JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

Applied Examples of Drug Safety Research

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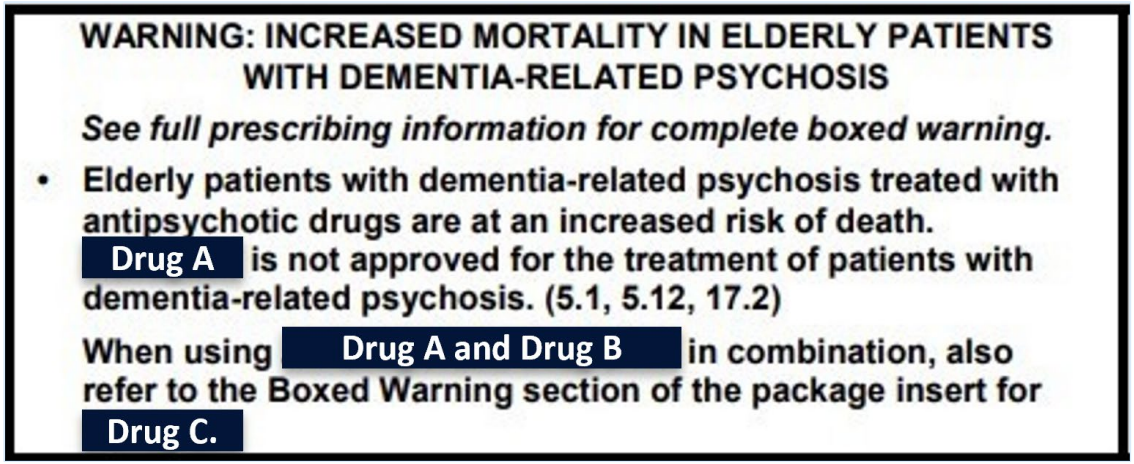
Contents

Example: Adverse Events and Boxed Warnings

Boxed Warnings (Formally Known as Black Box Warnings)



WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Drug A is not approved for the treatment of patients with dementia-related psychosis. (5.1, 5.12, 17.2)**

When using Drug A and Drug B in combination, also refer to the Boxed Warning section of the package insert for Drug C.

- The highest safety-related warning from the U.S. Food and Drug Administration (FDA) that medications can have since 1979
- The name originates from the prominent black border surrounding FDA-specified cautionary information on drug labels
- A definite causal connection need not be established

Sources:

Greiwe, J., Honsinger, R., Hvisdas, C., Chu, D. K., Lang, D. M., Nicklas, R., & Apter, A. J. (2022). Boxed warnings and off-label use of allergy medications: Risks, benefits, and shared decision making. *The Journal of Allergy and Clinical Immunology. In Practice*, *10*(12), 3057–3063. https://doi.org/10.1016/j.jaip.2022.08.033

Downing, N. S., Shah, N. D., Aminawung, J. A., Pease, A. M., Zeitoun, J.-D., Krumholz, H. M., & Ross, J. S. (2017). Postmarket safety events among novel therapeutics approved by the US Food and Drug Administration between 2001 and 2010. *JAMA*, *317*(18), 1854–1863. https://doi.org/10.1001/jama.2017.5150

Image source: Adapted from ZYPREXA (olanzapine) Label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020592s062021086s040021253s048lbl.pdf

Boxed Warnings

- Reasonable evidence of an association of a serious hazard with the drug
- The boxed warning is usually based on postmarketing and premarketing clinical data, but serious animal toxicity may also lead to a boxed warning when there are not clinical data
- Usually, the boxed warning is located at the beginning of the labeling
- The FDA can mandate it for prescription drugs
- Medications can have boxed warning added, taken away, or updated

Boxed Warning Process

What Will Happen After a Boxed Warning?

- The FDA does not regulate the practice of medicine
- It is up to the individual physician to make the clinical decision to prescribe or not to prescribe a drug with a boxed warning, after risk/benefit consideration

Example of a Drug Safety Study (Keane et al., 2001)

The New England Journal of Medicine

TUBERCULOSIS ASSOCIATED WITH INFLIXIMAB, A TUMOR NECROSIS FACTOR α–NEUTRALIZING AGENT

JOSEPH KEANE, M.D., SHARON GERSHON, PHARM.D., ROBERT P. WISE, M.D., M.P.H., ELIZABETH MIRABILE-LEVENS, M.D., JOHN KASZNICA, M.D., WILLIAM D. SCHWIETERMAN, M.D., JEFFREY N. SIEGEL, M.D., AND M. MILES BRAUN, M.D., M.P.H.

Source: Keane, J., Gershon, S., Wise, R. P., Mirabile-Levens, E., Kasznica, J., Schwieterman, W. D., Siegel, J. N., & Braun, M. M. (2001). Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *The New England Journal of Medicine*, *345*(15), 1098–1104. https://doi.org/10.1056/NEJMoa011110.

Infliximab (Remicade)

- A humanized monoclonal antibody against tumor necrosis factor α (TNF-α)
- The FDA approved infliximab in 1998 for the treatment of Crohn's disease and in 1999 for the treatment of rheumatoid arthritis
- In 2001:
  - Approximately 147,000 patients throughout the world had received infliximab
  - In the United States, 45,000 patients and 76,000 patients had received infliximab for rheumatoid arthritis and Crohn's disease, respectively

Source: Keane, J., Gershon, S., Wise, R. P., Mirabile-Levens, E., Kasznica, J., Schwieterman, W. D., Siegel, J. N., & Braun, M. M. (2001). Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *The New England Journal of Medicine*, *345*(15), 1098–1104. https://doi.org/10.1056/NEJMoa011110.

Image source: Johnson & Johnson.

Safety Concerns in Infliximab: Risk of Tuberculosis

- In animal models, TNF-α is important in the host response against tuberculosis (e.g., granuloma formation and containment of disease)
- Antibodies against TNF-α reactivate tuberculosis in a mouse model of latent tuberculosis infection
- However, the role of TNF-α in human immune response to tuberculosis was unclear

Source: Keane, J., Gershon, S., Wise, R. P., Mirabile-Levens, E., Kasznica, J., Schwieterman, W. D., Siegel, J. N., & Braun, M. M. (2001). Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *The New England Journal of Medicine*, *345*(15), 1098–1104. https://doi.org/10.1056/NEJMoa011110.

One Case of Tuberculosis After Infliximab Therapy in a Clinical Trial (Maini et al., 1999)

- In a phase III randomized clinical trial, 340 patients with active rheumatoid arthritis received infliximab, versus 88 who received placebo
- During the 30-week trial, there were no tuberculosis cases
- In the continuing second 6 months of the trial, one patient on infliximab developed tuberculosis
  - Disseminated tuberculosis
  - Died despite treatment with antituberculosis drugs

Source: Maini, R., St Clair, E. W., Breedveld, F., Furst, D., Kalden, J., Weisman, M., Smolen, J., Emery, P., Harriman, G., Feldmann, M., & Lipsky, P. (1999). Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: A randomised phase III trial. ATTRACT Study Group. *Lancet (London, England)*, *354*(9194), 1932–1939. https://doi.org/10.1016/s0140-6736(99)05246-0

Methods (Keane et al., 2001)—1

- Data from the U.S. FDA's Adverse Event Reporting System (AERS)
  - Spontaneous reports of suspected adverse drug reactions through the MedWatch program and pharmaceutical manufacturers
  - 70 reports of tuberculosis with infliximab between infliximab's approval (August 24, 1998) and May 29, 2001
- Patients were included if during or after treatment with infliximab, they had received a diagnosis of tuberculosis based on clinical, radiological, and laboratory findings

Source: Keane, J., Gershon, S., Wise, R. P., Mirabile-Levens, E., Kasznica, J., Schwieterman, W. D., Siegel, J. N., & Braun, M. M. (2001). Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *The New England Journal of Medicine*, *345*(15), 1098–1104. https://doi.org/10.1056/NEJMoa011110.

Methods (Keane et al., 2001)—2

- The researchers evaluated whether preexisting latent infection with *Mycobacterium tuberculosis* (i.e., a prior positive tuberculin skin test) was present in each case report
- Lung-tissue samples from the index patient treated with infliximab were compared with archival lung tissue from a patient with tuberculosis who had not received an anti–TNF-α agent
- Samples were examined for the presence of TNF-α–mediated apoptosis, a feature of normal granulomatous response to tuberculosis in the absence of an anti–TNF-α agent

Source: Keane, J., Gershon, S., Wise, R. P., Mirabile-Levens, E., Kasznica, J., Schwieterman, W. D., Siegel, J. N., & Braun, M. M. (2001). Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *The New England Journal of Medicine*, *345*(15), 1098–1104. https://doi.org/10.1056/NEJMoa011110.

Characteristics of 70 Patients With Tuberculosis After Infliximab (Keane et al., 2001)—1

Characteristic	Value
Age, years, median (range)	57 (18–83)
Female	32 (45%)
Indication	
Crohn's disease	18 (26%)
Rheumatoid arthritis	47 (67%)
Other	5 (7%)
Recent immunosuppressant use	55 (79%)
Interval between first dose of infliximab and diagnosis, weeks, median (range)	12 (1–52)
Recent exposure to tuberculosis	2 (3%)
History of tuberculosis infection of disease	8 (11%)
Report from countries with a low incidence* of tuberculosis	64 (91%)

* <20 cases per 100,000 population per year.

Source: Keane, J., Gershon, S., Wise, R. P., Mirabile-Levens, E., Kasznica, J., Schwieterman, W. D., Siegel, J. N., & Braun, M. M. (2001). Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *The New England Journal of Medicine*, *345*(15), 1098–1104. https://doi.org/10.1056/NEJMoa011110.

Characteristics of 70 Patients With Tuberculosis After Infliximab (Keane et al., 2001)—2

Characteristic	Value
Clinical manifestation of disease	
Pulmonary	22 (31%)
Extrapulmonary, not disseminated	23 (33%)
Extrapulmonary, disseminated*	17 (24%)
Not reported	8 (11%)

57% extrapulmonary

*Forms of tuberculosis that are associated with marked immunosuppression

- In comparison, among tuberculosis cases that are not associated with HIV infection, 18% accounts for extrapulmonary disease and <2% accounts for disseminated disease

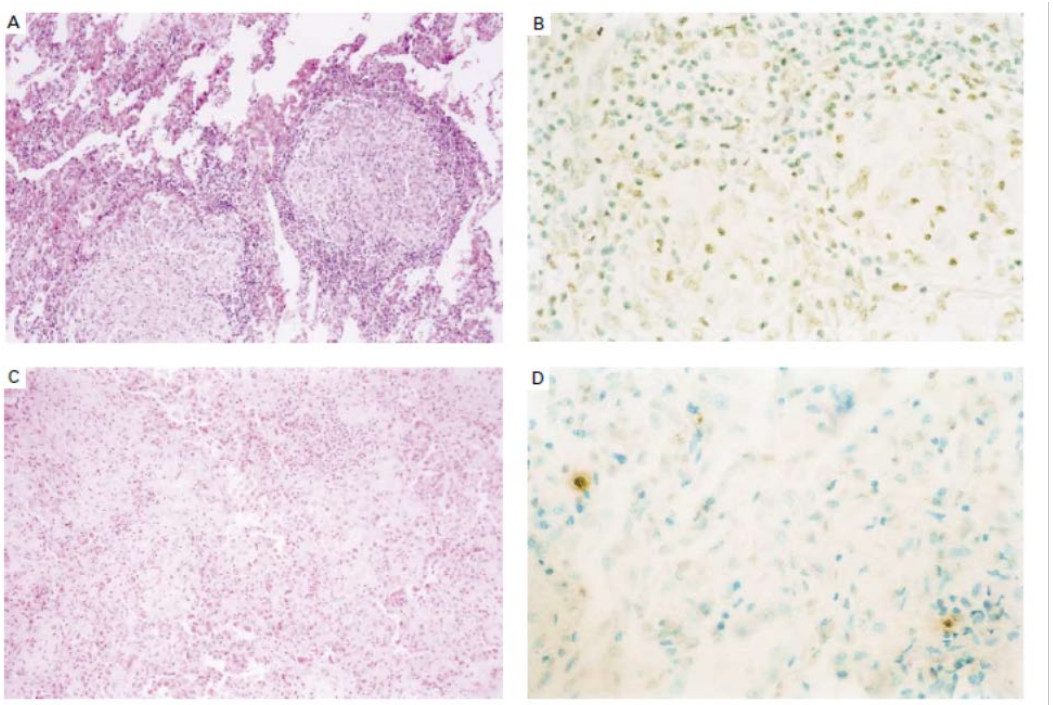
Source: Keane, J., Gershon, S., Wise, R. P., Mirabile-Levens, E., Kasznica, J., Schwieterman, W. D., Siegel, J. N., & Braun, M. M. (2001). Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *The New England Journal of Medicine*, *345*(15), 1098–1104. https://doi.org/10.1056/NEJMoa011110.

Results (Keane et al., 2001)

- On the basis of the data from the FDA's AERS, the estimated rate of tuberculosis among patients with rheumatoid arthritis in the United States who had received infliximab therapy within the previous year was **24.4 cases per 100,000**
- On the basis of the data from the prospective cohort study of 10,782 patients with rheumatoid arthritis, the background rate of tuberculosis among patients with rheumatoid arthritis in the United States was **6.2 cases per 100,000 per year**
- Twelve patients died, and at least 4 of these deaths appear to have been directly related to tuberculosis
- Other serious opportunistic infections (e.g., listeriosis, *Pneumocystis carinii* pneumonia, and *Candida* infections) have been reported, but tuberculosis was more common

Source: Keane, J., Gershon, S., Wise, R. P., Mirabile-Levens, E., Kasznica, J., Schwieterman, W. D., Siegel, J. N., & Braun, M. M. (2001). Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *The New England Journal of Medicine*, *345*(15), 1098–1104. https://doi.org/10.1056/NEJMoa011110.

Lung Tissue: A Patient With Tuberculosis After Infliximab (Keane et al., 2001)



Source: Figure 3, "Photomicrographs of lung specimens from a patient with tuberculosis who did not receive infliximab (panels A and B) and the index patient with tuberculosis who did receive infliximab (panels C and D)." In: Keane, J., Gershon, S., Wise, R. P., Mirabile-Levens, E., Kasznica, J., Schwieterman, W. D., Siegel, J. N., & Braun, M. M. (2001). Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *The New England Journal of Medicine*, *345*(15), 1098–1104. https://doi.org/10.1056/NEJMoa011110.

Authors' Conclusion (Keane et al., 2001)

"Our data suggest an association between treatment with infliximab and the development of tuberculosis. Although passive surveillance data are often insufficient to prove a causal relation between an adverse event and a drug, we believe this association is not coincidental, because of the large number of reports of tuberculosis in close temporal association with the initiation of treatment and the increased rate of tuberculosis among patients treated with infliximab, as compared with available data on background rates."

Source: Keane, J., Gershon, S., Wise, R. P., Mirabile-Levens, E., Kasznica, J., Schwieterman, W. D., Siegel, J. N., & Braun, M. M. (2001). Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *The New England Journal of Medicine*, *345*(15), 1098–1104. https://doi.org/10.1056/NEJMoa011110.

A Boxed Warning Was Added in October 2001

It took 3.1 years from infliximab's approval to add this boxed warning

REMICADE®
(infliximab)

for IV Injection

WARNING:

RISK OF INFECTIONS

TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE *WARNINGS*).

PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST. [1] TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE.

Source: REMICADE (infliximab) for IV Injection. https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/inflcen022702LB.pdf

Example: Adverse Events and Prescribing Practice Change

Rosiglitazone (Avandia)

- An insulin-sensitizing agent for the treatment of type 2 diabetes
- It is in the thiazolidinediones class of medications
- It was approved in 1999 by the U.S. Food and Drug Administration (FDA) and widely used as monotherapy or in fixed-dose combination with metformin or glimepiride (a type of sulfonylurea)

Image source: GlaxoSmithKline.

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death From Cardiovascular Causes (Nissen and Wolski, 2007)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Source: Nissen, S. E., & Wolski, K. (2007). Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *The New England Journal of Medicine*, *356*(24), 2457–2471. https://doi.org/10.1056/NEJMoa072761

Motivation for the Study (Nissen and Wolski, 2007)

- At the time of the study, three medications in this class were introduced:
  - Troglitazone: removed from the market because of hepatotoxicity
  - Rosiglitazone
  - Pioglitazone

- The initial approval for rosiglitazone in 1999 was based on efficacy in glycemic control (blood glucose and hemoglobin A1c)

- Initial studies were not adequately powered to determine the effects of rosiglitazone on microvascular and macrovascular complications of diabetes, including cardiovascular morbidity and mortality

Source: Nissen, S. E., & Wolski, K. (2007). Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *The New England Journal of Medicine*, *356*(24), 2457–2471. https://doi.org/10.1056/NEJMoa072761

Summary of the Study (Nissen and Wolski, 2007)

- Meta-analysis of 42 clinical trials (phase 2, 3, or 4)
- 15,565 patients randomly assigned to regimens that included rosiglitazone vs. 12,282 patients assigned to regimens that did not include rosiglitazone
- The mean age of the participants was 56 years
- The mean baseline hemoglobin A1c was 8.2%

Source: Nissen, S. E., & Wolski, K. (2007). Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *The New England Journal of Medicine*, *356*(24), 2457–2471. https://doi.org/10.1056/NEJMoa072761

Risk of Myocardial Infarction and Death From Cardiovascular Causes (Nissen and Wolski, 2007)

Study	Rosiglitazone group, No. of events / total No. (%)	Control group, No. of events / total No. (%)	Odds ratio (95% CI)	*P* values
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6,106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2,634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2,895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3,980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2,634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2,895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

Source: Nissen, S. E., & Wolski, K. (2007). Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *The New England Journal of Medicine*, *356*(24), 2457–2471. https://doi.org/10.1056/NEJMoa072761

Limitations (Nissen and Wolski, 2007)

- Most trials did not centrally adjudicate cardiovascular outcomes
- Definitions of myocardial infarction were not available
- Many of the trials included were small and short term, with few cardiovascular events or death
- Results were based on publicly available summary data, not individual-level trial data
- The lack of access to source data did not allow the authors to perform time-to-event analysis

Source: Nissen, S. E., & Wolski, K. (2007). Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *The New England Journal of Medicine*, *356*(24), 2457–2471. https://doi.org/10.1056/NEJMoa072761

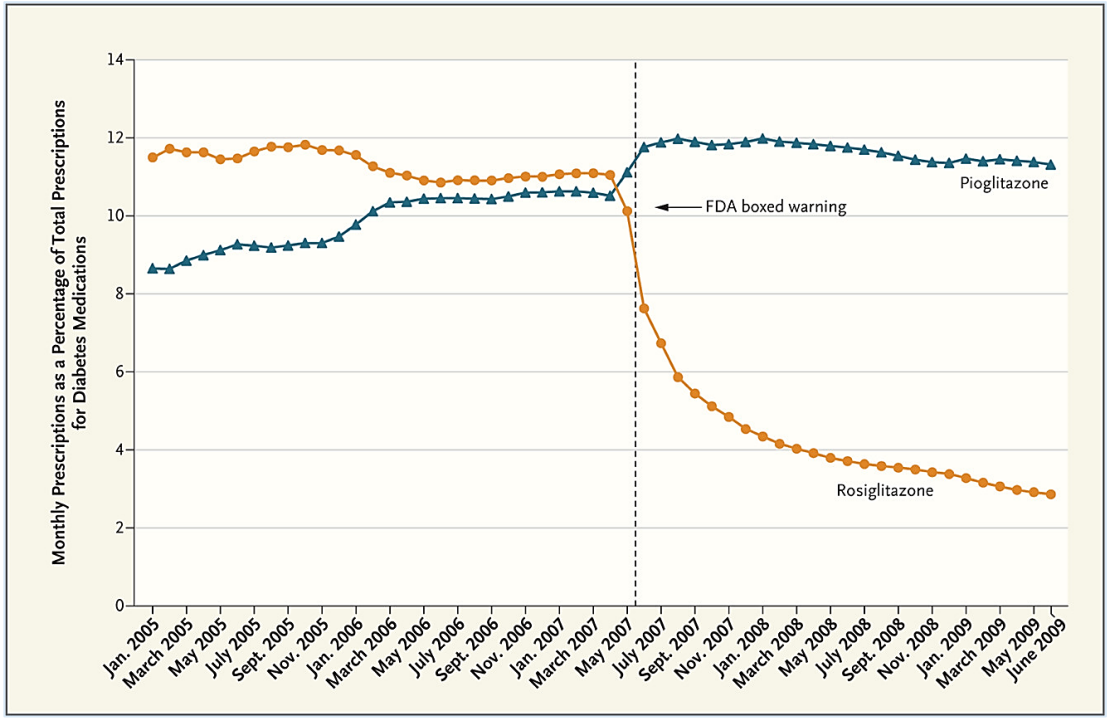
Conclusion and Consequence (Nissen and Wolski, 2007)

- This study suggested the urgent need for comprehensive evaluation to clarify the cardiovascular risks of rosiglitazone
- The authors also emphasized the necessity of making source data for completed clinical trials available to an external academic coordinating center for systematic analysis

- In July 2007, the Endocrinologic and Metabolic Drug Advisory Committee (EMDAC) and the Drug Safety and Risk Management Advisory Committee of the FDA held a joint meeting and concluded that rosiglitazone was associated with an increased risk of myocardial ischemia
- The committee also recommended more studies to refine the risk estimate, including a complete analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial and large observational cohort studies
- Subsequently, the FDA added a boxed warning about myocardial ischemia to the drug label

Source: Nissen, S. E., & Wolski, K. (2007). Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *The New England Journal of Medicine*, *356*(24), 2457–2471. https://doi.org/10.1056/NEJMoa072761

Prescription Patterns After FDA Boxed Warning



In June 2009, there were ~3.8 million rosiglitazone prescriptions per year

Source: Graph, "Monthly prescriptions for rosiglitazone and pioglitazone as a percentage of total prescriptions for diabetes medications (excluding insulin), United States." In: Shah, N. D., Montori, V. M., Krumholz, H. M., Tu, K., Alexander, G. C., & Jackevicius, C. A. (2010). Responding to an FDA warning—Geographic variation in the use of rosiglitazone. *The New England Journal of Medicine*, *363*(22), 2081–2084. https://doi.org/10.1056/NEJMp1011042

Results of RECORD Trial

Patients (*n* = 4,447) with type 2 diabetes on metformin or sulfonylurea monotherapy were assigned to addition of rosiglitazone (*n* = 2,220) or to a combination of metformin and sulfonylurea (*n* = 2,227)

	Rosiglitazone	Active control	Hazard ratio	Rate difference per 1,000 person-years	*P*
CV death or CV hospitalization	321	323	0.99 (0.85 to 1.16)	−0.2 (−4.5 to 4.1)	0.93
All-cause death	136	157	0.86 (0.68 to 1.08)	−1.7 (−4.3 to 0.9)	0.19
CV death	60	71	0.84 (0.59 to 1.18)	−0.9 (−2.7 to 0.9)	0.32
Myocardial infarction	64	56	1.14 (0.80 to 1.63)	0.6 (−1.1 to 0.2)	0.47
Stroke	46	63	0.72 (0.49 to 1.06)	−1.4 (−3.1 to 0.2)	0.10
CV death, myocardial infarction, or stroke	154	165	0.93 (0.74 to 1.15)	−1.0 (−3.9 to 1.9)	0.50
Heart failure	61	29	2.10 (1.35 to 3.27)	2.6 (1.1 to 4.1)	0.001

CV = cardiovascular.

Source: Home, P. D., Pocock, S. J., Beck-Nielsen, H., Curtis, P. S., Gomis, R., Hanefeld, M., Jones, N. P., Komajda, M., McMurray, J. J. V., & RECORD Study Team. (2009). Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): A multicentre, randomised, open-label trial. *Lancet (London, England)*, *373*(9681), 2125–2135. https://doi.org/10.1016/S0140-6736(09)60953-3

Rosiglitazone Revisited

56 randomized clinical trials of rosiglitazone at least 24 weeks in duration;
19,509 patients received rosiglitazone, and 16,022 patients received control therapy

Method	No. of studies	Rosiglitazone group	Control group	Peto OR (95% CI)	*P* value
Risk of myocardial infarction					
Including RECORD trial	41	159/17,258	136/14,449	1.28 (1.02–1.63)	0.04
Excluding RECORD trial	40	95/15,038	80/12,222	1.29 (1.02–1.89)	0.04
Risk of cardiovascular mortality					
Including RECORD trial	26	105/13,672	100/12,175	1.03 (0.78–1.36)	0.86
Excluding RECORD trial	25	45/11,452	29/9,949	1.46 (0.92–2.33)	0.11

Source: Nissen, S. E., & Wolski, K. (2010). Rosiglitazone revisited: An updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Archives of Internal Medicine*, *170*(14), 1191–1201. https://doi.org/10.1001/archinternmed.2010.207

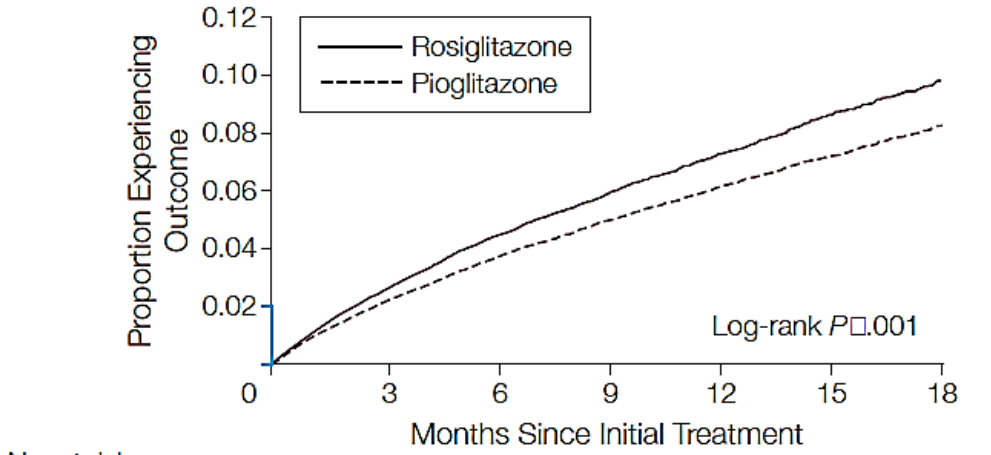
Evidence From Observational Study (Graham et al., 2010)—1

- Medicare beneficiaries (*n* = 227,571; mean age: 74.4 years) who initiated rosiglitazone or pioglitazone between 2006 and 2009 (new user, active comparator study design)
- Median days of follow-up: 105 days

Source: Graham, D. J., Ouellet-Hellstrom, R., MaCurdy, T. E., Ali, F., Sholley, C., Worrall, C., & Kelman, J. A. (2010). Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA*, *304*(4), 411–418. https://doi.org/10.1001/jama.2010.920

Evidence From Observational Study—2

Figure 2. Kaplan-Meier cumulative incidence of time to event for the composite of acute myocardial infarction, stroke, heart failure, and all-cause mortality in elderly Medicare patients treated with rosiglitazone or pioglitazone



No. at risk							
Rosiglitazone	67 593	36 544	19 237	11 164	6606	4261	3063
Pioglitazone	159 978	86 281	47 929	31 096	21 083	14 486	10 132

- Adjusted HR (95% CI) = 1.18 (1.12–1.23)
- Number needed to harm (95% CI) = 60 (48–79) treated for 1 year
- Segment of y-axis shown in blue indicates the range of 0 to 0.02 cumulative proportion

Source: Figure 2. In: Graham, D. J., Ouellet-Hellstrom, R., MaCurdy, T. E., Ali, F., Sholley, C., Worrall, C., & Kelman, J. A. (2010). Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA*, *304*(4), 411–418. https://doi.org/10.1001/jama.2010.920

Complex Regulatory Life Cycle of Rosiglitazone

- In September 2010, the FDA announced that only patients who were already successfully treated with rosiglitazone or had not adequately controlled their blood sugar on other medications could receive it
- In November 2011, as part of an FDA Risk Evaluation and Mitigating Strategy (REMS) program, patients could receive rosiglitazone only through specialty mail-order pharmacies
- However, in November 2013, the FDA **required removal** of some prescribing and dispensing restrictions for rosiglitazone
  - In 2010, the FDA required a comprehensive readjudication (expert reevaluation) of the results from the RECORD trial
  - The readjudicated RECORD trial failed to show increased risk of myocardial infarction, stroke, or cardiovascular death

Source: U.S. FDA. (2021). FDA Drug Safety Communication: Updated Risk Evaluation and Mitigation Strategy (REMS) to Restrict Access to Rosiglitazone-containing Medicines including Avandia, Avandamet, and Avandaryl. *FDA*. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-updated-risk-evaluation-and-mitigation-strategy-rems-restrict-access

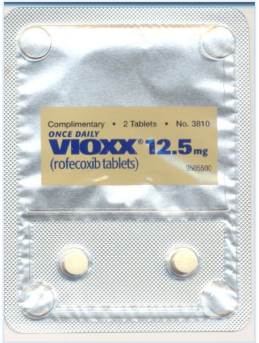
Effects of Removing Rosiglitazone's Restricted Access Program

- After the restricted access program was implemented, rosiglitazone initiation dropped below 1% and remained below 1%, even after the safety decisions were reversed
- Once a treatment falls out of favor with patients, prescribers, and payers, reversing safety decisions might not change utilization patterns

Source: Hickson, R. P., Cole, A. L., & Dusetzina, S. B. (2019). Implications of removing rosiglitazone's black box warning and restricted access program on the uptake of thiazolidinediones and dipeptidyl peptidase-4 inhibitors among patients with type 2 diabetes. *Journal of Managed Care & Specialty Pharmacy*, *25*(1), 72–79. https://doi.org/10.18553/jmcp.2019.25.1.072

Example: Phase 4 Clinical Trials

Rofecoxib (Vioxx)



- A nonsteroidal anti-inflammatory drug (NSAID) that is specific for cyclo-oxygenase 2 (COX-2)—a COX-2 inhibitor
- It was approved for the relief of arthritis symptoms in 1999 by the U.S. Food and Drug Administration (FDA)
- Since the early development of rofecoxib, there were some concerns about cardiovascular safety
  - It alters the ratio of prostacyclin (antithrombotic) to thromboxane (prothrombotic)
- None of the rofecoxib trials in the new drug application to the FDA were designed to study cardiovascular safety
- The approval was based on data from trials lasting 3 to 6 months and involving patients at low risk of cardiovascular disease

Source: Krumholz, H. M., Ross, J. S., Presler, A. H., & Egilman, D. S. (2007). What have we learnt from Vioxx? *BMJ (Clinical Research Ed.)*, *334*(7585), 120–123. https://doi.org/10.1136/bmj.39024.487720.68

Image source: Merck.

Vioxx Gastrointestinal Outcomes Research (VIGOR) Study in 2000—1

- To study whether rofecoxib is better for the digestive system than a nonselective NSAID
- Patients (*n* = 8,076; ≥50 years of age) with rheumatoid arthritis were randomized to receive either rofecoxib (COX-2 inhibitor) or naproxen (nonselective NSAID)
- The median follow-up was 9 months
- Excluded patients with history of stroke, myocardial infarction, or coronary artery bypass graft surgery or who were on aspirin or a gastroprotective agent
- Primary end point: upper gastrointestinal events

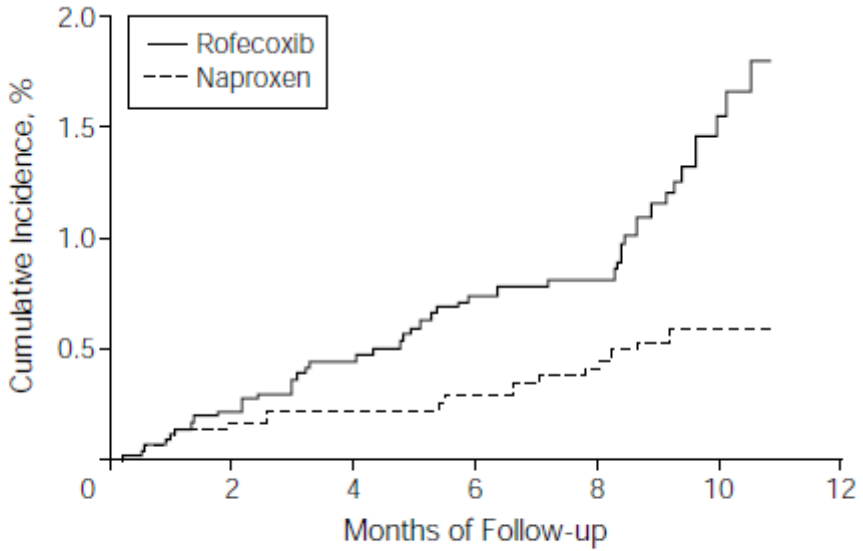
Sources:

Bombardier, C., Laine, L., Reicin, A., Shapiro, D., Burgos-Vargas, R., Davis, B., Day, R., Ferraz, M. B., Hawkey, C. J., Hochberg, M. C., Kvien, T. K., Schnitzer, T. J., & VIGOR Study Group. (2000). Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *The New England Journal of Medicine*, *343*(21), 1520–1528, 2 p following 1528. https://doi.org/10.1056/NEJM200011233432103

Mukherjee, D., Nissen, S. E., & Topol, E. J. (2001). Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA*, *286*(8), 954–959. https://doi.org/10.1001/jama.286.8.954

Vioxx Gastrointestinal Outcomes Research (VIGOR) Study in 2000—2

Figure 1. Time to cardiovascular adverse event in the VIGOR trial



No. at Risk							
Rofecoxib	4047	3643	3405	3177	2806	1067	531
Naproxen	4029	3647	3395	3172	2798	1073	514

Relative risk (95% confidence interval) = 2.38 (1.39–4.00); $P < .001$.

Sources:

Bombardier, C., Laine, L., Reicin, A., Shapiro, D., Burgos-Vargas, R., Davis, B., Day, R., Ferraz, M. B., Hawkey, C. J., Hochberg, M. C., Kvien, T. K., Schnitzer, T. J., & VIGOR Study Group. (2000). Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *The New England Journal of Medicine*, *343*(21), 1520–1528, 2 p following 1528. https://doi.org/10.1056/NEJM200011233432103

Image source: Figure 1, "Time to cardiovascular adverse event in the VIGOR trial." In: Mukherjee, D., Nissen, S. E., & Topol, E. J. (2001). Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA*, *286*(8), 954–959. https://doi.org/10.1001/jama.286.8.954

Manufacturer Response and FDA Response

- Manufacturer:
  - Did not undertake a dedicated phase 4 cardiovascular safety trial of rofecoxib
  - Proposed alternative explanation
    - The excess in myocardial infarction cases observed in the VIGOR study was due to a cardioprotective effect of naproxen

- FDA:
  - This was before the 2007 FDA Amendments Act (FDAAA)
  - FDA could not require the manufacturer to conduct a cardiovascular safety trial of rofecoxib

Source: Karha, J., & Topol, E. J. (2004). The sad story of Vioxx, and what we should learn from it. *Cleveland Clinic Journal of Medicine*, *71*(12), 933–934, 936, 938–939. https://doi.org/10.3949/ccjm.71.12.933

Adenomatous Polyp Prevention on Vioxx (APPROVE) Trial

- To evaluate the effect of 3 years of treatment with rofecoxib on the risk of recurrent adenomatous polyps among patients with a history of colorectal adenomas
- Patients (*n* = 2,600) were randomized to receive either rofecoxib or placebo for 3 years
- Potential thrombotic cardiovascular events were adjudicated, and cardiovascular findings were also reported

Source: Bresalier, R. S., Sandler, R. S., Quan, H., Bolognese, J. A., Oxenius, B., Horgan, K., Lines, C., Riddell, R., Morton, D., Lanas, A., Konstam, M. A., Baron, J. A., & Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. (2005). Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *The New England Journal of Medicine*, *352*(11), 1092–1102. https://doi.org/10.1056/NEJMoa050493

Cardiovascular Events With Rofecoxib in a Colorectal Adenoma Chemoprevention Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial

Robert S. Bresalier, M.D., Robert S. Sandler, M.D., Hui Quan, Ph.D., James A. Bolognese, M.Stat., Bettina Oxenius, M.D., Kevin Horgan, M.D., Christopher Lines, Ph.D., Robert Riddell, M.D., Dion Morton, M.D., Angel Lanas, M.D., Marvin A. Konstam, M.D., and John A. Baron, M.D., for the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators*

Source: Bresalier, R. S., Sandler, R. S., Quan, H., Bolognese, J. A., Oxenius, B., Horgan, K., Lines, C., Riddell, R., Morton, D., Lanas, A., Konstam, M. A., Baron, J. A., & Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. (2005). Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *The New England Journal of Medicine*, *352*(11), 1092–1102. https://doi.org/10.1056/NEJMoa050493

APPROVE Trial Confirmed Increased Cardiovascular Risk With Rofecoxib

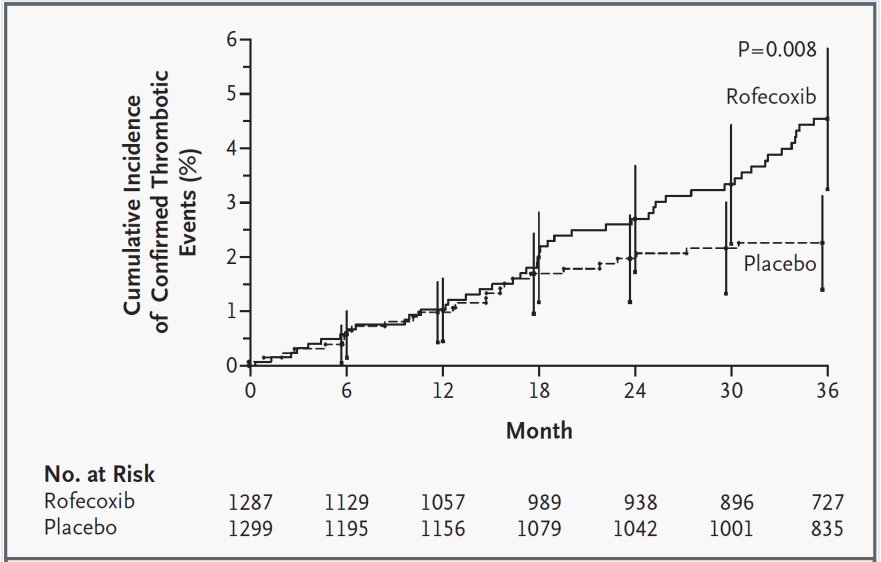


Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of Confirmed Serious Thrombotic Events.

Vertical lines indicate 95 percent confidence intervals.

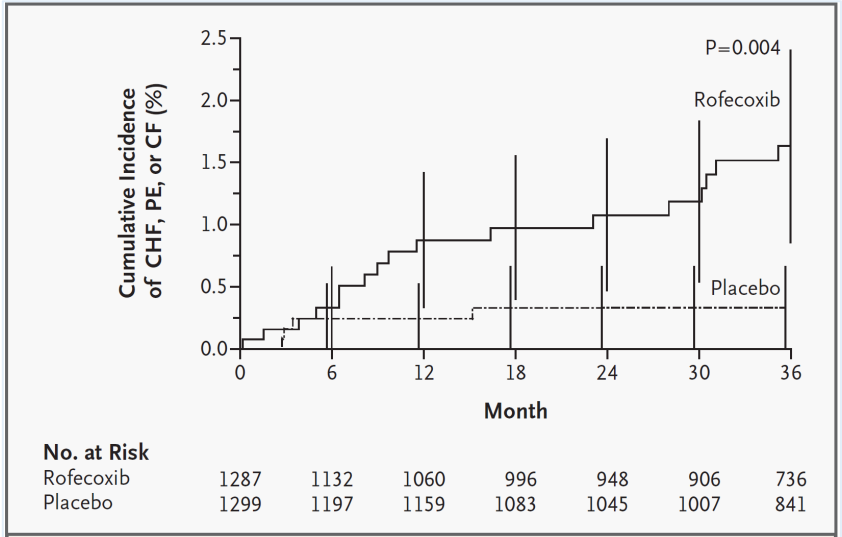


Figure 3. Kaplan–Meier Estimates of the Cumulative Incidence of Investigator-Reported Congestive Heart Failure (CHF), Pulmonary Edema (PE), or Cardiac Failure (CF).

Vertical lines indicate 95 percent confidence intervals.

Image source: Figure 2, "Kaplan–Meier estimates of the cumulative incidence of confirmed serious thrombotic events," and Figure 3, "Kaplan–Meier estimates of the cumulative incidence of investigator-reported congestive heart failure (CHF), pulmonary edema (PE), or cardiac failure (CF)." In: Bresalier, R. S., Sandler, R. S., Quan, H., Bolognese, J. A., Oxenius, B., Horgan, K., Lines, C., Riddell, R., Morton, D., Lanas, A., Konstam, M. A., Baron, J. A., & Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. (2005). Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *The New England Journal of Medicine*, *352*(11), 1092–1102. https://doi.org/10.1056/NEJMoa050493

Consequences

- The manufacturer voluntarily withdrew rofecoxib from the market on September 30, 2004 (approved in May 20, 1999)
- By the time rofecoxib was withdrawn from the market, an estimated 20 million Americans had taken the drug
- An estimated 88,000 Americans had heart attacks from taking rofecoxib, and 38,000 of them died
- Thousands of lawsuits
- In November 2007, the manufacturer announced that it would pay $4.85 billion to end lawsuits over rofecoxib: the largest drug settlement ever at that time

Sources:

Prakash, S. (2007, November 10). Timeline: The rise and fall of Vioxx. *NPR*. https://www.npr.org/2007/11/10/5470430/timeline-the-rise-and-fall-of-vioxx

Graham, D. J., Campen, D., Hui, R., Spence, M., Cheetham, C., Levy, G., Shoor, S., & Ray, W. A. (2005). Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: Nested case-control study. *Lancet (London, England)*, *365*(9458), 475–481. https://doi.org/10.1016/S0140-6736(05)17864-7

Summary

- Boxed warning is the highest safety-related warning from the FDA that medications can have
- A definite causal connection is not needed for a boxed warning
- The FDA does not regulate the practice of medicine, but boxed warnings affect clinical practice
- Individual physicians make the clinical decision to prescribe or not to prescribe a drug with a boxed warning, after risk/benefit consideration
- Since the 2007 FDA Amendments Act, the FDA can require phase 4 postmarketing safety studies