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Requires Data Access? Yes

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2025/05/SV_57KskaKADT3U9Aq-R_1GKiw6gqe1C4XgB.pdf
https://yoda.yale.edu/wp-content/uploads/2025/05/SV_57KskaKADT3U9Aq-R_723fFbT3Rmo5ECN.pdf
https://yoda.yale.edu/wp-content/uploads/2025/05/COI-FORM-TN.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT02489318 - 56021927PCR3002 - A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Apalutamide Plus Androgen Deprivation Therapy (ADT) Versus ADT in Subjects With Metastatic Hormone-sensitive Prostate Cancer (mHSPC)
2. NCT01715285 - 212082PCR3011 - A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naive

Prostate Cancer (mHNPC)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Bayesian Reanalysis of Prostate Cancer trial

Narrative Summary:

We will take a fresh look at an earlier cancer-drug study (apalutamide and abiraterone) to learn how often serious heart problems--heart attack, stroke, heart failure, or death from heart disease- occur. Using a Bayesian approach, we will blend the study's raw patient data with large, up-to-date U.S. cancer-cardiology databases that include people of similar age, sex, cancer type, and treatment period. This mix creates realistic starting assumptions, which we will test with weaker assumptions to be safe. We will report the most likely number of heart-related events, show 95 % ranges for uncertainty, and state the chance that the drug raised risk compared with placebo. The result will give doctors, patients, and regulators a clearer, evidence-based view of the drug's heart safety.

Scientific Abstract:

Background: Apalutamide (TITAN, N=1,052) and abiraterone + prednisone (LATITUDE, N=1,199) each improved survival in metastatic castration-sensitive prostate cancer but reported few major cardiovascular (CV) events (e.g., ischemic heart disease 45 vs 13 and ischemic cerebrovascular events 18 vs 10 per 1,052 patients in TITAN; any-grade cardiac disorders 95 vs 52 per 1,199 in LATITUDE). Small counts and protocol exclusions for recent myocardial infarction, unstable angina, or class III/IV heart failure limit precision.
Objective:To re-estimate the incidence and drug-attributable excess risk of a composite of CV death, myocardial infarction, stroke, and heart-failure hospitalization in each trial using Bayesian evidence synthesis.
Study Design: Post-hoc individual-participant re-analysis of the TITAN and LATITUDE safety datasets supplied by YODA.
Participants: All randomised participants receiving >=1 dose of study drug or placebo.
Primary Outcome: Time to first major CV event.
Secondary Outcomes: Each component event, composite without heart failure, and all-cause mortality.
Statistical Analysis Hierarchical Bayesian proportional-hazards models will combine trial likelihoods with informative priors derived from contemporary SEER-Medicare and Cardio-Oncology registries matched on age, sex, cancer stage, androgen-deprivation duration, and calendar era; weakly informative priors will be used in sensitivity analyses. We will report posterior event counts, hazard ratios with 95 % credible intervals, and drug-specific probabilities that CV risk exceeds 10 % and 25 % thresholds.

Brief Project Background and Statement of Project Significance:

Intensifying androgen-deprivation therapy with apalutamide or abiraterone prolongs overall and radiographic progression-free survival in metastatic castration-sensitive prostate cancer. TITAN reduced death by 35 % despite 40 % crossover, with a median 44-month follow-up. LATITUDE likewise extended median overall survival from 36.5 to 53.3 months. These benefits have cemented both agents as first-line options, yet cardio-oncology concerns persist.

Even after four years of follow-up, TITAN recorded only 66 adjudicated ischemic events (45 ischemic heart disease and 18 ischemic cerebrovascular events in the apalutamide arm; 13 + 10 in placebo). LATITUDE's final analysis listed any-grade cardiac disorders in 16 % vs 9 % of patients, but only ten grade >= 3 events per arm. Trial protocols excluded patients with recent acute coronary syndromes, decompensated heart failure or thrombo-embolic events, thereby selecting a fitter cohort than typically encountered. Consequently, confidence intervals around hazard ratios for myocardial infarction or stroke remain wide, and clinicians lack incontrovertible safety data when counselling men with pre-existing cardiovascular disease who already face ADT-related metabolic toxicity.

Bayesian evidence synthesis offers a rigorous framework to merge these underpowered safety datasets with large observational cohorts. Brophy et al. showed that real-world priors halve uncertainty when re-analysing venous-thrombo-embolism risk. Applying the same methodology to major CV events will (i) yield tighter credible intervals, (ii) quantify treatment-specific probabilities of clinically important excess risk, and (iii) expose any prior-data conflict, thereby transparently communicating uncertainty. The resulting calibrated estimates will directly inform drug labels, cardio-oncology surveillance guidelines, shared-decision aids and the design of future pragmatic trials that include higher-risk patients.

Specific Aims of the Project:

Aim 1 -- Construct external priors. Using 2012-2024 SEER-Medicare and the US Cardio-Oncology Registry, derive age-, sex-, Charlson comorbidity- and treatment-era-matched prior distributions for myocardial infarction, stroke, heart-failure hospitalization, and CV death in men with mHSPC receiving ADT alone.

Aim 2 -- Trial-level Bayesian re-analysis. Fit hierarchical Bayesian Cox models to TITAN and LATITUDE IPD to obtain posterior event counts, hazard ratios, and the probability that apalutamide or abiraterone increases composite CV risk by >=10 % and >=25 % versus placebo.

Aim 3 -- Bayesian meta-analysis. Pool trial-specific posteriors via a random-effects model to estimate class-level CV risk and explore heterogeneity by baseline cardiovascular disease, age >= 75 years, and prior docetaxel.

Aim 4 -- Robustness checks. Repeat analyses with weakly informative priors, exclude heart-failure from the composite, and perform prior-data conflict assessment (Martin-Anderson metric).

Hypotheses. (a) Informative priors will narrow composite CV 95 % credible intervals by >=40 %; (b) the posterior probability of >=25 % excess risk will be <30 % for each agent overall but higher in men with pre-existing CV disease; (c) pooled analysis will show non-inferiority of early androgen-signalling inhibition if excess CV risk <10 %.

Study Design:

Individual trial analysis

What is the purpose of the analysis being proposed? Please select all that apply.

Confirm or validate previously conducted research on treatment effectiveness

Confirm or validate previously conducted research on treatment safety

Participant-level data meta-analysis

Meta-analysis using only data from the YODA Project

Other: Certain elements of Bayesian reanalysis is not covered above.

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

We will analyse individual-participant data (IPD) from two Janssen-sponsored phase 3 trials provided through the YODA Project: TITAN (NCT02489318; apalutamide + ADT vs placebo + ADT; 1 051 treated men) and LATITUDE (NCT01715285; abiraterone + prednisone + ADT vs placebo + ADT; 1 199 treated men). The study population for each re-analysis is the trial safety set (all randomised participants who received >= 1 dose of study drug or placebo). No additional exclusions will be imposed.

Key eligibility already built into TITAN: men >= 18 y with metastatic castration-sensitive prostate cancer (mCSPC) documented by >= 1 bone lesion, ECOG 0-1, ongoing ADT, <= 6 cycles of prior docetaxel, and no myocardial infarction, unstable angina, class III/IV heart failure, stroke or venous thrombo-embolism within six months before randomisation .

Key eligibility already built into LATITUDE: men >= 18 y with newly diagnosed (<= 3 mo) high-risk mCSPC, ECOG 0-2, and at least two of three adverse prognostic factors (Gleason >= 8, >= 3 bone lesions, or visceral metastases); baseline haematologic, hepatic and renal function within protocol limits; exclusion of clinically significant heart disease within six months and uncontrolled hypertension .

External data will not be merged at the record level. Instead, age-/sex-/year-matched cardiovascular (CV) event rates from SEER-Medicare and the U.S. Cardio-Oncology Registry will be summarised as prior parameters and imported into the secure YODA workspace as numeric vectors.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary outcome: time from randomisation to first major CV event, defined as any of (i) CV death, (ii) non-fatal myocardial infarction, (iii) non-fatal ischaemic or haemorrhagic stroke, or (iv) hospitalisation for new-onset or acutely decompensated heart failure. Events will be identified from adjudication case-report forms where available and otherwise from MedDRA-coded serious adverse-event terms mapped to Standardised MedDRA Queries "myocardial infarction," "cerebrovascular disorders," and "cardiac failure" .

Secondary outcomes:

1. Composite excluding heart failure (CV death/MI/stroke).
2. Each component event analysed individually.
3. Sudden cardiac/arrhythmic death identified via fatal SAE narrative review.
4. First occurrence of any serious ventricular arrhythmia.
5. All-cause mortality.
6. Net clinical benefit composite (primary CV outcome + progression-free survival event) to quantify efficacy-safety trade-off.

All outcomes will be treated as time-to-event variables, right-censored at last contact.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The principal exposure is the randomised treatment arm:

Trial-specific contrast -- apalutamide + ADT vs placebo + ADT (TITAN); abiraterone + prednisone + ADT vs placebo + ADT (LATITUDE).

Pooled contrast -- early androgen-signalling inhibition (ASI) vs placebo, modelled with a trial-level

random effect. Treatment is coded 1 = ASI, 0 = placebo; analysis follows the intention-to-treat principle.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Baseline covariates for descriptive balance checks and optional adjustment:

1. Demographics: age (continuous and >= 75 y), race, region.
2. Cancer burden: high- vs low-volume disease (per CHAARTED), visceral metastasis, baseline PSA, prior docetaxel (yes/no)
3. Cardiovascular history and risk factors: hypertension, diabetes, dyslipidaemia, current smoking, body mass index, prior coronary, cerebrovascular or peripheral arterial disease, baseline systolic/diastolic BP, serum creatinine, potassium, and haemoglobin.
4. Concomitant cardioactive medications: β-blocker, ACE/ARB, statin, antiplatelet, anticoagulant.
5. ECOG performance status, Functional Assessment of Cancer Therapy-Prostate (FACT-P) score, and Brief Pain Inventory worst-pain score at baseline
6. Treatment exposure: cumulative apalutamide or abiraterone dose, treatment discontinuation reasons, and crossover status.

Statistical Analysis Plan:

Descriptive statistics
- Summarise baseline characteristics by arm with means +/- SD or medians (IQR) for continuous variables and counts (%) for categorical variables.
- Crude incidence rates (events/100 patient-years) with 95 % exact Poisson CIs.

Frequentist screening
- Kaplan--Meier curves and log-rank P values for each outcome.
- Trial-level Cox models (Efron ties) to obtain unadjusted hazard ratios (HRs).

Bayesian primary analysis
- For each trial, fit a hierarchical Bayesian Cox model:
log h_i(t)=α(t)+β x Treatment_i+γ^T Z_i, where α(t) is a piece-wise exponential baseline (knots at quartiles of event times), β the log-HR of ASI, and Z_i optional baseline covariates.
- Prior for β: Normal(0,1.0) (weakly informative).
- Prior for baseline hazard pieces: log-Gamma(0.001,0.001).
- Informative external priors enter through a parallel baseline-hazard arm for the placebo group: hazard_placebo ~ Gamma(shape=k_ext, rate=t_ext), where k_ext and t_ext reproduce person-years and events from matched SEER-Medicare and Cardio-Oncology cohorts (approximate Beta-binomial conjugacy after discretisation). Sensitivity runs replace k_ext with 1 (flat).

Posterior estimands
- Trial-specific posterior HRs and risk differences at 12, 24, and 48 months with 95 % credible intervals.
- Probability P(HR > 1.10) and P(HR > 1.25) to quantify >= 10 % and >= 25 % excess risk.

Bayesian random-effects synthesis
- Combine log-HR posteriors via μ ~ Normal(θ, τ^2), θ = overall effect, τ ~ half-Normal(0.2).
- Report pooled HR, τ, and shrinkage estimates for each study.

Model implementation
- Stan 2.32 (rstan) executed inside the YODA secure environment; four chains, 2 000 warm-up + 4 000 sampling iterations; adapt δ = 0.9. We may use python or r-studio
- Convergence assessed with R-hat 500, graphical trace plots. Posterior predictive checks compare observed vs simulated event counts.

Sensitivity and subgroup analyses

1. Weakly informative priors only (Normal(0,2.5)).
2. Event-count (Beta-Binomial) model ignoring time; useful if proportional-hazards violated.
3. Competing-risk Fine-Gray model treating non-CV death as competing.
4. Subgroups: age >= 75 y, baseline CVD, high-volume metastases, prior docetaxel, baseline hypertension. Interaction terms drawn from Normal(0,1.5).
5. Prior-data conflict measured by the Martin--Anderson conflict-p statistic; if conflict > 0.2, rerun with down-weighted external prior (k_ext/4).

Multiplicity control
- Bayesian probabilities are interpreted directly; no α-spending required. Frequentist secondary analyses will be labelled exploratory.

Software provenance
- All code will adapt the open-source template used by Brophy et al. for cardiovascular re-analysis (github.com/brophyj/jama_intmed_code) and will be version-controlled in a public repository after YODA approval.

Data security and sharing
- All computations on Janssen/YODA servers; only aggregate posterior summaries exported. External prior construction uses de-identified registry data queried on institutional servers; no individual-level external data will enter YODA.

Software Used:

Python, R, RStudio

Project Timeline:

Data-use agreement executed / workspace opened: 26 May 2025

Weeks 1--3 (26 May -- 15 Jun 2025) -- Import TITAN and LATITUDE datasets, clean variables, build external-prior vectors; complete baseline descriptive tables. Draft and submit conference abstract to AHA Scientific Sessions 2025 by 15 June 2025.

Weeks 4--8 (16 Jun -- 20 Jul 2025) -- Fit primary and sensitivity Bayesian models; run convergence diagnostics and posterior-predictive checks; generate graphs and codebooks.

Weeks 9--12 (21 Jul -- 25 Aug 2025) -- Finalise analyses, interpret findings with clinical co-authors, prepare visualisations, and draft full manuscript by 25 August 2025.

Internal and co-author review: 26 Aug -- 5 Sep 2025

Manuscript submitted to JAMA Cardiology by 5 September 2025 (≈ 3 1/2 months after project start).

Revision cycle / anticipated acceptance: Nov 2025 -- Jan 2026

Report results to YODA Project within 30 days of journal acceptance, no later than 15 February 2026.

Data-access closure: by 26 May 2026, with extension requested only if peer-review requires new analyses.

Dissemination Plan:

Primary products

1. Peer-reviewed manuscript detailing Bayesian re-analysis of TITAN and LATITUDE cardiovascular events; target journal JAMA Cardiology (impact factor, cardio-oncology readership).
2. Conference abstract and moderated poster at AHA Scientific Sessions 2025; back-up venues:

ASCO-GU 2026, ACC 2026.

Secondary products

1. Short methodological note in BMJ Evidence-Based Medicine describing external-prior construction.
2. Plain-language summary for patients and advocacy groups (Prostate Cancer Foundation, Cardio-Oncology Society of North America) published on institutional website and linked on YODA results page.
3. Open-access, fully reproducible R/Stan code repository (GitHub) released upon journal acceptance under MIT licence.

Target audiences: cardio-oncologists, medical oncologists, clinical pharmacologists, regulators (FDA Office of Oncologic Diseases & Office of Cardiology, Hematology, Endocrinology, and Nephrology), guideline committees (NCCN, ESMO, AHA/ACC), and patient advocacy organisations.

Bibliography:

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4. Fizazi K, et al. Abiraterone plus prednisone in high-risk mCSPC. *N Engl J Med.* 2017;377:352-360; protocol NEJMOA1704174_protocol.pdf.

5. Lyon AR, et al. Cardio-oncology: principles, practices, and future directions. *Nat Rev Clin Oncol.* 2022;19:563-577.

Additional regulatory guidance, MedDRA documentation, and SEER-Medicare methodology will be cited in the final manuscript.