

Observational Studies

Effect of Antidiabetic Agent Choice on Cardiovascular Morbidity and Mortality in Type 2 Diabetes Mellitus

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Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the
Drug Safety and Risk Management Advisory Committee
July 26, 2007

Background

- AUG 2006 submission from GSK
 - Pooled AVANDIA clinical trials
 - Observational study from Ingenix
- DDRE review completed FEB 2007
 - Regulatory recommendations based on information at that time
- Two new observational studies from GSK not yet fully reviewed by FDA

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Overview – Observational Studies in Type 2 Diabetes Mellitus (T2DM)

- Methodologic challenges in studying cardiovascular outcomes in T2DM
- Published population-based studies of cardiovascular outcomes in T2DM
 - From Saskatchewan and Tayside
- FDA review of Ingenix study
 - Included in background package
- Two new observational studies from GSK
 - Received in June / July 2007
 - Preliminary FDA review will be presented
 - Not in FDA background package

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Observational Studies in T2DM – Methodologic Challenges

Can these observational studies provide sufficiently robust evidence to refute the safety signal identified in the meta-analysis of randomized controlled trials with rosiglitazone?

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Observational Studies in T2DM – Methodologic Challenges

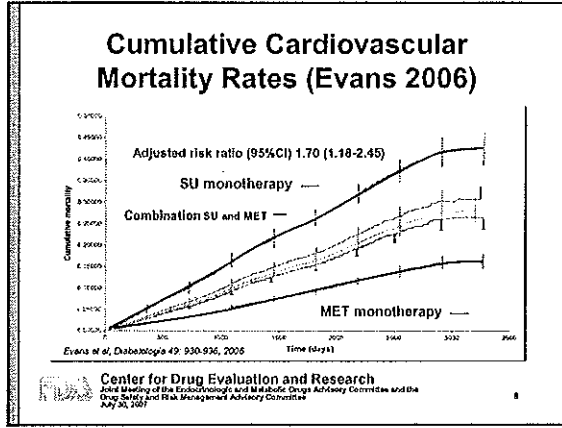
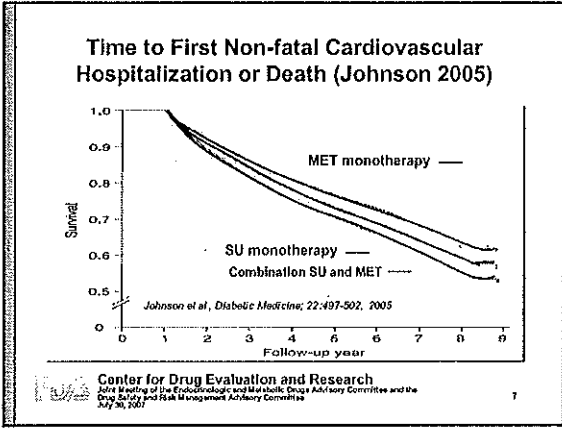
- **OUTCOME** – missing ascertainment of out of hospital cardiovascular deaths
- **EXPOSURE** misclassification
- Unmeasured **CONFOUNDING** and other sources of potential bias

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Published Observational Studies of Cardiovascular Morbidity and Mortality in Patients with T2DM

- Johnson et al. "Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with T2DM"
 - Saskatchewan Health Services Databases
 - *Diabetic Medicine*; 22:497-502, 2005
- Evans et al. "Risk of mortality and adverse cardiovascular outcomes in T2DM: a comparison of patients treated with sulfonylureas and metformin"
 - Tayside Medicines Monitoring Unit (MEMO)
 - *Diabetologia* 49: 930-936, 2006

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GSK Observational Study #1- Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents

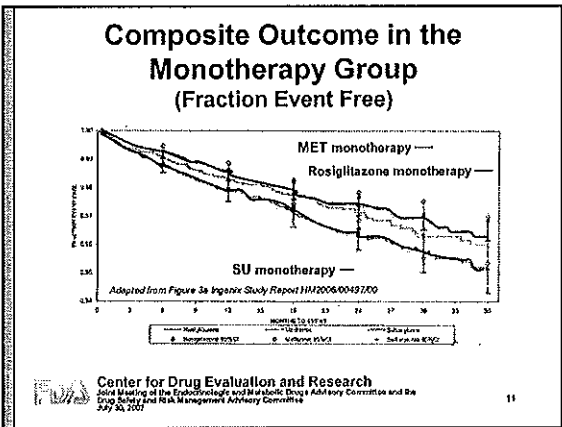
- Balanced Cohort Study
- Enrollees of United Healthcare health plans
- Drug initiators from JUL 2000 through DEC 2004
- Matched cohorts using multivariate balancing procedure (propensity score matching) to match comparable initiators for each study group
- New cases of myocardial infarction or coronary revascularization were identified up to JUN 2005

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Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents

- Outcomes identified in claims data:
 - Hospitalized fatal or nonfatal myocardial infarction (primary discharge diagnosis code ICD9 410.xx)
 - Coronary revascularization (based on procedure codes)
- Outcome does not include out-of-hospital cardiovascular deaths

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
GSK Observational Study #2- Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents in the Pharmetrics Database

- New users of specific antidiabetic therapies
- Pharmetrics aggregate of 80 US health plans
- Drug initiators from JUN 2000 through Mar 2007
- Pairwise comparisons stratified on pair-specific propensity scores
- New cases of myocardial infarction or coronary revascularization were identified from hospital insurance claims data

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
Study Limitations - General

- Study populations from both Ingenix and PharMetrics databases have relatively fewer patients ≥ 65 years of age compared to overall population of diabetics
- Limited generalizability to older (≥ 65 years of age) population

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
Major Limitation - Outcome

Outcome definition was not inclusive enough to capture the same events as the clinical trials

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
Proportion of Cardiovascular (CV) Deaths from AVANDIA RCTs Unlikely to be Ascertained in Claims Data

Cardiovascular Deaths	RSG N = 8604	Comparator N = 5633
Total	16	6
Out-of-hospital	10 (63%)	3 (50%)

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Proportion of Myocardial Ischemia SAEs from AVANDIA RCTs Unlikely to be Ascertained in Claims Data

Myocardial Ischemia SAEs	RSG N = 8604	Comparator N = 5633
Total	86	40
Out-of-hospital	9 (10.5%)	3 (7.5%)

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
Study Limitations - Exposure

- Definition of new user
 - Based on six month look back – long enough?
 - Depletion of susceptibles can lead to apparent dilution of risk in all exposure groups
- Exposure ascertainment
 - No documentation of actual compliance with prescribed therapy – poor adherence?
 - Switching among study cohorts – common in study #1, likely also in study #2
 - Leads to misclassification bias

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Study Limitations - Confounders

- Unmeasured confounding
- Definition and capture of events
 - Is six months long enough to capture information on confounders in claims data?
 - Completeness of the list of confounders (e.g. smoking, aspirin)?

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GSK Observational Study #3 – An Assessment of the Effect of Thiazolidinedione Exposure on the Risk of Myocardial Infarction in T2DM Patients

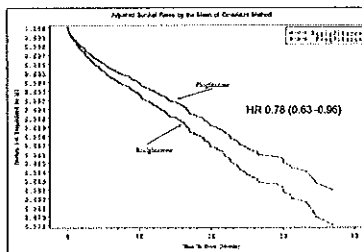
- Nested case-control study compares patients on TZD therapies to a reference group of patients on non-TZD therapies
- Integrated Healthcare Information Services (IHGIS) database for the years 1997 to 2006
- **Flawed Study Design and Analysis**
 - Reference group includes insulin patients who may have had more cardiovascular comorbidities
 - Unknown mix of therapies in exposure groups
 - No demonstration of adequate adjustment for baseline risk factors

Observational Studies Comparing Rosiglitazone and Pioglitazone

- **Pharmetrics study:**
Adjusted HR (95%CI) for RSG vs. PIO:
 - MI = 0.783 (0.519-1.180)
 - MI+CR = 0.966 (0.777-1.201)
- **Takeda study * (in press):**
Adjusted HR (95%CI) for PIO vs. RSG:
 - MI = 0.78 (0.63-0.96)
 - MI+CR = 0.85 (0.75-0.98)

* Has not been reviewed by FDA

A Comparison of Pioglitazone and Rosiglitazone for Hospitalization for MI in T2DM, Takeda study, in press



Summary

- Definition of **OUTCOME** inadequate
 - Out-of-hospital cardiovascular deaths seen in adjudicated pooled data from RCTs
 - Important "blind spot" in claims data relied on by GSK
- **EXPOSURE** mapping issues
 - Potential exposure-related misclassification
- Questions remain of unmeasured **CONFOUNDING** due to incomplete ascertainment of baseline risk factors

Conclusion

Available observational studies do not refute the signal for myocardial ischemia identified in the meta-analysis of randomized controlled trials with rosiglitazone

Acknowledgements

- Colleagues in DMEP and Office of Biostatistics
- **OSE/OB AVANDIA Observational Studies Analysis Team:**
 - Allen Brinker
 - Tarek Hammad
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 - Charles Cooper
 - Mark Levenson
 - Mark Avigan
 - George Rochester
 - David Graham
 - Gerald DalPan

Back-Up Slides

Study Limitations – Analytic Issues Propensity Score Approach

- Available adjustment variables limited by use of non-clinical (administrative) data
- Details on the adequacy of the propensity scores in achieving balance of adjustment variables are not given
- Effects for unmatched patients in Study #1 are not given.

Analyses – observational balanced cohort study

- Multivariate models adjusted with baseline covariates to account for potential confounding
- Propensity score matching procedure is intended to balance the distribution of characteristics within each cohort that may have influenced a physician's choice of therapy for an individual patient.

Sudden Death

- Many cases do not result in medical attention.
- If exposure cohorts are followed via health records, need to link with vital records to ascertain deaths.
- Death certificates may not have sufficient accuracy to differentiate between deaths of cardiovascular origin from other deaths.
- Death certificate cause of death will be more accurate if it mentions that an autopsy was performed.
- Coroner's reports are ideal for determining circumstances of death.

Slide courtesy Elizabeth B. Andrews, MPH, PhD, DSaRM AC Meeting, February 9, 2006

Out-of-Hospital Deaths from AVANDIA Pooled RCTs Not Likely to be Ascertained in Hospital Claims Data

Rosiglitazone Treatment Group

ID	Age/Sex	Cause of Death	Description	OCEAN ID
Pl 096-002-00349	52M	MI	Found dead in bed	A0219869A
Pl 011-043-00999	67F	MI	Died in bed sleep	A0267010A
Pl 079-006-05546	69M	MI	Found slumped in chair	A0270243A
Pl 094-005-04560	63F	MI	Found dead in a chair	A0274880A
Pl 082-037-13931	71M	MI	MI at home, pronounced dead at hospital	A0176423A

Out-of-Hospital Deaths from AVANDIA Pooled RCTs Not Likely to be Ascertained in Hospital Claims Data

Rosiglitazone Treatment Group (cont'd)

ID	Age/Sex	Cause of Death	Description	OCEAN ID
Pl 134-076-75235	51F	Cardiac arrest	Collapsed during activity, couldn't be resuscitated	A0312591A
Pl 132-002-00370	56M	MI	Collapsed at home, resuscitation not successful	B0228804A
Pl 136-701-74549	78M	MI	Died from a "suspected myocardial infarction"	B0230354A
Pl 163-001-86730	51M	VF, CHF	Died from "sudden heart failure, probably ventricular fibrillation"	B0244564A
Pl 1002-0049233	66M	Sudden death	Found dead in bed	B0309553A

Out-of-Hospital Deaths from AVANDIA Pooled RCTs Not Likely to be Ascertained in Hospital Claims Data

Comparator Treatment Group

ID	Age/Sex	Cause of Death	Description	OCRAM ID
P1 029-003-03618	71M	MI	Died suddenly "of an apparent heart attack"	A0265831A
P1 335-01377414	70M	Cardiac arrest	Developed dyspnea and was pronounced dead on arrival at hospital	A0339112A
P1 337-039-84000	78M	MI	Collapsed and could not be resuscitated	A0352432A

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