Pre-conference course - Pharmacovigilance

Research Methods for Evaluation of Drug Safety Surveillance Policies

藥物安全與風險管理政策評估研究方法

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Disclosures

- There is no potential conflict of interest relevant to this presentation.

Outline

1. The **decision making process** of safety warnings and RMP for post-marketing drugs
2. The **evaluation framework/methods** of safety warnings and RMP
3. Impacts of safety warnings and RMP:

   Examples of thiazolidinediones (rosiglitazone and pioglitazone)
4. **Conclusion**

1. The decision making process of safety warnings and RMP for post-marketing drugs

Post marketing Drug & Biologic Safety Evaluations

Phase-IV clinical trials
Case reports
Adverse event reports
Meta-analysis
Observational studies

→ **Safety warnings** → **FDA expert meeting** → **Requirement of REMS**

FDA expert meeting → **Withdraw**

Drug safety communication
Information for Health Care Professionals
(Black) box warning safety labeling
Safety Podcasts
Med Watch

Medication guides
Communication plan
Elements to assure safe use
Implementation system

2. The evaluation framework/methods of safety warnings and RMP – RE-AIM Framework

Factor	Description	Possible REMS assessment Domains
Reach	Proportion of the target population who participate	Distribution / availability Participation Medication access
Effectiveness	Success rate	Knowledge / awareness Drug Utilization Clinical Outcomes
Adoption	Proportion of settings that adopt the intervention	Attitude / intention Prescribing Behaviors
Implementation	Extent to which intervention is implemented as intended	Processes, Consistency Burden
Maintenance	Extent to which intervention is sustained over time	Persistency Failures

Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Glasgow, et. al. *Am. J. Public Health*, Sept. 1999, Vol. 89, No. 9.

3. Impacts of safety warnings and RMP: Examples of thiazolidinediones (rosiglitazone and pioglitazone)

Story of Thiazolidinediones

(1) History of Rosiglitazone

2007

The NEW ENGLAND JOURNAL of MEDICINE

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall	↑ 0.23%		1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall	↑ 0.08%		1.64 (0.98–2.74)	0.06

Story of Thiazolidinediones

(1) History of Rosiglitazone

2010

EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Journal (2010) **31**, 824–831
doi:10.1093/eurheartj/ehp604

CLINICAL RESEARCH
Heart failure/cardiomyopathy

Heart fa… diabetes… type 2 trial

Michel Koma… Markolf Hane… and Philip D. … on Gomis[5],

Table 1 Outcome of patients with heart failure events (fatal and non-fatal)

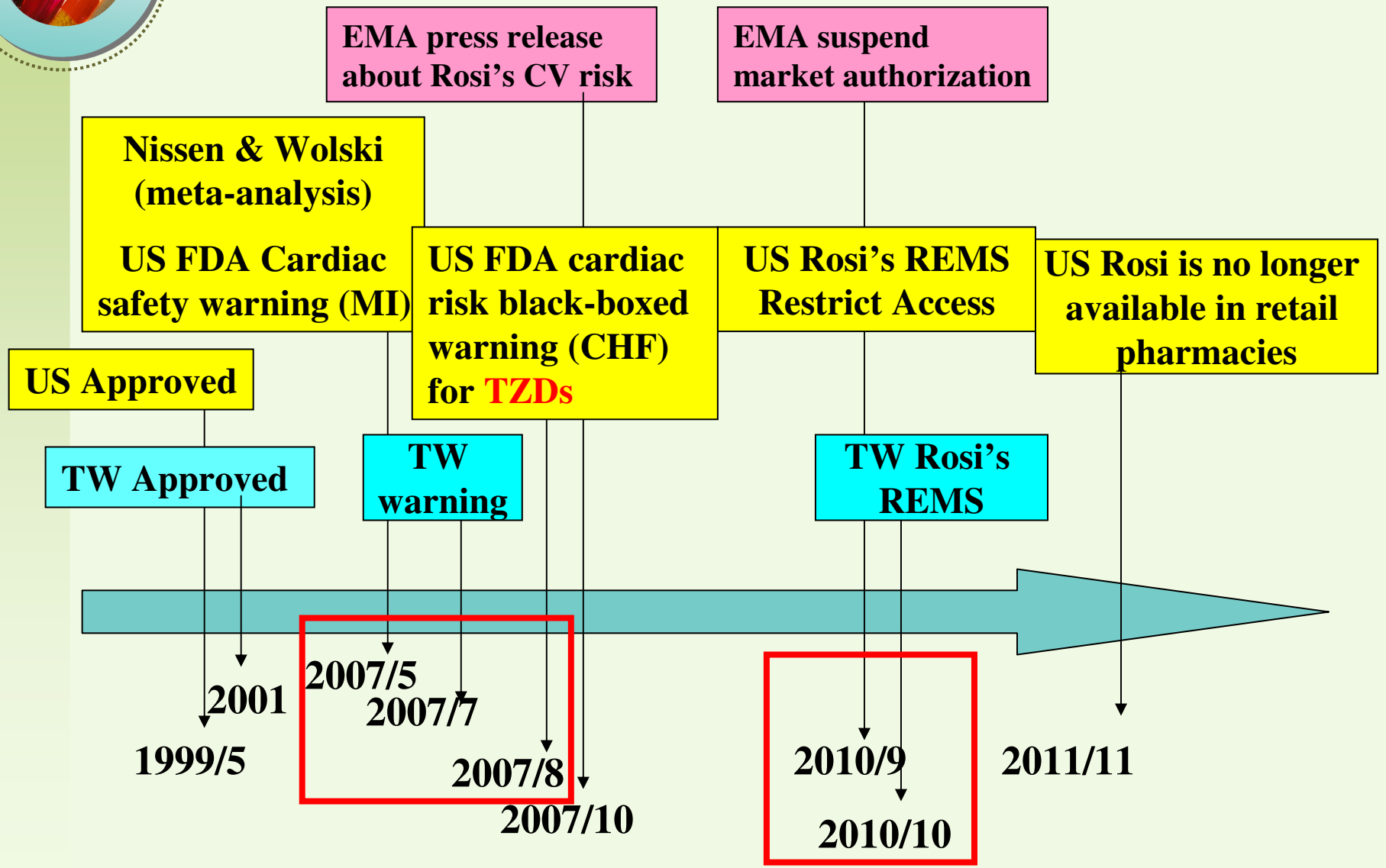
Metformin/SU

	Rosiglitazone (n = 2220)	Control (n = 2227)
Patients with HF events (fatal and non-fatal)	61 **2.75%**	29 **1.30%**
First HF event fatal	4	0
Survived first HF event	57	29
All-cause death (%)	17 (30)	8 (28)
HF death	6	2
Other CV death[a]	9	2
Other death	2	4
Further non-fatal HF event (%)	7 (12)	5 (17)
Other non-fatal CV event (%)	13 (23)	10 (34)
No other CV event (%)	26 (46)	15 (52)

↑ **1.45%**

Story of Thiazolidinediones

(1) History of Rosiglitazone



Story of Thiazolidinediones

(2) History of Pioglitazone

2005

Lancet

Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial

John A Dormandy, B
Pierre J Lefèbvre, Gor
László Korányi, Mark
Guntram Schernthar

Summary
Background Pati

05; 366: 1279–89

MI

	First events			Total events	
	Pioglitazone (n=2605)	Placebo (n=2633)	HR (95% CI)	Pioglitazone	Placebo
Death	177	186	0·96 (0·78–1·18)	177	186
Non-fatal MI (including silent MI)	119	144	0·83 (0·65–1·06)	131	157
Stroke	86	107	0·81 (0·61–1·07)	92	119
Major leg amputation	26	26	1·01 (0·58–1·73)	28	28
Acute coronary syndrome	56	72	0·78 (0·55–1·11)	65	78
Coronary revascularisation	169	193	0·88 (0·72–1·08)	195	240
Leg revascularisation	80	65	1·25 (0·90–1·73)	115	92
Total	..	..	..	803	900

Data refer to first event of that particular type. MI=myocardial infarction.

Table 4: Effect of pioglitazone and placebo on each component of the primary endpoint

Story of Thiazolidinediones

(2) History of Pioglitazone

2005

Lancet

Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial

John A Dormandy, Bernard Charbonnel, David J A Eckland, Erland Erdmann, Massimo Massi-Benedetti, Jan K Moules, Allan M Skene, Manuel J Tan, Pierre J Lefèbvre, Gordon D M..., László Korányi, Markku..., Guntram Schernthaner

Summary

Background Patients ...

Heart Failure

	Pioglitazone (n=2605)		Placebo (n=2633)		p
	Number of events	Number of patients	Number of events	Number of patients	
Any report of heart failure*	417	281 (11%)	302	198 (8%)	<0·0001
Heart failure not needing hospital admission*	160		117		0·003
Heart failure needing hospital admission*	209	149 (6%)	153	106 (4%)	0·007
Fatal heart failure†	25	25 (1%)	22	22 (1%)	0·634

*Not adjudicated. †Adjudicated cause of death.

Table 9: Reports of heart failure

10.79%

7.52%

↑ 3.27%

cet 2005; 366: 1279–89

Story of Thiazolidinediones

(2) History of Pioglitazone

2005

Secondary prevention of macrovascular events in patients with typ
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a randor

John A Dormandy,
Pierre J Lefèbvre, Gc
László Korányi, Ma
Guntram Schernth

Summary
Background Pa

Lancet

Bladder Cancer

	Pioglitazone (n=2605)		Placebo (n=2633)		p
	Number of events	Number of patients	Number of events	Number of patients	
Any serious adverse event	2720	1204 (46%)	2978	1275 (48%)	0·110
Endpoint events*	602	389 (15%)	686	434 (16%)	0·123
Non-endpoint events	2118	1079 (41%)	2292	1150 (44%)	0·099
Most common events (excluding endpoints)†					
Angina pectoris	107	89 (3%)	145	122 (5%)	0·025
Hospital admission for diabetes control	57	55 (2%)	99	91 (3%)	0·003
Accident	53	51 (2%)	50	49 (2%)	0·798
Atrial fibrillation	47	42 (2%)	60	51 (2%)	0·374
Pneumonia	57	53 (2%)	37	35 (1%)	0·047
Transient ischaemic attack	39	34 (1%)	42	39 (2%)	0·587
Neoplasms	118	112 (4%)	117	113 (4%)	
Malignant‡	103	97 (4%)	103	99 (4%)	
Colon/rectal	..	16 (1%)	..	15 (1%)	0·834
Lung		15 (1%)		12 (1%)	0·544
Bladder	..	14 (1%)	..	6 (<1%)	0·069
Bladder (after exclusion)§		6 (<1%)		3 (<1%)	0·309
Haematological		6 (<1%)		10 (<1%)	0·327
Breast		3 (<1%)		11 (<1%)	0·034
Other	..	47 (2%)	..	46 (2%)	0·876

0.54%

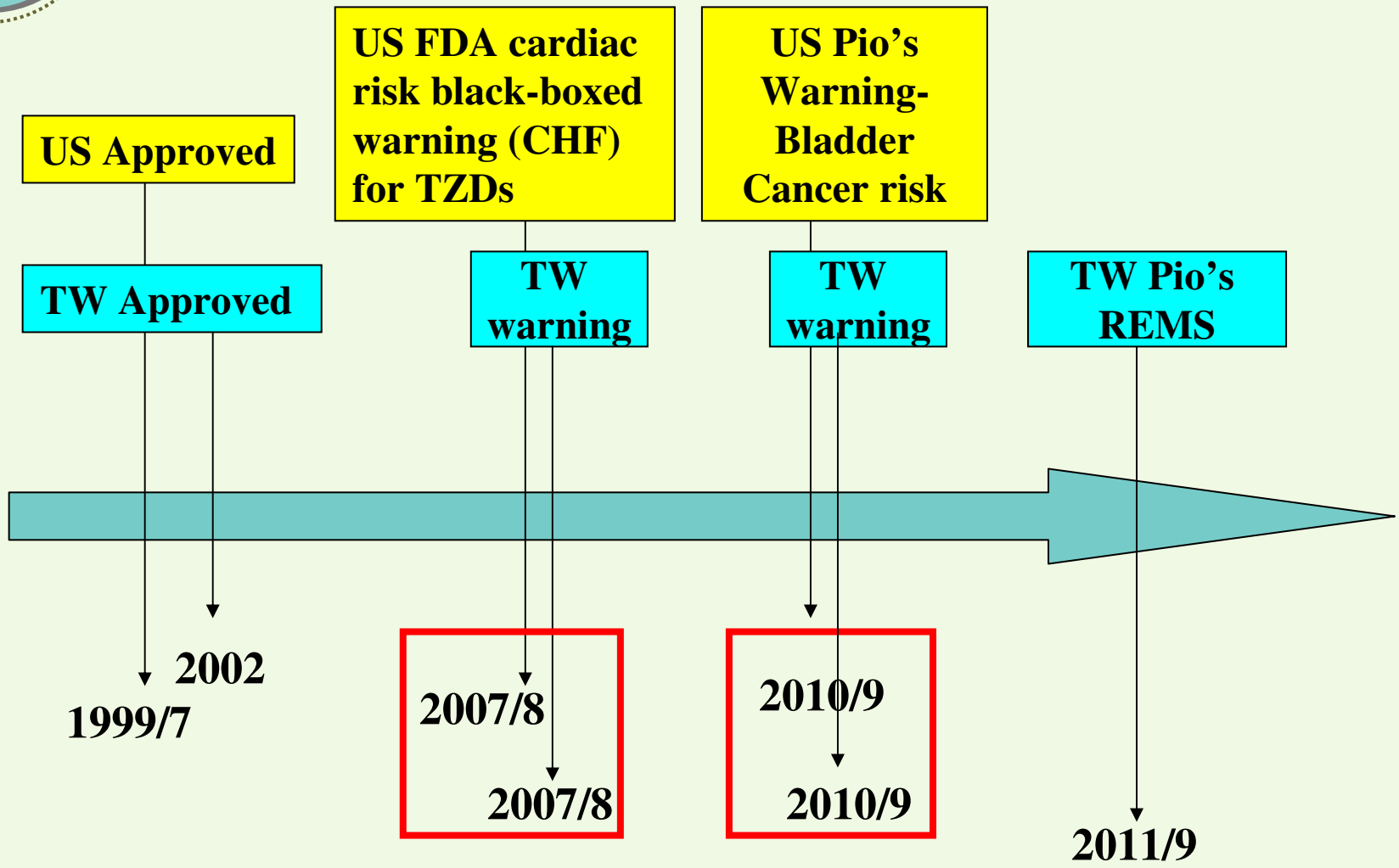
0.23%

↑ 0.31%

2005; 366: 1279–89

Story of Thiazolidinediones

(2) History of Pioglitazone



Shah (2010):

US TZDs' BBW in 2007 → The trend of TZDs utilization

Percentage of Total Prescriptions/Month

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

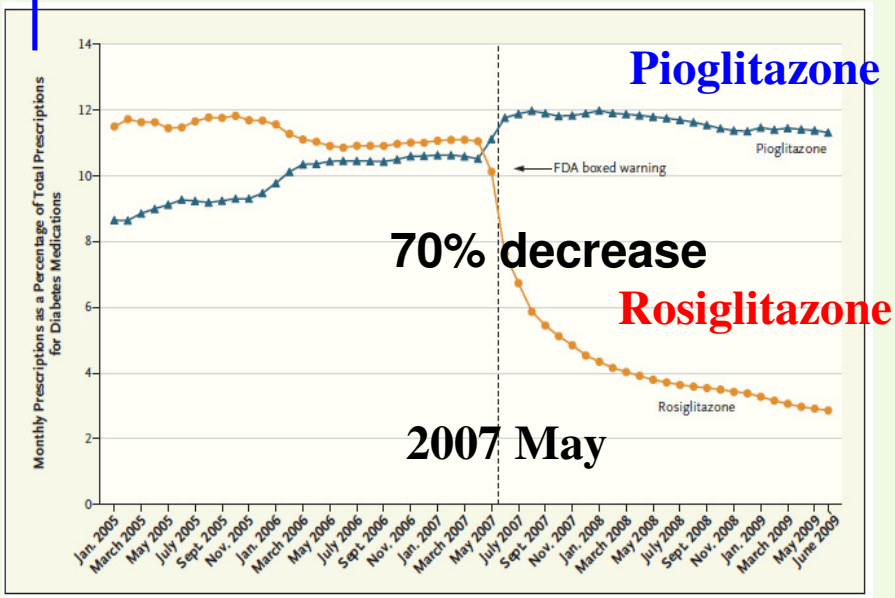
NOVEMBER 25, 2010

Responding to an FDA Warning — Geographic Variation in the Use of Rosiglitazone

Nilay D. Shah, Ph.D., Victor M. Montori, M.D., Harlan M. Krumholz, M.D., Karen Tu, M.D., G. Caleb Alexander, M.D., and Cynthia A. Jackevicius, Pharm.D.

On May 21, 2007, the Food and Drug Administration (FDA) issued a boxed warning in conjunction with the publication of a meta-analysis by Nissen and Wolski showing that the diabetes drug

for providers about how to incorporate the warning into clinical decision making. Warnings can be interpreted in a variety of ways, and patient protection may be inconsistent as a result. Variations



Pioglitazone

70% decrease

Rosiglitazone

2007 May

Monthly Prescriptions for Rosiglitazone and Pioglitazone as a Percentage of Total Prescriptions for Diabetes Medications (Excluding Insulin), United States.

Data are from the IMS Health National Prescription Audit, and data for 2009 are based on the period from January through June 2009.

Cohen (2010):

US TZDs' BBW in 2007 → The trend of TZDs utilization [Time series method]

Epidemiology/Health Services Research

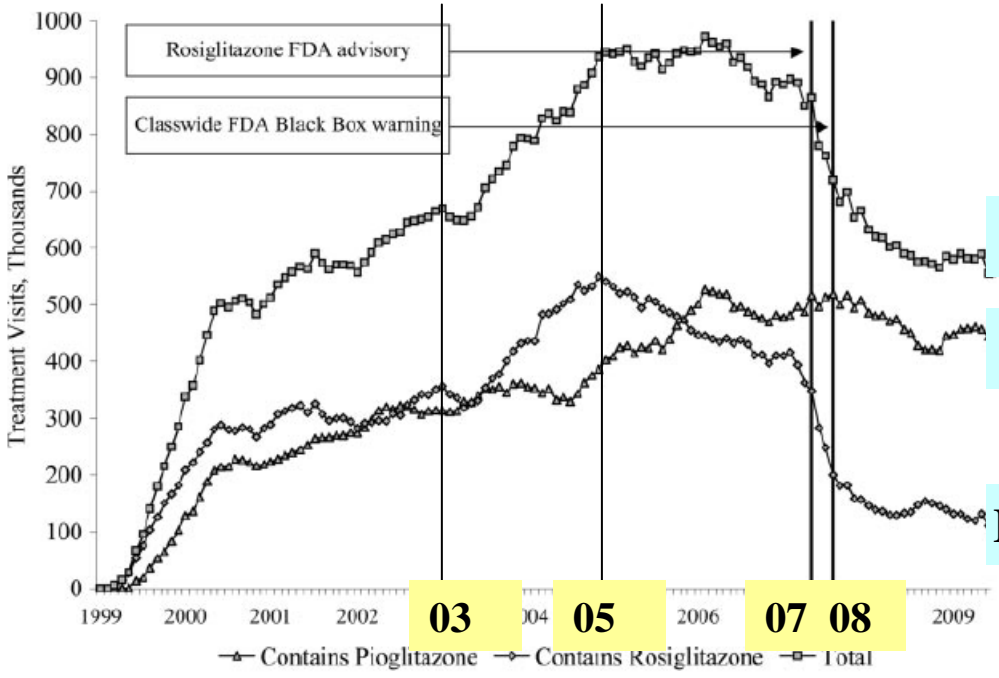
BRIEF REPORT

Changes in Glitazone Use Among Office-Based Physicians in the U.S., 2003–2009

ANDREW COHEN, BS[1]
ATONU RABBANI, PHD[2,3]
NILAY SHAH, PHD[4,5]
G. CALEB ALEXANDER, MD, MS[2,3,6,7]

was evidence that decreases in glitazone use following the FDA advisories oc-

Based on JointPoint Analysis



Total

Pioglitazone

Rosiglitazone

Ruiter (2012):

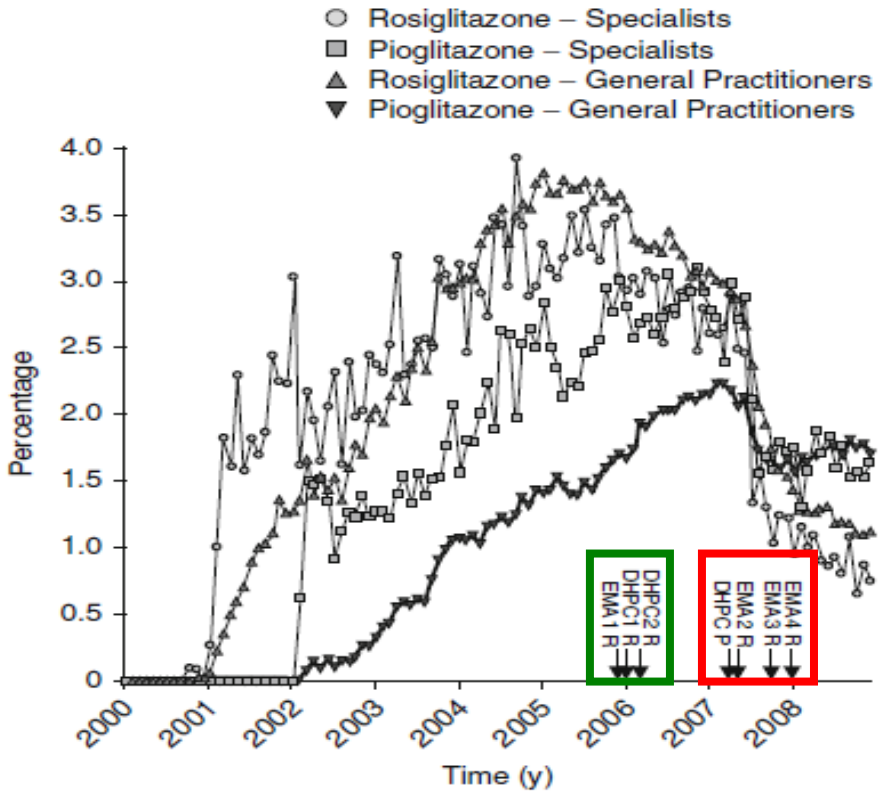
EMA rosiglitazone's press release in 2007

→ TZDs' utilization [Time series method]

Prescribing of Rosiglitazone and Pioglitazone Following Safety Signals

Analysis of Trends in Dispensing Patterns in the Netherlands from 1998 to 2008

Rikje Ruiter,[1,2] *. Geelhoed-*



Hurren (2011):
US TZDs' BBW in 2007 → TZDs' discontinuation

DIABETES RESEARCH AND CLINICAL PRACTICE 93 (2011) 49–55

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

ELSEVIER

International Diabetes Federation

Antidiabetic prescribing trends and predictors of thiazolidinedione discontinuation following the 2007 rosiglitazone safety alert☆

Kathryn M. Hurren, Thomas N. Taylor, Linda A. Jaber*

Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI, United States

Table 1 – Baseline characteristics of patients continuing or discontinuing TZDs.

	Rosiglitazone (n = 40,836)		Pioglitazone (n = 37,183)	
	Continued	Discontinued	Continued	Discontinued
Number of cases, n (%)	18,979 (45.5)	21,857 (53.5)	29,214 (78.6)	7969 (21.4)
Demographics				
Age, mean ± SD	54.4 ± 7.1	54.4 ± 7.4	55.0 ± 6.8	53.7 ± 7.7
Female, n (%)	7623 (40.2)	9726 (44.5)	11,305 (38.7)	3602 (45.2)

23%

<1%

6 months later

Starner (2008):
US 5 TZDs' sub-warnings in 2007 → TZDs' utilization

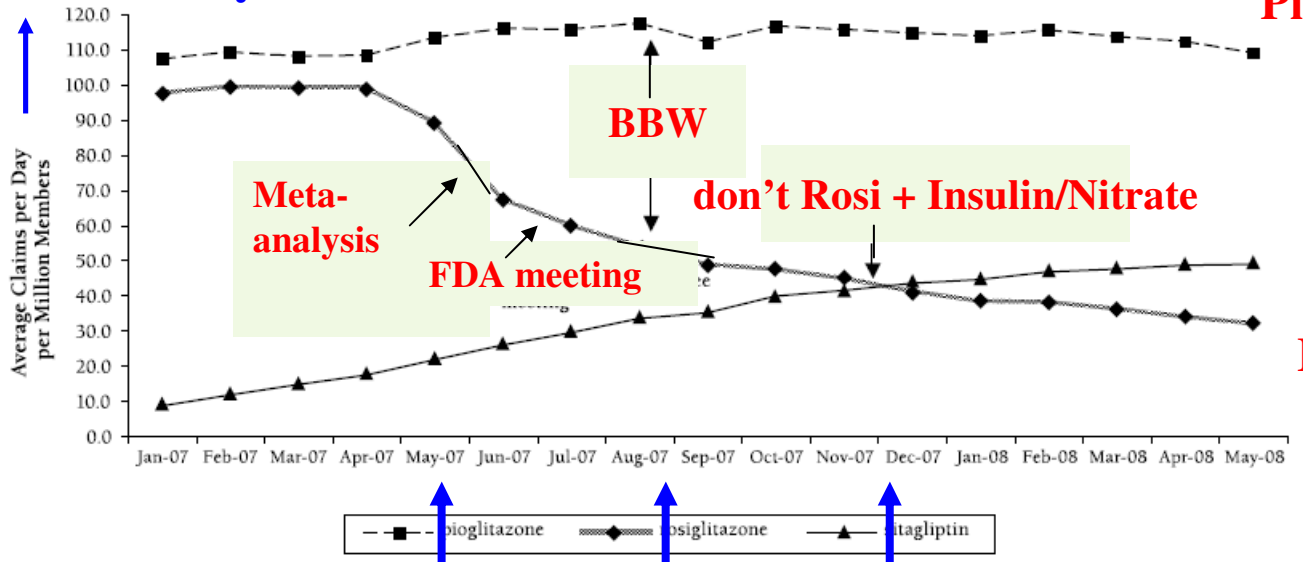
RESEARCH

Rosiglitazone and Pioglitazone Utilization from January 2007 Through May 2008 Associated With Five Risk-Warning Events

Catherine I. Starner, PharmD, BCPS, CGP; Jeremy A. Schafer, PharmD; Alan H. Heaton, PharmD; and Patrick P. Gleason, PharmD, BCPS, FCCP

FIGURE Rosiglitazone, Pioglitazone, and Sitagliptin Claims[a] per Million Members From January 1, 2007, Through May 31, 2008 (Represents Approximately 9 Million Commercially-Insured Members)

Average Claims/Day/Million Members



Shi (2011):
US TZDs BBW warning in 2007 → Clinical Outcome (HbA1c)

Impact of thiazolidinedione safety warnings on medication use patterns and glycemic control among veterans with diabetes mellitus☆,☆☆

Lizheng Shi[a,b,c,*], Yingnan Zhao[a,c], Keith Szymanski[d], Lillian Yau[a,c], Vivian Fonseca[b,c]

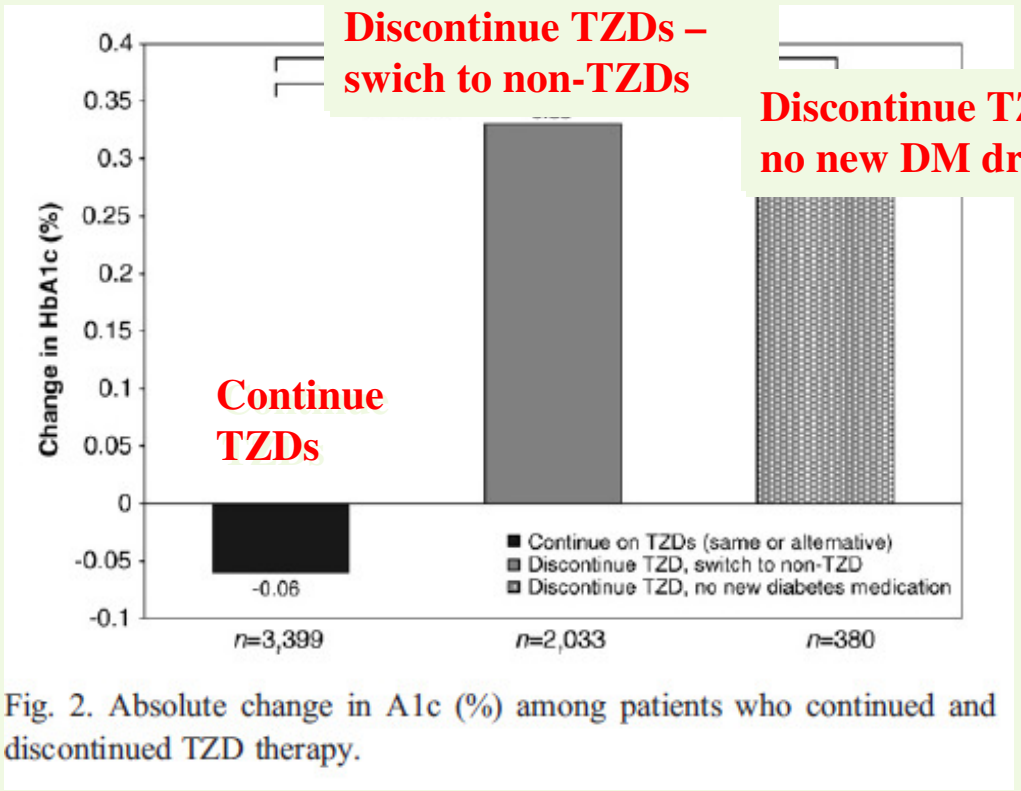


Fig. 2. Absolute change in A1c (%) among patients who continued and discontinued TZD therapy.

Rawson (2013):
Canada TZDs warning in 2007 →
Clinical Outcome (adverse events)

RESEARCH ARTICLE Open Access

Rosiglitazone use and associated adverse event rates in Canada between 2004 and 2010

Nigel SB Rawson[1,2] and Jorge A Ross Terres[1*]

Table 1 Estimated average monthly rates of adverse events per 100,000 patients in two time periods

	April 2004 - October 2007			November 2007 - December 2010		
	Average	Range	95% CI	Average	Range	95% CI
Adverse events	13.4	2.3-27.3	8.6-20.8	5.7	0.0-12.5	2.4-13.6
Serious adverse events	6.0	0.6-21.5	3.1-11.5	3.4	0.0-8.7	1.1-10.6
Cardiac adverse events	2.3	0.0-9.4	0.8-6.5	2.2	0.0-6.6	0.5-8.9

The evaluation framework/methods of safety warnings and RMP – RE-AIM Framework

Factor	Description	Possible REMS assessment Domains
Reach	Proportion of the target population who participate	Distribution / availability Participation Medication access
Effectiveness	Success rate	Knowledge / awareness Drug Utilization Clinical Outcomes
Adoption	Proportion of settings that adopt the intervention	Attitude / intention Prescribing Behaviors
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Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Glasgow, et. al. *Am. J. Public Health*, Sept. 1999, Vol. 89, No. 9.

Research Framework and Statistic Approaches

Safety Warning

RMP Policy

Prescribing Behaviors

Drug Utilization

Clinical Outcomes

Stratified Prescription Rate

Volume

Case Number

Changing Rate

Cost

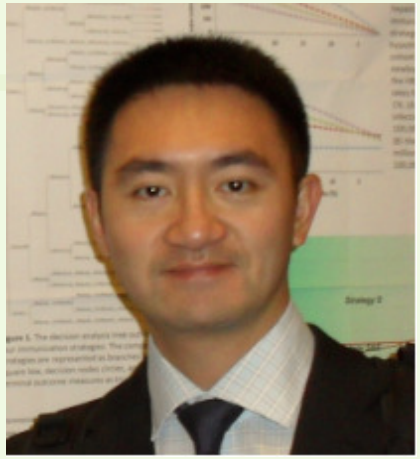
Incidence Rate

Pre-Post Analysis / Interrupted Time Series

Survival Analysis

4. Conclusion

- REMS policy might decrease the overall drug utilization and market share, regardless of patients with/without risk factors → REMS might not improve the quality of treatment.
- There might no dramatic reductions of incidences following the safety warnings or REMS due to the very rare event rates.
- The effects of future risk management policies (like REMS) for drugs to prevent the adverse events might be limited, since it might not been preferred anymore (may be switched to other classes of drugs).
- Other analyses, including medication access and burden of implication, are suggested for study.



THANK YOU!

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