Pain Relief in Osteoarthritis: Patients' Willingness to Risk Medication-Induced Gastrointestinal, Cardiovascular, and Cerebrovascular Complications

CHRIS G. RICHARDSON, ANDREW CHALMERS, HILARY A. LLEWELLYN-THOMAS, ALICE KLINKHOFF, ANNE CARSWELL, and JACEK A. KOPEC

ABSTRACT. ***Objective.*** Information concerning patients' preferences for the treatment of osteoarthritis (OA) is limited. We examined patients' attitudes toward the acceptability of gastrointestinal, cardiac, and cerebrovascular events in order to obtain pain relief from OA.

Methods. Patients responded to a set of threshold technique tasks. Each task described 2 treatment options, their levels of pain relief, and the risks of side effects. The risk for the side effect under investigation was then systematically increased to reveal the maximal acceptable risk increment associated with the pain reduction.

Results. Of 196 patients, 22.3% and 14.7% were unwilling to accept any additional risk of stomach bleed or heart attack/stroke for 2-point and 5-point pain reductions, respectively. Patients were willing to accept significantly more risk for a 5-point pain reduction than for a 2-point pain reduction in stomach bleed and heart attack/stroke scenarios. Patients also accepted significantly greater additional risks of stomach bleed compared to heart attack/stroke for 2-point and 5-point pain reductions.

Conclusion. Most patients with OA are willing to accept some additional risk of stomach bleed and heart attack/stroke to gain pain relief. Patients are willing to accept greater additional risk of stomach bleed than heart attack/stroke. However, there exists considerable variation in risk-taking attitudes across patients. We recommend that clinicians examine the risk attitude and treatment preferences of each patient on an individual basis when deciding on a treatment regimen. (First Release June 1 2007; J Rheumatol 2007;34:1569–75)

Key Indexing Terms:
OSTEOARTHRITIS ADVERSE EFFECTS RISK-TAKING PAIN/DRUG THERAPY
PATIENT ACCEPTANCE OF HEALTHCARE DECISION MAKING

Osteoarthritis (OA) is the most common form of arthritis, incurring substantial economic, social, and psychological costs[1,2]. Because it is strongly related to age and the population is getting older, the burden of OA is bound to increase[3]. Although there is no known cure, advances in symptomatic treatment have been made over the past few years. However, the optimal approach to therapy remains controversial; current treatments differ in effectiveness, side effects, and costs[4].

Several OA practice guidelines have been published[5-10] including one set that focuses entirely on a class of drugs, the selective cyclooxygenase-2 (COX-2) inhibitors[7]. Selective COX-2 inhibitors were developed in response to the belief that the inhibition of COX-1 isoenzymes by most traditional nonselective nonsteroidal antiinflammatory drugs (NSAID) results in harmful effects in the gastrointestinal (GI) tract. Research has shown that use of COX-2 inhibitors is associated with significantly fewer clinically important upper GI events[11]. Although a slight increase in cardiovascular risk has been associated with traditional nonselective NSAID use[12], recent research indicates that use of COX-2 inhibitors may be associated with a significant increase in risk of cardiac and cerebrovascular side effects. For example, patients receiving 25 mg of rofecoxib daily had a relative risk of confirmed thrombotic event of 1.92 [95% confidence interval (CI) 1.119–3.11] compared to placebo[13]. Similarly, compared to a placebo group, patients taking either 200 mg or 400 mg of celecoxib twice daily had a relative risk of death from cardio-

From the Arthritis Research Centre of Canada, Vancouver, British Columbia, Canada.

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A. Chalmers, MD; A. Klinkhoff, MD, Division of Rheumatology; C.G. Richardson, PhD, Postdoctoral Fellow, School of Nursing; J.A. Kopec, PhD, Associate Professor, Department of Health Care and Epidemiology, University of British Columbia, Vancouver; A. Carswell, PhD, School of Occupational Therapy, Faculty of Health Professions, Dalhousie University, Halifax, Nova Scotia, Canada; H.A. Llewellyn-Thomas, PhD, Professor, Center for the Evaluative Clinical Sciences, Department of Community and Family Medicine, Dartmouth Medical School, Dartmouth College, Hanover, New Hampshire, USA.

Address reprint requests to Dr. C.G. Richardson, School of Nursing, 302-6190 Agronomy Road, University of British Columbia, Vancouver, BC V6T 1Z3, Canada. E-mail: richardson_cg@yahoo.com

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vascular causes, myocardial infarction, stroke, or heart failure of 2.3 (95% CI 0.9–5.5) or 3.4 (95% CI 1.4–7.8), respectively[14].

Although published guidelines recommend fully informing patients about treatment options and specifically identify the need to balance the cardiovascular risks and GI benefits of COX-2 inhibitors[10], none address the issue of incorporating views of this patient population. Traditionally, the extent of patient involvement in medical decision-making has been minimal, at the micro level of the patient consultation with a doctor, and at the macro level of planning and developing practice policies and health services[15,16]. Recently, greater involvement of patients and communities has been advocated; in particular, the elicitation and integration of patient preferences into treatment decisions is increasingly considered an important step in enhancing healthcare outcomes and patients' overall quality of life[17,18].

Data about patients' preferences regarding OA treatments are limited; few studies have systematically elicited patients' attitudes toward the available medical options. One study compared preferences for acetaminophen with traditional NSAID, taking side effects into consideration[19]. Two others used conjoint analysis to elicit preferences in patients with OA of the knee and hip[20] and the knee[21], respectively. Both studies included traditional NSAID, and one included the newer COX-2 inhibitors. However, both studies focused on GI side effects, and neither study was designed to elicit patients' attitudes toward the cardiovascular/cerebrovascular risks associated with the newer COX-2 drugs[22]. More recently, researchers examining an elderly community cohort of patients with OA found that most patients were unsure; of those with an opinion, most correctly estimated the relative risk of heart attack, but tended to overestimate the absolute risk[23]. Although these studies provide some insight into patients' perceived cardiovascular risks and their preferences regarding possible GI side effects, little is known about the amount of cardiovascular and GI risk patients with OA are willing to accept to obtain pain relief.

Our main objective was to characterize patients' attitudes in terms of their acceptable risk levels for stomach bleed and for cardiac/cerebrovascular events in order to obtain different degrees of pain relief. (This project is part of a larger study examining the determinants of OA patients' risk attitudes toward a wide range of major side effects — including dyspepsia, fluid retention, and hypertension, as well as stomach bleed and cardiac/cerebrovascular events.)

MATERIALS AND METHODS

Study subjects. Eligible subjects were patients diagnosed with OA of the hip or knee (according to standard American College of Rheumatology criteria) who were between 45 and 74 years of age, able to understand English, mentally competent, and free of comorbid conditions causing chronic pain. Subjects were recruited from Vancouver rheumatologists (38%), from orthopedic surgeons (12%), and through newspaper advertising (50%). Subjects responding to newspaper advertising had their OA diagnosis confirmed by radiograph and examination by one of the investigating rheumatologists. Prospective participants received a letter explaining the purpose and structure of the study, then were contacted by telephone. At that time, a screening question was used to stratify patients into 3 categories of disease severity — mild, moderate, and severe — based on their self-reported usual level of pain (described by patients as mild, moderate, or severe). Sampling continued until an equal number of patients in each category had been recruited.

Data collection. All subjects provided written informed consent, and were reimbursed for travel and parking expenses. A trained professional interviewer collected the data, either at the Arthritis Research Centre or in the subject's home. For quality control, a sample of interviews was recorded and reviewed by the investigators. The interview was designed to collect demographic data, to obtain self-reports on the Western Ontario and McMaster University Osteoarthritis Index (WOMAC; a measure of OA pain, physical function, and stiffness)[24], and to estimate patients' "maximal acceptable risk increments."

Estimating maximal acceptable risk increments. This estimation process began by asking an individual to consider 2 treatment options, Option A or Option B. Each option was described in terms of: (1) type of treatment received; (2) cost of treatment; (3) level of pain experienced while undergoing treatment (using a 0 to 10 scale); (4) probability of dyspeptic symptoms; (5) probability of fluid retention symptoms; (6) probability of hypertension; (7) probability of stomach bleeding; and (8) probability of heart attack/stroke. The symptom probabilities represent estimates derived from a review of clinical and metaanalytic data and summaries from Canadian consensus conferences[9,25-29], and were presented as the percentage chance of experiencing the symptom.

An example of the initial presentation of the 2 options appears in Table 1. In this example, Option A could represent treatment with acetaminophen for moderate/severe OA, and Option B could represent treatment with a traditional NSAID (although to make the measurement task more generic, such specific treatment information was not provided). Note that the options differ only in the level of pain (5 for Option A vs 3 for Option B).

Once the respondent understood the 2 options, the interviewer asked the subject which he or she would choose. Since it offers better pain relief, the respondent chooses Option B.

Next, the Threshold Technique (TT) was used to elicit the respondent's maximal acceptable risk levels for obtaining Option B's lower pain level (e.g., a drop from 5 to 3 on a 10-point scale in Table 1). The TT is an adaptable method that is highly acceptable to patients in a variety of clinical contexts and yields reliable, internally consistent results[30-32]. To illustrate, in Table 1, the TT task revealing an individual's maximal acceptable risk level for stomach bleed proceeds by increasing Option B's probability of stomach bleed in small increments until he or she switches to Option A.

Each patient completed 4 such TT tasks, to reveal their maximal acceptable risk levels for 2-point and 5-point drops in pain levels for stomach bleed and for heart attack/stroke. A 2-point reduction was used because empirical evidence has indicated that this is the minimal clinically important difference in the intensity of chronic musculoskeletal pain, as assessed on a 0 to 10 scale[33]. A 5-point reduction was also used because it represents a clinically relevant effect size that is substantially greater than 2 points, yet is not so great that the initial presentation of the 2 options would involve starting the TT task at the extreme end of the pain scale.

After the interview, for each TT task, we subtracted Option A's risk from Option B's risk at the individual's switch point. These differences represent the maximal increments in the chances of experiencing a stomach bleed or a heart attack/stroke that the respondent would accept in exchange for a specified reduction in pain. For the rest of this report, we refer to each of these observations as the maximal acceptable risk increment for a particular side effect, given a particular drop in pain level.

Controlling for anchoring and adjustment effects. It is possible that an individual's reported switch point could be affected by a TT task's starting pain level and starting risk level[31]. For example, the "positive worth" of a 2-point difference in experienced pain may depend on whether it is initially presented as the difference between 5 versus 3, or the difference between 2 versus 0. Similarly, the "negative worth" of a 1% risk increment may depend on whether it is presented as an increment starting from 0%, or an increment starting from 3%.

Table 1. Initial presentation of options when eliciting the maximal acceptable risk increment for stomach bleed, under 2-point pain relief measurement condition.

Treatment	Option A	Option B
	Take 1 to 3 pills, spaced through the day	
Pain		
Pain experienced while walking after taking pills daily, on a 0–10 scale is...	5	3
Out-of-pocket cost	$ 0	$ 0
Risks and side effects		
Dyspepsia. Nausea, heartburn, stomach pain. These symptoms will disappear if you stop your arthritis medication	20%	20%
Fluid retention. Swelling ankles or legs. This side effect will disappear if you stop your arthritis medication	5%	5%
Heart attack/stroke. These conditions usually require hospitalization and may cause longterm disability. About 1 in 10 to 1 in 5 patients will die after heart attack/stroke	1%	1%
High blood pressure. Increase in blood pressure. This may be more severe in patients who already have high blood pressure, heart disease, or kidney problems. Treatment usually requires longterm medication, but will disappear if you stop your arthritis medication	10%	10%
Stomach bleed. Feeling unwell, vomiting blood. Treatment involves hospitalization, sedation for tests, a tube inserted down the throat, and blood transfusion. Hospital stay will be 2–7 days. You will be tired for about 3–4 weeks, on medication for 6 months. A small proportion of people may die from stomach bleeding	2%	Increase from 2% to maximal acceptable level = X%

To control for these possible anchoring and adjustment effects, respondents were randomly assigned to one of 4 different measurement conditions for the stomach bleed and heart attack/stroke TT tasks of interest here: (1) low starting pain and low starting side-effect risk; (2) low starting pain and high starting side-effect risk; (3) high starting pain and low starting side-effect risk; and (4) high starting pain and high starting side-effect risk level.

The pain levels for Options A and B in the "low starting pain" measurement condition were 2 versus 0 (2-point reduction) and 5 versus 0 (5-point reduction). In the "high starting pain" condition, these pain levels were 5 versus 3 (2-point reduction) and 8 versus 3 (5-point reduction).

For our stomach bleed and heart attack/stroke TT tasks, the risks of dyspepsia, fluid retention, and high blood pressure were set at 20%, 5%, and 10% in the "high starting side effect" condition, respectively. The risks of dyspepsia, fluid retention, and high blood pressure were all set to 0% in the "low starting side effect" condition. In the "high starting side effect risk" condition, the starting risk for stomach bleed was 2% and for heart attack/stroke was 1%. In the "low starting side effect risk" measurement condition, the starting risks for stomach bleed and for heart attack/stroke were 0%.

Statistical analyses. The distributions of maximal acceptable risk increments were described in terms of means and medians. Due to the skewed data distributions, nonparametric tests were used in the analyses. Mann-Whitney U-tests were employed to assess the influence of the 4 different TT protocols on reported maximal acceptable risk increments. To determine if maximal acceptable risk increments were larger with greater degrees of pain reduction, Wilcoxon signed-ranks tests were used to test for within-subject differences in maximal acceptable risk increments for: (1) stomach bleed, under 2- versus 5-point pain reduction conditions; and (2) heart attack/stroke, under 2- versus 5-point pain reduction conditions. To assess whether maximal acceptable risk increments were different for different side effects, Wilcoxon signed-ranks tests were used to test for within-subject differences in maximal acceptable risk increments for stomach bleed versus heart attack/stroke, given (1) a 2-point pain reduction, and (2) a 5-point pain reduction.

For each subject accepting some additional risk of both stomach bleed and heart attack/stroke, "risk ratios" were derived, by dividing the individual's maximal acceptable risk increment for stomach bleed by his/her maximal acceptable risk increment for heart attack/stroke. Thus, the individual could be characterized in terms of the relative acceptability of risk for stomach bleed compared to the risk for heart attack/stroke.

RESULTS

Participant characteristics. Of the 202 subjects who agreed to participate, 6 were excluded from the analyses due to missing data. The demographic characteristics of the remaining 196 patients appear in Table 2. The respondents were 56% female; 28% had severe and 33% had mild pain, and their WOMAC scores implied that this was a group with moderately severe OA.

Differences in maximal acceptable risk increments. We assessed whether the reported maximal acceptable risk increments were affected by measurement condition, by amount of pain relief offered, and by type of side effect.

Effects of measurement condition. There were 2 aspects to assessing the effects of measurement condition.

1. Pain levels: Starting high versus starting low. The Mann-Whitney U-tests for the effect of starting pain level on the accepted incremental risk of stomach bleed were not significant (2-point pain reduction: $Z = 0.5$, $p > 0.05$; and 5-point reduction: $Z = 1.1$, $p > 0.05$). The Mann-Whitney U-tests for the effect on the accepted incremental risk of heart attack/stroke were not significant (2-point reduction: $Z = 0.7$, $p > 0.05$; 5-point reduction: $Z = 1.6$, $p > 0.05$).

2. Side-effect risks: Starting high versus starting low. The Mann-Whitney U-tests for the effect of starting side-effect level on the accepted incremental risk of stomach bleed were

Table 2. Characteristics of study participants. Data are percentages unless otherwise indicated.

Characteristic	
Mean age, yrs (SD)	61 (8)
Sex	
Male	44
Female	56
Annual income	
$19,999 or less	10
$20,000–$39,999	20
$40,000–$59,999	24
$60,000–$99,999	26
$100,000 or more	20
Highest level of education	
High school	22
College	27
University	51
Mean years with diagnosed OA (SD)	12 (13)
Medication use	
Prescription	41
Over-the-counter	48
Herbal/natural remedies	48
Self-reported level of pain	
Mild	33
Moderate	39
Severe	28
Mean WOMAC Total* (SD)	37 (19)
Pain	37 (20)
Physical functioning	35 (20)
Stiffness	45 (22)

* Scores on a scale from 0 to 100. OA: osteoarthritis.

significant (2-point pain reduction: $Z = 5.0$, $p < 0.01$; 5-point pain reduction: $Z = 2.7$, $p < 0.01$). The Mann-Whitney U-tests for the effect of starting side-effect level on the accepted incremental risk of heart attack/stroke also were significant (2-point reduction: $Z = 7.2$, $p < 0.01$; 5-point reduction: $Z = 5.8$, $p < 0.01$).

These suggested that patients' reported maximal acceptable risk increments are not affected by the TT tasks' starting pain level but are affected by the starting side-effect risk level. Table 3 presents the median and mean maximal acceptable incremental risks for stomach bleed and for heart attack/stroke for 2-point and 5-point pain reductions in the high and low starting side-effect conditions.

Effects of amount of pain relief. The Wilcoxon signed-ranks tests for within-subject differences in maximal acceptable risk increments under 2-point versus 5-point pain reduction conditions were statistically significant for stomach bleed ($Z = 7.4$, $p < 0.01$) and for heart attack/stroke ($Z = 5.8$, $p < 0.01$). In both side-effect situations, respondents reported higher maximal acceptable risk increments in exchange for a 5-point pain reduction than for a 2-point pain reduction.

Effects of type of side effect. The Wilcoxon signed-ranks tests for within-subject differences in maximal acceptable risk increments for stomach bleed versus maximal acceptable risk increments for heart attack/stroke were statistically significant, in both the 2-point ($Z = 5.3$, $p < 0.01$) and 5-point ($Z = 6.7$, $p < 0.01$) pain reduction conditions. In both pain reduction situations, respondents reported higher maximal acceptable risk increments for stomach bleed. To illustrate these differences, Figure 1 presents box plots of the maximal acceptable risk increments for each of the side effect and pain reduction situations. The distributions tended to be quite skewed, with approximately half of the respondents reporting maximal acceptable risk increments of 2% or less.

Risk ratios. Of the 196 subjects, 22.3% would not accept any increase in either their risk of stomach bleed or their risk of heart attack/stroke in order to obtain a 2-point pain reduction; 14.7% would be similarly unwilling in order to obtain a 5-point pain reduction (Table 4).

On the other hand, 64.5% would be willing to accept some additional risk of both stomach bleed and heart attack/stroke in order to obtain a 2-point pain reduction, and 72.6% would be similarly willing in order to obtain a 5-point pain reduction. The median and mean risk ratios were 2.0 and 3.6 [standard deviation (SD) = 7.5] in the 2-point pain reduction condition, and 2.0 and 4.3 (SD = 8.0) in the 5-point pain reduction condition. In other words, among those who would accept some additional risks, subjects' maximal acceptable risk increment

Table 3. Maximum acceptable risk increments for stomach bleed and heart attack/stroke.

Threshold Task Measurement Conditions			Maximum Acceptable Risk Increments (expressed in absolute percentages)	
Amount of Pain Reduction* (points)	Side Effect	Starting Risk Level	Range (interquartile range)	Median
2	Stomach bleed	None (0.0)	100 (5.5)	0.0
		High (2.0)	38.5 (3.5)	3.5
2	Heart attack/ stroke	None (0.0)	50.5 (2.0)	0.0
		High (1.0)	19.5 (4.5)	1.5
5	Stomach bleed	None (0.0)	100 (7.5)	3.5
		High (2.0)	58.5 (6.5)	4.5
5	Heart attack/ stroke	None (0.0)	75.5 (3.5)	0.0
		High (1.0)	29.5 (4.5)	2.5

* On a 10-point scale.

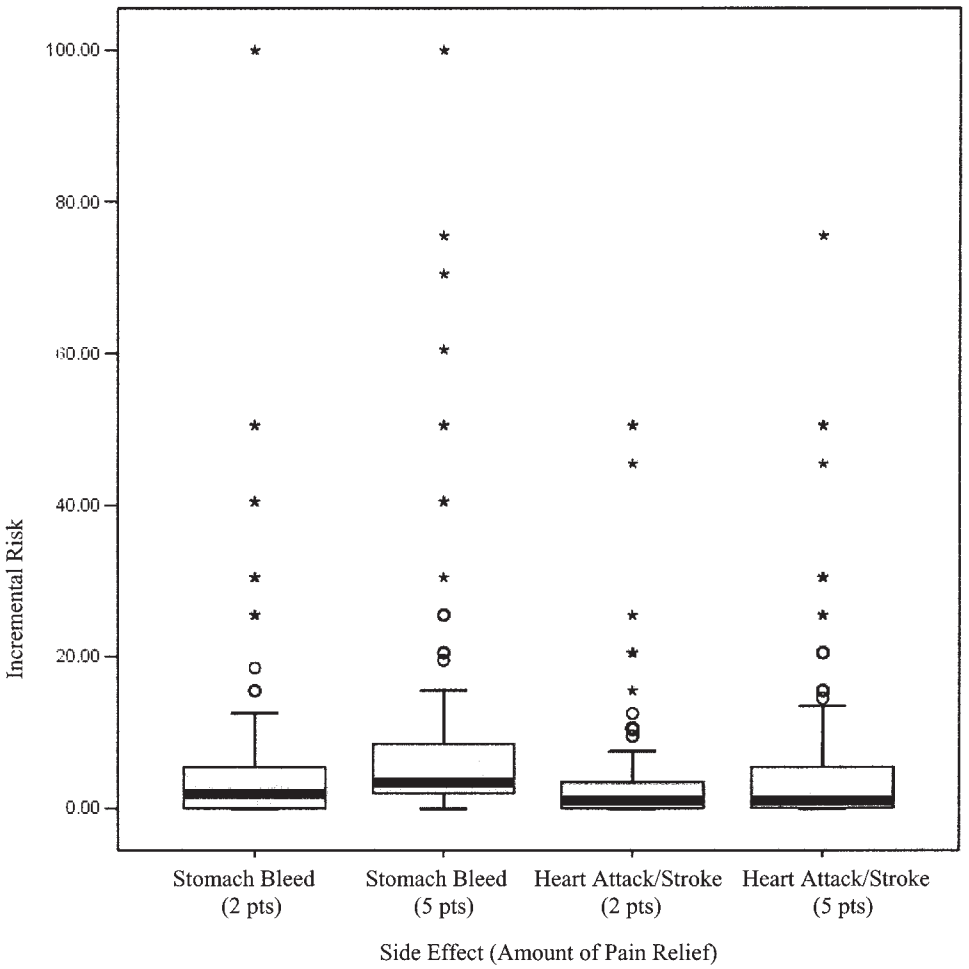

Figure 1. Maximal acceptable incremental risks for stomach bleed and heart attack/stroke, given 2- and 5-point reductions in pain. Ends of the box indicate quartiles; length of the box is the interquartile range (IQR). Line within the box indicates median; 2 vertical lines outside box extend to smallest and largest observations within 1.5× IQR of the quartiles. •: observations between 1.5× and 3× IQR. *: observations falling outside 3× IQR.

for stomach bleed was roughly 4 times greater than their maximal acceptable risk increment for heart attack/stroke, in both the 2-point and 5-point pain reduction conditions.

The potential range of ratios was also broken into categories derived using intuitive breaks, "buffers" of 0.1, and clusters of cases. These categories are presented in Table 5. Subjects with a ratio of less than 1 reported higher maximal acceptable risk increments for heart attack/stroke than for stomach bleed, given the same degree of pain reduction. Subjects with ratios greater than 1 reported higher maximal acceptable risk increments for stomach bleed than for heart attack/stroke. The different percentages of subjects in each of these categories illustrate the considerable variation in the size of the risk ratios.

DISCUSSION

Our study represents the first attempt to elicit patients' attitudes about treatment of OA of the hip and knee in a manner that explicitly focuses on the conditions under which side effects related to heart attack and stroke are acceptable or not. Two related studies have already appeared in the OA literature. One study, using conjoint analysis, suggested that respondents were more concerned with serious side effects than with mild to moderate side effects (even though the risks of these were small), and also indicated that the severity of joint aches and of reduced mobility were correlated with risk-taking attitudes[20]. Our study deals only with the serious side effects of stomach bleed and heart attack/stroke, but complements these observations in relationship to pain relief.

The second related study also used conjoint analysis to elicit overall treatment preferences across a broader range of treatment options, including 2 nonpharmacological options: capsaicin and glucosamine or chondroitin[21]. Even when it was described as least effective, capsaicin was preferred by 34% of patients. COX-2 inhibitors were preferred by 23%, but only when they were described as 3 times as effective as capsaicin and with a low prevalence of GI side effects. No patient preferred nonselective NSAID. Although these investigators

Table 4. Percentage of respondents willing to accept additional risk of heart attack/stroke or stomach bleed for a 2-point and 5-point reduction in pain.

Risk Acceptance Category	2-Pt Pain Reduction, n = 196	5-PT Pain Reduction, n = 196
Accepted no additional risks	22.3	14.7
Accepted additional risk of heart attack/stroke but not stomach bleed	5.6	2.5
Accepted additional risk of stomach bleed but not heart attack/stroke	7.6	10.2
Accepted additional risks of both stomach bleed and heart attack/stroke	64.5	72.6
Total percentage	100	100

Table 5. Percentage of respondents willing to accept some additional risk for stomach bleed and heart attack/stroke: percentage distributions into risk ratio* categories, under 2-point and 5-point pain reduction conditions.

Risk Ratio Categories	2-Pt Pain Reduction, n = 127	5-PT Pain Reduction, n = 143
0–0.8	18.1	15.4
0.9–1.1	8.7	11.9
1.2–1.8	14.2	14.7
1.9–2.1	29.9	20.3
2.2–5.0	16.5	21.7
> 5.0	12.6	16.1
Total percentage	100	100

* The ratio of maximal acceptable risk increment for stomach bleed to maximal acceptable risk increment for heart attack/stroke.

were not primarily focusing on acceptable side-effect risk levels, they did report that overall preferences were driven by trying to avoid both uncommon and common side effects.

In contrast, when focusing on serious adverse events, the majority of the patients examined in our study would accept some incremental risk of stomach bleed or heart attack/stroke for both 2-point and 5-point reductions in pain. However, our respondents were clearly more averse to the risk of heart attack/stroke than stomach bleed.

These contrasting risk attitudes may be due to differences in demographic characteristics; our patients tended to be younger (an average age of 60) than those in the earlier study (average age 70). The contrasts may also be due to the differences in the studies' measurement objectives and, by corollary, their elicitation techniques. Our objective was to measure the maximal acceptable risk increment for a side effect (e.g., risk of bleed) in order to obtain a particular treatment benefit (here, pain relief), while controlling for other factors[31,32]. The TT tasks were systematically designed to outline the full array of factors, to identify the specific side effect of particular interest, and to interactively pinpoint the maximal acceptable risk increment for that specific side effect. The advantages of this strategy are that the choices between therapeutic options are realistic and clinically relevant, there is no information overload, the preference-elicitation task is easy to understand, and the responses can be clearly interpreted. One potential limitation of the TT procedure is that it examines changes in a single attribute at a time and thus may not fully reflect decisions made in more complex real-world settings. Although more complex and cognitively demanding discrete choice techniques have been developed that simultaneously assess multiple attributes (e.g., conjoint analyses), we have found that the TT is practical and easy to use. Most patients, including the elderly, appear to understand the task and provide internally consistent and reliable responses[30,31]. An additional limitation to consider is that although respondents were randomly assigned to one of 4 different measurement conditions to control for possible anchoring and adjustment effects, the presentation order of TT tasks was the same for all patients. To help minimize potential order effects related to task familiarity (i.e., practice effects), interviewers were extensively trained in administering TT tasks and worked carefully with respondents during all TT procedures. It is also possible that patients' responses to the 5-point pain reduction may have been informed by their response to the previous 2-point TT scenario. Although we did not control for these order effects, we do not feel that they could have biased the results enough to significantly alter the findings of the study.

These observations carry implications for patients and clinicians. Our study results highlight the heterogeneity in patients' attitudes toward assuming risks, which should be recognized during the development of evidence-based practice guidelines and patients' decision aids for the treatment of OA of the hip and knee. These attitudinal differences also

should be revealed, acknowledged, and deliberately accommodated during decision-making in individual patient-physician dyads.

The recent withdrawal of one of the COX-2 drugs from the market was based in part on an increased risk of cardiac and cerebrovascular events. In one trial, 3.6% of patients taking rofecoxib (25 mg per day) experienced a serious thrombotic event compared to 2.0% in the placebo group[13]. Our study provides empirical support for the belief that many patients would accept this risk for pain relief if given the choice[17], and highlights the need to explicitly consider patients' attitudes toward maximal acceptable risk increments when helping them arrive at informed choices among optional therapies.

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