The CROWN Study: Cardiac outcomes with near-complete estrogen deprivation

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BACKGROUND

- Treatment for premenopausal women with high/ intermediate risk hormone receptor (HR)-positive breast cancer (BC) includes concurrent use of ovarian function suppression (OFS) and an aromatase inhibitor (AI) to induce near-complete estrogen deprivation (NCED).
- Long-term cardiovascular (CV) sequela for women treated with NCED is unknown and premature menopause in non-cancer populations is associated with CV disease.
- Given the overall CV morbidity associated with BC treatment and the future life-years of these women, the CV impact of NCED warrants further study.

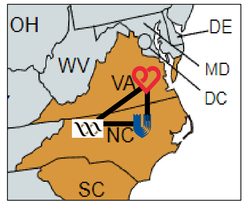
STUDY OBJECTIVES

The primary aim of this study is to understand the evolution of CV injury, as well as biomarker and demographic correlates for premenopausal women with BC treated with NCED, with the ultimate goal of developing tools to assess and mitigate CV risk.

METHODS

The CROWN Study is an NIH-funded prospective cohort study conducted at 3 US sites:

- Atrium Health Wake Forest Baptist Medical Center (Winston-Salem, NC)
- Duke University Medical Center (Durham, NC)
- Virginia Commonwealth University (Richmond, VA)



METHODS

Ninety women with stage I-III BC, age ≤55 who were premenopausal at the time of BC diagnosis have been enrolled in 2 cohorts. Enrollment has been increased to n=120 to enable more robust subgroup analyses.

- Cohort 1: HR-positive BC treated with NCED therapy that includes an aromatase inhibitor with medically or surgically induced menopause following completion of any planned chemotherapy, surgery and radiation (n=80)
- Cohort 2 (control): HR-negative BC within 3 months of completing planned chemotherapy, surgery and radiation (n=40)
- Women with human epidermal growth factor-2 (HER2) negative or HER2 positive BC are eligible.
- Patients may receive a CDK 4/6 inhibitor as part their cancer therapy and a selective-estrogen receptor degrader (SERD) rather than an AI.

STUDY MEASURES

- Annual study visits occur at baseline, Year 1, and Year 2 after enrollment with follow-up continuing through the end of the study (up to 5 years from enrollment).
- Each participant will undergo annual (Baseline, Year 1 and Year 2) adenosine stress CMRs to measure longitudinal changes in stress myocardial blood flow (Figure 1) as well as measures of aortic stiffness (Figure 2).
- The first primary statistical analyses will include testing hypotheses between group (NCED vs HR-negative) and within group (longitudinal changes within the NCED group).
- The second analyses involves developing predictive equations to determine if patient demographics, clinical parameters and serum biomarkers are associated with CV changes over time.

STUDY MEASURES

	Baseline	Year 1	Year 2
Questionnaires	X	X	X
Vitals	X	X	X
Cardiac MRI	X	X	X
CT Angiogram	X		X
EKG	X	X	X
Study Labs	X	X	X

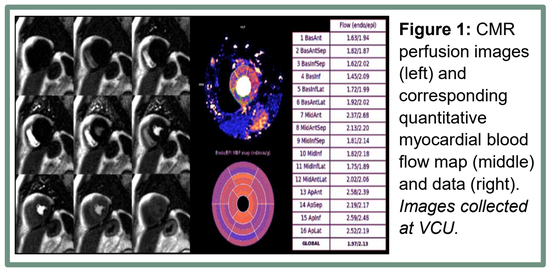


Figure 1: CMR perfusion images (left) and corresponding quantitative myocardial blood flow map (middle) and data (right). *Images collected at VCU.*

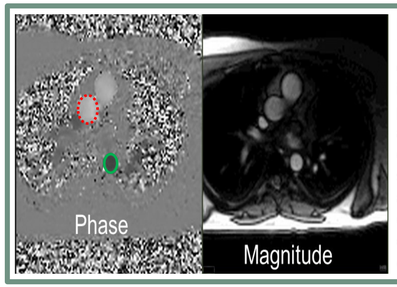


Figure 2: Thoracic phase contrast images in matched phase/flow (left) and magnitude (right) images showing the ascending aorta (red circle) and descending aorta (green circle).

- Complementary imaging for quantification of coronary plaque burden will be assessed with CT angiography at baseline and Year 2 for mechanistic validation and interpretation of CMR results.
- Predictive models to identify women at highest risk for developing deficits in myocardial perfusion will be developed with secondary study measures.

Results

This trial is open at 3 US sites. We have currently enrolled 100 women (80 HR-positive and 20 HR-negative). At this time, 12 patients have completed their Year 2 imaging and 36 have completed Year 1. Retention is a critical component of this study, as the analysis of both primary and secondary endpoints relies on longitudinal imaging data. To support this, we have successfully implemented several retention strategies, including offering "concierge" services, providing patient incentives and sending quarterly newsletters.

Conclusion

In this work, we are studying premenopausal women with serial CV imaging to increase our understanding of the impact of NCED treatment on small and large heart vessels. **This study may inform future CV risk mitigation strategies in premenopausal BC survivors.**

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