

VTE and cancer

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Overview

The association between cancer and thrombosis has been recognised for many years. VTE is a relatively common complication in patients with cancer, and is associated with both significant mortality and reduced survival^{1,2,3}. Epidemiological studies have identified cancer as an important VTE risk factor and show that cancer patients are at substantially increased risk of both initial and recurrent VTE events^{1,2,4,5}. The increase in risk is due to a number of factors, including chemotherapy, hormonal therapy and indwelling central venous catheters⁴; a persistent hypercoagulable state mediated by tumour activity is also considered a key feature in the pathogenesis of VTE⁶. The risk is higher for cancer surgery than in non-cancer patients undergoing surgery for benign disease. Overall, cancer increases the risk of thrombosis quite significantly by four- to six-fold⁴.

Many clinical questions regarding the care of cancer patients with VTE remain unanswered, but we are beginning to learn more about cancer and the risk of thrombosis *e.g.*, the IBIS 1 long-term follow-up study shows that the benefits of tamoxifen last 10 years, but the side effects, including the risk of VTE, fall away once treatment stops. Now, the VERITY database is large enough with sufficient cancer data to begin to make a difference in our understanding of which cancers are particularly associated with VTE, what cancers are associated with particularly poor survival if the patient has concomitant VTE and the role of D-dimer in identifying those VTE patients who may require cancer screening and further follow-up.

Final diagnosis and cancer

This year, we have data on 3,056 patients with cancer. More patients with a confirmed diagnosis of VTE had a diagnosis of cancer than VTE-negative patients: 13.4% (1,572 / 11,759) *versus* 4.5% (1,484 / 33,146), respectively. VTE occurred twice as frequently in patients with cancer than in the non-cancer patients (51.4% [1,572 / 3,056] *versus* 24.3% [10,187 / 41,849], respectively). These findings are as expected and similar to previous results.

Cancer

		Cancer status			
		No cancer	Cancer	Unspecified	All
Final diagnosis	DVT	9,356	1,457	643	11,456
	PE	627	79	62	768
	PE + DVT	204	36	20	260
	Non-VTE	31,662	1,484	1,742	34,888
	Unspecified	5,964	493	2,167	8,624
	All	47,813	3,549	4,634	55,996

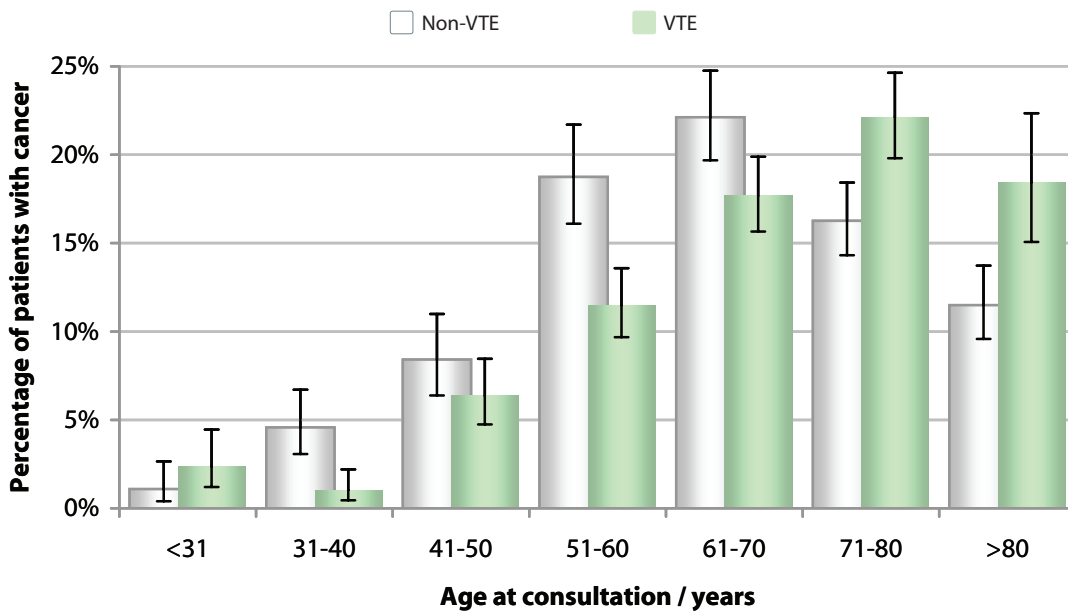
Cancer, age and gender in patients with VTE

The distributions of age, gender and cancer type are virtually identical to those presented in the last report and confirm that, overall, the rates of cancer and VTE increase with age as might be expected. The peak in the relative incidence of cancer in the female population occurs earlier (7th decade) than the peak in incidence for the male population (8th decade). As we noted in the last report, young patients with idiopathic VTE are highly unlikely to have an underlying malignancy.

		Gender and cancer status for patients with VTE								
		Female			Male			All		
		No cancer	Cancer	Unspecified	No cancer	Cancer	Unspecified	No cancer	Cancer	Unspecified
Age at consultation / years	<31	457	5	31	412	10	24	887	15	56
	31-40	543	26	43	675	7	46	1,232	34	91
	41-50	555	51	37	677	46	55	1,256	97	95
	51-60	633	146	50	955	124	55	1,618	277	109
	61-70	831	236	70	1,062	228	77	1,924	470	150
	71-80	1,076	209	73	915	260	59	2,020	480	136
	>80	847	110	53	376	85	32	1,244	199	88
	Unspecified	5	0	0	1	0	0	6	0	0
	All	4,947	783	357	5,073	760	348	10,187	1,572	725

Cancer

Cancer rates broken down by age and gender for patients with VTE (n=11,557)



Specific types of cancer and age for patients with VTE

The most common forms of cancer are breast, prostate, colorectal and lung. The age-specific findings for patients with VTE indicate that these common cancers make up around half of all cancer patients with VTE, and that the proportion increases as the population ages. In the 31-40 age-group, 41.2% of cancer patients with VTE had one of these four common cancers, rising with age by decade to 55.3% in those patients >80 years. Therefore, although these cancer types may not have especially high rates of VTE, they make up the large proportion of cancer patients presenting with VTE.

Prostate cancer is 100% gender specific to males and breast cancer is predominantly gender specific to females (only 1% of all breast cancers are in men); in the graph below we can see clear age-related differences in the peak incidence of VTE, with marked peaks in breast cancer-associated VTE in the 5th, 6th, 7th decades, but a marked peak for prostate cancer only in the 8th and 9th decades, and reflecting the peak incidence of these cancers.

Cancer

		Type of cancer for patients with VTE								
		Any cancer			Breast			Prostate		
		No	Yes	Unspecified	No	Yes	Unspecified	No	Yes	Unspecified
Age at consultation / years	<31	887	15	56	899	0	59	899	0	59
	31-40	1,232	34	91	1,255	7	95	1,262	0	95
	41-50	1,256	97	95	1,320	21	107	1,340	1	107
	51-60	1,618	277	109	1,823	41	140	1,848	16	140
	61-70	1,924	470	150	2,258	87	199	2,297	48	199
	71-80	2,020	480	136	2,394	62	180	2,363	93	180
	>80	1,244	199	88	1,378	43	110	1,377	44	110
	Unspecified	6	0	0	6	0	0	6	0	0
	All	10,187	1,572	725	11,333	261	890	11,392	202	890

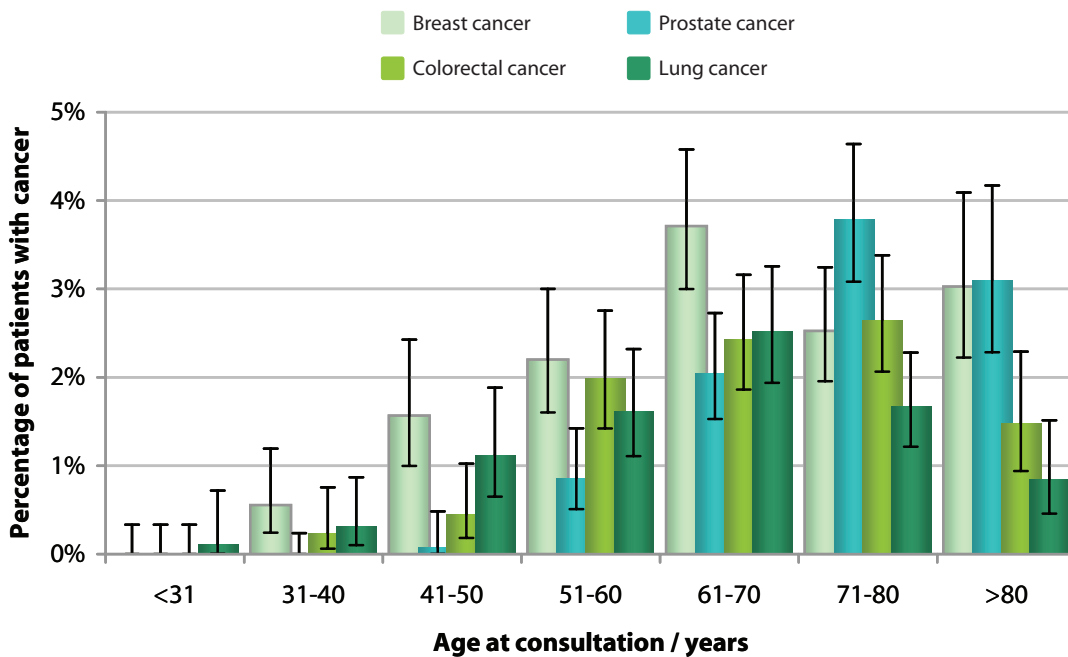
The age distribution of colorectal and lung cancer patients with VTE is shown in the table below. The highest rate of VTE occurs in the 8th decade in patients with colorectal cancer, and in the 7th decade in those with lung cancer.

Looking at the early age group, cancer is very uncommon in patients with VTE below the age of 40.

		Type of cancer for patients with VTE								
		Any cancer			Colorectal			Lung		
							Unspecified	No	Yes	Unspecified
Age at consultation / years	<31	887	15	56	899	0	59	898	1	59
	31-40	1,232	34	91	1,259	3	95	1,258	4	95
	41-50	1,256	97	95	1,335	6	107	1,326	15	107
	51-60	1,618	277	109	1,827	37	140	1,834	30	140
	61-70	1,924	470	150	2,288	57	199	2,286	59	199
	71-80	2,020	480	136	2,391	65	180	2,415	41	180
	>80	1,244	199	88	1,400	21	110	1,409	12	110
	Unspecified	6	0	0	6	0	0	6	0	0
	All	10,187	1,572	725	11,405	189	890	11,432	162	890

Cancer

Cancer rates broken down by age for the most frequently-occurring cancers in VERITY for patients with VTE (n=11,588)



Different cancers

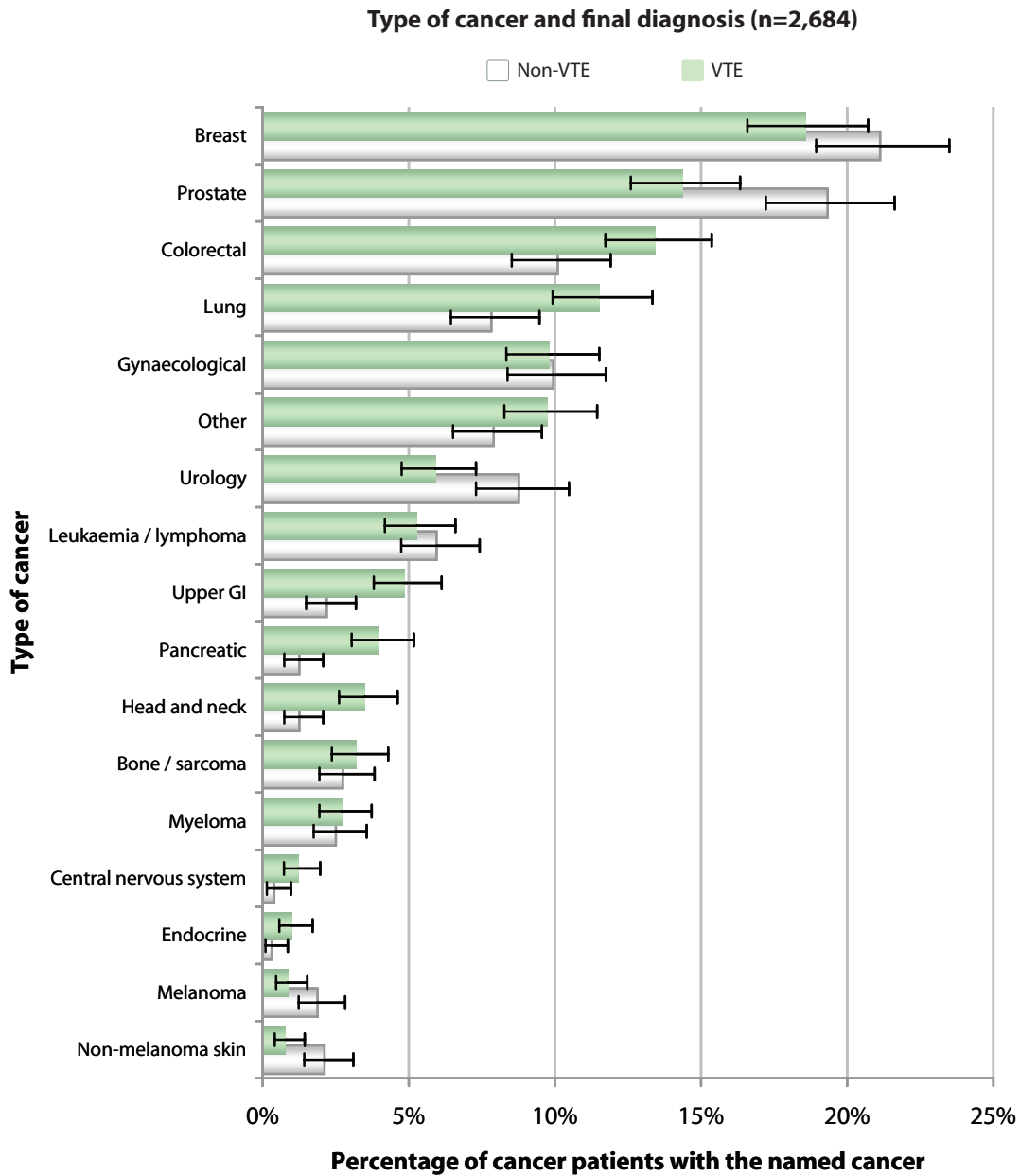
Specific types of cancer and final diagnosis

Compared with the last report, there are considerably more cancer data in the registry. In terms of absolute numbers of cancer patients, the most common forms of cancer in the general population (breast, prostate, colorectal and lung) again match the most common cancers with VTE found in the registry. In cases for which we know the cancer status and VTE diagnosis, these four cancers were associated with the highest overall number of patients with VTE. This can be seen clearly in the next figure showing the type of cancer and final diagnosis.

Cancer

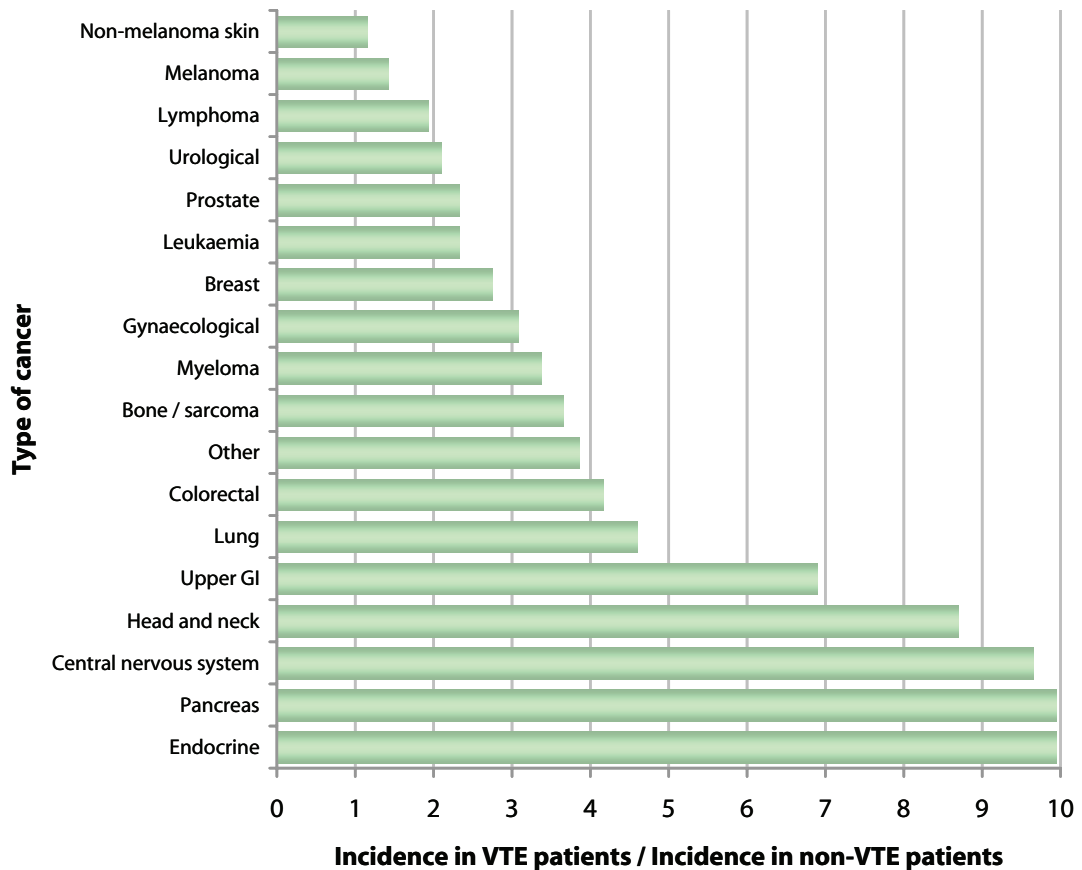
		Final diagnosis			
		Non-VTE	VTE	Unspecified	All
Type of cancer	No cancer	31,662	10,187	5,964	47,813
	Breast	270	261	74	605
	Prostate	247	202	67	516
	Colorectal	129	189	32	350
	Lung	100	162	42	304
	Other	101	137	33	271
	Gynaecological	127	138	52	317
	Urology	112	83	31	226
	Upper GI	28	68	11	107
	Bone / sarcoma	35	45	16	96
	Pancreatic	16	56	4	76
	Leukaemia / lymphoma	76	74	23	173
	Head and neck	16	49	7	72
	Myeloma	32	38	14	84
	Endocrine	4	14	3	21
	Central nervous system	5	17	1	23
	Melanoma	24	12	6	42
	Non-melanoma skin	27	11	10	48
	Unspecified cancer	206	166	112	484
	Unspecified	1,742	725	2,167	4,634
All	34,888	12,484	8,624	55,996	

This graph shows the percentages of each named cancer for the non-VTE and VTE patient-populations. There are now 2,446 patients with cancer type specified. These large numbers have resulted in tighter confidence intervals and allow us to identify three cancer types – upper GI tract cancer (as published in the previous VERITY report), pancreatic cancer and head and neck cancer – which are significantly more prevalent in the VTE patients than the non-VTE patients.



Comparing the incidence of each cancer type in the VTE patients to the non-VTE patients by calculating a ratio offers further insight into which cancers are particularly prevalent in the VTE population and therefore particularly associated with VTE. These findings presented below are very interesting and identify endocrine, pancreatic and CNS cancers as most strongly associated with VTE.

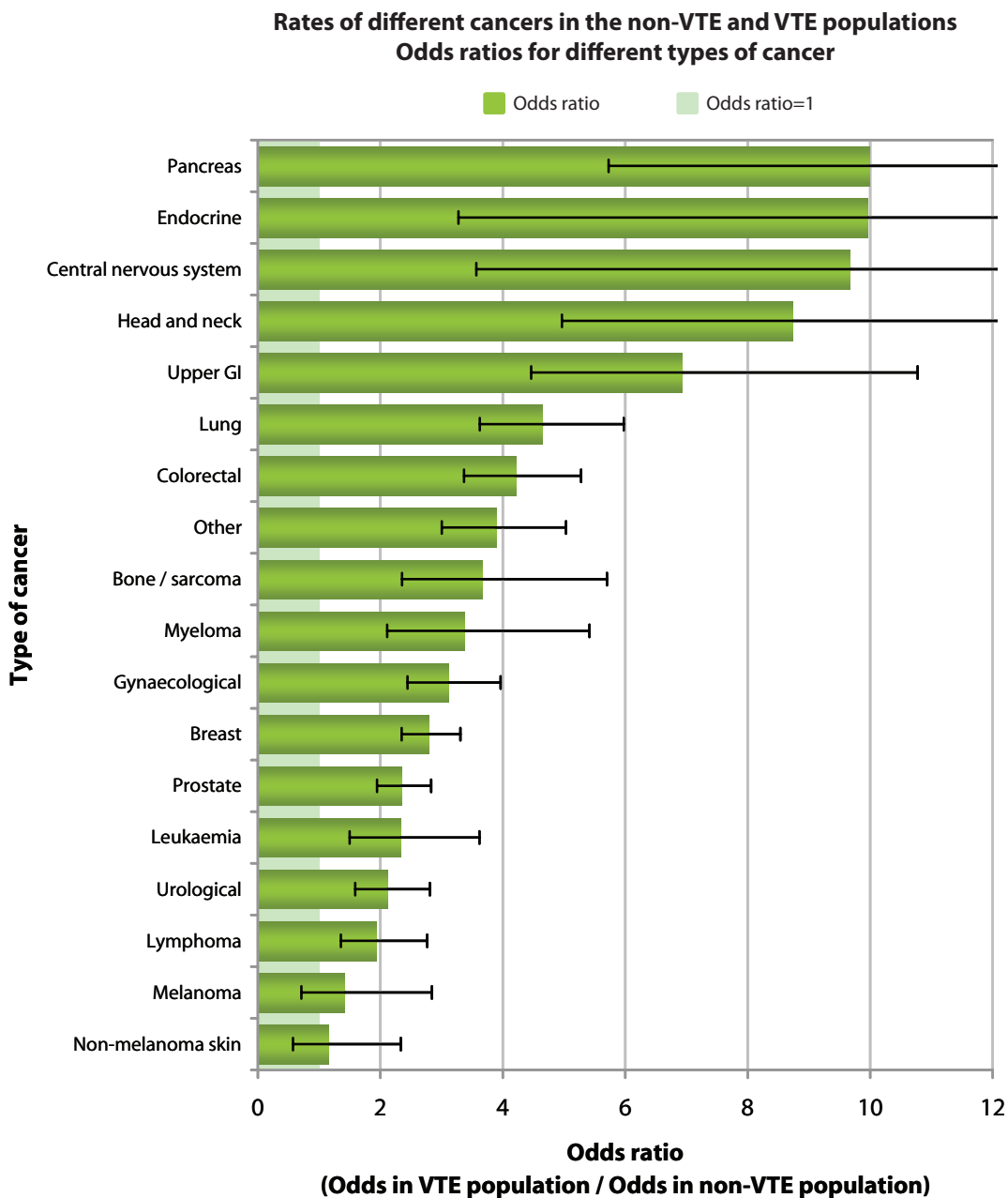
The ratio of the incidence of each type of cancer in the VTE patient population to the to the incidence in the non-VTE patient population



Cancer

Another way to present these data is to calculate odds ratios (OR) to compare the rates of different cancers in the non-VTE and VTE populations. OR is defined as the ratio of the odds of an event occurring in one group to the odds of it occurring in another group. An OR=1 indicates that a particular cancer is equally likely to be found in both groups. An OR>1 indicates that the cancer is more likely in the VTE group than the non-VTE group, if the 95% confidence intervals do not cross OR=1. This graph confirms that certain cancers are much more likely to be found in the VTE group, with pancreatic, endocrine and CNS tumours having an OR of around 10.

These findings are similar to those reported from the Californian Cancer Registry⁷. When linked to patient discharge data, it was shown that metastatic disease at the time of diagnosis was the strongest predictor of VTE and that the highest incidence of VTE (expressed as events / 100 patient-years) occurred during the first year of follow-up among cases with metastatic-stage pancreatic (20.0), stomach (10.7), bladder (7.9), uterine (6.4), renal (6.0), and lung (5.0) cancer.



Cancer

D-dimer and cancer

D-dimer testing in patients with cancer is particularly interesting from both a diagnostic and research viewpoint. D-dimer in conjunction with PTP remains a valid exclusion approach for VTE, even in a population of patients with cancer. But as we noted earlier (see page 27), we wish to move towards a quantitative D-dimer assessment in VERITY. Quantitative D-dimer is of particular interest in cancer patients both for identifying patients at potential risk of an occult cancer, and because of the recently established relationship between elevated D-dimer levels and poor outcome in cancer patients with VTE (see page 92).

D-dimer and pre-test probability

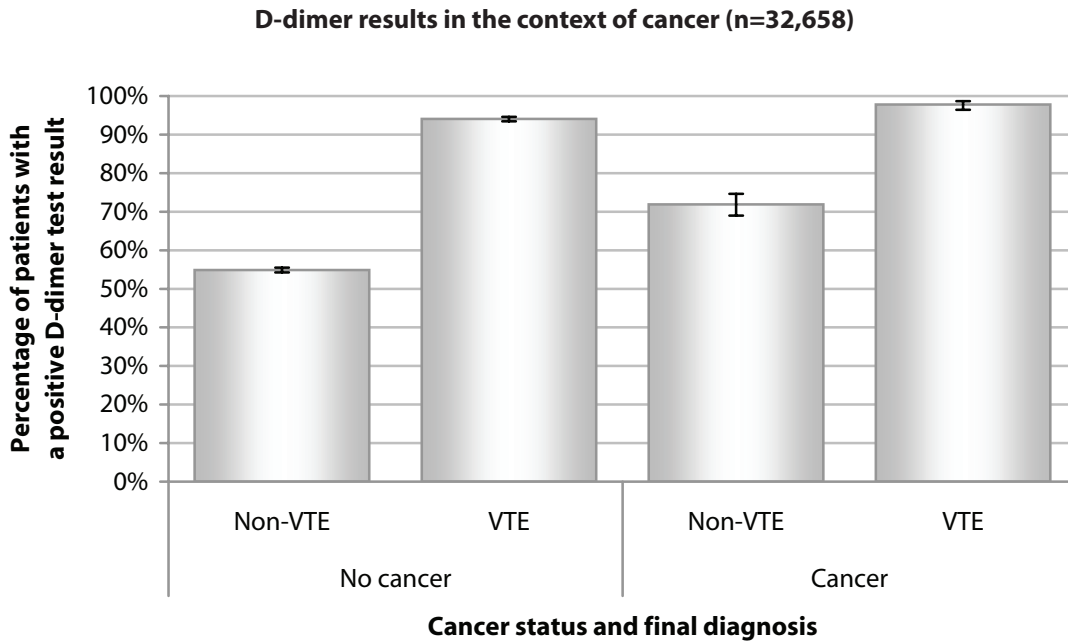
The assessment of PTP and D-dimer remains a valid investigation to exclude the diagnosis of DVT. In this table comparing cancer patients with non-cancer patients, the combination of negative D-dimer and low PTP had a negative predictive value of 100% - no cancer patients with negative tests were found to have VTE.

Cancer

				Final diagnosis					
				Non-VTE	DVT	PE	PE & DVT	Unspecified	All
Cancer status, D-dimer test results and DVT pre-test probability	No cancer	Negative D-dimer	Low <=0	6,449	80	13	1	375	6,918
			Moderate 1-2	1,494	143	0	2	153	1,792
			High >2	166	30	0	0	11	207
			Unspecified	2,827	117	7	1	771	3,723
		Positive D-dimer	Low <=0	6,348	706	112	14	565	7,745
			Moderate 1-2	2,955	2,211	26	68	423	5,683
			High >2	727	1,242	7	20	177	2,173
			Unspecified	3,275	1,674	120	39	1,342	6,450
		D-dimer not specified	Low <=0	3,497	241	93	4	620	4,455
			Moderate 1-2	1,685	1,243	14	18	470	3,430
			High >2	410	650	7	7	170	1,244
			Unspecified	1,829	1,019	228	30	887	3,993
	Cancer	Negative D-dimer	Low <=0	116	0	0	0	2	118
			Moderate 1-2	52	7	0	1	2	62
			High >2	28	8	0	0	5	41
			Unspecified	87	1	0	0	29	117
Positive D-dimer		Low <=0	207	16	8	0	25	256	
		Moderate 1-2	164	173	1	1	25	364	
		High >2	127	307	0	10	36	480	
		Unspecified	226	233	6	5	115	585	
D-dimer not specified	Low <=0	119	18	15	1	23	176		
	Moderate 1-2	118	139	8	8	48	321		
	High >2	96	261	0	1	59	417		
	Unspecified	144	294	41	9	124	612		

Comparison of D-dimer findings in cancer and non-cancer patients

This graph is very similar to the previous VERITY analysis and confirms that in patients who are excluded from the diagnosis of VTE, a significantly higher proportion of patients with cancer have a positive D-dimer than non-cancer patients. This is expected and confirms that D-dimer is often increased in cancer patients and more than in non-cancer patients.



Cancer

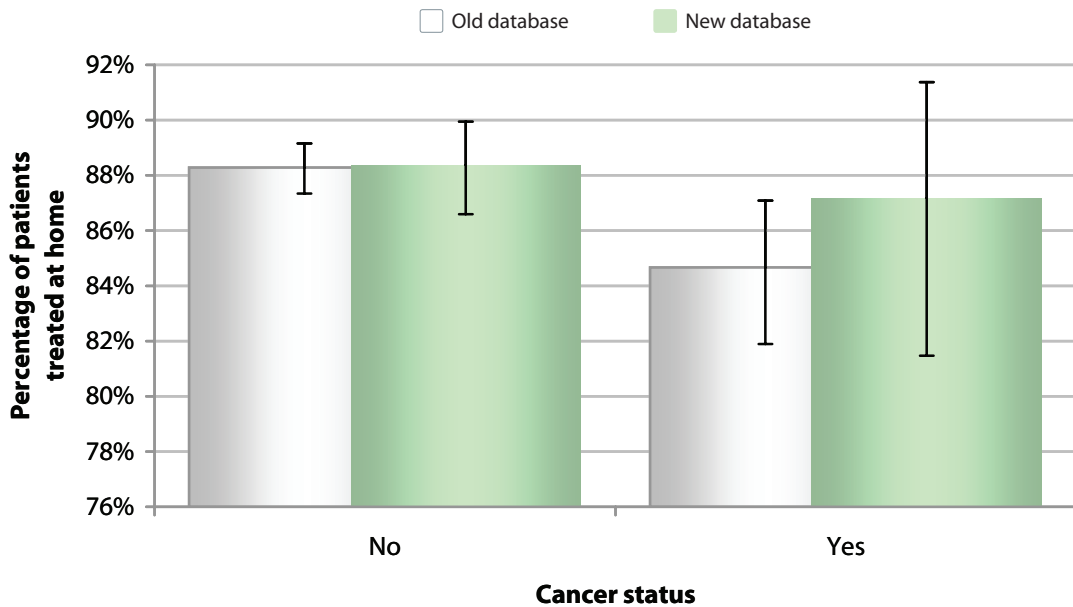
Treatment

Location of treatment

Despite the marked reduction in cancer given as a reason for not treating DVT out of hospital described on page 31, this has not yet manifested itself as an increase in the number of cancer patients treated out of hospital, with a slight decrease apparent in the graph below. Nonetheless, the proportion of cancer patients with DVT treated out of hospital remains quite high at 87%.

			Treated at home			
			No	Yes	Unspecified	All
Cancer status and database version	Old db	No cancer	581	4,376	237	5,194
		Cancer	119	657	40	816
		Unspecified	54	356	36	446
		All	754	5,389	313	6,456
	New db	No cancer	170	1,292	3,531	4,993
		Cancer	25	170	561	756
		Unspecified	21	57	201	279
		All	216	1,519	4,293	6,028

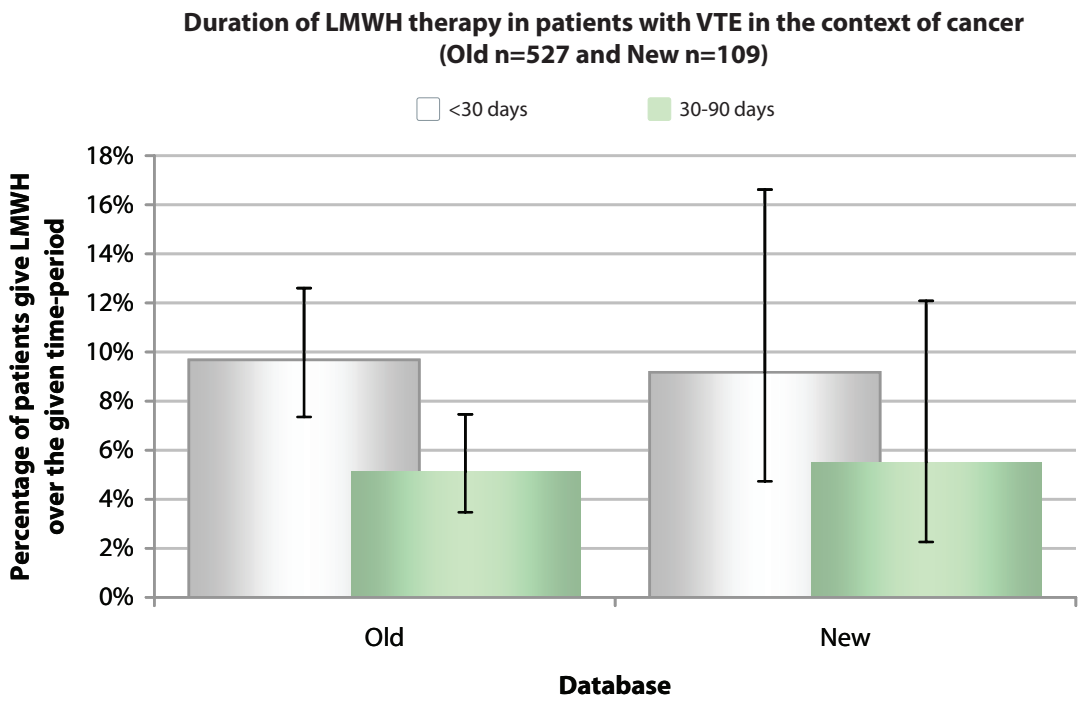
Location of treatment and cancer status for VTE patients (n=7,390)



Cancer

Duration of LMWH therapy and cancer

In patients with cancer who develop VTE, clinical guidelines recommend that secondary prevention should be with LMWH for 3 to 6 months⁸. However, reviewing the data shown below shows that only a small proportion of cancer patients receive extended treatment with LMWH. About 9% received treatment for longer than 30 days and only about 5% for longer than 90 days. Comparing the old and new databases shows little change over time. This suggests a slow uptake of the recommendation for LMWH to replace warfarin in the treatment of VTE in cancer patients. However, we are aware that two hospitals (Portsmouth and Derriford) have switched completely to LMWH for the treatment of DVT of cancer patients, and it is somewhat surprising that these changes have not yet manifested themselves in the overall database analysis.

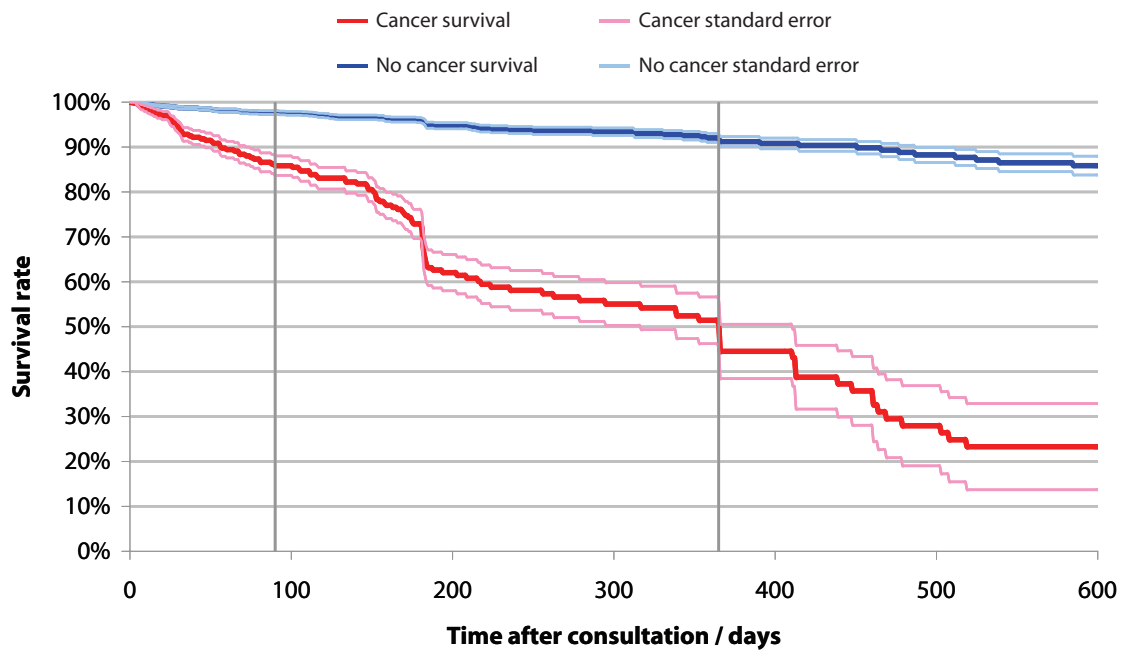


Cancer

Outcomes

The Kaplan-Meier survival curve below compares cancer patients with non-cancer patients in 2,772 patients with VTE. As shown in the last report, and as expected, VTE patients with cancer have a markedly poorer survival than cancer-free patients. This year, with more data available, the survival curve can be plotted to 600 days and shows that survival continues to fall to around 520 days, flattening out to day 600, with only 22% of patients alive at that time point.

Kaplan-Meier survival curves for patients with confirmed diagnoses of VTE according to the presence or absence of cancer (n=2,772)



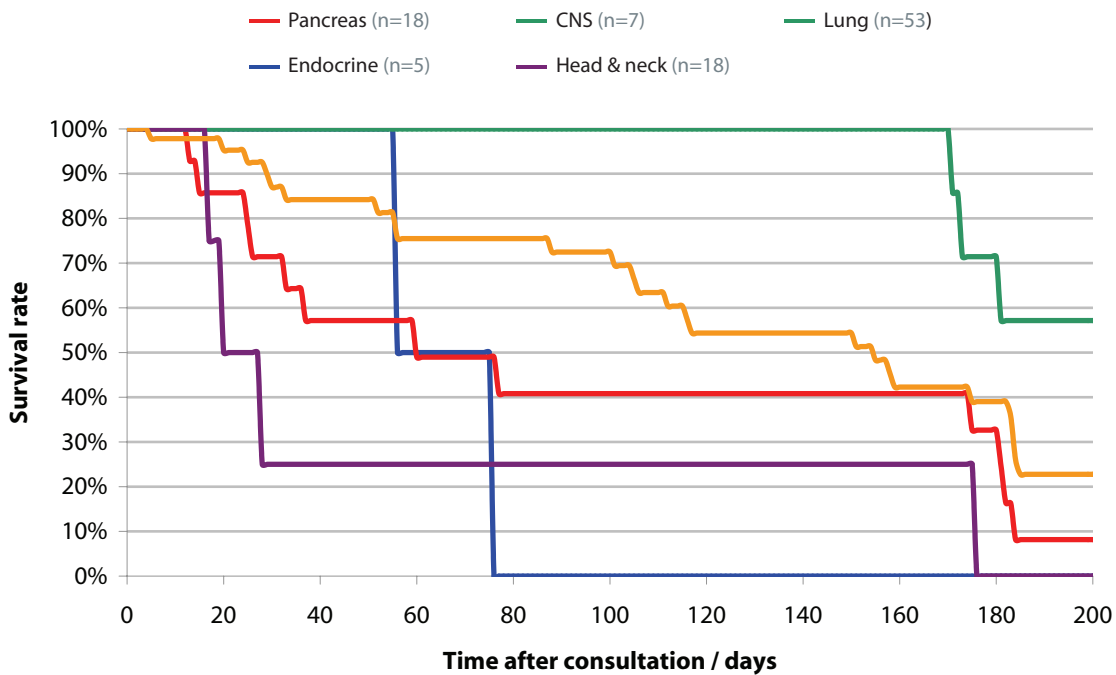
Cancer

Outcomes in VTE patients with different types of cancer

As described previously (see pages 83-85), certain cancer types are strongly associated with VTE. A key question we wish to answer is: what is the impact of VTE on survival in those particular cancer types? In this Kaplan-Meier survival curve, the numbers of cancers with follow up are quite small (endocrine n=5; pancreas n=18; CNS n=7; head and neck n=10; lung n=53) and we do not have comparisons of cancer patients' survival in the non-VTE population. However, we can begin to see a pattern, with particularly short survival associated with endocrine tumours, whereas with lung, the survival does not appear to be different from the overall cancer survival curve on the previous page. Clearly, these data are interesting and a VERITY project has been initiated to investigate further the association between cancer and VTE, with a particular focus on the impact of VTE on cancer survival.

The Californian Cancer Registry ⁷ again provides interesting data for current and future comparison. The Registry showed several interesting findings: that diagnosis of VTE was a significant predictor of decreased survival during the first year for all cancer types, and that metastatic disease at the time of diagnosis was the strongest predictor of VTE. With regard to staging, it is interesting to note that VTE was not a significant predictor of death for metastatic colorectal or breast cancer. VTE was a significant predictor of death among patients with local or regional-stage disease but not among patients with metastatic disease ^{9,10}.

Kaplan-Meier survival curves for patients with confirmed cancer according to the patients final diagnosis (n=597)



Cancer

Outcomes in VTE patients with elevated D-dimer

As noted earlier (see page 27), we wish to move towards a quantitative D-dimer assessment in VERITY. Quantitative D-dimer is of particular interest in cancer patients because of the recently established relationship between elevated D-dimer levels and poor outcome in cancer patients with VTE. The case report from The Walsgrave, presented in the last VERITY report, has now been published ¹¹ and confirms that high D-dimer is a marker of poor survival; the summary is presented below.

High D-dimer levels at presentation in patients with VTE is a marker of adverse clinical outcomes

S. Paneesha ¹, E. Cheyne ², K. French ², S. Bacchu ², A. Borg ¹ and P. Rose ^{1,2}

¹ Department of Haematology, Warwick Hospital, Warwick, and

² Department of Haematology, University Hospital Coventry and Warwickshire NHS Trust, Coventry, UK

Qualitative D-dimer results, together with clinical probability scores, are well established in the diagnosis of VTE. The predictive value of quantitative D-dimer levels for various clinical outcomes in VTE patients is not fully understood. D-dimer levels obtained at presentation were analysed in 699 (360 men; 339 women) VTE patients for survival and occurrence of malignancy. Patients were followed for a median of 23 months. 17.2% patients had a D-dimer level >8,000 ng FEU / ml at presentation, which was associated with decreased overall survival (OS; $p < 0.001$) and event-free survival (EFS; $p < 0.001$). 25.4% patients had malignancy and 4% subsequently developed malignancy following VTE. 29.9% of patients with VTE and malignancy had a D-dimer level >8 mg l⁻¹ when compared with 13.4% of patients with VTE without malignancy ($P < 0.001$). 50% of patients who developed subsequent malignancy following VTE had a presentation D-dimer >8,000 ng FEU / ml as compared with 13.3% of patients with VTE with out malignancy ($p = 0.009$).

In conclusion, D-dimer >8,000 ng FEU ml⁻¹ at presentation in patients with VTE is a marker of poor OS, EFS and underlying malignancy. Consideration of screening for malignancy is recommended in patients with VTE with a presentation D-dimer >8,000 ng FEU ml⁻¹ and age >60 years.

Outcomes in cancer patients with or without VTE

Cancer is known to be an adverse risk factor in patients with VTE but data on the potential adverse impact of VTE on survival in patients with malignancy is conflicting. In the previous report, we described an analysis of data from Walsgrave Hospital, that showed the impact of cancer on survival. This year, further analysis has been conducted using VERITY data and a summary of the data are presented below. These data were presented at the British Society of Haematology meeting in May 2007.

Venous thrombosis (VTE) has an adverse impact on the survival in patients with malignancy

This study included 902 (463 males; 439 females) patients from the prospectively maintained database of patients from UK venous thromboembolism registry (VERITY) between February 2001 and December 2006. Counterpart group included 2,263 (745 males; 1,518 female) consecutive patients without venous thrombosis from one site, between February 2001 and December 2005. All patients underwent a Doppler ultrasound examination to confirm the diagnosis and determine the extent of venous thrombosis. At presentation, D-dimer assays were done using Bio-Merieux kit containing mouse monoclonal antibody. The database was regularly updated (6 monthly) using hospital information systems, questionnaires and clinical review. Thrombosis recurrence was always confirmed by Doppler ultrasound examination. All Patients with thrombosis received standard treatment with low molecular weight heparin and warfarin. Statistical analysis was carried out using SPSS 13.0 for Windows software.

Median age at presentation was 66 years (range: 16-96 years). Median D-dimer level was 2,500 $\mu\text{g FEU ml}^{-1}$ (range: 100-40,000 $\mu\text{g FEU ml}^{-1}$). 17.3 % had D-dimer > 8,000 $\mu\text{g FEU ml}^{-1}$. 61% had above knee & 34% had below knee VTE. 522 patients had no malignancy, 89 had bowel, 61 prostate, 56 breast, 41 gynaecological, 29 lung and 102 had miscellaneous carcinoma. Median follow-up was 21 months (range: 0-74 years). Mean overall survival (OS) in non-VTE patients without malignancy was 56 months as compared to 54 months in VTE patients with malignancy. Mean OS in VTE patients with carcinoma breast was 34 months (counterpart group: 47 months). Median OS in VTE patients with carcinoma bowel was 9 months (counterpart group: 36 months). Median OS in VTE patients with carcinoma prostate was 31 months (counterpart group: 33 months). Median OS in VTE patients with gynaecological carcinoma was 17 months (counterpart group: 50 months). Median OS in VTE patients with miscellaneous carcinoma was 9 months (counterpart group: 30 months). Median OS in VTE patients with carcinoma lung was 5 months (counterpart group: 4 months). Median D-dimer levels in VTE patients without malignancy, Ca Breast, Ca bowel, Ca Prostate, Gynaecological Ca, Miscellaneous Ca and Ca Lung respectively were 2,200, 3,650, 4,100, 2,850, 3,140, 3,230 & 3,400 $\mu\text{g FEU ml}^{-1}$. D-dimer > 8,000 $\mu\text{g FEU ml}^{-1}$ was associated with shorter survival (Log rank test; p value < 0.001).

Our study shows occurrence of VTE shortens the survival in patients with malignancies. Our study also shows D-dimer > 8,000 $\mu\text{g FEU ml}^{-1}$ is associated with significant shorter survival. More studies are warranted to determine whether this adverse impact correlates with the thrombogenesis of underlying malignancy rather than recurrence and also can it be negated by optimum anticoagulant therapy.

Conclusions

Epidemiological studies have identified cancer as an important risk factor for VTE but many clinical questions remain unanswered. This year, we have data on 3,056 patients with cancer, 1,572 patients with VTE and 1,484 patients without VTE.

As previously, patients with VTE and the most common forms of cancer (breast, prostate, colorectal and lung) show interesting differences in age distribution, with breast cancer patients showing peaks in the middle age groups (4th, 5th and 6th decades). In calculating the ratio of the incidence of each cancer in the VTE population to the incidence in non-VTE patients, we can see that the particular cancers are particularly associated with VTE. The odds ratio is low for breast and prostate; for lung and colorectal cancers, the odds ratio is intermediate; but for endocrine, CNS and head and neck cancers, very high odds ratios are apparent. This is very interesting data and we will now attempt to correlate these findings with patient outcome.

With limited outcome data, it remains difficult to draw firm conclusions on the relationship between VTE and cancer. Nevertheless, VTE patients with cancer have a poorer outcome than patients without cancer. We would particularly like to assess the impact that VTE has on cancer survival, but the data are not extensive enough as yet. We hope that the VERITY cancer project that has been initiated will give sufficient data to begin to answer this important question.

Regarding the diagnosis and treatment of VTE in cancer patients, the findings validate combined PTP and D-dimer in this mixed population of cancer and non-cancer patients. Quantitative D-dimer now appears to be a valuable measure in cancer patients, with the publication by Walsgrave of a correlation between elevated D-dimer and survival. The proportion of cancer patients with VTE who were treated as outpatients was slightly less than VTE patients who did not have cancer, in keeping with the previous findings. As we suggested in the last report, the use of LMWH for secondary prophylaxis of VTE needs to be addressed. The use of guideline-recommended extended LMWH therapy in cancer patients remains limited, although we are aware that this practice has been adopted at two VERITY hospitals (Portsmouth and Derriford).

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