Efficacy of Rofecoxib, Celecoxib, and Acetaminophen in Patients with Osteoarthritis of the Knee. A Combined Analysis of the VACT Studies

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ABSTRACT. ***Objective.*** To compare efficacy among 1578 patients with osteoarthritis randomized to take acetaminophen 4000 mg (n = 269), celecoxib 200 mg (n = 523), rofecoxib 12.5 mg (n = 259), or rofecoxib 25 mg (n = 527) in a double blind trial [Vioxx, Acetaminophen, Celecoxib Trial (VACT2)]. Results were also pooled with the similarly designed VACT1 trial.

Methods. Patients evaluated over Days 1 to 6 and 6 weeks with Patient Global Assessment of Response to Therapy (PGART) and Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index.

Results. For VACT2, median time to good or excellent PGART response was 6, 5, 4, and 3 days for acetaminophen, celecoxib, rofecoxib 12.5 mg, and rofecoxib 25 mg (COX-2 inhibitors vs acetaminophen, $p \leq 0.035$; rofecoxib 25 mg vs celecoxib, $p = 0.01$). WOMAC response over the first 6 days was greater ($p < 0.05$) with both rofecoxib doses than acetaminophen and celecoxib. At Week 6, all COX-2 inhibitors provided significantly greater efficacy than acetaminophen. Good or excellent PGART was numerically, but not significantly, greater with rofecoxib 25 mg (55.4%) than celecoxib (50.6%) at Week 6; a significant difference was seen at Weeks 2 (6.9, $p = 0.022$) and 4 (6.7, $p = 0.027$) and over 6 weeks with analysis of all 5 PGART categories of response ($p = 0.035$). Rofecoxib 25 mg provided greater response ($p < 0.05$) than celecoxib on WOMAC subscales. Pooled analysis of VACT1/VACT2 demonstrated greater PGART ($p = 0.023$) with rofecoxib 25 mg (56.1%) than celecoxib (49.8%) at 6 weeks and greater response to all other PGART and WOMAC endpoints, and confirmed superiority of COX-2 inhibitors to acetaminophen. Overall, tolerability of the study medications was generally good and similar. There was no significant difference between treatment groups in the percentage of patients who experienced a clinical adverse experience (AE). The incidence of discontinuations due to an AE was significantly lower with celecoxib (2.5%) compared to rofecoxib 25 mg (6.3%, $p = 0.004$) or acetaminophen (7.8%, $p < 0.001$), and did not differ significantly from rofecoxib 12.5 mg (4.6%). Discontinuation rates due to edema and hypertension related AE were similar among all COX-2 inhibitors.

Conclusion. Rofecoxib and celecoxib provided superior efficacy to acetaminophen. There was a more rapid and greater response with rofecoxib 25 mg than celecoxib 200 mg. Rofecoxib 12.5 mg demonstrated greater efficacy than celecoxib 200 mg over the first 6 days, and was similar over 6 weeks. All study medications were generally well tolerated. (J Rheumatol 2005;32:1093–105)

Key Indexing Terms:

ROFECOXIB	CELECOXIB	ACETAMINOPHEN
EFFICACY	SAFETY	OSTEOARTHRITIS

Osteoarthritis (OA) affects roughly 43 million Americans, with associated costs of roughly $95 billion[1]. The cost of treatment alone in Western countries is 1%–2.5% of gross national product[2]. Symptomatic knee OA occurs in about 6% of adults over age 30 and 9.5% of adults ages 63–94 years (women 11.4% and men 6.8%)[3,4]. It is characterized by pain and inflammation that worsen with weight-bearing and activity and may improve with rest[5]. The American College of Rheumatology (ACR) guidelines recommend acetaminophen as first-line therapy for OA with nonselective cyclooxygenase (COX)-1 and COX-2-inhibiting nonsteroidal antiinflammatory drugs (NSAID) and COX-2 selective inhibitors available for patients who have not achieved a satisfactory response[5-7].

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Acetaminophen is categorized as a pure analgesic, while nonselective NSAID and COX-2 selective inhibitors provide both analgesic and antiinflammatory activity. Acetaminophen is considered a safer treatment option than nonselective NSAID, although not without risk[7-12]. Nonselective NSAID use in the chronic setting is limited by the potential of the class to cause gastrointestinal (GI) and renal side effects[13-16]. The former, in large part, can be circumvented by sparing inhibition of COX-1. COX-1 is responsible for the production of prostaglandins that regulate gastric mucosal protection and platelet aggregation[17-20]. Its inhibition increases the risk for GI erosion, perforation, ulceration, and bleeding that can increase morbidity and mortality and add to the cost of treating OA. COX-2 is responsible for the production of prostaglandins that regulate pain and inflammation[17-20]. Thus, COX-2 selective inhibition spares COX-1 related GI side effects, while providing similar relief of pain and inflammation as seen with nonselective NSAID.

The COX-2 selective inhibitors do not inhibit COX-1 when administered at therapeutic doses[21-23]. In clinical trials of patients with OA and with rheumatoid arthritis, COX-2 selective inhibitors demonstrated improved GI tolerability and comparable efficacy to NSAID, including ibuprofen, naproxen, and diclofenac[24-30]. Recommendations in current arthritis guidelines suggest that COX-2 selective inhibitors, like acetaminophen, be considered as a better tolerated treatment alternative to nonselective NSAID in patients at risk for GI side effects[31]. Although contrasting findings appear in the literature, recent studies suggest that nonselective NSAID and COX-2 selective inhibitors both provide greater efficacy than acetaminophen[5,31-33]. The Vioxx, Acetaminophen, Celecoxib Trial (VACT1) directly compared rofecoxib, celecoxib, and acetaminophen in patients with OA, and demonstrated efficacy advantages with both COX-2 selective inhibitors compared to acetaminophen[32].

The present VACT2 study was conducted to confirm the results of VACT1 in a larger patient population using the same clinical endpoints. Like the VACT1 study, efficacy endpoints included Patient Global Assessment of Response to Therapy (PGART) and functional improvement measured with the Western Ontario and McMaster Universities (WOMAC) OA Index evaluated over the first 6 days for onset of efficacy following an induced flare of symptoms and over 6 weeks for durability of response. Because the design of the 2 clinical trials was similar, including common efficacy endpoints, the data from both trials were pooled to document the total experience and increase precision of analysis. Data were also pooled for the analysis of safety endpoints.

MATERIALS AND METHODS

Patients. The VACT2 enrolled patients at 97 study sites in the United States. Patients were men and nonpregnant women with symptomatic OA of the knee as defined by investigator clinical diagnosis using American Rheumatology Association (ARA) clinical criteria, which were designated as the primary source of pain or disability in the lower extremity, for at least 6 months. Patients were at least 40 years of age, with a functional class rating of I, II, or III[34]. Patients eligible for inclusion were previous users of either a single prescription-strength nonselective NSAID or COX-2 selective inhibitor, or acetaminophen for control of OA symptoms for at least 30 days prior to study entry, who met baseline pain criteria.

Exclusion criteria included a concurrent medical or arthritic disease or abnormal laboratory results (values outside the normal reference range or determined by the investigator to be of clinical significance) that had the potential to confound or interfere with the efficacy evaluation or would contraindicate participation in the trial. Additionally, patients with a history of allergy to the study drugs, hypersensitivity to aspirin, any nonselective NSAID or sulfonamide-containing compounds, or who received an investigational drug within 30 days of screening, were excluded.

Study design. For both trials, at Visit 1 (screening), patients reviewed entry criteria; signed a written informed consent; provided a medical history and laboratory samples for complete blood count, serum chemistry, and urinalysis; underwent a physical examination; and completed a baseline WOMAC and Investigator Global Assessment of Disease Status (IGADS). To qualify to return for Visit 2, users of nonselective NSAID, COX-2 selective inhibitors, or acetaminophen were required to have at Visit 1 a WOMAC visual analog scale (VAS) score < 80 mm on a 100 mm scale for assessment of pain walking on a flat surface. Patients who satisfied these entry screening criteria were required to discontinue their prior nonselective NSAID or COX-2 selective inhibitor therapy according to a prespecified schedule (> 5 plasma half-lives of prior medication, from 4 to 15 days). Nonselective NSAID and COX-2 selective inhibitor patients returned to the study site for Visit 2 upon significant worsening of knee pain or related symptoms or at the end of their allowed washout period, whichever came first. Prior acetaminophen users were scheduled for Visit 2 within 3 to 7 days of screening. Prior acetaminophen, nonselective NSAID, or COX-2 selective inhibitor users were allowed to take up to 2600 mg daily of rescue acetaminophen (8 of the 325 mg tablets) during the washout phase. At Visit 2 (flare/randomization), all patients had to have a minimum WOMAC VAS score of 40 mm for the assessment of pain walking on a flat surface after discontinuing treatment. In addition, nonselective NSAID and COX-2 selective inhibitor users had to demonstrate a flare from screening in pain walking on a flat surface on WOMAC VAS score of at least 15 mm, and a worsening from screening in the IGADS (performed by the physician investigator) of at least 1 point on a 5-point Likert scale [range 0 (very well) to 4 (very poor)] at Visit 2. Because patients taking acetaminophen for OA potentially had milder disease consistent with previous clinical trials[5,31,32,35] and all patients had acetaminophen available as rescue between Visits 1 and 2, prior acetaminophen users were not required to meet a predefined WOMAC flare, but were required to exhibit an IGADS of not better than fair on 2 occasions while off therapy at least 24 hours. Rescue acetaminophen use was discontinued by all patients at least 12 hours before screening assessments to establish baseline values. Because all patients had symptomatic OA and all were assigned therapy previously shown to be effective, no other rescue medication was allowed during the study, to enhance the study's ability to detect differences between treatment groups.

At Visit 2, patients were randomly assigned (computer generated assignment) to the recommended once-daily doses for OA of rofecoxib (12.5 or 25 mg/day) and celecoxib (200 mg/day), or the highest recommended daily dose of acetaminophen (4000 mg, 1000 mg qid) in a 1:2:2:1 allocation. This distribution was chosen to ensure enrollment of an adequate number of patients for the primary comparison of rofecoxib 25 mg and celecoxib 200 mg. Patients and investigators were blinded to treatment using exact matching placebo tablets. Rofecoxib, celecoxib, or acetaminophen was taken each morning between 7 and 10 A.M., and matching placebo or the remaining acetaminophen doses were administered 3 more times daily to complete qid dosing. Clinical safety and efficacy data were collected and vital signs were recorded at 2, 4, and 6 week site visits. Blood pressure was measured at Weeks 2, 4, and 6 visits after patients had been in

a sitting position for 10 minutes. Early efficacy data were also collected by patient diary on Days 1 to 6. Compliance with study medication was assessed at visits at Weeks 2, 4, and 6, with acceptable compliance with study medication considered ≥ 80% (doses used divided by total possible study doses). Dosing was evaluated using patient diaries and counts of pills dispensed and returned.

Efficacy and safety. Efficacy was assessed over the first 6 days and over the entire 6 weeks of treatment. On Days 1 to 6, patients completed take-home forms with questions addressing the PGART, a 5-point categorical scale (range 0, "no response," to 4, "excellent response") and WOMAC OA Index Version VA 3.0 VAS (range 0, "best," to 100 mm, "worst"). Four individual WOMAC questions and the 3 predefined WOMAC subscales were included as study endpoints to assess specific components of response to treatment (pain and stiffness) and improvement in function[36], as a contrast to the global assessment provided by PGART. WOMAC endpoints through Day 6 included questions regarding pain walking on a flat surface (WOMAC Q1) and rest pain (Q4), completed at bedtime on Days 1 to 6, and night pain (Q3) and morning stiffness (Q6), completed prior to first dose of medication on Days 2 to 6. Patients completed the PGART and entire 24-question WOMAC during scheduled office visits at Weeks 2, 4, and 6. Specific WOMAC endpoints analyzed over 6 weeks included the pain subscale (WOMAC Q1–Q5), stiffness subscale (Q6 and Q7), and physical function subscale (remaining Q8–Q24). PGART assessed for Week 6 was the primary endpoint of the study. All these endpoints were utilized for analysis of the individual VACT2 results, as well as analysis of the pooled VACT1/VACT2 results.

Safety was assessed during physical examinations, and patient interviews were conducted as part of the Weeks 2, 4, and 6 office visits. Adverse experiences (AE) were recorded at these times and could be reported by patients at any time during the study. Cardiovascular and GI AE were adjudicated by an external committee that was blinded to treatment, as described[18].

Statistical analysis. An all-patients-treated approach, which included all patients randomized who took at least one dose of study medication, was used for all analyses performed in this trial. The analysis of efficacy variables was performed on changes from baseline, defined as the assessment obtained after discontinuation of prior NSAID or acetaminophen therapy. For the efficacy analyses, p values ≤ 0.05 were considered statistically significant. Because there was one primary endpoint and a hierarchy of additional endpoints, no adjustments for multiplicity were made for the analyses.

The primary hypothesis was that rofecoxib 25 mg would be superior to celecoxib 200 mg in terms of patients with a good or excellent PGART after 6 weeks of treatment. With 520 patients in the 2 treatment arms, there was 90% power to detect a difference in PGART between rofecoxib 25 mg and celecoxib 200 mg, assuming a true difference of at least 10 percentage points (50% vs 60%). The calculation was based upon a 2-sided test with an α level of 0.05. The analysis for data at a specific timepoint utilized a last observation carried forward (LOCF) approach for missing PGART and WOMAC data. Thus, if a patient provided a response at Week 2, but not at Week 4 or Week 6, the Week 2 value was used for Week 2 and also served as an imputed value for the missing values at Weeks 4 and 6. Baseline values were neither imputed, if missing, nor carried forward. Logistic regression with factors for baseline IGADS, previous OA medication strata, and treatment group was used to compare good or excellent responders by treatment group at Week 6, as well as at Weeks 2 and 4, and provide estimates of odds ratios, corresponding p values, and 95% confidence intervals. Pairwise comparisons of all remaining treatments were performed in a similar fashion. In addition, as a prespecified supportive analytical approach for the primary endpoint, a cumulative logistic regression model with factors for baseline IGADS, previous OA medication strata, and treatment group was performed to compare rofecoxib 25 mg and celecoxib 200 mg at Weeks 2, 4, and 6 to account for the ordered categorical responses of PGART (None, Poor, Fair, Good, or Excellent).

A time-to-event analysis was conducted for the PGART data over Days 1 through 6. The cumulative incidence of first report of a good or excellent PGART response was calculated using the Kaplan-Meier estimate. The Wilcoxon test for ranked survival data was used to make pairwise treatment comparisons in terms of the first report of a good or excellent response over Days 1 through 6.

For the 3 WOMAC composite subscales (i.e., pain, stiffness, and functional disability), analysis of variance (ANOVA) was used to assess statistical significance of treatment differences in mean changes from baseline to determine corresponding p values and 95% confidence intervals. The model included terms for baseline WOMAC scores, OA medication strata, and treatment group. An ANOVA including terms for baseline WOMAC scores, OA medication strata, and treatment group was also used to analyze the average change over Days 1 through 6 and the change from baseline to each timepoint for the 4 individual WOMAC question scores.

The analyses were performed as prespecified for the VACT2 study and were similarly applied in a post hoc analysis of the pooled VACT1/VACT2 combined results. Criteria for significance with between-treatment comparisons were consistent in both analyses. The analytical model for the VACT1/VACT2 analysis also included a term for trial.

Tabulations of the overall incidence of AE, serious AE, drug related AE, AE that caused discontinuation, edema and hypertension related AE causing discontinuation, congestive heart failure, and GI AE were performed in VACT-2 for all patients treated. Edema related AE were predefined to include the following collection of terms related to edema or fluid retention in any region of the body: edema, fluid retention, fluid overload, hand swelling, lower extremity edema, peripheral edema, and upper extremity edema. Hypertension related AE were also predefined to include the following terms related to hypertension or blood pressure increase: hypertension, borderline hypertension, diastolic hypertension, essential hypertension, hypertension uncontrolled with medication, hypertensive crisis, labile hypertension, malignant hypertension, secondary hypertension, systolic hypertension, uncontrolled hypertension, and increased blood pressure. Fisher's exact test was used to compare the incidence of prespecified AE between treatment groups. Pooled safety data were presented for all patients in the combined VACT1/VACT2 analysis, including evaluation of the same AE with statistical analysis by Fisher's exact test.

RESULTS

Patient characteristics and disposition. For VACT2, a total of 2146 patients were screened, 568 patients did not meet inclusion criteria, and 1578 patients were enrolled in the study (Figure 1). The treatment groups were similar with regard to demographic and baseline characteristics (Table 1). The patients were predominantly female (67%) and white (88%), with a mean age of 62 years. Most patients were prior NSAID or COX-2 inhibitor users (85%). In addition, 13% of the patients had a history of NSAID related GI AE; 10% had stopped arthritis medication due to stomach or abdominal problems; and 43% had a secondary diagnosis of hypertension. The investigators assessed 72% of the patients' disease status to be poor or very poor (baseline IGADS), with over 90% having OA in at least one additional joint besides the knee.

A total of 82% of the patients completed the study, with a higher percentage of completers among patients treated with a COX-2 inhibitor (82% to 84%) than acetaminophen (76%). Discontinuation rates were significantly greater ($p < 0.05$) with acetaminophen than rofecoxib 25 mg or celecoxib, and numerically greater with acetaminophen compared to rofecoxib 12.5 mg. Significantly ($p < 0.05$) more patients

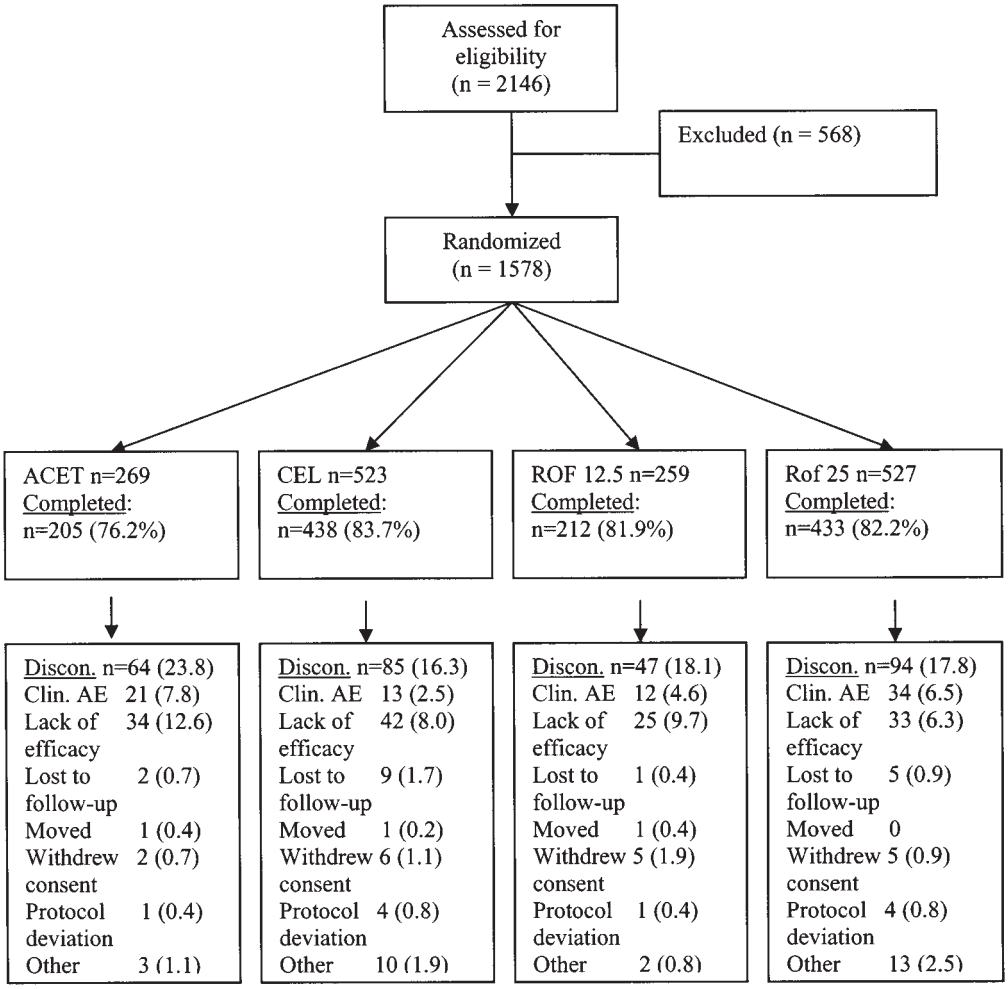

Figure 1. VACT2: patient disposition.

Table 1. Patient demographics and baseline characteristics (VACT2).

	Acetaminophen 4000 mg, (N = 269) n (%)	Celecoxib 200 mg, (N = 523) n (%)	Rofecoxib 12.5 mg, (N = 259) n (%)	Rofecoxib 25 mg, (N = 527) n (%)	Total, (N = 1578) n (%)
Sex					
Female	178 (66.2)	356 (68.1)	169 (65.3)	360 (68.3)	1063 (67.4)
Male	91 (33.8)	167 (31.9)	90 (34.7)	167 (31.7)	515 (32.6)
Age, yrs					
Mean (SD)	61.9 (10.70)	61.4 (9.89)	62.8 (10.80)	62.7 (10.34)	62.1 (10.34)
Median	62.0	61.0	64.0	63.0	62.0
Range	40–88	40–90	40–86	40–93	40–93
Race, n (%)					
White	240 (89.2)	460 (88.0)	229 (88.4)	455 (86.3)	1384 (87.7)
Hispanic American	6 (2.2)	23 (4.4)	13 (5.0)	21 (4.0)	63 (4.0)
Black	20 (7.4)	31 (5.9)	15 (5.8)	41 (7.8)	107 (6.8)
Other	3 (1.2)	9 (1.7)	2 (0.8)	10 (1.9)	24 (1.5)
Prior drug type, n (%)					
NSAID	225 (83.6)	450 (86.0)	218 (84.2)	450 (85.4)	1343 (85.1)
Acetaminophen	44 (16.4)	73 (14.0)	41 (15.8)	77 (14.6)	235 (14.9)

experienced a lack of efficacy with acetaminophen than rofecoxib 25 mg or celecoxib. Discontinuation was most commonly due to lack of efficacy (8.5% overall: acetaminophen 4000 mg, 12.6%; celecoxib 200 mg, 8.0%; rofecoxib 12.5 mg, 9.7%; and rofecoxib 25 mg, 6.3%) and clinical AE (5.1% overall: numbers by treatment provided in the Safety section). Mean compliance with treatment was 99% in all treatment groups, and over 97% of patients in each treatment group were at least 80% compliant with treatment.

The demographic and baseline characteristics of patients in this study were similar to patients in the VACT1 study and were combined for the pooled analyses. For the combined trial, a total of 2661 patients were screened, 1960 patients were randomized, and 81% completed the studies.

Onset of Efficacy

VACT2: PGART and WOMAC over first 6 days. In VACT2, the median times to first report of a good or excellent response were Days 6, 5, 4, and 3, respectively, for acetaminophen, celecoxib, rofecoxib 12.5 mg, and rofecoxib 25 mg. Each of the COX-2 inhibitors had a significantly quicker time to response than the acetaminophen group ($p \leq 0.035$). In addition, the difference between rofecoxib 25 mg and celecoxib was statistically significant ($p = 0.01$), whereas rofecoxib 12.5 mg was not significantly different from celecoxib or rofecoxib 25 mg. Separation between treatments was observed by the first time assessed on Day 1.

Over the first 6 days of treatment, rofecoxib 12.5 and 25 mg showed significant improvement on all WOMAC endpoints, pain walking on a flat surface, rest pain, night pain, and morning stiffness, compared to acetaminophen ($p \leq 0.01$) and celecoxib ($p \leq 0.05$; Table 2). Differences between treatment with celecoxib and acetaminophen were not significant for any of the WOMAC endpoints over the first 6 days of treatment with the exception of morning stiffness ($p = 0.046$). Numerically greater improvements with both rofecoxib doses compared to celecoxib and acetaminophen were seen as early as Day 1 and most were significant by Day 2. Improvements with rofecoxib 12.5 mg and 25 mg were generally similar for all WOMAC Days 1 to 6 endpoints.

Pooled VACT1/VACT2. PGART and WOMAC over first 6 days. For the pooled VACT1 and VACT2 study results, median time to a good or excellent PGART response was Day 6, 4, 4, and 3, respectively, for acetaminophen, celecoxib, rofecoxib 12.5 mg, and rofecoxib 25 mg. The COX-2 inhibitors had a significantly quicker time to response than the acetaminophen group ($p \leq 0.019$). Rofecoxib 25 mg was significantly quicker than celecoxib ($p = 0.008$). Rofecoxib 12.5 mg was not significantly different from celecoxib or rofecoxib 25 mg.

Pooled data revealed that both rofecoxib 12.5 mg and 25 mg provided significant improvement on all WOMAC endpoints over the first 6 days compared to acetaminophen ($p \leq 0.01$) and celecoxib ($p \leq 0.05$; Table 2). Celecoxib achieved significance ($p \leq 0.05$) compared to acetaminophen only for pain walking on a flat surface and morning stiffness. Similar response on WOMAC Days 1 to 6 endpoints was seen with rofecoxib 12.5 mg and 25 mg.

Overall Efficacy

VACT2. PGART over 6 weeks. For VACT2, the percentages of PGART responders (those with good or excellent response) at 6 weeks were 40.5%, 50.6%, 49.6%, and 55.4% for acetaminophen, celecoxib, rofecoxib 12.5 mg, and rofecoxib 25 mg, respectively (Figure 2). Differences between each COX-2 inhibitor and acetaminophen were significant (p values ≤ 0.038). The difference in the primary endpoint, the PGART, between rofecoxib 25 mg and celecoxib as assessed by logistical regression, was not significant (OR 1.22, 95% CI 0.96, 1.57, $p = 0.106$). Significantly greater PGART scores were reported with rofecoxib 25 mg compared to celecoxib at Week 2 (OR 1.33, 95% CI 1.04, 1.71, $p = 0.022$) and Week 4 (OR 1.32, 95% CI 1.03, 1.69, $p = 0.027$). In addition, the prespecified analysis based on cumulative logistical regression revealed a significant difference over 6 weeks when all 5 categories of PGART were analyzed ($p = 0.035$). Rofecoxib 12.5 mg and celecoxib did

Table 2. Change from baseline to Day 6 and over 6 weeks in individual WOMAC VAS scale scores: VACT2 and pooled VACT1/VACT2.

	Mean Change, mm							
	Acetaminophen, 4000 mg		Celecoxib 200 mg		Rofecoxib 12.5 mg		Rofecoxib 25 mg	
	VACT2	Pooled	VACT2	Pooled	VACT2	Pooled	VACT2	Pooled
First 6 days								
Night pain	–19.9	–19.4	–21.3	–20.5	–24.8**,†	–23.8**,†	–23.9**,†	–23.7**,††
Pain walking	–21.0	–20.9	–23.5	–24.3**	–26.5***,†	–27.2***,†	–27.0***,††	–28.1***,†††
Rest pain	–14.3	–13.7	–16.0	–15.7	–20.1***,††	–19.5***,††	–19.3***,††	–19.5***,†††
Morning stiffness	–23.3	–22.5	–26.5*	–26.0*	–30.6***,††	–29.8***,††	–30.2***,††	–29.9***,†††
6 weeks								
Pain subscale	–24.6	–24.7	–29.6**	–29.4***	–31.6***	–30.8***	–32.5***,†	–33.0***,††
Stiffness subscale	–25.3	–24.4	–30.6**	–30.0***	–32.6***	–31.5***	–34.0***,†	–34.0***,††
Function subscale	–20.0	–19.9	–25.7***	–25.6***	–27.5***	–26.7***	–28.7***,†	–28.8***,††

Compared to acetaminophen * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$. Compared to celecoxib † $p \leq 0.05$, †† $p \leq 0.01$, ††† $p \leq 0.001$.

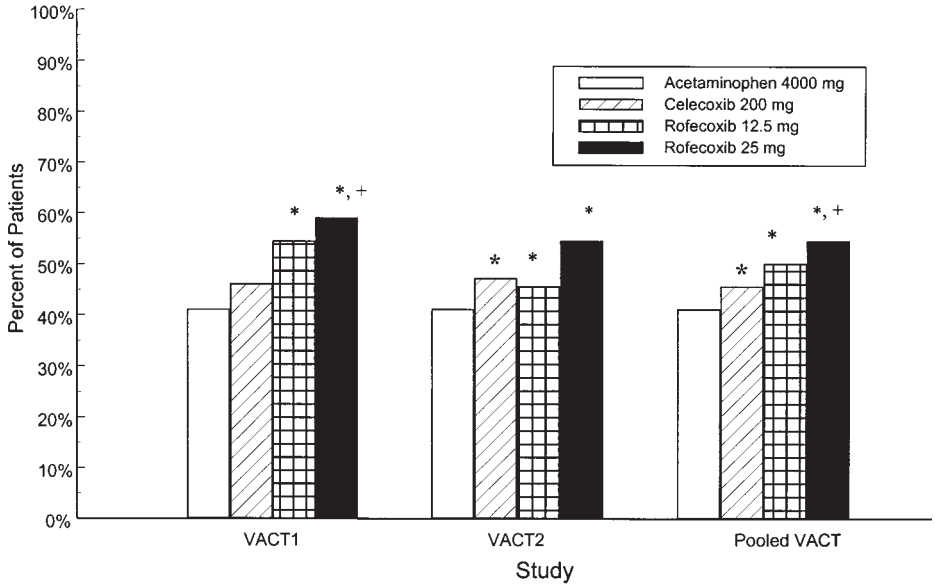

Figure 2. Percentage of patients with a good or excellent PGART: VACT1, VACT2, and pooled VACT1/VACT2. *p < 0.05 compared to acetaminophen; †p < 0.05 compared to celecoxib.

not differ significantly. PGART scores at 6 weeks were numerically but not significantly greater with rofecoxib 25 mg compared to rofecoxib 12.5 mg. Analyses of PGART for treatment interaction by previous OA medication (acetaminophen/COX-2 inhibitor or acetaminophen) or baseline IGADS were not significant, suggesting consistency of the results irrespective of prior OA therapy or disease severity.

WOMAC composite subscales over 6 weeks. In VACT2, the WOMAC pain, stiffness, and physical function subscales all showed significant ($p \leq 0.003$) improvement over 6 weeks with the COX-2 inhibitors compared to acetaminophen (Table 2, Figures 3A, 3B, 3C). Rofecoxib 25 mg provided significantly better improvements over 6 weeks than celecoxib on all measures of the WOMAC ($p \leq 0.030$). Differences in WOMAC subscales between rofecoxib 12.5 mg and celecoxib were not statistically significant. Rofecoxib 25 mg provided numerically greater response on the WOMAC subscales than rofecoxib 12.5 mg.

Pooled VACT1/VACT2. PGART over 6 weeks. Pooled VACT1 and VACT2 analysis showed that 40.2%, 49.8%, 51.4%, and 56.1% of patients in the acetaminophen, celecoxib, rofecoxib 12.5 mg, and rofecoxib 25 mg groups, respectively, reported a good or excellent PGART response at Week 6 (Figure 2). Each of the COX-2 inhibitors was statistically superior to acetaminophen ($p \leq 0.003$). The primary comparison of rofecoxib 25 mg to celecoxib at Week 6 was statistically significant ($p = 0.023$), as were comparisons at Weeks 2 and 4 ($p = 0.005$). Rofecoxib 12.5 mg and celecoxib did not differ significantly. Rofecoxib 25 mg provided numerical but not statistically significant advantages compared to rofecoxib 12.5 mg. Cumulative regression analysis was consistent with the primary analytical approach, and at all timepoints all COX-2 inhibitors provided significant improvement compared to acetaminophen (p values ≤ 0.001). In addition, rofecoxib 25 mg was superior to celecoxib at all timepoints ($p \leq 0.006$).

WOMAC composite subscales over 6 weeks. In the pooled VACT1 and VACT2 analysis of WOMAC subscales, findings were consistent with the results observed in VACT2, with significantly greater response ($p \leq 0.001$) on WOMAC endpoints over the 6-week treatment period with the COX-2 inhibitors compared to acetaminophen (Table 2, Figures 3A, 3B, 3C). Rofecoxib 25 mg provided significant improvements ($p \leq 0.01$) over 6 weeks on all WOMAC subscales compared to celecoxib. Differences between rofecoxib 12.5 mg and celecoxib were not statistically significant. Numerically better improvement in WOMAC subscales was seen with rofecoxib 25 mg compared to rofecoxib 12.5 mg.

Safety

VACT2. In VACT2, all 1578 patients who were randomized and took at least one dose of study medication were included in the safety analysis whether data for efficacy were available or not. There was no significant difference between treatment groups in the percentage of patients who experienced "any" clinical AE (acetaminophen 42%, celecoxib 37%, rofecoxib 12.5 mg 40%, and rofecoxib 25 mg 41%; Table 3). The most common AE included abdominal pain, diarrhea, headache, lower extremity edema, nausea, and upper respiratory infection, although none were reported in more than 5% of the overall population. The incidence of these events was similar between treatment groups (Table 3). Among the acetaminophen, celecoxib, rofecoxib 12.5

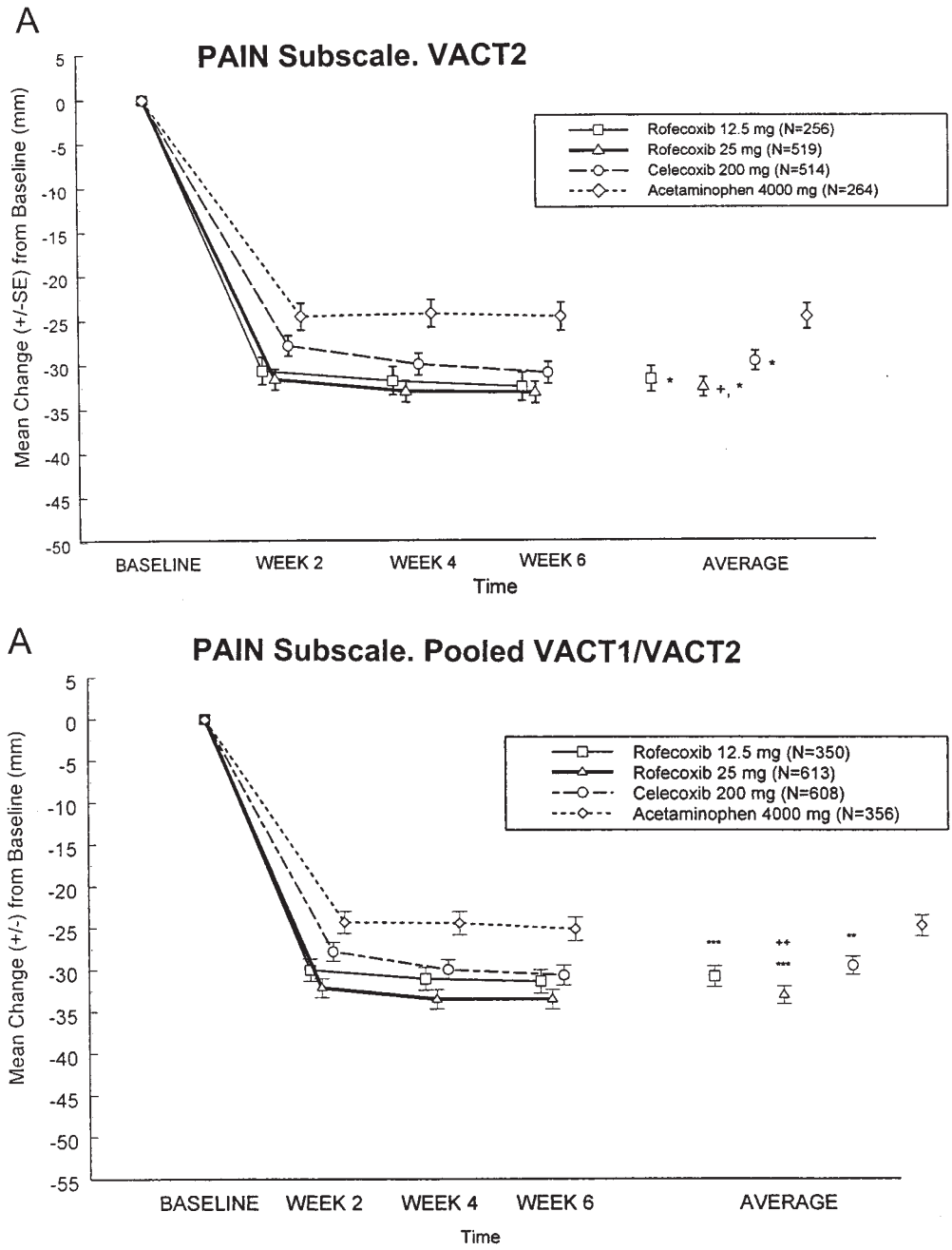

Figure 3A. Change from baseline at 2, 4, and 6 weeks and average change over 6 weeks in composite WOMAC VAS pain subscale scores: VACT2 (top) and pooled VACT1/VACT2 (bottom). Compared to acetaminophen * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$. Compared to celecoxib + $p \leq 0.05$, ++ $p \leq 0.01$, +++ $p \leq 0.001$.

mg, and rofecoxib 25 mg patients, the incidence of drug related AE (16.7%, 13.2%, 16.6%, and 16.7%, respectively) and serious AE (0, 0.4%, 1.2%, and 1.3%, respectively) did not differ significantly. The incidence of discontinuations due to an AE was significantly lower with celecoxib (2.5%) compared to rofecoxib 25 mg (6.3%; $p = 0.004$) or acetaminophen (7.8%; $p < 0.001$), and did not differ significantly from rofecoxib 12.5 mg (4.6%). Differences in GI AE incidence between acetaminophen (16.4%), celecoxib (12.0%), rofecoxib 12.5 mg (13.9%), and rofecoxib 25 mg (15.2%) were not significant.

The incidence of prespecified renal and vascular events, including discontinuations due to edema or hypertension related AE, and congestive heart failure was generally low. There were no significant differences between acetaminophen (0.4%), celecoxib (0%), rofecoxib 12.5 mg (0%), and rofecoxib 25 mg (0.6%) in discontinuations due to edema related AE. There was a significant difference between cele-

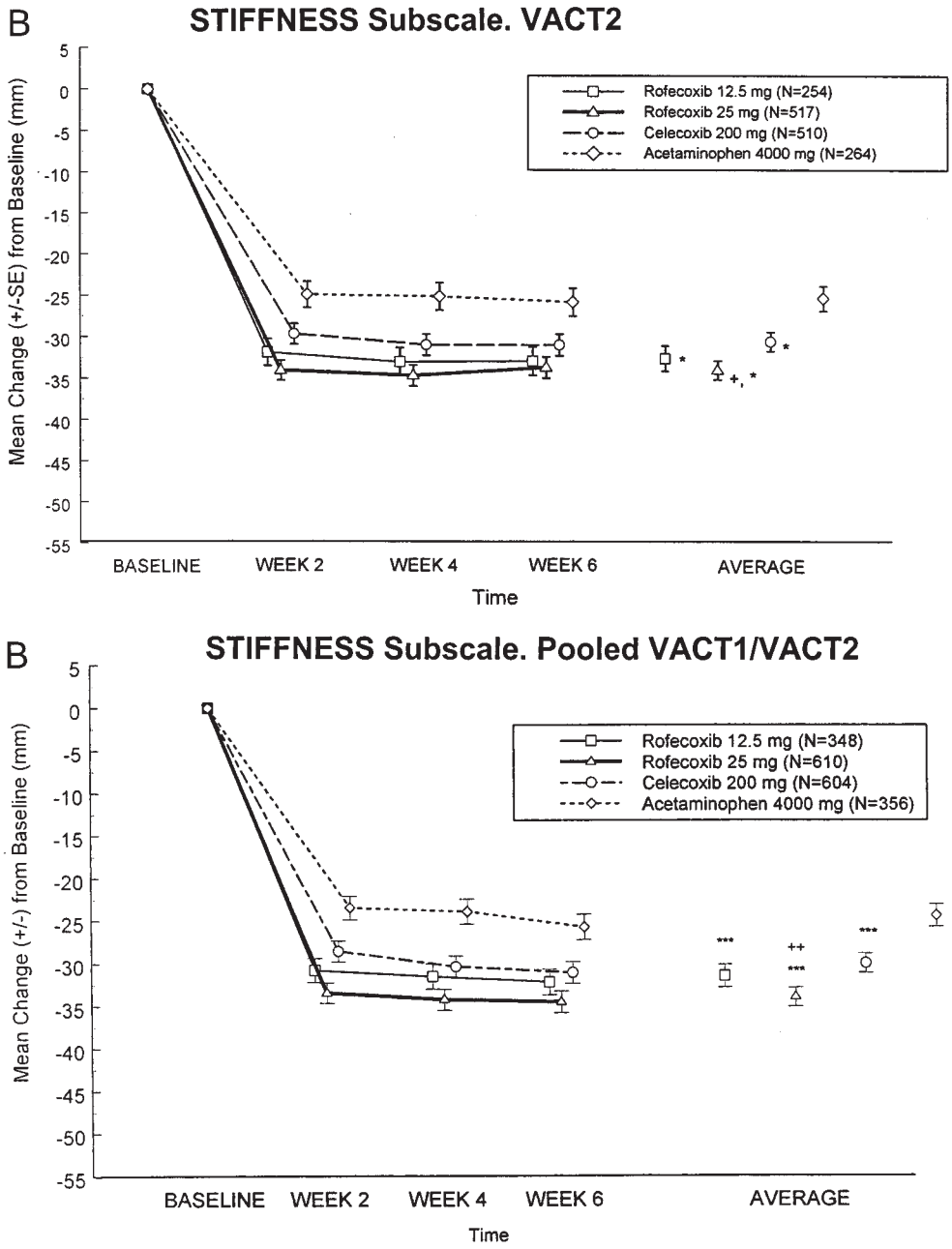

Figure 3B. Change from baseline at 2, 4, and 6 weeks and average change over 6 weeks in composite WOMAC VAS stiffness subscale scores: VACT2 (top) and pooled VACT1/VACT2 (bottom). Compared to acetaminophen * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$. Compared to celecoxib + $p \leq 0.05$, ++ $p \leq 0.01$, +++ $p \leq 0.001$.

coxib (0%) and acetaminophen (1.1%, $p = 0.039$), but not between celecoxib and rofecoxib 12.5 mg (0.8%) or rofecoxib 25 mg (0.2%) in discontinuations due to hypertension related AE. One patient, in the rofecoxib 12.5 mg treatment group, had congestive heart failure during the study that was considered not related to treatment by the investigator. The acetaminophen, celecoxib, rofecoxib 12.5 mg, and rofecoxib 25 mg treatment groups experienced a similar incidence of cardiovascular system AE (4.8%, 3.8%, 3.9%, and 2.7%, respectively), including events classified by the investigator specifically as hypertension (0.7%, 1.0%, 0.4%, and 0.8%, respectively).

Pooled VACT1/VACT2. The pooled VACT1/VACT2 safety population included all 1960 patients who were randomized and took at least one dose of study medication. There was no significant difference between treatment groups in the percentage of patients who experienced "any" clinical AE (acetaminophen 46%, celecoxib 39%, rofecoxib 12.5 mg 46%, and rofecoxib 25 mg 43%; Table 3). The most common AE in the pooled study population were also abdomi-

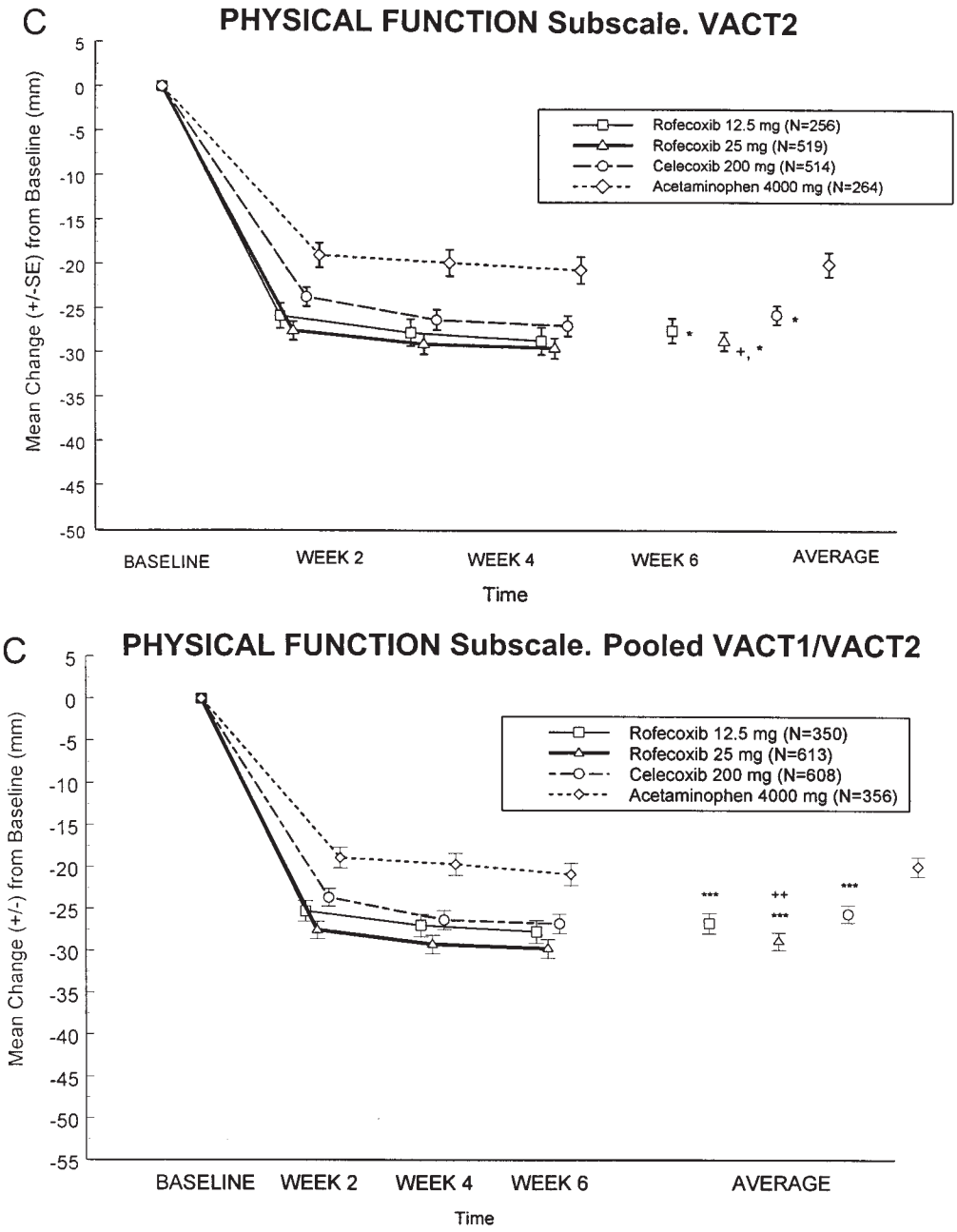

Figure 3C. Change from baseline at 2, 4, and 6 weeks and average change over 6 weeks in composite WOMAC VAS physical function subscale scores: VACT2 (top) and pooled VACT1/VACT2 (bottom). Compared to acetaminophen * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$. Compared to celecoxib + $p \leq 0.05$, ++ $p \leq 0.01$, +++ $p \leq 0.001$.

nal pain, diarrhea, headache, lower extremity edema, nausea, and upper respiratory infection. Incidence of drug related AE was also not significantly different between acetaminophen, celecoxib, rofecoxib 12.5 mg, and rofecoxib 25 mg (17.9%, 15.0%, 18.6%, and 16.7%, respectively). For serious AE, significantly more rofecoxib 12.5 mg (1.4%) and rofecoxib 25 mg (1.4%) patients than acetaminophen patients (0.0%; $p < 0.05$) experienced an event, while celecoxib (0.3%) was not significantly different from any of the other treatments. Serious AE were spread across a number of body systems, with no trends observed and no specific event or body system having the majority. Significantly more rofecoxib 25 mg (6.3%) and acetaminophen (7.4%) patients than celecoxib patients (2.7%; $p < 0.05$) discontinued due to an AE, while rofecoxib 12.5 mg (5.4%) was not significantly different from celecoxib. These events were also spread across body systems with no trends observed. There were no significant differences between treatments in incidence of GI AE (acetaminophen 18.2%, celecoxib 13.7%, rofecoxib 12.5 mg 16.6%, and rofecoxib 25 mg 15.4%).

Table 3. Most common clinical adverse events* (VACT2 and Pooled VACT1/VACT2).

	Acetaminophen 4000 mg n (%)	Celecoxib 200 mg n (%)	Rofecoxib 12.5 mg n (%)	Rofecoxib 25 mg n (%)
VACT2	N = 269	N = 523	N = 259	N = 527
Any clinical AE	114 (42.4)	194 (37.1)	104 (40.2)	218 (41.4)
Abdominal pain	9 (3.3)	8 (1.5)	4 (1.5)	10 (1.9)
Diarrhea	12 (4.5)	27 (5.2)	9 (3.5)	16 (3.0)
Headache	12 (4.5)	22 (4.2)	6 (2.3)	14 (2.7)
Lower extremity edema	3 (1.1)	9 (1.7)	9 (3.5)	16 (3.0)
Nausea	6 (2.2)	11 (2.1)	5 (1.9)	19 (3.6)
Upper respiratory infection	9 (3.3)	15 (2.9)	7 (2.7)	11 (2.1)
Pooled VACT1/VACT2	N = 363	N = 620	N = 355	N = 622
Any clinical AE	165 (45.5)	244 (39.4)	163 (45.9)	267 (42.9)
Abdominal pain	13 (3.6)	11 (1.8)	5 (1.4)	11 (1.8)
Diarrhea	20 (5.5)	35 (5.6)	19 (5.4)	21 (3.4)
Headache	20 (5.5)	33 (5.3)	10 (2.8)	21 (3.4)
Lower extremity edema	5 (1.4)	10 (1.6)	12 (3.4)	23 (3.7)
Nausea	11 (3.0)	14 (2.3)	12 (3.4)	23 (3.7)
Upper respiratory infection	14 (3.8)	21 (3.4)	8 (2.3)	14 (2.3)

* Defined as events that occurred in at least 3% of the patients in any treatment group.

Prespecified renal and vascular event rates in the pooled population were similar to those seen in VACT2. There were no significant differences between acetaminophen (0.6%), celecoxib (0%), rofecoxib 12.5 mg (0%), and rofecoxib 25 mg (0.6%) in discontinuations due to edema related AE. There were also no significant differences between acetaminophen (0.8%), celecoxib (0%), rofecoxib 12.5 mg (0.6%), and rofecoxib 25 mg (0.2%) in discontinuations due to hypertension related AE. There were no additional patients with congestive heart failure. The acetaminophen, celecoxib, rofecoxib 12.5 mg, and rofecoxib 25 mg treatment groups experienced a similar incidence of cardiovascular system AE (4.7%, 3.5%, 3.7%, and 3.2%, respectively) including events classified by the investigator specifically as hypertension (1.1%, 1.0%, 0.8%, and 0.8%, respectively).

DISCUSSION

The current recommendation for use of acetaminophen as first-line treatment for OA symptoms is largely in consideration of its generally good safety and, in particular, GI tolerability advantages compared to NSAID[5,6]. NSAID are useful in the segment of the OA population with symptoms unresponsive to even the highest recommended doses of acetaminophen. Our OA study demonstrates that the COX-2 selective inhibitors, rofecoxib and celecoxib, provide significant and sustained efficacy advantages compared to the maximum recommended daily dose of acetaminophen 4000 mg. Both rofecoxib 12.5 mg and 25 mg had a more rapid onset of action than acetaminophen or celecoxib 200 mg, with rofecoxib 25 mg showing the greatest overall efficacy across the combined study endpoints. Equally important is that the COX-2 selective inhibitors had safety profiles similar to acetaminophen. These results are consistent with the findings of the VACT1 study, and when combined provide efficacy and safety data that support the ACR recommendations for use of COX-2 inhibitors as an alternative to acetaminophen[31,32].

Acetaminophen and nonselective NSAID comparator trials have yielded conflicting results, possibly due to fundamental differences in study design[33,37-39]. Studies by Bradley, *et al* (n = 184) and Williams, *et al* (n = 178) comparing ibuprofen and naproxen, respectively, to acetaminophen suggested that a nonselective NSAID and acetaminophen provided similar efficacy in patients with OA[37,38]. Bradley, *et al* observed improvements in the Stanford Health Assessment Questionnaire pain scale (range 0 to 3) that were similar among treatment groups (0.30 and 0.35 with 1200 and 2400 mg of ibuprofen and 0.33 with acetaminophen) after 4 weeks[37]. Williams, *et al* described a significant difference favoring naproxen 750 mg compared to acetaminophen 2600 mg only in improvement in rest pain from among several 6 week endpoints[38].

Two recent studies that utilized the WOMAC OA Index, which was used in the VACT studies, demonstrated that NSAID provide efficacy benefits in OA patients compared to acetaminophen[33,39]. In Pincus, *et al* (n = 227), WOMAC target joint scores and Multidimensional Health Assessment Questionnaire (MDHAQ) pain scores significantly favored diclofenac/misoprostol 75/200 mg twice daily compared to acetaminophen 1000 mg four times daily [differences in improvement of -7.75 ± 1.81 ($p < 0.001$) and -14.6 ± 2.3 ($p < 0.001$), respectively] after 6 weeks[33]. Case, *et al* compared treatment with diclofenac sodium 150 mg (n = 25), acetaminophen 4000 mg (n = 29), and placebo daily[39]. At 2 and 12 week evaluations, significant improvement compared to baseline was achieved on WOMAC pain, stiffness, function, and summed scores with diclofenac ($p < 0.01$), but not acetaminophen ($p > 0.05$), which achieved changes similar to

placebo. The results of these more recent studies are supported by findings in a survey by Wolfe, *et al* of 1799 subjects with arthritis or fibromyalgia, in which 60% of patients preferred NSAID to 14% who preferred acetaminophen, with 26% having no preference[40]. Despite potentially better efficacy with nonselective NSAID compared to acetaminophen, acetaminophen has been the preferred first-line medication for OA due to the risk of GI side effects associated with nonselective NSAID.

To our knowledge, the VACT2 study is the largest study to directly compare COX-2 selective inhibitors and acetaminophen using recommended OA efficacy endpoints in an adequately powered clinical trial[41]. The demographic profile of patients in the VACT2 study is characteristic of the general OA population, increasing the external validity of the study and ability to extrapolate the results to the typical practice setting[1,5,42,43]. As recommended by prior consensus committees, both global assessment with PGART and WOMAC endpoints focusing on pain, stiffness, and physical function were evaluated over the recommended treatment period[32,33,37,38,41,44].

The VACT2 study demonstrated that over 6 weeks the COX-2 inhibitors provided greater efficacy in OA patients than acetaminophen consistently across study endpoints, as seen in VACT1. Further, rofecoxib 25 mg provided greater efficacy across the combined PGART and WOMAC endpoints than celecoxib 200 mg, despite a lack of significance in good or excellent PGART at 6 weeks. When the VACT1 and VACT2 results were pooled, significant advantages with rofecoxib 25 mg compared to celecoxib were observed on all efficacy measures. Efficacy differences between rofecoxib 25 mg and celecoxib 200 mg may be attributable to the longer half-life of rofecoxib or the need for a dose of celecoxib higher than 200 mg to achieve similar efficacy to rofecoxib 25 mg. In both VACT studies, rofecoxib 12.5 mg and celecoxib 200 mg were not significantly different over 6 weeks and should be considered equipotent.

An additional clinically important finding was the significant reduction in time to onset of efficacy over Days 1 to 6, observed on PGART and WOMAC, with both rofecoxib doses compared to acetaminophen. Following the prestudy flare period, patients' symptoms were required to be more severe for inclusion in the study, making it an appropriate time to measure the efficacy of a newly initiated treatment. Celecoxib showed significant improvement on PGART compared to acetaminophen, but on only a limited number of WOMAC endpoints. Both rofecoxib doses demonstrated significant advantages in onset compared to celecoxib.

Two additional 6 week, placebo controlled studies compared rofecoxib 25 mg to celecoxib 200 mg. In a study by McKenna, *et al*, 182 patients were assigned to treatment with rofecoxib 25 mg (n = 59), celecoxib 200 mg (n = 63), or placebo (n = 60)[45]. The study was powered to and did demonstrate the superiority of the 2 active drugs compared to placebo. Rofecoxib 25 mg and celecoxib 200 mg were determined to have similar efficacy based on mean OA pain improvement on VAS, improvement in total WOMAC score, and patient global assessment, all measured at 6 weeks. A study by Gibofsky, *et al*[46], powered to evaluate comparability between rofecoxib 25 mg (n = 190) and celecoxib 200 mg (n = 189), demonstrated comparable efficacy between the active treatments, as well as superior efficacy compared to placebo (n = 96) based on OA pain improvement on a VAS and the total WOMAC score, again measured at 6 weeks. Unlike these studies, the VACT studies evaluated efficacy over the entire 6 week period (assessments at 2, 4, and 6 weeks) and over Days 1 to 6 to measure efficacy when treating the potentially severe pain that follows a flare period. In addition, the VACT studies[32] utilized the generally accepted approach of evaluating the 3 WOMAC subscales and administering study medication in the morning, while McKenna[45] and Gibofsky[46] utilized total WOMAC scores and evening dosing.

The safety profiles of the COX-2 selective inhibitors in the VACT2 study were similar to acetaminophen, which is largely recommended as the first-line medication for OA because it is well tolerated. In the VACT2 study there were no significant differences between treatments in predefined AE categories. The similarity of GI AE rates with the COX-2 selective inhibitors and acetaminophen in this study is consistent with the GI safety advantages observed with the COX-2 selective inhibitors compared to the NSAID[24-30]. Findings were generally similar for the pooled VACT1/VACT2 analyses, although significantly more patients with both rofecoxib doses than acetaminophen experienced a serious AE, while more rofecoxib 25 mg and acetaminophen than celecoxib patients discontinued due to an AE. These differences were not due to the occurrence of any particular type of AE; serious AE and those causing discontinuation were few and spread across body systems. Overall, there were no significant differences between rofecoxib 12.5 mg and celecoxib.

The renal and cardiovascular safety profiles of the study medications were evaluated in VACT2 and were found to be similar when pooled with VACT1 data. There were no significant differences between treatments in discontinuations due to edema related or hypertension related AE, except for a lower incidence of discontinuations due to hypertension related AE with celecoxib compared to acetaminophen in the pooled analysis. Cardiovascular system AE, including hypertension, occurred in a low and similar incidence in the 4 treatment groups.

The safety findings in the VACT studies are generally similar to those in the studies by McKenna, *et al*[45] and Gibofsky *et al*[46], which also demonstrated similar tolerability of the study medications. These studies reported no significant differences between rofecoxib 25 mg or celecoxib 200 mg in overall, drug related, or serious AE. The only sig-

nificant difference between the active treatments in individual AE in either of these studies was a higher incidence of GI AE with rofecoxib (34%) compared to celecoxib (11%) in McKenna, *et al*; however, the study was designed as an efficacy study and, with roughly 60 patients per treatment arm, was smaller than either the VACT study or the Gibofsky study, which reported no such difference[45,46]. Thus, based on the findings in the VACT1/VACT2 studies and similar to what is reported in McKenna, *et al* and Gibofsky, *et al*, both rofecoxib and celecoxib were generally well tolerated in direct comparator clinical studies and had similar safety profiles to acetaminophen. All these studies were 6 weeks in length, and the safety profiles of the study medications in our report apply to that time period.

The results of the VACT2 study and pooled analyses of the VACT studies demonstrate the superior efficacy of the COX-2 inhibitors compared to acetaminophen in patients with OA. This includes both more rapid onset of symptom relief and maintained efficacy advantages over 6 weeks. Individual study results and pooled analysis also showed that rofecoxib 25 mg provides greater efficacy than celecoxib 200 mg on nearly all endpoints. Rofecoxib 12.5 mg showed greater efficacy compared to celecoxib 200 mg over the first 6 days of treatment, however, and provided similar symptom relief at Weeks 2, 4, and 6. The study medications were generally well tolerated, with the COX-2 selective inhibitors and acetaminophen having similar safety profiles. There was no significant difference between treatment groups in the percentage of patients who experienced a clinical adverse experience. The incidence of discontinuations due to an AE was significantly lower with celecoxib (2.5%) compared to rofecoxib 25 mg (6.3%; $p = 0.004$) or acetaminophen (7.8%; $p < 0.001$), and did not differ significantly from rofecoxib 12.5 (4.6%). Further studies and subgroup analyses may be helpful to identify patients with OA who would be predicted to respond differentially to the treatments studied in these trials.

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