Post-Approval

Benefit – Risk Assessment

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EDRA 543

Lecture, 2023

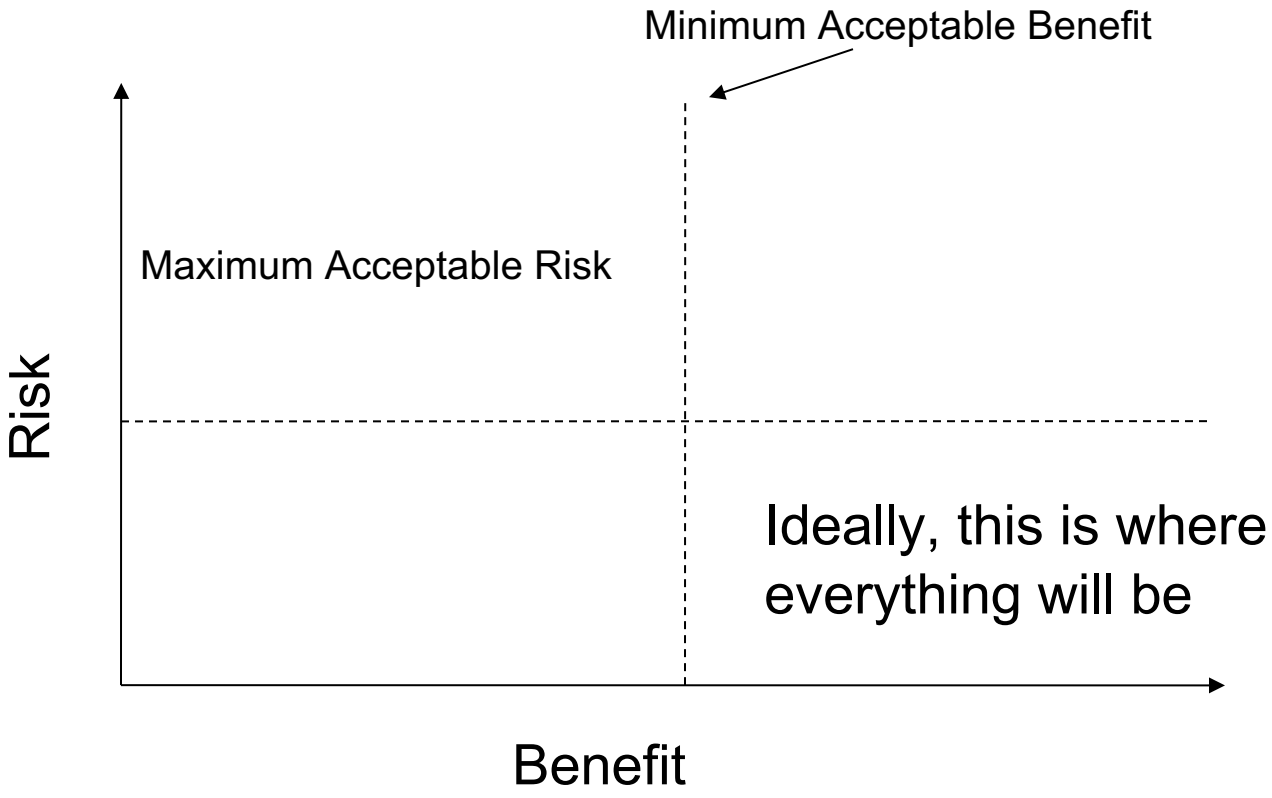
Outline

- Regulatory approaches & role of pharmacoepidemiology
- Examples:
  - signal detection and evaluation
  - benefit risk monitoring
  - evaluating effectiveness of risk minimization
- Current regulatory strategies

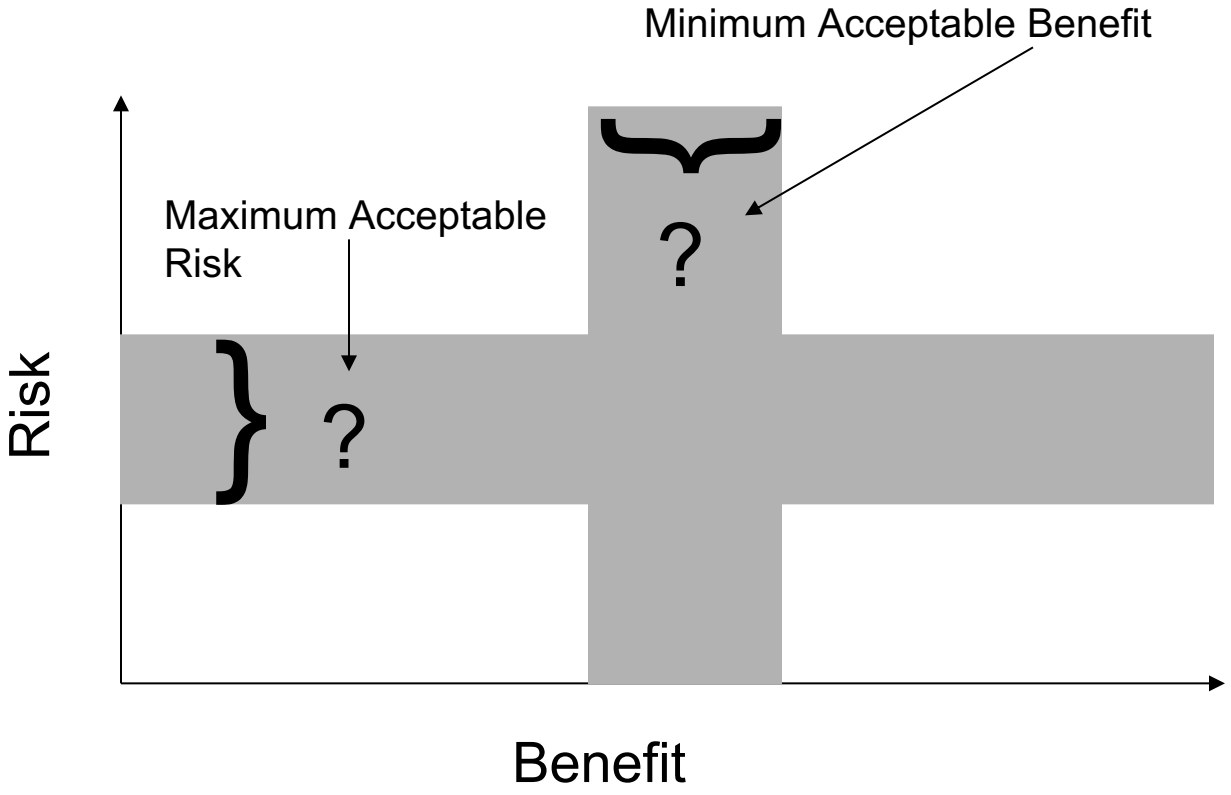
Role of the drug regulator

- Access to medicines
  - Assess efficacy, safety, quality
- Protection of the public
  - During clinical trials
  - Post-approval
- Information to the public
- Work within a legal/regulatory framework

Measuring benefits and risks



But things are never this clear



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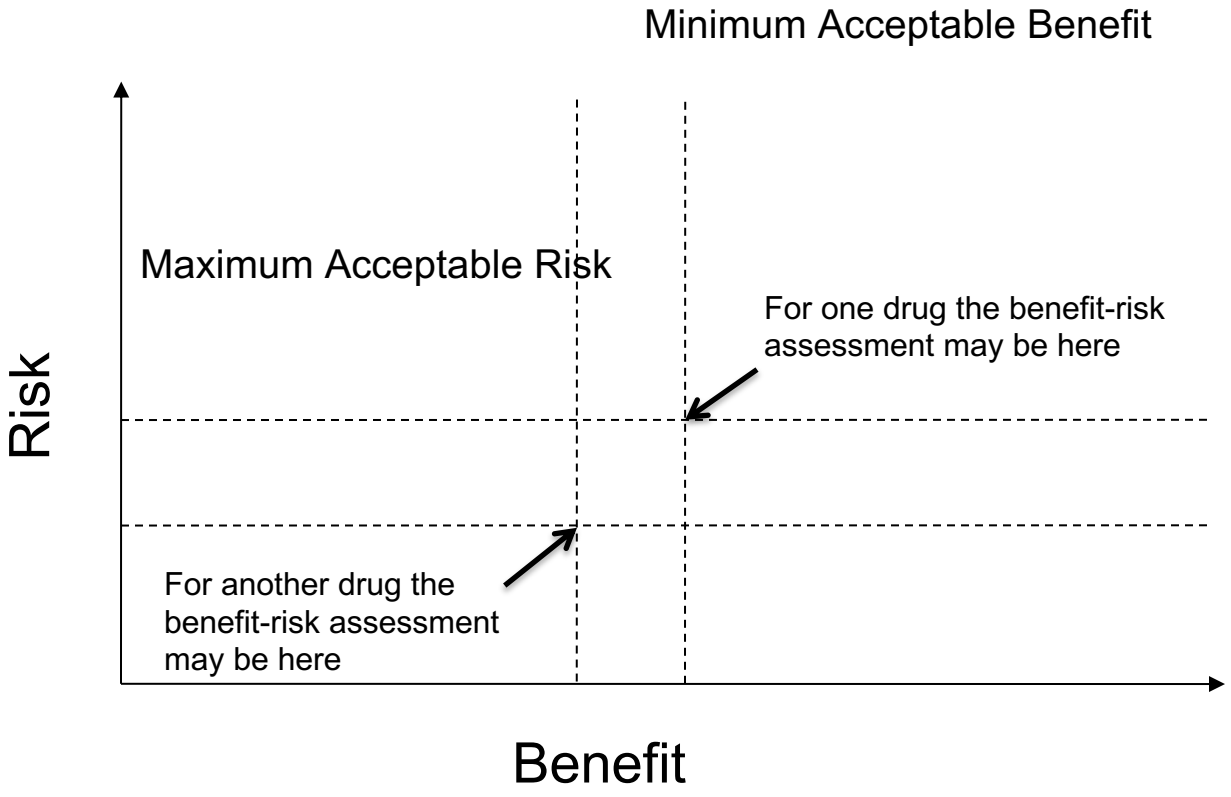

Why do these grey zones exist?

- Determining a “cut-off” for minimum acceptable benefit or maximum acceptable risk is not a strictly scientific process
  - It involves judgment
  - It involves imperfect, or non-existent, prior data
  - It involves values
- Regulators make decisions on efficacy and safety based on population data, but practitioners and patients look at their choices from an individual point of view.

Public health burden of medicines harms

- 5% of all hospital admissions due to ADRs
- 5% of all hospital patients experience an ADR
- ADRs 5th most common cause of hospital death
- 197,000 deaths per year in EU caused by ADRs

Clinical database before new drug approval

OPEN ACCESS Freely available online

PLOS | MEDICINE

Number of Patients Studied Prior to Approval of New Medicines: A Database Analysis

Ruben G. Duijnhoven[1,2], Sabine M. J. M. Straus[2,3], June M. Raine[4], Anthonius de Boer[1], Arno W. Hoes[5], Marie L. De Bruin[1,2]*

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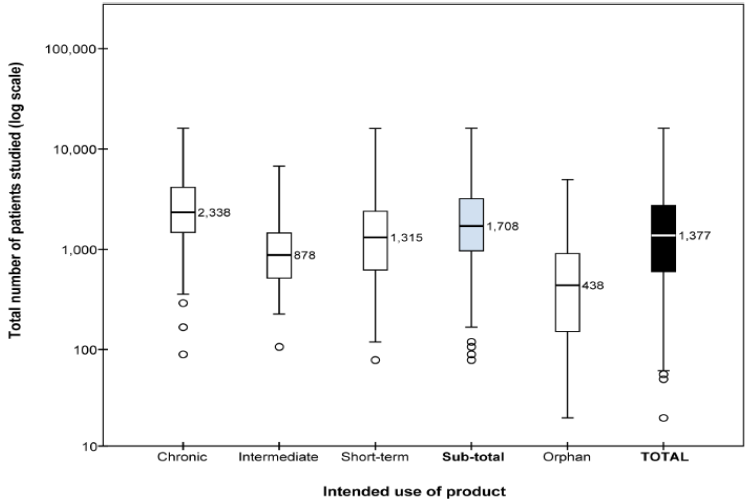
Abstract

Background: At the time of approval of a new medicine, there are few long-term data on the medicine's benefit–risk balance. Clinical trials are designed to demonstrate efficacy, but have major limitations with regard to safety in terms of patient exposure and length of follow-up. This study of the number of patients who had been administered medicines at the time of medicine approval by the European Medicines Agency aimed to determine the total number of patients studied, as well as the number of patients studied long term for chronic medication use, compared with the International Conference on Harmonisation's E1 guideline recommendations.

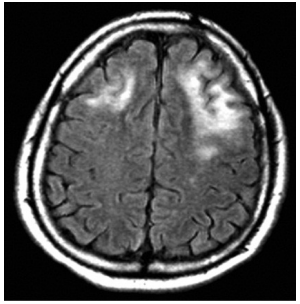


- For 200 new "standard" medicines median total no patients= **1708**
- For orphan drugs = **438** patients
- Safety and efficacy of chronic use was studied in fewer than 1,000 patients for at least 6 and 12 months of new medicines

Duijnhoven et al PLoS 2013

Important knowledge gaps to be filled

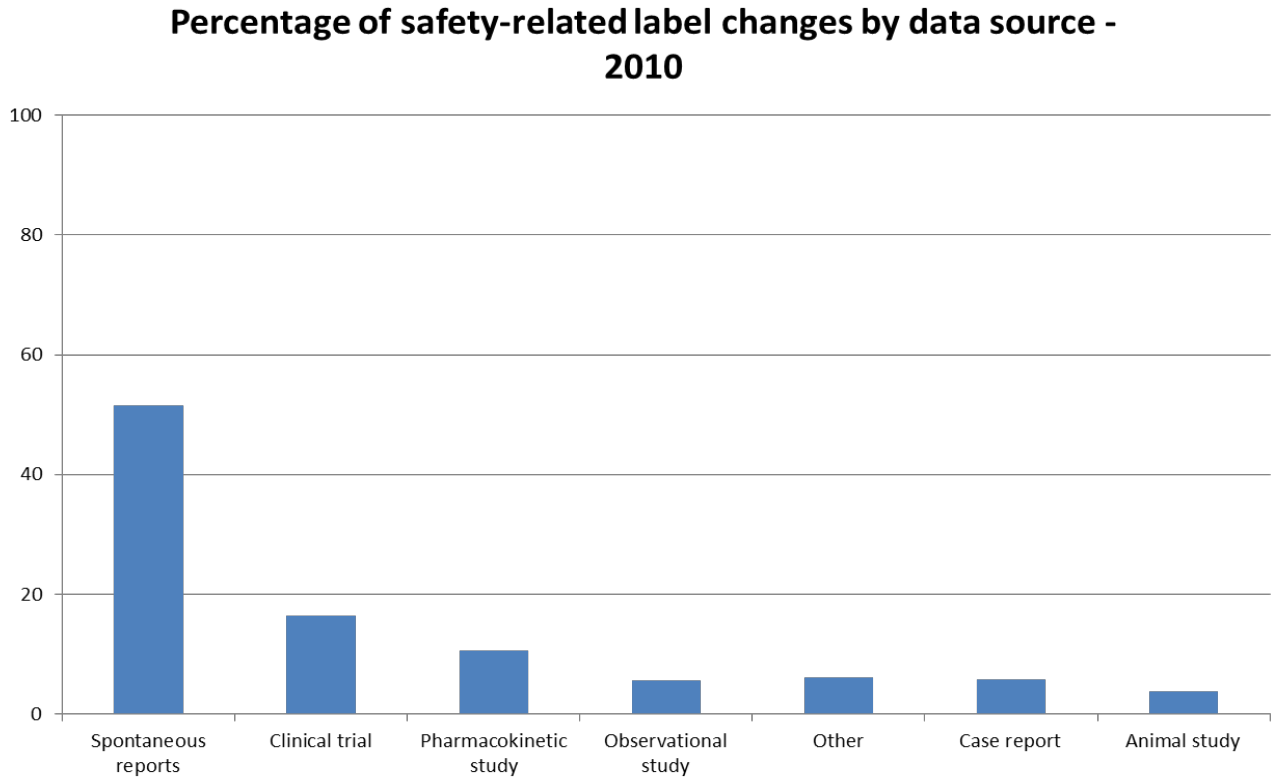
- Special populations
  - pregnancy
  - pediatrics
  - elderly
- At risk groups e.g. immunosuppressed
- Long term safety



Goals of Drug Safety Surveillance

- To identify previously unknown drug-related adverse events
- To learn more about known drug-related adverse events
- To learn more about how drugs are used in ways that may not promote safe use
- The method you use depends on what you are trying to learn
- To communicate findings about drug safety

Goals of Drug Safety Surveillance



Source: Lester J et al. Pharmacoepi Drug Safety (2013) 22:302-305

Causality in Drug Safety Surveillance

- If Event A is responsible for Outcome B, then Event A is said to cause Outcome B
- If Event A did not happen, then Outcome B would not have occurred

In causal assessments, this requires us to know what would have occurred if Event A had not happened. How do we handle this?

Association vs Causation

Events A and B are associated if:

1- A causes B

- Smoking and lung cancer
- Smoking causes lung cancer

2- B causes A (reverse causation)

- Low body-mass index and cancer
- People with very low body-mass index have a high rate of cancer diagnoses because (undiagnosed) cancer leads to low body-mass index (which leads to a medical evaluation that finds a cancer)

Association vs Causation

3- A causes B and B causes A

- Employee motivation and pay
- Motivated employees receive higher pay, and higher pay increases motivation

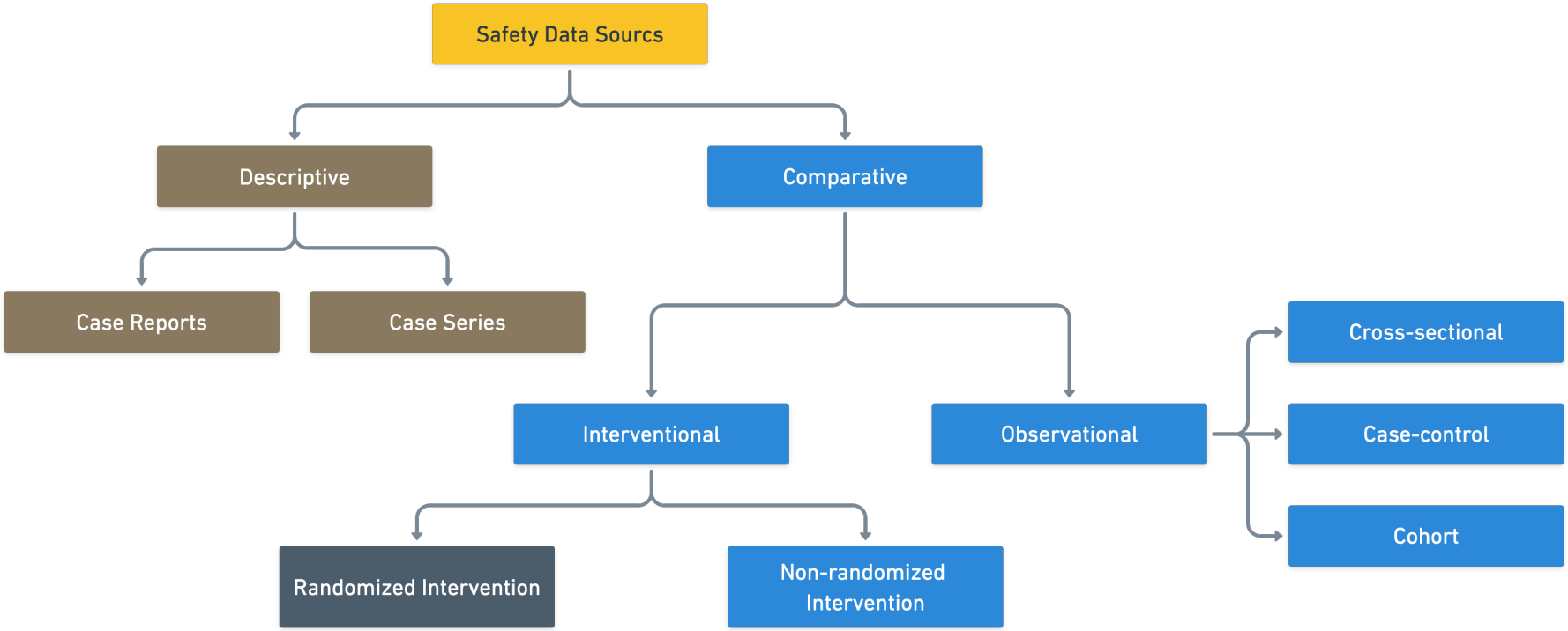
4- A third factor causes both A and B

5- A causes C and C causes B

- Urinary tract infection and rash
- Urinary tract infection leads to antibiotic treatment, which leads to rash

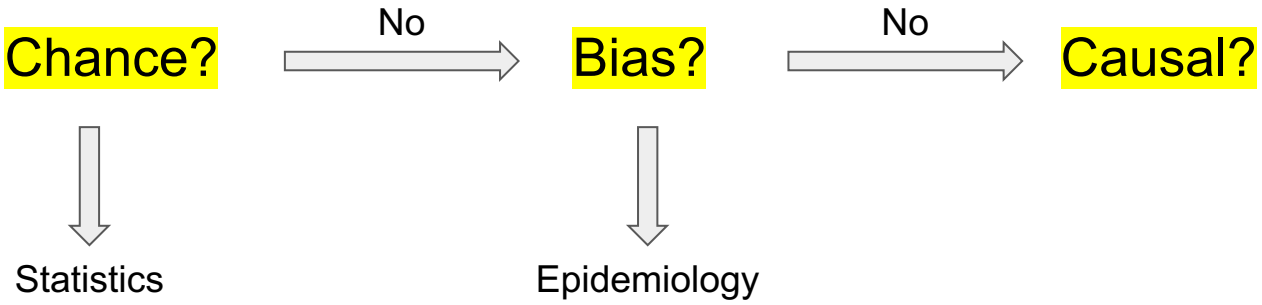
6- Coincidence

Association vs Causation



Chance, bias and causality

On their twitter and snapchat accounts, the CNN reported that a recent study showed that drinking coffee may cause cancer.



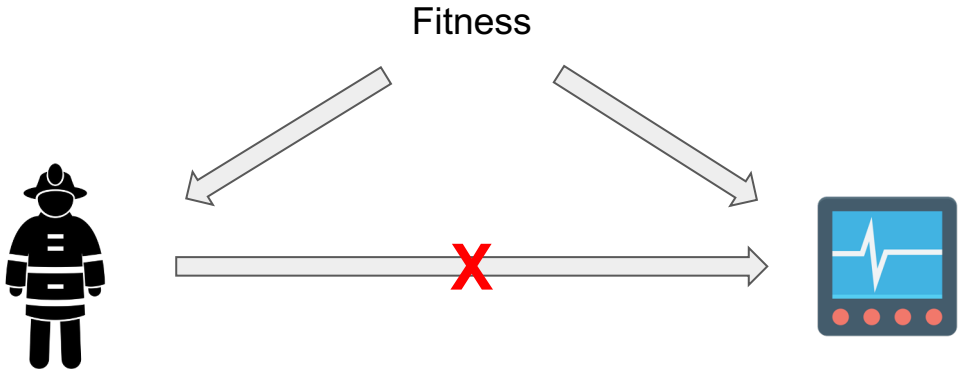
Confounding

Confounding is defined as a distorted relationship between two variables caused by a third variable. A confounder is the variable that distorts the association between two variables.

A study found that being a firefighter was associated with less heart disease compared to the general community they serve.

Does being a firefighter **decrease** your risk of developing heart diseases?

Confounding

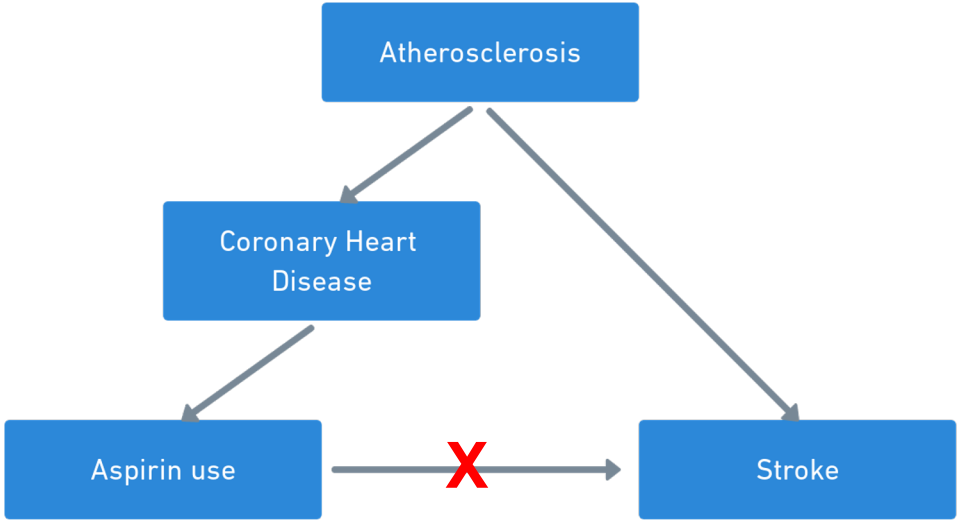


The association was distorted by a third variable. Being physically fit increases your chance to get accepted into organizations that provide firefighting services; it also prevents heart diseases.

Confounding in pharmacoepidemiology

A study found that using aspirin increases the risk of developing stroke. *The authors concluded that using aspirin may harm older patients who are at a higher risk of stroke*.

Confounding in pharmacoepidemiology



Atherosclerosis, a third variable, distorted the association between aspirin use and stroke. Atherosclerosis causes coronary heart disease which is an indication to initiate aspirin; it also causes stroke. This type of confounding is referred to as ***confounding by indication***

Prevalent User Bias

JOURNAL OF WOMEN'S HEALTH
Volume 15, Number 1, 2006

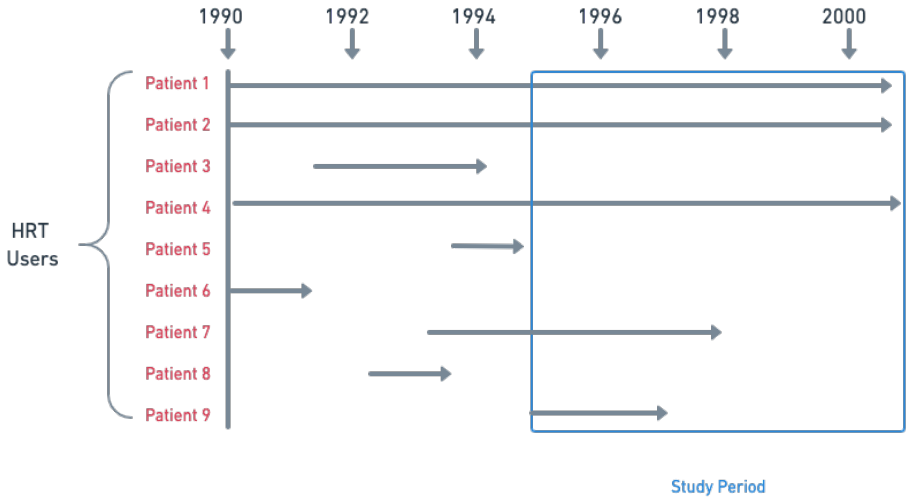
Hormone Therapy and Coronary Heart Disease: The Role of Time since Menopause and Age at Hormone Initiation

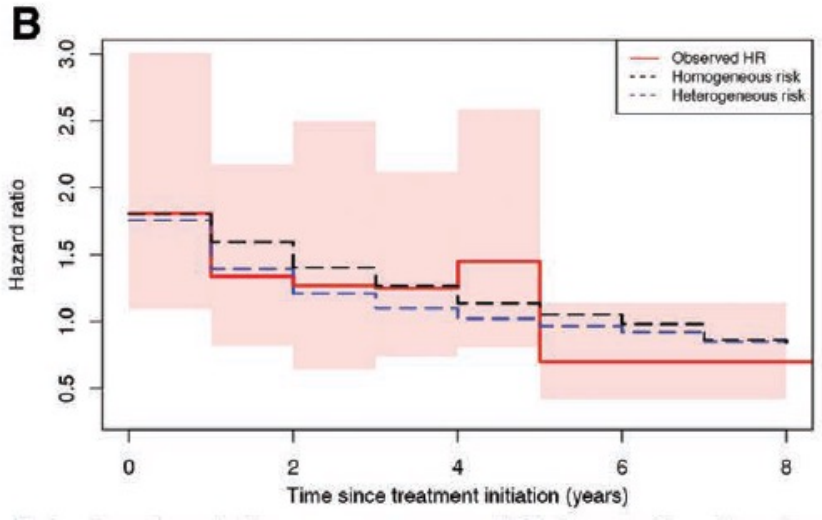
FRANCINE GRODSTEIN, Sc.D.,[1,3,4] JOANN E. MANSON, M.D., Dr.P.H.,[1,2,4] and MEIR J. STAMPFER, M.D., Dr.P.H.[1,4]

- In 2006, researchers conducted an observational study and found that postmenopausal hormone therapy significantly reduced coronary heart disease about 30% compared to postmenopausal women who never used hormone therapy.
  - *These results contradicted previous findings from an RCT that showed initiating hormone therapy increases the risk of CHD by 20% among postmenopausal women!! (Manson et al. NEJM, 2003)*

Prevalent User Bias

- Researchers *assumed* the CHD risk is constant during HRT exposure





Confounding in pharmacoepidemiology

- In 2008, the same data were re-analyzed to explain the discrepancies between RCTs and RWE findings.
- The researchers emulated an RCT by only including HRT initiators (new users). The only two differences between the RCT and the new re-analysis are:

  1- No randomization ad 2- No placebo assignment

	RCT (Women Health Initiative)	Observational data (Nurses' Health Study)
Overall (HR (95%CI))	1.23 (0.99 – 1.53)	1.05 (0.82 – 1.34)
Stratified by years of follow-up		
0 – 2 years (HR (95%CI))	1.51 (1.06 – 2.14)	1.43 (0.92 – 2.23)
> 2 years (HR (95%CI))	1.07 (0.81 – 1.41)	0.91 (0.72 – 1.16)

Hernán et al. *Epidemiology*. 2008;19(6):766-779. doi:10.1097/EDE.0b013e3181875e61

Factors May Assist in Causal Inference

Hill criteria:

- Strength of the association
- Consistency
- Specificity
- Temporality
- Biological gradient (dose response)
- Plausibility
- Coherence

Warnings and Precautions

Warnings and Precautions (21 CFR 201.57 (c)(6):

- "…the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established."

Adverse Reactions

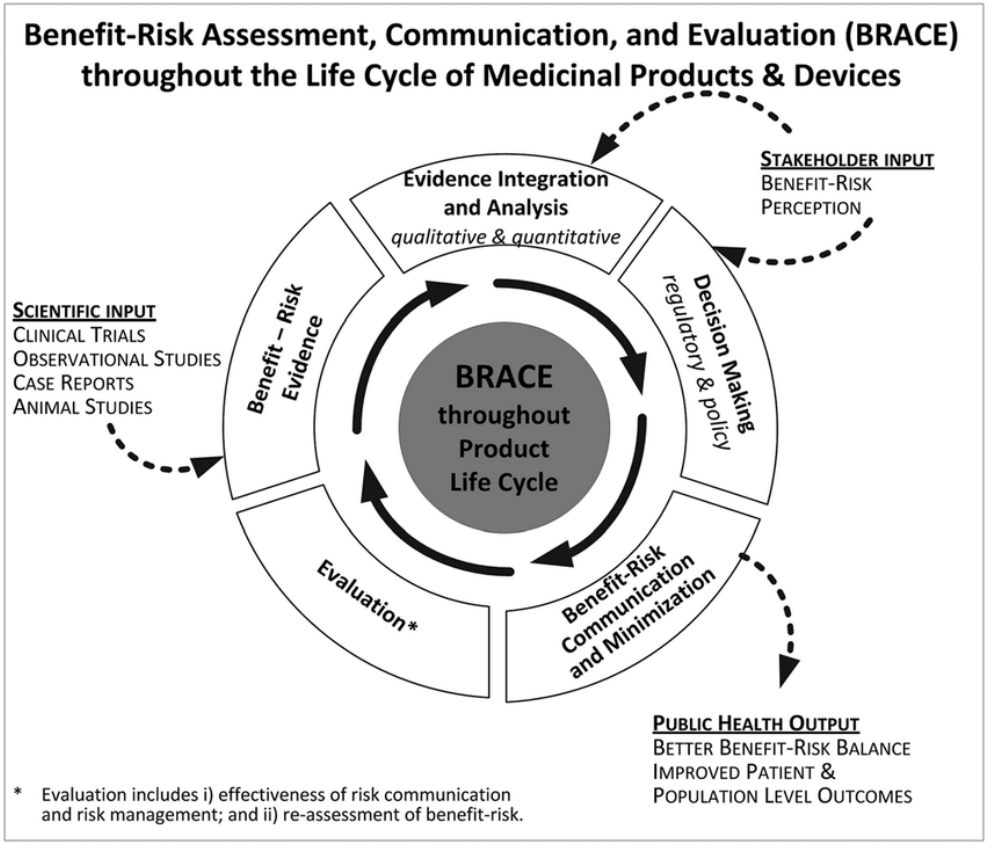
Adverse Reactions (21 CFR 201.57 (c)(7)

"…an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

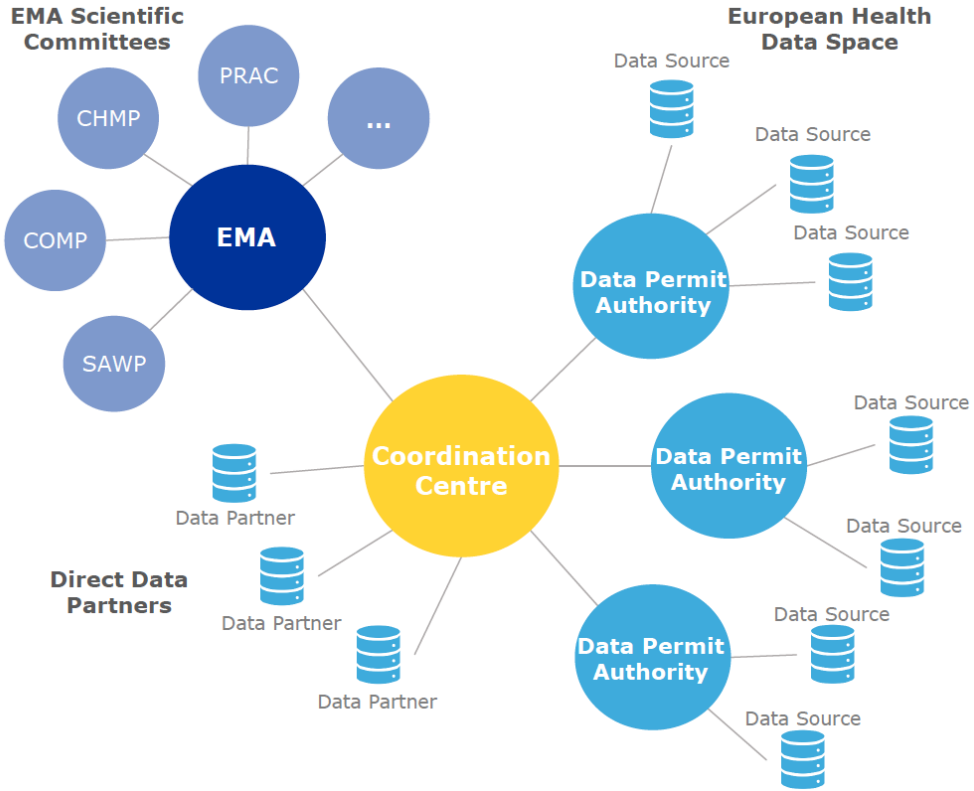
Regulatory activities

- **Detecting signals** of new or changing risks in clinical practice
- **Proactively generating data addressing uncertainties** and assessing changing risk benefit
- Implementing risk proportionate **risk minimizing measures** and evaluating their effectiveness
- Prompt decisions on basis of all available data taking into account the therapeutic context

Benefit Risk Assessment Cycle



Building Capacity for post-marketing BRACE



Case Examples

- All information presented here is publicly available in the published literature or on the FDA website

- These examples are for teaching purposes only – full details of FDA's actions and the rationale behind them are on the FDA website

Case Example: Felbamate

Felbamate

- Antiepileptic drug
- Approved in United States in July 1993
- Pre-approval data

  No evidence of significant, non-reversible hematologic abnormalities
- Within one year of approval, 20 cases of aplastic anemia were reported to FDA

  Three cases were fatal

Felbamate – Question 1

- Are you concerned?

- What do you do now?

Felbamate

- About 100,00 persons had taken felbamate during the time the 20 cases of aplastic anemia were reported

- Reporting ratio:

20/100,000 persons/year

= 200/1,000,000 persons/year

- Background incidence in the population:

1-2/1,000,000 persons/year

Felbamate – FDA Action

- FDA added warnings to the label

- Recommended that felbamate only be used if its benefits outweighed its risks, including the risk of aplastic anemia

Case Example: Dabigatran

Dabigatran

- An anti-coagulant
    - A direct thrombin inhibitor

- Approved October 19, 2010
- Indication of non-valvular atrial fibrillation
- Compared to warfarin in premarket clinical trials
- As with other anticoagulants, major risk is bleeding
    - No difference compared to warfarin in premarket clinical trials

Dabigatran

Bleeding Events in Pre-marketing Clinical Trials (per 100 patient-years)

	Dabigatran 150 mg twice daily N (%)	Warfarin N (%)	Hazard Ratio (95% CI**)
Randomized patients	6076	6022	
Patient-years	12,033	11,794	
Intracranial hemorrhage	38 (0.3)	90 (0.8)	0.41 (0.28, 0.60)
Life-threatening bleed	179 (1.5)	218 (1.9)	0.80 (0.66, 0.98)
Major bleed	399 (3.3)	421 (3.6)	0.93 (0.81, 1.07)
Any bleed	1993 (16.6)	2166 (18.4)	0.91 (0.85, 0.96)

Postmarket adverse event reports

- FDA received a large number of spontaneous adverse event reports of bleeding associated with dabigatran

- FDA received far fewer reports of bleeding associated with warfarin during the same time period

Safety Announcement

[11-02-2012] The U.S. Food and Drug Administration (FDA) has evaluated new information about the risk of serious bleeding associated with use of the anticoagulants (blood thinners) dabigatran (Pradaxa) and warfarin (Coumadin, Jantoven, and generics). Following the approval of Pradaxa, FDA received a large number of post-marketing reports of bleeding among Pradaxa users. As a result, FDA investigated the actual rates of gastrointestinal bleeding (occurring in the stomach and intestines) and intracranial hemorrhage (a type of bleeding in the brain) for new users of Pradaxa compared to new users of warfarin. This assessment was done using insurance claims and administrative data from FDA's Mini-Sentinel pilot of the Sentinel Initiative. The results of this Mini-Sentinel assessment indicate that bleeding rates associated with new use of Pradaxa do not appear to be higher than bleeding rates associated with new use of warfarin, which is consistent with observations from the large clinical trial used to approve Pradaxa (the RE-LY trial).[1] (see Data Summary). FDA is continuing to evaluate multiple sources of data in the ongoing safety review of this issue.

Pradaxa and warfarin are important medications used to reduce the risk of stroke and blood clots in patients with non-valvular atrial fibrillation (AF), the most common heart rhythm abnormality, which causes the heart (upper chambers or atria) to beat rapidly and irregularly. Although these drugs reduce the number of strokes in patients with non-valvular AF, they can cause bleeding, potentially leading to serious or even fatal outcomes. The risk of bleeding is a well-recognized risk of anticoagulant drugs.

Facts on Pradaxa

- Pradaxa is an anticoagulant medication used to reduce the risk of stroke and blood clots in patients with non-valvular atrial fibrillation (AF), the most common type of heart rhythm abnormality.
- The safety and efficacy of Pradaxa were studied in a clinical trial comparing Pradaxa with the anticoagulant warfarin. In the trial, patients taking Pradaxa had fewer strokes than those who took warfarin.[1]
- From approval in October 2010 through August 2012, a total of approximately 3.7 million Pradaxa prescriptions were dispensed, and approximately 725,000 patients received a dispensed prescription for Pradaxa from U.S. outpatient retail pharmacies.[2]

FDA has not changed its recommendations regarding Pradaxa. Pradaxa provides an important health benefit when used as directed. Healthcare professionals who prescribe Pradaxa should carefully follow the dosing recommendations in the drug label, especially for patients with renal impairment (when kidneys don't function normally) to reduce the risk of bleeding. Patients with atrial fibrillation should not stop taking Pradaxa without first talking to their healthcare professional. Stopping use of anticoagulant medications such as Pradaxa can increase the risk of stroke. Strokes can lead to permanent disability and death.

Postmarket adverse event reports

- How do you interpret the adverse event data?
- What more do you want to know?
- What do you do next?

Surveillance in Mini-Sentinel: ICH and GI Bleeding Outcomes/Events

New users of dabigatran and warfarin

During 183 days prior to index dispensing:

- No dispensings of either dabigatran or warfarin
- No occurrence of ICH or GIH in in-patient or emergency room setting
- Require a diagnosis of atrial fibrillation in any healthcare setting

Incidence Rate = events / 100,000 days at risk

Additional analyses

- Define new use by single drug
- Without the atrial fibrillation requirement
- Using 365 days instead of 183 days

Intracranial (ICH) and Gastrointestinal (GIH) Bleeding Events in New Users of Dabigatran and Warfarin: Mini-Sentinel

(Oct 2010 – Dec 2011, Incidence Rate =New Events/100,000 Days at Risk)

Dabigatran		Pre-existing Cond. Requirement	Warfarin	
N	Incidence Rate		N	Incidence Rate
10,599	1.6	Atrial Fibrillation – 183 days	43,541	3.5
9,241	1.4	Atrial Fibrillation – 365 days	34,962	3.7
12,195	1.6	No requirement – 183 days	119,940	3.1
10,493	1.6	No requirement – 365 days	97,669	3.3

Gastrointestinal (GIH) Bleeding Events in New Users of Dabigatran and Warfarin: Mini-Sentinel

(Oct 2010 – Dec 2011, Incidence Rate =New Events/100,000 Days at Risk)

Dabigatran		Pre-existing Cond. Requirement	Warfarin	
N	Incidence Rate		N	Incidence Rate
10,569	2.2	Atrial Fibrillation – 183 days	43,351	5.8
9,216	2.2	Atrial Fibrillation – 365 days	34,800	6.1
12,161	2.4	No requirement – 183 days	119,470	5.0
10,464	2.5	No requirement – 365 days	97,267	5.2

FDA Drug Safety Communication: FDA study of Medicare patients finds risks lower for stroke and death but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin

This information is in follow-up to the FDA Drug Safety Communication: Update on the risk for serious bleeding events with the anticoagulant Pradaxa (dabigatran) that was issued on November 2, 2012.

View and print full Drug Safety Communication (PDF - 103KB)

En español

Safety Announcement

[05-13-2014] In its ongoing review of the blood thinner Pradaxa (dabigatran), the U.S. Food and Drug Administration (FDA) recently completed a new study in Medicare patients comparing Pradaxa to the blood thinner warfarin (Coumadin, Jantoven, and generics), for risk of ischemic or clot-related stroke, bleeding in the brain, major gastrointestinal (GI) bleeding, myocardial infarction (MI), and death. Pradaxa and warfarin are used to reduce the risk of stroke and blood clots in patients with a common type of abnormal heart rhythm called non-valvular atrial fibrillation (AF).

The new study included information from more than 134,000 Medicare patients, 65 years or older, and found that among new users of blood-thinning drugs, Pradaxa was associated with a lower risk of clot-related strokes, bleeding in the brain, and death, than warfarin. The study also found an increased risk of major gastrointestinal bleeding with use of Pradaxa as compared to warfarin. The MI risk was similar for the two drugs.

Importantly, the new study is based on a much larger and older patient population than those used in FDA's earlier review of post-market data, and employed a more sophisticated analytical method to capture and analyze the events of concern. This study's findings, except with regard to MI, are consistent with the clinical trial results that provided the basis for Pradaxa's approval.

As a result of our latest findings, we still consider Pradaxa to have a favorable benefit to risk profile and have made no changes to the current label or recommendations for use. Patients should not stop taking Pradaxa (or warfarin) without first talking with their health care professionals. Stopping the use of blood-thinning medications such as Pradaxa and warfarin can increase the risk of stroke and lead to permanent disability and death. Health care professionals who prescribe Pradaxa should continue to follow the dosing recommendations in the drug label.

We urge both health care professionals and patients to report side effects involving Pradaxa or warfarin to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Regulation & Drug Safety & Data Science

Optimizing regulatory decision-making requires epidemiological tools, resources and expertise

Opportunities to access observational data from a wide range of sources

Regulatory challenge is developing capacity to proactively research safety issues

جامعة الملك سعود
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Thank you

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