Venous Thromboembolism in Bladder Cancer: Scope of the Problem and Patients' Perspectives (VTE-BC)

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Contents

Appendices

Figures

Tables

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Declaration

This thesis, presented for the degree of Doctor of Philosophy at the University of Warwick, contains no material, which has been accepted for any other degree in any university. This thesis contains no material written, or previously published, by any other person, except where due reference is given in the text and reviews.

Signature:

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Abstract = 298 words

Whole thesis without references and appendices = 52163 words

Abbreviations

ASCO	American Society of Clinical Oncology
BMI	Body Mass Index
BSREC	Biomedical & Scientific Research Ethics Committee
CASP	Critical Appraisal Skills Programme
CI	Confidence Interval
CNS	Clinical Nurse Specialist
CRF	Cancer-Related Factors
CRS	Cancer registration statistics
CT	Computed Tomography
CVC	Central Venous Catheter
DOACs	Direct Oral Anticoagulants
DOB	Date of Birth
DVT	Deep Venous Thrombosis
ESA	Erythropoietin Stimulating Agents
Hb	Haemoglobin
HES	Hospital Episode Statistics
HRA	Health Research Authority
INT	International
IRAS	Integrated Research Application System
ISTH	International Society of Thrombosis and Haemostasis
LMWH	Low Molecular Wight Heparin
MIBC	Muscle Invasive Bladder Cancer
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
Plt	Platelet
PE	Pulmonary Embolism

PRC	Packed Red Cells
PRF	Patient-Related Factors
PS	Performance Status
QEHB	Queen Elizabeth Hospital Birmingham
QoL	Quality of Life
RCT	Randomised Clinical Trial
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SSPE	Sub-Segmental Pulmonary Embolism
SUSAR	Suspected Unexpected Serious Adverse Reaction
TF	Tissue Factor
TNM	Tumour Node and Metastasis
TRF	Treatment-Related Factors
UC	Urothelial Cancer
UBC	Urothelial Bladder Carcinoma
UHCW	University Hospitals Coventry and Warwickshire
ULN	Upper Limit of Normal
US	Ultrasound
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism
WBC	White Blood Cell
WCC	White Cell Count
WCTU	Warwick Clinical Trials Unit

Abstract

Introduction: Venous thromboembolism (VTE) presents a challenge in the management of cancer patients and is a common cause of morbidity and mortality. Bladder cancer (BC) patients are at high risk of VTE; however, the problem is not well quantified. Patients' understanding of cancer-associated thrombosis (CAT) early in their cancer pathway has hitherto been neglected. The aims of this study, 'VTE-BC', are to investigate the scope of VTE in patients with BC in the UK and explore patients' understanding of CAT from their experience of having BC and treatments.

Methods: A sequential mixed-methods study was applied: i) quantitative (Phase I) to explore the incidence and risk factors for VTE in BC, by cohort and case-control analysis, followed by ii) qualitative (Phase II) through semi-structured interviews among patients with BC and healthcare professionals (HCPs), utilising thematic analysis.

Results: VTE incidence in patients with BC was around 6.0 per 1000 from national datasets, lower than previously published. Cystectomy and stage IV disease significantly increased the risk of VTE in BC patients; adjusted odds ratio (OR); OR 2.88 (95% CI 1.63-5.07), P < 0.001 and OR 4.41 (95%CI 1.85-10.50), P=0.002, respectively, while chemotherapy was found to have borderline significance as a risk factor; OR 2.56 (95% CI 1.03-6.32), P=0.041.

Patients had a lack of awareness of CAT; they received limited education on VTE. Three major themes emerged from the interviews: 'all about the cancer' (CAT was not a priority for patients with BC and HCPs), 'a labyrinthine process' (information about VTE was bewildering and compartmentalised) and 'improving the poor deal' (patients' and HCPs offered suggestions to improve communication around CAT).

Conclusions: VTE is an important clinical problem in patients with BC. HCPs can build on the findings of VTE-BC to improve individualised CAT care through multidisciplinary inclusion of CAT discussion inpatient encounters.

1. Introduction

This doctoral thesis is entitled “Venous Thromboembolism in Bladder Cancer: Scope of the Problem and Patients’ Perspectives”.

It is a sequential mixed-methods study which seeks explore the incidence rate and risk factors for VTE in bladder cancer patients, what bladder cancer patients understand about VTE, and how information around VTE can be best communicated.

This chapter outlines the challenges of bladder cancer (BC) and venous thromboembolism (VTE) and most importantly, the association between the two. An overview of VTE and BC is discussed. In addition, the research questions, aims and objectives.

Cancer, in general, is an uncontrolled proliferation of cells which behave in a different way to normal cells in the body and can grow into nearby tissue (Sonnenschein *et al.*, 2014). In bladder cancer, abnormal cells multiply without control, in the bladder and have the potential to spread to other parts of the body. The bladder is a hollow, muscular organ which filters waste products out of the blood and makes urine; it is located in the lower abdomen. The most common type of BC is urothelial carcinoma (UC), starting in the cells lining the inside of the urinary bladder (Kaufman *et al.*, 2009).

Patients with BC are at a high risk for developing VTE; thus, it is important to provide background information about bladder cancer and thrombosis.

1.1. Bladder cancer

Bladder cancer is the eleventh most common cancer in the UK and one of the most expensive to manage (CRUK, 2018, Svatek *et al.*, 2014). In the UK, more than 10,000 new cases of BC are diagnosed annually; however, 5,300 patients with BC die every year (CRUK, 2018). BC mainly affects individuals those over 55 years of age, and is more common in men than women; the peak of BC cases is at the age of 80 to 89 (CRUK, 2018). Genetic susceptibility, smoking, prior radiation therapy, exposure to certain chemicals and frequent bladder infections are the most common risk factors for developing BC (Burger *et al.*, 2013).

Bladder cancer is classified according to the type of cell it starts in (histology):

- Urothelial carcinoma (UC), also called transitional cell carcinoma, is the most predominant histological type of bladder cancer in the UK, representing 90-95% of cases.
- Squamous cell carcinoma represents about 5% of UK bladder cancers
- Adenocarcinoma accounts for 1 to 2% bladder cancers in the UK.
- Sarcoma of the bladder is very rare (CRUK, 2017)

In addition to its histological description, bladder cancer is described according to the stages of cancer as non-invasive, non-muscle-invasive, muscle-invasive, locally advanced or metastatic (Paner *et al.*, 2018).

- **Non-muscle-invasive (stage I):** only developed into the lamina propria, a thin layer of connective tissue and outer part of the mucosa, and not into the muscle.
- **Muscle-invasive (stage II):** developed into the bladder wall muscle and sometimes invades the fatty layers or surrounding tissue outside the bladder.
- **Locally advanced disease (stage III):** spread into the lymph nodes in the pelvis and the surrounding organs, such as the uterus and vagina in women, the prostate in men, and/or nearby muscles.
- **Metastatic disease (stage IV):** spread into the liver, bones, lungs, lymph nodes outside the pelvis or other parts of the body.

In regard to bladder cancer by stage at diagnosis in the UK, 73-76% of cases are at stages I or II, and 24-28% are at stages III or IV (CRUK, 2017).

According to Cancer Research UK (2017), in England, 80% of patients with non-muscle-invasive BC survive for five years or more after diagnosis, while in the muscle-invasive group, around 40% of patients survive for five years or more (after diagnosis). However, in metastatic BC patients, around 10% survive for five year or more after being diagnosed (CRUK, 2020).

In common with other cancer patients, those with bladder cancer experience many complications related to cancer or its related treatments

such as bleeding, anaemia, infection, thrombosis, gastrointestinal complications, urinary incontinence and cystectomy/neobladder-related complications (Avritscher *et al.*, 2006; Froehner *et al.*, 2009).

In summary, bladder cancer is a serious condition, usually involves multimodal treatments with optimal outcomes when picked up early. Patients with bladder cancer are in need of personalised care.

1.2. Thrombosis

Thrombosis is the formation of a blood clot within a blood vessel. The clot may block the blood vessel and prevent or reduce the flow of blood. Thrombosis is categorised according to the site where it occurs e.g. venous thrombosis (deep vein thrombosis, superficial vein thrombosis, renal vein thrombosis) or arterial thrombosis e.g. myocardial infarction, ischemic stroke, and the manifestation of peripheral arterial diseases (Albers *et al.*, 2008).

In pulmonary embolism, the thrombus usually forms in the deep vein of arms or legs, and breaks loose, travelling to the lungs before blocking the blood flowing through an artery in the lungs (Prandoni, 2009).

Commonly, arterial occlusions and events are caused when a process called atherosclerosis damages an artery. Fatty deposits on the walls of the arteries, which cause arteries to harden and narrow can lead to a blood clot in the artery and a heart attack or stroke (Prandoni, 2009). Arterial thrombosis is mostly present after the rupturing or slow destruction process of unstable atherosclerotic plaques in the arterial circulation (Jackson, 2011). Unlike arterial thrombosis, however, VTE and its complications do not usually arise due to vascular pathologies. Instead, VTE is linked with the dysregulation of coagulation proteins and/or venous stasis (Falanga & Russo, 2012).

A thrombus generally has two components: aggregated platelets and red blood cells that form a plug, and a mesh of cross-linked fibrin protein. A thrombus can form and can be divided into two types according to its composition and appearance: Arterial thrombus (white thrombus) is characteristically composed of platelet aggregates while a venous thrombosis (red thrombus) mostly be made of fibrin and red blood cells. Noticeably, most

thromboses in cancer patients are venous, and venous is the most common, but arterial also presents a challenge in cancer patients (Blann & Dunmore, 2011).

Cancer cells usually damage tissue in the body, which leads to inflammation and triggers thromboembolism. Thus, the lives of all people with a thrombosis are affected adversely; this is accentuated in the cancer patient.

1.3. Venous thromboembolism (VTE)

Venous thromboembolism is a disorder in which a clot or thrombus forms, mostly in the deep veins of lower and upper limbs, called a deep vein thrombosis (DVT) and it can move via blood vessels to the lungs and forming a pulmonary embolism (PE). DVT and PE are relatively common and known as VTE. Given its silent nature, the incidence and mortality rates of VTE are probably underestimated (Kniffin *et al.*, 1994; Phillippe, 2017).

VTE negatively affects quality of life and increases the risk of further complications such as recurrent VTE, bleeding and death (Khalil *et al.*, 2015). VTE is thus a risky, potentially deadly, medical disorder; it is known as the 'silent killer' as the first visible symptom could be sudden death (Donaldson, 2006). It has been estimated that 25,000 to 32,000 patients in England alone die annually from preventable VTE (Hansrani *et al.*, 2016). There are medical conditions leading to high risk of VTE such as hypertension, diabetes mellites, higher age, cancer and immobility, cancer being high on the list.

The key risk factors for VTE are major surgery, cancer, admission to hospital and immobility (Khorana *et al.*, 2007a). VTE is recognised as a complication of malignancy; moreover, it represents one of the most significant causes of morbidity and mortality in cancer patients (Puurunen *et al.*, 2016).

1.4. Cancer-associated thrombosis

Historically, Armand Trousseau (1801-1867) is acknowledged to be the first person to suggest that the association between malignancy and thrombosis may be integral to the cancer growth itself. A diagnosis of cancer alone has been acknowledged for decades as an independent risk factor for developing venous thromboembolism (Trousseau, 1865).

Cancer patients have a 5 to 7-fold increased risk of developing VTE, compared with the general population (Fennerty, 2006) and remarkably, cancer is responsible for 18-20% of all VTE cases (Blom *et al.*, 2006a; Lee, 2005).

In a study by the Dutch Cancer Registry, cancer patients with VTE had a two-fold increase in mortality as compared to those without VTE (Heit *et al.*, 2000). Indeed, more than 94% of cancer patients with VTE die within six months of initial hospital admission (Levitan *et al.*, 1999). Bladder cancer is thus one of the solid organ malignancies for which patients are considered to be at high risk of developing VTE (Ramos, 2017).

VTE is the second leading cause of death in the cancer population, and malignancy is the most prevalent reason for deaths in VTE patients (Fernandes *et al.*, 2019). Cancer patients who have VTE suffer from serious complications such as recurrent VTE, post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension in addition to the rising cost of management and adverse effects on the patients' quality of life (Noble & Pasi, 2010).

The cancer is only one factor in the development of VTE; there are additional factors that could increase the risk of developing VTE: cancer-related factors (e.g. the stage of cancer - advanced or metastatic), patient-related factors (e.g. obesity and immobility) and treatment-related factors (e.g. having surgery and receiving chemotherapy). These risk factors will be discussed in detail below.

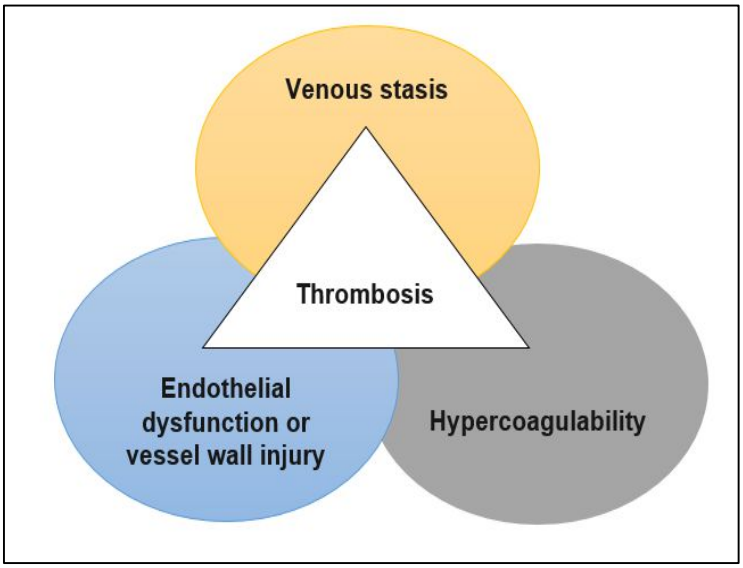
1.5. Pathophysiology of venous thromboembolism in cancer patients

The pathophysiology of VTE in cancer patients stems from a change in the processes of the coagulation system due to the tumour (Trousseau, 1865). Cancer cells release substances, such as tissue factor, that increase the risk of developing thrombosis (Manly *et al.*, 2011).

The body's homeostasis mechanism is maintained by a complex process of procoagulants, anticoagulants and fibrinolytic properties. In cancer, this delicate balance is disrupted. The development of a systemic hypercoagulable state is a basic pathogenic feature and is initiated by tumour expression of tissue factor (TF) and other procoagulants (Lee, 2002; Rickles *et al.*, 2003).

The coagulation system is usually initiated immediately in response to tear or injury of the endothelium, which allows exposure of blood to extravascular tissue (tissue-factor pathway). Prothrombotic factors are classified as intrinsic or extrinsic factors, as summed up by Virchow's Triad, Figure 1, (Kyrle & Eichinger, 2009). Extrinsic factors may include treatments and procedures (surgery, chemotherapy, CVC), which patients undergo for malignancy, causing injury of the blood vessel wall and releasing subendothelial TF, which is the primary initiator of the coagulation cascade (Dahlbäck, 2000). Additionally, extrinsic prothrombotic factors include decreased mobility causing stasis of the blood and tumour compression of the venous system e.g. from bulky tumours (Dahlbäck, 2000; Hicks & Selby, 2004). On the other hand, intrinsic factors are related to cancer biology and/or the body's reaction to malignancy.

Figure1: Pathogenesis of VTE (Virchow's triad)



Source: Author

What is known about the pathogenesis of VTE in cancer patients, is complex. Thrombosis is based on the interaction between the haemostatic system and procoagulant properties of malignant cells (Prandoni *et al.*, 2005).

In cancer patients, the thrombotic generation process is different from non-cancer patients (Fernandes *et al.*, 2019). Cell surface receptor protein tissue factor (TF), which is produced by malignant cells, causes oncologic progression and leads to the development of VTE. Tissue factor plays the role of activator for the coagulation pathway, resulting in the activation of factor X and then fibrin synthesis, as well as the activation of platelets. Malignant cells can produce other substances, for example, distinct cancer pro-coagulant factors which stimulate factor Xa and inflammatory cytokines which mediate endothelial dysfunction. Cancer cells also provide other tumorous substances, e.g. carcinoma mucins, that interfere in the coagulation cascade (Fernandes *et al.*, 2019). Moreover, thrombolysis and thrombin inhibition are inhibited by plasminogen activator inhibitor-1, which is produced by cancer cells. This disruption in the pro-anticoagulation balance causes CAT formation (Mukai & Oka, 2018).

Thus, the pathophysiology of CAT is complex, is much still unknown. What we do know needs to be understood by all clinicians for the individual management of patients.

1.6. Risk factors for venous thromboembolism in cancer patients

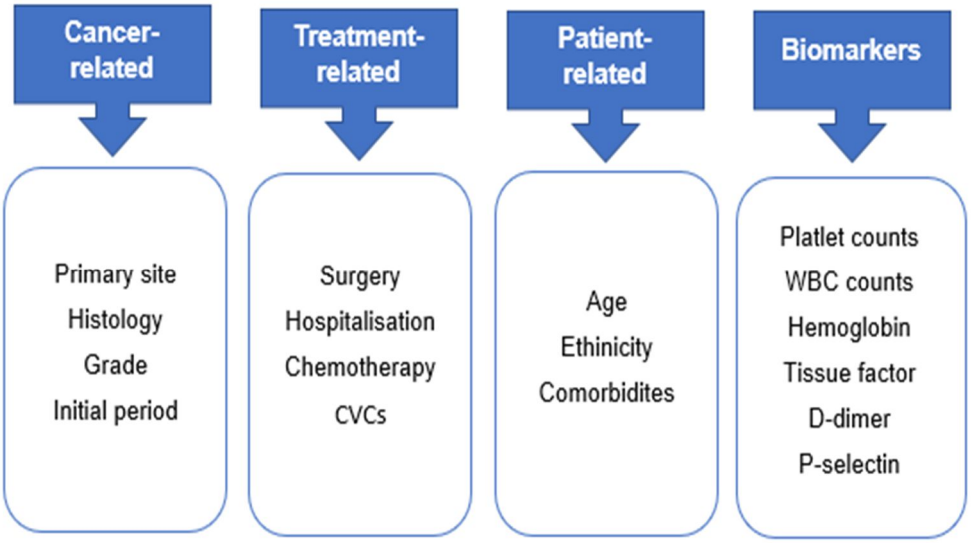
A risk factor in healthcare is any factor that could give rise to a person's probability of developing a certain condition. For example, cigarette smoking is a risk factor for lung cancer, and obesity is a risk factor for heart disease.

Indeed, a large percentage of terminal events in malignant diseases are thrombotic, supporting the thinking that cancer is a prothrombotic disease (Blann & Dunmore, 2011).

Cancer cells can develop VTE through several risk factors coexisting with cancer patients, such as surgery, chemotherapy and immobility, contributing to the increased risk cancer patients have of developing VTE compared with non-cancer patients (Abdol Razak *et al.*, 2018).

Cancer patients have different types of VTE risk factors, including biomarkers, best categorised into i) cancer-related factors (CRF) such as the histological subtype, site and stage of disease; ii) treatment-related factors (TRF) such as surgery, chemotherapy, antiangiogenic agents, hormonal treatment, erythropoiesis-stimulating agents, central venous catheters (CVCs) and hospitalisation and its consequences such as immobilisation, and iii) patient-related factors (PRF) such as comorbidities, advanced age, presence of infection, inherited prothrombotic mutations and performance status (PS) (Wun & White, 2009) and iv) candidate biomarkers such as elevated pre-chemotherapy platelet count, leucocyte count, D-dimer, TF, soluble P-selectin and C-reactive protein. Figure 2 provides a summary of risk factors and biomarkers for CAT (Sud & Khorana, 2009):

Figure 2: Examples of Risk Factors for VTE in Cancer Patients



CVCs=Central Venous Catheters

Source: Adapted from Sud and Khorana (Sud & Khorana, 2009)

Risk factors are crucial to explore in order to stratify individual patients into for optimal care and certain risk factors for VTE may help predict VTE in the individual patient.

1.6.1. Patient-related risk factors for VTE

1.6.1.1. Age

The incidence of VTE increases with age in the general population (Engbers *et al.*, 2010). Likewise, increasing age is a risk factor for VTE in cancer patients. This means that cancer patients aged 65 years or more have a larger chance of developing VTE compared with younger patients (Khorana *et al.*, 2007b). Similarly, in patients undergoing cancer surgery and chemotherapy, VTE risk increases noticeably after 65 years and 70 years respectively (Khorana *et al.*, 2007b; Königsbrügge *et al.*, 2014; Vergati M., 2013).

The effects of older age, irrespective of cancer, is accompanied by causes that increase one's risk of thrombosis, including diminished immobility, decreased exercise and increasing activation of blood coagulation (Lowe *et al.*, 1997; Rumley *et al.*, 2006). Hence, in BC patients, older age may have higher VTE risk than at a younger age.

1.6.1.2. Comorbidities

Medical comorbidities are common in elderly patients. Comorbid conditions such as severe respiratory disease, renal failure, cardiovascular disease and acute infection are associated with an increased risk of developing VTE in cancer patients (Khorana *et al.*, 2007b). The association between medical comorbidities and an increased risk of VTE in cancer patients has been investigated.

Sandhu and his colleagues (2010) found that there is a significant association between VTE incidence and comorbidities in the BC population (Sandhu *et al.*, 2010b).

1.6.1.3. Immobility

Immobility is closely associated with developing VTE in cancer patients. Being immobile for long periods increases the risk of VTE through stasis of venous blood flow (Cushman, 2007; Lowe, 2003). In this regard, it is well recognised that the regular exercise and avoidance of immobility reduces VTEs events (Lowe, 2003).

Mobility in cancer patients is a performance-based assessment higher rates of VTE were observed in cancer patients with poor performance status (Al Diab & therapy, 2010; Khorana *et al.*, 2005). Poor performance status has also been linked with higher rates of developing and recurrent VTE in cancer patients (Khorana & Connolly, 2009).

In general, an increase in the severity and duration of immobility leads to an increase in the risk of developing VTE (Hull, 2013).

1.6.1.4. Gender

The relationship between gender and developing VTE in cancer patients has been explored in a few studies. Retrospective studies show that females are at greater risk for VTE than males (Khorana *et al.*, 2007b). There are no studies that confirm the effect of gender on developing VTE in BC patients; hence, more studies are required to explore the effect of gender on developing VTE in the BC population group.

The varying methodologies in cancer patient-related risk factor studies together provide more detailed information on the risk for developing VTE.

1.6.2. Cancer-related risk factors for VTE

1.6.2.1. Site, histology and grade of the cancer

The incidence of VTE varies in different cancer types which may suggest that cancer-specific mechanisms play a role in cancer-associated thrombosis. The primary site of the cancer is frequently identified as a risk factor for VTE, with cancers of the pancreas, uterus, lung, stomach, bladder and kidney, and primary brain tumours associated with an increased risk of VTE (Khorana & Connolly, 2009). Patients with BC have a 5-fold higher risk of VTE than the general population (Sandhu *et al.*, 2010b). Histological subtypes of some types of cancer too have obvious links with the risk of VTE. For example, histological subtypes of lung and ovarian cancer show varying degrees of increased risk for VTE, while other histopathological subtypes of breast and colon cancer are non-predictive for VTE (Fuentes *et al.*, 2016).

Similarly, Ramos et al. (2017) reported that the VTE incidence in metastatic bladder cancer is significantly higher in non-urothelial histological subtype than in urothelial bladder carcinoma (Ramos *et al.*, 2017a).

Tumour grading may be another valuable histopathologic parameter to stratify patients into VTE risk groups (Ahlbrecht *et al.*, 2012). Accordingly, Ahlbrecht et al. (2012) confirmed that the tumour grade could affect the risk of VTE in a variety of solid tumours (Ahlbrecht *et al.*, 2012).

1.6.2.2. Stage of cancer

Stage of disease is likely to be the greatest risk factor for VTE (Khorana & Connolly, 2009). It is well known that patients with advanced-stage cancer have a higher risk of developing VTE (Connolly & Francis, 2013). A considerably higher risk of VTE in patients with the regional and distant disease than local disease was noted in the Vienna Cancer and Thrombosis Study (Dickmann *et al.*, 2013).

Distant metastatic disease is strongly associated with an increased risk for VTE. In this regard, the MEGA study revealed that cancer patients with

distant metastases had a 19.8-fold increased risk of VTE versus patients without metastases (Blom *et al.*, 2005). An analysis of the California Cancer Registry also revealed that the patients with metastatic disease at the time of cancer diagnosis had a 1.4- to 21.5-fold higher risk of developing VTE than patients with the localised disease for all cancer types (Chew *et al.*, 2006).

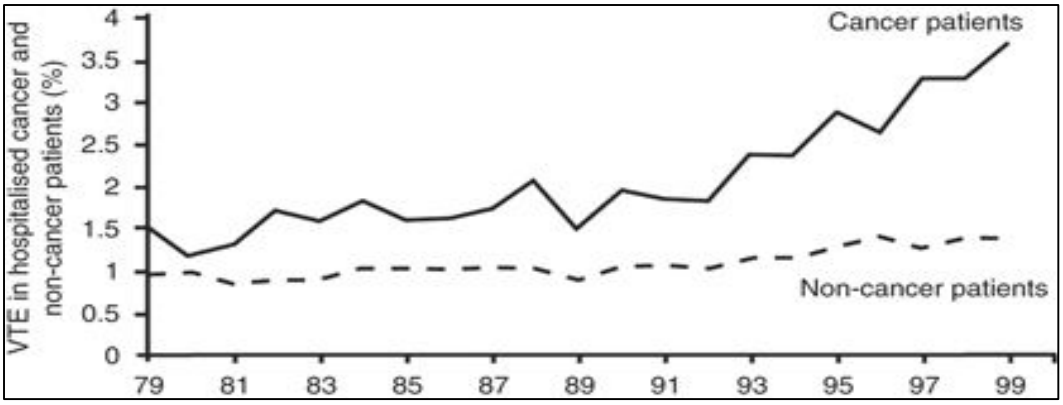
Thus, the higher the stage of the cancer, the greater risk of VTE. The histological type e.g. urothelial carcinoma in BC, affects the risk of VTE and subsequent management.

1.6.3. Treatment-related risk factors for VTE

1.6.3.1. Surgery and hospitalisation

It is well documented that hospitalisation is a risk factor for VTE in patients with cancer (Khorana *et al.*, 2013). Stein et al. found that the incidence of VTE in hospitalised cancer patients increased at a substantially sharper rate than was the case among hospitalised non-cancer patients, in a period between 1979 and 1999 (Stein *et al.*, 2006), (Figure 3).

Figure 3: Incidence of VTE rate between 1979 and 1999 in cancer and non-cancer patients



(Stein *et al.*, 2006)

The increased VTE incidence rate over time in patients with cancer, but not in those without cancer, could be due to the improved diagnostic modality of VTE and the increase in cancer interventions (Heit *et al.*, 2000; Khorana *et al.*, 2006; Stein *et al.*, 2006).

VTE incidence rate increases due to anticancer treatments, such as surgery and chemotherapy (Heit *et al.*, 2000). Surgery in cancer patients, especially pelvic and abdominal surgery, raises the risk of postoperative DVT 2-fold and PE greater than 3-fold when compared with similar operations carried out on non-cancer patients (Agnelli *et al.*, 2006). The precise mechanism by which surgery gives rise to VTE is poorly understood in patients; however, there are potential mechanisms that link surgical inflammation with VTE (Albayati *et al.*, 2015). Among patients undergoing surgery, an increase in the surgical procedure duration was directly associated with rising in the risk of developing VTE (Kim *et al.*, 2015). Postoperative immobility, meanwhile, has a significant association with developing VTE, thus early mobilisation post-surgery, in addition to pharmacologic thromboprophylaxis are key strategies to decrease the risk of developing VTE (Gould *et al.*, 2012).

1.6.3.2. Chemotherapy

Receiving systemic chemotherapy is one of the factors that lead to VTE among cancer patients and may reflect the increasing VTE incidence rate over the past few decades (Barni *et al.*, 2011; Khorana *et al.*, 2013).

Patients who had systemic chemotherapy as an initial treatment had an increased risk of VTE by a 6- to 7-fold over the first year following the start of chemotherapy compared within non-cancer patients (Blom *et al.*, 2006a; Khorana *et al.*, 2013). Cytotoxic drugs can increase the risk for VTE by several different mechanisms include damage to vessel walls; impairment coagulation inhibitors (reduced level of C and S proteins or antithrombin); platelet activation; increase the levels of procoagulant molecules; inducing tumour and endothelial cell apoptosis and cytokine release, both of which in turn leads to increased expression and activity of TF (Falanga & Russo, 2012; Haddad & Greeno, 2006).

One hypothesis suggests that chemotherapy causes cell-free DNA to be released from injured cells, leading to a hyper-coagulate state (Swystun *et al.*, 2011). Measuring cell-free DNA may add to the risk profile of the individual patient. Lastly, the vascular wall and, in particular, the endothelium may be

damaged by pressure coming from regional bulky lymph nodes or injuries from a CVC (Khalil *et al.*, 2015).

Previously, there was some controversy regarding the benefit of pharmacological thromboprophylaxis for cancer patients in the ambulant setting receiving chemotherapy. Some studies showed that there is not a significant advantage of thromboprophylaxis for ambulatory cancer patients who receive systemic chemotherapy (NICE, 2018), while other studies showed the worth of thromboprophylaxis for various high-risk tumour types, e.g. AVERT trial (Carrier et al., 2018,) and SAVE-ONCO trial (Agnelli *et al.*, 2012; Carrier *et al.*, 2018). Where the absolute reduction of risk of VTE is significant but small, drug regulatory authorities e.g. the US Food and Drug Administration (FDA) do not approve use, as happened with SAVE-ONCO.

Therefore, healthcare providers need to assess the risk of receiving systemic chemotherapy for developing VTE.

1.6.3.3. Central venous catheters

Central venous catheters (CVCs) comprise catheters inserted into a large vein in the neck (superior vena cava), chest (internal jugular or subclavian veins) or upper arm (cephalic or basilica veins) (Argoti-Velasco *et al.*, 2018). CVCs are used in hospitals and for outpatients who need long-term access to the central venous system for repeated procedures such as blood dialysis, receiving blood, fluids, nutrients, drugs and chemotherapy (Dougherty, 2000).

Catheter-related-thrombosis is the most important complication of CVC (Wall *et al.*, 2016). The indwelling of a CVC can also lead to local venous injury at the insertion site (Forauer *et al.*, 2006). The distortion of vessel integrity from the insertion procedure causes changes in the endothelium with subsequent production of procoagulant factors and activation of platelets and blood coagulation.

The risk of thrombosis in patients having CVCs (CRT) increases by:

- Primary thrombotic disorder such as factor V G1691A (Leiden) mutation
- Catheter tip malposition

- Thrombogenic catheter material
- Larger catheter diameter
- Left side placement
- Fibrinous catheter lumen occlusion
- Catheter-associated infections

  (Linenberger, 2006)

CVC insertion causes alterations in the endothelium with the resultant production of procoagulant factors and the activation of platelets and blood coagulation. These events may cause a thrombus which is reversible in the majority of patients (Geerts, 2014).

Correct position of CVCs by clinicians, using a small diameter catheter where possible catheter can also decrease the risk for VTE in cancer patients (Luciani *et al.*, 2001; Pittiruti *et al.*, 2009).

1.6.4. Biomarkers

An increase in platelet count in cancer patients has been identified as a novel marker of VTE. Patients with platelet counts of >350,000/mm^3 have a greater risk of VTE compared to patients with a prechemotherapy platelet count of <200,000/mm^3 (Sud & Khorana, 2009).

Elevated D-dimer levels are predictive of both primary and recurrent VTE. Furthermore, the elevation of TF and soluble P-selectin is considered as an independent predictive factor of VTE development. (Ay *et al.*, 2008; Sallah *et al.*, 2004; Uno *et al.*, 2007).

Many factors can increase the risk of developing VTE in cancer population. Some risk factors, such as major surgery, are sufficient on their own for thromboprophylaxis to be recommended. The use of risk assessment scores, utilising many risk factors e.g Khorana score (Khorana & Connolly, 2009) is the recommended way forward to assess individual risk VTE in patients with cancer in the ambulatory setting (Khorana *et al.*, 2019).

1.7. Clinical presentation of venous thromboembolism

Clinical diagnosis of DVT and PE is challenging because the clinical presentation is non-specific and varies substantially in individual patients (Bauersachs, 2012).

Patients with VTE may have the following features:

- Swelling in the affected leg
- Pain or tenderness often described as a cramp (especially at night)
- Reddish or bluish skin discolouration
- Leg (or arm) warmth to the touch
- Worsening leg pain when bending the foot
- Patients with PE mostly suffer from respiratory problems like:
- Shortness of breath that may occur suddenly
- Chest pain that may become worse with deep breathing or coughing
- Rapid heart rate
- Rapid breathing
- Sweating
- Coughing (maybe with blood)
- Fainting

Patients with VTE may or may not have all these symptoms. In the Multicentre Advanced Study for a Thromboembolism Registry (MASTER) study, a prospective cohort of 2,119 patients with VTE, the most common presenting symptoms and signs associated with DVT were reported as extremity oedema 80%, pain 75% and erythema 26%. Patients with PE suffered from dyspnoea 85%, chest pain 40%, rapid breathing (tachypnoea) 30% and increase heart rate (tachycardia) 23%. Syncope 10%, and haemoptysis, 2% were less common (Imberti *et al.*, 2008).

Given the life-threatening nature of VTE and the increased risk in cancer patients, patients should be made aware of VTE symptoms for their safety. Better education on VTE, DVT, and PE terms, risk factors, and preventive measures is needed to encourage active involvement by patients in treatment plans,

All healthcare professionals working with cancer patients including surgeons, medical oncologists, oncology nurses and patients' carers, should be familiar with the warning signs and symptoms that may indicate the patient has DVT or PE.

1.8. Venous thromboembolism in bladder cancer patients

Bladder cancer is one of several cancer types for which patients are considered to be at high risk for VTE development (Sandhu *et al.*, 2010a). VTE rates in BC patients range between 3% and 19.1% in patients who undergo cystectomy (Blom *et al.*, 2006; Tully *et al.*, 2016).

In patients with BC, a history of VTE before BC diagnosis is seen as the strongest risk factor for recurrent VTE, after cystectomy (Wallis *et al.*, 2017b). BC patients with VTE are at greater risk of recurrent VTE than those without cancer, and the risk of VTE further increases in the advanced stage of BC (Ramos, 2017). Comorbidities may increase the risk of VTE in BC patients. Medical comorbidities are also common in this predominantly elderly patient population (Wun & White, 2009).

According to Sundhu et al. (2010), the risk of VTE among BC patients is highest within the first six months of diagnosis (Sandhu *et al.*, 2010b). A population-based Canadian study has shown that over half of VTE events in BC patients who underwent radical cystectomy occur after hospital discharge, with a substantial incidence up to three months after cystectomy (Doiron *et al.*, 2016). The cumulative incidence of VTE continues to rise long after cystectomy, but the highest VTE incidence rates occur 20 days after surgery (Wallis *et al.*, 2017b).

In England and Wales, urologists and medical oncologists are expected to follow the National Institute for Health and Care Excellence (NICE) guidelines, and as such, treating BC patients might vary in relation to other countries. Moreover, there are limited data of VTE in BC patients. This study, VTE-BC, will consider VTE incidence in BC in the UK.

1.8.1. Venous thromboembolism and stage of bladder cancer

There is a direct association between VTE rate and the stage of bladder cancer. Non-muscle invasive (stage 1) BC, which is mainly treated with transurethral resection of bladder tumour (TURBT), does not appear to have a significant risk of VTE (CRUK, 2014). However, stages II, III, and IV of BC have a high risk of VTE. Sandhu et al. (2010) reported that the risk of VTE is significantly associated with advanced and metastatic BC (Sandhu *et al.*, 2010b). The VTE rates in stages II, III and IV BC cancer are 1.3%, 6.2% and 6.3%, respectively (Sandhu *et al.*, 2010b).

The treatment for muscle-invasive and locally advanced stages (stages II and III) is mainly cystectomy and chemotherapy. Systemic chemotherapy (generally platinum-based) remains the mainstay of treatment for metastatic cancer (stage IV). Both cystectomy and chemotherapy are further risk factors for VTE.

1.8.2. Prevention of venous thromboembolism in bladder cancer

VTE is a preventable condition in many cases anticoagulants can significantly decrease VTE incidence in cancer patients (Prandoni *et al.*, 2005). NICE clinical guideline (CG92, 2010) recommend that patients with cancer undergoing major abdominal or pelvic surgery should also receive 28 days (extended) postoperative, pharmacological thromboprophylaxis in addition to the perioperative thromboprophylaxis period (NICE, 2018). This means that patients undergoing radical cystectomy should receive an average of six weeks postoperative VTE prophylaxis to achieve a lower VTE events rate (Treasure & Hill, 2010).

An audit study group evaluated the recommendation of post-discharge thromboprophylaxis in UK pelvic cancer centres, consistent with national guidelines (Pridgeon *et al.*, 2015). The study found that after radical cystectomy, all pelvic cancer centres in the UK routinely use LMWH in the perioperative period, and 67% of them use post-discharge LMWH routinely, especially for patients undergoing cystectomy (Pridgeon *et al.*, 2015).

Usually, BC patients receive thromboprophylaxis after radical cystectomy for 14 days, or for an extended duration 28 days to decrease the

rate of VTE after radical cystectomy during the first month after surgery (Pariser *et al.*, 2017a). Using extended thromboprophylaxis (LMWH) after cystectomy causes a significant reduction in VTE events within BC patients (Bergqvist *et al.*, 2002). Exploring patients' experience and understanding of VTE and thromboprophylaxis measures may further reduce this reduction.

Despite the efficacy of anticoagulation therapy in high risk ambulatory BC patients, concerns about their related bleeding complications may prevent some BC patients from being prescribed or maintained on anticoagulant therapy for a long time. Anticoagulant therapy is thus accompanied by the risk of more bleeding in BC patients than non-cancer patients (Tikkinen *et al.*, 2014) and risk assessment therefore needs to achieve a balance between VTE and bleeding.

1.9. Venous thromboembolism and treatment of bladder cancer

Treatments of BC, e.g. surgery and chemotherapy, can raises the chance of experiencing VTE. Risk for developing a VTE depends mainly on the type of intervention or treatment received by BC patient like surgery, chemotherapy or both.

1.9.1. Venous thromboembolism in bladder cancer patients undergoing surgery

In bladder cancer patients, VTE is frequently seen as a major complication of open radical cystectomy. Radical cystectomy is associated with a 2.1-fold increase in the risk of developing VTE compared BC patients who did not undergo surgery (Alberts *et al.*, 2014; Dyer *et al.*, 2013a; Fantony *et al.*, 2016).

In a retrospective cohort study by Sun et al. (2015), around 4.7% of patients who underwent open radical cystectomy experienced VTE within three months post-surgery (Sun *et al.*, 2015b). Furthermore, Ording et al. (2016) found the VTE rate to be 7.5% within one year after cystectomy, in patients with bladder cancer.

Patients in both studies had variable regimens and drugs for thromboprophylaxis. Given the VTE rates in the above two studies, longer-term thromboprophylaxis should be considered postoperatively (Ording *et al.*, 2016a).

1.9.2. Venous thromboembolism in bladder cancer patients receiving chemotherapy

VTE events may increase in BC patients who receive perioperative chemotherapy. Sun et al (2015) found that the incidence rate of thromboembolic events in BC patients who received neoadjuvant chemotherapy was 14% with a significant difference between institutions, ranging from 5% up to 32% (Sun *et al.*, 2015b).

Platinum-based chemotherapy is widely used for the treatment of muscle-invasive and metastatic BC, which leads to a rise in the incidence of VTE in these patients, particularly in the first year after diagnosis (Tully *et al.*, 2016). Cisplatin and carboplatin can both increase VTE risk in BC patients (Tully *et al.*, 2016). The results of a post-hoc analysis of the PROTECHT study (2011) show that the highest rates of thromboembolism occurred in patients receiving gemcitabine (8.1%) or cisplatin-based gemcitabine with platinum chemotherapy increases the risk of thromboembolism to 10.2 % (Barni *et al.*, 2011). Furthermore, Moore et al. (2011) found that cisplatin has a high incidence of treatment-related VTE; in a retrospective study of 932 patients with various types of cancer who received cisplatin-based chemotherapy, around 18% of patients developed VTE (Moore *et al.*, 2011). Tully et al. (2016) stated that 24% of patients with carboplatin-based chemotherapy were diagnosed with VTE. This figure was 15% of the patients who had received cisplatin. The higher VTE incidence with carboplatin may be influenced by patient and tumour-related factors, as well as patients with adverse prognostic factors, higher tumour burden and those unable to have cisplatin (Tully *et al.*, 2016). Despite these increase rates with cisplatin in patients with BC, there is currently no standard thromboprophylaxis regime for outpatients receiving cisplatin-containing chemotherapy (NICE, 2010). This may again be due to the risk of haematuria (Yu *et al.*, 2017).

Bladder cancer patients at high risk of VTE should firstly be identified if possible and then be individually informed about measures to try and reduce the risk of VTE. Furthermore, patients need to know the signs and symptoms of VTE so they can seek urgent medical care if needed.

1.10. Patient education on Venous thromboembolism

Patient education on CAT can be defined for this study as information-giving on CAT to the patients during the clinical encounter e.g. at clinic, by using different channels such as verbal or written (e.g. leaflets). Patients and their caregivers also seek information from other sources e.g. internet and friends and family and so the patient prior knowledge on CAT was sought (Basch *et al.*, 2004; James *et al.*, 2007).

Patients need clear, concise and consistent information about their cancer, treatment options, and course of care. Information, open communication, and support from family and friends are, indeed, significant factors in supporting patients with cancer (Fitch *et al.*, 2010; McPherson *et al.*, 2001).

Education on VTE is assisting learning or gaining knowledge about VTE, providing some strategies that may prevent VTE and also the skills in picking up the signs and symptoms of VTE. The most common educational methods during clinical encounters i.e. generally at ‘clinic’, include brief information giving, discussion, encouraging self-learning e.g. on the internet and giving leaflets. Patients’ experiences are an education in themselves.

Communication of VTE is the act of sending information or ideas (around VTE in this study) via speech, visuals, writing or any other such method (Happ *et al.*, 2011; Heidbuchel *et al.*, 2015). In a health context, patient’s education is a fundamental part of patients’ management (McPherson *et al.*, 2001). The process of managing a patient requires a holistic approach which includes considerations beyond treating a disease. Information about the nature, course and prognosis of the disease is important (Ranjan *et al.*, 2015). Healthcare providers benefit from certain communication skills, along with medical expertise, to provide the best clinical care. Studies have shown that good communication skills on the part of the

healthcare provider improve patient's understanding, compliance, overall satisfaction, and delivery of high-quality care (Ha & Longnecker, 2010).

There are certain principles of practising effective communication between HCPs and patients. Mainly, communication of medical information is the responsibility of HCPs (McPherson *et al.*, 2001). HCPs are considered as sender of messages (information) to the receiver which are the patients and their caregivers. The message is sent via the channels (Figure 4) to facilitate the passage of information from HCPs to patients such as leaflets (written), clinical encounter (verbal) or video (audio-visual) (McPherson *et al.*, 2001) and guiding to peer-reviewed websites (Clayman *et al.*, 2008). Afterwards, the receiver receives the message using the channel that the sender used to send his message (Bhatnagar, 2011).

Figure 4: Communication Model

Source: (Sana, 2010)

However, communication is often a two-way process and many patients and their caregivers also find their own information e.g. via the internet and may or may not ask the HCPs for their opinion (Buckman, 2002).

Venous thromboembolism in BC patients is potentially preventable; therefore, BC patients benefit from effective communication regarding VTE empowering them and raising awareness e.g. to act quickly on VTE signs and symptoms. Venous thrombosis may be lessened through increased patient awareness, by providing BC patients with fundamental information about VTE signs, symptoms, risk factors, and thromboprophylaxis measures. Healthcare professionals wish to maximise patients' understanding of the information provided (Epstein *et al.*, 2004).

Checking patients' understanding is very important, and it is necessary to assess the effectiveness of communication between health professionals and their patients e.g. it is beneficial to ask the patients about their knowledge

(Debra, 2000). This helps to provide a summary of what they understand about their disease, risk, treatments, and prophylaxis, which may directly affect the level of compliance with health professionals' instructions (Debra, 2000).

A lack of understanding may mean that patients do not present early enough with the symptoms of VTE or bleeding, which leads to further complications (Debra, 2000). Levels of understanding are also influenced by numerous factors such as whether the patients receive accurately, and the right amount of, the information in the targeted population group (Debra, 2000).

Effective communication skills are powerful tools for all clinicians and essential for the delivery of high-quality healthcare (Kyle & Shaw, 2014). Communicating the risk of VTE includes providing the patient with a balanced, evidence-based summary of the risks and harms linked with BC and its treatment.

Information, open communication, and support from family and friends are also significant factors in supporting patients' adjustments (Fitch *et al.*, 2010). The views and experiences of patients and HCPs regarding the communication of VTE, as well as the prevention of VTE in patients with BC, are explored in this study. It will be significant to hear and act on BC patients' perceptions and views on the subject, so as to improve awareness for future patients (Petrie & Weinman, 2012).

Finding a systemic approach to this challenge of translating the evidence about the prevention of developing VTE into everyday clinical practice may provide a better outcome for BC patients.

1.11. Summary

Given the above, bladder cancer patients are known to have a high risk for VTE, in particular those patients who are undergoing cystectomy and/or receiving chemotherapy (Sun *et al.*, 2015b; Tully, 2016).

Patients' education on VTE plays an important part in helping patients to understand their condition and the risk of getting VTE which may lead to prevent developing VTE or assist in early diagnosis of VTE in order to save patients' lives.

Patients deserve to understand their risk for VTE and the consequences of VTE to adhere with anti-clotting measures. Many patients may be uncomfortable with self-injection or receiving injections of anti-clotting; hence, they should be helped to understand the importance and the side effects of thromboprophylaxis measures to enable shared decision-making with clinicians. It is essential to investigate the VTE incidence in the UK in order to compare with international data and discuss the UK data with patients and healthcare professionals (HCPs). This study strives to outline the scope of the VTE problem in a high-risk cancer population, understand the meaning of this problem for patients and HCPs and suggest what can be done to improve care. Patient education on VTE is a crucial part of shared decision making and evidence-based patient choice (Elwyn *et al.*, 2001).

Thus, it is important to do two reviews to find the available data on VTE in BC patients and studies explored the patients understanding of VTE. These two types of reviews are presented in the following chapter.

The research questions, aims and objectives were fully developed after the reviews in Chapter 2. They follow here as the background also contributed to the formulation of the research questions, aims and objectives.

1.12. Research questions

The research questions of this study are as follows:

- What is the scope of the problem of VTE in bladder cancer patients in the UK?
- What are the patients' understanding of VTE from their experience of having had BC and related treatments?

1.13. Aims and objectives.

The aims of VTE-BC study are to explore:

- the scope of the problem of VTE in bladder cancer patients in the UK
- the patients' understanding of VTE from their experience of having had BC and related treatments.

The objectives of VTE-BC study are to explore:

- the incidence of VTE in bladder cancer patients
- risk factors for VTE in bladder cancer patients through two local databases
- the content of the information on VTE communicated to BC patients
- the approaches by which VTE information can be more effectively communicated to the patients to facilitate informed choice
- patients' perspective and strive to influence clinicians' practice, ultimately to reduce the burden of VTE in the BC patient population

2. Literature reviews: Venous thromboembolism in bladder cancer patients

In order to identify, evaluate and summarise the findings of all relevant studies on VTE and find any gaps in the research and practice in this area of care, two literature reviews were carried out. This chapter provides a summary of the available primary research on i) venous thromboembolism (VTE) rate in bladder cancer (BC) patients within and outside the UK and ii) works of literature on patients' experiences and understanding of VTE. The chapter is made up of three sections, the first, a systematic review of the VTE rate in BC patients; the second, a scoping review to explore qualitative studies looking at communicating VTE between cancer patients and healthcare professionals (HCP). Having explored the literature, the rationale for the VTE-BC study then follows.

2.1. Systematic review of venous thromboembolism rates in patients with bladder cancer

2.1.1. Introduction

The background outlines the increase in morbidity and mortality in having both cancer and venous thromboembolism (VTE). Bladder cancer (BC) is classified as a high-risk tumour type for VTE, and surgery and chemotherapy are well-recognised risk factors for VTE in BC.

This systematic review was undertaken to summarise the contemporary evidence on the VTE rate in patients with BC according to the type of anti-cancer treatment and highlight the VTE rate in the UK vs other countries.

2.1.2. Rationale for a systematic review

The risk of VTE in BC may vary between different countries due to different guidelines followed in BC management e.g. ESMO guidelines are generally used in Europe, NCCN guidelines used internationally, in particular

in the USA and NICE guidelines generally used in the UK. Different treatment regimens are preferred in different countries e.g. using neoadjuvant chemotherapy or not before cystectomy, e.g. the USA and using thromboprophylaxis for 14 or 28 days post cystectomy (Fantony *et al.*, 2016).

Given the high risk of VTE for BC patients, compounded by patient, treatment and cancer-related risk factors for VTE, the study is centred in the UK. The author of the present thesis also works in the UK, hence it is deemed important to have UK data, and to compare such data with the rest of the world, so that healthcare professionals and patients may be informed and take appropriate action.

Optimising treatment plans to decrease the VTE risk while also reducing bleeding risk is crucial to influence both patients and the healthcare system. The clinician needs to consider the balance between the risk of VTE and the risk of bleeding before prescribing pharmacological thromboprophylaxis (Tikkinen *et al.*, 2017). This systematic review also reveals the rate of VTE in patients with BC according to the treatments and length of thromboprophylaxis in the UK and other countries to inform the optimisation of thromboprophylaxis.

Drawing on evidence gathered by previous studies, this current systematic review provides a comprehensive overview of the VTE rate in BC patients in and out of the UK. It is useful to have national (UK) and global (all other countries with relevant publications) data of the VTE in BC patients to recognise the similarities or differences.

2.1.3. Systematic review research questions

In patients with bladder cancer,

- What is the rate of venous thromboembolism (VTE), according to the stage of cancer and the anti-cancer treatments received in and out of the UK?
- What are the VTE rate differences between the UK and global data?

2.1.4. Aims and objectives of systematic review

Aims: **To find:**

- the incidence rate of venous thromboembolism (VTE), according to the anti-cancer treatments received, in and out of the UK.
- the VTE rate differences between the UK and global data.

Objectives: **To explore:**

- the VTE rate in BC patients in the UK and other countries
- the evidence available on VTE rate in non-muscle invasive, muscle invasive, and metastatic BC patients in the UK and non-UK countries
- the influence of the duration of pharmacological thromboprophylaxis on VTE rate in patients with BC undergoing cystectomy
- the knowledge gaps of VTE in BC that demand further studies in the UK and non-UK countries.

2.1.5. Methods for systematic review

The Centre for Reviews and Dissemination (CRD) Guidance for Undertaking Reviews in Healthcare (CRD, 2008) was utilised to guide this systematic review. A search was conducted in PubMed and Embase electronic databases (Appendix 1). In addition, conference proceedings of the American Society of Clinical Oncology and the American Urological Association, the two largest international meetings of cancer and urology, were screened for potentially relevant records.

2.1.5.1. Search inclusion and exclusion criteria

The main outcome of interest was any VTE, which included symptomatic or incidentally detected DVT and PE, diagnosed in patients with BC.

Inclusion criteria:

- Primary research which confirmed the diagnosis of DVT and/or PE in BC patients
- Papers in the English language
- From January 2000 until June 2020

Exclusion criteria:

- Case reports
- Studies reporting DVT or PE only
- Studies recorded in-hospital VTE only
- Studies occasionally reporting on VTE as one of the adverse effects of surgery or chemotherapy
- Studies reporting on a mix of arterial and venous thrombosis as a composite endpoint or lack of clarity on venous thrombosis only

2.1.5.2. Data sources and searches

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines and checklist were followed to develop this review (Moher *et al.*, 2009). The following terms were used: ((‘bladder cancer’ OR bladder carcinoma’ OR ‘bladder tumour’ OR ‘bladder urothelial carcinoma’ OR ‘transitional cell carcinoma’) AND (‘VTE’ OR ‘DVT’ OR ‘PE’ OR ‘venous thromboembolism’ OR ‘thrombosis’ OR ‘thromboembolism’ OR ‘deep vein thrombosis’ OR ‘pulmonary embolism’ OR ‘lung embolism’)).

Publications from January 2000 to June 2020 were included. Data on overall VTE incidence in BC patients were extracted from all related publications. These were the source data for the primary objective – incidence of VTE in BC patients. Reference list checking was carried out to identify further relevant studies. All titles and abstracts from the search were evaluated independently by two reviewers (DP and IM) and disagreements were resolved by a third arbitrator (AY).

2.1.5.3. Study quality assessment for systematic review

For each of the included studies, the risk of bias was evaluated using the Newcastle-Ottawa Scale (NOS) and Agency for Healthcare Research and Quality (AHRQ) standards and classified as good, fair, and poor. The NOS assigns up to a maximum of nine points for the least risk of bias in three domains: 1) selection of study groups (four points); 2) comparability of groups (two points); and 3) ascertainment of exposure and outcomes (three points) for cohort studies.

A maximum score of 2 can be awarded for comparability and a maximum score of 1 can be given for each of the remaining points. A study

can have the maximum possible quality score of 9. Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards were applied to have a clear view of quality assessment for each study (Appendix 2).

2.1.5.4. Ethical considerations for systematic review

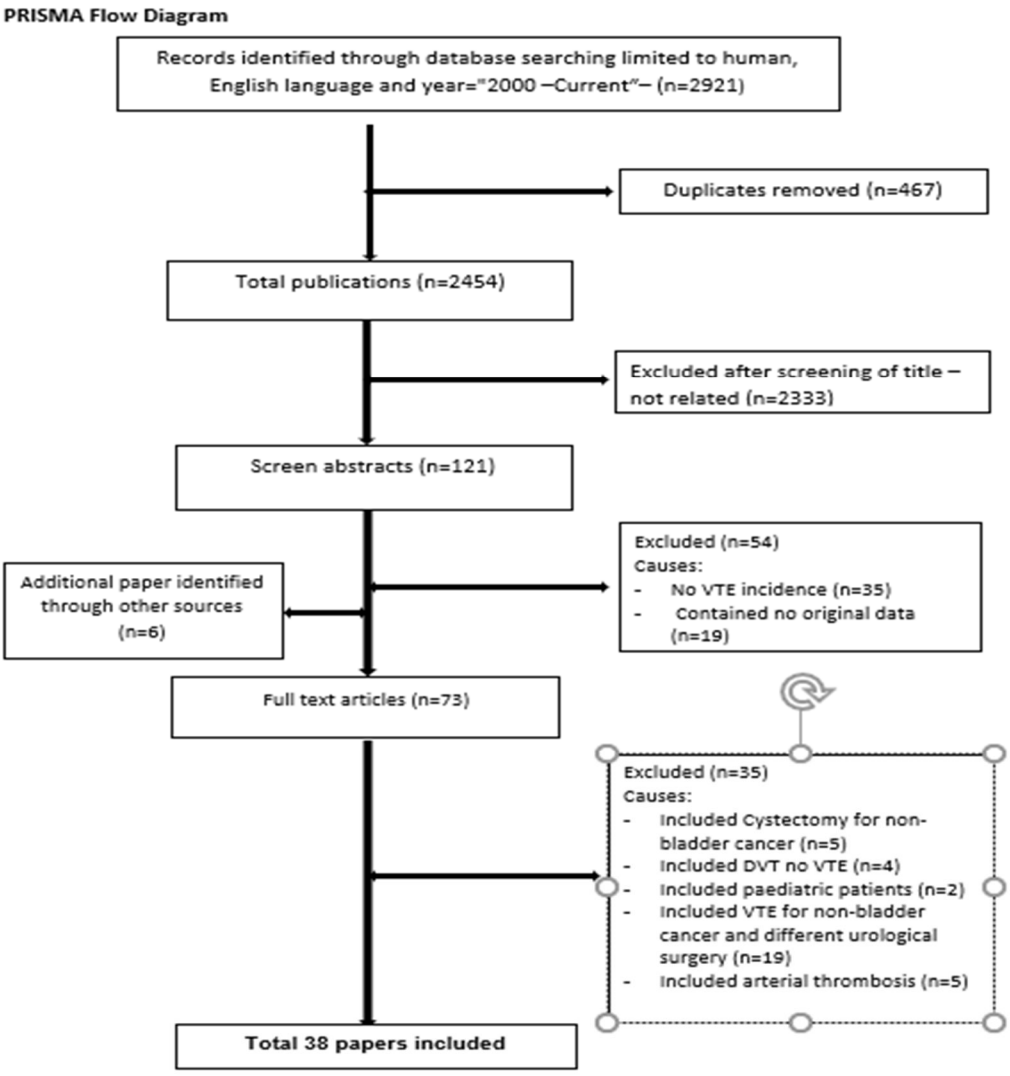
Ethics committee approval was not required for this systematic review as this methodology utilises only previously published material, is not primary research and does not involve humans or data collection.

2.1.6. Results of systematic review

2.1.6.1. Descriptive characteristics

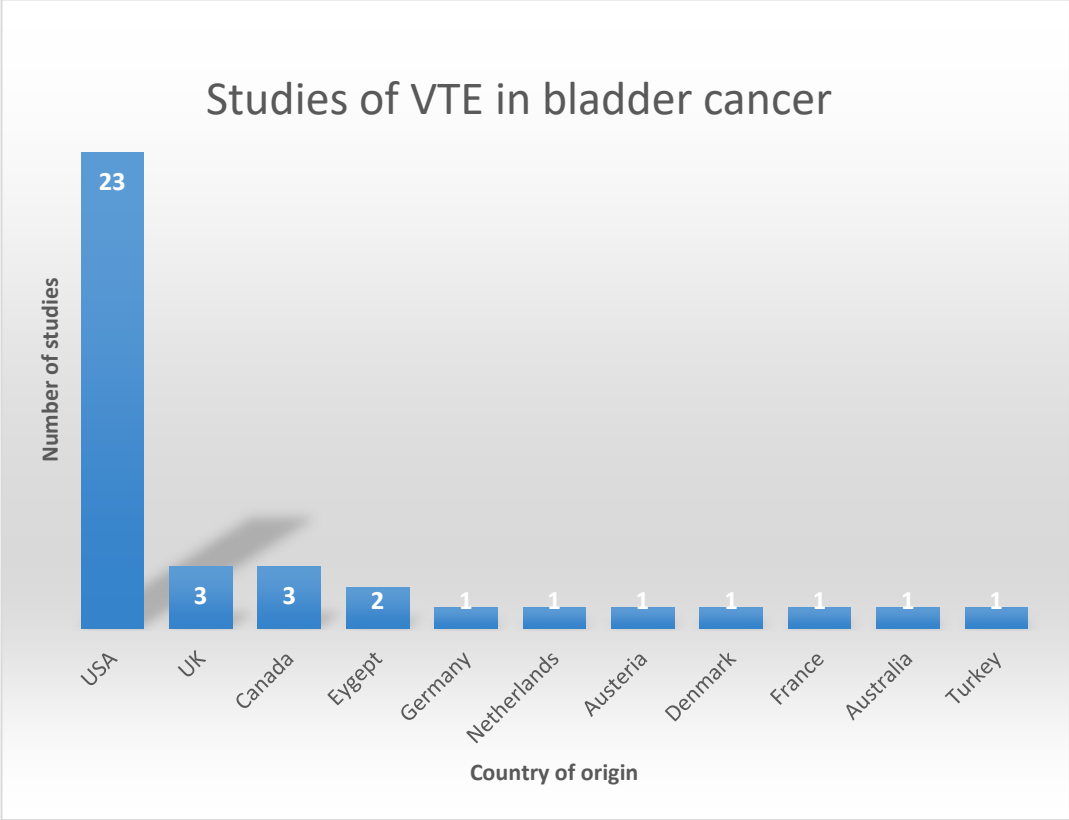
Of the 2921 publications, a total of 38 studies met the inclusion criteria and were selected for this systematic review. All stages of the extraction process are shown in the PRISMA flow diagram (Figure 5). In this current systematic review, all papers with one exception have good and fair quality according to the Newcastle-Ottawa Scale and AHRQ standards (Tables 1& 2).

Figure 5: Study selection process of systematic review



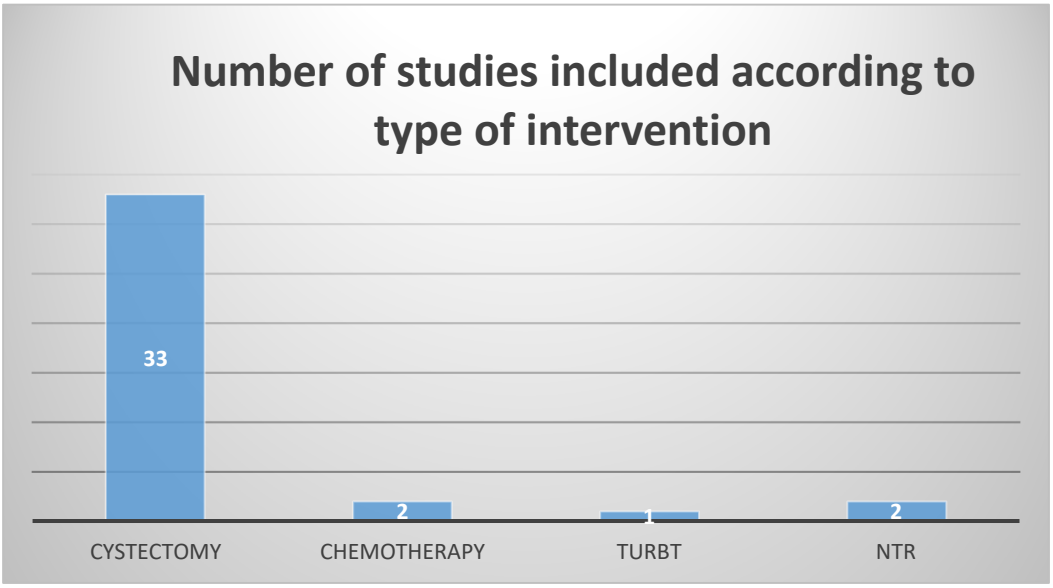
All publications were original research papers (cohort studies) in which the VTE rate was clearly stated. The cohort studies were generated in different countries: 'USA', 'Canada', 'Germany', 'France', 'Austria', 'Denmark', 'Netherlands', 'UK', 'Australia', 'Turkey', and 'Egypt'. The majority of the studies were carried out in the USA. The country of origin is summarised in Figure 6.

Figure 6: Summary of studies according to country of origin



The majority of papers included patients who had undergone cystectomy (n=33); (Figure 7). The further risk of VTE in patients receiving neoadjuvant or adjuvant chemotherapy (with curative intent) was only mentioned in four of the 33 papers (Brennan *et al.*, 2018; Doiron *et al.*, 2016; Nguyen *et al.*, 2018; Wallis *et al.*, 2017). There are no data on VTE in patients having multimodality treatments. Only two papers discussed the VTE risk in patients receiving chemotherapy only (Khorana *et al.*, 2013; Ramos *et al.*, 2017); two papers compared VTE rates in using thromboprophylaxis (TP) for two weeks and an extended duration of four weeks (Pariser *et al.*, 2017b; Schomburg *et al.*, 2017); and one paper included patients having a Transurethral Resection Bladder Tumour (TURBT) only (Zaffuto *et al.*, 2017).

Figure 7: Summary of VTE and BC studies by treatment



VTE-Venous Thromboembolism; TURBT-Transurethral Resection Bladder Tumour; NTR-No Treatment Recorded

2.1.6.2. VTE rate in patients with bladder cancer

This review identified 38 studies specifying the VTE rate in BC patients, with a total of 172,380 BC patients being included, according to the type of treatments (Figure 3) and country of origin; however, two studies stated the overall VTE rate with no data on anti-cancer therapies or TP regimes (Sandhu *et al.*, 2010a; Walker *et al.*, 2013a). A cohort study conducted in the UK explored the VTE rate in all cancer patients including 3152 BC patients, and the absolute rate per 1000 person years of VTE in BC was 15 (Walker *et al.*, 2013b). In the US, Sandhu et al (2010) carried out a retrospective cohort study for 24,861 patients with BC to look at VTE rate over 6-years. The 1-year and 2-year rate of VTE after cancer diagnosis was 1.6% and 1.9%, respectively (Sandhu *et al.*, 2010a). Taking both studies together, VTE rates in BC patients were an average of 1.9 to 4.7% (mean = 3.3%) within two years of BC diagnosis. The VTE rate in BC patients in the UK was more than double in the USA.

2.1.7. VTE rate in non-muscle-invasive bladder cancer undergoing transurethral resection bladder tumour

The effect of minimally invasive surgery, TURBT, on the VTE rate in BC patients has rarely been investigated. A single study used the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database, which explored the VTE rate in patients who had TURBT for non-muscle invasive bladder cancer patients. The study reviewed data from 1988 to 2009 for 50,125 patients treated with TURBT; 2.8% of patients experienced VTE within 90 days post TURBT (Zaffuto *et al.*, 2017). In non-muscle-invasive BC undergoing TURBT, no thromboprophylaxis was utilised due to lack of evidence on the VTE risk as well as concerns around bleeding.

2.1.8. VTE in patients with bladder cancer undergoing cystectomy

The data from 33 studies of patients with BC undergoing cystectomy (invasive surgery) (Tables 1 & 2) were extracted to find the rate of VTE in patients undergoing cystectomy alone and patients having a cystectomy plus chemotherapy and in and out with the UK. The VTE rates at different time points post-cystectomy were identified - 30 days, 90 days, 180 days, 1 year or 2 years. All studies included found an elevated risk of VTE among patients undergoing cystectomy. The rates of VTE in BC patients who had cystectomy were between 1.3% and 23.2% (mean=4.9%) (Table 1). In the UK, two studies explored the rate of VTE in patients undergoing cystectomy and the VTE rates were 2.5% and 2.9% mean=2.7% (Dyer *et al.*, 2013b; Khan *et al.*, 2012). Three Canadian studies and one from Turkey demonstrated a VTE rate of BC patients treated with chemotherapy and cystectomy of between 1.3% and 9% (mean=5.1%) (Table 1). There were no studies that explored the VTE rate in BC patients having cystectomy and chemotherapy.

Regarding thromboprophylaxis post-cystectomy, 30 studies did not clearly discuss thromboprophylaxis regimens for BC patients undergoing cystectomy (Table 1). However, two studies from the USA explored thromboprophylaxis effectiveness in BC patients with cystectomy in the post-surgical period (Table 2). These two studies grouped patients by receiving thromboprophylaxis for 14 days or 28 days post-cystectomy. The patients were followed for 90 days duration. A substantial reduction in VTE rate (from

17.6% to 5%) was recorded in the extended thromboprophylaxis (28 days) group in comparison to the control group (14 days); extended chemoprophylaxis significantly reduced the incidence of VTE (P value= 0.021) (Schomburg *et al.*, 2017). No UK studies explored the impact of using extended thromboprophylaxis on the VTE rate in BC patients who have had cystectomy.

2.1.9. VTE in bladder cancer patients undergoing chemotherapy

Only two studies exploring the VTE in muscle-invasive BC who received chemotherapy were found, and the VTE rates were 5.1% and 8.1% (mean=6.6%) (Khorana *et al.*, 2013; Ramos *et al.*, 2017b). The VTE rate within six months from diagnosis of metastatic urothelial cancer (not specifically bladder cancer) is 3.2%, and VTE rate in metastatic urothelial cancer and receiving chemotherapy is 5.1% (Ramos *et al.*, 2017). No data exclusively relating to patients with BC who have had chemotherapy only were found to assess the benefits or drawbacks of thromboprophylaxis in this population. The studies around VTE rate in BC patients who were undergone cystectomy and/or chemotherapy treatment are summarised in Table 1.

Table 1: Studies included information on VTE rate in bladder patients undergoing cystectomy and/or chemotherapy treatment

References	Study Origin	VTE rate (%)	Follow up (days)	Enrolment Period	Participants	Study type	Intervention	Quality
(De Martino *et al.*, 2012)	USA	4.9	30	2007-2009	307	Retrospective	Cyst.	Fair
(Alberts *et al.*, 2014)	USA	5.5	30	2005-2012	2065	Retrospective	Cyst.	Fair
(Soave *et al.*, 2016)	Germ-any	3	30	2007-2014	201	Retrospective	Cyst.	Poor
(Vukina *et al.*, 2014)	USA	5.7	30	2005-2011	878	Prospective	Cyst.	Fair
(Mossanen *et al.*, 2014)	USA	5.5	30	2007-2012	8671	Retrospective	Cyst.	Fair
(Chen Emily *et al.*, 2015)	Austra-lia	7.7	30	2009-2013	53	Retrospective	Cyst.	Fair
(Lyon *et al.*, 2018)	USA	4.2	30	2011-2016	8241	Retrospective	Cyst.	Fair
(Van Dlac & Cowan, 2014)	USA	6.0	30	2005-2011	1307	Retrospective	Cyst.	Good
(Zaffuto *et al.*, 2017)	USA	2.8	90	1988-2009	50125	Retrospective	TURBT	Good
(Daneshman d *et al.*, 2014)	USA	5.4	30	2011-2012	110	Prospective	Cyst.	Good
(Cookson *et al.*, 2003)	USA	1.3	30	1995-2000	304	Retrospective	Cyst.	Poor
(Breau *et al.*, 2014)	USA	3.2	30	2006-2012	2303	Retrospective	Cyst.	Fair
(Tyson *et al.*, 2014)	USA	6.8	30	2005-2011	1792	Retrospective	Cyst.	Good
(de Vries *et al.*, 2012)	Nether-lands	2.3	30	2007-2008	85	Prospective	Cyst.	Good
(Nguyen *et al.*, 2018)	Turkey	1.3	30	2011-2015	74	Prospective	Cyst. + CT	Poor
(Brössner *et al.*, 2004)	Austria	3.2	30	1998-2002	92	Retrospective	Cyst.	Fair
(Hugen *et al.*, 2017)	USA	4.4	90	1985 - 2015	2694	Retrospective	Cyst.	Fair
(Doiron *et al.*, 2016)	Cana-da	5.4	90	1994 - 2008	3879	Retrospective	Cyst. + CT	Good
(Sun *et al.*, 2015a)	USA	4.7	90	1971-2012	2316	Retrospective	Cyst.	Good
(Khan *et al.*, 2012)	UK	2.5	90	2003-2008	158	Retrospective	Cyst.	Good
(Fairey *et al.*, 2008)	Cana-da	3.5	90	2000-2006	314	Retrospective	Cyst.	Good
(James *et al.*, 2013)	USA	6.3	90	2008-2010	2565	Retrospective	Cyst.	Good
(Laymon *et al.*, 2019)	Egypt	4	90	2004-2014	1737	Retrospective	Cyst.	Good
(Brennan *et al.*, 2018)	Cana-da	9	180	1994-2013	4205	Retrospective	Cyst. + CT	Good
(Ramos *et al.*, 2017)	USA	5.1	180	2000-2013	1762	Retrospective Cohort	CT	Good

References	Study Origin	VTE rate (%)	Follow up (days)	Enrolment Period	Participants	Study type	Intervention	Quality
(Khafagy *et al.*, 2006)	Egypt	3.3	180	1999-2001	60	Retrospective	Cyst.	Fair
(Khorana *et al.*, 2013)	USA	8.2	360	2004-2009	2001	Retrospective	CT	Good
Dyer (Dyer *et al.*, 2013b)	UK	2.9	360	2009 - 2010	1641	Retrospective	Cyst.	Fair
(Ording *et al.*, 2016b)	Den-mark	3.3	360	1995 - 2011	13809	Retrospective	Cyst.	Fair
(Wallis *et al.*, 2017)	Cana-da	4.5	720	2002 - 2014	3623	Retrospective	Cyst. + CT	Fair
(Walker *et al.*, 2013b)	UK	1.5	720	1987 - 2012	3152	Retrospective	NA	Fair
(Sandhu *et al.*, 2010b)	USA	1.9	720	1993-95 & 97-99	24861	Retrospective	NA	Fair
(Berneking *et al.*, 2013)	USA	10.3	------	2000-2010	359	Retrospective	Cyst.	Fair
(Mendiola *et al.*, 2007)	USA	2.3	----	1995-2003	42	Retrospective	Cyst.	poor
(Clément *et al.*, 2011)	France	23.2	---	2005-2009	86	Retrospective	Cyst.	Fair
(Cárdenas-Turanzas *et al.*, 2008)	USA	1.4	---	2000-2003	1493	Retrospective	Cyst.	poor

CT-Chemotherapy; Cyst. – Cystectomy, NCT-Neoadjuvant chemotherapy; INT-International; TURBT-Transurethral Resection Bladder Tumour, ACT-Adjuvant chemotherapy, NA-Not Applicable

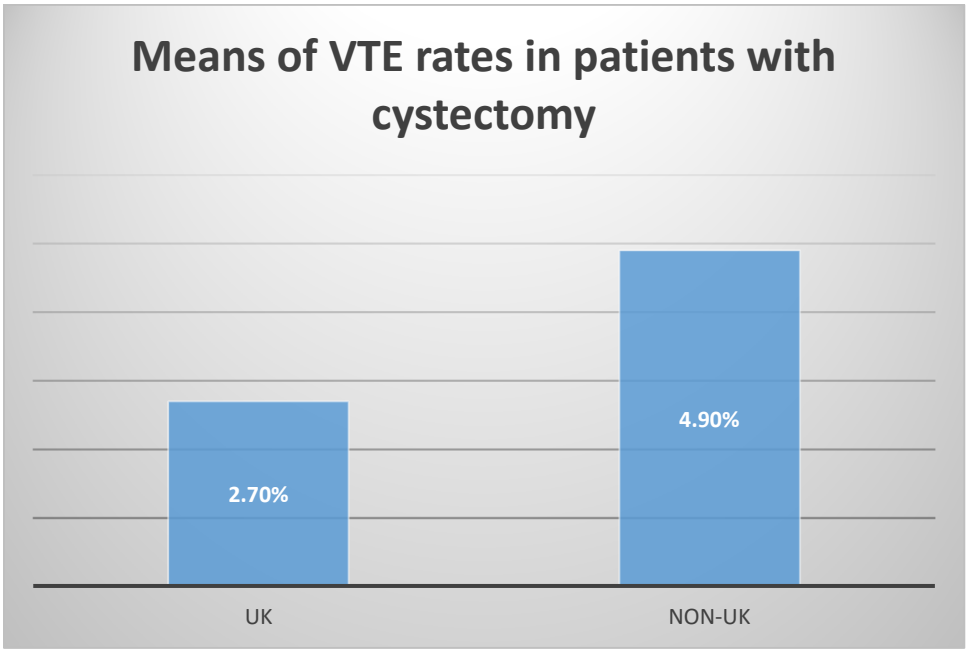
Table 2: VTE rate in bladder cancer patients receiving thromboprophylaxis

References	Study Origin	VTE rate (%) with ETP	VTE rate (%) without ETP	Follow-up (days)	Enrolment period	Participants	Type of study	Interventions	Quality
(Schomburg *et al.*, 2017)	USA	5	17.6	90	2012-2015	79-51	Retrospective	Cyst. ± TP	Good
(Pariser *et al.*, 2017b)	USA	5	12	90	2011-2014	402-234	Retrospective	Cyst. ± TP	Good

TP-Thromboprophylaxis; ETP-Extended Thromboprophylaxis, Cyst. - Cystectomy

The mean of VTE rates in BC patients who had undergone radical cystectomy in the UK was lower than in non-UK countries as a group (Figure 8).

Figure 8: Mean of VTE rates of BC patients who have had cystectomy, UK and other countries



2.1.10. Discussion of systematic review

This review explored the mean of VTE rates within and outside the UK and found the difference with the mean of VTE rates in non-UK countries according to type of treatments or VTE risk factors in patients with BC. The VTE rates were explored in BC patients according to the risk factors impacting on the rate of VTE such as surgery, chemotherapy and thromboprophylaxis in the UK and non-UK countries, where possible.

The review of the VTE rate in patients with BC elicited 38 prospective and retrospective studies that demonstrated VTE rates in different follow-up periods among BC patients who have had a radical cystectomy (Tables 1 & 2). Each study has a different rate of VTE and therefore a wide range of VTE rate in patients having cystectomy is noted (1.3% to 23.2%) in this current review (Tables 1 & 2). Regarding UK studies, they were only two studies that collected data on the VTE rate in BC patients who have had cystectomy in the UK and these studies were carried out some years ago (2012 and 2013).

Hence, due to lack of new and enough number of studies (more than four studies) in recent years, it would be unlikely to be beneficial to carry out a meta-analysis of VTE rate in BC patients based on country (UK vs non-UK countries). It is important to undertake new studies exploring the VTE rate in BC patients in the UK.

A previous systematic review was carried out on the risk of VTE and bleeding in patients having open radical cystectomy (Tikkinen *et al.*, 2017). Many studies included in Tikkinen's systematic review were occasionally reported the VTE rate as one of the adverse effects of surgery, and it seems that these studies did not check for VTE events carefully. These data may be at risk of information bias (Tikkinen *et al.*, 2017).

There are many possible explanations for the large variations in the rates of VTE observed within this group: for example, the heterogeneity of risk factors in this population that could affect the rate of VTE, such as minimal invasive (robotic) cystectomy or open radical cystectomy (Fantony *et al.*, 2016). Additionally, 30 of the included studies did not state, discuss or categories BC patients according to confounding factors that alter the rate of VTE, such as receiving surgical thromboprophylaxis for 14 or 28 days, which then makes it difficult to compare rates between studies (Alberts *et al.*, 2014; Berneking *et al.*, 2013; Breau *et al.*, 2014; Brennan *et al.*, 2018; Brossner *et al.*, 2004; Caglayan *et al.*, 2012; Chen Emily *et al.*, 2015; Clément *et al.*, 2011; Cookson *et al.*, 2003; Cárdenas-Turanzas *et al.*, 2008; Daneshmand *et al.*, 2014; De Martino *et al.*, 2012; de Vries *et al.*, 2012; Doiron *et al.*, 2016; Dyer *et al.*, 2013b; Fairey *et al.*, 2008; Hugen *et al.*, 2017; James *et al.*, 2013; Khafagy *et al.*, 2006; Khan *et al.*, 2012; Lyon *et al.*, 2018; Mendiola *et al.*, 2007; Mossanen *et al.*, 2014; Ording *et al.*, 2016b; Soave *et al.*, 2016; Sun *et al.*, 2015a; Tyson *et al.*, 2014; Van Dlac & Cowan, 2014; Vukina *et al.*, 2014; Wallis *et al.*, 2017). All included studies with the exception of two (Pariser *et al.*, 2017b; Schomburg *et al.*, 2017) did not clearly discuss or state the thromboprophylaxis measures employed. Having different thromboprophylaxis protocols may be the cause of variation in VTE rate between studies and countries using extended thromboprophylaxis 28 days post-surgery decrease VTE rate in BC patients with cystectomy (Table 1 & 2).

The timing of follow up differs between surgical studies. The minimum follow-up duration of patients undergoing cystectomy was 28 days and the VTE rates were 3% -7.7% (mean=5.6%). In this review, we excluded studies which only drew on data relating to VTE during in-hospital admission because the vast majority of VTEs (82.6%) occur after discharge from hospital; in other words, there was an inadequate follow-up for VTE in patients undergoing cystectomy (Alberts *et al.*, 2014). In our current review, the data from three studies that followed up the patients for three months after cystectomy revealed that VTE rates were still high; this may be due to patients having further treatment and hospitalisation (Blom *et al.*, 2006b; Brennan *et al.*, 2018; Ramos *et al.*, 2017b). According to the study by Wallis et al. (2017), the VTE rate peaks at 20 days after cystectomy in BC patients; however, patients continue to be at risk of VTE long after surgery (Wallis *et al.*, 2017). As found in this review, BC patients who had undergone cystectomy have an elevated risk of VTE for up to 3 months after surgery (Doiron *et al.*, 2016). Consideration should thus be given to offering thromboprophylaxis measures and caring for longer than 28 days post cystectomy, in particular, if chemotherapy has been added to the treatment plan or patients have other risk factors for VTE. The majority of BC guidelines typically suggest extended thromboprophylaxis for pelvic surgery including cystectomy for up to four weeks post-discharge (NICE, 2011; Streiff *et al.*, 2015). Interestingly, the mean of VTE rates in patients who have had cystectomy with chemotherapy is 5.0% (Brennan *et al.*, 2018; Doiron *et al.*, 2016; Van Dlac & Cowan, 2014), suggesting that systemic chemotherapy did not increase the VTE rate more than the already increased rate imposed by surgery.

Brennan and his team (2018) also mentioned that chemotherapy is not associated with an increased risk of VTE after RC (Brennan *et al.*, 2018). The presence of metastatic disease increases the VTE rate to the same extent as cystectomy by 5.1% (Gopalakrishna *et al.*, 2016). However, patients with metastatic BC who did not receive chemotherapy had an absolute VTE incidence rate of 3.2% (Ramos *et al.*, 2017b). The VTE rate in patients with metastatic BC who receive systemic chemotherapy further increased to 5.1% within 6 months. VTE rates based on the chemotherapy group demonstrated

no statistical difference when gemcitabine/cisplatin was used as the comparator (Ramos *et al.*, 2017b).

Gopalakrishna et al (2016) mentioned that the VTE rate differed significantly by country of origin among BC patients (Gopalakrishna *et al.*, 2016). This is likely to be due to differences in patients' characteristics, using preoperative chemotherapy, recording issues and using different protocols of thromboprophylaxis. Thus, it is of value to find the VTE rate in the UK and not depend on the data from non-UK countries, in order to scope the problem and strive to protect the patients from this debilitating condition. The VTE rates were 2.5% and 2.9% within one-year post-cystectomy as the UK study found (Dyer *et al.*, 2013b; Khan *et al.*, 2012).

The VTE rate in BC patients varies according to the type of treatment and the use of thromboprophylaxis. Additionally, the mean of VTE rates in BC patients in the UK is lower than the mean of non-UK countries, which indicates that there is a variation in VTE rates in BC patients between the UK and non-UK countries (Figure 4). According to the author, the VTE rate in BC patients in the UK seems lower than that of non-UK countries, perhaps due to the extended thromboprophylaxis regimens applied post cystectomy. More data in the UK are required to document the VTE rate in patients who have had a cystectomy and patients treated with cystectomy and chemotherapy. This current review has some limitations, however, as many studies included did not report all variables of interest e.g. thromboprophylaxis measures and chemotherapy prescribed, but mainly reported VTE rate and the country origin of study. The strengths of this current systematic review include the comprehensive search strategy, the risk of bias assessment and exploring other risk factors for VTE in the BC population.

In summary, this review found the VTE rates in patients with BC who have had cystectomy or chemotherapy are around 2.7% and 5.2%, respectively. There are no data on VTE in BC patients who have had radiotherapy, and very limited data regarding VTE in BC patients who have had cystectomy and chemotherapy in the UK. No data explored the radiotherapy risk factors for the VTE in BC patients.

2.1.11. Systematic Review - Conclusion

This review highlights the fact that VTE rate in BC varies between studies due to the heterogeneity of risk factors (cystectomy, chemotherapy and thromboprophylaxis) reported. The mean of VTE rates in BC patients who have had cystectomy in the UK seems lower than in non-UK countries.

The review also highlights the condition of VTE in BC patients, and thus will help to inform clinicians and patients about different VTE risk factors in this patient population. VTE rates in patients with BC are affected by the duration of thromboprophylaxis in patients who have had cystectomy, so this study supports extended anti-clotting prophylaxis in patients undergoing cystectomy.

The VTE rates obtained from this current review may contribute towards clinical decision-making on the duration of thromboprophylaxis in BC patients having a cystectomy. Standardisation of reporting may help improve the evaluation of risk.

2.1.12. Recommendation from the Systematic Review

Further studies to explore the VTE rate in patients with BC, undergoing cystectomy or receiving multimodality bladder preservation treatment, should be carried out in the UK, to garner more robust data to better protect patients from this debilitating condition. More studies on prophylactic measures for BC patients also would be required.

2.2. Cancer patients' experiences and understanding of venous thromboembolism: A scoping review

2.2.1. Introduction

As summarised in Chapter 1, VTE is a serious health challenge in patients with cancer; however, its severity is perhaps undervalued by healthcare professionals (HCPs) and oncologists (Khalil *et al.*, 2015).

Cancer patients are generally unaware of VTE, thromboprophylaxis measures and consequences of VTE. Two recent cancer patient surveys on VTE in cancer patients found that less than half of patients were aware of the increased risk of developing VTE with a malignancy (Lyman *et al.*, 2013a). The most up-to-date American Society of Clinical Oncology (ASCO) guidelines demand a better education regarding VTE in cancer patients who are at high risk for VTE (Key *et al.*, 2020b).

The prevention and treatment of VTE in cancer patients cannot be optimised without good awareness among patients. High-quality communication between HCPs and patients leads to a better VTE awareness in cancer patients. HCPs caring for cancer patients need to focus on educating patients on VTE, particularly in high risk settings such as major surgery and chemotherapy (Key *et al.*, 2020b).

In current oncology practice, prevention and treatment of VTE are practised according to international guidelines; the main challenge for healthcare providers is how to improve the awareness of cancer patients before VTE happens ultimately to strive to save lives (Donnellan & Khorana, 2017).

2.2.2. Rationale for scoping review

Cancer patients are well known to have a high risk of VTE, in particular, those patients who have had major surgery, chemotherapy and/or hormonal therapy (Khalil *et al.*, 2015). These groups of patients need to understand the risk factors of VTE and the prophylactic measures to prevent developing VTE.

To stimulate improvements in the supportive care of cancer patients and decrease VTE risk, and increased understanding and awareness

regarding VTE in cancer patients are required (Benelhaj *et al.*, 2018). A scoping review is a type of information synthesis that follows a systematic approach to map the literature on a subject and explore the types of evidence available, then determines gaps in that literature (Peterson *et al.*, 2017). This scoping review was conducted in an attempt to explore communication risk on VTE between cancer patients and health professionals before VTE diagnosis.

2.2.3. Research question for scoping review

What is known from the existing literature on patients' experiences of VTE regarding communication risk on VTE between cancer patients and HCPs?

2.2.4. Aims and objectives of scoping review

Aim:

To explore the literature on patients' experiences and understanding of VTE in cancer patients

Objectives:

- Highlight cancer patients' perspective on VTE
- Explore the content of the information on VTE communicated to cancer patient before VTE diagnosis
- Explore gaps in HCPs and cancer patient education regarding VTE

2.2.5. Methods for scoping review

A structured electronic search was conducted across three databases, which included Embase, Scopus and Medline, in July 2021 (Appendix 3). The search strategies combined with terms relating to venous thromboembolism, cancer-associated thrombosis, deep vein thrombosis, pulmonary embolism, anticoagulants, thromboprophylaxis, Low Molecular-weight Heparin, cancer and qualitative study. The electronic searches were limited to English language. No date restrictions were imposed, to ensure all relevant available literature pertaining to qualitative studies on cancer patient's understanding of VTE and their experience were identified. Bibliographies from relevant studies were examined for additional related studies.

2.2.6. Search inclusion and exclusion criteria for scoping review

Inclusion criteria:

- Studies of adult cancer patients with VTE
- Qualitative studies that explored the experience of cancer patients on VTE and related treatments

Exclusion criteria:

- Non-English language studies

2.2.7. Analysis of scoping review

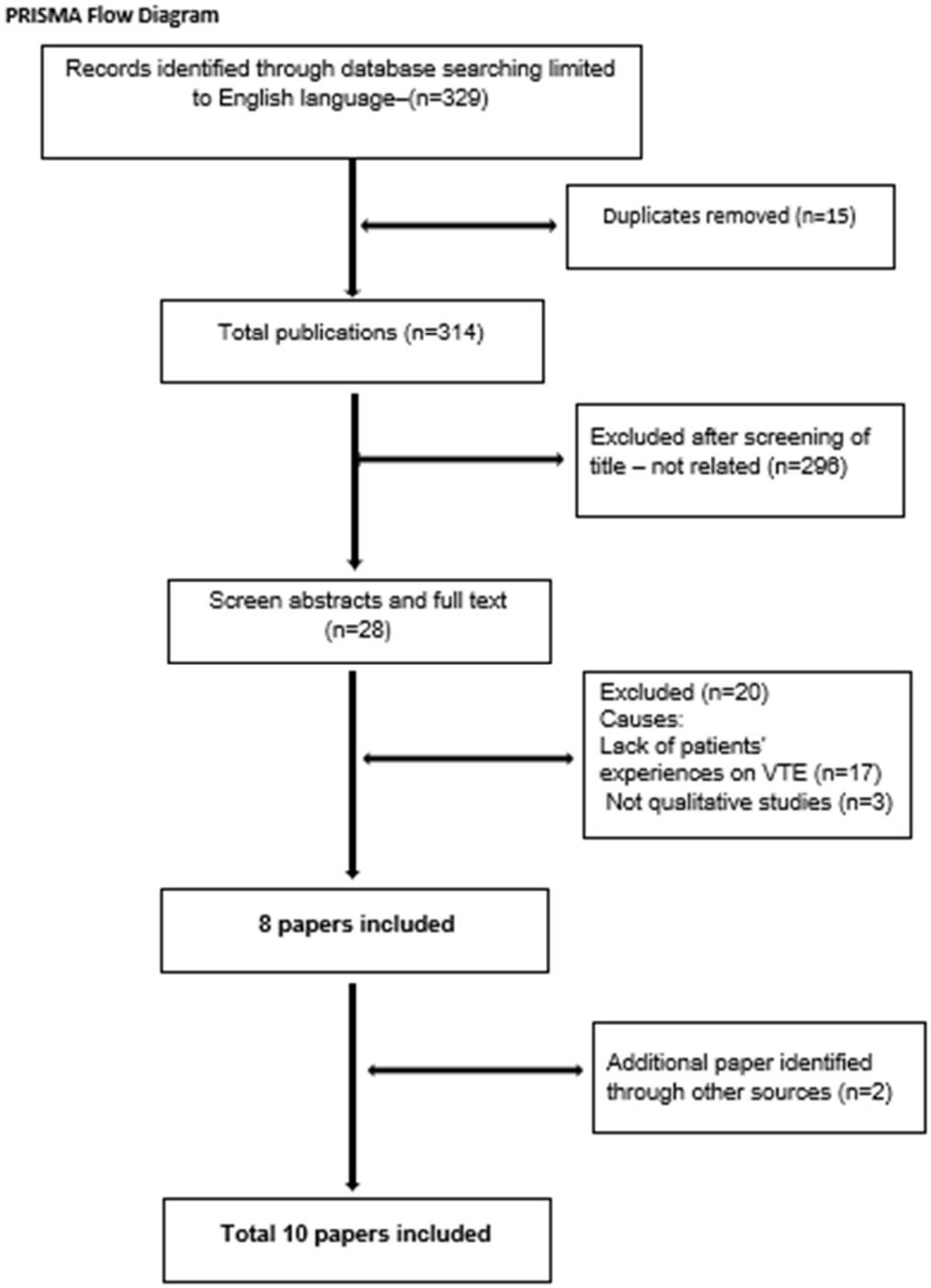
The results of this scoping review are presented in a descriptive manner. Included studies were selected according to a primary focus of the research in which the principles of thematic analysis were used to explore cancer patients' understanding of VTE from their experience of having had cancer and related treatments.

All qualitative studies regarding VTE in cancer patients were used to explore findings and evidence that answered the research questions. The researcher identified themes for knowledge synthesis using thematic analysis. For coding, the papers were read and re-read in order to become familiar with the data and discover codes. Direct quotes from cancer patients and the researcher comments were used from each study for coding and then developing themes related to the aims of this scoping review. Two reviewers independently checked selected themes; discrepancies were resolved through discussion.

2.2.8. Results of scoping review

Of the 329 publications, a total of ten met the inclusion criteria and were selected for this scoping review. All stages of the extraction process are shown in the PRISMA flow diagram (Figure 9).

Figure 9: Study selection process of scoping review



In total, ten qualitative studies discussing thrombosis and anti-thrombotic treatment in cancer patients were found. However, no studies explored patients' understanding of VTE in prophylactic settings in high-risk cancer patients.

Papers included in this review addressed patients' experiences of cancer-associated thrombosis (CAT) within the context of their cancer journey. A total of 152 cancer patients with VTE were contained within these studies. The participants represented a wide variety of cancer types and stages such as colorectal, breast, bladder, ovary, lung, renal, prostate and pancreas. All participants were adults of mixed gender, ranging from 32 to 84 years of age.

The number of participants in research-specific papers ranged from 8 to 40. Further characteristics of the eight papers reviewed as part of this scoping review are outlined in Table 1. Most studies originated in the UK. There was no published study before 2007; however, the majority of studies were published in the five years prior to this review being conducted (2015–2020). Of the articles recognised in this review, five discussed patients' experience of cancer-associated thrombosis and four were about anti-thrombotic treatments, such as low molecular weight heparin (LMWH) in cancer patients and its impact on their life. There are nine primary qualitative studies and one systematic review that explored cancer patients' experiences of living with VTE (Table 3):

Table 3: Qualitative studies of cancer-associated thrombosis

Study	Method	Setting	Aim	Analysis
(Noble & Finlay, 2005)	Semi-structured Interview	UK	Assessing the appropriateness of LMWH in palliative care patients and extent of daily injection burden	Thematic analysis
(Mockler *et al.*, 2012).	Semi-structured Interview	Canada	Exploring the experiences of patients with cancer who developed VTE	Thematic analysis
(Seaman *et al.*, 2014)	Semi-structured Interview	UK	Exploring the acceptability of long-term LMWH for the treatment of CAT	Thematic analysis
(Noble *et al.*, 2015a)	Semi-structured Interview	UK	Exploring patients' experiences of CAT within the context of cancer journey	Framwork analysis
(Noble *et al.*, 2016b)	Semi-structured Interview	UK	Impact of a dedicated CAT service on clinical outcomes	Thematic analysis
(Benelhaj *et al.*, 2018)	Systematic review	UK	Exploring patients' experience of CAT: an exploratory study	Thematic analysis
(Font *et al.*, 2018b)	Semi-structured Interview	Spain	Exploring patients' experience of CAT within a Spanish setting.	Framework analysis
(Noble *et al.*, 2019)	Semi-structured Interview	Canda	Exploring patients' experience of CAT within a Canadian setting	Framework analysis
(Noble *et al.*, 2015b)	Focus groups with clinicians; semi-structured interviews with patients and their relatives	UK	Explore clinicians' attitudes/patients' and relatives' experiences towards LMWH treatment for CAT versus cessation at 6 months in cancer patients; patients' perception of CAT and anticoagulation	Framwork analysis
(Woulfe *et al.*, 2020)	Semi-structured Interview	New Zealand	Exploring patients' experience of CAT within a New Zealand setting	Framework Analysis

CAT - Cancer-associated thrombosis, VTE - Venous thromboembolism

2.2.9. Synthesis of findings

The findings are presented as themes, as recognised from the included studies: these themes comprised: lack of meaningful information, cancer patients unaware of signs and symptoms of VTE and limited awareness of VTE amongst HCPs and acceptability of anti-coagulant:

Theme 1: Lack of meaningful information on CAT

Five studies explored patient information regarding VTE in cancer patients, known as cancer-associated thrombosis (CAT), in the context of patient's cancer journey (Font *et al.*, 2018b; Mockler *et al.*, 2012; Noble *et al.*, 2019; Noble *et al.*, 2015a; Woulfe *et al.*, 2020).

It is well known that VTE risk is elevated in cancer patients, and is higher with cancer treatments (surgery, chemotherapy and long in-hospital

admission). Although VTE may occur within the first few months of diagnosis of cancer, participants were often unaware of their high risk of developing VTE (Khorana & Connolly, 2009; Mockler *et al.*, 2012).

In more than one study, cancer patients reported that they had minimal information or support regarding CAT. Patients with cancer were not well informed about VTE, risk factors or their risk of VTE:

> *"Nobody really explained, […] 'coz they need the bed, you know. So, you don't feel as though erm, you know, I think if it was a little bit more relaxed er, they probably would've got somebody you know, from a department to come and explain it more." [VCC05] (Noble et al., 2015a).*
>
> *"During my cancer treatments, I was never told that there was a risk of getting a blood clot. I didn't know about it… I was pretty shaken up" (Mockler et al., 2012).*

When patients do not have background knowledge about VTE, they may have strong feelings and emotion during VTE diagnosis. Effective communication thus puts patients at ease:

> *"I have never heard of venous thromboembolism, so that's why I was so shocked" (Mockler et al., 2012).*

Patients explained about the moment the doctors told them they had VTE. It was noticeable that cancer patients felt worried and suffered from significant distress due to a lack of forewarning regarding the risk of VTE and possibility of death (Mockler *et al.*, 2012; Noble *et al.*, 2019; Noble *et al.*, 2015a). It is common for cancer patients to feel anxious about their health, about what investigations and treatments they might have to undergo and about what the future holds for them:

> *"The blood clot was a scary thing because I didn't know if I should have been looking for something and from what questions I have been asked, there was nothing that would have alerted me. … Because knowing nothing about clots, it just meant almost like a death sentence" [100-10] (Noble et al., 2019).*

"[…] but they don't tell you you're gonna get clots after chemo, that's the one thing they haven't, they never said but we, we just put it down to, it's just my breathing […] just that one item of information that we weren't aware of" [VCC07] (Noble et al., 2015a).

Conversely, patients with the right information about VTE, before VTE diagnosis, answered in a calm manner and looked for medical help directly after their doctors told them they had VTE. Thus, effective communication between HCPs and their patients reduces patients' anxiety and build their confidence:

"I was out of breath and I said to my partner, 'I think we are going to the hospital, without panic because I knew that it was something that could be rectified effectively" (Mockler et al., 2012).

As mentioned before, patients are receptive to having more knowledge and they need to know the truth (Font *et al.*, 2018b).

"There's nothing wrong with having a little more information." (LP03) (Font et al., 2018b).

"We told him that we wanted to know the truth, and in the clinic, I don't know whether they saw the attitude we had, but they have always told him the truth, always, because what I have, not knowing, doesn't solve anything. And in the clinic, they were very open right away." (LP18) (Font et al., 2018b).

In 2016, an evaluation of the development of a dedicated cancer-associated thrombosis (CAT) service was conducted: this revealed that some patients saw information leaflets as providing information and assurance (Noble *et al.*, 2016b):

"The knowledge you get by reading the, all the different literature makes it that much reassuring you know." (Noble et al., 2016b).

In the UK, a mixed-methods study described the development of a dedicated CAT service and its evaluation, and reported that the amount and

type of information given to cancer patients with thrombosis were enough for their required level of understanding (Noble *et al.*, 2016b):

> *"I think they told me what I could understand … I don't need… graphic details and chemical things. As long as they tell me…they think that's what caused it. That's the treatment we're going to give you, and it should sort it out, and this is what you need to look out for in the future." (Noble et al., 2016b).*

One embedded qualitative study within a randomised controlled trial (RCT) to identify the most clinically effective and cost-effective length of anticoagulation in the treatment of cancer-associated thrombosis (ALICAT) discussed the participants' understanding of their risk of having more VTE if they were randomised to the control arm of the ALICAT RCT and stopped receiving anticoagulant drugs (LMWH) (Noble *et al.*, 2015b). ALICAT study revealed that participants with a history of VTE might have an understanding of their ongoing risk of developing VTE (Noble *et al.*, 2015b). Three participants in this trial believed that they still had ongoing cancer and that they remained at risk of developing another VTE:

> *"I thought well the cancer is still there, there's still a possibility that I would get the clot back." [interview NC2] (Noble et al., 2015b)*

Clearly, the dominant reason, found in the ALICAT study for refusing to cease anticoagulant treatment was that patients believed that they would experience another VTE (Noble *et al.*, 2015b).

Cancer patients are receptive to receiving more information about VTE, but do not need very detailed information (Font *et al.*, 2018b).

> *"There's nothing wrong with having a little more information.' (LP03) (Font et al., 2018b).*

Theme 2: Cancer patients unaware of signs and symptoms of VTE

In two studies, patients reported that they had no information about the signs and symptoms of VTE (Mockler *et al.*, 2012; Noble *et al.*, 2015a). In Nobel et al.'s (2015) study, the patients stated that they were complaining about the delayed diagnosis of pulmonary embolism:

"They said it was probably pleurisy, gave me antibiotics […] it was a pain I'd never had before" (Noble et al., 2015a).

Two participants in Mockler et al.'s (2012) study suffered from sudden shortness of breath due to pulmonary embolism, but they diagnosed themselves wrongly with a heart attack:

"All of a sudden I couldn't breathe . . . I didn't know what was happening. . . . They wrote in the chart that it was a possible heart attack." (Mockler et al., 2012).

"I felt I was having a heart attack . . . that stress made [the symptoms] worse." (Mockler et al., 2012).

Informing cancer patients about CAT before developing VTE may support the patients for self-diagnosis and save their life. One of the patients in Mockler et al. (2012) mentioned that the awareness regarding VTE determines how the patient deal with symptoms of VTE and makes the patients to seek medical consultation:

"Prior knowledge of cancer-associated thrombosis risk and symptoms (or lack of knowledge) determined the patient's reaction to the symptoms of cancer-associated thrombosis" (Mockler et al., 2012).

Benelhaj et al. (2018) in their systematic review also confirmed that cancer patients have little awareness of the signs and symptoms of VTE:

"Cancer patients are still not routinely educated about the risk or warning symptoms/signs of venous thromboembolism which may otherwise be misattributed to cancer by patient and clinician alike."(Benelhaj et al., 2018)

Chemotherapy can cause unpleasant side effects, but it is difficult to predict what side effects patients would have. Cancer patients on chemotherapy usually have different side effects, making VTE very difficult to recognise. When VTE developed in patients who received chemotherapy, they therefore did not appreciate that their symptoms were due to VTE:

"[…] but um this time again first set of chemo, she felt terrible and the thing is, when we went back to hospital really desperate, the only problem we thought was that it was the chemotherapy that was causing it" [RG02] (Noble et al., 2015a).

Increasing patients' awareness on VTE and related symptoms may increase patients' recognition of serious adverse effects and promote fast reporting.

Theme 3: Limited awareness of VTE amongst HCPs

Nobel et al. (2015) stated that in their study of patients' experiences of living with cancer-associated thrombosis (PLICAN study), there was evidence of limited awareness of VTE and cancer among HCPs. Therefore, the limited knowledge regarding VTE in cancer patients was not restricted to patients (Noble *et al.*, 2015a). Moreover, the findings of the PELICAN study revealed that cancer patients reported delayed diagnosis of VTE, and on many occasions, alternative reasons or diagnosis were considered first:

"It just got bigger and bigger and bigger, over months really […] then they doubled them (diuretics), and then they trebled them" [RG05] (Noble et al., 2015a).

Regarding patients with shortness of breath associated with chest pain, these patients were often treated wrongly first with antibiotics for a supposed chest infection, which indicated doctors had limited information regarding VTE. One patient explained how his treating doctor reacted to his shortness of breath:

"I went to the doctor, and she listened and whatever and said it was probably pleurisy" [VCC12] (Noble et al., 2015a).

Theme 4: Acceptability of anticoagulant

In patients with cancer, LMWH has been preferable for prophylactic and treatment of VTE. Most patients were commenced on LMWH, and others were on warfarin but changed to LMWH due to the uncontrolled the international normalized ratio (INR), absorption difficulties, and VTE recurrence:

"With the warfarin, what was kind of crappy was that I had to do blood tests every two weeks. But with Low Molecular Weight Heparin no need for draws." (Mockler et al., 2012).

Cancer patients have different views regarding the duration of using LMWH; some patients who experienced VTE desired to take LMWH for longer than 6 months as long as the risk of VTE was still present. Others, meanwhile, wanted to cease LMWH injection after 6 months due to the pain and side effects of the injections and wished to continue their normal life without injections:

"I was just happy to get off of it, to be honest with you, um it was more or less the same time every night, um and the pain as I said eh to me was terrible, horrific and a lot of bruising and things." [Interview NC1] (Noble et al., 2015b)

"And so, I was very keen I have to say, I was predisposed I don't want any further injections once the treatments finished, I just want to try to get back to as much normality as I can." [Interview NC8] (Noble et al., 2015b).

For cancer patients with VTE, four studies estimated patients' responses to anticoagulation treatments, concentrating on the acceptability and tolerability of receiving anti-clotting injections (Mockler *et al.*, 2012; Noble & Finlay, 2005; Noble *et al.*, 2015b; Seaman *et al.*, 2014). All studies explored the experience of cancer patients who have already had VTE, with LMWH, but there are no studies exploring cancer patients' responses to use anticoagulants injection (LMWH) as a prophylactic measure. Anticoagulant had a good impact on patients' life, especially for those who had experienced distressing symptoms. Generally, the patients agreed to use LMWH to treat VTE.

"I really don't feel like pricking myself, but if it's that or dying well, I'd rather prick myself." (Mockler et al., 2012).

“The needles—it’s painful, but you have to do it.” (Mockler et al., 2012).

“It’s not a problem to inject myself; I’ll do that for as long as I have to.” [PT9] (Seaman et al., 2014).

Cancer patients found LMWH to be an acceptable measure for treating VTE despite reporting a variety of symptoms associated with injecting.

2.2.10. Discussion of scoping review

This scoping review was conducted in order to map the key concepts supporting research regarding patients’ experiences and understanding of CAT and explore related studies and the types of evidence available, as this subject was not reviewed comprehensively before.

Bladder cancer patients formed part of the wider group of cancer patients. Hence, this review addressed broader topics such as the communication risk of VTE in cancer patients, as well as the risk of communication of VTE between different types of cancer patients and HCPs. All the relevant literature were included regardless of study design.

The findings of this review provide in-depth coverage of available qualitative studies regarding cancer patients’ experiences and understanding of VTE in order to explore the communication of VTE between cancer patients and HCPs before VTE diagnosis.

Four main themes, which were developed from the included articles, describe the type of knowledge regarding VTE possessed by cancer patients.

Lack of meaningful information on CAT:

Although only patients with cancer who had experienced a VTE were interviewed in the qualitative studies, they still had limited awareness of CAT or VTE and received limited education regarding their condition. Cancer patients did not have enough knowledge regarding VTE and the risks of developing VTE in their case before VTE was diagnosed.

Poorly framed information on cancer, risk of treatments and interventions in developing VTE in cancer patients may impact negatively on

patients' involvement in VTE prevention and receiving thromboprophylaxis measures (Apenteng *et al.*, 2016). Moreover, a lack of awareness regarding the consequences and harms of VTE could lead to a misinterpretation of the prophylactic measures.

In Apenteng et al.'s (2016) qualitative study exploring patients' perceptions and experiences of the prevention of hospital-acquired thrombosis, they found patient participation to be an essential aspect of the VTE prevention acquired during long in-hospital admission (Apenteng *et al.*, 2016). Similarly, cancer patients play a prominent role in VTE prevention if they receive proper education regarding VTE. Cancer patients reported that a good understanding of their condition enhanced self-management, as well as improved access to support and information (Noble *et al.*, 2016b).

Improved communication regarding risk factors for VTE and VTE is likely to optimise the effectiveness of the prevention of VTE in cancer patients.

Cancer patients are not aware of signs and symptoms of VTE:

Benelhaj et al.'s (2018) study found that cancer patients were not usually educated about the signs/symptoms of VTE which may otherwise be misattributed to cancer (Benelhaj *et al.*, 2018).

Education regarding signs/symptoms of VTE for cancer patients may enable the patients to seek medical consultation and consequently lead to early diagnosis and saving their lives. Patients who received chemotherapy had difficulties in recognising VTE from other side effects produced by chemotherapy (Noble *et al.*, 2015a). They need to be able to differentiate between signs/symptoms of VTE from other chemotherapy-related side effects. Medical oncologists during consenting patients for chemotherapy need to make more effort to educate patients about sign/symptoms of VTE. Patients should be empowered with information on the signs and symptoms of VTE to enable them to recognise it as early as possible.

Limited awareness of VTE amongst HCPs:

Knowledge should not be limited to cancer patients, but HCPs need to be well informed regarding VTE in cancer patients in order to have the ability for early diagnosis and provide useful information regarding VTE, risk factors and VTEs' signs/symptoms. Noble et al. (2015) in the PELICAN study discovered there that limited understanding of VTE amongst HCPs led to alternative diagnosis and delayed VTE diagnosis (Noble *et al.*, 2015a). It is very important to diagnose pulmonary embolism (PE) as early as possible due to its rapid and serious consequences (Khorana *et al.*, 2007a). Hence, more attention is required for HCPs education, not only cancer patients. HCPs are the main source of information and they are considered as the senders of information. Thus, they should have good quality of information regarding VTE in order to diagnose VTE and educate their patients about VTE.

Acceptability of anticoagulant:

Anticlotting injections are mainly used to treat or prevent VTE and its complications. All included qualitative studies explored patients' experiences of using anti-clotting injections as treating measures.

The attitudes of cancer patients with VTE about VTE treatment were useful, in that they helped the patients adhere to their anti-clotting treatment. They considered anticoagulant self-injections as necessary, although unpleasant (Mockler *et al.*, 2012).

It is clear that receiving anti-clotting injections is not pleasant, but patients with VTE feel it is mandatory. Anticlotting injections, like LMWH, were considered to be an acceptable intervention despite the need to receive the injections long-term (Mockler *et al.*, 2012; Seaman *et al.*, 2014).

Some groups of high VTE risk cancer patients, such as those admitted to hospital or with major surgery, require anti-clotting injections. Their understanding of the role of anti-clotting injections (LMWH) makes them adhere more to the treatments. Hence, attitudes toward anticlotting measures and injections need to be explored in cancer patients who did not experience VTE but have a high risk of VTE and need anticlotting injections. Previous studies have established that increasing patient awareness of VTE increases

treatment adherence (Juthani *et al.*, 2018). Communicating VTE to cancer patients in a clear and balanced way is required, as expert panels in ASCO recommend that cancer patients need periodic reminders about VTE risks, and HCPs should educate patients about VTE and related signs and symptoms (Key *et al.*, 2020b).

VTE in cancer patients should be part of standard training and education for all HCPs caring for people with cancer. Physicians may use the results of this study to improve individual patient education.

2.2.11. Conclusion

In cancer patients who did not have VTE, there were no qualitative studies focusing on their understanding of VTE. All published studies explored patients' experience of having a VTE in the cancer context and showed that participants had limited information about VTE, VTE risk and signs and symptoms of VTE.

2.3. Rationale for the study

Before outlining the underlying philosophical framework or exploring the methodology used in VTE-BC, it is necessary to provide a rationale for undertaking this piece of research to justify the importance and novelty of the current study. The systematic review portrayed limitations in data which explored VTE incidence rate and VTE risk factors in patients with BC in the UK. It is important to have the most precise data possible in order to inform the oncology community, and ultimately strive to prevent VTE. It is also important to investigate if possible which group of BC patients are at higher risk of VTE. Hence, a retrospective descriptive study (Phase I) was chosen to enlighten the scope of the VTE problem within BC population in the UK by collecting data from Hospital Episode Statistics (HES) data and two local NHS trusts.

Patients with BC appear to have a high risk of VTE, in particular those patients who have had cystectomy and/or chemotherapy (Sun, 2015, Tully, 2016). The situation in the UK is not fully elucidated. Thus, patients with BC at high risk need to be identified, and then perhaps to follow the most

appropriate individual management plan to try and lower this risk of VTE. High-risk patients with VTE should firstly be identified if possible and then be individually well-informed about measures to try and reduce the risk of VTE; furthermore, they need to know the signs and symptoms of VTE so they can seek urgent medical care if needed. Communication of risk information is a crucial part of shared decision making and evidence-based patient choice (Elwyn et al., 2001).

Having patient and healthcare professionals' insights into VTE in BC patients is a first step towards a strategy for preventing VTE in BC patients. Therefore, a search through two medical databases, Embase and Pubmed, was carried out to look for qualitative studies exploring patients' understanding of VTE in the BC population; this revealed no published studies. In the cancer population, there were no qualitative studies focusing on their understanding of VTE before developing VTE. All previous literatures explored patients' experience of VTE in the cancer context. Noble et al. (2015) carried out a study to explore cancer patients' understanding of the risk of VTE which was found to be poor; however, no BC patients participated in this study (Noble et al., 2015a). Furthermore, there was no literature on understanding VTE in cancer patients before VTE diagnosis and no literature has explored with BC specifically. Therefore, by having a baseline knowledge of patient and HCP insights around VTE in BC, this may raise awareness and subsequently it may then be possible to improve patients' education on VTE, as well as improving thromboprophylaxis, as per international guidelines, ultimately to save the lives of BC patients.

Exploring patient's understanding of VTE risk factors and complications, with a discussion of their circumstances and past experiences, is likely to assist in finding the best to educate on VTE to future patients. Understanding these communication measures, at the very least, will raise awareness of the problem of VTE and identify factors. Whether this will make an impact on decreasing the VTE rate or not, it will require further research outside the scope of this study.

A scoping review on patients' experiences and understanding of VTE in cancer patients (all types of cancers including BC) was carried out to discover patients' education on VTE between cancer patients and HCPs before VTE diagnosis.

This scoping review explored the types of evidence available, then determined gaps. There are no studies that explored cancer patients' understanding of VTE. All studies explored patients' experience of VTE in the cancer context with patients having had a VTE, as shown in the scoping review above. Based on the above, this current qualitative study gives new data regarding BC patients understanding of VTE in the UK.

Current study, VTE-BC, may lead to the development of communication guidance for patients and healthcare professionals to aid the communication of VTE. A mixed-methods approach, starting with a quantitative phase I, and followed by a qualitative phase II, was chosen because one type of data would not be enough to provide fully effective answers to the research questions. The methodology, methods and study design which are applied in this VTE-BC study are discussed in detail in the next chapter (Chapter 3).

3. VTE-BC methodology and methods

3.1. Chapter outline

The methodology and methods chapter begins with an overview of the plan for the VTE-BC study. The philosophical approach and paradigm and study design are discussed in detail. Ethical considerations are then presented, before the final section, which concludes the chapter. The purpose of this chapter is to describe how this study was undertaken by discussing two elements: firstly, the philosophical framework, and secondly, the research design of VTE-BC study.

3.2. Plan of study

The current study, which is called VTE-BC study, consists of two Phases. Phase I embraces a quantitative paradigm and Phase II, qualitative. After completing the systematic review of venous thromboembolism (VTE) in patients with bladder cancer (BC) in the UK, Phase I of the VTE-BC study was undertaken. As outlined in Chapter 1, VTE is a serious and potentially life-threatening condition, and the main cause of mortality and morbidity in cancer patients (Heit *et al.*, 2000). However, VTE incidence and risk factors in BC patients in the UK have not been fully elucidated, and no research has explored the risks for VTE and prevention of VTE from the patient's perspective.

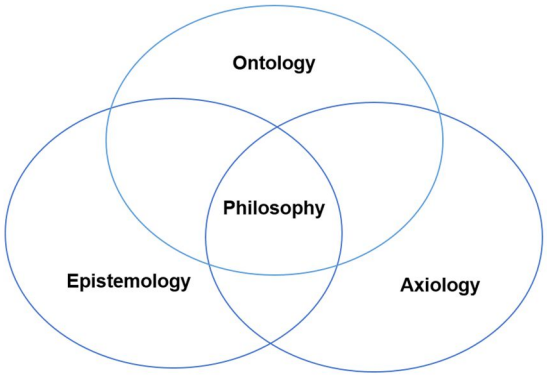
A systematic review of the VTE incidence rate in patients with BC by type of treatment was carried out, using available data from within the UK and elsewhere. From this review, it was clear that there are limitations in the data found on VTE incidence and risk factors in patients with BC in the UK, e.g., there are no data on VTE incidence rates in BC patients who have received chemotherapy or have stage IV disease in the UK.

Before Phase II, a scoping review on cancer patients' understanding of VTE was undertaken. The scoping revealed that there is limited awareness of VTE amongst cancer patients. Thus, the systematic review and scoping review in Chapter 2 highlighted limited data on the incidence of VTE in patients with BC and limited awareness of VTE in cancer patients, respectively.

3.3. Philosophical framework

Philosophy drives methodology and the methodology guides the choice of research methods (Pickard, 2013). Strong links were intentionally sought between the philosophy, the methodology and the methods of VTE-BC study. Hence, it is important to discuss the research philosophies used in the current research and to distinguish between them by considering the differences in the assumptions that each make. Three types of research assumptions distinguish research philosophies, namely ontology, epistemology and axiology (Figure 10).

Figure 10: Main components of research philosophy



Source: Author

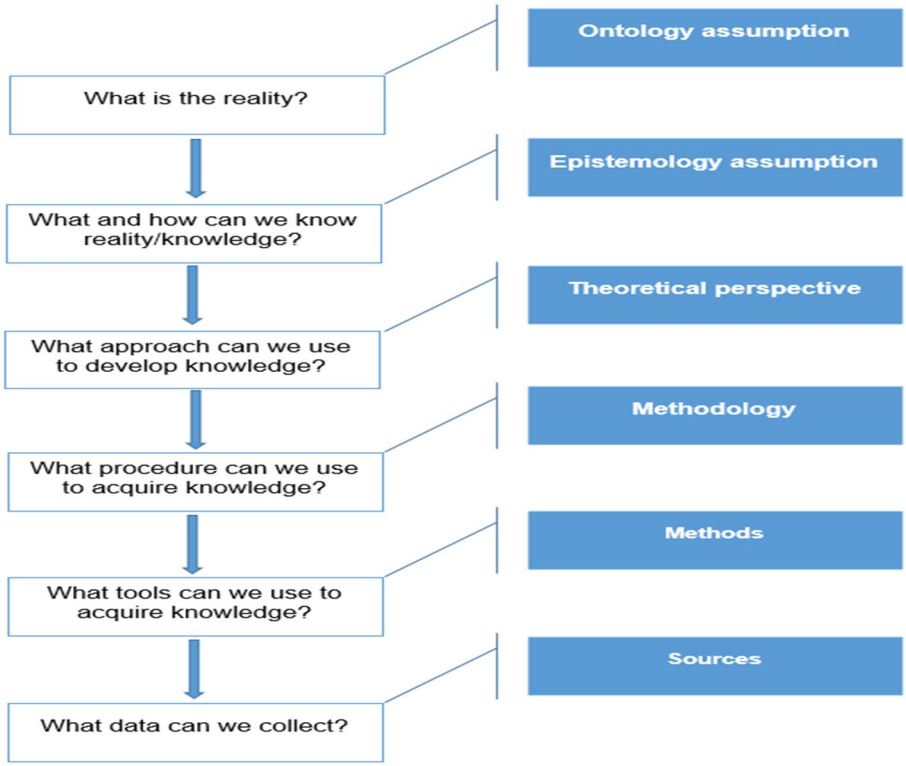
Every paradigm has its own ontological and epistemological assumptions. Various paradigms inherently include differing ontological and epistemological views; therefore, they have different assumptions in terms of reality and knowledge, which support their research approach and shape methodology and methods (Scotland, 2012).

3.4. Philosophical assumptions

At every stage of this study, underlying assumptions were considered. These included assumptions about realities in research (ontological assumptions), human knowledge (epistemological assumptions), and the extent (Figure 11) and the ways that factors influence the research process

(axiological assumptions). The following sections provide more details about the assumptions used in this study.

Figure 11: The relationship between the building blocks of research



Source: Adapted from (Grix, 2002)

3.4.1. Ontological assumptions

In VTE-BC, ontological assumptions establish objectivism for quantitative research strategies and subjectivism/constructivism for qualitative research. Moreover, they elucidate how these two types of research strategies are suitable for various intellectual purposes and conclude by discussing an alternative research strategy, namely pragmatic research (Bahari, 2010).

The entire study (VTE-BC) fits the ontology assumptions for studying phenomena and finding the reality of the VTE problem in BC patients, and the relevance of known phenomena in a new context of a pragmatic approach. Pragmatic researchers rely on the process of obtaining knowledge as part of a continuum, rather than two opposing and mutually exclusive poles that are either objective or subjective (Kaushik & Walsh, 2019).

Phase I of VTE-BC adopted a realistic ontology and followed the physical world, in which the researchers assumed the existence of a world of cause and effect, i.e. the researcher assumed that VTE existed in numbers and an approximation of the extent of VTE and risk factors could be found. The ontological position of Phase I is that there is a single truth which is objectively determined. However, the positivist ontology in Phase I of the VTE-BC study was not suitable for Phase II, because of the need to explore the communication of VTE risk between patients and healthcare professionals, and patients' understanding of VTE risk through contextual understanding. Therefore, a different ontology was applied to Phase II.

The ontology applied in Phase II was essentially that of a social world of meanings; a world populated by human beings who have their own thoughts, experiences, interpretations and explanations. The researcher's exploration of this world was clearly manifested in the use of different research methods and techniques of the interpretative paradigm, such as semi-structured interviews. Hence, Phase II was designed to explore knowledge in this discipline as being socially constructed (subjective) rather than objectively determined as in Phase I. In the next section, a different way of viewing a research philosophy (epistemology) will be discussed.

3.4.2. Epistemological assumption

Epistemological assumptions, therefore, concentrate on how knowledge can be created, acquired and communicated. Epistemological assumptions influence how researchers formulate their research in accordance with their manners to discover knowledge. Guba and Lincon (1994) explain that epistemology asks the following questions: What can one know? What are the sources of knowledge? How reliable are these sources? How does one know if something is true? (Guba & Lincoln, 1994). In the VTE-BC study, there were two sources of knowledge. The first was formulated based on reliable tools to explore the reality of the problem, VTE in BC patients in the UK, which was achieved by analysing the Hospital Episode Statistics (HES) database and two local NHS trusts. The second source involved interpreting reality by exploring the underlying meaning of events and activities that had been experienced by BC patients at high risk of VTE. The method to address the research questions needed to integrate the outcomes from these two approaches to give the most appropriate answer to the research question and avoid bias.

However, in Phase I of VTE-BC study, the observable evidence about VTE in BC patients was in the form of defensible scientific findings and facts derived from statistical analysis. Phase II of the VTE-BC study considered knowledge as social development, involving patients and healthcare professionals' views about the VTE, and influenced by various types of meaning determining the participants' knowledge of reality. Hence, an overarching epistemological approach or 'paradigm' based on pragmatism was followed.

3.4.3. Axiological assumptions

Axiology mainly focuses on personal character, rather than on universal rules or consequences and what the researcher's value is in his research. This is important because the values affect how specific research can be conducted and what the value is in the research findings (Guba & Lincoln, 1994). In phase I of the VTE-BC study, the research is carried out in an objective way, without any influence from the researcher. However, in

phase II, the value was placed in lived experience introduced and integrated into the research.

Table 4 summarises the axiology of Phase I in the VTE-BC research paradigm and highlights relevant methods of data collection.

Table 4: Axiology of Phase I in VTE-BC research and relevant methods of data collection

Paradigm	Axiology	Data Collection Techniques
Entire VTE-BC research is pragmatism	Values play a large role in interpreting results; the researcher adopts a subjective point of view	Mixed or multiple method designs, quantitative followed by qualitative research
Phase I is positivism	Research of phase I is undertaken in a value-free way, the researcher is independent of the data and maintains an objective stance	Highly structured, large samples, measurement, quantitative research
Phase II is interpretivism	Research of phase II is value bound, with the researcher being part of what is being researched, cannot be separated and so will be subjective	Small samples, in-depth investigations and exploration of patients' experience, qualitative research

Having recognised the ontology, epistemology and axiology governing the research, it is important to discuss the methodologies (Figure 3) applied during VTE-BC.

3.5. Research paradigm

Selecting the type of research paradigm was an important step for starting VTE-BC study. Research paradigms generally have one of two fundamental approaches to research: either the positivist approach or the interpretivist approach, to develop the research methodology through defined guidelines and to take on the research design in a way that is most appropriate (Wahyuni, 2012).

In VTE-BC, the study required a combination of more than one method to collect and analyse data and achieve its goals. Therefore, the *pragmatic paradigm* was chosen for VTE-BC. For more clarification, a summary of research philosophy is presented in the following table:

Table 5: Summary of research philosophy framework for VTE-BC

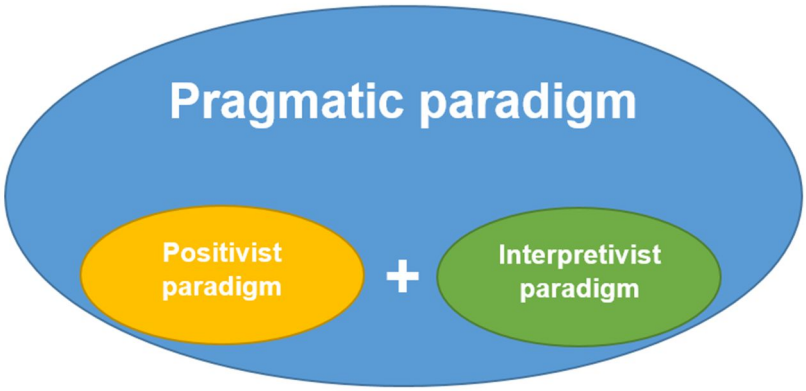
Paradigm	Ontology	Epistemology	Methodology and Method
Pragmatic	Truth is what is useful. Multiple assumptions to confirm the relevance of known phenomena in a new context	The proper method is one that solves the problems, which could be multi-approaches	Mixed methods Outcome from analysing of data used to specify the participants for interviews
Positivism	Explore the reality of problem from recorded data	Focus on reliable and valid tools to undercover reality that has been achieved from patients' recording	Quantitative Data collection from patients' records
Interpretivism	Reality and knowledge are explored by individuals	Interpretation of reality by finding the underlying meaning of events and activities that had experienced by patients	Qualitative Semi-structured Interviews of participants

A pragmatic paradigm is an overarching paradigm which draws on two others, positivism and interpretivism.

3.5.1. Pragmatic paradigm

Pragmatists believe that there is more than one reality, and they follow both positivism and interpretivism to seek answers to problems (Figure 12). However, pragmatists do not totally rely on the interpretivist or positivist approach (Mackenzie & Knipe, 2006).

Figure 12: Pragmatic paradigm



Source: Author

The pragmatic paradigm allows for more than one way to solve a problem, so a mix of approaches can better help to solve a problem and find the truth (Wahyuni, 2012). Therefore, this research paradigm would suggest a flexible approach, such as mixed-methods, to solve the research problem (Wahyuni, 2012).

Pragmatism is not logically contradictory, and quantitative and qualitative research are both beneficial, even if, at times, they appear to be opposing (Kaushik & Walsh, 2019).

Therefore, the pragmatic paradigm seeks to use reality that has been achieved from Phase I of this study, the VTE incidence rate and VTE risk factors in BC patients, to explore people's subjective experiences about the understanding and communication of risk of VTE in BC patients. In conclusion, Pragmatic paradigm encompasses positivist and Interpretivist paradigms.

3.5.2. Positivist paradigm

. 'Positivists' consider the outcomes of a specific study to be generalisable to another study of a similar kind, regardless of the environment and situation it is conducted in; there is little interest in investing in the meaning of a situation as it is not objectively measurable (Weaver & Olson, 2006). The term 'positivist' explains relationships and attempts to explore causes which influence outcomes (Creswell, 2009). This paradigm was used in the quantitative phase (Phase I) of the VTE-BC study in order to measure the objectives of the study, VTE incidence and risk factors in BC patients, and discover the relations between phenomena, particularly cause and effect. This approach cannot, however, be applied to phase II of study (the qualitative phase), as it does not serve to reveal the participants' experiences. Hence, an alternative approach is required to guide the qualitative element of the study.

3.5.3. Interpretivist paradigm

This approach Interpretivist paradigm is applied in the qualitative phase of the current study to explore the VTE risk communication and patients' understanding of VTE. In Phase II, meaning-oriented methodologies were used.

As mentioned before, one of the objectives of Phase II research in VTE-BC study is to explore the patients' understanding of VTE. Therefore, it is very important to assess the main components of VTE risk communication between HCPs and BC to find the gaps in the communication process if present. Both HCPs and BC patients are fallible humans, so the practice of healthy communication exchanges is needed to provide the best understanding of VTE risk and prevent developing VTE in BC patients group.

Communication is a transactional process and in a health context, it is a fundamental part of patients' management. The process of managing a patient requires a holistic approach which includes considerations beyond treating a disease. Proper information about the nature, course and prognosis of the disease is important (Ranjan *et al.*, 2015).

Healthcare providers need some skills along with medical expertise to provide the best clinical care. Studies have shown that good communication skills that the healthcare provider possesses improve patient's understanding, compliance, overall satisfaction and deliver high-quality care (Ha & Longnecker, 2010). After discussing the research paradigm, the details of the methodology of VTE-BC are explained.

3.6. Methodology

This study (VTE-BC) is pragmatic in nature and uses two methodologies. The most appropriate methodology for conducting Phase I of VTE-BC study was observational. The observational methodology is a fundamental part of epidemiological research. It is referred to as observational because the investigator observes individuals without manipulation or intervention.

However, for Phase II of VTE-BC study, grounded theory was chosen, because this methodology can construct theories through the methodical gathering and analysis of data (Strauss & Corbin, 1994). The fundamental goal of the ground theory is to generate a theory, rather than test hypotheses and formation of theory. The decision to consider the most suitable methodology depends on the aim of the research and the information needed.

Constructivist grounded theory can complete other approaches in relation to qualitative data analysis rather than stand in opposition to them (Charmaz, 2006).

3.6.1. Mixed methods

Mixed methods were seen as the most suitable approach for conducting a VTE-BC study, in that it involves collecting, analysing and integrating quantitative (descriptive and correlational) and qualitative (interviews) research. A mixed methods research was chosen as the qualitative study followed on from the results of the quantitative research and helped to understand what the figures meant in practice. This integrative approach to research was an attempt to gain an enhanced understanding of VTE in the bladder cancer population. Mixed-methods studies have been defined as studies involving 'the collection or analysis of both quantitative and/or qualitative data in a single study as in VTE-BC study" (Creswell & Clark, 2007).

Mixed methods studies are complex to plan and conduct. They require careful planning to describe all the characteristics of research, including the study sample for the qualitative and quantitative phase (identical, embedded, or parallel); timing (the sequence of qualitative and quantitative phases); and the strategy for integrating data.

Quantitative and qualitative materials are often used to complement each other and can be useful in understanding the contradictions between quantitative results and qualitative findings. The mixed methodologies of VTE-BC study gave a voice to study participants in Phase II and ensured that those study findings were grounded in participants' experiences. Creswell and Clark (2007) provided a good summary of mixed methods research:

> *"Mixed methods research is a research design with philosophical assumptions as well as methods of inquiry. As a methodology, it involves philosophical assumptions that guide the direction of the collection and analysis of data and the mixture of qualitative and quantitative data in a single study or series of studies. Its central premise is that the use of quantitative and qualitative approaches in combination provides a better understanding of research problems than either approach alone." (Creswell & Clark, 2007).*

In Phase I, the research sought to measure the magnitude of an event, to make predictions and develop causal explanations. To achieve this, a pre-established design based on a hypothesis and theories was utilised, an extensive data collection was conducted, and statistical data analysis developed.

In phase II, a qualitative methodology was chosen as a research method for gathering data through open-ended and conversational communication. The analysis of qualitative data was approached through a broadly social interactionist lens. Phase II was concerned with how patients and healthcare professionals communicate the VTE and related risk factors, in order to evaluate how patients with BC understand VTE and related risk factors from their experience of having BC.

Qualitative research allowed for in-depth and further probing and questioning of participants based on their answers. In this way, the researcher attempted to explore more information that could help in developing the best conclusion and understanding how healthcare professionals took decisions in informing VTE risk.

3.6.2. Challenges in mixed methods research

The main challenge in mixed methods research is the integration of ‘quantitative’ and ‘qualitative’ epistemologies, seen as two different disciplines in health research e.g. ‘positivist’ versus ‘interpretivist’ as mentioned above.

However, most researchers who use mixed methods now believe this total separation to be an obstacle to comprehensive results, and instead, concentrate on the ability of methods to provide the best answer for the research question at hand (Curry & Nunez-Smith, 2015). Creswell and Plano Clark (2011) also discussed the fact that as a pragmatic type of research, it is feasible for mixed methods researchers to include more than one worldview (Creswell *et al.*, 2011). Therefore, the VTE-BC study considers the scientific rigour of research components, before attempting to understand the trustworthiness of the findings of the mixed method.

3.6.3. Methods for VTE-BC – Phases I and II

Methods are the specific techniques and processes used to collect and analyse data (Crotty, 199833). Mixed methods research has been described as the third research paradigm, and can be used widely by health researchers (Tariq & Woodman, 2013). There are four fundamental types of mixed method design: triangulation, embedded, explanatory and exploratory design (Pansiri *et al.*, 2005). To answer the research questions (chapter 1), an explanatory followed by exploratory design was chosen to carry out VTE-BC study.

Using mixed methods research provides strengths that offset the weakness of both quantitative and qualitative research (Wahyuni, 2012). Each type of data has benefits and can extend in certain ways. This occurs when the researcher sequences the two types of methods, either qualitative first as exploratory, followed by quantitative as explanatory or vice versa (Johnson & Onwuegbuzie, 2004; Wahyuni, 2012). The main aim of combining two studies is to deploy both qualitative and quantitative research methods when generating knowledge (Onwuegbuzie *et al.*, 2009).

To provide a more detailed description and avoid the confusion between methods used in Phase I and II, the methods of each Phase will be discussed separately.

3.7. Phase I: Methods

Phase I of VTE-BC study is descriptive, relying on collecting descriptive data from a recorded database, and focuses on correlations between variable factors.

The purpose of the quantitative phase applied was to investigate the magnitude of VTE incidence and risk factors in patients with BC in the UK, close-ended information. To achieve this, a pre-established design based on a hypothesis was chosen.

In this phase, a quantitative method was applied to emphasise objective measurements before starting to analyse the statistical or numerical

analysis of data collected from patients' databases and arranged in Excel tables.

To achieve the aim and objectives of phase I of in VTE-BC study, the site and population group were specified. Since the group population is the UK only, two local NHS trusts were selected, for convenience, University Hospitals Coventry and Warwickshire (UHCW) and Queen Elizabeth Hospital Birmingham (QEHB). This selection enabled the sample to be large enough and to decrease bias. Moreover, a cohort study was conducted to provide an overview of the incidence rate of VTE in patients with BC in the UK which used Hospital Episode Statistics (HES) data.

3.7.1. Phase I: Patient eligibility

To explore the VTE in patients with BC, it was important to specify inclusion and exclusion criteria as follows:

Inclusion criteria:

- Histologically or clinically confirmed diagnosis of bladder cancer with or without VTE
- Adult patients aged 18 years old and over

Exclusion criteria:

- Patients with the history of VTE before BC diagnosis

3.7.2. Phase I: Aims and objectives

After identifying the research question (Chapter 1), aims and objectives were developed. The aim was to explore:

- the scope of the problem of VTE in bladder cancer patients in the UK

The objectives of the study were to explore:

- the incidence of VTE in bladder cancer patients
- risk factors for VTE in bladder cancer patients through two local databases

This helped to assess the extent of VTE in this population, as well as the risk factors for VTE. This information helped to identify the types of patients who would be approached to explore their understanding of the risk of VTE in bladder cancer patients, as well as to give strong background to discuss with

patients and healthcare professionals while carrying out quantitative phase of the study.

3.7.3. Study design

Phase I of the VTE-BC study was a quantitative research, carried out using two sources of data, 'England' and 'local data'.

For the 'UK' source, a quantitative retrospective cohort study was carried out to explore VTE incidence in BC patient groups. HES data were obtained for all patients with BC, who underwent systemic chemotherapy treatment and/or radical cystectomy between April 2013 and April 2018 to identify those re-attending with VTE within 12 months in NHS trusts throughout England. To obtain more detailed data, a case-control method was applied with local data from UHCW and QEHB.

With regard to local data, a quantitative, retrospective case-control study (1:2) of VTE was applied to assess whether there was a statistically significant difference in the rates of exposure to a defined risk factor (such as chemotherapy, surgery, and radiotherapy) between groups of BC. Odds ratio and p-values were used to find an association between risk factors and outcomes of interest.

Local data recorded at UHCW and QEHB for the last 10 and 7 years respectively, were collected. The duration of data collection differed between UHCW and QEHB due to the completeness and quality of data.

Local data provided descriptive and analytical information to identify:

- The VTE incidence rate in BC patients treated with or without systemic chemotherapy within 12 months of starting to receive chemotherapy
- VTE incidence in BC patients treated with or without cystectomy within 12 months post-surgery
- Any association between VTE events, odds ratio and VTE risk factors.

Local principal investigators (PI) at UHCW and QEHB agreed to provide anonymised data for patients with BC that had been previously recorded. Biomedical and Scientific Research Ethics Committee (BSREC)

plus Health Research Authority (HRA) approval were sought on 18th March 2018 (IRAS ID: 231338) at Warwick Medical School (Appendix 6).

3.7.4. Outcomes

The core outcomes of Phase I of VTE-BC study are:

- The incidence rate of VTE in patients with BC in England
- The trend in VTE incidence rate within 5 years in England
- The association between VTE and treatment, stage, comorbidities, gender, histology, and grade in patients with BC

3.7.5. Databases

More than one administrative dataset in the United Kingdom (UK) are presented, such as primary care datasets collected (GP-derived) and secondary care (hospital-derived), for example, the Clinical Practice Research Datalink (CPRD) which collects primary care patient interactions throughout the UK. Secondary care data are managed by the National Health Service (NHS) Digital in England and called HES (HES, 2018). Since cancer and VTE are generally not diagnosed and treated in primary care, HES data and local data from two NHS hospitals were used to carry out the current study.

In phase I of the VTE-BC study, the following data sources were used:

England data – In the NHS, data on healthcare services are recorded on statutorily defined datasets. These are recorded by providers and transferred to commissioners of care via electronic clearinghouses. The mechanism of data transfer has been changed from time to time, with the previous NHS Wide Clearing Service (NWCS) being replaced by the Secondary Uses Service (SUS), though at present, the data flows remain similar. Both NWCS/SUS data are cleaned and collated on a national basis to create HES data. HES started collecting admitted patient care records in 1987. However, outpatients and A&E data collection began in 2003 and 2007 respectively.

HES data records use computerised Patient Administration Systems. Each record is a subset of the record completed by the provider to

NWCS/SUS, and so defined in the NHS Data Dictionary. It is generally issued on an annual basis, though provisional data is now issued every four months.

HES data form a database which contains records for every NHS inpatient, outpatient and accident and emergency (A&E) managed in England (HES, 2018). These data are structured according to financial years. In this sense, HES data offer the opportunity to estimate population-based admission and procedure rates by condition and type of procedure used in managing the patients. In HES data, all diagnoses within the hospitalisation period (i.e. time they are admitted until the time they are discharged from the hospital) are recorded within episodes. The HES data registers healthcare activities in units entitled:

- Finished consultant episodes (FCE): FEC unit refers to a complete period for inpatient activity under only one consultant within one healthcare care provider
- Hospital spells: this unit is used for the whole period of hospital admission from the date of admission to the date of discharge, and may include one or more FECs
- Attendances: this is applied for a visit to outpatients' clinic or A&E

The HES record contains information regarding the patients who were admitted to NHS hospitals, including patients' characteristics, administrative information, clinical diagnosis and operation, treatments received and geographical information but there are no data regarding the progression of the disease, staging of cancer or treatment outcomes (HES, 2018). In the HES data, clinical diagnoses of all diseases are coded according to the International Classification of Diseases (ICD-10) and procedures are coded using Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS-4) (NHS, 2017; WHO, 2016).

HES data have frequently been used for research studies due to their universal coverage, long period of data collection and the ability to follow individuals over time. Hence, in VTE-BC study HES data were used to explore the incidence and trend of VTE in BC patients according to the intervention or treatment received for each patients group.

Local data – Each NHS trust records details of the care undertaken, and the data collection about patients and treatment should follow information standards (NHS, 2019). Information standards are an established set of instructions for capturing, processing, managing and sharing data and information of patients. Each hospital chosen (UHCW and QEHB) has a programme which was implemented to establish, deliver and ultimately manage a secure data service with linked combined data from all systems supporting direct health care. For local data analysis, oncology databases at UHCW and QEHB were used. A data collection form (Appendix 1), including patient demographics, patient-related, treatment and cancer-related risk factors for VTE, was utilised to find the outcome of interest.

At QEHB and UHCW, the information on each patient was written down on paper, held on a computer or a mixture of both.

3.7.6. Data Management

The required application processes were followed to request the relevant HES and local data. These processes will be discussed separately for HES and local data.

HES data management: The first process in acquiring HES data was to complete the Data Access Request Service (DARS). DARS application for the tabulation specification of NHS digital was approved after completing all the requirements. Anonymised data were received on 14/05/2019- reference number: NIC-121149-G4N1S. DARS information required the following:

- English version of 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes for VTE and bladder cancer were used to find the clinical codes for VTE and bladder cancer (Appendix 4). The Office of Population Censuses and Surveys (OPCS)-4.7, which performs clinical coding of Classification of Interventions and Procedures version 4, was used to find the codes for cystectomy and systemic chemotherapy regimen received by bladder cancer patients. Codes of all parameters required in the study were checked with allocated NHS Digital Case Manager before starting data collection.

- To discover VTE incidence of bladder cancer and related intervention, crosslinking of codes from ICD-10 and OPCS 4.7 was carried out and HES data were obtained for all patients who had BC and had cystectomy and chemotherapy for BC in NHS trusts throughout England for the last five years. The study followed patients revisiting with either DVT or PE (VTE) within 12 months of their surgery.

Regarding local data, to apply for UHCW and QEHB data, a protocol of the study was performed. The protocol was completed on 15/12/2017, after which a research application form on the Integrated Research Application System (IRAS) was completed on 14/02/2018 to obtain Health Research Authority (HRA) permissions and approvals for health and social care/community care research in the UK. HRA approval was confirmed on 13/03/2018, reference number 231338, before starting to apply for the capability and capacity confirmations to deliver the study at QEHB and UHCW NHS trusts.

The following documents were sent to the Research and Development offices of QEHB and UHCW:

- HRA Schedule of Events – Version 1-13/03/2018
- HRA Statement of Activities – Version 1-13/03/2018
- IRAS Application Form – 13/03/2018
- Letter from Sponsor – 01/11/2017
- Research Protocol – Version 2-15/12/2017
- Chief Investigator Declaration
- The Research Facilitation Group Approval (QEHB only)

The confirmation of the capacity and capability at UHCW NHS Trust to do the research was received on 18/04/2018, while at QEHB NHS Trust the confirmation of capacity and capability was obtained on 19/10/2018. A data form template was organised before being sent to the Principal Investigators (PIs) and information department to start data processing.

3.7.7. Data Collection

The records were identified by two PIs through the information departments at UHCW and QEHB NHS trusts. Spreadsheets of cohort data were received from PIs at each site, including NHS numbers of BC patients with or without VTEs. Subsequently, manual searches through patient records portal to identify all required details beside data input in excel sheets were conducted. The characteristics of BC patients and related risk factors were recorded in spreadsheets before commenced the analysis.

3.7.8. Data acquisition

Anonymised data collected during this study were handled and stored in accordance with the Data Protection Act 1998 and NHS standard operating procedures (SOPs). Data were analysed inside QEHB local trust and Clinical Sciences Building (CSB) at UHCW. Data were subjected to validity checks and additional data monitoring procedures to assure that the quality of data entry by supervisors and PIs were as high as possible.

Any data in paper form were stored in a lockable filing cabinet in a secure room, to which access is restricted to authorised personnel. Electronic data have been stored in a secure area of the computer with access restricted to staff working on the study at Warwick Medical School.

3.7.9. Data quality

In recent years, data quality has become an important focus of public health; furthermore, data quality checks are essential before existing and publishing to evaluate the recorded events and achieve greater confidence and satisfaction in the study results (Nutley & Reynolds, 2013).

Data quality is the state of completeness, validity and accuracy that make data appropriate and useful for collecting from the participating sites (UHCW and QEHB) and analysing in the current study.

- Regarding completeness, the most completed and useful data regarding VTE in bladder cancer and suggested risk factors are available from 2007 to 2018, and from 2011 to 2018 at UHCW and QEHB respectively. The

data collections were made by a service line review analyst at UHCW and by the informatics office team at QEHB.

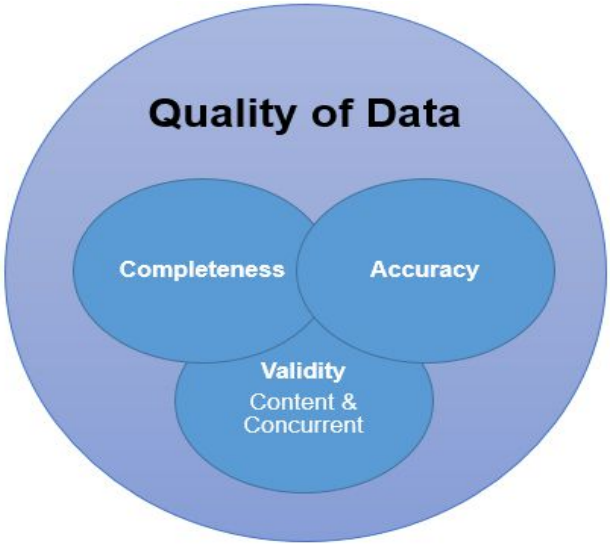
- In order to explore the validity of data that have been collected, it can be said that in general, validity in quantitative data collection means that study results truly represent the phenomenon which the study is claiming to measure (Kelley, 1927). There are four ways to check validity (Figure 5). While assessing the validity of data in the current study (VT-U-CAN) the following two ways were arranged, as they fit the current study VTE-U-CAN:
  - *Concurrent validity*: An attempt was made in this study to review and compare the study design and the methods of the applied research with other high-quality studies which were recognised in the systematic review (Chapter 2).
  - *Content validity:* The data that were collected and checked appear to fully represent the aims of the study. Indeed, data were available on the patients' recorded database at both hospitals, which were used to extract data of interest such as stage, histopathology, the grade of disease, medical interventions, and comorbidities. Data sources and collections were checked by my PhD supervisors in addition to the PIs at UHCW and QEHB. Moreover, the processes of data collection and results of this study were presented and discussed by the researcher at two multidisciplinary team meetings firstly at QEHB on 30/08/2019 then at the mid-term research meeting of SMDT/UHCW on 14/11/2019.
- For accuracy testing, an appraisal of methods used to collect data was conducted, and this provided satisfaction regarding the outcome. The required data were collected from the patient records portals at UHCW and QEHB.

At QEHB and UHCW NHS Trusts, all patients with BC and their events, investigations, treatments were recorded during hospital admissions and outpatients' clinics visiting which provide the actual number of VTE events within BC population during the specific time period.

After specifying the codes which are used for the diseases and interventions, including operations, chemotherapy and radiotherapy, all identified codes were checked to find if matching was relevant or not according to the ICD-10 and OPCS-4.7 clinical coding. Following this, the information delivery service desk was contacted (query number 270769) to confirm the accuracy of the codes selected for data collection. Consequently, the answer and resolution to query (270769) were received from the terminology and classification delivery service, which confirmed the accuracy of codes that used for data specification and collection for VTE in patients with BC. Finally, the accuracy of the codes required in VTE-U-CAN study was checked and confirmed before data processing was carried out.

The steps of data quality assessment are summarised in Figure 13.

Figure 13: Steps of data quality assessments in Phase I of VTE-BC study



Source: Author

3.7.10. Quality assessment for HES data

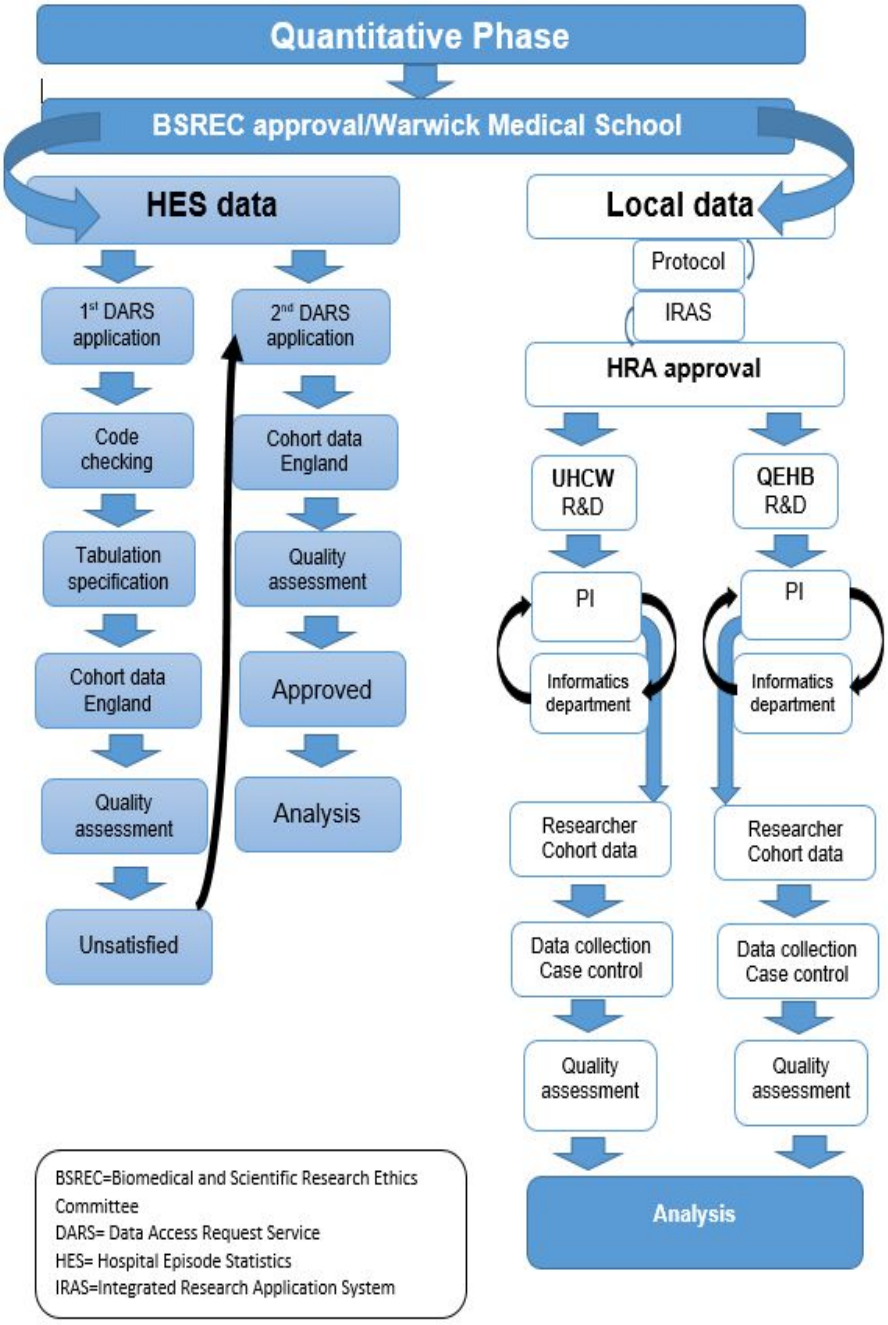
NHS Digital was contacted to discover the steps required to apply for HES data on 21/07/2017. The Data Applications Team (DAT) sent the paper application form (DARS-NIC-121149-G4N1S) to be completed, and this was done, and the document was sent back to DAT for a tabulation. After completing the DARS form and submitting the application (DARS-NIC-

121149-G4N1S-v0) on 10/04/2018, the HES data team confirmed which questions and information of data requested they could provide.

The data were received from HES team on 31/05/2018 which were checked against completeness, validity and accuracy. Unfortunately, the data gave the impression to the research team of neither accurate nor valid. The number of new bladder cancer patients in England each year was seven times higher than the number recorded in National Cancer Registry. So National Cancer Registry recorded around 8,000 new bladder cancer patients per year. In this regard, HES data team was contacted to check the real numbers and they confirmed that they had sent the number of episodes, not the crude number of bladder cancer patients. The HES data team agreed to resume data building on 27/02/2019 (DARS-NIC-121149-G4N1S-v1.1) and they re-sent the data of VTE in patients with BC on 14/05/2019.

The completeness, validity and accuracy were checked to assess the quality of new data. The data from the HES team regarding VTE in patients with BC were compared with data recorded in National Cancer Registrations. The number of cystectomy operations, receiving chemotherapy, age, gender of patients and the number of VTE events were also checked and compared with local data achieved from UHCW and QEHB. All details of the quantitative phase are presented in the following diagram:

Figure 14: Summary of Phase I



3.7.11. Data analysis of Phase I

Phase I data analysis consisted of statistically analysing event numbers which had been collected to answer the research questions. In the HES data, an estimation of the incidence rate and trend of VTE in patients with BC was conducted over 5 years, between 2013 and 2018.

However, for local data, the VTE incidences of patients with BC were estimated from the cohort data that had been received from informatics offices at QEHB and UHCW. After this, the case control study design was used to find the odds ratio to determine whether exposure to a specific confounder is a risk factor of VTE or not in crude and adjusted analysis. The confounders chosen were:

- Gender (Male, Female)
- Urothelial carcinoma (Yes, No)
- Grade (1,2,3)
- Has had chemotherapy (Yes, No)
- Has had surgery, cystectomy (Yes, No)
- Stage (non-muscle invasive, muscle invasive, metastatic)
- Has had chemotherapy plus cystectomy (Yes, No)
- Presence of comorbidities (Yes, No)

Multivariate linear and logistic regression were used to assess the independent associations between baseline VTE complications and possible risk factors. Risk estimates were calculated as odds ratios with 95% confidence and adjustment for the influence of the investigated potential confounders were carried out.

Comorbidities comprising hypertension, DM, heart failure, ischemic heart disease, COPD, pneumonia and second type of cancer, were considered confounders during the logistic regression analysis.

Subsequently, all data were re-analysed, with comorbidities split into comorbidities without a second type of cancer, and only included hypertension, DM, heart failure, ischemic heart disease and pneumonia, and second cancer. The 2nd cancer was analysed as a separate confounder to

see the real association of VTE with comorbidities not including second cancer in patients with BC.

3.8. Phase II method

In Phase II of VTE-BC research a qualitative research methodology was utilized, which applied a scientific method of observation to collect non-numerical data. Usually, qualitative research refers to the meanings, concepts, definitions, characteristics and description of things, and not to their counts or numerical data (Creswell & Clark, 2007). Thus, a method of data collection should be chosen that enables participants to express themselves openly and free of limitation.

This research is exploratory in nature and seeks to provide specific information by using data from the interviews. One-on-one semi-structured interviews with BC patients and HCPS were conducted in phase II of VTE-BC study. This was purely a conversational method and was an opportunity to gain in-depth views and experiences from the participants. The reason for using face–to-face interviews was to explore personal perceptions and individual experiences without the effect of other participants' views.

Several key questions were used in a semi-structured interview format, providing a common framework for all interviews, and defining those areas to explore in the studied topic (Appendix 5). The questions discussed the patients' knowledge of VTE, such as the information they had received and their understanding of VTE in a cancer context, patients' knowledge of how to identify VTE, the best way to inform patients about the risk of developing VTE and some further related questions about VTE. Interviews also sought to explore gaps in patient education that hinder any role in engagement around VTE prophylaxis. Patients and HCPs were free to introduce and elaborate any other information that they felt relevant, and any recommendations to improve communication around risk of VTE.

One specific advantage of a semi-structured interview is that it offers an opportunity to collect detailed data about what a specific population knows and what their motivations are (Blee & Taylor, 2002). This type of study can help collect meaningful data and provides insights into the problem. The

interviews could be done face-to-face or by phone. However, in the VTE-BC study, all interviews were carried out face-to-face, as the researcher preferred to have an opportunity to read the body language of the participants, to better grasp the answers. The participants were recruited from two sites, UHCW and QEHB, and the interviews took place in a quiet room, either at QEHB or UHCW. Each interview was conducted at place and time which was convenient for the participant. The patient's caregiver or 'significant other' were allowed by the researcher to join the patient during the interviews for support and to remind the patients of key details. All interviews were audio-recorded by means of an encrypted device, and transcribed verbatim by a transcriber.

3.8.1. Phase II: Aims and objectives

The aims and objectives of Phase II were to:

- Explore cancer patients' understanding of the risk of developing VTE from their experience of having had BC and related treatments.
- Highlight the patients' perspective and strive to influence clinicians' practice, ultimately to reduce the burden of VTE in the BC patient population.
- Explore the content of the information on VTE communicated to the patient
- Explore approaches by which VTE information can be more effectively communicated to the patients to facilitate informed choice
- Explore gaps in patient education that inhibit patients' role in VTE prophylaxis

3.8.2. Phase II: Study design and data collection

In qualitative research, there are several types of study design, these being: grounded theory, narrative research, historical, phenomenology, ethnographic and case studies (Petty *et al.*, 2012). The qualitative Phase of VTE-BC study concerns participants' own experiences of VTE communications and interprets what participants have mentioned. Two groups of participants (BC patients and HCPs) took part in this study.

A semi-structured interview approach was chosen by the researcher to interview each participant once. This type of interview enables an interviewer

to follow a non-strictly formalised list of questions (Leech & Politics, 2002). The interviewer asks more open-ended questions, permitting better discussion with the interviewee, rather than a direct question and answer format, and in addition, the interviewer can ask for more clarifications about answers (Ryan *et al.*, 2009). An interview approach to collect the data provides more independent and in-depth data (Leech & Politics, 2002).

An interview schedule or agenda is (generally) used to collect data in semi-structured interviews. An interview schedule consists of a small number of open-ended questions which encourage participants to talk about relevant concerns (Gill *et al.*, 2008). One of the advantages of interviews is that the interviewer can add some questions (prompts or probes) to discover and understand points that arise during the interview (Gill *et al.*, 2008). Usually, the interviewer decides when to use prompts and probes. Using prompts and probes enables the interviewer to cover a different aspect of the research topic and to provide different phrasing which might be more meaningful to the participant (Driedger *et al.*, 2006).

Following an exploration of the study design of qualitative Phase, it is mandatory to find a proper institution to conduct the study and recruit participants (interviewees).

3.8.3. Site participation

Phase I, the quantitative phase, was conducted with reference to two local NHS trusts in the UK, QEHB and UHCW. Hence, the same hospitals (UHCW and QEHB) were chosen by the researcher as research sites for conducting phase II. Research sites were recruited by directly contacting of Research and Development offices (R&D) at QEHB and UHCW.

On 04/06/2019, all the required documents were sent to the R&D offices at QEHB and UHCW, to include the following: protocol of study, all related consent forms and participants information sheet, sponsorship committee approval for phase II, favorable opinion of the NHS Research Ethics Committee (REC), Health Research Authority (HRA) & Health and Care Research Wales (HCRW) approval, HRA Statements of Activities, HRA and HCRW Schedule of Events, data transfer form. Confirmation of capacity and

capability at UHCW was approved on 27/06/2019. The capacity and capability of QEHB was approved on 21/10/2019. More time was needed to secure the confirmation of the capacity and capability at QEHB due to requirement for Research Facilitation Group review (CRFG) approval.

The recruiting of participants for interviews began at UHCW before QEHB due to have approval from UHCW before QEHB.

3.8.4. Sampling

In qualitative research, various sampling methods that one can use when recruiting participants. The two most popular sampling techniques are purposeful and convenience sampling.

Effective sampling practice and the sample size are key elements when seeking to answer any research question without bias (Collingridge & Gantt, 2008; Marshall, 1996). Sampling in a qualitative study is non-random; as the aim of qualitative research is to understand complex phenomena, participant selection should have a clear rationale and a specific purpose related to the research question (Cleary *et al.*, 2014).

In this study, purposive sampling was used to recruit the participants who were able to express their experiences regarding risk communication of VTE between BC patients and HCPs. In opportunistic sampling, the researcher needs to recruit participants with particular characteristics (Collingridge & Gantt, 2008; Marshall, 1996). Those BC patients with the characteristic of high VTE risk factors were chosen to be recruited for the study.

3.8.5. Phase II: Recruitment of participants

Patients and Healthcare professionals (medical oncologists, surgeons, and nurses) were recruited from two NHS trusts: UHCW and QEHB.

In the Phase I of VTE-BC study, high risk factors of VTE were specified, such as chemotherapy and surgery. Thereafter, in Phase II, only BC patients who had very high risk for VTE were chosen to take part in this study.

Recruitment of participants in this qualitative research was no easy task. Successful participant recruitment was, indeed, a significant aspect of conducting interviews in Phase II of VTE-BC study, and finding recruitment

methods suited for each group (HCPs and BC patients) proved to be a challenge. The researcher sought to find a convenient way to contact participants and encourage them to take part in this study. He held honorary contracts with UHCW and QEHB and was appropriately trained to undertake research and conduct interviews.

After receiving confirmation of capacity and capability approval from each site, the principal investigator (PI) at each site was directly contacted to arrange for the next step. PIs emailed their colleagues (HCPs) to invite them to participate in the study, and also contacted the clinical nurse specialist (CNS) in the urological and oncological departments to arrange for face-to-face meetings with CNS at each site (UHCW and QEHB) to discuss the processes of recruiting BC patients.

A clinical nurse specialist at each hospital circulated the invitation email to surgeons, medical oncologists, and nurses. I received 13 responses from HCPs within five months at both hospitals. All 13 HCPs were successfully interviewed.

Two strategies were followed to recruit the patients at both hospitals:

1. The CNS; they had the ability to access patients' records at urology and oncology departments in UHCW or QEHB, to screen the data of patients and specified which patients were eligible to participate in this study (according to inclusion and exclusion criteria). They then gave eligible patients the participant's information sheets and my contact details to contact me directly by email or phone. In this strategy, only two BC patients contacted me and agreed to do the interview.
2. Researcher near the outpatient's clinic: The nurse, urologist or oncologist, who was in the clinic asked the visiting and eligible patients to take part in this study; moreover, they offered them the opportunity to speak with me (researcher) directly to understand the study, steps of the interview and build trust between us. In implementing this strategy, 18 patients were recruited across the two hospitals.

The recruiting period for HCPs and patients started in July 2019 at UHCW and in October 2019 at QEHB and finished on 1st of March 2020 at both hospitals.

3.8.6. Developing and conducting the interview

As the protocol of this study states, before each interview took place, I (as a researcher) introduced myself and thanked the participant for taking part in his study. I then elicited preliminary questions from the participants. Furthermore, the participants were informed about the study in detail and given assurances about anonymity and confidentiality. This gave the participants some idea of what to expect from the interview. The interviews were carried out in an area free from distractions, and at times that were most suitable for each participant. Interviews were conducted in a quiet office at an outpatients' clinic departments at UHCW and QEHB.

To ensure that the interview would be as fruitful as possible, I attended a qualitative research module at Warwick Medical School, and I also drew advice from video samples of interviews; I also received insights from my supervisors in order to gain the necessary skills for conducting successful interviews and better collect comprehensive and representative data in the interviews. Interviews were recorded using an encrypted voice recorder. The audio-recorded interviews were transcribed. The reason for using face-to-face interviews was to explore personal perceptions and individual experiences without the effect of other participants' views.

During the interviews, I strove to listen attentively to what was being said and assisted the participants in recounting their experiences as fully as possible, without unnecessary interruptions. Notes were recorded during and immediately after each interview about the participant, observations and thoughts in the interview, since this can help in data analysing process.

3.8.7. Constructing research questions

Designing effective research questions or schedules for the interview is one of the most imperative components for successful qualitative results (Turner III, 2010).

The questions for interviewing HCPs and BC patients were prepared in order to gain maximum data about their experience and knowledge from interviews. To minimise bias, the questions were designed to be as open-ended as possible which allows focused, conversational, two-way communication, with a lack of value judgments in the wording.

The researcher used a guideline but was able to follow topical trajectories in the conversation that may have strayed from the guide when it seemed appropriate. Most questions were prepared and phrased ahead of time, while some questions followed with probes and prompts to gain more specific, in-depth information.

Mostly, the interviews questions came from related articles and clinical practice of the researcher. These questions were developed to answer the main research question and address the topic of study.

3.8.8. Phase II: Eligibility

To gain a greater understanding of VTE and risk of developing VTE in patients with BC, I conducted interviews with two groups of participants. These two groups were BC patients and HCPs.

For BC patients, the inclusion criteria were as follows:

- Patients age 18 and over
- Patients with histologically confirmed BC
- BC patients had cystectomy and/or chemotherapy.
- Patients were able to give informed consent and able to speak English

I excluded any participants who were not able to read or understand the information sheet or the consent form.

The inclusion criteria for healthcare professionals were as follows:

- Healthcare professional who was working at the University Hospitals Coventry and Warwickshire, Coventry and the Queen Elizabeth Hospital, Birmingham at the time of interview.
- Healthcare professionals who had clinical responsibility and delivered care to BC patients.

3.8.9. Data acquisition

Data collected during this study were handled and stored in accordance with the General Data Protection Regulation (GDPR), data protection act 2018 and NHS standard operating procedures (SOPs). All portable media (e.g. laptop and audio-recorder) were encrypted before use and any data downloaded. Special care was taken when moving data from a secure storage location.

An encrypted audio-recorder was used as a temporary storage device and data securely deleted once the audio-recorder were no longer required. The recorded interviews were downloaded onto a secure Warwick university computer and transcribed, after which the recordings were erased from the audio-recorder.

The audio-recorder (Olympus 7000) was borrowed from information technology (IT) services at Warwick Medical School and was pre-encrypted. Original copies of interviews were analysed within Warwick medical school and the researcher's home.

3.8.10. Confidentiality

In this VTC-BC study, the recorded interviews were regarded as strictly confidential, and the patients were informed of this. Their doctor, nurse or other people who worked at the hospital did not see or hear any of the information that was shared.

Regarding the confidentiality of personal data collected through interviews, research data were issued with a unique identification number to ensure anonymity and only members of the research team had the ability to identify individual participants by their identification number. Direct quotes were used in this thesis and publications but were anonymised.

This meant that all direct and indirect identifiers (email, phone no., name, and etc.) were removed from the research data before analysis.

3.8.11. Data storage and archiving

In line with GDPR principles 5 and 6, all electronic data records were stored on a secure, password protected network drive at the University of Warwick or on an encrypted, password protected device owned by researcher. Any additional paper versions of personal data used during the analysis were stored in a locked cupboard in the office building of the researcher (Farmhouse, Gibbet Hill). Only the researcher had access to the locker protected through one key. All potential identifiable data were pseudonymised. Consent forms and pseudonymised data in the form of paper will be securely keep for 10 years after the study is completed, at Warwick Medical School.

At the completion of the project, all data in paper form are to be given to my supervisor and safely stored in the data archive at Warwick Medical School. All electronic data, meanwhile, are to be securely stored in a shared drive at Warwick Medical School. All data will then be securely deleted from my laptop.

3.8.12. Consent

The researcher discussed the study in detail with each participant face to face before starting the interview. Participants had voluntarily agreed to take part in research, having been provided with all the information required to make their decision. Signed consent was obtained after I had explained the study and the participants were given opportunity to ask questions. Each signed consent form will be retained for the life of study and for the retention period of the data.

3.8.13. Right of withdrawal

Each patient or healthcare professional who participated in the current study was advised that they had the right to withdraw from the research process up to the time of data analysis and that after that point, data withdrawal would no longer be possible. Participants wishing to withdraw from the study could contact the researcher and any related data could potentially

have been deleted, in line with university protocols. However, in the circumstances, no one requested that their data be withdrawn.

3.8.14. Data analysis

The data generated by this study (Phase II of VTE-BC) were analysed by the researcher. The principle inductive strategy of the study analysis is grounded theory, which is used to produce and confirm theory emerging from empirical observation, rather than to test predetermined hypotheses (Kennedy & Lingard, 2006). Ground theory is a general research method which develops new theories or hypotheses from many observations. It emphasizes, in particular, the concept of induction, which moves from the particular to the general. It depends on context and never completely final (Charmaz & Belgrave, 2007). The findings of a grounded theory study are stated as a substantive theory: that is, as a set of concepts that are related to one another in a cohesive whole.

The researcher used thematic analysis to gain insights and knowledge from data gathered from the participants' interviews. This type of analysis is one of the commonest methods of looking at data in a qualitative study (Braun and Clarke, 2006). It emphasizes the need to define, test, and record themes that are regularly occurring across data sets, and which are important to enable a phenomenon to be articulated and related to the research questions (Braun and Clarke, 2006). Audio-recordings were transcribed by an expert working at the Clinical Trials Unit/Warwick Medical School. Prior to this, the researcher anonymised the interview data.

Thematic analysis of the data was then undertaken, in which the researcher compared within and between interview data to gain insights into participants' views and understandings of the risk of thrombosis.

This involved six main steps:

1- **Familiarisation of the whole interview**: During this stage, the researcher read and re-read the transcripts to familiarise himself with the data. The researcher also listened to the recorder on need.

2- **Coding:** During this stage, the researcher started to organise the data in a meaningful and systemic way to develop initial codes to interpret the data. Coding was done manually. Open coding approach was used,

meaning there was no pre-set codes but developed and modified the codes as the researcher worked through the coding process. An inductive approach was followed, whereby the researcher aimed to generate meanings from the data set collected in order to identify patterns and relationships to build a theory. Moreover, the researcher presented and interpreted the data according to Shannon and Weaver's model (1949), which divides the communication into four components: senders, massages, channels and receivers. Given this, the researcher coded each segment of data that was relevant to or captured something interesting about this research question. The initial idea about codes was developed from analyse eight interviews and the researcher discussed these codes with his supervisor and developed some preliminary ideas about codes. The researcher analysed and worked through each transcript and coded every segment of text that appeared to be relevant to study. Both electronic and hard copies of the transcripts were analysed, and codes were highlighted, leading to codes and relevant quotations being tabulated for each transcript.

3- Create themes: During this stage, the researcher developed themes by identifying what appeared to be significant within the data. The researcher then developed the contents of the transcript tables by grouping codes together that had equivalent meanings or had an association with one another. Following this grouping process, the codes were labelled based on the meaning or relationships shared. Some codes formed categories or sub-themes that were distributed over four components of communication: senders, massages, channels and receivers. Other codes, meanwhile, were discarded. At the end of this stage, a collection of sub-themes and themes was created.

4- Reviewing themes: This stage involved refining themes and subthemes. Some themes collapsed into other themes, whereas others needed to be broken down into smaller themes. Themes were reviewed against the data. This process confirmed that the themes and subthemes express the data without missing any important details.

5- **Naming and defining themes:** This process involved utilizing the labels created for the theme and providing a comprehensive name that described the relationship or meaning conveyed in the theme. This definition aimed to summarize the content of what was discussed within the theme. After continuous revision of themes in relation to the data, a final set of themes was produced.

6- **Producing final report:** The final report and results were written after the themes were defined and named. The quotes used in this study were anonymised and reflected the most typical comments of participants.

3.9. Ethical considerations for VTE-BC

This study fully meets the requirements of the University of Warwick's Biomedical and Scientific Research Ethics Committee (BSREC) agreement. The study obtained all mandatory ethical permissions and NHS Research and Development approvals before starting. The whole study was conducted according to the ethical guidelines for medical and health research involving human subjects and the ethical principles originating from the declaration of Helsinki (WMA, 2001). Each Phase had its own application and ethical approval. The Health Research Authority (HRA) application and Research Ethics Committee (REC) were applied to obtain approval for Phase I first then for Phase II. The following table shows the process and date of ethics committees' approval.

Table 6: Ethics committees' approval

Ethics	Study Title	Reference number	Submission	Approval
BSREC approval for phase I	Venous Thromboembolism in muscle invasive, locally advanced, or metastatic urothelial cancer, with or without chemotherapy (VT-U-CAN)	REGO-2017-2034	04/03/17	22/08/17
Sponsorship committee approval for phase I	Venous thromboembolism in muscle invasive, locally advanced, or metastatic urothelial cancer, with or without chemotherapy (VT-U- CAN)	SC.88/16-17	21/08/17	01/11/17
HRA approval for phase I	Venous thromboembolism in muscle-invasive, locally advanced or metastatic urothelial bladder carcinoma with or without chemotherapy (VT-U-CAN)	231338	14/02/18	13/03/18
Confirmation of capacity and capability at UHCW	Venous thromboembolism in muscle-invasive, locally advanced or metastatic urothelial bladder carcinoma with or without chemotherapy (VT-U-CAN)	AY372417	27/03/18	18/04/18
Confirmation of capacity and capability at QEHB	Venous thromboembolism in muscle-invasive, locally advanced or metastatic urothelial bladder carcinoma with or without chemotherapy (VT-U-CAN)	RRK 6296	11/03/18	19/10/18
Sponsorship committee approval for phase II	Venous Thromboembolism in Cancer Patients: patients' experiences (VTC-Exp)	SC.02/18-19	12/10/18	29/01/19
Favorable opinion of the REC	Venous Thromboembolism in Cancer Patients: patients' experiences (VTC-Exp)	19/LO/0940	13/03/19	31/05/19
HRA & HCRW Approval	Venous Thromboembolism in Cancer Patients: patients' experiences (VTC-Exp)	IRAS 256564	13/03/19	04/06/19
Confirmation of capacity and capability at UHCW	Venous Thromboembolism in Cancer Patients: patients' experiences (VTC-Exp)	RS445019	04/06/19	27/06/19
Confirmation of capacity and capability at QEHB	Venous Thromboembolism in Cancer Patients: patients' experiences (VTC-Exp)	RRK6707	04/06/19	21/10/19

3.10. Presenting the quantitative results and qualitative findings

As the VTE-BC study has two core questions, the scope of the problem and the patients' understanding of VTE in BC patients, two methods were used to answer the research questions. The quantitative results are presented in Chapter 4 and the qualitative finding in Chapter 5. The results of the quantitative part are numerical, while to understand the second core of VTE-BC study, the findings of the qualitative part are presented in a narrative manner. Following this, all the results and findings are brought together in one discussion chapter. Findings from both phases are presented discussion chapter of whole study to offer complementary information on the research problem.

3.11. Conclusion

The philosophical framework and system of methods used in VTE-BC study have been outlined in Chapter 3, the better to understand how each phase of the study was conducted. The philosophical assumptions and methodology of the research were then described, before exploring the methods, since understanding the relationship between research philosophy and methods was a key for the researcher and shaped the study design.

In order to discover the scope of VTE in bladder cancer patients in the UK, the incidence and risk factors of VTE required exploring; hence, a descriptive retrospective study including all adult bladder cancer patients recorded at HES data, QEHB and UHCW was carried out. Generating and analysing data in Phase I of study helped to specify which group of BC patients had a high risk of VTE and needed to be interviewed in Phase II. Additionally, data from Phase I could encourage HCPs to make more informed decisions and efforts to improve quality of diagnosis and management of patients with BC. Regarding Phase II, the data explore the communication component between HCPs and BC patients and find the patients understanding regarding VTE in BC context.

4. Venous thromboembolism in bladder cancer: scope of the problem

4.1. Chapter outline

The results of the quantitative component of VTE-BC study, Phase I, are presented in this chapter. This Chapter presents the data of venous thromboembolism (VTE) in bladder cancer (BC) patients from two sources: 1) Hospital Episode Statistics (HES) data relating to BC patients at NHS hospitals in England; and 2) Local data relating to BC patients from two big trusts Queen Elizabeth Hospital Birmingham (QEHB) and University Hospitals Coventry and Warwickshire (UHCW) in the UK. This chapter provides a comprehensive study of the extent of the VTE problem within BC patients by identifying the VTE incidence rate and risk factors of VTE in BC patients group in the UK.

4.2. Quantitative phase

Patients with BC have several disease-, patient- and treatment-related features that are well recognised as risk factors of VTE. To discover the scope of VTE in BC patients in the UK, it is necessary to explore the incidence and risk factors of VTE; hence, a descriptive retrospective study, including all adult bladder cancer patients recorded in HES data, QEHB and UHCW has been carried out. Generating and analysing data may allow HCPs to make more informed decisions and efforts to improve the quality of diagnosis and management of patients with BC. Based on the systematic review (chapter 2) there are insufficient meaningful data to gain an accurate picture of the number of new cases of VTE events in the BC population, as well as a lack of clear information regarding risk factors in the UK.

The current study and results may support NHS England and National VTE Prevention Program in providing updated data and information regarding VTE incidences and risk factors. The study has been conducted according to the ethical guidelines for medical and health research involving human subjects and the ethical principles originating from the declaration of Helsinki.

4.3. Results

To ascertain the scope of VTE problem in BC patients, a descriptive study was conducted to explore the incidence rate and risk factors of VTE in BC patients. The current study also aimed to discover the number of BC patients who were admitted for VTE treatment in the UK. A retrospective database was obtained with approval from the relevant institutional clinical governance committees.

4.3.1. HES data

HES data were used to explore the incidence rate of VTE in BC patients in England between 2013 and 2018. The number of new VTE recorded in HES data, for BC patients managed at NHS hospitals and NHS commissioned activity in the independent sector in England, was 1076 patients between 2013 and 2018.

HES data also provided the number of admission episodes of BC patients for different causes or events; the proportion of admissions due to VTE was 0.7% of all those admitted during the last 5 years (Table 7).

Table7: Bladder cancer patients' admissions between 2013 and 2018 in England

Reasons for admission	No. of admissions	No. of VTE's admissions	VTE admissions
Unspecified	151400	1045	0.7%
Undergoing cystectomy	7227	105	1.4%
Receiving systemic chemotherapy ± cystectomy	2614	77	2.9%

VTE — Venous Thromboembolism,

During the last 5 years, a total of 1045 BC patients were admitted for VTE events, which created an extra burden for affected BC patients, as well as the hospitals that treated them.

In England, according to HES data, 87% of bladder cancer patients were above 60 years old; 75% of BC patients were male and 25% were female, according to HES data from 2013 to 2018 (Figure 15 and 16).

Figure 15: Age distribution of bladder cancer patients according to HES data from 2012 to 2018

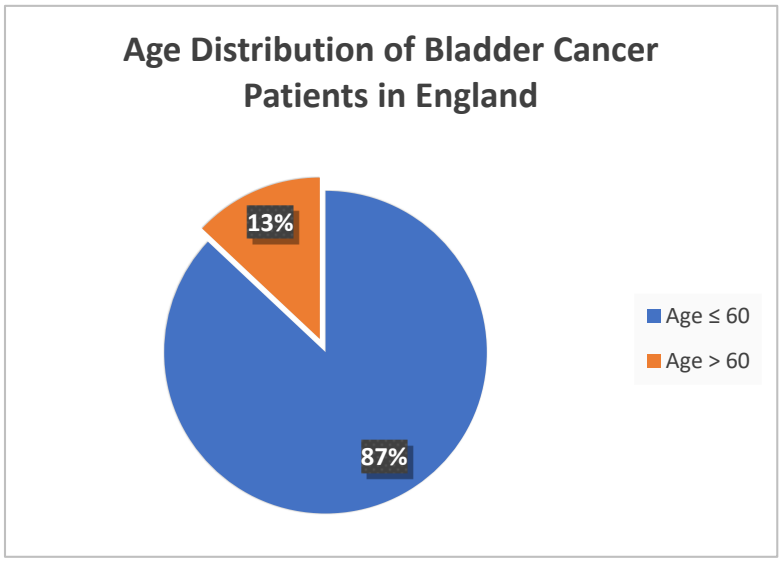
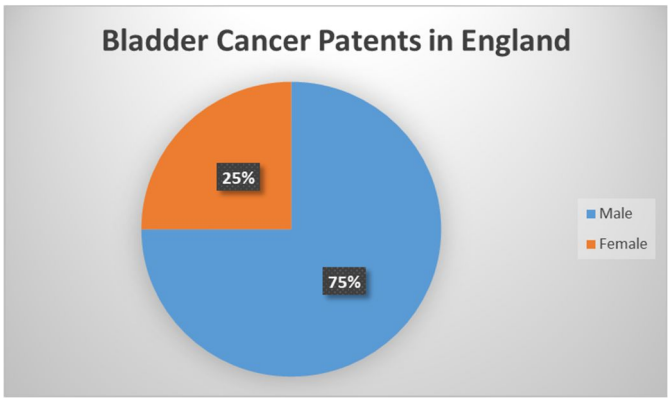


Figure 16: Male-female percentage of bladder cancer patients according to HES data from 2012 to 2018



In general, the annual VTE incidence in BC patients is 6.0 in every 1000 patients, while the VTE incidences in patients who had cystectomy and chemotherapy are 14 and 29 per 1000 respectively during a period from 2013 to 2018 in England (Table 8).

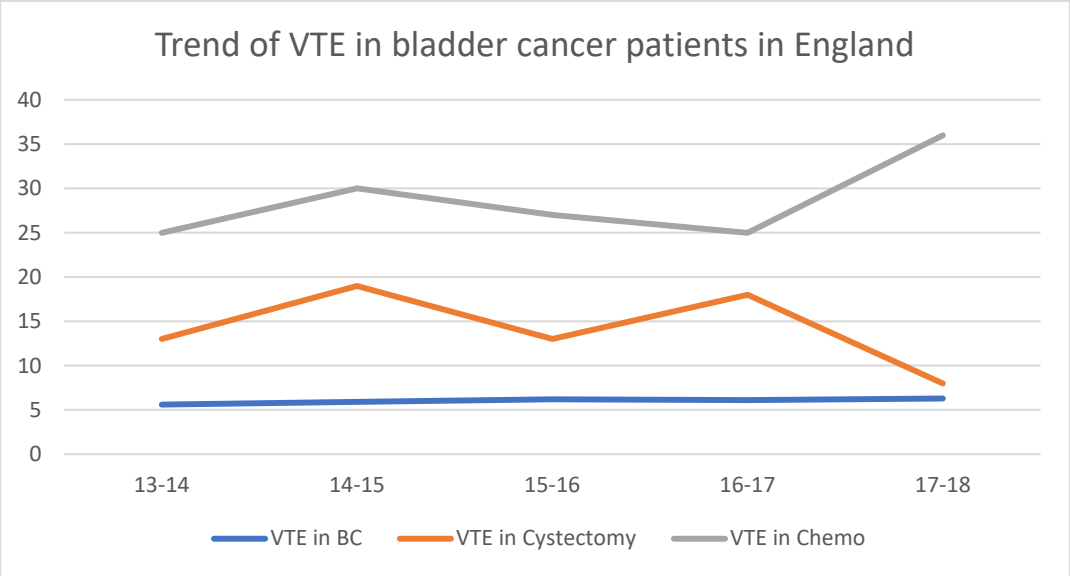
Table 8: Incidence of VTE cases per 1000 patients with bladder cancer

VTE incidence	Male	Female	Age ≤ 60	Age > 60	Total
		2013-2014			
Bladder cancer	5.0	7.1	7.4	5.4	5.6
Cystectomy	15	05	33	8.0	12
Chemotherapy	24	28	47	21	25
		2014-2015			
Bladder cancer	5.9	5.8	5.8	5.9	5.9
Cystectomy	18	21	7.0	22	19
Chemotherapy	28	47	20	32	30
		2015-2016			
Bladder cancer	5.5	8.2	5.3	6.3	6.2
Cystectomy	11	22	16	13	13
Chemotherapy	25	36	51	25	27
		2016-2017			
Bladder cancer	6.1	5.7	9.4	5.7	6.1
Cystectomy	20	9.0	19	18	18
Chemotherapy	30	9.0	16	26	25
		2017-2018			
Bladder cancer	6.2	6.7	7.1	6.1	6.3
Cystectomy	9.0	6.0	14	18	8.0
Chemotherapy	35	38	45	35	36

VTE — Venous Thromboembolism,

In order to provide a time-trend analysis of VTE incidence rate in bladder cancer patients to help conclude the effect of exposing to VTE risk factors and VTE prevention measures in BC patients in England, a comparison was made between groups in the last 5 years.

Figure 17: Time-trend of VTE Incidence rates per 1000 BC patients in England



BC — Bladder Cancer, VTE — Venous Thromboembolism, Chemo. — Chemotherapy The results from HES data reveal that the time-trend of VTE incidence rates in BC patients in England was practically unchanged from 2013 to 2018. However, the VTE incidence rates in BC patients who have had cystectomy fluctuated and bottomed out in 2018. The VTE incidence rate in BC patients receiving chemotherapy was at its highest in 2018 (Figure 17).

4.3.2. Local data

Retrospective cohort data of BC patients with or without VTE was received from the informatics departments at two local NHS trusts, QEHB and UHCW. There was a period difference in data collection between the two sites, for data quality reasons. The data was collected at QEHB from 2011 to 2018, but at UHCW from 2007 to 2018.

In total, 2892 patients with BC were recorded at both hospitals. The annual VTE incidence in patients with BC was around 6.1 per 1000 patients in both hospitals. The incidence rate of VTE in bladder cancer patients treated with radical cystectomy was 56 per 1000 and 76 per 1000 of chemotherapy, but VTE incidence was much higher for those who received chemotherapy and had undergone radical surgery, at 88 per 1000 cases. The median age of

diagnosis for BC was 73, the minimum age was 19, while the maximum was 103 (Figures 18 and 19).

Figure 18: Age distribution of bladder cancer patients at QEHB and UHCW

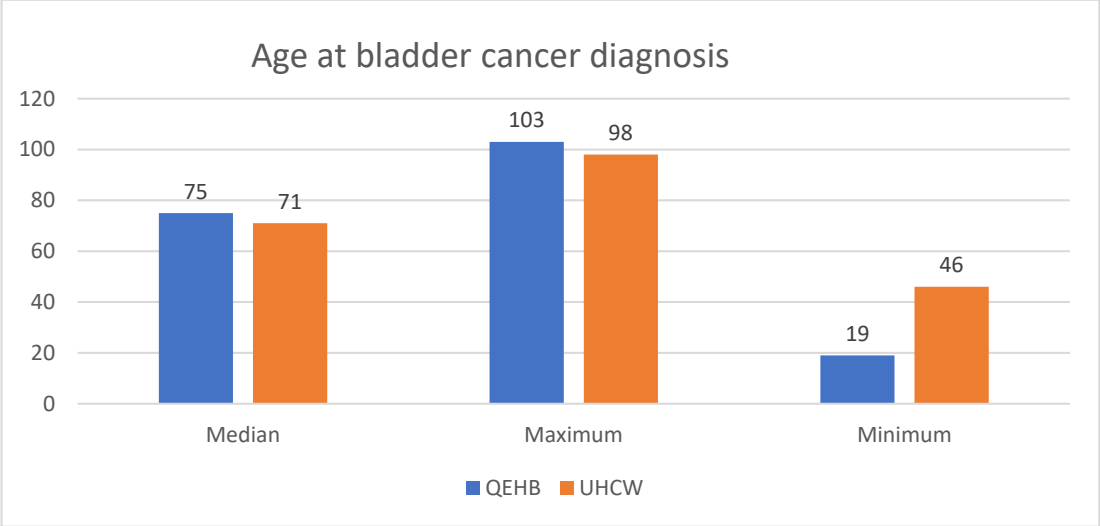
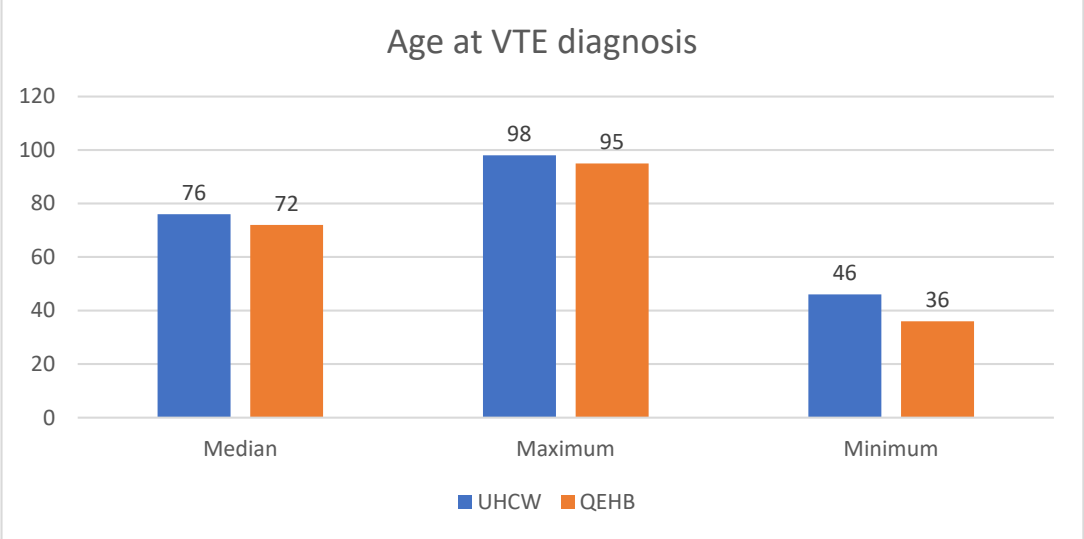


Figure 19: Age distribution of bladder cancer patients with VTE at QEHB and UHCW



Around 87.2% of patients with BC cancer were 60 years or older at the time of diagnosis and 73.7% of patients with BC were male. Both hospitals use multidisciplinary teams to treat BC and all patients with BC undergo TURBT for diagnosis or treating purpose. Only one-third of BC were

aggressive, muscle-invasive tumours (MIBC), receiving radical treatment which included systemic chemotherapy, radical cystectomy and/or radiotherapy (Table 13). Each type of treatment had its own risk for developing VTE. There was no significant difference in the percentage of VTE between QEHB and UHCW. However, the percentage of PE in patients with VTEs was higher than DVT, and most VTEs were symptomatic. A greater proportion (89%) of patients with BC and VTE were treated with only LMWHs, such as enoxaparin and dalteparin, while few patients received warfarin in addition to LMWHs tablet. Around 76% of patients with BC and VTE lived one year or more after VTE diagnosis. Around 96% of BC patients with VTE were admitted to the hospital for treatment. The characteristics of the 2892 patients with BC treated at QEHB and UHCW are given in Table 9.

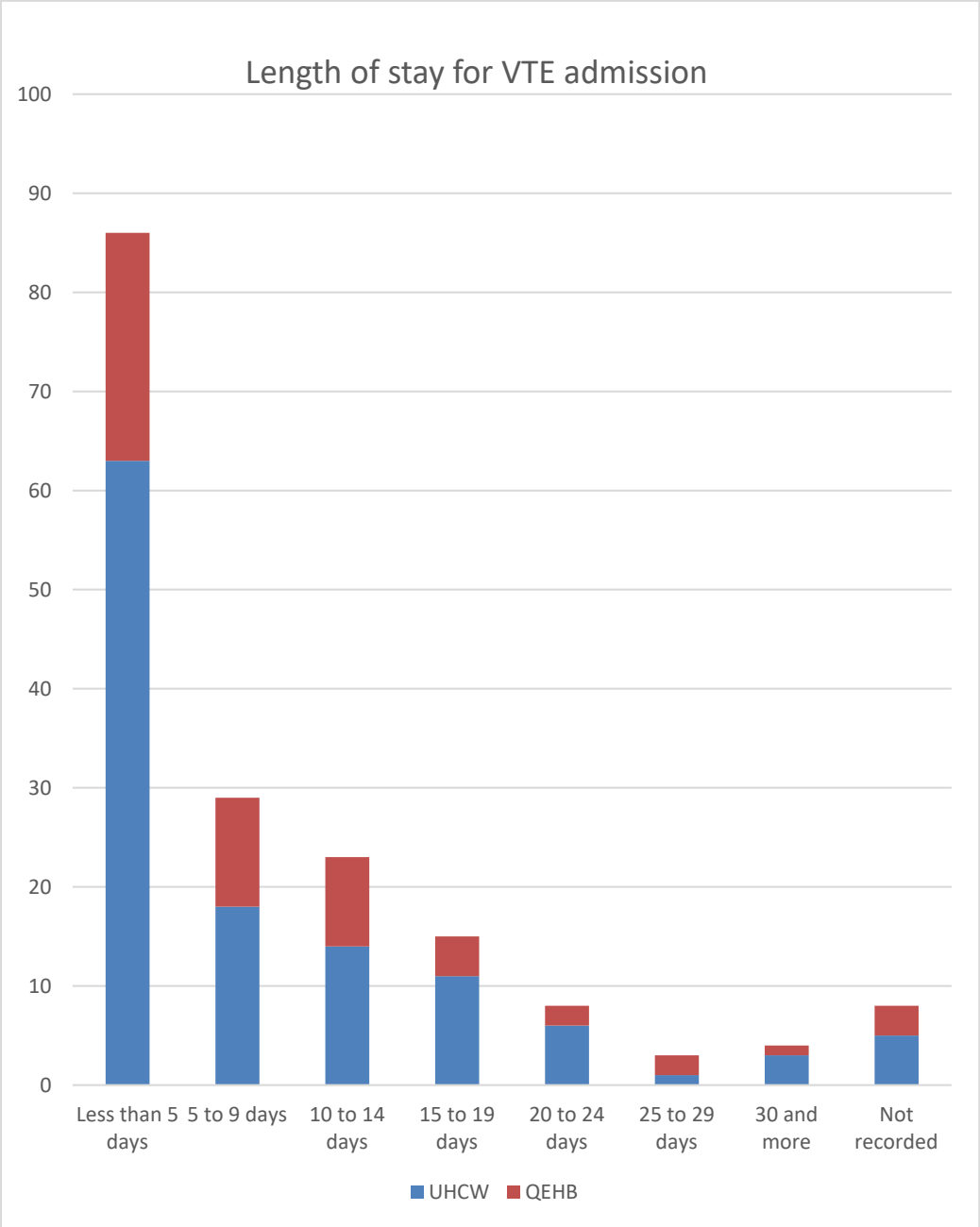
Table 9: BC patients' characteristics at UHCW and QEHB

	Variables (%)	UHCW (2007-2018)	QEHB (2011-2018)
1	Number of BC	1702	1190
2	Median age (mini-max)	75 (46-98)	71 (19-103)
3	Male	1244 (73.1%)	885 (74.3%)
4	Female	458 (26.8%)	305 (25.6%)
5	Cystectomy	277 (16.3%)	165 (13.8%)
6	Systemic chemotherapy	142 (8.4%)	294 (24.7%)
7	Radiotherapy	267 (15.7%)	150 (12.6%)
8	Radical Radiotherapy	125 (7.4%)	59 (4.9%)
9	Palliative Radiotherapy	139 (8.2%)	91 (7.6%)
10	VTE	121 (7.1%)	55 (4.6%)
11	DVT Incidental Symptomatic	33 (1.9%) 8 (24.2% of DVT) 25 (75.7% of DVT)	21 (1.7%) 3 (14.2% of DVT) 18 (85.7% of DVT)
12	PE Incidental Symptomatic	88 (5.1%) 16 (18.1% of PE) 72 (81.8% of PE)	36 (3%) 7 (19.4% of PE) 29 (80.5% of PE)
13	PE + DVT	7 (0.3%)	2 (0.1%)
14	VTE unspecified	0	4 (0.3%)

BC — Bladder Cancer, VTE — Venous Thromboembolism, DVT — Deep Vein Thrombosis, PE — Pulmonary Embolism

Regarding the duration of stay for VTE admission, 86% of patients were admitted for five days or less. Figure 20 below demonstrates the length of stay for VTE admission at both QEHB and UHCW.

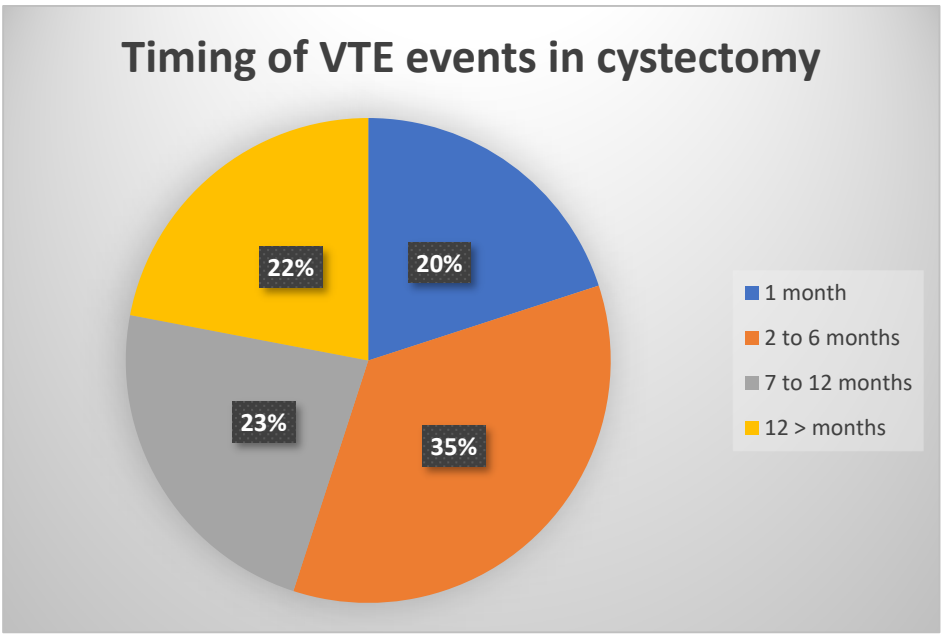
Figure 20: Length of stay for VTE admission



Regarding BMI data, there were insufficient data available in the patient database, with about 62% of BMI data not being accessible, and 77% of smoking history not being recorded within the database of patients with BC, whether at QEHB or UHCW. Hence, these two risk factors were omitted from the analysis. Around 22% of patients were diagnosed with VTE within one month of cystectomy, and 35% of patients acquired VTE within two to six

months period. 45% of patients were diagnosed with VTE after six months from cystectomy (Figure 21).

Figure 21: Percentage of patients diagnosed with VTE after cystectomy



At both NHS trusts (QEHB and UHCW), 176 patients with BC and VTE were recognised and matched with 352 control subjects to perform statistical analysis of this case-control study. Unadjusted and adjusted logistic regression were used to obtain odds ratios with 95% confidence intervals.

Unadjusted logistic regression analysis was used to explore the relations between VTE and each of one of following explanatory variables: treatment, stage, co-morbidities, gender, histology and grade of BC. Variables which had a significant association with VTE were chosen as predictors and fitted to a logistic regression model (Table 10). Treatment, stage and comorbidities appear to have a significant association with VTE in patients who have BC (Table 10).

Table 10: Association of VTE in patients with BC with treatment, stage, co-morbidities, gender, histology, and grade of BC at QEHB and UHCW

Variables	QEHB & UHCW		Unadjusted		*Adjusted	
	Cases (n=176)	Controls (n=352)	OR (95%CI)	P-value	OR (95%CI)	P-value
Treatment						
TURBT	68(38.6%)	237(67.3%)				≤0.001
Cyst.	57(32.3%)	80(22.7%)	2.48(1.60-3.83)	≤0.001	2.88(1.63-5.07)	≤0.001
Chemo.	18(10.2%)	22(6.2%)	3.30(1.64-6.64)	0.001	2.56(1.03-6.32)	0.041
CT + Cyst.	33(18.7%)	16(4.5%)	7.18(3.73-13.84)	≤0.001	8.26(3.51-19.45)	≤0.001
Stage						
NMIBC	82(46.5%)	245(69.6%)	1.84(1.22-2.77)			≤0.001
MIBC	60(34.0%)	99(28.1%)	10.15(4.80-	0.003	0.68(0.37-1.25)	0.221
Metastatic	34(19.3%)	10(2.8%)	21.46)	≤0.001	4.41(1.85-10.50)	0.002
Co-morbidities	91(51.7%)	134(38.0%)	0.58(0.40-0.84)	0.004	0.58(0.39-0.87)	0.009
Gender						
Male	124(70.4%)	256(72.7%)	1.02(0.69-152)	0.892		
Female	52(29.5%)	102(28.9%)				
Histology						
Uro	158(89.7%)	318(90.3%)	1.00(054-1.84)	1.000		
Non-Uro	18(10.2%)	35(9.9%)				
Grade						
1	11(6.2%)	18(5.1%)				
2	13(7.3%)	26(7.3%)	0.91(0.64-1.30)	0.629		
3	152(86.3%)	308(87.5%)				

OR-odds ratio, Cyst.-Cystectomy, Chemo.-Chemotherapy, Uro.-Urothelial

** Adjusted odds ratios were calculated from a multivariable logistic regression model that included treatments received (cystectomy, chemotherapy, cystectomy with chemotherapy), stage at diagnosis (expressed in non-muscle-invasive, muscle-invasive, and metastatic), comorbidities (have comorbidities vs no comorbidities).*

This regression model demonstrated that there was a significant association of treatment and stage with VTE P<0.001. However, muscle-invasive BC (MIBC) had no risk of VTE with OR=0.68 (95% CI=0.37-1.25) and P=0.221, this was only the case for the metastatic stage (Table 14).

The odds of VTE for patients with BC who had a cystectomy or chemotherapy was almost 3 times greater than in patients who had only TURBT, with statistically significant differences. Patients had cystectomy OR = 2.48 (95% CI=1.60-3.83) and P < 0.001 and for chemotherapy OR = 3.30 (95% CI=1.64-6.64) and P = 0.041. No doubt, for those patients who had both chemotherapy and cystectomy the odds ratio was about 7 times greater than

for those patients who had TURBT, the difference being statistically significant: OR = 7.18 (95% CI=3.73-13.84) and P < 0.001.

Another logistic regression model was fitted to explore the association of VTE with comorbidities without second type of cancer, second type of cancer, treatments and stage (Table 11). After splitting the comorbidities into comorbidities without 2nd cancer, the odds ratio of comorbidities revealed had no risk with VTE OR=0.98 (0.65-1.48) and P = 0.944; however, second type cancer had a high risk of VTE OR = 0.23 (95% CI=0.10-0.53) and P = 0.001, as well as chemotherapy demonstrated, had no risk of VTE with OR = 2.40 (0.96-5.99) and P = 0.061 (Table 11).

Table 11: Association of VTE in patients with BC with treatment, stage, co-morbidities without 2nd cancer and 2nd cancer at QEHB and UHCW

Variables	OR (95%CI)	P-value
Treatment		
TURBT		
Cystectomy	2.64 (1.49-4.68)	0.001
Chemo.	2.40 (0.96-5.99)	0.061
Chemo. & Cystectomy	7.45 (3.14-17.71)	≤0.001
Stage		
NMIBC		
MIBC	0.70 (0.38-1.30)	0.266
Metastatic	4.45 (1.86-10.62)	0.001
Co-morbidities no ca	0.98 (0.65-1.48)	0.944
2nd cancer	0.23 (0.10-0.53)	0.001

TURBT — Trans Urethral Resection of Bladder Tumour, Chemo. — Chemotherapy, MIBC — Muscle Invasive Bladder Cancer, MI — Muscle Invasive, NMIBC — Non-Muscle Invasive Bladder Cancer, MI — Muscle Invasive, Ca. — Cancer

Additional regression analysis was applied to QEHB and UHCW data separately to identify the differences between the results of the two NHS trusts. The logistic regression for each site demonstrated nearly the same results, as follows: radical cystectomy, radical cystectomy with chemotherapy, metastatic stage and 2nd cancer created a significant risk of VTE; however, chemotherapy, MIBC stage and comorbidities without second type of cancer had no risk of VTE in patients with BC (Tables 12 to 15).

Table 12: Association of VTE in patients with BC with treatment, stage, co-morbidities, gender, histology, and grade of BC at QEHB

			Unadjusted		*Adjusted	
Variables	QEHB (2011-2018)		OR (95%CI)	P=value	OR (95%CI)	P=value
	Cases (n=55)	Controls (n=110)				
Treatment						
TURBT	16 (29%)	79 (71.8%)				
Cyst.	20 (36.3%)	23 (20.9%)	4.29 (1.92-9.60)	0.012	4.61 (1.12-19.00)	0.034
Chemo.	4 (7.2%)	6 (5.4%)	9.87 (1.66-58.58)	≤0.001	4.81 (0.39-59.20)	0.220
Chemo & Cyst.	15 (27.2%)	6 (5.4%)	12.34(4.15-36.66)	≤0.001	11.89(1.91-73.84)	0.008
Stage						
NMIBC	18 (32.7%)	81 (73.6%)				
MIBC	22 (40.0%)	29 (26.3%)	3.66 (1.71-7.84)	0.001	0.70 (0.15-3.13)	0.643
Metastatic	15 (27.2%)	2 (1.8%)	33.75(7.08-160.82)	≤0.001	8.54 (1.32-55.22)	0.024
Co-morbidities	30 (54.5%)	40 (36.6%)	0.51(0.26-0.98)	0.046	0.76 (0.34-1.67)	0.496
Gender						
Male	42 (76.3%)	82 (74.5%)	0.90 (0.42-1.93)	0.799		
Female	13 (23.6%)	28 (25.4%)				
Histology						
Urothelial	52 (94.5%)	94 (85.4%)	0.33 (0.09-1.21)	0.097		
Non-urothelial	3 (5.4%)	17 (14.5%)				
Grade						
1	2 (3.6%)	6 (5.4%)				
2	2 (3.6%)	7 (6.3%)	1.36 (0.64-2.90)	0.422		
3	51 (92.7%)	97 (88.1%)				

OR — odds ratio, Cyst.— Cystectomy, Chemo.— Chemotherapy, Uro.-Urothelial TURBT — Trans Urethral Resection of Bladder Tumour, MIBC — Muscle Invasive Bladder Cancer, MI — Muscle Invasive, NMIBC — Non-Muscle Invasive Bladder Cancer, MI — Muscle Invasive

**Adjusted odds ratios were calculated from a multivariable logistic regression model that included treatments received (cystectomy, chemotherapy, cystectomy with chemotherapy), stage at diagnosis (expressed in non-muscle-invasive, muscle-invasive, and metastatic), comorbidities (have comorbidities vs no comorbidities).*

Table 13: Association of VTE in patients with BC with treatment, stage, co-morbidities without 2nd type cancer and 2nd type of cancer at QEHB

Variables QEHB	OR (95%CI)	P-value
Treatment		
TURBT		
Cystectomy	4.94 (1.18-20.70)	0.029
Chemo.	4.54 (0.34-60.07)	0.251
Chemo. and Cystectomy	10.94 (1.61-74.41)	0.014
Stage		
NMIBC		
MIBC	0.51 (0.11-2.43)	0.406
Metastatic	8.11 (1.20-54.49)	0.031
Co-morbidities no ca	0.98 (0.41-2.33)	0.980
2^{nd} ca	0.09 (0.01-0.50)	0.006

TURBT — Trans Urethral Resection of Bladder Tumour, Chemo. — Chemotherapy, MIBC — Muscle Invasive Bladder Cancer, MI — Muscle Invasive, NMIBC — Non-Muscle Invasive Bladder Cancer, MI — Muscle Invasive

Table 14: Association of VTE in patients with BC with treatment, stage, co-morbidities, gender, histology, and grade of BC at UHCW

			Unadjusted		*Adjusted	
Variables	UHCW (2007-2018)		OR (95%CI)	P-value	OR (95%CI)	P-value
	Cases (n=121)	Controls (n=242)				
Treatment						
TURBT	52 (42.9%)	158(65.2%)				
Cyst.	37 (30.5%)	57 (23.5%)	1.97 (1.17-3.31)	0.010	2.46 (1.31-4.63)	0.005
Chemo.	14 (11.5%)	16 (6.6%)	2.50 (1.15-5.42)	0.020	2.43 (0.91-6.52)	0.076
CT and Cyst.	18 (32.7%)	10 (4.1%)	5.46 (2.37-12.59)	0.000	7.58(2.72-21.09)	0.000
Stage						
NMIBC	64 (52.8%)	164(67.7%)				
MIBC	38 (31.4%)	70 (28.9%)	1.39 (0.85-2.26)	0.186	0.62 (0.32-1.23)	0.176
Metastatic	19 (15.7%)	8 (3.3%)	6.08 (2.53-14.60)	0.000	3.21 (1.17-8.77)	0.023
Co-morbidities	61 (50.4%)	94 (38.8%)	0.62 (0.40-0.97)	0.036	0.56 (0.34-0.89)	0.016
Gender						
Male	82 (67.7%)	174(71.9%)	1.08 (0.67-1.72)	0.749		
Female	39 (32.2%)	74 (30.5%)				
Histology	106 (87.6%)	224 (92.5%)	1.62 (0.78-3.39)	0.194		
Urothelial	15 (12.3%)	18 (7.4%)				
Non-urothelial						
Grade						
1	9 (7.4%)	12 (4.9%)				
2	11 (9.0%)	19 (7.8%)	0.81 (0.57-1.14)	0.233		
3	101(83.4%)	211(87.1%)				

TURBT — Trans Urethral Resection of Bladder Tumour, CT — Chemotherapy, NMIBC — Non-Muscle Invasive Bladder Cancer, MI — Muscle Invasive

**Adjusted odds ratios were calculated from a multivariable logistic regression model that included treatments received (cystectomy, chemotherapy, cystectomy with chemotherapy), stage at diagnosis (expressed in non-muscle-invasive, muscle-invasive, and metastatic), comorbidities (have comorbidities vs no comorbidities).*

Table 15: Association of VTE in patients with BC with treatment, stage, co-morbidities without 2nd cancer and 2nd cancer at UHCW

Variables UHCW	OR (95%CI)	P-value
Treatment		
TURBT		
Cystectomy	2.26 (1.20-4.28)	0.013
CT	2.06 (0.76-5.58)	0.152
CT and Cystectomy	6.97 (2.51-19.33)	0.000
Stage		
NMIBC		
MI	0.73 (0.37-1.43)	0.362
Metastatic	3.09 (1.11-8.56)	0.030
Co-morbidities no cancer	1.00 (0.62-1.61)	0.978
2nd cancer	0.07 (0.01-0.35)	0.001

TURBT — Trans Urethral Resection of Bladder Tumour, CT — Chemotherapy, NMIBC — Non-Muscle Invasive Bladder Cancer, MI — Muscle Invasive

Logistic regression analysis revealed that 2nd type of cancer was a risk factor of VTE and after splitting the comorbidities and reanalysing the data chemotherapy became a non-risk factor of VTE. The adjusted analysis yielded the association of each factor with VTE. The model, therefore, suggests that a patient with BC has more risk of VTE when he or she has had a metastatic stage, second type of cancer, cystectomy and/or chemotherapy.

4.4. Discussion

The extent of the VTE problem in patients with BC was explored and investigated before commencing the sequential qualitative component. Patients with BC have several disease-, patient- and treatment-related features that are well known as risk factors for developing VTE as well as candidate biomarkers (Sud & Khorana, 2009; Zareba *et al.*, 2018).

A descriptive retrospective study including all adult bladder cancer patients recorded at Hospital Episode Statistics (HES) data, Queen Elizabeth Hospital Birmingham (QEHB) and University Hospitals Coventry and Warwickshire (UHCW) was carried out.

4.4.1. HES data

The HES data collected between 2013 and 2018 showed that there were a significant number of BC patients needing hospital admission to manage VTE, which increased the burden on medical institutions, disrupted planned cancer treatment, and reduced quality of life. Moreover, BC with its related treatments and complications was seen to cause a major economic burden (Avritscher *et al.*, 2006; Kahn *et al.*, 2005; Lamping, 1997). Thus, cost-effective surveillance strategies for avoiding complications are mandatory for minimizing the disease's clinical and economic consequences (Avritscher *et al.*, 2006).

Previous literature shows that patients over 60 years old have a greater risk of developing VTE compared with young patients (Khorana *et al.*, 2007b). Yet the analysis of HES data in the current study revealed that there were no significant differences between the incidence of VTE rate in BC patients above or below 60 years. Age does not therefore seem to be a risk factor for VTE in BC patients.

Patients with BC who underwent radical cystectomy had a higher incidence rate of VTE compared with patients who did not undergo this surgical procedure. The VTE rate is convincingly higher in those patients who received only chemotherapy or chemotherapy with cystectomy than those who underwent radical cystectomy only. Changes in therapy, such as increasing use of chemotherapy or more aggressive chemotherapy treatment of later-stage patients may have influenced VTE rate in the last two years.

Looking at the HES data, the time-trend of VTE incidence rates among patients diagnosed with BC was practically unchanged from 2013 to 2018. This is because the VTE incidence rates in BC patients who had cystectomy fluctuated, bottoming out in 2018, but the VTE incidence rate in BC patients, who received chemotherapy was highest in 2018. The trend analysis of VTE in BC patients in England reflects that there was good control of VTE and good prophylactic measures in patients who underwent cystectomy. However, the increase of VTE rate in patients who received chemotherapy from 2016 to 2018 may indicate that surveillance strategies are still an option in addition to

awareness around VTE and focusing more on thromboprophylaxis measures in selected patients who receive systemic chemotherapy.

4.4.2. Local data

The VTE incidence rate found across UHCW and QEHB is 6.1 per 1000 patients which similar to the incidence rate that discovered in HES data, namely 6.0 per 1000 patients. However, the VTE incidence rate in BC patients in the current study VTE-BC varies from the previous study by Walker et al. (2013) which was 15 per 1000 person-years in the UK. There are two possible explanations for the variations in incidence rates of VTE in BC patients between this study (VTE-BC) and the study by Walker et. al. (2013). The stable incidence rates resulted from the longer duration of patient follow-ups in a study by Walker et al. (2013) who used two years in contrast to one year in the current VTE-BC study, and from the time of data collection (1987-2012) (Walker *et al.*, 2013a).

In the UK, the VTE incidence rate in BC patients is anticipated to be lower after 2010 because the National Institute for Health and Clinical Excellence (NICE) has produced guidelines back in 2010 recommending extending thromboprophylaxis for pelvic surgery including cystectomy for up to 28 days instead of 14 days post-surgery (NICE, 2010).

As expected, the rates of VTE varied greatly among patients with BC according to the type of treatments, stages and co-morbidities. This analysis demonstrated that there was a significant association of VTE with BC treatment, metastatic stage and co-morbidities (Table 10).

Transurethral resection of bladder tumour is carried out for diagnostic and treatment purposes and is considered a minimally invasive procedure and has not identified in the literature as a risk for VTE in BC patients, or indeed the current study. Patients who underwent radical cystectomy were significantly more likely to develop VTE compared with patients who received chemotherapy only.

When the analysis was adjusted for other risk factors, such as the second type of cancer, comorbidities without second cancer, stage and treatments (Chapter 4, table15), there was no significant association between chemotherapy and VTE in BC patients. However, patients who had both

cystectomy and chemotherapy appear to carry the highest risk of VTE, which is greater than those who underwent cystectomy only.

There were no significant differences between the confounders and risk for VTE after splitting the data of UHCW and QEHB and analyzing them separately, and chemotherapy had no significant association after the adjusted analysis.

The current study found that radical cystectomy increases VTE risk which similar to the findings of previous studies (Dyer *et al.*, 2013b; Ording *et al.*, 2016b). For this reason, health institutions follow the NICE guidelines (2018) to provide pharmacological and non-pharmacological thromboprophylaxis for patients who have undergone radical cystectomy (NICE, 2018). Patients who have had both chemotherapy and cystectomy had the highest association with VTE. As with previous studies, this study found that having metastatic disease led to increased VTE rates (Ording *et al.*, 2016a).

In this VTE-BC study, multivariable logistic regression was applied to explore the association of VTE with comorbidities without the second type of cancer, second cancer, treatments and stages (Table 15). After splitting the comorbidities into comorbidities without second cancer, the adjusted analysis revealed that the co-morbidities without second cancer had no significant association with VTE. Similarly, Ording et al. (2016) found that the comorbidities do not increase VTE rate (Ording *et al.*, 2016a). However, the adjusted analysis revealed that second cancer had a high risk of VTE.

Accordingly, for BC patients who undergo cystectomy with or without chemotherapy, and who have stage IV and/or second cancer, HCPs responsible for their care need to consider this risk. This implies (the need for) thromboprophylaxis, as well as informing their patients clearly about VTE and the risk of developing it.

There was no strong association between the chemotherapy and VTE, especially after adjusted analysis, while chemotherapy had no significant association with VTE. There was a strong association with VTE only when a patient had cystectomy plus chemotherapy (adjuvant and/or neo-adjuvant). Thus, NICE guidelines (2018) have not recommended thromboprophylaxis for ambulatory cancer patients who receive systemic chemotherapy. Systemic

chemotherapy in BC needs further investigation and studies to specify the risk for VTE, since there are studies revealed that the chemotherapy may increase VTE in cancer patients. Schomburg et al (2018), for instance, found that neoadjuvant chemotherapy increases subclinical DVT in BC patients (Schomburg *et al.*, 2018).

Around 55% of VTE events occur within the first six months post-cystectomy. This may be due to the effect of surgery or chemotherapy. Two studies confirmed that the VTE risk remains high for six months or more after cystectomy (Brennan *et al.*, 2018; Khafagy *et al.*, 2006). Thus, surveillance strategy and awareness around VTE may be required for more than six months post-cystectomy, and patients might benefit from extending the postoperative thromboprophylactic measures, especially for those who receive systemic adjuvant chemotherapy.

Finally, there were insufficient data available at QEHB and UHCW regarding specific patient characteristics such as weight, body mass index, smoking, or activity level to measure their influence in developing of VTE. The results of Phase II of the VTE-BC study identified which group of BC patients are at higher risk of VTE and the need for awareness around VTE.

4.5. Conclusion

Our analysis revealed that cystectomy, metastatic stage and second cancer type have a strong association with VTE in BC patients. Systemic chemotherapy requires further investigation and research to confirm the requirement for thromboprophylaxis in BC patients. BC patients who have undergone radical cystectomy need long duration (six months or more post-cystectomy) of surveillance strategy for VTE and increased awareness around VTE, and patients might benefit from extending of thromboprophylactic measures postoperatively. The current study and results could support the NHS England and National VTE Prevention Program in providing updated data and information regarding VTE incidences and risk factors.

5. Findings and discussion of Phase II

5.1. Chapter outline

The findings of the qualitative component of VTE-BC, Phase II, are presented and discussed in this chapter. Major themes and related subthemes were elicited from the interviews of bladder cancer (BC) patients and healthcare professionals (HCPs), the methods for which is explained in Chapter 3.

5.2. Introduction

As outlined in Chapter 2, cancer-associated thrombosis (CAT) is known to be a serious and potentially life-threatening condition and the leading cause of mortality and morbidity in cancer patients (Heit *et al.*, 2000). The scoping literature review in Chapter 3 revealed that there were no qualitative studies exploring BC patients' understanding of VTE. To this end, a qualitative approach was employed to examine this aspect of care. The interviews sought to examine how communication happen around venous thromboembolism (VTE) and BC patients' understanding of VTE. Interviews also sought to explore gaps in patient education that hinder engagement with VTE prophylaxis. Patients and HCPs were free to introduce and elaborate on any other information that they felt was relevant, and on any recommendations, to improve communication around VTE.

A thematic analysis approach was applied; the steps of the analysis are discussed in Chapter 3. In this chapter, patients' understanding of cancer-associated thrombosis (CAT) from their experience of cancer pathway and HCPs' perspectives of CAT along the BC care continuum were analysed.

5.3. Stating the case

Patients with BC have a high risk of developing VTE, and the risk may increase with risk factors such as cystectomy and metastatic stage (Tikkinen *et al.*, 2017; Tully, 2016; Zareba *et al.*, 2018). These patients need to be aware of VTE and its related risk factors. Moreover, they need to understand how they can prevent VTE from developing, and how they can diagnose it themselves to save their lives (Benelhaj *et al.*, 2018). Previous studies have shown that increasing patients' education about VTE leads to improved compliance with medical instructions, and improves adherence to treatment (Juthani *et al.*, 2018).

Education around VTE is assisting learning or gaining knowledge of VTE, some strategies that may prevent VTE and skills in picking up the signs and symptoms of VTE. The most common educational methods in clinical interactions include brief teaching, discussion and encouraging self-learning through information giving. Patients' experiences are an education in themselves. Effective VTE education remains elusive as little research has been done to determine what information patients must know about VTE, and how such information can be provided most effectively (Juthani *et al.*, 2018).

Effective education around CAT is important for preventing and treating CAT. However, in this study it is evident that venous thromboembolism as a complication of cancer is not a priority for HCPs and patients and is not addressed as should be. Patients in this study were overwhelmed with their cancer; in this regard, HCPs and patients are more concerned about cancer than VTE. Bladder cancer diagnosis brings a range of emotions including fear, anxiety, worry and depression, which in turn affect patients' understanding of VTE. Improving communicating about VTE between HCPs and patients is required after addressing the gaps and issues that may affect an understanding of VTE. The findings from interviews with all participants are presented in detail and discussed below.

5.4. Findings from Interviews

5.4.1. Participant characteristics

Patient group: Patients with muscle-invasive BC (at higher risk of VTE) who have undergone a cystectomy and/or received systemic chemotherapy (n=18) were represented in this qualitative study. They were advised that the study involved seeking their thoughts and understanding of VTE, and their experiences of how VTE is communicated, as well as what they have been informed about cancer-associated thrombosis (CAT) or VTE in the BC context. Five of the 18 patients had metastatic BC and four out of 18 patients had experienced a VTE. BC patients with non-muscle-invasive BC (at lower risk of VTE) were not represented (Table 17).

Caregivers were permitted to support the patients by taking an active part in the discussions during the interview should the patient agree. Thirteen patient's caregivers or 'significant others' joined the BC patients for the interviews. All patients who had undergone a cystectomy received anti-clotting injections during the post-operative period for 28 days.

Healthcare professionals' group: Thirteen HCPs were recruited for interviews; four clinical nurse specialists (CNS), five urologists (urology surgeons) and four clinical oncologists (chemotherapy and radiotherapy specialists). Healthcare professionals were advised that the study involved seeking their thoughts and experiences about "communication of VTE" and how they informed their BC patients about CAT or VTE in the BC context.

Table 16: Patient characteristics

Code	Age	Sex	Date of Diagnosis	Trust	Ethnicity	PS	stage	DVT PE	CT	Cyst
P001	56	F	2017	UHCW	White	0-1	MI	-------	No	Yes
P002	67	M	2017	UHCW	White	0	Met	DVT +PE	Yes	Yes
P003	72	M	2013	UHCW	White	1	MI	PE	No	Yes
P004	46	F	2019	QEHB	White	0	MI	-----	No	Yes
P005	56	F	2009	QEHB	White	0	MI	----	No	Yes
P006	62	M	2019	QEHB	White	1	MI	---	No	Yes
P007	57	M	2019	QEHB	White	0	MI	----	Yes	Yes
P008	60	M	2019	UHCW	White	1	MI	PE	Yes	Yes
P009	63	F	2017	QEHB	White	1	MI	------	No	Yes
P0010	57	M	2017	UHCW	White	1	MI	---	No	Yes
P0011	77	M	2015	UHCW	White	1	MI	---	No	Yes
P0012	84	F	2018	UHCW	White	1	MI	---	No	Yes
P0013	74	F	2016	UHCW	White	1	MI	DVT	No	Yes
P0014	--	F	2019	UHCW	White	1	MI	---	No	Yes
P0015	81	M	2018	UHCW	White	1	Met	---	No	Yes
P0016	78	M	2018	UHCW	White	1	Met	---	Yes	Yes
P0017	70	F	2018	QEHB	White	1	Met	---	No	Yes
P0018	34	M	2017	QEHB	White	1	Met	---	No	Yes

M-Male, F-Female, MI-Muscle invasive, Met-Metastatic, DVT-Deep vein thrombosis, PE-Pulmonary embolism, QEHB-Queen Elizabeth Hospital Birmingham, UHCW-University Hospital Coventry and Warwickshire

5.4.2. Findings from qualitative analysis

Codes, categories, subthemes and major themes were elicited from the data (Figure 21 and 22). Three major themes, namely 'All about the cancer', 'A labyrinthine in process', and 'Improving the poor deal' describe the communication around VTE and patients' understanding of VTE.

The analytic phases undertaken to identify these themes are outlined below (Figure 21) and the findings are presented in summary form (Figure 22). The themes are illustrated by patient quotes and have been selected to illustrate the findings.

Figure 22: Steps leading to main themes

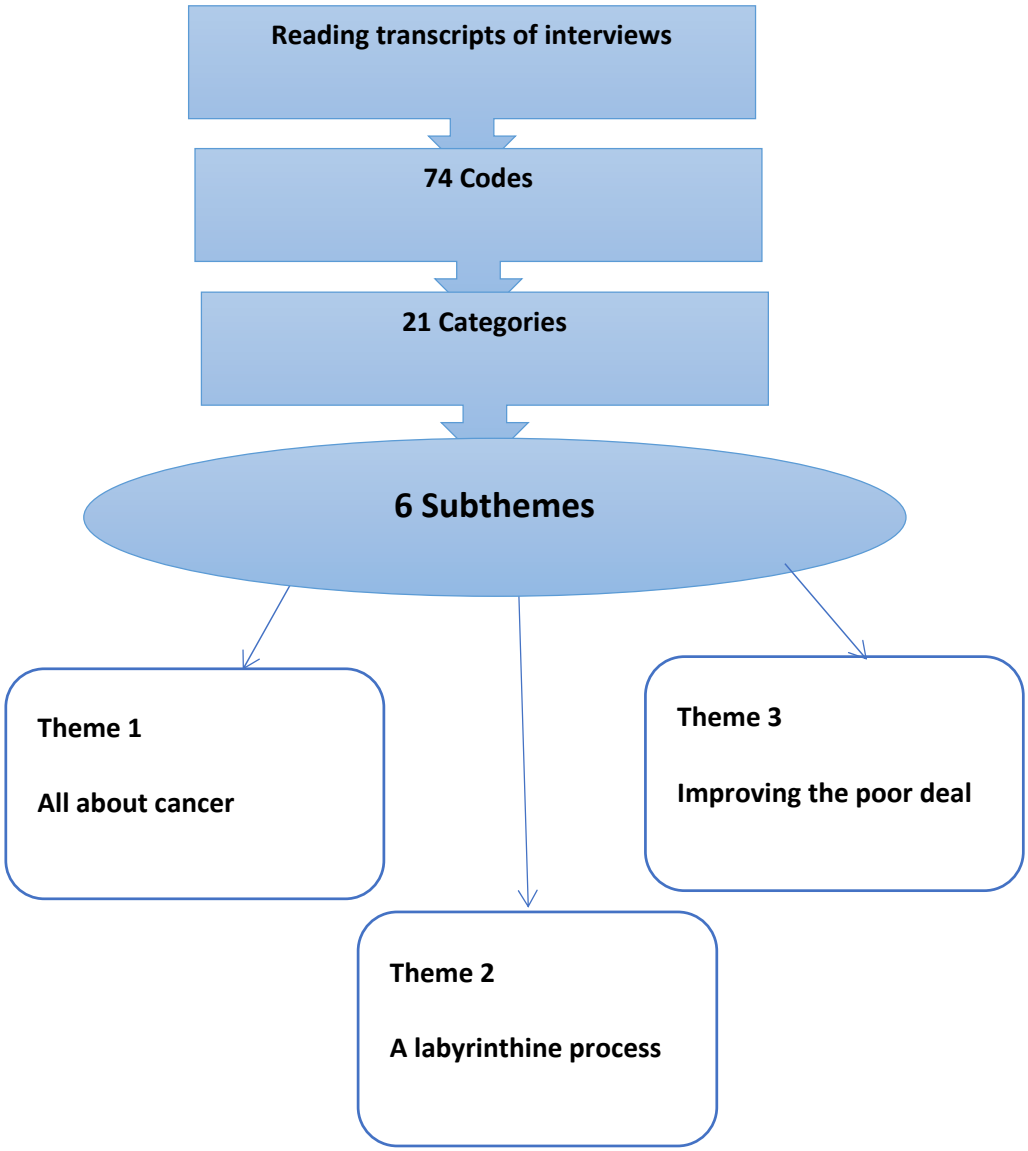
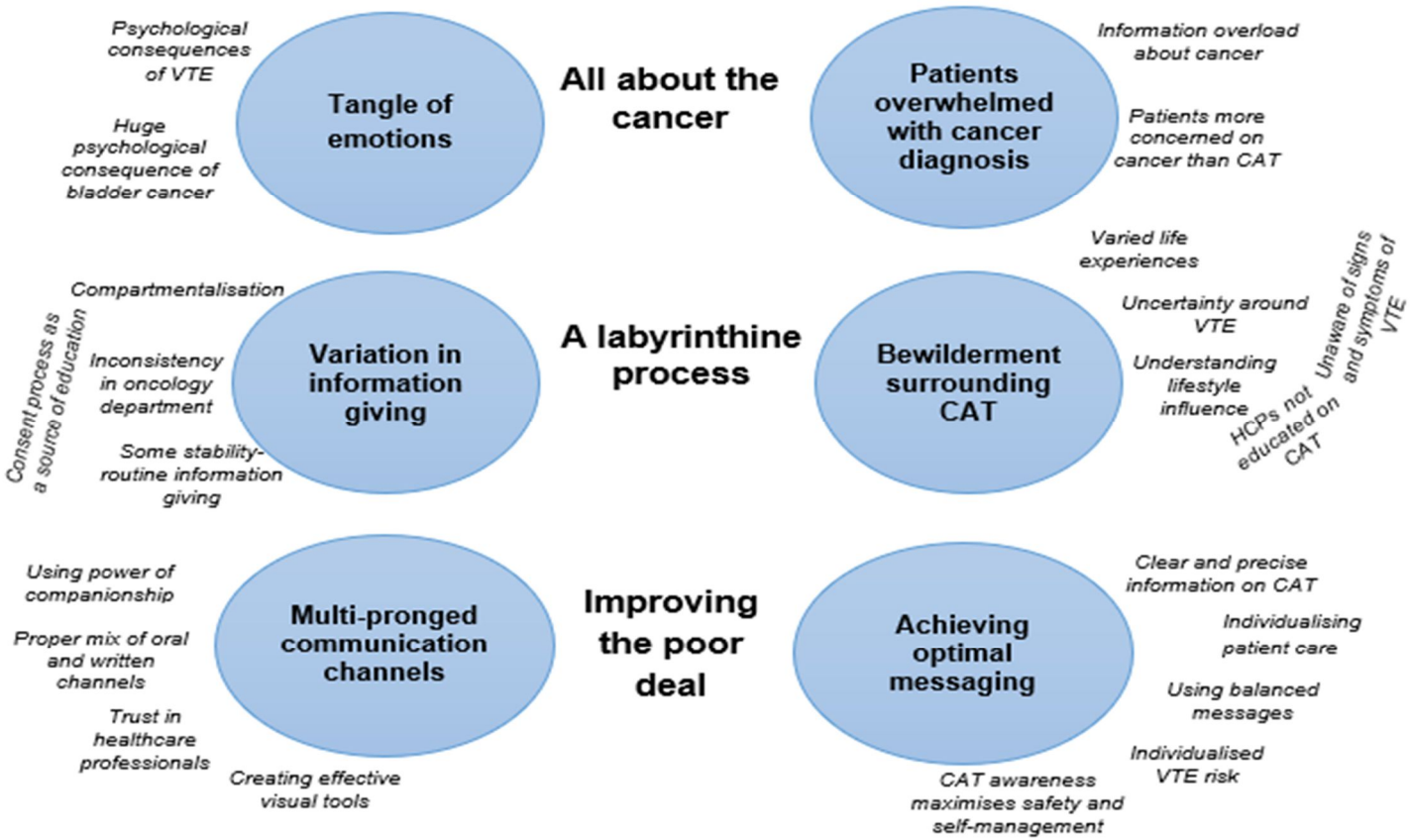


Figure 23: Categories, subthemes and main themes



Each theme with its related subthemes and categories is presented in the following sections:

Theme 1: 'All about cancer'

Bladder cancer is a life-threatening disease, which requires a number of consultations, interventions, investigations and treatments. There is an abundance of information about cancer that needs to be understood by patients. In addition, cancer diagnosis brings with it complex feelings, which may make affect a patient ability to notice, understand and remember information on VTE when facing difficulties.

Receiving a cancer diagnosis is scary and may cause great shock accompanied by psychological distress. Patients may experience a flood of emotions and feel overwhelmed due to the large amount of information transmitted via the cancer management pathway. Furthermore, the burden of cancer on patients leads to a decrease in focus and a reduced ability to absorb information about VTE. Moreover, HCPs focus more on cancer investigation and treatments.

Subtheme 1: Patients overwhelmed with the cancer diagnosis

Bladder cancer patients were generally overwhelmed with their cancer diagnosis and felt anxious, fearful and confused. The daughter of one of the patients (P009) confirmed that her mum was overwhelmed with cancer and therefore did not consider blood clots:

"She was overwhelmed by cancer and didn't worry about anything else!"
RE009

Patient (P009) received too much information regarding her cancer disease and an overload of information, which made her struggle to focus on information about blood clots. This was the case with most patients that were interviewed in this study. Also, patients emphasised cancer more than other health problems during their treatment journey.

Patients more concerned about cancer than CAT: Patients talked about their cancer diagnosis, investigations, treatments, and follow up appointment in such a way that it was clear that the patients were more concerned about cancer and its treatment.

"I was more concerned about the bladder cancer than I was the blood clots so it was just part of the process as far as I could see… yes, there were too many other emotions going on to focus on one particular aspect of it… it was more the cancer risk than thrombosis risk!" P014

Bladder cancer patients were clearly preoccupied with the cancer and thus they faced 'difficult to hear' information about blood clots during their appointment with HCPs. They were absorbed by cancer and its treatments; therefore, BC patients may consider blood clots as a small problem, and the blood clots were not their main concern:

"Mmm… but there are so many other things going on in your mind you may not you know… that was probably the least of the worries at the time… so I don't recall it though… I don't recall it" P017

Like patients' answers, HCPs also noticed that the cancer and related treatments were the priority for most patients. Neither had they, as HCPs, been sufficiently attentive to the blood clots. Patients focused more on their treatment, as HCPs noticed:

"The experience I've had with you know patients when we've talked about blood clots, they are more focussed on having their cancer treated…" HC011

"They are primarily focussed on cancer, and they want to you know get to the treatment and put it behind them as best as they can so most people would listen to that and take the advice… occasionally some people are alarmed but most people are too focussed on cancer." HC012

"You've told them they've got cancer… the whole DVT thing is I think quite a small part of their… almost once you tell someone they've got cancer they… they don't hear much else until you've sorted that out… mmm… yeah I don't think it impacts them any worse than what they've already heard that day!" HC008

Patients also focused on their changed lives and their survival since the cancer diagnosis; however, they did not realise that the blood clots could affect their life.

Oncologists were the ones that noted that BC patients are more concerned about cancer-related treatment and how long they will live, rather than VTE:

"They tend to be more interested in… err… in what survival would be or how much… how likely they are to respond to treatment and that sort of thing…" HC009

"The feelings they would have regarding that probably wouldn't be as strong to what the life expectancy questions that are going through their mind do you see and treatment options…" HC011

Clots are therefore not the priority for patients in the context of cancer. Patients are more interested in receiving information on BC and related treatments.

Information overload about cancer: Patients with BC experienced a high burden of cancer information at all stages of the cancer care continuum- diagnosis, investigations, treatments, treatment-related effects and self-care demands. They were therefore struggling to focus on VTE and had difficulties recalling any information provided on VTE (whether this was given before or after treatment). Patients felt that they received too much verbal information during physical encounters with HCPs e.g. at a clinic, and too many documents ('other' communication encounters) about cancer to read. This stopped them from being able to pay full attention to any VTE information.

"Well like I say I don't remember much about it. I remember the doctor telling me there's a chance (of VTE) when he was explaining the rest of the surgery…but then my mind blanked out, and I didn't take much more in, and I don't remember them telling me on the ward much about the blood clots." P001

"No, it was like an information overload on bladder cancer that's why (my mind)…Err… no going back to it as I say we had an information overload… we had that much information leaflets… verbal…" P007

Patients' companions also did not wish to overload the patients, feeling that the overload of information on cancer would affect their loved ones in a negative way:

"I didn't want to overload him with information…he was pretty depressed, and you can't give too much information to a patient at that stage!" RE008

Some patients did not wish to ‘exhaust themselves’ by receiving a large amount of extra information e.g. on blood clots.

> *“I was aware that there was a risk of blood clotting, but I guess with everything else going on it wasn’t top of the ones to absorb because he said if you inject yourself daily that would reduce the blood clots, so that was good enough for me, I didn’t really look at it any more than that!” P014*

The wife of one of the participants who accompanied her husband during treatment and to the interview mentioned that it was challenging for non-medical people to receive and understand a large amount of medical information, owing to the amount of information and technical language:

> *“It's very difficult to… when you're just an ordinary person like not medical… it's very difficult to take all the information in you know it's put in a way that you are supposed to be able to…” RE002*

Information overload on cancer treatment and side-effects may be one cause of patients being overwhelmed, which can lead to difficulty in recalling and understanding information on other complications, including VTE.

Subtheme 2: Tangle of emotions

A cancer diagnosis brought about different emotions, e.g. fear, anger and sadness, as a result of which patients may find it difficult to notice, understand and remember the information on VTE. Patients may feel anxious/scared and depressed after receiving bad news or because of uncertainty regarding the future. Bladder cancer patients must manage their emotions after their cancer diagnosis, during investigations and treatments.

Psychological consequences of having bladder cancer: As already pointed out in subtheme 1, some patients expressed the view that they were depressed and worried about cancer and its related treatment; hence, some of them did not focus on blood clots, and they could not remember the information regarding blood clots.

Bladder cancer overshadowed the importance of blood clots, and this diagnosis made the patients less concerned about other problems – even life-threatening problems:

"Well I concentrated more on cancer….on trying to get rid of the cancer you know than anything else… that was like the forefront of me thoughts…I want to get this cancer out me body you know that sort of thing…like rather than think about the side-effects." P006

Patients and HCPs confirmed that BC and its related treatments can aggravate feelings of anxiety. After a diagnosis of BC, most patients express a range of feelings, including fear, anxiety and depression. This is normal.

"Possibly I mean you know having cancer is an anxiety driven emotion, anyway, isn't it?" HC002

"I was worried (about bladder cancer), but I was more worried about the surgery!" P001

Bladder cancer patients commented that cancer was the main source of their worry, more so than blood clots. One of the patients stated that he was worried about blood clots, but more worried about cancer:

"…you know so… in that way it's not more… it's not… it is worrying but not like you would if you had the cancer." P009

"Yeah, your minds always on the bigger things which is the cancer isn't it!" P018

Anxiety is influenced by certain triggers, e.g. when patients visit their doctors for any problems, taking certain treatment, for instance, injections. Their worry is heightened:

"Most of them think 'oh God I've got to inject' so it's scary… it's the thought of giving self-injection." HC003

"Yes, anxious but I think I was more anxious about the actual surgery, and everything connected with that… you just take your chances, don't you?!" P010

"The trouble is whenever anyone comes up to see a doctor their naturally anxious and worried" HC011

Similarly, one of the oncologists mentioned that discussing the side effects of chemotherapy makes the patients anxious. The risk of VTE should be part of a holistic needs assessment for cancer patients. It is difficult to confirm if communication around blood clots, as a single entity, increases anxiety in patients:

> *"We talk about chemotherapy, in general it is enough to make the person anxious, OK, so probably everybody would dread to go through the side-effects of the treatment… I don't mention specifically about blood clots." HC010*

All healthcare professionals stated that the patients can also feel anxious/scared if they become aware of certain risk(s) without having been pre-warned or without having considered how to deal with it. Patients should be aware on the problem to prevent or manage:

> *"Well, I think if you tell them there's an increased risk and don't do anything about it then yes, I think it would increase their anxiousness or their anxiety." HC007*

One of the ways in which the staff manage anxiety among BC patients is through increasing patients' awareness/knowledge about the treatment they take to empower the patient, ultimately for self-management if possible:

> *"We give them a lot of instruction before they go home, I know we've talked about getting an information pack." HC003*

The content and context of communication between HCPs and patients can often generate challenging and difficult emotions. However more than this, BC patients were on an 'emotional rollercoaster', often a normal reaction after being diagnosed with BC. Diagnosis of BC brings together a mass of confusedly interlaced feelings about cancer, investigations, treatments and complications, initially with less emotion toward blood clots. However, the psychological implications of VTE may receive less attention.

Psychological consequences of VTE: The emotional reactions of BC patients on blood clots were investigated during interviews and the diagnosis of VTE can be shocking. Patients reported depression and anxiety as a result of the VTE:

"…became anxious" P003

"I was really shocked… depressed" P008

"Well, it (blood clot) just makes you feel wary that it's the possibility that could happen" P015

As discussed in the category above, patients with BC feel many different emotions, including anxiety, depression and distress. Blood clots could increase these psychological issues in those patients affected.

Patients who had blood clots did not receive enough information about VTE before it happen, and what measures could be taken in advance to prevent developing VTE. They were not informed about the risk of BC and related treatments; nor did they expect that they would have a blood clot, and they did not therefore adopt any specific precautions.

One patient (P008) had a blood clot, post chemotherapy, in his lung, pulmonary embolism (PE). This PE was associated with shortness of breath, and initially diagnosed wrongly as a chest infection, but the computerised tomography (CT) scan accidentally revealed the presence of PE. He was frustrated with the process:

"Yeah, I know about blood clots yeah, but I didn't expect to get them on the chemotherapy!... Before chemotherapy, they told us risks, but they didn't mention blood clots" P008

His wife, who accompanied the patient, described how they had an unpleasant experience and were shocked when her husband was admitted to hospital, and diagnosed wrongly with a chest infection in the beginning. The PE in this patient was diagnosed because his wife had a medical background, and she insisted on a scan being done for his chest. She explained in the interview:

"Yeah, I have a nursing background he became very ill… extremely ill and we were told he had a chest infection… he was admitted to hospital and put on a nebuliser twice and there was no improvement and they wanted discharge him because they dehydrated him and he was retaining food and fluid and I said I would like a scan done on him!" RE008

However, the lack of awareness of blood clots in BC context led to delay in the diagnosis of PE. The patient stated:

"…they weren't going to do a scan, they were just going to discharge him without it, but I insisted that they did it and the registrar came back, and he said, you have multiple PEs in both lungs!" P008

According to this patient (P008), the knowledge of awareness of the patient's companion assisted in PE diagnosis and saved his life.

One of patients expressed that he was not satisfied because he did not know how to recognise blood clots. He understood that the information regarding signs and symptoms could enable him to diagnose blood clots early and save his life:

"Well perhaps a little more information on self-diagnosis… mmm… it's… if you don't know what you're feeling… what it might be… if you leave it… it might be too late so but if you know what to look for it could save your life!" P015

Regarding VTE education for patients, most patients felt that receiving information about blood clots could make them worried and scared:

"I am a worrier if you tell me anything… I'll go home and I'll think… oh my God I'm gonna get a blood clot." P004

"Well, I'd be a bit scared (of blood clots) … that would be scary" P005

Moreover, BC patients may feel sad and down if the risk of developing VTE is mentioned:

"You're sort of depressed a bit." P007

Interviews with patients revealed that many emotions were apparent with VTE diagnosis on top of the cancer – disappointment, frustration, depression, anger, and shock. The blood clot experience can bring negative emotions for patients, with a few patients reporting depression and several more reporting increased anxiety.

This was a strong patient-centred theme. The patients were overwhelmed, with their cancer diagnosis tangled up in emotions around cancer and lack of information around VTE. Patients were dissatisfied with the level of information they received.

Their understanding of patents around VTE will be explored in greater depth in Theme 2: A labyrinthine in process.

Theme 2: A labyrinthine process

Bladder cancer patients' awareness of VTE was explored carefully in the interviews. Patients generally had poor or limited information on VTE and its relationship with BC, they were confused about VTE. HCPs provided their patients with detailed information about BC and highlighted the most common side effects and risks anticipated by specific medical interventions e.g. surgery or chemotherapy.

However, the communication process around VTE between HCPs and BC patients varied, and not all patients received the same amount and quality of information or discussion about VTE.

Subtheme 3: Variation in in information giving

Bladder cancer patients needed to be treated in more than one department such as a urology department and an oncology department. HCPs in each department have their own approach regarding communication about VTE. HCPs in this study did not discuss the treatments and complications that may happen in other departments or with other specialities. Cancer care tends to be multidisciplinary, involving team meetings for every patient diagnosed with cancer, and each stage along the continuum is important.

Some stability - routine information giving: HCPs weighed up the risk of VTE for patients and informed them according to their individual risk factors.

In the urology department, nurses and urologists took a while to inform each BC patient about the risk factors and complications of the surgical (cystectomy) procedure. They explained the risk of clots as part of the routine information they provided (often a checklist) in their pre-surgical counselling to patients who had a cystectomy and generally explained how VTE can be prevented. Two nurses noted:

> *"…for the patients that are undergoing open surgery then I spend an hour… I'll have already met them in the consultant's clinic but I then spend an hour with them and whoever family members they want to bring with them to go through what it means for them and their family unit to go*

through cystectomy, and as part of that, I mention… mmm… leg exercises…risk of avoiding DVT." HC001

"Just depending on the surgery if they are coming for the pre-op counselling for major surgery which is either cystectomy or neo-bladder or partial cystectomy or urinary diversions or something like that… it's part of the information that we give them." HC004

Nurses usually reported the risk of VTE undergoing a cystectomy, more than one time in pre- and post-operative period and during administering anticoagulant injections. It is probable that patients have a better understanding when they receive information regarding VTE reinforced by HCPs during different visits.

The communication about VTE between HCPs and patients could save patients' lives. Effective communication of VTE encourages patients to follow medical instructions and adhere to thromboprophylactic measures assumed to be important by HCPs:

"I do mention that they will have to have Clexane injections and that they'd be expected to do that at home… the only information I give my patients is to say that they will need some blood thinning injections because of the risk of thrombosis and basically that's it. I don't go into any great detail." HC003

Furthermore, patients who had surgery received blood clot awareness again in the post-operative period, when giving them anti-clotting injections and helping patients with anti-clotting socks, all by nurses. Patients recalled the information regarding the VTE risk during surgery due to mentioning it more than once:

"I think it was Mr [urologist] who mentioned blood clots and the nurses after the operation because you have to have those socks on don't you, they explained that was to help prevent them." P001

"I think maybe Mr [urologist] mentioned it… mmm… the anaesthetist before the operation mentioned it and probably the nurses on the ward as well… mmm… yeah so it was spoke about." P005

Thromboprophylactic treatments also are discussed routinely with patients who will undergo a cystectomy. The HCPs in this study talked about anticlotting injections and stockings:

"I only mention about thromboembolism risks in detail if I'm considering these patients for a radical cystectomy… cos there these risks are real… err… I'm sure they are real." HC005

"Yes, specifically when they're having surgery…a bladder removal operation and tell them about the measures that we take to prevent thromboembolism such as Heparin prophylaxis and compression stockings." HC007

"Only in as if as much they came for surgery, we would talk to them about perioperative thromboprophylaxis." HC013

The quotations above (HC005, HC007, HC013) indicate that urologists also explain VTE and thromboprophylaxis measures in terms of the type of surgery, and its risk of VTE.

Some HCPs commented that they routinely focused on providing lifestyle advice in face-to-face encounters which encourage patients to be active after cystectomy to prevent developing VTE. They advise their patients to use coping methods which can help them to deal with cancer and avoid developing VTE:

"The best they can do is to you know mobilise and that plays a role…so I think that there is only so much they can do." HC006

"If they maintain activity then the risk can be reduced but beyond that I don't give them any formal information it's just a short discussion… it's a short conversation about it." HC0010

In urology departments, HCPs only (tend to) inform their patients about VTE before and after a cystectomy. Urologists explained that the highest level of risk of developing VTE occurred within 30 days after cystectomy, and they provide the information on VTE within 30 days post-cystectomy. Urologists believe that patients do not need reminding about VTE during management and follow-up appointments after 30 days post-cystectomy, because the peak of VTE incidence is before this.

"All the evidence which is there so far indicates that the highest risk is within 30 days of surgery." HC005

However, VTE risk may still be higher than normal up to one-year post-cystectomy; thus, HCPs may need to remind their BC patients about VTE during long and short follow up. After cystectomy and during follow up of the patients up to one year, HCPs did not check if their patients remembered the instructions regarding VTE or not. HCPs also stated that they were unsure if reminding their patients about VTE would benefit the patient or not:

"I don't know is the honest answer… I hope they do but I don't know there's no… mmm… I've never checked their understanding… mmm… you know days, weeks, months down the line I like to think that… mmm… when I consent them that they understand at the time and they're able to retain the information. I don't think they necessarily need to retain the information you know forever…" HC007

HCPs expected that the risk for VTE in BC patients, who underwent cystectomy, to be low after 30 days post. Therefore, HCPs did not remind their patients on VTE after 30 days post-cystectomy.

There is routine provision of VTE information for patients treated with cystectomy from nurses and urologists at urology departments. Patients know that surgery is a main risk for VTE. Only patients having a cystectomy however received anti-clotting measures, as well as advice on VTE. This routine information giving is not the same in the oncology (cancer specialists in chemotherapy and radiotherapy) department.

Inconsistency of CAT information in oncology department: Unlike the surgical nurses and surgeons, the interviews with HCPs working in oncology departments and giving systemic chemotherapy for patients, demonstrated that HCPs only infrequently inform their patients about blood clots. Not all medical oncologists and chemotherapy nurses discussed blood clots with their patients as one of the systemic chemotherapy risk factors, possibly because of their incomplete understanding of the contemporary incidence of VTE.

> *"No, I don't actually… I don't… I don't talk to them about it (blood clot)… because all… most of the cancers that I treat have that… mmm… and it's not really a standard thing that we do maybe we should do that but you know it's not a standard thing." HC009*

Most of the medical oncologists did not focus on blood clots as a potential adverse effect of chemotherapy. The oncologists revealed that they informed their patients before chemotherapy about treatment and complications, but they did not focus on blood clots because they did not consider chemotherapy as a high-risk factor. This is interesting, as the surgeons indicated that their oncology colleagues would indeed impart some information on risk of VTE:

> *"Everybody would dread to go through the side-effects of chemotherapy… I don't mention specifically about blood clots" HC010*

As with oncologists, nurses in the oncology department explained to their patients the risks and complications of systemic chemotherapy. Nurses here did not focus specifically on blood clot risk factors while communicating the side effects of systemic chemotherapy. However, they highlighted other complications such as neutropenic fever:

> *"The thing is it's about getting key risks over so if you've given patient chemotherapy your number one key risk that you are worrying about is neutropenic sepsis so you" HC002*

However, two medical oncologists recognised the potential risk of VTE associated with receiving platinum-based systemic chemotherapy, and this is the way they informed their patients who received specifically platinum-based chemotherapy about VTE risk:

"Of course, many times I see patients in the palliative setting and again Platinum could be used in those scenarios… or… and always they informed the risk of blood clots as a potential complication that can happen." HC0011

"Yes, I mean platinum-based chemotherapy is thrombogenic and I would mention it to them, and it is mentioned in all of the leaflets I give them for the chemotherapy" HC01

Patients who received systemic chemotherapy did not recall that HCPs had informed them about the risk of chemotherapy:

"I don't know…I can't remember saying about a clotting risk with chemotherapy." P016

"No, I don't recall it before chemo… although they may've done then…I didn't really remember" P017

The communication around blood clots with patients who received chemotherapy therefore was not routinely delivered, and HCPs did not consider or know that systemic chemotherapy is a risk factor for blood clots. Patients who received systemic chemotherapy still need more information and discussion regarding VTE.

There was inconsistent reinforcement of information regarding blood clots with patients between surgical and oncology departments which may lead to the labyrinth in understanding of CAT and thus taking any preventive measures.

Consent process as a source of education: In the consent form that patients must sign before operation or chemotherapy, there is much information on the side effects of surgery or chemotherapy. Patients had difficulties in understanding all information during the consent session. Mentioning blood clots during consent to treatment is arguably not sufficient 'education' around blood clots. Awareness of VTE is not just a box ticking exercise; patients need verbal discussion around blood clots along the cancer pathway, in addition to the consent form:

"Well there's so much you go through and so much you know instruction manuals and all the side-effects… it's really difficult to keep track. So many

things they go through there must be I mean there must be 20 or 30 things on that list they go through." P002.

Correspondingly, HCPs in oncology department stated that blood clots might only be mentioned during consenting and informing on chemotherapy as one of the chemotherapy complications:

"…it's always myself the number of risks are outlined to the patients, and the risk of you know PE is one of the risks that are very… very stringently outlined to the patient and this is especially stringently outlined if the patient is going on to chemotherapy because obviously while there is a risk in just having cancer itself, it obviously carries on when you start giving chemotherapy." HC002

One oncologist stated that he his patients had been informed about blood clots before receiving chemotherapy; however, he did not speak or focus on blood clots in the conversation with the patient:

"When I do consent for chemotherapy… I consent people for venous thromboembolism, but I don't… I don't speak to all patients about thromboembolism as a specific thing" HC009

Paper consent forms may thus be inefficient in providing enough information on blood clots. The consent process was found to be an ineffective source of 'education' for patients, although the HCPs may have thought so.

Individualising patient care: HCPs in urology and oncology departments did not inform every BC patient on VTE. They selected specific group of patients to communicate blood clot information depending on the type of intervention and the risk of that intervention.

HCPs in urology departments believed that non-muscle invasive patients are not at high risk for blood clots and do not need a major operation (cystectomy). Moreover, they do not consider transurethral resection of bladder tumour (TURBT) a risk factor for VTE. Hence, they do not discuss VTE with patients requiring only TURBT:

"Ok I probably don't talk about that for the non-muscle invasive group unless somebody's at risk cos I did have somebody that had a DVT (deep vein thrombosis) prior to their diagnostic VTE so they were on VTE therapy while they were undergoing BCG with me so we had to work around that…" HC001

"As far as the TURBT's are concerned or the diagnostics aspects of this operation is concerned it's minimally invasive… we actually do not go through any specific consents other than mentioning that these patients are at risk of DVT…" HC005

Similarly, for intra-bladder (intravesical) chemotherapy, HCPs believe that giving intravesical chemotherapy does not bear high risk for VTE and there was no evidence to confirm that intravesical chemotherapy increases the risk of developing VTE. Thus, they do not discuss VTE with BC patients who are treated by intravesical chemotherapy:

"We give Mitomycin to the bladder intravesical, but we don't tend to discuss...it's not really… from what I can remember on the side-effects it's not really one of the major side-effects with intravesical." HC004

HCPs considered that major surgery increased risk of blood clots; thus, HCPs educated their patients having a cystectomy on VTE.

"I personally would tell them if they were coming in for major surgery…" HC001

"No, we don't choose which type of patients other than if they are having major surgery" HC004

Patient selection of whom to discuss VTE with or with whom not to do so did not depend on patient characteristics (weight, mobility, smoking, family history, etc.), but mainly on the type of treatment and related risk of VTE:

"We don't choose whether they're male or female or anything like that it's just that if they have that surgery then yes, we'll go through it with them." HC004

Medical oncologists did not routinely report non-cancer related VTE risk factors (smoking, vascular problems). They expressed that the oncologists should look for the patients' related risk factor such as smoking, and they should focus on discussing high VTE risk with their patients in future. They felt that is better to individualise risk factors of VTE:

> *"I think perhaps we should emphasise to patients who have inherent risk factors of blood clots like smoking history or some vascular problems, or previous history of spotting this thromboembolic phenomenon. I don't particularly do that all the time, but I do say that in planning. I don't particularly say that well if there is a risk and you are at a greater risk; I don't particularly say that." HC010*

Thus, by carrying out interviews, the researcher awakened the HCPs interest to discuss awareness of VTE including blood clots, risk factors for developing blood clots, thromboprophylaxis measures and the importance of the communication process to minimise the risk of VTE. Additionally, the researcher awakened patients' attention to have more information on VTE and the preventive measures.

Individualising patient information is key to good patient care. However, this was not always evident throughout the stages of the patient pathway.

Compartmentalisation: As previously mentioned, HCPs within each department bear responsibility only on the treatments given by them to ensure a good healthcare encounter. For example, the nurses and urologists in the urology department explain the risk of blood clots from having surgery but they do not discuss the risk of blood clots from having chemotherapy.

The HCPs in the urology department considered that they are not responsible for providing information on complications from having systemic chemotherapy. They expected that the CNS and oncologists in the oncology department describe to their patients that the systemic chemotherapy may increase the risk blood clots:

> *"We're the ones supporting them for their surgery so we will discuss the risks of surgery but when they have chemotherapy they are seen by the oncologist and the oncologist has a specialist… err… clinical nurse service attached to them and also we assume that the chemotherapy*

department… should go through all that with the patients… hopefully!" HC004

"I wouldn't necessarily inform them about risks of clots with chemotherapy. I would assume that that's done by the oncologist who are the chemotherapy specialists." HC007

There were also concerns voiced from some HCPs that they felt they were not sufficiently qualified to give information:

"I don't because I don't see the chemo they go from here and they're referred then to oncology and the nurses there… I'm quite sure… would talk to them about it… mmm… I don't… cos they will often ask about the chemotherapy itself and I don't know enough about the chemotherapy to go to tell them so I would refer them then onto their oncology nurse if they're going for chemotherapy." HC003

"I don't think we are qualified to do that because we're not chemo…we are not the one's administering the chemotherapy" HC004

Healthcare professionals in oncology departments believed that with regards to the awareness of the risk of cystectomy in developing VTE, the responsibility automatically fell to HCPs in the urology department, based on the assumption that oncologists were primarily responsible for the complication of chemotherapy.

"I don't do surgery, so I don't talk to them about that but certainly as the main parts of the discussion most of the patients are patients having chemotherapy so… mmm… definitely that's something that we talk about with the risk associated with those treatments you know." HC009

HCPs at each department tried not to deliver information that lay outside their expertise because they did not want to misinform their patients. They considered that they were only responsible of what type of treatment that they provide for their patients at their department. Although VTE risk may increase with providing more than one type of treatments, such as surgery with chemotherapy, they seem not take this point into consideration.

The responsibility for information provision when it came to CAT was unclear; there were some stable points of provision; nevertheless, overall, the communication process on VTE was inconsistent. One reason for this is that the HCPs may not be aware of CAT. Compartmentalisation with patients may cause some confusion in providing the information for patients and a labyrinthine in understanding of VTE.

Subtheme 4: Bewilderment surrounding VTE information

Patients with BC have incomplete and limited information regarding VTE. This confusion around VTE was developed due to some issues surrounding giving information about VTE.

Uncertainty around VTE: Interviews with BC patients revealed that most did not know much about blood clots:

"I don't know a lot about them, but they start in your leg" P007

"Mmm… not really I just assumed that it's… mmm… your blood becomes thicker" P011

Patients in general, had been given poor information on VTE during face-to-face encounters and via other sources (leaflets, internet etc.).

Some patients believed that they knew what blood clots were; however, they were still unclear:

"They spoke to me about blood clots…well, I presumed it would be something to do with the surgery, but I don't know what causes it… no!" P005

"To be honest I don't really know too much… I don't know how it forms… I don't know… I don't really know to be honest!" P018

A few patients could not recall any significant knowledge of blood clots, evident through the different ways in which patients described VTE, showing uncertainty around knowledge and awareness of VTE:

"So, they told me… I've never known what they did or how it comes." P002

"I'm not really sure what… what they are or what causes them to be honest with you!" P004

“I don’t remember anything significantly discussed about it!” P014

For some patients, there had been one year and more between the cancer diagnosis and interviews and the challenges in recall were evident:

“… I say it was a year ago so it’s hard to recall but I don’t remember anyone mentioning percentages or a greater risk or a lesser risk or anything like that it was just a risk.” P014

“You know you just have this treatment and there’s that much to take in that you can’t remember everything... He might’ve mentioned it but they mention that much stuff you… you know you just forget you can only absorb so much!” P016

Many patients knew that blood clots may lead to serious condition. However, few patients understood that blood clots formed in the legs could move to the lungs:

"Possibly start in your legs because of the non-movement… non-flowing of blood and the clotting up of the blood." P007

“Not a lot just that if you get one, they can travel up to your lung or brain and kill you that’s about it really… so I don’t know a lot about them!” P010

“(What do you know about blood clots?) …Well, if they reach your heart, is it or your lungs it will kill you!” P017

The informing patients about VTE was inconsistent and not all BC patients received the same amount and quality of information or discussion about VTE. Hence, patients' perceptions around VTE varied. Patients with BC in general had poor information about CAT.

Varied life experiences: Patients received information about blood clots from different input sources, physical encounters including HCPs, friends, relatives and ‘others’ including leaflets. Information about blood clots can come from virtually anywhere, such as media, personal experiences, other experience, expert opinions, and web pages.

Patients' life-related (not including cancer) experiences were highlighted. A few patients said that they themselves had received information about blood clots, or had received it from their family, with regard to long-haul air travel and age:

"Even just flying in an aeroplane, you can get a blood clot… my niece just got one coming back from abroad. it's just superficial" P002

"Everybody thinks of blood clots of going on a plane that's how I get blood clots… that's the way people think of blood clots…" P008

"You know about blood clots anyway; you know if you travel on a plane, and you have to be aware especially as you get older" P017

Some patients reported that they were informed by other people and their experiences with VTE (e.g. relatives, friends). In this case, patients' knowledge was based on what happened to others. These patients were not able to adequately explain VTE, what the risk factors were, and how they could be diagnosed. They only knew that a blood clot is a clot in the blood vessels. The following comments reflect what some patients knew about VTE:

"My ex-husband had one in his leg in the calf of his leg… it was a few years ago now, so that was the very first time that I'd ever heard about it properly yeah." P005

"There's a couple of friends of mine who have had blood clots, and they've been in the hospital like… mmm… you know having treatment like to try and thin them out… the clots out." P006

One patient (P012) mentioned that her son was diagnosed with VTE and she knew about VTE and related treatments. When she had BC, she experienced VTE as well, but she mentioned her condition, or the symptom were different:

"My son has recently had a thrombosis in his legs, so I know what treatment he had but 'touch wood' I haven't had any experience of it up until now!" P012

Although she knew about blood clots from her son, she did not know the risk of surgery of VTE. So the information from other experience would be incomplete.

Another main source of information regarding VTE is a previous diagnosis with VTE or cardiac problem. The following comments are examples of patients who had experience of blood clots. Two patients reported that they had had blood clot before they were diagnosed with BC, the patient said:

"I've had blood clots following a fracture to my left ankle" P011

"I had blood clots in 1996…" P013

A few patients mentioned that they had had cardiac problems before they were diagnosed with BC:

"Quite a high possibility I would've thought (of getting a clot) regarding my age and… mmm… and I had also… got systemic heart disease which I'd had before" P011

"Well, the heart people said due to the irregular heartbeat there was the possibility of stroke…due to a clot" P015

Patients with history of VTE (not cancer-related) remembered where the clots were found, how the clot are diagnosed, and the treatments to prevent blood clot:

"They did tell me where they were… one was in the lung and one was in the… but I never ever felt any in there cos they say they develop in the leg don't they normally…I've had no pain passing one or anything like that… I didn't know I had them… they found them when they did the X-rays!" P002

"I've had blood clots following a fracture to my left ankle and I didn't know I'd got them because I didn't have any pain, they just found it when they did a scan." P011

"I had blood clots in 1996…but since then I've been fine… it was only after having the operation. I was fine within two weeks after that developed clot." P013

Patients with cardiac problems were educated about blood clot in general, and they received anti-clotting drugs to prevent developing blood clot as patients

described. The following comments are examples of patients' knowledge regarding blood clot:

"I had a heart attack in 2007 and I'm always on a 75mg of Clopidogrel anyway, I've got a blood thinner there in the needle." P006

"I was having shortage of breath etc and… mmm… they diagnosed a heart murmur and they decided that I should have to go on… mmm… blood thinners for that condition……straight away… mmm… but in-between times I'm diagnosed with the cancer" P015

One of the patients (P003) had a pacemaker (a high risk for VTE), and he did not realise cancer and related treatment would increase the risk of developing blood clots further:

"I don't know nothing I've never even thought about it… never even… ever realised I could get blood clots! So, I'd like to add that I'm on these blood-thinning tablets it's because I've got the pacemaker" P003

Some patients experienced blood clots or someone around them had blood clots, but the majority of them had poor knowledge on the risk factors for developing blood clots. Not all BC patients realised that cancer itself could increases the risk of VTE and reported the following:

"I don't think anybody's…nobody's ever mentioned the risk of bladder cancer" P003

"I don't really know what causes them or anything like that I probably don't know that." P004

Most patients and their companion rely on the information conveyed to them by HCPs and it is possible that providing patients with adequate information not only permits informed decision making but also help in earlier diagnosis and improves coping of VTE. The patients who had a history of blood clots referred to their experiences as well as how they could protect themselves.

Understanding lifestyle influence: There are many risk factors for developing blood clots in BC patient, including, immobility, age, smoking, surgery and certain medications. Patients' understanding of blood clots risk in BC was explored carefully in this study. For non-cancer related risk factors, most of the patients were aware of

risk factors other than cancer and its related treatments (e.g. hospitalisation, old age, sedentary lifestyle, immobility):

"I think probably if you are older and sedentary lifestyle… mmm… you're more… probably more likely to develop a blood clot." P017

Some patients considered that smoking leads to increase the risk of developing blood clots; for this reason, they talked about stopping smoking:

"Yes, smoking yeah… yeah it was one of them yeah. And sedentary lifestyle...yeah…That's all I can remember actually you know like keep moving…." P006

"I yeah I don't smoke so… yeah… but yeah I know they say smoking and… smoking really is for everything I think!" P017

Some patients realised that the immobility and smoking increase the risk for VTE (non-cancer factors) and what they could do to protect themselves from blood clots. Thus, they expressed their willingness to stop smoking, keeping active and doing exercise in order to decrease the risk of developing blood clots which means. The patients also seemed to know how they could protect themselves against blood clots:

"…walking, exercising walking the dogs, at work I do between 8,000 and 12,000 just at work, so I think that the risk of blood clots in the next year is nothing… I've had no pains no aches…" P007
"Yes, when you're not moving around!" P011
"If you you're more active I'd say you're probably less likely." P017

Patients thought that some lifestyle or non-cancer factors could increase the risk for developing blood clots and they attempted to cope them.

Unaware of signs and symptoms of VTE: HCPs confirmed that informing patients on signs and symptoms of blood clots is very important. However, in interviews with HCPs, it appeared that most HCPs did not enlighten their patients about the early signs of blood clots and how to monitor themselves:

"I don't I must confess I don't tell them to look for signs of swelling in the leg as a routine… no I don't… because I concentrate mostly in the first four

weeks but no, I think that's a good point actually maybe I should tell them the signs… no I don't!" HC006

The vast majority of HCPs did not tell their patients about the signs and symptoms of blood clots, due to time limit during the consultation:

"That's a very good point not really we do not actually go in and say that if you get these (symptoms)… because time doesn't permit us to do that and secondly as we know that for the first month when the patients at their highest risk it's already covered by DVT prophylaxis." HC005

However, a few HCPs mentioned to their patients that VTE may lead to swelling and pain in the leg and shortness of breath when it moves to the lung:

"So, I talk about that and then shortness of breath which could be a symptom of disease recurrent… it could be all sorts of different things… mmm… so generally they're (patients) encouraged to report symptoms if there are problems… yeah." HC009

"I usually tell them the symptoms of breathlessness if they have it in the lungs but about of swelling and of pain and you know those kind of symptoms if they get a clot in the legs and that is all I tell them yeah…I tell them a few signs and symptoms for the chest as well as for the legs, but I don't go into too much detail no not in my routine practice." HC012

From a patient perspective, most confirmed that they were not informed about how to identify VTE and what the symptoms of VTE were. For instance, patients were unable to distinguish any clinical symptoms of DVT and PE. They frequently commented that they could not remember, or they stated that no one explained signs and symptoms of blood clots for them.

"Not that I remember no. I don't remember." P001

"No…I don't think anyone told me what the symptoms would be to self-diagnose a blood clot." P015

In some cases, patients tried to give the impression that they would have remembered the symptoms of blood clots, and they were keen to know how to finds clots. The patients reported the following:

"Yeah I mean obviously (better to know) yeah…keen to know." P004

A small number of patients understood the symptoms of blood clots in the leg, namely redness, swelling and pain. But only one of patients revealed that the shortness of breath could be a symptom of blood clot located in the lung (PE).

"I think if they told me it could get red and swollen, I'd have been watching out for it just in case, but I don't remember it." P001

"Shortness of breath that was in… that was in the… what I read… shortness of breath that was definitely one of the things" P005

Self-diagnosis and seeking treatment for blood clots may save patients' lives and prevent subsequent serious complications. HCPs relayed the importance of giving the information:

"…I think if they look out for the early warning signs then you can treat it." HC001

"To catch early signs… yes definitely to save their lives…" HC004

"Yes definitely…yeah so I think that would be a very good idea… so I presume if you catch the clot whilst it's in the leg and treat them before they get a PE then that's got to be good." HC008

"Yeah, I think the main thing is about symptom reporting, so if they get leg swelling they report it and then we investigate it properly so I think if we did it badly patients would have symptoms and not report them… mmm… and if that's deliberate that's fine but if that's because we haven't made it clear what symptoms to report and how to report them that's something that we could improve on." HC009

This seems to be a missed opportunity for HCPs to explain how the patient can look out for signs and symptoms of VTE. Detailed explanation of blood clots symptoms and how to report them to HCPs are very important for BC patients in order to look for early symptoms of blood clots and inform the HCPs as early as possible.

Limited information and recall, varied life experiences, not taking account of lifestyle and the consent process as a source of education all lead to the bewilderment

of patients. In summary, compartmentalisation in information giving and patient bewilderment about information on VTE and CAT illustrates the labyrinth in understanding.

Theme 3: Improving the poor deal

Findings above indicated that the BC patients had poor awareness about VTE, this was as a result of improper VTE education.

Subtheme 5: Achieving optimal messaging

Informing BC patients about blood clots may impact their outcome and may empower them to take the right decisions for their care and adhere to medical advice from their HCPs to prevent blood clots:

> *"Well, it's a 'carrot and stick' situation isn't it… if you haven't got the information you can't deal with it so first and foremost you must have the information and then you must be supported to understand it…" P008*

Thus, it is important to provide important information regarding VTE for patients to support them in preventing VTE.

Using balanced messages: Establishing a balance between warning messages and constructive messages was recommended by two HCPs. They wished to give some warning messages in a constructive manner:

> *"I think just to inform people how it is and what they can do to try and stop it from happening… that's what I would prefer…" P005*

> *"It depends on how everything's received but all additional information (on VTE) is good providing the patient can understand and receive really." HC011*

Patients believed that the blood clots risk message needs to be a factual message, and at the same time, a warning message. During physical encounters and other sources of information, both were welcomed:

> *"It's gotta be a balance you've gotta be in fear of it to understand it… to read… if you not frightened of it, you're not gonna read your leaflet you know if they paint a bright picture of… oh it's only a DVT it's only gonna kill ya… oh I'll read the leaflet, but if you say this can kill, so I think a*

mixture, don't be too upset, but it can happen, and it does happen, so I think to give it hard makes you read the leaflet and listen to the information more!" P007

"I think probably equal balance. I think you need to have like that initial like this what could happen this is fear" RE018

One patient mentioned that he needed the facts without adding any emotion as he believed the facts represent the reality:

"I think just the message… add fear to it I mean if you lay out the facts… the facts will speak for themselves there's no need to put a fear factor into it I just need to know the information!" P014

In striving to achieve optimal messaging, most HCPs and patients agreed that giving constructive-information and warning messages about blood clots was likely to increase the likelihood that patients would protect themselves from developing blood clots. Patients said that communication around blood clots in a simple manner may lead to make them feel more at ease, recall better and increase their attentiveness about blood clots.

Clear and precise information on CAT: Patients revealed that they were happy with the leaflets received from their HCPs, as leaflets were not complicated or technical and written in plain language:

"Mmm…it (leaflet) was very good because it wasn't all technical." P001
"I got that information and I read it thoroughly, so I did understand…" P012

Patients expressed that the information should be in simple/plain English (less technical), as communicating complicated messages may lead to patients not being able to follow.

"It was in quite plain English which helps a lot cos if you start getting technical you lose a lot of people… they don't want to know… but no that was quite… once my daughter read it all to me I understood most of it… probably forgot it but understood it at the time!" P010

Healthcare professionals also preferred to give leaflets which include clear information regarding blood clots in addition to verbal discussion of blood clots. They

noted that the leaflets were helpful for patients, particularly as they improved recall of what was said during the consultation:

"Yeah I think a good comprehensive information leaflet with the things spelt out you know as a basic sort of you know the ground situation laid out would be useful yeah!... I think also these… the risks and the problems preferably discussed by the urologist specialist nurse before the patient comes to us." HC012

Most HCPs stated that communicating the risk in terms of percentages may be a hard concept for many patients to grasp:

"For some people it is, but for many people are not bothered about numbers, but some people will ask about numbers." HC016

"So, I think a lot of patients don't understand percentages so there's not going to be one optimal way for… mmm… for us to present this…" HC009

From the patients' perspective, the vast majority preferred not to use numbers/percentages to communicate blood clots related risks, as this can sometimes be interpreted wrongly.

"I don't think percentages particularly have much of an impact on people. I think if they're given the facts and told how they could try to not allow it to happen, I think that's more… that's better information than saying well one in one hundred or whatever because I don't think that always works you know." P005

However, a few of patients chose to know the risk of blood clots in percentages:

"Probably percentages…yeah it's a worrying number but it's a real thing." P010

"…but it's nice to have the information perhaps on a percentage basis" P015

Patients had different perceptions of percentages. Most patients considered less than 4 percent to be low risk of having VTE. Only two patients thought 4 percent was a high percentage.:

"Four out of a hundred people who could get blood clots I'd still think that is a low percentage… yeah!" P018

"That's quite high really" P010

Using percentages to explain VTE risk is thus not ideal, and may indeed confuse the patients. To improve the communication, using facts without using numbers or percentages was preferred by patients.

HCPs noticed that the BC patients were happy to receive anti-clotting measures to decrease the risk of VTE.

"They are happy to go along with the things we impose like the stockings and the Clexane" HC008

It is interesting to note that this HCP used the word 'impose', as if she/he felt the information was enforced. However, according to HCPs, patients were comfortable with having anti-clotting injections or wearing anti-clotting stocking and generally happy with following the advice.

CAT awareness maximises safety and self-management: Views of HCPs are important to explore their confidence in educating patients regarding blood clots, firstly around VTE risk, and secondly, to help patients' awareness of early diagnosis of blood clots.

In general, HCPs assumed that effective communication around blood clots may encourage self-care and awareness:

"Yes, potentially yes…. I think it's something that they can actually do, something for themselves." HC001

"I would like to think my patients do because you know I think I'm quite to the point." HC002

"We're giving them the anticlotting sometimes we encourage mobility...I suppose if you make them aware of the risks that they might exercise a bit more… far enough." HC004

Discussing blood clots may encourage patients to look for early signs of thrombosis and seek medical advice and treatment.

"I think if you do mention specifically to the patient that yeah look out for these things if you notice any swelling or something that could be a clot get in touch and then we'll see you soon." HC010

According to the above quote, the emphasis on VTE specifically and explaining the related signs and symptoms may increase patients' monitoring and subsequently, diagnose VTE at the earliest stage. The main role in VTE awareness comes from HCPs. Without effective communication around VTE, patients may be unable to understand VTE and how they can prevent it.

Subtheme 6: Multi-pronged communication channels

Communication channels for clear and effective information giving are key to service improvement, in this case, information on CAT.

Mix of oral and written channels: The main benefit of using mix oral and written channels of communication is the reinforcement of the information. Also, when the patient misses or is unable to recall the information from oral education, he or she may be able to refer to the leaflet.

BC patients stated that they were informed verbally and received leaflets and a consent form regarding BC, related treatments and side-effects including VTE. Patients stated that leaflets strengthened and clarified the verbal message, as well as helping in understanding blood clots:

"Oh yeah verbally and I got several leaflets about it yeah." P002

"Yes, I read all of it yeah…I think it's good… I think you should be informed about everything like that before… there was a lot of information that I had to read, and I read all of it and I felt like it was very clear." P005

"Well, both… it's nice to have… you've got the leaflet that you can look at and have it explained to you as well is good." P011

However, use of both channels of information were not consistent:

"…no, I think they just told me about it… Verbally…no I don't remember any leaflets." P004

"No, I didn't have no booklet when I left the hospital…" P009

"I believe prior to the operation I was given a lot of books about the surgery and all the complications and I read them religiously…so there was obviously some mention of blood clots in that form, but I haven't had it spoken to me." P012

"Unless they gave them me and I… I misplaced them but verbally a lot of people…"P009

The vast majority of patients preferred a combination of verbal and written communication. Patients extract more information from reading because the leaflets remind them about the information they may have missed during verbal communication:

"I think it would be best to have it written down… cos I think people take it in more when they're reading it rather than listening…I think if they've got something to read keep picking up and reading about it I think that's… rather than… I think that's better than just being told… cos you can be told, and you can walk out and there it's gone!" P016

In addition to verbal education, patients preferred to read leaflets because they had more time to read and check the information:

"…yeah leaflets things like that you know and talk to them directly you know things like that…I've got more time to sit down you know when I've got time I sit down and read them… I read the leaflets rather than… cos with everything else that's going on…" P006

HCPs confirmed that they used a combination of verbal and written communication to inform their patients on BC with related treatments and side-effects. In addition to the discussion during consultation, they provide leaflets which include some explanation on VTE:

"I give them verbal information and I also give them written information on chemotherapy from the Macmillan cancer websites that contains blood clots and well as the toxic effect and then bring them back to the patient again at a later date to formally sign the form." HC0010

"Yeah so verbally… both really, so in the way when anyone's coming onto chemotherapy they get another counselling chat with the chemotherapy sisters before they start treatment…and they run through all the side-effects again but by then they've also read through the information leaflet and the consent form and specific in that it does mention about blood clots really." HC011

HCPs proposed to include VTE information within the leaflets to discuss BC, related treatments and side effects. They did not wish to provide a specific and separate leaflet on VTE to minimise information overload:

"I think it would certainly be worth having some sort of a document or including it in there so everyone who is newly diagnosed with cancer gets a booklet about… in this case bladder cancer and it would seem reasonable to have within there a chapter or paragraph or two on thromboembolic disease and what they can do to prevent it and what they should look out for we would need to give them would ideally be part of the document they're already being given and a brief concise summary I think the idea of giving them an extra booklet about the thromboembolic disease is probably excessive…" HC013

Both patients and HCPs agreed that using written as well as verbal communication about BC and CAT may help patients to have a better understanding. The provision of information on CAT was found to be poor during physical encounters, and other sources of information were not utilised to the full.

Creating effective visual tools: Most HCPs suggested using visual tools such as pictures and figures to explain what VTE is and what the risk factors are for developing VTE. HCPs expected the viewer to grasp and understand clearly what VTE is and its related risk by using pictures and figures:

"So, the ideal is using pictures…"" HC005

"Right I feel the best thing would be pictures and your figures so pictures and figures together will make a huge difference. You tell them what thromboembolism is and why you get thromboembolism and the ways that we can reduce the risks of thromboembolism." HC006

One of the HCPs stated that using pictures and figures of VTEs' signs could help with self-diagnosis of VTE and the early catching of blood clots:

"What are the signs and symptoms of thromboembolism and if you have said a picture of a swollen leg saying yeah you know this is any pain… swelling in the leg you know the risk of DVT is there and they get short of breath… they need to be immediately aware that there is a risk of thromboembolism." HC006

Another HCP suggested putting short videos about cancer and its related treatments with complications on the web to be seen by patients and give them a better description of their disease and treatments:

"I'm sure we should be able to you know have something on the Web that they could look at… you know just a little video about your upcoming operation or your chemotherapy or whatever!" HC008

Visual tools for explaining VTE could be an option to improve patients' perceptions of CAT.

The power of companionship: Cancer patients have many moments in which they become overwhelmed with various emotions (e.g. fear, anxiety, frustration), as mentioned before.

Ten patients mentioned that they were accompanied by third person during hospital sessions. These patients stated that they preferred to take a companion with them. The third persons accompanying patients are family members in most cases:

"My son with me like most of the time…" P006

"My wife." P008

"No, I've had my granddaughter (…) or someone's with me." P009

"My husband…" P017

Patients noticed that they had difficulties in recalling the instructions that were given by HCPs during hospital visits, which may be anticipated to huge amount of information related to cancer and its treatment as well as to their psychological feeling:

"You forget what the doctor says to you at times." P006

"Yeah and I used to bring my granddaughter with me so she could… cos I couldn't remember half the things what they said see!" P009

"When they told me my mind just went blank, I didn't take anything in really…" P010

Some patients described that their minds were fuzzy after the operation, and that they could not take any information in during the post-operative phase. They revealed that it is difficult to receive information during the post-operative time:

"They might've done, but I'm not gonna be a lot of help I'm afraid cos like I said when they told me my mind just went blank, I didn't take anything in reality!" P001

"Yeah, your minds in a fuzz, isn't!" P008

"They explained a lot of it on the day that I went back to the ward… my head was still very fuzzy I wasn't quite with it so I didn't understand a lot of what they were saying." P010

Due to the huge psychological impact of cancer, treatments and side effects BC patients suffered from some difficulties in recalling medical advice. Thus, the presence of the companion during their visits to the clinic/hospital or reading leaflets, can remind and reinforce the information and provide psychological support:

"You know I bring a relative with me cos there's a lot you'll be shown you know what I mean if you not computing what's been said at least you've got a relative there that might… you know have picked up on that…if I've forgot something, he'll… he'll tell me like you know… you've got to do this or have a go at that." P006

"Yeah well… cos you just reminded me bits now which didn't remember but I think it is necessary to have someone with you……when they're explaining things to you so." P009

Caregivers or relatives who accompanied their patients sometimes supported HCPs in explaining medical instruction for patients:

"Yeah I… you know I bring a relative with me cos there's a lot you'll be shown you know what I mean if you are not computing what's been said at least you've got a relative there that might… you know have picked up on that." P006

"I think it's better to be with somebody…" P017

"Yeah… yeah, every time because two sets of ears are better than one set of ears! She reminded about things I'd forgotten because when you've got the disease yourself, you're not 100% concentrating on what they're saying you know you're in your own little… you're sort of depressed a bit, so you're not listening to everything they're saying." P007

The same patient (007) confirmed this:

"So my wife's listening on my behalf…you know so we're both listening… we get home, and we say… 'what did he say about this… he said this' well I didn't hear him say that cos you sometimes go off inside your head you know!" P007

Other patients expressed similar thoughts:

"…yes I think so because quite often you know you've got this awful disease you're gonna have this you're quite het up and things don't always register so it's better to have somebody with you to take note I think… to you know because so they'll probably remember things that maybe you don't!" P017

"…to take things in… because if it's just me I've got things going on in my mind… I'm the patient……and I need…Extra ears.…other ears to hear things that I might not hear!" P018

Companions are central to the psychological and physical support of cancer patients, albeit some patients do not have companions. Cancer patients required mental support as much as they needed medical support.

In summary, according to patients and HCPs, using a mix of oral and written information and creating some visual tools i.e. multipronged communication channels, companionship, where possible, improves the communication process. Having a

companion, alongside optimal messaging and multipronged communication channels, could enhance patients' understanding of CAT.

Patients and HCPs had many suggestions for improving the apparent poor deal that patients receive about CAT. Patient involvement and engagement is therefore crucial for strategies to improve every stage of the CAT patient experience health promotion in awareness, prevention strategies, during diagnosis and treatment of cancer and CAT, and life after CAT in survivorship.

5.5. Discussion of themes

Bladder cancer is one of several cancer types for which patients are considered to be at high risk of developing VTE, especially after undergoing cystectomy and chemotherapy (Sandhu *et al.*, 2010a). The perceptions of patients experiencing a thrombosis have been studied before. and CAT is both under-recognised and given insufficient prominence along the continuum of cancer care (Font *et al.*, 2018b; Mahé *et al.*, 2020; Noble *et al.*, 2020; Woulfe *et al.*, 2020); however, this is the first time that perceptions of patients on the prevention of thrombosis has been studied. The findings of this study provide novel insights into the communication and perceptions around VTE in the bladder cancer population.

Three themes emerged from this study, focusing on the issues related to communication and understanding of VTE in BC patients: 'All about the cancer', 'A labyrinthine process', and 'Improving the poor deal'.

The current study has shown that there are some issues and gaps in communication around blood clots which affect patients' ability to recognise and understand this complication. These issues impact patients' perception of VTE; hence, HCPs wish to resolve these challenges and improve communication regarding blood clots, to give their patients a better chance of comprehending and acting on the advice given. For more clarifications around these findings and themes, each theme has been addressed and discussed as follows:

Theme 1: All about the cancer

During the BC management journey, the communication between BC patients and their HCPs was mainly around BC and its related treatments. Healthcare professionals placed greater emphasis on bladder cancer itself and its related

management. Most patients gave greater attention to cancer diagnosis than other complications relating to cancer and its treatments. Moreover, a previous study has demonstrated that cancer takes primacy over thrombosis, even after a CAT diagnosis in cancer patients (Font *et al.*, 2018a).

Correspondingly, previous studies have revealed that the information exchange between HCPs and patients is critical during clinical consultation and management (Elwyn *et al.*, 2001). Indeed, safe and effective treatment can only be maintained if all the relevant information has been shared and understood properly (Elwyn *et al.*, 2001).

Bladder cancer patients were confused by a large amount of information on cancer and often suffered from information overload. Patients were overwhelmed with cancer, which affected their capacity to take in more information other than bladder cancer. Similarly, the National Cancer Institute (2003) conducted a survey which confirmed that cancer patients were overloaded with cancer information, while information overload is also a common problem for physicians and patients (Kim *et al.*, 2007). However, there was poor VTE education for patients, with all education focusing on BC and treatments.

A further problem may be discovered from patients' interviews that could affect the focus of patients during communication around VTE, namely psychological distress. Psychological distress after bladder cancer diagnosis includes anxiety, fear, worries, depression and feelings of loss, all common amongst patients in this (VTE-BC) study, and relevant to all cancer patients, as some studies have disclosed (Ryan *et al.*, 2005). It is not surprising that different emotions can be developed when a patient is diagnosed with cancer, such as shock, fear, anxiety, distress (Strong *et al.*, 2007). Additionally, in VTE-BC study, it has been found that BC patients received insufficient information regarding VTE along the continuum of cancer management and initial diagnosis with CAT, leading to increased distress.

These unpleasant emotions make understanding complex information difficult and affect patients' understanding of CAT because strong emotions experienced by cancer patients may lead to difficulty in concentrating and absorbing information (McPherson *et al.*, 2001; Strong *et al.*, 2007). Insufficient information and communication may cause much distress for cancer patients as well (Fallowfield &

Jenkins, 1999). However, providing more information and support could minimise the distress of CAT as the previous article suggested (Noble *et al.*, 2015a).

In general, cancer patients should not be misled regarding the seriousness of their condition and disease (Fallowfield, 1997). Simple communicating around VTE might lead to making them feel at ease and ignore advice related to CAT.

To cope with strong feelings, it is crucial to be informed about their disease, treatments, complications and preventive measures. Most patients can feel better when they learn facts (Fallowfield, 1997). Educating BC patients on VTE is mandatory, and it is also worthwhile to minimise their fear and anxiety around VTE if happened. Information is classed as therapy because communicating adequate information enables patients to improve their way of coping, and leads to better psychological health (Mallinger *et al.*, 2005). Most HCPs and patients agreed with giving constructive information and warning messages about blood clots to make them follow the instructions and protect themselves from developing VTE. Proper VTE awareness is an important priority to prevent developing VTE and improving patient care.

From this study, it is readily apparent that there was no emphasis on VTE education, with all communications between patients and HCPs focusing (primarily on) cancer itself. This is not the only problem, however; other problems relate to the patients' understanding, as discussed in the theme 2.

Theme 2: A labyrinthine process

Patients with BC deserve effective education around VTE. Educating patients about VTE is not only imparting information, it needs to be understandable and include the motivation for patients to follow medical advices and protect themselves from VTE. Not all BC patients have high-risk factors for VTE and need education around VTE. Moreover, some areas of VTE risk communication still lack strong evidence, such as in systemic chemotherapy. There are also variations in providing information around VTE, with groups of patients receiving information about VTE, and others not.

Healthcare professionals mainly provided information around VTE for patients who were undergoing cystectomy, because there is clear evidence here that cystectomy is a risk factor for VTE (Tikkinen *et al.*, 2017). Additionally, they followed NICE guidelines (2010) and considered cystectomy as a high risk for VTE (NICE, 2010; NICE, 2018). Thus, they recommended pharmacological thromboprophylaxis

measures for BC patients who had cystectomy and explained to patients why they wanted to give them thromboprophylaxis (NICE, 2010; NICE, 2018).

This was not the same for patients undergoing chemotherapy. In this case, HCPs in oncology departments did not focus on the VTE, and mostly they did not inform their patients about VTE. Although some evidence states that systemic chemotherapy may increase VTE rate within cancer patients, there is no guideline for recommending thromboprophylaxis injections or stockings for ambulatory BC patients who have received chemotherapy (Lyman *et al.*, 2013b). Lack of thromboprophylaxis recommendation in the guidelines could be the main cause of neglecting communication around VTE with patients who have received systemic chemotherapy.

HCPs tended to provide information about their own aspect of the cancer pathway, and this could lead to patients receiving inconsistent information on the risk factors of blood clots. HCPs should learn more about all the risk factors of VTE and communicate effective information with their patients.

Patients with BC had a poor understanding of VTE and its relationship with cancer. Moreover, patients did not know the warning signs of blood clots. Lack of communicating signs and symptoms of blood clots constituted a major gap in communication around VTE. Patients could not recognise and diagnose VTE by themselves. However, awareness regarding signs and symptoms of VTE helps for early detection and save patients' lives. Similarly, some qualitative studies about CAT in cancer patients have revealed that cancer patients were unaware of signs and symptoms of VTE (Noble *et al.*, 2015a).

After identifying and discussing all the issues and obstacles in VTE education which affected patients' understanding (previous two themes), it is helpful to present all participants' suggestions regarding improving communication around VTE. The content of messages and how HCPs convey the messages to BC patients need to be improved. In the third theme, below, improving the poor deal patients receive is discussed.

Theme 3: Improving the poor deal

Bladder cancer patients had limited information about CAT, and all communication revealed information deficits. Effective communication around CAT is, however, crucial for preventing and treating CAT. Bladder cancer patients need more information regarding CAT, such as symptoms and how to find them. Patients need to be aware of CAT and understand what they can do to be an active partner in their care. BC patients need more and better communications and information around VTE to enable them to improve coping with VTE.

An effective VTE educational tool remains elusive, however, because there is a lack of sufficient evidence in terms of what information patients need to know or how such information could be delivered most effectively (Juthani *et al.*, 2018). To have an effective healthcare encounter, there should be a meaningful information exchange between HCPs and patients. Generally, cancer patients and their companions play a significant role in VTE prevention if they receive proper education regarding VTE (Noble *et al.*, 2016a). For better collaborative practice around protecting patients from blood clots and its consequences, effective communication is thus required. This type of communication is about more than just exchanging messages or information. It involves identifying the emotions and determining the intent behind the massage (Buckman, 2002). Communicating around blood clots to cancer patients in a clear way is essential in treating cancer patients, as expert panels in ASCO have recommended (Key *et al.*, 2020a).

This said, there are both technical issues and gaps in communicating about VTE with BC patients which affect patients' ability to recognise and understand VTE. Moreover, some studies have found that there are many patients who leave consultations unsure about their disease, treatments and complications (Fallowfield & Jenkins, 1999).

Thus, HCPs use multiple channels to communicate with their BC patients, using verbal and written communication. Using written as well as verbal communication about BC and related consequences in this way may help patients to have a better understanding of the key issues. Written communication has the advantage of being able to help patients to remember and comprehend medical instructions.

Healthcare professionals and BC patients suggest using visual tools such as pictures and figures to explain what blood clots are and the risk factors for developing blood clots. Showing short educational videos online about CAT may provide patients with a better description, and this video can be online.

Third-person accompanying can play an important role in patient-centred communication for BC patients (Mitchell *et al.*, 2020). All participants addressed the fact that the companions of patients can be considered as another channel for communicating VTE.

In addition to their role in supporting their patients psychologically during medical consultations, companions can remind and explain to their patients what a blood clot is, and any preventive measures. Wolff and his team (2008) also found that the presence of companions with patients during consultation provide emotional, informational and practical support (Wolff & Roter, 2008).

There is no emphasis on CAT education, however, and communication focused predominantly on the specifics of cancer management. Miscommunication or suboptimal communication can hinder patients' understanding, expectations of treatment, involvement in the treatment planning and represent the largest source of preventable issues (Brindley *et al.*, 2014).

As anticipated, bladder cancer brought up a wide range of feelings and emotions which were difficult for patients to deal with. Thus, improving communication around CAT by using multi-channels communication processes would be very helpful. The presence of companions with patients during medical consultations and treatments, utilizing visual stimuli tool and adding an optimal online educational tool about VTE have been suggested by participants to gain a better understanding of VTE.

5.6. Chapter Summary

The findings and discussion relating to the qualitative component of VTE-BC, Phase II, explored patients' perception around CAT and revealed that there is poor CAT education for BC patients and no forewarning for patients about VTE. More attention is required from HCPs in educating VTE for BC patients. Using different tools for VTE education is advisable.

6. Discussion - drawing the phases together

6.1. Chapter outline

In Chapters 4 and 5, separate discussions for the two phases of the study were set down, following the results and findings. In Phase I, the incidence of venous thromboembolism (VTE) in BC patients from HES and local data was more than 50% lower than the previous UK literature had shown. This was likely to be due to applying extended prophylaxis for surgical patients (the vast majority had muscle-invasive BC and thus, underwent cystectomy). For Phase II, BC patients generally were not aware of cancer associated thrombosis (CAT) and attendant risks and were not informed about CAT throughout their BC pathway and thus did not look out for signs and symptoms of VTE.

This final chapter links together all components of this mixed-methods study (reviews, Phase I and Phase II) and discusses the important findings that run throughout the VTE-BC study, in the context of the contemporary literature. The conclusions, recommendations, strengths and limitations of the study, are also presented in this chapter.

6.2. Introduction

From the previous chapters, it is apparent that VTE for people with cancer is a significant clinical problem often overlooked and neglected due to the overwhelming attention given to anticancer treatments and 'surviving' cancer. Knowing that VTE is the second most common cause of death in ambulant cancer patients (Khorana *et al.*, 2007a) affords a standpoint for change, using the perspectives of both patients and healthcare professionals. Choosing to focus on a cancer type, e.g. bladder cancer (BC), where people are at high risk for VTE (Pariser *et al.*, 2017a; Ramos, 2016; Zareba *et al.*, 2018; Zareba *et al.*, 2014) and where there has been no extensive research as yet, has the potential to increase the clinical impact of the study. Venous thromboembolism in BC patients increases the burden on medical institutions, disrupts planned cancer treatments, and reduces the quality of life (Lamping, 1997; Kahn*, et al.*, 2005). The cost of patients' treatment of VTE, in addition to the cost of BC treatment, adds up to one of the highest cost treatments in cancer care (Lyman *et al.*, 2018; Mossanen & Gore, 2014). For BC patients, it is crucial to explore which groups

are at higher risk of VTE and put effort into striving to decrease VTE rates, thus reducing adverse effects of VTE, with reduced costs to the healthcare system. Accordingly, patient-, tumour- and treatment-specific factors were examined for the risk of VTE and then appraised for the use of any thromboprophylaxis measures.

The researcher chose to focus on exploring the perspectives of patients and HCPs before a VTE event happened (in the preventative setting) as this is a crucial period to influence the CAT pathway. This is a novel topic as patient experience studies thus far have been focussed on 'living with CAT' (Benelhaj *et al.*, 2018), that is, after the event.

The literature suggests that it is possible to prevent many VTE episodes in cancer patients but not all (Sun, 2015). Prevention is better than cure (except when it comes to paying for it) (Buck, 2018). However, in the UK, with a universal healthcare system, there has been a push over the last decade, for research into the prevention of cancer (Forman *et al.*, 2018; Wiseman, 2008) and indeed prevention of VTE, to save lives and decrease unnecessary drug treatments and side effects (Agnelli, 2019; Carrier *et al.*, 2019; Farge *et al.*, 2019). Prevention of VTE where possible would therefore be a favoured strategy for patients and the healthcare organisation in contrast to treating VTE because the adverse effects of VTE are serious and the presence of VTE is associated with lower survival rates in cancer patients (Khorana *et al.*, 2020; Lyman, 2011). According to NICE guidelines (2018), pharmacological thromboprophylaxis in surgical patients with malignancy is a standard in the UK (NICE, 2018). However, in medical patients, pharmacological thromboprophylaxis has not been proven to be effective and/or cost-effective for all patients at risk of VTE (Du & Wu, 2020; Farge *et al.*, 2019). There are also consequences to pharmacological thromboprophylaxis with anticoagulants, most commonly bleeding, so thromboprophylaxis is a complex area of care in the medical cancer population with international guidelines at present only recommending consideration of using thromboprophylaxis for high-risk medical patients (Farge *et al.*, 2019; Streiff *et al.*, 2018; Verso & Di Nisio, 2020).

In summary, by interviewing patients and healthcare professionals on their perspectives of VTE in the BC population prior to any VTE event, the findings of this study may have more clinical impact.

6.3. The Build-up to the research

6.3.1. Literature reviews

Before starting this mixed-methods study, two reviews were carried out. Firstly, a systematic review of VTE rates in bladder cancer patients showed that the VTE rate in BC varies between studies due to the heterogeneity of risk factors (cystectomy, chemotherapy) and where relevant, the duration of perioperative thromboprophylaxis (Zareba*, et al.*, 2018). This is likely to be due to differences in patients' characteristics, recording issues and using different protocols of thromboprophylaxis (Gopalakrishna, 2016). The systematic review (Chapter 2) revealed that there was a research gap in studying incidence and specific risk factors for VTE in BC patients, in the UK where the researcher works. VTE in BC patients is still a neglected area of practice worldwide and an important topic to address because of the potentially life-threatening nature of the combination of BC and VTE with an attendant predicted shorter survival (Sandhu*, et al.*, 2010).

Secondly, a scoping review on cancer patients' experiences and understanding of VTE indicated that cancer patients have limited information of VTE and are unaware of signs and symptoms of VTE. No studies have explored the patients' understanding of VTE in patients prior to a VTE happening (Section 2.2). Phase II of this study was therefore shaped by the scoping review of qualitative studies of cancer patients with VTE. The lived experience of patients having BC and related anti-cancer treatments before developing a VTE (albeit four patients interviewed had a VTE post-treatment), and the lived experiences of HCPs caring for patients with BC was a crucial backdrop to exploring what patients understand about VTE.

6.3.2. A mixed-methods study

The rationale for collecting and analysing both types of data within one study is that neither quantitative nor qualitative methods are sufficient, by themselves, to provide answers to the research questions (Chapter 1) of this VTE-BC study, to explore the scope of the VTE problem in BC patients and the patients' and HCPs' perspectives of VTE along the BC care continuum.

VTE in BC patients was therefore explored using two different methodologies and allowed for more robust analysis, capitalising on the strengths of each. The principal link between Phases I and II arose from striving to translate the large challenge of VTE in BC patients identified in Phase I into meaningful clinical practice, by exploring the optimal approach to improving the education of patients about CAT as called for by many authors (Benelhaj *et al.*, 2018; Noble *et al.*, 2015a). This was best done in sequential stages via mixed methods (Cameron, 2009; Ivankova *et al.*, 2006). However, there were some issues in choosing a sequential mixed-methods approach; it took a long time (16 months) because it was not possible to start with Phase II until completing Phase I. Moreover, the application for two ethics committees' approval was required before starting the research; this was burdensome and took double the time of one application.

After outlining the consequences of the literature reviews and mixed methods above, the findings and results from both phases of VTE-BC are discussed in the context of contemporary literature.

6.4. The Research - venous thromboembolism challenges in bladder cancer patients

The huge challenges of cancer-associated thrombosis (CAT) for BC patients such as the high risk, the lack of awareness for patients and some HCPs and the poor deal the patients experienced with regard to a smooth CAT pathway, outlined throughout the thesis, can be turned into opportunities for patients, caregivers and HCPs to prevent developing VTE, as discussed below.

Phase I: Thromboembolic events in patients with bladder cancer

Incidence rate and risk factors: The statistical analysis of the national and local data on VTE in BC patients (Chapter 4) revealed that the VTE incidence in the UK was lower than has been found in the previous UK literature (Dyer et al., 2013b; Walker*, et al.*, 2013). A credible explanation suggested for this difference in the surgical setting was that an extended thromboprophylaxis regimen after-radical cystectomy was found to decrease the rate of VTE from 12% to 5% (Pariser, et al., 2017). Extended thromboprophylaxis peri-cystectomy concurs with the results of three systematic reviews of abdominal-pelvic surgery for malignancy using mainly low molecular weight heparins (LMWH) (Carrier *et al.*, 2018; Fagarasanu *et al.*, 2016; Rasmussen *et al.*, 2009). However, in this study, VTE-BC, not all surgical BC patients were found to have a high risk of VTE e.g those with non-muscle invasive BC who had undergone TURBT surgery, and therefore careful and individual patient selection is required for pharmacological thromboprophylaxis, also taking into account the risk of bleeding from anticoagulation.

The logistic regression analysis of Phase I showed cystectomy, cystectomy with systemic chemotherapy, metastatic stage and a second type of cancer (in addition to BC) are associated with a significantly increased risk for VTE (Table 14). In BC patients, radical cystectomy has been shown to increase the risk for VTE (Dyer, et al., 2013; Zareba, et al., 2014; Ording, et al., 2016; Tikkinen, et al., 2017) and giving chemotherapy increases the risk for VTE beyond the already present risk imposed by cystectomy and metastasis (Duivenvoorden *et al.*, 2016). Moreover, this VTE-BC study demonstrated that patients who had both cystectomy and chemotherapy appeared to carry the highest risk for VTE; greater than those who underwent cystectomy only. A systematic review and meta-analysis of chemotherapy risk of VTE in BC showed similar results, that is systemic chemotherapy raises the risk for VTE beyond the already increased risk imposed by surgery and cancer (Gopalakrishna, 2016).

The finding of having a second type of cancer, e.g. prostate cancer, lymphoma or other types of cancer increasing the risk of VTE, is a novel observation for BC patients. The higher risk of VTE may be due to the fact that those patients with a second cancer are likely to receive further surgery and/or chemotherapy further

increasing the risk for VTE. Future clinical trials will confirm the worth of thromboprophylaxis on BC patients who have a second type of cancer.

Thromboprophylaxis and patient education on VTE: Phase I of this study helps to specify which patients are at high risk for VTE and who may benefit from thromboprophylaxis measures and education on VTE.

Although surgical thromboprophylaxis is routine, in the ambulant setting, the decision to give thromboprophylaxis to ambulatory cancer patients receiving chemotherapy mainly depends on the weighting the benefits (e.g. prevention of VTE) and harms (e.g. bleeding) of pharmacological thromboprophylaxis (Mulder *et al.*, 2020). The European Society for Medical Oncology (ESMO) (Frere & Farge, 2016) and The National Institute for Health and Care Excellence (NICE) guidelines (NICE, 2018) do not routinely recommend thromboprophylaxis for ambulatory bladder cancer patients specifically who receive systemic chemotherapy. Moreover, the most recent American Society of Clinical Oncology (ASCO) (Key *et al.*, 2020a) and NCCN (Streiff *et al.*, 2018) guidelines recommend considering a validated risk score for VTE (e.g. 'Khorana Score' of 2 or higher) before the use of pharmacological thromboprophylaxis in ambulatory cancer patients who receive chemotherapy

Recommendations from national and international guidelines may conflict due to not being updated frequently enough which may be one of the reasons for the large differences in the use of VTE prophylaxis within and between countries (Violette *et al.*, 2016); nevertheless, as the guidelines are updated, there is a greater agreement.

There is an opportunity here for all clinicians to put into practice simple steps during patient encounters, despite conflicting opinion regarding which patients require thromboprophylaxis. Patient education on VTE including how to prevent VTE and how to recognise signs and symptoms of VTE could be offered to all patients receiving anti-cancer treatments with a high-risk for VTE, regardless of the use of thromboprophylaxis or not. All patients with BC could be assessed for their risk for VTE as part of a standard procedure and then individualised CAT information may be offered.

In Phase II of VTE-BC, only patients who had a high risk for VTE were interviewed, to maximise the relevance and impact on patients as 'patient awareness of VTE' may alter the morbidity and mortality rate associated with VTE (Font *et al.*,

2018a; Khorana *et al.*, 2019). Knowing the scope of the problem, we must listen to the patients and the HCPs to improve practice. In Phase II, how to improve practice was explored, as discussed below.

Phase II: Patients have limited awareness about CAT

Patients had limited information on the risk factors for VTE. Most BC patients interviewed 'grumbled' at the lack of forewarning of the risk for VTE and there were information deficits around VTE such as lack of informing the patients about signs and symptoms of VTE. This concurs with the findings of previous qualitative studies regarding patients' experiences and understanding of VTE where patients had experienced a VTE; those cancer patients with a VTE had limited information on CAT and were unaware of the signs and symptoms of VTE (Font *et al.*, 2018a; Mahé *et al.*, 2020; Noble *et al.*, 2015a).

Novel approaches to sharing information on VTE symptoms and how they can recognise them (e.g. pain, tenderness, warmth, redness, heavy sensation in the leg and oedema, for deep vein thrombosis; and dyspnoea, chest pain and cough with blood for pulmonary embolism) (Bauersachs, 2012) may add to an overall VTE prevention strategy and decrease the risk adverse consequences of a VTE (Young & Watson, 2006).

Lack of VTE awareness might lead to patients feeling falsely at ease. Studies have established that VTE education can affect patient's adherence to the thromboprophylaxis measures and suggested that patients need effective communication around VTE to cope with VTE (Abboud *et al.*, 2020; Juthani *et al.*, 2018). Awareness of VTE can promote patients' involvement in protecting themselves by encouraging participation in recommended actions such as mobilising, keeping hydrated, having anti-clotting injections where appropriate and wearing anti-clotting socks where appropriate (Juthani *et al.*, 2018). Education on VTE is essential for BC patients who are at high-risk for VTE. It allows patients to self-assess, self-report VTE symptoms and to obtain timely medical assistance (Le Sage et al., 2008). Thus, the opportunity arises to raise awareness of VTE in BC for HCPs through discussing studies at conferences or journal clubs, and for patients, at encounters with HCPs at the beginning and throughout the BC care continuum. Other factors of patient should be considered in these patients/clinic encounters as discussed below.

Patients are overwhelmed with cancer: The participants in VTE-BC study confirmed that the HCPs and patients understandably focus mostly on their cancer. Thus, educating on VTE in the BC context and encouraging patients' involvement in VTE prevention must be given more attention to ensure prevention of VTE and high quality of care.

Some patients in VTE-BC could not recall being told about VTE, and others showed uncertainty about whether they were told or not. They stated that this was due to being overwhelmed with their cancer, the related investigations and treatments. They received a huge amount of information on their cancer which perhaps swamped taking in any other information. Information overload on cancer is well documented in the literature and predictors of cancer information overload have been studied (Kim *et al.*, 2007), an overwhelmed mental state in cancer patients may affect patients' ability to take into account all aspects of medical information, including VTE preventive measures, and to make good decisions (Bester *et al.*, 2016). In this study, patients with BC focussed on cancer and not on CAT; anxious patients selectively hear the information about life threats and recall more of the information related to life threats than any other information (Beck & Clark, 1988; Bradley *et al.*, 1995).

Some patients in this VTE-BC study experienced psychological distress including fear, anxiety, stress, and depression. This is consistent with the results of other studies which found that cancer brings strong emotions and affects the mental health of patients e.g. fear, worry (Derry *et al.*, 2019). These strong emotions can make the comprehension of complex information difficult and may affect patients' perceptions of CAT (Fallowfield *et al.*, 1994). A good mental health state helps patients to understand medical information and cope with problems (Arora, 2003; Kessels, 2003; Meyers, 2000). As BC patients are often under huge psychological distress, psychological support is key to survivorship and maintaining wellbeing and as important as medical or physical support (Naughton & Weaver, 2014).

The HCP participants in VTE-BC were experienced oncology professionals in whom the patients showed trust. The HCPs displayed sensitivity and awareness of the patients being overwhelmed with their cancer and the attendant psychological impact. Nevertheless, there is an opportunity for CAT to be discussed in an equally sensitive manner as part of the wider discussions of adverse effects of cancer and anticancer

treatments along the continuum of BC care. The importance of information along the whole pathway of care is discussed below.

Compartmentalisation of information giving: According to the current study, patients who had undergone cystectomy received VTE education, whilst patients with other risks factors generally did not receive information about VTE, such as patients who had a metastases, comorbidities, a second type of cancer or have received chemotherapy.

HCPs did not consider the risk factors for VTE during encounters with their patients before or during systemic chemotherapy. In fact, some of the HCPs were unaware themselves that systemic chemotherapy may increase the risk of developing VTE, they had not considered that patients having systemic chemotherapy and cystectomy are at the highest risk for developing VTE (Chapter 5) (Gopalakrishna, 2016). This could be due to 'compartmentalisation' of information giving; healthcare professionals within each department educated the patients only on the treatments relevant to their expertise and not the whole pathway. They understandably focussed on adverse events that were familiar to them e.g. neutropenic sepsis but did not consider risks of VTE when patients received more than one type of treatment such as cystectomy and chemotherapy (shown as high risk from Phase I). Three out of the four patients participants who revealed that they had had a CAT diagnosis, had received both systemic chemotherapy and cystectomy prior to their VTE and although this is a small sub-sample, it is a signal for HCPs to strengthen both the opportunities to discuss VTE before it happens, and strengthen the information given to 'patients' at high-risk for VTE.

Patient participants stated that they only received information about VTE pre- and post-cystectomy. They did not have ongoing information about VTE. The literature suggests that patients need periodic reminders about VTE as the risk for VTE continues after 30 days post-surgery up to more than 1-year post-cystectomy (Brennan *et al.*, 2018; Duivenvoorden *et al.*, 2016). Cancer patients benefit from periodic reminders about VTE risks, and therefore the opportunity to discuss VTE with patients and keep the messages flowing along the continuum of care including follow up are vital.

To mitigate against the apparent compartmentalisation in VTE education that the patients and HCPs strongly noted, in particular between surgery and oncology departments, a discussion around VTE at all multidisciplinary team meetings with the whole team including nurses may be prudent (Mauger *et al.*, 2020). The nurses are often the patients' keyworkers and, from the interviews with the nurses, it is clear that they have a window of opportunity to discuss VTE at the pre-chemotherapy educational session, once they are themselves educated in CAT. Approaches to communication around CAT are discussed in the next section.

Effective communication in cancer-associated thrombosis: To improve patients' understanding of CAT, HCPs suggested using verbal and written channels to educate their patients on CAT as well as informing their patients on credible on-line resources**.** Patient participants in the interviews in this study recommended using figures and pictures to demonstrate signs of VTE for patients and provide a better demonstration. Maddock et al. (2011) explored the cancer patients' wish for a wide variety of easy to find, easy to understand accurate cancer information online. This general principle supports the suggestion from patients and HCPs' of the use of the internet as another channel for education on VTE (Maddock *et al.*, 2011)**.**

Communication between patients and HCPs is a two-way process; listening to the patient, hearing and acting upon what is heard is a key component of this process (Buckman, 2002). This two-way process should include VTE, related investigations and treatments for VTE and complications of having a VTE to make patients aware of VTE. Effective communication is crucial to good cancer care and this should involve the prevention of VTE, ideally as part of an overall discussion of the side effects of treatment (Uitterhoeve *et al.*, 2010).

There is much agreement in the literature on the importance of effective communication in cancer care. It has been demonstrated that effective communication can reduce emotional stress, anxiety, fear and uncertainty in patients (Uitterhoeve *et al.*, 2010). Effective communication between HCPs and cancer has been studied and found that the effective communication can create a good interpersonal relationship, facilitate the exchange of information, and includes patients in decision making (Bredart *et al.*, 2005). Communication within oncology is considered as a core of clinical management and poor communication may cause disappointment for patients

and their companion, who often need more information than is usually given (Fallowfield and Jenkins, 1999). Thus, the advanced communication skills of the HCPs can effectively be utilised for the two-way discussion on CAT. Another pair of ears always helps the understanding for the patient (Mitchell *et al.*, 2020). This was also highlighted in the Phase II findings.

Attending appointments/consultations with a companion: Most patients in this study expressed their gratitude for having a companion during their clinical appointment and visiting their HCPs. The supportive upshots of having a companion during clinical consultations also improved patients' awareness of CAT (Mitchell *et al.*, 2020). The interviews showed that the companions can also act as a 'communication channel' for patients and they can participate in increasing patients' awareness about CAT. The role of the companion is vital for cancer patients (Ellingson, 2002). Wolff and his team (2008) also found that the presence of companions with patients during consultation provide emotional, informational and practical support (Wolff & Roter, 2008).

VTE-BC uncovered the scope of the problem of VTE in bladder cancer patients in the UK and the patients' understanding of VTE from their experience of having had BC and related treatments. At the end of this study, both aims and all objectives as stated in Chapter 1, were achieved with the possible exception of one objective were achieved during the study. The incidence of VTE in BC patients was found to be 6.0 per 1000 BC patients from the national database, with cystectomy, metastatic stage and second type of cancer as risk factors for VTE in patients with BC from two local databases. Information on VTE was communicated effectively to patients with BC only at certain points along their pathway. Patients and HCPs noted that information on VTE can be more effectively communicated to the patients to facilitate informed choice. The patients' perspective, most notably of lack of awareness of CAT and generally receiving a poor deal with respect to information and communication around CAT, was heard loud and clear.

However, influencing clinicians' practice, ultimately to reduce the burden of VTE in the BC patient population, was encouraged and noted by the HCPs but requires further research.

6.5. Conclusions

The principal message from this study is that VTE in BC patients presents a challenge to patients and HCPs. Bladder cancer patients are not generally aware of the risk of VTE as a result of their cancer; they are generally only briefly informed about clots before major surgery and they do not know how to recognise a VTE event if it happened. Patients in this study mostly did not receive effective information on CAT from HCPs along their whole care pathway. The psychological and emotional state of BC patients had a big impact on patients understanding. Therefore, people with BC generally got a 'poor deal' on CAT.

This VTE-BC study, to the researcher's knowledge, is the first mixed-methods study which explores the incidence rate and risk factors for VTE in BC patients. Moreover, this study addresses an important aspect of VTE prevention and identifies gaps in patient education that hinder the patients' role in VTE prevention.

By presenting the scope of the problem and significant risk factors of VTE from UK data, followed by the perspectives of BC patients, this study may contribute to prevent CAT from increased awareness around VTE. However, this hypothesis was not tested in BC-VTE.

Bladder cancer patients have poor awareness of VTE. Many lacked important knowledge on the risk factors for VTE (apart from those patients undergoing cystectomy), symptom recognition of DVT and PE and evidence-based thromboprophylaxis measures. Emotional factors may also impact patients' awareness of VTE such as being overwhelmed with their cancer. Effective communication between HCPs and patients was found to be key; this involved more than providing information, e.g. attracting patients' attention to major risk factors and any preventive measures along the whole continuum of care. This is likely to encourage patients and caregivers to seek more information on CAT from other trusted sources, e.g., recommended UK charities e.g. Macmillan Cancer Support (Macmillan, 2019) and CAT websites e.g. CancerClot website (CancerClot, 2020)

In the patients' at high risk for VTE (Khorana & Connolly, 2009), the lack of awareness of VTE symptoms may lead to an increase in the length of time to diagnosis should a VTE develop and may put patients at risk of adverse consequences of VTE.

Indeed, it is beneficial for the patients to have at least a basic understanding of VTE from their HCPs and learn how to recognise DVT or PE by themselves, to be empowered to seek help quickly. Improved patient education incorporating VTE risk is also likely to motivate adherence to VTE prophylaxis, and education on recognition of symptoms will equip patients to self-assess and self-report possible VTE events.

Participants in this study offered some suggestions to improve communication about VTE at patient/ HCP encounters, all of which suggests the great need for improved awareness as an integral part of a UK national strategy to prevent and treat VTE in cancer patients.

This study in itself raised awareness amongst those HCPs interviewed from urology and oncology departments, some of whom said they would change practice, to provide effective information around VTE and consider thromboprophylaxis measures for this patient population. Patients trusted their HCPs and thus HCPs can be influential in striving to prevent VTE.

6.6. Clinical implications of VTE-BC

This study has a direct clinical significance for the BC population as some clinical opportunities stem from the challenges and opportunities of the bladder cancer.

During interviews with participants, the researcher awakened the HCPs interest to discuss the CAT and encouraged HCPs to raise blood clots awareness for BC patients. This is a first study focusing on patients' perceptions of VTE before a VTE diagnosis and it has provided useful suggestions to improve communication around VTE that may give a better understanding of VTE, encourage patients' adherence to thromboprophylaxis and decrease VTE events within this group. HCPs can use the finding of this study to improve their own and patients' understanding of VTE and encourage people with BC to adhere to the preventing measures. VTE-BC has the potential to make a large impact on the VTE control in the BC group and potentially save patients' lives, using the opportunities for CAT discussion along the BC pathway and ensuring the recommendations are implemented.

6.7. Strengths and limitations of VTE-BC

To the best of the researcher's knowledge, this study is the first mixed-methods study exploring VTE in BC patients in the UK. Face-to-face interviews with BC patients and their HCPs provided an in-depth understanding of the issues from both parties in Phase II, set against the updated knowledge of the incidence and risk factors in Phase I. The data from both the HCPs (mostly senders) and patients (mostly receivers) in Phase II also elicited different perceptions to improve the quality of patient/HCP encounters. The researcher, therefore, capitalised on two approaches to explore a clinically important problem, striving to strengthen future patient/HCP encounters. Both the quantitative and qualitative analyses were enhanced by the researcher's clinical background with the ability to describe, explain and interpret clinical data and information.

The uniqueness of exploring the clinical challenge of VTE in cancer patients and HCPs before the event happens provides a greater impetus for patients, their caregivers and the healthcare team to prevent VTE, given widespread dissemination of the results and recommendations. Allowing patients' families or caregivers to join some interviews (requiring appropriate ethics committees' amendments) helped support those patients in answering the questions.

This study is not without limitations and the potential limitations found in reviews, and in quantitative and qualitative phases. In the systematic review, most studies which included were retrospective studies. Retrospective studies may have some bias and have inferior level of evidence compared with prospective studies. In the scoping review, there are no studies that explored cancer patients' understanding of VTE prior to having a VTE. All studies explored patients' experience of VTE in the cancer context with patients having had a VTE. In the systematic review, most studies which included were retrospective studies. Retrospective studies may have some bias and have inferior level of evidence compared with prospective studies. In scoping review, there are no studies that explored cancer patients' understanding of VTE. All studies explored patients' experience of VTE in the cancer context with patients having had a VTE.

The main limitations of the Phase I component are its retrospective nature and a small absolute number of VTE events on which to base the analysis. Information

regarding confounding variables for VTE, e.g. smoking status and body weight, was not readily available in patients' records and therefore their influence on VTE events is unknown. Improving the process of documentation is necessary for quality improvement of patients' data recorded and basic services. Recording comprehensive, timely and accurate information in a patients' files is an essential part to have most accurate results in clinical research.

One of the drawbacks associated with Phase II was the difficulty in recruiting participants, in particular HCPs because they were extremely busy with clinical care, had no time and perhaps, little interest in taking part in the project. Thus, different strategies for recruiting participants should have been considered earlier by the researcher to obtain a diverse sample. The recruitment of patients was also difficult because of the logistics of patient recruitment at the clinic and the wide inclusion criteria of patients with BC had to be balanced against recruitment of the sufficient number of patients and the wish to minimise distress and the burden of time with the interview.

Most BC patients were evidently overwhelmed from their cancer diagnosis and treatments, and they were more interested in discussing their cancer pathway than VTE; some of them had difficulty in recalling their experiences. This limitation was turned into a strength by permitting caregivers or companions to join the interviews and garner more and specific data.

Due to the limited time to complete the PhD, there was not an opportunity to implement the findings. An implementation strategy will form part of future work.

6.8. Recommendations for future research

To execute:

1. A health promotion study to explore optimal approaches for raising awareness on the association between VTE and cancer including the consequences of VTE and any prophylactic measures advised
2. A service improvement study on multidisciplinary input to information giving on prevention of VTE along the cancer care continuum including follow up.
3. An observational study on the association of systemic chemotherapy (and any novel targeted and immunotherapy treatment) and VTE in bladder cancer patients.
4. Further clinical trials to confirm the requirement for pharmacological thromboprophylaxis in ambulatory patients with BC with safety as a co-primary endpoint.
5. Further clinical trials to confirm the requirement for pharmacological thromboprophylaxis in patients with two types of cancer.
6. Further quantitative studies to improve VTE risk assessment tool for VTE in cancer patients.
7. A UK-wide service evaluation of the effectiveness of the multidisciplinary communication of CAT throughout the cancer care continuum, including the two local hospitals in Phase II of this study.
8. Measuring bleeding and mortality rate due to VTE in BC patients in 'VTE-BC' would have been extremely valuable; these data required further applications to the national and local registries utilised and thus more resources. Further research with bleeding and mortality data as outcomes for patients with BC would elucidate the balance between thrombosis and bleeding and helps the shared decision-making between patient and clinician for any therapeutic intervention.

6.9. Motivation and reflection

In this section, I will share my motivation and personal reflection on the journey of conducting the VTE-BC study for a PhD,

6.9.1. Motivation for the research

I am a specialist in Medical Haematology-Oncology with over a decade of experience working as a physician in Iraq.

I obtained a Bachelor of Medicine (MB ChB) from the University of Mosul, College of Medicine in 2009. After a clinical internship programme, I decided to join the growing field of oncology at the only cancer centre in my home city, the Oncology and Nuclear Medicine Hospital, Mosul and then successfully completed a structured training programme, the High Diploma in Haematology-Oncology (HDHO) in Sulaymaniyah-Iraq (2011-2013).

Prior to registering for a PhD Fellowship with Warwick Medical School (WMS), I was primarily responsible for managing cancer patients, in particular, genitourinary malignancies and breast cancer. During this time, I noted, in the cancer patients I was caring for, that cancer-associated thrombosis was common.

Hence, when enrolling on the PhD programme to improve my research skills, I was fortunate to find some experts in cancer-associated thrombosis in the UK and at Warwick Medical School. In discussion with these experts, I recognised that, if possible, thromboprophylaxis was better for the patient than the treatment of thrombosis when the consequences are more serious. As well as novel research methods, I was keen to understand the experience of VTE understanding from cancer patients' and healthcare professionals' viewpoints. Their insights into VTE are, indeed, crucial in identifying strategies for the prevention of VTE. Thus, my chosen career in oncology, academic curiosity and endeavour to make a difference to cancer patient care all led to VTE-BC study.

6.9.2. Reflection

As a physician and oncologist, I experienced many challenges with the supportive care of cancer patients in Iraq around 2015. One of the most devastating complications of treatment for cancer patients I noted was thrombosis, which was not generally acknowledged or dealt with in any depth by the cancer team, although our patients with cancer and VTE were miserable.

In 2016, I was fortunate to gain a fellowship at Warwick Medical School which seemed a good fit for my interests. My supervisors were leaders in urological cancers and thrombosis and busy people. Unfortunately, I lost my first supervisor after 18 months but gained two more supervisors as my studies moved along. The continuity of the original second supervisor helped the overall study move along. Every supervisor has their own experience, skill and personality.

Coming out of clinical practice and doing full-time research in a new country with English as my second language meant that I had a ‘baptism of fire’; a good one. I completed 15 general clinical research and specific cancer, thrombosis, and qualitative methods courses. I was then able to start my systematic review and scoping review to enable me to get to the crux of the research.

One of the greatest challenges was the ethics approval processes in the UK. The ethics applications were lengthy; the national ethics approval systems and processes underwent major changes in the middle of my applications, Integrated Research Application System (IRAS) to Health Research Authority (HRA). This felt tedious and took nine months between the 2 Phase applications. Having gone through the process with some help from the University of Warwick administrators who were also new to this process and gained successful approval, I felt that it was a good experience for me as this was central to my PhD and stood me in good stead for the future. Moreover, the applications made by me to request Hospital Episode Statistics (HES) data and collection of local data from the two hospitals was clearly a completely different process. This also had a cost. I found the first package of HES data did not give me some vital patient-level data and I had to negotiate with the HES team.

After doing the literature reviews and taking on the helpful comments from the MPhil upgrade panel, I saw the need for two methods for VTE-BC to strive to make the study meaningful for patients. I had some experience with quantitative research

before, but the qualitative component was very odd for me at the beginning. I read extensively on qualitative methodology, study examples and how to apply qualitative designs to studies in healthcare. As a physician, the qualitative part was the trickiest for me, coming from a different culture and health system where the doctor is obeyed and there is not much scope to explore or discuss patient feelings and involvement or partnership. The analysis was the most critical part for me because as I realised for the first time in my career, the potential for findings of qualitative research to influence healthcare and health policies. I am very happy to upskill in mixed methods in order to collaborate with others in the future, in particular, Middle Eastern colleagues.

The interviews with patients and HCPs uncovered varied views. Interviews with HCPs were more focused on the related information and shorter in duration than patient interviews. During interviews with patients, a lot of unrelated information was given, and I improved my interview technique as the study progressed at bringing the patients back to the main subject in order to have more related information. The main finding was that patients have limited awareness on VTE and are dealt a poor deal was alarming to me and will make me focus more and disseminate to colleagues on the importance of individualised assessment of risk factors for VTE and improving patient education on VTE along the continuum of care.

In the interviews, I felt the participants managed to give me frank answers and all of them were very cooperative. No-one became angry or upset from the interview or the questions. Most of all, I was aware of the huge pressures of time and concentration, in particular for the patients and their caregivers. I was humbled by their patience and remarks during what was an extremely difficult time for them. I am very thankful for the time and thoughts of all participants during the interviews.

I feel that my PhD journey will impact positively on future patients and all HCPs and indeed my own encounters with people with cancer.

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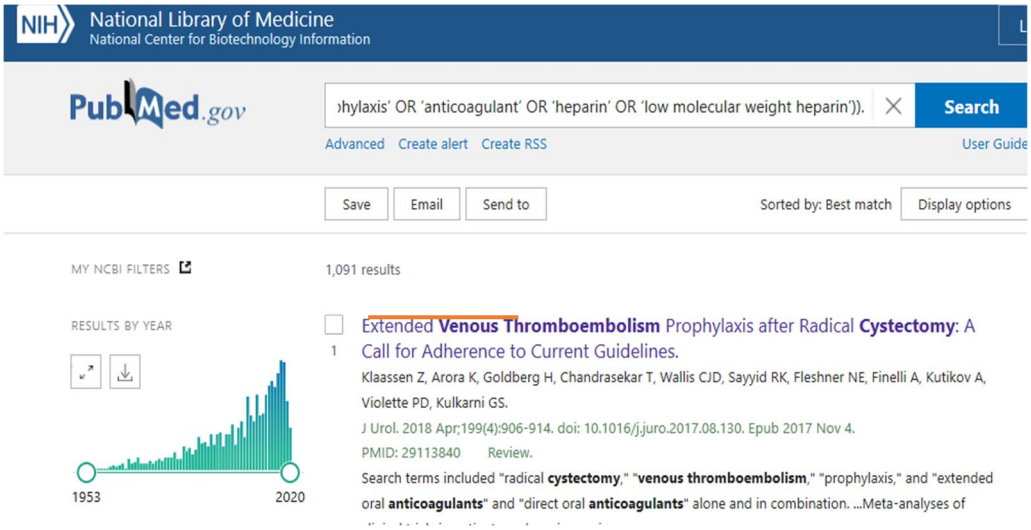
Appendices

Appendix 1: Sample of search of systematic review



Search History (19)

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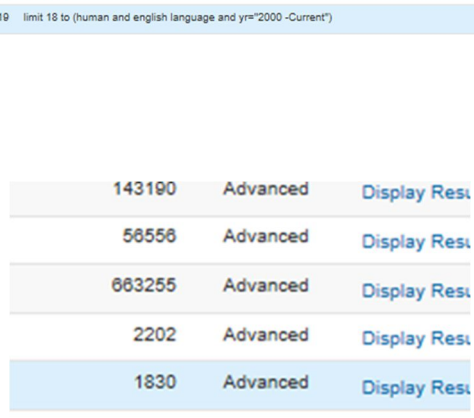
2	bladder urothelial carcinoma.mp. or exp transitional cell carcinoma/	28571	Advanced	Display Results | More
3	exp bladder/	109285	Advanced	Display Results | More
4	exp cancer chemotherapy/ or exp adjuvant chemotherapy/ or exp chemotherapy/ or exp neoadjuvant chemotherapy/	669137	Advanced	Display Results | More
5	exp "patient history of cystectomy"/ or exp cystectomy/	29671	Advanced	Display Results | More
6	exp anticoagulant agent/ or exp low molecular weight heparin/ or thromboprophylaxis.mp. or exp dalteparin/ or exp heparin/ or exp enoxaparin/	692978	Advanced	Display Results | More
7	3 and 4	4744	Advanced	Display Results | More
8	3 and 5	5076	Advanced	Display Results | More
9	3 and 6	951	Advanced	Display Results | More
10	1 or 2 or 7 or 8 or 9	109697	Advanced	Display Results | More
11	exp thrombosis/ or exp thrombosis prevention/ or exp vein thrombosis/ or exp deep vein thrombosis/	357593	Advanced	Display Results | More
12	exp thromboembolism/ or exp venous thromboembolism/	532917	Advanced	Display Results | More
13	VTE.mp.	21300	Advanced	Display Results | More
14	DVT.mp. or exp lung embolism/	112258	Advanced	Display Results | More
15	PE.mp.	143190	Advanced	Display Results | More
16	Pulmonary embolism.mp.	56556	Advanced	Display Results | More
17	11 or 12 or 13 or 14 or 15 or 16	663255	Advanced	Display Results | More
18	10 and 17	2202	Advanced	Display Results | More
19	limit 18 to (human and english language and yr="2000 -Current")	1830	Advanced	Display Results | More



Appendix 2: Newcastle-Ottawa quality assessment form

Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort

a) Truly representative (one star)

b) Somewhat representative (one star)

c) Selected group

d) No description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) Drawn from the same community as the exposed cohort (one star)

b) Drawn from a different source

c) No description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

a) Secure record (e.g., surgical record) (one star)

b) Structured interview (one star)

c) Written self-report

d) No description

e) Other

4) Demonstration that outcome of interest was not present at start of study

a) Yes (one star)

b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders

a) The study controls for age, sex and marital status (one star)

b) Study controls for other factors (list) _____ (one star)

c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

1) Assessment of outcome

a) Independent blind assessment (one star)

b) Record linkage (one star)

c) Self report

d) No description

e) Other

2) Was follow-up long enough for outcomes to occur

a) Yes (one star)

b) No

Indicate the median duration of follow-up and a brief rationale for the assessment above:_____

3) Adequacy of follow-up of cohorts

a) Complete follow up- all subject accounted for (one star)

b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (one star)

c) Follow up rate less than 80% and no description of those lost

d) No statement

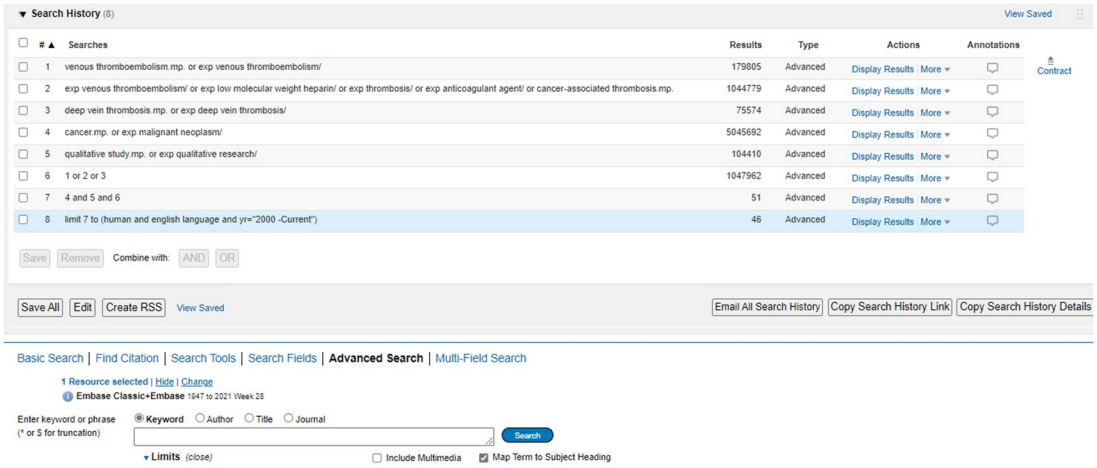
Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Appendix 3: Samples of search of scoping review (Embase, Scopus, Medline)



▼ Search History (8) View Saved

# ▲	Searches	Results	Type	Actions	Annotations
1	venous thromboembolism.mp. or exp venous thromboembolism/	179805	Advanced	Display Results | More	
2	exp venous thromboembolism/ or exp low molecular weight heparin/ or exp thrombosis/ or exp anticoagulant agent/ or cancer-associated thrombosis.mp.	1044779	Advanced	Display Results | More	
3	deep vein thrombosis.mp. or exp deep vein thrombosis/	75574	Advanced	Display Results | More	
4	cancer.mp. or exp malignant neoplasm/	5045692	Advanced	Display Results | More	
5	qualitative study.mp. or exp qualitative research/	104410	Advanced	Display Results | More	
6	1 or 2 or 3	1047962	Advanced	Display Results | More	
7	4 and 5 and 6	51	Advanced	Display Results | More	
8	limit 7 to (human and english language and yr="2000 -Current")	46	Advanced	Display Results | More	

Save | Remove | Combine with: AND | OR

Save All | Edit | Create RSS | View Saved | Email All Search History | Copy Search History Link | Copy Search History Details

Basic Search | Find Citation | Search Tools | Search Fields | **Advanced Search** | Multi-Field Search

1 Resource selected | Hide | Change
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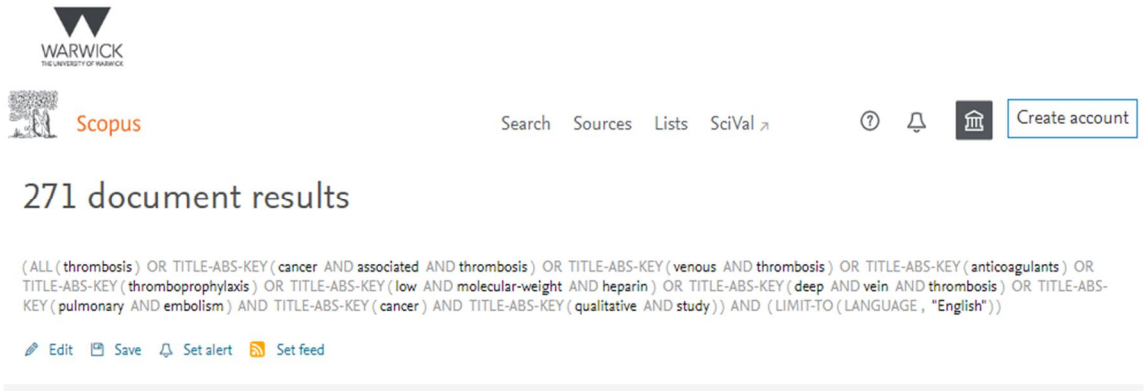
Enter keyword or phrase (* or $ for truncation) — Keyword | Author | Title | Journal — Search

▾ Limits (close) — Include Multimedia — Map Term to Subject Heading



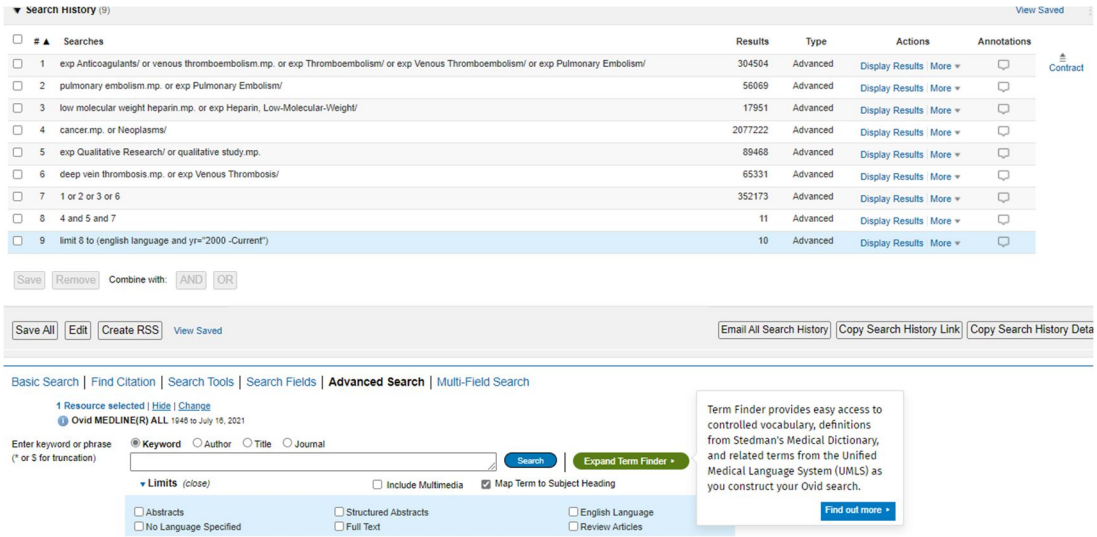
WARWICK

Scopus — Search | Sources | Lists | SciVal — Create account

271 document results

(ALL (thrombosis) OR TITLE-ABS-KEY (cancer AND associated AND thrombosis) OR TITLE-ABS-KEY (venous AND thrombosis) OR TITLE-ABS-KEY (anticoagulants) OR TITLE-ABS-KEY (thromboprophylaxis) OR TITLE-ABS-KEY (low AND molecular-weight AND heparin) OR TITLE-ABS-KEY (deep AND vein AND thrombosis) OR TITLE-ABS-KEY (pulmonary AND embolism) AND TITLE-ABS-KEY (cancer) AND TITLE-ABS-KEY (qualitative AND study)) AND (LIMIT-TO (LANGUAGE , "English"))

Edit | Save | Set alert | Set feed



▼ Search History (9) View Saved

# ▲	Searches	Results	Type	Actions	Annotations
1	exp Anticoagulants/ or venous thromboembolism.mp. or exp Thromboembolism/ or exp Venous Thromboembolism/ or exp Pulmonary Embolism/	304504	Advanced	Display Results | More	
2	pulmonary embolism.mp. or exp Pulmonary Embolism/	56069	Advanced	Display Results | More	
3	low molecular weight heparin.mp. or exp Heparin, Low-Molecular-Weight/	17951	Advanced	Display Results | More	
4	cancer.mp. or Neoplasms/	2077222	Advanced	Display Results | More	
5	exp Qualitative Research/ or qualitative study.mp.	89468	Advanced	Display Results | More	
6	deep vein thrombosis.mp. or exp Venous Thrombosis/	65331	Advanced	Display Results | More	
7	1 or 2 or 3 or 6	352173	Advanced	Display Results | More	
8	4 and 5 and 7	11	Advanced	Display Results | More	
9	limit 8 to (english language and yr="2000 -Current")	10	Advanced	Display Results | More	

Save | Remove | Combine with: AND | OR

Save All | Edit | Create RSS | View Saved | Email All Search History | Copy Search History Link | Copy Search History Deta

Basic Search | Find Citation | Search Tools | Search Fields | **Advanced Search** | Multi-Field Search

1 Resource selected | Hide | Change
Ovid MEDLINE(R) ALL 1946 to July 16, 2021

Enter keyword or phrase (* or $ for truncation) — Keyword | Author | Title | Journal — Search | Expand Term Finder

▾ Limits (close) — Include Multimedia — Map Term to Subject Heading

Abstracts | Structured Abstracts | English Language
No Language Specified | Full Text | Review Articles

Term Finder provides easy access to controlled vocabulary, definitions from Stedman's Medical Dictionary, and related terms from the Unified Medical Language System (UMLS) as you construct your Ovid search.

Find out more

Appendix 4: Codes used for HES data

Codes for ICD-10 and OPCS-4.8 clinical coding for:

Bladder Carcinoma

Venous thromboembolism

Chemotherapy

Cystectomy

A- Codes of bladder carcinoma

C67 Malignant neoplasm of bladder

C67.0 Malignant neoplasm of trigone of bladder

C67.1 Malignant neoplasm of dome of bladder

C67.2 Malignant neoplasm of lateral wall of bladder

C67.3 Malignant neoplasm of anterior wall of bladder

C67.4 Malignant neoplasm of posterior wall of bladder

C67.5 Malignant neoplasm of bladder neck

C67.6 Malignant neoplasm of ureteric orifice

C67.7 Malignant neoplasm of urachus

C67.8 Malignant neoplasm of overlapping sites of bladder

C67.9 Malignant neoplasm of bladder, unspecified

B- Codes of venous thromboembolism (VTE)

I82.2 Embolism and thrombosis of vena cava and other thoracic veins

I82.3 Embolism and thrombosis of renal vein

I82.4 Acute embolism and thrombosis of deep veins of lower extremity

I82.5 Chronic embolism and thrombosis of deep veins of lower extremity

I82.6 Acute embolism and thrombosis of veins of upper extremity

I82.7 Chronic embolism and thrombosis of veins of upper extremity

I82.A Embolism and thrombosis of axillary vein

I82.B Embolism and thrombosis of subclavian vein

I82.C Embolism and thrombosis of internal jugular vein

I82.8 Embolism and thrombosis of other specified veins

I82.9 Embolism and thrombosis of unspecified vein

I26 Pulmonary embolism

I26.0 Pulmonary embolism with acute cor pulmonale

I26.9 Pulmonary embolism without acute cor pulmonale

C- Codes of chemotherapy (OPCS 4.8.)

X70.1 Cisplatin + methotrexate + vinblastine (CMV)

X70.2 methotrexate + vinblastine + doxorubicin + cisplatin (MVAC)

X70.3 paclitaxel 7 day

X70.4 methotrexate + vinblastine + doxorubicin + cisplatin (MVAC) Accelerated

X71.1 Gemcitabine + Carboplatin days 1+8

X71.1 Gemcitabine 1000mg/m^2 D1, 8, 15

X71.1 paclitaxel 2 or 3 weekly

X71.2 Gemcitabine + cisplatin

X71.2 Gemcitabine 1250mg/m^2 D1, 8, 15

X71.3 paclitaxel (Abraxane)

X71.4 paclitaxel priming

X71.5 Gemcitabine + paclitaxel

D- Codes of Cystectomy (OPCS)

M34 cystectomy

M34.1 Cystoprostatectomy

M34.2 Cystourethrectomy

M34.3 Cystectomy (not elsewhere classified),

M34.4 Simple cystectomy

M34.8 Other specified total excision of bladder

M34.9 Unspecified total excision of bladder

Appendix 5: Interview topic guide

Patient Interview Topic Guide

Preamble / Introduction – thank you and purpose of the interview. What a venous thromboembolism is – deep vein thrombosis (DVT) and pulmonary embolism (PE)

1. Briefly introduction from the patient on themselves and their cancer pathway so far
2. Knowledge about clots associated with the cancer

If yes, Probe – e.g. causes of clot formation in your condition?

3. Knowledge on the possibility of getting a clot
4. Knowledge on how to identify if you have a clot
   (Probe: Do you know what the signs and symptoms are of having a clot?)
5. Knowledge about surgery and relation to clots as well as knowledge about medication and having the medication to prevent clots?

Probe – if yes, who, what, when, how, how long

6. Knowledge about chemotherapy and relation to clots? If yes, tell me if told about clots – who, what, when
7. Discussing anti-clotting treatment at any other time apart from surgery? (probe: injections or tablets) If no. go to Q10.
   If yes, the experience of receiving the blood thinners what, when, how long
8. If not mentioned above, knowledge patient has about the benefits and challenges or risks of anti-clotting treatment? Probe – heard about bleeding risk?
9. This research is hoping to improve how the risk of clots is communicated to cancer patients. Going back to the information you received from XYZ about clots, tell me a little bit about your experience of receiving this information. (probe: How did it make you feel? Is there anything that could be improved/changed to make the experience better?)
10. Discussion on the best way to inform patients about their risk of developing clots? Why? (probe: What is the best method of presenting risk information to patients? Using numbers, percentages, words, figure, combinations or all (present the tools), individual risk or average, fear messages or positive messages?).

Professional Healthcare Interview Topic Guide

1. Briefly introduction from participants on themselves and their speciality
2. What is the Knowledge about venous thromboembolism (DVT and PE) given to the patients?
3. Type of information given to the cancer patients about venous thromboembolism risk in cancer.

   Which will be answered by the following questions:

   a) Do you tell your cancer patients about the signs and symptoms of thromboembolism?
   b) Do you tell your cancer patients about different preventative approaches that could affect getting thromboembolism?
   c) Do you tell your cancer patients about the risk of chemotherapy for thromboembolism?
   d) Do you tell the patients about the risk of surgery for the thromboembolism?
   e) Do you inform your cancer patients about the benefits and challenges or risks of anti-clotting treatment? (probe: Do you inform your cancer patients about the bleeding risk?)
   f) This research is hoping to improve how the risk of thromboembolism is communicated to cancer patients. Could you tell me a little bit regarding your experience of informing cancer patients about this information? (probe: How did it make them feel? Is there anything that could be improved/changed to make the experience better?)
4. Discussion on the best way to inform patients about their risk of developing thromboembolism, Why? (probe: What is the best method of presenting risk information to patients? Using numbers, percentages, words, figure, combinations or all (present the tools), individual risk or average, fear messages or positive messages?).

Appendix 6: Definitions of research philosophy and related topics

- Research philosophy may be defined as a belief regarding the approach or way data about a phenomenon should be collected and analysed (Jabareen, 2009).

- Philosophical assumptions are the first ideas in developing a study. They shape how the research problems and questions are formulated, and how the researcher can search for information to answer the questions (Morehouse & Maykut, 20022).

- Philosophical assumption may be defined as the theoretical framework applied by researchers to gather and analyse the data that is collected in a study. This can determine the background applied for coming to conclusions or decisions (Saunders et al., 2009124; Wahyuni, 2012).

- Ontology is the nature of reality and the study of being. In other words, it is a study of existence (Crotty, 199810). Generally, ontology influences the selection of the research objectives, the research questions and how the research is conducted (Wahyuni, 2012).

- Epistemology is the study of the nature and scope of knowledge and how belief may be justified (Maynard, 1994). Being simply defined as the study of knowledge, it is concerned with the nature and forms of knowledge (Cohen *et al.*, 20077). It is about "how we know what we know" (Crotty, 19987).

- Axiology is a branch of philosophy that is concerned with the role of principles and values (Saunders *et al.*, 2012). More specifically, axiology is engaged with the assessment of the role of the researcher's own values at all stages of the research process (Wahyuni, 2012). Axiology primarily refers to the 'aims' of the research. This branch of research philosophy attempts to clarify if one is seeking to explain or predict the world or only seeking to understand it (Biddle & Schafft, 2015).
- Within the positivist paradigm, there is no place for values in research, as this may introduce bias; however, interpretative research is the process of interpersonal

revelation and therefore may have potential bias by its very nature (Guba & Lincoln, 1994).

- A paradigm, also known as a conceptual framework, has a set of fundamental beliefs and assumptions as to how the world is perceived and investigated (Wahyuni, 2012). A research paradigm is an approach or framework that guides research and makes judgements about its subjects and outcomes (Kawulich, 2012), and helps define the research philosophy.

- The interpretivist paradigm is concerned with an understanding of researchers interpretation of the research (McKenna *et al.*, 2011). Interpretivism leans towards qualitative research because its approach is based on the naturalistic approach of data collection such as observations and interviews (Wahyuni, 2012). Interpretivism is subjective and rejects absolute facts generally favoured by positivist (Wahyuni, 2012).
- Usually, interpretivism concerns people's subjective experiences on how they interact with or relate to each other, and in this approach, the knowledge is personally experienced, not only acquired from outside.

- Research paradigms are distinguished using the following ways of viewing a research philosophy: ontology, epistemology, methodology, and, methods. As a result, the ontology, epistemology, methodology and methods are the major components of any research (Grant & Giddings, 2002).

- The pragmatic paradigm started in the United States in the 19th century. Initially, the pragmatic paradigm was attributed to Charles Sanders Peirce (1839–1914) and William James (1842–1910) (Leary, 2009). The appearance of the pragmatic paradigm occurred concurrently with that of the mixed-methods approach (Wahyuni, 2012). The pragmatic paradigm typically endorses a mixed-method framework with acknowledgement to both objective and subjective phenomena depending on the research question (Wahyuni, 2012). Onwuegbuzie and Johnson, 2006 suggest that perhaps what is seen as contradictory are different perspectives that are complementary, and enable one to more fully to see one's world (Onwuegbuzie & Johnson, 200654).

- The positivist paradigm utilises objective scientific investigation and deductive methods to test a hypothesis based on an existing theory. This approach fits in with

quantitative research, as it considers empirical hypothesis testing. In quantitative research, the research follows a probabilistic model that is determined by previous research (Lee & Lings, 200828). 'Positivists' have a preference for quantitative methods such as social surveys, structured questionnaires and official statistics because these provide good reliability and representativeness.

- The interpretivist paradigm is concerned with an understanding of researchers interpretation of the research (McKenna *et al.*, 2011). Interpretivism leans towards qualitative research because its approach is based on the naturalistic approach of data collection such as observations and interviews (Wahyuni, 2012). Interpretivism is subjective and rejects absolute facts generally favoured by positivist (Wahyuni, 2012).
- Usually, interpretivism concerns people's subjective experiences on how they interact with or relate to each other, and in this approach, the knowledge is personally experienced, not only acquired from outside.

- A methodology is, in essence, a plan of action which lies behind the choice and use of particular methods, and concerns how the research will proceed (Crotty, 199833). Guba and Lincoln (1994) explain methodology as a means of asking the following question: how can the inquirer go about finding out whatever they believe can be known? (Guba & Lincoln, 1994108).
- *"A methodology is a collection of procedures, techniques, tools and documentation aids, supported by a philosophy which help the system developers in their efforts to implement a new information system" (Avison & Fitzgerald, 2003)*

Appendix 7: BSREC ethical approval

WARWICK
THE UNIVERSITY OF WARWICK

PRIVATE
Dr Omar Abdullah
Warwick Medical School
University of Warwick
Coventry
CV4 7AL

22 August 2017

Dear Dr Abdullah,

Study Title and BSREC Reference: *Venous Thromboembolism in muscle invasive, locally advanced, or metastatic urothelial cancer, with or without chemotherapy (VT U CAN)* REGO-2017-2034

Thank you for submitting your revisions to the above-named study to the University of Warwick's Biomedical and Scientific Research Ethics Sub-Committee for approval.

I am pleased to confirm that approval is granted and that your study may commence.

In undertaking your study, you are required to comply with the University of Warwick's *Research Data Management Policy*, details of which may be found on the Research and Impact Services' webpages, under "Codes of Practice & Policies" » "Research Code of Practice" » "Data & Records" » "Research Data Management Policy", at:
http://www2.warwick.ac.uk/services/ris/research_integrity/code_of_practice_and_policies/research_code_of_practice/datacollection_retention/research_data_mgt_policy

You are also required to comply with the University of Warwick's *Information Classification and Handling Procedure*, details of which may be found on the University's Governance webpages, under "Governance" » "Information Security" » "Information Classification and Handling Procedure", at:
http://www2.warwick.ac.uk/services/gov/informationsecurity/handling.
Investigators should familiarise themselves with the classifications of information defined therein, and the requirements for the storage and transportation of information within the different classifications:

Information Classifications:
http://www2.warwick.ac.uk/services/gov/informationsecurity/handling/classifications
Handling Electronic Information:
http://www2.warwick.ac.uk/services/gov/informationsecurity/handling/electronic/
Handling Paper or other media
http://www2.warwick.ac.uk/services/gov/informationsecurity/handling/paper/.

Please also be aware that BSREC grants **ethical approval** for studies. **The seeking and obtaining of *all* other necessary approvals is the responsibility of the investigator.**

www.warwick.ac.uk

These other approvals may include, but are not limited to:

1. Any necessary agreements, approvals, or permissions required in order to comply with the University of Warwick's Financial Regulations and Procedures.
2. Any necessary approval or permission required in order to comply with the University of Warwick's Quality Management System and Standard Operating Procedures for the governance, acquisition, storage, use, and disposal of human samples for research.
3. All relevant University, Faculty, and Divisional/Departmental approvals, if an employee or student of the University of Warwick.
4. Approval from the applicant's academic supervisor and course/module leader (as appropriate), if a student of the University of Warwick.
5. NHS Trust R&D Management Approval, for research studies undertaken in NHS Trusts.
6. NHS Trust Clinical Audit Approval, for clinical audit studies undertaken in NHS Trusts.
7. Approval from Departmental or Divisional Heads, as required under local procedures, within Health and Social Care organisations hosting the study.
8. Local ethical approval for studies undertaken overseas, or in other HE institutions in the UK.
9. Approval from Heads (or delegates thereof) of UK Medical Schools, for studies involving medical students as participants.
10. Permission from Warwick Medical School to access medical students or medical student data for research or evaluation purposes.
11. NHS Trust Caldicott Guardian Approval, for studies where identifiable data is being transferred outside of the direct clinical care team. Individual NHS Trust procedures vary in their implementation of Caldicott guidance, and local guidance must be sought.
12. Any other approval required by the institution hosting the study, or by the applicant's employer.

There is no requirement to supply documentary evidence of any of the above to BSREC, but applicants should hold such evidence in their Study Master File for University of Warwick auditing and monitoring purposes. You may be required to supply evidence of any necessary approvals to other University functions, e.g. The Finance Office, Research & Impact Services (RIS), or your Department/School.

May I take this opportunity to wish you success with your study, and to remind you that any Substantial Amendments to your study require approval from BSREC before they may be implemented.

Yours sincerely

pp. [redacted]

Professor John Davey
Chair
Biomedical and Scientific
Research Ethics Sub-Committee

Biomedical and Scientific
Research Ethics Sub-Committee
Research & Impact Services
University of Warwick
Coventry, CV4 8UW.
E: BSREC@Warwick.ac.uk

http://www2.warwick.ac.uk/services/ris/research_integrity/researchethicscommittees/biomed

Appendix 8: Sponsorship, University of Warwick act as research sponsor (Phase I)

WARWICK
THE UNIVERSITY OF WARWICK

Dr Maria De Santis
Warwick Medical School
University of Warwick
Coventry
CV4 7AL
United Kingdom

1 November 2017

Project Title: Venous Thromboembolism in muscle invasive, locally advanced, or metastatic urothelial cancer, with or without chemotherapy (VT U CAN)
Chief Investigator: Dr Maria De Santis
PhD Student: Omar Riyadh Abdullah Abdullah
Our Ref: SC.88/16-17

Dear Dr De Santis,

I confirm that the University of Warwick will act as research sponsor for the above project, in accordance with the Department of Health's Research Governance Framework for Health and Social Care (2005), and, where appropriate, UK Statutory Instrument Number 1031, that implements the Medicines for Human Use (Clinical Trials) Directive 2004 and subsequent amendments; effective from 1 November 2017.

I confirm that the University holds Public and Products Liability Insurance, and, where appropriate, Clinical Trial Insurance, which will provide cover for this study.

Any researcher involved in the project is required at all times to comply with the University of Warwick's Research Codes of Practice and Policies, available on the Research and Impact Services website via the following link:
http://www2.warwick.ac.uk/services/ris/research_integrity/code_of_practice_and_policies/

Researchers are also required to comply with all relevant requirements of Standard Operating Procedures (SOPs), which are applicable to all University of Warwick sponsored studies and are available via the following link:
http://www2.warwick.ac.uk/fac/med/research/hscience/ctu/conducting/planning/sop/

In particular, please ensure that you are familiar with the relevant safety and reporting requirements applicable to your study, as set out in SOP 17 'Safety Reporting' and SOP 31 'Deviations, Violations, Misconduct and Serious Breaches of GCP and/or Trial Protocol'.

As research sponsor the University of Warwick is committed to ensuring that studies carried out under its auspices are delivered to the highest standards, in order to ensure the safety of participants, the integrity of the study and compliance with applicable legislation, regulations and guidance. As part of this commitment, the University has established a programme of

Appendix 9: Sponsorship, University of Warwick act as research sponsor (Phase II)

Dr Deepak Parashar
Warwick Medical School
University of Warwick
Coventry
CV4 7AL
United Kingdom

29 January 2019

Project Title: Venous Thromboembolism in Cancer Patients: patients' experiences (VTC-Exp)
Chief Investigator: Dr Deepak Parashar
PhD student: Omar Abdullah
Our Ref: SC.02/18-19

Dear Dr Parashar,

I confirm that the University of Warwick will act as research sponsor for the above project, in accordance with the UK Policy Framework for Health & Social Care Research (2017) and, where appropriate, UK Statutory Instrument Number 1031, that implements the Medicines for Human Use (Clinical Trials) Directive 2004 and subsequent amendments; effective from 29 January 2019.

I confirm that the University holds Public and Products Liability Insurance, and, where appropriate, Clinical Trial Insurance, which will provide cover for this study.

Any researcher involved in the project is required at all times to comply with the University of Warwick's Research Codes of Practice and Policies, available on the Research and Impact *Services website via the following link:*
http://www2.warwick.ac.uk/services/ris/research_integrity/code_of_practice_and_policies/

If you have not already done so it is strongly recommended that you complete the on-line Research Integrity training available via the following link: www.warwick.ac.uk/ritraining

Researchers are also required to comply with all relevant requirements of Standard Operating Procedures (SOPs), which are applicable to all University of Warwick sponsored studies and are available via the following link:
https://warwick.ac.uk/fac/med/research/ctu/conducting/planning/sop2016

In particular, please ensure that you are familiar with the relevant safety and reporting requirements applicable to your study, as set out in SOP 17 'Safety Reporting' and SOP 31 'Deviations, Violations, Misconduct and Serious Breaches of GCP and/or Trial Protocol'.

Researchers processing (including collecting, storing, sharing or disposing of) personal data as defined in the General Data Protection Regulation (GDPR), including pseudonymised data, are required to comply with the principles set out in the GDPR. In addition, researchers are required to complete both the GDPR and Information Security Essentials e-learning courses prior to undertaking the research. Both courses and further GDPR guidance can be accessed via the following link to the Information & Data Compliance Team GDPR webpages: https://warwick.ac.uk/services/idc/other/

Prior to commencing your study you will be required to sign and return the completed 'Division of Sponsor Responsibilities Form', which sets out the study responsibilities delegated to you by the University as research sponsor. If you have not already done so please return the completed form to sponsorship@warwick.ac.uk

Please notify the Sponsor's Office via email to sponsorship@warwick.ac.uk of any key changes to your University sponsored study throughout its lifecycle, in particular if your study requires amendment, changes status, closes, is completed or if there are any changes to the proposed or anticipated closure date.

In addition, please copy the above email address into any Annual Progress Reports or End of Study Notifications sent to the Health Research Authority (HRA) or Research Ethics Committee (REC).

If you have any queries regarding these responsibilities or research sponsorship more generally, please contact the Sponsor's Office via email at: sponsorship@warwick.ac.uk

Kind regards,

[redacted]

Mathew Gane
Secretary, Sponsorship Committee

The University of Warwick
Coventry
CV4 7AL
E: sponsorship@warwick.ac.uk
T: [redacted]

Appendix 10: HRA approval for phase I

NHS
Health Research Authority

Professor Maria De Santis
University of Warwick
Clinical Trials Unit
Coventry/UK
CV4 7AL

Email: hra.approval@nhs.net

13 March 2018

Dear Professor De Santis

Letter of HRA Approval

Study title:	**Venous thromboembolism in muscle-invasive, locally advanced or metastatic urothelial bladder carcinoma with or without chemotherapy (VT-U-CAN)**
IRAS project ID:	**231338**
Protocol number:	**Sponsorship/SC.88/16-17**
Sponsor	**University of Warwick**

I am pleased to confirm that **HRA 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 from the HRA.

How should I continue to work with participating NHS organisations in England?
You should now provide a copy of this letter to all participating NHS organisations in England, 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 should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of HRA assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

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, Scotland and Wales?
HRA Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland, Scotland and Wales.

IRAS project ID	231338

If you indicated in your IRAS form that you do have participating organisations in one or more devolved administration, the HRA has sent the final document set and the study wide governance report (including this letter) 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 Northern Ireland, Scotland and Wales.

How should I work with participating non-NHS organisations?
HRA 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 attached document *"After HRA Approval – guidance for sponsors and investigators"* gives detailed guidance on reporting expectations for studies with HRA Approval, 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.

I am a participating NHS organisation in England. 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: Ms Jane Prewett
Tel: [redacted]
Email: sponsership@warwick.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 **231338**. Please quote this on all correspondence.

Yours sincerely

Kevin Ahmed
Assessor

Telephone: [redacted]
Email: hra.approval@nhs.net

Appendix 11: HRA approval for phase II

Dr Deepak Parashar
Division of Health Sciences, Warwick Medical School
University of Warwick
Coventry/UK
CV4 7AL

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

04 June 2019

Dear Dr Parashar

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

Study title:	**Venous Thromboembolism in Cancer Patients: Patients' Experiences**
IRAS project ID:	**256564**
Protocol number:	**2**
REC reference:	**19/LO/0940**
Sponsor	**University of Warwick**

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.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

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 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) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

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.

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 **256564**. Please quote this on all correspondence.

Yours sincerely,

Natalie Wilson
Approvals Specialist

Email: nrescommittee.london-camdenandkingscross@nhs.net

Copy to: *Mrs Jane Prewett, University of Warwick, Sponsor contact*
Mr Omar Abdullah, University of Warwick, Student researcher