Warfarin thromboprophylaxis in cancer patients with central venous catheters (WARP): an open-label randomised trial.

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Warfarin thromboprophylaxis in cancer patients with central venous catheters
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REPORT OF A RANDOMISED TRIAL OF THROMBOPROPHYLAXIS

WITH WARFARIN IN CANCER PATIENTS

WITH CENTRAL VENOUS CATHETERS: 'WARP'

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SUMMARY

Background: The role and dose of anticoagulants in thrombosis prophylaxis for cancer patients with central venous catheters (CVCs) is controversial.

Methods: 1590 cancer patients receiving chemotherapy via CVCs were randomised to no warfarin [control] vs warfarin [either daily fixed dose 1mg warfarin (FDW) or daily dose adjusted warfarin (DAW) to maintain International Normalised Ratio between 1.5 and 2.0]. Clinicians 'certain' of the benefit of warfarin randomised between FDW and DAW. The primary outcome measure is the incidence of radiologically proven, symptomatic catheter-related thrombosis (CRT); secondary outcome measures include toxicity, incidence of all thromboses and overall survival.

Findings: Compared to control, warfarin (79% FDW; 21% DAW) reduced neither CRT [5.9% vs 5.9%; relative risk (RR) 0.99, (95% Confidence Interval (CI) 0.57-1.72), p=0.98] nor all thrombotic events [7.4% vs 9.4%; RR 0.78 (95%CI 0.50-1.24), p=0.30]. However, compared to FDW only, DAW was superior in preventing CRT [2.8% vs 7.2%; RR 0.38, (95%CI 0.20-0.71), p=0.002] but not all thromboses [5.5% vs 7.9%; RR 0.70 (95%CI 0.43-1.14), p=0.15]. Major bleeding events were rare; an excess was observed with warfarin compared to control (7 vs 1, p=0.07) and with DAW compared to FDW (16 vs 7, p=0.09). A combined endpoint of thromboses and major bleeding showed no difference between warfarin and control or between DAW and FDW. No survival difference was demonstrated in either comparison.

Interpretation: Thrombosis rates were low (5.3%); there is no benefit in using warfarin in comparison to no warfarin for the prophylaxis of symptomatic CRT or other thromboses in cancer patients.

Summary: 250 words

INTRODUCTION

Venous thromboembolism (VTE) is a well documented complication of cancer and may be linked to tumoral production of a range of procoagulant factors, certain chemo and hormone therapies and the use of central venous catheters (CVCs). Evidence of VTE is found at post mortem in around 50% of cancer patients[1], but remains an under-diagnosed and under-treated condition in life. The last decade has seen an enormous increase in the use of CVCs to deliver infusional chemotherapy and, with this, recognition of catheter-related thrombosis (CRT) as a source of considerable morbidity[2].

Hitherto, trials of thromboprophylaxis for adult cancer patients undergoing chemotherapy with CVCs have not produced a clear consensus on the role of anticoagulation. Differing definitions of CRT and inconsistent assessment of VTE have made comparisons problematic.

Two early influential studies in the 1990s addressed the potential of anticoagulants to reduce the incidence of thrombotic events[3,4] and although small, suggested a benefit in using prophylactic anticoagulation, reducing thrombosis rates with minimal toxicity. However, trials since the turn of the century have challenged this thinking and have revealed no advantage of anticoagulant intervention in the reduction of thrombosis rates for patients having chemotherapy via CVCs[5,6,7,8].

A survey of clinical opinion of thromboprophylaxis in patients receiving infusional chemotherapy via a CVC was undertaken in 1999 and informed the design of this study. Completed by over 200 UK cancer clinicians, the results indicated that 60% of clinicians used warfarin routinely as a thromboprophylactic (95% of these clinicians prescribed 1mg warfarin daily) and 20% of clinicians were certain of the indication

for warfarin intervention and hence would not be willing to randomise to a comparison with a 'no warfarin' arm.

This paper reports the outcome of a large open label, multicentre trial, investigating the utility of warfarin in thromboprophylaxis, in cancer patients with CVCs.

Patients and Methods

Sixty-eight UK clinical centres with nursing teams dedicated to catheter care participated in the trial. The centres received ethical approval from West Midlands Multi-Centre Research Ethics Committee and all patients consented in writing.

Patient Eligibility

Patient eligibility covered the following inclusion criteria: histologically confirmed diagnosis of cancer; requirement for CVC insertion for administration of chemotherapy; aged at least 16 years and with adequate hepatic, renal and haematological function. Exclusion criteria comprised: patients with a contraindication to warfarin; patients taking warfarin and pregnant or lactating women.

Trial Design

The study was structured to encompass contemporary clinical opinion noted from the pre-trial survey. Clinicians who were 'uncertain' of the benefits of warfarin in thromboprophylaxis, randomised patients to no warfarin (control) *vs* daily 1mg fixed dose warfarin (FDW) *vs* daily 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, randomised patients between FDW and DAW. All preferences were those of clinicians. Initially, the 'uncertain indication'

preference had 3 arms, as previously described; however, investigators subsequently requested that a 2 arm option of control vs FDW be included (Figure 1). The trial design was amended accordingly by the Steering Committee after 141 patients had been randomised in the 3 arm comparison and 245 to the 'certain' preference. Randomisation was executed via a computerised block algorithm and accessed by telephone and fax. Stratification was based on three thrombosis risk factors; sclerosant potential of the cytotoxic regimen (low or high); site of placement of the catheter (peripheral or central); and duration of drug infusion (less than, or greater and equal to 24 hours; for duration of one chemotherapy cycle intravenous infusion).

This trial design enabled two key hypotheses to be tested: (i) whether warfarin reduces CRT relative to control ('warfarin evaluation' comparison) and (ii) whether DAW is superior to FDW ('dose evaluation' comparison).

Treatment Plan

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) 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$50x10^9/L). Agreed protocols for INR monitoring on all treatment arms were provided and treatment of VTE was carried out according to local practice.

Outcome Measures

The primary outcome measure reported is the incidence of radiologically confirmed symptomatic catheter-related thrombotic events, i.e. occurring in the venous system draining the catheter, or pulmonary emboli (PE) in patients who had catheter complications. Secondary outcome measures include non catheter-related thrombotic events (occurring in the arterial system, in the venous system not draining the catheter and PE in patients with no catheter complications), catheter patency, warfarin-related adverse events (bleeding and raised INR), overall survival, catheter-related infections and health service related costs (not reported here). All thromboses 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. Major bleeding episodes were defined as intracranial, retroperitoneal, requiring transfusion or hospitalisation or directly leading to death[9]. Increased INR was classified by the investigators as: mild (2<INR<5), moderate (5≤INR<8) or severe (INR≥8). Dates of death were obtained from the case record forms or from the Office of National Statistics (ONS) in April 2007.

Statistical methods

Sample size calculations were made on the following assumptions: the thrombotic event rate for patients on no warfarin was around 25% and if warfarin were to reduce this rate by 10%, this would be a medically worthwhile improvement. With 800

patients entered into the uncertain indication (400 no warfarin and 400 warfarin), there would be >90% power to detect a 10% difference. With 1000 patients randomised between warfarin doses, there would be 80% power to detect a difference of 7% in thrombotic event rates between the two dosing schedules. The trial had approximately 90% power to detect a 10% difference in long term survival comparing warfarin and no warfarin groups.

Rates of thrombotic events were compared using Mantel-Haenszel chi-square tests, stratified by randomisation option. Differences between treatments are expressed as relative risk (RR) with 95% confidence intervals (CI). The analysis was carried out on an intention-to-treat basis, with a small number of 'unknown outcome' patients combined with those not experiencing an event. Sensitivity analysis confirmed the validity of the assumption. CRT events were also analysed as time to event data with time to thrombosis censored at date of CVC removal in those with no event. In addition, time to thrombosis in patients with an event was compared using Wilcoxon tests. Duration of catheter patency was calculated as time from catheter insertion to thrombotic event or CVC complication and censored at CVC removal for those patients with no event. Overall survival, measured from date of randomisation to date of death or date last seen alive, was analysed using Kaplan-Meier[10] estimation and log-rank tests[11]. Major bleeding episodes were compared using Fisher's Exact test. All p-values are two-sided.

Role of the Funding Source

RESULTS

WARP recruited 1590 patients between October 1999 and December 2004; 812 were randomised to the 'uncertain' preference (404 to control, 408 to warfarin) and 778 to the 'certain' preference (389 to FDW and 389 to DAW). The design enabled 166 (10.4%) patients to contribute to both comparisons. Due to inclusion of the 'uncertain' indication 2-arm option (control vs FDW), of those patients randomised to the *warfarin* arm of the control comparison, 324 (79.4%) patients received FDW daily and 84 (20.6%) received DAW daily (Figure 1).

Patient and CVC characteristics

Baseline patient and CVC characteristics (Table 1) and are well balanced across the study arms. Peripherally inserted central catheters (PICCs) were used for 58% of patients, in keeping with a rising trend in practice. Patients were similar with respect to age, treatment length, performance status, disease site and stage of disease across all arms. 93% of patients had World Health Organisation (WHO) Performance Status of 0 and 1, although 65% had advanced disease; over 50% of patients presented with colorectal cancer.

Compliance

Protocol Compliance

Of 1590 patients, four were found to be ineligible, three on clinical parameters and one declining chemotherapy immediately post randomisation. Four additional patients did not have CVCs inserted post randomisation. Twelve further patients did not receive any allocated warfarin treatment (eight on warfarin 1mg and four on DAW), mostly due to patient choice. All were included in the analysis.

Warfarin Compliance

Of the 1139 patients who started warfarin, 26 (2.3%) patients and/or their clinicians did not conform to warfarin dose. Of these, for the five patients allocated FDW, the clinician chose to prescribe the variable dose; twenty out of 21 patients on DAW took 1mg warfarin daily either in error or by choice.

The protocol stated that warfarin should be taken until catheter removal or thrombosis; only 155 (10%) of patients started warfarin 3 days prior to catheter insertion and of the 1139 patients starting warfarin, 106 (9%) stopped 'early' (more than 7 days before the catheter was removed), largely due to their chemotherapy being completed and the CVC was still in situ but also because of patient choice or thrombocytopenia; this was balanced across treatment arms. Data on warfarin compliance were incomplete on 8% of patients.

The CONSORT diagram, available on-line, shows detailed compliance data.

Thrombotic events

Of the 1590 patients randomised, 85 (5.3%) had a radiologically confirmed CRT event. There were also 9 clinically suspected thromboses, not confirmed radiologically and classified as CVC complications. Warfarin (of which 79% was FDW) did not reduce the incidence of CRT relative to control (24 (5.9%) vs 24 (5.9%); RR=0.99, 95%CI 0.57–1.72, p=0.98) (Table 2a). In contrast, there were significantly fewer CRT in those patients allocated DAW compared to FDW (13 (2.8%) vs 34 (7.2%); RR=0.38; 95%CI 0.20–0.71, p=0.002). Analysis of this primary outcome as time-to-event data showed comparable results (Figure 2). A further 36 (2.3%) patients had a non-CRT event. Neither warfarin (compared to control) nor DAW (compared to FDW) have any significant impact (p=0.30 and p=0.15 respectively) on all thrombotic events (Table 2a). Comparisons of the FDW and DAW groups separately with control are shown in Table 3 – there are no significant differences.

The location of the 85 CRT were reported as follows: 32 upper limb, 17 axillary vein, 16 subclavian vein, 10 internal jugular, 4 superior vena cava, 2 pulmonary emboli, 2 catheter and 2 with site not stated. The location of the 36 non-CRT events presented as 18 lower limb, 9 pulmonary emboli, 4 upper limb, 2 inferior vena cava, 1 subclavian vein, 1 pulmonary vein and 1 portal vein. Non-CRT events were all venous with the exception of one upper limb arterial thrombosis.

Time to Thrombosis, Catheter – Patency and Infections

For the 85 patients with a CRT, median time to CRT was 32 days from randomisation (IQR=13 to 76 days). Median time to CRT did not significantly differ in the warfarin vs control (25 vs 32 days, p=0.71), or DAW vs FDW (60 vs 31 days, p=0.51) comparisons. Median time to all 121 thromboses (CRT and non-CRT) was 44 days (IQR=13-84 days). CVCs were patent for a median time of 13.9 weeks for all patients.   There was no significant difference in the median duration of catheter patency across treatments.   124 patients (7.8%) were categorised as having one or more catheter-related infections; there were no significant differences between treatments.

Major bleeding and INR

There was some evidence of an excess of major bleeding events in patients on warfarin vs control (RR=6.93, 95%CI 0.86-56.08, p=0.07) and in patients on DAW vs FDW (RR=2.28, 95%CI 0.95-5.48, p=0.09), although both failed to reach statistical significance.   An increase in moderately and severely raised INR *without* major bleeding was also demonstrated (Table 2b).   According to participating clinicians, warfarin may have contributed to the deaths of two patients receiving DAW; no thrombosis was reported as contributing to death.

Given the fine balance between the clinical consequences of thrombosis and major bleeding, we examined a combined endpoint of thrombotic events plus major bleeds. This analysis revealed no significant difference between treatment arms for both comparisons (Table 2c).

Detailed INR readings were analysed from one centre with 54 patients on FDW and 56 patients on DAW. 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 for FDW group was 1.10, (IQR 1.04-1.24); for DAW group was 1.69, (IQR 1.43-1.93).

Overall Survival

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. No overall survival advantage was found from taking warfarin compared to control (HR=0.98, 95%CI: 0.77-1.25, p=0.26) or found between the two dosing schedules (HR=0.91, 95% CI 0.73-1.14, p=0.53) (Figure 3).

Discussion

This trial demonstrates that warfarin (79% FDW, 21% DAW) does not have a useful role in the prophylaxis of CRT. The overall incidence of symptomatic CRT was relatively low (5.3%), in keeping with a general temporal trend[12] brought about by improved catheter design and care[13,14]. It is interesting to note that more clinicians than expected from the pre-trial survey were 'certain' of the indication for warfarin; they may have been influenced by the results of early studies and some were also high recruiters. When compared to control, warfarinisation does not offer any advantage in reducing CRT. Similarly, warfarin did not reduce the incidence of all thrombotic events or have any impact on survival. When FDW and DAW

respectively were compared directly with the control arm, there was no advantage demonstrated from either warfarin dose; however, the numbers in each arm are small (Table 3). Conversely, when compared to FDW, DAW did significantly reduce the number of symptomatic CRT but at an increased cost in terms of major bleeds and additional INR monitoring. This reduction in CRT events with DAW over FDW does not translate into a decrease in all thrombotic events and, in effect, is cancelled out when the combined endpoint of thrombosis plus major bleeding is observed. However, for clinicians still wishing to offer prophylactic oral anticoagulation to patients with CVCs, for example, those at high thrombotic risk[15,16,17] and who are prepared to accept the related toxicity profile, dose adjusted warfarin may be the more logical choice. Exploratory subgroup analysis will be the topic of a future paper.

Our findings are in keeping with the results of more recent studies on thromboprophylaxis in cancer patients with CVC. Bern et al (1990) compared 1 mg warfarin for 90 days to control in cancer patients with long term central venous catheters[4]. VTE were detected symptomatically and by routine venogram in 15 of 40 (37.5%) control patients in comparison to 4 of the 42 (9.5%) patients on warfarin (p<0.001). Monreal et al[3] (1996) randomised a similar group of patients to the low molecular weight heparin (LMWH), dalteparin (2500iu subcutaneously, daily for 90 days) or control. 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, in 1999, randomised 80 cancer patients with CVCs to 1mg warfarin vs control and reported thrombosis rates of 13% vs 29% respectively (p=0.07)[18]. Although small, these three trials suggested a

benefit in using prophylactic anticoagulation by reducing thrombosis rates with minimal toxicity. However, more recent trials have found no benefit from warfarin intervention. Heaton et al (2002) examined the effects of 1mg fixed daily dose of warfarin versus control on thromboprophylaxis in 88 haemato-oncology patients receiving chemotherapy via CVCs[5]. 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[6]. Overall CRT rates were low; 4.6% with warfarin and 4.0% with placebo (HR, 1.2, 95% CI, 0.37 – 3.94). It appears more difficult to keep cancer patients on warfarin within target INR range[20,21]. Our INR analysis showed a similar variability to other studies[20,21]. INR monitoring of patients receiving DAW was problematic in some centres

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 (measured at routine investigation) in a trial of enoxaparin (40mg once daily for 6 weeks) vs placebo[7]. In 385 cancer patients, thrombosis rates were found to be similar in both arms (14% enoxaparin vs 18% placebo, p=0.35). Karthaus and colleagues showed no symptomatic thromboprophylactic effect of dalteparin (5000iu/day) in comparison to placebo (3.7% and 3.4% respectively, p=0.88)[8]. Our results concur both with a recent pooled estimate of the Bern and Heaton trials[19], confirming a lack of benefit from warfarin. When WARP data were added to a previous meta-analysis of warfarin intervention vs control in the prophylaxis of thrombosis in cancer patients with CVCs[12], the earlier advantage seen for warfarin

(OR 0.58, CI 0.34-1.01; p=0.05) was reduced (OR 0.75, CI 0.5-1.1; p=0.1) (Figure 4).

Taking these trials in concert with this definitive report, it is noticeable that the incidence of symptomatic CRT reported in clinical trials has markedly declined over the past decade[12]. The improvements in catheter technology, placement and aftercare are contributing to this reduction[13,14]. The clinically relevant benefit/risk outcome of (prophylaxis of) thrombotic events plus major bleeding demonstrated no advantage in using any dose of warfarin. These findings only add to the assertion, 'it is time to move on from warfarin' for thromboprophylaxis in the cancer patient population.

MANUSCRIPT: 2995 WORDS

Table 1: Baseline Patient Characteristics

Comparison		Control		Dose evaluation	
Factor	**Grouping**	**No Warfarin** N (%) N=404 U3*: N=161 U2*: N=243	**Warfarin** N (%) N=408 U3*: N=166 U2*: N=242	**FDW** N (%) N=471 U3*: N=82 C2*: N=389	**DAW** N (%) N=473 U3*: N=84 C2*: N=389
Gender	Male	247 (61%)	252 (62%)	253 (54%)	265 (56%)
Age (yrs)	Median (IQR)	61 (53-68)	60 (53-68)	59 (51-66)	60 (53-67)
WHO Performance Status	0	221 (55%)	225 (55%)	263 (56%)	272 (58%)
	1	168 (42%)	151 (37%)	178 (38%)	161 (34%)
	2/3	10 (2%)	21 (5%)	23 (5%)	29 (6%)
	Not known	5 (1%)	11 (3%)	7 (1%)	11 (2%)
Stage of disease	No residual/early	130 (32%)	134 (33%)	171 (36%)	138 (29%)
	Advanced	273 (68%)	269 (66%)	294 (62%)	330 (70%)
	Not known	1 (0.3%)	5 (1%)	6 (1%)	5 (1%)
Disease site	Colorectal	201 (50%)	217 (53%)	226 (48%)	243 (51%)
	Upper GI	109 (27%)	92 (23%)	95 (20%)	98 (21%)
	Breast	32 (8%)	32 (8%)	82 (17%)	67 (14%)
	Other	50 (12%)	54 (13%)	52 (11%)	49 (10%)
	Not known	12 (3%)	13 (3%)	16 (3%)	16 (3%)
Catheter Placement	Central	146 (36%)	150 (37%)	226 (48%)	228 (48%)
	Peripheral	258 (64%)	258 (63%)	245 (52%)	245 (52%)
Sclerosant potential	Non-sclerosant	172 (43%)	169 (41%)	235 (50%)	236 (50%)
	Sclerosant	232 (57%)	239 (59%)	236 (50%)	237 (50%)
Treatment length	<24 hours	64 (16%)	68 (17%)	87 (18%)	86 (18%)
	≥24 hours	340 (84%)	340 (83%)	384 (82%)	387 (82%)

*U = Uncertain Indication for Warfarin; C= Certain Indication for Warfarin; 3= 3arm; 2= 2 arm

Table 2a: 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%)	
All thrombotic events (CRT& non-CRT)	**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 2b: Bleeding and raised INR (moderate and severe)

Major Bleeding & 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	

Table 2c: Combined Thrombosis Major and Bleeding

CRT Events	24	24		34	13	
Total Major Bleeding	1	7		7	16	
Total	**25 (6.2%)**	**31 (7.6%)**	**1.23** **(0.83,1.52)** **0.51**	**41(8.7%)**	**29(6.1%)**	**0.84** **(0.74,2.04)** **p=0.17**
All thrombotic events (CRT& non-CRT)	38	30		37	26	
Total Major Bleeding	1	7		7	16	
Total	**39 (9.7%)**	**37 (9.1%)**	**0.94** **(0.61,1.44)** **0.87**	**44 (9.3%)**	**42 (8.9%)**	**0.95** **(0.64,1.42)** **p=0.89**

Table 3: Thrombotic Events – Other Randomised Comparisons

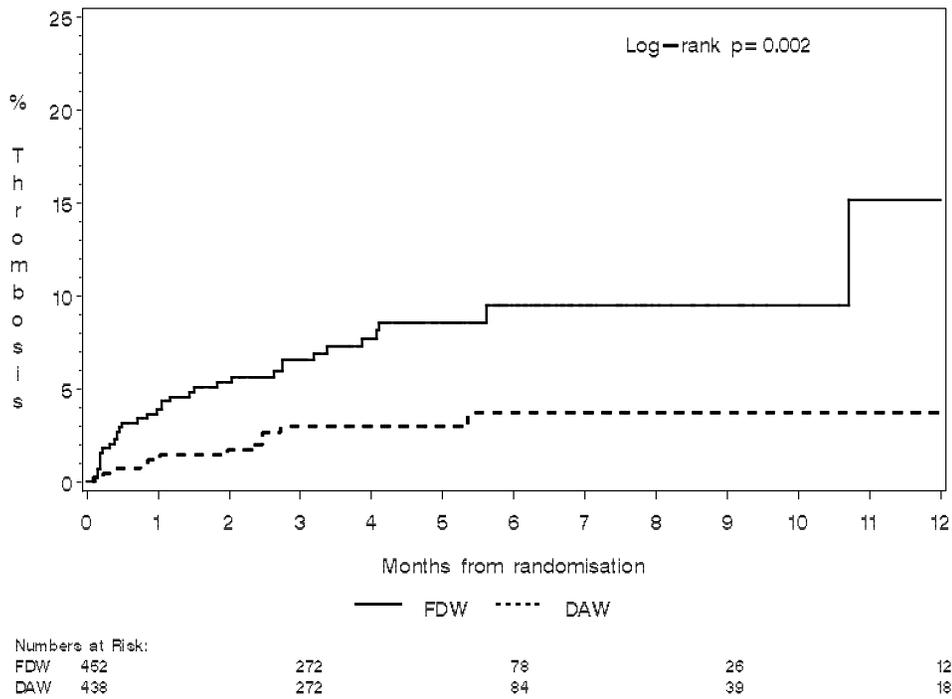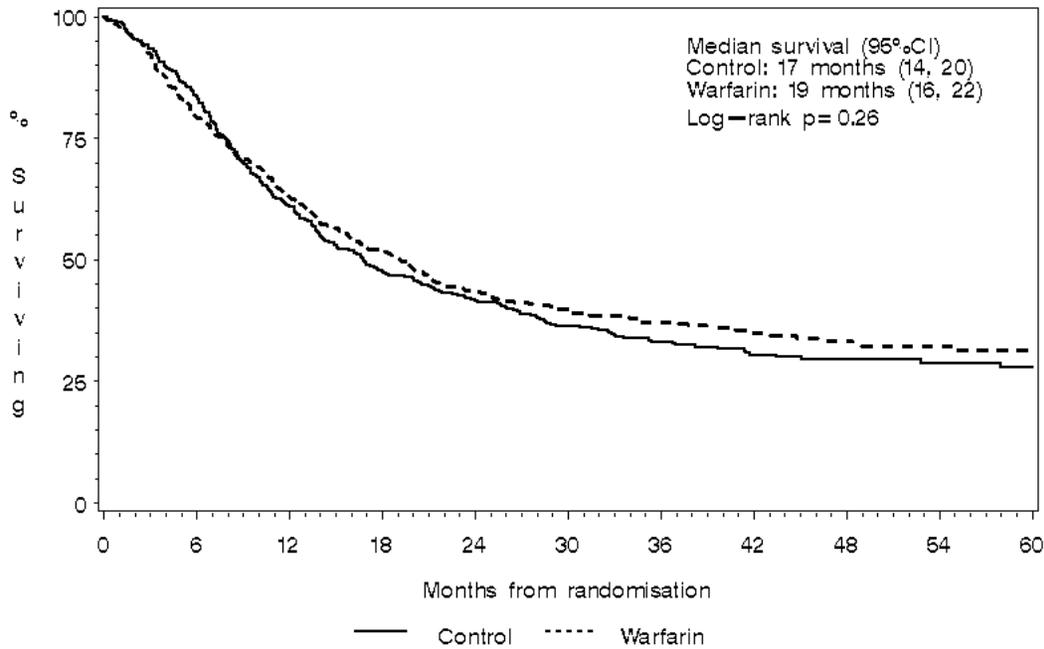|	Control vs FDW			Control vs DAW*		
	No Warfarin N=404	FDW N= 324	Relative Risk (95% CI) p-value	No Warfarin N= 161	DAW N= 84	Relative Risk (95% CI) p-value
CRT Events	24 (5.9%)	22 (6.8%)	1.10 (0.64, 1.89) p=0.72	5 (3.1%)	2 (2.4%)	0.77 (0.15, 3.87) p>0.99
All thrombotic events (CRT& non-CRT)	38 (9.4%)	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
Major Bleeding	1 (0.3%)	3 (0.9%)	3.74 (0.39, 35.79) p=0.33	0 (0%)	4 (4.8%)	Not calculable p=0.01
Total major bleeding and CRT events	25 (6.2%)	25 (7.7%)	1.25 (0.73, 2.13) p=0.51	5 (3.1%)	6 (7.1%)	2.30 (0.72, 7.32) p=0.19
Total major bleeding and all thrombotic events	39 (9.7%)	31 (9.6%)	0.99 (0.63, 1.55) p>0.99	13 (8.1%)	6 (7.1%)	0.88 (0.35, 2.24) p=0.99

Figure 1 – Trial Flow Diagram

Figure 1 - Trial Structure at Randomisation

Are you (clinician) certain or uncertain of the benefits of warfarin in the prophylaxis of thrombosis in cancer patients with CVCs?

Uncertain
n=812

Certain
n=778

Are you (clinician) willing to participate in the dose adjusted warfarin (DAW) arm?

YES – 3 arm study
n=327

NO – 2 arm study
n=485

No warfarin
n=161
CRT - 5

1mg warfarin od*
n=82
CRT - 8

DAW warfarin od*
n=84
CRT - 2

No warfarin
n=243
CRT - 19

1mg warfarin od*
n=242
CRT - 14

1mg warfarin od*
n=389
CRT - 26

DAW warfarin od*
n=389
CRT - 11

2 parallel randomised studies:

No warfarin
n=404
(161+243)
CRT - 24

vs

Warfarin
n=408
(242+82+84)
FDW; n=324
DAW; n=84

and

1mg warfarin
n=471
(82+389)
CRT - 34

vs

DAW warfarin
n=473
(84+389)
CRT - 13

* once daily: CRT – Catheter-related thromboses

Figure 2 – Time to Thrombosis

2a)

Numbers at Risk:
Control 376   212   66   15   6
Warfarin 379   211   58   15   8
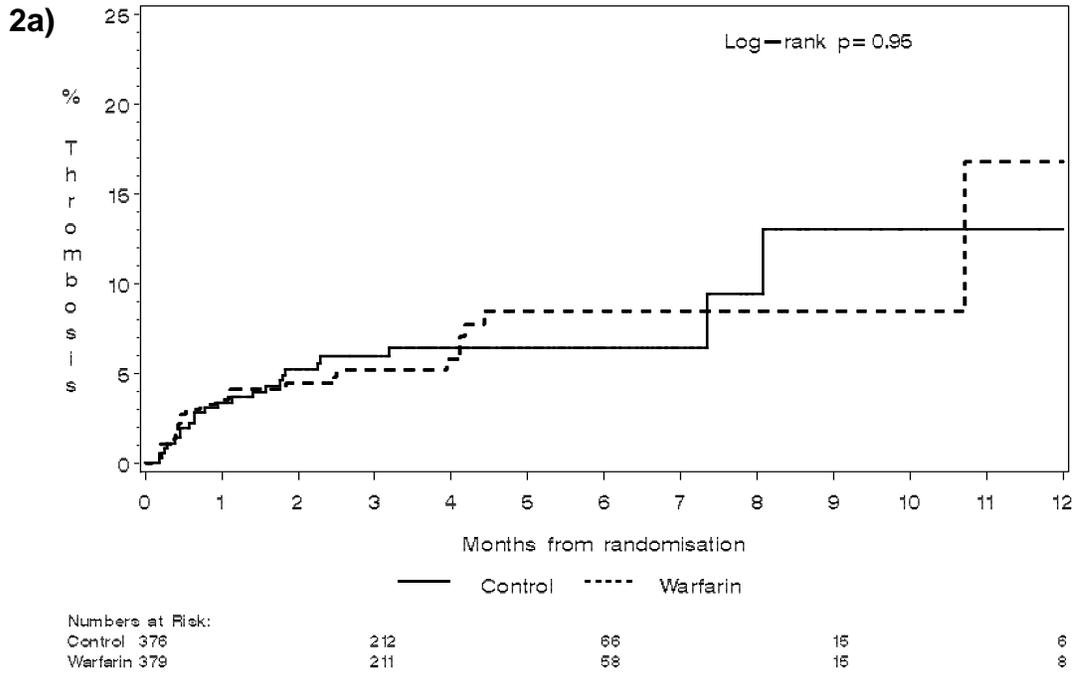
2b) Time to Thrombosis – FDW vs DAW

Numbers at Risk:
FDW   452   272   78   26   12
DAW   438   272   84   39   18

Figure 3: Overall survival

3a) Overall Survival - Control vs Warfarin

Median survival (95%CI)
Control: 17 months (14, 20)
Warfarin: 19 months (16, 22)
Log-rank p= 0.26

Months from randomisation

——— Control ⋅⋅⋅⋅⋅ Warfarin

Numbers at Risk:
Control 404	246	169	100	48	28
Warfarin 408	256	178	118	55	37

3b) Overall Survival - FDW vs DAW

Median survival (95%CI)
FDW: 21 months (17, 24)
DAW: 21 months (19, 25)
Log-rank p= 0.53

Months from randomisation

——— FDW ⋅⋅⋅⋅⋅ DAW
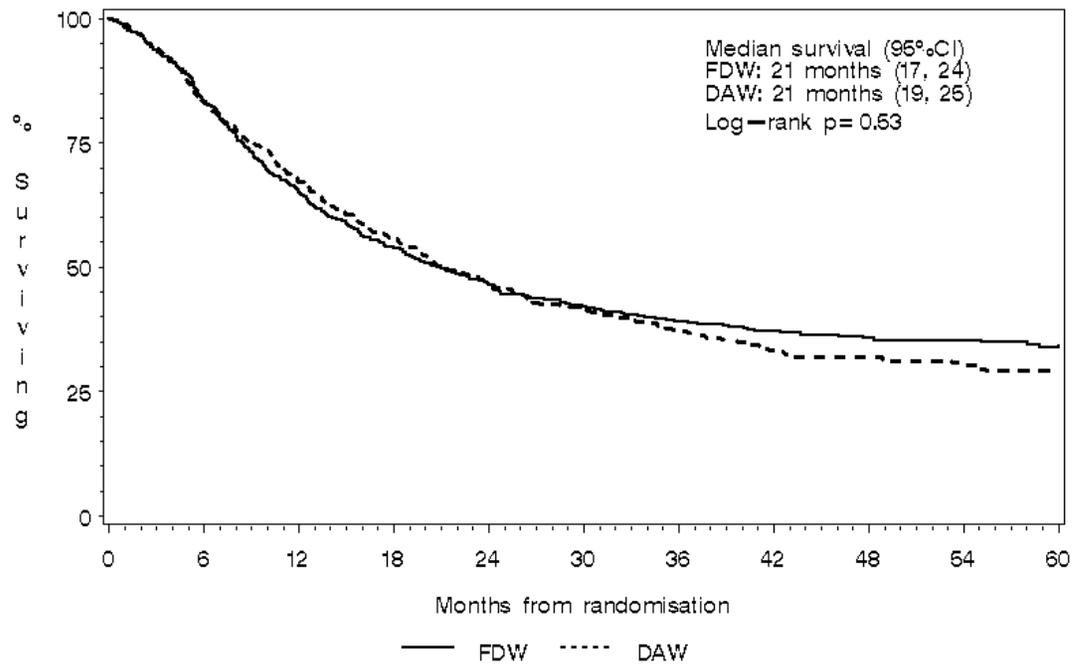
Numbers at Risk:
FDW 471	308	220	158	98	70
DAW 473	318	222	156	91	63

Figure 4

Meta-analysis of prevention of thrombosis with warfarin vs control in cancer patients

with CVCs
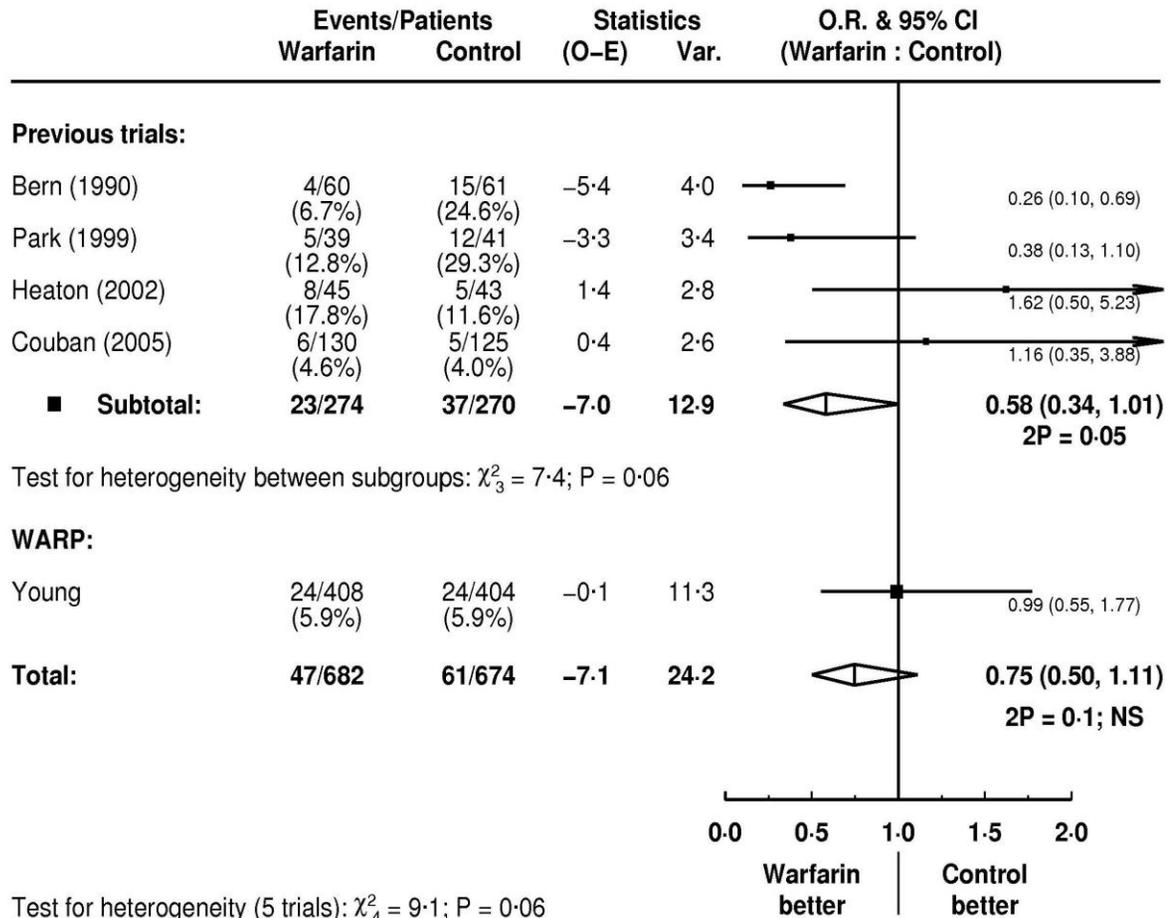
Test for heterogeneity (5 trials): $\chi^2_4 = 9\cdot1$; P = 0·06

Test for heterogeneity between subtotals: $\chi^2_1 = 1\cdot7$; P = 0·2; NS

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List of tables and figures

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Conflict of interest statement

There are no known conflicts of interest.

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