Thromboprophylaxis

in Cancer Patients

with Central Venous Catheters

by

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Dedicated to my family: David, my remarkable husband who put up with me hiding in the study night after night and my three wonderful and patient children, Stewart, Sarah and Fiona; my dad, two sisters, who care for me always and in memory of my mum who died in November 2008 and when well, constantly encouraged me to ‘go for it’.

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1. Glossary

5-FU	5-Fluorouracil
APC	Activated Protein C
AT	Antithrombin
CDG	Clinical Development Group
CI	Confidence Interval
CRF	Case Record Form
CRT	Catheter-related Thrombosis
CTC	Common Toxicity Criteria
CVC	Central Venous Catheter
DAW	Dose Adjusted Warfarin
DMC	Data Monitoring Committee
DVT	Deep Vein Thrombosis
FDW	Fixed Dose Warfarin
GCP	Good Clinical Practice
GP	Glycoprotein
ICAM	Intracellular Adhesion Molecule
ICH	International Conference on Harmonisation
INR	International Normalised Ratio
ITT	Intention to Treat
LMWH	Low Molecular Weight Heparin
LREC	Local Research Ethics Committee
MREC	Multicentre Research Ethics Committee

NCRN	National Cancer Research Network
NICE	National Institute of Health and Clinical Excellence
OR	Odds Ratio
PAI	Plasminogen Activator Inhibitor
PAR	Protease-activated Receptor
PE	Pulmonary Embolus / Emboli
PICC	Peripherally Inserted Central Catheter
PT	Prothrombin Time
RR	Relative Risk
SAE	Serious Adverse Event
SCLC	Small Cell Lung Cancer
SVC	Superior Vena Cava
TAFI	Thrombin Activatable Fibrinolysis Inhibitor
TF	Tissue Factor
TFPI	Tissue Factor Pathway Inhibitor
tPA	Tissue Plasminogen Activator
UFH	Unfractionated Heparin
V/Q; V-P	Ventilation/Perfusion (Scanning)
V-CAM	Vascular Cell Adhesion Molecule
VEGF	Vascular Endothelial Growth Factor
VTE	Venous Thromboembolism / Thromboemboli
vWF	von Willebrand Factor
WARP	WARfarin Prophylaxis

2. Abstract

This thesis focuses on a nurse-led trial assessing the thromboprophylactic utility of warfarin in cancer patients (n=1590) with central venous catheters and designed following a UK survey of practice.

Clinicians who were 'uncertain' of the benefits of warfarin, randomised patients to no warfarin *vs* fixed dose warfarin of 1mg (FDW) *vs* dose adjusted warfarin (DAW) to maintain the international normalised ratio (INR) between 1.5 and 2.0. Clinicians, who were 'certain', randomised patients between FDW and DAW. The primary endpoint was the number of symptomatic catheter-related thrombotic events (CRT).

Compared to no warfarin, warfarin (79% FDW; 21% DAW) did not reduce CRT [5.9% vs 5.9%; relative risk (RR) 0.99, (95% Confidence Interval (CI) 0.57-1.72), p=0.98]. However, compared to FDW, DAW was superior in preventing CRT [2.8% vs 7.2%; RR 0.38, (95%CI 0.20-0.71), p=0.002]. Major bleeding events were rare; an excess was observed with warfarin compared to no warfarin (7 vs 1, p=0.07) and with DAW compared to FDW (16 vs 7, p=0.09).

There is no benefit in using low dose warfarin in CRT prophylaxis. DAW shows benefit over FDW but at a cost of major bleeding events. Subsequent meta-analysis confirmed the primary finding. This research has changed clinical practice internationally.

3. Introduction and Background

3.1 *Introduction*

Venous thromboembolism (VTE) is well recognised as a complication of cancer. In comparison with other patient groups, the cancer population is distinctive because the pathogenesis of cancer-related VTE differs, the frequency and risk of recurrent of VTE is increased and the clinical management of prophylaxis and treatment is more complex.

There are three clinical goals for anticoagulation of cancer patients: primary prophylaxis, optimal management of VTE and to alter the natural history of the cancer by reducing the potential for metastasis, all of which pose difficult therapeutic challenges to the clinician. This thesis focuses on the first objective: the prophylaxis of thrombosis with warfarin in cancer patients receiving chemotherapy via central venous catheters (CVCs), in a clinical trial setting. This nurse-led clinical trial, WARP (acronym for WARfarin Prophylaxis) stemmed from empirical observations recording the increased frequency of VTE and wide variation in thromboprophylactic measures whilst nursing patients receiving chemotherapy via CVCs. A national pre-trial survey, based on this experience gathered in a single large cancer centre, was then undertaken to garner clinical views on thromboprophylaxis and whether a multicentre trial to address this problem was rational and timely. This resulted in WARP, a randomised, phase III trial assessing the utility of warfarin in this patient group. The study design, based on the uncertainty principle, was structured to encompass contemporary clinical opinion. Oncology nurses and physicians who were 'uncertain'

of the benefits of warfarin in thromboprophylaxis, could randomise patients to control (no warfarin) *vs* fixed dose warfarin of 1mg (FDW) *vs* dose adjusted warfarin (DAW) to maintain the international normalised ratio (INR) between 1.5 and 2.0. Clinicians, who were 'certain' of the indication for warfarin, and who did not support the need for a control arm, randomised patients between FDW and DAW. This pragmatic trial design united the entire clinical community and enabled two linked hypotheses to be tested: (i) whether warfarin (any dose) reduces catheter-related thrombosis (CRT) relative to no warfarin (warfarin evaluation) and (ii) whether DAW is superior to FDW (dose evaluation). The primary endpoint of the trial was the number of catheter-related thrombotic events with the secondary endpoints including the number of non-catheter-related thrombotic events, duration of catheter patency, trial-related adverse events, trial-related costs and patient mortality.

Although WARP was designed as the largest and therefore likely to be the most informative trial in the field, it was important to contextualise it relative to other trials evaluating the efficacy of pharmacologic thromboprophylaxis in patients with cancer; therefore meta-analyses of relevant trials were undertaken.

Increasingly, funding bodies are demanding that careful plans for dissemination of research findings are included with the primary trial proposal as part of a wider drive to accelerate conversion of research findings into practice. Following on from publication of this work, an invitation was received to contribute to the first UK thromboprophylaxis guidelines, 'Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital, thus

incorporating the results of this research into national guidelines and greatly increasing its visibility to frontline multidisciplinary teams.

3.2 *Aims and Objectives of Thesis*

There are three stepped aims of this thesis with linked objectives:

Aim 1: Conduct a national survey to identify:

- current clinical practices for prophylaxis of thrombosis in patients with CVCs
- ascertain if CRT was deemed an important clinical problem
- establish the interest in participation in a 3-arm clinical trial of no warfarin vs 1mg warfarin/day vs warfarin to maintain the INR between 1.5 and 2.0. This range was taken from earlier trials in which it was found to be safe. The initial trial design had been prepared in consultation with key opinion leaders in the field.

Aim 2: Design and deliver WARP, a pragmatic trial with the following objectives:

- determine the utility of any warfarin in reducing CVC-related thrombosis rates in cancer patients
- determine whether variable dose warfarin was superior to fixed dose warfarin in reducing CVC thrombosis rates
- assess warfarin-related toxicity and monitor the trial-related adverse events
- determine the effect of warfarin (fixed and variable dose) on overall thrombosis rates
- compare survival of patients in the warfarin and no warfarin arms

Aim 3: Conduct meta-analyses of published studies in this field:

- to provide a context for the results of WARP relative to other trials in the area

3.3 *Background*

3.3.1 Venous Thromboembolism

Venous thromboembolism (VTE) includes thrombosis of the deep veins (usually of the leg, thigh and pelvis), pulmonary embolus, thrombosis associated with central venous catheters (generally in the arm or veins draining the site of the catheter) and related sequelae of post-thrombotic syndrome and pulmonary hypertension. VTE is a condition in which a thrombus (blood clot) forms in a vein through which blood flow may be limited by the thrombus, causing swelling and pain. An embolism is created if all or part of the thrombus breaks off from the site of formation and travels through the venous system. An embolus blocking the pulmonary arteries (pulmonary embolism [PE]), arising from a deep vein thrombosis (DVT), causes most deaths. Untreated PE has a mortality rate of around 30%; treated, this mortality reduces to 2% (Douketis et al, 2007).

3.3.2 The Clotting Process

3.3.2.1 Introduction

The normal clotting process is discussed in detail as it is core to the understanding of the pathophysiology of catheter-related thrombosis (CRT) in cancer patients.

A vein consists of three layers: tunica intima, the innermost and in direct contact with venous flow, formed of a single layer of endothelial cells (the endothelium) to provide a smooth surface that is normally non-thrombogenic; tunica media, composed of connective tissue with muscular and elastic fibres to allow changes in pressure and flow and the tunica adventitia, the outer layer, composed of longitudinal elastic fibres and loose connective tissue (Egan Sansivero, 1998). Blood coagulation and

platelet-mediated primary haemostasis have evolved as important defence mechanisms against bleeding and are a dynamic, highly interwoven array of multiple processes (Furie and Furie, 2008). The coagulation system is usually triggered almost immediately in response to rupture of the endothelium, which allows exposure of blood to the extravascular tissue. The responses of the coagulation system are coordinated and, for ease, are outlined in four phases:

- Initiation and formation of the platelet plug (primary haemostasis)
- Cascade response of the coagulation factors (secondary haemostasis) which occurs simultaneously
- Termination by antithrombotic control mechanisms
- Removal of the clot by fibrinolysis

3.3.2.2 Primary Haemostasis

Platelets are activated at the site of vascular injury to form a plug that provides the initial haemostatic response to stop bleeding.

3.3.2.2.1 Platelet Activation

The functional response of activated platelets involves four processes: adhesion [the deposition of platelets on the subendothelial matrix]; aggregation [platelet-platelet cohesion]; secretion [the release of platelet granule proteins and procoagulant activity (the enhancement of thrombin generation] (Brass, 2003). Collagen and thrombin are the most potent platelet activators. The intact endothelium prevents adherence of platelets by the production of nitric oxide and prostacyclin. Intimal injury impairs the flow of platelets and exposes subendothelial elements e.g. collagen, microfibrils and laminin which lead to platelet adherence, activation and secretion. The two most important platelet collagen receptors are Glycoprotein (GP)Ia/IIa and GPIV, playing

critical roles in platelet adhesion and activation respectively. Platelet activation by thrombin (section 3.3.2.3.2) is mediated by a family of G-protein coupled protease-activated receptors (PARs) using dual platelet receptors, PAR1 and PAR4 (Brass, 2003) .

3.3.2.2.1.1 Platelet Adhesion

Following activation, platelets undergo significant shape changes, producing elongated pseudopods that make platelets extremely adhesive. Platelet adhesion is mediated by the large multimeric circulating protein von Willebrand factor (vWF) which forms links between the platelet GPIb,IX,V complex and collagen fibrils, further strengthened by the binding of collagen–specific GPIa/IIa receptor to collagen fibrils (Sixma et al, 1997).

3.3.2.2.1.2 Platelet Aggregation

Platelet activation results in exposure of and conformational changes in the GPIIb/IIIa receptor (an adhesive protein receptor of the integrin family), binding fibrinogen and immobolised vWF. The cytosolic portion of activated GPIIb/IIIa complex binds to the platelet cytoskeleton and can mediate platelet spreading and clot retraction, thus integrating receptor-ligand interactions with events inside the cell in a bidirectional fashion (Savage et al, 1992).

3.3.2.2.1.3 Platelet Secretion

The activated platelets then release the contents of their granules into the plasma: adenosine diphosphate (ADP) and serotonin stimulate and recruit other platelets (ADP activated platelets increase the surface expression of intercellular adhesion molecule (ICAM)-1 on endothelial cells); fibronectin and thrombospondin to reinforce and stabilise platelet aggregates; fibrinogen, providing a local source; thromboxane A_2, a prostaglandin metabolite, causing activation of new platelets and further

aggregation (Wu and Thiagarajan, 1996) and growth factors e.g. platelet derived growth factor which has potent mitogenic activity on smooth muscles cells as well as mediating tissue repair.

3.3.2.2.1.4 Platelet Procoagulant Activity

Platelet procoagulant activity is an important aspect of platelet activation and involves exposure of procoagulant phospholipids (section 3.3.2.3.3), primarily phosphatidylserine and the subsequent assembly of the clotting cascade (section 3.3.2.3) on the platelet surface. These complexes are an example of the close interrelationship between platelet activation and activation of the clotting cascade (Furie and Furie, 2008) which is examined in the next section.

3.3.2.3 Thrombotic Cascade

Thrombin (section 3.3.2.3.2) is the key effector enzyme of the coagulation system, having many biologically important functions such as the conversion of fibrinogen to a fibrin network, amplification of the feedback of coagulation and as discussed in section 3.3.2.2.1, activation of platelets. For review of thrombotic cascade, see (Provan D et al, 2009). The exact and balanced generation of thrombin is the result of an ordered series of reactions collectively referred to as the 'blood coagulation' (Figure 3.3.2.1). At each stage, a precursor protein (zymogen) and its glycoprotein co-factor are converted to an active protease by cleavage of one or more peptide bonds in the precursor molecule and then catalyse the next reaction in the cascade, ultimately resulting in cross-linked fibrin. Coagulation factors are indicated by Roman numerals, with 'a' indicating the active form.

Figure 3.3.2.1 Blood Coagulation and Fibrinolytic Pathway

Source: www.ganfyd.org (ganfyd, 2010)

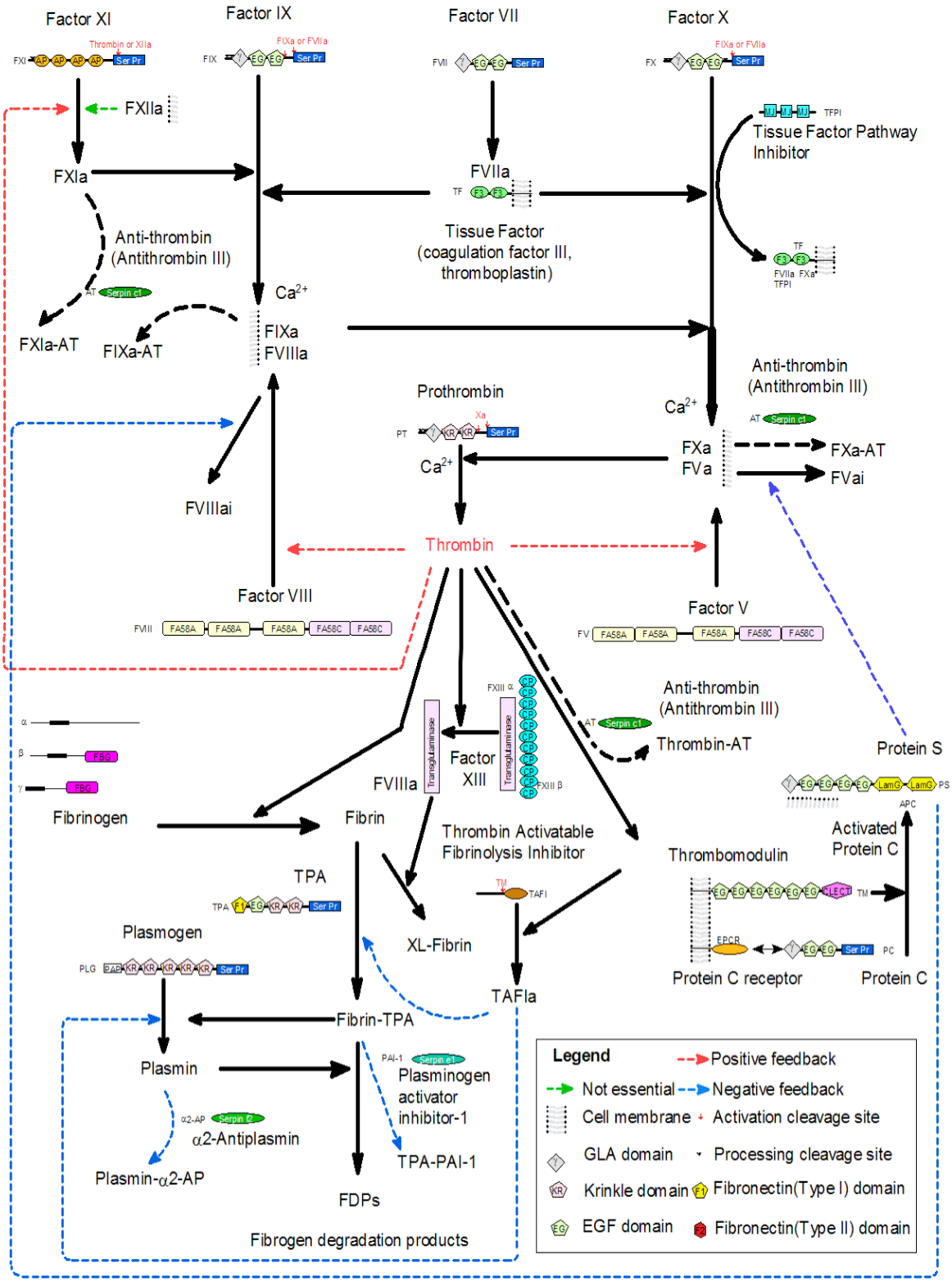


Figure 3.3.2.1 Tissue factor binds to Factor VIIa and activates factors IX and X. Factors IXa and Xa, together with factors VIIIa and Va respectively, form the tenase and prothrombinase complexes that activate factor X and prothrombin respectively. Thrombin-mediated activation of factor XI, factor V and factor VIII gives positive feedback amplification of the system. Thrombomodulin is present on endothelial cells. Thrombin generated in the vicinity of intact endothelial cells binds to thrombomodulin and efficiently activates protein C. Activated protein C (APC) and protein S form a complex on the plasma membrane of endothelial cells which inactivates factors Va and VIIIa, which results in downregulation of the coagulation system. The degradation of factor VIIIa by APC is stimulated by protein S and by factor V.

XL – cross-linked; GLA - γ-carboxyglutamic acid;

3.3.2.3.1 Tissue Factor

Tissue factor is the physiological initiator of coagulation (Figure 3.3.2.1). It is a membrane protein abundantly present in cells surrounding the vascular bed. It binds both zymogen and activated forms of factor VII (factor VIIa). A fraction of factor VII in blood circulates as active enzyme and the binding of this form to tissue factor triggers coagulation by converting factors IX and X to their active forms, IXa and Xa. Feedback amplification is achieved when factor VII bound to tissue factor is activated by factors VIIa, IXa and Xa. Factors IXa and Xa remain associated with the tissue-factor-bearing cell or diffuse into the blood and bind to the surface or nearby activated platelets which have formed the platelet plug. The activation of platelets (section 3.3.2.2.1), is associated with the exposure of negatively charged phospholipids which

have high potential to bind coagulation factors and assemble enzyme-cofactor complexes that are crucially important for efficient propagation of the system.

Prothrombin is activated to thrombin by the prothrombinase complex, which consists of the phospholipid-bound complex between the enzyme, factor Xa and its cofactor, activated factor V (Va). The substances that activate factor V are Xa (on the phospholipid surface) and thrombi (in solution and on the surface). Thrombin feedback amplifies the system by activating not only factor V, but also factors VIII and XI. Factor VIII circulates bound to vWF, the adhesive protein important for the generation of the initial platelet plug. After activation, factor VIIIa dissociates from vWf and forms a complex on the platelet surface with factor IXa; this complex (denoted the tenase complex) then activates factor X. Activation of factor XI by thrombin in the amplification loop, results in the generation of factor IXa, which in turn, activates factor X (Furie and Furie, 2008) (Figure 3.3.2.1).

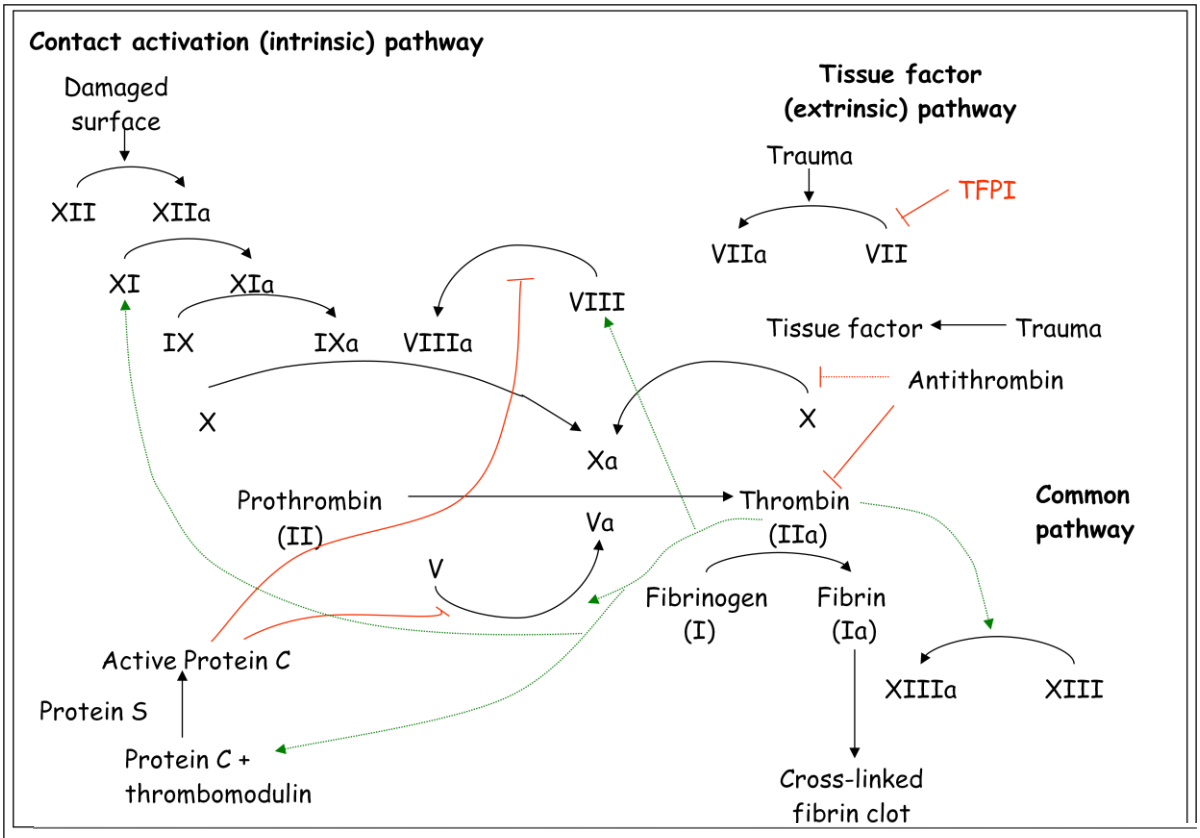
The initiation of coagulation via the exposure of tissue factor as described above is referred to as the tissue factor (extrinsic) pathway, the mechanism by which coagulation is initiated in vivo in response to trauma, including chemotherapy and central venous catheters. The contact activation (intrinsic) pathway is an alternative mechanism by which the coagulation can be initiated. It involves factors VIII, IX, X, XI and XII, high-molecular-weight kininogen (HK), prekallikrein (PK) and factor XI and results in the conversion of factor X to factor Xa (Figure 3.3.2.1).

Although the concept of intrinsic and extrinsic pathways served for many years as a useful model for coagulation, more recent evidence has shown that the pathways are

not, in fact, redundant but are highly interconnected, converging on a common pathway leading to clot formation. For example, the tissue factor/VIIa complex activates not only factor X but also factor IX of the intrinsic pathway. In addition, patients with severe factor VII deficiency may bleed even though the intrinsic pathway is intact (Kroll, 2001). Figure 3.3.2.2 shows the interrelationship between both pathways. The common part in both pathways is the activation of factor X to factor Xa. Factor Xa activates prothrombin (Factor II) to thrombin (Factor IIa) (Dahlback, 2000).

Figure 3.3.2.2 Schematic of extrinsic and intrinsic coagulation pathways

Source: Adapted from Ferguson et al, *Eur Heart J*, 1998; Suppl 19:8



Interrelationship between Intrinsic and Extrinsic Coagulation Pathways

3.3.2.3.2 Thrombin

Thrombin, in turn, converts fibrinogen to fibrin. Maximum thrombin generation occurs after the formation of the fibrin clot – for review of thrombotic cascade, see (Provan D et al, 2009). This thrombin is important for additional fibrin generation as well as for activation of factor XIII and the thrombin-activatable fibrinolysis inhibitor (TAFI). Activated factor XIII (XIIIa) is a transglutaminase that stabilises the clot by covalent cross-linking of fibrin. TAFI is a carboxypeptidase that releases carboxy-terminal lysines from fibrin and as these lysines are important for the binding of fibrinolytic enzymes to fibrin, activation of the inhibitor prevents fibrinolytic attack (Dahlback, 2000). Thrombin also binds to and leads to the release of G-protein-coupled PARs. The release of these proteins leads to the activation of numerous signalling cascades that, in turn, increases the release of the interleukins, IL-1 and IL-6. IL-6 releases secretion of the ICAM-1 and vascular cell adhesion molecule, vascular cell adhesion molecule (V-CAM)-1. ICAM-1 binds to three proteins (one of which is fibrinogen) and facilitates transmigration of leucocytes across vascular endothelia e.g. in extravasation. As well as adhesion of proteins to the vascular endothelium, V-CAM-1 is also involved in endothelial cell signalling transduction (Dugina et al, 2002).

3.3.2.3.3 Phospholipid Membrane

Early components of the clotting pathway circulate at lower concentrations than the factors that act at later stages. The assembly of enzyme-cofactor complexes on negatively charged phospholipid surfaces increases the local concentration of the coagulation components and counteracts regulation by anticoagulant mechanisms.

Phosphatidylserine is a negatively charged phospholipid required for the assembly of the tenase and prothrombinase complexes (Figure 3.3.2.1). Under normal conditions, phosphatidylserine is present in the inner layer of the plasma cell

membrane. During platelet activation, it is translocated from the inner to the outer layer of the membrane. In the tenase and prothrombinase complexes, all participating proteins (the enzymes - factor IXa and Xa, the cofactors VIII and Va, and the substrates factor X and prothrombin), have affinity for the negatively charged phospholipid surface. The enzymes and the substrates are vitamin-K dependant proteins that interact with the phospholipid membrane via their amino-terminal domains, which contain γ-carboxylation acid residues. The post-translationally modified glutamic acid residue is present only in the vitamin-K-dependent proteins. The residues are involved in calcium binding, important for the correct folding of the γ-carboxyglutamin acid domain. Inhibition of the γ-carboxylation reaction by antagonists of vitamin K results in defective calcium binding of the γ-carboxyglutamic acid domains and loss of ability to interact with the phospholipid membrane. This is the molecular basis for anticoagulant therapy with warfarin and other vitamin K antagonists (Provan D et al, 2009) – see warfarin section 3.3.3.1.

3.3.2.4 Regulation of blood coagulation by anticoagulant factors

Regulation of coagulation is exerted at each level of the pathway, either by enzyme inhibition or by modulation of the activity of the cofactors. The tissue-factor-pathway-inhibitor (TFPI) inhibits the reactions involving tissue factor and factor VIIa. This inhibitor is mostly bound to low density lipoprotein (LDL) in plasma or to haparan sulphate when associated with endothelial cells.

Most of the enzymes generated during activation of coagulation are inhibited by the serine-protease inhibitor, antithrombin [AT] (also called Antithrombin III).

AT preferentially inhibits free enzymes, whereas enzymes that are part of the tenase or prothrombinase complexes are less accessible for inhibition. The physiological role of AT is to limit the coagulation process to sites of vascular injury and to protect the circulation from liberated enzymes. AT is the most important thrombin inhibitor since it can also inhibit the activities of factors IXa, Xa, XIa and XIIa. Heparin and the heparin-like molecules that are present on the surface of endothelial cells stimulate its activity by the following means: heparin binds to the AT causing a conformational change which results in its active site being exposed. The activated AT then inactivates thrombin and other proteases involved in blood clotting, most notably factor Xa. The rate of inactivation of these proteases by AT increases 1000-fold due to the binding of heparin. AT binds to a specific pentasaccharide sulphation sequence contained within the heparin polymer. The conformational change in AT on heparin binding mediates its inhibition of factor Xa but for thrombin inhibition, thrombin must also bind to the heparin polymer at a site proximal to the pentasaccharide (Perry, 1994). The highly negative charge density of heparin contributes to its very strong interaction with thrombin. The formation of a ternary complex between AT, thrombin and heparin results in the inactivation of thrombin. For this reason, heparin's activity against thrombin is size dependent, the ternary complex requiring at least 18 saccharide units for efficient formation. In contrast, anti factor Xa activity only requires the pentasaccharide binding site (Dahlback, 2000).

The protein C anticoagulant system regulates coagulation by modulation of the activity of the two cofactors, VIIIa and Va. Protein C, the key component of the system, is a vitamin-K dependent zymogen to an anticoagulant protease. It is activated on the surface of intact endothelial cells by thrombin that has bound to the

membrane protein thrombomodulin. Thus thrombin has the capacity to express both procoagulant and anticoagulant functions depending on the context under which it is generated. At sites of vascular disruption, the procoagulant effects of thrombin are fully expressed. In contrast, in an intact vascular system, thrombin has anticoagulant function since it binds to thrombomodulin and activates protein C. Activated protein C (APC) can cleave the phospholipid-membrane-bound cofactors factors Va and VIIIa which results in inhibition of the coagulation system. A vitamin-K-dependent cofactor protein, protein S, supports the anticoagulant activity of APC. APC and free protein S form a membrane-bound complex, which can cleave factors VIIIa and Va, even when they are part or fully assembled tenase and prothrombinase complexes.

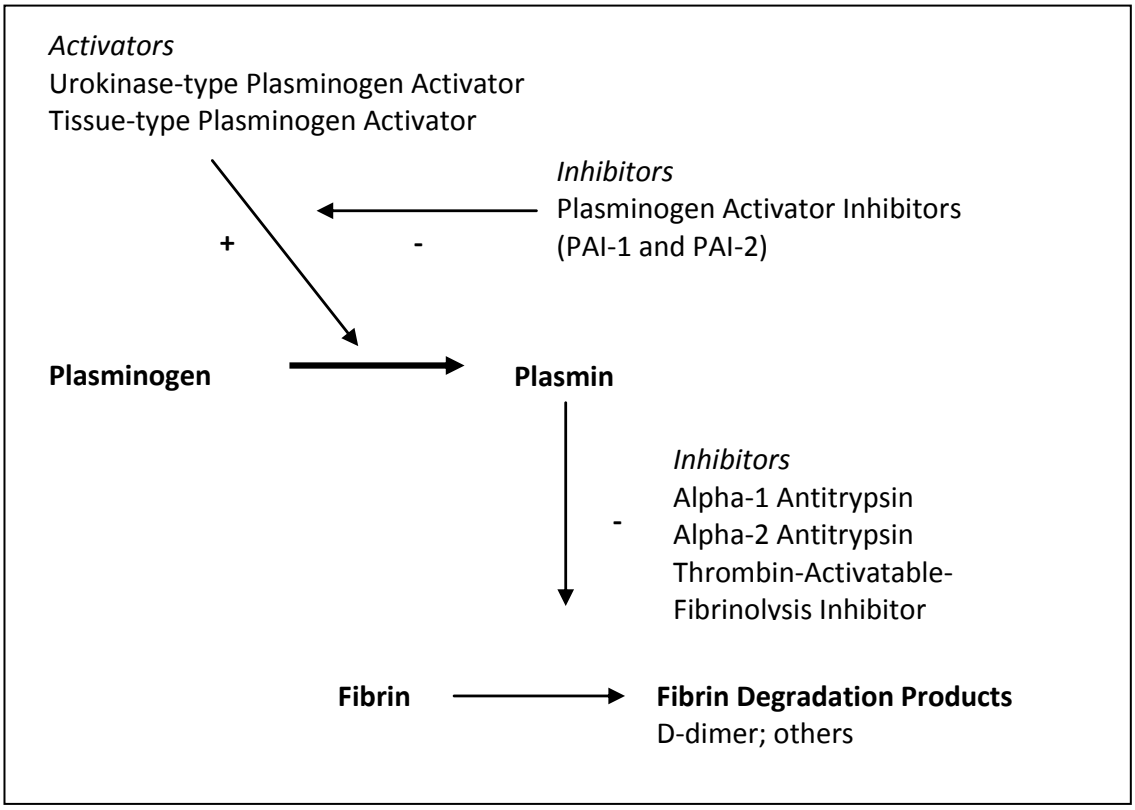
APC does not cleave intact factor VII because the binding of factor VII to vWF prevents it from interacting with the phospholipid membranes. In contrast, factor V binds phospholipids as well as factor Va does, and APC is able to cleave the intact form of factor V. The consequence of APC-mediated cleavage of factor V is the generation of anticoagulant factor V that functions in synergy with protein S and an APC cofactor in the degradation of factor VIIIa. Thus, factor V can function as a procoagulant and anticoagulant cofactor. The regulation of coagulation by anticoagulant factors is illustrated in Figure 3.3.2.1 as part of the whole cascade.

3.3.2.5 Removal of clot by fibrinolysis

Lastly, the degradation of fibrin clots is the function of plasmin, a serine protease that circulated as the inactive proenzyme, plasminogen. Plasminogen binds to both fibrin and fibrinogen, thereby, getting incorporated into the clot. Tissue plasminogen activator (tPA) and urokinase are serine proteases which convert plasminogen to

plasmin. Inactive tPA is released from vascular endothelial cells following injury, binding to fibrin and then activated. The inhibition of tPA activity results from binding to specific inhibitory proteins including plasminogen activator-inhibitors type 1 (PAI-1) and type 2 (PAI-2) (Dahlback, 2000). This process is seen in Figures 3.3.2.3.

Figure 3.3.2.3 The Fibrinolytic Pathway



In summary, prostacyclin and thromboxane are released from injured endothelial cells and modulate platelet adhesion and aggregation. Injured endothelial cells also express TF on their membrane, a receptor for the circulating coagulation factor VII, a serine protease that initiates the blood coagulation cascade, unleashing sequential activation of other serine proteases: coagulation factors X, IX, VIII, V and thrombin. The latter promotes conversion of circulating fibrinogen into fibrin monomer which polymerises and is then cross-linked to for the fibrin-gel matrix. This matrix acts as a

net, trapping platelets and various other cells into a clot that seals the wound and provides a scaffold for tissue repair (Mann KG, 1999). Finally, the clot is removed by fibrinolytic enzymes, mostly plasmin, which derives from plasminogen through action of uPA or tPA. Fibrinolysis is counteracted, among others, by PAI 1 and PAI 2.

Having explored the coagulation cascade, the mechanism of action and effects of the anticoagulant drugs, warfarin and low molecular weight heparin, trialled in the prophylaxis of catheter-related thrombosis in cancer patients, will be considered.

3.3.3 Anticoagulant Drugs

3.3.3.1 Warfarin

Warfarin, an oral anticoagulant, is still one of the most widely used drugs worldwide and is the most commonly prescribed anticoagulant in the UK (Sanger Institute, 2009).

3.3.3.1.1 Mechanism of action of warfarin

Warfarin occurs as a pair of enantiomers that are differently metabolised by human cytochrome P450 (CYP) isozymes. The dose-response relationship is influenced by genetic and environmental factors including a common mutation in the gene for a P450 enzyme (2C9), the hepatic enzyme responsible for oxidative metabolism of the warfarin S-isomer, and *VKORC1*, the gene for the enzyme Vitamin K epoxide reductase complex subunit 1 (see Figure 3.3.3.1) (Klein et al, 2009). Warfarin exerts its anticoagulant action by inhibiting the vitamin K-dependent post- translational modification of the coagulation proteins II, VII, IX, X and also regulatory proteins C & S that serve as natural inhibitors of coagulation. Before being released into the

circulation, these proteins undergo carboxylation, converting approximately 10 glutamic acid (Glu) residues in their N-terminal regions to gamma-carboxy glutamates (Gla). This process is catalysed by a carboxylase that requires molecular oxygen, carbon dioxide, and the reduced form of vitamin K (vitamin KH_2). During this reaction vitamin KH_2 is oxidised to vitamin K epoxide, which is recycled back to vitamin KH_2 by the actions of two reductases, vitamin K epoxide reductase and vitamin K reductase (Figure 3.3.3.1). Warfarin inhibits the former and probably also the latter reductase, resulting in depletion of vitamin KH_2 and thereby limiting the degree of carboxylation of the coagulation proteins. These under or non-carboxylated proteins are released from their site of production in the liver into the circulation and are inactive. Conversely, the presence of Gla residues allows the coagulation proteins to bind calcium, which in turn allows these proteins to undergo a conformational change essential for their ability to complex with their respective cofactors on phospholipid surfaces. The biological activity of these proteins is thus dependent upon the Gla residues (Ansell et al, 2008).

Figure 3.3.3.1 The Vitamin K cycle

Source: Hirsh J in Oral anticoagulants (Hirsh et al, 2001a)

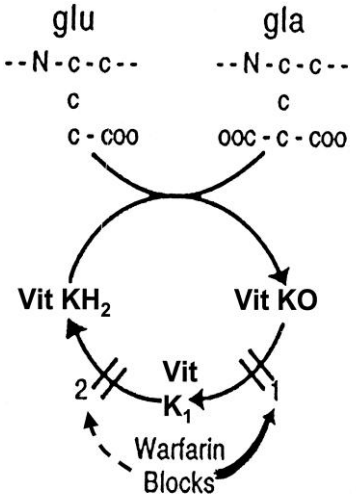


Figure 3.3.3.1 In the presence of calcium ions, carboxylation causes a conformational change in coagulation proteins that promotes binding to cofactors on phospholipid surfaces (section 3.2.3.3). The carboxylation reaction requires the reduced form of vitamin K (Vit KH_2), oxygen and carbon dioxide and is linked to the oxidation of Vit KH_2 to Vitamin K epoxide (VitKO). Vit KO is then recycled to to Vit KH_2 through two reductase steps. The first, which is sensitive to warfarin, reduces Vit KO to Vit K1, while the second, which is relatively insensitive to warfarin, reduces the VitK1 (the natural food form of vitamin K), to Vit KH_2.

Warfarin is readily absorbed from the gastrointestinal tract, has a predictable onset and duration of action, is extensively bound to plasma proteins and has a plasma half-life of 36 to 48 hours for the unaltered compound. It is metabolised in the liver and metabolites with negligible or no anticoagulation activity are excreted in the urine following reabsorption from bile. The pharmacological response to warfarin varies between individuals. Warfarin disposition (i.e. plasma concentration-time profiles)

and the effect of warfarin on vitamin K–dependent clotting factor production have been shown to be altered in cancer patients (Mousa, 2006; Hutten et al, 2000). The mechanisms for this alteration are complex and largely unknown.

Warfarin action occurs within 24 hours, peaks at 2-3 days and can last for up to 5 days. The anticoagulant effect of warfarin is delayed until all the clotting factors already in circulation are cleared: After achieving steady-state levels of warfarin, the anticoagulant effect overwhelms any potential hypercoagulability induced by decreasing protein C and/or protein S activity, although this may not be so in the first days following initiation of warfarin therapy. In addition, factors II, IX and X levels decline more slowly (48-72 hours) than factor VII and adequate degree of anticoagulation is only evident after this time (Hirsh et al, 2008). Given this pharmacokinetic profile, starting warfarin (where appropriate) three days prior to the insertion of a central venous catheter (CVC) allows time for exposure to warfarin prior to catheter insertion and the start of chemotherapy (Boraks et al, 1998).

Fixed dose warfarin (FDW) [1mg daily] probably affects the in-vivo function of the vitamin K-dependent proteins in ways as yet not always detectable by current ex-vivo assays (Magagnoli et al, 2005; Bern et al, 1990) and so monitoring FDW as well as higher doses is prudent.

3.3.3.1.3 Laboratory investigation for warfarin: International Normalised Ratio (INR)

Oral anticoagulant therapy is most commonly monitored by the prothrombin time (PT), a coagulation-based assay that is sensitive to depression of three of the four vitamin K-dependent procoagulants reduced in patients on warfarin therapy (factors

II, VII and X). The test is performed by adding a mixture of tissue factor and calcium to citrated plasma and measuring the time to fibrin formation. Tissue factor (section 3.3.2.3.1) is a protein-phospholipid tissue extract, derived typically from lung, brain or placenta. The responsiveness of tissue factors varies according to their source and method of preparation and determines the extent of PT prolongation. PT ratios derived from an individual on warfarin will vary, therefore, according to the particular tissue factor used to perform the test. Because of this unavoidable variability, the international normalised ratio (INR) is used. The INR incorporates a correction factor (international sensitivity index, ISI) into the PT ratio to account for the reactivity of the particular tissue factor used to perform the PT (Horsti, 2000).

3.3.3.1.4 Complications of warfarin therapy

Bleeding is the most common side-effect of warfarin therapy. Although the most common sites of bleeding from warfarin are the gastrointestinal and genitourinary systems, bleeding may occur at unusual sites and become manifest with atypical clinical presentations. Both major and minor bleeding rates are much lower with 'low-intensity' dose of warfarin than 'standard intensity' (target INR>2.0). Additionally, the risk of major and minor bleeding for an individual patient rises with the INR. Patient characteristics, e.g. dietary changes and cachexia, the use of interaction medications and non-compliance with warfarin also dictate bleeding risk to a large extent.

Other complications including warfarin–induced skin necrosis, alterations in calcium metabolism, rebound hypercoagulability, cholesterol embolisation, fever, nausea, vomiting, anorexia, abdominal cramp, diarrhoea, dermatitis, urticaria, alopecia and mouth ulcers have also been reported infrequently but must be considered alongside the side effects of concomitant medication, in particular, chemotherapy (British National Formulary, 2010).

3.3.3.1.5 INR variations in cancer patients

Given that the majority of patients in the WARP trial were on fluoropyrimidine-based chemotherapy, the following observation is of interest and strengthens the case for the recommendation in the protocol that regular INR monitoring in patients on both warfarin arms of WARP was undertaken. Masci et al (2003) analysed the incidence of alterations in INR and bleeding episodes in cancer patients receiving warfarin (1mg daily) during treatment with continuous infusional 5-Fluorouracil (5-FU). They evaluated 95 patients and found that 31 subjects (33%) had an INR>1.5, 18 of whom (19%) having an INR of >3.0. Twelve of the patients (12/31, 39%) had liver metastases and the incidence of distorted INR was more common in patients receiving the combination of infusional 5-FU, folinic acid and oxaliplatin (FOLFOX) (Masci et al, 2003). These authors concluded that a high incidence of INR abnormalities was observed in patients treated with infusional 5-FU and that regular measurement of INR should be undertaken. Following this, patients on WARP, receiving all chemotherapies, had their INRs closely monitored and warfarin doses adjusted according to written guidelines provided in the protocol (item 4.6). The protocol recommended monitoring patients more closely when they were taking, adding, stopping and changing dose of any medication known to interact with warfarin.

3.3.3.1.6 Interaction between warfarin and other drugs

3.3.3.1.6.1 Anticancer Drugs

There are frequent case reports, retrospective and prospective analyses on the interaction between warfarin and cytotoxic therapies, most recently with the oral fluoropyrimidine, 5-FU prodrug, capecitabine (Shah et al, 2006; Camidge et al, 2005). The summary of product characteristics for capecitabine has this year (2010) been

amended by the drug manufacturers, Roche, to include a warning and description of an interaction with warfarin (Roche, 2010). Altered coagulation parameters and/or bleeding have been reported in patients taking concomitant capecitabine and warfarin. These events occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within one month of it's cessation. In a clinical interaction study, after a single dose of 20mg warfarin, capecitabine treatment increased the area under the curve (AUC) of S-Warfarin by 57% with a 91% increase in international normalised ratio (INR) value. The manufacturers of capecitabine therefore recommend that patients on warfarin should be monitored regularly by INR test and careful consideration given to adjusting the anticoagulant dose accordingly (Roche, 2010). This is the consistent theme on the warfarin-cytotoxic drug interaction reports.

3.3.3.1.6.2 Non-anticancer drugs

Numerous drugs have been reported to potentiate or oppose the action of warfarin. Particularly relevant to cancer patients is the interaction of warfarin with antibiotics and antifungal agents, frequently used for side effects of chemotherapy or as a prophylactic measure. In a case control and case cross over study investigating warfarin interactions with anti-infectives and measuring gastrointestinal bleeds, using Medicaid data, warfarin users who had received an anti-infective agent showed a substantially increased risk of GI bleeding. However, a drug-drug interaction with warfarin was evident only for co-trimoxazole and fluconazole (Schelleman et al, 2008). It is of note that, in a retrospective analysis of 372 patients at end of life, the most common drug interactions involved warfarin and phenytoin. Most interactions were classified as being of moderate severity (59%). Older patients, those with comorbid conditions, brain tumour patients and those taking many medications were

at greater risk of drug interactions (Riechelmann et al, 2008). Again, the advice from these reports is to monitor warfarin vigilantly and not necessarily to cease one of the drugs.

Low molecular weight heparin (LMWHs), usually given subcutaneously, have been tested in the thromboprophylaxis of cancer patients with CVCs. In addition, the findings from an overview of six systematic reviews on anticoagulation (with warfarin, unfractionated heparin and LMWHs) and cancer (Akl et al, 2008), concluded i) current evidence does not support a specific anticoagulant for perioperative thromboprophylaxis and ii) that anticoagulants may improve survival but more data will be useful in deciding which subgroups benefit most. Therefore it is pertinent that other anticoagulants are examined, in particular, LMWH, in the following section. LMWH is a derivative of unfractionated heparin; unfractionated heparin is usually restricted to the hospital setting where its effect can be monitored and dosage adjusted frequently and, because of the limited use and patient inconvenience, is not covered in this section.

3.3.3.2 Low Molecular Weight Heparin

3.3.3.2.1 Mechanism of Action

Low molecular weight heparin (LMWHs) are derived from (unfractionated) heparin by chemical or enzymatic depolymerisation, yielding fragments approximately one third the size of heparin i.e. LMWHs have a mean molecular weight of 4,500 to 5,000 daltons. Like heparin, LMWHs produce their major anticoagulant effect by activating AT. The interaction with AT is mediated by a unique pentasaccharide sequence found on fewer than one third of LMWHs. Since a minimum chain length of 18

saccharides is required to form ternary complexes among heparin, AT and thrombin, only the minority of LMWHs that are above this critical chain length are available to inactivate thrombin. In contrast, all LMWH chains, containing the high affinity pentasaccharide, catalyse the inactivation of factor Xa.

3.3.3.2.2 Pharmacokinetic Profile

The LMWHs have half lives of some 2-4 fold larger than unfractionated heparin (UFH) (UFH half life is 30-150 minutes) and, coupled to their enforced bioavailability at low doses, means that a once daily subcutaneous dosing schedule provides a more convenient means of administration.

3.3.3.2.3 Side effects

The risk of heparin-induced bleeding is influenced by the administered dose, route of administration (usually subcutaneous injection but higher risk of bleeding with intravenous use), the concomitant use of aspirin and thrombolytic agents and the patient's clinical condition (e.g. history of peptic ulcer, thrombocytopenia, renal failure). The key non-haemorrhagic side effect is heparin induced thrombocytopenia, an antibody-mediated adverse reaction causing venous and arterial thrombosis which may have serious consequences. Long-term use of LMWH carries a risk of heparin-induced osteoporosis, although most studies investigating osteoporosis are with unfractionated heparin, known to cause more significant reduction in bone density and symptomatic vertebral fractures (Hirsh et al, 2001c).

3.3.3.3 New Anticoagulants

There are a number of new anticoagulants that have been studied in recent years, some of which are licensed for use in certain conditions including orthopaedic surgery (Levine, 2009). They target the active site of factor Xa or thrombin and are administered in a fixed dose. Fonadaparinux is a parenteral, indirect factor Xa

inhibitor; rivaroxaban is an oral direct, factor Xa inhibitor (directed again the active site of factor Xa); apixaban is also a direct, oral, factor X inhibitor. Dabigatran etexilate is an oral direct thrombin inhibitor which does not bind to plasma proteins and therefore has a more predictable anticoagulant effect than heparin . The new oral drugs are mentioned as they are attractive for patients with cancer because of the administration route, the fixed dose and the non-requirement for laboratory monitoring. It is vital that thromboprophylactic trials of the new anticoagulants are evaluated in the cancer population, given the high-risk of VTE.

Having examined the coagulation pathways utilised under normal circumstances as a defence against bleeding, their regulation by anti-coagulant pathways and the therapeutic anticoagulants widely used in clinical practice, the effects of cancer on these factors are now scrutinised.

3.3.4 Thrombotic Events Associated with Carcinogenesis

3.3.4.1 Introduction

Today, it is known that thrombosis and cancer are linked by multiple pathophysiological mechanisms and that tumour biology and coagulation mechanisms are integrally connected. The pathophysiology of thrombosis in the cancer patient is multifaceted, with the haemostatic process finely balanced between thrombosis, invasion and metastases and bleeding, involving a complex interaction between the tumour cell and the patient. The pathogenic mechanisms are dependent on the tumour type, extent of disease, host response, therapies used and other risk factors (section 3.3.5.5). VTE may indicate an occult cancer or a complication of a

known malignancy. In most studies of VTE and its treatment, a diagnosis of cancer is a poor prognostic sign and similarly, a diagnosis of a DVT in cancer patients also indicates a poor prognosis. Cancer patients who undergo surgery, receive chemotherapy or have CVCs inserted for the administration of chemotherapy are at increased risk of VTE, compared to non-cancer patients and cancer patients with established VTE are at increased risk of not only recurrent thromboembolism but also anticoagulant associated bleeding, in comparison to non-cancer patients. All these factors will be explored, with the molecular biology which underlies the clinical ramifications of thrombosis and malignancy briefly covered and the clinical factors pertinent to cancer patients with central venous catheters, examined in more detail.

3.3.4.2 Tumour Biology: Link between Cancer and Thrombosis

The cancer cell phenotype is characterised by loss of the normal features which control cell proliferation, a capacity to invade normal tissue and further to metastasise or spread to distant organs. The extraordinary advances in molecular biology which have been made over the last two decades have give an series of insights into the biochemical pathways and cascades which are mutated in cancer and contribute to its dysfunctional state. Perhaps the best characterised of the carcinogenic pathways has been described for colorectal cancer patients in which there are well recognised pre-malignant precursors which have been described by pathologists, the so-called adenoma-carcinoma sequence. Adenomas are benign, hyperproliferative wart-like lesions lining the large bowel. These accumulate further genetic mutations which eventually transform these lesions into fully invasive and metastatic cancer cells. Molecular biologists have characterised the approximate sequence of genetic events during the transition from normal to dysplastic to adenoma to carcinoma. Many of

these changes implicate pathways involved in cell cycle control (*C-MYC*, cyclins, p53), proliferation (*RAS*, MAP kinase, transforming growth factor-α), cell adhesion (matrix metalloproteinase overexpression) and angiogenesis (vascular endothelial growth factor [VEGF]). It is clear that cancer cells, in their de-differentiated state, can synthesise and secrete a number of factors which are otherwise strictly confined to specific normal tissues of stage of foetal development. There is therefore the potential to interact with proteins involved in the thrombotic cascade, outlined in section 3.3.2.3. It has only recently been recognised that the genetic mechanism responsible for neoplastic transformation, as in the example above (activation of tumour oncogenes e.g. *RAS* and inactivation of tumour suppressor genes e.g. p53), modulate the expression of genes at the core of haemostasis control. The thrombotic diathesis in the cancer patient may be induced by intrinsic or extrinsic factors.

3.3.4.3 Intrinsic Factors

The process of subclinical activation of the coagulation system has been widely described in untreated cancer patients (Bluff et al, 2008; Winter, 2006). In general, the subclinical activation of prothrombotic mechanisms reflects the host response to the growing cancer and is thought to arise from the activation of thrombin and fibrin formation; directly, by the release of procoagulants by the tumour cell and indirectly, through the activation of endothelial cells, leucocytes and platelets by augmenting pro-inflammatory cytokines and the production of factor X-activating cysteine protease, mucinous glycoproteins and circulating tissue factor-bearing microparticles (Petralia et al, 2005) [section 3.3.4.3.1.1].

3.3.4.3.1 Tissue Factor in Malignancy

As in non-malignancy, TF localises the coagulation serine protease factor VII/VIIa to the cell surface. The primary function of TF is to activate the clotting cascade (Section 3.3.2.3). TF expression has been reported in a number of cancers including glioma, pancreatic, non-small cell lung, colorectal, renal cell, ovarian, prostate, hepatocellular and breast (Rickles et al, 1995) with the level of TF expression varying among different types of cancer and, in general, increases with advanced cancer stage (Kakkar et al, 1995). The incidence of thrombosis in patients with tumours expressing higher levels of TF such as brain and pancreatic cancer is greater that those expressing lower levels such as breast (White et al, 2007), so the use of TF as a biomarker (Table 3.3.5.1) is currently being evaluated. TF expression by cancer cells is under the transcriptional control of oncogenes and tumour suppressor genes such as members of the epidermal growth factor receptor (*EGFR*) family, *RAS*, *p53*, and *PTEN* (Boccaccio and Comoglio, 2009).

Tumour-infiltrating macrophages also express tissue factor (TF) activity; activated macrophages produce interleukin-1 (IL-1) and tumour necrosis factor alpha (TNF-α), stimulating endothelial cell TF, downregulating endothelial cell anticoagulant activity and stimulating releases of fibrinogen/factor VIII (Sutherland et al, 2003). An increased fibrin formation supports the metastatic process (Falanga A et al, 2003). It has been proposed that anticoagulant therapy therefore might not only prevent vascular events but also may demonstrate anti-metastatic activity (Prandoni et al, 2005).

In addition to procoagulant activity, TF has signalling properties. TF can interact with Filamen A (a protein that participates in the anchoring of membrane proteins for the actin cytoskeleton), plasminogen activators and PAR 2 signalling (formation of the TF:VIIa complex on the surface of tumour cells leads to cleavage and activation of the G-protein coupled receptor, PAR2) and thereby enhance tumour growth, invasion, angiogenesis and haematogenous metastasis. Inhibition of the TF:VIIa complex suggests a novel approach to anticancer therapy, yet to be studied in patients (Kasthuri et al, 2009). *PAI-1 and COX-2* genes, both strongly upregulated by the *MET* oncogene, are other examples of mechanisms that link oncogene activation to the procoagulant activity of cancer cells. The measurement of COX-2 products, prostaglandins and thromboxane, may help assess the procoagulant properties of incipient neoplasia.

3.3.4.3.1.1 Microparticles and Selectins

Microparticles [MPs] (submicron phospholipid vesicles derived from apoptotic and/or activated cells) (Morel et al, 2006) and selectins (transmembrane molecules expressed on the surface of leucocytes and endothelial cells) may both initiate blood coagulation and also allow thrombin generation by providing a surface for the generation of fibrin. TF-bearing MPs seem to have a role not only in cancer-associated thrombosis but also cardiovascular disease, sepsis and diabetes.

P-selectin (CD62P), the largest of the selectins, is crucial for the localisation of MPs to areas of injury and inflammation.

3.3.4.4 Extrinsic Factors

The increased risk of thrombosis is associated with alterations in normal blood flow, injury to the vascular epithelium, and alteration in the constituents of the blood, the so-called, Virchow's triad. Stasis tends to be the result of extrinsic venous compression by locally advanced tumours, occurring by uncontrolled growth of the primary tumour or by a metastatic manifestation e.g. a large lymph node mass. 'Performance status', in relation to cancer patients, is an attempt to quantify their general wellbeing. Patients with advanced cancer and reduced performance status tend to be less mobile and more predisposed to bed rest than average and more prone to infection, through general immunosuppression to infection, all of which can lead to relative venous stasis and reduced clearance of activated clotting factors. CVCs by their invasive nature also cause alterations in blood flow. Vessel damage may be caused by intravenous medication including antineoplastics, erythropoietin and anti-angiogenic agents, CVCs and by direct tumour invasion.

3.3.5 Clinical Picture: Thrombosis and Carcinogenesis

3.3.5.1 Introduction

Around 145 years ago, Professor Armand Trousseau first recognised the association between thrombosis and cancer. He noted, "there appears in the cachexia…. a particular condition of the blood which predisposes it to spontaneous coagulation" and "Should you, when in doubt as to the nature of an affection of the stomach, when hesitating between chronic gastritis, simple ulcer, and cancer, observe a vein become inflamed in the arm or leg, you may dispel your doubt, and pronounce in a positive manner that there is a cancer" (Trousseau A, 1865).

Over the years, ‘Trousseau’s syndrome’ has been expanded from a recurrent and migratory pattern of superficial thrombophlebitis prior to the diagnosis of cancer, to any thromboembolic event linked to a malignancy. However, recently it has been proposed, “to restrict use of Trousseau’s syndrome to unexplained thrombotic events that precede the diagnosis of an occult visceral malignancy or appear concomitantly with the tumour” (Varki, 2007).

Thromboses have been found postmortem in up to 50% of patients with metastatic cancer (Walsh-McMonagle and Green, 1997). However, despite a small group of dedicated scientists and clinicians working together to elucidate the association between thrombosis and carcinogenesis in the laboratory since the 1970s and despite VTE being acknowledged as a common event in cancer patients by the medical and nursing communities, it remains an under-diagnosed and under-treated condition in life. It is really only in the last few years that the uniqueness of the thrombotic problem in cancer patients has become the focus of attention by the wider health community. This is in some part, due to:

- the steady increase in the overall burden of VTE because of ageing population and the increasing use of CVCs
- more routine staging using sensitive imaging techniques
- an expanded basic science research programme elucidating our understanding of the pathogenesis of thrombosis and cancer
- the study of newer anticoagulants in the cancer population
- more effective novel but prothrombotic anticancer agents, in particular the vascular endothelial growth factors (VEGF) inhibitors (Kamba and McDonald,

2007) and thalidomide and its derivatives, in which thrombosis has been found to be a significant complication of treatment, *and*

- UK governmental and associated bodies e.g. the Chief Medical Officer and the National Institute of Health and Clinical Excellence raising awareness of the problem by developing policies and guidelines.

3.3.5.2 The scale of the problem

The problem of VTE in general is large - each year 25,000 people in the UK are estimated to die from venous thromboembolism (VTE). This figure includes all types of patients admitted for medical care of serious illnesses, as well as, those admitted for surgery (House of Commons Health Committee, 2005). However, in comparison with other groups of patients, the cancer population is distinctive because virtually all patients with active malignancy demonstrate some degree of activation of the coagulation cascade, although the resulting hypercoagulable state only rarely results in overt disseminated intravascular coagulation (Lyman et al, 1978). The risk of VTE is therefore considerably elevated in cancer patients and significant morbidity may result from thrombotic events as well as a result of therapeutic interventions. It is difficult to compare the incidence of VTE in cancer patient population because of the varied study methods, varied populations covered and varied methods of detecting and reporting VTE but the population-based studies, hospital discharge data, cancer registries, retrospective cohorts and prospective observational studies, all give a sense of a widespread problem.

3.3.5.2.1 Incidence of Venous Thromboembolism in Cancer Patients

In a population-based study looking at risk factors of VTE, Heit et al found that patients with cancer account for almost 20% of all patients with VTE (Heit et al, 2002) and that cancer patients were found to have an overall 4-6-fold increased risk of thrombosis compared to non-cancer patients (Heit et al, 2000) . An even higher risk was reported in a later Dutch population-based case control study of 3220 patients presenting with a first DVT or PE and 2131 control patients, revealing the overall VTE risk was increased 7-fold in patients with a malignancy (OR 6.7; 95% CI 5.2-8.6) vs persons without a malignancy (Blom et al, 2005b). In retrospective cohort studies, thrombosis was found to be the second most common but often preventable cause of death in outpatients with cancer, after death from the cancer itself (Khorana et al, 2007b). Levitan et al reported an analysis of Medicare claims data for patients over 65 years between 1988 and 1990 and found an established VTE rate of 0.6%, significantly higher than the comparison group with no malignancy (Levitan et al, 1999). A later smaller study including hospitalised patients with solid tumours demonstrated an higher incidence of VTE of 7.8% over 26 months for this specific population (Sallah et al, 2002). The largest patient hospital discharge analysis of over 40 million cancer patients who were hospitalised between 1979 and 1999, found a DVT rate of 2% and PE rate of 1%; this was twice the rate of VTE observed in patients with no malignancy (Stein et al, 2006). The highest rates of VTE, however, were found in hospitalised neutropenic patients (6.4%) (Khorana et al, 2006) and in patients admitted to an oncology unit (VTE rate 7.8%) in the study by Sallah et al (2002), suggesting that the patients were on active treatment.

Finally, cancer-associated VTE is increasingly prevalent; the rate of VTE increased by 28% from 1995 to 2003 in a study of over one million hospitalised patients with cancer (Khorana et al, 2007c) a diagnosis of DVT and PE was made in 3.4% and 1.1% of patients respectively with an overall rate of VTE of 4.1%; the increase is due to many of the reasons postulated in the introduction (section 3.5.1).

3.3.5.3 Adverse Consequences of Venous Thromboembolism in Patients with Cancer

VTE is related to a variety of adverse physical and psychological consequences, including increased mortality. Cancer patients developing symptomatic VTE during chemotherapy are at a greater risk of early mortality than those without VTE (Kuderer et al, 2008). The risk of a developing a symptomatic pulmonary embolus (PE) from a deep vein thrombosis (DVT) in cancer patients is around 4% with approximately 1% of deaths during all DVT episodes related to the DVT and 1% due to the treatment for the DVT (Bergqvist et al, 2007; Elting et al, 2004). The mortality from PE is difficult to estimate as many PEs are not suspected clinically. However, in a retrospective study of all hospitalised patients, the mortality rate from PE was 14% and it was felt by clinicians that a significant number of cancer patient deaths compared with those of non-cancer patients may have been preventable (e.g.by the use of an inferior vena caval filter) (Scarvelis et al, 2010). Chew et al (2006), also reported that a diagnosis of a VTE during the first year of follow-up was a significant predictor of death for most cancer types and stages (Chew et al, 2006) and in a retrospective cohort analysis of cancer patients hospitalised with neutropenia, those with documented thromboembolism had a significantly greater in-hospital mortality than those patients without thromboembolism (Khorana et al, 2006). Lastly, VTE was found to be a

significant predictor of decreased 2 year survival in a study of over 100,000 patients with breast cancer (Chew et al, 2007).

Patients with cancer who suffer a VTE have an increased risk recurrent VTE, bleeding complications and increased utilisation of healthcare resources, in particular, hospitalisation (Elting et al, 2004; Prandoni et al, 2002). There are also significant morbidities related to having a VTE including reduced pulmonary function for patients with a PE and post-thrombotic syndrome for those with a DVT. Upon removal of CVCs from thrombosed vessels, thrombi often persist and 15% to 35% of patients with CRT were found to develop post thrombotic syndrome (Kuter, 2004). Symptoms can range from mild to severe and include calf pain, discomfort, swelling, and rashes with skin ulceration in severe cases. The long-term complications of this syndrome are hard to assess in the cancer population because of reduced life expectancy and co-morbidities. Chronic thromboembolic pulmonary hypertension is a rare but serious complication of PE (McNeil and Dunning, 2007) . VTE may also interrupt or complicate life-saving treatments e.g. chemotherapy, surgery and radiotherapy and profoundly affect the quality of life of the patient. The restriction on mobility and the emotional strain on patients and their families further diminishes quality of life. The financial burden from the management of VTE is also considerable, resulting from the expense of investigations, drugs, travel to the hospital to monitor anticoagulant therapies and loss of work productivity. The overall patient impact, not always considered as a totality, can therefore be considerable.

3.3.5.4 Clinical Presentation of Venous Thromboembolism

Given the high incidence of VTE in patients with cancer and the adverse consequences outlined above, oncology nurses, the clinical multidisciplinary team and the patients and their carers must remain vigilant for any signs and symptoms that may indicate the presence of DVT or PE. Clinical suspicion for VTE must reflect the entirety of the patient's risk profile including age, primary cancer site, histologic type and stage, recent major surgery, trauma, hospitalisation or serious medical illness, immobility and use of chemotherapy, radiotherapy, hormone or erythropeietic stimulatory agents, in addition to the presence of a thrombophilia or a past history of VTE. In the Multicenter 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 deep venous thrombosis were reported as extremity oedema (80%), pain (75%) and erythema (26%). Patients with pulmonary embolism reported dyspnoea (85%), chest pain (40%), tachypnoea (30%) and tachycardia (23%). Syncope (10%), and haemoptysis (2%) were less common (Imberti et al, 2008). The clinical picture of indwelling CVC-associated VTE is similar and outlined in Section 3.3.6.4

3.3.5.5 Risk Factors for Thrombosis in Cancer Patients

Clearly, multiple factors need to be considered when attempting to calculate an individual cancer patient's risk of developing thrombosis. Currently, there are few data to produce a specific algorithm; however, in general risk assessment tools for VTE, malignancy is considered moderate to high risk, with surgery of the abdomen and pelvis for cancer considered high risk (National Institute of Health and Clinical Excellence, 2010).

Cancer is an independent risk factor for thrombosis (Heit et al, 2000) with several molecular mechanisms for this finding being postulated in section 3.3.4.2. Despite the complexities with the studies on incidence of VTE in cancer patients, there is broad agreement in the literature around cancer, treatment and patient risk factors for cancer-associated VTE which will now be scrutinised. These evidence-based factors may be relevant to the multivariate analysis of risk factors in the WARP trial.

3.3.5.5.1 Cancer-related Risk Factors

3.3.5.5.1.1 Stage of Disease

Although some large cohort studies have identified advanced stage as a major risk factor (Sallah et al, 2002), other studies in patients with good performance status have not (Khorana et al, 2005). Stage may therefore be a surrogate for poor performance status (Khorana and Connolly, 2009).

3.3.5.5.1.2 Tumour Type

The incidence of VTE among patients with cancer varies between tumour types but the primary site of the cancer is consistently identified as a risk factor. Rates vary widely between cancer types and prevalent cancers contribute to the overall burden of VTE. Early case reports suggested that the 'mucin-producing' tumours were the most commonly associated with thrombosis. In men, pancreatic and lung cancers were particularly involved, whereas in women gynaecologic, pancreatic and colorectal cancer were most frequently associated with risk for thrombosis (Pineo et al, 1974). More recent and better designed studies have shown malignant brain tumours, haematological malignancies and adenocarcinomas of the pancreas, uterus, ovary stomach and kidney to confer the highest risk of VTE, (Blom et al, 2005a; Sallah et al, 2002; Thodiyil and Kakkar, 2002; Levitan et al, 1999). The US National Hospital Discharge survey (Stein et al, 2006) show that the highest incidence of VTE, 4.3%,

was in hospitalised patient with pancreatic cancer, followed by 3.5% in patients with brain tumours. Other tumour types were seen as high risk in a population-based case control study; patients with haematological malignancies were reported to have the highest risk of VTE (odds ratio [OR] = 28.0; 95% Confidence Interval [CI], 4.0 – 119.7), followed by lung (OR=22.2; 95% CI, 3.61-136.1) and gastrointestinal cancers [OR=20.3; 95% CI, 4.9-83.0] (Levitan et al, 1999). The results from current prospective registry data are awaited e.g. PERCEIVE, an international prospective, registry of newly diagnosed patients with cancers of the pancreas, lung, prostate, breast, colon and rectum and ovary to find out accurate clinical incidence, treatment and outcome of thromboembolic events in those patients. This study, in which the author is a principal investigator, aims to recruit 10,000 patients, to provide a more definitive answer to these questions.

3.3.5.5.2 Treatment-related Risk Factors

3.3.5.5.2.1 Surgery

Surgery is one of the cornerstones of cancer treatment and may be the only curative treatment for patients with advanced disease. The vast majority of cancer patients with CVCs for infusional chemotherapy have gastrointestinal or breast cancers, for which the first definitive treatment is generally surgery. Historically surgery and the extended postoperative period have been recognised as high risk but, in recent reports, surgery has not been found to be a major risk factor (Rodriguez et al, 2007; Alcalay et al, 2006; Blom et al, 2006), with some authors suggesting that there is high compliance with thromboprophylaxis guidelines (Khorana et al, 2009).

3.3.5.5.2.2 Chemotherapy and Hormone Therapy

The direct tissue toxicity from chemotherapy can in some cases be traced directly to vascular endothelial damage. Animal and tissue culture models are often used in

experimentation of the effects of chemotherapy on the endothelial cells (Nuver et al, 2010; Romanov et al, 2007).

In addition to the direct damage, there are several different mechanisms through which chemotherapy is capable of inducing a prothrombotic state (Haddad and Greeno, 2006):

- increasing the levels of procoagulant molecules and
- reducing the levels of endogenous anticoagulants
- inducing tumour and endothelial cell apoptosis and cytokine release, both of which in turn lead to increased expression and activity of TF
- inducing platelet activation
- inducing expression of monocyte–macrophage TF

The sclerosant potential of the chemotherapy drug (i.e. a vesicant – 'a drug which produces blisters' - or non-vesicant) was a simple method of classifying potential damage to the vein and was used as a stratification variable in the WARP trial. The clinical evidence for chemotherapy-induced thrombosis is compelling. Chemotherapy is an independent risk factor for VTE (Khorana et al, 2005). In the Olmstead County, Minnesota population-based study from 1996 through to 1990, the risk of VTE was increased 6.5-fold (95% CI 2.1-20.2) in patients with malignancy receiving chemotherapy and 4.1 fold (95% CI 1.9-8.5) in patients with malignancy not receiving chemotherapy, compared with patients without malignancy (Heit et al, 2000). In a retrospective record linkage cohort study, chemotherapy was also associated with a two to six fold increased risk of VTE compared with the general population (Blom et al, 2006).

Breast cancer patients were in the past the most widely prospectively studied population with a landmark study by Levine in 1998 showing chemotherapy contributes to VTE (Levine et al, 1988). Tamoxifen treatment increases the risk of VTE, especially during the first two years of exposure (Hernandez et al, 2009) and in combination with chemotherapy. In a randomised trial of cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy +/- to tamoxifen as adjuvant therapy in 705 postmenopausal women with breast cancer, thromboembolic events were reported to significantly increase in those women taking CMF plus tamoxifen in comparison with those who took CMF alone [$p<0.0001$] (Pritchard et al, 1997). Over the last five years, with the new era of anticancer drugs, several specific agents have been implicated in high rates of VTE. Thalidomide has been associated with VTE rates of 12%-28%, when given in combination with dexamethasone or chemotherapy (Rajkumar et al, 2006; Cavo et al, 2004). Zangari et al discovered that regimens containing doxorubicin, newly diagnosed disease and presence of chromosome 11 abnormality are predictors of thalidomide-associated VTE (Zangari et al, 2003). Lenalidomide, a thalidomide derivate, is similarly associated with high rates of VTE (Palumbo et al, 2008). A large individual data meta-analysis of bevacizumab, an antiangiogenic agent, demonstrated patient with cancer receiving bevacizumab, had a significantly increased risk of VTE (Nalluri et al, 2008), a feature found with other antiangiogenic class drugs (Kuenen et al, 2003).

3.3.5.5.3 Patient-related Risk Factors

Comorbid conditions, prior thromboses, prothrombotic mutations, age, gender and race, performance status and mobility have all been found to be high risk factors for VTE. Some factors, relevant to patients in WARP are described: Infection, often seen in patients with CVCs, was identified as one of the comorbidities mostly strongly associated with VTE among hospitalised cancer patients (Khorana et al, 2007c). Older age (≥ 65 years) is associated with a slightly elevated risk of VTE in hospitalised patients in the study above but not in the ambulatory setting with patients of good performance status (Khorana et al, 2005). Performance status has also been associated with higher rates of recurrent VTE in cancer patients (Sallah et al, 2004).

3.3.5.5.4 Prediction of Venous Thromboembolism Risk

Almost all studied cancer types have been associated with haemostatic abnormalities including thrombocythaemia, activated platelets, variation in prothombin and activated partial thromboplastin times, demonstration of circulating activated coagulation factors and elevation of fibrinogen and markers of thrombin generation. Similarly, suppression of fibrinolytic activity has been noted. Nevertheless, these markers do not yet correlate with prediction of thromboembolism or prognosis for the individual patient but exploratory studies have identified some ‘candidate’ biomarkers that may be predictive of VTE in cancer patients (Table 3.3.5.1).

Table 3.3.5.1. Candidate Clinical Biomarkers for Prediction of Venous Thromboembolism in Cancer Patients

Potential Biomarker	References
Blood Count Pre-chemotherapy Platelet Count ≥ 350,000/μL Prechemotherapy White Cell Count > 11,000/ μL	(Khorana et al, 2008; Simanek et al, 2007);
Tissue Factor High grade of TF expression by tumour cells Elevated systemic TF (antigen or activity)	(Tesselaar et al, 2009; Khorana et al, 2008; Tesselaar et al, 2007; Uno et al, 2007; Khorana et al, 2007a)
D -dimer	(Ay et al, 2009)
Soluble p-selectin	(Ay et al, 2008)
C-reactive protein	(Kroger et al, 2006)
Prothrombin fragment 1+2	(Ay et al, 2009)
Microparticles, selectin and d-dimer	(Chirinos et al, 2005)

3.3.5.6 The Impact of Anticoagulants on the Survival of Cancer Patients

Treatment of VTE for cancer patients is not discussed in this thesis as prophylaxis is the focus; however, since overall survival is a secondary endpoint of the WARP trial and there are mounting data suggesting that components of the clotting cascade and associated vascular factors play an integral part in tumour progression, invasion, angiogenesis and metastasis formation (section 3.3.5.6.1) and indeed that anticoagulants may have anticancer properties, the impact of anticoagulants on the survival of cancer patients will be explored briefly.

3.3.5.6.1 Impact of Haemostatic System on Cancer Growth and Progression

Patients presenting with idiopathic thrombosis are at increased risk of developing cancer in subsequent years (Sorensen et al, 1998; Prandoni et al, 1992). In addition, cancer diagnosed within one year of an idiopathic VTE is often associated with an advanced stage and a poorer survival than among patients with a newly diagnosed cancer without a preceding VTE event (Sorensen et al, 2000). Schulman and co-workers (2000) performed a prospective randomised study of the duration of anticoagulation (six weeks or six months) after a first episode of VTE. After a mean follow up of 8 years, they used the national Swedish Cancer Registry to identify all diagnosis of cancer and causes of death in the study population. Observed numbers of cancer cases were compared with expected national incidence rates, allowing calculation of standardised incidence ratios. They found that the standardised incidence ratio was 3.4 (95% CI, 2.2-4.6) during the first year after the VTE event and remained between 1.3 and 2.2 for the following 5 years. Interestingly, cancer was diagnosed in 66 of 419 patients who were treated with warfarin for 6 weeks, compared to 45 of 435 patients treated for 6 months (odds ratio, 1.6; 95% CI, 1.1-2.4). These data must be treated with some caution as the initial trial was not powered to detect small differences in cancer survival; nevertheless, these findings suggest that unexplained VTE is a risk factor for cancer development and that warfarin may have an antineoplastic effect (Schulman and Lindmarker, 2000). These data amongst other studies promulgated a number of trials in which anticoagulants were employed in prospective randomised controlled trials of patients, with and without established VTE, designed to determine whether they would enhance overall survival.

3.3.5.6.1.1 Anticoagulation as Cancer Therapy in Patients without Venous Thromboembolism

Warfarin was reported to improve survival in patients with small cell lung cancer in an early and small study of patients with lung, prostate, head and neck and colon cancers but this effect has not been subsequently confirmed (Zacharski et al, 1984). In a trial of 328 patients, Chahinian et al reported a significant improvement in time to tumour progression and in overall survival with warfarin versus no warfarin among small cell lung cancer patients, with no difference in other tumour types (Chahinian et al, 1989). Unfractionated heparin given to 277 patients receiving chemotherapy for five weeks, showed improved median survival (p=0.01) (Lebeau et al, 1994). However, a later study of warfarin in 347 patients with limited stage small cell lung cancer, demonstrated no significant improvement in response rate, disease-free or overall survival (Maurer et al, 1997). The most recent study in 84 patients with small cell lung cancer showed a median progression-free survival of 10 months with LMWH versus 6 months in the control arm of chemotherapy alone [p=0.01] (Altinbas et al, 2004). The majority of these studies are limited by their small size, heterogeneous cancer patient population and outdated chemotherapy.

In tumour types, apart from small cell lung cancer, there is some evidence to suggest that heparin and its low molecular weight derivatives (LMWH) may also lead to survival benefits for cancer patients. The Fragmin advanced malignancy outcome study (FAMOUS) was designed to investigate the efficacy of long term treatment with the LMWH dalteparin, compared with placebo in 385 patients with advanced cancer, randomised to 5000iu dalteparin or normal saline placebo subcutaneously, daily for a maximum of 1 year. The powered objective, namely a 15% improvement in 1 year

survival was not achieved but in a post hoc analysis of 102 patients still alive at 17 months, significant improvement in survival was found for patients receiving dalteparin (Kakkar et al, 2004). Post hoc, subgroup analyses must be treated with caution, but these data may suggest that further trials are warranted in patients with a minimal cancer burden. In another LMWH trial, 302 patients were randomly assigned to nandroparin or placebo for 6 weeks. With a mean follow up of one year, a significant improvement in overall survival was observed (p=0.02) among patients receiving nadroparin (Klerk et al, 2005). However, these findings were not confirmed by a later small trial in advanced solid tumour patients randomly assigned to standard treatment with or without dalteparin (Sideras et al, 2006). This study changed from placebo-controlled to open label part way through making the interpretation of the findings problematic (Section 5.3.2).

3.3.5.6.1.2 Anticoagulation Therapy in Cancer Patients with an Established Venous Thromboembolism

Most of the data in clinical trials of anticoagulation treatment in patient with an established VTE come from subgroups of studies with mixed disease types. A trial of initial treatment of patients with a proximal DVT with either LMWH or unfractionated heparin (UFH), demonstrated that 44% of the patients with cancer in the UFH group died compared with 7% of patients in the LMWH group (p=0.02). In a meta-analysis of nine trials, Hettiarachchi et al (1998), compared the mortality of LMWH vs UFH treatment using nine randomised controlled trials in patients with cancer; there were fewer deaths reported in the first three months with patients receiving LMWH compared to UHF (OR, 0.61; 95% CI, 0.40-0.93) (Hettiarachchi et al, 1998). Both LMWH and UHF were of brief duration and followed by warfarin in these patient groups. Again, because of the post hoc analyses of cancer patients, these findings

remain hypothesis generating only. A retrospective analysis of survival for cancer patients with established VTE and recruited to the CLOT trial (dalteparin versus coumarin derivative for 6 months), was undertaken (Lee et al, 2005). During the 12 month follow up period, 356 of 602 patients died. In a post-hoc analysis of patients with non-metastatic disease, the probability of death at one year was 20% (dalteparin) vs 36% (oral coumarin) (HR, 0.5; 95% CI 0.27-0.95, p=0.003). In patients with metastatic cancer (n=452), no statistically significant difference in mortality between the treatment groups was observed (72% and 69%, respectively; hazard ratio, 1.1; 95% CI, 0.87 to 1.4; p=0.46). The observed effects of dalteparin on survival were statistically significantly different between patients with and without metastatic disease (p= 0.02).

As survival was a secondary endpoint of the trial, a meta-analysis of the trials above in mortality in cancer patients treated with warfarin versus control or LMWH versus control was carried out as part of this thesis, in order to place the WARP survival results in context. Although plausible antineoplastic properties associated with LMWHs (inhibition of heparanase, disruption of P-selectin function, and inhibition of coagulation proteases) have been put forward, it is difficult to separate putative survival benefits which may be accrued from a direct anticancer effect leading to reduced rates of tumour progression, or by reduction in deaths from silent or asymptomatic VTE. Further, well designed trials, especially in the adjuvant setting, are required to provide a definitive proof of benefit or refutation thereof.

This thesis is based on a clinical trial on a specific population - cancer patients who have indwelling central venous catheters for the administration of chemotherapy. This patient population has the potential to fulfil the three categories in the triad of Virchow for risk of thrombosis: hypercoagulability due to the cancer cells and host reaction; blood stasis due to the catheter sitting in the vein; and injury to the vessel wall due to the catheter and/or or the vesicant nature of the chemotherapy. Central venous catheters have been recognised as an additional and independent risk factor for thrombosis in cancer patients and warrant close examination.

3.3.6 Central Venous Catheters and Thrombosis

3.3.6.1 Central Venous Catheters

Initial experiments with venous catheters in the mid-17th century, through which the physicians of the day administered animal blood, purgatives, ale and opiates, were plagued with controversy and iatrogenic deaths. Not surprisingly, intravenous therapy fell into abeyance for a few centuries. However, the last three decades have seen the development of much more sophisticated cannulation devices, particularly long-term catheters which can stay in place for months or years (summarised in Table 3.3.6.1). A central venous catheter by definition is one whose tip lies in the superior vena cava (Goodwin and Carlson, 1993). Central placement is direct insertion into a 'central vein usually on the chest wall, most commonly the internal jugular or subclavian veins and peripheral insertion is placement in the cephalic or basilic veins in arm – see Figure 3.3.6.1. Ultrasound guidance is commonly utilised during the placement procedure as suggested in the National Institute of Health and Clinical Excellence (NICE) Technology Appraisal Guidance (NICE, 2005) but, there is by no means, comprehensive use despite the national guidance. Traditionally, the insertion of tunneled catheters was the domain of surgeons, anaesthetists and radiologists; however, in the last decade, nurse-led services for centrally placed, as well as peripherally placed, have demonstrated high quality care (Hamilton, 2004; Kelly, 2003; Benton and Marsden, 2002).

Table 3.3.6.1 Types of Central Venous Catheters used for Intravenous Chemotherapy

Type of Device	Material	Veins Commonly Used	Number of Lumens	Associated non thrombotic complications
Peripherally Inserted Central Catheter (PICC)	Polyurethane Silicone	Basilic Cepahalic Median Cubital	Single or double	Phlebitis, infection, malposition, occlusion
Skin tunneled catheter	Polyurethane Silicone	Internal jugular Subclavian Femoral	Single, double or triple	Infection, thrombosis, occlusion
Implanted Port	Portal Body – titanium or plastic; Catheter - silicone	Internal jugular Subclavian Femoral	Single or double	Infection, thrombosis, extravasation

The type of central catheter employed by UK clinicians varies from centre to centre.

3.3.6.1.1 Types of Central Venous Catheters

The types of catheters, using a generic taxonomy, are shown in Table 3.3.6.1. Totally implanted devices tend to be utilised in routine practice more frequently within European countries other than the UK, e.g. in one of the largest cancer centres in France, Institut Gustave Roussy in Villejuif, where the author has worked, 99% of central venous devices inserted, are 'Port-a Caths' (implantable). However, these are becoming more popular in the UK in the last 5 years, because by their very nature, they are not exposed on the external skin and have an associated expected reduction in the risk of infection and less thrombosis than peripherally inserted catheters (odds ratio [OR] = 0.43; 95% CI, 0.23-0.80) (Saber et al, 2008). Catheter material, lumen number and internal tip forms are claimed by the manufacturers to be of differing thrombogenicity amongst other features and merit discussion.

3.3.6.1.1.1 Catheter Material

Polyurethane and polyvinylchloride (PVC) were used in the past due to their stiff nature that allowed for percutaneous insertion. However, they are associated with increased thrombogenicity due to the rigidity of the catheter. Polyurethane is now available as a rigid, semi-rigid and flexible material. Some of the newer polyurethane catheters soften after insertion in response to body temperature and some have silicone tips to reduce potential damage to the endothelium. Polyurethane has tensile strength that permits the catheter to be constructed with thinner walls and smaller external diameters, thereby reducing the foreign material in the vein and allowing higher infusion pressures through smaller catheters (Hadaway, 1995). Silicone, alternatively, is a very soft biocompatible material that floats within the vein and is less likely to cause damage to the wall of the vessel. The majority of CVCs are made

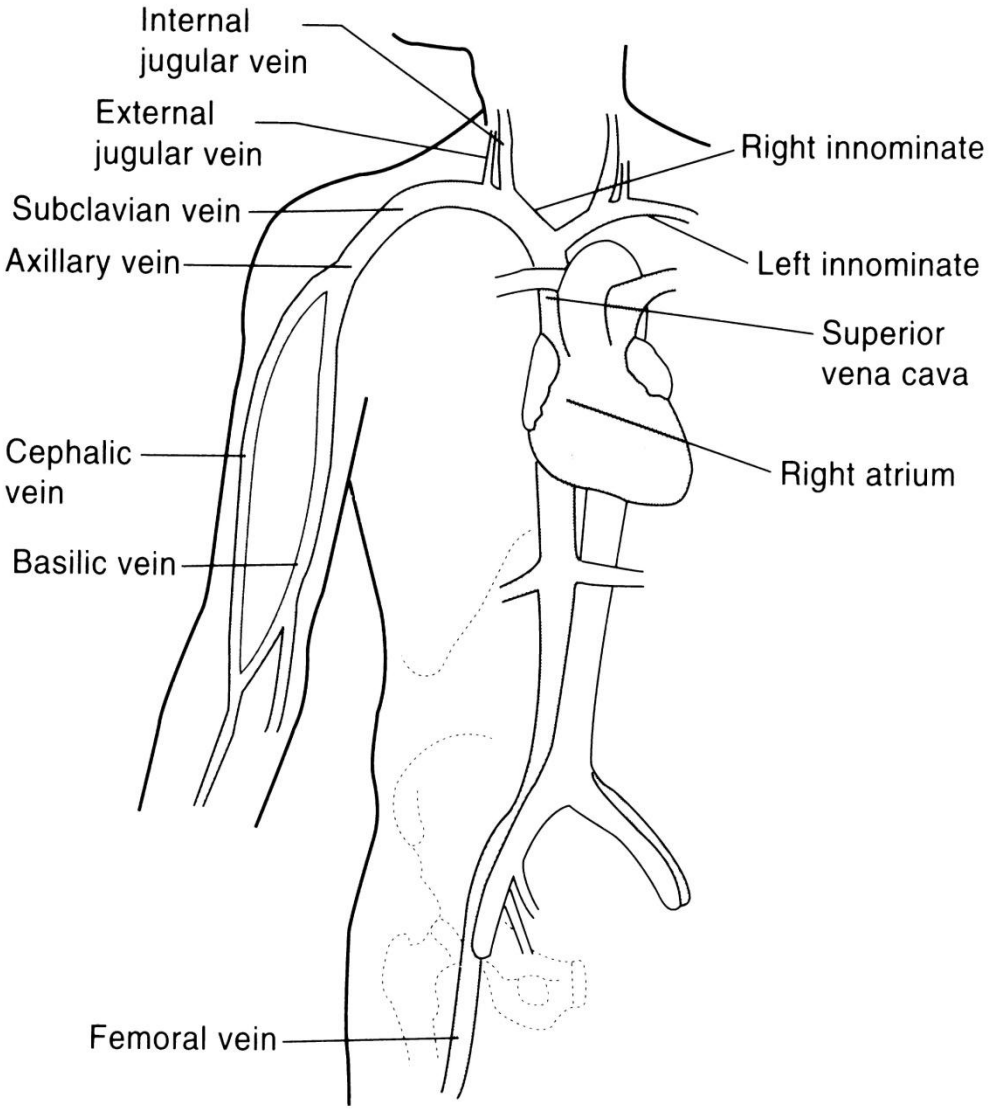
of silicone which necessitates thicker walls to achieve strength and therefore smaller internal diameters (Dougherty, 2006).

3.3.6.1.1.2 Further Catheter Variables

Catheters are available with a number of lumens for simultaneous infusion of incompatible agents; double lumens are usually required for complex chemotherapy regimens for patients with haematological malignancies; however, an increase in the number of lumens is associated with infection (Pratt et al, 2001). There are two types of internal tip endings: open, which can be cut to size and 'valved', developed to ensure there is no blood reflux when the catheter is not in use. The Groshong valve, in the tip of the catheter is pressure activated. Positive pressure connectors can also be added to the external catheter end to maintain pressure and minimize occlusion (Jacobs et al, 2004). Lastly, catheter size is measured in 'French' or in 'gauge'. French size is the outside diameter of the catheter (in millimeters, multiplied by three); gauge is the inner or outer diameter, ranging from 13-28 with the smallest number indicating the largest diameter.

Figure 3.3.6.1. The main veins used for central venous catheter placement

Source: Central Venous Access Devices (Dougherty, 2006) with author permission



3.3.6.2 CVC Use in Cancer Therapy

Long-term central venous catheters (CVCs) have been in clinical use for over 20 years for the administration of infusional cytotoxic therapy to patients with both haematological and solid malignancies. This practice is increasing rapidly due to ease of catheter insertion, novel high dose chemotherapy regimens requiring long term vascular access and increased use of ambulatory infusional regimens. Additional indications for placement of a CVC include poor venous access and the administration of chemotherapy drugs known to be venous sclerosants (vesicants).

3.3.6.2.1 Basis of infusional chemotherapy

The reason for giving infusional chemotherapy instead of bolus is based on the cell cycle and the chemotherapy's mode of action. The vast majority of cytotoxic drugs inhibit the synthesis of DNA, albeit, through a range of different molecular targets. Empirical observations on the shape of dose response curves for all the major antineoplastic agents led Skipper and Schabel (Wilcox et al, 1965) to postulate that there was a class of drugs which was cell cycle and phase specific. This implied that cancer cells were sensitive to these drugs for a limited period of time only. For example, if the cell cycle lasted, arbitrarily 24 hours and S-phase (the period during which the DNA doubles) is of 8 hours duration, then in a typically desynchronised cancer cell population, only one third of the cells would be in S-phase at any point; and therefore vulnerable to the cell killing effects of the anticancer drugs. A classical phase specific agent is the antimetabolite, 5-FU, used in on its own and in combination with other cytotoxic agents for the majority of patients having infusional chemotherapy. This prodrug is activated within cells to 5-fluorodeoxyuridine monophosphate (5-dUMP) which binds to and inhibits one of the key enzymes involved in DNA synthesis, thymidilate synthase (TS). There are good experimental

data which show that prolonged exposure to lower concentrations of 5-FU is much more effective at killing cancer cells than brief exposure to higher drug quantities. This is consistent with its S-phase specificity and would imply that prolonged exposure might be more effective that an intermittent, high dose regimen. 5-FU has a brief plasma half life of 10-15 minutes (Young et al, 1999), and has proven very difficult to formulate in a slow-release, pharmaceutically stable form. Infusional 5-FU is better tolerated, induces a higher tumour response rate and marginally improves survival compared to intermittent bolus injections (Louvet et al, 1992). These clinical data have supported a very large increase in infusional delivery of 5-FU, using a variety of schedules (48 hour infusion every 2 weeks; 24 hour infusion every week; 7 day continuous infusion, repeated for 8 weeks) for patients with advanced disease.

3.3.6.3 Catheter-related Thrombosis

CVCs are consistently identified as an independent risk factor for VTE (Heit et al, 2000) and a common cause of upper extremity or neck DVT. Using the data from a prospective multicentre US DVT registry, the 'DVT-FREE' steering group reported that an indwelling CVC was the strongest independent predictor of upper extremity DVT (odds ratio [OR], 7.3; 95% CI, 5.8 to 9.2). and risk factors for upper extremity VTE differ somewhat from the conventional risk factors for lower-extremity DVT (section 3.5.5) by virtue of the foreign body location (the catheter) (Joffe et al, 2004). A more recent multivariate analysis also demonstrated that the presence of a central venous catheter and no thromboembolic prophylaxis during hospitalisation were independently associated with VTE in patients with cancer (Seddighzadeh et al, 2007).

3.3.6.3.1 Pathophysiology of Catheter-related Thrombosis

The pathogenesis of CRT is multifactorial: injury to the vessel wall from placement, venous stasis around the catheter and vessel occlusion caused by size of the catheter in relation to the smaller veins of the upper extremity are all factors involved. The loss of vessel integrity from the insertion procedure causes changes in the endothelium with resultant production of procoagulant factors and activation of platelets and blood coagulation. These events may cause a thrombus which is reversible in the majority of patients but, in some, leads to the formation of collagen and stabilisation of the thrombus (Xiang et al, 1998).

3.3.6.3.2 Types of Catheter-related Thromboses

Venographic studies have shown that a catheter sleeve, an extraluminal adherent coating of fibrin and collagen that envelopes the CVC in up to 47% of patients, is formed within 24 hours (De Cicco et al, 1997). This sleeve is in itself a benign complication but can travel the whole length of the catheter, interfere with catheter function, produce a nidus for local infection and may lead to a mural thrombus, although formation of a sheath does not predict subsequent VTE (Starkhammar et al, 1992) (Figure 3.3.6.2). One other common thrombotic event is intraluminal clotting, most commonly noted when the infusional pump fails to work. The frequency of this event is probably significantly underreported as nursing staff readily handle this complication; initial management is thrombolysis with urokinase (or equivalent) or removal and replacement. Published figures suggest that 15-20% of patients suffer this inconvenience (Shivakumar et al, 2009). Lastly a fibrin tail occurs when fibrin, platelets and blood cells adhere to the end of the catheter, often lengthening. The ability to flush but not withdraw blood (‘ball valve effect’), is commonly experienced because of the tail which may lead to a luminal or vessel

thrombosis but again, is not predictive. Non-thrombotic mechanical problems commonly prevent blood flow. In an venographic study of patients with problems with blood withdrawal from catheters, 58% were found to have a thrombosis [and 42% did not have a thrombosis] (Stephens et al, 1995).

Figure 3.3.6.2 Types of Central Venous Catheter Thromboses

Source: Vascular Access Devices (Dougherty, 2000)

With permission from the author, Lisa Dougherty

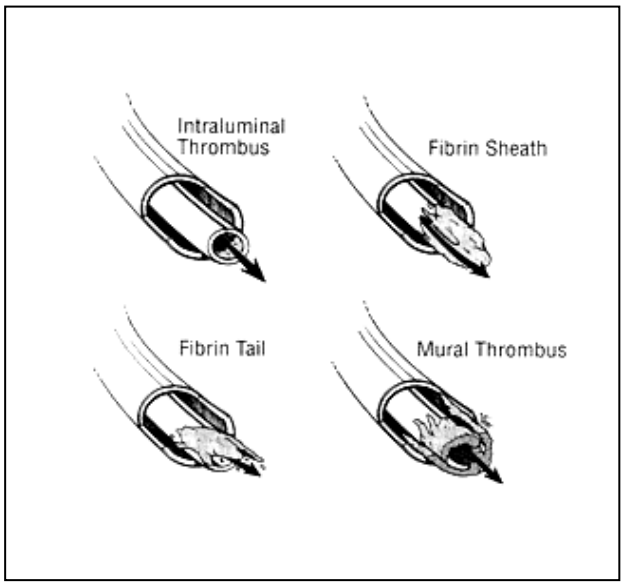


Figure 3.3.6.2 Types of Central Venous Catheter Thromboses

Intraluminal: within the catheter and often under-reported

Fibrin Tail: fibrin, blood cells and platelets adhere to the top of the catheter

Fibrin Sheath: an extraluminal fibrin sheath is formed normally around the top of the catheter and may extend back along the catheter

Mural Thrombosis: fibrin from the vessel wall attaches to the catheter

3.3.6.3.3 Incidence of Catheter-related Venous Thromboembolism

The incidence of catheter-related VTE has been described in a number of clinical observational and interventional studies; however, as with incidence of VTE in cancer patients, it is impossible to define incidence precisely, given the variation in a range of relevant factors that make an inter-study comparison difficult. These include differences in study design and the observed patient population, variation in the method of catheter type and insertion, inconsistent description of the thrombotic event, significant differences in patient follow up and the sensitivity and specificity of the radiological methods used to confirm the diagnosis. This gives a wide range in the published incidence of symptomatic CRT in adult cancer patients, from 0.7-28.3% (Table 3.3.6.2). If the study endpoint is venography- detected VTE, the thrombosis rate rises to a range of 3.7-66% (Table 3.3.6.3). In summary, from all published studies of VTE carried out in adult cancer patients with CVCs, since 1983, presented in Tables 3.3.6.2 and 3.3.6.3, a median of 6.75% of patients develop symptomatic thrombi. In those studies in which symptomatic plus venographically screened CRTs were measured, a median of 28% of patients develop a VTE. By extrapolation, for every one symptomatic VTE (mean 10.4%), there may be around two to three asymptomatic VTE (mean 27.7%).

With respect to timing, there are relatively few prospective studies with multiple venography. Di Cicco and coworkers reported a longtitudinal study with venography repeated 8, 30 and 105 days after CVC insertion. They found that 64% of thrombi occurred by day 8, and 98% by day 30 (De Cicco et al, 1997).

Table 3.3.6.2 Incidence of Symptomatic Catheter-related Thromboses in Adult Cancer Patients

Study Design	Sample Number	CRT %	Reference
Retrospective	53	28.3	(Lokich and Becker, 1983)
Prospective	826	28.7	(Raaf, 1985)
Retrospective	92	16.3	(Lokich et al, 1985)
Retrospective	115	7.8	(Stanislav et al, 1987)
Prospective	190	3.7	(Moss et al, 1989)
Prospective	168	17	(Anderson et al, 1989)
Prospective	123	4.1	(Jansen et al, 1990)
Prospective	162	12.9	(Haire et al, 1990)
Prospective	46	41	(Conlan et al, 1991)
Prospective	92	6.0	(Mueller et al, 1992)
Prospective	22	5.0	(Soh and Ang, 1993)
Prospective	322	10.0	(Eastridge and Lefor, 1995)
Prospective	50	21.0	(Horne, III et al, 1995)
Retrospective	223	3.0	(Laurenzi et al, 1996)
Prospective	18	26.0	(Cunningham et al, 1996)
Prospective	949	4.7	(Nightingale et al, 1997)
Retrospective	177	4.8	(Meisenberg et al, 1997)
Prospective	223	9.0	(Boraks et al, 1998)
Retrospective	110	9.0	(O'Neill et al, 1999)
Retrospective	409	2.2	(Lyon et al, 1999)
Prospective	923	3.1	(Schwarz et al, 2000)
Prospective	390	6.9	(Lagro et al, 2000)
Retrospective	209	11	(Minassian et al, 2000)
Retrospective	65	21	(Carr and Rabinowitz, 2000)
Prospective	100	5.0	(Povoski, 2000)
Prospective, RCT	304	6.6	(Biffi et al, 2001)
Prospective	98	2.1	(Coccaro et al, 2001)
Prospective	233	1.5	(Harter et al, 2002)

Study Design	Sample Number	CRT %	Reference
Prospective, RCT	88	14.7	(Heaton et al, 2002)
Prospective, RCT	255	4.3	(Couban et al, 2005)
Prospective	458	7.6	(Cortelezzi et al, 2005)
Prospective	247	1.8	(Magagnoli et al, 2005)
Prospective	443	4.3	(Lee et al, 2006)
Prospective	1390	2.5	(Fagnani et al, 2007)
TOTAL	**9573**		**Median Catheter-related thrombosis rate = 6.75%**

Interestingly, for the 34 ‘symptomatic CRT’ studies (Table 3.3.6.2), the sample size was found to be correlated with %CRT (spearman’s r = -0.48, p = 0.004); the larger the sample, the lower the CRT rate.

For the 13 venographically determined VTE rate studies (Table 3.3.6.3), sample size was not found to be correlated with %CRT (spearman's r = -0.43, p = 0.14). Caution should be applied in the interpretation of the above results because of the small numbers of studies.

Table 3.3.6.3 Incidence of Venographically determined Catheter-related Thromboses in Cancer Patients

Study Design	**Sample Number**	**CRT %**	**Authors**
Prospective, RCT	121	15.7	(Bern et al, 1990)
Prospective, match	17	35	(Haire et al, 1990)
Case Series, post mortem	72	36	(Raad et al, 1994)
Prospective	57	56	(Balestreri et al, 1995)
Retrospective, RCT	32	28	(Monreal et al, 1996)
Prospective, RCT	127	66.0	(De Cicco et al, 1997)
Prospective, RCT	80	21	(Park K et al, 1999)
Retrospective	319	35.1	(Frank et al, 2000)
Prospective, RCT	302	5.6	(Biffi et al, 2001)
Prospective, RCT	252	30	(van Rooden et al, 2004)
Prospective, RCT	385	16	(Verso et al, 2005)
Prospective	439	3.6	(Karthaus et al, 2006)
Prospective, RCT	87	12.6	(Niers et al, 2007)
TOTAL	**2203**		**Median Catheter-related thrombosis rate = 28%**

3.3.6.3.4 Risk Factors for Central Venous Catheter-related Thrombosis

Very few prospective randomised studies have been undertaken to compare different types of catheters, ports, surface coatings etc. in relation to CRT and therefore most of the published data on risk factors for CRT has come from retrospective multivariate analyses of sequential patient cohorts, others with historical controls. Although limited, these have suggested a number of plausible catheter-related risk factors (catheter and host associated). Data from randomised studies with sufficient power offer the most robust answers.

The factors found to be associated with an increased risk of CRT in patients with cancer include the type of malignancy e.g. ovarian (Tesselaar et al, 2004), lung (Anderson et al, 1989), metastatic vs localised disease (Verso et al, 2008); anticancer treatment type ((Verso et al, 2008; Bern et al, 1990; Baglin and Boughton, 1986); pre-existing haematological conditions e.g. Antithrombin III deficiency (De Cicco et al, 1995), and characteristics of the catheter itself e.g. previous insertion (Lee et al, 2006), tip position (Nightingale et al, 1997).

Catheter tip placement is an important risk factor for CRT. The optimal tip placement is the upper portion of the lower third of the superior vena cava (Eastridge and Lefor, 1995) – Figure 3.3.6.3

Figure 3.3.6.3 Optimal placement for central venous catheters

Source: Bard Catheters, 'PICC Training Poster' - with permission from the company

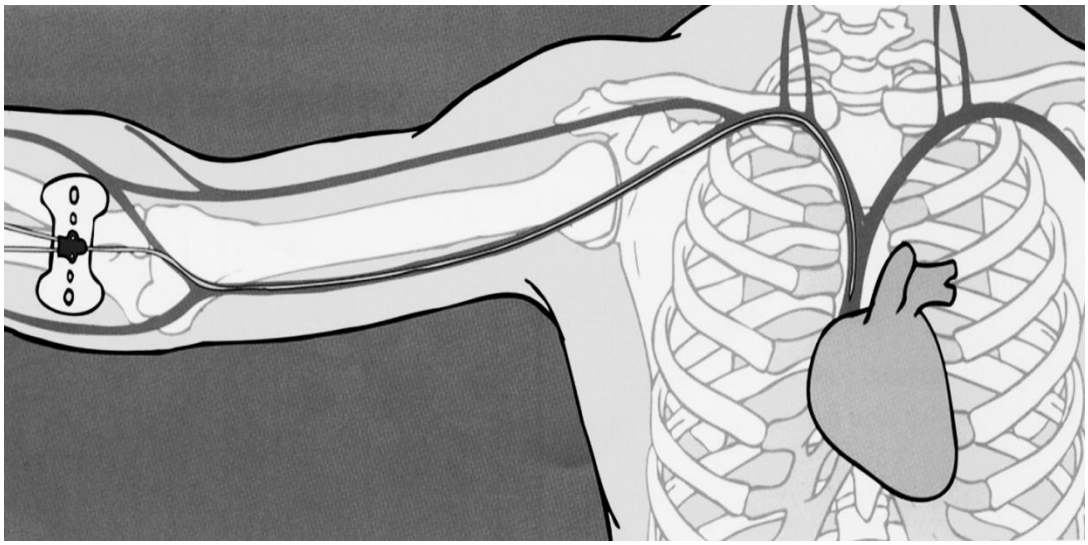


Figure 3.3.6.3 Schematic of optimal catheter placement: the upper portion of the lower third of the Superior Vena Cava. A peripherally inserted central catheter (PICC) is illustrated.

3.3.6.4 Clinical Presentation of Catheter-related Thrombosis

Around one third of VTE events in cancer patients with CVCs involve the upper limb (33%). Another third are in the veins feeding the superior vena cava (SVC) with the remainder in the SVC (3%), the leg (23%), pulmonary emboli (11%) and inferior vena cava (<1%). As previously mentioned, approximately 7% of patients screened by venography were symptomatic, presumably because thrombosis is more chronic and less likely to be occlusive. Patients typically present with upper extremity or head or neck swelling, erythema, and/or discomfort with congestion of subcutaneous

collateral veins. CVC dysfunction is also a common presentation although this can also result from a fibrin sheath in the catheter lumen itself. Less commonly, symptoms of PE, headache and distal parasthesiae are the first signs of a CVC thrombus (Linenberger, 2006). In addition to being a complication of CRT, pulmonary embolism may present as the first clinical manifestation of catheter thrombosis, with a reported incidence of 15-25% in adult cancer patients. These data are collected from three small prospective studies which recruited a total of 147 patients (Kuter, 2004).

3.3.6.5 Other Complications of Central Venous Catheters

Thrombotic complications are associated with CVCs. However, there are other sequelae of catheter insertion (summarised in Table 3.3.6.4). These may be early and associated with puncture wounds (arterial, pneumothorax, venous haemorrhage) and malposition (failure of insertion, arrhythmia, misplacement of reservoir) or later (infection, catheter fracture or migration of catheter tip). These complications are rarer than thrombosis but can nevertheless be the source of significant morbidity.

Table 3.3.6.4 – Non-thrombotic Complications of Central Venous Catheters

Source: Vascular Access Devices (Dougherty, 2000), with permission

	Incidence (%)
Early	
Arrhythmia	13
Arterial Puncture	2.8-3.8
Malposition of Reservoir	2
Pneumothorax	1-2
Wound dehiscence	1.5
Haemorrhage	1.2
Failure of Insertion	1.2
Late	
Infection	4-38
Catheter fracture and embolisation	3
Migration of catheter tip	7.4

3.3.6.6 Diagnosis of Venous Thromboembolism in Patients with Central Venous Catheters

The gold standard for diagnosis of VTE in patients with CVCs, remains contrast venography. This method has not been applied uniformly across the various epidemiologic studies of catheter related thrombotic risk, given its invasiveness, cost and requirement for contrast medium. In the case of clinical suspicion of upper limb VTE, modern ultrasound techniques (especially with Doppler and colour flow) are most widely used to confirm the diagnosis. A systematic review of the rather sparse literature has indicated that the specificity of duplex ultrasound varies between 56 to 100% and sensitivity from 94-99%. In patients with clinical suspicion of an upper limb VTE, a diagnostic accuracy rate of 82-95% has been reported for colour flow Doppler, compared to venography as standard. This has led clinicians instituting anticoagulant therapy in patients with a clinical suspicion of VTE and a positive

ultrasound examination, whereas it is recommended that patients with a negative ultrasound despite suspicious clinical factors, should have a venogram before the diagnosis of VTE is completely ruled out (Streiff, 2009).

3.3.6.7 Managing Established Catheter-related Thrombosis

Conventional therapy for a CVC blocked by an intraluminal thrombus only is local lytic therapy with a low dose of single or repeated bolus of urokinase, streptokinase or tissue plasminogen activator. This is effective in restoring patency in up to 85% of patients. If this proves ineffective, catheter removal and replacement, if chemotherapy is to continue, is mandated.

For other confirmed VTE, anticoagulant therapy is the treatment of choice, using protocols developed for lower limb VTE. Accordingly, treatment is generally initiated with adjusted dose unfractionated heparin or LMWH for 5-7 days and subsequently continued with oral warfarin. If there is some contraindication to warfarin, treatment is continued with subcutaneous administration of LMWH. This seems relatively straightforward, but given the lack of prospectively randomised trial data on this subject, there are areas of management which are open to local interpretation. Should the CVC be removed if it is still functioning? Clearly, this will depend on associated symptoms, whether further chemotherapy is required, platelet count etc and consideration given to the fact that insertion of a second CVC on the opposite side is often associated with considerable morbidity and cost.

What is the optimal duration of anticoagulant therapy? There are no guiding data to give a precise answer and there seem to be two camps of thought. One in which anticoagulation is discontinued after 6 months, especially if the patient has received curative therapy) or the other in which patients are treated indefinitely (particularly if they still have an active cancer burden). The cost-benefit ratio for either of these approaches has not been properly calculated and guidelines will therefore be based more on expert opinion than randomised trial evidence.

3.3.7 Prophylaxis of Venous Thromboembolism in Cancer Patients with Central Venous Catheters

The literature on which the WARP trial was based and the emerging evidence on anticoagulation in cancer patients with CVCs is outlined in the discussion (section 6.2.6.1), as background to the meta-analyses of thromboprophylaxis in cancer patients with CVCs.

4. Methods

4.1 *Survey of UK Practice of Thromboprophylaxis for Cancer Patients with CVCs (Pre-trial Survey)*

In May 1999, a postal questionnaire with a pre-paid envelope was sent out to 769 cancer clinicians and nurses, targeted through previous participation (i.e. selected population) in large-scale national trials of cancer chemotherapy. Clinicians who did not have personal experience of using catheters for the administration of chemotherapy were asked in the covering letter to pass questionnaires onto interested colleagues. This was a single postal survey and non-responders were not followed up due to postal costs and lack of efficiency in phoning clinicians. The survey consisted of a semi-structured questionnaire with nine main questions, five tick box categories and four open text sections for answers on types of catheters and drugs used, cancer sites and any other comments (Appendix 1). Respondents were asked about their current clinical practice, an estimate of incidence of thrombosis in their cancer patients, whether thrombosis in patients with central venous catheters (CVCs) receiving chemotherapy, represented an important clinical problem and also their confidence (certain or uncertain) in the thromboprophylactic use and dosage of warfarin.

Results were collated using a bespoke relational database (Microsoft Access) which enabled the analysis to be performed. These are summarised using descriptive statistics. A Wilcoxon rank sum test (used for a non-parametric comparison of two groups, making no assumptions on the underlying distribution) was utilised to

compare clinicians who documented that they used warfarin versus those who used no warfarin in practice for thromboprophylaxis in cancer patients with CVCs.

4.2 *WARP Trial*

The aims and outcomes for the WARP trial, taken directly from the protocol, were stipulated as:

4.2.1 Aims

4.2.1.1 Primary:

- To determine the utility of any warfarin in reducing CVC-related thrombosis rates in cancer patients
- To determine whether variable dose warfarin is superior to fixed dose warfarin in reducing CVC thrombosis rates

4.2.1.2 Secondary:

- To assess warfarin-related toxicity and monitor the trial-related adverse events
- To determine the effect of warfarin (fixed and variable dose) on total thrombosis rates
- To compare survival of patients in the warfarin and no warfarin arms

4.2.2 Outcomes

4.2.2.1 Primary:

- The number of catheter-related thrombotic events

4.2.2.2 Secondary:

- The number of other thrombotic events
- The duration of catheter patency
- The frequency and severity of trial-related adverse events
- The frequency of central venous catheter-related sepsis
- Costs (dependent upon primary outcome):
  - trial-related outpatient, inpatient and GP attendances
  - diagnostic procedures for confirmation of thrombosis and
  - cost incurred by patients and patient preference for alternative management options
- Patient survival

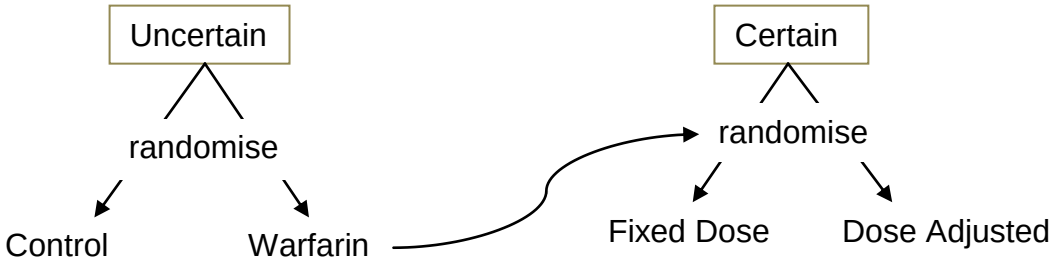
4.2.3 Trial Design

WARP was structured to encompass contemporary clinical opinion noted from the pre-trial survey described above. A randomised, phase III trial was chosen to assess the role of warfarin in the prophylaxis of catheter-related thrombosis in cancer patients having chemotherapy via a central venous catheter (CVC). The UK has promulgated the concept of large, pragmatic trials, designed to give clear answers to clinically relevant questions. The proponents of this approach to clinical trials stress that focussing on data collection of the key outcome measures, reduction in extraneous data input and recruiting sufficient subjects to give a greater degree of power and reliability, is more likely to deliver practice-changing science (Yusuf et al, 1984). The design of the trial was based on the principle of uncertainty i.e. if the clinician is certain or uncertain of the indication for the intervention, they are able to randomise to their preference (Freedman, 1987). This was an attempt to be

inclusive and provide a trial design which would allow clinicians to interpret the current literature in their own way and contribute patients to the trial question which they felt was the most relevant to their practice and the individual patient. The survey demonstrated three groups of clinicians with strongly-held views; those who give no warfarin; those who give 1mg of warfarin daily and those who anticoagulate further, to a target INR. The trial design chosen therefore was able to accommodate these three opinions with two questions in one linked trial: does warfarin add benefit or not in comparison to no warfarin in thromboprophylaxis in cancer patients with CVCs and, if so, what is the optimal dose of warfarin to use? This trial design, based on the principle of uncertainty, had been utilised successfully in the UK in a trial of 8,000 patients, 'QUASAR', a comparison of adjuvant chemotherapy vs control and optimal chemotherapy regime for patients with colorectal cancer (Kerr et al, 2000). QUASAR adopted a pragmatic trial design, with local clinical teams categorising patients as having either a clear or an uncertain indication for adjuvant chemotherapy. The indication for chemotherapy was decided by each patient's clinician, after consultation with the patient, rather than by any per-protocol definition. This design was adapted for WARP, in response to the national clinical survey and a desire to develop a pragmatic study that could be supported by the majority of clinical sites in the UK and therefore enhance recruitment. This design also allows some patients to contribute to both comparisons (Figure 4.2.3.1).

Figure 4.2.3.1 WARP Trial Design I

(based on the principle of uncertainty)



In WARP, clinicians who were 'uncertain' of the benefits of warfarin for thromboprophylaxis, could randomise patients to no warfarin, fixed dose warfarin at 1mg per day (FDW) or dose adjusted warfarin (DAW) daily, to maintain the international normalised ratio (INR) between 1.5 and 2.0. Clinicians who were 'certain' of the benefits of warfarin, could randomise patients to FDW or DAW. All preferences were those of the clinicians after consultation with the patient.

4.2.3.1 Blinding

The blinding (or masking) of an observer or patient so that neither can identify the assigned treatment is the ideal way of avoiding biased measurement (by the observer) or reporting (by the patient). This was not feasible in WARP as the treatments are generally distinguishable by the international normalised ratio (INR) [prothrombin time ratio] which must be made known to the assessor and the patient to treat accordingly to minimise bleeding and keep within range for the dose adjusted warfarin arm. Therefore, an open-label randomised trial was chosen as placebo-control was difficult to execute. The clinicians and the study patients were aware of the group to which they were assigned and different coagulation test (INR

or prothrombin time ratio) monitoring guidelines were in place as per protocol for different arms of the study.

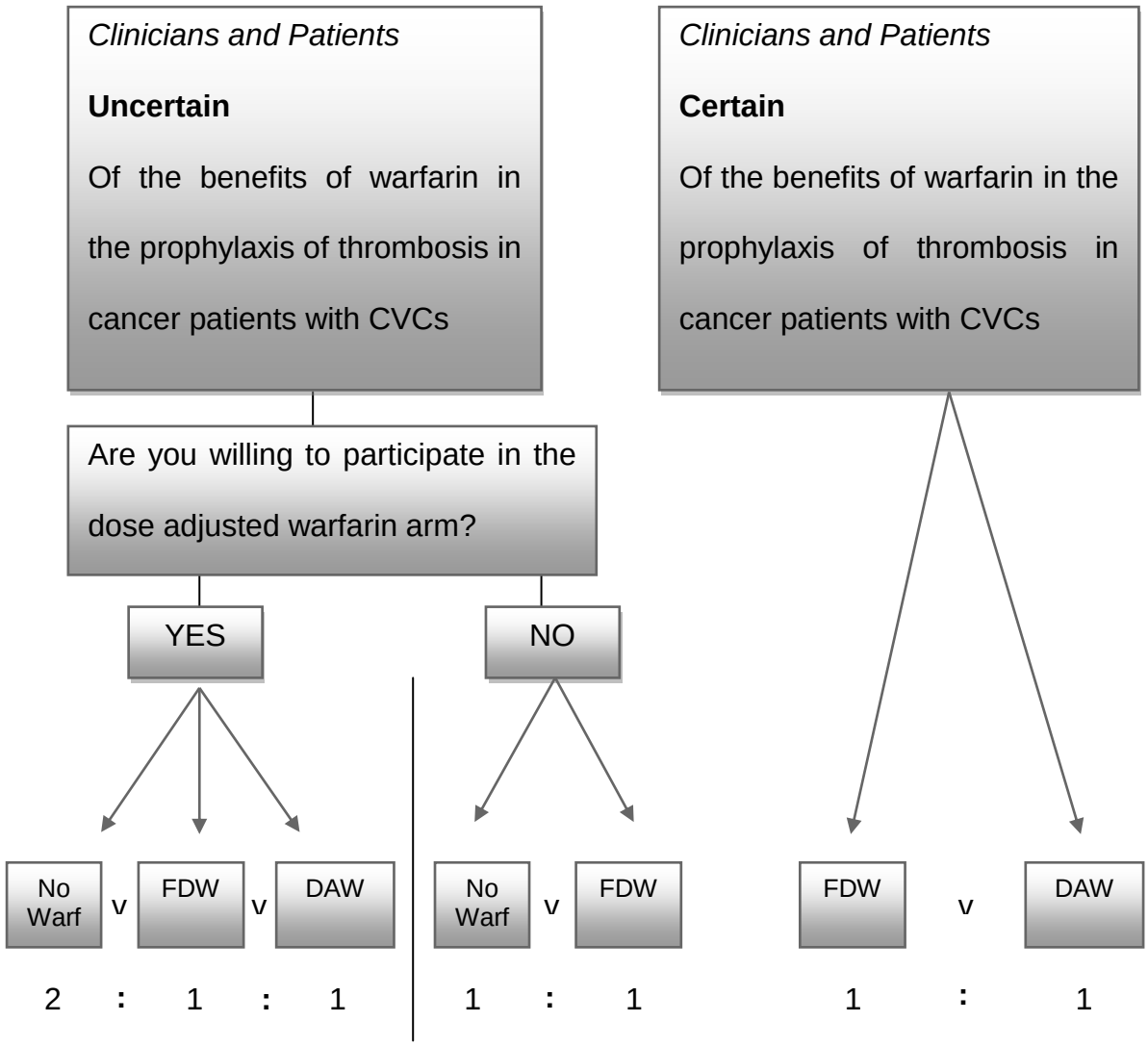
4.2.3.2 Trial Design Amendment

Initially, the 'uncertain indication' preference had three arms as described above; no warfarin *versus* FDW *versus* DAW. However, investigators subsequently requested that a two arm option of no warfarin vs FDW be included. There were two important reasons for this: firstly, patients randomised to DAW were monitored more closely, as recommended by the guidelines issued, in order to maintain their INR between 1.5 and 2.0. However, in some centres it proved difficult to monitor those on DAW, as patients often were reluctant to make extra journeys to anticoagulation clinics and clinicians were not always available to ensure vigilant monitoring and to change the warfarin dose, if appropriate. The trial design was amended accordingly by the steering committee after 378 patients had been randomised into the trial; 141 to uncertain three arm comparison and 245 to the certain preference group.

After this design amendment, clinicians had three different randomisation options to choose from depending on whether they were certain or uncertain of the benefits of warfarin and depending on whether they and their patients were willing to be entered into the dose adjusted warfarin arm (for uncertain indication). Figure 4.2.3.2 outlines the final trial design with Figure 4.2.3.3 showing the changes in trial design over time.

Figure 4.2.3.2 Final WARP Trial Design II

With principle of uncertainty



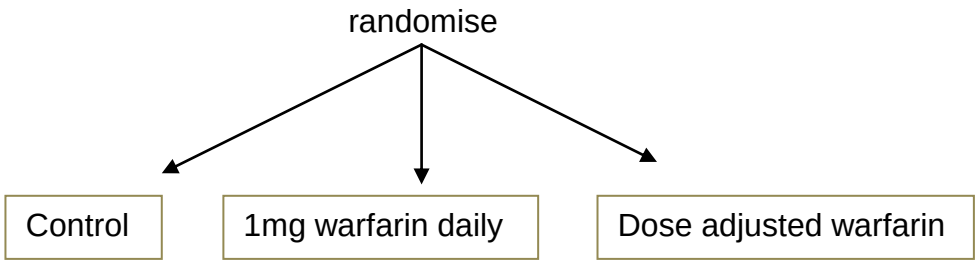
Warf – Warfarin; FDW – Fixed Dose Warfarin (1mg daily);

DAW – Dose Adjusted Warfarin (to maintain INR between 1.5 and 2.0)

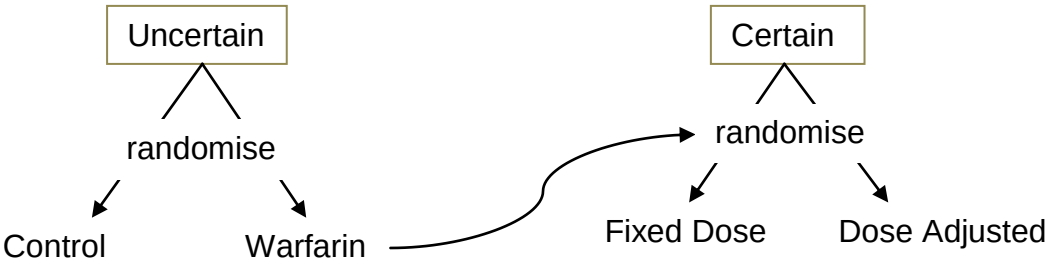
Figure 4.2.3.3 WARP Trial Design Adaptation over Time

YEAR

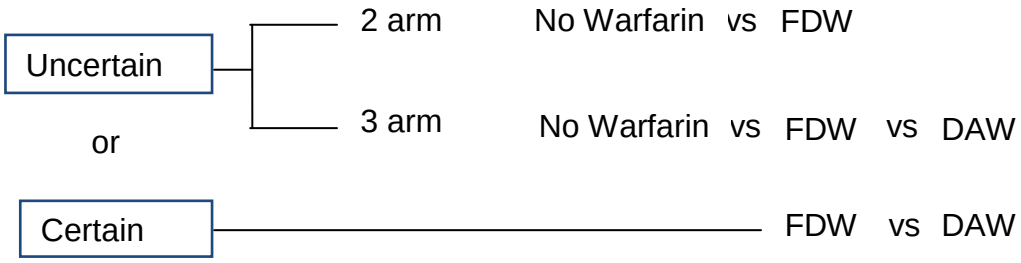
INITIAL TRIAL CONCEPT **1999**



TRIAL MODIFICATION POST SURVEY **1999**



PRAGMATIC TRIAL MODIFICATION POST SURVEY FOR CENTRES WHO REFUSED DOSE ADJUSTED WARFARIN **2001**



FDW – Fixed Dose Warfarin; DAW – Dose Adjusted Warfarin

Trial Completion **2004**

The final design enabled six key hypotheses to be tested:

Hypothesis 1:

Does warfarin (any dose) reduce the incidence of catheter-related thrombosis (CRT)? Endpoint, catheter-related thrombosis (CRT)

Hypothesis 2:

Is DAW superior to FDW in terms of reducing the incidence of CRT?

Endpoint, CRT

Hypothesis 3:

Does warfarin (any dose) reduce the incidence of any thrombotic events?

Endpoint , all thrombotic events

Hypothesis 4:

Is DAW superior to FDW in terms of reducing the incidence of any thrombotic events? Endpoint, all thrombotic events

Hypothesis 5:

Does warfarin (any dose) improve overall survival compared to control?

Endpoint, overall survival

Hypothesis 6:

Is DAW superior to FDW in terms of improving overall survival?

Endpoint, overall survival

Only randomised comparisons were used to infer results, no cross group comparisons were performed in any of these analyses.

4.2.4 Patient Eligibility

All patients, aged 16 years or over, who were having a CVC inserted for administration of cytotoxic therapy, were eligible for the WARP trial. All makes of catheter for both central and peripheral placement for anticancer therapy, were acceptable.

4.2.4.1 Inclusion Criteria

- Histologically or clinically confirmed diagnosis of cancer
- Patients who are due to have a CVC inserted for administration of chemotherapy
- Aged at least 16 years
- Adequate haematological function (recommended levels – haemoglobin (Hb) $\geq$ 10g/dl, white cell count (WCC) $\geq$ $2x10^9$/l, platelets $\geq$ 100 $x10^9$/l)
- Adequate hepatic and renal function – as determined locally
- Able to provide written informed consent

4.2.4.2 Exclusion Criteria

- Patients with contraindication to warfarin (including congenital bleeding disorders, anatomic lesions that bleed e.g. duodenal ulcers and profound concomitant therapy interaction)
- Patients currently on warfarin
- Patients who have previously been entered into WARP
- Use of CVC for additional purposes with the exception of antibiotic therapy and blood products
- Pregnant or lactating women

4.2.5 Treatment Plan

4.2.5.1.1 Overview

All types of CVCs were permitted in the study; the correct position of the catheter tip (at the junction of the superior vena cava and the right atrium – Figure 3.6.3.2) was checked by chest X-ray post CVC insertion. Randomisation and start of warfarin, if allocated, was permitted from 3 days prior to CVC insertion (to enable sufficient exposure to warfarin for the immediate post insertion period). Warfarin was taken daily until thrombosis or catheter removal for any reason and could be temporarily discontinued in the face of thrombocytopenia (platelets$\leq 50 \times 10^9$/L). Recommendations for monitoring warfarin therapy by carrying out the 'INR' (prothrombin time ratio) blood test were contained in the protocol for all treatment arms and treatment of venous thromboembolism (VTE) was carried out according to local practice. All other patient management was as per standard practice for the local centre. The simple trial plan from the protocol is shown in Table 4.2.5.1.

Table 4.2.5.1Trial Plan from the WARP Protocol

Pre-screening tests	**Randomise, if possible**	**Warfarin (arms B&C) Commences**	**Catheter Insertion (if INR < 1.3)**
-7 to 0 days	-7 to 0 days	-3 to 0 days	Day 0

Patient monitoring during trial*	**Catheter withdrawal or thrombosis**	**Follow-up**	**1 year data follow-up**
⟶	End of primary evaluation period	As per local practice	

4.2.5.1.2 WARP Catheter Care Guidelines

Regardless of the CVC utilised, the principles of catheter care remain the same. High quality catheter care is crucial to minimising thrombosis, infection and other catheter complication. The specialist teams caring for patients with CVCs were asked in the protocol to follow the manufacturer's instructions for the care of the specific catheter. However, around 20 enquires were made by trial centre nurses for guidelines for the care of central venous catheters and these were then developed - the 'WARP Catheter Care Guidelines'. These were published in 2000 and updated twice in 2002 and 2004 as new data emerged e.g. in late 2000, synerkinase replaced urokinase for thrombolysis therapy due to the withdrawal from the market of the latter because the manufacturers did not take adequate steps to test for infection in, or prevent contamination of, the kidney cells used to manufacture the drug (US Food and Drugs Administration, 1999). The WARP Catheter Care Guidelines were adapted from the Vascular Access Devices chapter of The Royal Marsden Hospital Manual of Clinical Nursing Procedures, 5th edition, 2000 (Dougherty, 2000) with permission from the author [Appendix 2]

4.2.6 Analytical Plan

4.2.6.1 Outcome Measures

In order to meet the aims and objectives of the trial (section 3.2.1), the following outcomes were measured:

- The number of catheter–related thrombotic events
- The number of other thrombotic events
- The duration of catheter patency
- The frequency and severity of trial-related adverse events
- The frequency of central venous catheter-related sepsis
- Death
- Combination of bleeding plus thrombotic events

The final outcome measure was added during analysis of the trial. As thrombosis and bleeding events were the two major adverse outcomes associated with central venous catheters and anticoagulants, it was felt that the effect of treatment on this composite endpoint would provide a more integrated approach to examine the disbenefit of bleeding versus the benefit of thromboprophylaxis. Clearly, the optimal situation would be a statistically significant reduction in thrombosis with treatment and a low bleeding rate. However, if the bleeding rate was sufficiently high to render the composite endpoint (which is clinically more important) statistically neutral, then this could be interpreted to mean that the therapeutic gains made by reduction in thrombosis rates would be offset by the adverse outcome, the bleeding.

4.2.6.2 Categorisation, Grading and Assessment of Thrombosis

A thrombosis was categorised as **non**-catheter-related if was:

- arterial; or
- located in the leg; or
- *known* to occur on the opposite side to the catheter; or
- occurred >5 days post catheter removal

Thromboses were only valid if they were radiologically confirmed. All thromboses were reviewed and classified as primary or secondary by the principal investigator and an independent second observer following a set of rules, agreed by the steering committee, outlined in Table 4.2.6.1:

Table 4.2.6.1 Categorisation of Thromboses

Primary Thrombosis	**Secondary Thrombosis**
Arm (Catheter Side)	Arm (non-catheter side)
Axillary Vein	Leg DVT
Internal Jugular Vein	Arterial
Subclavian Vein	Internal Vena Cava
Superior Vena Cava	Pulmonary Embolus with no documented catheter complications
Pulmonary Embolus with documented catheter complications	

Where the *catheter* side data were unknown (this information was not requested until 20 months after the start of the trial – amendment 2; Table 4.2.7.1), and where relevant (e.g. not in the case of PEs), these were assumed to be on the same side as the thrombosis. The steering committee advised that upper extremity thromboses are extremely rare when there is no catheter present and are highly likely to be catheter-related thromboses. Where the *thrombosis* side data were

unknown, these were assumed to be on the same side as the catheter for the same reason. Catheter related and other thromboses (primary and secondary endpoints) were radiologically confirmed by venogram, ultrasound or ventilation-perfusion (VQ) / Spiral CT and classified as CRT or non-CRT by two investigators, blinded to treatment allocation, using a central protocol. Thromboses that were suspected but not radiologically confirmed were recorded under CVC complications. Thromboses were graded according to the Common Toxicity Criteria (CTC) (National Cancer Institute, 1999) [Table 4.2.6.2].

Table 4.2.6.2 Grading of Phlebitis / Thromboembolic Events

Toxicity	**0**	**1**	**2**	**3**	**4**
Arterial	none	-	-	Transient events	Permanent Events
Venous	none	Super-ficial	DVT not requiring anticoagulation	DVT requiring anticoagulation	Pulmonary Embolus

Major bleeding episodes were defined as intracranial, retroperitoneal, requiring transfusion or hospitalisation or directly leading to death. Increased INR was classified by the investigators as: mild ($2<INR<5$), moderate ($5\leq INR<8$) or severe ($INR\geq 8$). Dates of death were obtained from the CRFs or from the Office of National Statistics (ONS) in April 2007.

4.2.6.3 Intention to treat

ITT is based on the initial treatment intent and not the treatment actually given and therefore all patients who are randomised to the trial are counted in the analysis, whether they took the allocated therapy or not. The analysis of toxicity data was done by ITT and not per protocol analysis. The same ITT population was used for

the analysis of the combination endpoint of bleeding plus thrombosis. A small number of unknown outcome patients were combined with those who did not have an event. A sensitivity analysis was carried out to test the validity of this assumption. Because major bleeding is life-threatening and all bleeding was found in the pre-trial survey to be one reason for clinicians to be hesitant about participation in the WARP Trial, an analysis of major bleeding was carried out restricted to only those patients who were known to comply with warfarin as well as in all patients. One further analysis of time to CRT was not carried out on an ITT basis because of missing data which may have confounded an analysis performed on the ITT population. The time to CRT analysis excluded 57 patients who had not had a thrombosis or had no data for thrombosis or not, *plus* no data for CVC removal.

4.2.6.4 A Priori Patient Numbers

The power function is the confidence with which the investigator can claim that a specified treatment benefit has not been overlooked. The level of significance is an indication of the degree of plausibility of the 'null hypothesis' i.e. thrombosis rates were the same in warfarin vs no warfarin arm. If the null hypothesis is deemed too implausible, it is rejected and the 'alternative hypothesis' that the treatments differ in their effect, is accepted. Conventional significance level of 5% is a useful guide. The significance level, p, is the probability of obtaining a result at least as unlikely as the observed one if the null hypothesis of no effect is true.

The thrombotic event rate for the control arm was estimated to be around 25%, using the published rates found in 1999, when the protocol was being developed: a

report (Bern et al, 1986), a historical study , a randomised trial with a low molecular weight heparin (LMWH) (Monreal et al, 1996) and a small randomised trial using low dose warfarin (Bern et al, 1990). Treatment with warfarin was hypothesised to reduce this rate by 10%, i.e. down to 15%, which would be a medically worthwhile improvement. With 800 patients entered into the uncertain indication part of the trial (400 no warfarin and 400 warfarin), there was greater than 90% power to detect a 10% difference at a 2-tailed p-value of 0.05. Differences between the two doses of warfarin were likely to be smaller than between warfarin versus not. With 1000 patients randomised between warfarin doses (initially calculated as 400 from arms B and C in the uncertain indication group, and 600 from arms B and C in the certain indication group), there was 80% power to detect a difference of 7% in thrombotic event rates between the two doses (at 2p=0.05). It was unrealistic to base the sample size calculations on effects that were larger than this, but, if bigger than anticipated differences were observed during the course of the trial, accrual to the trial could be modified on the recommendation of the DMC. The trial recruitment target for the primary endpoint gave approximately 90% power to detect (at 2p=0.05) a 10% difference in long term survival between the warfarin and no warfarin groups. This survival difference was extrapolated from the results of two small studies at the time, showing a trend towards a survival benefit for warfarin plus chemotherapy in comparison to chemotherapy alone (Maurer et al, 1997; Chahinian et al, 1989)

4.2.6.5 Number of Patients - Protocol Amendment

The trial was designed to recruit 1000 patients into the fixed versus adjusted dose treatment comparison. As above, it was planned that 600 of these patients would originate from recruitment to the certain indication option and a further 400 patients

from the two warfarin arms of the uncertain indication. The trial design was changed in 2001 to allow 'uncertain' participants to randomise into either a two-arm option (no warfarin and fixed dose warfarin) or the original three-arm design. Patients randomised via the new uncertain two-arm option could not be included in the fixed versus dose adjusted comparison creating a shortfall in patients originating from the uncertain option. This shortfall was addressed by increasing the target number of patients required from the certain indication option to an estimated 800 patients.

4.2.6.6 Randomisation and Randomisation Procedure

Randomisation is the only safeguard against selection bias – firstly, there can be neither unwitting or deliberate selection because there is no identifiable pattern in the process; secondly, it is an insurance, in the long run against accidental bias – the more patients entered, the larger the chance of patient characteristics being the same in every treatment group and lastly, the foundation for many statistical tests used in the analysis, is the premise that each patient could have received any one of the treatments allocated. Unequal randomisation of 2:1:1 for no warfarin : FDW : DAW, was utilised to ensure the balance of the numbers of patients in the no warfarin vs any warfarin (FDW and DAW) comparison (Figure 4.2.3.2).

Randomisation was executed via a computerised block algorithm and performed by randomisation officers at the central randomisation office in the departmental trials unit, accessed by telephone and fax. The patient's name, their hospital, the name of the person randomising and the lead investigator with overall responsibility for the patient were documented and patient eligibility was checked before the treatment allocation was given out. The date of the telephone call (or fax) is the date of

randomisation. Details were then confirmed in writing to the person randomising, who then submitted a CRF1 or 'on-study' form (parts A and B of CRF1) for the patient. There was a back-up of paper randomisation forms in case of electronic failure.

4.2.6.6.1 Timing of Randomisation

The protocol stated that randomisation was possible from 3 days prior to CVC insertion to enable sufficient exposure to warfarin for the immediate post insertion period. Permission to randomise up to 5 days after the insertion of the CVC was inserted was granted by the steering committee in July 2000 after requests by local coordinators who often discussed the trial with their patients after the CVC had been inserted at another centre. Although not clinically ideal, as insertion of catheter may cause trauma to the vein with the potential of a thrombosis, this was within protocol wording and did not require an amendment.

4.2.6.6.2 Stratification

Stratification by factors known to affect thrombosis is a safeguard against a chance imbalance between treatment groups with respect to an important variable. Stratification was based on three thrombosis risk factors, each with two levels:

- sclerosant potential of the cytotoxic regimen [low or high as defined in the protocol] (Salmon SE et al, 1998)
- site of catheter insertion (peripheral or central)
- duration of drug infusion (less than, or greater and equal to 24 hours; for duration of one chemotherapy cycle intravenous infusion).

The stratification variables define 8 (2x2x2) different strata and separate treatment lists were created for each. Lists of treatments were created using the method of random permuted blocks with a fixed block size of 12 for uncertain indication and 8

for certain indication. This guarantees that the numbers allocated to each treatment are equal at the end of each block.

The treatment lists were stored on computer and a computer programme was used to allocate the next treatment on the appropriate list.

4.2.6.7 Interim analysis

No patient should receive a treatment that has been established as inferior on the basis of substantial accumulated evidence and therefore interim analyses were planned, initially after 200 patients were entered and, subsequently, after approximately 500 more patients were recruited up to the target.

4.2.6.8 Health Economics

An academic health economist was recruited to be the health economics advisor for the WARP trial. The protocol stated that a societal health economics perspective would be adopted such that costs incurred by both the NHS and patients themselves would be recorded. Data on key elements of resource use, such as contacts with primary and secondary care, were requested on all trial patients. Analysis was planned to be descriptive.

4.2.6.9 Examination of INRs in one centre

The steering committee suggested that in order to ascertain if the patients in the DAW arm were within INR range (1.5-2.0) and the patients in the FDW arm did not breach this range (i.e. the arms were indeed separate in practice), that INRs from high recruiting centres should be analysed centrally. This analysis was, however, only possible for one centre, the highest recruiting centre, due to extra workload for

the local coordinators in collating and sending the INR data. The local coordinators in this centre forwarded anonymised INR data values on paper to the principal investigator for analysis. INR tests in this centre, were taken at baseline (prior to warfarin starting) and weekly for both FDW (1mg daily) and DAW; unless the result warranted more frequent monitoring patients receiving FDW, no further monitoring of this patient group was carried out. In contrast, patients on DAW were monitored weekly until catheter removal of thrombosis. The degree of differentiation between the two doses and, therefore, the interpretation of the primary outcome of the trial was examined, using descriptive statistics:

- Adherence to range for the DAW arm (INR between 1.5 and 2.0)
- Maintenance of the fixed dose warfarin arm below 1.5 as specified in the protocol

4.2.6.10 Statistical Tests Utilised

The analyses outlined below were performed using SAS statistical software (SAS Institute, SAS Circle, Cary, North Carolina, USA). These analyses were carried out by the trial statistician, supervised by the author. All frequency and descriptive analysis were performed using Microsoft Excel 2003 by the author.

4.2.6.10.1 Comparison of rates of thrombotic events

Rates of thrombotic events were compared using the Mantel Haenszel χ^2 test. This is a test suitable for testing the null hypothesis (no treatment effect) between two dichotomous variables – in this case, outcome (thrombotic event or no thrombotic event) and treatment [warfarin or no warfarin (or DAW or FDW)]. Therefore, the data consisted of several 2x2 tables (variables with two possible values) in order to compare treatment rates. Differences were expressed between treatments as

relative risk (RR) with 95% confidence intervals (CIs). The analysis was done on an intention-to-treat basis, with a small number of unknown-outcome patients combined with those who did not have an event. Therefore, radiologically confirmed thrombotic events were compared with no thrombotic events plus thrombotic event outcomes which were 'not known'.

4.2.6.10.2 Survival Analyses

Survival analysis applied to both catheter patency (survival) and death. Catheter-related events were analysed as time to event data with time to thrombosis censored at date of CVC removal in those patients without an event. The duration of catheter patency was calculated as the time from catheter insertion to a thrombotic event; CVC complication or CVC removal for those patients without an event. However, if there was no CVC removal date or thrombosis date, these patients were excluded from the analysis; this analysis was therefore not ITT. Patient survival time was from date of randomisation to the date of death or censored at the date the patient was last seen alive; the unknown-outcome patients were combined with those who were still alive. For the WARP trial, it was not possible to follow up all patients until death: firstly, some patients were lost to 'follow-up' for various reasons and, secondly, those entered into WARP towards the end of the study had only been followed up for 10 months when the analysis was carried out.

In analysing survival data, two functions that are dependent on time are of particular interest: i) the survival function S(t) is defined as the probability of surviving to at least time t and ii) the hazard function is the conditional probability of dying at time t having survived to that time. The graph of S(t) against t is called the survival curve. The statistical significance of any difference observed in a comparison of two

survival curves, was assessed by Kaplan Meier estimation (Kaplan EL and Meier P, 1958) and the log rank test. The Kaplan Meier estimator is the non-parametric likelihood estimate of the probability that a person from the WARP population will have a lifetime exceeding certain timepoints. The number 'at risk' just prior to time these timepoints and the number of deaths at timepoints are calculated. The log rank test is a special application of the Mantel-Haenszel χ^2 procedure, carried out by constructing a separate 2 x 2 tables for each interval in order to compare the proportions dying in each interval but does not allow for other explanatory variables to be taken into account. Cox's proportional hazards model is analogous to a multiple regression model (section 4.2.6.9.5.1) and enables the difference between survival times of particular groups of patients to be tested whilst allowing for other factors. In this model the response (dependent) variable is the hazard function. The hazard function describes the instant probability of dying given at a particular time that patients have survived up to that point.

4.2.6.10.3 Comparison of Time to thrombosis in patients with an event

A Wilcoxon Rank Sum Test, comparing a group against a hypothetical median, tests whether the two groups have equally large values without assuming any particular distribution (e.g. normal) [section 4.1]. This test was used for the comparison of the time to thrombosis in patients with an event.

4.2.6.10.4 Comparison of major and minor bleeding episodes

The Fisher's exact test was used to compare i) major (and minor) bleeding episodes between arms and ii) the randomised comparison of thrombotic events between FDW vs DAW. This test is utilised for the comparison of two treatment regimes where the number of events is small. The Fisher's exact test is based on calculating

the exact probabilities of the observed results and more extreme results that could occur by chance.

4.2.6.10.5 Exploratory Prognostic Modelling

4.2.6.10.5.1 Predictors of All Thromboses

Logistic regression allows both the inclusion of explanatory variables and the assessment of interaction between the variables. Logistic regression investigates the linear dependence of the logistic transformation of the proportion on several explanatory variables (e.g. heparin flush data, age, catheter type) where:

the logistic transformation or log odds $= \log_e \left[\frac{\text{proportion}}{1 - \text{proportion}} \right]$

Thrombosis was treated as a binary outcome. The risk factors were treated as categorical and dummy variables were created for each category. A separate category was created for missing data for each variable, and a dummy variable was created for this category and was included in the regression analyses. This category (missing data category) was never chosen to be the referent group for any of the analyses. Initially, pre-specified baseline factors were investigated univariately; a multivariate logistic regression was then conducted, using stepwise selection methods set at the 0.05 alpha level. The risks for thrombosis were expressed as odds ratios (OR), with corresponding 95% CIs. Due to an imbalance within factors, some of the factor groupings were combined for analysis.

4.2.6.10.5.2 Predictors of Catheter-related Thromboses

A second logistic regression analysis was performed to identify potential predictors of CRT which included catheter-related variables. A total number of 1547/1590 patients had complete CVC data and were included in analysis, of these 85 patients had suffered a CVC-related thrombosis. Explanatory variables included catheter placement (central vs peripheral), treatment length (<24 vs ≥24 hours) and sclerosant potential of chemotherapy (high vs low). CVC information was also considered, CVC lumen (single vs double/triple), CVC material (silicone vs other), type of CVC (valved vs non-valved), CVC size (<4 and ≥4). Forward, backward and stepwise regression techniques were applied; a 10% significance level was used for entering and removing the model.

4.2.6.10.5.3 Correlation between Number of Venous Thrombotic Events and Study Sample Number

In the collation of all studies investigating catheter-related VTE (Section 3.6.3.1), a Spearman's Rank Correlation Test was utilised to measure the statistical dependence (strength of the relationship) between the number of VTE events and study sample size. Spearman's rank correlation coefficient is used as a measure of linear relationship between two sets of ranked data (how tightly the ranked data cluster around a straight line). A correlation of +1 or -1 will arise if the relationship between the two variables is exactly linear. A correlation close to zero means there is no linear relationship between the ranks (Altman, 1991).

4.2.7 Trial Management

4.2.7.1 Ethical Considerations

The WARP protocol stated that the trial would be carried out, 'in accordance with the principles laid down by the 18th World Medical Assembly, Helsinki, 1964 (RICKHAM, 1964; World Medical Assembly, 1964) and subsequent amendments. This document, of which the 1996 and 2000 updates were pertinent to WARP, provides the ethical foundation of all subsequent European and International Directives. Whilst WARP was recruiting, on the 4th April 2001, The Clinical Trials Directive (2001/20/ EC) of the European Parliament and of the Council, was introduced for member states. The Medicines for Human Use (Clinical Trials) Regulations followed this in the UK, in May 2004, 'transposing' the European Clinical Trials Directive into law. These directives and legal documents relate to the implementation of good clinical practice (GCP) in the conduct of clinical trials on medicinal products for human use, aimed at maintaining an appropriate level of protection for patients. They seek to simplify and harmonise the administrative provisions governing clinical trials, by establishing clear and transparent procedures including: i) international recognised principles of good clinical practice (GCP); ii) good manufacturing practice (GMP); iii) GCP and GMP inspections and enforcement; iv) protection of incapacitated adults; v) protection of minors and vi) stringent pharmacovigilance arrangements. Although these procedures were not in place when WARP was initiated in the summer of 1999, the principles were recognised by the WARP trial management group, familiar with the Declaration of Helsinki. From April 2001, the documentary evidence to comply with the Clinical Trials Directive was collated; the WARP trial, 'A Multicentre Prospective Randomised Controlled Trial of Thrombosis Prophylaxis with Warfarin in Cancer

Patients with Central Venous Catheters' was registered as an International Standard Randomised Controlled Trial, number 50312145. The above regulatory documents and guidelines provided the framework for WARP trial teams to perform to optimal standards for the protection of their patients.

4.2.7.1.1 Informed Consent

The principles of the informed consent process for WARP and all other clincial trials, supported by the directives and guidances in section 4.2.7.1, were expected to be followed by all participating trials teams, who may be subject to monitoring by national or international auditors. The principles adhered to are as follows: The voluntary consent of the human subject is absolutely essential; this means that the person involved should have legal capacity to give consent; should be able to exercise free power of choice and should have sufficient knowledge and comprehension of the elements of the subject matter involved, to enable them to make an understanding and enlightened decision. Therefore the nature, duration, and purpose of the trial; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected and any effects upon their health or person which may possibly come from their participation, need to be explained.

The duty and responsibility for ascertaining the quality of the consent rested upon the WARP trial team and the participating lead investigators and coodinators who initiated, directed or engaged in the trial. It is a personal duty and responsibility which may not be delegated to another with impunity (Nuremburg Code, 1947). After entry, the patient must be free to withdraw from trial treatment at any time without giving reason or prejudicing further care. The physician (Declaration of

Helsinki, Section 1.9). or other delegated person (Clinical Trials Directive 2001) should then obtain the subject's freely given informed consent, preferably in writing. The local investigators were therefore responsible for obtaining informed consent in compliance with the above requirements, from each patient prior to entering the trial. In addition to verbal information, the patients were given sufficient time to read and comprehend the written information and to ask questions if necessary before making their decision. An example from the three Patient Information Sheets [uncertain (3-arm and 2-arm options) and certain preference for warfarin therapy] is included in Appendix 3. The Patient Consent Form is shown in Appendix 4.

4.2.7.1.2 Nurses Taking Informed Consent

During the course of WARP recruitment (October 1999 to December 2004), a number of specific informed consent procedures were updated and issued as part of the regulatory and guideline procedures in section 4.2.7.1. Due to the many different local rules for nurses taking informed consent in the participating centres, the principal investigator gathered the growing literature on consent and produced ‘Guidance for nurses; Informed Consent for the WARP Trial’, in November 2001. Because WARP was a nurse-led oncology trial and was then pushing the boundaries for nurses obtaining informed consent as sole signatories, WARP guidance for nurses obtaining informed consent was developed and sent to participating research nurses (Appendix 5).

4.2.7.1.3 Ethics Committees Approval

The trial was submitted on a standard form to the West Midlands Multicentre Research Ethics Committee (MREC) in July 1999 and approved in September 1999 via a letter to the principal investigator. There was one change in the patient information sheets (PISs) required before approval, namely the addition of some expanded contraceptive advice for patients and partners. This was added to the PIS and a final approval letter of Protocol Version 3 was received in September 1999.

The local coordinators then submitted this protocol and case record forms (CRFs) on their headed notepaper to their Local Research Ethics Committee on an MREC form, Annexe A, and were then requested to forward a copy of the LREC letter of approval, signed by the LREC Chairman, to the WARP Trial Office, prior to the start of recruitment.

4.2.7.1.4 Protocol Amendments

There were five were protocol amendments during the trial. These are acknowledged, where appropriate, in relevant sections and summarised below in Table 4.2.7.1.

Table 4.2.7.1 WARP Protocol Amendments

Amendment No.	Protocol Version	Date Submitted	Summary of Amendment
1	3 post-amendment	5th May 2000	Additions to CRF1, 2 and 3 to improve the quality of data collected: CRF1; *Will the patient be on any form of heparin whilst on WARP?* CRF3; monitoring of all thrombotic events (check), *'Has patient had a thrombosis? No/Yes: Date of thrombosis: Location of thrombosis:* Deletion in Patient Information Sheets (PISs) -. 'half of the doctors and nurses in the UK regularly prescribe warfarin' as Scottish nurses did not then do so.
2	4	28th March 2001	Addition on CRF1 and CRF2 of whether the catheter and the thrombosis respectively was on the left or right side. Trial design change to include no warfarin vs 1mg warfarin arm. New figure in protocol.
3	5	20th January 2003	Change to duration of study in protocol: Protocol page 6, Study Duration, 'The planned study initiation is October 1999; completion around September 2004'.
4	6	16th July 2003	Change in contact details and updated personnel in protocol
5	7	2nd December 2003	PIS: Contraceptive advice changed to, "If you are allocated warfarin and become pregnant, you must contact your doctor to arrange to stop the warfarin as soon as the pregnancy is confirmed, as warfarin can damage the baby in the first part of pregnancy; protocol deletion of exclusion criterion: *"Fertile persons not taking adequate contraceptive measures"*.

4.2.7.2 Regulatory Considerations

4.2.7.2.1 Trial Monitoring

Monitoring is defined as 'the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded and reported in accordance with the protocol, Standard Operating Procedures, GCP and the applicable regulatory requirements' (MHRA, 2010). The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial. There was no external on-site or central monitoring requested for WARP. However, other University of Birmingham Cancer Research UK Trials Unit studies were externally monitored during this period and although WARP was not identified as one of trials to be examined in detail, all trials in the unit were prepared for inspection. The internal monitoring approach for the WARP trial was as follows:

4.2.7.2.1.1 WARP Trial Management Group

The Trial Management Group included those individuals responsible for the day-to-day management of WARP - the principal investigator (PI), statistician and the trial coordinator - and they met weekly with e-mail communication in-between. The group monitored all aspects of the conduct and progress of the trial, ensuring that the protocol was adhered to and took appropriate action to safeguard participants and the quality of the trial itself. Day-to-day monitoring by the PI and the trial coordinator typically included the following checks, that:

- data collected are consistent with adherence to the trial protocol
- CRFs are only being completed by authorised personnel; no key data are missing
- data appear to be valid (for example, range and consistency checks)

• recruitment rates are appropriate, withdrawals and losses to follow-up overall and by clinical site are documented

4.2.7.2.1.2 The Steering Committee

Sixteen experts in the field of clinical trials and thromboprophylaxis in cancer patients, were invited by the principal investigator to sit on the WARP Trial Steering Committee, prior to protocol development. They WARP Trial Steering Committee provided overall supervision of the trial and ensured that it was being conducted in accordance with the principles of GCP. There were five steering committee face to face meetings with full reports prepared by the trial management team: 8th March 2001, 13th March 2002, 15th October 2002, 18th September 2003 and 24th June 2004. The trial steering committee reports included feedback from the data monitoring committee if appropriate, new literature, overall, per centre and per lead investigator recruitment, data completion and quality, patient characteristics and compliance, adverse events, serious adverse events and overall thrombotic rate.

4.2.7.2.1.3 Independent Data Monitoring Committee

The role of the WARP Data Monitoring Committee (DMC) was to review the accruing trial data and to assess whether there were any safety issues that should be brought to investigators' attention or any reasons for the trial not to continue. The DMC was independent of the investigators and the funders and was the only committee that had access to unblinded data. There were three national experts in thrombosis, cancer or trials on the DMC, chaired by a Professor of Statistics. There were four DMC meetings throughout the trial – 26th February 2002, 30th September 2002, 28th January 2003 and February 12th 2004, each confidential with an open and closed component and report. The

closed component contained a discussion of the interim analysis of unblinded data with the trial statistician in discussion with the DMC members. The formal open report contained:

- Literature Update – new relevant randomised controlled trials, related and unpublished studies
- Actual and target recruitment by indication, treatment and randomisation strata. Recruitment by centre and lead investigator
- Centres with approval, time from LREC approval and centres awaiting approval
- Case Record Form return rates and quality
- Overall patient baseline characteristics, compliance, timing and duration of warfarin with reasons for stopping early and catheter patency data
- Toxicity and serious adverse events
- Overall frequency of thrombotic events and location of events
- Overall survival
- Reasons for rejecting event as a serious adverse event (SAE) [only toxicity that could be associated with warfarin was required and the expert clinical advisors transferred non-SAE events as defined in the protocol to the correct data field e.g. thrombosis and toxicity]

The closed report incorporated the additional unblinded WARP analysis.

The notes from the open DMC committee meeting were shared with the steering committee.

4.2.7.3 Data Handling

In order to collect the key data but keep the task of form completion as simple as possible thereby hoping to increase the comprehensiveness of data return, three one-page CRFs were designed - baseline, primary evaluation period (from randomisation to catheter removal or thrombosis) and follow up (one year post randomisation or death) [Appendix 6]. These were requested to be returned at certain time points (Table 4.2.7.2). For the same reasons, follow-up data were only requested from centres at one year from randomisation. Survival data not obtained on the CRFs were obtained from the Office of National Statistics. Randomisation data were entered on-line by the randomisation officers at time of randomisation and data were 'cleaned' (investigate missing data and outliers) by the trial coordinator and the author. A standard letter for missing data, identifying the missing section, was sent to relevant coordinators on two occasions and then followed up by a phonecall, should the data not have been sent. If still no data were forthcoming, the case was generally closed and noted as missing data with the exception of two data fields – has the patient had a thrombosis and is the patient still alive? These two crucial data fields were pursued vigorously by personal phonecalls to the local investigators.

Table 4.2.7.2 (from protocol) Trial Plan with Case Record Form Return Schedule

Pre-screening tests	**Randomise, if possible**	**Warfarin (arms B&C) commences, if possible**	**Catheter Insertion (if INR < 1.3)**	**Patient monitoring during trial***	**Catheter withdrawal or thrombosis**	**Follow-up***	**One year follow-up (for survivors)**
-7 to 0 days	-7 to 0 days	-3 to 0 days	Day 0	⟶	End of primary evaluation period		
	CRF1 randomisation details completed		*CRF1* completed and sent to study office		*CRF2* completed and sent to study office	*CRF3* completed and sent to study office if patient dies	*CRF3* completed and sent to study office

CRF – Case Record Form; * as per normal practice for institution;

4.2.7.3.1 Adverse Event Reporting

Adverse events which were trial-related i.e. due to warfarin or to thrombosis were collected at the end of trial on CRF2. The Common Toxicity Criteria (National Cancer Institute, 1999) was chosen as the grading system for adverse events. In the case of a Serious Adverse Event (SAE) - i.e. any untoward medical occurrence that is fatal, life threatening, disabling/ incapacitating, requires hospitalisation or is an overdose - believed to be due to trial therapy (i.e. warfarin) [or bleeding in no warfarin arm], the local investigator was asked to fill out an SAE form and send within 24 hrs, preferably by fax, a signed and dated SAE form to the WARP Study office (the clinical trials unit). In the case of death or life-threatening events, investigators were asked to phone the trials office in office hours or a hospital switchboard out of hours, in order to notify the principal investigator. In the case of a trial-related SAE, surviving patients were followed up until clinical recovery was complete or until death occurred. This information was relayed to the WARP office at resolution of the serious event or death by faxing an SAE form and ticking the box marked 'follow-up'. SAEs that were not considered to be related to warfarin did not need to be reported on an SAE form. Two expert clinical advisors reviewed all SAEs, rejected non-SAEs and agreed the rejected SAEs with the local coordinators who had originally sent the data. These were then transferred to the accurate category e.g. thrombosis or toxicity.

4.2.7.4 Database and Construction

The case record and adverse event forms were created by the principal investigator on an electronic template. Initially, the fields were transferred on to a password protected relational database (Access 2000) for data input by the WARP trial coordinator. In November 2001, when 584 patients had been randomised, an electronic shared SQL (Structured Query Language) relational database for all ongoing trials at the Clinical Trials Unit in Birmingham was created by the programming team and WARP data were transferred to this electronic data capture system. SQL is the International Organization for Standardization (ISO) standard language used for creating, updating and querying relational database management systems and therefore compatibility and consistency were ensured. The new system enabled quick and secure data entry and storage.

4.2.7.5 Trial Funding

The trial was funded by the Medical Research Council (MRC) [clinical fellowship for the author] and Cancer Research UK (CRUK) [trial coordinator salary]. The author applied successfully to both charities for the funding. The MRC or CRUK had no role in study design, data collection, data analysis, data interpretation or writing the ensuing publications.

4.2.7.6 Building and sustaining the trials network

4.2.7.6.1 Centre Visits

Patients from centres in the UK with nursing teams dedicated to catheter care including those who indicated interest in the pre-trial survey, were approached by post, telephone and e-mail to participate in the trial. A personal visit was made to interested clinicians and trials teams at their UK cancer centres, prior to the start of recruitment at the centre. Sixty-four centres were visited to educate staff about the trial, review understanding of the protocol and trial procedure, verify for relevant centres that the staff at the site have access to the necessary documents to conduct the trial, confirm that the required pharmacy and laboratory resources are in place to start the trial. A presentation was generally given to the audience of nurses, doctors and trials teams.

4.2.7.6.2 Newsletters

Over the five years of start up, recruitment and evaluation, 12 WARP newsletters were produced updating the local trials teams on items such as recruitment, trial amendments, new recommendations, newly published literature and related news items such as conferences. This was an excellent means of thanking the local coordinators for their participation. An example of a newsletter is shown in Appendix 7.

4.3 *Meta-analysis*

4.3.1 Overview

A meta-analysis is defined as a statistical summary of the data (Lau et al, 1997). The statistical methods of meta-analysis aim to evaluate the heterogeneity (diversity) amongst the results of certain studies, explore and explain the observed heterogeneity and estimate a common pooled effect with increased precision. This involves the comparison of the number of events observed (O) amongst the treatment-allocated patients with the number expected (E) under the null hypothesis of no treatment effect. When this is done for similar trials, the O-E could well be positive or negative and if their sum was close to zero, these treatments had no effect but if treatment really reduced the outcome (thrombosis or mortality), then the (O-E)s would tend to be negative. This may be obscured by chance in individual studies but stand out clearly when the total of (O-E)s is calculated (Peto, 1987).

For binary response variables e.g. thrombosis or no thrombosis, dead or alive, odds ratios are utilised as the measure of treatment effect, providing an estimate of the relative efficacy of the anticoagulant. Pooling estimates into an overall estimate can increase statistical power to lead to more precise estimates of the treatment effect. Each study is given a weight according to the precision of its results. Studies with narrow confidence intervals are weighted more heavily than studies with greater uncertainty. The precision is generally expressed by the inverse of the variance of the estimate of each study. The variance has two components: the variance of the individual study and the variance between

different studies. When the between-study variance is found to be or assumed to be zero, each study is weighted by the inverse of its own variance which is a function of the study size and the number of events in the study (Yusuf, 1987).

A fixed effects model - i.e. where a single true treatment effect of anticoagulation is assumed - was utilised. The summary statistics from the individual studies were used without requiring access to the full data set. Results were combined to estimate overall treatment effects on CRT or VTE and mortality for the following treatment subgroup comparisons:

- warfarin versus no warfarin
- low molecular weight heparin (LMWH) versus no LMWH
- LMWH versus oral anticoagulants

Differences in treatment effects between trials and subgroups were assessed using tests of heterogeneity. A test for trend over trials was utilised to investigate whether results have changed over time. The results are presented in Forest Plots (also known as odds ratio plots), showing number of events and confidence intervals. No bleeding analyses were carried out as different trials used different criteria to measure bleeding and there were many missing data.

4.3.2 Protocol for Meta-analysis

4.3.2.1 PRISMA Reporting System

This systematic approach to the description of meta-analytical data was introduced in 2009. However, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) approach undertaken in this thesis conformed with their published checklist (Liberati et al, 2009). Their data flow diagram has been adapted and included in the results (Section 5.3.1).

4.3.2.2 Data Sources and Searches

The following databases were searched: MEDLINE, EMBASE, CINAHL (Cumulative Index to Nursing and Allied Health), ISI The Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL); Scientific meetings databases, which include American Society of Hematology and American Society of Clinical Oncology; and Google scholar. Experts in the field were also consulted to identify additional studies.

The following search terms were used for the thromboprophylaxis and catheter analysis: central venous catheterisation (text and MeSH – Medical Subject Headings) OR thrombosis, thromboembolism (text and MeSH) NOT haemodialysis, renal dialysis, hemodialysis, dialysis (text and MeSH) AND cancer AND randomised controlled trials (text, MeSH, Publication type) AND 1980-2008. The following search terms were used for the VTE studies for efficacy and survival: cancer (text and MeSH – Medical Subject Headings) AND thrombosis, thromboembolism (text and MeSH) AND low molecular weight heparin OR warfarin AND randomised controlled trials (text, MeSH, Publication

type) AND 1980-2009. The MEDLINE electronic component of the searches was updated between March 2005 and October 2009.

4.3.2.3 Study Selection – Inclusion and Exclusion Criteria

The title and abstract were used to select the articles. A study was eligible for the quality assessment if it met all the following inclusion criteria: (1) a randomised clinical trial with stated endpoint as CRT rates or VTE rates or survival; and (2) published between 1980 and 31st October, 2009. Studies were excluded if they met any one of the following exclusion criteria: (3) conducted mainly in children ≤16 years of age (because of tiny doses of drug in comparison to adults); (4) did not use objective testing to confirm a diagnosis of VTE; (5) were duplicate publications containing data reported in later studies. For the catheter meta-analysis, the studies that dealt mainly with fibrin sheath formation and not with catheter-related deep vein thrombosis (DVT) and those that included non-cancer patient populations (e.g. all hospitalised patients) were also excluded.

4.3.2.4 Quality Assessment

Two people (the chief investigator and the trial statistician) independently and then together, evaluated the methodological quality of the different studies using criteria described by Jadad et al. for randomised clinical trials (Jadad et al, 1996). This quality assessment was not used to weigh the studies differently during the analyses.

4.3.2.5 Data Extraction

Data were extracted by two independent reviewers (the chief investigator and a statistician from the University of Birmingham Trials Unit) and included the type of, the dose and duration of treatment (warfarin or LMWH), whether it was primary or secondary VTE prophylaxis, the number of thrombotic events during the trial and whether the endpoint in the catheter analysis was symptomatic or the composite endpoint of 'asymptomatic (venographically screened) and symptomatic', VTE.

4.3.2.6 Data Synthesis and Analysis

Catheter Thromboprophylaxis Meta-analysis: For subjects who received more than one catheter during the course of any of the studies, only outcomes observed while they had their first device in place, were evaluated.

All Meta-analyses: The analyses were carried out using a standard meta-analytic in-house (University of Birmingham Trials Unit) software, by the trials statistician with advice from the chief investigator.

5. Results

5.1 *Pre-WARP Survey*

The summary of the pre-trial survey responses are summarised in Table 5.1.1. Overall, there was an informative response from 27% (213/769) of clinicians (73% oncologists or haematologists; 27% were oncology/haemato-oncology nurses), representing the majority of cancer hospitals (60%, n=116) involved in the delivery of cancer care in the UK. Nearly two thirds of respondents who described the catheters they used according to site of placement, employed centrally placed (they referred to as 'Hickman') catheters rather than peripherally inserted central catheters (PICCs) to treat common solid tumours (50% gastrointestinal ; 21% breast; 10% range of other types) and haematological malignancies (15%). Most clinicians routinely used warfarin prophylaxis for venous catheters (62% vs 26%); the majority of whom (121/131; 92%) used fixed, low dose warfarin at 1mg/day. Only 3% (4/131) of clinicians who used warfarin, adjusted the dose to maintain an INR of 1.5-2.0. The respondents were asked to estimate the likely thrombosis rate in their practice, a mean of 13% (IQR 5% to 15%). A Wilcoxon test on the thrombosis rates split by use of prophylactic warfarin demonstrated that estimated thrombosis rates were higher in the clinical group prescribing warfarin group than in the non-warfarin group (p=0.006). Importantly, there was considerable interest in the question of warfarin prophylaxis within the medical community; 80% of all respondents felt that the questions addressed were of importance, and 70% expressed interest in a clinical trial of warfarin prophylaxis with 150 clinicians providing names of lead

contacts at their centres. Ninety-seven of 213 clinicians provided additional comments. These ranged from,

"we are keen to participate" to "we cannot participate as most of our patients are in other trials with pre-set medication";

"this [thrombosis] is a huge problem" to "we have very little problem with thrombosis".

Of the survey lead contacts, 82 (55%) subsequently participated in WARP. The largest category of comments, however, were 19 respondents (9%; 20% of all those who commented) who noted that they would *not* randomise to a 'no warfarin' arm, as they were substantially certain of the benefits of thromboprophylaxis. Their comments included,

"I would be uncomfortable with a no warfarin arm" and

"it is unethical to have a study with a 'no warfarin' arm".

The results of this survey informed the design of WARP as follows:

Interest was high, supporting the concept of WARP as a multicentre study

WARP design would be a three arm randomisation: no warfarin, a fixed dose of 1mg of warfarin/day, and an adjusted dose, to keep the INR in the range 1.5-2.0.

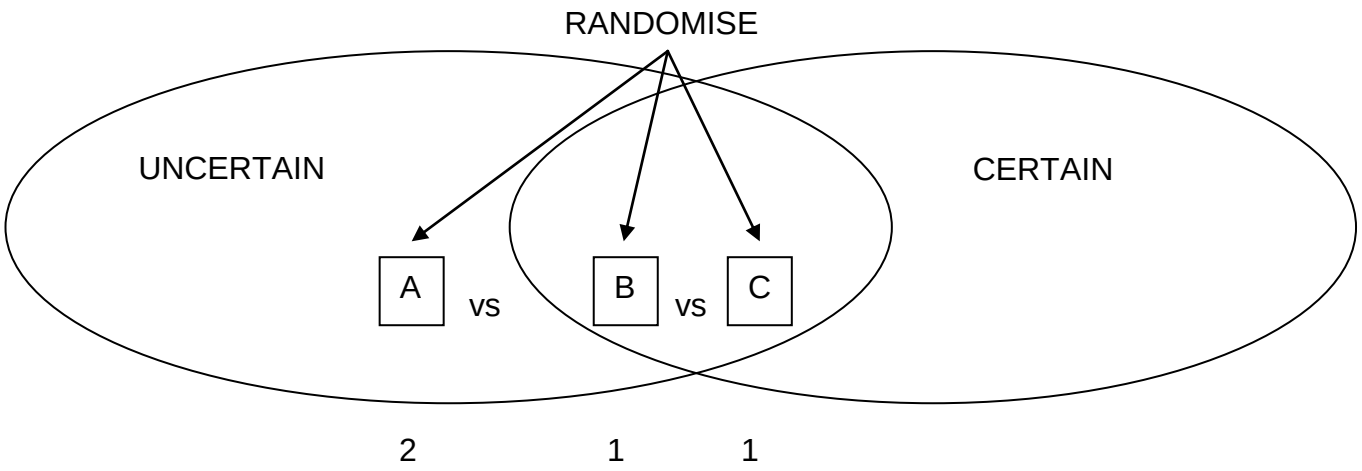
As the no warfarin arm was highlighted by some respondents as difficult to participate in, the principle of uncertainty was adopted: For clinicians who felt there was a clear benefit for warfarin, the randomisation was restricted to the last two treatment groups – see Figure 5.1.1

Table 5.1.1 Summary of pre-trial Survey Responses

Question **n= total number of responses to question**	**No. of Respondents Completing Question (% of total respondents)**	**Answers** **(% of total respondents, n=213)**			
Section 1	**n=213**	**1**	**2**	**3**	**4**
Types of CVCs used for chemotherapy n=345	n=213 (100%)	61% described site of CVC insertion (63% Hickman 27% PICC)	20% described catheter design (75% Groshong; 24% Portocaths)	12% described manufacturers (44% BARD; 32% VYGON)	7% 'other'
Types of cancer in which CVCs used n= 447	n=213 (100%)	gastrointestinal cancers n=224 (50%)	breast cancer n= 94 (21)%	haematological cancers n=69 (15%)	other cancers n=60(13%)
Drugs used via CVCs n=268	n=213 (100%)	Colorectal: continuous 5-FU / De Gramont Gastro-oesphageal: epirubicin /cisplatin	FEC	All	Various
Do you routinely use warfarin for arterial catheters? n=1	n=1 (<1%)	YES n=1 (<1%)	-		
If yes, dose used, n=1		1mg/day			
Do you routinely use warfarin for venous catheters? n=187	n=187 (88%)	NO n=56 (26%)	YES n=131 (62%)		

Question **n= total number of responses to question**	**No. of Respondents Completing Question (% of total respondents)**	**Answers** **(% of total respondents, n=213)**			
If yes, dose used n=131	n=131 (62%)	1mg/day n=121 (57%)	Variable dose for INR 1.5-2.0 n=4 (2%)	Other n=6 (3%)	
What percentage of your patients with CVCs develop a thrombosis? n=151	n=151 (70%)	Median: 10% (IQR 5%-15%)	Mean rate: 13% develop a thrombosis		
Time to thrombosis n=151	n=151 (70%)	over 28days n=88 (41%)	14-28 days n=33 (15%)	7-14days n=22 (10%)	0-7days n=6 (3%)
Section 2					
Is this an important clinical question? n=180	n=180 (85%)	YES n=171 (80%)	NO n=9 (4%)	-	
Are you interested in participating in a trial of thromboprohylaxis? n=176	n=176 (83%)	YES n=150 (70%)	NO n=26 (12%)		

Figure 5.1.1 WARP Trial Design after the Results of the pre-Trial Survey



A – no warfarin; B – fixed dose warfarin, 1mg daily; C – Dose adjusted warfarin, to maintain the INR between 1.5 and 2.0

5.2 *WARP Trial*

5.2.1 Overall Recruitment

The trial opened for recruitment in October 1999 with first patient recruited on 19th October 1999 and closed for recruitment in December 2004, with the last patient recruited on 17th December 2004 when protocol target number of patients was reached; 812 patients were randomised to the uncertain preference (404 to no warfarin, 408 to warfarin; 324 to Fixed Dose Warfarin (FDW) and 84 to Dose Adjusted Warfarin to maintain the INR between 1.5 and 2.0 [DAW]) and 778 to the certain preference (389 to FDW and 389 to DAW). The imbalance in the numbers of patients in the uncertain preference warfarin arms (324 patients receiving FDW and 84 receiving DAW) was due to the popularity, by the randomising clinicians in discussion with the patients, of the 2 arm option (no warfarin vs FDW), over the 3 arm option (no warfarin vs FDW vs DAW). This was possible after the trial design amendment. The design enabled 166 (10.4%) patients to contribute to both comparisons (Figure 5.2.1.1).

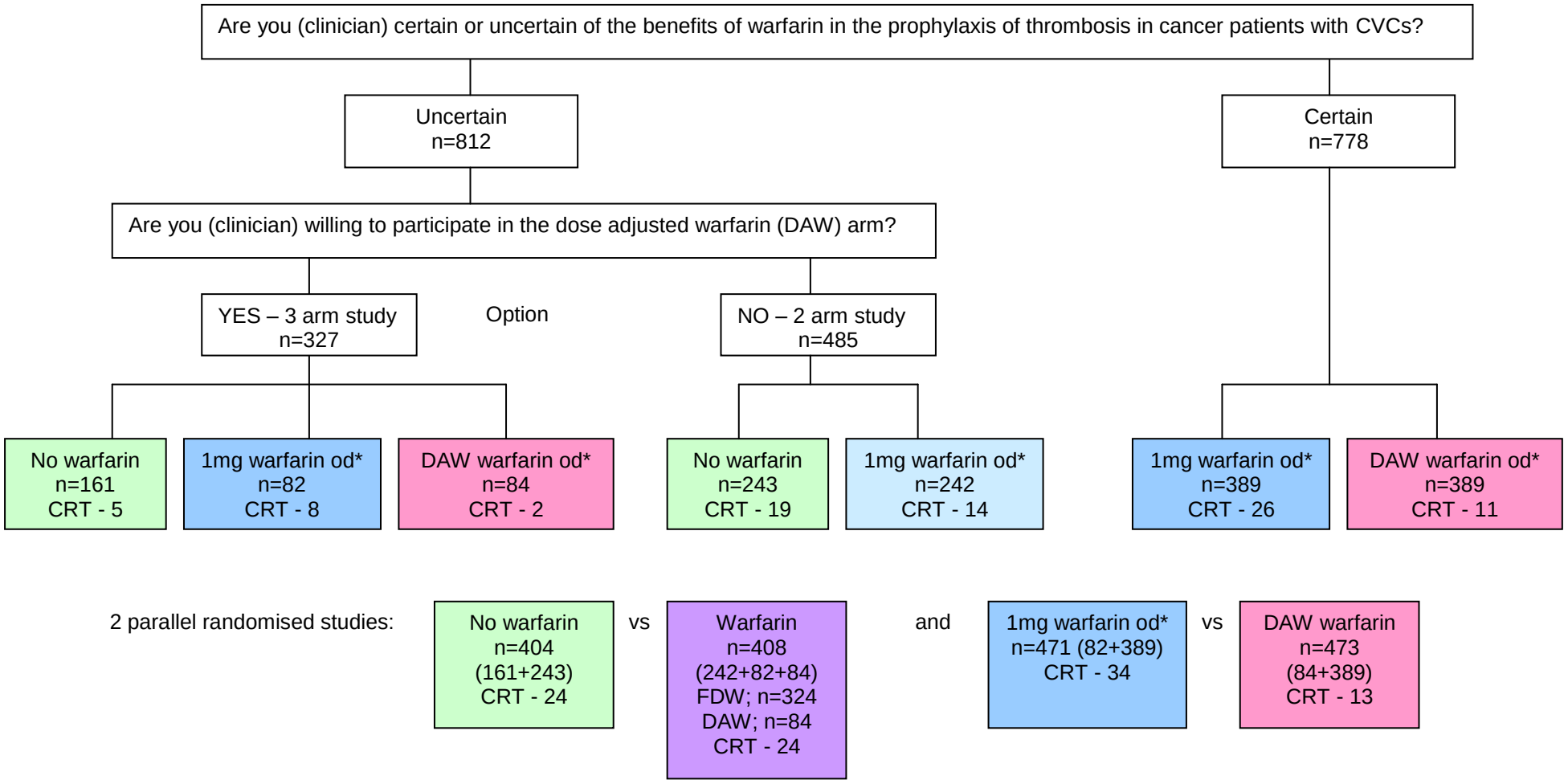
Yearly, quarterly and monthly recruitment is shown in Tables 5.2.1.1 – 5.2.1.4. Average monthly recruitment was 25 patients and ranged (after the first two months) from 4 midway through the trial (August 2002) to 69 in September 2003 (Table 5.2.1.1). During this period of 5.25 years, 1593 randomisations took place. Three of these were excluded from the analysis because they were invalid randomisations (see section 5.2.1.3).

Table 5.2.1.1 Yearly, Quarterly and Monthly Recruitment

	Number of time periods	**Mean**	**Median**	**Range**
Yearly	5.25	265	279	15 – 475
Quarterly	21	76	72	15 – 165
Monthly	63	25	25	4 – 69*

* recruitment not including the first two months, when there were 2 and 4 patients recruited respectively

Figure 5.2.1.1 Numbers of Patients Randomised to Uncertain/Certain Preference by Arm



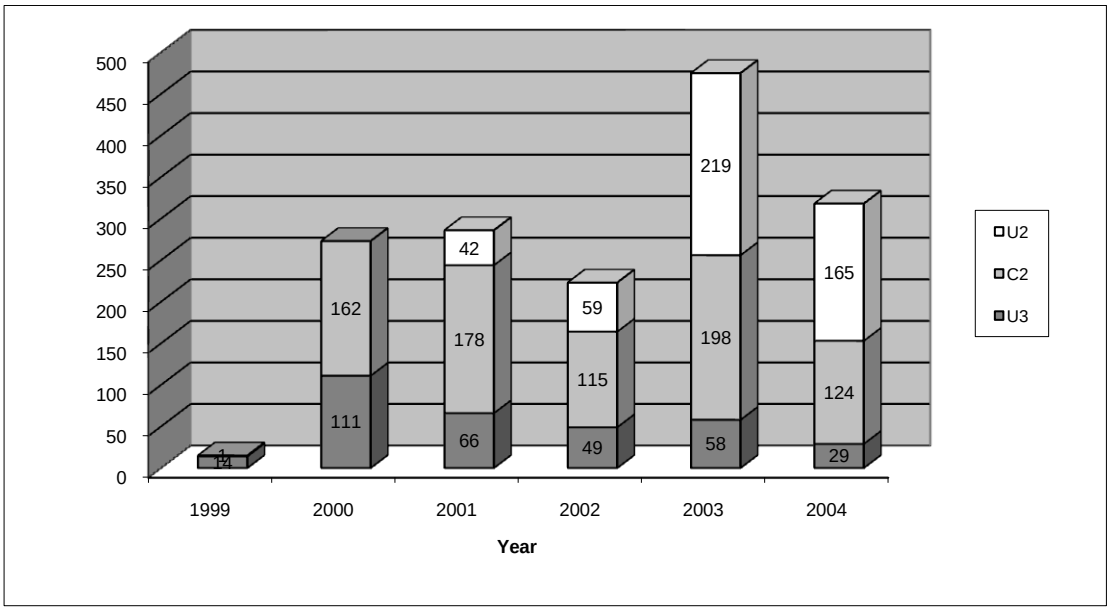
DAW – Dose Adjusted Warfarin; *od - once daily; FDW – Fixed Dose Warfarin (1mg daily); CRT – Catheter-related Thrombosis

Recruitment was greatest in 2003 (Table 5.2.1:2), with 277 patients assigned to the uncertain preferences (79% to 2 arm option) and 198 to the certain preference (Figure 5.2.1.2)

Table 5.2.1.2 Total Yearly Recruitment

Year	Number of Patients Recruited
1999	15
2000	273
2001	286
2002	223
2003	475
2004	318

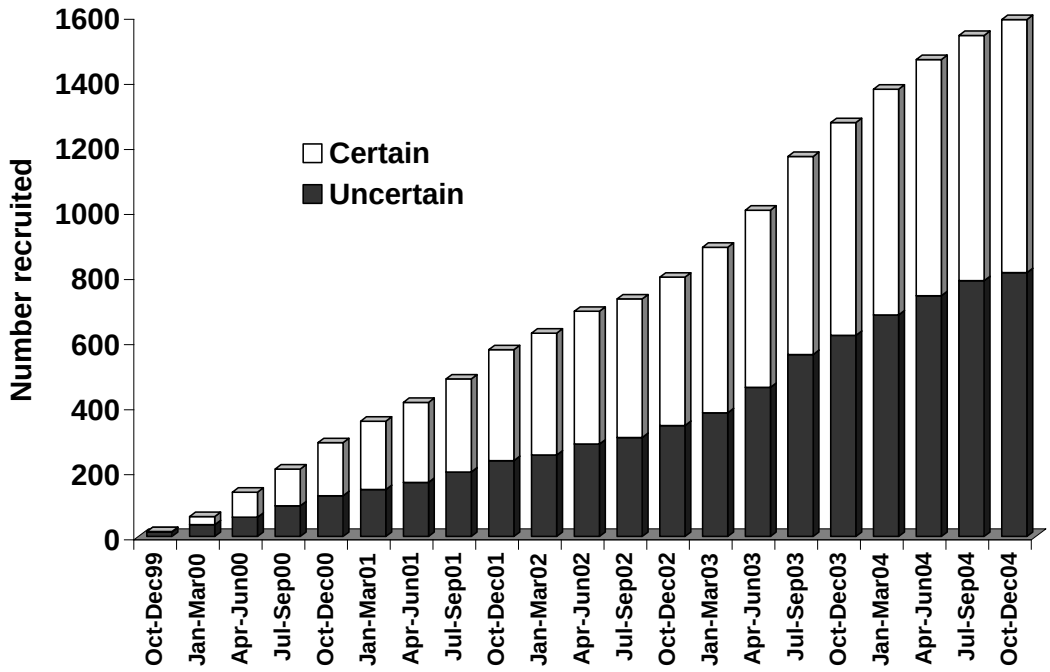
Figure 5.2.1:2 Yearly Recruitment by uncertain/certain preference



*U – uncertain preference; C – certain preference; 3- 3-arm option; 2 – 2 arm option

The quarterly recruitment demonstrates broadly that clinicians were evenly split on their preference on the benefits of warfarin in thromboprophylaxis (Figure 5.2.1.3)

Figure 5.2.1.3 Quarterly Cumulative Recruitment by Preference



The recruitment rates by centre and clinician are summarised in Table 5.2.1.3. The trial involved 68 participating centres from the United Kingdom with 12 centres recruiting more than 50 patients and 52% of all patients were recruited by the top 10 recruiting centres (Appendix 8). The trial involved 175 lead investigators (LIs), 98% of whom were consultant oncologists, with 4 (2%) senior nurses. In contrast, the randomising clinicians were predominantly research or clinical specialist nurses (82%) with oncologists at 12 centres supporting the nurses in this role.

Seventy six percent of clinicians always chose certain (35%) or uncertain (41%) preference for the benefit of warfarin whilst the remainder (24%) selected patients for randomisation to both certain and uncertain preferences. Within centres, different clinicians randomised patients under different preferences and options. The recruitment rates per centre are documented in Appendix 8.

Table 5.2.1.3 Total Patient Recruitment by Centres and Clinicians

Recruitment (number of patients)	**Mean**	**Median**	**Range**
Centres; n=68	23	12	1 – 214
Lead Investigators; n=175	9	4	1 – 128

5.2.1.1 Recruitment by Randomised Treatment Arm

Table 5.2.1.4 illustrates how the 1590 randomisations were split according to uncertain or certain preference and assigned treatment.

Table 5.2.1.4 Number of patients randomised by preference and by treatment arm

Indication/option	**No Warfarin**	**FDW**	**DAW**	**Total**
Uncertain 3 arm	161	82	84	327
Uncertain 2 arm	243	242	0	485
Certain 2 arm	0	389	389	778
Total	**404**	**713**	**473**	**1590**

5.2.1.2 Stratification Variables

Stratification variables (central *or* peripheral site of insertion, chemotherapy sclerosant *or* non-sclerosant potential and infusion of less than *or* greater than or equal to 24 hours) were balanced across allocated treatments. The uncertain 3 arm was proportionally assigned 2:1:1 for no warfarin; fixed dose warfarin of 1mg/day (FDW); dose-adjusted warfarin (DAW), daily, (Table 5.2.1.5).

Table 5.2.1.5 Balance of Patients per Stratification Variable

Preference and Option	No Warfarin	FDW	DAW
Central, <24, non-sclerosant (n=35)			
Uncertain; 3 arm study	3	1	2
Uncertain; 2-arm study	5	5	0
Certain	0	10	9
Central, <24, sclerosant (n=128)			
Uncertain; 3 arm study	8	3	5
Uncertain; 2-arm study	10	12	0
Certain	0	46	44
Central, 24+, non-sclerosant (n=203)			
Uncertain; 3 arm study	25	12	12
Uncertain; 2-arm study	20	21	0
Certain	0	56	57
Central, 24+, sclerosant (n=301)			
Uncertain; 3 arm study	47	24	24
Uncertain; 2-arm study	28	29	0
Certain	0	74	75
Peripheral, <24, non-sclerosant (n=33)			
Uncertain; 3 arm study	2	3	2
Uncertain; 2-arm study	10	8	0
Certain	0	4	4
Peripheral, <24, sclerosant (n=86)			
Uncertain; 3 arm study	6	3	3
Uncertain; 2-arm study	20	20	0
Certain	0	17	17
Peripheral, 24+, non-sclerosant (n=477)			
Uncertain; 3 arm study	35	18	18
Uncertain; 2-arm study	72	70	0
Certain	0	132	132
Peripheral, 24+, sclerosant (n=327)			
Uncertain; 3 arm study	35	18	18
Uncertain; 2-arm study	78	77	0
Certain	0	50	51

5.2.1.3 Randomisation Procedures

At randomisation, the following parameters were checked with the randomising clinician specifically confirming that the patient conformed to six of these criteria:

- Histologically or clinically confirmed diagnosis of solid or haematological malignancy
- Patient is due to have (or has had within last 7 days) a central venous catheter inserted for chemotherapy
- Adequate haematological, hepatic and renal function
- No contraindication to warfarin and not on warfarin
- Not pregnant or lactating and taking adequate contraceptive measures if appropriate
- Signed consent for WARP

The electronic computer randomisation procedure malfunctioned ('crashed') on four occasions over the four years of recruitment. Paper copies of the seven randomisations were documented and later added to the electronic database. The randomising officers found a duplication of three paper randomisation records on the electronic database. These were deleted and not included in any analysis.

5.2.1.4 Timing of Randomisation

Randomisation and start of warfarin, if allocated, was permitted from 3 days prior to CVC insertion for 1186 patients who were randomised to warfarin. After requests from some trial coordinators whose patients had their CVCs inserted in peripheral units before having their treatment administered at the regional

centres where WARP was recruiting, the steering committee permitted randomisation to take place after central venous catheter (CVC) insertion.

There were 10% of patients assigned to FDW and 17% of patients assigned to DAW who started warfarin up to 3 days prior to randomisation. However, 8% of patients assigned FDW and 10% of patients assigned DAW started warfarin >3 days prior to randomisation. The majority of patients (59%) on warfarin started on the day of randomisation (Tables 5.2.1.6. and 5.2.1.7).

Table 5.2.1.6 Timing of warfarin start in relation to randomisation

(for patients assigned to warfarin, n=1186)

Timing of start of warfarin	**FDW (n=713)**	**DAW (n=473)**
>3 days prior to randomisation	59 (8%)	45 (10%)
3 days prior to randomisation	34 (5%)	38 (8%)
1-2 days prior to randomisation	36 (5%)	36 (8%)
Same day as randomisation	447 (63%)	259 (55%)
1- 3 days after randomisation	50 (7%)	34 (7%)
4+ days after randomisation	41 (6%)	32 (7%)
Missing data - start of warfarin	46 (6%)	29 (6%)

Table 5.2.1.7 Timing of warfarin start in relation to randomisation by preference and by treatment

Preference:	**Uncertain**		**Certain**	
Timing in relation to randomisation	FDW (n=324)	DAW (n=84)	FDW (n=389)	DAW (n=389)
>3 days prior to randomisation	10 (3%)	3 (4%)	49 (13%)	42 (11%)
3 days prior to randomisation	5 (2%)	1 (1%)	29 (7%)	37 (10%)
1-2 days prior to randomisation	17 (5%)	5 (6%)	19 (5%)	31 (8%)
Warfarin started same day	202 (62%)	49 (58%)	245 (63%)	210 (54%)
1- 3 days after randomisation	35 (11%)	7 (8%)	15 (4%)	27 (7%)
4+ days after randomisation	28 (9%)	12 (14%)	13 (3%)	20 (5%)
Missing data - start of warfarin	27 (8%)	7(8%)	19 (5%)	22 (6%)

5.2.1.5 Eligibility

Eligibility is specified in section 4.2.4; patients with any malignancy, receiving chemotherapy via a central venous catheter and clinically fit to receive warfarin.

All patients recruited into the trial were confirmed by the local coordinators to be eligible at the time of randomisation. Immediately following randomisation, of the 1590 patients, four were found to be ineligible, three on clinical parameters and one declining chemotherapy post randomisation (Table 5.2.1.8). Four additional patients did not have CVCs inserted post randomisation. All patients were included in the analysis.

Table 5.2.1.8 Ineligible Patients* and Patients who had no Catheter Inserted after Randomisation

Preference and option	**Treatment Arm**	**Reason for ineligibility for trial**
Uncertain; 3-arm study	DAW	Platelet count not adequate to give warfarin*
Uncertain; 2 arm study	No warfarin	No line inserted due to technical difficulties
	FDW	After randomisation, lab results showed high values of liver enzymes ALT and AST* Patient was withdrawn from study but did receive warfarin for 3 days
		No line inserted
		No line inserted
Certain	DAW	Ulcerated tumour found post randomisation which is a contraindication to warfarin*
		Patient had no chemotherapy after randomisation*
		Line could not be inserted due to technical difficulties

FDW – Fixed Dose Warfarin (1mg daily); DAW – Dose Adjusted Warfarin *ineligible patients

5.2.2 Baseline Characteristics

Patient baseline characteristics are presented in Table 5.2.2.1 and are well balanced across the study arms. 58% of all patients had peripherally inserted central catheters (PICCs), in keeping with a rising trend in usage. Patients were similar with respect to age, treatment length, performance status, disease site and stage of disease across all arms. 93% of patients had WHO Performance Status of 0 and 1, although 65% had advanced disease and 73% of patients had gastrointestinal cancer. Over 50% of patients presented with colorectal cancer, reflecting an established European and increasing US practice for infusional chemotherapy with 5-FU, folinic acid and oxaliplatin or irinotecan. There were only 57 (3.6%) patients in total with haematological malignancies.

Of the 3% of patients who were on tamoxifen before the trial, 76% (39/51) stopped this hormone treatment and 24% (12/51) patients continued.

Table 5.2.2.1 Baseline Characteristics of Patients in WARP Trial

		Warfarin Evaluation		Dose Evaluation	
	Overall n=1590	**No Warfarin n=404**	**Warfarin n=408**	**FDW n=471**	**DAW n=473**
Sex:					
Male	913 (57%)	247 (61%)	252 (62%)	253 (54%)	265 (56%)
Female	677 (43%)	157 (39%)	156 (38%)	218 (46%)	208 (44%)
Age (yrs):					
Median	60	61	60	59	60
Age IQ Range	53-67	53-68	53-68	51-66	53-67
Age Range	16-91	16-86	19-87	19-85	20-91
WHO PS:					
0	890 (56%)	221 (55%)	225 (55%)	263 (56%)	272 (58%)
1	591 (37%)	168 (42%)	151 (37%)	178 (38%)	161 (34%)
2	71 (5%)	9 (2%)	20 (5%)	22 (5%)	25 (5%)
3	7 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	4 (1%)
Not Known	31 (2%)	5 (1%)	11 (3%)	7 (1%)	11 (2%)
Disease Stage					
No residual or Early	534 (34%)	130 (32%)	134 (33%)	171 (36%)	138 (29%)
Advanced	1040 (65%)	273 (68%)	269 (66%)	294 (62%)	330 (70%)
Not Known	16 (1%)	1 (<1%)	5 (1%)	6 (1%)	5 (1%)
Disease Site:					
Colorectal	810 (51%)	201 (50%)	217 (53%)	226 (48%)	243 (51%)
UGI (total)	352 (22%)	109 (27%)	92 (23%)	95 (20%)	98 (21%)
Oesophagus	*188 (12%)*	*67 (16.6%)*	*46 (11.3%)*	*46 (10%)*	*49 (10%)*
Gastric	*113 (7.1%)*	*33 (8.2%)*	*32 (8%)*	*36 (8%)*	*27 (6%)*
Pancreatic	*30 (1.9%)*	*2 (<1%)*	*7 (2%)*	*9 (2%)*	*17 (4%)*
*Upper GI**	*13 (1%)*	*4 (1%)*	*6 (1%)*	*2 (<1%)*	*3 (1%)*
Cholangio	*7 (<1%)*	*3 (1%)*	*1(<1%)*	*2 (<1%)*	*1 (<1%)*
Hepatic	*1 (<1%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*	*1 (<1%)*
Breast	202 (13%)	32 (8%)	32 (8%)	82 (17%)	67 (14%)
Other	174 (11%)	50 (12%)	54 (13%)	52 (11%)	49 (10%)
Lymphoma	29 (2%)	10 (2%)	12 (3%)	6 (1%)	5 (1%)

		Warfarin Evaluation		Dose Evaluation	
	Overall n=1590	**No Warfarin n=404**	**Warfarin n=408**	**FDW n=471**	**DAW n=473**
Ovarian	26 (2%)	3 (1%)	4 (1%)	15 (3%)	7 (1%)
Myeloma	19 (1%)	7 (2%)	5 (1%)	4 (1%)	6 (1%)
Sarcoma	12 (1%)	2 (<1%)	7 (2%)	6 (1%)	3 (1%)
Renal	10 (1%)	2 (<1%)	4 (1%)	3 (1%)	3 (1%)
Bladder	9 (1%)	2 (<1%)	4 (1%)	2 (<1%)	5 (1%)
Leukemia	9 (1%)	4 (1%)	5 (1%)	1 (<1%)	4 (1%)
Melanoma	7 (<1%)	2 (<1%)	1 (<1%)	3 (1%)	2 (<1%)
Head & Neck	4 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)	0
Cervical	3 (<1%)	0	0	1 (<1%)	2 (<1%)
Lung	3 (<1%)	2 (<1%)	1 (<1%)	0	0
Testicular	3 (<1%)	0	0	1 (<1%)	2 (<1%)
Prostate	1 (<1%)	0	0	1 (<1%)	0
Ophthalmic	1 (<1%)	0	1 (<1%)	1 (<1%)	0
Other	38 (2%)	14 (3%)	8 (2%)	7 (1%)	10 (2%)
Not Known	52 (3%)	12 (3%)	13 (3%)	16 (3%)	16 (3%)
CUO	37 (2%)	10 (2%)	9 (2%)	11 (2%)	11 (2%)
Blank	15 (1%)	2 (<1%)	4(1%)	5 (1%)	5 (1%)
Pre-trial Tamoxifen:					
No	1523 (96%)	393 (97%)	396 (97%)	449 (95%)	444 (94%)
Yes	51 (3%)	9 (2%)	7 (2%)	16 (3%)	24 (5%)
Stopped on trial	39 (2%)	8 (2%)	5 (1%)	12 (3%)	17 (4%)
Continue on trial	12 (<1%)	1 (<1%)	2 (<1%)	4 (<1%)	7 (1%)
Not Known	16 (1%)	2 (<1%)	5 (1%)	6 (1%)	5 (1%)

WHO PS – WHO Performance Status; Cholangio – cholangiocarcinoma;

CUO – Cancer of Unknown Origin; UGI – Upper Gastrointestinal;

*broad classification given; *Italics denotes specific UGI tumour types*

5.2.3 Protocol Compliance

5.2.3.1 Return of Case Record Forms

CRF return was excellent; there was 100% of mandatory baseline information on CRF1 including treatment arm and trial number. The remaining baseline data on CRF1 (permitted to be completed after randomisation) were returned in 99.2% of cases, 98.1% of cases for CRF2 and 98.2% of cases for CRF3. Table 5.2.3.1 shows the CRF return across preferences; there are no differences in return of any CRF between preferences. Overall, 4.4% of CRFs were missing (including part C of CRF1) and 0.4% of all patients had both CRF1 and CRF2 missing.

5.2.3.2 Assigned Treatment Compliance

Of 1186 patients who were allocated warfarin, 12 (0.1%) did not receive any allocated warfarin treatment (eight on warfarin 1mg and four on DAW), mostly due to patient choice (n=7). The reasons for not starting warfarin were: one refusal to take warfarin after consent, one patient had a slight nose bleed before treatment and withdrew, one patient was taking aspirin (permissible at low doses) and so withdrew, one patient did not start warfarin as was concerned about vaginal bleeding and three patients gave no reason. Clinician error contributed to one patient not starting warfarin with clinician request to two patients not to start warfarin, because of risk of bleeding and disease progression. One patient left hospital without warfarin and one omitted to start, both then withdrawing from treatment. Only one patient out of 404 who were allocated no warfarin (0.0025%) was known to start warfarin because of a suspected thrombosis. All these patients were included in the analysis. Assigned treatment compliance is summarised in Figure 5.2.3.1

Table 5.2.3.1 CRF Return

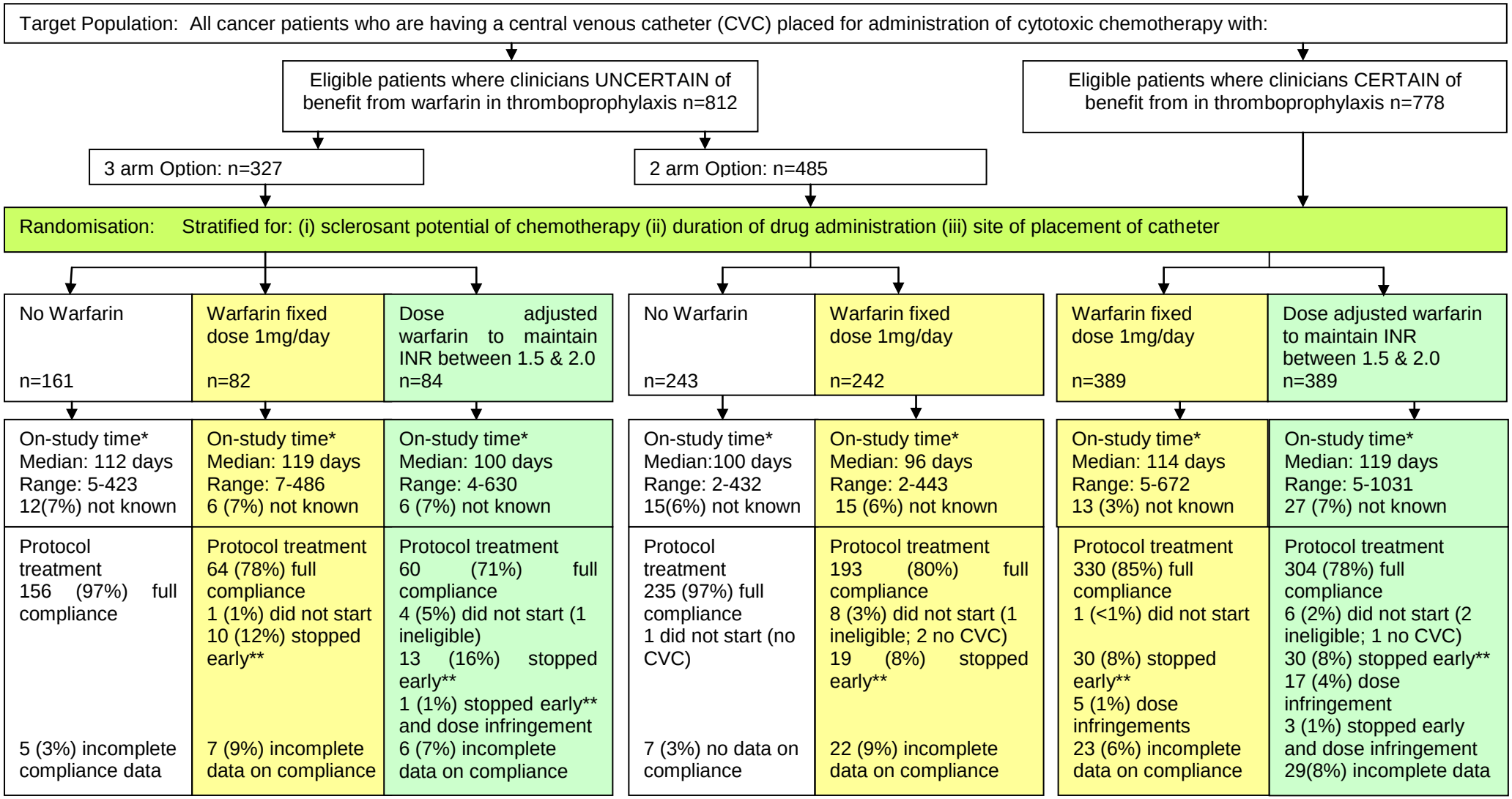
Preference and Option:		**Uncertain 3-arm**			**Uncertain 2-arm**		**Certain**		**Total**
Case Record Form (CRF)	**Time CRF completed and returned**	**No Warfarin**	**FDW**	**DAW**	**No Warfarin**	**FDW**	**FDW**	**DAW**	
CRF1 Randomisation Form Part A, B	**At randomisation (total no. of CRFs)**	**161**	**82**	**84**	**243**	**242**	**389**	**389**	**1590**
CRF1 Randomisation Form Part C	Baseline data after randomisation	160 (1)	81 (1)	84 (0)	243 (0)	239 (3)	385 (4)	386 (3)	1478 (12)
CRF2 End of Primary Evaluation Period Form	At catheter removal or thrombosis	156 (5)	82 (0)	82 (2)	238 (5)	234 (8)	386 (3)	382 (7)	1560 (30)
CRF3 Follow-up Form*	One year after randomisation or death	157 (4)	81 (1)	81 (3)	237 (6)	237 (5)	386 (3)	383 (6)	1562 (28)
CRF2 and CRF3 missing		(3)	(0)	(1)	(1)	(0)	(0)	(1)	(6)
Total CRFs Missing*		(10)	(2)	(5)	(11)	(16)	(10)	(16)	(70)[4.4%]

(number of patients missing in brackets); * includes part C of CRF1

5.2.3.3 Warfarin Dose Compliance

Of 1186 patients allocated to warfarin, 1139 were known to have started treatment (20 did not start and there were no data for 27). Of the 1139 patients who started warfarin, 26 (2.3%) patients and/or their clinicians did not conform to warfarin dose. For five patients allocated FDW, the clinician chose to prescribe the variable dose; for 21 patients on DAW, five took 1mg warfarin in error, 12 patients decided jointly with their clinician to change to FDW daily, three were prescribed 1mg warfarin in error and one reason for shifting to FDW remained unknown. Of the 1139 patients taking warfarin, 106 (9%) stopped taking their prescribed medication early (over 7 days before the catheter was removed), 59 patients (56%) on FDW and 47 patients (44%) on DAW. The majority (80%) of these patients stopped taking warfarin at the end of their chemotherapy course, but over 7 days before their catheter was removed. For the other patients, warfarin was stopped early due to patient choice or thrombocytopenia; data on warfarin compliance were incomplete on 8% of patients. Compliance with warfarin dose is summarised in Figure 5.2.3.1.

Figure 5.2.3.1 WARP Flow Chart (Consort Diagram)



5.2.4 Primary Endpoint

5.2.4.1 Catheter – related thrombotic events

Comparisons can only be made for randomised groups, hence those receiving warfarin under the certain preference, could not be included in the assessment of warfarin vs no warfarin. Of the 1590 patients randomised, 85 (5.3%) had a radiologically confirmed CRT, occurring most frequently in the upper limb. There were also 9 clinically suspected CRT in 7 patients, not confirmed radiologically and therefore classified as CVC complications and not CRT. Warfarin - any dose (79% was 1mg; 21% DAW) - did not reduce the incidence of CRT thrombotic events relative to no warfarin [24(5.9%) vs 24(5.9%); Relative Risk (RR)=1.00, 95% Confidence Interval (CI) 0.74–1.34, p=0.98]

In contrast, there were significantly fewer CRT events in those patients allocated DAW compared to FDW [13(2.8%) vs 34(7.2%); RR=0.67; 95% CI 0.56–0.81, p=0.002] (Table 5.2.4.1). When randomised comparisons were analysed for no warfarin (n=404) vs FDW (n=324), there were no significant differences in CRT; [24(5.9%) vs 22(6.8%), RR=1.10; 95%CI 0.64-1.89, p=0.7]. Similarly, between no warfarin (n=161) and DAW (n=84), DAW demonstrated no significant reduction in CRT [5(3.1%) vs 2(2.4%), RR=0.77, 95%CI 0.15-3.87, p>0.99] (Table 5.2.4.2).

Table 5.2.4.1: Catheter-Related Thrombotic Events

	Warfarin Evaluation			Dose Evaluation		
	No Warfarin n=404	**Warfarin n= 408**	**Relative Risk (95% CI) p-value**	**FDW n= 471**	**DAW n= 473**	**Relative Risk (95% CI) p-value**
CRT Events	24 (5.9%)	24 (5.9%)	0.99 (0.57, 1.72) p=0.98	34 (7.2%)	13 (2.8%)	0.38 (0.20, 0.71) p=0.002
No event	370 (91.6%)	372 (91.2%)		433 (91.9%)	448 (94.7%)	
Not known	10 (2.5%)	12 (2.9%)		4 (0.9%)	12 (2.5%)	

Table 5.2.4.2 Other Randomised Comparisons of Catheter Related Thrombotic Events

	No warfarin vs FDW			No warfarin vs DAW*		
	No Warfarin n=404	FDW n= 324	Relative Risk (95% CI) p-value	No Warfarin n= 161	DAW n= 84	Relative Risk (95% CI) p-value
CRT Events U3 U2	24 (5.9%) 5 19	22 (6.8%) 8 14	1.10 (0.64, 1.89) p=0.72	5 (3.1%)	2 (2.4%)	0.77 (0.15, 3.87) p>0.99*
No Events + not known	380 (94.1%)	303 (93.5%)		156 (96.9%)	82 (97.6%)	

5.2.4.2 Location of Catheter-related Events

The locations of the 85 CRT events were reported as follows:

32 (38%) upper limb; 17 (20%) axillary vein; 16 (19%) subclavian vein;

10 (12%) internal jugular; 4 (5%) superior vena cava; 2 (2%) pulmonary emboli;

2 catheter and 2 with site not stated. These are presented with type of venous thromboembolism (VTE) assessment, side of catheter and side of thrombosis if known (Table 5.2.4.3).

5.2.4.3 Assessment Technique for Diagnosis of Catheter-related Events

The most common assessment technique used for diagnosing CRT was ultrasound [45 (53%)], followed by venogram [32 (40%)]. Six 'other' assessment techniques were used (including Ventilation-Perfusion [V-P] Scintigraphy and Computerised Tomography [CT] scans for the diagnosis of PE, and 2 assessments were carried out but not specified (one of these CRTs occurred less than five days after the removal of the catheter) [Table 5.2.4.3].

5.2.4.4 Side of Thrombosis

The thrombosis was on the same side as the catheter in all cases (as per definition of CRT) unless the data were unknown (n=4) and these were assumed to be on the same side as the catheter. There were 43 left-sided thromboses, 32 right-sided and six in which the side was not applicable [4 in superior vena cava (SVC) and 2 PEs].

5.2.4.5 Removal of catheters in relation to Catheter-related thrombosis

The catheters were removed after the thrombosis occurred in 57 cases; on the same day in 26 cases, and in 4 patients, the thrombosis occurred within 1-5 days after the removal of the catheter (which was the duration after catheter removal still categorised as a CRT).

5.2.4.6 Time-to-event analysis: Catheter-related Thrombosis

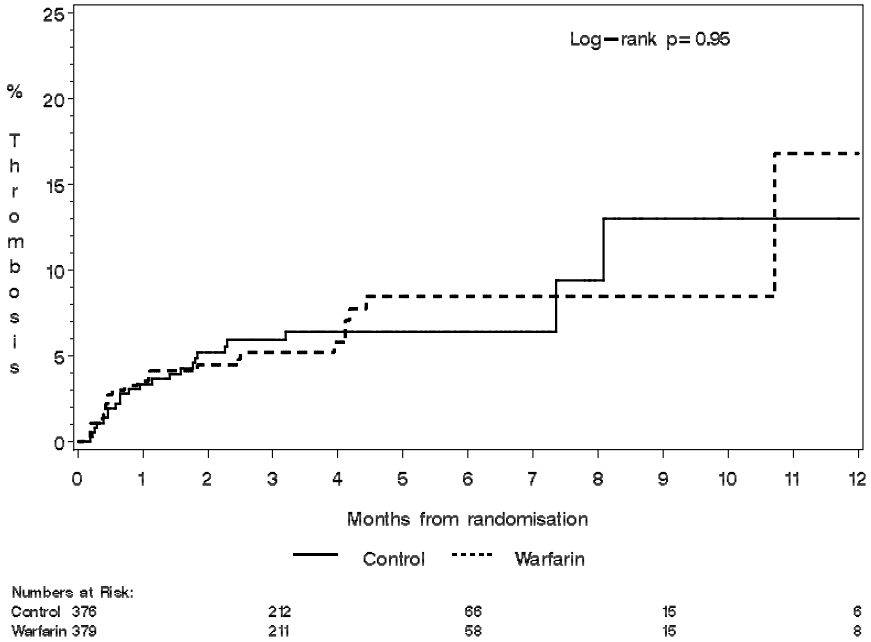
Kaplan-Meier estimates of cumulative thrombosis rates for CRT were calculated using all patients, by treatment and shown as curves in Figure 5.2.4.1. The numbers of patients at risk of thrombosis over time are shown below the curves. Analysis of this primary outcome as time-to-event data is comparable to the χ-square tests shown in Table 5.2.4.1 and demonstrate no difference in the proportion of thromboses over time between no warfarin and warfarin (log rank p=0.95), whereas for the FDW versus DAW comparison, there was a significant advantage for the DAW group (log rank p=0.002) There are 57 patients who either did not have thrombosis or in whom the outcome was not known or who have not got a date of CVC removal (28 allocated to no warfarin and 29 to warfarin) who were excluded from the analysis i.e. the numbers of patients at risk at the (Figure 5.2.4.1).

5.2.4.7 Time to Catheter-related Thrombosis

For patients with a CRT event, median time to CRT was 32 days from randomisation (IQR=13 to 76 days). Median time to CRT did not differ in the warfarin vs no warfarin (25 vs 32 days, p=0.71), or DAW vs FDW (60 vs 31 days, p=0.51) studies.

Figure 5.2.4.1 Time to Catheter-Related Thrombosis by Treatment

a) No Warfarin (labelled control) vs Warfarin



b) Fixed dose warfarin versus dose adjusted warfarin

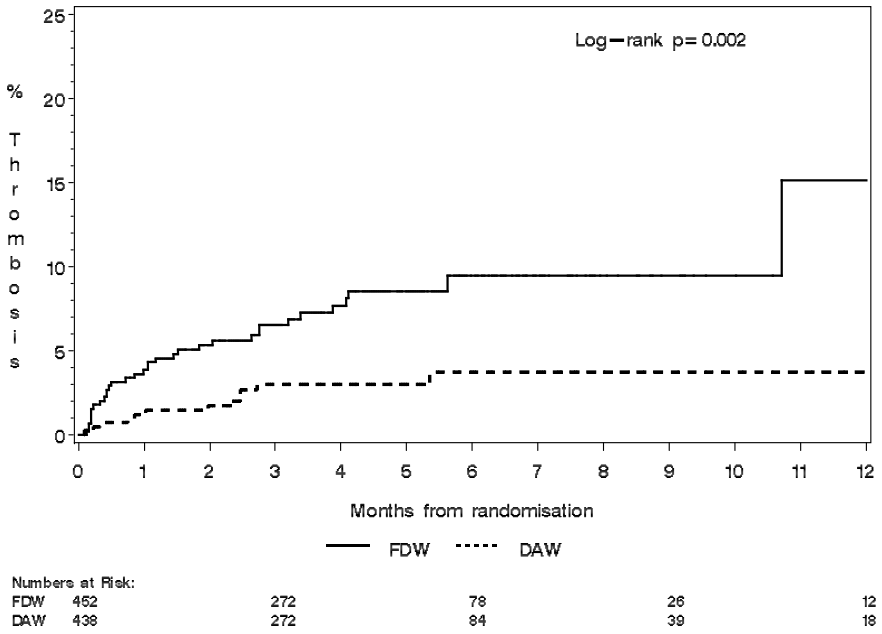


Table 5.2.4.3 Details of Catheter Related Thromboses

Location	Diagnosis	Time in relation to CVC removal	Side Catheter: Thrombosis	n
Arm (n=32)	Venogram	Before	LL	1
			RR	2
			UL	2
			UR	2
		Same	LL	1
			RR	2
			RU	1
			UL	3
	Ultrasound	Before	LL	4
			RR	5
			UL	3
			UR	1
		Same	RR	1
			UL	1
	Other	Before	RR	1
		Same	RR	1
	NK	5 days	UU	1
Axillary Vein (n=17)	Venogram	Before	LL	1
			UL	1
			UR	1
		Same	UL	2
	Ultrasound	Before	LL	5
			UL	1
			UR	1
		Same	LL	3
		1-5 after	RR	1
	Other	Before	UU	1
Internal Jugular (n=10)	Ultrasound	Before	RR	1
			UL	2
			UR	1
		Same	RR	2

Location	Diagnosis	Time in relation to CVC removal	Side Catheter: Thrombosis	n
		1-5 after	LL	1
		NK	RR	1
			UR	1
	Other	Before	RR	1
Subclavian Vein (n=16)	Venogram	Before	RR	2
			UL	1
			UU	1
		Same	LL	1
			RR	1
		1-5 after	UL	1
	Ultrasound	Before	RR	2
			UL	1
			UR	1
		Same	LL	3
		NK	LL	1
	Other	Same	LL	1
SVC (n=4)	Venogram	Before	R NA	1
			U NA	1
	Ultrasound	Same	RU	1
	Other	NK	R NA	1
Lung - PE (n=2)	Other after venogram and ultrasound	Before	U NA	1
		Same	U NA	1
Catheter (end) n=2	Venogram	Before	RR	1
		Same	LL	1
NK (n=2)	NK	Same	UL	1
	Venogram	Same	UL	1

NK – not known; L – left; R- right; U – unknown; NA – not applicable

5.2.4.8 Grading of Catheter-related Venous Thromboses

The majority (64%) of CRT were deep vein thromboses, requiring anticoagulants [grade 3] (Table 5.2.4.4].

Table 5.2.4.4 Grade of Catheter-related Thromboses

CTC Grade	1	2	3	4	NK
(n=85)	3 (4%)	8 (9%)	54 (64%)	4 (5%)	16 (19%)

5.2.5 Secondary Outcomes

5.2.5.1 All thrombotic events

36 (2.3%) patients had a non catheter-related thrombosis (CRT), giving a total of 121 VTE in 1590 patients (7.6%). Neither warfarin (compared to no warfarin) nor DAW (compared to FDW) have any significant impact (p=0.30 and p=0.15 respectively) on all thrombotic events (Table 5.2.5.1). The inclusion of clinically suspected thromboses (including two non-CRT) that were not confirmed radiologically (one in any warfarin group vs four in no warfarin group; one in DAW vs five in FDW), in a sensitivity analysis of all thromboses showed that there was no advantage from taking warfarin over no warfarin (p=0.17) or DAW over FDW (p=0.06). When randomised comparisons were analysed for no warfarin (n=404) vs FDW (n=324), there were no significant differences in all thrombotic events, [38(9.4%) vs 28(8.6%), RR=0.91, 95%CI 0.57-1.45, p=0.7]. Similarly, between no warfarin (n=161) and DAW (n=84), DAW demonstrated no significant reduction in all thrombotic events [13(8.1%) vs 2(2.4%), RR=0.29, 95%CI 0.07-1.28, p=0.10] (Table 5.2.5.2).

5.2.5.2 Location of non-Catheter Related Thromboses

The location of the 36 non-CRT events presented as: 18 (50%) lower limb; 10 (28%) pulmonary emboli; 4 (14%) upper limb (opposite side from catheter by definition), 2 (5%) inferior vena cava, 1(3%) subclavian vein, and 1 portal vein. Non-CRT events were all venous with the exception of one upper limb arterial thrombosis. Details of non-CRT are included in Table 4.2.5.3.

5.2.5.3 Assessment Technique for Diagnosis of All Thromboses

All thromboses were diagnosed by various assessment techniques, owing to the number of PEs. Other methods (including V-P Scintigraphy and CT scan for assessment of PEs) were used for 14 patients, ultrasound for 13 patients and venogram in 9 patients (Table 5.2.5.3).

5.2.5.4 Removal of Catheters in relation to non-Catheter-related Thromboses

After the occurrence of a non-catheter-related thrombosis, 7 catheters were removed on the same day and 25 at least a day after the thrombosis. There were no catheter removal data for 4 patients (Table 5.2.5.3).

5.2.5.5 Time to All Thromboses

For those patients who had a thrombosis, median time to all thromboses (CRT and non-CRT) was 44 days (IQR=13-84 days). Median time to all thromboses did not differ in the warfarin vs no warfarin (34 vs 45 days, p=0.80), or DAW vs FDW (73 vs 31 days, p=0.14) studies.

Table 5.2.5.1 All Thrombotic Events

	Warfarin Evaluation			Dose Evaluation		
	No Warfarin n=404	Warfarin n= 408	Relative Risk (95% CI) p-value	FDW n= 471	DAW n= 473	Relative Risk (95% CI) p-value
All thrombotic events	38 (9.4%)	30 (7.4%)	0.78 (0.50, 1.24) p=0.30	37 (7.9%)	26 (5.5%)	0.70 (0.43,1.14) p=0.15
No event	356 (88.1%)	368 (90.2%)		430 (91.3%)	438 (92.6%)	
Not known	10 (2.5%)	12 (2.9%)		4 (0.9%)	12 (2.5%)	

Table 5.2.5.2 All thrombotic events – no warfarin vs fixed dose warfarin and no warfarin vs dose adjusted warfarin

	No warfarin vs FDW			No warfarin vs DAW		
	No Warfarin n=404	FDW n= 324	Relative Risk (95% CI) p-value	No Warfarin n= 161	DAW n= 84	Relative Risk (95% CI) p-value*
All thrombotic events (CRT& non-CRT)	38 (9.4%)	28 (8.6%)	0.91 (0.57, 1.45) p=0.69	13 (8.1%)	2 (2.4%)	0.29 (0.07,1.28) p=0.10
No event + not known	366 (90.6%)	296 (91.4%)		148 (91.9%)	82 (97.6%)	

Table 5.2.5.3 Details of non-Catheter Related Thromboses

Location	Type	Diagnosis	Time relating to CVC removal	Side Catheter/ Thrombosis	n
Arm (n=4)	Venous	Venogram	Before	LR	1
				RL	1
		Ultrasound	Same	LR	1
	Arterial	Ultrasound	Before	UL	1
Leg (n=18)	Venous	Venogram	Before	RL	1
				UR	1
			Same	UR	1
			NK	RR	2
				UU	1
		Ultrasound	Before	LL	3
				LR	2
				UL	1
				UR	2
			Same	UU	1
				UL	1
		Other	Before	LL	1
				UR	1
Subclavian Vein (n=1)	Venous	Ultrasound	Same	RL	1
IVC (n=2)	Venous	Venogram	Same	UR	1
		Other	Before	RL	1
Portal Vein (n=1)	Venous	Other	NK	LR	1
Lung - PE (n=10)	Venous	Other	Before	R NA	8
				L NA	1
			Same	R NA	1

NK – not known; L – left; R- right; U – unknown; NA – not applicable

5.2.5.6 Grading of All Thromboses

Grading of venous and arterial thrombosis was requested according to CTC criteria as specified in the protocol. Given that there was only one known arterial secondary thrombosis, the majority of VTE (71%) were grades 3 and 4, with 8% classified as not requiring anticoagulation.

Table 5.2.5.4 Grades of All Thromboses

Grade	CRT (n=85)	Non-CRT (n=36)	All Thromboses (n=121)
1	3 (4%)	1 (3%)	4 (3%)
2	8 (9%)	2 (6%)	10 (8%)
3	54 (64%)	17 (47%)	71 (59%)
4	4 (5%)	10 (28%)	14 (12%)
NK	16 (19%)	6 (17%)	22 (18%)

CRT – catheter-related thromboses; NK – not known

5.2.5.7 Exploratory Multivariate Analysis – Patient Factors; All Thromboses

Table 5.2.5.5 shows the factors entered into the analytic model.

Table 5.2.5.5 Exploratory Prognostic Modelling for All Thromboses: Patient Groupings with Explanatory Variables

Grouping	Variable	Number of Patients	Percentage
Catheter Insertion Site	Central	667	42
	Peripheral	923	58
Duration of Drug Infusion *not included in modelling*	<24 hours	283	18
	>24Hours	1307	82
Sclerosant Potential	Non-Sclerosant	746	47
	Sclerosant	884	53
Disease Stage	No Residual/ Early	534	34
	Advanced	1040	66
Tumour Site	Other	765	49
	Colorectal	810	51
Type of Chemotherapy	5FU*- containing	346	24
	Non- 5FU-containing	1105	76
WHO Performance Status	0	890	57
	1+	663	43
Heparin Flushing	No	1059	67
	Yes	513	33

* 5-FU – 5-Fluorouracil; shaded are stratification factors

The overall catheter-related thrombosis (CRT) rate in the WARP trial was 7.6%. In total, there were 121 thrombotic events. Only one tumour site out seven risk factors above in the univariate prognostic modelling, was found to be significant. These are post-hoc groupings which were developed from the results of the trial. The result is presented in Table 5.2.5.6

Table 5.2.5.6 Univariate Analysis for Site of Disease

Risk Factor	Odds Ratio (OR)	95% CI for OR	p-value
Tumour Site: Colorectal vs other	0.65	0.44, 0.94	0.02

A multivariate logistic regression analysis for all thrombosis demonstrated that colorectal cancer against all other tumour sites remains an independent prognostic factor in the presence of all the other factors. This is a subgroup analysis with the post-hoc groupings, based on results.

5.2.5.8 Trial-related toxicities

5.2.5.8.1 Major Bleeding

Major bleeding occurred in 28 of 1590 (2%) patients. There was evidence of an excess of major bleeding events in patients on warfarin compared to no warfarin [7(0.3%) vs 1(1.7%), RR=6.93, 95%CI 0.86-56.08, p=0.07] and in patients on DAW compared to FDW [16(3.4%) vs 7(1.5%) RR=2.28, 95%CI 0.95-5.48, p=0.09], although both failed to reach statistical significance (Table 5.2.5.7). The results from the analysis restricted to only those patients known to comply with their randomised treatment, showed a significant difference between major bleeding between no warfarin and warfarin respectively (7/376 (0.2%) vs 1/390 (0.03%); p=0.04) and an excess was seen in patients receiving DAW in comparison to FDW [14/423 (0.03%) vs 6/451 (0.01%); p= 0.07]. According to participating clinicians, warfarin may have contributed to the deaths of two patients receiving DAW who had a major bleed, one with raised INR and one without raised INR; no thrombosis was reported as contributing to death.

Table 5.2.5.7 Toxicity - Summary of Major Bleeding and Raised INR

	Warfarin Evaluation			Dose Evaluation		
	No Warfarin n=404	**Warfarin n=408**	**Relative Risk (95% CI); p value**	**FDW n=471**	**DAW n=473**	**Relative Risk (95% CI); p value**
Major Bleeding and no reported raised INR	1	3		5	7	
Major Bleeding & raised INR	0	4		2	9	
Total Major Bleeding	**1 (0.3%)**	**7 (1.7%)**	**6.93 (0.86,56.08) p=0.07**	**7 (1.5%)**	**16 (3.4%)**	**2.28 (0.95,5.48) p=0.09**
Moderate and severe raised INR & no major bleeding	0	3		1	12	

Tables 5.2.5.8 – 5.2.5.10 illustrate the total number of trial-related toxicities. These are categorised into: i) raised INR and no reported bleeding (Figure 5.2.5.8); ii) major bleeding and no reported raised INR (Figure 5.2.5.9) and iii) major bleeding and raised INR (Figure 5.2.5.10). Reported Serious Adverse Events (SAE) are shaded. There were 30 trial-related SAEs reported on SAE forms, each discussed with two physicians independently and then together, in order to verify the data. Other trial-related toxicities, e.g. minor bleeding or raised INR, were reported on CRF2 and, if within 5 days of thrombosis or catheter removal, on CRF3. An increase in moderately and severely raised INR *without* major bleeding was documented for 13 patients, in whom three were deemed a SAE. Warfarin was stopped by the local investigators in all cases (Table 5.2.5.8).

Table 5.2.5.8 Toxicity - Raised INR and no Reported Major Bleeding

Severity	Treatment	Preference	Details
Moderate (INR=5-<8)	DAW	C2	INR=5.4
	DAW	U3	INR=6.8
	DAW	C2	INR=5.8
	DAW	U3	Unable to stabilise INR (max = 5.5)
	DAW	U3	Unable to control (INR=5.9)
	DAW	C2	INR=6.2, disease progression
	FDW	C2	INR=5.4
	DAW	C2	INR=6.6 due to wrong dose
Severe (INR=8+)	DAW	C2	SAE: INR=8 (moderate) but no signs of bleeding
	DAW	C2	SAE: INR=9.3 plus vomiting and diarrhoea
	DAW	C2	SAE: INR>10, alerted by haematoma
Value not stated	DAW	C2	Unable to stabilise INR
	FDW	C2	No further information available

Major bleeding also occurred in this patient population (patients with cancer, receiving chemotherapy with CVCs) with no reported raised INR in 19 patients, 14 of whom were deemed to have a SAE. Warfarin was a contributory factor in the death of one of the patients with major bleeding but no reported raised INR, in the opinion of the local investigators. Six of the 14 SAE major bleeds were reported as tumour-related (Table 5.2.5.9).

Table 5.2.5.9 Toxicity – Major Bleeding and No Reported Raised INR

Severity	Treatment	Preference	Details
Grade 3	0W	U2	Haematemesis
	FDW	C2	Rectum bleed, anaemia
	DAW	C2	Nose bleeding
	DAW	C2	Rectal bleed
Grade 4	FDW	C2	Tumour-related
SAE - moderate	FDW	C2	Tumour-related
	FDW	C2	Tumour-related
	FDW	C2	Tumour-related
	FDW	C2	Tumour-related
	FDW	C2	Tumour-related
	FDW	C2	Tumour-related
	FDW	C2	Tumour-related
SAE – severe	DAW	U3	Acute UGI bleed (INR=1.3)
	DAW	C2	Acute upper GI bleed (perforated ulcer)
	DAW	C2	GI bleed; patient has oesophageal carcinoma
	FDW	C2	Abdominal pain and haematemesis, 2 units of blood given (recorded as moderate)
	DAW	C2	Bleeding from stoma site,

Severity	Treatment	Preference	Details
SAE -severe			warfarin stopped (recorded as moderate)
	DAW	C2	Admitted with haematemesis; confirmed myocardial infarction
	FDW	C2	Admitted with raised blood pressure and confusion. CT showed bleed in parietal lobe consistent with intracerebral haemorrhage
	FDW	U2	Patient Haemoglobin 6.0 g/dL on admission to hospital (RT sided abdominal pain) leading to cardiac arrest and death; warfarin may have contributed to death.

In the group of 14 patients with major bleeding and raised INR, all but one were reported as SAEs. The major bleeding was deemed severe in 4 patients, one of whom was reported to have 'warfarin sensitivity' and, in another, warfarin was thought to have contributed to their death (Table 5.2.5.10).

Table 5.2.5.10 Toxicity – Major Bleeding and Raised INR

Severity	Treatment	Preference	Details
Grade 2 & Moderate INR	DAW	C2	Rectal bleed and INR=5.2
SAE-Mild	DAW	C2	INR=8.7; bleeding into knee;
SAE-Moderate	DAW	U3	INR=6.1; melaena
	DAW	U3	INR>8; melaena;
	DAW	C2	INR>12; haemoptysis, splinter haemorrhages, leg bleed; extreme breathlessness.
	DAW	C2	Patient had epistaxis, INR=4.4
	DAW	U3	Melaena for 24 hours; INR=4.4
	DAW	C2	INR=8.3; haematuria and bruising to hip. Hb=8.9
	FDW	U2	INR=11, mild epistaxis for 2 weeks, fatigue. 2 units of fresh frozen plasma (FFP). Infection
	FDW	C2	INR=4.8, Patient admitted with increasing confusion and headaches, CT showed sub-dural bleed. Patient given 4 units FFP and made full recovery.
SAE-Severe	DAW	C2	INR=11-23; renal failure and shock; warfarin sensitivity
	DAW	C2	INR>15; Per rectum (PR) bleed;

Severity	Treatment	Preference	Details
SAE - severe			warfarin may have contributed to death.
	FDW	C2	INR=9.9; history of nausea and PR bleeding (possible GI bleed).
	DAW	C2	INR=6.1, Patient unwell after chemotherapy, severe diarrhoea (melaena), exhaustion, pain in right shoulder, requiring resuscitation on admission; patient died next day.

Key to Tables 5.2.5.8 – 5.2.5.10

0W – no warfarin; FDW – FDWed dose warfarin; DAW – dose adjusted warfarin

U – uncertain; C – certain. U2 – 2 arm study (no warfarin vs FDW);

U3 – 3 arm study (no warfarin vs FDW vs DAW) SAE – serious adverse event

GI – gastrointestinal; UGI – upper gastrointestinal; g/dL – grams per decilitre

5.2.5.8.2 Minor Bleeds

There were 47 minor bleeds reported; 22 nasal, 12 rectal, 3 stoma, 3 haematuria, 3 haematemesis and 4 ‘other’ (wound, conjunctiva, haemorrhoid and knee joint). There was a significant increase in minor bleeding with any warfarin in comparison to no warfarin (p=0.001) but no difference in minor bleeding between the FDW and DAW arms [p=0.53] (Table 5.2.5.11).

Table 5.2.5.11 Toxicity - Minor Bleeds by Treatment Arm

		Warfarin Evaluation p=0.001*		**Dose Evaluation** p=0.53*	
Minor bleeding	Overall (n=1590)	No Warfarin (n=404)	Warfarin (n=408)	FDW (n=471)	DAW (n=473)
Yes	47	1 (0.3%)	13 (3%)	18 (4%)	22 (5%)

*Fisher's Exact Test

5.2.5.8.3 Composite Endpoint – Bleeding plus CRT

In view of the fine balance between the clinical consequences of thrombosis and major bleeding, a combined endpoint of thrombotic events plus major bleeds was assessed. No significant difference between treatment arms was found in either evaluation (Table 5.2.5.12).

Table 5.2.5.12 Composite Endpoint: Catheter-related Thromboses plus Major Bleeding; All Thromboses plus Major Bleeding

	Warfarin Evaluation			Dose Evaluation		
	No Warfarin n=404	**Warfarin n=408**	**Relative Risk (95% CI); p value**	**FDW n=471**	**DAW n=473**	**Relative Risk (95% CI); p value**
Total major bleeding and CRT	25 (6.2%)	31 (7.6%)	1.23 (0.83, 1.52) p=0.51	41 (8.7%)	29 (6.1%)	2.30 (0.72, 7.32) p=0.17
Total major bleeding and all thromboses	39 (9.7%)	37 (9.1%)	0.94 (0.61, 1.44) p=0.87	44(9.3%)	42(8.9%)	0.95 (0.64, 1.42) p=0.89

5.2.5.9 Overall Survival

Mortality data were collected on the follow up CRF3. This consisted of whether the patient had died or not, when the date patient was last seen alive or date of death and the cause of death. At the time of analysis, 532 patients were still alive with a median follow-up of 45 months (range 26 to 88 months). Of the 1058 reported deaths, 921 (87%) were due to cancer; 53 (5%), other causes; and 84 (8%), cause unknown.

For the patients in the warfarin evaluation study, median survival was 19 months no warfarin group (95% CI 14–20) and 17 months for patients receiving warfarin (95% CI 16–22). For the patients in the dose evaluation study, median survival was 21 months (95% CI 19–25) in the DAW group and 21 months in the FDW group (95% CI 17-24). No overall survival advantage was found from taking warfarin compared to no warfarin (HR=0.98, 95%CI: 0.77-1.25, p=0.26) [Figure 5.2.5.1] or found between the two dosing schedules (HR=0.91, 95% CI 0.73-1.14, p=0.53) [Figure 5.2.5.2].

Figure 5.2.5.1 Survival – no warfarin vs warfarin

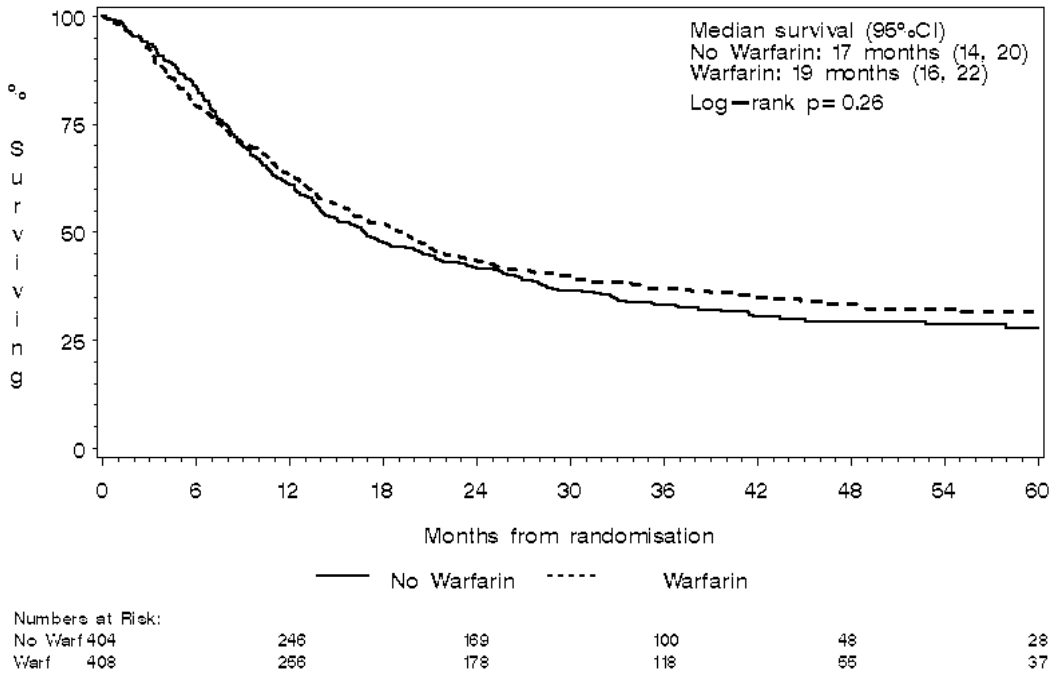
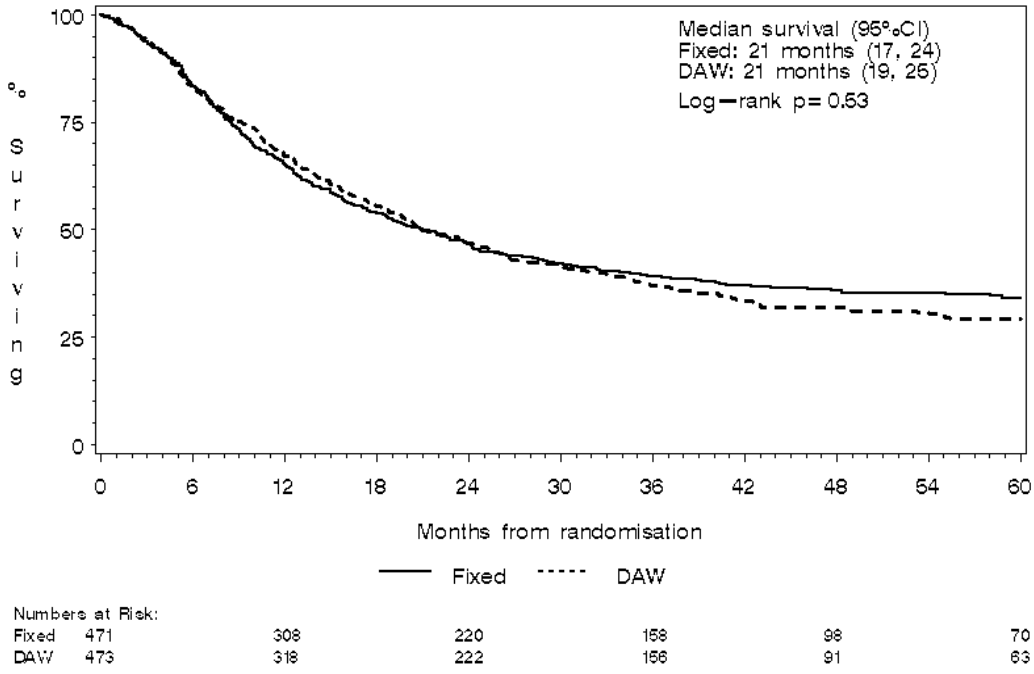


Figure 5.2.5.2 Survival - fixed dose warfarin vs dose adjusted warfarin



5.2.6 INR Values and Maintenance from One Centre

All INR test results were analysed from one centre with five randomising clinicians and three coordinators - 54 patients on FDW and 56 patients on DAW. Trial number, date, INR result and warfarin dose were collected on paper and entered into patient notes from April 2000 until April 2005 at a minimum of 2 weekly timepoints for FDW and weekly for DAW. Timepoints for each test carried out were assigned to individual patients e.g. baseline (pre-trial), timepoint 2 at one week, timepoint 3 at 2 weeks, timepoint 4 at 4 weeks etc. The timepoints were on average at two weekly intervals, apart from the first two timepoints which were weekly intervals; this concurred with the monitoring of warfarin guidelines in section 4.6 of the WARP protocol. One hundred and seven out of 110 patients had a baseline INR recorded (timepoint 1). The number of INR tests that individual patients underwent varied greatly, according to the dose of warfarin assigned and the length of time they were on treatment e.g. 5 patients on FDW and 1 on DAW had one entry only (baseline INR) and one patient on DAW had entries for 2 years and 8 months (94 timepoints). INR determinations were taken on average, 6 times for FDW and 19 times for DAW groups over a median timespan of 1.8 months and 5.1 months respectively. Median INR was 1.10 (IQR 1.04-1.24) for the patients on FDW and 1.69 (IQR 1.43-1.93) for the DAW group. The 'loading dose' for patients assigned to DAW recommended in WARP guidelines was 3mg given for 3 days. In this one centre with 5 named investigators, there was a variation seen in the loading dose for those patients on DAW with just over half of patients being started on 3mg warfarin. The variation is likely down to clinician choice (Table 5.2.6.1).

Table 5.2.6.1 Warfarin Loading Dose for Dose Adjusted Warfarin in One Centre

Warfarin Loading Dose for patients assigned DAW	Number of Patients; n=56	% of Total Number of Patients
1mg	6	11
2mg	10	18
2.5mg	2	4
3mg	29	52
4mg	4	7
4.5mg	2	4
5mg	3	5

5.2.6.1 Fixed Dose Warfarin Analysis

Timepoints 3 (3rd blood test for INR) and 8 (8th blood test for INR) were chosen for further analysis. At timepoint 3, the INR values were likely to have sufficient exposure to warfarin to be stable (for FDW) or to be within target (for DAW); at timepoint 8, there were still sufficient patients having INR tests to carry out a meaningful analysis. For those 18 patients on FDW (1mg daily) with INR results for timepoint 3 (INR range 0.9-3.2) and timepoint 8 (INR range 0.9-1.7), the change in INRs in individual patients between timepoints ranged from -1.5 to 0.4, with median of 0.1. There was only one patient on FDW, identified at both timepoints 3 and 8, who was classified with 'mild' INR toxicity (2<INR<5). Three patients over all timepoints had 'labile' INRs on FDW; and were monitored throughout their study time. The protocol stated that should the INR go above 1.5, then warfarin may be reduced to 0.5mg/day (or 1mg every two days); this was adhered to in the three patients with labile INRs on FDW. The INR was > 1.5 (above the upper specified limit and in the range of the DAW arm) in an

average of 8% of tests for patients on FDW. INR results for the first 8 timepoints for patients on FDW are summarised in Table 5.2.6.2

Table 5.2.6.2 Summary of INR results on patients on Fixed Dose Warfarin in One Cancer Centre for first eight timepoints

Timepoint	No of patients	INR median	INR IQR	INR Range	No of patients over INR of 1.5
1 – pre warfarin baseline	53	1.0	1.0 - 1.1	0.9-1.3	0
2	47	1.1	1.0 - 1.2	0.9-1.8	2 (4%)
3	38	1.1	1.0-1.2	0.9-3.2	1 (3%)
4	34	1.1	1.0-1.3	1.0-3.7	4 (12%)
5	32	1.15	1.1-1.25	1.0-5.4	3 (9%)
6	27	1.2	1.0-1.2	1.0-1.8	3 (11%)
7	20	1.1	1.0-1.35	1.0-3.4	2 (10%)
8	18	1.1	1.1-1.4	0.9-1.7	1 (6%)

5.2.6.2 Dose Adjusted Warfarin Analysis

There were 50 patients who were assigned to DAW who had INR results for timepoint 3 (INR range 1.0-3.8) and timepoint 8 (INR range 1.1-7.6). The change in individual patient INRs between the two timepoints ranged from -1.0 to 6.6, with median of 0.6. At these two timepoints for patients on DAW, there were 17 patients with mild INR toxicity (2<INR<5), and one patient with moderate INR toxicity (5≤INR<8). At any one timepoint, there were <50% of patients within the specified INR range for DAW. At timepoint 4, there were still 56% of patients with an INR< 1.5. At later timepoints (6, 7 and 8), around one third of patients had an INR>2.0. DAW results for the first 8 timepoints are summarised in Table 5.2.6.3.

Table 5.2.6.3 Proportion of Patients on Dose Adjusted Warfarin in INR Target Range over Time

Timepoint	No of patients INR < 1.5	No of patients INR within range (1.5-2.0)	No of patients INR >2.0
1	53 (98%)	1(2%)	0
2	45(85%)	7 (13%)	1 (2%)
3	40 (73%)	10 (18%)	5 (9%)
4	30 (56%)	17 (31%)	7 (12.9%)
5	17 (31%)	25(46%)	12 (22%)
6	14 (26%)	21 (38%)	19 (35%)
7	15 (28%)	21 (39%)	17 (32%)
8	7(14%)	25 (49%)	19 (37%)

5.2.7 Central Venous Catheters

5.2.7.1 Central Venous Catheter Baseline Characteristics

The Central Venous Catheter (CVC) variables are balanced across all arms (Table 5.2.7.1) with the exception of CVC placement side (left or right), in particular in the dose evaluation study in which 89 (36%) of patients on FDW against 65 (27%) on DAW had left-sided placements. Over 40% of the placement side data are unknown. The stratification variables were known from the literature or from clinical experience to be of clinical importance to CRT:

i) out of 1590 patients, 58% of all patients had peripherally inserted central catheters (PICCs); ii) the chemotherapy regimens utilised were an equal balance of high and low sclerosant potential and iii) infusional administration (administered over 24 hours or more) was favoured (82%). From the data submitted, central insertion of catheters was most commonly on the right side of the chest (49% versus 11%) [away from the heart] and the left arm was used more frequently for PICCs, (35% versus 23%) [right handedness is more common]. Most catheters were made of silicone (92%) rather than polyurethane (5%) or other materials and over half the catheters used were Groshong (with Groshong valve – section 3.6.1.1.2); only 4 catheters out of 1590 were implantable ports. Lastly, single lumen catheters were by far, the most commonly used in the WARP trial (78% of patients) [Table 5.2.7.1].

Table 5.2.7.1 Central Venous Catheter Baseline Characteristics by Treatment Arm

		Total n=1590	No Warfarin n=404	Warfarin n=408	FDW n=471	DAW n=473
Length of infusion:	<24 hours	283 (18%)	64 (16%)	68 (17%)	87 (18%)	86 (18%)
	24hours+	1307 (82%)	340 (84%)	340 (83%)	384 (82%)	387 (82%)
Sclerosant:	No	746 (47%)	172 (43%)	169 (41%)	235 (50%)	236 (50%)
	Yes	844 (53%)	232 (57%)	239 (59%)	236 (50%)	237 (50%)
Catheter Placement:	Central	667 (42%)	146 (36%)	150 (37%)	226 (48%)	228 (48%)
	Peripheral	923 (58%)	258 (64%)	258 (63%)	245 (52%)	245 (52%)
CVC Side:	Left	395 (25%)	111 (27%)	105 (26%)	113 (24%)	86 (18%)
	Right	534 (34%)	140 (35%)	156 (38%)	143 (30%)	144 (30%)
	Unknown	661 (42%)	153 (38%)	147 (36%)	215 (46%)	243 (51%)
CVC Side for Central:	Total	667	146	150	226	228
	Left	72 (11%)	17 (12%)	16 (11%)	24 (11%)	21 (9%)
	Right	324 (49%)	74 (51%)	80 (53%)	109 (48%)	99 (43%)
	Not Known	271 (41%)	55 (38%)	54 (36%)	93 (41%)	108 (47%)
CVC Side for Peripheral:	Total	923	258	258	245	245
	Left	323 (35%)	94 (36%)	89 (35%)	89 (36%)	65 (27%)
	Right	210 (23%)	66 (26%)	76 (29%)	34 (14%)	45 (18%)
	Not Known	390 (42%)	98 (38%)	93 (36%)	122 (50%)	135 (55%)
CVC Lumen:	Single	1242 (78%)	353 (87%)	332 (81%)	346 (73%)	346 (73%)
	Double	323 (20%)	49 (12%)	66 (16%)	117 (25%)	116 (25%)

		Total n=1590	No Warfarin n=404	Warfarin n=408	FDW n=471	DAW n=473
CVC Lumen continued	Triple	5 (<1%)	0 (0%)	3 (<1%)	1 (<1%)	4 (<1%)
	Not Known	20 (1%)	2 (<1%)	7 (2%)	7 (1%)	7 (1%)
CVC Material:	Silicone	1462 (92%)	368 (91%)	357 (88%)	436 (93%)	441 (93%)
	Polyurethane	79 (5%)	28 (7%)	35 (9%)	19 (4%)	13 (3%)
	Other	17 (1%)	3 (<1%)	1 (<1%)	6 (1%)	8 (2%)
	Not Known	32 (2%)	5 (1%)	15 (4%)	10 (2%)	11 (2%)
CVC Make:	BARD	935 (59%)	223 (55%)	207 (51%)	295 (63%)	287 (61%)
	Vygon	439 (28%)	136 (34%)	133 (33%)	117 (25%)	121 (26%)
	Kimal	8 (<1%)	1 (<1%)	5 (1%)	2 (<1%)	5 (1%)
	Other	171 (11%)	35 (9%)	48 (12%)	46 (10%)	48 (10%)
	Not Known	37 (2%)	9 (2%)	15 (4%)	11 (2%)	12 (3%)
CVC Type:	Groshong	888 (56%)	217 (54%)	201 (49%)	267 (57%)	275 (58%)
	Hickman	220 (14%)	59 (15%)	59 (14%)	66 (14%)	69 (15%)
	Lifecath	195 (12%)	66 (16%)	63 (15%)	51 (11%)	48 (10%)
	PICC	51 (3%)	11 (3%)	16 (4%)	13 (3%)	14 (3%)
	Leader Cuff	21 (1%)	9 (2%)	10 (2%)	5 (1%)	3 (<1%)
	Bardport	2 (<1%)	0 (0%)	0 (0%)	1 (<1%)	1 (<1%)
	Portocath	2 (<1%)	0 (0%)	0 (0%)	0 (0%)	2 (<1%)
	Other	189 (12%)	39 (10%)	52 (13%)	60 (13%)	54 (11%)
	Not Known	22 (1%)	3 (<1%)	7 (2%)	8 (2%)	7 (1%)

5.2.7.2 Catheter-specific risk factors for thrombosis:

A univariate analysis identified the number of CVC lumens as a potential risk factor for CRT; patients with catheters with double or triple lumens were more likely to suffer a thrombosis than those with a single-lumen CVC (p=0.03). CVC material appeared to have some importance with silicone CVCs less likely to suffer a CVC-related thrombosis than those with CVCs made of polyurethane or other materials (p=0.05) [Table 5.2.7.2]. No other factor: catheter placement (central vs peripheral), treatment length (<24 vs ≥24 hours), sclerosant potential of chemotherapy (high vs low), type of CVC (valved vs non-valved) or CVC size (<4 and ≥4) was found to be significant at the p=0.1 level of significance. A multivariate logistic regression analysis for CRT was not undertaken due to the small number of events.

Table 5.2.7.2 Univariate Analysis of Catheter Risk Factors for Thrombosis

Risk Factor	**Odds Ratio (OR)**	**95% Confidence Interval for OR**	**p-value**
CVC lumen: Single vs double or more	1.73	1.06 – 2.82	0.03
CVC material: Silicone vs polyurethane and other	2.11	1.02-4.39	0.05

5.2.7.3 CVC Patency

CVCs were patent for a median time of 13.9 weeks for all patients. There was no difference in the median duration of catheter patency in the warfarin vs no warfarin (13.1 vs 13.4 weeks, p=0.55) and the DAW vs FDW (13.3 vs 14.7 weeks, p=0.27) studies.

5.2.7.4 Catheter Complications

Of the 1590 patients in the trial, details were not available on CVC complications for 30 patients because CRF2s were not returned, including 4 patients who withdrew from the trial early because CVC was not inserted. In a further 11 patients, the CRF2s were available but no CVC data were recorded and thus in this case, the absence of any CVC complication was regarded as missing. In 1212 patients, details on CVC insertion and removal dates were included but no CVC complication was recorded and this absence of information is assumed to imply that no complication was experienced. In total, 411 catheter complications were reported in 327 different patients. Over 40% of all complications were due to infection which occured in 9.1% of all patients (Table 5.2.7.3).

Most patients who experienced a CVC complication only experienced one but one patient experienced as many as 6 different complications with a mean number of complications per patient of 1.4. The per-patient complication rate is the number of patients who experienced at least one catheter complication out of all patients randomised and is calculated to be 327/1590 x100 (20.6%).

Table 5.2.7.3 Central Venous Catheter Complication Type

Complication	Compli-cations (n = 411)	% of Total Compli-cations	Patients (n=327)	% of total patients n=1590
Infection	171	41.6	144	9.1
Suspected Fibrin Sheath / Blocked Catheter	46	11.2	32	2.0
Inflammation / Erythema / Rash / Phlebitis	44	10.7	37	2.3
Damaged or Kinked / Line Leaking (not exit site)	43	10.5	39	2.5
Misplaced or Migrated Catheter and Pneumothorax	38	9.2	29	1.8
Line fell or pulled out	31	7.5	23	1.4
Exit site leaking / bleeding	12	2.9	7	0.4
Suspected Catheter Thrombosis	9	2.7	7	0.4
Other	6	1.0	3	0.2
Pain	11	2.7	6	0.4
Total	**411**	**100**	**327**	**20.6**

5.2.7.4.1 Infection

144 patients (9.1%) were categorised as having one or more catheter-related infections. Infection as the first complication caused a further catheter complication in 14.6% (21/144) patients. Eight patients who had an infection as a catheter complication, also had a CRT - i.e. 9.4% (8/85) of all patients who had a primary event also had a catheter infection and 5.6% (8/144) of all patients with infection as a catheter complication went on to have a CRT. Two patients with

infection as a catheter complication also developed a non-catheter-related thrombosis.

5.2.7.5 Flushing, Fibrinolytic Locks and Positive Pressure Devices

As an anticoagulant, heparin flushing is a potential confounding factor, not stratified for, but is required at very low concentrations to flush non-valved catheters. A fibrinolytic solution (e.g. urokinase) may also be used as a 'lock' to try and prevent CRT. Positive pressure devices may also be used to minimise occlusion (section 3.6.1.1.2). Around one third of patients had their catheters flushed with heparin and 17% of patients had planned use of catheter positive pressure devices or fibrinolytic locks. Table 5.2.7.4 shows the heparin flushing and use of positive pressure devices and fibrinolytic locks by treatment.

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Table 5.2.7.4 Flushing of Catheters by Treatment

			Warfarin Evaluation		Dose Evaluation	
		Overall n=1590	No Warfarin n=404	Warfarin n=408	FDW n=471	DAW n=473
Flushing of catheter:	No	1059 (67%)	253 (63%)	252 (62%)	331 (70%)	326 (69%)
	Yes	513 (32%)	148 (37%)	149 (37%)	133 (28%)	143 (30%)
	Heparin & Saline	438 (28%)	124 (31%)	118(29%)	121 (26%)	127 (27%)
	Sodium/Saline	*24 (2%)*	*14 (3%)*	*9 (2%)*	*2 (<1%)*	*0 (0%)*
	Clexane	3 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)
	Unspecified	48 (3%)	9 (2%)	20 (5%)	9 (2%)	15 (3%)
	Not Known	18 (1%)	3 (<1%)	7 (2%)	7 (1%)	4 (<1%)
Planned use of fibrinolytic locks or positive pressure devices:	No	1062 (67%)	269 (67%)	269 (66%)	309 (66%)	308 (65%)
	Yes	267 (17%)	84 (21%)	82 (20%)	60 (13%)	61 (13%)
	Not Known	261 (16%)	51 (13%)	57 (14%)	102 (22%)	104 (22%)

5.2.8 Health Resource Usage

Data entry for the number of inpatient stays, outpatient attendances and GP attendances was extremely poor. These data were missing on 66% of CRF2s and deemed unreliable and therefore an economic analysis was not undertaken. The coordinators from the trial centres noted that it was time consuming to find these data with any accuracy, unless the patients had had a SAE. The results of the two studies above signified that a detailed health economic analysis was not necessary. This was pre-specified in the protocol for the conditions that resulted:

i) there was no advantage from taking any warfarin in comparison to no warfarin in thromboprophylaxis and increased major bleeding was seen in the warfarin group. On balance, warfarin is therefore harmful and is not recommended. Cancer patients with CVCs will be safer without warfarin and will be able to save time on the extra hospital and GP visits required for INR testing (a mean of 6 visits for those on FDW in one trial centre during warfarin treatment). Patients were hospitalised for the management of major bleeds thought to be caused by warfarin; 28 patients had a major bleed documented (Tables 5.2.5.9 and 5.2.5.10). Hospitalisation is a key element of NHS resource and this resource may be saved by patients not taking warfarin.

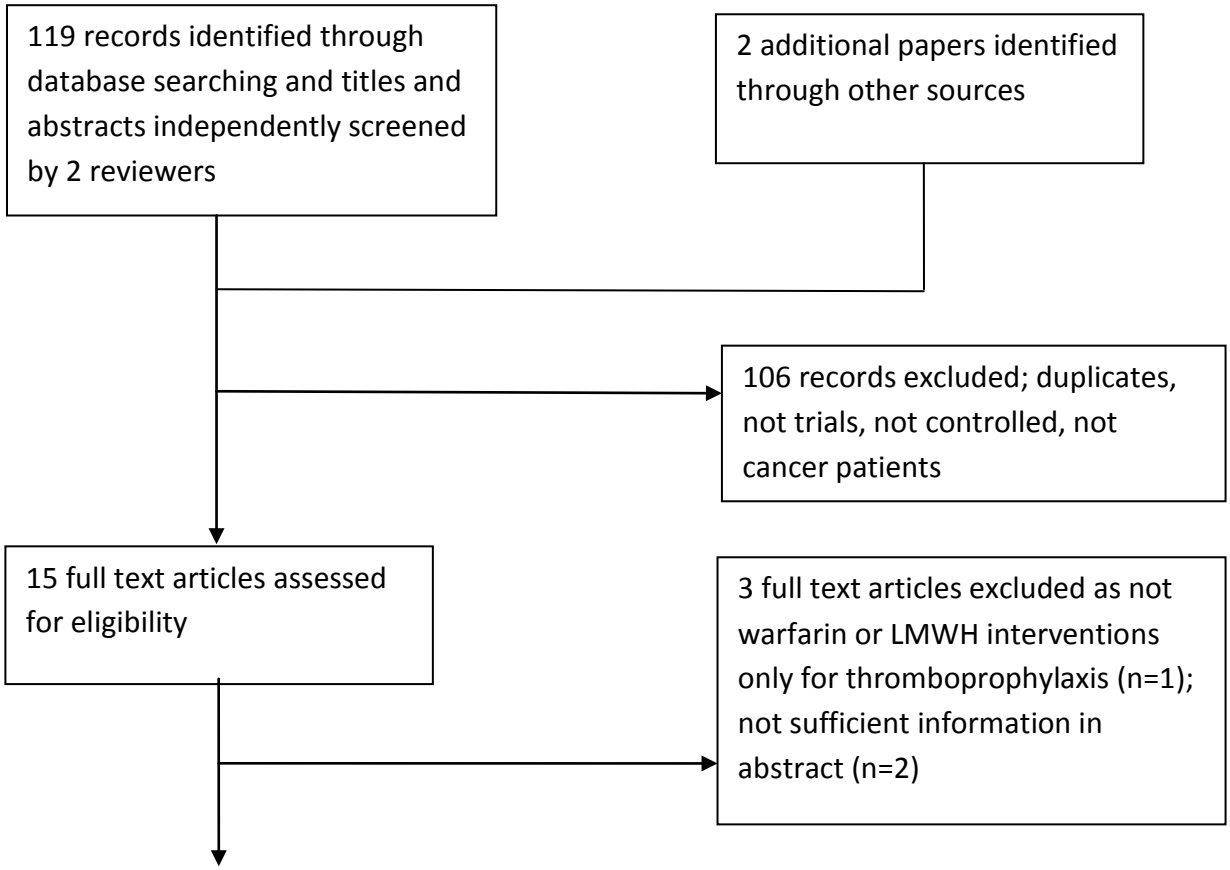
ii) DAW was superior to FDW but at a cost of more bleeding. On balance, DAW is harmful. The extra visits required for INR testing (a mean of 19 visits for patients on DAW in one centre during warfarin treatment) will be saved and as above, the health resource consequences of the management of the excess bleeding seen with DAW, may be saved.

5.3 *Meta-analyses*

5.3.1 Thromboprophylaxis for Cancer Patients having Chemotherapy

5.3.1.1 Flow of Information through the Meta-Analysis

Figure 5.3.1.1 Thromboprophylaxis Meta-analysis Study Selection



No of studies included in quantitative synthesis **n=12**

Primary Thromboprophylaxis:

Patients with CVCs – warfarin vs no warfarin,	n=5	Figure 5.3.1.1
Patients on Chemotherapy – warfarin vs no warfarin	n=1	(not in meta-analysis)
Patients with CVCs – LMWH vs control	n=4	Figure 5.3.1.3
Patients on Chemotherapy – LMWH vs control	n=2	Figure 5.3.1.4

5.3.1.2 Patients with Central Venous Catheter - Warfarin vs No Warfarin

Of the 121 citations identified in the search, five RCTs were included with 1356 patients with CVCs. The pooled data provide no clear evidence of benefit from warfarin thromboprophylaxis (odds ratio [OR] 0.7, 95%CI 0.5-1.1; p=0.1) in cancer patients with central venous catheters. These five trials are discussed in detail in section 6.2.6.1, 'Contextualising WARP'. The two studies in which patients were screened for VTE and also underwent venography when symptomatic [denoted as 'asymptomatic' in the figures] (Park K et al, 1999; Bern et al, 1990) did contribute to a VTE rate reduction of 70% (p=0.001) whereas warfarin confers no advantage in the trials in which only symptomatic VTE is measured (10% increase in risk of VTE; p=0.7) [Figure 5.3.1.2]. It is important to note that there is a large difference in event rates in the control arms when comparing thrombosis rates in the asymptomatic plus symptomatic group (27/102, 26%) with only symptomatic VTE subjects (34/572, 6.5%). For trials of cancer patients with CVCs, the addition of the WARP trial reduces the overall effect of warfarin such that statistical significance pre-WARP (OR 0.6; 95%CI 0.3,1.0; p=0.05), is lost (OR=0.7; 95%CI: 0.5,1.1; p=0.1) [Figure 5.3.1.3]. There was some heterogeneity seen across the five trials, p=0.06, and none between pre-WARP and WARP subgroups, p=0.2.

5.3.1.3 All patients; warfarin versus no warfarin

There was only one study identified (Levine et al, 1994) in thromboprophylaxis with warfarin in ambulatory patients and therefore no meta-analysis was carried out.. This was the first study of low dose warfarin in women with metastatic breast cancer receiving chemotherapy in which 311 women were given either low dose warfarin (1mg for 6 weeks followed by adjusted dose to a target INR 0f 1.5) or placebo, whilst on chemotherapy. There was an 85% risk reduction (p = 0.031) with a thrombosis rate of 4.4% in the placebo arm versus 1% in the warfarin arm, with no increase in bleeding.

5.3.1.4 Patients with Central Venous Catheters - Low molecular weight heparin vs control

From 121 records identified in the search, four RCTs were identified in this category. Based on the pooled estimates, LMWH therapy was not associated with a significant reduction in VTE (OR 0.7; 95%CI 0.5, 1.1; p=0.2) [Figure 5.3.1.4]. However, the test for heterogeneity was significant between the trials (p=0.03). Mismetti et al also reported on a small pilot study of 59 cancer patients randomised to LMWH (nadroparin) versus warfarin in which there was found to be no difference in VTE between the two groups [p=0.48] (Mismetti et al, 2003). This paper was rejected from the meta-analysis

5.3.1.5 All patients – Low Molecular weight heparin vs control

Primary Prophylaxis: There have been four primary prophylaxis studies in cancer patients, using LMWHs but only one fully published article. Firstly, Agnelli et al randomly assigned 1150 ambulatory patients with metastatic or locally advanced solid tumours receiving chemotherapy to nadroparin 3800IU anti Xa or placebo with a composite endpoint of symptomatic venous and arterial thrombotic events (Agnelli et al, 2009). Nadroparin reduced the incidence of thrombotic events in comparison to placebo (2% vs 3.9%; p=0.02). Around 40% of the patients in this study had a central venous catheter. Secondly, a higher dose of the same LMWH, nadroparin (5000 anti Xa units), was compared with placebo in 389 patients with newly diagnosed glioma in a study, still in abstract form, which showed objectively confirmed VTE during the first 6 months: 9 on LMWH and 12 on placebo (11% and 17% respectively; HR=0.7, 95% CI: 0.37-1.5, p=0.3). Over the 12 months there were 5 (5.1%) major bleeds with LMWH and 1 (1.2%) with placebo (HR=4.0, 95%CI: 0.5-34, p=0.2) (Perry et al, 2007). The authors acknowledged that the study was underpowered. The pooling of these two studies showed a significant benefit for thromboprophylaxis from LMWH [OR 0.5; 95%CI: 0.3, 0.9; p=0.03] (Figure 5.3.1.5). There was no heterogeneity between the two trials (p=0.6). Lastly, in the TOPIC (Thromboembolism Prevention in Cancer) I trial, 353 patients with metastatic breast cancer were randomised to 6 months of certoparin 3000 anti-Factor Xa units or placebo. Patients were screened for DVT every 4 weeks. VTE rate was 4% in each treatment group. In TOPIC II, 547 patients with stage III or IV non-small-cell lung cancer were randomised as TOPIC I patients.

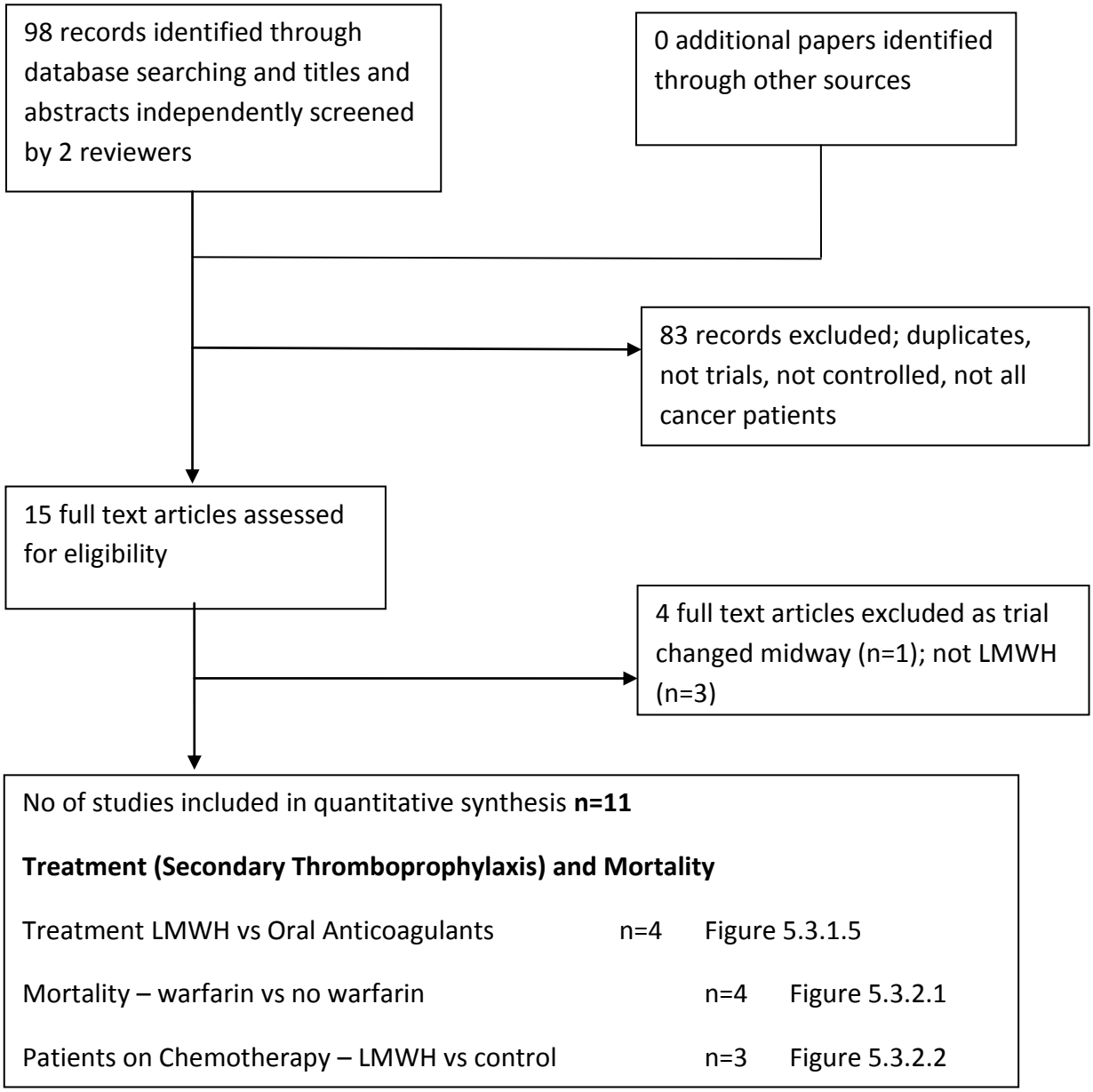
The VTE rate was 4.5% in the LMWH arm and 8.3% in placebo patients (p=0.7). In a post-hoc subgroup analysis involving stage IV lung cancer patients, there was a statistically significant reduction in VTE with the LMWH (10.1% vs 3.5%; p=0.03). The TOPIC study results are published in one abstract (Haas et al, 2005) and are not included in the meta-analysis as there are no data to support how many patients are in each arm. Assuming equal numbers in each arm (450 vs 450), the pooled analysis of the four trials with a total of 2,252 patients, reaches greater significance in favour of LMWH (OR 0.6, 95%CI: 0.4, 0.9; p=0.008).

Secondary Prophylaxis: From the 98 records retrieved through database searching for treatment of VTE and mortality in patients receiving chemotherapy, four studies tested LMWH (long-term) versus short-term LMWHs, followed by long-term warfarin, (with one exception: Hull et al used IV unfractionated heparin as the short term heparin before warfarin) for the treatment of VTE (Deitcher et al, 2006; Hull et al, 2006; Lee et al, 2003; Meyer et al, 2002). LMWH provided a statistically significant reduction in VTE (OR 0.5; 95%CI: 0.3,0.7; p=0.001) [Figure 5.3.1.6]. There was no heterogeneity between the four trials (p=1.0).

5.3.2 Anticoagulant Effect on Mortality in Patients having chemotherapy

5.3.2.1 Flow of Information through the Meta-analysis

Figure 5.3.2.1 Treatment and Mortality Meta-analysis Study Selection



Flow Charts, Figures 5.3.1.1 and 5.3.2.1, are adapted from Liberati et al, 2009 'PRISMA', (Liberati et al, 2009)

5.3.2.2 Warfarin vs No Warfarin

From the 98 records retrieved through database searching for treatment of VTE and mortality in patients receiving chemotherapy, seven trials met the inclusion criteria and were included in the meta-analysis with a total of 2,453 patients including three trials in cancer patients with CVCs with published mortality data. The effect of warfarin on reduction in mortality was statistically significant (OR 0.9; 95%CI 0.8, 1.0; p=0.03) [Figure 5.3.2.2].

5.3.2.3 Low Molecular Weight Heparin vs Control

Three trials met the inclusion criteria for this meta-analysis. A trial by Sideras et al (Sideras et al, 2006) in 138 patients with advanced cancer initially compared a LMWH vs placebo. The placebo arm was eliminated part way through because of low accrual and therefore was deemed unreliable and the trial was excluded from the meta-analysis by the reviewers. Low molecular weight heparin is associated with a statistically significant survival benefit (OR 0.8; 95%CI 0.7, 0.9; p=0.001) [Figure 5.3.2.3].

5.3.2.4 Summary of the Results of the Meta-analyses

A summary of the results of the meta-analyses is outlined in Table 5.3.2.1.

An overall test for trend over the trials (carried out in the analyses with no subgroups) demonstrated that the results have significantly changed over time in the thromboprophylaxis of CRT in cancer patients using LMWH (p=0.02) [Figure 4.3.1.3]. There was a significant trend between trials in the pre-WARP thromboprophylaxis trials of cancer patients with CVCs p=0.02 [Figure 4.3.1.2]. No other significant changes over time were found in the meta-analyses.

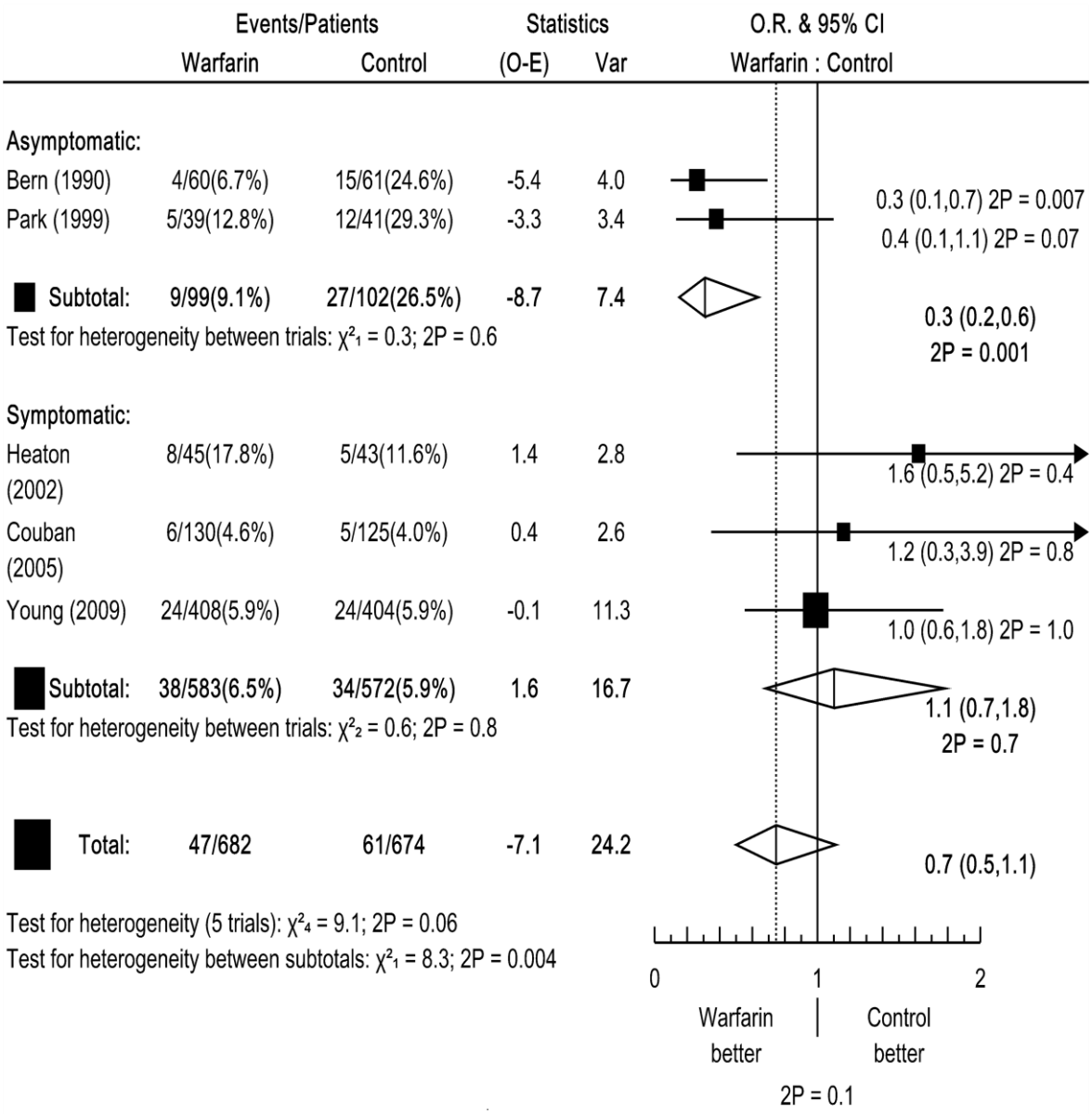
Table 5.3.2.1Summary of Meta-analyses Results

Outcome	***Warfarin vs no Warfarin***	***LMWH vs no LMWH***	***Warfarin vs LMWH***	**Figure Reference**
Primary Prophylaxis CRT events	OR: 0.7; CI 0.5,1.1 ***p=0.1*** TTT: p=0.02 (4.3.1.2)	OR: 0.7; CI 0.5,1.1 ***p=0.2*** *OTT: p=0.02*		5.3.1.2 and 5.3.1.3 - *warfarin* 5.3.1.4 - *LMWH*
Primary Prophylaxis VTE events	-	OR: 0.5; CI 0.3, 0.9; ***p=0.03*** *OTT: p=0.6*	-	5.3.1.5 - *LMWH*
Secondary Prophylaxis			OR 0.4; CI 0.3,0.6 ***p<0.001*** *OTT: p=0.6*	5.3.1.6 – *LMWH* vs warfarin
Mortality	OR: 0.9; CI 0.8,1.0; ***p=0.03***	OR: 0.8, CI 0.7,0.9 ***p=0.001*** *OTT: 0.4*		5.3.2.2 – *warfarin* 5.3.2.3 - *LMWH*

OR – odds ratio; CI confidence interval; CRT – catheter-related thrombosis; LMWH – low molecular weight heparin;

Overall test for trend (OTT); Test for trend between trials (TTT)

Figure 5.3.1.2 Meta-analysis of Thromboprophylaxis in Cancer Patients with Central Venous Catheters: Warfarin versus Control; Symptomatic and Asymptomatic* plus Symptomatic Event Subgroups



*asymptomatic + symptomatic events are denoted as ‘asymptomatic’

Figure 5.3.1.3 Meta-analysis of Thromboprophylaxis in Cancer Patients with Central Venous Catheters: Warfarin versus Control; Pre and Post WARP Subgroups

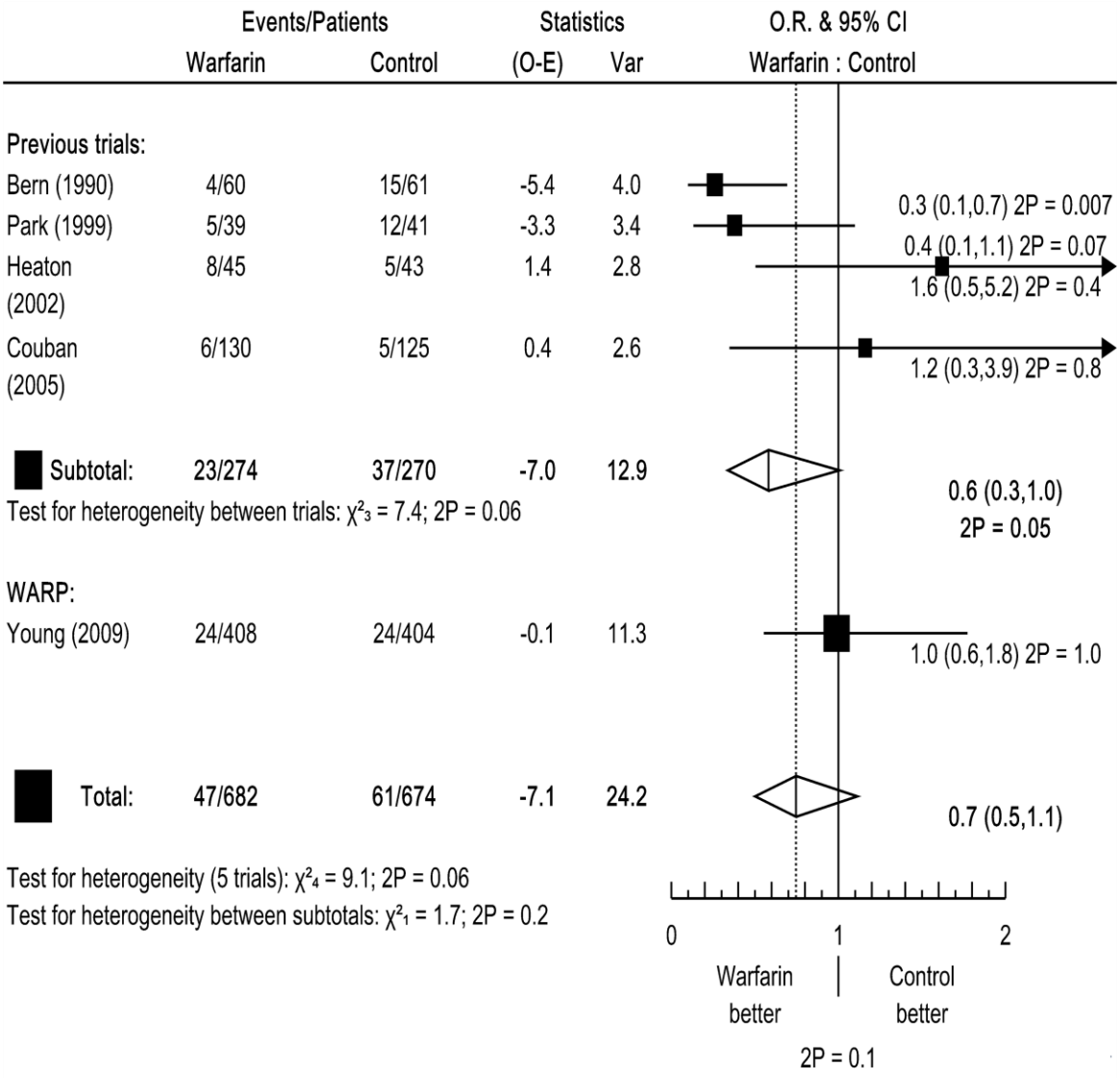


Figure 5.3.1.4 Meta-analysis of Thromboprophylaxis in Cancer Patients with Central Venous Catheters: Low Molecular Weight Heparin versus Control

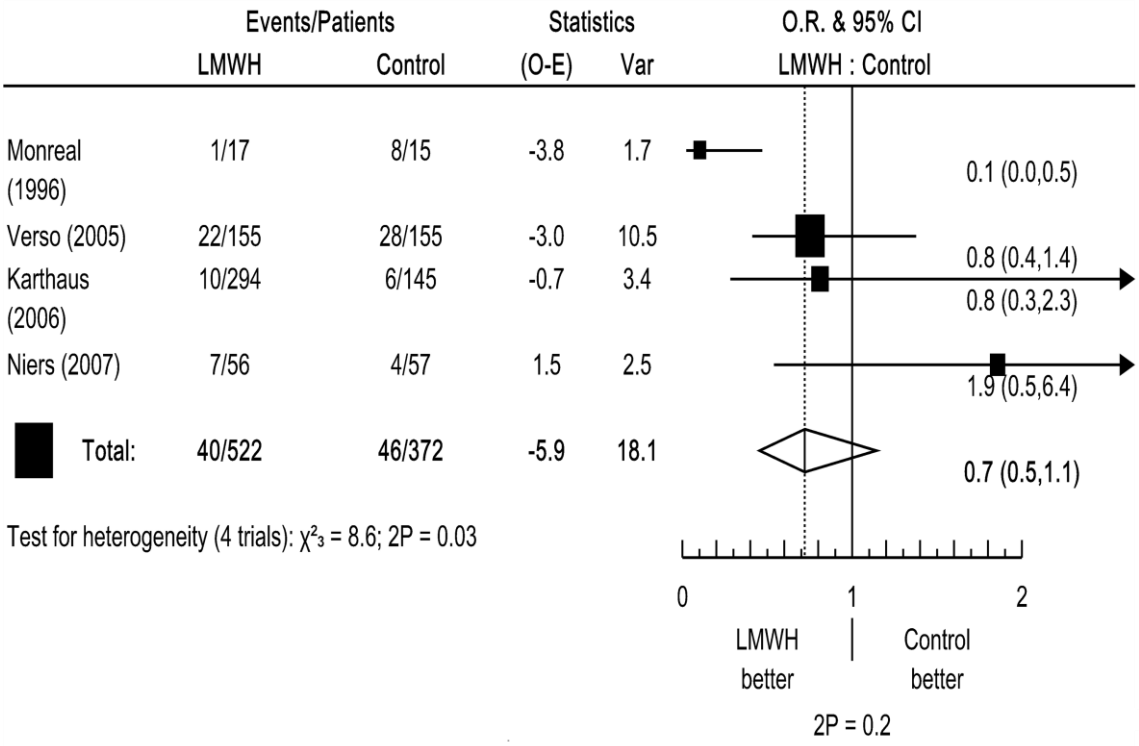


Figure 5.3.1.5 Meta-analysis of Primary Thromboprophylaxis in Cancer Patients receiving Chemotherapy: Low Molecular Weight Heparin versus Control

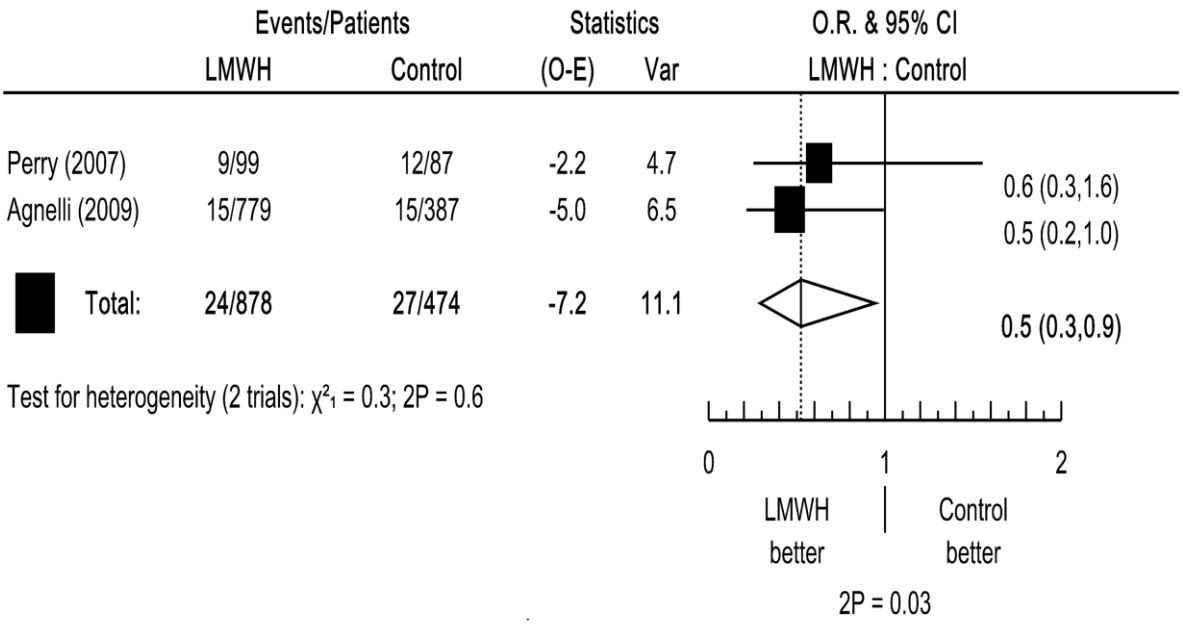
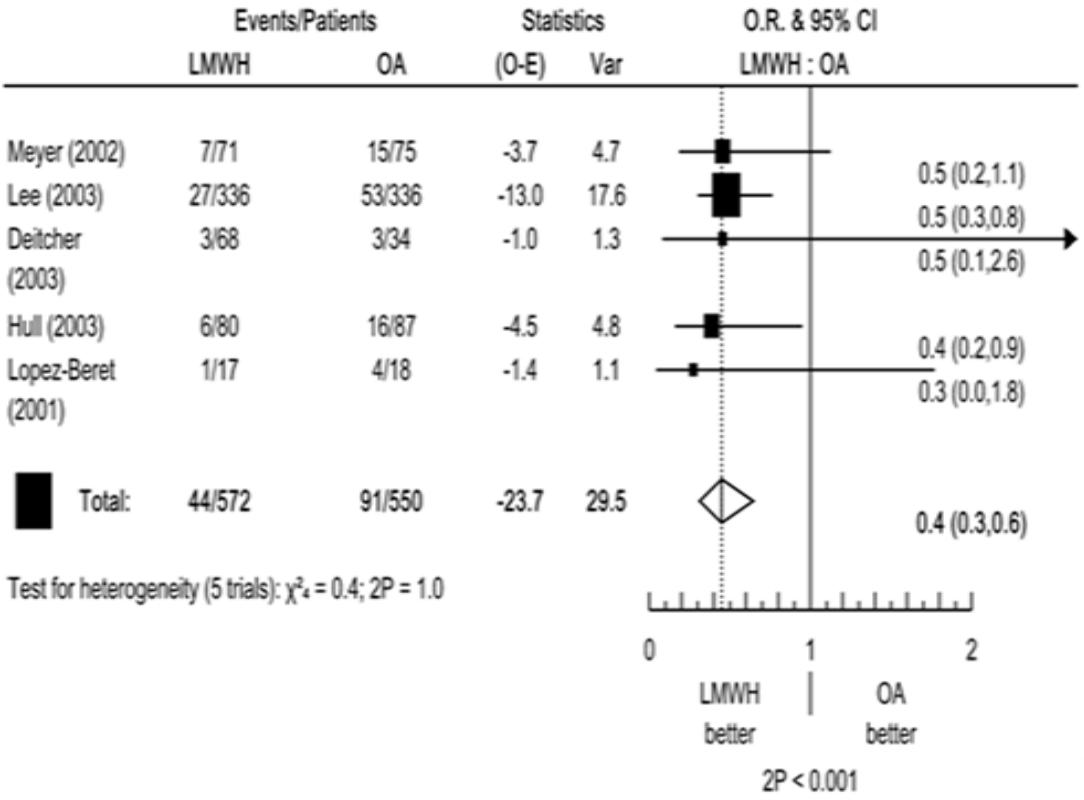


Figure 5.3.1.6 Meta-analysis of Secondary Thromboprophylaxis in Cancer Patients: Low Molecular Weight Heparin versus short-term Low Molecular Weight Heparin then Oral Anticoagulant



Events are subsequent VTE.

Figure 5.3.2.2 Meta-analysis of Mortality in Cancer Patients receiving Chemotherapy: Warfarin versus No Warfarin

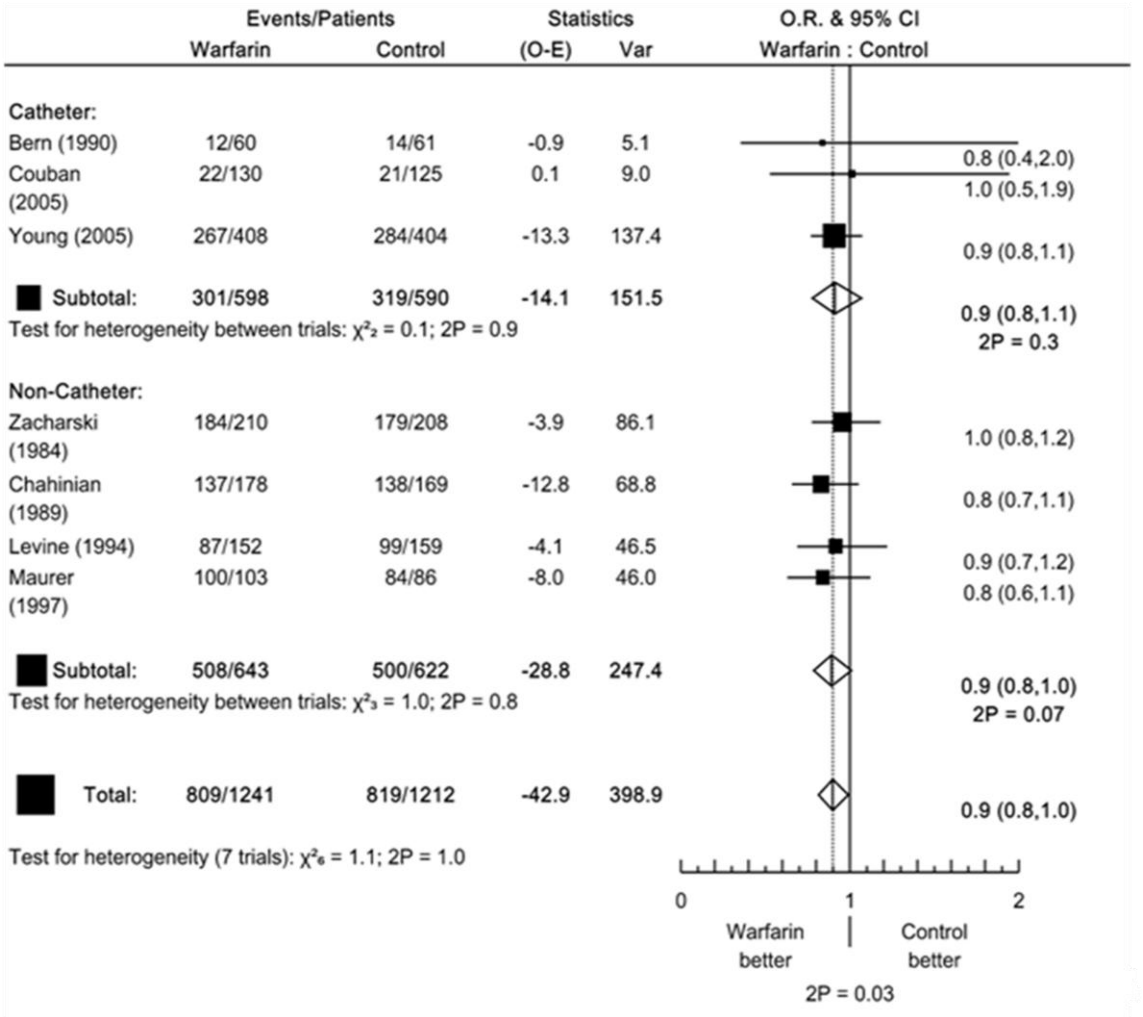
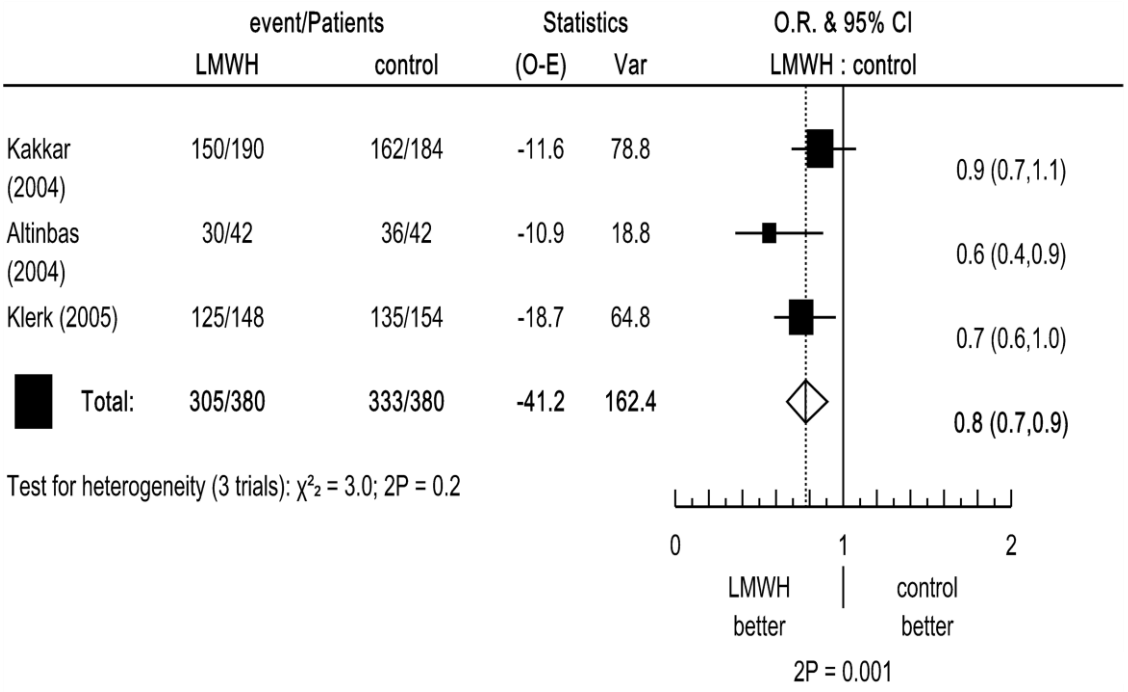


Figure 5.3.2.3 Meta-analysis of Mortality in Cancer Patients receiving Chemotherapy: Low Molecular Weight Heparin versus Control



6. Discussion

This thesis focuses on the prophylaxis of thrombosis in cancer patients receiving chemotherapy via central venous catheters (CVCs) and includes the largest study yet completed defining the role of warfarin as a thromboprophylactic for this specific group of patients. The WARP trial adds to the new evidence published over the last decade on this topic and has the potential to change international clinical practice. The three components of the thesis are now discussed in the context of contemporary evidence and practice.

6.1 *National Survey of Anticoagulant Prescribing Practice*

This was the first survey undertaken in the UK with respect to thromboprophylactic practice for cancer patients with CVCs. The survey provided invaluable data which were used to frame the questions to be answered by WARP, namely:

- Does warfarin have any role to play in the prevention of CVC thrombosis? This question was primarily aimed at clinicians in equipoise.
- Is dose-adjusted warfarin superior to fixed dose warfarin (1mg/day)? This question was looking towards the clinical community who have been sufficiently convinced by pre-existing trial data to routinely prescribe warfarin.

The national survey strongly influenced the design of the WARP study and identified a network of interested clinicians with around 50% of the survey clinicians actually participating in WARP. Twenty percent (19/93) of respondents who completed the

open comments box (93/213 [44%]) stated that they would not randomise to a 'no warfarin' arm, four commented that this was "unethical" and two felt "uncomfortable". On the back of the substantial interest in the trial and these comments, the steering committee adapted the design of the trial, based on the principle of uncertainty. The 1999 survey indicated that 62% of clinicians used warfarin routinely for thromboprophylaxis (this could be termed presumptive 'certainty') and 14.5% (19/131) of these clinicians voluntarily stated that they would not randomise to a 'no warfarin' arm. In practice in the WARP trial, fewer clinicians chose the certain preference: thirty five percent of clinicians were consistently certain of the benefit of warfarin whilst 24% chose either certain and uncertain.

In the survey, a comparison of estimated thrombosis rates, split by clinicians using warfarin or not, revealed a significantly higher thrombosis rate at the centres where the clinicians prescribed warfarin. This is not a randomised comparison and must be open to question because of selection and reporting biases. This small survey was successful in its objectives of identifying the current clinical practice in 1999 for thromboprophylaxis in patients with CVCs, ascertaining if catheter-related thrombosis (CRT) was an important clinical problem and garnering interest in participation in a national clinical trial. However, the open question on CVC types generated ambiguity in the meaning of 'type' with answers including manufacturers, trade names used by the companies and slang. This warranted careful consideration of the categorisation of catheter type for the WARP trial and highlighted the importance for clinicians in using generic terms for catheters to minimise confusion. Generic categories will be utilised for a future national survey,

aiming at assessing the uptake and implementation of the NICE thromboprophylaxis guidelines (National Institute of Health and Clinical Excellence, 2010).

Since the pre-WARP national survey was completed, there have been two other surveys on thrombosis and malignancy, one in the UK and the other, an international on-line survey. These offer some indication of clinical opinion on CVCs and thrombosis. A small UK survey was reported when WARP was recruiting (Kirwan et al, 2003). The survey was sent by post to 166 oncologists in the North of England with a 64% response rate. From the 106 acceptably completed responses, more than a quarter of oncologists did not recognise the thrombogenic effects of treatments for cancer, and thromboprophylaxis was rarely used in patients undergoing treatment for cancer. Nine out of the 10 oncologists who used prophylaxis in chemotherapy noted CVCs as a thrombotic risk factor. Only three oncologists mentioned that they were, 'randomising patients with CVCs to different warfarin regimens' (i.e. participating in the WARP trial). Oncologists estimated a surprisingly low percentage of their patients were receiving prophylaxis, bearing in mind that half of respondents mentioned previous VTE and immobility as indications for routine prophylaxis. The response from a third of oncologists that VTE does not pose a risk was reported as being biased by 'low risk' specialties such as paediatrics. However, although the thrombotic risk for children with cancer is lower than adults, 60% of childhood deep vein thromboses (DVTs) are associated with CVCs (Massicotte and Mitchell, 2006) and paediatrics should not perhaps be classed as low thrombotic risk speciality. The North of England survey was a small survey without specific questions on CVCs but nevertheless demonstrates a lack of awareness of the thrombogenic effects of the treatments for cancer at this time.

The international survey, FRONTLINE (Fundamental Research in Oncology and Thrombosis), was designed in part to evaluate thromboprophylaxis regimens currently practiced by clinicians worldwide for both surgical and medical patients with cancer (Kakkar et al, 2003). Over 3800 responses were received and demonstrated that patients undergoing surgery for their malignancy commonly receive thromboprophylaxis but medical patients with cancer do not, with the exception of patients with a central venous catheter in place. The majority of respondents (80%) perceived an increased risk for venous thromboembolism (VTE) in patients with indwelling CVCs. Regionally, there were substantial differences in the perception of risk. In North America, most clinicians thought that up to 30% of their patients with CVCs would develop VTE without thromboprophylaxis. In Europe, and the rest of the world, the perceived risk was lower (Figure 6.1.1). Thromboprophylaxis was generally considered normal practice for cancer patients with CVCs, particularly in North America and Eastern Europe ($p<0.05$), compared with other geographical regions (Figure 6.1.2). However, 10-20% of clinicians do not employ any thromboprophylaxis for their patients with CVCs. LMWH was the antithrombotic of choice for patients with CVCs, except in North America, where low dose oral anticoagulation was the most common means employed (Table 6.1.1). In Eastern Europe, a notable proportion of clinicians gave aspirin to reduce the risk of CRT. Another regional difference noted was that in North America, compared with Europe and the rest of the world, there was much less reliance on heparin flushes to prevent VTE. In summary, in the section of the FRONTLINE survey relevant to CVCs, there was a perceived association between CVCs and the risk of VTE with regional variations in the perception of that risk (North America suggesting a higher risk than the rest of the world). The prophylactic regimens for patients with CVCs

vary, with North American clinicians using low dose oral anticoagulants rather than LMWH (presumably because of higher cost), as used by Western Europe and the rest of the world.

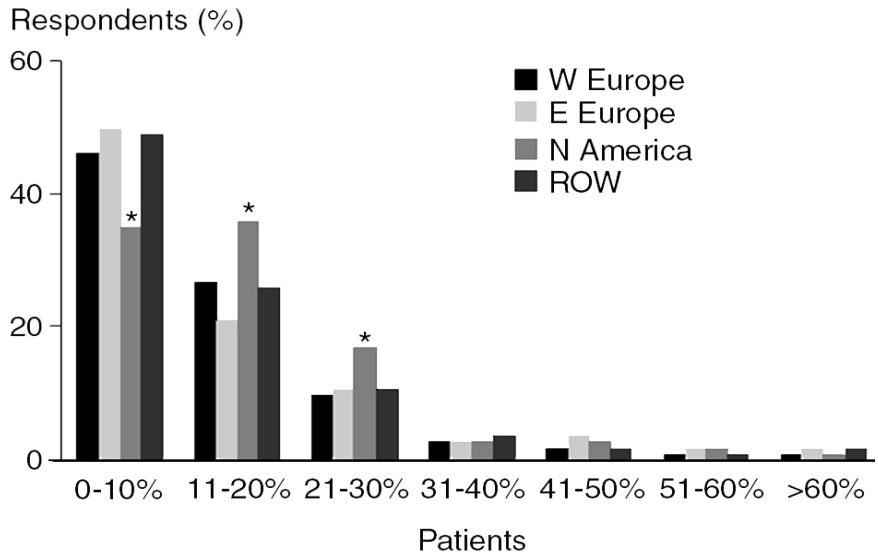
The North of England postal survey response rate was more than double that of the pre-WARP survey, perhaps because it was confined to one region in the UK where clinicians knew of the research team or their institution. It is impossible to gauge a response rate for on-line surveys such as FRONTLINE but the number of overall responses (n=3899) suggests a sufficient sample size for analysis. National (UK) guidelines on prophylaxis for VTE during cancer treatment were requested in the publication from the North of England survey in 2003 and generic guidelines with a specific section on cancer patients, have only recently been published in 2010 (National Institute of Health and Clinical Excellence, 2010). Like the pre-WARP survey, the subsequent two surveys on thrombosis and cancer demonstrated a large variation in thromboprophylactic practice, a lack of standards and guidelines in this area and the need for more research into thrombosis and malignancy, including thromboprophylaxis with CVCs.

Table 6.1.1 Central Venous Catheter and Thrombosis Data from the FRONTLINE survey

Treatment of patients with CVCs for thromboprophylaxis			Thromboprophylaxis regimen used in patients with CVCs	
	Use of Thrombo-prophylaxis	Removal of Line when thrombosis	LMWH	52%
Never	19%	4%	Fixed low dose OA	28%
Rarely	26%	13%	Adjusted dose OA	14%
Sometimes	22%	31%	Aspirin	14%
Usually	31%	46%	s.c. UFH	13%
Never	2%	6%	Heparin Flushes	27%

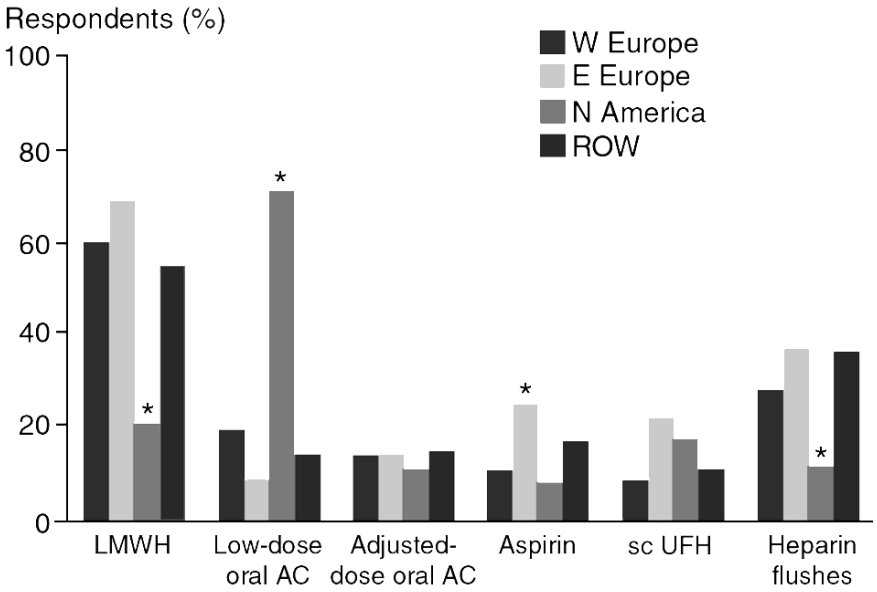
OA – oral anticoagulant

Figure 6.1.1 FRONTLINE Survey Data of Clinicians' Perception of Risk of Thrombosis in Patients with Cancer and a Central Venous Catheter



n = 3891. *p<0.05 compared with other regions. ROW - rest of the world

Figure 6.1.2 FRONTLINE Survey Data of Thromboprophylaxis Regimens used in Patients with Cancer and a Central Venous Catheter



Total number of respondents to survey = 3891.

*p < 0.05 compared with other regions. ROW - rest of the world

6.2 *WARP Trial*

6.2.1 Integrated Approach to Trial Implementation

6.2.1.1 Trials Infrastructure - Teamwork

The sound infrastructure of an established multidisciplinary clinical trials unit and strong multiprofessional clinical teams enabled WARP, the largest UK-wide trial of its kind, to be designed, recruited to, analysed and published. Whilst all the local coordinators in the 68 centres participating in WARP were nurses with the exception of one radiographer, only four (one oncology nurse consultant and three senior oncology trials nurses) were named as lead investigator, even though nurses were encouraged to take on this role by the principal investigator. From the randomisation sheets (Case Record Form [CRF] 1) and the day to day communications with trials centres, it was clear that the lead coordinators (nurses) were carrying out the vast majority of randomisation procedures in addition to coordinating the care pathway of the trial patient (including international normalised ratio [INR] monitoring, informing the patient of their trial responsibilities and being their first point of contact if needed) and completing the CRFs but not taking on the responsibility, traditionally that of the doctor, of the lead investigator (LI).

6.2.2 Trial Design

6.2.2.1 Certain / Uncertain Preferences

The clinicians' preference for being 'certain' of the benefit of warfarin was reflected most strongly in the pattern of randomisations over the first two years of the WARP trial; in 2000, 69% of clinicians were certain for the indication for warfarin, and in 2001, 61% chose the certain preference - Figure 4.2.1.2. This initial pattern of certainty was similar to that of the trial QUASAR (Kerr et al, 2000), where the majority of clinicians opted for the certain indication for chemotherapy preference over the uncertain indication. The QUASAR clinicians found it more practical to randomise patients into a trial comparing chemotherapy A with chemotherapy B (certain indication), rather than chemotherapy versus control (uncertain indication). They logged the fact that only one in five patients approached for the uncertain indication agreed to participate in the study. In WARP, the clinician choice for the certain preference for warfarin at the start of the trial, may have been due to: i) the perception that they were benefiting the patient by offering a 'treatment' rather than no treatment; ii) reliance on anecdotal evidence from their own practice or iii) that they were influenced by the available literature at the time, a single, small study showing benefit for 1mg of warfarin per day over control (Bern et al, 1990). However, after the major protocol amendment, with introduction of the 'more straightforward' uncertain 2-arm option (no warfarin versus 1mg warfarin) at the end of 2001, recruitment to certain and uncertain preferences were evenly balanced in 2002, with uncertain being the majority choice for clinicians and patients in 2003 and 2004 (Figure 5.2.1.3).

One external statistical peer reviewer of one of the WARP publications commented that the principles of certainty and uncertainty,

> "should be used more frequently in trial design to get the best evidence from the largest number of clinicians in the shortest time".

The design enabled 166 patients to be counted in both the warfarin and dose evaluations, less than initially calculated, due to the introduction of the uncertain 2-arm option and was a pragmatic means of encompassing contemporary clinical opinion. This is borne out by the adaptations over time; the initial design was a 3-arm study which after the survey was adapted to a trial of certain and uncertain indication. Even that design was difficult to deliver in practice and so the 2-arm uncertain option was introduced (Figure 4.2.3.2). This pragmatic approach hastened recruitment, whilst allowing the original research questions to be answered.

The key question of the whole study was, 'does warfarin reduce catheter related thrombotic events or not?' i.e. the uncertain preference. After initiating recruitment to the WARP trial, two small and underpowered studies failed to show a difference in the reduction of CRTs with 1mg warfarin daily (Heaton et al, 2002; Park K et al, 1999). These data may also have contributed to the rise in uncertain preference recruitment after the first couple of years. Early WARP newsletters highlighted the uncertain preference as the most important clinical question. For example, the chair of the DMC published a statement in the April 2002 newsletter as follows:

“The DMC believes that the lack of apparent benefit from warfarin in 3 small previous studies – when considered alongside the potential risks from warfarin – make the ‘uncertain indication’ randomisation between warfarin and no warfarin a more appropriate option than the ‘clear indication’ option for most patients, and that participants should be encouraged to support the ‘uncertain indication”.

(Newsletter in Appendix 7).

6.2.2.2 Design Amendment

Following a case conference on one early serious adverse event (where in the opinion of the local lead investigator, warfarin may have contributed to the death of the patient), it became apparent that the monitoring of the dose adjusted arm (DAW) to maintain the INR between 1.5. and 2.0 was causing concern in some centres. The patients were finding the additional time and effort travelling for tests (to the cancer centre or to the general practitioner [GP]), troublesome and expensive of time and finance. Although there were clear guidelines on monitoring INRs in the WARP protocol, specific practices varied between centres, and GPs were often asked to monitor INRs without robust systems being set up. The need for a boost in the uncertain preference recruitment as discussed above and the extra burden of monitoring the INR for those patients assigned to the DAW arm, persuaded the WARP steering committee to apply to the ethics committee in March 2001 for a two arm option of no warfarin vs 1mg warfarin, which was granted two months later. Following this protocol design amendment, of those patients randomised to any warfarin vs no warfarin, 79.4% of patients received fixed dose warfarin (FDW) and 20.6% received DAW daily, reflecting the intellectual position of randomising clinicians but also their capacity to offer DAW to their patients. The rate of recruitment into the trial and the uncertain preference, increased mid-2003 due to the availability of the two arm option (Figures 5.2.1.1.and 5.2.1.3). In 2003, 277 out of 475 patients (58.3%) were randomised against a no warfarin arm, 79% of clinicians choosing the two arm option.

6.2.2.3 Blinding

The open label trial design of WARP was suboptimal as the observer and the patient are aware of the assigned treatment arm and this may lead to prejudging the side effects of a particular treatment arm e.g. the unconsciously biased reporting of bleeding. To blind a trial using warfarin, it is possible to undertake 'sham' INR testing for a placebo control arm (Levine et al, 1994) but at a huge cost to the patients in undergoing unnecessary tests and cost to the organisation for the manufacture of a placebo, extra coagulation tests and the coordination of the monitoring a 'sham'. Therefore, an open-label randomised trial was chosen as placebo-controlled was difficult to execute and the cost was prohibitive.

6.2.3 Trial Recruitment

WARP recruited 1590 patients over five years and three months, between October 1999 and December 2004; 812 were randomised to the uncertain preference (404 to no warfarin, 324 to warfarin 1mg and 84 to DAW) and 778 to the certain preference (389 to warfarin 1mg and 389 to DAW). There was an annual mean of 265 randomisations with a surge in 2003 of 475 patients randomised. The changing pattern of certain/uncertain preference accrual is described above. Recruitment was constantly being addressed by the WARP trial monitoring groups, as it lagged behind predicted recruitment from the start, specified in the early versions of the protocol for completion, by March 2002. This was a large overestimation of monthly accrual figures by the local investigators and principal investigator as it took another 2 years and 9 months to reach target recruitment. Consequently, the steering committee and the data monitoring committee (DMC) prioritised recruitment analyses and discussed recruitment strategies at all meetings. The DMC did not, at any point, change the recruitment target which may have been an option for dealing with the low event rate, discussed in detail in section 5.2.6.3. The design change along with a good communications plan of site visits, regular newsletters with relevant literature, and open access to the principal investigator and trial coordinator by phone or e-mail for support, facilitated the attainment of the accrual target, albeit with a lower event rate than forecast.

6.2.3.1 Recruitment by clinicians and centres

There were 175 clinical lead investigators from the 68 centres. Seventy six percent always chose the same preference (41% always uncertain and 35% always certain)

whilst the remaining 24% randomised patients to both certain and uncertain preferences, presumably taking the condition or the opinion of the individual patient into consideration. In the pre-trial survey, 38% of clinicians did not use warfarin as a thromboprophylactic measure and yet more than half of clinicians seemed unwilling to randomise to a no warfarin (control) arm when the trial was initiated. Using or not using warfarin as a thromboprophylactic measure pre-trial when the evidence was scanty and in equipoise, did not directly translate to being 'certain' or 'uncertain' of the benefit when it came to randomisation preferences in the actual trial. The National Cancer Research Network (NCRN) infrastructure for the organisational delivery of clinical trials in the UK started in 2001 and introduced a recruitment incentive for clinicians to support NCRN-accredited trials. WARP automatically became NCRN-accredited as it had been previously peer reviewed by the Medical Research Council and the then Cancer Research Campaign (now Cancer Research UK) and there is no doubt that this NCRN incentive encouraged clinicians to recruit to WARP.

6.2.4 WARP Baseline Characteristics

Baseline patient details are presented in Table 5.2.2.1 and were similar with respect to performance status, age, treatment length, disease site and stage of disease across all arms. The numbers of patients randomised to the stratification variables were equally balanced across all arms, confirming the quality of the electronic randomisation programme. There is a preponderance of males (57%), reflecting the dominant tumour types (gastrointestinal cancers are more common in men) mandating chemotherapy via central venous catheters (CVCs). Clinicians reported

that 93% of patients had WHO Performance Status of 0 and 1 which seems high, given that 65% of patients had advanced disease but may be generally be expected of patients considered sufficiently fit to undergo infusional cytotoxic chemotherapy. Patient self-reported performance status is now in common practice throughout UK cancer centres and would perhaps be a more reliable measure than that of the clinician. It is interesting to note that the median age of the patients recruited to the trial is 60 years, similar to other large reported trials of chemotherapy for advanced and early gastrointestinal cancers. This is a reproducible factor; even although three quarters (74%) of cancer diagnoses are in people aged 60 and over, and more than a third of cases are in people aged 75 and over (ONS, 2009), it is common to find an age difference of a decade lower in patients entered into national and international trials of chemotherapy for patients with solid tumours. It is likely that this reflects the consistent degree of selection bias that operates against elderly patients receiving chemotherapy (Schrag et al, 2001), which may relate to comorbidity, polypharmacy, or reduced performance status. However, warfarin is safe in the elderly and the doses used in WARP are lower than the recommended starting doses for the elderly in The American College of Chest Physician Guidelines for management of anticoagulants (Ansell et al, 2008).

The majority (51%) of patients entered in the study had early or advanced colorectal cancer, reflecting the predilection for 48-hour 5-flourouracil (5-FU)-based chemotherapy, promulgated by Professor Aimery de Gramont (Louvet et al, 1992). Colorectal cancer is a ‘thrombotic’ tumour type (Mandala et al, 2009) [section 3.5.5.1.2] and although 5-FU was classed as ‘non-sclerosant’ in the stratification strata, there have been some animal and human case reports on the cytotoxic

effects of 5-FU on the vascular endothelium (Tham and Albertsson, 2004; Cwikiel et al, 1996); therefore, this significant cohort of patients represented a true test of the thromboprophylactic worth of warfarin. Cancers of the pancreas, stomach, uterus, kidney, lung, primary brain and haematological malignancies are associated with the highest rates of VTE (Khorana and Connolly, 2009) and constituted another 16% of WARP patients (Table 5.2.2.1). Many of the clinicians in the pre-trial survey stated that all their patients with haematological malignancies had a CVC inserted for chemotherapy. VTE rates in patients with haematological malignancies are comparable with high risk tumours (Falanga and Marchetti, 2009) and, even in the absence of active thrombosis and/or bleeding, present with laboratory signs of a hypercoagulable condition or chronic disseminated intravascular coagulation. Different degrees of laboratory haemostatic abnormalities can occur, particularly in patients with acute leukaemia. Clinical manifestations range from localised small thromboses to diffuse bleeding and anticoagulant therapy is complicated in patients with haematological cancer. However, only 3.6% of patients recruited to WARP had a haematological malignancy which perhaps reflects the reluctance of the haematologists to use warfarin for the reasons outlined above. The expected low platelet counts in these patients also mean having to stop and start warfarin frequently. It is only recently that in patients with multiple myeloma, thromboprophylaxis with low molecular weight heparin (LMWH) is employed due to the high thrombotic risk of thalidomide and lenalidomide (section 3.5.5.2.2).

6.2.5 Compliance

Compliance is outlined in Figure 4.2.3.1 and split into compliance with i) the assigned treatment and ii) warfarin dose. CRF return was excellent at 97.4% overall (Table 5.2.3.1) and was pursued rigorously. There were more cases of patient/clinician non-compliance in the DAW arm (20/473; 4%), than in FDW (5/471; 1.1%), this finding supports the concerns of the local coordinators and patients who were anxious about monitoring warfarin in the DAW arm. Only 6% of patients (72/1186) started warfarin at 3 days prior to catheter insertion which was recommended in the protocol but in practice, was not easy to execute (Table 5.2.1.6). Of the 1139 patients starting warfarin, 106 (9%) stopped 'early' (more than 7 days before the catheter was removed), largely due to the completion of their chemotherapy and choosing to stop warfarin at the same time, even although the CVC was still in situ and they were still potentially at risk of thrombosis but, having gone that far without a thrombosis, the patients may not have been either aware or concerned about the risk. Warfarin also had to be stopped when thrombocytopenia developed and, in two cases, was not restarted.

6.2.6 Catheter-related Thromboses

Of the 1590 patients randomised, 85 (5.3%) had a radiologically confirmed CRT, occurring most frequently (38%) in the upper limb. There were also 9 clinically suspected CRT, not confirmed radiologically and therefore classified as CVC complications and not thromboses. Any warfarin (of which 79% was 1mg and 21% DAW) did not reduce the incidence of CRT relative to no warfarin [24 (5.9%) vs 24 (5.9%), p=0.98] but there were significantly fewer CRT events in those patients allocated DAW compared to FDW (13 (2.8%) vs 34 (7.2%), p=0.002).

The no warfarin versus FDW and no warfarin versus DAW comparisons are post hoc analyses; the trial was not powered to address these comparisons, patient numbers are low in the latter comparison and therefore the analyses are exploratory only. A combined endpoint of thrombosis and major bleeding was assessed to investigate any change in risk (of bleeding): benefit (of thromboprophylaxis) ratio. The dose effect of warfarin (DAW superior to FDW) is reduced when the combined endpoint was assessed (Table 5.2.5.12). One interpretation of this finding of a statistically significant advantage for DAW over FDW in the reduction of CRT (p=0.002) to no advantage seen for DAW over FDW when bleeding plus CRT is examined, is that the therapeutic gains made by the reduction in thrombosis rates with DAW are offset by the higher bleeding rates overall and it is not worth the risk of using a higher dose of warfarin. This analysis helped frame the conclusion of the dose evaluation study. This is an interesting approach to analysis of risk: benefit, focussing on the balance of toxicity and efficacy within a single clinical trial.

The incidence of CRT was lower than expected, but is in keeping with a temporal trend caused by improved catheter design and care. The low event rate restricts the power of the warfarin evaluation comparison and is discussed in detail (section 6.2.6.3). In the analysis of patients with a CRT event only, median time to CRT thrombosis was 32 days from CVC insertion (IQR=13 to 76 days). Given that CVCs were patent for a median of 13.9 weeks, most CRT occurred early. Median time to CRT did not differ in the warfarin vs no wafarin (25 vs 32 days, p=0.71), or DAW vs 1mg (60 vs 31 days, p=0.51) evaluations. Analysis of the primary outcome as time to event data (with time to thrombosis in those who do not experience the event censored at the time of CVC removal), warfarin did not reduce the rate of CRT compared to no warfarin (log-rank, p=0.95); by contrast, significantly fewer CRT occurred in patients assigned to DAW compared to FDW (log-rank, p=0.002). The time to event results were in keeping with the χ^2 test comparison of thrombotic events.

The analyses of the primary endpoints indicate, therefore, that low dose warfarin does not have a useful role in the prophylaxis of CRT. This is a finding of major clinical import, given the survey findings that 62% of the UK's oncologists and haematologists routinely prescribed warfarin 1mg to prevent catheter thrombosis prior to WARP. There is now no justification for this practice. However, WARP was the first study in which there was a dose comparison of warfarin. Interestingly, DAW conferred a significant advantage in comparison to FDW in the reduction of CRT. Counterbalancing the therapeutic benefit was the doubling of major bleeding events (16 [3%] versus 7 [1%]) (p=0.09); likewise when the composite endpoint of major bleeding plus CRT was examined in the dose evaluation study, there was no

difference between DAW and FDW. More powerfully for clinicians, warfarin was thought by the lead investigators to contribute to at least two deaths of patients who were assigned to DAW, giving a mortality rate of 0.4% which is similar to the toxic death rate in chemotherapy for adjuvant colorectal trials (Twelves, 2006). So, on balance, there does not appear to be a role for the regular use of warfarin in thromboprophylaxis of cancer patients with CVCs in any dose. However, with vigilant monitoring of patients, clinicians may wish to offer prophylaxis to specific patients at high risk of thrombosis, for example, those who have had a previous history of DVT (Saber et al, 2008) or have one of a number of risk factors identified e.g. ovarian cancer (Lee et al, 2006) or more than one insertion attempt, a previous CVC insertion or a peripherally inserted central catheter [PICC] (Saber et al, 2008), outlined in Table 3.6.3.3. Then DAW would seem the most logical choice but more research is needed for this high risk group. Identifying patients with cancer and CVCs who are most at risk of VTE is essential to better target thromboprophylaxis with the eventual aspiration of reducing VTE and reducing the sometimes devastating adverse consequences of VTE for this group of patients e.g. a pulmonary embolus (PE), interruption of treatment or post-thrombotic syndrome.

6.2.6.1 Contextualising WARP

Our findings are in keeping with the results of the more recent studies on thromboprophylaxis in cancer patients with CVCs and have challenged the outcomes of three early studies. Bern et al compared 1 mg warfarin for 90 days to control in cancer patients with long term central venous catheters (Bern et al, 1990). VTE were detected symptomatically and by routine venogram in 15 of 40 (37.5%) no warfarin patients in comparison to 4 of the 42 (9.5%) patients on warfarin ($p<0.001$). Monreal et al randomised a similar group of patients to the low molecular weight heparin (LMWH), dalteparin (2500iu subcutaneously, daily for 90 days) or control (Monreal et al, 1996). Early trial closure was precipitated by differential upper limb thrombosis rates (1/16 dalteparin arm vs 8/13 in control patients, $p=0.002$), confirmed by routine venography. A Korean group randomised 80 cancer patients with CVCs to 1mg warfarin vs control and reported thrombosis rates of 13% vs 29% respectively, $p=0.07$, (Park K et al, 1999). Although small, these three trials suggested a benefit in using prophylactic anticoagulation, reducing thrombosis rates with minimal toxicity. However, from the turn of the century trials have not demonstrated a benefit for anticoagulation intervention for cancer patients with CVCs. Heaton et al (Heaton et al, 2002) examined the effects of 1mg fixed daily dose of warfarin versus control on thromboprophylaxis in 88 patients with a haematological malignancy receiving chemotherapy via CVCs. No significant difference in symptomatic thromboses (18% vs 12% respectively, $p=0.4$) was demonstrated. Similarly, Couban and colleagues recorded the number of symptomatic thrombotic events in a trial of 255 patients (80% with haematological malignancies) receiving warfarin 1mg or placebo for 9 weeks (Couban et al, 2005).

Overall CRT rates were low; 4.6% with warfarin and 4.0% with placebo (HR, 1.2, 95% CI, 0.37 – 3.94).

LMWHs, recently evaluated in trials, have also proven no more effective than control in the prophylaxis of CRT. Verso et al adopted a primary endpoint of thrombosis (by routine investigation) in a trial of enoxaparin (40mg once daily for 6 weeks) vs placebo (Verso et al, 2005) . In 385 cancer patients, thrombosis rates were not found to be significantly different in both arms (14% enoxaparin vs 18% placebo, p=0.35). Karthaus and colleagues similarly revealed no symptomatic thromboprophylactic effect of dalteparin (5000iu/day) in comparison to placebo (3.7% and 3.4% respectively, p=0.88) (Karthaus et al, 2006). Interestingly, the Verso, Karthaus and Couban studies were powered on baseline event rates of around 30-32.5%, in keeping with older studies.

In summary, recent single trials of thromboprophylaxis in cancer patients with CVCs have shown no benefit in using an anticoagulant – warfarin or LMWH versus control. WARP supports these data and is the largest study in this population. DAW has not been previously tested in this population but given the increase in bleeding associated with DAW, the 'hassle factor' identified in WARP by the patients travelling for coagulation testing, DAW should not be routinely used. In order to put WARP in context of the multiple thromboprophylaxis studies undertaken and to take advantage of the large sample size resulting from the pooling of the results from these studies, meta-analyses were undertaken, allowing for greater accuracy and statistical power.

6.2.6.1.1 Thromboprophylaxis Meta-analyses

The meta-analysis of thromboprophylaxis in cancer patients with CVCs comparing 1mg warfarin versus control, provides no clear evidence for using warfarin (OR 0.7; 95% Confidence Interval (CI) 0.5, 1.1; p=0.1) [Figure 5.3.1.2] . Likewise, the four randomised controlled trials that compared LMWH with placebo or no intervention, demonstrated no statistically significant reduction in the rates of VTE (OR 0.5; 95%CI, 0.5, 1.1; p=0.2) [Figure 5.3.1.4]. In meta-analysis, each study is weighted by the inverse of its own variance which is a function of the study size and the number of events in the study. The corollary for thromboprophylaxis studies is that when asymptomatic venographically screened plus symptomatic VTE (i.e. both types of event) are measured as an endpoint, these carry more weight than studies which measure only symptomatic events, and make comparisons difficult. Although 'both events' and symptomatic only events were subgroups of the thromboprophylactic analyses, combining the events in one meta-analysis has to be viewed with caution. However, there were an inadequate number of trials with either symptomatic or both events measured separately, to perform a separate meta-analysis, for warfarin versus control and LMWH versus control comparisons. An alternative analysis would have been for both prophylactic anticoagulant interventions (warfarin and LMWH) to be combined in a symptomatic event only analysis and look at the different anticoagulants as subgroups. As the WARP trial was a warfarin only intervention, it was important to observe any influence that WARP results had on the previous findings using warfarin only and so the separate anticoagulant type analyses were carried out. WARP was by far the largest contributory study in the warfarin thromboprophylaxis meta-analysis and therefore gathers greatest statistical weight. It was therefore of little surprise to find that the

inclusion of WARP reduced the odds ratio from 0.6 to 0.7 with an associated loss of statistical significance (p=0.1) [Figure 5.3.1.3]. As any anticoagulant intervention increases the risk of bleeding, a further limitation of the meta-analyses was that bleeding data were not included and therefore the risk / benefit ratio for thrombosis and bleeding could not be considered as a whole from the multiple trials. Lastly, even with multiple studies, the lack of effect in some instances could be due to the small number of studied patients and events. Even with the WARP trial, the analysis of warfarin as a thromboprophylactic intervention in cancer patients with CVCs only had 682 patients with 47 events versus 674 control patients with 61 events, p=0.1 and would be strengthened by increased numbers of patients.

The protocol-driven approach with the double checking of searches, the acceptable overall methodological quality found in the studies, combined with the consistency of the results (lack of significant heterogeneity in the warfarin intervention trials) and a low likelihood of publication bias because of the searching method (e.g. asking the experts and inclusion of relevant abstracts), increase the confidence in the internal validity of the results. However, a variation between study outcomes in the four trials using LMWH intervention was found (test for heterogeneity, p=0.03), suggesting 'non-combinability' and that the pooled results carry a warning to that effect. The decrease in the baseline risk of asymptomatic plus symptomatic VTE events with LMWH over the years is notable (section 6.2.6.2). There was also a general progressive decrease in the effect size in the thromboprophylaxis studies by year of publication, particularly in the LMWH studies. This may have been due to the smaller sizes of earlier studies as it has been reported that small trials exaggerate intervention effects compared with large trials (Kjaergard et al, 2001). Another

explanation could be that the trial with 32 patients by Monreal was stopped early because of the benefit. The early cessation of trials for benefit has been shown to cause questionably large treatment effects (Montori et al, 2005).

There have been several systematic reviews of thromboprophylaxis in cancer patients receiving chemotherapy with CVCs. A 2003 review in this population (Klerk et al, 2003) identified two trials (Monreal et al, 1996; Bern et al, 1990) and concluded in contradiction to the thromboprophylaxis meta-analyses in this thesis that warfarin 1mg daily or LMWH significantly reduce the incidence of CRT. The disparity is likely to be due to these two trials including screening detected thromboses and the later studies showing a smaller effect with a greater number of patients. The findings of the primary thromboprophylaxis meta-analyses in patients with CVCs illustrated in Figures 5.3.1.2 to 5.3.1.4 are in keeping with Akl et al who published a Cochrane systematic review of anticoagulation for thromboprophylaxis in cancer patients with CVCs (Akl et al, 2007c). They found the use of heparin in cancer patients (LMWH plus unfractionated heparin (UHF) [UFH is not used in practice now because it generally requires an inpatient stay and therefore was not included in the meta-analyses carried out in this thesis] was associated with a trend towards a reduction in symptomatic DVT (relative risk (RR),0.43; 95% CI, 0.18-1.06). However, their pooled results of all different types of anticoagulants [including one study of unfractionated heparin (Abdelkefi et al, 2004)] showed that the symptomatic only DVT rates were significantly reduced in cancer patients with CVCs (RR 0.56; 95%CI 0.34, 0.92), concluding that the risk / benefit ratio of anticoagulant burden against anticoagulant benefit should be considered by patients. Because the results of the meta-analyses in section 5.3.1.2 were strongly influenced by WARP and the

bleeding data from WARP are now known and noteworthy, the recommendation from the pooled data in the thesis is not to use warfarin 1mg/day, routinely. The meta-analysis evidence suggests that LMWH should also not be used routinely in the thromboprophylaxis of cancer patients with CVCs.

6.2.6.2 Time Trend of Decreasing Incidence of Catheter-related Thrombosis

The incidence of VTE associated with long-term CVCs in cancer patients has been assessed in a number of studies (Tables 3.6.3.1 and 3.6.3.2). CRT are commonly asymptomatic, highlighted by the difference in CRT rates in the two tables, one measuring symptomatic only CRT and the other, measuring both symptomatic and screened CRT. However, careful definition of CRT incidence has been hampered by inconsistent factors that make inter-study comparison difficult. Over time, there has been a general decrease in the incidence of CRT in patients with cancer. This can be seen in the decline in CRT rates in the control arms of the thromboprophylaxis meta-analyses by year (Figures 5.3.1.2.and 5.3.1.4). The effect is also observed in the incidence of VTE in all catheter studies in cancer patients, listed in Tables 3.6.3.1 and 3.6.3.2. After the turn of the century, there is approximately a halving of the rate of CRT compared to trials done before 2000, in studies measuring both symptomatic and asymptomatic events (a mean VTE rate of 37% before 2000 and 17.2% from 2000) and in studies measuring symptomatic only events (a mean VTE rate of 11.7% before 2000 and 6.6% from 2000).

6.2.6.3 Low Event Rate

The overall low symptomatic CRT rate of 5.3% in the WARP trial which was reflective of the more recent studies, led the Data Monitoring Committee (DMC) and Trial Steering Committee to discuss this matter in detail at their reviews. No formal futility analysis was presented and the trial did not have formal stopping rules but, on every occasion, the DMC considered stopping or extending the trial and decided that the trial should continue as planned. To deliver a similar proportional reduction as was envisaged in the initial power calculation in WARP (25% to 15%) and given the event rate of 5.9% in the control arm, 750 patients in each arm would be required to detect a reduction in thrombosis rate to 3% (80% power, 5% level of significance, 2-sided test). To increase the patient recruitment target would probably not have been feasible, as the WARP trialists were mindful of the two small trials published after WARP started showing no benefit for 1mg of warfarin daily and made aware of one non-published study from Wake Forest Comprehensive Cancer Centre stopped by their DMC because of low event rates and no differences in event rates between warfarin and no warfarin (Owen, 1999). In the final year of recruitment, the clinicians seemed less enthusiastic about the WARP trial, perhaps because of the emerging data and because it had been open to recruitment for so long. On the other hand, in the WARP dose evaluation study, the statistical power at the end of the study was 87%, with a CRT rate of 7.2%, brought down to 2.8% with DAW, at the 5% level of significance (2-sided) with 470 patients in each arm. This was therefore a well powered comparison, using the predicted recruitment numbers.

6.2.6.3.1 Differences in Event Rates due to Thrombosis Assessment

Clearly, in the studies in which CRT are assessed on clinical presentation and on regular screening by venography (symptomatic and asymptomatic respectively), the rates are higher than assessment on symptomatic events only (27% vs 6.5% respectively in the meta-analysis – Figure 5.3.1.2). Although asymptomatic VTE is, by definition, covert, these thrombi can embolise to the lungs (Kuter, 2004). Studies have also shown that asymptomatic DVT is strongly associated with the development of symptomatic VTE and is also associated with an increased risk of death (Cronin et al, 2007). It is therefore important to consider assessing both asymptomatic and symptomatic DVT when looking at the effectiveness of prophylactic strategies. However, thrombosis screening was not carried out in the WARP trial due to the extra diagnostic tests involved and their cost. There are surprisingly few data on the natural history of asymptomatic CVC thrombosis, although there are indirect data that these may lead to PE (Kearon, 2001; Black et al, 1993). It is of note that two cases of PE were documented in patients with catheter complications whereas 10 were found in those with no obvious catheter complications. This ratio of 5:1 corresponds with the approximate ratio of symptomatic: asymptomatic VTE in the meta-analysis. These data are inferential; a greater understanding of the natural history as to whether screened thrombotic events have the same propensity for PE compared to symptomatic is required.

6.2.6.4 Risk Factors – Multivariate and Univariate Analyses

When investigating baseline risk factors for CRT in a prospective cohort study, Lee et al found more than one insertion attempt, previous CVC insertion and ovarian cancer to be significant (Lee et al, 2006). The first two factors suggest that vessel wall trauma or endothelial damage predispose to CRT. Kraybill and Allen have made similar observations; they found that 42% of patients with a history of long-term central venous access had evidence of thrombosis on duplex scanning (Kraybill and Allen, 1993). From an individual patient data-level meta-analysis, a multivariate logistic regression analysis revealed the use of implanted ports as compared with peripherally implanted central venous catheters (PICC), decreased CRT risk (OR = 0.43; 95% CI, 0.23-0.80), whereas past history of deep vein thrombosis (DVT) (OR = 2.03; 95% CI, 1.05-3.92), subclavian venipuncture insertion technique (OR = 2.16; 95% CI, 1.07-4.34), and improper catheter tip location (OR = 1.92; 95% CI, 1.22-3.02), increased CRT risk (Saber et al, 2008). Many other risk factors for CRT have been hypothesised using smaller studies (Table 3.6.3.3).

In WARP, no data on insertion attempts and previous CVC insertion were collected. Of the seven factors that were entered into the univariate analysis for CRT, double lumen catheters (OR 1.73; p=0.03) and catheters made of polyurethane (OR 2.11; p=0.05) were associated with a greater likelihood of CRT. The other factors, showing non-significant results do not indicate that the factors tested were not prognostic of CRT; it may reflect an underpowered analysis due to the low number of events and the limited number of patients in some of the categorised factors. This is somewhat in keeping with previous literature in this field (Gallieni et al, 2008; Eastridge and Lefor, 1995).

6.2.6.5 Central Venous Catheters

Fifty eight percent of all patients had peripherally inserted central catheters (PICCs), in keeping with a rising trend in usage; only 4 patients had implantable ports. After recruitment to WARP had ended and within the last three years, implantable ports are being increasingly utilised in the UK, perhaps because of their low thrombogenicity (Heibl et al, 2010).

As mentioned above, CVCs were not fully categorised in the pre-trial survey and it was difficult to differentiate between catheter types from the differing terminologies. The CVC data collection component of CRF2 was therefore designed with an expert group of specialist central venous access device nurses and contained text boxes to document catheter manufacturer, size, type, number of lumens and material. This removed the ambiguity in all but the 'type' category where the data collected were not definitive (Lifecath, Groshong, Hickman, PICC, Bardport, Portocathand and Leader cuff) for any meaningful analysis. A detailed log of different catheters used at different centres and used generic terms (PICC, central placement, valved or non-valved, skin-tunnelled or non-tunnelled and implanted port) was therefore documented. These were used for the CVC analysis with the exception of skin-tunnelled and non-tunnelled as the majority of data were unknown. However, catheters which are required for over 14 days, should always be tunnelled. Any future survey or clinical trial with CVC data collection (e.g. a duration of herceptin trial, 'Persephone'), will use generic terms, minimising ambiguity.

6.2.7 All thromboses

A further 36 (2.3%) patients had a non-CRT thrombosis, making a total of 121 (7.6%) thromboses in 1590 patients. Neither warfarin (compared to no warfarin) nor DAW (compared to FDW) had any significant impact (p=0.30 and p=0.15 respectively) on *all* thrombotic events - Table 5.2.5.1. Median time to all thromboses (CRT and non-CRT) was 44 days (IQR=13-84 days) which was not statistically different from the median time of 32 days for CRT. The reduction in CRT events seen with DAW in comparison to FDW did not translate into a decrease in all thrombotic events and, in effect, is cancelled out when the composite endpoint of thrombosis plus major bleeding is considered. The rates of all thromboses in the no warfarin arm of the randomised comparisons (no warfarin vs warfarin and no warfarin vs 1mg warfarin) is the same at 9%; the FDW arm of the two randomised comparisons of FDW are similar - 9% (FDW vs DAW) and 8% (no warfarin vs FDW). This bears out the uniformity of the groups. However, in a non-randomised comparison, for the FDW arm of the dose evaluation study there is a doubling of the rate seen for CRT from 13 (2.8%) to 26 (5.5%) seen for all thromboses (taken from Tables 5.2.4.1 and 5.2.5.1). This begs the question of whether warfarin may be less effective in non-CRT. The natural history and size of CRT and non-catheter-related thrombosis need further investigation and this effect may be due to chance as the suggestion stems from a non-randomised comparison.

All thromboses are clinically important and risk factors include the tumour, the chemotherapy as well as CVCs (section 3.5.5). The incidence of non-CRT was 2.3% and is a clinically significant issue. All thromboses, including pulmonary

emboli, should be considered as the primary endpoint of future thromboprophylactic catheter trials in cancer patients, as all thromboses require immediate attention, with pulmonary emboli (PE) carrying the greatest risk of mortality. PE were once thought to be a rare complication of upper extremity deep vein thrombosis because of the smaller lumen of upper extremity veins but a prospective study of 86 patients with CRT all of who underwent ventilation/perfusion (V/Q) scanning within 24 hours of diagnosis, found a 16% incidence of symptomatic and asymptomatic PE, combining clinical and radiological findings (Monreal et al, 1994). In studies in which V/Q scans were performed on all patients with upper extremity deep vein thrombosis (DVT), irrespective of pulmonary symptoms, the total PE rate of 11% was twice that of the symptomatic PE rate (Monreal and Davant, 2001; Prandoni et al, 1997; Monreal et al, 1991), comparable to asymptomatic PE seen in patients with lower extremity DVT. The reported incidence of pulmonary embolism in WARP was 0.8% (12/1590); 14% of all thromboses, two of which were related to a catheter complication [Tables 5.2.4.3 and 5.2.5.3].

6.2.7.1 Risk Factors for All Thromboses – Exploratory Multivariate and Univariate Analyses

Risk factors identified from the literature, for all thromboses, were categorised into patient, treatment, cancer and catheter related and explored in detail in sections 3.5.5 and 3.6.3.4. In WARP, there was one significant risk factor for all thromboses. Only two risk factors were found to be significant in the univariate analysis for CRT and this is most likely to be reflective of the low number of events and the limited number of patients in some of the categorised factors. 'Colorectal' was found to be a significant risk factor for all thromboses compared with all other tumour sites in the univariate analysis and should be explored further in trials with anticoagulants.

6.2.8 Major Bleeding Events

Although there are potential risks associated with pharmacologic prophylaxis, major bleeding complications are reported to be very rare and the consequences of not preventing VTE are thought to be greater (Geerts et al, 2004). There was an excess of major bleeding events in patients on warfarin vs no warfarin (RR=4.01, 95%CI 0.64-25.11, p=0.07) and in patients on DAW vs FDW (RR=1.66, 95%CI 0.90-3.08, p=0.09). An increase in moderately and severely raised INR *without* major bleeding was also demonstrated (Table 5.2.5.8). According to participating clinicians, warfarin may have contributed to the deaths of two patients receiving DAW; no thrombosis was reported as contributing to death. The case histories of the two patients who died and in whom warfarin may have contributed to their deaths were fully investigated by the principal investigator, with site visits and a case conference with key members of the multidisciplinary team including the research nurse. Both patients were not monitored as per the WARP trial protocol; in one case, the GP had failed to follow up on an INR in the severe range and, in the other, the bank holiday had prevented the patient from having a coagulation test. The major haemorrhage rate in over 13,000 patients receiving warfarin for non-valvular atrial fibrillation (AF) was 1.1% with intracranial haemorrhage associated with 90% of deaths from warfarin-associated haemorrhage (Fang et al, 2007). The overall major haemorrhage rate in WARP was found to be 0.6%, which is less than the result from the above AF cohort study in which the doses of warfarin were greater than WARP. It has been possible to demonstrate that DAW to maintain the INR between 1.5.and 2.0 significantly reduces catheter thrombosis rated compared to 1mg daily dose of warfarin, but at the cost of an increase in major bleeding events. The absolute

reduction in CRT thrombosis seen in this study was 4.4% and the increase in major bleeding events was 2% with DAW in comparison to FDW, making it unlikely that most clinicians would offer routine DAW in this setting. However, for patients at higher than average risk of thrombosis, then the patient must be prepared to accept the related toxicity profile. This extrapolated subgroup of high risk of thrombosis patients discussed in section 6.2.6.4 was not sufficiently well represented in the present study to offer definitive advice on prescription of DAW; therefore this guidance is indirect and conjectural.

6.2.9 Survival

At the time of analysis, 532 patients were still alive with a median follow-up of 45 months (range 26 to 88). Of the 1058 reported deaths, 921 (87%) were due to cancer; 53, other causes and 84, cause unknown. No benefit in overall survival was found from taking warfarin compared to no warfarin (HR=0.98, 95%CI: 0.77-1.25, p=0.26) or between the two dosing schedules (HR=0.91, 95% CI 0.73-1.14, p=0.53). It is perhaps unsurprising that warfarinisation had no impact on overall survival as the incidence of life threatening thrombotic events was low and the mechanistic data linking the action of warfarin to direct, antitumour effects are scanty and fewer than LMWH (Kuderer et al, 2009). This hypothesis might be better tested in a clinical trial of a more homogenous group of patients, say with pancreatic cancer (who are at high risk of VTE), in which a factorial design would allow incorporation of a chemotherapy question, regime A vs regime B, and a second randomisation between anticoagulant and control, properly powered to detect a significant difference in overall survival in the adjuvant setting.

The two treatment survival curves (no warfarin and warfarin) in the warfarin evaluation cross over at around 8 months. This could mean that the harmful effects of warfarin (i.e. bleeding) are seen early on (in the first 8 months) and that the benefit is seen after this time. This is highly speculative, given that CVCs were patent for a median of only 13.9 weeks (3.5 months).

The survival findings from the WARP trial, examining 1mg warfarin versus control are not consistent with the mortality meta-analysis performed (Figure 5.3.2.2) where a significant reduction in mortality was seen (meta-analysis, p=0.03). The results from a meta-analysis of oral anticoagulation in patients with cancer (Akl et al, 2007a) concur with the WARP trial findings of no survival benefit from warfarin, although they suggested a survival benefit at six months from warfarin in a subgroup of patients with small cell lung cancer (SCLC), particularly when the disease was extensive. Subgroup studies are often unreliable. When investigated further in another analysis, the authors concluded that the decision for a patient with extensive SCLC to start warfarin for survival benefit should balance that benefit with the downsides of increased bleeding risk in light of patient values for these outcomes (Akl et al, 2007b). LMWH was also associated with a statistically significant survival benefit in cancer patients (Figure 5.3.2.3). Akl et al demonstrated a survival benefit with all heparins (LMWH and UFH) in this population [Hazard Ratio (HR) 0.77; 95% CI 0.65, 0.91] (Akl et al, 2007d) and found, in their subgroup analysis, that patients with limited SCLC experienced a clear survival benefit with all heparins, not seen in extensive disease. Future research should investigate the survival benefit of different types of anticoagulants including the new oral agents in patients with different tumour types and stages of cancer.

6.2.10 INR analysis

The results of all the INRs for patients entered into WARP and documentation of any action taken were collected and collated for all patients manually in one book in the highest recruiting centre. This systematic approach to monitoring INRs suggests that the monitoring was thorough. The WARP newsletters emphasised vigilant monitoring frequently as the case discussions of severe or 'high INR' serious adverse events suggested that INR monitoring could be improved and in particular, the coordination and systems between primary and secondary care. Hospital monitoring was therefore recommended unless general practitioners, patients and local coordinators had a robust system in place. The sample of INR results (110/1590; 6.9%), taken from a single centre, demonstrated that 8% of patients taking FDW at any one time, had INR>1.5 for which the protocol recommends reducing warfarin by 50% to differentiate between arms. The individual variability of INR with warfarin in cancer patients is known to be high and the cross-over into the comparator arm of DAW (INR between 1.5 and 2.0) is concerning but perhaps to be expected in this population. More worryingly, it took at least five weeks for around half of the patients receiving DAW to reach their target INR range of 1.5-2.0 and, at this timepoint, 31% of patients still had an INR below lower range limit. At around 4 months, 49% of patients were within the DAW range and the proportion of patients with an INR<1.5 had reduced to 14%. These data cannot be extrapolated to other participating centres but given the documentary evidence that the monitoring was regular and by implication, stringent, there is a poor INR target achievement for patients on DAW which may have reduced the benefit found in the FDW vs DAW comparison.

6.2.11 Continuing Relevance of Central Venous Catheters

Even with the increasing use of oral chemotherapy drugs for many cancers, as witnessed over the last five years, CVCs are still required for the majority of regimens noted in the pre-trial survey. The exception to this would be the replacement of infusional 5-flourouracil with oral capecitabine for colorectal, breast and some upper-gastrointestinal cancers. However, in some cases, clinicians and patients still prefer a CVC for the administration of the other combination drugs given with capecitabine, e.g. anthracyclines and taxanes for early breast cancer, and with an increase in use for patients with haematological cancers in particular. Millions of CVCs are used worldwide for the administration of chemotherapies (McGee and Gould, 2003) and thrombotic events are a common problem. Thromboprophylaxis in cancer patients with CVCs is still an important clinical question.

6.3 *Corollary of WARP Trial*

6.3.1 NICE Guidelines

6.3.1.1 International Guidelines

The international consensus guidelines on the prevention of VTE from the American College of Chest Physicians (ACCP) in 2000 (Hirsh et al, 2001b) were available during the WARP trial and recommended: i) thromboprophylaxis for surgical patients with cancer and ii) thromboprophylaxis for acutely ill medical patients. These have since been updated twice (Geerts et al, 2008; Geerts et al, 2004) with the latest edition including a limited discussion of patients with cancer. Several international oncology societies have also produced guidelines specifically on prevention of VTE in patients with cancer: The National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), the Italian Association of Medical Oncology and the French National Federation of the League of Centres Against Cancer, summarised a consensus and disagreement paper on all the above guidelines, carried out by a working group from all panels (Khorana et al, 2009). There are other general guidelines on thromboprophylaxis and the treatment of thrombosis which include cancer as a topic, with individual countries developing their individual guidelines. Despite all these guidelines and the evidence of increased risk of VTE amongst cancer patients and the benefit of thromboprophylaxis in particular high risk settings, surveys of oncologists and their colleagues have demonstrated poor compliance, (Joffe et al, 2004; Kakkar et al, 2003) with the most recent survey showing that less

than 40% of at-risk hospitalised medical patients receive ACCP recommended prophylaxis (Bergmann et al, 2010).

6.3.1.2 National Institute of Health and Clinical Excellence (NICE) Guidelines on Thromboprophylaxis

After the WARP trial and the meta-analysis results were published in abstract form at the ASCO and the American Society of Haematology (ASH) meetings in 2005, and presented at the annual UK National Cancer Research Institute (NCRI) Conference Thrombosis and Malignancy workshop, the author was invited, after interview, in 2007 to participate in the National Institute of Health and Clinical Excellence (NICE) clinical development group (CDG) to produce guidelines on, “Venous thromboembolism: reducing the risk. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital” (National Institute of Health and Clinical Excellence, 2010) and advise on the cancer related topic areas and central venous catheters. The guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in 'The Guidelines Manual' (National Institute of Health and Clinical Excellence, 2009). Clinical questions were developed to guide the literature searching process and to facilitate the development of recommendations by the CDG, based around, ‘What is the effectiveness of X vs Y in reducing the incidence of VTE, where X and Y are the mechanical, other non-pharmacological (e.g. exercise and foot elevation) and pharmacological prophylaxis interventions?’ The primary outcomes comprised all cause mortality, deep-vein thrombosis (DVT) [symptomatic and asymptomatic], pulmonary embolism (PE), and major bleeding events, similar to the WARP study. Secondary endpoints sought

were post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension, heparin-induced thrombocytopenia, neurological events, quality of life, survival and length of stay. The methods utilised for the guidelines generally followed that of the meta-analyses outlined in section 4.3.1 but over a broader range of conditions with a larger variety of interventions (including warfarin and LMWH). The CDG reviewed the results of these but also of 'network' meta-analyses (combining direct and indirect evidence).

6.3.1.3 Recommendations

Risk assessment is crucial for all patients attending hospital including daycase patients.

6.3.1.3.1 Patients with cancer

Offer pharmacological VTE prophylaxis to patients with cancer who are assessed to be at increased risk of VTE. Choose any one of:

- Fondaparinux sodium
- Low Molecular Weight Heparin
- Unfactionated Heparin (for patients with renal failure)

Start pharmacological VTE prophylaxis as soon as possible after a risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.

Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with cancer having oncological treatment who are ambulant.

Warfarin is not included in this list as LMWHs have been shown to be of greater efficacy in primary thromboprophylaxis (Figure 5.1.2.5).

6.3.1.3.2 Patients with central venous catheters

- Do not routinely offer pharmacological or mechanical VTE prophylaxis to patients with central venous catheters who are ambulant.
- Consider offering pharmacological VTE prophylaxis with LMWH (or UFH for patients with renal failure) to patients with central venous catheters who are at increased risk of VTE.

All patients are to be assessed for risk of VTE and bleeding

Again, warfarin is not included in this list.

6.3.1.4 Assessing the risks of VTE and bleeding

Assess all patients on admission to identify those who are at increased risk of VTE. Reassess patients' risks of bleeding and VTE within 24 hours of admission and whenever the clinical situation changes.

Medical patients are considered being at increased risk of VTE if they:

- have had or are expected to have significantly reduced mobility for 3 days or more **or** are expected to have ongoing reduced mobility relative to their normal state **and**
- have one or more of the risk factors shown in Table 6.3.1.1

Surgical patients are considered as being at increased risk of VTE if they meet one of the following criteria:

- surgical procedure with a total anaesthetic and surgical time of more than 90 minutes, or 60 minutes if the surgery involves the pelvis or lower limb

- acute surgical admission with inflammatory or intra-abdominal condition expected significant reduction in mobility
- one or more of the risk factors shown in Table 6.3.1.1

Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis. Do not offer pharmacological VTE prophylaxis to patients with any of the risk factors for bleeding shown in Table 6.3.1.2, unless the risk of VTE outweighs the risk of bleeding.

Table 6.3.1.1 Risk Factors for Venous Thromboembolism

Active cancer or cancer treatment	One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
Age over 60 years	Personal history or first-degree relative with a history of VTE
Critical care admission	Use of hormone replacement therapy
Dehydration	Use of oestrogen-containing contraceptive therapy
Known thrombophilias	Obesity (body mass index [BMI] over 30 kg/m2)

Table 6.3.1.2 Risk Factors for Bleeding

Active bleeding	Acute stroke
Acquired bleeding disorders (such as acute liver failure)	Thrombocytopenia (platelets less than 75 x 10^9/l)
Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with international normalised ratio [INR] higher than 2)	Uncontrolled systolic hypertension (230/120 mmHg or higher)
Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours	Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)
Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours	

Updating guidelines on a regular basis is crucial to safe practice. Separate institutions and organisations in many countries are compiling guidelines from first principles such as the UK NICE guidelines, using the same evidence; an international effort with member state representation is called for to provide consistency.

Despite the evidence for increased risk of VTE among patients with cancer and the benefit of prophylactic anticoagulation in high risk areas e.g. surgery, surveys of clinicians have demonstrated low rates of compliance with guidelines. Further efforts are underway in the NHS to improve the implementation and utilisation of the NICE thromboprophylaxis guidelines in order to bring clinical practice in concert with the current recommendations. This is being monitored nationally and carries financial disincentives for non-compliance.

6.3.2 Conclusion

Cancer related VTE in general is increasingly prevalent, with a 28% increase found in hospitalised patients between 1995 and 2003 (Khorana et al, 2007c), although CRT rates have reduced markedly in the last two decades. The past few years has seen an increasing recognition amongst health providers of the impact of thrombotic complications on cancer patients including catheter-related thrombosis and, with this, important strides in research in this field. WARP surpassed existing trials and provided the data necessary to influence clinical practice. There is no role for fixed dose warfarin (1mg daily) in thromboprophylaxis in cancer patients with central venous catheters. Our study was unique in that for the first time a variable dose arm (DAW) was investigated for efficacy of thromboprophylaxis. This was found to be superior to FDW; however, offsetting this therapeutic benefit, was the increase in bleeding incidence. But perhaps more tellingly, there were two deaths from bleeding in which warfarin was a contributory factor and therefore, in balance, there does not appear to be a role for warfarin in any dose in the thromboprophylaxis in cancer patients with central venous catheters. With vigilant monitoring, clinicians may wish to choose DAW in high risk cases. However, warfarin is not recommended for use in this setting in the recent NICE guidelines (2010) and LMWH may be a more appropriate choice for this population of patients only. The risk / benefit ratio is always going to be the sine qua non with respect to anticoagulation therapy.

To reduce the public health burden of VTE in cancer patients with CVCs, it is vital to identify patients at greatest risk, for whom prophylaxis may benefit. On the other hand, the majority of patients in WARP who did not have a VTE (low risk) should

over time be excluded from prophylaxis studies to protect them from unnecessary treatment. Risk models and markers of thrombosis will therefore become increasingly important in order to reduce the often devastating adverse effects of thrombosis. The outcomes from WARP and associated research in this thesis played an important role in defining relevant parts of national thromboprophylaxis guidelines, thus completing the research cycle from initial empirical observation to implementation of national guidance.

6.3.3 Future Research

From the evidence presented in this thesis; firstly, that low dose warfarin confers no advantage over no warfarin in the thromboprophylaxis of cancer patients with CVCs, secondly, that warfarin (adjusted to maintain the dose between 1.5 and 2.0) does reduce the thrombotic rates in comparison to warfarin 1mg daily but has a propensity towards higher major bleeding events and thirdly, from the meta-analysis performed, that LMWH does not reduce the thrombotic rates in this population, the focus of future thromboprophylaxis research in cancer patients is likely to be around the utility of the novel, emerging oral anticoagulant agents. The scientific rationale for continued research of thromboprophylaxis and survival with anticoagulants, outlined in section 3.3.5.6, remains compelling. With the improvements in catheter placement and insertion, reduced thrombosis rates and an increasing use of oral fluoropyrimidines, the emphasis of future research will switch from catheter-related thromboprophylaxis to the investigation of the effect of these novel agents on VTE, cancer recurrence and survival in the adjuvant setting.

However, one final international study of a novel oral anticoagulant in the prophylaxis of VTE in cancer patients with CVCs is being discussed at the International Society of Thrombosis and Haemostasis Malignancy Subgroup. This study will require around 1000 patients in each arm to detect differences from 5% to 2.5% with 80% power at the 5% significance level (2-sided test). This could only be achieved with international collaboration, led by the newly formed Warwick Cancer and Thrombosis Network.

Colorectal cancer emerged as a significant risk factor for thrombosis in comparison to all other tumour sites (grouped together) and colorectal tumours are known to be hypercoagulable (Alcalay et al, 2006). To this end, a randomised phase II trial of placebo versus two doses of a novel oral anticoagulant, has been designed, firstly to investigate safety and pharmacokinetics parameters in patients with advanced colorectal cancer, before progressing into a large phase III trial in the adjuvant setting. The development of the Warwick Cancer and Thrombosis Network which includes internationally renowned experts in this field, has the potential to provide useful insight into the natural history of colorectal cancer and the role of anticoagulants in changing its metastatic potential.

Finally, an audit of NICE Guidelines will be executed to investigate the impact of the guidelines on clinical practice in the UK. This will include specific questions on CVC thromboprophylaxis which can then be compared with the national survey described in this thesis.

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8. Publications and Peer-reviewed Presentations

8.1 *Pre-trial Survey*

Key results as part of WARP Trial, in publication below.

8.2 *WARP Trial*

1. **Young, AM**., Begum, G., Billingham, L J., Hughes, AI., Kerr, DJ., Rea, D., Stanley, A., Sweeney, A., Wheatley, K., Wilde, J., WARP Collaborative Group, UK. WARP - A multicentre prospective randomised controlled trial (RCT) of thrombosis prophylaxis with warfarin in cancer patients with central venous catheters (CVCs)**.** *J Clin Oncol* (Meeting Abstracts) 2005 23: LBA8004 – oral presentation (Young et al, 2005).

2. **Young, AM**., Billingham, LJ., Begum, G., Kerr, DJ, Hughes, AI, Rea, DW, Shepherd, S, Stanley, A, Sweeney, A, Wilde, J & Wheatley, K. (2009) Warfarin thromboprophylaxis in cancer patients with central venous catheters (WARP): an open-label randomised trial. *Lancet*, 373 (9663): 567-574. (Young et al, 2009).

3. Central Venous Catheters and Thrombosis in Cancer Patients
   Young AM, Begum G, Billingham LJ, Hughes AI, Sweeney A, Wronski S, Ashton A, (2007) NCRI Conference # A185. (Young et al, 2007)
   Poster [Appendix 9]

8.3 *Meta-analyses*

1. Wheatley, K, Gross, LE., Hills, R. K., & **Young, AM**. 2005, "Meta-Analyses of Randomised Controlled Trials (RCT) of Warfarin and Low Molecular Weight Heparin (LMWH) for the Prevention of Venous Thromboembolism (VTE) and Death in Cancer Patients", *ASH Annual Meeting Abstracts*, 106 (11) Abstract 909. (Wheatley et al, 2005) Poster [Appendix 9]
2. Independent Risk Factors of Catheter-Related Thrombosis (CRT) in Adult Cancer Patients: An Individual Patient-Level Data (IPD) Meta-Analysis of Randomized Clinical Trials and Prospective Cohort Study. Saber W, Moua T, Williams EC, Verso M, Agnelli G, Couban S, **Young AM**, De Cicco M, Biffi R et al. (2010) *Journal of Thrombosis and Haemostasis 9 (2): 312-319* (Saber et al, 2011); Abstract Form: (Saber et al, 2008)

8.4 *Guidelines*

National Institute of Health and Clinical Excellence. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. National Collaborating Centre for Acute and Chronic Conditions Chapters 26, 27 and 28. Clinical Guideline 92. 2010. (National Institute of Health and Clinical Excellence, 2010)

8.5 *Other*

Young A and Stanley A. Primary Prevention of Venous Thromboembolism in Medical and Surgical Oncology Patients. (2010)

British Journal of Cancer **102**: S10-S16

9. Appendices

Appendix 1	Pre-trial Survey
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APPENDIX 1

Pre-trial Survey

A Randomised Study Comparing Two Warfarin Prophylactic Regimes Against No Warfarin in Oncological Patients With Indwelling Central Vascular Access Devices

Please take a few moments to complete this questionnaire to let us know your current clinical practice

Name:

Address: *Tel:*

Fax:

Section 1

A: What types of central venous/arterial catheters do you use for administration of cytotoxic drugs? Please list.

_____

_____

_____

B: When using such catheters, which drugs do you use and for which diseases? Please list.

Disease	**Drug**
_____	_____
_____	_____
_____	_____
_____	_____

C: Do you routinely administer oral warfarin for prevention of thrombosis after insertion of central venous catheters?

YES ☐ what dose? ___mgs How frequently? _____per day

NO ☐ please state your reasons briefly

_____

D: Do you routinely administer oral warfarin for prevention of thrombosis after insertion of central arterial catheters?

YES ☐ what dose? ___mgs How frequently? _____per day

NO ☐ please state your reasons briefly

_____

E: Roughly, what percentage of patients with central venous/arterial catheters in your practice do you estimate have a thrombosis?

At what time, post insertion of catheter, do these most commonly occur?

☐ 0-7 days ☐ 7-14 days ☐ 14-28 days ☐ Over 28 days

Section 2

We are planning to address the question:, "Does the administration of warfarin – either 1mg/day or adjusted to keep INR at 1.4-2.0 – post insertion of catheter, prevent thrombosis?"

1. Do you think this is an important question? ☐ **YES** ☐ **NO**

2. Would you be interested in finding out more about the trial with a view to participation? ☐ **YES** ☐ **NO**

3. If so, who would be the principal contact(s) at your hospital?

Any other comments?

_____

_____

_____

_____

_____

_____

_____

Please return this questionnaire in the pre-paid envelope or send to

Annie Young, Research Nurse Manager, Clinical Trials Unit, Clinical Research Block, CRC Institute for Cancer Studies, The Medical School, University of Birmingham B15 2TA

Thank you for your time

APPENDIX 2

WARP Catheter Care Guidelines

WARP Catheter Care Guidelines

September 2004 Version 3

adapted from Vascular Access Devices Chapter in The Royal Marsden Hospital Manual of Clinical Nursing Procedures, 5th edition, 2000 (Dougherty L, 2000)

Contents:

Deciding on the choice of line and where to insert

1. Preventing Infection
2. Maintaining a closed intravenous system
3. Maintaining Patency
4. Preventing Damage to the CVC
5. Discharging patients with a CVC in situ
6. Removing the CVC safely

1. Deciding on the choice of line and where to insert

The clinician responsible for the patient will decide upon choice of line and insertion site. If the clinician is not trained in the insertion of the particular line required, or is unsure what is required, advice from an expert IV team, should be sought. Choosing the anatomical site:

Internal jugular vein

The internal jugular route is more straightforward than the subclavian in terms of procedural difficulty. Internal jugular lines are more mobile than subclavian lines. However, the use of specially designed skin fixation devices, such as the Statlock™, can improve the stability of fixation of internal jugular lines and this has been shown to reduce the rate of infection (Crnich CJ and Maki DG, 2002) . Their use should be considered.

Subclavian vein

In general, subclavian lines are less likely to get infected because there is less movement of the catheter in the skin at the site of insertion. They are however, associated with more complications. There is a greatly increased risk of pneumothorax compared to the internal jugular route as the pleura lies immediately below the subclavian vein and artery (Galloway S and Bodenham A, 2004). Should inadvertent arterial puncture occur, it can be more difficult to control bleeding. Because of the increased risk of arterial puncture with the subclavian route, and the inherent difficulty of controlling haemorrhage, the patient should have clotting results and platelet count checked if there is a perceived or known risk of bleeding (Hadaway LC, 2001; Perucca R, 2001; Egan Sansivero G, 1998).

Femoral vein

In rare circumstances, the femoral venous route may be necessary, but this is associated with a higher rate of infection by virtue of the anatomical location.

Larger peripheral veins

PICC lines will frequently be inserted into veins at or around the antecubital fossa.

Ultrasound guidance

Ultrasound guidance should be considered whenever an internal jugular line is placed, as the technique has been shown to be safer and more efficient than the traditional landmark technique. This, however, depends on the appropriate

equipment being available and the user being competent in its use, as in unskilled hands, ultrasound could be more dangerous than the landmark technique. Certain ultrasound devices (e.g. Sonosite) also allow the patency of the vein to be assessed, using Colour Power Doppler techniques. Ultrasound can be used to help identify the location, route and patency of the subclavian vein but the technique is limited by the presence of the clavicle, which blocks ultrasound transmission. NICE guidance is awaited.

Choosing the type of line

When CVC access is needed for more than two weeks:

Because of the increased risk of colonisation or line-related septicaemia, if a CVC is needed for more than two weeks, consideration should be given to inserting a tunnelled line. This will usually require a patent subclavian vein (the left is easier anatomically than the right). Internal jugular lines can be tunnelled but it is technically more difficult and there could be a greater incidence of line occlusion due to the more circuitous route. If more than one lumen is necessary, then a more specialised line such as a multilumen Groshong or Hickman line will be necessary.

Preventing Infection

Bloodstream infections associated with the insertion and maintenance of CVC's are among the most dangerous infections that can occur further compromising a patient's health and often requiring hospitalisation (Emerson et al 1996).

Maximum barrier precautions should be utilised during the insertion of CVC's in order to minimise the risk of an insertion related infection to the patient.

Cleaning solutions of preferably a 2% Chlorhexidine Gluconate in 70% Isopropyl Alcohol, should be used for skin cleaning prior and post CVC Insertion and for cleaning the needle-free devices (e.g. Bionector/interlink system) prior to accessing the line. If any line is not compatible, 2% aqueous solution must be used as an alternative. If the patient is allergic to chlorhexidine, a povidine iodine based product can be utilised however the time frame that povidine iodine is efficacious is significantly diminished (Maki DG, Ringer M et al, 1991).

It is recommended that the potential insertion site be cleansed in concentric circles moving from intended site out towards the periphery (Baranowski L, 1993).

An aseptic technique in line with each trust's infection control policy should be used wherever the line is accessed and during procedures involving the exit site. This includes hospital wards. Sterile powder free gloves and a non-touch technique should always be used when handling a CVC. Hickman and Groshong lines are held in place with sutures following insertion. The top sutures should remain in place for 7 days and the sutures around the exit site for a minimum of 14 days. As it is likely that there will be some bleeding from the exit site following insertion of a CVC it is recommended that the dressing is changed within 24 hours of insertion. Following this initial dressing change a transparent semi permeable occlusive dressing (e.g. IV 3000, Smith and Nephew) allows for moisture vapour transmission whilst enabling daily inspection for any signs of infection. It is recognised that some patients may be sensitive to this type of dressing and therefore other dressings may be required which require closer monitoring. Where dressings are utilised, they should be inspected regularly and renewed immediately should it become soiled, wet or detached. If the dressing is intact with no signs of complications weekly dressings can be undertaken. If the exit site is red, painful or exudating, a minimum of daily dressing is required. Any signs of systemic or local infection should be referred to the specialist intravenous (IV) team for advice.

If the patient develops pyrexia of unknown origin, then catheter sepsis should be suspected. In this scenario blood cultures should be taken from each lumen of the CVC as well as peripheral cultures.

Patients should be advised that whilst a CVC is in situ it is advisable that a shower is taken in preference to a bath. However if patients wish to bathe they should be advised that the exit site should be kept out of the bathwater. Patients with a CVC should be advised against swimming.

2. Maintaining a Closed Intravenous System

If equipment becomes accidentally disconnected, there is a risk of air emboli or profuse blood loss. Fatal air emboli may occur when small bubbles accumulate and form tenacious bubbles that block the pulmonary capillaries. Due to the physiology of respiration and its impact on the central veins, if a central catheter is inserted and becomes open to the atmosphere air will be sucked into the circulatory system at a rate of up to 100ml/second (Phifer TJ, Bridges M et al, 1991). All equipment used with vascular access devices should be Luerlock to minimise the risk of disconnection. A needleless system is the preferred method for accessing any venous access device; the manufacturer's recommendations for frequency of changing of these systems must be adhered to. The in line clamp or external clamp should be used to close the catheter when changing equipment. Air in line detectors should be used to monitor for air bubbles in administration sets when delivered via an electronic infusion device. Infusions, which are not administered via an electronic device, should be monitored very closely to prevent the infusion running dry particularly where an air inlet is utilised to enable infusion.

The removal of a central line is a time of high risk for air emboli as for a brief period the vein is open to the atmosphere. When patients are able they should lie supine or in the Trendelenberg position for removal of a CVC. If a patient is unable to lie flat the line should be removed whilst the patient performs the Valsalva manoeuvre or during expiration. The patient should remain lying flat if possible for 30 minutes after catheter removal (Drewett SR, 2000). When removing the line gentle digital pressure should be applied to the exit site until haemostasis is achieved. It is documented there is a risk of an air emboli for up to 72 hours following a central line removal, this risk proportionally increases with the length of time the catheter remained in situ. This would appear to be due to the persistence of the skin tract to the vein (Hanley PC, Click RL et al, 1984). It is therefore recommended that an occlusive dressing be applied to the site for 24-72 hours until epithialisation has occurred (Drewett SR, 2000).

3. Maintaining Patency

Prior to the catheter being utilised the patency, position and correct functioning of the line should be established. It is imperative that the patency of the catheter is maintained at all times, a blockage predisposes to device damage, infection and potential delay in treatment. The patency of any vascular access device should be established prior to administration of medicines. The health care practitioner should aspirate the catheter and check for blood return to confirm patency. If a vesicant is to be administered the location of the tip must be confirmed prior to utilisation if blood return is absent (Masoorli S and Angeles T, 2002).

There is no requirement to withdraw blood prior to routine flushing of a CVC unless blood samples or blood cultures are required. All lumens of indwelling CVC's should be flushed at established intervals and in accordance with manufacturer's guidance. Flushing with 0.9% sodium chloride should be performed before, between and after the administration of each different medication/solution to prevent precipitation inside the lumen. The volume of sodium chloride should be at least twice the volume of the catheter. Any unused lumen should be flushed at least once a week even if other lumens are being utilised. Heparinised saline unless contra-indicated is the preferred solution for maintaining patency of non-valve central venous catheters for intermittent use. The concentration of heparin should be the lowest possible that will maintain patency which is usually 10 iu/1ml 0.9% sodium chloride. Groshong lines do not require a heparinised flush due to their patented non-return valve.

Flushing of the central catheter should utilise a pulsated flush, which creates turbulence within the catheter lumen thereby removing debris from the internal catheter wall (Todd J, 1998; Goodwin ML et al, 1993). A positive pressure technique should be maintained when completing the flushing procedure, which helps prevent blood entering the catheter after flushing. This is accomplished either by clamping the line as the last 0.5ml are infused, maintaining pressure on the end of syringe whilst removing from the injection cap or utilising positive pressure injection caps.

4. Preventing damage to the Central Venous Catheter

Whenever accessing a CVC, only syringes of 10ml and above must be utilised as anything smaller may lead to a rupture of the catheter. To prevent accidental damage to CVC, scissors or toothed forceps should never be used on or near the CVC's. If the catheter has a clamp this should be moved at regular intervals to reduce the risk of damage at one point. Patients should be informed not to wear brooches in the vicinity of their CVC. Vacuum blood collection bottles should not be used without consulting the manufacturer's literature as these may create too much internal pressure within the catheter therefore increasing the risk of rupture.

5. Discharging Patients Home with a Central Venous Catheter in situ

Patients discharged home with a CVC should be educated regarding the care and maintenance of the device. Patients should be educated on potential complications of CVC's and initial management. Patients should be given 24-hour contact numbers to seek professional advice in case of any anxieties regarding CVC.

An initial catheter care pack should be supplied with the patient on discharge, which includes equipment for flushing of the line and dressing change. If patients have a peripherally inserted central catheter (PICC) in situ they should be educated regarding the importance of not placing anything heavy or sharp over the external portion of the PICC. Community nurses should be informed of patients who are at home with a CVC in situ. Written information should be sent from the hospital to the community nurses stating the exact position of the catheter tip, whether blood return has ever been obtained and potential signs and symptoms of catheter complications. If PICC is in situ, community nurses should also be informed of the length of PICC externally visible so that monitoring for migration can be undertaken at every visit.

6. Removing the Central Venous Catheter

Removal should only be undertaken by appropriately trained personnel to minimise pain, trauma, risk of air emboli and infection. This is an aseptic procedure. Prior to the procedure a full blood count and clotting screen may be required dependent upon diagnosis, treatment and concurrent medications. Following removal the CVC should be inspected to ensure complete removal has occurred. If there is any uncertainty a CXR should be performed to assess for radio opaque fragments, any fragments will require surgical removal. Following removal of CVC the tip may be sent to microbiology for bacterial culture and sensitivity assessment. This is particularly pertinent if catheter related infection is suspected or patient has pyrexia of unknown origin.

These guidelines were issued to the local coordinators when updated. No external monitoring of adherence to the guidelines was undertaken.

References in Section 7

APPENDIX 3

Example of Patient Information Sheet

Uncertain Preference - 3-arm Option

Patient Information Sheet

WARP –DOES WARFARIN PREVENT CATHETER CLOTS?

We would like to invite you to take part in a large clinical trial called the WARP study. We hope to involve 1400 cancer patients who are having a long tube or line (called a central venous catheter or CVC) inserted into a large vein so that chemotherapy may be given more easily. This sheet tells you about the study and what joining it would involve. You do not have to decide at once and you may wish to take this sheet away with you and discuss it with your relatives and friends first. Taking part in this study is entirely voluntary. If you do not want to take part, simply say so. Your nurses and doctors will respect your decision and your current and future care will not be affected in any way.

Why are we doing the WARP study?
One of the complications of giving chemotherapy through a CVC is that a blood clot (a thrombosis) may sometimes occur, either in the tube or in the vein leading from the tube. If this happens, it can cause discomfort and will interrupt your chemotherapy treatment for a short while. Very rarely, the clot can extend to the lungs and this may be life-threatening.
We want to find out if warfarin – a blood-thinning drug – given in very low doses, safely reduces the risk of getting a catheter clot. At the moment, around half of the doctors in the UK regularly prescribe warfarin for this purpose and the other half do not. We do not know if warfarin makes any difference or not in stopping clots forming. We are doing the WARP study to try and find out the most effective and safest way of preventing clots in and around the lines.

What is the study about?
There are three different treatments that we are comparing –

Treatment 1 **No warfarin** and

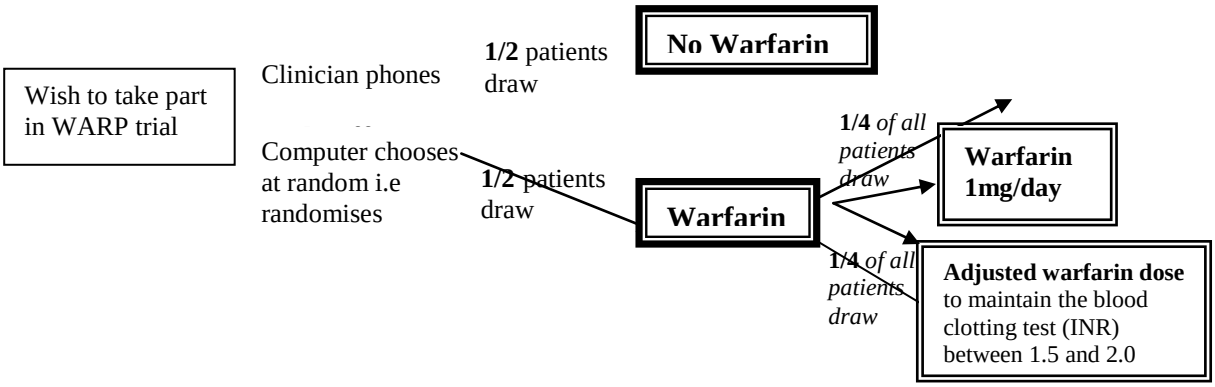
Treatment 2 **Warfarin - 1mg/day**

Treatment 3 **Adjusted** small doses of warfarin - to keep the blood clotting test
(the 'INR') between 1.5 and 2.0. The actual adjusted dose will be different for different patients. It will probably mean taking more than more than 1mg/day and if necessary, changing the dose up or down periodically, to get your blood clotting time in the range of 1.5 – 2.0.

Why is WARP important?
We want to find out the most effective and safest way of preventing clots in and around CVCs. To do this, we need to collect accurate information about large numbers of patients being treated by the three methods. We will be looking at differences in the number of clots and the intensity of any side-effects in the different groups.

What are the alternatives?
If you decide not to take part in the trial, your nurse or doctor will advise you of what their normal practice is with regard to prevention of clotting.

What would taking part involve?
If you agree to take part in the trial, we will telephone the Trials Office before you have your CVC inserted. They will tell us which 'treatment' you have been allocated. In order to make the choice of treatments for patients as fair as possible, the computer will choose one of the three treatments (no warfarin; warfarin 1mg/day or adjusted doses of warfarin) for you at random, i.e. 'randomise' you in the trial. Half the patients will draw no warfarin and half will draw warfarin. So you have a 50:50 chance of getting either one. If you are allocated *warfarin* treatment, you will then have another 50:50 chance of receiving either warfarin 1mg/day or the adjusted dose of warfarin:



If you are allocated to have no warfarin (treatment 1), your central line may be inserted anytime. If you are allocated warfarin (treatments 2 and 3), you should, if possible, start taking the warfarin tablets 3 days before the line is inserted and have your blood 'clotting' checked again on the day or the day before your line is placed.
For the patients who have been allocated treatments 1or 2, there should be no extra visits for monitoring clotting. If you are allocated the *adjusted* dose of warfarin (treatment 3), there will likely be a few more visits to the hospital outpatient clinic (or your GP's 'anticoagulant' clinic if they have one) to monitor your blood clotting time. This may be around 2 visits per month and can often be made to coincide with chemotherapy checks or treatments. Unfortunately we are unable to cover the costs of these extra clinic visits.
If you are allocated treatments 2 or 3, you should take warfarin until your CVC is removed or a clot occurs (the end of the trial), unless your doctor or nurse advises you otherwise. Your doctor and nurse may feel it is appropriate to continue your warfarin medication after the end of the trial, for an indefinite period, at the same dose. They will discuss that with you nearer the time. If warfarin is continued, you will be monitored as you were on the trial.

If you are allocated warfarin and become pregnant, you must contact your doctor to arrange to stop the warfarin as soon as the pregnancy is confirmed, as warfarin can damage the baby in the first part of the pregnancy.

In some centres only, you may be asked to give one extra blood sample (4 ml, a teaspoon) to be taken at the same time as routine bloods, on three occasions, for a special clotting factors test. These extra tests are entirely optional – if you are asked and do not wish to give the blood, please just tell the nurse or doctor.

Your nurses and doctors are very interested in WARP and, therefore, your progress will be followed very closely.

What are the side-effects ?
The side-effects of the your particular chemotherapy and the risks of having the line inserted will have already been explained to you. You will also have been told how to care for your line to avoid any infection in or near the line. If you have any questions about these procedures, please ask your nurse.

You should report any tenderness, swelling, or change in colour in the arm or the side where the line is as these may be early signs of a clot forming.
If you are allocated warfarin, we are not expecting any adverse effects at the small doses prescribed in this trial but we will monitor your blood clotting very carefully to minimise the possibility of any minor bleeding– a side-effect associated with this drug.
Very rarely, the bleeding may be large or may be life-threatening. We will ask therefore you to tell us immediately of any changes in the colour of your urine or stools and of any new pains. Also, some medicines that you may be taking may interfere with the action of warfarin so you must tell your nurse or doctor of all medications you are taking at all times.

What happens to the information?
We will give your GP information relating to this trial, only if you give permission.
Information about you collected for the trial will be kept at the Cancer Research UK Trials Unit at the University of Birmingham and is totally confidential. Only authorised members of the research team will have access to your medical records in order to collect the information we need for the study.
Results of the study will be published but nothing that could identify you individually will be reported.

Will participation in the study affect my legal rights?
There are no special arrangements for compensation in the event of you suffering any adverse event from taking part in the study. But, whether or not you take part, you would retain the same legal rights as any other patient treated in the National Health Service.

How do I join the study?
This is a decision for you to make and if you wish to take part, you should read this leaflet carefully and ask your nurse or doctor if there are things that you do not understand. If you choose to join the study, you will be asked to sign a consent form and then the nurse or doctor will call the study organisers and enter you into WARP. You may still change your mind and leave the study at any time you wish without any problem.

What happens at the end of the study?
After the trial, when your CVC is removed or there is a clot, your progress will be monitored as usual. We will do the analysis for all the patients and will inform interested patients of the results some time after the study has finished.

Could warfarin be a treatment for cancer?
Warfarin has been investigated as a cancer treatment for many years. There is little evidence to suggest that it makes any difference to the growth of different cancers. We will monitor this in WARP.

Contact Numbers
The nurse at your hospital will give you the local contact numbers.

Your local nurse contact is: _____ Tel: _____

You may also contact the lead investigator **Annie Young** in Birmingham, pager number: [redacted].

In addition, if you would like to discuss the study with an independent person, you can phone

……

We thank you for taking time to read this leaflet and consider the study, the answer to which will make it a lot easier for us to advise on how best to prevent catheter clots in future patients

APPENDIX 4

Consent Form

A MULTICENTRE PROSPECTIVE RANDOMISED CONTROLLED TRIAL OF THROMBOSIS PROPHYLAXIS WITH WARFARIN IN CANCER PATIENTS WITH CENTRAL VENOUS CATHETERS

Patient Consent Form

To be completed by the nurse/doctor

I have explained the nature of the WARP study to ……

I have explained the trial to my patient and he/she has agreed to enter the study. I have made it clear that he/she may withdraw at any time without giving a reason and without affecting any future care. The patient has been given the opportunity to ask any questions about the study and his/her treatment.

Nurse's / Doctor's name (print)…… Date……

Signature ……..

To be completed by the patient

I have read and received a copy of the information sheet provided. ☐

I confirm that I am satisfied with the information provided about the WARP study. ☐

I have had the opportunity to ask any questions that I have about the study. ☐

I understand that I am free to withdraw from the study at any time without giving a reason. If I decide to leave the study I understand that this will not affect my future care. ☐

I also understand that my medical records and any data collected as part of the study will remain confidential and will only be handled by authorised personnel associated with the study. ☐

Your signature indicates that you have read the patient information sheet and this form, have had any questions relating to the study answered satisfactorily, and willingly consent to participate.

Patients signature …… Date …….

Witness name (print) …… Status ……..……

Witness signature ……. Date

APPENDIX 5

Guidance for Nurses Taking Informed Consent

Guidance for Nurses Taking Informed Consent

In many centres, nurses are key to the ongoing informed consent process within their oncology/haematology research team. Nurses obtaining written informed consent add significant advantages (including continuity of care and reduced waiting times) to centres and patients. Nurses are also accountable for their actions in their own professional practice. The logical corollary from these statements is that if the nurse has explained the nature of the trial to the patient, then they should be the person signing to say this and not another party on their behalf.

The signature on the WARP consent form confirms that:

1) the description/implications of the trial have been given to the patient, highlighting that they may withdrawal at any time.

2) the person taking consent has given the patient the opportunity to ask questions:

See WARP consent form - extract below:

To be completed by the nurse/doctor

I have explained the nature of the WARP study to ……

I have explained the trial to my patient and he/she has agreed to enter the study. I have made it clear that he/she may withdraw at any time without giving a reason and without affecting any future care. The patient has been given the opportunity to ask any questions about the study and his/her treatment.

Nurse's / Doctor's name (print)…… Date……

Signature ……..

The principal investigator and the steering committee recommend therefore that those nurses (and indeed other healthcare professionals) who are sole professional signatory on the consent form should:

1. be deemed competent (knowledge and experience) in 'taking informed consent'
2. have endorsement from their employer with indemnity made clear (The Royal College of Nursing (RCN) indemnity cover is available for nurses who are involved in the informed consent process for research purposes).

Since WARP started, the team through the principal investigator has encouraged and supported nurses in the informed consent process, backed up by numerous professional guidelines and frameworks. During the trial, some helpful documents have been prepared and published on the attendant responsibilities of the nurse in 'seeking' and 'obtaining' informed consent (knowledgable explanation of trial, signature on form and ongoing availability to answer questions as they arise). These are cited below:

Consultation Document – RCN Guidance on Informed Consent in Health and Social Care Research (Royal College of Nursing, 2001) – the WARP principal investigator is one of the authors of this Guidance

The NCRN Clarification Statement and Briefing Paper re: 'Nurse Involvement in the Informed Consent Process'

http://www.ncrn.org.uk/downloads/informed_consent.pdf (last accessed December 2005).

A summary of the background to nurses participating in the informed consent process is given below:

- ICH (International Conference on Harmonisation, 2000) Guidelines for Good Clinical Practice (GCP) state that informed consent process and the associated responsibility of being the sole signatory on a consent from may be delegated by a physician.
- The Declaration of Helsinki (World Medical Assembly, 1964) states that obtaining consent should be done by a physician – this Declaration is currently a guideline and not law.
- The Department of Health Good Practice in Consent Implementation Guide: the law in England (Department of Health, 2001), point 6, states: 'It is always best for the person actually treating the patient to seek the patient's consent. However, you may seek consent on behalf of colleagues if you are capable performing the procedure in question or if you have been specifically trained to seek consent for that procedure'.
- The Department of Health, 'Good Practice in Consent Implementation Guide: Who should seek consent' (Department of Health, 2001) says that the same legal principles apply when seeking consent for research purposes as when seeking consent for investigations or treatment
- The Nursing and Midwifery Council (NMC), Code of Professional Conduct (Nursing and Midwifery Council, 1992) states: You (nurses) are professionally accountable for your practice. This means that you are answerable for your omissions, regardless of advice or directions from another professional.

This guidance was sent to all lead coordinators and lead investigators.

APPENDIX 6

Case Records Forms
1, 2 and 3

RANDOMISATION FORM – CRF 1

Patient Name:		Centre Name:	
Hospital No:		Responsible Clinician:	
Date of Birth:		Person Randomising:	

Sex: Male Female *please circle*

Part A – This section must be completed prior to randomisation

ELIGIBILITY CHECKLIST

All questions must be answered YES for the patient to be eligible.

	No	Yes
Histologically or clinically confirmed diagnosis of solid or haematological malignancy	☐	☐
Patient is due to have (or has had within last 7 days), a central venous catheter inserted for chemotherapy	☐	☐
Adequate haematological, hepatic and renal function	☐	☐
No contraindication to warfarin and not on warfarin	☐	☐
Not pregnant or lactating and taking adequate contraceptive measures, if appropriate	☐	☐
Signed consent for WARP	☐	☐

CENTRAL VENOUS CATHETER

Centrally placed ☐ **Peripherally placed** ☐ | **Left** ☐ **Right** ☐

CHEMOTHERAPY

Length of single treatment/infusion:	Bolus or under 24 hours ☐	24 hours and over ☐		
Scleroscant potential of regimen:	Sclerosant ☐	Non – sclerosant ☐	see appendix 1 in protocol	

INDICATION FOR WARFARIN

Is the indication for warfarin: UNCERTAIN: ☐ CLEAR: ☐

If UNCERTAIN, are you happy to randomise between no warfarin, fixed dose and individualised dose warfarin? **N** ☐ **Y** ☐

or (IF NO,) are you happy to randomise between fixed dose warfarin and no warfarin only? **N** ☐ **Y** ☐

If CLEAR, are you happy to randomise between fixed dose and individualised dose warfarin? **N** ☐ **Y** ☐

Part B – to be filled in at randomisation

Treatment Allocated: ☐ A: No Warfarin ☐ B: Warfarin 1mg/day ☐ C: Warfarin– to maintain INR between 1.5 and 2.0

WARP Trial No: ☐

Part C – this section may be filled in after randomisation

Central Venous Catheter Type:

Single/*Double/Triple Size e.g. 4f* ☐ *Material e.g. Silicone* ☐ *Type e.g. Groshong* ☐ *Manufacturer e.g. Bard* ☐

Do you use any type of fibrinolytic locks or positive pressure devices ? ***Yes*** ☐ ***No*** ☐

If yes please give details ……..

WHO Perf Status:

0 ☐ 1 ☐ 2 ☐ 3 ☐

Disease:

Primary Site: ☐

Stage of disease:

No residual disease / early disease ☐

or advanced disease ☐

Was the patient on tamoxifen pre-trial? **N** ☐ **Y** ☐ If yes, is the patient continuing with tamoxifen whilst on WARP? **N** ☐ **Y** ☐

For this patient are you using any form of heparin whilst on WARP, **including flushing of line** ? **N** ☐ **Y** ☐

If yes, please detail type, dose and frequency

……..

Signed (randomising clinician)**:** …….. **Date:** ____/____/__

Please return this form to: [redacted], Cancer Research UK Trials Unit
Institute for Cancer Studies, University of Birmingham, B15 2TT FAX: [redacted]

Randomisation telephone or fax: [redacted] or telephone [redacted] (toll free in UK)

END OF PRIMARY EVALUATION PERIOD FORM – CRF 2

Please complete (with patient if possible), at time of catheter removal

Patient Name: *or* Affix sticker here

Centre Name:

Date of Birth:

Consultant:

Today's date:

WARP Trial No:

All patients:

Chemotherapy:

Please continue overleaf if necessary

DRUG:	**DOSE** (mg/m^2)**:**	**DATES:**

Central Venous Catheter - Date of catheter insertion: ☐ Date of catheter removal: ☐

Any catheter-related complications (excluding thrombosis)? Detail below with dates:

Has patient had a thrombosis? **No** ☐ **Yes** ☐ please specify below :

Date of thrombosis: ☐ Diagnosed by: venogram ☐ ultrasound ☐

Location of thrombosis: ☐ position: **Left** ☐ **Right** ☐ (type) **Venous** ☐ **Arterial** ☐

Was the patient hospitalised due to thrombosis? **No** ☐ **Yes** ☐ for ☐ days

Was patient prescribed long-term anticoagulation? **No** ☐ **Yes** ☐

If **Yes**, oral ☐ subcut ☐ for ☐ months – please approximate

Grade of Thrombosis (circle worst grade only): 1 2 3 4

Duration of this grade (*in days*)

.....

Other Toxicity:
Only if potentially related to warfarin **CTC criteria** *on page 30 of protocol*

Toxicity	Site *or* description	Grade (circle worst grade only)	Duration of this grade *(in days)*
Bleeding:		1 2 3 4 *and* major ☐ minor ☐	.....
Other:		1 2 3 4	.....

	Due to: **warfarin** therapy	**thrombosis**
Trial-related* inpatient stays– total *in days*:	☐ *days*	☐ *days*
Total number of trial-related* outpatient attendances:	☐	☐
Total number of trial-related* GP visits:	☐	☐

*Trial-related means due to ***thrombosis or warfarin therapy*** (monitoring and adverse events) i.e. **'EXTRA'** visits due to WARP trial

Has the patient received warfarin? **NO** ☐ **YES** ☐ If yes, please detail below:

Date warfarin started: ☐ Date warfarin stopped: ☐

Was dose/range as per protocol **NO** ☐ **YES** ☐ Continuing at dose/range: ☐

If no, state dose/range achieved and reason for alteration and non compliance..... Reason warfarin stopped: ☐

Signed:..... **Date:**___/___/___

Please return to: [redacted], Cancer Research UK Trials Unit
Institute for Cancer Studies, University of Birmingham, B15 2TT FAX: [redacted]

FOLLOW-UP FORM - CRF 3

To be completed one year after randomisation date or on death of patient

Patient's Name: ..... **Date of Birth:** ____/____/____

Clinician: ..... **Centre Name:** .....

WARP Trial Number:

Since the last form (CRF2) was sent,

Has the patient had any late complication of warfarin treatment?

No ☐ **Yes** ☐ **N/A** ☐ If yes, please specify type and dates:

.....

Since the last form (CRF2) was sent,

Has patient had a thrombosis since CRF2 has been completed? No ☐ **Yes** ☐ please specify below :

Date of thrombosis:

Location of thrombosis:

Has the patient had any specialist referral or hospital admission for late toxicity? No ☐ **Yes** ☐

If yes, please specify:

.....

Since CRF2 was completed, has the patient received warfarin?

No ☐ **Yes** ☐ If yes, the current dose is ..... *or* date stopped____/____/___

Has the patient died? No ☐ Date patient last seen / contacted: ____/____/____

Yes ☐ please give details:

Date of Death: ___/___/___

Cause(s):

Cancer ☐ Site: .....

Possibly trial-related ☐ Please specify: .....

Other ☐ Please specify: .....

.....

Signed: ..... **Date:** ____/____/____

Please return to: [redacted], Cancer Research UK Trials Unit

Institute for Cancer Studies, University of Birmingham, B15 2TT FAX: [redacted]

APPENDIX 7

Example of WARP Newsletter

- **Please circulate this newsletter to all colleagues who may be interested in WARP**

WARP? Newsletter

March 2004

RECRUITMENT TO 15TH MARCH 2004

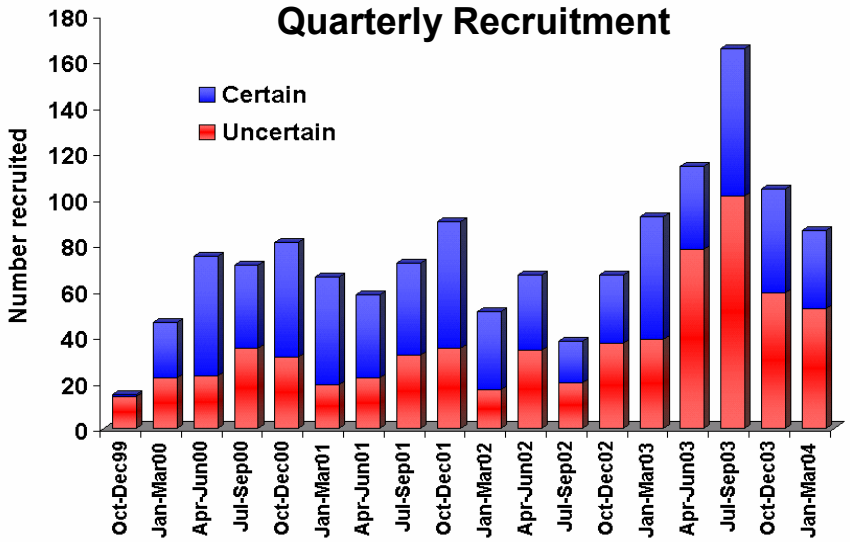
1358 Patients Entered **688** Certain indication *and* **670** Uncertain Indication

Thank you !

WARP NEEDS YOU! 242 PATIENTS TO GO!!

WARP has experienced a remarkable increase in recruitment in 2003, in particular to the uncertain indication (2-arm option). Recruitment figures doubled going from an average monthly recruitment of 19 patients in 2002 to an average monthly recruitment of 41 patient in 2003. We need to maintain the momentum. In the past two months, the number of patients entered into WARP has decreased slightly. Only 29 out of 64 centres have recruited patients in 2004. What's happened to the other 35?

Let's all give a last push to reach the recruitment target by September 2004!



Thank you to all the centres for your help and support

What about WARP II?

What is your next related clinically important question? Suggestions please to Annie Young

RECRUITMENT: TREATMENT BY INDICATION

	Treatment allocation			
	No Warfarin	Warfarin 1mg	Warfarin INR	Total
Uncertain Indication 3 arm	154	80	79	313
Certain Indication	0	345	343	688
Uncertain Indication 2 arm	178	179	0	357
Total	332	604	422	1358

Contacts: [redacted] - tel: [redacted], e-mail: [redacted]
Annie Young - tel: [redacted] e-mail: [redacted]

WARP is an NCRN-approved trial

TRIAL FORMS

Return of forms has been good so far, please remember to send forms in as soon as possible to [redacted] at CRUK Clinical Trials Unit, Institute for Cancer Studies, University of Birmingham, Birmingham, B15 2TT.

So far we have received
1227 forms returned for CRF1: Section c (1358 expected)
930 for CRF2 (1080 expected) and
703 for CRF3 (846 expected)

Keep them coming!

RECRUITMENT IN 2004 (UNTIL 15TH MARCH). THANKS AGAIN!

Centre	No. patients randomised	Centre	No. patients randomised
Royal Berkshire Hospital	12	Pinderfields Hospital	2
Western General Hospital	9	Princess Royal Hospital	2
Belfast City Hospital	8	Russells Hall Hospital	2
Cheltenham Hospital	6	Churchill Hospital	1
St Mary's Hospital. Portsmouth	6	Eastbourne District General Hospital	1
New Cross Hospital	5	Huddersfield Royal Infirmary	1
The Alexandra Hospital	4	Newcastle General Hospital	1
Royal Free Hospital	4	North Hampshire Hospital	1
Broomfield Hospital	3	Queen Elizabeth Hospital. London	1
St. Luke's Cancer Centre	3	South Tyneside District Hospital	1
Stoke Mandeville Hospital	3	St Mary's Hospital. Newport	1
Diana Princess of Wales Hospital	2	Walsgrave Hospital	1
Great Western Hospital	2	Wexham Park Hospital	1
Oldchurch Hospital	2	Worcester Royal Hospital	1
		Wycombe Hospital	1

Protocol amendments

Amendment No 5:
Protocol v. 7 - 2nd December 2003
Patient Information Sheets v. 6 - 2nd December 2003

! *Please remember to report any bleeding events in patients on the* ***no warfarin*** *arm as well as the other two arms*

Reported SAE's since October 2003

Type of Event	Requiring Hospitalisation	Life Threatening	Details	Recovery
Raised INR but no reported bleeding	✓	✓	INR>10, knock on arm that resulted in haematoma. Chest infection	✓
Bleeding & raised INR	✓	X	Malaena, INR=4.4, Hb=8.4, WBC=6.0, duodenal ulcer diagnosed	✓
Bleeding & raised INR	✓	X	INR=8.3, Hb=8.9, haematuria and bruising to hip, required blood transfusion	✓

Contacts: [redacted] - **tel:** [redacted], **e-mail:** [redacted]
Annie Young - tel: [redacted], **e-mail:** [redacted]

Thrombosis?

Radiologically confirmed thrombotic events that are deemed to be catheter-related are the primary endpoint for the trial, whilst those that are not thought to be catheter-related are secondary endpoints. Thromboses that are suspected but not radiologically confirmed are recorded and reported under CVC complications.

A thrombosis is categorised as non-catheter-related if:

- It is arterial; or
- It is located in the leg; or
- It is known to occur on the opposite side of the catheter; or
- It occurs >5 days post catheter removal

All thromboses are reviewed and classified as primary or secondary by an independent second observer (Dr Daniel Rea) as follows:

Primary Thrombosis	Secondary Thrombosis
Arm (Catheter side)	Arm (not Catheter side)
Axilliary	Leg DVT
Internal jugular	Arterial
Subclavian	IVC
SVC	
PE (most likely)	
Catheter	

How much do you know about WARP?

Take our quiz and you could win a £10 voucher

1. Which month did the WARP trial open to recruitment?
2. 2003 has without doubt been WARP's record-breaking year, but can you estimate how many patients were randomised into WARP in 2003?
3. What is the recent literature demonstrating for prophylaxis of thrombosis in cancer patients with CVCs? - Warfarin or not?
4. What does the WARP acronym stand for?

If you think you know the answers, you could win a £10 Boots voucher.

Send your answers to [redacted]
by post or e-mail: [redacted]
before 30th April 2004

All correct answers will be entered into the draw,
and the lucky winner will be picked at random and notified on 3rd May 2004

Good Luck!

Contacts: [redacted] - **tel:** [redacted], **e-mail:** [redacted]
Annie Young - tel: [redacted], **e-mail:** [redacted]

Literature Update

Randomised Trials

2003 Abstract - (full paper submitted to JCO). *Look out for this publication which was listed in last Newsletter but still unpublished*

Anderson D, Goodyear M, Burnell M, Dolan S, Wasi P, Barnes D, MacLeod D, Burton E, Andreou P and Couban S. A randomised double blind placebo-controlled study of low dose warfarin for the prevention of symptomatic central venous catheter-associated thrombosis in patients with cancer. *Journal of Thrombosis and Haemostasis* 2003; *Supplement 1 July* (abstract no. P1982).

255 patients with solid (70%) and haematological malignancies were randomised between 1mg and no warfarin (placebo). There were 11(4%) symptomatic CVC-associated thromboses; 5/125 (4%) in the placebo group and 6/130 (4.6%) in the warfarin group p=NS. Low dose warfarin did not reduce the incidence of symptomatic CVC-associated thrombosis in patients with cancer. 75% of patients' treatment was interrupted, usually because of thrombocytopenia.

Related Studies

1. Cancer Patients: LMWH - Primary Prophylaxis

Reichardt P, Kertzshmar A, Biakhov M et all: A phase III randomised, double-blind placebo controlled study evaluation the efficacy and safety of daily low-molecular-weight –heparin (dalteparin sodium) in prevention catheter-related complications (CRCs) in cancer patients with central venous catheters (CVCs). *Proc Am Soc Clin Oncol* 21: 369a, 2002 (abstract 1474)

The endpoint of this study was 'clinically overt' CRCs including thrombotic events requiring anticoagulant or thrombolysis, clinically overt PE and CVC obstruction requiring CVC removal. 425 patients were randomised to 5000iu dalteparin or placebo for 16 weeks within 5 days of CVC insertion. There was no benefit in the reduction of CRCs in the treatment arm as compared with placebo (3.7% vs 3.4%; p=0.9) A venographically determined endpoint may like WARP, may have resulted in a higher rate of venous thromboembolic events.

Largo SW, Verdonck LF, Borel Rinkes IH, et al: No effect of nadroparin prophylaxis in the prevention of CVC-associated thrombosis in bone marrow transplant recipients. *Bone Marrow Transplant* **26**:1103-1106, 2000

2. Heparin vs warfarin

Low – molecular-weight heparins or oral anticoagulation for the secondary prevention of deep vein thrombosis in cancer patients

Lee AY, Levine MN, Baker RI, BowdenC, Kakkar AK, Prins M, Julian JA, Haley S, Kovacs MJ and Gent M. Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer *N. Eng. J Med* 2003 349 (2): 146-153

In patients with cancer and acute venous thromboembolism, dalteparin was more effective than an oral anticoagulant in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding.

3. Interaction between warfarin and chemotherapy

Given the high percentage (~65 %) of patients in WARP are on fluorouracil-based chemotherapy, the following observations are of interest and strengthen the case for regular INR monitoring in patients on both warfarin arms of WARP and also make us consider the way our SAE collection (we request that no chemo-related SAEs be sent).

Masci G, Magagnoli M, Zucali PA, Castagna L, Carnaghi C, Sarina B, Pedicini V, Fallini M and Santoro A. Minidose warfarin for catheter-associated thrombosis in cancer patients: can it be safely associated with fluorouracil-based chemotherapy? *Journal of Clinical Oncology* **21**(4):736-739; 2003
A high incidence of INR abnormalities was observed in this cohort of patients

Review

Venous Thromboembolism Associated with Long Central Venous Catheters in Cancer Patients *JCO* **21**(1): 3665-3675; 2003.
Excellent review

APPENDIX 8

Recruitment Rates

Per Centre

Recruitment Rates per Centre

Centre	Frequency	%
Cheltenham General Hospital	214	13.5
St.Mary's, Portsmouth	93	5.8
Newcastle General Hospital	76	4.8
Belfast City Hospital Trust	75	4.7
Royal Berkshire Hospital	70	4.4
Western General Hospital	70	4.4
Queen Elizabeth Hospital, Birmingham	59	3.7
Exeter Oncology Centre	58	3.6
Diana Princess of Wales Hospital	57	3.6
Birmingham Heartlands Hospital	56	3.5
Huddersfield Royal Infirmary	54	3.4
Russells Hall Hospital	53	3.3
Cumberland Infirmary	46	2.9
St Luke's Cancer Centre	42	2.6
Singleton Hospital	39	2.5
St James's Hospital	32	2.0
Great Western Hospital	28	1.8
New Cross Hospital	26	1.6
Royal Sussex County Hospital	25	1.6
Churchill Hospital	24	1.5
Velindre Hospital NHS Trust	24	1.5
Charing Cross Hospital	20	1.3
The Essex County Hospital	20	1.3
Princess Royal Hospital	16	1.0
Royal Free Hospital	15	0.9
Royal South Hants Hospital	15	0.9
St George's Hospital	15	0.9
Wycombe Hospital	15	0.9
Walsall Manor Hospital	14	0.9
Cookridge Hospital	13	0.8
Princess Alexandra Hospital	13	0.8
South Tyneside District Hospital	13	0.8
The Alexandra Hospital	13	0.8
St Marys Hospital	12	0.8
Whiston Hospital	12	0.8
Plymouth Oncology Centre	11	0.7
Walsgrave Hospital	11	0.7
University College Hospital	10	0.6
Broomfield Hospital	9	0.6
Oldchurch Hospital	9	0.6
Addenbrookes Hospital	8	0.5
Pinderfields Hospital	8	0.5
Queen Elizabeth Hospital London	8	0.5
City Hospital NHS Trust	7	0.4

Royal Lancaster Infirmary	7	0.4
Stoke Mandeville Hospital	7	0.4
Guy's Hospital	6	0.4
Mount Vernon Hospital	6	0.4
Ninewells Hospital	6	0.4
Hammersmith Hospital	5	0.3
North Hampshire hospital	5	0.3
Derbyshire Royal Infirmary	4	0.3
Eastbourne District General Hospital	4	0.3
South Cleveland Hospital	4	0.3
Wexham Park Hospital	4	0.3
Worcestershire Royal Hospital	4	0.3
Aberdeen Royal Infrimary	3	0.2
Glasgow Royal Infirmary	3	0.2
Ipswich Hospital NHS Trust	3	0.2
Royal Gwent Hospital	3	0.2
Good Hope Hospital	1	0.1
North Devon District Hospital	1	0.1
Princess Royal University Hospital	1	0.1
Royal Hampshire County Hospital	1	0.1
Royal Preston Hospital	1	0.1
Sandwell Hospital	1	0.1
Warwick Hospital	1	0.1
West Cumberland Hospital	1	0.1

APPENDIX 9

Publications

Central Venous Catheters and Thrombosis in Cancer Patients

Annie Young[1], Gulnaz Begum[2], Anita Ashton[1], Sue Anderson[1], Lucinda Billingham[3], Ana Hughes[3], Debbie Hunter[1], Keith Wheatley[3]

[1] 3 Counties Cancer Network, [2] University of Warwick, [3] University of Birmingham

Background

Central Venous Catheters (CVCs) present a stress test to the coagulation system in cancer patients. The major thrombotic complication of CVCs is venous thromboembolism (VTE) and in the majority of cases, is asymptomatic.

However, catheter-related thrombosis (CRT) is a source of considerable morbidity, the most severe of which is pulmonary embolism. The last decade has seen an enormous increase in the use of CVCs to deliver infusional chemotherapy for a range of malignancies. Novel catheter designs are revolutionising patient care with attendant improvements in catheter care and placement.

The aetiology of CRT is multifactorial - trauma of catheter insertion, endothelial damage from chemotherapy, size and rigidity of catheter, stasis of blood flow around the catheter are factors which have been proposed but few randomised studies have been executed. Two significant risk factors for CRT, identified from a cohort study, were i) having had a previous catheterisation and ii) more than one attempt at insertion[1] – 'see Risk Factors'.

As part of the largest randomised trial of thromboprophylaxis with warfarin, in cancer patients with CVCs, named WARP, we examined catheter-specific risk factors for thrombosis.

Clinical Features of Thrombosis

Clinical features of thrombosis are variable and may not become apparent until total occlusion of the vessel occurs. Early symptoms include skin erythema overlying at catheter, oedema, discomfort, pyrexia and pain in arm on the catheter placement side. Later symptoms include facial swelling, neck distension and arm swelling. CRT is still an important clinical problem.

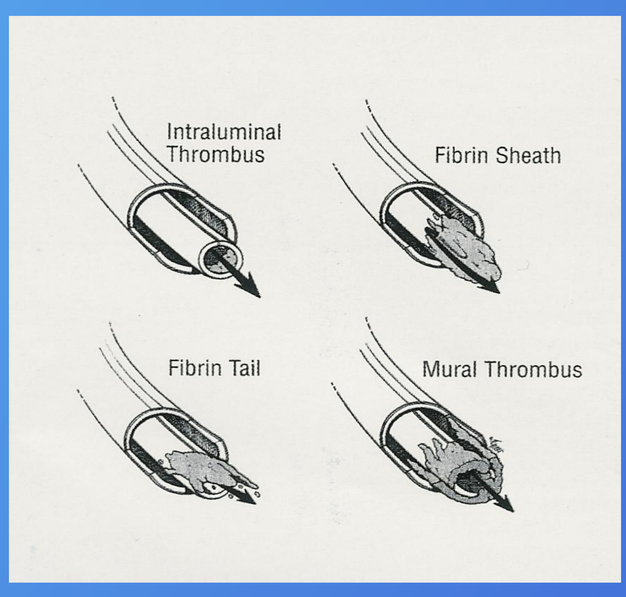
Types of Catheter Thrombosis

Intraluminal: within the catheter and often under-reported

Fibrin Tail: fibrin, blood cells and platelets adhere to the top of the catheter (often acting as a ball valve)

Fibrin Sheath: an extraluminal fibrin sheath is formed normally around the top of the catheter and may extend back along the catheter

Mural Thrombosis: fibrin from the vessel wall attaches to the catheter surface and is often a total occlusion



Methods

A logistic regression analysis was performed to identify potential predictors of a CVC-related thrombosis. Explanatory variables included stratification variables, catheter placement (central vs peripheral, treatment length (<24 vs 24 hours), sclerosant potential of chemotherapy (sclerosant vs non-sclerosant). CVC information was also considered, CVC lumen (single vs double/triple), CVC material (silicone vs other), Type of CVC (valved vs non-valved), CVC size (F). Forward, backward and step-wise regression techniques were applied, a 10% significance level was used for entering and removing from the model. A total number of 1547/1590 patients had complete CVC data and were included in analysis, of these 83 patients had suffered a CRT. Due to the small number of events this analysis was viewed as an exploratory exercise only and results are to be treated with caution. All analyses were performed using SAS statistical software (SAS Institute, SAS Circle, Cary, North Carolina, USA).

Results

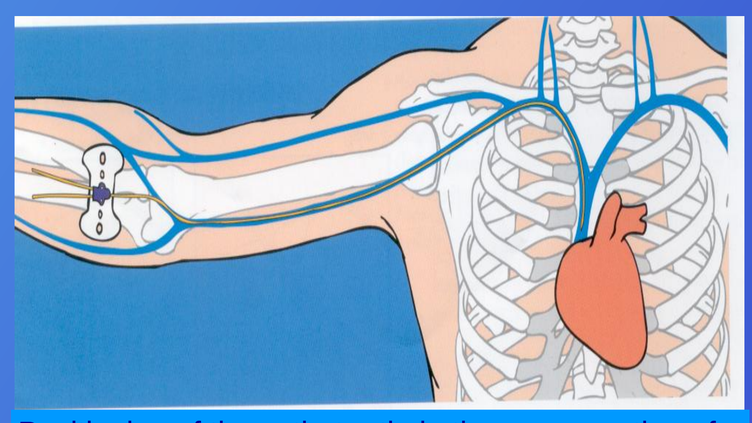
Of the 1590 patients randomised from 68 UK centres, the overall CRT rate was 5.3%. Warfarin demonstrated no apparent benefit over no warfarin (5.9% vs 5.9%, p=0.98). 916 (58%) of catheters inserted, were PICCs. 78% had single lumens; 92% were silicone; 40% >4F; 56% had non-return valves and 32% of catheters required heparin flushes. 21% of patients had catheter complications, 37% of whom had CVC infections. Median time to thrombosis was 37 days; IQR 13-80 days. Logistic regression identified CVC lumen as a potential predictor of a CVC-related thrombosis, with patients with double or triple lumen CVCs more likely to suffer a thrombosis than those with a single lumen. CVC material appeared to have some importance, showing CVCs made of silicone less likely to have a CRT than those made of polyurethane or other material. CVC infection, CVC insertion site, CVC type and CVC size were unrelated to the occurrence of CRT.

Conclusion

Overall, CRT rates are low, with warfarin adding no apparent benefit. This multivariate analysis demonstrates the only catheter-specific risk factor for thrombosis is a double or triple lumen catheter compared to single lumen, with non-silicone catheters showing a trend towards higher thrombotic potential.

Risk factors of Catheter Related Thrombosis

Very few prospective randomised studies have been undertaken to compare different types of catheters, ports, surface coatings etc. A number of potential risk factors for development of CRT have been suggested including CVC bioavailability (chemical and surface structure, rigidity, diameter, additive agents), number of lumens (3, 2 or 1), catheter tip, position, previous CVC insertions and site of insertion, insertion technique, CVC related infection and high platelet count. In the prospective single centre cohort study of Lee et al (2006)[2] significant baseline factors for CRT were: more than one insertion attempt, (p=0.03), ovarian cancer (p=0.01) and previous CVC insertion (p=0.03).



Positioning of the catheter tip in the upper portion of the lower third of the Superior Vena Cava is crucial. Other positions may increase the risk of thrombosis[2]

WARP Trial – Catheter Complications

Complication	n	%
Infection	152	47
Suspected thrombosis	6	2
Exit site leaking \ Bleeding	6	2
Inflammation \ Erythema \ Rash \ Bruising	22	7
Damaged or kinked \ Line leaking	33	10
Fibrin sheath \ Blocked catheter	29	9
Misplaced line \ Migrated	14	4
Line fell \ Pulled out	21	7
Other	37	12

References

For contact details contact Annie Young on e-mail: a.young@bham.ac.uk

1. **Incidence, Risk Factors, and Outcomes of Catheter-Related Thrombosis in Adult Patients With Cancer**
Agnes Y.Y. Lee, Mark N. Levine, Gregory Butler, Carolyn Webb, Lorrie Costantini, Chushu Gu, Jim A. Julian
JCO Mar 20 2006: 1404-1408

2. **Venous Thromboembolism Associated With Long-Term Use of Central Venous Catheters in Cancer Patients**
Melina Verso, Giancarlo Agnelli
JCO Oct 1 2003: 3665-3675

Meta-Analyses of Randomised Controlled Trials (RCTs) of Warfarin and Low Molecular Weight Heparin (LMWH) for the Prevention of Venous Thromboembolism (VTE) and Death in Cancer Patients

Wheatley K[1], Gross LE[1], Hills RK[1] and Young AM[2]

Birmingham Clinical Trials Unit, University of Birmingham, UK[1] CRUK Trials Unit, University of Birmingham, UK[2]

INTRODUCTION

Venous thromboembolism (VTE) is a common clinical problem in cancer patients. Uncertainty remains as to whether treatment with oral anticoagulants (OA - mainly warfarin) or low molecular weight heparin (LMWH), given by subcutaneous injection, is beneficial in primary and secondary thromboprophylaxis and practice varies widely. It has been proposed that anticoagulant therapy may also improve survival in cancer patients. Several randomised trials have investigated warfarin for VTE in cancer patients; other trials have looked at LMWH.

The largest trial of VTE prophylaxis in cancer patients with central venous catheters (CVCs), WARP, has just been completed and showed no apparent benefit for low dose warfarin. Among 811 patients randomised to low dose warfarin versus not, the VTE rate was 5% in both arms (OR = 1.04, 95% CI = 0.56-1.92, p=1.0) and mortality was not reduced (OR=1.02, CI=0.74-1.4, p=0.8) (Young *et al.*, ASCO, 2005, LBA8004). With this result needing to be put in the context of other RCTs of anticoagulants, we performed meta-analyses to evaluate the effect of warfarin and LMWH on primary and secondary VTE rates and mortality.

METHODS

TRIAL IDENTIFICATION AND ELIGIBILITY

A comprehensive computerised literature search was undertaken to identify relevant trials. This included searching abstracts on MedLine, Embase, NCI trials register and ACSO, ISTA and ASH meeting websites. Studies were eligible for inclusion if they were randomised trials of cancer patients comparing either treatment (warfarin or LMWH) with no treatment or one treatment with another (OA v LMWH) in the management of primary or secondary prophylaxis. These included studies using central venous catheters.

OUTCOME MEASURES

Data extracted by two independent reviewers included the type of, the dose and duration of treatment (warfarin or LMWH), whether it was primary or secondary VTE prophylaxis, the number of VTEs and deaths during the trial and whether the endpoint was symptomatic or asymptomatic (venographically determined) VTE.

ANALYSIS

Results were combined using standard meta-analytic techniques to estimate overall treatment effects for both VTE and mortality rates for the following treatment subgroup comparisons:

- **warfarin vs no warfarin**
- **LMWH vs no LMWH**
- **LMWH vs OA**

Differences in treatment effects between trials and subgroups were assessed using tests of heterogeneity. We also used a test for trend over trials to investigate whether results have changed over time in the warfarin v no-warfarin comparison.

TRIALS

14 eligible trials were identified with data on VTEs (total of 4154 patients) and 14 were identified with mortality data (total of 3790 patients). Trials were classified according to treatment comparison.

Ref	Author	Year	Endpoint	Prophylaxis	Subgroups	Placebo	Duration of Warfarin	Patients
1	Zacharski	1984	Mortality	-	-	-	Mean of 26.4 wks	NSC lung, colorectal. H&N, prostate, SCLC
2	Chahinian	1989	Mortality	-	-	-	Median of 162 days	SCLC
3	Bern	1990	Asymptomatic & Mortality	Primary	CVC	No	90 days	Mixed – mainly solid tumour
4	Maurer	1997	Mortality	-	-	-	113 or 197 days (protocol amended part way through)	SCLC
5	Park	1999	Asymptomatic	Primary	CVC	No	63 days	Solid
6	Heaton	2002	Symptomatic & Mortality	Primary	CVC	No	90 days	All haematological
7	Couban	2005	Symptomatic & Mortality	Primary	CVC	Yes	63 days	80% haematological
8	Young (WARP)	2005	Symptomatic & Mortality	Primary	CVC	No	100 days	Mixed – 98% solid tumour; 50% colorectal

Table 1: Warfarin v No Warfarin Trials

Ref	Author	Year	Endpoint	Prophylaxis	Subgroups	Placebo	Dur/Dose of LMWH	Patients
9	Monreal	1996	Asymptomatic & Mortality	Primary	CVC	Yes	Fragmin 2500iu/day for 90 days	Solid Tumour
10	Reichardt	2002	Symptomatic	Primary	CVC	Yes	Dalteparin 5000iu for 16 wks	Unknown
11	Kakker	2004	Mortality	-	-	Yes	Dalteparin 5000iu/day for 1year	Solid Tumour
12	Altinbas	2004	Mortality	-	-	-	Dalteparin 5000iu/day for 18 wks	SCLC
13	Haas	2005	Asymptomatic	Primary	Breast/ Lung	Yes	Certoparin 3000iu/day for 6 months	Breast, Lung
14	Klerk	2005	Mortality	-	-	Yes	Nadroparin according to weight.	Solid tumour
15	Verso	2005	Asymptomatic	Primary	CVC	Yes	Enoxaparin 40mg/day for 6 wks	90% solid tumour

Table 2: LMWH v No LMWH Trials

Ref	Author	Year	Endpoint	Prophylaxis	LMWH	Duration of OA	Patients
16	Meyer	2002	Symptomatic & Mortality	Secondary	Enoxoparin 1.5mg/kg/day	3 months	90% Solid Tumour, 10% malignancies
17	Deitcher	2003	Symptomatic	Primary CVC	Enoxoparin 1mg/kg for 5 days	180 days post 5 days enoxaparin	Solid Tumour
18	Lee	2003	Symptomatic	Secondary	Dalteparin 200iu/kgday for 5-7 days (then warfarin) v 1 month dalteparin 200iu/kg+5 months of 150iu/kg/day for 4 months	5-7 daysLMWH then 6 mnths warfarin	90% Solid Tumour, 10% malignancies
19	Mismetti	2003	Symptomatic	Secondary	Nadroparin 2850iu/day	90 Days	Solid Tumour
20	Hull	2003	Symptomatic	Secondary	Tinzaparin 175 antiXa U/kg (84 days)	5 days heparin then 84 days warfarin	Cancer subgroup

Table 3: LMWH v OA Trials

RESULTS

WARFARIN VERSUS NO WARFARIN

Data was available on VTEs in 5 trials (1355 patients). There was no significant difference between warfarin and no-warfarin treated patients in the incidence of VTEs (Odds Ratio (OR) = 0.75, 95% Confidence Interval (CI)=0.5 to 1.13; p=0.2) (Figure 1). There was some evidence of heterogeneity between the treatment comparisons (p=0.05) and of a trend over time in trial outcomes (p=0.01).

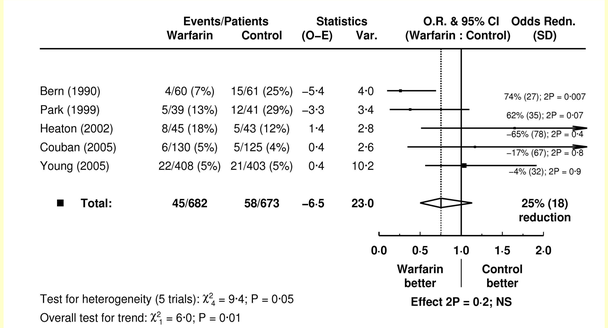


Figure 1: VTEs in Warfarin v No Warfarin Trials

An additional 3 trials had survival data (2033 patients in 7 trials in total). There was no clear evidence of a difference in mortality rates for warfarin compared to no-warfarin treated patients (OR = 0.2, CI = 0.81 to 1.01; p = 0.07) (Figure 2).

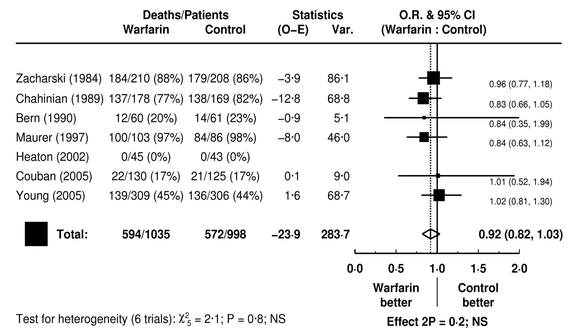


Figure 2:Mortality Rates in Warfarin v No-Warfarin Trials

LMWH VERSUS NO LMWH

4 eligible trials comparing LMWH with no treatment for VTEs were found with a total of 1667 patients. There is evidence that VTE rate is reduced in patients treated with LMWH as compared to no treatment (OR = 0.64, CI = 0.44 to 0.94; p = 0.02) (Figure 3).

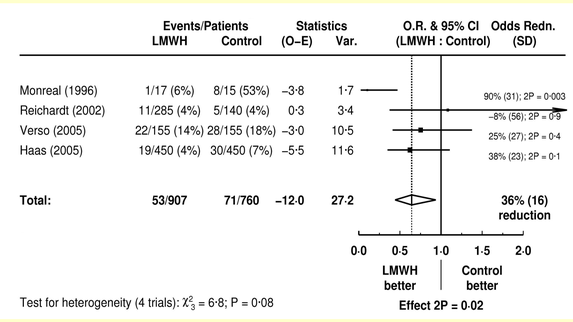


Figure 3: VTEs in LMWH v No LMWH Trial

One of the VTE studies and an additional 3 other trials had mortality data available (772 patients). Mortality rates in LMWH patients were reduced by 23% (OR = 0.77, CI = 0.66 to 0.90; p=0.001) (Figure 4).

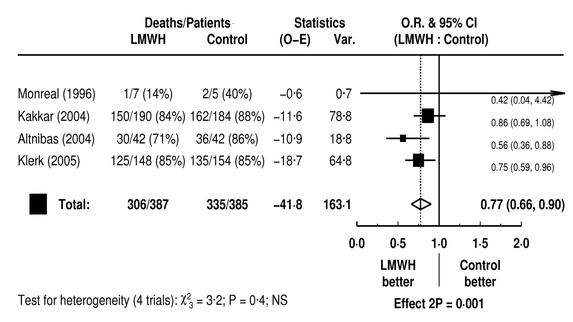


Figure 4: Mortality in LMWH v No-LMWH Trials

LMWH VERSUS ORAL ANTICOAGULANTS (OA)

5 trials (1132 patients) were found to be eligible for investigating VTE rates in patients treated with LMWH compared to oral anticoagulants. VTE rates decrease significantly more in patients treated with LMWH with 9% occurring on LMWH compared to 16% occurring on OA (OR = 0.50, CI = 0.35 to 0.72; p=0.0001) (Figure 5).

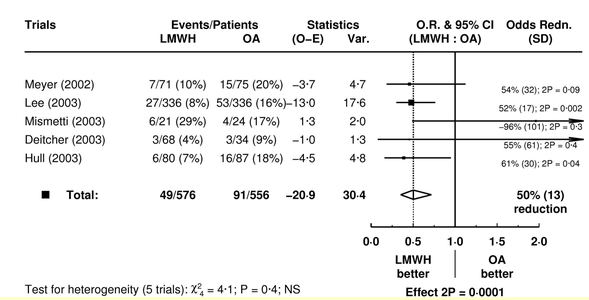


Figure 5: VTEs in LMWH v OA Trials

With 3 of the 5 VTE trials also containing mortality data (985 patients in total), no significant difference was found in mortality rates between LMWH and OA treated patients (OR = 0.89, CI = 0.74 to 1.10; p = 0.3) (Figure 6).

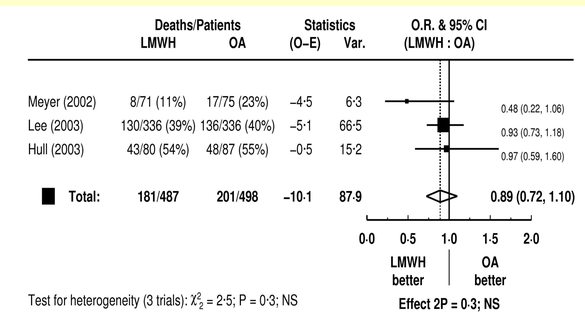


Figure 6: Mortality Rates in LMWH v OA Patients

CONCLUSION

The results of these preliminary meta-analyses suggest that LMWH is the preferred form of prophylaxis for VTE in cancer patients since it was shown to be superior to both no treatment and to oral anticoagulants (mainly warfarin). There may also be an anti-tumour effect, leading to a survival benefit, but further research is needed to confirm or refute this.

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