



FDA Advisory Committee Meeting Trilipix® & The ACCORD-Lipid Trial

Eric Colman, MD

Division of Metabolism and Endocrinology Products

U.S. Food and Drug Administration

May 19, 2011

Introduction

- Fibrates
- Trilipix plus a statin
- ACCORD-Lipid trial
- Today's agenda
- Discussion points and questions

Fibrates Approved in U.S.

- Gemfibrozil
 - Initial approval 1981
 - Numerous generics
- Fenofibrate
 - Initial approval 1993
 - Numerous generics
- Fenofibric acid (active ingredient of fenofibrate)
 - Trilipix approved 2008
 - No generics.....thus far

Fenofibrate

- Indications:
 1. Treat severe hypertriglyceridemia
 2. To reduce elevated LDL-C, Total-C, TG, and Apo B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia

Fenofibric Acid - Trilipix®

- Indications:
 1. Treat severe hypertriglyceridemia
 2. To reduce elevated LDL-C, Total-C, TG, and Apo B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia

Fenofibric Acid -Trilipix®

- Indications:
 3. In combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal

ACCORD-Lipid Trial

- Randomized, double-blind, placebo-controlled add-on trial
- Simvastatin plus fenofibrate vs. simvastatin plus placebo
- Primary outcome: major cardiovascular events (MACE) defined as CVD death plus nonfatal MI and stroke
- 5518 subjects with type 2 diabetes
- Mean follow-up 4.7 years

ACCORD Lipid – Primary Outcome

Table 2. Prespecified Primary and Secondary Outcomes.

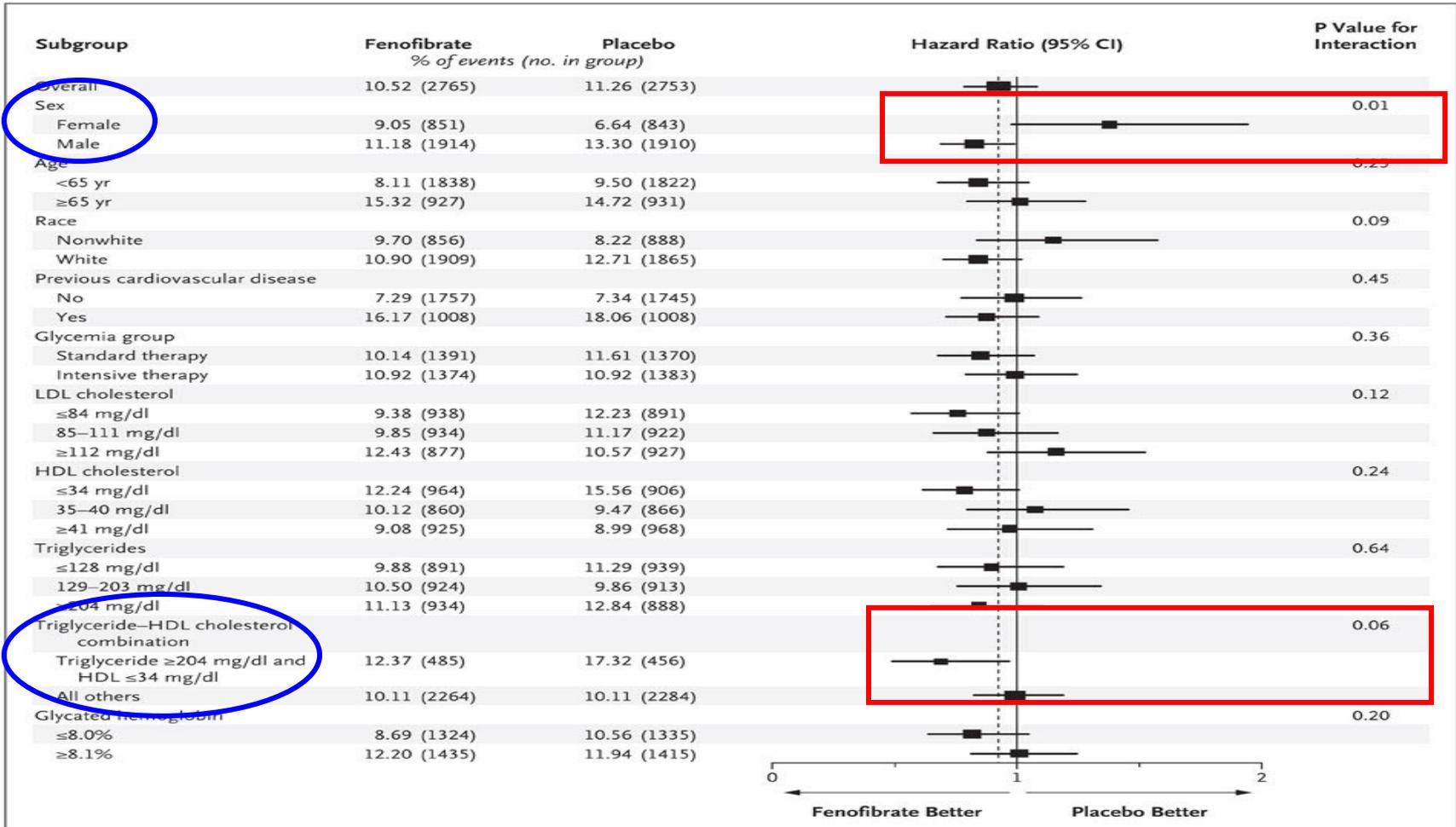
Outcome	Fenofibrate (N = 2765)		Placebo (N = 2753)		Hazard Ratio (95% CI)	P Value
	no. of events	rate/yr	no. of events	rate/yr		
Primary outcome (major fatal or nonfatal cardiovascular event)	291	2.24	310	2.41	0.92 (0.79–1.08)	0.32*
Secondary outcomes						
Primary outcome plus revascularization or hospitalization for congestive heart failure	641	5.35	667	5.64	0.94 (0.85–1.05)	0.30
Major coronary disease event†	332	2.58	353	2.79	0.92 (0.79–1.07)	0.26
Nonfatal myocardial infarction	173	1.32	186	1.44	0.91 (0.74–1.12)	0.39
Stroke						
Any	51	0.38	48	0.36	1.05 (0.71–1.56)	0.80
Nonfatal	47	0.35	40	0.30	1.17 (0.76–1.78)	0.48
Death						
From any cause	203	1.47	221	1.61	0.91 (0.75–1.10)	0.33*
From cardiovascular cause	99	0.72	114	0.83	0.86 (0.66–1.12)	0.26
Fatal or nonfatal congestive heart failure	120	0.90	143	1.09	0.82 (0.65–1.05)	0.10

* P values were adjusted for interim monitoring.

† A major coronary disease event was defined as a fatal coronary event, nonfatal myocardial infarction, or unstable angina.



ACCORD Lipid – Subgroup Analyses



Today's Agenda

- Henry Ginsberg, MD, Columbia University
- Abbott Laboratories and Peter Jones, MD
- FDA
 - Vicky Borders-Hemphill, PharmD
 - Christian Hampp, PhD
 - Iffat Chowdhury, MD
- Open Public Hearing
- Discussion and Questions

Discussion Point 1

- Discuss your interpretation of the primary efficacy results from ACCORD-Lipid, specifically as they relate to Trilipix's indication for coadministration with a statin.

Discussion Point 2

- In the subgroup of women from ACCORD-Lipid, the incidence of MACE in patients randomized to simvastatin plus placebo was 6.6% compared to 9.1% in patients randomized to simvastatin plus fenofibrate (interaction p-value 0.01 vs. men).
- Discuss your interpretation of this subgroup finding, specifically as it relates to Trilipix's indication for coadministration with a statin.

Discussion Point 3

- In the subgroup of patients from ACCORD-Lipid with baseline levels of TG \geq 204 mg/dl and HDL-C \leq 34 mg/dl, the incidence of MACE in patients randomized to simvastatin plus placebo was 17.3% compared to 12.4% in patients randomized to simvastatin plus fenofibrate (interaction p-value 0.06 vs. all others).
- Discuss your interpretation of this subgroup finding, specifically as it relates to Trilipix's indication for coadministration with a statin.

Discussion Point 4

- Discuss the safety profile of fenofibrate/fenofibric acid, specifically as it relates to Trilipix's indication for coadministration with a statin.

Discussion Point 5

- Discuss the benefit-risk profile of Trilipix when used in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD equivalent who are on optimal statin therapy to achieve their LDL-C goal.

Questions

Taking into account all relevant data and levels of evidence:

A. Should FDA require the conduct of a clinical trial designed to test the hypothesis that, in high-risk men and women at LDL-C goal on a statin with residually high TG and low HDL-C, add-on therapy with Trilipix versus placebo significantly lowers the risk for MACE?

Vote Yes or No and provide the rationale for your recommendation

B. Which regulatory action do you recommend FDA take regarding Trilipix's indication for coadministration with a statin?

1. Allow continued marketing of Trilipix's indication for coadministration with a statin without revision of the labeling
2. Withdraw approval of Trilipix's indication for coadministration with a statin
3. Allow continued marketing of Trilipix's indication for coadministration with a statin with revision of the labeling to incorporate the principal findings from ACCORD Lipid

Vote 1, 2, or 3 and provide the rationale for your recommendation

Reminder

- Today's discussion will influence not only the statin coadministration indication for Trilipix, but also the Division's approval standards and regulatory policy for combinations of statins and fibrates in general
- Prior to publication of ACCORD Lipid, several companies expressed interest in obtaining approval of statin-fibrate products based on changes in TG and HDL-C
- Generics of Trilipix



Fibrate and Statin Concurrency Analyses

CDR Vicky Borders-Hemphill, PharmD
Drug Utilization Analyst
Division of Epidemiology
Office of Surveillance and Epidemiology

OUTLINE

- National estimates of Fibrate and Statin Patient Counts
- Concurrent Claims Analysis
- Limitations
- Summary

Data Source:

- ***Wolters Kluwer SOURCE Lx[®] database***
 - Longitudinal patient data source
 - U.S. adjudicated medical and prescription claims
 - Commercial plans, Medicare Part D plans, Cash and Medicaid claims.
 - 4.8 billion paid, non-reversed prescriptions claims linked to over 172 million unique prescription patients
 - Medical claims history of which nearly 91 million prescription drug patients are linked to medical claims
 - The overall sample represents 27,000 pharmacies (retail/specialty/mail order), 1,000 hospitals, 800 clinics/outpatient facilities, and 80,000 physician practices.

Methodology

- Patients with a fibrate or statin prescription claim during years 2007 – 2010
- Concurrency: Patients with fibrate prescription claim with overlapping days supply* of a statin prescription claim

** days supply = add the number of therapy days to the date of prescription dispensing*

Methodology

- A 50% grace period was allowed for the days supply time window to adjust for delays in prescription filling[†]
- The number of *therapy days* is estimated by dividing the number of tablets or capsules dispensed by the number of tablets or capsules estimated to be consumed per day.

†total days of therapy for a claim with 30 days supply would be 45 days

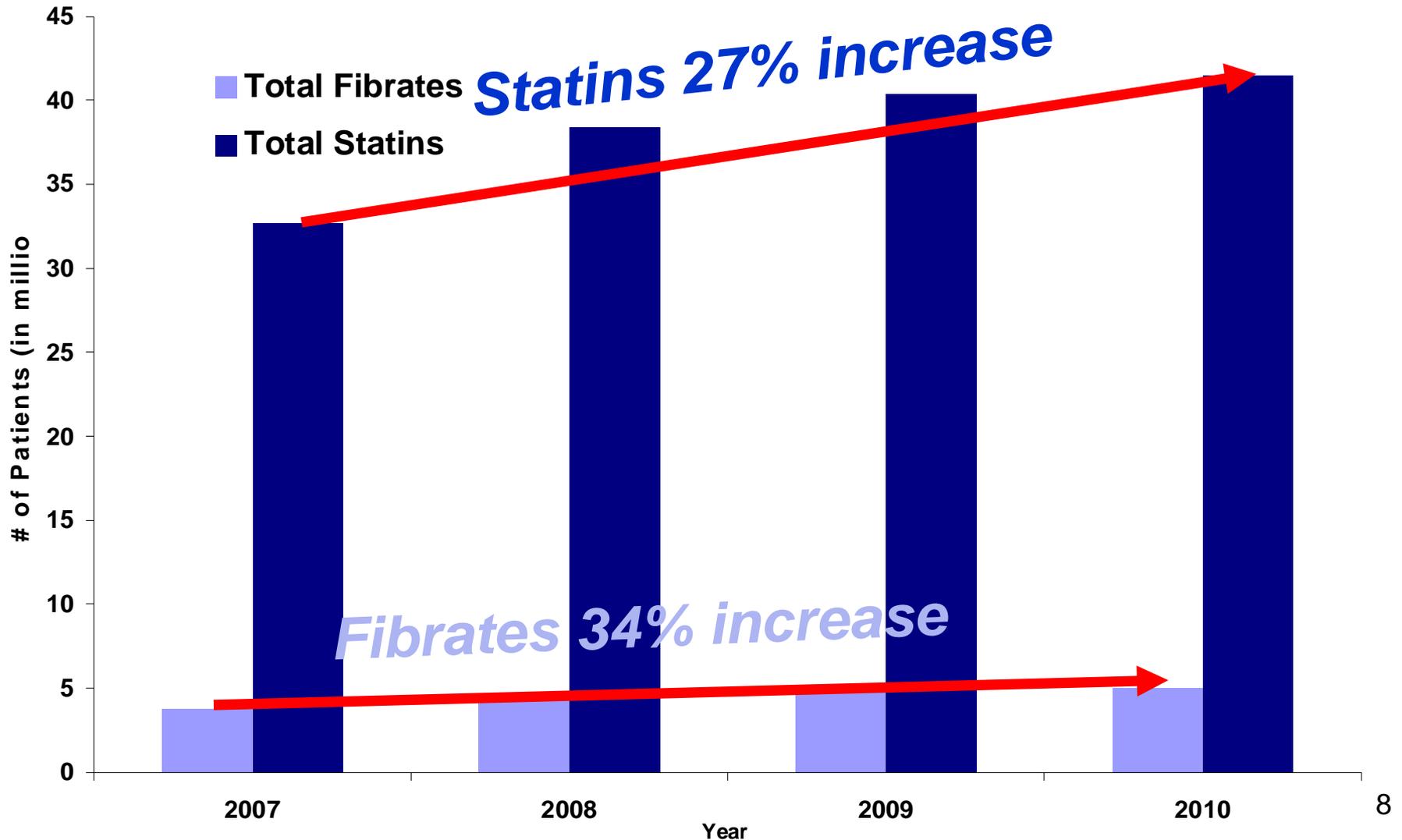
Fibrate Products Included:

- Gemfibrozil/Lopid
- Trilipix (choline fenofibrate/fenofibric acid)
- Other fenofibrates:
 - Fenofibrate
 - Antara
 - Fenoglide
 - Lipofen
 - Tricor
 - Triglide
 - Fenofibric acid
 - Fibracor

Statin Products Included:

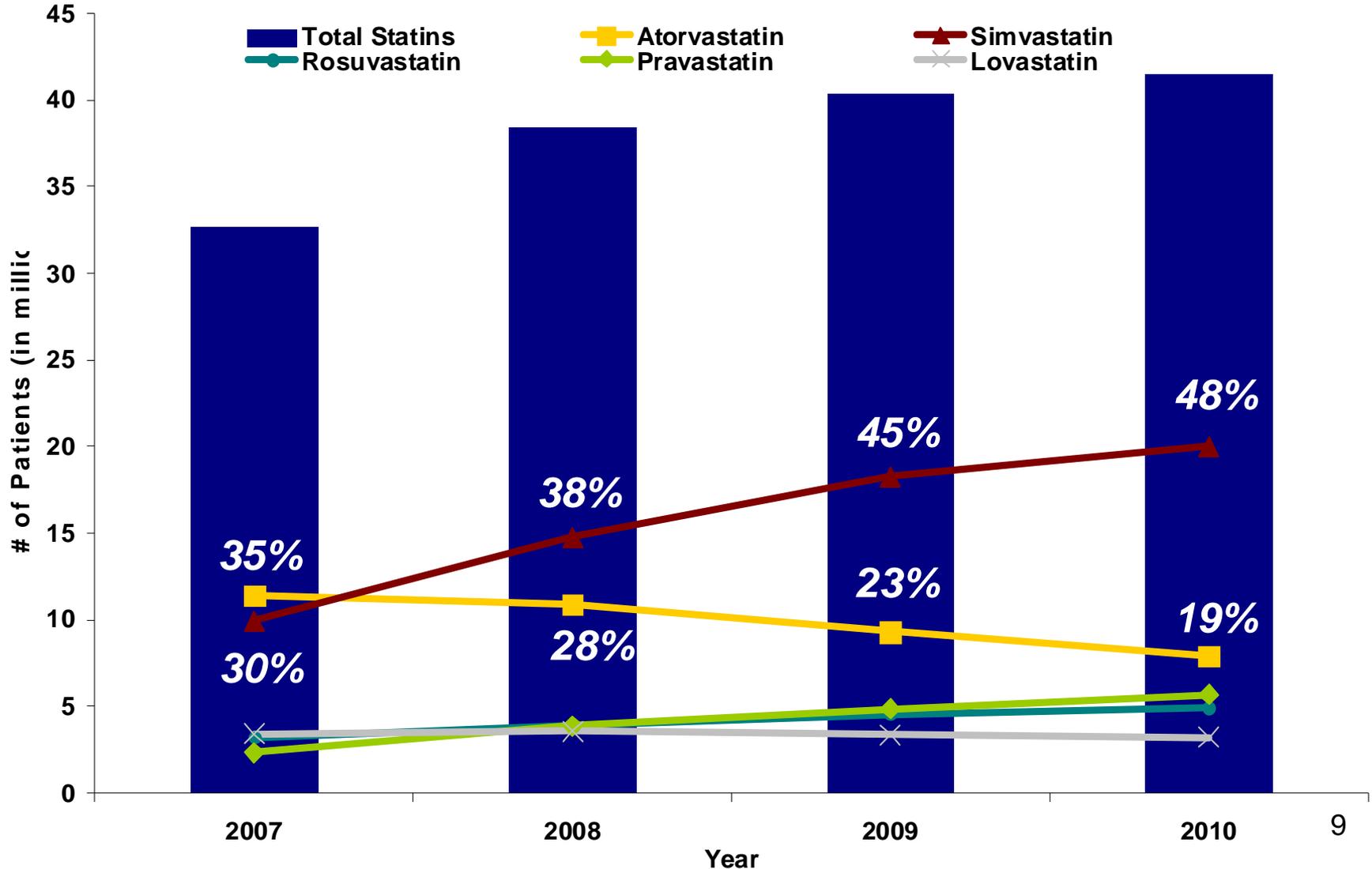
- Single ingredient Statins
 - Simvastatin
 - Atorvastatin
 - Rosuvastatin
 - Fluvastatin
 - Pitavastatin
 - Lovastatin
 - Pravastatin
- Combination Statins
 - Caduet (atorvastatin-amlodipine)
 - Vytorin (ezetimibe-simvastatin)
 - Advicor (niacin-lovastatin)
 - Simcor (niacin-simvastatin)

Patients with a Fibrate or Statin Claim



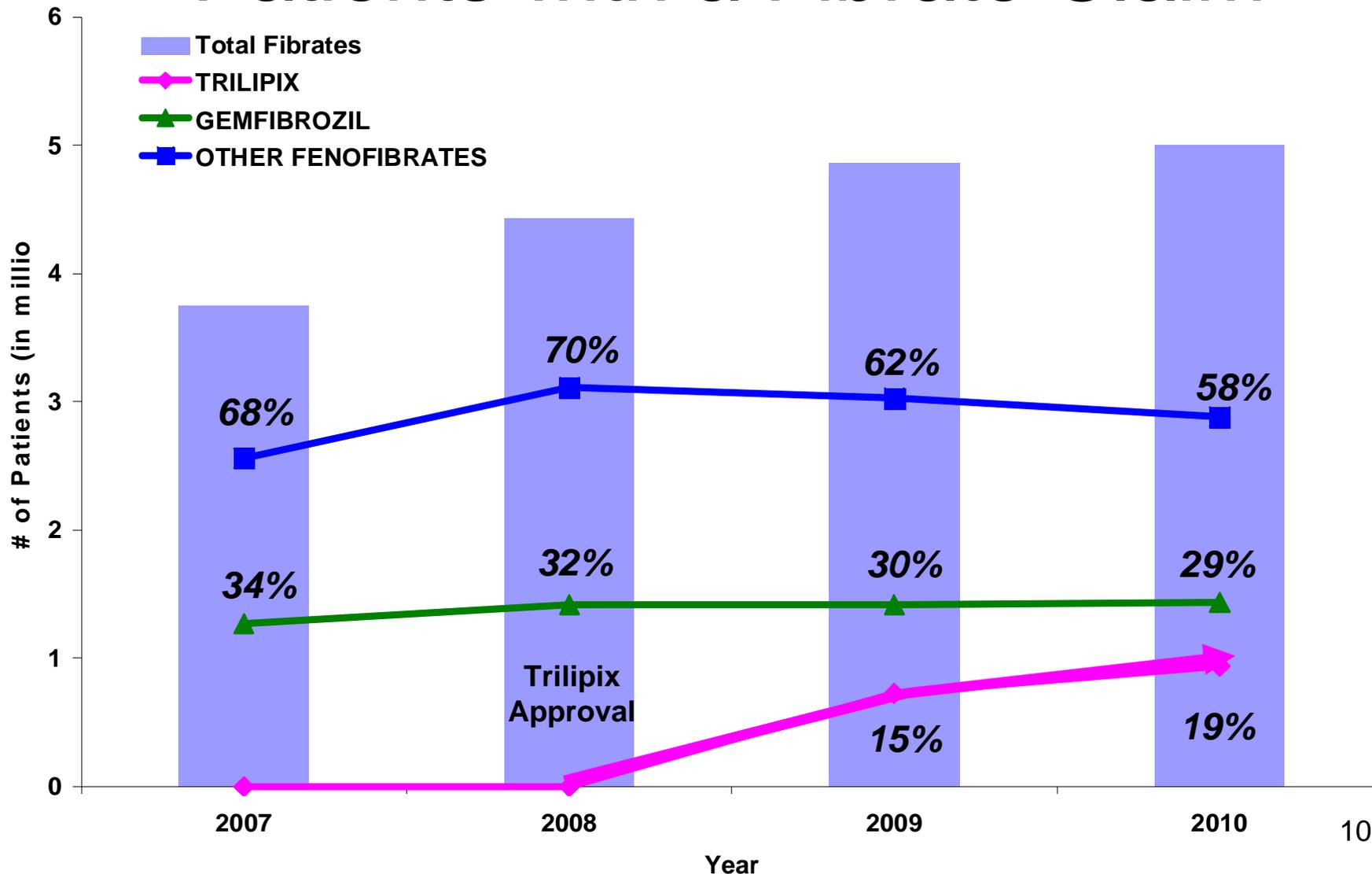
Source: Wolters Kluwer Health's Source® Lx. CPA tool Years 2007-2010. Extracted March 2011.

Patients with a Statin Claim



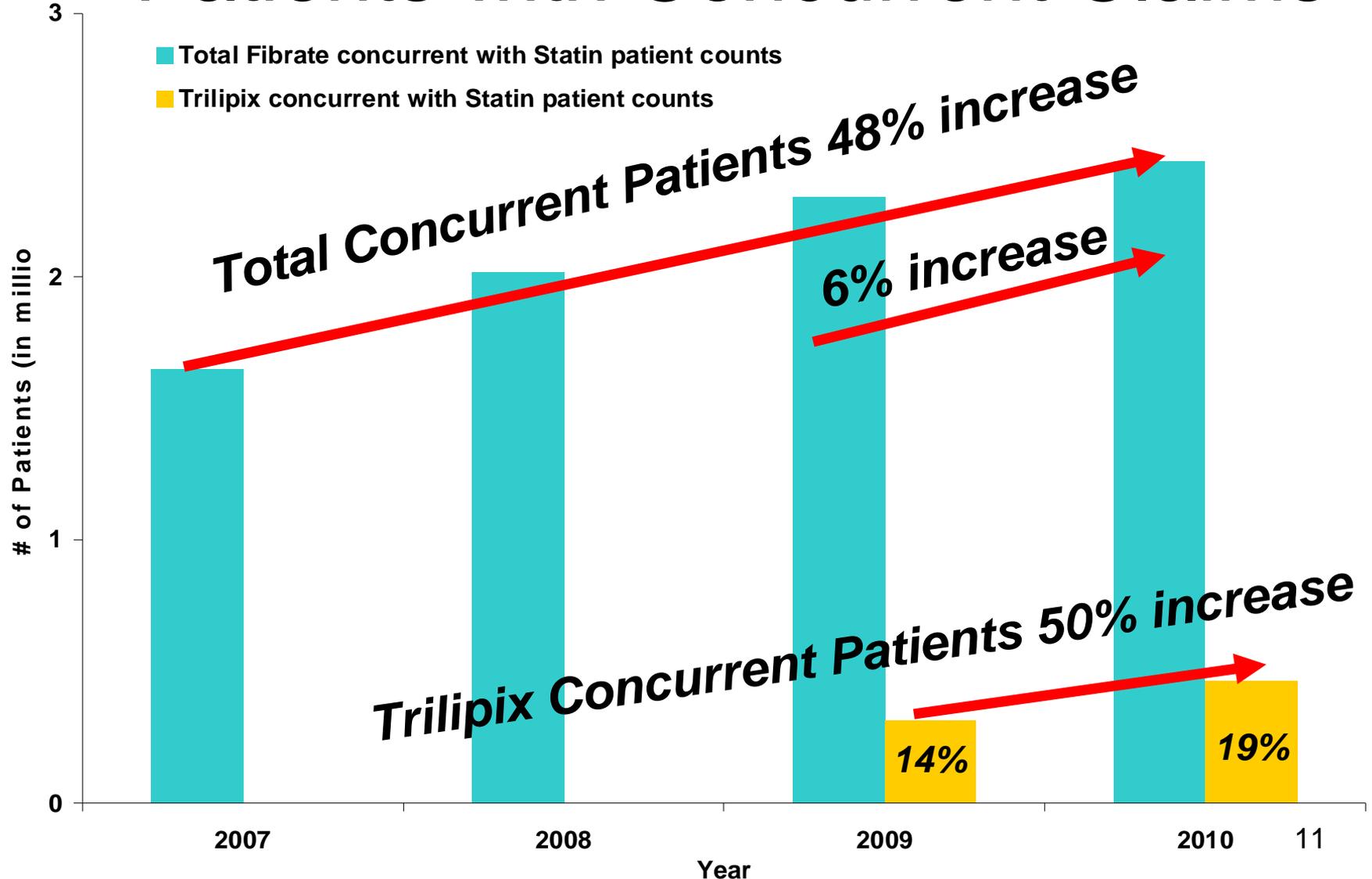
Source: Wolters Kluwer Health's Source® Lx. CPA tool Years 2007-2010. Extracted March 2011.

Patients with a Fibrate Claim



Source: Wolters Kluwer Health's Source® Lx. CPA tool Years 2007-2010. Extracted March 2011.

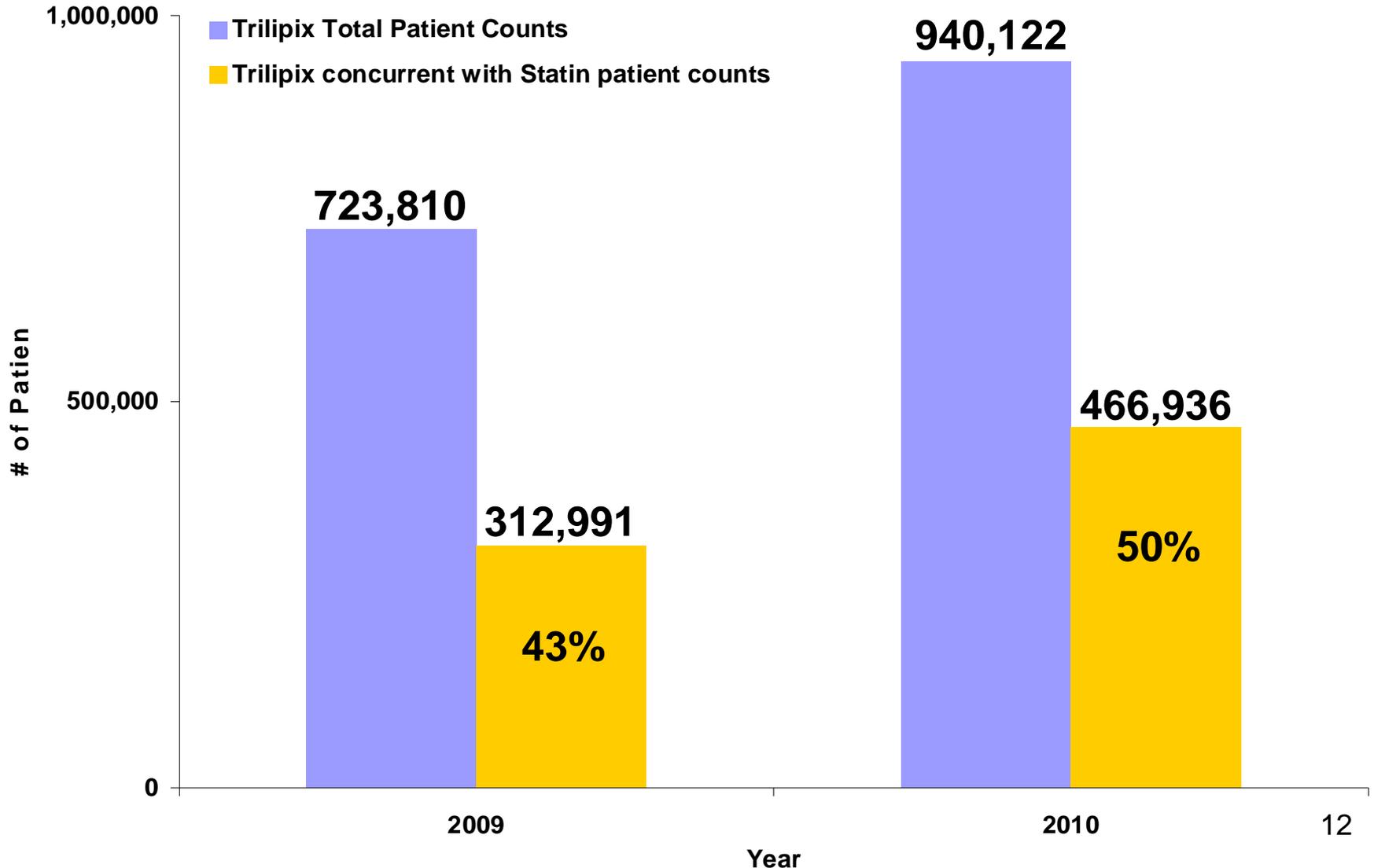
Patients with Concurrent Claims



Source: Wolters Kluwer Health's Source® Lx. CPA tool Years 2007-2010. Extracted March 2011.



Trilipix Patients: Total & Concurrent Claims



Source: Wolters Kluwer Health's Source® Lx. CPA tool Years 2007-2010. Extracted March 2011.

Concurrent Patients: Trilipix/Statin Year 2010

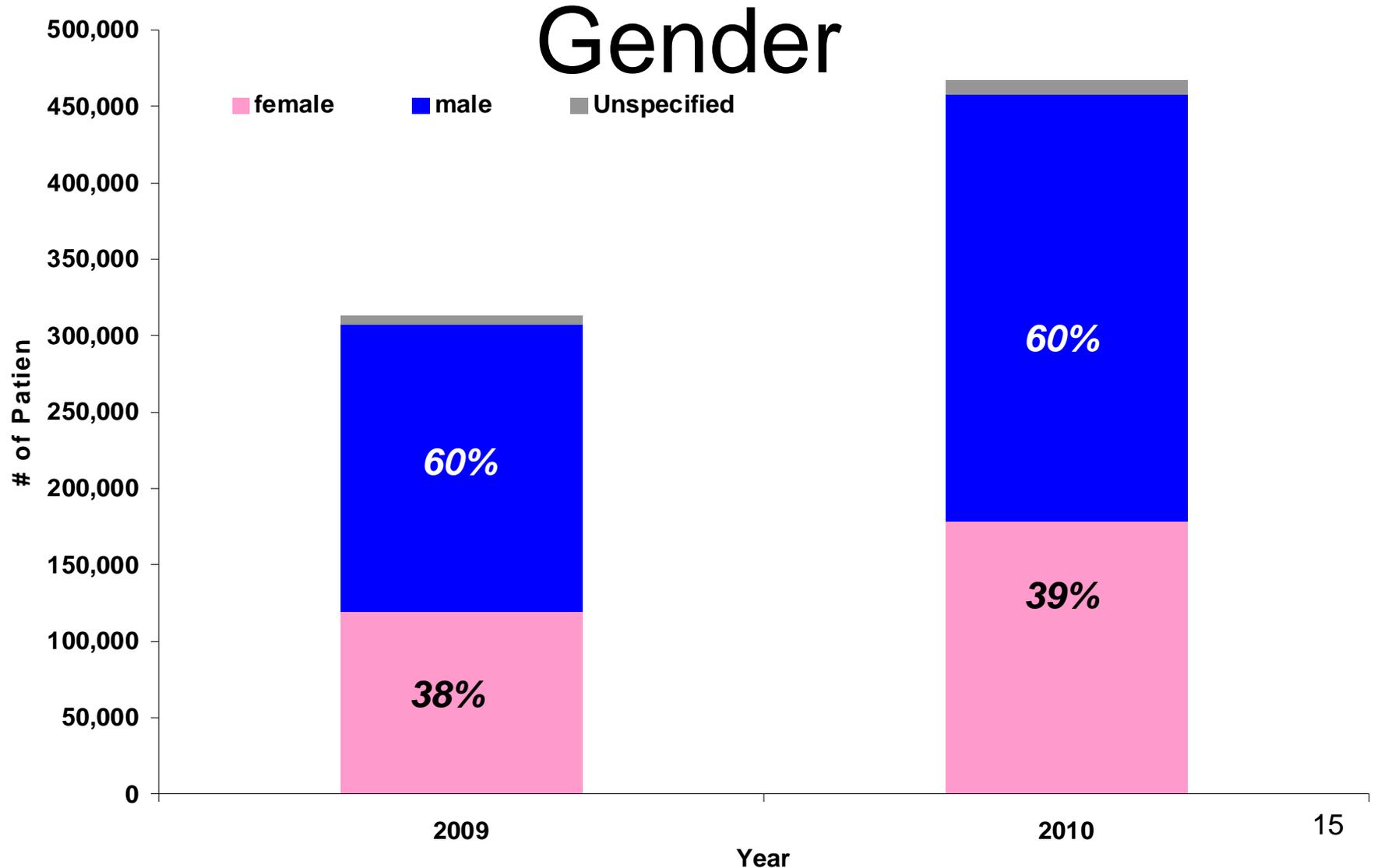
- Patients with concurrent Trilipix and Statin claims:
 - simvastatin (36%)
 - rosuvastatin (27%)
 - atorvastatin (19%)
 - pravastatin (11%)
 - Vytorin (6%)

Concurrent Patients: Trilipix/Statin Year 2010

- Concurrent Trilipix and Statin claims by strength:
 - simvastatin 40 mg (18%)
 - rosuvastatin 10 mg (12%)
 - simvastatin 20 mg (11%)
 - rosuvastatin 20 mg (10%)
 - simvastatin 80 mg (7%)



Concurrent Patients: Trilipix/Statin



Source: Wolters Kluwer Health's Source® Lx. CPA tool Years 2007-2010. Extracted March 2011.

Limitations

- Concurrency Analysis:
 - Mail order data excluded
 - Do not add patient counts across years
 - No statistical tests performed
 - Assumptions:
 - (1) patient is taking prescription(s) as recommended; and
 - (2) recorded days supply reflects how the patient is actually taking the prescription.
- Indications for use are unknown

Summary

- Year 2010: 41.5 million patients with Statin claim and 5 million patients with fibrate claim
 - 940,000 patients had a Trilipix claim
 - 467,000 (50%) Trilipix patients had a concurrent claim for a statin
- Trilipix utilization increased since marketing
 - Greatest proportion of concurrent claims were with simvastatin 40 mg (18%)
 - Females accounted for around 40% of patients



Hospitalized Rhabdomyolysis with Combined Statin/Fibrate Use

*Observational evidence submitted by the sponsor
in the context of the Trilipix Postmarketing Requirement*

*Endocrinologic and Metabolic Drugs Advisory Committee Meeting
May 19, 2011*

Christian Hampp, PhD

Division of Epidemiology I
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
US Food and Drug Administration

Outline

- Postmarketing Requirement (PMR) for Trilipix NDA (2008)
- FDA observational study (Graham et al., *JAMA* 2004)
- Assessment of i3 study on rhabdomyolysis submitted as part of Trilipix PMR
- Published i3 study on additional safety outcomes for combinations of statins and fibrates (Enger et al., *Am J Cardiol* 2010)

Postmarketing Requirement for Trilipix NDA

- FDA required sponsor to conduct **“an observational study to estimate the incidence and risk factors for hospitalized rhabdomyolysis** in patients treated with a **fibrate in combination with a statin**, versus **statin or fibrate monotherapy**.
- FDA recommended methodology used in **“Incidence of Hospitalized Rhabdomyolysis in Patients Treated with Lipid-Lowering Drugs** by **Graham and Staffa**, published in JAMA December 1, 2004.”

Graham et al. (2004)

- Methodology
 - Inception cohort based on data from 11 US health plans
 - Study period: 1/1/1998 – 6/30/2001
 - 180 days baseline period free of drug use for each exposure cohort
 - Exposure based on days of supply + 30 days
 - Outcome: hospitalized rhabdomyolysis, identified from claims data search and validated through medical record review

Findings, Graham et al. (2004)

- 252,460 patients with 225,640 person-years of monotherapy and 7,300 person-yrs of combined therapy
- 194 potential cases and 24 confirmed cases of hospitalized rhabdomyolysis

Exposure	Cases	IR /100,000 p-yrs	95% CI
None	0	0	0 – 4.8
Atorvastatin	7	5.4	2.2 – 11.2
Cerivastatin	4	53.4	16.4 – 136.8
Pravastatin	0	0	0 – 11.1
Fluvastatin	0	0	--
Lovastatin	0	0	--
Simvastatin	2	4.9	0.6 – 17.6
Fenofibrate	0	0	0 – 145.8
Gemfibrozil	3	37.0	7.6 – 108.2
Atorvastatin + fenofibrate	1	224.5	5.7 – 1250
Fenofibrate + atorvastatin		168.6	4.3 – 936.0
Cerivastatin + gemfibrozil	3	10 350.0	3890 – 21,170
Gemfibrozil + cerivastatin	3	7 890.0	1660 – 21,380
Simvastatin + gemfibrozil	1	187.3	4.7 – 1040



Occurrence of Rhabdomyolysis with Fibrate and Statin Use

PMR Report by i3 drug safety

Prepared 01/26/2010, revised 06/17/2010

Objectives

To estimate and compare the incidence of hospitalized rhabdomyolysis during periods of use of **statins, fenofibrate, and gemfibrozil monotherapy, concomitant use of statins and fibrates,** and periods of **non-use** (no statins or fibrates)

Data Source

- Normative Health Informatics (NHI) database based on 44 major markets or health plans
- Medical and pharmacy data for >60 million current and past members from 01/1993-12/2009
- 12 million members in Jan 2006, ~3-4% of US population
- Population over 65 is underrepresented (8% in database vs. 12% of US population)
- Average length of membership: 18 months
- Medical record abstraction is possible

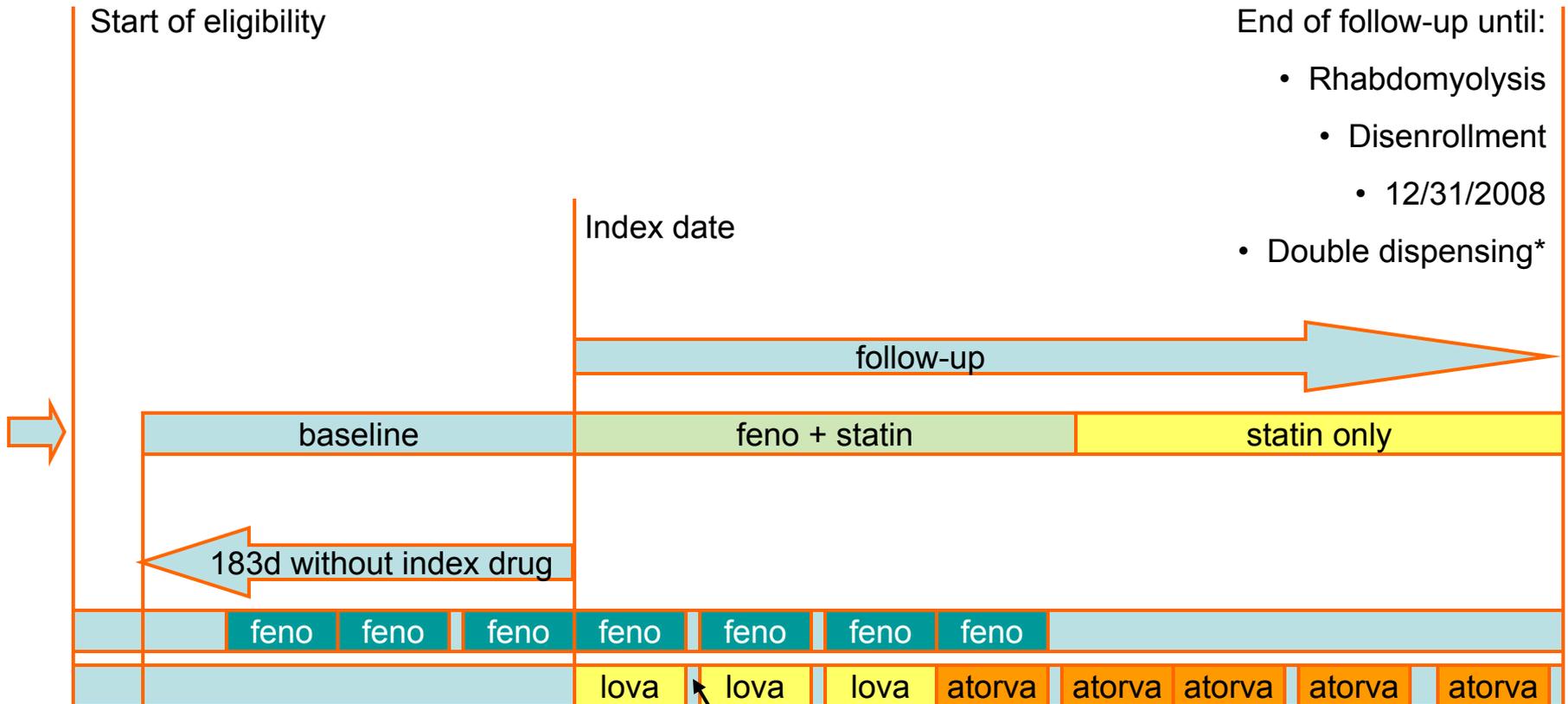
Study Design

- Retrospective cohort study
- New user design
- Study period: 1/1/1998-12/31/2008
- Inclusion criteria:
 - Age >17 years
 - Commercial insurance coverage with medical and pharmacy benefits
 - >183 days of continuous enrollment
 - At least one dispensing of a statin (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin) or fibrate (fenofibrate, gemfibrozil)
- Exclusion criteria:
 - Receipt of cerivastatin or clofibrate
 - Claims-based diagnosis of rhabdomyolysis during baseline period

Study Design: Exposure

- Index date: 1st prescription of fibrate, statin, or both, that was preceded by 183 days without a drug in the same class
- Follow-up: each day was categorized by current exposure to statin and/or fibrate
- Exposure duration: current days of supply + 20%

Study Design: Exposure

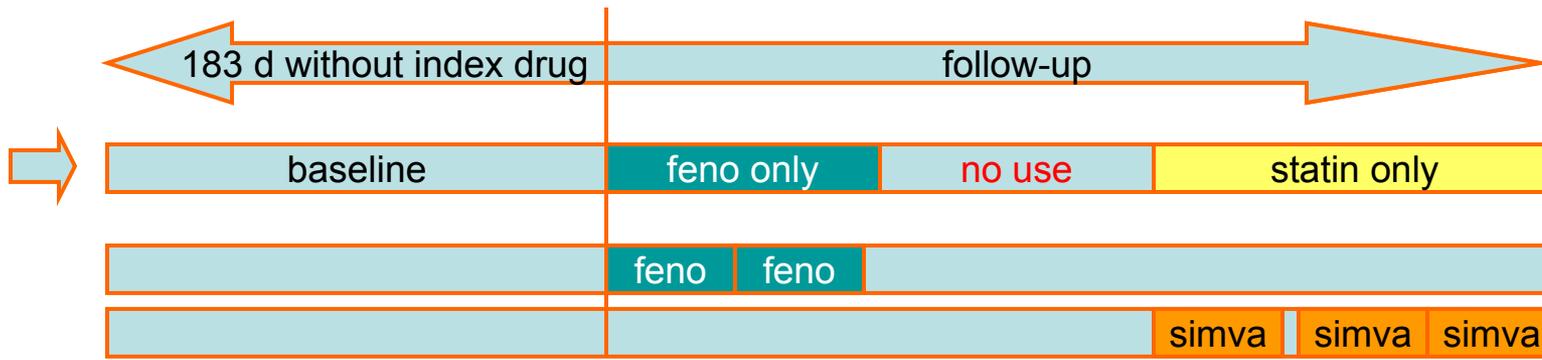


- End of follow-up until:
- Rhabdomyolysis
 - Disenrollment
 - 12/31/2008
 - Double dispensing*

Exposure duration: current days of supply + 20%

* Two statins or two fibrates on the same day

Exposure: No Use



- No use is a period without lipid-lowering drug use
- No use period is preceded by lipid-lowering drug use (-> inclusion criteria)

Study Design: Outcomes

- Outcome: hospitalized rhabdomyolysis
- 3 steps:
 1. medical claims: 1st or 2nd position of inpatient claims :

ICD-9-CM Code	ICD-9-CM Description
710.4	Polymyositis
791.3	Myoglobinuria
728.88	Rhabdomyolysis
728.89	Other disorder of muscle, ligament, and fascia
728.9	Unspecified disorder of muscle, ligament, and fascia
729.1	Myalgia and myositis
729.8x	Musculoskeletal symptoms of the limb
359.4, 359.8, 359.9	Myopathy
E942.2	Adverse effect of antihyperlipidemic agents

Study Design: Outcomes cont'd

2. claims profile review: Clinical consultant blinded to exposure excluded obvious false-positives
3. medical record review by blinded clinical consultants:

Rhabdomyolysis

- 1) **Creatine kinase increase to ≥ 10** x laboratory upper limit of normal (ULN), with **concomitant muscle symptoms** (e.g., weakness, aching, tenderness) and **no obvious acute alternate etiology** (e.g., burns, crush injury); **AND**
- 2) Creatinine elevation to \geq laboratory ULN, or new clinical diagnosis of **renal insufficiency** or renal failure*

Requires hospitalization

* 2) narrows the definition of rhabdomyolysis and selects only very severe cases. Only 33-51% of hospitalized rhabdomyolysis cases have acute renal failure (Melli G. et al., *Medicine*, 2005)

Data Analysis

- Incidence rates: confirmed cases of rhabdomyolysis divided by person-years of exposure
- Crude and adjusted incidence rate ratios (IRR):
Poisson regression, considering *baseline* values of:

age

sex

region

year

total cost

statin use

fibrate use

diabetes

hypertension

hypothyroidism

renal or

hepatic disease

recent exposure to

contrast dye

number of:

hospitalizations

primary care visits

specialty visits

prescription drugs

laboratory tests

procedures

Results

- 1,116,805 subjects initiated
 - statin: 86.6%
 - fibrate: 12.9%
 - both 0.5%
- 2,389,466 person-yrs of follow-up, current exposure:
 - statin monotherapy: 47.6%
 - fibrate monotherapy: 4.7%
 - statin + fibrate combination: 2.9%
 - periods without lipid-lowering drug use: 44.8%

Potential and Confirmed Cases of Hospitalized Rhabdomyolysis

- potential cases based on claims data	2309 in 2171 pts	- 939
- selected for medical record review <i>based on claims profile review</i>	1232 (57%)	- 290
- medical record obtained	942 (76%)	- 872
- confirmed cases	70 (7.4%)	

- 4 of the confirmed cases died within 1 day to 6 months of case diagnosis. Neither exposure information nor causes of death were provided



Selected Sample Characteristics Based on Drug Initiated

Baseline Characteristics		Statin Initiators	Fibrate Initiators	Statin + Fibrate Initiators
Sample	N	967,602	143,907	5,296
	%	86.6	12.9	0.47
Age	<40	13.3	19.2	18.9
	>70	4.4	3.0	2.6
Gender	% male	56.4	68.1	73.2
Number of hospitalizations	0	90.6	93.2	85.7
	2+	0.9	0.8	1.2
Number of medications dispensed	0-2	22.6	17.7	9.8
	>8	17.8	24.6	26.1
Overweight, obesity and other hyperalimentation	%	4.8	5.8	7.3
History of diabetes	%	16.3	21.5	22.6
Other forms of chronic ischemic heart disease	%	11.5	10.0	15.5
Angina pectoris	%	3.4	2.5	4.5
Acute myocardial infarction	%	3.0	1.1	4.4

Results: Hospitalized Rhabdomyolysis with Renal Impairment

Current Exposure	Cases	P-years	IR, per 100,000 p-yrs	(95% CI)
No lipid-lowering drug use	24	1,069,324	2.24	1.44 - 3.34
Statin only	28	1,137,968	2.46	1.64 - 3.56
Fenofibrate only	5	80,654	6.20	2.01 - 14.47
Gemfibrozil only	1	31,964	3.13	0.08 - 17.43
Statin and Fenofibrate	7	56,593	12.37	4.97 - 25.48
Statin and Gemfibrozil	5	12,963	38.57	12.52 - 90.01
Gemfibrozil and Fenofibrate	-	-		-
Statin and Fenofibrate and Gemfibrozil	-	-		-

Crude and Adjusted Incidence Rate Ratios for Rhabdomyolysis

Current Exposure	Crude IRR	95% CI	Adj. IRR*	95% CI
Compared to statin monotherapy				
Statin only	ref	ref	ref	ref
Fenofibrate only	2.52	0.97 – 6.52	2.25	0.85 – 5.95
Gemfibrozil only	1.27	0.17 – 9.34	1.41	0.19 – 10.50
Statin + Fenofibrate	5.03	2.20 – 11.51	3.26	1.21 – 8.80
Statin + Gemfibrozil	15.68	6.05 – 40.60	11.93	3.96 – 35.93

•Adjusted for: age, sex, year of cohort entry, use of statins/fibrates, diagnosis of diabetes/hypertension, number of specialty visits, prescriptions, and total cost during baseline period

•**Bolded: statistically significant at $\alpha < 0.05$**

Comparison of Study Results

Exposure	Graham et al., 2004*			i3 report, 2010		
	Cases	IR [†] 95% CI	Crude IRR 95% CI	Cases	IR [†] 95% CI	Crude IRR 95% CI
Statin monotherapy	9	4.34 1.98 – 8.23	ref	28	2.46 1.64 – 3.56	ref
Fibrate monotherapy	3	28.2 5.67 – 82.45	6.51 1.76 – 24.0	6	5.32 1.95 – 11.60	2.17 0.90 – 5.23
Statin + fibrate	2	58.5 6.58 – 211.3	13.50 2.92 – 62.46	12	17.23 8.89 – 30.10	7.00 3.56 – 13.77

*Graham et al.: statins include: atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. Cerivastatin was excluded from this table.

[†]per 100,000 person-years

Bolded: statistically significant at $\alpha < 0.05$

Attributable Risk and Number Needed to Harm

For hospitalized rhabdomyolysis with renal impairment based on i3 study, compared to **statin monotherapy**:

- Fenofibrate + statin
 - **Attributable risk: 5.6 [95%CI, 0.9 – 35.3]** additional cases per 100,000 person-yrs of exposure
 - **Number needed to harm (NNH): 17,987 [95% CI, 2,833 – 114,218]** person-yrs of combination exposure to observe one additional case of hospitalized rhabdomyolysis
- Gemfibrozil + statin
 - **Attributable risk: 26.9 [95%CI, 7.4 – 98.0]** additional cases per 100,000 person-yrs of exposure
 - **NNH: 3,719 [95%CI, 1,020 – 13,558]** person-yrs of combination exposure to observe one additional case of hospitalized rhabdomyolysis

Strengths of i3 Study

- **Size:** ~2.4 million person-years of follow-up and 70 confirmed cases of rhabdomyolysis
- **Medical record review:** validation of hospitalized rhabdomyolysis cases to eliminate false-positives

Limitations of i3 Study

- Not an actual new-user design
 - Concern: **depletion of susceptibles**
- Outcomes were compared based on **current exposure** but baseline characteristics were provided by **initiated drug**
 - Example: **2.9% of person-time** occurred during statin and fibrate combination therapy, but only **0.5% of patients were initiators** of combination therapy
 - Concern: cannot evaluate appropriateness of multivariate adjustment

Limitations cont'd

- **Underrepresentation of elderly** who are at higher risk for rhabdomyolysis
 - Concern: Incidence rates and attributable risk could be underestimated
- Possible **misclassification of exposure**, especially in “no exposure” cohort

Limitations cont'd

Adjustment

- Adjustment changed IRRs significantly, suggesting the presence of **confounding**. It is unclear whether adjustment was sufficient
- Information on risk factors, e.g. **alcohol use, strenuous physical activity, and BMI** was **not included** in analysis, potentially resulting in residual confounding

Limitations cont'd

- Potential cases with **missing medical records** (24%) were treated as non-cases
- Case definition requiring renal impairment only selected the **most severe cases** of hospitalized rhabdomyolysis
- Study was **underpowered** to investigate specific **drugs and doses**

Pharmacoepidemiology Safety Study of Fibrate and Statin Concomitant Therapy

Am J Cardiol 2010;106:1594-1601
And Sponsor's Final Report, 7/31/2009

Study by i3 drug safety for Abbott Laboratories

Study Design

- Cohort study in NHI database
- Cohort design comparable to PMR study, except:
 - Shorter study period: 1/1/2004-12/31/2007, instead of 1/1/1998-12/31/2008 in previous study
 - No unexposed cohort
 - Safety outcomes:
 - Rhabdomyolysis
 - Myopathy
 - Renal impairment
 - Renal failure requiring renal replacement (dialysis or transplant)
 - Hepatic injury
 - Pancreatitis
 - For some outcomes, models were adjusted for biliary disease

Results – Renal Impairment

Current exposure	Cases	P-years	IR* 95% CI	Crude IRR 95% CI	Adj IRR † 95% CI
Renal impairment					
Statin Only	494	453,744	108.87 99.59 - 118.79	ref	ref
Fenofibrate Only	53	35,831	147.92 112.00 - 191.90	1.36 1.02 - 1.80	1.33 1.00 - 1.77
Gemfibrozil Only	19	10,381	183.03 113.88 - 279.95	1.68 1.06 - 2.66	1.61 1.02 - 2.54
Statin and Fenofibrate	60	26,504	226.38 174.39 - 289.28	2.08 1.59 - 2.72	1.47 1.12 - 1.93
Statin and Gemfibrozil	12	4,808	249.58 136.29 - 422.73	2.29 1.29 - 4.06	1.49 0.84 - 2.65

* per 100,000 person-years

† adjusted for age, gender, diabetes, hypertension, number of comorbidities

Results – Renal Failure

Current Exposure	Cases	P-years	IR* 95% CI	Crude IRR 95% CI	Adj IRR † 95% CI
Renal failure requiring renal replacement (transplant or dialysis)					
Statin Only	121	453,744	26.67 22.23 - 31.74	ref	ref
Fenofibrate Only	5	35,831	13.95 5.29 - 30.59	0.52 0.21 - 1.28	0.48 0.20 - 1.18
Gemfibrozil Only	3	10,381	28.90 8.00 - 77.1	1.08 0.34 - 3.41	0.98 0.31 - 3.08
Statin and Fenofibrate	14	26,504	52.82 30.25 - 86.26	1.98 1.14 - 3.44	1.29 0.74 - 2.26
Statin and Gemfibrozil	3	4,808	62.40 17.27 - 166.47	2.34 0.74 - 7.36	1.41 0.45 - 4.45

* per 100,000 person-years

† adjusted for age, gender, diabetes, hypertension, number of comorbidities

Results – Hepatic Injury

Current Exposure	Cases	P-years	IR* 95% CI	Crude IRR 95% CI	Adj IRR † 95% CI
Hepatic injury					
Statin Only	39	454,846	8.57 6.19 - 11.59	ref	ref
Fenofibrate Only	5	35,943	13.91 5.28 - 30.49	1.62 0.64 - 4.12	1.65 0.65 - 4.20
Gemfibrozil Only	0	10,424	0 0 - 23.64	---	---
Statin and Fenofibrate	3	26,660	11.25 3.11 - 30.02	1.31 0.41 - 4.25	1.23 0.38 - 4.00
Statin and Gemfibrozil	1	4,833	20.69 1.88 - 96.47	2.41 0.33 - 17.56	2.31 0.32 - 16.88

* per 100,000 person-years

† adjusted for age, gender, number of comorbidities

Results - Pancreatitis

Current Exposure	Cases	P-years	IR* 95% CI	Crude IRR 95% CI	Adj IRR † 95% CI
Pancreatitis					
Statin Only	208	454,531	45.76 39.86 - 52.3	ref	ref
Fenofibrate Only	45	35,879	125.42 92.66 - 166.23	2.74 1.99 - 3.78	2.67 1.93 - 3.69
Gemfibrozil Only	9	10,400	86.54 42.74 - 157.95	1.89 0.97 - 3.69	1.82 0.93 - 3.55
Statin and Fenofibrate	42	26,592	157.94 115.41 - 211.34	3.45 2.48 - 4.81	2.87 2.05 - 4.02
Statin and Gemfibrozil	4	4,813	83.11 27.78 - 197.59	1.82 0.68 - 4.88	1.45 0.54 - 3.92

* per 100,000 person-years

† adjusted for age, gender, biliary disease, diabetes, hypertension, number of comorbidities

Conclusions

Observational data suggest:

- Increased risk for hospitalized rhabdomyolysis with **statin + fibrate combination** therapy vs. **statin monotherapy**
- Moderate to large increase on relative scale:
 - **Fenofibrate: IRR, 3.26** [95% CI, 1.21 – 8.80]
 - **Gemfibrozil: IRR, 11.93** [95% CI, 3.96 – 35.93]
- Small increase on absolute scale:
 - **Fenofibrate: 5.6** additional cases **per 100,000 person-yrs** of exposure
 - **NNH = 17,987**
 - **Gemfibrozil: 26.9** additional cases **per 100,000 person-yrs** of exposure
 - **NNH = 3,719**

Conclusions cont'd

- Increased risk of **renal impairment** associated with the use of **fibrates**, and **pancreatitis** associated with use of **fenofibrate** compared to statin monotherapy, but **no further increase** when **combined with statins**

Conclusions cont'd

- Success of statistical adjustment potentially limited by small case numbers and lack of information on important risk factors
- Residual confounding could lead to **overestimated IRR** associated with combination therapy
- Missed cases and rhabdomyolysis case definition requiring renal impairment could lead to **underestimated IRs** and **attributable risks**



Endocrinologic and Metabolic Drugs Advisory Committee Meeting
Silver Spring, Maryland
May 19, 2011

Statin-Fenofibrate Combination Therapy after the ACCORD-Lipid Trial

Iffat Nasrin Chowdhury, M.D.
Medical Officer
Division of Metabolism and Endocrinology Products
Office of New Drugs
CDER

Outline

- General characteristics of fibrates
- Fibrate cardiovascular outcomes trials
- Trilipix® New Drug Application
- ACCORD-Lipid trial
- Subgroup analyses
- Summary
- Conclusion

Fibrates

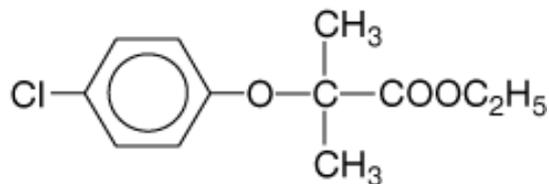
- Fibrates: synthetic peroxisome proliferator activated receptor (PPAR) α agonists
- PPAR α : subfamily of nuclear receptors
 - Increases lipoprotein lipase and decreases Apo CIII
 - Reduces TG
 - Increases Apo AI and AII
 - Increases HDL-C

Fibrates

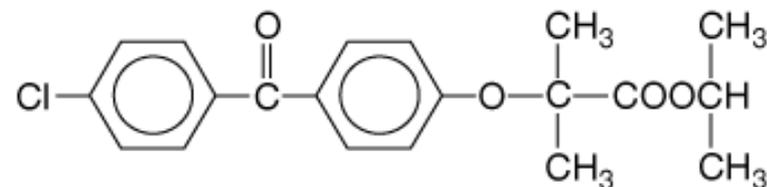
- Metabolic effects:
 - Reduce TG ~ 20-50%
 - Increase HDL-C ~ 10-35%
 - Variable effects on LDL-C
- Adverse effects:
 - Myopathy
 - Cholelithiasis/cholecystectomy
 - Pancreatitis
 - VTE

Structures of the Fibrates

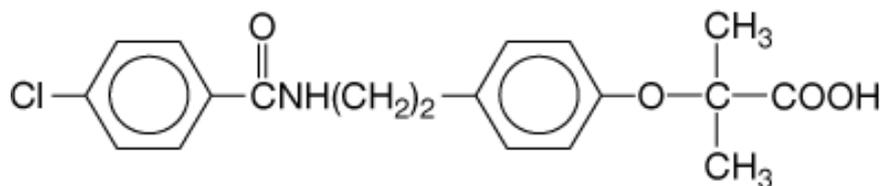
CLOFIBRATE



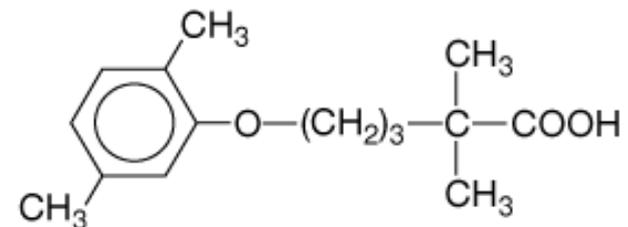
FENOFIBRATE



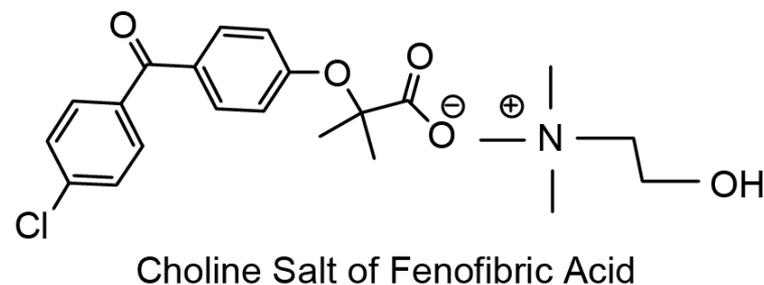
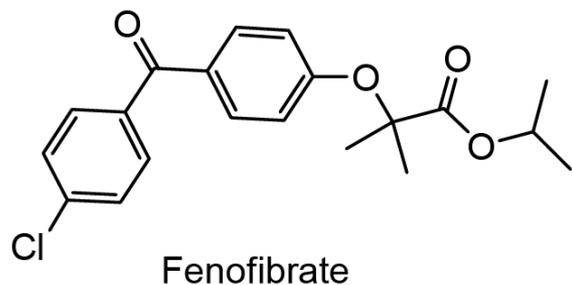
BEZAFIBRATE



GEMFIBROZIL

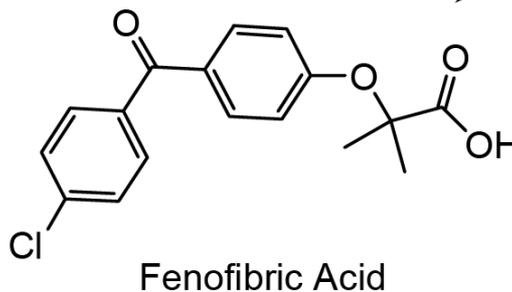


Fenofibrate and Fenofibric Acid



Enzymatic conversion
in the intestine and
via a single pass
through the liver

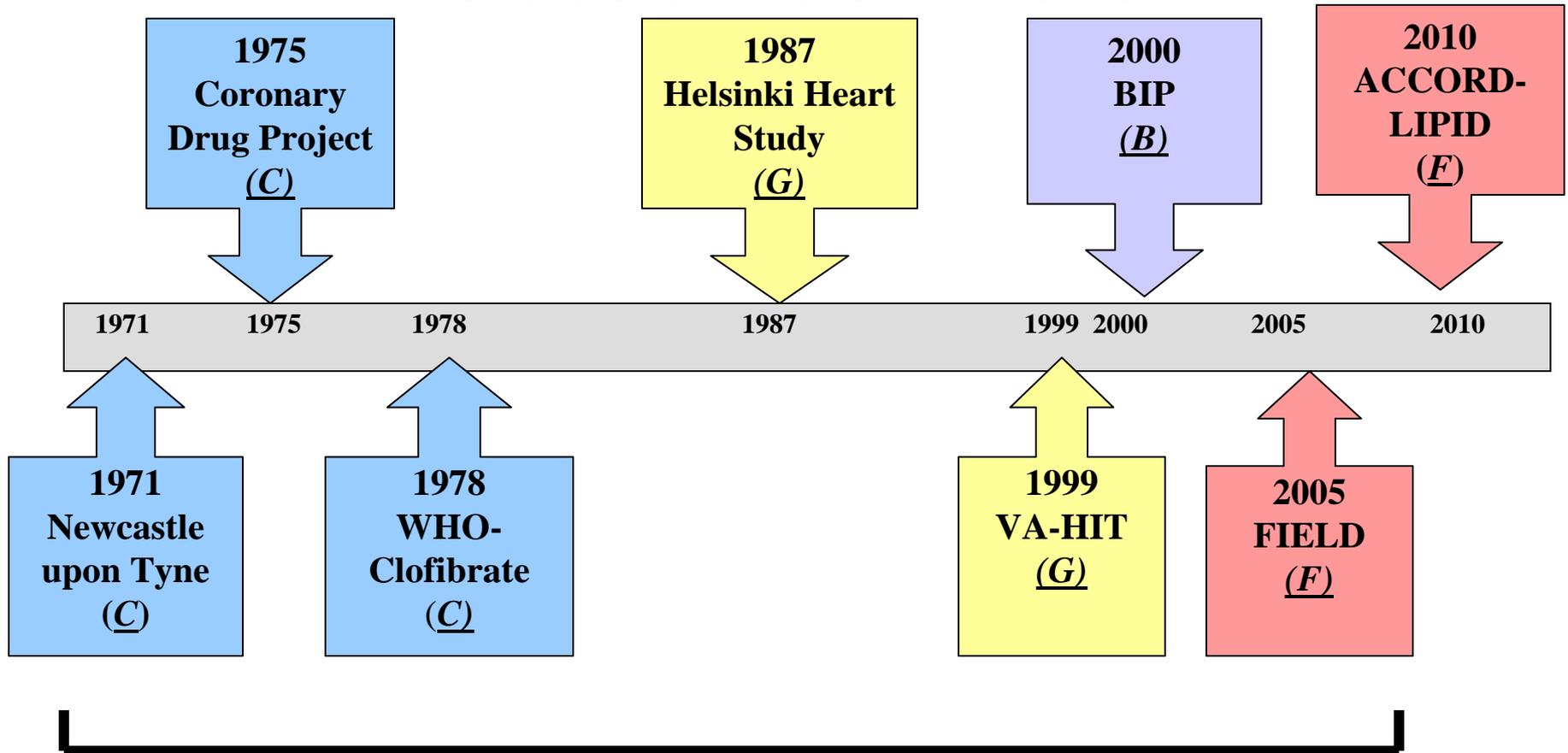
Chemical disassociation
in gastrointestinal tract





Fibrate Cardiovascular Outcomes Trials

Fibrate Cardiovascular Outcomes Trials



Fibrate Monotherapy Trials

Fibrate Monotherapy Trials

Trial	Fibrate	Population	Primary Endpoint	Reduction in events
HHS	Gemfibrozil 1200 mg	Primary Prevention	Fatal + non-fatal MI + cardiac death	↓ 34% (p<0.02)
VA-HIT	Gemfibrozil 1200 mg	Secondary Prevention	Nonfatal MI + CHD Death	↓ 22% (p=0.006)
BIP	Bezafibrate 400 mg	Secondary Prevention	Fatal + non-fatal MI + sudden death	↓ 9.4% (p=0.26)
FIELD	Fenofibrate 200 mg	Primary & Secondary Prevention	Non-fatal MI + CHD death	↓ 11% (p=0.16)

Helsinki Heart Study (HHS) 1987

- 5-year RCT of gemfibrozil 600 mg twice daily vs. placebo
- Enrolled 4081 men without CHD between 40-55 years of age
- Inclusion criterion: non-HDL-C ≥ 200 mg/dL
- Primary end point: fatal and nonfatal MI + cardiac death

HHS Population

- Type 2 diabetes ~ 3% of study population
- Men = 100% of study population
- Mean Baseline Lipids
 - LDL-C = 189 mg/dL
 - Non-HDL-C = 242 mg/dL
 - TG = 176 mg/dL
 - HDL-C = 47 mg/dL

HHS Results

- Relative to placebo, gemfibrozil treatment
 - Decreased LDL-C ~ 8%
 - Increased HDL-C ~ 10%
 - Decreased TG ~ 35%
 - Decreased non-HDL-C ~ 12%
- Primary endpoint: 34% relative risk reduction (RRR) in fatal and nonfatal MI + cardiac death ($p < 0.02$)

Veterans Affairs High-Density Lipoprotein Cholesterol Intervention (VA-HIT) 1999

- 5-year RCT of gemfibrozil 1200 mg daily vs. placebo
- Enrolled 2531 men with coronary heart disease
- Inclusion criteria:
 - HDL-C \leq 40 mg/dL, LDL-C \leq 140 mg/dL, and TG \leq 300 mg/dL
- Primary end point: non-fatal MI + death from coronary heart disease

VA-HIT Population

- Type 2 diabetes ~ 25% of study population
- Men = 100% of study population
- Mean age = 64 years
- Mean Baseline Lipids
 - LDL-C = 112 mg/dL
 - HDL-C = 32 mg/dL
 - TG = 160 mg/dL

VA-HIT Results

- Relative to placebo, gemfibrozil treatment
 - Decreased TG ~ 31%
 - Increased HDL-C ~ 6%
 - No change in LDL-C
- Primary endpoint: 22% RRR in non-fatal MI + CHD death ($p=0.006$)

Bezafibrate Infarction Prevention (BIP) 2000

- 6-year RCT of bezafibrate 400 mg daily vs. placebo
- 3090 men and women with CAD not on lipid-lowering medication
- Inclusion criteria:
 - TG \leq 300 mg/dL, HDL-C \leq 45 mg/dL and LDL-C \leq 180 mg/dL
- Primary end point: fatal or non-fatal MI + sudden death

BIP Population

- Type 2 diabetes ~ 10% of study population
- Women ~ 10% of study population
- Mean age = 60 years
- Mean Baseline Lipids
 - LDL-C = 148 mg/dL
 - TG = 145 mg/dL
 - HDL-C = 35 mg/dL

BIP Results

- Relative to placebo, bezafibrate treatment
 - Increased HDL-C ~ 18%
 - Decreased LDL-C ~ 7%
 - Decreased TG ~ 21%
- Primary endpoint: 9.4% RRR in nonfatal + fatal MI + sudden death (p=0.26)

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) 2005

- 5-year RCT of fenofibrate 200 mg daily vs. placebo
- Enrolled 9795 men and women not on lipid-lowering therapy
- Inclusion criteria:
 - TC 116 - 250 mg/dL plus either
 - TG 89 - 442 mg/dL or TC to HDL-C ratio ≥ 4.0
- Primary endpoint: non-fatal MI + CHD death

FIELD Population

- Type 2 diabetes = 100%
- Median HbA1c = 6.9%
- Mean age = 62 years
- Women = 37% of study population
- History of CVD events = 22%
- Mean Baseline Lipids
 - LDL-C = 119 mg/dL
 - HDL-C = 43 mg/dL
 - TG = 154 mg/dL (median)

FIELD Results

- Relative to placebo, fenofibrate treatment
 - Decreased LDL-C ~ 6%
 - Increased HDL-C ~ 1%
 - Decreased TG ~ 22%
- Primary endpoint: 11% RRR in non-fatal MI + CHD death (p=0.16)

FIELD Safety Findings

	Fenofibrate	Placebo
Rhabdomyolysis	3 (0.06%)	1 (0.02%)
Pancreatitis	40 (0.8%)	23 (0.5%)
Pulmonary embolism	53 (1%)	32 (0.7%)
Deep venous thrombosis	67 (1%)	48 (1%)
Serum creatinine >2.26 mg/dL	73 (2%)	48 (1%)



Trial	Fibrate	Population	Primary Endpoint	Reduction in events
HHS	Gemfibrozil 1200 mg	Primary Prevention	Fatal + non-fatal MI + cardiac death	↓ 34% (p<0.02)
VA-HIT	Gemfibrozil 1200 mg	Secondary Prevention	Nonfatal MI + CHD Death	↓ 22% (p=0.006)
BIP	Bezafibrate 400 mg	Secondary Prevention	Fatal + non-fatal MI + sudden death	↓ 9.4% (p=0.26)
FIELD	Fenofibrate 200 mg	Primary & Secondary Prevention	Non-fatal MI + CHD death	↓ 11% (p=0.16)



Trilipix® (fenofibric acid) New Drug Application (NDA)

Trilipix® (fenofibric acid) NDA

- Fenofibric acid is the active ingredient of fenofibrate
- Three pivotal trials: 12 weeks, 6 arms
 - Fenofibric acid monotherapy
 - Statin (low dose, moderate dose, high dose) monotherapy
 - Fenofibric acid + statin combination therapy (only with low and moderate dose statin)
- Enrolled 2698 men and women

Trilipix® (fenofibric acid) NDA Population

- Inclusion criteria:
 - TG \geq 150 mg/dL
 - HDL-C < 40 / 50 mg/dL
 - LDL-C \geq 130 mg/dL
- Type 2 diabetes ~ 22%
- Women ~ 52%
- Mean age = 55 years

Trilipix® (fenofibric acid) NDA

- Primary endpoints = lipid changes
 - TG: Fenofibric acid + statin vs. statin monotherapy
 - HDL-C: Fenofibric acid + statin vs. statin monotherapy
 - LDL-C: Fenofibric acid + statin vs. fenofibric acid monotherapy

Trilipix® (fenofibric acid)

Lipid Changes

	Low Dose Statin	FF + Low Dose Statin	Moderate Dose Statin	FF + Moderate Dose Statin	High Dose Statin	FF
HDL-C	7%	18%	9%	18%	8%	16%
TG	-17%	-44%	-24%	-42%	-28%	-31%
LDL-C	-34%	-33%	-41%	-35%	-47%	-5%

Trilipix® (fenofibric acid) Safety 12-Week Controlled Trials

- No cases of rhabdomyolysis
- Pancreatitis: 1 (0.2%) patient on combination of fenofibric acid + statin
- DVT: 2 (0.4%) patients on fenofibric acid monotherapy

Trilipix® (fenofibric acid) Approval 2008

- Co-administration indication: In combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal
- Limitations of use: No incremental benefit of Trilipix on cardiovascular morbidity and mortality over and above that demonstrated for statin monotherapy has been established



ACCORD-Lipid

ACCORD-Lipid Design

- The ACCORD-Lipid Trial was not designed to answer the question of whether the addition of fenofibrate to subjects at LDL-C goal on a statin with elevated TG levels (\pm low HDL-C) reduces the risk for major cardiovascular events
- e.g., subjects with TG <200 mg/dL enrolled in study

ACCORD-Lipid Safety

- Myopathy
 - 4 (0.1%) Fenofibrate vs. 3 (0.1%) Placebo
- Pancreatitis
 - 5 (0.2%) Fenofibrate vs. 4 (0.1%) Placebo
- Pulmonary embolus and deep venous thrombosis
 - No cases

ACCORD-Lipid Safety

- Serum creatinine increase in women >1.3 mg/dL
 - 28% fenofibrate vs. 19% placebo
- Serum creatinine increase in men > 1.5 mg/dL
 - 37% fenofibrate vs. 18% placebo
- Reduced dose or discontinued from masked study drug for “Low GFR/elevated serum creatinine”
 - 18% fenofibrate vs. 8% placebo



Subgroup Analyses from ACCORD-Lipid, VA-HIT, BIP, and FIELD

ACCORD-Lipid Results

- Primary endpoint: composite of non-fatal MI, non-fatal stroke and CVD death
- No significant difference in hazard for the primary endpoint between combination of fenofibrate + statin therapy vs. statin monotherapy
 - HR = 0.92 (95%CI 0.79-1.08; p=0.32)



ACCORD-Lipid Risk of Non-fatal MI, Non-fatal Stroke, and CVD death by Baseline Lipids and Gender

	Placebo	Fenofibrate	HR	Interaction P-value
Male	13.3%	11.2%	0.82	0.01
Female	6.6%	9.0%	1.38	
≤ 34 mg/dL HDL ≥ 204 mg/dL TG	17.3%	12.4%	0.69	0.06
All Others	10.1%	10.1%	0.99	

VA-HIT – Risk for CHD Death, Nonfatal MI, and Stroke by Baseline Lipid Levels

	Placebo	Gemfibrozil	HR	Interaction P-value
HDL-C				
< 31.5 mg/dl	28%	21%	0.70	0.59
≥ 31.5 mg/dl	23%	18%	0.76	
TG				
< 151 mg/dl	25%	19%	0.72	0.84
≥ 151 mg/dl	27%	20%	0.73	

BIP – Risk of Fatal and Nonfatal MI and Sudden Death by Baseline Lipids

	Bezafibrate	Placebo	HR	Interaction P-value
HDL <35 mg/dL and TG ≥150 mg/dL	18.1%	19.4%	0.95	0.87
All Others	12.0%	13.5%	0.88	
HDL <35 mg/dL and TG ≥200 mg/dL	13.0%	22.3%	0.55	0.05
All Others	13.8%	14.3%	0.96	



FIELD – Risk of CVD Death, MI, Stroke, and Revascularization by Baseline Lipids and Gender

	Placebo	Fenofibrate	HR	Interaction P-value
TG > 150 mg/dl & HDL < 40 mg/dl ♂ HDL < 50 mg/dl ♀	16.3%	14.0%	0.86	0.6
All Others	12.6%	11.6%	0.92	
Male	16.6%	15.4%	0.93	0.3
Female	9.5%	7.7%	0.81	

Summary

- Mixed results from fibrate monotherapy cardiovascular outcome trials
 - Gemfibrozil monotherapy trials: “positive”
 - Fenofibrate monotherapy trials: “negative”
- Trilipix NDA approved based on favorable HDL and TG changes
- ACCORD-Lipid trial
 - Fenofibrate plus statin vs. statin: “negative”
 - Suggestion of harm for women
 - Not observed in the FIELD Trial
 - Suggestion of benefit for TG ≥ 204 mg/dL and HDL-C ≤ 34 mg/dL
 - Some post-hoc analyses of fibrate monotherapy CV trials may suggest benefit in patients with TG > 200 mg/dL and HDL < 35 mg/dL

Conclusion

- “The results of the ACCORD Lipid subgroup analysis, together with those of previous fibrate trials, support the hypothesis that fibrate therapy may reduce cardiovascular events among patients with clinically significant dyslipidemia (i.e., hypertriglyceridemia and low HDL cholesterol levels).”

Ginsberg H, et al. *N Engl J Med* 2010;363:692-5.

Conclusion

- “A definitive clinical trial involving such persons would provide critical information regarding this issue.”

Ginsberg H, et al. *N Engl J Med* 2010;363:692-5.



END