

**Cardiovascular Risk of Celecoxib in Six Randomized Placebo-controlled Trials:
The Cross Trial Safety Analysis**

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Abstract

Background Observational studies and randomized trials have reported increased cardiovascular risk associated with cyclooxygenase-2 inhibitors. Prior placebo-controlled randomized studies had limited ability to assess the relationship of either celecoxib dose or pretreatment cardiovascular status to risk associated with celecoxib. Our aim was to assess the cardiovascular risk associated with celecoxib in three dose regimens and to assess the relationship between baseline cardiovascular risk and effect of celecoxib on cardiovascular events.

Methods and Results We performed a patient-level pooled analysis of adjudicated data from 7950 patients in six placebo controlled trials comparing celecoxib to placebo for conditions other than arthritis with a planned follow-up of at least 3 years. Patients were administered celecoxib in three dose regimens - 400mg qd, 200mg bid or 400mg bid. From the pooled data, we calculated a hazard ratio for all dose-regimens combined and individual hazard ratios for each dose regimen, and examined whether celecoxib-related risk was associated with baseline cardiovascular risk. The primary endpoint was the combination of cardiovascular death, myocardial infarction, stroke, heart failure or thromboembolic event.

With 16,070 patient-years of follow-up, the hazard ratio for the composite endpoint combining the tested doses was 1.6 (95% confidence interval 1.1 to 2.3). The risk, which increased with dose regimen ($p = 0.0005$), was lowest for the 400mg qd dose (hazard ratio 1.1, 95% confidence interval 0.6 to 2.0), intermediate for the 200mg bid dose (hazard ratio 1.8, 95% confidence interval 1.1 to 3.1), and highest for the 400mg bid dose (hazard ratio 3.1, 95% confidence interval 1.5 to 6.1). Patients at highest baseline

risk demonstrated disproportionately greater risk of celecoxib-related adverse events (p-interaction = 0.034).

Conclusions We observed evidence of differential cardiovascular risk as a function of celecoxib dose regimen and baseline cardiovascular risk. By further clarifying the extent of celecoxib-related cardiovascular risk, these findings may help guide treatment decisions for patients who derive clinical benefit from selective Cox-2 inhibition.

Keywords: non-steroidal anti-inflammatory drugs outcomes

Introduction

Observational studies and randomized controlled trials have reported increased cardiovascular risk associated with cyclooxygenase-2 (cox-2) inhibitors (coxibs)^{1,2,3,4,5,6,7,8,9,10}. Moreover, numerous experimental studies have supported a strong biologic basis for this risk¹¹. While most clinical studies with these agents have compared coxibs with active comparators in relatively short-term arthritis trials, initial evidence of increased cardiovascular risk associated with rofecoxib⁷, valdecoxib⁸ and celecoxib⁹ emerged from longer duration, placebo-controlled trials designed to study the role of coxibs in other therapeutic areas. In December 2004, two months after the withdrawal of rofecoxib because of increased cardiovascular risk observed in a polyp-prevention trial⁷, the report of an increased risk of cardiovascular events in the NCI- and Pfizer-sponsored Adenoma Prevention with Celecoxib (APC) trial¹² led to stopping drug administration in that trial⁹. Immediately afterwards, drug administration was withheld in five other long-term trials comparing celecoxib to placebo – the Prevention of Sporadic Adenomatous Polyps (PreSAP) trial¹³, the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)¹⁴, the MA-27 trial, the Celecoxib Diabetic Macular Edema (CDME) trial, and The Celecoxib/Selenium Trial.

The relatively low cardiovascular event rate in all coxib-cardiovascular risk analyses to-date has limited the ability to elucidate the relationship between coxib dose or pre-treatment cardiovascular status to drug-associated cardiovascular risk. Observational and randomized trial data suggest that coxib-associated cardiovascular risk may be dose related⁵, and that both dose and dosing interval may be important factors in cardiovascular risk¹⁰. Prior trials have had too few cardiovascular events to assess

whether the cardiovascular risk associated with celecoxib use risk varies according to a patient's baseline cardiovascular risk.

To understand more fully the cardiovascular risk profile associated with long-term use of celecoxib, the National Institutes of Health asked investigators in four long-term, placebo-controlled trials with a planned follow-up of 3 years or greater to submit their data for central adjudication and combined analysis by the same process used to analyze the APC and PreSAP studies. This report presents the results of the Celecoxib Cross Trial Safety Analysis, an NCI commissioned meta-analysis of six randomized trials focused on cardiovascular safety.

METHODS

Patients

Prior to collecting data we specified that trials included in the analysis would have the following properties: (1) they would be randomized, double blind, and placebo-controlled, 2) the planned follow-up for each participant would be at least three years. We searched the public literature for such trials and asked the National Institutes of Health (NIH) and Pfizer to identify any unpublished trials with those characteristics. In addition to APC and PreSAP, the search identified four such trials. All trials fulfilling these two criteria studied the therapeutic potential of celecoxib for a condition other than arthritis. We obtained patient-level data from these four trials, which we combined with data obtained from the two studies previously adjudicated, analyzed, and reported (APC and

PreSAP)^{9,10}. Table 1 shows brief descriptions of each trial, randomization scheme, stratification factors, and follow-up time. Informed consent was obtained from all patients enrolled in each of the studies presented.

Procedures

Following approval of the statistical analysis plan, each participating trial submitted to Statistics Collaborative patient-level data consisting of randomization code, baseline clinical characteristics, length of follow-up, and data on events to be classified. While each study collected different types of baseline data, for the purposes of a patient-level meta-analysis we re-categorized, according to the prespecified plan, certain baseline data (e.g., race, ethnicity, cardiovascular risk factors) to provide common definitions.

The adjudication team consisted of two cardiovascular specialists with experience in cardiovascular endpoint adjudication (PVF and SDS). Each study's research team identified possible cardiovascular or cerebrovascular events and sent summaries to the reviewers. The adjudication team reviewed each summary and requested source documentation for all deaths and all events deemed potentially cardiovascular in nature. We developed uniform endpoint definitions as guidelines for adjudication as previously described¹⁵. The reviewers, masked to treatment allocation, categorized each event as definite, probable, or possible, depending on the availability and apparent reliability of the source documentation.

Statistical Analysis

The primary analysis for each trial categorized composite outcomes hierarchically as described previously⁹, with events added to the hierarchy by virtue of increasing subjectivity of diagnosis. For the purposes of this analysis, the statistical analysis plan prespecified that the principal outcome would be the composite of cardiovascular death, myocardial infarction, stroke, heart failure, or a thromboembolic event, and that the hierarchy of composite events would be reported.

As prespecified in our analysis plan, for the six studies we calculated separately the incidence of each outcome and rate per 1000 patient-years by treatment group. We constructed Kaplan-Meier curves for the principal composite endpoint for each study and used Cox models stratified by the study-specific strata to calculate the hazard ratio of each celecoxib dose group relative to the placebo group in the same study along with its 95 percent confidence interval. Pooled analyses assessed both the overall risk of any dose of celecoxib and the dose-specific risk. The estimated hazard ratio for the overall effect of celecoxib across studies was derived from the antilog of the pooled log-hazard ratio, which was calculated as the average of the log-hazard ratio from each individual trial weighted by the inverse of its variance. We assessed reliability of this estimate by comparing an ordinary Mantel-Haenszel pooled odds ratio and that of a Cox model stratified by study and baseline aspirin use with the plan to explore potential reasons for discrepancy if this analysis differed substantially from the primary method.

To assess the effect of dose regimen, we grouped studies according to dose regimen as follows: 400mg qd: PreSAP and The Celecoxib/Selenium trial; 200mg bid: ADAPT, APC (low dose), and CDME; 400mg bid: APC (high dose) and MA27. As

prespecified, we tested for an interaction between dose regimen and the risk associated with celecoxib adjusting for baseline cardiovascular risk (see below), and tested for the presence of a linear trend among dose regimens. Our primary method was an intention-to-treat analysis, with follow-up for cardiovascular events occurring as long as the participant remained in the study, even if the participant stopped taking celecoxib or placebo. Our primary analysis included only those events the adjudication team judged “definite.”

We created a “three-category” risk score using variables in the Framingham Heart Study risk model¹⁶ modified to conform to the availability of data from these studies: *low*: no known risk factor; *moderate*: one of the following: age > 75; hypertension or on hypertensive medication; hyperlipidemia or using lipid-lowering medication; current smoker; using low-dose aspirin; *high*: diabetes, prior history of cardiovascular disease, or two or more of the risk factors used in isolation to define “moderate” risk. Our analysis plan had called for a four category risk score, but because so few participants in the studies fell into the lowest risk group, we redefined the score into three categories. For the MA27 study, which did not collect data on current smoking status, we assumed that no participant was a smoker. We did not have data from the Celecoxib/Selenium Trial on use of lipid-lowering medication; for that study we defined “hyperlipidemic” as total cholesterol of 240 or greater, LDL-cholesterol of 160 or greater, or the ratio of total to HDL-cholesterol of 5 or greater. As prespecified in our analysis plan, we used the risk score in two different ways. First, we constructed a Cox model, stratified by study, using the risk score as a categorical variable and combining all treatment groups to confirm that the ratios of successive hazard ratios in this grouping were at least 1.5. We then used this

score as a continuous variable in a Cox model with an interaction term to gain a better understanding of the relationship between cardiovascular risk and celecoxib use. We further assessed the effect of baseline aspirin use on celecoxib risk.

We used Akaike's Information Criterion (AIC)¹⁷ to assess whether addition of terms improved the fit of the Cox model. We considered a decrease of at least two in the AIC as evidence that a model with an additional term produced a better fit. Because the CDME study had only three outcomes and only patients at high cardiovascular risk, we did not include it in the Cox models that assessed baseline risk. Because we had a single principal hypothesis, its associated two-sided p-value and 95% confidence interval need no correction for multiplicity. We view all other analyses as providing insights into questions of interest. Their reported p-values are two-sided; all confidence limits are 95%; they are not corrected for multiplicity.

Statement of Responsibility

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

RESULTS

The baseline characteristics of the six trials showed some notable differences (Table 2). In particular, patients in the ADAPT trial were older (mean age 75 in ADAPT vs 61 for the other trials combined), and patients in the CDME were more diverse in

ethnic origin (67% white in CDME; nearly 95% for the other trials combined). All patients in the CDME trial were diabetic, while the prevalence of diabetes was similar (less than 10%) across the other trials. Baseline cardiovascular risk differed among the trials. All patients in the CDME trial were deemed at high cardiovascular risk because all were diabetic. Among the other trials, patients in the ADAPT trial were at highest cardiovascular risk, partly because they were all at least 70 years old, followed by the Celecoxib/Selenium Trial. The CDME and ADAPT trials had the highest frequencies of low-dose aspirin use, likely reflecting the increased cardiovascular risk in these patient cohorts.

All trials combined had a total of 16,070 patient years of follow-up, with individual trials ranging from 101 patient-years (CDME) to 6234 patient-years (APC) (Table 2). An important difference among the trials was the follow-up time. The percentage with 3 years of follow-up was 90 percent in APC and 43 percent in PreSAP. By contrast, the median follow-up times for ADAPT, The Celecoxib/Selenium Trial, CDME, and MA27 were 24, 21, 15, and 5 months, respectively.

Event rates and hazard ratios for the principal composite endpoint for each individual trial (irrespective of dose) are shown in Table 3. The CDME trial, which randomized 86 participants, had the fewest events, with 3 principal composite endpoints in the placebo group and none in the celecoxib group.

For the principal composite endpoint of cardiovascular death, myocardial infarction, stroke, heart failure or thromboembolic events, the overall pooled hazard ratio considering all dose regimens together and including the CDME trial was 1.6 (95% confidence intervals 1.1, 2.3). See Figure 1 for Kaplan-Meier curves for each trial. We

obtained virtually identical overall hazard ratios and confidence intervals regardless of whether we utilized the inverse variance method, Cox regression, or the Mantel-Haenszel estimate to estimate the pooled hazard ratio (data not shown). Pooled event rates and hazard ratios for each of the composite events in the prespecified event hierarchy are shown in Table 4.

Effect of Dose

We calculated hazard ratios for each dose regimen, adjusted for baseline cardiovascular risk and stratified by study-specific randomization strata (Table 3; Figure 2). The highest observed risk was for the 400mg bid dose (hazard ratio 3.1, 95% confidence intervals 1.5 to 6.1), with the 200mg bid dose demonstrating intermediate risk (hazard ratio 1.8, 95% confidence interval 1.1 to 3.1), and the 400mg qd dose demonstrating the lowest risk (hazard ratio 1.1, 95% confidence interval 0.6 to 2.0). Pairwise comparison using Cox regression stratified by study and adjusted for cardiovascular baseline risk demonstrated increased risk associated with the 400mg bid dose regimen compared to the 400mg once-daily dose regimen (hazard ratio 2.5, 95% confidence interval 1.1 to 5.5; $p = 0.029$). Comparison of either twice-daily dose to the once-daily dose suggested an increased risk (hazard ratio 2.0, 95% confidence interval 1.0 to 4.1; $p = 0.062$). A linear trend model testing for increased risk associated with dose regimen showed a significant trend for increased risk progressing from placebo to 400mg qd to 200mg bid to 400 mg bid (P -trend = 0.0005; hazard ratios ranging from 1, by definition, for placebo to 2.5 for 400mg bid). Because of the small number of events contributed by the CDME trial, we performed the analyses including or excluding those

data, and the overall hazard ratio and the individual dose-related hazard ratios were nearly identical in both analyses.

Effect of Baseline Cardiovascular Risk

The overall event rate increased across the three baseline risk categories regardless of the use of celecoxib, with a doubling of risk between the low and moderate risk groups (hazard ratio 2.0, 95% confidence interval 1.5 to 2.6) and a further doubling between the moderate and high risk groups (hazard ratio high risk to low risk: 3.9, 95% confidence interval 2.3 to 6.7) (Figure 3). The use of celecoxib in any dose tested was associated with adverse cardiovascular risk even after adjusting for baseline risk (hazard ratio celecoxib versus placebo: 1.7, 95% confidence interval 1.2 to 2.4), virtually the same as the pooled estimate that did not include baseline risk. With all doses pooled, the data suggested an interaction between celecoxib use and baseline risk with respect to outcomes (p -interaction = 0.16); the three dose regimens in an ordered model provided more evidence of such an interaction (p = 0.034), with patients in the highest risk category demonstrating the greatest hazard with respect to celecoxib use (Figure 3). Celecoxib was associated with increased risk irrespective of baseline aspirin use.

Discussion

The Cross Trial Safety Analysis provides an assessment of cardiovascular risk associated with three dose regimens of celecoxib based on over 16,000 patient years of follow-up from six randomized placebo-controlled trials. The data show evidence of dose and regimen differences in risk, as well as evidence of an interaction between baseline

cardiovascular risk and celecoxib dose, suggesting that the adverse effect of dose is most pronounced in higher risk patients. The increase in the number of patients and events afforded by this analysis adds substantively to the understanding of the role of dose regimen and baseline cardiovascular risk on celecoxib-related risk. Since celecoxib, which currently carries an FDA-mandated black-box warning, remains the only coxib available in the United States, and is the most commonly used cox-2 inhibitor worldwide, these data have important implications for treating patients who derive clinical benefit from coxibs.

The increased risk observed in this analysis needs to be considered in light of the high doses of celecoxib tested. All the tested doses are higher than the doses of celecoxib typically used in osteoarthritis patients (recommended daily dose 200mg); however, our data are directly relevant to doses recommended in the current celecoxib prescribing guidelines for patients with rheumatoid arthritis (up to 200mg bid), acute pain and dysmenorrhea (400mg qd or 200mg bid or higher if needed), familial adenomatous polyposis (400mg bid)¹⁸, as well as doses currently being tested for non-arthritic conditions. Moreover, some patients enrolled in the ongoing PRECISION trial – a 20,000 patient clinical trial comparing celecoxib, naproxen and ibuprofen with osteoarthritis or rheumatoid arthritis – will be titrated up to the 200mg bid dose of celecoxib. Our data do not, however, address whether doses lower than those tested in any of these trials would lead to lower cardiovascular risk, or whether non-selective non-steroidal anti-inflammatory agents would be associated with similar risk.

Several mechanisms have been proposed to explain the cardiovascular risk attributed to cyclooxygenase-2 inhibitors^{11, 19}. A coxib-induced imbalance between

prostacyclin and thromboxane production due to inhibition of cox-2 generated prostacyclin without an opposing reduction in thromboxane has been one of the most widely discussed mechanisms to support cardiovascular risk^{20,21}. Coxibs, and other nonsteroidal anti-inflammatory agents can also increase blood pressure by a variety of mechanisms, including through disruption of Cox-2²². Although we have reported significant increases in blood pressure in the APC trial at both the 200mg bid and 400mg bid doses¹⁰, we did not have blood pressure data from the additional studies included in this analysis so the extent to which coxib-related blood pressure elevation contributes to individual patient risk remains unknown. That the majority of adverse cardiovascular events observed – including strokes - were thromboembolic in nature suggests that while elevation in blood pressure may be related to the same mechanisms of Cox-2 disruption, blood pressure elevation in individual patients is unlikely to explain much of the observed cardiovascular risk.

The addition in this analysis of more trials and events over previous placebo-controlled analyses clarifies the role of dose and regimen on celecoxib risk. The approach we used allowed us to answer questions that would have been difficult or impossible to address from a single randomized clinical trial. The results of a single prior study (PreSAP) suggesting a lower hazard with the 400mg once daily dose¹⁰ are supported by an even lower point estimate in another 400mg once daily dose regimen trial, The Celecoxib/Selenium Trial. Nevertheless, the wide confidence intervals around the overall point estimate for the 400mg once daily dose do not exclude hazard with this dose, and are consistent with as much as a 40% risk reduction or a doubling of risk. The linear trend in cardiovascular risk observed among the three dose regimens studied supports

differences related to dose with respect to cardiovascular risk, and suggests that the risk associated with the 200mg twice daily dose may be intermediate between the 400mg once daily dose and the 400mg twice daily dose.

Whereas differences in risk associated with different total daily doses are easily explainable, the finding that a once-daily dose might be associated with lower cardiovascular risk than a twice-daily dose – a finding that is concordant with the prior observation that blood pressure increased with a 200 mg twice daily dose but not with a 400mg once-daily dose – requires further explanation¹⁰. Eicosanoids such as PGE₂, prostacyclin, and thromboxane are “rapid response” molecules, immediately elaborated upon activation by appropriate stimuli and then rapidly degraded to prevent sustained effect. Pharmacodynamic studies show that, following a single oral celecoxib dose, the maximal plasma concentration is achieved in approximately 90 minutes, and the mean half-life of the drug is 1.5 hours²³. Similarly, human volunteer dosing studies of celecoxib have suggested recovery of prostacyclin levels between 12-24 hours after dosing²⁴, raising the possibility that partial prostacyclin recovery might explain an observed lower risk with a once-daily regimen, a mechanism that has been hypothesized by Grosser et al¹¹. If production of thromboxane within the arterial wall under pathologic conditions is a mechanism underlying celecoxib-mediated thrombosis, once daily dosing may be safer than twice daily dosing because this regimen is associated with a shorter duration of exposure of susceptible atherosclerotic tissue to effects of high celecoxib doses, although this hypothesis remains highly speculative. Additionally, significant individual variability in the response to coxibs has been observed in volunteers²⁵, and a variety of candidate genes, including CYP2C9, have been associated with marked

variability in response to coxibs²⁶. While the importance of genetic variability with respect to cardiovascular risk remains unknown, clinicians should be aware of the potential marked individual variability that might affect either efficacy or safety.

Previous analyses of the APC and PreSAP trials did not find significant heterogeneity in the risk associated with celecoxib as a function of baseline cardiovascular risk; this may be explained by the smaller number of events and a less comprehensive method of assigning cardiovascular risk. In the current analysis, we combined several baseline characteristics to obtain an individual measure of cardiovascular risk for each patient, and observed that patients with the highest baseline risk were not only at greatest absolute risk as would be expected, but also at greatest relative risk for adverse cardiovascular events associated with celecoxib, particularly in the highest doses. This finding would not be expected if the relative risk were the same regardless of an individual's baseline risk and is consistent with a mechanism of risk that postulates a coxib-induced imbalance between thromboxane and prostacyclin, which would likely be most important under thrombogenic conditions. As no available compelling data suggest coxibs increase atherosclerotic burden – and recent evidence showing reduction in restenosis rates after PCI in patients randomized to celecoxib²⁷ may suggest the opposite – potential imbalances between thromboxane and prostacyclin production would likely be most meaningful in a patient predisposed to pathologic thrombus formation. Thus, patients with preexisting atherosclerotic plaque might be most susceptible to the risk imposed by coxibs, and in the presence of a plaque rupture, coxib use might increase the likelihood of sustained thrombosis.

The finding that both the relative and absolute risks of cardiovascular events increases with baseline cardiovascular risk has important implications for clinical decision making, as it may provide more comfort in prescribing the drug in patients with very low baseline risk, and would argue for more caution in prescribing the drug in patients with higher baseline risk. Nevertheless, while baseline risk factors may serve as a surrogate of risk, more precise noninvasive measurement of vascular disease might better identify a patient at increased risk for coxib-related adverse events^{28,29,30}. Our data support the recent American Heart Association scientific position statement³¹ suggesting that physicians should prescribe the lowest doses of celecoxib possible, especially in higher risk patients.

Our study followed previous analyses of safety data from the APC and PreSAP studies which, in total, had 90 cardiovascular outcomes contained in the primary composite outcome. The other four studies added a total of 63 events, 15 to the 400 mg qd dose, 39 to the 200mg dose group, and 9 to the 400 mg bid dose. For each of the four additional studies, the estimated hazard ratio for each dose is lower than the hazard ratios observed in the APC and PreSAP studies. While the APC trial stopped celecoxib use early because of an observed increase in cardiovascular risk, all participants – except a very few who were lost to follow-up – were followed for the full planned three years of the trial, and cardiovascular events were collected for that entire period. Therefore, the estimated hazard ratio associated with celecoxib use in the APC trial was an unbiased estimate of the true hazard ratio. Because the five other trials stopped celecoxib in response to the excess risk observed in the APC trial, the early stopping of drug administration in those trials also produce unbiased estimates of the hazard ratios. Of note,

our results differ from those reported by the ADAPT investigators¹⁴ because their primary outcome included transient ischemic attacks (TIAs) and excluded thromboembolic events, and the process of adjudicating outcomes differed in the two analyses. The primary outcome in our previous analyses had been cardiovascular death, myocardial infarction, stroke or heart failure. In designing this analysis, we prespecified a primary outcome that added thromboembolic event to the previous outcome; analysis using the previous primary outcome, or using a stricter ATPC endpoint excluding heart failure, showed qualitatively similar results.

Some additional limitations of our analyses should be noted. First, none of the trials included in this analysis was designed or powered with the intent of assessing cardiovascular risk. As a result, we used data collected for other purposes to assess the effect of celecoxib on cardiovascular outcomes. We must therefore be cautious in interpreting the results with regard to hazard or safety of particular doses, or with regard to extrapolation to doses not tested. Our method of assessing baseline cardiovascular risk was imprecise since we did not have identical baseline data for each study and we lacked more direct measures of vascular disease that could better predict risk.

While our data suggest an interaction with respect to baseline risk and celecoxib dose, we are limited by small numbers of events in the lowest risk groups, and therefore our estimates of risk lack precision. Indeed, even in the lowest risk groups, we cannot exclude as much as a 50% increased hazard in the 400mg qd dose group or as much as a nearly three-fold hazard in the 400mg bid dose group. Moreover, the majority of the long-term data came from a subset of trials so that our inferences are heavily influenced by ADAPT, APC, and PreSAP. The model that forms the basis of our main conclusions

assumes a linear relationship among the four dose regimens – placebo, 400 mg qd, 200 mg bid, and 400 mg bid; although other assumptions about the relationship among the regimens would lead to different estimated hazard ratios, we tested a number of models which all produced similar estimated hazard ratios. While we included heart failure in our composite endpoint in order to obtain an estimate of overall cardiovascular risk, we recognize that the mechanism for risk induced by heart failure – including fluid retention common to all non-steroidal anti-inflammatory agents – is likely distinct from the mechanisms that may underlie the thrombotic risk. The series of composite endpoints shown in table 4 demonstrate that the hazard ratios were similar whether or not heart failure was included.

In summary, a pooled analysis of six randomized trials comparing celecoxib to placebo, with over 16,000 patient-years of follow-up, shows an increase in cardiovascular risk associated with these tested doses, with evidence for differences in risk based on the dose regimen of celecoxib. Importantly, the data showed evidence of an interaction between baseline cardiovascular risk and the effect of celecoxib, suggesting that patients at highest baseline risk had an increased relative risk for celecoxib-related adverse cardiovascular events. Although the doses tested were higher than those used for the most common conditions for which celecoxib is prescribed, because celecoxib remains the only cox-2 inhibitor available to clinicians in the United States, these findings will help guide rational clinical decisions regarding celecoxib use.

Conflict of Interest Disclosures

Drs. Solomon, Wittes, Finn, Lance, Obara, Hawk, Viner, Meinert, Martin, Chew, Kim, Mr. Fowler, Ms. Arndt report no conflicts of interest with respect to this manuscript. Drs. Bertagnolli, Arber, Levin, Pater report research support from Pfizer. Dr. Levin reports receiving consulting honoraria from Pfizer. Dr. Goss reports receiving speaker's honorarium from Pfizer.

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Table 1. Description of each study in the Cross Trial Safety Analysis

Study	Sponsor	Description	Randomization / Dose	Stratification	Planned follow-up time
Adenoma Prevention with Celecoxib (APC)	NCI and Pfizer	Comparison of two doses of celecoxib to placebo for the prevention of colorectal adenoma recurrence	Celecoxib 200mg bid or celecoxib 400mg bid or placebo	Center; Low dose aspirin use	37 months
PreSAP	Pfizer	Comparison of celecoxib to placebo for the prevention of colorectal adenoma recurrence	Celecoxib 400mg qd or placebo	Country; Low dose aspirin use	37 months
MA27	NCI, NCI of Canada, and Pfizer	Factorial design comparing two aromatase inhibitors with or without celecoxib in post-menopausal women with breast cancer	Factorial Design: exemestane (2.5mg/ day) or anastrozole (1mg/day); celecoxib (400 mg bid) or placebo	Lymph node status at diagnosis; adjuvant chemotherapy; Low dose aspirin use	Participants would take celecoxib for 3 years after randomization but were to be followed until the study end which was the time of ending treatment with aromatase inhibitor.
ADAPT	NIA	Multi-center clinical trial comparing naproxen sodium, celecoxib, and placebo for the prevention of Alzheimer's disease and the attenuation of age-related cognitive decline	Naproxen sodium (220 mg bid), celecoxib (200 mg bid), or placebo	Field site; Age category: 70-74; 75-79; 80+	Up to 7 years
CDME	NEI	Factorial design comparing laser diode photocoagulation to focal photocoagulation and celecoxib or placebo for three months prior to and following laser coagulation	Celecoxib (200mg bid) or placebo .	None	Three years
The Celecoxib/Selenium Trial	NCI	Factorial design study comparing celecoxib to placebo and selenium to placebo for the prevention of colonic polyp recurrence	Factorial Design: Celecoxib (400 mg qd) or placebo; selenium (200 µg/day) or placebo	Clinical center; Low dose aspirin use	Three to five years after randomization. The planned length of follow-up depended on the recommendation by the participant's gastrointestinal physician for a follow-up colonoscopy.

Table 2. Common baseline characteristics across trials

Baseline characteristic	Study							Total N = 7950 16070 pt-years
	ADAPT N = 1809 3530 pt-years	APC N = 2035 6234 pt-years	CDME N = 86 101 pt-years	MA27 N = 1635 ¹ 695 pt-years	PreSAP N = 1561 4141 pt-years	Celecoxib/Selen ium N = 824 ² 1369 pt-years		
Age (years), mean (SD)	75 (4)	59 (10)	59 (9)	64 (9)	60 (10)	63 (9)	64 (10)	
Male, n (%)	979 (54)	1387 (68)	53 (62)	0	1035 (66)	559 (68)	4013 (50)	
Race								
White	1753 (97)	1863 (92)	58 (67)	1503 (94)	1392 (89)	778 (96)	7347 (93)	
Black	24 (1.3)	112 (5.5)	19 (22)	54 (3.4)	34 (2.2)	16 (2.0)	259 (3.3)	
Asian	8 (0.4)	15 (0.7)	3 (3.5)	26 (1.6)	96 (6.1)	12 (1.5)	160 (2.0)	
Other	22 (1.2)	45 (2.2)	6 (7.0)	8 (0.5)	39 (2.5)	4 (0.5)	124 (1.6)	
Diabetes	133 (7.4)	194 (9.5)	86 (100)	100 (6.1)	159 (10)	62 (7.5)	734 (9.2)	
HTN or on anti-HTN medication	725 (40)	834 (41)	53 (62)	561 (34)	582 (37)	297 (36)	3052 (38)	
Hyperlipidemia or on lipid-lowering medication	589 (33)	769 (38)	47 (55)	280 (17)	269 (17)	270 (33) ³	2224 (28)	
Current smoker	55 (3.0)	337 (17)	Not collected	Not collected	368 (24)	79 (16)	839 (14)	
Low-dose aspirin use	907 (50)	637 (31)	53 (62)	226 (14)	268 (17)	370 (45)	2461 (31)	
Prior CV event	232 (13)	292 (14)	1 (1.2)	113 (6.9)	198 (13)	116 (14)	952 (12)	
Low CV risk	261 (14)	491 (24)	0	820 (50)	506 (32)	154 (19)	2232 (28)	
Moderate CV risk	477 (26)	582 (29)	0	372 (23)	480 (31)	252 (31)	2163 (27)	
High CV risk	1071 (59)	962 (47)	86 (100)	443 (27)	575 (37)	418 (51)	3555 (45)	

Notes: Denominators are the number of participants with applicable data.

¹ Column header counts are the number of participants randomized through 12/22/2004.

² Column header counts are the number of participants randomized before 12/20/2004.

³ Based on any of the following lipid thresholds: total cholesterol \geq 240, LDL \geq 160, or total to HDL cholesterol ratio \geq 5.

⁴ Depending on the study, may include atherosclerotic heart disease, angina, cerebrovascular disease, CHF, MI, stroke, TIA, TE, or aortic valve disease.

⁵ Limited relevant medical history collected.

Table 3. Event rates per 1000 patient-years and pooled hazard ratios with 95% confidence intervals for the principal composite endpoint of cardiovascular death, myocardial infarction, stroke, heart failure, or thromboembolism for each individual trial, for each dose regimen, and for all the trials combined., adjusted for baseline cardiovascular risk

Study	Median follow-up time	Events/Participants		Event rate/ 1000 pt years		Hazard ratio	95% CI	Relative weight ^a
		Placebo	Celecoxib	Placebo	Celecoxib			
400 mg qd								
PreSAP	36	12/628	23/933	7.2	9.4	1.3	(0.6, 2.5)	7.9
Selenium/Celecoxib	21	8/410	7/414	11.8	10.3	0.9	(0.3, 2.4)	3.7
<i>Pooled 400 mg qd</i>	35	20/1038	30/1347	8.6	9.6	1.1	(0.6, 2.0)	
200 mg bid								
ADAPT	24	18/1083	18/726	8.6	12.8	1.5	(0.8, 2.9)	9.0
APC	37	8/679	20/685	3.9	9.7	2.5	(1.1, 5.7)	5.7
CDME	15	3/47	0/39	54.3	0.0	0.0	- ²	0.0
<i>Pooled 200mg bid</i>	36	29/1809	38/1450	6.9	10.8	1.8^b	(1.1, 3.1)^a	
400 mg bid								
<i>APC</i>	37	8/679	27/671	3.9	13.4	3.6	(1.6, 8.0)	6.2
MA27	5	3/817	6/818	8.7	17.2	1.8	(0.4, 7.3)	2.0
<i>Pooled 400 mg bid</i>	11	11/1496	33/1489	4.6	13.9	3.1	(1.5, 6.1)	
<i>Pooled all doses</i>	31	52/3664^d	101/4286	7.5	11.2	1.6^c	(1.1, 2.3)^c	

a. The relative weights are the inverses of the variances of the estimated log hazard ratios.

- b. The relative risk and 95% confidence intervals in the table exclude the CDME trial. Including it, but not adjusting for baseline cardiovascular risk, gives a hazard ratio of 1.8 and a 95% confidence interval of (1.1, 3.0).
- c. The relative risk and 95% confidence intervals in the table exclude the CDME trial. Including it, but not adjusting for baseline cardiovascular risk, gives the same hazard ratio and 95% confidence limits.
- d. The placebo group in the APC study is only counted once.

Table 4. Overall pooled event rates for the hierarchy of events.

Composite endpoint	Placebo			Celecoxib 400 mg QD			Celecoxib 200 mg bid			Celecoxib 400 mg bid		
	<i>N</i> = 3664 6943 pt-years			<i>N</i> = 1347 3159 pt-years			<i>N</i> = 1450 3563 pt-years			<i>N</i> = 1489 2404 pt-years		
	<i>n</i> (%)	Rate / 1,000 pt- years		<i>n</i> (%)	Rate / 1,000 pt- years	Hazard ratio* (95% CI)	<i>n</i> (%)	Rate / 1,000 pt- years	Hazard ratio* (95% CI)	<i>n</i> (%)	Rate / 1,000 pt- years	Hazard ratio* (95% CI)
Cardio/cerebrovascular (CV) death	13 (0.4)	1.9		5 (0.4)	1.6	0.5 (0.2, 1.7)	8 (0.6)	2.2	1.7 (0.6, 4.9)	6 (0.4)	2.5	2.7 (0.7, 10.2)
CV death or non-fatal MI	29 (0.8)	4.2		16 (1.2)	5.1	1.0 (0.5, 2.1)	24 (1.7)	6.8	1.9 (1.0, 3.5)	16 (1.1)	6.7	2.4 (1.1, 5.1)
CV death, non-fatal MI, or stroke	44 (1.2)	6.4		25 (1.9)	8.0	1.0 (0.6, 1.9)	28 (1.9)	7.9	1.4 (0.8, 2.5)	22 (1.5)	9.3	2.0 (1.1, 3.9)
CV death, non-fatal MI, stroke, or heart failure	46 (1.3)	6.7		28 (2.1)	8.9	1.2 (0.6, 2.1)	31 (2.1)	8.8	1.5 (0.9, 2.5)	26 (1.7)	11.0	2.2 (1.2, 4.0)
CV death, non-fatal MI, stroke, HF, or TE	52 (1.4)	7.5		30 (2.2)	9.6	1.1 (0.6, 2.0)	38 (2.6)	10.8	1.6 (1.0, 2.6)	33 (2.2)	13.9	2.5 (1.4, 4.4)
CV death, non-fatal MI, stroke, HF, TE, or angina	72 (2.0)	10.5		44 (3.3)	14.1	1.2 (0.8, 2.0)	49 (3.4)	14.0	1.6 (1.0, 2.3)	35 (2.4)	14.8	2.0 (1.2, 3.2)
CV death, non-fatal MI, stroke, HF, TE, angina, or CV procedure	91 (2.5)	13.3		54 (4.0)	17.4	1.3 (0.8, 2.0)	68 (4.7)	19.5	1.6 (1.1, 2.3)	44 (3.0)	18.7	1.9 (1.2, 2.9)
Any cardio/cerebrovascular event	144 (3.9)	21.2		73 (5.4)	23.7	1.3 (0.9, 2.0)	95 (6.6)	27.6	1.3 (1.0, 1.7)	65 (4.4)	27.9	1.6 (1.1, 2.3)

Notes: Within each row, follow-up is truncated at the first event. The column header pt-year counts reflect complete follow-up.

* Calculated using Cox regressions stratified by study and baseline aspirin use. Each dose group is estimated independently within one regression.

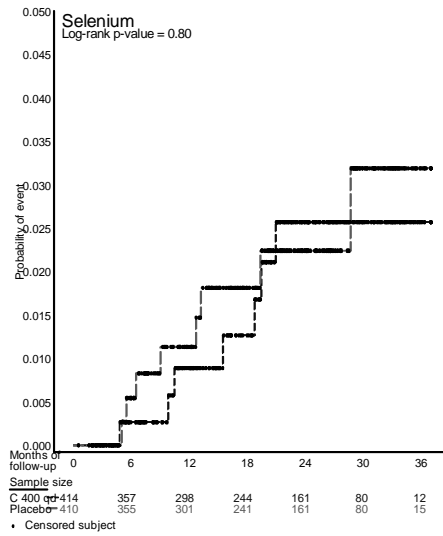
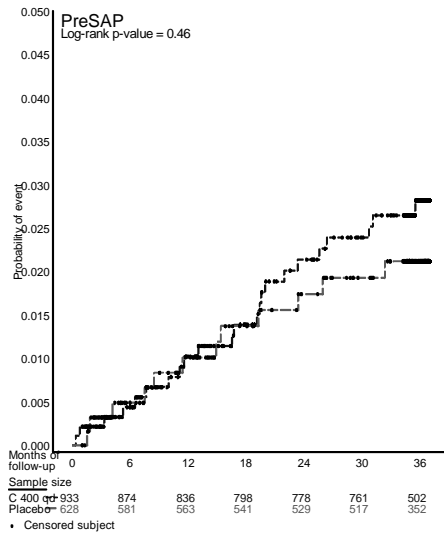
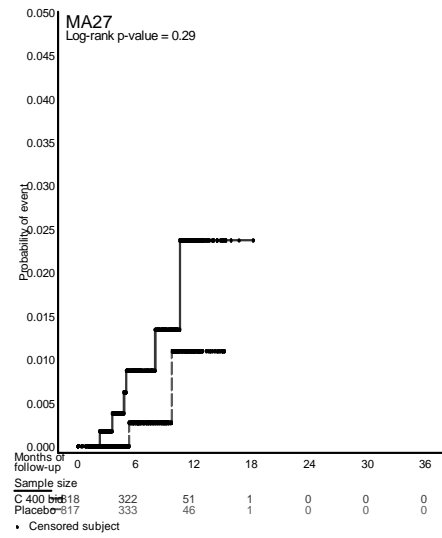
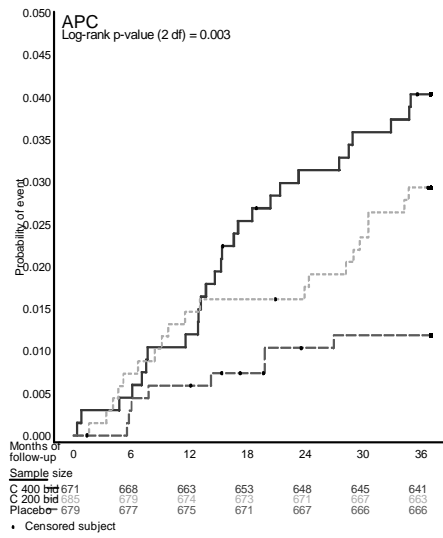
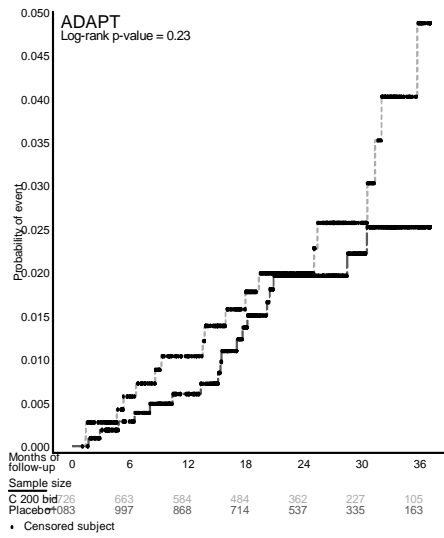
CV=cardio-cerebrovascular; MI=myocardial infarction; HF=heart failure; TE=thromboembolic event

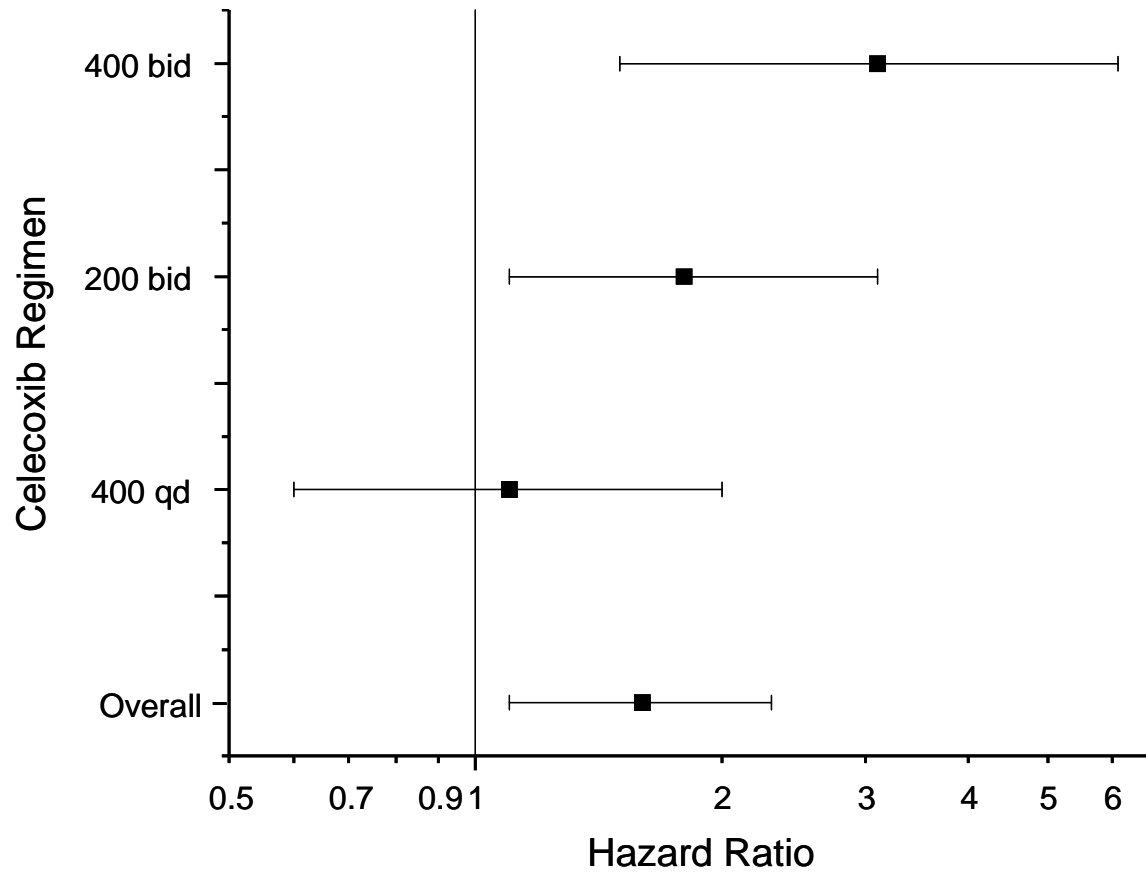
Figures

Figure 1. Kaplan-Meier curves for individual trials in ANALYSIS. Note CDME had too few events to plot.

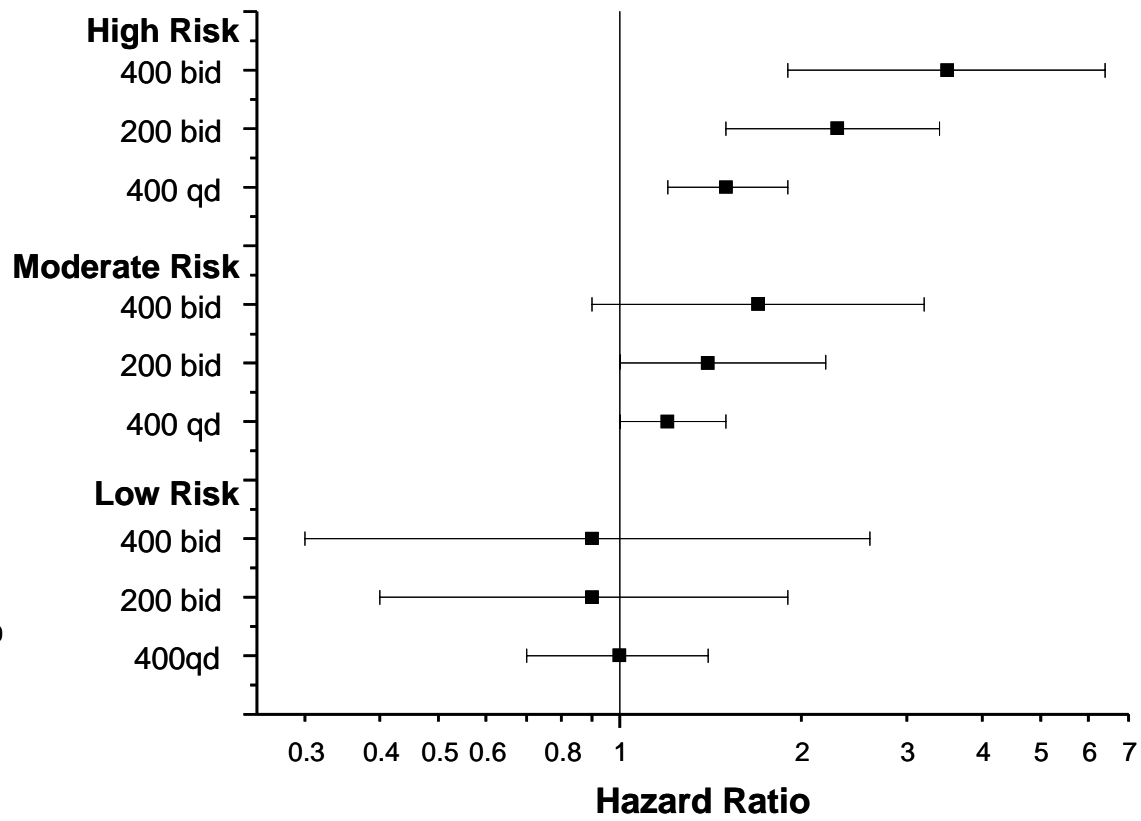
Figure 2. Hazard ratios for each dose-regimen and the combined overall hazard ratio with 95% confidence intervals.

Figure 3. Relationship between celecoxib dose, baseline cardiovascular risk and the principal combined outcome of cardiovascular death, myocardial infarction, stroke, heart failure or thromboembolic event.





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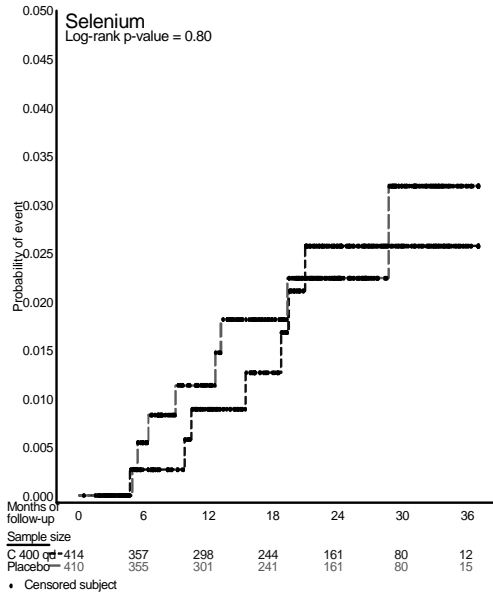
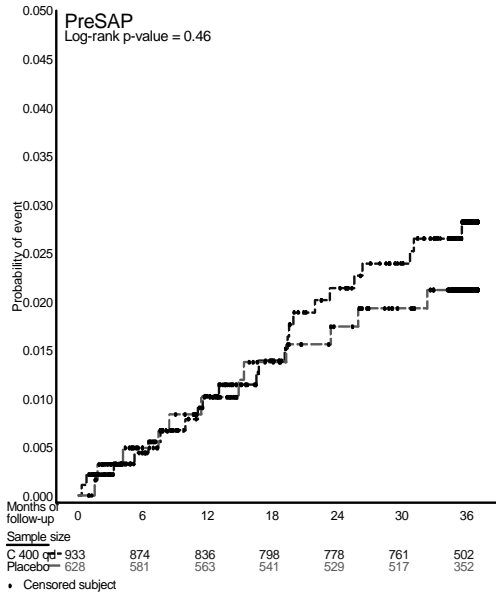
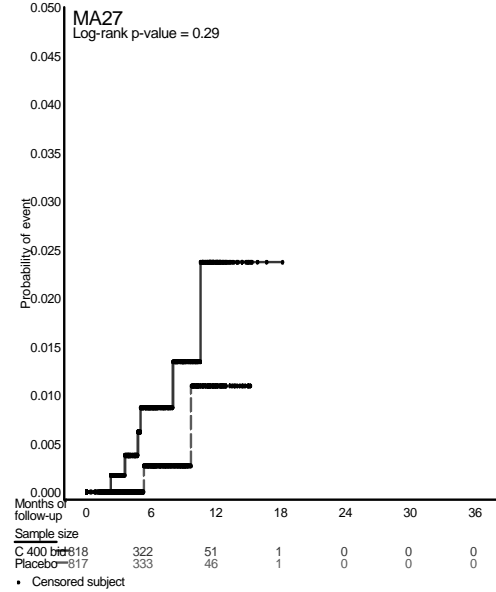
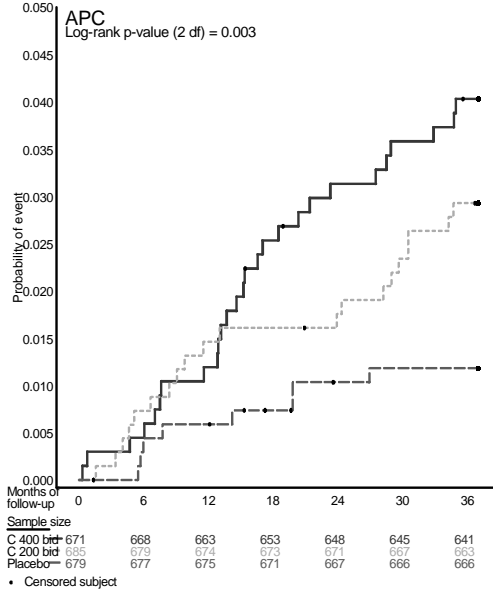
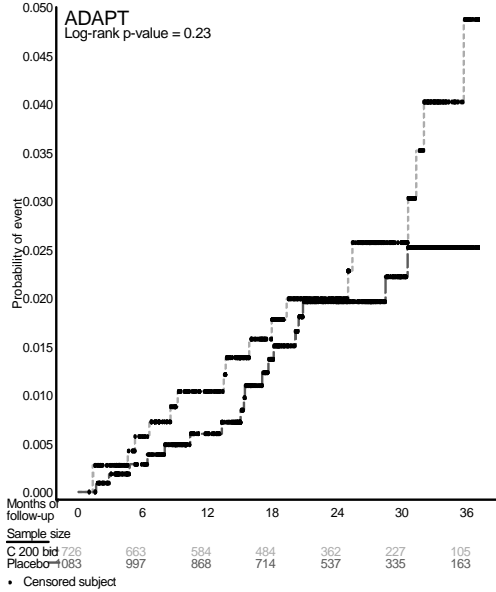
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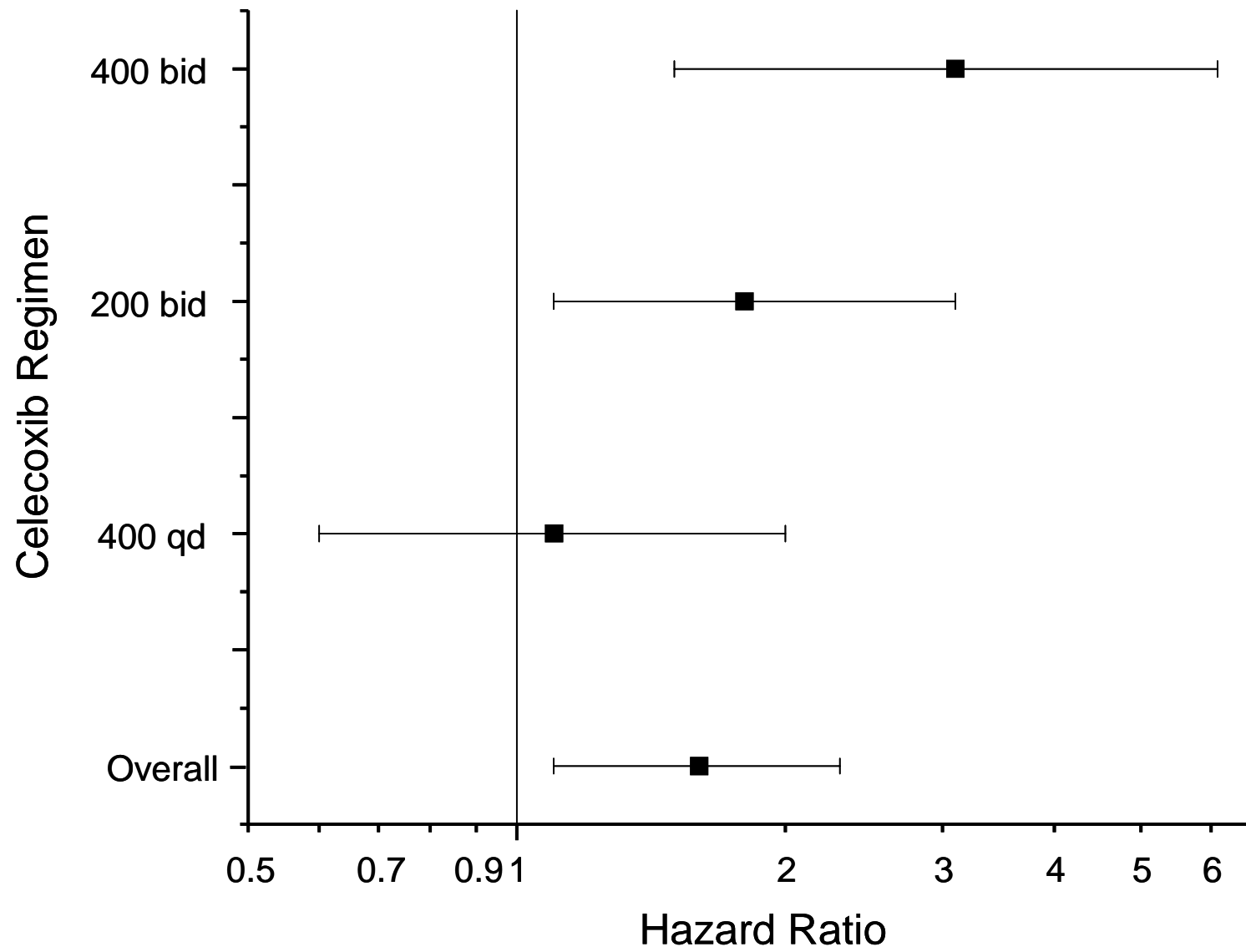
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