U.S. FOOD & DRUG ADMINISTRATION

Cardiac Safety Signals:
Case Examples

- Testosterone
- Peripherally-acting mu-receptor antagonist
  - PAMORAs
- Dabigatran (Pradaxa)

Testosterone

- Testosterone replacement therapy is approved for men with low levels of testosterone related to certain conditions
- Demonstrated effect:“Normalization” of testosterone levels
- Safety/efficacy not established in age-related hypogonadism
- CV Safety Signal
  - 2 Observational studies showed increased risk of death, MI, stroke
  - MOA?: adverse effect on BP; lipids; inflammatory marketers

http://www.fda.gov/downloads/Drugs/DrugSafety/UCM436270.pdf

Testosterone: CV Safety Signal

Study	Database	Endpoint	Risk (TRT vs. control)
Xu, et al (MA #1; 2013)	27 RCT	"CV related events"	OR: 1.5 (1.1, 2.1)
Corona, et al (MA #2; 2014)	26 RCT	CV death; non-fatal MI; stroke; ACS; HF	OR: 1.01 (0.57, 1.77)
**Vigen, et al (Obs #1; 2013)*	*VA system (angiog plus low t)*	*Death, MI, stroke*	*HR 1.29 (1.04, 1.58)* *RD: 5.8% (-1.4, 13.1)*
**Finkle, et al (Obs #2; 2014)*	*Commercial claims (pre vs. post rx)*	*Non-fatal MI*	*RR: 1.36 (1.03, 1.81)* • *Age effects* *RD: 1.27/1000 pt-yrs*
Shores, et al (Obs #3; 2012)	VA system	Mortality	HR: 0.61 (0.42, 0.88) RD: -2.3/100 pt-yrs
Muraleedharan (Obs #4; 2013)	Hypogonadism study	Mortality	HR 0.43 RD: 10.8%
Baillargeon (Obs #5; 2014)	Medicare sample	MI	HR: 0.84 (0.69, 1.02)

http://www.fda.gov/downloads/Drugs/DrugSafety/UCM436270.pdf posted 3/3/2015.

Investigating the CV signal

- Advisory Committee held in 2014
  - Safety signal is weak
  - Use in age related hypogonadism inappropriate
  - Only a prospective, well-controlled clinical trial could determine whether testosterone causes cardiovascular harm.
    - Differing views on studied population
- FDA required RCT to investigate signal

A randomized, double-blind, placebo-controlled clinical trial to evaluate the effect of testosterone replacement therapy on the incidence of major adverse cardiovascular events in men. We recommend that this trial also assess other important safety and efficacy outcomes associated with testosterone therapy.

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/ucm404895.htm

PAMORAs

- Peripherally acting mu-opioid receptor antagonists
  - Opioid induced constipation; post-operative ileus
    - Entereg (alvimopan); Relistor (methylnaltrexone); Movantik (naloxegol)
  - Abuse deterrent opioids
    - Targiniq (naloxone+oxycodone)

PAMORAs: CV Safety Signal

- Signal originated from alvimopan
  - Imbalance in MIs in 12 month controlled trial for opioid induced constipation
  - MOA?: opioid withdrawal, vasoconstriction, class effect?
- No CV signal for Movantik in development program
  - 2 12-week placebo controlled studies (n=1300)
  - 1 52-week controlled safety study (n=800)
- Lack of signal for Relistor (4 weeks); Targiniq

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm390304.htm

Investigating the signal

- Advisory committee on PAMORAs (2014)
  - No dedicated controlled, pre-approval CVOT needed because signal weak
  - 12 month controlled, “modestly sized”, pre-approval trial
  - Reassuring to collect post-marketing data on cardiac safety via observational studies
- FDA required postmarket observational studies for Movantiq, Relistor, and Targiniq

FDA required study

2779-1 A post-marketing, observational epidemiologic study comparing MOVANTIK (naloxegol) to other treatments of opioid induced constipation in patients with chronic non-cancer pain. The study's primary outcome is a composite of major adverse cardiovascular events (MACE): cardiovascular (CV) death, nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes include, but are not limited to, CV death, nonfatal myocardial infarction, and nonfatal stroke separately. Specify concise case definitions and validation algorithms for the primary and secondary outcomes. Justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to MOVANTIK (naloxegol)-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, MACE risk among MOVANTIK (naloxegol) users relative to comparator(s) considering important potential confounders including lifestyle risk factors and over the counter (OTC) medications with potential for cardiovascular effects, with a pre-specified statistical analysis method. For the MOVANTIK (naloxegol)-exposed and comparator(s), clearly define the new user clean period, including any exclusion and inclusion criteria. Ensure an adequate number of patients with at least 12 months of MOVANTIK (naloxegol) exposure at the end of the study.

Dabigatran

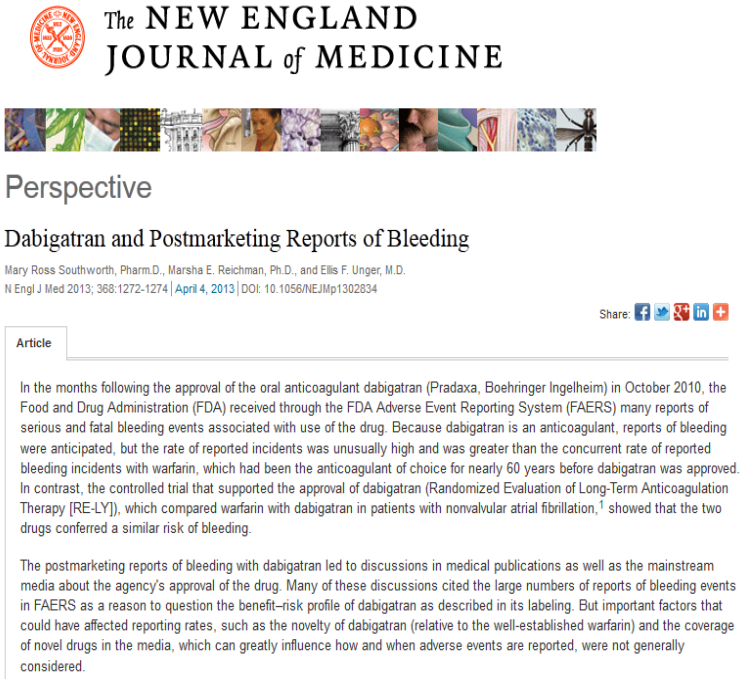
- Direct thrombin inhibitor approved (2010) for prevention of stroke in patients with NVAF
  - First anticoagulant approved since warfarin (1954)
- Postmarketing reports of bleeding signaled concerns
  - FAERS reports numerous (10,000 in first year)
  - Literature reports
  - Regulatory Authority alerts

FDA actions

- Modular programs run in Mini-Sentinel
  - October 2011 (too little exposure)
  - October 2012 (basis for drug safety communication and NEJM article)

"…large numbers of reported cases of bleeding with dabigatran is an example of stimulated reporting. The Mini-Sentinel assessment suggests that bleeding rates with dabigatran are not higher than those with warfarin, a finding that is consistent with the results of RE-LY"

-April 2013



The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Dabigatran and Postmarketing Reports of Bleeding

Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.

N Engl J Med 2013; 368:1272-1274 | April 4, 2013 | DOI: 10.1056/NEJMp1302834

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Article

In the months following the approval of the oral anticoagulant dabigatran (Pradaxa, Boehringer Ingelheim) in October 2010, the Food and Drug Administration (FDA) received through the FDA Adverse Event Reporting System (FAERS) many reports of serious and fatal bleeding events associated with use of the drug. Because dabigatran is an anticoagulant, reports of bleeding were anticipated, but the rate of reported incidents was unusually high and was greater than the concurrent rate of reported bleeding incidents with warfarin, which had been the anticoagulant of choice for nearly 60 years before dabigatran was approved. In contrast, the controlled trial that supported the approval of dabigatran (Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY]), which compared warfarin with dabigatran in patients with nonvalvular atrial fibrillation,[1] showed that the two drugs conferred a similar risk of bleeding.

The postmarketing reports of bleeding with dabigatran led to discussions in medical publications as well as the mainstream media about the agency's approval of the drug. Many of these discussions cited the large numbers of reports of bleeding events in FAERS as a reason to question the benefit–risk profile of dabigatran as described in its labeling. But important factors that could have affected reporting rates, such as the novelty of dabigatran (relative to the well-established warfarin) and the coverage of novel drugs in the media, which can greatly influence how and when adverse events are reported, were not generally considered.

Observational Study in Medicare

Table 2. Outcome Event Counts, Incidence Rates, and Adjusted Hazard Ratios With 95% CIs Comparing Propensity Score–Matched New-User Cohorts of Dabigatran and Warfarin Treated for Nonvalvular Atrial Fibrillation, With Warfarin as the Reference Group

	No. of Events		Incidence Rate per 1000 Person-Years		Adjusted Hazard Ratio (95% CI)	*P* Value
	Dabigatran	Warfarin	Dabigatran	Warfarin		
Primary outcomes						
Ischemic stroke	205	270	11.3	13.9	0.80 (0.67–0.96)	0.02
Major hemorrhage	777	851	42.7	43.9	0.97 (0.88–1.07)	0.50
Gastrointestinal	623	513	34.2	26.5	1.28 (1.14–1.44)	<0.001
Intracranial	60	186	3.3	9.6	0.34 (0.26–0.46)	<0.001
Intracerebral	44	142	2.4	7.3	0.33 (0.24–0.47)	<0.001
Acute myocardial infarction	285	327	15.7	16.9	0.92 (0.78–1.08)	0.29
Secondary outcomes						
All hospitalized bleeds	1079	1139	59.3	58.8	1.00 (0.92–1.09)	0.97
Mortality*	603	744	32.6	37.8	0.86 (0.77–0.96)	0.006

*For 1064 deaths not preceded by a primary study outcome, the adjusted hazard ratio (95% confidence interval [CI]) was 0.89 (0.79–1.00; *P*=0.051), whereas for 283 deaths occurring within 30 days after a primary outcome, the adjusted hazard ratio (95% CI) was 0.77 (0.61–0.98; *P*=0.03).

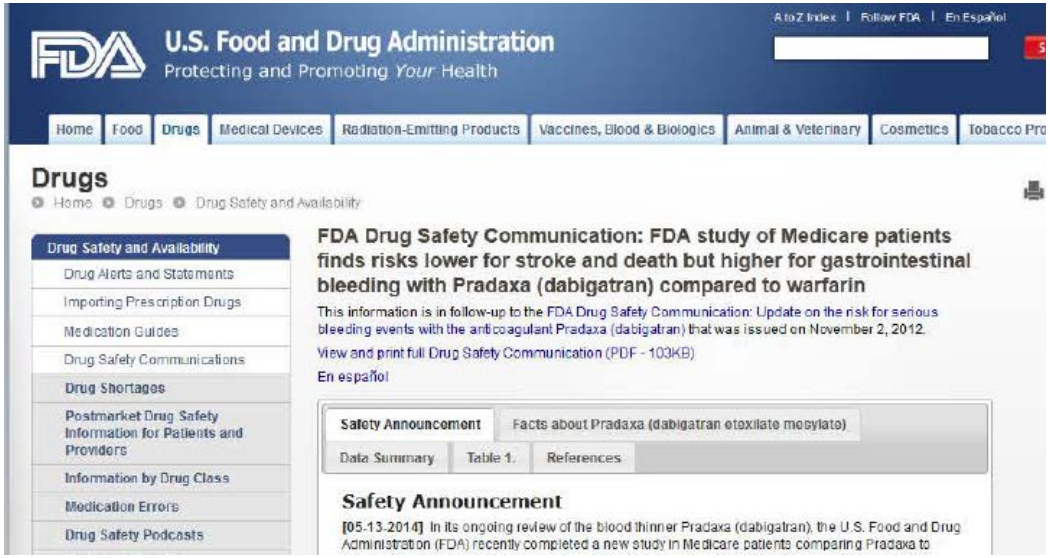
Graham DJ et al, Circulation 2015.

FDA actions

- CMS Observational Study (basis for drug safety communication)

"In this study…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."

-May 2014



Other CV signals investigated

- NSAIDS
- Weight loss drugs
- Chantix (Varenicline)
- PAMORAs
- Zelnorm (Tegaserod)
- Benicar (Olmesartan)
- Diabetes drugs
- Stalevo (entacapone)
- Azithromycin
- Loperamide

Summary

- Inconsistent results limit confidence in observational studies
  - Risk vs. No Risk vs. Protective Effect
  - Implausible subgroup findings
  - Results differ based on methodology used
- When Observational study consistent with RCT
  - Use methodology/database to investigate similar signals?
- Need for/Approach to safety study affected by
  - Baseline risk of the treated population
  - Benefit demonstrated
  - Strength of signal
  - Feasibility
  - Risk aversion attitudes
  - Policy
- Parameters stipulated in required studies are broad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