Drug Safety and Vioxx® Controversy

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Outline

- Drug safety
- Accelerated approval
- Development of COX2 selective inhibitors
- Vioxx® controversy
- Statistical issues in design and analysis
- Conclusion

Post-Marketing Safety Surveillance

- Adverse events (AEs) account for more than 100,000 deaths/year in the US
- Size of typical clinical trials prevents detection of all but the most common AEs prior to approval
- Over half of all new drugs have undetected serious toxicities at the time of FDA approval
- Many serious AEs not identified until after on market for several years

Inadequacy of RCTs for Assessment of Adverse Events

Hunter. N Engl J Med 2006;354:329-31.

- Trials powered for efficacy may be too small to detect adverse events.
- Monitoring of adverse events may not be sensitive or specific for the actual events caused.
- Stopping rules in clinical trials may further shorten the duration of exposure after randomization.
- Enrollment criteria may exclude susceptible subgroups.
- For industry-sponsored trials, head-to-head comparison of adverse events due to drugs from different manufacturers may not be available.
- Follow-up studies to detect adverse events that involve the denial of an efficacious medication to patients may be deemed unethical. Patients may not wish to enroll in such a study.
- Funding to conduct trials solely to quantify adverse events may be difficult to obtain.

The Drug Approval Pendulum

- "It just breaks my heart when I think of American citizens having to go to Switzerland or Mexico to get the drugs and devices they need to stay alive because the Washington bureaucracy won't approve them" – Rep. Thomas Bliley (R-VA), 1995

- "When the FDA approves a drug, it should be a Good Housekeeping seal of approval … Consumers shouldn't have to second-guess the safety of what's in their medicine cabinet." – Sen. Chuck Grassley (R-IA), 2005

Accelerated Approval

NEWS 12/08/1992

P92-37
FOR IMMEDIATE RELEASE

Food and Drug Administration
Monica Revelle - (301) 443-4177

The Food and Drug Administration today announced that it will soon publish new rules to speed the approval of drugs for patients with serious or life-threatening illnesses, such as AIDS, cancer and Alzheimer's disease.

"These final rules will help patients who are suffering the most serious illnesses to get access to new drugs months or even years earlier than would otherwise be possible," said HHS Secreatry Louis W. Sullivan, M.D. "The effort to accelerate FDA review for these drugs has been a long-term commitment and indeed a hallmark of this administration."

These rules establish procedures for the Food and Drug Administration to approve a drug based on "surrogate endpoints" or markers. They apply when the drug provides a meaningful benefit over currently available therapies. Such endpoints could include laboratory tests or physical signs that do not in themselves constitute a clinical effect but that are judged by qualified scientists to be likely to correspond to real benefits to the patient.

Use of surrogate endpoints for measurement of drug efficacy permits approval earlier than if traditional endpoints -- such as relief of disease symptoms or prevention of disability and death from the disease -- are used.

The new rules provide for therapies to be approved as soon as safety and effectiveness, based on surrogate endpoints, can be reasonably established. The drug's sponsor will be required to agree to continue or conduct

-MORE-

Challenges in AA

- Surrogate Endpoints
  - Validation based on both in-depth biological and clinical insights and empirical evidence
  - Effects on biological or disease markers would accurately predict if treatment truly provides clinical benefits
  - "A Correlate Does Not A Surrogate Make"
- Major difficulties enrolling patients in a post-marketing validation/safety study

Media's Reactions to AA

- Once 'too slow,' FDA approvals called 'too fast' – The Boston Globe, 4/10/05
- The Drug Approval Pendulum – Washington Post, 4/13/05

Influence from Industry

- Prescription Drug User Fee Act (PDUFA) 1992
- User fee charged to industry to augment FDA budget
  - $707 million from industry to FDA in 2011 alone, a quarter of FDA's total spending
- Decrease in the median approval time for standard: from 27 months in 1993 to 14 months in 2001
- Increase in drug recall: from 1.56% for 1993-1996 to 5.35% for 1997-2001

COX2 Selective Inhibitors

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Effective in arthritis, dysmenorrhea and headache
  - Long-term use limited by gastrointestinal (GI) effects: dyspepsia, abdominal pain and gastric/duodenal perforation or bleeding
- GI effects believed to be due to cyclooxygenase 2 (COX2) enzyme
- Development of the coxibs to address the undesirable therapeutic profiles, i.e. side effects
- First generation COX2 selective inhibitors:
  - Celebrex® (celecoxib)
  - Vioxx® (rofecoxib)

Selectivity of COX2 inhibition

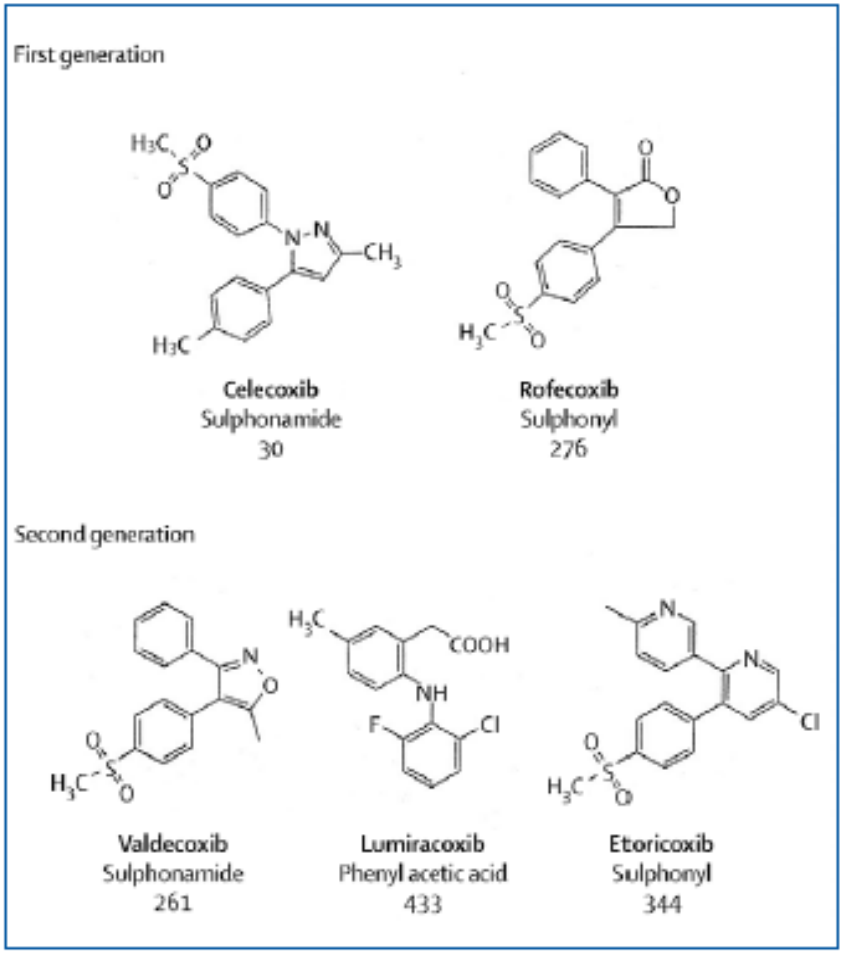


Figure: **Molecular structure of first and second generation coxibs**
Name and type of structure given. Number corresponds to quantification of COX2:COX1 selectivity.

Topol EJ, Falk GW. Lancet 2004;364:639-40.

THE UNIVERSITY of WISCONSIN MADISON

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20-998

Trade Name: CELEBREX

Generic Name:(celecoxib)

Sponsor: G.D. Searle

Approval Date: December 31, 1998

Indication: Provides for the use of CELEBREX (celecoxib capsules) 100mg and 200 mg for the signs and symptoms of osteoarthritis and rheumatoid arthritis.

THE UNIVERSITY of WISCONSIN MADISON

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 021042 and 021052

Trade Name: VIOXX TABLETS 12.5 MG and 25 MG, VIOXX ORAL SUSPENSION 12.5 MG/mL and 25MG/mL

Generic Name: ROFECOXIB TABLETS AND ORAL SUSPENSION

Sponsor: MERCK RESEARCH LABORATORIES

Approval Date: 05/20/99

INDICATION(s): FOR RELIEF OF SIGNS AND SYMPTOMS OF OSTEOARTHRITIS, THE MANAGEMENT OF ACUTE PAIN, AND THE TREATMENT OF PRIMARY DYSMENORRHEA.

Vioxx®

- History of its development
- Thrombotic cardiovascular adverse events
- The Adenomatous Polyp PRevention On Vioxx (APPROVe) Trial
- Statistical Issues: Design and analysis
  - Period of follow-up
  - Proportional hazards assumption
  - Exposure on interpretation of hazard

Vioxx® Timeline

- Nov 1998: New Drug Application (NDA) submitted to the US FDA based on data from ~5,400 osteoarthritis patients from eight double-blind, randomized and controlled studies
- Jan 1999: VIoxx Gastrointestinal Outcomes Research (VIGOR) trial initiated
- May 1999: Approved by FDA
- Feb 2000: APPROVe enrollment began
- Nov 2000: VIGOR reported in N Engl J Med. 2000 Nov 23;343(21):1520-8.
- Nov 2001: APPROVe enrollment completed

Vioxx® Timeline

- Apr 2002: Vioxx In Colorectal Cancer Therapy: definition of Optimal TheRapy (VICTOR) enrollment begins
- May 2002: First lawsuit filed against Merck
- Jun 2003: Vioxx in Prostate Cancer (ViP) enrollment began
- Sep 2004: APPROVe Data and Safety Monitoring Board recommends termination based on increase in cardiovascular (CV) risks
- Sep 2004: APPROVe, ViP and VICTOR terminated early
- Sep 2004: Voluntarily withdrawn from the market
- Nov 2007: $4.85 billion settlement reached with 47,000 plaintiff groups involving 26,600 lawsuits after 12 verdicts in favor of and 5 against Merck

News Release

Media Contact: Anita Larsen (908) 423-6022

Investor Contact: Michael Rabinowitz (908) 423-5185

Merck Announces Voluntary Worldwide Withdrawal of VIOXX®

WHITEHOUSE STATION, N.J., Sept. 30, 2004 – Merck &. Co., Inc. today announced a voluntary worldwide withdrawal of VIOXX® (rofecoxib), its arthritis and acute pain medication. The company's decision, which is effective immediately, is based on new, three-year data from a prospective, randomized, placebo-controlled clinical trial, the APPROVe (Adenomatous Polyp Prevention on VIOXX) trial.

The trial, which is being stopped, was designed to evaluate the efficacy of VIOXX 25 mg in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas. In this study, there was an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in the patients taking VIOXX compared to those taking placebo. The results for the first 18 months of the APPROVe study did not show any increased risk of confirmed cardiovascular events on VIOXX, and in this respect, are similar to the results of two placebo-controlled studies described in the current U.S. labeling for VIOXX.

The New York Times
nytimes.com

November 9, 2007

Merck Agrees to Pay $4.85 Billion for Vioxx Claims

By ALEX BERENSON

Three years after withdrawing its pain medication Vioxx from the market, Merck announced today that it will pay $4.85 billion to settle 27,000 lawsuits by people who contend they or their family members suffered injury or died after taking the drug.

The settlement, one of the largest ever in civil litigation, comes after nearly 20 Vioxx civil trials over the last two years from New Jersey to California. After losing a $253 million verdict in the first case, Merck has won most of the rest of the cases that reached juries, giving plaintiffs little choice but to settle.

The settlement will help put Vioxx behind Merck, as well as sharply reduce its Vioxx-related legal defense fees, which are now running at more than $600 million annually.

Judges in Louisiana, New Jersey and California, who oversee nearly all the lawsuits, had pressed for a deal before a new wave of trials was scheduled to begin in January.

The APPROVe Trial

- A multi-center, randomized, placebo-controlled, double-blind study designed to evaluate the efficacy of 156 weeks (three years) of treatment with Vioxx® 25 mg in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas, a precursor to colorectal cancer
- 2,586 patients randomized
- Follow-up for AEs terminated 14 days after off-treatment
- Bresalier et al. N Engl J Med 2005 Mar 17;352(11): 1092-102.

Analysis of CV Data

- No statistical analysis plans for the thrombotic CV data from APPROVe alone
- Merck planned to combine the CV data from APPROVe with data from two other placebo-controlled studies, VICTOR and ViP
- Given the decision to stop APPROVe early, its CV data were analyzed separately

The New York Times
nytimes.com

May 22, 2006

Why the Data Diverge on the Dangers of Vioxx

By ANDREW POLLACK and REED ABELSON

Eighteen months.

Ever since Merck pulled its arthritis painkiller Vioxx off the market in September 2004 on evidence that it could cause strokes or heart attacks, the company and its lawyers have stood by the premise that it was dangerous only to patients who took it for at least 18 months.

So it was news last week when prominent medical experts said that new data from Merck indicated that Vioxx's risks started to emerge after only four months of use. The controversy is the latest illustration of how widely open to interpretation and potential corporate pressure the results of clinical trials can be — even when reported in a leading medical journal.

Critics say it is now clear that the previous data analysis was done in a way that minimized the risks of the drug. Some also say that Merck and its academic collaborators should have known about that four-month threshold and made the earlier risks clearer in a medical journal article in March 2005.

It was the first scientific report of the clinical trial results that had prompted the company to withdraw the drug. That article, in The New England Journal of Medicine, concluded: "The increased relative risk became apparent after 18 months of treatment."

The New York Times

May 22, 2006

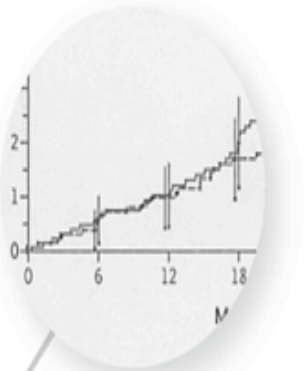
A Second Look

Merck has long contended that its painkiller Vioxx did not pose significant risks of strokes or heart attacks unless a person took the drug for at least 18 months, as the first chart, published in March 2005 in The New England Journal of Medicine indicates. But in a more recent look at the data, which the company recently submitted to the Food and Drug Administration as part of a follow-up study, Vioxx's risks seem to begin showing up after only about four months of use. Merck says the difference is insignificant, but some critics say otherwise.

The first study

Published March 17, 2005

In this study, patients taking Vioxx begin to show a consistently higher rate of cardiovascular problems than those who took a placebo at about 18 months . . .



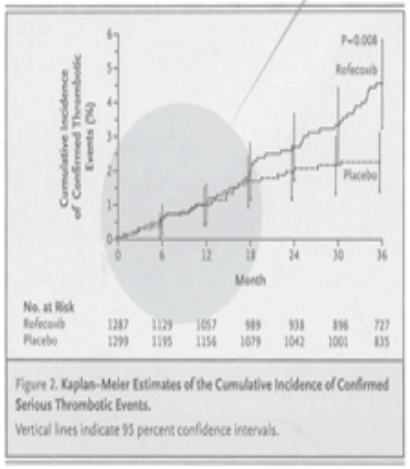


Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of Confirmed Serious Thrombotic Events.

Vertical lines indicate 95 percent confidence intervals.

These two charts show:

VERTICAL SCALE

The cumulative percentage of patients taking rofecoxib (the chemical name for Vioxx) who had heart attacks, strokes or other so-called thrombotic events.

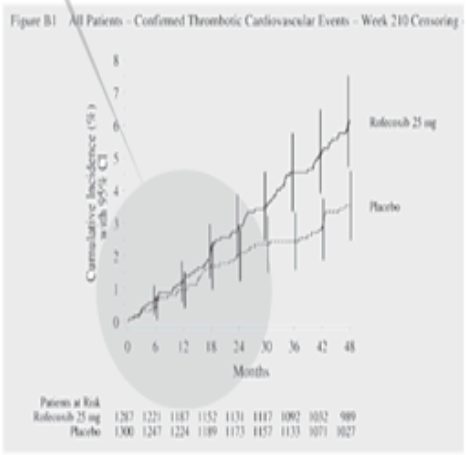
HORIZONTAL SCALE

Time since patients took their first dose of the drug, in months

A more recent study

Submitted this month

. . . but in this chart, patients taking Vioxx show higher rates of cardiovascular problems beginning at about four months.



Perspective
JULY 13, 2006

STATISTICS AND MEDICINE

Time-to-Event Analyses for Long-Term Treatments — The APPROVe Trial

Stephen W. Lagakos, Ph.D.

The Adenomatous Polyp Prevention on Vioxx (APPROVe) trial[1] compared rofecoxib with placebo in the prevention of recurrent colorectal polyps, but the researchers also collected data on adverse cardiovascular events, including confirmed serious thrombotic events. Assessment of the cardiovascular data raises important issues about the analysis and interpretation of a time-to-event end point in a randomized, placebo-controlled trial evaluating a long-term treatment. These issues include the appropriate period of follow-up for safety outcomes after the discontinuation of treatment; the purpose and implications of checking the assumption of proportional hazards, which underlies the commonly used log-rank test and Cox model; and what the results of a trial examining long-term use imply about the safety of a drug if it were given for shorter periods.

With regard to the first issue, the distribution of the time to an event is described by the cumulative incidence function, I(t), which for every time t after the start of treatment gives the cumulative probability that the event occurred in a patient. I(t) is usually estimated by the Kaplan–Meier method.

Time-to-event analyses of a safety end point sometimes count only events that occur during the scheduled treatment period, T_s, or during a limited window of time afterward, T_w. For example, in the APPROVe trial, T_s was 36 months and T_w was 14 days, so data on cardiovascular events were scheduled to be collected for a total of 36 months and 14 days after the initiation of treatment. There are several reasons why using such windows might be desirable. First, events occurring during treatment or the subsequent window period might be the most relevant clinically for assessing the safety of the treatment. Second, any increased risk attributable to the treatment might diminish shortly after the discontinuation of treatment, so the power of the log-rank or Cox test might be diluted if events that occurred after the window period were counted. And third, patients might receive other therapy after the discontinuation of the study treatment that could affect their risk of a safety end point.

Two important considerations are the length of T_w and the duration of follow-up for patients who discontinue treatment prematurely. Suppose that all patients continue to receive treatment until the end of the scheduled period

Lagakos SW. N Engl J Med 2006;355:113-7.

Disclaimer

I have a great subject [statistics] to write upon, but feel keenly my literary incapacity to make it easily intelligible without sacrificing accuracy and thoroughness.

— Sir Francis Galton

Statistical Issues

- Period of follow-up after off-treatment
- Proportional hazards assumption
  - Log-rank test and Cox models
- Exposure on interpretation of hazard
- All three issues hightened by litigations

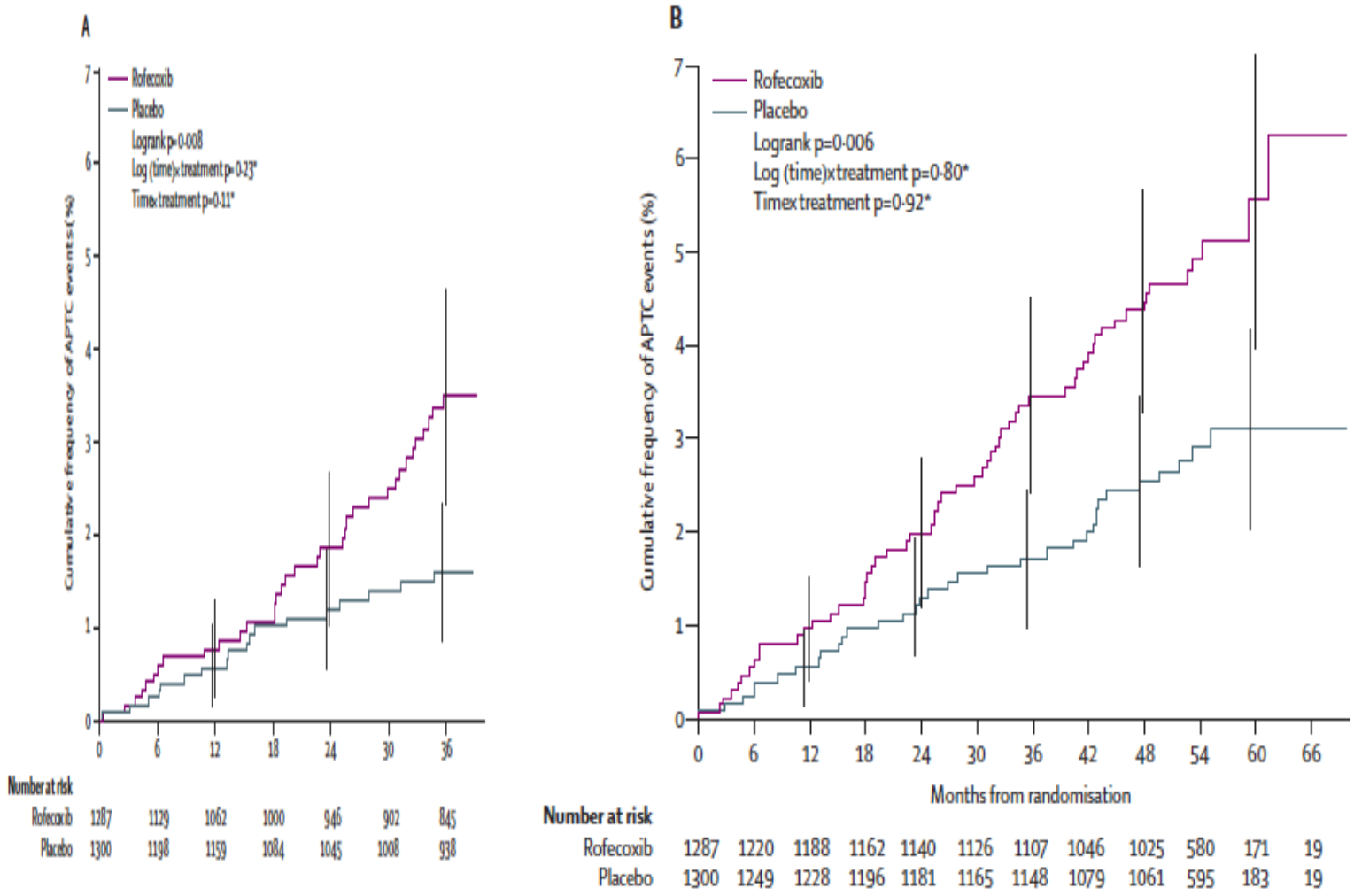
Follow-Up after Off-Treatment

- CV events collected for a total of up to T_s=36 months plus T_w=14 days after going off-treatment
  - Most relevant clinically for safety
  - Any increased risk attributable to the treatment might diminish shortly after off-treatment
  - Other therapy after off-treatment
- Might cause a real difference to be obscured by the differential exclusion of events that occur after the 14-day window
- Premature discontinuation due to adverse events may bias the Kaplan-Meier estimates
  - 32% on rofecoxib *vs* 25% on placebo

Follow-Up after Off-Treatment

- Issues of censoring with follow-up for events
  - The primary analysis for on-drug through 14 days post off-treatment
  - A common practice in many disease trials
- Two off-treatment extension analyses
  - Same follow-up time
    - CV events through week 210 for each patient
    - Freedman LS. Stat Med. 1982 Apr-Jun;1(2):121-9.
  - Same calendar follow-up termination (variable follow-up time)
    - CV events through 31 October 2005
    - Common practice in cancer clinical trials

APPROVe Final Results



Baron et al. Lancet. 2008 Nov 15;372(9651):1756-64.

Proportional Hazards Assumption

- Tested to determine whether a non-significant difference might have been due to a treatment effect that does not satisfy the assumption
- Cumulative incidence curves diverge throughout
  - Constancy of treatment effect over time
- Initially reported linear time by treatment interaction (p=0.01)
  - Claimed that the cumulative incidence rates were equivalent for the first 18 months
- Later corrected based on logarithm of time by treatment interaction (p=0.07)

Proportional Hazards Assumption

- The estimated relative risk based on the Cox model represents a time-averaged hazard ratio and thus may not adequately describe the difference when the proportional hazards assumption does not hold
- Confidence bands for the excess risk to capture the difference between the two groups
- Many plausible differences (Fig. 1)
  - A separation of the curves at times both before and after 18 months
  - A consistently higher or lower cumulative incidence on rofecoxib before 18 months

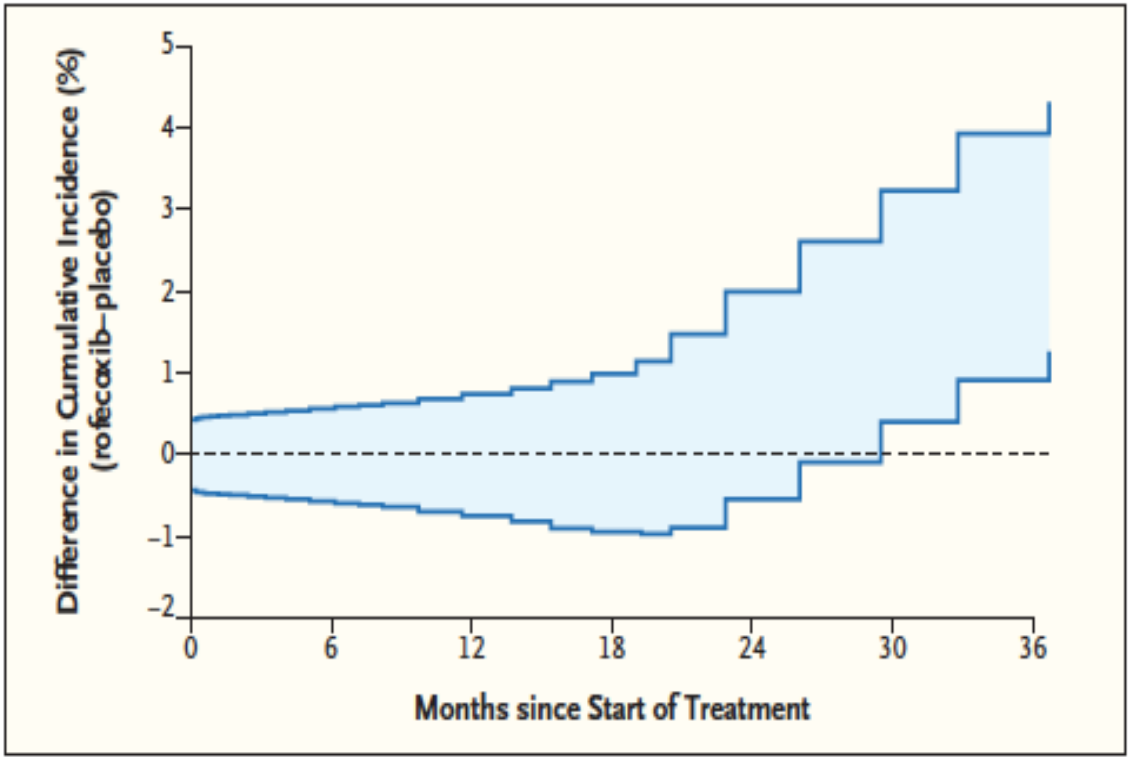


Figure 1. Hypothetical 95 Percent Confidence Band for the Difference, $I_{36}(t) - I_p(t)$, between the Cumulative Incidence Curves for the Rofecoxib (I_{36}) and Placebo (I_p) Groups, Constructed from the Results of the APPROVe Trial.

Differences lying partly or completely outside the shaded region are inconsistent with the data. Differences lying wholly within the shaded region include the following: separation of the cumulative incidence curves in the two groups at times both before and after 18 months, and consistently higher or lower cumulative incidence in the rofecoxib group before 18 months.

Exposure on Interpretation of Hazard

- Implications of analyses of long-term use (36 months) for the safety of shorter-term use (say 12 months due to adverse events)
- The initial APPROVe results misinterpreted to mean that treatment with rofecoxib for less than 18 months poses no excess CV risk
- Let $I_{12}(t)$, $I_{36}(t)$and $I_p(t)$ denotes the cumulative incidence functions for 12 and 36-mo course and for placebo
- Under the monotonicity assumption when the 36-mo course increases risk
  - $I_p(t) \leq I_{12}(t) \leq I_{36}(t)$, $t \geq 0$

Exposure on Interpretation of Hazard

- Suppose $I_{36}(t)$ and $I_p(t)$ are known and the same for $t \leq 18$ mo and diverge afterwards
- Given the monotonicity assumption (Fig. 2),
  - $I_{12}(t) \equiv I_p(t)$, $t \leq 18$
  - $I_p(t) \leq I_{12}(t) \leq I_{36}(t)$, $t > 18$
- The excess risk, $I_{12}(t) - I_p(t)$, associated with a 12-mo course (Fig. 3)
- One cannot rule out that a shorter course of rofecoxib increases CV risk

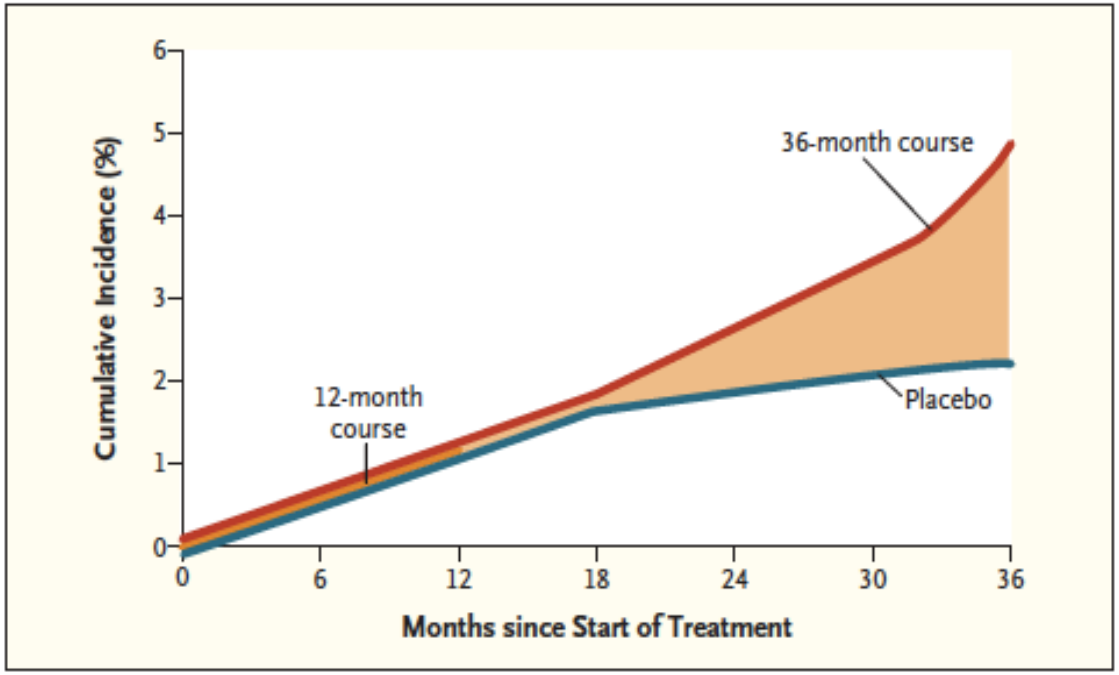


Figure 2. Logical Inferences about the Cumulative Incidence Function, $I_{12}(t)$, for a 12-Month Course of Rofecoxib, Based on Known Values for $I_{36}(t)$ and $I_p(t)$ That Are Identical for 18 Months before Diverging.

If monotonicity is assumed, so that $I_p(t) \leq I_{12}(t) \leq I_{36}(t)$, then $I_{12}(t)$ must equal $I_p(t)$ for first 18 months and be somewhere in the shaded region after 18 months. The lower edge of the shaded region corresponds to the absence of an increased risk with the 12-month course; all other scenarios in the shaded region correspond to an excess risk with the 12-month course that occurs only after the discontinuation of treatment. If monotonicity is not assumed, nothing can be inferred about $I_{12}(t)$ beyond month 12; however, the 12- and 36-month courses are identical for the first 12 months, so that, all other things being equal, $I_{12}(t)$ must equal $I_{36}(t)$, and thus $I_p(t)$, through month 12. Although drawn as separate curves to be visually informative, the inferences are based on the assumption that the cumulative incidence functions overlap for the first 18 months.

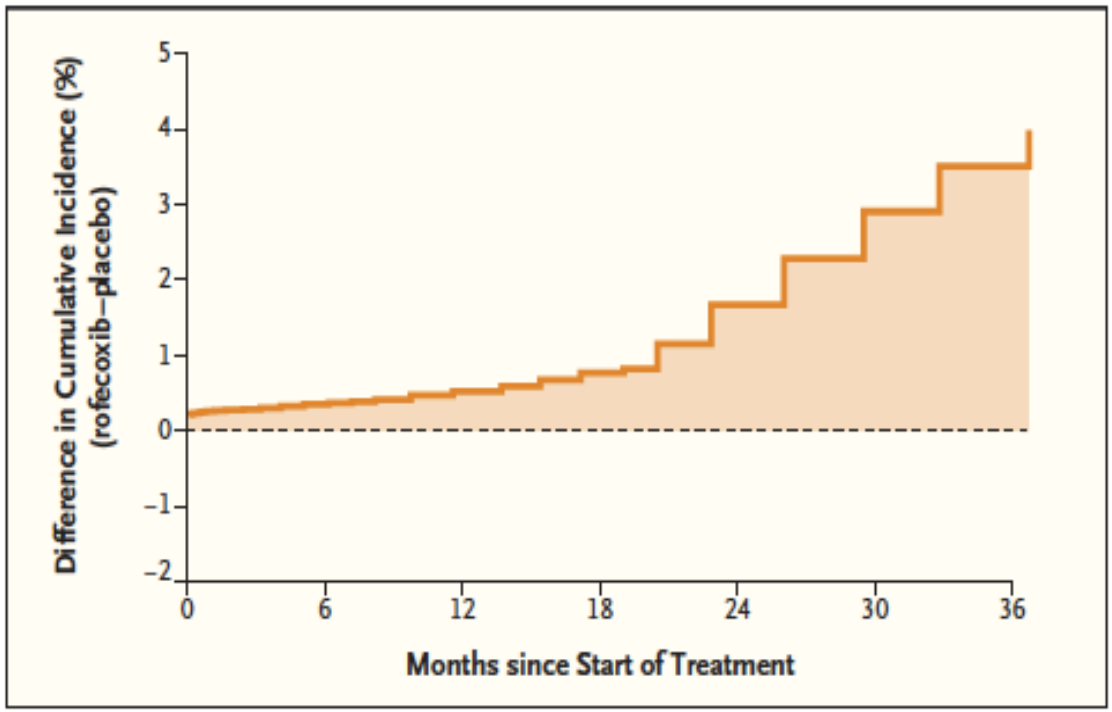


Figure 3. Statistical Inferences about the Excess Risk, $I_{12}(t) - I_p(t)$, Associated with a 12-Month Course of Rofecoxib, Based on the Hypothetical Results of a Trial Comparing a 36-Month Course of Rofecoxib with Placebo.

The upper edge of the shaded region represents an upper 95 percent bound for $I_{36}(t) - I_p(t)$, constructed from the trial results. If monotonicity is assumed, this edge also represents an (at least) 95 percent upper bound for $I_{12}(t) - I_p(t)$. The assumption of monotonicity also implies that $I_{12}(t) - I_p(t) \geq 0$, so that the shaded region represents an (at least) 95 percent confidence band for $I_{12}(t) - I_p(t)$. If monotonicity is not assumed, nothing can be inferred about $I_{12}(t) - I_p(t)$ beyond month 12; however, since the 12- and 36-month courses are identical for the first 12 months, the first 12 months of the confidence band in Figure 1 also represents, all other things being equal, a confidence band for $I_{12}(t) - I_p(t)$ over this period.

Conclusion

- Drug safety a vexing and difficult problem
- A rigorous post-marketing surveillance system and an investment in clinical informatics
- No short-term solutions
  - Biology is one thing
  - Clinical science is another matter altogether
- National investment necessary
  - US system haphazard
  - UK's NHS model
- Many challenges in time-to-event analysis
  - Proportional hazards assumption