How Do Physicians Weigh Benefits and Risks Associated with Treatments in Patients with Osteoarthritis in the United Kingdom?

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ABSTRACT. ***Objective.*** To quantify the relative importance that UK physicians attach to the benefits and risks of current drugs when making treatment decisions for patients with osteoarthritis (OA).

Methods. Physicians treating at least 10 patients with OA per month completed an online discrete-choice experiment survey and answered 12 treatment-choice questions comparing medication profiles. Medication profiles were defined by 4 benefits (reduction in ambulatory pain, resting pain, stiffness, and difficulty doing daily activities) and 3 treatment-related risks [bleeding ulcer, stroke, and myocardial infarction (MI)]. Each physician made medication choices for 3 of 9 hypothetical patients (varied by age, history of MI, hypertension, and history of gastrointestinal bleeding). Importance weights were estimated using a random-parameters logit model. Treatment-related risks physicians were willing to accept in exchange for various reductions in ambulatory and resting pain also were calculated.

Results. The final sample was 475. A reduction in ambulatory pain from 75 mm to 25 mm (1.6 units) was 1.1 times as important as an increase in MI risk from 0% to 1.5% (1.5 units). The greatest importance was for eliminating a 3% treatment-related risk of MI or stroke. On average, physicians were willing to accept an increase in bleeding ulcer risk of 0.7% (95% CI 0.4%–1.7%) for a reduction in ambulatory pain of 75 mm to 50 mm.

Conclusion. When presented with well-known benefits and risks of OA treatments, physicians placed greater importance on the risks than on the analgesic properties of the drug. This has implications for the reporting of the results of clinical research to physicians. (First Release March 15 2012; J Rheumatol 2012;39:1056–63; doi:10.3899/jrheum.111066)

Key Indexing Terms:
OSTEOARTHRITIS | NONSTEROIDAL ANTIINFLAMMATORY DRUGS
OUTCOME ASSESSMENT | PHYSICIAN PRACTICE PATTERNS | RISK

Osteoarthritis (OA) is the most common form of arthritis, affecting about 8.5 million people in the United Kingdom[1]. The prevalence of OA increases markedly with age and is a significant contributor to disability in the elderly. It is characterized by pain, bony enlargement, reduced joint mobility, and intermittent joint swelling and can occur most commonly in the knees, hips, hands, and spine. Due to joint pain and stiffness, patients with OA often have limitations in their ability to conduct their usual physical or social activities.

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Currently, there is no cure for OA, and treatment is focused on controlling pain and improving function. Published treatment guidelines by the European League Against Rheumatism (EULAR) and the Osteoarthritis Research Society International (OARSI)[2,3] recommend a treatment algorithm starting with paracetamol and progressing to nonsteroidal antiinflammatory drugs (NSAID) or cyclooxygenase-2 (COX-2) inhibitors and to adjuvant analgesics and opioids as needed.

Paracetamol and NSAID are the most commonly used treatments for OA[4,5]. Although both are effective in reducing pain, paracetamol is less effective than NSAID[3]. In addition to the known risk of hepatotoxicity with paracetamol, more recent data suggest that high-dose paracetamol also may be associated with an increased risk of gastrointestinal (GI) side effects[6]. It is well known that NSAID are associated with GI side effects, the most common being nausea, vomiting, dyspepsia, and abdominal pain[6,7,8]. In high doses and in patients with risk factors, more serious GI side effects, such as gastroduodenal ulceration, bleeding, obstruction, and perforation, can occur at rates of about 1%

to 2%, on average, and up to 10% per annum in high-risk patients[7]. COX-2 inhibitors were developed to reduce the risk of GI side effects, compared with nonselective NSAID[9]. NSAID also are associated with increases in blood pressure, especially in patients with preexisting hypertension[9,10,11,12]. More recently, both nonselective NSAID and selective COX-2 inhibitors have been linked to an increased risk of thrombotic cardiovascular (CV) events, such as myocardial infarctions (MI) and strokes, when compared with no treatment[13,14,15,16,17].

Despite the associated GI, blood pressure, and CV risks, NSAID are still widely used to treat patients with OA. However, EULAR and the OARSI guidelines recommend using NSAID only after careful assessment of a patient's GI and CV risk factors[9,11,12,13]. While these recommendations are clinically helpful, nevertheless there is little published data on how physicians balance the benefits and known side effects of drugs when making treatment decisions for their patients with OA. Given how risk is communicated in the general media and medical literature, both patients and physicians can easily become confused about how to compare risks and how to make judgments about the relative balance between benefits and risks among different treatment options[18].

Direct comparisons between therapeutic benefits and risks are difficult because endpoints are dissimilar. Regulatory agencies such as the US Food and Drug Administration and the European Medicines Agency are evaluating quantitative approaches to inform decisions involving benefit-risk tradeoffs. Quantifying physicians' benefit-risk tradeoff judgments can make implicit weights attached to endpoints more transparent and help regulators, physicians, and patients make better-informed and more consistent decisions about treatment options. Therefore, our primary aim was to quantify the relative importance that physicians attach to the benefits and risks of current options when making a treatment decision for patients with OA. A secondary aim was to determine whether certain patient characteristics influence a physician's decision-making regarding treatments for patients with OA.

MATERIALS AND METHODS

Study sample. Physicians were recruited from Harris Interactive's (Rochester, NY, USA) online physician panel. Physicians were recruited to the panel by direct telephone contact at their workplace. All participating physicians were required to be board-eligible or board-certified general practitioners, internists, orthopedic surgeons, and rheumatologists in the United Kingdom who treat at least 10 patients with OA per month. Physicians were recruited by an e-mail invitation asking them to participate in the online survey. Subsequent reminder e-mails were sent within a week of the invitation. If a physician did not complete the survey, Harris Interactive followed up with a telephone reminder. Harris Interactive administered the 20-minute online survey in August 2009. The Office of Research Protection and Ethics at Research Triangle Institute granted a consent exemption for our study.

Discrete-choice experiments. Discrete-choice experiments have been used increasingly to quantify decision criteria for attributes of health, healthcare, and healthcare policy[19,20,21,22,23,24]. Discrete-choice experiment is a systematic method of eliciting tradeoffs to quantify the relative importance that healthcare decision makers assign to various treatment attributes and outcomes. Discrete choice experiments are based on the premise that medical interventions are composed of a set of attributes or outcomes (efficacy, side effects, mode of administration) and that the ability of a particular intervention to satisfy the needs or wants of an individual is a function of these attributes[25,26,27,28]. In a discrete-choice experiment, respondents are presented with a series of questions in which they are asked to choose a preferred alternative from a set of hypothetical treatment profiles. Each treatment profile is defined by varying levels of treatment attributes and outcomes.

Survey instrument. We identified 7 attributes (4 benefits and 3 risks) to describe the OA medication profiles in our study (Table 1). Each of the 4 benefits (easing of ambulatory pain, resting pain, stiffness, and daily activities) and 3 treatment-related risks (bleeding ulcer, stroke, and MI) were varied across 4 possible clinically meaningful levels, as well as across different patient demographic characteristics (age, history of MI, hypertension, and history of GI bleeding). The benefits were developed to correspond to 3 domains of the Western Ontario and McMaster (WOMAC) Index of Osteoarthritis (pain, stiffness, and physical function) because these domains are commonly used as clinical trial endpoints in OA studies[29]. Using clinician recommendations, we considered 2 independent pain attributes — resting pain and ambulatory pain — because these 2 pain types have different effects on patients.

CV risks (MI and stroke) and GI risk (bleeding ulcer) were included because, as described, these are the most common and potentially worrisome severe adverse events. The salience and completeness of these attributes in describing OA medication outcomes was confirmed with one-to-one, face-to-face interviews with 10 physicians and 10 patients in the United Kingdom.

To create medication profiles for the treatment-choice questions, we used a main effects D-efficient experimental design that resulted in 30 hypothetical medication pairs[30,31,32,33,34]. The final experimental design consisted of 3 survey versions, each containing 10 treatment-choice questions (the order of the treatment-choice questions was randomized for each respondent). Two treatment-choice questions from each version were randomly repeated for different patient profiles to determine whether patient characteristics affected physicians' preferences. Each physician was randomly assigned to 1 of the 3 versions and was asked to consider 3 of the 9 possible hypothetical patient profiles. Thus, each physician answered 12 choice questions in total: 4 treatment-choice questions for each of 3 patient profiles randomly selected from the 9 patient profiles. The 9 hypothetical patient profiles varied by age, history of MI, hypertension, and history of GI bleeding (Appendix). Thus, the patient profiles varied by comorbid conditions and clinically relevant risk factors for treatment-related risks. In each treatment-choice question, physicians were asked to choose between 2 hypothetical medication profiles (Figure 1). In addition, the survey collected demographic information about the physicians, including sex, years in practice, type of practice, and medical specialty.

Statistical analysis. The pattern of physicians' choices was analyzed using a random-parameters logit model. In such a model, the dependent variable is discrete treatment choice, and the explanatory variables include the levels of the attributes included in the study. The resulting importance-weight parameter estimates quantify the relative importance of each attribute level[35,36,37]. All analyses were conducted using NLOGIT 4.0 (Econometric Software Inc., Plainview, NY, USA).

For efficacy benefits, physicians perceived level of difficulty in doing daily activities and level of ambulatory pain as being closely related. The reported importance weights for ambulatory pain thus incorporated the combined effect of pain severity and the corresponding limitation on daily activities. Although importance weights for the treatment-related bleeding ulcer risk varied from 0% to 10% and were reported in our estimates, we present only the most clinically relevant values (0%, 1%, and 2.5%). We

Table 1. Attributes and levels used in the survey instrument.

Physician Attribute Labels	Abbreviated Label	Levels*
Pain while moving around 1 hour after taking the medication	Ambulatory pain	None (0 mm) Mild (25 mm) Moderate (50 mm) Severe (75 mm)
Pain while sitting, lying down, or sleeping 1 hour after taking the medication	Resting pain	None (0 mm) Mild (25 mm) Moderate (50 mm) Severe (75 mm)
Stiffness 1 hour after taking the medication	Stiffness	None (0 mm) Mild (25 mm) Moderate (50 mm) Severe (75 mm)
Difficulty doing daily activities 1 hour after taking the medication	Difficulty doing daily activities	None (0 mm) Mild (25 mm) Moderate (50 mm) Severe (75 mm)
Risk of a bleeding ulcer requiring an operation within the next year because of the medication	Bleeding-ulcer risk	None 10 out of 1000 (1.0%) 50 out of 1000 (5.0%)† 100 out of 1000 (10.0%)†
Incremental, treatment-related risk of a heart attack/stroke within the next 5 years††	Heart-attack risk/stroke risk	No chance 5 out of 1000 (0.5%) 15 out of 1000 (1.5%) 30 out of 1000 (3.0%)

*On a 0–100mm visual analogue scale, unless stated otherwise. †Not clinically relevant levels. ††Heart attack and stroke risks are both cardiovascular risks and could not be included at the same time because they are inherently correlated. In the discrete-choice survey, heart attack risk was shown half the time and stroke risk was shown the other half.

used a linear interpolation between 1% and 5% to calculate the importance weight for 2.5%.

We tested the effect of a patient's risk factors (age, history of MI, hypertension, and history of GI bleeding) on physicians' evaluation of treatment-related risks (MI risk, stroke risk, and bleeding ulcer risk). Specifically, if the patient profile included CV risk factors (history of MI and hypertension), we estimated the independent effect of treatment-related CV risks (MI risk and stroke risk) as well as the incremental effect of increased patient risk factors on physicians' treatment choices. The incremental effect of patient CV risk factors was estimated by multiplying the treatment-related CV risk levels presented in each treatment-choice question with a dummy variable equal to 1 if the patient profile included CV risk factors. Similarly, we estimated both the independent effect of treatment-related bleeding ulcer risk and the incremental effect of a patient having a history of GI bleeding. Similarly, the incremental effect of patient age was estimated for all treatment-related risks.

The data are presented in Figure 2 and may be interpreted in 3 primary ways. First, the vertical distance between the importance weights for the best and worst levels of any attribute represents the importance of that attribute over the range of levels included in the study relative to the importance of any other attribute included in the study. Second, differences between adjacent importance weights indicate the relative importance of moving from 1 level of an attribute to an adjacent level of that attribute: the greater the difference, the more important is the change from 1 level to the next. Third, the difference between adjacent importance weights of 1 attribute can be compared with the difference between adjacent importance weights of a different attribute for purposes of understanding whether the magnitude of the importance of a given change is comparable across attributes. If the confidence intervals do not overlap for adjacent levels in a particular attribute, the mean estimates are statistically different from each other at the 5% level of significance or better.

RESULTS

Physician sample characteristics. Harris Interactive sent e-mail invitations to 3428 physicians. Of the 3428 invitations, 771 physicians responded (response rate = 22%). Information on the physicians who did not respond is not available. Of the 771 physicians who responded, 482 met the inclusion criteria and 477 consented to participate in the survey. Table 2 presents the summary statistics for the 477 physicians who completed the survey. The majority of respondents were men, had a mean (SD) age of 43 (10.1) years, and had been practicing medicine for at least 10 years. In addition, 61% reported being in a general practice and saw a mean number of 127 patients per month.

Two physicians (0.4%) with no variation in their responses to the choice questions were deleted from the sample, as this lack of variation suggested that these physicians did not pay attention to the treatment-choice questions. Thus, the final physician number used for analysis was 475.

Importance weights. Figure 2 presents the estimated importance weights and 95% confidence intervals for the 7 included attributes. The mean estimates demonstrated a more positive importance weight for treatments that result in lower residual pain and improved function and with the lowest risk of side effects. The greatest importance was attached to eliminating a 3% treatment-related risk of heart attack or stroke.

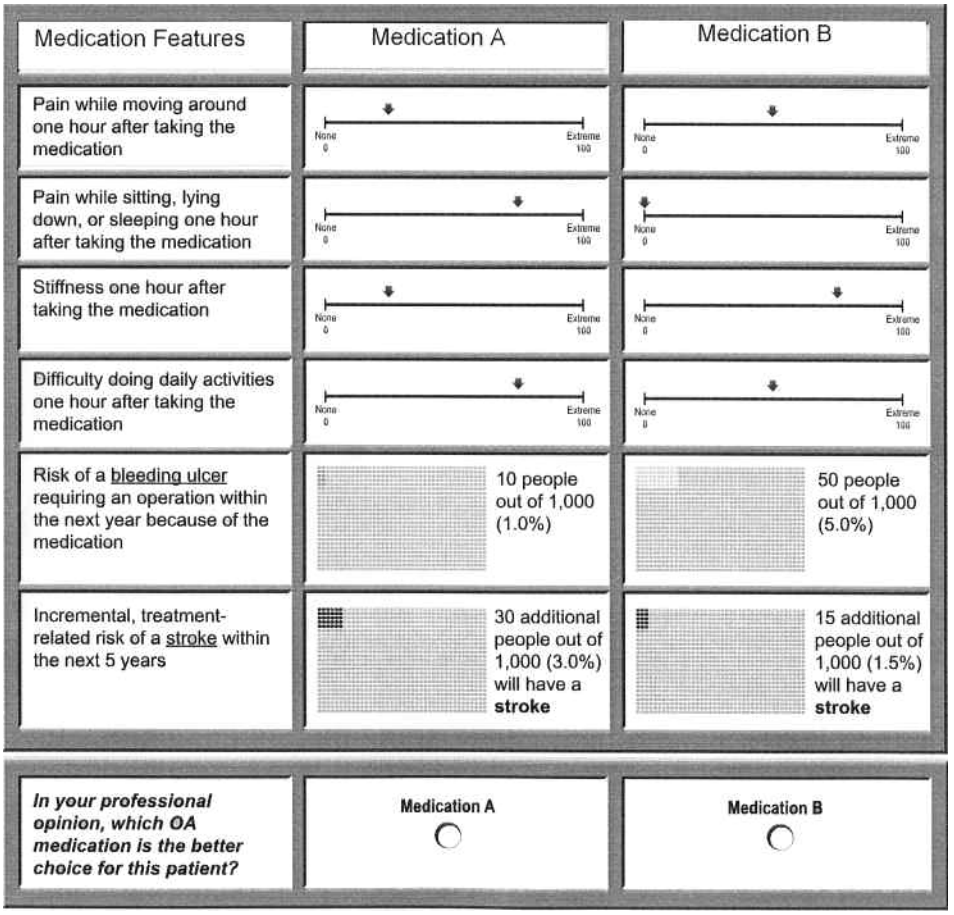

Figure 1. Example of a treatment-choice question. Patient profile 1: A 55-year-old patient with severe osteoarthritis (OA; e.g., hip or knee). The patient's health is otherwise good (high performance status), with no history of kidney disease and no significant comorbidities.

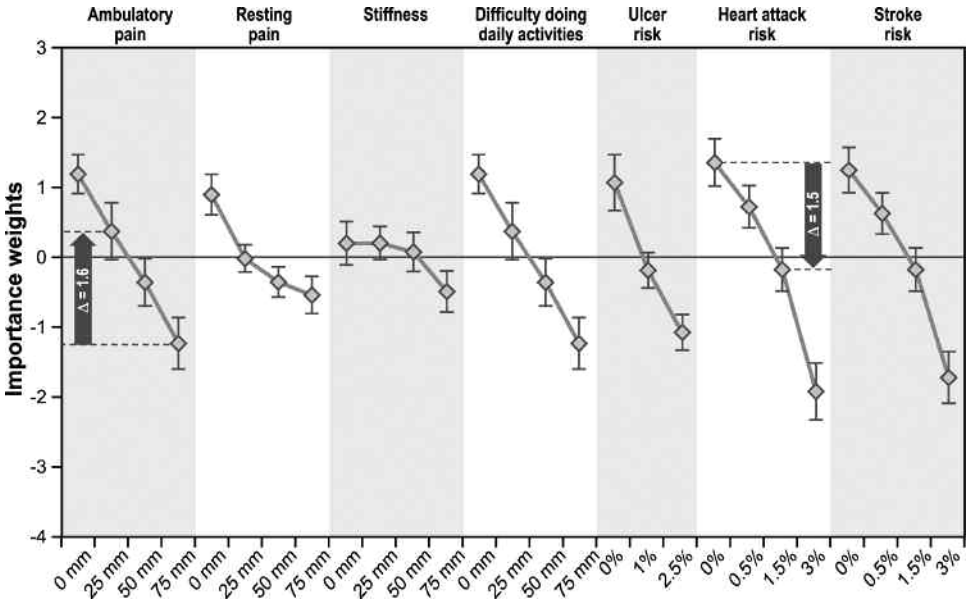

Figure 2. Importance weights for the 7 attributes. Only relative differences matter when interpreting importance weights. The differences between adjacent weights indicate the relative importance of moving from 1 level of an attribute to an adjacent level of that attribute. The vertical lines around each mean importance weight denote the 95% CI of the point estimate.

Table 2. Demographic and clinical characteristics of physicians (n = 477).

Category	No. Physicians (%)
Gender	
Male	356 (74.6)
Female	121 (25.4)
Age, yrs, mean (SD)	43 (10.1) NA
How many years have you been in practice since completing your medical training?	
< 1	1 (0.2)
1–3	18 (3.8)
4–6	55 (11.5)
7–9	81 (17.0)
10–15	107 (22.4)
16–20	67 (14.0)
21–25	68 (14.3)
> 25	80 (16.8)
Which of the following best describes your practice?	
NHS university hospital	108 (22.6)
Other NHS hospital	61 (12.8)
Private hospital	1 (0.2)
Both private and NHS hospitals	17 (3.6)
General practice	289 (60.6)
Other	1 (0.2)
Which of the following best describes your specialty?	
Orthopedics	89 (18.7)
Rheumatology	72 (15.1)
General practice	291 (61.0)
Internist	25 (5.2)
Patients seen per month, mean (SD)	127 (104.4) NA

NA: not applicable; NHS: UK National Health Service.

For benefits, the order of importance (from most to least) was eliminating severe ambulatory pain and eliminating severe difficulty doing daily activities, followed by eliminating severe resting pain and then eliminating severe stiffness. With respect to differences between adjacent importance weights within 1 attribute, the importance of reducing MI risk from 3% to 1.5% (a difference in importance weights of about 2.1 units) was the most important from a safety perspective. A similar result was seen for reduction in stroke risk from 3% to 1.5%. A reduction in resting pain from 25 mm to 0 mm was considered the most important treatment benefit (a difference in importance weights of about 0.9 units).

With respect to comparisons of the magnitude of the differences in weights across attributes, Figure 2 indicates that the differences in importance weights for a reduction from 75 mm to 25 mm in ambulatory pain and an increase in MI risk from 0% to 1.5% were similar, with differences in importance weights of 1.6 and 1.5, respectively. Thus physicians' perceived benefit of the 50-mm improvement in the pain endpoint over this range had about the same value as a 1.5% absolute increase in the perceived risk of an MI. Physicians generally attached greater importance to reducing or eliminating side effects than reducing pain. Within the positive drug attributes, physicians attached more importance to the reduction of ambulatory pain and reduction in difficulty doing daily activities than to the reduction in resting pain; little importance was attached to reducing stiffness.

Table 3 presents the level of treatment-related risks physicians were willing to accept in exchange for various improvements in ambulatory and resting pain. For example, on average, physicians were willing to accept an increase in bleeding ulcer risk of 0.7% (95% CI 0.4%–1.7%), for an improvement in ambulatory pain of 75 mm to 50 mm. Generally, physicians were willing to accept similar risks for ulcers, MI, and strokes. Interestingly, the acceptable risk associated with a 25-mm reduction in pain is dependent on the baseline level and the type of pain: physicians would accept the greatest risk of side effects when moving from 75 mm to 50 mm, with smaller risk being acceptable when moving from 50 mm to 25 mm.

For resting pain, the greatest acceptable risk was associated with a 25-mm reduction in pain when moving from 25 mm to 0 mm, with smaller risk being acceptable when moving from 50 mm to 25 mm; the smallest risk was acceptable when moving from 75 mm to 50 mm. In contrast, the differences in a 25-mm reduction in ambulatory pain were much less dependent on baseline level, but a trend for 75 mm to 50 mm was associated with the largest acceptable risk. This risk was similar for the reduction from 25 mm to 0 mm of resting pain.

Table 3. Mean risks physicians are willing to accept in exchange for various reductions in ambulatory and resting pain. For example, on average, physicians are willing to accept an increase in bleeding ulcer risk of 0.7% (95% CI 0.4%–1.7%) for an improvement in ambulatory pain of 75 mm to 50 mm (severe to moderate). All risks are given in percentages.

Improvement in Benefit	Bleeding Ulcer Risk (95% CI)	Heart Attack Risk (95% CI)	Stroke Risk (95% CI)
Ambulatory pain			
75 mm to 50 mm	0.72 (0.35, 1.65)	0.76 (0.27, 1.48)	0.74 (0.26, 1.52)
50 mm to 25 mm	0.55 (0.06, 1.18)	0.52 (0.06, 1.57)	0.49 (0.06, 1.62)
25 mm to 0 mm	0.66 (0.27, 1.56)	0.68 (0.22, 1.33)	0.65 (0.21, 1.36)
Resting pain			
75 mm to 50 mm	0.17 (0.01, 0.50)	0.16 (0.01, 0.51)	0.15 (0.01, 0.48)
50 mm to 25 mm	0.27 (0.03, 0.58)	0.26 (0.03, 0.67)	0.24 (0.03, 0.66)
25 mm to 0 mm	0.75 (0.50, 1.17)	0.80 (0.37, 1.51)	0.78 (0.34, 1.56)

Figure 3 presents the results of the analysis when comparing responses between general practitioners and specialists. There were no significant differences in the importance weights between these 2 groups. Further, none of the incremental effects of CV or GI risk factors or patient ages were significant (indicating that patient risk factors were not an importance influence on physicians' treatment choices).

DISCUSSION

To our knowledge, these results provide the first systematic evaluation, using benefit-risk tradeoffs, of UK physicians' attitudes in deciding which treatments to use in managing patients' OA symptoms. It is also the first study to define specific side effects associated with the drugs commonly used to manage OA pain. Our study had several important results. First, when presented with well-known benefits and risks of treatment for OA, UK physicians placed greater importance on the risks than on the analgesic properties of the drug. Second, physicians considered reductions in ambulatory pain to be more important than the same reductions in resting pain (except for the improvement from mild to no pain). Third, UK physicians placed little importance on reducing moderate pain to mild pain. Fourth, UK physicians weighted the benefits and risks of treatment similarly, regardless of patient characteristics, when analyzed by physician specialty.

Previous discrete-choice studies have examined patient preferences[20,21,22,23,24] but none has examined physician importance weighting or detailed side effect attributes. Ratcliffe, *et al*[21] concluded that the level of joint aches, level of physical mobility, and serious treatment-related side effect risks were most influential on the treatment preferences of patients with OA. Fraenkel, *et al*[23] found that older patients with knee OA were willing to accept lesser efficacy in exchange for a lower risk of adverse events. Fraenkel and Fried[24] concluded that patients with knee OA preferred exercise to prescription drugs, due to the patients' unwillingness to accept adverse event risks.

Our study shows that both primary care and specialist physicians place greater importance on side effects than on the treatment benefits of the drug. This is an important finding and has several potential explanations. The adverse publicity and subsequent litigation regarding the adverse effects of COX-2 inhibitors, traditional NSAID, and opiates may have focused the physicians on the side effects of these medications and thus may explain the decline in prescribing NSAID COX-2 inhibitors for patients with OA in the second half of the last decade. It also may reflect the fact that physicians underestimate the effect of pain on patients' overall quality of life.

The risks that physicians were willing to accept differed by the type of pain. They accepted a similar risk for a 25-mm reduction in ambulatory pain, irrespective of the baseline level of the pain. Results for resting pain, however, were very different, with higher risk being accepted for eliminating mild pain than for reducing pain from higher baseline levels. It is possible that physicians may have realized that an absolute reduction in pain of 25 mm results in a much greater relative reduction in pain when moving from 75 mm to 50 mm. However, the levels of a similar trend for ambulatory pain would argue against this. It is possible that physicians equated resting pain with night pain that affects

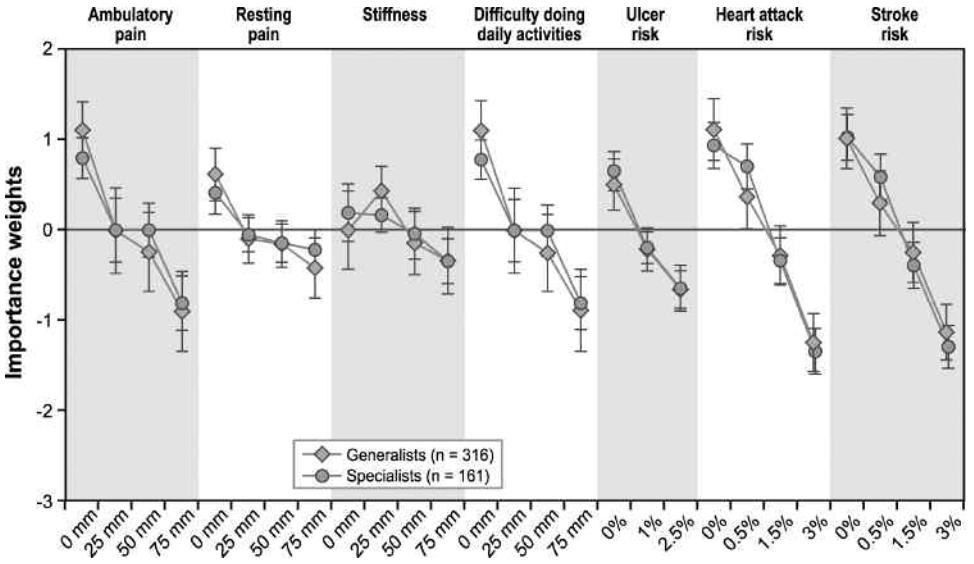

Figure 3. Importance weights for attribute levels by specialty. Only relative differences matter when interpreting importance weights. The differences between adjacent weights indicate the relative importance of moving from 1 level of an attribute to an adjacent level of that attribute. The vertical lines around each mean importance weight denote the 95% CI of the point estimate.

sleep disturbance and therefore elimination of resting pain would be the most important outcome. Physicians were willing to accept greater risks of side effects when moving a patient from mild resting pain to a pain-free state, compared with either moving from severe to moderate resting pain or from moderate to mild resting pain. Research has shown that healthcare providers consistently underestimate the severity of pain and its effect on patients. This lack of appreciation for the experience of pain may in part explain these results.

Physician importance weights were similar across a range of patient profiles, including patients with CV and GI risk factors. Although this finding may be due to limited statistical power to detect such differences in baseline CV and GI risk factors, we designed this large discrete-choice experiment study so that it could detect differences in importance weights at the 5% significance level between treatment-related outcomes. This does not mean that physicians do not include a patient's baseline level of risk in their decision-making, rather that they assessed the risks and benefits of a drug in a similar manner across a range of risk profiles and that there was no significant interaction between baseline CV and GI risk factors and the treatment outcomes of interest.

In spite of the increasing use of discrete-choice methods in health applications to elicit preferences and assess health-related quality of life, discrete choice has several potential limitations. One inherent limitation is that the physicians evaluate hypothetical treatment and patient profiles. These constructed choices are intended to simulate plausible clinical decisions, but they do not have the same clinical and potential legal consequences of actual choices. We have attempted to minimize such differences by offering alternatives that mimic real-world tradeoffs as closely as possible.

Further, it is not clear whether UK physicians' responses indicated their appraisal of their patients' risk tolerance, their personal risk tolerance, adherence to established treatment guidelines, or some combination of these. In addition, although the sample was large and the sampling procedure was not inherently biased, we cannot fully judge how representative our physician sample was of specialists and general practitioners in the UK, and we cannot be certain that our results are generalizable to all UK physicians involved in managing patients with OA. Physicians could not evaluate difficulty in doing daily activities and ambulatory pain independently, and thus it was not possible to estimate the relative importance of these outcomes separately. This is not surprising; as with the patient-completed WOMAC questionnaire, the questionnaire most commonly used as a validated outcome for knee and hip OA, there is a very strong correlation between the pain and function domain[29].

Our study provides evidence that UK physicians, regardless of specialty, place greater weight on potential side effects than benefits when considering treatment choices for patients with OA. The adverse effect of greatest concern to UK physicians in considering treatment for OA was that of MI or stroke. With respect to the benefits of OA treatment, UK physicians considered reduction of ambulatory pain to be the most important clinical outcome. Moreover, these findings apply consistently over the range of patient profiles included in our study. When clinical data are presented to physicians, it is important to present both efficacy and side effect data in a clear and comparable format.

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APPENDIX. Patient profiles.

1. A 55-year-old patient with severe osteoarthritis (OA; e.g., hip or knee). The patient's health is otherwise good (high performance status), with no history of kidney disease and no significant comorbidities.
2. A 70-year-old patient with severe OA (e.g., hip or knee). The patient's health is otherwise good (high performance status), with no history of kidney disease and no significant comorbidities.
3. A 55-year-old patient with severe OA (e.g., hip or knee) and a history of gastrointestinal bleeding. The patient's health is otherwise good (high performance status).
4. A 70-year-old patient with severe OA (e.g., hip or knee). The patient has had a myocardial infarction within the past 12 months. The patient's health is otherwise good (high performance status).
5. A 55-year-old patient with severe OA (e.g., hip or knee). The patient's blood pressure is persistently elevated above 140/90 mm Hg and has not been adequately controlled. The patient's health is otherwise good (high performance status).
6. A 55-year-old patient with severe OA (e.g., hip or knee). The patient has had a myocardial infarction within the past 12 months. The patient's blood pressure is persistently elevated above 140/90 mm Hg and has not been adequately controlled. The patient's health is otherwise good (high performance status).
7. A 55-year-old patient with severe OA (e.g., hip or knee) and a history of gastrointestinal bleeding. The patient has had a myocardial infarction within the past 12 months. The patient's health is otherwise good (high performance status).
8. A 70-year-old patient with severe OA (e.g., hip or knee) and a history of gastrointestinal bleeding. The patient's blood pressure is persistently elevated above 140/90 mm Hg and has not been adequately controlled. The patient's health is otherwise good (high performance status).
9. A 70-year-old patient with severe OA (e.g., hip or knee) and a history of gastrointestinal bleeding. The patient has had a myocardial infarction within the past 12 months. The patient's blood pressure is persistently elevated above 140/90 mm Hg and has not been adequately controlled. The patient's health is otherwise good (high performance status).

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