Real world evidence for the use of androgen deprivation therapy in prostate cancer

George, Gincy

Awarding institution:
King's College London

REAL WORLD EVIDENCE FOR THE USE OF ANDROGEN DEPRIVATION THERAPY IN PROSTATE CANCER

Thesis presented in accordance with the requirements for the degree of Doctor of Philosophy by

Gincy Elsa George
Translational Oncology and Urology Research
School of Cancer and Pharmaceutical Sciences
King's College London

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B. ABSTRACT

Background

Androgen deprivation therapy (ADT) is the mainline treatment for men with advanced prostate cancer (PCa), with some men remaining on ADT for up to two decades. Prolonged use of Gonadotropin Releasing Hormone (GnRH) agonists may be associated with survival benefits, but also with potential side-effects in men with PCa. One of the more recently investigated side-effects of ADT is an increased risk of cardiovascular disease (CVD). Observational studies that have explored CVD effects following GnRH agonists have found consistent positive associations whereas GnRH antagonists have shown less metabolic characteristics of CVD in preclinical models. Moreover, patterns of non-adherence to GnRH agonists among men with PCa may be associated with worse prognosis. This thesis used real world data to investigate risk of CVD following GnRH agonists and antagonists and to explore patterns and factors influencing adherence to GnRH agonists in men with PCa.

Methods

Data from six countries (United Kingdom (UK) excluding Scotland, Scotland, Belgium, the Netherlands, France and Canada) was extracted to evaluate the association between GnRH agonists or GnRH antagonists and the risk of CVD. Country-specific hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using multivariable adjusted Cox proportional hazards models and then

pooled using a random effects meta-analysis model. Meta-analytical models included stratifications by history of CVD indicator (HCVDi) and age.

In order to identify patterns affecting non-adherence to GnRH agonists, data from Sweden and UK were collated considering determinants at 3 years following GnRH agonists' initiation. Non-adherence was determined by a medication possession ratio (MPR) of < 80%. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated using logistic regression. Factors contributing to adherence in men with PCa on GnRH agonists in the UK were also thematically analysed using qualitative data from interviews with men with PCa on GnRH agonists and focus groups with their clinicians.

Results

Men with PCa on GnRH antagonists had an increased risk of developing any CVD (HR = 1.22; 95% CI = 1.03-1.45), arrhythmia (HR = 1.39; 95% CI = 1.13-1.72) and heart failure (HF) (HR = 1.33; 95% CI = 1.12-1.58) compared to men on GnRH agonists. In men on GnRH antagonists and with a HCVDi, there was an increased risk of developing arrhythmia (HR = 1.48; 95% CI = 1.03-2.13), HF (HR = 1.06; 95% CI = 1.05-1.07) and stroke (HR = 1.04; 95% CI = 1.03-1.05). Stratification by age showed an increased risk of developing any CVD (HR = 1.24; 95% CI = 1.04-1.48), ischaemic heart disease (IHD) (HR = 1.22; 95% CI = 1.03-1.45), arrhythmia (HR = 1.43; 95% CI = 1.19-1.73) and HF (HR = 1.39; 95% CI = 1.12-1.73) in those aged ≥ 75 years.

MPRs showed an increased adherence both for men with PCa on primary (Sweden = 88%; UK = 75%) and secondary (Sweden = 84%; UK = 70%) GnRH agonists after 3 years on the treatment. Analysis from both countries showed that an increased age and longer injection intervals were associated with increased adherence to primary and secondary GnRH agonists. In Sweden, increased adherence was also observed in men with PCa given anti-androgens (OR = 1.53; 95% CI = 1.21-1.93) and radiotherapy (OR = 1.77; 95% CI =1.39-2.27) as prior PCa treatment before GnRH agonists compared to deferred PCa treatment.

Qualitative analysis of interviews and focus groups in the UK showed that some multi-factorial reasons such as side-effects, strong patient belief system and quality over quantity of life contributed to non-adherence in some men.

Conclusion

Men with PCa and a HCVDi who were on GnRH antagonists may be at an increased risk of developing certain CVD subtypes compared to men on GnRH agonists. Pooling data from different countries can be challenging in the real world setting and results from both real world data and randomised controlled trials may be useful to better understand adverse effects of a drug. Therefore, results from the PRONOUNCE trial are required to fully address the potential of indication bias in this observational setting.

Factors such as age, injection intervals and prior PCa treatments can influence adherence patterns to GnRH agonists in the PCa population. Moreover, employing different strategies by clinicians to support non-adherent men and keeping them

engaged with the health care system may lead to the eventual acceptance of treatment whilst also acknowledging their reasons for non-adherence.

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ABBREVIATIONS

ACTH: Adrenocorticotrophic hormone

ADT: Androgen deprivation therapy

AMI: Acute myocardial infarction

AR: Androgen receptor

ATC: Anatomical Therapeutic Chemical

BCR: Belgian Cancer Registry

BD4BO: Big Data for Better Outcomes

BMI: Body mass index

BRCA 2: Breast cancer susceptibility gene 2

CCI: Charlson Comorbidity Index

CHAARTED: Chemohormonal Androgen Ablation Randomized Trial for Extensive Disease in prostate cancer

CI: Confidence interval

CNS: Clinical Nurse Specialist

CVD: Cardiovascular disease

CYP17: Cytochrome P450 17A1

DCIR: *Données de Consommation Inter-Régimes* or Inter-Scheme Consumption Data

DDD: Defined Daily Dose

DHT: Dihydrotestosterone

DNA: Deoxyribonucleic acid

EAU: European Association of Urology

EBRT: External beam therapy

EU: European union

FDA: Food and Drug Administration

FSH: Follicle stimulating hormone

GnRH: Gonadotropin-releasing hormone

HCVDi: History of cardiovascular disease indicator

HDR: High-dose rate

HF: Heart failure

HR: Hazard ratio

HRA: Health Research Authority

HTA: Health Technology Assessment

ICD: International Classification of Diseases

IHD: Ischaemic heart disease

IMI: Innovative Medicines Initiative

IMRT: Intensity-modulated external-beam radiotherapy

INSEE: *Institut national de la statistique et des études économiques* (National Institute of Statistics and Economic Studies)

ISUP: International Society of Urological Pathology

LATITUDE:

LDR: Low-dose rate

LH: Luteinizing hormone

MPR: Medication Possession Ratio

MRI: Magnetic resonance imaging

NHSS: National Health Service Scotland

NICE: National Institute for Clinical Excellence

NPCR: National Quality Register on Prostate Cancer

NRSI: Non-randomised studies of interventions

OR: Odds ratio

PCa: Prostate cancer

PCBaSe^{Traject}: Prostate Cancer data Base Sweden^{Traject}

PIONEER: Prostate cancer dIagnOsis and treatmeNt Enhancement through the power of big data in EuRope

PIVOT: Prostate Cancer Intervention versus Observation Trial

PMSI: *Médicalisation des Systèmes d'Information* or the National Hospital discharge Summaries database system

PSA: Prostate-specific antigen

PRONOUNCE: A Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Advanced Prostate Cancer and Cardiovascular Disease

ProtecT: Prostate Testing for Cancer and Treatment

RANKL: Receptor Activator of Nuclear factor κB Ligand

RAMQ: Régie de l'assurance maladie du Québec

ROBINS-I: Risk Of Bias In Non-randomised Studies – of Interventions

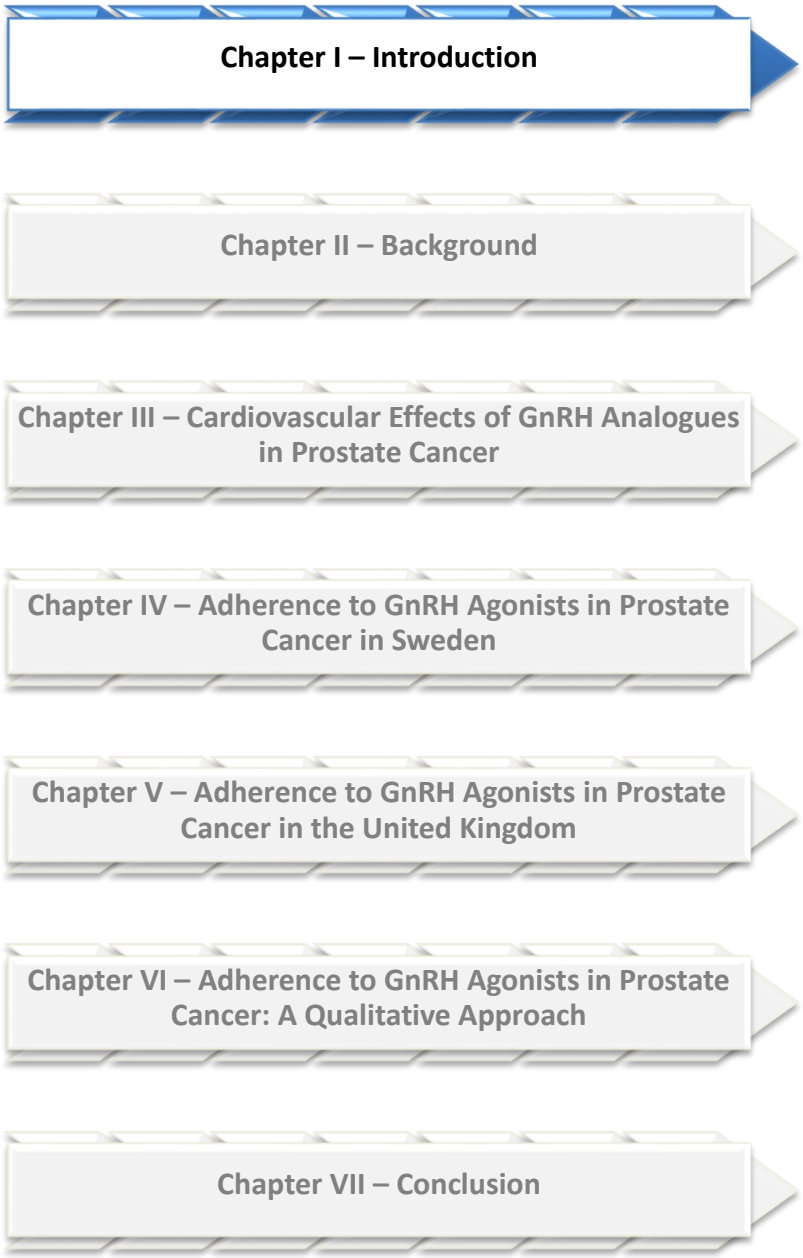
SES: Socio-economic status

SNIIRAM: *Systeme National d'Informations Inter Regimes de l'Assurance Maladie* (The French National Health Database)

SPCG-4: Scandinavian Prostate Cancer Group Study Number 4

STAMPEDE: Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy

VMAT: Volumetric arc external-beam radiotherapy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1. CHAPTER I – INTRODUCTION

1.1 RESEARCH OBJECTIVES AND STRUCTURE OF THESIS

Prostate cancer (PCa) is the second most common cause of cancer death in men, with almost 70% of PCa cases occurring in developed countries (1). The incidence of clinically significant disease is on a steady increase worldwide. The increasing ageing population worldwide means that men diagnosed with PCa will increase substantially in the next two decades (2). Age-standardised mortality rates for PCa per 100,000 men between 1971-2017 have remained stable in the United Kingdom (UK) for those aged < 70 years, whereas the rates have decreased by 11% for those between 70-79 years and increased by 45% in those aged > 80 years. The increasing mortality rates for PCa in men aged > 80 years may reflect the rising incidence and stable survival of men with PCa (3).

Several risk factors have been established for PCa, with age being the greatest contributing factor. The prevalence of microscopic PCa is approximately 80% in men aged 80 years or over. Other contributing factors can include family history, genetic polymorphisms, environmental factors (i.e. Westernised diet) and geographic and ethnic variations (2). The risk of developing PCa is higher in black men than Caucasian men suggesting a link between ethnicity and PCa (2).

Geographic variations have also shown to influence the risk of developing PCa. The risk is highest in North America and northern Europe and lowest in Asia. However, migration studies have shown that the incidence of PCa in men emigrating from low- (i.e. Asia) to high-risk (i.e. North America) areas increases to that of the local population within two generations. This suggests that environmental factors, such

as diet, as well as differences in healthcare systems may also have an effect in detecting clinically significant PCa (4).

Considering that a large proportion of PCa population may be on hormonal treatment or androgen deprivation therapy (ADT), it is important to understand the impact of long-term treatment with ADT on PCa-related outcomes and quality of life (5, 6).

This thesis therefore aims to provide more insights into the impact of long-term ADT in men with PCa. More specifically, this thesis focuses on the use of real world data to investigate adverse effects of hormonal treatment and adherence to hormonal treatment on the quality of life in men with PCa through the following four projects:

1. ***Project 1:*** Data from six countries (The Health Improvement Network (THIN) database from the UK (excluding Scotland), National Health Service Scotland (NHSS) from Scotland, Belgian Cancer Registry (BCR) from Belgium, PHARMO Database Network from the Netherlands, Systeme National d'Informations Inter Regimes de l'Assurance Maladie (SNIIRAM) database from France and Régie de l'assurance maladie du Québec (RAMQ) database from Canada) were used to compare the cardiovascular disease (CVD) effects of Gonadotropin-releasing hormone (GnRH) agonists and GnRH antagonists in men with PCa.
2. ***Project 2:*** Data from Prostate Cancer data Base Sweden^{Traject} (PCBaSe^{Traject}), version 4.0 was used to identify patterns of adherence to GnRH agonists in men with PCa in Sweden.

3. ***Project 3:*** Data from THIN was used to identify patterns of adherence to GnRH agonists in men with PCa in the UK.
4. ***Project 4:*** Qualitative study based on interviews with men with PCa on GnRH agonists and focus groups with their healthcare professionals to better understand factors influencing adherence and non-adherence to GnRH agonists in men with PCa.

The next chapter (chapter II) briefly introduces the concept of real world evidence and provides a background to PCa, including the anatomy, histology and diagnosis and treatment of PCa, epidemiology of PCa, use of ADT and its side-effects and a brief introduction into the four projects of this thesis. Chapters III-VI describe the methods and results of the four projects outlined above, in chronological order. Finally, chapter VII provides an overall conclusion, with interpretation of results and suggestions for future research directions.

2. CHAPTER II – BACKGROUND

This chapter introduces the concept of real world evidence and gives an overview of PCa including its epidemiology. A summary of ADT, significance of adverse effects following ADT and the concept of adherence to long-term ADT is also explored.

2.1 REAL WORLD EVIDENCE

The term real world evidence is now widely used in the medical field and has become an important part of research. The primary characteristic that distinguishes real world evidence from other kinds of scientific evidence is the setting in which the evidence is gathered. Real world evidence must originate from clinical care, home or community settings rather than research-intensive or academic settings (7). Real world data includes information derived from multiple sources such as; electronic healthcare records, claims and insurance data, disease registries including cancer registries, product and pharmacy registries and even data collected through personal devices and healthcare applications (8, 9).

Clinical trials remain a powerful tool for generating scientific evidence regarding the safety and efficacy of newly formulated drugs. Trials are needed to understand the biological and therapeutic action of drugs in patients. However, the generalisability of the internal validity attained by trial studies remain uncertain because the study population recruited to clinical trials are different to those seen in clinical practice (7). One reason for this distinction in study populations can be due to the selection

of healthier patients in trial data because of the rigorous recruitment criteria employed in many clinical trials, especially those that include an intervention.

There is a growing interest among academic and trial researchers, drug companies and medical-product developers to integrate clinical research with real world settings by increasing access to data from various real world data sources. Whereas registries and claims databases provide a platform for data collected at point of care, data from personal devices and healthcare applications allow continuous monitoring (7, 10).

The mutual interest for gathering real world evidence among various individual institutions has also given rise to consortiums aspiring to increase the quality of real world data available. For example, the GetReal Initiative was launched by the European Union (EU) in 2018, with the aim of increasing the quality of real world evidence in drug development and regulatory and Health Technology Assessment (HTA) processes across Europe. The consortium consists of pharmaceutical companies, academia, HTA agencies and regulators and patient organisations (11).

Therefore, real world evidence is a means of incorporating diverse types of real world data to increase the general applicability of results in studies. This thesis largely includes the use of real world data from electronic healthcare records, claims and insurance databases, hospital databases, cancer registries and pharmacy registries. Moreover, a small element of the thesis also includes the use of qualitative approaches in the real world setting.

2.2 ANATOMY, HISTOLOGY AND PHYSIOLOGY OF THE NORMAL PROSTATE

The prostate gland is part of the male reproductive system and is located between the bladder and the urethra (Figure 1) (12). It is approximately 20 to 30 grams in volume and resembles the size of a walnut (13). The prostate is surrounded by part of the urethra (called the prostatic urethra) which explains some of the common symptoms such as urinary retention, decreased force of stream or urinary frequency reported for prostate-related pathologies (14).

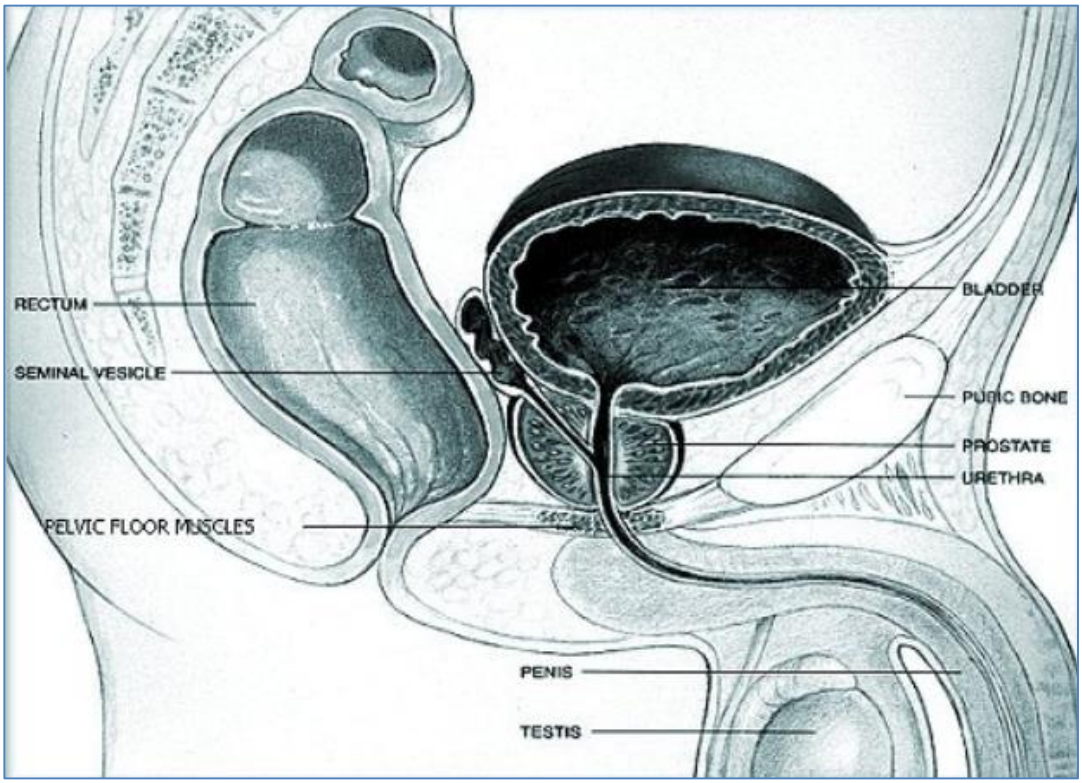

Figure 1: *Anatomy of the prostate gland (12).*

The prostate tissue can be divided into three zones: the transition zone, central zone and the peripheral zone (15). The transition zone represents 10% of the prostate glandular tissue and the central zone, that surrounds the ejaculatory ducts, represents 20% of the prostate glandular tissue. 70% of the prostate is represented by the peripheral zone which is located in the posterior and lateral segments of the prostate. PCa arises in the glandular tissue as adenocarcinomas, developing from the acini of the prostatic ducts (16). Adenocarcinomas can develop in all three zones of the prostate, with 20% of adenocarcinomas occurring in the transition zone, 1-5% in the central zone and 70% in the peripheral zone (14).

The primary function of the prostate is the production of an important liquefying component of the semen which nourishes the sperm. Once sperm is produced in the testicles, it is stored in the seminal vesicles until time of ejaculation. At the time of ejaculation, sperm mixes with fluid secreted by the prostate to become semen (13).

Prostate cells need androgens to develop and function normally. 95% of androgens originate from the testes, with 5-10% originating from adrenal glands via the adrenocorticotropic hormone (ACTH) pathway (Figure 2) (17). Testosterone is the androgen that is produced in the testes which is highly bound to plasma proteins with 40% bound to sex hormone-binding globulin, 60% bound with low affinity to albumin, leaving only 2% as free, unbound hormone (17, 18). Testosterone is converted to dihydrotestosterone (DHT) by the enzyme 5 α-reductase in the prostate and is the active metabolite of testosterone that is involved in the endocrine feedback loop (19).

The hypothalamic-pituitary-gonadal axis or the endocrine feedback loop (Figure 2) controls the secretion of testosterone. Pulsatile release of GnRH every 90-120 minutes from the hypothalamus stimulates the anterior pituitary gland to release luteinizing hormone (LH) and follicle stimulating hormone (FSH), which in turn promotes the synthesis and liberation of testosterone and inhibin. The 5α-DHT binds onto the androgen receptor (AR) located on the nuclear membrane of the prostate cells, thus contributing to normal prostate function and development (17).

Hypothalamic secretion of GnRH and pituitary secretion of LH is controlled by a negative feedback loop system. The release of testosterone and inhibin from the testes causes a negative effect on the hypothalamus and the pituitary gland, which results in the downregulation of testosterone synthesis (17).

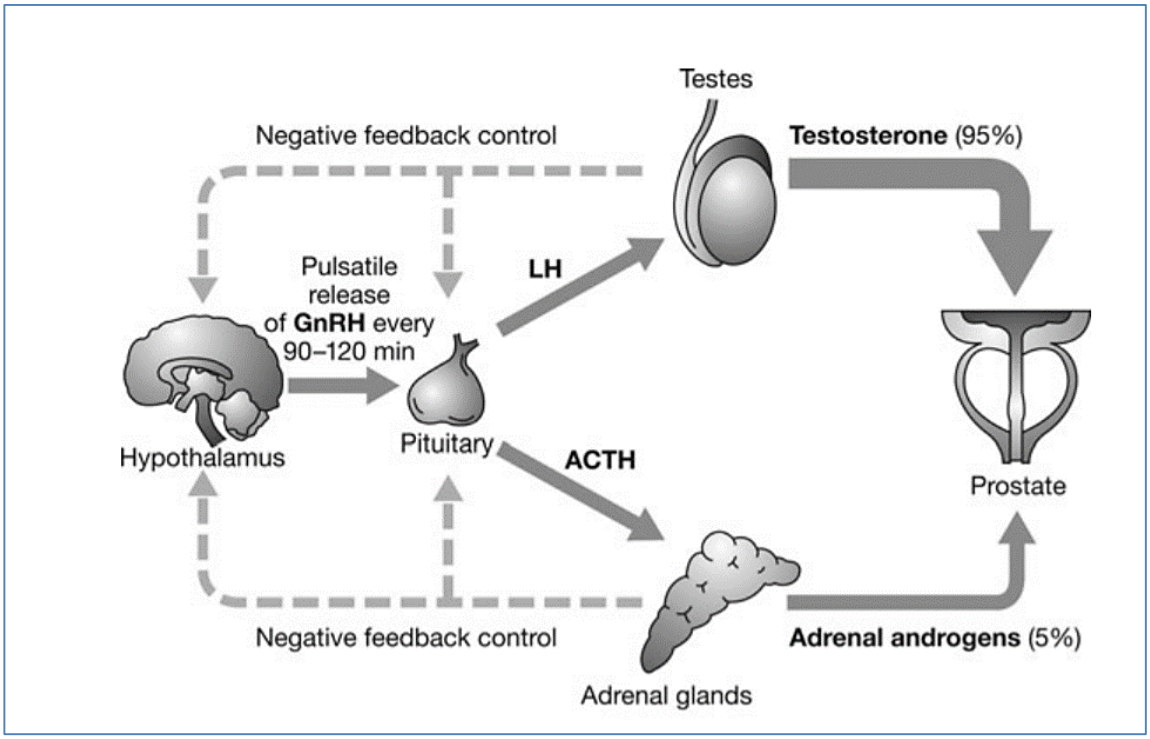

Figure 2: *The hypothalamic-pituitary-gonadal axis (17).*

2.3 PROSTATE CANCER

PCa occurs when cells in the prostate gland divide uncontrollably into cancer cells. Nearly all PCa cases diagnosed are adenocarcinomas, which arise in the glandular tissue of the prostate. Some rare cases of prostatic transitional cell carcinomas (developing from urothelial cells in the prostatic urethra) and neuroendocrine or squamous cell carcinomas also exist. These rare cases develop and behave differently to prostatic adenocarcinomas and therefore require distinctive management options to the adenocarcinomas (20).

2.3.1 Diagnosis of prostate cancer

2.3.1.1 Prostate-specific antigen screening

The primary method for PCa detection is through a simple blood test aimed to screen for a molecule found in prostate cells, the prostate-specific antigen (PSA), that is measured in the blood. An elevated PSA of 3.0-4.0 ng/mL is considered as an abnormal PSA. Although a raised PSA level can be a sign of PCa, some men can also have an elevated PSA due to an inflammation or enlargement of the prostate (21).

Most PCa cases are diagnosed in men who are asymptomatic due to increasing use of PSA testing. PCa cases detected through PSA tests are usually organ-confined and may not require immediate medical intervention (active surveillance described in section 2.3.2.1) (22). Men with advanced PCa may present with urinary-related symptoms, dramatic weight loss, bone pain or other symptoms of metastasis including spinal cord compression (23, 24). A physician also performs a digital rectal examination to determine the size, consistency and physical abnormalities on the

posterior surface of the prostate. Many cancers can be palpated on digital rectal examination because they occur in the peripheral zone (22).

2.3.1.2 Pathological investigation

Typically, men with persistent elevated PSA levels will undergo a pathological investigation through biopsy of the prostate tissue, which is usually the confirmatory test (21). Differences in histological characteristics in the biopsy are scored based on the grade to which the abnormal cell has differentiated compared to the normal prostatic tissue. Based on the appearance of cancer cells in the biopsy sample, the pathologist assigns two most common cancer patterns identified – Gleason scores (e.g. 3+4). More advanced and more rapidly growing cancers are given a higher Gleason grade (21). Gleason scores can range from 2 (non-aggressive) to 10 (very aggressive) and Gleason grades can range from 1 (well differentiated) to 5 (poorly differentiated or anaplastic) (Figure 2).

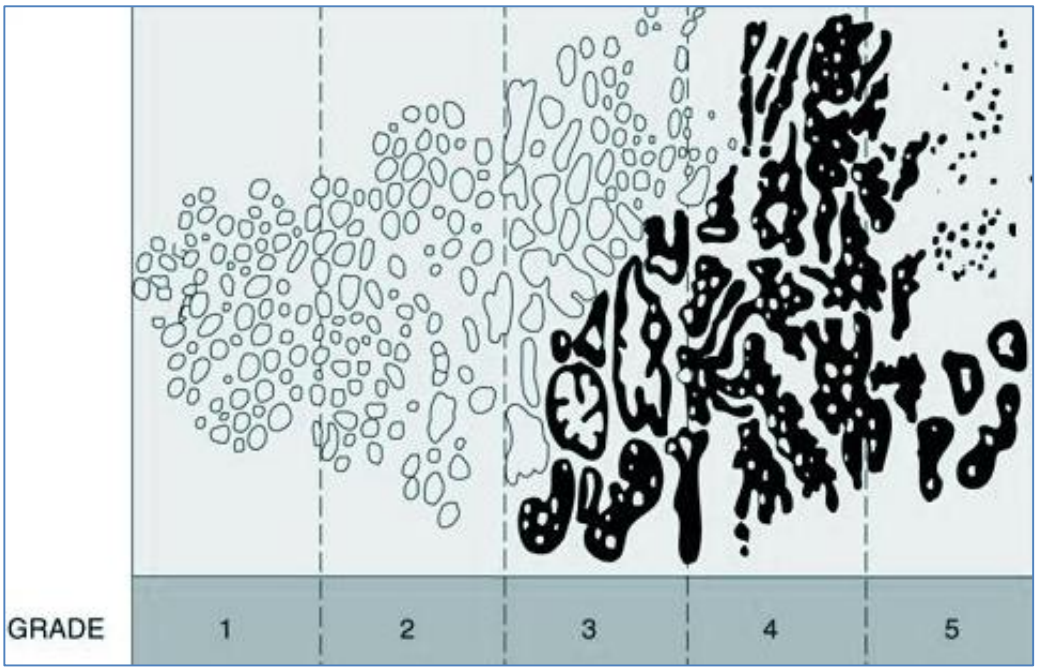

Figure 3: *The Gleason grading system can help physicians to predict how rapidly the cancer is likely to spread (21).*

Recently, a new Gleason grading system was endorsed by International Society of Urological Pathology (ISUP) in 2014 to simplify the grading system and improve accuracy of grade stratification (Figure 3) (25). The new system is grouped as follows:

- **Grade Group 1:** *(Gleason score 3+3 = 6)* Individual, discrete, well-formed glands.
- **Grade Group 2:** *(Gleason score 3+4 = 7)* Largely well-formed glands with lesser component of poorly formed or fused or cribriform glands.
- **Grade Group 3:** *(Gleason score 4+3 = 7)* Largely poorly formed or fused or cribriform glands with lesser component of well-formed glands.
- **Grade Group 4:** *(Gleason score 8)* (i) Only poorly formed/fused/cribriform glands or (ii) largely well-formed glands and lesser component lacking glands or (iii) largely lacking glands and lesser component of well-formed glands.
- **Grade Group 5:** *(Gleason scores 9-10)* Lack of gland formation with (or without) necrosis or with (or without) poorly formed or fused or cribriform glands.

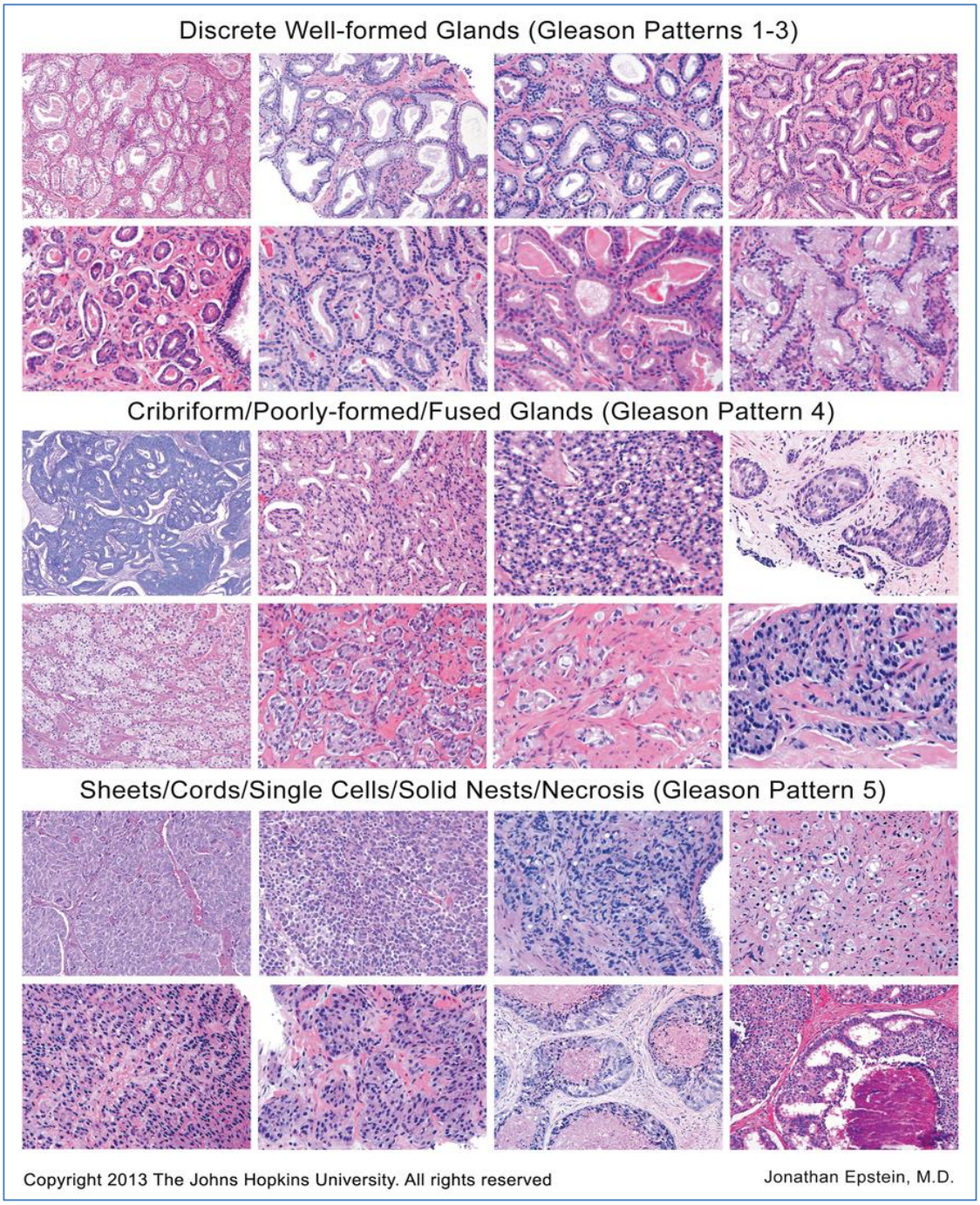

Figure 4: *A new contemporary prostate cancer grading system – the Epstein Gleason grading system (25).*

Currently, Gleason scores are reported along with the new grading system until the new system becomes widely practiced (for example, Gleason score 3+3=6 (Grade Group 1)) (25). Further diagnostic imaging tests such as magnetic resonance

imaging (MRI), bone scan, ultrasonography and computed tomography may be performed in men presenting with high risk disease to assess for extent of disease spread (21).

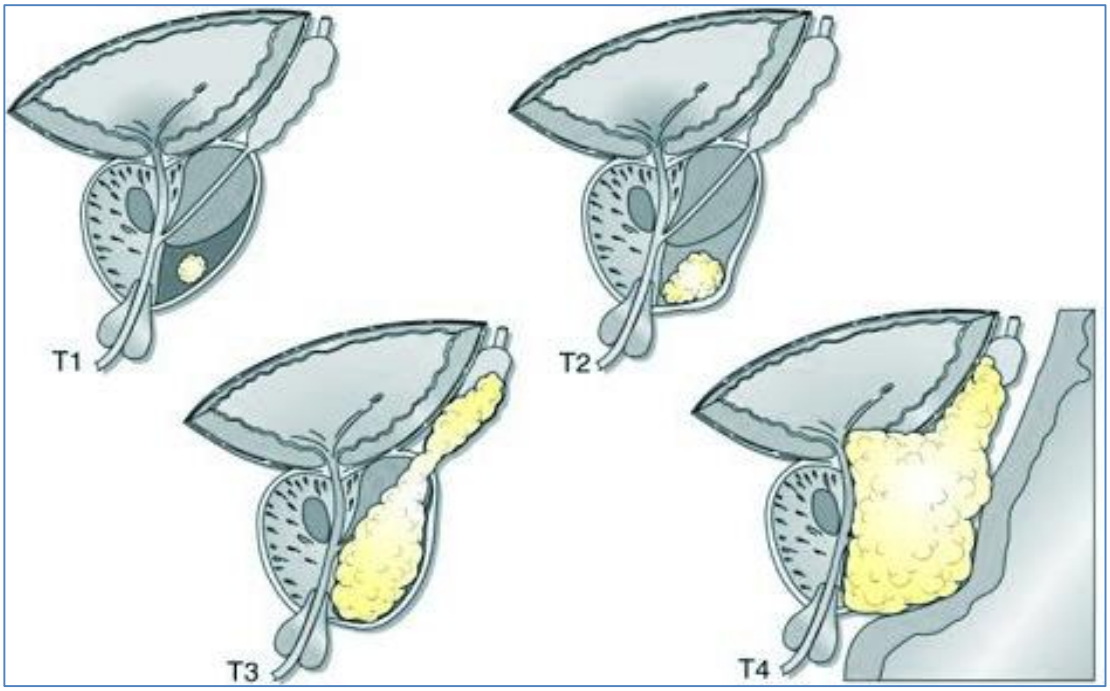

Figure 5: *Stages of prostate cancer. This is the extent of disease spread classified by all the diagnostic tests. PCa uses the Tumour Node Metastasis (TNM) system based on the American Joint Committee on cancer. T1 means that the cancer is too small to be detected on a scan or through digital rectal examination. T2 is where the cancer is contained within the prostate gland. T3 means that the cancer has broken through the capsule surrounding the prostate and spread into the seminal vesicles. T4 is where the cancer has spread into other body organs. N0 and N1 determine the involvement of lymph nodes and M0 and M1 determine the involvement of other body organs.*

2.3.2 Management of prostate cancer

Management options for men with detected PCa can include active surveillance (regular monitoring for low-risk PCa) or watchful waiting, a prostatectomy (surgical removal of the prostate), hormonal treatment or radiation therapy depending on stage (Figure 5) and Gleason pattern of PCa (Figures 3 and 4) (21).

2.3.2.1 Deferred treatment

Deferred treatment can include active surveillance or watchful waiting. Active surveillance is a treatment option for men with low-risk PCa. This includes a treatment plan that monitors the cancer periodically through repeated biopsies, digital rectal examination and PSA testing. The purpose of active surveillance is to reduce overtreatment in men with low-risk PCa with minimal other health complications and only offer curative treatment when the cancer progresses or if the patient decides to undergo treatment (26).

PSA screening has led to an increased detection of early-stage PCa (27, 28). Treating these early-stage cancers using the therapies described below cause unwanted risks and side-effects that may outweigh the benefits of immediate treatment. Disease progression for men who are initially diagnosed with low-risk PCa is slow enough that radical treatments can be delayed without reducing overall survival (29, 30). Therefore, the aim of active surveillance is to monitor an individual with low-risk PCa to the extent where treatment can be avoided permanently because the rate of cancer growth is gradual enough that the individual may be more likely to die of other causes than PCa.

Moreover, evidence from trials such as the Prostate Testing for Cancer and Treatment (ProtecT) trial have reinforced active surveillance as a valid form of treatment for men with low-risk PCa. In the ProtecT trial, effects of active surveillance, radical prostatectomy and radical radiotherapy on PCa mortality was assessed at a median follow-up of 10 years. No significant difference was observed

for overall mortality for men in the active surveillance group compared to the other groups (30).

Currently, no standard protocol for active surveillance exists and institutional guidelines determine the clinical and pathological parameters required to offer men with PCa the option of active surveillance. However, most active surveillance protocols require men to have the following characteristics of cancer to be considered for active surveillance: T1-T2 organ-confined cancer with Gleason score ≤6, ≤ 3 biopsies with cancer and 50% of each biopsy with cancer and a PSA of < 10 ng/mL (31).

In men diagnosed with PCa who have a limited life expectancy due to other health conditions, another form of deferred treatment called watchful waiting is used which consists of monitoring symptoms of PCa. In cases where life expectancy is limited and PCa progresses, palliative treatment is offered (26).

2.3.2.2 Curative treatments

Curative treatment options can include radical prostatectomy and radiotherapy. Radical prostatectomy is the surgical removal of the prostate in men with localised PCa (32). Since the adoption of radical prostatectomy in the mid-1980s, the technique has evolved to now include laparoscopic radical prostatectomy (33) and robotic radical prostatectomy (34). The procedure can involve removing the entire prostate with its capsule intact and seminal vesicles (refer to Figure 1 for anatomy of the prostate). Side-effects of radical prostatectomy can include: urinary incontinence, erectile dysfunction, complications with bowel, injuries relating to the

rectum, urethra or bladder, neurological injuries and thromboembolic complications (35).

Three prospective randomised-controlled trials (RCTs) (30, 36, 37) have so far compared oncological outcomes for radical prostatectomy over deferred treatment in organ-confined disease:

1. Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) (36)
2. Prostate Cancer Intervention versus Observation Trial (PIVOT) (37)
3. Prostate Testing for Cancer and Treatment (ProtecT) trial (30)

SPCG-4 was the only study that showed a benefit for radical prostatectomy compared to watchful waiting (36). The three trials (30, 36, 37) highlighted the importance of risk stratifying men diagnosed with low-risk, localised PCa so that they are managed and treated appropriately.

The two main types of radiotherapy offered for low-risk PCa are external beam radiation therapy (EBRT) and brachytherapy. Although EBRT can also include intensity-modulated external-beam radiotherapy (IMRT) and volumetric arc external-beam radiotherapy (VMAT), IMRT is considered the gold standard for EBRT. Brachytherapy is usually given in early stages of the disease and can include two types: low-dose rate (LDR) brachytherapy and high-dose rate (HDR) brachytherapy (38). Whereas LDR brachytherapy uses radioactive seeds permanently implanted into the prostate, HDR brachytherapy uses a radioactive source temporarily introduced into the prostate to deliver radiation (39). Erectile

dysfunction, urinary incontinence, issues with bowel movements and nocturia are some negative effects of radical radiotherapy reported by patients (40).

The type of curative treatment offered depends on the stage of PCa, as well as other factors such as comorbidities, age and patient choice.

2.3.2.3 Hormonal treatment

ADT interrupts the pathway that leads to the production of testosterone (described below in section 2.5). PCa cells can be deprived of androgens in two ways: either by suppressing the secretion of androgens from the testes or by inhibiting the action of circulating androgens in the blood at their receptor level (39). Detailed description including the mechanisms of action for GnRH agonists and GnRH antagonists can be found in section 2.5.

Castration can be achieved by surgical removal of the testes in a process called an orchiectomy which leads to a considerable decline in testosterone levels and the treatment is irreversible. In addition to orchiectomy, hormonal treatments can also include, oestrogens, GnRH (also known as luteinising-hormone-releasing hormone (LHRH)) agonists and antagonists (section 2.5.1) and anti-androgens. Oestrogens are no longer considered as standard first-line therapy due to severe side-effects such as thromboembolic complications even at low doses (39).

Anti-androgens are oral compounds that compete with androgen receptors and inhibit their interaction with testosterone and dihydrotestosterone (41). Androgen receptor blockade induces programmed cell death in PCa cells. Structurally, anti-androgens can be divided into steroidal and non-steroidal anti-androgens.

Cyproterone acetate is the most commonly used steroidal anti-androgen that competitively inhibit androgen receptors thus lowering LH secretion by a negative feedback effect. Steroidal anti-androgens also bind to other steroid receptors, such as those for glucocorticoids and progestin, leading to non-specific effects. Non-steroidal anti-androgens such as bicalutamide, flutamide and nilutamide also interrupt the negative feedback of testosterone on GnRH secretion but is specific to androgen receptors. This difference in modes of mechanisms explain why non-steroidal anti-androgens have lesser sexual side-effects than steroidal anti-androgens. However, the excess testosterone after treatment with non-steroidal anti-androgens are converted into oestrogens which lead to side-effects such as gynaecomastia (41). Anti-androgens are used in combination with GnRH agonists to prevent the clinical 'flare' associated with GnRH agonists (17) (explained in section 2.5.1). In some countries such as Sweden, anti-androgens are also given as a monotherapy (41).

ADT can be given as a primary treatment in advanced staged disease, or as a secondary treatment when PCa progresses after a curative treatment. It can also be given in conjunction with a curative treatment in an adjuvant setting (usually with radiotherapy) (39).

2.3.2.4 Other treatments

PCa eventually develops into castrate-resistant PCa over time. This is where an adaptive mechanism over time leads to increased intracellular androgen levels compared to androgen sensitive cells, in addition to an overexpression of androgen receptors (42). Abiraterone acetate is approved for treatment of metastatic

castrate-resistant PCa. Synthesis of androgens inside the PCa cells and at the adrenal level are inhibited by the Cytochrome P450 17A1 (CYP17) enzyme inhibitor, Abiraterone acetate. Moreover, the Food and Drug Administration (FDA) has also approved for the use of Sipuleucel-T vaccine containing the antigen-presenting cell from the patient for the treatment of castrate-resistant PCa (43).

Enzalutamide and apalutamide are novel anti-androgens with higher affinity for androgen receptors than the ones described above (44). Docetaxel and cabazitaxel are chemotherapeutic antimircotubule drugs shown to improve overall survival in men with very advanced disease (45). In men with very advanced disease and in high risk category for bone-related injuries due to bone metastasis, treatment with monoclonal antibodies such as denosumab has also shown to be successful because the downstream pathway for denosumab acts as a primary signal to promote bone renewal (20).

2.3.2.5 Combination treatment modalities

Combination treatment modalities for advanced PCa have been part of several study investigations. Clinical trials such as the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) (46), Chemohormonal Androgen Ablation Randomized Trial for Extensive Disease in prostate cancer (CHAARTED) (47) and LATITUDE (48) have investigated and reported practice-changing results that showed improvement in PCa disease control and life-expectancy by adding docetaxel or abiraterone acetate to ADT. Moreover, the STAMPEDE trial has been investigating several research questions including combination treatment modalities since 2005 (49). In 2018, STAMPEDE also showed

a substantial improvement in survival of men with low metastatic burden of PCa who were given radiotherapy along with ADT (HR = 0.68, 95% CI = 0.52–0.90) (50). The trial is currently exploring two research questions:

1. whether the addition of metformin, the diabetic drug, to the treatment of PCa can improve life expectancy in non-diabetic men with PCa and
2. whether hormone patches can be used to substitute hormonal injections so as to avoid some of the side-effects associated with the injections (49).

2.3.2.6 Prostate cancer treatment by disease stages

PCa is categorised into six risk groups based on serum PSA values, clinical stage and biopsy scores: low-risk, intermediate risk, high-risk localised, high-risk locally-advanced, metastatic and castrate-resistant PCa. The risk group of PCa will determine the type of treatment given for men with PCa (39). Table 1 provides a brief summary of the EAU treatment guidelines for the describe above. In addition to the therapies discussed in Table 1, additional treatments can be given in an adjuvant setting to decrease the risk of PCa recurrence. For example, men with node-positive PCa may be offered adjuvant ADT or adjuvant ADT with additional radiotherapy, after a radical prostatectomy with an extended lymph node dissection. Moreover, adjuvant EBRT may also be offered to men with PCa at an increased risk of local relapse (T3 N0 with positive margins and/or invasion of seminal vesicle), after a radical prostatectomy (39).

Table 1: *Treatment guidelines by PCa stages. Summarised from European Association of Urology guidelines on prostate cancer, 2018 (39).*

PCa risk groups	Definition of stage	Guidelines for treatment
Low-risk	PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a	• WW: Asymptomatic men with low-risk PCa with a life expectancy of more than 10 years based on comorbidities • AS: Men with low-risk PCa suitable for curative treatment but with low-risk PCa • Active treatment: Surgery or radiotherapy as alternatives to AS • Radiotherapy: Low-dose brachytherapy, IMRT without ADT • Other treatment options: Cryotherapy, focal therapy
Intermediate risk	PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b	• AS: Only to highly selected men with intermediate-risk PCa (i.e., < 10% pattern 4) • Radical prostatectomy: Men with intermediate-risk PCa and a life expectancy > 10 years. Perform pelvic node dissection if estimated risk is > 5% for a positive lymph node • Radiotherapy: Low-dose rate brachytherapy, EBRT • Other treatment options: cryotherapy, focal therapy
High-risk localised	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c	• Radical prostatectomy: Men with high-risk localised PCa with a life expectancy of more than 10 years as part of multi-modal therapy and with extended pelvic lymph node dissection • Radiotherapy: EBRT + long-term ADT (2-3 years), EBRT + brachytherapy boost + long-term ADT
High-risk locally-advanced	Any PSA, any GS (any ISUP grade), cT3-4 or cN+	• Radical prostatectomy: Only to highly selected men with cT3b-T4 N0 or any T N1 disease as part of multi-modal therapy with extended pelvic lymph node dissection • Radiotherapy: Radiotherapy + long-term ADT for men with high-risk locally advanced PCa (cN0)

		• Other treatment options: ADT monotherapy only for men with high-risk locally advanced PCa who refuse or are unable to receive any form of local treatment
Metastatic	M1	• ADT with chemotherapy (docetaxel) to men with metastatic PCa who are fit enough to be administered docetaxel • Abiraterone acetate with glucocorticoid (prednisone) • ADT with or without an anti-androgen (instead of the first two options) to unfit or unwilling men with metastatic disease • GnRH antagonists: men with metastatic PCa with risk of spinal cord compression • Intermittent therapy: Asymptomatic men with metastatic PCa with major PSA response after induction period (PSA level < 4 ng/mL after six-seven months)
Metastatic castration-resistant	Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L and either a biochemical progression or a radiological progression	• Men with non-metastatic castration-resistant treated within a clinical trial setting • Life-prolonging treatments in men with metastatic castration-resistant PCa based on the earlier choice of treatment for hormone-sensitive metastatic PCa, performance status, comorbidities, symptoms, disease extent and location and patient preference

* GS: Gleason score; ISUP: International Society for Urological Pathology; PSA: Prostate-specific antigen; WW: Watchful waiting; AS: Active surveillance; EBRT: External-beam radiotherapy; Biochemical progression: Three consecutive rises in PSA one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL; Radiological progression: appearance of new lesions in bone scans.

2.4 EPIDEMIOLOGY OF PROSTATE CANCER

PCa is the most common cancer among men in Europe and has the third highest projected rate in Europe (51, 52) . In England, there is a subtle increase in incidence

in age-standardised rates for PCa (Figure 6) (52). Age-standardised rate mortality has continued to fall since 2001, which may be attributed to several shifts in treatment regimens of men with PCa.

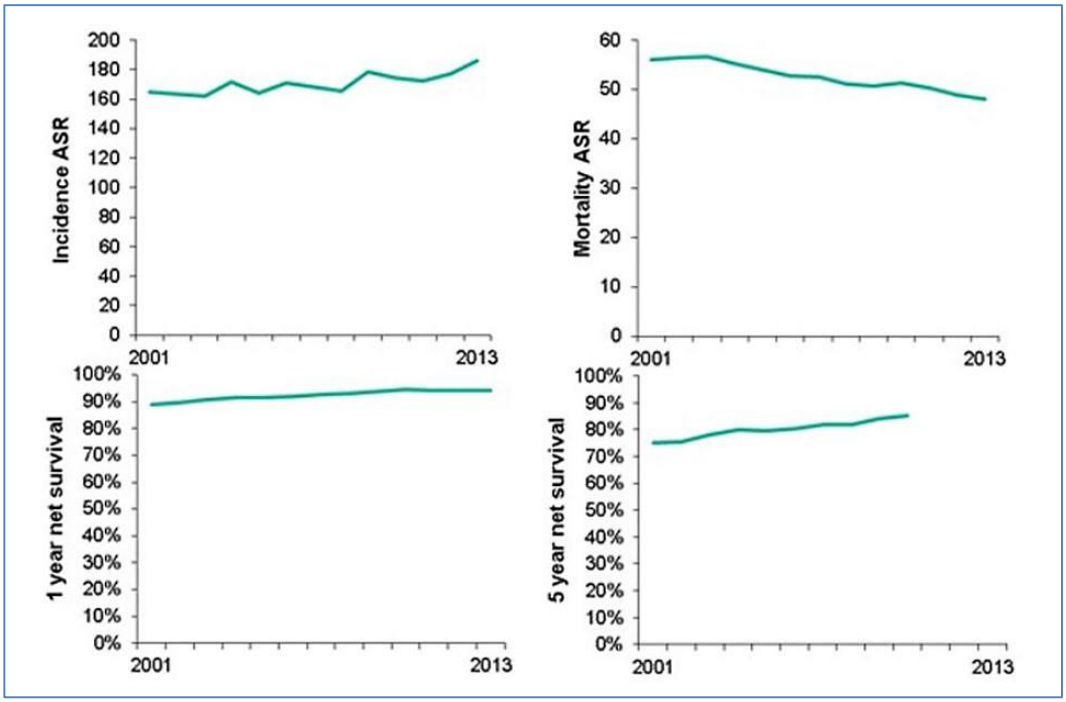

Figure 6: *Prostate cancer incidence and mortality age-standardised rates, and one- and five-year net survival, for England (52).*

2.4.1 Risk factors

In most cases, PCa is a slow growing tumour that is most commonly detected in the adult and elderly population. Ageing is the most important risk factor for developing PCa. Autopsy studies most often report PCa which was never even diagnosed (53, 54). PCa incidence varies with age and age-specific incidence curves reveal that after the age of 55 years, PCa risk begins to rise dramatically reaching a peak in the 70s (52). As a natural process of ageing in most body tissues, there is an increased

frequency of deoxyribonucleic acid (DNA) damage that result in tumorigenesis due to an accumulation of cellular oxidants, such as free radicals and reactive oxygen species (55).

Another risk factor contributing to PCa is ethnicity. The overall prevalence of PCa is significantly higher in men with a Black origin than any other ethnic group. Several explanations have been put forward to understand the cause of higher rates of PCa in men with a Black origin:

- there is a downregulation of androgen receptors in the stromal cells of the prostate in men with Black origin (56)
- higher testosterone levels in men with a Black origin may contribute to PCa pathogenesis (57)
- higher prevalence of polymorphisms in the genes of different enzymes that regulate the production, metabolism and function of PCa cells (58)

In addition to the mentioned risk factors, a 2.3-fold increased risk of developing PCa has been associated with a family history of PCa in both a father and brother(s) (59). Moreover, the presence of genetic mutations such as the ones present in the tumour suppressor gene, breast cancer susceptibility gene 2 (BRCA2), can also increase the risk of developing PCa from five to seven-fold (60). Although specific dietary components such as refined carbohydrates (61) and animal and dairy products (62) have been suggested to increase the risk of PCa, the evidence is less conclusive. Other studies investigating reduced fat intake (63) and increased consumption of lycopene, vitamin E, cruciferous vegetables and zinc to lower the risk of PCa have also shown inconclusive results (20, 64, 65).

2.5 ANDROGEN DEPRIVATION THERAPY

Testosterone is a type of androgen which is a prerequisite for the proliferation and progression of PCa (66). Testosterone is produced downstream in a pathway that is initiated in the hypothalamus (Figure 7) (67). The dependence of PCa cells on androgens was first discovered by Huggins et al. in 1941 (5). In fact, AR signalling determine carcinogenesis and progression in PCa (68). As mentioned in section 2.3.2.3, ADT interrupts the pathway that leads to the production of testosterone: either by suppressing the secretion of androgens from the testes or by inhibiting the action of circulating androgens in the blood at their receptor level (39). It is the mainstream treatment for symptomatic metastatic PCa; more specifically, ADT is commonly used in men with biochemical relapse after radical prostatectomy, locally advanced PCa and metastasis (69, 70). This thesis mainly focuses on two types of ADT, GnRH agonists and GnRH antagonists which are discussed in more detail below.

2.5.1 GnRH agonists and GnRH antagonists

ADT aims to reduce the production of testosterone by interfering at various points in the AR signalling pathway (67). One such mode by which ADT works is by competing with GnRH or LHRH for their receptors. GnRH is then prevented from binding onto the GnRH receptor; thus ensuring a block which obstructs the production of testosterone (67).

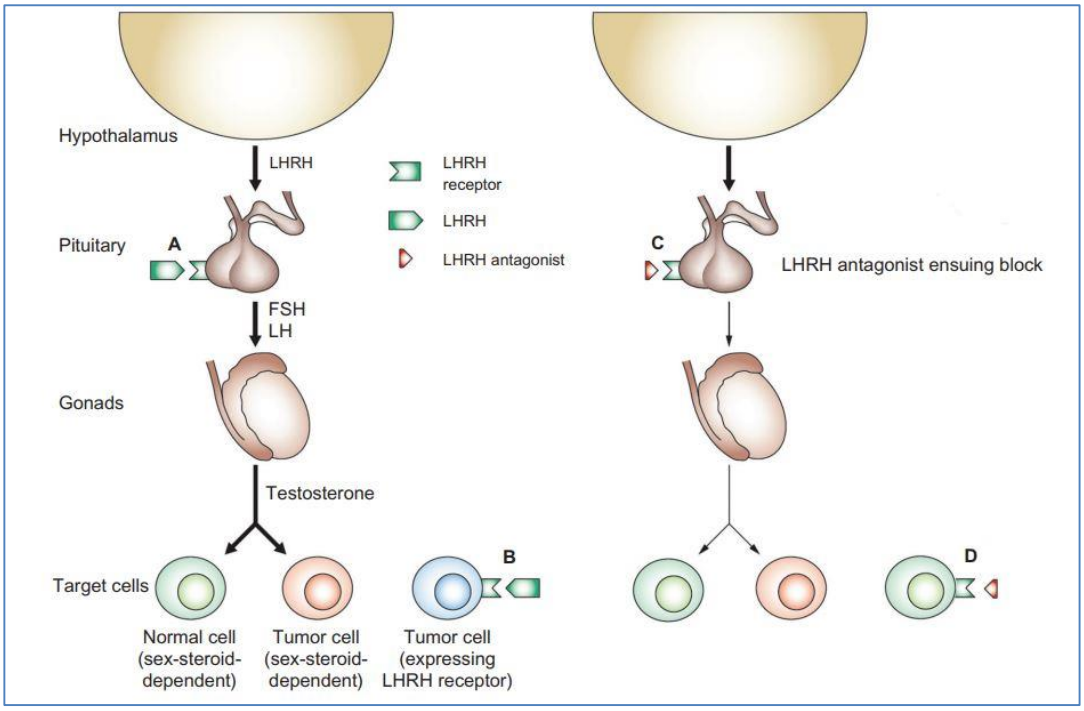

Figure 7: *Mode of action of antagonists of luteinizing hormone-releasing hormone (LHRH).* ***(a)*** *LHRH secreted by the hypothalamus binds to its receptor in the pituitary and stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones, in turn, stimulate the release of sex steroids, which can stimulate growth and development of both normal and tumour cells.* ***(b)*** *Some tumours express LHRH receptors and can respond directly to LHRH; cells in these tumours can be sex-steroid-dependent or sex-steroid-independent.* ***(c)*** *LHRH antagonists induce a state of sex steroid deprivation by competitive blockade of pituitary LHRH receptors, whereas LHRH agonists achieve a similar effect by downregulation of the pituitary receptors for LHRH. Consequently, levels of FSH and LH, and subsequently levels of sex steroids, are lowered. The decrease in the levels of sex steroids inhibits the proliferation of both benign and malignant sex-steroid-dependent cells.* ***(d)*** *In tumours that express LHRH receptors, both antagonists and agonists of LHRH may exert direct effects mediated by these LHRH receptors. Modified from Engel JB and Schally AV with permission.18 Copyright 2013 Nature Publishing Group (67).*

2.5.1.1 Differences in modes of mechanism

Although GnRH agonists and GnRH antagonists are both forms of ADT and stimulate the reduction of testosterone, they differ in their mechanism of action (Figure 8) (17). As seen in Figure 7, GnRH agonists bind to GnRH receptors in the pituitary gland and overproduce LH and FSH, thus leading to an increase in testosterone. Persistent overstimulation of the pituitary gland by GnRH agonists overrides the pulsatile control of LH and FSH release by natural GnRH, leading to a

downregulation of GnRH receptors and desensitising of the pituitary gland to GnRH. The desensitising process eventually leads to a decrease in the tumour growth factor, testosterone. In comparison, GnRH antagonists block the GnRH receptors in the pituitary gland, immediately stopping the downstream pathway (Figure 8). The blocking effect of GnRH antagonists therefore prevents the initial testosterone surge and clinical 'flare' (marked by symptoms such as hot flushes) in the disease that is associated with GnRH agonists (17).

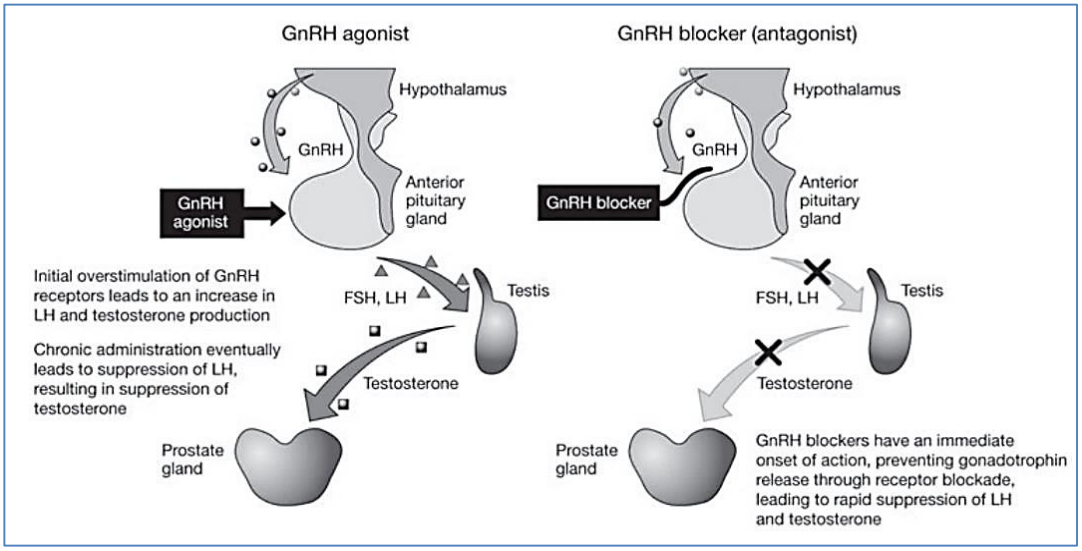

Figure 8: *Mechanism of action of gonadotropin-releasing hormone (GnRH) agonists and blockers (antagonists) (17).*

Degarelix was developed by Ferring Pharmaceuticals and obtained FDA approval in 2009 (71). It was the first GnRH antagonist that showed weaker histamine-releasing properties than other GnRH antagonists that were developed (such as Abarelix) (72). Following subcutaneous injection, degarelix immediately forms a gel-like depot and the drug is released into the circulation in a controlled manner prolonging the

clinical effect of the drug (73). Efficacy and dose-finding studies have established an initial dosage of 240mg and maintenance doses of 80mg or 160mg for degarelix (73-75). These studies (73-75) were carried out in comparison to the GnRH agonist, leuprolide, with respect to achieving and maintaining testosterone suppression.

2.6 ADVERSE EFFECTS OF ANDROGEN DEPRIVATION THERAPY

Adverse effects of ADT are numerous and require pro-active prevention and treatment. These adverse effects can include: hot flushes, sexual dysfunction, obesity, osteoporosis, cognitive decline, CVD, diabetes and hypercholesterolemia (76).

2.6.1 Hot flushes

About 80% of men on ADT report hot flushes, most often described as diaphoresis and facial discomfort (77). The reduction in testosterone due to ADT causes an instability in the hypothalamic thermoregulatory center which in turn results in sudden fluctuations in body temperatures. Hot flushes can last for a considerable length of time and cause significant discomfort in men on ADT (78). Hot flushes can be managed by avoiding triggers such as increased exposure to hot temperatures or eating spicy food (77).

2.6.2 Sexual dysfunction

The biggest component affecting the quality of life of men on ADT for PCa is sexual dysfunction (79). Loss of libido was reported by 58-91% of men on GnRH agonists. Additionally, men on ADT have also reported erectile dysfunction and cessation of

sexual activity as side-effects (77). Reduction or complete elimination of sexual activity can lead to couples having a reduced expression of affection for each other, which in turn can lead to relationship issues (80). 50% of patients (n = 15) interviewed for a qualitative study investigating effects of ADT on body, sexuality and spousal ties, experienced marital erosion after ADT administration (81). This suggests that sexual dysfunction is a cause for concern in men on ADT which may lead to issues such as non-adherence to ADT because a negative attitude towards a treatment can to influence adherence to a treatment (82). Management options for sexual dysfunction can include counselling for couples and intracavernosal injections (76).

2.6.3 Obesity

70% of men on ADT experience some form of weight-related issues. Men on ADT experience a reduced muscle mass and increased gain of adiposity. This phenomenon is known as sarcopenic obesity. Sarcopenic obesity can in itself lead to a loss of muscle strength, fatigue and quality of life (83, 84). Men on ADT can therefore benefit from referral to dieticians and exercise physiologists (76).

2.6.4 Bone health

In men with PCa, there is an absolute bone mass density loss of around 5% within the first year of ADT administration. Bone mass density loss leads to increased risk for fractures which underscores the importance of preventing bone mass density loss at an early stage (85). The results of an observational study that investigated the effects of ADT on fracture risk also showed that the mortality risk doubled after a fracture in men with PCa (86). Bisphosphonates are given to men on ADT to

reduce bone mass density loss because bisphosphonates weaken the activity of osteoclasts that is involved in breaking down bone tissue (87). Zoledronic acid is a bisphosphonate that shown an increase of 4% in bone mass density in the hip and spinal area within a year (88). A human monoclonal antibody, Denosumab, has also been approved by the FDA for the treatment of bone metastases in PCa and in ADT-induced osteoporosis. Denosumab works by targeting the receptor activator of nuclear factor κB ligand (RANKL), which has a pivotal role in osteoclast activity and bone loss in osteoporosis (89).

2.6.5 Cognitive decline

Newly diagnosed men with metastatic PCa reported a steady decline in their mood over the first 12 months after diagnosis (90). The hormonal effects from ADT immediately after diagnosis may also add to the distress levels that men in this group experience (76). Moreover, a RCT showed a significant decline in cognition in 50% of men with PCa after six months on ADT (91). Interventions in the form of education packages and patient-support groups can therefore aid to increase the overall patient satisfaction and quality of life in men on ADT (92).

Exposure to ADT was also associated with a subsequent diagnosis of dementia or Alzheimer's disease in men with PCa over a 10-year follow-up period (93). Therefore, the risk of dementia needs to be considered in men before ADT initiation.

2.6.6 Cardiovascular disease

In 2010, the FDA issued a requisite for GnRH agonists, a main form of ADT for locally advanced and metastatic PCa, to carry a safety warning on the drug labels after

several observational studies (94-100) and systematic reviews (101) showed an increased risk of CVD in individuals on GnRH agonists. Keating et al. (2013) showed that men with PCa on ADT were at an increased risk of developing CVD (especially myocardial infarction). Risk factors for myocardial infarction (such as hypertension, renal insufficiency and prior CVD) were also associated with developing myocardial infarction during ADT (102). Similar results have also been demonstrated by a nationwide Danish population-based cohort study that showed that ADT was associated with a 31% increased risk of developing myocardial infarction (103). Although observational studies (101) have shown evidence for association between ADT and CVD, no association was identified in RCTs (104). Therefore, the association between ADT and CVD has been explored in greater depth in chapter III of this thesis.

2.6.7 Diabetes

A substantial increase in fasting insulin was identified in a clinical trial with men on ADT, with 13.5 mU/L at baseline to 17 mU/L at 3 months (105). An observational study also showed that treatment with ADT may be associated with an increased risk of incident diabetes (94). Moreover, in men with pre-existing diabetes, glycaemic control declined over time on ADT because of an increase in the levels of glycosylated haemoglobin (106). Lifestyle interventions including exercise and weight loss programmes, smoking cessation and reduction of alcohol intake may help maintain glycaemic control in men with pre-existing diabetes (76).

2.6.8 Hypercholesterolemia

An 11% increase in total cholesterol was observed within six months of ADT administration in men with PCa in a RCT. An increase in triglyceride levels (27%), low-density lipoprotein (LDL) (7%) and high-density lipoprotein (HDL) (10%) was also observed in these men (105). Although an increase in HDL may be cardio-protective, the rise in the other three cholesterol markers can have an adverse effect on men with PCa on ADT. Moreover, rising fasting cholesterol levels can be an independent risk factor for CVD, regardless of the presence or absence of PCa(105). Therefore, cholesterols levels need to be monitored in men with PCa on ADT along with engaging them with the lifestyle interventions discussed above (section 2.6.7).

2.7 ADHERENCE TO GNRH AGONISTS IN PROSTATE CANCER

The term adherence refers to the resolve a patient requires to follow their course of therapy. Although other terms such as 'compliance' and 'concordance' are used to describe patients taking their prescribed drugs in pharmacology, they are less commonly used in the literature (107).

As adherence to a treatment regimen contributes to the success of that treatment, the loss of adherence to treatment is a global concern that has both clinical and economic consequences. Considering that a large proportion of men diagnosed with PCa may remain on ADT for the rest of their PCa treatment, there is a need for more studies focusing on factors contributing to non-adherence in men with PCa on ADT (108, 109).

The remaining sections of this chapter provides a brief background for the four projects of this thesis:

- Cardiovascular effects of GnRH analogues in PCa
- Adherence to GnRH agonists in PCa in Sweden
- Adherence to GnRH agonists in PCa in the United Kingdom
- Adherence to GnRH agonists in PCa – a qualitative approach

2.8 CARDIOVASCULAR EFFECTS OF GNRH ANALOGUES IN PROSTATE CANCER

The first project of this thesis investigated the CVD effects of GnRH analogues that are routinely used in men with PCa. Several studies have shown an increased risk of developing CVD in men with PCa on ADT (94-98). Regardless of the CVD history of men with PCa, standardized incidence ratios for CVD in men on ADT were elevated (99). Results from these studies (94-99) prompted the FDA to add safety labels on drug labels warning ADT users of the risk of developing CVD in 2010. However, these results have been challenged due to contradictory results from RCTs and observational studies. Whereas meta-analysis of RCTs (104) have shown no associations between GnRH agonists and CVD, meta-analysis of observational studies (101) have shown an increased risk of developing CVD following GnRH agonists' administration. Moreover, the newly formulated GnRH antagonist, degarelix, has shown less atherosclerotic effects in pre-clinical mouse models (110). Although risk of side-effects exists, PCa progression is inevitable if the disease is left

untreated. Therefore, it is important to compare the CVD effects of GnRH agonists and GnRH antagonists to reduce the risk of CVD from GnRH analogues in the long-term in men with PCa.

2.9 ADHERENCE TO GNRH AGONISTS IN PROSTATE CANCER IN SWEDEN

The second project investigated patterns of adherence to GnRH agonists in men with PCa in Sweden. Medication adherence is usually quantified by the Medication Possession Ratio (MPR) which is the sum of the days' supply for all fills of a given drug in a particular time period, divided by the number of days in the time period (111).

Factors contributing to patterns of non-adherence to a particular medication may be manifold (82). Some key factors extensively discussed in the literature include: decreasing the frequency of doses and physician visits (112, 113), side-effects associated with medication (114, 115), combination treatment modalities (116), social support and forgetfulness (117) and degree of behavioural change required (82, 118). Since medication non-adherence is generally associated with worse prognosis of a disease, it is important to investigate this in men with PCa on GnRH agonists (108, 109).

Currently, recommendations for PCa in Sweden are set by the regional clinical care guidelines based on national recommendations. GnRH agonists are offered to men with high-risk PCa, metastatic PCa and castration-resistant PCa. Adjuvant GnRH

agonists can also be given after radical prostatectomy and radiotherapy for high-risk PCa depending on other clinical characteristics such as PSA value and Gleason grade. As per the guidelines, once GnRH agonists had been initiated as a treatment for metastatic PCa, it should not be discontinued. The injection intervals for GnRH agonists can include 30 days, 90 days, 180 days and 365 days implants (119).

2.10 ADHERENCE TO GNRH AGONISTS IN PROSTATE CANCER IN THE UNITED KINGDOM

The third project investigated patterns of adherence to GnRH agonists in men with PCa in the UK. As country-specific guidelines may also influence patterns of adherence to a medication, data from the UK was used to understand patterns of adherence to GnRH agonists in men with PCa in the UK.

Currently, ADT is offered to men with locally advanced and advanced PCa in the UK (NICE NG131) (120) (refer to Table 1 for a detailed overview for the use of GnRH agonists by disease stages in the UK). The injection dosages for GnRH agonists include 3mg, 11.25mg and 22.5mg formulations given every 28 days, 90 days and 180 days, respectively (National Institute for Clinical Excellence (NICE) ESNM30) (121). The injection is given intramuscularly at the above dosage intervals by local health care professionals (most often nurses).

2.11 ADHERENCE TO GNRH AGONISTS IN PROSTATE CANCER: A QUALITATIVE APPROACH

The fourth project investigated factors contributing to adherence and non-adherence to GnRH agonists in men with PCa in the UK by applying qualitative methods. Quantitative methods quantify adherence as the MPR (111) which uses a relatively simple calculation to quantify adherence. Although MPR is useful in understanding the factors contributing to adherence using real world data from cancer registries and other national databases, they do not provide sufficient insight into reasons contributing to adherence from a patient's or clinician's perspective.

Therefore, both quantitative (using data from Sweden and UK) and qualitative (using data collected from a hospital in the UK) methods were used to explore adherence to GnRH agonists in men with PCa. Whereas quantitative methods using data from Sweden and UK investigated the patterns of adherence to GnRH agonists in PCa men, qualitative methods explored the reasons why PCa men on GnRH agonists may not adhere to their treatment regimen. Currently, no studies have fully investigated patterns of adherence to GnRH in men with PCa. Therefore, the three projects on adherence aim to:

- employ quantitative and qualitative methods to identify whether non-adherence is an issue among men with PCa on GnRH agonists
- identify whether country-specific guidelines influence the observed patterns of adherence and non-adherence
- understand patient and clinician perspectives on the issue of adherence and non-adherence to GnRH agonists in men with PCa.

3. CHAPTER III – CARDIOVASCULAR EFFECTS OF GNRH ANALOGUES IN PROSTATE CANCER

This chapter focuses on adverse effects of GnRH analogues used in men with PCa specifically with respect to CVD. Several observational studies and RCTs have investigated the CVD effects of GnRH analogues in the literature with contradictory results. This chapter aims to use real world data from six different countries to compare the risk of developing CVD following GnRH agonists and GnRH antagonists in men with PCa. The methods used for this study has already been published (122) (section 9.3.2.1, Appendix).

3.1 BACKGROUND

Prevention and management of adverse effects of ADT is important for men who are on some form of long-term ADT. A number of metabolic side-effects have been reported for GnRH agonists including, increased body weight, insulin resistance, dyslipidemia and hyperglycemia (94, 123-125). The adverse effects of ADT, differences between GnRH agonists and GnRH antagonists and CVD effects of the GnRH analogues has already been explored in sections 2.5 and 2.6 of chapter II. The next two sections discuss in more detail studies previously conducted on CVD effects of GnRH agonists and GnRH antagonists.

3.1.1.1 Cardiovascular effects of GnRH agonists

One of the more recently investigated side-effects of GnRH agonists is an increased risk of CVD, which is believed to be due to a reduced cardio-protective effect of testosterone (94-98). A study using the Swedish National PCa Register and

Prescribed Drug Register indicated an increased risk of developing CVD within the first year of initiating GnRH agonist therapy or orchiectomy. These results were identified specifically in patients who had experienced a CVD event one year before commencing ADT (100). Moreover, research by Van Hemelrijck et al. (2010) showed that standardized incidence ratios for CVD were elevated in all men with PCa, with the highest for those undergoing ADT treatment, independent of CVD history (99). In 2010, the findings from these studies (94-100) prompted the FDA to issue a new requirement for manufacturers of certain types of GnRH agonists to add safety information to drug labels in order to warn users of the CVD risks involved.

A meta-analysis of observational studies that focused on the risk of developing CVD following ADT administration found consistent positive associations, especially with GnRH agonists compared with men not treated with ADT (101). In contrast, a meta-analysis of RCTs showed that ADT use was not associated with an increased risk of cardiovascular death (104). This contrast with meta-findings from RCTs (104), in comparison to observational studies (101), may be due to differences in study designs. RCTs typically exclude older patients or those with a higher number of comorbidities, which are two common characteristics of PCa patients (126). Real world data used in observational studies do not need to exclude these patients (127), which may result in findings that are more applicable to the general population. RCTs conducted till date to assess risk of CVD following GnRH agonists have lacked power and have insufficient follow-up as they were not designed to ascertain cardiovascular outcomes as a primary endpoint (other than death) (104). Observational studies, when well conducted, have been shown to provide similar

estimates of side-effects to RCTs – which is the rationale behind phase IV studies (128).

3.1.1.2 Cardiovascular effects of GnRH antagonists

Following observations of an increased risk of CVD in men on GnRH agonists, a meta-analysis of six pooled RCTs' results found that degarelix (a GnRH antagonist) was associated with lower risk of developing CVD compared to GnRH agonists (129). The findings for a lower risk of CVD following degarelix administration are also supported by pre-clinical mouse models showing less atherosclerosis and characteristics of metabolic syndrome in those treated with degarelix as compared to those with orchiectomy or GnRH agonists (110). Based on the contradictory findings from meta-analyses that primarily focused on GnRH agonists and the risk of CVD in observational (101) and RCT settings (104); there is a need to also investigate the risk of CVD following degarelix using real world data.

GnRH antagonists also have a similar impact on PCa progression in comparison to the commonly used GnRH agonists (130). A review by UK-based clinicians highlighted that when making treatment decisions, clinicians should consider comorbidities, particularly CVD (131). They further suggested that GnRH antagonists may be appropriate in the class of patients with significant CVD risk, existing osteopenia, lower urinary tract symptoms and significant metastatic disease.

3.1.1.3 GnRH agonists versus GnRH antagonists

Studies comparing GnRH agonists and GnRH antagonists have shown PCa outcome-specific results. Phase II and phase III studies showed no difference in terms of efficacy and baseline testosterone levels in men receiving GnRH antagonists

compared to men receiving various GnRH agonists for their PCa (132). Comparison of CVD safety profile of men on GnRH agonists and antagonists have yielded inconclusive results (101, 104), however CVD was not set as a primary outcome (133).

A RCT comparing the risk of cardiovascular morbidity between GnRH agonist and GnRH antagonists among men with PCa showed that there was a lower risk of developing subsequent CVD events in men on GnRH antagonists with a pre-existing CVD event as compared to men on GnRH agonists (134). However, cardiovascular biomarkers were used as a surrogate endpoint (which are intended to replace clinical endpoints when it can be measured more conveniently and cheaply (135)) in the RCT rather than a CVD event.

Only one observational study has been conducted to date directly comparing risk of CVD between GnRH agonists and GnRH antagonists. Scailteux et al. (2017) showed no difference in risk of developing stroke and myocardial infarction in men with PCa, however overall CVD was not investigated as a specific outcome in the study (136). Currently, a phase III RCT (A Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Advanced Prostate Cancer and Cardiovascular Disease (PRONOUNCE); ClinicalTrials.gov identifier: NCT02663908) is recruiting to compare risk of fatal or non-fatal CVD in 900 men with PCa receiving degarelix or leuprolide (GnRH agonist) as primary treatment over a year (137) as the increase in risk of developing a CVD event is apparent within the first year of treatment initiation (94, 97, 138).

Therefore, since the impact of GnRH antagonists on PCa progression has been shown to be similar to that of commonly used GnRH agonists (130), there is a need to identify whether its suggested reduced risk of CVD is also observed in real world data. This project is the first to assess real world data for the risk of CVD in men with PCa following GnRH agonists versus GnRH antagonist.

3.1.1.3.1 Switch between GnRH analogues

There is a possibility of a switch from GnRH agonists to GnRH antagonists or vice-versa in men with PCa on the GnRH analogues. Switch between the GnRH analogues showed stable disease control and no adverse clinical or oncological effects. However, one reason that men on GnRH antagonists switch to a GnRH agonist can be due to the adverse effects of GnRH antagonists (skin rash at injection site) and the more frequent visits required for the monthly administration of the injection (139). Therefore, it is important to consider the switch in comparison studies of GnRH analogues.

3.1.1.4 ROBINS-I tool and the target trial

Risk of bias should be considered when designing an observational study to assess effects of different types of drugs. Risk of bias in non-randomised studies of interventions (NRSIs) can be evaluated using the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool (140). Sterne et al. (2016) first developed the ROBINS-I tool in 2016 to assess risk of bias in systematic reviews of non-randomised studies using the idea of developing a 'target trial'. A target trial renders a pragmatic approach to emulate a hypothetical randomised controlled-trial in NRSIs. The ROBINS-I tool mimics a hypothetical randomised trial covering

seven specific domains through which any bias may be introduced into the study design. However, the resulting hypothetical randomised trial may not necessarily be feasible or ethical. For example, a target trial may randomly assign no smoking to one group of the study population and smoking to the comparative group. The aim of the target trial is to design the ideal study where minimal risk of bias exists.

The seven specific domains of the ROBINS-I tool address details of the study population, experimental intervention, comparator and the outcomes of interest at pre-, during and after intervention (140). For this study, the ROBINS-I tool was modified to emulate a target trial for the risk of CVD following GnRH agonists and GnRH antagonists in men with PCa.

The aim of this study was to investigate the risk of developing CVD following GnRH agonists and GnRH antagonists in PCa using real world data from six countries: UK (excluding Scotland), Scotland, Belgium, the Netherlands, France and Canada.

3.2 METHODS

3.2.1 Study population

Men with PCa entered the study on the date of ADT (GnRH agonists or antagonists) initiation. A diagnosis of advanced or metastatic PCa was also used as an inclusion criterion in countries where data on PCa stage was available (Belgium and the Netherlands). Following cohort entry into either treatment regimen, men were assumed to be on that regimen until time of censoring.

3.2.2 Data

Six different databases from six countries for the following study periods were used in this project:

1. THIN database from the United Kingdom between 2010-2016
2. NHSS database from Scotland between 2010-2017
3. BCR from Belgium between 2010-2013
4. PHARMO database from the Netherlands between 2010-2015
5. SNIIRAM database from France between 2010-2013
6. RAMQ database from Canada between 2011-2019

3.2.2.1 United Kingdom

The THIN database used in this study covers 6.2% of the UK population and comprises anonymised longitudinal data from patients that is processed and validated by Cegedim Strategic Data Medical Research UK. Data is extracted from more than 500 general practices in England, Wales, Scotland and Northern Ireland using the VISION healthcare interface system (In Practice Systems, London, UK) (141-144). Contribution to THIN by GPs is as simple as signing a data sharing agreement with VISION. THIN medical records include information on demographics, medical diagnoses, prescriptions, referrals to specialists in hospitals, laboratory results and some lifestyle factors (145).

The THIN data was provided for the project by IQVIA (previously known as QuintilesIMS) following ethical approval from the Scientific Research Committee. The data provided was organised into seven different files in the 'data' folder along with their descriptions in a separate folder, 'ancil'. The ancil folder is linked to the

data folder by standardised readcodes or medcodes (146) and Anatomical Therapeutic Chemical (ATC) (147) codes or drugcodes. Each of the seven files (Figure 9) in the THIN data folder is linked by patient identification codes (patid) and GP identification codes (pracid) which meant that patients may have a unique identifier within a GP but not across the dataset. As a result, patid and pracid were combined to form a combination identification code called combid so that each patient in the database had unique identifiers.

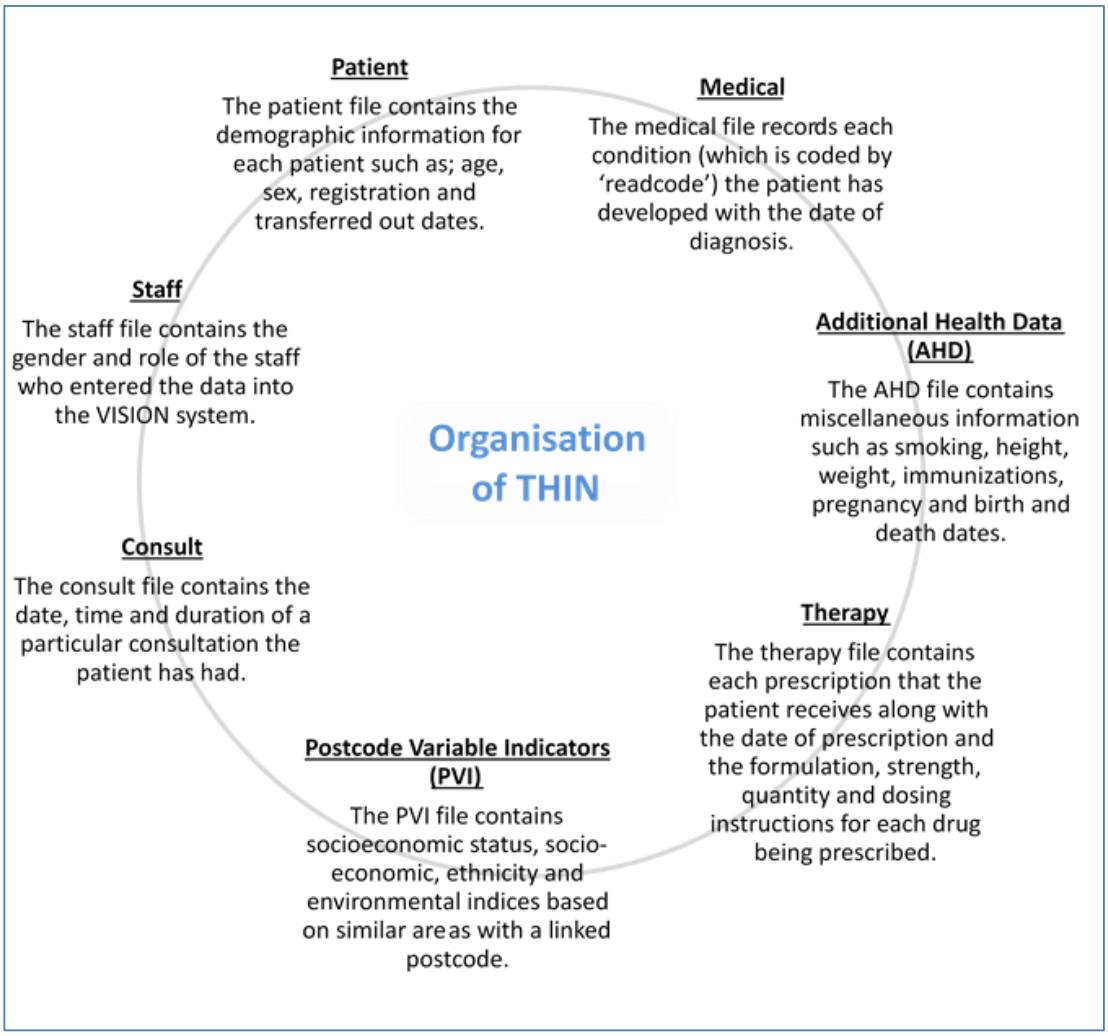

Figure 9: *Organisation of The Health Improvement Network database (122).*

3.2.2.2 Scotland

The NHSS (148) consists of: The Scottish Cancer Registry, the Scottish National Prescribing Information System, the General or Acute Inpatient and Day Case dataset (SMR01), the Outpatient Attendance dataset (SMR00) and the National Records of Scotland Death Records. These five databases are linked by a unique identifier, Community Health Index Number. The NHSS captures information on PCa diagnosis and treatment the Scottish National Prescribing Information System, the General or Acute Inpatient and Day Case dataset (SMR01), the Outpatient Attendance dataset (SMR00) and the National Records of Scotland Death Records (148). As Scotland is in the UK and there may have been some overlap of men with PCa in the UK THIN and Scottish NHSS databases, men with PCa with a postcode in Scotland were excluded from THIN. This study included men with PCa from NHSS on GnRH agonists and antagonists from 2010-2015 with follow-up until 2017.

3.2.2.3 Belgium

The BCR (Figure 10) comprises population-based clinical and pathological information on newly diagnosed cancer cases in Belgium. As all newly diagnosed cancer cases in Belgium are legally required to be registered in the BCR, the registry offers an almost complete coverage of the Belgian population from 2004 onwards (149). The BCR links BCR data with data from health insurance companies (150) and hospital discharge data (151) using the national social security number which is a unique patient identifier (Figure 5). Whereas the data from health insurance companies cover information regarding date and type of diagnostic and therapeutic procedures (including the amount and dosages of dispensed medications) over a period between one year before until five years after cancer diagnosis date, hospital

discharge data covers information on hospital admission and discharge dates, diagnoses and procedures. Moreover, cause of death for the Belgian population is coupled to the BCR data, provided by the three different Belgian regions (150, 151).

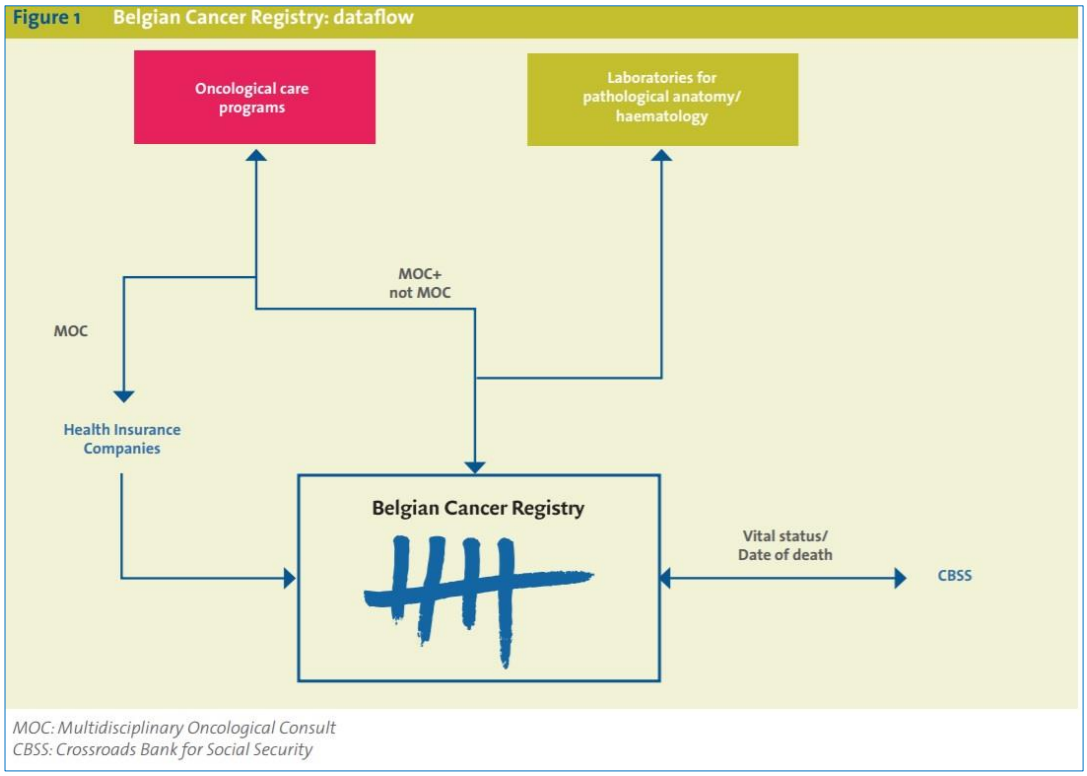

Figure 10: *Organisation of Belgian Cancer Registry (150, 151).*

3.2.2.4 Netherlands

PHARMO is a population-based network of healthcare databases and combines data from both primary and secondary healthcare settings in the Netherlands (151). For this study, data from the Out-patient Pharmacy Database, Hospitalisation Database and Cancer Registry was used which are linked on a patient level (Figure 11) (152). The Cancer Registry comprises information on newly diagnosed cancer patients from the Netherlands [(151)]. The Hospitalisation Database comprises hospital admissions from the Dutch Hospital Data Foundation for >24 hours and admissions

for <24 hours for which a bed is required. The Out-patient Pharmacy Database comprises detailed information on GP or specialist prescribed healthcare products dispensed by out-patient pharmacies. Detailed information on the methodology and the validation of the record linkage method used in PHARMO can be found elsewhere (152). The study period used for the Netherlands was from 2010-2015.

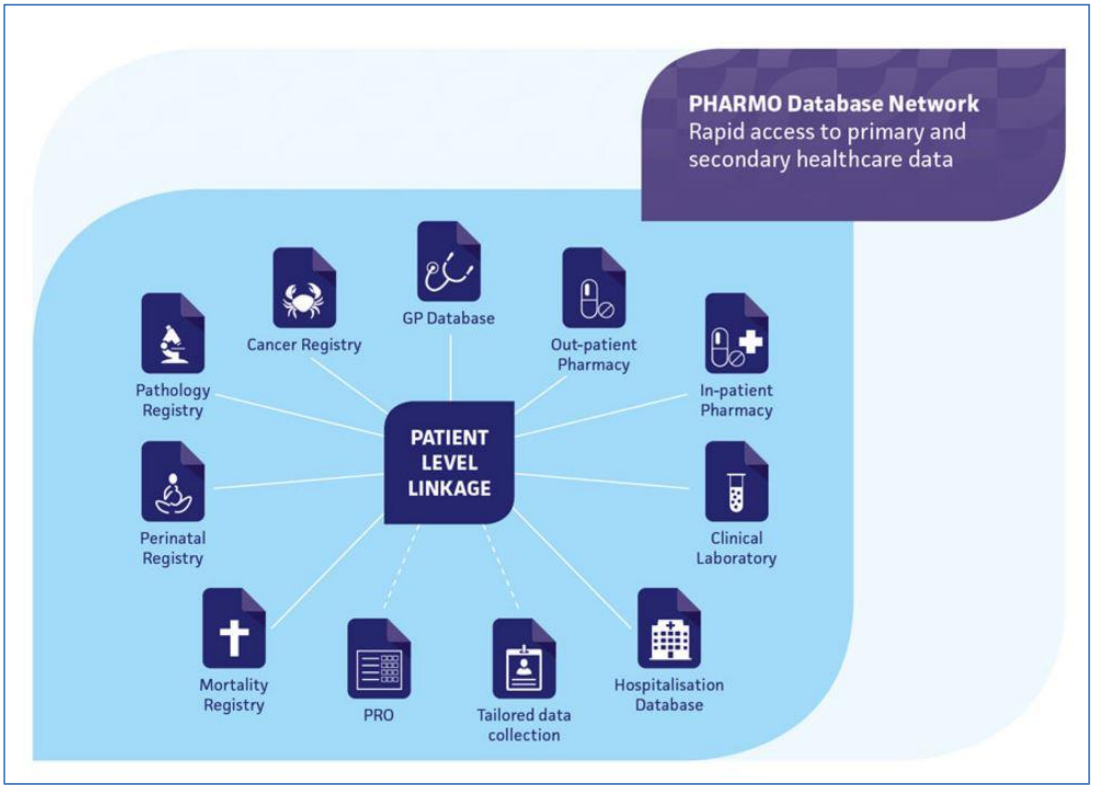

Figure 11: *The organisation of the PHARMO Database Network where different healthcare databases are linked together by patient level linkage. The PHARMO Database Network includes; the Cancer Registry, General Practice Database, Out-patient Pharmacy, In-patient Pharmacy, Clinical Laboratory, Hospitalisation Database, Tailored data collection, PRO (patient reported outcomes), Mortality Registry, Perinatal Registry and the Pathology Registry (152).*

3.2.2.5 France

SNIIRAM (Figure 12) is the French National Health Database based on claims data which combines reimbursed claims from insurance plans with the National Hospital discharge Summaries database system (PMSI) (153). The PMSI datamart stems from

all private or public hospitals and are provided to the *caisse nationale de l'assurance maladie des travailleurs salariés* (CNAMTS) or the National Health Insurance Fund for linkage to the SNIIRAM. The SNIIRAM database includes 98.8% of the French population with information on patient demographics, linked and associated diagnoses (identified by International Classification of Diseases (ICD)-10 codes) of chronic medical conditions extracted from hospital and clinical visits. SNIIRAM provides patient-level linkage based on a unique civil registration number assigned to all French residents (154). Data of a given individual are linked through a unique identification number called *numéro d'identification au repertoire*, which is a unique identifier for each insured person. However, this unique identifier is not accessible in the SNIIRAM in order to preserve the identity of patients. The Données de Consommation Inter-Régimes (DCIR) datamart includes all outpatient reimbursed health expenditures (Figure 12) (153).

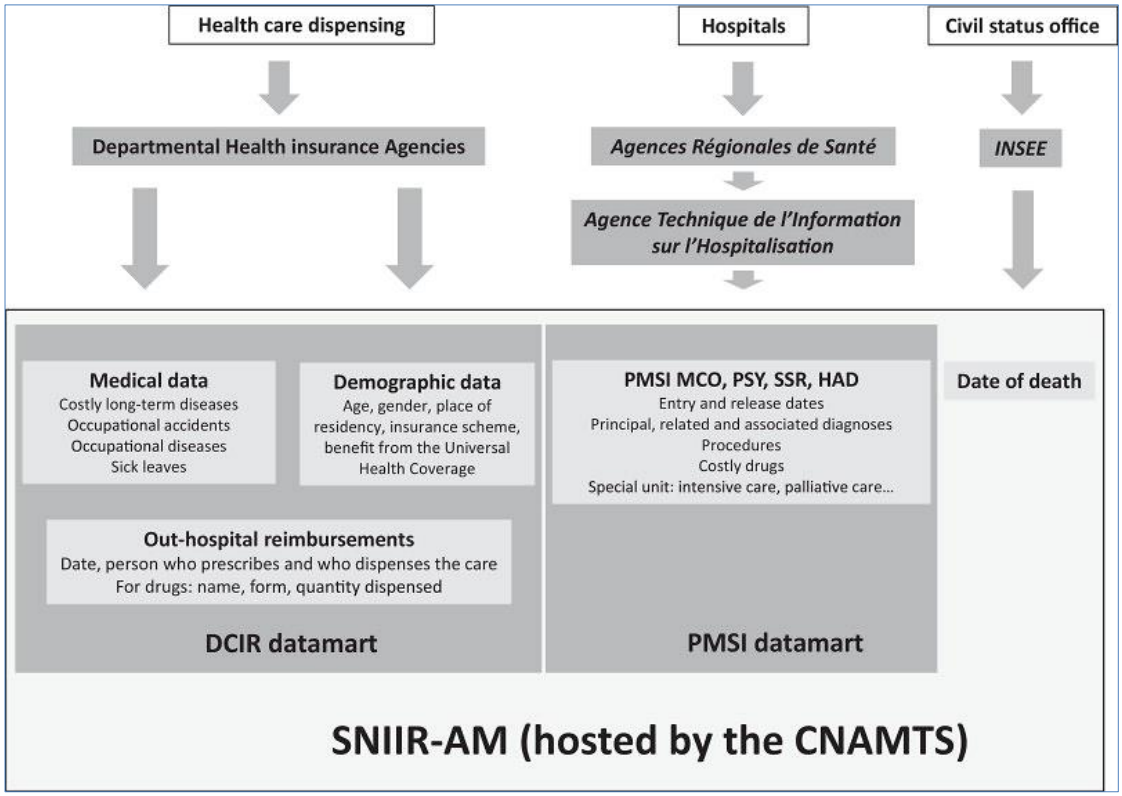

Figure 12: *Organisation of the SNIIRAM database in France that contains Médicalisation des Systèmes d'Information or the National Hospital discharge Summaries database system (PMSI) and Données de Consommation Inter-Régimes or Inter-Scheme Consumption Data (DCIR) datamarts (154). The three main sources the data is gathered from are the healthcare dispensations, hospitals and civil status office or Institut national de la statistique et des études économiques (INSEE) translated to National Institute of Statistics and Economic Studies.*

3.2.2.6 Canada

The RAMQ database combines the following databases from the province of

Québec based on medical claims using unique identifiers between 2011-2016:

- Beneficiaries database provides the demographic information
- Medical services provide data from the inpatient and ambulatory services
- Admissibility database derives prescriptions from the Prescription Drug Insurance Plan

- Pharmaceutical database provides information on drug dispensation data (155).

3.2.3 Exposures

The exposure for this large observational study was defined as the first prescription or dispensation of GnRH agonists or GnRH antagonists. Men with PCa who were hormone treatment naïve were followed up until censoring point (defined below). Once an individual was on one drug, they were assumed to be on that drug until censoring (defined below).

3.2.4 Outcomes

The outcome was defined as the first incident or fatal CVD event following exposure to GnRH agonists or GnRH antagonists. The following CVD outcomes were explored separately: any CVD (ICD-10: I20-I99, G45 or ICD-9 equivalent), ischaemic heart disease (IHD) (ICD-10: I20-I25), acute myocardial infarction (AMI) (ICD-10: I21), arrhythmia (ICD-10: I44-I49), heart failure (HF) (ICD-10: I50, I97.710, I97.790, I11.0) and stroke (ICD-10: I60-64, G45).

3.2.5 Censoring Point

Censoring point was defined as any of the following, which ever occurred first: switch between GnRH agonists and antagonists and vice-versa, orchiectomy, end of study period or death from other causes than CVD death during the study period. For example, when IHD was studied as an outcome, men were censored at first incident or fatal IHD. Any CVD, AMI, arrhythmia, HF and stroke after treatment initiation were overlooked, even if these had occurred before the IHD event. Men with PCa were censored at switch between the GnRH analogues because the

percentage of men with PCa who made the switch across the six countries were low.

3.2.6 Other study variables

Age, follow-up time, year of PCa diagnosis, stage of PCa, total Gleason score, PSA, any prior PCa treatment, type of ADT, ADT specifics, history of CVD indicator (HCVDi), number of previous CVD events and other socio-demographic variables were extracted for the five countries. Detailed data extracted for each country and where relevant, reasons data was not extracted for variables are outlined in Table 2 below. ICD codes, ATC codes, readcodes and drugcodes used to extract study variables for each country has been published (122) (section 9.3.2.1, Appendix).

Table 2: *Data extraction for other study variables in the six included countries.*

Study Variables	Data Extraction in the United Kingdom, Scotland, Belgium, the Netherlands, France and Canada
Age	Age was considered as a timescale in all analytical models on the date of study entry (i.e. GnRH agonists or antagonists' initiation). In the UK THIN database, 5,562 out of 17,073 men with PCa had missing date of births. For these men, multiple imputation was used to impute the missing date of births by creating five plausible imputed datasets and combining results from each of the five datasets. The PHARMO database in the Netherlands only contained the year of birth for all men with PCa on the exposures. Therefore, age for all men in the Netherlands was calculated using the same random day (12^{th}) and month (June).
Follow-up Time	Follow-up began on the date of treatment initiation and ended when any of the censoring criteria was reached. The median, lower and upper quartiles for follow-up time were calculated for UK, Scotland, Belgium, the Netherlands, France and Canada.
Year of PCa Diagnosis	Year of PCa diagnosis was available for UK, Scotland, Belgium and the Netherlands.

Stage of PCa	PCa stage at diagnosis was available for Scotland, Belgium and the Netherlands. Stage of PCa was defined as locally advanced (T3a/bT4 N0M0) and metastatic (TxNxM1) because most PCa men on long-term GnRH analogues are usually categorized into these stages. In Belgium, the stage categories were further split into: TxNxM1, TxN1M0, T3aNxMx, T3bNxMx and T4NxMx.
Total Gleason Score	Total Gleason score was available for Scotland and the Netherlands and was divided into Gleason 5-6, 7, 8, 9-10 and missing. In the Netherlands, men with invalid Gleason score (nine patients) were included in the missing category.
Prostate Specific Antigen (PSA)	PSA, only available for the Netherlands, was categorised into: ≤10, 11-20, 21-50 and >50 ng/ml at GnRH at study entry.
Any Prior PCa Treatment	This was one of the most heterogeneous variable across the six countries as only some information was available for all the included countries. The main categories were divided into: radical prostatectomy, radiotherapy and anti-androgens. Radical prostatectomy and adjuvant or salvage radiotherapy was an additional category in Belgium. Moreover, in Belgium, radiotherapy was further split into palliative radiotherapy (1-10 fractions) and long course external beam radiotherapy +/- brachytherapy). Chemotherapy regimen prior to study entry was only available in the Netherlands. In Canada, brachytherapy and external beam therapy was also included in the variable.
Type of ADT	Type of ADT was defined so that GnRH agonists or antagonists as to distinguish whether GnRH was given as a primary, adjuvant, neo-adjuvant treatment or other (Belgium only). In the UK no distinction was made between primary, neo-adjuvant and adjuvant ADT due to lack of data availability on full radiotherapy profile given to men on the GnRH analogues. In Belgium and Scotland, a prescription of GnRH agonists or antagonists was considered neo-adjuvant if it had appeared in the databases within one month before PCa incidence and the date of surgery or radiotherapy. An adjuvant prescription was defined as a prescription of GnRH agonists or antagonists within a six months' period following surgery or radiotherapy. In Belgium, men with PCa for whom a GnRH treatment was discovered but had not fulfilled the definitions of primary, adjuvant or neo-adjuvant ADT treatment (e.g. GnRH treatment started more than six months following surgery), were classed into the 'other' category. The cancer registry in the PHARMO Database Network in Netherlands only extracted treatment information given at PCa diagnosis and six months after diagnosis. Moreover, combination treatment modalities

	were not derived for the study. As information for radiotherapy dosages was not available in France, a distinction between primary, adjuvant and neo-adjuvant was not made.
ADT Specifics	This variable was defined as with PCa who had received anti-androgens as flare protection or combined androgen blockade. Flare protection was defined as receiving anti-androgens for ≤ 30 days, whereas combined androgen blockade was defined as receiving anti-androgens for more than 30 days.
History of CVD Indicator (HCVDi)	HCVDi was defined as any of the following 12 months prior to entering the cohort: any CVD event (ICD-10 codes: I20-I99, G45), hypertension (ICD-10 and ATC codes), dyslipidaemia (ATC codes or drugcodes) or diabetes (ATC codes or drugcodes). HCVDi was further sub-categorised to specifically indicate history of hypertension, dyslipidemia or diabetes 12 months prior to study entry.
Number of Previous CVD Events	The number of CVD events prior to entering the cohort were coded as 0, 1, 2 or ≥ 3 CVD events. As data in Belgium was only available one year before first ADT prescription, previous CVD events and time of last previous CVD was limited to the 12 months prior to entering the cohort. Previous history of CVD was stratified as time of last previous CVD, defined as: No CVD, 0-3 months, 4-6 months, 7-12 months prior to treatment initiation.
Other Socio-Demographics	Body Mass Index (BMI), socio-economic status (SES), civil status, smoking status and ethnicity were extracted in the UK using the readcodes (122) (section 9.3.2.1, Appendix for specific codes). BMI was defined as: underweight at ≤ 18.5 kg/m^2, normal at 18.6-24 kg/m^2, overweight at 25-30 kg/m^2 and obese at ≥ 30 kg/m^2. Townsend scores (156) were used to extract the SES of the study population. Townsend scores incorporated four different variables: unemployment, non-car ownership, non-home ownership and household overcrowding. The Townsend scores were given as quintiles (i.e. five groups of equal size ranging from 1 (least deprived) to 5 (most deprived) (156). In THIN, civil status was coded as 12 different codes that were combined to form three categories: single, married and unknown (section 9.3.2.1, Appendix for specific codes). Smoking status was defined as: current smokers, non-smokers and past smokers. Ethnicity was defined as men with an origin of: Caucasian, Black, Asian and other (readcodes other than these three categories).

3.2.7 Analysis

3.2.7.1 ROBINS-I tool and target trial

To ensure a clinically applicable research design for this real world study, a modified version of the ROBINS-I tool was used. The modified version compared study variables and trial characteristics between a target trial and the current study. The focus of the target trial was to understand the different types of biases when assessing risk of CVD following GnRH agonists and GnRH antagonists in men with PCa in six different countries and highlight the challenges encountered in addressing these biases.

3.2.7.2 Stage 1: Country-specific analysis

Multivariable Cox proportional hazard models were used to estimate country-specific HRs with age as a timescale. Men with PCa entered the cohort at baseline age (left-truncation) and exited at CVD event age or censoring age. Stage one analysis was conducted using age as a timescale for: (i) outcomes, (ii) stratified analysis for those with HCVDi, (iii) stratified analysis for those without HCVDi, (iv) stratified analysis for men aged < 75 years and (v) stratified analysis for men aged ≥ 75 years.

3.2.7.3 Stage 2: Meta-analysis

Country-specific HRs for risk of CVD following GnRH agonists and GnRH antagonists were log-transformed and pooled in a random-effects meta-analytical model. The I^2 statistic from the meta-analysis assessed the percentage of variation between the databases. Each country in the meta-analysis was weighted by the inverse of its variance (i.e. HRs), and adjustment to the weight was made based upon the degree

of heterogeneity between the six countries. Heterogeneity in the assessment of exposure and outcome data was further evaluated by performing sensitivity analyses. This included only those countries that had collected data in a similar way – incident CVD (ICD-9-CM codes) sourced from hospital discharge date and fatal CVD (ICD-10 codes) sourced from death certificates in Belgium, ICD-10 codes in Scotland, the Netherlands, France and Canada versus readcodes in the UK. Additional stratifications by HCVDi as well as age (< 75 and ≥ 75 years) were conducted to assess effect modification in all countries.

3.2.8 Results

3.2.8.1 ROBINS-I tool and target trial

A target trial was emulated to assess the risk of CVD following GnRH agonists and GnRH antagonists in men with PCa using the ROBINS-I tool (140) (Table 3).

Table 3: *Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool was used to emulate a target trial to assess the risk of CVD following GnRH agonists and GnRH antagonists in men with PCa (122).*

Types of bias addressed	Trial Characteristics		Challenges Encountered
	Target Trial	This Study	
Randomisation Distribution	50/50 split	Uneven number of patients in GnRH agonists and GnRH antagonists	Observational data does not guarantee even distribution between trial arms.
Information Bias	Information on compliance to treatment	An individual is assumed to be in the same cohort at end of study as they are in at start of the study	There is no information on compliance in most observational databases.
Unmeasured Confounding	Lifestyle and socio-demographic factors	Information used for lifestyle and socio-demographic variables	Lifestyle factors are often not well-recorded in healthcare databases leading to an unmeasured

			confounding. UK was the only country with data on some lifestyle (BMI, smoking status) and socio-economic (Townsend scores) factors recorded. However, due to high missing data, these variables were not added to the analytical models.
Unmeasured Confounding	Concomitant medications, history of specific diseases	History of CVD indicator	Although CVD risk factors such as hypertension, diabetes and dyslipidaemia were stratified through the variable HCVDi, other unmeasured concomitant medications may be present that have not been accounted for, leading to some unmeasured confounding.
Channeling Bias	GnRH antagonists to patients with no history of CVD	Men with a history of CVD may be prescribed GnRH antagonists	GnRH antagonists may have been preferentially "channeled" to patients who may have been at risk of a CVD leading to a channeling bias. This must be considered when interpreting the results of this study.
Classification bias	Uniform coding system to define exposure and outcome variables	Readcodes & drugcodes for UK and ATC codes & ICD codes for Scotland, Belgium, the Netherlands, France and Canada	It was difficult to homogenise the coding system fully across the six countries in this study, due to heterogeneity in the data collection methods.
Immortal time bias	Information on GnRH agonists and GnRH antagonists' dispensation	Prescription database in the UK. Dispensing database in Scotland, Belgium, the	Prescription databases usually do not hold information on whether the patient has adhered to their

		Netherlands, France and Canada	prescribed treatment. For example, a man with PCa may be prescribed GnRH antagonists on 1st November but may not visit their health care professional on the same day for their injection. This introduces a lag time between the prescription date and dispensation or injection date resulting in an immortal time bias. A sensitivity analysis excluding the UK may have accounted for this immortal time bias.
Immeasurable time bias	Medications given at hospital visits during the follow-up time	Hospital data was not available for the UK and medications from the in-patient pharmacy was not available for France and the Netherlands	Immeasurable time bias can arise from the presence of an unidentified hospitalisation within a database (157). Records of medications administered during a hospital visit may not have been available during the study period. Data for unidentified hospitalisation was not available in the six countries.

*BMI: Body Mass Index; CVD: cardiovascular disease; HCVDi: history of cardiovascular disease indicator; ATC: anatomical therapeutic chemical, ICD: international classification of diseases.

Table 4 shows the study period, number of men and median follow-up time for men on GnRH agonists and GnRH antagonists in the UK, Scotland, Belgium, the Netherlands, France and Canada.

Table 4: *Study period, number of men and median follow-up time for men on GnRH agonists and GnRH antagonists in the United Kingdom (excluding Scotland), Scotland, Belgium, the Netherlands, France and Canada.*

	United Kingdom (excluding Scotland)		Scotland		Belgium		Netherlands		France		Canada	
	Men on GnRH Agonists	Men on GnRH Antagonist	Men on GnRH Agonists	Men on GnRH Antagonist	Men on GnRH Agonists	Men on GnRH Antagonists	Men on GnRH Agonists	Men on GnRH Antagonists	Men on GnRH Agonists	Men on GnRH Antagonist	Men on GnRH Agonists	Men on GnRH Antagonist
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Study period	2010-2016		2010-2017		2010-2015		2010-2015		2010-2013		2011-2016	
Number of men with PCa	16955 (99.3)	118 (0.7)	9114 (94.8)	495 (5.2)	1860 (78.1)	522 (21.9)	1187 (92.5)	97 (7.6)	19641 (83.9)	912 (3.9)	10201 (94.6)	584 (5.4)
Follow-up time, years												
Median	0.6	0.5	2.1	0.8	1.7	1.3	2.3	1.5	2.2	2.1	2.1	1.5
Lower quartile	0.2	0.1	1.1	0.6	0.8	0.9	1.5	1.2	0.7	0.8	1.2	0.8
Upper quartile	1.8	1.2	2.9	1.1	3.0	1.8	3.4	2.2	2.7	2.6	3.7	2.7

3.2.8.2 Patient characteristics

Table 5 shows demographic and clinical characteristics of men with PCa on GnRH agonist and GnRH antagonists. As seen in the table, demographic variables and lifestyle factors were not available for most countries. Moreover, clinical characteristics of PCa were also not uniformly available in all countries. Therefore, these variables are reported in this thesis for descriptive purposes and no further analyses were conducted using these variables.

***Table 5**: Baseline characteristics for men with prostate cancer from the six included databases in the United Kingdom (excluding Scotland), Scotland, Belgium, the Netherlands, France and Canada.*

Demographic or Clinical Characteristic	United Kingdom (excluding Scotland)		Scotland		Belgium		Netherlands		France		Canada	
	Men on GnRH Agonists	Men on GnRH Antagonists	Men on GnRH Agonists	Men on GnRH Antagonists	Men on GnRH Agonists	Men on GnRH Antagonists	Men on GnRH Agonists	Men on GnRH Antagonists	Men on GnRH Agonists	Men on GnRH Antagonists	Men on GnRH Agonists	Men on GnRH Antagonists
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Age, years												
Mean	75	74	73	74	73.5	72.3	71.9	72.5	74.2	73.4	74.7	74.1
SD	9.6	10.1	8.4	9.2	9.3	9.8	8.3	9.6	8.6	9.8	8.2	9.1
≤ 65	1627 (9.6)	21 (17.8)	1641 (18.0)	84 (10.9)	390 (21.0)	130 (24.9)	276 (23.3)	24 (24.7)	3016 (15.4)	191 (20.9)	1278 (12.5)	92 (15.8)
66-74	3543 (20.9)	43 (36.4)	3895 (43.0)	192 (25.0)	555 (29.8)	162 (31.0)	452 (38.1)	33 (34.0)	6358 (32.4)	278 (30.5)	3792 (37.2)	224 (38.4)
75-84	4322 (25.5)	33 (28.0)	1852 (20.3)	99 (12.9)	697 (37.5)	177 (33.9)	387 (32.6)	26 (26.8)	8124 (41.4)	318 (34.9)	3863 (37.9)	192 (32.9)
≥ 85	1901 (11.2)	21 (17.8)	1726 (18.9)	120 (15.6)	218 (11.7)	53 (10.2)	72 (6.1)	14 (14.4)	2143 (10.9)	125 (13.7)	1268 (12.4)	76 (13.0)
Missing	5562 (32.8)	0	0	0	0	0						
Year of PCa diagnosis												
< 2010	1815 (10.7)	4 (3.4)	0	0			0	0	N/A	N/A	N/A	N/A
2010	1719 (10.1)	4 (3.4)	1490 (16.3)	8 (1.6)	496 (26.7)	41 (7.9)	256 (21.6)	27 (27.8)	N/A	N/A	N/A	N/A
2011	1508 (8.9)	14 (11.9)	1638 (18.0)	23 (4.6)	494 (26.6)	108 (20.7)	275 (23.1)	23 (23.7)	N/A	N/A	N/A	N/A
2012	1582 (9.3)	13 (11.0)	1431 (15.7)	60 (12.1)	433 (23.3)	143 (27.4)	236 (19.9)	14 (14.4)	N/A	N/A	N/A	N/A
2013	1532 (9.0)	15 (12.7)	1614 (17.7)	91 (18.4)	437 (23.5)	230 (44.1)	238 (20.1)	22 (22.7)	N/A	N/A	N/A	N/A
2014	1241 (7.3)	24 (20.3)	1535 (16.8)	166 (33.5)	0	0	182 (15.3)	11 (11.3)	N/A	N/A	N/A	N/A
2015	821 (4.8)	31 (26.3)	1406 (15.4)	147 (29.7)	0	0	0	0	N/A	N/A	N/A	N/A

2016	183 (1.1)	7 (5.9)	0	0	0	0	0	0	N/A	N/A	N/A	N/A
Missing	6,554 (38.7)	6 (5.1)	0	0	0	0	0	0	N/A	N/A	N/A	N/A
Stage of PCa												
Locally Advanced (T3a/bT4 N0M0)	N/A	N/A	N/A	N/A	879 (47.3)	137 (26.3)	N/A	N/A	N/A	N/A	N/A	N/A
Advanced (TxNxM1)	N/A	N/A	N/A	N/A	981 (52.7)	385 (73.8)	N/A	N/A	N/A	N/A	N/A	N/A
PCa stage subgroups												
TxNxM1	N/A	N/A	N/A	N/A	981 (52.7)	385 (73.8)	N/A	N/A	N/A	N/A	N/A	N/A
TxN1M0	N/A	N/A	N/A	N/A	315 (16.9)	60 (11.5)	N/A	N/A	N/A	N/A	N/A	N/A
T3aNxMx	N/A	N/A	N/A	N/A	287 (15.4)	25 (4.8)	N/A	N/A	N/A	N/A	N/A	N/A
T3bNxMx	N/A	N/A	N/A	N/A	153 (8.2)	15 (2.9)	N/A	N/A	N/A	N/A	N/A	N/A
T4NxMx	N/A	N/A	N/A	N/A	124 (6.7)	37 (7.1)	N/A	N/A	N/A	N/A	N/A	N/A
T3 (Netherlands)	N/A	N/A	N/A	N/A	N/A	N/A	417 (35.8)	9 (9.6)	N/A	N/A	N/A	N/A
T4 (Netherlands)	N/A	N/A	N/A	N/A	N/A	N/A	748 (64.2)	85 (90.4)	N/A	N/A	N/A	N/A
Missing	N/A	N/A	N/A	N/A	0	0	22 (1.9)	3 (3.1)	N/A	N/A	N/A	N/A
Total Gleason Score												
Gleason 5-6	N/A	N/A	989 (10.9)	25 (5.1)	N/A	N/A	52 (4.4)	4 (4.1)	N/A	N/A	N/A	N/A
Gleason 7	N/A	N/A	3023 (33.2)	72 (14.5)	N/A	N/A	228 (19.2)	14 (14.4)	N/A	N/A	N/A	N/A
Gleason 8	N/A	N/A	1154 (12.7)	40 (8.1)	N/A	N/A	194 (16.3)	19 (19.6)	N/A	N/A	N/A	N/A
Gleason 9-10	N/A	N/A	2139 (23.5)	257 (51.9)	N/A	N/A	240 (20.2)	22 (22.7)	N/A	N/A	N/A	N/A
Missing	N/A	N/A	2815 (30.9)	374 (75.6)	N/A	N/A	473 (39.9)	38 (39.2)	N/A	N/A	N/A	N/A
PSA												

≤10	N/A	N/A	N/A	N/A	N/A	N/A	192 (16.2)	8 (8.3)	N/A	N/A	N/A	N/A
11-20	N/A	N/A	N/A	N/A	N/A	N/A	186 (15.7)	7 (7.2)	N/A	N/A	N/A	N/A
21-50	N/A	N/A	N/A	N/A	N/A	N/A	237 (20.0)	12 (12.4)	N/A	N/A	N/A	N/A
>50	N/A	N/A	N/A	N/A	N/A	N/A	479 (40.4)	51 (52.6)	N/A	N/A	N/A	N/A
Missing	N/A	N/A	N/A	N/A	N/A	N/A	93 (7.8)	19 (19.6)	N/A	N/A	N/A	N/A
Any prior PCa treatment												
Radical prostatectomy	292 (1.7)	3 (2.5)	229 (3.0)	<5.0	51 (2.7)	6 (1.2)	62 (5.2)	2 (2.1)	1000 (5.1)	35 (3.8)	2932 (28.7)	133 (22.8)
Radical prostatectomy + Adjuvant/Salvage Radiotherapy	N/A	N/A	N/A	N/A	14 (0.8)	1 (0.2)	N/A	N/A	29 (0.2)	1 (0.11)	N/A	N/A
Radiotherapy	305 (1.8)	3 (2.5)	4281 (47.0)	145 (29.0)			403 (34.0)	9 (9.3)	269 (1.37)	13 (1.42)	N/A	N/A
Radiotherapy ≤ 6 months prior to ADT initiation	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	55 (20.5)	4 (30.8)	N/A	N/A
Radiotherapy > 6 months prior to ADT initiation	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	214 (79.5)	9 (69.2)	N/A	N/A
Palliative radiotherapy (1-10 fractions)	N/A	N/A	N/A	N/A	108 (5.8)	67 (12.8)	N/A	N/A	N/A	N/A	N/A	N/A
Long course external beam radiotherapy +/- brachytherapy	N/A	N/A	N/A	N/A	453 (24.4)	56 (10.7)	N/A	N/A	N/A	N/A	N/A	N/A
Chemotherapy	N/A	N/A	N/A	N/A	N/A	N/A	14 (1.2)	1 (1.0)	N/A	N/A	N/A	N/A
AA	4214 (24.9)	7 (5.9)	N/A	N/A	990 (53.2)	42 (8.1)	1037 (87.4)	67 (69.1)	N/A	N/A	N/A	N/A
Previous AA 0-3 month	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1669 (87.8)	39 (92.9)	N/A	N/A
Previous AA 3-6 month	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	145 (7.6)	1 (2.4)	N/A	N/A
Previous AA 6-9 month	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	71 (3.7)	1 (2.4)	N/A	N/A
Previous AA 9-12 month	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	16 (0.8)	1 (2.4)	N/A	N/A

Brachytherapy	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	9 (0.1)	0
EBRT	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	927 (9.1)	70 (12.0)
Other/none	12144 (71.6)	105 (89.0)			244 (13.1)	350 (67.1)	N/A	N/A	N/A	N/A	6333 (62.1)	381 (65.2)
ADT specifics (with GnRH agonists)												
Anti-androgens – flare protection	3764 (22.2)	4 (3.4)	N/A	N/A	506 (27.2)	13 (2.5)	402 (33.9)	20 (20.6)	8527 (43.4)	41 (4.5)	N/A	N/A
Anti-androgens – combined androgen blockade	276 (1.6)	1 (0.9)	N/A	N/A	953 (51.2)	44 (8.4)	635 (53.5)	47 (48.5)	4199 (21.4)	53 (5.8)	N/A	N/A
No anti-androgens	12741 (75.1)	111 (94.1)	N/A	N/A	401 (21.6)	465 (89.1)	150 (12.6)	30 (30.9)	6805 (34.7)	795 (87.2)	N/A	N/A
Unknown*	174 (1.03)	2 (1.7)	N/A	N/A	0	0			11 (0.56)	23 (2.5)	N/A	N/A
History of CVD indicator												
Yes	8288 (48.9)	70 (59.3)	2876 (31.6)	119 (24.0)	1364 (73.3)	361 (69.2)	741 (62.4)	64 (66.0)	14011 (71.3)	625 (68.5)	3137 (30.8)	213 (36.5)
No	8667 (51.1)	48 (40.7)	6238 (68.4)	376 (76.0)	496 (26.7)	161 (30.8)	446 (37.6)	33 (34.0)	5630 (28.7)	287 (31.5)	7064 (69.2)	371 (63.5)
CVD risk factors 12 months prior to ADT initiation												
Hypertension	5729 (33.8)	42 (35.6)	5375 (59.0)	319 (64.4)	1124 (60.4)	280 (53.6)	481 (40.5)	47 (48.5)	10251 (52.2)	457 (50.1)	3298 (32.3)	377 (64.6)
Dyslipidaemia	4547 (26.8)	36 (30.5)	4224 (46.3)	268 (54.1)	714 (38.4)	197 (37.7)	446 (37.6)	32 (33.0)	8852 (45.1)	369 (40.5)	4380 (42.9)	293 (50.2)
Diabetes Mellitus	1173 (6.9)	11 (9.3)	912 (10.0)	64 (12.9)	277 (14.9)	97 (18.6)	163 (13.7)	10 (10.3)	3343 (17.0)	152 (16.7)	7847 (76.9)	127 (21.7)
Number of previous CVD events, 12 months prior to ADT initiation												
0	16540 (97.6)	113 (95.8)	8725 (95.7)	451 (91.1)	1551 (83.4)	437 (83.7)	1128 (95.0)	91 (93.8)	18541 (94.4)	838 (91.9)	6610 (64.8)	337 (57.7)
1	98 (0.6)	2 (1.7)	158 (1.7)	16 (3.2)	155 (8.3)	50 (9.6)	18 (1.5)	1 (1.0)	944 (4.8)	66 (7.2)	1956 (19.2)	120 (20.5)
2	119 (0.7)	0	111 (1.2)	10 (2.0)	92 (5.0)	25 (4.8)	5 (0.4)	2 (2.1)	130 (0.7)	6 (0.7)	889 (8.7)	69 (11.8)

3+	198 (1.2)	3 (2.5)	120 (1.3)	18 (3.6)	62 (3.3)	10 (1.9)	36 (3.0)	3 (3.1)	26 (0.1)	2 (0.2)	746 (7.3)	58 (9.9)
Time of last previous CVD, 12 months prior to ADT initiation												
No CVD	16540 (97.6)	113 (95.8)	N/A	N/A	1551 (83.4)	437 (83.7)	1128 (95.0)	91 (93.8)	18541 (94.4)	838 (91.9)	N/A	N/A
0-3m	141 (0.8)	3 (2.5)	N/A	N/A	254 (13.7)	71 (13.6)	16 (1.4)	3 (3.1)	365 (1.9)	32 (3.5)	N/A	N/A
4-6m	98 (0.6)	0	N/A	N/A	29 (1.6)	8 (1.5)	15 (1.3)	0	274 (1.4)	14 (1.5)	N/A	N/A
7-12m	176 (1.0)	2 (1.7)	N/A	N/A	26 (1.4)	6 (1.2)	28 (2.4)	3 (3.1)	461 (2.4)	28 (3.1)	N/A	N/A
BMI / obesity												
Normal weight (18.5-24)	76 (0.5)	2 (1.7)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Underweight (<18.5)	2 (0.01)	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Overweight (25-30)	165 (1.0)	2 (1.7)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Obese (>30)	103 (0.6)	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Missing	16609 (98.0)	114 (96.6)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Socio-economic Status												
Lowest or least deprived (Townsend 1)	3402 (20.1)	18 (15.3)	1380 (15.1)	105 (21.2)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Low (Townsend 2)	2638 (15.6)	32 (27.1)	1708 (18.7)	108 (21.8)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Middle (Townsend 3)	2223 (13.1)	16 (13.6)	1939 (21.3)	113 (22.8)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
High (Townsend 4)	1700 (10.0)	18 (15.3)	2132 (23.4)	95 (19.2)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Highest or most deprived (Townsend 5)	975 (5.8)	10 (8.5)	1951 (21.4)	73 (14.7)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
French "poor income"	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	550 (2.8)	22 (2.4)	N/A	N/A
Missing	6017 (35.5)	24 (20.3)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Civil Status												

Single	114 (0.7)	2 (1.7)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Married	556 (3.3)	5 (4.2)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Missing	16285 (96.1)	111 (94.1)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Smoking Status												
Current Smokers	3729 (22.0)	30 (25.4)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Non-smokers	78 (0.5)	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Past Smokers	195 (1.2)	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Missing	12953 (76.4)	88 (74.6)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ethnicity												
Caucasian	7392 (43.6)	57 (48.3)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Black	360 (2.1)	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Asian	226 (1.3)	1 (0.9)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Other	152 (0.9)	1 (0.9)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Missing	8825 (52.1)	59 (50.0)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

*Unknown: Received anti-androgens before GnRH initiation however cannot make a distinction between flare or combined androgen blockade; N/A: Not available.

3.2.8.3 Stage 1: Country-specific Cox proportional hazard models

Tables 6-11 show country-specific HRs and 95% CIs for the six included countries.

3.2.8.3.1 United Kingdom

In the UK, 16,955 (99.3%) men with PCa were on GnRH agonists and 118 (0.7%) men with PCa were on GnRH antagonists (Table 4). Country-specific HRs and 95% CI from the UK (Table 6) showed an increased risk of developing arrhythmia in men with PCa on GnRH antagonists compared to GnRH agonists (HR = 4.05; 95% CI = 1.03 – 15.9).

Table 6: *Hazard ratios and 95% confidence intervals from Cox proportional hazard models including different stratifications for any CVD, ischaemic heart disease, acute myocardial infarction, arrhythmia, heart failure and stroke for the United Kingdom.*

Outcome	HR for all men (95% CI)	HR for men with *HCVDi (95% CI)	HR for men without HCVDi (95% CI)	HR for men < 75 years (95% CI)	HR for men ≥ 75 years (95% CI)
Any CVD	2.18 (0.69 – 6.84)	1.69 (0.47 – 6.12)	4.02 (0.80 – 20.12)	1.09 (0.25 – 4.72)	1.85 (0.49 – 7.07)
Ischaemic Heart Disease	0.61 (0.10 – 3.62)	0.30 (0.03 – 2.92)	2.17 (0.23 – 20.83)	–	0.85 (0.13 – 5.45)
Acute Myocardial Infarction	–	–	–	–	–
Arrhythmia	4.05 (1.03 – 15.9)	2.94 (0.71 – 12.2)	7.29 (1.19 – 44.51)	2.89 (0.53 – 15.6)	2.79 (0.60 – 13.0)
Heart Failure	0.43 (0.05 – 3.67)	0.48 (0.05 – 4.13)	–	–	0.41 (0.05 – 3.5)
Stroke	0.44 (0.05 – 3.81)	–	3.1 (0.34 – 28.65)	–	0.48 (0.05 – 4.36)

* HR: hazard ratio; CI: confidence interval; HCVDi: history of CVD indicator; GnRH agonists (reference group). The (-) indicates where analyses were not conducted due to no number of events in GnRH agonists or antagonist group.

3.2.8.3.2 Scotland

In Scotland, 11,929 (94.0%) men with PCa were on GnRH agonists and 768 (6.0%) men with PCa were on GnRH antagonists (Table 4). Results from Scotland (Table 7) showed an increased risk of developing any CVD (HR = 1.52; 95% CI = 1.19 – 1.94) and arrhythmia (HR = 2.24; 95% CI = 1.35 – 3.72) in men with PCa on GnRH antagonists and a previous HCVDi as compared to men on GnRH agonists. Moreover, there was an increased risk of developing any CVD in men with PCa on GnRH antagonists regardless of age, as compared to men on GnRH agonists. In men aged < 75 years who were on GnRH antagonists, there was also an increased risk of developing arrhythmia (HR = 2.10; 95% CI = 1.03 – 4.28) as compared to those on GnRH agonists.

Table 7: *Hazard ratios and 95% confidence intervals from Cox proportional hazard models including different stratifications for any CVD, ischaemic heart disease, acute myocardial infarction, arrhythmia, heart failure and stroke for Scotland.*

Outcome	HR for all men (95% CI)	HR for men with *HCVDi (95% CI)	HR for men without HCVDi (95% CI)	HR for men < 75 years (95% CI)	HR for men ≥ 75 years (95% CI)
Any CVD	1.57 (1.25 – 1.96)	1.52 (1.19 – 1.94)	1.49 (0.85 – 2.59)	1.64 (1.18 – 2.27)	1.50 (1.10 – 2.04)
Ischaemic Heart Disease	1.48 (1.00 – 2.19)	1.42 (0.93 – 2.16)	1.40 (0.44 – 4.42)	1.28 (0.68 – 2.40)	1.63 (0.99 – 2.70)
Acute Myocardial Infarction	1.45 (0.83 – 2.53)	1.24 (0.66 – 2.33)	2.50 (0.78 – 8.03)	1.40 (0.57 – 3.42)	1.50 (0.74 – 3.05)
Arrhythmia	1.89 (1.14 – 3.12)	2.24 (1.35 – 3.72)	–	2.10 (1.03 – 4.28)	1.69 (0.83 – 3.44)
Heart Failure	1.72 (0.88 – 3.37)	1.75 (0.89 – 3.44)	–	0.96 (0.13 – 6.97)	1.85 (0.90 – 3.79)

Stroke	0.73 (0.35 – 1.55)	0.63 (0.26 – 1.55)	1.1 (0.27 – 4.52)	0.27 (0.04 – 1.96)	1.03 (0.46 – 2.34)

* HR: hazard ratio; CI: confidence interval; HCVDi: history of CVD indicator; GnRH agonists (reference group). The (-) indicates where analyses were not conducted due to no number of events in GnRH agonists/antagonist group.

3.2.8.3.3 Belgium

1,860 (78.1%) men with PCa were on GnRH agonists and 522 (21.9%) men with PCa were on GnRH antagonists in Belgium (Table 4). Results from Belgium (Table 8) showed an increased risk of developing any CVD in men on GnRH antagonists with a HCVDi (HR = 1.37; 95% CI = 1.07 – 1.76) as compared to men on GnRH agonists. There was also an increased risk of developing AMI in men on GnRH antagonists with a HCVDi (HR = 2.19; 95% CI = 1.16 – 4.16) and those aged < 75 years (HR = 2.99; 95% CI = 1.24 – 7.19) as compared to men on GnRH agonists.

Table 8: *Hazard ratios and 95% confidence intervals from Cox proportional hazard models including different stratifications for any CVD, ischaemic heart disease, acute myocardial infarction, arrhythmia, heart failure and stroke for Belgium.*

Outcome	HR for all men (95% CI)	HR for men with *HCVDi (95% CI)	HR for men without HCVDi (95% CI)	HR for men < 75 years (95% CI)	HR for men ≥ 75 years (95% CI)
Any CVD	1.27 (1.00 – 1.62)	1.37 (1.07 – 1.76)	1.26 (0.47 – 3.40)	1.40 (0.99 – 1.97)	1.13 (0.81 – 1.58)
Ischaemic Heart Disease	1.35 (0.88 – 2.08)	1.42 (0.91 – 2.23)	2.15 (0.40 – 11.57)	1.30 (0.70 – 2.40)	1.36 (0.74 – 2.49)
Acute Myocardial Infarction	2.03 (1.07 – 3.84)	2.19 (1.16 – 4.16)	–	2.99 (1.24 – 7.19)	1.30 (0.49 – 3.44)
Arrhythmia	1.57 (0.96 – 2.55)	1.65 (1.00 – 2.73)	3.11 (0.28 – 35.25)	1.47 (0.66 – 3.26)	1.56 (0.84 – 2.88)
Heart Failure	1.13 (0.62 – 2.05)	1.17 (0.63 – 2.17)	2.72 (0.24 – 30.96)	1.09 (0.41 – 2.87)	1.08 (0.51 – 2.31)

Stroke	1.19 (0.64 – 2.23)	1.21 (0.62 – 2.39)	1.81 (0.36 – 9.09)	1.52 (0.56 – 4.14)	1.01 (0.45 – 2.26)

* HR: hazard ratio; CI: confidence interval; HCVDi: history of CVD indicator; GnRH agonists (reference group). The (-) indicates where analyses were not conducted due to no number of events in GnRH agonists/antagonist group.

3.2.8.3.4 The Netherlands

In the Netherlands, there were 1,187 (92.5%) men with PCa were on GnRH agonists and 97 (7.6%) men with PCa were on GnRH antagonists (Table 4). Country-specific HRs and 95% Cis from the Netherlands (Table 9) showed no significant risks for any CVD or CVD subtypes in both comparison groups.

Table 9: *Hazard ratios and 95% confidence intervals from Cox proportional hazard models including different stratifications for any CVD, ischaemic heart disease, acute myocardial infarction, arrhythmia, heart failure and stroke for the Netherlands.*

Outcome	HR for all men (95% CI)	HR for men with *HCVDi (95% CI)	HR for men without HCVDi (95% CI)	HR for men < 75 years (95% CI)	HR for men ≥ 75 years (95% CI)
Any CVD	1.14 (0.62 – 2.10)	1.61 (0.70 – 3.71)	0.75 (0.23 – 2.44)	1.01 (0.38 – 2.71)	1.03 (0.45 – 2.34)
Ischaemic Heart Disease	0.46 (0.09 – 2.45)	–	1.62 (0.14 – 18.31)	0.60 (0.11 – 3.36)	–
Acute Myocardial Infarction	–	–	–	–	–
Arrhythmia	1.56 (0.21 – 11.70)	1.41 (0.08 – 23.57)	–	1.56 (0.21 – 11.70)	–
Heart Failure	1.56 (0.21 – 11.70)	–	–	–	1.56 (0.21 – 11.70)
Stroke	0.73 (0.08 – 7.08)	–	–	–	0.73 (0.08 – 7.08)

* HR: hazard ratio; CI: confidence interval; HCVDi: history of CVD indicator; GnRH agonists (reference group). The (-) indicates where analyses were not conducted due to no number of events in GnRH agonists/antagonist group.

3.2.8.3.5 France

19,641 (83.9%) men with PCa were on GnRH agonists and 912 (3.9%) men with PCa were on GnRH antagonists in Belgium (Table 4). Results from France (Table 10) showed a decreased risk of developing IHD in men with PCa on GnRH antagonists and aged ≥ 75 years as compared to those on GnRH agonists (HR = 0.86; 95% CI = 1.73 – 4.43).

Table 10: *Hazard ratios and 95% confidence intervals from Cox proportional hazard models including different stratifications for any CVD, ischaemic heart disease, acute myocardial infarction, arrhythmia, heart failure and stroke for France.*

Outcome	HR for all men (95% CI)	HR for men with *HCVDi (95% CI)	HR for men without HCVDi (95% CI)	HR for men < 75 years (95% CI)	HR for men ≥ 75 years (95% CI)
Any CVD	0.91 (0.70 – 1.16)	0.95 (0.72 – 1.25)	1.84 (0.47 – 1.15)	0.92 (0.62 – 1.36)	0.90 (0.65 – 1.24)
Ischaemic Heart Disease	0.93 (0.57 – 1.54)	0.78 (0.43 – 1.41)	2.09 (0.84 – 5.20)	1.02 (0.50 – 2.07)	0.86 (1.73 – 4.43)
Acute Myocardial Infarction	1.41 (0.62 – 3.19)	1.57 (0.64 – 3.86)	1.13 (0.15 – 8.42)	2.42 (0.87 – 6.56)	0.77 (0.19 – 3.12)
Arrhythmia	1.02 (0.60 – 1.74)	1.30 (0.76 – 2.22)	–	0.94 (0.35 – 2.53)	1.06 (0.57 – 1.99)
Heart Failure	1.39 (0.85 – 2.52)	1.30 (0.76 – 2.22)	2.39 (0.74 – 7.74)	2.58 (1.19 – 5.57)	1.04 (0.55 – 1.95)
Stroke	0.78 (0.39 – 1.57)	0.64 (0.26 – 1.55)	1.25 (0.40 – 3.98)	0.57 (0.14 – 2.30)	0.89 (0.40 – 2.01)

* HR: hazard ratio; CI: confidence interval; HCVDi: history of CVD indicator; GnRH agonists (reference group). The (-) indicates where analyses were not conducted due to no number of events in GnRH agonists/antagonist group.

3.2.8.3.6 Canada

10,201 (94.6%) men with PCa were on GnRH agonists and 584 (5.4%) men with PCa were on GnRH antagonists in Canada (Table 4). In Canada (Table 11), there was increased risk of developing all CVD outcomes regardless of HCVDi. For men with a HCVDi there was an increased risk of developing any CVD (HR = 1.04; 95% CI = 1.03 – 1.04), IHD (HR = 1.03; 95% CI = 1.02 – 1.03), AMI CVD (HR = 1.05; 95% CI = 1.04 – 1.06), arrhythmia (HR = 1.05; 95% CI = 1.04 – 1.05), HF (HR = 1.06; 95% CI = 1.05 – 1.07) and stroke (HR = 1.04; 95% CI = 1.03 – 1.05) in men on GnRH antagonists with a HCVDi as compared to men on GnRH agonists. Moreover, there was increased risk of developing any CVD (HR = 1.39; 95% CI = 1.18 – 1.64), arrhythmia (HR = 1.43; 95% CI = 1.15 – 1.79), HF (HR = 1.48; 95% CI = 1.14 – 1.92) and stroke (HR = 1.46; 95% CI = 1.01 – 2.13) in men aged $\geq$ 75 years and on GnRH antagonists as compared to men on GnRH agonists.

Table 11: *Hazard ratios and 95% confidence intervals from Cox proportional hazard models including different stratifications for any CVD, ischaemic heart disease, acute myocardial infarction, arrhythmia, heart failure and stroke for Canada.*

Outcome	HR for all men (95% CI)	HR for men with *HCVDi (95% CI)	HR for men without HCVDi (95% CI)	HR for men < 75 years (95% CI)	HR for men ≥ 75 years (95% CI)
Any CVD	1.17 (1.04 – 1.33)	1.04 (1.03 – 1.04)	1.04 (1.03 – 1.05)	1.08 (0.90 – 1.30)	1.39 (1.18 – 1.64)
Ischaemic Heart Disease	1.08 (0.92 – 1.25)	1.03 (1.02 – 1.03)	1.02 (1.01 – 1.04)	1.03 (0.82 – 1.29)	1.19 (0.97 – 1.46)
Acute Myocardial Infarction	1.04 (0.68 – 1.58)	1.05 (1.04 – 1.06)	1.06 (1.02 – 1.10)	0.87 (0.43 – 1.76)	1.25 (0.74 – 2.09)
Arrhythmia	1.27 (1.07 – 1.51)	1.05 (1.04 – 1.05)	1.06 (1.04 – 1.08)	1.21 (0.91 – 1.60)	1.43 (1.15 – 1.79)
Heart Failure	1.32 (1.08 – 1.63)	1.06 (1.05 – 1.07)	1.06 (1.03 – 1.09)	1.26 (0.90 – 1.78)	1.48 (1.14 – 1.92)
Stroke	1.37 (1.03 – 1.82)	1.04 (1.03 – 1.05)	1.05 (1.02 – 1.07)	1.34 (0.86 – 2.09)	1.46 (1.01 – 2.13)

* HR: hazard ratio; CI: confidence interval; HCVDi: history of CVD indicator; GnRH agonists (reference group). The (-) indicates where analyses were not conducted due to no number of events in GnRH agonists/antagonist group.

Stage 2: Meta-analysis

Table 12 shows pooled HRs from UK, Scotland, Belgium, the Netherlands, France and Canada, including stratifications to evaluate the use of GnRH agonists compared to GnRH antagonists according to HCVDi and age.

Table 12: *Hazard ratios from random-effects meta-analytical models including different stratification for any CVD, ischaemic heart disease, acute myocardial infarction, arrhythmia, heart failure and stroke for six included countries.*

Outcome	HR for all men (95% CI)	HR for men with *HCVDi (95% CI)	HR for men without HCVDi (95% CI)	HR for men < 75 years (95% CI)	HR for men ≥ 75 years (95% CI)
Any CVD	1.22 (1.03 – 1.45)	1.21 (1.00 – 1.46)	1.05 (0.91 – 1.23)	1.21 (1.00 – 1.46)	1.24 (1.04-1.48)
Ischaemic Heart Disease	1.12 (0.98 – 1.28)	1.10 (0.89 – 1.36)	1.02 (1.01 – 1.04)	1.07*[1] (0.88 – 1.29)	1.22*[2] (1.03 – 1.45)
Acute Myocardial Infarction	1.34*[3] (1.00 – 1.78)	1.31*[3] (0.92 – 1.86)	1.09*[4] (0.89 – 1.33)	1.63*[3] (0.91 – 2.94)	1.28*[3] (0.88 – 1.85)
Arrhythmia	1.39 (1.13 – 1.72)	1.48 (1.03 – 2.13)	2.19*[5] (0.58 – 8.26)	1.32 (1.04 – 1.67)	1.43*[2] (1.19 – 1.73)
Heart Failure	1.33 (1.12 – 1.58)	1.06*[2] (1.05 – 1.07)	1.21*[6] (0.77 – 1.89)	1.39*[3] (1.01 – 1.91)	1.39 (1.12 – 1.73)
Stroke	1.17 (0.93 – 1.47)	1.04*[3] (1.03 – 1.05)	1.05*[2] (1.03 – 1.08)	1.11*[3] (0.65 – 1.88)	1.22 (0.91 – 1.62)

* HR: hazard ratio; CI: confidence interval; HCVDi: history of CVD indicator; GnRH agonists (reference group). History of CVD indicator was defined as any of the following 12 months prior to entering the cohort: any CVD event, hypertension, dyslipidaemia or diabetes.
*[1] UK was excluded due to low number of events for country-specific analysis.
*[2] Netherlands was excluded due to low number of events for country-specific analysis.
*[3] UK and the Netherlands were excluded due to low number of events for country-specific analysis.
*[4] UK, Belgium and the Netherlands were excluded due to low number of events for country-specific analysis.
*[5] Scotland, the Netherlands and France were excluded due to low number of events for country-specific analysis.
*[6] UK, Scotland and the Netherlands were excluded due to low number of events for country-specific analysis.

Men with PCa on GnRH antagonists had an increased risk of developing any CVD (HR = 1.22; 95% CI = 1.03-1.45), arrhythmia (HR = 1.39; 95% CI = 1.13-1.72) and HF (HR = 1.33; 95% CI = 1.12-1.58) compared to men on GnRH agonists. Stratification by HCVDi also showed an increased risk of developing arrhythmia (HR = 1.48; 95% CI = 1.03-2.13; Figure 13 (a)), HF (HR = 1.06; 95% CI = 1.05-1.07; Figure 13 (b)) and stroke (HR = 1.04; 95% CI = 1.03-1.05; Figure 13 (c)) for men on GnRH antagonists

with a HCVDi. For men who were on GnRH antagonists without a HCVDi, there was an increased risk of developing IHD (HR = 1.02; 95% CI = 1.01-1.04) and stroke (HR = 1.05; 95% CI = 1.03-1.08) compared to those on GnRH agonists.

Stratification by age showed an increased risk of developing any CVD (HR = 1.24; 95% CI = 1.04-1.48; Figure 14 (a)), IHD (HR = 1.22; 95% CI = 1.03-1.45; Figure 14 (b)), arrhythmia (HR = 1.43; 95% CI = 1.19-1.73; Figure 14 (c)) and HF (HR = 1.39; 95% CI = 1.12-1.73; Figure 14 (d)) in those aged ≥ 75 years.

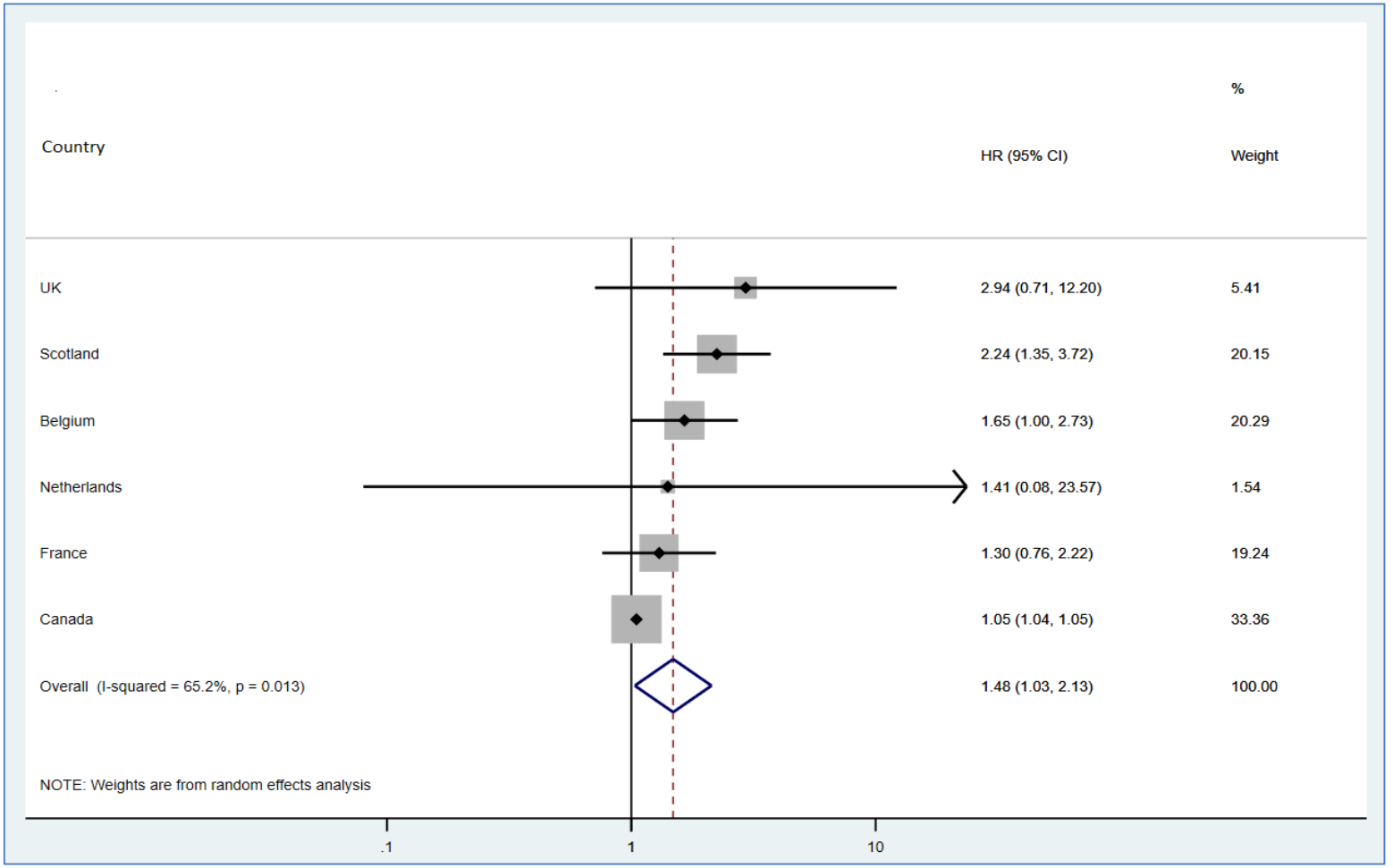

Figure 13 (a): *Pooled results from meta-analysis for PCa men with a HCVDi developing arrhythmia including UK, Scotland, Belgium, the Netherlands, France and Canada.*

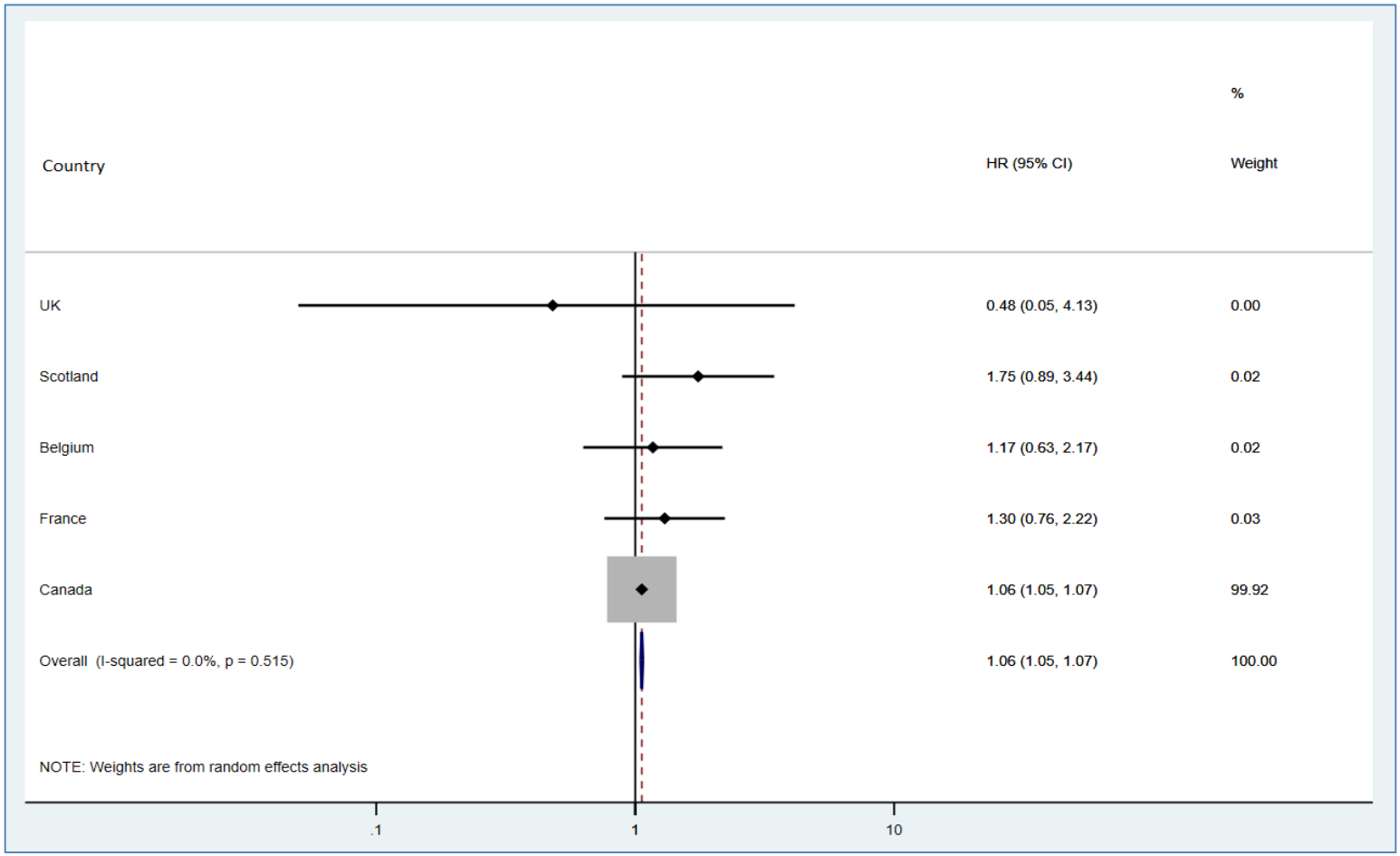

Figure 13 (b): *Pooled results from meta-analysis for PCa men with a HCVDi developing heart failure including UK, Scotland, Belgium, France and Canada.*

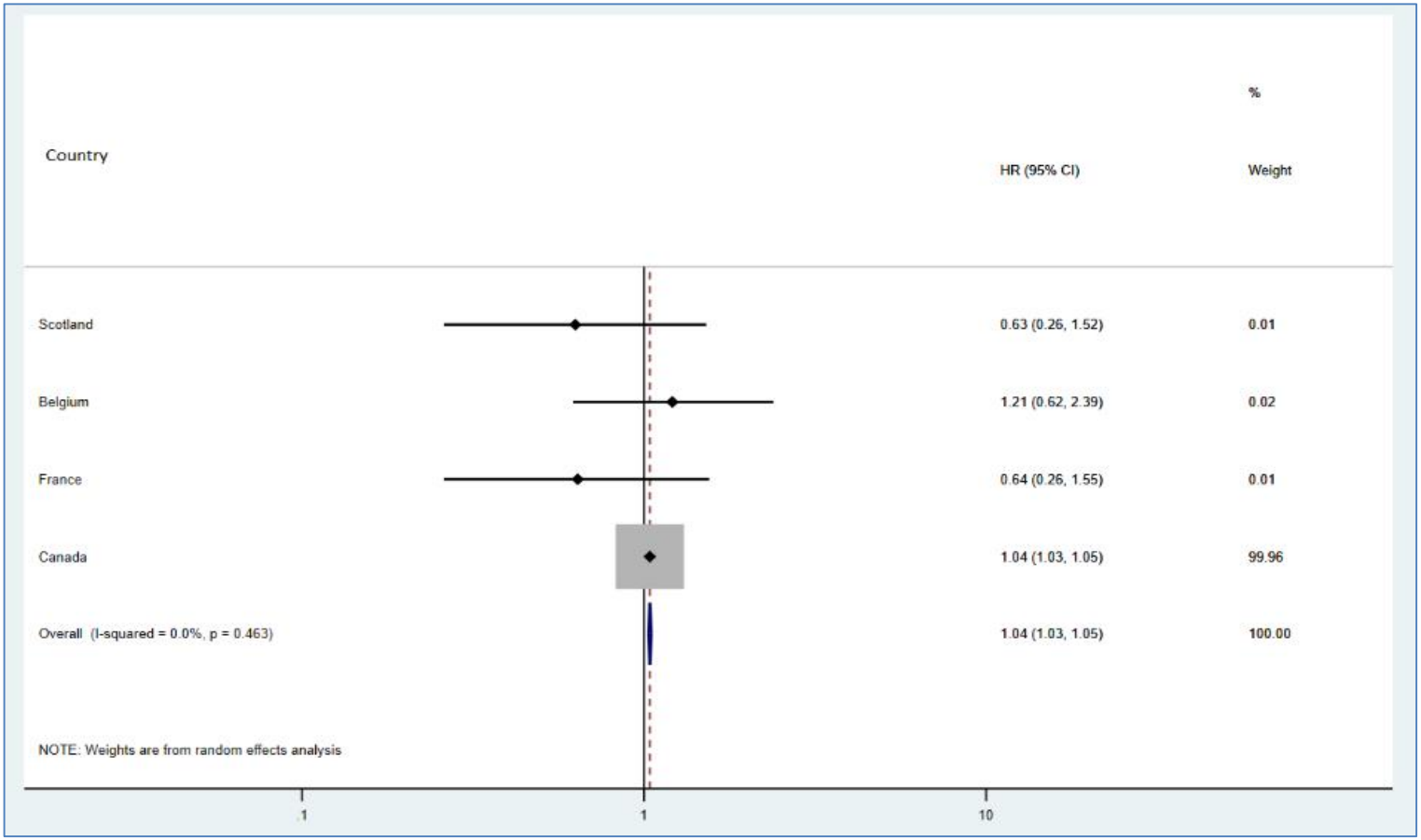

Figure 13 (c): *Pooled results from meta-analysis for PCa men with a HCVDi developing stroke including Scotland, Belgium, France and Canada.*

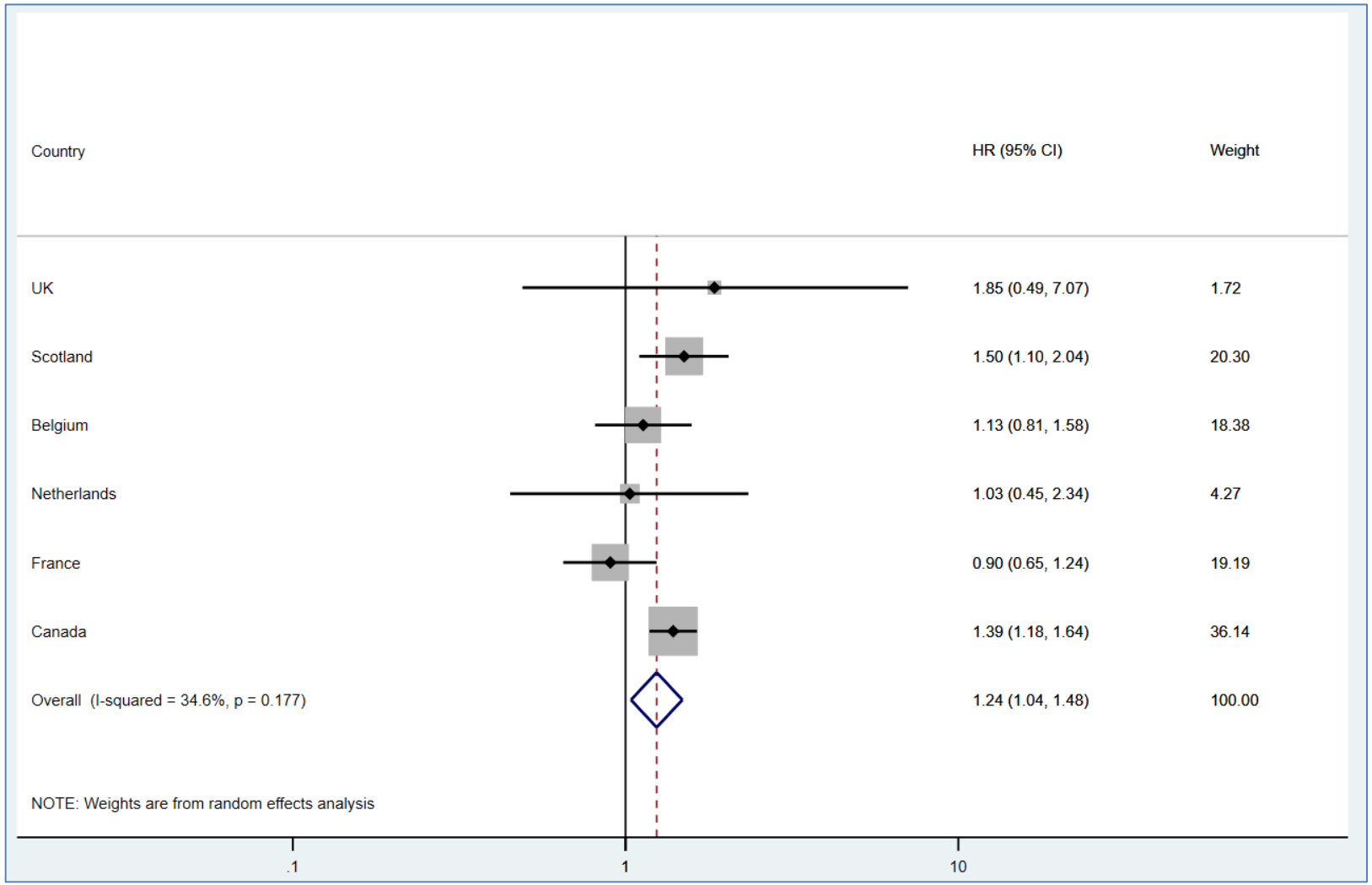

Figure 14 (a): *Pooled results from meta-analysis for PCa men aged ≥ 75 years developing any CVD including UK, Scotland, Belgium, the Netherlands, France and Canada.*

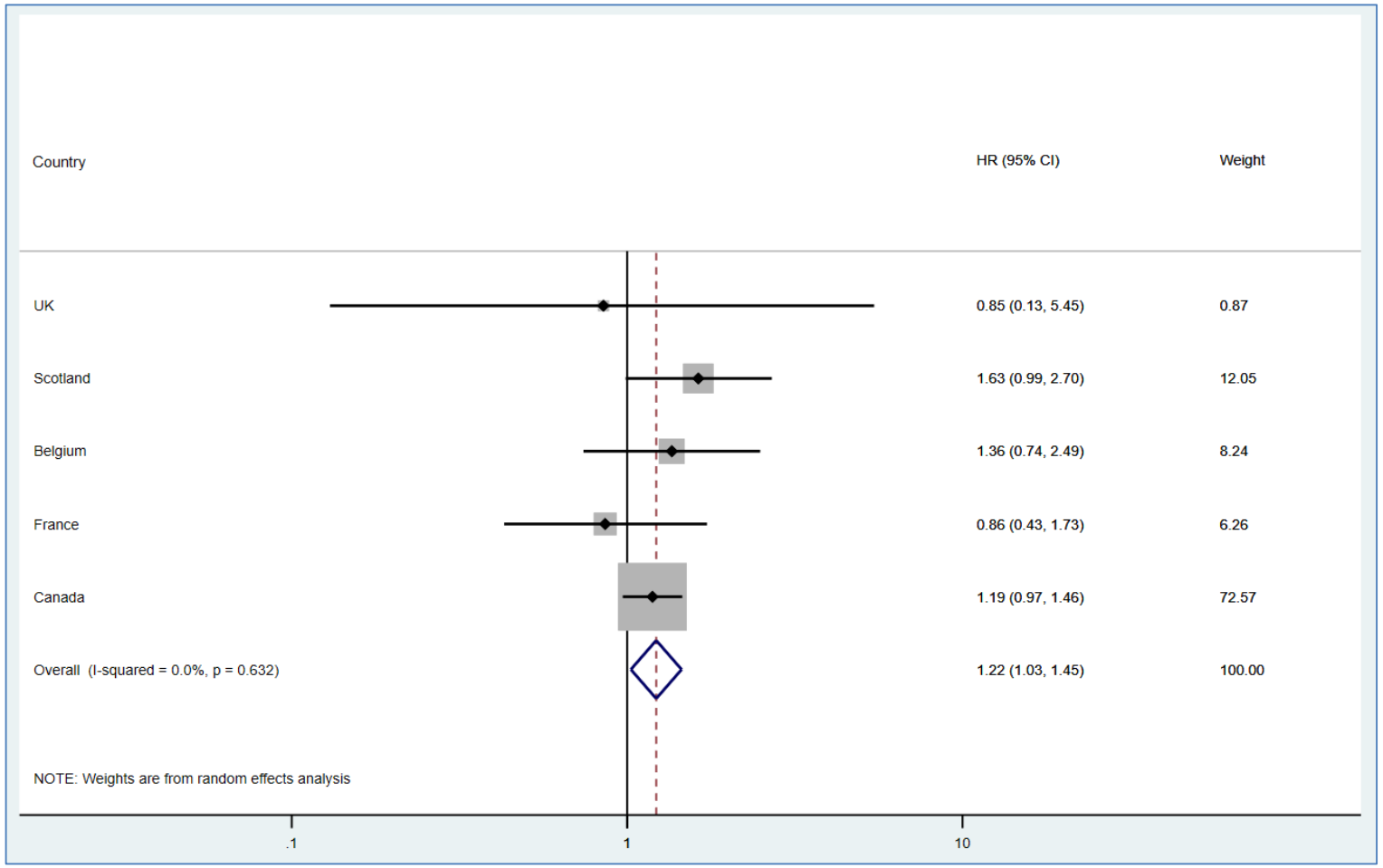

Figure 14 (b): *Pooled results from meta-analysis for PCa men aged ≥ 75 years developing ischaemic heart disease including UK, Scotland, Belgium, the Netherlands, France and Canada.*

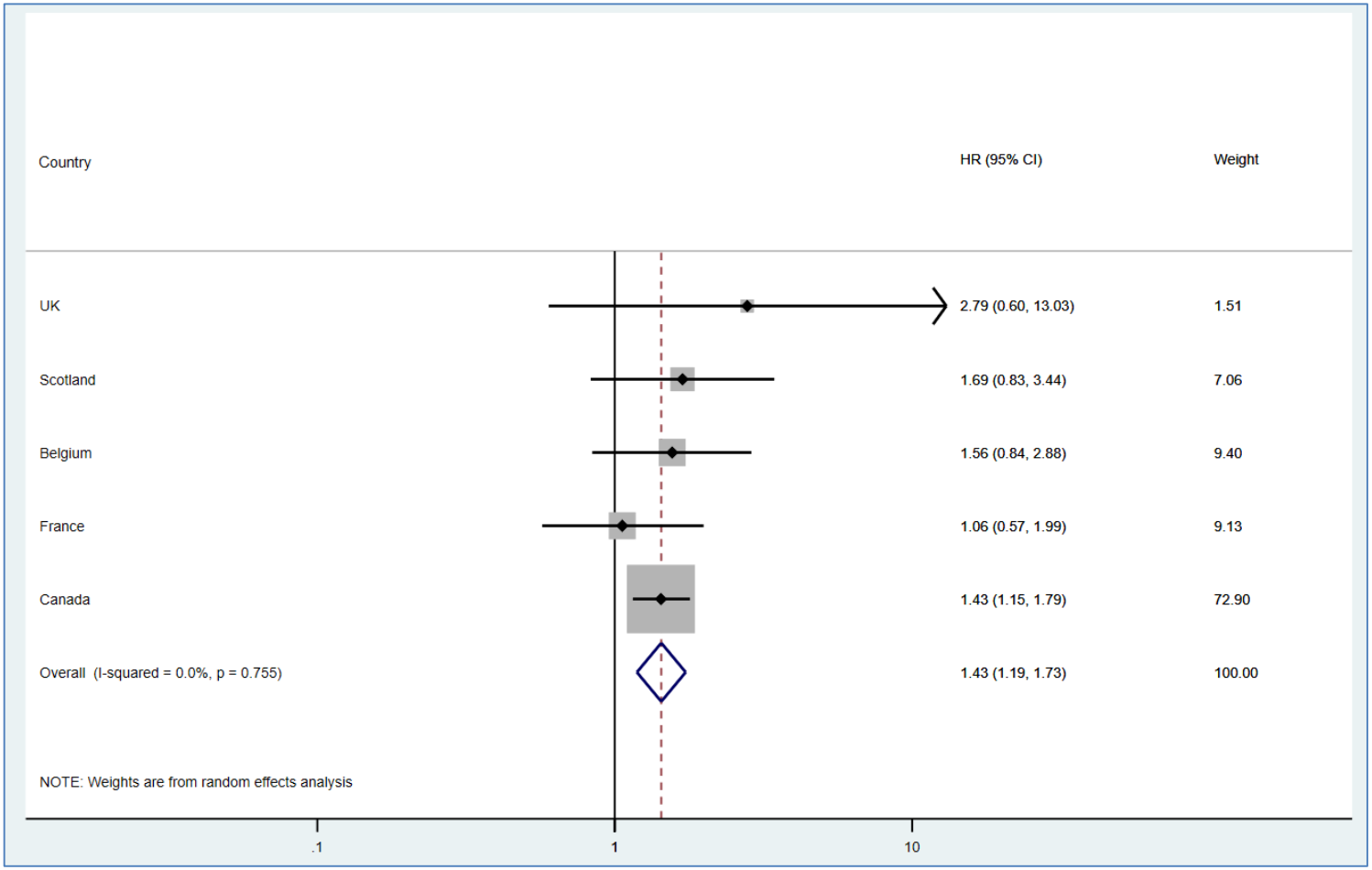

Figure 14 (c): *Pooled results from meta-analysis for PCa men aged ≥ 75 years developing arrhythmia including UK, Scotland, Belgium, the Netherlands, France and Canada.*

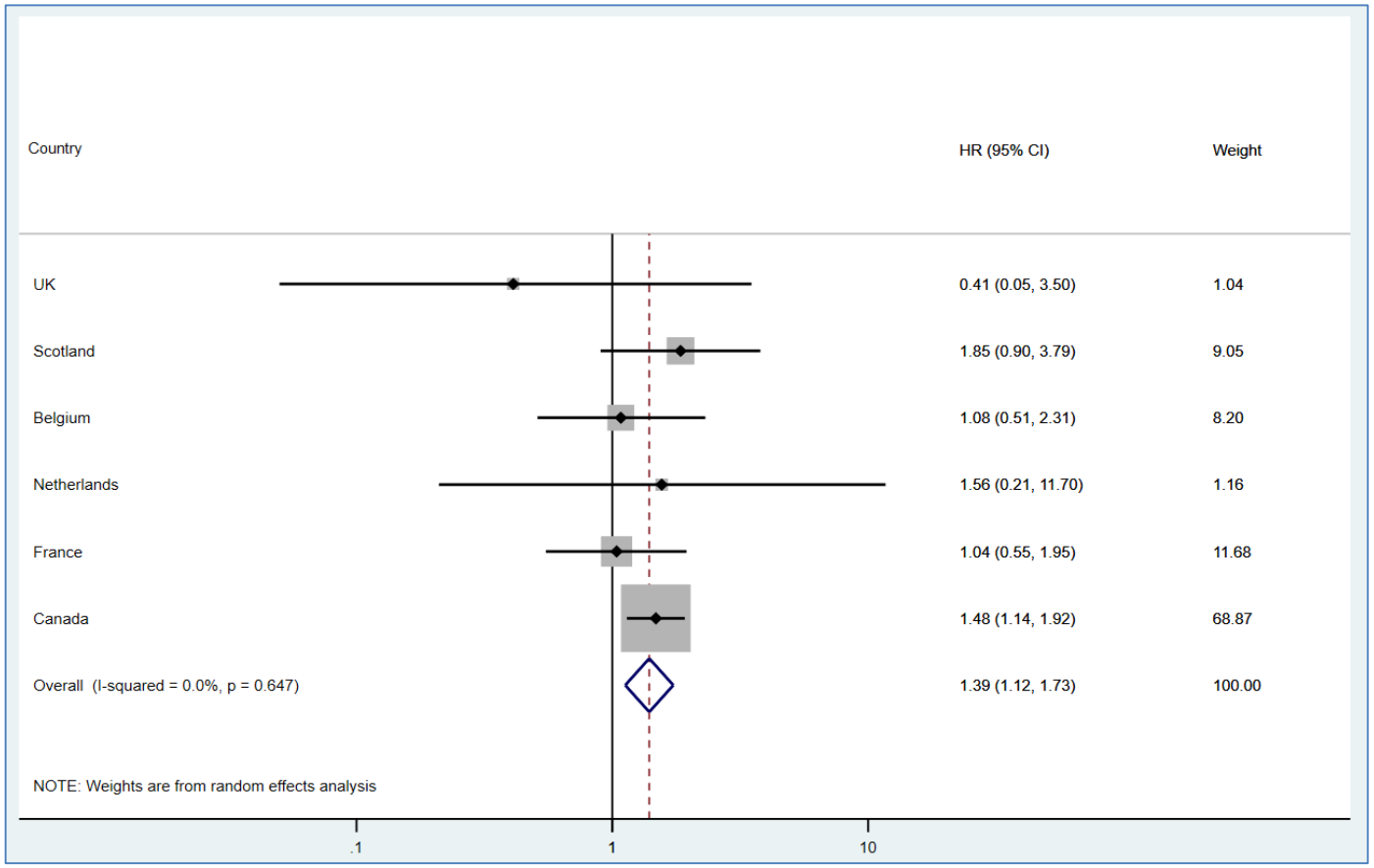

Figure 14 (d): *Pooled results from meta-analysis for PCa men aged ≥ 75 years developing heart failure including UK, Scotland, Belgium, the Netherlands, France and Canada.*

3.2.8.3.7 Sensitivity analyses

Sensitivity analyses excluding UK showed some differences (Table 13) in the results as compared to main analysis (Table 12). HR for all men remained similar in the sensitivity analysis excluding UK as compared to the main analysis. For men on GnRH antagonists, there was still an increased risk of developing any CVD (HR = 1.21; 95% CI = 1.01-1.43), arrhythmia (HR = 1.32; 95% CI = 1.14-1.53), HF (HR = 1.34; 95% CI = 1.12-1.59) and stroke (HR = 1.16; 95% CI = 0.91-1.49) as compared to men on GnRH agonists after excluding UK. For men on GnRH antagonists with a HCVDi, there was an increased risk of developing HF (HR = 1.06; 95% CI = 1.05-1.07) and stroke (HR = 1.04; 95% CI = 1.03-1.05) as compared to men on GnRH agonists, similar to the results in the main analysis. There was also an increased risk of developing IHD (HR = 1.02; 95% CI = 1.01-1.04) and stroke (HR = 1.05; 95% CI = 1.03-1.08) in men on GnRH antagonists without a HCVDi as compared to men on GnRH agonists, similar to the results in the main analysis. However, exclusion of UK also showed an increased risk of developing arrhythmia (HR = 1.06; 95% CI = 1.04-1.08) in men on GnRH antagonists with a HCVDi as compared to men on GnRH agonists. In men aged < 75 years and on GnRH antagonists, there was an increased risk of developing arrhythmia (HR = 1.30; 95% CI = 1.01-1.65) as compared to men on GnRH agonists. These results were similar to the results in the main analysis. Finally, in men aged ≥ 75 years and on GnRH antagonists, there was an increased risk of developing any CVD (HR = 1.23; 95% CI = 1.01-1.48), IHD (HR = 1.22; 95% CI = 1.03-1.46), arrhythmia (HR = 1.42; 95% CI = 1.17-1.72) and HF (HR = 1.41; 95% CI = 1.14-1.76) as compared to men on GnRH agonists. These results were similar to the results in the main analysis.

Table 13: *Hazard ratios from sensitivity analyses using random-effects meta-analytical model including different stratifications any CVD, ischaemic heart disease, acute myocardial infarction, arrhythmia, heart failure and stroke for Scotland, Belgium, the Netherlands, France and Canada.*

Outcome	HR for all men (95% CI)	HR for men with *HCVDi (95% CI)	HR for men without HCVDi (95% CI)	HR for men < 75 years (95% CI)	HR for men ≥ 75 years (95% CI)
Any CVD	1.21 (1.01 – 1.43)	1.20 (0.99 – 1.46)	1.04 (1.03 – 1.05)	1.21 (0.98 – 1.50)	1.23 (1.01 – 1.48)
Ischaemic Heart Disease	1.14 (0.97 – 1.34)	1.11*[1] (0.90 – 1.37)	1.02 (1.01 – 1.04)	1.07 (0.88 – 1.29)	1.22*[1] (1.03 – 1.46)
Acute Myocardial Infarction	1.34*[1] (1.00 – 1.78)	1.31*[1] (0.92 – 1.86)	1.09*[2] (0.89 – 1.33)	1.63*[1] (0.91 – 2.94)	1.28*[1] (0.88 – 1.85)
Arrhythmia	1.32 (1.14 – 1.53)	1.42 (0.99 – 2.04)	1.06*[3] (1.04 – 1.08)	1.30 (1.02 – 1.65)	1.42*[1] (1.17 – 1.72)
Heart Failure	1.34 (1.12 – 1.59)	1.06*[1] (1.05 – 1.07)	1.21*[4] (0.77 – 1.89)	1.39*[1] (1.01 – 1.91)	1.41 (1.14 – 1.76)
Stroke	1.16 (0.91 – 1.49)	1.04*[1] (1.03 – 1.05)	1.05*[1] (1.03 – 1.08)	1.11*[1] (0.65 – 1.88)	1.24 (0.93 – 1.65)

* HR: hazard ratio; CI: confidence interval; HCVDi: history of CVD indicator; GnRH agonists (reference group). History of CVD indicator was defined as any of the following 12 months prior to entering the cohort: any CVD event, hypertension, dyslipidaemia or diabetes

*[1] Netherlands was excluded due to low number of events for country-specific analysis.

*[2] Belgium and the Netherlands were excluded due to low number of events for country-specific analysis.

*[3] Scotland, the Netherlands and France were excluded due to low number of events for country-specific analysis.

*[4] Scotland and the Netherlands were excluded due to low number of events for country-specific analysis.

3.3 DISCUSSION

This is the first study to combine real world data from the UK, Scotland, Belgium, Netherlands, France and Canada to compare the risk of CVD following GnRH agonists and GnRH antagonists in men with PCa. This study shows contradictory results to what has been previously reported in meta-analyses of RCTs and observational studies. The modified ROBINS-I tool emphasised three main forms of biases for the current study design: misclassification of study variables, channeling or indication and unmeasured confounding. Pooled results from the six countries showed that men with PCa given GnRH antagonists with history of CVD event or a CVD indication had a 48% higher chance of developing arrhythmia, 6% higher chance of developing HF and 4% higher chance of developing stroke compared to men on GnRH agonists. Age stratification showed that men on GnRH antagonists aged ≥ 75 years had a 24% higher chance of developing any CVD and 39% higher chance of developing HF compared to men on GnRH agonists.

The methodological protocol for this study has been published already (122). The purpose of the methodological protocol was to reduce heterogeneity in the definitions for the study variables extracted from the six databases. In the protocol, a modified version of the ROBINS-I tool was used to assess the study design which emphasised three main forms of biases: misclassification of study variables, channeling or indication and unmeasured confounding. By following a standard protocol (122) to extract study variables from the different databases of the six countries, misclassification bias was avoided, to a certain extent.

Channeling bias is a term used to describe indication bias in pharmacoepidemiology and is one of the most common types of bias found in this setting. Channeling bias occurs when a physician prescribes specific drugs to patients with certain characteristics such as disease severity or age (158). Channeling bias was highlighted by the ROBINS-I tool in the study design phase of this study (Table 2). This means that GnRH antagonists may have been channelled to men with a prior CVD event or risk of CVD based on previous evidence (32). Although stratifying meta-analyses (stage 2) by HCVDi attempted to resolve channeling bias, it was impossible to fully avoid channeling bias in this study because no information for physician preferences for medications was available in the six countries.

The channeling bias in this observational setting may be addressed by the PRONOUNCE trial which is currently recruiting to compare risk of fatal or non-fatal CVD in 900 men with PCa receiving degarelix or leuprolide (GnRH agonist) as primary treatment over a year (137). However, the follow-up period for the PRONOUNCE trial is limited to a year, whereas the average median follow-up time (for six included countries) for this real world study is more than a year, allowing for the detection of CVD events occurring 12 months after treatment initiation.

The ROBINS-I tool highlighted some other evident and unavoidable biases associated with observational data such as uneven randomization distribution and unmeasured confounding (159). Unmeasured confounding occurs when certain factors may not be considered in analyses due to unavailability of data. For example, lifestyle factors are often not well-recorded in healthcare databases leading to an unmeasured confounding. Although the UK had data available on

some lifestyle (BMI, smoking status) and socio-economic (Townsend scores) factors, these variables were not added in the analytical models due to high percentage of missing data. Therefore, unmeasured confounding should be taken into consideration while interpreting the results of this study.

Preliminary findings from this study which included four countries (UK, Belgium, the Netherlands and France) showed a decreased risk of developing any CVD in men on GnRH antagonists with a HCVDi compared to GnRH agonists (presented at the European Association of Urology (EAU), 2018, section 9.3.1.1, Appendix) (160). The inconsistency in the preliminary results and the final results can be explained by the difference in methods used and the addition of Scotland and Canada. Whereas proportions of men developing a CVD event in both exposure groups were investigated (without including age or follow-up period in the models) in the EAU report (160), the current methodology pooled country-specific HRs with adjustment to age and follow-up period, thus accounting for the heterogeneity in study population and follow-up periods across the six countries.

Moreover, the potential differences in prescription and delivery of GnRH antagonists between UK, Scotland, Belgium, the Netherlands, France and Canada may have also influenced the results of the study. In the UK, GnRH antagonists were prescribed to men with advanced hormone-dependent PCa until 2016 (NICE CG175) (161-163). As a NICE review of GnRH antagonists was still in progress during the study period (2010-2016), only a few men were prescribed the new and expensive drug in the UK, explaining the low number of men on GnRH antagonists in the UK.

Similar non-specific guidelines on the definition of advanced stage and risk factors were followed by the other countries in this study (78, 164, 165). This may have left room for physicians to decide to prescribe GnRH antagonists to men with PCa based on PCa severity, risk factors for CVD and other comorbidities and previous evidence (32), thus introducing possible heterogeneity in prescription patterns of GnRH antagonists across the six countries. Stage of PCa may have also driven treatment decisions for men on the GnRH analogues thus influencing the results of this study. Since stage of PCa was not available across the six countries, it was not included in the analyses. In addition to these factors, adherence patterns to treatment regimens especially in men with a prior history of CVD may have also affected the results of this study because non-adherence to CVD medications is a leading risk factor for poor outcomes (166).

Interpretation of results for some subtypes of CVD is limited due to the data sources that they were obtained from. For example, AMI is usually recorded in an acute setting (such as a hospital) due to the acute nature of the event (167). Whereas Scotland, Belgium, the Netherlands, France and Canada used hospital settings to extract AMI, the UK had no AMI events in the GnRH antagonists' group which may be attributed to THIN's origin from primary healthcare settings. Although sensitivity analysis excluding UK showed no significant findings (Table 13), further assessment of dedicated hospital registries may better inform clinicians on the risk of AMI in PCa men on GnRH analogues.

One strength of this large prospective study cohort was the use of different types of databases (primary healthcare, secondary healthcare and claims databases) which ensured the inclusion of rare, adverse events that may not have been identified in a

RCT. However, it was difficult to fully homogenise study variables. Although a standard protocol eliminated some possible heterogeneity, the use of varied data sources from the six countries made it difficult to fully homogenise definitions for the study variables. For example, exclusive derivation of data from primary health care settings made the UK THIN database the most distinctive (i.e. use of readcodes instead of ICD-codes) of the six databases.

The potential for real world evidence is very large in the healthcare setting. Reconfiguration of data from different healthcare settings with regulatory supervision is required for real world data to achieve its full potential (168). Addressing heterogeneity across different institutional data is an issue at the centre of many Innovative Medicines Initiative 2 (IMI)'s ongoing collaborative projects such as the GetReal Initiative (11) and Prostate cancer dIagnOsis and treatmeNt Enhancement through the power of big data in EuRope (PIONEER) (169), which are part of the Big Data for Better Outcomes (BD4BO) (170). The collective aims of these projects are to combine and analyse 'big data' from databases across different institutions and countries into a single data platform using novel data analytical techniques. This would ensure the use of big data for research focused on disease-related and health-economic outcomes across different healthcare systems in a move towards standardising healthcare pathways across Europe (11, 169, 170). As a result, the current study was useful in understanding the challenges involved in the process of obtaining access to different data sources in different countries, homogenising study variables and developing methodologies that are most appropriate for the data available in the real world setting.

3.4 CONCLUSION

This large-scale real world study suggests that GnRH antagonists are also associated with an increased risk of CVD. However, results from the PRONOUNCE RCT may address the potential of indication bias in this observational setting even though the trial only covers a one-year follow-up period.

4. CHAPTER IV – ADHERENCE TO GNRH AGONISTS IN PROSTATE CANCER IN SWEDEN

Chapter IV introduces the concept of medication adherence and investigates patterns of adherence to GnRH agonists in men with PCa in Sweden. Adherence means the resolve a patient requires to follow their course of therapy and adherence to a treatment regimen is the primary determinant of the success of that treatment. The loss of adherence to medication is a global concern that has medical and economic consequences which makes it an important area of research, particularly to improve clinical outcomes of a treatment (107-109).

4.1 BACKGROUND

ADT is the standard form of treatment for men with advanced PCa. Considering that a large proportion of men diagnosed with PCa may remain on ADT for the rest of their PCa treatment, there is a need to understand factors related to adherence to ADT (6). No study has fully investigated patterns of adherence to GnRH agonists, the most common ADT in men with PCa. We assessed this using data from PCBaSe^{Traject} version 4.0 (171).

Previous studies in breast cancer have reported side-effects to be a major cause for non-adherence to ADT. 46% women who underwent hormonal therapy for breast cancer withdrew from their treatment due to unwanted side-effects associated with the hormonal therapy (172). Side-effects associated with prolonged use of GnRH agonists such as; fatigue, hot flushes, low bone density (leading to increased risk of

fractures) and even psychological issues may also be a factor contributing to non-adherence for men on hormone therapy for PCa (114, 115).

Intermittent GnRH agonists may be given to some men with PCa to minimise the side-effects attributed to the medication while maintaining anti-tumour efficacy (173, 174). Active treatment periods during an intermittent regimen may be separated by periods without any form of treatment. These active treatment periods by GnRH agonists may last for 6-9 months or until a PSA nadir of < 4 μg/ml has been reached (175).

Although one study has highlighted that there is an issue of non-adherence to GnRH agonists in men with PCa (176), no studies in the literature have fully investigated patterns of adherence to GnRH agonists in PCa. Therefore, the aim of this study was to identify patterns influencing adherence to GnRH agonists in men with PCa over 3 years in PCBaSe^{Traject}.

4.2 METHODS

4.2.1 Study population

The National Quality Register on Prostate Cancer of Sweden (NPCR) is linked to other healthcare registries and demographic databases by PCBaSe (177, 178). Healthcare registries such as the Swedish Cancer Registry, the Cause of Death Register, the Prescribed Drug Register and the National Patient Register are linked to NPCR by PCBaSe using the unique Swedish Personal Identity Number (171). NPCR

includes information on tumour stage, Gleason grading, serum level PSA and primary treatment for PCa (177).

PCBaSe has undergone a number of extensions with more cases, longer follow-up, family history of PCa and a selection of men free of PCa at the time of sampling (PCBaSe 2.0), with the latest version (PCBaSe^{Traject}, version 4.0) including men diagnosed with between 1998-2016 (177, 178). This study included men with PCa who initiated GnRH agonists between 2006-2013.

Recommendations for PCa treatment during this study period were set by regional clinical care guidelines based on national recommendations from the National Board of Health and Welfare in Sweden. The guidelines stated that once castration by ADT is initiated, it should not be discontinued (119).

4.2.2 Exposures

Men with PCa who started GnRH agonists between 2006-2013 were included in the study. Men with PCa on GnRH agonists were divided into two treatment groups: primary and secondary. Primary GnRH agonists was defined as the first form of PCa treatment. Secondary GnRH agonists was defined as men who received other forms of PCa treatments prior to GnRH agonists. Men entered the study 45 days (run-in period) following initiation of GnRH agonists and exited at 3 years (and 6 years for sensitivity analysis). 45 days was used as a run-in period to avoid overestimating adherence 90 days' injection interval was the most commonly prescribed GnRH agonists (11.25 mg) in PCBaSe^{Traject}. Only men who had at least a 3-year follow-up were considered because men with shorter follow-up may show better adherence

to GnRH agonists, thus overestimating adherence in this group of men. A detailed description of the inclusion and exclusion criteria can be found in Figure 15.

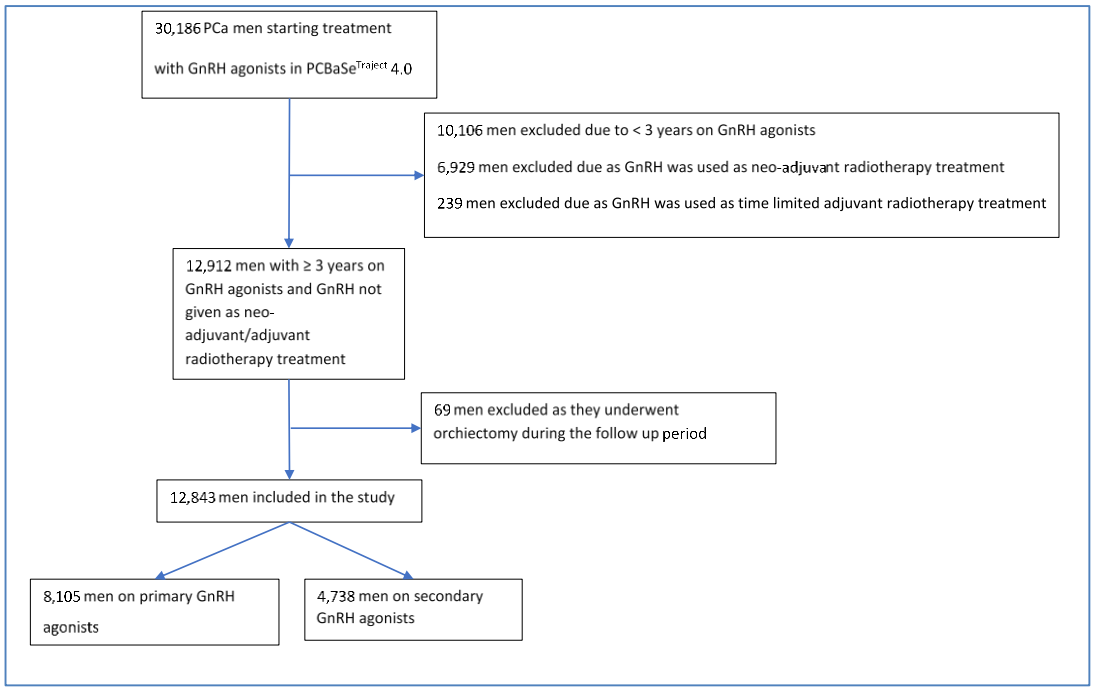

Figure 15: *Consort diagram showing the inclusion and exclusion criteria used to select men with PCa on GnRH agonists from PCBaSe.*

4.2.3 Outcomes

A binary outcome of adherent versus non-adherent was quantified by MPR (179), with a MPR of ≥ 80% defined as adherent and < 80% as non-adherent. MPR was used to quantify adherence by using the following equation:

$$\frac{\text{Days of prescribed/dispensed supply}}{\text{Number of days in the study period}} \text{ X } 100\ \%$$

4.2.4 Other study variables

In addition to the exposures and the outcomes, age, injection intervals, risk group at diagnosis, change in Charlson Comorbidity Index (CCI) since diagnosis, year of GnRH agonists' initiation, prior PCa treatment and civil status were extracted from PCBaSe (Table 14).

Table 14: *Detailed definitions for other study variables extracted from PCBaSe^{Traject} for this study.*

Study Variables	Data Extraction in PCBaSe^{Traject}
Age	Age was calculated using date of births for men on GnRH agonists. The age categories used were: ≤ 65 years, 66-74 years, 75-84 years and ≥ 85 years.
Injection Intervals	Injection intervals was defined as 90 days, 180 days, 365 days and mixed. The dosages were defined by the defined daily dose (DDD) number in PCBaSe^{Traject}. The DDD is defined as the average maintenance dose per day assumed for a drug for its indicated use (180). For DDD < 55, the injection interval was defined as 30 days, DDD of 55-99 was defined as 90 days, 100-199 was defined as 180 days and DDD ≥ 200 was defined as 365 days. Low number of men in the 30 days' injection interval group (primary GnRH agonists = 23; secondary GnRH agonists = 19) resulted in merging the 30 days' injection interval group with the 90 days' injection interval group. The mixed group included men who started GnRH agonists therapy at a 'short-acting depot' and proceeded to a 'long-acting depot' over the course of three years.
Risk Group at Diagnosis	Risk group at diagnosis in PCBaSe^{Traject} was defined as low risk, medium or intermediate risk, high risk, regionally metastatic and distant metastatic.
Change in Charlson Comorbidity Index	Charlson Comorbidity Index (CCI) was first developed in the 1980's as a weighted index accounting for the number and seriousness of comorbidities and classifying them to estimate risk of death from these comorbidities in longitudinal studies (181). Change in CCI for this study was calculated as a difference between CCI at diagnosis and CCI at 3 years following GnRH agonists. It was defined as no change, change by 1, change by 2, change by 3 and change by ≥ 4.
Year of GnRH agonists' Initiation	Year of GnRH agonists' initiation was defined from date of first prescription of GnRH agonists for men with PCa in PCBaSe^{Traject}.

Prior PCa Treatment	Prior PCa treatment was defined as those who had received PCa treatments such as deferred treatment, anti-androgens, radical prostatectomy only (i.e. without radiotherapy), radiotherapy < 1 year after radical prostatectomy and radiotherapy ≥ 1 years after radical prostatectomy.
Primary and Secondary GnRH agonists	Prior PCa treatment was used to differentiate between men who received GnRH agonists as primary for their PCa treatment and those who had received GnRH agonists as secondary treatment. Secondary treatment also included men who had received more than one form of PCa treatment prior to GnRH agonists' initiation. All analyses were conducted separately for primary and secondary GnRH agonists.
Civil Status	Civil status was available for all men included in the study and was defined as those who were single and married at study entry.

* ATC: Anatomical Therapeutic Chemical; DDD: Defined Daily Dose; CCI: Charlson Comorbidity Index.

4.3 ANALYSIS

4.3.1 Main analysis

Multivariable logistic regression analyses were conducted separately for men with PCa receiving primary and secondary GnRH agonists with the odds in the regression models expressing the odds of being adherent. A MPR of ≥ 80% was defined as adherent and < 80% defined as non-adherent. Models for primary GnRH agonists included: age, injection intervals, risk group at diagnosis, change in CCI since diagnosis, year of GnRH agonists' initiation and civil status. For secondary GnRH agonists the following variables were included: age, change in CCI since diagnosis, prior PCa treatment and civil status. Adherence was defined over 3 years following GnRH agonists.

The distinction between flare protection and CAB (defined in chapter III) was difficult to make in PCBaSe^{Traject} because anti-androgens were only recorded

intermittently in the database and no precise definition could be made. Therefore, flare-protection and CAB were combined as anti-androgens given to men with PCa as prior PCa treatment.

4.3.2 Sensitivity analyses

Adherence over a longer follow-up (6 years) was also calculated for men with PCa who were on GnRH agonists for 6 years in PCBaSe^{Traject}, thus including a higher proportion of long-time survivors on GnRH agonists. Multivariable logistic regression was conducted with a MPR of ≥ 80% being adherent and < 80% being non-adherent.

The chance of non-adherent men with a MPR of < 80% being on an intermittent regimen for GnRH agonists was explored in a sensitivity analysis. The reason for low MPR observed in these men may be due to an intermittent treatment regimen (common in men treated with GnRH agonists) or their decision to quit the treatment for various reasons. An intermittent treatment regimen for GnRH agonists was determined as a gap of < 9 months between the last and second last prescriptions in PCBaSe^{Traject} (174). Men on GnRH agonists with ≥ 9 months' gap were defined as having ended their treatment and classed as non-adherent. Once the outcomes (adherent vs non-adherent) were reclassified after considering the intermittent treatment regimen, the logistic regression models were repeated for primary and secondary GnRH agonists, with a MPR of ≥ 80% being adherent and < 80% being non-adherent.

Evidence suggests that testosterone levels may remain suppressed for a longer period of time after treatment with GnRH agonists than previously thought (182).

To account for this evidence, a sensitivity analysis was conducted by running the logistic regression models again using redefined outcomes. The redefined outcomes used a MPR of $\geq$ 50% for being adherent and < 50% for being non-adherent.

4.4 RESULTS

4.4.1 Main analysis

8,105 men with PCa starting on primary GnRH agonists and 4,738 men with PCa starting on secondary GnRH agonists between 2006 and 2013 from PCBaSe were determined to be eligible for the study (Figure 15).

Table 15 shows patient characteristics for the study after 3 years on GnRH agonists. 79% were adherent on primary GnRH agonists after 3 years. 71% were adherent on secondary treatment after 3 years. The mean age was similar for primary (adherent = 77, SD = 7.8; non-adherent = 76, SD = 8.4) and secondary (adherent = 76, SD = 7.8; non-adherent = 75, SD = 8.0) GnRH agonists.

Table 15: *Characteristics for men with PCa on primary and secondary GnRH agonists after 3 years.*

Patient Characteristics	3 Years			
	Primary GnRH agonists		Secondary GnRH agonists	
	Adherent (%)	Non-adherent (%)	Adherent (%)	Non-adherent (%)
n	6432 (79.4)	1673 (20.6)	3376 (71.3)	1362 (28.8)
Age (Years)				
Mean	76.5	75.9	76.0	75.1
SD	7.8	8.4	7.8	8.0
Age Groups (Years)				
≤ 65	612 (9.5)	190 (11.4)	348 (10.3)	185 (13.6)
66-74	1719 (26.7)	465 (27.8)	999 (29.6)	419 (30.8)
75-84	3169 (49.3)	762 (45.6)	1580 (46.8)	599 (44.0)
≥ 85	932 (14.5)	256 (15.3)	449 (13.3)	159 (11.7)
***Injection Interval (Days)**				
90	4519 (70.3)	1404 (83.9)	2388 (70.7)	1135 (83.3)
180	374 (5.8)	46 (2.8)	203 (6.0)	33 (2.4)
365 (Implant)	648 (10.1)	66 (4.0)	347 (10.3)	62 (4.6)
Mixed	891 (13.9)	149 (8.9)	438 (13.0)	116 (8.5)
Missing	0	8 (0.5)	0	16 (1.2)
Risk Groups at Diagnosis				
Low Risk	98 (1.5)	65 (3.9)	437 (12.9)	244 (17.9)
Medium Risk	695 (10.8)	226 (13.5)	1003 (29.7)	404 (29.7)
High Risk	2305 (35.8)	638 (38.1)	1332 (39.5)	503 (36.9)
Regional Metastasis	1064 (16.5)	273 (16.3)	402 (11.9)	135 (9.9)
Distant Metastasis	2235 (34.8)	457 (27.3)	164 (4.9)	56 (4.1)
Missing	35 (0.5)	14 (0.8)	39 (1.1)	20 (1.5)
Prior PCa Treatment				
*Deferred Treatment	N/A	N/A	1509 (44.7)	641 (47.1)
Anti-androgens	N/A	N/A	649 (19.2)	198 (14.5)
Radical Prostatectomy only	N/A	N/A	269 (8.0)	148 (10.9)
Radiotherapy	N/A	N/A	719 (21.3)	279 (20.5)
Radiotherapy after Radical Prostatectomy				
< 1 year	N/A	N/A	109 (3.2)	54 (4.0)
≥ 1 year	N/A	N/A	121 (3.6)	42 (3.1)

Change in *CCI since CCI at diagnosis				
No change	4636 (72.1)	1244 (74.4)	2485 (73.6)	1014 (74.5)
Change by 1	920 (14.3)	223 (13.3)	439 (13.0)	170 (12.5)
Change by 2	533 (8.3)	132 (7.9)	288 (8.5)	115 (8.4)
Change by 3	215 (3.3)	47 (2.8)	102 (3.0)	35 (2.6)
Change by ≥ 4	128 (2.0)	27 (1.6)	62 (1.8)	28 (2.1)
Civil Status				
Single	2374 (36.9)	649 (38.8)	1061 (31.4)	472 (34.7)
Married	4058 (63.1)	1023 (61.2)	2315 (68.6)	890 (65.4)
Missing	0	1 (0.1)	0	0
Year of GnRH agonists' Initiation				
2006-2007	2026 (31.5)	558 (33.4)	842 (24.9)	344 (25.3)
2008-2009	1747 (27.2)	471 (28.2)	869 (25.7)	336 (24.7)
2010-2011	1474 (22.9)	362 (21.6)	894 (26.5)	328 (24.1)
2012-2013	1185 (18.4)	282 (16.9)	771 (22.8)	354 (26.0)

* Deferred treatment includes men who underwent active surveillance and watchful waiting; N/A: Not applicable; CCI: Charlson Comorbidity Index; Injection interval at 90 days included 7 adherents (primary = 6, secondary = 1) and 35 non-adherent (primary = 17, secondary = 18) PCa men given 30 days dosages due to low number in the 30 days group.

4.4.1.1 Primary GnRH agonists

Table 16 outlines the results of a logistic regression on primary GnRH agonists. Increased adherence was observed in the age-groups 66-74 (OR = 1.27; 95% CI = 1.04-1.54) and 75-84 (OR = 1.49; 95% CI = 1.23-1.81) compared to group ≤ 65 years. Men with PCa on the 365 days' hydrogel implant were three times more likely to be adherent than men on 90 days' injection interval (OR = 3.29; 95% CI = 2.52-4.30).

Table 16: *Logistic regression analyses showing odds ratios (OR) and 95% confidence intervals (CI) for men with PCa after 3 years on primary GnRH agonists.*

Patient Characteristics	3 Years			
	Univariate		Multivariable	
	OR	95% CI	OR	95% CI
Age Groups (Years)				
≤ 65	1.00	Ref.	1.00	Ref.
66-74	1.15	0.95-1.39	1.27	1.04-1.54
75-84	1.29	1.08-1.55	1.49	1.23-1.81
≥ 85	1.13	0.91-1.40	1.24	0.99-1.56
***Injection interval (Days)**				
90	1.00	Ref.	1.00	Ref.
180	2.53	1.85-3.45	2.61	1.89-3.59
365 (Implant)	3.05	2.35-3.96	3.29	2.52-4.30
Mixed	1.86	1.55-2.23	1.93	1.60-2.32
Risk Groups at Diagnosis				
Low Risk	1.00	Ref.	1.00	Ref.
Medium Risk	2.04	1.44-2.89	1.88	1.32-2.69
High Risk	2.40	1.73-3.32	2.34	1.68-3.26
Regional Metastasis	2.59	1.84-3.63	2.69	1.90-3.82
Distant Metastasis	3.24	2.33-4.51	3.56	2.54-5.00
Change in *CCI since CCI at diagnosis				
No change	1.00	Ref.	1.00	Ref.
Change by 1	1.11	0.94-1.30	1.12	0.95-1.33
Change by 2	1.08	0.89-1.32	1.12	0.91-1.38
Change by 3	1.23	0.89-1.69	1.19	0.86-1.66
Change by ≥ 4	1.27	0.84-1.94	1.21	0.79-1.86
Civil Status				
Single	1.00	Ref.	1.00	Ref.
Married	1.08	0.97-1.21	1.08	0.97-1.21
Year of GnRH agonists' initiation				
2006-2007	1.00	Ref.	1.00	Ref.
2008-2009	1.02	0.89-1.17	0.86	0.75-1.00
2010-2011	1.12	0.97-1.30	0.88	0.75-1.03
2012-2013	1.16	0.99-1.36	0.85	0.72-1.01

* OR: Odds ratio; CI: Confidence interval; Non-adherent (reference group); CCI: Charlson Comorbidity Index; Injection interval at 90 days included 7 adherents (primary = 6, secondary = 1) and 35 non-adherent (primary = 17, secondary = 18) PCa men given 30 days' dosages due to low number in the 30 days' group.

4.4.1.2 Secondary GnRH agonists

Table 17 shows the results of a logistic regression for secondary GnRH agonists. Increased age was associated with increased adherence in men who were given GnRH agonists as a secondary treatment for their PCa with the most adherent in men aged ≥ 85 years (OR = 1.65; 95% CI = 1.23-2.22). An increased adherence was observed in men who were given anti-androgens (OR = 1.50; 95% CI = 1.23-1.82) and radiotherapy (OR = 1.35; 95% CI =1.11-1.64) as primary treatment prior to GnRH agonists' initiation compared to deferred treatment. Men who were given radiotherapy ≥ 1 year after undergoing radical prostatectomy were also more likely to be adherent to secondary GnRH agonists compared to no radiotherapy (OR = 1.54; 95% CI = 1.04-2.28).

Table 17: *Univariate and multivariable logistic regression analyses showing odds ratios (OR) and 95% confidence intervals (CI) for men with PCa after 3 years on secondary GnRH agonists.*

Patient Characteristics	3 Years			
	Univariate		Multivariable	
	OR	95% CI	OR	95% CI
Age Groups (Years)				
≤ 65	1.00	Ref.	1.00	Ref.
66-74	1.27	1.03-1.57	1.27	1.02-1.58
75-84	1.40	1.15-1.72	1.46	1.16-1.84
≥ 85	1.50	1.16-1.94	1.65	1.23-2.22
Injection Interval (Days)				
90	1.00	Ref.	1.00	Ref.
80	2.92	2.01-4.25	2.83	1.95-4.13
365 (Implant)	2.66	2.01-3.52	2.65	2.00-3.51
Mixed	1.79	1.45-2.23	1.82	1.46-2.26
Change in *CCI since CCI at diagnosis				
No change	1.00	Ref.	1.00	Ref.
Change by 1	1.05	0.87-1.28	1.05	0.86-1.27
Change by 2	1.02	0.81-1.28	0.99	0.78-1.25
Change by 3	1.19	0.80-1.76	1.15	0.77-1.71
Change by ≥ 4	0.90	0.57-1.42	0.84	0.53-1.34
Civil Status				
Single	1.00	Ref.	1.00	Ref.
Married	1.16	1.01-1.32	1.15	1.00-1.32
Prior PCa Treatment				
*Deferred Treatment	1.00	Ref.	1.00	Ref.
Anti-androgens	1.39	1.16-1.67	1.50	1.23-1.82
Radical Prostatectomy only	0.77	0.62-0.96	0.91	0.71-1.67
Radiotherapy	1.09	0.93-1.29	1.35	1.11-1.64
Radiotherapy < 1 year after Radical Prostatectomy	0.86	0.61-1.20	1.17	0.81-1.71
Radiotherapy ≥ 1 year after Radical Prostatectomy	1.22	0.85-1.76	1.54	1.04-2.28

* OR: Odds ratio; CI: Confidence interval; Non-adherent (reference group); Deferred treatment includes men who underwent active surveillance and watchful waiting; CCI: Charlson Comorbidity Index; Injection interval at 90 days included 7 adherent (primary = 6, secondary = 1) and 35 non-adherent (primary = 17, secondary = 18) PCa men given 30 days dosages due to low number in the 30 days group.

4.4.2 Sensitivity analyses

4.4.2.1 Longer Study Period

After 6 years on GnRH agonists, 3,611 men with PCa were on primary treatment and 1,967 were on secondary treatment (Table 18).

***Table 18**: Patient characteristics for men with PCa on primary and secondary GnRH agonists after 6 years.*

Patient Characteristics	6 Years			
	Primary GnRH Agonists		Secondary GnRH agonists	
	Adherent (%)	Non-adherent (%)	Adherent (%)	Non-adherent (%)
n	2636 (73.0)	975 (27.0)	1232 (62.6)	735 (37.4)
Age (Years)				
Mean	75.5	74.8	75.2	74.0
SD	7.2	7.9	7.3	7.7
Age Groups (Years)				
≤ 65	254 (9.6)	132 (13.5)	139 (11.3)	115 (15.7)
66-74	797 (30.2)	296 (30.4)	389 (31.6)	245 (33.3)
75-84	1342 (50.9)	444 (45.5)	598 (48.5)	325 (44.2)
≥ 85	243 (9.2)	103 (10.6)	106 (8.6)	50 (6.8)
***Injection Interval (Days)**				
90	1752 (66.5)	797 (81.7)	832 (67.5)	606 (82.5)
180	88 (3.3)	18 (1.9)	50 (4.1)	8 (1.1)
365 (Implant)	233 (8.8)	38 (3.9)	92 (7.5)	38 (5.2)
Mixed	563 (21.4)	118 (12.1)	258 (20.9)	77 (10.5)
Missing	0	4 (0.4)	0	6 (0.8)
Risk Groups at Diagnosis				
Low Risk	61 (2.3)	53 (5.4)	172 (13.9)	134 (18.2)
Medium Risk	382 (14.5)	170 (17.4)	394 (32.0)	200 (27.2)
High Risk	1003 (38.1)	382 (39.2)	466 (37.8)	286 (38.9)
Regional Metastasis	449 (17.0)	163 (16.7)	133 (10.8)	81 (11.0)
Distant Metastasis	724 (27.5)	201 (20.6)	53 (4.3)	24 (3.3)

Missing	17 (0.6)	6 (0.6)		
Prior PCa Treatment				
*Deferred Treatment	N/A	N/A	615 (49.9)	343 (46.7)
Anti-androgens	N/A	N/A	213 (17.3)	73 (9.9)
Radical Prostatectomy only	N/A	N/A	108 (8.8)	77 (10.5)
Radiotherapy	N/A	N/A	218 (17.7)	185 (25.2)
Radiotherapy < 1 year after Radical Prostatectomy	N/A	N/A	41 (3.3)	36 (4.9)
Radiotherapy ≥ 1 year after Radical Prostatectomy	N/A	N/A	37 (3.0)	21 (2.9)
Change in *CCI since CCI at diagnosis				
No change	1536 (58.3)	577 (59.2)	733 (59.5)	454 (61.8)
Change by 1	522 (19.8)	166 (17.0)	211 (17.1)	140 (19.1)
Change by 2	322 (12.2)	129 (13.2)	150 (12.2)	75 (10.2)
Change by 3	146 (5.5)	56 (5.7)	82 (6.7)	39 (5.3)
Change by ≥ 4	110 (4.2)	47 (4.8)	56 (4.6)	27 (3.7)
Civil Status				
Single	903 (34.3)	365 (37.4)	352 (28.6)	240 (32.7)
Married	1733 (65.7)	610 (62.6)	880 (71.4)	495 (67.4)
Year of GnRH agonists' initiation				
2006-2007	1056 (40.1)	433 (44.4)	456 (37.0)	272 (37.0)
2008-2009	851 (32.3)	283 (29.0)	403 (32.7)	232 (31.6)
2010-2011	729 (27.7)	259 (26.6)	373 (30.3)	231 (31.4)
2012-2013	0	0	0	0

* OR: Odds ratio; CI: Confidence interval; Non-adherent (reference group); Deferred treatment includes men who underwent active surveillance and watchful waiting; N/A: Not applicable; CCI: Charlson Comorbidity Index; Injection interval at 90 days included PCa men given 30 days dosages due to low number in the 30 days group.

4.4.2.1.1 Primary GnRH agonists

After 6 years on GnRH agonists, men with PCa aged 66-74 (OR = 1.60; 95% CI = 1.23-2.07) and 75-84 (OR = 1.88; 95% CI = 1.45-2.42) showed an increased adherence compared to men with PCa aged ≤ 65 years (Table 19). Increased adherence was also observed with increased injection intervals (180 days OR = 2.18; 95% CI = 1.30-3.67; 365 days OR = 2.94; 95% CI = 2.03-4.25 and mixed OR = 2.27; 1.82-2.83, as compared to 90 days' injection intervals), increased risk groups at diagnosis and change in CCI by 1 compared to no change in CCI in the 3 years.

Table 19: *Univariate and multivariable logistic regression analyses showing odds ratios (OR) and 95% confidence intervals (CI) for men with PCa after 6 years on primary GnRH agonists.*

Patient Characteristics	6 Years			
	Univariate		Multivariable	
	OR	95% CI	OR	95% CI
Age Groups (Years)				
≤ 65	1.00	Ref.	1.00	Ref.
66-74	1.40	1.09-1.80	1.60	1.23-2.07
75-84	1.57	1.24-1.99	1.88	1.45-2.42
≥ 85	1.23	0.90-1.67	1.37	0.98-1.91
***Injection interval (Days)**				
90	1.00	Ref.	1.00	Ref.
180	2.22	1.33-3.72	2.18	1.30-3.67
365	2.79	1.96-3.97	2.94	2.03-4.25
Mixed	2.17	1.75-2.69	2.27	1.82-2.83
Risk Groups at Diagnosis				
Low Risk	1.00	Ref.	1.00	Ref.
Medium Risk	1.95	1.30-2.94	1.90	1.24-2.90
High Risk	2.28	1.55-3.36	2.44	1.63-3.64
Regional Metastasis	2.39	1.59-3.60	2.77	1.81-4.23
Distant Metastasis	3.13	2.10-4.67	3.85	2.53-5.84
Change in *CCI since CCI at diagnosis				
No change	1.00	Ref.	1.00	Ref.
Change by 1	1.18	0.97-1.44	1.23	1.00-1.52
Change by 2	0.94	0.75-1.17	0.95	0.75-1.21
Change by 3	0.98	0.71-1.35	0.93	0.67-1.29
Change by ≥ 4	0.88	0.62-1.25	0.89	0.61-1.28
Civil Status				
Single	1.00	Ref.	1.00	Ref.
Married	1.15	0.99-1.34	1.12	0.96-1.31
Year of GnRH agonists' initiation				
2006-2007	1.00	Ref.	1.00	Ref.
2008-2009	1.23	1.04-1.47	1.07	0.90-1.29
2010-2011	1.15	0.96-1.38	0.91	0.75-1.10
2012-2013	N/A	N/A	N/A	N/A

* OR: Odds ratio; CI: Confidence interval; Non-adherent (reference group); CCI: Charlson Comorbidity Index; Injection interval at 90 days included PCa men given 30 days' dosages due to low number in the 30 days' group.

4.4.2.1.2 Secondary GnRH agonists

In comparison to deferred treatment, increased adherence was observed in men who were given anti-androgens (OR = 1.67; 95% CI = 1.22-2.29) as prior PCa treatment, whereas decreased adherence was observed in men who underwent radiotherapy (OR = 0.73; 95% CI = 0.56-0.97) (Table 20).

Table 20: *Univariate and multivariable logistic regression analyses showing odds ratios (OR) and 95% confidence intervals (CI) for men with PCa after 6 years on secondary GnRH agonists.*

Patient Characteristics	6 Years			
	Univariate		Multivariable	
	OR	95% CI	OR	95% CI
Age Groups (Years)				
≤ 65	1.00	Ref.	1.00	Ref.
66-74	1.31	0.98-1.76	1.23	0.90-1.68
75-84	1.52	1.15-2.02	1.32	0.94-1.84
≥ 85	1.75	1.16-2.66	1.55	0.96-2.49
***Injection Interval (Days)**				
90	1.00	Ref.	1.00	Ref.
80	4.55	2.14-9.67	4.83	2.26-10.35
365 (Implant)	1.76	1.19-2.61	1.69	1.13-2.51
Mixed	2.44	1.85-3.21	2.40	1.81-3.17
Change in *CCI since CCI at diagnosis				
No change	1.00	Ref.	1.00	Ref.
Change by 1	0.93	0.73-1.19	0.90	0.70-1.16
Change by 2	1.24	0.92-1.67	1.25	0.92-1.71
Change by 3	1.30	0.87-1.94	1.27	0.84-1.92
Change by ≥ 4	1.28	0.80-2.06	1.24	0.76-2.01
Civil Status				
Single	1.00	Ref.	1.00	Ref.
Married	1.21	0.99-1.48	1.22	1.00-1.50
Prior PCa Treatment				
*Deferred Treatment	1.00	Ref.	1.00	Ref.
Anti-androgens	1.63	1.21-2.19	1.67	1.22-2.29

Radical Prostatectomy only	0.78	0.57-1.08	0.86	0.60-1.23
Radiotherapy	0.66	0.52-0.83	0.73	0.56-0.97
Radiotherapy < 1 year after Radical Prostatectomy	0.64	0.40-1.01	0.76	0.45-1.27
Radiotherapy ≥ 1 year after Radical Prostatectomy	0.98	0.57-1.71	1.08	0.59-1.97

* OR: Odds ratio; CI: Confidence interval; Non-adherent (reference group); Deferred treatment includes men who underwent active surveillance and watchful waiting; CCI: Charlson Comorbidity Index; Injection interval at 90 days included PCa men given 30 days' dosages due to low number in the 30 days' group.

4.4.2.2 Reclassification of Outcomes

In this analysis, outcomes were reclassified according to men who received intermittent GnRH agonists or who discontinued treatment. As discussed above, an intermittent treatment regimen for GnRH agonists was determined as a gap of < 9 months between the last and second last prescriptions in PCBaSe^{Traject}. Following reclassification, 89% (7,227/8,105) men with PCa on primary GnRH agonists were adherent and 11% (878/8,105) were non-adherent. 86% (4,049/4,738) men with PCa on secondary GnRH agonists were adherent and 15% (689/4,738) were non-adherent (Appendix Table 1, Appendix).

4.4.2.2.1 Primary GnRH agonists

Table 21 shows odds ratios and 95% Cis estimated using logistic regression models on the reclassified outcomes. Increased age, injection interval and risk groups showed an increased adherence in men on primary GnRH agonists. Reclassification of outcomes in the primary GnRH agonists' group showed that change in CCI by 3 compared to no change in CCI (OR = 1.95; 95% CI = 1.15-3.33) was also statistically significant which was not observed in the original analysis.

Table 21: *Univariate and multivariable logistic regression analyses showing odds ratios (OR) and 95% confidence intervals (CI) for men with PCa after 3 years on primary GnRH agonists, following reclassification of outcomes based on those on an intermittent GnRH agonists therapy.*

Patient Characteristics	3 Years			
	Univariate		Multivariable	
	OR	95% CI	OR	95% CI
Age Groups (Years)				
≤ 65	1.00	Ref.	1.00	Ref.
66-74	1.39	1.10-1.75	1.71	1.34-2.18
75-84	1.64	1.31-2.04	2.26	1.78-2.88
≥ 85	1.52	1.17-1.99	1.94	1.46-2.58
***Injection Interval (Days)**				
90	1.00	Ref.	1.00	Ref.
180	1.45	1.02-2.04	1.43	1.00-2.05
365 (Implant)	1.74	1.30-2.33	1.81	1.34-2.45
Mixed	2.55	1.92-3.39	2.65	1.99-3.54
Risk Groups at Diagnosis				
Low Risk	1.00	Ref.	1.00	Ref.
Medium Risk	2.39	1.64-3.48	2.20	1.49-3.24
High Risk	3.29	2.31-4.67	3.16	2.20-4.53
Regional Metastasis	4.33	2.96-6.33	4.70	3.18-6.96
Distant Metastasis	5.45	3.80-7.84	6.49	4.45-9.47
Change in *CCI since CCI at diagnosis				
No change	1.00	Ref.	1.00	Ref.
Change by 1	1.09	0.89-1.34	1.07	0.86-1.32
Change by 2	1.09	0.84-1.42	1.12	0.86-1.47
Change by 3	2.08	1.23-3.53	1.95	1.15-3.33
Change by ≥ 4	1.18	0.69-2.02	1.13	0.65-1.96
Civil Status				
Single	1.00	Ref.	1.00	Ref.
Married	0.92	0.80-1.07	0.93	0.80-1.08
Year of GnRH agonists' initiation				
2006-2007	1.00	Ref.	1.00	Ref.
2008-2009	1.26	1.05-1.51	1.11	0.92-1.35
2010-2011	1.11	0.92-1.34	0.91	0.75-1.11
2012-2013	1.30	1.05-1.60	0.98	0.79-1.22

* OR: Odds ratio; CI: Confidence interval; Non-adherent (reference group); CCI: Charlson Comorbidity Index; Injection interval at 90 days included PCa men given 30 days' dosages due to low number in the 30 days' group.

4.4.2.2.2 Secondary GnRH agonists

For the men on secondary GnRH agonists (Table 22), similar patterns as the original analysis was observed with age, injection intervals and prior PCa treatments (anti-androgens, radiotherapy and radiotherapy ≥ 1 year after radical prostatectomy) affecting adherence patterns.

***Table 22**: Univariate and multivariable logistic regression analyses showing odds ratios (OR) and 95% confidence intervals (CI) for PCa men after 3 years on secondary GnRH agonists, following reclassification of outcomes based on those on an intermittent GnRH agonists therapy.*

Patient Characteristics	3 Years			
	Univariate		Multivariable	
	OR	95% CI	OR	95% CI
Age Groups (Years)				
≤ 65	1.00	Ref.	1.00	Ref.
66-74	1.11	0.86-1.45	1.14	0.86-1.51
75-84	1.31	1.02-1.69	1.49	1.10-2.01
≥ 85	1.68	1.20-2.35	2.10	1.42-3.09
***Injection Interval (Days)**				
90	1.00	Ref.	1.00	Ref.
180	1.98	1.25-3.11	1.87	1.18-2.96
365 (Implant)	1.35	0.99-1.83	1.34	0.98-1.83
Mixed	3.03	2.11-4.36	3.18	2.20-4.58
Change in *CCI since CCI at diagnosis				
No change	1.00	Ref.	1.00	Ref.
Change by 1	1.17	0.91-1.51	1.15	0.89-1.49
Change by 2	1.10	0.82-1.48	1.06	0.78-1.43
Change by 3	1.69	0.95-3.02	1.62	0.90-2.90
Change by ≥ 4	1.05	0.58-1.90	1.01	0.55-1.84
Civil Status				
Single	1.00	Ref.	1.00	Ref.
Married	1.08	0.91-1.28	1.08	0.90-1.28
Prior PCa Treatment				

*Deferred Treatment	1.00	Ref.	1.00	Ref.
Anti-androgens	1.71	1.32-2.20	1.92	1.47-2.50
Radical Prostatectomy only	0.65	0.50-0.83	0.81	0.60-1.08
Radiotherapy	1.34	1.07-1.67	1.84	1.42-2.38
Radiotherapy < 1 year after Radical Prostatectomy	0.95	0.62-1.45	1.50	0.93-2.44
Radiotherapy ≥ 1 year after Radical Prostatectomy	1.27	0.79-2.04	1.88	1.11-3.18

* OR: Odds ratio; CI: Confidence interval; Non-adherent (reference group); Deferred treatment includes men who underwent active surveillance and watchful waiting; CCI: Charlson Comorbidity Index; Injection interval at 90 days included PCa men given 30 days' dosages due to low number in the 30 days' group.

4.4.2.3 Redefinition of Outcomes

Tables 23 and 24 show odds ratios and 95% confidence intervals after 3 years on GnRH agonists, following redefinition of adherent and non-adherent. In this analysis, a MPR of ≥ 50% was considered as adherent and a MPR of < 50% was considered as adherent to GnRH agonists.

4.4.2.3.1 Primary GnRH agonists

Following redefinition of outcomes, 88% (7,140/8,105) men on primary GnRH agonists were adherent and 12% (965/8,105) were non-adherent (Appendix Table 2, Appendix). Increased age, longer injection interval and higher risk groups showed an increased adherence in men on primary GnRH agonists (Table 22).

Table 23: Univariate and multivariable logistic regression analyses showing odds ratio (OR) and 95% confidence intervals (CI) for men with PCa after 3 years on primary GnRH agonists, following redefinition of adherence.

Patient Characteristics	3 Years			
	Univariate		Multivariable	
	OR	95% CI	OR	95% CI
Age Groups (Years)				
≤ 65	1.00	Ref.	1.00	Ref.
66-74	1.20	0.96-1.50	1.43	1.13-1.82

75-84	1.62	1.31-2.01	2.12	1.68-2.68
≥ 85	1.49	1.15-1.94	1.82	1.38-2.40
***Injection Interval (Days)**				
90	1.00	Ref.	1.00	Ref.
180	1.97	1.36-2.85	2.01	1.37-2.94
365 (Implant)	3.35	2.35-4.79	3.44	2.39-4.95
Mixed	2.48	1.90-3.22	2.60	1.99-3.39
Risk Groups at Diagnosis				
Low Risk	1.00	Ref.	1.00	Ref.
Medium Risk	2.52	1.73-3.65	2.28	1.56-3.35
High Risk	3.31	2.34-4.67	3.16	2.21-4.51
Regional Metastasis	3.60	2.49-5.19	3.91	2.67-5.71
Distant Metastasis	5.33	3.74-7.61	6.41	4.42-9.29
Change in *CCI since CCI at diagnosis				
No change	1.00	Ref.	1.00	Ref.
Change by 1	1.11	0.91-1.36	1.08	0.88-1.32
Change by 2	1.20	0.93-1.56	1.22	0.93-1.59
Change by 3	1.54	0.99-2.41	1.44	0.92-2.26
Change by ≥ 4	1.32	0.77-2.26	1.24	0.72-2.14
Civil Status				
Single	1.00	Ref.	1.00	Ref.
Married	1.08	0.94-1.24	1.10	0.95-1.26
Year of GnRH agonists' initiation				
2006-2007	1.00	Ref.	1.00	Ref.
2008-2009	1.26	1.06-1.50	1.06	0.88-1.27
2010-2011	1.23	1.02-1.48	0.94	0.78-1.14
2012-2013	1.24	1.02-1.51	0.87	0.71-1.07

* OR: Odds ratio; CI: Confidence interval; Non-adherent (reference group); CCI: Charlson Comorbidity Index; Injection interval at 90 days included PCa men given 30 days' dosages due to low number in the 30 days' group.

4.4.2.3.2 Secondary GnRH agonists

84% (3,959/4,738) men on secondary GnRH agonists were adherent and 16% (779/4,738) were non-adherent (Appendix Table 2, Appendix). For men on

secondary GnRH agonists (Table 24), increased adherence was observed with increased age, injection intervals and those who were given anti-androgens or radiotherapy as PCa treatment before GnRH agonists.

Table 24: *Univariate and multivariable logistic regression analyses showing odds ratio (OR) and 95% confidence intervals (CI) for PCa men after 3 years on secondary GnRH agonists, following redefinition of adherence.*

Patient Characteristics	3 Years			
	Univariate		Multivariable	
	OR	95% CI	OR	95% CI
Age Groups (Years)				
≤ 65	1.00	Ref.	1.00	Ref.
66-74	1.25	0.97-1.60	1.24	0.96-1.62
75-84	1.42	1.12-1.81	1.53	1.15-2.02
≥ 85	1.56	1.14-2.12	1.81	1.27-2.59
***Injection Interval (Days)**				
90	1.00	Ref.	1.00	Ref.
180	2.45	1.54-3.91	2.39	1.49-3.81
365 (Implant)	2.43	1.70-3.47	2.44	1.71-3.50
Mixed	2.02	1.51-2.70	2.09	1.56-2.80
Change in *CCI since CCI at diagnosis				
No change	1.00	Ref.	1.00	Ref.
Change by 1	1.15	0.91-1.46	1.14	0.89-1.46
Change by 2	1.13	0.85-1.50	1.08	0.80-1.44
Change by 3	1.55	0.91-2.63	1.49	0.87-2.55
Change by ≥ 4	1.11	0.62-1.98	1.05	0.59-1.89
Civil Status				
Single	1.00	Ref.	1.00	Ref.
Married	1.16	0.99-1.37	1.15	0.97-1.36
Prior PCa Treatment				
*Deferred Treatment	1.00	Ref.	1.00	Ref.
Anti-androgens	1.36	1.08-1.70	1.50	1.18-1.90
Radical Prostatectomy only	0.70	0.54-0.90	0.87	0.65-1.15
Radiotherapy	1.42	1.15-1.77	1.90	1.48-2.45

Radiotherapy < 1 year after Radical Prostatectomy	0.77	0.52-1.14	1.16	0.75-1.80
Radiotherapy ≥ 1 year after Radical Prostatectomy	0.98	0.64-1.48	1.34	0.85-2.11

* OR: Odds ratio; CI: Confidence interval; Non-adherent (reference group); Deferred treatment includes men who underwent active surveillance and watchful waiting; CCI: Charlson Comorbidity Index; Injection interval at 90 days included PCa men given 30 days' dosages due to low number in the 30 days' group.

4.5 DISCUSSION

This population-based register study was the first to investigate patterns of adherence to GnRH agonists in men with PCa in Sweden. Increased adherence to primary GnRH agonists was observed with increased age, a longer injection interval and a diagnosis of high risk or metastatic PCa after 3 years. Adherence to secondary GnRH agonists was stronger with increased age and prior use of anti-androgens and radiotherapy. Reclassification and redefinition of outcomes showed similar patterns as above and no remarkable differences in associations were observed with a longer study period of 6 years.

An increased age was associated with increased adherence to GnRH agonists in this study. Several studies (183, 184) on heart failure medication support the findings of the current study. Individuals who were older with chronic illnesses were shown to have an increased adherence to heart failure medications than their younger counterparts. In the current study, older men with PCa showed an increased adherence regardless of whether they received primary or secondary GnRH agonists. Older men may be able to cope better with side-effects such as erectile dysfunction than their younger counterparts. A review (185) on the experiences of

men after PCa treatment has shown that side-effects such as erectile dysfunction had minimal impact in older men because they had already experienced sexual dysfunction due to another chronic or co-morbid disease. Moreover, erectile dysfunction was an “ill-effect’ that older men could live with and had minimal impact on their masculinity.

Men with PCa with 365 days (50mg) intervals between their GnRH agonists injections showed three times increased adherence as compared to men receiving the injection with 90 days’ interval. This can be attributed to the reduced number of visits required to deliver the injections at higher doses, which means that men on the longer injection intervals may simply be more receptive to the less frequent and more convenient injection schedules (113). This warrants further discussion among clinicians into 365 days’ implants to be offered as an alternative to men encountering difficulties organising appointments at set intervals for injection administration.

A three-fold increased adherence was observed in men with metastatic PCa at diagnosis compared to men diagnosed with low risk PCa. One reason for this increase may be that men with metastatic PCa were more likely to adhere to their cancer treatment in order to relieve disease symptoms such as bone pain, since disease severity is most often associated with more severe symptoms (186). However, the predominant reason for this increase may be due to the influence of stage-specific treatment guidelines in Sweden. For example, some men with low risk PCa may be on GnRH agonists with an elective intent (i.e. men with low risk PCa may be given treatment instead of no treatment) leading to the low adherence

observed this group (187). Moreover, this study did not account for oestrogens as it was extremely uncommon in the dataset although guidelines (187) in Sweden suggested the use of oestrogens for metastatic PCa because of similar effects to GnRH agonists at a lower cost.

An increased adherence was also observed in men who had received radiotherapy prior to GnRH agonists' initiation compared to those who were on deferred treatment. In men who had undergone radiotherapy for PCa, having radiotherapy ≥ 1 year after their radical prostatectomy improved adherence to GnRH agonists which may reflect the treatment regimen for an advanced or recurrent PCa. Recommended therapies for localised PCa in Sweden include: radical prostatectomy, radiation therapy (188), anti-androgen monotherapy (189) or a combination of any of these based on cancer risk category and life expectancy. GnRH agonists can be given after a radical prostatectomy to reduce the risk of recurrence and to men who have a PSA relapse. In some of these cases, once PSA is under control, physicians may decide to discontinue GnRH agonists (190). Differences in the radiotherapy regimens between localised and advanced or recurrent PCa therefore explain the adherence patterns discussed above.

Men given anti-androgens prior to their GnRH agonists were also more adherent than those on deferred treatment. Although some men can continue anti-androgens in combination with GnRH agonists (for one month or longer) because it can help relieve the side-effects caused by GnRH agonists (191), further research is required to understand how patterns of adherence to GnRH agonists is related to different anti-androgen regimens in men with PCa.

No remarkable differences to adherence patterns were observed following reclassification of outcomes suggesting that adherence in men on primary or secondary GnRH agonists was not affected by whether they were on intermittent therapy (Tables 21-22). In order to minimise (or reduce) the risk of side-effects due to GnRH agonists, men on GnRH agonists may be placed on an intermittent treatment regimen all the while maintaining anti-tumour efficacy (173, 174). These men may have lower adherence to GnRH agonists due to a longer gap in their treatment regimen. Therefore, it was important to conduct a sensitivity analysis using reclassified outcomes accounting for the possibility of an intermittent treatment. However, the lack of a standard definition for intermittent therapy for men on GnRH agonists means that the 9 months' gap explored in this study warrants further research.

Redefining adherence to a MPR of 50% cut-off (Tables 23-24) showed no remarkable differences compared to the original analysis (Tables 16-17). Nevertheless, it was important to investigate Pettersson et al.'s (2006) report on the longer-lasting effects of testosterone suppression by GnRH agonists than previously documented in this study (182).

The possibility of a switch in treatment regimens from GnRH agonists to other forms of ADT was not explored in this study since very few men switched treatments in the dataset. One could argue about the generalisability of the study population in PCBaSe^{Traject} being limited to a single country as differences in healthcare settings exist in different countries, especially limited by its ethnic diversity. However,

treatment with GnRH agonists may not differ significantly among men with PCa globally and therefore the results of this study may be applicable globally.

Future research assessing predictive factors once men stop adhering to the treatment may also offer explanations to the patterns observed in PCBaSe^{Traject}. Factors that are patient-related were not explored in this study because this was beyond the information available in PCBaSe^{Traject}. Patient-related factors such as forgetfulness, side-effects of GnRH agonists and 'white-coat compliance' may also contribute to the adherence patterns in men on GnRH agonists (82). Therefore, this thesis also comprises of a qualitative study (chapter VI) exploring the reasons contributing to non-adherence to GnRH agonists, both from a patient's and clinician's perspective to better understand overall adherence in men with PCa on long-term GnRH agonists.

4.6 CONCLUSION

This study identified increased age, advanced cancer stage at diagnosis, longer injection intervals and prior PCa treatment as patterns contributing to increased adherence to GnRH agonists in men with PCa. The patterns observed in this study provides evidence for some common factors already known from other disease settings that can contribute to adherence in men on GnRH agonists. Further research on data from other countries (chapter V) and qualitative research (chapter VI) are needed to reinforce the findings of this study.

5. CHAPTER V – ADHERENCE TO GNRH AGONISTS IN PROSTATE CANCER IN THE UNITED KINGDOM

Chapter IV introduced the concept of adherence and explored patterns of adherence to GnRH agonists in men with PCa in Sweden. This chapter will employ the same methods to investigate this in the UK population and briefly explore the differences or similarities in the patterns identified between the Swedish and UK populations.

5.1 BACKGROUND

Patterns of adherence to GnRH agonists have not been investigated previously in the UK. Considering that a large proportion of men with PCa are on GnRH agonists or some form of ADT, possibly for the rest of their lives, it is important to better understand adherence patterns in this population (6).

In the UK, ADT is offered to men with locally advanced and advanced PCa (NICE NG131) (120). Furthermore it is recommended that men continue with GnRH agonists treatment along with Docetaxel chemotherapy in castrate-resistant PCa (NICE 1.5.12, NG131) (120) because GnRH agonists increases the expression of the pro-apoptotic protein, Bax, which leads to re-sensitising castrate-resistant PCa cells to the cytotoxic activity of Docetaxel (192).

As mentioned in chapter IV, side-effects associated with prolonged use of ADT have shown to be a major cause of non-adherence to ADT in previous breast cancer studies (172). Some side-effects reported to be associated with ADT include:

fatigue, hot flushes, low bone density (leading to increased risk of fractures) and even psychological issues (114, 115). These may also affect adherence to treatment among men with PCa.

Other factors identified from the literature that may be associated with medication adherence and have not already been discussed in chapter IV include; socio-demographic information and lifestyle factors of an individual such as ethnicity, socio-economic status, smoking status and alcohol intake (117, 193). These factors are explored in more detail below.

Several studies have reported ethnicity to be an important factor contributing to the adherence status of an individual. A literature review (82) identified 16 studies that included ethnicity as a factor contributing to medication adherence. The results of this review showed Caucasians to have an increased adherence to medication compared to other ethnic minorities. This was attributed to the plausible explanation of language barriers and lower socio-economic statuses of the minorities included in the countries studied (82). Ethnicity was not investigated in PCBaSe^{Traject} (chapter IV) because more than 90% of population in PCBaSe^{Traject} had a Caucasian origin (194).

Adherence to medication has also been shown to be associated with lifestyle factors such as smoking status and alcohol intake. Individuals who smoked or had an increased alcohol intake were more likely to be non-adherent to medication (117, 193). Smoking status was not available in PCBaSe^{Traject} and was not investigated in chapter IV. The introduction of the April 2004 contract for UK GPs resulted in a substantial increase in GPs recording the smoking status of patients

attending general practices across UK (195). Although this raises the possibility of investigating smoking status as a non-adherent factor in the UK THIN database (141), detailed investigation of smoking status in chapter III has already shown a high percentage of missing data for this variable in the THIN database.

Although issues surrounding non-adherence to GnRH agonists in men with PCa in Sweden has been explored in chapter IV of this thesis, country-specific factors such as treatment guidelines may influence the patterns observed in chapter IV. This study will therefore aim to investigate patterns of adherence to GnRH agonists in PCa in the UK population using the primary healthcare database, THIN (141).

5.2 METHODS

5.2.1 Study Population

Men with PCa on GnRH agonists were identified from the THIN database using drugcodes for GnRH agonists. Detailed structure of the THIN database has been discussed in chapter III. The THIN (141) database covers more than 500 GP practices across UK representing prescription patterns relevant to the UK population. In addition to the prescription data; the database comprises other relevant data elements such as: age, frequency of prescriptions, combination treatment modalities, civil status, smoking status, BMI, ethnicity and social deprivation index (Townsend scores) (141). This study included men starting on GnRH agonists between 1990-2013.

5.2.2 Exposure

Men with PCa on GnRH agonists entered the cohort 45 days after GnRH agonists' initiation date. In order to avoid overestimating adherence in men with a shorter follow-up, only men with a minimum of 3 years on GnRH agonists were considered for the study. Men in the study were divided into two groups: those who had received GnRH agonists as the first-line treatment for their PCa were grouped as primary GnRH agonists and those who had received GnRH agonists following other PCa treatments were grouped as secondary GnRH agonists. The distinction between primary and secondary GnRH agonists in the THIN database was made using the variable, prior PCa treatment. Prior PCa treatment was created using readcodes (146) for curative treatments such as radical prostatectomy and radiotherapy and drugcodes (chapter III) for anti-androgens.

5.2.3 Outcome

Similarly to the study using PCBaSe^{Traject} in chapter IV, the outcome was defined as adherent and non-adherent using the MPR (179). MPR was used to quantify adherence by using the following equation:

$$\frac{\text{Days of prescribed/dispensed supply}}{\text{Number of days in the study period}} \text{ X } 100\ \%$$

A MPR of ≥ 80% was classified as adherent and a MPR of < 80% as non-adherent.

5.2.4 Analysis

5.2.4.1 Main analysis

The frequency of patterns for GnRH agonists' use in PCa men was analysed separately depending on whether men with PCa were given primary or secondary

GnRH agonists. Logistic regression analyses were conducted in both groups to estimate ORs and 95% CIs of adherence to GnRH agonists. The regression models for primary GnRH agonists included age groups and injection intervals. For secondary GnRH agonists, the regression models included age groups, injection intervals and prior PCa treatment. Study variables civil status, smoking status, ethnicity, SES and BMI were not included in the regression models due to a high percentage of missing information.

5.2.4.2 Sensitivity analyses

The sensitivity analyses conducted for this study were also similar to chapter IV which included a longer follow-up period of six years, reclassification and redefinition of outcomes. Multivariable logistic regression was conducted with a MPR of ≥ 80% being adherent and < 80% being non-adherent was conducted for men who were on GnRH agonists for six years in THIN.

In a further sensitivity analysis, logistic regression models were repeated for primary and secondary GnRH agonists following reclassification of outcomes. This sensitivity analysis was conducted to determine whether an intermittent regimen resulted in low MPR in some men on GnRH agonists. A gap of < 9 months between the last and second last prescriptions in THIN was defined as intermittent medication in THIN (174).

Finally, logistic regression models for primary and secondary GnRH agonists were also repeated using redefined outcomes (MPR of ≥ 50% for being adherent and < 50% for being non-adherent). As mentioned in chapter IV, the rationale behind this sensitivity analysis was to account for evidence that suggests that testosterone

levels may remain suppressed for a longer period of time after treatment with GnRH agonists than previously thought (182).

5.3 RESULTS

5.3.1 Main Analysis

4,923 men with PCa starting on primary GnRH agonists and 423 men with PCa starting on secondary GnRH agonists between 1990 and 2013 were extracted from THIN. Table 25 shows patient characteristics after 3 years on GnRH agonists. 75% were adherent on primary GnRH agonists and 70% were adherent on secondary treatment after 3 years. The mean age was similar for primary (adherent = 76, SD = 8.0; non-adherent = 75, SD = 8.2) and secondary (adherent = 74, SD = 8.3; non-adherent = 71, SD = 8.2) GnRH agonists.

Table 25: *Patient characteristics for men with PCa on primary and secondary GnRH agonists after 3 years.*

Patient Characteristics	Primary GnRH Agonists		Secondary GnRH Agonists	
	Adherent (%)	Non-adherent (%)	Adherent (%)	Non-adherent (%)
n	3712 (75.4)	1211 (24.6)	295 (69.7)	128 (30.3)
Age (Years)				
Mean (SD)	76	75	74	71
SD	8.0	8.2	8.3	8.2
Age Groups (Years)				
≤ 65	368 (9.9)	147 (12.1)	57 (19.3)	33 (25.8)
66-74	1003 (27.0)	310 (25.6)	87 (29.5)	58 (45.3)
75-84	1759 (47.4)	438 (36.2)	123 (41.7)	29 (22.7)
≥ 85	442 (11.9)	107 (8.8)	28 (9.5)	8 (6.3)
Missing	140 (3.8)	209 (17.3)	0	0
Injection Interval (Days)				
28	920 (24.8)	547 (45.2)	62 (21.0)	34 (26.6)
90	2641 (71.2)	649 (53.6)	224 (75.9)	90 (70.3)
180	151 (4.1)	15 (1.2)	9 (3.1)	4 (3.1)

Prior PCa Treatment				
Radical prostatectomy	N/A	N/A	95 (32.2)	51 (39.8)
Radiotherapy	N/A	N/A	148 (50.2)	64 (50.0)
Anti-androgens	N/A	N/A	52 (17.6)	13 (10.2)
Civil Status				
Single	17 (0.5)	3 (0.3)	4 (1.4)	0
Married	39 (1.1)	6 (0.5)	6 (2.0)	2 (1.6)
Missing	3656 (98.5)	1202 (99.3)	285 (96.6)	126 (98.4)
Smoking Status				
Current Smokers	634 (17.1)	205 (16.9)	43 (14.6)	15 (11.7)
Non-Smokers	22 (0.6)	8 (0.7)	2 (0.7)	3 (2.3)
Past Smokers	48 (1.3)	12 (1.0)	6 (2.0)	4 (3.1)
Missing	3008 (81.0)	986 (81.4)	244 (82.7)	106 (82.8)
Ethnicity				
Caucasian	1279 (34.5)	382 (31.5)	105 (35.6)	41 (32.0)
Black	34 (0.9)	9 (0.7)	1 (0.3)	0
Asian	6 (0.2)	4 (0.3)	1 (0.3)	0
Other	7 (0.2)	5 (0.4)	1 (0.3)	0
Missing	2386 (64.3)	811 (67.0)	187 (63.4)	87 (68.0)
Socio-economic Status				
Lowest or least deprived (Townsend 1)	172 (4.6)	41 (3.4)	16 (5.4)	6 (4.7)
Low (Townsend 2)	179 (4.8)	39 (3.2)	16 (5.4)	8 (6.3)
Middle (Townsend 3)	139 (3.7)	26 (2.2)	7 (2.4)	1 (0.8)
High (Townsend 4)	109 (2.9)	13 (1.1)	7 (2.4)	2 (1.6)
Highest or most deprived (Townsend 5)	63 (1.7)	18 (1.5)	6 (2.0)	0
Missing	3050 (82.2)	1074 (88.7)	243 (82.4)	111 (86.7)
BMI / obesity				
Normal weight (18.5-24)	7 (0.2)	1 (0.1)	1 (0.3)	0
Underweight (<18.5)	0	0	0	0
Overweight (25-30)	20 (0.5)	1 (0.1)	2 (0.7)	1 (0.8)
Obese (>30)	7 (0.2)	2 (0.2)	0	0
Missing	3678 (99.1)	1207 (99.7)	292 (99.0)	127 (99.2)

* BMI: Body Mass Index; N/A: Not available.

5.3.1.1 Primary GnRH agonists

Table 26 outlines the results of a logistic regression for men receiving primary GnRH agonists. Increased adherence was observed in the age groups 75-84 (OR = 1.47; 95% CI = 1.18-1.83) and ≥ 85 (OR = 1.50; 95% CI = 1.13-2.00) as compared to the group ≤ 65 years. Men with PCa on the 90 days' injection interval (OR = 1.87; 95% CI = 1.61-2.16) and 180 days' injection interval (OR = 4.13; 95% CI = 2.43-7.02) were more likely to be adherent than men on 28 days' injection interval.

Table 26: *Univariate and multivariable logistic analyses showing odds ratios (OR) and 95% confidence intervals (CI) for men with PCa after 3 years on primary GnRH agonists.*

Patient Characteristics	Univariate		Multivariable	
	OR	95% CI	OR	95% CI
Age Groups (Years)				
≤ 65	1.00	Ref.	1.00	Ref.
66-74	1.29	1.03-1.63	1.23	0.97-1.55
75-84	1.60	1.29-1.99	1.47	1.18-1.83
≥ 85	1.65	1.24-2.19	1.50	1.13-2.00
Injection Interval (Days)				
28	1.00	Ref.	1.00	Ref.
90	2.43	2.12-2.79	1.87	1.61-2.16
180	5.62	3.32-9.52	4.13	2.43-7.02

* OR: Odds ratio; CI: Confidence interval; non-adherent (reference group).

5.3.1.2 Secondary GnRH agonists

Table 27 shows the results of a logistic regression for men on secondary GnRH agonists. Increased adherence was observed in men aged 75-84 (OR = 2.55; 95% CI = 1.41-4.61) compared to men aged ≤ 65. Injection interval and prior PCa treatment had no influence on adherence status.

Table 27: *Univariate and multivariable logistic regression analyses showing odds ratios (OR) and 95% confidence intervals (CI) for men with PCa after 3 years on secondary GnRH agonists.*

Patient Characteristics	Univariate		Multivariable	
	OR	95% CI	OR	95% CI
Age (Years)				
≤ 65	1.00	Ref.	1.00	Ref.
66-74	0.87	0.50-1.49	0.86	0.49-1.47
75-84	2.46	1.36-4.43	2.55	1.41-4.61
≥ 85	2.03	0.83-4.96	2.21	0.88-5.51
Injection Interval (Days)				
28	1.00	Ref.	1.00	Ref.
90	1.36	0.84-2.22	1.51	0.91-2.50
180	1.23	0.35-4.31	1.27	0.34-4.63
Prior PCa Treatment				
Radical prostatectomy	1.00	Ref.	1.00	Ref.
Radiotherapy	1.21	0.63-2.35	1.29	0.80-2.08
Anti-androgens	1.16	0.74-1.82	1.33	0.80-2.08

* OR: Odds ratio; CI: Confidence interval; non-adherent (reference group).

5.3.2 Sensitivity analyses

5.3.2.1 Longer follow-up period

After six years on GnRH agonists, 1,828 men with PCa were on primary treatment and 174 were on secondary treatment (Table 28). Mean age was 75 years (SD = 7.7) for adherent and 73 years (SD = 7.2) for non-adherent men on primary GnRH agonists. For men on secondary GnRH agonists, mean age was 72 years (SD = 7.9) for adherent men and 69 years (SD = 7.5) for non-adherent men.

Table 28: *Patient characteristics for men with PCa on primary and secondary GnRH agonists after 6 years.*

Patient Characteristics	6 years			
	Primary GnRH Agonists		Secondary GnRH Agonists	
	Adherent (%)	Non-adherent (%)	Adherent (%)	Non-adherent (%)
n	1296 (70.9)	532 (29.1)	119 (68.4)	55 (31.6)
Age (Years)				

Mean (SD)	75	73	72	69
SD	7.7	7.2	7.9	7.5
Age Groups (Years)				
≤ 65	128 (9.9)	67 (12.6)	24 (20.2)	14 (25.5)
66-74	446 (34.4)	172 (32.3)	48 (40.3)	30 (54.6)
75-84	612 (47.2)	194 (36.5)	40 (33.6)	9 (16.4)
≥ 85	88 (6.8)	21 (4.0)	7 (5.9)	2 (3.6)
Missing	22 (1.7)	78 (14.7)	0	0
Injection Intervals (Days)				
28	341 (26.3)	231 (43.4)	26 (21.9)	14 (25.5)
90	911 (70.3)	294 (55.3)	91 (76.5)	41 (74.6)
180	44 (3.4)	7 (1.3)	2 (1.7)	0
Prior PCa Treatment				
Radical prostatectomy	N/A	N/A	34 (28.6)	23 (41.8)
Radiotherapy	N/A	N/A	65 (54.6)	24 (43.6)
Anti-androgens	N/A	N/A	20 (16.8)	8 (14.6)
Civil Status				
Single	4 (0.3)	1 (0.2)	4 (3.4)	0
Married	8 (0.6)	3 (0.6)	0	0
Missing	1284 (99.1)	528 (99.3)	115 (96.6)	55 (100)
Smoking Status				
Current Smokers	227 (17.5)	103 (19.4)	20 (16.8)	8 (14.6)
Non-Smokers	9 (0.7)	4 (0.8)	1 (0.8)	1 (1.8)
Past Smokers	15 (1.2)	6 (1.1)	4 (3.4)	1 (1.8)
Missing	1045 (80.6)	419 (78.8)	94 (79.0)	45 (81.8)
Ethnicity				
Caucasian	452 (34.9)	172 (32.3)	44 (37.0)	20 (36.4)
Black	11 (0.9)	4 (0.8)	0	0
Asian	2 (0.2)	1 (0.2)	0	0
Other	1 (0.1)	4 (0.8)	1 (0.8)	0
Missing	830 (64.0)	351 (66.0)	74 (62.2)	35 (63.6)
Socio-economic Status				
Lowest or least deprived (Townsend 1)	17 (1.3)	7 (1.3)	1 (0.8)	1 (1.8)
Low (Townsend 2)	23 (1.8)	8 (1.5)	1 (0.8)	0
Middle (Townsend 3)	21 (1.6)	3(0.6)	2 (1.7)	0
High (Townsend 4)	18 (1.4)	3 (0.6)	0	0
Highest or most deprived (Townsend 5)	6 (0.5)	6 (1.1)	2 (1.7)	0
Missing	1211 (93.4)	505 (94.9)	113 (95.0)	54 (98.2)
BMI / obesity				
Normal weight (18.5-24)	3 (0.2)	1 (0.2)	1 (0.8)	0
Underweight (<18.5)	0	0	0	0

Overweight (25-30)	7 (0.5)	1 (0.2)	1 (0.8)	0
Obese (>30)	2 (0.2)	0	0	0
Missing	1284 (99.1)	530 (99.6)	117 (98.3)	55 (100)

* BMI: Body Mass Index; N/A: Not available.

5.3.2.1.1 Primary GnRH agonists

For men on primary GnRH agonists, increased age was associated with increased adherence with the most adherent age group being ≥ 85 years (OR = 2.08; 95% CI = 1.18-3.65) compared to ≤ 65 years (Table 29). An increased adherence was also observed in men who were administered injections at 90 days' intervals (OR = 1.55; 95% CI = 1.23-1.95) and 180 days' intervals (OR = 2.97; 95% CI = 1.31-6.77) as compared to 28 days.

Table 29: *Univariate and multivariable logistic regression analyses showing odds ratios (OR) and 95% confidence intervals (CI) for men with PCa after 6 years on primary GnRH agonists.*

Patient Characteristics	6 Years			
	Univariate		Multivariable	
	OR	95% CI	OR	95% CI
Age (Years)				
≤ 65	1.00	Ref.	1.00	Ref.
66-74	1.36	0.96-1.91	1.31	0.92-1.85
75-84	1.65	1.18-2.31	1.53	1.09-2.15
≥ 85	2.19	1.25-3.84	2.08	1.18-3.65
Injection Interval (Days)				
28	1.00	Ref.	1.00	Ref.
90	2.10	1.70-2.60	1.55	1.23-1.95
180	4.26	1.89-9.62	2.97	1.31-6.77

* OR: Odds ratio; CI: Confidence interval; non-adherent (reference group).

5.3.2.1.2 Secondary GnRH agonists

For men on secondary GnRH agonists, increased adherence was observed in men aged 75-84 years (OR = 2.94; 95% CI = 1.08 -8.03) compared to men aged ≤ 65 years (Table 30). Injection interval 180 days had low number of men on GnRH agonists in the two outcome groups for analysis (adherent = 2; non-adherent = 0). Prior PCa treatment had no influence on the adherence status of men on secondary GnRH agonists.

Table 30: *Univariate and multivariable logistic regression analyses showing odds ratios (OR) and 95% confidence intervals (CI) for men with PCa after 6 years on secondary GnRH agonists.*

Patient Characteristics	6 years			
	Univariate		Multivariable	
	OR	95% CI	OR	95% CI
Age (Years)				
≤ 65	1.00	Ref.	1.00	Ref.
66-74	0.93	0.42-2.08	1.02	0.45-2.34
75-84	2.59	0.97-6.90	2.94	1.08-8.03
≥ 85	2.04	0.37-11.22	2.54	0.45-14.4
Injection Interval (Days)				
28	1.00	Ref.	1.00	Ref.
90	1.20	0.57-2.52	1.22	0.56-2.66
180	* -	-	* -	-
Prior PCa Treatment				
Radical prostatectomy	1.00	Ref.	1.00	Ref.
Radiotherapy	1.83	0.90-3.71	1.97	0.95-4.08
Anti-androgens	1.69	0.64-4.49	1.44	0.52-3.97

* * OR: Odds ratio; CI: Confidence interval; non-adherent (reference group); Injection interval 180 days had low number of men on GnRH agonists in the two outcome groups for analysis (Adherent = 2; Non-adherent = 0)

5.3.2.2 Reclassification of outcomes

Patient characteristics after reclassification of outcomes are provided in (Appendix Table 3, Appendix). Following reclassification based on intermittent GnRH agonists

therapy, 78% (3,833/4,923) men with PCa on primary GnRH agonists were adherent and 22% (1,090/4,923) were non-adherent. 72% (303/423) men with PCa on secondary GnRH agonists were adherent and 28% (120/423) were non-adherent. Mean age was similar for men on primary (adherent = 76, SD = 8.0; non-adherent = 74, SD = 8.1) and secondary GnRH agonists (adherent = 74, SD = 8.4; non-adherent = 70, SD = 7.8).

5.3.2.2.1 Primary GnRH agonists

Table 31 shows odds ratios and 95% CIs estimated using logistic regression models on the reclassified outcomes. Increased age and injection intervals showed an increased adherence in men on primary GnRH agonists.

Table 31: *Univariate and multivariable logistic regression analyses showing odds ratios (OR) and 95% confidence intervals (CI) for men with PCa after 3 years on primary GnRH agonists, following reclassification of outcomes based on those on an intermittent GnRH agonists therapy.*

Patient Characteristics	3 Years			
	Univariate		Multivariable	
	OR	95% CI	OR	95% CI
Age Groups (Years)				
≤ 65	1.00	Ref.	1.00	Ref.
66-74	1.38	1.09-1.74	1.33	1.05-1.68
75-84	1.71	1.37-2.13	1.60	1.28-2.00
≥ 85	1.96	1.45-2.64	1.83	1.35-2.47
Injection Interval (Days)				
28	1.00	Ref.	1.00	Ref.
90	2.06	1.79-2.37	1.55	1.33-1.81
180	4.40	2.60-7.46	3.16	1.86-5.39

* OR: Odds ratio; CI: Confidence interval; non-adherent (reference group).

5.3.2.2.2 Secondary GnRH agonists

For the men on secondary GnRH agonists (Table 32), increased age was associated with increased adherence with the most adherence observed in ≥ 85 year olds (OR = 3.97; 95% CI = 1.38-11.42). Injection intervals and prior PCa treatment had no influence on adherence patterns in men on secondary GnRH agonists which was similar to the patterns observed in the original analysis (Table 27).

Table 32: *Univariate and multivariable logistic regression analyses showing odds ratios (OR) and 95% confidence intervals (CI) for men with PCa after 3 years on secondary GnRH agonists, following reclassification of outcomes based on those on an intermittent GnRH agonists.*

Patient Characteristics	3 Years			
	Univariate		Multivariable	
	OR	95% CI	OR	95% CI
Age Groups (Years)				
≤ 65	1.00	Ref.	1.00	Ref.
66-74	0.92	0.53-1.58	0.91	0.53-1.57
75-84	2.81	1.54-5.12	2.88	1.57-5.28
≥ 85	3.59	1.27-10.13	3.97	1.38-11.42
Injection Interval (Days)				
28	1.00	Ref.	1.00	Ref.
90	1.21	0.73-1.98	1.34	0.80-2.25
180	1.02	0.29-3.59	1.05	0.29-3.87
Prior PCa Treatment				
Radical prostatectomy	1.00	Ref.	1.00	Ref.
Radiotherapy	1.13	0.71-1.79	1.34	0.82-2.17
Anti-androgens	1.31	0.66-2.59	1.50	0.73-3.07

* OR: Odds ratio; CI: Confidence interval; non-adherent (reference group).

5.3.2.3 Redefinition of outcomes

In this analysis, a MPR of ≥ 50% was considered as adherent and a MPR of < 50% was considered as adherent to GnRH agonists. Appendix Table 4 (Appendix) shows characteristics of men following redefinition of outcomes. 86% (4,246/4,923) men on primary GnRH agonists were adherent and 14% (677/4,923) were non-adherent. 83% (352/423) men on secondary GnRH agonists were adherent and 17% (71/423) were non-adherent. Mean age was similar for men on primary (adherent = 76, SD = 8.0; non-adherent = 74, SD = 8.1) and secondary GnRH agonists (adherent = 74, SD = 8.4; non-adherent = 70, SD = 7.6).

5.3.2.3.1 Primary GnRH agonists

Following redefinition of outcomes (Table 33), increased age and longer injection interval showed an increased adherence in men on primary GnRH agonists.

Table 33: *Univariate and multivariable logistic regression analyses showing odds ratio (OR) and 95% confidence intervals (CI) for men with PCa after 3 years on primary GnRH agonists, following redefinition of adherence.*

Patient Characteristics	3 Years			
	Univariate		Multivariable	
	OR	95% CI	OR	95% CI
Age Groups (Years)				
≤ 65	1.00	Ref.	1.00	Ref.
66-74	1.39	1.05-1.83	1.30	0.98-1.72
75-84	1.82	1.40-2.38	1.64	1.25-2.15
≥ 85	2.52	1.71-3.72	2.26	1.53-3.35
Injection Interval (Days)				
28	1.00	Ref.	1.00	Ref.
90	2.90	2.45-3.42	2.11	1.76-2.53
180	5.47	2.76-10.82	3.77	1.89-7.50

* OR: Odds ratio; CI: Confidence interval; non-adherent (reference group).

5.3.2.3.2 Secondary GnRH agonists

For men on secondary GnRH agonists (Table 34), increased adherence was observed with increased age and longer injection intervals. Prior PCa treatment had no influence on the adherence status.

Table 34: *Univariate and multivariable logistic regression analyses showing odds ratio (OR) and 95% confidence intervals (CI) for men with PCa after 3 years on secondary GnRH agonists, following redefinition of adherence.*

Patient Characteristics	3 Years			
	Univariate		Multivariable	
	OR	95% CI	OR	95% CI
Age Groups (Years)				
≤ 65	1.00	Ref.	1.00	Ref.
66-74	0.66	0.34-1.25	0.65	0.34-1.24
75-84	2.30	1.07-4.92	2.41	1.12-5.18
≥ 85	3.96	0.87-18.11	4.17	0.89-19.45
Injection Interval (Days)				
28	1.00	Ref.	1.00	Ref.
90	1.59	0.90-2.83	1.78	0.98-3.24
180	0.93	0.24-3.70	1.02	0.24-4.27
Prior PCa Treatment				
Radical prostatectomy	1.00	Ref.	1.00	Ref.
Radiotherapy	1.01	0.58-1.77	1.22	0.68-2.19
Anti-androgens	1.02	0.45-2.27	1.22	0.52-2.86

* OR: Odds ratio; CI: Confidence interval; non-adherent (reference group).

5.4 DISCUSSION

This is the first study to use a primary healthcare database to assess patterns of adherence to GnRH agonists in men with PCa in the UK. Increased adherence was observed in men with older age and longer injection intervals for primary GnRH

agonists in all analyses. For men on secondary GnRH agonists, increased age was the single most contributing factor to increased adherence in all analyses. The results of this study support some of the findings observed in for Sweden using the PCBaSe^{Traject} database (chapter IV). Adherence in both Sweden and UK was influenced by an increased age and a longer injection interval.

Increased adherence was observed with increased age regardless of whether men were on primary or secondary GnRH agonists. The increased adherence observed in older men remained significant even with longer follow-up period, reclassification and redefinition of outcomes. Previous studies (183, 184) have also shown that older individuals have an increased medication adherence, especially in chronic illnesses. Moreover, the results from this study support the results from PCBaSe^{Traject} (chapter IV), which reinforces that increased age is a contributing factor to increased adherence in men with PCa on GnRH agonists.

Adherence status was also influenced by injection intervals, particularly for men on primary GnRH agonists. Longer injection intervals of 90 days and 180 days showed an increased adherence as compared to the shorter 28 days' injection intervals, similar to the findings observed in PCBaSe^{Traject} (chapter IV). As discussed in chapter IV, this may be explained by the reduced number of visits required by an individual on GnRH agonists to be administered the injections. Men on the longer injection intervals may simply be more receptive to the less frequent and more convenient injection schedules (113).

A key strength of this study was that it made use of a primary healthcare database which covered men attending primary care to be administered GnRH agonists'

injections. However, a high percentage of missing information on socio-demographic variables and no information being available on stage of PCa in the THIN database limited the applicability of the results of this study.

Further research is required with more data on socio-demographic variables and stage of PCa to complement the preliminary findings of this study. Moreover, it is important to understand factors contributing to adherence and non-adherence from a patient's and their clinician's perspective. Therefore, a qualitative study exploring different perspectives will help to better understand overall adherence patterns to GnRH agonists in men with PCa in the UK.

5.5 CONCLUSION

The results of this study confirm findings from chapter IV that increased age and longer injection intervals influence adherence patterns to GnRH agonists in men with PCa. Further research is required to reinforce the preliminary findings of this study. For this thesis, a qualitative approach (chapter VI) was employed to data collected from a UK hospital, to better understand the socio-demographic aspects, patient and clinician perspectives contributing to adherence patterns to GnRH agonists in men with PCa.

6. CHAPTER VI – ADHERENCE TO GNRH AGONISTS IN PROSTATE CANCER: A QUALITATIVE APPROACH

In chapters IV and V of this thesis, adherence to GnRH agonists in men with PCa was investigated in Sweden and the UK using quantitative methods. The aim of this chapter is to better understand factors influencing adherence and non-adherence to GnRH agonists in men with PCa using qualitative methods. Most methods of measuring adherence only consider quantitative methods. Although this may inform patterns of non-adherence, it provides little insight into the reasons contributing to non-adherence in patients. The qualitative data in this chapter includes measures such as patient and clinician perspectives of factors contributing to adherence and non-adherence, which are outside the scope of quantitative databases, thus providing an overall representation of the subject being investigated.

6.1 BACKGROUND

A qualitative review by Jin et al. (2008) identified various factors from the literature between 1970 to 2005 contributing to therapeutic non-compliance or non-adherence to medication in general. The review categorised the factors identified into patient-centred factors, therapy-related factors, social and economic factors, healthcare system factors and disease factors (82). Jin et al.'s (2008) review formed the basis for the qualitative research carried out in this project. For the purpose of this project, the main factors identified from Jin et al.'s (2008) review were combined into patient-related and clinician-related factors (Figures 16 and 17).

6.1.1.1 *Patient-related factors*

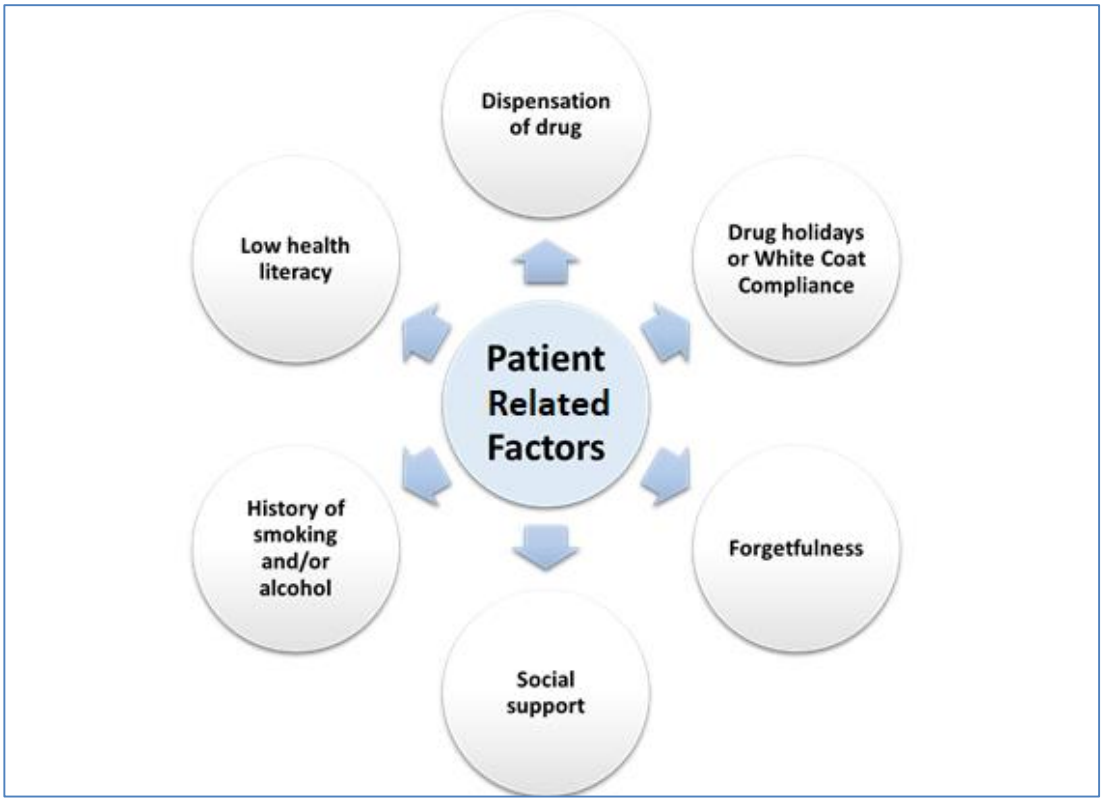

***Figure 16**: Patient-related factors influencing non-adherence highlighted in literature review by Jin et al. (2008) (82).*

Patient-related factors can include the demographics of a patient such as the age, ethnicity, gender, education and marital status. They can also cover factors that may arise from the patient himself such as forgetfulness, skipping medications and lack of dispensation of a drug. Lack of dispensation of a drug occurs when a patient has not collected their prescribed medication from the pharmacy (82).

Reasons such as 'drug holidays' or 'white-coat compliance' may also contribute to the lack of adherence to medication. Drug holidays occur when a patient takes short intervals of time from their medication routine before resuming their medication

due to no reason. White-coat compliance is a phenomenon whereby medication adherence is positively associated with clinical appointments (196).

The extent of social support from a spouse or other family members may also influence the adherence status of a patient. Having a partner or a family member to remind the patient about taking their medication on time and taking care of the patient's health in general may contribute to an increased medication adherence in these patients.

6.1.1.2 Clinician-related factors

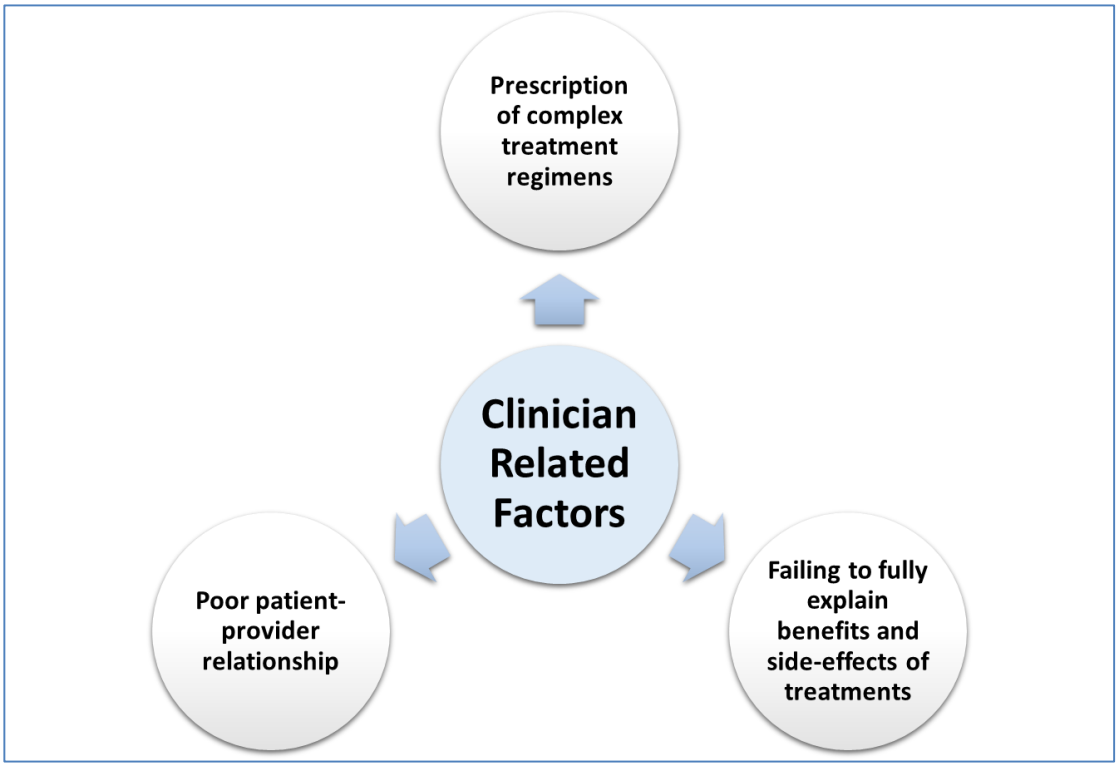

Figure 17: *Clinician-related factors influencing non-adherence highlighted in literature review by Jin et al. (2008) (82).*

Prescribing complex treatment regimens may be one reason how clinicians may influence a patient's adherence to medication. A poor patient-provider relationship may also influence medication adherence because it can lead to clinicians not having a chance to fully explain the benefits and side-effects of a treatment to a patient unwilling to cooperate (197-200).

The term patient-related care suggests that patients may adhere to their medications after making an informed decision in a supportive healthcare environment (201). In order to address clinician-related factors contributing to non-adherence to a medication, it is important to establish a therapeutic alliance between a patient and their physician (107, 202). Vlasnik et al. (2005) even proposes that a patient having multiple physicians prescribing medication may decrease the patient's confidence in the prescribed treatment. One way to build a healthy relationship between a patient and their provider is to actively involve patients in their treatment plans right from the beginning (201). Shared decision making can help patients to actively engage in their care. Therefore, a positive relationship between a patient and their clinician is important to help patients understand their disease and the need to adhere to their therapy.

It is therefore imperative to understand both patient and clinician perspectives when it comes to medication adherence. No study has fully investigated adherence to GnRH agonists in men with PCa using qualitative methods (such as interviews with patients and focus groups with clinicians). Taking into consideration factors contributing to medication adherence that are discussed above, this project aimed

to understand factors contributing to adherence and non-adherence to GnRH agonists in men with PCa.

6.2 METHODS

The project was divided into three main stages: validation of themes contributing to non-adherence by an Oncologist Specialist, interviews with men with PCa on long-term GnRH agonists and focus groups with healthcare professionals treating men with PCa on GnRH agonists. This study was conducted in Guy's Hospital (Guy's and St Thomas' Foundation Trust), a large teaching hospital treating around 1,000 men with PCa per year.

6.2.1.1 Stage 1: Validation

The purpose of validation in qualitative research is to ensure that the research question is valid for the desired outcome, that the methodology chosen is appropriate for answering the research question and that the study design is suitable for the methodology applied (203). This concept was modified for this study to validate the methodology and reasons contributing to medication non-adherence highlighted by Jin et al.'s (2008) review (82). For the validation process, an Oncology Specialist with 10 years of experience treating men on GnRH agonists at the hospital, went through the study protocol and highlighted any additional reasons for non-adherence in relation to the population being studied in this project.

6.2.1.2 Stage 2: Interviews

Men with PCa on GnRH agonists were identified by oncology specialists and clinical nurse specialists (CNS) from the direct care team. Once identified, eligible men were offered the study participant information sheet (section 9.4.2, Appendix) by the research team. After an informed consent was obtained, semi-structured interviews were held on a one-to-one basis using a topic guide (section 9.4.2, Appendix). The interview topic guide included topics discussed in Figures 16 and 17 and any further topics highlighted by the validation process in stage 1. Questions were open-ended with participants being encouraged to initiate topics that they deemed were important. All men were assured that the researchers were interested in understanding their views regardless of their adherence status. Each interview lasted for a maximum of 45 minutes and were audio recorded, transcribed verbatim and anonymised. A total of ten men on GnRH agonists were interviewed where no new emerging themes were identified (204).

6.2.1.3 Stage 3: Focus groups

Focus groups were conducted for healthcare professionals treating men on GnRH agonists. The aim of the focus groups was to identify factors related to adherence and non-adherence in the study that were not identified in the literature review (82), the validation process (section 9.4.2, Appendix) or the interview stage. Moreover, the focus groups also provided a clinical perspective to factors contributing to adherence and non-adherence to GnRH agonists in men with PCa. The focus groups were held in two separate sessions: one with oncology specialists or registrars and one with CNS. The clinicians were invited by their managers to the focus groups using the study participant information sheet (section 9.4.2,

Appendix). Once informed consent was obtained, the focus groups were run using a topic guide (section 9.4.2, Appendix) for a maximum of two hours. The focus groups were audio recorded and anonymously transcribed verbatim. Three clinicians per focus group were recruited, as the minimum number of members required for a focus group is between 3-5 participants (204).

6.2.1.4 Ethical approval

Ethical approval was obtained from the Health Research Authority (HRA) using the Integrated Research Application System before the start of the study. The HRA approved documents are provided in section 9.4.2 of the Appendix.

6.2.1.5 Analysis

All audio recordings were anonymised and given a unique study ID during transcription. Interviews (stage 2) and focus groups (stage 3) were analysed using thematic analysis as described by Braun and Clarke (2006) (205) which include:

1. familiarising yourself with your data (includes transcription of audio recording)
2. generating initial codes by identifying repeated patterns in extracts of your data
3. searching for themes by combining the initial codes to form overarching themes
4. reviewing themes to identify coherent themes
5. defining and naming themes
6. producing the report which should provide a concise, coherent, logical and non-repetitive explanation of the themes.

Following familiarisation with the data, initial codes were generated by working systematically through the interview and focus group transcripts. Each code was determined by the language used by the participant. For example, if the participant said, "*The fatigue meant that it was very difficult for me to work properly*", the sentence was coded under the overarching code, "fatigue". The initial codes were then organised into potential themes (Figure 18) using the software NVIVO (section 9.2, Appendix). Following discussion of themes with other qualitative researchers in the team, the themes were reviewed into coherent themes.

Men in the interview stage (stage 2) were classified as adherent or non-adherent by the clinicians identifying them for the study. All men interviewed were recommended to go on the GnRH agonists by their clinician. Men who had never missed an injection intentionally were classed as adherent and men who were reported to have missed or discontinued their injection without recommendation from the clinician were classed as non-adherent.

6.3 RESULTS

Following validation (stage 1) by an Oncology Specialist of themes highlighted in the systematic review by Jin et al. (2008) (82), one-to-one interviews (stage 2) were conducted with men with PCa on GnRH agonists. All themes identified until stage 2 were then discussed with their healthcare professionals in focus groups (stage 3).

There was a substantial overlap between the themes identified by the interviews (stage 2) and focus groups (stage 3). The key themes identified from both the

interviews and focus groups were side-effects of treatment, patient belief system, benefits outweigh harm, quality of life over quantity of life, social support and patient-clinician relationship (Figure 18).

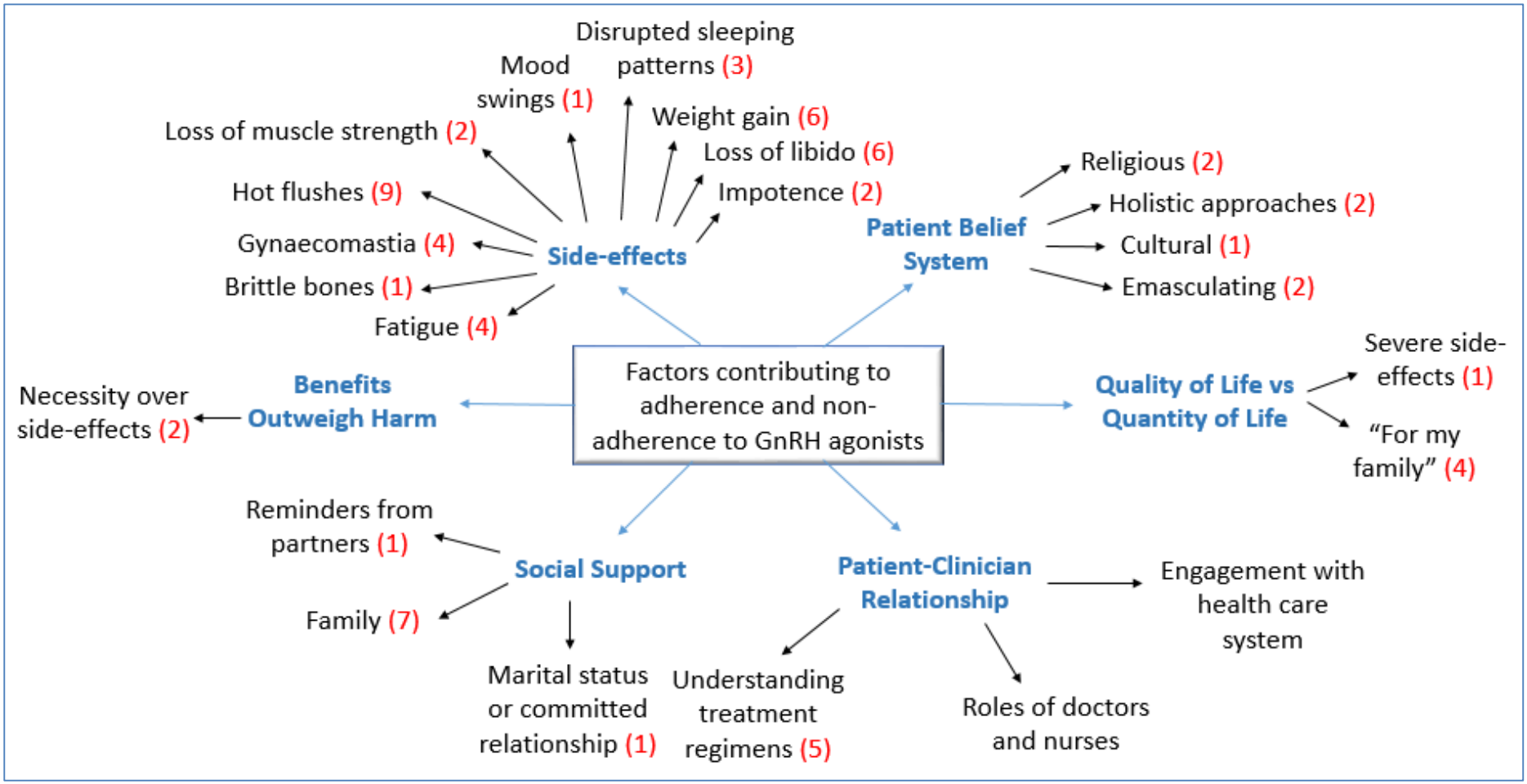

Figure 18: *Key themes identified from the interviews and focus groups. The number in brackets next to the sub-themes show the number of men in interviews who highlighted the issue. Sub-themes without a number was highlighted by focus groups.*

6.3.1.1 Stage 1: Validation

The validated protocol is shown in section 9.4.2, Appendix. In addition to the patient-centred factors contributing to non-adherence emphasised by Jin et al. (2008) (82), the Oncology Specialist highlighted other factors such as: the mixed health beliefs of patients on GnRH agonists, the desire to avoid side-effects resulting from the hormonal treatment and major life events in the patients' lives that may contribute to non-adherence (for example, a partner being diagnosed with cancer or other chronic conditions).

6.3.1.2 Stage 2: Interviews

Clinic lists were screened by the direct care team for men with PCa on GnRH agonists. Once identified, eligible men were offered the participant information sheet by the research team, outlining the purpose of the interviews. Men with PCa on GnRH agonists who agreed to take part in the study were interviewed for the study. Semi-structured interviews were conducted on a one-to-one basis using a topic guide. The interviews lasted on average for 45 minutes. No new emerging themes were identified after ten interviews. Table 35 shows the patient characteristics for the men interviewed. Seven men were classed as adherent and three were classed as non-adherent.

Table 35: *Characteristics of study participants from the interviews.*

Study ID	Age	Ethnicity	Marital Status	Adherence Status at Recruitment
ADT-001	63	White-British	Married	Adherent
ADT-002	76	White-British	Married	Adherent
ADT-003	56	White-British	Married	Adherent
ADT-004	66	Black-British	Single	Adherent
ADT-005	63	Black-British	Single	Non-adherent
ADT-006	53	Black-Other African	Single	Non-adherent

ADT-007	64	Black-British	Married	Non-adherent
ADT-008	83	White-British	Married	Adherent
ADT-009	53	Black-Caribbean	Single	Adherent
ADT-010	63	White-British	Married	Adherent

Themes identified from the interview stage were: side-effects of treatment, patient belief system, benefits outweigh harm, quality of life over quantity of life, social support and patient-clinician relationship.

Side-effects of treatment

Nine out of ten men interviewed mentioned hot flushes as a side-effect which they found quite challenging and embarrassing. Hot flushes at night also led to disrupted sleeping patterns.

> *"Another side-effect that people think, it's a bit of a laugh I guess is the hot flushes. I myself thought of that but it is, it can be quite debilitating. Um, example, every night it wakes me up at least half a dozen times."*
>
> (ADT-003, 56, adherent)

One of the most important driving forces for non-adherence in men prescribed GnRH agonists were side-effects of the treatment. Six out of ten men interviewed agreed that loss of libido was the biggest factor they found difficult to come to terms with.

> *"If you ask any man, white, black, if once you have.. you don't have libido. If you ask a woman, if you're a woman and the man is staying with you without having the urge, the craving for sex, it's.. what's the point."*

(ADT-006, 53, non-adherent)

Loss of libido also affected those who were in a committed relationship. Often men felt that they were letting their partners down.

"Yes I thought uh um I thought I was letting her down and it became very difficult to uh explain to anyone what was happening."

(ADT-008, 83, adherent)

Other side-effects that the men interviewed mentioned were weight gain (n = 6), mood swings (n = 4), fatigue (n = 4), gynaecomastia (n = 4), impotence (n = 2), loss of muscle strength (n = 2), memory loss (n = 1), brittle bones (n = 1) and painful injection site (n = 1).

Patient belief system

Some men held strong beliefs about their disease that influenced their adherence status. Some men believed that GnRH agonists contained "female" hormones that they were not willing to be injected with.

"I don't believe in this female hormones. There are all these symptoms. The ideology you know what it is no? [Interviewer: Yeah] Female hormones in a man."

(ADT-007, 64, non-adherent)

Men who held strong religious views believed in a higher deity in keeping them alive rather than taking GnRH agonists.

"The oestrogen will not stop me from dying tomorrow. So I'm not going to put my trust in the oestrogen for my life, I put my trust in God."

(ADT-007, 64, non-adherent)

In addition to believing in God to keep them alive, some men even sought out faith healers who they believed could cure their disease.

"I went to Brazil at one point to see um John of God, this guy who is supposed to be able to heal people and stuff.."

(ADT-009, 53, adherent)

Aside from religious and cultural views, stigmas against cancer, healthcare services and pharmaceutical companies can form barriers against adherence.

"And I hate to say it but a lot of these things is not materialistic. A lot of these things is not for the benefit [laughs] of the person but because of the money made from it….. They probably found a cure 15 years ago. And stop this and start that. But they're not gonna produce something that's going to solve the problem if it's not financially beneficial for them. And I'm aware of these things."

(ADT-007, 64, non-adherent)

Some men believed in herbal medications and holistic approaches rather than 'Western' medicine.

"… growing up in Jamaica, learning about plants, as a youngster growing up, about bush, natural herbs, I think that also helps me a lot. Because.. I drink…

I've been drinking a lot of bush when I first started, when I first found out that I had cancer"

(ADT-005, 63, non-adherent)

Benefits outweigh harm

All adherent men recognised having treatment as a necessity to stop their PCa from progressing. For them, side-effects were a price to pay for the benefits of having the treatment.

"It seems to be well-established that for most men and for me that it seems to be working effectively at containing the identified prostate cancer. Um you might say that that's the price to pay and that would be how I would view it."

(ADT-001, 63, adherent)

Quality of life over quantity of life

Although majority of the men interviewed felt that the necessity of having hormonal injections for their cancer outweighed their side-effects, some felt that the benefits of having treatments were outweighed by side-effects that they may experience or have already experienced.

"I may live longer but what will be the quality of my life…. I'd rather live long, naked, happy and content than go through misery."

(ADT-007, 64, non-adherent)

Men discontinued treatment due to severe side-effects that they had experienced which hindered their quality of life. For example, most men found hot flushes quite embarrassing and frustrating.

> *"Because I hate going out and I've been walking with a towel and I'm walking, I'm on the bus and mopping up.. mopping up myself [Interviewer: Yeah]. I hate it."*
>
> (ADT-005, 63, non-adherent)

Whereas other men were willing to compromise their quantity of life over quality of life for their family.

> *"I'd much rather have more time with my family even if the quality of that is a bit of the best."*
>
> (ADT-003, 56, adherent)

Social support

Having a supportive social unit, whether it is family or friends, was deemed to be an important factor influencing adherence by adherent men.

> *"An understanding family or close unit connection, I think is really important."*
>
> (ADT-001, 63, adherent)

One individual discussed about his wife's role in reminding him about his medication.

"But yes, certainly my wife particularly is brilliant at helping me remember stuff. Um reminding me to, I mean, just taking the medication. It's a bit of a challenge for somebody who has never really taken medication before. So she's very supportive in that."

(ADT-003, 56, adherent)

On the other hand, non-adherent men who were single or not in a committed relationship felt that side-effects such as loss of libido worsened if they did not have an understanding or stable partner, which in turn, influenced their decision to not have the treatment.

"*There's a lot of difference. And.. if you don't have… one single partner [Interviewer: Mmm], it makes it even worse…… if you're separated.. you haven't got somebody you trust… it's killing …… Because you don't want something you do and it will affect your libido, sometimes you want to escape it. Maybe a girl is coming to you, you don't want anything to.."*

(ADT-006, 53, non-adherent)

Patient-clinician relationship

Understanding treatment regimens

Understanding treatment regimens influenced treatment decisions in some men in choosing to adhere to GnRH agonists.

"It wouldn't get me to the point where I am today if I didn't understand."

(ADT-002, 76, adherent)

Misinterpretation of the prescribed treatment in one individual meant that he failed to have the injection on time.

> *"…. He literally thought that I was still taking the injection… But I said no… he's saying to me that, he thinks that I should be taking the injection as well."*
>
> (ADT-005, 63, non-adherent)

In addition to the themes identified above, the one-to-one interviews also included discussions on change in lifestyle factors such as smoking status, alcohol intake and exercise. Men who made changes to their lifestyle made these changes because of cancer diagnosis rather than initiating GnRH agonists. No direct link was therefore identified for these lifestyle factors contributing to adherence or non-adherence.

6.3.1.3 Stage 3: Focus groups

Six clinicians attended two focus groups which lasted for a maximum of one hour. Table 36 shows the gender and role of the clinicians.

Table 36: *Characteristics of study participants from the focus groups.*

Study ID	Gender	Professional Role
CNS-001	Female	Nurse specialist
CNS-002	Female	Nurse specialist
CNS-003	Female	Nurse specialist
ONC-001	Female	Registrar
ONC -002	Female	Consultant
ONC -003	Male	Consultant

The themes identified from the focus groups included side-effects of treatment, patient belief system, quality of life over quantity of life, social support and patient-clinician relationship.

Side-effects of treatment

Patients' views on loss of libido were in concordance with assessments made by clinicians which were discussed in the focus groups.

> *"Yeah and it's born out of all our holistic needs assessments, if you look at the top concern, month in, month out, it's the sex…… But the problem is that, it's libido, sex drive. And you can't replace that. So it involves counselling, it involves couple therapy, it involves work, it involves adapting to the fact that everything's changed and you've got to move forward."*
>
> (CNS-001, nurse specialist)

Patient belief system

Clinicians from the focus groups also agreed that strong beliefs held by men prescribed GnRH agonists also influenced their adherence status.

> *"I think that cultural thing can be around the cultural view of you as a man. In terms of your facility, in terms of your potency, in terms of your body shape, all those things. … And you hear people say "I don't want female hormones" and no matter how many times you say it's not female hormones [CNS-002: Mmm], it's perceived as feminising and demasculating."*
>
> (CNS-001, nurse specialist)

"I'm thinking some… ethnic groups, especially the African people, some beliefs that uh.. they can be in control umm of their disease, they can pray a lot and that will control the cancer."

(ONC-003, consultant oncologist)

Quality of life over quantity of life

Clinicians were also aware that some men preferred a better quality of life over a quantity of life.

"And this is a life-limiting condition and for some people, they'd rather have very short-term life with quality."

(CNS-001, nurse specialist)

Social support

Men who were adherent also had an "efficient family" who provided support by reminding these men to have their injection on time.

"Moderator: So there's no sort of reminders out there, at this point [CNS-002: No] to um –

CNS-002: Other than efficient family.

CNS-001: Because yeah, I think family."

(CNS-001, CNS-002, nurse specialists)

Patient-clinician relationship

Understanding treatment regimens

From the clinician's perspective, some men fail to understand the importance of their medication.

> *"I don't think they comprehend why they're on it, you know the importance of it and that it matters that if they miss it."*
>
> (CNS-002, nurse specialist)

Even after educating men repeatedly, some men simply did not retain the information given to them.

> *"No I don't think we can educate them that much more. I think some of it is just retention. … they'll probably attend a seminar … written information. So we do give them… all this information.. But some of it, I don't think, can retain it or.."*
>
> (CNS-003, nurse specialist)

Differences in roles between doctors and nurses

Role differences between doctors and nurses were highlighted both in the interviews and focus groups. Whereas doctors focus on oncological and treatment outcomes in their consultations with men on GnRH agonists, nurses address functional issues and side-effects in special clinics such as the sexual dysfunction clinic and seminars such as the 'Healthy on Hormones' seminar run every four months at Guy's hospital.

According to the clinicians, men attending these clinics seemed to be aware of what issues to discuss with different healthcare professionals even though some men in the interviews felt that there was no "continuity" in which doctor they saw in clinic.

> *"I think it can be done in a different forum… a seminar setting.. in a offline setting. Not in a clinic where they are making treatment decisions and where they are hearing about their latest scans and all of that. I think they'd much rather discuss what their latest scan shows … first and then talk about hormone thing which is kind of an ongoing issue and very rarely is acute problem."*
>
> (ONC-001, registrar)

Engagement with the health care system

Clinicians in both focus groups were in concordance about the importance of keeping non-adherent men engaged within the health care system.

> *".. for me it's about leaving the door open, it's about acknowledging their concerns… not trying to change their mind but just very much introducing different alternatives … making sure that they're still engaged. Because some people will change their minds."*
>
> (CNS-001, nurse specialist)

Keeping non-adherent men engaged from different perspectives and reminding them of the consequences of being non-adherent based on evidence may at some point convince them to have the treatment.

".. it's their decision… but we have to make sure that they fully understand the, the repercussions."

(ONC-002, consultant oncologist)

6.4 DISCUSSION

The results of this qualitative study provide insights into factors contributing to adherence and non-adherence to GnRH agonists in men with PCa. Loss of libido was the most important factor contributing to non-adherence in some men. Adherent men who reported side-effects such as hot flushes, disrupted sleeping patterns and weight gain found ways to cope with the side-effects as they saw that benefits of the treatment outweighed the harms. However, men who struggled to cope with the side-effects wanted a better quality of life than quantity of life and were more likely to be non-adherent. Moreover, some men held strong cultural, religious or other personal views that contributed to their non-adherence or complete refusal of initiating the treatment that they were prescribed. Social support, understanding treatment regimens and patient-clinician relationship were other factors that influenced adherence to treatment in this study.

Loss of libido strongly influenced some men's decision to not adhere to the treatment that they were prescribed. One of the interviewees viewed loss of libido as the single most important factor for being non-adherent because it was affecting his chances of finding a partner. Loss of libido was also reported as a concern in 58-91% of men on GnRH agonists in a literature review of studies investigating adverse effects of ADT (77). Moreover, 50% of married men on ADT interviewed experienced some extent of marital erosion after ADT administration (81). This suggests that loss of libido is a cause for concern in both men who are single and in a committed relationship.

Nurses in the focus group also emphasised that loss of libido was the biggest concern that men on GnRH agonists highlighted in their holistic needs assessments forms. Sexuality can be influenced by other factors such as body image and self-perceived masculinity in addition to loss of libido in these men. Based on previous evidence, 60% of men receiving hormonal treatment had negative views of their body image and felt a loss of their masculinity (206).

A strong belief system of men in this study also appear to influence adherence to treatment. Some men believed that GnRH agonists were "female hormones" which they found emasculating to be treated with. In a previous study, 50% men reported feeling less masculine after only three months on ADT (207). Psychological factors including patients' beliefs, motivation and a negative attitude towards their treatment were found to influence adherence to a treatment in other studies (82). Moreover, a negative attitude towards "Western" medication may also be heightened by an increased confidence in herbal or natural remedies leading to non-adherence to medication in certain cultures, especially in men of Black origin (208), which was also reported in the current study.

The results of this study show that ethnic origin and cultural views of men may influence non-adherence to GnRH agonists and this warrants further investigation. Out of the sixteen studies identified on ethnicity within Jin et al.'s review (82), Caucasians showed an increased adherence to medication compared to other ethnicities. This was attributed to the plausible explanation of language barriers and lower socio-economic statuses of the minorities included in the study countries.

In the current study, all non-adherent men were of Black origin who held strong beliefs and stigmas against cancer and 'Western' cancer treatments (refer to quotes by ADT-005 and ADT-006). Addressing non-adherence to GnRH agonists in this ethnic group is particularly important because men of Black origin are diagnosed with more aggressive PCa which can affect treatment-outcomes (209). Although these belief systems may be challenged it is also important to acknowledge these beliefs in order to keep non-adherent men engaged with the healthcare system.

Men in the interviews who struggled with their side-effects wanted a better quality of life than quantity of life. On the other hand, men who were determined to cope with their side-effects held a completely opposite viewpoint and believed that the benefits of the treatment outweighed the side-effects of the treatment. These two groups who belonged to the opposite ends of the spectrum were also observed in Moon et al.'s (2017) study on adherence in women with breast cancer (210).

Adherent men believed that social support in the form of a spouse or other family members helped with their adherence in this study. This was also suggested by several studies included by Jin et al. (2008) to be the reason why married patients were more adherent to medication compared to single patients (82).

According to clinicians who attended the focus groups in this study, some men simply failed to retain information despite being educated. For example, CNS-003 who is a nurse specialist, thought, *"No I don't think we can educate them that much more. I think some of it is just retention*". Although one may expect that a well-educated patient may be able to better comprehend the therapy they are receiving for their disease, Senior et al. (2004) showed that patients without a formal

educational qualification had better adherence to cholesterol-lowering medication than those with higher educational qualifications (211). Therefore, education level and the level of retention in the men interviewed may be explored in future studies to determine the role of education in non-adherence to GnRH agonists.

Having a good patient-clinician relationship contributed to understanding treatment regimens and differences in roles of healthcare professionals. Whereas some men had a good understanding of their treatment regimens and even tailored their discussions corresponding to the roles of their clinicians, understanding treatment regimens proved to be too complicated and led to misinterpretations of the regimen in other men. Clinicians in this study also felt that it was important to use different strategies to keep non-adherent men engaged with the healthcare system. As side-effects of GnRH agonists were reported to be one reason for non-adherence to GnRH agonists in this study, offering intermittent therapy (a gap between GnRH agonists' injections to minimise the side-effects of GnRH agonists discussed in more detail on page 123-124, chapter 4) may lead to the eventual acceptance of treatment in these men whilst also acknowledging their reasons for non-adherence.

6.5 CONCLUSION

In this single-centred study, adherence to GnRH agonists in men with PCa was identified to be due to a positive patient-clinician relationship and an understanding of treatment regimens among patients. Several multi-factorial reasons such as side-effects, strong patient belief system and quality over quantity of life were identified as contributing to non-adherence in some men. Reasons leading to non-adherence

can be multifactorial and unique to each patient. Therefore, supporting non-adherent men and keeping them engaged with the health care system by employing different strategies such as the use of intermittent therapy by clinicians may lead to the eventual acceptance of treatment whilst also acknowledging their reasons for non-adherence. Further multi-centre studies including larger sample sizes representative of care across UK and GP perspectives are required to fully understand adherence in men with PCa on GnRH agonists.

7. CHAPTER VII – CONCLUSION

The aim of this thesis was to use real world data to investigate adverse events of ADT and to identify patterns and factors influencing adherence to GnRH agonists in men with PCa. This chapter provides a summary of the results of the four projects.

The first project (chapter III) of this thesis was the first study to use real world data from six countries to compare the CVD effects of GnRH agonists and GnRH antagonists in men with PCa. The results of this study showed that there was an increased risk of developing CVD (arrhythmia, HF and stroke) in men with PCa on GnRH antagonists who had a HCVDi compared to men on GnRH agonists. This finding was contradictory to the pre-clinical studies comparing these GnRH analogues and thus requires further investigation. Moreover, this study highlighted the challenges of using real world data across the different countries. The results emphasised the importance of homogenous definitions for study variables when aiming to answer research questions using pooled data from different countries, especially in cases where country-specific data is limited. Therefore, the results of the first project require further investigation using updated data from countries with a larger sample size, including acute CVD events from hospital-based databases and information on prescription patterns of GnRH antagonists to address channeling bias. Finally, results from the PRONOUCE RCT may also address the potential of channeling bias in this observational setting even though the trial only covers a one-year follow-up period in which the long-term CVD effects may not be addressed.

The purpose of the three adherence projects of this thesis was to identify patterns of adherence to GnRH agonists in men with PCa in Sweden (chapter IV) and the UK (chapter V) and explore reasons for non-adherence from both patient and clinician perspectives (chapter VI). The results from PCBaSe^{Traject} Sweden identified increased age, advanced cancer stage at diagnosis, longer injection intervals and prior PCa treatment as factors contributing to increased adherence. Two of these factors were also identified in the analyses based on the UK THIN database: increased age and longer injection intervals. This provides evidence for some common factors already known from other disease settings that can contribute to adherence in men on GnRH agonists.

Moreover, employing thematic analysis to qualitative data collected from one-to-one interviews with patients and focus groups with clinicians from a hospital setting provided further insight into factors contributing to adherence and non-adherence to GnRH agonists in men with PCa. The results of the three projects showed that whilst men on long-term GnRH agonists may benefit from longer injection intervals, the reasons that lead to non-adherence are multifactorial and unique to each patient. Several multi-factorial reasons such as side-effects, strong patient belief system and quality over quantity of life were identified as contributing to non-adherence in some men. Ethnicity also played a major role in non-adherence to GnRH agonists, with an increased number of men of Black origin failing to adhere to GnRH agonists than men of other origins. Addressing non-adherence in this ethnic group is especially important because men of Black origin are diagnosed with more aggressive PCa and have worse disease-related and treatment-related outcomes.

Although the strong belief systems held by non-adherent men may be challenged, acknowledging their role in decision-making concerning their treatments and employing strategies such as the use of intermittent treatment regimens to keep non-adherent men engaged with the healthcare system may eventually lead to an acceptance of treatment. Further multi-centre studies including larger sample sizes and GP perspectives are required to fully understand factors contributing to adherence and non-adherence in men with PCa on GnRH agonists.

In conclusion, the findings from six countries highlight the importance of adverse effects of ADT in men with PCa on GnRH analogues. For the first time, results have shown an increased risk of developing CVD in men with PCa on GnRH antagonists as compared to GnRH agonists which requires further clarification from RCTs. If the findings are confirmed in further studies and RCTs, it may influence hormonal treatment of PCa in men with a prior history of CVD. Moreover, this thesis provides insights into methodological issues and challenges of data heterogeneity encountered when using real world data. The projects on adherence provide evidence for multi-factorial reasons such as side-effects and strong patient belief system contributing to non-adherence in men with PCa on GnRH agonists. This highlights the importance of using qualitative methods to complement quantitative measures in healthcare research.

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9. APPENDIX

9.1 TABLES

Appendix Table 1: *Patient characteristics for men with PCa on primary and secondary GnRH agonists after 3 years following reclassification of outcomes based on intermittent medication in PCBaSe^{Traject}.*

Patient Characteristics	3 Years			
	Primary GnRH agonists		Secondary GnRH agonists	
	Adherent (%)	Non-adherent (%)	Adherent (%)	Non-adherent (%)
n	7227 (89.2)	878 (10.8)	4049 (85.5)	689 (14.5)
Age (Years)				
Mean	76.5	75.2	75.9	74.7
SD	7.8	8.5	7.8	7.8
Age Groups (Years)				
≤ 65	681 (9.4)	121 (13.8)	440 (10.9)	93 (13.5)
66-74	1936 (26.8)	248 (28.3)	1192 (29.4)	226 (32.8)
75-84	3546 (49.1)	385 (43.9)	1877 (46.4)	302 (43.8)
≥ 85	1064 (14.7)	124 (14.1)	540 (13.3)	68 (9.9)
Injection Interval (Days)				
90	5197 (71.9)	726 (82.7)	2955 (73.0)	568 (82.4)
180	383 (5.3)	37 (4.2)	215 (5.3)	21 (3.1)
365 (Implant)	661 (9.2)	53 (6.0)	358 (8.8)	51 (7.4)
Mixed	986 (13.6)	54 (6.2)	521 (12.9)	33 (4.8)
Missing	0	8 (0.9)	0	16 (2.3)
Risk Groups at Diagnosis				
Low Risk	113 (1.6)	50 (5.7)	531 (13.1)	150 (21.8)
Medium Risk	777 (10.8)	144 (16.4)	1179 (29.1)	228 (33.1)
High Risk	2594 (35.9)	349 (39.8)	1604 (39.6)	231 (33.5)
Regional Metastasis	1213 (16.8)	124 (14.1)	488 (12.1)	49 (7.1)
Distant Metastasis	2490 (34.5)	202 (23.0)	200 (4.9)	20 (2.9)
Missing	40 (0.6)	9 (1.0)	47 (1.2)	11 (1.6)
Prior PCa Treatment				
Deferred Treatment	N/A	N/A	1810 (44.7)	340 (49.4)
Anti-androgens	N/A	N/A	763 (18.8)	84 (12.2)
Radical Prostatectomy only	N/A	N/A	323 (8.0)	94 (13.6)
Radiotherapy	N/A	N/A	875 (21.6)	123 (17.9)
Radiotherapy after Radical Prostatectomy				
< 1 year	N/A	N/A	136 (3.4)	27 (3.9)
≥ 1 year	N/A	N/A	142 (3.5)	21 (3.1)
Change in CCI* since CCI at diagnosis				

No change	5220 (72.2)	660 (75.2)	2972 (73.4)	527 (76.5)
Change by 1	1024 (14.2)	119 (13.6)	529 (13.1)	80 (11.6)
Change by 2	596 (8.3)	69 (7.9)	347 (8.6)	56 (8.1)
Change by 3	247 (3.4)	15 (1.7)	124 (3.1)	13 (1.9)
Change by ≥ 4	140 (1.9)	15 (1.7)	77 (1.9)	13 (1.9)
Civil Status				
Single	2710 (37.5)	313 (35.7)	1300 (32.1)	233 (33.8)
Married	4516 (62.5)	565 (64.4)	2749 (67.9)	456 (66.2)
Missing	1 (0.01)	0		
Year of GnRH agonists' Initiation				
2006-2007	2270 (31.4)	314 (35.8)	1019 (25.2)	167 (24.2)
2008-2009	1998 (27.7)	220 (25.1)	1051 (26.0)	154 (22.4)
2010-2011	1633 (22.6)	203 (23.1)	1056 (26.1)	166 (24.1)
2012-2013	1326 (18.4)	141 (16.1)	923 (22.8)	202 (29.3)

*CCI: Charlson Comorbidity Index.

Appendix Table 2: *Patient characteristics for men with PCa on primary and secondary GnRH agonists after 3 years following redefinition of outcomes at 50% in PCBaSe[Trajet].*

Patient Characteristics	3 Years			
	Primary GnRH agonists		Secondary GnRH agonists	
	Adherent (%)	Non-adherent (%)	Adherent (%)	Non-adherent (%)
n	7140 (88.1)	965 (11.9)	3959 (83.6)	779 (16.4)
Age (Years)				
Mean	76.5	75.1	75.9	74.7
SD	7.8	8.5	7.8	7.9
Age Groups (Years)				
≤ 65	675 (9.5)	127 (13.2)	423 (10.7)	110 (14.1)
66-74	1888 (26.4)	296 (30.7)	1173 (29.6)	245 (31.5)
75-84	3522 (49.3)	409 (42.4)	1842 (46.5)	337 (43.3)
≥ 85	1055 (14.8)	133 (13.8)	521 (13.2)	87 (11.2)
Injection Interval (Days)				
90	5095 (71.4)	828 (85.8)	2871 (72.5)	652 (83.7)
180	388 (5.4)	32 (3.3)	216 (5.5)	20 (2.6)
365 (Implant)	681 (9.5)	33 (3.4)	374 (9.5)	35 (4.5)
Mixed	976 (13.7)	64 (6.6)	498 (12.6)	56 (7.2)
Missing	0	8 (0.8)	0	16 (2.1)
Risk Groups at Diagnosis				
Low Risk	110 (1.5)	53 (5.5)	526 (13.3)	155 (19.9)
Medium Risk	773 (10.8)	148 (15.3)	1173 (29.6)	234 (30.0)
High Risk	2569 (36.0)	374 (38.8)	1555 (39.3)	280 (35.9)
Regional Metastasis	1179 (16.5)	158 (16.4)	464 (11.7)	73 (9.4)
Distant Metastasis	2469 (34.6)	223 (23.1)	195 (4.9)	25 (3.2)

Missing	40 (0.6)	9 (0.9)	46 (1.2)	12 (1.5)
Prior PCa Treatment				
Deferred Treatment	N/A	N/A	1775 (44.8)	375 (48.1)
Anti-androgens	N/A	N/A	733 (18.5)	114 (14.6)
Radical Prostatectomy only	N/A	N/A	320 (8.1)	97 (12.5)
Radiotherapy	N/A	N/A	869 (22.0)	129 (16.6)
Radiotherapy after Radical Prostatectomy				
< 1 year	N/A	N/A	128 (3.2)	34 (4.5)
≥ 1 year	N/A	N/A	134 (3.4)	29 (3.7)
Change in CCI* since CCI at diagnosis				
No change	5151 (72.1)	729 (75.5)	2904 (73.4)	595 (76.4)
Change by 1	1014 (14.2)	129 (13.4)	517 (13.1)	92 (11.8)
Change by 2	595 (8.3)	70 (7.3)	341 (8.6)	62 (8.0)
Change by 3	240 (3.4)	22 (2.3)	121 (3.1)	16 (2.1)
Change by ≥ 4	140 (2.0)	15 (1.6)	76 (1.9)	14 (1.8)
Civil Status				
Single	2648 (37.1)	375 (38.9)	1259 (31.8)	274 (35.2)
Married	4491 (62.9)	590 (61.1)	2700 (68.2)	505 (64.8)
Missing	1 (0.01)	0	0	0
Year of GnRH agonists' Initiation				
2006-2007	2235 (31.3)	349 (36.2)	989 (25.0)	197 (25.3)
2008-2009	1973 (27.6)	245 (25.4)	1027 (25.9)	178 (22.9)
2010-2011	1629 (22.8)	207 (21.5)	1033 (26.1)	189 (24.3)
2012-2013	1303 (18.3)	164 (17.0)	910 (23.0)	215 (27.6)

*CCI: Charlson Comorbidity Index.

Appendix Table 3: *Patient characteristics for men with PCa on primary and secondary GnRH agonists after 3 years following reclassification of outcomes based on intermittent medication in THIN.*

Patient Characteristics	Primary GnRH Agonists		Secondary GnRH Agonists	
	Adherent (%)	Non-adherent (%)	Adherent (%)	Non-adherent (%)
n	3833 (77.9)	1090 (22.1)	303 (71.6)	120 (28.4)
Age (Years)				
Mean	76	74	74	70
SD	8.0	8.1	8.4	7.8
Age Groups (Years)				
≤ 65	375 (9.8)	140 (12.8)	57 (18.8)	33 (27.5)
66-74	1003 (27.0)	280 (25.7)	89 (29.4)	56 (46.7)
75-84	1803 (47.0)	394 (36.2)	126 (41.6)	26 (21.7)
≥ 85	461 (12.0)	88 (8.1)	31 (10.2)	5 (4.2)
Missing	161 (4.2)	188 (17.3)	0	0

Injection Interval (Days)				
28	1001 (26.1)	466 (42.8)	66 (21.8)	30 (25.0)
90	2681 (70.1)	608 (55.8)	228 (75.3)	86 (71.7)
180	151 (3.9)	16 (1.5)	9 (3.0)	4 (3.3)
Prior PCa Treatment				
Radical prostatectomy	N/A	N/A	99 (32.7)	49 (40.8)
Radiotherapy	N/A	N/A	153 (50.5)	56 (46.7)
Anti-androgens	N/A	N/A	51 (16.8)	15 (12.5)
Civil Status				
Single	17 (0.4)	3 (0.3)	4 (1.3)	0
Married	40 (1.0)	5 (1.5)	6 (2.0)	2 (1.7)
Missing	1082 (99.3)	1082 (99.3)	293 (96.7)	118 (98.3)
Smoking Status				
Current Smokers	656 (17.1)	186 (17.1)	43 (14.2)	15 (12.5)
Non-Smokers	24 (0.6)	8 (0.7)	2 (0.7)	3 (2.5)
Past Smokers	46 (1.2)	9 (0.8)	6 (2.0)	4 (3.3)
Missing	3107 (81.1)	887 (81.4)	252 (83.2)	98 (81.7)
Ethnicity				
Caucasian	1308 (34.1)	350 (32.1)	106 (35.0)	39 (32.5)
Black	37 (1.0)	8 (0.7)	1 (0.3)	0
Asian	7 (0.2)	3 (0.3)	1 (0.3)	0
Other	8 (0.2)	5 (0.5)	2 (0.7)	0
Missing	2473 (64.5)	724 (66.4)	193 (63.7)	81 (67.5)
Socio-economic Status				
Lowest or least deprived (Townsend 1)	179 (4.7)	34 (3.1)	16 (5.3)	6 (5.0)
Low (Townsend 2)	179 (4.7)	39 (3.6)	16 (5.3)	8 (6.7)
Middle (Townsend 3)	141 (3.7)	24 (2.2)	7 (2.3)	1 (0.8)
High (Townsend 4)	111 (2.9)	11 (1.0)	7 (2.3)	2 (1.7)
Highest or most deprived (Townsend 5)	66 (1.7)	15 (1.4)	6 (2.0)	0
Missing	3157 (82.4)	967 (88.7)	251 (82.8)	103 (85.8)
BMI / obesity				
Normal weight (18.5-24)	7 (0.2)	1 (0.1)	1 (0.3)	0
Underweight (<18.5)	0	0	0	0
Overweight (25-30)	22 (0.6)	1 (0.1)	2 (0.7)	1 (0.8)
Obese (>30)	6 (0.2)	1 (0.1)	0	0
Missing	3798 (99.1)	1087 (99.7)	300 (99.0)	119 (99.2)

* BMI: Body Mass Index; N/A: Not available.

Appendix Table 4: *Patient characteristics for men with PCa on primary and secondary GnRH agonists after 3 years following redefinition of outcomes at 50% in THIN.*

Patient Characteristics	Primary GnRH Agonists		Secondary GnRH Agonists	
	Adherent (%)	Non-adherent (%)	Adherent (%)	Non-adherent (%)
n	4246 (86.3)	677 (13.8)	352 (83.2)	71 (16.8)
Age (Years)				
Mean	76	74	74	70
SD	8.0	8.1	8.4	7.6
Age Groups (Years)				
≤ 65	426 (10.0)	89 (13.2)	17 (23.9)	73 (20.7)
66-74	1141 (26.9)	172 (25.4)	107 (30.4)	38 (53.5)
75-84	1971 (46.4)	226 (33.4)	138 (39.2)	14 (19.7)
≥ 85	507 (11.9)	42 (6.2)	34 (9.7)	2 (2.8)
Missing	201 (4.7)	148 (21.9)	0	0
Injection Interval (Days)				
28	1119 (26.4)	348 (51.4)	75 (21.3)	21 (29.6)
90	2969 (70.0)	320 (47.3)	267 (75.9)	47 (66.2)
180	158 (3.7)	9 (1.3)	10 (2.8)	3 (4.2)
Prior PCa Treatment				
Radical prostatectomy	N/A	N/A	119 (33.8)	29 (40.9)
Radiotherapy	N/A	N/A	175 (50.0)	34 (47.9)
Anti-androgens	N/A	N/A	58 (16.5)	8 (11.3)
Civil Status				
Single	19 (0.5)	1 (0.2)	4 (1.1)	0
Married	42 (1.0)	3 (0.4)	6 (1.7)	2 (2.8)
Missing	4185 (98.6)	673 (99.4)	342 (97.2)	69 (97.2)
Smoking Status				
Current Smokers	724 (17.1)	118 (17.4)	50 (14.2)	8 (11.3)
Non-Smokers	26 (0.6)	6 (0.9)	4 (1.1)	1 (1.4)
Past Smokers	47 (1.1)	8 (1.2)	10 (2.8)	0
Missing	3449 (81.2)	545 (81.0)	288 (81.8)	62 (87.3)
Ethnicity				
Caucasian	1450 (34.2)	208 (30.7)	121 (34.4)	24 (33.8)
Black	43 (1.0)	2 (0.3)	1 (0.3)	0
Asian	9 (0.2)	1 (0.2)	1 (0.3)	0
Other	20 (0.2)	3 (0.4)	2 (0.6)	0
Missing	2734 (64.4)	463 (68.4)	227 (64.5)	47 (66.2)
Socio-economic Status				
Lowest or least deprived (Townsend 1)	192 (4.5)	21 (3.1)	19 (5.4)	3 (4.2)
Low (Townsend 2)	198 (4.7)	20 (3.0)	20 (5.7)	4 (5.6)
Middle (Townsend 3)	152 (3.6)	13 (1.9)	8 (2.3)	0
High (Townsend 4)	120 (2.8)	2 (0.3)	7 (2.0)	2 (2.8)
Highest or most deprived (Townsend 5)	70 (1.7)	11 (1.6)	6 (1.7)	0
Missing	3514 (82.8)	610 (90.1)	292 (83.0)	62 (87.3)

BMI / obesity				
Normal weight (18.5-24)	7 (0.2)	1 (0.2)	1 (0.3)	0
Underweight (<18.5)	0	0	0	0
Overweight (25-30)	22 (0.5)	1 (0.2)	2 (0.6)	1 (1.4)
Obese (>30)	7 (0.2)	0	0	0
Missing	4210 (99.2)	675 (99.7)	349 (99.1)	70 (98.6)

* BMI: Body Mass Index; N/A: Not available.

9.2 CODES FROM NVIVO

NVivo version 12 was used to collect codes from stage 2 interviews and stage 3 focus groups and form themes. The following two sections show figures of the codes identified.

9.2.1 Stage 2: Interviews

Nodes

Name	Files	References
Benefits outweigh harm	2	3
Quality over quantity	1	3
Family	4	6
Severe side-effects	1	3
Side-effects	2	2
Brittle bones	1	2
Disrupted sleeping patterns	3	5
Fatigue	4	6
Gynaecomastia	4	5
Hot flushes	9	15
Impotence	2	2
Loss of libido	6	20
Loss of muscle strength	2	2
Mood swings	1	1
Weight gain	6	8
Social support	1	1
Family	7	25
Marital	1	1
Reminders from spouse	1	1
Strong belief system	0	0
Cultural	1	7
Female-like	1	2
Holistic	2	2
Religious	2	4
Understanding of treatment	5	6

9.2.2 Stage 3: Focus groups

Nodes

Name	Files	References
Beliefs	2	12
Cultural	1	3
Emasculating	1	1
Holistic	1	1
Educating patients	2	13
Keep them engaged with the system	2	6
Compromise by Bicalutamide	1	1
Forgetfulness	1	2
Holiday	2	2
Negotiations & compromises	1	1
Non-adherent men want to be monitored	1	3
Offering too many options lowers compliance	1	1
PC progression can be the trigger	1	1
Trying to change someone's mind	2	4
Quality over quantity	1	1
Role differences between onc & cns	1	4
Communication between primary & secondary	1	2
Focus on oncology outcomes rather than side-effects	1	3
Not an issue for majority of patients	1	1
Orchidectomy	1	1
Patient-clinician relationship	2	15
Time restrictions in clinic or capacity	1	6
Underestimation from clinicians	1	3
Side-effects	2	20
Social support	1	4
Marital status	1	1
Understanding treatment regimens	2	12

9.3 PUBLICATIONS

9.3.1 Abstracts

9.3.1.1 Abstract presented as expert-guided poster presentation at the 33rd Annual European Association of Urology Congress, 2018, Copenhagen.

33rd Annual EAU Congress Copenhagen

PT088

The risk of cardiovascular disease following GnRH agonists versus antagonists: Real-world evidence from four European countries

Eur Urol Suppl 2018; 17(2);e1850

George G. [1], Scailteux L-M. [2], Garmo H. [1], Balusson F. [3], De Coster G. [4], De Schutter H. [4], Kuiper J. [5], Oger E. [3], Verbeeck J. [4], Van Hemelrijck M. [1]

[1]King's College London, Dept. of Translational Oncology and Urology Research , London, United Kingdom, [2]Rennes Hospital University, Pharmacovigilance Pharmacoepidemiology and Drug Information Center, Rennes, France, [3]Rennes University, UPRES EA 7449 REPERES Pharmacoepidemiology and Health Services Research, Rennes, France, [4]Belgian Cancer Registry, Brussels, Belgium, [5]PHARMO Institute for Drug Outcomes Research, Utrecht, Netherlands, The

Introduction & Objectives: While observational studies have shown an increased risk of developing cardiovascular disease (CVD) after initiation of GnRH agonists in men with prostate cancer (PCa), no associations were found in randomised controlled trials. Pre-clinical mouse models showed that a recently approved GnRH antagonist (Degarelix) resulted in less atherosclerosis and fewer characteristics of metabolic syndrome, as compared to GnRH agonists. This is the first study to combine real-world data from four European countries to compare risk of CVD following GnRH agonists and Degarelix in men with PCa.

Materials & Methods: Men with PCa who started on GnRH agonists or Degarelix were identified from the UK THIN (The Health Improvement Network) database, French National Database (SNIIRAM), Belgian Cancer Register and Dutch PHARMO Database Network. A CVD event was defined as: Any first incident or fatal CVD (ICD-10: I20-I99, G45) after cohort entry. A random-effects meta-analysis was conducted to calculate the pooled risk ratio (RR) for CVD comparing Degarelix with GnRH agonists (reference). Follow-up time started from date of GnRH agonists or Degarelix initiation. Analyses were stratified by history of CVD indicator defined as: Any CVD (ICD-10: I20-I99, G45) event or a prescription for: hypertension, dyslipidaemia or diabetes, within 12 months prior to treatment initiation. Effect modification by age was assessed using 75 years as a cut-point.

Results: 17.9% of men on GnRH agonists (7,159/39,998) and 16.9% of men on Degarelix (272/1,342) developed CVD after GnRH agonists or Degarelix initiation. The pooled analysis resulted in a RR of 1.08 (95% CI: 0.67-1.74). Due to heterogeneity (I^2 = 94%, p<0.001), data from the UK and the Netherlands were excluded, resulting in 21,463 men on GnRH agonists and 1,324 men on Degarelix. The pooled RR from France and Belgium resulted in 0.80 (95% CI: 0.60-1.08) with an improved heterogeneity (I^2 = 72%, p = 0.06). In stratified analysis, a stronger inverse association was observed for those with CVD history 12 months prior to treatment initiation 0.72 (95% CI: 0.49-1.05) than those without 0.86 (95% CI: 0.68-1.57). Stratification by age did not show any effect modification.

Conclusions: Our meta-analyses show less risk of CVD events in men on Degarelix than men on GnRH agonists who had a previous history of CVD. Since our findings are based on real-world data, they may be more applicable to the general population. Future work will look into subtypes of CVD as well as differences in prescription patterns between countries.

9.3.2 Peer-reviewed journal articles

9.3.2.1 Methodological protocol

doi: 10.1111/fcp.12454

ORIGINAL ARTICLE

Real-world insights into risk of developing cardiovascular disease following GnRH agonists versus antagonists for prostate cancer: a methodological protocol to a study using five European databases

Gincy George[a]*, Lucie-Marie Scailteux[b,c], Hans Garmo[a], Frédéric Balusson[c], Christopher Cardwell[d], Greet De Coster[e], Harlinde De Schutter[e], Josephina G. Kuiper[f], Úna McMenamin[d], Julie Verbeeck[e], Mieke Van Hemelrijck[a]

[a]Translational Oncology and Urology Research, King's College London, London, UK
[b]Pharmacovigilance, Pharmacoepidemiology and Drug Information Center, Rennes Hospital University, Rennes, France
[c]REPERES (Pharmacoepidemiology and Heath Services Research), Rennes University, EA 7449, F-35000, Rennes, France
[d]Centre for Public Health, Institute for Health Sciences, Queen's University Belfast, Belfast, Northern Ireland
[e]Belgian Cancer Registry, Brussels, Belgium
[f]PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands

Keywords
cardiovascular disease, GnRH agonists, GnRH antagonists, prostate cancer, real-world evidence

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*Correspondence and reprints: gincy.e.george@kcl.ac.uk

Joint first authors: Gincy George, Lucie-Marie Scailteux.

ABSTRACT

One of the more recently investigated adverse long-term side effects of gonadotropin-releasing hormone (GnRH) agonists for prostate cancer (PCa) is cardiovascular disease (CVD). Studies suggest lower risk of CVD following GnRH antagonists (degarelix) than GnRH agonists. This protocol describes precise codes used to extract variables from five European databases for a study that compares risk of CVD following GnRH agonists and antagonists for PCa. PCa men on primary GnRH agonists or antagonists were identified from the UK THIN (The Health Improvement Network) database, National Health Service (NHS) Scotland, Belgian Cancer Registry (BCR), Dutch PHARMO Database Network and French National Database (SNIIRAM). Cohort entry was defined as date of treatment initiation. CVD event was defined as any first incident or fatal CVD after cohort entry. Readcodes in THIN and ICD codes in NHS Scotland, BCR, PHARMO and SNIIRAM were used to extract variables. Risk of Bias in Non-randomised studies of Interventions (ROBINS-I) tool was used to assess the potential risk of biases in this study. 51 572 men with a median follow-up time of 2 years started on GnRH agonists and 2 417 men with a median follow-up time of 1 year started on GnRH antagonists between 2010 and 2017 in the UK, Scotland, Belgium, the Netherlands and France. Data from five countries improved the study power and internal validity required to compare risk of CVD between GnRH agonists and antagonists, the latter being a fairly new drug with limited data in individual countries.

INTRODUCTION

Prostate cancer (PCa) is the most common cancer among men in Europe, with a further increase in projected incidence rates [1,2]. By decreasing male hormone levels, androgen deprivation therapy (ADT) serves as the mainstream treatment for symptomatic PCa. More specifically, ADT is commonly used in

men with biochemical relapse after radical prostatectomy (RP), locally advanced PCa and metastasis [3,4].

Several metabolic side effects have been reported for ADT, including increased body weight, insulin resistance, dyslipidaemia and hyperglycaemia [5–8]. One of the more recently investigated side effects of ADT is an increased risk of cardiovascular diseases (CVD), which is believed to be due to a reduced cardio-protective effect of testosterone [6,9–12]. In 2010, the findings from several observational studies [6,9–14] prompted the Food and Drug Administration (FDA) to issue a new requirement for manufacturers of certain types of ADT (gonadotropin-releasing hormone (GnRH) receptor agonists) to add safety information to drug labels in order to warn users of the potential CVD risks involved.

It is therefore of interest to note that degarelix, a newly introduced GnRH receptor antagonist (2010), was suggested to be associated with a lower risk of CVD in PCa men [15,16]. These observations were also supported by preclinical mouse models showing less atherosclerosis and characteristics of metabolic syndrome in mice treated with degarelix as compared to those with orchiectomy or GnRH agonists [17]. Even though a recent systematic review [18] suggested that GnRH antagonists may be appropriate for those men with significant CVD risk, existing osteopenia, lower urinary tract symptoms and significant metastatic disease, no results from randomized clinical trials (RCTs) are available to compare the risk of CVD between GnRH agonists and antagonists. The PRONOUNCE trial (ClinicalTrials.gov identifier: NCT02663908), a phase III RCT comparing CVD safety of leuprolide (GnRH agonist) and degarelix (GnRH antagonist), is currently recruiting patients with an anticipated completion date in December 2020 [19]. An observational study, which directly compared the risk of CVD between GnRH antagonists and GnRH agonists, detected no difference in risk of developing stroke and myocardial infarction (MI). However, overall CVD was not investigated as a specific outcome [20].

Even though the results of the PRONOUNCE trial will inform the long-term side effects of GnRH analogues, it is equally important that any results obtained are applicable to the general PCa population. Observational studies, when well conducted, provide similar estimates of side effects to RCTs – which is the rationale behind phase IV studies [21]. Elderly participants and those with comorbidities, two common characteristics of PCa patients receiving ADT, are often excluded from RCTs [22].

Therefore, we designed a study using real-world evidence from five countries to provide results that are more applicable to the general PCa population. Moreover, as degarelix was only licensed in 2010, there was a need to combine data from different countries (the United Kingdom (UK), Scotland, Belgium, the Netherlands and France) to obtain a sufficient sample size. Preliminary results of this study were presented at the Annual Meeting of the European Association of Urology, 2018 [23] and the Global Cardio-Oncology Summit, 2018 [24].

This study describes a methodological protocol which accounts for heterogeneity in the five databases by making study variables and analyses as homogenous as possible. In this protocol, we describe the codes used to extract study variables from the databases and the processes and challenges encountered in collecting and analysing real-world data. When designing the protocol for this observational study, we followed the design of a target trial to assess all potential biases by using the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool [25].

MATERIALS AND METHODS

Study design

To investigate the association between GnRH agonists or GnRH antagonists and risk of CVD, we designed a prospective cohort study using databases (described in the 'databases' section below) from the UK, Scotland, Belgium, the Netherlands and France. The protocol was designed to obtain country-specific hazard ratios (stage 1), which were pooled in a meta-analysis (stage 2).

Target trial

A target trial is a pragmatic trial that emulates a hypothetical RCT in non-randomized studies of interventions (NRSIs) and can thus be considered useful when designing an observational study to assess effects of different types of drugs. The results of NRSIs can be evaluated for any risk of bias (RoB) by using the ROBINS-I tool [25]. The latter is based on seven specific bias domains that address biases at pre-intervention, during intervention and after intervention [25]. To ensure a clinically applicable study design for our real-world study, we used a modified version of

the ROBINS-I tool to emulate a target trial for risk of CVD following GnRH agonists or GnRH antagonists in men with PCa.

Study population

Men with PCa entered the cohort on the date of treatment (GnRH agonists or GnRH antagonists) initiation. In addition to exposure variable, cohort entry was also determined by the presence of advanced or metastatic PCa where stage of PCa was available (Belgium and the Netherlands). Once an individual entered the cohort, they stayed on that treatment regime until time of censoring.

Databases

The health improvement network. The Health Improvement Network (THIN) database is an electronic database that covers more than 11 million patients in the UK and is representative of 6.2% of the UK population [26,27]. The database comprises of longitudinal, anonymized data processed and validated by Cegedim Strategic Data (CSD) Medical Research UK. THIN is organized into seven different files (*Figure 1*), which are extracted from general practices (GP) in the UK using the VISION [28] system. The data are coded using standardized codes called the 'readcodes' [29] or 'medcodes' and 'drugcodes'. As some individuals may be present in both THIN and National Health Service (NHS) Scotland databases, PCa men from Scotland were excluded from THIN. The study period used for this project extended from 2010 to 2016.

National health service Scotland. Data were linked from five databases in Scotland [30]: the Scottish Cancer Registry, the Scottish National Prescribing Information System (PIS), the General or Acute Inpatient and Day Case dataset (SMR01), the Outpatient Attendance dataset (SMR00) and the National Records of Scotland Death Records (NRSDR) using the unique identifier number, Community Health Index Number. The resulting dataset captures information on PCa diagnosis and treatment (from the Scottish Cancer Registry), community prescriptions in Scotland (PIS), hospital diagnoses and operations (SMR01), diagnoses and procedures from outpatient clinics (SMR00) and the date and cause of death (NRSDR) [30]. Men diagnosed with PCa from 2010 to 2015 with follow-up until 2017 were part of this study.

Belgian cancer registry. All new cancer cases are legally required to be registered in Belgium in the Belgian Cancer Registry (BCR) [31]. The database constitutes of population-based clinical–pathological information on new cancer diagnoses with almost complete coverage of the Belgian population since 2004. Administrative data on reimbursed medical acts and dispensed in- and outpatient medications are provided to the BCR by the health insurance companies (HIC), covering a period from 1 year before until 5 years after the date of cancer diagnosis [32]. The HIC data contain information regarding the date and type of charged diagnostic and therapeutic procedures, and regarding the date, amount and dosages of dispensed medications. Following specific authorizations, hospital discharge data (HDD) covering hospitalizations of the patients registered by BCR from the year prior to the incidence date onwards are made available using specific codes [33]. These records contain information on hospital admission and discharge dates, diagnoses and procedures for each hospitalization. Both HIC and HDD data are deterministically coupled to the BCR database, using the national social security number as a unique patient identifier. Cause of death information for all Belgian inhabitants is provided by the three different Belgian regions and probabilistically coupled to the BCR data (coupling percentage 98%). The current project used data from 2010 to 2013.

PHARMO Database Network. The PHARMO Database Network is a population-based network of healthcare databases combining data from both primary and secondary healthcare settings in the Netherlands [34]. These different data sources, including data from GPs, in- and outpatient pharmacies, clinical laboratories, hospitals, the cancer registry, pathology registry and perinatal registry, are linked on a patient level through validated algorithms. Detailed information on the methodology and the validation of the used record linkage method can be found elsewhere [35]. For this study, data from the Out-patient Pharmacy Database, Hospitalisation Database and Cancer Registry were used. The Out-patient Pharmacy Database includes detailed information on GP or specialist prescribed healthcare products dispensed by outpatient pharmacies. The dispensing records include information on type of product, date, strength and dosage regimen, quantity, route of administration, prescriber specialty and costs. The Hospitalisation Database comprises of hospital admissions for more than 24 hours and admissions for less than 24 hours, for which a bed was required (i.e. inpatient records) from the Dutch Hospital

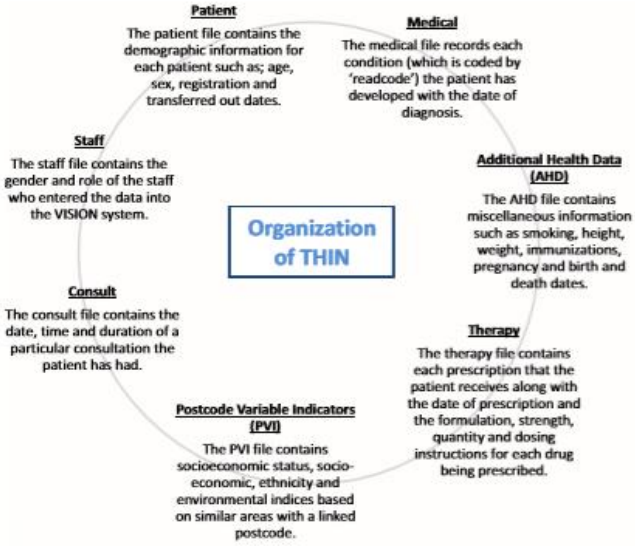

Figure 1 Organization of data in the THIN database.

Data Foundation. The records include information on hospital admission and discharge dates, discharge diagnoses and procedures. The Cancer Registry comprises information on newly diagnosed cancer patients in the Netherlands [34]. For the current project, we used data from 2010 to 2015.

French Health National Database (SNIIRAM). The French Health National Database based on claims data called the Système National d'Informations Inter-Régimes de l'Assurance Maladie (SNIIRAM) was used for this study [36]. SNIIRAM combines reimbursed claims from insurance plans with the National Hospital discharge Summaries database system (PMSI). As of 2016, the SNIIRAM includes 98.8% of the French population with follow-up from birth to death [37]. The database includes information on patient demographics, hospital and clinical visits, diagnoses of hospitalized patients (extracted using ICD-10 codes from hospital visits) and chronic medical conditions. Data between 2010 and 2013 were used for this study.

Study variables

Exposure variable

The exposure variable was defined as prescription or dispensation of GnRH agonists or GnRH antagonists. PCa men who were hormone-treatment naïve were followed from date of first prescription or dispensation until censoring (defined below).

Outcome variables

The outcome variable was defined as first (incident or fatal) CVD event (ICD-10: I20-I99, G45 or ICD-9 equivalent) following GnRH agonists or antagonists initiation. In addition to overall CVD, the following five types of CVD were considered: ischaemic heart disease (IHD) (ICD-10: I20-I25), acute myocardial infarction (AMI) (ICD-10: I21), arrhythmia (ICD-10: I44-I49), heart failure (HF) (ICD-10: I50, I97.710, I97.790, I11.0) and stroke (ICD-10: I60-64, G45). The THIN database made use of already published readcodes [29] similar to the ICD codes.

Censoring

The censoring point was defined as any of the first occurring among the following: outcome, switch between GnRH agonists and antagonists and vice versa, orchiectomy, end of study period or death from other causes than CVD death during the study period, whichever came first. Since the six CVD outcomes were studied separately, only the first event of the interested outcome at the time of analysis was considered. For example, when IHD was studied as an outcome, men

were censored at first incident or fatal IHD. Any CVD, AMI, arrhythmia, heart failure and stroke after treatment initiation were overlooked, even if these had occurred before the IHD event.

Other study variables

Age. Age was considered as a timescale in all analytical models and was defined at date of GnRH agonists or antagonists' initiation. 5 562 men in THIN had missing date of births which were imputed using multiple imputation. Age for all men in PHARMO was calculated using the same random day and month (12th June) as it only contained the year of birth.

Follow-up time. The median follow-up time and upper and lower quartiles were calculated for all countries. Follow-up time began on the date of treatment initiation and ended when they reached any of the censoring criteria discussed above.

Year of PCa diagnosis. Year of PCa diagnosis was extracted for all countries except for France, where data for the year of PCa diagnosis was not available.

Stage of PCa. PCa stage was available for Scotland, Belgium and the Netherlands, recorded at the time of PCa diagnosis. It was defined as locally advanced (T3a/bT4 N0M0) and metastatic (TxNxM1), as most men with PCa on long-term GnRH analogues are categorized into these stages. Further PCa stage subgroups were distinguished as: TxNxM1, TxN1M0, T3aNxMx, T3bNxMx and T4NxMx in Belgium.

Total Gleason Score. Total Gleason Score (GS) was available for Scotland and the Netherlands and was divided into Gleason 5–6, 7, 8, 9–10 and missing. In the Netherlands, men with invalid GS (nine patients) were included in the missing category.

Prostate-specific antigen. Prostate-specific antigen (PSA), only available for the Netherlands, was categorized into ≤ 10, 11–20, 21–50 and > 50 ng/mL.

Any prior PCa treatment. Some information on PCa treatment before GnRH initiation was available for all five countries. This included men who had undergone any form of PCa treatment prior to GnRH initiation such as radical prostatectomy, radical prostatectomy and adjuvant or salvage radiotherapy (Belgium only), radiotherapy, chemotherapy (the Netherlands only) and anti-androgens. In Belgium, radiotherapy was further split into palliative radiotherapy (1–10 fractions) and long course external beam radiotherapy (+/- brachytherapy).

Type of ADT. This variable indicated whether ADT (only in the form of GnRH agonists or antagonists) was given as primary, adjuvant, neo-adjuvant treatment or other (Belgium only). No distinction between primary, neo-adjuvant and adjuvant ADT was made in the UK due to a lack of accurate data availability on radiotherapy given to men on ADT. An ADT prescription in Belgium and Scotland was considered neo-adjuvant if it appeared in the database within 1 month before PCa incidence and the date of surgery or radiotherapy. An adjuvant ADT prescription was defined as a prescription of GnRH agonists or antagonists within a 6 months' period following surgery or radiotherapy. PCa men for whom a treatment (ADT) was found but had not fulfilled the definitions of primary, adjuvant or neo-adjuvant ADT treatment (e.g. ADT treatment started more than 6 months following surgery) were classed into the 'other' category. In the Netherlands, the cancer registry only had treatment information given at PCa diagnosis and 6 months after diagnosis and combination treatment modalities were not derived for the study. In France, information for radiotherapy (especially dosages) was not available, and therefore, a distinction between primary, adjuvant and neo-adjuvant was not made.

ADT specifics. This variable showed whether ADT was prescribed in combination with anti-androgens as flare protection or combined androgen blockade (CAB). Flare protection was defined as receiving anti-androgens for ≤ 30 days, whereas CAB was defined as receiving anti-androgens for more than 30 days.

History of CVD indicator. History of CVD indicator (HCVDi) was defined as any of the following 12 months prior to entering the cohort: any CVD event (ICD-10 codes: I20-I99, G45), hypertension (ICD-10 and ATC codes – *Figure 2*), dyslipidaemia (ATC codes or drugcodes – *Table III*) or diabetes (ATC codes or drugcodes – *Table III*). HCVDi was further subcategorized to specifically indicate history of hypertension, dyslipidaemia or diabetes 12 months prior to ADT initiation.

Number of previous CVD events. The number of CVD events prior to entering the cohort was coded as 0, 1, 2 or ≥ 3 CVD events. As data in Belgium were only

available 1 year before first ADT prescription, previous CVD events and time of last previous CVD were limited to the 12 months prior to entering the cohort. The previous history of CVD was stratified as time of last previous CVD, defined as no CVD, 0–3 months, 4–6 months, 7–12 months prior to treatment initiation.

Socio-demographic variables. Body mass index (BMI), socio-economic status (SES), civil status, smoking status and ethnicity were extracted in the UK using the readcodes (*Table II* for specific codes). BMI was defined as: underweight at ≤ 18.5 kg/m^2, normal at 18.6–24 kg/m^2, overweight at 25–30 kg/m^2 and obese at ≥ 30 kg/m^2. Townsend scores [38] were used to extract the SES of the study population. Townsend scores incorporated four different variables: unemployment, non-car ownership, non-home ownership and household overcrowding. The Townsend scores were given as quintiles (i.e. five groups of equal size ranging from 1 (least deprived) to 5 (most deprived) [38]). In THIN, civil status was coded as 12 different codes that were combined to form three categories: single, married and unknown (*Table II*). Smoking status was defined as: current smokers, non-smokers and past smokers. Ethnicity was defined as men with an origin of: Caucasian, Black, Asian and other (readcodes other than these three categories).

Analysis

The analysis was conducted in two stages: stage 1 analysis was used to assess heterogeneity and prescription patterns in different countries and stage 2 was a pooled analysis of PCa cohorts from five countries using meta-analytical techniques to pool the results. Results of the meta-analysis will be reported in the main study article.

Stage 1 analysis

Country-specific estimates of hazard ratios were calculated using Cox proportional hazard models with age as a timescale. When using age as a timescale, men entered the cohort at baseline age (left-truncation) and exited at CVD event age or censoring age. Stage 1 analysis was conducted in four separate steps: (i) age-adjusted analysis with CVD as outcome, (ii) stratified analysis based on HCVDi, (iii) multivariable analysis including HCVDi and (iv) multivariable analysis including HCVDi and number of previous CVD events.

Stage 2 analysis

In the second stage, a random-effects meta-analytic model was performed to compare the pooled log-transformed country-specific hazard ratios for CVD following GnRH agonists and GnRH antagonists. The percentage of variation between the databases was assessed using the I^2 statistic. Each country in the meta-analysis was weighted by the inverse of its variance (i.e. hazard ratios), and adjustment to the weight was made based upon the degree of heterogeneity between the five countries. Heterogeneity in the assessment of exposure and outcome data was further evaluated by performing sensitivity analyses. This included only those countries that had collected data in a similar way – incident CVD (ICD-9-CM codes) sourced from hospital discharge date and fatal CVD (ICD-10 codes) sourced from death certificates in Belgium, ICD-10 codes in Scotland, the Netherlands and France versus readcodes in the UK. Additional stratifications by HCVDi as well as age (< 75 and ≥ 75 years) were conducted to assess effect modification in all countries.

RESULTS

Table I shows the modified ROBINS-I tool used to compare a target trial with this study. This informed the inclusion/exclusion criteria for the real-world study population as well as the definitions of all relevant exposures, outcomes and study variables. The aim of using the ROBINS-I tool was to understand the types of biases and challenges involved when dealing with real-world, heterogeneous data sources. The ROBINS-I tool highlighted unmeasured confounding, channelling and misclassification biases.

Table II shows the study period, number of men with PCa on GnRH agonists and antagonists and follow-up time (median and quartiles) for the UK, Scotland, Belgium, the Netherlands and France. Total median follow-up time for the UK, Scotland, Belgium, the Netherlands and France was 2 (1.1–2.8) years for GnRH agonists and 1 (0.7–1.8) year for GnRH antagonists. High missing numbers for socio-demographic confounders (BMI, SES, smoking status and civil status) resulted in an exclusion of these variables from the analytical models. *Table III* shows detailed codes used to extract study variables from four databases.

An algorithm of ICD and ATC codes (*Figure 2*) in Belgium, the Netherlands and France was used to identify men with hypertension as using ICD codes alone resulted in a very low number of hypertensive men in an aged population.

Panel 1

If in the previous year, ICD-10 code « I10 » in the main or related or associated diagnosis OR
If patient has a « long term disease » with ICD-10 code « I10 » OR Reimbursement for HTA drugs (ATC classes C02A + C02B + C02CA06 + C02D + C02L + C03 + C07 (**exclusion** of propranolol = C07AA05) + C08 + C09) but patients **without** history of:

- ischemic stroke: ICD10 codes in main diagnosis "I63",
- and/or myocardial infarction: ICD10 codes in main diagnosis "I21",
- and/or coronaropathy diseases: ICD10 codes in main diagnosis "I20% / I21% / I22% / I23%/ I24%/ I25%",
- and/or congestive heart failure (thanks to French Quan* algorithm) defined as, in main or related or associated diagnosis (but excluding ICD-10 code "I25", already in Coronaropathy disease algorithm) or long-term disease with the following ICD10 codes:
- I099/I110/I130/I132/I420/I425/I426/I427/I428/I429/I43%/I50%/P290;
- and/or arterial thrombosis diseases: main diagnosis with ICD10 codes "I74" + and/or medical acts (CCAM) for thrombosis:

```
('EEAF%' or 'ECPF%' or 'ECFA%' or 'EBFA%' or     'EENF%' or 'EEPF%' or 'EEFA%' or
 'EECA%' or 'ENNF%'or 'ENFA%' or     'DGAF%' or 'EDAF%' or 'DGPF%' or 'EDPF%' or '
DGFA%' or 'EDFA%' or 'DGCA%' or 'EDCA%'or 'EDPF%' or 'EDJF%' or 'EDEA%' or 'EDEA%
' or     'EDLF%' or 'EDNF%' or 'EDPF%' or 'EDJF%' or'EDMA%' or                cdc_act
in    ('EANF002', 'ECNF002', 'ECJF001', 'ECCA007', 'ECCA009', 'ECCA003',    'ECCA0
02', 'ECMA001', 'ECKA002', 'EBNF001', 'EDEA001', 'EDLF007', 'EEJF001', 'EDCA005',
 'ENAF001','ENAF002', 'DGKA004', 'EDNF003', 'EDKA002'.)
```

Panel 2

If in the previous year, ICD-9 code « 4010 - 4011 - 4019 » (= ICD10 I10) in the main or related or associated diagnosis OR Reimbursement for HTA drugs (ATC classes C02A + C02B + C02CA06 + C02D + C02L + C03 + C07 + C08 + C09) but patients **without** history of:

- ischemic stroke: ICD9 codes in main diagnosis "43321 – 43311 – 43391 – 43301 – 43401 – 43411 – 43491 – 43331 - 43381" (=ICD10 I63),
- and/or myocardial infarction: ICD10 codes in main diagnosis "41000 – 41001 – 41002 – 41010 – 41011 – 41012 – 41030 – 41031 – 41032 – 41020 – 41021 – 41022 – 41040 – 41041 – 41042 – 41050 – 41051 – 41052 – 41060 – 41061 – 41062 – 41080 – 41081 – 41082 – 41090 – 41091 – 41092 – 41070 – 41071 - 41072" (=ICD10 I21),
- and/or coronaropathy diseases: ICD10 codes in main diagnosis "I20% / I21% / I22% / I23%/ I24%/ I25%" converted into ICD9 :
- I20 : 4111 – 4131 – 4130 – 4139 - 4139
- I21 :
- 41000 – 41001 – 41002 – 41010 – 41011 – 41012 – 41030 – 41031 – 41032 – 41020 – 41021 – 41022 – 41040 – 41041 – 41042 – 41050 – 41051 – 41052 – 41060 – 41061 – 41062 – 41080 – 41081 – 41082 – 41090 – 41091 – 41092 – 41070 – 41071 - 41072
- I22 : /
- I23 : 42979
- I24 : 41181 – 4110 - 41189
- I25 : 41400 – 41401 – 4292 – 412 – 41410 – 41419 – 41411 – 41412 – 4148 – 41402 – 41403 – 41404 – 41405 – 41406 – 41407 – 4142 – 4143 – 4144 – 4148 – 4148 – 4149
- and/or congestive heart failure defined as, in main or related or associated diagnosis (but excluding ICD-10 code "I25" (=ICD9 41400 – 41401 – 4292 – 412 – 41410 – 41419 – 41411 – 41412 – 4148 – 41402 – 41403 – 41404 – 41405 – 41406 – 41407 – 4142 – 4143 – 4144 – 4148 – 4148 – 4149), already in Coronaropathy disease algorithm) or long-term disease with the following ICD9 codes:
- I099 : 39890
- I110 : 40201 – 40211 - 40291
- I130 : 40401 – 40411 - 40491
- I132 : 40403 – 40413 - 40493
- I420 : /
- I425 : 4254
- I426 : 4255
- I427 : 4259
- I428 : 4252 - 4254
- I429 : /
- I43% : 4257 - 4258
- I50% : 4281 – 42820 – 42821 – 42822 – 42823 – 42830 – 42831 – 42832 – 42833 – 42840 – 42841 – 42842 – 42843 – 4280 - 4289
- P290 : 77989 ;
- and/or arterial thrombosis diseases: main diagnosis with ICD9 codes "44401 – 44409 – 4441 – 44421 – 44422 – 44481 – 44489 - 4449" (ICD10 I74)

*Quan algorithm for congestive heart failure (ICD-10 codes): I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x. P29.0.

Figure 2 Algorithm to define hypertension (HTA) used by France and the Netherlands (Panel 1) and modified algorithm used by Belgium (Panel 2).

Table I Target trial using ROBINS-I [25] tool.

	Trial characteristics		
Types of bias addressed	Target trial	This study	Challenges encountered
Randomization distribution	50/50 split	Uneven number of patients in GnRH agonists and GnRH antagonists	Observational data do not guarantee even distribution between trial arms
Information bias	Information on compliance to treatment	An individual is assumed to be in the same cohort at end of study as they are in at start of the study	There is no information on compliance in most observational databases
Unmeasured confounding	Lifestyle and socio-demographic factors	Information used for lifestyle and socio-demographic variables	Lifestyle factors are often not well recorded in healthcare databases leading to an unmeasured confounding. The UK was the only country with data on some lifestyle (BMI, smoking status) and socio-economic (Townsend scores) factors recorded. However, due to high missing data, these variables were not added to the analytical models
Unmeasured confounding	Concomitant medications, history of specific diseases	History of CVD indicator	Although CVD risk factors such as HTN, DM and DYS were adjusted for in HCVD), there may be other unmeasured concomitant medications that we may not have taken into account, leading to unmeasured confounding. This will be addressed in the main study article by calculating E-values to assess the strength of unmeasured confounding in our study
Channeling bias	GnRH antagonists to patients with no history of CVD	Men with a history of CVD may be prescribed GnRH antagonists	GnRH antagonists may have been preferentially 'channeled' to patients who may have been at risk of a CVD leading to a channeling bias. This has to be considered when interpreting the results of this study
Classification bias	Uniform coding system to define exposure and outcome variables	Readcodes & drugcodes for UK and ATC codes & ICD codes for Scotland, Belgium, the Netherlands and France	It was difficult to homogenize the coding system fully across the five countries in this study, due to heterogeneity in the data collection methods
Immortal time bias	Information on GnRH agonists and GnRH antagonists dispensation	Prescription database in the UK; Dispensing database in Scotland, Belgium, the Netherlands and France	Prescription databases usually do not hold information on whether the patient has adhered to their prescribed treatment. For example, a man with PCa may be prescribed GnRH antagonists on 1st November but may not visit their health care professional on the same day for their injection. This introduces a lag time between the prescription date and dispensation/injection date resulting in an immortal time bias. A sensitivity analysis excluding the UK accounted for immortal time bias
Immeasurable time bias	Medications given at hospital visits during the follow-up time	Hospital data were not available for the UK and medications from the inpatient pharmacy was not available for France and the Netherlands	Immeasurable time bias arises from the presence of an unidentified hospitalization within a database [49]. Records of medications administered during a hospital visit may not have been available during the study period. Data for unidentified hospitalization were not available in the five countries

HTN, Hypertension; DYS, dyslipidaemia; DM, diabetes mellitus.

Table II Study period, number of men with prostate cancer on GnRH agonists and antagonists, and median follow-up time five European databases: the United Kingdom, Scotland, Belgium, the Netherlands and France.

	United Kingdom (excluding Scotland)		Scotland		Belgium		Netherlands		France	
	Men on GnRH agonists N (%)	Men on GnRH antagonists N (%)	Men on GnRH agonists N (%)	Men on GnRH antagonists N (%)	Men on GnRH agonists N (%)	Men on GnRH antagonists N (%)	Men on GnRH agonists N (%)	Men on GnRH antagonists N (%)	Men on GnRH agonists N (%)	Men on GnRH antagonist N (%)
Study period	2010-2016		2010-2017		2010-2015		2010-2015		2010-2013	
Number of PCa men	16 955 (99.3)	118 (0.7)	11 929 (94.0)	768 (6.0)	1 860 (78.1)	522 (21.9)	1 187 (92.5)	97 (7.6)	19 641 (83.9)	912 (3.9)
Follow-up time, years										
Median	0.6	0.5	2.1	0.8	1.7	1.1	2.1	1.3	2.4	2.3
Lower quartile	0.2	0.1	1.1	0.6	0.8	0.5	1.1	0.6	2.1	1.9
Upper quartile	1.8	1.2	2.9	1.1	3.0	1.8	3.4	2.2	2.7	2.6

DISCUSSION

This is the first study to combine real-world data from five European countries to compare risk of CVD following GnRH agonists and GnRH antagonists in men with PCa. The ROBINS-I tool allowed detailed investigation of our real-world study design with an emulated RCT in an attempt to avoid misclassification and unmeasured confounding biases. Extraction of baseline and clinical characteristics defined variables that were to be included in country-specific analytical models. Homogenous variables in the five countries were then used in the meta-analytical models.

Real-world data or population-based observational studies have enabled large-scale studies that allow linkages between databases, such as cancer registries, hospital records and epidemiological databases [39]. According to Booth and Tannock, the way forward in research is to apply RCTs and real-world data in a complementary manner. Whereas RCTs provide information on how to improve efficacy and quality of life of cancer patients (because they collect lifestyle factors along with other measurements), real-world data provide evidence of improvement in outcome (including safety) at the level of the general population [39]. Therefore, the ROBINS-I tool helped generate a pragmatic approach to our study design to mimic a target trial. It specifically allowed a detailed investigation of trial characteristics, types of biases involved and challenges encountered when using different databases. The ROBINS-I tool highlighted some evident and unavoidable biases associated with observational data such as uneven randomization distribution and unmeasured confounding. Although unmeasured confounding is often unavoidable in real-world data, VanderWeele (2017) suggests a 'straightforward' E-value calculation to quantify the minimum strength of association that an unmeasured confounder would need to have with treatment and outcome in order to explain the treatment-outcome association [40]. For example, higher E-values suggest stronger unmeasured confounder associations to explain the estimated effect.

ROBINS-I tool further highlighted indication bias also known as channeling bias in pharmacoepidemiology. Qayyim Said in Yang and West-Strum (2010) describes channeling bias as one of the most common type of bias found in pharmacoepidemiology studies. Channeling bias arises when the physician treating patients for a particular disease prescribes certain drugs

Table III Codes used for the databases from the UK, France, Belgium and the Netherlands to extract study variables.

Variables	Definitions	Codes used			
		United Kingdom	France	Belgium[a]	Netherlands
Exposures defined by drugcodes in UK and ATC codes in France, Belgium and the Netherlands					
GnRH agonists	Prescription or dispensation of: Leuprorelin Acetate (Eligard), Leuprorelin Acetate (Lucrin), Leuprorelin Acetate (Generics)	Drugcodes: 39797978, 42604978, 61916979, 61917979, 61918979, 61919979, 88842998, 88845998, 92404979, 92405979, 92412979, 96945998, 97368998, 81332998, 81333998	ATC: L02AE02	ATC: L02AE02	ATC: L02AE02
	Prescription or dispensation of: Goserelin (Zoladex)	Drugcodes: 82646998, 91057998, 91058998, 92434979, 92436979, 92439979, 92444979, 94894998, 94895998	ATC: L02AE03	ATC: L02AE03	ATC: L02AE03
	Prescription or dispensation of: Buserelin	Drugcodes: 94133997, 94133998, 97430997, 97430998	ATC: L02AE02	ATC: L02AE02	ATC: L02AE02
	Triptorelin (Decapeptyl or Gonapeptyl Depot)	Drugcodes: 81648998, 81649998, 81699998, 81700998, 87670998, 87671998, 87744998, 87745998, 91336998, 91337998	ATC: L02AE04	ATC: L02AE04	ATC: L02AE04
GnRH antagonist	Prescription or dispensation of: Degarelix	Drugcodes: 82881998, 82882998, 82886998, 82887998	ATC: L02BX02	ATC: L02BX02	ATC: L02BX02
Outcomes defined by readcodes in UK and ICD codes in France, Belgium and the Netherlands					
Any CVD	First incident or fatal any CVD	G3...00, G3...11, G3...12, G3...13, G30..00, G30..12, G30..13, G30..15, G30..16, G30..17, G300.00, G301.00, G301000, G301100, G301z00, G302.00, G303.00, G304.00, G305.00, G306.00, G307.00, G3070000, G3071100, G308.00, G309.00, G308.00, G30X.00, G30X000, G30y.00, G30y100, G30y200, G30yz00, G30z.00, G31..00, G310.00, G310.11, G311.00, G311.11, G311.12, G311.13, G311.14, G3110000, G3111011, G3111100, G3112200, G3113000, G3115500, G3112z00, G31y.00, G31y000, G31y200, G31y300, G31yz00, G32..00, G32..11, G32..12, G33..00, G330.00, G330000, G330z00, G331.00, G331.11, G332.00, G33z.00, G33z000, G33z100, G33z200, G33z300, G33z400, G33z500, G33z600, G33z700, G33zz00, G34..00, G340.00, G340.11, G340.12, G340000, G340100, G342.00, G343.00, G344.00, G34y.00, G34y000, G34y100, G34yz00, G34z.00, G34z000, G35..00, G350.00, G351.00, G353.00, G35X.00, G360.00, G362.00, G363.00,	ICD 10: I20-I99, G45	ICD 10: I20-I99; G45ICD 9 : 4111 - 4131 - 4130 - 4139 – 41000 - 41001 - 41002 - 41010 - 41011 - 41012 - 41030 - 41031 -41032 - 41020 - 41021 - 41022 - 41040 - 41041 - 41042 - 41050 – 41051 - 41052 - 41060 - 41061 -41062 - 41080 - 41081 - 41082 – 41090 - 41091 - 41092 - 41070 - 41071 - 41072 - 42979 - 41181 –4110 - 41189 - 41400 - 41401 - 4292 - 412 - 41410 - 41419 – 41411 - 41412 - 4148 - 41402 – 41403 - 41404 - 41405 - 41406 – 41407 - 4142 - 4143 - 4144 -4149 -	ICD 10: I20-I99, G45

Table III. Continued

Variables	Definitions	Codes used			
		United Kingdom	France	Belgium[a]	Netherlands
		G364.00, G365.00, G38..00, G380.00, G381.00, G384.00, G38z.00, G3y..00, G3z..00, G574011, G575.00, G575.11, G575.12, G575000, G575100, G575z00, G61..00, G61..11, G61..12, G610.00, G611.00, G612.00, G613.00, G614.00, G615.00, G616.00, G617.00, G618.00, G61X.00, G61X000, G61X100, G61z.00, G63..00, G63..11, G632.00, G63y000, G63y100, G64..12, G64..13, G640.00, G640000, G641.00, G641.11, G641000, G64z.00, G64z.11, G64z.12, G64z000, G64z111, G64z200, G64z300, G64z400, G66..00, G66..11, G66..12, G66..13, G661.00, G662.00, G663.00, G664.00, G665.00, G666.00, G667.00, G668.00, G671.00, G671000, G671z00, G676000, G6W..00, G6X..00, G70..00, G700.00, G73..00, G73..12, G73y.00, G73y200, G73z.00, G73z000, G73z011, G73zz00, G742z00, G74y300, G76z000, Gyu3.00, Gyu3200, Gyu3300, Gyu3400, Gyu3600, Gyu6200, Gyu6300, Gyu6400, Gyu6F00, Gyu6G00, Gyu7400		42611 - 42612 - 42613 – 4260 - 42610 - 42650 - 4262 – 4263 - 4264 - 42651 - 42652 - 42653 - 42654 - 4266 – 4267 - 42681 - 42682 - 42689 –4269 - 4275 - 4270 - 4271 - 4272 – 42731 - 42732 - 42741 - 42742 – 42761 - 42769 - 42760 - 42781 –42789 - 4279 - 4281 - 42820 – 42821 - 42822 - 42823 - 42830 – 42831 - 42832 - 42833 - 42840 – 42841 - 42842 - 42843 - 4280 – 4289 - 9971 - 40201 - 40211 – 40291 - 430 - 431 - 4321 - 4320 –4329 - 43321 - 43311 - 43391 – 43301 - 43401 - 43411 - 43491 – 43331 - 43381 - 4350 - 4351 –4353 - 4358 - 4377 - 4352 – 4359	
Ischaemic Heart Disease	First incident or fatal IHD	G3...00, G3...11, G3...12, G3...13, G30..00, G30..11, G30..12, G30..13, G30..14, G30..15, G30..16, G30..17, G300.00, G301.00, G301000, G301100, G301z00, G302.00, G303.00, G304.00, G305.00, G306.00, G307.00, G3070000, G3071100, G308.00, G309.00, G30A.00, G30B.00, G30X.00, G30X000, G30y.00, G30y000, G30y100, G30yz00, G30yz100, G30z.00, G31..00, G310.00, G310.11, G311.00, G311.11, G311.12, G311.13, G311.14, G311000,, G311011, G311100, G311200, G311300, G311400, G311500, G311z00, G312.00, G31y.00, G31y000, G31y100, G31yz00, G31yz100, G31yz200, G31yz300, G31yz00, G32..00, G32..11, G32..12, G33..00, G330.00, G330000, G330z00, G331.00, G331.11, G332.00, G33z.00, G33z000, G33z100, G33z200, G33z300, G33z400,G33z500,	ICD 10: I20-I25	ICD 10: I20-I25iCD 9 : 4111 - 4131 - 4130 – 4139 - 41000 - 41001 - 41002 – 41010 - 41011 - 41012 - 41030 – 41031 - 41032 - 41020 - 41021 – 41022 - 41040 - 41041 - 41042 – 41050 - 41051 - 41052 - 41060 – 41061 - 41062 - 41080 - 41081 – 41082 - 41090 - 41091 - 41092 – 41070 - 41071 - 41072 - 42979 – 41181 - 4110 - 41189 - 41400 – 41401 - 4292 - 412 - 41410 – 41419 - 41411 -	ICD 10: I20-I25

Table III. Continued

Variables	Definitions	Codes used				
		United Kingdom	France	Belgium[a]	Belgium[a]	Netherlands
		G33z600, G33z700, G33zz00, G34..00, G340.00, G340.11, G340.12, G3400000, G3401100, G342.00, G343.00, G344.00, G34y.00, G34y000, G34y100, G34yz00, G34z.00, G34z000, G35..00, G350.00, G351.00, G353.00, G35X.00, G36..00, G360.00, G361.00, G362.00, G363.00, G364.00, G365.00, G366.00, G38..00, G380.00, G381.00, G384.00, G38z.00, G3y..00, G3z..00		41412 - 4148 – 41402 - 41403 - 41404 - 41405 – 41406 - 41407 - 4142 - 4143 – 4144 - 4149		
Acute Myocardial Infarction	First incident or fatal AMI	323..00, 3233.00, 3234.00, 3235.00, 3236.00, 323Z.00, 889A.00, G30..00, G30..11, G30..12, G30..13, G30..14, G30..15, G30..16, G30..17, G300.00, G301.00, G301000, G3011100, G301z00, G302.00, G303.00, G304.00, G305.00, G306.00, G307.00, G307000, G307100, G308.00, G309.00, G30A.00, G30B.00, G30X.00, G30XX000, G30y.00, G30y000, G30y100, G30yz00, G30yz00, G30z.00, G310.11, G31y100, G35..00, G350.00, G351.00, G353.00, G35X.00, G36..00, G360.00, G361.00, G362.00, G363.00, G364.00, G365.00, G366.00, G38..00, G380.00, G381.00, G384.00, G38z.00, G501.00, Gyu3400	ICD 10: I21	ICD 10: I21ICD 9 : 41000 - 41001 - 41002 – 41010 - 41011 - 41012 - 41030 – 41031 - 41032 - 41020 - 41021 –41022 - 41040 - 41041 - 41042 – 41050 - 41051 - 41052 - 41060 – 41061 - 41062 - 41080 - 41081 -41082 - 41090 - 41091 - 41092 – 41070 - 41071 – 41072	ICD 10: I21
Arrhythmia	First incident or fatal arrhythmia	14AN.00, 14AR.00, 212R.00, 327..00, 3272, 3273, 328..00, 3282, 328Z.00, 6625.00, 6A9..00, 7936A00, 8CMW200, 8HTy.00, 9Os..00, 9Os0.00, 9Os1.00, 9Os2.00, 9Os3.00, 9Os4.00, 9nF..00, 9nF1.00, G559.00, G55A.11, G56..00, G56..11, G567400, G56y.00, G56y000, G56z200, G57..00, G57..11, G570.00, G570000, G570100, G570200, G570300, G570z00, G571.00, G571.11, G572.00, G572000, G572z00, G573.00, G573000, G573100, G573200, G573300, G573400, G573500, G573600, G573z00, G574.00, G574100, G574z00, G576300, G576400, G576500, G57y.00, G57y600, G57y900, G57yA00, G57yz00, G57z.00, Gyu5a00, I45.6, I47, I47.0, I47.1, I47.2, I47.9, I48, I49, I49.0, I49.1, I49.2, I49.3, I49.4, I49.5, R00.0	ICD 10: I44- I49	ICD 10: I44- I49ICD 9 : 42611 - 42612 - 42613 – 4260 - 42610 - 42650 - 4262 – 4263 - 4264 - 42651 - 42652 – 42653 - 42654 - 42650 - 4266 – 4267 - 42681 - 42682 - 42689 –4269 - 4275 - 4270 - 4271 - 4272 – 42731 - 42732 - 42741 - 42742 – 42761 - 42769 - 42760 - 42781 –42789 – 4279	ICD 10: I44- I49
Heart Failure	First incident or fatal HF	1O1..00, 402 C, 4270, 4270C, 4270CC, 4270D, 4270DR, 4270LW, 4270R, 4271, 4271A, 4271H, 428 A, 7824A, 7824AC, 7824FC, 7824FH, G1yz100, G232.00,	ICD 10: I50, I97.710, I97.790, I11.0	ICD 10: I50, I97.710, I97.790, I11.0ICD 9 :4281 - 42820 - 42821 – 42822 - 42823 -	ICD 10: I50, I97.710, I97.790, I11.0	

Table III. Continued

Variables	Definitions	Codes used			
		United Kingdom	France	Belgium[a]	Netherlands
		G234.00, G58..00, G58..11, G580.00, G580.11, G580.12, G580.13, G580.14, G580000, G580100, G580200, G580300, G581.00, G581.11, G581.12, G581.13, G581000, G582.00, G582.12		42830 - 42831 – 42832 - 42833 - 42840 - 42841 – 42842 - 42843 - 4280 - 4289 – 9971 - 40201 - 40211 – 40291	
Stroke	First incident or fatal stroke	4350AT, 4359AT, 4360A, 4360B, 4369A, 4369AL, 4369AR, 4369B, 4369BN, G61..00, G61..11, G61..12, G610.00, G611.00, G612.00, G613.00, G614.00, G615.00, G616.00G618.00, G61X.00, G61X000, G61X100, G61z.00, G63y000, G63y100, G64..00, G64..11, G64..12, G64..13, G640.00, G640000, G641.00, G641.11, G641000, G64z.00, G64z.11, G64z.12, G64z000, G64z100, G64z111, G64z200, G64z300, G64z400, G65..00, G65..11, G65..12, G65..13, G650.00, G650.11, G651.00, G651000, G652.00, G653.00, G654.00, G656.00, G65y.00, G65z.00, G65z000, G65z100, G65z200, G66..00, G66..11, G66..12, G66..13, G660.00, G661.00, G662.00, G663.00, G664.00, G665.00, G666.00, G667.00, G668.00, G6W..00, G6X..00, Gyu6200, Gyu6300, Gyu6400, Gyu6500, Gyu6600, Gyu6G00, L440.11, L440.12	ICD 10: I60-64, G45	ICD 10: I60-64, G45ICD 9 : 430 - 431 - 4321 - 4320 – 4329 - 43321 - 43311 - 43391 – 43301 - 43401 - 43411 - 43491 –43331 - 43381 - 4350 - 4351 – 4353 - 4358 - 4377 - 4352 – 4359	ICD 10: I60-64, G45
Other variables defined by readcodes or drugcodes in UK and ICD or ATC codes in France, Belgium and the Netherlands					
Hypertension	At baseline	Algorithm using readcodes, ATC codes, BNF codes and drugcodes	Panel 1 (Figure 2)	Panel 2 (*Figure 2*) + ATC codes :C09AA01 - C09AA02 - C09AA03 – C09AA04 - C09AA05 - C09AA06 – C09AA07 - C09AA08 - C09AA09 –C09AA10 - C09AA11 - C09AA12 – C09AA13 - C09AA14 - C09AA15 – C09AA16 - C07AA01 - C07AA02 – C07AA03 - C07AA05 - C07AA06 – C07AA07 - C07AA12 - C07AA14 - C07AA15 - C07AA16 -	Panel 1 (*Figure 2*)

Table III. Continued

Variables	Definitions	Codes used			
		United Kingdom	France	Belgium[a]	Netherlands
				C07AA17 –C07AA19 -	
				C07AA23 - C07AA27 –	
				C07AB01 - C07AB02 -	
				C07AB03 – C07AB04 -	
				C07AB05 - C07AB06 –	
				C07AB07 - C07AB08 -	
				C07AB09 – C07AB10 -	
				C07AB11 - C07AB12 –	
				C07AB13 - C07AB14 -	
				C08CA01 –C08DB01 -	
				C08CA02 - C08CA03 –	
				C08CA04 - C08CA05 -	
				C08CA55 – C08DA01 -	
				C08DA51 - C03AA01 –	
				C03AA02 - C03AA03 -	
				C03AA04 – C03AA05 -	
				C03AA06 - C03AA07 –	
				C03AA08 - C03AA09 -	
				C03AA13 –C03AB01 -	
				C03AB02 - C03AB03 –	
				C03AB04 - C03AB05 -	
				C03AB06 – C03AB07 -	
				C03AB08 - C03AB09 -	
				C07BA02 - C07BA05 -	
				C07BA06 – C07BA07 -	
				C07BA12 - C07BA68 –	
				C07BB02 - C07BB03 -	
				C07BB04 –C07BB06 -	
				C07BB07 - C07BB12 –	
				C07BB52 - C09CA09 -	
				C09CA06 – C09DB07 -	
				C09DA06 - C09CA02 –	
				C09DA02 - C09CA04 -	
				C09DB05 – C09DA04 -	
				C09CA01 - C09DB06 –	
				C09DA01 - C09CA08 -	
				C09DB02 –C09DA08 -	

Table III. Continued

Variables	Definitions	Codes used			
		United Kingdom	France	Belgium[a]	Netherlands
				C09DX03 - C09CA07 –	
				C09DB04 - C09DA07 -	
				C09CA03 – C09DX02 -	
				C09DB01 - C09DA03 –	
				C09DB08 - C09DX04 -	
				C09DX01 – C02AA01 -	
				C02AA02 - C02AA03 –	
				C02AA04 - C02AA05 -	
				C02AA06 –C02AA07 -	
				C02AA52 - C02AA53 -	
				C02AA57 - C02AB01 -	
				C02AB02 – C02AC01 -	
				C02AC02 - C02AC04 –	
				C02AC05 - C02AC06 -	
				C02BA01 – C02BB01 -	
				C02CA01 - C02CA02 –	
				C02CA03 - C02CA04 -	
				C02CA06 –C02CC01 -	
				C02CC02 - C02CC03 –	
				C02CC04 - C02CC05 -	
				C02CC06 – C02CC07 -	
				C02DG01 - C02DA01 –	
				C02DB01 - C02DB02 -	
				C02DB03 – C02DB04 -	
				C02DC01 - C02DD01 –	
				C02KA01 - C02KB01 -	
				C02KC01 –C02KD01 -	
				C02KX01 - C02KX02 –	
				C02KX03 - C02KX04 -	
				C02KX05 – C02LA01 -	
				C02LA02 - C02LA03 –	
				C02LA04 - C02LA07 -	
				C02LA08 – C02LA09 -	
				C02LA50 - C02LA51 -	
				C02LA52 - C02LA71 -	
				C02LB01 –C02LC01 -	
				C02LC05 - C02LC51 –	

Table III. Continued

Variables	Definitions	Codes used			
		United Kingdom	France	Belgium[a]	Netherlands
				C02LE01 - C02LF01 - C02LG01 – C02LG02 - C02LG03 - C02LG51 – C02LG73 - C02LK01 - C02LL01 – C02LX01 - C02BC - C02LN - C02N	
Dyslipidaemia	At baseline	Algorithm using readcodes, ATC codes, BNF codes and drugcodes	ICD 10: E78	ATC codes : C10AA01 - C10AA02 – C10AA03 - C10AA04 - C10AA05 – C10AA06 - C10AA07 - C10AA08 – C10AB01 - C10AB02 - C10AB03 – C10AB04 - C10AB05 - C10AB06 – C10AB07 - C10AB08 - C10AB09 – C10AB10 - C10AB11 - C10AC01 – C10AC02 - C10AC03 - C10AC04 – C10AD01 - C10AD02 - C10AD03 – C10AD04 - C10AD05 - C10AD06 – C10AD52 - C10AX03 - C10AX05 – C10AX06 - C10AX07 - C10AX08 – C10AX09 - C10AX10 - C10AX11 – C10AX12 - C10AX13 - C10AX14	ICD 10: E78
Diabetes	At baseline	Algorithm using readcodes, ATC codes, BNF codes and drugcodes	ICD 10: E10-E14	ATC codes : A10BA02 - A10BD02 – A10BD03 - A10BD05 - A10BD07 – A10BD08 - A10BD10 - A10BD11 – A10BD13 - A10BD14 - A10BD15 – A10BD16 - A10BD17 - A10BD18 – A10BD20 - A10BB01 - A10BB02 – A10BB03 - A10BB04 -	ICD 10: E10-E14

Table III. Continued

Variables	Definitions	Codes used			
		United Kingdom	France	Belgium[a]	Netherlands
				A10BB05 –A10BB06 - A10BB07 - A10BB08 – A10BB09 - A10BB10 - A10BB11 – A10BB12 - A10BB31 - A10AB	
Prior PCa Treatment	Radical prostatectomy before GnRH initiation	Readcodes: 7820000, 7B20200, 7B36.00, 7B36.11, 7B36000, 7B36100, 7B36111, 7B36200, 7B36300, 7B36400, 7B36411, 7B36500, 7B36600, 7B36700, 7B36y00, 7B36z00, 7B36z11, 7B37.00, 7B37000, 7B37200, 7B37y00, 7B37z00, 7B3E.00, 7B3Ez00	ICD 10: M6180, M6182, M34.1, M61.2, M61.3, M61.4	Nomenclature codes (from health insurance companies : http://ondpanon.riziv.fgov.be/nomenfr/search) :261796 – 2618006946l0 - 6946211154851 - 154862777114 - 777125	ICD 10: M6180, M6182, M34.1, M61.2, M61.3, M61.4
Prior PCa Treatment	Radiotherapy	5149, 5151., 59...00, 597..00, 5971.00, 597Z.00, 59Z..00, 5A...11, 5A1..00, 5A16.00, 5A16.11, 5A16.12, 5A17.00, 5A1Z.00, 5A2..00, 5A27.00, 5A28.00, 5A2Z.00, 5A3..00, 5A33.00, 5A3Z.00, 5A4..00, 5A59.00, 5A65.00, 5A8Z.00, 7M37100, XaIpH	ICD 10: M70.6, M71.2, Z42.2, Z42.2	Nomenclature codes (from health insurance companies : http://ondpanon.riziv.fgov.be/nomenfr/search):444113 - 444124444135 - 444146444150 - 444161444172 - 444183444216 - 444220444253 - 444264444290 - 444301444312 - 444323	ICD 10: M70.6, M71.2, Z42.2, Z42.2
Smoking Status	Current smokers	Readcodes: 137%, 8CAL%, 8H%, BIAj.00, 9NS0200, 9ko%	N/A	N/A	N/A
Smoking Status	Non-smokers	Readcodes: 1371%, 9kn%	N/A	N/A	N/A
Smoking Status	Smokers	Readcodes: 1377, 1378, 1379, 137(A,B,F,K,N,O,S,T)., 1371.00, 9 km%	N/A	N/A	N/A
Ethnicity	Caucasian	Readcodes: 951%, 95A9%, 95I%, 9I1%, 9I2%	N/A	N/A	N/A
Ethnicity	Black	Readcodes: 952%, 953%, 954%, 958%, 9C%, 9C%, 9C%, 9D%	N/A	N/A	N/A
Ethnicity	Asian	Readcodes: 956%,957%,958%,95A8%,95H%,9I8%,9I9%,9IA%	N/A	N/A	N/A
Ethnicity	Other	Readcodes: 955%, 959%,95A2%,95A4%,95AA%, 958%,95J%,9J3%-9J6%,9JA3%,9JA7%,9JE%,9JF%	N/A	N/A	N/A
BMI	underweight at ≤ 18.5	Readcodes: 22K3.00, 22K6.00, EMISNQBO29	N/A	N/A	N/A
BMI	normal at 18.6–24	Readcodes: 22K1.00, 22K8.00, JHCBO5	N/A	N/A	N/A

Table III. Continued

Variables	Definitions	Codes used			
		United Kingdom	France	Belgium[a]	Netherlands
BMI	overweight at 25–30	Readcodes: 22K2.00, 22K4.00	N/A	N/A	N/A
BMI	obese at ≥ 30	Readcodes: 22KC.00, 22KD.00, 22KE.00, 22K7.00, 22K5.00	N/A	N/A	N/A
Socio-economic Status	Lowest	1 - least deprived	N/A	N/A	N/A
Socio-economic Status	Low	2	N/A	N/A	N/A
Socio-economic Status	Middle	3	N/A	N/A	N/A
Socio-economic Status	High	4	N/A	N/A	N/A
Socio-economic Status	Highest	5 - most deprived	N/A	N/A	N/A
Socio-economic Status	French 'poor income'	N/A		N/A	N/A
Civil Status	Single	Single (01), widowed (03), divorced (04), separated(05)	N/A	N/A	N/A
Civil Status	Married	Engaged (07), co-habiting (08), remarried (09), stable relationship (10), civil partnership (11)	N/A	N/A	N/A

[a]Further information on nomenclature in Belgium can be found on the RIZIV/INAMI [50].

based on patient characteristics such as severity of disease, age or gender [41]. We accounted for channeling bias by conducting a stratified meta-analysis by HCVDi. Stratification by HCVDi allowed for estimating hazard ratios across two strata: those who had a history of CVD and those who had no history of CVD.

The use of different codes in the five databases proved difficult to fully homogenize variable definitions. While readcodes and drugcodes were used to identify study variables in the UK, ICD and ATC codes were used in Scotland, Belgium, the Netherlands and France. Moreover, due to missing observations in socio-demographic data in the UK, further analyses of lifestyle factors were not possible.

An algorithm combining ICD and ATC codes (*Figure 2)* in Belgium, the Netherlands and France was used to extract hypertensive men as using ICD codes alone resulted in a very low number of hypertensive men in an aged population. We attempted to avoid classification biases in the five databases by ensuring that data availability, study variable definitions and cohort definitions were as uniform as possible (*Table III*). As information on compliance to treatment was not available in our databases, this information bias will have to be accounted for when interpreting the results of stage 1 and stage 2 analyses.

The representativeness of the European PCa population by incorporating five different databases across Europe adds strong value to this study. THIN is a primary healthcare database which represents approximately 6.2% of the UK population [39]. Whereas THIN is a primary healthcare database, data in the other four databases were of other origins. NHS Scotland provides nationwide medical record linkages between cancer registry, hospital inpatient and outpatient admission, dispensed medications and death certificates [30]. BCR derives information from standard cancer registration, health insurance companies, hospital discharge data and cause of death data [31]. The PHARMO Database Network obtains data from both primary and secondary healthcare settings which meant that both cancer registration and follow-up visits were reliably available for a patient [35]. The SNIIRAM database combines a claims database (derived from insurance funds) with hospital-derived data to form a large database representative of the French population [36]. The use of primary healthcare, secondary healthcare and claims databases thus ensured the inclusion of rare, adverse events that may not have been identified in a RCT and adds additional strength to the study.

We used a two-stage approach for the study by investigating heterogeneity in country-specific analysis. The country-specific analysis was used to describe prescription patterns and the PCa population in the five countries. Stage 2 meta-analysis assessed the risk of outcome due to the two exposures investigated. As there was no possibility of combining data at the individual level (due to legal and ethical restrictions), using pooled log-transformed hazard ratios of CVD outcomes were the only way to combine the data. In addition to creating a homogenous study protocol, we attempted to further account for heterogeneity using stratified and sensitivity analyses, as described in the methods section.

The effect of other treatment modalities in addition to GnRH agonists or antagonists needs to be considered when assessing the risk of CVD. This was not considered in detail for this study because full chemotherapy and radiotherapy profiles were not available for all countries. Chemotherapy and radiotherapy are treatment modalities given in a hospital setting, and our data source was limited in this aspect. As a result, we were not able to consider other combination treatment modalities that may have affected CVD outcome. Moreover, data on follow-up treatment modalities affecting CVD outcome were missing and were therefore a limitation to the study.

A further limitation to the study was that CVD history was only considered 12 months prior to GnRH initiation. Although Belgium received information on CVD history for a maximum of 12 months prior to PCa diagnosis, the first GnRH prescription was given immediately or a maximum of four months after PCa diagnosis (90%). In France, access to CVD history was only available during the study period (2010–2013) and accurate information on PCa diagnosis date was not available. As CVD history was not consistently available for more than 12 months across the countries, we defined CVD history to be 12 months prior to first GnRH prescription. Therefore, all men included in the study had a minimum of 12 months of CVD history. In order to keep study definitions homogenous across the five countries, we assessed history of CVD using the variable HCVDi.

The variations in prescription patterns of GnRH antagonists in the five included countries may have influenced the delivery of GnRH antagonists to a specific class of PCa men who were predisposed by factors such as comorbidities and physician preferences. For instance, a physician may have prescribed GnRH antagonists to an individual with a history of CVD based on previous evidence [42]. This means that GnRH antagonists may have been channeled to this class of PCa men (channeling bias discussed in *Table I*). Channeling may also explain the different proportions of PCa men on GnRH antagonists across the five countries. A lower number of men on GnRH antagonists was observed in the UK compared to the other four countries, owing to specific guidelines (CG175) [43,44] only allowing the use of GnRH antagonists in certain PCa men. Although these specific guidelines determined the prescription of GnRH antagonists to advanced hormone-dependent PCa men during the study period, current UK National Institute of Clinical Excellence (NICE) guidelines suggest that GnRH antagonists should be prescribed to advanced staged PCa men with a spinal metastasis (NICE TA404) [45].

In Belgium, GnRH antagonists were specified for advanced stage hormone-dependent PCa; however, no specifications were made concerning the exact definition of advanced stage, which left room for interpretation by the physician [46]. In France, although set regulations defined classes of patients for whom GnRH antagonists were prescribed, the decisions were steered mostly by the physicians who may have included PCa men with all T-stages with nodal involvement and metastatic disease [47]. In the Netherlands, the need for rapid testosterone decline was achieved by using GnRH antagonists, with switch to a GnRH agonist after a few months [48]. Potential differences in prescription and delivery of GnRH antagonists between UK, Scotland, Belgium, the Netherlands and France may thus explain the data heterogeneity between the countries.

CONCLUSION

When considering the potential heterogeneity introduced by the variation in the means of recording real-world data, pooling data from five different databases were found to be a challenge. However, for the first time we were able to use databases from the UK, Scotland, Belgium, the Netherlands and France to include a heterogeneous PCa population (in contrast to the selected PCa population in RCTs) across Europe to provide results that are more applicable to the general PCa population. The results from this study will help us understand the variations in risk of long-term CVD outcomes following GnRH agonists and GnRH antagonists in men with PCa.

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9.4 HEALTH RESEARCH AUTHORITY APPLICATION AND ARRPOVED STUDY DOCUMENTS

The Health Research Authority (HRA) grants ethical approval for studies conducted in England. The HRA approval requires the completion of a research application form on the Integrated Research Application System (IRAS) and submission to HRA along with the relevant study documents. Once HRA approval, Research and Development approval (from the site of study) and Capacity and Capability of research team approval (from site of study) is in place, recruitment can begin. The following sections include approval letter from the HRA and study documents including participant information sheets and consent forms.

9.4.1 Approval letter from the HRA

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Mieke Van Hemelrijck
Translational Oncology & Urology Research
3rd Floor, Bermondsey Wing, Great Maze Pond
Guy's Hospital
SE1 9RT

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

11 January 2019

Dear Dr Van Hemelrijck

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Adherence Patterns of GnRH Agonists in Prostate Cancer**
IRAS project ID:	**251396**
REC reference:	**18/EM/0370**
Sponsor	**Guy's and St Thomas' NHS Foundation Trust**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations in England and Wales that are ***recruiting patients*** should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter. You should then work with each organisation that has confirmed capacity and capability and provide clear instructions when research activities can commence.

Participating NHS organisations in England and Wales that are ***recruiting NHS staff*** **will not** be required to formally confirm capacity and capability before you may commence research activity at site. As such, you may commence the research at each organisation 35 days following sponsor provision to the site of the local information pack, so long as:

- You have contacted participating NHS organisations (see below for details)
- The NHS organisation has not provided a reason as to why they cannot participate
- The NHS organisation has not requested additional time to confirm.

You may start the research prior to the above deadline if the site positively confirms that the research may proceed.

If not already done so, you should now provide the local information pack for your study to your participating NHS organisations. A current list of R&D contacts is accessible at the NHS RD Forum website and these contacts MUST be used for this purpose. After entering your IRAS ID you will be able to access a password protected document (password: **Redhouse1**). The password is updated on a monthly basis so please obtain the relevant contact information as soon as possible; please do not hesitate to contact me should you encounter any issues.

Commencing research activities at any NHS organisation before providing them with the full local information pack and allowing them the agreed duration to opt-out, or to request additional time (unless you have received from their R&D department notification that you may commence), is a breach of the terms of HRA and HCRW Approval. Further information is provided in the "*summary of assessment*" section towards the end of this document.

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

IRAS project ID	251396

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Professor Reza Razavi
Tel: +44 (0)207 8483224
Email: reza.razavi@kcl.ac.uk

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **251396**. Please quote this on all correspondence.

Yours sincerely

Joanna Strickland
Assessor

Email: hra.approval@nhs.net

Copy to: *Professor Reza Razavi [sponsor contact]* *reza.razavi@kcl.ac.uk*
Jennifer Boston, Guy's and St Thomas' NHS Foundation Trust [Lead R&D contact] R&D@gstt.nhs.uk
Student: *gincy.e.george@kcl.ac.uk*

IRAS project ID	251396

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Covering letter on headed paper [Letter to Committee]		
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Kings College London Insurance Certificate]		
HRA Schedule of Events [dated]	1	26 October 2018
HRA Statement of Activities [dated]	1	26 October 2018
Interview schedules or topic guides for participants [Adherence Interview Topic Guide]	1.0	03 December 2018
Interview schedules or topic guides for participants [Adherence Focus Groups Topic Guide]	1.0	03 December 2018
IRAS Application Form [IRAS_Form_17102018]		17 October 2018
IRAS Application Form XML file [IRAS_Form_17102018]		17 October 2018
Letter from sponsor [Sponsor Letter]		
Participant consent form [amended_clean]	4	09 January 2019
Participant consent form [Adherence Consent Form (Patient)]	3.0	03 December 2018
Participant information sheet (PIS) [Adherence Participant Information Sheet (Patients)]	3.0	03 December 2018
Participant information sheet (PIS) [amended_clinician_GDPR_clean]	6	09 January 2019
Research protocol or project proposal [amended-clean]	6	09 January 2019
Summary CV for Chief Investigator (CI) [CI CV]		
Summary CV for student [Student CV]		
Summary CV for supervisor (student research) [Dr Mieke Van Hemelrijck]		

IRAS project ID	251396

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	Compliant with HRA standards
2.1	Participant information/consent documents and consent process	Yes	Compliant with HRA standards
3.1	Protocol assessment	Yes	Compliant with HRA standards
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	A statement of activities (SoA) has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used. Confirmation of capacity and & capability of the NHS site is expected for recruiting patients. Although formal confirmation of capacity and capability is not expected of the NHS site recruiting NHS staff, it will be assumed that the NHS site will confirm their capacity and capability should they not respond to the contrary, we would ask that these organisations pro-actively engage with the sponsor in order to confirm at as early a date as possible. Confirmation in such cases should be by email to the CI and Sponsor confirming participation based on the relevant Statement of Activities and information within this letter.
4.2	Insurance/indemnity arrangements assessed	Yes	Compliant with HRA standards.

Section	Assessment Criteria	Compliant with Standards	Comments
4.3	Financial arrangements assessed	Yes	There has been no application for external funding and no funding is available to the NHS site.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	The clinician participant information sheet (PIS) has been updated in accordance with GDPR as a non-substantial amendment. The clinician consent form and study protocol have also been updated as a non-substantial amendment to reflect the amended version of the clinician PIS.
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	Compliant with HRA standards
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	Compliant with HRA standards
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England and Wales

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
There is one NHS site type acting as a full research site, performing all the research activities as stated in the schedule of events and study protocol. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the

research management function at the participating organisation. Where applicable, the local LCRN contact should also be copied into this correspondence.

If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS, the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and Wales, and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A local PI is expected to be in place to oversee the research activities. GCP training is not a generic training expectation, in line with the HRA/HCRW/MHRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
The student has an honorary contract with the NHS site. Standard DBS checks and occupational health clearance is required for interviewing patients. Pre-engagement checks including occupational health clearance are not required for NHS staff.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales to aid study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

9.4.2 Study documents

9.4.2.1 Study protocol

Adherence Patterns of GnRH Agonists in Prostate Cancer

Study Protocol

Introduction

Gonadotropin-releasing hormone (GnRH) agonists, a form of androgen deprivation therapy (ADT), remains the standard treatment for men with advanced prostate cancer (PCa). About 50% of all men diagnosed with PCa receive ADT at some stage after diagnosis and some may even remain on ADT for the rest of their PCa treatment (1, 2). Non-adherence to a treatment regimen may be associated with clinical and economic consequences. In men with PCa, non-adherence to GnRH agonists may also be associated with worse prognosis (3, 4).

Non-adherence to GnRH agonists has been a concern early on with patients on long-term GnRH agonists. GnRH agonists were first developed as 3-monthly depots, however 6-monthly depots were developed soon after in order to increase patient compliance and decrease the number of physician visits required for injections (5). Unwanted side-effects that are commonly associated with ADT such as, low bone density, fatigue and hot flushes, has been suggested to lead to non-adherence to treatment regimens (6, 7).

Patient-related Factors Contributing to Non-adherence

Previous research has outlined many different factors contributing to non-adherence to medication. A common reason attributed to medication non-adherence was lack of dispensation of a drug. This occurs when a patient has not collected his/her prescribed medication from the pharmacy. Reasons such as “drug holidays” or “white-coat compliance” may also contribute to non-adherence. Drug holidays refers to short intervals of time where a patient becomes non-adherent before resuming their treatment regimen. White-coat compliance refers to the phenomenon whereby patient adherence is positively associated with clinical appointments (8). Forgetfulness and skipping medication doses are other patient-related causes that may contribute to non-adherence (9).

The psychological state of an individual may also be positively associated with adherence to a treatment regimen. A patient's adherence may be improved by the extent of social support that he or she may receive, be it from a spouse or other family members (10). Moreover, an individual with an excessive drinking or smoking history may require a high degree of behavioural change to their current lifestyle in order to adhere to a systematic treatment regimen (11).

Low health literacy and a lack of understanding of the role of treatment regimens has been associated with poor adherence to medication in patients (12, 13). For instance, PCa men on intermittent GnRH agonists may not be able to fully understand the definition of intervals between injections leading to missed doses. Therefore, educating patients about their disease, the role of their treatment in disease suppression and the treatment regimen increases their active participation in treatment (14).

Clinician-related Factors Contributing to Non-adherence

Several clinician-related factors may also contribute to non-adherence to medication (9). By prescribing complex treatment regimens, physicians may contribute to a patient's adherence. Moreover, failing to fully explain the benefits and side-effects of treatments and having a poor patient-provider relationship are other factors that may contribute to medication non-adherence (15-18). To address clinician-related factors contributing to non-adherence, establishing a therapeutic alliance between the physician and patient is important and this is known as 'concordance'. According to Bell et al. (2007), concordance is synonymous with patient-centred care. And concordance may be one mechanism by which non-adherence can be better understood (19, 20).

Quantitative and Qualitative Approaches

Most traditional methods of measuring adherence only take into account quantitative methods that although may inform patterns of adherence, provide little insight into the reasons contributing to non-adherence. Whereas a quantitative study will investigate the patterns of adherence to GnRH agonists, a qualitative study will explore the reasons why men on GnRH agonists may not adhere to their treatment regimen. We are currently investigating patterns of adherence to GnRH agonists in the UK primary care database, The Health Improvement Network and a national Swedish PCa database, PCBaSe. We will now use qualitative methods to better understand reasons contributing to non-adherence to GnRH agonists in men with PCa. We used patient-related and clinician-related factors mentioned above as the background for this study. Some factors from Jin et al.'s (2008) review are shown in Figure 1 (21).

Methods

The factors identified by Jin et al.'s literature review will be validated by an experienced specialist oncologist before being used to devise topic guides for interviews. The project is divided into two stages: interviews and focus groups (Figure 2).

Interviews

Clinic lists will be screened by the direct care team for men with PCa on GnRH agonists for a minimum of six months. Once identified, eligible men will be offered participant information sheet (PIS) by the research team, outlining the purpose of the interviews (Participant Information Sheet (Patient), v.3 dated 03/12/2018). Semi-structured interviews will be conducted using a topic guide. The interviews will last for approximately 45 minutes and will be audio recorded, anonymised, transcribed verbatim and thematically analysed. The interviews will be held in the Urology Centre or Cancer Centre at Guy's Hospital.

Study participants in this stage are at risk of being distressed when discussing sensitive topics during the interview. All participants will be informed by the researcher (in the study PIS, consent form and at the beginning of the interview) that they may ask the interviewer to stop at any point during the interview. Should there still arise a situation where a participant is distressed, the researcher will cease the interview immediately and seek the help of the participant's clinical care team to further support the distressed individual.

Focus Groups

Focus groups will be conducted for healthcare professionals treating PCa men on GnRH agonists in stage one. The focus groups will be held in 2 separate sessions: one with oncology specialists and the other with Clinical Nurse Specialists. The aim of the focus groups will be to identify any new themes that were not previously identified by the literature review [21] and the interviews. The focus groups for staff will be held at the Urology Seminar Room at Guy's Hospital. Staff at and St Thomas' Foundation Trust who have regular contact with PCa men on GnRH agonists will be invited to take part. Clinicians will be invited to the focus groups by their managers who will first introduce the study and give out the Participant Information Sheet (Clinician),v.6 dated 09/01/2019. Clinicians who are interested in taking part will then contact the researcher through the contact details given in the PIS. Once agreed, the clinicians will sign the Consent Form (Clinician), v.4 dated09/01/2019. The focus groups will last between 1-2 hours and will be audio recorded and transcribed anonymously.

Sample Size

We will aim to interview a minimum of 10 men with PCa on GnRH agonists and keep interviewing more men until there are no new emerging themes. This will be the point of saturation for our interviews stage. We will aim to recruit at least 3-5 clinicians per focus group as this seen as the minimum number of members required for a focus group [22].

Inclusion and Exclusion Criteria

All men with PCa on GnRH agonists for a minimum of six months will be included in the interviews and all clinicians who have direct contact with PCa men on GnRH agonists will be invited to take part in the focus groups. No further exclusion criteria will be implemented.

Data Management

The audio recordings from the interviews and focus groups will be directly saved onto a trust computer or laptop and will be destroyed one year following the end of study period. Once data is collected from both interviews and focus groups, the audio recordings will be transcribed anonymously by the researcher into a password-protected excel file on the trust server. The password-protected excel file containing the anonymised transcriptions will only be available to the research team and will be held on the trust server for five years after the end of study period. The end of study period will be 12 months following the recruitment of first participant in the interview stage. Both the transcription and analysis process will be conducted by the researcher and no external body will be involved in this study.

Analysis

Data collected from the semi-structured interviews and focus groups will be analysed using thematic analysis. Thematic analysis is a widely used method for analysing qualitative data where the analysis aims to identify patterns of meaning across a dataset, which can then be used to generate themes. We will identify themes in this study through a process of data familiarisation, data coding, theme development and revision of themes (following each interview) (23). For this study, we will use the six phases of thematic analysis illustrated by Braun and Clarke (2006) which include:

1. familiarising yourself with your data (includes transcription of audio recording)
2. generating initial codes by identifying repeated patterns in extracts of your data
3. searching for themes by combining the initial codes to form overarching themes
4. reviewing themes to identify coherent themes
5. defining and naming themes
6. producing the report which should provide a concise, coherent, logical and non-repetitive explanation of the themes

Thematic analysis is the ideal method to evaluate the data collected for this study because through thematic analysis of data collected from both the focus groups and interviews, we will achieve a coherent interpretation of patterns of non-adherence in men with PCa on GnRH agonists.

Expected Results

Although reasons contributing to non-adherence to GnRH agonists in men with PCa is known among clinicians, this is the first qualitative study to investigate this at a large hospital. This study will enable clinicians to understand the barriers and challenges to adhering to GnRH agonists so as to better target care pathways to improve adherence.

Dissemination of Results

The results of the study will be published in peer-reviewed articles and conferences.

References

1. Huggins C, Stevens R, Hodge C. Studies on prostate cancer: II. The effects of castration on advanced carcinoma of the prostate gland. Arch Surg. 1941;43:209-23.
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21. Jin J, Sklar GE, Min Sen Oh V, et al. Factors affecting therapeutic compliance: A review from the patient's perspective. Ther Clin Risk Manag. 2008;4(1):269-86.
22. Francis JJ, Johnston M, Robertson C, et al. What is an adequate sample size? Operationalising data saturation for theory-based interview studies. Psychol Health. 2010;25(10):1229-45.
23. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3(2):77-101.

Figures

Figure 1: Factors influencing non-adherence (Jin et al., 2008).

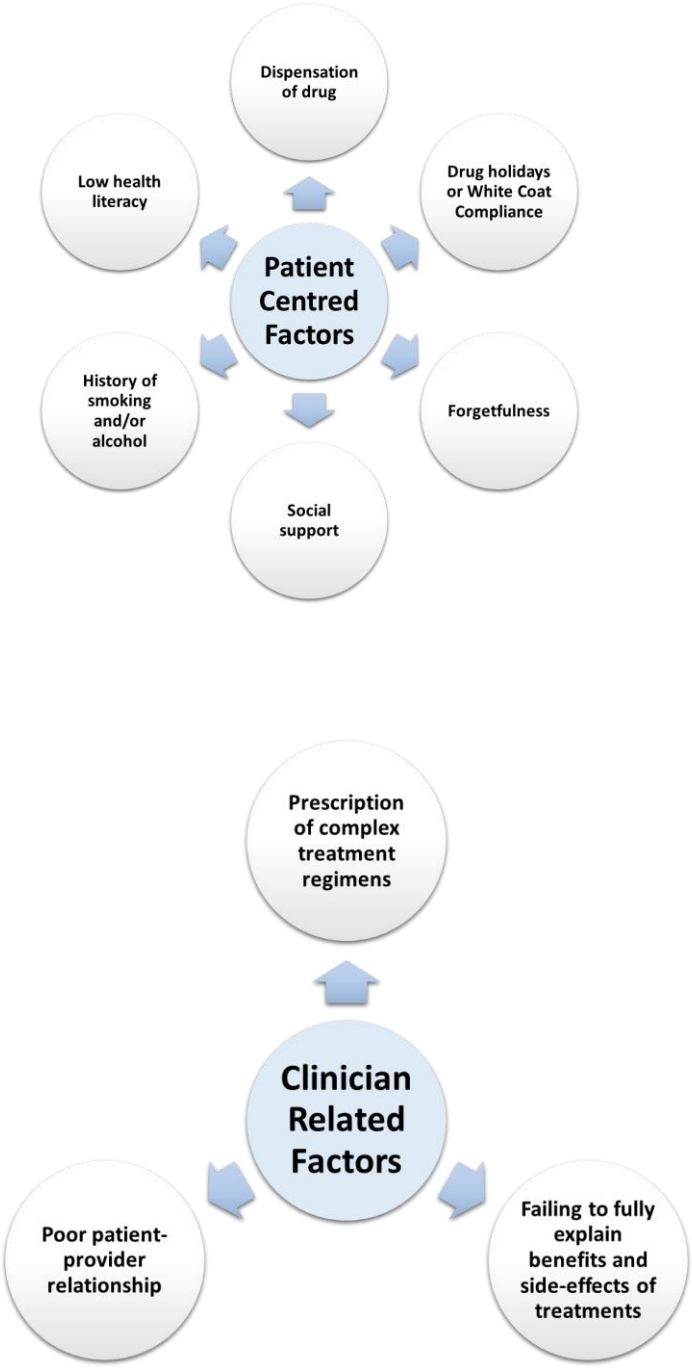
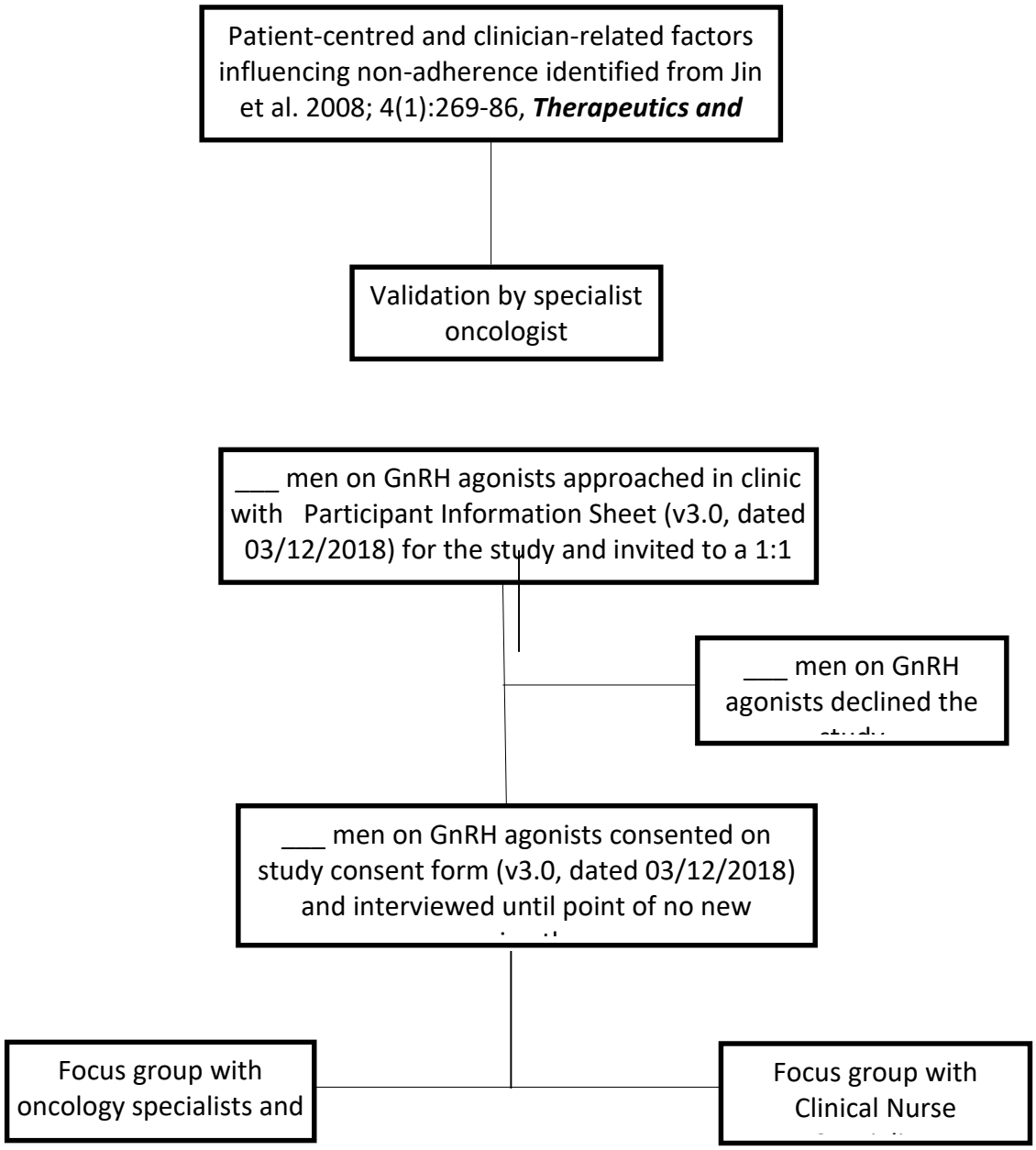


Figure 2: Flow chart of study design.



Guy's and St Thomas' NHS
NHS Foundation Trust

Adherence Patterns of GnRH Agonists in Prostate Cancer

Study Protocol

Introduction

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References

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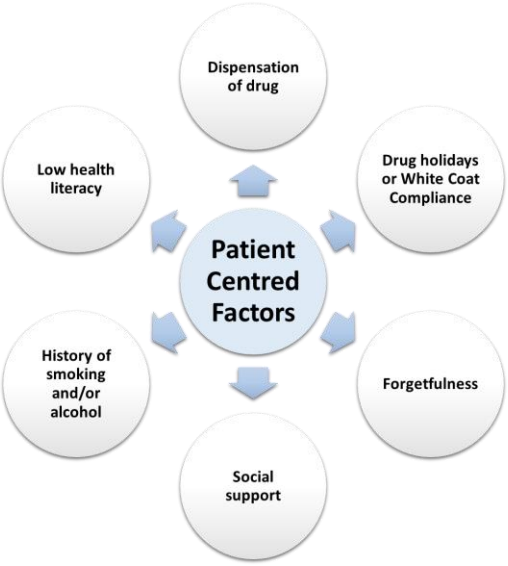
Figures

Figure 1: Factors influencing non-adherence (Jin et al., 2008).



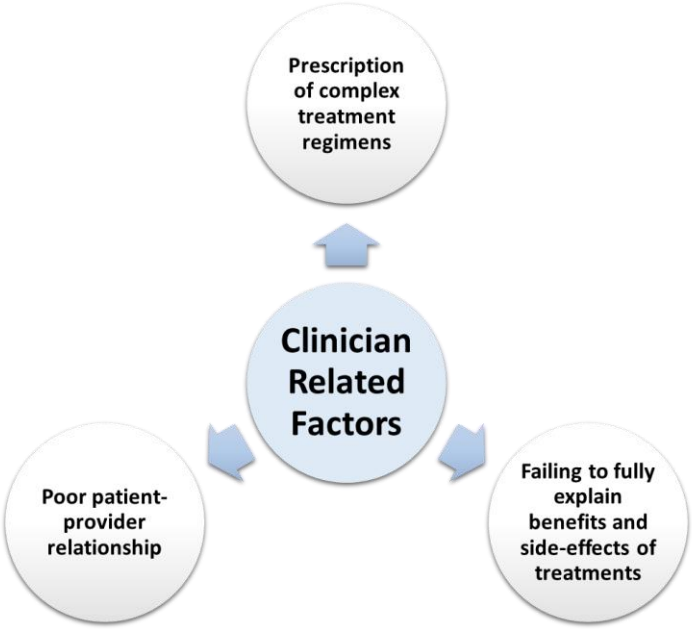
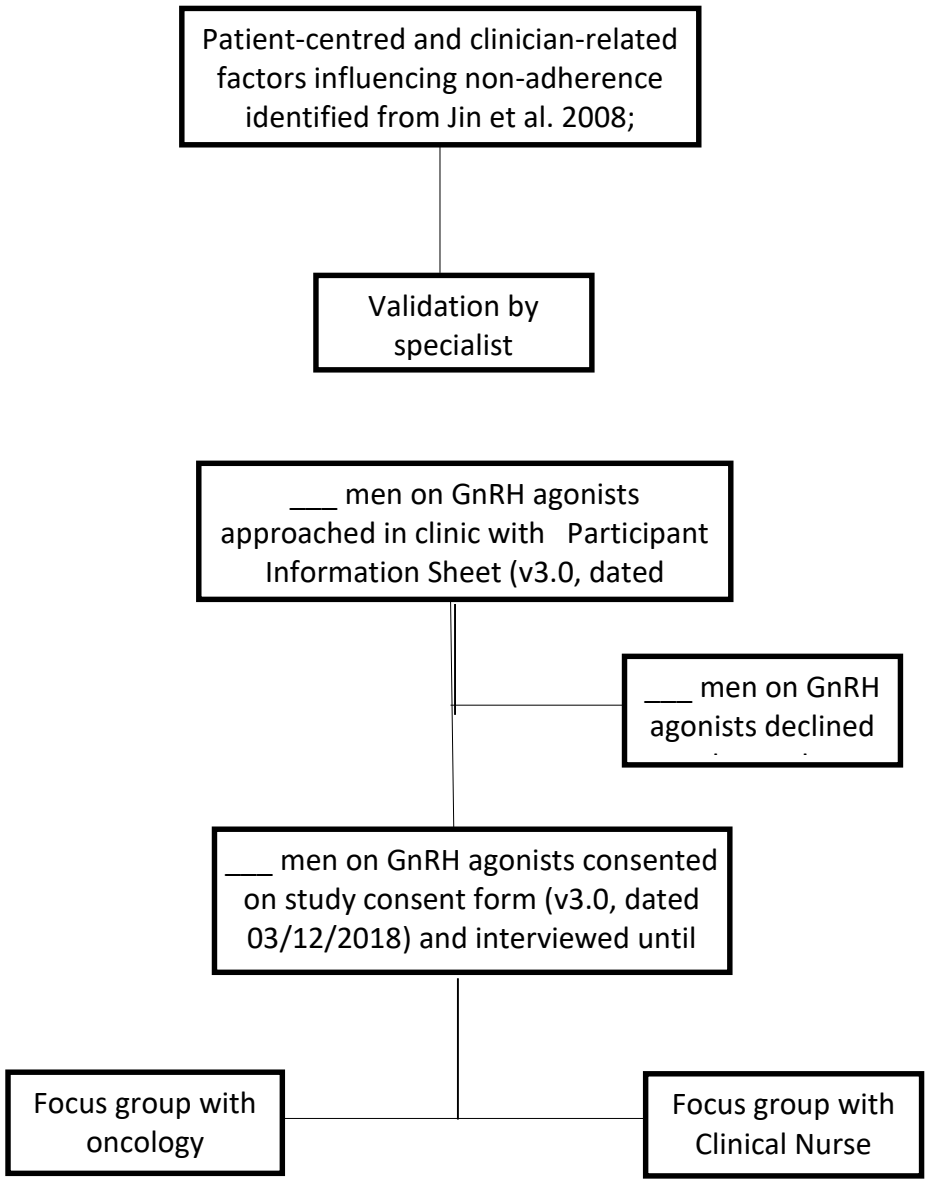


Figure 2: Flow chart of study design.



Comment from oncologist

Other patient centred factors contributing to non-adherence for patients who are on long-term GnRH agonists may include:

- Mixed health beliefs of patients
- Desire to avoid side-effects
- Major life events that a patient may have to go through (for example, a partner being diagnosed with cancer or other chronic condition)

9.4.2.3 Topic guides

9.4.2.3.1 Stage 2: Interviews

KING'S College LONDON

Guy's and St Thomas' NHS
NHS Foundation Trust

Adherence Patterns of GnRH Agonists in Prostate Cancer

TOPIC GUIDE FOR SEMI-STRUCTURED INTERVIEWS

Name of Institution:	**Guy's and St Thomas' NHS Trust**
Principle Investigator:	**Dr Sarah Rudman**
Phone Number and Contact Details:	**Gincy George**
	Clinical Trials Coordinator
	02071887188 | Ext. 57380

The aim of this 1:1 interview is to explore various factors contributing to non-adherence to the treatment in men with prostate cancer on the GnRH agonists.

The interview will follow a semi-structured approach with prostate cancer men on GnRH agonists for a minimum of six months. The interviewer is not required to strictly adhere to the structure below and may ask the following questions in no particular order. The interviews will take place in Guy's Hospital and should last no more than a maximum of 45 minutes per study participant.

Some questions to consider during the 1:1 interview:

The interviewer may ask the following main questions (in no particular order) and if needed, ask clarifying questions to cover a topic fully.

Main Questions	Clarifying Questions
Have you encountered any issues in the past with taking your injections?	• Would you mind clarifying what you meant when you said… please? • Would you mind expanding a little on… please? • Would you mind giving an example of… please?
Have you made any changes to your lifestyle to help you take your injections? Can explore lifestyle factors such as smoking and alcohol intake here.	
What makes it difficult for you to have your injection on time?	
What strategies have you used to overcome these difficulties?	
What happens when you do something 'out of routine' e.g. go on holiday?	
Do you experience any side-effects from your treatment? If so, do you think this is contributing to your difficulty to having your injection on time?	
Does a family member/spouse help you remember to take your injections?	
Do you think you understand your treatment regimen and how the injections help treat your prostate cancer? May explore clinician-patient relationship here if the participant is willing to talk about this.	

KING'S College LONDON

Guy's and St Thomas' NHS
NHS Foundation Trust

Adherence Patterns of GnRH Agonists in Prostate Cancer

TOPIC GUIDE FOR FOCUS GROUPS

Name of Institution:	**Guy's and St Thomas' NHS Trust**
Principle Investigator:	**Dr Sarah Rudman**
Phone Number and Contact Details:	**Gincy George**
	Clinical Trials Coordinator
	02071887188 | Ext. 57380

The aim of these focus groups is to explore various factors contributing to non-adherence to the treatment in men with prostate cancer on the GnRH agonists. The focus groups will be conducted with clinicians from Guy's and St Thomas' Foundation Trust who treat prostate cancer men on GnRH agonists. The focus groups will take place at Guy's hospital in two 1-2 hours sessions:

- Session 1: focus group with a minimum of 3 clinical oncologists or registrars
- Session 2: focus with a minimum of 3 clinical nurse specialists

The focus groups may follow the structure set below, in no particular order.

Some questions to consider during the focus groups:

- Do you think there is an issue with non-adherence to GnRH agonists in men with prostate cancer in clinic?
- How does your role help prostate cancer men adhere to their treatment?
- Do you think men on the treatment fully understand the consequences of not taking their injections?
- How can you as clinicians help with better adherence in to GnRH agonists?
- From your experience of treating prostate cancer men with GnRH agonists, what factor do you think is the most important in contributing to non-adherence?

Discussion of results from 1:1 interviews

In the last 30-40 minutes of the focus groups, summarise the results from 1:1 interviews with prostate cancer men on GnRH agonists and discuss the results with the clinicians. Conclude with what they as clinicians can do to tackle factors highlighted in the interviews to improve adherence to GnRH agonists in men with prostate cancer.

9.4.2.4 Participant information sheets

9.4.2.4.1 Stage 2 interviews: Participant information sheet (patient)

Adherence Patterns of GnRH Agonists in Prostate Cancer

Participant Information Sheet (Patient)

Name of Institution:	**Guy's and St Thomas' NHS Trust**
Principle Investigator:	**Dr Sarah Rudman**
Phone Number and Contact Details:	**Gincy George**
	Clinical Trials Coordinator
	02071887188 | Ext. 57380

You are being invited to take part in an optional research study. Please take the time to read the information provided below and ask questions. It is important that you understand the risks and benefits of participating in this study so that you can make a decision that is right for you. This process is known as Informed Consent.

You do not have to take part in this study and if you do not take part, it will have no effect on your care now or in the future.

If you do decide to take part, you can change your mind at any time without having to give a reason and without any effect on the care you will receive from the medical staff.

WHY IS THIS STUDY BEING DONE?

Men with prostate cancer who have hormonal injections as part of their treatment may sometimes not take their injections on time. They may also eventually stop taking their injections due to various reasons. We are trying to understand the reasons why men may stop taking their injections. This study is being conducted for educational purposes as the anonymised results will form part of a PhD project. Gincy George (Clinical Trial Coordinator) is a PhD student working as part of the Translational Oncology and Urology Research at King's College London whose PhD primarily focuses on men with prostate cancer on long-term hormonal treatment.

WHO IS ORGANISING AND FUNDING THIS STUDY?

This study is being conducted by the medical teams in Guy's and St Thomas' NHS Trust in collaboration with Kings College London (KCL).

HOW WILL IT BE CARRIED OUT?

This study will take place in Guy's and St Thomas' NHS Trust in the United Kingdom. Men with prostate cancer who are known to have advanced disease and are on hormonal injections will be invited to take part.

WHAT WILL HAPPEN TO ME IF I AGREE TO TAKE PART?

If you decide to join the study you will be asked to:

1. Sign the consent form for the study
2. Spare approximately 45 minutes in a 1:1 interview with the researcher who will discuss with you difficulties that you may have come across with being on long-term hormonal injections as part of your prostate cancer treatment

The interviews will be carried out, audio recorded and transcribed by Gincy George (Clinical Trial Coordinator). The interviews will take place in the oncology department at Guy's Hospital, Great Maze Pond, London, SE1 9RT. All transcriptions from the interviews will be made anonymous and analysed by Gincy George.

WHAT ARE THE BENEFITS OF TAKING PART IN THIS STUDY?

If you take part in the study, you may help the researchers to understand why men with prostate cancer find being on long-term hormonal injections so challenging. It is important for you to realise that this research study is designed to increase doctors' knowledge of men's perception of being on hormonal injections and the difficulties and challenges they come across which may deter them from discontinuing these hormonal injections.

WHAT ARE THE RISKS OF TAKING PART IN THIS STUDY?

The study involves spending approximately 45 minutes in a 1:1 interview with the researcher asking you questions on what may be sensitive topics.

It is important for you to realise that should at any point during the interview you may become uncomfortable, you have the right to ask the interviewer to stop the interview and seek to destroy the data collected on you so far.

CONFIDENTIALITY ISSUES

The interviews will be audio recorded. The audio recordings of the study will be transcribed anonymously by Gincy George (Clinical Trial Coordinator) and the recordings will be destroyed at the end of the study. All data collected from you will be given an identification number and will not be labelled with your name or any other information that directly identifies you. The connection between the identification number and you will only be stored on a password-protected Guy's and St Thomas' Trust computer as per NHS trust policies.

King's College London is the sponsor for this study based in London, United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. When all analysis is complete, the audio recordings from the interviews will be destroyed by the research team after 1 year following the end of study period. The anonymised data (i.e. the transcriptions) from the interviews will be archived on the password-protected Guy's and St Thomas' Foundation Trust server (co-sponsor) for five years following the end of study period.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at www.kcl.ac.uk/innovation/research/support/ethics/how-does-gdpr-affect-ethics/king's-college-london-statement-on-use-of-personal-data-in-research.aspx (sponsor) and https://www.guysandstthomas.nhs.uk/research/patients/about.aspx (co-sponsor) and/or by contacting Clinical Trials Coordinator Gincy George on gincy.george@gstt.nhs.uk or 0207 188 7188 | Ext 57380.

Guy's and St Thomas Foundation Trust will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from King's College London (contracted to Guy's and St Thomas' Foundation Trust) may look at your medical records to check the accuracy of the research study. Guy's and St Thomas Foundation Trust will pass these details to King's College London along with the information collected from you and/or your medical records. The only people in King's College London

who will have access to information that identifies you will be researchers from the research team who need to contact you to invite you to the interview.

WHO HAS REVIEWED THE STUDY?

The study has been reviewed by the Nottingham 1 Research Ethics Committee.

WHO DO I CONTACT IF I REQUIRE FURTHER INFORMATION OR HAVE ANY CONCERNS?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact: Principle Investigator Dr Sarah Rudman, via Clinical Trials Coordinator Gincy George on gincy.george@gstt.nhs.uk or 0207 188 7188 | Ext 57380.

WHAT IF THERE IS A PROBLEM?

If you have a complaint, you should talk to your research doctor (Dr Sarah Rudman) who will do their best to answer your questions. If you remain unhappy, you can make a formal complaint through the NHS complaints procedure. Details can be obtained through the Guy's and St Thomas' Patient Advisory Liaison Service (PALS) on 0207 1887188, address: PALS, KIC, Ground floor, north wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH . This study is insured by Guy's & St Thomas' NHS Foundation Trust under the Clinical Negligence Scheme for trials.

All professional staff involved in the study hold professional indemnity to work within Guy's and St Thomas' NHS Trust. In the event that you are harmed during the research and this is due to negligence then you may have grounds for legal action for compensation against Guy's and St Thomas NHS Trust but you may have to pay your legal costs. The normal NHS complaints mechanisms are still available to you.

9.4.2.4.2 Stage 3 focus groups: Participant information sheet (clinician)

Participant Information Sheet (Clinician)

Name of Institution:	**Guy's and St Thomas' NHS Trust**
Principle Investigator:	**Dr Sarah Rudman**
Phone Number and Contact Details:	**Gincy George**
	Clinical Trials Coordinator
	02071887188 | Ext. 57380

Aim of the study

Non-adherence to GnRH agonists has been a concern early on with patients on long-term GnRH agonists. Our aim is to determine the factors contributing to non-adherence to GnRH agonists in men with prostate cancer. This study is being conducted for educational purposes as the anonymised results will form part of a PhD project. Gincy George (Clinical Trial Coordinator) is a PhD student working as part of the Translational Oncology and Urology Research at King's College London whose PhD primarily focuses on men with prostate cancer on long-term hormonal treatment.

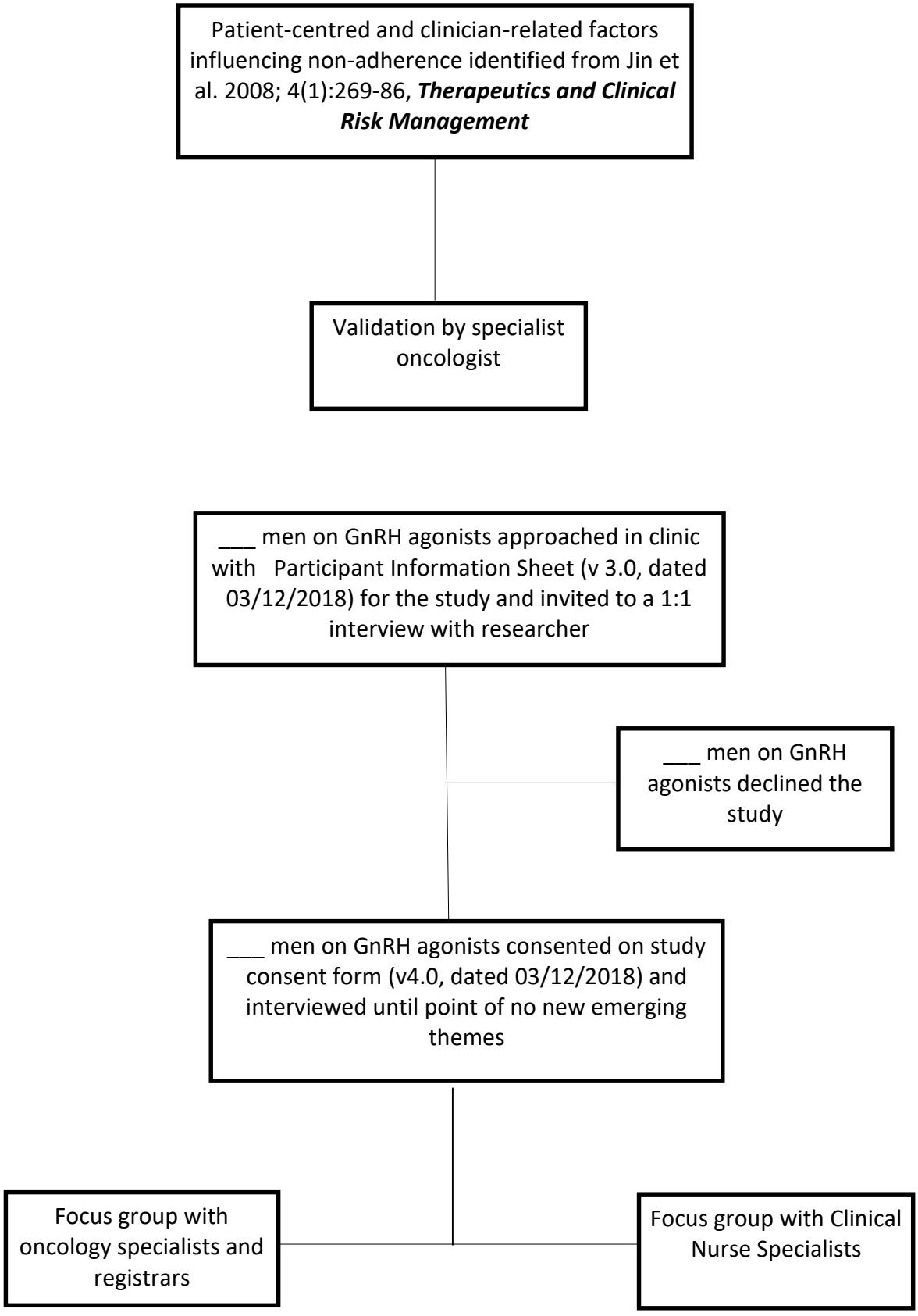
Methods

This study is divided into two stages: interviews and focus groups (Figure 1).

Results from the literature will be firstly validated by an oncologist and will be used to devise a topic guide for the interviews. Following the validation process, 1:1 interviews will be conducted with PCa men on GnRH agonists. Men with PCa on GnRH agonists for a minimum of six months will be invited to the interview stage. Semi-structured interviews will be conducted using a topic guide that covers all themes identified from the previous stages. The interviews will last for approximately 45 minutes and will be audio recorded, anonymised, transcribed verbatim and thematically analysed. The interviews will be held in the Urology Centre or Cancer Centre at Guy's Hospital.

Focus groups will be conducted for healthcare professionals treating PCa men on GnRH agonists in stage one. The focus groups will be held in 2 separate sessions: one with oncology specialists and the other with Clinical Nurse Specialists. The aim of the focus groups will be to identify any new themes that were not previously identified by in the literature. The focus groups for staff will be held at the Urology Seminar Room at Guy's Hospital and staff at Guy's hospital who have regular contact with the patient population described above will be invited to take part.

Figure 1: Flow chart of study design.



Analysis Plan

Data collected from the semi-structured interviews and focus groups will be analysed using thematic analysis. Thematic analysis is a widely used method for analysing qualitative data where the analysis aims to identify patterns of meaning across a dataset, which can then be used to generate themes. We will identify themes in this study through a process of data familiarisation, data coding, theme development and revision of themes (following each interview).

Your involvement

As health care professionals treating PCa men on GnRH agonists, you are being invited to join the focus groups that will be held in two separate sessions: one with oncology specialists and the other with Clinical Nurse Specialists. Taking part in this study is completely voluntary and you can withdraw from the study at any stage during the study, without giving a reason. If you are interested in taking part, please contact Gincy George (Clinical Trials Coordinator) via email at gincy.george@gstt.nhs.uk or by phone on 02071887188, Ext. 57380. Once you have agreed to take part in the study, you will be invited to a focus group that will last between 1-2 hours. Before taking part in the focus group, you will be asked to sign the study consent form. The focus group will be audio recorded and transcribed anonymously.

Confidentiality issues

The focus groups will be audio recorded. The audio recordings of the study will be transcribed and made anonymous by Gincy George (Clinical Trial Coordinator). When all analysis is complete, the audio recordings from the focus groups will be destroyed by the research team after 1 year following the end of study period. The anonymised data (i.e. the transcriptions) from the focus groups will be archived on the password-protected Guy's and St Thomas' Foundation Trust server for five years following the end of study period.

King's College London is the sponsor for this study and Guy's and St Thomas' will be the co-sponsor for this study who are both based in England, United Kingdom. King's College London will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The co-sponsor, Guy's and St Thomas' Foundation Trust will keep identifiable information from you for five years following the end of study period. Only anonymised information will be kept on the King's College (sponsor) server. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at www.kcl.ac.uk/innovation/research/support/ethics/how-does-gdpr-affect-

ethics/king's-college-london-statement-on-use-of-personal-data-in-research.aspx (sponsor) and https://www.guysandstthomas.nhs.uk/research/patients/about.aspx (co-sponsor) and/or by contacting Clinical Trials Coordinator Gincy George on gincy.george@gstt.nhs.uk or 0207 188 7188 | Ext 57380.

If there is a problem

If there are any issues or complaint about the conduct of the study, please contact the Chief Investigator of the study, Dr Sarah Rudman on gincy.george@gstt.nhs.uk who will do their best to resolve any issues. If you remain unhappy, a formal complaint can be made through the NHS complaints procedure. Details can be obtained through the Guy's and St Thomas' Patient Advisory Liaison Service (PALS) on 0207 1887188, address: PALS, KIC, Ground floor, north wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH . This study is insured by Guy's & St Thomas' NHS Foundation Trust under the Clinical Negligence Scheme for trials.

All professional staff involved in the study hold professional indemnity to work within Guy's and St Thomas' NHS Trust. In the event that you are harmed during the research and this is due to negligence then you may have grounds for legal action for compensation against Guy's and St Thomas NHS Trust but you may have to pay your legal costs. The normal NHS complaints mechanisms are still available to you.

Study review

This study has been reviewed by the Nottingham 1 Research Ethics Committee.

9.4.2.5 Consent forms

9.4.2.5.1 Stage 2 interviews: Consent form (patient)

Guy's and St Thomas' NHS
NHS Foundation Trust

CONSENT FORM (PATIENT)

Participant Identification Number: _____

Name of Institution: **Guy's and St Thomas' NHS Trust**

Principle Investigator: **Dr Sarah Rudman**

Phone Number and Contact Details: **Gincy George**

Clinical Trials Coordinator

02071887188 | Ext. 57380

Please write your initials in each box

1. I have read the attached Participant Information Sheet (Patient) (Version 3.0, dated 03/12/2018) on 'Adherence Patterns of GnRH Agonists in Prostate Cancer' and have been given a copy to keep. The information has been fully explained to me and I have had an opportunity to ask questions about the project and understand why the research is being done and any foreseeable risks or consequences involved. I also understand that no guarantee can be given about the possible results. ☐

2. I give permission to be contacted regarding participating in an interview as part of this study. I understand that my participation is voluntary, and any contribution I make within these sessions will be anonymised. ☐

3. I give permission for my interview to be audio recorded. All information collected will be transcribed, stored and analysed anonymously. I understand that the data will be protected by the principles of confidentiality and both national and EU data protection legislation. ☐

4. I give permission for individuals from regulatory authorities or from the NHS Trust to look at relevant sections of my medical notes and data collected during the study for audits or research monitoring purposes. I give permission for these individuals to have access to my records for these purposes. ☐

5. I give permission to take part and I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, and without my medical care or legal rights being affected. ☐

6. I know how to contact the research team if I need to. ☐

7. I agree to take part in the above study. ☐

Name of participant (BLOCK CAPITALS)	Date	Signature
Name of researcher	Date	Signature

KING'S College LONDON

Guy's and St Thomas' NHS
NHS Foundation Trust

Adherence Patterns of GnRH Agonists in Prostate Cancer

CONSENT FORM (CLINICIAN)

Participant Identification Number:	_____
Name of Institution:	**Guy's and St Thomas' NHS Trust**
Principle Investigator:	**Dr Sarah Rudman**
Phone Number and Contact Details:	**Gincy George**
	Clinical Trials Coordinator
	02071887188 | Ext. 57380

Please write your initials in each box

1. I have read the attached Participant Information Sheet (Clinician) (Version 6.0, dated 09/01/2019) on 'Adherence Patterns of GnRH Agonists in Prostate Cancer' and have been given a copy to keep. The information has been fully explained to me and I have had an opportunity to ask questions about the project and understand why the research is being done and any foreseeable risks or consequences involved. I also understand that no guarantee can be given about the possible results. ☐

2. I give permission to be contacted regarding the study. I understand that my participation is voluntary, and any contribution I make within these sessions will be anonymised. ☐

8. I give permission for the focus groups that I am a part of to be audio recorded. All information collected will be transcribed, stored and analysed anonymously. I understand that the data will be protected ☐

by the principles of confidentiality and both national and EU data protection legislation. ☐

9. I give permission to take part and I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, and without my legal rights being affected. ☐

10. I know how to contact the research team if I need to. ☐

11. I give permission to take part in the above study. ☐

Name of participant (BLOCK CAPITALS)	Date	Signature

Name of researcher	Date	Signature