UC Irvine

UC Irvine Electronic Theses and Dissertations

Title

Long Term Assessment of Adverse Cardiovascular Events in Men Receiving Androgen Deprivation Therapy Following Radical Prostatectomy

Permalink

https://escholarship.org/uc/item/0w86h0f3

Author

Tran, Joshua

Publication Date

2022

Supplemental Material

https://escholarship.org/uc/item/0w86h0f3#supplemental

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, availalbe at https://creativecommons.org/licenses/by/4.0/

Peer reviewed|Thesis/dissertation

eScholarship.org Powered by the California Digital Library
University of California

UNIVERSITY OF CALIFORNIA,
IRVINE

Long Term Assessment of Adverse Cardiovascular Events in Men Receiving Androgen Deprivation Therapy Following Radical Prostatectomy

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Biomedical and Translational Science

by

Joshua K. Tran

Thesis Committee:
Professor Thomas E. Ahlering, Chair
Professor Robert Wilson
Professor Sheldon Greenfield

2022

© 2022 Joshua K. Tran

DEDICATION

To

my family, friends, and mentors

in recognition of their sacrifices and support

To staying strong and keeping your eyes forward

It matters not how strait the gate,
How charged with punishments the scroll,
I am the master of my fate,
I am the captain of my soul.

(William Ernest Henley
Invictus)

and knowing your "why"

People don't buy what you do; they buy why you do it.

Simon Sinek
Start with Why: How Great Leaders
Inspire Everyone to Take Action

TABLE OF CONTENTS

		Page
LIST OF FIGURES		iv
LIST OF TABLES		v
LIST OF ABBREVIATIONS		vi
ACKNOWLEDGEMENTS		vii
ABSTRACT OF THE THESIS		viii
CHAPTER 1:	Introduction	1
	Background	1
	Conflicting Literature	2
	Randomized Control Trials	3
	Observational Studies	4
	Specific Aims and Objectives	5
CHAPTER 2:	Patients and Methods	6
	Methods	7
	Statistical Methods	9
CHAPTER 3:	Results	12
	Results of Analysis	12
CHAPTER 4:	Discussion	21
	ADT and Adverse Cardiovascular Event	21
	Interpretation	22
	Limitations	24
	Future Directions	25
CHAPTER 5:	Summary and Conclusions	26
REFERENCES		27

LIST OF FIGURES

		Page
Figure 1.0	Inclusion and Exclusion Criteria for patient population	7
Figure 2.0	15-year Kaplan-Meier Analysis of ACE survival Between AO and TG groups	17
Figure 3.A	15-year Kaplan-Meier Analysis of ACE survival Stratified By Types of Treatment	18
Figure 3.B	15-year Kaplan-Meier Analysis of ACE survival Stratified By Types of Treatment. Time to ACE calculated from time of treatment	19

LIST OF TABLES

		Page
Table 1.0	Descriptive statistics of AO and TG groups	9
Table 2.0	Univariate Logistic Regression Model for ACE	13
Table 3.0	Multivariate Logistic Regression Model for ACE	14
Table 4.0	Multivariate Logistic Regression Model for ACE Stratified by patients on treatment	15
Table 5.0	Multivariate Logistic Regression Model for ACE Including Smoking Status	16
Table 6.0	Type of ACE stratified by AO or TG	20

LIST OF ABBREVIATIONS

PC	Prostate Cancer
RP	Radical Prostatectomy
PSA	Prostate Specific Antigen
BCR	Biochemical Recurrence
ADT	Androgen Deprivation Therapy
BMI	Body Mass Index
Pre-PSA	Preoperative PSA
CVD	Cardiovascular Disease
CM	Cardiovascular Mortality
ACE	Adverse Cardiovascular Event
OM	Overall Mortality
AO	Active Observation
CCI	Charlson Comorbidity Index
TG	Treatment Group
RCT	Randomized Control Trial
RT	Radiation Therapy
GGG	Gleason Grade Group
p-stage	Pathological Stage
CAD	Coronary Artery Disease
MI	Myocardial infarction
CHF	Congestive Heart Failure
DVT	Deep Venous Thrombosis
PE	Pulmonary Embolism
PVD	Peripheral Vascular Disease

ACKNOWLEDGEMENTS

I would like to express the deepest appreciation to my committee chair, Dr. Thomas Ahlering, without whom this thesis would not be possible. I have had the honor to work with and witness your admirable passion for urology and the field of research. He has inspired me to pursue academic medicine and to help others if I can.

I would like to thank my committee members, Dr. Robert Wilson, and Dr. Sheldon Greenfield, for their patients and advice throughout the year. The wisdom and teachings you shared with me have become invaluable in my pursuit of this master's degree and my future aspirations.

I would also like to give a special recognition to Linda Huynh; The first person to take a chance on me and give me the opportunity to succeed. It is no small exaggeration to say that what I have accomplished today is thanks to her.

Erica Huang - from stranger, to teacher, to friend. Without her support and guidance, I would not have been able to survive the journey this past year. I wish you the best in your future endeavors and the first steps toward becoming a physician.

Finally, I would like to thank my family - especially my parents. I have been able to pursue greater things thanks to your support and teachings throughout my life.

ABSTRACT OF THE THESIS

Long Term Assess of Adverse Cardiovascular Events in Men Receiving Androgen Deprivation Therapy Following Radical Prostatectomy

by

Joshua K. Tran

Master of Science of Biomedical and Translational Sciences

University of California, Irvine, 2022

Professor Thomas Ahlering, Chair

Introduction: Androgen deprivation therapy (ADT) or radiation therapy (RT) with ADT is frequently recommended for biochemical recurrence (BCR) following a radical prostatectomy (RP). Probably the most severe life-threatening complication of ADT is an adverse cardiovascular event (ACE) such as acute myocardial infarction, stroke, etc. Because the literature is conflicted as to whether ADT increase ACEs. This study seeks to assess relationship of ACE in men undergoing ADT following RP.

Methods: Retrospective review of prospectively collected data (n = 1895) from patients who underwent robot-assisted radical prostatectomy (RARP) performed by a single surgeon. 308 patients with a biochemical recurrence (BCR) and adequate follow-up data were analyzed for ACE. 189 men in the "treatment group" (TG) were managed with ADT or RT/ADT. The comparator group consisted of 119 men undergoing active observation (AO) with BCR but received no ADT or RT/ADT. Differences between AO and TG were analyzed utilizing student t-test and chi-squared (Table 1). Logistic regression was used to find predictors of ACE. Kaplan-Meier survival curves were generated to find time to ACE event and the percentage of patients that did not have an event.

Results: At baseline, time of surgery, there was no significant difference in Charlson comorbidity index (CCI) but there was a trend in favor of AO (4.14 versus 4.38). In follow-up following BCR significant predictors of ACE in univariate analysis were age, CCI, body mass index (BMI), treatment status (AO vs TG), and smoking status (non-smoker vs previous smoker). 15-year Kaplan-Meier (KM) analysis showed a statistically significant increase in ACEs (TG 54.4% and AO 41.8%, p = 0.02). The driving factors for the increase in ACEs was coronary artery disease and arrhythmia. In the TG, there were no differences in ACE between ADT versus RT+ADT (55.4% versus 53.8%, p = 0.68). In adjusted multivariate logistic regression analysis, CCI and BMI were significant predictors for ACE with treatment status trending toward significance.

Conclusions: There is an association between treatment for BCR and subsequent cardiovascular morbidity (as measured by ACE). Treatment may not undoubtedly cause ACE but that it may carry a higher risk of ACE. This effect may be attributed to time, or increasing the risk of particular types of ACE, but not to other types of ACE. We also saw the importance of BMI and CCI as a prognosticating tool for ACE, over treatment status.

INTRODUCTION

1.1 Background

Prostate cancer (PC) is the most commonly diagnosed non-cutaneous cancer in men, with about 1.3 million incident cases in 2018. Prostate cancer is also the fifth most common cause of cancer death globally with an estimated 360,000 deaths in 2018[1].

Current guidelines suggest that primary treatment of PC includes radiation or surgical therapy[2]. The most common surgical treatment for PC is a radical prostatectomy (RP). Following RP, patients with an elevated serum prostate specific antigen (PSA; 0.2ng/ml x2) are considered to have a biochemical recurrence (BCR). BCR following primary treatment is quite common and occurring in about 20-40% of patients[3]. Patients with BCR are frequently recommended to receive radiation therapy (RT) and/or androgen deprivation therapy (ADT).

With technological and medical improvements occurring every year, physicians and patients are presented with a wide range of medication options for ADT. These medications can be separated into different classes depending on the pharmacokinetics of these medications. The main class of ADT are Gonadotropin-releasing hormone agonists[4] which create castrate levels of testosterone. While these medications are effective in treating BCR, side effects due to no testosterone are associated with reduced muscle mass, increased belly fat and a host of harmful complications. Probably the most severe complication for patients taking ADT following RP are the effects of increasing cardiovascular disease (CVD). According to the CDC, heart disease is the leading cause of death for men in the United States[5]. Most prostate cancer patients with more advanced disease leading to BCR are already at a higher risk of CVD. Although it is very intuitive that men are at risk of ACEs due to their disease status, this risk should be increased with secondary effects ADT. However, there is significant controversy surrounding this issue.

1.2 Conflicting Literature

There are several studies that have assessed the use of hormonal therapy and risks of cardiovascular mortality (CM). One of the most well-known publications on this topic is a science advisory from the American Heart Association, American Cancer Society, and American Urological Association that was published in 2010[6]. Despite the growing literature on the relationship between PC patients on ADT and increased risk of CVD, the consensus states that "there may be a relationship" but does not believe that patients should be referred to additional specialists or perform any additional tests to ensure safety.

In 2021, Zhang et al. analyzed 49,634 patients from the FDA adverse event reporting system and found that patients had a adverse cardiovascular event (ACE) rate of 12.6% on hormone monotherapy and 26.1% on combination therapy. They also found that patients utilizing second generation ARI in combination with GnRH antagonists were associated with higher rates of ACE[7].

The extent in which ADT is associated with CVD and CM are largely conflicting. This is especially true when large meta-analyses compare randomized control trials (RCT) and observational studies. Nguyen et al. in 2011, reported a meta-analysis of 11 RCTs that found no significant difference in CM between patients receiving ADT vs control[8]. They also found that ADT was associated with lower overall mortality (OM). These trials were not designed to ascertain CVD outcomes as exclusion criteria may remove patients common in PC patients (e.g. elderly or those with comorbidities). Observational studies are also able to examine CVD outcomes other than death. In order to address this, Bosco et al. in 2015 performed A meta-analysis on observational studies that found eight studies reporting on at least one type of ADT and a nonfatal or fatal CVD outcome. They found that observational studies consistently show a positive association between ADT use and risk of CVD [CITE]. These conflicting results show the need to further explore this topic.

1.3 Randomized Control Trials

RCTs have long been accepted as the "golden standard" for clinical research[9]. As such, we will first be reviewing several RCTs that include use of ADT in PC patients that reported CVD or CM.

In 2008, D'Amico et al. (DFCI 95-096) reported the results of an RCT between radiation therapy (RT) and RT+ADT[10]. Their study included 206 men with unfavorable-risk PC and had a median follow-up of 7.6 years. Over this time period, 44 deaths occurred in the RT group and 30 deaths in the RT+ADT group. Of these, 13 patients in each group (26 total) were attributed to a CM. They found that the addition of ADT did not increase the overall rate of CM.

In a larger trial reported by Efstathiou et al. (RTOG 85-31) on CM was published in 2009[11]. 945 patients received either RT alone or RT+ADT with a median follow-up of 8.1 years. Both arms did not have any statistically different prevalence of cardiovascular disease (CVD), hypertension, or diabetes in their preoperative demographics. In their regression analysis, the addition of ADT to treatment was not significantly associated with increased risk of CM ($p = 0.16$). In a subgroup analysis of this trial, there were no differences in CM for patients with preoperative CVD or preoperative diabetes or age >70 years old. They confirmed that ADT did not increase CM in men with locally advanced PC.

Bolla Et al. (EROTIC 22863) analyzed 208 patients in the RT group and 207 in the RT+ADT group[12]. Of the 192 deaths in the trial, 39 were CM with 17 and 22 in the RT and RT+ADT group, respectively. In patients with previous CVD, CM was not significantly different in the RT (11/63) and RT+ADT (8/53) group ($P=0.60$). In patients without preexisting CVD, similar results were found between the two groups (6/145 and 14/154 in the RT and RT+ADT groups, respectively; $p = 0.25$).

An Australian-New Zealand study (TROG 96.01) reported on 818 men receiving either RT or RT+ADT[13]. At 10-year follow-up, they observed no differences in cardiac related death with 23

deaths in the RT alone group and 36 in the RT+ADT group. This study agrees with many previously published RCTs that show no differences of CM in patients receiving treatment.

All of the RCTs reported here, and many more not mentioned, all agree that ADT use does not increase CM in patients. The “golden standard” of medicine shows that there is no association between treatment and CM. While RCTs are considered one of the highest levels of evidence, the observational studies on this have differing results.

1.4 Observational Studies

Observational studies are more typically numerous in publications than RCTs but are considered a lower level of evidence. Despite this, an argument has been made that observational studies are more easily accessible and cheaper to look at safety and effectiveness[9]. Some have argued that observational studies more accurately reflect the “real clinical world” more so than RCTs.

One of the larger studies that sparked the concern for ADT use and CVD was published in the mid-2000s[14]. Utilizing the Surveillance, Epidemiology and End Results (SEER) Medicare database, 73,196 patients were analyzed to assess diabetes, coronary heart disease (CHD), myocardial infarction (MI), and sudden cardiac death. They found that compared to no treatment, ADT use was significantly associated with incidence of diabetes, CHD, MI, and sudden CM.

Another review of the SEER database by Hu et al. was reported and published in 2012, to identify the use of ADT and peripheral arterial disease and venous thromboembolism[15]. They found that treatment with ADT was significantly associated with both peripheral arterial disease and venous thromboembolism. This group also considered smoking status as a possible confounder based on previous reports. They concluded that the actual effect of smoking status depended too heavily on the prevalence of smoking status in both groups. Especially in the ADT group, with lower estimates being significantly different, but higher estimates would not be.

A report on the Swedish national health care registers analyzed 41, 362 men with PC on ADT compared with an age-matched, PC-free comparison cohort[16]. They found that men on ADT

were at a higher risk of CVD compared to the comparison cohort. Patients with at least two cardiovascular events before therapy were at a higher risk of CVD during the first six months of ADT. While these results support pre-existing observational studies, it should be noted that the comparator group consisted of patients who were not diagnosed with PC.

A multi-center, cross-sectional study from 30 Italian institutions reported on the occurrence of CVD (CHOICE study) in patients receiving ADT (concordant (n = 790) and discordant (n = 285) ADT groups)[17]. Cardiovascular complications were seen at a rate of 32.7%; Surprisingly, patients who were discordant (according to EAU guidelines) showed a greater probability of cardiovascular complication than concordant patients. The majority of discordant patients had a Charlson Comorbidity Index (CCI) >2 (81.8%). They suggest that the risk of side effects from ADT in this subgroup may “exceed clinical benefit”.

30,923 patients with PC from the Norwegian health registry were analyzed for ADT use (n = 8,449) and subsequent CVD and overall mortality[18]. They reported an association between ADT and increased risk of CVD (MI, stroke, and heart failure). Patients who received ADT for a longer duration and those with some CVD risk factors at time of diagnosis were noted to have a stronger association with CVD events.

1.5 Specific Aims and Objectives

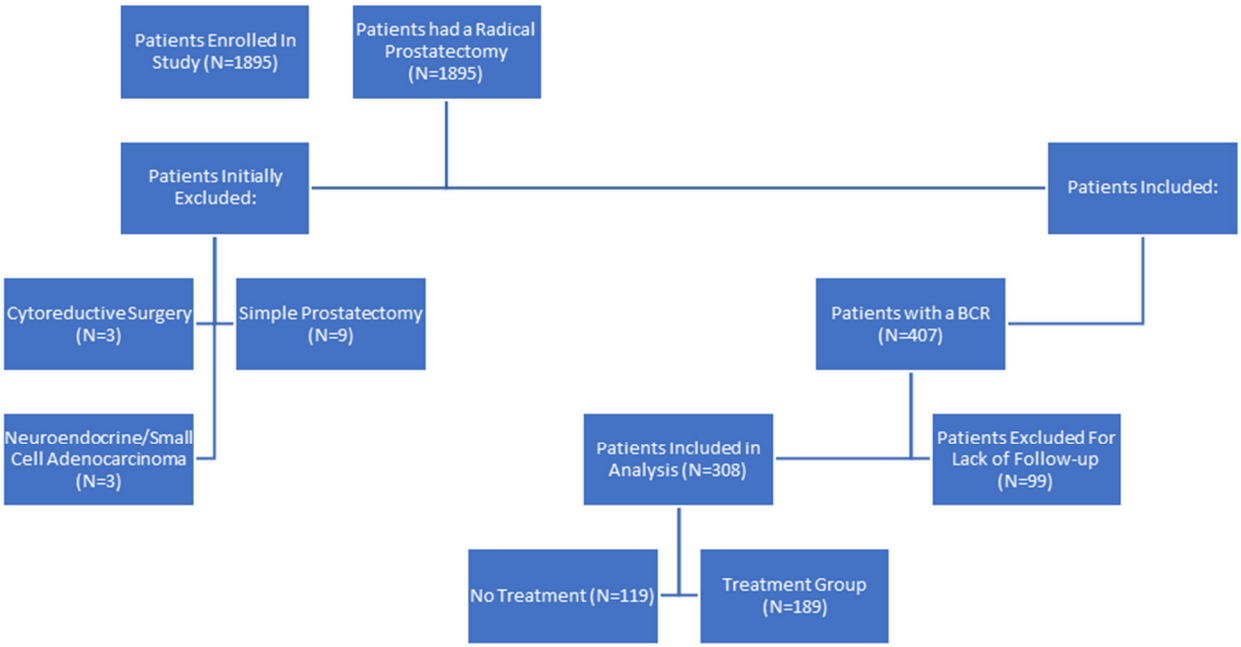
It is apparent that there exists a divide between results on the association between ADT use and cardiovascular morbidity in PC patients. This divide has only been growing with EAU guidelines stating that level I evidence on both sides conclude conflicting results and therefore can only give advice on “non-specific measures such as loss of weight, increased exercise minimizing alcohol intake, and smoking cessation.” This study seeks to assess the relationship of adverse cardiovascular events (ACE) in men undergoing ADT and/or RT and men that did not, following a BCR post-RP.

PATIENTS AND METHODS

2.0 Methods

Retrospective review of prospectively collected data from patients who underwent robot-assisted RP performed by a single surgeon at a single institution between June 2002 and September 2019. Data included preoperative demographics, oncologic information, and long-term follow-up data on cardiovascular events were prospectively recorded in an anonymized, electronic database, under approved institutional review board protocol at the University of California, Irvine (HS#1998-84). All data collection was conducted in compliance with the Health Insurance Portability and Accountability Act and federal guidelines for informed consent were followed.

Figure 1. Inclusion and Exclusion Criteria for Patient Population



1895 patients were included in the study (Figure 1). Patients were screened and excluded if they underwent simple prostatectomy (N=9) or cytoreductive prostatectomy (N=3), and if they had neuroendocrine or small cell adenocarcinoma (N=3). Inclusion criteria included patients who

had PC, received a primary treatment of RP, and subsequently experienced a BCR (N=407). After review of the patient's chart, 99 patients were excluded due to lack of follow-up. The final cohort (n=308) with a BCR either received treatment (TG; Treatment Group, N=189) or did not receive treatment (AO; Active Observation, N=119) (Table 1). The database was frozen for follow-up through March 29, 2021.

The primary outcome was defined as the presence or absence of at least one adverse cardiovascular event (ACE). An “event” date was noted only if an ACE occurred post-RP in the AO group and post-ADT in the treatment group. ACE was transformed into a categorical variable with “1” defined as at least one ACE and “0” defined as no ACE. ACE was measured according to Zhang et al. based on the FDA Adverse Event Reporting System[7] and the Charlson Comorbidity Index (CCI)[19]. ACE included coronary artery disease (CAD), arrhythmia, myocardial infarction (MI), ischemic stroke, congestive heart failure (CHF), deep venous thrombosis (DVT), pulmonary embolism (PE), and peripheral vascular disease (PVD). While some ACE are included in the CCI, these events were not counted unless an additional event was noted post-RP.

A CCI sum was calculated according to Charlson et al. The CCI analyzed age, MI, CHF, PVD, cerebrovascular accident, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes, hemiplegia, chronic kidney disease, solid tumor, leukemia, lymphoma, and AIDS[19]. The CCI sum was utilized as a discrete independent variable in our analysis along with other continuous and categorical variables described in Table 1.

Clinically relevant data addressing aggressiveness and progression of PC includes pathological outcomes utilizing the Gleason grading system and the TNM staging system. The Gleason grade refers to how abnormal or differentiated PC cells look under a microscope. The Gleason grade group (GGG) represents 5 different levels of disease aggressiveness with 5 being the most aggressive. Grade is represented in pairs with the most common pattern of cells included

first followed by the second most common pattern (GGG; 1 = 3+3, 2 = 3+4, 3 = 4+3, 4 = 4+4, and 5 = anything with a grade 5 disease).

A backward stepwise logistic regression model was utilized to find independent predictor variables of ACE. Continuous variables in our model included age, preoperative PSA (pre-PSA), body mass index (BMI), and years of follow-up. Pathologic outcomes were transformed into categorical variables and included in our model; GGG and pathologic stage (pT2 = 0 and pT3 = 1). Additional categorical variables in our model included ACE (0 = no ACE and 1 = at least one ACE) along with rounds of treatment (0 = only one round of treatment, number of events, and 1 = more than one round of treatment) and smoking status (0 = non-smoker and 1 = current (N=16) or previous smoker (N=87)). Descriptive statistics of these variables included frequency and percentages for categorical variables and mean and standard deviations for discrete and continuous variables, as shown in Table 1.

Table 1. Descriptive statistics of AO (n = 119) and TG (n = 189) groups.

	No Treatment (N=119)	Treatment (N=189)	Overall (N=308)	P-value
Age				0.2919
Mean(SD)	63.3 (7.34)	64.2 (7.25)	63.8 (7.29)	
Median [Min, Max]	64.0 [44.3, 79.7]	63.6 [43.1, 80.8]	63.9 [43.1, 80.8]	
Adjusted Pre-PSA				**0.0056**
Mean (SD)	8.19 (5.30)	12.9 (17.9)	11.1 (14.6)	
Median [Min, Max]	6.50 [1.20, 32.4]	7.80 [2.30, 221]	7.40 [1.20, 221]	
Adjusted Gleason Grade Group				**<0.0001**
1	14 (11.8%)	1 (0.5%)	15 (4.9%)	
2	42 (35.3%)	35 (18.5%)	77 (25.0%)	
3	41 (34.5%)	57 (30.2%)	98 (31.8%)	
4	12 (10.1%)	13 (6.9%)	25 (8.1%)	
5	10 (8.4%)	83 (43.9%)	93 (30.2%)	
Adjusted Pathologic Stage				**<0.0001**
0	59 (49.6%)	46 (24.3%)	105 (34.1%)	
1	60 (50.4%)	143 (75.7%)	203 (65.9%)	
Charlson Comorbidity Index				0.0845
Mean (SD)	4.15 (1.04)	4.38 (1.19)	4.29 (1.14)	
Median [Min, Max]	4.00 [2.00, 9.00]	4.00 [2.00, 10.0]	4.00 [2.00, 10.0]	
Missing	0 (0%)	1 (0.5%)	1 (0.3%)	
BMI				1.0000
Mean (SD)	27.2 (3.80)	27.2 (3.91)	27.2 (3.86)	
Median [Min, Max]	26.5 [20.3, 39.4]	26.8 [18.1, 46.3]	26.6 [18.1, 46.3]	
Missing	2 (1.7%)	10 (5.3%)	12 (3.9%)	
Follow-Up (Yrs)				0.5210
Mean (SD)	7.37 (3.98)	7.69 (4.42)	7.57 (4.25)	
Median [Min, Max]	7.36 [0.967, 16.8]	7.41 [0.214, 17.6]	7.38 [0.214, 17.6]	
1 vs More Than 1 Round of Treatment				
0	0 (0%)	98 (51.9%)	98 (31.8%)	
1	0 (0%)	91 (48.1%)	91 (29.5%)	
Missing	119 (100%)	0 (0%)	119 (38.6%)	
Patients with at least 1 Cardio Event				0.0625
0	97 (81.5%)	135 (71.4%)	232 (75.3%)	
1	22 (18.5%)	54 (28.6%)	76 (24.7%)	
Number of Events				**0.0391**
0	100 (84.0%)	136 (72.0%)	236 (76.6%)	
1	15 (12.6%)	28 (14.8%)	43 (14.0%)	
2	4 (3.4%)	17 (9.0%)	21 (6.8%)	
3	0 (0%)	3 (1.6%)	3 (1.0%)	
4	0 (0%)	5 (2.6%)	5 (1.6%)	
Non-Smoker vs Previous Smoker				0.8613
0	78 (65.5%)	127 (67.2%)	205 (66.6%)	
1	41 (34.5%)	62 (32.8%)	103 (33.4%)	

2.1 Statistical Methods

Table 1 displays the demographics between the TG and AO groups. Student's t-tests were utilized for continuous and discrete variables (age, pre-PSA, CCI sum, BMI, and follow-up years) with significance defined as p-value <0.05. Categorical variables (GGG, p-stage, rounds of

treatment, patients with at least 1 cardio event, number of events, smoking status) were analyzed using chi-squared to evaluate differences between AO and TG.

Logistic regression analysis was used in determining predictors of the primary outcome (ACE). In our multivariate models, independent variables were initially chosen a priori - based on clinical practice and/or current literature. A backwards logistic regression model was performed where variables were first inputted into the multivariate model and then eliminated one at a time based on the largest p-value. This was re-run until a final model was reached with only statistically significant variables along with our primary exposure variable(s). The initial multivariate model included preoperative age, Pre-PSA, CCI sum, and BMI along with oncologic covariates such as GGG and p-stage. The primary exposure variable was treatment status (1 = TG vs 0 = AO).

Subsequent analysis included smoking status and subgroup analysis of only the TG. These analyses utilized logistic regression analysis utilizing the same predictors, or independent variables, as the primary analysis with additional covariates - smoking status or rounds of treatment. Secondary analysis of smoking status included smoking status as an additional independent variable. Thus, the primary exposure variables in this secondary analysis consisted of smoking status and treatment status. Subgroup analysis included only patients that received treatment with primary exposure variable as rounds of treatment.

Another secondary analysis was performed in comparing the type of ACE between the TG and AO groups. This analysis focused on separating each classification of ACE. Chi-squared analysis was utilized in interpreting any statistical difference between the two groups. ACE included in this analysis consisted of CAD, arrhythmia, MI, ischemic stroke, CHF, DVT, PR, and PVD (Table 6).

15-year cardiac event survival assessment was performed with Kaplan-Meier analysis and stratified between the TG and AO groups. Patients were censored at the last known follow-up or death. Further analysis was performed utilizing Kaplan-Meier analysis stratified by type of treatment (ADT vs ADT+RT). Statistical significance was defined as a p-value <0.05 for all

statistical testing. All statistical tests and figures were conducted and produced in R statistical package (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

3.0 Results of Analysis

Table 1 displays the demographic results of AO versus TG and no differences were observed other than pre-PSA, GGG, and p-stage. Table 2 describes the univariate regression models of predictors for ACE. In the univariate models, age, CCI, BMI, treatment status, and smoking status were statistically significant predictors of ACE. Conversely, GGG, pre-PSA, rounds of treatment (only for treatment patients), and p-stage, were not statistically significant predictors of ACE. Results showed that for every year of increased age, patients had 8% higher odds of an ACE. For every unit increase in CCI sum, patients had 67% increased odds of an ACE. When compared to AO, patients on treatment were 76% more likely to have an ACE. Further, patients who were previous or current smokers were 2.06 times more likely to have a ACE, when compared to non-smokers.

Table 2. Univariate logistic regression model for ACE and independent variables

Variable		OR	95% CI	p-value
Age		1.08	1.04, 1.12	**<0.001**
Adjusted Gleason Grade Group				
	1	—	—	
	2	1.22	0.34, 5.78	0.78
	3	1.16	0.33, 5.41	0.83
	4	2.25	0.54, 11.8	0.29
	5	1.39	0.40, 6.48	0.63
Charlson Comorbidity Index		1.67	1.32, 2.14	**<0.001**
BMI		1.10	1.03, 1.18	**0.005**
Treatment				
	AO	—	—	
	TG	1.76	1.02, 3.14	**0.047**
Adjusted Pre-PSA		1	0.97, 1.01	0.7
Adjusted Pathologic Stage				
	pT2	—	—	
	pT3	1.49	0.85, 2.67	0.17
Non-Smoker vs Previous Smoker				
	Non-Smoker	—	—	
	Previous Smoker	2.06	1.21, 3.51	**0.008**
Rounds of Treatment				
	Only 1 Round	—	—	
	More than 1 Round	0.66	0.34, 1.24	0.20

OR = Odds Ratio, CI = Confidence Interval

In multivariate analysis (Table 3), the final model indicated that CCI sum and BMI were significant predictors of ACE. All other independent variables fell out of the model according to the backward stepwise regression analysis. The Pearson correlation coefficient for CCI sum and BMI was not significant ($p = 0.8334$). It is important to note that although treatment status was not statistically significant in the final model, the variable was trending toward significance ($p = 0.10$).

Table 3. Multivariate logistic regression model of ACE, adjusting for covariates that affect aggressiveness of disease and cardiovascular morbidity.

Model	Variables		OR	95% CI	p-value
Initial Model	Age		1.06	1.01, 1.12	**0.033**
	Adjusted Gleason Grade Group				
		1	—	—	
		2	0.8	0.19, 4.30	0.78
		3	0.47	0.10, 2.57	0.34
		4	1.16	0.22, 7.18	0.86
		5	0.43	0.09, 2.52	0.32
	Adjusted Pre-PSA		0.99	0.96, 1.01	0.58
	Adjusted Pathologic Stage				
		pT2	—	—	
		pT3	1.12	0.57, 2.24	0.74
	Charlson Comorbidity Index		1.38	0.98, 1.95	0.062
	BMI		1.14	1.06, 1.24	**<0.001**
	Treatment				
		AO	—	—	
		TG	2.18	1.12, 4.41	**0.025**
Final Model	Charlson Comorbidity Index		1.7	1.31, 2.23	**<0.001**
	BMI		1.12	1.04, 1.20	**0.003**
	Treatment				
		AO	—	—	
		TG	1.65	0.91, 3.07	0.1

OR = Odds Ratio, CI = Confidence Interval

Table 4 illustrates a subgroup analysis of only TG patients that examined the impact of the number of rounds of ADT treatment on ACE. Backwards regression analysis showed that CCI sum and BMI were the only significant predictors of ACE in our final model.

Table 4. Multivariate logistic regression model of ACE stratified by patients on treatment, adjusting for covariates that affect aggressiveness of disease and cardiovascular morbidity.

Model	Variables		OR	95% CI	p-value
Initial Model	Age		1.07	1.00, 1.14	0.058
	Adjusted Gleason Grade Group				
		1	—	—	
		2	221,699	0.00, NA	0.99
		3	112,457	0.00, NA	0.99
		4	288,487	0.00, NA	0.99
		5	125,911	0.00, NA	0.99
	Adjusted Pre-PSA		0.99	0.95, 1.02	0.70
	Adjusted Pathologic Stage				
		pT2	—	—	
		pT3	0.82	0.34, 2.04	0.66
	Charlson Comorbidity Index		1.46	0.98, 2.17	0.062
	Treatment Group				
		ADT	—	—	
		ADT+RT	1.23	0.53, 2.81	0.62
	Rounds of Treatment				
		Only 1 Round	—	—	
		More than 1 Round	0.69	0.32, 1.48	0.35
	BMI		1.13	1.03, 1.25	**0.015**
Final Model	Charlson Comorbidity Index		1.78	1.31, 2.47	**<0.001**
	Treatment Group				
		ADT	—	—	
		ADT+RT	1.1	1.50, 2.37	0.81
	Rounds of Treatment				
		Only 1 Round	—	—	
		More than 1 Round	0.68	0.32, 1.42	0.31
	BMI		1.10	1.01, 1.20	**0.037**
	OR = Odds Ratio, CI = Confidence Interval				

Table 5 is an analysis adding smoking status to the existing covariates and the risk ACE. An interim model was included during this analysis in order to outline a significant trend between age and CCI sum. While the final model had CCI sum fall out, it was close to statistical significance and should remain an important factor to consider. The final model for this analysis with age and

BMI remaining significant predictors or ACE with treatment status trending, but no longer being a statistically significant predictor.

Table 5. Multivariate logistic regression model of ACE, adjusting for covariates that affect aggressiveness of disease and cardiovascular morbidity. Initial multivariate model with smoking status. Interim multivariate model. Final Multivariate Model.

Model	Variables		OR	95% CI	p-value
Initial Model	Age		1.06	1.00, 1.12	**0.043**
	Adjusted Gleason Grade Group				
		1	—	—	
		2	0.73	0.17, 3.88	0.68
		3	0.44	0.10, 2.39	0.298
		4	1.06	0.20, 6.56	0.945
		5	0.43	0.09, 2.47	0.306
	Adjusted Pre-PSA		0.99	0.96, 1.02	0.64
	Adjusted Pathologic Stage				
		pT2	—	—	
		pT3	1.11	0.56, 2.22	0.771
	Charlson Comorbidity Index		1.37	0.97, 1.94	0.07
	Treatment				
		AO	—	—	
		TG	2.14	1.09, 4.34	**0.03**
	BMI		1.14	1.06, 1.23	**<0.001**
	Non-Smoker vs Previous Smoker				
		Non-Smoker	—	—	
		Previous Smoker	1.46	0.78, 2.69	0.228
Interim Model	Age		1.05	1.00, 1.11	0.061
	Charlson Comorbidity Index		1.36	0.97, 1.91	0.073
	Treatment				
		AO	—	—	
		TG	1.7	0.93, 3.18	0.089
	BMI		1.13	1.05, 1.22	**0.001**
	Non-Smoker vs Previous Smoker				
		Non-Smoker	—	—	
		Previous Smoker	1.59	0.87, 2.87	0.127
Final Model	Age		1.08	1.04, 1.13	**<0.001**
	Treatment				
		AO	—	—	
		TG	1.73	0.96, 3.22	0.074
	BMI		1.13	1.05, 1.22	**0.001**
	Non-Smoker vs Previous Smoker				
		Non-Smoker	—	—	
		Previous Smoker	1.58	0.87, 2.83	0.127
	OR = Odds Ratio, CI = Confidence Interval				

Figure 2 illustrates the 15-year Kaplan-Meier curve for ACE between AO and TG groups. There was a statistically significant higher ACE incidence 54.4% TG versus 41.8% AO (p = 0.026).

Figure 2. 15-year Kaplan-Meier analysis of ACE survival between AO and TG. Time to ACE calculated from time of RP.

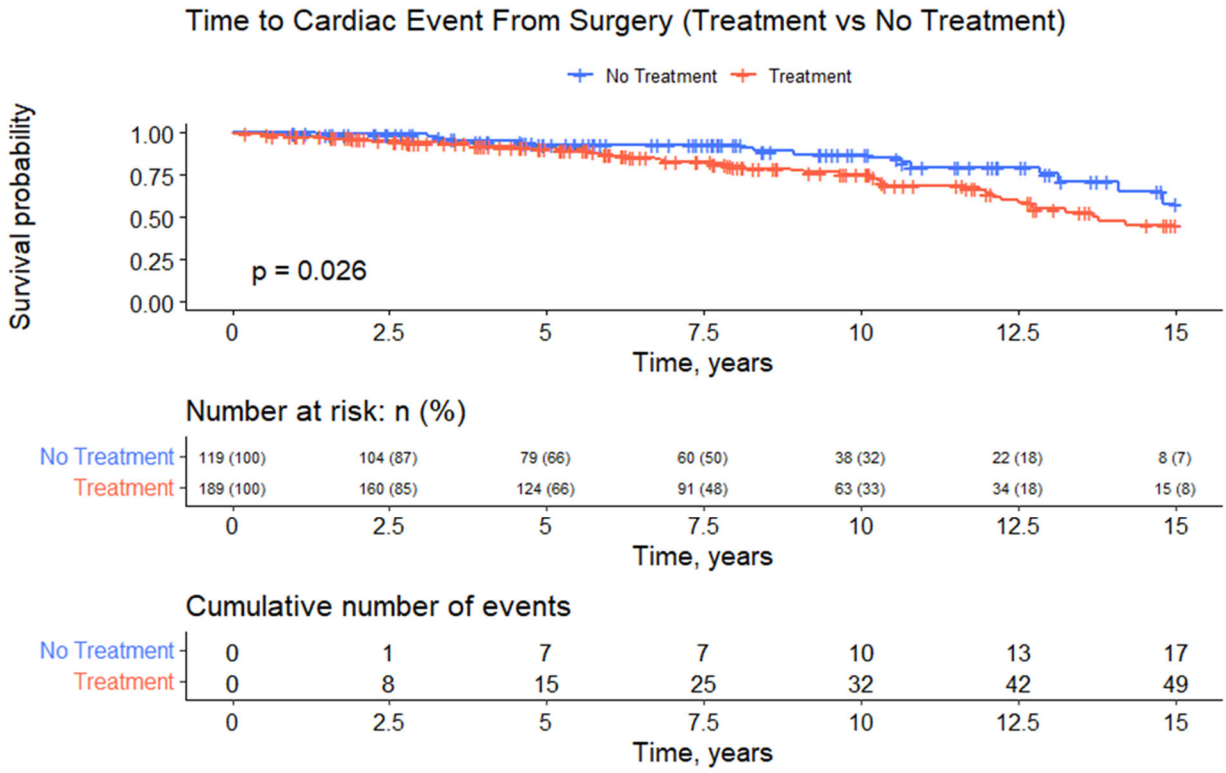


Figure 3A demonstrates a subgroup analysis of ACE stratified by treatment types of the TG post-RP. This Kaplan-Meier analysis showed no significant differences between ADT and ADT + radiation therapy (RT) (p = 0.68). In order to account for any lead time bias, a secondary Kaplan-Meier analysis was performed that calculated the time to ACE after treatment (Figure 3B). This analysis continued to show that there was no significant difference between the two treatment cohorts (p = 0.68).

Figure 3A. 15-year Kaplan-Meier analysis of ACE survival stratified by treatment types of ADT versus ADT + RT. Time to ACE calculated from time of RP.

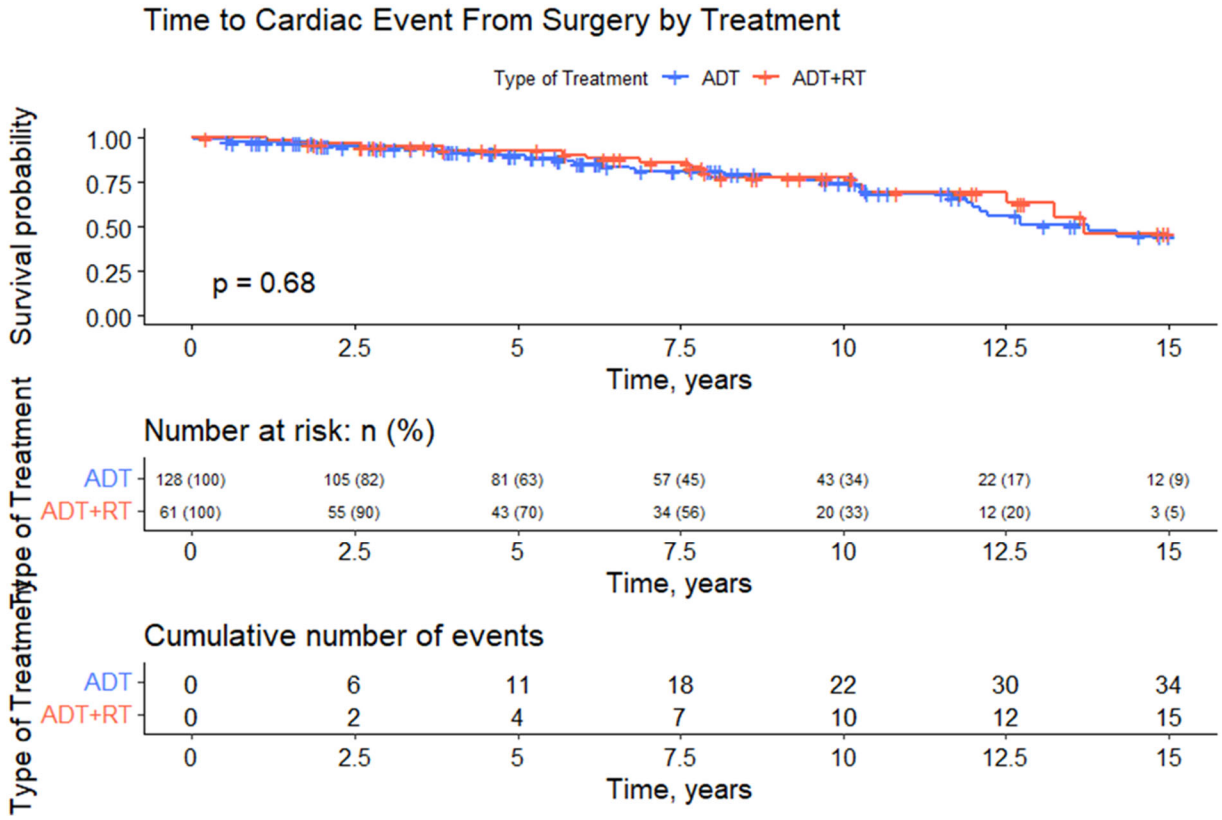


Figure 3B. 15-year Kaplan-Meier analysis of ACE survival stratified by treatment types ADT versus ADT + RT. Time to ACE calculated from time of treatment.

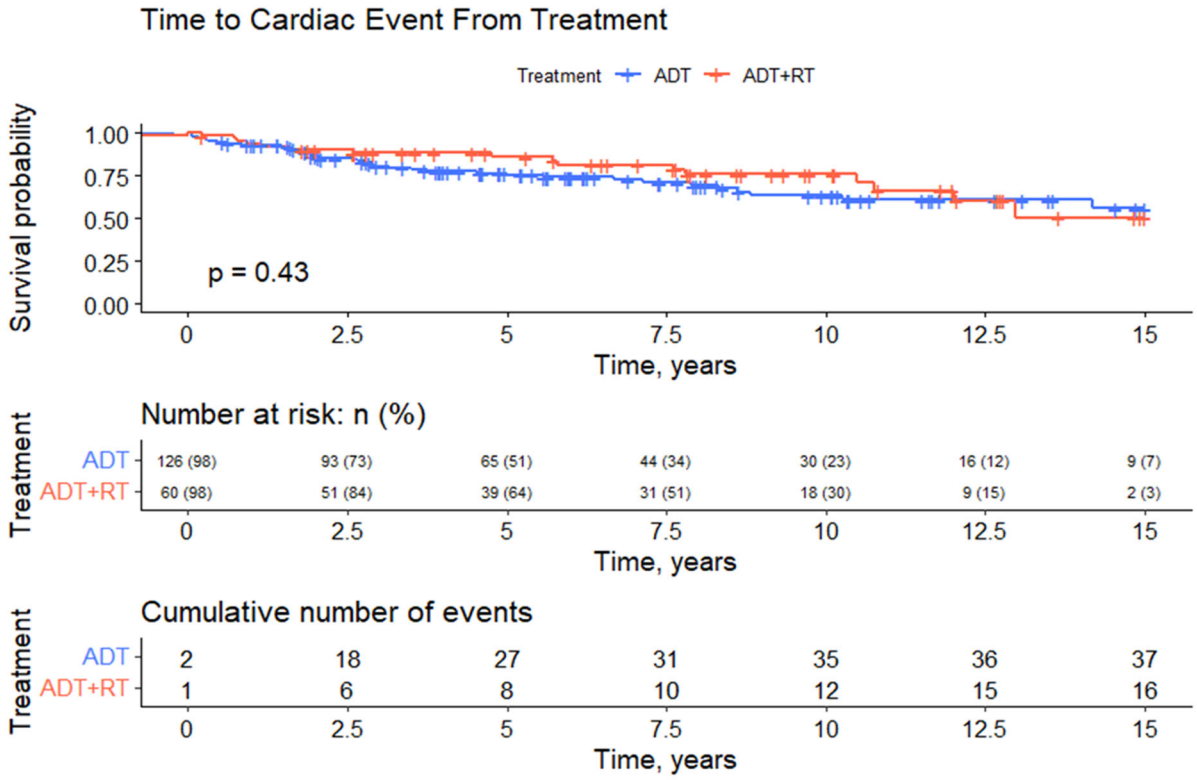


Table 6 outlines the differences between AO and TG based on the type of ACE. No statistical differences were found in MI, ischemic stroke, CHF, DVT, PE, and PVD. A statistically significant difference was observed in CAD (p = 0.0009) and arrhythmia (p = 0.05).

Table 6. Type of ACE stratified by AO versus TG.

	No Treatment (N=119)	Treatment (N=189)	Overall (N=308)	P-value
Coronary Artery Disease				**0.0009**
0	115 (96.6%)	158 (83.6%)	273 (88.6%)	
1	4 (3.4%)	31 (16.4%)	35 (11.4%)	
Arrhythmia				**0.05**
0	110 (92.4%)	159 (84.1%)	269 (87.3%)	
1	9 (7.6%)	30 (15.9%)	39 (12.7%)	
Myocardial Infarction				0.3755
0	116 (97.5%)	179 (94.7%)	295 (95.8%)	
1	3 (2.5%)	10 (5.3%)	13 (4.2%)	
Ischemic Stroke				0.3442
0	118 (99.2%)	183 (96.8%)	301 (97.7%)	
1	1 (0.8%)	6 (3.2%)	7 (2.3%)	
Congestive Heart Failure				0.212
0	116 (97.5%)	177 (93.7%)	293 (95.1%)	
1	3 (2.5%)	12 (6.3%)	15 (4.9%)	
Deep Venous Thrombosis				0.3442
0	119 (100%)	183 (96.8%)	302 (98.1%)	
1	0 (0%)	6 (3.2%)	6 (1.9%)	
Pulmonary Embolism				0.5988
0	116 (97.5%)	187 (98.9%)	303 (98.4%)	
1	3 (2.5%)	2 (1.1%)	5 (1.6%)	
Peripheral Vascular Disease				0.1728
0	107 (89.9%)	179 (94.7%)	286 (92.9%)	
1	12 (10.1%)	10 (5.3%)	22 (7.1%)	

DISCUSSION

4.0 ADT and Adverse Cardiovascular Event

According to guidelines, patients are recommended systemic treatment following a serial elevation of PSA (BCR)[2]. Systemic treatments normally consist of ADT or ADT + RT. EAU guidelines state that several studies have shown that ADT is associated with an increased risk of cardiovascular morbidity. They cite several studies that expand on the conflicting results between trials and observational studies. While a concern is noted, their recommendations defer to the FDA consensus paper from the American Heart Association, American Cancer Society, and American Urological Association[6]. They concede that there may exist a relationship between ADT and ACE, but there is no definitive determination.

Despite the growing literature since the release of the consensus paper, no definitive answer can be supported by both parties. We believe that our study lends well to bridging this divide as our results have aspects that support both sides. Initial comparison of ACE between AO and TG showed no difference between the groups with TG patients at a higher risk (Table 1). This result was contrasted with univariate analysis showing treatment status to be a statistically significant predictor of ACE (Table 2). This result is in agreement with previously established observational studies[14–18].

Utilization of multivariate logistic regression analysis models our study closer to a RCT as we are controlling for significant risk factors such as age, CCI, and BMI. In secondary analysis, we also controlled for smoking status as it is an important factor for cardiovascular morbidity[20]. Therefore, we are able to utilize the benefits of both RCT and observational studies. The nature of our study design (retrospective review of prospectively collected data) lends to the elimination, or reduction, of confirmation bias when interpreting the data. This allows us to control for one of the largest biases associated with observational and retrospective studies.

4.1 Interpretation

In multivariate modeling when controlling for age, adjusted GGG, adjusted Pre-PSA, adjusted p-stage, CCI sum, BMI and the primary exposure variable (treatment status), only BMI and CCI sum were significant predictors of ACE (Table 3). While treatment status was no longer significant, it was still trending toward significance. Therefore, treatment status no longer lends to a conclusive outcome, but would still outline the importance for physicians to consider when managing a patient's care. Correlation analysis utilizing the Pearson correlation coefficient for CCI sum and BMI showed no statistically significant results ($p = 0.8334$); reinforcing that CCI sum and BMI are independent predictors of ACE.

Another important outcome observed in the analysis was outlined in Table 5. The interim multivariate regression modeling that included smoking status displayed age, CCI sum, and treatment status as trending toward significance (Table 5B). When adjusting for smoking status, covariates age, CCI sum, treatment status, and BMI were all significant or very close to statistical significance. This result outlines the importance of considering all of the covariates as important predictors of ACE in patients post-RP. In our final model, age was a more important predictor. Smoking status is shown to be an important factor for physicians to consider when managing a patient's treatment plan, despite the lack of statistical significance.

None of our regression models were able to associate disease aggressiveness (GGG, Pre-PSA, p-stage) with the primary outcome. While there was a statistical difference in these variables, our analysis reflects that the differences in patient's demographics are not a contributing factor to ACE. Despite our results, treatment status may be a mediator between disease aggressiveness and ACE. This is outside the scope of this study but poses a fascinating direction for future studies.

Patients in the treatment group (TG) were more likely to experience CAD and arrhythmia (Table 6). The differences in event type between the two groups are quite large. While we are able to identify a definitive difference in event type between the two groups, there were only a few

overall events when compared to the sizes of each group, so it is possible that these results could be confounded by the small total number of these events. With the major differences in events seen mostly in CAD and arrhythmia, these would significantly affect a patient's quality of life but may not be reflected in larger studies where the primary endpoint is mortality. This may explain why there are negative results from large RCTs where mortality is the primary endpoint[8].

A 15-year Kaplan-Meier analysis showed a statistical significance for ACE between AO and TG (Figure 2). When considering previous analysis, treatment status was often no longer statistically significant in our final regression models. Figure 2 shows that there may be a time-varying component to the outcome variable that is not included in regression analysis. The Kaplan-Meier curve displays a growing difference between AO and TG patients' ACE survival as time increases. Emphasizing this result is paramount as patients often live beyond 10-years post-RP and do not die from PC[21]. Our analysis showed a statistically significant difference in ACE incidence at 12.5 years post-RP (P=0.017) with a difference of 19.3% (Supplemental Figure 1). Patients that are expected to live longer than 10-years post-RP are at a significantly higher risk of experiencing an ACE if they have received treatment.

Results from the Kaplan-Meier analysis may explain why there is such a stark difference in results between RCT and observational studies. RCTs, especially those funded by grants, are not often designed to follow patients beyond several years. Our model shows that patients are more likely to experience an ACE beyond 10 years and this risk increases as time continues. As stated above, there may also be a fundamental issue with the design of RCTs as their primary endpoint is often mortality.

In our subgroup analysis of treatment patients, rounds of treatment were not a significant predictor of ACE (Table 4). This regression model reinforced the necessity and driving force behind CCI sum and BMI. A concern our study team had was the effect of the different types of secondary treatments a patient can receive and its effects on ACE. Figures 3A-B show that there is no statistical difference between ADT alone and ADT + RT when adjusting for time to ACE.

This result shows that hormonal therapy (ADT) is the main driving force behind cardiovascular morbidity in patients. While RT may affect other aspects of a patient's quality of life, it may not influence the cardiovascular system. If there is an effect, it may be overshadowed by ADT's effect on ACE. We are not able to differentiate between these two possible results.

4.2 Limitations

As mentioned above, a limitation of this study was inability to isolate the effect of RT on cardiovascular morbidity. Further subgroup analysis is required in order to determine definitive effects of RT.

Another limitation of this study is the large number of patients that had missing follow-up (n = 99) (Figure 1). While unlikely, it is possible that the patients lost to follow-up may have had more ACE. While we were still able to follow and analyze the majority of the patients (n = 308), we cannot discount the possibility that the results could have been impacted if the missing data had been available for inclusion in the study.

The particular effects of treatment and the subsequent types of ACE are not fully characterized in our analysis. For example, we were unable to determine if or how treatment may affect PVD or PE. While we did observe an association and significant difference in the occurrence of CAD and arrhythmia, there was an overall small occurrence of such events in the AO patients. Future studies are required to first determine if treatment affects specific types of ACE and secondly how it is affected to definitely prove a causal relationship.

The last limitation of this study is the inability to analyze the effect of AO and TG on cardiovascular related mortality. Our cohort experienced a relatively low number of mortality (14.6%) and an even lower number of cardiovascular related mortality (2.6%) (Supplement Table 1.). Future studies would be needed in order to determine treatment effects on cardiovascular related mortality.

4.3 Future Directions

Future studies are required to fill the gaps of our limitations. While our work has concluded an importance on predictors of ACE, many aspects of our study can be utilized as the basis for future studies. Possible future studies may wish to look at different thresholds for BMI, CCI, and age. Analysis of thresholds may lend to advising physicians of what may be considered a “high” risk patient. Grouping these patients into different groups may also change the outcome of similar analyses performed in this study.

Another possible future direction is to utilize a combined aggregate or composite for cardiovascular events. An example is to use major adverse cardiovascular events (MACE) composite outcome or a similar tool in order to measure ACE.

It might also be pertinent to further study the interactions between RT and ADT. As our analysis combined all treatments of hormonal therapy into one group, the addition of radiation therapy may have a combined effect with ADT that is not reflected in our analysis.

5.0 Conclusion

The present study establishes that there is an association between treatment for biochemical recurrence following radical prostatectomy in PC patients and subsequent cardiovascular morbidity (as measured by ACE). Significant predictors of ACE are established illustrating the importance of BMI and CCI sum in relation to our primary exposure variable. Treatment status remains an important risk factor, as it continues to be trending toward statistical significance in most of our models. Utilizing these predictors, we can stratify patients into different risk groups for ACE based on information collected at time of RP. These patients would need to be carefully examined in order to determine if the risks of disease progression outweigh the risks of cardiovascular morbidity. A previous study by Huang et al. shows that a subset of patients can be observed without need for treatmens[22]. If patients fall into this group and are at a higher risk of cardiovascular morbidity, it may be more advantageous for that subgroup of patients to not receive treatment.

The current literature is divided between trusting the “golden standard” of RCT or following recommendations offered by observational studies. Our study positions itself in between the two and offers that treatment may not undoubtedly cause ACE but that it may carry a higher risk of ACE. This effect can be related to time or increasing the risk of particular ACE, such as CAD and arrhythmia, but may not increase the risk of the other types of ACE examined in our study. Future work is required to rigorously inform potential modifications to guidelines for prognosticating the effect of treatment on patients to help inform physicians of the possible risks of post-treatment ACE.

Similar to many previous studies on the effects of ADT on cardiovascular morbidity (as measured by ACE) we did not find evidence supporting ADT increasing risk of ACE and CM. After extensive evaluation we conclude that If there is an effect of ADT on ACE and CM, it is a small effect, or only affecting a small subset of patients.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424. doi:10.3322/caac.21492

2. Cornford P, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II-2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. *Eur Urol*. 2021;79(2):263-282. doi:10.1016/j.eururo.2020.09.046

3. Ahlering T, Huynh LM, Kaler KS, et al. Unintended consequences of decreased PSA-based prostate cancer screening. *World J Urol*. 2019;37(3):489-496. doi:10.1007/s00345-018-2407-3

4. Campbell CM, Zhang KW, Collier A, et al. Cardiovascular Complications of Prostate Cancer Therapy. *Curr Treat Options Cardio Med*. 2020;22(12):69. doi:10.1007/s11936-020-00873-3

5. CDC. Men and Heart Disease. Centers for Disease Control and Prevention. Published July 12, 2022. Accessed August 29, 2022. https://www.cdc.gov/heartdisease/men.htm

6. Levine GN, D'Amico AV, Berger P, et al. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. *Circulation*. 2010;121(6):833-840. doi:10.1161/CIRCULATIONAHA.109.192695

7. Zhang KW, Reimers MA, Calaway AC, et al. Cardiovascular Events in Men with Prostate Cancer Receiving Hormone Therapy: An Analysis of the FDA Adverse Event Reporting System (FAERS). *J Urol*. 2021;206(3):613-622. doi:10.1097/JU.0000000000001785

8. Nguyen PL, Je Y, Schutz FAB, et al. Association of Androgen Deprivation Therapy With Cardiovascular Death in Patients With Prostate Cancer: A Meta-analysis of Randomized Trials. *JAMA*. 2011;306(21):2359-2366. doi:10.1001/jama.2011.1745

9. Faraoni D, Schaefer ST. Randomized controlled trials vs. observational studies: why not just live together? *BMC Anesthesiol*. 2016;16:102. doi:10.1186/s12871-016-0265-3

10. D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA*. 2008;299(3):289-295. doi:10.1001/jama.299.3.289

11. Efstathiou JA, Bae K, Shipley WU, et al. Cardiovascular Mortality After Androgen Deprivation Therapy for Locally Advanced Prostate Cancer: RTOG 85-31. *J Clin Oncol*. 2009;27(1):92-99. doi:10.1200/JCO.2007.12.3752

12. Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol*. 2010;11(11):1066-1073. doi:10.1016/S1470-2045(10)70223-0

13. Denham JW, Steigler A, Lamb DS, et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. *Lancet Oncol*. 2011;12(5):451-459. doi:10.1016/S1470-2045(11)70063-8

14. Keating NL, O'Malley AJ, Smith MR. Diabetes and Cardiovascular Disease During Androgen Deprivation Therapy for Prostate Cancer. *JCO*. 2006;24(27):4448-4456. doi:10.1200/JCO.2006.06.2497

15. Hu JC, Williams SB, O'Malley AJ, Smith MR, Nguyen PL, Keating NL. Androgen-deprivation therapy for nonmetastatic prostate cancer is associated with an increased risk of peripheral arterial disease and venous thromboembolism. *Eur Urol*. 2012;61(6):1119-1128. doi:10.1016/j.eururo.2012.01.045

16. O'Farrell S, Garmo H, Holmberg L, Adolfsson J, Stattin P, Van Hemelrijck M. Risk and timing of cardiovascular disease after androgen-deprivation therapy in men with prostate cancer. *J Clin Oncol*. 2015;33(11):1243-1251. doi:10.1200/JCO.2014.59.1792

17. Morgia G, Russo GI, Tubaro A, et al. Prevalence of Cardiovascular Disease and Osteoporosis During Androgen Deprivation Therapy Prescription Discordant to EAU Guidelines: Results From a Multicenter, Cross-sectional Analysis From the CHOsIng Treatment for Prostate canCEr (CHOICE) Study. *Urology*. 2016;96:165-170. doi:10.1016/j.urology.2016.06.024

18. Forster RB, Engeland A, Kvåle R, Hjellvik V, Bjørge T. Association between medical androgen deprivation therapy and long-term cardiovascular disease and all-cause mortality in nonmetastatic prostate cancer. *Int J Cancer*. 2022;151(7):1109-1119. doi:10.1002/ijc.34058

19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8

20. Kondo T, Nakano Y, Adachi S, Murohara T. Effects of Tobacco Smoking on Cardiovascular Disease. *Circ J*. 2019;83(10):1980-1985. doi:10.1253/circj.CJ-19-0323

21. Rosario E, Rosario DJ. Localized Prostate Cancer. In: *StatPearls*. StatPearls Publishing; 2022. Accessed May 20, 2022. http://www.ncbi.nlm.nih.gov/books/NBK563248/

22. Huang E, Huynh LM, Tran J, Gordon AM, Chandhoke R, Morales B, Skarecky D, Ahlering TE. Active Observation of Biochemical Recurrence without Treatment following Radical Prostatectomy: Long-Term Analysis of Outcomes. Cancers. 2022; 14(17):4078. https://doi.org/10.3390/cancers14174078