# Using The Right Tool For the Right Tree in the Forest

Gen Pan, Roche

PharmaSUG China 2016
Paper #37

# Section 1:
# Right Tree in the Forest

# Why Forest Plot

- Quick overview instead of potentially producing many more pages with summary tables

- Useful catalyst for timely and informed decision making on potential further analysis

# Two Kinds of the Forest Plot

- Meta-Analysis for Displaying Treatment Effects
- Subgroup Analysis in Randomized Controlled Trials

# Questions Being Addressed #Meta-Analysis

- In a Meta-Analysis, results comes from different clinical trials
- To combine the results of separate analyses

# Questions Being Addressed #Subgroup Analysis

- In a Subgroup Analysis, patients are typically grouped according to common baseline characteristics

- To assess the homogeneity of a result across different patient subgroups (e.g. to demonstrate the result applies equally to all patient subgroups)
- To identify subgroups of patients in which the treatment effect differs from that of the main analysis

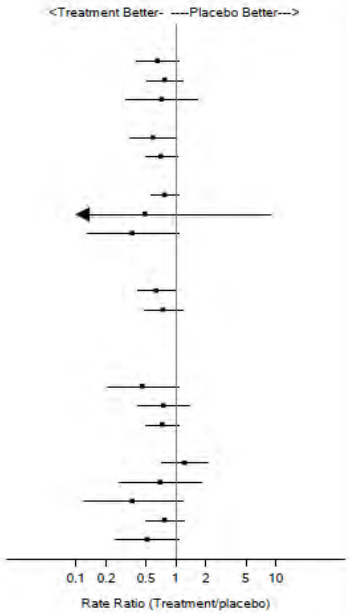
# Section 2:
# Using the Right Tool

# Case Study

- To create a custom Forest Plot to display Table Columns, Statistics, and Line Chart with arrow

Forest Plot for Rate Ratio of Asthma Exacerbations by Demographic or Baseline Characteristic Subgroup (Treatment vs. Placebo)

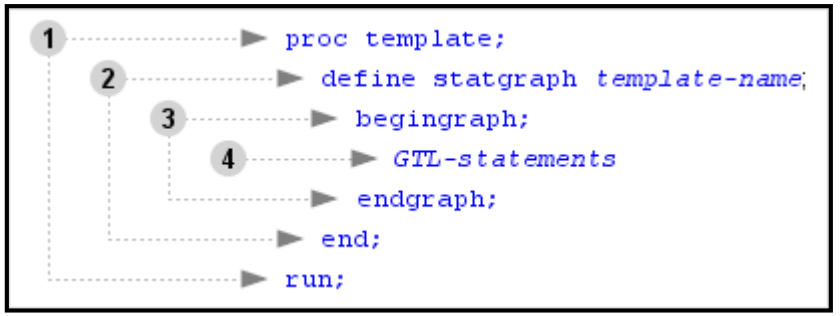
| Subgroup | Placebo N | Placebo Rate (per year) | Treatment N | Treatment Rate (per year) | Treatment vs. Placebo Rate Ratio (95% CI) | Rate Reduction |
|---|---|---|---|---|---|---|
| **Age (years)** | | | | | | |
| 18 to <50 | 107 | 0.99 | 101 | 0.66 | 0.66 (0.41, 1.07) | 34% |
| 50 to <65 | 116 | 0.85 | 112 | 0.67 | 0.78 (0.52, 1.17) | 22% |
| >=65 | 33 | 0.82 | 42 | 0.60 | 0.73 (0.32, 1.64) | 27% |
| **Sex** | | | | | | |
| Male | 90 | 0.89 | 77 | 0.53 | 0.60 (0.35, 1.02) | 40% |
| Female | 166 | 0.97 | 178 | 0.70 | 0.72 (0.50, 1.04) | 28% |
| **Race** | | | | | | |
| White | 191 | 0.89 | 209 | 0.69 | 0.78 (0.57, 1.06) | 22% |
| Black or African American | 20 | 0.41 | 7 | 0.21 | 0.50 (0.03, 8.76) | 50% |
| Asian | 40 | 1.49 | 34 | 0.55 | 0.37 (0.13, 1.06) | 63% |
| **Baseline ICS dose >=1000 ug/day plus LABA** | | | | | | |
| Yes | 107 | 1.15 | 118 | 0.73 | 0.64 (0.42, 0.97) | 36% |
| No | 149 | 0.78 | 137 | 0.59 | 0.75 (0.49, 1.16) | 25% |
| **Number of asthma exacerbations in the 12 months prior to study entry** | | | | | | |
| 0 | 92 | 0.48 | 97 | 0.23 | 0.47 (0.21, 1.06) | 53% |
| 1 | 74 | 0.61 | 65 | 0.47 | 0.76 (0.42, 1.38) | 24% |
| >=2 | 90 | 1.68 | 93 | 1.24 | 0.74 (0.50, 1.09) | 26% |
| **Geographic region** | | | | | | |
| North America | 72 | 0.68 | 65 | 0.83 | 1.23 (0.72, 2.11) | -23% |
| Latin America | 18 | 0.76 | 26 | 0.53 | 0.70 (0.27, 1.81) | 30% |
| Asia | 33 | 1.68 | 28 | 0.63 | 0.37 (0.12, 1.16) | 63% |
| Central and Eastern Europe | 105 | 0.72 | 98 | 0.56 | 0.78 (0.50, 1.22) | 22% |
| Western Europe plus Rest of World | 28 | 1.54 | 38 | 0.80 | 0.52 (0.25, 1.09) | 48% |




footnote1
footnote2
footnote3
footnote4
Program: $HOME/cdt3637e/gb28688/g_forest_ratio.sas Output: $HOME/cdt3637e/p28688a/reports/g_forest_ratio.pdf 07SEP2016 4:58

# Using the SAS 9.4 Graph Template Language (GTL)

- Define the structure of the graph using the GTL syntax in a **DEFINE STATGRAPH** block in a **TEMPLATE** procedure statement



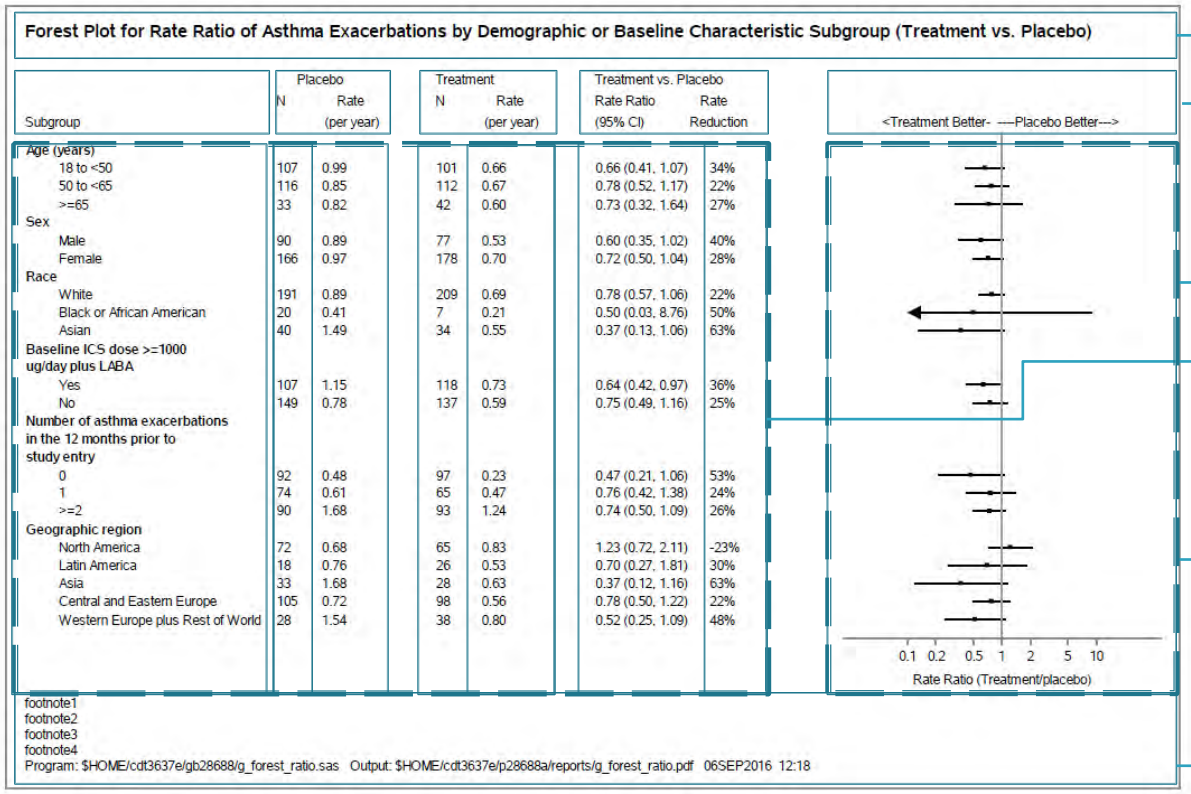

- Run the **TEMPLATE** procedure

- Run an **SGRENDER** procedure statement

```
proc sgrender data = data-source template = template-name;
run;
```

# Structured Building-Block Approach

- To create a forest plot as below




entrytitle

sidebar
layout lattice / columns = 5
entry

layout lattice/ columns =8

layout overlay
axistable

layout overlay
highlowplot
scatterplot
referenceline

entryfootnote

# Input Dataset

- What you see is what you get

| | GROUP | N_P | Rate_P | N_125 | Rate_125 | Ratio_CI_125 | Reduction_12 | Ratio_N_125 | Low_N_125 | High_N_125 | ZERO | INDENT | GROUPLEVE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Age (years) | | | | | | | . | . | . | 0 | 0 | 1 |
| 2 | 18 to <50 | 107 | 0.99 | 101 | 0.66 | 0.66 (0.41, 1.07) | 34% | 0.66 | 0.41 | 1.07 | 0 | 2 | 1 |
| 3 | 50 to <65 | 116 | 0.85 | 112 | 0.67 | 0.78 (0.52, 1.17) | 22% | 0.78 | 0.52 | 1.17 | 0 | 2 | 1 |
| 4 | >=65 | 33 | 0.82 | 42 | 0.60 | 0.73 (0.32, 1.64) | 27% | 0.73 | 0.32 | 1.64 | 0 | 2 | 1 |
| 5 | | | | | | | | . | . | . | 0 | 0 | 2 |
| 6 | Sex | | | | | | | . | . | . | 0 | 0 | 2 |
| 7 | Male | 90 | 0.89 | 77 | 0.53 | 0.60 (0.35, 1.02) | 40% | 0.6 | 0.35 | 1.02 | 0 | 2 | 2 |
| 8 | Female | 166 | 0.97 | 178 | 0.70 | 0.72 (0.50, 1.04) | 28% | 0.72 | 0.5 | 1.04 | 0 | 2 | 2 |
| 9 | | | | | | | | . | . | . | 0 | 0 | 3 |
| 10 | Race | | | | | | | . | . | . | 0 | 0 | 3 |
| 11 | White | 191 | 0.89 | 209 | 0.69 | 0.78 (0.57, 1.06) | 22% | 0.78 | 0.57 | 1.06 | 0 | 2 | 3 |
| 12 | Black or African American | 20 | 0.41 | 7 | 0.21 | 0.50 (0.03, 8.76) | 50% | 0.5 | 0.03 | 8.76 | 0 | 2 | 3 |
| 13 | Asian | 40 | 1.49 | 34 | 0.55 | 0.37 (0.13, 1.06) | 63% | 0.37 | 0.13 | 1.06 | 0 | 2 | 3 |
| 14 | | | | | | | | . | . | . | 0 | 0 | 4 |
| 15 | Baseline ICS dose >=1000 | | | | | | | . | . | . | 0 | 0 | 4 |
| 16 | ug/day plus LABA | | | | | | | . | . | . | 0 | 0 | 4 |
| 17 | Yes | 107 | 1.15 | 118 | 0.73 | 0.64 (0.42, 0.97) | 36% | 0.64 | 0.42 | 0.97 | 0 | 2 | 4 |
| 18 | No | 149 | 0.78 | 137 | 0.59 | 0.75 (0.49, 1.16) | 25% | 0.75 | 0.49 | 1.16 | 0 | 2 | 4 |
| 19 | | | | | | | | . | . | . | 0 | 0 | 5 |
| 20 | Number of asthma exacerbations | | | | | | | . | . | . | 0 | 0 | 5 |
| 21 | in the 12 months prior to | | | | | | | . | . | . | 0 | 0 | 5 |
| 22 | study entry | | | | | | | . | . | . | 0 | 0 | 5 |
| 23 | 0 | 92 | 0.48 | 97 | 0.23 | 0.47 (0.21, 1.06) | 53% | 0.47 | 0.21 | 1.06 | 0 | 2 | 5 |
| 24 | 1 | 74 | 0.61 | 65 | 0.47 | 0.76 (0.42, 1.38) | 24% | 0.76 | 0.42 | 1.38 | 0 | 2 | 5 |
| 25 | >=2 | 90 | 1.68 | 93 | 1.24 | 0.74 (0.50, 1.09) | 26% | 0.74 | 0.5 | 1.09 | 0 | 2 | 5 |
| 26 | | | | | | | | . | . | . | 0 | 0 | 6 |
| 27 | Geographic region | | | | | | | . | . | . | 0 | 0 | 6 |
| 28 | North America | 72 | 0.68 | 65 | 0.83 | 1.23 (0.72, 2.11) | -23% | 1.23 | 0.72 | 2.11 | 0 | 2 | 6 |
| 29 | Latin America | 18 | 0.76 | 26 | 0.53 | 0.70 (0.27, 1.81) | 30% | 0.7 | 0.27 | 1.81 | 0 | 2 | 6 |
| 30 | Asia | 33 | 1.68 | 28 | 0.63 | 0.37 (0.12, 1.16) | 63% | 0.37 | 0.12 | 1.16 | 0 | 2 | 6 |
| 31 | Central and Eastern Europe | 105 | 0.72 | 98 | 0.56 | 0.78 (0.50, 1.22) | 22% | 0.78 | 0.5 | 1.22 | 0 | 2 | 6 |
| 32 | Western Europe plus Rest of World | 28 | 1.54 | 38 | 0.80 | 0.52 (0.25, 1.09) | 48% | 0.52 | 0.25 | 1.09 | 0 | 2 | 6 |

# Some of the Code

- Add Error Bars
  - By using **ScatterPlot** Statement with **xErrorLower** and **xErrorUpper**
- Replace Error bars with caps for outlier value
  - Pre-processing for the input dataset
  - By using **HighLowPlot** Statement with **HighCap** and **LowCap**

```
layout overlay /    xaxisopts =( type=log  label='Rate Ratio (Treatment/placebo)' labelattrs = (size = 7)
                                 tickvalueattrs=(size = 7)  offsetmin = 0.2 offsetmax = 0.2
                                 logopts=(tickintervalstyle =  linear   minorticks=true   tickvaluepriority=true
                                          viewmin = 0.1 viewmax = 10 tickvaluelist =  (0.1 0.2 0.5 1 2 5 10) )
                               )
                    yaxisopts = (reverse=true display=none) walldisplay=none;
       highlowplot y=GROUP high=HIGH_N_125 low=LOW_N_125 /
                        outlineattrs = (pattern=solid)
                        fillattrs = (color = black)
                        lineattrs = (color = black)
                        type=line
                        highcap = CAP_H lowcap = CAP_L;

       scatterplot y=group x=Ratio_N_125 /
                        markerattrs=(color=black symbol=squarefilled) ;
       referenceline x=1;
endlayout;
```

# Conclusions

- Time-Cost
  - Do not need to know anything about templates to create statistical graphics
  - With just a little knowledge of the graph and style template languages
- Users' Experience
  - Easy to use
  - Easy to modify based on stakeholders' comments
- Traceability
  - What you see is what you get

## References:


- How to interpret the sample forest plot
- What is an effect size?

  Center For Evidence-Based Intervention
  Department of Social Policy and Intervention
  University of OXFORD

- Forest plots and the interpretation of subgroups

  Jack Cuzicka, Cancer Research UK Centre for Epidemiology, Mathematics and Statistics, Wolfson Institute of Preventive Medicine, Charterhouse Square, London EC1M 6BQ, UK, The Lancet, Volume 365, Issue 9467, 9–15 April 2005, Pages 1308