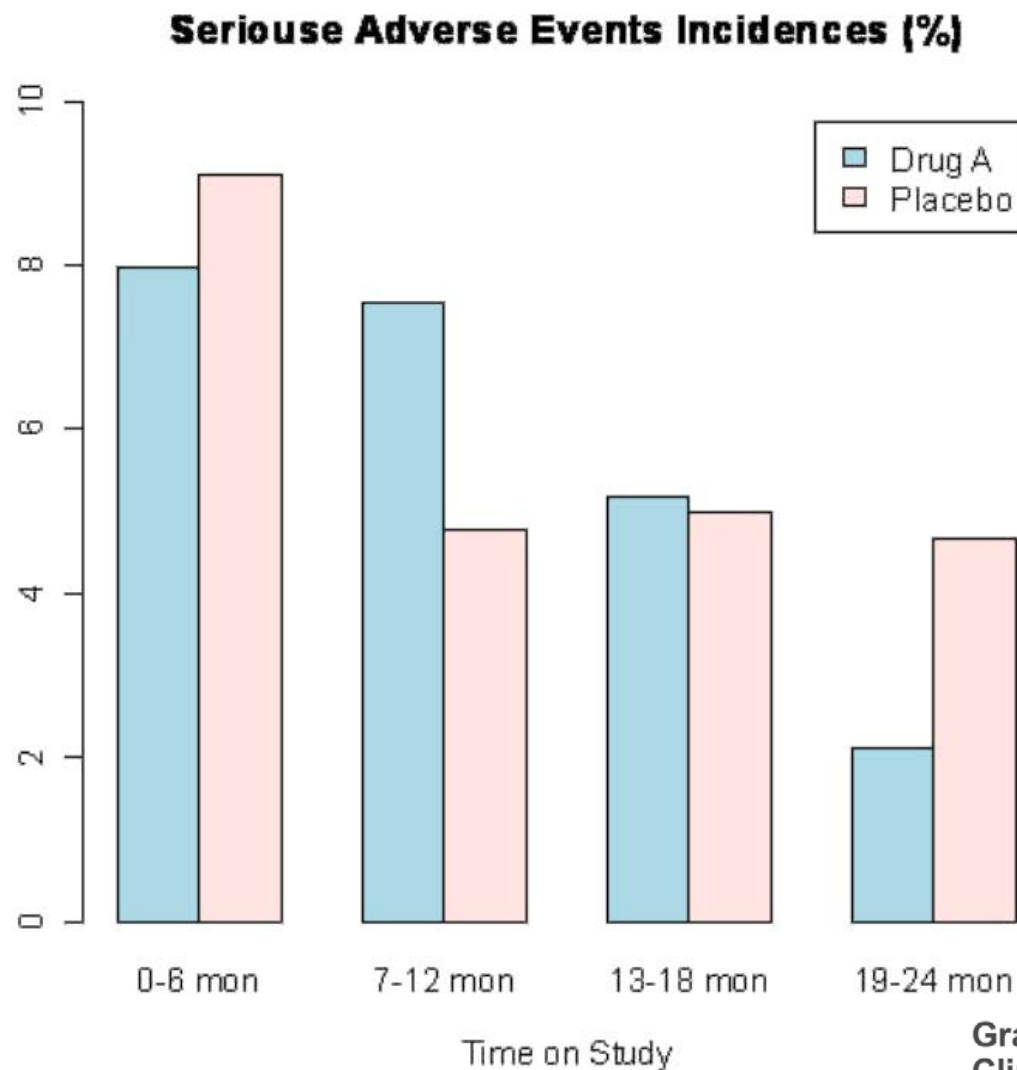


## Clinical Question: Incidence of AE ?



**Graphical Analyses of  
Clinical Trial Safety Data**

Haijun Ma, PhD and Amy Xia, PhD

Amgen Inc.  
11/20/2008

# Clinical Question: Incidence of AE ?

## Most Frequent On-Therapy Adverse Events

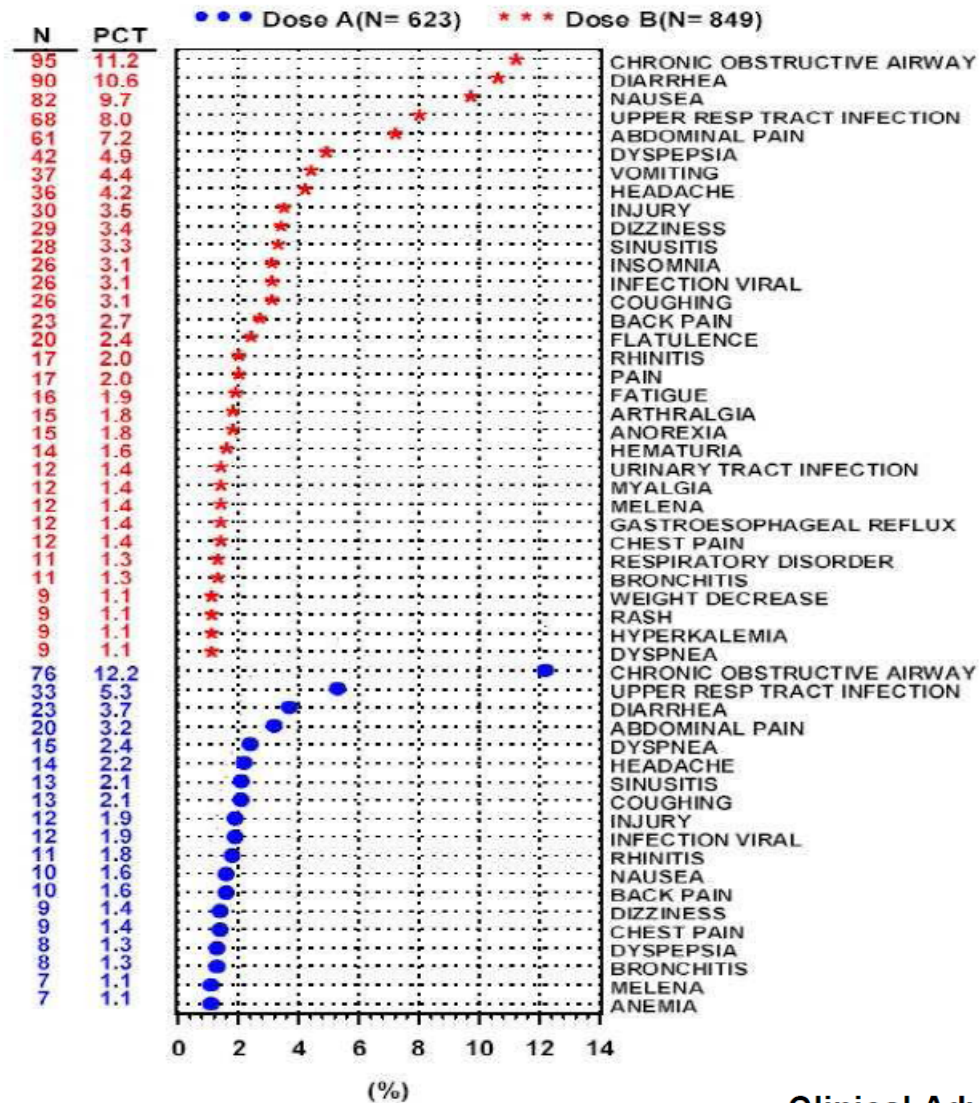


Figure 3. Sample AE Dot Plot

## Clinical Adverse Events Data Analysis and Visualization

Shi-Tao Yeh, GlaxoSmithKline, King of Prussia, PA.

## Clinical Question: Incidence of AE ?

The AE summary table shown in Table 1 can be presented in the bar charts display shown in Figure 1.

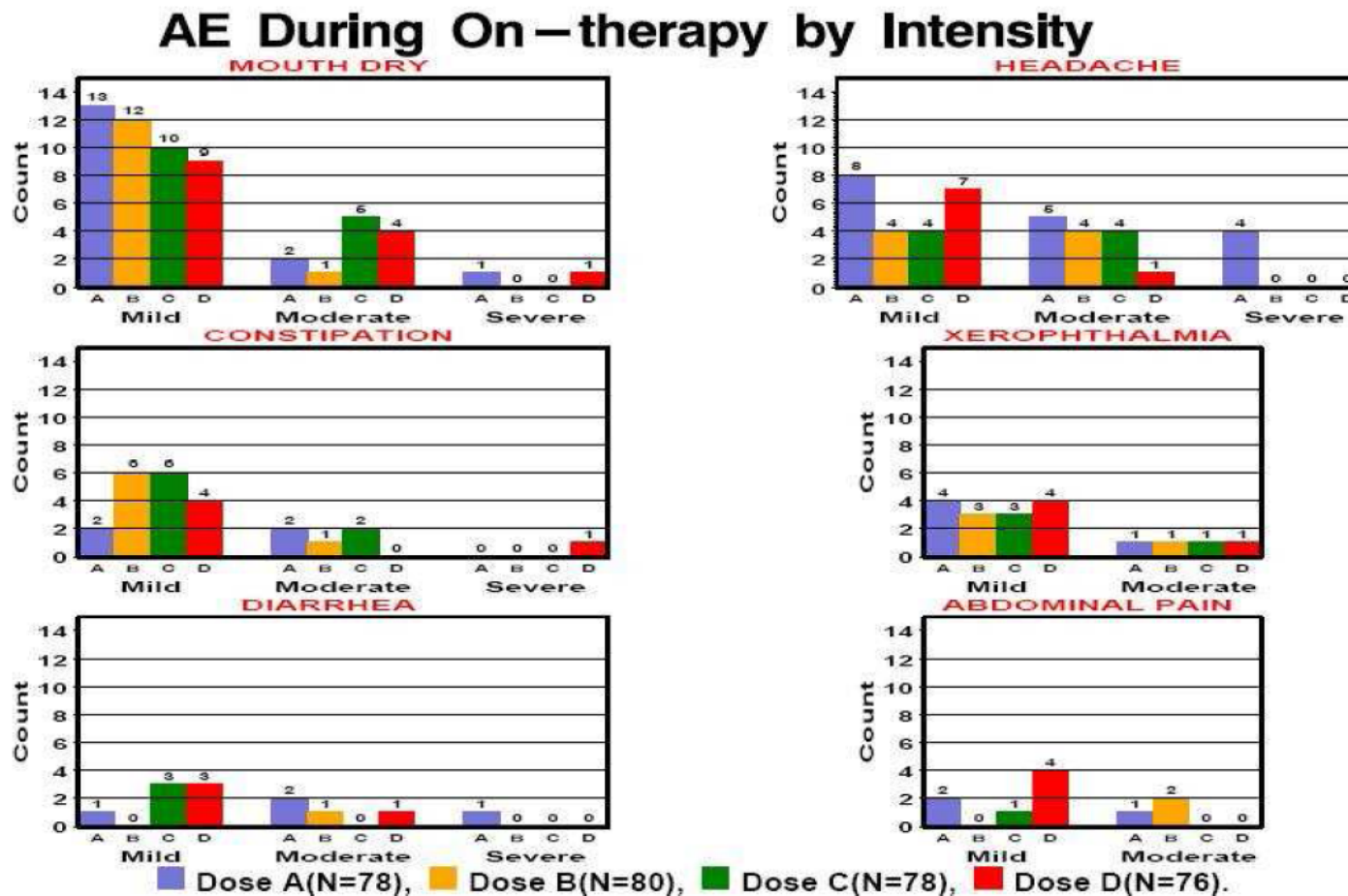
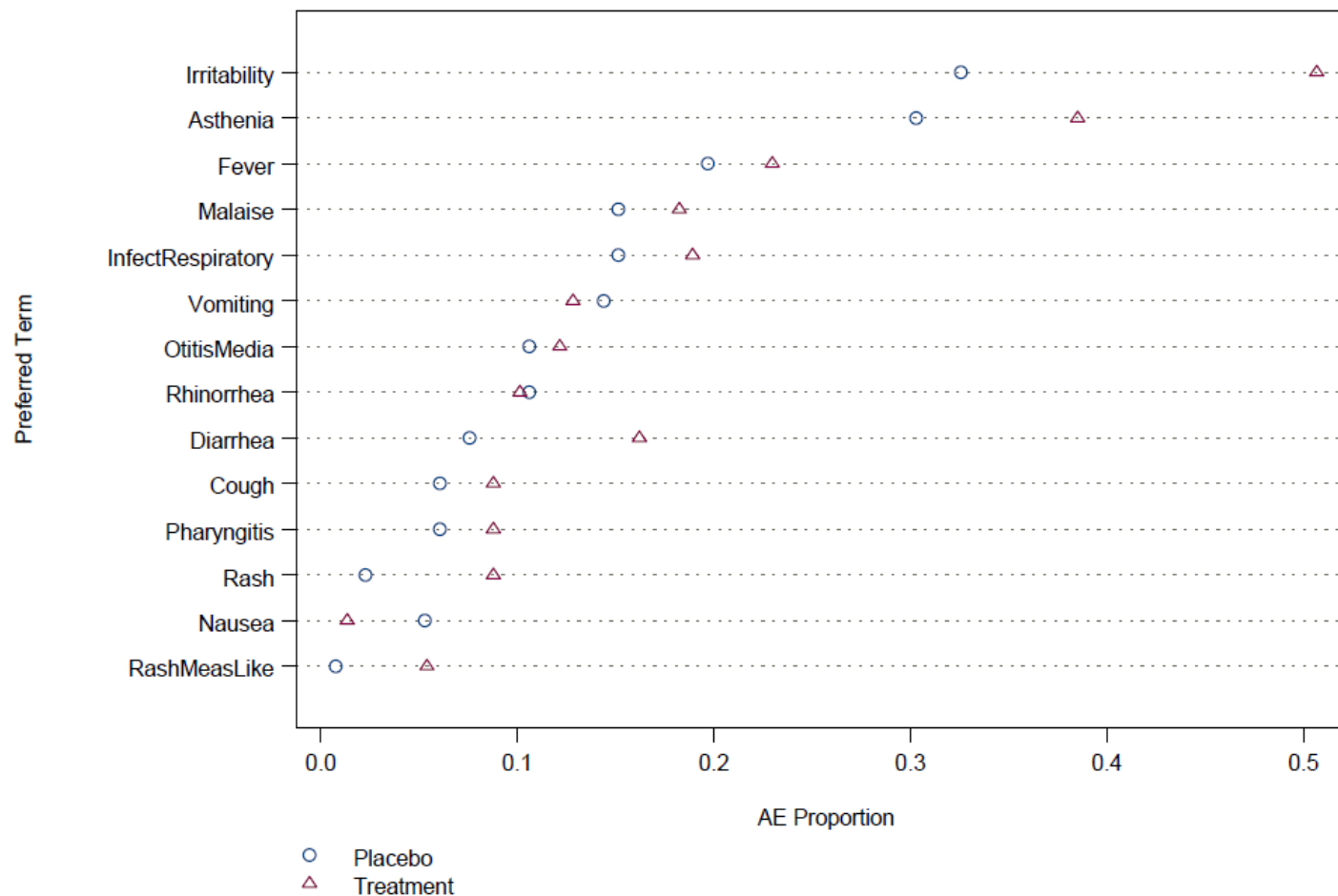


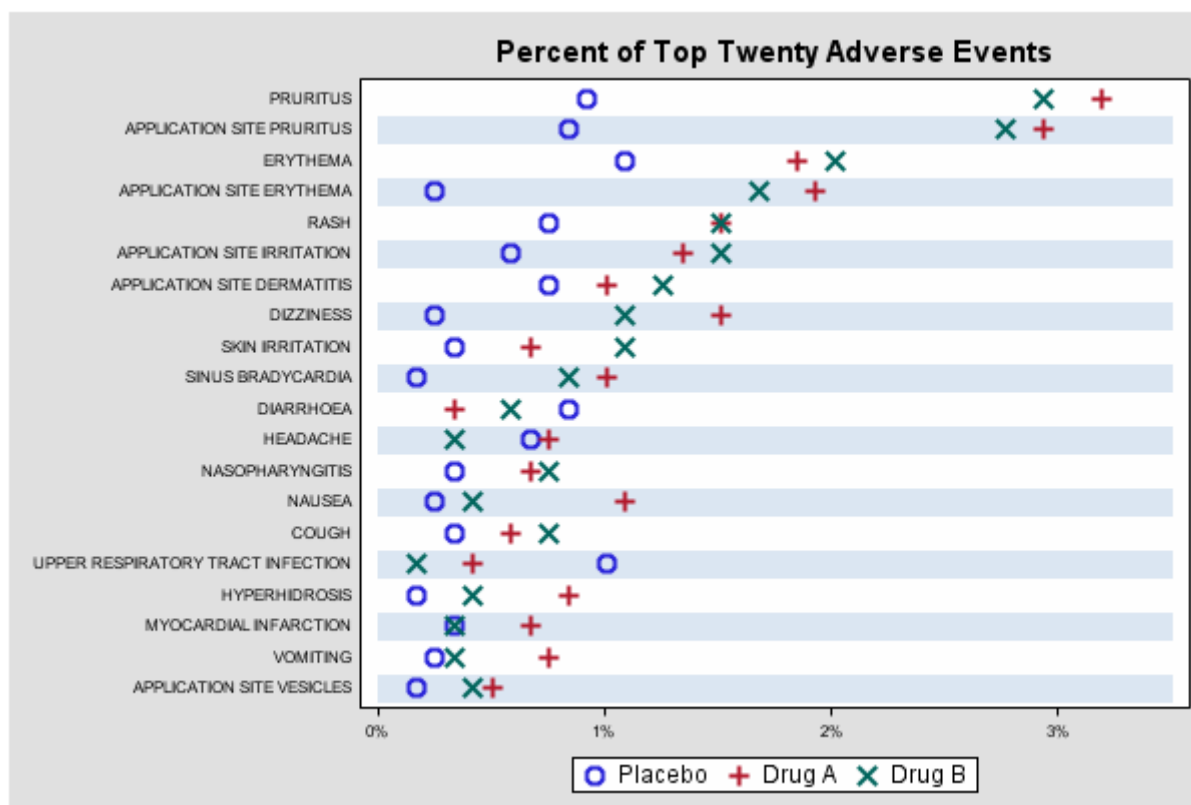
Figure 1. Bar Chart Display of AE by Intensity

# Clinical Question: Which AEs are elevated in treatment vs. control?

## Grouped Dotplot



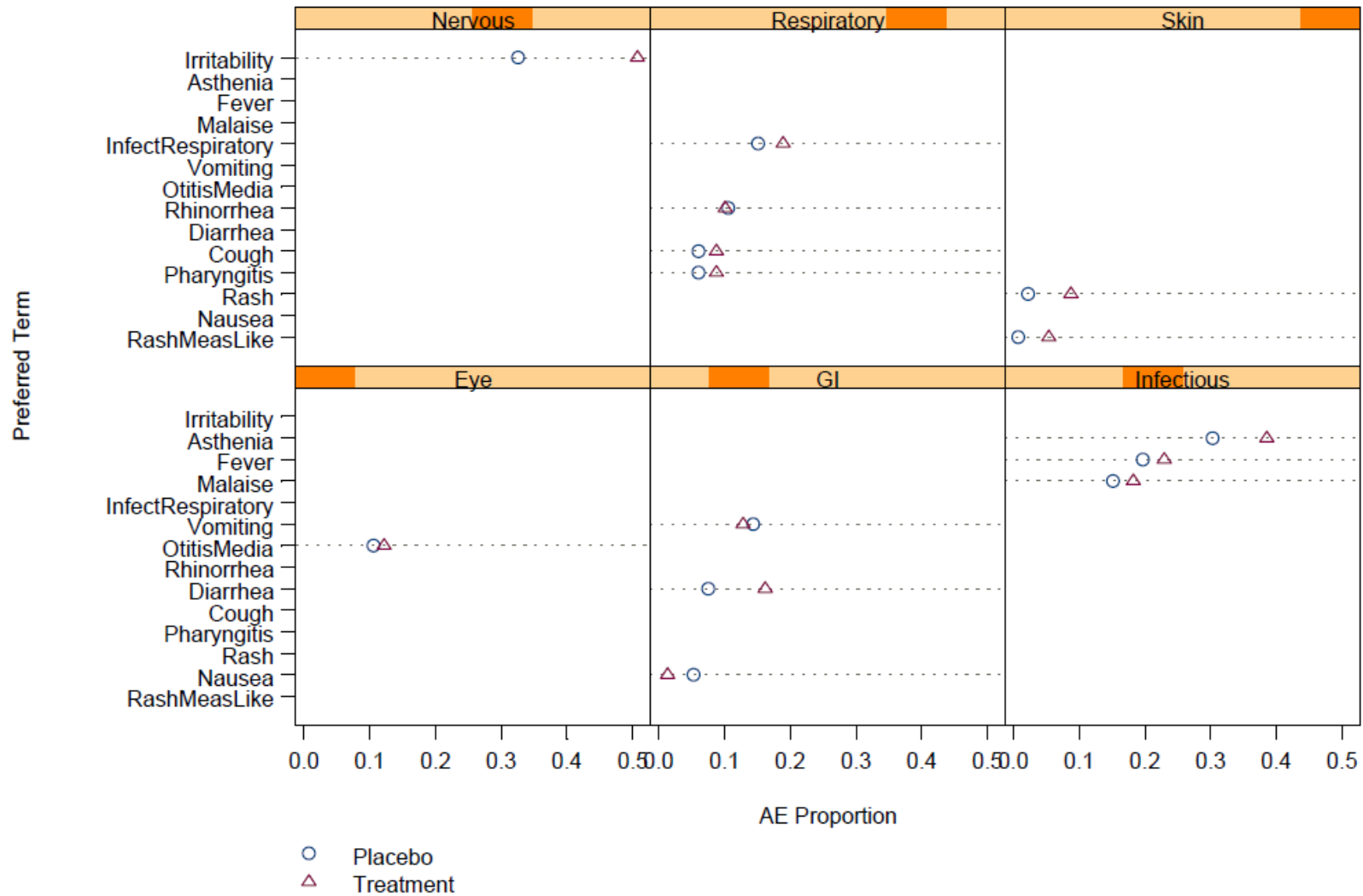
# Clinical Question: Which AEs are elevated in treatment vs. control?



[http://support.sas.com/sassamples/graphgallery/Health\\_and\\_Life\\_Sciences\\_Industry.html](http://support.sas.com/sassamples/graphgallery/Health_and_Life_Sciences_Industry.html)  
With SAS code

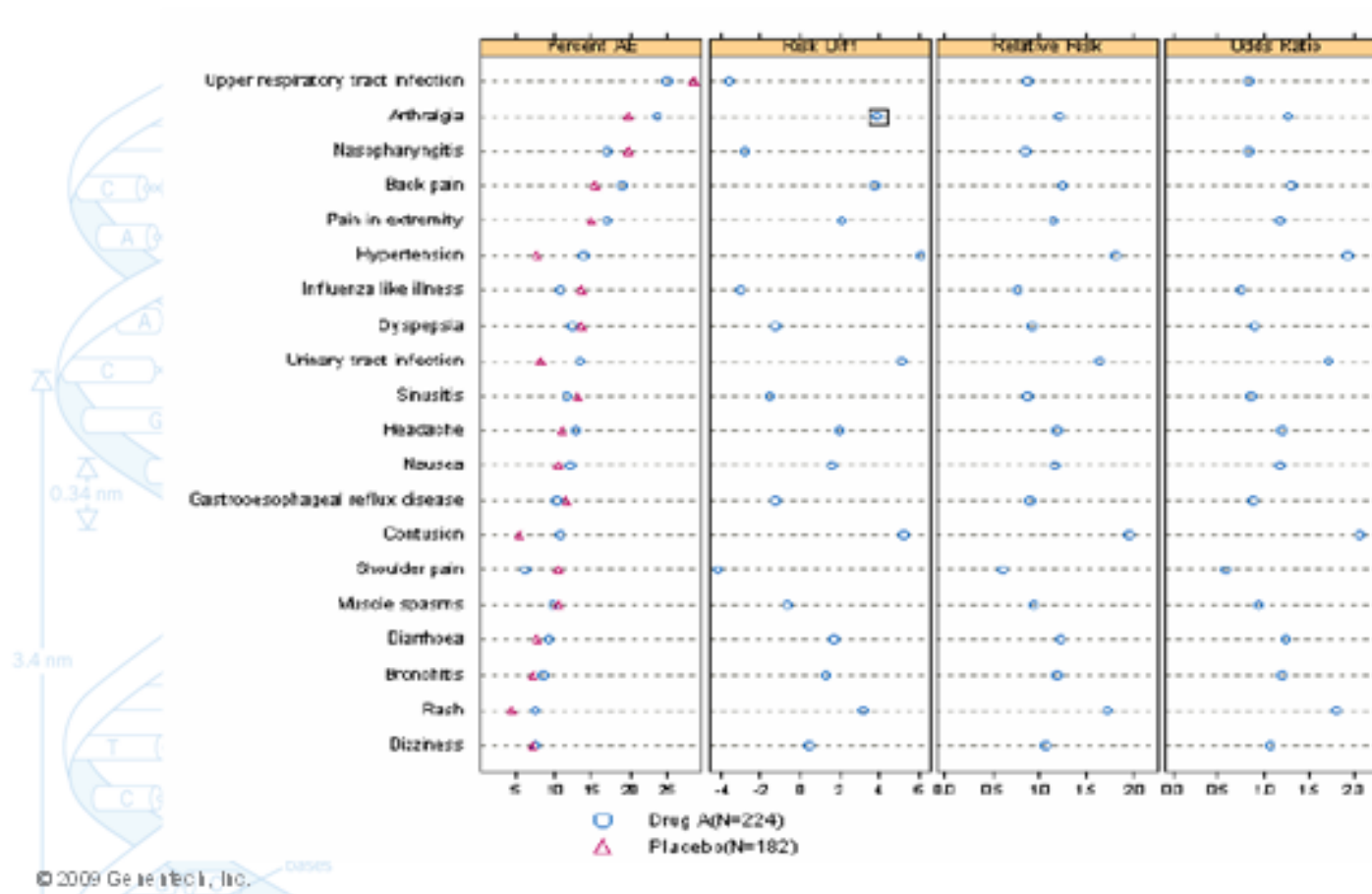
Clinical Question: Which AEs are elevated in treatment vs. control?

**Grouped Trellis Dotplot**



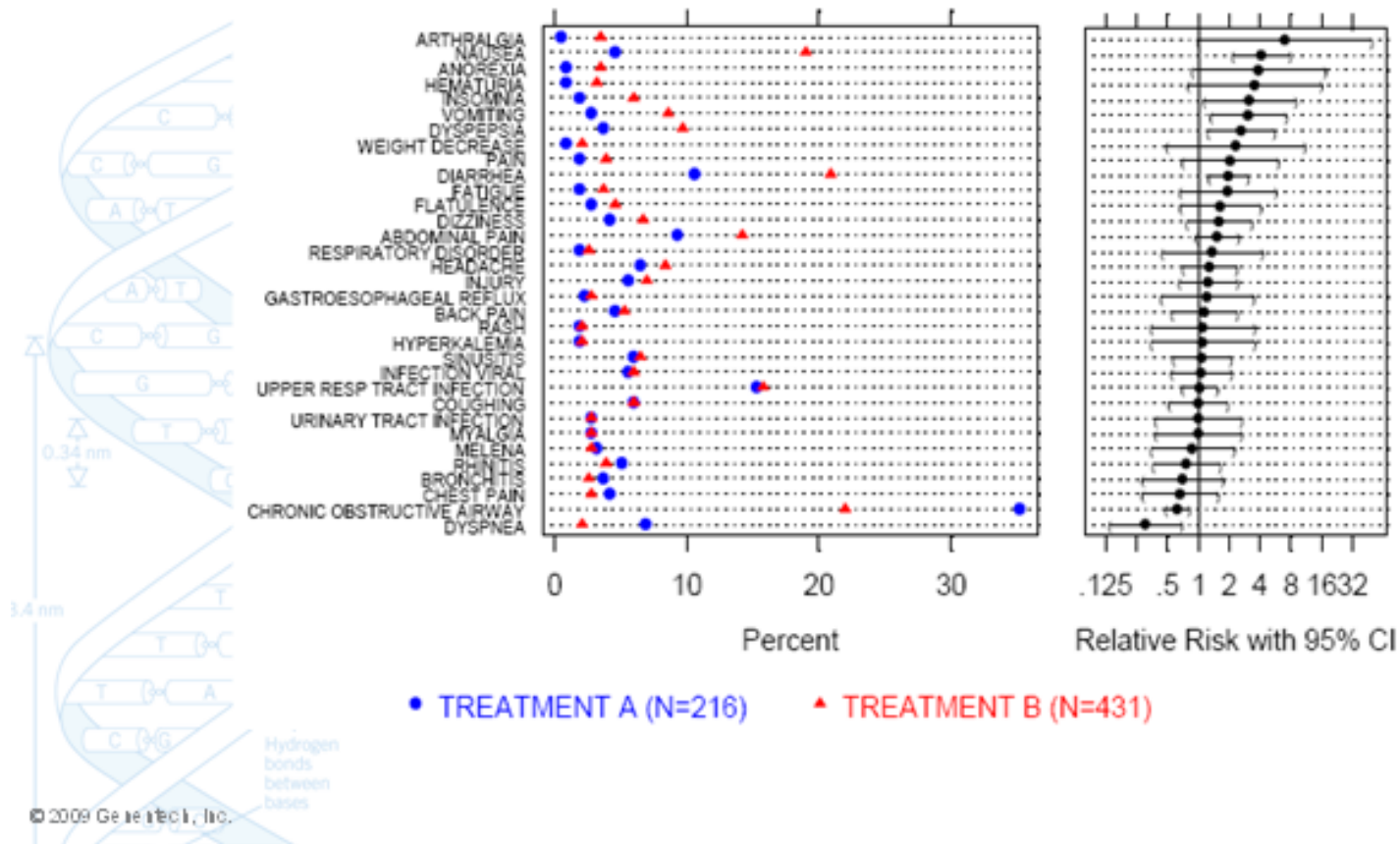
# Clinical Question: Which AEs are elevated in treatment vs. control?

Figure 2. Adverse Event  $\geq 5\%$  by Preferred Term in Descending Order of Frequency



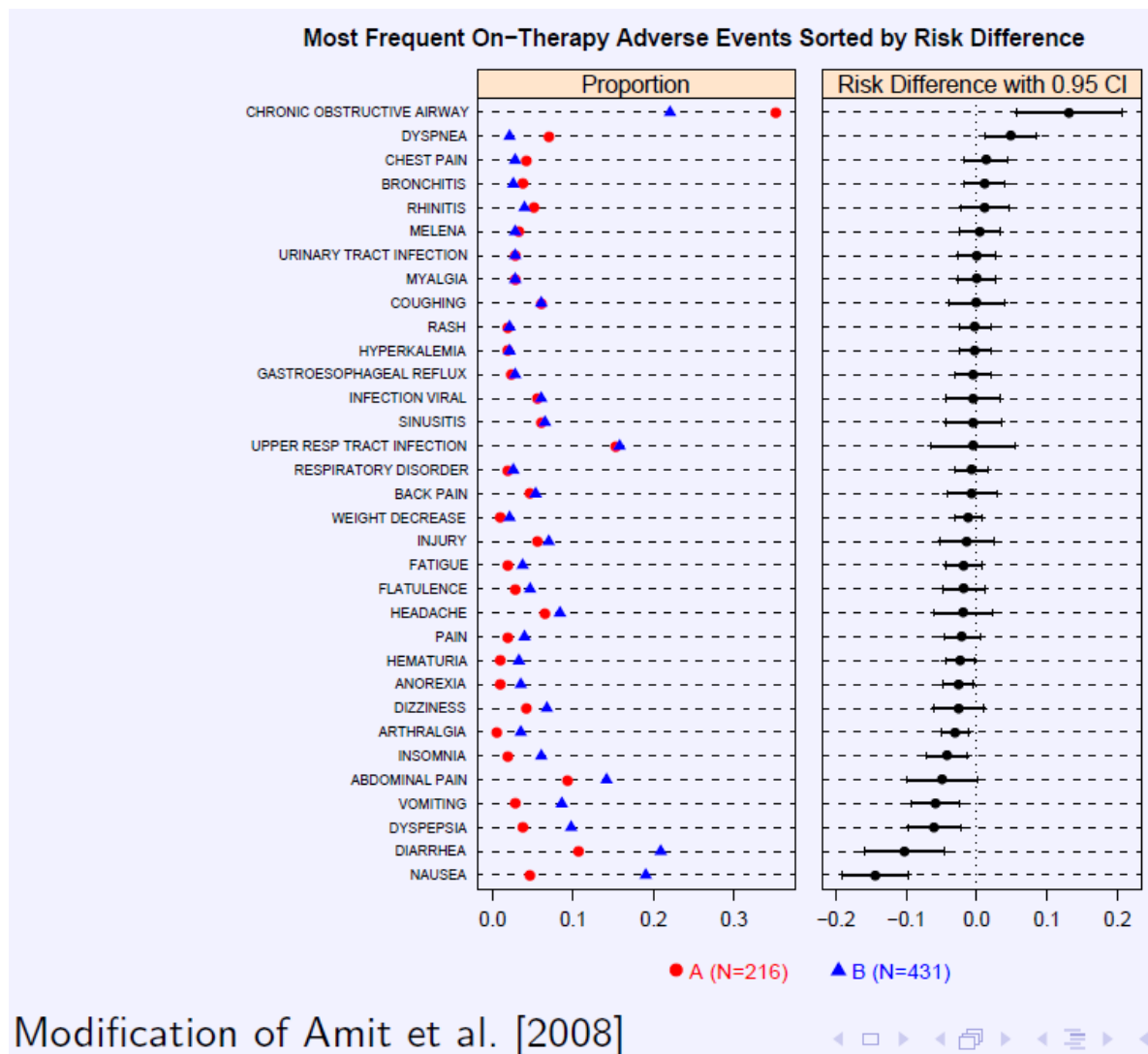
# Clinical Question: Which AEs are elevated in treatment vs. control?

Figure 1. Dot Plot to compare incidence rate and relative risk





# Clinical Question: Which AEs are elevated in treatment vs. control?



## Clinical Question: Which AEs are elevated in treatment vs. control?

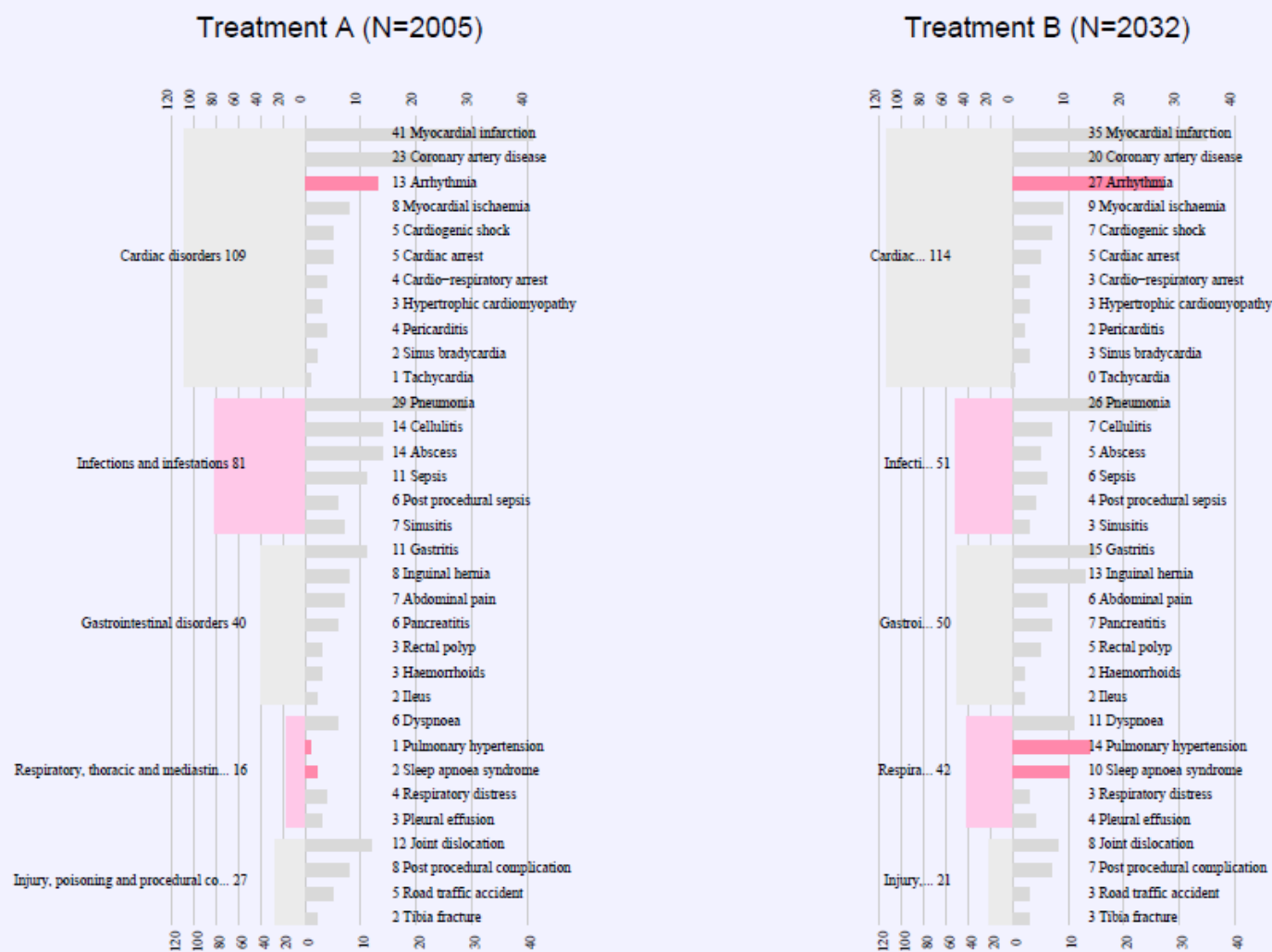
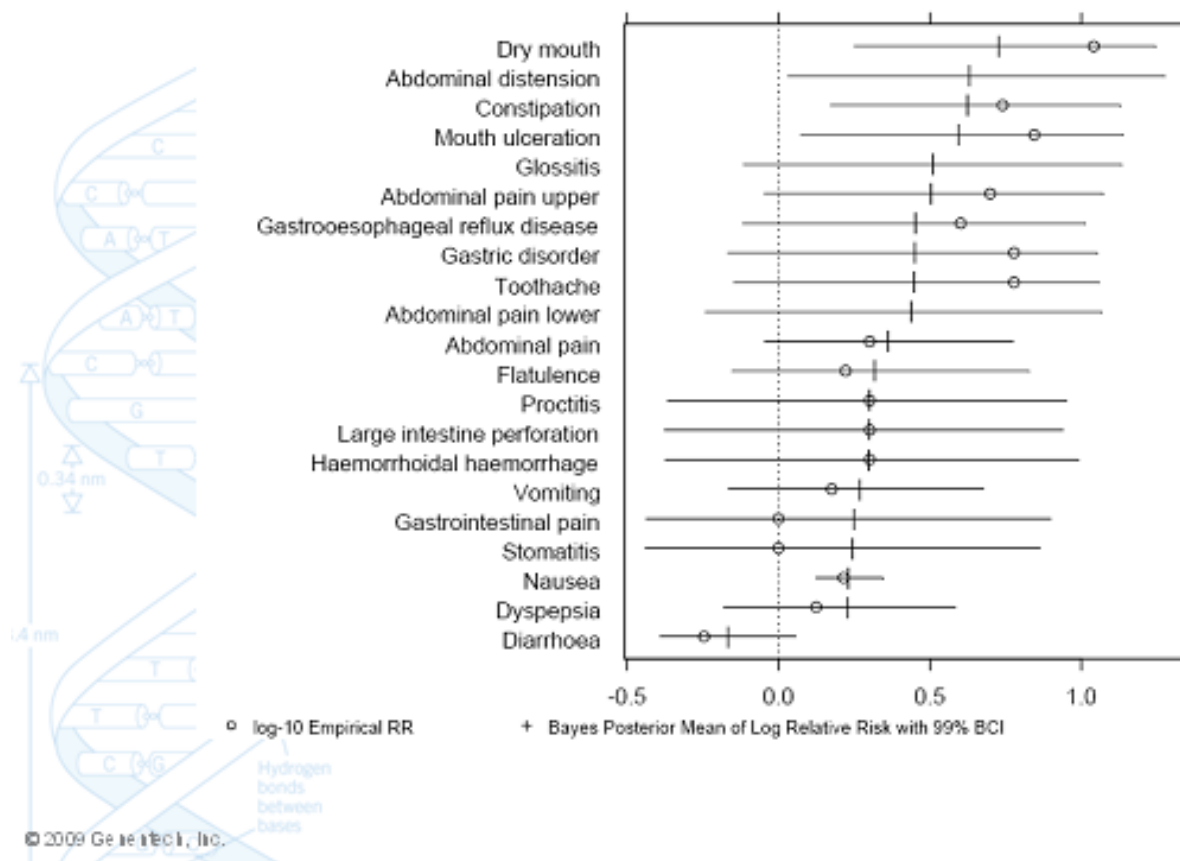


Figure 2.20: Serious AE frequency display by body system and preferred term. Widths of body system rectangles is proportional to the number of subjects having an event in that body system. The small bars denote the number of subjects who had a particular event. If the between-treatment difference in proportions of subjects having events is significant ( $P < 0.05$ ), the corresponding rectangles/bar charts in both treatment groups are pink/red. Graphic designed and implemented in R in the `rreport` package by Svetlana Eden, VU Dept. of Biostatistics.

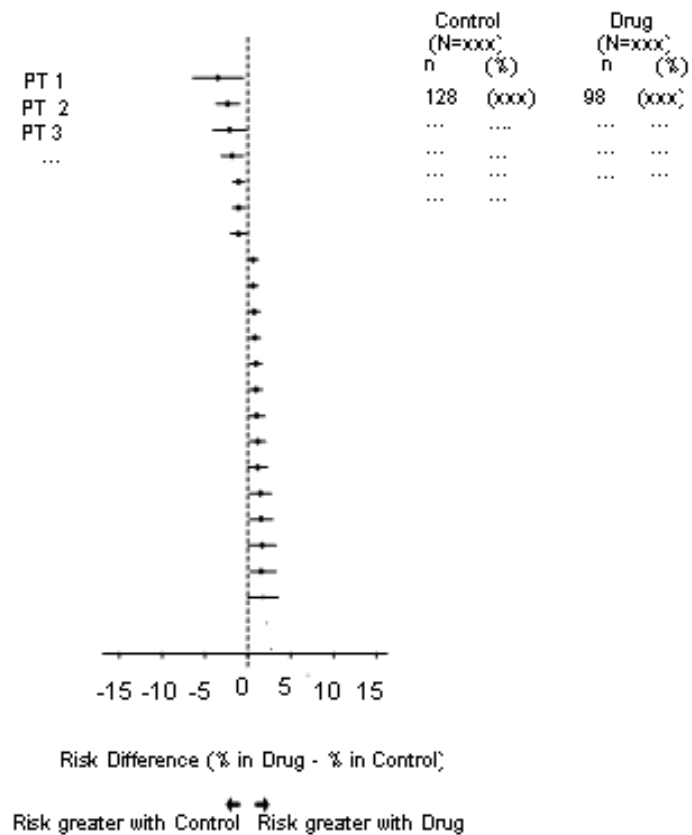
# Clinical Question: Which AEs are elevated in treatment vs. control?

Figure 3. AE Dot Plot with Interval Pattern

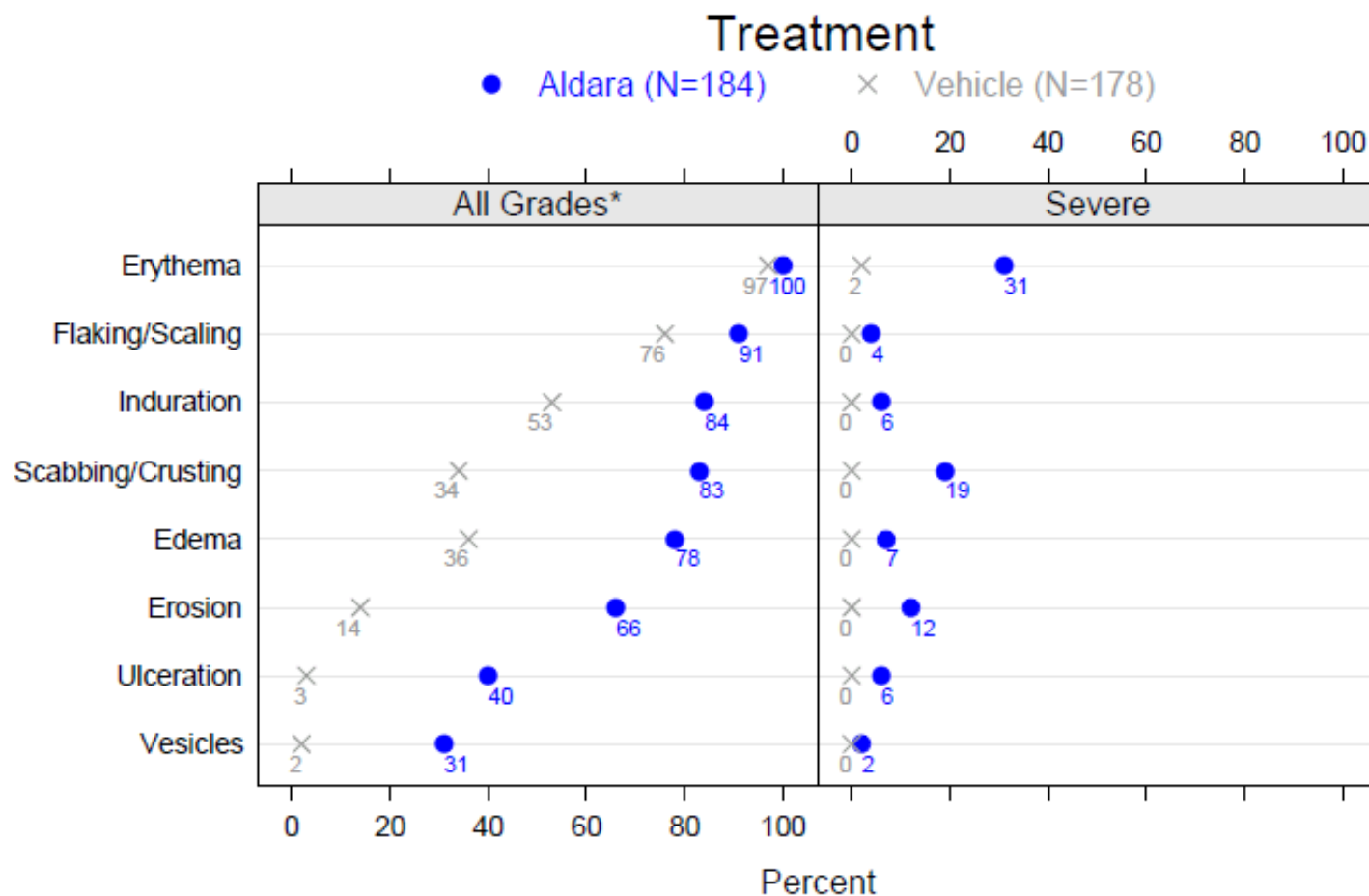


# Clinical Question: Which AEs are elevated in treatment vs. control?

## Forest Plot of Adverse Events with Unadjusted P-value <0.05



*Clinical Question: Which AEs are elevated in treatment vs. control?*



\*Mild, Moderate, or Severe

*Clinical Question: Which AEs are elevated in treatment vs. control?*

(%) Comparison of On-Therapy Serious Adverse Events By Treatment

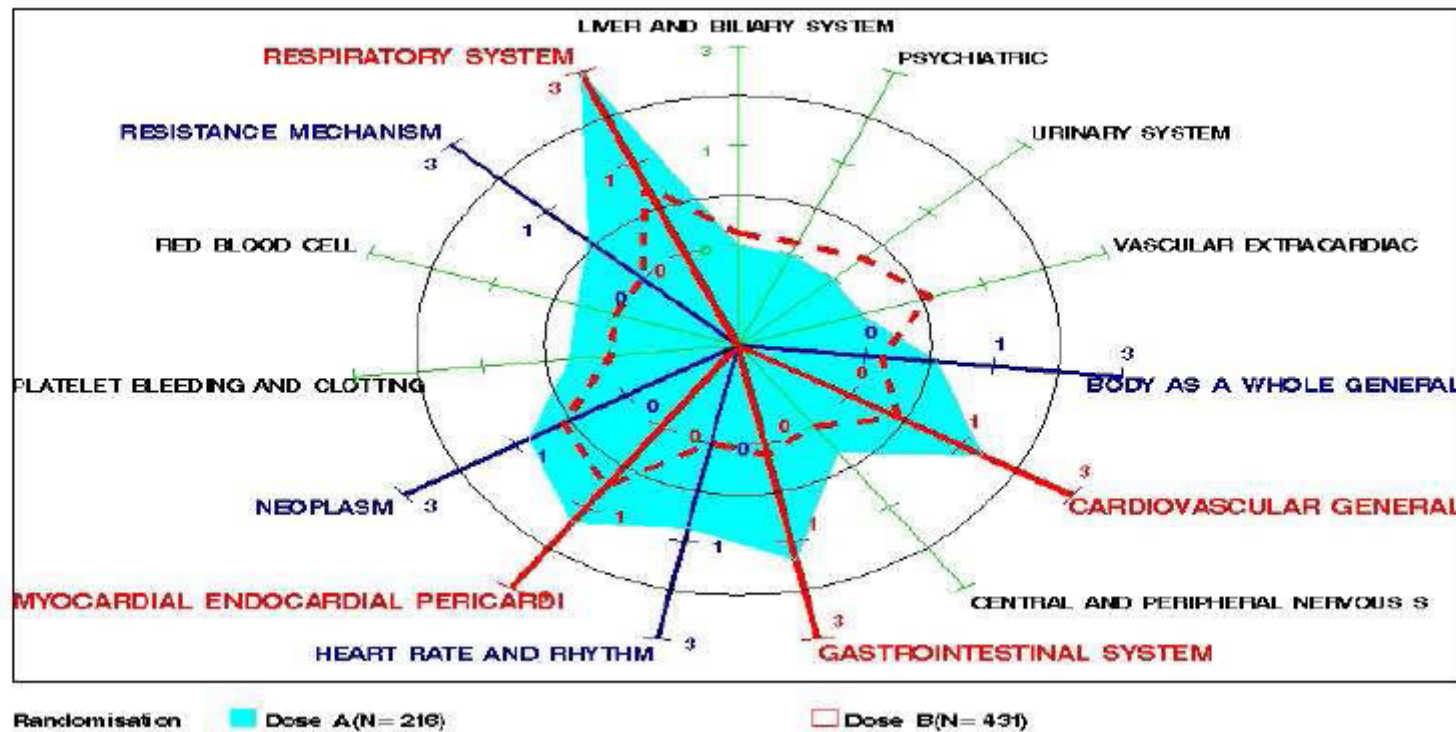
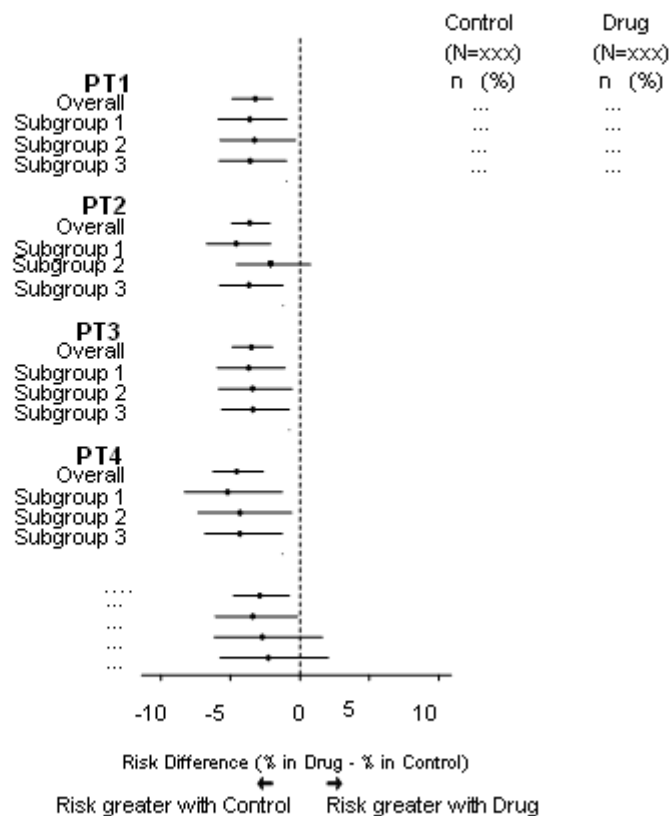


Figure 11 Radar Chart for Serious AEs Display

# Clinical Question: Which adverse events are elevated in patient subgroups?

Forest Plot of Adverse Events with Unadjusted P-value <0.05 (Overall and Subgroup)



## Clinical Question: Which adverse events are elevated in patient subgroups?

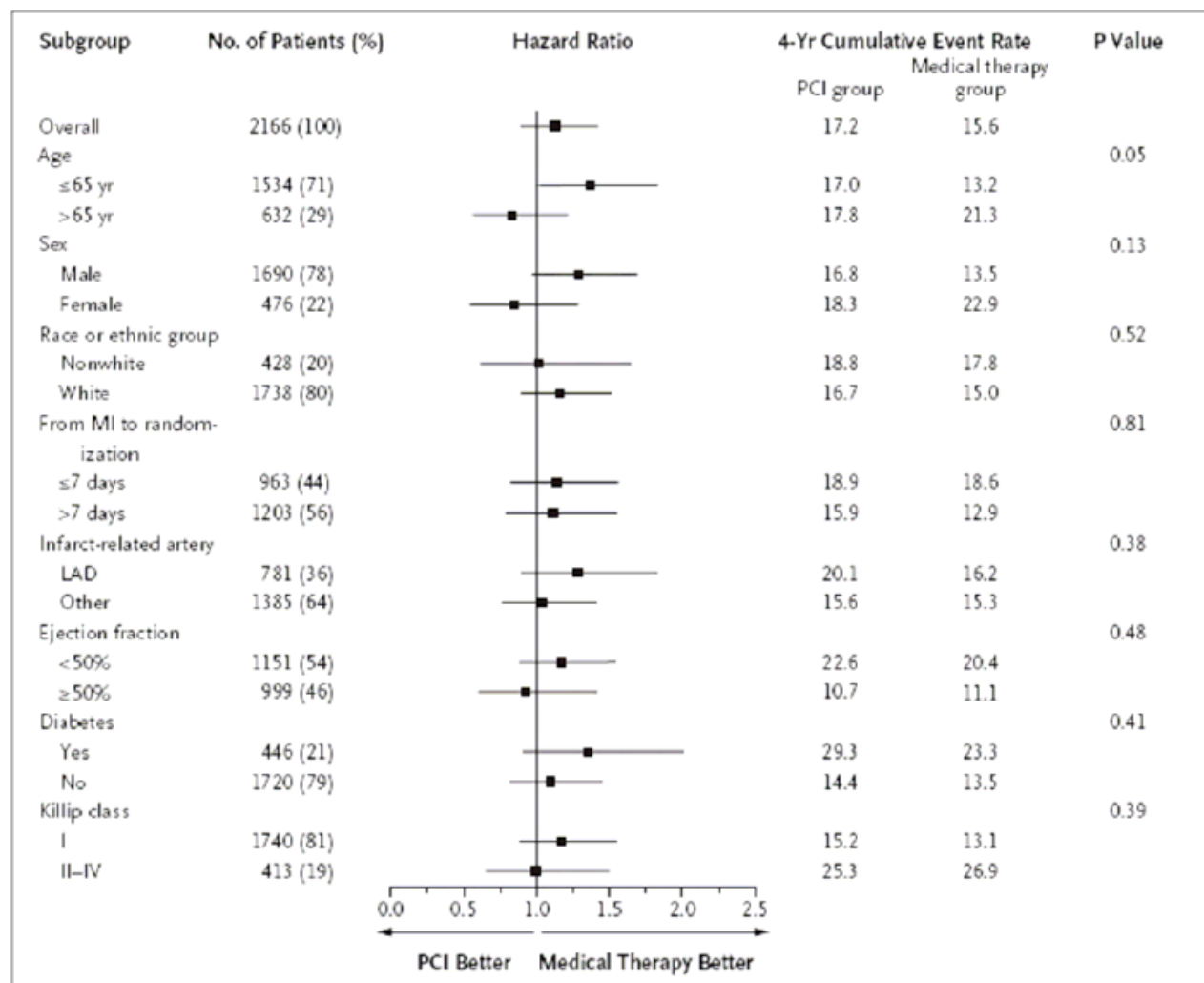


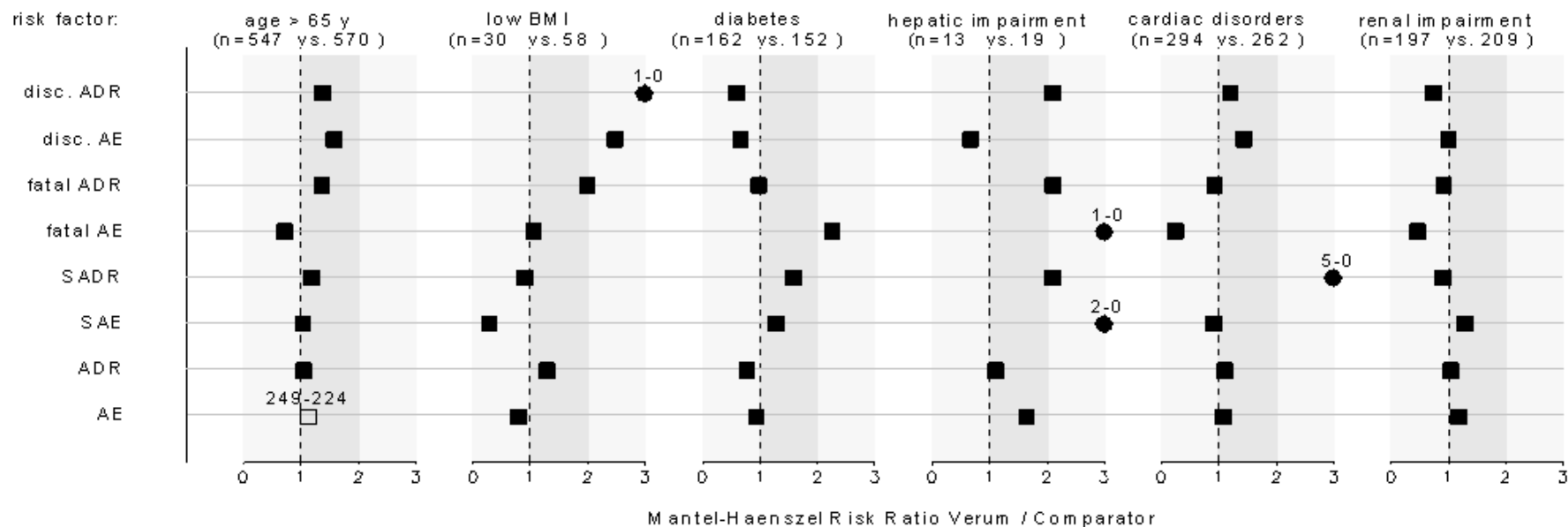
Figure 10  
Subgroup Analysis. Hazard ratios (black squares), 95% CIs (horizontal lines), P values for the interaction between the treat-

**Figures in clinical trial reports: current practice & scope for improvement**

Stuart J Pocock\*<sup>1</sup>, Thomas G Trivison<sup>2</sup> and Lisa M Wruck<sup>2,3</sup>

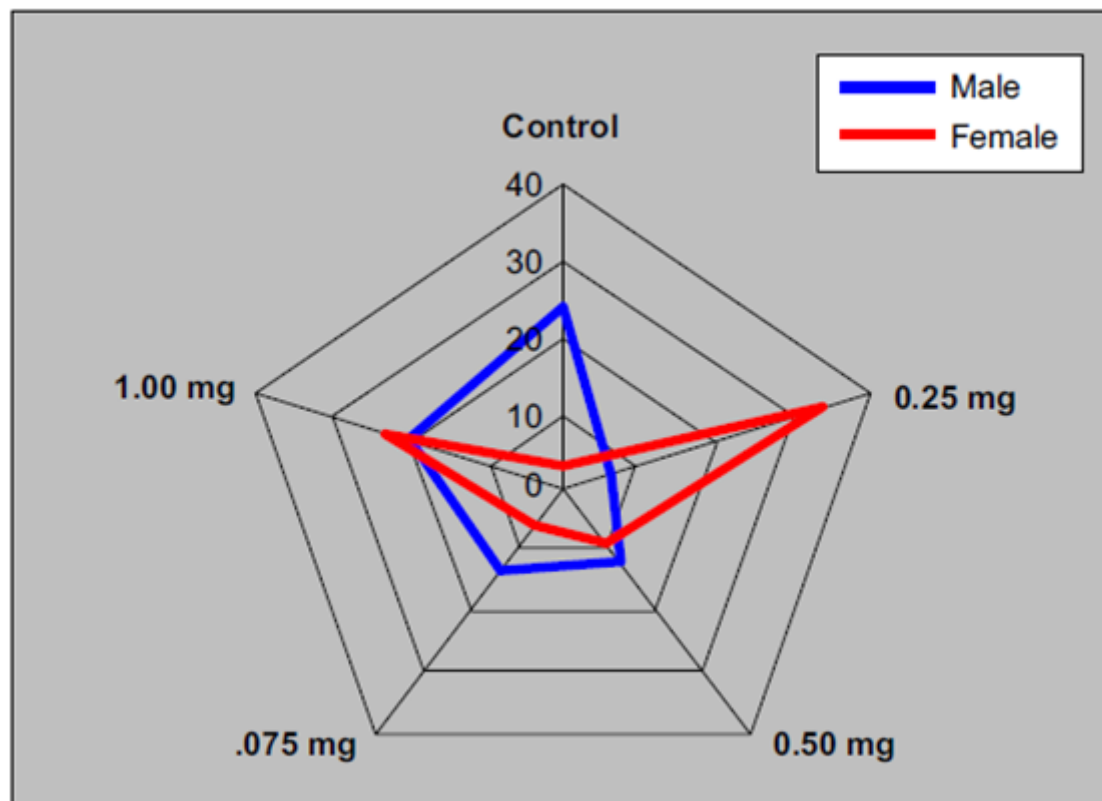


# Clinical Question: Which adverse events are elevated in patient subgroups?



Note: Stratified Mantel-Haenszel Risk Ratio estimates were calculated with a continuity correction of 0.1.  
 Note: A circle indicates a Mantel-Haenszel Risk Ratio estimate above three.  
 Note: An empty symbol indicates a lower confidence limit bound above one.

*Clinical Question: Which adverse events are elevated in patient subgroups?*

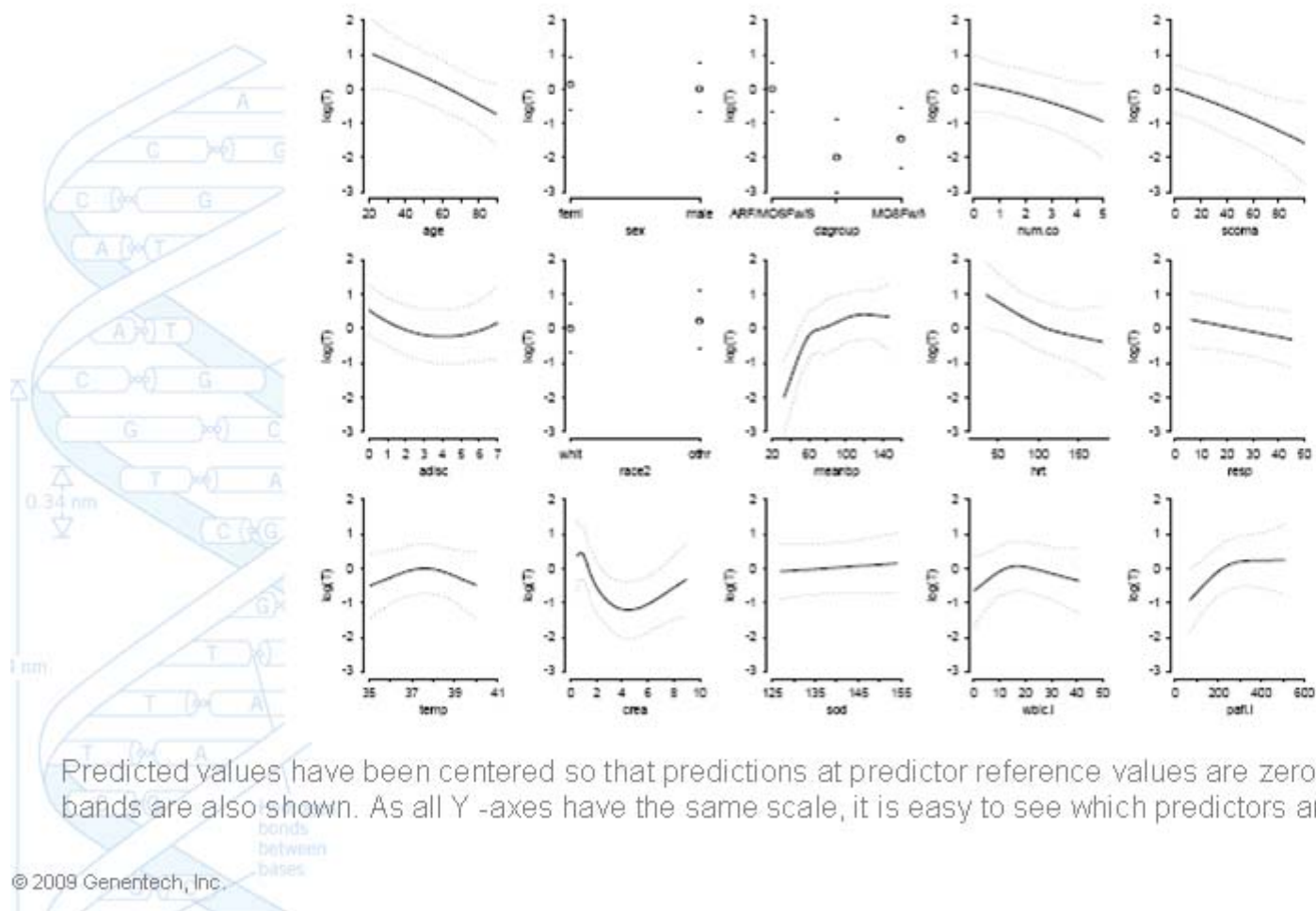


Radar plots: a useful way for presenting multivariate health care data

M. Joan Saary<sup>a,b,\*</sup>

## Clinical Question: **Potential risk factors or temporal relationship of AE?**

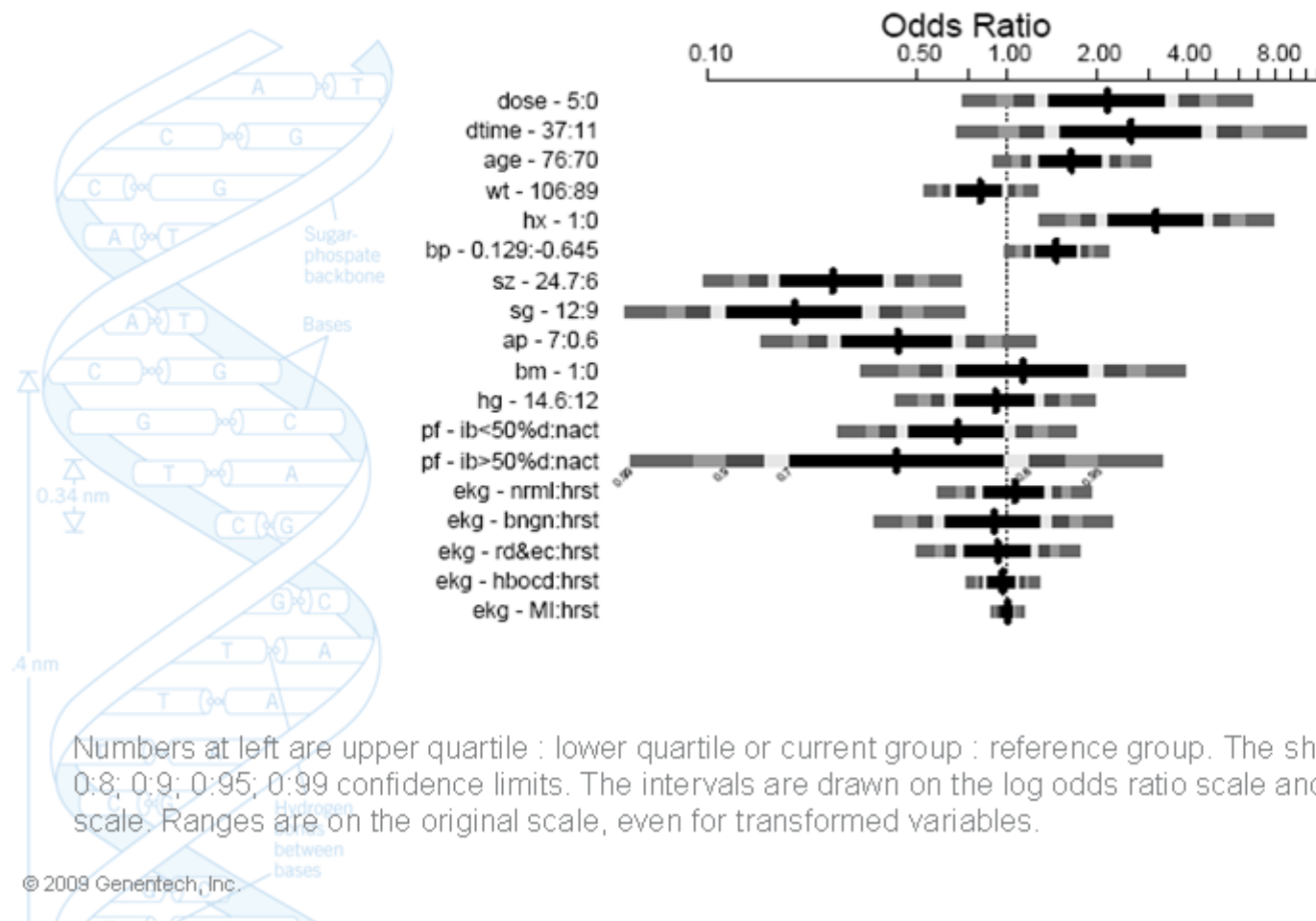
Figure 1. Effect of each predictor on log survival time



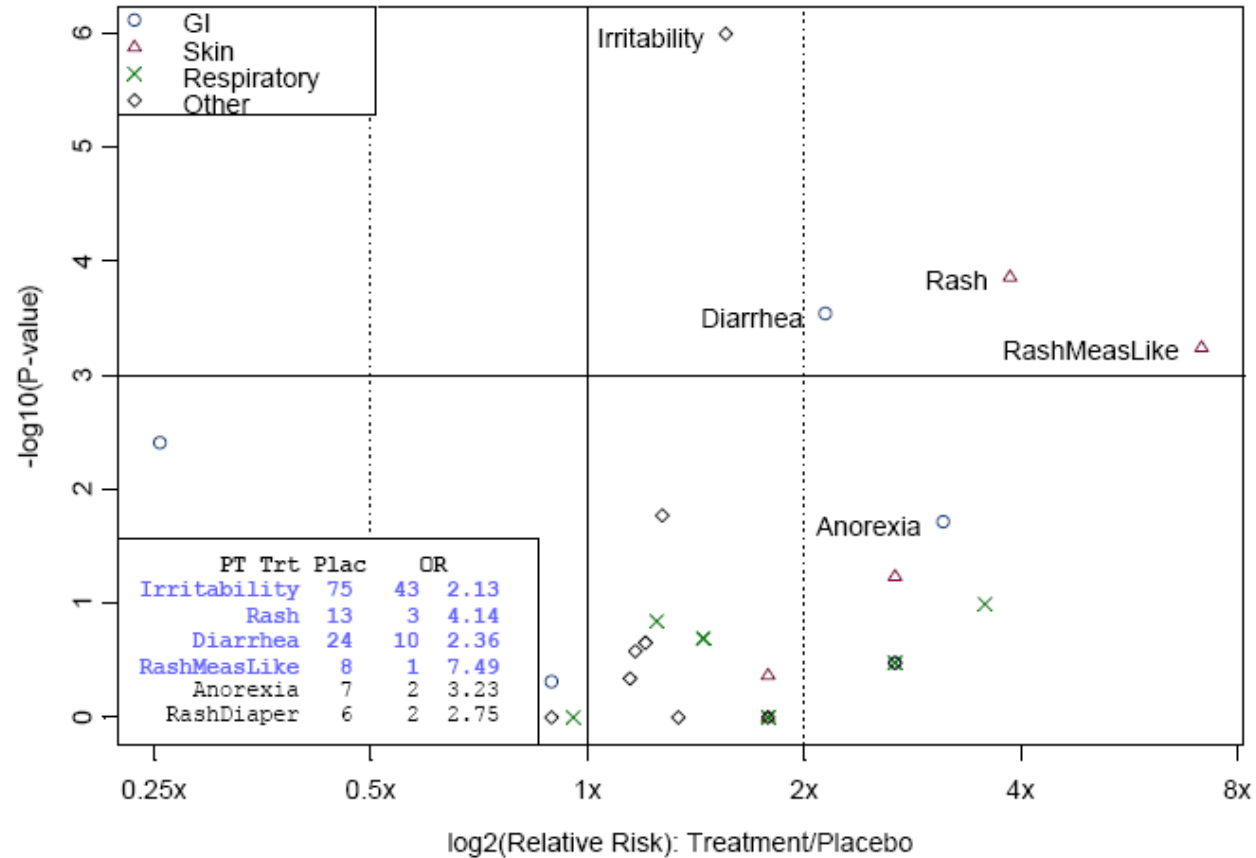
## Clinical Question: **Potential risk factors or temporal relationship of AE?**

### Risk Factors in Relation to AEs

Figure 2. Inter-quartile-range odds ratios for continuous predictors and simple odds ratios for categorical predictors



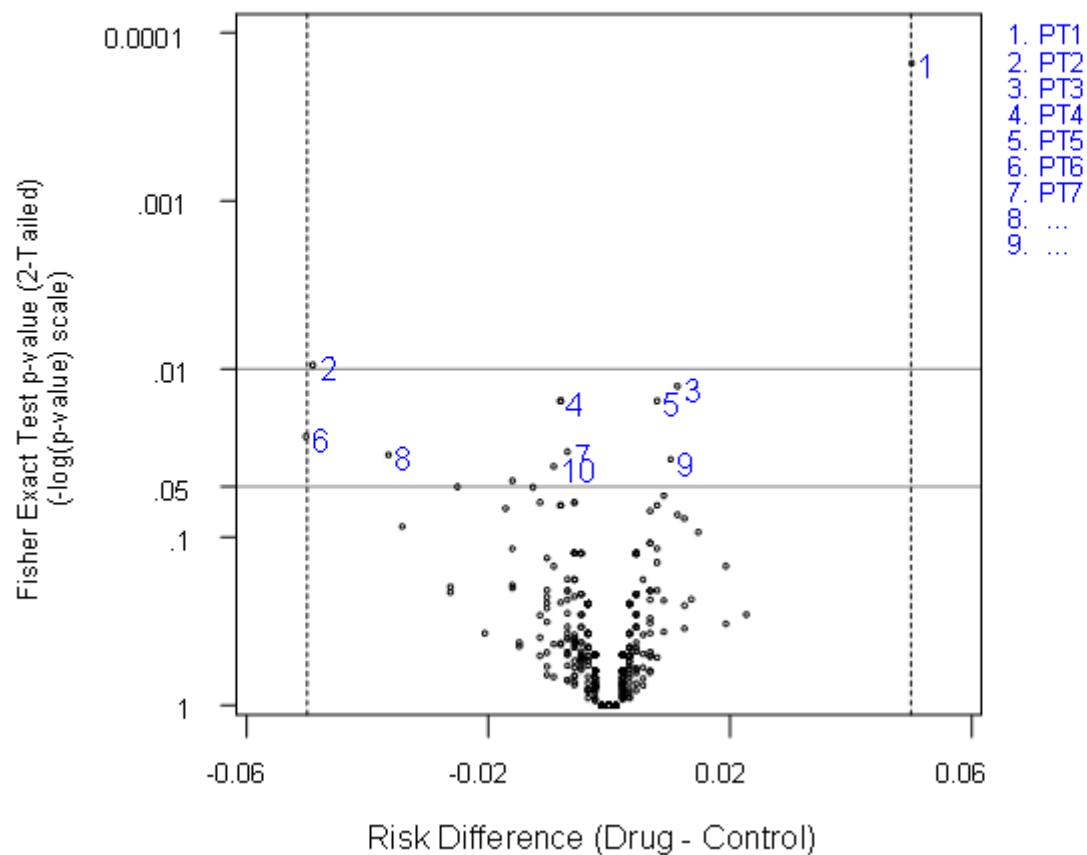
*Clinical Question: Which AEs are elevated in treatment vs. control?*  
*Clinical Question: What is the safety profile of the drug?*  
 Volcano Plot



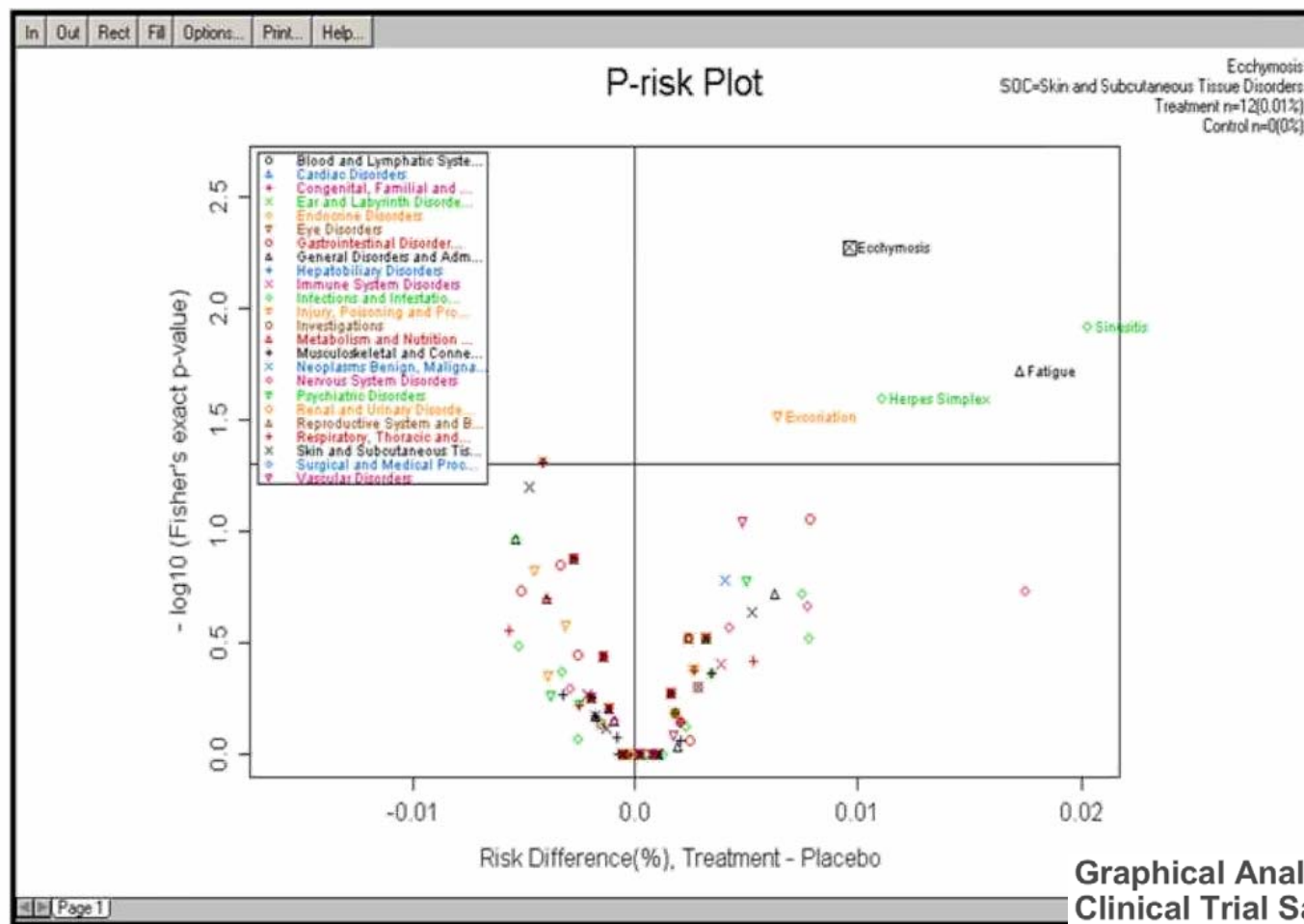
\*It shows the relative risk or ratio of the adverse event rates on the x-axis and the p-value comparing treatment and control on the y-axis. The additional information on the p-value of the treatment effect is important since it incorporates the number of observed events and confidence in the treatment effect.

*Clinical Question: Which AEs are elevated in treatment vs. control?*  
*Clinical Question: What is the safety profile of the drug?*  
Volcano Plot

Relationship Between Risk Difference and P-value for Adverse Events by Preferred Term



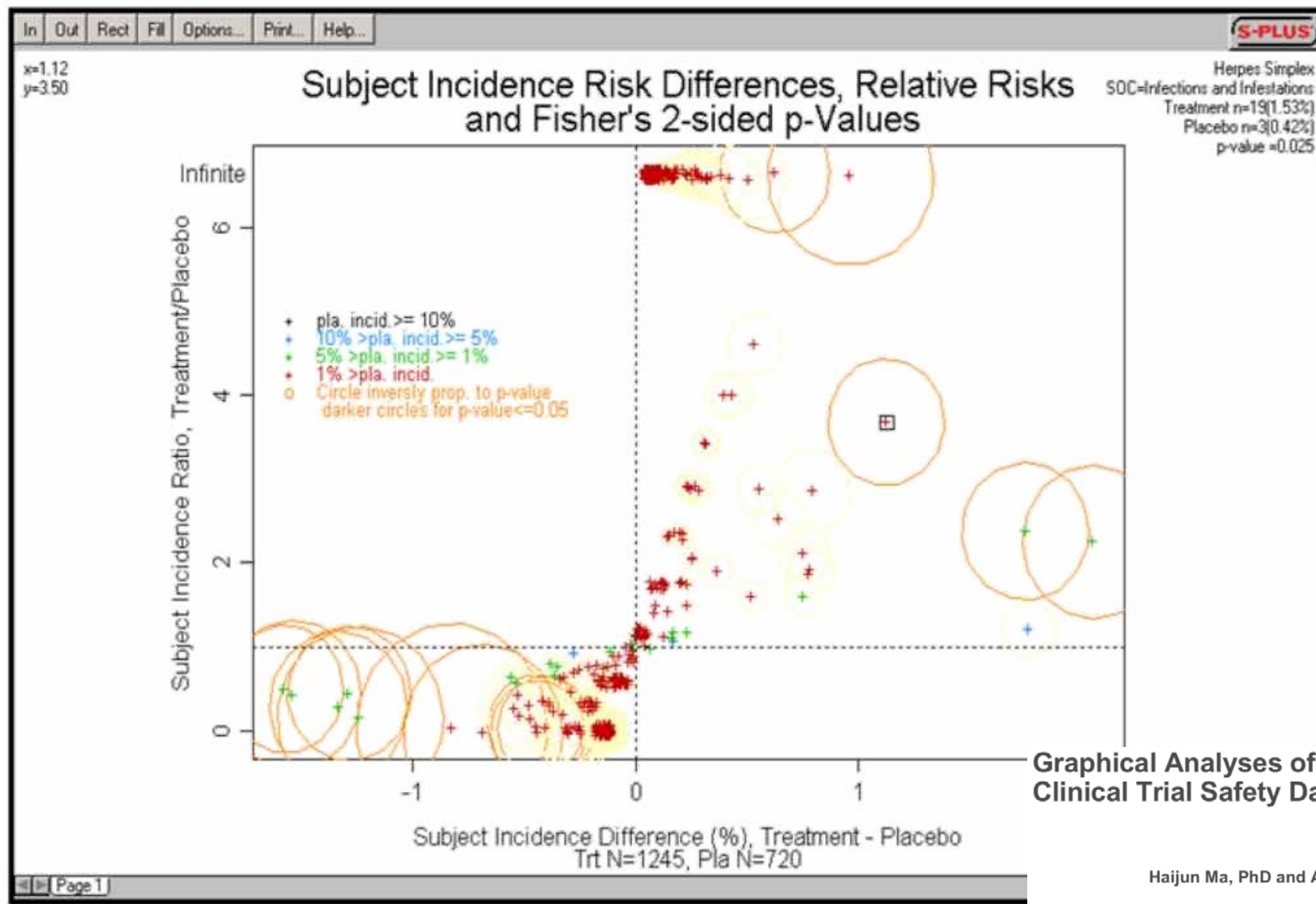
*Clinical Question: Which AEs are elevated in treatment vs. control?*  
*Clinical Question: What is the safety profile of the drug?*  
 Volcano Plot



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Clinical Question: Which AEs are elevated in treatment vs. control?  
 Clinical Question: What is the safety profile of the drug?

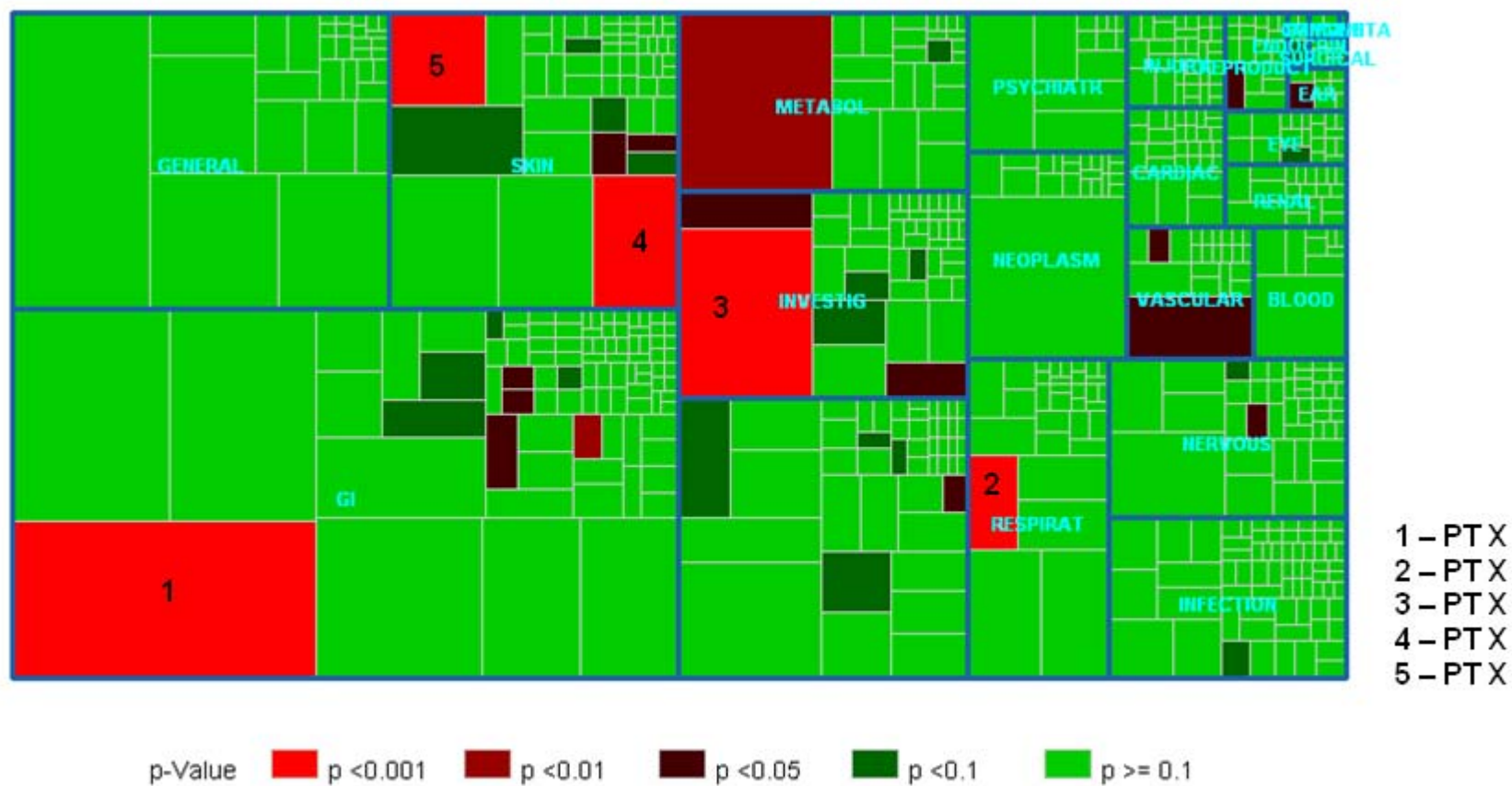


Graphical Analyses of Clinical Trial Safety Data

Haijun Ma, PhD and Amy Xia, PhD

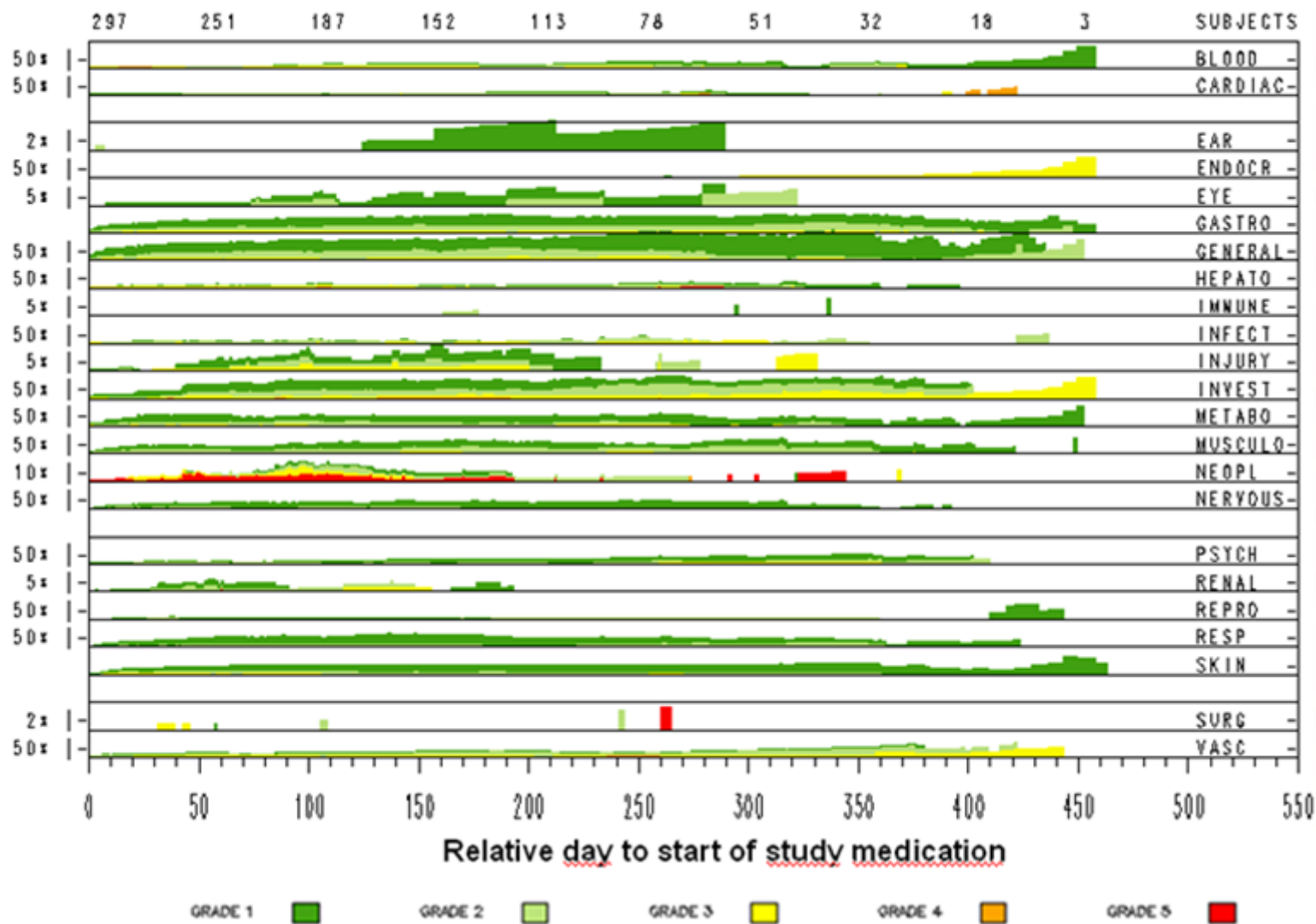


Clinical Question: Which AEs are elevated in treatment vs. control?  
 Clinical Question: What is the safety profile of the drug?  
 Treemap

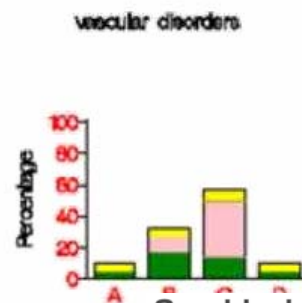
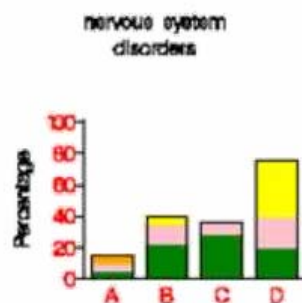
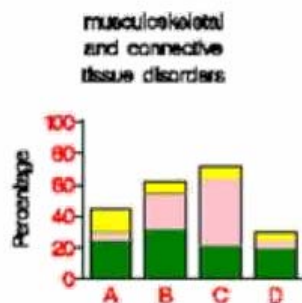
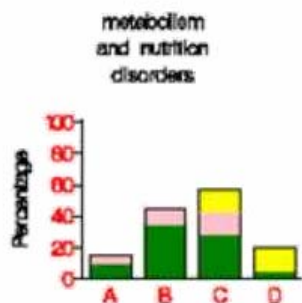
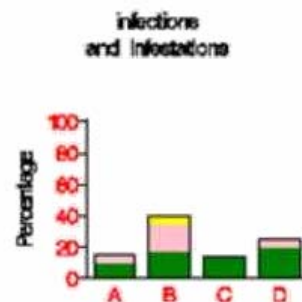
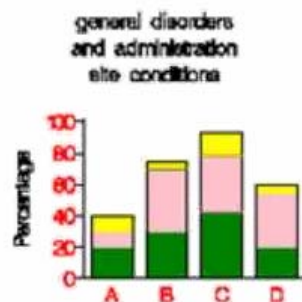
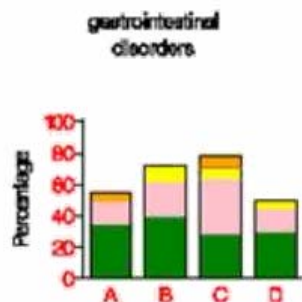
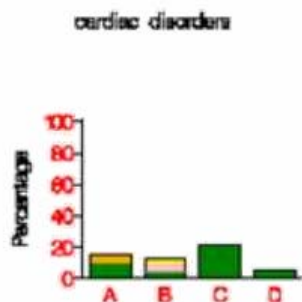


# Clinical Question: What is the safety profile of the drug?

## Horizon Plot



# Clinical Question: What is the safety profile of the drug?

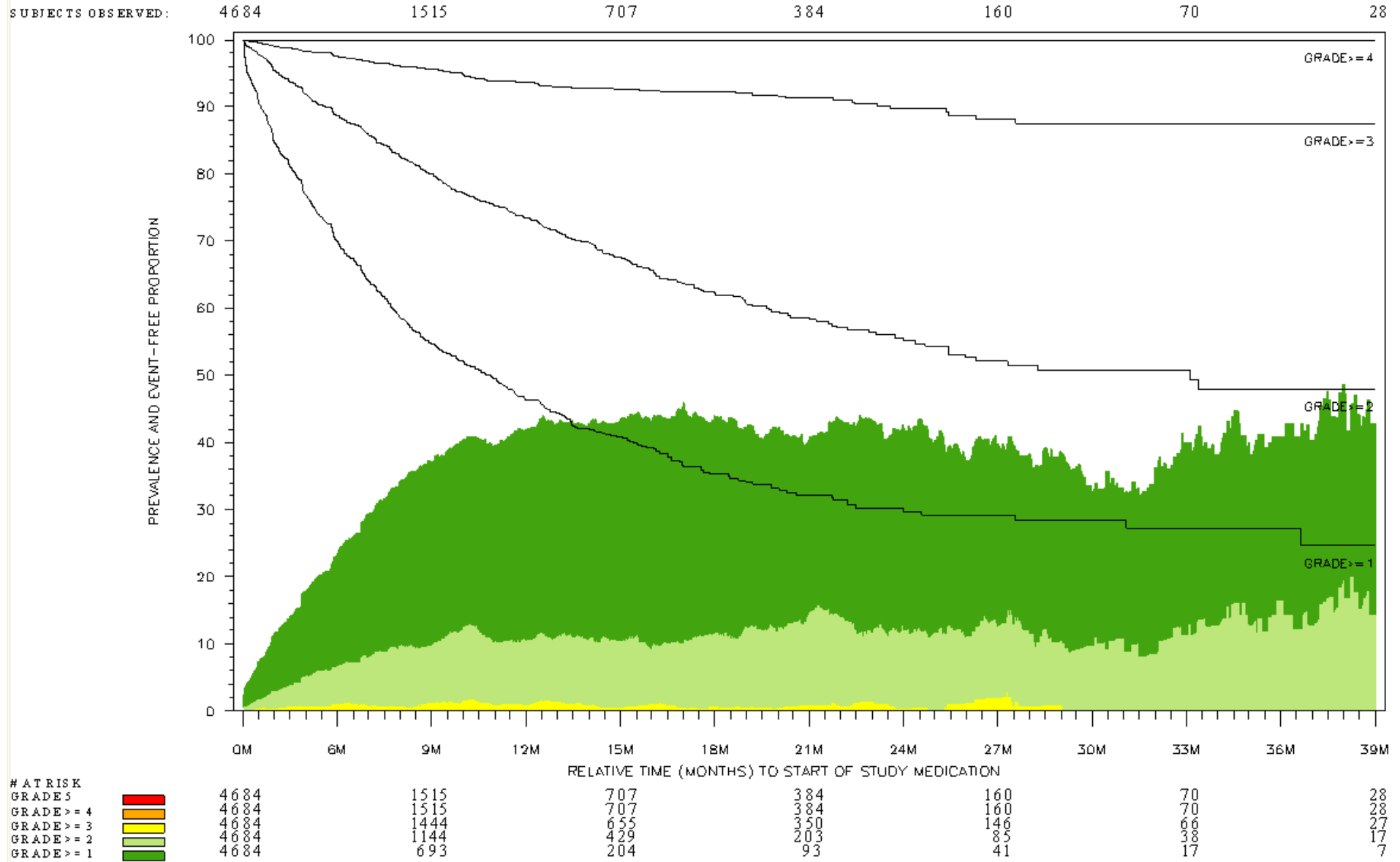


Graphical Analyses of Clinical Trial Safety Data

Haijun Ma, PhD and Amy Xia, PhD

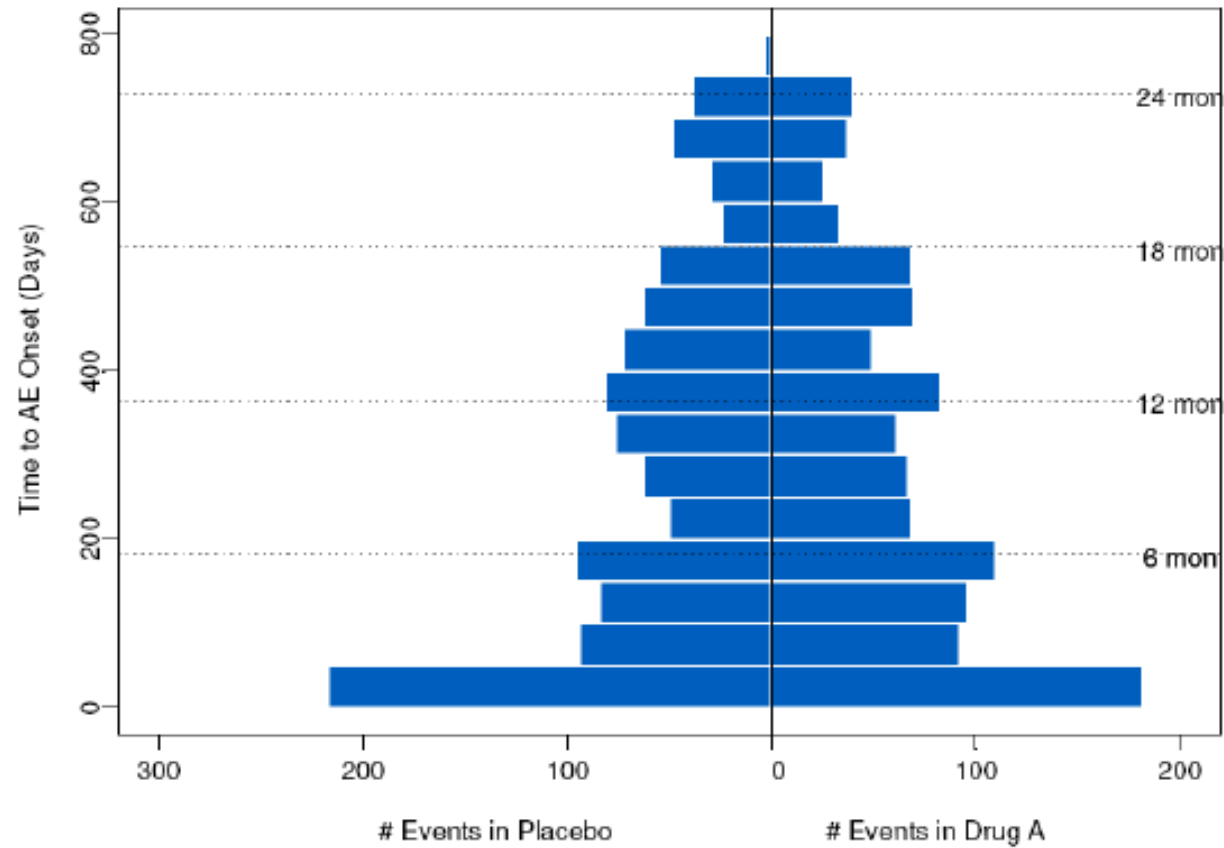
# Clinical Question: AE occurrence over time

## Incidence - Prevalence Plots



## Clinical Question: AE occurrence over time

Distribution of Days on Study to AE Onset for Subjects with AE



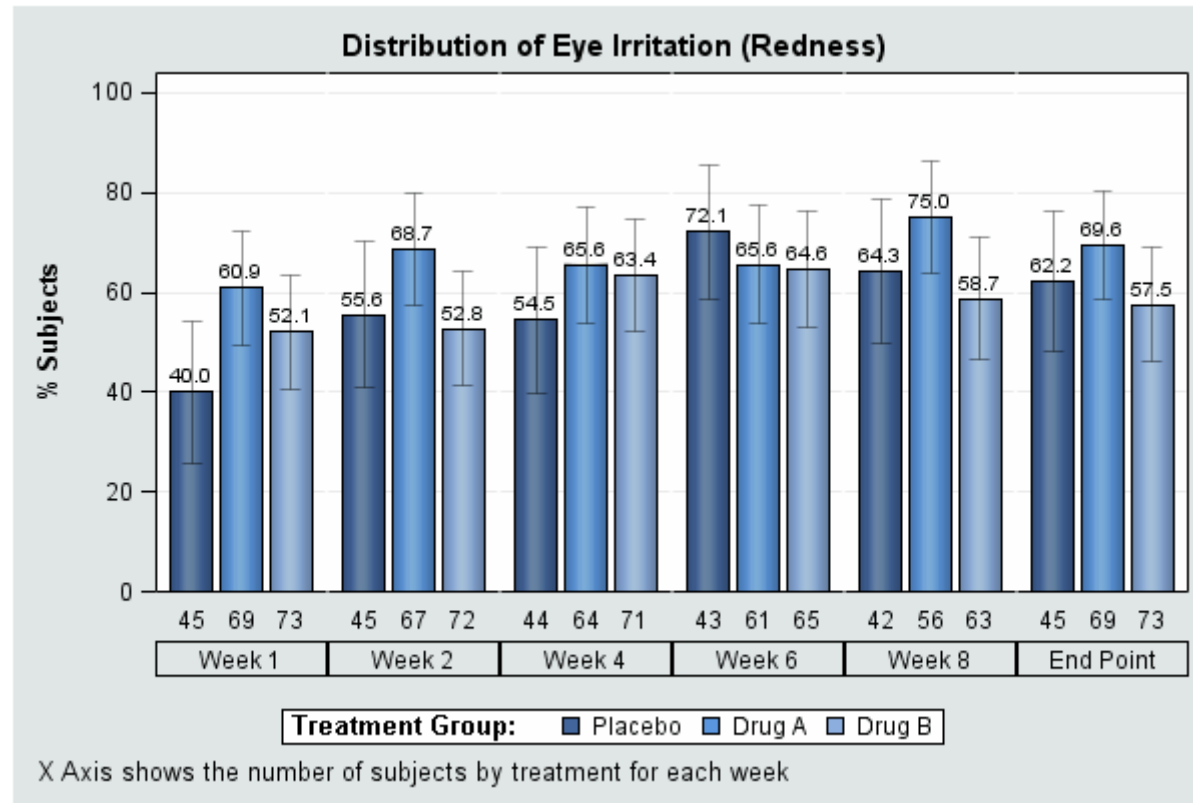
21

Graphical Analyses of  
Clinical Trial Safety Data

Haijun Ma, PhD and Amy Xia, PhD

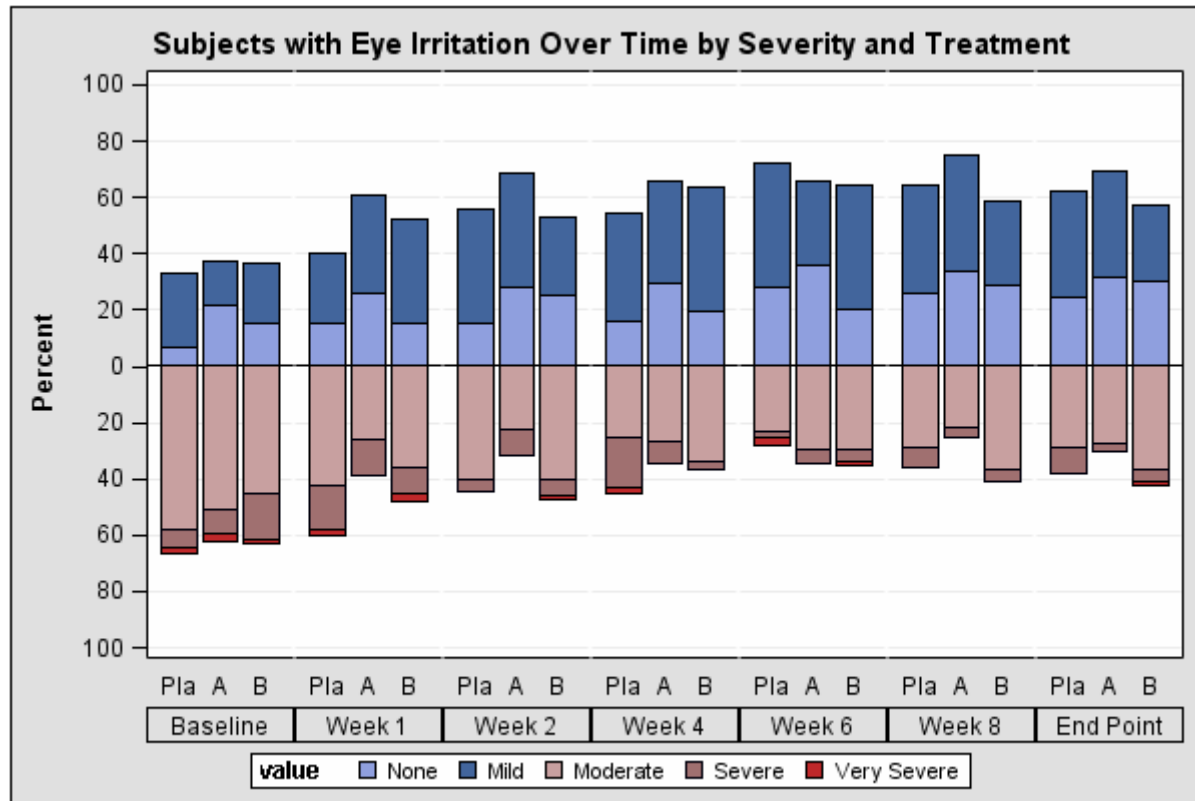
Amgen Inc.

## Clinical Question: AE occurrence over time



[http://support.sas.com/sassamples/graphgallery/Health\\_and\\_Life\\_Sciences\\_Industry.html](http://support.sas.com/sassamples/graphgallery/Health_and_Life_Sciences_Industry.html)  
With SAS code

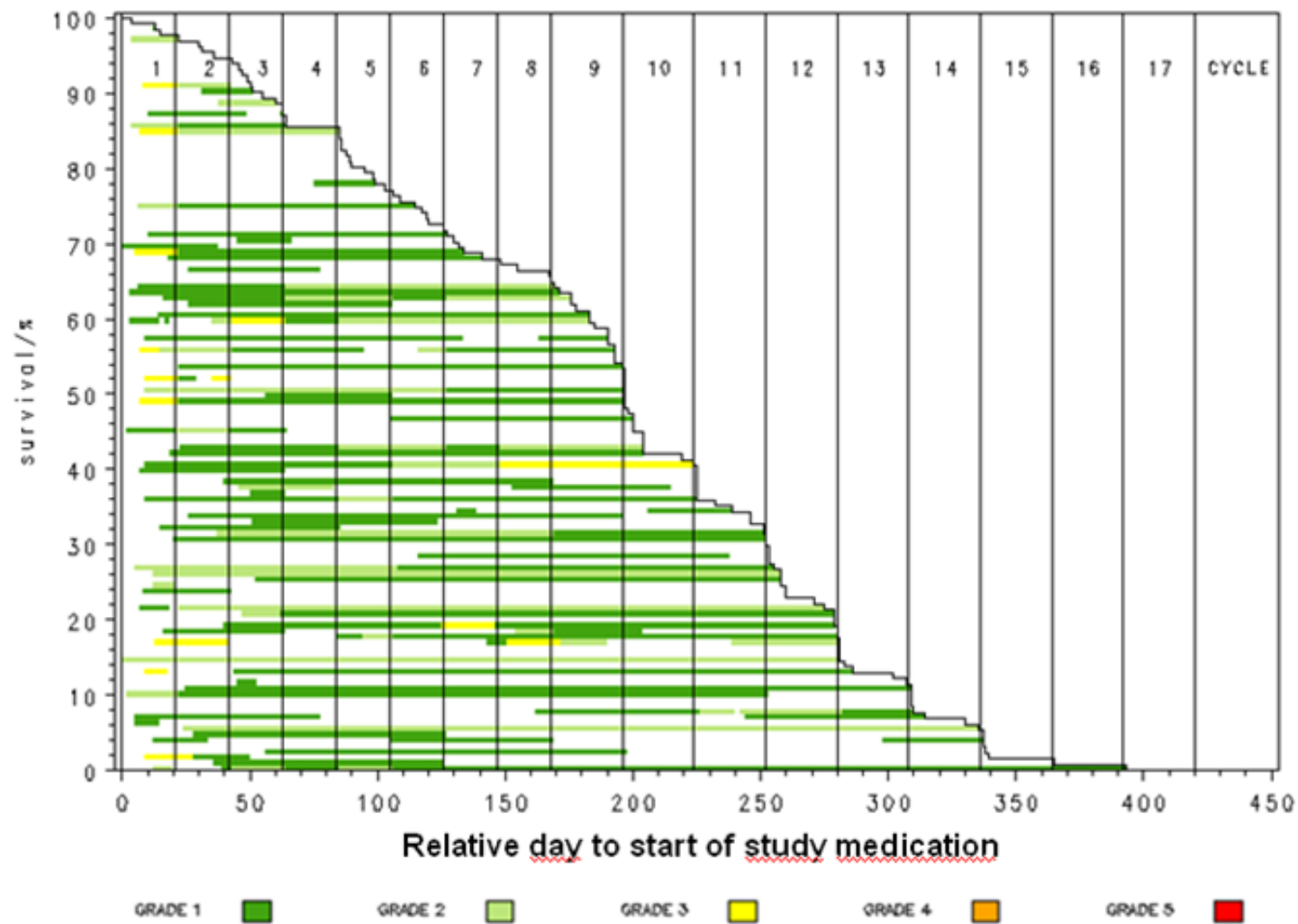
## Clinical Question: AE occurrence over time



[http://support.sas.com/sassamples/graphgallery/Health\\_and\\_Life\\_Sciences\\_Industry.html](http://support.sas.com/sassamples/graphgallery/Health_and_Life_Sciences_Industry.html)  
With SAS code

# Clinical Question: AE occurrence over time

## Event History Graphs





Clinical Question: AE occurrence over time

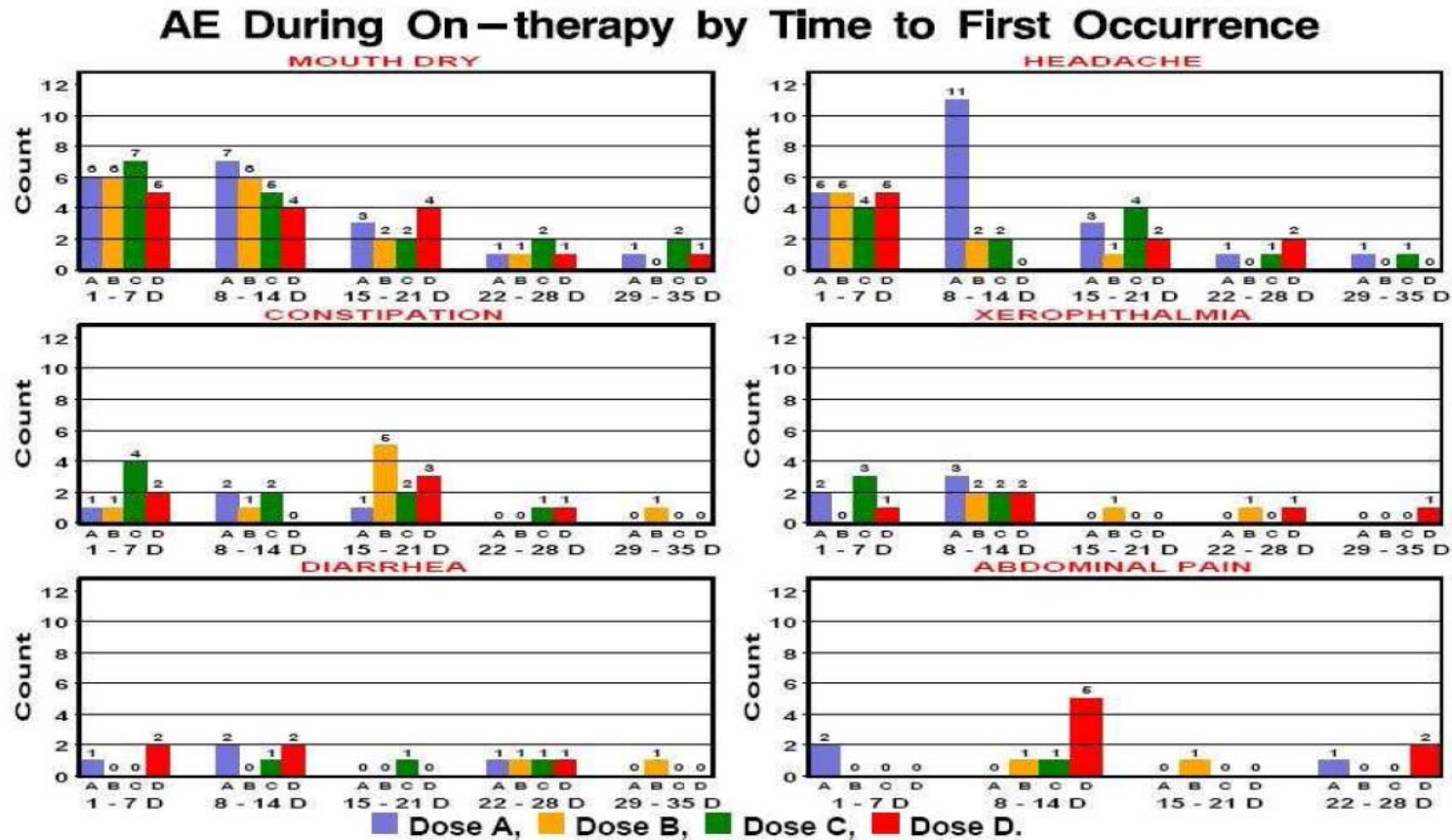


Figure 2. Sample AE Display of Time to First Occurrence

## Clinical Adverse Events Data Analysis and Visualization

Shi-Tao Yeh, GlaxoSmithKline, King of Prussia, PA.

# Clinical Question: AE occurrence over time

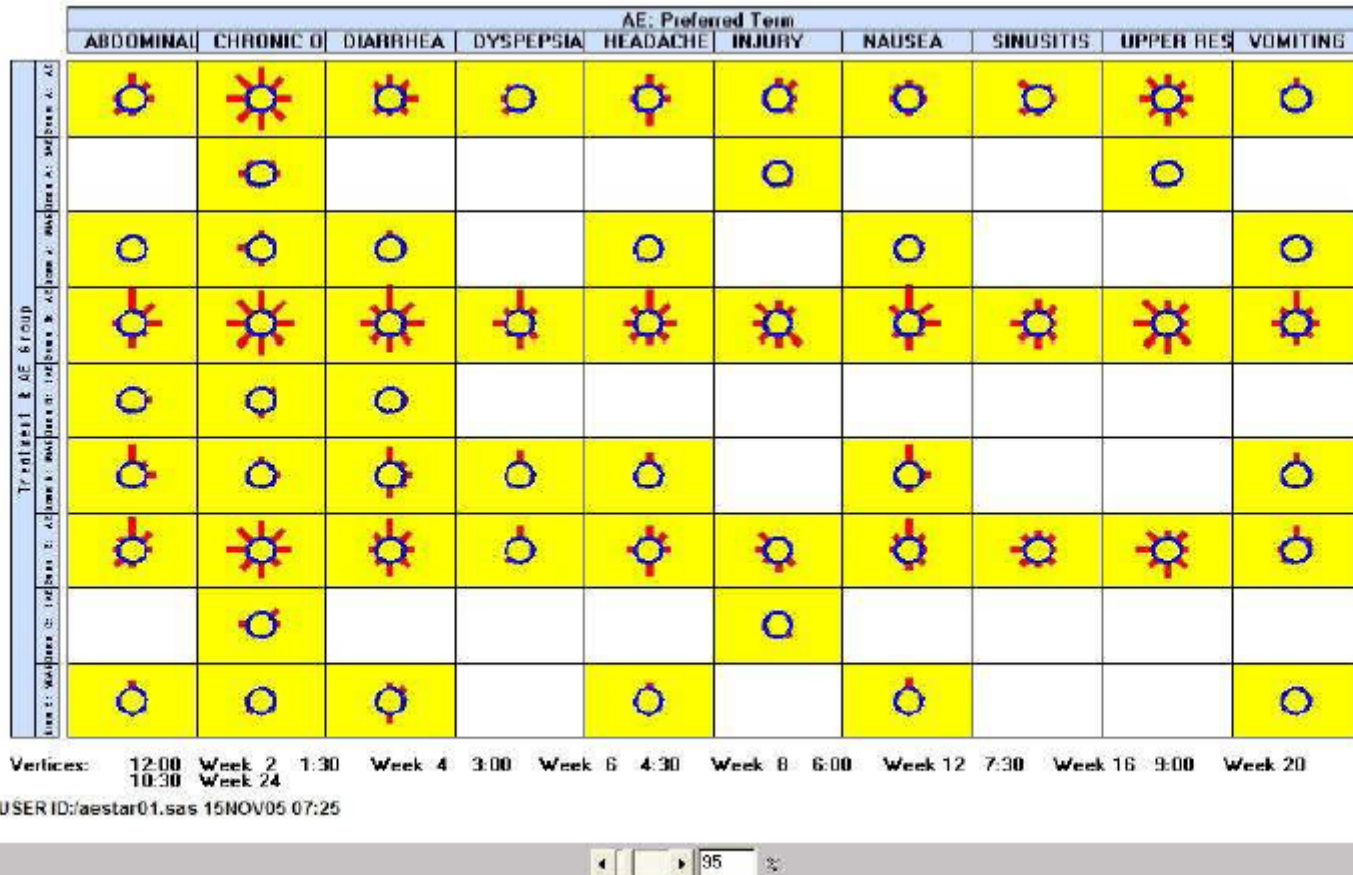
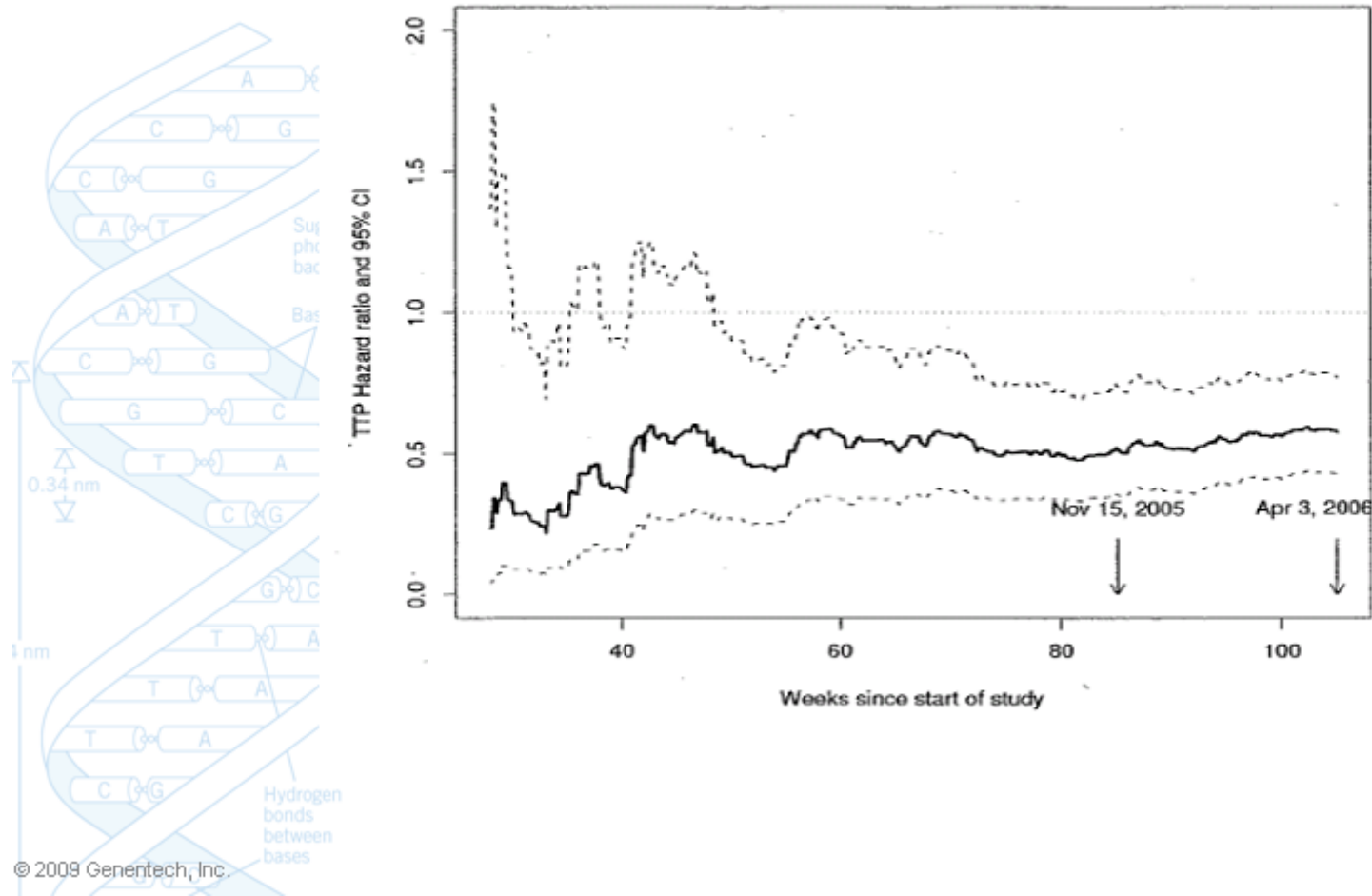


Figure 12 Time Trends in Incidence of AEs

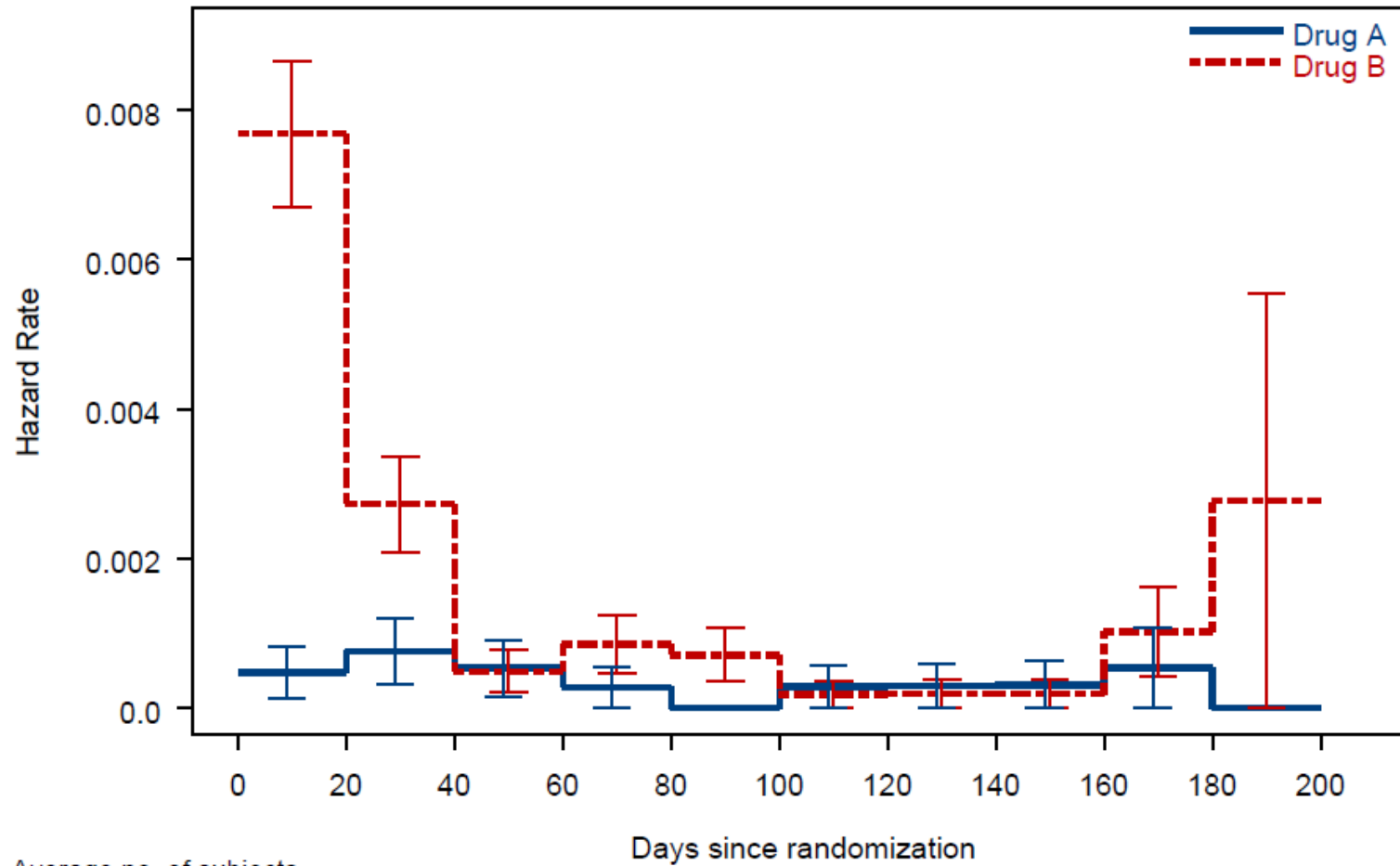
# Clinical Question: AE occurrence over time

## KM Graphs

Figure 4. Hazard Ratio and 95% CI for IRC Time Progression Over Time



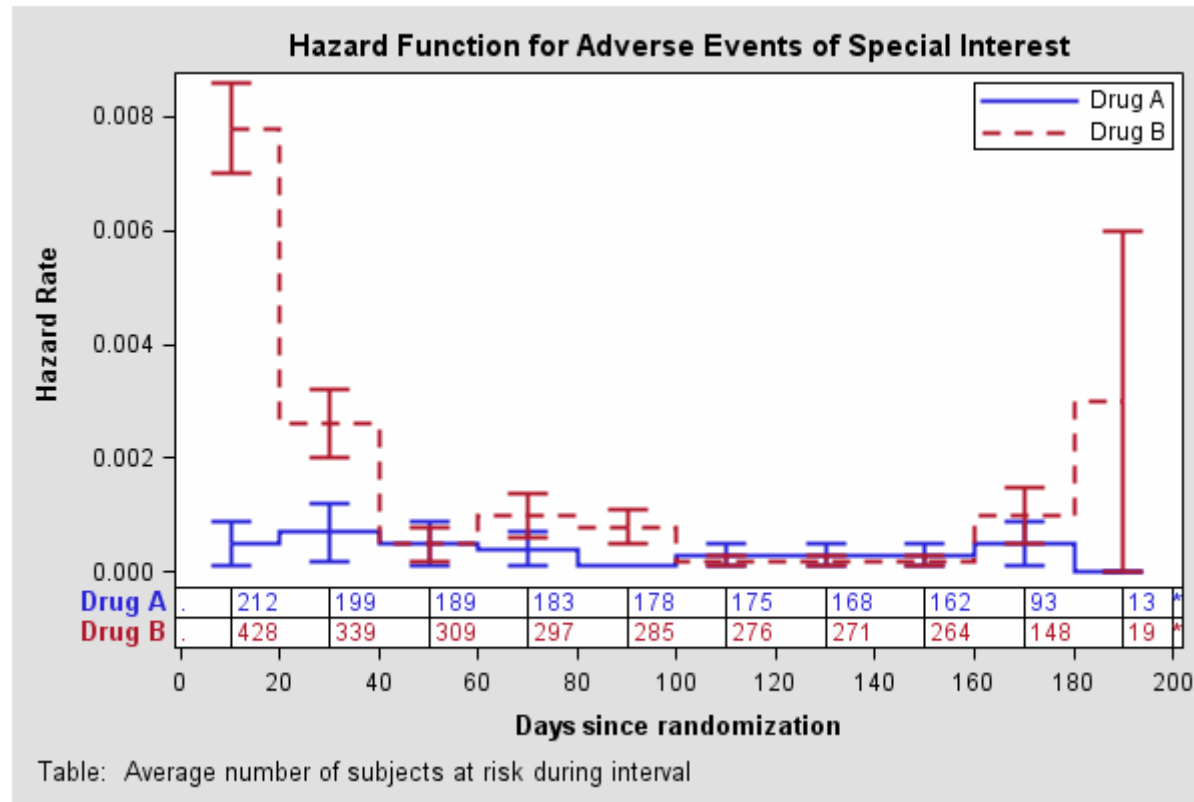
*Clinical Question: AE occurrence over time*  
 KM Graphs



Average no. of subjects at risk during interval

	0	20	40	60	80	100	120	140	160	180	200
Drug A	210	200	190	180	180	170	170	160	93	13	
Drug B	430	340	310	300	280	280	270	260	150	18	

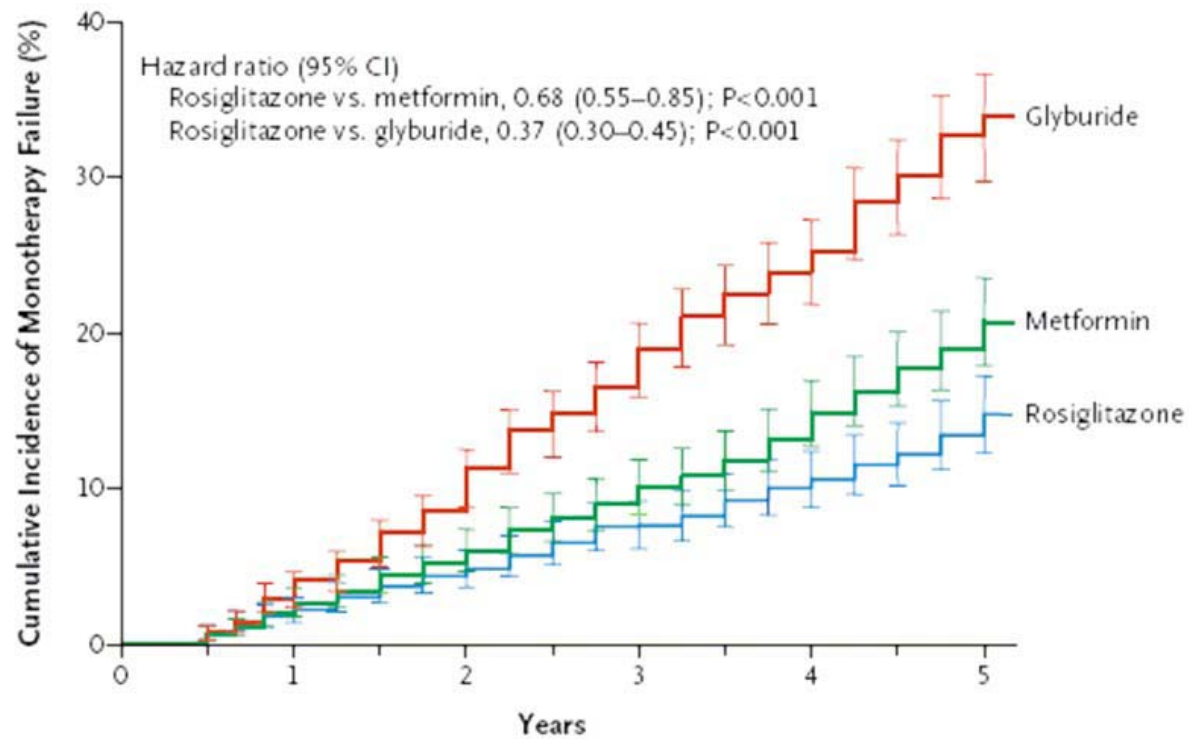
*Clinical Question: AE occurrence over time*  
 KM Graphs



[http://support.sas.com/sassamples/graphgallery/Health\\_and\\_Life\\_Sciences\\_Industry.html](http://support.sas.com/sassamples/graphgallery/Health_and_Life_Sciences_Industry.html)  
 With SAS code

## Clinical Question: AE occurrence over time

### KM Graphs



No. at Risk						
Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glyburide	1337	1114	958	781	617	218

**Figures in clinical trial reports: current practice & scope for improvement**

Stuart J Pocock\*<sup>1</sup>, Thomas G Trivison<sup>2</sup> and Lisa M Wruck<sup>2,3</sup>

## Clinical Question: AE occurrence over time

### KM Graphs

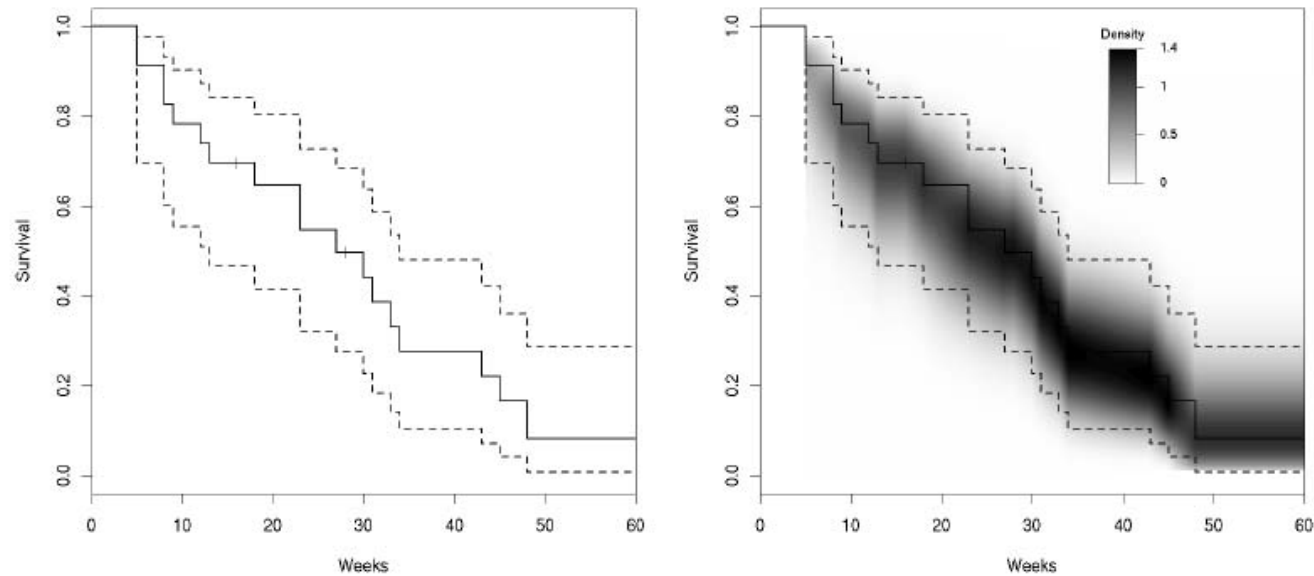


Figure 4. Kaplan–Meier estimates of survival for patients with acute myelogenous leukemia, with 95% confidence limits (left) and also uncertainty represented by shading proportional to density (right), calculated using Greenwood standard errors and a normal approximation to  $\log(-\log(\text{survival}))$ .

## Statistical Computing and Graphics

### Displaying Uncertainty With Shading

## Clinical Question: AE occurrence over time

### KM Graphs

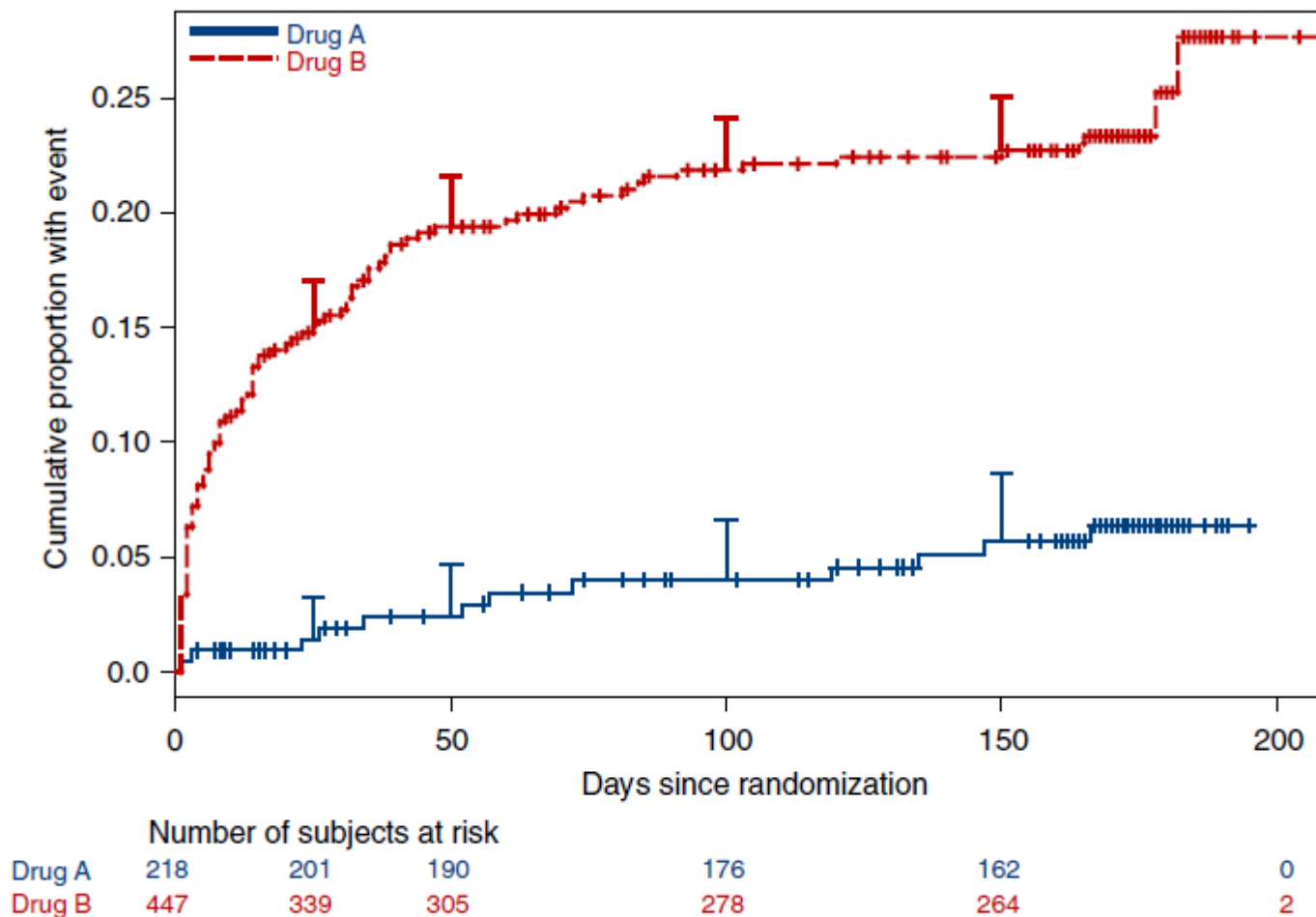


Figure 10. Cumulative distribution (with SEs) of time to first AE of special interest.

### *Graphical Approaches to the Analysis of Safety Data from Clinical Trials*

Ohad Amit<sup>1</sup>, Richard M. Heiberger<sup>2,3</sup> and Peter W. Lane<sup>3,\*</sup>

<sup>1</sup>Oncology Medicine Development Center, GlaxoSmithKline, USA

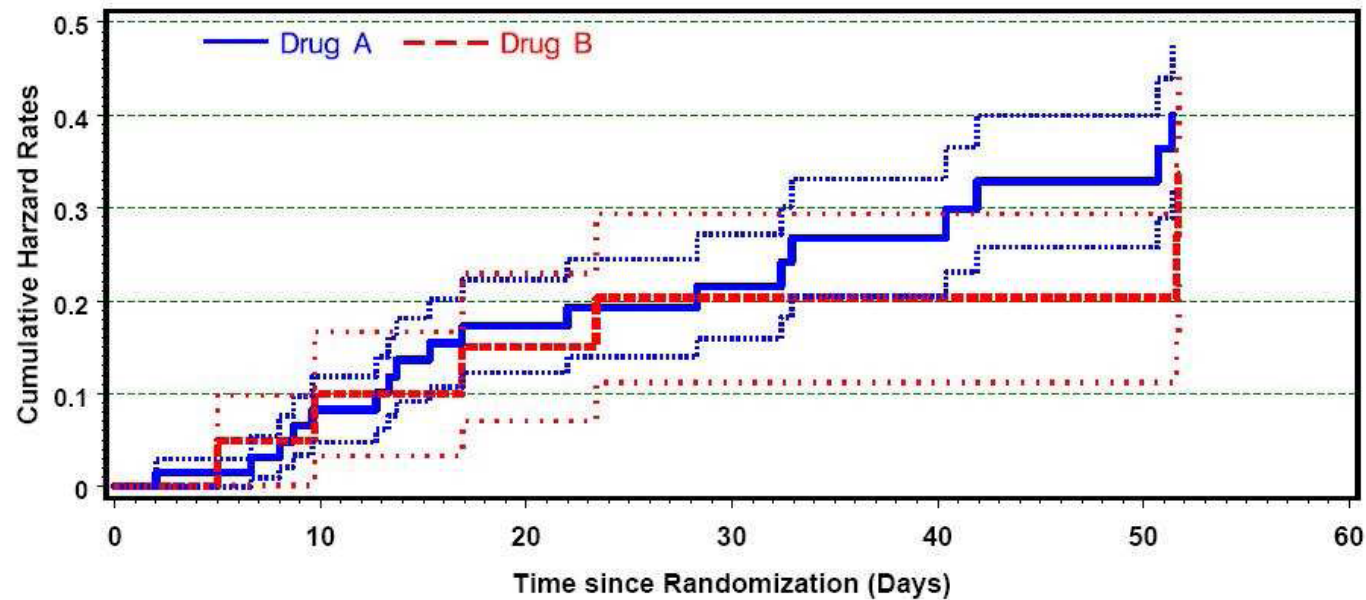
<sup>2</sup>Department of Statistics, Temple University, USA

<sup>3</sup>Research Statistical Unit, GlaxoSmithKline, UK



*Clinical Question: AE occurrence over time*  
 KM Graphs

Cumulative Incidence (SE) of Gastrointestinal Adverse Events of Concern by Time of Initial Onset



Subjects At Risk

Drug A	67	53	42	33	24	19	14
Drug B	20	18	16	15	13	12	10

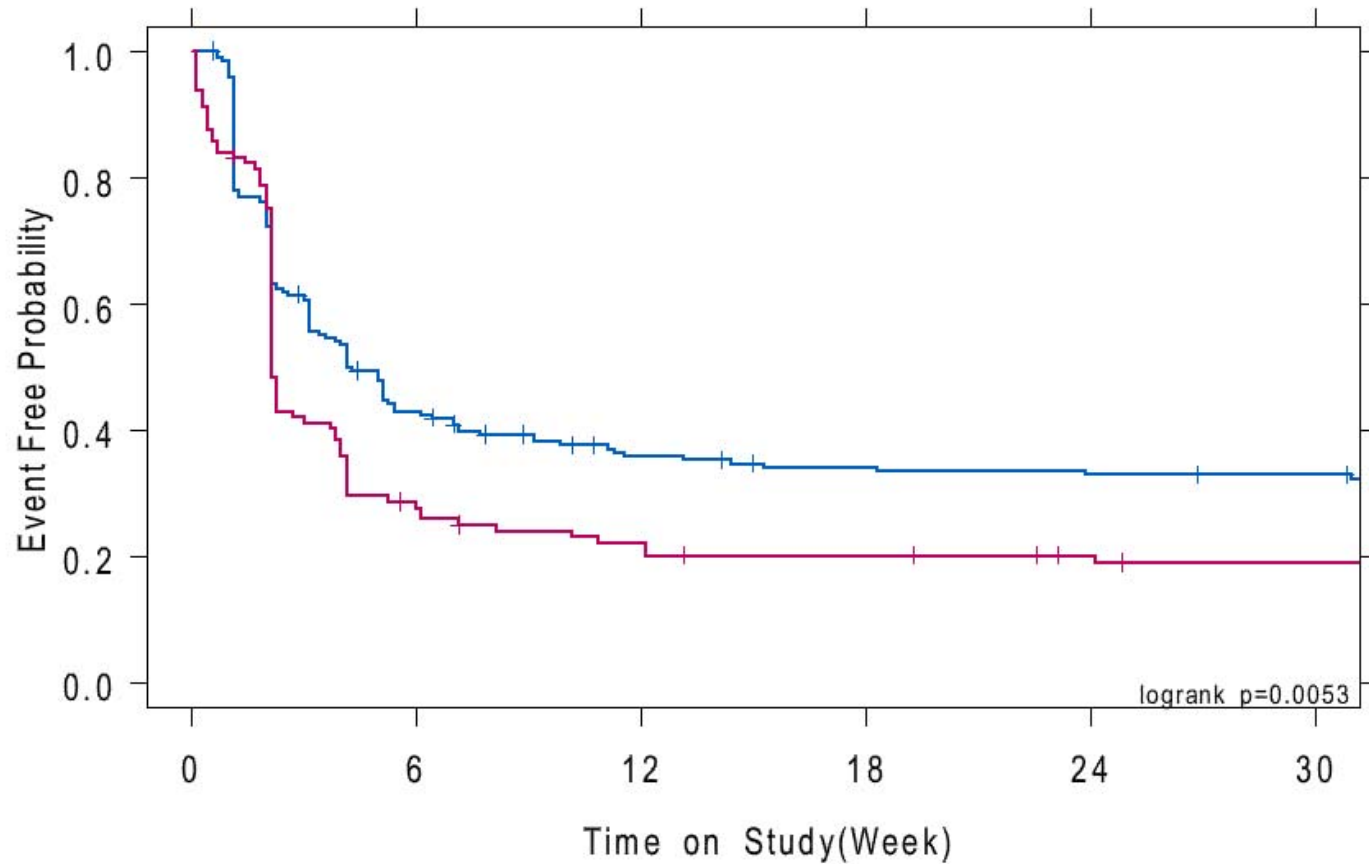
Note: Gastrointestinal AE of Concern are: Nausea, Abdominal Pain, Diarrhea, and Vomiting.

**Clinical Adverse Events Data Analysis and Visualization**

Shi-Tao Yeh, GlaxoSmithKline, King of Prussia, PA.

*Clinical Question: AE occurrence over time*  
 KM Graphs

Kaplan-Meier Survival Plot for AE

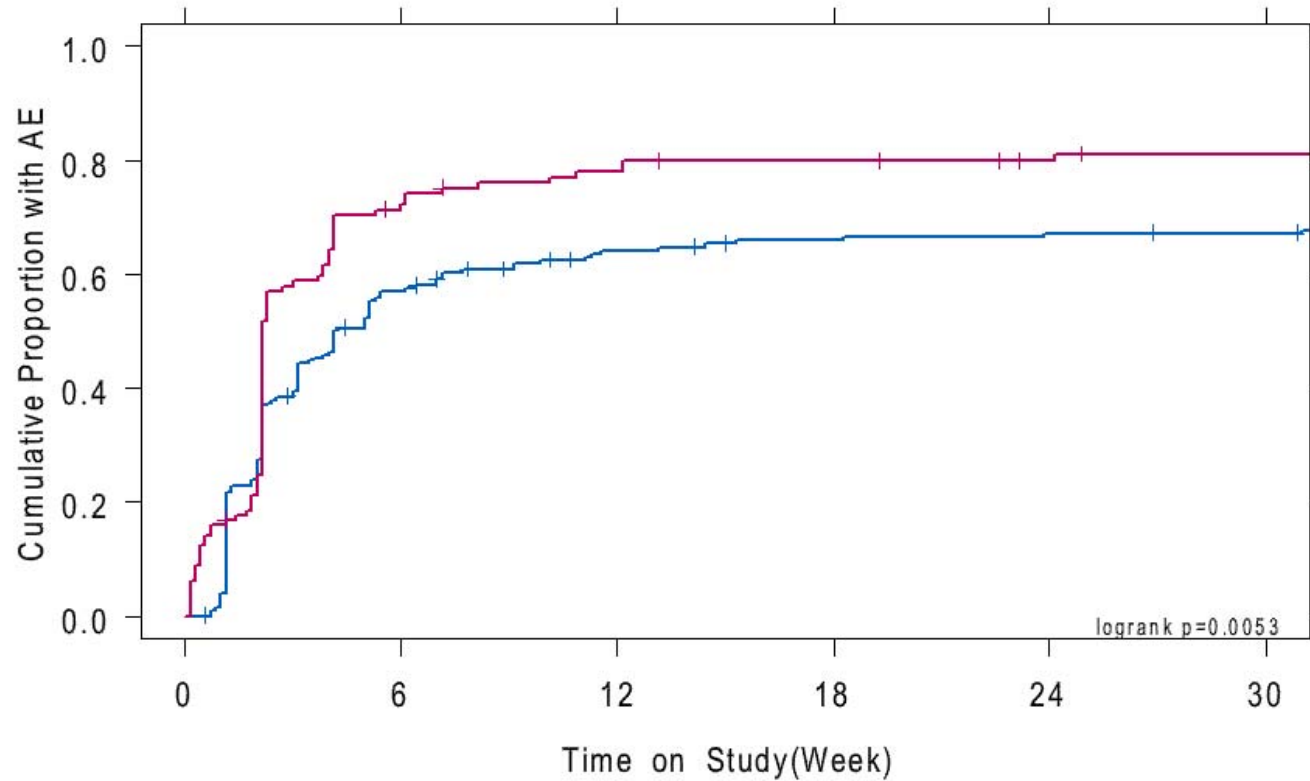


	Subjects At Risk				
Treatment	194	81	62	57	55
Control	113	31	23	20	17

Graphical Analyses of  
 Clinical Trial Safety Data

*Clinical Question: AE occurrence over time*  
 KM Graphs

Cumulative Incidence of AE



	Subjects At Risk	0	6	12	18	24	30
Treatment	194	81	62	57	55	54	
Control	113	31	23	20	17	15	

Graphical Analyses of  
 Clinical Trial Safety Data

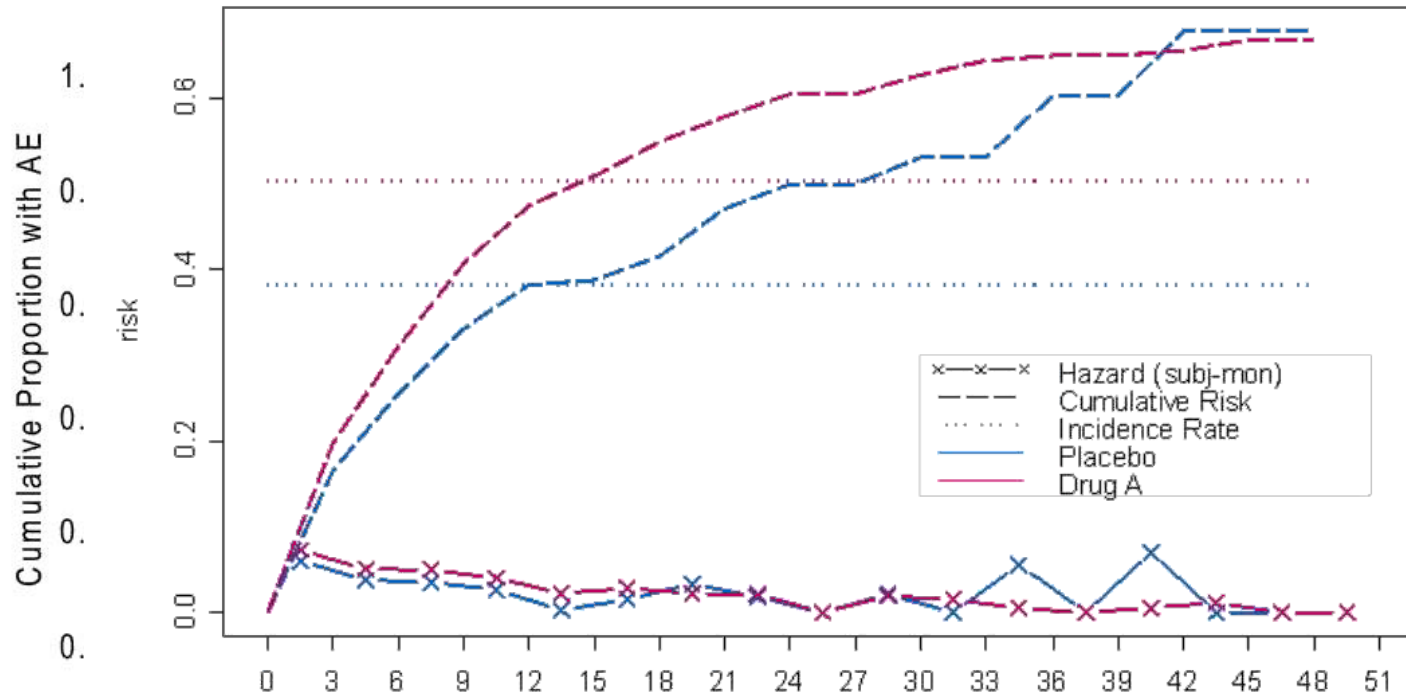
Haijun Ma, PhD and Amy Xia, PhD

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 11/20/2008

# Clinical Question: AE occurrence over time

## KM Graphs

### Risk Over Time Plot for Infection



	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Num. Events:		104	56	46	25	1	1	2	1	0	1	0	2	0	2	0	0	0
Num. At Risk:	632	520	459	409	213	22	21	19	17	16	15	13	11	11	8	8	5	
Num. Events:		241	135	112	67	20	14	10	8	0	4	3	1	0	1	2	0	0
Num. At Risk:	1229	971	810	681	423	172	156	141	107	71	67	62	61	59	58	56	33	

Treatment ————  
Control ———— 113

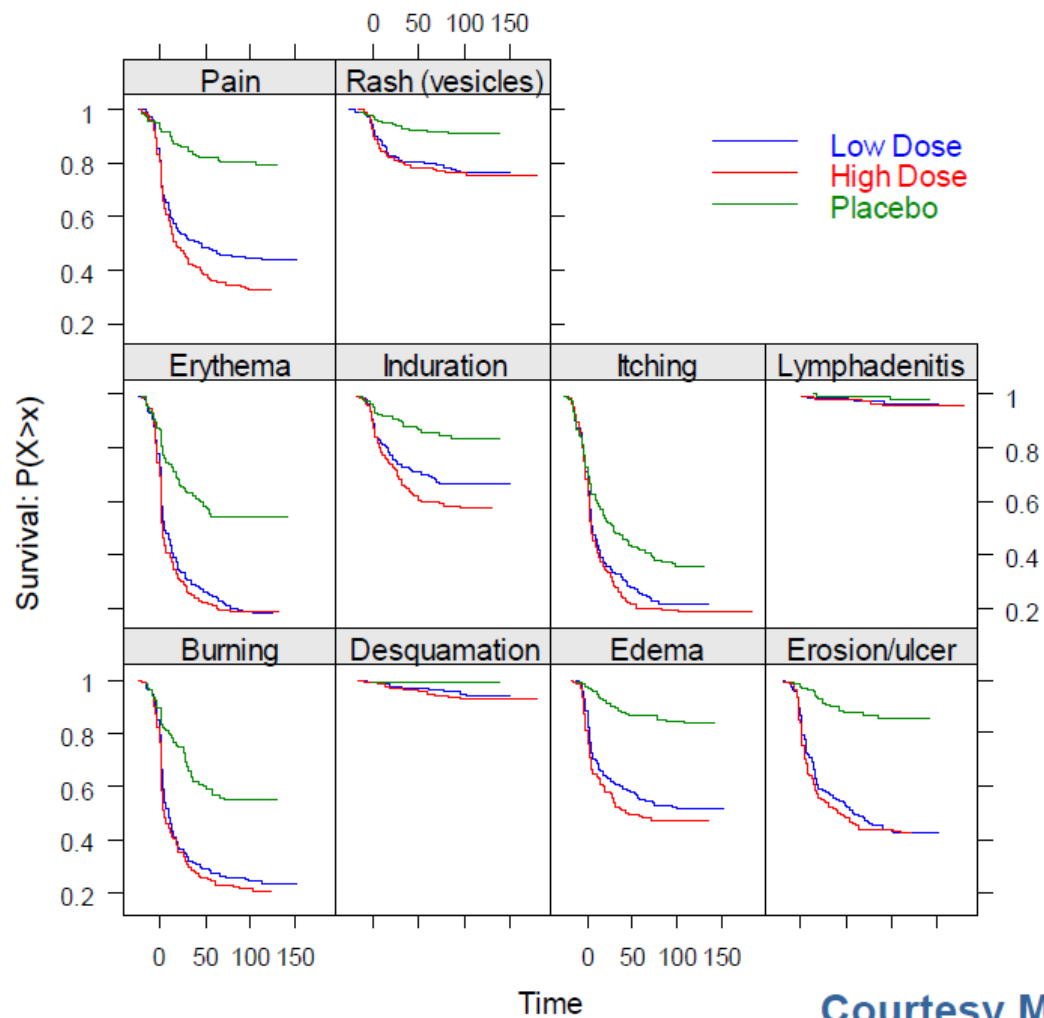
Graphical Analyses of  
Clinical Trial Safety Data

Haijun Ma, PhD and Amy Xia, PhD

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11/20/2008

Clinical Question: AE occurrence over time  
KM Graphs

**Grouped Trellis Kaplan Meier Plot**



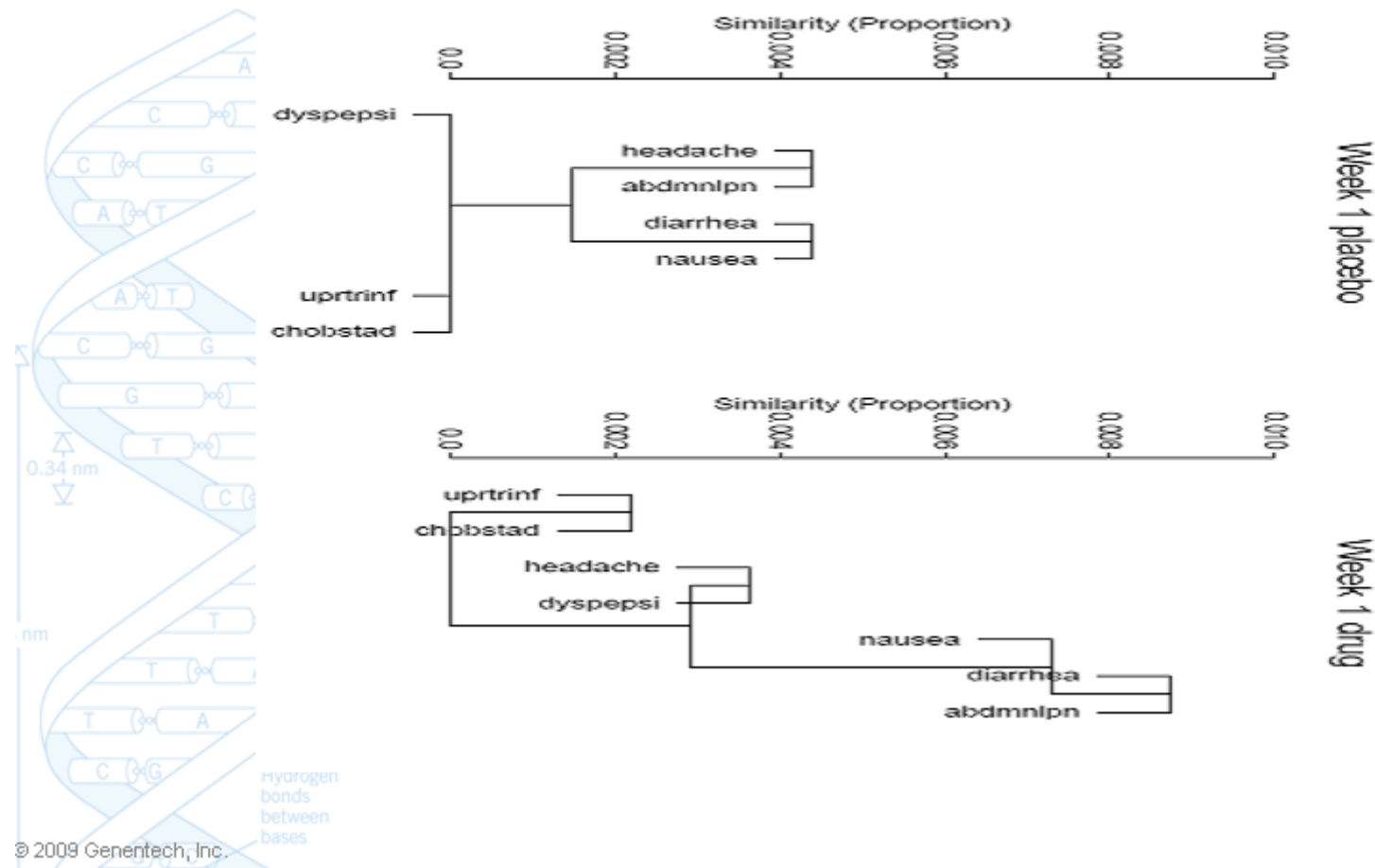
Courtesy Matt Soukup, FDA

Graphical Analysis and Reporting  
of Safety Data

Michael O'Connell, Ph.D.

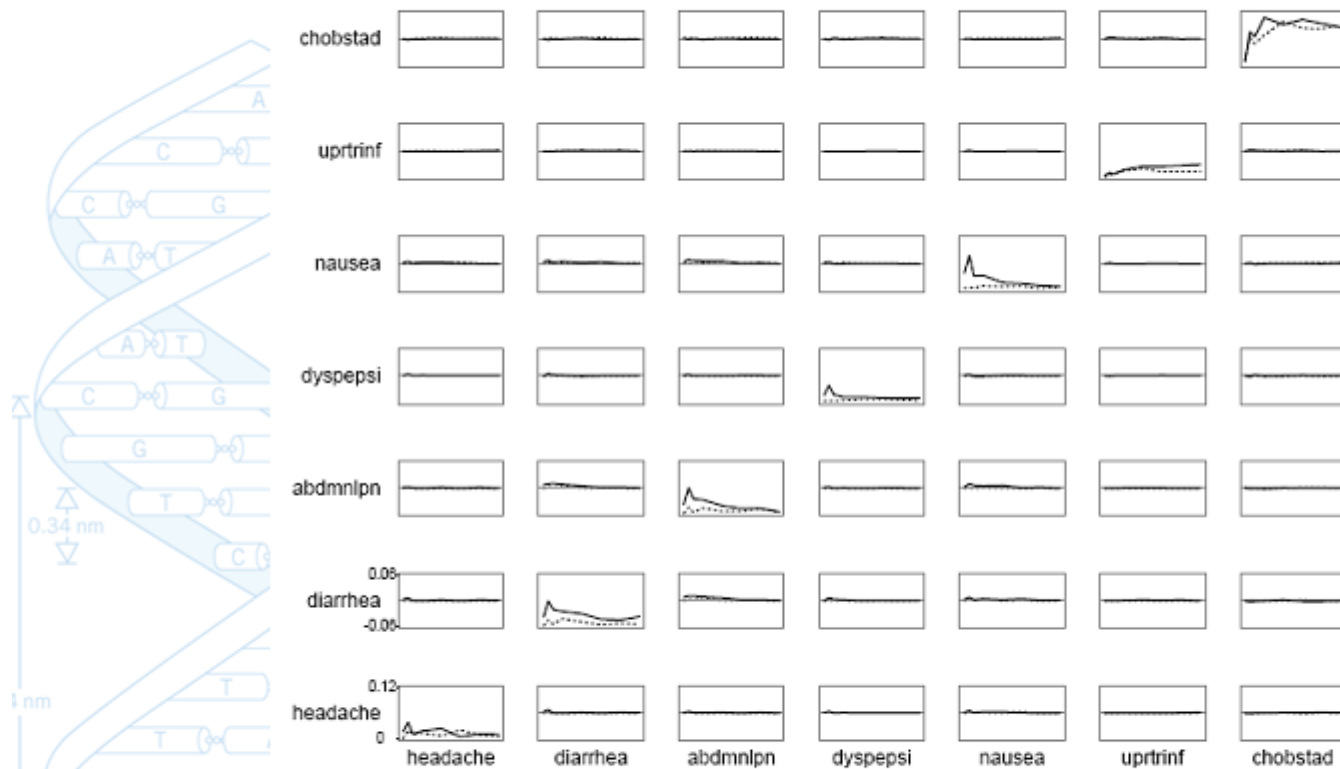
## Clinical Question: Relationship of one AE with other Concurred AEs

Figure 2. Variable Clustering of AEs at Week 1, Using Proportion of Patients Had AEs as Similarity



## Clinical Question: Relationship of one AE with other Concurrred AEs

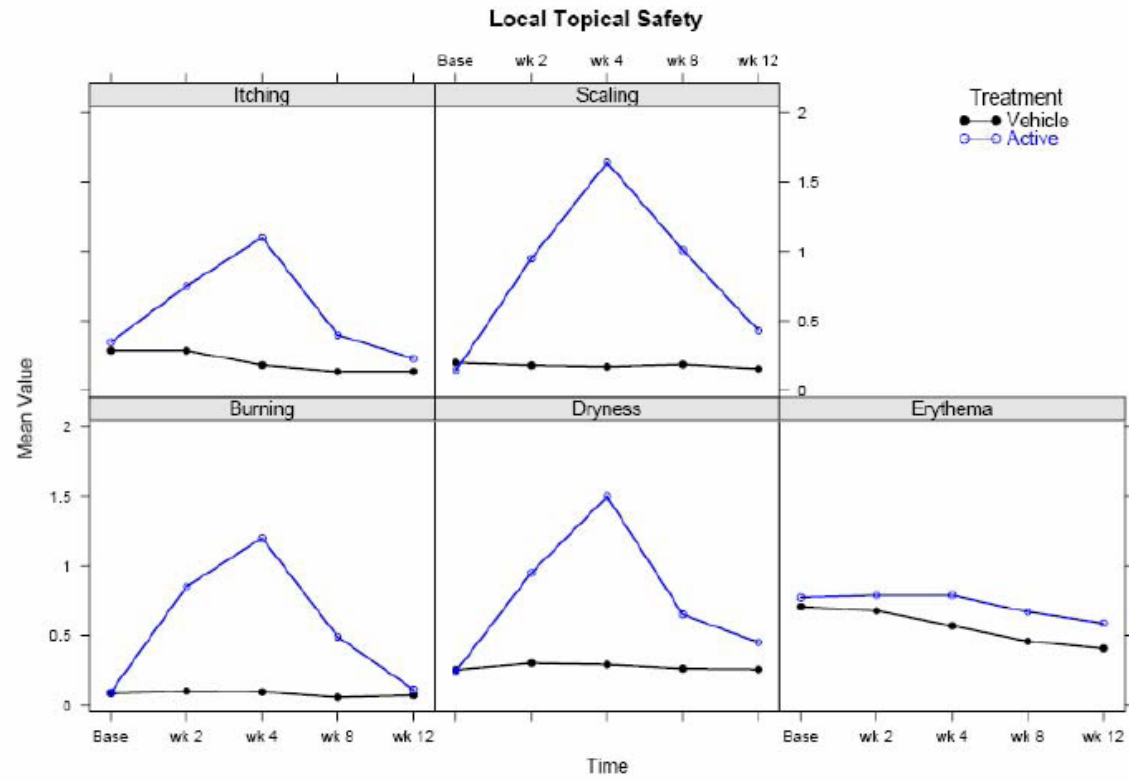
Figure 1. Time Trends in Incidence of AEs (diagonal) and chance-corrected joint incidence (off-diagonal)



\*Solid lines represent drug and dotted lines placebo. Horizontal reference lines are at zero (chance level of joint incidence).

Week is on x-axis

# Clinical Question: Relationship of one AE with other Concurred AEs





## Clinical Question: Relationship of one AE with other Concurred AEs

A cluster plot is a technique for conducting point pattern analysis. It is a bivariate plot visualizing a partition or clustering of the data. It plots the data points and a representation of the located cluster.

We can use hierarchical clustering to run on a variety of similarity matrices based on pairwise similarity measures. Spearman  $\rho^2$  is selected for similarity measure. It measures the proportion of subjects having both AEs. The SAS procedure DISTANCE is used to produce a proximity matrix. The procedures CLUSTER and TREE are used to produce the hierarchical clustering tree. Figure 5 shows a sample AE cluster tree.

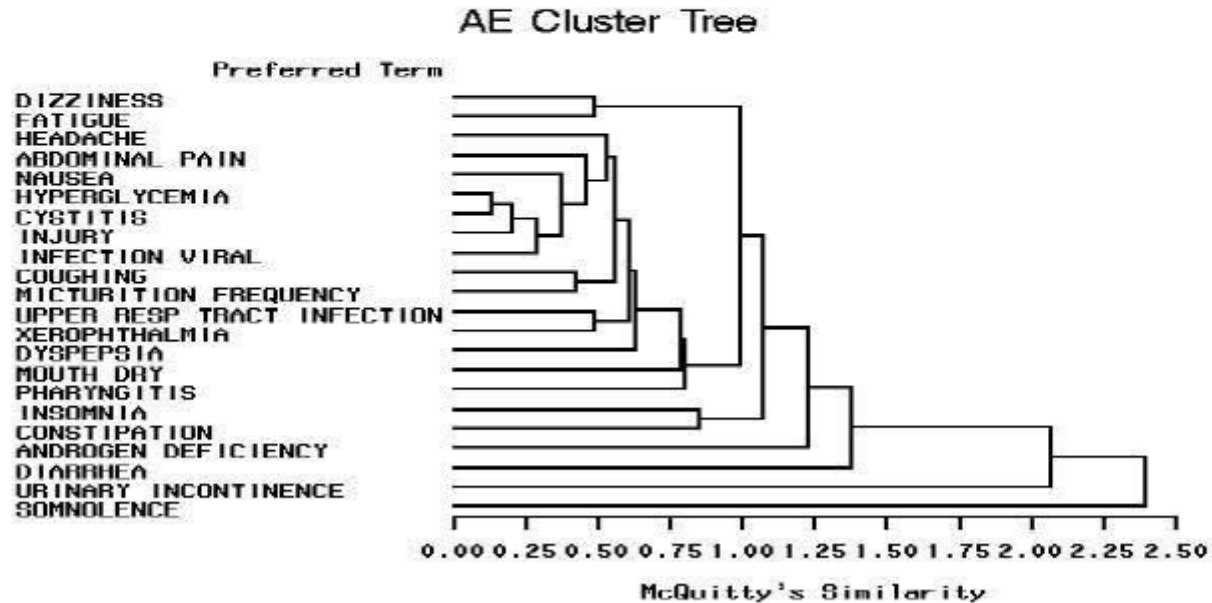


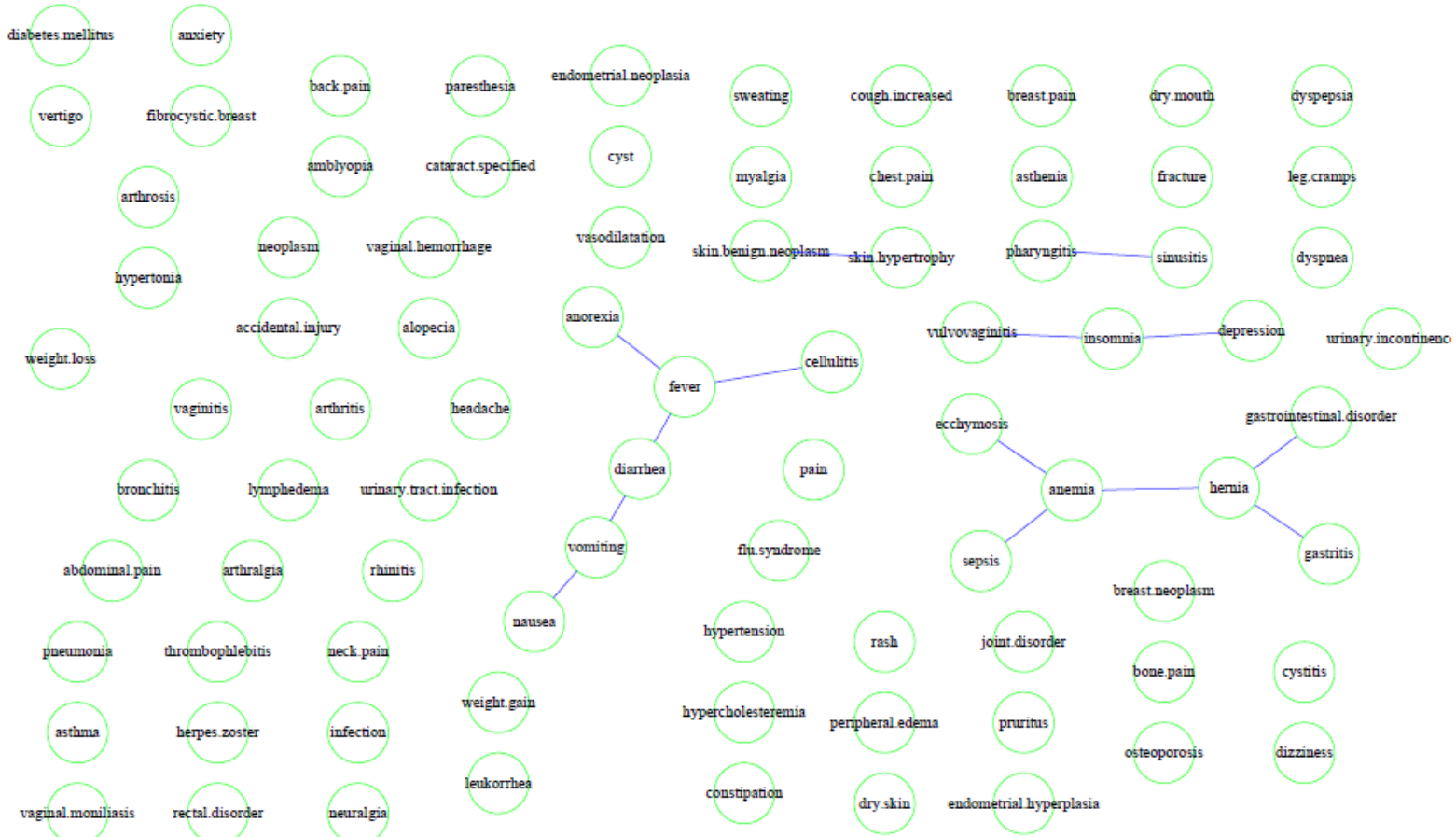
Figure 5. Sample AE Cluster Plot

## Clinical Adverse Events Data Analysis and Visualization

Shi-Tao Yeh, GlaxoSmithKline, King of Prussia, PA.

# Clinical Question: Relationship of one AE with other Concurred AEs

Tr A: labels, FDR  $\alpha = 0.10$



Finding independence graphs for clinical trial adverse event data

March 2010

Joe Whittaker and Lucy Bradshaw (Lancaster University)

Harry Southworth (AstraZeneca)

# Clinical Question: AE onset Sequence

AE Onset Sequence Diagram Dose B

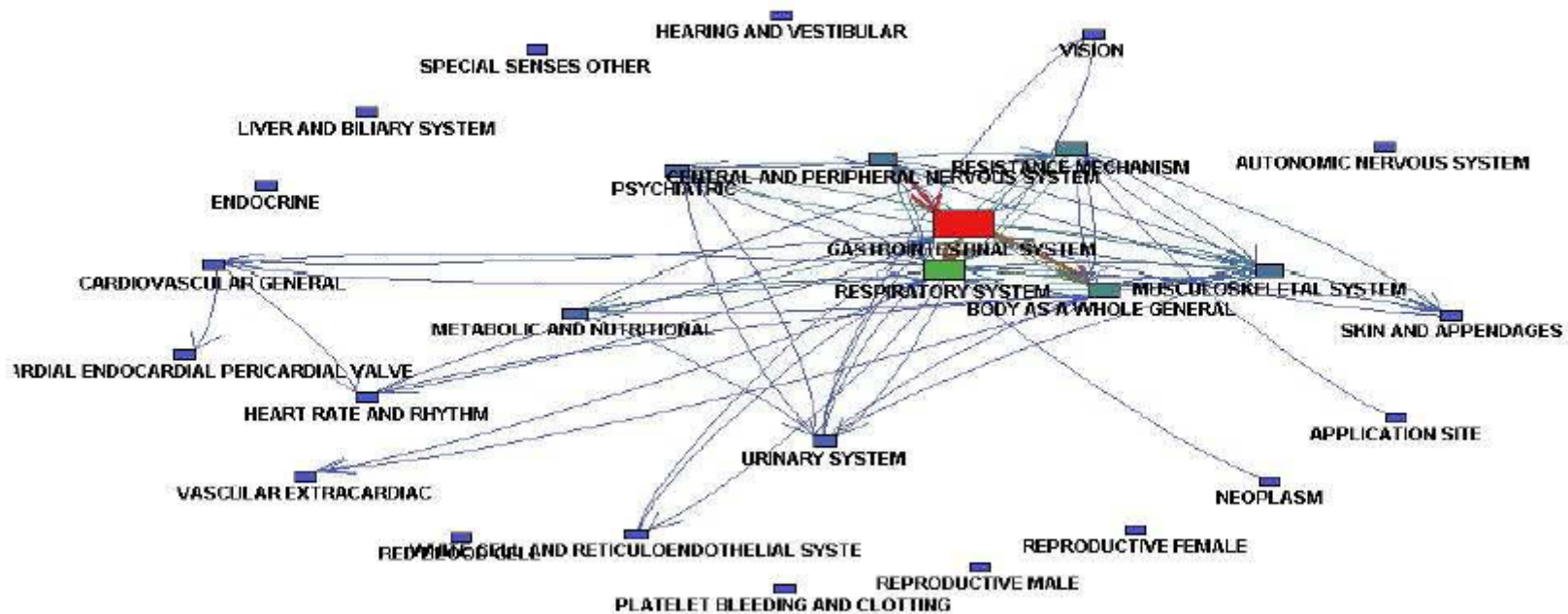


Figure 13. Constellation Display of AE Onset Sequence

## Clinical Question: Patient Profile

- Different symbols/colors to distinguish severity, seriousness
- Arrow to indicate whether AE/conMed resolved

### Lab Values



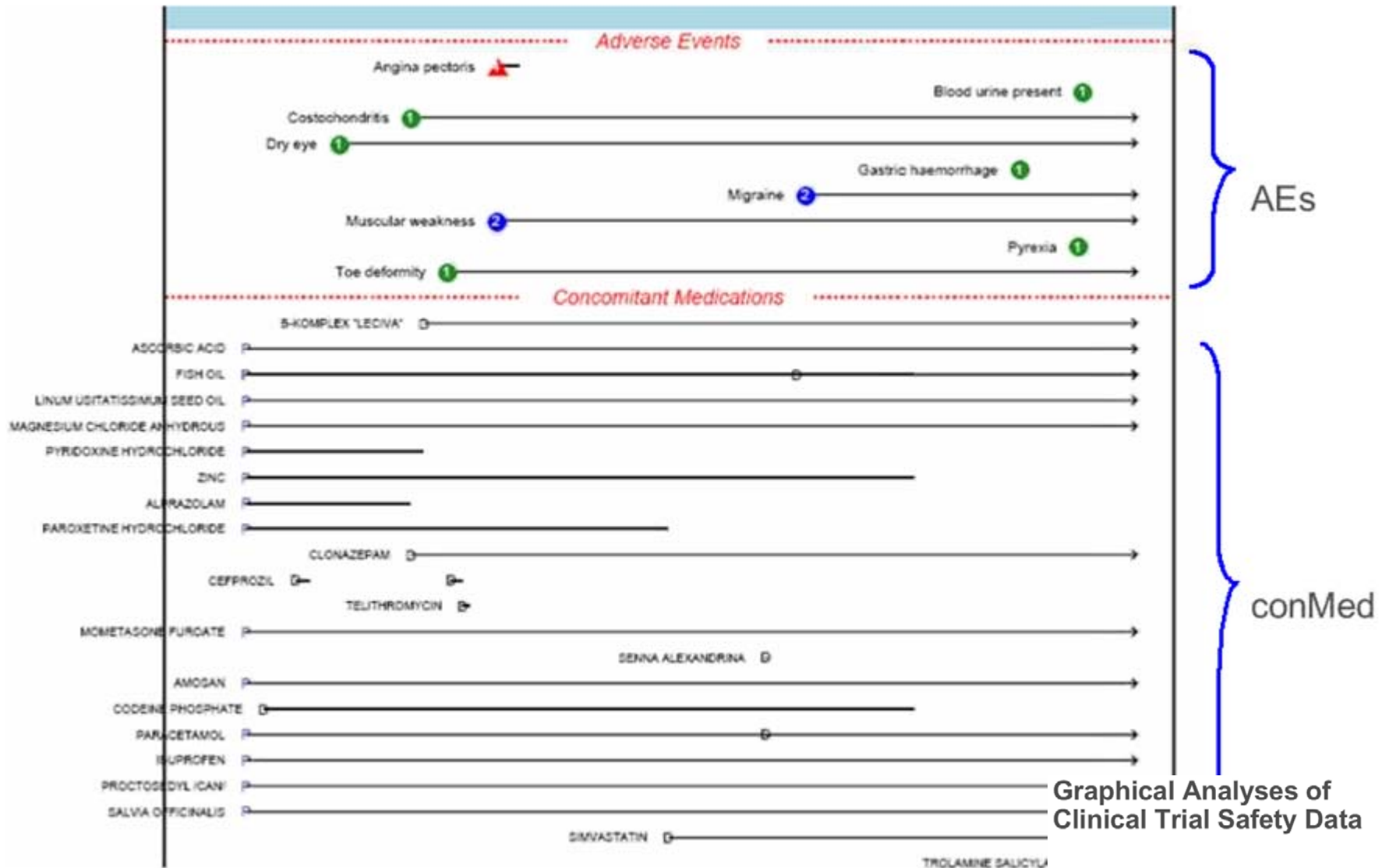
### CTDB AE/SAE Records



### Graphical Analyses of Clinical Trial Safety Data

Haijun Ma, PhD and Amy Xia, PhD

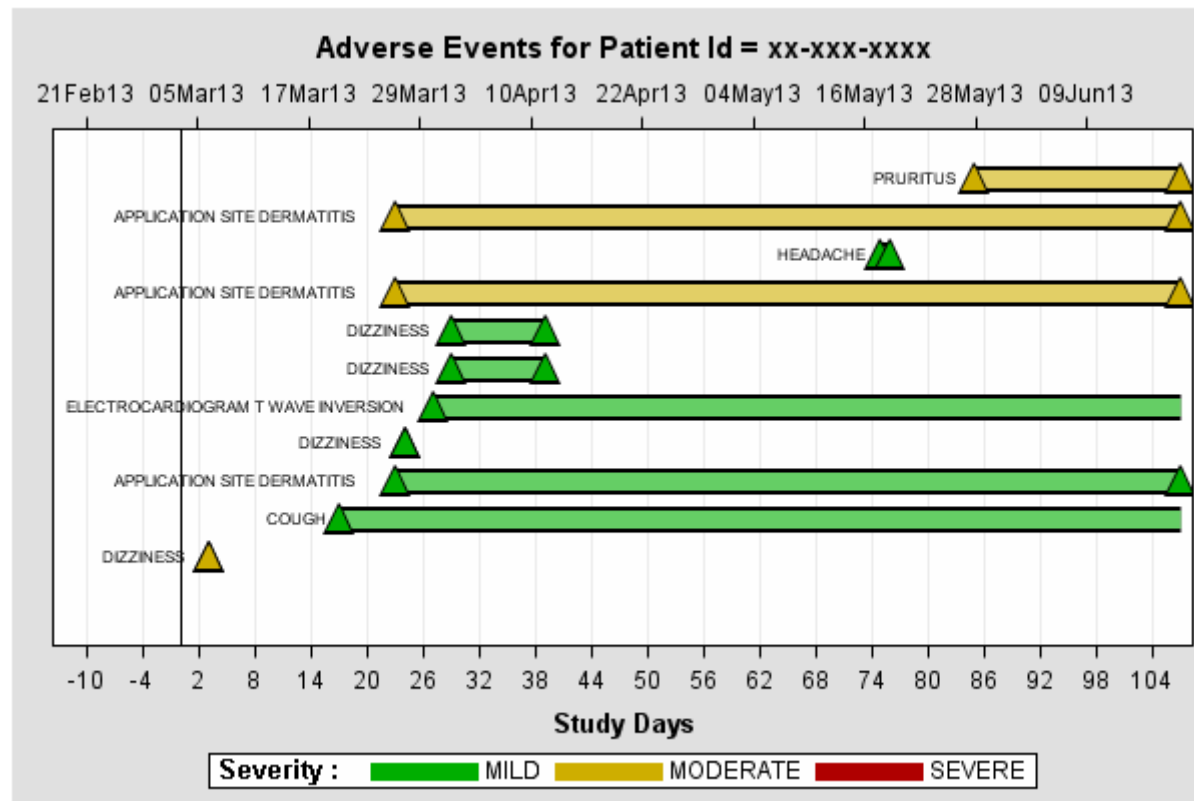
# Clinical Question: Patient Profile



Graphical Analyses of Clinical Trial Safety Data

Haijun Ma, PhD and Amy Xia, PhD

## Clinical Question: Patient Profile



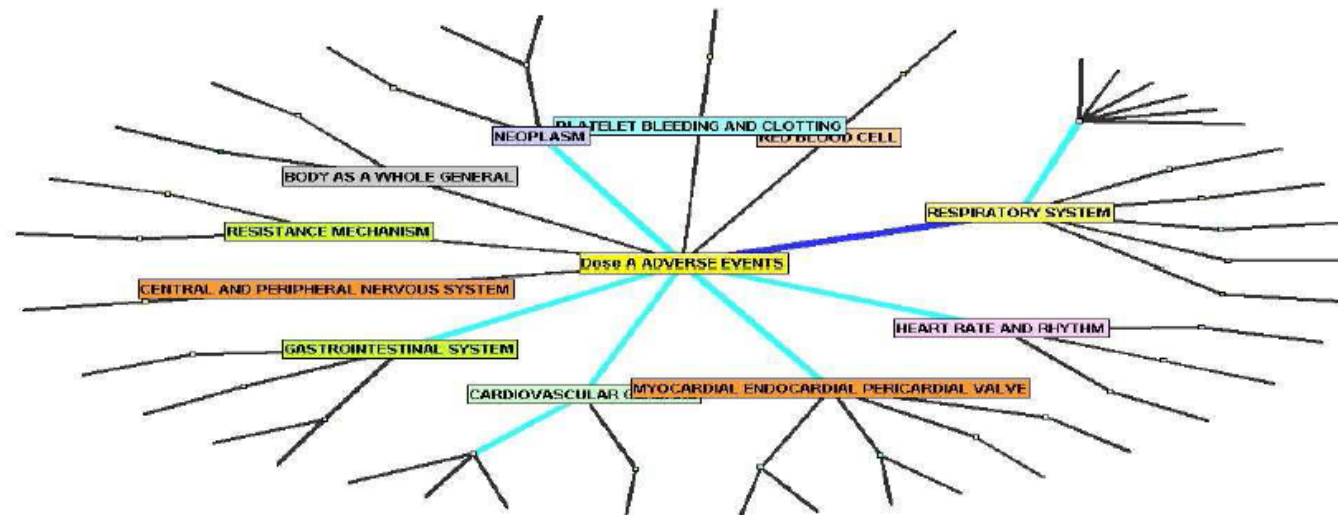
[http://support.sas.com/sassamples/graphgallery/Health\\_and\\_Life\\_Sciences\\_Industry.html](http://support.sas.com/sassamples/graphgallery/Health_and_Life_Sciences_Industry.html)  
With SAS code

## Clinical Question: ?

A tree structure is a method of representing the hierarchical structure in a graphical form. It is named a “tree structure” because the graph looks like a tree. In graph theory, a tree is a collection of connected nodes. Every finite tree structure has a member that has no superior. This node is called the “root” node. The lines connecting nodes are called “branches” or “links”. Nodes without children are called “leaves” or “end-nodes”. A node is a “parent” of another node if it is one step higher in the hierarchy and closer to the root node.

Tree structures are used in many applications, such as hierarchical organizational structures, binary search tree, decision tree, partition tree, etc. There are many ways of visually representing tree structures. The most commonly used method is a classical node-link diagram, that connects nodes together with line segments. Figure 9 shows a tree structure from a Treeview applet with a root node in the center of the presentation. Figure 10 shows a recursive partition tree for AE occurrence prediction.

Treeview of Serious AE - Dose A



## Clinical Adverse Events Data Analysis and Visualization

Shi-Tao Yeh, GlaxoSmithKline, King of Prussia, PA.

# Clinical Question: ?

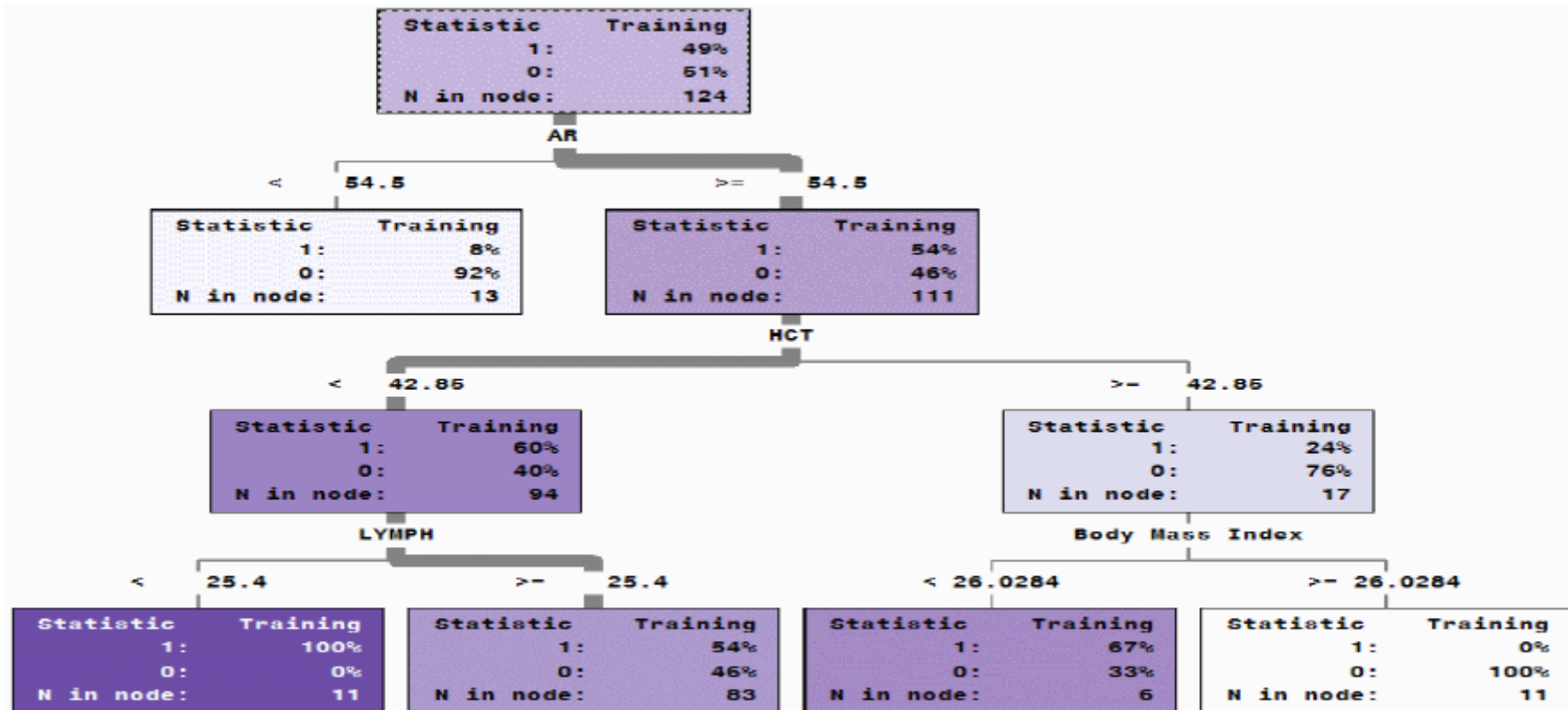


Figure 10. A Recursive Partition Tree for AE Occurrence Prediction



# Clinical Question: ?

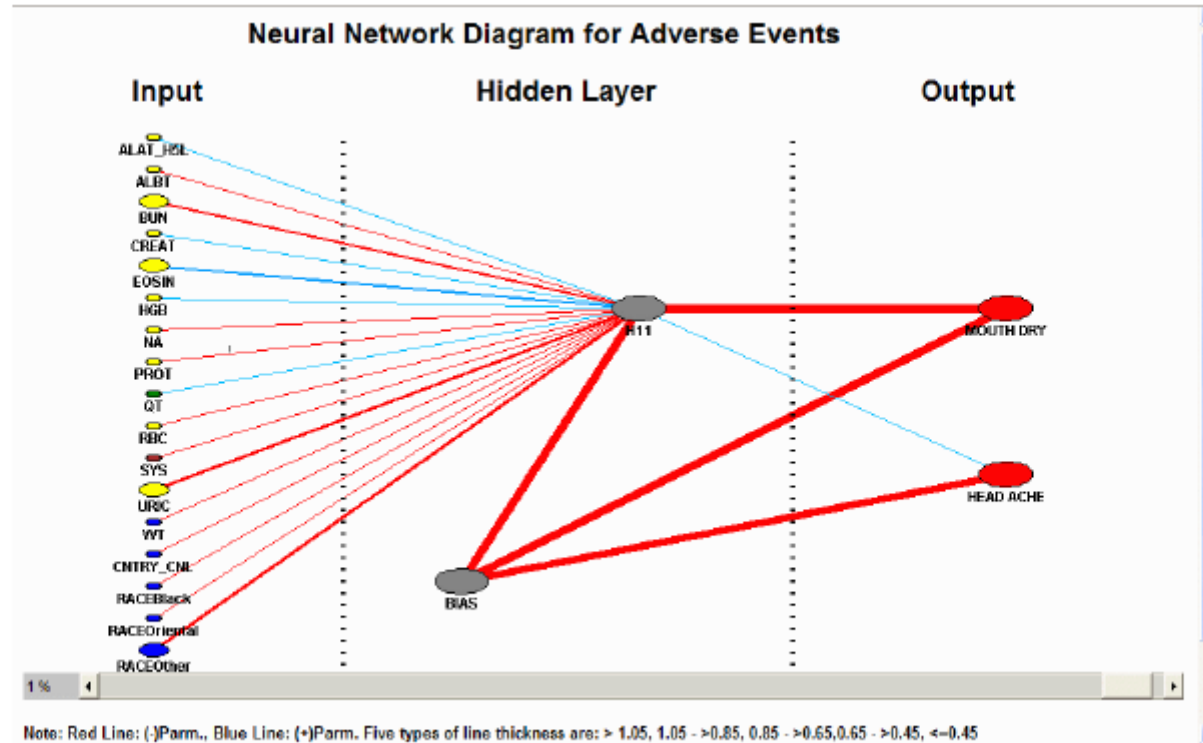


Figure 15. Neural Network Diagram for AE Events