Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial

ADAPT Research Group*

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ABSTRACT **Objective:** To evaluate the efficacy and safety of naproxen and celecoxib for the primary prevention of Alzheimer disease (AD). **Methods:** Randomized, placebo-controlled, double-masked clinical trial conducted at six US dementia research clinics. Volunteers aged 70+ years, with cognitive screening scores above designated cut-offs and a family history of AD, were randomly assigned to celecoxib 200 mg BID, naproxen sodium 220 mg BID, or placebo. Enrollment began in early 2001. The main outcome measure was diagnosis of AD after randomization. **Results:** On December 17, 2004, treatments were suspended. Events while on treatment yielded hazard ratios vs placebo of 1.99 (95% CI 0.80 to 4.97; $p = 0.14$) for celecoxib and 2.35 (0.95 to 5.77; $p = 0.06$) for naproxen. Imperfect screening measures led to enrollment of 7 individuals with dementia and 46 others with milder cognitive syndromes. Their (prevalent) illness was detected at enrollment and diagnosed within 6 months following randomization. Secondary analyses that excluded the 7 cases of prevalent dementia showed increased hazard ratios for AD with both treatments. Neither treatment produced a notable effect on the incidence of milder cognitive syndromes. **Conclusions:** These results do not support the hypothesis that celecoxib or naproxen prevent Alzheimer dementia, at least within the early years after initiation of treatment. Masked long-term follow-up of these participants will be essential.
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While the causes of Alzheimer disease (AD) are not well understood,[1,2] neuropathologic evidence indicates that inflammatory processes are involved.[3] Inflammatory mechanisms are also suggested by epidemiologic findings that users of nonsteroidal anti-inflammatory drugs (NSAIDs) show reduced incidence of Alzheimer dementia.[4] A recent meta-analysis yielded a hazard ratio (HR) for incident AD of 0.42 (95% CI 0.26 to 0.66) among individuals with 2 or more years of sustained NSAID exposure, compared with nonusers.[5]

Interest in NSAIDs as a treatment for AD was initially reinforced by a promising randomized controlled trial.[6] However, several subsequent trials have shown no benefit from treatment of AD with rofecoxib,[7,8] naproxen,[8] nimesulide,[9] or diclofenac.[10] A trial of rofecoxib to prevent progression to AD in those with mild cognitive impairment (often a prodromal phase of AD) was similarly disappointing.[11] However, trials have not tested the hypothesis, suggested by epidemiologic data, that NSAIDs may be useful for the primary prevention of AD, i.e., for reducing its incidence in individuals with normal cognition. The AD Anti-inflammatory Prevention Trial (ADAPT) was designed to investigate whether the selective cyclooxygenase-2 (COX-2) inhibitor celecoxib (Celebrex, Pfizer) or the dual-inhibitor NSAID naproxen sodium (Aleve, Bayer) could prevent AD or delay cognitive decline. We report ADAPT results on occurrence of AD by treatment group, with secondary outcomes of the incidence of all-cause dementia and AD prodromes including amnestic mild cognitive impairment (aMCI). ADAPT results with regard to safety of the treatments are reported elsewhere.[12]

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METHODS

Design overview. ADAPT is a randomized, placebo-controlled, multicenter, primary prevention trial. Specifics regarding study design and eligibility criteria are available elsewhere.[13,14] Registered on ClinicalTrials.gov (#NCT00007189), ADAPT is investigator-initiated and sponsored by the National Institute on Aging (NIA) via a cooperative agreement. Recruitment was accomplished primarily through mailings to Medicare beneficiaries targeted by age and by zip code to areas surrounding the trial's six field sites (Baltimore, MD; Boston, MA; Rochester, NY; Seattle, WA; Sun City, AZ; and Tampa, FL). Eligible participants (see below) were aged ≥70 years and had a history of at least one first-degree relative with Alzheimer-like dementia. Persons regularly using NSAIDs were excluded, but regular aspirin use was allowed in dosage ≤81 mg per day. All pertinent institutional review boards (IRBs) approved the study protocol. Consent for participation was obtained from each person and a collateral informant. Enrollment began in March 2001.

Participants were randomly assigned to receive celecoxib (200 mg twice daily), naproxen sodium (220 mg twice daily), or matching placebos. The randomization scheme used permuted blocks with assignment ratio 1:1:1.5. Randomization was stratified by three age groups (ages 70 to 74, ages 75 to 79, and ages 80+) and by the six field sites, using a distributed computerized system that released treatment assignment only after baseline data were keyed and eligibility confirmed.

The study's Treatment Effects Monitoring Committee (TEMC) met twice yearly to review efficacy and safety data by treatment assignment. The Committee comprised five members external to ADAPT (voting), and three representatives of the ADAPT Steering Committee (non-voting).

Procedures. Study staff reviewed the eligibility of prospective participants using specified health criteria and cut-off scores on an Eligibility Battery of cognitive tests, which included the Modified Mini-Mental State Examination (3MS-E),[15] the Hopkins Verbal Learning Test-Revised (HVLT-R),[16] and the informant-based Dementia Severity Rating Scale (DSRS).[17] Eligible individuals returned for an enrollment visit at which time their baseline cognitive and functional abilities were assessed using a more elaborate Cognitive Assessment Battery (CAB) that included the 3MS-E, Digit Span Test, Generative Verbal Fluency (name as many supermarket items as possible in 1 minute), narratives from the Rivermead Behavioral Memory Test,[18] HVLT-R, Brief Visuospatial Test–Revised,[19] self-rating of memory functions,[20] Geriatric Depression Scale,[21] and the informant-rated DSRS. This same battery (with equivalent alternate test forms for some items) was used each year thereafter in follow-up screening for incident cognitive syndromes.

Participants and collateral informants were interviewed at 1 month and 6 months after randomization and annually thereafter. Telephone interviews were conducted with participants and informants approximately every 6 months between visits, starting at month 3. Interviews focused on health history and treatment compliance, but also collected information about change in cognitive or functional abilities.

Outcome assessment. Suspected cognitive syndromes were identified using a sensitive cut-off procedure on annual CAB assessments (including baseline measures) or, occasionally, upon referral from study clinicians. Participants with a suspected cognitive syndrome were invited to return for a dementia evaluation (DE). Expert physicians, trained study nurses, and psychometrists conducted the DEs following a protocol that included a detailed history from participants and informants, physical, neurologic, and mental status examinations, and a detailed psychometric assessment battery. The latter again included the informant-rated DSRS, and also the Dementia Questionnaire–clinical revision[22]; the Neuropsychiatric Inventory[23]; the CERAD cognitive test battery[24]; Trail Making Test[25]; Logical Memory[26]; Benton Visual Retention Test[27]; Controlled Oral Word Association Test[28]; Symbol Digit Modalities Test[29]; Shipley Vocabulary[30]; and Self-rating of Memory Functions.[20] Where appropriate, participants with a cognitive syndrome were referred for laboratory testing and neuroimaging for differential diagnosis.

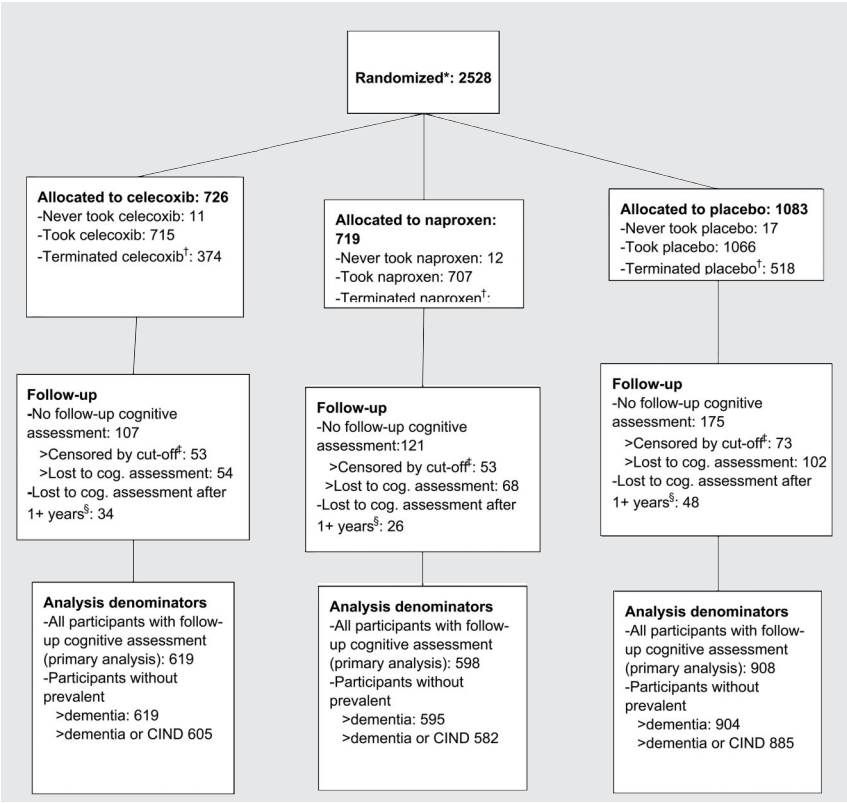
All resulting DE, laboratory, and neuroimaging data were then reviewed by a diagnostic panel of experts including the examining clinicians, other ADAPT physicians, and senior site neuropsychologists. Where appropriate, participants with abnormal cognition received diagnoses of dementia using the Diagnostic and Statistical Manual of Mental Disorders–IV criteria,[31] or Alzheimer's dementia using the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria.[32] Among the remaining cognitively impaired individuals, we identified instances of aMCI[13] or, in some participants who did not meet the specific criteria for MCI, other mild cognitive disorders suggestive of prodromal AD (prAD), as used in the Cache County study.[33] To promote diagnostic consistency across the field sites, several cases from each site were reviewed at semi-annual meetings of the ADAPT clinical personnel.

By convention, the date of onset of any cognitive syndrome was taken as the date of the relevant DE visit. Notably, seven CABs administered at enrollment triggered DEs, conducted over the following 6 months, that resulted in a diagnosis of dementia. Another 46 enrollment CABs resulted in DEs that identified diagnoses of aMCI or prAD.[34]

Treatment discontinuation. On December 17, 2004, the National Cancer Institute–sponsored Adenoma Prevention with Celecoxib (APC) trial announced significantly increased cardiovascular risk with celecoxib. On the same day, the ADAPT Steering Committee suspended treatment with celecoxib and naproxen, and suspended enrollment. On March 31, 2005, the Steering Committee made these suspensions permanent.[35]

Data analysis. Because we performed cognitive screening only once a year, and treatment termination took place in the middle of an annual cycle of follow-up assessments, we analyzed outcomes ascertained at DEs that were triggered by CABs conducted on or before June 17, 2005, 6 months after termination of treatments. To contribute an "event," DEs must then have been completed within 3 months of this date and outcomes entered into the ADAPT database by December 17, 2005. Outcome analyses included only participants with at least one cognitive assessment after enrollment. Person-time was censored after participants' last completed cognitive assessment. By design, active treatments were compared individually with placebo and not with each another. In all instances, we used the principle of intention-to-treat (ITT) when comparing the occurrence of diagnostic outcomes by assigned treatment. In addition to the primary analyses of AD identified following randomization, we conducted analyses (specified a priori) of the incidence of AD or all-cause dementia after exclusion of seven participants who had passed the screening eligibility battery but had dementia (diagnosed later) that had been detected at their enrollment visit. In other analyses we esti-

Figure 1 Participant flow (CONSORT) chart



*Numbers available only for those randomized, not those screened for eligibility.
†Participants considered to have terminated study drug if study drug had been started but was no longer being issued prior to December 17, 2004; does not include temporary interruptions.
‡Participants considered administratively censored if their 1-year visit window had not closed by June 17, 2005.
§Participants considered lost to cognitive assessment after 1 or more years if they did not have cognitive assessment data in the 1.5 years before June 17, 2005; losses include deaths.

mated post hoc the incidence of aMCI or suspected prAD after exclusion of all individuals with cognitive impairment identified at enrollment and diagnosed within the subsequent 6 months. We evaluated time-to-occurrence of each outcome using Kaplan-Meier plots, with p values of associated log-rank χ^2 tests. Cox proportional hazards regression models permitted adjustment for the stratification variables of age group and field site and semi-parametric estimation of the relative treatment effects. Resulting adjusted HRs were estimated with 95% CIs and Wald p values. These analyses used the PHREG routine in SAS, version 8.

RESULTS

Study population. As of December 17, 2004, ADAPT had recruited 2,528 participants. Figure 1 shows the flow of these participants from randomization forward. Some 403 participants did not contribute to the analyses for one of three reasons: 1) their observations were censored before their first annual follow-up (179); 2) they did not return for cognitive follow-up (210); or 3) no information on cognition was available because they had refused or not completed a requested Dementia Evaluation.[14] These losses were distributed proportionally across treatment groups (Fisher exact $p = 0.54$). The seven participants with dementia at enrollment and the 46 with other cognitive syndromes identified at enrollment were also distributed proportionally by treatment group ($p = 0.23$ and 0.89). There were 51 deaths: 17 in those receiving celecoxib (2.3%); 16 in the naproxen-treated group (2.2%); and 18 in those on placebo (1.7%) ($p = 0.38$ for naproxen vs placebo, and 0.30 for celecoxib). Median follow-up times following treatment assignment were 733 days for celecoxib-, 734 days for naproxen-, and 734.5 days for placebo-assigned participants. Participants reported that they actually took celecoxib for a median 561 days (25th percentile = 358, 75th percentile = 829), with corresponding figures of 546 days (350, 813) for naproxen, and 559 days (353, 848.5) for placebo (exact $p = 0.31$). While taking the study treatments, 85.6% of participants on celecoxib reported taking drug always or almost always or most of the time, compared with 86.1% on naproxen and 87.9% on placebo. Among participants assigned to celecoxib, 10.7% reported taking proscribed doses of aspirin or NSAID medications at least once, compared with 9.9% of participants on naproxen and 13.3% on placebo.

Table 1 provides baseline and demographic characteristics by treatment group for the 2,528 randomized participants and for the 2,128 who contributed to the analyses of cognitive outcomes. More men than women were enrolled. Race/ethnicity was predominantly white. Over three-quarters of the population had more than a high school education, and most had a Karnofsky score of 100. Baseline characteristics, including rates of cardiovascular diseases, were similar for the three treatment groups.

Diagnostic rates by treatment assignment. Table 2 displays counts, rates, and 95% CIs of diagnostic events per person year of follow-up by treatment group. In addition to occurrence of AD following randomization, the table displays rates of AD and all-cause dementia after exclusion of the seven participants with dementia detected at enrollment. Also shown are crude rates for incidence of MCI or prAD in a secondary analysis that excluded the 53 participants with any cognitive impairment syndrome at enrollment. Neither treatment was associated with reduction in the incidence of AD, all cause-dementia, or the AD prodromes. Instead, there was a suggestion of increase in the incidence of AD with both treatments.

Time-to-event analyses. The primary analyses of time to onset of AD are shown in the Kaplan-Meier plot of figure 2. The associated log-rank tests compare each treatment with placebo. A similar time-to-onset analysis that excluded the seven prevalent cases of dementia (not shown) produced log rank χ^2 p values of 0.02 for celecoxib vs placebo and 0.04 for naproxen vs placebo. These results do not suggest a reduction in the occurrence of AD with either NSAID but, if anything, the reverse. Figure 3 shows little difference across treatments in time-to-event analyses of incident MCI or prAD.

Table 1 Study population at entry: all participants randomized and participants who contributed to the analyses of cognitive outcome

	Total	Celecoxib	Naproxen	Placebo
All participants randomized				
No. randomized	2,528	726	719	1,083
Age, percentiles, y				
50	74	74	74	74
25, 75	72, 77	72, 77	72, 77	72, 77
0, 100	70, 90	70, 90	70, 88	70, 90
Gender, %				
Female	45.9	47.1	45.9	45.1
Male	54.1	52.9	54.1	54.9
Ethnic group, %				
White, non-Hispanic	97.0	96.1	97.1	97.4
African American	1.5	1.8	1.8	1.0
Hispanic	0.7	1.4	0.3	0.6
Other	0.8	0.6	0.7	0.9
Refused	0.1	0.1	0.1	0.1
Marital status, %				
Married	71.9	70.2	75.0	71.0
Widowed	18.2	19.7	16.1	18.7
Divorced/separated	7.3	7.3	6.1	8.0
Single	2.6	2.8	2.8	2.3
Education, %				
Less than high school	4.0	3.9	4.9	3.6
High school degree	19.9	20.8	17.5	20.9
College, no degree	27.5	27.7	28.4	26.8
College degree	19.2	19.2	17.0	20.6
Post-graduate	29.4	28.5	32.3	28.2
Karnofsky functional rating				
% Scoring 100	82.3	84.3	80.1	82.5
% Scoring 90	15.3	13.5	18.2	14.6
% Scoring 80	2.2	2.1	1.4	2.8
% Scoring 60–70	0.2	0.1	0.3	0.0
History of medical conditions, %				
Myocardial infarction	5.1	5.4	3.8	5.9
Diabetes	8.0	8.3	8.6	7.5
Hypertension treatment	39.8	39.4	39.2	40.5
Heart failure	0.9	1.4	0.7	0.6
Transient ischemic attack	3.5	3.2	3.2	3.9
Stroke	1.1	1.5	1.0	1.0
Participants who contributed to the analyses of cognitive outcome				
No. randomized	2,125	619	598	908
Age, percentiles, y				
50	74	74	74	74
25, 75	72, 77	72, 77	72, 77	72, 77
0, 100	70, 90	70, 90	70, 88	70, 90
Gender, %				
Female	45.3	47.2	45.6	43.8
Male	54.7	52.8	54.4	56.2
Ethnic group, %				
White, non-Hispanic	96.8	96.1	97.0	97.1
African American	1.6	2.1	1.8	1.2
Hispanic	0.8	1.3	0.3	0.7
Other	0.7	0.5	0.7	0.9
Refused	0.1	0.0	0.2	0.1
Marital status, %				
Married	71.7	69.8	74.6	71.0
Widowed	18.8	20.5	16.6	19.1
Divorced/separated	6.8	6.8	5.7	7.6
Single	2.7	2.9	3.2	2.3
Education, %				
Less than high school	4.2	3.9	5.0	3.8
High school degree	19.7	21.2	17.2	20.4
College, no degree	27.0	27.3	27.9	26.1
College degree	19.4	19.1	17.6	20.8
Post-graduate	29.7	28.6	32.3	28.8
Karnofsky functional rating				
% Scoring 100	83.8	85.1	82.6	83.7
% Scoring 90	14.3	12.9	16.6	13.8
% Scoring 80	1.7	1.8	0.8	2.3
% Scoring 60–70	0.1	0.2	0.0	0.2

Table 2 Rates of cognitive outcomes by treatment group

	Placebo (n = 908)		Celecoxib (n = 619)		Naproxen (n = 598)		Total (n = 2125)	
	Events	Rate (95% CI)*	Events	Rate (95% CI)	Events	Rate (95% CI)	Events	Rate (95% CI)
Analysis including all participants with known follow-up cognitive status								
Alzheimer dementia	9	0.005 (0.002, 0.009)	11	0.009 (0.004, 0.015)	12	0.010 (0.005, 0.017)	32	0.007 (0.005, 0.010)
Analyses excluding participants with dementia at enrollment								
		(n = 904)		(n = 619)		(n = 595)		(n = 2,118)
Alzheimer dementia	5	0.003 (0.001, 0.006)	11	0.009 (0.004, 0.016)	9	0.007 (0.003, 0.014)	25	0.006 (0.004, 0.008)
All-cause dementia	7	0.004 (0.001, 0.008)	12	0.009 (0.005, 0.017)	11	0.009 (0.004, 0.016)	30	0.007 (0.005, 0.010)
Analysis excluding participants with any cognitive syndrome at enrollment								
		(n = 885)		(n = 605)		(n = 582)		(n = 2,072)
MCI or prAD	18	0.010 (0.006, 0.015)	16	0.013 (0.007, 0.021)	15	0.012 (0.007, 0.020)	49	0.011 (0.008, 0.015)

*Rate = Total number of events per person-year; CIs are based on an exact Poisson distribution.
MCI = mild cognitive impairment; prAD = prodromal Alzheimer disease.

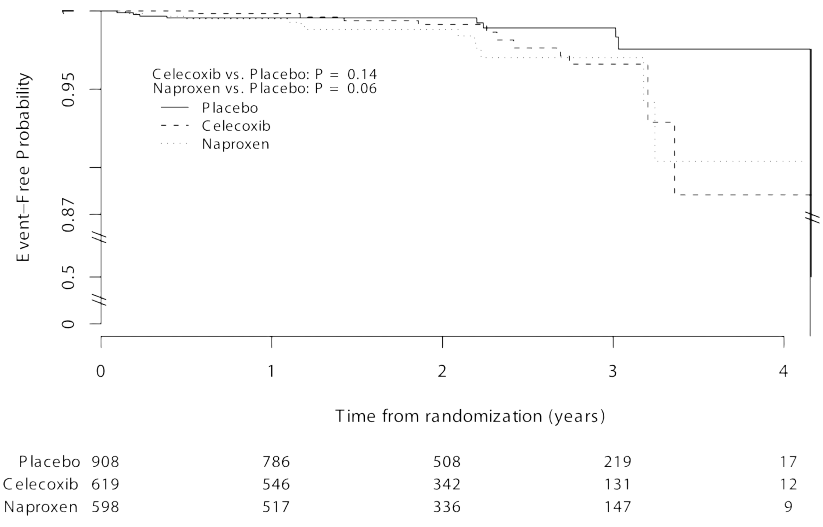
Table 3 shows results from corresponding proportional hazards models. In the primary analyses of all events following randomization, the hazard for AD was approximately doubled with either celecoxib or naproxen, but the related CIs included the null value of 1. Analyses that excluded the seven cases of prevalent AD yielded HRs further from the null, with significant *p* values. The HR for the composite of MCI and prodromal AD did not differ much from unity.

Table 4 displays results from proportional hazards models estimating the risk of AD or death (composite outcome, death being an obvious censoring variable). The results do not change the conclusion from table 3 of no benefit with the study treatments.

DISCUSSION Although ADAPT was conducted to test the hypothesis that celecoxib or naproxen reduce the incidence of AD, these results indicate no such effect, at least over the study's period of observation. Based on these findings, the lower bounds of the HR CIs in the primary analyses, 0.80 for celecoxib and 0.95 for naproxen, imply with 95% confidence that the treatments conferred no more than 20% (celecoxib) or 5% (naproxen) reduction in risk of AD. Using similar reasoning, the treatments provided no more than 24% or 28% protection against aMCI or prAD.

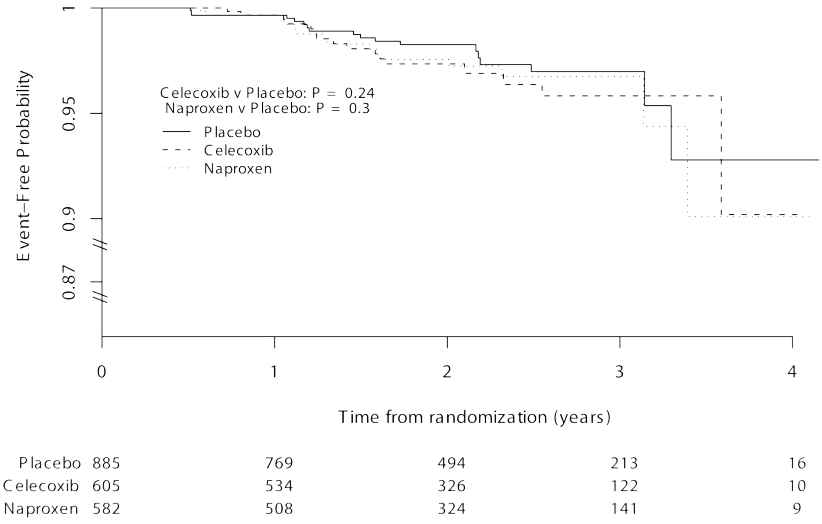
The primary analyses that included all events following randomization showed an inconclusive trend toward increased AD incidence with either NSAID treatment. Owing to the imperfect sensitiv-

Figure 2 Time-to-event plot for Alzheimer dementia following randomization



Time-to-event plot for Alzheimer dementia following randomization, comparing placebo-, celecoxib-, and naproxen-treated groups, with *p* values from the log-rank χ^2 tests comparing each treatment with placebo.

Figure 3 Time-to-event plot for secondary analyses of Alzheimer-like prodromes



Placebo	885	769	494	213	16
Celecoxib	605	534	326	122	10
Naproxen	582	508	324	141	9

Time-to-event plot for secondary analyses of Alzheimer-like prodromes, comparing placebo-, celecoxib-, and naproxen-treated groups, with *p* values from log-rank χ^2 tests comparing each treatment to placebo. Individuals with any cognitive impairment syndrome detected at enrollment were excluded.

ity of our screening protocol, these events included seven cases of AD whose dementia, although diagnosed later, was present at the time of randomization. While it makes little sense clinically to include these individuals with prevalent AD in the at-risk pool, their inclusion in the primary analyses is warranted by a fundamental objective of clinical trials: freedom from bias. Nevertheless, we recognized that the inclusion of these seven individuals could potentially dilute any treatment effects. This concern, magnified here by the small number of events, led to a decision a priori to conduct additional analyses that excluded these individuals. As predicted, these latter analyses yielded HRs that were more extreme (table 3). Despite the reduction in number of events from 32 (a small number) to 25 (a smaller number), the corresponding *p* values also met conventional criteria for statistical significance, even though a power analysis with 25 events would have suggested that only a very extreme HR could be reliably detected as "significant."

It is probably noteworthy that the effects of the two treatments seem broadly interchangeable. This fact would seem to reduce the probability that the observed HRs are attributable purely to chance. Furthermore, the findings trend in the same direction as the results of a recent trial of the selective COX-2 inhibitor rofecoxib in patients with MCI,[11] and also the results of a widely cited trial of naproxen and rofecoxib for treatment of Alzheimer dementia[8] that showed trends toward negative effects of rofecoxib.

These findings from a randomized controlled trial therefore appear to be inconsistent with epidemiologic findings suggesting reduced AD incidence following sustained NSAID use.[4] A common explanation for such divergent results posits that the inverse association in the observational work reflects the effects of unknown variables confounded with NSAID use. Another explanation might be that the ADAPT findings relate specifically to celecoxib or naproxen but not to other NSAIDs such as ibuprofen, a common exposure in observational studies, because the ADAPT treatments do not lower production of amyloidogenic Aβ 42,[36] a probable early step in the development of AD pathology.

A more speculative explanation that may tie together the epidemiologic and clinical trials findings posits that the effects of NSAID exposures differ with the stage of brain disease progression. NSAIDs suppress brain inflammatory mechanisms, particularly the secretion by activated microglia of proinflammatory cytokines that are widely thought to promote AD pathogenesis. Especially given the extended presymptomatic period of AD neurodegeneration,[2] it is therefore possible that NSAID suppression of microglial activation might exert

Table 3 Hazard ratios (HRs) for cognitive outcomes

	Celecoxib vs placebo		Naproxen vs placebo	
Diagnosis	HR* (95% CI)	*p* Value	HR* (95% CI)	*p* Value
Analyses of all participants with known cognitive status				
Alzheimer dementia	1.99 (0.80, 4.97)	0.14	2.35 (0.95, 5.77)	0.06
Analyses excluding participants with dementia at enrollment				
Alzheimer dementia	4.11 (1.30, 13.0)	0.02	3.57 (1.09, 11.7)	0.04
All cause dementia	3.04 (1.13, 8.17)	0.03	2.83 (1.04, 7.72)	0.04
Analyses excluding participants with any cognitive syndrome at enrollment				
MCI or prAD	1.52 (0.76, 3.05)	0.24	1.46 (0.72, 2.97)	0.30

*Common HRs across clinic and age strata from proportional hazards models for risk of a cognitive diagnosis. Estimates account for stratification factors without subjecting them to the proportional hazards assumption.
MCI = mild cognitive impairment; prAD = prodromal Alzheimer dementia.

Table 4 Hazard ratios (HRs) for risk of death or Alzheimer disease (composite)

	Celebrex vs placebo		Naproxen vs placebo	
Patient subset (n)	HR* (95% CI)	*p* Value	HR* (95% CI)	*p* Value
All patients with available follow-up (2,501)	1.53 (0.90, 2.60)	0.11	1.63 (0.96, 2.77)	0.07
Excluding those who refused DEVs (2,470)	1.58 (0.92, 2.73)	0.10	1.75 (1.02, 3.00)	0.04
Cognitive follow-up population (2,125)	1.75 (0.98, 3.14)	0.06	1.60 (0.87, 2.94)	0.13

*HRs across clinic and age strata from Cox proportional hazards models for risk of death or Alzheimer dementia. Estimates account for stratification factors without subjecting them to the proportional hazards assumption.

protective effects when given years before the development of symptoms. Once extensive Aβ deposits have occurred, however, microglia-mediated inflammatory mechanisms may be essential to their clearance. At this later stage, when symptoms may be imminent or evident, NSAID suppression of microglial activity could have mixed effects or even accelerate the disease process, thus precipitating the onset of dementia.

This last explanation is consistent with data from both the Rotterdam and Cache County observational studies.[5,37] Both studies suggest no protection with NSAIDs used in the last 2 years before dementia onset. If timing of exposure determines whether NSAIDs produce benefit or harm, the ADAPT results should logically be compared with observational study subjects having only recent NSAID exposure, i.e., those for whom the observational studies do not suggest protection. In this way, the emerging evidence base on AD protection with NSAIDs may simulate the findings with hormone replacement therapy (HRT) in women. HRT observational studies suggest that hormones may prevent AD if given years before the typical age at onset,[38-40] but may increase risks when used later in life.[20,41] Like the women who developed incident dementia in the Women's Health Initiative Memory Study[40] (WHIMS), the incident AD cases in ADAPT developed their symptoms within a few years of exposure to the intervention. In both trials, those who developed dementia within a short span of time were likely to have had advanced pre-clinical Alzheimer brain changes when the intervention was administered.

Because the observational data suggest that NSAIDs may have protective effects for individuals with "healthier" brains (i.e., for those whose onset of AD would be some years in the future), continued observations in the ADAPT cohort could show mitigation—or even reversal—of the treatment effects that presently appear null or negative. This idea should be tested directly through continued masked follow-up of the ADAPT cohort. For now, we suggest that the ADAPT treatments are not indicated for the prevention of AD. By contrast, our findings are too limited to be considered evidence that persons at risk for AD should avoid these or other NSAIDs when used for their approved indications.

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APPENDIX

ADAPT Steering Committee: Chair—Curtis Meinert, PhD, Johns Hopkins Bloomberg School of Public Health, Baltimore (through February 2005), Denis Evans, MD, Rush-Presbyterian-St. Luke's Medical Center, Chicago (since March 2005); Resource center representatives/Study officers (voting)—John Breitner, MD, MPH (Study Chair), Veteran Affairs Puget Sound Health Care System and University of Washington School of Medicine, Seattle, Neil Buckholtz, PhD (Project Officer), National Institute on Aging, Bethesda, Barbara Martin, PhD (Coordinating Center Deputy Director), Johns Hopkins Bloomberg School of Public Health, Baltimore, Curtis Meinert, PhD (Coordinating Center Director), Johns Hopkins Bloomberg School of Public Health, Baltimore, Susan Molchan, MD (Project Officer), National Institute on Aging, Bethesda; Field site directors (voting)—Suzanne Craft, PhD, Veteran Affairs Puget Sound Health Care System and University of Washington School of Medicine, Seattle, Robert C. Green, MD, MPH, Boston University School of Medicine, Boston, Constantine Lyketsos, MD, MHS, Johns Hopkins School of Medicine, Baltimore, Michael Mullan, MD, PhD, The Roskamp Institute Memory Clinic, Tampa, Marwan Sabbagh, MD, Sun Health Research Institute, Sun City, AZ, Pierre Tariot, MD, Banner Health System, Phoenix AZ (through October 2005), M. Saleem Ismail, MD, University of Rochester School of Medicine, Rochester, NY (since December 2005); Other voting members—Jason Brandt, PhD, Johns Hopkins School of Medicine, Baltimore, Steven Piantadosi, MD, PhD, Johns Hopkins School of Medicine, Baltimore; Staff—Janette Negele and Melissa Montero, Veteran Affairs Puget Sound Health Care System, Seattle, Bonnie Piantadosi, MSW, MPH, Johns Hopkins Bloomberg School of Public Health, Baltimore; Consultants—Themistocles Dassopoulos, MD, Johns Hopkins School of Medicine, Baltimore, Claudia Kawas, MD, University of California Irvine, Leon Thal, MD, University of California San Diego, La Jolla, Kathleen Welsh-Bohmer, PhD, Duke University Medical Center, Durham, Andrew Whelton, MD, Hunt Valley, MD. Treatment Effects Monitoring Committee: Voting members—C. Morton Hawkins, PhD (Chair), Frontier Science & Technology Research Foundation, Madison, Bernard Carroll, MBBS, PhD, FRCPsych, Pacific Behavioral Research Foundation, Carmel, CA, Ronald Petersen, PhD, MD, Mayo Clinic, Rochester, MN, Thomas Schnitzer, MD, PhD, Northwestern University, Chicago, Dallas High, PhD, retired (through June 2004); Non-voting members—Neil Buckholtz, PhD, National Institute on Aging, Bethesda, Denis Evans, MD, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Curtis Meinert, PhD, Johns Hopkins Bloomberg School of Public Health, Baltimore. Other members of Research Group: Resource centers—Chairman's Office, Veteran Affairs Puget Sound Health Care System, Seattle: John Breitner, MD, Director; Janette Negele, Coordinator; Melissa Montero, Coordinator; Elizabeth Aigbe, MS; Jill Dorje; Brenna Cholerton, PhD;

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