A Step-Down Approach to Analyzing Electrocardiogram (ECG) Endpoints For *In Vivo* Regulatory Toxicology Studies

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Outline

- ECG Endpoints in Regulatory Toxicology Studies
  - Rationale, Design
- Current Analysis Methodology
- Assessment of Power
  - Dunnett's Test
  - Step-Down version of Dunnett's Test
  - Linear Trend Test

Regulatory Toxicology ECGs

Rationale

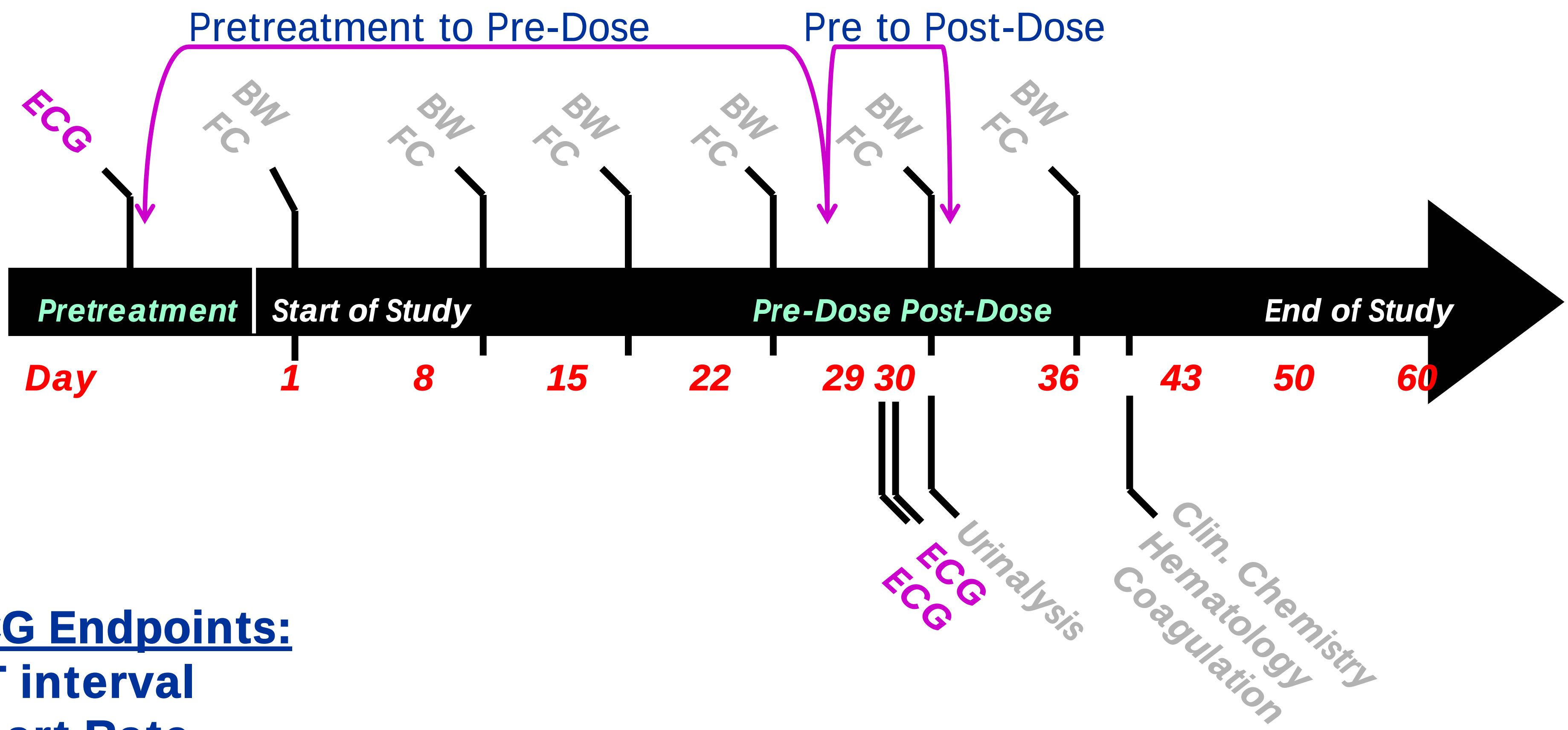
- ID long term changes in CV parameters
  - Large Animals (Canines & NHP)
- Mandatory to Evaluate CV safety for Regulatory Review
  - Combined with Safety Pharmacology data to support FIH studies

Study Design

- Parallel Group
  - Control & 3 Treatment Groups (same drug, escalating doses)
  - Sample Size: n=3/sex/group
- Analysis: ANOVA with Step-Down Dunnett's Procedure
  - Sexes analyzed separately

1-Month General Tox Study with 1-Month Recovery

Analyze Changes



ECG Endpoints:

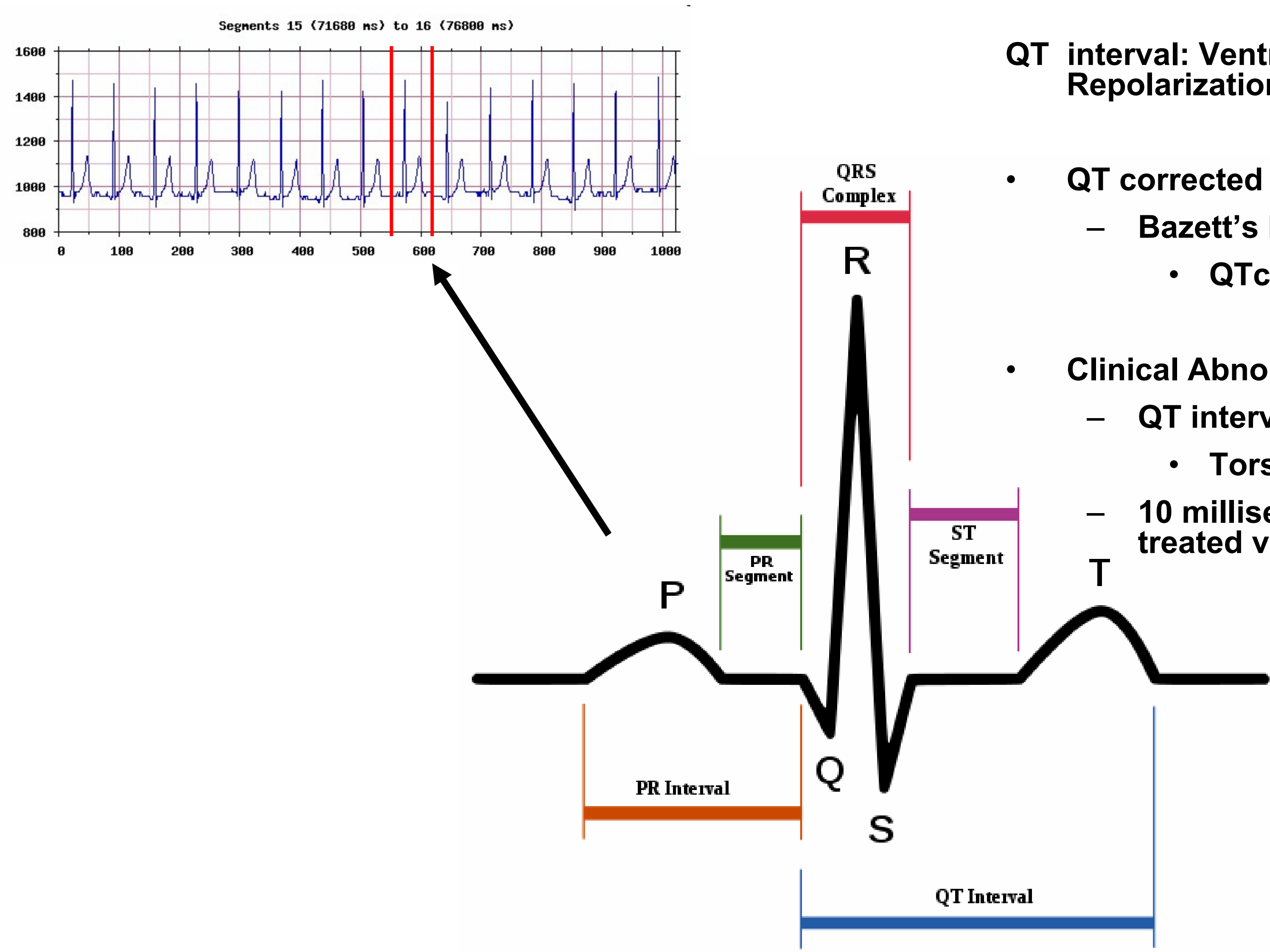
QT interval

Heart Rate

PR interval

QRS interval

ECG Endpoints- QT interval



QT interval: Ventricular Repolarization Time

- QT corrected for Heart Rate:
  - Bazett's Formula
    - QTc= QT/√RR interval
- Clinical Abnormality:
  - QT interval Prolongation
    - Torsades de Pointes
  - 10 millisec prolongation treated versus control

Have you Heard?

Biaxin

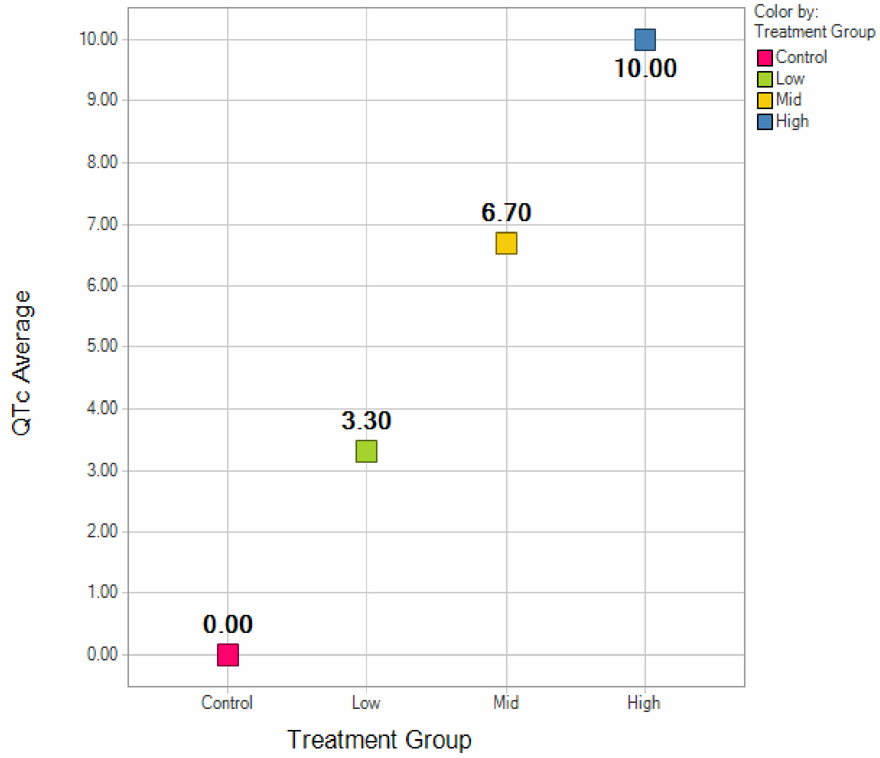
Geodon

Tykerb

Symbicort

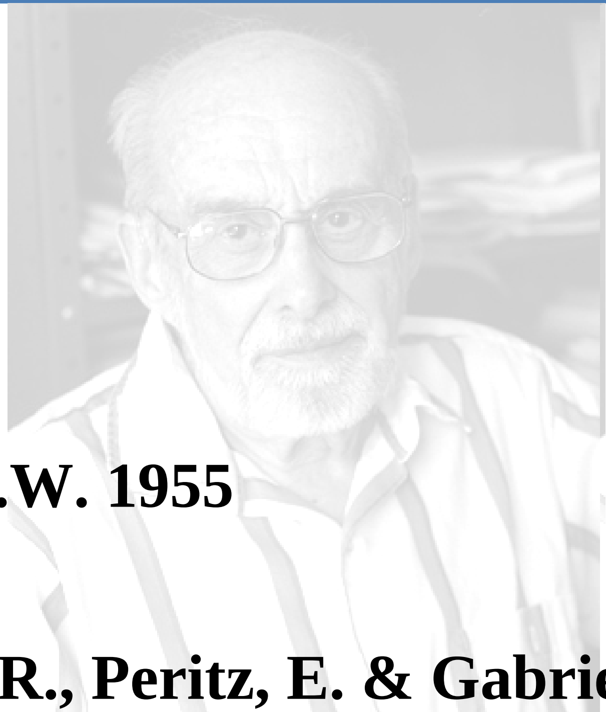
Analyzing and Evaluating QTc Data

1. Estimated σ from in-house historical control data n=63
   1. pre-dose to post-dose changes
   2. σ ≈ 6
2. Produced 1000 simulations of 3 monotonic patterns with varying σs, sample sizes (n), and mean changes from control
3. Linear Pattern most Scientifically Relevant
4. Analyzed data in SAS – *GLM* Procedure to obtain Dunnett's adjusted p- values
   1. PROBMC function in SAS to obtain 2-sided Dunnett critical values for Step-Down procedure



How does Step-Down Dunnett's Test perform against Dunnett's Test?

Step-Down Dunnett's Procedure



Dunnett, C.W. 1955

Marcus, R., Peritz, E. & Gabriel, K.R. 1976.

Dunnett, C.W.; Tamhane, A.C 1991

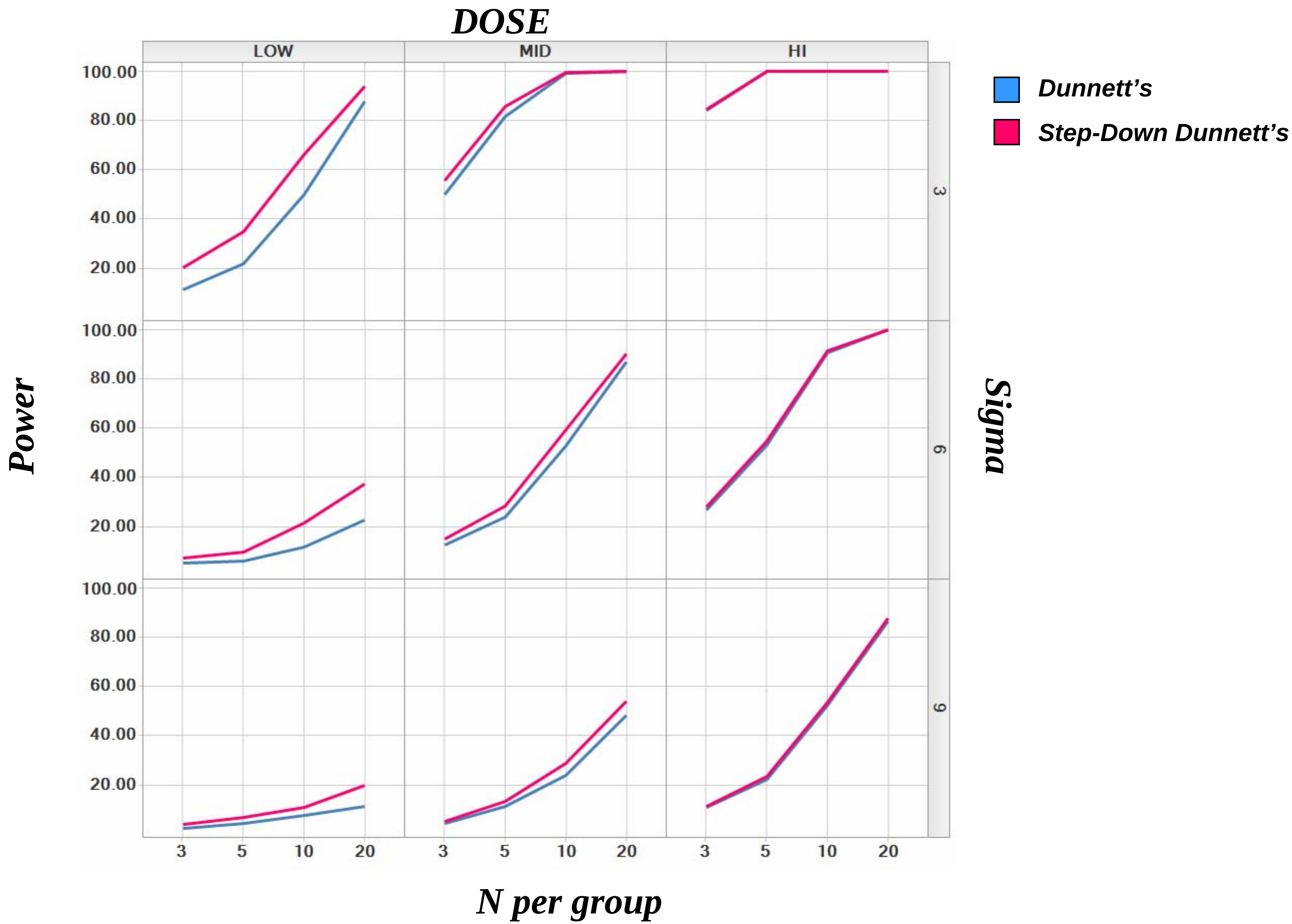
Dunnett's Step-Down Procedure

1. Order the means by the t-values of their differences from the control (tdiff) so that $t_{(1)} < t_{(2)} < t_{(3)}$.
2. Compare $t_{(3)}$ to $c_{(3)}$. If smaller, then stop and retain all inequalities. Otherwise, reject $\mu_0 = \mu_{(3)}$ and proceed to step 3.
3. Compare $t_{(2)}$ to $c_{(2)}$. If smaller, then stop and retain all inequalities. Otherwise, reject $\mu_0 = \mu_{(2)}$ and proceed to step 4.
4. Compare $t_{(1)}$ to $c_{(1)}$. If smaller, then stop and retain all inequalities. Otherwise, reject $\mu_0 = \mu_{(1)}$.

Enhanced power by modifying the critical points from one step to the next

Westfall , Peter H., Randall D. Tobias, Dror Rom, Russell D. Wolfinger, and Yosef Hochberg. 1999. *Multiple Comparisons and Multiple Tests Using SAS*, Cary, NC: SAS Institute, Inc.

Line Chart of Power for Dunnett's and Step-Down Dunnett's, Stratified by Dose and Sigma



QTc Simulation Results
Dunnett's vs. Step-Down Dunnett's

CASE: LINEAR		LOW- 3.3 Δ in milliseconds			MED- 6.7 Δ in milliseconds			HI- 10.0 Δ in milliseconds		
σ	n	Power from Dunnett's	Power from Step-Down Dunnett's	↑ in Power	Power from Dunnett's	Power from Step-Down Dunnett's	↑ in Power	Power from Dunnett's	Power from Step-Down Dunnett's	↑ in Power
3	3	11.4	20.4	9.0	49.8	55.7	5.9	84.3	84.7	0.4
3	5	22.0	35.0	13.0	81.8	85.9	4.1	99.8	99.8	0.0
3	10	49.9	66.4	16.5	99.1	99.4	0.3	100.0	100.0	0.0
3	20	87.8	94.0	6.2	100.0	100.0	0.0	100.0	100.0	0.0
6	**3**	**5.0**	**7.2**	**2.2**	**12.5**	**15.0**	**2.5**	**26.8**	**28.0**	**1.2**
6	5	5.9	9.6	3.7	23.9	28.3	4.4	53.3	54.9	1.6
6	10	11.8	21.6	9.8	52.8	59.3	6.5	90.8	91.4	0.6
6	20	22.7	37.5	14.8	86.9	90.2	3.3	99.9	99.9	0.0
9	3	2.3	3.8	1.5	4.2	5.1	0.9	10.8	11.2	0.4
9	5	4.5	6.7	2.2	11.4	13.4	2.0	22.4	23.5	1.1
9	10	7.6	10.9	3.3	23.9	28.7	4.8	52.2	53.6	1.4
9	20	11.3	19.9	8.6	48.1	54.2	6.1	86.7	87.6	0.9

QTc Simulation Results
Dunnett’s vs. Step-Down Dunnett’s

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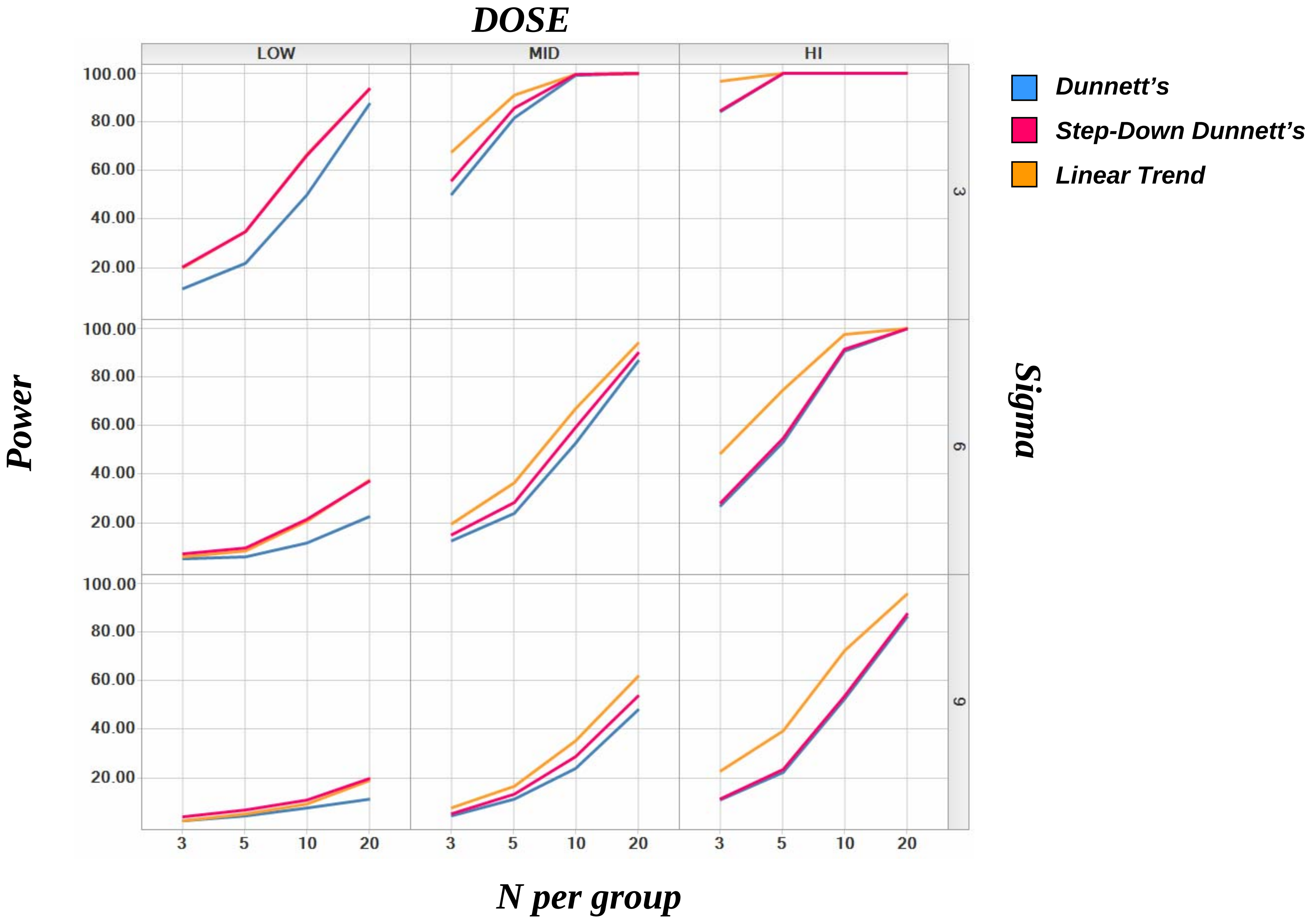
Line Chart of Power for Dunnett's, Step-Down Dunnett's, and Linear Trend Stratified by Dose and Sigma



What about Linear Trend Tests?

CASE: LINEAR		LOW- 3.3 Δ in miliseconds			MED- 6.7 Δ in miliseconds			HI- 10.0 Δ in miliseconds		
σ	n	Power From Dunnett's	Power from Step-Down Dunnett's	Power From Linear Contrasts	Power From Dunnett's	Power from Step-Down Dunnett's	Power From Linear Contrasts	Power From Dunnett's	Power from Step-Down Dunnett's	Power From Linear Trend Test
3	3	11.4	20.4	19.9	49.8	55.7	67.3	84.3	84.7	96.6
3	5	22.0	35.0	34.9	81.8	85.9	90.9	99.8	99.8	100.0
3	10	49.9	66.4	66.5	99.1	99.4	99.6	100.0	100.0	100.0
3	20	87.8	94.0	94.0	100.0	100.0	100.0	100.0	100.0	100.0
6	3	5.0	7.2	5.9	12.5	15.0	19.5	26.8	28.0	48.4
6	5	5.9	9.6	8.5	23.9	28.3	36.6	53.3	54.9	74.8
6	10	11.8	21.6	20.5	52.8	59.3	67.2	90.8	91.4	97.4
6	20	22.7	37.5	37.6	86.9	90.2	94.1	99.9	99.9	100.0
9	3	2.3	3.8	2.4	4.2	5.1	7.4	10.8	11.2	22.6
9	5	4.5	6.7	5.1	11.4	13.4	16.7	22.4	23.5	39.5
9	10	7.6	10.9	9.2	23.9	28.7	35.3	52.2	53.6	72.5
9	20	11.3	19.9	19.0	48.1	54.2	62.1	86.7	87.6	96.1

Conclusions

- **Step-Down Dunnett's resulted in 2-3 percentage point increase in power for relevant sigma/n**
  – Relevant?
- **Well powered cases (>80% at High Dose) resulted in <1 % gain in power**
- **Step-Down Dunnett's test fares better when detecting small differences**
  – up to ~6% gain in power for well powered cases
  – up to ~16% gain in power for moderately powered cases
- **Linear Trend Tests More Powerful but Step-Down Dunnett's prevails at low dose**

Dose	Power	Average Gain in Power by Step-Down Dunnett's Test
LO	< 40	6.8
	50-60	16.5
	75+	6.2
MID	< 30	3.5
	40-60	6.2
	75+	3.2
HI	< 30	0.9
	40-60	1.5
	75+	0.3

References

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- **Dunnett, C.W.; Tamhane, A.C. *Step Down Multiple Testing for comparing treatments with a control in unbalanced one-way layouts.* Stat. Med 1991, 10, 939-947.**
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- **Marcus, R., Peritz, E. & Gabriel, K.R. 1976. *On closed testing procedures with special reference to ordered analysis of variance.* Biometrika 63,655-60**
- **Westfall , Peter H., Randall D. Tobias, Dror Rom, Russell D. Wolfinger, and Yosef Hochberg. 1999. *Multiple Comparisons and Multiple Tests Using SAS*, Cary, NC: SAS Institute, Inc.**
- Web resource: http://drugs.emedtv.com/medicine/qt-prolonging-medications.html

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