Summarizing the Incidence of Adverse Events Using Volcano Plots and Time Windows

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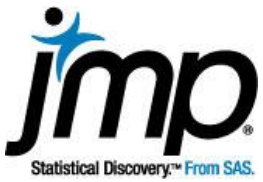


Adverse Events

- Understanding the risk of AEs is a critical component for describing the safety profile of a new medication
- When safety is most critical, insight is more difficult
  - Disease severity
  - Trial duration
  - Number of subjects
- AEs occur spontaneously during the course of the trial
- Multiplicity adjustment to reduce false positive findings
  - How to account for this without overly affecting power
- Some therapeutic areas or drug classes allow one to predict events likely to occur
- Doesn't help novel drug classes or orphan diseases

Traditional Adverse Event Summaries

Table XX.XX.XX: Incidence of Treatment Emergent Adverse Events

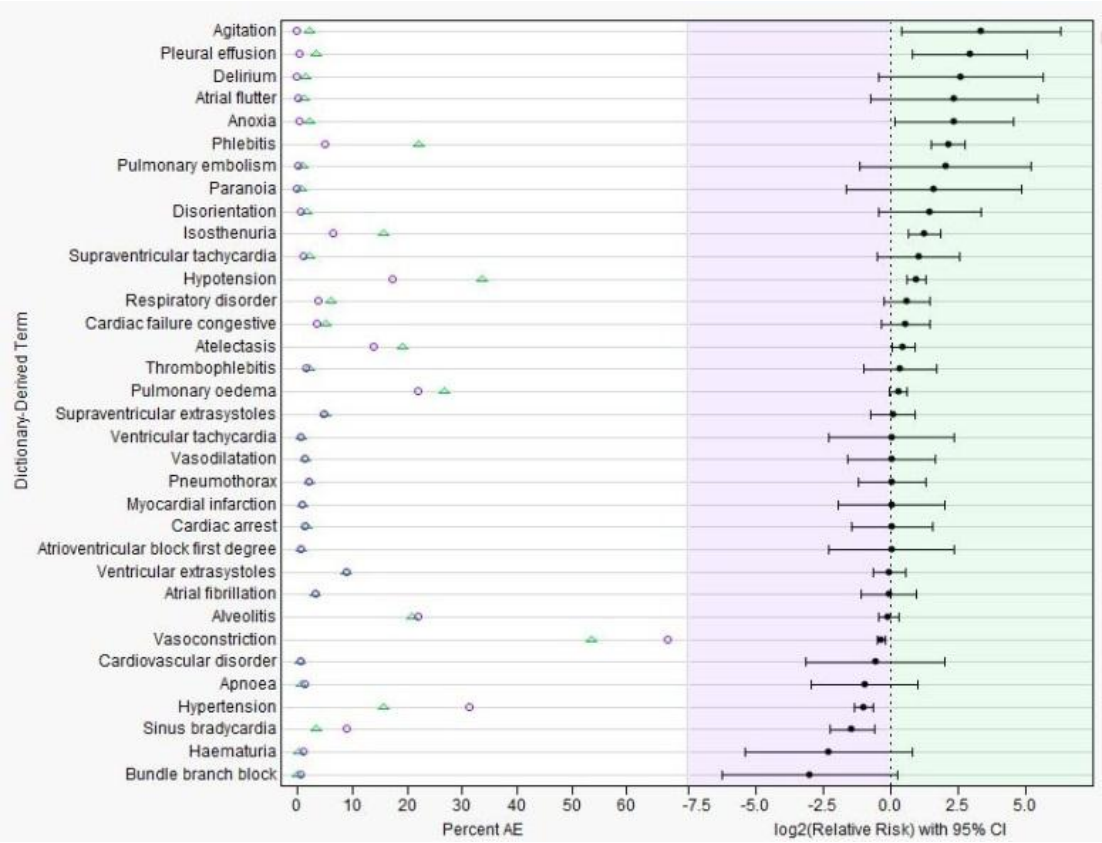
	Nicardipine (n=447)	Placebo (n=455)
Blood & Lymphatic System Disorders	195 (44)	203 (45)
Anaemia	137 (31)	160 (35)
Platlet Destruction Increased	29 (6)	16 (4)
... (5 more)		
Cardiac Disorders	156 (35)	175 (38)
Ventricular Extrasystoles	39 (9)	41 (9)
Sinus Bradycardia	15 (3)	41 (9)
.... (22 more)		
Gastrointestinal Disorders	95 (21)	90 (20)
Vomiting	59 (13)	61 (13)
Gastrointestinal haemorrhage	17 (4)	10 (2)
... (14 more)		
19 more System Organ Classes		
160 more Preferred Terms		

Data from a clinical trial of Nicardipine. Haley EC, Kassell NF and Torner JC (1993).

Traditional Adverse Event Summaries

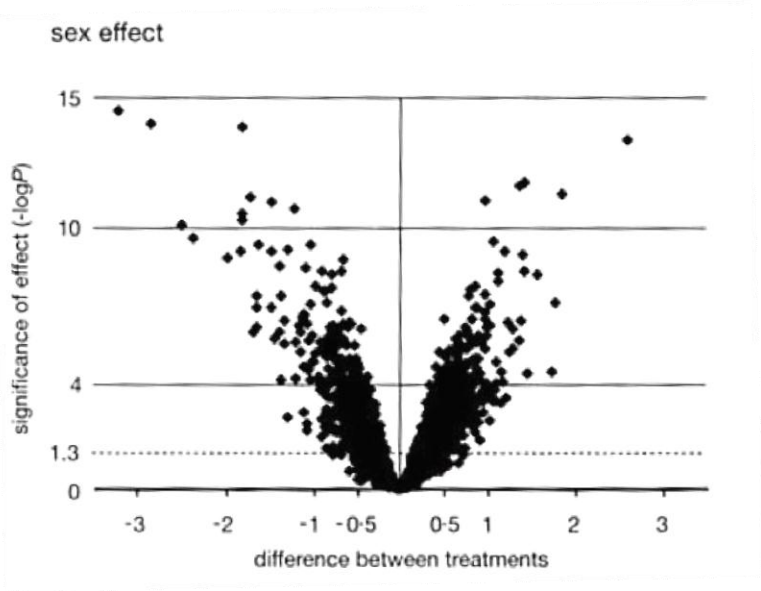
- Previous table may summarize overall risk of TEAEs
- Additional Tables for
  - AEs by event severity
  - AEs by relationship to study medication
  - AEs by study periods
    - » Pre-treatment
    - » Treatment phase
    - » Off-treatment follow-up
  - AEs of Special Interest
    - » Ocular AEs for ophthalmics / pulmonary exacerbation for CF
    - » Combinations of events
    - » Grouping of events

Traditional Relative Risk Plots



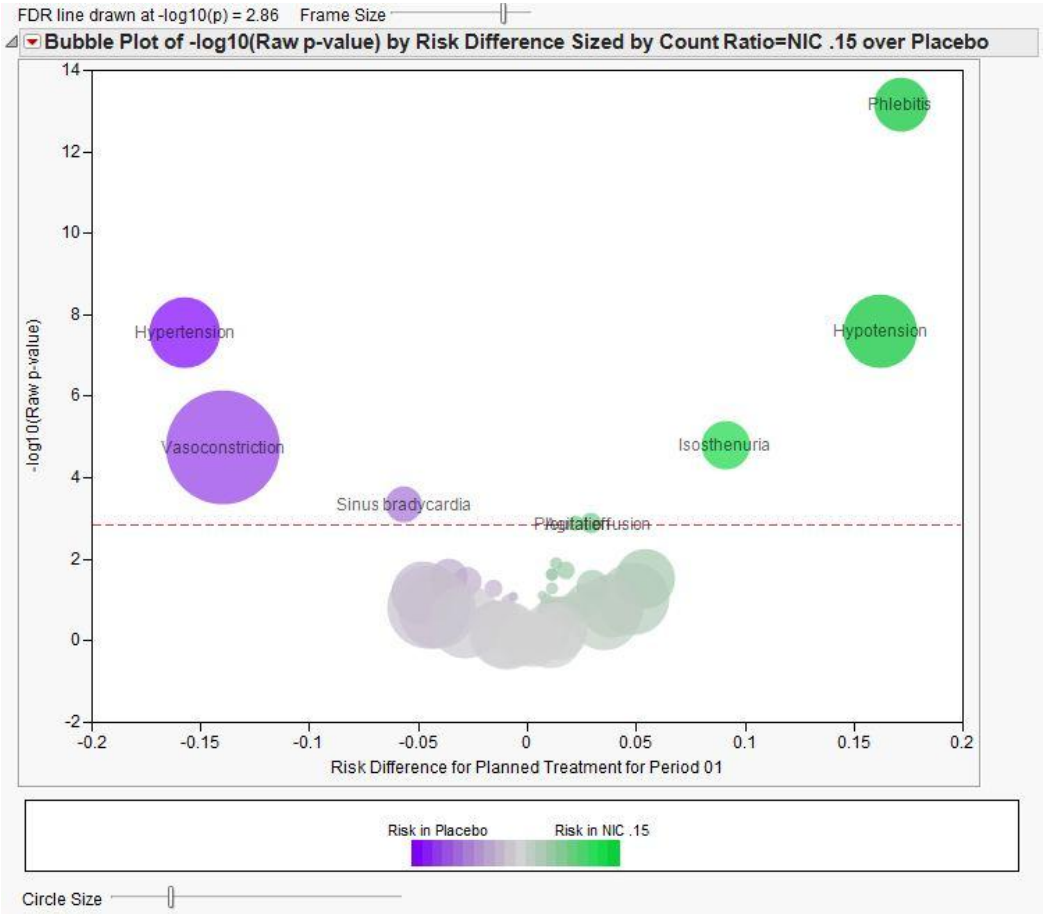
- Traditional Relative Risk Plot (Amit et al. 2008)
- Recommended as standard display for reporting adverse event incidence

Volcano Plots



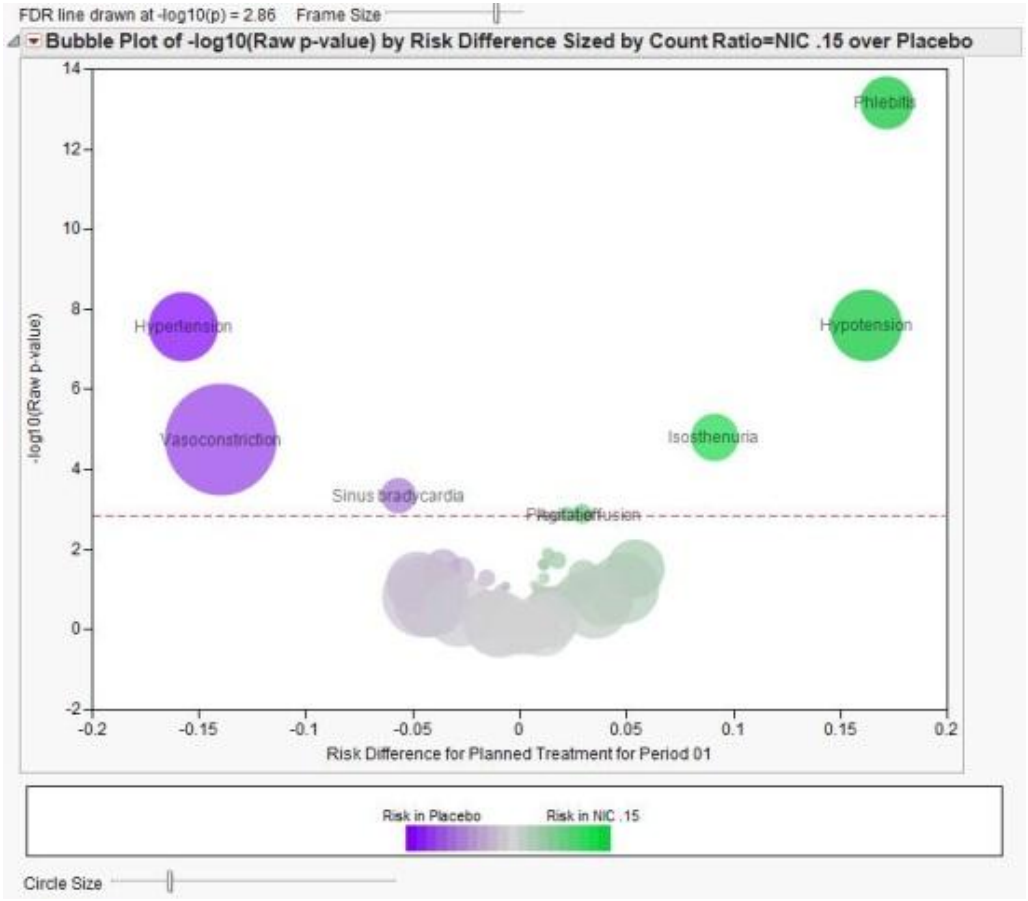
- First described in Jin et al. (2001) *Nature Genetics*
- X-axis is difference in LS means of $\log_2$ gene expression, a relative measure of RNA abundance
- Y-axis is $-\log_{10}$(p-value)
  - *p*-value of 1 equals 0
  - *p*-value of 0.1 equals 1
  - *p*-value of 0.01 equals 2
  - *p*-value of 0.001 equals 3
  - *p*-value of 0.0001 equals 4
- Diamonds represent one of 3931 genes
- Look for large, significant differences that occur towards upper corners

Enhanced AE Volcano Plots



- Bubble size represents frequency of AE on study
- Color used to illustrate which treatment exhibits higher incidence
- Difference can be
  - Difference in proportions
  - Log_2(relative risk)
  - Log_2(odds ratio)
- Space-constrained view of 201 AEs which highlights interesting signals

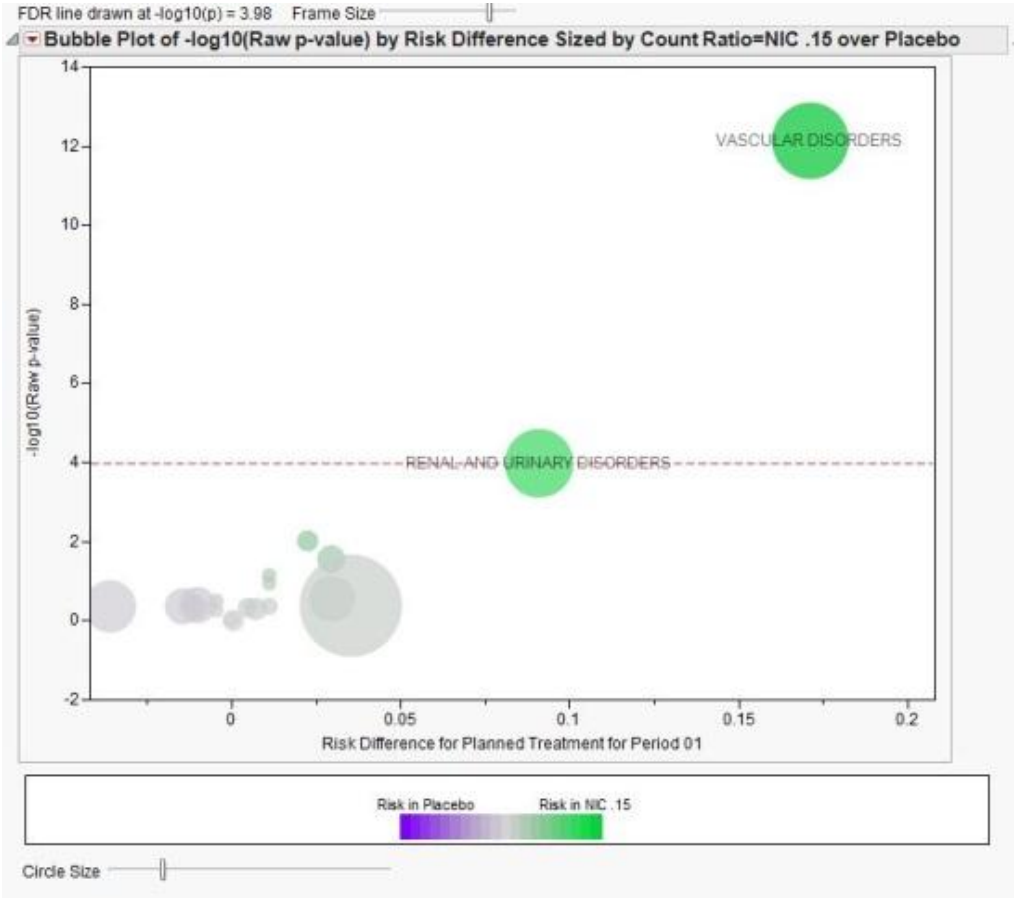
Multiplicity Concerns



Bubbles with center above the dotted red line are significant adjusting for multiple comparisons.

- Crowe et al. (2009). Should strike a balance to limit false positives without sacrificing too much power
- False discovery rate (FDR). Benjamini & Hochberg (1995)
- $10^{-2.86} = 0.0014$ on p-value scale
- Controls FDR: proportion of erroneous inferences
- Not FWE: probability of any erroneous inferences

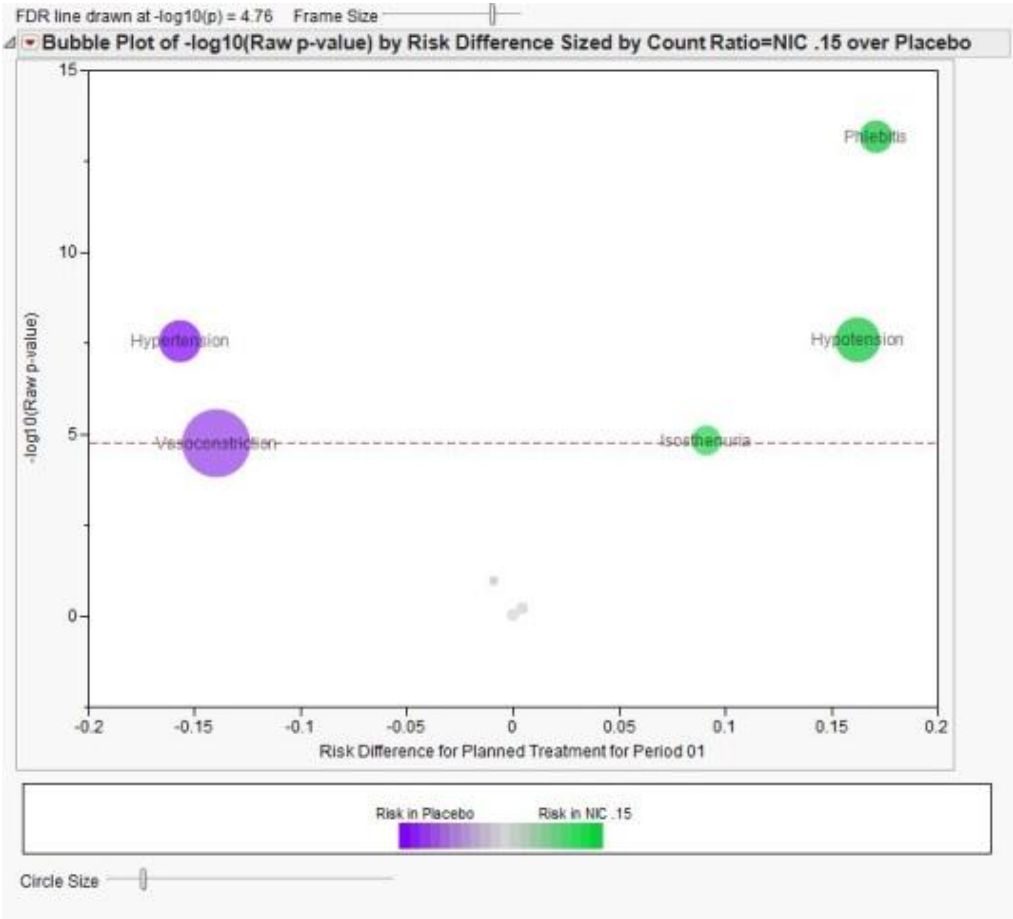
Multiplicity Concerns



Initial bubble plot displays most significant term from each group (here, system organ class)

- Double FDR
  - Mehrotra & Heyse (2004)
  - Mehrotra & Adewale (2012)
- Accounts for a classification variable such as MedDRA system organ class
- Method considers whether related terms show differences between the treatments and upweights or downweights the significance of an individual term accordingly.

Multiplicity Concerns



- First plot illustrates significant groupings or body systems
- Second plot displays terms from significant systems

Note how Sinus Bradycardia (Cardiac Disorders), Pleural Effusion (Respiratory, Thoracic and Mediastinal Disorders) and Agitation (Psychiatric Disorders) are no longer significant using Double FDR.

These SOCs had 12, 8, and 3 other non-significant terms, respectively.

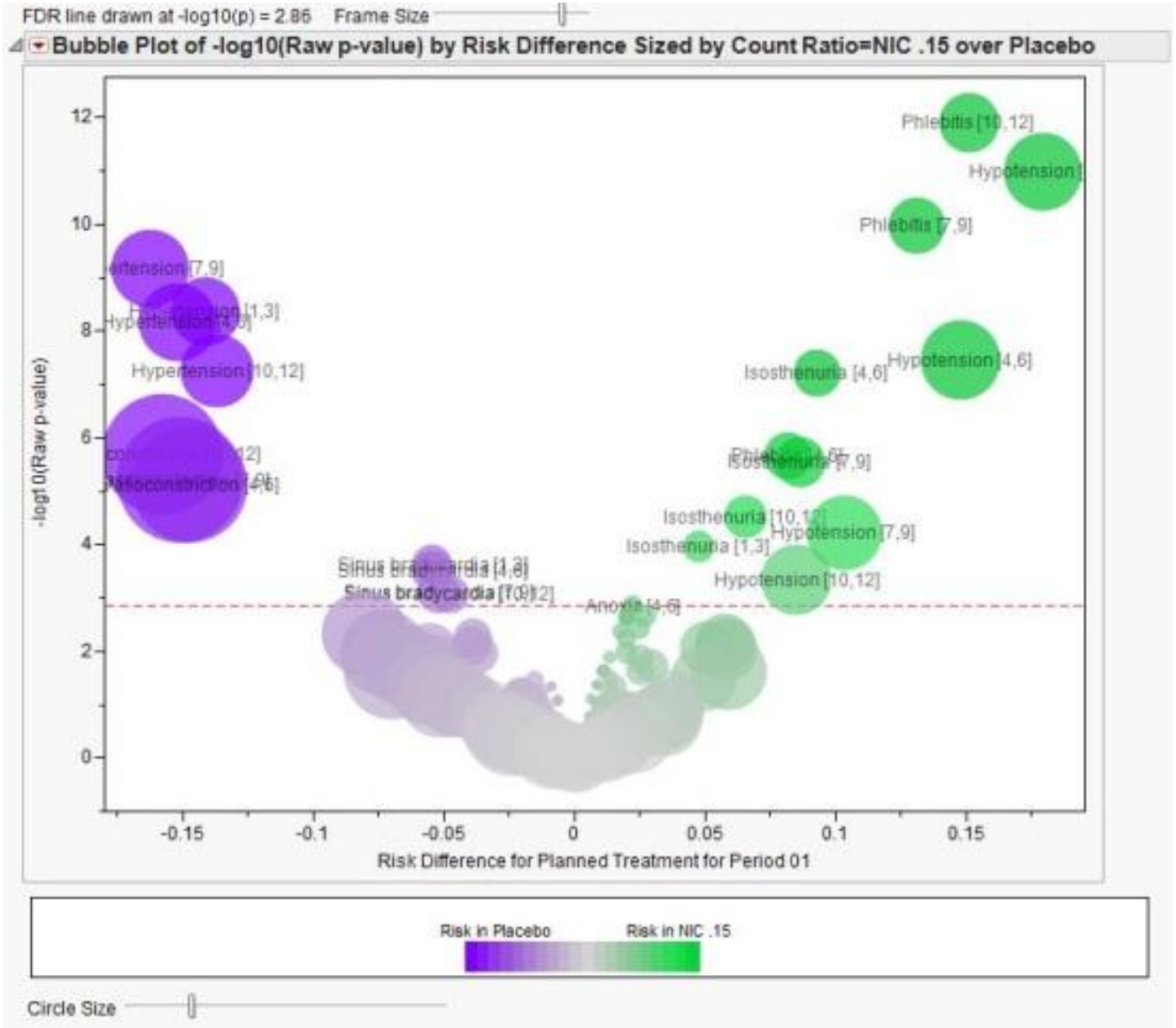
Incorporating Time Windows

- Time is related to drug exposure
- Influence of time on AE incidence tends to be ignored
  - Rarity of most adverse events could make breaking the study into mutually exclusive time periods rather pointless
  - Rarely sufficient space within a journal to report all findings of interest
  - Sheer scope of events makes it difficult to summarize results meaningfully
- AEs occur spontaneously during the course of the trial
- Can define time windows
  - Mutually exclusive time periods
  - Calculate incidence separately within each window
  - For example, windows of 3 day duration: [1,3] [4,6] [7,9] [10,12]

Incorporating Time Windows

- Provides insight into how risk changes over time
  - Increased exposure could lead to higher risk of adverse events
  - Body could adjust to presence of drug with events resolving naturally

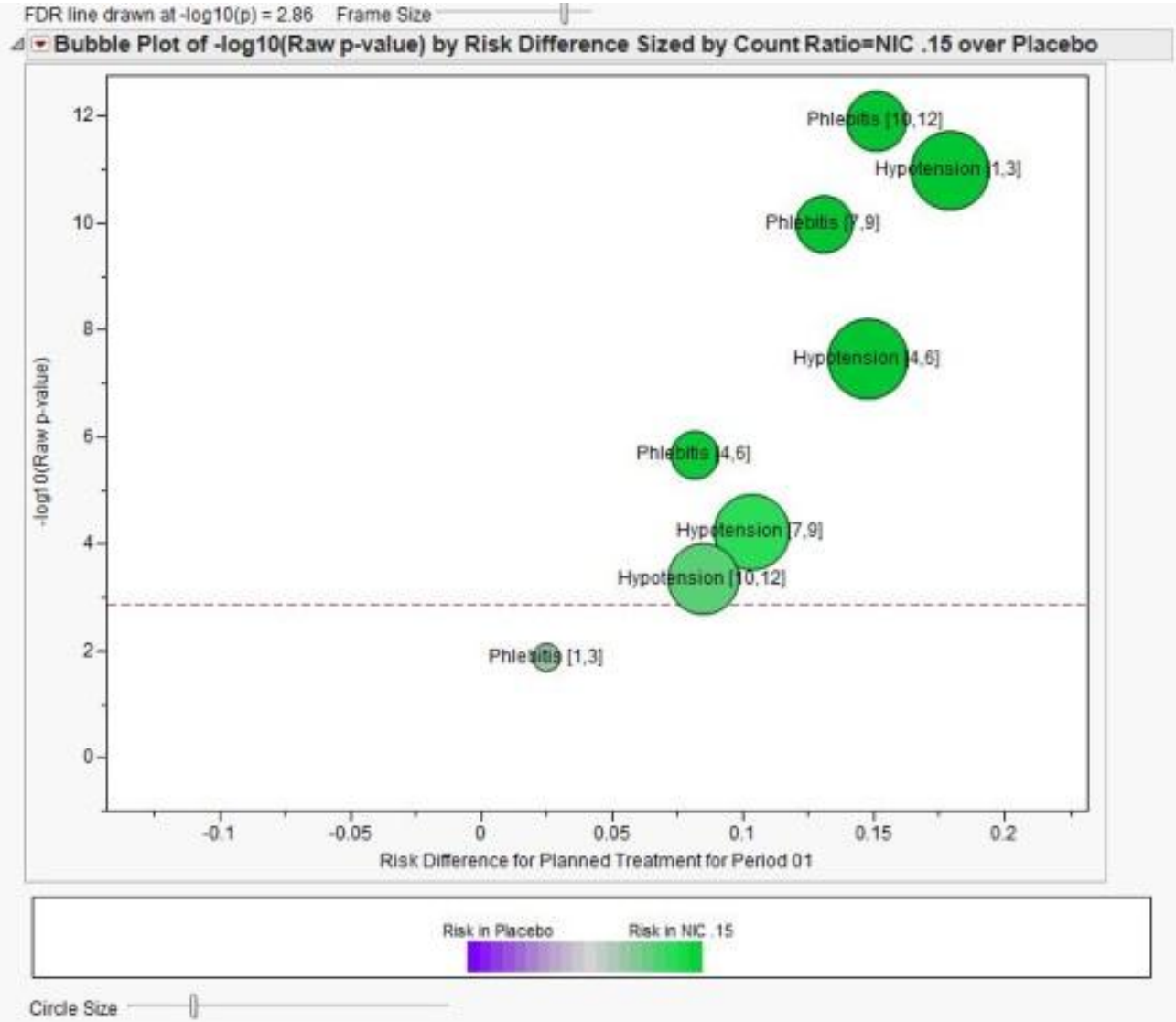
Incorporating Time Windows



Get one bubble per preferred term and time window

Four windows here are [1,3] [4,6] [7,9] [10,12] based on study day

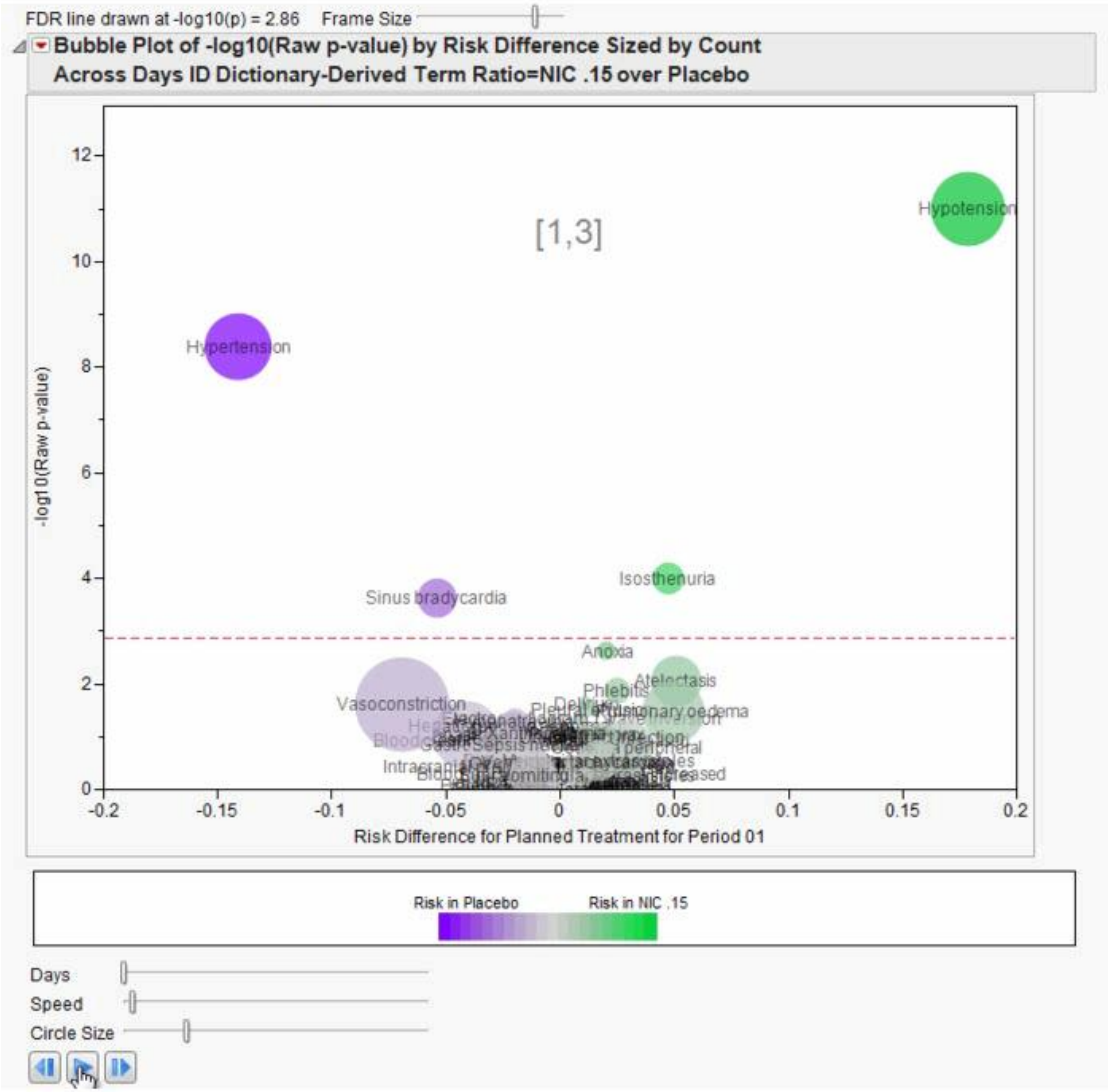
Incorporating Time Windows



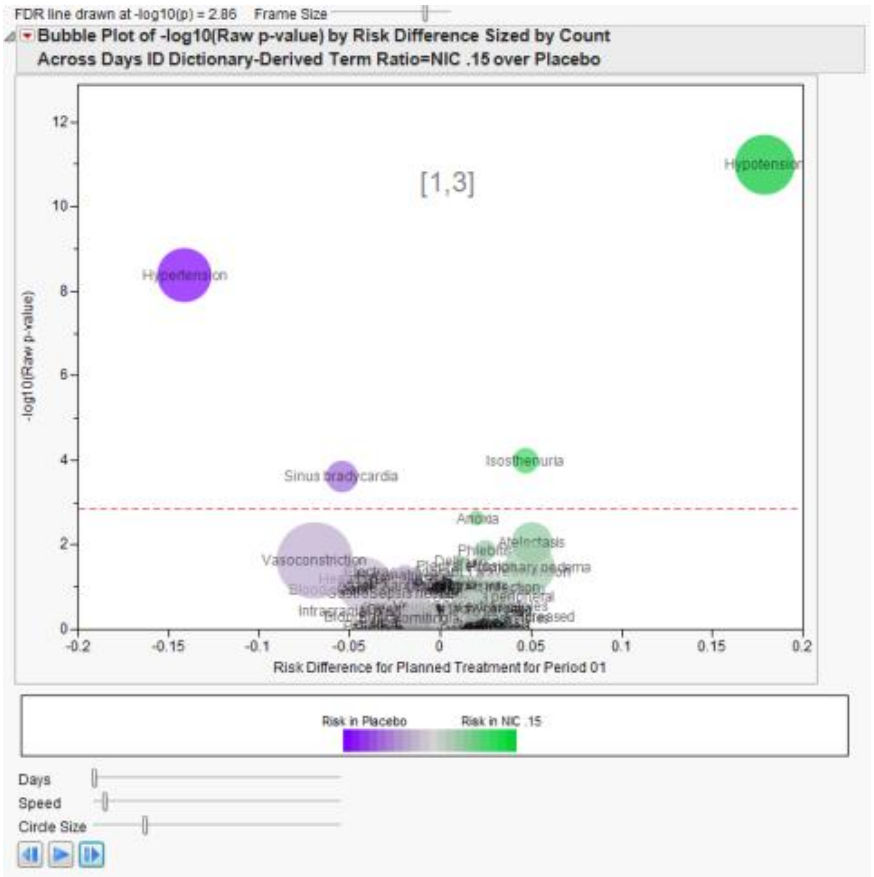
Hypotension risk for Nicardipine reduces over time. Number of cases appears to reduce slightly.

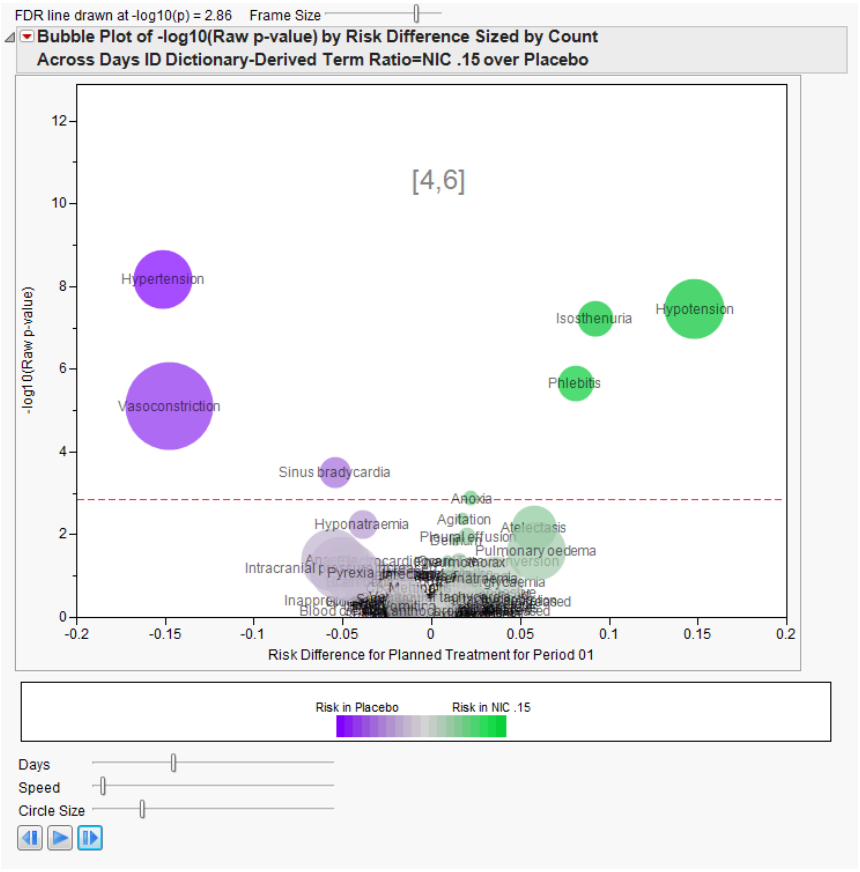
Phlebitis risk for Nicardipine increases over time. Number of cases increases.

Exploding or Erupting Volcano Plots

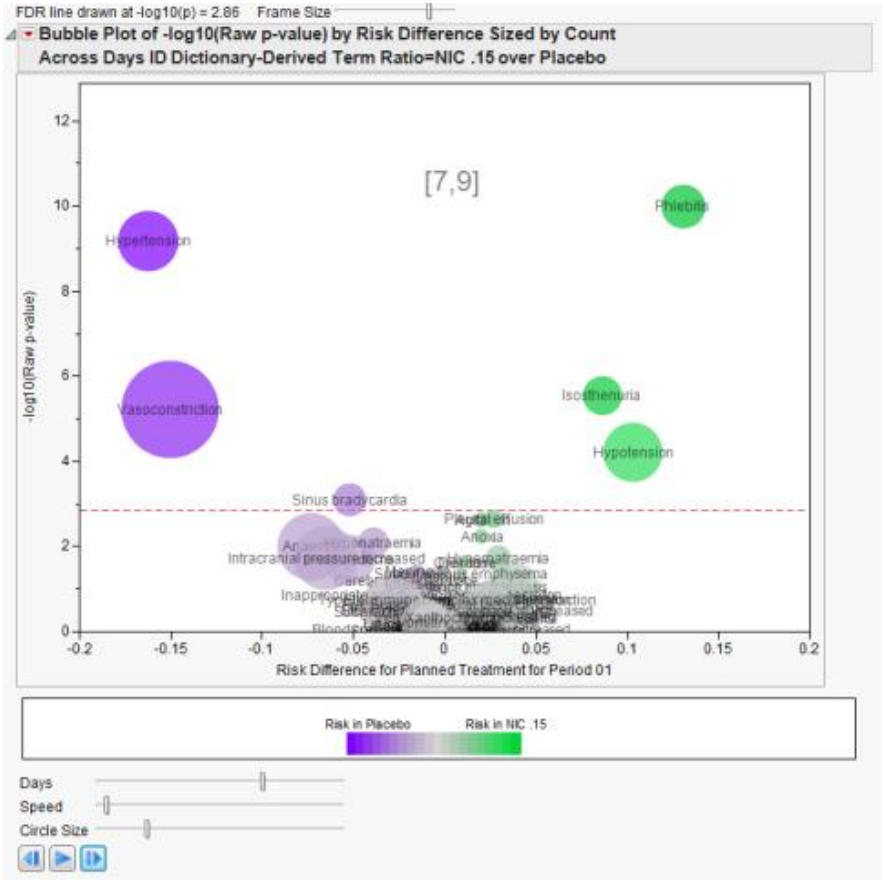


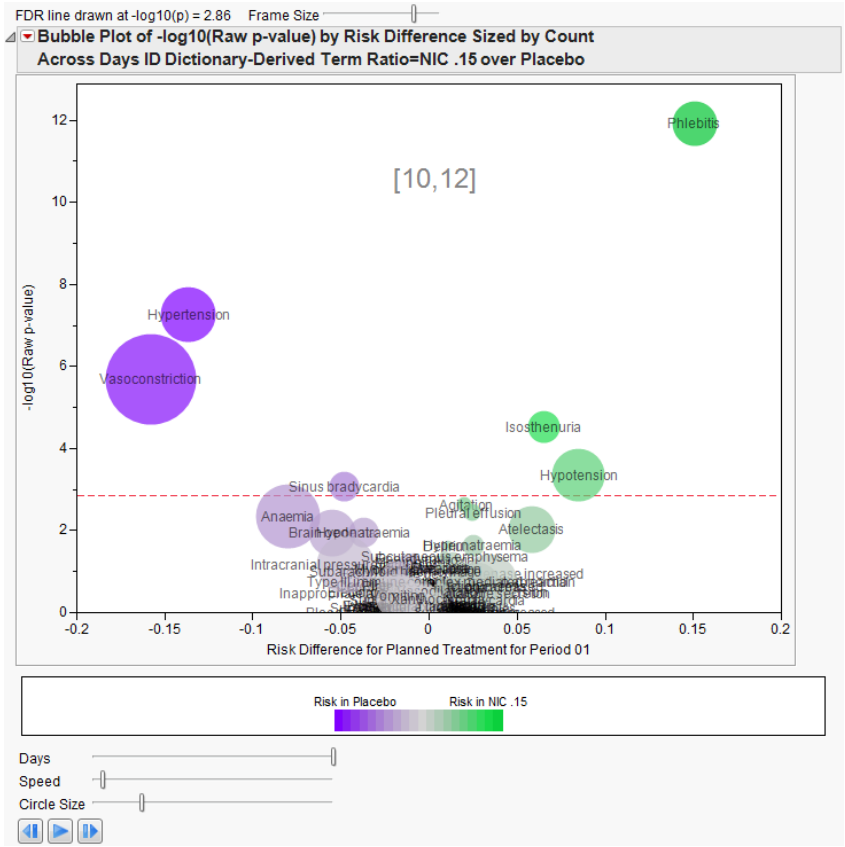
Multiple Plots





Multiple Plots





Comparison with Traditional RR Plots

- Relative risk plot less space constrained
  - Space for 201 rows needed
- More difficult to assess how frequent the AE is unless individual rates are presented (left panel)
- RR plot presents either unadjusted or adjusted values. Volcano plots prints unadjusted values with significance threshold based on multiple comparisons
- Both figures limit discussion to pairs of treatments, can do a 3D volcano with three treatments or use a trellis of all pairs
- Difficult to incorporate time changes with RR Plot

Conclusions

- Volcano plots are a space-constrained view which can be used to summarize AE incidence
- Quickly draws attention to the important safety signals
- Straightforward to incorporate multiplicity adjustment
- With time windows, volcano plots provide insight into how risk changes over time
- Since no confidence intervals displayed, perhaps more straightforward for clinical interpretation
- How many time windows should be specified?
- Plots generated with **JMP Clinical**

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