# Rethinking Endpoints in Antianginal Trials:
## From Exercise Time to Patient-Centered Outcomes

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## INTRODUCTION & AIMS

Regulatory approval of antianginal therapies has historically relied on exercise treadmill test (ETT) endpoints, yet ETT reflects functional capacity influenced by non-anginal factors and may not directly capture patient-experienced angina burden.

We analyzed data from ORBITA-2[1] (PCI vs placebo; n = 301) and ORBITA-COSMIC[2] (coronary sinus reducer vs placebo; n = 50) to evaluate how commonly used endpoints relate to underlying clinical constructs and how endpoint choice influences the detection of treatment effects.

**Primary Aim:**

- To determine how choice of primary endpoint influences power to detect treatment effects in double-blind, placebo-controlled antianginal trials

**Additional Aims:**

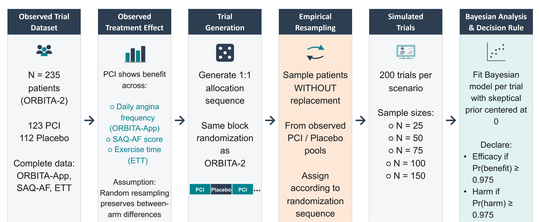
- To compare clinical construct alignment of ETT and ORBITA-App–recorded daily angina frequency
- To evaluate how the Seattle Angina Questionnaire (SAQ) Angina Frequency score reflects true angina episode frequency over its recall window

## METHODS

**Data Sources:**

- ORBITA-2 dataset (PCI vs placebo; n = 301)
- ORBITA-COSMIC dataset (coronary sinus reducer vs placebo; n = 50)

**Empirical Resampling Framework for Power Estimation:**




**Construct Alignment Analyses:**

- Baseline associations quantified using Somers' D from Bayesian ordinal logistic models
- Outcomes: ORBITA-App daily angina frequency; ETT exercise time
- Predictors: SAQ domains, Canadian Cardiovascular Society (CCS) angina class, ROSE angina typicality, age and sex
- Combined ORBITA-2 and ORBITA-COSMIC datasets (n = 351)

**SAQ Anchoring and Recall Period Analyses:**

- SAQ Angina Frequency related to ORBITA-App recorded angina episode counts
- App data summarized over preceding weekly windows (final week to 3 weeks prior)
- Somers' D used to assess recency bias within 4-week recall period
- Combined ORBITA-2 and ORBITA-COSMIC datasets (n = 351)

**Clinically Meaningful Estimand Derivation from ORBITA-App Daily Angina Frequency Models:**

- Bayesian ordinal logistic model[3,4] of daily angina frequency (ORBITA-2)
- Conditional on previous-day frequency (first-order Markov)[3]
- Transition probabilities marginalized over prior-day distributions[3]
- From marginal state probabilities, we derived:
  - **Expected reduction in angina episodes attributable to PCI**
  - **Expected additional angina-free days attributable to PCI**
  - **Net days with reduced symptom burden attributable to PCI**

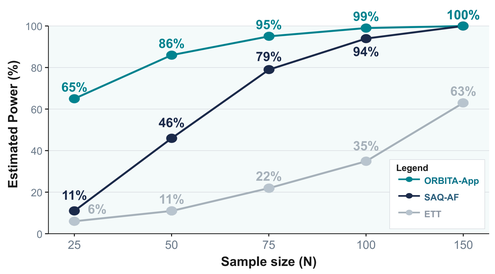
## DISCUSSION

- ETT, SAQ and ORBITA-App reflect **distinct but overlapping clinical constructs**
- Exercise-based endpoints primarily capture **functional capacity, which is influenced by both anginal and non-anginal factors,** whereas daily symptom tracking enables **high-resolution longitudinal assessment of angina dynamics** not accessible through exercise testing or recall-based questionnaires
- Limitation: ORBITA-App data were modeled using a **first-order Markov** structure[3]; misspecification of temporal dependence may affect precision and inflate type I error
- **Future work:**
  - Evaluate temporal dependence assumptions (e.g. comparison with higher-order Markov structures and alternative temporal aggregation)
  - Perform empirical null resampling to calibrate type I error under Bayesian decision rules

## RESULTS

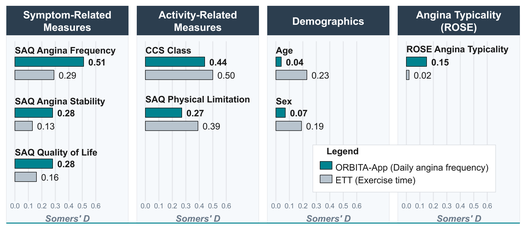
### Endpoint Power and Clinical Construct Alignment

**Figure 1.** Endpoint Choice Influences Power to Detect Treatment Effects




*Empirical power from 200 resampled trials at observed ORBITA-2 effect size. Decision rule: Pr(benefit) ≥ 0.975. Pr(benefit) = Pr(PCI better than placebo).*

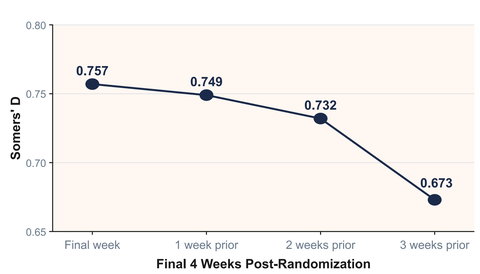
**Figure 2.** ORBITA-App Angina Frequency and ETT Exercise Time Reflect Distinct Underlying Clinical Constructs (Somers' D)




*Symptom-related measures aligned more strongly with ORBITA-App; activity-related measures aligned with ETT. ORBITA-App data showed weaker associations with demographic factors and stronger alignment with angina typicality.*

### SAQ Angina Frequency: Recall Behavior and Symptom Interpretation

**Figure 3.** SAQ Reflects Recent Angina Frequency More Strongly Than Earlier Symptoms Within the 4-Week Recall Period




*SAQ-AF showed strongest association with most recent ORBITA-App symptom frequency, with attenuation for earlier weeks (recency bias).*

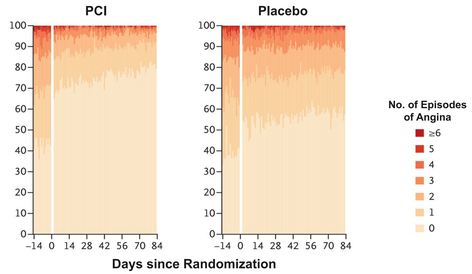
**Table 1.** Expected Angina Episode Counts by SAQ Angina Frequency Score Across Weeks of the 4-Week Recall Period

| SAQ-AF Score | Final Week (95% CrI) | 1 Week Prior (95% CrI) | 2 Weeks Prior (95% CrI) | 3 Weeks Prior (95% CrI) | 4-Week Average (95% CrI) |
|---|---|---|---|---|---|
| **0** | 22.7 (16.1–29.7) | 21.4 (15.9–26.9) | 21.0 (15.2–26.8) | 21.1 (15.8–26.9) | 20.4 (16.5–24.8) |
| **20** | 16.6 (13.3–20.2) | 16.1 (13.0–19.2) | 15.9 (12.9–19.1) | 15.6 (12.6–18.5) | 15.6 (13.4–18.0) |
| **40** | 11.7 (10.0–13.5) | 11.5 (10.0–13.3) | 11.5 (9.9–13.2) | 11.0 (9.3–12.5) | 11.6 (10.3–13.1) |
| **60** | 6.9 (5.7–8.2) | 7.0 (5.8–8.1) | 7.2 (6.0–8.4) | 6.7 (5.5–8.0) | 7.2 (6.2–8.3) |
| **80** | 2.1 (1.6–2.7) | 2.4 (1.9–2.9) | 2.6 (2.1–3.1) | 2.7 (2.2–3.3) | 2.4 (1.9–2.9) |
| **100** | 0.17 (0.06–0.31) | 0.23 (0.11–0.38) | 0.28 (0.14–0.44) | 0.51 (0.29–0.79) | 0.19 (0.10–0.31) |

*Estimated angina episodes vary across weeks of the recall period for the same SAQ-AF score, limiting interpretation of absolute symptom burden from SAQ alone. Estimates represent posterior medians with 95% credible intervals (CrI).*

### ORBITA-App: Daily Angina Dynamics and Treatment Effect Estimands

**Figure 4.** Distribution of Daily Angina Frequency Over Time in ORBITA-2 by Treatment (PCI vs Placebo)




*Daily symptom distributions show lower burden with PCI vs placebo, supporting derived patient-centered estimands.*

**Table 2.** Clinically Meaningful Treatment Effect Estimands Derived from Daily Angina Data

| Estimand | Treatment Effect (95% CrI) | Pr(benefit) |
|---|---|---|
| **Total expected angina episodes over follow-up (PCI - placebo)** | −31.4 (−35.2 to −26.9) | >0.99 |
| **Total expected angina-free days over follow-up (PCI - placebo)** | 14.5 (12.7 to 16.2) | >0.99 |
| **Expected days with better symptom burden on PCI vs placebo** | 30.8 (29.2 to 32.1) | >0.99 |
| **Expected days with worse symptom burden on PCI vs placebo** | 15.0 (14.0 to 15.9) | >0.99 |
| **Net days with improved symptom burden attributable to PCI (PCI − placebo)** | 15.8 (13.9 to 17.7) | >0.99 |

*All estimands show posterior Pr(benefit) >0.99. Daily angina data enables clinically intuitive measures of treatment effect magnitude. Estimates represent posterior medians with 95% credible intervals (CrI). Pr(benefit) = Pr(PCI better than placebo).*

## CONCLUSIONS

- **Endpoint choice determines both trial power and clinical interpretation of treatment effects**
- Exercise-based endpoints may **underestimate treatment effects on angina burden**
- SAQ Angina Frequency scores **do not capture dynamic symptom trajectories** and are **disproportionately influenced by recent symptoms**, limiting accurate representation of overall angina burden
- Daily symptom tracking provides **greater statistical power and clinically intuitive estimates of treatment effect on anginal symptoms**

**Daily symptom tracking endpoints should be adopted as primary efficacy measures in future antianginal trials**

## DISCLOSURE INFORMATION

M. Mohsin and M. Shun-Shin report no relevant disclosures. M. Foley reports speaker fees from Menarini and Philips. R. Al-Lamee reports advisory board roles with Janssen Pharmaceuticals, Abbott, and Philips, and speaker honoraria from Abbott, Philips, Medtronic, Servier, Omniprex, and Menarini.

These relationships had no role in the design, conduct, analysis, or interpretation of this study.

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