our findings did not show any meaningful difference in cardiovascular events in aspirin users between celecoxib and naproxen. With our findings of a significantly increased risk of upper gastrointestinal bleeding with naproxen in patients at high risk of gastrointestinal events, which can itself lead to cardiovascular compromise and mortality,[30] we believe that naproxen should be avoided in patients at high risk of both cardiovascular and gastrointestinal events.

Our study had limitations. First, our study was not powered to assess the cardiovascular safety of celecoxib. Nevertheless, we have extended our study period to 18 months to capture any delayed cardiovascular outcomes. Second, naproxen at lower doses might have an improved gastrointestinal safety profile, but this speculation needs to be confirmed in future prospective trials. In view of the uncertain cardiovascular and gastrointestinal safety of low-dose naproxen, we cannot recommend low-dose naproxen to high-risk patients. Third, we acknowledge the limitations of our single-centre study design although we found no evidence that the susceptibility to gastrointestinal toxicity in patients given NSAIDs has significant ethnic or geographic variations. Fourth, the study had a long recruitment time and possible confounders might have arisen during this time. We anticipate that our randomised study design will reduce the bias that might have been caused by such confounders. Furthermore, both the demographics of patients and the vigilance of adjudication (shown by the proportions of suspected gastrointestinal events adjudicated as confirmed gastrointestinal events) were not different between the early periods and later periods of the study (data not shown).

In conclusion, celecoxib plus proton-pump inhibitor is the preferred treatment to reduce the risk of recurrent upper gastrointestinal bleeding in patients at high risk of both cardiovascular and gastrointestinal events who require aspirin and NSAID for cardiovascular and anti-inflammatory therapies. Contrary to present guidelines, naproxen should be avoided despite its perceived cardiovascular benefit. Our findings provide novel data toward future practice guidelines in NSAID choice for very high-risk patients.

Contributors

FKLC designed the study. AL, HC, VWSW, and KL recruited and followed up patients. KWLA, PKC, BYS, and KMK coordinated patient follow-up and collected clinical data. VL was responsible for monitoring the quality of study drug production. YKT analysed the data. JYLC was responsible for monitoring. GLHW, SCN, and JCYW were members of the adjudication committee. The manuscript was prepared by FKLC, MHK, YKT, and JYLC without editorial support. All authors read, revised, and approved the final report.

Declaration of interests

FKLC has served as a consultant to Eisai, Pfizer, Takeda, and Otsuka, and has been paid lecture fees by Eisai, Pfizer, AstraZeneca, and Takeda. SCN has been paid lecture fees by Ferring and Takeda. JCYW has received grant support from the US National Institute of Health and has been paid lecture fees by AstraZeneca and Takeda. All other authors declare no competing interests.

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