United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510-6200

July 12, 2010

Via Electronic Transmission

The Honorable Margaret A. Hamburg
Commissioner
U.S. Food and Drug Administration
White Oak Building 1
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Hamburg:

As Chairman and Ranking Member of the United States Senate Committee on Finance (Committee), we have a special responsibility to protect the health of the approximately 100 million Americans who receive health care through the Medicare and/or Medicaid programs, as well as to ensure that taxpayer and beneficiary dollars are appropriately spent on safe and effective drugs and devices. These responsibilities include overseeing the U.S. Food and Drug Administration (FDA) whose mission is, among other things, to protect the public health by assuring the safety, efficacy, and security of our nation's drug supply.

We would like to update you about our concerns regarding Avandia, a drug marketed by GlaxoSmithKline (GSK) to treat diabetes. As part of our oversight duties, we have requested documents from GSK that may shed light on safety and efficacy concerns with Avandia. Our staff reviewed those internal GSK documents and found the following:

- **GSK apparently failed to publish studies in a timely manner that found problems with Avandia**

- **Avandia was part of GSK's ghostwriting program**

In the following pages, we have provided further information on these topics for your review and consideration. We have also attached pertinent documents for FDA's review.

GSK APPARENTLY FAILED TO PUBLISH STUDIES THAT FOUND PROBLEMS WITH AVANDIA

As far back as 2000, internal emails show that GSK executives sought to downplay scientific findings, which raised questions about the safety of Avandia. For example, in an internal email sent on October 23, 2000, a GSK executive sought to

downplay the fact that Avandia gave a worse lipid profile[1] than the competitor, ACTOS. At the time, GSK executives were concerned about a GSK study of ACTOS, called Study 175. In that email, a GSK executive wrote, "This was done for the US business, way under the radar and we lost in terms of LDL and Tgs….Per Sr. Mgmt request, these data should not see the light of day to anyone outside of GSK." [ATTACHMENT A]

In another email sent on July 6, 2001, GSK executives discussed not wanting to do a head to head trial between Avandia and ACTOS because of Study 175. In that email, a GSK executive wrote, "I agree that there is no benefit in doing a head to head study with [ACTOS] as the best result would be equivalence." [ATTACHMENT B] We have attached a copy of Study 175 for your review. [ATTACHMENT C]

We are concerned that Study 175 was not turned over to the FDA in a timely manner. A deputy director at the FDA Office of Drug Safety was asked whether it would "have been important…to know that in 2001 GlaxoSmithKline found that they lost against its competitor Actos" and responded:

> …any information pertaining to a serious adverse event, such as myocardial infarction, and especially death, is a high alert for any safety officer at the FDA. So any information, including something like this, because the lipid profile go to some biological mechanism by which maybe one drug may have more safety –adverse event than another within the same drug class, it would be extreme important information for someone in my position to consider.[*sic*] [ATTACHMENT D]

On a separate occasion, GSK executives discussed, in email, whether to publish two GSK studies that also found problems with Avandia. In an email sent on July 20, 2001, a GSK executive responded, "Not a chance. These put Avnadia [sic] in quite a negative light when folks look at the response of the [Avandia] arm. It is a dificult [sic] story to tell and we would hope that these do not see the light of day. We have already published the better studies." [ATTACHMENT E]

Finally, GSK told Committee investigators that GSK examined Avandia for heart attack risk in 2001. GSK told Committee investigators that they never provided this document to FDA, but they did provide the underlying data to FDA. We have attached that 2001 report to this letter, in case the information may prove important to the FDA. [ATTACHMENT F]

[1] According to the Mayo Clinic: It's important to keep your cholesterol levels within healthy limits. And if

AVANDIA WAS PART OF GSK'S GHOSTWRITING PROGRAM

As reported by the *Associated Press*, GSK created a "sophisticated ghostwriting program to promote its antidepressant Paxil." GSK called this program CASPPER.[2] Avandia was also part of GSK's CASPPER program and GSK created at least one ghostwritten article for an academic. While this behavior is not illegal, we would like to apprise you of what we found. In an internal GSK memo written on September 13, 2000, GSK explained the value of CASPPER. According to the document:

> CASPPER provides you the ability to offer assistance in the preparation and publication of case studies and other short communications relevant to the clinical use of Avandia….Your participation can help establish or enhance your relationships with your physicians or other healthcare professionals. [ATTACHMENT G]

Other documents show that GSK prepared at least one ghostwritten manuscript. For example, in an email sent on August 13, 2001, a GSK employee wrote, "[S]ee attached manuscript that has been ghost written for Haffner." Further down, the email continued, "Please find attached the Haffner manuscript….The manuscript is currently in a rough format that has not gone to the author yet." [ATTACHMENT H]

We have attached several drafts of the ghostwritten document for FDA to review, a draft of a letter with the study that is addressed to the journal Circulation, and copy of the study that was published in July 2002 in the journal *Circulation*. [ATTACHMENT I]

We appreciate your review of these documents. If you have any questions, please do not hesitate to contact Christopher Law of Senator Baucus's staff or Paul Thacker of Senator Grassley's staff at (202) 224-4515.

Sincerely,

Max Baucus
Chairman

Charles E. Grassley
Ranking Member

Attachments

[2] Perrone, Matthew, "Glaxo Used Ghostwriting Program to Promote Paxil," *Associated Press*, August 19, 2009.

ATTACHMENT A

From: Martin I Freed/DEV/PHRD/SB_PLC

To: Stuart C Dollow/GB1/GlaxoWellcome@ExchangeUK @ SB

CC: Ameet Nathwani-1/DEV/PHRD/SB_PLC@SB_PHARM_RD@SB;
Christine L Blumhardt/SB-OTHER/PHRD/SB_PLC@SB_PHARM_RD@SB;
Colette M Bellin/HEP/WSO/SB_PLC@SB;
Hilary M Malone/TRAC/PHRD/SB_PLC@SB_PHARM_RD@SB;
JaiKrishna Patel/US1/GlaxoWellcome@ExchangeUS@SB;
Joanna M Balcarek/DEV/PHRD/SB_PLC@SB_PHARM_RD@SB

Subject: Re: [redacted]

Date: 03/29/2001 08:08:18 (GMT-05:00)

There was no Avandia v Actos study performed in exSB. Study 175 was an Actos only study performed to give us enough info using historical comparison to make a decision about large scale H-H. This was done for the US business, way under the radar and we lost both in terms of LDL and Tgs. Per Sr Mgmt request, these data should not see the light of day to anyone outside of GSK.

Marty

From: Stuart C Dollow/GB1/GlaxoWellcome@ExchangeUK on 29-Mar-2001 03:44

To: Joanna M Balcarek, Martin I Freed, Ameet Nathwani-1, Colette M Bellin, Hilary M Malone, Christine L Blumhardt
cc: JaiKrishna Patel
Subject: [redacted]

[redacted]

I have heard also that there was an Avandia vs Actos study performed in ex SB, but have not seen the data from this. can someone send me the data so that I can have as comprehensive a package as possible for Mike Ferris

Many thanks

Regards

Stuart

Dr Stuart Dollow
Global Clinical Head
Metabolic and Musculoskeletal Clinical Development
GlaxoSmithKline

Tel [redacted]
Fax [redacted]
email [redacted]

Attachments:
Revised Study 175 Headline Results Summary.doc

ATTACHMENT B

Sharon W Shapowal
12-Jul-2001 10:08

Regulatory Affairs North America Franklin Plaza, FP-1010 8-288-3434

To: Susan Weill
cc:
Subject: Re: 175 Freezer study -- post-hoc lipid analyses

Have you seen these data?
---------- Forwarded by Sharon W Shapowal/SB-OTHER/PHRD/SB_PLC on 07/12/2001 10:07 ----------

Murray W Stewart
06-Jul-2001 09:03

To: Martin I Freed
cc: Ameet Nathwani-1, Peter W Letendre, Stuart C Dollow, David M Brand, Lisa E Porter, Lisa Menci-1, Margaret M Kreider, Joanna M Balcarek, Sharon W Shapowal, Jo F Dole, Nandita Biswas-1, Rhona A Berry, Alexander R Cobitz, Nigel P Jones
Subject: Re: 175 Freezer study -- post-hoc lipid analyses

Dear Marty

I would just like to confirm that the data with Pio does show an improvement in LDL particle density to more lighter particles and the change in LDLchol/LDLApoB suggests increase in particle size. Along with the increase in HDL2 these changes are very similar to that shown in 108 and therefore I agree that there is no benefit in doing a head to head with PIO as the best result would be equivalence. I support your additional mechanistic study with lipases particularly following John Brunzell talk at the Avandia medical marketing meeting.

Murray
Martin I Freed

Martin I Freed 05-Jul-2001 21:23

Pulmonary/Diabetes Therapeutic Unit Mail Code - UP 4310; E-mail [redacted]

To: Ameet Nathwani-1, Murray W Stewart, Peter W Letendre, Stuart C Dollow
cc: David M Brand, Lisa E Porter, Lisa Menci-1, Margaret M Kreider, Joanna M Balcarek, Sharon W Shapowal, Jo F Dole, Nandita Biswas-1, Rhona A Berry, Alexander R Cobitz
Subject: 175 Freezer study -- post-hoc lipid analyses

All - many thanks to Lisa Menci and Marge for pulling these data together!! Please find

enclosed a copy of the post-hoc lipid analyses from study 175 - the Actos-only study. Recall that we did this study in lieu of a H2H due to our concerns of what we might see. We have previously put together an SPS for a H2H RSG vs PIO study, pending these data. You will note that the apparent effects of Actos on lipid subfractions were similar to that observed with RSG (esp wrt Rf and HDL2). What is not shown in these slides are the full DGUC data for Tgs which showed a demonstrable reduction in VLDL Tgs with Pio - remember, we wree unable to get those data with Avandia.

These data should be discussed at the next Avandia CMT or PT (whichever comes first) - Murray and I have discussed these data briefly and I think that we are aligned that we should NOT proceed with a lipid H2H; however, we both feel quite strongly that an additional study more fully characterizing the effects of RSG on subfractions, including chol and Tg in the DGUC, as well as looking at LPL, HL and CETP in the same cohort will be needed. Please review and feed any questions back to Lisa and myself. We will also show these data to the CST when we get that scheduled.

Regards,

Marty

---------- Forwarded by Martin I Freed/DEV/PHRD/SB_PLC on 07/05/2001 16:11 ----------

Lisa Menci-1 05-Jul-2001 15:07

Clinical R&D - Pulmonary-Diabetes TU Room UP 4-3257M phone: [redacted] fax: [redacted]

To: Martin I Freed
cc: Margaret M Kreider
Subject: 175 Freezer study -- post-hoc lipid analyses

Marty,

Marge asked me to review the post-hoc lipid analyses from the Study 175 stored samples, and display key data in a manner which may be easily conveyed to groups outside of Clinical. When reviewing the attached graphs and tables, please note the following:

- Data included in the post-hoc lipid analyses are from a subset of patients, and represent approximately 65-70% of patients who participated in Study 175.

- For point of reference, demographic characteristics and changes in glycemic parameters for the entire study population are provided in the attachment below. Data for the subset of patients are not available.

Please let me know if additional data are needed.

Lisa


175_post-hoc_lipid_analysis.p


175_demog_eff.doc

ATTACHMENT C

Study 175 Headline Results Summary

Background/Rationale

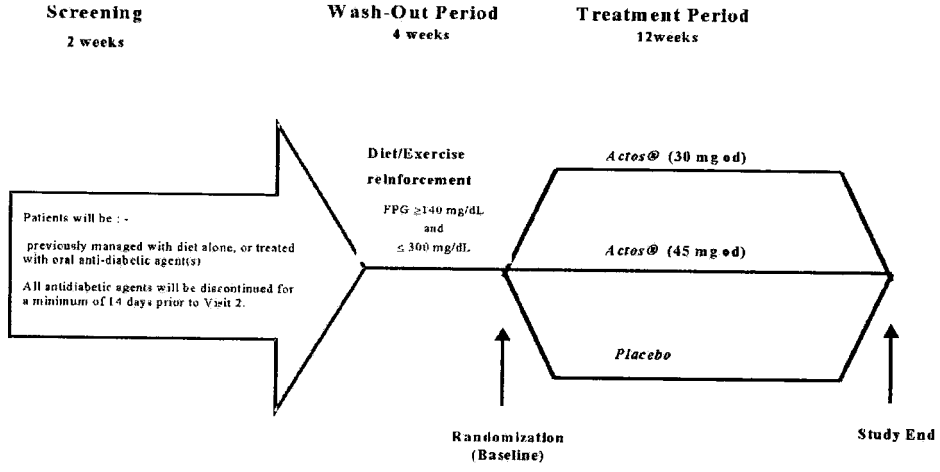
Clinical/BDS were asked in September 1999 to assess the risk/benefit of performing an Avandia vs. Actos head-to-head trial comparing glycemic control and/or lipid effects. We concluded that such a study would entail very high risk for the following reasons:

- Differences in glycemic efficacy between the two drugs were likely to be small, and therefore a very large sample size would be required to demonstrate a statistical superiority which may not be considered clinically relevant.
- Baseline differences in the Avandia and Actos patient populations precluded comparisons, therefore it was not possible to predict whether apparent differences in lipid effects were due to a true drug effect.

We therefore undertook an Actos only trial in a population which was very similar to the Avandia clinical trials population, with the intent of comparing lipid effects to the Avandia **historical data** from studies 011 and 024. A statistical rationale based on the historical comparison was developed for a go/no-go decision on whether to proceed with a direct head-to-head trial.

Methods

The purpose of study 175 was to determine the effect of Actos on LDL and TGs when given to patients with similar baseline characteristics as patients in the Avandia phase 3 clinical program. The study design is shown below.



In order to enroll a patient population similar to the 011 and 024 clinical trials population, inclusion/exclusion criteria were identical to studies 011 and 024 with the following additions: Patients with triglycerides >400 mg/dL or LDL cholesterol >250 mg/dL were excluded. These additional criteria were added to ensure that patients in study 175 were similar to the majority of patients in our existing monotherapy database. A placebo arm was included in study 175 to assess any potential unknown study differences.

The go/no-go decision for proceeding with a direct head-to-head trial was based on change from baseline in LDL and Triglycerides at week 12, compared to the historical Avandia data. The two primary comparisons were:

Avandia 8 mg od (n = 159) vs. pooled 30 mg and 45 mg Actos groups (n = 60)
Avandia 4 mg bd (n = 314) vs. pooled 30 mg and 45 mg Actos groups (n = 60)

The go/no-go objective was to show that Avandia was non-inferior to Actos for the change from baseline in LDL and triglycerides at week 12 with a non-inferiority margin of:

no more than 10% greater for LDL (upper limit of the 90% C.I. $\leq$ 10%)
no more than 25% greater for TGs (upper limit of the 90% C.I. $\leq$ 25%)

The "go" decision requires that both criteria are met.

The estimation of between group differences was based on an analysis of covariance (ANCOVA) which included covariates that were identified as being associated with lipid changes in the Avandia database.

Results

RSG 4 mg bd and 8 mg od did not meet the criteria for non-inferiority to the combined PIO group in the percent change from baseline at week 12 in either LDL or triglycerides.

Mean Percentage Difference in Change from Baseline at Week 12 - LDL cholesterol

	Point Estimate	90% Confidence Interval
RSG 4 mg bd vs. pooled PIO	11.1%	6.61, 15.86
RSG 8 mg od vs. pooled PIO	11.2%	6.30, 16.32

Mean Percentage Difference in Change from Baseline at Week 12 - Triglycerides		
	Point Estimate	**90% Confidence Interval**
RSG 4 mg bd vs. pooled PIO	22.9%	12.96, **33.67**
RSG 8 mg od vs. pooled PIO	25.6%	14.73, **37.58**

Baseline Demographics and Metabolic Parameters:
The baseline and demographic characteristics of the study 175 population were similar to the characteristics of the patient populations in studies 011 and 024. There was little difference in the placebo groups among the three studies.

Mean Demographic Characteristics at Baseline

	PIO 30 mg	**PIO 45 mg**	**PIO Pbo**	**RSG 8 od**	**RSG 4 bd (011, 024)**	**011 Pbo**	**024 Pbo**
Age (yr)	61	55	61	59	62,58	60	58
Female (%)	44	29	33	33	34,32	37	30
BMI	31	31	30	30	29,30	30	29
*Prior Therapy (%)	94	68	82	69	74,74	70	76
LLA** (%)	35	18	21	23	20,15	11	19

*Any prior oral antidiabetic therapy
**Lipid lowering agent use at baseline

Mean Baseline Values for Lipid and Glycemic Parameters

	PIO 30 mg	**PIO 45 mg**	**PIO Pbo**	**RSG 8 od**	**RSG 4 bd (011, 024)**	**011 Pbo**	**024 Pbo**
LDL (mg/dL)	118	137	127	128	131, 126	131	127
Trigs (mg/dL)	174	162	162	185	186, 182	183	179
HDL (mg/dL)	42	45	44	44	43, 45	44	45
HbA1c (%)	8.6	8.6	8.7	8.9	8.8, 9.1	8.8	8.8
FPG (mg/dL)	207	190	208	226	220, 231	225	222

Change from Baseline in Lipid Parameters

The mean percent change from baseline in primary lipid parameters (LDL and triglycerides) and the mean change from baseline in secondary lipid parameters (HDL and FFA) are shown below for study 175, along with the historical Avandia data from studies 011 and 024.

Mean Percent Change from Baseline at Week 12 in Primary Lipid Parameters (Geometric mean and 95% C.I.)

	Study 175 data			
	PIO 30 mg	**PIO 45 mg**	**PIO Pbo**	
LDL (mg/dL)	**+4.9** (-1.34, 11.61)	**-6.5** (-13.19, 0.67)	**+0.8** (-5.40, 7.39)	
Trigs (mg/dL)	**-4.6** (-18.25, 11.45)	**-15.8** (-25.77, -4.42)	**+5.6** (-7.35, 20.45)	
	Historical Avandia data			
	RSG 8 od	**RSG 4 bd (011, 024)**	**011 Pbo**	**024 Pbo**
LDL (mg/dL)	**+12.0** (7.59, 16.56)	**+15.7** (11.70, 19.94) **+8.7** (4.81, 12.66)	**+1.6** (-0.98, 4.33)	**+1.6** (-1.07, 4.40)
Trigs (mg/dL)	**+11.0** (3.66, 18.92)	**+5.9** (-1.31, 13.61) **+11.0** (3.63, 18.85)	**+3.9** (-2.16, 10.29)	**+1.3** (-4.28, 7.31)

Mean Change from Baseline at Week 12 in Secondary Lipid Parameters (Mean and S.D.)

	Study 175 data			
	PIO 30 mg	**PIO 45 mg**	**PIO Pbo**	
HDL (mg/dL)	**-1.0** (5.2)	**+1.5** (8.7)	**+0.2** (4.4)	
FFA (mg/dL)	**-2.3** (6.0)	**-5.1** (7.9)	**1.6** (7.5)	
	Historical Avandia data			
	RSG 8 od	**RSG 4 bd (011, 024)**	**011 Pbo**	**024 Pbo**
HDL (mg/dL)	**+4.3** (7.2)	**+3.1** (6.7) **+5.3** (8.2)	**+1.0** (6.3)	**+2.4** (5.5)
FFA (mg/dL)	**-4.6** (6.5)	**-4.8** (7.0), **-4.8** (6.8)	**0.2** (6.5)	**-0.7** (6.4)

Change from Baseline in Glycemic Parameters

Mean Change from Baseline at Week 12 in Glycemic Parameters (Mean and S.D.)

	Study 175 data			Historical Avandia data			
mean (SD)	PIO 30 mg	PIO 45 mg	PIO Pbo	RSG 8 od	RSG 4 bd (011, 024)	011 Pbo	024 Pbo
HbA1c (%)	-0.3 (0.8)	-0.6 (1.1)	+0.4 (1.0)	0.0 (1.1)	-0.2 (1.2) –0.3 (1.3)	+0.8 (1.1)	+0.7 (1.0)
FPG (mg/dL)	-27.9 (36.3)	-34.5 (44.2)	-8.0 (51.2)	-44.5 (47.3)	-51.5 (49.6), -56.7 (50.8)	14.9 (49.5)	6.5 (45.1)

Safety Summary

The proportion of patients with on-therapy adverse experiences in the PIO 30 mg od and 45 mg od groups (40% and 48%, respectively), was similar to placebo (40%)

On-therapy Adverse Experiences by Preferred Term Reported by ≥ 5% of Patients in Any Treatment Group

	Treatment Group		
AEs by Preferred Term, n (%)	Placebo (N =40)	PIO 30mg od (N = 38)	PIO 45mg od (N = 40)
Patients with at least one AE	**16 (40.0)**	**15 (39.5)**	**19 (47.8)**
Fatigue	2 (5.0)	0	4 (10.0)
Dyspnea	0	0	2(5.0)
Edema dependent	1 (2.5)	0	2 (5.0)
Edema generalized	0	0	2 (5.0)
Headache	0	0	2 (5.0)
URTI	1 (2.5)	2 (5.3)	2 (5.0)
Weight Increase	0	0	2 (5.0)
Arthralgia	0	3 (7.9)	1 (2.5)
Micturition frequency	4 (10.0)	0	0
Thirst	2 (5.0)	0	0

NOTE: Sorted by highest dose of pioglitazone.

No patients treated with PIO reported on-therapy serious adverse events. Withdrawals due to adverse experiences were rare (2.6% of patients treated with either dose of PIO withdrew due to AEs).

The mean increase in weight at week 12 was 0.05 kg in the PIO 30 mg od group, and 1.61 kg in the PIO 45 mg od group. (The placebo group had a mean decrease in weight of 1.35 kg at week 12.)

Hemoglobin and hematocrit decreased from baseline in both PIO groups. At week 12, the mean change from baseline for hemoglobin was -0.8 g/dl for both doses of PIO. The mean change from baseline for hematocrit was –1.4% for the PIO 30 mg od group, and –2.0% for the PIO 45 mg od group.

Conclusion

Study objectives were met and a population similar to the Avandia historical population was enrolled enabling a valid comparison. The study results support a "no-go" decision, therefore we recommend not proceeding with a head-to-head lipid and/or glycemic efficacy trial.

ATTACHMENT D

Videotaped Deposition of Rosemary Johann-Liang, M.D.
Rockville, Maryland
May 26, 2010

ATTACHMENT E

From: Martin I Freed/DEV/PHRD/SB_PLC

To: Rhona A Berry/DEV/PHRD/SB_PLC@SB_PHARM_RD

CC: David 8 Harrison/GB1/GlaxoWellcome@ExchangeUK

BCC: Alexander R Cobitz/DEV/PHRD/SB_PLC

Subject: Re: Publications for 079 and 096

Date: 07/20/2001 13:37:11 (GMT-05:00)

Rhona - Not a chance. These put Avnadia in quite a negative light when folks look at the response of the RSG monotherapy arm. It is a dificult story to tell and we would hope that these do not see the light of day. We have already published the better studies...015 (?can't rmember ..maybe Gomis?) and 094 (Fonseca).

Marty

Rhona A Berry 20-Jul-2001 13:28

Metabolic CDPS UP 4310 tel [redacted] fax [redacted]
To: Martin I Freed
cc: David 8 Harrison
Subject: Publications for 079 and 096

Marty,

Are NAMA planning to publish manuscripts for studies 079 and 096?

Best regards,

Rhona
---------- Forwarded by Rhona A Berry/DEV/PHRD/SB_PLC on 07/20/2001 13:27 ----------
From: David 8 Harrison/GB1/GlaxoWellcome@ExchangeUK on 20-Jul-2001 07:52

To: Rhona A Berry
cc:
Subject: Publications

Hi Rhona,

I've been asked by EMA whether there are any plans to publish manuscripts based on studies 079 and 096. From CPMS it appears that both studies finished in 1998. Any ideas or ideas on who to contact?

Thanks - see you on Monday!

David

David Harrison
Avandia Publication Strategy Manager
GlaxoSmithKline
Greenford Building 6 Room G12
Phone [redacted] ([redacted] int)
Fax [redacted] ([redacted] int)

Attachments: embedded picture.tif

Study No.: 49653/079			
Title: A 26-week Randomized, Double-Blind, Double-Dummy, Multicentered Study to Evaluate the Efficacy, Safety and Tolerability of Rosiglitazone when Administered to Patients with Non-Insulin Dependent Diabetes Mellitus (NIDDM) who are Inadequately Controlled on a Maximal Dose (20 mg/day) of Glyburide.			
Rationale: This study examined the safety and efficacy of rosiglitazone (RSG) when given for the treatment of type 2 diabetes mellitus (T2DM) in combination with the sulfonylurea, glyburide (glibencamide [Gly]), and determined whether the two drugs act synergistically to improve glycemic control.			
Phase: IIIA			
Study Period: 19-Apr-1997 - 29-Mar-1998			
Study Design: Multicenter, randomized, double-blind, double-dummy parallel group, placebo (Pbo)-controlled.			
Centres: 41 in the US.			
Indication: T2DM			
Treatment: During a single-blind run-in, subjects received Gly 10 mg bd + RSG-Pbo bd. During double-blind treatment subjects received either RSG-Pbo bd + Gly 10 mg bd, RSG 2 mg bd# + Gly-Pbo bd, or RSG 2 mg bd# + Gly 10 mg bd # Denotes treatment regimens approved in the US and at least one country in the European Union.			
Objectives: The primary objective was to evaluate the efficacy of RSG in combination with Gly in reducing hyperglycemia when added to the therapy of subjects with T2DM who were inadequately controlled on a maximal dose (20 mg/day) of Gly alone as assessed by changes in glycolysated hemoglobin (HbA1c) after 26 weeks of treatment.			
Primary Outcome / Efficacy Variable: The primary efficacy parameter was the reduction from baseline (Visit 4) in HbA1c after 26 weeks of treatment in the RSG /Gly combination group compared with the glyburide and rosiglitazone monotherapy groups.			
Secondary Outcome / Efficacy Variable(s): The secondary efficacy parameters were change from baseline in fasting plasma glucose (FPG), fructosamine, C-peptide, immunoreactive insulin, leptin and serum lipids; HbA1c and FPG responder rates in each treatment group; the proportion of subjects in each group who achieved the target FPG.			
Statistical Methods: For the assessment of differences between the treatment groups with regard to continuous variables, an analysis of covariance (PROC GLM or MIXED in SAS), with terms for treatment, region (states) and baseline measurement, was employed. The assumptions of the statistical model were tested before it was applied. If there were significant departures from the assumptions, either a model using heterogenous variance or the Wilcoxon Rank Sum Test was used. Pairwise comparisons using Hochberg's multiple comparison procedure (with an overall significance level of 0.05) were performed to compare the two monotherapy groups to the combination group for the evaluation of efficacy. The proportion of patients who achieved fasting glucose <140mg/dL was described in each treatment group. The Intent to Treat (ITT) population consisted of all randomized patients who had at least one valid observation for an efficacy variable while on treatment. All patients who received at least one dose of medication were assessed for clinical safety and tolerability and were denoted the "All Randomized Patients" population.			
Study Population: Males and females, aged 40-80 years with a diagnosis of NIDDM, treated with a maximum dose of Gly for ≥30 days prior to screening, and have a fasting plasma glucose (FPG) of ≥140 mg/dL and ≤300 mg/dL, and fasting C-peptide ≥0.8 ng/mL during the Pbo run-in.			
Number of Subjects:	Gly	RSG 2 mg bd	Gly + RSG 2 mg bd
Planned, N	65	65	65

Randomised, N	106	104	99
Completed, n (%)	71 (67.0)	46 (44.2)	78 (78.8)
Withdrawn, n (%)	35 (33.0)	58 (55.8)	21 (21.2)
Withdrawn due to Adverse Events n (%)	10 (9.4%)	21 (20.2%)	7 (7.1%)
Withdrawn due to Lack of Efficacy n (%)	7 (6.6%)	21 (20.2%)	2 (2.0%)
Withdrawn for other reasons n (%)	18 (17%)	16 (15.4%)	12 (12.1%)
Demographics	Gly	RSG 2 mg bd	Gly + RSG 2 mg bd
N (ITT)	99	99	98
Females: Males	33:66	36:63	30:68
Mean Age in Years (SD)	58.5 (9.12)	59.1 (9.80)	57.7 (9.60)
Race - White, n (%)	68 (68.7)	69 (69.7)	69 (70.4)
Primary Efficacy Results:			
	Gly	RSG 2 mg bd	Gly + RSG 2 mg bd
N	99	99	98
Mean HbA1c (%) Baseline (SD)	9.3 (1.43)	9.1 (1.14)	9.2 (1.34)
Mean HbA1c (%) Week 26 (SD)	10.1 (1.76)	11.0 (1.95)	8.7 (1.60)
Comparison with Baseline: Mean (SD)	0.9 (1.17)	1.9 (1.71)	-0.5 (1.14)
95% CI	(0.6, 1.1)	(1.5, 2.2)	(-0.7, -0.3)
p value	<0.0001	<0.0001	<0.0001
Comparison with Gly + RSG 2 mg bd: adjusted mean	-1.4	-2.4	-
95% CI	(-1.7, -1.1)	(-2.8, -2.0)	-
p value	<0.0001	<0.0001	-
Secondary Efficacy Results:			
	Gly	RSG 2 mg bd	Gly + RSG 2 mg bd
FPG, mg/dL	(n = 99)	(n = 98)	(n = 98)
Baseline mean	219.8	224.5	221.7
Change from baseline, mean (SD)	24.0 (50.96)	52.5 (65.80)	-31.0 (60.53)
95% CI	(13.8, 34.1)	(39.3, 65.7)	(-43.1, -18.8)
Difference from RSG + Gly (adjusted mean)	-55.6	-85.6	
95% CI	(-71.5, -39.6)	(-101.6, -69.6)	
	Gly	RSG 2 mg bd	Gly + RSG 2 mg bd
Fructosamine, mcmol/L	(n = 99)	(n = 97)	(n = 98)
Baseline mean	365.4	374.2	365.1
Change from baseline, mean (SD)	26.1 (59.91)	87.1 (96.88)	-23.7 (54.85)
95% CI	(14.1, 38.0)	(67.5, 106.6)	(-34.7, -12.7)
Difference from RSG + Gly (adjusted mean)	-49.2	-113.2	
95% CI	(-65.2, -33.2)	(-135.8, -90.6)	
C-peptide, nmol/L	(n = 92)	(n = 85)	(n = 92)
Baseline (mean)	1.26	1.19	1.14
Change from baseline, mean (SD)	-0.17 (0.378)	-0.35 (0.478)	-0.08 (0.416)
95% CI	(-0.25, -0.09)	(-0.45, -0.25)	(-0.17, 0.01)
Difference from RSG + Gly (adjusted mean)	0.03	0.24	
95% CI	(-0.07, 0.14)	(0.13, 0.36)	
Immunoreactive insulin, pmol/L	(n = 94)	(n = 90)	(n = 91)

Baseline mean	178.0	162.3	141.0
Change from baseline, mean (SD)	-7.9 (109.98)	-55.4 (118.01)	22.2 (133.03)
95% CI	(-30.5, 14.6)	(-80.1, -30.7)	(-5.5, 49.9)
Difference from RSG + Gly (adjusted mean)	15.1	69.0	
95% CI	(-14.0, 44.2)	(35.4, 102.7)	
Leptin, ng/mL	(n = 84)	(n = 76)	(n = 84)
Baseline mean	16.9	15.1	15.9
Change from baseline, mean (SD)	-2.3 (8.57)	-3.3 (5.14)	1.9 (7.27)
95% CI	(-4.2, -0.5)	(-4.4, -2.1)	(0.3, 3.5)
Difference from RSG + Gly (adjusted mean)	4.0	4.9	
95% CI	(1.8, 6.1)	(2.7, 7.1)	
Total cholesterol, mg/dL	(n = 99)	(n = 98)	(n = 98)
Baseline mean	219.1	209.8	213.2
Change from baseline, mean (SD)	8.4 (38.16)	43.5 (51.53)	33.3 (47.64)
95% CI	(0.7, 16.0)	(33.2, 53.9)	(23.8, 42.9)
Difference from RSG + Gly (adjusted mean)	24.1	-9.5	
95% CI	(9.2, 39.0)	(-22.5, 3.5)	
HDL-cholesterol, mg/dL	(n = 99)	(n = 98)	(n = 98)
Baseline mean	44.7	43.8	43.7
Change from baseline, mean (SD)	1.0 (7.32)	3.2 (8.07)	2.2 (8.22)
95% CI	(-0.4, 2.5)	(1.6, 4.8)	(0.5, 3.8)
Difference from RSG + Gly (adjusted mean)	1.0	-1.2	
95% CI	(-1.2, 3.1)	(-3.7, 1.2)	
LDL-cholesterol, mg/dL	(n = 92)	(n = 79)	(n = 85)
Baseline mean	131.7	124.7	121.0
Change from baseline, mean (SD)	0.3 (23.45)	21.9 (27.26)	13.1 (24.69)
95% CI	(-4.6, 5.1)	(15.8, 28.0)	(7.7, 18.4)
Difference from RSG + Gly (adjusted mean)	10.5	-9.4	
95% CI	(3.2, 17.8)	(-17.0, -1.7)	
Total cholesterol/HDL ratio	(n = 99)	(n = 98)	(n = 98)
Baseline mean	5.14	5.07	5.12
Change from baseline, mean (SD)	0.18 (1.605)	0.63 (1.406)	0.72 (2.007)
95% CI	(-0.14, 0.50)	(0.35, 0.91)	(0.31, 1.12)
Difference from RSG + Gly (adjusted mean)	0.514	0.114	
95% CI	(-0.032, 1.059)	(-0.363, 0.592)	
LDL/HDL ratio	(n = 92)	(n = 79)	(n = 85)
Baseline mean	3.05	2.89	2.81
Change from baseline, mean (SD)	-0.07 (0.646)	0.24 (0.667)	0.15 (0.814)
95% CI	(-0.21, 0.06)	(0.09, 0.39)	(-0.03, 0.32)
Difference from RSG + Gly (adjusted mean)	0.14	-0.11	
95% CI	(-0.09, 0.37)	(-0.32, 0.10)	
VLDL-cholesterol, mg/dL	(n = 99)	(n = 98)	(n = 98)
Baseline mean	21.8	21.9	24.4
Change from baseline, mean (SD)	8.1 (19.00)	14.9 (37.83)	15.5 (26.98)
95% CI	(4.3, 11.9)	(7.4, 22.5)	(10.1, 20.9)
Difference from RSG + Gly (adjusted mean)	7.7	0.6	
95% CI	(-1.7, 17.2)	(-7.7, 8.9)	

Triglycerides, mg/dL	(n = 99)	(n = 98)	(n = 98)
Baseline mean	248.0	264.3	271.2
Change from baseline, mean (SD)	32.3 (182.02)	77.5 (301.93)	59.5 (278.74)
95% CI	(-4.0, 68.6)	(17.0, 138.1)	(3.6, 115.4)
Difference from RSG + Gly (adjusted mean)	31.2	-16.2	
95% CI	(-53.4, 115.9)	(-90.2, 57.8)	
Free fatty acids, mg/dL	(n = 99)	(n = 98)	(n = 98)
Baseline mean	16.8	15.9	16.3
Change from baseline, mean (SD)	1.0 (6.73)	0.6 (9.69)	-1.6 (7.13)
95% CI	(-0.3, 2.4)	(-1.3, 2.6)	(-3.1, -0.2)
Difference from RSG + Gly (adjusted mean)	-3.1	-2.2	
95% CI	(-5.0, -1.3)	(-4.0, -0.3)	
HbA1c response rate, reduction ≥0.7%	(n = 99)	(n = 99)	(n = 98)
Total responder rate, n (%)	10 (10.1)	5 (5.1)	37 (37.8)
Difference from RSG + Gly	27.7	32.7	
95% CI	(17.7, 37.6)	(22.8, 42.6)	
Odds-ratio	5.9	11.6	
95% CI	(2.7, 13.1)	(4.3, 31.5)	
FPG response rate, reduction ≥30%	(n = 99)	(n = 98)	(n = 98)
Total responder rate, n (%)	10 (10.1)	10 (10.2)	49 (50.0)
Difference from RSG + Gly	39.9	39.8	
95% CI	(29.2, 50.6)	(29.1, 50.5)	
Target FPG	(n = 99)	(n = 98)	(n = 98)
Subjects achieving <140 mg/dL at Week 26, n (%)	4 (4.0)	4 (4.1)	21 (21.4)

Safety Results: On therapy Adverse events were events with onset on or after the start date of double-blind study medication but not later than one day after the last date of double-blind study medication.

Most Frequent Adverse Events -On Therapy	Gly	RSG 2 mg bd	Gly + RSG 2 mg bd
N	106	104	99
Subjects with an AE(s), n (%)	85 (80.2)	75 (72.1)	80 (80.8)
Dizziness	1 (0.9%)	5 (4.8%)	12 (12.1%)
Upper respiratory tract infection	9 (8.5%)	5 (4.9%)	9 (9.1%)
Injury	11 (10.4%)	4 (3.8%)	8 (8.1%)
Hypoglycemia	6 (5.7%)	0	8 (8.1%)
Hypercholesterolemia	0	5 (4.8%)	7 (7.1%)
Headache	5 (4.7%)	4 (3.8%)	7 (7.1%)
Sinusitis	6 (5.7%)	3 (2.9%)	7 (7.1%)
Hypertriglyceridemia	2 (1.9%)	4 (3.8%)	6 (6.1%)
Urinary tract infection	7 (6.6%)	2 (1.9%)	6 (6.1%)
Dyspepsia	5 (4.7%)	1 (1.0%)	6 (6.1%)
Hyperglycemia	9 (8.5%)	23 (23.1%)	5 (4.0%)
Infection viral	5 (4.7%)	3 (2.9%)	3 (3.0%)
Pain	5 (4.7%)	5 (4.8%)	2 (2.0%)
Back pain	7 (6.6%)	2 (1.9%)	1 (1.0%)
Diabetes mellitus aggravated	4 (3.8%)	7 (6.7%)	0
Fatigue	3 (2.8%)	7 (6.7%)	0

Serious Adverse Events, n (%) [# considered by the investigator to be related to study medication]:			
	Gly	RSG 2 mg bd	Gly + RSG 2 mg bd
Subjects with nonfatal SAEs, n (%)	6 (5.7%)	6 (5.8%)	4 (4.0%)
Basal cell carcinoma	0	0	1 (1.0%) [0]
Colon carcinoma	0	0	1 (1.0%) [0]
Depression	0	0	1 (1.0%) [0]
Skin ulceration	0	0	1 (1.0%) [0]
Vertigo	0	0	1 (1.0%) [0]
Pneumonia	0	2 (1.9%) [0]	0
Chest pain	1 (0.9%)[0]	1 (1.0%) [0]	0
Dehydration	0	1 (1.0%) [0]	0
Hyperglycemia	0	1 (1.0%) [0]	0
Ketosis	0	1 (1.0%) [0]	0
Skin neoplasm malignant	0	1 (1.0%) [0]	0
Cellulitis	1 (0.9%) [0]	0	0
Claudication intermittent	1 (0.9%) [0]	0	0
Hypocalcemia	1 (0.9%) [0]	0	0
Pancreatitis	1 (0.9%) [1]	0	0
Skin disorder	1 (0.9%) [0]	0	0
Vascular disorder	1 (0.9%) [0]	0	0
Subjects with fatal SAEs, n (%)	1	1	0
Myocardial infarction	1 (0.9%) [0]	1 (1.0%) [0]	0

Conclusions:

In patients with type 2 diabetes mellitus who were previously inadequately controlled on a maximum dose glyburide alone or in combination with other oral antidiabetic agents, low-dose rosiglitazone, 2mg bd, in combination with glyburide produced clinically and statistically significant decreases in HbA1c and FPG compared to treatment with either glyburide or rosiglitazone alone and compared to baseline. Treatment with combination therapy was more effective than treatment with glyburide alone or with low-dose rosiglitazone alone, which were both associated with deterioration of glycemic control.
Combination therapy had effects on lipid parameters that were consistent with those described in the RSG prescribing information.
There was a higher incidence of edema in the combination and rosiglitazone monotherapy groups than in the glyburide group. The incidence of hypoglycemia in the combination therapy group was similar to that in the glyburide monotherapy group.

Date Updated: 13-Sep-2004

Publications

No Publications

Study No: 49653/096
Title: A 26-week Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Evaluate the Efficacy, Safety and Tolerability of Rosiglitazone when Administered Once Daily to Patients with Non-Insulin Dependent Diabetes Mellitus (NIDDM) who are Inadequately Controlled on At Least Half-Maximal Dose (≥10 mg/day) of Glyburide.
Rationale: The purpose of this study was to examine the safety and efficacy of low dose (≤ 4 mg/day) rosiglitazone (RSG) in combination with glyburide (Gly), a sulfonylurea, in the management of type 2 diabetes mellitus (T2DM).
Phase: IIIA
Study Period: 28-April-1997-March-1998.
Study Design: This was a randomized, double-blind, placebo-controlled, parallel group, multicenter study.
Centres: 33 in the US.
Indication: Type 2 diabetes mellitus (T2DM)
Treatment: # Denotes treatment regimens approved in the US and at least one country in the European Union During double-blind treatment, subjects received one tablet of oral RSG 2mg#, oral RSG 4mg#, or placebo (Pbo) daily (od) while they continued to receive Gly at a dose ≥10 mg/day.
Objectives: To evaluate the efficacy of RSG in combination with Gly in improving glycemic control, as assessed by a reduction in gycosylated hemoglobin (HbA1c), when added to the therapy of T2DM subjects who were inadequately controlled on at least half-maximal dose (≥10 mg/day) of Gly.
Primary Outcome/Efficacy Variable: Mean change from Baseline in HbA1c at the end of the double-blind treatment period (treatment Week 26).
Secondary Outcome/Efficacy Variable(s): Secondary outcome variables included: the mean change from Baseline in fasting plasma glucose (FPG), fructosamine, immunoreactive insulin, C-peptide, and serum lipids (i.e., total cholesterol, HDL-cholesterol, LDL-cholesterol, cholesterol/HDL ratio, LDL/HDL ratio, VLDL-cholesterol, free fatty acids and triglycerides) at the end of the double-blind treatment period (treatment Week 26); comparison of two types of responder rates in each treatment group, one with respect to HbA1c and the other with respect to fasting glucose; definition of the safety and tolerability of RSG with respect to changes in physical examination, vital signs, body weight, clinical laboratory tests, AEs, and electrocardiograms; and examination of the proportion of subjects in each group who achieved normalization of FPG (<140mg/dL).
Statistical Methods: An analysis of covariance procedure, which included terms for treatment, center and baseline value, was used to assess the differences between glyburide plus rosiglitazone treatment groups and glyburide plus placebo for continuous variables. Dunnett's multiple comparison was performed to evaluate the efficacy for each glyburide plus rosiglitazone group relative to glyburide plus placebo. The differences between the treatment groups in the analysis of HbA1c and FPG responders were assessed by a categorical analysis procedure. The primary analysis was the intent-to-treat (ITT), with last observation carried forward. Additional analyses were conducted to assess the robustness of the results.
Study Population: Males and females of non-childbearing potential, aged 40-80 years, with a diagnosis of T2DM and FPG of ≥140mg/dL and ≤300mg/dL at screening. Subjects with significant renal or hepatic disease, anemia, leukopenia, thrombocytopenia, severe angina, coronary insufficiency, or heart failure were excluded as were subjects with a fasting C-peptide level ≥0.8ng/mL and Body Mass Index <22 or >38kg/m^2.

Number of Subjects:	Gly + RSG 2mg od	Gly + RSG 4mg od	Gly + Pbo
Planned, N	65	65	65
Randomised, N	116	116	115
Completed, n (%)	95 (81.9)	102 (87.9)	94 (81.7)
Withdrawn, n (%)	21 (18.1)	14 (12.1)	21 (18.3)
Demographics	Gly + RSG 2mg od	Gly + RSG 4mg od	Gly + Pbo
N (ITT)	115	116	115
Females: Males	35:80	40:76	38:77
Mean Age in Years (SD)	59.33 (8.75)	60.23 (9.73)	60.33 (9.07)
White, n (%)	85 (73.9)	93 (80.2)	90 (78.3)
Primary Efficacy Results:			
HbA1c, %	Gly + RSG 2mg od	Gly + RSG 4mg od	Gly + Pbo
N	115	116	115
Baseline, mean (SD)	9.33 (1.541)	9.10 (1.478)	8.94 (1.401)
Week 26, mean (SD)	9.33 (1.732)	8.79 (1.814)	9.55 (1.512)
Comparison with baseline: median of difference	0.00	-0.30	0.55
(95% CI)	(-0.2, 0.3)	(-0.6, -0.1)	(0.4, 0.7)
p-value	0.7962	0.0054	<0.0001
Comparison with Gly + Pbo: median of difference	-0.60	-0.80	-
(95% CI)	(-0.90, -0.30)	(-1.10, -0.60)	-
p-value	0.0001	0.0001	-
Secondary Outcome Variables:			
HbA1c responder analysis			
Reduction in HbA1c at Week 26, n (%)	Gly + RSG 2mg od	Gly + RSG 4mg od	Gly + Pbo
N	115	116	115
Non-responders			
<0.5%	77 (67.0)	64 (55.2)	104 (90.4)
0.5- <0.7%	6 (5.2)	18 (15.5)	4 (3.5)
Responders			
0.7 - <1%	13 (11.3)	7 (6.0)	3 (2.6)
1 - ≤1.5%	10 (8.7)	6 (5.2)	2 (1.7)
1.5 - <2%	3 (2.6)	11 (9.5)	1 (0.9)
≥ 2%	6 (5.2)	10 (8.6)	1 (0.9)
Total Responders, n (%)	32 (27.8)	34 (29.3)	7 (6.1)
Change in Fasting Plasma Glucose and Fructosamine at Week 26 Compared To Baseline and Placebo			
Glycemic Parameter	Gly + RSG 2mg od	Gly + RSG 4mg od	Gly + Pbo

Plasma glucose reference range: 13-49 years, 70-115mg/dL; 50 >years, 70-125 mg/dL			
N	114	116	115
Baseline, mean (SD)	222.2 (53.68)	213.6 (50.39)	209.1 (56.81)
Baseline, median	224.0	203.0	203.0
Week 26 mean (SD)	211.7 (57.86)	188.4 (67.78)	232.1 (56.77)
Week 26, median	209.5	180.0	231.0
Change from baseline, mean (SD)	-10.5 (51.38)	-25.2 (62.23)	23.0 (48.10)
(95% CI)	(-20.0, -1.0)	(-36.7, -13.8)	(14.1, 31.9)
Difference from Gly, adjusted mean	-28.7	-46.8	-
95% CI	(-44.0, -13.4)	(-61.9, -31.6)	-
Fructosamine, µmol/L			
N	115	116	115
Baseline, mean (SD)	371.9 (72.33)	361.3 (68.61)	344.9 (65.84)
Baseline, median	366.0	357.0	337.0
Week 26, mean (SD)	373.4 (79.99)	340.5 (82.12)	371.5 (71.88)
Week 26, median	356.0	321.0	360.0
Change from Baseline, mean (SD)	1.5 (63.71)	-20.8 (62.41)	26.6 (52.81)
(95% CI)	(-10.3, 13.2)	(-32.2, -9.3)	(16.9, 36.4)
Difference from Gly, adjusted mean	-19.3	-44.0	-
(95% CI)	(-36.4, -2.2)	(-60.9, -27.2)	-
Fasting Plasma Glucose (FPG) Responder Analysis (ITT Population)			
Reduction in FPG at Week 26, n(%)	Gly + RSG 2mg od	Gly + RSG 4mg od	Gly + Pbo
N	114	116	115
Non-responders			
<30 mg/dL	72 (63.2)	63 (54.3)	100 (87.0)
Responders			
30 - <40mg/dL	7 (6.1)	13 (11.2)	3 (2.6)
40 -<50 mg/dL	11 (9.6)	11 (9.5)	5 (4.3)
≥ 50 mg/dL	24 (21.1)	29 (25.0)	7 (6.1)
Total responders	42 (36.8)	53 (45.7)	15 (13.0)
Comparison with Gly			
Diff in proportion (%) of responders	23.8	32.6	-
(95% CI)	(10.7, 36.9)	(19.6, 45.7)	-
Odds ratio	3.873	6.772	-
(95% CI) for odds ratio	(1.8, 8.6)	(3.1, 15.0)	-
Subjects who achieved FPG <140 mg/dL at week 26, n (%)	9 (7.9)	26 (22.4)	4 (3.5)
Change in Measures of Endogenous Insulin Production at Week 26 Compared To Baseline and Placebo (ITT)			
Glycemic Parameter	Gly + RSG 2mg od	Gly + RSG 4mg od	Gly + Pbo
Immunoreactive insulin, pmol/L			

N	113	115	115
Baseline, mean (SD)	130.36 (67.26)	141.88 (91.00)	133.64 (70.05)
Baseline, median	114.80	121.97	114.80
Week 26, mean (SD)	148.83 (233.20)	138.32 (86.70)	125.91 (52.04)
Week 26, median	107.63	121.97	114.80
Change from Baseline, mean (SD)	18.48 (218.75)	-3.56 (73.17)	-7.73 (55.18)
(95% CI)	(-22.30, 59.25)	(-17.08, 9.95)	(-17.92, 2.46)
Difference From Gly, adjusted mean	27.12	5.67	-
(95% CI)	(-13.59, 67.83)	(-34.71, 46.06)	-
C-peptide, nmol/L			
N	84	87	82
Baseline, mean (SD)	1.04 (0.43)	1.10 (0.57)	1.10 (0.46)
Baseline ,median	0.99	0.96	0.99
Week 26, mean (SD)	1.00 (0.82)	0.95 (0.45)	0.95 (0.42)
Week 26, median	0.87	0.86	0.87
Change From Baseline, mean (SD)	-0.04 (0.70)	-0.16 (0.36)	-0.15 (0.34)
(95% CI)	(-0.19, 0.11)	(-0.23, 0.08)	(-0.23, -0.08)
Difference From Gly, adjusted mean	0.12	0.00	-
(95% CI)	(-0.05, 0.29)	(-0.16, 0.17)	-
Changes in Secondary Lipid Parameters at Week 26 Compared To Baseline and Placebo (ITT Population)			
Lipid parameter	Gly + RSG 2mg od	Gly + RSG 4mg od	Gly + Pbo
Total cholesterol, mg/dL			
N	115	116	115
Baseline, mean (SD)	210.4 (40.65)	207.0 (42.71)	211.6 (45.18)
Baseline, median	208.0	200.0	205.0
Week 26, mean (SD)	230.5 (48.43)	235.2 (88.15)	217.1 (47.2)
Week 26, median	229.0	228.5	213.0
Change From Baseline, mean (SD)	20.2 (28.75)	28.3 (72.88)	5.4 (32.86)
(95% CI)	(14.8, 25.5)	(14.9, 41.7)	(-0.6, 11.5)
Difference from Gly, adjusted mean	15.0	22.4	-
(95% CI)	(0.5, 29.6)	(7.9, 37.0)	-
HDL-cholesterol, mg/dL			
N	115	116	115
Baseline, mean (SD)	45.1 (12.40)	45.0 (16.59)	45.0 (12.81)
Baseline, median	43.0	41.5	43.0
Week 26, mean (SD)	46.2 (14.02)	45.0 (12.45)	45.2 (13.34)
Week 26, median	43.0	43.0	44.0
Change From Baseline, mean (SD)	1.1 (9.64)	0.0 (13.72)	0.3 (6.60)
(95% CI)	(-0.6, 2.9)	(-2.5, 2.6)	(-0.9, 1.5)
Difference from Gly, adjusted mean	1.1	-0.1	-
(95% CI)	(-1.7, 3.8)	(-2.8, 2.6)	-
Total Cholesterol/HDL-Cholesterol Ratio			
N	115	116	114

Baseline, mean (SD)	4.918 ±1.36	4.881 ±1.35	5.005 ±1.60
Baseline, median	4.688	4.572	4.759
Week 26, mean (SD)	5.341 (1.68)	5.427 (1.83)	5.130 (1.87)
Week 26, median	5.064	4.929	4.772
Change From Baseline, mean (SD)	0.338	0.386	0.088
(95% CI)	(0.174, 0.516)	(0.159, 0.61)	(-0.047, 0.223)
Difference from Gly, adjusted mean	0.241	0.252	-
(95% CI)	(-0.005, 0.485)	(-0.038, 0.548)	
LDL-cholesterol, mg/dL			
N	107	106	105
Baseline, mean (SD)	124.4 (33.72)	119.8 (29.93)	121.8 (35.40)
Baseline, median	125.0	119.5	116.0
Week 26, mean (SD)	135.9 (37.36)	137.8 (39.32)	124.8 (38.95)
Week 26, median	134.0	136.0	123.0
Change From Baseline, mean (SD)	11.5 (23.79)	18.0 (31.93)	3.0 (24.11)
(95% CI)	(7.0, 16.1)	(11.8, 24.1)	(-1.7, 7.6)
Difference from Gly, adjusted mean	9.1	14.8	-
(95% CI)	(0.9, 17.3)	(6.6, 23.0)	-
LDL/HDL-Cholesterol Ratio			
N	107	106	105
Baseline, mean (SD)	2.845 (0.90)	2.796 (0.85)	2.860(1.11)
Baseline, median	2.807	2.684	2.765
Week 26, mean (SD)	3.044 (0.96)	3.120 (1.16)	2.874 (1.12)
Week 26, median	2.845	3.011	2.706
Change From Baseline, mean (SD)	0.199 (0.67)	0.324 (0.91)	0.014 (0.63)
(95% CI)	(0.070, 0.328)	(0.149, 0.500)	(-0.109, 0.136)
Difference from Gly, adjusted mean	0.170	0.295	-
(95% CI)	(-0.058, 0.398)	(0.068, 0.522)	-
VLDL-cholesterol, mg/dL			
N	115	116	115
Baseline, mean (SD)	19.1 (12.28)	22.0 (20.33)	24.6 (18.68)
Baseline, median	15.9	17.9	19.9
Week 26, mean (SD)	30.0 (21.25)	33.7 (27.25)	30.2 (23.38)
Week 26, median	23.9	26.9	22.9
Change From Baseline, mean (SD)	10.9 (15.68)	11.7 (21.65)	5.6 (17.41)
(95% CI)	(8.0, 13.8)	(7.7, 15.7)	(2.4, 8.8)
Difference from Gly, adjusted mean	5.0	5.9	-
(95% CI)	(-0.6, 10.6)	(0.4, 11.5)	-
Free Fatty Acids, mg/dL			
N	115	116	115
Baseline, mean (SD)	16.136 (6.0915)	15.846 (6.4443)	16.443 (7.0545)
Week 26, mean (SD)	15.279 (5.9948)	15.895 (6.5827)	18.858 (7.3760)

Change from Baseline, mean (SD)	-0.857 (6.3739)	0.049 (6.7372)	2.415 (6.9575)
(95% CI)	(-2.035, 0.320)	(-1.190, 1.288)	(1.129, 3.700)
Difference From Glyburide, adjusted mean	-3.463	-2.643	-
(95% CI)	(-5.147, -1.780)	(-4.317, -0.968)	-
Triglycerides, mg/dL			
N	115	116	115
Baseline, mean (SD)	213.7 (147.22)	248.8 (294.11)	266.6 (298.83)
Week 26, mean (SD)	262.2 (186.39)	308.0 (688.13)	279.3 (281.17)
Change from Baseline, mean (SD)	48.5 (111.74)	59.3 (540.78)	12.6 (193.87)
(95% CI)	(27.9, 69.1)	(-40.2, 158.7)	(-23.2, 48.4)
Difference From Glyburide, adjusted mean	48.0	47.9	-
(95% CI)	(-52.7, 148.8)	(-51.8, 147.6)	-

Safety Results:			
	Gly + RSG 2mg od	Gly + RSG 4mg od	Gly + Pbo
Most Frequent Adverse Events - On-Therapy			
Subjects with any AE(s), n (%)	88 (75.9)	88 (75.9)	79 (68.7)
Upper respiratory tract infection	8 (6.9)	14 (12.1)	15 (13.0)
Arthralgia	3 (2.6)	10 (8.6)	2.(1.7)
Injury	11 (9.5)	9 (7.8)	8 (7.0)
Sinusitis	8 (6.9)	9 (7.8)	7 (6.1)
Edema	3 (2.6)	8 (6.9)	1 (0.9)
Pain	8 (6.9)	8 (6.9)	2 (1.7)
Urinary tract infection	4 (4.3)	6 (5.2)	4 (3.5)
Infection viral	5 (4.3)	6 (5.2)	2 (1.7)
Fatigue	4 (3.4)	6 (5.2)	2 (1.7)
Chest pain	1 (0.9)	6 (5.2)	1 (0.9)
Hypertension aggravated	0	6 (5.2)	2 (1.7)
Dizziness	2 (1.7)	5 (4.3)	4 (3.5)
Hyperglyceridemia	4 (3.4)	4 (3.4)	2 (1.7)
Diarrhea	1 (0.9)	4 (3.4)	4 (3.5)
Anxiety	0	4 (3.4)	3 (2.6)
Back pain	7 (6.0)	3 (2.6)	4 (3.5)
Hypoglycemia	7 (6.0)	3 (2.6)	2 (1.7)
Headache	4 (3.4)	3 (2.6)	8 (7.0)
Hyperglycemia	2 (1.7)	3 (2.6)	5 (4.3)
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]			
Subjects with non-fatal SAEs, n (%)	5 (4.3)	8 (6.9)	2 (1.7)
Angina pectoris aggravated	1 (0.9) [0]	2 (1.7) [0]	0
Cardiac failure	0	2 (1.7) [0]	1 (0.9) [0]
Alcohol intolerance	0	1 (0.9) [0]	0
Arthritis	0	1 (0.9) [0]	0

Basal cell carcinoma	0	1 (0.9) [0]	0
Depression	0	1 (0.9) [0]	0
Tendon disorder	0	1 (0.9) [0]	0
Thrombosis coronary	0	1 (0.9) [0]	0
Adenocarcinoma	1 (0.9) [0]	0	0
Angina pectoris	1 (0.9) [0]	0	0
Cerebral hemorrhage	1 (0.9) [0]	0	0
Injury	1 (0.9) [0]	0	0
Necrosis ischemic	1 (0.9) [0]	0	0
Chest pain	0	0	1 (0.9) [0]
Fibrillation atrial	0	0	1 (0.9) [0]
Osteomyelitis	0	0	1 (0.9) [0]
Pneumonia	0	0	1 (0.9) [0]
Subjects with fatal SAEs, n (%)	0	0	0

Conclusions:

Treatment with rosiglitazone at total daily doses of 2mg and 4mg once daily in combination with glyburide produced statistically and clinically significant reductions in HbA1c and FPG compared to placebo and to baseline. Also, there were greater proportions of HbA1c and FPG responders in the glyburide plus rosiglitazone treatment groups than in the glyburide plus placebo treatment group.
Combination therapy had effects on lipid parameters that were consistent with those described in the RSG prescribing information. Relative to patients treated with glyburide plus placebo there was an increased incidence of edema in the glyburide plus rosiglitazone groups. Relative to the glyburide plus placebo group and relative to baseline, the decrease in hemoglobin and hematocrit was statistically significant at week 26 in both glyburide plus rosiglitazone treatment groups.

Date Updated: 23-Aug-2004

Publications

No Publications

Net Sales Upside

Cause of Upside	Probability H/M/L	Net Sales Impact ($mm) 2002	2003	2004	Total
Consensus conference supports early TZD use	M/H/H	$100	$175	$200	$475
Successful reframing of lipid story to HDL	L/M/M	$50	$100	$200	$350
LFT monitoring requirement relaxed to quarterly	M/M/L	$100	$150	$150	$400
LFT monitoring requirement relaxed to semi-annual	L/L/L	$200	$200	$100	$500
IMT/IVUS studies document CV benefits of Avandia	(n/a)/M/M	-	$100	$200	$300
Metformin/Avandia IR/IR approved and launched	(n/a)/H/H	-	$150	$225	$375
Avandia achieves HDL indication	L/L/L	$150	$150	$150	$450
Avandia /Amaryl combination launched	(n/a)/(n/a)/H	-	-	$25	$25
Actos CV labeling changes	M/H/H	$50	$100	$150	$300
Actos loses insulin indication	L/L/L	$75	$100	$150	$325
Total		$725	$1,225	$1,550	$3,500

Net Sales Downside

Cause of Downside	* Probability H/M/L	Net Sales Impact ($mm) 2002	2003	2004	Total
Actos Solidifies Lipid Profile	M/M/M	$200	$250	$300	$750
No reduction of LFT Monitoring	M/L/L	100	150	200	$450
Glucovance exceeds new pt. Starts	L/M/M	75	100	150	$325
Lantus use as 3rd line agent	L/L/L	50	75	75	$200
Deep Managed Care Discounting	H/H/H	75	100	100	$275
CV Safety issue intensifies	L/M/M	100	200	300	$600
Insulin indication not attained	L/L/L	150	250	300	$700
Metformin/Glipizide combo launched by BMS	(n/a)/H/H	-	75	75	$150
Actos achieves HDL Indication	(n/a)/M/M	-	200	300	$500
Actos/glipizide XL launched	(n/a)/(n/a)/H	-	-	50	$50
Takeda/Lilly increase SOV (due to generic Prozac)	H/H/H	50	75	100	$225
Total		$800	$1,475	$1,950	$4,225

* Probability represent chronological likelihood from 2002 through 2004

Note: These assumptions should relate to those specified in the *Lifecycle Vision* (Template 2) and the *3 Year Objectives & Key Assumptions*

ATTACHMENT F

Confidential

SmithKline Beecham

Avandia and Myocardial Infarction

Laraine M Caponi, RN, BSN*

*Clinical Safety & Pharmacovigilance

Signatory: _____
Jeffrey D Freid, MD

Issue Date: October 2001

Table of Contents

List of Appendices

List of Tables

Supporting Safety Data

1 Issue

Evaluation and review of reports of myocardial infarction during rosiglitazone therapy was completed to determine if there is a safety signal regarding this event. This document presents a summary of these reports.

2 Introduction

Rosiglitazone is a member of the thiazolidinedione class of antidiabetic agents. It improves glycemic control by improving insulin sensitivity at key sites of insulin resistance, namely adipose tissue, skeletal muscle and liver. Rosiglitazone improves metabolic control by lowering blood glucose, circulating insulin and free fatty acids.

Rosiglitazone is indicated for the treatment of type 2 diabetes mellitus (non-insulin dependent diabetes mellitus [NIDDM]). It is effective as monotherapy in patients inadequately controlled by diet and exercise and in combination with sulfonylureas and metformin to improve glycemic control.

Rosiglitazone was first approved in Mexico in April, 1999 and launched in the US in June 1999.

Cardiovascular events are very common in type 2 diabetes, as the disease results in premature and accelerated atherosclerosis. Diabetes mellitus, both non-insulin dependent and insulin-dependent, carries a substantially increased risk of atherosclerosis affecting the arteries that supply the heart, brain, legs and other organs. Most deaths in NIDDM are due to cardiovascular disease, and especially coronary artery disease. Overall, the age-adjusted, cause-specific mortality for coronary heart disease is two to four times higher in diabetic subjects than in comparable non-diabetic control groups. Diabetes itself may confer 75-90% of the excess risk of coronary heart disease in diabetic subjects, and enhances the deleterious effects of the other major cardiovascular risk factors, namely smoking,

hypertension and hypercholesterolemia. (Source: Textbook of Diabetes, 2nd Edition. 1997. Chapter 57)

3 Methodology

The sources of information reviewed for inclusion in this paper are as follows:

- Information from database of completed clinical trials (Safety Update 2000 issued October 31, 2000)
- GlaxoSmithKline (GSK) Clinical Safety Database (AEGIS)
- Published literature

The GSK Safety Database (AEGIS) was searched for all reports of events coded to the WHO Code adverse event *myocardial infarction.* An additional verbatim event, *heart attack,* was also searched. The output included reports received from clinical and spontaneous sources received at GSK as of September 19, 2001.

The above data was reviewed and is presented in the following sections.

4 Results

4.1 Information from Database of Completed Clinical Trials

Clinical Data - Introduction

Clinical trial data reviewed is derived from the latest Safety Update 2000 which was issued on October 31, 2000. The clinical cutoff date for this update was July 07, 2000.

The data integrated in the Safety Update 2000 are from all completed double blind and all ongoing open-label phase II, IIIA and IIIB studies conducted in North America and Europe. The Safety Update 2000 database includes all studies in the Integrated Summary of Safety (ISS) for NDA 21-071 (submitted February 25, 2000), the 120-day Safety Update (submitted March 31, 1999), the rosiglitazone plus sulfonylurea sNDA (submitted June 02, 1999), and the Second Safety Update

(submitted February 25, 2000). In addition, the Safety Update database includes two new completed double-blind studies, and one new, ongoing open label extension (OLE) study.

- Study 044 - A 26-week, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of rosiglitazone when administered twice daily to patients with non-insulin dependent diabetes mellitus (NIDDM) who are inadequately controlled on a maintenance dose (2.5g/day) of metformin

- Study 127 – A 26-week, double-blind, placebo-controlled study to evaluate the safety, efficacy, and tolerability of rosiglitazone 8 mg/day (4 mg bd) versus placebo in combination with glyburide in patients with type 2 diabetes mellitus who are inadequately controlled on maximum dose glyburide.

- Study 133 – An open-label extension study to assess the long-term safety, tolerability and efficacy of rosiglitazone when administered twice daily in combination with glyburide (Open label extension for patients from study 127).

Clinical Data - Patient Exposure

In total, more than 5300 patients have been exposed to rosiglitazone (as monotherapy, or in combination with sulfonylurea, metformin or insulin), with more than 2900 patients treated for one year or more, over 1800 patients treated for two years or more, and approximately 645 patients for 3 years or more. As of July 2000, exposure to rosiglitazone had increased to greater than 7000 patient years.

Clinical Data - Specific Cardiac Groupings

In order to examine fully specific types of cardiac events, selected preferred terms were collapsed into the category of cardiac ischemia as detailed below.

Rates per 100 patient years with the associated 95% confidence intervals were generated for cardiac ischemic events and cardiac failure events. The confidence intervals were based on exact probabilities from the Poisson distribution. The rates per 100 patient years were calculated for the successive population/datasets available from the time of submission of the sNDA through this current update. These datasets include a mixture of accumulating data from ongoing patients and data from newly exposed patients as described in the following bullets:

- the double blind comparator group from the ISS
- the double blind population/dataset from the ISS (DB),
- the double-blind and open label population/dataset from the ISS (DB/OL). This dataset includes not only accumulated data on patients who continued in the open-label extension on the **same dose or a higher dose of rosiglitazone** but also data on patients who previously received insulin alone and were newly exposed to rosiglitazone in the open-label extension.
- the double blind and open label population/dataset from the safety update 2000 (SU 2000). **This dataset includes only accumulated data from ongoing patients**.

On therapy reporting rates for myocardial infarction during the clinical trials in the Safety Update 2000 are as follows:

Table 1 On-Therapy Reports of Cardiovascular Events* - Rosiglitazone Monotherapy

	RSG Monotherapy Update 2000 N = 3172 4095.7 Pt Yrs			Placebo Updates N = 601 169.5 Pt Yrs
Preferred Term*	**n**	**%**	**Rate/100 Pt Yrs**	**Rate/100 Pt Yrs**
Myocardial infarction	42	1.3	1.0	0.6

* In any RSG group, sorted by Safety Update 2000 population.
Data Source: Safety Update 2000 Table 4.2.1.1a.

Table 2 On-Therapy Reports of Cardiovascular Events* - Rosiglitazone and Metformin Combination

	RSG + MET Update 2000 N = 651 896.1 Pt Yrs			MET Updates N = 276 118.9 Pt Yrs
Preferred Term*	**n**	**%**	**Rate/100 Pt Yrs**	**Rate/100 Pt Yrs**

Myocardial infarction	10	1.5	1.1	0.8

* In any RSG group, sorted by Safety Update 2000 population.
Data Source: Safety Update 2000 Tables 4.2.3.1.a.

Table 3 On-Therapy Reports of Cardiovascular Events* - Rosiglitazone and Sulfonylurea Combination

	RSG + SU			SU
	Update 2000 N = 1076 1364.6 Pt Yrs			Updates N = 903 679.6 Pt Yrs
Preferred Term*	**n**	**%**	**Rate/100 Pt Yrs**	**Rate/100 Pt Yrs**
Myocardial infarction	19	1.8	1.4	1.0

* In any RSG group, sorted by Safety Update 2000 population.
Data Source: Safety Update 2000 Table 4.2.2.1.a.

Table 4 On-Therapy Reports of Cardiovascular Events - Rosiglitazone in Combination with Insulin**

	RSG + INS						INS
	sNDA N = 541 Pt Yrs = 325.5			Update 2000 N = 549 Pt Yrs = 681.2			Update N = 203 Pt Yrs = 91.4
Preferred Term*	**n**	**%**	**Rate/100 pt yrs**	**n**	**%**	**Rate/100 pt yrs**	**Rate/100 pt yrs**
Myocardial infarction	6	1.1	1.8	10	1.8	1.5	0

** A patient could have more than one cardiovascular event.
Data Source: RSG + INS sNDA ISS Tables 4.2.4.1.a and 4.2.4.1.b; Safety Update 2000 Tables 4.2.4.1.a and 4.2.4.1.b

Summary

The profile of cardiovascular events was typical of a type 2 diabetic population. The rate per 100 patient years was similar across the treatment groups; for most events, rates were decreased or unchanged, with continuing exposure to study medication, indicating no accumulating increase in events.

4.2 Information from the GSK Clinical Safety Database (AEGIS)

This report contains the following information from the GSK safety database (AEGIS):

- All serious and non-serious reports from spontaneous sources.
- All reports which contain one or more serious events (attributable to the drug by either the investigator or GSK, or not specified) reported during clinical studies, PMS studies or named-patient ("compassionate") use. These cases may also contain individual non-serious adverse events. Those clinical reports in which the patient was taking the comparator agent or did not receive active drug were excluded from the following analysis.
- All serious reports from regulatory authorities.

Adverse events reviewed in this report are those received by GSK from all geographic locations worldwide. In the line listings of adverse experiences, AEs are recorded in terms of a "diagnosis" where known. If no diagnosis is recorded then the AEs are recorded in terms of "signs and symptoms". To avoid duplication, signs and symptoms associated with a "diagnosis" are not provided in the line listings or included in the total counts.

4.2.1 All Reports of Myocardial Infarction

A review of the AEGIS database as of September 19, 2001 identified 174 reports of events coded to the event of myocardial infarction in patients receiving rosiglitazone therapy. All 174 reports were classified as serious and were from clinical, postmarketing, unsolicited and regulatory sources. Reports of myocardial infarction as reported by source are as follows in Table 1:

Table 5 Reports of Myocardial Infarction from the GSK Clinical Safety Database AEGIS

Source	Number of Reports
Clinical	114
Spontaneous *	37
Postmarketing	23
Total	174

* Includes reports from unsolicited and regulatory sources.

Of the 174 reports of myocardial infarction, 126 were reported to have occurred in males, 45 in females and three did not report the gender of the patient. The age range of the patients was between 32 to 86 years. In those reports where the age was provided (n=164), 29% (n=47) fell between the age of 40 to 60 years. Seventy-one percent (n=117) fell between the age of 61 to 90 years. The dosage of rosiglitazone therapy ranged between 2 and 16 mg daily at the time of the event.

One hundred and one (58%) of the 174 reports described an outcome of recovered, 17 (10%) noted that the patient had not yet recovered at the time of the report, and 11 (6%) reported an outcome of unknown. There were 45 (26%) reports with a fatal outcome which are further discussed in section 4.2.2 Report of Myocardial Infarction with a Fatal Outcome.

One hundred forty-two (82%) of the 174 reports also reported a significant concurrent or past medical condition affecting the cardiovascular system. These conditions included the following: previous myocardial infarction, hypertension, ventricular dysfunction, alcohol abuse, cardiomegaly, coronary artery disease, congestive heart failure, hypercholesterolemia, coronary artery bypass surgery, hyperlipidemia, hypertriglyceridemia, ischemic heart disease, atrial fibrillation,

supraventricular tachycardia, obesity, recurrent pneumonia, chronic obstructive pulmonary disease, tobacco use, previous angioplasty, cerebrovascular accident, rheumatic fever, asthma, cerebral thrombosis, pulmonary embolism, congenital heart disease (NOS), blocked carotid artery, ventricular tachycardia, chronic anemia, tuberculosis, pulmonary disease (NOS), asbestosis, valvular insufficiency (tricuspid, mitral, aortic), transient ischemia attacks, placement of a pacemaker for atrioventricular heart block and fluid retention.

4.2.2 Reports of Myocardial Infarction with a Fatal Outcome

Of the 174 reports of myocardial infarction, 45 (26%) reported an outcome of death, three of which underwent autopsy.

Thirty-seven (82%) of these 45 reports described the cause of death to be due to a myocardial infarction occurring either alone or with a concurrent cardiac or medical condition. Three (7%) of the 45 reports with a fatal outcome (**1997002849-1, 1998021297-1, 2001018767-1**) reported the patient's death was possibly, probably or suspected to be due to a myocardial infarction.

Five (11%) of the 45 reports described the cause of death to be attributed to other conditions. Two reports (**2000037114-1, 2001006895-1**) indicated the cause of death to be congestive heart failure secondary to a recent myocardial infarction. The cause of death as confirmed by an autopsy in report **1998009128-1** was coronary heart disease and a possible myocardial infarction. The cause of death was reported as unknown in report **2001012407-1** as no autopsy was performed, however it was reported that the patient had experienced congestive heart failure following a myocardial infarction. Report **1999027997-1** noted the cause of death to be small cell carcinoma. This patient had a myocardial infarction two years earlier but recovered from this event.

Of the 45 reports with a fatal outcome, 41 (92%) listed a significant past or concurrent medical condition, two (4%) were poorly documented and two (4%) denied a previous cardiac history.

The significant past or concurrent medical conditions associated with cardiovascular function noted in the 41 reports with a fatal outcome include the following: previous myocardial infarction, coronary artery bypass graft surgery, hypertension, coronary artery disease, pulmonary embolism, left ventricular dysfunction,

hypertriglyceridemia, chronic angina, hypercholesterolemia, hyperlipidemia, peripheral vascular disease, atrial fibrillation, atrial flutter, cardiomegaly, unspecified arrhythmia, cerebral thrombosis, chronic bronchitis, ischemic heart disease, nicotine abuse, blocked carotid arteries, ventricular tachycardia, stroke, obesity, occlusive arterial disease, tuberculosis, aortic valve insufficiency, mitral valve insufficiency and tricuspid valve insufficiency.

The reporters' assessments of causality to rosiglitazone therapy in the 45 reports of myocardial infarction with a fatal outcome are as follows: 22 (49%) unrelated, 18 (40%) unlikely related/probably unrelated, 4 (9%) not specified and 1 (2%) was unassessable.

4.3 Information from the Published Literature

An extensive review of the literature was undertaken. No reports of myocardial infarction in association with rosiglitazone therapy have been reported in the published literature.

4.4 Prescribing Information

4.4.1 Master Data Sheet

The Master Data Sheet (MDS) does not include any statements regarding myocardial infarction in the Undesirable Effects or Contraindication sections.

4.4.2 US Prescribing Information

The US Prescribing Information (USPI) does not include myocardial infarction as an expected event, however, it contains the following warning statement in the contraindication section regarding cardiovascular effects:

Cardiac Failure and Other Cardiac Effects: *Avandia*, like other thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be observed for signs and symptoms of heart failure. *Avandia* should be discontinued if any deterioration in cardiac status occurs.

Patients with New York Heart Association (NYHA) Class 3 and 4 cardiac status were not studied during the clinical trials. *Avandia* is not recommended in patients with NYHA Class 3 and 4 cardiac status.

In two 26-week U.S. trials involving 611 patients with type 2 diabetes, *Avandia* plus insulin therapy was compared with insulin therapy alone. These trials included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions, including peripheral neuropathy (34%), retinopathy (19%), ischemic heart disease (14%), vascular disease (9%), and congestive heart failure (2.5%). In these clinical studies an increased incidence of cardiac failure and other cardiovascular adverse events were seen in patients on *Avandia* and insulin combination therapy compared to insulin and placebo. **The use of Avandia (rosiglitazone maleate) in combination therapy with insulin is not indicated (see ADVERSE REACTIONS).**

5 Patient Exposure

The total marketed exposure to rosiglitazone since launch to May 2001 is estimated to be 978,822 patient years. In addition, a total of approximately 20,800 patients have received rosiglitazone in clinical trials or postmarketing studies since the start of the clinical trials program. Total marketed exposure to rosiglitazone is in excess of 2.3 million patients.

The number of patient days was derived from the number of tablets sold and an average dose in mg per day for each formulation strength. The dose in mg per day was calculated using the average daily dose in terms of standard units (tablets) for each strength and multiplying this by the strength in milligrams. The data source used to obtain this information was IMS Health.

6 Discussion

Clinical trial data reviewed in the Safety Update 2000 issued on October 31, 2000 revealed the incidence of myocardial infarction was similar across all treatment groups. (Source: ISS 8.H.12.4)

A review of the AEGIS database as of September 19, 2001 identified 174 reports coded to the event of myocardial infarction in patients receiving rosiglitazone therapy. All (100%) of these 174 reports were classified as serious. There were 45 reports with a fatal outcome.

Of the 174 reports of myocardial infarction, 126 (72%) were reported to have occurred in males. In those reports where the age was provided (n=164), seventy-one percent (n=117) fell between the age of 61 to 90 years. The male sex and advanced age are two nonreversible risk factors for arteriosclerosis which can precipitate ischemic myocardial necrosis. (Source: The Merck Manual. Seventeenth Edition, 1999. Chapter 201)

Major reversible or modifiable risk factors include abnormal serum lipid levels, hypertension, cigarette smoking, diabetes mellitus, obesity and physical inactivity. (Source: The Merck Manual, Seventeenth Edition. 1999. Chapter 201) The majority (82%) of the 174 reports retrieved from AEGIS were found to have had a past or concurrent medical condition which may have contributed to the event including smoking, obesity, hypertension, hyperlipidemia and hypercholesterolemia, in addition to having diabetes mellitus, which is itself a major risk factor for the development of acute myocardial infarction.

Of the 174 reports of myocardial infarction, 45 (26%) reported an outcome of death. Three of these 45 reports noted that autopsies were performed which confirmed the cause of death as being due to acute myocardial infarction. Thirty-seven (82%) of these 45 reports described the cause of death to be due to a myocardial infarction occurring either alone or with a concurrent cardiac or medical condition. Three (7%) of the 45 reports with a fatal outcome reported the patient's death was possibly, probably or suspected to be due to a myocardial infarction. Five (11%) of the 45 reports described the cause of death to be attributed to other conditions.

Considering the total market exposure to rosiglitazone which is in excess of 2.3 million patients since launch to May 2001, the receipt of reports of myocardial infarction at GSK would be considered very rare (<1/10,000 or <0.001%) per the CIOMS Working Committee Guidelines.

The current MDS and USPI do not contain information specifically regarding myocardial infarction as an expected event.

An extensive review of the literature was undertaken. No reports of myocardial infarction in association with rosiglitazone therapy were in the published literature.

In summary, cardiovascular events are very common in diabetic patients as the disease results in premature and accelerated atherosclerosis. Evaluation of these 174 reports from AEGIS provides limited information and does not demonstrate a serious signal of myocardial infarction during rosiglitazone therapy. No evidence was found from the literature or the data received at GSK that indicates that patients receiving rosiglitazone are at risk for myocardial infarction.

An independent cardiologist associated with a major US university currently reviews all reports of cardiovascular events, including myocardial infarctions, occurring in patients prescribed Avandia. In a recent review of reports, he noted that no other cardiovascular events have been clearly related to Avandia, although the relatively high frequency of cardiovascular events in patients with diabetes would make it difficult to detect a relationship from the spontaneous reporting system, most particularly for events like acute MI or other acute coronary syndrome. As of September 19, 2001, no clear signal has been generated which would like the occurrence of acute MI to the prescription of Avandia.

7 List of References

Sorrier LA, et al. Rosiglitazone maleate. Antidiabetic, insulin sensitize. Drugs of the Future (Spain). 1998. Vol. 23/9. Pages 977-985.

The Merck Manual, 17th Edition, 1999. Chapter 201.

Textbook of Diabetes, 2nd Edition. 1997. Chapter 57.

Appendix 1 Line Listing Of All Reports of Myocardial Infarction

Appendix 2 Line Listing of Reports of Myocardial Infarction with a Fatal Outcome

ATTACHMENT G

SB's Treatment for Type 2 Diabetes

Avandia rosiglitazone maleate

AVANDIA

September 13, 2000

To: All Avandia Consultants

From: Nejla Abbed
Avandia Product Management

CC: Avandia Product Team
D. Brand
D. Pernock
D. Tasse'
IHD Area Directors
Managed Care Segment Directors
RBAs
RSOAs
RVPs

Subject: ***Avandia*** **CASPPER**

Highlights:

- In your field mail envelope, you will find a brochure to introduce you to the CASPPER program being sponsored by SmithKline Beecham and Avandia Product Management.

Avandia Product Management is launching CASPPER, Case Study Publications for Peer Review. This innovative program is a tool for you to bring value to your customers and gives you the opportunity to work closely on issues important to them. CASPPER provides you the ability to offer assistance in the preparation and publication of case studies and other short communications relevant to the clinical use of *Avandia*. SmithKline encourages publications to broaden the knowledge of Avandia and provide credible answers to competitive issues.

Your participation can help you establish or enhance your relationships with your physicians or other healthcare professionals. CASPPER supports your sales efforts by providing a valuable service to your customers and by increasing the literature for *Avandia*.

ATTACHMENT H

From: Julia M Eastgate
Date Sent: 8/13/2001 2:44:57 PM
To: Murray W Stewart
CC: Arvind Agrawal-1
Subject: Haffner - CV review article

Murray - see attached manuscript that has been ghost written for Haffner. I think it is VERY poorly written....what are your thoughts? Also, I notice that the US refer to the '5 modifiable CV risk factors' but do not mention obesity. We have obesity down as one of our 5 modifiable risk factors and have combined the lipid factors under the umbrella 'dyslipidemia'. Am I correct in believing that the US have 'cherry picked' here because they do not want to address obesity?
Thanks
Julia

Dear All,

Please find attached the Haffner manuscript, 'Modifying cardiovascular risk in the Type 2 diabetes patient'. The manuscript is currently in a rough format that has not gone to the author yet. However, Michael DiMatteo would appreciate your comments at this time. The manuscript is to be targeted to the American Journal of Cardiology.

Please review the manuscript by close of business on Wednesday 15th August and return any comments to Michael with a copy to me.

Thanks, once more, for your review.

Regards

David

David Harrison
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Modifying Cardiovascular Risk in the Type 2 Diabetes Patient

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ABSTRACT

Patients with type 2 diabetes (NIDDM) are at increased risk for cardiovascular disease (CVD), including myocardial infarction (MI) and stroke. For this reason, such patients should be monitored with respect to 5 main risk factors that contribute to coronary heart disease (CHD) and other cardiovascular (CV) events, even if they do not present with clinical signs. **There are more than 5 risk factors/main risk factors, but these are the 5 "modifiable" risk factors.** These 5 risk factors are: elevated low-density lipoprotein (LDL), elevated glycosylated hemoglobin, reduced high-density lipoprotein (HDL), hypertension, and smoking. Insulin resistance, evident in the majority of patients with type 2 diabetes, also complicates the clinical prognosis of such patients. Strategies to prevent the development of coronary heart disease (CHD) in the patient with type 2 diabetes should emphasize a multifactorial approach that includes: a) improved control of glycemia that incorporates dietary modifications; b) aggressive treatment of risk factors for CHD, including dyslipidemia, hypertension, and smoking; and c) the use of ~~insulin sensitizers, such as the~~ **(suggests that there are others besides TZDs)** thiazolidinediones (TZDs), that improve insulin sensitivity and may limit CV risk factors.

Key words: Type 2 diabetes, cholesterol, coronary heart disease, hypertension, insulin resistance, ACE inhibitors, thiazolidinediones

INTRODUCTION

The prevalence of type 2 diabetes mellitus is very high and increasing worldwide. Sixteen Million Americans are now estimated to have this disorder that shortens life expectancy by up to 15 years [National, 1998]. The World Health Organization (WHO) predicts that between 1995 and 2005, the global pervasiveness **[quantify this with a specific number]** of diabetes in adults will increase from 4.0% to 5.4% **(look at actual numbers in the US per year)** [King, 1998]. In comparison with the incidence of other multifactorial diseases—such as heart disease, stroke, and many forms of cancer, which have declined or remained stable—the age-adjusted mortality rate for diabetes in the United States has increased 30% since 1980 [National, 1998].

Type 2 diabetes is associated with a high risk **(use a number as a reference point)** for microvascular (retinopathy and neuropathy) and macrovascular (~~amputation~~ **(CVD and CHD)** complications as well as with a high risk for premature death [Kohner, 1998; DCCT, 1993; Klein, 1995; Nelson, 1988; Lee, 1993]. Data from the Framingham study suggest that hyperglycemia is an independent risk factor for coronary heart disease (CHD) [Garcia, 1974; Kannel, 1974; Gordon, 1977; Kannel, 1979; Abbott, 1988; Brand, 1989; Kannel, 1990]. Frequently, patients with diabetes have additional risk factors that contribute to CHD, such as hypertension and low high-density lipoprotein cholesterol (HDL-C) [ADA, 2001]. In fact, once a patient with type 2 diabetes develops clinically evident CHD, cardiac complications occur with increased frequency **(what is the**

number? Use a figure.), as do morbidity and mortality as compared to non-diabetic patients with CHD [Wingard & Barrett-Connor, 1995].

The majority of **patients with type 2 diabetes [make global change from diabetics]** have multiple CV risk factors. The Third Report of the National Cholesterol Educational Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), or NCEP ATP III, raises patients with type 2 diabetes without diagnosed CHD to the level of CHD risk equivalent, the highest category of risk [National, 2001]. Diabetes is considered a CHD threat because it can directly contribute to new CHD **(of what event, Dx?)** within 10 years **(years before T2DM, IR is present)** due in part to its association with other risk factors.

IR is associated with CV risk. At the time of T2DM diagnosis, most already have CV risk factors.

Speak to the clustering of the phenomena. Metabolic syndrome as secondary target in NCEP. For the above reasons, a patient with type 2 diabetes is ostensibly a patient with multiple CV risk factors even before the manifestation of clinical signs [Stamler, 1993]. Type 2 diabetes is associated with a 2- to 4-fold increased risk of CHD, compared to non-diabetic persons [Haffner, 1997]. Patients with type 2 diabetes without previous myocardial infarction (MI) have as high a risk for MI as non-diabetic patients with previous MI. This group

should be treated as aggressively for CV risk factors as their MI-experienced peers [Haffner, 1998]. Predictably, patients with type 2 diabetes with previous MI are at more risk for mortality and have a correspondingly poor prognosis **[numbers/stats to support]** following MI [Malmberg, 1999; Abbud, 1995; Orlander, 1994].

Patients with type 2 diabetes must therefore be monitored **[strengthen --- treat, assumed to have...]** with regard to the traditional CV risk factors. However, emerging risk factors such as LDL-C particle size, PAI-1, and C-reactive protein **[strengthen the following]** must also be considered so that patients with the highest risk can be identified and treated. In addition, medications exist, specifically the thiazolidinediones, that not only help to control blood glucose, but **[and]** also have a complementary effect when coupled with other treatments for the modification of CV risk. **May want to quickly elaborate on the effects that complementary existing therapies (decreased HTN/particle distribution [LDL/HDL]/microalbuminuria/surrogate hs-CRP, PAI-1, etc.). Make the complementary point emphasized.**

Rationale for Modifying Key Risk Factors for CHD in Type 2 Diabetes

In the treatment and prevention of CVD in type 2 diabetes, a multifactorial approach is necessary to minimize excess risk [Laakso, 1999; Haffner, 1997]. Hence, the first step is to identify the risks. According to the United Kingdom Prospective Diabetes Study (UKPDS 23) survey of over 3,000 middle-aged patients (median age 52 years) with recently diagnosed type 2 diabetes mellitus and without evidence of disease related to atheroma, there are 5 risk factors that contribute most significantly to CVD in type 2 diabetes patients. Those risk factors are: ~~high~~ elevated low-density lipoprotein cholesterol (LDL-C), low HDL-C, high glycosylated hemoglobin (HbA_{1c}), high systolic blood pressure (SBP), and smoking [Turner, 1998] **[Table 1]**.

LDL-C

How many diabetics have small, dense LDL (Haffner or Brunzell)? Reduce talk of LDL; more on LDL morphology and the danger in T2DM.

It is imperative that LDL-C levels be monitored in patients with type 2 diabetes. Epidemiologic studies have highlighted a direct relationship between LDL-C concentrations and the risk of CHD [Castelli, 1984; Stamler, 1986]. However, the ability to effectively identify individuals at high risk for CHD, based solely on LDL-C levels, has been challenged by reports suggesting that as many as 50% of patients with LDL-C concentrations in the normal range also have coronary artery disease (CAD) [Genast, 1992; Ginsburg, 1991]. The 5-year prospective data from the Québec Cardiovascular Study (QCS) has shown that LDL-C particle

diameter may be a more effective predictor of ischemic heart disease (IHD) than the actual LDL-C plasma concentration [Lamarche, 1997]. In **the** QCS, patients who had the smaller, denser LDL-C particles had a [redacted] **(double check this number)** increase (95% CI, 1.5 to 8.8) in the risk of IHD. These compacted particles (LDL-C_{3-5} subfractions) are believed to be more atherogenic than larger LDL-C particles (LDL-C_{1-2} subfractions) because of their greater susceptibility to oxidation [de Graaf, 1991] and their reduced affinity for LDL-C receptors in the liver [Nigon, 1991]. Therefore, for the insulin resistant patient with type 2 diabetes, (**add low HDL and HTN** overweight, physically inactive, with elevated triglycerides), smaller LDL-C particle size may identify heightened CV risk at an early stage, even if LDL-C levels are normal **(make this point earlier - on page 6)**. Research has shown that insulin resistant patients have smaller LDL-C particles than insulin sensitive individuals ($P<.05$) **(Characterize patient here.)**[Haffner, 1999]. While at the present time, LDL-C particle size is not part of a typical cholesterol screen and larger population-based studies need to be completed to further define the impact of small LDL-C particle size, patients who have type 2 diabetes or who are pre-diabetic should be considered as having this condition. This emerging risk factor underscores the multi-faceted nature of developing CHD and may, in time, eclipse the importance of serum LDL-C concentration as a predictive factor for CVD in the person with diabetes.

Conclusion: Assume that all patients with T2DM have small, dense LDL. But do not need to measure.

HDL-C

A large body of evidence in patients with type 2 diabetes indicates that a low concentration of HDL-C is a major risk factor for CHD [Miller and Miller, 1975; Gordon, 1989; Stampfer, 1991; Goldbourt, 1997]. In fact, some research has shown that reduced HDL-C levels are more ~~characteristic~~ **meaning what? predictive?** of CHD than elevated LDL-C [Genest, 1992; Lamarche and Despres et al, 1996]. Reduced HDL-C levels ~~without elevated~~ with acceptable normal LDL-C levels characterize as many as 30% of CHD patients, equivalent to several million **(How many?)** Americans [Rubins, 1995; Genest, 1991]. The NCEP ATP III has raised the categorical low for HDL-C from <35 mg/dL to <40 mg/dL because the higher level is a better measure of depressed HDL-C [National, 2001]. The causes of low HDL-C include insulin resistance, cigarette smoking, very high intake of carbohydrates (>60% of calories), and drugs like beta-blockers, anabolic steroids, and progestational **(Is this ovulatory products, or do you mean progestins? Check.)** agents [National, 2001].

While the concentration of LDL-C in patients with type 2 diabetes is not significantly different from non-diabetic individuals, the most common pattern of dyslipidemia in patients with type 2 diabetes is decreased HDL-C [UKPDS 27, 1997]. ~~Baseline data from the UKPDS showed that decreased HDL, in addition to elevated LDL, predicted CHD [Turner, 1998].~~ **Previous sentence refutes what was just said.** The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) demonstrated the need for therapeutic intervention for

HDL-C levels ≤36 mg/dL in men and ≤40 mg/dL in women, including those study participants with type 2 diabetes, to reduce the risk for the first acute major coronary event [Downs, 1998]. The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) included 2,531 men with CHD, about 25% of whom had type 2 diabetes. VA-HIT demonstrated that a 6% increase in HDL-C was associated with a 22% reduction in death and both fatal and non-fatal MI, a therapeutic benefit that ~~eclipses~~ is equivalent to/mirrors the benefit associated with LDL-C reduction [Robins, 2001]. Consequently, for patients with CHD whose primary lipid abnormality is low HDL-C, a condition that can occur in diabetes, correcting this aspect of dyslipidemia can potentially ~~prevent~~ reduce the mortality associated with CHD. **Qualify this last statement to make it realistic; too broad of a statement as is.**

HbA_{1c}

Glycosylated hemoglobin (HbA_{1c}), an indicator of average blood glucose concentration over 3 months, has been recommended as a screening tool for diabetes [McCance, 1994; Haffner, 1998; Marshall and Barth, 2000]. This parameter has also been shown to be an indicator of mortality in men with type 2 diabetes. In the Norfolk Cohort of European Prospective Investigation into Cancer and Nutrition (EPIC-Norfolk), a 1% increase in HbA_{1c} was associated with a 28% (P = .002) increased risk of death independent of age, blood pressure, serum cholesterol, body mass index, and cigarette smoking [Khaw, 2001]. **Although this was data prospective/intervention trial, it is suggestive of**

strong involvement of glucose and glucose control in CVD. Not a treatment study—it was an observation that suggested . . . need a qualifier. Kuusisto and colleagues showed a significant increase in the risk of CHD death and all CHD events in type 2 diabetes subjects with HbA_{1c} levels higher than 7.0% compared to subjects with type 2 diabetes with lower values **53% of patients in U.S. not at goal (check ADA)** [Kuusisto, 1994]. Long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study showed that HbA_{1c} was the most powerful predictor of poor in-hospital outcome in patients with type 2 diabetes who have suffered MI, ~~although the power of this indicator dissipated in patients who were on intensive insulin therapy~~ [Malmberg, 1999]. UKPDS 35 demonstrated that any reduction in HbA_{1c} was likely to moderate the risk of CV complications associated with diabetes, such as MI and stroke, with the lowest risk being in those patients with HbA_{1c} <6.0% [Stratton, 2000]. ~~In addition, LDL-C particle size is associated with HbA_{1c} levels regardless of the patient's plasma lipid levels, suggesting that small LDL-C particles would be present in subjects with type 2 diabetes regardless of plasma lipid concentrations [Okumura, 1998].~~ **Does this fit here? Restate or change; repetitive of LDL section. HbA1c—correlate with decreased insulin sensitivity = increased HbA1c.**

Blood pressure

Over 11 million Americans have both diabetes and hypertension [USRDS, 2000]—co-morbid conditions that strongly predispose individuals to both renal

and CV damage. For the patient with type 2 diabetes, hypertension is a major risk factor for the sequelae of diabetes, contributing to as much as 75% of all such complications, including nephropathy and end-stage renal disease [Bild and Teutsch, 1987]. As the UKPDS study demonstrated, diabetes patients whose blood pressure is tightly controlled (144/82 mmHg) can reduce their risk of CV events more effectively than those whose blood pressure is less tightly controlled (154/87 mmHg; *P*<.0001) [UKPDS 38, 1998].

The Hypertension Optimal Treatment (HOT) trial showed that patients with diabetes demonstrated a 51% reduction in major cardiovascular events when diastolic pressures were ≤80 mmHg compared to those patients with type 2 diabetes with diastolic pressures of ≤90 mmHg (*P* for trend=.005) [Hansson, 1998]. However, [redacted] **Place in table.**

Smoking

Smoking is related to the premature development of both macrovascular and microvascular complications of diabetes and may have a role in the development of type 2 diabetes [Haire-Joshu, 1999]. Cigarette smoking is also associated with

increased hepatic lipase activity, insulin resistance, dyslipidemia, and early atherosclerosis in type 2 diabetes [Kong, 2001]. Compared to non-smokers, men who smoke cigarettes have a higher level of fibrinogen, a risk factor closely related to plaque progression and thrombosis, an effect that appears more pronounced in males with diabetes or hypertension [Tuut & Hense, 2001]. While smoking has decreased over the last decade as a result of extensive public health efforts, over 47 million American adults—24% of the all people 18 years of age and older—continue to smoke [Centers for Disease Control, 2000]. These figures mirror the prevalence of tobacco use among individuals with diabetes [Haire-Joshu, 1999]. **Add sentence to summarize top 5 modifiable risk factors, then triglycerides may be considered.**

Triglycerides [deleted whither]

Support controversy surrounding this in text. [redacted] **Short section—focus therapy on 5 modifiable risk factors. Include that Framingham showed that HDL more than triglycerides are a predictor of CHD risk. Austin [who? Use study name or clearer description]** looked at 17 prospective population-based studies published between 1965 and 1994, involving more than 57,000 patients. Austin concluded that increased triglyceride level is a risk factor for CVD, independent of HDL-C level [Austin, 1994]. [redacted]

Triglycerides alert you to risk. In UKPDS 23, triglyceride concentration was a

risk factor for CAD after adjustment for age and sex, but it was not an independent risk factor when other variables were included in the model [Turner, 1998]. This finding was in agreement with other studies, possibly because of the greater biological variability of triglyceride than of HDL-C measurements [Grundy, 1998; Robins, 2001]. In the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT), triglyceride levels did not predict CVD risk, either at baseline or during the trial [Robins, 2001]. The Framingham study showed that HDL-C is a more consistent and reliable predictor of increased CHD than are triglyceride concentrations [Grundy, 1998].

As control of plasma triglyceride and HDL-C is interlaced through lipoprotein lipase and hepatic lipase activities, it may not be possible to separate the contributions of triglyceride and HDL-C to CAD. Results from the Helsinki Heart Study [Manninen, 1992] and the Prospective Cardiovascular Münster (PROCAM) Study [Assman, 1992] show that the impact of elevated triglyceride levels is increased only **(need to convey it is only a part of the whole picture)** when combined with elevated LDL-C and reduced HDL-C. This cluster of risk factors may represent the metabolic condition most demonstrative of CVD risk [Assman, 1994].

~~Cardiovascular Risk Factors Associated with Insulin Resistance~~ **Impact of IR on Cardiovascular Risk**

Persons with type 2 diabetes are typically characterized by peripheral insulin resistance, ß-cell failure, and elevated hepatic glucose production [DeFronzo, 1988]. A study by DeFronzo and colleagues demonstrated that the majority of patients with type 2 diabetes are insulin resistant, and that both hepatic and peripheral resistance to the action of insulin contributes to diabetic hyperglycemia [DeFronzo, 1982].

Insulin resistance has been flagged as a potential etiologic factor for CVD. In 1988, Reaven argued **?[postulated/hypothesized]** that insulin resistance may well support a cluster of disorders—including hypertension, dyslipidemia, CHD, visceral adiposity, increased PAI-1, and small, dense LDLs—many of which contribute to a condition called the metabolic syndrome [Reaven, 1988]. The metabolic syndrome, which identifies subjects with increased CV morbidity and mortality, is defined as the presence of at least 2 of the following risk factors: obesity, hypertension, dyslipidemia, or microalbuminuria [Isomaa, 2001]. Diagnosing patients as having ? or using ? to describe a way to determine which patients are at increased risk for CVD **Clarify intent of sentence.**

Components of the metabolic syndrome can be directly linked to diabetes. For example, Groop and colleagues examined the relationship between type 2

diabetes and hypertension and determined that elevated blood pressure was associated with a 27% reduction in the rate of total glucose metabolism, compared to normotensive patients with type 2 diabetes (both P <.001) [Groop, 1993]. Associations between insulin resistance and dyslipidemia, notably decreased HDL-C, as well as other emerging risk factors **(insert risk factors here in brackets)**, have also been noted in patients with type 2 diabetes [Groop, 1993; Chaiken, 1991; Widen, 1992]. Lamarche and colleagues assessed the ability to predict IHD using a cluster of emerging metabolic risk factors that included elevated fasting insulin [Lamarche, 1998]. They noted that elevated fasting insulin was prevalent in over 30% of the patients, yielding a 2-fold increase in the odds ratio of developing IHD in men and with increased fasting insulin compared with less atherogenic [Lamarche, 1998] **Speaks to increased insulin but compares to euglycemic. Elevated fasting insulin = increased odds ratio for IHD. Can't compare to patients who are not hyperglycemic.** In the Insulin Resistance Atherosclerosis Study (IRAS), the relationship between insulin resistance and CV risk factors was examined in patients with type 2 diabetes [Haffner, 1997]. The results of IRAS showed that insulin-resistant subjects with type 2 diabetes have a more atherogenic CV risk factor profile than insulin-sensitive subjects with type 2 diabetes. The insulin-resistant subjects with type 2 diabetes **(insert data)** had increased levels of very low density lipoprotein (VLDL) cholesterol, fibrinogen, PAI-1, and fasting glucose, lower HDL-C level and more compact **[change to small, dense]** LDL size, even when serum LDL-C measurements were within the normal range. **Define what**

IMT is and significance as indicative of vessel wall damage and plaque development Carotid intimal-medial thickness (IMT) was greater in insulin-resistant than in insulin-sensitive subjects, but this difference was not statistically significant. Howard and associates concurred with these findings by showing that the increased insulin resistance was associated with increased atherosclerosis in Hispanics and in non-Hispanic whites, but not in [redacted] **[African Americans? Check study]** [Howard, 1996]. A substantial relationship was noted between [redacted] **(explain why substantial—quantify)**, a relationship that persisted even when risk factors for the insulin resistance [redacted] **Confused. Explain here.**

~~More work needs to be done to explore the pathways that lead from insulin resistance to atherosclerosis, as well as to determine the effects insulin resistance has, if any, in the [redacted]~~ **African American** ~~population, a group that suffers from a [redacted]~~ **better word?** ~~of diabetes mellitus [Cowie & Eberhardt, 1995]. Specific measurements of insulin resistance are needed in these endeavors, as well as detailed measurements of specific insulin, proinsulin, and insulin-like molecules [Haffner, 1996].~~

Rework Conclusion: Majority of patients are insulin resistant. Insulin resistance means more at risk—characterized by HTN, low HDL, small, dense LDL. Global change—Metabolic syndrome.

Emerging Cardiovascular Risk Factors/Predictors

Give credibility here. "Recent evidence has shown . . ." While most patients will be evaluated with regard to the major risk factors, several other parameters [redacted] **? are coming to the forefront of risk evaluation** watching, primarily due to their increased prevalence in the presence of diabetes.

C-reactive protein

Beef up this section. C-reactive protein is an acute-phase reactant that is a marker for underlying vascular inflammation, and elevated plasma concentrations have been reported in acute ischemia [Berk, 1990], myocardial infarction [de Beer, 1982; Pietila, 1993; Liuzzo, 1994; Thompson, 1995], and fatal coronary disease in smokers [Kuller, 1996]. In a study that included patients with type 2 diabetes who had experienced major CV events, Ridker and associates found that C-reactive protein predicts the risk of a first MI and ischemic stroke 6 years or more before the event independently of other risk factors [Ridker, 2001 **may cite newer literature like 2001 Ridker paper on CRP**]. **IR link to CRP**

PAI-1 spell out

Fibrinolysis counteracts the occlusion of blood vessels by blood clots and is involved in the lysis of thrombi upon vessel repair. Its basic substrate is plasminogen that coverts to plasmin; this conversion is regulated via [redacted] **TPA activator/inhibitor**, such as plasminogen activator inhibitor type-1 (PAI-1) **Conversion is inhibited by PAI-1/TPA is the activator**. Hypercoagulability and

impaired fibrinolysis are ~~possible candidates~~ additional factors/disorders linking insulin resistance with atherosclerotic disease. Lau and colleagues concluded that ~~hypofibrinolysis~~ impaired/decreased fibrinolytic activity leading to a risk of thrombosis might be caused by elevated PAI-1 activity [Lau, 1993]. **Any IR data linking to PAI-1?** A study by Festa and associates linked elevated PAI-1 levels to increases in insulin, while decreased insulin sensitivity was independently associated with higher PAI-1 and fibrinogen levels [Festa, 1999]. ~~Impaired fibrinolysis and elevated PAI-1 are associated with atherothrombosis via insulin resistance and obesity~~ **reversed? IR and obesity are associated with atherothrombosis and fibrinolysis and PPAR-gamma.** [Juhan-Vague, 2000]. Thus, circulating PAI-1 levels that are elevated in patients with CHD, particularly those who are insulin resistant, may be predictive of the development of atherothrombosis. **Conclusion: Majority of T2DM patients will have elevated PAI-1. Reinforce link to T2 and Metabolic Syndrome.**

MMP spell out

Thrombus formation usually occurs because of a physical disruption of atherosclerotic plaque [Libby, 2000]. The majority of coronary thromboses are caused by a rupture of the plaque's protective fibrous cap, culminating in contact between blood and the highly thrombogenic material located in the lesion's lipid core. Interstitial collagen accounts for most of the tensile strength of the plaque's fibrous cap. Matrix metalloproteinases (MMPs), particularly MMP-9, are involved in the degradation of extracellular collagen; thus, dysregulated MMP activity,

probably due to an imbalance of endogenous inhibitors, could be involved in the mechanisms of [redacted] **or do you mean its rupture?**. [redacted] **PPAR-gamma agonists act as anti-inflammatory agents. PPAR-gamma is the receptor that is expressed in adipose. PPAR-gamma is the receptor; MMP is the agonist.** Some drug classes such as TZDs **(check what ref says)**can modulate PPAR activity so that the MMPs are better controlled [Deeb, 1998].

Sections appear to be written in a vacuum and do not relate back to previous sections. They should appear as a continuum and it should be clear that they are related. More connection -- pulled through by the metabolic syndrome.

Dandona – ADA abstract

Vascular dysfunction

Insulin resistance is associated with an increased risk of CVD that is probably related to abnormalities of vascular wall function. An analysis of the IRAS revealed that ~~established~~ more progressed patients with type 2 diabetes with CAD had the greatest amount of [redacted] **vessel** and [redacted] **measure**, while non-diabetic patients with no CAD had the least **What?** [Wagenknecht, 1998]. This increase in carotid IMT suggests that the rate of CHD in patients with diabetes

but ~~without~~ absent of detectible vascular disease at baseline may be due to accelerated atherosclerosis. **Dandona—ADA 2001 abstract**

A study by Cabellero and associates showed that vascular reactivity in both the micro- and macrocirculation was reduced not only in study subjects with diabetes, but also in those with impaired glucose tolerance ~~as well as in the~~ and in normoglycemic individuals with **high ??** potential genetic risk for diabetes [Caballero, 1999]. This suggests that these vascular abnormalities develop at an early stage and ~~probably~~ are linked not only to hyperglycemia but also to other factors independent of hyperglycemia (i.e., dyslipidemia and hypertension) that occur before the onset of a impairments in glucose metabolism ~~impairment~~.

Microalbuminuria

In a study by Kim and colleagues, microalbuminuria was associated with insulin resistance independent of type 2 diabetes [Kim, 2001]. In subjects with metabolic syndrome, the risk for CHD and stroke increased 3-fold (P <.001) **compared to who?**. Cardiovascular mortality was also markedly increased in subjects with the metabolic syndrome as compared to those without the syndrome (12.0% versus 2.2%, P<.001). Of the individual components of the metabolic syndrome, microalbuminuria conferred the strongest risk of CV death (RR 2.80; P=.002) and can be another marker of CV risk **? it IS another marker, not can be** in the patient with type 2 diabetes.

Summary and transition, please. Moving from traditional to emerging risk factors.

Use the word "modify" in place of "control"

Management of Risk Factors in Patients with Type 2 Diabetes

Physicians should address the aforementioned risk factors in patients with type 2 diabetes, even if the patient does not present with clinical signs. **Refer to figure used—use as a transition to the 5 emerging risk factors.** Strategies to prevent the development of CHD in diabetic, as well as possibly pre-diabetic, patients should emphasize a multifactorial approach that includes: [redacted] **Link all back to Table 2.** Guidelines for controlling risk factors associated with CHD in the patient with type 2 diabetes can provide a therapeutic foundation for this vulnerable patient population **[Table 2]**.

Control of dyslipidemia

Make the point that conventional statin therapy is not doing enough. No clinical trial has been done regarding the effects of lipid-lowering agents specifically on subsequent CHD exclusively in subjects with type 2 diabetes. **Complimentary message.** However, a number of major studies have included small numbers of subjects with type 2 diabetes. In the Scandinavian Simvastatin Survival Study (4S) trial, the HMG-CoA reductase inhibitor, simvastatin, significantly reduced CHD incidence and total mortality in subjects with type 2

diabetes with high LDL-C and with previous clinical CHD [Scandinavian, 1994]. In the Cholesterol and Recurrent Events (CARE) study, pravastatin significantly reduced CHD incidence in subjects with type 2 diabetes with average LDL-C levels and with previous clinical CHD [Sacks, 1996]. **Table 2 shows management—link to Table 3 TZD.** In the Helsinki Heart Study, the fibric acid derivative, gemfibrozil, was associated with CHD reduction, albeit not statistically significant, in subjects with type 2 diabetes without prior CHD [Koshkinen, 1992]. In the VA-HIT, gemfibrozil was associated with a 24% decrease in CV events in subjects with type 2 diabetes with prior CVD by increasing HDL-C in patients with low LDL-C and with low HDL-C [Robins, 2001].

The NCEP ATP III states that, since diabetes is a CHD risk equivalent, the LDL-C goal of therapy should be <100 mg/dL and that the HMG-CoA reductase inhibitors (statins) are the drug class that can most significantly lower LDL-C levels [National, 2001]. However, there is evidence that serum LDL-C does not necessarily correlate with CV risk, and that LDL-C particle size may be the better determinant.

A large body of evidence exists to demonstrate that LDL-C particle size and insulin resistance can be effectively altered by diet and exercise [William, 1990; Despres and Lamarche, 1993]. ~~In addition, therapy with fibric acid derivative [Yuan, 1994; Guerin, 1996] can result in a modest increase in LDL-C particle size.~~ **Mention TZDs.**

Control of blood pressure

The Multiple Risk Factor Intervention Trial (MRFIT) identified highly significant associations between blood pressure and the rate of renal dysfunction, thereby establishing a causal role for hypertension in the development of renal disease [Klag, 1996]. The current therapeutic paradigm states that the use of angiotensin converting enzyme inhibitors (ACEIs) in patients with type 2 diabetes not only controls hypertension, but can also prevent the progression of microalbuminuria to overt proteinuria, reduce proteinuria in patients with overt diabetic nephropathy, slow glomerular filtration rate (GFR) deterioration, and delay the progression to end stage renal disease [Lewis, 1993]. A meta-analysis of 41 studies showed that while all the available antihypertensive drug classes lowered blood pressure to a greater extent than placebo, the ACEIs lowered urinary protein excretion more than the other classes [Gansevoort, 1995]. This renoprotective effect of ACEIs appears to be independent of their antihypertensive action. The Heart Outcomes Prevention Evaluation (HOPE) study showed that ramipril, an ACEI, significantly reduced the mortality rate, as well as the rate of MI and stroke, in a broad range of high-risk patients. [redacted] **Check accuracy of statement.** Thus, by using the ACEIs, patients with type 2 diabetes ~~profit~~ benefit from the drug's renal benefits in tandem with a lowered CV risk.

Control of smoking

A significant rise in blood pressure accompanies the smoking of each cigarette [Greenberg, 1987]. The CV benefits of discontinuing tobacco use can be seen within a year in all age groups [US Dept of Health and Human Services, 1990]. Accordingly, patients must be encouraged to stop smoking. Nicotine replacement systems accompanied by behavior modification counseling can help in this regard. A nurse-managed smoking cessation intervention study in patients with type 2 diabetes showed that patients who were educated and counseled about the negative effects of cigarette smoking were more than 7 times more likely to quit smoking than their non-counseled peers [Canga, 2000].

Control of glucose

Reductions in blood glucose or HbA_{1c} concentrations through tight blood glucose control in people with diabetes lessen the risk of microvascular disease [DCCT, 1993; DCCT, 1995; DCCT, 1996; UKPDS 33, 1998], although the relationship with macrovascular outcomes—CHD and stroke—is less clear [Eschwege, 1985; Pyorala, 1985; Ohlson, 1986;]. ~~UKPDS 51 showed that metformin, a biguanide, extends life expectancy when used as first-line pharmacotherapy in overweight (>120% ideal body weight) patients with type 2 diabetes [Clarke, 2001].~~ **Use figures. Current agents do not sustain control. Within 3 years, 50% of patients need combination. Emphasize that it must be the right combination—metformin + sulfonylurea increases by 90% MI/CVD.** UKPDS 33 demonstrated that intensive glucose control by either sulfonylureas or insulin

therapy substantially decreases the risk of microvascular complications, but not macrovascular disease, in patients with type 2 diabetes [UKPDS 33, 1998].

The role of thiazolidinediones in modifying cardiovascular risk

The thiazolidinediones—a class of type 2 diabetes treatment agents that includes rosiglitazone, pioglitazone, and formerly available troglitazone—reduce insulin resistance [Raskin, 2001; Patel, 1999; Phillips, 2001; Satiel & Olefsky, 1996; Polonsky, 1996; Tokuyama, 1995]. These agents reduce ~~glucose~~ insulin resistance at the level of the muscle adipose and, in turn, increase glucose uptake and decrease insulin resistance and glucose production in the liver [Maggs, 1998]. **Insulin resistance is the heart of the metabolic syndrome.** [redacted] **Changes bad effects by improving size, improving . . .** In addition, they can positively impact emerging CV risk factors **[Table 3].** Through their effects in both addressing insulin resistance and CV risk-factor modification, TZDs may serve to complement other agents, such as statins and ACEIs, customarily used to treat CV risk factors commonly associated with type 2 diabetes. **Add 108 data table—to rosiglitazone.**

[DREAM study = ACEI] While a rare type of hepatic failure led to the withdrawal of troglitazone from clinical use [Shibuya, 1998; Neuschwander-Teri, 1998; Gidin,

1998], trials with rosiglitazone and pioglitazone have not been associated with an excessive rate of liver function abnormalities [Parulkar, 2001]. **FDA abstract at endocrine society meeting—Michael to send abstract.**

Insulin resistance may be the connection between CVD and type 2 diabetes. If this is proven true via continued research, then this unique drug class with its profound risk-modifying effects on lipid metabolism, can directly reduce the risk for CVD. Thus, as with the dual action of the ACEIs to control blood pressure and protect the kidneys, the TZDs have a novel mechanism of action that may not only impact hyperglycemia, but may also impact CVD, for which the patient with type 2 diabetes is at enhanced risk.

SUMMARY

The patient with type 2 diabetes is now, by definition, threatened with a greatly increased likelihood of developing CVD. Therefore, attention must be given to controlling CV risk factors early in the patient's life before the sequelae of diabetes and CHD occur. **[i.e., can't just control LDL levels and think you're managing the patient!]** Lifestyle modifications, such as increased exercise and a low-fat, high-fiber diet, have both physical and psychological advantages, and they place the patient in a more proactive position for the long road ahead in managing diabetes. Careful selection of pharmacologic agents that have been proven to manage some of the problems for which the patient may be at highest risk can reduce the morbidity and mortality associated with type 2 diabetes. The

TZDs, with their insulin-sensitizing and cardiovascular-defending capacities, may well complement the effects of other agents, such as statins and ACEIs, used in managing the risk-factor profile of the patient with type 2 diabetes.

Restate links—triglycerides are not as significant. Need to consider other agents, right combination . . .

TABLES

Goals—guidelines for traditional and emerging risk factors. CV risk factors and break into traditional and emerging in table.

Table 1: Key risk factors for coronary artery disease (CAD) in type 2 diabetes patients according to UKPDS 23 [Turner, 1998]

Risk factor	Impact
LDL-C	A 57% increase in CAD risk per increment of 1 mmol/L **[give mg/dL conversion in parens]** in LDL-C is equal to a 36% risk reduction for a decrement of 1 mmol/L **[give mg/dL conversion in parens]** [Turner, 1998].
HDL-C	The 15% decrease in CAD risk associated with a 0.1 mmol/L **[give mg/dL conversion in parens]** increment in HDL-C is compatible with the 8–12% reduction in risk reported from other prospective studies [Gordon, 1989].
HbA_{1c}	**State normal.** An increase in the risk of CAD has been noted with HbA_{1c} >6.2%, the upper range of normal values, in accord with other studies that infer hyperglycemia increases the risk for macrovascular disease [Jarrett, 1976; Folsom, 1997].
Blood pressure	A 10 mmHg reduction in SBP is associated with 15% decreased risk for CHD [MacMahon, 1990]. **HOPE data? What mm Hg reduction associated here?**
Smoking	The estimated CAD hazard ratio for CAD is 41% higher among

Check on specific to T2DM	current smokers than non-smokers (95% CI, 6–88%); the hazard ratio among smokers for fatal or non-fatal MI is 58% (95% CI, 11%-25%) [Turner, 1998].

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; HbA_{1c} = glycosylated hemoglobin; SBP = systolic blood pressure; 95% CI = 95% confidence interval

Add emerging in this table.

Table 2: Guidelines for cardiac risk factors goals in diabetes

Risk factor	Guideline source	Specifications
LDL-C	NCEP (National Cholesterol Education Program) Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) [National, 2001] **Mention particle size—check. Based on existing literature, best to reduce small, dense LDL, TZD, fibric acid--?**	- The LDL-C goal of therapy for most persons with diabetes is <100 mg/dL. - When LDL-C is ≥130 mg/dL, most persons with diabetes will require LDL-lowering drugs simultaneously with lifestyle modifications to achieve LDL-C goal. - When LDL-C levels are 100-129 mg/dL at baseline or on treatment, therapeutic options include: increasing intensity of LDL-lowering therapy, adding a drug to modify atherogenic dyslipidemia (fibrate or nicotinic acid), or intensifying control of other risk factors including hyperglycemia.

HDL-C	NCEP (National Cholesterol Education Program) Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) [National, 2001]	- Low HDL cholesterol is now defined as <40 mg/dL instead of the previously recommended <35 mg/dL cut-off because the higher value is a better measure of a depressed HDL. - HDL-C ≥60 mg/dl **verify** is considered an abnormally high level.
HbA_{1c}	American Diabetes Association [ADA, 2001] **Check ADA and combination therapy.**	- Normal HbA_{1c} <6%. - Goal HbA_{1c} <7%. - If HbA_{1c} >8%, action must be taken to control glycemia. - Approach diabetes treatment as multifactorial: nutrition control, weight loss, exercise, and use of oral glucose-lowering agents with careful attention given to CV risk factors (hypertension, smoking, dyslipidemia, and family history).
Hypertension	JNC VI (The Sixth Report of	- In patients with diabetes,

	the Joint National Committee On Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) [Joint, 1997]	antihypertensive drug therapy should be initiated along with lifestyle modifications, especially weight loss, to reduce blood pressure to <130/85 mmHg. - ACEIs, alpha-blockers, calcium antagonists, and low-dose diuretics are preferred because of fewer adverse effects on glucose homeostasis, lipid profiles, and renal function. - Beta-blockers also show reduction in CHD risk but may not always be appropriate in poorly managed patients with type 2 diabetes.
Smoking	US Department of Health and Human Services, 1990	- Patients must be encouraged to stop smoking. - The cardiovascular benefits **what are the benefits?** of discontinuing tobacco use can be seen within a year in all age groups.

Complementary. Impact—use rosiglitazone references. Please use Avandia references throughout this table. Reorganize table.

Table 3: Effects of thiazolidinediones on cardiovascular risk factors

Risk factor	**Cardiovascular effect**
Coagulation and fibrinolysis	Decrease in PAI-1 and fibrinogen levels [Ehrmann, 1997; Nordt, 2000]
Direct effects on the vasculature **Separate HDL and triglycerides.** **What is the resultant effect on risk--% decrease in parameters**	- Decrease in IMT [Minamikawa, 1998] - Decreases in blood pressure [Ogihara, 1995; Sung, 1999; Ghazzi, 1997] - Increase in cardiac output, stroke volume, and peripheral vascular resistance [Ghazzi, 1997] - Acts as PPAR-gamma agonist to directly affect the molecular mechanisms of atherosclerosis, including PPAR-gamma found in human arterial lesions [Satoh, 1999; Marx, 1998]
Lipids	- Increase in HDL-C and decrease in triglycerides [Ghazzi, 1997; Suter, 1992; Antonucci, 1997] - Decrease in LDL-C oxidation and increase in particle size [Tack, 1998; Cominacini, 1998; Cominacini, 1997]

Microalbuminuria	Decrease in microalbuminuria [Imano, 1998]
Platelets	Decrease in platelet aggregation [Ishizuka, 1998]

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From: Diane Fuell/DEV/PHRD/SB_PLC

To: David S Krause/DEV/PHRD/SB_PLC@SB_PHARM_RD

CC: Martin I Freed/DEV/PHRD/SB_PLC@SB_PHARM_RD

Subject: Re: Freezer study

Date: 10/23/2000 10:47:27 (GMT-05:00)

DAvid

We did measure LP-PLA2 in the freezer study but the values increased on treatment and seemed to be tracking increases in LDL. The suggestion to measure LP_PLA2 came from the PERL lab at Presby as they had the assay available. We decided to make the results available for anyone within SB who is interested but, until we understood the role of lipids better, not to persue the results further for the Avandia story

Diane

ATTACHMENT I

From: Sarah Mooney([redacted])
Date Sent: 7/2/2002 3:06:34 PM
To: ""[redacted]"" <[redacted]>
CC:
Subject: FW: Haffner Revised

> Hello Michael and Denise -- Attached is the file containing the reworked
> paper by Dr. Haffner. Again, the word count has been reduced to meet the
> Clinical Cardiology publication requriements. The article was originally
> approximately 10,000 words, Dr. Haffner cut it to 8,800, and we have
> modified it to meet the 5,000 word requirement. We are currently at 4,974
> words.
>
> Please contact Melissa directly to discuss, as I will be on vacation until
> July 16th.
>
> Thanks so much and have a great 4th!
>
> Sarah and Melissa
>
> <<39-3376-LF Haffner with EndNote cuts.doc>>

- 39-3376-LF Haffner with EndNote cuts.doc

Modifying Cardiovascular Risk in the Type 2 Diabetes Patient

Short title: Modifying Cardiovascular Risk in Diabetes

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Condensed Abstract

Type 2 diabetes mellitus (T2DM) patients are at increased risk for cardiovascular disease (CVD). Strategies to reduce CVD risk in patients with T2DM should be multifactorial: a) improve glycemic control, incorporating behavioral and pharmacologic interventions; b) aggressively treat risk factors, including dyslipidemia and hypertension; and c) carefully select pharmacologic agents that complement the effects of such treatment to better manage these risk factors.

Abstract

Type 2 diabetes mellitus (T2DM) patients are at increased risk for cardiovascular disease (CVD). The Third Report of the National Cholesterol Educational Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP III) elevated T2DM to a CVD risk equivalent. T2DM patients should be monitored with respect to 5 modifiable risk factors that contribute to CVD: elevated low-density lipoprotein cholesterol (LDL-C), elevated glycosylated hemoglobin, reduced high-density lipoprotein cholesterol (HDL-C), hypertension, and smoking. Several other risk factors have been identified, including small, dense LDL particle size and reduced levels of the HDL_2 subfraction, and should be considered as well.

Strategies to reduce CVD risk in T2DM patients should emphasize a multifactorial approach: a) improved glycemic control, incorporating behavioral and pharmacologic interventions; b) aggressive treatment of risk factors, including dyslipidemia and hypertension; and c) careful selection of pharmacologic agents that complement the effects of such treatment to better manage these risk factors. Combined, these strategies may reduce the morbidity and mortality associated with T2DM.

Insulin resistance, evident in most patients with T2DM may support the risk factor cluster known as the metabolic syndrome, now recognized by NCEP as a secondary target in reducing cardiovascular risk.

Agents that target insulin resistance, such as the thiazolidinediones (TZDs), may be used to address the atherogenic risk factors of the metabolic syndrome and reduce the risk of CVD in patients with T2DM. Used as monotherapy or in combination, these agents control blood glucose levels and also may contribute independent benefits.

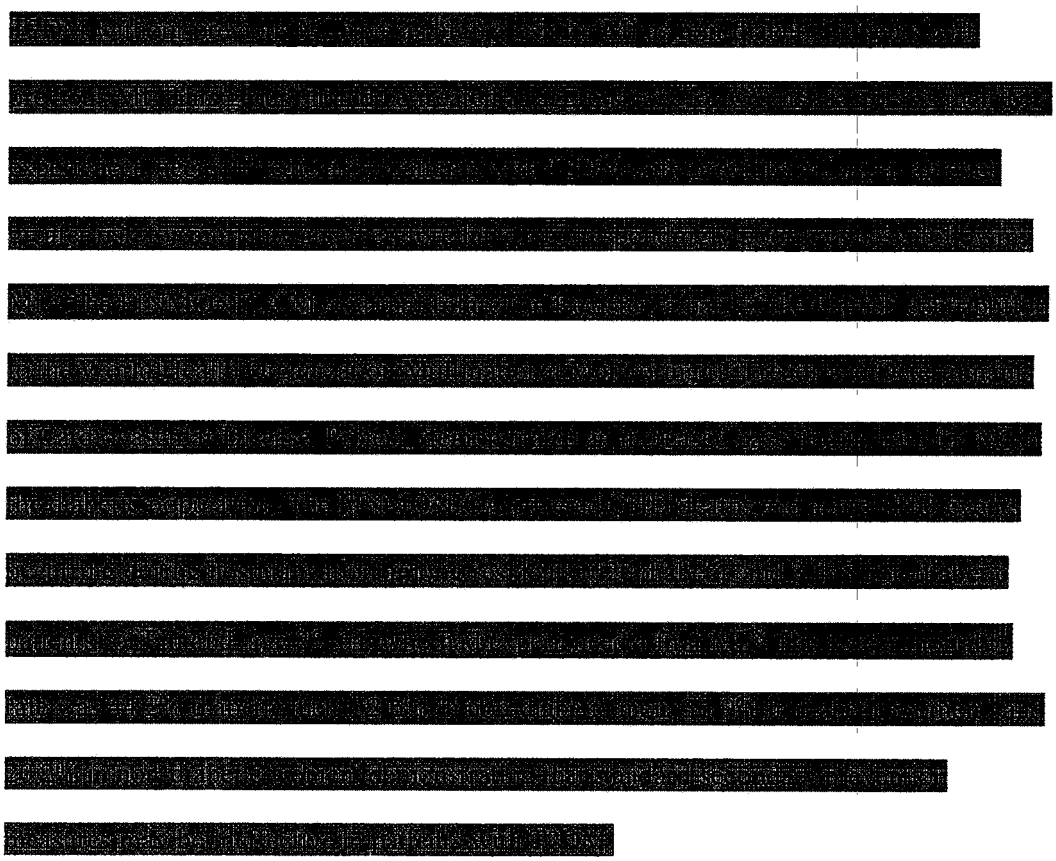
Key words: Type 2 diabetes, coronary heart disease, insulin resistance, dyslipidemia

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is high and increasing worldwide. [redacted].[1] The World Health Organization (WHO) predicts that between 1995 and 2025, the global pervasiveness of diabetes in adults will increase from 135 million to 300 million. [redacted][1]

Frequently, patients with T2DM have additional risk factors that contribute to CHD, such as hypertension and reduced high-density lipoprotein cholesterol (HDL-C).[3] For these reasons, The Third Report of the National Cholesterol Educational Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NCEP ATP III), elevates patients with T2DM to the same risk level as those already diagnosed with CHD. This is the highest category of risk designated by the NCEP.[4]

[redacted]



Due to this considerably increased risk for CHD and related complications in patients with T2DM, CV risk factors must be managed in this population to ensure optimal outcomes and to reduce potential cardiac-related morbidity and mortality. Medications that may have effects beyond glycemic control, specifically the thiazolidinediones (TZDs) and metformin, not only help to control blood glucose, but also have complementary effects on CV risk when used in combination with each other.

Discussion

Impact of insulin resistance on cardiovascular risk

Insulin resistance, present in the majority of patients with impaired glucose tolerance (IGT) and T2DM, has been identified as a CVD risk factor and is believed to support a cluster of disorders—including hypertension; dyslipidemia; diabetes; visceral adiposity; small, dense low-density lipoprotein cholesterol (LDL-C) particles; and CHD.[9] This risk factor cluster, known as the metabolic syndrome, identifies subjects with increased CV morbidity and mortality and has also been recognized by the NCEP ATP III as a secondary treatment target in reducing CV risk. [redacted]

Components of the metabolic syndrome can be directly linked to diabetes. For example, associations among insulin resistance and dyslipidemia, notably decreased HDL-C have also been observed in patients with T2DM. (INSERT ref 10-ADA. Standards. S57) In the Insulin Resistance Atherosclerosis Study (IRAS), the relationship between insulin resistance and CV risk factors was examined in patients with T2DM.[11] The insulin-resistant subjects had increased levels of very low density lipoprotein cholesterol and fasting glucose, lower HDL-C level, and smaller, denser LDL-C particles, even when serum LDL-C measurements were within the normal range.

As insulin resistance is both an independent CV risk factor and the common link to the atherogenic elements of the metabolic syndrome, as well as a core defect in T2DM, insulin resistance may indeed be the key underlying factor in the link between diabetes and increased CHD risk.

Identifying cardiovascular risk in patients with insulin resistance

[redacted]

Four of the 5 traditional modifiable risk factors are also elements of the metabolic syndrome; which may be linked by insulin resistance.

The NCEP ATP III has outlined specific criteria to identify those patients who may have the metabolic syndrome. These criteria consist of assessments and laboratory parameters that are simple to perform and commonly obtained (Table I). Patients who fit this profile may be assumed to have the other components of the metabolic syndrome; therefore, a

targeted treatment strategy may be implemented to effectively modify their risk-factor profile (Table IV).[4]

Management of risk factors in patients with T2DM

Strategies to reduce CHD risk in patients with T2DM, as well as possibly pre-diabetic patients, should emphasize a multifactorial approach. Since obesity, smoking, and sedentary living contribute to the risk, patients should be guided in appropriate dietary and lifestyle modifications.

Modifying dyslipidemia

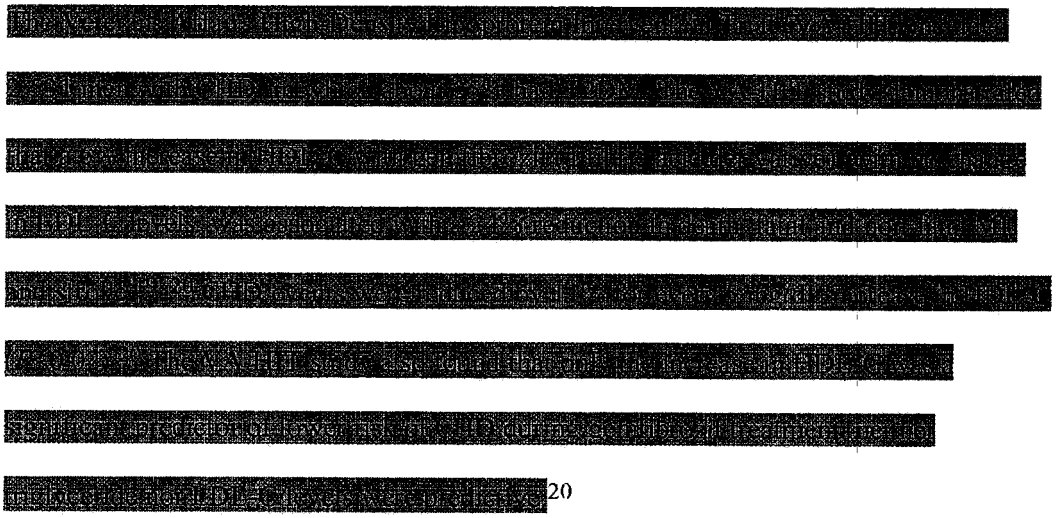
The NCEP ATP III indicates that LDL-C is the primary target of therapy in diabetic dyslipidemia and suggests the LDL goal of <100 mg/dL. Recent clinical trials of cholesterol lowering have demonstrated that reducing LDL-C in persons with diabetes does lower the incidence of CHD.[14, 15]

However, awareness of the unique dyslipidemia common among patients with T2DM plays a key role in the identification of cardiovascular risk in this population, as in theFramingham study notes that LDL-C is not elevated in about 1 in 4 individuals with diabetes.[16]

[redacted][11]

The Québec Cardiovascular Study (QCS) has shown that LDL-C particle diameter may be a more effective predictor of IHD than the actual LDL-C plasma concentration.[17] In this 5-year prospective study, patients who had the smaller, denser LDL-C particles had a 2.5-fold increase (95% CI, 1.0 to 6.6) in the risk of IHD.

In some studies, HDL-C levels are as predictive of CHD than are elevated LDL-C levels.[18]



[20]

It has also been suggested that HDL subfractions, specifically HDL_2, are responsible for the cardioprotective benefits of HDL-C.[21] Study results have demonstrated that low levels of HDL_2 are associated with an increased risk of CVD.[21] As HDL_2 has been found to be reduced in patients with diabetic dyslipidemia, the HDL_2 subfraction may also be a target for reducing CVD risk in patients with T2DM.

Becauase it may not be possible to separate the contributions of triglyceride and HDL-C to CAD. Rather than a predictor of risk, increased levels of triglycerides may be used as a cue to the clinician to investigate other lipid abnormalities, such as low HDL-C or small, dense LDL-C.

Though no clinical trial has been conducted exclusively in subjects with T2DM regarding the effects of lipid-lowering agents on subsequent CHD, a number of major studies have included diabetic patients. [redacted] in patients with T2DM.[22]

The NCEP ATP III states that statins are the class of drug that can most significantly lower LDL-C levels.[4] Statins are very effective in lowering LDL-C, and in one study, selectively reduced the number of small, dense LDL-C particles.[23] However, they have only modest effects on increasing HDL-C.[23]

[redacted][24]

[redacted]

[redacted].[26]

Modifying blood pressure

For patients with T2DM, hypertension is a major risk factor for the sequelae of diabetes, contributing to as much as 75% of all such complications, including nephropathy and end-stage renal disease.[27] As UKPDS demonstrated, diabetes patients whose blood pressure is tightly controlled (144/82 mm Hg) can reduce their risk of CV events more effectively than those whose blood pressure is less tightly controlled (154/87 mm Hg; $P<0.0001$).[28]

The Heart Outcomes Prevention Evaluation (HOPE) study, which involved 3,577 people with diabetes, showed that treatment with ramipril (an angiotensin converting enzyme [ACE] inhibitor) provided cardioprotective benefits that surpassed the benefit of its role as an antihypertensive agent.[29] After adjustment for both SBP and DBP, the ACE inhibitor lowered the risk of the combined primary outcome—the development of MI, stroke, or CV death—by 25–30% ($P<0.001$), possibly because of the protective effect of ACE inhibitors on the arterial wall.[30] Thus, the use of an ACE inhibitor may lower the risk of CV events in patients with T2DM, both by lowering blood pressure and by directly protecting the vasculature.

[redacted].[31] Thus, the

addition of an ACE inhibitor or ARB to T2DM therapy provides renal benefits in tandem with a lowered CV risk.

Control of hyperglycemia

Glycosolated hemoglobin (HbA_{1c})

[redacted]6, 32

Since CAD is the major cause of death in diabetes, several studies have examined the link between HbA_{1c} and CV risk. [redacted].7

Therefore, lowering elevated glucose levels to the ADA's goal of <7% is an important goal in the management of T2DM . In addition to lifestyle modifications, there are a number of pharmacological approaches which may be taken.

The sulfonylureas increase insulin secretion and substantially decrease the risk of microvascular complications, but not macrovascular disease, in patients with T2DM.[34] Metformin, in contrast, has been associated with a reduction in mortality and is often

regarded as initial therapy in overweight patients with T2DM. A biguanide, metformin works primarily through suppressing endogenous glucose output, and to a lesser extent through increasing peripheral insulin sensitivity. (insert ref 63- Inzucchi)

[redacted] These agents—rosiglitazone, pioglitazone, and the formerly available troglitazone—are effective when given alone[36-40] or when given in combination with certain other oral antidiabetes agents such as metformin.[41, 42]

[redacted] [35, 42, 43]

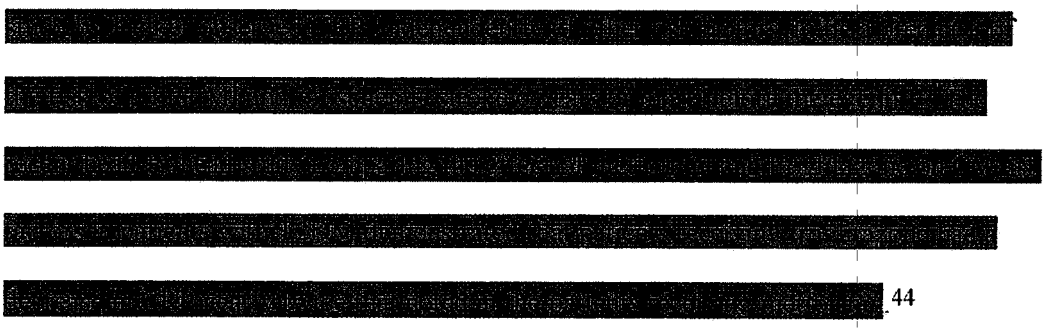
The role of TZDs in modifying cardiovascular risk

Through their effects in both glycemic control and CV risk-factor modification, TZDs may serve to complement other antidiabetes agents as well as agents customarily used to treat CV risk factors in T2DM in order to address the metabolic syndrome. A recent head-to-head study compared the effect of metformin and troglitazone on CV risk factors in patients with T2DM and poor glycemic control (HbA_{1c} >8.5%) despite glyburide therapy. The study found that troglitazone therapy increased both LDL particle size and

HDL-C while decreasing triglyceride. Subjects who received metformin, however, did not have significant changes in LDL-C, LDL particle size, HDL-C, or triglyceride.[44]

Statins effectively reduce LDL-C but have a less pronounced effect on other related lipid risk factors (HDL-C, HDL_2, and LDL-C particle size/density). However, combination use of TZDs with statin therapy positively affects these lipid parameters, as demonstrated in a study evaluating rosiglitazone in combination with atorvastatin.[45] In this study, subjects with T2DM received TZD (rosiglitazone) open-label monotherapy for 8 weeks. Of those subjects who presented with smaller, denser LDL-C particles, 71% shifted to a predominance of large, buoyant LDL-C particles after 8 weeks. In addition, there was a 17% increase in the cardioprotective HDL_2 subfraction and only a minimal change in the HDL_3 subfraction compared with pre-run-in measurements.[46] With the addition of atorvastatin 10 mg and 20 mg for 16 weeks, patients experienced a 33% and 40% decrease in LDL-C respectively while maintaining the benefits with regard to HDL-C and LDL-C particle size experienced during the first 8 weeks of rosiglitazone alone.[45] It is important to note that the effects of TZDs on HDL-C are often larger than those found with fibric acid derivatives, although head-to-head studies have not been carried out. Studies have shown a 16%–33% increase in HDL-C with TZD therapy.[47-49] This effect may be compared to that of gemfibrozil, as illustrated in the VA-HIT study, which yielded only a 6% increase in HDL-C.[19]

[redacted]



Women with gestational diabetes mellitus (GDM) have an increased risk of developing T2DM.[52] Results from a recent study of Hispanic women with a history of GDM showed that reducing insulin resistance by using a TZD, lowered the incidence of T2DM in this population.[53] Results from the Diabetes Prevention Program further supports the evidence that improving insulin sensitivity reduces the risk of developing T2DM. Non-diabetic patients with elevated fasting and post-load plasma glucose concentrations who had undergone a regimen of diet and exercise were less likely to develop T2DM when compared to patients either taking metformin or who had no intervention.[54]

A number of large outcomes studies are currently in progress to assess the effects of TZDs on CV risk in diabetic patients.

Conclusions

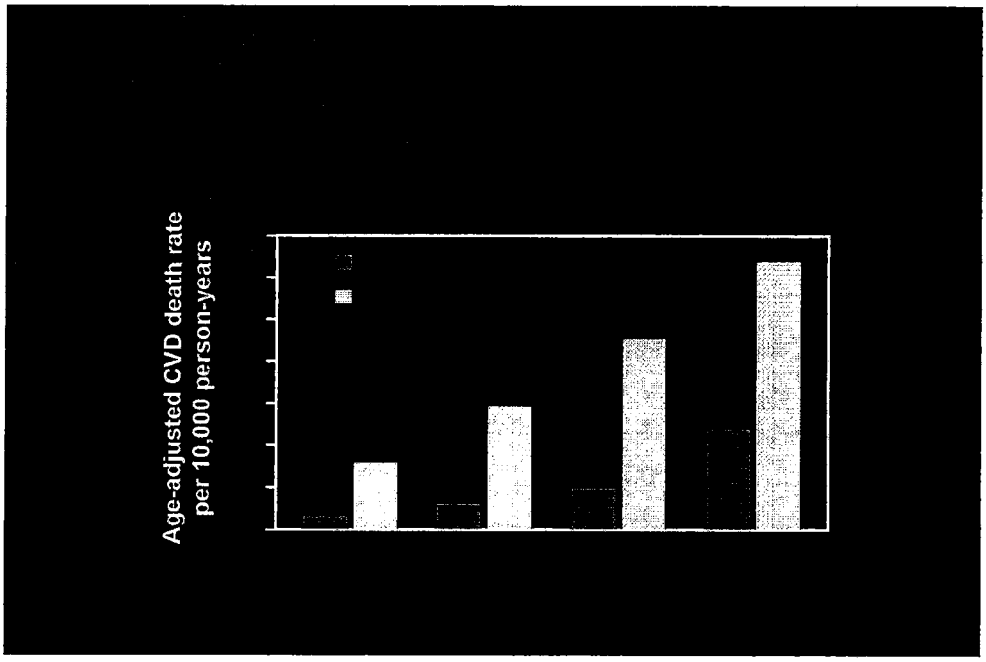
The patient with T2DM has a greatly increased likelihood of developing CVD due to the likelihood of having significant and independent risk factors for CVD. Among these risk factors are the various components of the metabolic syndrome, notably smaller LDL-C

particles and lower HDL-C levels. Evidence is indicating that these may be key underlying factors in the link between diabetes and increased CHD risk.

Thus, effective risk modification in patients with T2DM includes attention to the entire metabolic syndrome, particularly 4 of the 5 top modifiable CV risk factors in T2DM (LDL-C particle number, low HDL-C, hypertension, and hyperglycemia) as well as other elements such as small, dense LDL-C particles and HDL-C subfractions. Lifestyle modifications, such as increased exercise and a low-fat, high-fiber diet, have both physical and psychological advantages, and they place the patient in a more proactive position in managing diabetes.

Careful selection of pharmacologic agents that have been proven to manage some of the problems for which the patient may be at highest risk can reduce the morbidity and mortality associated with T2DM. Metformin is useful, as it reduces weight and has been shown in the UKPDS to reduce mortality. The TZDs offer added benefits, such as modifying LDL-C particle size and density, increasing HDL-C, and reducing blood pressure and CRP. The combination of TZDs and metformin improves glycemic control, insulin sensitivity, and beta-cell function more effectively than treatment with metformin alone. The TZDs also complement the effects of lipid-lowering agents such as statins. Alone or in combination, the TZDs appear beneficial in decreasing the risks of CHD in patients with T2DM.

Figure 1: Age-adjusted CVD death rates according to the number of risk factors for men screened for MRFIT, with and without diabetes at baseline.



Reprinted from *American Journal of Medicine*, vol. 80, Stamler et al, Prevalence and prognostic significance of hypercholesterolemia in men with hypertension. Prospective data on the primary screenees in the Multiple Risk Factor Intervention Trial, pp 33-39, with permission from Excerpta Media Inc.

Figure Legends

Figure 1: Age-adjusted CVD death rates according to the number of risk factors for men screened for MRFIT, with and without diabetes at baseline.

Table I: Guidelines for cardiac risk factor goals in diabetes

Risk Factor	Guideline Source	Specifications
LDL-C	Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III - (NCEP ATP III)[4]	For most persons with diabetes: LDL-C goal: <100 mg/dL. When LDL-C is ≥130 mg/dL, most will require LDL-lowering drugs along with lifestyle modifications to achieve goal. When LDL-C levels are 100–129 mg/dL at baseline or on treatment, therapeutic options include increasing intensity of LDL-lowering therapy, adding a drug to modify atherogenic dyslipidemia (fibrate or nicotinic acid), or intensifying control of other risk factors including hyperglycemia.
HDL-C	NCEP ATP III[4]	Low HDL-C is now defined as <40 mg/dL instead of the previously recommended <35 mg/dL cut-off because the higher value is a better

		measure of a depressed HDL.
HbA_{1c}	American Diabetes Association[3]	Normal HbA_{1c} <6%. Goal HbA_{1c} <7%. If HbA_{1c} >8%, action must be taken to control glycemia. Approach diabetes treatment as multifactorial: nutrition control, weight loss, exercise, and use of oral glucose-lowering agents with careful attention given to CV risk factors (hypertension, smoking, dyslipidemia, and family history).
Hypertension	The Sixth Report of the Joint National Committee On Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI)[55]	In patients with diabetes, antihypertensive drug therapy should be initiated along with lifestyle modifications, especially weight loss, to reduce blood pressure to <130/85 mm Hg. ACE inhibitors, alpha-blockers,

		calcium antagonists, and low-dose diuretics are preferred because of fewer adverse effects on glucose homeostasis, lipid profiles, and renal function. Beta-blockers also show reduction in CHD risk but may not always be appropriate in poorly managed patients with T2DM.
Smoking	U.S. Department of Health and Human Services	Patients must be encouraged to stop smoking. The cardiovascular benefits of discontinuing tobacco use can be seen within a year in all age groups.

Table II: Clinical identification of the metabolic syndrome

(National Cholesterol Education Program: Adult Treatment Panel III)

Three or more required for diagnosis

Risk Factor	Defining Level
Abdominal Obesity (waist circumference) Men Women	 • 102 cm (>40 in) • >88 cm (>35 in)
Triglycerides	≥150 mg/dL
High-density Lipoprotein Cholesterol Men Women	 • <40 mg/dL • <50 mg/dL
Blood Pressure	≥130/≥85 mg/dL
Fasting Glucose	≥110 mg/dL

Adapted from: National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of The Third Report of The National Cholesterol Education Program Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*.2001;285(19):2486-2497. Permissions pending.

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March 5, 2002

Dr. James Willerson
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Dear Dr. Willerson,

We are pleased to submit the revision of our paper "Effect of Rosiglitazone Treatment on Nontraditional Markers of Cardiovascular Disease in Patients with Type 2 Diabetes", MS 01-0454 2BR. We found the reviewers comments extremely helpful and feel our paper is now considerably improved. In order to respond to the reviewers request for additional analysis and discussion, we have expanded our paper so it will accommodate additional discussion and analysis (one new tables). Our paper is now at the limit for a brief report (2,375 words). A list of suggested reviewers for the additional review is enclosed (none were included in the initial list). Also enclosed is the original and three copies.

We thank the reviewers for their comments and look forward to your decision.

Sincerely,

Steven M. Haffner
Professor

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COMMENTS – REVIEWER 1

General Comments

1. We have added a caveat on the interpretation of the relevance of CRP and MMP-9 levels as representing reduced CHD risk in the discussion. We now say "reductions in markers for cardiovascular risk (page 8, paragraph 2).

Specific Comments

1. The absolute levels....seem to be higher. The reviewer is correct. First, in the initial version, we reported CRP in μg/mL whereas most authors report data in mg/dl which are 10% of μg/mL. We have changed our revised report to report CRP in mg/dl. For instance, in Pradhan's paper in women on baseline CRP predicting diabetes in the Women's Health Study, the median CRP was 0.69 mg/dl in subjects who later developed type 2 diabetes versus 0.29 mg/dl in subjects who did not later develop type 2 diabetes. The median BMI (kg/m^2) and median fasting insulin (pmol/l) in the converters was 31.8 kg/m^2 and 77.5 pmol/l versus 25.6 kg/m^2 and 39.3 pmol/l in the non-converters (Reference 7). Thus, obesity and insulin resistance are major factors determining CRP levels. The current report which includes moderately hyperglycemic, obese diabetic subjects might be expected to have even higher levels. We reported a median of 0.76 in women. These results probably reflect a selected population. Our data from the Insulin Resistance Atherosclerosis Study (IRAS) in non-diabetic subjects (Reference 6) also shows a dramatic increase in CRP (mg/dl) in subjects who have more metabolic degraders (n=0, 0.1; n=1, 0.5; n=2, 0.9; n=3, 1.3 and n=4, 1.4). We thank the reviewer for calling this to our attention to this issue which is now addressed in the discussion (Page 7, Paragraph 2).

2. Log CRP correlated within gender. This was confusing. We now show the median and geometric mean (catalog of log transformed variables) for gender in Table 1. In our study, as in other studies, CRP levels were higher in women than in men. There was no gender difference for IL-6, MMP-9 or WBC (Page 6, Paragraph 1).

3. Evidence linking MMP-9 to plaque stability. Most data have been collected on MMP-9 in plaque rather than in plasma or serum (Reference 15). There are, however, a number of reports suggesting increased MMP-9 in patients following a) cardiopulmonary bypass (Steinberg J et al. J Extra Corpor Technol 2000; 33:218-22.); b) premature coronary atherosclerosis (Nojix et al. Clin Chem Lab Med 2001; 39:380-4.); c) acute coronary syndrome (Kai H et al. JACC 1998; 32:368-77.). We cite the latter two papers. (Page 6, Paragraph 3)

4. Please define HOMA IS. The formula is:

$$\frac{\text{fasting insulin } (\mu U/ml) \times \text{fasting insulin } (mmol/l)}{22.5}$$

This formula is now given in the Methods section (Page 4, Paragraph 1).

5. The authors describe a long list of associations both positive and negative that they hardly discuss. We added Table 2a for baseline correlations and Table 2b for changes from 0 to 26 weeks.

6. Placebo group in Appendix. To simplify the paper, we report correlations only in the overall group in paper but show the RSG and placebo in the Appendix A for the reviewers. The correlations in the RSG group and the overall group are very similar.

7. Correlation between markers. The reviewer is correct. We have mentioned this point in the discussion and additionally performed multiple linear regression analyses (shown in Appendix B and mentioned on Page 6, Paragraph 2).

8. References 18-27. We are uncertain about whether different TZD's differ in their effects on atherosclerosis. We substituted a few references (References 21-23) showing a positive effect with all TZD's (troglitazone, pioglitazone and rosiglitazone) on atherosclerosis.

9. The interpretation of CRP in overweight diabetic subjects. We agree with the reviewers comments and "softened" the statement and suggested that the comparisons of TZD's and statins need to be done in a factorial design. (Page 6, Paragraph 4)

   One interesting issue is whether statin use attenuates the effect of TZD's on CRP levels. Only 15% of the subjects in the study were on statins at baseline. No subjects changed their statin use during the 26 weeks. However, the placebo users, the CRP declined -1.8 mg/dl in non-statin users and –1.6 mg/dl among statin users. In the RSG group, CRP declined 3.2 mg/dl in the non-statin users and 5.1 mg/dl in the statin users. Although the numbers are small (and we prefer not to include this data in the paper), this data suggests that the use of statins does not attenuate the effect of TZD's on CRP levels.

COMMENTS – REVIEWER 2

Specific Comments

1. How many subjects did not complete the study? The number of subjects in the current report study was 356 versus 493 subjects in the original cohort. One hundred sixty eight subjects withdrew before the final visit. Eight subjects did not have plasma for the analyses at the final visit. The "no change" analysis brought the n for each measurement up to that of the ITT population, but assumed for the "missing" patients that the baseline and endpoint values for each parameter were equal to the population mean, giving a "change" of zero. By adding in these values for the missing patients, we are actually diluting the mean change seen in those patients that did have values. This secondary analysis is intended to provide greater confidence in our results.

2. No dose response. We are uncertain as to why there is no dose response. The weight increase with RSG 8 mg may have blunted a possible dose response. See Appendix C (Page 6, Paragraph 3). It is not clear that a dose response should be expected for all

parameters. The maximum treatment effect for CRP may be achieved at 4 mg RSG. There is no statistically significant correlation between change in CRP and change in HbA1c or fasting glucose; thus dose effect on glycemic parameters should not imply dose effect on another. There does appear to be a dose response for MMP-9.

3. A Table should.... We have added tables on baseline correlations (Table 2a and change from 0 to 26 weeks in Table 2b) in the overall population. Data on the separate groups are shown in the Appendix A and B. Note the relatively small sample size in the placebo group. Data on fasting glucose, HOMA IS (which is very highly correlated with fasting insulin [r=.95]), WBC are now included. Change in glucose (or HBA1c) correlated significantly with WBC, MMP-9 and BMI (-) (Table 2b). In the change data, the MMP-9 did not correlate with changes in lipids. (Please also see Page 6, Paragraph 2). FFA data are shown in Appendix C. FFA did decline significantly in the RSG 4 and 8 mg group but not in the placebo group.

4. Weight. Weight did increase in the RSG groups. (Please see Appendix C, Page 5, Paragraph 3). However, adjustment for weight change did not significantly change the results (larger effects for CRP and smaller effects for MMP-9 but all still significant). FFA also decreases with RSG. See Appendix C.

5. Is circulating MMP-9..... Little data is available on plasma levels. However the data that is available suggests an increase in premature atherosclerosis and unstable angina (see Page 6, Paragraph 3). Other markers were not examined because of the lack of samples although this is being studied prospectively in other populations.

Appendix Table A1. Pearson correlations in changes among subjects in the **placebo group (n=95).**

	IL6	MMP9	WBC	BMI	HDL	TG	LDL-C	HbA_{1c}	FG	HOMA-IS	FFA
CRP	**0.25**	0.16	-0.01	0.14	-0.17	0.02	-0.07	-0.08	-0.03	-0.11	**-0.24**
IL6		**0.26**	0.19	-0.02	-0.15	0.01	-0.03	-0.12	-0.10	0.17	-0.04
MMP9			0.05	-0.19	-0.04	-0.20	-0.07	-0.12	-0.06	0.02	0.02
WBC				0.02	**0.25**	**-0.21**	0.15	**-0.25**	-0.07	-0.20	0.10
BMI					0.13	0.17	0.01	-0.15	**0.23**	**-0.25**	-0.05
HDL						**-0.38**	-0.03	**-0.36**	-0.06	-0.13	-0.11
TG							0.05	**0.23**	0.20	-0.07	**0.38**
LDL-C								0.08	0.07	-0.06	0.08
HbA_{1c}									**0.49**	0.13	**0.23**
FG										**-0.30**	**0.22**
HOMA-IS											0.01

All **bolded** coefficients $p < 0.05$. If |coefficient| > 0.26, $p < 0.01$; |coefficient| > 0.33, $p < 0.001$

Appendix Table A2. Pearson correlations in changes among subjects in the **treatment groups (n=258).**

	IL6	MMP9	WBC	BMI	HDL	TG	LDL-C	HbA_{1c}	FG	HOMA-IS	FFA
CRP	**0.54**	**0.19**	**0.23**	0.04	**-0.17**	0.01	-0.07	0.05	0.05	**-0.15**	0.09
IL6		**0.23**	**0.42**	0.02	**-0.13**	0.04	-0.11	0.02	0.09	**-0.13**	0.11
MMP9			**0.48**	**-0.18**	-0.02	0.03	0.02	**0.13**	**0.20**	-0.12	0.09
WBC				**-0.17**	-0.01	0.07	0.08	**0.14**	**0.26**	**-0.20**	0.05
BMI					-0.05	-0.06	0.01	**-0.35**	**-0.19**	-0.12	-0.02
HDL						**-0.34**	-0.01	0.03	-0.05	**0.16**	-0.07
TG							-0.07	0.08	**0.24**	-0.07	**0.17**
LDL-C								0.12	**0.16**	-0.08	0.10
HbA_{1c}									**0.59**	0.09	0.06
FG										-0.11	**0.16**
HOMA-IS											0.03

All **bolded** coefficients $p < 0.05$. If |coefficient| > 0.15, $p < 0.01$; |coefficient| > 0.20, $p < 0.001$

Appendix Table B1. Stepwise regression results from baseline measures.

Dependent variable	step	Predictor	Coefficient estimate	Standard error	p-value	Partial R^2	Model R^2
Ln(CRP)	.	Intercept	-2.48279	0.47827	<.0001	.	.
	1	Ln(IL-6)	1.04748	0.12474	<.0001	0.2192	0.2192
	2	DM_BMI	0.06263	0.01262	<.0001	0.0589	0.2781
	3	Ln(WBC)	0.65156	0.20161	0.0014	0.0215	0.2996
Ln(IL-6)	.	Intercept	0.04112	0.17651	0.8159	.	.
	1	Ln(CRP)	0.16647	0.01871	<.0001	0.2192	0.2192
	2	Ln(WBC)	0.21539	0.07952	0.0032	0.0196	0.2388
	3	Age	0.00519	0.00203	0.0111	0.0143	0.2531
Ln(MMP-9)	.	Intercept	5.10911	0.38690	<.0001	.	.
	1	Ln(WBC)	0.92917	0.09350	<.0001	0.2177	0.2177
	2	Ln(LDL-C)	-0.16743	0.07560	0.0274	0.0111	0.2288
Ln(WBC)	.	Intercept	-0.01907	0.23499	0.9354	.	.
	1	LOG_MMP9	0.22252	0.02368	<.0001	0.2177	0.2177
	2	Ln(IL-6)	0.09933	0.03204	<.0001	0.0515	0.2692
	3	Ln(CRP)	0.02578	0.01247	0.0092	0.0144	0.2836
	4	HOMA S	-0.00031	0.00014	0.0440	0.0085	0.2922
	5	Ln(LDL-C)	0.07865	0.03707	0.0346	0.0093	0.3015

Appendix Table C. Analysis of covariance

Change in:	Placebo	RSG 2 mg	RSG 4 mg	p-values overall	p-values trend
weight (kg)	-1.13	1.77	3.51	**<.0001**	**<.0001**
FFA*	-0.9	-4.2	-4.5	**0.0227**	**0.0347††**
CRP (%)†	-13.93%	-40.55%	-35.60%	**0.0075**	**0.0296**
adjusted for change in weight	0.00%	-41.14%	-41.73%	**<.0001**	**0.0004**
IL-6 (%)†	-4.88%	-6.76%	-4.88%	0.9397	0.9670
adjusted for change in weight	-4.88%	-6.76%	-5.82%	0.9289	0.9295
MMP-9 (%)†	2.02%	-10.42%	-21.34%	**0.0001**	**<.0001**
adjusted for change in weight	-3.92%	-10.42%	-18.13%	**0.0500**	**0.0149**
WBC, cells/mm^3 x 10	0.04	-0.52	-0.64	**<.0001**	**<.0001**
adjusted for change in weight	-0.08	-0.52	-0.56	**0.0085**	**0.0082**

† ANCOVA of the difference in natural logarithms (or equivalently the logarithm of the ratio of follow-up level to baseline level) and presented as percentage change (antilog – 1).
†† All ANCOVAs of rank transformations of the measurements were concordant with the results presented above (i.e. both $p < 0.05$ or both $p > 0.05$ and comparisons in the same direction) except that FFA trend $p = 0.1256$ and weight-adjusted FFA overall $p = 0.0281$.
*FFA levels changed in the 4 mg and 8 mg group ($p<0.001$) but not in the placebo group ($p<0.160$).

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Clinical Investigation and Reports

Effect of Rosiglitazone Treatment on Nontraditional Markers of Cardiovascular Disease in Patients With Type 2 Diabetes Mellitus

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Abstract

▲ Top
▪ Abstract
▼ Introduction
▼ Methods
▼ Results
▼ Discussion
▼ References

Background— Markers of systemic inflammation (eg, C-reactive protein [CRP] and interleukin-6 [IL-6]) have been proposed to be "nontraditional" risk factors for cardiovascular disease in patients with type 2 diabetes mellitus. Matrix metalloproteinase-9 (MMP-9) has been implicated in the pathogenesis of atherosclerotic plaque rupture, which raises the possibility of the use of MMP-9 levels as a marker for future myocardial infarction or unstable angina. In vitro and animal studies suggest that thiazolidinediones can reduce the expression of these markers. The purpose of this analysis was to determine whether rosiglitazone alters serum concentrations of CRP, IL-6, MMP-9, and white blood cell count (WBC) and to examine the relationship of these effects with demographic and disease variables.

Methods and Results— CRP, IL-6, MMP-9, and WBC were analyzed from stored frozen serum samples obtained from patients with type 2 diabetes who completed a 26-week randomized, double-blind, placebo-controlled study. After 26 weeks of rosiglitazone treatment, the percentage reductions in mean CRP, MMP-9, and WBC levels were statistically significant compared with baseline and placebo ($P<0.01$). The percentage reduction in mean IL-6 was small and similar in the rosiglitazone and placebo groups. The change in each inflammatory marker from baseline to week 26 was significantly correlated ($P<0.05$) with each of the other markers, as well as with the homeostasis model assessment estimate of insulin resistance.

Conclusions— Rosiglitazone reduces serum levels of MMP-9 and the proinflammatory marker CRP in patients with type 2 diabetes, which indicates potentially beneficial effects on overall cardiovascular risk.

Key Words: atherosclerosis • cardiovascular diseases • diabetes mellitus • inflammation • risk factors

Introduction

▲ Top
▲ Abstract
▪ Introduction
▼ Methods
▼ Results
▼ Discussion
▼ References

Cardiovascular disease (CVD) accounts for ≈50% of all deaths worldwide. Type 2 diabetes mellitus is one of the most potent independent risk factors for the development of CVD and is seemingly related to accelerated atherosclerosis compared with the nondiabetic population.[1,2] It is clear that alterations in traditional risk factors (eg, abnormal lipids and raised blood pressure) alone cannot explain the excess incidence of CVD in patients with type 2 diabetes.[3]

There is increasing recognition that chronic subclinical vascular inflammation plays a role in the pathogenesis of atherosclerosis, insulin resistance, and type 2 diabetes.[4–6] Markers of subclinical inflammation, in particular C-reactive protein (CRP) and interleukin-6 (IL-6), have been shown to be powerful independent predictors of diabetes and CVD risk.[5,7,8] In addition, elevated white blood cell count (WBC) may be a marker for inflammation and may predict future coronary heart disease and mortality.[9]

Preclinical studies demonstrate that peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists may affect inflammatory pathways through transcriptional mechanisms. These effects, seen in monocytes, macrophages, T-lymphocytes, and vascular smooth muscle cells, include decreases in cytokines, chemokines,

and matrix metalloproteinases (MMPs).[10] Treatment with troglitazone, a PPAR-γ agonist, is associated with declines in plasminogen activator inhibitor-1 levels.[11] Taken together, these anti-inflammatory effects raise the prospect of reduced cardiovascular risk, either through improved metabolism or directly by activation of PPAR-γ in vascular or atherosclerosis-associated cells.[12] To follow up these preclinical observations, we investigated the effects of rosiglitazone (RSG) on markers of inflammation (CRP and IL-6) and plaque stability (MMP-9) in patients with type 2 diabetes. Effects on WBC were analyzed as well. Potential relationships between effects on these markers and variables associated with type 2 diabetes were also examined.

Methods

▲ Top
▲ Abstract
▲ Introduction
▪ Methods
▼ Results
▼ Discussion
▼ References

Subject Material

Serum biomarkers were analyzed with samples obtained from 357 patients with type 2 diabetes mellitus who completed a 26-week randomized, double-blind, placebo-controlled study to assess the efficacy and safety of RSG (4 or 8 mg/d).[13] Patients received instruction on a weight-maintenance diet throughout the study. Prior antidiabetic medications taken by patients were discontinued for a minimum of 4 weeks before randomization. Serum samples were obtained on the day of randomization (baseline) and at week 26 and stored at -70°C until analyzed.

Analyses

Serum levels of IL-6 and MMP-9 were measured by ELISA (R&D Systems), and serum levels of CRP were assayed by another ELISA (Diagnostic Systems Laboratory Inc). Baseline and week 26 paired samples for any patient were assayed in the same batch to minimize interassay variability. The marker of insulin resistance, homeostasis model assessment estimate of insulin resistance (HOMA-IR),[14] is defined as follows: equation

$$\frac{\text{Fasting plasma insulin } (\mu\text{U/mL}) \times \text{fasting glucose (mmol/L)}}{22.5}$$

Statistical Analyses

Within-treatment comparisons of mean change from baseline to week 26 of CRP, MMP-9, IL-6, and WBC levels; point estimates; and 95% CIs were presented for different treatment groups. For the assessment of differences between each RSG dosage group and placebo group with regard to continuous variables, an ANCOVA (using PROC MIXED in SAS software) with terms for treatment and baseline measurement was used that was based on log-transformed data. To determine whether analysis of only those who completed the study might bias our results, the same comparisons were also made for the study population as a whole. Patients missing values for an analyte were assumed to have had no change in that analyte.[15]

Pearson correlation coefficients were calculated to examine the relationships of analyte levels at baseline with prespecified disease and metabolic variables (Table 1). Correlations were determined for baseline variables (Table 2) and the relationship of percentage changes from baseline to week 26 with CRP, IL-6, MMP-9, and

WBC with the prespecified changes in metabolic variables (Table 3). Baseline levels of analytes and the changes in analytes were nonnormally distributed; therefore, log-transformed data were used for determination of Pearson correlation coefficients.

View this table: **Table 1.** Demography and Baseline Characteristics
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View this table: **Table 2.** Baseline Pearson Correlations in the Entire Population (n=357)
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View this table: **Table 3.** Pearson Correlations in Changes Among All Individuals
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[in a new window]

Results

▲ Top
▲ Abstract
▲ Introduction
▲ Methods
▪ Results
▼ Discussion
▼ References

Each treatment group displayed similar demographic and baseline characteristics (Table 1), and there was no difference between this patient cohort and the original intent-to-treat study population (n=493) in terms of the magnitude of improvement in mean [SD] of glycosylated hemoglobin (HbA_{1c}; RSG 4 mg/d, -0.6% [1.2%]; RSG 8 mg/d, -0.9% [1.2%]; placebo 0.6% [1.1%]) and fasting plasma glucose (RSG 4 mg/d, -2.5 [2.6] mmol/L; RSG 8 mg/d, -3.1 [2.9] mmol/L; placebo 0.2 [2.6] mmol/L).[13] Median CRP levels were higher in women than in men (0.76 versus 0.39 mg/dL, $P<0.001$). There were no sex differences in IL-6, WBC, or MMP-9 levels.

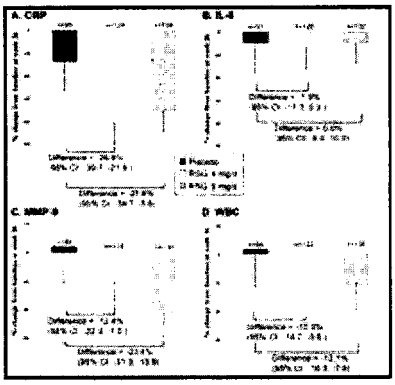
Relationship of Baseline Values With Metabolic and Disease Variables

As shown in Table 2, the natural logarithm (ln) of CRP was significantly ($P<0.001$) correlated with ln IL-6 ($r=0.44$) and ln MMP-9 ($r=0.17$) at baseline. Baseline ln CRP and ln IL-6 both correlated positively with body mass index ($r=0.30$ and $r=0.11$, respectively) and WBC ($r=0.28$ and $r=0.27$, respectively). Ln CRP was correlated with ln HOMA-IR ($r=0.21$), as was reported in other studies.[6] Additionally, ln HOMA-IR was correlated with WBC ($r=0.13$) and ln IL-6 ($r=0.13$). Baseline ln MMP-9 showed a statistically significant positive correlation with baseline ln WBC ($r=0.47$) but was only weakly correlated with baseline triglycerides ($r=0.07$) and LDL cholesterol ($r=0.07$).

Effects of RSG Treatment on Weight, CRP, IL-6, MMP-9, and WBC

After 26 weeks of RSG treatment, patients in the placebo group lost 1.1 kg as opposed to a 1.8-kg increase in

the RSG 4 mg/d group and a 3.5-kg increase in the RSG 8 mg/d group ($P<0.001$ compared with baseline). Both RSG treatment groups showed statistically significant ($P<0.05$) mean percentage reductions in CRP levels from baseline and placebo (Figure, A). The reductions in CRP did not appear to be dose related. There was no significant difference between the percentage reductions in CRP in the RSG 4- and 8-mg/d groups. After adjustment for the greater weight increases in the RSG groups, the decline in CRP was -0.15 mg/dL in the placebo group, -0.52 mg/dL in the RSG 4-mg/d group, and -0.54 mg/dL in the RSG 8-mg/d group. There was no significant percentage change in CRP from baseline in the placebo group (Figure, A). Mean percentage changes in IL-6 level were small and similar between the RSG and placebo groups (Figure, B). Statistically significant ($P<0.05$) and dose-ordered reductions from baseline and placebo were observed for MMP-9 in the RSG treatment groups, whereas no change was observed in the placebo group (Figure, C). WBC also declined significantly with RSG (Figure, D).



Effect of RSG on levels of CRP (A), IL-6 (B), MMP-9 (C), and WBC (D). All percentages represent 1 subtracted from antilogs of mean difference between baseline and week 26 log-transformed levels.

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To determine whether focusing this analysis on only those who completed the study introduced a bias into the results, the analysis of changes from baseline and treatment effects was repeated with the total study population (n=493), assuming no change from baseline to week 26 where analytical values were missing. As expected, this secondary analysis of the data also demonstrated slightly smaller but still significant reductions from baseline and placebo for CRP and MMP-9 in both RSG treatment groups compared with the analysis shown in the Figure.

Correlations Between Changes From Baseline to Week 26 in CRP, IL-6, and MMP-9 and Metabolic Variables

The change in ln CRP from baseline to week 26 was significantly ($P<0.05$) positively correlated with changes in IL-6 ($r=0.53$), MMP-9 ($r=0.19$), WBC ($r=0.19$), and HOMA-IR ($r=0.13$) and inversely correlated with changes in HDL cholesterol ($r=-0.17$; Table 3). The change in MMP-9 was significantly correlated with change in IL-6 ($r=0.22$), WBC ($r=0.40$), HbA_{1c} ($r=0.14$), fasting plasma glucose ($r=0.19$), and free fatty acids ($r=0.11$). Change in IL-6 was correlated with change in WBC ($r=0.36$), HDL cholesterol ($r=-0.12$), and HOMA-IR ($r=0.09$). Multivariate analyses of the change from weeks 0 to 26 also illustrated that the strongest correlates of change were between CRP, MMP-9, WBC, and IL-6 (data not shown).

Discussion

▲ Top
▲ Abstract
▲ Introduction
▲ Methods
▲ Results
▪ Discussion
▼ References

These data show that RSG treatment significantly reduced serum CRP, MMP-9, and WBC compared with placebo. Elevation in CRP levels has been associated with both the development of type 2 diabetes and an increased risk of CVD.[5–8,16] MMPs, in addition to being a known acute-phase reactant that increases inflammation, have also been implicated in plaque rupture.[17] Interestingly, thiazolidinediones have been shown to decrease MMP-9 expression in vascular smooth muscle cells,[10] with evidence for a transcriptional mechanism demonstrated by changes in protein and mRNA levels. Despite these intriguing data, there is no evidence to suggest elevated serum MMP-9 levels reflect MMP-9 levels in the arterial walls and only limited evidence to suggest an increased propensity for plaque rupture. Increased blood levels of MMP-9 have been reported in premature atherosclerosis[18] and in patients with acute coronary syndrome.[19] After the initiation of cardiopulmonary bypass (a high-stress condition), circulating MMP-9 increased more than 6-fold.[20] Reductions of MMP-9, CRP, and WBC could thus possibly be interpreted as reflecting a reduction in overall CVD risk, although this possibility should be tested in clinical controlled studies.

The percentage reductions in CRP with RSG in the present study were of a similar magnitude to those seen with the lipid-lowering statins.[21] However, patients in the present study were diabetic and were more obese than in the typical CRP study with statins,[21] and direct comparisons between the effect of statins and PPAR-γ agonists in CRP levels should be done with a factorial study design. It is possible that the decrease of CRP in obese diabetic patients could reflect changes in insulin resistance rather than a vasculoprotective effect. Changes in CRP were independent of changes in LDL cholesterol, similar to the effect of statins on CRP. Additionally, RSG treatment effects on CRP and MMP-9 were still evident in a second, more conservative analysis of the study data in which patients with missing values were assumed to have no change in that parameter, which increases our confidence in these results.

CRP levels in the present report were higher than in some previous reports,[6,7] which may reflect the present study population, who had diabetes and who were quite obese. In data from the Women's Health Study report,[7] which examined CRP in relation to the incidence of diabetes, median CRP was 0.67 mg/dL in patients who developed diabetes compared with 0.26 mg/dL in patients who did not develop diabetes. Median CRP in women in the present study was 0.76 mg/dL. Because glucose levels were also associated with higher CRP levels,[6] it would be expected that the present population might have even higher levels than the obese prediabetic patients in the Women's Health Study.[7]

Although there was a positive correlation between changes in CRP and IL-6 in both the RSG and placebo treatment groups, there was no apparent effect of either treatment on serum IL-6 levels. Thiazolidinediones have been shown to reduce mRNA induction and expression of IL-6 in a mouse model of type 2 diabetes.[22] Subcutaneous adipose tissue is a significant source of IL-6 expression,[23] whereas thiazolidinedione treatment has been associated with weight gain and increases in subcutaneous fat. It is possible that our inability to detect differences between RSG and placebo with respect to this parameter may be related to the observed weight decrease in the placebo group (possibly leading to reductions in subcutaneous fat) and weight gain in

the RSG group.

The correlations we observed between changes in CRP, IL-6, and MMP-9 were consistent with potential anti-inflammatory and antiatherogenic actions of various PPAR-γ agonists observed in preclinical and clinical studies.[24–26] The correlation between HOMA-IR and the inflammatory markers IL-6 and MMP-9 at baseline in diabetic patients may suggest a relationship between insulin resistance and a chronic inflammatory state, as shown for CRP and insulin resistance with the frequently sampled intravenous glucose tolerance test in nondiabetic individuals.[6]

The decrease of WBC with RSG is consistent with the positive correlation of WBC with decreased insulin sensitivity in the Insulin Resistance Atherosclerosis Study (IRAS).[8] In the West of Scotland Coronary Prevention Study (WOSCOPS),[27] WBC was associated with the development of type 2 diabetes[16,27] in univariate models. Additionally, WBC has been shown to predict CVD.[6]

Relatively few data are available on correlations of circulating MMP-9 with demographic or metabolic variables. In the present report, MMP-9 was correlated with WBC, IL-6, and CRP at baseline. Baseline MMP-9 was positively but weakly correlated with baseline triglyceride and LDL cholesterol levels. However, changes in MMP-9 were correlated with changes in several other variables. Changes in MMP-9 were correlated with changes in CRP, IL-6, WBC, HbA_{1c}, fasting plasma glucose, insulin resistance, and body mass index. The strongest correlations between 0 and 26 weeks for CRP were with other inflammatory factors. In one report, baseline MMP-9 was associated with lower HDL cholesterol, [19] but no association of MMP-9 and HDL cholesterol was observed in another report.[28] A positive association of MMP-9 and WBC was observed in one report.[28]

These data support the potential beneficial effects of insulin-sensitizing interventions such as use of thiazolidinediones on levels of markers for cardiovascular risk. Additional investigations of the effects of antidiabetic agents on cardiovascular outcomes are ongoing.

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Footnotes

Drs Weston, Chen, and Freed are employees of GlaxoSmithKline.

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▲ Top