Matters of the heart : An exercise medicine approach to counteracting the adverse effects of androgen deprivation therapy in men with prostate cancer

Bigaran, Ashley Sammantha

Matters of the heart: An exercise medicine approach to counteracting the adverse effects of androgen deprivation therapy in men with prostate cancer

Submitted by
Ms. Ashley Sammantha Bigaran
Bachelor of Applied Science (Human Movement)
Bachelor of Exercise and Sports Science (Honours)
Master of Clinical Exercise Physiology

A thesis submitted in total fulfilment of the requirements of the degree of
Doctor of Philosophy (with publication)

Exercise & Nutrition Research Program
Mary MacKillop Institute for Health Research
Faculty of Health
Australian Catholic University
July 2022

STATEMENT OF AUTHORSHIP AND SOURCES

This thesis contains no material that has been extracted in whole or in part from a thesis that I have submitted towards the award of any other degree or diploma in any other tertiary institution.

No other person's work has been used without due acknowledgment in the main text of the thesis.

All research procedures reported in the thesis received the approval of the relevant Ethics/Safety Committees (where required).

The extent to which other persons contributed to work arising from this thesis is specified in **Appendix A**.

Ashley S. Bigaran
July 2022

STATEMENT OF APPRECIATION

Several individuals were a part of the design, development, and contributions of this thesis that I would like to thank and express gratitude to sincerely:

Firstly, to my PhD supervisory team of Dr Eva Zopf, Dr Erin Howden, A/Prof Michael Baker, and A/Prof Prue Cormie. I am privileged and grateful for the extensive time, efforts, and support each of you provided throughout my PhD and the hours spent critically evaluating my work, all while trying to keep me on track (as difficult as that can be). I certainly think you deserve a medal for helping me reach the finish line. Although the project start-up and study deliverables felt like an ongoing battle (including a 100-year pandemic), I have learned an astonishing amount over the last few years. From the research upskilling to navigating my PhD's countless twists and turns, you provided ample support to help me find solutions, move past manuscript rejections, and grant outcomes, and redirect my focus to the end goal. My fascination for endocrine/hormone therapies will continue beyond this PhD, particularly concerning cardiovascular health. I very much owe that ongoing fascination to all of you (but Erin, you get the kudos for this one). While we set out to undertake an ambitious series of experimental studies, I hope you are proud of the results and body of work as I am.

To Mark, Kelcey, and Louise, it has been a pleasure working with you, and I hope that after I depart the 'tute', you can finally get some work done without me distracting you. From all the office pranks (and great nicknames) to the ample amounts of coffee drinking, I cannot thank you enough for supporting the study deliverables, training my participants and for your friendships over the years. I felt that the bonds we formed during the fun times made the difficult times a breeze.

To Evelyn, Bridge, John, Orly and the ENRP team at ACU, thank you for your encouragement and support over the years. The start-up of the EX-HEART trial would not have been possible without each of you. Also, thanks to Gabi, Pauline, and Angela for all the coffee chats, fashion critiques of the MET Gala and the online shopping that broke my bank account a few times.

To Andre, Kristel, Leah, Rachel, Steve, and the Sports Cardiology Team, thank you for your support over the years. I have been incredibly fortunate to be a part of this team for almost seven years (luckily not as old as Andre), and I have seen this team go from strength to strength. To the original

supervisory team of Andre, Steve Fraser, and Steve Selig, I cannot thank you enough for convincing me to return to study and undertake an honours degree in breast cancer and exercise oncology. This monumental pivot has changed my career trajectory. Your generous support and mentoring and the out-of-the-blue emails telling me how proud you are of me (especially after being awarded the 2022 Female Leader in Exercise and Sports Science) have never gone unnoticed. To the incredible Sports Cardiology team support staff, thank you for your support over the years. My long testing days could not have gone as smoothly if not for Anniina, Amy, Imogen, and Kristel. Hayley, thank you for making me constantly laugh and keeping my underlying anxiety on alert whenever I open your text messages. To Liz Paratz, thank you for the comic relief, the brunches with Alex and Esther and being my favourite dismissive cardiologist.

To our collaborators at Austin Health (Carla D'Amico, A/Prof Joseph Ischia), Peter MacCallum Cancer Centre (Prof Declan Murphy, Marc Diomerc, Elizabeth Medhurst), Australian Prostate Centre (Dr Jane Crowe, Helen Crowe, Kimberley Hobson) and Alfred Health (A/Prof Jeremy Millar), the EX-HEART trial would not have been possible without your support. Carla, you have been a pillar of support, and I am incredibly fortunate to work alongside you at Austin Health (aka Hawaii). I would also like to extend many thanks to the participants who took part in the EX-HEART trial. I could not have completed my PhD without your willingness to take part.

To Pat Owen, Niamh Mundell, and Donny Camera, thank you for listening, being present and setting weekly deadlines to help me finish my PhD. Your support over the last 12 months has been critical to reaching this deadline, and I hope one day I can return the very generous favour. As we have both mentioned on several occasions, we would do the same thing for each other if ever we were in need. To other friends and colleagues, Sofie Lionett, Daniel Romeo, Christian Pitcher, John Waters, Jason Gardner, Kelly Spence, Holly Austin, Bec Hallam, Gemma Houston, Steve Foulds, and Emma Little, thank you for your support and constant comic relief throughout my PhD.

To my parents, my brother Rhys, cousins (Steph, Mark, Ilaria and the other Bigaran et al. Innes), grandparents, aunts, and uncles, this could not have been possible without your support, and encouragement and always making sure I was looking after myself. Mum and Dad, I can confirm that I am done studying after this. Even though there were many times when I wanted to step away, revaluate my perspectives, or start a bougie coffee business, you always convinced me to keep

going, especially after my ADHD and dyslexia diagnosis. To the two beautiful dogs in my life, Keeper (rest in peace), and Remi, thank you for crashing my zoom meetings and pestering me to go on daily neighbourhood walking adventures.

Lastly, I feel fortunate and humbled to lead the Exercise Oncology team at Austin Health. To Penny Sanderson, thank you for allowing me to take the lead and supporting my vision of the exercise oncology service over the past 12 months. You have been incredibly patient since I started at Austin Health and provided ample support during the busiest time of my PhD. To the Exercise Oncology dream team of Grace Williams and Clare O'Donnell, thank you for making me laugh, breaking my brain on a Wednesday afternoon, and always supporting my crazy ideas. I cannot wait to see what we do next. Many thanks to Lisa Garetto, Carlene Wilson and the entire Wellness and Supportive Care Team; thank you for welcoming me as one of your own, and I feel so humbled to work with each of you.

Table of Contents

LIST OF PUBLICATIONS ARISING FROM THIS THESIS ..... **x**
CONFERENCE PROCEEDINGS ARISING FROM THIS THESIS ..... **xi**
ADDITIONAL PRESENTATIONS ARISING FROM THIS THESIS ..... **xii**
POSTER PRESENTATIONS ARISING FROM THIS THESIS ..... **xii**
PODCAST ..... **xii**
LIST OF ABBREVIATIONS ..... **xiii**
LIST OF FIGURES ..... **xvi**
LIST OF TABLES ..... **xvii**
ABSTRACT ..... **xix**
CHAPTER ONE: Overview, introduction, and literature review **1**
1.1. Prostate and prostate cancer 1
1.2. Epidemiology of prostate cancer 1
1.3. Prostate cancer diagnosis, detection, and treatment 3
1.4. Adverse effects of prostate cancer treatments 7
1.5. Cardiovascular disease in prostate cancer 10
1.6. Abnormal cardiovascular risk profiles in ADT-treated men 12
1.7. Possible mechanisms linking adverse cardiovascular consequences and cardiovascular disease incidence in men treated with ADT. 17
1.8. Management of cardiovascular risk in prostate cancer 21
1.9. Assessing cardiovascular health: an innovative detection strategy 23
1.10. Interventions to address the cardiovascular and metabolic disease risk burden in non-cancer populations 26
1.11. Preliminary evidence to address cardiometabolic health in ADT-treated men. 29
1.12. Conclusion 30
1.13. Overall aims of this thesis. 30
1.14. Aims of this thesis 31
1.15. Specific hypotheses: 31
1.16. Thesis Structure 32
CHAPTER TWO: The influence of pre-existing cardiovascular disease on cardiovascular morbidity and mortality in men with prostate cancer treated with androgen deprivation therapy **33**

2.1. Introduction 36
2.2. Materials and methods 37
2.3. Results 38
2.4. Qualitative synthesis 47
2.5. Discussion 61
2.6. Conclusions 64
CHAPTER THREE: The effect of exercise training on cardiometabolic health in men with prostate cancer receiving androgen deprivation therapy. 70
3.1. Summary and linking section. 97
CHAPTER FOUR: General Methods 98
4.1. Methodology 99
4.1.1. Overview of study design for Chapter Five 99
4.1.2. Overview of study design for Chapter Six 100
4.2. Outcome measures 101
4.2.1. Blood biochemical markers 101
4.2.2. Cardiovascular risk 101
4.2.3. Body composition 102
4.2.4. Resting cardiovascular function 102
4.2.5. Arterial stiffness 103
4.2.6. Central blood pressure and augmentation index 103
4.2.7. Ventricular structure and function (echocardiogram) 104
4.2.8. Ventricular structure (cardiac magnetic resonance imaging) 105
4.2.9. Physical function 106
4.2.10. Cardiopulmonary exercise testing 107
4.2.11. Patient-reported outcomes 108
4.3. Exercise attendance and adherence. 110
4.4. Adverse events 111
4.5. Exercise intervention 113
4.6. Usual care 114
4.7. Summary 116
CHAPTER FIVE: Cardiovascular risk profile of men with prostate cancer initiating androgen deprivation therapy related to aged-matched controls: a cross-sectional study. 117

5.1. Abstract 118
5.2. Introduction 120
5.3. Methods 122
5.3.1. Study design 122
5.4. Outcomes measures 122
5.5. Statistical analysis 123
5.6. Results 124
5.6.1. Participant characteristics 124
5.6.2. Vascular health and central and peripheral haemodynamic indices 126
5.6.3. Blood biochemical biomarkers 127
5.6.4. Resting cardiovascular structure and function 128
5.6.5. Body composition 128
5.6.6. Cardiorespiratory fitness 128
5.6.7. Associations between cardiorespiratory fitness and cardiovascular health 132
5.6.8. Predictors of cardiorespiratory fitness 133
5.7. Discussion 134
5.8. Strengths and limitations 138
5.9. Conclusions 139
CHAPTER SIX: Evaluating the impact of exercise training on cardiac remodelling in men with prostate cancer undergoing androgen deprivation therapy: a randomised controlled trial. 140
6.1. Abstract 141
6.2. Introduction 143
6.3. Methods 145
6.3.1. Study design 145
6.3.2. Participants and recruitment 145
6.3.3. Exercise training intervention 146
6.3.4. Exercise attendance and adherence 146
6.3.5. Adverse events 146
6.3.6. Outcomes measures 147
6.3.7. Sample size calculation 149
6.3.8. Randomisation and blinding 149

6.3.9. Usual care 149
6.3.10. Statistical analysis 149
6.4. Results 150
6.4.1. Recruitment 150
6.4.2. Participant characteristics 153
6.4.3. Study attrition, attendance, and adherence 153
6.4.4. Adverse events 154
6.4.5. Resting cardiac structure and function 157
6.4.6. Cardiorespiratory fitness and physical function 163
6.4.7. Body composition 168
6.4.8. Vascular health 170
6.4.9. Patient-reported outcomes 170
6.5. Discussion 177
6.6. Strengths and limitations 181
6.7. Conclusions 183
CHAPTER SEVEN: Summary, key findings, strengths, limitations, and conclusions 185
7.1. Summary 185
7.2. Key findings 187
7.3. Strengths and Limitations 191
7.4. Concluding remarks 193
REFERENCES 198
APPENDIX A 240
APPENDIX B 246

LIST OF PUBLICATIONS ARISING FROM THIS THESIS

Bigaran A, Zopf E, Gardner J, La Gerche A, Murphy DG, Howden EJ, et al. The effect of exercise training on cardiometabolic health in men with prostate cancer receiving androgen deprivation therapy: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2021;24(1):35-48. DOI: 10.1038/s41391-020-00273-5

Submitted

Bigaran A, Zopf EM, Gardner J, Howden EJ, Baker MK, Cormie, P. The influence of pre-existing cardiovascular disease on cardiovascular morbidity and mortality in men with prostate cancer treated with androgen deprivation therapy. A systematic review.
Submitted to *Acta Oncologica*

In preparation

Bigaran A, Zopf EM, La Gerche A, Baker MK, Cormie P, Howden EJ. Evaluating vascular health in men with prostate cancer commencing androgen deprivation therapy: a cross-sectional study.

Bigaran A, Zopf EM, La Gerche A, Baker MK., Howden EJ, Cormie P. The impact of exercise training on cardiac remodelling in men with prostate cancer undergoing androgen deprivation therapy: A randomised controlled trial.

CONFERENCE PROCEEDINGS ARISING FROM THIS THESIS

Bigaran A. The impact of exercise training on cardiac remodelling in men with prostate cancer undergoing androgen deprivation therapy: A randomised controlled trial.
Invited presentation: Psych Oncology Grand Rounds, Department of Integrative Cancer Services, Austin Health, June 2022, Melbourne, Australia.

Bigaran A, Zopf EM, La Gerche A, Romeo D, Trevaskis M, Bland K, Baker MK, Howden EJ, Cormie P. The impact of exercise training on cardiac remodelling in men with prostate cancer undergoing androgen deprivation therapy: A randomised controlled trial.
Exercise and Sports Science Australia National Conference, May 2022, Perth, Australia (Virtual Conference)

Bigaran A. Using exercise to counteract the adverse side effects of prostate cancer treatments: Latest evidence and research update.
Invited presentation: Asia Pacific Prostate Cancer Conference, November 2021, Melbourne, Australia

Bigaran A. Using exercise to counteract the cardiotoxic effects of androgen deprivation therapy.
Invited presentation: Surgical Uro-Oncology Symposium (sponsored by MundiPharma Pty Limited), August 2019, Gold Coast, Australia

ADDITIONAL PRESENTATIONS ARISING FROM THIS THESIS

Bigaran A. Using exercise to identify and prevent cardiotoxicity in men with prostate cancer undergoing androgen deprivation therapy.
Department of Radiation Oncology Research Symposium, Alfred Health, November 2019, Melbourne, Australia; Department of Urology, Austin Health, May 2019, Melbourne, Australia, Department of Urology, Alfred Health, November 2019; Department of Genitourinary Cancer, Peter MacCallum Cancer Centre, Melbourne Australia; Australian Prostate Centre and Royal Melbourne Hospital, November 2019, February 2020, October 2020.

Bigaran A. Prescribing exercise training for men with prostate cancer
Victorian Prostate Cancer Nurses Association (sponsored by AbbVie Pty Limited) November 2021, Melbourne, Australia

POSTER PRESENTATIONS ARISING FROM THIS THESIS

Bigaran A, Zopf, EM, Wiggins L, La Gerche A, Baker MK, Cormie P, Howden EJ. Cardiovascular Health is Impaired in Men with Prostate Cancer Commencing Androgen Deprivation Therapy.
Clinical Oncology Society of Australia, Annual Scientific Meeting, November 2020 (Virtual Conference).
Exercise and Sports Science Australia National Conference, May 2021, Perth, Australia (Virtual Conference).

PODCAST

Bigaran A, Ischia D, Zopf EM, Ischia J. So, you're going to recommend exercise for men with prostate cancer on androgen deprivation therapy and chemotherapy?
Talking Urology (sponsored by AbbVie Pty Limited) November 2019
https://www.talkingurology.com.au/syg/exercise-for-men-with-pc/

LIST OF ABBREVIATIONS

ADT	Androgen Deprivation therapy
AIx	Augmentation index
AIx [HR75]	Augmentation index at heart rate 75 bpm
ARKO	androgen receptor knockout mice
ASR	Age-standardised rate
BSI-18	Brief Symptom Index
cfPWV	Pulse wave velocity
CMR	Cardiac magnetic resonance
CON	Age-matched control group
COVID	Coronavirus disease
CPET	Cardiopulmonary exercise testing
CV	Coefficient of variation
CVD	Cardiovascular disease
CYP17	Cytochrome gene
DT	deceleration time
DXA	Dual-energy x-ray absorptiometry
E	Peak early diastolic flow velocity
E/A	The ratio of early diastolic inflow to late diastolic inflow
E/e’	mitral annular velocity
e’	Peak early diastolic tissue velocity
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EORTC-QLQ C30	European Organisation for Research and Treatment of Cancer, Quality of Life of Cancer Patients
EORTC-QLQ PR25	Quality of life of prostate cancer patients
d	Cohen’s *d* effect size
EX	Exercise training group
FACIT-F	Functional Assessment of Chronic Illness Therapy
FMD	Flow-mediated dilation
FSH	Follicle-stimulating hormone

GLS	Global longitudinal strain
GNRH	Gonadotropin-releasing hormone
HIIT	High-intensity interval training
HR	Hazard ratio
LAVI	Left atrial volume and indexed value
LH	Luteinising hormone
LHRH analogues	Luteinising hormone-releasing hormone
LV	Left ventricular
LVCOi	LV cardiac output
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVM: V	Left ventricular mass to volume ratio
LVSVi	LV stroke volume index
MD	Mean difference
MET	Metabolic equivalent
MSS	Maximal steady-state
NT-BNP	N-terminal probe-type natriuretic peptide
OR	Odds Ratio
PCa	Prostate cancer
PSQI	Pittsburgh Sleep Quality Index
QoL	Quality of life
REDCap	Research Electronic Data Capture
RM	Repetition maximum
RR	Relative risk
SD	Standard deviation
SEER	Surveillance, Epidemiology and End Results Database
UC	Usual care group
VCO_2	Expired volume of carbon dioxide
VE/VCO_2	The slope of minute ventilation in proportion to the expired volume of carbon dioxide
VO_2max	Maximal oxygen uptake
VO_2peak	Peak oxygen uptake

VT	Ventilatory threshold
WMD	Weighted mean difference

LIST OF FIGURES

Figure 1.1: Managing cardiovascular risk in ADT-treated men. 22
Figure 2.1: Study selection process for the influence of pre-existing cardiovascular disease on cardiovascular morbidity and mortality in men with prostate cancer treated with ADT. 39
Figure 4.1: Cross-sectional study design and protocol for the study presented in *Chapter Five* 99
Figure 4.2: Randomised controlled trial design and protocol for the study presented in *Chapter Six* 100
Figure 5.1 A & B: Arterial stiffness assessed by pulse wave velocity and augmentation index assessed by pulse wave analysis in men commencing ADT, compared to age-matched controls. 126
Figure 5.2: A, B & C: Cardiorespiratory fitness and peak power output determined by cardiopulmonary exercise testing (VO_2peak) in men commencing ADT, compared to age-matched controls. 131
Figure 6.1: Flow diagram of the EX-HEART trial including men commencing ADT randomised to exercise training or usual care control for three months. 152
Figure 6.2 A, B & C: Resting cardiac structure assessed by CMR imaging between exercise training and usual care in ADT-treated men. 159
Figure 6.3 A & B: Cardiorespiratory fitness and peak power output assessed by cardiopulmonary exercise testing between exercise training and usual care in ADT-treated men. 164

LIST OF TABLES

Table 1.2: Summary of long-term and late effects of prostate cancer and its treatment 8
Table 2.1: Characteristics of studies investigating the association of pre-existing cardiovascular disease with all-cause mortality, cardiovascular mortality and cardiovascular events in prostate cancer patients treated with androgen deprivation therapy. 42
Table 2.2: All-cause mortality and cardiovascular mortality in prostate cancer patients with pre-existing cardiovascular disease and treated with androgen deprivation therapy. 48
Table 2.3: Incidence of cardiovascular events in prostate cancer patients with pre-existing cardiovascular disease and treated with androgen deprivation therapy. 56
Supplementary Table s2.1: Methodological quality of included cohort studies according to the Newcastle-Ottawa quality assessment scale 66
Supplementary Table s2.2: Search terms 67
Table 4.1: Summary of data collection methodology 112
Table 4.2: Summary of exercise intervention 115
Table 5.1: Demographics and baseline characteristics 125
Table 5.2: Comparisons of arterial stiffness and central and peripheral haemodynamic indices between men with prostate cancer commencing ADT and age-matched controls 127
Table 5.3: Comparisons of traditional and novel blood biochemical markers between men with prostate cancer commencing ADT and age-matched controls. 128
Table 5.4: Comparisons of cardiac structure and function, body composition, and cardiorespiratory fitness between men with prostate cancer commencing ADT and age-matched controls. 130
Table 5.5: Bivariate correlations between VO_2peak and other clinically relevant variables 132
Table 5.6: Multiple linear regression model for the association between VO_2peak and cardiovascular and clinical characteristics in men commencing ADT and age-matched controls (n=33) 133
Table 6.1: Baseline characteristics 155
Table 6.2: Mean baseline and three-month change values for CMR-derived indices between exercise training and usual care groups 160
Table 6.3: Mean baseline and three-month change values for echocardiographic outcomes between exercise training and usual care groups 162
Table 6.4: Mean baseline and three-month change values for CPET and physical function parameters between exercise training and usual care groups 166

Table 6.5: Mean baseline and three-month change values for body composition parameters between exercise training and usual care groups.....169
Table 6.6: Mean baseline and three-month change values for vascular and haemodynamic parameters between exercise training and usual care groups.....171
Table 6.7: Mean baseline and three-month change values for quality-of-life parameters between exercise training and usual care groups.....173
Table 6.8: Mean baseline and three-month change values for physical activity, fatigue, psychological distress, sleep quality and prostate-cancer-specific quality of life outcomes between exercise training and usual care groups.....175
Table 7.1 Implications and recommendations resulting from this thesis for managing the cardiovascular and metabolic side effects in men with PCa treated with ADT. 196

ABSTRACT

Androgen deprivation therapy (ADT) is commonly prescribed for men with prostate cancer (PCa). Despite its clinical effectiveness, ADT is associated with several deleterious effects, including cardiovascular disease (CVD). Whilst epidemiological data suggests that ADT-treated men have an increased risk of all-cause and cardiovascular mortality and cardiovascular events, the underlying mechanisms are poorly understood. As CVD is the leading cause of death unrelated to PCa, elucidating these mechanisms would aid in identifying therapeutic targets for preventative strategies.

The primary aim of this thesis was to explore the underlying mechanisms of cardiovascular risk and the therapeutic role of exercise training in ADT-treated men. To achieve this, two systematic reviews, a cross-sectional study, and a randomised controlled trial were completed. *Chapter One* provides an overview, introduction and review of the literature related to this thesis. *Chapter Two* presents the results of a systematic review that comprehensively examined the influence of pre-existing CVD on all-cause mortality, cardiovascular mortality, and cardiovascular events in ADT-treated men. This review included prospective and retrospective cohort studies and randomised controlled trials that reported risk estimates separately for groups with pre-existing CVD diagnoses in ADT-treated men and included at least one endpoint for all-cause and cardiovascular mortality and cardiovascular events. Chapter *Three* presents the results of a published systematic review and meta-analysis, which evaluated the "effect of exercise training on cardiometabolic health in men with PCa receiving ADT." Chapter *Four* presents the methodological approach for the experimental studies performed in Chapters *Five and Six*. Chapter *Five* presents the results of a cross-sectional study (assessments performed in parallel with the randomised controlled trial in Chapter *Six*) that compared measures of vascular health in 31 men commencing ADT (age: 66.5±9.9 years) and ten age-matched controls (age: 64.8±8.7 years). Chapter *Six* randomly assigned ADT-treated men (age: 66.6±9.2 years, n=16) to a three-month thrice-weekly aerobic and resistance exercise program or usual care (age: 66.3±10.2 years, n=15). Outcomes of Chapters *Five and Six* included blood biochemical markers, resting echocardiography, cardiac magnetic resonance imaging, body composition, vascular health, cardiorespiratory fitness, physical function, and a series of patient-reported outcomes. Lastly, Chapter *Seven* presents the thesis's strengths, limitations, and future directions.

Men with pre-existing CVD (chronic heart failure or prior myocardial infarction) treated with ADT reported higher rates of all-cause mortality than men without pre-existing CVD or those not treated with ADT (Chapter *Two*). Despite the inconsistencies and notable between-study clinical and methodological heterogeneity, observations regarding the risk of cardiovascular mortality or cardiovascular events in ADT-treated men with pre-existing CVD were inconclusive. In addition, the meta-analysis in Chapter *Three* showed that exercise training improved some, but not all, cardiometabolic health markers in ADT-treated men. While statistically significant effect estimates were observed between the exercise training and usual care groups, these estimates did not reach clinically meaningful thresholds, which suggested that the lower aerobic exercise training intensities were insufficient to induce beneficial cardiometabolic effects in ADT-treated men. Chapter *Five* showed that novel CVD (functional) markers, such as peak oxygen uptake (VO_2peak; 23.7±4.5 vs. 32.8±8.3 ml/kg/min; P<0.001) and body fat percentage (29.8±6.8 vs. 23.9±9.4%; P=0.03) were statistically different between men commencing ADT and age-matched controls. Predictors of better cardiovascular health appear best reflected in those with a higher cardiorespiratory fitness level in all participants. Chapter *Six* showed that incorporating a three-month periodised aerobic and resistance training exercise intervention, including high-intensity interval training, mitigated adverse cardiac remodelling and improved VO_2peak in ADT-treated men compared to usual care.

Overall, this thesis provides the foundation for future investigative studies to explore the impact of pre-existing CVD/risk factors in ADT-treated men and the potential influence on subclinical markers of CVD along the hypothesised clinical pathway to CVD events. These findings suggest that incorporating subclinical CVD markers and higher-intensity exercise regimens known to increase VO_2peak may help reduce the CVD risk burden in ADT-treated men.

CHAPTER ONE: Overview, introduction, and literature review

1. Overview

This chapter provides an overview of the epidemiology of prostate cancer (PCa) and the public health issue faced by many men in Australia and worldwide. A commonly prescribed treatment, androgen deprivation therapy (ADT), is an effective cancer therapy in appropriately selected men yet is often associated with adverse effects on cardiovascular risk. This introductory chapter will thoroughly synthesise the available evidence regarding the cardiovascular risks of ADT. This chapter will also summarise the epidemiological evidence concerning cardiovascular disease (CVD) incidence in this population and discuss potential mechanisms contributing to this heightened risk. In addition, this chapter will then review current and potential strategies to identify and prevent the cardiovascular effects associated with ADT. Given that *Chapters Two* and *Three* of this thesis are systematic reviews, a brief overview of the latest research evidence will also be presented before integrating these manuscripts.

1.1. Prostate and prostate cancer

The prostate gland is a reproductive organ composed of muscular and connective tissue below the bladder and the vas deferens [1]. The production and secretion of seminal fluid, which is necessary for male reproduction, is the sole function of the prostate gland in the body. PCa is an adenocarcinoma originating within the prostate gland. It occurs via a malignant replication of prostatic cells surrounding the prostate tissue, which results in tumour formation. Upon diagnosis, prostate adenocarcinoma may be considered localised (within the prostate gland), spread beyond the prostate gland (locally advanced), or metastasise to bones or lymph nodes (metastatic PCa) [2].

1.2. Epidemiology of prostate cancer

Incidence

PCa is the most prevalent male cancer diagnosis worldwide [3, 4]. Since 2019, approximately 1.4 million new cases and over 370,000 deaths have been attributed to PCa globally [4]. As the global burden of PCa in developed nations remains high, the incidence of PCa in 2040 is projected to exceed 2.3 million [4]. Epidemiological evidence suggests that PCa incidence varies considerably across geographic regions. Currently, Northern Europe (age-standardised rates [ASR], 83.4), Western Europe (ASR 77.6), the Caribbean (ASR 75.8), Australia/New Zealand (ASR 75.8) and North Americas (ASR 73) have the highest age-standardised rates of PCa per 100,000 people

worldwide [3, 4], which may stem from the availability and emphasis on testing and early detection, respectively. Australia has the highest incidence and prevalence of PCa, with approximately 18,110 cases recorded in 2021, representing 23 %of all new male cancer diagnoses [5].

Overall Mortality

Compared to the general population, men diagnosed with PCa have an increased risk of all-cause and non-cancer-related mortality [6-8]. Notably, in Australian contexts, the risk of all-cause and non-cancer-related mortality has proportionally increased, with data from the Queensland Cancer Registry indicating that over 30% of men with PCa are more likely to die from non-cancer-related causes than the age-matched general population [7]. This data was consistent with recent evidence from a South Australian study by Koczwara et al.[9], whereby men with PCa had the highest rates of all-cause mortality (54.7 per 1000 person-years) and non-cancer-related mortality (30.0 per 1000 person-years) compared with the general population and other cancer cohorts.

Cancer-specific mortality

PCa is the second leading cause of cancer-related mortality among adult males, accounting for an estimated 3.8% of all cancer-related deaths worldwide [3, 4]. Since 2018, there has been a steady decline in age-standardised mortality rates in Australia, with an expected decrease of approximately 2.1% in 2021 (23.8 deaths in 2018 vs. 21.7 deaths per 100,000 males expected in 2021) [5]. PCa was projected to account for roughly 3,323 male cancer-related deaths in Australia in 2020 [5]. This accounts for roughly 12 % of all male cancer fatalities in Australia [5].

Cardiovascular-specific mortality

With increasing survival rates among men with PCa nationally and internationally, men now live long enough to experience age-related comorbid conditions such as cardiovascular disease (CVD). A large cohort study of 3,234,256 cancer survivors from the United States Surveillance, Epidemiology and End Results databases (SEER) reported that 76% of deaths were related to CVD, of which 16% were PCa survivors [10]. This data was consistent with the above Australian study, which revealed that death from CVD causes exceeded cancer-related deaths in men with PCa 13 years following their diagnosis [9]. While observational data reports that PCa-related death is declining, deaths from CVD and other non-cancer-related conditions continue to rise [10, 11]. Overall, these findings suggest that men with PCa have a higher risk of dying from CVD than PCa.

Therefore, to improve survival in this vulnerable population, PCa care should consider shifting its emphasis to managing modifiable co-morbid conditions such as CVD.

Survival

Globally, the five-year survival rate of PCa has markedly improved, with many countries reporting five-year survival rates of greater than 90% [12]. With greater access to detection and treatment, developed countries such as Australia have observed proportional increases in the five-year survival rate from 58% to 96% over the past three decades [5].

1.3. Prostate cancer diagnosis, detection, and treatment

In an Australian context, the most common first-line assessment for PCa detection is conducted via a blood test, which measures the prostate-specific antigen concentration. While the prostate-specific antigen measurement is the first-line level of inquiry regarding a PCa diagnosis, additional, more informative assessments may also be required. Further investigations may include a digital rectal exam, prostate gland biopsy (removal of tissue from the prostate gland for histopathological examination), computed tomography, multi-parametric magnetic resonance imaging and metastatic screening, including bone imaging (if beyond Gleason 4 histopathology patterns and International Society of Urological Pathology [ISUP] grade 2-5) [13, 14]. Once PCa is histologically confirmed, primary staging (using the tumour, node, and metastasis classification) and the Gleason score and s the ISUP grade of the adenocarcinoma are included. The Gleason Score is a grading system based on the histopathological architecture of PCa tumours derived from a PCa biopsy. The Gleason score is calculated based on the summation of the most extensive and second most common histological tumour pattern [13, 14]. The Gleason score ranges from 2-10 (ISUP grade group 1-5). A Gleason score of 6 or less is considered low grade, and a score from 8-10 is considered high-grade PCa [13, 14]. Upon staging, an appropriate oncological treatment pathway is determined. Current PCa treatments are dependent on PCa staging, Gleason score, age, comorbidities and expected survival; patients may undergo active surveillance/watchful waiting, surgery (radical prostatectomy), radiation therapy (low or high dose brachytherapy, external beam radiation therapy) or be prescribed a combination of neoadjuvant or adjuvant ADT with or without radiation therapy or chemotherapy [12, 14]. However, the PCa treatment pathway changed in 2018 following the results of the STAMPEDE trial [15], whereby men with low-volume metastatic PCa now receive upfront ADT with docetaxel chemotherapy. These data guide clinical decision-making and treatment

pathways, particularly for men with locally advanced or metastatic disease. PCa treatments may now include a combination of neoadjuvant or adjuvant ADT with radiation therapy or chemotherapy.

Androgen deprivation therapy

The different types of ADT are outlined in Table 1.1. ADT is a frequently prescribed surgical or medical castration treatment for PCa worldwide. While data concerning the current usage rates of ADT in Australia is limited [12, 16, 17], data from the Prostate Cancer Outcome Registry Victoria estimated that 50-64% (2% received surgical castration) of men with locally advanced or metastatic PCa received ADT (medical castration) in conjunction with other treatments such as radiation therapy [18]. ADT aims to reduce circulating androgen levels, such as testosterone, to castration levels [12, 19]. Although medical castration via ADT is commonly prescribed, an alternate surgical option, such as surgical orchiectomy (permanent removal of the testicles), can also achieve castration levels of testosterone [14]. Medical castration is generally favoured over surgical orchiectomy due to the reversibility of hypogonadism symptoms following treatment cessation [14]. Pharmacological treatments, such as ADT, are commonly administered via subcutaneous implant (injection) or tablets of luteinising hormone-releasing hormone analogues (LHRH), antagonists, anti-androgens and, more recently, cytochrome P450 17Y inhibitor (outlined in Table 1.1). These treatments are commonly combined with radiotherapy and chemotherapy or minimally in isolation following neoadjuvant treatment periods. The treatments are designed to palliate symptoms, reduce biochemical recurrence, and improve survival [14].

LHRH agonists (also known as Gonadotropin-releasing hormone, GnRH) continue to be the most frequently prescribed form of ADT for locally advanced, metastatic, and castrate-resistant PCa [12]. As mentioned previously, the data pertaining to the usage of ADT type is limited; the European Urological Association states that the frequency of use for choosing any particular ADT type is associated with the practicalities of administering the depots (depots may require reconstitution or subcutaneous or intramuscular injection) and storage (e.g., freezer temperature storage) in clinical settings [12].

LHRH agonists such as Leuprolide and Goserelin are administered monthly, quarterly, or semi-annual depot injections via subcutaneous implant [12]. Although it is well-established that the initial

depot causes a testosterone surge, LHRH agonists are typically prescribed in conjunction with anti-androgen tablets (Flutamide or Bicalutamide) for approximately four weeks.

LHRH antagonists (Degarelix or newer agents Relguolix) can also be administered via monthly subcutaneous depot or tablets; however, a key difference is the known rapid reduction in LH compared to LHRH agonists without the testosterone flare [20, 21]. Although this may be advantageous given the immediate reduction in LH, there is insufficient evidence to suggest that PCa-free survival is superior in those treated with LHRH antagonists when compared with LHRH agonists [22-25].

The use of second-generation non-steroidal anti-androgens (apalutamide, enzalutamide, and darolutamide) and CYP17 inhibitors (abiraterone) in the treatment of metastatic castrate-resistant PCa is increasing annually and plays a significant role in the treatment of PCa [26-30]. Indeed, second-generation anti-androgens and CYP17 inhibitors have improved PCa-specific and overall survival and metastatic-free survival in men with PCa [26-29, 31]. However, the efficacy of these medications on additional survival parameters remains a subject of ongoing investigation.

While there are various ADT modalities to treat non-metastatic and metastatic PCa, the evidence for using ADT as a standalone treatment minimally exists [32]. In recent years, standard care treatment for advanced PCa has changed following the results of the STAMPEDE [33], CHARRTED [34] and LATTITUDE [35, 36] trials. These trials observed clinically significant improvements in PCa-specific survival and delayed metastatic disease progression following chemo-hormonal therapy (including newer hormonal agents targeting castrate-resistant PCa) relative to standalone ADT or combined ADT and radiation therapy. These studies have shown translational benefits with this treatment regime and are now considered first-line treatment for advanced metastatic PCa.

Table 1.1: Different types of ADT

Treatment type	Description	Treatment/Drug name	Diagnostic stage
Surgical orchiectomy	A surgical procedure in which one or both testicles are removed.	Orchiectomy	Locally advanced, advanced
LHRH (or GnRH) analogues)	LHRH analogues cause hypothalamus hyperstimulation, resulting in testosterone overstimulation (commonly known as the testosterone flare). Eventually, LHRH results in desensitisation and downregulation of LH and FSH, which results in a time to castration of four weeks. This effectively regresses tumour growth [37].	Leuprolide, Goserelin, Triptorelin	Locally advanced, metastatic
LHRH (or GnRH) antagonist	LHRH antagonists such as Degarelix have a similar mechanism of action to LHRH analogues; however, the primary difference is that LHRH antagonists lower testosterone faster without the tumour flare [38, 39].	Degarelix, Relguolix	Locally advanced, metastatic
CYP17 inhibitor	In addition to LHRH agonists and antagonists, PCa cells can still produce small quantities of testosterone, which can cause tumour growth [37]. CYPI7 are administered to reduce testosterone production, causing subsequent tumour growth [40].	Abiraterone	Castrate resistant
Anti-androgens (steroidal and non-steroidal)	Anti-androgens are designed to inhibit androgens (i.e. testosterone and dihydrotestosterone) from mediating tumour growth [40]. The mechanism of action is to immediately block the androgen receptor by inhibiting and/or suppressing the production of androgens [40].	Steroidal Cyproterone acetate Non-steroidal Flutamide, Bicalutamide, Enzalutamide, Apalutamide, Darolutamide	Locally advanced, metastatic Castrate resistant

Abbreviations: LH (luteinising hormone), LHRH analogues (luteinising hormone-releasing hormone), PCa (prostate cancer), GnRH (gonadotropin hormone-releasing hormone), FSH (follicle-stimulating hormone), CYP17 (cytochrome gene)

1.4. Adverse effects of prostate cancer treatments

Despite advances in PCa diagnosis, detection, and treatment, ADT is associated with substantial adverse effects [41], which can significantly impact quality of life (QoL) among men with PCa. Adverse effects include deleterious changes to bone mineral density [42], body composition [43-45], physical function [43, 44], and inflammatory/cardiovascular risk factors such as insulin and fasting blood glucose levels [46, 47]. Men also experience sexual complications and increased psychological distress [41]. The deleterious impact of ADT-related adverse effects on health-related QoL and the abundance of cross-sectional and longitudinal evidence led influential organisations such as the American Cancer Society, American Society of Clinical Oncology, and the European Association of Urology to publish guidelines describing health-related issues affecting survivorship care [48]. Although these guidelines are primarily based on PCa survivorship care (Table 1.2), several research gaps, mainly related to CVD, require additional research to facilitate more robust treatment and management strategies. Thus, managing the adverse effects of PCa treatments represents and remains a significant challenge.

Overall, the focus of this chapter is not to detail the broader documented adverse effects of ADT, as this has been detailed extensively elsewhere [41, 44, 48-51]. The following sections will focus on the cardiovascular effects of ADT and the specific impact on CVD during ADT.

Table 1.2: Summary of long-term and late effects of prostate cancer and its treatment

TREATMENT TYPE	LONG-TERM EFFECTS	LATE EFFECTS
Surgery (Radical prostatectomy: open, laparoscopic, robot assisted)	Urinary dysfunction • Urinary incontinence (stress) • Urinary symptoms (urgency, frequency, nocturia, dribbling) • Urethral structure formation (scarring at the urethra) • Sexual dysfunction • ED • Lack of ejaculation • Orgasm changes (without erection, associated with incontinence) • Penile shortening	Disease progression
Radiation (External beam or brachytherapy)	Urinary dysfunction • Urinary incontinence • Urinary symptoms (dysuria, urgency, frequency, nocturia, dribbling) • Haematuria • Urethral stricture • Sexual dysfunction • Progressive ED • Decreased semen volume. • Bowel dysfunction • Faecal urgency • Blood in stool • Rectal inflammation, pain	Urinary dysfunction • Urethral structure • Haematuria due to small blood vessel changes • Sexual dysfunction • ED can be delayed in onset 6 to 36 mo. after therapy. • Bowel dysfunction • Rectal bleeding secondary to thinning/small blood vessel changes of anterior rectal wall mucosa. • Disease progression

Hormone
(Androgen deprivation therapy)
	• Sexual dysfunction
	• Loss of libido
	• ED
	• Other
	  ○ Hot flushes/sweats
	  ○ Weight gain, abdominal obesity
	  ○ Change in body image.
	  ○ Excessive emotional reactions and frequency of mood changes
	  ○ Depression
	  ○ Fatigue/decreased activity.
	  ○ Gynecomastia
	  ○ Anaemia
	  ○ Body hair loss
	  ○ Dry eyes
		• Osteoporosis, fractures
		• Metabolic syndrome
		• Cardiovascular disease (possible increased risk of myocardial infarction)
		• Diabetes; decreased sensitivity to insulin and oral glycaemic agents.
		• Increased cholesterol
		• Increased fat mass and decreased lean muscle mass/muscle wasting.
		• Venous thromboembolism
		• Vertigo
		• Cognitive dysfunction
		• Disease progression

Expectant management (active surveillance or watchful waiting[a]	• Stress, anxiety, worry. • Risks associated with repeat biopsy (active surveillance) • PSAs and DREs • Symptoms associated with disease progression	• Disease progression
GENERAL PSYCHOSOCIAL LONG-TERM AND LATE EFFECTS		
• Depression, depressive symptoms • Distress (multifactorial unpleasant experience of psychological, social and/or spiritual nature) • Worry, anxiety.		

• Fear of recurrence • Pain-related concerns • End-of-life concerns: death and dying. • Changes in sexual function and/or desire • Challenges with body image (secondary to surgery, hormone therapy) • Challenges with self-image • Relationship and other social role difficulties • Return to work concerns and financial challenges.

ED indicates erectile dysfunction; PSA, prostate-specific antigen; DRE, digital rectal examination. [a]According to the National Cancer Institute Dictionary of Cancer Terms, active surveillance indicates a treatment plan that involves closely watching a patient's condition but not giving treatment unless there are changes in test results that show the condition is getting worse. Active surveillance may be used to avoid or delay the need for treatments such as radiation therapy or surgery, which can cause side effects or other problems. During active surveillance, certain exams and tests are done on a regular schedule. It may be used in the treatment of certain types of cancer, such as prostate cancer. It is a type of expectant management. Watchful waiting indicates closely watching a patient's condition but not giving treatment unless symptoms appear or change. Watchful waiting is sometimes used in conditions that progress slowly. It is also used when the risks of treatment are greater than the possible benefits. During watchful waiting, patients may be given certain tests and exams. Watchful waiting is sometimes used in prostate cancer. It is a type of expectant management.

Table 1.2: Summary of the commonly reported long-term effects of PCa treatments. Reproduced and re-drawn with permission by Skolarus et al. [48] and John Wiley and Sons with license number 5291591242468.

1.5. Cardiovascular disease in prostate cancer

For men with PCa, CVD is the leading cause of death unrelated to cancer [10]. Cardiovascular risk factors, such as hypertension, dyslipidaemia, and hyperglycaemia, are prevalent in approximately 68% of men commencing ADT, of which 30-50% of men have previously experienced a cardiovascular event (e.g., myocardial infarction or stroke) [52]. Following ADT treatment, data from prospective and retrospective studies [52-59] observed proportional increases in all-cause/cardiovascular mortality rates and further incident cardiovascular events (myocardial infarction, stroke) up to five years following ADT. Although PCa is commonly diagnosed in men 68 years and older, the increased prevalence of cardiovascular risk factors and the biochemical changes associated with ADT may increase the risk of additional morbidity in this susceptible population. Biochemical changes associated with low testosterone may implicate cardiovascular risk or disease [46, 50, 51, 60], yet CVD incidence mechanisms remain unknown. Therefore, it is critical to determine the physiological and biological factors predisposing ADT-treated men to CVD.

The following section of this chapter will briefly address the epidemiological evidence associated with the risk of developing cardiovascular morbidity and mortality in ADT-treated men. This has been extensively described in the systematic review presented in *Chapter Two*.

Epidemiological evidence associated with cardiovascular morbidity and mortality.

Several prospective, retrospective, and randomised controlled trials have demonstrated that GnRH agonists are associated with higher all-cause mortality, cardiovascular mortality, and cardiovascular event rates than GnRH antagonists [53, 54, 61-64]. However, not all studies support these observations [53, 65-67]. The association between ADT and cardiovascular events was first identified in a large retrospective study by Keating et al. [68] from the SEER database. This study found that ADT was associated with an "increased risk of diabetes mellitus (adjusted hazard ratio [HR] 1.34, 95% confidence interval [CI] 1.34, 1.55), coronary artery disease (HR 1.16, 95% CI 1.10, 1.21), myocardial infarction (HR 1.11, 95% CI 1.01,1.21), and sudden cardiac death (HR 1.16, 95% CI 1.05, 1.27)" [68]. This initial evidence prompted concerns amongst the medical community, leading to the scientific advisory statement by American Urology Association, American Heart Association, American Cancer Society and American Society for Radiation Oncologists, indicating that "ADT may be associated with cardiovascular events and death" [69]. However, since this initial observation and the meta-analytic evidence by Nguyen et al. [54], the association of ADT with

cardiovascular mortality (relative risk [RR] of cardiovascular death ADT vs. control, 0.93, 95% CI, 0.79-1.10) has been the subject of intense investigation and criticism among the scientific community.

Emerging evidence from randomised controlled trials and prospective cohort studies suggests that the effects of ADT on cardiovascular risk may differ by the mechanisms of action of the pharmaceutical drug type, especially in men with pre-existing CVD [24, 53, 55-57, 65-67, 70-77]. For example, a pooled analysis of Ferring Pharmaceutical trials (six, phase three randomised controlled trials, comparing GnRH agonist to GnRH antagonist) observed fewer cardiac events in men with pre-existing CVD treated with GnRH antagonists (6.5%) compared with GnRH agonists (14.7%) [64]. Notably, after 12 months of ADT, the risk of cardiac events or death was substantially lower by approximately 56% (HR 0.44; 95% CI 0.26–0.74) in men treated with GnRH antagonists than in men treated with GnRH agonists [64]. Additionally, the results of a phase III trial randomly assigning Relguolix (GnRH antagonist) or Leuprolide to men with pre-existing CVD reported higher cardiovascular event incidence among men treated with Leuprolide (6.2%) than those treated with Relguolix (2.9%) following a two-year follow-up period [24]. The above study and other observations [64] suggest that men treated with GnRH antagonists tend to experience fewer major adverse cardiovascular events independent of baseline cardiovascular risk. However, more recent data suggest that the cardiovascular risk profile of GnRH antagonists remains less conclusive. Despite accounting for cardiovascular confounders, recent data from the PRONOUNCE trial [70]found negligible differences in the risk of developing major adverse cardiovascular events when comparing Degarelix and Leuprolide. However, it is essential to note that this trial ceased short of its intended sample size due to recruitment barriers. As a result, wide confidence intervals related to cardiovascular deaths were observed (HR 1.28, 95% CI, 0.59-2.79)[70]. While the association between ADT and cardiovascular events has been extensively studied, the available evidence is typically derived from cohort studies or randomised controlled trials that exclude non-ADT treated groups or do not separate participants groups by pre-existing CVD diagnoses; this, therefore, limits the generalisability and comparability of the results to the general population.

1.6. Abnormal cardiovascular risk profiles in ADT-treated men

Cancer

Emerging evidence from studies conducted in humans suggests that CVD and cancer share several biological risk factors, which may increase the risk of CVD in this population [78, 79]. While the mechanisms may be unclear, it was hypothesised that a higher prevalence of cardiovascular risk factors (e.g., smoking, obesity, hypercholesterolaemia), coupled with biological changes (e.g., inflammation or oxidative stress) associated with cancer, may predispose individuals with cancer to cardiovascular morbidity and events [78, 80-82]. Inflammation is a well-known mediator of disease progression in both CVD and cancer, with multiple studies demonstrating that elevated inflammatory markers such as C-reactive protein (CRP) or interleukin-6 are associated with poorer prognosis and/or clinical endpoints such as PCa-specific mortality, biochemical failure-free survival, or metastatic disease progression [82-86]. In a prospective cohort study [87] of 524 men scheduled for a PCa biopsy that investigated the association between metabolic syndrome, CRP, testosterone levels, and risk of PCa, it was found that men who were subsequently diagnosed with a more aggressive form of PCa had several metabolic syndrome characteristics and higher serum CRP levels. While we cannot rule out the possibility that higher serum CRP levels are already elevated due to subclinical PCa, the combination of metabolic syndrome characteristics and higher CRP levels observed in this study relative to other observations [84] makes it more likely that cancer and CVD share biological risk factors.

Moreover, several literature reviews [88-91] have detailed biochemical markers such as insulin-like growth hormone factor, interleukin-6 and tumour necrosis factor, leptin, and adiponectin, particularly in individuals with metabolic syndrome, which may be potential mediators of PCa incidence. Evidence from a meta-analytic study of cohort and case-control studies found that elevated levels of insulin-like growth hormone factor were associated with a marked incidence of PCa (odds ratio [OR] 1.83, 95 % CI 1.03, 3.36) when compared to patients whose insulin-like growth hormone factor levels were lower [92]. Considering that CVD is highly prevalent among men beginning ADT [52], it is possible that perturbations associated with CVD and cancer and cancer treatments may collectively amplify cardiovascular risk in this population. However, whether this may be the case in PCa is yet to be elucidated.

Age, gender, and cardiovascular risk

Uncontrollable cardiovascular risk factors, such as gender, age, and ethnicity, are known risk factors for CVD and cancer [78, 93, 94]. While there is some evidence to suggest that hormone dysregulation may be linked to the progression of cancer and CVD, older age (>60 years) is a consistent independent variable for both diseases [95-97]. A prospective study of 3,526 older and younger men treated with ADT reported that the combination of older age (mean age,76 years) and prolonged ADT exposure (>2 years) was related to a higher risk of diabetes mellitus (OR, 2.1 95%CI 1.0-4.4) and CVD (OR, 1.9 95% CI 1.0-3.5), compared to younger ADT-treated men [98]. While it is known that cardiovascular comorbidities are common in older men, prolonged ADT exposure markedly increased the incidence of diabetes mellitus and CVD compared with the younger cohort [98]. This suggests that increasing age, baseline cardiovascular risk, and ADT duration are critical in understanding cardiovascular morbidity in this vulnerable population.

ADT, insulin resistance and metabolic syndrome

Data from several observational studies have consistently shown that ADT increases insulin resistance [41, 69, 99-101]. Glucose intolerance and insulin resistance are linked to endothelial dysfunction and arterial stiffness, both of which are associated with an increased risk of CVD in this population [102-104]. Longitudinal studies in PCa have shown that ADT is associated with insulin resistance and elevated fasting blood glucose, leptin, and glycated haemoglobin [105, 106]. A meta-analysis, including nine cross-sectional studies in ADT-treated men, found that metabolic syndrome (RR 1.75, 95%CI 1.27,1.41) and diabetes mellitus (RR 1.36, 95%CI 1.17,1.58) were positively associated with ADT, compared to controls [107]. These results were consistent with a small cross-sectional study of 20 ADT-treated men, 18 non-ADT, and 20 non-cancer controls, which found the incidence of metabolic syndrome was markedly higher in ADT-treated men (55%) than with non-ADT treated men (22%) and non-cancer controls (20%). Importantly, the drivers of metabolic syndrome were primarily related to fasting blood glucose (13%) and waist circumference (15%) among ADT-treated men [108]. While the mechanisms that underpin ADT (e.g., insulin resistance and metabolic syndrome) may be more evident than other cardiovascular risk factors, the degree by which insulin resistance or diabetes mellitus, particularly in the context of PCa and cardiovascular outcomes, is unclear.

Furthermore, experimental evidence in men who develop diabetes mellitus following ADT seems to have higher visceral fat mass composition [44, 49] and abnormal blood lipid profile values (triglycerides, low-density lipoprotein) [50, 109, 110] compared to PCa non-ADT controls. Moreover, few studies have reported increased fasting blood lipid profile, including total cholesterol, high-density lipoprotein triglycerides and low-density lipoprotein in ADT-treated men [50, 109, 110]. For example, a longitudinal study of 32 men treated with ADT was evaluated for 48 weeks [106]. The percentage change from baseline to 48 weeks demonstrated marked increases in total cholesterol (percentage change, 9.0 ±2.1%), high-density lipoprotein (11.3±2.6%), triglycerides (26.5±10.0%) and low-density lipoprotein (7.3±3.5%) [106]. Interestingly, high-density lipoprotein appeared to increase, thus limiting the parallels to the conventional metabolic syndrome classification. Although higher high-density lipoprotein values are considered cardioprotective [111], the breadth of evidence is limited to small samples with no comparator groups, therefore making it difficult to conclude whether the observed changes were typical rather than a result of ADT.

ADT and body composition

The effect of ADT on body composition and adiposity is well-established, with a preponderance of evidence demonstrating unfavourable reductions in whole-body lean mass and increases in fat mass and body fat percentage [44, 45, 49, 99, 101, 106, 112-114], which may render this susceptible population to adverse effects on cardiovascular risk. For example, pooled data from 14 cohort studies and two randomised controlled trials showed changes from baseline increase in body weight (MD 2.1%, 95% CI 1.4, 2.9), body mass index (2.2%, 95% CI 1.2, 3.1), fat mass (7.7%, 95% CI, 4.3, 11.2) and reductions in lean mass (MD -2.8%, 95% CI -3.6, -2.0) favouring ADT in all participants across all time points [115]. Interestingly, the most pronounced effects on body composition (by timepoint and ADT type) were observed between three and six months for body weight and body mass index and further impacted at 12 months for all measurements of body composition (all, $p<0.0001$)[115]. While changes in body composition and adiposity are attributable to heightened cardiovascular risk and incident cardiovascular events and mortality in non-cancer populations [116], the impact of these effects, particularly in the context of cardiovascular risk in PCa, has been minimally examined. Furthermore, men treated with newer hormonal agents (i.e., metastatic castrate-resistant PCa) may experience further deleterious effects on whole-body lean mass and fat mass than conventional therapies, suggesting newer hormonal agents coupled with

prior therapies may have additional detrimental effects [117]. Notably, the reductions in whole-body lean mass and subsequent increases in fat mass exceed age-related reference values (ADT-treated 2.8% vs. age-matched controls, 0.9%, *P*=0.03) [113], thus amplifying fragility and functional disability in a rapidly aging population. While prior observations support the adverse consequences of ADT on body composition and adiposity, prospective studies are required to establish causality with heightened cardiovascular risk and the implications on cardiovascular outcomes in ADT-treated men.

ADT and cardiovascular toxicity

Population-based studies have observed higher rates of cardiovascular toxicity, including cardiovascular events (ischaemic heart disease, stroke, chronic heart failure, arrhythmias, atherosclerotic events)[118-120]) and cardiovascular risk factors (hypertension, hyperglycaemia, obesity) in ADT-treated men administered with second class hormonal agents [24, 118, 119, 121, 122]. There are no cardiovascular toxicity risk calculators or consensus definitions for ADT-treated men, but cardiovascular side effects include hypertension, Type II diabetes, and ischaemic heart disease[123, 124]. A large meta-analysis of ~8,660 men investigating the cardiovascular toxic effects of abiraterone and enzalutamide plus prednisolone showed a two-fold increase in all-grade cardiovascular toxicity (RR 1.36, 95% CI 1.13,1.64) and all-grade hypertension (RR 1.98, 95% CI 1.62,1.2.43), compared with placebo study arms [118]. Additionally, when comparing the incidence and relative risk by treatment, abiraterone use was shown to have a higher frequency of all-grade and high-grade hypertension (abiraterone, 26.2% and 6.9%) related events when compared with placebo (15% and 5%) [118]. Despite the observed epidemiological increases in all-grade and high-grade cardiovascular toxicity and hypertension in men treated with newer hormonal agents, the evidence associated with widely available conventional therapies, for example, LHRH analogues or antagonists, is less conclusive, with most studies focused on arterial compliance and stiffness rather than hypertension in this population [100, 125-127]. Arterial stiffness is a prognostic indicator of cardiovascular mortality and cardiovascular events in the general and clinical CVD population [128]. Thus, its use alongside cardiovascular risk stratification models is becoming widely accepted in primary cardiovascular care. Despite this, evidence from a small number of cross-sectional studies have reported higher arterial stiffness values ~12 m/s (determined by central pulse wave velocity, cfPWV) and alterations in waveform characteristics, including augmentation index (AIx) (24-29%) during varying durations of ADT (GnRH agonists and antagonists) [127, 129]. Although

cfPWV values >10 m/s are categorised as high cardiovascular risk [130], ADT-men and their comparators (age-matched controls, non-ADT treated men with PCa) seem to exhibit similar levels of arterial stiffening [100, 125, 127]. While older age could be a pivotal contributor to higher cfPWV values in PCa, other determinants of higher arterial stiffness in this population remain unknown.

ADT and physical activity (cardiorespiratory fitness, physical function)

Many observational studies have shown that individuals with cancer who participate in regular physical activity experience lower rates of all-cause and cancer-specific mortality [131, 132]. Pooled analyses of 136 studies examining the effect of pre-and post-diagnosis physical activity in all cancers, including PCa, showed enhanced survival benefits in all cancers (pre-diagnosis, low versus high volumes of physical activity HR 0.82, 95% CI 0.79 -0.86; post-diagnosis physical activity, HR 0.63 95% CI 0.53 to 0.75), with similar reductions in all-cause mortality for all-cancers and particularly PCa [132]. This was consistent with an observational study investigating exercise dosages (<9 Metabolic equivalents [MET]-hours per week [h/wk.] vs >9 MET-h/wk.) on all-cause mortality in men with PCa. This study found marked reductions in all-cause mortality (HR 0.67, 95% CI 0.56-0.82) in those that completed higher volumes of physical activity (>9 MET-h/wk.) than those men that participated <9 MET-h/wk. [133]. While it is essential to encourage men with PCa to increase their physical activity, men treated with short-term and long-term ADT report difficulty meeting/exceeding guideline recommendations due to treatment-related effects [49, 117, 134-137].

Longitudinal studies evaluating physical function by distance-based walking tests or the short physical performance battery have shown that ADT has detrimental effects on walking velocities [134, 138], gait speed [49], chair rise time [49, 117, 135] and walk distance [49, 117, 134-137], compared with non-ADT treated men or age-matched controls. Notably, impaired physical function also correlates with reduced physical activity levels, whole-body lean mass, and higher adiposity in men on longer-term ADT, especially those treated with newer hormonal agents [49, 117]. While the assessment of physical function by the above outcome measures is widely used to assess clinical status or cardiorespiratory fitness in clinical practice, the degree to which it can provide detailed prognostic insights [139, 140], specifically related to cardiovascular health outcomes, is unclear. On the contrary, assessing peak oxygen uptake (VO_2peak), determined by a cardiopulmonary exercise

test, may offer pathophysiological insights into detecting therapy-related dysfunction and stratifying cardiovascular risk in this population [141]. Although these preliminary results are supported by prior observations [100, 142], the prognostic value of reduced cardiorespiratory fitness and the physiological mechanisms contributing to reduced cardiorespiratory fitness and cardiovascular risk in PCa remains yet to be elucidated.

1.7. Possible mechanisms linking adverse cardiovascular consequences and cardiovascular disease incidence in men treated with ADT.

Testosterone is the primary male sex hormone responsible for regulating anabolic functions, such as promoting and maintaining muscle mass, muscle strength, bone mineral density, blood pressure, and vascular function in men [143, 144]. Serum testosterone levels reach maximal by 30 years in men, with longitudinal studies showing reductions by approximately 1 to 2% per year thereafter [145-147]. However, it is not entirely clear whether clinical features of androgen deficiency are also caused by ageing or age/lifestyle-related comorbidities in older men. [145-147]. Low endogenous testosterone levels are early markers of poorer prognosis, cardiovascular risk factors and all-cause mortality in older men, according to accumulating evidence [148-151]. In a nested study of 794 men (age: range 50-91 years), low endogenous testosterone levels (lowest quartile) independent of age and baseline cardiovascular were associated with a markedly higher risk of all-cause mortality (HR 1.44, 95% CI 1.12, 1.84) [152], relative to men with higher/normative endogenous testosterone levels. These results were supported by several other population-based studies and meta-analyses [149, 150, 153, 154]. Specifically, in a population-cohort study of Tromso participants (n=1,548 men), LV mass by height was correlated with total testosterone (r=-0.10; P<0.001), systolic blood pressure (r=0.26; P <0.001), diastolic blood pressure (r=0.24; p<0.001) and body mass index (r=0.39; P <0.001), which all remained independent predictors after multiple linear regression analyses [155]. In addition, studies examining the association between low endogenous testosterone and cardiovascular endpoints have shown that incident hypertension and all-cause/cardiovascular mortality rates are higher in men with low testosterone levels [156-158]. Intriguingly, the authors hypothesised that the increased incidence of hypertension and all-cause/cardiovascular mortality might be related to LV hypertrophy, specifically concentric cardiac remodelling. Based on the mechanistic literature proposing that androgens are highly sensitive to cardiomyocytes, it could be quite possible that low endogenous testosterone levels may alter LV geometry [159, 160]. A large cohort study of 5,098 of the Multi-Ethnic Study of Atherosclerosis) observed that concentric

remodelling (quantified by LV mass to volume ratio [LVM: V]) was associated with incident coronary heart disease (adjusted HR 2.1, 95% CI 1.1-4.1), stroke (adjusted HR 4.2, 95% CI 1.5-11.2), chronic heart failure (adjusted HR 2.3, 95% CI 0.8-6.1) in asymptomatic populations [161]. While this evidence may provide interesting parallels to ADT, the mechanisms underpinning CVD in men with PCa require additional investigative studies to establish causality. The section that follows will provide an overview of the available evidence and hypothesised mechanisms underlying CVD in this population.

The effect of ADT on cardiac remodelling (animal studies)

Cardiac remodelling (concentric or maladaptive cardiac remodelling) is an adaptive response associated with increased cardiac afterload (increase/unchanged LV mass and decrease in chamber volumes), primarily driven by physiological and pathological changes associated with hypertension and atherosclerosis [162, 163]. Although cardiac remodelling is a known precursor of future cardiovascular events in other settings [164-166], its potential association with the incidence of cardiovascular events in PCa is yet to be elucidated. However, the mechanistic basis for this hypothesis is widely documented in animal studies. Animal studies examining the role of androgen receptors in cardiomyocytes *in vivo* have consistently shown that haemodynamic, endocrine, and paracrine factors mediate cardiac hypertrophy, specifically cardiomyocyte elongation [159]. However, studies of mammalian cardiac tissue *in vitro* suggest otherwise. An *in vitro* found that in mammalian cardiac tissues, including humans, androgen receptors are expressed explicitly in cardiomyocytes and that testosterone and dihydrotestosterone were directly responsible for the cardiac hypertrophic response in cardiomyocytes [159]. This suggests that androgen receptors are highly sensitive to androgen availability and regulate cardiac hypertrophy response in addition to other mediating factors above [159]. In the context of androgen deprivation, Malhotra et al.[167] showed that surgical castration (gonadectomy) led to marked declines in cardiac weight/mass (~17%) and increased cardiac hypertrophic response in gonadectomised mice. This hypertrophic pattern has been similarly observed in medical castration studies, which suggest that reductions in androgen availability may have a compensatory hypertrophic effect on maintaining hemodynamic load [160, 168]. Despite preliminary evidence suggesting cardiomyocytes and cardiac hypertrophic stimuli are particularly susceptible to androgens, no clinical trials have specifically examined the effects of ADT on the cardiovascular system in men with PCa.

The effect of ADT on cardiac function

Compared with cardiac remodelling, the direct effects of low testosterone (ADT, medical and surgical castration) on cardiac function is primarily limited to animal studies [160, 167-169]. Low testosterone is associated with decreased LVEF and is crucial to the aetiology of chronic heart failure in older men [170-173]. In gonadectomised male rodents, androgens seem to regulate cardiac performance [159]. Several studies in gonadectomised male rats *in vivo* have exhibited reductions in heart weight, lower LVEF, LV cardiac output (LVCO), reduced cardiac contractility and delayed cardiomyocyte stretch recoil activity, which resulted in impaired cardiac performance [167, 168]. Specifically, 16 weeks of surgical castration resulted in compromised calcium regulatory proteins and contractility properties, including myocyte excitation-contraction coupling, peak shortening (14%), and time to peak shortening (16%) in *ex vivo* isolated myocytes [174]. Furthermore, animal studies examining myocyte excitation-contraction coupling in gonadectomised and medically castrated rodent models observed higher quantities of slow adenosine triphosphate β-myosin heavy chain isoforms and lower quantities of short adenosine triphosphate phase α-myosin heavy chain isoforms in male ventricles [167, 168]. This suggests that testosterone suppression by surgical or medical castration may influence adenosine triphosphate β-myosin heavy chain quantities and may impair cardiac performance. These features have also been similarly observed in animal studies of heart failure [175-177]. However, limited evidence exists regarding the impact of ADT on cardiac function in humans, with only a single trial of 43 men evaluating its effect on N-terminal probe-type natriuretic peptide (NT-proBNP; a cardiac marker indicating ventricle stretch in response to pressure and volume overload), compared to a non-ADT PCa control. NT-proBNP values increased substantially from baseline to three months across both drug groups (Goserelin, the median baseline 66 ng/L vs. three-months 87 ng/L vs. Bicalutamide baseline 55 ng/L vs. 101 ng/L vs. control baseline 60 ng/L vs. three-months 53 ng/L; P=0.006), with Bicalutamide continuing to rise by ~17% after five months [178]. It was somewhat surprising that markers of systolic function (LVEF, global longitudinal strain [GLS]) remained unchanged, despite the documented increase in rising NT-proBNP throughout the study period. However, no other data exists concerning the effect of systolic or diastolic function, and thus, conclusions remain inconclusive.

The effect of ADT on vascular function

Emerging evidence supports the hypothesis that ADT worsens atherosclerosis and endothelial cell function compared with non-ADT treated men or age-matched controls [179, 180]. However, the mechanism by which ADT may influence endothelial cell function is limited to animal studies. For example, studies examining testosterone supplementation in orchiectomised mice observed that testosterone mediates atherosclerosis lesion size compared with placebo [181]. Animal research utilising androgen receptor (AR) knockout mice (ARKO) (testosterone deficient) revealed marked increases in the diameter of atherosclerotic lesions when compared to AR-intact mice [180]. However, when testosterone deficiency was reversed (testosterone supplementation), authors observed a blunt response and reduced atherosclerotic lesion size in ARKO mice compared with AR-intact mice [180]. This suggests that atherogenic mechanisms associated with biochemical testosterone concentrations are AR-dependent and independent [180]. A further study investigating the differing effects of atherosclerosis and metabolic syndrome by ADT drug types (GnRH agonist, antagonist, and orchiectomy) in ADT-treated and sham surgery mice models reported differences in the severity of metabolic syndrome and the manifestation of atherosclerosis across all drug types [179]. Further, the most distinct effects on atherosclerotic plaque size and neurotic plaque core areas were observed in orchiectomised and GnRH agonist-treated mice after four months [179]. While these data provide preliminary evidence of a possible association between ADT and atherogenic changes related to CVD, the applicability to human clinical trials is limited.

Compared with animal models of ADT, human studies have shown that ADT may increase arterial stiffness, alter waveform characteristics, and impair endothelial function [100, 126, 129, 182]. In comparison with age-matched controls, men treated with long-term ADT exhibited non-significant increases in cfPWV and impaired flow-mediated dilation (FMD) [100, 126, 129, 182]. In addition, a recent cross-sectional study of 98 men with PCa (12 of 51 men who received ADT for 13.6 months) revealed no statistically significant differences in cfPWV (PCa 12.0 m/s vs. age-matched control 11.7 m/s; P=0.16), AIx (24.8% vs. 25.7 %; P=0.90) compared with control [127]. However, men with PCa seemed to exhibit a similar degree of arterial stiffening to men of a similar age according to age-appropriate reference guidelines (>10 m/s) [183]. Although it is unknown to what extent ADT amplifies cfPWV men with PCa, other factors such as physical activity, cardiorespiratory fitness, and obesity may provide additional insight into mechanisms that underpin cardiovascular risk in this population.

1.8. Management of cardiovascular risk in prostate cancer

The adverse cardiovascular and metabolic effects of ADT, such as hyperglycaemia, obesity, hyperlipidaemia, and postulated mechanisms, such as atherosclerosis and LV hypertrophy, are sinister and may be linked to the higher epidemiological increases in CVD observed in this population [41]. Despite the limited pragmatic data to definitively characterise the impact of ADT on the cardiovascular system, the critical pathway to reducing further cardiovascular morbidity and mortality is via primary and secondary prevention strategies. The current algorithm (Figure 1.1) represents a potential strategy to manage cardiovascular risk in ADT-treated men per the American College of Cardiology and American Heart Association's key recommendations [124]. This scientific statement suggests that increasing awareness of cardiovascular risk factors in ADT-treated men [124] should follow the Awareness/Aspirin, Blood pressure, Cholesterol/Cigarettes, Diabetes Mellitus/Diet and Exercise (ABCDE). However, this approach was primarily devised without formal guidelines for preventing and managing CVD in ADT-treated men. The ABCDE approach extends the primary and secondary prevention strategy used to identify and manage CVD in the general population. These guidelines[124, 184], comparable to other ADT-specific recommendations [69, 120], suggest that a combination of pharmacotherapy and lifestyle interventions should be recommended for men commencing or receiving ADT. However, whether this combined approach is offered to all patients treated with ADT is unknown. In light of the recommendations above, evidence from Europe suggests that men initiating ADT are not 1) routinely assessed for cardiometabolic risk factors or disease, 2) provided with treatment information about cardiometabolic side effects, or 3) advised of treatment options to counteract/manage the cardiovascular and metabolic side effects of ADT [69, 185, 186]. This extensive European survey of radiation oncologists, medical oncologists and urologists found that clinicians primarily communicated loss of libido and sexual dysfunction (90%), hot flushes (85%) and minimal communication concerning metabolic syndrome (41%) and cardiovascular morbidity and death (31%) to their patients [187]. In addition, the assessment of metabolic risk performed by clinicians was limited, with only 33% of clinicians assessing fasting blood glucose, blood lipid profile and blood pressure in men initiating ADT [187]. While there is limited evidence suggesting clinicians assess some cardiovascular risk factors, the integration and uptake of these strategies vary widely.

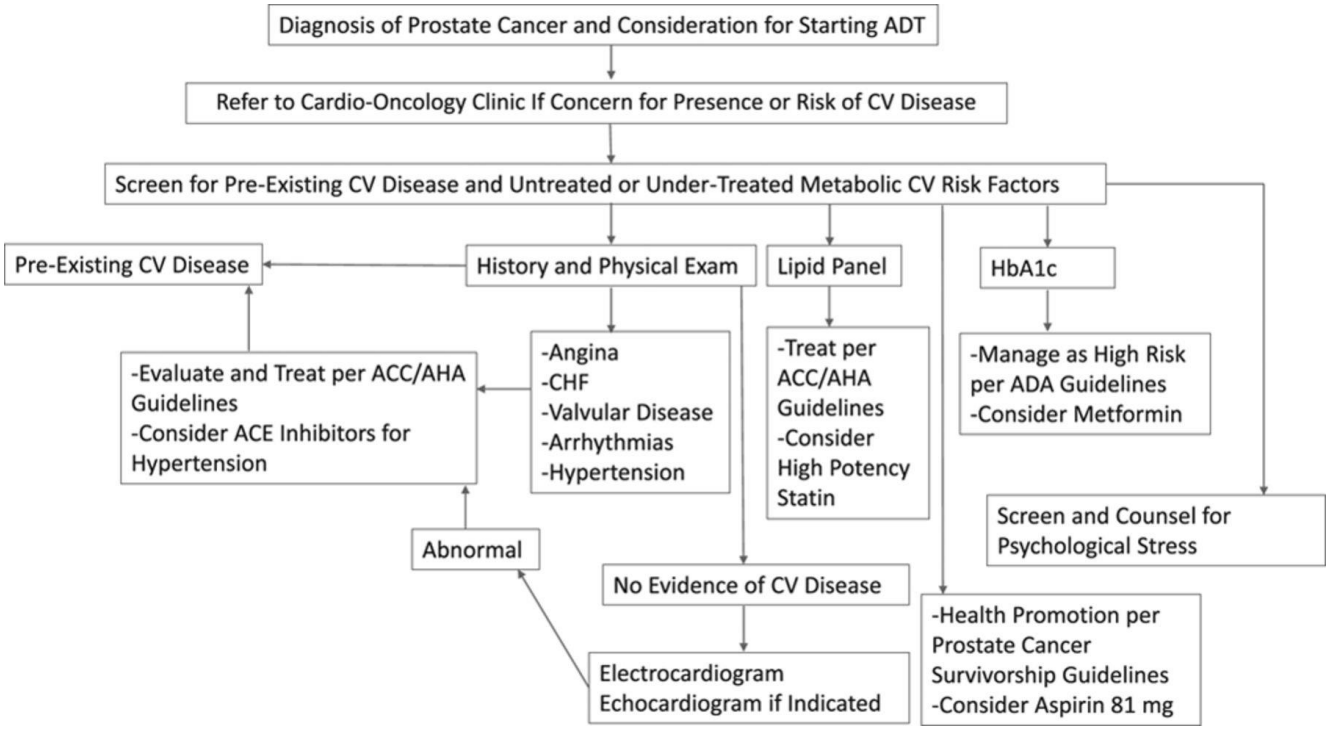


Figure 1.1: Managing cardiovascular risk in ADT-treated men.
Reproduced with permission by Bhatia et al.[124] and Wolters Kluwer Health Inc. with license number 5300431511347.

Furthermore, the assessment of traditional cardiovascular risk factors by cardiovascular risk profiling methods has been investigated with varying results [52]. These variations may be partly explained by the influence of older age on cardiovascular risk prediction tools. For example, the commonly used Framingham Risk Score tool [188] was examined in ~2 492 ADT naive and ADT-treated men [52]. Most participants included in this study were deemed to have a higher cardiovascular risk (Framingham Risk Score, 29%) than non-ADT treated men (21%), and this was mainly due to older age independent of cardiovascular risk factors [52]. This suggests that irrespective of ADT (prior to or undergoing treatment), the higher cardiovascular risk noted in this population, particularly in the context of cardiovascular risk prediction tools, seems primarily driven by older age. This indicates that current methods for detecting CVD risk do not adequately explain heightened CVD risk/disease among men with PCa. Importantly, this could mean that the effects of ADT on traditional CVD risk factors may be too imprecise or operate through different

mechanistic pathways that fail to explain the heightened risk of CVD in this population. Therefore, the section below will provide an overview of possible identification and preventative strategies that could potentially detect and prevent the adverse cardiovascular effects of ADT.

1.9. Assessing cardiovascular health: an innovative detection strategy

Assessing cardiac structure and function

According to population-based studies, LV cardiac remodelling (LV mass, LVEDV, and LVM: V) is a crucial precursor of cardiovascular events [161, 166, 189]. Notably, these associations are evident in those with and without pre-existing CVD [161, 166, 189]. A large cohort study of 5,098 participants that evaluated the association of concentric remodelling (quantified by CMR imaging) with cardiovascular events found that CMR imaging detected subtle changes in LVM: V, and these were associated with coronary heart disease (adjusted HR 2.1 g/ml, 95% CI 1.1-4.1), stroke (adjusted HR 4.2 g/ml, 95% CI 1.5-11.2) and a markedly higher risk of developing heart failure (adjusted HR 1.4 g/m^2, 95% CI 11.2-1.5) when quantified by LV mass/LV hypertrophy [161]. In a similar study from the same cohort of 2,935 participants (mean age, 69 years) without CVD at baseline (follow-up 9.4 years), variables related to systolic blood pressure, body mass index, and smoking history were responsible for proportional increases in LV mass over time and a key predictor of cardiovascular events in this population [166]. While these results are consistent with CMR imaging studies, not all studies agree, and this is primarily due to different imaging techniques [161, 166, 190-192]. Most epidemiological studies have primarily investigated LV structural changes by echocardiography to determine increasing cardiovascular risk and cardiovascular event incidence in the general population [161, 166, 190-192]. Although established in cardiovascular care, echocardiography does have several limitations and may be unable to detect subtle changes in sub-clinical CVD. For example, LV mass quantified by echocardiogram requires a >30g change from baseline (~17%, relative), and LVEF requires a >10% change from baseline to be considered clinically meaningful compared to gold standard techniques such as CMR imaging (~7% change from baseline) [193, 194]. Despite advancements in echocardiographic techniques, two-dimensional echocardiography is the most commonly used for estimating LV mass by length and truncate methods during end-diastole. However, the imprecision of these techniques is well-documented, with some trials reporting substantially higher interobserver and intraobserver variability (37% and 19%, respectively) in older men when compared to CMR imaging (intra and interobserver variability, 7% and 8%, respectively) [193, 194]. Although CMR imaging has a high

degree of accuracy and precision, its broader utility in other settings, such as cancer, is still emerging.

Assessing vascular health

Compared with CMR imaging and echocardiography, the higher prevalence of traditional cardiovascular risk factors in ADT-treated men does not explain the observed epidemiological increases in cardiovascular event incidence in this population [52, 107]. The assessment of vascular health, including arterial stiffness (cfPWV) and waveform characteristics (pulse wave analysis), are relatively simple, non-invasive procedures that could provide additional information concerning the factors that precede/contribute to alterations in traditional cardiovascular risk factors [130, 195]. cfPWV is considered the gold standard assessment for determining central aortic stiffness via non-invasive applanation tonometry [130, 196]. Compared with cfPWV, pulse wave analysis uses a similar technique to estimate central aortic pressure and calculate AIx (a measure of arterial rigidity of the peripheral wave reflection from the ascending pressure waveform and is derived from the peak amplitude of the reflective wave augmentation pressure/pulse pressure) via the central pressure waveform [130, 197, 198]. Collectively, both techniques measured in clinical cohorts have excellent accuracy (cfPWV, r>0.90; AIx, intraclass correlation: 0.97) and reproducibility (cfPWV CV: <5%, AIx, CV: 5-8.4%)[195, 199-201]. While the repeatability of cfPWV appears excellent (cfPWV, CV: 4.7-10.5%), several studies have reported rather large CV ranges for AIx across several clinical populations, including CVD and chronic kidney disease (AIx, CV: 15-25%) [195, 199-201]. This has been primarily due to some trials only taking one measurement per participant; however, when multiple (average of three) are taken, the AIx CV falls within normal limits [195, 199-201]. Despite the variance in CVs linked to AIx reported in the above studies, the utility of this clinical measure in cardiovascular care is still evolving.

In addition, the majority of research has centred on arterial stiffness and wave reflection in other settings, demonstrating that it is a reliable indicator of future cardiovascular events, all-cause mortality, and precursors of hypertension and cardiac remodelling in ageing and CVD cohorts [128, 196, 197, 202-208]. Meta-analytic evidence from 17 cohort studies observed that high cfPWV was associated with an increased risk of cardiovascular events (RR 2.26, 95% CI 1.89-2.70) [128] compared to control groups with lower cfPWV values. In addition, it was also found that for every one-meter per-second increase in cfPWV translates to a ~14% (1.14, 95% CI 1.09-1.20) increase in

cardiovascular events [128]. Higher all-cause and cardiovascular mortality rates were also associated with high cfPWV values [128]. Recent meta-analytic evidence from 19 prospective and cross-sectional studies examining the effect of cancer treatments on arterial stiffness was consistent with these findings [209]. Notably, administration of any cancer therapy, for example, anthracycline chemotherapy, showed a markedly higher increase in cfPWV values compared to baseline/pre-treatment levels (MD 1.505 m/s, 95% CI 0.789-2.221)[209]. Similar results were reported in cross-sectional evidence in PCa, suggesting ADT may influence arterial stiffness [100, 125-127]. These data indicate that arterial stiffness and waveform characteristics may be central to further understanding vascular health and its implications on target organs and elevated cardiovascular risk in this population.

Assessing cardiorespiratory fitness

Resting measures of cardiovascular structure, function and vascular health cannot adequately explain impairments in integrative cardiovascular function or reliably predict VO_2peak [196, 210]. Cardiorespiratory fitness is an important prognostic marker of CVD, all-cause mortality, survival, and poorer prognoses in the general and clinical cohorts [141, 211-213]. Recent meta-analytic evidence involving 13 studies (n=6,486 adults with cancer) [214] found that individuals with a higher cardiorespiratory fitness level (categorised as high, intermediate, and low based on their corresponding unit of measurement) were associated with a reduction in all-cause mortality (HR 0.52, 95% CI 0.35-0.77) independent of cancer type in adults. However, this reduction was not consistent with the intermediate or low cardiorespiratory fitness levels groups [214]. Furthermore, a large cohort study of 616 men with localised high-risk PCa men examined the impact of cardiorespiratory fitness (measured by exercise treadmill testing) on cardiovascular mortality and ADT duration [215]. Men on long-term ADT (<6 months) had a higher risk of cardiovascular mortality (adjusted HR 3.87, 95% CI 1.16-12.96) [215] when adjusted for cardiorespiratory fitness and other common confounders. However, no significant differences in cardiovascular mortality rates were detected in men on short-term ADT, despite the higher frequency of low cardiorespiratory fitness noted among all patients [215]. Although the benefits of maintaining a high VO_2peak are well-established in other clinical settings [216], the prognostic value of VO_2peak in identifying cardiovascular risk in PCa is poorly defined, even though the measurement (CPET) has excellent test-retest reliability (r=0.94; P<0.001) [217] in this population.

Assessing cardiac biomarkers

In addition to cardiac and vascular imaging methods, cardiovascular biomarkers of myocardial injury and LV wall stress may be helpful in further elucidating cardiovascular disease in this population. Despite blood-based biomarkers being widely available and easily accessible, there are no consensus or guideline recommendations for clinical-decision making beyond primary prevention recommendations[124, 218]. Current recommendations by leading organisations such as the European Society of Cardiology and the American Heart Association suggest that Troponin I and NT-BNP be assessed during chemotherapeutic treatments to facilitate the detection of myocardial damage [219, 220]. Whilst minimal evidence exists regarding their utility during ADT, more research is required to understand whether CVD biomarkers related to the shared biological risk factors between CVD and cancer, such as inflammatory markers (c-reactive protein), should be considered during ADT [78].

1.10. Interventions to address the cardiovascular and metabolic disease risk burden in non-cancer populations

Aerobic exercise training, resistance training, and combined exercise interventions have superior beneficial effects on cardiorespiratory fitness (measured by VO_2peak), cardiac structure (LV mass, LVEDV, cardiac remodelling), cardiovascular risk factors (blood pressure, blood lipid profile), diabetes mellitus, and adiposity, according to randomised controlled trial evidence in non-cancer populations [221]. Further, burgeoning data favour higher intensity aerobic exercise training, for example, long interval high-intensity interval training (HIIT) (four minutes of high intensity, coupled with three minutes of active recovery), medium interval HIIT (one to two minutes of high intensity, coupled with one to three minutes of active recovery), short HIIT (15-60 seconds of high, coupled with 15 seconds to two minutes of active recovery) over moderate continuous exercise training (moderate intensity of 30-60 minutes) to reduce cardiovascular risk burden in patients with cardiovascular and metabolic disease [221, 222]. While the beneficial effects of higher-intensity aerobic exercise training have been investigated minimally during ADT, the effect of HIIT in CVD populations is extensive [141, 221, 223]. A meta-analysis of 273 patients with established cardiovascular and metabolic disease found a statistically significant difference in VO_2peak (+3.03 ml/kg/min, 95% CI 2.0-4.07), in favour of HIIT, compared with moderate continuous exercise training [221]. These results were consistent with a more recent meta-analysis involving 949 cardiac rehabilitation patients investigating the effect of HIIT interval durations on VO_2peak [222]. The

results of this review found that change from baseline values in participants assigned to the moderate interval HIIT (MD 4.02 ml/kg/min, 95% CI 1.29-6.76) and long interval HIIT (MD 1.36 ml/kg/min, 95% CI 0.71-2.02) for three-months reported beneficial effects on VO_2peak, compared with moderate continuous exercise training [222]. These data indicate that exercise training intensity and interval type are central to improving VO_2peak in patients with cardiovascular disease.

In addition to VO_2peak, the favourable effects of aerobic exercise training on cardiac structure have been thoroughly investigated in clinical and non-clinical cohorts. Specifically, aerobic exercise training has shown similar benefits to pharmacologically-induced anti-cardiac remodelling, especially in clinical cohorts with chronic heart failure [224-226]. In a meta-analysis of 14 trials (n=812 patients with chronic heart failure), significant improvements in LVEDV (weighted mean difference [WMD], -11.5 ml, 95% CI -19.9-3.02) and LV end-systolic volume (LVESV) (WMD -12.8 ml, 95% CI -17.8-7.93) were observed when resistance exercise training and combined exercise interventions were compared [224]. While the authors also examined the effect of resistance exercise training and combined aerobic and resistance exercise training on cardiac structure, no beneficial effects were observed between groups. This suggests that exercise intensity may be a key mediator of cardiac structure in CVD populations [224]. In addition, a prospective study of 12 previously sedentary adults with minimal comorbidities participated in a novel athletic style periodised exercise training intervention (aerobic exercise intensities such as base pace, 1-20 bpm below maximal steady-state, maximal steady-state, and HIIT [4x4 method >95% of heart rate maximum]) induced physiological cardiac remodelling (a term used to describe exercise-induced changes in LV mass, LVEDV, LVESV and LVCO) and significantly improved maximal oxygen uptake (VO_2max) by~20% from baseline to 12 months (P<0.00001) [226]. Notably, this was primarily the result of proportional increases in left ventricular stroke volume (LVSV) and LVCO, which were likely related to the resultant increases in VO_2peak, LV mass, and LVEDV. Similar results were observed in a randomised controlled trial of 61 (48% male) previously sedentary middle-aged participants (age 53±5 years), by which physiological cardiac remodelling (magnitude of difference, LVEDV ~17% after ten months, P<0.05), VO_2peak (~18%, P<0.001) and LV stiffness markedly improved from baseline, compared with attention control [225]. Therefore, a multi-modal aerobic training program consisting of varied aerobic exercise training intensities is vital and key to inducing physiological cardiac remodelling in clinical (for example CVD) and non-clinical cohorts.

Exercise interventions aimed at improving vascular health, particularly arterial stiffness, wave reflections and endothelial function, have shown favourable effects on mitigating cardiovascular risk in clinical and non-clinical cohorts [227, 228]. However, the beneficial effects of exercise training seem to differ by exercise mode. Specifically, aerobic and combined aerobic and resistance exercise training significantly reduced cfPWV in adults with hypertension. (Aerobic, MD -0.70 m/s, 95% CI -12.0, -0.19 and combined MD -0.74 m/s 95% CI -1.41, -0.08) compared to usual care [229]. In addition, no beneficial effects were observed for resistance exercise training alone among trials included (14 randomised controlled trials, n=642) [229]. While the review mentioned above is the first to highlight the benefits of combined aerobic and resistance exercise training interventions on cfPWV in adults with hypertension, substantial heterogeneity exists and may partly be explained by different methodological approaches and the exercise interventions prescribed in other studies [227]. Furthermore, exercise interventions targeting vascular health, particularly endothelial function [228, 230] in healthy adults and CVD populations, vary widely [231, 232]. Multiple studies have found that regular, moderate-intensity aerobic exercise training (stationary cycling) improves endothelial function, particularly nitric oxide-mediated forearm resistance vessel function, after a brief aerobic exercise intervention (range, four to six weeks) in sedentary adults with minimal comorbidities [233, 234]. However, not all studies support these observations [235-238]. A possible reason for the discrepancy may be related to the time course of structural and functional arterial remodelling and the fixed exercise duration. An eight-week aerobic exercise training intervention involving 13 young, healthy men and seven inactive controls resulted in a ~3.5% (P<0.01) improvement in brachial artery FMD response from baseline to four weeks; however, FMD returned to baseline following study cessation [239]. Interestingly, conduit dilator capacity (a marker of arterial remodelling) gradually increased throughout the study period (~2.5%, P<0.05) [239]. Overall, studies by Tinken et al.[239] and others [240] have demonstrated that functional arterial remodelling precedes structural arterial remodelling. Therefore, this may explain the discrepancy in exercise-induced vascular adaptations associated with cfPWV and endothelial function in human populations [241].

Although exercise training has been extensively examined in non-cancer populations concerning cardiac structure and function, cardiorespiratory fitness and vascular health [221, 225-228, 242], the impact of higher-intensity aerobic exercise training, combined with resistance training in ADT-treated men and other cancer cohorts is limited [243]. Despite this, a solid theoretical rationale

suggests that more intensively prescribed exercise may be an effective therapy for enhancing cardiorespiratory fitness, vascular function, and cardiac structure and function during and after PCa treatments.

1.11. Preliminary evidence to address cardiometabolic health in ADT-treated men.

The effect of exercise training prescribed concurrently with ADT is well-established and supports the notion that exercise training has favourable effects on minimising the deleterious effects of ADT [244-246]. Specifically, combined aerobic and resistance training interventions initiated concurrently with ADT are effective at preventing loss of lean mass and increased fat mass, bone mineral density, fatigue, sexual dysfunction, health-related QoL, and certain cardiovascular risk factors, including fasting blood glucose, insulin sensitivity, and c-reactive protein [244-246]. However, limited evidence exists regarding the beneficial effects of combined aerobic and resistance exercise interventions on cardiometabolic health outcomes in ADT-treated men (extensively detailed in *Chapter Three*). In a randomised controlled trial of 62 men commencing ADT involving a three-month combined moderate to vigorous aerobic exercise training intervention, appendicular lean mass significantly improved by 0.4 kg (95% CI 0.1-0.7, P=0.01), markers of adiposity (all, P<0.01) as well as high-density lipoprotein: total cholesterol (-0.52 mmol/L 95% CI -0.97,-0.06, P=0.02) in ADT-treated men, compared with usual care [247]. Similar results were observed in a larger randomised controlled trial involving 97 ADT-treated men who participated in a combined higher-intensity aerobic exercise intervention versus standard care [248]. This study showed subtle improvements in VO_2peak (+0.11 L/min, 95% CI 0.04-0.19, P=0.033), fasting blood glucose (-0.5 mmol/L, 95%, CI, 0.3-2.3, P= 0.037) as well fat oxidation and whole-body fat mass [248]. However, arterial stiffness and wave reflection measures showed no favourable effects as a result of the combined exercise intervention [248]. Although there is a preponderance of evidence demonstrating different effects of combined aerobic and resistance exercise training [244-246] on key outcomes, the breadth of evidence is limited to relatively homogenous exercise prescriptions that have demonstrated negligible effects on key cardiometabolic health outcomes.

Furthermore, a recent randomised controlled trial [249] of 26 ADT-treated men, including a high-intensity aerobic interval exercise training program, found that higher intensity aerobic exercise training attenuated declines in absolute VO_2peak (exercise training, -6.0% vs. -10.9% usual care,

P=0.05) after 17 weeks. Although this trial included a small number of ADT-treated men, the data suggest that enhancing or progressively increasing the aerobic exercise training stimulus may be a more effective way to prevent the adverse effects of ADT [249]. Although future research is required to determine whether more vigorous combined aerobic and resistance exercise training interventions can improve cardiometabolic health in ADT-treated men, the potential for using exercise training as a method to reduce the CVD burden is an important prospect, given the heightened risk of developing cardiovascular events in this population.

1.12. Conclusion

The five-year survival rate of PCa in Australia has increased from 58% in 1988 to 96% in 2021[5]. Consequently, PCa patients live long enough to experience age-related medical conditions, particularly CVD [53]. ADT is an effective cancer therapy that reduces biochemical recurrence, PCa mortality and extends survival [2]. Despite its effectiveness, evidence suggests that ADT increases the risk of all-cause and cardiovascular mortality and cardiovascular events in men with PCa [54-56, 59, 107, 250]. Animal studies and trials in clinical hypogonadism suggest that androgen deprivation may negatively affect the heart and vasculature [159, 160, 168, 169], potentially increasing the risk of additional cardiovascular illness in this vulnerable population group. Given that males with PCa had a greater risk of dying from CVD than from PCa [10], optimal detection and preventative strategies to reduce the CVD burden in ADT-treated men are lacking. Exercise training is an effective management strategy to counteract cardiovascular risk and is supported by a plethora of evidence in other settings [221, 222, 225-227]. However, additional research is necessary to evaluate the effect of more vigorous exercise interventions on the cardiovascular/metabolic effects of ADT in men with PCa [247, 248, 251-254]. Thus, a multidisciplinary strategy incorporating novel detection methods and preventative strategies, including HIIT, could represent a powerful means of improving cardiovascular health outcomes in this susceptible population.

1.13. Overall aims of this thesis.

The primary focus of this thesis is to provide insight into the mediators of cardiovascular risk in men commencing ADT (*Chapter Five*) while also investigating an exercise medicine strategy targeting cardiovascular health for three months in men randomly assigned to exercise training or

usual care/non-intervention control *(Chapter Six)*. The preceding chapters *(Chapters Two* and *Three)* synthesised the evidence concerning the influence of pre-existing CVD on cardiovascular morbidity and mortality in men treated with ADT and the "effect of exercise training on cardiometabolic health in men with PCa receiving ADT." This dissertation seeks to generate new knowledge regarding the cardiovascular effects of ADT and identify diagnostic and preventive strategies to improve the management of ADT-treated men with PCa.

1.14. Aims of this thesis

Specifically, this PhD aimed to:

1. To examine the influence of pre-existing cardiovascular disease on cardiovascular events, cardiovascular mortality, and all-cause mortality in ADT-treated men (*Chapter Two*).
2. To examine the impact of exercise training on cardiometabolic health in men with PCa receiving ADT (*Chapter Three*).
3. To compare markers of vascular health in men with PCa, compared to age-matched controls (*Chapter Five*).
4. To determine the relationship between cardiorespiratory fitness, vascular health, cardiac structure and function, traditional CVD risk factors and body composition in all participants (*Chapter Five*)
5. To evaluate the effects of a three-month exercise intervention initiated concurrently with ADT on (1) cardiac remodelling, (2) resting cardiovascular function and (3) cardiorespiratory fitness in men with PCa (*Chapter Six*).
6. To evaluate the impact of three months of ADT on (1) cardiac remodelling, (2) resting cardiovascular function and (3) cardiorespiratory fitness in men with PCa (*Chapter Six*).

1.15. Specific hypotheses:

1. Men with pre-existing cardiovascular disease/risk who receive ADT will have an increased incidence of cardiovascular events compared with non-ADT treated men without pre-existing cardiovascular disease.
2. ADT-treated men who participate in an exercise intervention will have improved cardiometabolic health compared with usual care.
3. Men with PCa commencing ADT will have impaired vascular health relative to age-matched controls.

4. Higher cardiorespiratory fitness will be associated with better vascular health in all participants.
5. Exercise training will attenuate (1) concentric remodelling, (2) resting cardiovascular dysfunction, and (3) improve cardiorespiratory fitness in men receiving ADT.
6. ADT will result in (1) concentric remodelling, (2) resting cardiovascular dysfunction, and (3) reduced cardiorespiratory fitness in men with PCa at three months.

1.16. Thesis Structure

This PhD thesis comprises of seven chapters. *Chapter Two* presents the results of a systematic review comprehensively synthesising the available literature on the influence of pre-existing CVD on cardiovascular morbidity and mortality in men treated with ADT. *Chapter Three* presents a published systematic review and meta-analysis focusing on the "effect of exercise training on cardiometabolic health in men with PCa undergoing ADT." *Chapter Four* provides an overview of the experimental study's methodology. The first experimental study outlined in *Chapter Five* compared measures of vascular health in men with commencing ADT to the age-matched non-cancer control group, as well as determined the relationship between cardiorespiratory fitness, vascular health, cardiac structure and function, traditional CVD risk factors and body composition in all participants. The second experimental chapter outlined in *Chapter Six* presents the randomised controlled trial results, evaluating the impact of exercise training on cardiac remodelling in men undergoing ADT. This experimental study employed a novel periodised exercise medicine approach to optimise cardiovascular and metabolic health in men undergoing ADT. *Chapter Seven* gives a broad discussion and review of the findings of this thesis, with a particular focus on key findings, strengths, limitations, and the significance of these findings. *Appendix A* details the research portfolio, including the statement of contributions, additional publications (unrelated to the thesis) and presentations completed during the PhD. *Appendix B* includes a copy of human research ethics approval from Alfred Health.

CHAPTER TWO: The influence of pre-existing cardiovascular disease on cardiovascular morbidity and mortality in men with prostate cancer treated with androgen deprivation therapy.

2. Overview

This chapter presents a systematic review that synthesised the evidence concerning the influence of pre-existing CVD on cardiovascular morbidity and mortality in ADT-treated men.

Bigaran A, Zopf EM, Gardner J, Baker MK, Howden EJ, Cormie P. The influence of pre-existing cardiovascular disease on cardiovascular morbidity and mortality in men with prostate cancer treated with androgen deprivation therapy. A systematic review.

This chapter has been submitted to *Acta Oncologica* for formal consideration. Due to its manuscript format, the following chapter contains its own abbreviations section.

Influence of pre-existing cardiovascular disease on morbidity and mortality in men with prostate cancer undergoing androgen deprivation therapy: A systematic review

Ashley Bigaran MSc.[a,b]*, Eva Zopf PhD[a], Jason Gardner MSc[c], Michael K Baker PhD[d], Erin J Howden PhD[b], Prue Cormie PhD[e,f]

[a]Mary MacKillop Institute for Health Research, Australian Catholic University, Victoria, Australia
[b]Human Integrative Physiology Laboratory, Baker Heart and Diabetes Institute, Victoria, Australia
[c] School of Exercise and Nutrition Sciences, Deakin University, Victoria, Australia
[d]School of Behavioural and Health Sciences, Australian Catholic University, Sydney, Australia
[e]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
[f]Sir Peter MacCallum Department of Oncology, The University of Melbourne, Victoria, Australia

Correspondence to: Ashley Bigaran
Mary MacKillop Institute for Health Research, Australian Catholic University
Level 5, 215 Spring Street, Melbourne, Victoria 3000 Australia
Ph:+61 39230 8268
Fax:+61 39963 5726
Email: ashley.bigaran@acu.edu.au
Keywords: prostate cancer; androgen deprivation therapy; cardiovascular morbidity; cardiovascular mortality
Word count of text: 3,852 words
Word count of abstract: 296 words

Abstract

Background Observational evidence suggests androgen deprivation therapy (ADT) increases the risk of cardiovascular disease (CVD) in prostate cancer (PCa) patients. While some studies have shown that pre-existing CVD may mediate this risk, the influence of pre-existing CVD on cardiovascular morbidity and mortality has yet to be systematically evaluated.

Objective: To investigate the influence of pre-existing CVD on all-cause mortality, cardiovascular mortality, and cardiovascular events in ADT-treated men.

Methods: A systematic search of MEDLINE, EMBASE, CINHAL, SCOPUS, and WEB OF SCIENCE to May 2022 was performed to summarise the available evidence on the associations between pre-existing CVD and all-cause mortality, cardiovascular mortality, and cardiovascular events in PCa patients treated with ADT.

Results: Eleven studies were included, with data originating from seven databases. A total of 363,431 participants with PCa treated with ADT were included. Studies were mainly of high quality; however, they were heterogeneous in their pre-existing CVD definitions, cardiovascular endpoints, length of follow-up, and statistical approaches. In addition, there was a study population cohort overlap in six studies, which precluded our ability to conduct a meta-analysis. Six studies observed a significant increase in the risk of all-cause mortality in men with pre-existing CVD treated with neoadjuvant ADT compared to PCa patients not treated with ADT. However, there is insufficient evidence of the relationship between pre-existing CVD and ADT with cardiovascular events and mortality.

Conclusions: Significant increases in the risk of all-cause mortality were observed in men with existing chronic heart failure or prior myocardial infarction subsequently treated with neoadjuvant ADT from the studies assessed; however, the influence of pre-existing CVD on cardiovascular mortality and cardiovascular events remains unclear. Future studies are necessary to clarify if a causal relationship between pre-existing CVD and cardiovascular morbidity and mortality exists.

2.1. Introduction

Androgen deprivation therapy (ADT) is an effective PCa treatment that decreases PCa-specific mortality [32, 255, 256]. However, the adverse effects of ADT are profound and include changes in bone mineral density, sexual health, psychosocial health, and detrimental declines in health-related QoL [41, 47]. Further, ADT-treated men also experience adverse effects on body composition (increased fat mass and reduction in lean muscle mass), blood lipid profile, C-reactive protein, insulin sensitivity, and vascular function, which may increase the risk of cardiovascular morbidity and premature mortality [41, 43, 44, 68, 106, 112].

For over a decade, the relationship between ADT and all-cause mortality, cardiovascular mortality and cardiovascular events has been the subject of investigation [32, 53, 54, 63]. However, the available evidence remains inconsistent [54, 58, 63, 68]. A potential reason for the inconsistent findings is that prior evidence has mostly been derived from secondary analyses of randomised controlled trials, which generally exclude patients with pre-existing cardiovascular disease (CVD) and may not reflect the general population of men with PCa [67]. Despite the inconsistent findings, a pooled analysis of six pharmaceutical trials [64] and recent prospective data [257] suggest that the excess mortality risk (all-cause and cardiac-specific mortality) may be influenced by the presence of pre-existing CVD conditions in men treated with ADT [64]. This raises the question of whether there is a susceptible sub-group of men with pre-existing CVD who may be at a higher risk of cardiovascular complications following exposure to ADT. Despite the high prevalence of cardiovascular comorbidities in PCa patients commencing ADT [46, 52], limited evidence exists regarding the influence of pre-existing CVD on cardiovascular morbidity and mortality.
While ADT's association with cardiovascular events and mortality has been extensively reviewed [41, 53, 54, 218], none specifically focused on men with pre-existing CVD. Therefore, this systematic review aims to provide a comprehensive summary of the literature examining the influence of pre-existing CVD on all-cause mortality, cardiovascular mortality, and cardiovascular events in ADT-treated men. We theorise that men with pre-existing CVD treated with ADT will have an increased risk of all-cause mortality, cardiovascular mortality, and cardiovascular events compared to men without a history of CVD treated with ADT.

2.2. Materials and methods

Search Strategy and Study Eligibility

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (PRISMA)[258] and was prospectively registered with PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=162520). A protocol deviation was submitted concerning the attempt to perform a meta-analysis; however, the amendment remains pending due to the sheer volume of submissions and applications. Literature searches were carried out from the inception of the database to May 2022 by systematically searching MEDLINE, EMBASE, CINAHL, SCOPUS, and WEB of SCIENCE. Prospective and retrospective cohort studies and randomised controlled trials (RCT), including ADT-treated men (gonadotropin-releasing hormone agonists and antagonists, anti-androgens) or orchiectomy with or without radiotherapy, were considered. To be eligible for this systematic review, studies had to separately report risk estimates (hazard ratios [HR], standard incident ratios) and 95% confidence intervals for participant groups with pre-existing CVD diagnoses (for example, ADT with or without pre-existing CVD type). Studies also had to report at least one endpoint for the incidence of all-cause mortality, cardiovascular mortality, or cardiovascular events (specifically by the type of cardiovascular event). Studies were excluded if the study sample included: 1) participants receiving chemotherapy or 2) participants with other cancer types unless data for PCa participants could be separately identified. Studies were limited to the English language only. A single study author (AB) performed the literature search, and two study authors (JG and AB) screened all studies independently, and any disagreement was discussed until consensus was achieved. If data was not presented as described in the inclusion criteria, these studies were not included in the systematic review.

Data Extraction and Quality Assessment

Data extraction was completed by a single author (AB) using tabulated data extraction forms. Study characteristics, including study authors, database, participants, follow-up period, ADT type, ADT duration, the definition of CVD, and the primary outcome of each study (including all-cause mortality, cardiovascular mortality, and cardiovascular events), were extracted.

Each study's quality was assessed using the Newcastle-Ottawa quality assessment scale (NOS) for cohort studies [259]. The NOS scale assesses study quality by assigning scores ranging from zero (poor-quality studies) to nine (high-quality studies). The scale awards nine points for each cohort

study (four for selection, two for comparability and three for the outcome and adequate follow-up). A study was classified as high quality if it achieved >7 points (Supplementary Table s2.1).

2.3. Results

Literature search

The systematic literature search results, screening process and search terms are outlined in Figure 2.1 and Supplementary Table s2.1. The initial search identified 1144 articles. After duplicates were removed and abstracts and titles screened, 59 articles were assessed for eligibility. Six retrospective [55, 59, 71, 72, 74, 75] and five prospective [56, 57, 73, 76, 77] cohort studies met the eligibility criteria. They provided at least one endpoint of interest: all-cause or cardiovascular mortality or cardiovascular events for men with pre-existing CVD treated with ADT. Although randomised controlled trials were identified in the literature search, the primary reason for exclusion was the inability to separate hazard ratios by pre-existing subtypes on endpoints of interest in this review.

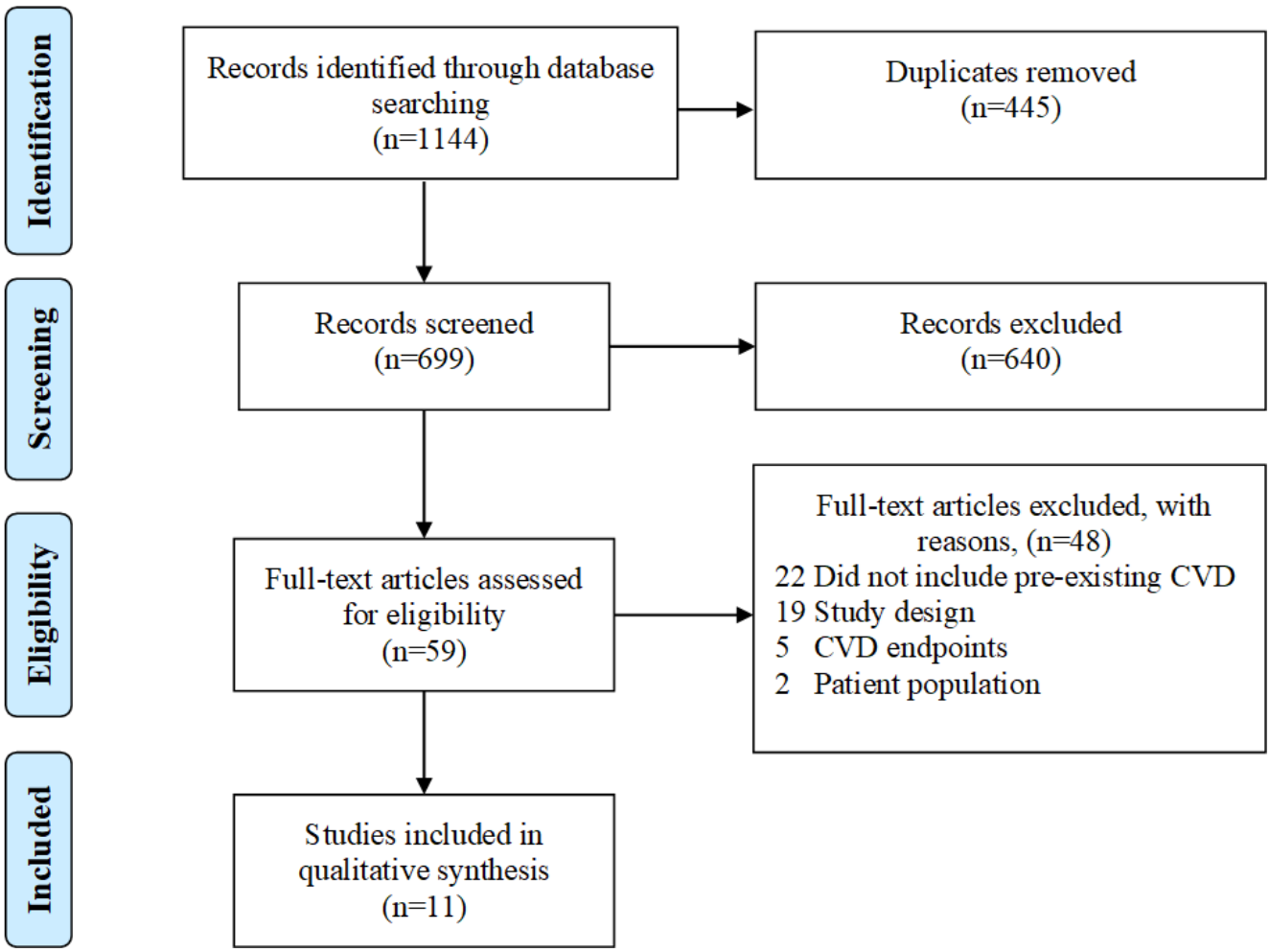


Figure 2.1: Study selection process for the influence of pre-existing cardiovascular disease on cardiovascular morbidity and mortality in men with prostate cancer treated with ADT.
Abbreviations: CVD (cardiovascular disease)

Risk of bias

The tabulated risk of bias assessment related to the studies included is presented in Supplementary Table s2.1. Studies were mainly of high quality [56, 57, 76]. The average NOS score of the cohort studies included in this review was 7.4 out of 9. The primary difference between studies was the cohort comparability based on whether the studies controlled for essential confounders that may have affected the primary outcome.

Characteristics of included studies

The key characteristics, including participant characteristics and the methodology of the included studies, are presented in Table 2.1. Six studies reported the association between pre-existing CVD and all-cause mortality [55, 59, 71, 73-75]. Two studies investigated the association between pre-existing CVD and cardiovascular mortality in ADT-treated men [72, 77]. Four studies examined the association between ADT and cardiovascular events in men with pre-existing CVD [56, 57, 76, 77]. A single study combined the hazard risk estimates for fatal and non-fatal cardiovascular events (myocardial infarction and stroke); however, the authors stated that the risk estimates were similar and did not affect the results [76].

Nine of the included studies were conducted in the United States. They included data from either Surveillance, Epidemiology and End Results Programs (SEER) [56, 57], Chicago Prostate Centre [72, 75], Kaiser Permanente [56], 21st Century Oncology practices or a combination of 21st Century Oncology Practices and Chicago Prostate Cancer Centre, respectively [55, 59, 71, 73, 74]. The remaining two studies were conducted in Sweden and Denmark and included data from the Danish National Cancer Registry or the Swedish National Prostate Cancer Registry [76, 77]. A total of 363,431 participants with PCa were included in this review, and participants' age ranged from 65-85 years. Follow-up periods ranged from 3.3 to 4.8 years.

PCa stage varied among the studies included. All studies included men with low-risk, intermediate and high-risk PCa; however, most participants included in the analyses had intermediate-risk disease. Treatments included gonadotropin-releasing hormone (GnRH) agonists, orchiectomy, anti-androgens, or a combination of these. Eight studies included patients who received short-term ADT (neoadjuvant ADT in conjunction with external beam radiotherapy or interstitial brachytherapy) [55, 59, 71-75]. ADT duration varied among studies, ranging from three months for studies

including men receiving neoadjuvant ADT to 450 days [96-804 days] for a single study examining longer-term ADT. The most reported pre-existing CVD conditions were myocardial infarction, stroke, and chronic heart failure [59, 74, 75].

The studies reported the following methods for determining pre-existing CVD: 1) individual medical consultations with referring physicians before initiation of ADT; 2) extraction of inpatient and outpatient electronic medical records; 3) World Health Organisation International statistical classification codes of diseases (ICD) to report pre-existing CVD diagnoses before ADT, and 4) Charlson comorbidity score. Keating et al. [57] modified the Charlson comorbidity score to stratify patients by their baseline cardiovascular comorbidities. Van Hemelrijck et al. [77] extracted pre-existing CVD diagnoses from the National Prostate Cancer Registry of Sweden.

The method of statistical analysis differed widely. Nine studies used adjusted Cox proportional hazard models, adjusting for age and PCa-specific covariates. Van Hemelrijck et al. [77] calculated standardised incident and mortality ratios by comparing the observed events to the Swedish population. Ziehr et al. [72] conducted a Fine and Gray competing risks analysis to evaluate ADT's association with cardiovascular-specific mortality while adjusting for standardised covariates and treatment propensity scores.

Table 2.1: Characteristics of studies investigating the association of pre-existing cardiovascular disease with all-cause mortality, cardiovascular mortality and cardiovascular events in prostate cancer patients treated with androgen deprivation therapy.

Reference	Database	Participants	Follow up	ADT type	ADT duration	Definition of CVD	Primary outcome
Hayes et al.[73]	"Chicago Prostate cancer (or one of 20 community-based centres within 21st Century Oncology located in Florida, New York, and North Carolina)" (1991-2007)	Overall cohort, n = 12,792. ADT with MI/CVA, n = 2,040. No MI/CVA with ADT, n = 2,491	3.8 years	GnRH agonist, with A or GnRH agonist alone	Neoadjuvant 4 months (IQR 3-5 months)	Consultation with referring physicians for MI or stroke	All-cause mortality
Haque et al.[56]	Kaiser Permanente, South Carolina (1998-2008); SEER database	Overall cohort, n = 7,637 SEER data base: ADT, n = 2,170	3.4 years	GnRH agonist, AA, GnRH agonist with AA	NR	CVD (ICD-9 and ICD-10)	Cardiovascular events
Jespersen et al.[76]	Danish National Cancer Registry (2002-2010)	Overall cohort, n = 31, 571. ADT, n = 9,204 and Orchiectomy, n = 2,060	3.3 years	GnRH agonist or AA or orchiectomy	NR	MI and stroke were characterised before PCa diagnosis throughout the study period. MI (ICD -8 410.09-410.99) and ischaemic stroke	Cardiovascular events

						(ICD-8 433.09/99, 434.09/99, 436.01/436. 90, ICD-10 DI63, x and DI64, x). Fatal events were identified using ICD-10 D121.x and DI46.x) for MI and stroke (ICD-10 DI63.x and DI64.x)	
Keating et al.[57]	SEER database for men > 65 years with PCa (1992-2007)	Overall cohort, n = 185,106	NR	GnRH agonist or orchiectomy	450 days (96-804)	AMI and DM were identified using dx and procedure codes. Comorbid conditions were characterised by pre-diagnosis or throughout the study period. HTN (ICD -9 401-405.99) and obesity (ICD-9 278,278,278.01, 278.02) in addition to the Charlson score.	Cardiovascular events
Nanda et al. [75]	"Chicago prostate cancer centre (1997-2006)"	Overall cohort, n = 5,077. ADT, n = 1,521	4.8 years	LHRH agonist with AA	Neoadjuvant 4 months (IQR 3-4 months)	Individual consultation with referring physicians	All-cause mortality

						for CHF, MI, CVD risk factors	
Nanda et al. [74]	"Chicago prostate cancer centre (or one of 20 community-based medical centres within the 21st Century Oncology establishment located within Florida, New York, and North Carolina (1991-2006)"	Overall cohort, n = 11,166 ADT, n = 5,071	Low-risk PCa 4.1 years Intermediate PCa risk 4.4 years High-risk PCa 4.6 years	NR	Neoadjuvant 4 months (IQR 3-4 months)	Consultation with referring physicians for CAD risk factors	All-cause mortality (in low-risk prostate cancer)
Nguyen et al. [71]	"US Community-based practices located in Florida, New York, and North Carolina (21st Century Oncology) (1991-2006)"	Overall cohort, n = 7,839	4.1 years	LHRH agonist with or without AA	Neoadjuvant 4 months	Consultation with referring physicians for CHF, MI with or without revascularisation	All-cause mortality
Nguyen et al.[59]	21st Century Oncology "(one of 20 community-based medical	Overall cohort, n = 14,594	4.3 years	LHRH agonist with or without AA	Neoadjuvant 4 months (IQR 3-5 months)	Consultation with referring physicians for CHF, MI	All-cause mortality

	centres within the 21st Century Oncology establishment located within Florida, New York, and North Carolina) (1991-2007)."						
Parekh et al.[55]	21st Century Oncology (one of 20 community-based centres) (1993-2008)"	Overall cohort, n = 5,972	3.9 years	LHRH agonist with or without AA	Neoadjuvant 4 months (IQR 3-5 months)	Consultation with referring physicians for CHF, MI, and CAD risk factors with or without revascularisation	All-cause mortality
Van Hemelrijck et al.[77]	NPCR PCBaSE Sweden, (1997-2007)	Overall cohort, n=76,600. ADT, n = 30,642 AA, n = 3,391; Orchiectomy, n = 5,340	3.5 years	GnRH agonist, GnRH agonist plus AA, Orchiectomy, AA only	NR	"Ischaemic heart disease (ICD -10:120-I25) AMI (ICD-10: I21), Arrhythmia (ICD-10: I44-I49), Heart failure (ICD-I50), stroke (ICD -10 I60-I64, G45)"	Cardiovascular events and Cardiovascular mortality
Ziehr et al.[72]	Chicago prostate cancer centre (1997-2006)	Overall cohort, n = 5,077, ADT, n = 1,521	4.8 years	GnRH agonist with AA	Neoadjuvant 4 months (IQR 3-4 months)	Hospital consultation for CHF, AMI, and CVD risk factors	Cardiovascular mortality

Abbreviations: SEER (Surveillance, Epidemiology, and End Results), NPCR/PCBaSe (National Prostate Cancer Registry, Sweden), PCa (Prostate cancer), IQR (interquartile range), ADT (Androgen deprivation therapy), NR (Not reported), GnRH (gonadotropin-releasing hormone), AA (anti-androgen), LHRH (Luteinising hormone-releasing hormone), ICD (International Classification of Diseases), HTN (hypertension), CVD (cardiovascular disease), CAD (coronary artery disease), AMI (acute myocardial infarction), MI (myocardial infarction), CHF (chronic heart failure)

2.4. Qualitative synthesis

The main results of the included studies examining the association between pre-existing CVD and all-cause mortality, cardiovascular mortality and cardiovascular events are depicted in Tables 2.2 and 3.3.

The association between pre-existing CVD and all-cause mortality

Six cohort studies [55, 59, 71, 73-75] examined the association of pre-existing CVD with all-cause mortality in men with low and high-risk PCa treated with neoadjuvant ADT. Four of the six studies originated from 21st Century Oncology practices and/or Chicago Prostate Cancer Centres [55, 59, 73, 74]. While these studies varied in recruitment periods, study locations and pre-existing CVD diagnoses, there was likely study population overlap (Table 2.2). PCa participants with pre-existing CVD were compared to men with PCa who did not receive ADT and those with and without pre-existing CVD. A significantly higher risk of all-cause mortality was observed in PCa patients with chronic heart failure or prior myocardial infarction (HR range from 1.73-1.96) [59, 71, 75], chronic heart failure or prior myocardial infarction with (HR 2.06; 95%CI [0.02-4.17]; *P* =0.04) and without coronary revascularisation (HR range from 1.48-1.83) [55, 71], prior myocardial infarction or stroke (HR 1.20; 95%CI [1.05-1.38]; *P*=0.008) [73] and in men with at least one coronary artery disease risk factor (HR 1.36; 95%CI [1.07-1.74]; *P* =0.01) [74] treated with neoadjuvant ADT. There was no proportional increase in the risk of all-cause mortality in PCa patients with existing hypertension and high cholesterol (HR 0.87; 95%CI [0.67-1.12]; *P*=0.28) [55], diabetes Mellitus, hypertension and high cholesterol (1.04; 95%CI [0.72-1.43]; *P*=0.82) [75] or without coronary disease risk factors (HR 1.19; 95% CI [0.95-1.51]; *P*=0.13) [74] or existing chronic heart failure or prior acute myocardial infarction (HR 0.78; 95% CI [0.53-1.15]; *P*=0.21)[55] treated with neoadjuvant ADT, compared to PCa patients without pre-existing CVD and not treated with ADT.

Table 2.2: All-cause mortality and cardiovascular mortality in prostate cancer patients with pre-existing cardiovascular disease and treated with androgen deprivation therapy.

Outcome	Author	ADT with or no pre-existing CVD	N (subgroup)	N (events)	Adjusted HR* [95% CI]	P-value
All-cause mortality	Hayes et al.[73]	No ADT with previous AMI or stroke	NR	NR	1.0 [Reference]	
		No ADT with no previous AMI or stroke	NR	NR	0.74 [0.65-0.85]	**<0.001**
		ADT with no previous AMI or stroke	NR	NR	0.79 [0.67-0.92]	**0.003**
		ADT with previous AMI or stroke	NR	NR	1.2 [1.05-1.38]	**0.008**
	Nanda et al.[75]	No ADT with no pre-existing CVD	2653	125	1.0 [Reference]	
		ADT with no pre-existing CVD	2653	75	0.97 [0.72-1.32]	0.86

		ADT with pre-existing T2DM, HTN and HChol	2168	69	1.04 [0.75-1.43]	0.82
		ADT with pre-existing CHF or previous AMI	256	25	1.96 [1.04-3.71]	**0.04**
	Nanda et al.[74]	No ADT with no pre-existing CVD	2678	325	1.0 [Reference]	
		ADT with a single CAD risk factors	NR	NR	1.36 [1.07-1.74]	**0.01**
		ADT with no CAD risk factors	NR	NR	1.19 [0.95-1.51]	0.13
	Nguyen et al [71]	No ADT with pre-existing CHF or previous AMI	NR	NR	1.0 [Reference]	
		ADT with pre-existing CHF or previous AMI	NR	NR	1.73 [1.13-2.64]	**0.012**
		No ADT with pre-existing CHF or previous AMI, no revascularisation	NR	NR	1.0 [Reference]	
		ADT with pre-existing CHF or	NR	NR	1.48 [1.01-2.18]	**0.047**

		previous AMI or no revascularisation				
		No ADT with pre-existing CHF or previous AMI with revascularisation	NR	NR	0.51 [0.28-0.93]	**0.028**
		No ADT with pre-existing CVD	NR	NR	1.0 [Reference]	
		ADT with CHF/AMI	NR	NR	1.76 [1.32-2.34]	**0.0001**
	Parekh et al.[55]	No ADT with no pre-existing CVD	NR	NR	1.0 [Reference]	
		ADT with no pre-existing CVD	2727	NR	0.97 [0.82-1.15]	0.71
		ADT with pre-existing HTN, HChol, no DM	1740	NR	0.87 [0.67-1.12]	0.28
		ADT with pre-existing CAD (No AMI/CHF)	549	NR	0.78 [0.53-1.15]	0.21
		ADT with pre-existing CHF or previous AMI or	245	NR	1.83 [1.05-3.20]	**0.03**

		no revascularisation				
		ADT with pre-existing CHF or previous AMI with revascularisation	250	NR	2.06 [0.02-4.17]	**0.04**
Cardiovascular mortality	Van Hemelrijck al. [77]	Swedish male population	NR	NR	[Reference]	
		ADT with no baseline circulatory disease (AMI)	NR	569	1.32 [1.22-1.44]	NR
		ADT with baseline circulatory disease (AMI)	NR	622	1.19 [1.10-1.28]	NR
		ADT with no baseline circulatory disease (arrhythmia)	NR	98	1.21 [0.98-1.47]	NR
		ADT with baseline circulatory disease (arrhythmia)	NR	90	0.85 [0.68-1.04]	NR

		ADT with no baseline circulatory disease (IHD)	NR	1085	1.18 [1.11-1.26]	NR	
		ADT with baseline circulatory disease (IHD)	NR	1012	1.23 [1.16-1.31]	NR	
		ADT with no baseline circulatory disease (CHF)	NR	171	1.22 [1.04-1.42]	NR	
		ADT with baseline circulatory disease (CHF)	NR	201	1.26 [1.09-1.45]	NR	
		ADT with no baseline circulatory disease (stroke)	NR	209	1.08 [0.94-1.24]	NR	
		ADT with baseline circulatory disease (stroke)	NR	337	1.36 [1.21-1.51]	NR	
	Ziehr et al. [72]	No ADT with no pre-existing CVD	1873	24	1.0 [Reference]		

		ADT with no pre-existing CVD	780	12	0.83 [0.39-1.78]	0.640
		No ADT with pre-existing DM, HTN and HChol	1552	256	1.0 [Reference]	
		ADT with pre-existing DM, HTN and HChol	646	18	1.33 [0.70-2.53]	0.390
		No ADT with pre-existing CHF or AMI	161	4	1.0 [Reference]	
		ADT with pre-existing CHF or AMI	95	8	3.28 [1.01-10.64]	**0.048**

*Note: Van Hemelrijck reported incidence data as standard mortality rates compared to the general population of men with prostate cancer in Sweden.

Abbreviations: NR (Not reported), ADT (androgen deprivation therapy), CVD (cardiovascular disease), CAD (coronary artery disease), AMI (acute myocardial infarction), CHF (chronic heart failure), DM (diabetes mellitus), HTN (hypertension), HChol (hypercholesterolemia), PAD (peripheral artery disease), IHD (ischaemic heart disease), NR (not reported)

The association between pre-existing CVD and cardiovascular mortality

Two cohort studies [72, 77] examined the association between pre-existing CVD and cardiovascular mortality in ADT-treated men (Table 2.2). Ziehr et al. [72] reported a higher risk of cardiovascular mortality rates in men with coronary artery disease-induced chronic heart failure or myocardial infarction treated with neoadjuvant ADT (HR 3.28; 95% CI [1.01-10.64]; *P*=0.048], compared with men with coronary artery disease-induced chronic heart failure or myocardial infarction not treated with ADT. No significant differences in cardiovascular mortality were observed in other groups with Diabetes Mellitus, hypertension and high cholesterol (HR 1.33; 95%CI [0.70-2.53]; *P*=0.390) or those without pre-existing CVD and treated with ADT (HR 0.83; 95% CI [0.39-1.78]; *P*=0.640) [72]. In contrast, Van Hemelrijck et al. [77] found limited evidence to suggest that baseline circulatory disease (heart disease) increased cardiovascular mortality rates in ADT-treated men compared to PCa patients without baseline circulatory disease or the general Swedish population. It is important to note that this trial included all types of medical (anti-androgen, GnRH agonists and/or short-term anti-androgens) and surgical castration (orchiectomy) interventions to treat PCa.

The association between pre-existing CVD and cardiovascular events

Four prospective cohort studies [56, 57, 76, 77] examined the association between pre-existing CVD and several cardiovascular events, including myocardial infarction, cardiac arrest, stroke, arrhythmia, conduction disorders, heart failure, cardiomyopathy, and ischaemic heart disease (Table 2.3). For the risk of developing myocardial infarction, ADT was associated with a higher risk of cardiovascular events in PCa patients with pre-existing CVD; however, this risk increased to a similar extent in PCa patients without pre-existing CVD or those with pre-existing CVD that did not receive ADT [56, 57, 76, 77]. Further, two of these studies [56, 57] stratified by a comprehensive set of cardiovascular covariates similarly reported that the risk of developing myocardial infarction was similar between groups and was not mediated by the presence of pre-existing CVD or ADT use.

Two studies investigated the association between pre-existing CVD, cardiac arrhythmias, and conduction disorders in men treated with ADT. Haque et al. [56] observed a significantly higher "risk of developing arrhythmias (HR 1.44; 95% CI [1.02-2.01]) and conduction disorders (HR 3.11; 95% CI [1.22-7.9])" in ADT-treated men with pre-existing CVD, relative to men without pre-existing CVD. Van Hemelrijck et al. [77] similarly observed a higher non-significant increase in

arrhythmias in PCa patients treated with any ADT type; however, this risk was independent of baseline circulatory disease. For the remaining studies, there was a non-significant increase in cardiovascular event incidence (cardiac arrest, stroke, heart failure, cardiomyopathy and ischaemic heart disease) in PCa patients with pre-existing CVD treated with ADT; however, this risk was similar to PCa patients without pre-existing CVD treated with or without ADT [56, 57, 76, 77]. Notably, some studies could not adjust their hazard ratio estimates for significant clinical CVD covariates relevant to the primary outcome [76, 77].

Table 2.3: Incidence of cardiovascular events in prostate cancer patients with pre-existing cardiovascular disease and treated with androgen deprivation therapy.

Cardiovascular outcome	Author	ADT with or no pre-existing CVD	N (total population)	N (events)	Adjusted HR* [95% CI]	P-value
Myocardial infarction	Haque et al.[56]¥	No ADT with no pre-existing CVD	NR	NR	1.0 [Reference]	
		ADT with no pre-existing CVD	NR	NR	1.24 [0.93-1.64]	NR
		ADT with pre-existing CVD	NR	NR	1.14 [0.78-1.65]	NR
	Jespersen et al.[76]	No ADT with no previous AMI or stroke	18283	NR	1.0 [Reference]	
		ADT with no previous AMI or stroke	8175	NR	1.33 [1.15-1.53]	NR
		ADT with previous AMI or stroke	1029	NR	1.20 [0.90-1.60]	NR
	Keating et al.[57]†	No ADT with no pre-existing CVD	NR	NR	1.0 [Reference]	
		ADT with no pre-existing CVD	NR	NR	1.09 [1.02-1.16]	P<0.05
		No ADT with previous AMI	NR	NR	1.72 [1.51-1.97]	P<0.05
		ADT with previous AMI	NR	NR	1.75 [1.41-2.16]	P<0.05

		No ADT with pre-existing CHF	NR	NR	2.00 [1.88-2.13]	P<0.05
		ADT with pre-existing CHF	NR	NR	2.15 [1.94-2.39]	P<0.05
		No ADT with pre-existing PAD	NR	NR	1.39 [1.30-1.50]	P<0.05
		ADT with pre-existing PAD	NR	NR	1.41 [1.24-1.59]	P<0.05
		No ADT with previous stroke	NR	NR	1.29 [1.20-1.38]	P<0.05
		ADT with previous stroke	NR	NR	1.44 [1.27-1.62]	P<0.05
		No ADT with pre-existing HTN	NR	NR	1.08 [1.03-1.14]	P<0.05
		ADT with pre-existing HTN	NR	NR	1.17 [1.06-1.29]	P<0.05
	Van Hemelrijck et al. [77]	Swedish male population	NR	NR	1.0 [Reference]	
		ADT with no baseline circulatory disease	NR	955	1.40 [1.31-1.49]	NR
		ADT with baseline circulatory disease	NR	1125	1.15 [1.08-1.22]	NR
Incident cardiac arrest	Haque et al.[56]¥	No ADT with pre-existing CVD	NR	NR	1.0 [Reference]	
		ADT with no pre-existing CVD	NR	NR	1.29 [0.61-2.76]	NR

		ADT with pre-existing CVD	NR	NR	0.85 [0.25-2.83]	NR
Incident stroke	Haque et al.[56]¥	No ADT with no pre-existing CVD	NR	NR	1.0 [Reference]	
		ADT with no pre-existing CVD	NR	NR	0.93 [0.46-1.88]	NR
		ADT with pre-existing CVD	NR	NR	1.62 [0.64-4.12]	NR
	Jespersen et al.[76]	No ADT with no previous AMI or stroke	NR	NR	1.0 [Reference]	
		ADT with no previous AMI or stroke	NR	NR	1.21 [1.05-1.39]	NR
		ADT with previous AMI or stroke	NR	NR	1.08 [0.84-1.39]	NR
	Van Hemelrijck et al.[77]	Swedish male population	NR	NR	1.0 [Reference]	
		ADT with no baseline circulatory disease	NR	991	1.29 [1.21-1.37]	NR
		ADT with baseline circulatory disease	NR	1628	1.24 [1.18-1.30]	NR
Incident arrhythmia	Haque et al.[56]¥	No ADT with no pre-existing CVD	NR	NR	1.0 [Reference]	
		ADT with no pre-existing CVD	NR	NR	1.07 [0.84-1.37]	NR

		ADT with pre-existing CVD	NR	NR	**1.44 [1.02-2.01]**	NR
	Van Hemelrijck et al.[77]	Swedish male population	NR	NR	1.0 [Reference]	
		ADT with no baseline circulatory disease	NR	816	1.32 [1.23-1.41]	NR
		ADT with baseline circulatory disease	NR	876	1.11 [1.04-1.18]	NR
Incident conduction disorders	Haque et al.[56]¥	No ADT with no pre-existing CVD	NR	NR	1.0 [Reference]	
		ADT with no pre-existing CVD	NR	NR	1.08 [0.57-2.03]	NR
		ADT with pre-existing CVD	NR	NR	**3.11 [1.22-7.91]**	NR
Incident heart failure	Haque et al.[56]¥	No ADT with no pre-existing CVD	NR	NR	1.0 [Reference]	
		ADT with no pre-existing CVD	NR	NR	1.81 [1.40-2.32]	NR
		ADT with pre-existing CVD	NR	NR	1.00 [0.78-1.29]	NR
	Van Hemelrijck et al.[77]	Swedish male population	NR	NR	1.0 [Reference]	
		ADT with no baseline circulatory disease	NR	1212	1.66 [1.57-1.76]	NR
		ADT with baseline circulatory disease	NR	1601	1.04 [0.98-1.11]	NR

Incident cardiomyopathy	Haque et al.[56]¥	No ADT with no pre-existing CVD	NR	NR	1.0 [Reference]	
		ADT with no pre-existing CVD	NR	NR	2.25 [0.74-6.78]	NR
		ADT with pre-existing CVD	NR	NR	1.51 [0.51-4.46]	NR
Incident ischaemic heart disease	Van Hemelrijck et al.[77]	Swedish male population	NR	NR	1.0 [Reference]	
		ADT with no baseline circulatory disease	NR	1663	1.29 [1.23-1.36]	NR
		ADT with baseline circulatory disease	NR	1601	1.35 [1.28-1.42]	NR

Abbreviations: ADT (androgen deprivation therapy), CVD (cardiovascular disease), AMI (acute myocardial infarction), CHF (chronic heart failure), HTN (hypertension), PAD (peripheral artery disease), NR (not reported).

*Note: Van Hemelrijck et al. [77] reported incidence data as standard incidence rates compared to the general population of men with prostate cancer in Sweden.

†Bold hazard ratios for Keating et al.[57] were considered statistically significant $P<0.05$ compared to the reference group (No ADT with no comorbidity). The interaction between ADT and no ADT by comorbidity was only statistically significant for peptic ulcer disease (data not shown). ¥Bold hazard ratio values for Haque et al.[56] were considered statistically significant at $P<0.05$.

2.5. Discussion

This systematic review synthesised the evidence, evaluating the association of pre-existing CVD with all-cause mortality, cardiovascular mortality, and cardiovascular events in ADT-treated men. This review included 11 prospective and retrospective cohort studies that evaluated these outcomes in more than 360,000 PCa patients. The findings suggest that PCa patients with pre-existing chronic heart failure and prior myocardial infarction that undergo neoadjuvant ADT have a 73-96% increase in the risk of all-cause mortality than men without a history of chronic heart failure or coronary artery disease [55, 59, 71, 73-75]. Overall, the magnitude of the effect was significant for all-cause mortality only. For cardiovascular mortality or cardiovascular events outcomes, a small number of studies with inconclusive results suggest the risks associated with these outcomes were not any different from the general population of men without PCa [56, 57, 72, 76, 77]. Therefore, insufficient evidence exists to determine if pre-existing CVD modulates the risk of cardiovascular mortality and cardiovascular events in ADT-treated men.

The most consistent finding to emerge from this systematic review was that neoadjuvant ADT increases the risk of all-cause mortality in PCa patients with a history of chronic heart failure or prior myocardial infarction (HR range from 1.73-1.96) [55, 59, 71, 73-75]. While these results are consistent with previous findings [64], the risk identified should be interpreted with caution because four studies [55, 59, 73, 74] originated from the same databases, preventing us from conducting a meta-analysis. However, these findings have important clinical implications for clinicians treating men with PCa with pre-existing CVD initiating neoadjuvant ADT. PCa patients with pre-existing CVD conditions seem to die earlier and have higher cardiovascular-related mortality rates than the general population [10, 32, 63, 64, 260]. It is well-established that pre-existing CVD conditions such as chronic heart failure and prior myocardial infarction increase the risk of all-cause mortality rates in non-cancer populations [94, 128, 261]. These pre-existing CVD conditions are likely to worsen prognosis, independent of PCa or neoadjuvant ADT. While there was substantial study population cohort overlap and methodological heterogeneity [55, 59, 71, 73], the increased mortality risk associated with pre-existing CVD seems solely related to neoadjuvant ADT. It should be considered when weighing up the risk versus benefits of commencing neoadjuvant ADT in men with a history of chronic heart failure and prior myocardial infarction. Broader multi-disciplinary team involvement, including cardiovascular care practitioners, may enhance clinical decision-

making and increase access to cardiovascular screening and management practices to reduce the risk of increased mortality noted in this population.

Another key finding of this systematic review was that available evidence examining the influence of pre-existing CVD on cardiovascular mortality outcomes in ADT-treated men is limited. A retrospective trial reported a significantly higher risk of cardiovascular mortality in PCa patients with chronic heart failure or prior myocardial infarction treated with neoadjuvant ADT [72]. In contrast, a prospective trial observed no effect or greater risk of cardiovascular mortality from any type of ADT than the general Swedish population [77]. Although the two studies investigating cardiovascular mortality are inherently different [72, 77], the subtle increases in cardiovascular mortality following neoadjuvant ADT observed in a more representative study sample with pre-existing CVD should not be disregarded. A possible explanation for the discrepancies could be related to the duration of ADT and pre-existing CVD diagnoses. Consistent with the aforementioned all-cause mortality rates [55, 59, 71, 73-75], the available evidence indicates that neoadjuvant ADT, specifically in men with an extensive cardiovascular history, report higher cardiovascular mortality rates compared to those not treated with any ADT. While the mechanisms are unclear, the combination of shared risk factors between cancer and CVD accompanied by the distinct physiological effects of ADT, even in the short term, may uniquely affect pre-existing CVD conditions [78]. Further research investigating the cardiovascular effects of ADT duration (short-term and long-term ADT) in men with pre-existing CVD on primary cardiovascular outcomes are needed.

This review revealed that the risk of cardiovascular events in ADT-treated with pre-existing CVD remains inconsistent. Data from a single prospective study [56] reported a significant increase in the risk of developing arrhythmias and conduction disorders in men with pre-existing CVD; however, three prospective studies observed no effect. Moreover, the results indicated that pre-existing cardiovascular disease did not increase or influence the risk of cardiovascular events [57, 76, 77]. While the findings are consistent with recent [70] and prior observations [57, 218], the lack of differences should be interpreted with caution as significant heterogeneity was associated with pre-existing CVD definitions, surrogate comorbidity scores, and statistical approaches, which also precluded our ability to conduct a meta-analysis or sensitivity analysis. Nevertheless, the findings of this review have important implications for future investigations and clinicians prescribing ADT.

Most studies included in this review have relatively short follow-up periods for men treated with neoadjuvant ADT. We theorise that the relatively short follow-up period may be insufficient to detect adverse changes to pre-existing CVD or cardiovascular risk factors and, therefore, limit the ability to detect signals evident in observational trials with extended follow-up periods [58, 68]. In addition, it is important to note that most men regain normal androgen levels following neoadjuvant treatment cessation (within ~3-6 months) [262]. Therefore, it could be entirely possible that no clear distinction between ADT and cardiovascular risk or time to cardiovascular events can be made due to the nature of the short follow-up periods. There are numerous unanswered questions regarding the association between ADT and cardiovascular events in men with pre-existing CVD, and the evidence currently available does not provide additional clarity [57, 76, 77]. Hence, further research that prospectively monitors cardiovascular risk factors and pre-existing CVD conditions over more extended study periods is necessary to understand better whether pre-existing CVD influences the risk of cardiovascular events in ADT-treated men.

Aside from recent results of the PRONOUNCE trial [70], no long-term studies have prospectively tracked the effect of ADT's short- and long-term effects on pre-existing CVD diseases and CVD risk factors or whether the distinct physiological effects of ADT alter cardiovascular-related prognosis. Given that CVD mortality is more likely than PCa [10], future investigations should expand prior studies and investigate the cardiovascular effects of short-term versus long-term ADT in men with pre-existing CVD conditions and whether there is a minimum exposure time that may affect cardiovascular risk factors negatively. Such evidence will help further understand if the duration of ADT is a critical determinant in mediating pre-existing CVD conditions and, therefore, increasing the risk of cardiovascular morbidity and mortality. In the interim, PCa clinicians may consider collecting prospective cardiovascular risk data by using the ABCDE (“awareness, aspirin, blood pressure, cholesterol, cigarette cessation, diet, diabetes mellitus and exercise”) approach outlined in the recent American Heart Association Scientific statement [184] as a prerequisite for men with pre-existing CVD initiating any type of ADT. Incorporating prospective cardiovascular monitoring may identify those men with an increased risk of developing cardiovascular events and potentially reduce the competing risks of non-cancer-related mortality observed in this population.

Several limitations are noteworthy and should be considered when interpreting the results of this review, and several factors that may partly explain the inconsistencies between the included studies

and the broader scientific evidence. First, the trials included in this review were primarily retrospective cohort study designs from similar databases, which resulted in study population overlap and mostly homogenous cardiovascular outcomes. Notably, an attempt to contact the corresponding authors for outcomes including myocardial infarction and stroke was made; however, they could not provide our team with the data required to perform the analyses. This precluded our ability to appropriately conduct a meta-analysis and estimate the mortality risk in the population. Second, as previously acknowledged, there were inconsistencies related to CVD definitions and reporting of cardiovascular outcomes across studies. Four of eleven studies [56, 57, 76, 77] used coding systems to extract or document pre-existing CVD and cardiovascular endpoints, whereas other studies used in-person consultations. Lastly, most participants included in this review were diagnosed with intermediate-risk disease and treated with neoadjuvant ADT (4-5 months in duration) with relatively short follow-up periods. In contrast, observational studies such as the Framingham Heart Study or the Whitehall II study are long-duration studies spanning ~40 years that prospectively examine cardiovascular incidence in the general population [93, 94]. These studies established that cardiovascular risk factors and conditions are likely to manifest for many years before becoming apparent [93, 94]. Finally, there was homogeneity related to participants (western populations only) and substantial heterogeneity related to ADT type and combinations of other treatments, such as radiation therapy, within the included studies. While there is emerging evidence to suggest in cancers other than PCa that radiation therapy may increase the risk of CVD and death [263, 264], radiation-induced CVD appears primarily linked to the volume of the myocardium irradiated, total radiation dose, and use of cardiotoxic chemotherapies such as anthracyclines. In contrast, ADT-treated men receiving radiation therapy may receive similar radiation doses; however, the anatomical landmarks related to the radiation field and the use of cardiotoxic treatments differ widely.

2.6. Conclusions

In conclusion, this systematic review synthesised the available evidence on whether pre-existing CVD increases the risk of all-cause mortality, cardiovascular mortality, and cardiovascular events in ADT-treated men. Men with existing chronic heart failure or prior myocardial infarction treated with neoadjuvant ADT appear to have a significant increased risk of all-cause mortality. In contrast, there is little and conflicting evidence to assess if pre-existing CVD affects the risk of cardiovascular mortality and cardiovascular events in ADT-treated men. While some associations are present, the results should be interpreted carefully as there is considerable heterogeneity in study

designs, methodology and documented analyses. Despite these limitations, we cannot exclude that the observational evidence continues to highlight the heightened risk of cardiovascular morbidity and mortality observed in this population, independent of pre-existing CVD. Future studies using prospective observational designs and RCTs should include patients with pre-existing CVD, more precise pre-existing CVD definitions, document and report ADT duration (short term vs long term) and incorporate more extended follow-up periods to understand further the influence of pre-existing CVD on cardiovascular morbidity and mortality in ADT-treated men. In the midst, clinicians may consider incorporating baseline cardiovascular risk screening for men commencing ADT in conjunction with broader multi-disciplinary team involvement.

Acknowledgments

"PC is the recipient of a Victorian Government Mid-Career Research Fellowship through the Victorian Cancer Agency."

Author contributions

Conceptualization AB, MB, EH and PC; data acquisition and extraction AB, JG; data analysis and interpretation, AB, EZ, MB, EH and PC; data preparation and drafting of manuscript AB; critical revisions and final approval AB, EZ, JG MB, EH and PC.

Ethical declarations

Conflict of interest

"PC is the Founder and Director of EX-MED Cancer Ltd, a not-for-profit organization that provides exercise medicine services to people with cancer. PC is the Director of Exercise Oncology EDU Pty Ltd, a company that provides fee-for-service training courses to upskill exercise professionals in delivering exercise to people with cancer."

Supplementary Table s2.1: Methodological quality of included cohort studies according to the Newcastle-Ottawa quality assessment scale

	Selection				Comparability	Outcome			Score†
Reference	**Representativeness of the exposed cohort**	**Selection of the non-exposed cohort**	**Ascertainment of the exposure**	**Demonstration that outcome of interest was not present at the start of the study***	**Comparability of cohorts based on the design or analysis (i.e., age or other confounders) ******	**Assessment of primary outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow-up of cohorts**	
Hayes et al.[73]	+	+	+	-	+	+	+	+	7
Haque et al. [56]	+	+	+	+	++	+	+	+	9
Jespersen et al.[76]	+	+	+	+	+	+	+	+	8
Keating et al. [57]	+	+	+	+	++	+	-	+	8
Nanda et al. [75]	+	+	+	-	+	+	+	+	7
Nanda et al. [74]	+	+	+	-	+	+	+	+	7
Nguyen et al. [71]	+	+	+	-	+	+	+	+	7
Nguyen et al. [59]	+	+	+	-	+	+	+	+	7
Parekh et al. [55]	+	+	+	-	+	+	+	+	7
Van Hemelrijck et al. [77]	+	-	+	+	+	+	+	+	7
Ziehr et al.[72]	+	+	+	-	+	+	+	+	7

Note: * -"The presence of disease/incident at the beginning of the study does not earn a star (Newcastle Ottawa scale manual [259])."
**A maximum of 2 stars can be allotted in this category, one for the most critical factors (age) and two for other important confounders (e.g., cardiovascular confounders).
†A study was high quality if it achieved >7 points."

Supplementary Table s2.2: Search terms

	Cardiovascular disease	Prostate cancer	Androgen Deprivation therapy	Mortality	Cardiovascular events
TITLE/ABSTRACT TERMS MEDLINE CINAHL EMBASE WEB OF SCIENCE SCOPUS	TI ("cardio-vascular disease*" OR "cardiovascular disease*" OR diabet* OR cholesterol OR "vascular malformations" OR hypotension OR hypertension OR "myocardial ischaemia" OR "myocardial ischemia" OR "cardiac output" OR "heart output" OR "heart valve disease*" OR "heart disease*" OR "ischemic heart disease*" OR "myocardial disease*" OR "valvular heart disease*" OR "heart muscle ischemia" OR cardiomyopath* OR "congestive heart failure" OR "angina pectoris" OR "coronary disease*" OR "coronary artery disease" OR "vascular disease*" OR "ventricular dysfunction" OR "heart ventricle function") OR AB ("cardio-vascular disease*" OR "cardiovascular disease*" OR diabet* OR cholesterol OR "vascular malformations" OR hypotension OR hypertension OR "myocardial ischaemia" OR "myocardial ischemia" OR "cardiac	TI ((prostat*) N3 (cancer* OR neoplasm* OR oncolog* OR tumor* OR tumour*)) OR AB ((prostat*) N3 (cancer* OR neoplasm* OR oncolog* OR tumor* OR tumour*))	TI ("androgen deprivation therap*" OR "androgen deprivation" OR "hormone therap*" OR "androgen suppression" OR "hormone suppression" OR "hormone ablation" OR hypo-gonadism OR hypogonadism OR "low testosterone" OR zolodex OR luprin) OR AB ("androgen deprivation therap*" OR "androgen deprivation" OR "hormone therap*" OR "androgen suppression" OR "hormone suppression" OR "hormone ablation" OR hypo-gonadism OR hypogonadism OR "low testosterone" OR zolodex OR luprin)	TI (death* OR die OR dead OR fatal* OR "fatal outcome" OR mortality OR died OR "sudden cardiac death" OR "cancer mortality" OR "cardiovascular mortality" OR "premature mortality" OR "hospital mortality" "cause of death") OR AB (death* OR die OR dead OR fatal* OR "fatal outcome" OR mortality OR died OR "sudden cardiac death" OR "cancer mortality" OR "cardiovascular mortality" OR "premature mortality" OR "hospital	TI ("myocardial infarct*" OR arryhthmi* OR "heart arrhythmi*" OR "cardiac arrhythmi" OR angina OR stroke* OR "cerebro-vascular accident*" OR "cerebrovascular accident*" OR CVA OR "vascular dysfunction" OR "tachycardia" OR "myocardial ischemia" OR "myocardial ischemia" OR "heart infarction" OR "acute coronary syndrome" OR "sudden cardiac death" OR cardiotoxicit* OR "heart death*" OR "heart ventricle fibrillation" OR "heart infarct*" OR "heart failure*" OR "acute heart failure" OR "diastolic dysfunction*" OR "heart ventricle failure" OR "systolic dysfunction*" OR "heart ventricle function" OR hypertension OR hypotension OR cardiomyopath* OR "coronary artery disease" OR "long QT syndrome") AB ("myocardial infarct*" OR arryhthmi* OR "heart arrhythmi*" OR "cardiac arrhythmi" OR angina OR stroke* OR "cerebro-vascular accident*" OR "cerebrovascular accident*" OR CVA

	output" OR “heart output” OR “heart valve disease*” OR “heart disease*” OR “ischemic heart disease*” OR “myocardial disease*” OR “valvular heart disease*” OR “heart muscle ischemia” OR cardiomyopath* OR “congestive heart failure” OR “angina pectoris” OR “coronary disease*” OR “coronary artery disease” OR “vascular disease*” OR “ventricular dysfunction” OR “heart ventricle function”) TI ((heart OR coronary OR vascular) N3 (fail* OR attack* OR disease* OR arrest) OR AB (heart OR coronary OR vascular) N3 (fail* OR attack* OR disease* OR arrest))			mortality” "cause of death")	OR "vascular dysfunction" OR “heart arrhythmi*”OR "tachycardia" OR "myocardial ischaemia" OR “myocardial ischemia” OR “heart infarction” OR "acute coronary syndrome" OR “sudden cardiac death” OR cardiotoxicit* OR “heart death*” OR “heart ventricle fibrillation” OR “heart infarct*” OR “heart failure*” OR “acute heart failure” OR “diastolic dysfunction*” OR “heart ventricle failure” OR “systolic dysfunction*” OR “heart ventricle function” OR hypertension OR hypotension OR cardiomyopath* OR “coronary artery disease” “long QT syndrome”)
MEDLINE/CINAHL MeSH terms	(MH “Cardiovascular Diseases”) OR (MH "Vascular Malformations) OR (MH "Cardiac Output, High") OR (MH "Cardiac Output, Low") (MH Cardiac output) OR (MH "Heart Valve Diseases+") OR (MH "Myocardial Ischemia+") OR (MH "Angina Pectoris+") OR (MH "Coronary Disease+”) ((MH “Cardiac output”)OR (MH "Ventricular Dysfunction+") OR (MH "Vascular Diseases")	(MH "Prostatic Neoplasms")	(MH "Hypogonadism")	(MH "Mortality") OR (MH "Mortality, Premature") OR (MH "Hospital Mortality") OR (MH "Cause of Death") OR (MH "Fatal Outcome") OR (MH "Death") OR (MH "Death, Sudden, Cardiac")	(MH "Death, Sudden, Cardiac") OR (MH "Heart Failure+") OR (MH "Tachycardia") OR (MH "Ventricular Fibrillation") OR (MH "Long QT Syndrome+") OR (MH "Arrhythmias, Cardiac+") OR (MH "Myocardial Infarction+") OR (MH "Hypertension+") (MH "Cardiomyopathies) OR (MH "Hypotension")

EMBASE **MeSH terms**	heart disease/ OR cardiovascular disease/ OR ischemic heart disease/ OR myocardial disease/ OR valvular heart disease/ OR heart output OR cardiomyopathy OR congestive heart failure/ OR heart muscle ischemia/ OR angina pectoris/ OR coronary artery disease/ OR heart ventricle function/ OR vascular disease/	prostate tumor/ OR prostate cancer/	androgen deprivation therapy/ OR hypogonadism/	cancer mortality/ OR cardiovascular mortality/	cardiotoxicity/ OR heart death/ OR heart arrhythmia OR long QT syndrome OR tachycardia OR heart ventricle fibrillation OR sudden cardiac death/ OR heart infarction OR heart failure OR acute heart failure/ OR diastolic dysfunction/ OR heart ventricle failure/ OR systolic dysfunction OR hypertension/ OR hypotension/ OR coronary artery disease/

CHAPTER THREE: The effect of exercise training on cardiometabolic health in men with prostate cancer receiving androgen deprivation therapy.

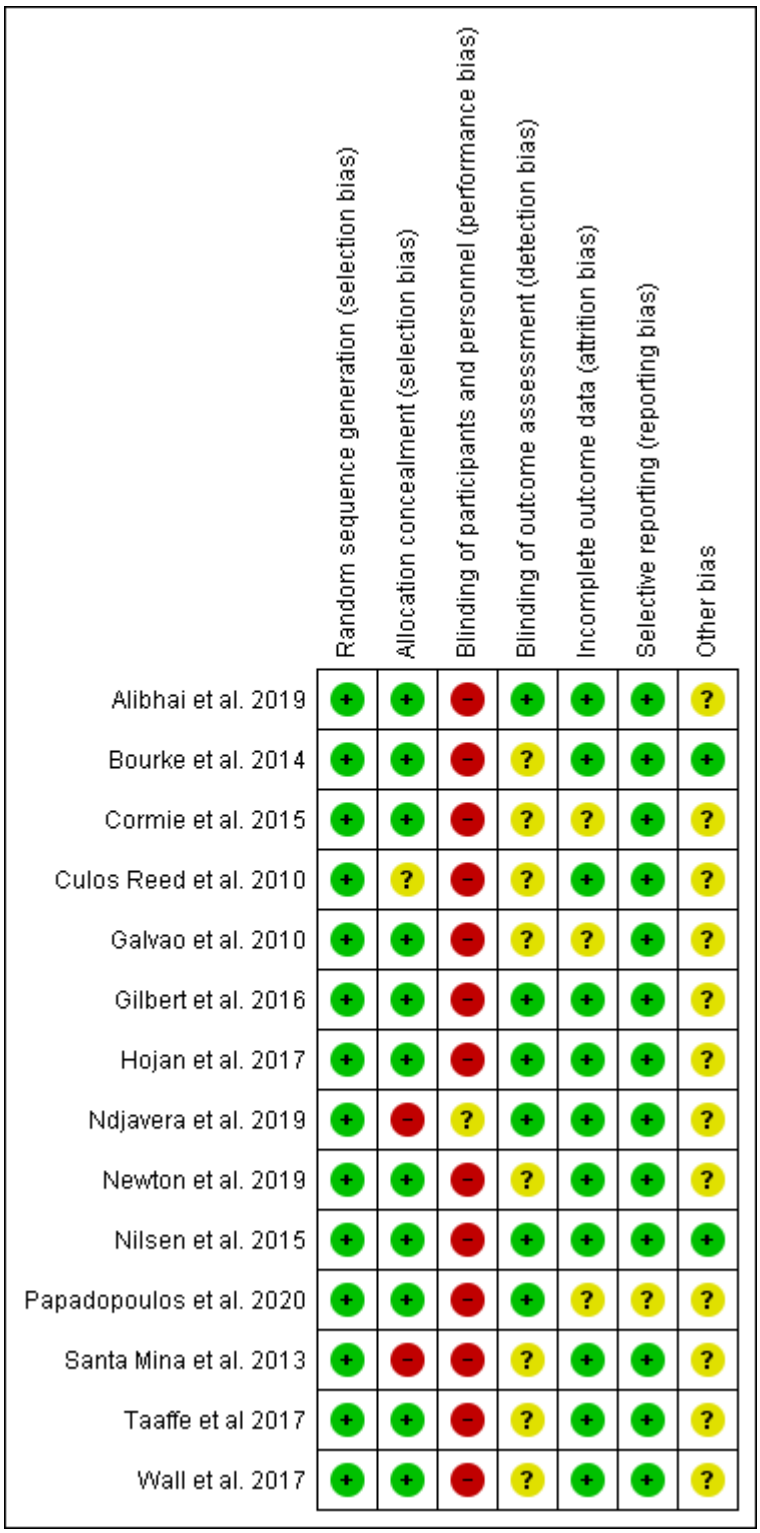
3. Overview

This section comprehensively synthesises the available evidence on the "effect of exercise training on cardiometabolic health in men with PCa receiving ADT" through a *published systematic review and meta-analysis*.

Bigaran A, Zopf E, Gardner J, La Gerche A, Murphy DG, Howden EJ, et al. The effect of exercise training on cardiometabolic health in men with prostate cancer receiving androgen deprivation therapy: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2021;24(1):35-48. DOI: 10.1038/s41391-020-00273-5

Appendix I

Figure 1: Risk of bias of the included studies according to the Cochrane Collaboration tool



Appendix II

Table 2: Search terms for MEDLINE database

Literature search strategies. Medical subject headings were developed using the following terms: prostate neoplasms, hypogonadism, exercise training and cardiometabolic health. For SCOPUS and WEB of SCIENCE, the search was restricted to articles involving human trials

	Prostate cancer	Androgen deprivation therapy	Exercise	Cardiometabolic health
Title/Abstract terms MEDLINE	TI ((prostat*) N3 (cancer* OR neoplasm* OR oncolog* OR tumor* OR tumour*)) OR AB ((prostat*) N3 (cancer* OR neoplasm* OR oncolog* OR tumor* OR tumour*))	TI ("androgen deprivation therap*" OR “androgen deprivation” OR “androgen suppression” OR “hormone suppression” OR “hormone ablation " OR hypo-gonadism OR hypogonadism OR "low testosterone" OR zolodex OR luprin) OR AB ("androgen deprivation therap*" OR "hormone therap*" OR hypo-gonadism OR hypogonadism OR "low testosterone" OR zolodex OR luprin)	TI (exercis* OR "physical activit*" OR aerobic OR fitness OR fit OR sport* OR swim* OR run OR runner* OR running OR jog OR jogging OR jogger* OR cycle OR cycling OR cyclist* OR walk* OR “physical endurance” OR “therapeutic exercise” OR “kinesiotherapy” OR “weight lifting" OR "strength training" OR "resistance training") AB (exercis* OR "physical activit*" OR aerobic OR fitness	TI (heart* OR coronary* OR cardio* OR cardiac* OR angiocardio* OR angio-cardio* OR "exercise test" OR "walk test" OR "peak oxygen consumption" OR "maximal oxygen consumption" OR "exercise capacity" OR echocardiograph* OR electrocardiograph* OR submaximal OR sub-maximal OR maximal OR "flow mediated dilatation" OR "flow-mediated dilatation" OR FMD

		OR fit OR sport* OR swim* OR run OR runner* OR running OR jog OR jogging OR jogger* OR cycle OR cycling OR cyclist* OR walk* OR “physical endurance” OR “therapeutic exercise” OR “kinesiotherapy” OR “weight lifting" OR "strength training" OR "resistance training")	OR "vascular function" OR "arterial stiffness" OR “cardiopulmonary exercise testing” OR “V˙O2max” OR cholesterol OR dyslipidaemia OR hyperlipidaemia OR hypertension OR HDL OR LDL OR “low-density lipoprotein” OR “high-density lipoprotein” OR "blood pressure" OR diabet* OR pre-diabetic OR glucose OR "body composition" OR "body fat" or adipose OR “weight gain” OR "lean muscle mass" OR DEXA OR “dual energy x-ray” OR "body mass index" OR BMI OR "waist circumference" OR waist OR weight OR inflammation OR "c-

		reactive protein*" OR interleukin-6 OR “waist-height-ratio” OR “body weight” OR testosterone OR hemoglobin OR haemoglobin) OR AB (heart* OR coronary* OR cardio* OR cardiac* OR angiocardio* OR angio-cardio* OR "exercise test" OR "walk test" OR "peak oxygen consumption" OR "maximal oxygen consumption" OR "exercise capacity" OR echocardiograph* OR electrocardiograph* OR submaximal OR sub-maximal OR maximal OR "flow mediated dilation" OR "flow-mediated dilation" OR FMD OR "vascular function" OR "arterial

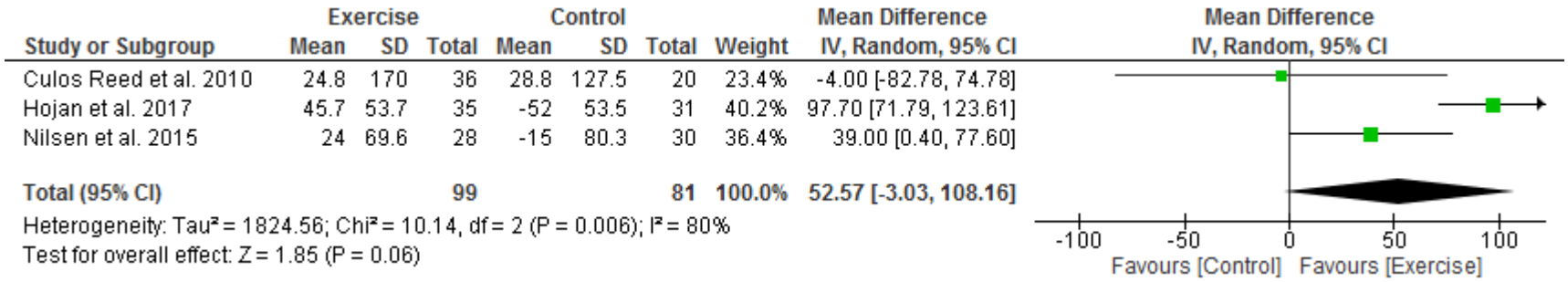
		stiffness" OR “cardiopulmonary exercise testing” OR “V˙O2max” OR cholesterol OR dyslipidaemia OR hyperlipidaemia OR hyperlipidaemia OR hypertension OR “HDL” OR “LDL” OR “low-density lipoprotein” OR “high-density lipoprotein” OR "blood pressure" OR diabet* OR pre-diabetic OR glucose OR "body composition" OR "body fat" OR adipose OR “weight gain” OR "lean muscle mass" OR DEXA” OR “dual energy x-ray” OR "body mass index" or BMI or "waist circumference" OR waist OR weight OR inflammation

				OR "c-reactive protein*" OR "interleukin-6 OR “waist-height-ratio” OR “Body Weight” OR testosterone OR hemoglobin OR haemoglobin))
MEDLINE MeSh terms	(MH "Prostatic Neoplasms")	(MH "Hypogonadism")	(MH "Exercise+") OR (MH "Exercise Test") OR (MH "Exercise Therapy") OR (MH "Exercise Tolerance") OR (MH "Physical Fitness") OR (MH "Sports")	(MH "Exercise Test+") OR (MH "Heart Function Tests+") OR (MH "Echocardiography") OR (MH "Electrocardiography")

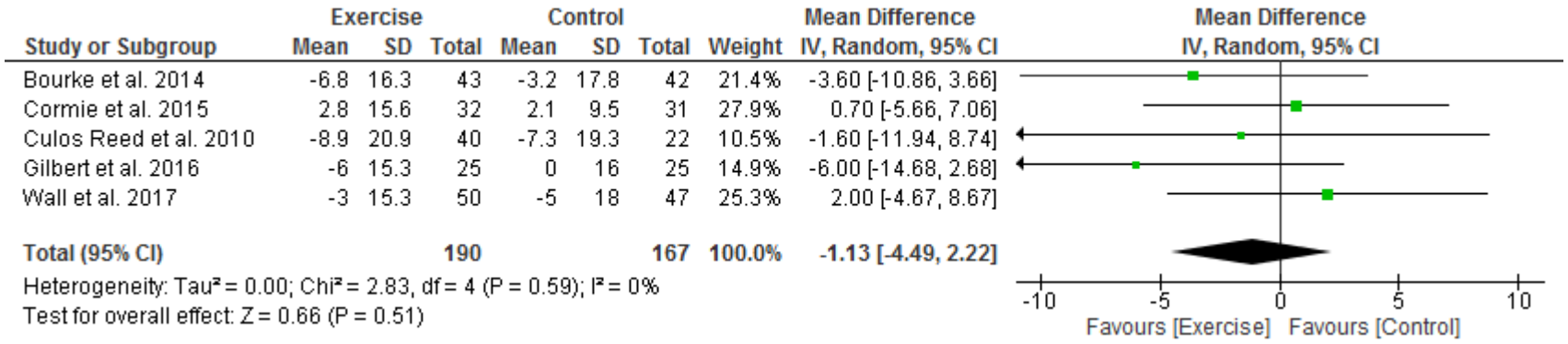
Appendix III

Figure 2: Forest plots (A-I) of randomised controlled trials observing non-significant effects following exercise training

(A) 6-minute walk test (metres)



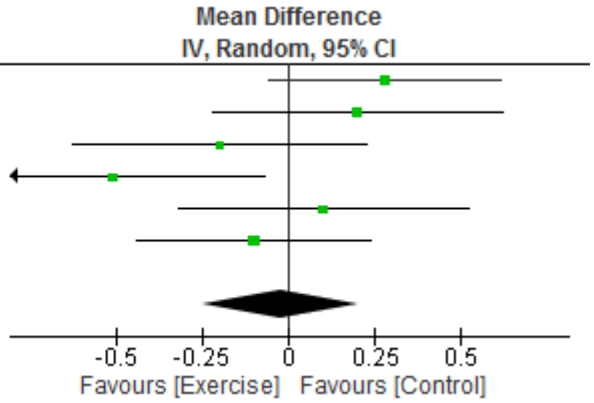
(B) Systolic blood pressure (mmHg)



(C) Total cholesterol (mmol/L)

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Cormie et al. 2015	0.31	0.79	32	0.03	0.55	31	19.4%	0.28 [-0.06, 0.62]
Galvao et al. 2010	0.1	0.88	29	-0.1	0.73	28	15.7%	0.20 [-0.22, 0.62]
Gilbert et al. 2016	-0.1	0.88	25	0.1	0.65	25	15.3%	-0.20 [-0.63, 0.23]
Hojan et al. 2017	-0.14	0.86	35	0.37	0.96	31	14.8%	-0.51 [-0.95, -0.07]
Ndjavera et al. 2019	0.2	0.74	24	0.1	0.78	26	15.6%	0.10 [-0.32, 0.52]
Wall et al. 2017	0.2	0.86	50	0.3	0.85	47	19.2%	-0.10 [-0.44, 0.24]
Total (95% CI)			**195**			**188**	**100.0%**	**-0.02 [-0.25, 0.20]**

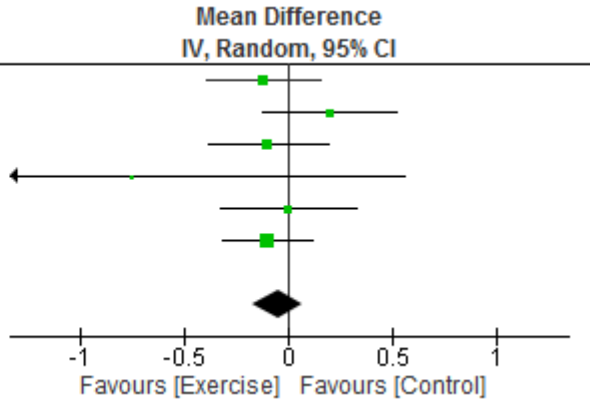
Heterogeneity: Tau² = 0.04; Chi² = 10.04, df = 5 (P = 0.07); I² = 50%
Test for overall effect: Z = 0.21 (P = 0.84)



(D) Low-density lipoprotein (mmol/L)

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Cormie et al. 2015	0.12	0.61	32	0.24	0.48	31	20.6%	-0.12 [-0.39, 0.15]
Galvao et al. 2010	0	0.7	29	-0.2	0.53	28	14.6%	0.20 [-0.12, 0.52]
Gilbert et al. 2016	0.1	0.51	25	0.2	0.53	25	18.1%	-0.10 [-0.39, 0.19]
Hojan et al. 2017	0.05	0.77	35	0.8	3.65	31	0.9%	-0.75 [-2.06, 0.56]
Ndjavera et al. 2019	0.1	0.6	24	0.1	0.59	26	13.8%	0.00 [-0.33, 0.33]
Wall et al. 2017	0	0.53	50	0.1	0.56	47	32.0%	-0.10 [-0.32, 0.12]
Total (95% CI)			**195**			**188**	**100.0%**	**-0.05 [-0.18, 0.07]**

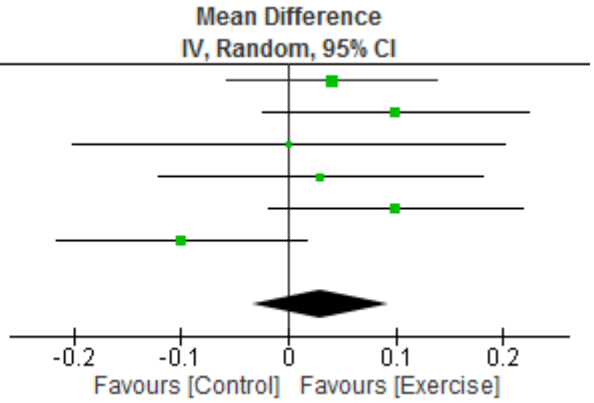
Heterogeneity: Tau² = 0.00; Chi² = 4.08, df = 5 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.40)



(E) High-density lipoprotein (mmol/L)

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Cormie et al. 2015	0.11	0.21	32	0.07	0.19	31	23.3%	0.04 [-0.06, 0.14]
Galvao et al. 2010	0	0.24	29	-0.1	0.24	28	17.5%	0.10 [-0.02, 0.22]
Gilbert et al. 2016	0	0.32	25	0	0.4	25	8.5%	0.00 [-0.20, 0.20]
Hojan et al. 2017	-0.02	0.25	35	-0.05	0.36	31	13.3%	0.03 [-0.12, 0.18]
Ndjavera et al. 2019	0.1	0.22	24	0	0.21	26	18.5%	0.10 [-0.02, 0.22]
Wall et al. 2017	0	0.29	50	0.1	0.3	47	18.9%	-0.10 [-0.22, 0.02]
Total (95% CI)			**195**			**188**	**100.0%**	**0.03 [-0.03, 0.09]**

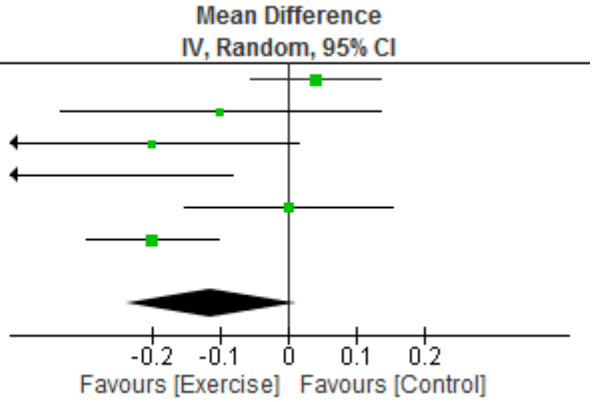
Heterogeneity: Tau² = 0.00; Chi² = 7.35, df = 5 (P = 0.20); I² = 32%
Test for overall effect: Z = 0.93 (P = 0.35)



(F) Triglycerides (mmol/L)

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Cormie et al. 2015	0.13	0.2	32	0.09	0.19	31	22.7%	0.04 [-0.06, 0.14]
Galvao et al. 2010	0.1	0.31	29	0.2	0.56	28	13.6%	-0.10 [-0.34, 0.14]
Gilbert et al. 2016	-0.3	0.31	25	-0.1	0.45	25	14.8%	-0.20 [-0.41, 0.01]
Hojan et al. 2017	-0.14	1.06	35	0.34	0.53	31	7.2%	-0.48 [-0.88, -0.08]
Ndjavera et al. 2019	0	0.27	24	0	0.28	26	18.9%	0.00 [-0.15, 0.15]
Wall et al. 2017	0.1	0.22	50	0.3	0.26	47	22.8%	-0.20 [-0.30, -0.10]
Total (95% CI)			**195**			**188**	**100.0%**	**-0.11 [-0.24, 0.01]**

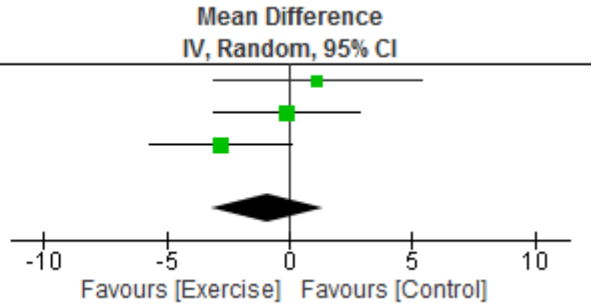
Heterogeneity: Tau² = 0.02; Chi² = 18.07, df = 5 (P = 0.003); I² = 72%
Test for overall effect: Z = 1.79 (P = 0.07)



(G) Insulin (mU/L)

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Cormie et al. 2015	1.12	9.06	32	-0.02	8.22	31	22.3%	1.14 [-3.13, 5.41]
Galvao et al. 2010	0.8	6.02	29	0.9	5.43	28	37.8%	-0.10 [-3.07, 2.87]
Wall et al. 2017	0.4	4.34	50	3.2	9.06	47	39.9%	-2.80 [-5.66, 0.06]
Total (95% CI)			**111**			**106**	**100.0%**	**-0.90 [-3.15, 1.35]**

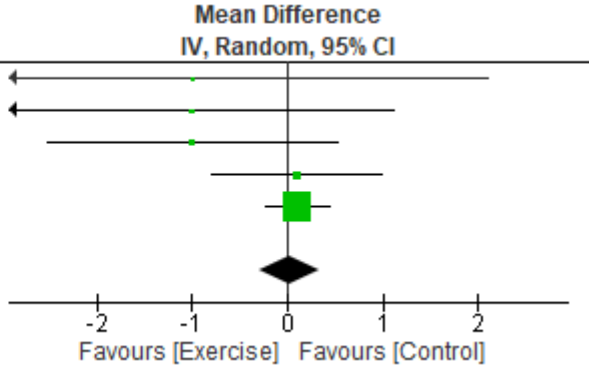
Heterogeneity: Tau² = 1.19; Chi² = 2.84, df = 2 (P = 0.24); I² = 30%
Test for overall effect: Z = 0.78 (P = 0.43)



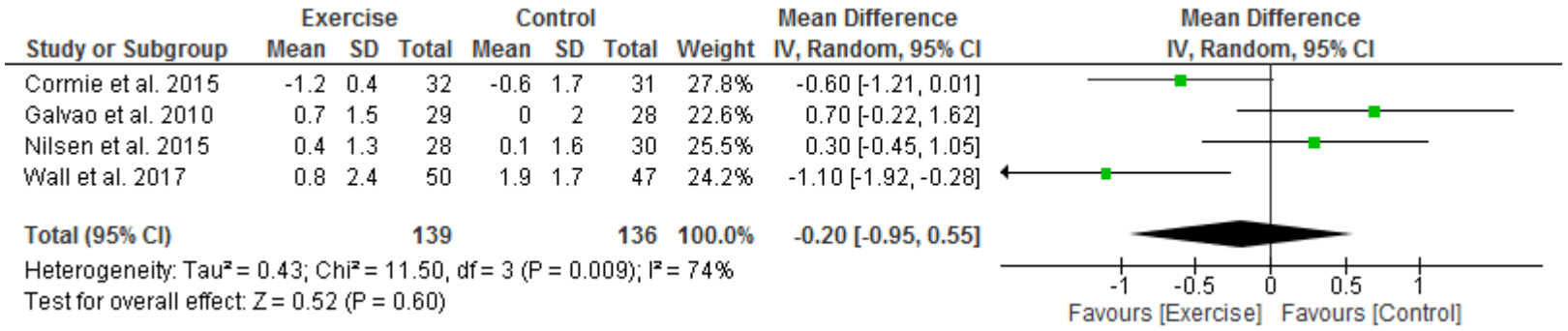
(H)) Body mass index (kg/m^{-2})

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Bourke et al. 2014	-0.8	6.8	44	0.2	7.8	42	1.0%	-1.00 [-4.10, 2.10]
Culos Reed et al. 2010	-0.2	1	41	0.8	5	22	2.1%	-1.00 [-3.11, 1.11]
Gilbert et al. 2016	-0.8	2.7	25	0.2	2.8	25	4.1%	-1.00 [-2.52, 0.52]
Hojan et al. 2017	0.1	1.8	35	0	1.9	31	11.7%	0.10 [-0.80, 1.00]
Nilsen et al. 2015	0.1	0.8	30	0	0.5	28	81.1%	0.10 [-0.24, 0.44]
Total (95% CI)			**175**			**148**	**100.0%**	**0.02 [-0.29, 0.33]**

Heterogeneity: Tau² = 0.00; Chi² = 3.27, df = 4 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)



(I) Whole body total mass (kilograms)



Study or Subgroup	Exercise Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cormie et al. 2015	-1.2	0.4	32	-0.6	1.7	31	27.8%	-0.60 [-1.21, 0.01]
Galvao et al. 2010	0.7	1.5	29	0	2	28	22.6%	0.70 [-0.22, 1.62]
Nilsen et al. 2015	0.4	1.3	28	0.1	1.6	30	25.5%	0.30 [-0.45, 1.05]
Wall et al. 2017	0.8	2.4	50	1.9	1.7	47	24.2%	-1.10 [-1.92, -0.28]
Total (95% CI)			**139**			**136**	**100.0%**	**-0.20 [-0.95, 0.55]**

Heterogeneity: Tau² = 0.43; Chi² = 11.50, df = 3 (P = 0.009); I² = 74%

Test for overall effect: Z = 0.52 (P = 0.60)

Mean Difference
IV, Random, 95% CI

-1 -0.5 0 0.5 1

Favours [Exercise] Favours [Control]

3.1. Summary and linking section.

Overall, the findings from *Chapters One* and *Two* highlighted that CVD is a significant public health issue among men commencing ADT and in ADT-treated men. The evidence presented in *Chapter One* suggests that mortality is more likely from CVD than PCa [53, 218], particularly in those with pre-existing CVD [41]. However, the available methods to detect changes in cardiovascular risk status do not fully explain the heightened epidemiological increases in cardiovascular events, all-cause and cardiovascular mortality observed in this population [52]. It could be theorised that the currently available methods used to assess cardiovascular risk may not accurately reflect the mechanistic pathway from risk factors to cardiovascular events, therefore providing an avenue for future investigative studies focused on markers of subclinical CVD. Moreover, exercise training is a well-known management strategy for mitigating the widely documented adverse effects of ADT [244, 245, 265]; however, the effect of exercise training on cardiometabolic health has yet to be systematically evaluated. The results of *Chapter Three* (as described in *Chapter One*) found that "exercise training (combined aerobic and resistance exercise training interventions, or standalone) improved some but not all markers of cardiometabolic health among ADT-treated men [243]." While the reason for this could be partly explained by substantial clinical and methodological heterogeneity, it may be possible that the exercise interventions, specifically aerobic exercise training intensities, were insufficient to mitigate markers of cardiometabolic health in ADT-treated men. While we acknowledge that the search and results of *Chapter Three* were published over two years ago, recent evidence [266, 267] has offered similar conclusions in that evidence for the effect of exercise training on cardiovascular and metabolic health remains limited. Recognising the foregoing and accepting that ADT-treated men are likely to be at a high risk of CVD (*Chapters One, Two and Three),* given the profound effects of severe hypogonadism, there are no clear strategies to identify and prevent the cardiovascular and metabolic effects of ADT in men with PCa across the scientific literature. Therefore, this thesis focuses on a proposed strategy to assess cardiovascular health (*Chapter Five*) and prevent the cardiovascular effects of ADT (*Chapter Six*) in men with PCa. The following Chapters will describe the methodological approach of the two experimental studies presented in *Chapters Five* and *Six*.

CHAPTER FOUR: General Methods

4. Overview

This Chapter provides the methodological details for the measures used in two experimental studies. The first experimental chapter (*Chapter Five*) details a cross-sectional study that evaluated markers of vascular health in men with PCa commencing ADT compared to age-matched controls. This study also examined the relationship between cardiorespiratory fitness, cardiac structure and function, vascular health, traditional CVD markers and body composition in all participants, as these factors increase CVD risk. The second experimental chapter (*Chapter Six*) details a three-month randomised controlled trial that evaluated the impact of exercise training on cardiac remodelling compared to usual care control in a cohort of men with PCa commencing ADT. Outcomes were cardiac remodelling, resting cardiovascular function and cardiorespiratory fitness in men with PCa.

Given the similarities in methods between the two aforementioned studies and the same PCa cohort was used for both the cross-sectional study and randomised controlled trial, methodological procedures are provided in detail within this chapter and only briefly in *Chapters Five and Six*.

4.1. MethodologyOverview of study design for Chapter Five

The methodological processes and procedures for study three *(Chapter Five)* are presented in Figure 4.1. Study three (*Chapter Five*) evaluated measures of vascular health in men with PCa commencing ADT compared to an age-matched control group. Additionally, the relationship between cardiorespiratory fitness (quantified by VO_2peak), cardiac structure and function, vascular health, traditional CVD risk factors, and body composition were evaluated in all participants to examine further which variables correlated with cardiorespiratory fitness. Data was collected between 2019 and 2021 at Australian Catholic University and the Baker Institute (Melbourne, Australia), parallel with the randomised controlled trial presented in *Chapter Six.*

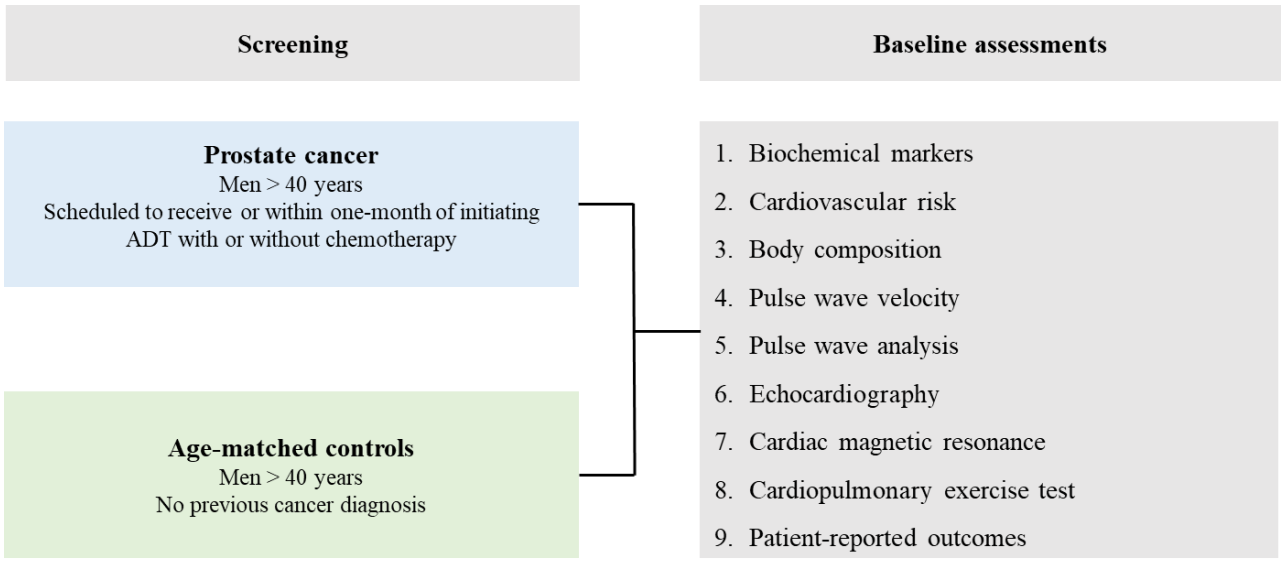


Figure 4.1: Cross-sectional study design and protocol for the study presented in *Chapter Five*.

4.1.2. Overview of study design for Chapter Six

Study four evaluated the effect of exercise training on cardiac remodelling in men with PCa receiving ADT as part of the EX-HEART trial conducted at Australian Catholic University and the Baker Institute (Melbourne, Australia; Figure 4.2 – Chapter Six). This two-arm randomised controlled trial aimed to evaluate whether a three-month combined aerobic and resistance exercise training program initiated at the commencement of ADT could attenuate cardiac remodelling, cardiac dysfunction, and cardiorespiratory fitness compared to usual care control. In brief, men aged 40 years and older with histologically confirmed PCa and scheduled to receive or within one month of initiating ADT with or without chemotherapy were included. Participants attended a comprehensive series of cardiovascular assessments at baseline and three months. Following baseline assessments, men with PCa were randomly assigned to exercise training or usual care control for three months using a 1:1 group allocation method. Participants were stratified by age ≥ 68 years or < 68 years old.

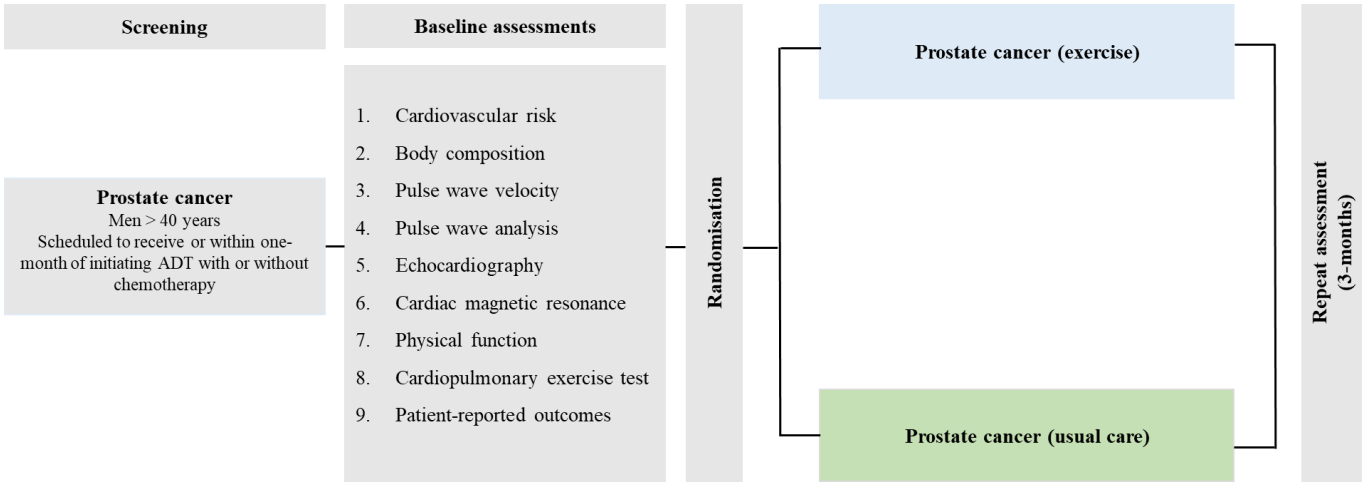


Figure 4.2: Randomised controlled trial design and protocol for the study presented in *Chapter Six*

It is important to note that the PhD candidate made significant contributions to the cross-sectional study and RCT and performed the majority of the baseline and post-outcome measurements, including blood collection (venepuncture & blood processing), body composition (DXA), arterial stiffness (cfPWV, PWA), CPET, CMR analysis, physical function, and exercise training sessions for all participants with assistance from the respective research teams.

4.2. Outcome measures

Participant preparation

A tabulated summary of the methodology included in this thesis is presented in Table 4.1. All participants reported to the laboratory for blood collection after an overnight fast (minimum of 12 hours). In addition, participants were required to be voided for body composition assessments. Before each assessment session, all participants were advised to abstain from caffeine, alcohol, and strenuous physical activity for 24 hours. Participants were contacted 24 hours before the assessment session and completed a questionnaire (located on the paper-based data collection sheet), denoting whether or not they adhered to the pre-testing control procedures. Participants completed clinical and demographical questionnaires before attending the assessment session, and the research staff reviewed each questionnaire.

4.2.1. Blood biochemical markers

Blood sample collections were standardised according to the Australian Laboratory standards and collected in a fasted state on the morning of each assessment session. Approximately 15 mL of blood was collected using ethylenediaminetetraacetic acid (EDTA), serum and heparin tubes to measure serum lipid markers (total cholesterol, low-density lipoprotein, high-density lipoprotein, non-high-density lipoprotein, triglycerides,), fasting blood glucose and inflammatory markers (C-reactive protein). EDTA blood samples (3 mL) were centrifuged (AWEL-MF-20R Centrifuge) immediately following blood collection for 10 minutes in order to obtain plasma samples. Alternatively, serum blood samples were rested at room temperature for 30 minutes before centrifuging. All samples were transferred by pipette to Eppendorf tubes and stored at -80°C for subsequent batched analysis. All samples were analysed by Alfred Health NATA Accredited Pathology laboratory per the Australian laboratory standards.

4.2.2. Cardiovascular risk

Cardiovascular risk was determined by the Australian Absolute Cardiovascular Risk Calculator [268], which uses the Framingham Heart Study cardiovascular risk equation [269]. The Framingham risk score algorithm is a widely accepted and validated cardiovascular risk profile tool that includes age, gender, systolic blood pressure, smoking status, total cholesterol, high-density lipoprotein, diabetes diagnosis (self-reported) and whether the patient has established LV hypertrophy (confirmed by electrocardiogram) to estimate cardiovascular risk, as a percentage

[269]. Higher percentage scores (>15%) are categorised as high cardiovascular risk [269]. Older adults >74 years and individuals with diabetes mellitus are automatically categorised as high cardiovascular risk [268].

4.2.3. Body composition

Whole-body total mass (kilograms, kg), lean mass (kg), fat mass (kg), trunk fat mass (kg), whole-body fat percentage (%), regional fat mass (kg) and fat-free mass (kg) were assessed by dual-energy x-ray absorptiometry (DXA) (eCore CoreScan software version 16, Lunar iDXA, GE Lunar Corp, Madison, Wisconsin, United States of America). DXA is a capable and cost-effective body composition assessment with relatively high precision (whole-body lean mass and fat mass coefficient of variation [CV] range, 3-6%) compared to gold standard approaches such as the four-compartment model. Height and weight were measured by standard anthropometry before initiating the assessment. Participants were instructed to lay supine and were positioned in the centre of the imaging bed (spine in line with the centre line and the participant's head positioned three centimetres below the horizontal line). Each participant was instructed to rest quietly and remain still for the duration of the body composition scan of 10-15 minutes. A researcher analysed each DXA scan following each examination per standard procedures and recommendations [270]. The researcher analysing each DXA scan was not blinded to group assignment due to limited resources. The technologist's short-term CV for repeated measures (baseline and three-months via the Lunar iDXA) of whole-body lean and fat mass in a sample of ten aged-matched controls was between 1-4%. Our CV is consistent with other trials using a Lunar iDXA in similar cohorts of ADT-treated men and healthy controls [271, 272]. Due to the impact of the COVID-19 pandemic on the original testing location, Australian Catholic University, and the inability to restart the trial at this site, the Baker Institute Lunar iDXA (same make/model) was used for the remainder of the study.

4.2.4. Resting cardiovascular function

All resting cardiovascular function assessments, including arterial stiffness, central blood pressure and AIx, echocardiogram, and CMR imaging, were performed in a dark, temperature-controlled quiet room and repeated within four hours across all timepoints. Of note, the supervising radiographer screened all participants for CMR eligibility prior to initiating the scan.

4.2.5. Arterial stiffness

Arterial stiffness was evaluated using applanation tonometry (SphygmoCor CvMS, ATCOR, Sydney, Australia) to measure cfPWV. cfPWV is a validated non-invasive method for measuring arterial stiffness [273], with a high degree of precision (r>0.90) [195, 199, 200], excellent reproducibility (CV: <5%) [201] and repeatability (CV: 4.7-10.5%) in elderly patients and those with chronic renal disease [195, 274]. All measurements were duplicated in accordance with standardised procedures and recommendations [130, 196]. Participants were instructed to lay quietly (supine) and rest for 20 minutes. Following rest, a gated three-lead electrocardiogram (ECG) was placed on the patient to record heart rate and pulse wave recordings [130, 183]. An automated blood pressure device (HEM-7320, Omron Corp, Kyoto, Japan) was placed on the dominant arm and recorded following each measurement (in duplicate). Carotid and femoral pulse sites were located and marked, and the distances between each site were measured using a measuring tape. Two distances determined the arterial length: 1) transcutaneous distance between the carotid pulse site and sternal notch and 2) measuring the distance between the sternal notch and the femoral pulse site. In order to determine cfPWV, a separate recording was taken from each of the carotid and femoral pulse sites using the tonometer. The measurement was acquired by gently placing the handheld tonometer over each pulse site and slowly adjusting it until the strongest pulse was detected. Each measurement was recorded for 10 seconds (equating to 10 cardiac cycles) [130, 196]. Following each measurement, resting brachial blood pressure and the arterial length distances between the carotid and femoral pulse sites were recorded and entered into the Sphygmocor system [130, 196]. All data were analysed immediately via the Sphygmocor software system. The technologist's short-term CV for repeated measures of cfPWV in a sample of ten aged-matched controls was approximately 4%.

4.2.6. Central blood pressure and augmentation index

Pulse wave analysis (SphygmoCor CvMS, AtCor, Sydney, Australia) via radial artery applanation tonometry was performed and calibrated with brachial blood pressure to estimate central blood pressure and derive the AIx [196, 275]. Pulse wave analysis possesses a higher degree of precision (intraclass correlation: 0.97) [195, 199, 200], reproducibility (CV: 5-8.4%) [201] and repeatability (CV: 15-25%) in chronic disease populations [195, 274]. Following the cfPWV measurement, the participant's limb was repositioned to perform radial artery applanation tonometry. The handheld tonometer was gently placed over the radial artery and repositioned until the strongest radial

waveform was detected [183, 196]. The SphygmoCor system uses radial tonometry to record the peripheral arterial pressure waveform from the radial artery. A validated generalised transfer function is applied via the SphygmoCor system to reconstruct the central aortic pressure waveform [201, 275]. Ten consecutive radial artery waveforms (in line with the SphygmoCor system) were recorded in duplicate and calibrated with brachial blood pressure (HEM-7320, Omron Corp, Kyoto, Japan) to estimate central blood pressure and calculate AIx. In addition, other haemodynamic parameters, including pulse pressure, augmented pressure, and heart rate, are also derived from this measurement. It is important to note that AIx is influenced by HR; therefore, the adjusted value HR of 75 bpm (AIx [HR75]) was also included in the analysis. According to guideline recommendations and procedures [201, 275], each consecutive waveform was assessed for consistency in pulse wave height, baseline and pressure deviation and was equal to or less than 5% [183, 276]. A quality index >80% was deemed acceptable. All data were analysed using the SphygmoCor software. The technologist's short-term CV for repeated measures of AIx in a sample of ten aged-matched controls was approximately 3%.

4.2.7. Ventricular structure and function (echocardiogram)

A comprehensive transthoracic echocardiogram (Vivid E95, General Electric Medical Systems Milwaukee, WI, USA) was used to evaluate ventricular structure and function. A transthoracic echocardiogram is a diagnostic tool for screening and monitoring of cardiac complications associated with LV structure and function [120, 277]. It is commonly used to detect resting cardiovascular dysfunction in general and clinical cohorts and those receiving cancer therapy [120, 278]. Generally, a comprehensive echocardiogram is the first-line diagnostic assessment used to detect cardiotoxicity in cancer patients [120]. In accordance with standard clinical care for both cancer treatment and CVD detection, all participants underwent an echocardiogram on this basis. Despite its widely accepted use, two-dimensional echocardiography has modest interobserver and intraobserver variability for evaluating LV mass (CV: 37% and 19%, respectively), which may require greater detectable differences over time (>17% clinically meaningful change) to identify LV structural abnormalities [279, 280]. For Study Three and Four, a comprehensive echocardiogram including doppler and three-dimensional volumetric acquisitions, novel torsion, strain, and strain rate were acquired across all study time points [279, 280]. Three-dimensional quantification of LVEDV, LVESV and LVEF were acquired and measured per standardised protocols [280, 281]. Two-dimensional GLS was acquired across three apical views, and the average negative GLS score

was reported. The Simpsons biplane approach was used to estimate LV cardiac volumes using apical two- and four-chamber images. The LV mass was determined using the 2D linear technique. The left atrial volume and indexed value (LAVI) were determined using the area-length approach from the four-chamber and two-chamber images. The apical four-chamber view was used to evaluate peak early (E), late diastolic flow (A), and deceleration time (DT) using pulse-waved doppler. Peak early diastolic tissue velocity (e'), mitral annular velocity (E/e'), and the ratio of early diastolic inflow to late diastolic inflow (E/A) were measured using pulsed-wave tissue Doppler imaging to evaluate diastolic function and were analysed according to guideline suggestions [280, 281]. All echocardiographic measures were performed and analysed by two certified sonographers and reported by two staff cardiologists. The certified sonographers and cardiologists were blinded to the group allocation across all timepoints. All images were analysed using Echopac v13.0.00 GE, Norway, and digitally acquired for offline analysis. LVEDV, LVESV, and LV mass values were adjusted for body surface area and presented as the indexed value. It is important to note that these research echocardiograms were performed by staff certified sonographers employed within the Baker Institute echocardiography service. The echocardiographic variables reported in this thesis aligned with standard recommendations [280]. Based on this, inter-rater reliability related to the certified sonographers that performed these acquisitions is unavailable.

4.2.8. Ventricular structure (cardiac magnetic resonance imaging)

CMR imaging was performed using a Siemens MAGNETOM Prisma 3.0T CMR system with a five-element phased array coil. CMR imaging is the gold standard measurement of biventricular cardiac structure [282], with excellent temporal and spatial resolution throughout numerous cardiac cycles. The fundamental advantage, compared with transthoracic echocardiography, is CMR's ability to assess ventricular geometry in three dimensions in real-time, thereby permitting global and regional analyses of LV structure and function at the same time point with greater precision (r=0.99) and minimal intra and inter-observer variability of 7% and 8%, respectively [193, 194]. Our group previously described the methodological detail related to CMR sequences [210, 283]. In brief, the “resting, ungated, real-time, steady-free, precision cine imaging breath-hold technique (without cardiac or respiratory gating)” was carried out. “Every 36-38 milliseconds, 40 to 75 consecutive frames were acquired for each of the 13 to 18 contiguous 10 mm slices in the short and long axes; 50 consecutive slices were acquired using the exact temporal resolution for 11 to 15

contiguous eight-millimetre slices [210, 283].” The same cine techniques were used to acquire long-axis views of the LV to facilitate anatomical cross-referencing.

Images were analysed by a single researcher using CVi42 version 5.14 (Circle Cardiovascular Imaging, Calgary, Canada). In the short-axis view, the endocardial and epicardial contours of the LV were automatically traced (and manually adjusted). In the horizontal long-axis view, the points of transection were located. This allowed for anatomical cross-referencing. LV volumes were calculated using the same automated contouring technique in the end-diastole and end-systole of each cardiac cycle to derive LVEDV and LVESV. LVSV (LVEDV minus LVESV) was calculated to derive LVEF (SV/EDV) [284, 285]. LV mass was calculated using the same contouring method; however, total myocardial wall volume was multiplied by the gravity of the myocardium and indexed to body surface area [284, 285]. LVM: V was calculated by dividing LV mass by LVEDV. Trabeculations and papillary muscles were included in LV mass and LV volume calculations via the summation of disk method [286]. This thesis presents all LV outcomes as raw and body surface area indexed values. The technologist’s short-term CV for repeated measures for LVM: V, LVEDV and LVM in a sample of ten aged-matched controls was between 4-6%.

4.2.9. Physical function

Timed stair climb power test.

Lower limb muscular power was assessed using the timed stair climb power test. The timed stair climb power test is a therapeutically practical and realistic assessment of functional independence with excellent test-retest reliability (intraclass correlation, 0.94 to 0.99) in older adults and clinical cohorts with pulmonary disease [287-290]. Participants were instructed to ascend a flight of stairs (12 steps per flight, 17-centimetre step) without using a handrail [291, 292]. Using the start command “Ready, set, go”, the participant was instructed to ascend the stairs quickly and safely. Once both feet reached the top of the last platform, the timing was stopped. Each participant was given two attempts, and the average of the two attempts was calculated within the nearest 0.1 seconds. A recovery period of two minutes was employed between each attempt. Stair climb time and the vertical height of the step were used to calculate velocity (velocity equals distance divided by time). Gravity, body mass and acceleration were used to calculate force (force equals body mass multiplied by acceleration) [291]. Stair climb power was calculated by force multiplied by velocity.

4.2.10. Cardiopulmonary exercise testing

Peak oxygen uptake (VO_2peak)

A cardiopulmonary exercise test was performed to determine VO_2peak. CPET is the gold standard clinical assessment for accurately determining cardiorespiratory fitness, with superior test-retest reliability for body-weight indexed VO_2peak (intraclass correlation: 0.90, P<0.001) and absolute VO_2peak (intraclass correlation: 0.93, P<0.001) in men with PCa following radical prostatectomy [217]. The methodology related to this assessment has been described previously [210, 283]. An incremental ramp protocol test on an electronically braked cycle ergometer (Lode, Groningen, the Netherlands) with continuous cardiac monitoring (NORAV, PC-ECG1200, Digital RF Wireless system) was conducted. A respiratory gas analysis (Jaeger, Vyntus CPX, CareFusion, Hochberg, Germany) was performed using a metabolic measurement system. Resting measures were obtained for two minutes before the test commenced (including blood pressure and resting heart rate). Once the test commenced, a one-minute warm-up was undertaken at 10-25 Watts, and then the test was progressively increased by 10-30 Watts per minute until volitional fatigue. Each incremental ramp test protocol was individually assigned to align with a fatigue-limited test duration of approximately eight to 12 minutes [293]. Blood pressure (SunTech BP Tango M2, SunTech Medical, North Carolina, USA) was measured every two minutes throughout the test [294]. An identifiable plateau in oxygen uptake (plateau in VO_2 despite work rate/watts continuing to increase) was used to quantify the achievement of VO_2max [293]. The secondary criteria were used without an identifiable plateau [293]. VO_2peak was achieved if at least two of the following conditions were met: >85% of age-predicted heart rate maximum, respiratory exchange ratio (RER) >1.10 or volitional fatigue [293-295]. The test was terminated early if the supervising cardiologist deemed the test unsafe to proceed (e.g. systolic blood pressure exceeded >250 mmHg; diastolic blood pressure exceeded >115 mmHg) per the American College of Sports Medicine absolute contraindications to exercise testing criteria [296]. Several other parameters were determined from the CPET, including absolute VO_2peak (L/min), VT, slope in minute ventilation (V_E) in proportion to the expired volume of carbon dioxide (V_E/VCO_2), peak power output at VT, resting systolic and diastolic blood pressure, peak systolic and diastolic blood pressure, resting and peak heart rate, peak power output and RER. [297]. VO_2peak was defined as the 30-second moving average of the six highest oxygen consumption values measured over five seconds [210]. The V slope method was used to determine VT, and VO_2 at VT was expressed as an absolute value of each participant's VO_2peak. V_E in proportion to the expired VCO_2 was used to calculate V_E/VCO_2 slope [293, 297-

299]. Linear regression analyses were used to calculate V_E/VCO_2 slope from exercise test initiation to VT [298]. The short-term test-retest CV for maximal CPET has been reported between 4.0-4.7% [142, 217, 248] in a sample of ADT-treated men and PCa survivors. The technologist's short-term CV for repeated measures for VO_2peak (ml/kg/min) in a sample of ten aged-matched controls was approximately 4%.

4.2.11. Patient-reported outcomes

The Research Electronic Data Capture (REDCap) platform at Australian Catholic University collected and managed all patient-reported outcomes, including clinical and sociodemographic characteristics and the questionnaires described below [300]. Electronic questionnaires were administered across time points and had to be completed before attending all assessment sessions. Using electronic questionnaires, the usage of prescription medications, including medication type, dosage, and frequency, was also documented. Age-matched controls did not complete the questionnaires related to cancer.

Health-related quality of life

Health-related QoL was evaluated by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire and the EORTC-QLQ-PR25 [301, 302]. The EORTC QLQ-C30 evaluates general health-related QoL and compromises of a global health status/overall QoL scale, five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, nausea, and vomiting), and five single-item scales that assess additional, commonly reported symptoms (dyspnoea, appetite, constipation, diarrhea), and financial impact [301]. Each item is rated on a four-point Likert scale, except for the global health status scale, which was rated from 1-7. All scores are converted to 0-100. Questionnaire responses were analysed per the official scoring manual provided by the EORTC [301]. Higher values (functional scales only) reflect higher/better functioning, while higher symptom scores indicate a higher prevalence of symptoms.

PCa-specific QoL was evaluated using the EORTC QLQ-PR25. The questionnaire measures symptom-related effects on QoL, specifically in PCa [302], and includes four symptom scales (urinary symptoms, bother to use incontinence aids, bowel symptoms, hormone treatment-related symptoms) and two functional scales (sexual activity and sexual functioning) [302]. Questionnaire

responses were analysed as per the official scoring manual provided by the EORTC [303, 304]. Higher scores reflect a more significant symptom burden or higher levels of functioning (sexual).

Cancer-related fatigue

Using the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale, cancer-related fatigue was evaluated [305, 306]. The FACIT-F is a 13-item questionnaire that assesses fatigue levels during usual daily activities over the past seven days. Responses are recorded on a five-point Likert scale [305, 306]. Total scores are summed, forming the FACIT-F score, which ranges from 0 to 52. Questionnaire responses were analysed per the FACIT scoring manual [305, 306]. A score of less than 30 reflects severe fatigue, while higher scores indicate less fatigue [305, 306].

Psychological Distress

The Brief Symptom Inventory (BSI-18) was used to evaluate psychological distress in men undergoing ADT and age-matched controls. This questionnaire asked participants to rate how much they have been bothered by a symptom on a five-point Likert scale within the past seven days [307]. The BSI-18 contains three subscales: somatisation, depression, and anxiety, ranging from 0 to 24. These sub-scales are reported separately. The total scores of the three subscales are summed, forming the global severity index (GSI) (range: 0-72) [307]. Questionnaire responses were analysed per the BSI-18 scoring manual [307]. Higher scores on the subscales and the GSI indicates psychological distress.

Sleep quality and disturbance

The Pittsburgh Sleep Quality Index (PSQI) measured sleep quality and disturbance in men beginning ADT and controls of the same age [308-310]. The PSQI assesses sleep quality and disturbance using seven sub-scores, including sleep quality, onset latency, duration, efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. All responses are summed, forming the global PSQI score (0-21). Questionnaire responses were analysed per the PSQI scoring manual. Higher scores on the global PSQI reflect worse sleep quality and disturbance.

Physical activity

The modified Godin Leisure-Time Exercise questionnaire evaluated the duration and frequency of mild, moderate, and vigorous-intensity aerobic training completed over the last seven days [311, 312]. According to the method described by Godin et al. [313], the Godin Leisure-Time Index is computed by multiplying mild, moderate, and vigorous aerobic exercise intensity by three, five, and nine, respectively, and summing the overall values. Weekly total exercise training duration and frequency were calculated by multiplying the total exercise training duration by frequency for mild, moderate, and vigorous aerobic exercise training. Higher scores (<24 units or more) on the Godin Leisure-Time Exercise questionnaire indicate that participants are physically active [313]. Questionnaire responses were analysed in accordance with the Godin Leisure-Time Exercise Score manual [311, 312]. The total volume of exercise training completed in a typical week (sum of total minutes completed of mild, moderate, and vigorous moderate-intensity exercise training) to determine whether participants met the physical activity recommendations for individuals with cancer [314, 315].

4.3. Exercise attendance and adherence.

The exercise physiology team recorded attendance and adherence to the exercise training programme. Attendance was determined by dividing the number of sessions attended by the number of required sessions. For aerobic training, adherence was calculated as a percentage by comparing each session's average intensity (average session heart rate) to the prescribed intensity for each participant. In addition, whether participants also adhered to the prescribed aerobic exercise training duration will also be reflected as a percentage. For resistance training, volume load was determined by multiplying the completed sets by the repetitions by the external load (weight lifted), yielding a total volume load in kilograms or tonnes [316, 317]. As described previously [316, 317], the overall

volume load was calculated by adding each subject's leg press, seated row, and chest press, yielding the cumulative volume load. The overall adherence was expressed as a percentage of exercise doses completed versus prescribed [316, 317]. A home-based exercise training diary was provided to EX participants. They were encouraged to complete an additional 60 minutes of moderate aerobic continuous exercise training each week throughout the twelve weeks. The home-based exercise training diary was monitored throughout the intervention period rather than formally documented, given that the Godin Leisure-Time Exercise Questionnaire was completed across all timepoints.

4.4. Adverse events

The study coordinator or exercise physiology team documented any adverse events associated with exercise testing or the supervised exercise program following each assessment and training session. Participants in the exercise training group were required to inform the study coordinator of any adverse events during their involvement in the study. If the adverse event were related to an assessment procedure or the exercise intervention (supervised or unsupervised), the investigator team and study doctors (cardiologists) would discuss the seriousness of the adverse event and report the adverse event to the local Human Research Ethics Committee. Before recommencing the exercise intervention, the participant needed to be deemed safe to return to exercise training by their treating clinician.

Table 4.1: Summary of data collection methodology

Outcome	Outcome descriptors	Timepoint	
		Baseline	**3-months**
Blood biochemical markers	Blood lipids, fasting blood glucose, and c-reactive protein	X	X
Body composition	DXA whole-body total and regional lean muscle and fat mass	X	X
Arterial stiffness	cfPWV	X	X
Central blood pressure and Augmentation index	Central systolic and diastolic blood pressures, AIx[HR75], pulse pressure, augmented pressure, heart rate	X	X
Ventricular structure and function	Echocardiogram for the quantification of LVEF, GLS, LV chamber volumes, diastolic function	X	X
Ventricular structure	CMR imaging for the quantification of LVM: V and LV chamber volumes	X	X
Physical function	Timed stairs climb power test	X	X
Peak oxygen uptake	Peak oxygen uptake determined by a cardiopulmonary exercise test	X	X
Patient-reported outcomes	Clinical and demographic questionnaires, FACIT-F, EORTC QLQ-C30, EORTC QLQ-PR25, BSI-18, PSQI, Godin Leisure-Time Exercise Questionnaire	X	X
Exercise program adherence	Adherence to targeted HR ranges, assigned volume load and RPE; Monitored weekly for adherence and compliance	Collected throughout the intervention	
Adverse events	Adverse event reporting	Monitored throughout the intervention	

Abbreviations: DXA (dual-energy x-ray absorptiometry), cfPWV (carotid to femoral pulse wave velocity), AIx [HR75] (augmentation index at HR 75 bpm), LVEF (left ventricular ejection fraction), GLS (global longitudinal strain), CMR (cardiac magnetic resonance imaging), LV (left ventricular), LVM: V (left ventricular mass to volume ratio), FACIT- F (Functional Assessment of Chronic Illness Therapy – Fatigue), EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire), PR-25 (PCa), BSI-18 (Brief symptom inventory) and PSQI (Pittsburgh Sleep Quality Index).

4.5. Exercise intervention

Aerobic exercise training

A tabulated summary of the exercise intervention performed in the study is presented in Table 4.2. Participants randomly assigned to the exercise intervention underwent a periodised and progressive combined aerobic and resistance training program three times per week for three months at one of five community-based gymnasiums in Melbourne, Victoria, or via video-delivered telehealth sessions during the COVID-19 pandemic lockdown periods (between March 2020 and September 2020; February 2021 and July 2021). All exercise training sessions were supervised by an accredited exercise physiologist and performed in small groups of up to five participants or individually. Each training session was 60 minutes in duration. All exercise sessions included a five-minute warm-up and cool-down period. Aerobic exercise training was performed on either a stationary cycle ergometer, elliptical or treadmill. The accredited exercise physiologist determined the mode of aerobic exercise training. Aerobic exercise intensities were determined at VT during the CPET (maximal steady-state, MSS) as described previously [225, 318, 319]. Based on the MSS heart rate, three heart rate training zones were determined; base pace (1-20 beats below MSS), MSS and HIIT (>95% heart rate peak achieved during the CPET) [225, 318, 319]. The first training phase (phase one) focused on general preparation (aerobic endurance) and consistency, of which participants performed three 30-minute moderate continuous (base pace) sessions per week. In the second training phase (phase two), one MSS and one HIIT session replaced two weekly moderate continuous base pace sessions. Hence, participants performed one moderate continuous base pace, HIIT, and MSS weekly during this phase. The HIIT intervals were progressed from a 2 x 2 interval session (2 minutes of HIIT at >95% heart rate peak repeated four times followed by 2 minutes of active recovery at 60-70% of heart rate peak) to a 4 x 4 interval session at the same intensities above for four minutes and repeated four times. A three-minute recovery followed this at 60-75% of HR peak. In the final training phase (phase three), participants performed a single base pace session and two HIIT sessions per week to align with the primary outcome (cardiac remodelling). The training load and intensity remained unchanged for the remainder of the program, but progressive overload was applied throughout the three-month intervention. Heart rate monitors were worn during each training session. In accordance with the guideline recommendations, all participants were encouraged to perform an additional 60 minutes of moderate continuous aerobic exercise training each week throughout the intervention period [314, 315].

Resistance exercise training

Resistance training included whole-body progressive resistance training, including six to eight upper body and lower body exercises (e.g., leg press, latissimus dorsi pulldown/seated row, chest press, shoulder press, seated leg extension, seated leg curl, triceps pulldown and biceps curl). Participants performed three 30-minute resistance training sessions (phase one) to supplement the aerobic exercise training for the first month. In months two and three (phases two and three), participants performed two weekly resistance training sessions. For each exercise, a 10-repetition maximum (RM) (the most amount of weight-lifted for ten repetitions) was performed to determine the initial resistance training intensity. The initial intensity was set between ~60-75% of predicted 1-RM following a 10-RM test, and participants completed two to four sets of 12-8 RM with progressions of ~5-10% applied each week [296, 314, 315]. The sessional rating of perceived exertion (applied at the end of the training session) was used to guide progressive overload. Volume load (volume multiplied by load) [316, 320] was calculated after each session and used as a guide for exercise tolerability and the application of progressive overload. Due to the impact of the COVID-19 pandemic and the transition to video-delivered telehealth exercise sessions, not all volume load calculations could be completed as indicated previously.

Due to the worldwide pandemic (COVID-19), some participants were required to complete their exercise intervention at their place of residence. Participants in this study had access to an online exercise programme and completed their supervised exercise intervention using video conferencing software (Zoom Meetings, Zoom Video Communications). The online video-delivered exercise training program mirrored the supervised, in-person exercise training program with minor alterations depending on access to exercise equipment. During the COVID-19 pandemic lockdown times, participants had access to resistance training equipment, such as a compact gym station, and aerobic training equipment, such as an elliptical or stationary cycle ergometer.

4.6. Usual care

Research investigators gave no specific advice regarding physical activity to participants randomly assigned to the usual care group (UC). After completing the three-month follow-up evaluation, all participants were offered an optional consultation with an exercise physiologist who developed an individualised exercise program.

Table 4.2: Summary of exercise intervention

Exercise intervention												
				Aerobic training				Resistance training				
Microcycle	**Weeks**	**Session number**	**Duration, min**	**Sessions p/wk.**	**Session type**	**HR range**	**Duration, min**	**Sessions p/wk.**	**Sets**	**Repetitions**	**Rest**	**% RM**
Phase one	1-4	1-12	60	3	Base pace	1-20 bpm below MSS	30	3	2-3	10-12	45 secs - 1 min	~60-75%
Phase two	5-8	13-24	30-60	3	Base pace MSS HIIT	1-20 bpm below MSS MSS (VT) >95% HRpeak	30 20-25 20-25	2	3-4	8-10	1-2 min	~60-85%
Phase three	9-12	25-36	30-60	3	Base pace HIIT HIIT	1-20 bpm below MSS >95% HRpeak >95% HRpeak	30 20-25 20-25	2	3	10-12	45 secs - 1 min	~60-75%

Note Exercise Prescription: Base pace (20 beats per minute below maximal steady-state), MSS (maximal steady-state, ventilatory threshold [VT]), HIIT (high-intensity interval training, >95% HRpeak). Progressions included duration and intensity from weeks five to 12. High-intensity interval training started with four by two minutes at >95% HR peak, followed by two minutes of moderate-intensity recovery at 65%-75% HR peak. From weeks 7-8, the interval duration was increased; to four by three minutes at >95% HR peak, followed by three minutes of moderate-intensity recovery at 65%-75% HR peak. For the final block (weeks 9-12), the interval duration was increased by four minutes at >95% HR peak, followed by three minutes of moderate-intensity recovery at 65%-75% HR peak.

4.7. Summary

In summary, this chapter describes in detail the robust and rigorous assessments included in study three (a cross-sectional study parallel to a randomised controlled trial that compared vascular health in men with PCa commencing ADT to age-matched controls) and study four (a three-month randomised controlled trial that evaluated the impact of exercise training on cardiac remodelling in men with PCa receiving ADT relative to usual care control). These strengths include a novel range of assessments used to assess the cardiovascular effects of ADT, which were evaluated for the first time within a cohort of PCa patients undergoing ADT.

It is important to note that this study was initially conducted across two sites: Australian Catholic University and the Baker Institute. Due to the COVID-19 pandemic and the subsequent suspension of all study procedures from March 2020 to October 2020, the entire experimental protocol was transferred to the Baker Institute, which had formalised policies, procedures, and processes to ensure participant safety during the COVID-19 pandemic. Therefore, the first 18 participants in the randomised controlled trial completed baseline and three-month follow-up assessments for blood collection and processing, DXA and the timed stair climb at Australian Catholic University. The remainder underwent all assessment processes at the Baker Institute. Additionally, the DXA machine located at the Baker Institute is the same make and model as the DXA used at Australian Catholic University. While we recognise that this may have resulted in a certain amount of systematic error, the processes and procedures were identical at both locations. The same researchers carried out all assessments across all timepoints.

CHAPTER FIVE: Cardiovascular risk profile of men with prostate cancer initiating androgen deprivation therapy related to aged-matched controls: a cross-sectional study.

5. Overview

This chapter presents the results of the first experimental study included in this thesis. This study compared measures of vascular health in men with PCa commencing ADT with that of age-matched controls. This chapter also explores whether vascular health, traditional cardiovascular risk factors, cardiac structure and function and body composition predict cardiorespiratory fitness in all participants.

5.1. Abstract

Background: CVD is the leading non-cancer cause of death among men with PCa. Preliminary evidence suggests that CVD and cancer may share biological risk factors, which may exacerbate baseline CVD risk factors and/or pre-existing CVD in this vulnerable population. However, no study has fully characterised the cardiovascular risk profile (vascular health, cardiac structure and function, body composition, and biochemical markers) in men with PCa. Therefore, this study aimed to: (1) compare measures of vascular health in men with PCa commencing ADT to age-matched non-cancer controls (CON) and (2) examine the relationship between cardiorespiratory fitness, vascular health, cardiovascular risk factors, cardiac structure/function, and body composition among groups to determine predictors of cardiorespiratory fitness in the total sample.

Methods: Men with PCa commencing ADT (n=31; mean [SD] age: 66.5±9.9 years) and CON (n=10; age: 64.8±8.7 years) were examined. Biochemical blood markers of fasting blood glucose, total cholesterol, high-density lipoprotein, low-density lipoprotein, non-high-density lipoprotein, triglycerides, and c-reactive protein were collected in a fasted state. cPWV and waveform characteristics (central and peripheral blood pressures, AIx) were also assessed. LVEF and GLS were measured via echocardiography. LV mass and LVEDV were assessed via CMR imaging. Cardiorespiratory fitness (VO_2peak), determined via CPET, and body composition (determined via DXA) were also examined. Correlates for VO_2peak were assessed by multiple linear regression analyses in the total sample.

Results: There was a statistically significant difference between PCa patients and CON for VO_2peak (23.7±4.5 vs. 32.8±8.3 ml/kg/min; P<0.001),body fat percentage (29.8±6.8 vs. 23.9±9.4%; P=0.03), resting heart rate (64±9 vs. 54±5 bpm; P=0.006) and serum triglycerides (median 1.3 mmol/L, interquartile range [0.85-1.7] vs. 0.7 mmol/L [0.7-1.0], P=0.001). Other CPET-derived indices also reached statistical significance (p<0.01). No statistically significant between-group differences were observed for cfPWV, AIx, LV mass, LVEDV, LVEF, GLS, most biochemical blood markers and central and peripheral haemodynamic values. In the total sample, LV mass, heart rate, and cfPWV predicted VO_2peak (R^2 = 0.35, P=0.002).

Conclusion: The results of this study found that there was a significant difference in cardiorespiratory fitness and body fat percentage between men commencing ADT and CON. In addition, significant differences in resting heart rate and serum triglycerides were noted between groups; however, the clinical or practical significance of the findings is unclear. Further, multiple linear regression analyses revealed that a higher VO_2peak was associated with better cardiovascular

health (LV mass, heart rate and cfPWV) in all participants. These findings emphasise the need for prospective studies to evaluate traditional and subclinical CVD markers, such as cardiorespiratory fitness, to better understand the intermediary steps between CVD risk factors and events in this population.

5.2. Introduction

CVD is the most common cause of non-cancer-related death in PCa [10]. While CVD risk and/or the incidence of cardiovascular events are the subject of intense debate in PCa, growing evidence from clinical cohorts suggests that CVD and cancer may share comparable biological risk factors such as obesity, diabetes mellitus and inflammation, oxidated stress, which may contribute to the heightened CVD risk in this population [78]. Several systematic reviews and meta-analyses [88-91] have revealed that common CVD biochemical markers, such as insulin-like growth hormone factor, interleukin-6 and tumour necrosis factor, leptin, and adiponectin are associated with a higher incidence of PCa [92]. Given the higher prevalence of CVD morbidity and mortality in men with PCa initiating ADT [52], the mechanisms underlying the comparable shared biological risk factors between CVD and cancer may contribute to the increased CVD risk in this vulnerable population [78]. Nonetheless, it is essential to identify underlying mechanisms and potential identification strategies that may aid in the identification of therapeutic intervention targets.

Men with pre-existing CVD treated with or without ADT appear to have an increased risk of cardiovascular events and/or death [54, 56, 67, 72], although not all studies support these observations [54]. Previous retrospective and prospective cohort studies have included heterogeneous cohorts of PCa patients with notable inconsistencies concerning the characterisation of CVD, including CVD definitions, reporting cardiovascular outcomes, and data extraction techniques [56, 57, 76, 77]. Given that the evidence above and recent observations appear to contribute to these notable inconsistencies (*Chapter Two*), it is possible that current methods to characterise CVD prior to initiating ADT do not adequately reflect the potential shared biological CVD risk or could under- or overestimate CVD risk in this population.

Moreover, emerging experimental evidence [94, 104, 161, 189, 207, 321-332] characterising CVD in other clinical populations has focused on markers of subclinical CVD such as arterial stiffness, wave reflection characteristics, VO_2peak, adiposity and cardiac structure and function [46, 50, 52]. These markers, such as cfPWV and waveform characteristics (pulse wave analysis), are gold-standard techniques and relatively straightforward procedures with proven clinical utility [196, 198]. They also appear to provide mechanistic insight into the intermediary steps (early atherogenesis) in the pathway from traditional CVD risk factors to cardiovascular events in clinical cohorts [128, 276, 333, 334]. While evaluating arterial stiffness and wave reflection characteristics may provide additional insight into shared biological risk factors between CVD and cancer, these

subclinical CVD markers have been minimally examined in men prior to commencing ADT [100, 126, 127]. Therefore, it remains uncertain whether the CVD risk has been appropriately characterised and, therefore, a key contributor to increased CVD morbidity and mortality in this vulnerable population.

There is a growing consensus in cancer that traditional CVD risk factors, especially in older adults or those with high average CVD risk, are poorly associated with cardiorespiratory fitness, adiposity, and cardiac remodelling [141, 223]. Importantly, CPET (VO_2peak) is the gold standard measurement of integrative cardiovascular function [293] and is associated with an increased risk of CVD in the general population [212, 216, 335]. Further, the utility of VO_2peak may increase our understanding of the factors mediating CVD risk and clinical events in this population [141]. Furthermore, several studies have shown that subclinical CVD markers such as VO_2peak, and arterial stiffness may be more sensitive to detecting subtle changes to CVD risk than traditional CVD risk factors [141, 204, 207, 209, 216, 336]. Based on this, international organisations [141, 196, 198] have endorsed the inclusion of these subclinical CVD markers in future research trials due to the fact that they may also provide additional biological and physiological value in quantifying cardiovascular risk in clinical populations. In addition, these subclinical markers may also provide a therapeutic target for intervention, given that higher cardiorespiratory fitness is associated with a lower risk of incident CVD in the general population and clinical cohorts [212, 213, 216, 335]. Thus, evaluating vascular health in men with PCa seems logical, given that no study has comprehensively evaluated the CVD risk profile in men with PCa commencing ADT compared with matched controls.

Therefore, this cross-sectional study aimed to: (1) compare vascular health (cfPWV, AIx) in men with PCa commencing ADT to age-matched non-cancer controls (CON), and (2) examine the relationship between cardiorespiratory fitness, vascular health, traditional cardiovascular risk factors, cardiac structure and function and body composition in men with PCa commencing ADT and CON. We hypothesised that 1) men with PCa commencing ADT would have impaired vascular health relative to CON, and 2) higher cardiorespiratory fitness would be associated with better vascular health in all participants.

5.3. Methods

5.3.1. Study design

This cross-sectional study compared two groups: 1) men with PCa commencing ADT and 2) aged-matched control (CON). Participants were eligible for the PCa group if they were aged >40 years, had histologically confirmed PCa, and were currently receiving (<one month of initiating therapy) or scheduled to receive ADT with or without chemotherapy. Participants were excluded if they had: 1) an unstable heart condition determined by the study doctor and/or general practitioner), 2) previously received ADT or chemotherapy for the treatment of previous cancer, 3) acute illness or any musculoskeletal, cardiovascular or neurological disorder that could inhibit exercise or put participants at risk during exercise testing, or 4) a permanent metallic implant, cardiac pacemaker or implantable cardioverter which are considered a contraindication to MRI imaging. Participants requiring an MRI-screening X-ray (at the discretion of the radiographer) were excluded from the study. Participants were referred by treating PCa clinicians in Melbourne, Victoria, from March 2019 to July 2021 and screened for eligibility prior to the provision of written informed consent. Ten CON were recruited via convenience sampling at a 3:1 (PCa patients: CON) ratio [337, 338] from the Baker Institute Healthy Hearts clinic. This clinical service includes an accessible database of subjects who have attended a cardiovascular health screening and consented to be contacted about future research study participation at the Baker Institute. Participants were contacted and assessed for eligibility if they were male and had no prior history of a cancer diagnosis. The 3:1 non-probability sampling ratio was selected for the following reasons: 1) feasibility, 2) accessible cohort, 3) budgetary constraints, 4) PhD candidature timeline and 5) impact of the COVID-19 pandemic. These reasons are consistent with the broader scientific evidence related to the recruitment of convenience samples when resource and financial constraints exist [339, 340]. The exclusion criteria for CON were the same as for the PCa group. Age matching was based on the nearest age of the PCa patients (>68 years or $\leq$68 years) included in the study, which aligns with the age of men with PCa. This study was approved by the Alfred Health Human Research Ethics Committee (HREC/18/Alfred/4), Peter MacCallum Cancer Centre (18-205), Austin Health and Australian Catholic University (2018-70R). All procedures in this study conformed to the standards set by the Declaration of Helsinki.

5.4. Outcomes measures

The outcome measures of this study are given in detail in *Chapter Four* (see Methodology Section 4.1.1 and 4.2). In brief, all participants attended an assessment session that included a

comprehensive series of cardiovascular assessments. All participants were overnight fasted, voided and refrained from caffeine, alcohol and strenuous exercise 24 hours before reporting to the laboratory.

Clinical, demographical and lifestyle data were assessed by questionnaire. Arterial stiffness was evaluated by applanation tonometry (SphygmoCor CvMS, ATCOR, Sydney, Australia) to measure cfPWV [130]. Pulse wave analysis via radial applanation tonometry was used to estimate central blood pressures and calculate AIx as well as other haemodynamic variables, including adjusted augmentation index (AIx[HR75 bpm]), pulse pressure, augmented pressure, and heart rate [130]. Blood samples assessed biochemical markers (specifically, fasting blood glucose, total cholesterol, high-density lipoprotein, low-density lipoprotein, non-high-density lipoprotein, triglycerides, and c-reactive protein) in a fasted state on the morning of the assessment session and used as part of the cardiovascular risk score. Cardiovascular risk was determined using the Australian Absolute Cardiovascular Risk Calculator. Cardiac structure, including LV mass and LVEDV, were quantified by CMR imaging. A comprehensive echocardiogram assessed cardiac function, including function indices such as LVEF and GLS [280]. It is important to note that only LVEF and GLS were included and analysed in this cross-sectional study. The reasoning is that LVEF and GLS are considered key diagnostic measures critical to detecting and monitoring cancer-related cardiotoxicity in oncology populations [120, 341]. In this instance, the use of these variables aligns with the recommendations outlined by the European Society of Cardiology and the American Heart Association [120, 341] clinical guidelines for detecting cancer therapy-related cardiotoxicity. DXA was used to assess body composition, particularly whole-body lean mass and body fat percentage. Cardiorespiratory fitness, determined by VO_2peak, was assessed using a CPET with continuous cardiac monitoring, 12-lead electrocardiography and respiratory gas analysis [293]. Several parameters were collected during the CPET, including VO_2 (L/min), VE/VCO_2, peak power output (Watts), peak power output at VT, peak heart rate, systolic and diastolic blood pressure, and RER. Habitual physical activity was assessed by a self-reported questionnaire, the modified Godin Leisure-Time Exercise Questionnaire [313].

5.5. Statistical analysis

Statistical analyses were performed using SPSS (v27, IBM Australia Ltd, Sydney NSW, Australia). Data were expressed as mean, SD, median and IQR for continuous data. Categorical variables were expressed as frequency and percentage. Visual inspection of Q-Q plots of residuals was used to assess

the normality of distribution. Between-group comparisons were assessed using independent *t*-tests for continuous variables with assumed normal distribution and the Mann-Whitney test *U* test for continuous variables with assumed alternative distribution. Chi-square tests were performed for dichotomous variables. A hypothesis-driven correlation analysis was conducted based on the established relationship between a higher VO_2peak and better cardiovascular health in the general population and clinical cohorts [216, 223, 323, 332, 335]. Therefore, a multiple linear regression analysis was performed using the total sample to test the secondary hypothesis noted in Chapter Five. For this reason, strengths and associations between VO_2peak and markers of cardiovascular health were assessed by Spearman's correlation coefficient in the total sample. Markers of cardiovascular health related to the dependant variable, such as bodyweight indexed VO_2peak, were excluded. Multiple linear regression analyses were hypothesis-driven and based on statistically significant bivariate associations with VO_2peak or statistically determined cut points and entered (backward method) into the multiple linear regression analyses. No adjustments for multiple comparisons were performed as this would increase the risk of Type II error given the small sample size. An alpha of 0.05 was adopted for all analyses.

5.6. Results

5.6.1. Participant characteristics

The demographics and baseline characteristics of participants are outlined in Table 5.1. Collectively, 31 men with PCa (age: 66.5±9.9 years) and ten CON (age: 64.8±8.7 years) were examined. There appeared to be no differences between groups for age, body mass and body mass index (all: $P>0.05$; Table 5.1). Habitual physical activity (evaluated by Godin-Leisure Exercise Time activity score) was 58% lower in the PCa group than CON, with only ten of 31 PCa participants (32%) meeting the physical activity guidelines for individuals with cancer (≥150 minutes per week)[314]. The PCa group had a higher prevalence of hypertension relative to CON (55% vs. 10%). For men with PCa, the most common PCa stage at diagnosis was localised (48%) and locally advanced PCa (35%), with fewer men diagnosed with metastatic disease (16%). Previous PCa treatments included radical prostatectomy (29%) and radiation therapy (13%). Due to the COVID-19 pandemic lockdown periods, it is important to note that three participants completed their baseline assessments outside the strict four-week window.

Table 5.1: Demographics and baseline characteristics

	Prostate cancer (n=31)	Age-matched controls (n=10)	*P* value
Age, years	66.5±9.9	64.8±8.7	0.63
Height, m	1.74±0.06	1.74±0.04	0.77
Body mass, kg	79.6 (74.0-97.7)	78 (68.4-89.8)	0.37
Body mass index, kg/m^2	26.3 (24.2-32.04)	25.5 (23.7-28.1)	0.26
Standard modifiable risk factors, n (%)			
Hypertension	17 (55)	1 (10)	**0.01**
Hyperlipidaemia	11 (35)	1 (10)	0.12
Smoking	2 (6.5)	0	0.41
Diabetes mellitus	2 (6.5)	0	0.41
Cardiovascular risk score, %	9.6±4.8	8.3±5.1	0.98
Medications n (%)			
Betablockers	2 (6.5)	0	0.41
Angiotensin II inhibitor	13 (42)	1 (10)	0.06
Angiotensin Receptor blocker	2 (6.5)	0	0.41
Statin	6 (19)	0	0.13
Anti-arrhythmic	1 (3)	0	0.56
Calcium channel blocker	4 (13)	0	0.23
Anti-coagulant	2 (6.5)	0	0.41
Diuretic	1 (3)	0	0.56
Metformin	1 (3)	0	0.56
Physical activity			
Godin Leisure-Time Activity Score	26.3±24.5	53.3±25.3	**0.005**
Meets physical activity guidelines, n (%) †	10 (32)	9 (90)	**0.001**
Prostate cancer stage at diagnosis, n (%)			
Localised	15 (48)	-	
Locally advanced	11 (35)	-	
Metastatic	5 (16)	-	
Time since diagnosis, months	19.1±32.7	-	
Previous treatments, n (%)			
Previous radiation therapy	4 (13)	-	
Previous radical prostatectomy	9 (29)	-	

Data presented as mean ± standard deviation or median (interquartile range, 25th and 75th percentile) unless stated otherwise.

†Self-reported physical activity via the Godin Leisure-Time Activity Score >150 min/week of moderate-intensity aerobic exercise training [314, 315]

5.6.2. Vascular health and central and peripheral haemodynamic indices

Differences in vascular health and haemodynamic indices between PCa and CON are presented in Figure 5.1 and Table 5.2. cfPWV and pulse wave analysis could not be acquired in two PCa participants. The AIx of one participant (CON) was negative, and this individual data point was removed from the primary analysis based on established guidelines [130, 196, 342]. There was a significant difference between PCa and CON for resting sting heart rate (absolute difference, +9 bpm; (P=0.006) only. However, no statistically significant differences in arterial stiffness or haemodynamic variables were found (all: P>0.05; Table 5.2).

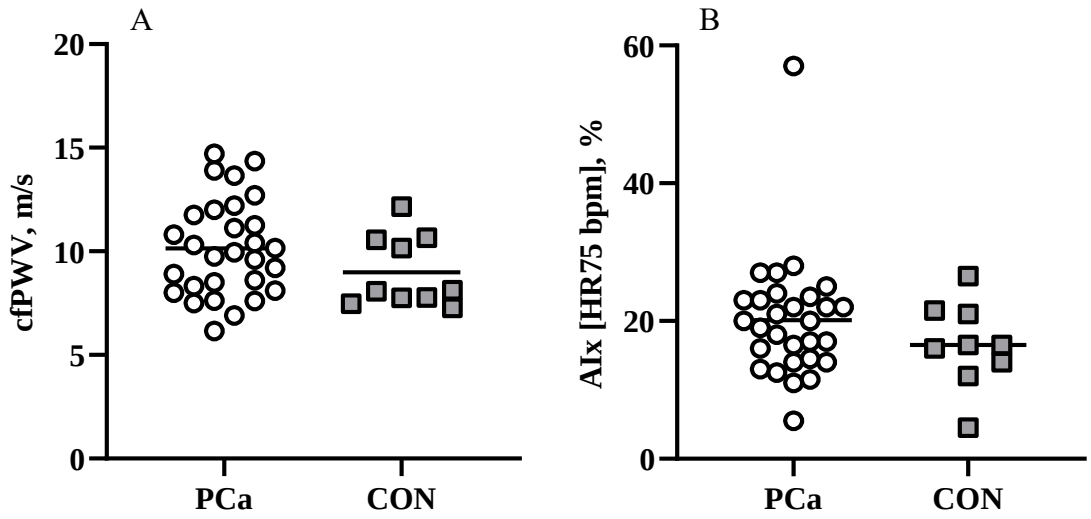


Figure 5.1 A & B: Arterial stiffness assessed by pulse wave velocity and augmentation index assessed by pulse wave analysis in men commencing ADT, compared to age-matched controls.

Group comparisons demonstrate that men with PCa had similar arterial stiffness (cfPWV, P=0.13) and augmentation index values (AIx [HR75]%, P=0.26) compared to CON.

Abbreviations: ADT (androgen deprivation therapy), PCa (prostate cancer), cfPWV (carotid to femoral pulse wave velocity), AIx [HR75], augmentation at heart rate 75 bpm.

Table 5.2: Comparisons of arterial stiffness and central and peripheral haemodynamic indices between men with prostate cancer commencing ADT and age-matched controls.

	Prostate cancer	Age-matched controls	*P*-value
***Pulse wave velocity*[1]**			
Aortic pulse wave velocity, m/s	10.2±2.3	8.9±1.7	0.13
***Haemodynamics*[2]**			
Brachial systolic blood pressure, mmHg	134±19	124±11	0.16
Brachial diastolic blood pressure, mmHg	74±10	73±9	0.79
Central systolic blood pressure, mmHg	116 (112-130)	115 (99-124)	0.22
Central diastolic blood pressure, mmHg	76±9	71±7	0.21
Resting heart rate, bpm	64±9	54±5	**0.006**
Augmentation index, %	24±6	27±7	0.32
Augmentation index [HR75], %	20±9	16±6	0.26
Augmented pressure, mmHg	10 (7-13)	11 (8-15)	0.78
Pulse Pressure, mmHg	61±17	51±7	0.09

Data presented as mean ± standard deviation, median (interquartile range, 25th and 75th percentile)

[1]Aortic pulse wave velocity measurement included 29 men with PCa commencing ADT and ten age-matched controls.

[2]Haemodynamic indices included 29 men with PCa commencing ADT and nine age-matched controls.

5.6.3. Blood biochemical biomarkers

The results for traditional (fasting blood glucose, total cholesterol, high-density lipoprotein, low-density lipoprotein, non-high-density lipoprotein, and triglycerides) and novel (C-reactive protein) blood biochemical cardiovascular risk factors for both groups are presented in Table 5.3. Six baseline blood samples in the PCa group were lost due to freezer malfunction beyond the control of the research team. Most blood biochemical markers did not reach statistical significance between groups except for higher serum triglycerides, which was significantly different and in favour of the PCa group when compared with CON (absolute difference, 0.6 mmol/L, *P*=0.001).

Table 5.3: Comparisons of traditional and novel blood biochemical markers between men with prostate cancer commencing ADT and age-matched controls.

	Prostate cancer	Age-matched controls	*P*-value
***Blood biochemical markers*[1]**			
Fasting blood glucose, mmol/L	5.4 (2.1-5.9)	5.5 (5.0-5.9)	0.95
Total cholesterol, mmol/L	5.1±1.3	5.7±0.7	0.20
High-density lipoprotein, mmol/L	1.2 (1.0-1.5)	1.4 (1.2-2.2)	0.12
Low-density lipoprotein, mmol/L	3.3±0.9	3.5±0.7	0.66
Non-high-density lipoprotein, mmol/L	3.9±1.1	4.0±0.6	0.93
Triglycerides, mmol/L	1.3 (0.85-1.7)	0.7 (0.7-1.0)	**0.001**
C-reactive protein, mg/L	1.0 (1.0-3.0)	1.0 (1.0-1.7)	0.37

Data presented as mean ± standard deviation, median (interquartile range, 25th and 75th percentile)

[1]Blood biomarkers included 25 men with PCa commencing ADT and ten age-matched controls.

5.6.4. Resting cardiovascular structure and function

The results for resting echocardiographic and CMR-derived indices for both groups are presented in Table 5.4. Two participants did not undertake CMR imaging due to claustrophobia in the PCa group. No between-group differences were detected in CMR-derived measures of cardiac structure (LV mass and LVEDV) and echocardiographic-derived functional measures resting LVEF and GLS.

5.6.5. Body composition

The results for DXA measures of whole-body lean mass and body fat percentage for both groups are presented in Table 5.4. There were no differences in whole-body lean mass between groups. PCa had a significantly higher body fat percentage than CON (absolute difference, 6.1%, *P*=0.03).

5.6.6. Cardiorespiratory fitness

Between-group differences in cardiorespiratory fitness and other CPET parameters are presented in Figure 5.2 and summarised in Table 5.4. Twenty-eight PCa and ten CON met the CPET criteria for peak effort, as determined by an RER >1.1, ≥85% of aged-predicted heart rate maximum, or volitional fatigue. Two participants did not complete the test due to 1) claustrophobia associated with the mask and 2) elevated resting systolic blood pressure, deemed unsafe to proceed by the supervising cardiologist (>200 mmHg). No participants achieved VO_2max or completed an invalid test (such as failing to reach VT). A single test was ceased prematurely due to an exaggerated systolic blood pressure response and asymptomatic ST changes during the CPET. Therefore, it did

not meet the eligibility criteria for a peak effort. Both absolute (absolute difference, -0.5 L/min, P=0.04) and bodyweight-indexed VO_2peak (absolute difference -9.1 ml/kg/min, P<0.001) were significantly different when comparing PCa to CON. In addition, peak workload (absolute difference -75 Watts, P=0.001), peak workload at VT (absolute difference -53 Watts, P=0.003) and peak heart rate (absolute difference -15 bpm, P=0.006) were significantly lower in PCa. In contrast, both groups had similar systolic and diastolic blood pressure, VE/VCO_2, and RER. Taking into account age, gender, height, and bodyweight, predicted VO_2peak was significantly lower in PCa, at 83% of predicted VO_2peak, compared to 102% of predicted VO_2peak in CON (P=0.005).

Table 5.4: Comparisons of cardiac structure and function, body composition, and cardiorespiratory fitness between men with prostate cancer commencing ADT and age-matched controls.

	Prostate cancer	Age-matched controls	*P* value
Cardiac structure and function[1]			
LV mass, g/m^2	52±10	55±12	0.44
LVEDV, ml//m^2	84±14	91±19.6	0.29
LVEF, %	60 (58-63)	61 (56-62)	0.75
GLS, %	-19 (18-20)	-19 (19-21)	0.45
Body composition[2]			
Whole-body lean mass, kg	54.4 (51.7-58.1)	55 (52.7-61.4)	0.54
Body fat percentage, %	30.0 ±6.7	23.9 ±9.5	**0.03**
Cardiorespiratory fitness[3]			
VO_2peak ml/kg/min, % predicted*	83.4 (72.4-96.9)	102.4 (87.9-116.7)	**0.005**
Peak heart rate, bpm	148±19	163±11	**0.006**
Peak power at VT, watts	89 (70-121)	142 (113-203)	**0.003**
VE/VCO_2	28.2±3.3	26.4±2.8	0.13
Respiratory exchange ratio	1.22±0.09	1.21±0.06	0.69
Peak systolic blood pressure, mmHg	201 (185-215)	209 (203-219)	0.16
Peak diastolic blood pressure, mmHg	85±12	93±20	0.29

Data presented as mean ± standard deviation or median (interquartile range, 25th and 75th percentile) unless stated otherwise. Abbreviations: LV (left ventricle), LVEF (left ventricular ejection fraction), GLS (global longitudinal strain), LV EDV (left ventricular end-diastolic volume), VO_2peak (peak oxygen uptake), VT (ventilatory threshold), VE/VCO_2 (minute ventilation to carbon dioxide output).

*Predicted VO_2peak was calculated using the FRIEND registry reference equation for maximal aerobic power [343]

[1]Cardiac structure (CMR-derived indices) included 29 men with PCa commencing ADT and ten age-matched controls, and cardiac function (echocardiographic indices) included 31 men with PCa commencing ADT and ten age-matched controls.

[2]Body composition measurement included 31 men with PCa commencing ADT and ten age-matched controls.

[3]Cardiorespiratory fitness measurement included 28 men with PCa commencing ADT and ten age-matched controls.

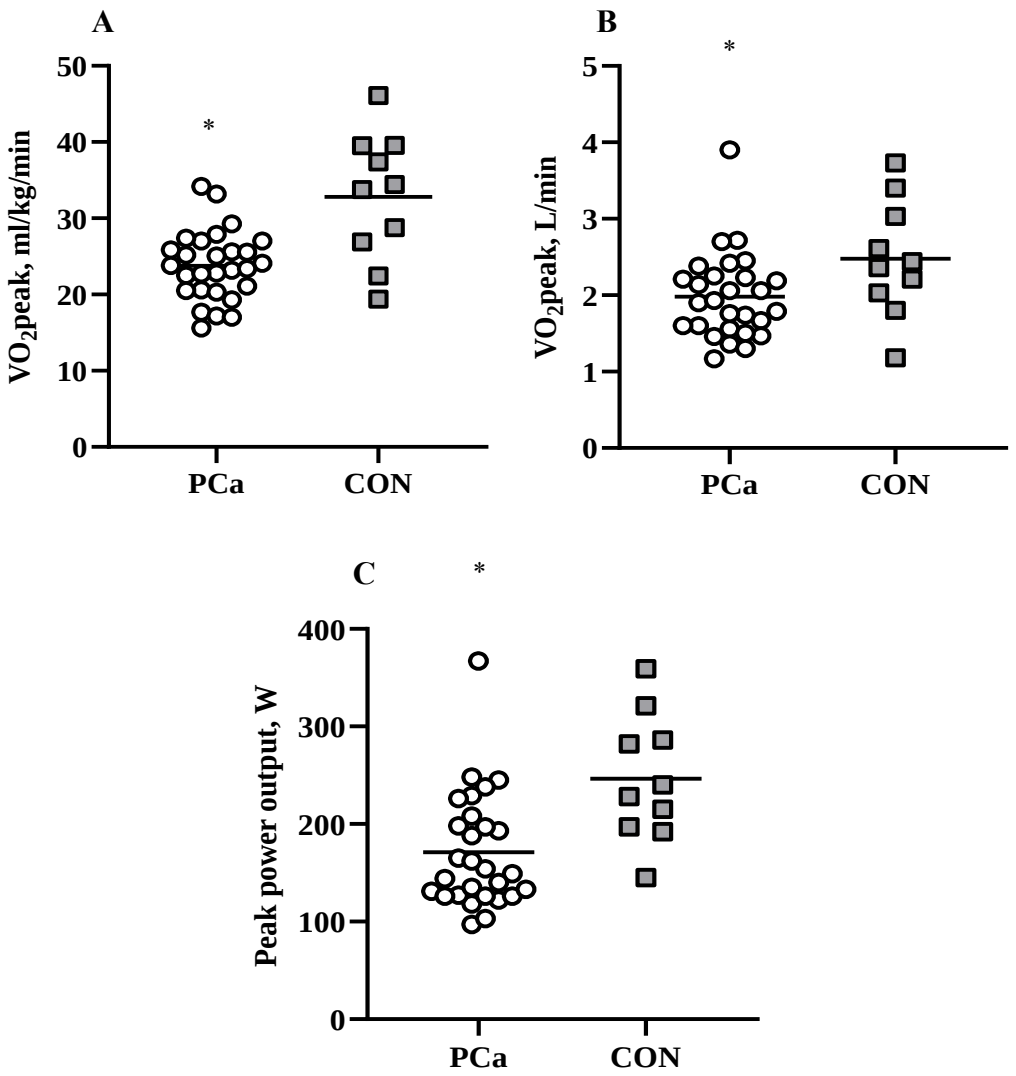


Figure 5.2: A, B & C: Cardiorespiratory fitness and peak power output determined by cardiopulmonary exercise testing (VO_2peak) in men commencing ADT, compared to age-matched controls.
Group comparisons demonstrate that men with PCa have a significantly lower bodyweight-indexed VO_2peak ml/kg/min (P<0.001)*, absolute VO_2peak L/min (P=0.04)* and lower peak power output (P=0.001)* than CON.
Abbreviations: ADT (androgen deprivation therapy), PCa (prostate cancer), VO_2peak (peak oxygen uptake), CON (age-matched controls).

5.6.7. Associations between cardiorespiratory fitness and cardiovascular health

Associations between VO_2peak and other clinically relevant variables are presented in Table 5.5. Bivariate correlations showed VO_2peak was strongly associated with physical activity levels (r_s=0.32, *P*=0.04), C-reactive protein (r_s=-0.62, *P*<0.001), LVEDV (r_s=0.59, *P*<0.001), LV mass (r_s=0.48, *P*=0.003), high-density lipoprotein (r=0.39, *P*=0.02) and resting heart rate (r_s=-0.53, *P*<0.001) in all participants. Other bivariate associations did not reach statistical significance.

Table 5.5: Bivariate correlations between VO_2peak and other clinically relevant variables

Outcome variable	Correlation coefficient	P-value
VO_2peak, ml/kg/min	1.0	-
Age, years	-0.26	0.10
Height, m	0.11	0.50
Physical activity	0.32	**0.04**
Fasting blood glucose, mmol/L	0.14	0.42
Total cholesterol, mmol/L	0.27	0.12
High-density lipoprotein, mmol/L	0.39	**0.02**
Low-density lipoprotein, mmol/L	0.09	0.59
Non-high-density lipoprotein, mmol/L	0.05	0.75
Triglycerides, mmol/L	-0.24	0.18
C-reactive protein, mg/L	-0.62	**<0.001**
LVEF, %	0.18	0.26
GLS, %	0.06	0.68
LVEDV, ml//m^2	0.59	**<0.001**
LV mass, g/m^2	0.48	**0.003**
Pulse wave velocity, m/s	-0.28	0.09
Peripheral SBP, mmHg	-0.31	0.06
Peripheral DBP, mmHg	-0.09	0.58
Heart rate, bpm	-0.53	**<0.001**
Augmented Pressure, mmHg	0.16	0.36
Pulse pressure, mmHg	-0.33	0.05
Augmentation index, %	0.22	0.21
Augmentation index [HR75], %	-0.14	0.41
Central SBP, mmHg	-0.09	0.58
Central DBP, mmHg	-0.18	0.29

Data presented as Spearman's correlation coefficients (rs). Abbreviations: VO_2peak (peak oxygen uptake), LV (left ventricle), LVEF (left ventricular ejection fraction), GLS (global longitudinal strain), LVEDV (end-diastolic volume), SBP (systolic blood pressure), and DBP (peripheral diastolic blood pressure).

5.6.8. Predictors of cardiorespiratory fitness

The hypothesis-driven multiple linear regression model, including VO_2peak, LV mass, heart rate and cfPWV, is presented in Table 5.6. VO_2peak remained independently associated with LV mass, heart rate and cfPWV (R^2 = 0.35, *P*=0.002) in the total sample. A multiple linear regression model adjusting for physical activity levels was also performed; however, including this variable did not affect the model.

Table 5.6: Multiple linear regression model for the association between VO_2peak and cardiovascular and clinical characteristics in men commencing ADT and age-matched controls (n=33)

	ß	*P*-value	ß	*P*-value
LV mass, g/m^2	0.30	0.06	0.33	**0.04**
HR, bpm	-0.43	**0.01**	-0.39	**0.01**
cfPWV, m/s			-0.19	0.22
R^2 models	***R^2 = 0.32 P=0.001***		***R^2 = 0.35 P=0.002***	

Data are presented as standardised ß coefficient and p-values related to the independent variables in the models.

Note: Models included both participants (PCa patients commencing ADT and CON).

Abbreviations: LV (left ventricular), HR (heart rate), cfPWV (central pulse wave velocity).

5.7. Discussion

This is the first study to comprehensively assess vascular health and compare cardiac structure and function, vascular health, traditional cardiovascular risk factors, body composition, and cardiorespiratory fitness outcomes in men with PCa commencing ADT. The results indicate that men commencing ADT had a markedly lower VO_2peak and a higher body fat percentage than CON, despite the limited differences in vascular health and cardiac structure and function outcomes between groups. Resting heart rate and serum triglycerides were also significantly higher in men with PCa commencing ADT compared with CON. Further, in all participants, a higher VO_2peak was positively associated with LV mass and inversely associated with a lower resting heart rate and cfPWV.

This study did not detect significant differences in arterial stiffness or waveform characteristics between men commencing ADT and CON, despite the differences in resting heart rate between groups. While there is a paucity of experimental studies evaluating arterial stiffness or waveform characteristics in men commencing ADT, our findings are consistent with a previous study [127] in 51 men with PCa (ADT and non-ADT treated men), which also observed non-significant differences in cfPWV or AIx, compared with 47 controls. Of note, our findings and others [127] highlighted that despite similar CVs and negligible differences, cfPWV values were abnormal (> ten m/s) and considered high CVD risk in men with PCa. While this study and others have focused on single imaging approaches such as cfPWV [100, 127] to evaluate vascular health, it may be entirely possible that the pathways or mechanisms by which increase cardiovascular risk in this setting are not adequately reflected in cfPWV or AIx values [202, 344]. In contrast, there is a plethora of epidemiological evidence demonstrating the association of cfPWV, AIx and other haemodynamic values, such as central blood pressure, on cardiovascular events in the general population and clinical cohorts, including cancer [128, 209, 345-347]. Differences may be in part explained by patient demographics and larger samples. In contrast, FMD, a subclinical measure of endothelial dysfunction, may be more sensitive to detecting functional changes that precede arterial structural remodelling (e.g., arterial stiffness) [239, 240]. Therefore, variables targeting vascular structure such as cfPWV, particularly in the context of the negligible results reported in ADT-treated men [100, 125-127], may not adequately reflect the physiological or mechanistic pathways that contribute to increased CVD risk in this population. While the evaluation of vascular health in PCa

and cancer is still emerging, our observations highlight that measures of vascular function, such as FMD, should be considered when prospectively examining cardiovascular risk in future trials.

There is a growing notion in cardio-oncology and our prior work that current traditional cardiovascular assessments do not fully explain the prevalence of CVD in this population [66, 67, 348]. Traditional risk factors, especially in older adults or those with pre-existing CVD, correlate poorly with subclinical CVD markers such as VO_2peak [141, 223]. In this study, we investigated the utility of VO_2peak and found that VO_2peak was significantly lower among men commencing ADT, with an approximate difference of ~9.1 ml/kg/min between groups. Notably, the predicted VO_2peak values varied significantly between groups. The VO_2peak of men commencing ADT was approximately 17% below age-related reference values[343], whereas the VO_2peak of CON was 100% of the predicted value [343]. Compared to a relatively healthy CON, the significant difference between groups may be due to a higher prevalence of cardiovascular risk factors or pre-existing CVD, lower physical activity levels, and greater adiposity. Nevertheless, our results align with the growing notion [210, 348] that VO_2peak may help quantify the intermediary steps in the pathway from traditional CVD risk factors to cardiovascular events [210, 348]. Importantly, epidemiological studies have demonstrated that for every one-unit MET (3.5 ml/kg/min) decline in VO_2peak, cardiovascular events (heart failure or atherosclerotic disease) and all-cause and cardiovascular mortality in older adults with coronary disease increase two- to fivefold [141, 349-352]. Although we have highlighted that low physical activity levels and high adiposity may have influenced the lower VO_2peak value in the PCa group, we could speculate that the magnitude of the difference of 9.1 ml/kg/min, particularly in the context of the negligible results of other subclinical CVD markers, places men commencing ADT at a higher CVD risk than CON. However, the predictive value of VO_2peak in PCa and other cancers in terms of CVD risk remains to be determined, and the findings above require additional validation.

Compared with reduced VO_2peak, this study also found that men commencing ADT had a substantially higher body fat percentage (+6.1%, P=0.03), despite similar values for whole-body lean mass observed between groups. This is consistent with previous studies before radical prostatectomy and during active surveillance [353, 354], in which higher adiposity correlates with poorer post-surgical outcomes, disease progression and cardiometabolic risk factors [353, 354].

Obesity is a recognised CVD risk factor in other populations [355]; however, it does not explain the lower absolute VO_2peak (independent of body mass) observed in this cohort. In a cohort study of 505 women and 417 men (age range: 70-77 years), the combination of lower cardiorespiratory fitness and higher adiposity (body mass index, waist circumference) was associated with an increased risk of cardiometabolic disease compared to individuals with higher cardiorespiratory fitness and lower adiposity values [323]. Based on this study and others, it seems the body composition assessment alone may underestimate CVD risk burden in broader populations as well as PCa. Therefore, our observations highlight that cardiorespiratory fitness and body composition (adiposity) should be considered when designing future trials and implementing cardiovascular risk assessments in clinical settings.

This study is the first to examine the relationship between VO_2peak and clinically significant correlates in men commencing ADT and CON. A high VO_2peak was correlated positively with LV mass and negatively with resting heart rate and cfPWV. The above correlates may be important targets for future trials in men commencing ADT. Moreover, given the strong and consistent evidence that a higher VO_2peak may offset cardiovascular morbidity, all-cause and cardiovascular mortality in older adults [141, 212, 216, 223, 323, 332, 335], targeting this outcome may confer substantial beneficial effects on CVD burden in men commencing ADT. While recent evidence has shown the value of implementing exercise interventions targeting VO_2peak on PCa-specific outcomes during active surveillance [356], our findings highlight the urgent need for future trials to target cardiometabolic health. Considering that a higher VO_2peak seems to be associated with positive cardiovascular health outcomes in other settings, using VO_2peak as a diagnostic and therapeutic tool may help reduce the risk of CVD in this population.

By contrast, no differences were observed between groups for cardiac structure (LV mass, LVEDV), cardiac function (LVEF, GLS) and most blood biochemical markers. Although serum triglycerides were markedly higher in PCa, these differences appear trivial, especially given that conventional CVD risk factors assessed in this study were within normal ranges according to arbitrary CVD risk factors cut-off values [357]. This further supports the notion that traditional CVD risk factors do not adequately reflect the higher prevalence of CVD risk in this population and, therefore, may underestimate CVD risk, particularly in the context of reduced VO_2peak, higher adiposity, and abnormal arterial stiffness values (non-significant difference) observed in this study and others.

Notably, there is ample evidence from prospective cohort studies in several population settings [128, 207, 328, 333, 358-362], including cancer [210, 295, 348, 363, 364] that have shown that subclinical CVD markers such as reduced VO_2peak tend to be more sensitive to detecting cardiovascular impairment, despite traditional CVD risk factors values. Although additional prospective studies evaluating traditional and subclinical CVD markers are necessary, the current standard care approaches still rely on traditional risk factors to determine CVD risk. However, based on the above findings and others [125-127, 248], this may underestimate CVD risk in this population by omitting other more sensitive markers that may partially explain the higher prevalence of CVD risk in this population.

While the results of the RADICAL-PC trial [52] have shown that CVD risk factors are highly prevalent across the PCa continuum, no prospective studies have examined the utility of traditional and subclinical CVD risk factors and whether they enhance our understanding of the pathways between risk factors and incident CVD in this population. Consistent with evidence from other settings [128, 207, 328, 333, 358-362], we found that traditional CVD risk factors did not adequately reflect the cardiovascular and metabolic impairments identified by subclinical CVD markers, notably reduced VO_2peak and higher adiposity included in this study. The subclinical CVD risk observed between groups places men with PCa commencing ADT at a higher risk of CVD, despite normal traditional risk factor values. Our findings suggest that subclinical CVD markers such as VO_2peak, adiposity and vascular health should be considered alongside assessing traditional risk factors in men with PCa [53, 65-67]. While decades of compelling evidence in cardiovascular settings [189, 207, 232, 365, 366] have shown that subclinical CVD markers such as cfPWV and AIx provide further mechanistic detail concerning clinical pathways not typically identified by traditional cardiovascular risk factors, the findings of this study and others [100, 127] does not appear consistent with the scientific literature. While the inclusion of subclinical CVD markers and traditional risk factors offers clinicians vital information and the opportunity to detect and manage risk while improving patient care in this susceptible population, the timing of these assessments may be more important (coinciding with medical castration 0.07 mmol/L rather than the initiation of ADT), given the wide variation in ADT mechanisms and medications currently prescribed. Therefore, future studies should consider the timing of their assessments to better characterise subclinical and traditional CVD risk in this population.

5.8. Strengths and limitations

The current study is strengthened by including a comprehensive series of objective assessments using gold standard techniques to thoroughly evaluate cardiovascular structure and function (CMR and echocardiogram), vascular health, body composition, and cardiorespiratory fitness in men with PCa commencing ADT. However, numerous limitations should be considered when interpreting the findings of this study. First, only a small number of men commencing ADT for PCa were studied, and power calculations were based on our randomised controlled trial *(Chapter Six)*. This was primarily due to the significant impact of the COVID-19 pandemic and our inability to actively recruit, enrol and conduct study assessments between 2020 and 2021. This led to the early cessation of study recruitment short of the intended sample size. In addition, three of 31 PCa participants completed their baseline assessments outside the strict four-week window due to the lockdown periods. While our inability to perform the baseline assessments for these participants was out of the candidate's control, the duration of ADT, particularly testosterone suppression preceding the baseline assessments for these three participants, may have influenced the results. Second, PCa patients commencing ADT were volunteers for an exercise training intervention study and may not represent the broader population group, given a potential penchant for exercise. Third, the CON was recruited via the community and a convenience sample of men who underwent regular cardiovascular health screenings at the Baker Heart and Diabetes Institute. These participants represented men interested in cardiovascular health and physical activity. While the 3:1 non-probability sampling ratio was chosen for the reasons mentioned above in Section 5.3, we acknowledge that it is not ideal compared to superior probability sampling ratios of 1:1 or 2:1[367, 368], which would have been more representative of the target population. Therefore, these results limit the CON's generalisability to the general population and the overall comparability to men with PCa. Fourth, it is also impossible to exclude that the CON recruitment bias has influenced the observed differences in cardiovascular health and cardiorespiratory fitness. Fifth, limitations associated with vascular health assessments are well-documented, specifically in established/severe pre-existing vascular disease and negative AIx. For these reasons, individual data points were excluded from the primary analysis in line with recommendations [130, 196, 342] and sensitivities analyses were performed to confirm these findings. Sixth, prior PCa treatments, including surgery or radiotherapy, differed widely among participants. While it may be challenging to undertake sub-group analyses given the small sample size, we cannot refute that these differences, especially previous radiation therapy or surgery, may have influenced the functional measures included in this

study. Seventh, although the sample was smaller than prior studies [100, 127] and included a comprehensive series of cardiovascular outcome measures due to its alignment with the randomised controlled trial in *Chapter Six* [100, 142], the possibility of Type I statistical error cannot be disregarded. Eighth, as detailed in the Methodology section (Section 4.2.3), this study used two DXA machines to analyse body composition. Therefore, the variation between DXA machines, despite using the same make/model and the same assessor across all timepoints, cannot be disregarded. Lastly, the cross-sectional design of this study hindered our ability to ascertain the clinical implications of our findings. Although it is possible to theorise by using exploratory analyses to compare with other contexts, causality cannot be inferred from these findings, which require further validation in prospective trials.

5.9. Conclusions

This cross-sectional study utilised gold standard outcome measures to quantify the clinical pathways that partly explain the higher frequency of traditional CVD risk factors among men initiating ADT. This study showed that VO_2peak, resting heart rate, serum triglycerides, and body fat percentage were key points of difference between men commencing ADT and CON. However, the clinical relevance of the statistical differences is unclear. Moreover, VO_2peak appears to be associated with better cardiovascular health in all participants included in this study. Future research would benefit from exploring the prognostic value of VO_2peak and other subclinical CVD markers on cardiovascular risk burden and endpoints in men with PCa. Given that CVD is highly prevalent among men with PCa, clinicians and supportive care staff should consider lifestyle counselling, including exercise interventions, to address this population's growing cardiovascular risk burden.

CHAPTER SIX: Evaluating the impact of exercise training on cardiac remodelling in men with prostate cancer undergoing androgen deprivation therapy: a randomised controlled trial.

6. Overview

This chapter presents the results of the EX-HEART trial, a randomised controlled trial that evaluated the effects of exercise training on cardiac remodelling in men with PCa undergoing ADT, compared to a non-exercise training usual care group. Comparisons between groups were evaluated via a generalised linear mixed model.

It is important to note that this study was markedly impacted by various challenges associated with research contract delays (ethics approved March 2018, research office and hospital contract delays from March 2018 to February 2019), ongoing recruitment difficulties (March 2019 to March 2020; October 2020 to May 2021), and the COVID-19 pandemic (March 2020 to October 2020; February 2021 to July 2021; ceased recruitment in July 2021). These obstacles were beyond the PhD candidate's control, causing the supervisory team to prematurely cease active recruitment, allowing the PhD candidate to concentrate on thesis preparations and remaining follow-up assessments for enrolled individuals.

6.1. Abstract

Introduction: ADT may increase CVD risk in men with PCa, partly stemming from treatment-related deleterious cardiac remodelling. Exercise training is known for its beneficial effects on counteracting adverse cardiac remodelling in CVD populations; therefore, we sought to evaluate the impact of exercise training on cardiac remodelling and other markers of cardiometabolic health in men undergoing ADT.

Methods: ADT-treated men were randomly assigned to exercise training (EX; n=16) or usual care (UC; n=15). EX completed a thrice-weekly aerobic and resistance training program for three months at moderate to vigorous intensities, including HIIT. All assessments were completed before or within one month of initiating ADT (baseline) and at a three-month follow-up. The primary outcome was cardiac remodelling (LVM: V) by CMR imaging. Secondary cardiovascular outcomes included LV mass index (LVMi), LVEDV index, LVSV index and LVCOi measured by CMR imaging and LVEF, GLS, LVMi, LVEDV, E/A, E/e', DT, and LAVI quantified by echocardiogram. Cardiorespiratory fitness (VO_2peak) was measured via a graded CPET (cycle ergometry). Other CPET-derived indices were also reported (peak power output, peak power output at VT, peak systolic and diastolic blood pressure, heart rate, VE/VCO_2, and RER). Vascular function was assessed by cfPWV and pulse wave analysis (AIx and other central and peripheral haemodynamic). Body composition via DXA and a series of patient-reported outcomes, including health-related QoL (EORTC QLQ C30 and QLQ PR25), cancer-related fatigue (FACIT-F), psychological distress (BSI-18), sleep disturbance (PSQI) and physical activity (Godin-Leisure Time Exercise Questionnaire) were also assessed. All analyses were completed using an intention-to-treat approach. Repeated measures analysis was performed between groups using a generalised linear mixed model.

Results: Mean EX attendance was 85% (range, 58-100%). Compared with UC, between-group differences for LVM:V (net difference, -0.13 ml/g, 95% CI -0.23, -0.03, group by time P=0.01; Cohens d effect estimate [d]=1.29), LVEDVi (13 ml/m^2, 95% CI 7.2, 18.4, P<0.001; d=0.90), LVSVi (11 ml/m^2, 95% CI 6, 17, P<0.001; d=1.21) and LVCOi (0.7 ml/m^2, 95% CI 0.3, 1.0, P<0.001; d=1.24) were detected in favour of the EX-group. In addition, a statistically significant between-group difference of 3.5 ml/kg/min (95% CI, 1.9, 5.0, P<0.001; d=0.71) for VO_2peak in favour of EX was detected when compared with UC. Similar between-group differences were noted for absolute VO_2peak (0.2 L/min, 95% CI, -0.1, 0.4, P<0.001; d=0.55) and peak power output (32 Watts, 95% CI 13, 51, P=0.001; d=0.66). Diastolic and central systolic blood pressure increased from baseline to three months in the UC group, resulting in a significant difference between groups

(all group by time P=0.04; d=0.39-0.62). No between-group differences were detected for cardiovascular outcomes quantified by echocardiogram, body composition, physical function, arterial stiffness, AIx, and most patient-reported outcomes (all; group by time P >0.05). In addition, a significant between-group difference in the EORTC-QLQ C30 score related to insomnia (18.6, 95% CI 1.8, 35.6, P=0.03; d=-0.81) was observed, which was related to the rise in insomnia symptoms reported in the EX-group only.

Conclusion: Exercise training prevented adverse cardiac remodelling and improved cardiorespiratory fitness in men undergoing ADT compared with UC. The findings from this study suggest that more vigorous exercise interventions initiated at the commencement of ADT are feasible, tolerable and appear efficacious in reducing cardiovascular risk burden in ADT-treated men. However, future trials with larger sample sizes are required to confirm these initial findings.

6.2. Introduction

ADT improves survival rates for men diagnosed with locally advanced and metastatic PCa [32]. Nonetheless, the adverse effects of ADT may impact health-related QoL in men with PCa [41]. Most randomised controlled trials, including exercise interventions, have focused on attenuating the adverse effects of ADT on body composition, bone mineral density, cardiorespiratory fitness, health-related QoL and psychological distress [247, 248, 251, 265, 369-374]. In contrast, limited investigative studies have focused on the cardiovascular effects of ADT [243], despite CVD affecting approximately 40% of men with PCa [53] and being the leading cause of non-cancer-related death worldwide [10]. While the association of ADT with CVD remains uncertain [65-67], many men will develop hypertension (45-61%), type II diabetes mellitus (16-25%) and obesity (30-48%) in the short-term [46, 52, 53, 375], and a small proportion (6-10%, with a wider confidence interval reported as high as 40% [67]) of men may experience cardiovascular events years following ADT [63, 77, 376, 377]. Hence, identifying strategies to detect and interventions to prevent these treatment-related adverse effects is critical.

Existing research recognises the critical role of androgens, such as testosterone, on the cardiovascular system [378]. Several epidemiological studies have discovered that low testosterone correlates with a higher frequency of CVD risk factors, thus increasing the risk of cardiovascular events and mortality in clinical cohorts [379-381]. Several prospective studies have shown that clinical hypogonadism may result in resting cardiovascular dysfunction, including impaired LV systolic function and adverse concentric cardiac remodelling (increase/decrease LV mass, decrease LVEDV) [155, 157, 158]. It has been hypothesised that these LV geometric patterns may be associated with incident hypertension and all-cause/cardiovascular mortality. Interestingly, data [161, 166, 189, 326, 382, 383] from the Multi-Ethnic Study of Atherosclerosis cohorts observed that adverse/concentric cardiac remodelling patterns were predictive of incident coronary artery disease, stroke and chronic heart failure in asymptomatic populations [161]. Notably, pre-clinical studies in animal models of PCa treated with ADT [159, 160, 168, 169] appear to reflect similar impairments in LV systolic function and adverse LV geometric patterns to those documented in trials of clinical hypogonadism and early echocardiographic studies in ADT-treated men. Emerging observational evidence in ADT-treated men indicates that men appear to have impaired resting cardiovascular dysfunction (GLS), with a 15% reduction from baseline in approximately 56% of participants during the first six months of treatment [384]. While this may be considered a sign of cardiotoxicity,

given the magnitude of change reported by Gheorghe et al.[384], the evidence concerning resting cardiovascular dysfunction in ADT-treated men remains inconclusive.

Based on the above, the effect of androgen deprivation seems to be more pronounced within the first few months of ADT, raising the question of whether the heightened CVD risk/events in ADT-treated men could be related to resting cardiovascular dysfunction or adverse cardiac remodelling [161, 166, 190]. Despite the preponderance of evidence linking the relationship between low testosterone, resting cardiovascular dysfunction and adverse cardiac remodelling to cardiovascular morbidity and mortality [161, 189, 326, 379, 381, 382, 385, 386], there has been no detailed investigation directly evaluating the impact of ADT on cardiac structure (cardiac remodelling), resting cardiovascular function (global systolic function) or associated cardiovascular risk factors in men with PCa. Whilst a few cross-sectional evaluations have focused on traditional cardiovascular risk factors in ADT-treated men and their potential association with cardiovascular events [52, 120], without more sensitive assessments, the evidence for this relationship remains yet to be elucidated.

Randomised controlled trial evidence has established the efficacy and effectiveness of exercise training in preventing some of the adverse effects of ADT [244, 266, 387, 388]. Notably, the combined effects of aerobic and resistance exercise training have shown beneficial effects on body composition, cardiorespiratory fitness, cardiovascular risk factors such as fasting blood glucose and insulin sensitivity, as well as patient-reported outcomes such as fatigue and health-related quality of life [243, 244, 246, 265]. While the beneficial effects of exercise training are considerable and widely documented, most clinical trial evidence has explicitly focused on body composition and assigning exercise training interventions that target this outcome (see *Chapter Three*) [243, 247, 251, 254]. Furthermore, higher-intensity aerobic exercise training has also been shown to prevent resting cardiovascular dysfunction and adverse cardiac remodelling, enhance cardiorespiratory fitness and decrease arterial stiffness in the general population, hypogonadal, sedentary ageing and CVD population groups [221, 225, 226, 389-392]. Intervention studies in hypogonadal older men and those receiving endogenous testosterone have shown that higher-intensity aerobic exercise training alone can induce superior cardiovascular benefits on cardiorespiratory fitness and cardiovascular function, induce physiological cardiac remodelling, and reduce cardiovascular risk factors, compared to testosterone supplementation alone [393, 394]. Therefore, despite hypogonadism, moderate continuous and HIIT may prevent age or sedentary-related cardiac

remodelling, improve cardiorespiratory fitness and cardiovascular function, and reduce CVD risk/event burden in this susceptible population group [225, 393].

Given that androgen deficiency in both hypogonadism and asymptomatic cohorts appears to increase the prevalence of CVD risk factors, resting cardiovascular dysfunction and adverse cardiac remodelling and that HIIT appears to elicit an appropriate physiological stimulus to overcome resting cardiovascular dysfunction and adverse cardiac remodelling [393, 395, 396], it seems reasonable to investigate the application of periodised more vigorous exercise interventions targeting resting cardiovascular function, physiological cardiac remodelling and cardiometabolic health in ADT-treated men. Therefore, this two-arm randomised controlled trial aimed to evaluate the effect of a three-month exercise intervention initiated concurrently with ADT compared with UC on (1) cardiac remodelling, (2) resting cardiovascular function and (3) cardiorespiratory fitness in men with PCa. The second aim of this randomised controlled trial was to determine the effect of three months of ADT on (1) cardiac remodelling, (2) resting cardiovascular function, and (3) cardiorespiratory fitness in men with PCa. We hypothesise that three months of exercise training will attenuate (1) concentric remodelling, (2) resting cardiovascular dysfunction, and (3) improve cardiorespiratory fitness in men receiving ADT and treatment with ADT would result in (1) concentric remodelling, (2) resting cardiovascular dysfunction and (3) reduced cardiorespiratory fitness in men with PCa.

6.3. Methods

The methodological approach for this investigation is described in detail in *Chapter Four*. This document has been prepared according to the CONSORT statement [397].

6.3.1. Study design

The trial detailed below is a two-arm parallel randomised controlled trial, whereby men with PCa either scheduled to receive or commencing ADT with or without chemotherapy were randomly assigned (stratified by age, >68 years or ≤68 years; randomisation [1:1]) to either EX or UC for an intervention period lasting three-months.

6.3.2. Participants and recruitment

The details regarding the participants, recruitment and eligibility criteria are detailed in *Chapter Five*. In brief, men aged 40 years and older with histologically confirmed PCa and currently

receiving ADT (within one month of initiating ADT) or scheduled to receive ADT with or without chemotherapy were eligible. Participants were excluded if they had: 1) an unstable heart condition determined by the study doctor and/or general practitioner, 2) previously received ADT or chemotherapy for the treatment of a previous cancer, 3) acute illness or any musculoskeletal, cardiovascular or neurological disorder that could inhibit exercise or put participants at risk during exercise testing, or 4) a permanent metallic implant, cardiac pacemaker, implantable cardioverter which is a contraindication to MRI imaging. A trial modification was undertaken in 2020 due to the results of the STAMPEDE trial [15], whereby men with low-volume metastatic PCa received ADT with chemotherapy. The trial was conducted at the Australian Catholic University and the Baker Institute (Melbourne, Australia) and eligible participants were referred by treating PCa clinicians from March 2019 to July 2021 (Figure 6.1). This trial was approved by the Alfred Health Human Research Ethics Committee (HREC/18/Alfred/4), Peter MacCallum Cancer Centre (18-205), Austin Health and Australian Catholic University (2018-70R), and all participants provided written informed consent before participating. This trial was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12618001155280). All procedures undertaken in this trial conformed to the standards set by the Declaration of Helsinki.

6.3.3. Exercise training intervention

The specific details related to the exercise intervention prescribed in this study are outlined in *Chapter Four (Methodology).* In brief, participants performed a thrice-weekly aerobic and resistance training exercise program for three months.

6.3.4. Exercise attendance and adherence.

The specific details related to exercise attendance and adherence calculation are outlined in *Chapter Four (Methodology).*

6.3.5. Adverse events

The specific details related to the adverse event reporting are outlined in *Chapter Four (Methodology).* Any adverse events during the exercise testing or three-month exercise intervention were recorded.

6.3.6. Outcomes measures

Chapter Four (Methodology 4.1.2) outlines the outcome measures related to this study. In brief, all participants attended an assessment session that included a comprehensive series of cardiovascular assessments. All participants were overnight fasted, voided and refrained from caffeine, alcohol and strenuous physical activity 24 hours before reporting to the laboratory.

The primary outcome of this study was LVM:V. In general populations and clinical cohorts, LVM:V is a prognostic marker of concentric remodelling and predictor of future cardiovascular events [161, 189, 382, 383]. Secondary outcomes included LV mass, LVEDV, LVESV, LVSV, LVCO, and LVEF were quantified by CMR imaging. CMR-derived variables are presented in raw form and body surface-indexed values.

A comprehensive echocardiogram assessed cardiac structure and function, including LVEF, GLS, LVM index, LVEDV, E/A, E/e', DT, and LAVI [280]. LVEF is a standard care outcome measure for detecting chemotherapy-induced cardiotoxicity (LV cardiotoxicity is defined as a 10% decline in LVEF to <50% or an overall >20% decline in LVEF) in individuals with cancer [277]. More recently, studies suggest that GLS may detect early signs of chemotherapy-induced cardiotoxicity in individuals with cancer [398]. This was supported by the recent European Society for Medical Oncology guidelines [399, 400], which suggests an absolute decline by >5% (relative decline of 12%) in GLS may be indicative of cardiotoxicity in individuals with cancer.

CPET measured cardiorespiratory fitness by determining VO_2peak with continuous cardiac monitoring, 12-lead electrocardiography, and respiratory gas analysis [293]. VO_2peak is the gold standard measure of integrative cardiovascular function and predictor of functional disability [141], cardiovascular events and all-cause and cardiovascular mortality in the general population and clinical cohorts [212, 216, 335]. Several other parameters were collected during the CPET, including VO_2peak (L/min), V_E/VCO_2, peak power output (Watts), peak power output at VT(watts), peak heart rate, and peak systolic and diastolic blood pressure, and RER. Physical function was assessed using the timed stair-climb power test [292, 401].

Arterial stiffness was evaluated using applanation tonometry (SphygmoCor CvMS, AtCor, Sydney, Australia) to measure cfPWV [130]. Pulse wave analysis via radial applanation tonometry was used

to estimate central blood pressure and calculate AIx. Other haemodynamic variables were collected during pulse wave analysis, including central systolic and diastolic blood pressure, brachial systolic and diastolic blood pressure, pulse pressure, augmented pressure, resting heart rate, and AIx (HR75) [130]. cfPWV is a reliable and accurate measure of arterial stiffness and a precursor of future cardiovascular events in the general population [128, 158]. Arterial stiffening and changes to pulsatile pressures are known contributors to adverse cardiac remodelling in the general and clinical populations with pre-existing CVD [158].

DXA was used to assess body composition (body mass index, whole-body total mass, lean mass, fat mass, body fat percentage, regional fat mass, fat-free mass, and trunk fat mass). Reductions in whole-body lean and fat mass are known to negatively affect body composition in ADT-treated men [44, 49]. They are also considered key contributors to cardiovascular events, all-cause and cardiovascular mortality, independent of their association with traditional CVD risk factors in the general population [185, 402-405]. Epidemiological evidence suggests that obese patients also exhibit higher cardiac output (as well as higher peripheral systolic blood pressures) than those with relatively normal body fat distributions. This is often associated with adverse (concentric) cardiac remodelling [321, 325, 404].

A comprehensive series of questionnaires were used to evaluate general and PCa-specific QoL, sleep, physical activity, and psychological distress. QoL was assessed using the EORTC QLQ-C30 and PCa-specific EORTC-QLQ-PR25 [302-304]. FACIT-F was used to assess cancer-related fatigue. Psychological distress was assessed using the Brief Symptom Inventory (BSI-18)[307]. The Pittsburgh Sleep Quality Index (PSQI) measures sleep quality and disturbance [309, 310]. Modified Godin Leisure-Time Exercise Questionnaire evaluated habitual physical activity [313]. Blood biochemical markers such as total cholesterol and high-density lipoprotein were assessed at baseline and measured as a part of the Australian Absolute Cardiovascular Risk calculation. The issue documented in *Chapter Five* regarding blood biochemical markers was the primary reason follow-up samples were not included in the below results. This issue was out of the research team's control. Clinical, demographical and lifestyle data were assessed by questionnaire.

6.3.7. Sample size calculation

Sample size calculations were based on limited research evidence evaluating the effect of exercise training on cardiac remodelling (LVM: V) in patients with CVD [226, 318, 389, 406, 407]. Clinical trials evaluating the effect of exercise training on LVM: V after three months revealed a moderate-to-large effect (d = 0.50-0.82) relative to the UC group [226, 318, 389, 406, 407]. A priori, 25 men in each group provided 80% power (P< 0.05, two-tailed) to detect a between-group difference in LVM: V. To ensure we acquired a complete dataset and accounted for participant withdrawal, we increased our sample size to 31 participants per group (attrition rate of 25%). Prior experience in exercise oncology trials indicated that a maximum attrition rate of 20% over three months was necessary to obtain a complete dataset [247]. The power calculation was completed using G*Power (v3.1.9.2) [408, 409].

6.3.8. Randomisation and blinding

Participants were randomised to EX or UC after the baseline evaluation. Participants were stratified by age (>68 years or ≤68 years) [410] and randomly allocated to each group in an allocation ratio of 1:1 using a computer-generated random number generator. The allocation sequence was concealed from research personnel (cardiac sonographers, radiographers, and research assistants) who participated in the assessment and training of study participants.

6.3.9. Usual care

UC participants were instructed to maintain their typical physical activity for three months and received no formal exercise training advice. Following the three-month study period, all participants (EX and UC arm) were offered a consultation with an exercise physiologist to develop an individualised exercise training program following the primary intervention period.

6.3.10. Statistical analysis

Statistical analyses were performed using SPSS (v27, IBM Australia, Sydney, NSW). Unless otherwise specified, data are displayed as mean SD for normally distributed data and median and interquartile range (IQR) for assumed non-normally distributed data. Categorical variables were presented as frequency and percentage. The normality of distribution was assessed by examining Q-Q plots of residuals. Independent t-tests or Mann-Whitney U tests assessed baseline characteristics between EX and UC pending normality of distribution. Chi-square tests were performed for

dichotomous variables at baseline only. The primary analyses were performed using the intention-to-treat methodology. A generalised linear mixed model for repeated measures was performed to determine the effect of the exercise training intervention on changes in primary (LVM: V) and secondary outcome variables between EX and UC. The generalised linear mixed models included a random effect (participants) to evaluate within-and between-group changes by group and group-by-time interactions (fixed effects), including baseline values for age, physical activity and VO_2peak (included for physiological assessments only). Within-group and between-group changes are presented as mean (absolute) change (95% CI) relative to baseline. The calculation of the net difference reflects the within-group mean change of the UC group from baseline subtracted by the within-group mean change of the EX-group from baseline. The link function determined the best-fitting models, as determined by visual inspection of the residual plot and the Akaike Information Criteria [411], which determines the appropriate covariance structure for mixed models. Clinically meaningful changes were estimated as effect estimates according to Cohen et al.[368] where *d* equals 0 to 0.2 (trivial effect size), 0.2 to 0.49 (small effect size), 0.5-0.79 (medium effect size) and >0.8 (large effect size). Effect estimates were derived by dividing the mean difference by the aggregate standard deviation. The missing data were not imputed because the generalised linear mixed model uses robust estimation methods to account for missing data. An α of 0.05 was adopted for all analyses.

6.4. Results

6.4.1. Recruitment

One hundred twenty-two patients were referred to the study and assessed for eligibility (Figure 6.1), and 31 participants were enrolled in the study (recruitment rate: 25%). A total of 55 participants were deemed ineligible (45% of referred participants). Previous ADT treatment was the most common reason for ineligibility (n=21, 17% of participants referred). Ten participants due to commence chemotherapy were also excluded, as the trial initially excluded participants who were scheduled to receive chemotherapy (recruitment initiation March 2019 until June 2019). However, due to advances in PCa treatment and the results of the STAMPEDE trial [33], concurrent ADT and chemotherapy are now considered standard care for men with low-volume metastatic disease at diagnosis. Therefore, we amended our inclusion criteria to include PCa patients receiving chemotherapy to reflect advances in medical treatment and clinical practice.

Thirty-Six (54%) eligible participants declined to participate for the following reasons: not interested (n=9), work commitment (n=4), personal/holiday commitment (n=9), unable to travel (n=10), COVID-19 restrictions (n=3), and acute illness (n=1). It is important to note that this study was considerably affected by the COVID-19 pandemic, which resulted in study closure from March 2020 to October 2020. This prevented three eligible participants from enrolling in the study. Moreover, the study was paused until further notice from July 2021 due to the escalating COVID-19 situation in Melbourne, Australia.

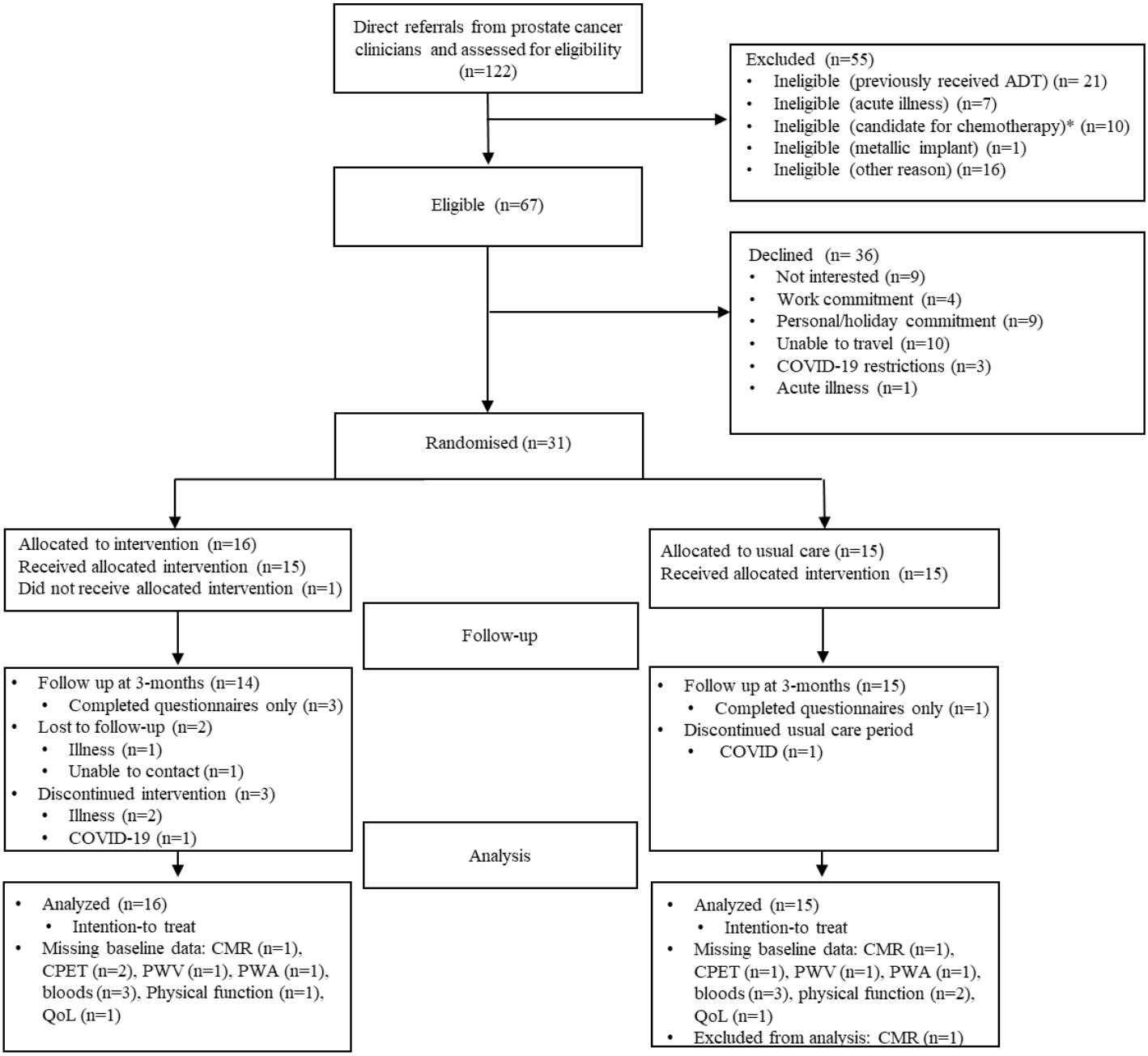


Figure 6.1: Flow diagram of the EX-HEART trial including men commencing ADT randomised to exercise training or usual care control for three months.

Abbreviations: ADT (androgen deprivation therapy), CMR (cardiac magnetic resonance), CPET (cardiopulmonary exercise test), PWV (pulse wave velocity), PWA (pulse wave analysis), QoL (quality of life),

6.4.2. Participant characteristics

Table 6.1 details the baseline characteristics of the 31 PCa participants involved in this study. Across EX and UC groups, most participants had completed post-secondary education (69% and 67%, respectively), were employed full-time (37% and 27%) and were married (81% and 60%). Alcohol consumption was similar between groups. Participants reported consuming alcohol two or more days per week (37% and 27%, respectively). Among PCa participants allocated to the EX-group, 19% of participants reported currently smoking. Cardiovascular comorbidities were highly prevalent in the UC group, with 53% and 33% of participants diagnosed with hypertension and hypercholesterolemia. In addition, men included in this study were deemed to have a medium CVD risk according to the Australian Absolute Cardiovascular risk score. Further, participants were mainly treated for hypertension with angiotensin-converting enzyme inhibitors (36-50% across both groups) and statin therapy (13-25%). Among men allocated to the UC group, 20% of participants were treated with calcium channel blockers. Compared to UC, men in the EX -group tended to be more physically active and reported higher adherence to the physical activity guidelines for individuals with cancer [314, 315] (47% vs. 15%). PCa staging was reported by the Gleason score, which was similar between groups. The most prescribed ADT were LHRH agonists (81% and 93%, respectively), and between 25-27% of participants have been prescribed both an LHRH agonist and anti-androgens. Three participants were scheduled to receive ADT and chemotherapy regimens following study enrolment. Prior PCa-specific treatments included surgery (radical prostatectomy) or radiation therapy.

6.4.3. Study attrition, attendance, and adherence

Thirty-one men commencing ADT were randomised to either the EX (n=16) or UC (n=15). From baseline to the three-month follow-up evaluation, participant retention was 93% (29 of 31 participants). Two participants were considered lost to follow-up (they did not complete physical assessments and questionnaires), and three participants discontinued the exercise intervention in the EX-group. The reasons for exercise intervention discontinuation in the EX-group were illness (n=2) and the COVID-19 pandemic lockdown periods (n=1). One participant allocated to the UC group discontinued the intervention period due to study closures during the COVID-19 pandemic between March 2020 and September 2020; however, they did complete the three-month follow-up questionnaires. The average time between initiation of ADT and baseline assessments was 17 days (range, 1-41 days). Importantly, the maximum range of time between ADT initiation and baseline

assessment was attributable to the three participants who performed their baseline assessment outside of the strict four-week window. This was due to the COVID-19 closure period in 2020. The follow-up evaluation was completed within 3.4 months. Chapters Five and Six had a 100 percent compliance rate across all timepoints for the pre-testing preparation requirements of fasting, voiding, abstaining from caffeine, alcohol, and strenuous exercise for 24 hours. The mean session attendance to the prescribed exercise training program was 85% (range, 58-100%). Adherence to the prescribed aerobic exercise training intensity was 83% (range, 59-100%) and aerobic exercise training duration was 82% (range, 60-100%). Similarly, adherence to the prescribed resistance training intervention was 98% (range 93-100%). Three of sixteen participants successfully completed their hybrid exercise intervention via videoconferencing and in-person sessions. Attendance and adherence to the hybrid exercise intervention were replicable to the face-to-face exercise intervention; consequently, attendance and adherence outcomes were included in the above calculations. The mean sessional rating of perceived exertion was 13/20.

6.4.4. Adverse events

No serious adverse events were related to the exercise testing and training intervention. A single intermediate-risk event occurred during a prescribed exercise training session. A participant with significant pre-existing CVD (chronic heart failure and atrial fibrillation; deemed safe by our study doctors) had an atrial fibrillation episode (n=1) in the warmup stage of his aerobic exercise training session. Immediately following this episode, the participant consulted his general practitioner and was referred to a cardiologist for review. Following medical clearance, the participant returned to the prescribed intervention after session modification. Two minor adverse events related to the exercise intervention were reported in two participants. These included a calf strain (non-specific)(n=1) and a bicep femoris strain (n=1). The aforementioned two minor adverse events were reported in participants undergoing the hybrid exercise intervention during the COVID-19 lockdown perio

Table 6.1: Baseline characteristics

	All participants (n=31)	Exercise training (n=16)	Usual care (n=15)
Age, years	66.5±9.5	66.6±9.2	66.3±10.2
Height, m	1.7±0.06	1.7±0.05	1.7±0.08
Body mass, kg	79.6 (74.0-97.7)	81.9 (74.0-98.8)	75.3 (73.3-95.2)
Body mass index, kg/m^2	26.3 (24.2-32.0)	27.0 (24.3-32.0)	25.2 (23.5-32.6)
Post-secondary education, n (%)	21 (68)	11 (69)	10 (67)
Employment full time, n (%)	10 (32)	6 (37)	4 (27)
Married, n (%)	22 (71)	13 (81)	9 (60)
Alcohol consumption, n (%)			
Two or more days per week	17 (55)	8 (47)	9 (53)
Current smoker n (%)	3 (9)	3 (19)	0 (0)
Cardiovascular comorbidities, n (%)			
Hypertension	14 (45)	6 (37)	8 (53)
Hyperlipidaemia	9 (30)	4 (27)	5 (33)
Chronic heart failure	1 (3)	1 (6)	0 (0)
Aortic stenosis	1 (3)	1 (6)	0 (0)
Prior myocardial infarction	1 (3)	0 (0)	1 (6)
Prior stroke	2 (6)	1 (6)	1 (6)
Diabetes	2 (6)	1 (6)	1 (6)
Cardiovascular medications, n (%)			
Beta-blockers	2 (6)	1 (7)	1 (6)
Angiotensin II inhibitor	13 (42)	8 (50)	5 (36)
Angiotensin Receptor blocker	2 (6)	0 (0)	2 (13)
Statins	6 (19)	4 (25)	2 (13)
Anti-arrhythmic	1 (3)	1 (6)	0 (0)
Calcium channel blocker	4 (13)	1 (6)	3 (20)
Anti-coagulant	2 (6)	1 (6)	1 (7)
Diuretic	1 (3)	0 (0)	1 (7)
Metformin	1 (3)	0 (0)	1 (7)
Cardiovascular risk score, %	9.6 ± 4.8	10.5±4.3	8.7 ± 5.5
Physical activity			
Godin Leisure-Time Exercise Score	26.3 ±24.5	32.6±28.0	19.5±18.7
Meets physical activity guidelines, n (%)	9 (31)	7 (47)	2 (15)
Prostate cancer			
Gleason score	7.9±1.0	8.0 ±1.0	7.8±1.0
Time since diagnosis, months	19 ±32.7	12.0 ±25.6	26.0 ±38.1

Prostate cancer treatment n (%)			
LHRH agonist	27 (87)	13 (81)	14 (93)
LHRH antagonist	5 (16)	3 (19)	2 (13)
Anti-androgen	7 (23)	4 (25)	3 (20)
LHRH agonist plus anti-androgen	8 (26)	4 (25)	4 (27)
LHRH agonist plus chemotherapy	3 (9)	2 (12)	1 (7)
Previous prostate cancer treatments, n (%)			
Previous radiation therapy	4 (13)	2 (13)	2 (13)
Previous radical prostatectomy	9 (29)	5 (31)	4 (27)
Previous chemotherapy	0 (0)	0 (0)	0 (0)
Other previous cancers	0 (0)	0 (0)	0 (0)

Data presented as mean ± standard deviation or median (interquartile range, 25th and 75th percentile) unless stated otherwise.

Abbreviations: LHRH (luteinizing hormone-releasing hormone). †Self-reported physical activity level of $\geq$ 150 min/week.[314, 315]

6.4.5. Resting cardiac structure and function

The effect of exercise training on resting cardiac structure and function are presented in Table 6.2, Table 6.3, and Figure 6.2. Post-CMR imaging was not available for seven participants due to high body mass index (n=1) (CMR contraindication; beyond pre-specified bodyweight thresholds), illness (n=2) COVID-19 (n=2) and loss to follow-up (n=2). A single participant was excluded from the analysis due to poor imaging quality (n=1). Compared to UC, between-group differences for the primary outcome of LVM: V resulted in a statistically significant difference between groups of -0.13 ml/g (95% CI, -0.2, 0.03; group by time interaction, *P*=0.01), in favour of the EX-group. In addition, a statistically significant between-group difference in LVEDVi (13 ml/m^2 95% CI, 7, 18; group by time *P*<0.001) was observed favouring the EX-group (9 ml/m^2, 95% CI, 5, 13) compared with UC (-4 ml/m^2, 95% CI, -8, 0.2). Favourable changes in LVEDVi and LVM: V were accompanied by proportional increases in LVSVi favouring EX compared to UC, which also resulted in a statistically significant between-group difference of 11 ml/m^2 (95% CI, 6, 17, group by time *P*<0.001). In contrast, UC was associated with a reduction in LVCOi (-0.5 ml/m^2, 95% CI, -0.7, 0.3), which was maintained in the EX-group (0.2 ml/m^2, 95% CI, 0.1, 0.4). This led to a statistically significant between-group difference of 0.7 ml/m^2 (95% CI, 0.3, 1.0; group by time *P*<0.001) for LVCOi. No between-group differences were observed for LVMi or LVEF. A time effect for LVESVi (time, *P* = 0.01) was reported between groups; however, this was related to the significant increase in LVESVi in the EX-group only (3 ml/m^2, 95% CI 0.7, 6). Between-group differences were similarly reflected in raw and non-body surface-indexed values. The results were consistent with the Cohen's *d* effect estimates observed in the analysis of body-surfaced indexed CMR-derived values, demonstrating large effects for LVM:V (Cohens *d* [*d*] =1.29), LVEDVi (*d* =0.90), LVSVi (*d*= 1.21) and LVCOi (*d*=1.44) in favour of the EX-group. These Cohens *d* effect estimates were also similar for the non-bodyweight indexed CMR values.

There were no statistically significant differences or low, medium, or large effect estimates related to exercise training for echocardiographic measures (Table 6.3). Both EX and UC groups showed similar resting cardiac structure and function values. There was a time effect (*P*=0.007) for an increase in GLS from baseline to three months, which appeared in the EX-group only (1.5 %, 95% CI, 0.4, 2.6).

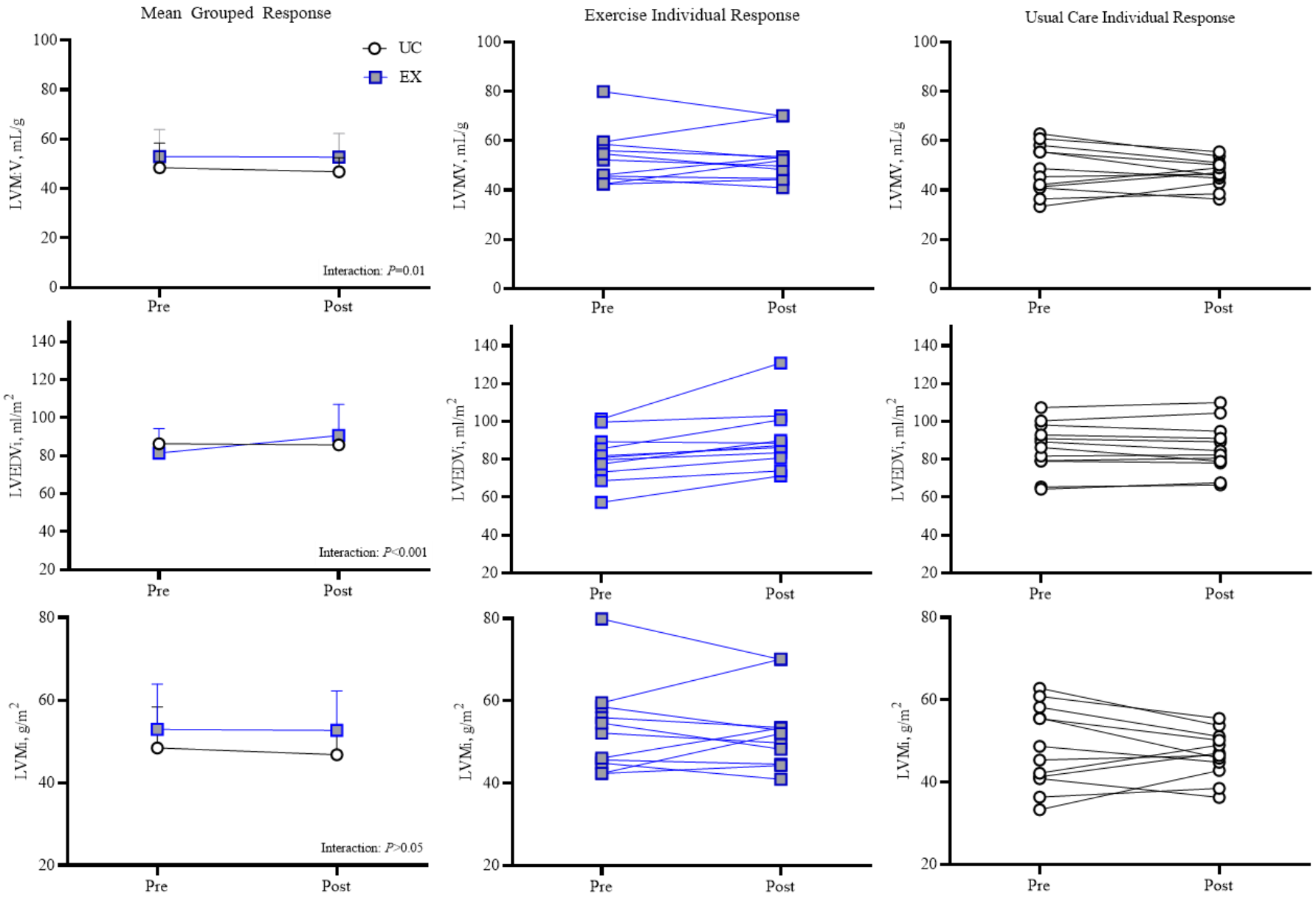

Mean Grouped Response
Exercise Individual Response
Usual Care Individual Response
UC
EX
LVMV, mL/g
LVEDVi, ml/m2
LVMi, g/m2
Interaction: P=0.01
Interaction: P<0.001
Interaction: P>0.05
Pre
Post

Figure 6.2 A, B & C: Resting cardiac structure assessed by CMR imaging between exercise training and usual care in ADT-treated men. Group comparisons and individual responses demonstrate that exercise training significantly improved LVM: V (P=0.01) and LVEDVi (P<0.001) compared to UC. No significant effects were detected for LV mass (P>0.05) (Figure A-C). Grouped data is presented as mean ± SD.

Abbreviations: CMR (cardiac magnetic resonance), ADT (androgen deprivation therapy), LVM:V (left ventricular mass to volume ratio), LVEDVi (left ventricular end-diastolic volume index), LVMi (left ventricular mass index).

Table 6.2: Mean baseline and three-month change values for CMR-derived indices between exercise training and usual care groups.

Outcome	Exercise	Usual Care	Net difference (95% CI)	Time, P	Group x Time interaction , P	Cohens *d* Effect sizes
LVEDV, mL						
Baseline	164±34	175±30				
Δ 3-months	18 (11, 25)§	-5 (-12, -1)□	24 (14, 34)	**<0.001**	**<0.001**	0.92
LVESV, mL						
Baseline	62±22	68±16				
Δ 3-months	6 (-0.9, 11)*	4 (-0.8, 9)	2 (-5, 9)	**0.02**	0.63	0.05
LVSV, mL						
Baseline	102±27	108±19				
Δ 3-months	12 (4, 20)□	-10 (-18, -3)*	22 (11, 34)	**0.004**	**<0.001**	1.21
LVCO, mL						
Baseline	6.1±1.5	6.8±0.9				
Δ 3-months	0.4 (-0.0, 0.8)	-1.0 (-1.4, 0.5)§	1.3 (0.6, 2.0)	0.12	**<0.001**	1.24
LVM, g/m^2						
Baseline	109±29	99±22				
Δ 3-months	-4 (-16, 7)	5 (-6, 17)	-10 (-26, 7)	0.45	0.23	0.47
LVESVi, ml/m^2						
Baseline	31±12	33±8				
Δ 3-months	3 (0.7, 6)*	2 (-0.7, 4.5)	1 (-2, 5)	**0.01**	0.41	-0.05
LVSVi, ml/m^2						
Baseline	51±11	53±9				
Δ 3-months	6 (2, 10)□	-5 (-9, -1)□	11 (6, 17)	**0.005**	**<0.001**	1.21
LVEF, %						
Baseline	62±11	57±17				
Δ 3-months	-0.2 (-3, 3)	-4 (-7, 0.7)*	3 (-0.7, 8)	0.89	0.10	0.81
LVCOi, mL/m^2						
Baseline	3.0±0.8	3.0±0.5				
Δ 3-months	0.2 (-0.1, 0.4)	-0.5 (-0.7, 0.3)§	0.7 (0.3, 1.0)	0.14	**<0.001**	1.44

Data presented as unadjusted baseline mean ± standard deviation or median (interquartile range, 25th and 75th percentile) unless stated otherwise. Within-group means to change (baseline to three months) presented as mean change (95% CI) relative to baseline (statistical significance from baseline; *P<0.05, □P<0.01, §P<0.001). Adjusted mean (95% CI) (including baseline values as covariates for age, habitual physical activity and VO_2peak) and net difference are presented as the difference between baseline and three months for exercise and usual care. Effect estimates are presented as Cohen's *d* effect sizes. LVEDV (end-diastolic volume), LVESV (end-systolic volume), LVSV (stroke volume), CO (cardiac output), LVM (mass), LVEF (ejection fraction).

Table 6.3: Mean baseline and three-month change values for echocardiographic outcomes between exercise training and usual care groups

Outcome	Exercise	Usual Care	Net difference (95% CI)	Time, P	Group x Time interaction , P	Cohens *d* Effect sizes
LVEF, %						
Baseline	60 (55-64)	60 (58-62)				
Δ 3-months	0.6 (-2, 3)	0.3 (-3, 2)	0.3 (-3, 4)	0.66	0.86	0.15
GLS, %						
Baseline	18.1±3.6	19.2±1.1				
Δ 3-months	1.5 (0.4, 2.6)□	0.8 (-0.1, 1.7)	0.5 (-0.8, 1.8)	**0.007**	0.32	0.02
LVMi g/m^2						
Baseline	84±17	92±14				
Δ 3-months	1 (-8, 11)	-6 (-15, 3)	7 (-6, 21)	0.76	0.28	0.53
LVEDVi, ml/m^2						
Baseline	53 (47-65)	58 (49-66)				
Δ 3-months	1 (-7, 9)	-5 (-13, 3)	6 (-6, 17)	0.86	0.32	0.06
E/A						
Baseline	0.8 (0.7-1.5)	0.8 (0.7-1.0)				
Δ 3-months	-0.0 (-0.3, 0.1)	-0.0 (-0.2, 0.2)	0.0 (-0.3, 0.2)	0.35	0.51	-0.13
E/e’						
Baseline	8.6±2.7	7.7±2.0				
Δ 3-months	-0.6 (-1.6, 0.3)	0.1 (-0.9, 0.8)	-0.7 (-2.0, 0.6)	0.19	0.30	-0.30
DT, cm/s						
Baseline	249.1±50.2	245.5±48.9				
Δ 3-months	28.8 (-13.4, 71.0)	1.5 (-44.3, 41.3)	27.3 (-32.8, 87.4)	0.17	0.36	-0.39
LAVi, ml/m^2						
Baseline	44±22	40±11				
Δ 3-months	3 (-2, 9)	2 (-8, 3)	1 (-7, 9)	0.25	0.79	-0.08

Data presented as unadjusted baseline mean ± standard deviation or median (interquartile range, 25th and 75th percentile) unless stated otherwise. Within-group means to change (baseline to three months) presented as mean change (95% CI) relative to baseline (statistical significance from baseline; **P*<0.05, □*P*<0.01, §*P*<0.001. Adjusted mean (95% CI) (including baseline values as covariates for age, habitual physical activity and VO_2peak) and net difference are presented as the difference between baseline and three months for exercise and usual care. Effect estimates are presented as Cohen’s *d* effect sizes. LV (left ventricular), LVEF (left ventricular ejection fraction), GLS (global longitudinal strain), LVMi (left ventricular mass index), LVEDV (end-diastolic volume), E/A (ratio of early and late diastolic filling velocity), E/e’ (ratio of early mitral inflow velocity to mitral annual early diastolic velocity), DT (deceleration time), LAVi (left atrial index).

6.4.6. Cardiorespiratory fitness and physical function

The effect of exercise training on cardiorespiratory fitness, other CPET parameters and physical function are presented in Figure 6.3 and summarised in Table 6.4. Nine participants did not perform the three-month follow-up CPET assessment due to the following reasons: declined (n=1), radiotherapy contraindication (gold brachytherapy seed insertion) (n=1), peak systolic blood pressure deemed unsafe to proceed by supervising cardiologist (>250 mmHg) (n=1), illness (n=2), COVID-19 (n=2), and lost to follow-up (n=2). No participants reached VO_2max or completed invalid tests (for example, failed to achieve VT). Twenty-three participants met the CPET criteria for VO_2peak [296]. VO_2peak increased by 8% in the EX-group after three months of ADT, compared to a 7% reduction in the UC group, which resulted in a significant between-group difference of 3.5 ml/kg/min (95% CI, 1.9, 5.0; group by time, P<0.001). This significant difference was similarly reflected in absolute VO_2peak (0.25 L/min, 95% CI, -0.12, 0.38; group by time, P<0.001) and peak power output (32 Watts 95% CI, 13, 51; group by time, P=0.001) between groups. Other CPET and physical function measures did not reach statistical significance between groups.

The Cohen's *d* effect estimates were consistent with the above analyses showing medium effects for body-weight indexed VO_2peak (d =0.71), absolute VO_2peak (d =0.55) and peak power output (d= 0.66) in favour of exercise training.

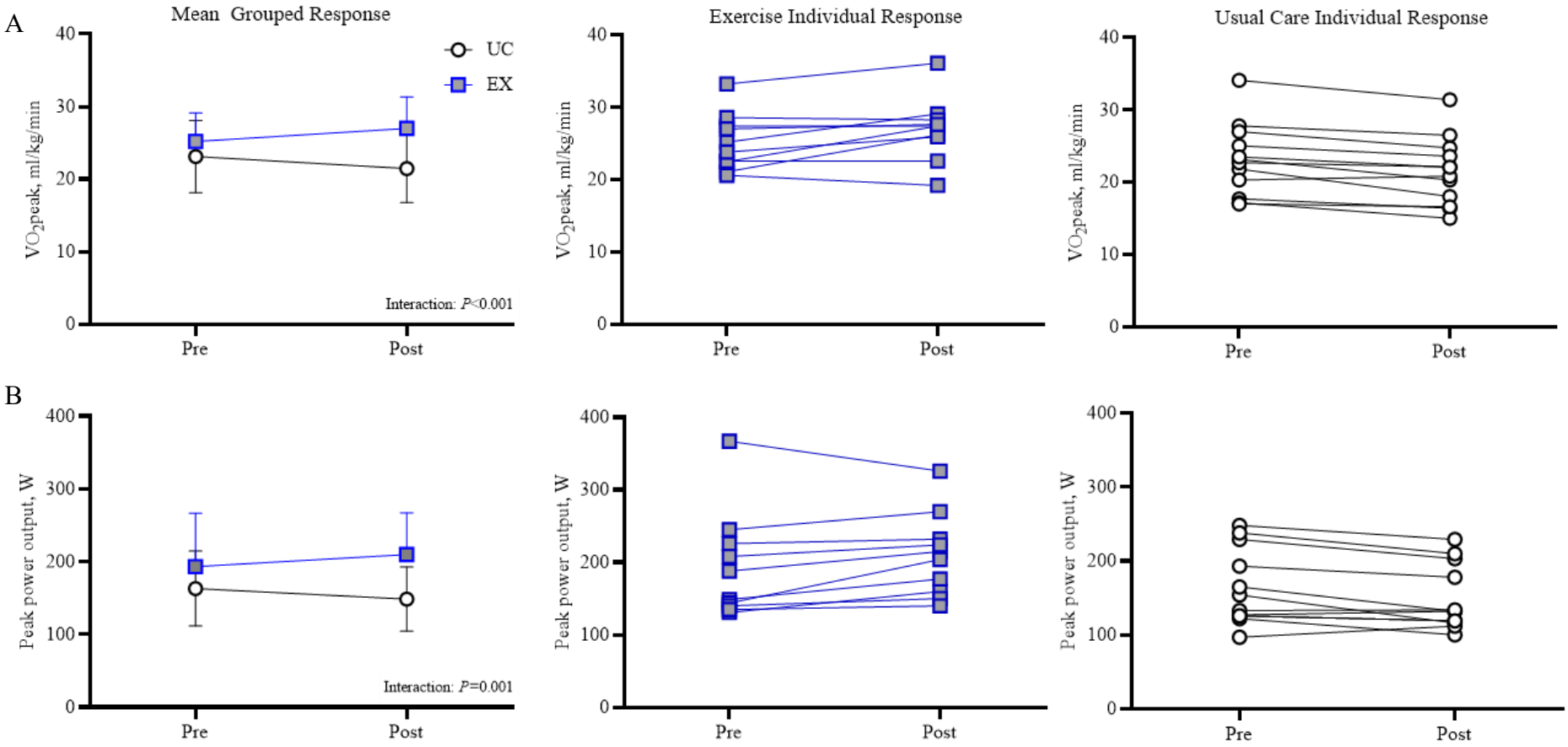


Figure 6.3 A & B: Cardiorespiratory fitness and peak power output assessed by cardiopulmonary exercise testing between exercise training and usual care in ADT-treated men.

Group comparisons and individual responses showed that exercise training significantly improved VO_2peak and peak power output compared to UC, resulting in a statistically significant difference of 3.5 ml/kg/min (P<0.001) and 32 Watts (P=0.001), respectively, in favour of the EX-group (Figure A and B). Group data is presented as mean ± SD.

Abbreviations: ADT (androgen deprivation therapy), VO_2peak (peak oxygen uptake), UC (usual care), EX (exercise)

Table 6.4: Mean baseline and three-month change values for CPET and physical function parameters between exercise training and usual care groups

Outcome	Exercise	Usual Care	Net difference (95% CI)	Time, P	Group x Time interaction, P	Cohens *d* Effect sizes
VO_2peak, L/min						
Baseline	2.1±0.7	1.9±0.4				
Δ 3-months	0.1 (0.4, 0.2)§	-0.1 (-0.2, -0.0)□	0.2 (-0.1, 0.4)	**0.008**	**<0.001**	0.55
Peak HR, bpm						
Baseline	154±21	141±16				
Δ 3-months	-1 (-8, 7)	-5 (-2, 12)	4 (-6, 14)	0.87	0.41	-0.02
VE/VCO_2, ml/min						
Baseline	28.6 (26.0-30.1)	28.6 (26.1-30.0)				
Δ 3-months	0.6 (-0.8, 2.1)	0.2 (-1.1, 1.6)	0.4 (-1.6, 2.4)	0.37	0.69	0.17
PPO at VT, Watts						
Baseline	114±69	93±29				
Δ 3-months	4 (-11,19)	-10 (-25, 5)	14 (-7, 35)	0.59	0.18	0.50
RER						
Baseline	1.24 (1.17-1.33)	1.19 (1.14-1.20)				
Δ 3-months	0.0 (-0.06, 0.06)	-0.0 (-0.06, 0.06)	0.0 (-0.09, 0.09)	0.91	0.98	-0.56
Peak SBP, mmHg						
Baseline	206±29	199±18				
Δ 3-months	-7 (-19, 5)	4 (-8, 16)	-10 (-28, 7)	0.28	0.23	0.46
Peak DBP, mmHg						
Baseline	84±15	84±7				
Δ 3-months	-8 (-16, -0.2)	0.4 (-7, 8)	-9 (-20, 3)	0.05	0.14	0.61
Physical function						
Stair climb, seconds						
Baseline	4.2 (3.5-5.7)	5.1 (4.1-6.3)				
Δ 3-months	-0.2 (-0.8, 0.3)	-0.1 (-0.5, 0.8)	0.3 (-1.2, 0.6)	0.44	0.42	0.24
Stair climb power, N						
Baseline	3578±1269	3041±935				
Δ 3-months	163 (-255, 582)	81 (-362, 525)	83 (-527, 692)	0.43	0.78	0.16

Data presented as unadjusted baseline mean ± standard deviation or median (interquartile range, 25th and 75th percentile) unless stated otherwise. Within-group means to change (baseline to three months) presented as mean change (95% CI) relative to baseline (statistical significance from baseline; **P*<0.05, □*P*<0.01, §*P*<0.001. Adjusted mean (95% CI) (including baseline values as covariates for age and habitual physical activity) and net difference are presented as the difference between baseline and three months for exercise and usual care. Effect estimates are presented as Cohen's *d* effect sizes. VO_2peak (peak oxygen uptake), HR (heart rate), minute ventilation, ventilatory carbon

dioxide (V_E/VCO_2), respiratory exchange ratio (RER), systolic blood pressure (SBP), and diastolic blood pressure (DBP), PPO at VT (peak power output at ventilatory threshold).

6.4.7. Body composition

The results for measures of body composition are presented in Table 6.5. Three-month follow-up assessments were not obtained in six participants due to illness (n=2), COVID-19 (n=2) and loss to follow-up (n=2). Overall, there were no statistically significant effects (including trivial effect estimates) of exercise training on any marker of body composition. However, there was a trend toward significance between groups for the net decline in trunk fat mass of -1.5 kg (95% CI, -3.0, 0.1; group by time, *P*=0.06).

Table 6.5: Mean baseline and three-month change values for body composition parameters between exercise training and usual care groups

Outcome	Exercise	Usual Care	Net difference (95% CI)	Time, P	Group x Time interaction, P	Cohens *d* Effect size
BMI, kg/m^2						
Baseline	28.0 (24.2-32.3)	25.4 (23.3-36.5)				
Δ 3-months	0.11 (-0.5, 0.7)	0.3 (-0.2, 0.9)	-0.2 (-1.0, 0.6)	0.69	0.59	0.07
Total mass, kg						
Baseline	84.3±15.1	87.2±19.5				
Δ 3-months	0.03 (-1.7, 1.8)	1.4 (-0.29, 3.1)	1.4 (-3.8, 1.0)	0.98	0.26	0.05
Lean mass, kg						
Baseline	55.9±7.6	57.0±8.8				
Δ 3-months	-0.2 (-0.9, 0.5)	-0.7 (-1.4, -0.8)*	0.5 (-0.4, 1.5)	0.47	0.86	0.19
Fat mass, kg						
Baseline	25.4±8.9	27.2±11.5				
Δ 3-months	0.3 (-1.4, 2.0)	2.1 (0.4, 3.7) □	-1.8 (-4.2, 0.53)	0.71	0.13	0.11
Body fat, %						
Baseline	30.2±6.3	31.2±7.1				
Δ 3-months	0.6 (-0.7, 1.9)	1.9 (0.6, 3.2) □	-1.3 (-3.2, 0.5)	0.39	0.14	0.14
Regional fat mass. k						
Baseline	29.1±6.1	30.0±6.9				
Δ 3-months	0.6 (-0.6,1.9)	2.0 (0.75, 3.2)□	-1.36 (-3.1,0.49)	0.32	0.14	0.14
Fat-free mass, kg						
Baseline	58.9±8.0	60.0±9.2				
Δ 3-months	-0.25 (-0.94, 0.4)	-0.5 (-1.3, 0.01)	0.39 (-0.56, 1.36)	0.46	0.10	0.20
Trunk fat mass, kg						
Baseline	15.3±6.2	16.4 ± 8.3				
Δ 3-months	-0.2 (-1.4, 1.0)	1.4 (-0.2, 2.4) □	-1.5 (-3.1, 0.1)	0.75	0.06	0.19

Data presented as unadjusted baseline mean ± standard deviation or median (interquartile range, 25th and 75th percentile) unless stated otherwise. Within-group means to change (baseline to three months) presented as mean change (95% CI) relative to baseline (statistical significance from baseline; *P<0.05, □P<0.01, §P<0.001. Adjusted mean (95% CI) (including baseline values as covariates for age, habitual physical activity and VO_2peak) and net difference are presented as the difference between baseline and three months for exercise and usual care. Effect estimates are presented as Cohen's *d* effect sizes. Abbreviations: Body mass index (BMI).

6.4.8. Vascular health

The effect of exercise training on vascular health and haemodynamic indices is presented in Table 6.6. Six participants did not complete the follow-up measurements for pulse wave analysis and cfPWV due to illness (n=2), COVID-19 (n=2) and loss to follow-up (n=2). A statistically significant difference between groups in brachial diastolic blood pressure of -5 mmHg (95% CI, -10, -0.2; group by time, *P*=0.04) was observed. Also, central systolic (-10 mmHg, 95% CI, -19, -0.1; group by time, *P*=0.04) and diastolic blood pressure (5 mmHg, 95% CI, -10, -0.2; group by time, *P*=0.04) were statistically significant between groups. Cohen's *d* effect estimates were consistent with the above analyses demonstrating small and medium effects on brachial diastolic blood pressure (*d*=0.39), central systolic (*d* =0.62) and diastolic blood pressure (*d* =0.39). No differences in other markers of vascular health, including cfPWV or AIx, were observed, with both groups exhibiting similar cfPWV and AIx values after three months.

6.4.9. Patient-reported outcomes

The results for patient-reported outcomes are presented in Tables 6.7 and 6.8. Two participants did not complete the questionnaires due to loss of follow-up. Changes in insomnia (EORTC-QLQ-C30) differed between groups, with the EX-group reporting greater rates of insomnia than the UC after three months (18.6, 95% CI, 1.8, 35.6, group by time, *P*=0.03). In contrast, Cohen's *d* effect estimates for the effect of exercise training on insomnia (*d* =-0.81) were considered trivial between groups. No differences were reported between groups for other patient-reported outcomes, including QoL, physical activity, psychological distress, fatigue, and sleep quality.

Table 6.6: Mean baseline and three-month change values for vascular and haemodynamic parameters between exercise training and usual care groups

Outcome	Exercise	Usual Care	Net difference (95% CI)	Time, P	Group x Time interaction, P	Cohens *d* Effect size
cfPWV, m/s						
Baseline	10.4±2.2	9.8 ±2.4				
Δ 3-months	-0.6 (-1.7, 0.4)	0.4 (-0.6, 1.5)	-1.1 (-2.5, 0.5)	0.24	0.17	0.48
Brachial SBP, mmHg						
Baseline	138±23	130±13				
Δ 3-months	- 3 (-10, 4)	5 (-2, 13)	-8 (-18, 2)	0.44	0.11	0.50
Brachial DBP mmHg						
Baseline	76±10	72±9				
Δ 3-months	-1 (-5, 2)	4 (0.1, 7)*	-5 (-10, -0.2)	0.37	**0.04**	0.39
Pulse pressure, mmHg						
Baseline	62±19	58 ±11				
Δ 3-months	-1 (-7, 5)	2 (-4, 8)	-3 (-12, 6)	0.71	0.50	0.35
Central SBP mmHg						
Baseline	125±21	118±14				
Δ 3-months	-2 (-9, 4)	7 (-0.4, 14)*	-10 (-19, -0.1)	0.46	**0.04**	0.62
Central DBP mmHg						
Baseline	77±10	73±9				
Δ 3-months	-2 (-5, 2)	3 (-0.7, 7)*	-5 (-10, -0.2)	0.35	**0.04**	0.39
Resting HR, bpm						
Baseline	61±9	66±10				
Δ 3-months	-2 (-8, 4)	1 (-5, 8)	-3 (-12, 5.5)	0.57	0.45	0.24
AIx, %						
Baseline	25±6	24 ±8				
Δ 3-months	-0.5 (-4, 3)	3.8 (-0.5, 6.7)	3 (-9, 1)	0.79	0.16	0.45
AIx [HR75], %						
Baseline	19±6	20±6				
Δ 3-months	-0.1 (-3, 3)	2 (-0.5, 5)	-2 (-7, 2)	0.94	0.22	0.44
AP, mmHg						
Baseline	11 (8-17)	10 (7-13)				
Δ 3-months	-0.1 (-3, 3)	3 (-0.3, 6)*	-3 (-7, 1)	0.90	0.10	0.46

Data presented as unadjusted baseline mean ± standard deviation or median (interquartile range, 25th and 75th percentile) unless stated otherwise. Within-group means to change (baseline to three months) presented as mean change (95% CI) relative to baseline (statistical significance from baseline; *P<0.05, □P<0.01, §P<0.001. Adjusted mean (95% CI) (including baseline values as covariates for age, habitual

physical activity and VO_2peak) and net difference are presented as the difference between baseline and three months for exercise and usual care. Effect estimates are presented as Cohen's *d* effect size. Pulse wave velocity (cfPWV), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean pressure (MP), Augmentation index (AIx), Augmentation index [heart rate 75 bpm] (AIx[HR75]), augmented pressure (AP).

Table 6.7: Mean baseline and three-month change values for quality-of-life parameters between exercise training and usual care groups

Outcome	Exercise	Usual Care	Net difference (95% CI)	Time, P	Group x Time interaction, P	Cohens *d* effect size
QLQ-C30						
Global health status						
Baseline	73.3±22.7	62.5±22.10				
Δ 3-months	4.8 (-5.8, 15.5)	-3.6 (-14.4, 7.0)	8.5 (-6.6, 23.6)	0.36	0.26	0.27
Physical functioning						
Baseline	94.6±6.7	85.2±13.8				
Δ 3-months	1.4 (-5.8, 8.6)	-4.3 (-11.5, 2.8)	5.7 (-4.4, 15.9)	0.70	0.26	0.53
Role functioning						
Baseline	93.3±25.8	77.3±24.6				
Δ 3-months	1.6 (-15.0, 18.2)	-2.3 (-19.1, 14.4)	3.9 (-19.7, 27.6)	0.84	0.73	-0.15
Emotional functioning						
Baseline	91.1±10.1	78.5±28.1				
Δ 3-months	0.6 (-4.9, 6.2)	1.9 (-3.6, 7.5)	-1.3 (-9.2, 6.5)	0.82	0.73	-0.04
Cognitive functioning						
Baseline	93.3±8.4	77.3±16.8				
Δ 3-months	-3.8 (-11.9, 4.3)	3.4 (-4.6, 11.3)	-7.1 (-18.5, 4.2)	0.35	0.21	-0.64
Social functioning						
Baseline	92.2±25.8	82.1±20.1				
Δ 3-months	-2.0 (-15.5, 11.4)	-4.11 (-17.6, 9.3)	-2.1 (-17, 21.3)	0.76	0.82	0.08
Symptoms						
Fatigue						
Baseline	13.3±14.1	35.7±30.2				
Δ 3-months	5.5 (-3.1, 14.2)	1.7 (-7.0, 10.4)	3.8 (-8.4, 16.1)	0.20	0.52	-0.28
Nausea						
Baseline	1.1±4.3	0.0				
Δ 3-months	2.7 (-2.2, 7.7)	3.6 (-1.3, 8.6)	-0.88 (-7.6, 6.0)	0.27	0.80	-0.28
Pain						
Baseline	11.1±22.4	19.0±22.5				
Δ 3-months	-2.6 (-15.4, 10.2)	1.0 (-11.8, 14.0)	-3.7 (-21.9, 14.5)	0.68	0.68	0.15
Dyspnoea						
Baseline	4.4±11.7	16.6±21.6				
Δ 3-months	2.4 (-5.9, 10.6)	6.3 (-1.8, 14.50)	-3.9 (-15.6, 7.7)	0.56	0.50	-0.27

Insomnia						
Baseline	17.7±21.3	35.7±33.2				
Δ 3-months	14.4 (2.6, 26.2)*	-4.1 (-16.0, 7.7)	18.6 (1.8, 35.6)	**0.01**	**0.03**	-0.82
Appetite loss						
Baseline	2.2±8.6	7.1±19.2				
Δ 3-months	2.3 (-2.5, 7.7)	2.4 (-2.6, 7.4)	0.2 (-7.0, 7.3)	0.31	0.96	0.21
Constipation						
Baseline	4.4±17.2	14.2±31.2				
Δ 3-months	0.4 (-10.5, 11.4)	-4.8 (-15.7, 6.6)	5.0 (-10.7, 20.7)	0.93	0.52	0.19
Diarrhoea						
Baseline	4.4±11.7	4.7±12.1				
Δ 3-months	0.21 (-5.0, 5.4)	-0.0 (-5.2, 5.2)	0.2 (-17.1, 7.6)	0.93	0.95	0.06
Financial difficulties						
Baseline	2.2±8.6	19.9±24.8				
Δ 3-months	3.9 (8.6, 16.5)	4.7 (-7.7, 17.2)	0.8 (-18.5,16.8)	0.53	0.92	0.15

Data presented as unadjusted baseline mean ± standard deviation or median (interquartile range, 25th and 75th percentile) unless stated otherwise. Within-group means to change (baseline to three months) presented as mean change (95% CI) relative to baseline (statistical significance from baseline; *P<0.05, □P<0.01, §P<0.001. Unadjusted mean (95% CI) net difference for the difference between baseline and three months for exercise and usual care control. Effect estimates are presented as Cohen's *d* effect size.

Table 6.8: Mean baseline and three-month change values for physical activity, fatigue, psychological distress, sleep quality and prostate-cancer-specific quality of life outcomes between exercise training and usual care groups

Outcome	Exercise	Usual Care	Net difference (95% CI)	Time, P	Group x Time interaction, P	Cohens *d* effect size
Godin Scale Score						
Baseline	32.6±28.0	19.5±18.7				
Δ 3-months	10.7 (-4.4, 26.0)	-2.4 (-18.4, 13.6)	13.1 (-8.9, 35.1)	0.16	0.23	0.49
Fatigue						
Baseline	47.4±2.6	39±12.1				
Δ 3-months	-0.6 (-3.3, 2.0)	-0.5 (-3.2, 2.2)	-0.1 (-3.9, 3.6)	0.62	0.93	0.00
BSI-18						
GSI						
Baseline	3.0±3.0	9.0±12				
Δ 3-months	0.2 (-2.3, 2.8)	1.4 (-1.1, 4.0)	-1.2 (-4.8, 2.4)	0.87	0.51	0.09
Depression						
Baseline	1.3±1.9	3.4±4.7				
Δ 3-months	-0.3 (1.4, 0.8)	0.2 (-1.0, 1.3)	-0.5 (-2.1, 1.2)	0.61	0.57	-0.08
Anxiety						
Baseline	2.0±4.4	3.0±4.2				
Δ 3-months	0.2 (-1.0, 1.4)	-0.7 (-1.9, 5.2)	0.9 (-0.8 ,2.5)	0.74	0.31	0.45
Somatisation						
Baseline	0.6±0.9	2.7±3.5				
Δ 3-months	0.4 (-0.8, 1.6)	1.9 (-0.6, 3.1)	-1.5 (-3.2, 0.2)	0.54	0.09	-0.09
QLQ-PR25						
Urinary symptoms						
Baseline	15.5±17.4	21.4±12.6				
Δ 3-months	-2.4 (-9.8, 4.9)	0.9 (-6.5, 8.3)	3.4 (-13.8, 7.0)	0.50	0.51	0.35
Incontinence aid						
Baseline	2.2±8.6	7.6±14.6				
Δ 3-months	7.9 (-5.4, 21.3)	1.8 (-11.2, 15.0)	6.1 (-12.7, 24.8)	0.23	0.51	-0.81
Bowel symptoms						
Baseline	2.7±5.1	7.1±14.5				
Δ 3-months	-0.5 (-4.0, 3.0)	0.1 (-3.4, 3.7)	-0.6 (-5.6, 4.3)	0.77	0.79	-0.04
ADT symptoms						
Baseline	8.1±9.1	13.0±8.3				

Δ 3-months	3.4 (-2.1, 9.0)	6.3 (0.80, 11.9)*	-2.9 (-10.8, 9.0)	0.22	0.45	-0.39
Sexual activity						
Baseline	42.2±26.6	28.5±22.0				
Δ 3-months	-9.8 (-22.5, 2.9)	-10.9 (-23.6, 1.6)	1.1 (-16.8, 19.1)	0.12	0.89	-0.20
Sexual function						
Baseline	57.2±20.1	53.8±20.8				
Δ 3-months	-5.3 (-18.3, 7.7)	-8.8 (-21.9, 4.2)	3.5 (-14.9, 21.9)	0.41	0.38	-0.17
PSQI scores						
Baseline	4.9±3.8	7.2±3.14				
Δ 3-months	-0.8 (-2.5, 0.9)	-0.6 (-2.4, 1.1)	-1.7 (-2.6, 2.2)	0.34	0.88	-0.09
Sleep quality						
Baseline	0.9±0.6	1.4±0.7				
Δ 3-months	0.2 (-0.2, 0.6)	-0.04 (-0.5, 0.4)	0.2 (-0.4, 0.8)	0.40	0.43	0.34
Sleep duration						
Baseline	0.7±1.0	0.4±0.6				
Δ 3-months	-0.3 (-0.7, 0.1)	0.1 (-0.3, 0.5)	- 0.4 (-1.0, 0.2)	0.17	0.16	0.43
Sleep efficiency						
Baseline	0.9±1.3	1.1±0.9				
Δ 3-months	-0.4 (-0.9, 0.2)	0.2 (-0.4, 0.2)	- 0.5 (-1.3, 0.3)	0.19	0.19	0.48
Sleep latency						
Baseline	0.4±0.6	1.1±0.82				
Δ 3-months	0.1 (-0.2, 0.5)	0.1 (-0.2, 0.5)	0.0 (-0.5, 0.5)	0.43	0.95	-0.12
Sleep disturbance						
Baseline	1.2±0.45	1.5±0.6				
Δ 3-months	-0.0 (-0.4, 0.5)	-0.3 (-0.7, 0.2)	0.3 (-0.3, 0.9)	0.83	0.36	0.46
Sleep medication						
Baseline	0.3±0.9	0.7±1.2				
Δ 3-months	-0.1 (-0.5, 0.2)	-0.3 (-0.7, 0.0)	0.2 (-0.3, 0.7)	0.43	0.44	-0.24
Daytime dysfunction						
Baseline	0.3±0.5	0.8±0.87				
Δ 3-months	-0.0 (-0.4, 0.4)	-0.4 (-0.7, 0.0)	0.4 (-0.2, 1.0)	0.92	0.17	0.44

Data presented as unadjusted baseline mean ± standard deviation or median (interquartile range, 25th and 75th percentile) unless stated otherwise. Within-group means to change (baseline to three months) presented as mean change (95% CI) relative to baseline (statistical significance from baseline; *P<0.05, □P<0.01, §P<0.001. Unadjusted mean (95% CI) net difference for the difference between baseline and three-months for exercise and usual care control. Effect estimates are presented as Cohen's d effect size. Abbreviations: Global Severity index (GSI)

6.5. Discussion

This is the first randomised controlled trial to evaluate the effects of exercise training on cardiac remodelling in ADT-treated men. Compared with UC, periodised aerobic and resistance exercise training initiated concurrently with ADT prevented adverse cardiac remodelling and improved VO_2peak.

A periodised exercise intervention, including HIIT, prevented adverse cardiac remodelling and improved VO_2peak in ADT-treated men.

Exercise training prevented adverse cardiac remodelling and improved LVEDV and other CMR-derived variables compared with UC. While we are unaware of any previous studies evaluating the impact of exercise training on cardiac remodelling in ADT-treated men, our results align with prior observations in animal studies and hypogonadal men with or without testosterone supplementation [168, 393, 412, 413], which showed aerobic exercise training offset changes in LV geometry and reversed cardiac remodelling in orchiectomised and ADT-treated mice. In contrast, the changes to LV geometry observed in the UC group surpassed age-related longitudinal reference values (increase in LV mass, LVM: V and declines in LVEDV, LVSV) generally expected within five to 10 years [49]. These adverse changes may confer a markedly higher risk of cardiovascular events than the EX-group, which abrogated age-related declines in LV cardiac remodelling despite severe hypogonadism [164]. This is important as the chronic, repeated high-intensity exercise stimulus, primarily responsible for inducing physiological cardiac remodelling, was a normal physiological response to haemodynamic demand, which has been similarly observed in other settings [390, 394, 414]. While our findings have highlighted the beneficial effects of higher-intensity aerobic exercise training on cardiac remodelling in ADT-treated men, its relation to CVD risk reduction remains speculative. Our findings suggest that integrating higher-intensity exercise training could offer substantial cardiovascular benefits by preventing age-related or ADT-induced declines in LV remodelling in ADT-treated men [164]. However, future prospective studies with larger sample sizes, longer durations, and more vigorous exercise interventions must confirm our initial findings.

VO_2peak is a known marker of integrative cardiovascular function strongly associated with poor prognoses, all-cause and cardiovascular mortality in the clinical and general population cohorts [212-214, 216, 223, 415-418]. However, the effects of exercise training on VO_2peak in ADT-treated men are limited [243]. Our study showed that a combined aerobic exercise and resistance training

intervention, including HIIT, markedly improved VO_2peak by 8% (between-group difference of 3.5 ml/kg/min) in the EX-group. These results differ from a prior trial in 97 ADT-treated men, who found that combined aerobic and resistance training exercise interventions, including moderate to vigorous exercise intensities, led to modest improvements in VO_2peak (~1-2%) after six months [248]. Notably, our trial prescribed a combination of moderate continuous training and HIIT, which has been shown to have greater cardiovascular benefits in the general population and clinical cohorts than moderate continuous training interventions alone [141, 225, 226, 389, 392, 419, 420]. Notably the 3.5 ml/kg/min difference between the EX and UC groups is particularly notable, given that for every one-unit MET (3.5 ml/kg/min) increase in VO_2peak, the risk of all-cause and cardiovascular mortality in the general population is reduced by 13% and 15%, respectively [212, 213, 216]. We, therefore, contend that the magnitude of difference observed in our study is clinically meaningful [216]. It may confer substantial cardiovascular benefits for ADT-treated men, especially given the higher prevalence of CVD reported in this population group. Therefore, our findings highlight that incorporating a combination of moderate continuous exercise intensities combined with HIIT and resistance training may reduce the CVD burden in this population.

Favourable changes in VO_2peak and cardiac remodelling could not be explained by arterial stiffness.

Arterial stiffness and wave reflection measurements are important predictors and often precursors of future cardiovascular events in the general population and those with pre-existing CVD [128, 130]. However, the effect of the optimised, more vigorous exercise intervention on cfPWV and wave reflection appeared limited in our cohort. No differences were observed between groups after three months in ADT-treated men. Our results align with data from 97 ADT-treated men who reported no effects of a six-month combined exercise intervention on arterial stiffness or wave reflection values [248]. Nevertheless, the lack of detectable differences in this trial and others [248] may partly be explained by being underpowered to detect statistically significant values. Despite the absence of statistical differences, medium effect sizes (d = >0.5) in favour of exercise training were observed for most vascular health indices in this trial, suggesting that the absence of detectable differences is likely due to the small sample size. Moreover, another possible explanation for the lack of differences may be related to the time-course of exercise-induced arterial remodelling [239-241]. Studies in healthy and CVD populations examining the time course of vascular adaptations suggest that functional and structural arterial remodelling occurs at different time points throughout an

exercise intervention period [239-241]. For example, changes in conduit artery function (first two to four weeks) precede structural adaptations, followed by a gradual increase in vascular structure (four to eight weeks) in response to repeated exercise-induced shear stress [239]. While biological risk factors associated with cancer, ADT and CVD [78] may impede vasodilator capacity, the time-course of exercise-induced structural arterial remodelling may have differential effects in ADT-treated men, possibly explaining the negligible effects of short-term exercise interventions on arterial stiffness in this population group [100, 127, 248]. Our findings highlight the need for future studies to include multi-modal vascular imaging to fully elucidate functional and structural vascular adaptations (e.g., FMD) across different time points throughout a prescribed exercise intervention during ADT. This may help guide the design of future exercise intervention trials targeting vascular health in ADT-treated men.

Negligible differences between groups were detected for body composition and most patient-reported outcomes. This lack of difference in body composition differs from previous exercise intervention trials [247, 248, 254] in ADT-treated men and the results from our meta-analysis [243], in which combined exercise interventions improved whole-body lean mass and reduced fat mass and other markers of adiposity [243]. Although the resistance exercise training prescription was similar to prior observations [247, 248, 254, 266], the greater emphasis on higher intensity aerobic exercise training assigned to participants and smaller sample size may partially explain the non-significant results, especially in light of negligible effect size estimates. In addition, it is noteworthy that two different DXA machines (same make/model) were used for this study across different sites. While the technologist ensured the procedures were the same across both sites, all participants were assessed using the same machine at baseline and three-months. However, we cannot exclude that using two different DXA machines may result in high inter and intra-variation and may have influenced the results.
Furthermore, several studies have reported small beneficial effects of exercise training on fatigue, and health-related QoL, including sexual function in ADT-treated men [247, 370, 374]; this trial found no statistical differences between groups for patient-reported outcomes of QoL or fatigue. Although several systematic reviews and meta-analyses have shown small positive effects of exercise training on QoL and fatigue in men with PCa [265, 421, 422], the lack of detectable differences may be potentially related to the small sample size given that small to medium effect sizes observed in favour of exercise training for the EORTC QLQC30 and EORTC QLQPR25

functional and symptoms scales. While the larger body of evidence indicates that exercise training has shown small but significant effects on fatigue in men with PCa [265, 421-423], our observation was inconsistent with the broader evidence. One possible explanation may be related to the fact that participants included in this trial were least fatigued at baseline compared to other cancer populations [304, 305, 423]. Future studies, especially those investigating the effect of exercise training on cancer-related fatigue, should include participants experiencing fatigue [424, 425] to understand better the impact of HIIT in this susceptible population.

Moreover, we found higher insomnia symptoms in the EX compared to the UC group in the subgroup of the EORTC QLQC30. While other systematic reviews and guideline recommendations have shown the beneficial effects of exercise training on sleep and insomnia symptomatology [314, 426, 427], limited data exist regarding the effect of exercise training, particularly HIIT, on sleep quality in ADT-treated men [428] and other cancers [429]. Therefore, the reported significant differences appear entirely coincidental in light of the small sample size and the negligible effect size. In light of the prevalence of fragmented sleep quality in ADT-treated men [430], future research is required to evaluate the effect of exercise training on insomnia and insomnia-related symptom clusters in ADT-treated men to understand the therapeutic benefits of exercise training better.

Cardiac contributions could be central to VO_2peak improvements.

The results of this trial also extend prior observations [248, 431] to provide preliminary evidence for the mechanism for improvement in VO_2peak in ADT-treated men. While we could speculate that the central contributions to VO_2peak improvements could be partially attributable to the chronic, intense exercise stimulus resulting in higher haemodynamic demand [141, 225, 226], further investigations focusing on the integrative assessment of VO_2peak (exercise stress) in ADT-treated men should be considered. Understanding the central and peripheral contributions to VO_2peak may help improve therapeutic exercise training strategies, given the association of VO_2peak with cardiovascular morbidity, all-cause and cardiovascular mortality in older men. However, our findings remain critical for future investigation [216].

Clinical implications

This randomised controlled trial was conducted in ADT-treated men with a history of cardiovascular risk factors and pre-existing CVD conditions. Despite several barriers, the periodised exercise training intervention was well-tolerated and had high attendance and adherence compared to other trials [247, 248, 254]. While the ongoing recruitment challenges present in this trial are similar to others [271], the adverse events related to the intervention were minimal and similar to other trials (see Chapter Three [243]). The periodised exercise training intervention was assigned at moderate to vigorous exercise intensities, including HIIT and was progressively increased over three months, as similarly assigned in other settings [225, 226, 319, 389]. Our findings indicate that assigning a higher intensity combined exercise intervention prevented adverse cardiac remodelling and improved VO_2peak compared with UC. As adverse cardiac remodelling and VO_2peak are predictors of cardiovascular events and mortality [216, 223], our findings suggest that moderate continuous exercise training and HIIT could be cardioprotective and should be considered the preferred approach to reducing the CVD risk burden in ADT-treated men. Given that the 3.5 ml/kg/min difference between EX and UC translates to a risk reduction in all-cause and cardiovascular mortality by ~13% and 15% [216], the long-term implications of the above results on cardiovascular outcomes still need to be determined. While the literature provides examples of heterogenous exercise prescriptions that have demonstrated some beneficial effects on cardiovascular risk factors [243], assigning exercise interventions targeting cardiometabolic health (e.g., including HIIT) may offset the cardiovascular effects of ADT and potentially reduce future CVD risk in this susceptible population. However, future trial designs should consider including reliability studies and the calculations of a minimal clinically important change to provide more congruent practical and clinical interpretations of the findings related to exercise training on cardiovascular and metabolic health markers in ADT-treated men.

6.6. Strengths and limitations

There are several strengths and limitations worthy of comment and should be considered when interpreting the results of this study. This study expands on prior work [247, 248, 251, 254, 369, 370, 432, 433] by investigating the effect of exercise training on mitigating cardiovascular risk in men treated with ADT. This study also addressed a clinically relevant question related to identifying and mitigating markers of cardiovascular health driven by potential changes to LV cardiac mass and volumes, as similarly investigated and established in CVD populations [225,

226, 390].This study included a series of gold-standard objective assessments and patient-reported outcomes to thoroughly examine the impact of a highly effective periodised exercise training intervention on cardiac remodelling, vascular health, cardiorespiratory fitness, physical function, body composition and patient-reported outcomes in ADT-treated men. The above was strengthened by our strict inclusion criteria, which specifically allowed us to investigate the cardiovascular effects of ADT. However, certain limitations should be considered when interpreting the outcomes of this trial. First, due to recruitment difficulties exacerbated by the COVID-19 pandemic, we ceased recruitment short of the intended sample size. This resulted in a modest drop-out rate and difficulty completing scheduled follow-up assessments during the COVID-19 lockdown periods between March 2020 to October 2020 and February 2021 to July 2021. Second, although we used several recruitment pathways to recruit participants, our recruitment uptake was hindered by project initiation barriers (contract delays) and the COVID-19 lockdown periods in Melbourne, Victoria, which limited the continuity of recruitment and our ability to be present or remind clinicians of the trial. This resulted in many potential participants screened deemed ineligible as they had previously received ADT or were outside the strict four-week window. Due to the COVID-19 study closure period between March 2020 and October 2020, three participants completed their baseline assessment outside the strict four-week window. While the above protocol deviation was out of our control, these participants would have achieved testosterone suppression (independent of ADT type). Therefore, the impact of testosterone suppression in these participants may have influenced the results. Third, participants volunteered for an exercise training intervention trial and may not be representative or generalisable to the broader community of men with PCa commencing ADT. Fourth, several participants included in the trial had previously undergone radical prostatectomy or radiotherapy, and some participants received radiotherapy and/or chemotherapy concurrently during the intervention period. Therefore, the impact of prior or concurrent treatments may have influenced the results of all outcomes reported in this thesis. In addition, it is important to note the variance in ADT type (87% received LHRH analogues vs. 16% received LHRH antagonists) included in this study. While most participants were administered with LHRH analogues, the time course to testosterone suppression differs widely and especially in those administered with LHRH antagonists. While it would be prudent to perform a sub-group analysis related to ADT type, the differences in the pharmacokinetics and clinical response time to castration levels may have influenced the results [12, 434]. Fifth, another limitation was the inability to blind all outcome assessors conducting the

assessments for three months due to resource limitations and financial constraints. This included the PhD candidate performing most of the baseline and post-assessment sessions, including blood collection (venepuncture), body composition (DXA), vascular function (PWA, PWV), and CPET, as well as the exercise training sessions with some support. However, for the assessments that included multiple assessors (CPET) or diagnostic examinations, e.g., CMR imaging or echocardiography, the research assistants, sonographers, and cardiologists were to refrain from asking the study coordinator or participants their group allocation. Sixth, despite the importance of cardiovascular and physiological measurements to the overall conclusions of the study, no formal reliability study, including clinically meaningful changes, was conducted or incorporated into the study design; only CVs were reported. While this is doubtlessly a limitation of the study design, the CVs reported in Chapter Four were consistent with trials performed in PCa [142, 217] and cardiovascular cohorts [435-438]. Seventh, as mentioned in the Methodology and Section 6.5, two DXA machines (same make/model) were used for this trial due to the transfer of the trial to be completely performed at the Baker Institute rather than ACU. While the short-term repeated CVs for DXA remain within normal limits, the high variation between machines cannot be excluded. Lastly, due to the ongoing COVID-19 pandemic and widespread closures of gymnasiums, the delivery of the exercise training intervention shifted to video-delivered telehealth. Although participants were supervised and had access to appropriate equipment (e.g., heart rate monitoring), the intensity of resistance training was likely inferior to the intended prescription. Despite these limitations, we detected between-group differences in the primary outcome (LVM: V), likely due to the use of the gold standard and highly sensitive measures (CMR imaging). This may mean that the initially calculated sample size from a non-cancer population may have been overestimated. Although we may have been underpowered to detect changes in vascular health, body composition and other outcome measures were also included in this study.

6.7. Conclusions

This trial demonstrated that a periodised exercise training intervention, including HIIT, prevented adverse cardiac remodelling and improved VO_2peak in ADT-treated men. Future research would benefit from longer-duration exercise interventions and prolonged follow-up to examine whether the considerable cardiovascular benefits observed in this trial remained after 12 months. Given that our study showed minor intervention-related adverse events, clinicians, and supportive care staff within PCa care should consider recommending exercise training at the commencement of

ADT to manage cardiovascular risk and other ADT-related concerns throughout their treatment continuum.

CHAPTER SEVEN: Summary, key findings, strengths, limitations, and conclusions

7. Overview

The final chapter of this thesis presents an integrated overview of key findings from the two systematic reviews (*Chapters Two and Three)*, a cross-sectional study (*Chapter Five*), and a randomised controlled trial (*Chapter Six*) reported in this dissertation. This chapter also briefly addresses the overall strengths and limitations of the experiments and, by extension, this thesis before highlighting recommendations for further research.

7.1. Summary

ADT is an effective cancer treatment that reduces biochemical recurrence and PCa-specific mortality and extends survival [32]; however, ADT is associated with several adverse effects [41] (e.g. CVD [53]). It has been widely theorised that the heightened risk of CVD may be related to the biochemical changes induced by ADT, such as those deleteriously altering cardiac geometry and vascular function [159, 160, 169]. This line of inquiry is supported by observational data [159, 160, 169] and prompted decades of investigative trials to determine the association of ADT with incident cardiovascular events. Despite these efforts, the association of ADT with cardiovascular morbidity and mortality remains unclear [54, 57, 76, 77]. Moreover, it is known that traditional cardiovascular risk factors correlated with cardiovascular events are mainly a consequence of and mediated by subclinical CVD markers (e.g., arterial stiffness, cardiorespiratory fitness) [439]. While some of the emphasis has shifted towards investigating the effect of ADT on subclinical CVD markers [100, 126, 182], the degree to which subclinical CVD markers evaluated in prior studies adequately reflect the clinical pathways/mechanisms by which alter CVD risk factors remains unclear [243]. Given that CVD is the primary cause of mortality among men with PCa [10] and that cardiovascular and metabolic toxicities are highly prevalent within the first 12 months of ADT [44], investigating the effect of exercise training on markers of cardiovascular and metabolic health is clinically relevant and has important implications for men with PCa throughout the cancer treatment continuum. Furthermore, emerging evidence supports the concurrent prescription of combined aerobic and resistance exercise training to counteract the adverse effects of ADT and, to a lesser extent, markers of cardiometabolic health in ADT-treated men [244, 265, 387]. However, most exercise interventions in prior clinical trials [247, 248, 251, 254] have applied lower aerobic exercise training intensities compared with guideline-driven advice in other settings [221, 440-442], which may partly explain the trivial effects observed on markers of cardiometabolic health to

date. Therefore, this PhD aimed to generate new knowledge and provide insight into the mediators of cardiovascular risk (subclinical CVD markers) while investigating the effects of a combined aerobic and resistance exercise training intervention, including HIIT, on markers of cardiovascular and metabolic health in ADT-treated men. The following section will address each key finding separately, followed by the overall experimental work strengths, limitations, and conclusions.

To address some of the gaps above, the specific aims of this thesis were:

1. To investigate the influence of pre-existing CVD on all-cause mortality, cardiovascular mortality, and cardiovascular events in PCa patients treated with ADT *(Chapter Two)*
2. "To evaluate the effect of exercise training on cardiometabolic health in men with PCa receiving ADT *(Chapter Three)*."
3. To evaluate measures of vascular health in men with PCa commencing ADT relative to age-matched non-cancer controls *(Chapter Five)*.
4. To examine the relationship between cardiorespiratory fitness, body composition, cardiovascular structure and function, traditional cardiovascular risk factors and vascular health in men with PCa commencing ADT and age-matched controls *(Chapter Five)*.
5. To evaluate the effects of a three-month exercise intervention initiated concurrently with ADT on (1) cardiac remodelling, (2) resting cardiovascular function and (3) cardiorespiratory fitness in men with PCa (*Chapter Six*).
6. To evaluate the impact of three months of ADT on (1) cardiac remodelling, (2) resting cardiovascular function and (3) cardiorespiratory fitness in men with PCa (*Chapter Six*).

The key findings from the thesis are:

1. ADT-treated men with pre-existing chronic heart failure or prior myocardial infarction had increased all-cause mortality rates compared with non-ADT controls and those without pre-existing CVD. The evidence linking pre-existing CVD to cardiovascular events or mortality in ADT-treated men was less conclusive *(Chapter Two)*.
2. In a subset of randomised controlled trials and non-randomised studies, exercise training improved body composition (lean and fat mass/size), diastolic blood pressure, cardiorespiratory fitness, fasting blood glucose and c-reactive protein. However, exercise training did not improve other traditional cardiovascular risk factors such as systolic blood pressure and blood lipid profile *(Chapter Three)*.

3. Men commencing ADT exhibited similar degrees of arterial stiffening to age-matched controls. Moreover, VO_2peak, body fat percentage, resting heart rate and serum triglycerides were significantly different between men commencing ADT and CON. Furthermore, LV mass, heart rate and arterial stiffness positively correlated with a higher VO_2peak *(Chapter Five)*.
4. A three-month multi-modal exercise intervention initiated at the commencement of ADT prevented adverse cardiac remodelling (LVM: V), increased LVEDV and improved VO_2peak, compared to UC (*Chapter Six*).

7.2. Key findings

Pre-existing CVD in ADT-treated men was associated with an increased risk of all-cause mortality; however, there was limited evidence to suggest that pre-existing CVD increased the risk of cardiovascular events and mortality in ADT-treated men.

The systematic review presented in *Chapter Two* addressed the influence of pre-existing CVD on cardiovascular morbidity and mortality in ADT-treated men. Based on five prospective [56, 57, 73, 76, 77] and six retrospective studies [55, 59, 71, 72, 74, 75], the results indicated that men with pre-existing CVD (chronic heart failure or prior myocardial infarction) treated with neoadjuvant ADT had higher all-cause mortality rates compared to men not treated with ADT or those men without pre-existing CVD [55, 59, 71, 73-75]. However, there was inconsistent evidence to suggest that ADT-treated men with pre-existing CVD had an increased risk of experiencing a cardiovascular event [56, 57, 76, 77] or cardiovascular mortality [72, 77]. A potential explanation may be that ADT duration and short-term follow-up periods may be insufficient to detect signals evident in observational studies with more extended follow-up periods. This is important to elucidate, particularly in light of the HERO trial [24], which detected higher cardiovascular event incidence rates in ADT-treated men (Leuprolide) with a history of CVD compared to Relguolix after two years. However, the association of ADT with CVD remains a subject of an ongoing investigation, particularly in light of the recent pharmaceuticals trial data that showed neither Leuprolide nor Degarelix increased the risk of developing cardiovascular events in men with pre-existing CVD [24, 70]. Conclusions are therefore limited regarding whether the presence or absence of pre-existing CVD in ADT-treated men mediates incident cardiovascular events and cardiovascular mortality. Nevertheless, the results of this systematic review indicated a need for future trials to shift the

emphasis to evaluating the intermediary/mediating effects (subclinical CVD markers), as this may highlight the mechanistic pathways from pre-existing CVD/risk factors to cardiovascular events in ADT-treated men. Future trials would value from including larger generalisable samples of men with PCa, consistent definitions of pre-existing CVD conditions and cardiovascular events and differentiating by ADT type and duration.

Current exercise training interventions improve some but not all markers of cardiometabolic health in men with prostate cancer treated with ADT.

In *Chapter Three*, a systematic review and meta-analysis synthesised available evidence regarding the "effects of exercise training on cardiometabolic health in men with PCa receiving ADT." This analysis indicated for the first time that current exercise training approaches improved some but not all cardiometabolic health markers in ADT-treated men. [247, 251-254, 292, 370, 373, 431-433, 443-448]. Specifically, exercise training, when compared to non-exercise training control, improved the 400-metre walk test "(−10.11 s, 95%CI [−14.34, −5.88]), diastolic blood pressure (−2.22 mmHg, [−3.82, −0.61), fasting blood glucose (−0.38 mmol/L, [−0.65, −0.11]), C-reactive protein (−1.16 mg/L, [−2.11, −0.20]) and body composition (whole-body lean mass 0.70 kg, [0.39, 1.01], appendicular lean mass 0.59 kg, [0.43, 0.76], whole-body fat mass −0.67 kg, [−1.08, −0.27]), whole-body fat percentage −0.79%, [−1.16, −0.42]), and trunk fat mass −0.49 kg, [−0.87, −0.12])." However, other markers of cardiometabolic health, such as systolic blood pressure and serum blood lipids, remained unchanged [247, 248, 251, 252, 433]. While these results are promising for select markers of cardiometabolic health, this review was limited by a small subset of randomised controlled trials and non-randomised studies, of which none included cardiometabolic health as a primary outcome. In addition, substantial clinical heterogeneity was present, which included differences in participant characteristics (comorbidities), ADT timing and duration, the timing of exercise testing procedures, exercise intervention characteristics and the exercise dose prescribed, thus making it difficult to conclude whether the overall effect was attributable to the exercise intervention. Lastly, the cardiovascular risk profile of participants included in this review was considered normal according to age-appropriate reference ranges [357], which could be related to recruitment bias. This may be one of the key reasons small effects were observed for some key markers of cardiometabolic health. Despite these limitations, the insights from this systematic review and meta-analysis have important clinical considerations for designing exercise interventions targeting cardiometabolic health. Future studies should consider incorporating higher-

intensity exercise interventions as it may represent a powerful means of counteracting ADT-induced biochemical changes that increase CVD risk in men with PCa.

Men with PCa exhibited similar levels of arterial stiffening compared to controls; however, VO_2peak, body fat percentage, resting heart rate and serum triglycerides differed between groups.

The cross-sectional study presented in *Chapter Five* compared markers of vascular health between men commencing ADT and age-matched controls. It also examined the relationship between vascular health, traditional CVD risk factors, cardiac structure and function, body composition, and cardiorespiratory fitness in all participants by correlation analyses. The prevalence of CVD and CVD events in PCa is widely documented [53]. However, it is currently unknown whether the higher prevalence of CVD may be linked to the shared biological risk factors between CVD and cancer [78]. It is well-documented that sub-clinical markers of CVD may mediate adverse changes in cardiovascular risk factors and/or cardiovascular events, particularly by changes in arterial stiffness [128, 130, 439]. Arterial stiffness and other subclinical CVD markers have strong prognostic value and are considered important predictors of cardiovascular events in the general population and chronic disease cohorts [128, 161, 216, 327]. However, the degree to which subclinical CVD markers could help explain the higher prevalence of traditional risk factors in men with PCa is currently unknown. In a cross-sectional study of 31 men commencing ADT, we found no statistically significant differences in arterial stiffness or wave reflection characteristics compared to age-matched controls (n=10). However, body-weight indexed VO_2peak, body fat percentage, resting heart rate, and serum triglycerides were significantly different between men commencing ADT and CON. This may indicate that subclinical CVD markers of cardiorespiratory fitness and adiposity may be a critical intermediary/mediating pathway in further elucidating the deleterious effects on traditional cardiovascular risk factors in men with PCa. While it was surprising that arterial stiffness and wave reflection characteristics were indifferent, it may be possible that these subclinical CVD measures could not capture the attributable risks related to the higher prevalence of cardiovascular risk factors noted in this population. Moreover, while the reduced VO_2peak observed in this cohort of men may be attributable to lower physical activity levels and higher adiposity [141], the magnitude of difference in VO_2peak by 38% is clinically significant. Given that VO_2peak was lower than normative values in men commencing ADT [343, 449], we theorise that the PCa cohort has a higher CVD risk over time than the control group, which

exceeded the predicted reference values. Furthermore, the utility of VO_2peak as a potential therapeutic target indicative of better cardiovascular health was also examined. When groups were combined, a higher VO_2peak was positively correlated with LV mass and negatively correlated with resting heart rate and arterial stiffness, indicating that a higher VO_2peak has beneficial effects on cardiovascular health markers. Nevertheless, from a clinical standpoint, our findings suggest that integrative indicators of subclinical CVD, such as VO_2peak, may assist in quantifying the intermediate steps in the pathways leading from traditional CVD risk factors to clinical CVD events and potentially with understanding the shared biological risk factors between cancer and CVD. Further, it reemphasises the growing notion, specifically in cancer, that assessing cardiorespiratory fitness can improve patient management and identify those needing targeted lifestyle interventions designed to reduce cardiovascular risk in men with PCa.

A three-month multi-modal exercise intervention initiated at the commencement of ADT prevented adverse cardiac remodelling, increased LVEDV and improved cardiorespiratory fitness compared to UC.

The study presented in *Chapter Six* was a randomised controlled trial that evaluated the impact of exercise training on cardiac remodelling in ADT-treated men. There is a growing consensus that exercise training initiated concurrently with ADT can prevent various ADT-related adverse effects in men with PCa [243, 244]. Evidence in older adults with CVD supports the beneficial effects of exercise training on preventing adverse cardiac remodelling and other lifestyle-related cardiovascular conditions [221, 222, 225, 226]. However, as mortality in men with PCa is more common from CVD than PCa, as described in *Chapter One*, exercise interventions targeting cardiac remodelling or lifestyle-related cardiovascular risk factors are limited [243]. This trial showed concurrent prescription of aerobic and resistance exercise training-induced changes in LVM: V, which were reflected in improvements in LVEDVi, LVSV and LVCO. In addition, exercise training favourably improved bodyweight-indexed VO_2peak by ~8% and power output by 32 Watts, compared with UC. These findings were consistent with prior observations related to VO_2peak improvements in ADT-treated men [248]; however, we present the first evidence that VO_2peak improvements coincided with CMR indices induced by exercise training as similarly reported in sedentary aging and athletic population studies [225, 226]. Considering the higher prevalence of CVD in this population and the fact that VO_2peak may be a viable target for reducing the risk of CVD (discussed in *Chapter Five*), the difference between groups (3.5 ml/kg/min) is noteworthy.

Observational studies suggest that for every 3.5 ml/kg/min (one unit MET), improvement in VO_2peak is associated with a risk reduction in all-cause and cardiovascular mortality by 13% and 15% in the general population and chronic disease cohorts [216]. Based on this, we could theorise that men assigned to the EX-group have substantially reduced their future CVD event risk compared with the UC group. Furthermore, it is essential to note that the observed LV geometry changes (trends towards concentric cardiac remodelling) in the UC group surpassed age-related longitudinal reference values generally expected within five to 10 years, which was attenuated with exercise training. No significant effects of exercise training were observed for body composition, cfPWV, AIx and most patient-reported outcomes between groups, except for insomnia symptoms which were higher in the EX-group. The addition of effect estimates, particularly for measures of vascular health and patient-reported outcomes, was able to further explain that, despite the non-significant values, small and medium effects favouring exercise training were present. Thus, the inability to achieve statistical significance was likely due to the small sample size. Therefore, exercise training maintained some markers of cardiometabolic health in ADT-treated men. Despite our reduced sample size, we observed significant between-group differences in CMR indices (LVM: V, LVEDV, LVSV, LVCO) and VO_2peak, thus supporting the utility of more sensitive metrics to evaluate the effect of ADT (and cardioprotective advantages) in men with PCa. Therefore, these initial findings suggest that exercise interventions targeting cardiometabolic health, including HIIT, should be considered to reduce the CVD burden in men with PCa.

7.3. Strengths and Limitations

Several strengths and limitations in the experimental studies undertaken in this thesis are worthy of comment. Notably, the trial (*Chapters Five and Six)* was strengthened by the randomised design, novel objective assessments and tailored exercise intervention targeting cardiometabolic health, which addressed key limitations noted across the scientific literature (as discussed in *Chapter Three*). The comprehensive diagnostic and preventative strategy and using robust assessments (e.g., CMR imaging) and the quantification of vascular health (e.g., cfPWV and AIx), VO_2peak and body composition was an additional strength of this trial design. The magnitude of effect between groups was large, resulting in favourable effects on the primary outcome (LVM: V) and other secondary outcomes, including VO_2peak, thus suggesting that the beneficial effects observed are biologically plausible rather than a result of statistical error. This strategy showed that the combined effects of a higher intensity aerobic and resistance training intervention were cardioprotective on the integrative

components of VO_2peak. Another strength of this study was the broader inclusion of men with a wide range of pre-existing CVD conditions or cardiovascular risk factors. This is important as most trials have excluded men with PCa with pre-existing CVD. This enhances the generalisability and comparability of these findings to men of similar age with PCa. The flexibility of the study design, especially during the COVID-19 pandemic, was the delivery of community-based exercise training and the uptake of video-delivered telehealth during the COVID-19 pandemic lockdown periods between March 2020 to May 2021. Despite these strengths, several limitations may affect the overall interpretation of these findings. First, this trial was markedly impacted by the COVID-19 pandemic and subsequent 'lockdown' periods within Melbourne, Australia. Unfortunately, due to these barriers, the study ceased recruitment short of the intended sample size. Although the sample was smaller than prior studies [100, 127] and included several outcome measures due to its alignment with the randomised controlled trial in *Chapter Six* [100, 142], this may have increased the likelihood of Type I statistical error. Despite this, we detected statistically significant changes in a range of cardiovascular outcomes, partly due to the use of gold standard and highly sensitive measures (CMR imaging, VO_2peak) [195, 200, 217, 274]. Second, although our strict inclusion criteria were viewed as a strength of this study, the four-week window may have posed a barrier for clinicians and supportive care staff to identify, discuss, and refer patients to our study within a pre-specified timeframe. In addition, while we altered our inclusion criteria to reflect the current medical management of ADT-treated men due to the STAMPEDE trial, this modification did not seem to improve our recruitment uptake. Third, the population under investigation, ADT-treated men and CON were volunteers for a randomised controlled trial with an exercise training arm. These participants had higher rates of physical function and a general interest in exercise training. This may have limited the generalisability of our findings to broader, less health-conscious individuals. Specifically, the age-matched controls were recruited via a 3:1 non-probability convenience sample of men who regularly attend the Baker Institute Healthy Hearts clinic to assess cardiovascular risk. It is known that non-probability sampling through convenience samples is feasible, cost-effective, and easily accessible, particularly in time-sensitive trials such as PhD programmes; however, the results limit the comparison to the general population of men with and without PCa due to the small sample size and sampling method. In line with this, these participants were physically active and exceeded age-related reference ranges for VO_2peak, which again limits the generalisability of this cohort to the typical male of a similar age [182, 449]. Fourth, complications related to the assessment of pulse wave analysis and cfPWV are well-documented,

especially in patients with arrhythmias or younger adult populations. Despite the reported CVs being in line with other PCa [100, 127] and other clinical cohorts [199, 275], these abnormal individual data points (negative AIx) were excluded from the primary analysis in line with recommendations [130, 196, 342]. Due to site closures during the COVID-19 pandemic (Australia Catholic University), two DXA machines were also utilised as part of this study. Even though the two DXA machines were of the same make and model, machine-to-machine variation is considered high; consequently, the body composition results may have been affected by using two different DXA machines. Fifth, the short duration of the exercise intervention and follow-up periods may have hindered our ability to detect changes in other cardiometabolic health markers (arterial stiffness, central and peripheral blood pressures, body composition) as similarly observed in other studies, therefore, may only provide a 'snapshot' of exercise-induced changes in cardiometabolic health markers. Sixth, some participants had previously undergone PCa treatments other than ADT, including surgery or radiotherapy and also were administered with combined therapies such as ADT and radiation/chemotherapy during the trial. While recent evidence suggests that the impact of these treatments is minimal [450], the impact on physical function and quality of life outcomes cannot be disregarded. In addition, different types of ADT were prescribed to participants in this study. While most participants were administered with LHRH analogues, the timing of testosterone suppression differs significantly between LHRH analogues and LHRH antagonists, which may have influenced the results. Some were medicated for pre-existing CVD and risk factors, which may have influenced these results. Lastly, the trial's design limited our ability to determine our findings' clinical and prognostic value. Although we can compare and speculate the implications of our findings, the findings of the experimental studies included in this thesis need to be validated in future trials.

7.4. Concluding remarks

An overview of the concluding remarks and implications of the findings of this thesis is outlined in Table 7.1. This thesis provided novel insight into the degree to which measures of subclinical CVD may partly explain the higher prevalence of CVD and the impact of enhanced, more vigorous exercise interventions on cardiac remodelling in ADT-treated men. The key findings of this thesis were that measures of functional (integrative) subclinical CVD, such as VO_2peak, provided a more sensitive means of detecting underlying cardiovascular dysfunction and may provide some insight into the intermediary clinical pathways or mechanisms not adequately reflected by traditional cardiovascular risk factors or anatomic subclinical CVD measures. This discrepancy is important as subclinical CVD

markers, such as arterial stiffness, evaluated in this study and those prior [100, 127] could not explain the higher prevalence of CVD reported in this cohort [328, 451]. Furthermore, this highlights the need for future research designs to assiduously focus on examining traditional and subclinical markers of CVD in parallel with clinically determined medical castration (<0.7 mmol/L). However, before undertaking any future designs, studies should consider measuring risk factors and subclinical CVD markers beyond a single time point, as singular measures do not robustly reflect changes in subclinical disease. Prospective designs spanning many timepoints between diagnosis and respective treatments are necessary. Consideration should also be given to comprehensive evaluations of PCa progression and clinically determined medical castration via ADT, as these observations would facilitate a clearer understanding of the aetiology of CVD progression in men with PCa. Evidence from such designs would help validate prognostic associations between traditional and subclinical markers of CVD and quantify the intermediate steps in the clinical pathways from traditional risk factors to clinical events in men with PCa.

Whilst functional (integrative) measures of subclinical CVD (VO_2peak) highlighted a markedly lower VO_2peak in men commencing ADT, it was surprising that the results of other prognostic markers were negligible. Although arterial stiffness did not reach statistical significance in men commencing ADT, we could speculate that the severity of traditional and subclinical markers of CVD could be offset by increasing VO_2peak. Based on this notion, there is a need for further research studies to evaluate the effect of more vigorous exercise interventions targeting cardiometabolic health in PCa. Our meta-analysis in *Chapter Three* explicitly highlighted this, whereby the physiological stimulus was insufficient to elicit beneficial effects on cardiometabolic health outcomes in ADT-treated men. Recognising the above and accepting that ADT-treated men are likely to be at a higher risk of CVD *(Chapter Two and Chapter Five),* given the known impact of severe hypogonadism, the clinically significant findings of *Chapter Six* demonstrated that an enhanced periodised approach, including HIIT targeting cardiometabolic health, prevented adverse cardiac remodelling, and improved VO_2peak in ADT-treated men compared to UC. It is worth noting that this trial was the first to provide evidence for the mechanism of improvement in VO_2peak, which suggests the cardiovascular benefits from exercise training could be related to improvements in LVCO and LVSV. In contrast, decrement declines observed in the UC group are noteworthy, specifically concerning trends toward concentric cardiac remodelling, reduced VO_2peak, and negative alterations in other cardiovascular health markers, including central and

peripheral haemodynamic and adiposity. While the trial results provide an avenue for future investigative work, the cardiovascular benefits observed in a short-term intensive exercise intervention prescribed concurrently with ADT profoundly affected traditional and subclinical markers of CVD. Future prospective designs should include robust assessments to determine underlying integrative system-level limitations associated with ADT before prescribing exercise interventions. While these precision-based approaches are well-studied in breast cancer [210, 295, 316, 363, 452-455], particularly in integrative cardiovascular impairment, PCa has received limited attention. The application of precision-based exercise approaches targeting physiological limitations via the evaluation of cardiac function under stress (stress echocardiogram or exercise cardiac MRI) across the duration of ADT may potentially yield superior exercise benefits for ADT-treated men. However, before embarking on future trial designs, examining the association between exercise dosage and cardiovascular risk/event reduction in ADT-treated men would be of interest using prospective cohort designs as similarly conducted by others in breast and childhood cancers [456, 457]. This approach could not only unveil targeted strategies to minimise the distinct short-term and long-term cardiovascular effects experienced by men during ADT, but it would also provide a far more informative clinical trial design to address cardiovascular risk reduction in this susceptible population.

Therefore, the questions addressed in this thesis and the unique experimental methodologies show a thorough review of the subject field of cardiovascular risk in ADT-treated men. While this series of experimental studies in this thesis contained multiple secondary outcomes, it may have raised the likelihood of Type I statistical error. Nevertheless, the results of this thesis provide an initial step and basis for future work to understand further the higher prevalence of CVD in ADT-treated men and its influence on subclinical markers of CVD in the postulated pathway to cardiovascular events. The utility of comprehensively evaluating traditional and subclinical markers of CVD, specifically VO_2peak, holds promise as a therapeutic tool to identify and mitigate cardiovascular impairment before and during ADT. Moreover, it is hoped that the results of this thesis direct our focus to investigate the effects of more vigorous exercise interventions targeting cardiometabolic health in ADT-treated men. While comparative effectiveness exercise intervention trials could best achieve this, evidence from such designs could play a critical role in defining which interventions should be recommended or prioritised throughout the PCa treatment continuum, mainly to reduce the CVD risk burden in this susceptible population.

Table 7.1 Implications and recommendations resulting from this thesis for managing the cardiovascular and metabolic side effects in men with PCa treated with ADT.

Men with prostate cancer commencing or undergoing ADT. **Cardiovascular risk** • Prior to commencing ADT, men should discuss the cardiovascular and metabolic side effects of ADT with clinical staff, which may include performing a cardiovascular risk screening [120, 341]. These measures should be completed yearly or even six-monthly, dependent on 10-year cardiovascular risk until ADT is ceased. **Exercise Training** • It is also recommended that clinicians treating men with PCa commencing or undergoing ADT seek advice on appropriate and individualised exercise prescription for managing ADT-related side effects. The current recommendations for individuals with cancer are: • Aerobic exercise training, which includes cycling, walking, rowing, and cross-training for 30 minutes 5-7 days per week, is recommended. • Progressive resistance exercise training should follow established exercise oncology literature for ADT-treated men [247, 254, 314, 315]. Whole-body progressive resistance training be performed at least twice per week, including 8-10 upper and lower body exercises at moderate to vigorous exercise intensity (12-6 repetition maximum). It is recommended that progressive overload should be applied each week (2-10% increase in training load) where appropriate [314]. • In the context of the thesis findings, more vigorous aerobic exercise training interventions should be considered to reduce the cardiovascular and metabolic side effects of ADT [243]. Before participating in more vigorous exercise interventions, referral to an exercise physiologist should be considered, given that participating in vigorous aerobic exercise interventions carries a higher risk of exercise-related events.
Exercise professionals working with ADT-treated men with PCa. • It is recommended that exercise professionals working with ADT-treated men ensure that a cardiovascular risk screening (e.g., CVD risk calculator) via the patient's general physician has been performed prior to prescribing an exercise intervention. • Before commencing ADT and participating in an exercise intervention, exercise capacity (e.g., symptom-limited exercise test) should be assessed to identify adverse signs and symptoms across various exercise intensities. • A submaximal/symptom-limited exercise tests can predict baseline exercise capacity using VO_2peak prediction equations and, therefore, should be considered given that men commencing ADT appear to have a substantially lower exercise capacity compared to age-gender reference values. • It is recommended that men with PCa work towards meeting or exceeding the guideline-recommended advice for exercise training for individuals with cancer [314]. The results of this thesis have shown that multi-modal exercise interventions consisting of moderate-intensity continuous (20 beats per minute below

ventilatory threshold), maximal steady state (ventilatory threshold) and high-intensity interval training (>95% of heart rate maximum) using the individual heart rate training zones appears feasible, well-tolerated and efficacious in this population [225]. A general preparation period of four weeks of moderate continuous exercise training is recommended before adding intensive efforts.

- Before administering these more intensive exercise interventions to ADT-treated men, ensure a medical clearance has been provided, and there has been no change in their cardiovascular risk factors.

Researchers investigating the impact of exercise training on the adverse effects of ADT, particularly cardiovascular and metabolic health.

- Further evaluation of cardiovascular risk profiling prior to and during ADT is recommended. While this study comprehensively evaluated cardiovascular risk using both traditional and novel assessments, the impact of ADT in men with PCa remains unknown. Studies with larger sample sizes using traditional and novel CVD risk assessment methods would be recommended for future research in this area. In addition, determining the reliability, sensitivity, and validity of traditional and novel cardiovascular assessments, specifically in this population, would be interesting.
- The value of measuring arterial stiffness and pulse wave reflection prior to and throughout ADT based on the results of this thesis remains unclear. While the results of this thesis, particularly the baseline values, are consistent with others [100, 127], the impact of ADT on arterial stiffness and pulse wave reflection appears trivial, and the reasoning for this is most likely related to the small sample size and the timing of assessments. Future studies with larger sample sizes should consider performing arterial stiffness and pulse wave reflection measures at baseline and once medical castration has been achieved (complete androgen blockade; minimum testosterone level of 0.7 mmol/L). This may offer additional insights as to whether adverse arterial structure and function changes may affect CVD risk in this population.
- Cohort studies focusing on the dose-response relationship between cardiovascular risk/events and exercise dose would be highly recommended. Studies conducted by Scott et al.[456] and Jones et al.[457] may provide insight into the dose-response relationship between exercise training and CVD risk/event mitigation in ADT-treated men.
- Given that HIIT appears efficacious in ADT-treated men, future studies should assign longer exercise intervention periods using this multimodal exercise intervention to determine if more extended intervention periods have beneficial effects on body composition and patient-reported outcomes, such as fatigue and quality of life.

REFERENCES

1. Knudsen BS, Vasioukhin V. Mechanisms of prostate cancer initiation and progression. Adv Cancer Res. 2010;109:1-50.

2. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2021;79(2):243-62.

3. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.

4. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.

5. Australian Institute of Health and Welfare. Australian Cancer Incidence and Mortality (ACIM) Books: Prostate Cancer. AIWH, editor. Canberra: AIWH.; 2021.

6. Schröder FH, Hugosson J, Roobol MJ, Tammela TLJ, Ciatto S, Nelen V, et al. Prostate-Cancer Mortality at 11 Years of Follow-up. N Engl J Med. 2012;366(11):981-90.

7. Baade PD, Fritschi L, Eakin EG. Non-Cancer Mortality among People Diagnosed with Cancer (Australia). Cancer Causes & Control. 2006;17(3):287-97.

8. Ye Y, Otahal P, Marwick TH, Wills KE, Neil AL, Venn AJ. Cardiovascular and other competing causes of death among patients with cancer from 2006 to 2015: An Australian population-based study. Cancer. 2019;125(3):442-52.

9. Koczwara B, Meng R, Miller MD, Clark RA, Kaambwa B, Marin T, et al. Late mortality in people with cancer: a population-based Australian study. Med J Aust. 2021;214(7):318-23.

10. Sturgeon KM, Deng L, Bluethmann SM, Zhou S, Trifiletti DM, Jiang C, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. Eur Heart J. 2019;40(48):3889-97.

11. Epstein MM, Edgren G, Rider JR, Mucci LA, Adami HO. Temporal trends in cause of death among Swedish and US men with prostate cancer. J Natl Cancer Inst. 2012;104(17):1335-42.

12. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol. 2017;71(4):630-42.

13. Horwich A, Parker C, de Reijke T, Kataja V, Group EGW. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6(suppl_6):vi106-14.
14. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2017;71(4):618-29.
15. James ND, Spears MR, Clarke NW, Dearnaley DP, De Bono JS, Gale J, et al. Survival with newly diagnosed metastatic prostate cancer in the "docetaxel era": data from 917 patients in the control arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019). Eur Urol. 2015;67(6):1028-38.
16. Gordon LG, Tuffaha HW, James R, Keller AT, Lowe A, Scuffham PA, et al. Estimating the healthcare costs of treating prostate cancer in Australia: A Markov modelling analysis. Urol Oncol. 2018;36(3):91 e7- e15.
17. Mervin MC, Lowe A, Gardiner RA, Smith DP, Aitken J, Chambers SK, et al. What does it cost Medicare to diagnose and treat men with localized prostate cancer in the first year? Asia Pac J Clin Oncol. 2017;13(3):152-9.
18. Ong WL, Foroudi F, Evans S, Millar J. Large institutional variations in use of androgen deprivation therapy with definitive radiotherapy in a population-based cohort of men with intermediate- and high-risk prostate cancer. BJU Int. 2017;120(S3):35-42.
19. Huggins C, Hodges CV. Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. J Urol. 2002;168(1):9-12.
20. Carter NJ, Keam SJ. Degarelix: a review of its use in patients with prostate cancer. Drugs. 2014;74(6):699-712.
21. Clinton TN, Woldu SL, Raj GV. Degarelix versus luteinizing hormone-releasing hormone agonists for the treatment of prostate cancer. Expert Opin Pharmacother. 2017;18(8):825-32.
22. Klotz L, Boccon-Gibod L, Shore ND, Andreou C, Persson BE, Cantor P, et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int. 2008;102(11):1531-8.
23. Klotz L, Miller K, Crawford ED, Shore N, Tombal B, Karup C, et al. Disease control outcomes from analysis of pooled individual patient data from five comparative randomised clinical trials of degarelix versus luteinising hormone-releasing hormone agonists. Eur Urol. 2014;66(6):1101-8.

24. Shore ND, Saad F, Cookson MS, George DJ, Saltzstein DR, Tutrone R, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. N Engl J Med. 2020;382(23):2187-96.
25. Sciarra A, Fasulo A, Ciardi A, Petrangeli E, Gentilucci A, Maggi M, et al. A meta-analysis and systematic review of randomized controlled trials with degarelix versus gonadotropin-releasing hormone agonists for advanced prostate cancer. Medicine (Baltimore). 2016;95(27):e3845.
26. Mostaghel EA. Abiraterone in the treatment of metastatic castration-resistant prostate cancer. Cancer Management and Research. 2014;6:39-51.
27. Scher HI, Fizazi K, Saad F, Taplin M-E, Sternberg CN, Miller K, et al. Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy. N Engl J Med. 2012;367(13):1187-97.
28. Shore ND, Chowdhury S, Villers A, Klotz L, Siemens DR, Phung D, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. The Lancet Oncol. 2016;17(2):153-63.
29. Tombal B, Borre M, Rathenborg P, Werbrouck P, Van Poppel H, Heidenreich A, et al. Enzalutamide monotherapy in hormone-naive prostate cancer: primary analysis of an open-label, single-arm, phase 2 study. Lancet Oncology. 2014;15(6):592-600.
30. Fakhrejahani F, Madan RA, Dahut WL. Management Options for Biochemically Recurrent Prostate Cancer. Current Treatment Options in Oncology. 2017;18(5):26.
31. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med. 2018;378(15):1408-18.
32. 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):289-95.
33. Parker CC, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet. 2018;392(10162):2353-66.
34. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med. 2015;373(8):737-46.
35. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. The Lancet Oncology. 2019;20(5):686-700.

36. Feyerabend S, Saad F, Perualila NJ, Van Sanden S, Diels J, Ito T, et al. Adjusting Overall Survival Estimates for Treatment Switching in Metastatic, Castration-Sensitive Prostate Cancer: Results from the LATITUDE Study. Target Oncol. 2019;14(6):681-8.
37. Board. PATE. Prostate Cancer Treatment (PDQ(R)): Health Professional Version. PDQ Cancer Information Summaries. Bethesda (MD): National Cancer Institute (US); 2002.
38. Angelucci C, Lama G, Iacopino F, Ferracuti S, Bono AV, Millar RP, et al. GnRH receptor expression in human prostate cancer cells is affected by hormones and growth factors. Endocrine. 2009;36(1):87-97.
39. Moul JW. Utility of LHRH antagonists for advanced prostate cancer. Canadian Journal of Urology. 2014;21:22-7.
40. Kluth LA, Shariat SF, Kratzik C, Tagawa S, Sonpavde G, Rieken M, et al. The hypothalamic-pituitary-gonadal axis and prostate cancer: implications for androgen deprivation therapy. World J Urol. 2014;32(3):669-76.
41. Nguyen PL, Alibhai SM, Basaria S, D'Amico AV, Kantoff PW, Keating NL, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol. 2015;67(5):825-36.
42. Dalla Via J, Daly RM, Owen PJ, Mundell NL, Rantalainen T, Fraser SF. Bone mineral density, structure, distribution and strength in men with prostate cancer treated with androgen deprivation therapy. Bone. 2019;127:367-75.
43. Galvao DA, Spry NA, Taaffe DR, Newton RU, Stanley J, Shannon T, et al. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. BJU Int. 2008;102(1):44-7.
44. Spry NA, Taaffe DR, England PJ, Judge JS, Stephens DA, Peddle-McIntyre C, et al. Long-term effects of intermittent androgen suppression therapy on lean and fat mass: a 33-month prospective study. Prostate Cancer Prostatic Dis. 2013;16(1):67-72.
45. Owen PJ, Daly RM, Livingston PM, Fraser SF. Lifestyle guidelines for managing adverse effects on bone health and body composition in men treated with androgen deprivation therapy for prostate cancer: an update. Prostate Cancer Prostatic Dis. 2017;20(2):137-45.
46. Cheung AS, Pattison D, Bretherton I, Hoermann R, Lim Joon D, Ho E, et al. Cardiovascular risk and bone loss in men undergoing androgen deprivation therapy for non-metastatic prostate cancer: implementation of standardized management guidelines. Andrology. 2013;1(4):583-9.

47. Grossmann M, Hamilton EJ, Gilfillan C, Bolton D, Joon DL, Zajac JD. Bone and metabolic health in patients with non-metastatic prostate cancer who are receiving androgen deprivation therapy. Med J Aust. 2011;194(6):301-6.
48. Skolarus TA, Wolf AM, Erb NL, Brooks DD, Rivers BM, Underwood W, 3rd, et al. American Cancer Society prostate cancer survivorship care guidelines. CA Cancer J Clin. 2014;64(4):225-49.
49. Galvao DA, Taaffe DR, Spry N, Joseph D, Turner D, Newton RU. Reduced muscle strength and functional performance in men with prostate cancer undergoing androgen suppression: a comprehensive cross-sectional investigation. Prostate Cancer Prostatic Dis. 2009;12(2):198-203.
50. Grossmann M, Zajac JD. Androgen deprivation therapy in men with prostate cancer: how should the side effects be monitored and treated? Clin Endocrinol (Oxf). 2011;74(3):289-93.
51. Grossmann M, Wittert G. Androgens, diabetes and prostate cancer. Endocr Relat Cancer. 2012;19(5):F47-62.
52. Leong DP, Fradet V, Shayegan B, Duceppe E, Siemens R, Niazi T, et al. Cardiovascular risk in men with prostate cancer: insights from the RADICAL PC Study. J Urol. 2020;203(6):1109-16.
53. Bosco C, Bosnyak Z, Malmberg A, Adolfsson J, Keating NL, Van Hemelrijck M. Quantifying observational evidence for risk of fatal and nonfatal cardiovascular disease following androgen deprivation therapy for prostate cancer: a meta-analysis. Eur Urol. 2015;68(3):386-96.
54. Nguyen PL, Je Y, Schutz FA, Hoffman KE, Hu JC, Parekh A, 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):2359-66.
55. Parekh A, Chen MH, D'Amico AV, Dosoretz DE, Ross R, Salenius S, et al. Identification of comorbidities that place men at highest risk of death from androgen deprivation therapy before brachytherapy for prostate cancer. Brachytherapy. 2013;12(5):415-21.
56. Haque R, UlcickasYood M, Xu X, Cassidy-Bushrow AE, Tsai HT, Keating NL, et al. Cardiovascular disease risk and androgen deprivation therapy in patients with localised prostate cancer: a prospective cohort study. Br J Cancer. 2017;117(8):1233-40.
57. Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Does comorbidity influence the risk of myocardial infarction or diabetes during androgen-deprivation therapy for prostate cancer? Eur Urol. 2013;64(1):159-66.
58. Keating NL, O'Malley A, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst. 2012;104(19):1518-23.

59. Nguyen PL, Chen MH, Beckman JA, Beard CJ, Martin NE, Choueiri TK, et al. Influence of androgen deprivation therapy on all-cause mortality in men with high-risk prostate cancer and a history of congestive heart failure or myocardial infarction. Int J Radiat Oncol Biol Phys. 2012;82(4):1411-6.

60. Davey RA, Grossmann M. Androgen Receptor Structure, Function and Biology: From Bench to Bedside. Clin Biochem Rev. 2016;37(1):3-15.

61. Scailteux LM, Vincendeau S, Balusson F, Leclercq C, Happe A, Le Nautout B, et al. Androgen deprivation therapy and cardiovascular risk: No meaningful difference between GnRH antagonist and agonists-a nationwide population-based cohort study based on 2010-2013 French Health Insurance data. Eur J Cancer. 2017;77:99-108.

62. Scailteux LM, Naudet F, Alimi Q, Vincendeau S, Oger E. Mortality, cardiovascular risk, and androgen deprivation therapy for prostate cancer: A systematic review with direct and network meta-analyses of randomized controlled trials and observational studies. Medicine (Baltimore). 2016;95(24):e3873.

63. D'Amico AV, Denham JW, Crook J, Chen MH, Goldhaber SZ, Lamb DS, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. J Clin Oncol. 2007;25(17):2420-5.

64. Albertsen PC, Klotz L, Tombal B, Grady J, Olesen TK, Nilsson J. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. Eur Urol. 2014;65(3):565-73.

65. Bourke L, Chico TJ, Albertsen PC, Hamdy FC, Rosario DJ. Cardiovascular risk in androgen suppression: underappreciated, under-researched and unresolved. Heart. 2012;98(5):345-8.

66. Rosario DJ, Bourke L. Cardiovascular Disease and the Androgen Receptor: Here We Go Again? Eur Urol. 2020;77(2):167-9.

67. Rosario DJ, Bourke L, Keating NL. Androgen deprivation therapy and cardiovascular harm: are all men created equal? Eur Urol. 2014;65(3):574-6.

68. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol. 2006;24(27):4448-56.

69. Levine GN, D'Amico AV, Berger P, Clark PE, Eckel RH, Keating NL, 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):833-40.

70. Lopes RD, Higano CS, Slovin SF, Nelson AJ, Bigelow R, Sorensen PS, et al. Cardiovascular safety of degarelix versus leuprolide in patients with prostate cancer: the primary results of the PRONOUNCE Randomized Trial. Circulation. 2021;144(16):1295-307.
71. Nguyen PL, Chen MH, Goldhaber SZ, Martin NE, Beard CJ, Dosoretz DE, et al. Coronary revascularization and mortality in men with congestive heart failure or prior myocardial infarction who receive androgen deprivation. Cancer. 2011;117(2):406-13.
72. Ziehr DR, Chen MH, Zhang D, Braccioforte MH, Moran BJ, Mahal BA, et al. Association of androgen-deprivation therapy with excess cardiac-specific mortality in men with prostate cancer. BJU Int. 2015;116(3):358-65.
73. Hayes JH, Chen MH, Moran BJ, Braccioforte MH, Dosoretz DE, Salenius S, et al. Androgen-suppression therapy for prostate cancer and the risk of death in men with a history of myocardial infarction or stroke. BJU Int. 2010;106(7):979-85.
74. Nanda A, Chen MH, Moran BJ, Braccioforte MH, Dosoretz D, Salenius S, et al. Neoadjuvant hormonal therapy use and the risk of death in men with prostate cancer treated with brachytherapy who have no or at least a single risk factor for coronary artery disease. Eur Urol. 2014;65(1):177-85.
75. Nanda A, Chen MH, Braccioforte MH, Moran BJ, D'Amico AV. Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction. JAMA. 2009;302(8):866-73.
76. Jespersen CG, Norgaard M, Borre M. Androgen-deprivation therapy in treatment of prostate cancer and risk of myocardial infarction and stroke: a nationwide Danish population-based cohort study. Eur Urol. 2014;65(4):704-9.
77. Van Hemelrijck M, Garmo H, Holmberg L, Ingelsson E, Bratt O, Bill-Axelson A, et al. Absolute and relative risk of cardiovascular disease in men with prostate cancer: results from the Population-Based PCBaSe Sweden. J Clin Oncol. 2010;28(21):3448-56.
78. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. Circulation. 2016;133(11):1104-14.
79. Handy CE, Quispe R, Pinto X, Blaha MJ, Blumenthal RS, Michos ED, et al. Synergistic opportunities in the interplay between cancer screening and cardiovascular disease risk assessment: together we are stronger. Circulation. 2018;138(7):727-34.
80. De Marzo AM, Platz EA, Sutcliffe S, Xu J, Gronberg H, Drake CG, et al. Inflammation in prostate carcinogenesis. Nat Rev Cancer. 2007;7(4):256-69.

81. Graff JN, Beer TM. The role of C-reactive protein in prostate cancer. Cancer. 2013;119(18):3262-4.
82. Van Hemelrijck M, Jungner I, Walldius G, Garmo H, Binda E, Hayday A, et al. Risk of prostate cancer is not associated with levels of C-reactive protein and other commonly used markers of inflammation. Int J Cancer. 2011;129(6):1485-92.
83. Elsberger B, Lankston L, McMillan DC, Underwood MA, Edwards J. Presence of tumoural C-reactive protein correlates with progressive prostate cancer. Prostate Cancer Prostatic Dis. 2011;14(2):122-8.
84. Stark JR, Li H, Kraft P, Kurth T, Giovannucci EL, Stampfer MJ, et al. Circulating prediagnostic interleukin-6 and C-reactive protein and prostate cancer incidence and mortality. Int J Cancer. 2009;124(11):2683-9.
85. Liu ZQ, Chu L, Fang JM, Zhang X, Zhao HX, Chen YJ, et al. Prognostic role of C-reactive protein in prostate cancer: a systematic review and meta-analysis. Asian J Androl. 2014;16(3):467-71.
86. Zhou K, Li C, Chen T, Zhang X, Ma B. C-reactive protein levels could be a prognosis predictor of prostate cancer: A meta-analysis. Front Endocrinol (Lausanne). 2023;14:1111277.
87. Gomez-Gomez E, Carrasco-Valiente J, Campos-Hernandez JP, Blanca-Pedregosa AM, Jimenez-Vacas JM, Ruiz-Garcia J, et al. Clinical association of metabolic syndrome, C-reactive protein and testosterone levels with clinically significant prostate cancer. J Cell Mol Med. 2019;23(2):934-42.
88. Vansaun MN. Molecular pathways: adiponectin and leptin signaling in cancer. Clin Cancer Res. 2013;19(8):1926-32.
89. Gallagher EJ, LeRoith D. Epidemiology and molecular mechanisms tying obesity, diabetes, and the metabolic syndrome with cancer. Diabetes Care. 2013;36 Suppl 2(Suppl 2):S233-9.
90. Matsuda M, Shimomura I. Increased oxidative stress in obesity: implications for metabolic syndrome, diabetes, hypertension, dyslipidemia, atherosclerosis, and cancer. Obes Res Clin Pract. 2013;7(5):e330-41.
91. Scheid MP, Sweeney G. The role of adiponectin signaling in metabolic syndrome and cancer. Rev Endocr Metab Disord. 2014;15(2):157-67.
92. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet. 2004;363(9418):1346-53.

93. Marmot M, Brunner E. Cohort Profile: the Whitehall II study. Int J Epidemiol. 2005;34(2):251-6.
94. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. Lancet (London, England). 2014;383(9921):999-1008.
95. Henley SJ, Singh S, King J, Wilson R, Ryerson B, Centers for Disease C, et al. Invasive cancer incidence - United States, 2010. MMWR Morb Mortal Wkly Rep. 2014;63(12):253-9.
96. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. Diabetes care. 2010;33(7):1674-85.
97. Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. Int J Cancer. 2007;121(7):1571-8.
98. Morgans AK, Fan KH, Koyama T, Albertsen PC, Goodman M, Hamilton AS, et al. Influence of age on incident diabetes and cardiovascular disease in prostate cancer survivors receiving androgen deprivation therapy. J Urol. 2015;193(4):1226-31.
99. Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. J Clin Endocrinol Metab. 2006;91(4):1305-8.
100. Wall BA, Galvao DA, Fatehee N, Taaffe DR, Spry N, Joseph D, et al. Reduced cardiovascular capacity and resting metabolic rate in men with prostate cancer undergoing androgen deprivation: a comprehensive cross-sectional investigation. Adv Urol. 2015;2015:976235.
101. Smith MR. Androgen deprivation therapy and risk for diabetes and cardiovascular disease in prostate cancer survivors. Curr Urol Rep. 2008;9(3):197-202.
102. Niebauer J, Pflaum CD, Clark AL, Strasburger CJ, Hooper J, Poole-Wilson PA, et al. Deficient insulin-like growth factor I in chronic heart failure predicts altered body composition, anabolic deficiency, cytokine and neurohormonal activation. J Am Coll Cardiol. 1998;32(2):393-7.
103. Giltay EJ, Lambert J, Gooren LJ, Elbers JM, Steyn M, Stehouwer CD. Sex steroids, insulin, and arterial stiffness in women and Men. Hypertension. 1999;34(4 Pt 1):590-7.
104. Shah RV, Abbasi SA, Heydari B, Rickers C, Jacobs DR, Jr., Wang L, et al. Insulin resistance, subclinical left ventricular remodeling, and the obesity paradox: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2013;61(16):1698-706.

105. Basaria S, Muller DC, Carducci MA, Egan J, Dobs AS. Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy. Cancer. 2006;106(3):581-8.

106. Smith MR, Finkelstein JS, McGovern FJ, Zietman AL, Fallon MA, Schoenfeld DA, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab. 2002;87(2):599-603.

107. Bosco C, Crawley D, Adolfsson J, Rudman S, Van Hemelrijck M. Quantifying the evidence for the risk of metabolic syndrome and its components following androgen deprivation therapy for prostate cancer: a meta-analysis. PLoS One. 2015;10(3):e0117344.

108. Braga-Basaria M, Dobs AS, Muller DC, Carducci MA, John M, Egan J, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol. 2006;24(24):3979-83.

109. Grossmann M, Cheung AS, Zajac JD. Androgens and prostate cancer; pathogenesis and deprivation therapy. Best Pract Res Clin Endocrinol Metab. 2013;27(4):603-16.

110. Hamilton EJ, Gianatti E, Strauss BJ, Wentworth J, Lim-Joon D, Bolton D, et al. Increase in visceral and subcutaneous abdominal fat in men with prostate cancer treated with androgen deprivation therapy. Clin Endocrinol (Oxf). 2011;74(3):377-83.

111. Bolu E, Sonmez A, Tapan S, Taslipinar A, Aydogdu A, Meric C, et al. HDL cholesterol subfractions and the effect of testosterone replacement in hypogonadism. Horm Metab Res. 2013;45(6):443-8.

112. Smith MR, Lee H, McGovern F, Fallon MA, Goode M, Zietman AL, et al. Metabolic changes during gonadotropin-releasing hormone agonist therapy for prostate cancer: differences from the classic metabolic syndrome. Cancer. 2008;112(10):2188-94.

113. Smith MR, Saad F, Egerdie B, Sieber PR, Tammela TL, Ke C, et al. Sarcopenia during androgen-deprivation therapy for prostate cancer. J Clin Oncol. 2012;30(26):3271-6.

114. Smith MR. Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. Urology. 2004;63(4):742-5.

115. Haseen F, Murray LJ, Cardwell CR, O'Sullivan JM, Cantwell MM. The effect of androgen deprivation therapy on body composition in men with prostate cancer: systematic review and meta-analysis. J Cancer Surviv. 2010;4(2):128-39.

116. Powell-Wiley TM, Poirier P, Burke LE, Despres JP, Gordon-Larsen P, Lavie CJ, et al. Obesity and cardiovascular disease: A Scientific Statement From the American Heart Association. Circulation. 2021;143(21):e984-e1010.

117. Hanson ED, Stopforth CK, Alzer M, Carver J, Lucas AR, Whang YE, et al. Body composition, physical function and quality of life in healthy men and across different stages of prostate cancer. Prostate Cancer Prostatic Dis. 2021;24(3):725-32.

118. Iacovelli R, Ciccarese C, Bria E, Romano M, Fantinel E, Bimbatti D, et al. The cardiovascular toxicity of abiraterone and enzalutamide in prostate cancer. Clin Genitourin Cancer. 2018;16(3):e645-e53.

119. Iacovelli R, Verri E, Cossu Rocca M, Aurilio G, Cullura D, De Cobelli O, et al. The incidence and relative risk of cardiovascular toxicity in patients treated with new hormonal agents for castration-resistant prostate cancer. Eur J Cancer. 2015;51(14):1970-7.

120. Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. Eur J Heart Fail. 2020;22(11):1945-60.

121. Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015;16(2):152-60.

122. Shore ND, Chowdhury S, Villers A, Klotz L, Siemens DR, Phung D, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. Lancet Oncol. 2016;17(2):153-63.

123. Guan J, Khambhati J, Jones LW, Morgans A, Allaf M, Penson DF, et al. ABCDE steps for heart and vascular wellness following a prostate cancer diagnosis. Circulation. 2015;132(18):e218-e20.

124. Bhatia N, Santos M, Jones LW, Beckman JA, Penson DF, Morgans AK, et al. Cardiovascular effects of androgen deprivation therapy for the treatment of prostate pancer: ABCDE steps to reduce cardiovascular disease in patients with prostate cancer. Circulation. 2016;133(5):537-41.

125. Dockery F, Bulpitt CJ, Agarwal S, Donaldson M, Rajkumar C. Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. Clinical science (London, England : 1979). 2003;104(2):195-201.
126. Dockery F, Rajkumar C, Agarwal S, Waxman J, Bulpitt CJ. Androgen deprivation in males is associated with decreased central arterial compliance and reduced central systolic blood pressure. J Hum Hypertens. 2000;14(6):395-7.
127. Jones LM, Wilson R, Stoner L, Baldi JC. Arterial stiffness as a cardiovascular risk factor in prostate cancer survivors: a case–control study. J Sci Med Sport. 2019;3(2):171-8.
128. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;55(13):1318-27.
129. Smith JC, Bennett S, Evans LM, Kynaston HG, Parmar M, Mason MD, et al. The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. J Clin Endocrinol Metab. 2001;86(9):4261-7.
130. Chowienczyk PJ, Donald A, Segers P, Boutouyrie P, Schillaci G, McEniery CM, et al. ARTERY Society guidelines for validation of non-invasive haemodynamic measurement devices: Part 1, arterial pulse wave velocity. Artery Res. 2010;4(2):34-40.
131. Friedenreich CM, Wang Q, Neilson HK, Kopciuk KA, McGregor SE, Courneya KS. Physical activity and survival after prostate cancer. Eur Urol. 2016;70(4):576-85.
132. Friedenreich CM, Stone CR, Cheung WY, Hayes SC. Physical activity and mortality in cancer survivors: A systematic review and meta-analysis. JNCI Cancer Spectr. 2020;4(1):pkz080.
133. Kenfield SA, Stampfer MJ, Giovannucci E, Chan JM. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. J Clin Oncol. 2011;29(6):726-32.
134. Alibhai SM, Breunis H, Timilshina N, Johnston C, Tomlinson G, Tannock I, et al. Impact of androgen-deprivation therapy on physical function and quality of life in men with nonmetastatic prostate cancer. J Clin Oncol. 2010;28(34):5038-45.
135. Clay CA, Perera S, Wagner JM, Miller ME, Nelson JB, Greenspan SL. Physical function in men with prostate cancer on androgen deprivation therapy. Phys Ther. 2007;87(10):1325-33.
136. Gonzalez BD, Jim HSL, Small BJ, Sutton SK, Fishman MN, Zachariah B, et al. Changes in physical functioning and muscle strength in men receiving androgen deprivation therapy for prostate cancer: a controlled comparison. Support Care Cancer. 2016;24(5):2201-7.

137. Levy ME, Perera S, van Londen GJ, Nelson JB, Clay CA, Greenspan SL. Physical function changes in prostate cancer patients on androgen deprivation therapy: a 2-year prospective study. Urology. 2008;71(4):735-9.
138. Alibhai SM, Breunis H, Timilshina N, Marzouk S, Stewart D, Tannock I, et al. Impact of androgen-deprivation therapy on cognitive function in men with nonmetastatic prostate cancer. J Clin Oncol. 2010;28(34):5030-7.
139. Guazzi M, Dickstein K, Vicenzi M, Arena R. Six-minute walk test and cardiopulmonary exercise testing in patients with chronic heart failure: a comparative analysis on clinical and prognostic insights. Circ Heart Fail. 2009;2(6):549-55.
140. Guazzi M, Myers J, Vicenzi M, Bensimhon D, Chase P, Pinkstaff S, et al. Cardiopulmonary exercise testing characteristics in heart failure patients with and without concomitant chronic obstructive pulmonary disease. Am Heart J. 2010;160(5):900-5.
141. Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BA, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: A Scientific Statement From the American Heart Association. Circulation. 2016;134(24):e653-e99.
142. Wall BA, Galvao DA, Fatehee N, Taaffe DR, Spry N, Joseph D, et al. Maximal exercise testing of men with prostate cancer being treated with androgen deprivation therapy. Med Sci Sports Exerc. 2014;46(12):2210-5.
143. Herring MJ, Oskui PM, Hale SL, Kloner RA. Testosterone and the cardiovascular system: a comprehensive review of the basic science literature. J Am Heart Assoc. 2013;2(4):e000271.
144. Oskui PM, French WJ, Herring MJ, Mayeda GS, Burstein S, Kloner RA. Testosterone and the cardiovascular system: a comprehensive review of the clinical literature. J Am Heart Assoc. 2013;2(6):e000272.
145. Beattie BJ, Smith-Jones PM, Jhanwar YS, Schoder H, Schmidtlein CR, Morris MJ, et al. Pharmacokinetic assessment of the uptake of 16beta-18F-fluoro-5alpha-dihydrotestosterone (FDHT) in prostate tumors as measured by PET. J Nucl Med. 2010;51(2):183-92.
146. Beattie MC, Chen H, Fan J, Papadopoulos V, Miller P, Zirkin BR. Aging and luteinizing hormone effects on reactive oxygen species production and DNA damage in rat Leydig cells. Biol Reprod. 2013;88(4):100.
147. Beattie MC, Adekola L, Papadopoulos V, Chen H, Zirkin BR. Leydig cell aging and hypogonadism. Exp Gerontol. 2015;68:87-91.

148. English KM, Mandour O, Steeds RP, Diver MJ, Jones TH, Channer KS. Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. Eur Heart J. 2000;21(11):890-4.

149. Khaw KT, Dowsett M, Folkerd E, Bingham S, Wareham N, Luben R, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. Circulation. 2007;116(23):2694-701.

150. Ohlsson C, Barrett-Connor E, Bhasin S, Orwoll E, Labrie F, Karlsson MK, et al. High serum testosterone is associated with reduced risk of cardiovascular events in elderly men. The MrOS (Osteoporotic Fractures in Men) study in Sweden. J Am Coll Cardiol. 2011;58(16):1674-81.

151. Zhao SP, Li XP. The association of low plasma testosterone level with coronary artery disease in Chinese men. Int J Cardiol. 1998;63(2):161-4.

152. Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. J Clin Endocrinol Metab. 2008;93(1):68-75.

153. Haring R, Volzke H, Steveling A, Krebs A, Felix SB, Schofl C, et al. Low serum testosterone levels are associated with increased risk of mortality in a population-based cohort of men aged 20-79. Eur Heart J. 2010;31(12):1494-501.

154. Vikan T, Schirmer H, Njolstad I, Svartberg J. Endogenous sex hormones and the prospective association with cardiovascular disease and mortality in men: the Tromso Study. Eur J Endocrinol. 2009;161(3):435-42.

155. Svartberg J, von Muhlen D, Schirmer H, Barrett-Connor E, Sundfjord J, Jorde R. Association of endogenous testosterone with blood pressure and left ventricular mass in men. The Tromso Study. Eur J Endocrinol. 2004;150(1):65-71.

156. Vlachopoulos C, Ioakeimidis N, Miner M, Aggelis A, Pietri P, Terentes-Printzios D, et al. Testosterone deficiency: a determinant of aortic stiffness in men. Atherosclerosis. 2014;233(1):278-83.

157. Vlachopoulos C, Ioakeimidis N, Terentes-Printzios D, Aznaouridis K, Rokkas K, Aggelis A, et al. Plasma total testosterone and incident cardiovascular events in hypertensive patients. Am J Hypertens. 2013;26(3):373-81.

158. Vlachopoulos C, Pietri P, Ioakeimidis N, Aggelis A, Terentes-Printzios D, Abdelrasoul M, et al. Inverse association of total testosterone with central haemodynamics and left ventricular mass in hypertensive men. Atherosclerosis. 2016;250(Supplement C):57-62.

159. Marsh JD, Lehmann MH, Ritchie RH, Gwathmey JK, Green GE, Schiebinger RJ. Androgen receptors mediate hypertrophy in cardiac myocytes. Circulation. 1998;98(3):256-61.
160. Golden KL, Marsh JD, Jiang Y, Brown T, Moulden J. Gonadectomy of adult male rats reduces contractility of isolated cardiac myocytes. Am J Physiol Endocrinol Metab. 2003;285(3):E449-53.
161. Bluemke DA, Kronmal RA, Lima JA, Liu K, Olson J, Burke GL, et al. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. J Am Coll Cardiol. 2008;52(25):2148-55.
162. Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. Circulation. 2000;101(25):2981-8.
163. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol. 2000;35(3):569-82.
164. Cheng S, Fernandes VR, Bluemke DA, McClelland RL, Kronmal RA, Lima JA. Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: the Multi-Ethnic Study of Atherosclerosis. Circ Cardiovasc Imaging. 2009;2(3):191-8.
165. Chung CC, Kao YH, Chen YJ, Chen YJ. Androgen modulates cardiac fibrosis contributing to gender differences on heart failure. Aging Male. 2013;16(1):22-7.
166. Eng J, McClelland RL, Gomes AS, Hundley WG, Cheng S, Wu CO, et al. Adverse left ventricular remodeling and age assessed with cardiac MR Imaging: The Multi-Ethnic Study of Atherosclerosis. Radiology. 2016;278(3):714-22.
167. Malhotra A, Buttrick P, Scheuer J. Effects of sex hormones on development of physiological and pathological cardiac hypertrophy in male and female rats. Am J Physiol. 1990;259(3 Pt 2):H866-71.
168. Hydock DS, Wonders KY, Schneider CM, Hayward R. Androgen deprivation therapy and cardiac function: effects of endurance training. Prostate Cancer Prostatic Dis. 2006;9(4):392-8.
169. Hydock DS, Lien CY, Schneider CM, Hayward R. Effects of voluntary wheel running on cardiac function and myosin heavy chain in chemically gonadectomized rats. Am J Physiol Heart Circ Physiol. 2007;293(6):H3254-64.
170. Jankowska EA, Biel B, Majda J, Szklarska A, Lopuszanska M, Medras M, et al. Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. Circulation. 2006;114(17):1829-37.

171. Jankowska EA, Filippatos G, Ponikowska B, Borodulin-Nadzieja L, Anker SD, Banasiak W, et al. Reduction in circulating testosterone relates to exercise capacity in men with chronic heart failure. J Card Fail. 2009;15(5):442-50.
172. Jankowska EA, Tkaczyszyn M, Wegrzynowska-Teodorczyk K, Majda J, von Haehling S, Doehner W, et al. Late-onset hypogonadism in men with systolic heart failure: prevalence, clinical associates, and impact on long-term survival. ESC Heart Fail. 2014;1(1):41-51.
173. Malkin CJ, Pugh PJ, Morris PD, Asif S, Jones TH, Channer KS. Low serum testosterone and increased mortality in men with coronary heart disease. Heart. 2010;96(22):1821-5.
174. Golden KL, Marsh JD, Jiang Y, Brown T, Moulden J. Gonadectomy of adult male rats reduces contractility of isolated cardiac myocytes. American Journal of Physiology - Endocrinology And Metabolism. 2003;285(3):E449-E53.
175. Gupta MP. Factors controlling cardiac myosin-isoform shift during hypertrophy and heart failure. J Mol Cell Cardiol. 2007;43(4):388-403.
176. Lowes BD, Minobe W, Abraham WT, Rizeq MN, Bohlmeyer TJ, Quaife RA, et al. Changes in gene expression in the intact human heart. Downregulation of alpha-myosin heavy chain in hypertrophied, failing ventricular myocardium. J Clin Invest. 1997;100(9):2315-24.
177. Miyata S, Minobe W, Bristow MR, Leinwand LA. Myosin heavy chain isoform expression in the failing and nonfailing human heart. Circ Res. 2000;86(4):386-90.
178. Dockery F, Bulpitt CJ, Agarwal S, Vernon C, Nihoyannopoulos P, Kemp M, et al. Anti-androgens increase N-terminal pro-BNP levels in men with prostate cancer. Clin Endocrinol (Oxf). 2008;68(1):59-65.
179. Hopmans SN, Duivenvoorden WC, Werstuck GH, Klotz L, Pinthus JH. GnRH antagonist associates with less adiposity and reduced characteristics of metabolic syndrome and atherosclerosis compared with orchiectomy and GnRH agonist in a preclinical mouse model. Urol Oncol. 2014;32(8):1126-34.
180. Nathan L, Shi W, Dinh H, Mukherjee TK, Wang X, Lusis AJ, et al. Testosterone inhibits early atherogenesis by conversion to estradiol: critical role of aromatase. Proceedings of the National Academy of Sciences of the United States of America. 2001;98(6):3589-93.
181. Bourghardt J, Wilhelmson AS, Alexanderson C, De Gendt K, Verhoeven G, Krettek A, et al. Androgen receptor-dependent and independent atheroprotection by testosterone in male mice. Endocrinology. 2010;151(11):5428-37.

182. Gilbert SE, Tew GA, Bourke L, Winter EM, Rosario DJ. Assessment of endothelial dysfunction by flow-mediated dilatation in men on long-term androgen deprivation therapy for prostate cancer. Exp Physiol. 2013;98(9):1401-10.
183. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006;27(21):2588-605.
184. Okwuosa TM, Morgans A, Rhee JW, Reding KW, Maliski S, Plana JC, et al. Impact of hormonal therapies for treatment of hormone-dependent cancers (breast and prostate) on the cardiovascular system: effects and modifications: A Scientific Statement From the American Heart Association. Circ Genom Precis Med. 2021;14(3):e000082.
185. Gupta D, Lee Chuy K, Yang JC, Bates M, Lombardo M, Steingart RM. Cardiovascular and metabolic effects of androgen-deprivation therapy for prostate cancer. J Oncol Pract. 2018;14(10):580-7.
186. Bultijnck R, Van de Caveye I, Rammant E, Everaert S, Lumen N, Decaestecker K, et al. Clinical pathway improves implementation of evidence-based strategies for the management of androgen deprivation therapy-induced side effects in men with prostate cancer. BJU Int. 2018;121(4):610-8.
187. Bultijnck R, Surcel C, Ploussard G, Briganti A, De Visschere P, Futterer J, et al. Practice patterns compared with evidence-based strategies for the management of androgen deprivation therapy-induced side effects in prostate cancer patients: results of a European web-based survey. Eur Urol Focus. 2016;2(5):514-21.
188. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-53.
189. Liu CY, Lai S, Kawel-Boehm N, Chahal H, Ambale-Venkatesh B, Lima JAC, et al. Healthy aging of the left ventricle in relationship to cardiovascular risk factors: The Multi-Ethnic Study of Atherosclerosis (MESA). PLoS One. 2017;12(6):e0179947.
190. Lai YH, Lo CI, Wu YJ, Hung CL, Yeh HI. Cardiac remodeling, adaptations and associated myocardial mechanics in hypertensive heart diseases. Acta Cardiol Sin. 2013;29(1):64-70.
191. Santos AB, Gupta DK, Bello NA, Gori M, Claggett B, Fuchs FD, et al. Prehypertension is associated with abnormalities of cardiac structure and function in the atherosclerosis risk in communities study. Am J Hypertens. 2016;29(5):568-74.

192. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med. 1990;322(22):1561-6.
193. Mor-Avi V, Sugeng L, Weinert L, MacEneaney P, Caiani EG, Koch R, et al. Fast measurement of left ventricular mass with real-time three-dimensional echocardiography: comparison with magnetic resonance imaging. Circulation. 2004;110(13):1814-8.
194. Chuang ML, Beaudin RA, Riley MF, Mooney MG, Mannin WJ, Douglas PS, et al. Three-dimensional echocardiographic measurement of left ventricular mass: comparison with magnetic resonance imaging and two-dimensional echocardiographic determinations in man. Int J Card Imaging. 2000;16(5):347-57.
195. Frimodt-Moller M, Nielsen AH, Kamper AL, Strandgaard S. Reproducibility of pulse-wave analysis and pulse-wave velocity determination in chronic kidney disease. Nephrol Dial Transplant. 2008;23(2):594-600.
196. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, et al. Recommendations for improving and standardizing vascular research on arterial stiffness: A Scientific Statement From the American Heart Association. Hypertension. 2015;66(3):698-722.
197. Doupis J, Papanas N, Cohen A, McFarlan L, Horton E. Pulse wave analysis by applanation tonometry for the measurement of arterial stiffness. Open Cardiovasc Med J. 2016;10:188-95.
198. Wilkinson IB, Maki-Petaja KM, Mitchell GF. Uses of Arterial Stiffness in Clinical Practice. Arterioscler Thromb Vasc Biol. 2020;40(5):1063-7.
199. Hwang MH, Yoo JK, Kim HK, Hwang CL, Mackay K, Hemstreet O, et al. Validity and reliability of aortic pulse wave velocity and augmentation index determined by the new cuff-based SphygmoCor Xcel. J Hum Hypertens. 2014;28(8):475-81.
200. Elliot CA, Hamlin MJ, Lizamore CA. Inter-operator reliability for measuring pulse wave velocity and augmentation index. Front Cardiovasc Med. 2020;7:72.
201. Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR, et al. Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. Journal of hypertension. 1998;16(12 Pt 2):2079-84.
202. AlGhatrif M, Strait JB, Morrell CH, Canepa M, Wright J, Elango P, et al. Longitudinal trajectories of arterial stiffness and the role of blood pressure: the Baltimore Longitudinal Study of Aging. Hypertension. 2013;62(5):934-41.

203. Kingwell BA, Cameron JD, Gillies KJ, Jennings GL, Dart AM. Arterial compliance may influence baroreflex function in athletes and hypertensives. Am J Physiol. 1995;268(1 Pt 2):H411-8.
204. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension. 2001;37(5):1236-41.
205. Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation. 2006;113(5):657-63.
206. McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR, et al. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). J Am Coll Cardiol. 2005;46(9):1753-60.
207. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation. 2010;121(4):505-11.
208. Thijssen DH, Carter SE, Green DJ. Arterial structure and function in vascular ageing: are you as old as your arteries? J Physiol. 2016;594(8):2275-84.
209. Parr SK, Liang J, Schadler KL, Gilchrist SC, Steele CC, Ade CJ. Anticancer therapy-related increases in arterial stiffness: a systematic review and meta-analysis. J Am Heart Assoc. 2020;9(14):e015598.
210. Howden EJ, Bigaran A, Beaudry R, Fraser S, Selig S, Foulkes S, et al. Exercise as a diagnostic and therapeutic tool for the prevention of cardiovascular dysfunction in breast cancer patients. Eur J Prev Cardiol. 2019;26(3):305-15.
211. Imboden MT, Harber MP, Whaley MH, Finch WH, Bishop DL, Kaminsky LA. Cardiorespiratory fitness and mortality in healthy men and women. J Am Coll Cardiol. 2018;72(19):2283-92.
212. Laukkanen JA, Lakka TA, Rauramaa R, Kuhanen R, Venalainen JM, Salonen R, et al. Cardiovascular fitness as a predictor of mortality in men. Arch Intern Med. 2001;161(6):825-31.
213. Laukkanen JA, Zaccardi F, Khan H, Kurl S, Jae SY, Rauramaa R. Long-term change in cardiorespiratory fitness and all-cause mortality: a population-based follow-up study. Mayo Clin Proc. 2016;91(9):1183-8.
214. Ezzatvar Y, Ramirez-Velez R, Saez de Asteasu ML, Martinez-Velilla N, Zambom-Ferraresi F, Lobelo F, et al. Cardiorespiratory fitness and all-cause mortality in adults diagnosed with cancer systematic review and meta-analysis. Scand J Med Sci Sports. 2021;31(9):1745-52.

215. Gong J, Payne D, Caron J, Bay CP, McGregor BA, Hainer J, et al. Reduced cardiorespiratory fitness and increased cardiovascular mortality after prolonged androgen deprivation therapy for prostate cancer. JACC CardioOncol. 2020;2(4):553-63.
216. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA. 2009;301(19):2024-35.
217. Scott JM, Hornsby WE, Lane A, Kenjale AA, Eves ND, Jones LW. Reliability of maximal cardiopulmonary exercise testing in men with prostate cancer. Med Sci Sports Exerc. 2015;47(1):27-32.
218. Hu JR, Duncan MS, Morgans AK, Brown JD, Meijers WC, Freiberg MS, et al. Cardiovascular effects of androgen deprivation therapy in prostate cancer: contemporary meta-analyses. Arterioscler Thromb Vasc Biol. 2020;40(3):e55-e64.
219. Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2017;35(8):893-911.
220. Curigliano G, Cardinale D, Dent S, Criscitiello C, Aseyev O, Lenihan D, et al. Cardiotoxicity of anticancer treatments: Epidemiology, detection, and management. CA Cancer J Clin. 2016;66(4):309-25.
221. Weston KS, Wisloff U, Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. Br J Sports Med. 2014;48(16):1227-34.
222. Yue T, Wang Y, Liu H, Kong Z, Qi F. Effects of high-intensity interval vs. moderate-intensity continuous training on cardiac rehabilitation in patients with cardiovascular disease: a systematic review and meta-analysis. Front Cardiovasc Med. 2022;9:845225.
223. Mehta A, Kondamudi N, Laukkanen JA, Wisloff U, Franklin BA, Arena R, et al. Running away from cardiovascular disease at the right speed: The impact of aerobic physical activity and cardiorespiratory fitness on cardiovascular disease risk and associated subclinical phenotypes. Prog Cardiovasc Dis. 2020;63(6):762-74.
224. Haykowsky MJ, Liang Y, Pechter D, Jones LW, McAlister FA, Clark AM. A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: the benefit depends on the type of training performed. J Am Coll Cardiol. 2007;49(24):2329-36.

225. Howden EJ, Sarma S, Lawley JS, Opondo M, Cornwell W, Stoller D, et al. Reversing the cardiac effects of sedentary aging in middle age-a randomized controlled trial: implications for heart failure prevention. Circulation. 2018;137(15):1549-60.
226. Arbab-Zadeh A, Perhonen M, Howden E, Peshock RM, Zhang R, Adams-Huet B, et al. Cardiac remodeling in response to 1 year of intensive endurance training. Circulation. 2014;130(24):2152-61.
227. Ashor AW, Lara J, Siervo M, Celis-Morales C, Mathers JC. Effects of exercise modalities on arterial stiffness and wave reflection: a systematic review and meta-analysis of randomized controlled trials. PLoS One. 2014;9(10):e110034.
228. Ashor AW, Lara J, Siervo M, Celis-Morales C, Oggioni C, Jakovljevic DG, et al. Exercise modalities and endothelial function: a systematic review and dose-response meta-analysis of randomized controlled trials. Sports Med. 2015;45(2):279-96.
229. Lopes S, Afreixo V, Teixeira M, Garcia C, Leitao C, Gouveia M, et al. Exercise training reduces arterial stiffness in adults with hypertension: a systematic review and meta-analysis. J Hypertens. 2021;39(2):214-22.
230. You Q, Yu L, Li G, He H, Lv Y. Effects of different intensities and durations of aerobic exercise on vascular endothelial function in middle-aged and elderly people: a meta-analysis. Front Physiol. 2021;12:803102.
231. Green DJ, Maiorana A, O'Driscoll G, Taylor R. Effect of exercise training on endothelium-derived nitric oxide function in humans. J Physiol. 2004;561(Pt 1):1-25.
232. Green DJ, Smith KJ. Effects of exercise on vascular function, structure, and health in humans. Cold Spring Harbor perspectives in medicine. 2018;8(4).
233. Kingwell BA, Sherrard B, Jennings GL, Dart AM. Four weeks of cycle training increases basal production of nitric oxide from the forearm. Am J Physiol. 1997;272(3 Pt 2):H1070-7.
234. Hambrecht R, Adams V, Erbs S, Linke A, Krankel N, Shu Y, et al. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. Circulation. 2003;107(25):3152-8.
235. Maiorana A, O'Driscoll G, Cheetham C, Dembo L, Stanton K, Goodman C, et al. The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. J Am Coll Cardiol. 2001;38(3):860-6.

236. Maiorana A, O'Driscoll G, Dembo L, Cheetham C, Goodman C, Taylor R, et al. Effect of aerobic and resistance exercise training on vascular function in heart failure. Am J Physiol Heart Circ Physiol. 2000;279(4):H1999-2005.
237. Thijssen DH, de Groot PC, Smits P, Hopman MT. Vascular adaptations to 8-week cycling training in older men. Acta Physiol (Oxf). 2007;190(3):221-8.
238. Ostergard T, Nyholm B, Hansen TK, Rasmussen LM, Ingerslev J, Sorensen KE, et al. Endothelial function and biochemical vascular markers in first-degree relatives of type 2 diabetic patients: the effect of exercise training. Metabolism: clinical and experimental. 2006;55(11):1508-15.
239. Tinken TM, Thijssen DH, Black MA, Cable NT, Green DJ. Time course of change in vasodilator function and capacity in response to exercise training in humans. J Physiol. 2008;586(20):5003-12.
240. Black MA, Cable NT, Thijssen DH, Green DJ. Importance of measuring the time course of flow-mediated dilatation in humans. Hypertension. 2008;51(2):203-10.
241. Naylor LH, Weisbrod CJ, O'Driscoll G, Green DJ. Measuring peripheral resistance and conduit arterial structure in humans using Doppler ultrasound. J Appl Physiol (1985). 2005;98(6):2311-5.
242. Williams CJ, Gurd BJ, Bonafiglia JT, Voisin S, Li Z, Harvey N, et al. A multi-center comparison of VO2peak trainability between interval training and moderate intensity continuous training. Front Physiol. 2019;10(19):19.
243. Bigaran A, Zopf E, Gardner J, La Gerche A, Murphy DG, Howden EJ, et al. The effect of exercise training on cardiometabolic health in men with prostate cancer receiving androgen deprivation therapy: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2021;24(1):35-48.
244. Gardner JR, Livingston PM, Fraser SF. Effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving androgen-deprivation therapy: a systematic review. J Clin Oncol. 2014;32(4):335-46.
245. Lopez P, Taaffe DR, Newton RU, Buffart LM, Galvao DA. What is the minimal dose for resistance exercise effectiveness in prostate cancer patients? Systematic review and meta-analysis on patient-reported outcomes. Prostate Cancer Prostatic Dis. 2021;24(2):465-81.
246. Lopez P, Taaffe DR, Newton RU, Galvao DA. Resistance exercise dosage in men with prostate cancer: systematic review, meta-analysis, and meta-regression. Med Sci Sports Exerc. 2021;53(3):459-69.

247. Cormie P, Galvao DA, Spry N, Joseph D, Chee R, Taaffe DR, et al. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. BJU Int. 2015;115(2):256-66.
248. Wall BA, DA GA, Fatehee N, Taaffe DR, Spry N, Joseph D, et al. Exercise improves VO2max and body composition in androgen deprivation therapy-treated prostate cancer patients. Med Sci Sports Exerc. 2017;49(8):1503-10.
249. Harrison MR, Davis PG, Khouri MG, Bartlett DB, Gupta RT, Armstrong AJ, et al. A randomized controlled trial comparing changes in fitness with or without supervised exercise in patients initiated on enzalutamide and androgen deprivation therapy for non-metastatic castration-sensitive prostate cancer (EXTEND). Prostate Cancer Prostatic Dis. 2022;25(1):58-64.
250. Tsai HT, Keating NL, Van Den Eeden SK, Haque R, Cassidy-Bushrow AE, Ulcickas Yood M, et al. Risk of diabetes among patients receiving primary androgen deprivation therapy for clinically localized prostate cancer. J Urol. 2015;193(6):1956-62.
251. Bourke L, Gilbert S, Hooper R, Steed LA, Joshi M, Catto JW, et al. Lifestyle changes for improving disease-specific quality of life in sedentary men on long-term androgen-deprivation therapy for advanced prostate cancer: a randomised controlled trial. Eur Urol. 2014;65(5):865-72.
252. Culos-Reed SN, Robinson JW, Lau H, Stephenson L, Keats M, Norris S, et al. Physical activity for men receiving androgen deprivation therapy for prostate cancer: benefits from a 16-week intervention. Support Care Cancer. 2010;18(5):591-9.
253. Hojan K, Kwiatkowska-Borowczyk E, Leporowska E, Milecki P. Inflammation, cardiometabolic markers, and functional changes in men with prostate cancer. A randomized controlled trial of a 12-month exercise program. Pol Arch Intern Med. 2017;127(1):25-35.
254. Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. J Clin Oncol. 2010;28(2):340-7.
255. Denham JW, Steigler A, Lamb DS, Joseph D, Turner S, Matthews J, 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):451-9.
256. Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff RO, Storme G, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med. 1997;337(5):295-300.

257. Lu-Yao G, Nikita N, Keith SW, Nightingale G, Gandhi K, Hegarty SE, et al. Mortality and hospitalization risk following oral androgen signalling inhibitors among men with advanced prostate cancer by pre-existing cardiovascular comorbidities. Eur Urol. 2020;77(2):158-66.
258. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
259. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603-5.
260. Brown BW, Brauner C, Minnotte MC. Noncancer deaths in white adult cancer patients. J Natl Cancer Inst. 1993;85(12):979-87.
261. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PWF, et al. Prediction of Lifetime Risk for Cardiovascular Disease by Risk Factor Burden at 50 Years of Age. Circulation. 2006;113(6):791-8.
262. Nascimento B, Miranda EP, Jenkins LC, Benfante N, Schofield EA, Mulhall JP. Testosterone recovery profiles after cessation of androgen deprivation therapy for prostate cancer. J Sex Med. 2019;16(6):872-9.
263. Guo Y, Dong X, Yang F, Yu Y, Wang R, Kadier A, et al. Effects of Radiotherapy or Radical Prostatectomy on the Risk of Long-Term Heart-Specific Death in Patients With Prostate Cancer. Frontiers in Oncol. 2020;10.
264. Liu E, Guan X, Wei R, Jiang Z, Liu Z, Wang G, et al. Association Between Radiotherapy and Death From Cardiovascular Disease Among Patients With Cancer: A Large Population-Based Cohort Study. JAMA. 2022;11(6):e023802.
265. Bourke L, Smith D, Steed L, Hooper R, Carter A, Catto J, et al. Exercise for men with prostate cancer: a systematic review and meta-analysis. Eur Urol. 2016;69(4):693-703.
266. Lopez P, Newton RU, Taaffe DR, Singh F, Lyons-Wall P, Buffart LM, et al. Interventions for improving body composition in men with prostate cancer: a systematic review and network meta-analysis. Med Sci Sports Exerc. 2022;54(5):728-40.
267. Ligibel JA, Bohlke K, May AM, Clinton SK, Demark-Wahnefried W, Gilchrist SC, et al. Exercise, diet, and weight management during cancer treatment: ASCO Guideline. J Clin Oncol. 2022;40(22):2491-507.
268. O'Callaghan CJ, Rong P, Goh MY. National guidelines for the management of absolute cardiovascular disease risk. Med J Aust 2012.

269. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General Cardiovascular Risk Profile for Use in Primary Care. The Framingham Heart Study. 2008;117(6):743-53.

270. Hangartner TN, Warner S, Braillon P, Jankowski L, Shepherd J. The Official Positions of the International Society for Clinical Densitometry: acquisition of dual-energy X-ray absorptiometry body composition and considerations regarding analysis and repeatability of measures. Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry. 2013;16(4):520-36.

271. Dalla Via J, Owen PJ, Daly RM, Mundell NL, Livingston PM, Rantalainen T, et al. Musculoskeletal responses to exercise plus nutrition in men with prostate cancer on androgen deprivation: A 12-Month RCT. Med Sci Sports Exerc. 2021;53(10):2054-65.

272. Owen PJ, Daly RM, Dalla Via J, Mundell NL, Livingston PM, Rantalainen T, et al. Does use of androgen deprivation therapy (ADT) in men with prostate cancer increase the risk of sarcopenia? Calcif Tissue Int. 2019;105(4):403-11.

273. Chen CH, Nevo E, Fetics B, Pak PH, Yin FC, Maughan WL, et al. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. Circulation. 1997;95(7):1827-36.

274. Grillo A, Parati G, Rovina M, Moretti F, Salvi L, Gao L, et al. Short-term repeatability of noninvasive aortic pulse wave velocity assessment: comparison between methods and devices. Am J Hypertens. 2017;31(1):80-8.

275. Sharman JE, Lim R, Qasem AM, Coombes JS, Burgess MI, Franco J, et al. Validation of a generalized transfer function to noninvasively derive central blood pressure during exercise. Hypertension. 2006;47(6):1203-8.

276. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness; definitions and reference values. Am J Hypertens. 2002;15(5):426-44.

277. Zamorano JL, Lancellotti P, Rodriguez Munoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(36):2768-801.

278. Hamo CE, Bloom MW, Cardinale D, Ky B, Nohria A, Baer L, et al. Cancer Therapy-Related Cardiac Dysfunction and Heart Failure: Part 2: Prevention, Treatment, Guidelines, and Future Directions. Circulation Heart failure. 2016;9(2):e002843.
279. Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M, et al. Recommendations on the use of echocardiography in adult hypertension: a report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE)dagger. Eur Heart J Cardiovasc Imaging. 2015;16(6):577-605.
280. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39 e14.
281. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277-314.
282. Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol. 2002;90(1):29-34.
283. Foulkes SJ, Howden EJ, Bigaran A, Janssens K, Antill Y, Loi S, et al. Persistent impairment in cardiopulmonary fitness after breast cancer chemotherapy. Med Sci Sports Exerc. 2019;51(8):1573-81.
284. Hundley WG, Li HF, Willard JE, Landau C, Lange RA, Meshack BM, et al. Magnetic resonance imaging assessment of the severity of mitral regurgitation. Comparison with invasive techniques. Circulation. 1995;92(5):1151-8.
285. Katz J, Milliken MC, Stray-Gundersen J, Buja LM, Parkey RW, Mitchell JH, et al. Estimation of human myocardial mass with MR imaging. Radiology. 1988;169(2):495-8.
286. American College of Cardiology Foundation Task Force on Expert Consensus D, Hundley WG, Bluemke DA, Finn JP, Flamm SD, Fogel MA, et al. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol. 2010;55(23):2614-62.

287. Gagliano-Juca T, Li Z, Pencina KM, Traustadottir T, Travison TG, Woodhouse L, et al. The stair climb power test as an efficacy outcome in randomized trials of function promoting therapies in older men. J Gerontol A Biol Sci Med Sci. 2020;75(6):1167-75.
288. LeBrasseur NK, Bhasin S, Miciek R, Storer TW. Tests of muscle strength and physical function: reliability and discrimination of performance in younger and older men and older men with mobility limitations. J Am Geriatr Soc. 2008;56(11):2118-23.
289. Ni M, Brown LG, Lawler D, Bean JF. Reliability, validity, and minimal detectable change of four-step stair climb power test in community-dwelling older adults. Phys Ther. 2017;97(7):767-73.
290. Marks T, Raskin JM, Fioriello D, Talreja R, Rey C, Isom S, et al. The reliability and validity of the timed stair climbing test as an outcome measure for individuals with pulmonary disease. Cardiopulmonary Physical Therapy Journal. 2014;25(4).
291. Bean JF, Kiely DK, LaRose S, Alian J, Frontera WR. Is stair climb power a clinically relevant measure of leg power impairments in at-risk older adults? Arch Phys Med Rehabil. 2007;88(5):604-9.
292. Galvao DA, Nosaka K, Taaffe DR, Spry N, Kristjanson LJ, McGuigan MR, et al. Resistance training and reduction of treatment side effects in prostate cancer patients. Med Sci Sports Exerc. 2006;38(12):2045-52.
293. American Thoracic S, American College of Chest P. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167(2):211-77.
294. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation. 2010;122(2):191-225.
295. Jones LW, Courneya KS, Mackey JR, Muss HB, Pituskin EN, Scott JM, et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. J Clin Oncol. 2012;30(20):2530-7.
296. American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription. 8th ed. Thompson WR, editor. Baltimore, Maryland, USA: Lippincott Williams & Wilkins; 2014.
297. Bard RL, Gillespie BW, Clarke NS, Egan TG, Nicklas JM. Determining the best ventilatory efficiency measure to predict mortality in patients with heart failure. J Heart Lung Transplant. 2006;25(5):589-95.

298. Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. Am Heart J. 2004;147(2):354-60.
299. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol. 1986;60(6):2020-7.
300. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
301. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.
302. van Andel G, Bottomley A, Fossa SD, Efficace F, Coens C, Guerif S, et al. An international field study of the EORTC QLQ-PR25: a questionnaire for assessing the health-related quality of life of patients with prostate cancer. Eur J Cancer. 2008;44(16):2418-24.
303. Fayers P, Bottomley A. Quality of life research within the EORTC—the EORTC QLQ-C30. European Journal of Cancer. 2002;38:125-33.
304. Scott NW, Fayers P, Aaronson NK, Bottomley A, de Graeff A, Groenvold M, et al. EORTC QLQ-C30 reference values manual. 2008.
305. Cella D, Davis K, Breitbart W, Curt G, Fatigue C. Cancer-related fatigue: prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. J Clin Oncol. 2001;19(14):3385-91.
306. Cella D, Nowinski CJ. Measuring quality of life in chronic illness: the functional assessment of chronic illness therapy measurement system. Arch Phys Med Rehabil. 2002;83(12 Suppl 2): S10-7.
307. Derogatis LR KL. The SCL-90-R and Brief Symptom Inventory (BSI) in primary care. Minneapolis, USA: Routledge.; 2000.
308. Hanisch LJ, Gooneratne NS, Soin K, Gehrman PR, Vaughn DJ, Coyne JC. Sleep and Daily Functioning during Androgen Deprivation Therapy for Prostate Cancer. Eur J Cancer. 2011;20(4):549-54.
309. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193-213.

310. Backhaus J, Junghanns K, Broocks A, Riemann D, Hohagen F. Test–retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. J Psychosomatic Res. 2002;53(3):737-40.

311. Cerin E, Cain KL, Oyeyemi AL, Owen N, Conway TL, Cochrane T, et al. Correlates of agreement between accelerometry and self-reported physical activity. Med Sci Sports Exerc. 2016;48(6):1075-84.

312. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35(8):1381-95.

313. G. Godin. The Godin-Shephard lesuire-time physical activity questionnarie. Health & Fitness Journal of Canada. 2011;4(1):18-22.

314. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. Med Sci Sports Exerc. 2019;51(11):2375-90.

315. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010;42(7):1409-26.

316. Bigaran A, Howden EJ, Foulkes S, Janssens K, Beaudry RI, Haykowsky MJ, et al. Prescribing Exercise in Early-Stage Breast Cancer During Chemotherapy: A Simple Periodized Approach to Align With the Cyclic Phases of Chemotherapy. J Strength Cond Res. 2022;36(10):2934-41.

317. Fairman CM, Nilsen TS, Newton RU, Taaffe DR, Spry N, Joseph D, et al. Reporting of resistance training dose, adherence, and tolerance in exercise oncology. Med Sci Sports Exerc. 2020;52(2):315-22.

318. Howden EJ, Perhonen M, Peshock RM, Zhang R, Arbab-Zadeh A, Adams-Huet B, et al. Females have a blunted cardiovascular response to one year of intensive supervised endurance training. J Appl Physiol (1985). 2015;119(1):37-46.

319. Iwasaki K, Zhang R, Zuckerman JH, Levine BD. Dose-response relationship of the cardiovascular adaptation to endurance training in healthy adults: how much training for what benefit? J Appl Physiol (1985). 2003;95(4):1575-83.

320. McBride JM, McCaulley GO, Cormie P, Nuzzo JL, Cavill MJ, Triplett NT. Comparison of methods to quantify volume during resistance exercise. J Strength Cond Res. 2009;23(1):106-10.

321. Burke GL, Bertoni AG, Shea S, Tracy R, Watson KE, Blumenthal RS, et al. The impact of obesity on cardiovascular disease risk factors and subclinical vascular disease: the Multi-Ethnic Study of Atherosclerosis. Arch Intern Med. 2008;168(9):928-35.
322. Kuller LH, Arnold AM, Psaty BM, Robbins JA, O'Leary DH, Tracy RP, et al. 10-year follow-up of subclinical cardiovascular disease and risk of coronary heart disease in the Cardiovascular Health Study. Arch Intern Med. 2006;166(1):71-8.
323. Sandbakk SB, Nauman J, Lavie CJ, Wisloff U, Stensvold D. Combined association of cardiorespiratory fitness and body fatness with cardiometabolic risk factors in older Norwegian adults: The Generation 100 Study. Mayo Clin Proc Innov Qual Outcomes. 2017;1(1):67-77.
324. Chaves PH, Kuller LH, O'Leary DH, Manolio TA, Newman AB, Cardiovascular Health S. Subclinical cardiovascular disease in older adults: insights from the Cardiovascular Health Study. Am J Geriatr Cardiol. 2004;13(3):137-51.
325. Abbasi SA, Hundley WG, Bluemke DA, Jerosch-Herold M, Blankstein R, Petersen SE, et al. Visceral adiposity and left ventricular remodeling: The Multi-Ethnic Study of Atherosclerosis. Nutr Metab Cardiovasc Dis. 2015;25(7):667-76.
326. Heckbert SR, Post W, Pearson GD, Arnett DK, Gomes AS, Jerosch-Herold M, et al. Traditional cardiovascular risk factors in relation to left ventricular mass, volume, and systolic function by cardiac magnetic resonance imaging: the Multiethnic Study of Atherosclerosis. J Am Coll Cardiol. 2006;48(11):2285-92.
327. Myers J, McAuley P, Lavie CJ, Despres JP, Arena R, Kokkinos P. Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: their independent and interwoven importance to health status. Prog Cardiovasc Dis. 2015;57(4):306-14.
328. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA. 2012;308(8):788-95.
329. Yoneyama K, Venkatesh BA, Bluemke DA, McClelland RL, Lima JAC. Cardiovascular magnetic resonance in an adult human population: serial observations from the multi-ethnic study of atherosclerosis. J Cardiovasc Magn Reson. 2017;19(1):52.
330. Zavodni AE, Wasserman BA, McClelland RL, Gomes AS, Folsom AR, Polak JF, et al. Carotid artery plaque morphology and composition in relation to incident cardiovascular events: the Multi-Ethnic Study of Atherosclerosis (MESA). Radiology. 2014;271(2):381-9.

331. Adams SC, DeLorey DS, Davenport MH, Stickland MK, Fairey AS, North S, et al. Effects of high-intensity aerobic interval training on cardiovascular disease risk in testicular cancer survivors: A phase 2 randomized controlled trial. Cancer. 2017;123(20):4057-65.
332. Laukkanen JA, Rauramaa R, Salonen JT, Kurl S. The predictive value of cardiorespiratory fitness combined with coronary risk evaluation and the risk of cardiovascular and all-cause death. J Intern Med. 2007;262(2):263-72.
333. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159-219.
334. Green DJ, Jones H, Thijssen D, Cable NT, Atkinson G. Flow-mediated dilation and cardiovascular event prediction: does nitric oxide matter? Hypertension (Dallas, Tex : 1979). 2011;57(3):363-9.
335. Laukkanen JA, Pukkala E, Rauramaa R, Makikallio TH, Toriola AT, Kurl S. Cardiorespiratory fitness, lifestyle factors and cancer risk and mortality in Finnish men. Eur J Cancer. 2010;46(2):355-63.
336. Chirinos JA, Segers P, Hughes T, Townsend R. Large-Artery stiffness in health and disease: JACC state-of-the-art review. J Am Coll Cardiol. 2019;74(9):1237-63.
337. Bornstein MH, Jager J, Putnick DL. Sampling in developmental science: situations, shortcomings, solutions, and standards. Dev Rev. 2013;33(4):357-70.
338. Cochran WG. Sampling techniques. 3rd Edition, ed. New York: John Wiley & Sons; 1977.
339. Bornstein MH, Jager J, Putnick DL. Sampling in Developmental Science: Situations, Shortcomings, Solutions, and Standards. Dev Rev. 2013;33(4):357-70.
340. Jager J, Putnick DL, Bornstein MH. II. More than just convenient: the scientific merits of homogeneous convenience samples. Monogr Soc Res Child Dev. 2017;82(2):13-30.
341. Lyon AR, Lopez-Fernandez T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. 2022;43(41):4229-361.
342. Hughes AD, Park C, Davies J, Francis D, Mc GTSA, Mayet J, et al. Limitations of augmentation index in the assessment of wave reflection in normotensive healthy individuals. PLoS One. 2013;8(3):e59371.

343. de Souza ESCG, Kaminsky LA, Arena R, Christle JW, Araujo CGS, Lima RM, et al. A reference equation for maximal aerobic power for treadmill and cycle ergometer exercise testing: Analysis from the FRIEND registry. Eur J Prev Cardiol. 2018;25(7):742-50.
344. Meyer ML, Tanaka H, Palta P, Cheng S, Gouskova N, Aguilar D, et al. Correlates of Segmental Pulse Wave Velocity in Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study. Am J Hypertens. 2016;29(1):114-22.
345. Chirinos JA, Zambrano JP, Chakko S, Veerani A, Schob A, Willens HJ, et al. Aortic pressure augmentation predicts adverse cardiovascular events in patients with established coronary artery disease. Hypertension. 2005;45(5):980-5.
346. Chirinos JA, Kips JG, Jacobs DR, Jr., Brumback L, Duprez DA, Kronmal R, et al. Arterial wave reflections and incident cardiovascular events and heart failure: MESA (Multiethnic Study of Atherosclerosis). J Am Coll Cardiol. 2012;60(21):2170-7.
347. Li WF, Huang YQ, Feng YQ. Association between central haemodynamics and risk of all-cause mortality and cardiovascular disease: a systematic review and meta-analysis. J Hum Hypertens. 2019;33(7):531-41.
348. Howden EJ, Foulkes S, Dillon HT, Bigaran A, Wright L, Janssens K, et al. Traditional markers of cardiac toxicity fail to detect marked reductions in cardiorespiratory fitness among cancer patients undergoing anti-cancer treatment. Eur Heart J Cardiovasc Imaging. 2021;22(4):451-8.
349. Lee CD, Blair SN, Jackson AS. Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. Am J Clin Nutr. 1999;69(3):373-80.
350. Blair SN, Kohl HW, 3rd, Paffenbarger RS, Jr., Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA. 1989;262(17):2395-401.
351. Blair SN, Shaten J, Brownell K, Collins G, Lissner L. Body weight change, all-cause mortality, and cause-specific mortality in the Multiple Risk Factor Intervention Trial. Ann Intern Med. 1993;119(7 Pt 2):749-57.
352. Wei M, Gaskill SP, Haffner SM, Stern MP. Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality. The San Antonio Heart Study. Diabetes Care. 1998;21(7):1167-72.
353. Wilson RL, Shannon T, Calton E, Galvao DA, Taaffe DR, Hart NH, et al. Efficacy of a weight loss program prior to robot assisted radical prostatectomy in overweight and obese men with prostate cancer. Surg Oncol. 2020;35:182-8.

354. Wilson RL, Taaffe DR, Newton RU, Hart NH, Lyons-Wall P, Galvao DA. Obesity and prostate cancer: A narrative review. Crit Rev Oncol Hematol. 2022;169:103543.
355. Ortega FB, Lavie CJ, Blair SN. Obesity and Cardiovascular Disease. Circulation research. 2016;118(11):1752-70.
356. Kang DW, Fairey AS, Boule NG, Field CJ, Wharton SA, Courneya KS. Effects of exercise on cardiorespiratory fitness and biochemical progression in men with localized prostate cancer under active surveillance: The ERASE randomized clinical trial. JAMA Oncol. 2021;7(10):1487-95.
357. Banks E, Crouch SR, Korda RJ, Stavreski B, Page K, Thurber KA, et al. Absolute risk of cardiovascular disease events, and blood pressure- and lipid-lowering therapy in Australia. Med J Aust. 2016;204(8):320.
358. Vlachopoulos C, Xaplanteris P, Aboyans V, Brodmann M, Cifkova R, Cosentino F, et al. The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: Endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. Atherosclerosis. 2015;241(2):507-32.
359. Jae SY, Heffernan KS, Fernhall B, Oh YS, Park WH, Lee MK, et al. Association between cardiorespiratory fitness and arterial stiffness in men with the metabolic syndrome. Diabetes Res Clin Pract. 2010;90(3):326-32.
360. Lin JS, Evans CV, Johnson E, Redmond N, Coppola EL, Smith N. Nontraditional risk factors in cardiovascular disease risk assessment: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2018;320(3):281-97.
361. Ferreira I, Twisk JW, Stehouwer CD, van Mechelen W, Kemper HC. Longitudinal changes in VO2max: associations with carotid IMT and arterial stiffness. Med Sci Sports Exerc. 2003;35(10):1670-8.
362. Berry JD, Liu K, Folsom AR, Lewis CE, Carr JJ, Polak JF, et al. Prevalence and progression of subclinical atherosclerosis in younger adults with low short-term but high lifetime estimated risk for cardiovascular disease: the coronary artery risk development in young adults study and multi-ethnic study of atherosclerosis. Circulation. 2009;119(3):382-9.
363. Haykowsky MJ, Beaudry R, Brothers RM, Nelson MD, Sarma S, La Gerche A. Pathophysiology of exercise intolerance in breast cancer survivors with preserved left ventricular ejection fraction. Clinical science (London, England : 1979). 2016;130(24):2239-44.

364. Beaudry RI, Howden EJ, Foulkes S, Bigaran A, Claus P, Haykowsky MJ, et al. Determinants of exercise intolerance in breast cancer patients prior to anthracycline chemotherapy. Physiol Rep. 2019;7(1):e13971.
365. Thanassoulis G, Lyass A, Benjamin EJ, Larson MG, Vita JA, Levy D, et al. Relations of exercise blood pressure response to cardiovascular risk factors and vascular function in the Framingham Heart Study. Circulation. 2012;125(23):2836-43.
366. Kokkinos P, Myers J, Faselis C, Panagiotakos DB, Doumas M, Pittaras A, et al. Exercise capacity and mortality in older men: a 20-year follow-up study. Circulation. 2010;122(8):790-7.
367. Grimes DA, Schulz KF. Compared to what? Finding controls for case-control studies. The Lancet. 2005;365(9468):1429-33.
368. Cohen J. Statisical power analysis for Behavioural Sciences. 2nd ed. London, UK1988.
369. Galvao DA, Spry N, Denham J, Taaffe DR, Cormie P, Joseph D, et al. A multicentre year-long randomised controlled trial of exercise training targeting physical functioning in men with prostate cancer previously treated with androgen suppression and radiation from TROG 03.04 RADAR. Eur Urol. 2014;65(5):856-64.
370. Taaffe DR, Newton RU, Spry N, Joseph D, Chambers SK, Gardiner RA, et al. Effects of different exercise modalities on fatigue in prostate cancer patients undergoing androgen deprivation therapy: a year-long randomised controlled trial. Eur Urol. 2017;72(2):293-9.
371. Gaskin CJ, Fraser SF, Owen PJ, Craike M, Orellana L, Livingston PM. Fitness outcomes from a randomised controlled trial of exercise training for men with prostate cancer: the ENGAGE study. J Cancer Surviv. 2016;10(6):972-80.
372. Owen PJ, Daly RM, Livingston PM, Mundell NL, Dalla Via J, Millar JL, et al. Efficacy of a multi-component exercise programme and nutritional supplementation on musculoskeletal health in men treated with androgen deprivation therapy for prostate cancer (IMPACT): study protocol of a randomised controlled trial. Trials. 2017;18(1):451.
373. Nilsen TS, Raastad T, Skovlund E, Courneya KS, Langberg CW, Lilleby W, et al. Effects of strength training on body composition, physical functioning, and quality of life in prostate cancer patients during androgen deprivation therapy. Acta Oncol. 2015;54(10):1805-13.
374. Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. J Clin Oncol. 2009;27(3):344-51.

375. Morgia G, Russo GI, Tubaro A, Bortolus R, Randone D, Gabriele P, 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;96:165-70.
376. Van Hemelrijck M, Garmo H, Holmberg L, Stattin P, Adolfsson J. Multiple events of fractures and cardiovascular and thromboembolic disease following prostate cancer diagnosis: results from the population-based PCBaSe Sweden. Eur Urol. 2012;61(4):690-700.
377. 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):1243-51.
378. Kloner RA, Carson C, 3rd, Dobs A, Kopecky S, Mohler ER, 3rd. Testosterone and Cardiovascular Disease. J Am Coll Cardiol. 2016;67(5):545-57.
379. Corona G, Rastrelli G, Monami M, Guay A, Buvat J, Sforza A, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. Eur J Endocrinol. 2011;165(5):687.
380. Ruige JB, Mahmoud AM, De Bacquer D, Kaufman JM. Endogenous testosterone and cardiovascular disease in healthy men: a meta-analysis. Heart. 2011;97(11):870-5.
381. Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA. Clinical review: Endogenous testosterone and mortality in men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2011;96(10):3007-19.
382. Lieb W, Gona P, Larson MG, Aragam J, Zile MR, Cheng S, et al. The natural history of left ventricular geometry in the community: clinical correlates and prognostic significance of change in LV geometric pattern. JACC Cardiovascular imaging. 2014;7(9):870-8.
383. Lindroos M, Kupari M, Heikkila J, Tilvis R. Echocardiographic evidence of left ventricular hypertrophy in a general aged population. Am J Cardiol. 1994;74(4):385-90.
384. Gheorghe ACD, Ciobanu A, Hodorogea AS, Radavoi GD, Jinga V, Rascu ASC, et al. Subclinical left ventricular dysfunction in men under androgen deprivation therapy for prostate cancer, revealed by speckle-tracking-derived parameters, repolarization, and myocardial injury markers. Echocardiography. 2021;38(4):632-40.
385. Subramanya V, Zhao D, Ouyang P, Lima JA, Vaidya D, Ndumele CE, et al. Sex hormone levels and change in left ventricular structure among men and post-menopausal women: The Multi-Ethnic Study of Atherosclerosis (MESA). Maturitas. 2018;108(Supplement C):37-44.

386. Rosen BD, Edvardsen T, Lai S, Castillo E, Pan L, Jerosch-Herold M, et al. Left ventricular concentric remodeling is associated with decreased global and regional systolic function. Circulation. 2005;112(7):984-91.

387. Ostergren PB, Kistorp C, Bennedbaek FN, Faber J, Sonksen J, Fode M. The use of exercise interventions to overcome adverse effects of androgen deprivation therapy. Nat Rev Urol. 2016;13(6):353-64.

388. Cormie P, Zopf EM. Exercise medicine for the management of androgen deprivation therapy-related side effects in prostate cancer. Urol Oncol. 2020;38(2):62-70.

389. Fujimoto N, Prasad A, Hastings JL, Arbab-Zadeh A, Bhella PS, Shibata S, et al. Cardiovascular effects of 1 year of progressive and vigorous exercise training in previously sedentary individuals older than 65 years of age. Circulation. 2010;122(18):1797-805.

390. Wisloff U, Stoylen A, Loennechen JP, Bruvold M, Rognmo O, Haram PM, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation. 2007;115(24):3086-94.

391. Moholdt TT, Amundsen BH, Rustad LA, Wahba A, Lovo KT, Gullikstad LR, et al. Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life. Am Heart J. 2009;158(6):1031-7.

392. Moholdt T, Aamot IL, Granoien I, Gjerde L, Myklebust G, Walderhaug L, et al. Aerobic interval training increases peak oxygen uptake more than usual care exercise training in myocardial infarction patients: a randomized controlled study. Clin Rehabil. 2012;26(1):33-44.

393. Scott JM, Martin D, Ploutz-Snyder R, Downs M, Dillon EL, Sheffield-Moore M, et al. Efficacy of exercise and testosterone to mitigate atrophic cardiovascular remodeling. Med Sci Sports Exerc. 2018;50(9):1940-9.

394. Chasland LC, Yeap BB, Maiorana AJ, Chan YX, Maslen BA, Cooke BR, et al. Testosterone and exercise: effects on fitness, body composition, and strength in middle-to-older aged men with low-normal serum testosterone levels. Am J Physiol Heart Circ Physiol. 2021;320(5):H1985-H98.

395. Edwards J, Shanmugam N, Ray R, Jouhra F, Mancio J, Wiles J, et al. Exercise Mode in Heart Failure: A Systematic Review and Meta-Analysis. Sports Medicine - Open. 2023;9(1):3.

396. Adams SC, DeLorey DS, Davenport MH, Fairey AS, North S, Courneya KS. Effects of high-intensity interval training on fatigue and quality of life in testicular cancer survivors. British Journal of Cancer. 2018;118(10):1313-21.

397. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.
398. Negishi T, Thavendiranathan P, Negishi K, Marwick TH, investigators S. Rationale and design of the strain surveillance of chemotherapy for improving cardiovascular outcomes: The SUCCOUR Trial. JACC Cardiovascular imaging. 2018;11(8):1098-105.
399. Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, Sandri MT, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol. 2012;23 Suppl 7(suppl_7):vii155-66.
400. Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol. 2020;31(2):171-90.
401. Bean JF, Kiely DK, LaRose S, Alian J, Frontera WR. Is Stair Climb Power a Clinically Relevant Measure of Leg Power Impairments in At-Risk Older Adults? Archives of Physical Medicine and Rehabilitation. 2007;88(5):604-9.
402. Bandini M, Gandaglia G, Briganti A. Obesity and prostate cancer. Curr Opin Urol. 2017;27(5):415-21.
403. Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. Sarcopenic obesity and risk of cardiovascular disease and mortality: a population-based cohort study of older men. J Am Geriatr Soc. 2014;62(2):253-60.
404. Aurigemma GP, de Simone G, Fitzgibbons TP. Cardiac remodeling in obesity. Circ Cardiovasc Imaging. 2013;6(1):142-52.
405. Despres JP. Body fat distribution and risk of cardiovascular disease: an update. Circulation. 2012;126(10):1301-13.
406. Izeli NL, Santos AJ, Crescencio JC, Goncalves AC, Papa V, Marques F, et al. Aerobic Training after Myocardial Infarction: Remodeling Evaluated by Cardiac Magnetic Resonance. Arq Bras Cardiol. 2016;106(4):311-8.
407. Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, et al. Effect of aging and physical activity on left ventricular compliance. Circulation. 2004;110(13):1799-805.
408. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods. 2009;41(4):1149-60.

409. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39(2):175-91.
410. Alberga AS, Segal RJ, Reid RD, Scott CG, Sigal RJ, Khandwala F, et al. Age and androgen-deprivation therapy on exercise outcomes in men with prostate cancer. Support Care Cancer 2012;20(5):971-81.
411. Glatting G, Kletting P, Reske SN, Hohl K, Ring C. Choosing the optimal fit function: comparison of the Akaike information criterion and the F-test. Med Phys. 2007;34(11):4285-92.
412. Baumfalk DR, Opoku-Acheampong AB, Caldwell JT, Butenas ALE, Horn AG, Kunkel ON, et al. Effects of high-intensity training on prostate cancer-induced cardiac atrophy. Am J Transl Res. 2021;13(1):197-209.
413. Baumfalk DR, Opoku-Acheampong AB, Caldwell JT, Ade CJ, Copp SW, Musch TI, et al. Effects of prostate cancer and exercise training on left ventricular function and cardiac and skeletal muscle mass. J Appl Physiol. 2019;126(3):668-80.
414. Scott JM, Zabor EC, Schwitzer E, Koelwyn GJ, Adams SC, Nilsen TS, et al. Efficacy of exercise therapy on cardiorespiratory fitness in patients with cancer: a systematic review and meta-analysis. J Clin Oncol. 2018;36(22):2297-305.
415. Vainshelboim B, Chan K, Chen Z, Myers J. Cardiorespiratory fitness and cancer in men with cardiovascular disease: Analysis from the Veterans Exercise Testing Study. Eur J Prev Cardiol. 2021;28(7):715-21.
416. Myers J, Kokkinos P, Chan K, Dandekar E, Yilmaz B, Nagare A, et al. Cardiorespiratory Fitness and Reclassification of Risk for Incidence of Heart Failure: The Veterans Exercise Testing Study. Circ Heart Fail. 2017;10(6).
417. Jones LW, Watson D, Herndon JE, 2nd, Eves ND, Haithcock BE, Loewen G, et al. Peak oxygen consumption and long-term all-cause mortality in nonsmall cell lung cancer. Cancer. 2010;116(20):4825-32.
418. Blair SN, Kampert JB, Kohl HW, 3rd, Barlow CE, Macera CA, Paffenbarger RS, Jr., et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA. 1996;276(3):205-10.
419. Molmen-Hansen HE, Stolen T, Tjonna AE, Aamot IL, Ekeberg IS, Tyldum GA, et al. Aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients. Eur J Prev Cardiol. 2012;19(2):151-60.

420. Wisloff U, Ellingsen O, Kemi OJ. High-intensity interval training to maximize cardiac benefits of exercise training? Exerc Sport Sci Rev. 2009;37(3):139-46.
421. Vashistha V, Singh B, Kaur S, Prokop LJ, Kaushik D. The Effects of Exercise on Fatigue, Quality of Life, and Psychological Function for Men with Prostate Cancer: Systematic Review and Meta-analyses. European urology focus. 2016;2(3):284-95.
422. Tsou P-H, Lan T-C, Tam K-W, Huang T-W. Essential of Immediate Exercises on Cancer-Related Fatigue in Patients with Prostate Cancer Receiving Androgen Deprivation Therapy: A Meta-Analysis of Randomized Controlled Trials. Seminars in Oncology Nursing. 2023;39(3):151368.
423. Potosky AL, Reeve BB, Clegg LX, Hoffman RM, Stephenson RA, Albertsen PC, et al. Quality of life following localized prostate cancer treated initially with androgen deprivation therapy or no therapy. J Natl Cancer Inst. 2002;94(6):430-7.
424. Twomey R, Martin T, Temesi J, Culos-Reed SN, Millet GY. Tailored exercise interventions to reduce fatigue in cancer survivors: study protocol of a randomized controlled trial. BMC Cancer. 2018;18(1):757.
425. Brownstein CG, Twomey R, Temesi J, Medysky ME, Culos-Reed SN, Millet GY. Mechanisms of Neuromuscular Fatigability in People with Cancer-Related Fatigue. Medicine and science in sports and exercise. 2022;54(8):1355-63.
426. Hayes SC, Newton RU, Spence RR, Galvao DA. The Exercise and Sports Science Australia position statement: Exercise medicine in cancer management. J Sci Med Sport. 2019;22(11):1175-99.
427. Fuller JT, Hartland MC, Maloney LT, Davison K. Therapeutic effects of aerobic and resistance exercises for cancer survivors: a systematic review of meta-analyses of clinical trials. Br J Sports Med. 2018;52(20):1311.
428. Teleni L, Chan RJ, Chan A, Isenring EA, Vela I, Inder WJ, et al. Exercise improves quality of life in androgen deprivation therapy-treated prostate cancer: systematic review of randomised controlled trials. Endocr Relat Cancer. 2016;23(2):101-12.
429. Lavín-Pérez AM, Collado-Mateo D, Mayo X, Liguori G, Humphreys L, Copeland RJ, et al. Effects of high-intensity training on the quality of life of cancer patients and survivors: a systematic review with meta-analysis. Sci Rep. 2021;11(1):15089.
430. Mondal S, Edwards S, Wibowo E, Ahmed H, Wassersug RJ, Ellis J, et al. Evaluating Patterns and Factors Related to Sleep Disturbances in Prostate Cancer Patients. Healthcare (Basel). 2022;10(5).

431. Alibhai SMH, Santa Mina D, Ritvo P, Tomlinson G, Sabiston C, Krahn M, et al. A phase II randomized controlled trial of three exercise delivery methods in men with prostate cancer on androgen deprivation therapy. BMC Cancer. 2019;19(1):2.
432. Newton RU, Galvao DA, Spry N, Joseph D, Chambers SK, Gardiner RA, et al. Exercise mode specificity for preserving spine and hip bone mineral density in prostate cancer patients. Med Sci Sports Exerc. 2019;51(4):607-14.
433. Gilbert SE, Tew GA, Fairhurst C, Bourke L, Saxton JM, Winter EM, et al. Effects of a lifestyle intervention on endothelial function in men on long-term androgen deprivation therapy for prostate cancer. Br J Cancer. 2016;114(4):401-8.
434. Van Poppel H, Abrahamsson PA. Considerations for the use of gonadotropin-releasing hormone agonists and antagonists in patients with prostate cancer. Int J Urol. 2020;27(10):830-7.
435. Holland DJ, Sacre JW, McFarlane SJ, Coombes JS, Sharman JE. Pulse Wave Analysis Is a Reproducible Technique for Measuring Central Blood Pressure During Hemodynamic Perturbations Induced by Exercise. Am j Hypertens. 2008;21(10):1100-6.
436. Hwang MH, Yoo JK, Kim HK, Hwang CL, Mackay K, Hemstreet O, et al. Validity and reliability of aortic pulse wave velocity and augmentation index determined by the new cuff-based SphygmoCor Xcel. J Hum Hypertens. 2014;28(8):475-81.
437. Ni M, Brown LG, Lawler D, Bean JF. Reliability, Validity, and Minimal Detectable Change of Four-Step Stair Climb Power Test in Community-Dwelling Older Adults. Physical therapy. 2017;97(7):767-73.
438. Smith-Ryan AE, Mock MG, Ryan ED, Gerstner GR, Trexler ET, Hirsch KR. Validity and reliability of a 4-compartment body composition model using dual energy x-ray absorptiometry-derived body volume. Clinical Nutr. 2017;36(3):825-30.
439. McGill HC, Jr., McMahan CA, Gidding SS. Preventing heart disease in the 21st century: implications of the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study. Circulation. 2008;117(9):1216-27.
440. Pelliccia A, Sharma S, Gati S, Back M, Borjesson M, Caselli S, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. Eur Heart J. 2021;42(1):17-96.
441. Price KJ, Gordon BA, Bird SR, Benson AC. A review of guidelines for cardiac rehabilitation exercise programmes: Is there an international consensus? Eur J Prev Cardiol. 2016;23(16):1715-33.

442. Way KL, Terada T, O'Neill CD, Vidal-Almela S, Keech A, Reed JL. Practical recommendations for high-intensity interval training for adults with cardiovascular disease. ACSM's Health & Fitness Journal. 2021;25(5).
443. Culos-Reed SN, Robinson JL, Lau H, O'Connor K, Keats MR. Benefits of a physical activity intervention for men with prostate cancer. J Sport Exerc Psychol. 2007;29(1):118-27.
444. Ndjavera W, Orange ST, O'Doherty AF, Leicht AS, Rochester M, Mills R, et al. Exercise-induced attenuation of treatment side-effects in patients with newly diagnosed prostate cancer beginning androgen-deprivation therapy: a randomised controlled trial. BJU Int. 2020;125(1):28-37.
445. Papadopoulos E, Mina DS, Culos-Reed N, Durbano S, Ritvo P, Sabiston CM, et al. Effects of six months of aerobic and resistance training on metabolic markers and bone mineral density in older men on androgen deprivation therapy for prostate cancer. J Geriatr Oncol. 2020;11(7):1074-7.
446. Mina DS, Matthew AG, Trachtenberg J, Tomlinson G, Guglietti CL, Alibhai SMH, et al. Physical activity and quality of life after radical prostatectomy. Can Urol Assoc J. 2010;4(3):180-6.
447. Hvid T, Winding K, Rinnov A, Dejgaard T, Thomsen C, Iversen P, et al. Endurance training improves insulin sensitivity and body composition in prostate cancer patients treated with androgen deprivation therapy. Endocr Relat Cancer. 2013;20(5):621-32.
448. Zabegalina NS, Henderickx M, Lamotte V, Segers B, Stassijns G, De Wachter S, et al. Effects of a six-month supervised physical exercise program on physical and cardio-metabolic profile and quality of life in patients with prostate cancer on androgen deprivation therapy: a pilot and feasibility study. Cent European J Urol. 2018;71(2):234-41.
449. Kaminsky LA, Arena R, Myers J. Reference standards for cardiorespiratory fitness measured with cardiopulmonary exercise testing: data from the fitness registry and the importance of exercise national database. Mayo Clin Proc. 2015;90(11):1515-23.
450. Schumacher O, Galvao DA, Taaffe DR, Spry N, Joseph D, Tang C, et al. Effect of exercise adjunct to radiation and androgen deprivation therapy on patient-reported treatment toxicity in men with prostate cancer: a secondary analysis of 2 randomized controlled trialss. Pract Radiat Oncol. 2021;11(3):215-25.
451. Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegenthart R, Verwoert GC, et al. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. Ann Intern Med. 2012;156(6):438-44.

452. Scott JM, Thomas SM, Peppercorn JM, Herndon JE, 2nd, Douglas PS, Khouri MG, et al. Effects of exercise therapy dosing schedule on impaired cardiorespiratory fitness in patients with primary breast cancer: a randomized controlled trial. Circulation. 2020;141(7):560-70.
453. Scott JM, Iyengar NM, Nilsen TS, Michalski M, Thomas SM, Herndon J, 2nd, et al. Feasibility, safety, and efficacy of aerobic training in pretreated patients with metastatic breast cancer: A randomized controlled trial. Cancer. 2018;124(12):2552-60.
454. Jones LW, Eves ND, Peddle CJ, Courneya KS, Haykowsky M, Kumar V, et al. Effects of presurgical exercise training on systemic inflammatory markers among patients with malignant lung lesions. Appl Physiol Nutr Metab. 2009;34(2):197-202.
455. Jones LW, Eves ND, Peterson BL, Garst J, Crawford J, West MJ, et al. Safety and feasibility of aerobic training on cardiopulmonary function and quality of life in postsurgical nonsmall cell lung cancer patients: a pilot study. Cancer. 2008;113(12):3430-9.
456. Scott JM, Li N, Liu Q, Yasui Y, Leisenring W, Nathan PC, et al. Association of exercise with mortality in adult survivors of childhood cancer. JAMA Oncol. 2018;4(10):1352-8.
457. Jones LW, Habel LA, Weltzien E, Castillo A, Gupta D, Kroenke CH, et al. Exercise and risk of cardiovascular events in women with nonmetastatic breast cancer. J Clin Oncol. 2016;34(23):2743-9.

APPENDIX A

A.1. Research Portfolio

Australian Catholic University High Degree Research requests a statement of contributions detailing each co-author's intellectual input into publications included in this doctoral thesis.

The statement of contributions (next page) relates to the following peer-review publication.

Bigaran A, Zopf E, Gardner J, La Gerche A, Murphy DG, Howden EJ, et al. The effect of exercise training on cardiometabolic health in men with prostate cancer receiving androgen deprivation therapy: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2021;24(1):35-48. DOI: 10.1038/s41391-020-00273-5

Statement of contributions

Bigaran A, Zopf E, Gardner J, La Gerche A, Murphy DG, Howden EJ, et al. The effect of exercise training on cardiometabolic health in men with prostate cancer receiving androgen deprivation therapy: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2021;24(1):35-48. doi: 10.1038/s41391-020-00273-5

I acknowledge that my contribution to the above paper is 60 percent.

A. Bigaran: [redacted] Date: 20/06/2022

I acknowledge that my contribution to the above paper is 5 percent.

E. Zopf: [redacted] Date: 28/6/2022

I acknowledge that my contribution to the above paper is 5 percent.

J. Gardner: [redacted] Date: 21/6/2022

I acknowledge that my contribution to the above paper is 5 percent.

A. La Gerche: [redacted] Date: 28/6/2022

I acknowledge that my contribution to the above paper is 5 percent.

D. G. Murphy: [redacted] Date: 27/6/2022

I acknowledge that my contribution to the above paper is 5 percent.

E.J. Howden: [redacted] Date: 24/6/2022

I acknowledge that my contribution to the above paper is 5 percent.

M.K. Baker: [redacted] Date: 22/6/2022

I acknowledge that my contribution to the above paper is 10 percent.

P. Cormie: [redacted] Date: 28/6/2022

A.2. Evidence of journal submission

The manuscript presented in *Chapter Two* (listed below) has been submitted to *Acta Oncologica*.

Submitted

Bigaran A, Zopf EM, Gardner J, Howden EJ, Baker MK, Cormie, P. The influence of pre-existing cardiovascular disease on cardiovascular morbidity and mortality in men with prostate cancer treated with androgen deprivation therapy. A systematic review.

Evidence of this submission is attached.

Ashley Bigaran

From: Acta Oncologica <onbehalfof@manuscriptcentral.com>
Sent: Friday, 1 July 2022 11:18 AM
To: Ashley Bigaran
Subject: Acta Oncologica - Manuscript ID SONC-2022-0399

30-Jun-2022

Dear Miss Ashley Bigaran:

Your manuscript entitled "Influence of pre-existing cardiovascular disease on morbidity and mortality in men with prostate cancer undergoing ADT: A systematic review" has been successfully submitted online and is presently being given full consideration for publication in the Acta Oncologica.

Your manuscript ID is SONC-2022-0399.

Please mention the above manuscript ID in all future correspondence.
If there are any changes in your street address or e-mail address, please log in to Manuscript Central at https://aus01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fmc.manuscriptcentral.com%2Fsonc&data=05%7C01%7Cashley.bigaran%40acu.edu.au%7Cb9d4579ac62042f26aa608da5aff853c%7C429af009f196448fae7958c212a0f2ce%7C0%7C0%7C637922350813292595%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=LdZolKiqFWlimCyJ6k%2BMDWrMMBiX6K6aAhBL3Xk%2Fjzo%3D&reserved=0 and edit your user information as appropriate.

You can also view the status of your manuscript at any time by checking your Author Center after logging in to https://aus01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fmc.manuscriptcentral.com%2Fsonc&data=05%7C01%7Cashley.bigaran%40acu.edu.au%7Cb9d4579ac62042f26aa608da5aff853c%7C429af009f196448fae7958c212a0f2ce%7C0%7C0%7C637922350813292595%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=LdZolKiqFWlimCyJ6k%2BMDWrMMBiX6K6aAhBL3Xk%2Fjzo%3D&reserved=0

Additionally, please do follow the Journal on Twitter (@actaoncol) for the latest articles and updates from the society.

Thank you for submitting your manuscript to the Acta Oncologica.

Sincerely,
Lena Andreasson-Haddad and Åsa Sjoblad

Acta Oncologica Editorial Office

A.3. Additional publications

Bigaran A, Howden EJ, Foulkes S, Janssens K, Haykowsky MJ, Beaudry R, et al. Prescribing exercise in early-stage breast cancer during chemotherapy: a simple periodized approach to align with the cyclic phases of chemotherapy. J Strength Cond Res (2021). DOI: 10.1519/JSC.0000000000003990

Howden EJ, Foulkes S, Dillon HT, **Bigaran A**, Wright L, Janssens K, et al. Traditional markers of cardiac toxicity fail to detect marked reductions in cardiorespiratory fitness among cancer patients undergoing anti-cancer treatment. Eur Heart J Cardiovasc Imaging. 2021;22(4):451-8. DOI: 10.1093/ehjci/jeaa421

Bland KA, **Bigaran A**, Campbell KL, Trevaskis M, Zopf EM. Exercising in Isolation? The Role of Telehealth in Exercise Oncology During the COVID-19 Pandemic and Beyond. Phys Ther. 2020;100(10):1713-6. DOI: 10.1093/ptj/pzaa141

Costello BT, Roberts TJ, Howden EJ, **Bigaran A**, Foulkes SJ, Beaudry RI, et al. Exercise Attenuates Cardiotoxicity of Anthracycline Chemotherapy Measured by Global Longitudinal Strain. JACC CardioOncol. 2019;1(2):298-301. DOI: 10.1016/j.jaccao.2019.09.002.

Foulkes SJ, Howden EJ, **Bigaran A**, Janssens K, Antill Y, Loi S, et al. Persistent Impairment in Cardiopulmonary Fitness after Breast Cancer Chemotherapy. Med Sci Sports Exerc Medicine 2019;51(8). DOI: 10.1249/MSS.0000000000001970.

Howden EJ, **Bigaran A,** Beaudry R, Fraser S, Selig S, Foulkes S, et al. Exercise as a diagnostic and therapeutic tool for the prevention of cardiovascular dysfunction in breast cancer patients. Eur J Prev Cardiol. 2019;26(3):305-15. DOI: 10.1177/2047487318811181.

Beaudry RI, Howden EJ, Foulkes S, **Bigaran A**, Claus P, Haykowsky MJ, et al. Determinants of exercise intolerance in breast cancer patients prior to anthracycline chemotherapy. Physiol Rep. 2019;7(1):e13971. Physiol Rep. (2019). DOI: 10.14814/phy2.13971**.**

A.4. Additional presentations

Bigaran, A. Using exercise to counteract the adverse side effects of cancer treatments.

Bigaran A, Howden, EJ, Janssens K, Selig SE, Fraser SF, La Gerche A. The effect of chemotherapy

- **Invited presentation:** Department of Medical Oncology Grand Rounds, Department of Medical Oncology, Austin Health, February 2022, Melbourne, Australia.

on aerobic power and cardiac function in early-stage breast cancer patients.
Australian Cardiovascular Health and Rehabilitation Scientific Meeting, August 2017, Perth, Australia.
Awards: This presentation was presented in the research finalist prize session as one of the top four ranked abstracts in the conference.

Bigaran, A. Using exercise to counteract the adverse side effects of breast cancer treatments.
Department of Medical Oncology, Genesis Care, November 2020, Melbourne, Australia

Bigaran, A. Clinical and practical implications of exercise-delivered telehealth interventions for cancer patients: where to from here?
Invited presentation: Little Big Forum (international), June 2020, Melbourne, Australia (Virtual Conference)

Bigaran A, Howden EJ, Janssens K, Selig SE, Fraser SF, La Gerche A. The Effect of Exercise Training on Aerobic Power in Early-stage Breast Cancer Patients undergoing Anthracycline-Chemotherapy.
Australian Society of Medical Research Symposium, November 2017, Melbourne, Australia.

APPENDIX B

B.1. Ethics approval

Human Research Ethics Approval – Alfred Health 2018

ETHICS COMMITTEE CERTIFICATE OF APPROVAL

This is to certify that

Project Number: HREC/18/Alfred/4 (Local Reference: Project 19/18)

Project Title: Evaluating the impact of exercise on cardiac remodeling in men with prostate cancer undergoing androgen deprivation therapy

Coordinating Principal Investigator: A/Professor Prue Cormie

*was considered under the Victorian Streamlined Ethical Review Process (SERP) by the Ethics Committee on **30-Jan-2018**, meets the requirements of the National Statement on Ethical Conduct in Human Research (2007) and was **APPROVED** on **9-Mar-2018**.*

It is the Coordinating Principal Investigator's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Coordinating Principal Investigator is required to notify the Secretary of the Ethics Committee, via amendment or progress report, of

- Any significant change to the project and the reason for that change, including an indication of ethical implications
  (if any);
- Serious adverse effects on participants and the action taken to address those effects;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Coordinating Principal Investigator to continue in that role, or any other change in research personnel involved in the project;
- Any expiry of the insurance coverage provided with respect to sponsored clinical trials and proof of re-insurance;
- A delay of more than 12 months in the commencement of the project; and,
- Termination or closure of the project.

Additionally, the Coordinating Principal Investigator is required to submit

- A Progress Report on the anniversary of approval and on completion of the project.

The Ethics Committee may conduct an audit at any time.

All research subject to the Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Hospital Ethics Committee is a properly constituted Human Research Ethics Committee in accordance with the National Statement on Ethical Conduct in Human Research (2007).

SPECIAL CONDITIONS

None

APPROVED DOCUMENTS

Documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Protocol	1.1	24-Jan-2018
MASTER Participant Information Sheet & Consent Form (Patient)	1.3	31-Jan-2018
MASTER Participant Information Sheet & Consent Form (Control)	1.4	31-Jan-2018
Advertisement – Flyer (Patient)	1.1	24-Jan-2018
Advertisement – Flyer (Control)	1.1	24-Jan-2018
Phone screening	1.0	10-Jan-2018
Questionnaires	1.0	10-Jan-2018
Data Management Plan	-	10-Jan-2018
Budget	-	10-Jan-2018
Section 4 – Use of Ionising Radiation (ACU & Alfred Health)	-	-

APPROVED SITES

Approval is given for this research project to be conducted at the following sites and campuses:

1. Alfred Health
2. Austin Health
3. Baker Heart & Diabetes Institute
4. Peter MacCallum Cancer Centre
5. Royal Melbourne Hospital

The Alfred Hospital Ethics Committee has approved the study but does not take responsibility for research governance processes at the participating sites. It is the responsibility of each participating site to create and implement research governance practices to adequately authorise, monitor and oversee the conduct of the study at their site.

Site-Specific Assessment (SSA)
SSA authorisation is required at all sites participating in the study. SSA must be authorised at a site before the research project can commence.

The completed Site-Specific Assessment Form and a copy of this ethics approval letter must be submitted to the Research Governance Officer for authorisation by the Chief Executive or delegate. This applies to each site participating in the research.

The HREC wishes you and your colleagues every success in your research.

SIGNED:

Chair, Ethics Committee (or delegate)

Please quote project number and title in all correspondence