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Effect of testing for cancer on cancer- and venous thromboembolism (VTE)-related mortality and morbidity in patients with unprovoked VTE

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ABSTRACT

Background

Venous thromboembolism (VTE) is a collective term for two conditions: deep vein thrombosis (DVT) and pulmonary embolism (PE). A proportion of patients with VTE have no underlying or immediately predisposing risk factors and the VTE is referred to as unprovoked. Unprovoked VTE can often be the first clinical manifestation of an underlying malignancy. This has raised the question of whether patients with an unprovoked VTE should be investigated for an underlying cancer. Treatment for VTE is different in cancer and non-cancer patients and a correct diagnosis would ensure that patients received the optimal treatment for VTE to prevent recurrence and further morbidity. Furthermore, an appropriate cancer diagnosis at an earlier, potentially curative stage could avoid the risk of cancer progression and thus lead to improvements in cancer-related mortality and morbidity.

Objectives

To determine whether testing for undiagnosed cancer in patients with a first episode of unprovoked VTE (DVT or PE) is effective in reducing cancer and VTE-related mortality and morbidity and to establish which tests for cancer are most useful.

Search methods

The Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched January 2015) and the Cochrane Register of Studies (CRS) (2014, Issue 12). Clinical trials databases were searched. The reference lists of relevant articles were also checked.

Selection criteria

Randomised and quasi-randomised trials in which patients with an unprovoked VTE were allocated to receive specific tests for cancer or clinically indicated tests only were eligible for inclusion in this review. Primary outcomes included all-cause mortality, cancer-related mortality and VTE-related mortality.
Data collection and analysis
Selection of the studies, quality assessment and data extraction were completed independently by two review authors. Any disagreements were resolved by discussion.

Main results
Two studies with a combined total of 396 patients met the inclusion criteria for this review. Both studies assessed the effect of testing for cancer versus clinically indicated tests only in patients with an unprovoked VTE. The quality of the evidence was moderate because although the studies were judged to be at a low risk of bias, there was concern that the studies were small as reflected in the wide confidence intervals (CIs). Pooled analysis showed that testing for cancer was consistent with either a benefit or no benefit on cancer-related mortality (odds ratio (OR) 0.49, 95% CI 0.15 to 1.67, P = 0.26). One study showed that, overall, malignancies were less advanced in patients belonging to the extensive screening group than in patients of the control group (64% versus 20%, P = 0.047) and that tested patients were diagnosed earlier than untreated patients (mean 1 month versus 11.6 months to cancer diagnosis from the time of diagnosis of VTE). Standard deviations were not provided for time to diagnosis, so it was not possible to perform an independent statistical analysis on this association. Neither study measured all-cause mortality, VTE-related morbidity and mortality, side effects of anticoagulation, side effects of cancer tests or patient satisfaction.

Authors’ conclusions
Testing for cancer in patients with idiopathic VTE leads to earlier diagnosis of cancer at an earlier stage of the disease. However, there is currently insufficient evidence to draw definitive conclusions concerning the effectiveness of testing for undiagnosed cancer in patients with a first episode of unprovoked VTE (DVT or PE) in reducing cancer and VTE-related morbidity and mortality. The results are imprecise and could be consistent with either harm or benefit. Further good-quality large-scale randomised controlled trials are required before firm conclusions can be made.

Plain Language Summary
Effect of testing for cancer (on cancer and blood clot-related death and illness) in patients with unprovoked blood clots in the legs and lungs

Venous thromboembolism (VTE) refers to blood clots in leg veins (known as deep venous thrombosis (DVT)), which can travel to the lungs (causing pulmonary embolism (PE)). PE can often be fatal. Signs of DVT include pain and swelling of the leg while signs of PE include breathlessness and chest pain. Risk factors for VTE include surgery, prolonged bed rest, trauma, a family history, pregnancy and blood deficiencies. However, sometimes a VTE happens for no apparent reason (it is unprovoked). In such patients an undetected cancer may be the cause of the VTE. This has raised the question of whether patients with an unprovoked VTE should be investigated for underlying cancer. This is potentially important as the management of VTE in patients with and without cancer differs. A cancer diagnosis would ensure that patients received the optimal treatment to reduce the risk of another VTE. A diagnosis could also lead to the cancer being treated earlier, at a more curable stage.

This review assessed whether testing for undiagnosed cancer in patients with a first unprovoked VTE (DVT or PE) was effective in reducing cancer and VTE-related illness and death. We found two studies with a combined total of 396 patients. Both studies compared cancer tests with no tests. One study used a complete range of tests while the second study performed fewer tests. The quality of the evidence was moderate because although the studies were judged to be at a low risk of bias, the studies were small. Combining the results of the two studies showed that testing had no effect on the number of cancer-related deaths. Additionally, testing did not identify more people with cancer. However, testing did identify cancers at an earlier stage (approximately 10 months earlier). Neither study looked at the number of deaths due to any cause, deaths and illness associated with VTE, side effects of cancer tests, side effects of VTE treatment nor patient satisfaction. This review found that there are too few trials to determine whether testing for undiagnosed cancer in patients with a first unprovoked VTE (DVT or PE) is effective in reducing cancer and VTE-related deaths and illness. Further good-quality and large-scale studies are required.
BACKGROUND

Description of the condition

Venous thromboembolism (VTE) is the collective term for the clinical conditions deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is the formation of a blood clot (thrombus) in a deep vein, predominantly in the legs. Symptoms include pain, tenderness, erythema and swelling of the affected leg. PE occurs when part or all of the thrombus breaks off (embolizes) and travels up to the lungs blocking the pulmonary arteries. Symptoms of PE include breathlessness and chest pain (Blann 2006).

Guidelines published by the UK National Institute for Health and Clinical Excellence (NICE) recommend that patients with a suspected DVT should be risk stratified using the Wells score, undergo a D-dimer test, and have a proximal leg vein ultrasound scan based on the risk of DVT (NICE 2012a). Similarly, patients with a suspected PE should be assessed using the Wells PE risk score, D-dimer test and a computed tomography pulmonary angiogram (CTPA) depending on the PE risk. The NICE guidelines recommend that anticoagulant therapy with low molecular weight heparin (LMWH) should be administered in the interim until these diagnostic investigations are carried out if the leg ultrasound is expected to take longer than four hours, or if a CTPA cannot be performed immediately (NICE 2012a). Patients with confirmed VTE should receive LMWH or fondaparinux for at least the initial five days and also started on a vitamin K antagonist. The LMWH should be stopped when the international normalised ratio (INR) has been above 2 for at least 24 hours. Vitamin K antagonists should be continued for at least three months in these patients. In patients with an unprovoked VTE consideration should be given to extending anticoagulation beyond three months based on an assessment of the risk of VTE recurrence and complications of anticoagulation. However, patients with cancer-associated VTE should be treated with LMWH from the initial diagnosis for a period of six months, and considered for continuation of anticoagulation with either LMWH or a vitamin K antagonist based on the status of the underlying cancer and risks of anticoagulation (NICE 2012a). More recently, rivaroxaban has been used for the treatment of DVT and prevention of recurrent DVT and PE (NICE 2012b). Guidelines by NICE recommend that rivaroxaban should be administered at a dose of 15 mg twice daily for the first 21 days followed by a continued dose of 20 mg once daily to prevent recurrence. Evidence from the EINSTEIN-DVT study showed that, in a subgroup of patients with active cancer, there was a trend indicating that rivaroxaban was less effective than LMWH at preventing VTE recurrence (hazard ratio 1.32, 95% confidence interval (CI) 0.06 to 32.3) but it was associated with fewer major bleeding events (Einstein Investigators).

The difference in management of patients with a cancer-associated VTE is due to their significantly higher risk of VTE recurrence, which is estimated to be three time higher than in patients with VTE in the absence of cancer (Levitan 1999). The underlying pathophysiology of cancer and thrombosis involves a complex process of several mechanisms including a “release of inflammatory cytokines, activation of the clotting system, expression of haemostatic proteins on tumour cells, inhibition of natural anticoagulants and impaired fibrinolysis” as described by Rodrigues 2010. Activation of the clotting system has also been implicated in cancer-associated angiogenesis, tumour metastasis and aggressiveness. Indeed, patients with cancer and an associated VTE have a poorer overall prognosis compared to patients without a VTE, with a 12% one-year survival from the diagnosis of VTE (Kakkar 1969; Ruiz 2003).

A proportion of patients with VTE have no underlying or immediately apparent cause and the VTE is referred to as idiopathic or unprovoked. Unprovoked VTE can suggest underlying malignancies such as cancer of the blood, kidney, ovary, pancreas, stomach and lung (Bick 1978; Kakkar 2003; Lee 2003a; P randoni 1997; White 2005). Results from a Swedish prospective cohort study of almost 62,000 patients determined that the standardised incidence ratio of a cancer diagnosis within the first two years of an unprovoked VTE was 4.4 (Baron 1998), and there was an overall absolute incidence of cancer of 11% (NICE 2012a). A study of 339 patients with a first episode of an unprovoked VTE determined that the relative risk (RR) of cancer-related mortality at two years was 0.52 (95% CI 0.10 to 2.75) in patients undergoing intensive investigations compared to routine tests, while the RR for early-stage cancer detection was 3.21 (95% CI 0.88 to 11.79) (Piccioli 2004a).

Patients who present with an apparent unprovoked VTE therefore have a significant underlying risk of malignancy or cancer-associated VTE, with significant implications for the management of the VTE itself (three months vitamin K antagonist versus six months LMWH), the prognosis related to risk of VTE recurrence, and the precipitating cancer. This has raised the question of whether patients with an unprovoked VTE should be investigated for an underlying cancer. Some authors have referred to this as ‘screening for cancer’ although this is somewhat misleading as screening refers to the investigation of asymptomatic patients. Instead, patients with VTE are better regarded as presenting with symptoms suggestive of an underlying cancer and the aim of investigations is to refine the diagnosis of VTE based on the underlying cause, so that the patient may receive a more accurate diagnosis and appropriate treatment for their VTE. In this context, VTE represents a symptom rather than a diagnosis per se. So, to what extent should patients with an unprovoked VTE be investigated for a potential underlying cancer?

Description of the intervention

The NICE Guidelines on venous thromboembolic disease (NICE 2012a) recommend that all patients presenting with a first episode of unprovoked VTE (DVT or PE) should undergo a history and
physical examination directed to detecting an underlying malignancy, and further tests guided by the history and examination including blood tests (complete blood count, serum calcium and liver function tests), urinalysis and chest X-ray. If none of these initial investigations suggest signs and symptoms of cancer then further tests including abdomino-pelvic CT scan (and a mammogram for women) are recommended in patients over 40 years (NICE 2012a). It is the value of these additional tests which is the subject of this review.

How the intervention might work

The interventions for detecting an underlying cancer will enable a diagnosis of cancer-associated VTE to be made. This will enable the patient to receive appropriate anticoagulation with LMWH versus vitamin K antagonist, for six versus three months respectively, and for the underlying cancer to be treated promptly without the need for additional symptoms to emerge before it is diagnosed. One study has shown that the combination of tests recommended by NICE detects cancer in approximately 10% of patients with a first episode of unprovoked VTE and with no prior cancer diagnosis (Piccioli 2004a). However, tests for cancer also have the potential for harm, from the pain and inconvenience of blood tests to more serious complications due to radiation exposure from X-rays and CT scans.

Why it is important to do this review

The pharmacological management of VTE in patients with and without cancer is considerably different, both in terms of choice of agent and duration of anticoagulation. Therefore, an appropriate cancer diagnosis would ensure that patients received the optimal form and duration of anticoagulation, which, in turn, could reduce the overall population VTE recurrence rate and associated morbidity. Establishing whether a patient with an apparently unprovoked VTE has an underlying cancer is important since this may lead to cancer diagnosis at an earlier, potentially curative stage, avoiding the risk of cancer progression whilst waiting for additional symptoms. This may, in turn, lead to improvements in cancer-related mortality and morbidity. To date, no systematic review has been conducted to measure the effectiveness of testing for cancer in patients with an unprovoked VTE. This review provides evidence as to whether such tests for underlying cancer, followed by appropriate alteration in the management or treatment of VTE, or both, are effective in reducing morbidity (VTE recurrence) and mortality (VTE- and cancer-associated).

OBJECTIVES

1. To determine whether testing for undiagnosed cancer in patients with a first episode of unprovoked VTE (DVT or PE) is effective in reducing cancer mortality and morbidity

2. To determine whether testing for undiagnosed cancer in patients with a first episode of unprovoked VTE (DVT or PE) is effective in reducing VTE-related mortality and morbidity

3. To determine which tests for cancer are most useful

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised trials in which patients with an unprovoked VTE were allocated to receive different tests for cancer or tests as per physician discretion. We looked primarily at randomisation within three months of a VTE, as used in the SOMIT trial (Piccioli 2004a). However, trials where randomisation occurred at different time points would also be included as a subgroup analysis. We included published studies and studies in progress if preliminary results were available. Non-English language studies were also eligible for inclusion in the review.

Types of participants

Patients with a first episode of unprovoked VTE (DVT or PE) with no pre-existing or clinically apparent cancer diagnosis.

Types of interventions

Tests for cancer (for example complete blood count, serum calcium, liver function test, urinalysis, chest X-ray, all forms of CT imaging, mammogram, tumour markers, sputum cytology, ultrasonography, positron emission tomography (PET) scan and colonoscopy) versus no tests for cancer or alternative tests, followed by appropriate treatment for cancer or change in VTE treatment regime, or both. Studies where these tests were routinely used in all arms were not included. However, we included any study that focused on some other aspect of care than cancer only if the test for cancer was the subject of randomisation.

Types of outcome measures

Primary outcomes

1. All-cause mortality (death due to any cause).

2. Cancer-related mortality (defined as death due to a malignant disease itself, or death due to complications of treatments or procedures to diagnose or treat the cancer).
3. VTE-related mortality (fatal PE). PE diagnosed "on the basis of a lung scan indicating a high probability of its presence, as indicated by the presence of new or enlarged areas of segmental perfusion defects with ventilation-perfusion mismatch; an abnormal perfusion scan with documentation of new or recurrent deep-vein thrombosis; the presence of non-
enhancing filling defects in the central pulmonary vasculature on helical computed tomography; a finding of intraluminal filling defects on pulmonary angiography; or evidence of fresh pulmonary embolism at autopsy" (Lee 2003b). Fatal PE including probable fatal PE and unexplained sudden death were used if reported, as defined by individual studies.

Secondary outcomes

1. VTE-related morbidity (e.g. frequency of recurrent VTE). Recurrent PE or DVT was diagnosed if a previously compressible proximal venous segment or segments could no longer be compressed on ultrasonography or if there were constant intraluminal filling defects in two or more projections on venography. Unequivocal extension of the thrombus required for the diagnosis of recurrence if the results were abnormal on previous testing (Lee 2003b).

2. Complications of anticoagulation (e.g. warfarin versus LMWH-associated bleeding). We reported on major bleeding and minor bleeding if reported in the included studies. Major bleeding includes bleeding associated with death, bleeding at a critical site (intracranial, intraspinal, intracocular, retroperitoneal or pericardial area), bleeding resulting in a need for a transfusion of at least two units of blood, or bleeding leading to a drop in haemoglobin of at least 2.0 g/dL (Lee 2003b). Minor bleeding includes any other bleeding.

3. Side effects of cancer tests (e.g. radiation exposure, bleeding, as defined in included studies).

4. Characteristics of diagnosed cancer (e.g. primary tumour, stage, localised (curable) versus advanced (palliative) as defined in included studies).

5. Time to cancer diagnosis, as defined in included studies.

6. Frequency of an underlying cancer diagnosis (that is the number of times cancer was diagnosed through screening following an unprovoked VTE as defined in included studies) at the time of VTE presentation and overall over the follow-up period.

7. Patient satisfaction (if assessed in individual studies, we reported results descriptively using the definition provided by the trialists).

Search methods for identification of studies

There was no restriction on date or language of publication.

Electronic searches

The Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched January 2015) and the Cochrane Register of Studies (CRS) (http://www.metaxis.com/CRSWeb/Index.asp) (2014, Issue 12). See Appendix 1 for details of the search strategy used to search the CRS. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane Peripheral Vascular Diseases Group module in the Cochrane Library (www.cochranelibrary.com).

The TSC searched the following trial databases (January 2015) for details of ongoing and unpublished studies using the terms ((cancer or neoplasm) and screening and thrombosis):

- World Health Organization International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/);
- ClinicalTrials.gov (http://clinicaltrials.gov/);

Searching other resources

Reference lists of relevant articles retrieved by the electronic searches were searched for additional citations. Furthermore, we searched the conference proceeding abstracts of the following societies:

- International Society for Thrombosis and Haemostasis (ISTH) (from 2003 to 2014);
- The American Society for Hematology (ASH) (from 2004 to 2014).

Data collection and analysis

Selection of studies

One review author (LR) used the selection criteria to identify trials for inclusion. The second review author (SEY) independently confirmed this selection and any disagreements were resolved by discussion.

Data extraction and management

Two review authors (LR, SEY) independently extracted the data. Information about the trial design, VTE definition and investigations to confirm diagnosis, baseline characteristics of patients and tests for cancer was recorded. All-cause mortality, cancer-related mortality and VTE-related mortality data were recorded as...
the primary outcome measures. Information on VTE-related morbidity (for example frequency of recurrent VTE), complications of anticoagulation (for example warfarin- versus LMWH-associated bleeding), side effects of cancer tests (for example radiation exposure, bleeding), characteristics of diagnosed cancer (for example primary tumour, stage, localised (curable) versus advanced (palliative)), time to cancer diagnosis, frequency of an underlying cancer diagnosis and patient satisfaction was collected in accordance with the secondary outcome measures. Authors of included studies were contacted for further information if clarification was required. Any disagreements in data extraction and management were resolved by discussion.

Assessment of risk of bias in included studies
Two review authors (LR, SEY) independently used the Cochrane Collaboration’s tool (Higgins 2011) to assess the risk of bias for each of the included studies. The tool provides a protocol for judgements on sequence generation, allocation methods, blinding, incomplete outcome data, selective outcome reporting and any other relevant biases. We judged each of these domains as either at high, low or unclear risk of bias according to Higgins 2011 and provided support for each judgement. The conclusions are presented in a ‘Risk of bias’ table. Any disagreements were resolved by discussion.

Measures of treatment effect
We planned to base the analysis on intention-to-treat data from the individual clinical trials. The majority of outcomes were binary measures (mortality, morbidity, complications, side effects, characteristics of diagnosed cancer, frequency of an underlying cancer diagnosis). For these outcomes we computed odds ratios (ORs) using a random-effects model and calculated the 95% confidence intervals (CI) of the effect sizes. For time to cancer diagnosis we aimed to compute hazard ratios (HR) while for patient satisfaction we planned to report results descriptively (Deeks 2011).

Unit of analysis issues
The unit of analysis within each trial was the individual participant.

Dealing with missing data
We sought information about dropouts, withdrawals and other missing data and, if not reported, we contacted the study authors.

Assessment of heterogeneity
We assessed the heterogeneity between the pooled studies by visual examination of the forest plot to check for overlapping CIs, and used the Chi² test for homogeneity with a 10% level of significance. We used the I² statistic to measure the degree of inconsistency between the studies. An I² value of over 50% may represent moderate to substantial heterogeneity (Deeks 2011).

Assessment of reporting biases
We planned to assess reporting biases such as publication bias using funnel plots (Sterne 2011). However, as only two studies were included in the review it was not possible to test for funnel plot asymmetry.

Data synthesis
The review authors independently extracted the data. One review author (LR) entered the data into RevMan (RevMan 2014). A second review author (SEY) cross-checked data entry and any discrepancies were resolved by consulting the source publication. We used a random-effects model for meta-analysis of the data. We planned to stratify analyses according to the individual cancer test being assessed and also the combination of tests as used in the SOMIT trial (Piccioli 2004a).

Subgroup analysis and investigation of heterogeneity
Where possible, we planned to analyse clinically relevant subgroups based on the following:
1. DVT or PE;
2. cancer site;
3. treatment post-investigation with vitamin K antagonist or LMWH;
4. duration of anticoagulation (e.g. three or six months);
5. age and gender of patients (comparing those in age and gender groups for national screening programmes to those not in these age and gender groups);
6. time of randomisation after VTE diagnosis (within three months compared with after three months).

Sensitivity analysis
We planned to conduct a sensitivity analysis by excluding studies at a high risk of bias to measure the effect on the results.

RESULTS

Description of studies

Results of the search
See Figure 1
Figure 1. Study flow diagram.

1196 reports from CRS search
5 records for 4 studies found from World Health Organization International Clinical Trials Registry
10 studies found in ClinicalTrials.gov
24 studies found in ISRCTN register

4 records identified from Specialised Register

1187 reports when duplicates removed screened by authors

1183 not relevant

4 full-text articles assessed for eligibility

1 ongoing study

2 studies (3 reports) included in qualitative synthesis

2 studies included in quantitative synthesis (meta-analysis)
Included studies

Two studies (Piccoli 2004; Piccoli 2012) were deemed relevant and included in the review. See Characteristics of included studies

One study (Piccoli 2004) was a randomised multicentre study of 201 apparently cancer-free patients with acute idiopathic venous thromboembolism (VTE). Extensive investigations for occult malignant disease were compared with testing at the physician’s discretion. Ninety-nine patients were randomised to the extensive screening group and 102 were randomised to the control arm. Patients in the extensive investigations group were offered ultrasound and CT scans of the abdomen and pelvis, gastroscopy or double contrast barium swallowing, colonoscopy or sigmoidoscopy followed by a barium enema, haemoccult test, sputum cytology and tumour markers including carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP) and CA125. Women also underwent mammography and Pap smears while men had transabdominal ultrasound of the prostate and a total prostate specific antigen (PSA) test. All tests were completed within a four-week period from the diagnosis of VTE. Patients in the control group were investigated at the physician’s discretion. If the investigations suggested the presence of a malignant process, further investigations were performed according to current standards. Patients were followed up at 3, 12 and 24 months following the diagnosis of VTE. The primary outcome was cancer-related morbidity, defined as death due to a malignant disease itself, or death due to complications of diagnostic or surgical procedures performed to diagnose or treat cancer. A secondary outcome of this study consisted of the cluster of cancer-related mortality and documented residual malignancy or recurrent malignancy at 24 months. The authors also measured the frequency of an underlying cancer diagnosis including type and stage as well as mean time to cancer diagnosis.

The second study (Piccoli 2012) was a randomised study in which 195 patients with a first episode of unprovoked VTE were randomised to extensive investigations (n = 98) or a discretionary diagnostic approach excluding CT scans (n = 97). Extensive investigations comprised a CT scan of the thorax, abdomen and pelvis together with faecal haemoccult testing. Patients were followed for 24 months to document the incidence of newly discovered cancer and cancer-related mortality. At the time of writing this review, this study had only been published as an abstract.

Excluded studies

There were no studies excluded from the review.

Ongoing studies

There was one ongoing study which is not expected to finish until 2015 (NCT00773448).

Risk of bias in included studies

See Figure 2 and Figure 3

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**Figure 2.** Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Although both studies were randomised, the study by Piccoli 2012 did not provide any information on the method of randomisation used and therefore the risk of selection bias could not be assessed. The study by Piccoli 2004 used a Zelen approach and therefore was at low risk of selection bias. In terms of concealing the allocation of treatment, the study by Piccoli 2004 performed randomisation centrally while the study by Piccoli 2012 did not report the methods used.

Blinding

As the study groups in both the Piccoli 2004 and Piccoli 2012 trials were randomised to extensive screening or no further testing, it was impossible to blind patients and study personnel. However, we believe it was unlikely that the lack of blinding would have affected the outcome and, therefore, both studies were judged to be at a low risk of performance bias.

In the Piccoli 2004 trial, the physician at the follow-up examination was unaware of the allocation of a patient and therefore detection bias for outcome assessors was low. For Piccoli 2012 there was insufficient information about the blinding of outcome
assessors to permit a judgment on the risk of detection bias.

Incomplete outcome data
The two treatment groups in Piccioli 2004 were well-balanced with respect to baseline characteristics, completion of the study protocol and discontinuation of treatment. Furthermore, all missing data were accounted for and reported. Therefore, the study was judged to be at low risk of attrition bias. The study by Piccioli 2012 did not provide enough information to assess the risk of attrition bias.

Selective reporting
Piccioli 2004 clearly pre-specified all primary and secondary outcomes and data on all outcomes were reported. The study by Piccioli 2012 was reported as a conference abstract and there was insufficient information to determine the risk of reporting bias.

Other potential sources of bias
The Piccioli 2004 study was deemed to be at low risk from other sources of bias while the risk of bias in the Piccioli 2012 study was unclear due to lack of information.

Effects of interventions
Both studies (Piccioli 2004; Piccioli 2012) measured the primary outcome cancer-related mortality. In the study by Piccioli 2004, 2 out of 99 patients in the extensive testing group died of cancer compared to 4 out of 102 in the group who underwent no further tests (OR 0.51, 95% CI 0.09 to 2.82). In the second study (Piccioli 2012), two tested and four untested patients died of cancer (OR 0.48, 95% CI 0.15 to 1.67) in favour of testing, which did not reach statistical significance (P = 0.26) (Analysis 1.1). However, neither of the included studies (Piccioli 2004; Piccioli 2012) measured the review’s other primary outcomes of all-cause mortality and VTE-related mortality, and the secondary outcomes VTE-related morbidity, complications of anticoagulation, side effects of cancer tests and patient satisfaction.

One study (Piccioli 2004) looked at the location of the malignancy and found no difference in the incidence of any particular cancer between the tested and untested groups: lung (OR 2.08, 95% CI 0.19 to 23.34), bladder (OR 2.08, 95% CI 0.19 to 23.34), stomach (OR 1.03, 95% CI 0.06 to 16.71), kidney (OR 3.12, 95% CI 0.13 to 77.75), adrenal gland (OR 3.12, 95% CI 0.13 to 77.75), liver (OR 3.12, 95% CI 0.13 to 77.75), uterus (OR 3.12, 95% CI 0.13 to 77.75), breast (OR 1.03, 95% CI 0.06 to 16.71), ovary (OR 3.12, 95% CI 0.13 to 77.75), colon (OR 0.51, 95% CI 0.05 to 5.72), prostate (OR 0.51, 95% CI 0.05 to 5.72) and pancreas (OR 0.20, 95% CI 0.01 to 4.26) (Analysis 1.2). Piccioli 2004 compared the characteristics of the diagnosed cancer by assessing the proportion of early stage malignancies, defined as T1 or T2 without loco-regional or distant metastases (N0 M0). Overall, malignancies were less advanced in patients who had undergone extensive testing. One patient in the tested group was found to have stage T3 compared with four patients of the control group. In total, 9 of the 14 patients with cancer in the tested group had a T1 or T2 stage malignancy without loco-regional or distant metastases compared to two out of 10 patients in the control group (64% versus 20%, P = 0.047).

Time to cancer diagnosis (measured from the time of diagnosis of VTE) was measured in one study (Piccioli 2004), reported as a mean of 1 month in tested patients compared to 11.6 months in untested patients (P < 0.001). Standard deviations for these means were not given. Attempts were made to contact the author for this data but no response was received.

Both studies measured the frequency of an underlying cancer diagnosis. In the study by Piccioli 2004, underlying cancer was detected in 13 out of 99 patients who underwent extensive testing, whereas it became symptomatic in 10 out of 102 untested patients (OR 1.39, 95% CI 0.58 to 3.34). In the study by Piccioli 2012, cancer was detected in 2 of the 98 patients who had further tests and it became apparent in 2 out of the 97 patients who were not tested (OR 0.99, 95% CI 0.14 to 7.17). The combined incidence of an underlying cancer diagnosis was 15/197 in the tested group and 12/199 in the non-tested group (OR 1.32, 95% CI 0.59 to 2.93) (Analysis 1.3). Therefore, after 24 months of follow-up, the incidence of cancer was not different in the tested and control groups.

Overall, only two studies with a combined total of 396 patients were included in this review. Furthermore, the data in the two included studies were limited and therefore it was not possible to perform all pre-defined subgroup analyses.

Of the two studies included in this review, one (Piccioli 2004) was at a low risk of bias and the other (Piccioli 2012) did not provide enough information to make a judgement on the level of bias. Therefore, it was not feasible to perform a sensitivity analysis based on the quality of the included studies.

DISCUSSION

Summary of main results
Only two studies were found which fulfilled the eligibility criteria for inclusion in this review. Both studies measured the effectiveness of testing for cancer on cancer-related mortality in patients with a first unprovoked VTE. The study by Piccioli 2004 performed an extensive list of tests while the study by Piccioli 2012 carried out fewer tests. In total, 396 patients were studied. Pooled analysis showed that testing for cancer was consistent with either a benefit or no benefit on cancer-related mortality. Testing did not
increase the frequency of an underlying cancer diagnosis. However, the time to cancer diagnosis was shorter in tested patients (mean 1 month versus 11 months). Furthermore, malignancies were less advanced in patients belonging to the extensive screening group than those of the control group (Piccioli 2004). However, standard deviations for the mean time to diagnosis were not reported and therefore it was not possible to independently test the statistical significance of this result. Neither study measured all-cause mortality, VTE-related morbidity and mortality, side effects of anticoagulation, side effects of cancer tests nor patient satisfaction.

**Overall completeness and applicability of evidence**

At present, there is limited evidence concerning whether testing for undiagnosed cancer in patients with a first episode of unprovoked VTE (DVT or PE) is effective in reducing cancer- and VTE-related mortality and morbidity and which tests for cancer are most useful. Only two studies (Piccioli 2004; Piccioli 2012) met the inclusion criteria for this review. The number of patients in each study was relatively small and pooled analysis is based on a total of 396 patients. Furthermore, the two studies primarily looked at cancer-related mortality and incidence of cancer diagnosis as their main outcomes. Other outcomes of interest for this review, such as all-cause mortality, VTE-related morbidity and mortality, side effects of anticoagulation and side effects of cancer tests, were not studied and, therefore, remain unknown. The Piccioli 2012 study was reported as an abstract only and therefore had limited information. Written communication with the author revealed that the full results of this study are to be published soon and, therefore, it may be possible to include data on other outcomes in future updates of this review. A third study (NCT00773448) was eligible for inclusion in this review but is ongoing and not expected to finish until 2015.

**Quality of the evidence**

The study by Piccioli 2012 was a conference abstract and therefore there was insufficient information to make any judgements on the methodological quality of the study. Written communication with the author revealed that full results of this study are due to be published soon and therefore it may be possible to assess the quality of the study in a future update of the review. The other study included in the review (Piccioli 2004) was judged to be at low risk of bias. While the study had a robust design and consistent results, there are concerns with regards to the precision of the results, particularly for the analysis by cancer site, where there were wide confidence intervals (Analysis 1.2). Therefore the quality of the evidence in this review was considered to be moderate.

**Potential biases in the review process**

None of the authors of this review were involved in any of the included or excluded studies. Furthermore, none have any commercial or other conflict of interest. The search was as comprehensive as possible, and all studies were independently assessed for inclusion by two review authors. We are confident that we have included all relevant studies and we have attempted to reduce bias in the review process by performing data extraction and assessing study quality independently. However, the possibility remains that we may have missed studies which have not been published. We judged blinding of investigators and participants to be at low risk of bias. It would have been impossible to blind participants and staff to tests such as scans. There is, therefore, a risk of crossover bias in participants in the control arm with them having further tests. The effect of this, however, would be to minimize the apparent benefit from testing that was observed, and therefore this does not detract from the conclusions of the study or review.

**Agreements and disagreements with other studies or reviews**

To date, no other systematic review has assessed the effectiveness of testing for cancer on cancer-related mortality in patients with an unprovoked VTE.

**Authors’ conclusions**

**Implications for practice**

At present, there is insufficient evidence as to whether testing for undiagnosed cancer in patients with a first episode of unprovoked VTE (DVT or PE) is effective in reducing cancer- and VTE-related mortality and morbidity, and which tests for cancer are most useful. The decision whether to screen for cancer or not in a first episode of unprovoked VTE remains for individual clinicians and patients to decide on a case by case basis. Based on the current data which show a reduction in time to cancer diagnosis and cancer detection at an earlier, potentially more curable stage, and since the diagnosis of cancer has significant implications for patients, in particular pharmacological treatment of their VTE, there is a potential rationale for patients choosing to be tested even in the absence of evidence of a survival benefit.

**Implications for research**

The low number of studies in this systematic review confirms the need for further methodologically sound and large randomised controlled trials. They should be adequately powered to look at key endpoints including mortality, as well as addressing questions concerning the types of test to be used, quality of life and patient preference.
ACKNOWLEDGEMENTS
The review authors would like to thank the Cochrane Peripheral Vascular Disease (PVD) Group for their guidance for this review.

REFERENCES

References to studies included in this review

Piccioli 2004 {published data only}

Piccioli 2012 {published data only}

References to ongoing studies

NCT00773448 {published data only}

Additional references

Baron 1998

Bick 1978

Blann 2006

Deeks 2011

Einstein Investigators

Higgins 2011

Kakkar 1969

Kakkar 2003

Lee 2003a

Lee 2003b

Levitan 1999

NICE 2012a

NICE 2012b
NHS National Institution for Health and Clinical Excellence. Rivaroxaban for the treatment of deep VTE (Review)

Effect of testing for cancer on cancer- and venous thromboembolism (VTE)-related mortality and morbidity in patients with unprovoked VTE (Review)
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**Piccoli 2004a**

**Prandoni 1997**

**RevMan 2014**

**Rodrigues 2010**

**Ruiz 2003**

**Sterne 2011**

**White 2005**

* Indicates the major publication for the study
## Characteristics of included studies  [ordered by study ID]

### Piccioli 2004

| Methods | Study design: Randomised multicentre clinical trial  
Source of funding: Associazione Italiana per le Ricerca sul Cancro |
|---------|----------------------------------------------------------|
| Participants | Country: Italy  
Setting: Hospital  
Number of centres: Not stated  
No: 201  
Age (mean (SD)): Screening group 66.2 (13.1) years, no screening group 66.6 (13.1) years  
Sex: Screening group 54 M, 45 F; no screening group 46 M, 56 F  
Inclusion criteria: Apparently cancer-free patients with a documented idiopathic first episode of symptomatic deep vein thrombosis of the lower extremity or pulmonary embolism  
Exclusion criteria: Recognised risk factor for VTE (malignant disease, trauma of the leg, surgical procedures or immobilisation within 6 months, confirmed spontaneous VTE in a first degree relative, deficiency of antithrombin, protein C or S, presence of circulating lupus anticoagulant, oestrogen use, pregnancy or childbirth), previously documented VTE, malignant disease identified at routine physical examination, history taking, laboratory assessment or chest X-ray at referral, unable to attend follow-up due to geographic inaccessibility and age below 25 years |
| Interventions | Screening procedure: Combination of ultrasound and CT scan of abdomen and pelvis, gastroscopy or double contrast barium swallow, flexible sigmoidoscopy or rectoscopy followed by barium enema or colonoscopy, haemoccult, sputum cytology and tumour markers including carcinoembryonic antigen (CEA), -fetoprotein (-FP) and CA 125. In addition, women had a gynaecological examination, Pap smear and mammography. Men had a transabdominal ultrasound of the prostate and total specific prostatic antigen (PSA) test  
Control: No tests for cancer  
Duration: 2-year follow-up |
| Outcomes | Primary outcomes: Cancer-related mortality defined as death due to a malignant disease itself, or death due to complications of diagnostic or surgical procedures performed to diagnose or treat cancer  
Secondary outcomes: Cluster of cancer-related mortality and presence of objectively documented residual malignancy or recurrent malignancy at 24 months and sensitivity of the diagnostic work-up for occult malignancy |

### Notes

#### Risk of bias

| Bias | Authors’ judgement | Support for judgement |
Random sequence generation (selection bias) | Low risk | Quote: “According to the Zelen design, patients randomised to...”

Allocation concealment (selection bias) | Low risk | “Randomisation was performed centrally”

Blinding of participants and personnel (performance bias) | Low risk | “Patients randomised to extensive screening were informed about the study. As patients allocated to the control group were not informed about the study, patients and their physicians were not discouraged to search for malignant disease”
Comment: Blinding of the patients in the extensive screening group and study personnel was not done but review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding

Blinding of outcome assessment (detection bias) | Low risk | “To avoid diagnostic suspicion bias, the medical history concerning general health, hospital admission and occurrence of signs and symptoms of cancer were obtained on a standardised form by a physician unaware of allocation of the patient”
Comment: Outcome assessors were blinded to the study allocation

Incomplete outcome data (attrition bias) | Low risk | All patients completed the two-year follow-up. No missing data

Selective reporting (reporting bias) | Low risk | Primary and secondary outcomes are clearly pre-specified and reported

Other bias | Low risk | The study appears to be free from other sources of bias

Piccoli 2012

Methods | Study design: Randomised controlled trial

Participants
Country: Italy
Setting: Hospital
Number of centres: Not stated
No: 195
Age (mean): Extensive screening group 67 years, control group 71 years
Sex: Extensive screening group 54 M, 44 F; control group 47 M, 50 F
Inclusion criteria: Patients with a first episode of unprovoked VTE, in whom a routine initial screening for cancer was normal
### Exclusion criteria
Not stated

### Interventions
**Screening procedure:** Extensive screening with mandatory CT scan of the thorax, abdomen and pelvis together with haemoccult test or any test at physician's discretion according to good clinical practice

**Control:** No screening

**Duration:** 2-year follow-up

### Outcomes
**Primary outcomes:** Cancer-related mortality and incidence of newly discovered cancer

**Secondary outcomes:** None

### Notes
Conference abstract

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Insufficient evidence to permit judgement of high or low risk</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Insufficient evidence to permit judgement of high or low risk</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Comment: Blinding of the patients in the extensive screening group and study personnel was not done but review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding</td>
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</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
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<td>Insufficient evidence to permit judgement of high or low risk</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Insufficient evidence to permit judgement of high or low risk</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Insufficient evidence to permit judgement of high or low risk</td>
</tr>
</tbody>
</table>

CT: computed tomography  
SD: standard deviation  
VTE: venous thromboembolism
### Characteristics of ongoing studies  
*ordered by study ID*

**NCT00773448**

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Screening for occult malignancy in patients with idiopathic venous thromboembolism (SOME)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised, open label, parallel assignment efficacy study</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Patients with a new diagnosis of unprovoked proximal DVT or PE</td>
</tr>
<tr>
<td></td>
<td>Unprovoked VTE is defined as the absence of any known cancer, recent (less than 3 months) paralysis, paresis or plaster immobilisation of the lower extremities, recently bedridden for period of 3 or more days, major surgery within the previous 12 weeks requiring general or regional anaesthesia, previous unprovoked VTE or known thrombophilia. Exclusion criteria if aged under 18 years, refusal or inability to provide informed consent, greater than 21 days post-diagnosis of idiopathic VTE, index VTE event of unusual site DVT, diagnosis of SSPE in the absence of above or below knee DVT, allergy to contrast media, creatinine clearance &lt; 60 mL/min, claustrophobia or agoraphobia, weight &gt; 130 kg, diagnosis of ulcerative colitis or glaucoma, current pregnancy</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Limited malignancy screening: a complete medical history and physical examination, complete blood count, liver function tests (AST, ALT, ALP, bilirubin, LDH), renal function test (creatinine), chest X-ray (if not performed in the past year. In women, a Pap smear or pelvic examination (if &gt; 18 and &lt; 70 years old and not performed during the past year), a mammogram (&gt; 50 years old) will be performed if not conducted in the last year. In men, prostate examination ± PSA testing (&gt; 40 years old) will be performed if not conducted in the past year Extensive malignancy screening: comprehensive CT of the abdomen or pelvis, virtual colonoscopy and gastroscopy, a biphasic enhanced CT for hepatoma and renal cell carcinoma, parenchymal pancreatogram with minimum intensity projection (MinIP) reformation for pancreatic carcinoma, and uniphasic enhanced CT of distended bladder for bladder and ovarian carcinoma</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Primary outcome: Previously undiagnosed malignancy missed by malignancy screening, defined as biopsy proven tissue diagnosis of malignancy diagnosed from the time of malignancy screening completion to the end of the 1-year follow-up period Secondary outcomes: overall mortality, recurrent VTE, early malignancy (T1-2N0M0 as per the World Health Organization TNM classification system), QALYs gained, incremental cost-effectiveness ratio and adverse events with cCT. All secondary outcome measured at one year</td>
</tr>
<tr>
<td><strong>Starting date</strong></td>
<td>September 2008</td>
</tr>
<tr>
<td><strong>Contact information</strong></td>
<td>Marc Carrier: <a href="mailto:mcarrier@ottawahospital.on.ca">mcarrier@ottawahospital.on.ca</a></td>
</tr>
</tbody>
</table>
| **Notes**           | CT: computed tomography  
DVT: deep vein thrombosis  
PE: pulmonary embolism  
QALY: quality-adjusted life year  
SSPE: subsegmental pulmonary embolism  
VTE: venous thromboembolism |
### DATA AND ANALYSES

**Comparison 1. Tests for cancer versus no tests**

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
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<tr>
<td>1 Cancer-related mortality</td>
<td>2</td>
<td>396</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.49 [0.15, 1.67]</td>
</tr>
<tr>
<td>2 Characteristics of diagnosed cancer: Type of cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.1 Lung</td>
<td>1</td>
<td>201</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>2.08 [0.19, 23.34]</td>
</tr>
<tr>
<td>2.2 Bladder</td>
<td>1</td>
<td>201</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>2.08 [0.19, 23.34]</td>
</tr>
<tr>
<td>2.3 Stomach</td>
<td>1</td>
<td>201</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.03 [0.06, 16.71]</td>
</tr>
<tr>
<td>2.4 Kidney</td>
<td>1</td>
<td>201</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>3.12 [0.13, 77.55]</td>
</tr>
<tr>
<td>2.5 Adrenal gland</td>
<td>1</td>
<td>201</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>3.12 [0.13, 77.55]</td>
</tr>
<tr>
<td>2.6 Liver</td>
<td>1</td>
<td>201</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>3.12 [0.13, 77.55]</td>
</tr>
<tr>
<td>2.7 Uterus</td>
<td>1</td>
<td>201</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>3.12 [0.13, 77.55]</td>
</tr>
<tr>
<td>2.8 Breast</td>
<td>1</td>
<td>201</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.03 [0.06, 16.71]</td>
</tr>
<tr>
<td>2.9 Ovary</td>
<td>1</td>
<td>201</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>3.12 [0.13, 77.55]</td>
</tr>
<tr>
<td>2.10 Colon</td>
<td>1</td>
<td>201</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.51 [0.05, 5.72]</td>
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<tr>
<td>2.11 Prostate</td>
<td>1</td>
<td>201</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.51 [0.05, 5.72]</td>
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<tr>
<td>2.12 Pancreas</td>
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<td>201</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.20 [0.01, 4.26]</td>
</tr>
<tr>
<td>3 Frequency of underlying cancer diagnosis</td>
<td>2</td>
<td>396</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.32 [0.59, 2.93]</td>
</tr>
</tbody>
</table>

**Analysis 1.1. Comparison 1 Tests for cancer versus no tests, Outcome 1 Cancer-related mortality.**

Review: Effect of testing for cancer on cancer- and venous thromboembolism (VTE)-related mortality and morbidity in patients with unprovoked VTE

Comparison: 1 Tests for cancer versus no tests

Outcome: 1 Cancer-related mortality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>No tests</th>
<th>Tests</th>
<th>Odds Ratio (Non-event)</th>
<th>Weight</th>
<th>Odds Ratio (Non-event)</th>
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<tr>
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<td>n/N</td>
<td>n/N</td>
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<td>M-H, Random, 95% CI</td>
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<tr>
<td>Piccioli 2004</td>
<td>4/102</td>
<td>2/99</td>
<td>0.51 [0.09, 2.82]</td>
<td>50.0 %</td>
<td>0.51 [0.09, 2.82]</td>
</tr>
<tr>
<td>Piccioli 2012</td>
<td>4/97</td>
<td>2/98</td>
<td>0.48 [0.09, 2.71]</td>
<td>50.0 %</td>
<td>0.48 [0.09, 2.71]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>199</strong></td>
<td><strong>197</strong></td>
<td><strong>0.49 [0.15, 1.67]</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.49 [0.15, 1.67]</strong></td>
</tr>
</tbody>
</table>

Total events: 8 (No tests), 4 (Tests)
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.97); I^2 = 0.0%
Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Not applicable
### Analysis 1.2. Comparison 1 Tests for cancer versus no tests, Outcome 2 Characteristics of diagnosed cancer: Type of cancer.

**Review:** Effect of testing for cancer on cancer- and venous thromboembolism (VTE)-related mortality and morbidity in patients with unprovoked VTE

**Comparison:** 1 Tests for cancer versus no tests

**Outcome:** 2 Characteristics of diagnosed cancer: Type of cancer

<table>
<thead>
<tr>
<th>Study or subgroup</th>
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<th>No tests</th>
<th>Odds Ratio</th>
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<td>M- H(Random, 95%) CI</td>
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<td>1 Lung</td>
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<td></td>
</tr>
<tr>
<td>Piccioli 2004</td>
<td>2/99</td>
<td>1/102</td>
<td>2.08 [ 0.19, 23.34 ]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>99</strong></td>
<td><strong>102</strong></td>
<td><strong>2.08 [ 0.19, 23.34 ]</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>2.08 [ 0.19, 23.34 ]</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>2 Bladder</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piccioli 2004</td>
<td>2/99</td>
<td>1/102</td>
<td>2.08 [ 0.19, 23.34 ]</td>
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<td></td>
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<td></td>
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<tr>
<td>3 Stomach</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Piccioli 2004</td>
<td>1/99</td>
<td>1/102</td>
<td>1.03 [ 0.06, 16.71 ]</td>
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<tr>
<td></td>
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<td>4 Kidney</td>
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<td></td>
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<tr>
<td>Piccioli 2004</td>
<td>1/99</td>
<td>0/102</td>
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<td>100.0 %</td>
<td></td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>99</strong></td>
<td><strong>102</strong></td>
<td><strong>3.12 [ 0.13, 77.55 ]</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>3.12 [ 0.13, 77.55 ]</strong></td>
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(Continued...)
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<td>n/N</td>
<td>M-H Random 95% CI</td>
<td>M-H Random 95% CI</td>
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<td>6 Liver</td>
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<td>0/102</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>3.12 [ 0.13, 77.55 ]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td>102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Uterus</td>
<td>1/99</td>
<td>0/102</td>
<td>100.0 %</td>
<td>100.0 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.12 [ 0.13, 77.55 ]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>99</td>
<td>102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 Breast</td>
<td>1/99</td>
<td>1/102</td>
<td>100.0 %</td>
<td>100.0 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.03 [ 0.06, 16.71 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>99</td>
<td>102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Ovary</td>
<td>1/99</td>
<td>0/102</td>
<td>100.0 %</td>
<td>100.0 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.12 [ 0.13, 77.55 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>99</td>
<td>102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 Colon</td>
<td>1/99</td>
<td>2/102</td>
<td>100.0 %</td>
<td>100.0 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.51 [ 0.05, 5.72 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>99</td>
<td>102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 Prostate</td>
<td>1/99</td>
<td>2/102</td>
<td>100.0 %</td>
<td>100.0 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.51 [ 0.05, 5.72 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>99</td>
<td>102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Pancreas</td>
<td>1/99</td>
<td>2/102</td>
<td>100.0 %</td>
<td>100.0 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.51 [ 0.05, 5.72 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>99</td>
<td>102</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 1 (Tests), 0 (No tests)
Heterogeneity: not applicable
Test for overall effect: Z = 0.69 (P = 0.49)

6 Liver
Piccioli 2004

Subtotal (95% CI)

7 Uterus
Piccioli 2004

Subtotal (95% CI)

8 Breast
Piccioli 2004

Subtotal (95% CI)

9 Ovary
Piccioli 2004

Subtotal (95% CI)

10 Colon
Piccioli 2004

Subtotal (95% CI)

11 Prostate
Piccioli 2004

Subtotal (95% CI)

12 Pancreas

Effect of testing for cancer on cancer- and venous thromboembolism (VTE)-related mortality and morbidity in patients with unprovoked VTE (Review)
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Continued

Study or subgroup | Tests | No tests | Odds Ratio | Weight | Odds Ratio |
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Random,95% CI</td>
<td></td>
<td>M-H,Random,95% CI</td>
</tr>
<tr>
<td>Piccioli 2004</td>
<td>0/99</td>
<td>2/102</td>
<td>100.0 %</td>
<td>0.20 [ 0.01, 4.26 ]</td>
<td></td>
</tr>
</tbody>
</table>

Subtotal (95% CI) | 99 | 102 | 100.0 % | 0.20 [ 0.01, 4.26 ] |

Total events: 0 (Tests), 2 (No tests)
Heterogeneity: not applicable
Test for overall effect: Z = 1.03 (P = 0.30)

Analysis 1.3. Comparison 1 Tests for cancer versus no tests, Outcome 3 Frequency of underlying cancer diagnosis.

Review: Effect of testing for cancer on cancer- and venous thromboembolism (VTE)-related mortality and morbidity in patients with unprovoked VTE

Comparison: 1 Tests for cancer versus no tests
Outcome: 3 Frequency of underlying cancer diagnosis

Study or subgroup | Tests | No test | Odds Ratio | Weight | Odds Ratio |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Random,95% CI</td>
<td></td>
<td>M-H,Random,95% CI</td>
</tr>
<tr>
<td>Piccioli 2004</td>
<td>13/99</td>
<td>10/102</td>
<td>83.7 %</td>
<td>1.39 [ 0.58, 3.34 ]</td>
<td></td>
</tr>
<tr>
<td>Piccioli 2012</td>
<td>2/98</td>
<td>2/97</td>
<td>16.3 %</td>
<td>0.99 [ 0.14, 7.17 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) | 197 | 199 | 100.0 % | 1.32 [ 0.59, 2.93 ] |

Total events: 15 (Tests), 12 (No test)
Heterogeneity: Tau² = 0.0; Chi² = 0.09, df = 1 (P = 0.76); P² =0.0%
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable
### Appendix 1. Cochrane Register of Studies search strategy

<table>
<thead>
<tr>
<th>Search run on Tue Jan 20 2015</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>#1</strong></td>
<td>MESH DESCRIPTOR Thrombosis</td>
</tr>
<tr>
<td><strong>#2</strong></td>
<td>MESH DESCRIPTOR Thromboembolism</td>
</tr>
<tr>
<td><strong>#3</strong></td>
<td>MESH DESCRIPTOR Venous Thromboembolism</td>
</tr>
<tr>
<td><strong>#4</strong></td>
<td>MESH DESCRIPTOR Venous Thrombosis EXPLODE ALL TREES</td>
</tr>
<tr>
<td><strong>#5</strong></td>
<td>(thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*):TI,AB,KY</td>
</tr>
<tr>
<td><strong>#6</strong></td>
<td>MESH DESCRIPTOR Pulmonary Embolism EXPLODE ALL TREES</td>
</tr>
<tr>
<td><strong>#7</strong></td>
<td>(PE or DVT or VTE):TI,AB,KY</td>
</tr>
<tr>
<td><strong>#8</strong></td>
<td>((vein* or ven*) near thromb*):TI,AB,KY</td>
</tr>
<tr>
<td><strong>#9</strong></td>
<td>(blood near3 clot*):TI,AB,KY</td>
</tr>
<tr>
<td><strong>#10</strong></td>
<td>(pulmonary near3 clot*):TI,AB,KY</td>
</tr>
<tr>
<td><strong>#11</strong></td>
<td>(lung near3 clot*):TI,AB,KY</td>
</tr>
<tr>
<td><strong>#12</strong></td>
<td>#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11</td>
</tr>
<tr>
<td><strong>#13</strong></td>
<td>MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES</td>
</tr>
<tr>
<td><strong>#14</strong></td>
<td>malignan*:TI,AB,KY</td>
</tr>
<tr>
<td><strong>#15</strong></td>
<td>neoplas*:TI,AB,KY</td>
</tr>
<tr>
<td><strong>#16</strong></td>
<td>cancer*:TI,AB,KY</td>
</tr>
<tr>
<td><strong>#17</strong></td>
<td>(carcinoma* or adenocarcinoma*):TI,AB,KY</td>
</tr>
<tr>
<td><strong>#18</strong></td>
<td>(tumour* or tumor*):TI,AB,KY</td>
</tr>
<tr>
<td>#19</td>
<td>Trouseau:TL,AB,KY</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>#20</td>
<td>#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19</td>
</tr>
<tr>
<td>#21</td>
<td>MESH DESCRIPTOR Mass Screening EXPLODE ALL TREES</td>
</tr>
<tr>
<td>#22</td>
<td>MESH DESCRIPTOR Early Diagnosis EXPLODE ALL TREES</td>
</tr>
<tr>
<td>#23</td>
<td>screen*:TL,AB,KY</td>
</tr>
<tr>
<td>#24</td>
<td>diagnos*:TL,AB,KY</td>
</tr>
<tr>
<td>#25</td>
<td>assess*:TL,AB,KY</td>
</tr>
<tr>
<td>#26</td>
<td>investigat*:TL,AB,KY</td>
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<tr>
<td>#27</td>
<td>test:TL,AB,KY</td>
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<tr>
<td>#28</td>
<td>testing:TL,AB,KY</td>
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<tr>
<td>#29</td>
<td>#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28</td>
</tr>
<tr>
<td>#30</td>
<td>#12 AND #20 AND #29</td>
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**Contributions of Authors**

LR: drafted the protocol, selected studies for inclusion, assessed the quality of studies, carried out data extraction, performed data analysis and wrote the review

SEY: selected studies for inclusion, assessed the quality of the studies and carried out data extraction

GS: provided clinical input into the review

RA: contributed to the protocol; and provided clinical input into the review
DECLARATIONS OF INTEREST

LR: none known
SEY: none known
GS: none known
RA: none known

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  The PVD Group editorial base is supported by the Chief Scientist Office.
- National Institute for Health Research (NIHR), UK.
  The PVD Group editorial base is supported by a programme grant from the NIHR.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The primary outcome ‘Non-cancer-related mortality (death due to some cause other than cancer or cancer-related treatment)’ was re-phrased to ‘all-cause mortality’ for clarity.