

## Use of Rosiglitazone in the BARI 2D Trial

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## BARI 2D Trial

PI: Sheryl Kelsey, University of Pittsburgh  
 Study Chair: Robert Frye, Mayo Clinic  
 Study Co-Chair: Saul Genuth, Case Western Reserve

- Support:**
- NHLBI
  - NIDDK
  - GlaxoSmithKline
  - Many in-kind contributors

## BARI 2D Trial

Bypass Angioplasty Revascularization Investigations 2 - Diabetes

- Multi-center 2x2 factorial RCT
  - Elective Revascularization + Medical Rx versus Medical Rx only
  - Insulin Sensitization versus Insulin Provision
- 2368 patients with type 2 diabetes and stable CAD (high risk)
- 5 years mean follow-up
- HbA1c goal < 7.0%
- End Points:
  - Primary: All-cause mortality (300 expected)
  - Secondary: All-cause mortality + nonfatal MI and stroke

## Glycemia Management Strategy Drugs Used in BARI 2D at Year 1

<u>Drug Class</u>	<u>IS</u>	<u>IP</u>
TZD (mainly rosiglitazone)	69%	3%
Metformin	79%	7%
Sulfonylureas	14%	57%
Insulin	24%	53%

## Glycemia Management Strategy Risk Factor Control in BARI 2D at Year 1

- HbA1c: 7.1%
- LDL-C: 83 mg/dL (93% on statins)
- TG: 151 mg/dL
- BP: 127/72 mm Hg
- Current Smokers: 10.1%
- BMI: 32 kg/m/m

## BARI 2D DSMB

- Appointed by and advisory to Director NHLBI
  - NHLBI-appointed Executive Secretary (separate from project officer)
- Meets at least twice per year
- Monitors
  - Safety of participants
  - Integrity of data collection
  - Evidence for differential efficacy
    - From trial - O'Brien-Fleming stopping rule (annual "looks")
    - From external data
  - Futility - No formal stopping rule

## BARI 2D DSMB Expertise

- Cardiology
- Diabetes
- Cardiothoracic Surgery
- Biostatistics
- Clinical Trials
- Bioethics

## Rosiglitazone - Past DSMB Recommendations (1)

- **January 9 2006: Ad hoc conference call to review preliminary GSK trial data analysis (provided unsolicited to Executive Secretary)**
  - Letter to BARI 2D investigators alerting them to HF risk of rosiglitazone (even without insulin)
  - Improve monitoring for HF in BARI 2D
  - Additional analyses of existing BARI 2D data
- **March 24, 2006: Regularly scheduled DSMB meeting**
  - Disclosure statement of HF risk of rosiglitazone to be presented to and signed by participants at their next BARI 2D visit

## Rosiglitazone - Past DSMB Recommendations (2)

- **October 23, 2006: Regularly scheduled DSMB conference call**
  - Encourage BARI 2D patients should to have an ophthalmologic examination (with dilation) yearly.
  - Add a question to data form to ascertain whether macular edema was identified.
- **January 29, 2007: Ad hoc conference call to discuss ADOPT fracture data**
  - Additional prospective and retrospective data collection on fractures in BARI 2D

## BARI 2D DSMB Review

- IS versus IP (intention-to-treat)
- Does being on rosiglitazone at Year 1 predict CV events, death? (Cox model)
- Does recent rosiglitazone use predict CV events, death? (time-dependent Cox model)
  - Control for baseline CV risk factor levels
  - Control for baseline insulin use
  - Control for use of other diabetes drugs during trial
  - Control for HbA1c, CV risk factor levels during trial

## Expanded Meta-Analysis CV Death

CV Death	N	Events	Odds Ratio	95% CI
Nissen-Wolski	27833	61	1.67	0.99 to 2.82
RECORD	4447	83	0.80	0.52 to 1.24
Total	32280	144	1.09	0.77 to 1.53

BARI 2D                      2368                      180\*

\* Expected by the end of the BARI 2D trial, based on BARI 1 experience. Approximately 60% of follow-up completed as of 12/31/06.

## Expanded Meta-Analysis Myocardial Infarction

MI	N	Events	Odds Ratio	95% CI
Nissen-Wolski	27883	158	1.49	1.06 to 2.11
RECORD	4447	89	1.23	0.81 to 1.88
Total	32280	247	1.40	1.06 to 1.83

BARI 2D                      2368                      270\*

\* Expected by the end of the BARI 2D trial, based on the BARI 1 experience. Approximately 60% of follow-up completed as of 12/31/06.

## DSMB Statement (1)

- The members of the BARI 2D Data and Safety Monitoring Board (DSMB), who have extensive expertise in patient care, safety, and ethics, met on May 30, 2007, to review the safety information from the trial.
- The Board thoroughly reviewed the recently published data on heart attacks and deaths in patients receiving rosiglitazone (Avandia®).

## DSMB Statement (2)

- In the research setting of BARI 2D, the Board made no observations that would justify a recommendation to terminate treatment with rosiglitazone.
- The Board was very satisfied with the coordinated care of BARI 2D patients.
- The trial participants are strongly encouraged to adhere to their recommended treatments for diabetes, hypertension, and dyslipidemia.
- The Board is not in a position to comment on the use of rosiglitazone in routine clinical practice.

## BARI 2D and ACCORD Trials NHLBI Public Statement (6/15/07)

- NHLBI Statement on Use of Rosiglitazone in Two NHLBI-Funded Clinical Trials  
<http://public.nhlbi.nih.gov/newsroom/home/GetPressRelease.aspx?id=267>
- Questions and Answers: Use of Rosiglitazone (Avandia) in the National Heart, Lung, and Blood Institute's Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trials  
<http://www.nhlbi.nih.gov/new/press/07-rosi-qa.htm>

## Extra Slides

## Nissen/Wolski Meta-Analysis CV Death

CV Death	N		Events		Odds Ratio	95% CI
	Avandia	Control	Avandia	Control		
40 Small Trials	11465	6748	25	7	2.59	1.23 to 5.49
DREAM	2635	2634	12	10	1.20	0.52 to 2.77
ADOPT	1456	2895	2	5	0.80	0.17 to 3.86
Total	15556	16724	39	22	1.67	0.99 to 2.82

## Nissen/Wolski Meta-Analysis Myocardial Infarction

MI	N		Events		Odds Ratio	95% CI
	Avandia	Control	Avandia	Control		
40 Small Trials	11465	6748	44	22	1.49	0.86 to 2.51
DREAM	2635	2634	15	9	1.65	0.74 to 3.68
ADOPT	1456	2895	27	41	1.33	0.80 to 2.21
Total	15556	19092	86	72	1.49	1.06 to 2.11