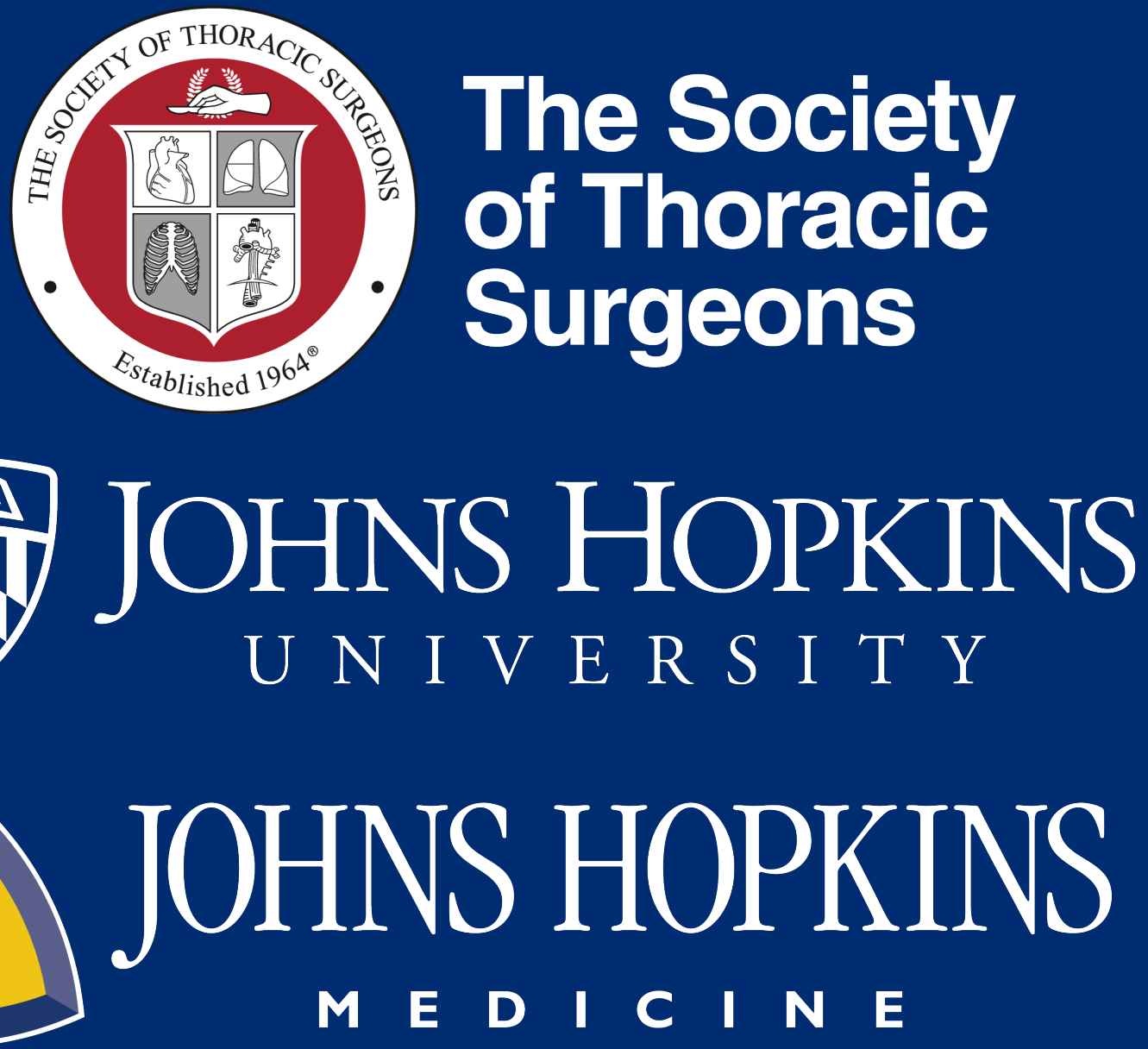


Acute Kidney Injury During X-Clamp in Cardiopulmonary Bypass Surgery: A Novel Causal Machine Learning Framework for Analyzing Causes, Mechanisms, and Prevention

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Introduction

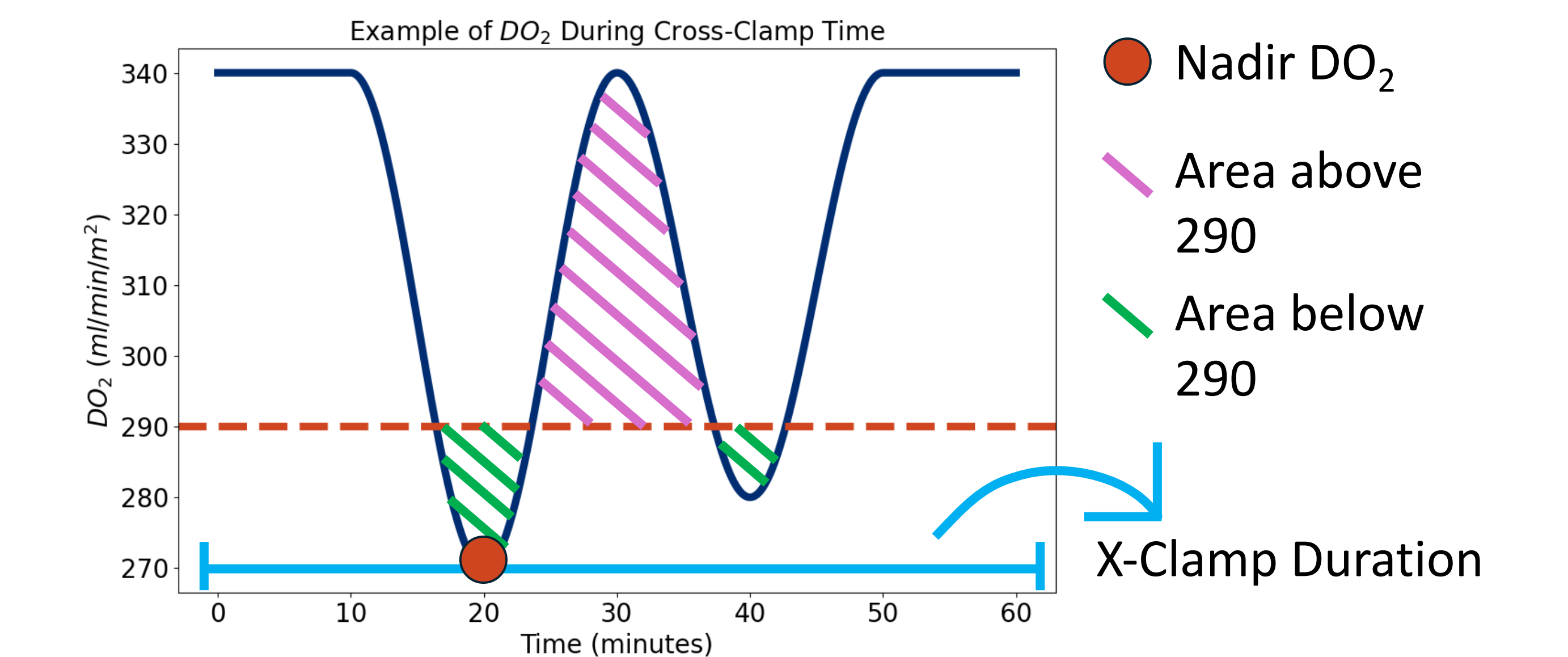
- Cardiopulmonary bypass (CPB) surgery is associated with post-operative acute kidney injury (POAKI).
- Existing studies have found that higher nadir oxygen delivery (DO₂) reduces the incidence of POAKI [4, 5].
- However, causality between DO₂ and POAKI has not been shown due to the impossibility of randomization.
- We use causal inference techniques that emulate randomized controlled trials (RCTs) to evaluate the effect of DO₂ on POAKI.

Hypothesis

Insufficient intraoperative oxygen delivery (DO₂) during X-clamp (XC) causes POAKI, and this causal effect is mediated by kidney injury as witnessed by renal ischemia biomarker release.

Selecting Features of DO₂

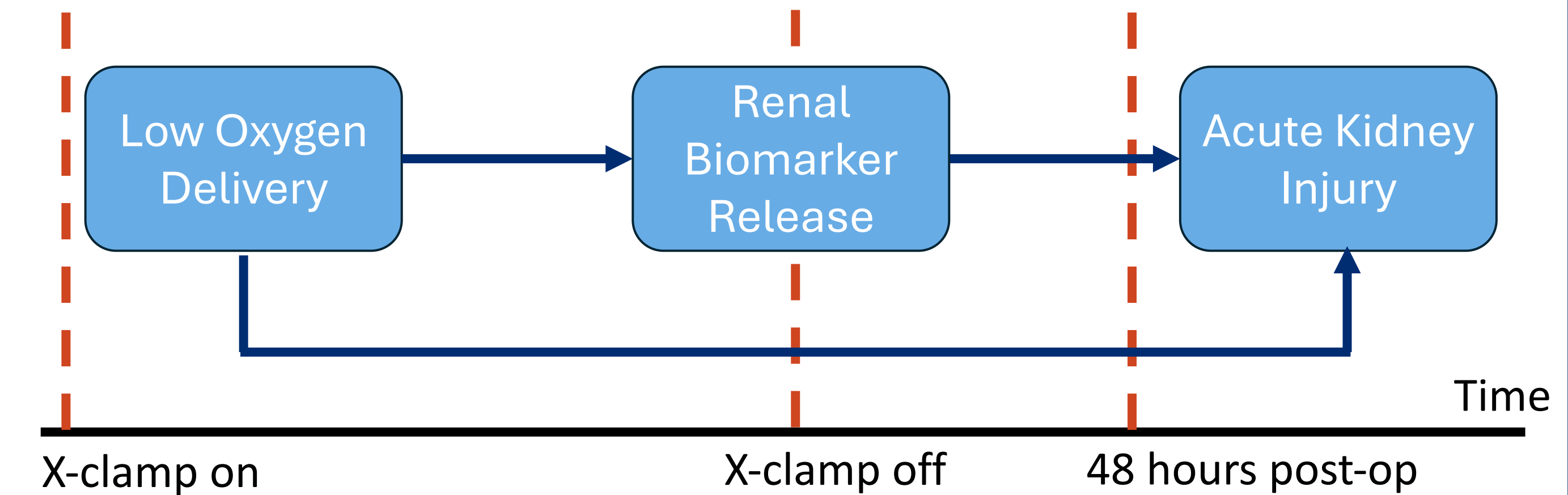
- During XC, we assessed the **area below** 170, 190, 210, 230, 250, 270, 290, and 300 ml/min/m² of DO₂; **area above** 400, 450, and 500 ml/min/m² of DO₂; **number of dips** below 50, 170, 220, and 270 ml/min/m² of DO₂; **nadir DO₂**; and **X-clamp duration** as potential causes POAKI (17 total features).



- The above figure illustrates a hypothetical patient's DO₂ curve and its features that are plausible causes of POAKI.
- We developed a novel scoring method – inspired by the Bayesian information criterion [3] - that determines whether each of the 17 features of DO₂ is causal for POAKI as if the data came from an RCT. We then followed the Greedy Equivalence Search algorithm [1] to select a subset of causally relevant features of DO₂.

Renal Ischemia Biomarkers

- We assessed the release of the renal ischemia biomarkers KIM-1, MCP-1, NGAL, and YKL-40 at baseline and at release of X-clamp as measures of **immediate kidney injury (IKI)**.
- These biomarkers allow us to compute the proportion of the causal effect of poor DO₂ on POAKI attributed to IKI.

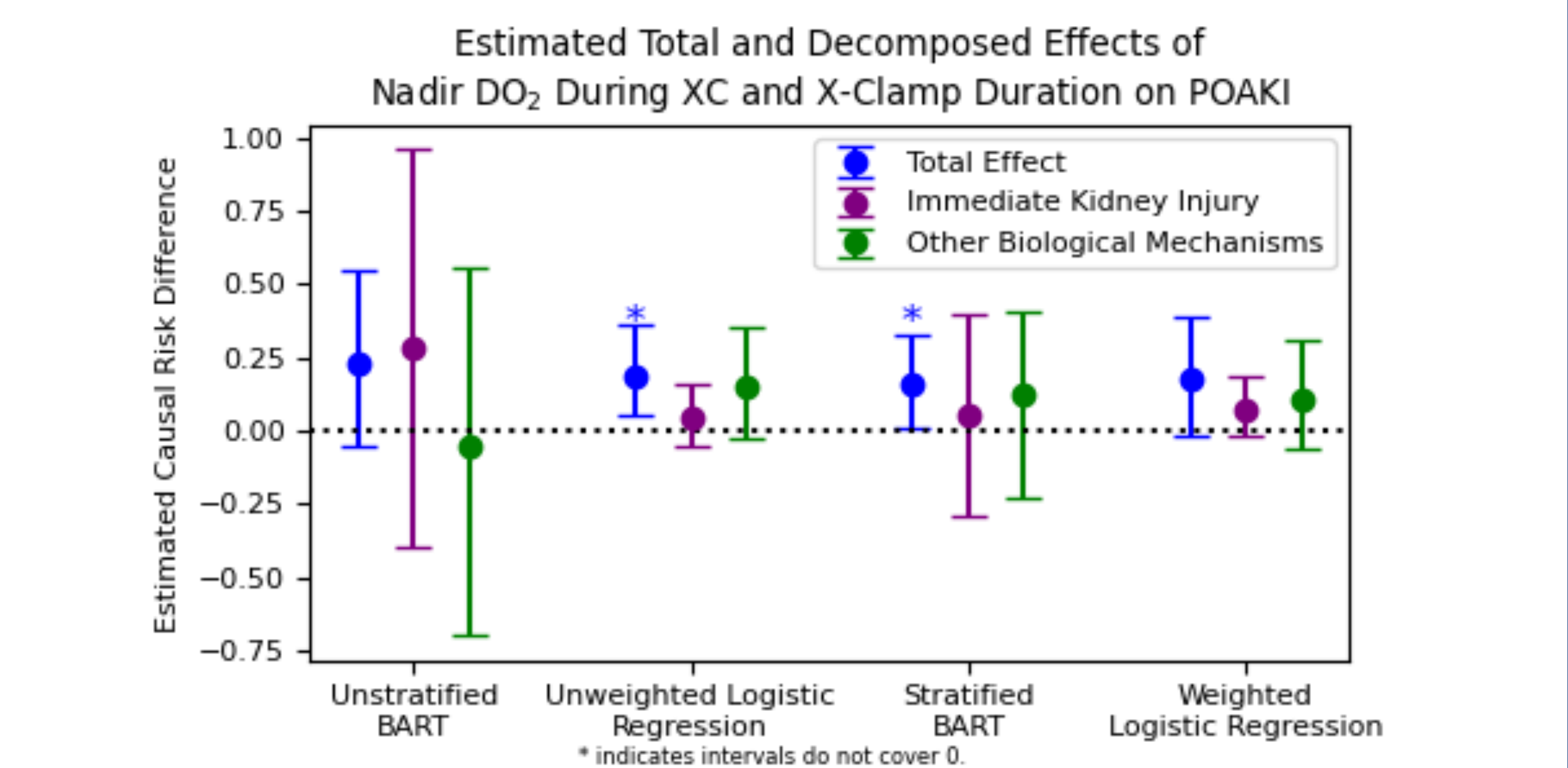


- The causal diagram above shows time on the x-axis and three key time points: X-clamp on, X-clamp off, and 48 hours post-operation.
- The first causal pathway from Low Oxygen Delivery, to Renal Biomarker Release, to POAKI represents the proportion of overall POAKI attributed to IKI.
- The second causal pathway from Low Oxygen Delivery directly to POAKI represents the proportion of overall POAKI attributed to all **other biological mechanisms (OBM)**.

Dataset and Analysis

- We analyzed a combined cohort of 1661 patients undergoing CPB, 434 of whom experienced POAKI and 136 for whom we collected intraoperative renal ischemia biomarkers.
- To assess the causal effect of DO₂ during XC on POAKI, we used **inverse-weighted logistic regression** and **stratified Bayesian additive regression tree (BART)** [2] models that control for **confounding**, a type of bias that arises from the lack of randomization of DO₂ during XC.
- BART models avoid **model misspecification bias**, a type of bias that arises when the statistical model's underlying assumptions are incorrect (e.g. using linear regression when the underlying relationship is parabolic).
- For comparison with purely **associational analyses**, we also compute the causal effect of DO₂ during XC on POAKI using unweighted logistic regression and unstratified BART.

Results



- Our model scoring procedure showed that, out of 17 pre-defined features, **nadir DO₂ during XC and X-clamp duration** were causal risk factors for POAKI.
- Stratified BART models showed that low nadir DO₂ during XC and prolonged X-clamp duration increase the risk of POAKI by **0.16 (0.01, 0.33)**. IKI accounts for 31.3% of the total effect (0.05/0.16). Credible intervals for IKI and OBM are not statistically significant.
- Estimates from logistic regressions for the total effect do not significantly change after adjusting for confounding bias – 0.18 vs. 0.19 – but estimates for BART do change significantly.

Conclusions

- Nadir DO₂ during XC and X-clamp duration are causally significant factors for POAKI, corroborating previous results while adding X-clamp duration as an additional risk factor.
- IKI during XC may play a causal role.
- Minimizing significant drops in DO₂ during XC and reducing X-clamp duration may reduce the risk of POAKI.

References

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Financial and Regulatory Disclosure

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