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

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[Intervention Review]

Effect of testing for cancer on cancer- or venous thromboembolism (VTE)-related mortality and morbidity in people 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 people 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 people 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 people received the optimal treatment for VTE to prevent recurrence and further morbidity. Furthermore, an appropriate cancer diagnosis at an earlier stage could avoid the risk of cancer progression and lead to improvements in cancer-related mortality and morbidity. This is the third update of the review first published in 2015.

Objectives

To determine whether testing for undiagnosed cancer in people with a first episode of unprovoked VTE (DVT of the lower limb or PE) is effective in reducing cancer- or VTE-related mortality and morbidity and to determine which tests for cancer are best at identifying treatable cancers early.

Search methods

The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase and CINAHL databases and World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials registers to 5 May 2021. We also undertook reference checking to identify additional studies.

Selection criteria

Randomised and quasi-randomised trials in which people with an unprovoked VTE were allocated to receive specific tests for identifying cancer or clinically indicated tests only were eligible for inclusion.

Data collection and analysis

Two review authors independently selected studies, assessed risk of bias and extracted data. We assessed the certainty of the evidence using GRADE criteria. We resolved any disagreements by discussion. The main outcomes of interest were all-cause mortality, cancer-related mortality and VTE-related mortality.

Main results

No new studies were identified for this 2021 update. In total, four studies with 1644 participants are included. Two studies assessed the effect of extensive tests including computed tomography (CT) scanning versus tests at the physician's discretion, while the other two studies assessed the effect of standard testing plus positron emission tomography (PET)/CT scanning versus standard testing alone. For extensive tests including CT versus tests at the physician's discretion, the certainty of the evidence, as assessed according to GRADE, was low due to risk of bias (early termination of the studies). When comparing standard testing plus PET/CT scanning versus standard testing alone, the certainty of evidence was moderate due to a risk of detection bias. The certainty of the evidence was downgraded further as detection bias was present in one study with a low number of events.

When comparing extensive tests including CT versus tests at the physician's discretion, pooled analysis on two studies showed that testing for cancer was consistent with either benefit or no benefit on cancer-related mortality (odds ratio (OR) 0.49, 95% confidence interval (CI) 0.15 to 1.67; 396 participants; 2 studies; low-certainty evidence). One study (201 participants) showed that, overall, malignancies were less advanced at diagnosis in extensively tested participants than in participants in the control group. In total, 9/13 participants diagnosed with cancer in the extensively tested group had a T1 or T2 stage malignancy compared to 2/10 participants diagnosed with cancer in the control group (OR 5.00, 95% CI 1.05 to 23.76; low-certainty evidence). There was no clear difference in detection of advanced stages between extensive tests versus tests at the physician's discretion: one participant in the extensively tested group had stage T3 compared with four participants in the control group (OR 0.25, 95% CI 0.03 to 2.28; low-certainty evidence). In addition, extensively tested participants were diagnosed earlier than control group (mean: 1 month with extensive tests versus 11.6 months with tests at physician's discretion to cancer diagnosis from the time of diagnosis of VTE). Extensive testing did not increase the frequency of an underlying cancer diagnosis (OR 1.32, 95% CI 0.59 to 2.93; 396 participants; 2 studies; low-certainty evidence). Neither study measured all-cause mortality, VTE-related morbidity and mortality, complications of anticoagulation, adverse effects of cancer tests, participant satisfaction or quality of life.

When comparing standard testing plus PET/CT screening versus standard testing alone, standard testing plus PET/CT screening was consistent with either benefit or no benefit on all-cause mortality (OR 1.22, 95% CI 0.49 to 3.04; 1248 participants; 2 studies; moderate-certainty evidence), cancer-related mortality (OR 0.55, 95% CI 0.20 to 1.52; 1248 participants; 2 studies; moderate-certainty evidence) or VTE-related morbidity (OR 1.02, 95% CI 0.48 to 2.17; 854 participants; 1 study; moderate-certainty evidence). Regarding stage of cancer, there was no clear difference for detection of early (OR 1.78, 95% 0.51 to 6.17; 394 participants; 1 study; low-certainty evidence) or advanced (OR 1.00, 95% CI 0.14 to 7.17; 394 participants; 1 study; low-certainty evidence) stages of cancer. There was also no clear difference in the frequency of an underlying cancer diagnosis (OR 1.71, 95% CI 0.91 to 3.20; 1248 participants; 2 studies; moderate-certainty evidence). Time to cancer diagnosis was 4.2 months in the standard testing group and 4.0 months in the standard testing plus PET/CT group (P = 0.88). Neither study measured VTE-related mortality, complications of anticoagulation, adverse effects of cancer tests, participant satisfaction or quality of life.

Authors' conclusions

Specific testing for cancer in people with unprovoked VTE may lead 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 people with a first episode of unprovoked VTE (DVT or PE) in reducing cancer- or VTE-related morbidity and mortality. The results could be consistent with either benefit or no benefit. Further good-quality large-scale randomised controlled trials are required before firm conclusions can be made.

PLAIN LANGUAGE SUMMARY

Does testing for cancer in people with unprovoked blood clots in the legs and lungs reduce cancer- and blood clot-related death and illness?

Key message

This review found that there are too few trials to determine whether testing for undiagnosed cancer in people with a first unprovoked venous thromboembolism (VTE) is effective in reducing cancer- and VTE-related deaths and illness. Further good-quality and large-scale studies are required.

Why is this question important?

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, family history, pregnancy, and blood deficiencies. Sometimes a VTE happens for no apparent reason (it is unprovoked). In such people, undetected cancer may be the cause of the VTE. This has raised the question of whether people with an unprovoked VTE should be investigated for underlying cancer. This is important as the management of VTE in people with and without cancer differs. A cancer diagnosis would ensure people receive 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.

What did we do?

We searched for randomised controlled studies that assessed whether testing for undiagnosed cancer in people with a first unprovoked VTE (DVT or PE) was effective in reducing cancer and VTE-related illness and death. In randomised controlled studies the treatments or tests people receive are decided at random and these usually give the most reliable evidence about treatment effects.

What did we find?

We found four studies with 1644 participants. Two studies compared extensive cancer tests with tests carried out at the physician's discretion and two studies compared cancer tests plus scanning with cancer tests alone. Combining the results of the two studies showed that extensive testing had no effect on the number of cancer-related deaths. Additionally, extensive testing did not identify more people with cancer. However, extensive testing did identify cancers at an earlier stage (approximately 10 months earlier) and cancers were less advanced in people in the extensive testing group than in people in the group with tests carried out at the physician's discretion. 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 or participant satisfaction. Two studies that compared tests plus scanning with tests alone showed that adding computed tomography scanning had little or no effect on the number of deaths, cancer-related deaths, illness associated with VTE; nor did it identify more people with cancer, or show a clear difference in time to diagnosis or stages of cancer diagnosed. Neither study looked at deaths associated with VTE, side effects of cancer tests, side effects of VTE treatment, participant satisfaction or quality of life.

How certain are we in the evidence?

When comparing extensive tests versus tests at the physician's discretion, the certainty of the evidence was low due to bias caused by two of the studies stopping early. When comparing tests plus PET/CT scanning with tests alone, the certainty of the evidence ranged from low to moderate due to issues with how the studies were designed, imprecision caused by a low number of events and bias due to lack of blinding of people assessing the effects.

How up to date is this evidence?

This Cochrane review updates our previous evidence. The evidence is current to May 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Extensive tests versus tests at the physician's discretion

Extensive tests versus tests at the physician's discretion

Patient or population: people with unprovoked VTE

Setting: hospital

Intervention: extensive tests

Comparison: tests at the physician's discretion

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with tests at physician's discretion	Risk with extensive tests				
All-cause mortality [1]	See comment	See comment	See comment	See comment	See comment	No study measured this outcome.
Cancer-related mortality [2]	Study population		OR 0.49 (0.15 to 1.67)	396 (2 RCTs)	⊕⊕⊖⊖ **Low** [3]	-
	40 per 1000	20 per 1000 (6 to 65)				
VTE-related mortality [4]	See comment	See comment	See comment	See comment	See comment	No study measured this outcome.
VTE-related morbidity [5]	See comment	See comment	See comment	See comment	See comment	No study measured this outcome.
Stage of cancer - early [6]	Study population		OR 5.00 (1.05 to 23.76)	201 (1 RCT)	⊕⊕⊖⊖ **Low** [7]	-
	20 per 1000	91 per 1000 (21 to 322)				
Stage of cancer - advanced [8]	Study population		OR 0.25 (0.03 to 2.28)	201 (1 RCT)	⊕⊕⊖⊖ **Low** [7]	-
	39 per 1000	10 per 1000 (1 to 85)				

Time to cancer diagnosis [9]	See comments	See comments	See comments	201 (1 RCT)	See comments	Time to cancer diagnosis (measured from time of diagnosis of VTE) measured in 1 study (Piccioli 2004b), and reported as a mean of 1 month with extensive tests compared to 11.6 months with tests at physician's discretion (P < 0.001). Standard deviations for these means not given. Attempts to contact author for these data made but no response received.
Frequency of underlying cancer diagnosis [10]	60 per 1000	78 per 1000 (36 to 158)	OR 1.32 (0.59 to 2.93)	396 (2 RCTs)	⊕⊕⊖⊖ **Low** [3]	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **RCT:** randomised controlled trial; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Death due to any cause.
[2] Defined as death due to malignant disease itself, or death due to complications of treatments or procedures to diagnose or treat cancer.
[3] Risk of bias was high in two included studies (Piccioli 2004b; Prandoni 2016). Piccioli 2004b terminated early after inclusion of only 201 participants after 5 years for several reasons. First, only five of more than 40 potential participating centres could contribute participants to study. Second, some medical ethics committees rejected the protocol because of absence of screening for occult cancer in the control group, other centres could not start because the proposed extensive screening was judged unethical. Finally, identification of cancer at an apparent early stage in extensive screening group led to an increasing tendency among physicians in participating hospitals to initiate screening for cancer in control participants. Prandoni 2016 study terminated early due to low recruitment rate and failure to show an appreciable advantage of CT-based strategy over control strategy for detection of cancer.
[4] Fatal pulmonary embolism (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 (DVT); 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 PE at autopsy" (Lee 2003b). Fatal PE including probable fatal PE and unexplained sudden death used if reported, as defined by individual studies.
[5] Frequency of recurrent VTE. Recurrent PE or DVT 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 diagnosis of recurrence if results abnormal on previous testing (Lee 2003b)
[6] Early-stage malignancies, defined as T1 or T2 without locoregional or distant metastases (N0 M0).
[7] Certainty of evidence downgraded for imprecision due to low number of events. Evidence downgraded further as risk of bias high in Piccioli 2004b. Study terminated early after inclusion of only 201 participants after five years for several reasons. First, only five of more than 40 potential participating centres could contribute participants to study. Second, some medical ethics committees rejected the protocol because of absence of screening for occult cancer in the control group, other centres could not start because the proposed

extensive screening was judged unethical. Finally, identification of cancer at an apparent early stage in extensive screening group led to an increasing tendency among physicians in participating hospitals to initiate screening for cancer in control participants.

[8] Advanced-stage malignancies, defined as T3 with locoregional or distant metastases (N1 or M1).

[9] Time to cancer diagnosis, as defined in included studies.

[10] Frequency of an underlying cancer diagnosis (i.e. number of times cancer diagnosed through screening following an unprovoked VTE as defined in included studies) at time of VTE presentation and overall over follow-up period.

Summary of findings 2. Standard testing plus PET/CT scanning versus standard testing alone

Standard testing plus PET/CT scanning versus standard testing alone

Patient or population: people with unprovoked VTE

Setting: hospital

Intervention: standard testing + PET/CT scanning

Comparison: standard testing alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard testing alone	Risk with standard testing + PET/CT scanning				
All-cause mortality [1]	Study population		OR 1.22 (0.49 to 3.04)	1248 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [2]	-
	14 per 1000	17 per 1000 (7 to 42)				
Cancer-related mortality [3]	Study population		OR 0.55 (0.20 to 1.52)	1248 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [2]	-
	18 per 1000	10 per 1000 (4 to 26)				
VTE-related mortality [4]	See comment	See comment	See comment	See comment	See comment	No study measured this outcome.
VTE-related morbidity [5]	Study population		OR 1.02 (0.48 to 2.17)	854 (1 RCT)	⊕⊕⊕⊖ **Moderate** [6]	-
	32 per 1000	33 per 1000 (16 to 68)				

Stage of cancer - early	Study population		OR 1.78 (0.51 to 6.17)	394 (1 RCT)	⊕⊕⊖⊖ **Low** [2,6]	-
	20 per 1000	36 per 1000 (10 to 113)				
Stage of cancer - advanced	Study population		OR 1.00 (0.14 to 7.17)	394 (1 RCT)	⊕⊕⊖⊖ **Low** [2,6]	-
	10 per 1000	10 per 1000 (1 to 69)				
Time to cancer diagnosis [7]	See comments	See comments	See comments	854 (1 RCT)	See comments	Time to cancer diagnosis measured in Carrier 2015 as 4.2 months in standard testing group and 4.0 months in standard testing + PET/CT group (P = 0.88). However, standard deviations for these means not given. Attempts made to contact author for these data but no response received.
Frequency of an underlying cancer diagnosis [8]	Study population		OR 1.71 (0.91 to 3.20)	1248 (2 RCTs)	⊕⊕⊕⊖ **Moderate** [2]	-
	29 per 1000	48 per 1000 (26 to 86)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **PET/CT:** positron emission tomography/computed tomography; **RCT:** randomised controlled trial; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Death due to any cause.
[2] Certainty of evidence downgraded as risk of detection bias high for one study as outcome assessors not blinded to treatment (Robin 2016).
[3] Defined as death due to malignant disease itself, or death due to complications of treatments or procedures to diagnose or treat cancer.
[4] Fatal pulmonary embolism (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 (DVT); 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 PE at autopsy" (Lee 2003b). Fatal PE including probable fatal PE and unexplained sudden death used if reported, as defined by individual studies.

[5] Frequency of recurrent VTE. Recurrent PE or DVT 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.

[6] Certainty of evidence downgraded for imprecision due to low number of events.

[7] Time to cancer diagnosis, as defined in included studies.

[8] Frequency of an underlying cancer diagnosis (i.e. number of times cancer diagnosed through screening following an unprovoked VTE as defined in included studies) at time of VTE presentation and overall over follow-up period.

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 the thrombus breaks off (embolises) 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 Care Excellence (NICE) recommend that people with a suspected VTE should be risk stratified using various diagnostic investigations. Anticoagulant therapy with low molecular weight heparin (LMWH) should be administered in the interim. People with confirmed VTE should receive LMWH or fondaparinux for at least the initial five days and be started on a vitamin K antagonist. The LMWH should be stopped when the international normalised ratio has been above 2 for at least 24 hours. Vitamin K antagonists should be continued for at least three months. In people with an unprovoked VTE, consideration should be given to extending anticoagulation beyond three months. However, people 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 2020). Direct oral anticoagulants (DOACs) such as rivaroxaban have been used for the initial treatment and prevention of recurrent VTE. Two systematic reviews have shown that DOACs may be as safe and effective as conventional anticoagulation for the prevention of recurrent VTE in people with cancer but, direct comparisons to the current standard of care with LMWH are limited (Carrier 2014; Vedovati 2015).

The difference in management of people with a cancer-associated VTE is due to their significantly higher risk of VTE recurrence, which is estimated to be three times higher than in people with VTE in the absence of cancer (Levitan 1999). Furthermore, people with cancer and an associated VTE have a poorer overall prognosis compared to people without a VTE (Sorensen 2000).

A proportion of people with VTE have no underlying or immediately apparent cause and the VTE is referred to as 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; Prandoni 1997; White 2005). Results from one Swedish prospective cohort study of almost 62,000 participants 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 2012). One study of 339 participants with a first episode of an unprovoked VTE determined that the risk ratio (RR) of cancer-related mortality at two years was 0.52 (95% confidence interval (CI) 0.10 to 2.75) in people 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).

Therefore, people who present with an apparent unprovoked VTE 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. NICE guidelines recommend that all people presenting with a first episode of unprovoked VTE (DVT or PE) should undergo a medical history review and baseline blood test results including full blood count, renal and hepatic function, PT and APTT, and offer a physical examination (NICE 2020). This is consistent with other guidelines (ISTH 2017). If these initial investigations suggest signs and symptoms of cancer then further tests including abdomino-pelvic computed tomography (CT) and positron emission tomography (PET) scans and ultrasound, are recommended. For people presenting with VTE at unusual sites (e.g. splanchnic vein thrombosis), further imaging tests are not recommended because the CT scans used for the initial diagnosis would be adequate for occult cancer detection. Given the higher prevalence of JAK2 mutation in patients with splanchnic vein thrombosis, JAK2V617F mutation testing to screen for a myeloproliferative disorder should be considered in patients with unprovoked events (ISTH 2017).

Detection of cancer at an earlier stage enables more effective treatment. This has raised the question of whether people with an unprovoked VTE should be investigated for 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 people. Instead, people with VTE are better regarded as presenting with symptoms suggestive of underlying cancer and the aim of investigations is to refine the diagnosis of VTE based on the underlying cause, so that the person 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 people with an unprovoked VTE be investigated for a potential underlying cancer? It is the value of these additional tests which is the subject of this review.

Description of the intervention

A number of imaging techniques are used in the detection of cancers including computed tomography (CT), positron emission tomography (PET) and ultrasound (US).

CT scans use x-rays to produce cross-sectional, three-dimensional, images of structural changes due to malignancy. An intravenous, iodine agent is used to increase the contrast between the tumour and normal tissue. CT provides a very high spatial resolution but is limited in its ability to accurately distinguish between benign and malignant tissue on the basis of structural information alone, and image interpretation can be difficult where normal anatomy is distorted (Chin 2008).

A PET scan uses low-dose radiation to measure the activity of cells, producing images that represent the functional rather than anatomical characteristics of disease. 18F-fluoro-2-deoxy-D-glucose (FDG) is used as a contrast agent as it is taken up strongly by many aggressive malignant tumours, but weakly by any normal physiological structures of the human body, resulting in an excellent lesion-to-background contrast (Buthiau 2003). FDG-PET imaging alone is limited by a lack of anatomical data so it is combined with CT in a single machine that performs both imaging techniques. Integrated PET/CT images combining the anatomical data of CT with the functional data of PET imaging, can detect

lesions smaller than 1 cm which other imaging techniques cannot clearly classify as benign or malignant (Buthiau 2003; Chen 2004; Schöder 2007).

Ultrasound scanning uses high frequency sound waves to build up a picture of internal organs. The sound waves echo differently when bounced off healthy and abnormal tissue. While US can distinguish fluid-filled cysts from solid tumours, it cannot tell if a tumour is malignant. The images are not as detailed as CT or MRI scan images and it is limited to specific parts of the body as the waves cannot travel through air (the lungs) or bone. US is one of the most common imaging methods used in the diagnosis of tumours in the thyroid, breast, prostate, liver, pancreatic, ovarian, uterine and kidney (Fass 2008).

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 person 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 people 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 people 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 people 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 person 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 while 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 people 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). This is the third update of the review first published in 2015.

OBJECTIVES

To determine whether testing for undiagnosed cancer in people with a first episode of unprovoked VTE (DVT of the lower limb or PE) is effective in reducing cancer- and VTE-related mortality and morbidity and to determine which tests for cancer are best at identifying treatable cancers early.

The detailed objectives are as follows:

- to determine whether testing for undiagnosed cancer in people with a first episode of unprovoked VTE (DVT of the lower limb or PE) is effective in reducing cancer mortality and morbidity (cancer morbidity being the need for cancer treatment and effects producing reduced quality of life);
- to determine whether testing for undiagnosed cancer in people with a first episode of unprovoked VTE (DVT or PE) is effective in reducing VTE-related mortality and morbidity;
- to determine which tests for cancer are best at identifying treatable cancers early.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised and quasi-randomised trials (where a method of allocation was used that was not truly random) in which people 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, we also included trials where randomisation occurred at different time points 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

We included people with a first episode of unprovoked VTE (DVT of the lower limb or PE) with no pre-existing or clinically apparent cancer diagnosis.

Types of interventions

We included tests for cancer (e.g. 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 regimen, or both. We excluded studies where these tests were routinely used in all groups. 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

- All-cause mortality (death due to any cause).
- 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).
- 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 DVT; the presence of non-enhancing filling defects in the central pulmonary vasculature on helical CT; a finding of intraluminal filling defects on pulmonary angiography; or evidence of fresh PE 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

- 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).
- 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 included bleeding associated with death, bleeding at a critical site (intracranial, intraspinal, intraocular, 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 included any other bleeding.
- Adverse effects of cancer tests (e.g. radiation exposure, bleeding, as defined in included studies).
- Characteristics of diagnosed cancer (e.g. primary tumour, stage, localised (curable) versus advanced (palliative) as defined in included studies).
- Time to cancer diagnosis, as defined in included studies.
- Frequency of an underlying cancer diagnosis (i.e. 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.
- Participant satisfaction (if assessed in individual studies, we reported results descriptively using the definition provided by the trialists).
- Quality of life.

Search methods for identification of studies

There were no restrictions on date or language of publication.

Electronic searches

The Cochrane Vascular Information Specialist conducted systematic searches of the following databases for randomised controlled trials and quasi-randomised trials.

- The Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web searched on 5 May 2021).
- The Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Register of Studies Online (CRSO 2021, Issue 4).
- MEDLINE (Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE) (searched from 11 July 2018 to 5 May 2021).
- Embase Ovid (searched from 11 July 2018 to 5 May 2021).
- CINAHL Ebsco (searched from 11 July 2018 to 5 May 2021).
- AMED Ovid (searched from 11 July 2018 to 5 May 2021).

The Information Specialist modelled search strategies for other databases on the search strategy designed for CENTRAL. Where appropriate, they were combined with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 6, Lefebvre 2011). Search strategies for major databases are provided in Appendix 1.

The Information Specialist searched the following trials registries on 5 May 2021:

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

Searching other resources

We searched the reference lists of relevant articles retrieved by the electronic searches for additional citations.

Data collection and analysis

Selection of studies

Two review authors (LR, CB) independently used the selection criteria to identify trials for inclusion. We resolved any disagreements by discussion.

Data extraction and management

Two review authors (LR, SEY) independently extracted the data and recorded information about the trial design, VTE definition and investigations to confirm diagnosis, baseline characteristics of participants and tests for cancer. All-cause mortality, cancer-related mortality and VTE-related mortality data were recorded as the primary outcome measures. Information on VTE-related morbidity (e.g. frequency of recurrent VTE), complications of anticoagulation (e.g. warfarin- versus LMWH-associated bleeding), adverse effects of cancer tests (e.g. radiation exposure, bleeding), characteristics of diagnosed cancer (e.g. primary tumour, stage, localised (curable) versus advanced (palliative)), time to cancer diagnosis, frequency of an underlying cancer diagnosis and participant satisfaction was collected in accordance with the secondary outcome measures. Where more than one publication of one study existed, reports were grouped together and the most recent or most complete data set were used. We contacted authors of included studies for further information if clarification was required. We resolved any disagreements in data extraction and management by discussion.

Assessment of risk of bias in included studies

Two review authors (LR, SEY) independently used the Cochrane tool to assess the risk of bias for each of the included studies (Higgins 2011). 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 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, adverse 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% CI of

the effect sizes. For time to cancer diagnosis, we aimed to compute hazard ratios (HR), while for participant 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 heterogeneity between the pooled studies by visual examination of the forest plot to check for overlapping CIs, and used the Chi^2 test for homogeneity with a 10% level of significance. We used the I^2 statistic to measure the degree of inconsistency between the studies. An I^2 result 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 when there were more than 10 studies in the meta-analyses (Sterne 2011). However, as there were only four studies 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 Review Manager 5 (RevMan 2014). A second review author (SEY) cross-checked data entry and resolved any discrepancies 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 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:

- DVT or PE at time of randomisation;
- cancer site;
- treatment post-investigation with vitamin K antagonist or LMWH;
- duration of anticoagulation (e.g. three or six months);
- age and gender of participants (comparing those in age and gender groups for national screening programmes to those not in these age and gender groups);
- time of randomisation after VTE diagnosis (within three months compared with after three months).

However, due to lack of data in the studies, it was not possible to perform subgroup analysis.

Sensitivity analysis

We planned to conduct a sensitivity analysis by excluding studies at high risk of bias to measure the effect on the results. We were not able to carry out sensitivity analysis due to the limited number of studies in each comparison.

Summary of findings and assessment of the certainty of the evidence

We presented the main findings of the review results concerning the certainty of evidence, the magnitude of effect of the interventions examined and the sum of available data for all outcomes of this review (Types of outcome measures) in a Summary of findings table, according to the GRADE principles as described by Higgins 2011 and Atkins 2004. We calculated assumed control intervention risks from the mean number of events in the control groups of the selected studies for each outcome. We used the GRADEprofiler (GRADEpro) software to assist in the preparation of the Summary of findings table.

RESULTS

Description of studies

Results of the search

No new studies were identified for inclusion in this 2021 update. See Figure 1.

Figure 1. Study flow diagram.

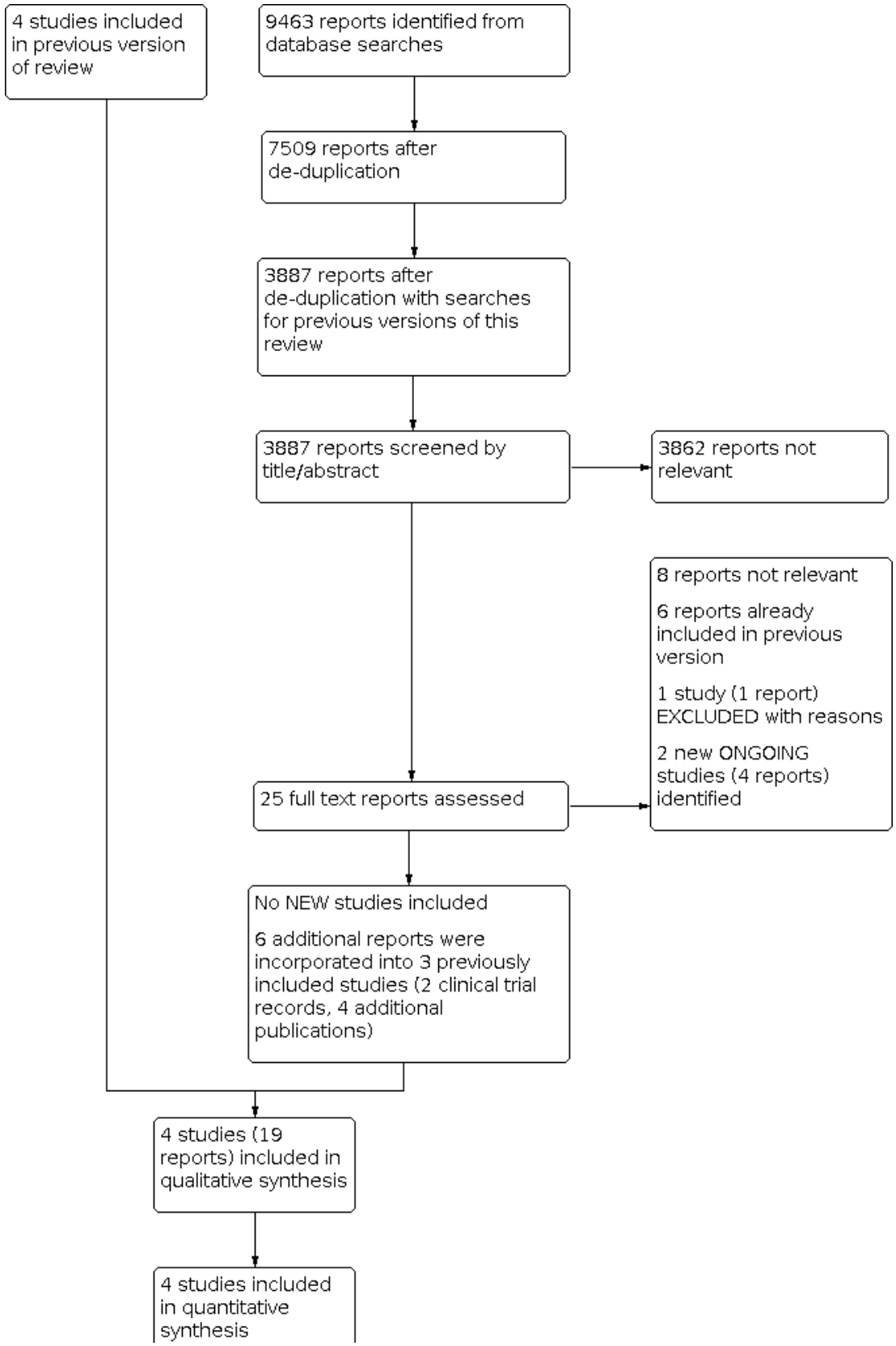
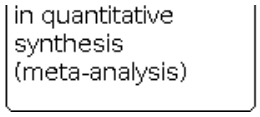


Figure 1. (Continued)



We identified four additional reports relating to the previously included study Robin 2016 (Robin 2017a; Robin 2017b; Robin 2018; Robin 2020); and one additional report each for Carrier 2015 (NCT00773448) and Prandoni 2016 (NCT00361647). One new study was assessed as excluded (Kraaijpoel 2018). We identified two new ongoing studies (EUCTR2018-003958-25-ES; EUCTR2020-002210-41-FR).

Included studies

Four studies fulfilled the eligibility criteria for inclusion in this review (Carrier 2015; Piccioli 2004b; Prandoni 2016; Robin 2016).

See Characteristics of included studies table.

The first study was a randomised multicentre study of 201 apparently cancer-free people with acute unprovoked VTE (Piccioli 2004b). Extensive investigations for occult malignant disease were compared with testing at the physician's discretion. Ninety-nine participants were randomised to the extensive screening group and 102 were randomised to the control group. Participants in the extensive investigations group were offered ultrasound and CT scans of the abdomen and pelvis, 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 (α-FP) and CA125. Women also underwent mammography and Papanicolaou (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. Participants 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. Participants 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 was a randomised study in which 195 participants with a first episode of unprovoked VTE were randomised to extensive investigations (98 participants) or a discretionary diagnostic approach excluding CT scans (97 participants) (Prandoni 2016). Extensive investigations comprised a mandatory CT scan of the thorax, abdomen and pelvis together with faecal haemoccult testing or any test at physician's discretion according to good clinical practice. Participants allocated to the discretionary diagnostic approach or personalised strategy underwent additional testing based on physicians' judgements and participants' preferences, including a 'no-further testing' option. Participants were followed at 3, 6, 12 and 24 months to document the incidence of newly discovered cancer and cancer-related mortality. The primary outcomes were cancer-related mortality (defined as death due to malignancy, or death due to the complications of the diagnostic or surgical procedures performed to diagnose or treat cancer) and incidence of newly discovered cancer. The secondary outcomes were cancer stage, using the tumours-nodes-metastases classification, at which tumours were diagnosed in the two study groups and the incidence of cancer-related mortality in the two randomisation groups,

The third study was an open-label randomised study in which 854 participants with a first episode of unprovoked VTE were randomised to limited occult-cancer screening plus CT scanning of the abdomen and pelvis (423 participants) or limited occult-cancer screening alone (431 participants) (Carrier 2015). The limited occult-cancer screening comprised complete history and physical examination, measurement of complete blood counts and serum electrolyte and creatinine levels, liver-function testing and chest radiography. Sex-specific screening was conducted if it had not been performed in the previous year. A breast examination, mammography, or both were performed in women over 50 years of age and Pap testing and a pelvic examination were performed in women 18 to 70 years of age who had ever been sexually active. A prostate examination, PSA test, or both were performed in men over 40 years of age. The additional CT investigations comprised a virtual colonoscopy and gastroscopy, biphasic enhanced CT of the liver, parenchymal pancreatography and uniphasic enhanced CT of the distended bladder. Participants were followed up for one year to document the incidence of newly diagnosed cancer, type of cancer diagnosed, one-year cancer-related mortality, one-year overall mortality, time to cancer diagnosis and incidence of recurrent VTE.

The fourth study was an open-label randomised study in which 394 participants with a first episode of unprovoked VTE were randomised to a limited screening strategy (197 participants) or a screening strategy consisting of the limited strategy plus an 18-fluorodeoxyglucose (^{18}F-FDG) PET/CT scan of the chest, abdomen and pelvis (197 participants) (Robin 2016). The limited screening comprised medical history taking, physical examination, routine laboratory tests (including complete blood count, erythrocyte sedimentation rate or C-reactive protein, aminotransferases, alkaline phosphatase and calcium), chest radiograph, and recommended age-specific and sex-specific cancer screening tests (i.e. PSA in men older than 50 years, mammography in women older than 50 years and Pap smear in all women). Participants were followed up for two years to determine the proportion of people with a cancer diagnosis in each group after the initial screening assessment.

Excluded studies

We identified one new excluded study (Kraaijpoel 2018). See Characteristics of excluded studies.

Studies that were not randomised controlled trials were deemed not relevant and therefore not listed as an excluded study.

Ongoing studies

We identified two new ongoing studies (EUCTR2018-003958-25-ES; EUCTR2020-002210-41-FR). See Characteristics of ongoing studies.

Risk of bias in included studies

See Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

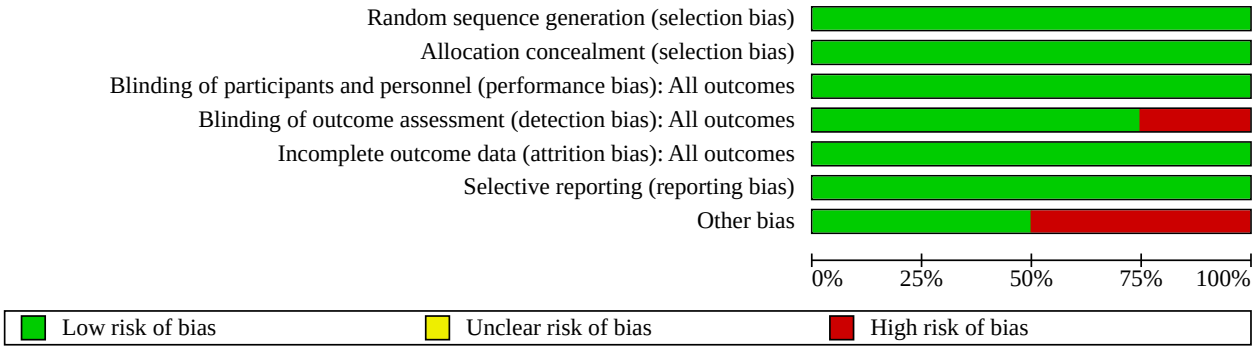
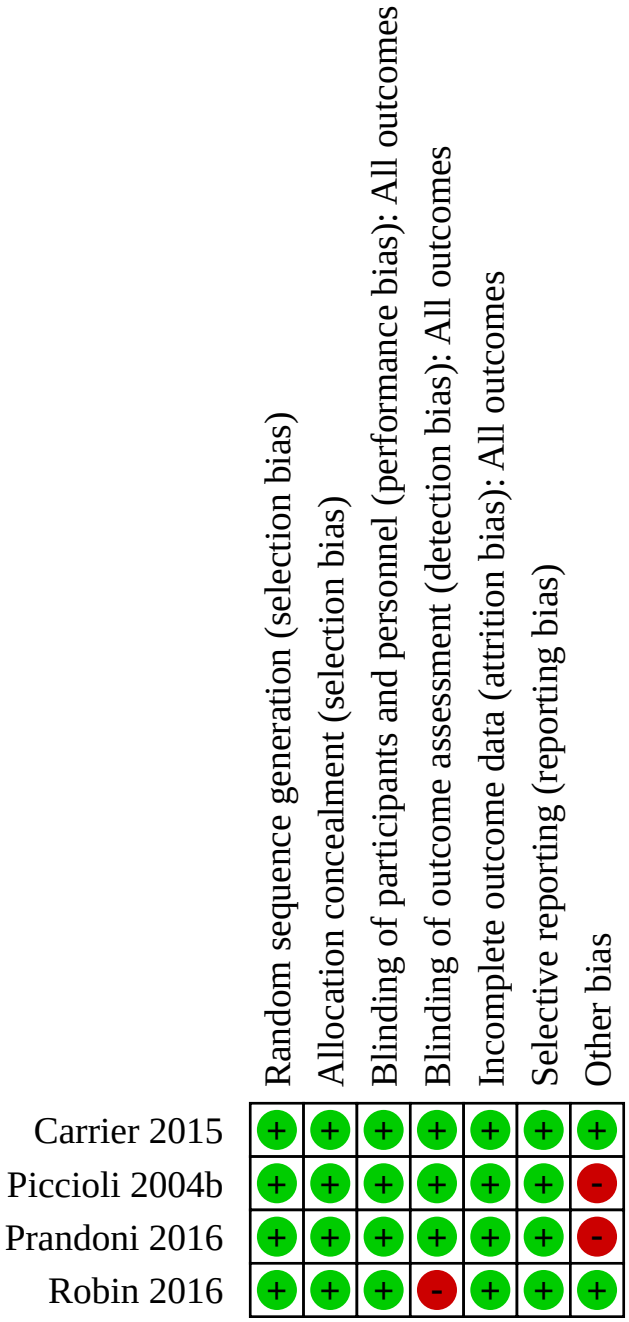


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All four studies were randomised. Prandoni 2016 used envelopes. Piccioli 2004b used a Zelen approach (participants are randomised to either the treatment or control group before giving informed consent), Carrier 2015 used random number tables and Robin 2016 used a computer random number generator. Therefore, these four studies were judged at low risk of selection bias. In terms of concealing the allocation of treatment, Piccioli 2004b performed randomisation centrally and Carrier 2015 and Robin 2016 used a central web-based randomisation system and, therefore, these

three were judged at low risk of selection bias. The Prandoni 2016 study used serially numbered, opaque, sealed envelopes to conceal allocation and was, therefore, judged at low risk of selection bias too.

Blinding

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

In Piccioli 2004b, the physician at the follow-up examination was unaware of the allocation of participants and, therefore, detection bias for outcome assessors was low. Similarly, for Carrier 2015 a blinded adjudication committee reviewed all suspected outcome events and, therefore, the risk of detection bias was low. Robin 2016 did not blind outcome assessors to treatment allocation and was, therefore, judged at high risk of detection bias. In Prandoni 2016, investigators performing the follow-up visits were blinded to the participants' randomisation group and the study was, therefore, judged at low risk of detection bias.

Incomplete outcome data

The treatment groups in all four studies 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, all four studies were judged at low risk of attrition bias (Carrier 2015; Piccioli 2004b; Prandoni 2016; Robin 2016).

Selective reporting

All four studies clearly prespecified all primary and secondary outcomes and data on all outcomes were reported (low risk of reporting bias) (Carrier 2015; Piccioli 2004b; Prandoni 2016; Robin 2016).

Other potential sources of bias

Two studies were deemed at low risk (Carrier 2015; Robin 2016), and two studies were deemed to be at high risk of other bias (Piccioli 2004b; Prandoni 2016). The study by Piccioli 2004b was terminated early after the inclusion of only 201 participants after five years for several reasons. First, only five of the more than 40 potential participating centres could contribute participants to the study. Second, some medical ethics committees rejected the protocol because of the absence of screening for occult cancer in the control group, other centres could not start because the proposed extensive screening was judged to be unethical. Finally, the identification of cancer at an apparent early stage in the extensive screening group led to an increasing tendency among physicians in the participating hospitals to initiate screening for cancer in the control participants. The study by Prandoni 2016 was judged at high risk of bias as results of an interim analysis, scheduled after the inclusion of approximately half of the planned sample size, showed no appreciable advantage of the CT-based strategy over the control strategy for detection of occult cancers. In addition, there was a low recruitment rate, so the study promoters decided to terminate the study early.

Effects of interventions

See: **Summary of findings 1** Extensive tests versus tests at the physician's discretion; **Summary of findings 2** Standard testing plus PET/CT scanning versus standard testing alone

Extensive tests versus tests at the physician's discretion

Two studies assessed the effect of testing for cancer versus clinically indicated tests only (Piccioli 2004b; Prandoni 2016).

Both studies measured the primary outcome cancer-related mortality. In Piccioli 2004b, 2/99 participants in the extensive testing group died of cancer compared to 4/102 in the group who underwent tests at the physician's discretion (OR 0.51, 95% CI 0.09 to 2.82). In Prandoni 2016, 2/98 participants who underwent extensive testing and 4/97 participants who underwent tests at the physician's discretion died of cancer (OR 0.48, 95% CI 0.09 to 2.71). Meta-analysis showed an OR of 0.49 (95% CI 0.15 to 1.67; low-certainty evidence) in favour of extensive testing, which did not reach statistical significance (P = 0.26) (Analysis 1.1).

However, neither Piccioli 2004b nor Prandoni 2016 measured the review's other primary outcomes of all-cause mortality and VTE-related mortality, or the secondary outcomes VTE-related morbidity, complications of anticoagulation, adverse effects of cancer tests, participant satisfaction and quality of life.

Piccioli 2004b looked at the location of the malignancy and found no clear difference in the incidence of any particular cancer between participants who underwent extensive tests and participants who were tested at the physician's discretion (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 77.55; adrenal gland: OR 3.12, 95% CI 0.13 to 77.55; liver: OR 3.12, 95% CI 0.13 to 77.55; uterus: OR 3.12, 95% CI 0.13 to 77.55; breast: OR 1.03, 95% CI 0.06 to 16.71; ovary: OR 3.12, 95% CI 0.13 to 77.55; colon: OR 0.51, 95% CI 0.05 to 5.72; prostate: OR 0.51, 95% CI 0.05 to 5.72; pancreas: OR 0.20, 95% CI 0.01 to 4.26) (Analysis 1.2).

Piccioli 2004b compared the characteristics of the diagnosed cancer by assessing the proportion of early-stage malignancies, defined as T1 or T2 without locoregional or distant metastases (N0 M0). Overall, malignancies were less advanced in participants who had undergone extensive testing. In total, 9/13 participants diagnosed with cancer in the tested group had a T1- or T2-stage malignancy without locoregional or distant metastases compared to 2/10 participants diagnosed with cancer in the control group (OR 5.00, 95% CI 1.05 to 23.76; P = 0.04; low-certainty evidence). There was no difference in detection of advanced stages between groups: one participant in the tested group had stage T3 compared with four participants in the control group (OR 0.25, 95% CI 0.03 to 2.28; P = 0.22; low-certainty evidence) (Analysis 1.3).

One study measured time to cancer diagnosis (measured from the time of diagnosis of VTE) (Piccioli 2004b), reported as a mean of one month in tested participants compared to 11.6 months in participants who were tested at the physician's discretion (P < 0.001). Standard deviations for the means were not given. We attempted to contact the author for these data but received no response.

Both studies measured the frequency of an underlying cancer diagnosis. Piccioli 2004b detected underlying cancer in 13/99

participants who underwent extensive testing, whereas it became symptomatic in 10/102 control participants (OR 1.39, 95% CI 0.58 to 3.34). Prandoni 2016 detected cancer in 2/98 participants who had further tests and it became apparent in 2/97 participants who were tested at the physician's discretion (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 control group (OR 1.32, 95% CI 0.59 to 2.93; low-certainty evidence) (Analysis 1.4). Therefore, after 24 months of follow-up, the incidence of cancer was no different in the tested and control groups.

Standard testing plus PET/CT scanning versus standard testing alone

Two studies assessed the effect of standard testing plus PET/CT scanning versus standard testing alone (Carrier 2015; Robin 2016).

Both studies measured the primary outcome all-cause mortality. In the standard testing plus CT scanning group, 11/620 participants died during follow-up compared to 9/628 participants who received standard testing alone (OR 1.22, 95% CI 0.49 to 3.04; moderate-certainty evidence) (Analysis 2.1).

Carrier 2015 and Robin 2016 also measured cancer-related mortality and reported an incidence of 6/620 participants with standard testing plus CT scanning compared to 11/628 participants who received standard testing alone (OR 0.55, 95% CI 0.20 to 1.52; moderate-certainty evidence) (Analysis 2.2).

The study by Carrier 2015 measured VTE-related morbidity. The incidence of recurrent VTE was 14/423 participants who underwent standard testing plus CT scanning compared to 14/431 participants who had standard testing alone (OR 1.02, 95% CI 0.48 to 2.17; moderate-certainty evidence) (Analysis 2.3).

Carrier 2015 and Robin 2016 also looked at the location of the malignancy and found no clear difference in the incidence of any particular cancer between the two groups (acute leukaemia: OR 1.62, 95% CI 0.20 to 13.22; gynaecological: OR 2.39, 95% CI 0.43 to 13.36; melanoma: OR 1.02, 95% CI 0.06 to 16.34; colorectal: OR 0.43, 95% CI 0.08 to 2.40; prostate: OR 2.52, 95% CI 0.48 to 13.12; pancreatic: OR 4.81, 95% CI 0.55 to 42.48; cholangiocarcinoma: OR 0.51, 95% CI 0.05 to 5.63; lymphoma: OR 0.74, 95% CI 0.09 to 5.83; breast: OR 0.20, 95% CI 0.01 to 4.24; urological: OR 0.62, 95% CI 0.03 to 12.32; liver: OR 0.33, 95% CI 0.01 to 8.19; head and neck: OR 3.02, 95% CI 0.12 to 74.47; lung: OR 3.02, 95% CI 0.12 to 74.47; unknown primary origin: OR 0.34, 95% CI 0.01 to 8.34) (Analysis 2.4).

Robin 2016 also measured the stage of cancer. Early-stage cancer was detected in 7/197 participants who underwent standard testing plus CT scanning compared to 4/197 participants who underwent standard testing alone (OR 1.78, 95% CI 0.51 to 6.17; low-certainty evidence), while advanced-stage cancer was detected in two participants in each group (OR 1.00, 95% CI 0.14 to 7.17; low-certainty evidence) (Analysis 2.5).

Time to cancer diagnosis was 4.0 months in the standard testing plus PET/CT group and 4.2 months in the standard testing group in one study (P = 0.88) (Carrier 2015). However, standard deviations for these means were not given. We attempted to contact the author for these data but received no response. Robin 2016 did not measure time to cancer diagnosis.

Carrier 2015 and Robin 2016 measured the frequency of underlying cancer diagnosis. Underlying cancer was detected in 30/620 participants who underwent standard testing plus CT scanning compared to 18/628 participants who underwent standard testing alone (OR 1.71, 95% CI 0.91 to 3.20; moderate-certainty evidence) (Analysis 2.6).

The studies by Carrier 2015 and Robin 2016 did not measure the other review outcomes of VTE-related mortality, complications of anticoagulation, adverse effects of cancer tests, participant satisfaction or quality of life.

DISCUSSION

Summary of main results

Four studies fulfilled the eligibility criteria for inclusion in this review (Carrier 2015; Piccioli 2004b; Prandoni 2016; Robin 2016). In total, 1644 participants were studied. We found no studies that were potentially eligible but then excluded.

Extensive tests versus tests at the physician's discretion

Two studies compared the effectiveness of testing for cancer on cancer-related mortality in people with a first unprovoked VTE (Piccioli 2004b; Prandoni 2016). Piccioli 2004b performed an extensive list of tests while Prandoni 2016 carried out fewer tests. 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 participants (mean: one month with extensive tests versus 11 months with tests at the physician's discretion). Furthermore, more people had a detection of early-stage cancer with extensive tests compared to people who were tested at the physician's discretion (Piccioli 2004b). However, standard deviations for the mean time to diagnosis were not reported and, therefore, it was impossible to independently test the statistical significance of this result. Neither study measured all-cause mortality, VTE-related morbidity and mortality, adverse effects of anticoagulation, adverse effects of cancer tests, participant satisfaction or quality of life.

Standard testing plus PET/CT scanning versus standard testing alone

Two studies compared limited screening plus PET/CT scanning of the abdomen and pelvis with limited screening alone in people with a first unprovoked VTE (Carrier 2015; Robin 2016). Standard testing plus PET/CT scanning was consistent with either a benefit or no benefit on all-cause mortality, cancer-related mortality and VTE-related morbidity. Extensive testing did not increase the frequency of an underlying cancer diagnosis. Furthermore, there was no clear difference in the incidence of particular types of cancer or the stage of cancer between the extensive and standard testing groups. One study measured time to cancer diagnosis but standard deviations for the mean time to diagnosis were not reported and, therefore, it was impossible to independently test the statistical significance of this result (Carrier 2015). Carrier 2015 and Robin 2016 did not measure VTE-related mortality, adverse effects of anticoagulation, adverse effects of cancer tests, participant satisfaction or quality of life.

A follow-up publication to Robin 2016 assessed the cost-effectiveness of screening plus PET/CT in comparison with

limited screening from the publicly-funded health care systems perspective (Ontario, Canada and France; Robin 2018). This post-hoc analysis found that the addition of PET/CT scan to screening for occult cancer diagnosis is more expensive than standard screening (screening and follow-up total cost per patient (SD): Ontario health system screening plus PET/CT CAD 1324.08 (236.89) versus standard screening CAD 211.75 (315.51); French health system screening plus PET/CT EUR 817.52 (111.43) versus standard screening EUR 96.89 (187.81)). Compared to standard screening, the incremental cost per quality-adjusted life year (QALY) gained was CAD 3412.85 (95% CI 1463.89 to 13,935.88) from the Ontario health system perspective, and EUR 2162.83 (95% CI 958.78 to 10,544.42) from the French health system perspective (Robin 2018).

Overall completeness and applicability of evidence

At present, there is limited evidence concerning whether testing for undiagnosed cancer in people 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 four studies met the inclusion criteria for this review (Carrier 2015; Piccioli 2004b; Prandoni 2016; Robin 2016). While the losses to follow-up were equally balanced within each study, the number of participants in each study was relatively small and pooled analysis is based on 1644 participants. Furthermore, the four 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 VTE-related mortality, adverse effects of anticoagulation, adverse effects of cancer tests and quality of life, were not studied and, therefore, remain unknown.

Quality of the evidence

One study included in the review was judged at low risk of bias (Carrier 2015). Piccioli 2004b was judged at high risk of bias as the study was terminated early for several reasons. First, only five of the more than 40 potential participating centres could contribute participants to the study. Second, some medical ethics committees rejected the protocol because of the absence of screening for occult cancer in the control group, other centres could not start because the proposed extensive screening was judged to be unethical. Finally, the identification of cancer at an apparent early stage in the extensive screening group led to an increasing tendency among physicians in the participating hospitals to initiate screening for cancer in the control participants. Prandoni 2016 was judged at low risk for all domains except other bias, where the risk was deemed to be high as, based on an interim analysis, the study was terminated early because of the low recruitment rate and of the failure to show an appreciable advantage of the CT-based strategy over the control strategy for detection of cancers. Robin 2016 was judged at low risk for all domains except detection bias, where the risk was deemed high due to lack of blinding of outcome assessors.

For the comparison extensive tests for cancer versus tests at the physician's discretion, the certainty of the evidence for cancer-related mortality and frequency of an underlying cancer diagnosis was downgraded to low as there was a high risk of bias in both studies due to them both being terminated early. However, the outcome was direct and effect estimates were consistent and precise, as reflected in the narrow CIs around the ORs (Summary of findings 1). The certainty of evidence for type of cancer are presented in a Summary of findings table (Appendix 2). For type of cancer, the evidence was downgraded to low certainty as there was imprecision due to low number of events combined with the study being terminated early.

For the comparison standard testing plus PET/CT scanning versus standard testing alone, the certainty of the evidence was graded as moderate for all-cause mortality and cancer-related mortality due to the high risk of detection bias in Robin 2016. For VTE-related morbidity, the certainty of the evidence was downgraded to moderate as only one study measured this outcome. For stage of cancer, the evidence was downgraded to low as there was imprecision due to low number of events and there was a high risk of detection bias (Summary of findings 2). The certainty of evidence for type of cancer are presented in a summary of findings table in Appendix 3. For type of cancer, the evidence was judged to be moderate if there was imprecision due to low number of events or where the study was at high risk of detection bias. Where both imprecision and detection bias occurred together, the certainty of the evidence was downgraded to low.

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 conflicts 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 that 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. Therefore, there is a risk of cross-over bias in participants in the control group with them having further tests. However, the effect of this would be to minimise the apparent benefit from testing that was observed, and, therefore, this does not detract from the conclusions of the study or review.

In this review, we presented the studies by Piccioli 2004b and Prandoni 2016 together as both studies compared extensive tests for cancer versus "tests at the physicians discretion". The studies by Carrier 2015 and Robin 2016 were reported in a separate analysis as both studies compared limited screening plus PET/CT scanning versus limited screening alone. Combining all four studies in a meta-analysis would have been problematic due to the different definitions of the comparator groups. However, the control group of the Carrier 2015 and Robin 2016 studies included some of the tests in the test group of the studies by Piccioli 2004b and Prandoni 2016, which may account for why there was no clear difference observed, along with participation of all people in breast and colorectal cancer screening programmes. This may also be the reason for the very low incidence of cancer in the studies by Carrier 2015 and Robin 2016 compared to the studies by Piccioli 2004b and Prandoni 2016.

Agreements and disagreements with other studies or reviews

To date, three other systematic reviews have assessed the effectiveness of testing for cancer on cancer-related mortality in people with an unprovoked VTE. van Es 2017 conducted a

systematic review and meta-analysis of individual patient data from ten prospective studies. Only two of these were randomised controlled trials, both of which were also included in our meta-analysis (Carrier 2015; Robin 2016). The primary outcome was prevalence of occult cancer in patients with an unprovoked VTE. The prevalence of cancer 12 months after VTE diagnosis was 5.2% (95% CI 4.1% to 6.5%). The prevalence of cancer was higher in patients who had extensive testing than in those who had more limited testing initially (OR 2.0, 95% CI 1.2 to 3.4) but not at 12 months (OR 1.4 95% CI 0.89 to 2.1). Furthermore, the prevalence of cancer increased with age, and was seven-fold higher in patients aged 50 years or older, than in younger patients (OR 7.1, 95% CI 3.1 to 16.0). Systematic reviews by Klein 2017 and Zhou 2017 evaluated the efficacy of an extensive testing strategy for occult malignant diseases in patients with unprovoked VTE. Both reviews included five studies; the same four studies included in our review (Carrier 2015; Piccioli 2004b; Prandoni 2016; Robin 2016) and a fifth study which was a prospective cohort study (van Doormaal 2011). This did not meet the inclusion criteria for our review as we considered randomised controlled trials only. Neither review demonstrated a significant difference between extensive and limited testing for all-cause mortality (with risk ratios (RR) of 0.86, 95% CI 0.58 to 1.27 and RR 0.86, 95% CI, 0.58 to1.27 for Klein 2017 and Zhou 2017, respectively), nor cancer-related mortality (RR 0.93, 95% CI 0.54 to 1.58 and RR 0.86, 95% CI, 0.46 to 1.62 for Klein 2017 and Zhou 2017, respectively). Zhou 2017 found no significant difference between the extensive and limited testing groups with regard to risk of missed cancer diagnosis (RR 0.51, 95% CI 0.20 to 1.28). However, Klein 2017 determined that extensive testing yielded more diagnoses of cancer (RR 2.17, 95% CI 1.42 to 3.32). A more recent narrative review reported similar findings to this Cochrane Review as well as highlighting ongoing studies involving high-risk patients (D'Astous 2020). These ongoing studies were identified in our searches and will be included in future updates of this Cochrane Review. D'Astous 2020 also mentioned that other means of occult cancer detection, such as biomarkers, are being investigated. Biomarkers may allow more targeted screening, and platelet RNA profiling is currently being evaluated in a prospective cohort study to detect occult cancer in patients with unprovoked VTE (NCT02739867).

AUTHORS' CONCLUSIONS

Implications for practice

At present, there is insufficient evidence as to whether testing for undiagnosed cancer in people with a first episode of unprovoked venous thromboembolism (VTE) (deep vein thrombosis (DVT) of the lower limb or pulmonary embolism (PE)) is effective in reducing cancer- and VTE-related mortality and morbidity, and which tests for cancer are best at identifying treatable cancers early. The decision whether to screen for cancer or not in a first episode of unprovoked VTE remains for individual clinicians and participants to decide on a case-by-case basis. The diagnosis of cancer has significant implications for participants and may alter the pharmacological treatment of their VTE, and some may wish to be investigated even in the absence 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 participant preference.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Carrier 2015

Study characteristics	
Methods	Study design: multicentre, open-label, randomised controlled trial.
Participants	Country: Canada. Setting: hospital. Number of centres: 9. Number of participants: 854. Age (mean (SD)): screening + CT group: 53.4 (14.2) years; screening only group: 53.7 (13.8). Sex: screening + CT group: 299 M/124 F; screening only group: 277 M/154 F. Inclusion criteria: people with new diagnosis of first unprovoked VTE (proximal lower-limb deep vein thrombosis, pulmonary embolism, or both). Unprovoked VTE defined as VTE in absence of known overt active cancer, current pregnancy, thrombophilia (hereditary or acquired), previous unprovoked VTE or a temporary predisposing factor in the previous 3 months, including paralysis, paresis or plaster immobilisation of the legs, confinement to bed for ≥ 3 days or major surgery. Exclusion criteria: aged < 18 years, refusal or inability to provide informed consent, allergy to contrast media, creatinine clearance < 60 mL per minute, claustrophobia or agoraphobia, weight > 130 kg, ulcerative colitis or glaucoma.
Interventions	Screening procedure: complete history and physical examination, measurement of complete blood counts and serum electrolyte and creatinine levels, liver-function testing and chest radiography. Sex-specific screening conducted if it had not been performed in previous year. Breast examination, mammography, or both performed in women > 50 years of age and Pap testing and a pelvic examination

Carrier 2015 *(Continued)*

	performed in women 18-70 years of age who had never been sexually active. Prostate examination, PSA test, or both performed in men aged > 40 years. Also comprehensive CT of abdomen and pelvis (virtual colonoscopy and gastroscopy, biphasic enhanced CT of liver, parenchymal pancreatography, and uniphasic enhanced CT of distended bladder). Control: complete history and physical examination, measurement of complete blood counts and serum electrolyte and creatinine levels, liver-function testing and chest radiography. Sex-specific screening conducted if it had not been performed in previous year. Breast examination, mammography, or both performed in women > 50 years of age and Pap testing and a pelvic examination performed in women 18-70 years of age who had ever been sexually active. Prostate examination, PSA test, or both performed in men aged > 40 years. Duration: 1 year follow-up.
Outcomes	Primary outcomes: newly diagnosed cancer during the follow-up period in people who had a negative screening result for occult cancer. Secondary outcomes: total number of occult cancers diagnosed and total number of early cancers (T_{1-2}, N_0, M_0 according to the World Health Organization TNM classification system) diagnosed by occult-cancer screening and during subsequent 1-year follow-up, 1-year cancer-related mortality, 1-year overall mortality, time to cancer diagnosis and incidence of recurrent VTE.
Funding	Heart and Stroke Foundation of Canada.
Declarations of interest	Quote: "Dr. Lazo-Langner reports receiving honoraria from Pfizer, LEO Pharma, and Bayer and grant support from Alexion and participating in research studies funded by Pfizer, LEO Pharma, Boehringer Ingelheim, Bayer, Daiichi Sankyo, Novartis, and Celgene. Dr. Douketis reports receiving fees for serving on advisory boards from Biotie Therapies, Portola Pharmaceuticals, and The Medicines Company; honoraria from Bristol-Myers Squibb, Pfizer, and Sanofi-Aventis; consulting fees from Boehringer Ingelheim, Bayer, Janssen, Bristol-Myers Squibb, Daiichi Sankyo, and Actelion Pharmaceuticals; and grant support from Boehringer Ingelheim. Dr. Wells reports receiving lecture fees from Bayer HealthCare and grant support from Bristol-Myers Squibb/Pfizer. No other potential conflict of interest relevant to this article was reported."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The trial statistician generated the randomisation list using random-number tables."
Allocation concealment (selection bias)	Low risk	Quote: "A central Web-based randomisation system ensured assignment concealment."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: blinding of participants and study personnel not done but review authors judged that outcome and outcome measurement not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A central adjudication committee whose members were unaware of the study-group assignments reviewed all suspected outcome events." Comment: outcome assessors blinded to study allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all losses to follow-up accounted for.

Carrier 2015 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: primary and secondary outcomes clearly prespecified and reported.
Other bias	Low risk	Comment: study appeared free from other sources of bias.

Piccioli 2004b

Study characteristics	
Methods	Study design: randomised multicentre clinical trial.
Participants	Country: Italy. Setting: hospital. Number of centres: not stated. Number of participants: 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 people with a documented unprovoked 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 aged < 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, α-fetoprotein and CA125. In addition, women had gynaecological examination, Pap smear and mammography. Men had a transabdominal ultrasound of prostate and total PSA test. Control: tests at physician's discretion. Duration: 2-year follow-up. At these visits, special attention paid to recent medical history. To avoid diagnostic suspicion bias, medical history concerning general health, hospital admission, and occurrence of signs and symptoms of cancer obtained on a standardised form by a physician unaware of allocation of participant. If malignant disease had become apparent during follow-up, information from the attending specialist sought after consent of participant.
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.
Funding	Associazone Italiana per le Ricerca sul Cancro.
Declarations of interest	Declarations not reported.

Piccioli 2004b *(Continued)*

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	Quote: "Randomisation was performed centrally."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "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 participants in extensive screening group and study personnel not done but review authors judged that outcome and outcome measurement not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "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 blinded to study allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants completed the 2-year follow-up. No missing data.
Selective reporting (reporting bias)	Low risk	Comment: primary and secondary outcomes clearly prespecified and reported.
Other bias	High risk	Comment: study terminated early after inclusion of only 201 participants after 5 years for several reasons. First, only 5 of the more than 40 potential participating centres could contribute participants to the study. Second, some medical ethics committees rejected the protocol because of the absence of screening for occult cancer in the control group, other centres could not start because the proposed extensive screening was judged to be unethical. Finally, identification of cancer at an apparent early stage in the extensive screening group led to an increasing tendency among physicians in participating hospitals to initiate screening for cancer in control participants.

Prandoni 2016

Study characteristics

Methods	Study design: multicentre, randomised controlled trial.
Participants	Country: Italy. Setting: hospital. Number of centres: 5.

Prandoni 2016 *(Continued)*

	Number of participants: 195 Age (mean (SD)): extensive screening group: 69.3 (14) years; control group: 69.0 (14) years. Sex: extensive screening group: 54 M/44 F; control group: 47 M/50 F. Inclusion criteria: people with an objectively diagnosed, first episode of unprovoked VTE, in whom a routine initial screening for cancer was normal. Exclusion criteria: history of previous documented episodes of VTE, aged < 18 years, pregnant, unable to attend follow-up visits because of geographic inaccessibility, had known allergy to contrast medium or had a CT scan of torso for any reasons within 6 months from presentation.
Interventions	Screening procedure: extensive screening with mandatory CT scan of thorax, abdomen and pelvis together with haemoccult test or any test at physician's discretion according to good clinical practice. Control: personalised strategy consisting of additional testing based on physicians' judgements and participants' preferences, including a 'no-further testing' option. Duration: 3, 6, 12 and 24 months' follow-up in which participants were asked about general health, history of recent hospital admissions and occurrence of signs and symptoms suggestive of cancer. Cancer outcomes that presented during follow-up were detected based on clinical features that would prompt diagnostic imaging or cancers that were occasionally detected by screening that was independent of the diagnosis of VTE.
Outcomes	Primary outcomes: cancer-related mortality (defined as death due to malignancy or death due to the complications of the diagnostic or surgical procedures performed to diagnose or treat cancer) and incidence of newly discovered cancer. Secondary outcomes: cancer stage, using the TNM classification, at which tumours were diagnosed in the 2 study groups; and incidence of cancer-related mortality in the 2 randomisation groups.
Funding	None. Quote: "This was a spontaneous, unfunded, nonsponsored study."
Declarations of interest	Quote: "None."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Concealed allocation was ensured by employing serially numbered, opaque, sealed envelopes. Each participating centre was initially assigned a lot of 20 envelopes, while subsequent allocations were in lots of 10, as needed."
Allocation concealment (selection bias)	Low risk	Quote: "Concealed allocation was ensured by employing serially numbered, opaque, sealed envelopes. Each participating centre was initially assigned a lot of 20 envelopes, while subsequent allocations were in lots of 10, as needed."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: blinding of participants in extensive screening group and study personnel not done but review authors judged that outcome and outcome measurement were not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: investigators performing the follow-up visits blinded to participants' randomisation groups'.

Prandoni 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all losses to follow-up accounted for.
Selective reporting (reporting bias)	Low risk	Comment: primary and secondary outcomes clearly prespecified and reported.
Other bias	High risk	Comment: interim analysis scheduled after inclusion of approximately half of planned sample size. Based on results of this analysis, study promoters decided to stop study enrolment because of low recruitment rate and of failure to show an appreciable advantage of CT-based strategy over control strategy for detection of occult cancers.

Robin 2016

Study characteristics	
Methods	Study design: open-label, multicentre, randomised study.
Participants	Country: France. Setting: hospital. Number of centres: 4. Number of participants: 394. Age (mean (range)): screening group: 64 (48-77) years; limited screening group: 62 (50-75) years. Sex: screening group: 105 M/92 F; limited screening group: 102 M/95 F. Inclusion criteria: aged ≥ 18 years, diagnosed with unprovoked VTE. VTE defined as objectively confirmed proximal deep vein thrombosis or pulmonary embolism. Unprovoked VTE defined as VTE not provoked by major inherited or acquired risk factor including surgery, trauma or fracture during 3 months before VTE event, known antiphospholipid antibody syndrome or known deficiency in antithrombin, protein C or protein S. Exclusion criteria: ongoing pregnancy, active malignant disease (defined as known malignant disease which was active or treated during previous 5 years), not insured under French National Social Security programme, hypersensitivity to ^{18}F-FDG or any of the excipients according to summary of product characteristics in France, or unable or unwilling to give consent.
Interventions	Screening procedure: screening strategy consisting of limited strategy + ^{18}F-FDG PET/CT scan of chest, abdomen and pelvis. Control: limited screening strategy (physical examination, usual laboratory tests and basic radiographs). Duration: 2 years.
Outcomes	Primary outcomes: proportion of people with a cancer diagnosis in each group after the initial screening assessment. Secondary outcomes: subsequent cancer diagnosis in people with negative initial screening, proportion of early-stage versus advanced-stage tumours at initial screening and during follow-up, overall mortality and cancer-related mortality during follow-up.
Funding	Programme Hospitalier de Recherche Clinique (French Department of Health).

Robin 2016 *(Continued)*

Declarations of interest	Quote: "OS reports grants, personal fees, and non-financial support from Bayer, grants from Daiichi Sankyo, personal fees from BMS, grants and personal fees from Boehringer Ingelheim, personal fees and non-financial support from Chiesi, non-financial support from GSK, and grants, personal fees, and non-financial support from Actelion, outside the submitted work. None of the other authors declare any competing interests."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation list was created centrally using computer-generated block sizes of six, stratified by centre, and concealed from investigators. We used a secure, dedicated, central web-based randomisation system (Clinsight)."
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation list was created centrally using computer-generated block sizes of six, stratified by centre, and concealed from investigators. We used a secure, dedicated, central web-based randomisation system (Clinsight). A unique study participant number and study group allocation was given after patients' basic information and eligibility criteria were entered by the study personnel."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants and physicians giving the intervention, assessing outcomes, and analysing the data were not masked to study group assignment." Comment: blinding of participants and study personnel not done but review authors judged that outcome and outcome measurement not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Physicians giving the intervention, assessing outcomes, and analysing the data were not masked to study group assignment." Comment: outcome assessors not blinded to outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all losses to follow-up accounted for.
Selective reporting (reporting bias)	Low risk	Comment: primary and secondary outcomes clearly prespecified and reported.
Other bias	Low risk	Comment: study appeared free from other sources of bias.

CT: computed tomography; F: female; FDG: fluorodeoxyglucose; M: male; Pap: Papanicolaou; PET: positron emission tomography; PSA: prostate-specific antigen; SD: standard deviation; TNM: tumour-node-metastasis; VTE: venous thromboembolism.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Kraaijpoel 2018	Participants not randomised by test. This was a post hoc evaluation of the RIETE and SOME scores for occult cancer detection in patients with acute VTE. Data from the Hokusai-VTE study where participants were randomised to edoxaban or warfarin for the treatment of acute VTE.

RIETE: Registro Informatizado de Pacientes con Enfermedad TromboEmbólica
SOME: Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism
VTE: venous thromboembolism

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2018-003958-25-ES

Study name	Screening for cancer with PET/CT in patients with unprovoked venous thromboembolic disease with a high risk of developing cancer. Open randomized clinical trial
Methods	Randomised, parallel, open label clinical trial
Participants	650 participants with unprovoked venous thromboembolic disease at high risk of developing cancer at follow-up
Interventions	Limited screening: complete clinical history, along with routine physical, analytical examination (creatinine, sodium, potassium, red series, white series, liver and calcium profile) and chest x-ray Limited screening plus 18FDG PET-CT
Outcomes	Number of neoplasms diagnosed using extended screening (after 3 years) Number of neoplasms diagnosed in early phase using extended screening (after 3 years) Overall survival of patients with high-risk unprovoked thromboembolic disease performing limited/extended screening (after 3 years) European Quality of Life-5 (EQ-5D scale validated in Spanish) of patients with high-risk unprovoked thromboembolic disease performing limited/extended screening (baseline and after 90, 180 and 365 days of follow-up)
Starting date	1 June 2019
Contact information	Principal Investigator: Luis Jara Palomares, MD/PhD; DHospitales Universitarios Virgen del Rocío Clara M Rosso Fernández, MD/PhD; Fundación Pública Andaluza para la gestión de la Investigación en Sevilla
Notes	IDs: EudraCT2018-003958-25, NCT03937583 Individual participant data to be shared with the centre participants once the study is officially finished in the foreseen period of three years.

EUCTR2020-002210-41-FR

Study name	Screening for occult malignancy using 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (FDG PET/CT) in patients with unprovoked venous thromboembolism
Methods	Randomised, parallel, open label clinical trial
Participants	1276 participants, higher risk patients (≥ 50 year-old) with a first unprovoked VTE
Interventions	Limited cancer screening compared to limited cancer screening plus FDG PET/CT The limited cancer screening will include: 1) a complete medical history and physical examination; 2) complete blood count; 3) liver function tests; and 4) chest X-ray In women, a breast examination, Pap smear/pelvic examination (if < 70 years old and previously sexually active) and mammogram will be performed, if not conducted in last year In men, similarly, prostate examination and PSA testing will be performed, if not conducted in the last year

EUCTR2020-002210-41-FR *(Continued)*	All patients will undergo colon cancer screening as per local practice
Outcomes	Occult cancer missed by screening strategies (1 year) Occult cancer diagnosed by screening strategies (1 month) Early vs advanced-stage cancers (1 year) Cancer-related mortality (5 years) Cost-effectiveness analysis (1 year) Recurrent VTE (1 year) Decision aid to assist patients in the decision of cancer screening (1 year) Additional tests (1 year)
Starting date	8 September 2020
Contact information	Pierre-Yves Salaun; University Hospital, Brest, France Florence Morvan, CHRU de Brest, France
Notes	IDs: EUCTR2020-002210-41-FR, NCT04304651, 29BRC20.0021, MVTEP2/SOME2

FDG PET/CT: fluorodeoxyglucose positron emission tomography/computed tomography
PSA: prostate-specific antigen
VTE: venous thromboembolism

DATA AND ANALYSES

Comparison 1. Extensive tests versus tests at the physician's discretion

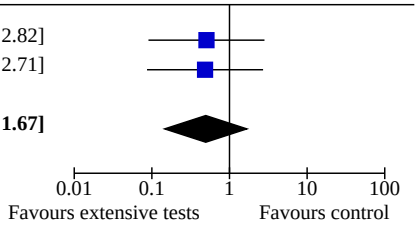
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Cancer-related mortality	2	396	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.15, 1.67]
1.2 Characteristics of diagnosed cancer: type of cancer	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.2.1 Lung	1	201	Odds Ratio (M-H, Random, 95% CI)	2.08 [0.19, 23.34]
1.2.2 Bladder	1	201	Odds Ratio (M-H, Random, 95% CI)	2.08 [0.19, 23.34]
1.2.3 Stomach	1	201	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.06, 16.71]
1.2.4 Kidney	1	201	Odds Ratio (M-H, Random, 95% CI)	3.12 [0.13, 77.55]
1.2.5 Adrenal gland	1	201	Odds Ratio (M-H, Random, 95% CI)	3.12 [0.13, 77.55]
1.2.6 Liver	1	201	Odds Ratio (M-H, Random, 95% CI)	3.12 [0.13, 77.55]
1.2.7 Uterus	1	201	Odds Ratio (M-H, Random, 95% CI)	3.12 [0.13, 77.55]
1.2.8 Breast	1	201	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.06, 16.71]
1.2.9 Ovary	1	201	Odds Ratio (M-H, Random, 95% CI)	3.12 [0.13, 77.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.10 Colon	1	201	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.05, 5.72]
1.2.11 Prostate	1	201	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.05, 5.72]
1.2.12 Pancreas	1	201	Odds Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.26]
1.3 Characteristics of diagnosed cancer: stage of cancer	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.3.1 T1 or T2 (N0 M0)	1	201	Odds Ratio (M-H, Random, 95% CI)	5.00 [1.05, 23.76]
1.3.2 T3	1	201	Odds Ratio (M-H, Random, 95% CI)	0.25 [0.03, 2.28]
1.4 Frequency of underlying cancer diagnosis	2	396	Odds Ratio (M-H, Random, 95% CI)	1.32 [0.59, 2.93]

Analysis 1.1. Comparison 1: Extensive tests versus tests at the physician's discretion, Outcome 1: Cancer-related mortality

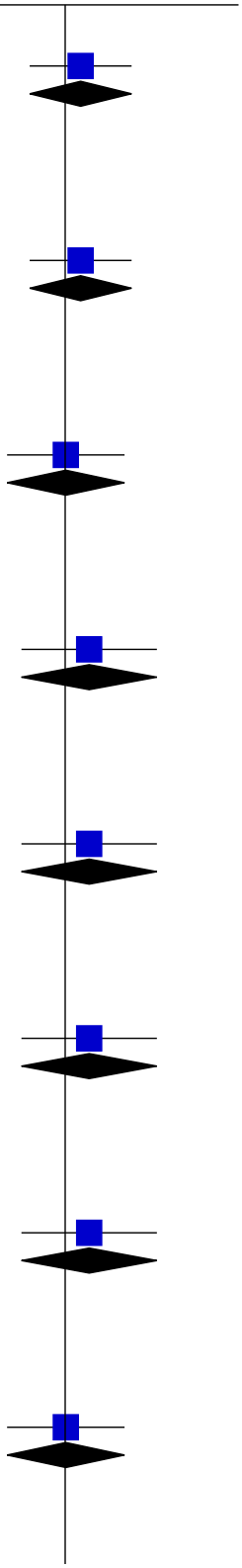
Study or Subgroup	Extensive tests Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Piccioli 2004b	2	99	4	102	50.0%	0.51 [0.09 , 2.82]
Prandoni 2016	2	98	4	97	50.0%	0.48 [0.09 , 2.71]
Total (95% CI)		**197**		**199**	**100.0%**	**0.49 [0.15 , 1.67]**
Total events:	4		8			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Not applicable

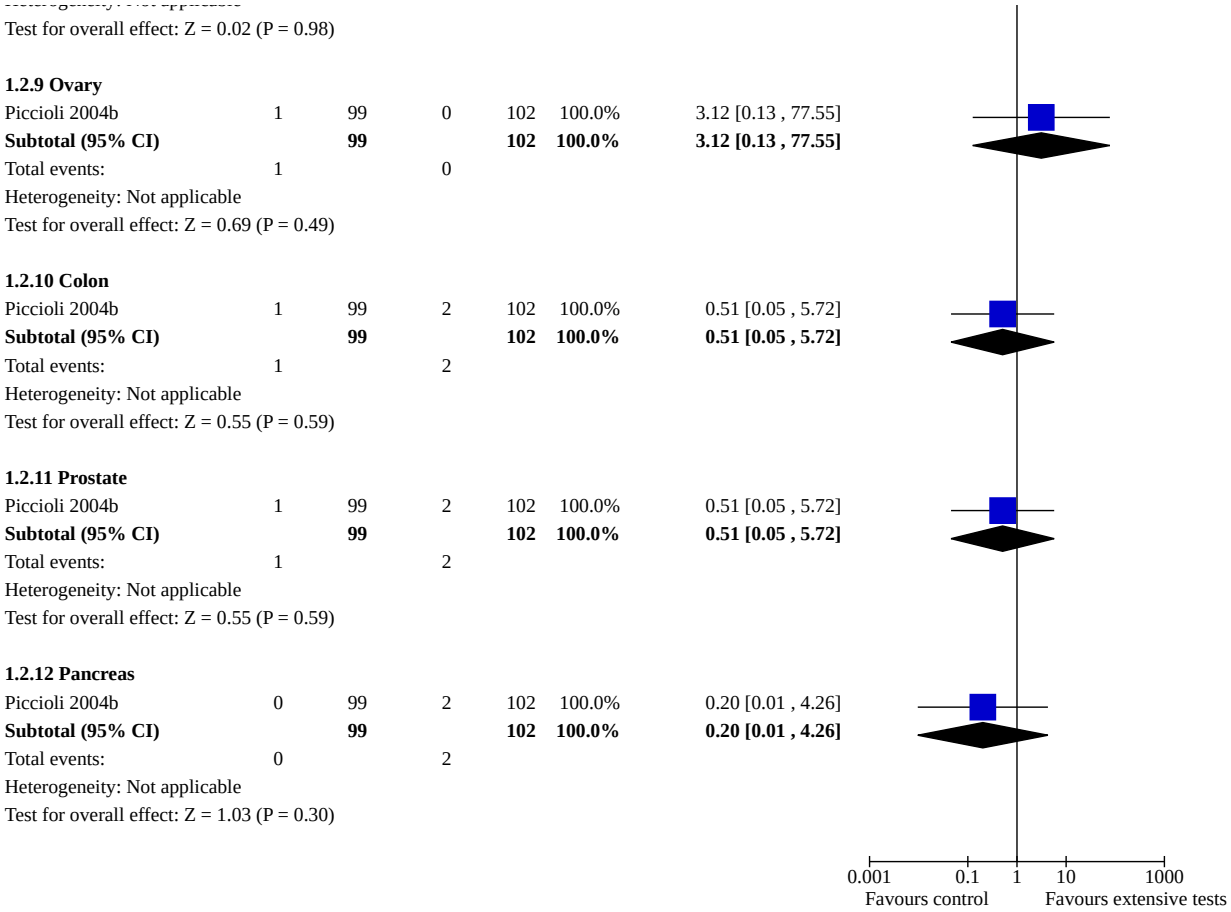


Analysis 1.2. Comparison 1: Extensive tests versus tests at the physician's discretion, Outcome 2: Characteristics of diagnosed cancer: type of cancer

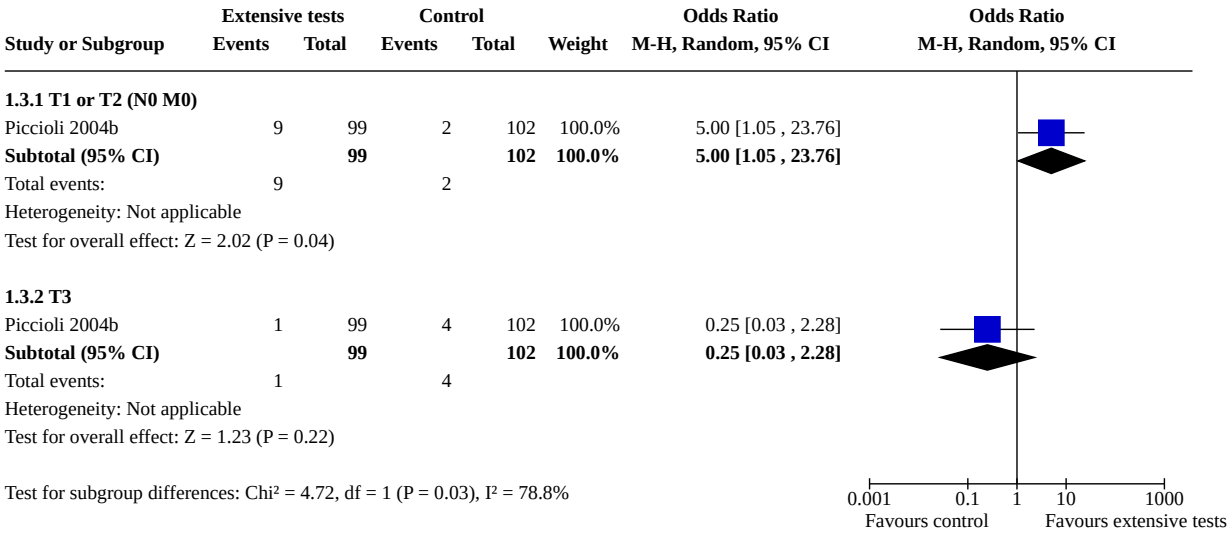
Study or Subgroup	Extensive tests Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 Lung						
Piccioli 2004b	2	99	1	102	100.0%	2.08 [0.19 , 23.34]
Subtotal (95% CI)		**99**		**102**	**100.0%**	**2.08 [0.19 , 23.34]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.55)						
1.2.2 Bladder						
Piccioli 2004b	2	99	1	102	100.0%	2.08 [0.19 , 23.34]
Subtotal (95% CI)		**99**		**102**	**100.0%**	**2.08 [0.19 , 23.34]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.55)						
1.2.3 Stomach						
Piccioli 2004b	1	99	1	102	100.0%	1.03 [0.06 , 16.71]
Subtotal (95% CI)		**99**		**102**	**100.0%**	**1.03 [0.06 , 16.71]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						
1.2.4 Kidney						
Piccioli 2004b	1	99	0	102	100.0%	3.12 [0.13 , 77.55]
Subtotal (95% CI)		**99**		**102**	**100.0%**	**3.12 [0.13 , 77.55]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
1.2.5 Adrenal gland						
Piccioli 2004b	1	99	0	102	100.0%	3.12 [0.13 , 77.55]
Subtotal (95% CI)		**99**		**102**	**100.0%**	**3.12 [0.13 , 77.55]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
1.2.6 Liver						
Piccioli 2004b	1	99	0	102	100.0%	3.12 [0.13 , 77.55]
Subtotal (95% CI)		**99**		**102**	**100.0%**	**3.12 [0.13 , 77.55]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
1.2.7 Uterus						
Piccioli 2004b	1	99	0	102	100.0%	3.12 [0.13 , 77.55]
Subtotal (95% CI)		**99**		**102**	**100.0%**	**3.12 [0.13 , 77.55]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
1.2.8 Breast						
Piccioli 2004b	1	99	1	102	100.0%	1.03 [0.06 , 16.71]
Subtotal (95% CI)		**99**		**102**	**100.0%**	**1.03 [0.06 , 16.71]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						



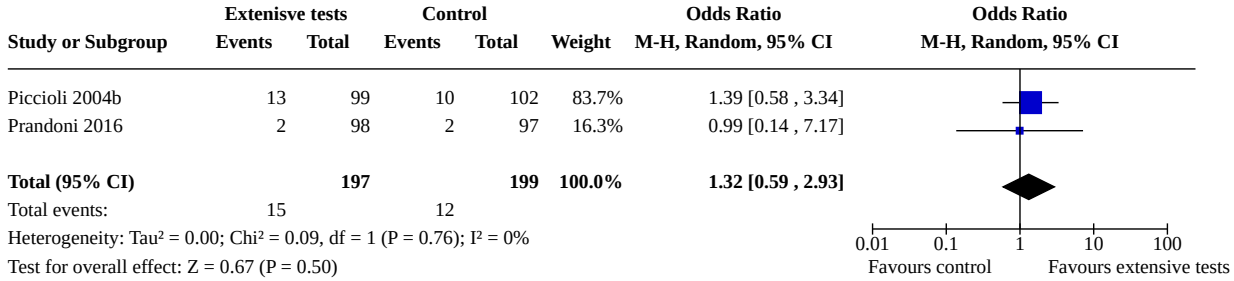
Analysis 1.2. (Continued)



Analysis 1.3. Comparison 1: Extensive tests versus tests at the physician's discretion, Outcome 3: Characteristics of diagnosed cancer: stage of cancer



Analysis 1.4. Comparison 1: Extensive tests versus tests at the physician's discretion, Outcome 4: Frequency of underlying cancer diagnosis



Comparison 2. Standard testing plus PET/CT scanning versus standard testing alone

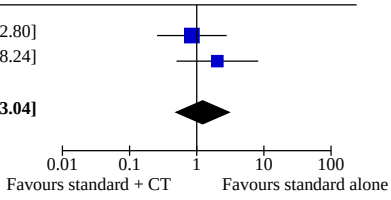
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality	2	1248	Odds Ratio (M-H, Random, 95% CI)	1.22 [0.49, 3.04]
2.2 Cancer-related mortality	2	1248	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.20, 1.52]
2.3 Venous thromboembolism-related morbidity	1	854	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.48, 2.17]
2.4 Characteristics of diagnosed cancer: type of cancer	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.4.1 Acute leukaemia	2	1248	Odds Ratio (M-H, Random, 95% CI)	1.62 [0.20, 13.22]
2.4.2 Gynaecological	2	1248	Odds Ratio (M-H, Random, 95% CI)	2.39 [0.43, 13.36]
2.4.3 Skin: melanoma	1	854	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.06, 16.34]
2.4.4 Colorectal	2	1248	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.08, 2.40]
2.4.5 Prostate	2	1248	Odds Ratio (M-H, Random, 95% CI)	2.52 [0.48, 13.12]
2.4.6 Pancreatic	2	1248	Odds Ratio (M-H, Random, 95% CI)	4.81 [0.55, 42.48]
2.4.7 Cholangiocarcinoma	1	854	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.05, 5.63]
2.4.8 Lymphoma	2	1248	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.09, 5.83]
2.4.9 Breast	1	854	Odds Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.24]
2.4.10 Urological	2	1248	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.03, 12.32]
2.4.11 Liver	1	394	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.19]
2.4.12 Head and neck	1	394	Odds Ratio (M-H, Random, 95% CI)	3.02 [0.12, 74.47]
2.4.13 Lung	1	394	Odds Ratio (M-H, Random, 95% CI)	3.02 [0.12, 74.47]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4.14 Unknown primary	1	854	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.34]
2.5 Characteristics of diagnosed cancer: stage of cancer	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.5.1 Early	1	394	Odds Ratio (M-H, Random, 95% CI)	1.78 [0.51, 6.17]
2.5.2 Advanced	1	394	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.14, 7.17]
2.6 Frequency of an underlying cancer diagnosis	2	1248	Odds Ratio (M-H, Random, 95% CI)	1.71 [0.91, 3.20]

Analysis 2.1. Comparison 2: Standard testing plus PET/CT scanning versus standard testing alone, Outcome 1: All-cause mortality

Study or Subgroup	Standard testing + CT Events	Total	Standard testing alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Carrier 2015	5	423	6	431	57.9%	0.85 [0.26 , 2.80]
Robin 2016	6	197	3	197	42.1%	2.03 [0.50 , 8.24]
Total (95% CI)		**620**		**628**	**100.0%**	**1.22 [0.49 , 3.04]**
Total events:	11		9			

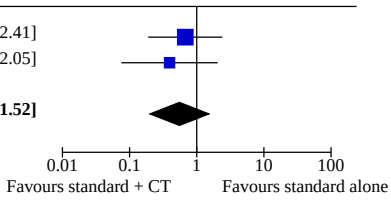
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 0.44 (P = 0.66)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Standard testing plus PET/CT scanning versus standard testing alone, Outcome 2: Cancer-related mortality

Study or Subgroup	Standard testing + CT Events	Total	Standard testing alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Carrier 2015	4	423	6	431	62.8%	0.68 [0.19 , 2.41]
Robin 2016	2	197	5	197	37.2%	0.39 [0.08 , 2.05]
Total (95% CI)		**620**		**628**	**100.0%**	**0.55 [0.20 , 1.52]**
Total events:	6		11			

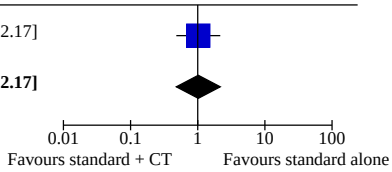
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.15 (P = 0.25)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Standard testing plus PET/CT scanning versus standard testing alone, Outcome 3: Venous thromboembolism-related morbidity

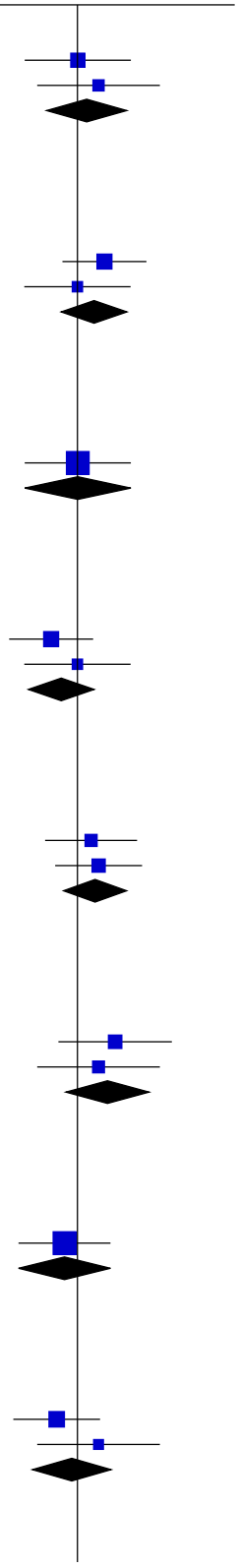
Study or Subgroup	Standard testing + CT Events	Total	Standard testing alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Carrier 2015	14	423	14	431	100.0%	1.02 [0.48 , 2.17]
Total (95% CI)		**423**		**431**	**100.0%**	**1.02 [0.48 , 2.17]**
Total events:	14		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable



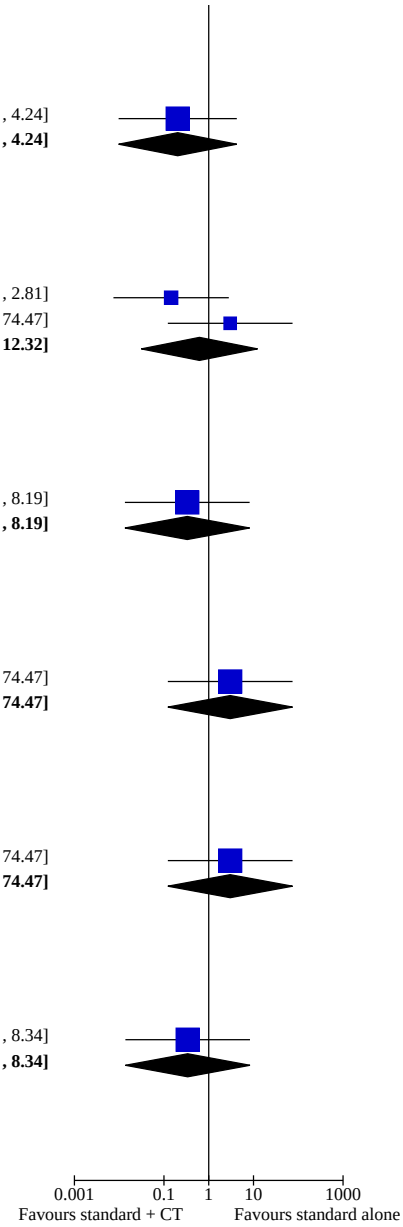
Analysis 2.4. Comparison 2: Standard testing plus PET/CT scanning versus standard testing alone, Outcome 4: Characteristics of diagnosed cancer: type of cancer

Study or Subgroup	Standard testing + CT Events	Total	Standard testing alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
2.4.1 Acute leukaemia						
Carrier 2015	1	423	1	431	57.2%	1.02 [0.06 , 16.34]
Robin 2016	1	197	0	197	42.8%	3.02 [0.12 , 74.47]
Subtotal (95% CI)		**620**		**628**	**100.0%**	**1.62 [0.20 , 13.22]**
Total events:	2		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.65)						
2.4.2 Gynaecological						
Carrier 2015	4	423	1	431	61.6%	4.11 [0.46 , 36.88]
Robin 2016	1	197	1	197	38.4%	1.00 [0.06 , 16.10]
Subtotal (95% CI)		**620**		**628**	**100.0%**	**2.39 [0.43 , 13.36]**
Total events:	5		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.99 (P = 0.32)						
2.4.3 Skin: melanoma						
Carrier 2015	1	423	1	431	100.0%	1.02 [0.06 , 16.34]
Subtotal (95% CI)		**423**		**431**	**100.0%**	**1.02 [0.06 , 16.34]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
2.4.4 Colorectal						
Carrier 2015	1	423	4	431	61.6%	0.25 [0.03 , 2.27]
Robin 2016	1	197	1	197	38.4%	1.00 [0.06 , 16.10]
Subtotal (95% CI)		**620**		**628**	**100.0%**	**0.43 [0.08 , 2.40]**
Total events:	2		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.96 (P = 0.34)						
2.4.5 Prostate						
Carrier 2015	2	423	1	431	47.2%	2.04 [0.18 , 22.61]
Robin 2016	3	197	1	197	52.8%	3.03 [0.31 , 29.39]
Subtotal (95% CI)		**620**		**628**	**100.0%**	**2.52 [0.48 , 13.12]**
Total events:	5		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.10 (P = 0.27)						
2.4.6 Pancreatic						
Carrier 2015	3	423	0	431	53.9%	7.18 [0.37 , 139.49]
Robin 2016	1	197	0	197	46.1%	3.02 [0.12 , 74.47]
Subtotal (95% CI)		**620**		**628**	**100.0%**	**4.81 [0.55 , 42.48]**
Total events:	4		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 1.41 (P = 0.16)						
2.4.7 Cholangiocarcinoma						
Carrier 2015	1	423	2	431	100.0%	0.51 [0.05 , 5.63]
Subtotal (95% CI)		**423**		**431**	**100.0%**	**0.51 [0.05 , 5.63]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						
2.4.8 Lymphoma						
Carrier 2015	1	423	3	431	64.0%	0.34 [0.04 , 3.26]
Robin 2016	1	197	0	197	36.0%	3.02 [0.12 , 74.47]
Subtotal (95% CI)		**620**		**628**	**100.0%**	**0.74 [0.09 , 5.83]**
Total events:	2		3			
Heterogeneity: Tau² = 0.39; Chi² = 1.19, df = 1 (P = 0.27); I² = 16%						
Test for overall effect: Z = 0.28 (P = 0.78)						



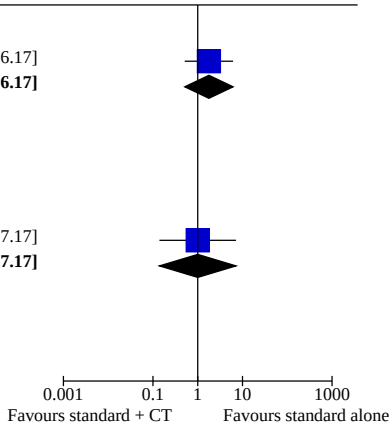
Analysis 2.4. (Continued)

Heterogeneity: Tau² = 0.39; Chi² = 1.19, df = 1 (P = 0.27); I² = 16%						
Test for overall effect: Z = 0.28 (P = 0.78)						
2.4.9 Breast						
Carrier 2015	0	423	2	431	100.0%	0.20 [0.01 , 4.24]
Subtotal (95% CI)		**423**		**431**	**100.0%**	**0.20 [0.01 , 4.24]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
2.4.10 Urological						
Carrier 2015	0	423	3	431	52.1%	0.14 [0.01 , 2.81]
Robin 2016	1	197	0	197	47.9%	3.02 [0.12 , 74.47]
Subtotal (95% CI)		**620**		**628**	**100.0%**	**0.62 [0.03 , 12.32]**
Total events:	1		3			
Heterogeneity: Tau² = 2.18; Chi² = 1.88, df = 1 (P = 0.17); I² = 47%						
Test for overall effect: Z = 0.31 (P = 0.75)						
2.4.11 Liver						
Robin 2016	0	197	1	197	100.0%	0.33 [0.01 , 8.19]
Subtotal (95% CI)		**197**		**197**	**100.0%**	**0.33 [0.01 , 8.19]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
2.4.12 Head and neck						
Robin 2016	1	197	0	197	100.0%	3.02 [0.12 , 74.47]
Subtotal (95% CI)		**197**		**197**	**100.0%**	**3.02 [0.12 , 74.47]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
2.4.13 Lung						
Robin 2016	1	197	0	197	100.0%	3.02 [0.12 , 74.47]
Subtotal (95% CI)		**197**		**197**	**100.0%**	**3.02 [0.12 , 74.47]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
2.4.14 Unknown primary						
Carrier 2015	0	423	1	431	100.0%	0.34 [0.01 , 8.34]
Subtotal (95% CI)		**423**		**431**	**100.0%**	**0.34 [0.01 , 8.34]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
Test for subgroup differences: Chi² = 8.44, df = 13 (P = 0.81), I² = 0%						



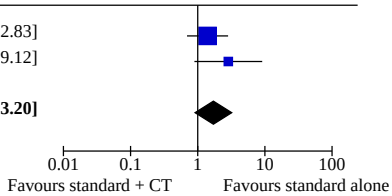
Analysis 2.5. Comparison 2: Standard testing plus PET/CT scanning versus standard testing alone, Outcome 5: Characteristics of diagnosed cancer: stage of cancer

Study or Subgroup	Standard testing + CT Events	Total	Standard testing alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
2.5.1 Early						
Robin 2016	7	197	4	197	100.0%	1.78 [0.51 , 6.17]
Subtotal (95% CI)		**197**		**197**	**100.0%**	**1.78 [0.51 , 6.17]**
Total events:	7		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.91 (P = 0.37)						
2.5.2 Advanced						
Robin 2016	2	197	2	197	100.0%	1.00 [0.14 , 7.17]
Subtotal (95% CI)		**197**		**197**	**100.0%**	**1.00 [0.14 , 7.17]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%						



Analysis 2.6. Comparison 2: Standard testing plus PET/CT scanning versus standard testing alone, Outcome 6: Frequency of an underlying cancer diagnosis

Study or Subgroup	Standard testing + CT Events	Total	Standard testing alone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Carrier 2015	19	423	14	431	71.9%	1.40 [0.69 , 2.83]
Robin 2016	11	197	4	197	28.1%	2.85 [0.89 , 9.12]
Total (95% CI)		**620**		**628**	**100.0%**	**1.71 [0.91 , 3.20]**
Total events:	30		18			
Heterogeneity: Tau² = 0.01; Chi² = 1.06, df = 1 (P = 0.30); I² = 5%						
Test for overall effect: Z = 1.68 (P = 0.09)						
Test for subgroup differences: Not applicable						



APPENDICES

Appendix 1. Sources searched and search strategies

Source	Search strategy	Hits retrieved
VASCULAR REGISTER IN CRSW	#1 venous thromboembolism or vte AND INREGISTER AND 02/01/2017_TO_11/07/2018:CRSCREATED #2 cancer or malignan* or tumour or tumor AND INREGISTER AND 02/01/2017_TO_11/07/2018:CRSCREATED #3 screen* or test* AND INREGISTER AND 02/01/2017_TO_11/07/2018:CRSCREATED #4 #1 AND #2 AND #3	April 2019: 0 May 2021: 30
CENTRAL via CRSO	#1 MESH DESCRIPTOR Thrombosis 1623 #2 MESH DESCRIPTOR Thromboembolism 1130	April 2019: 157 May 2021: 1427

(Continued)

	#3 MESH DESCRIPTOR Venous Thromboembolism 460 #4 MESH DESCRIPTOR Venous Thrombosis EXPLODE ALL TREES 2383 #5 (thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*):TI,AB,KY 23592 #6 MESH DESCRIPTOR Pulmonary Embolism EXPLODE ALL TREES 876 #7 (PE or DVT or VTE):TI,AB,KY 6410 #8 ((vein* or ven*) near thromb*):TI,AB,KY 8228 #9 (blood near3 clot*):TI,AB,KY 4086 #10 (pulmonary near3 clot*):TI,AB,KY 11 #11 (lung near3 clot*):TI,AB,KY 7 #12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 30819 #13 MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES 66085 #14 malignan*:TI,AB,KY 15050 #15 malignan*:TI,AB,KY 15050 #16 cancer*:TI,AB,KY 109032 #17 (carcinoma* or adenocarcinoma*):TI,AB,KY 34396 #18 tumour* or tumor* 53285 #19 Trousseau 116 #20 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 159584 #21 MESH DESCRIPTOR Mass Screening EXPLODE ALL TREES 3452 #22 MESH DESCRIPTOR Early Diagnosis EXPLODE ALL TREES 1383 #23 screen*:TI,AB,KY 37148 #24 diagnos*:TI,AB,KY 155907 #25 assess*:TI,AB,KY 345626 #26 investigat*:TI,AB,KY 191309 #27 test:TI,AB,KY 164229 #28 testing:TI,AB,KY 36477 #29 #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 627438 #30 #12 AND #20 AND #29 3087 #31 01/01/2017 TO 11/07/2018:CD 297578 #32 #30 AND #31 988	
Clinicaltrials.gov	screening and thrombosis | Neoplasms | Start date on or after 01/01/2017 | Last update posted on or before 07/11/2018	April 2019: 0 May 2021: 9
ICTRP Search Portal	screen* and thromb* AND (cancer OR neoplas*)	April 2019: 0

(Continued)

		May 2021: 3
MEDLINE	1 THROMBOSIS/ 65754	April 2019: 436
	2 THROMBOEMBOLISM/ 22598	May 2021: 910
	3 Venous Thromboembolism/ 8353	
	4 exp Venous Thrombosis/ 51491	
	5 (thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).ti,ab. 300204	
	6 exp Pulmonary Embolism/ 36266	
	7 (PE or DVT or VTE).ti,ab. 47179	
	8 ((vein* or ven*) adj thromb*).ti,ab. 61230	
	9 (blood adj3 clot*).ti,ab. 10069	
	10 (pulmonary adj3 clot*).ti,ab. 189	
	11 (lung adj3 clot*).ti,ab. 48	
	12 or/1-11 388932	
	13 exp NEOPLASMS/ 3057674	
	14 malignan*.ti,ab. 512186	
	15 neoplas*.ti,ab. 240131	
	16 cancer*.ti,ab. 1517621	
	17 (carcinoma* or adenocarcinoma*).ti,ab. 677364	
	18 (tumour* or tumor*).ti,ab. 1502982	
	19 Trousseau.ti,ab. 313	
	20 or/13-19 3885141	
	21 exp Mass Screening/ 116649	
	22 exp Early Diagnosis/ 40905	
	23 screen*.ti,ab. 641466	
	24 diagnos*.ti,ab. 2165172	
	25 assess*.ti,ab. 2516167	
	26 investigat*.ti,ab. 3065445	
	27 test.ti,ab. 1289871	
	28 testing.ti,ab. 471233	
	29 or/21-28 7959109	
	30 12 and 20 and 29 25950	
	31 randomized controlled trial.pt. 463720	
	32 controlled clinical trial.pt. 92491	

(Continued)

	33 randomized.ab. 415764	
	34 placebo.ab. 190130	
	35 drug therapy.fs. 2028849	
	36 randomly.ab. 293491	
	37 trial.ab. 432571	
	38 groups.ab. 1811637	
	39 or/31-37 2880739	
	40 exp animals/ not humans.sh. 4472147	
	41 39 not 40 2578287	
	42 30 and 41 5263	
	43 (2017* or 2018*).ed. 1443224	
	44 42 and 43 549	
	45 from 44 keep 1-549 54	
Embase	1 thrombosis/ 124873	April 2019: 2446
	2 thromboembolism/ 64224	May 2021: 3595
	3 venous thromboembolism/ 31164	
	4 exp vein thrombosis/ 118502	
	5 (thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).ti,ab. 432307	
	6 exp lung embolism/ 84483	
	7 (PE or DVT or VTE).ti,ab. 75463	
	8 ((vein* or ven*) adj thromb*).ti,ab. 91606	
	9 (blood adj3 clot*).ti,ab. 13282	
	10 (pulmonary adj3 clot*).ti,ab. 289	
	11 (lung adj3 clot*).ti,ab. 75	
	12 or/1-11 615807	
	13 exp neoplasm/ 4123701	
	14 malignan*.ti,ab. 709885	
	15 neoplas*.ti,ab. 315603	
	16 cancer*.ti,ab. 2121608	
	17 (carcinoma* or adenocarcinoma*).ti,ab. 902868	
	18 (tumour* or tumor*).ti,ab. 2002209	
	19 Trousseau.ti,ab. 492	
	20 or/13-19 5009281	

(Continued)

21 12 and 20 121984

22 exp mass screening/ 214485

23 exp early diagnosis/ 94736

24 screen*.ti,ab. 885407

25 diagnos*.ti,ab. 3075877

26 assess*.ti,ab. 3532058

27 investigat*.ti,ab. 3881465

28 test.ti,ab. 1807591

29 testing.ti,ab. 653679

30 or/22-29 10515417

31 21 and 30 59125

32 randomized controlled trial/ 509418

33 controlled clinical trial/ 460076

34 random$.ti,ab. 1318239

35 randomization/ 78687

36 intermethod comparison/ 236961

37 placebo.ti,ab. 274806

38 (compare or compared or comparison).ti. 471921

39 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 1766840

40 (open adj label).ti,ab. 64885

41 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 210042

42 double blind procedure/ 151638

43 parallel group$1.ti,ab. 21941

44 (crossover or cross over).ti,ab. 93462

45 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. 284838

46 (controlled adj7 (study or design or trial)).ti,ab. 296995

47 (volunteer or volunteers).ti,ab. 225436

48 trial.ti. 252721

49 or/32-48 3971781

50 31 and 49 14132

51 (2017* or 2018*).em. 3704407

52 50 and 51 3042

(Continued)

	53 from 52 keep 3001-3042 42	
CINAHL	S45 S43 AND S44 64 S44 EM 2017 OR EM 2018 375,192 S43 S29 AND S42 1,031 S42 S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 342,779 S41 MH "Random Assignment" 38,773http://web.b.ebscohost.com/Legacy/Views/UserControls/Ehost/ S40 MH "Single-Blind Studies" or MH "Double-Blind Studies" or MH "Triple-Blind Studies" 32,756 S39 MH "Crossover Design" 11,217 S38 MH "Factorial Design" 920 S37 MH "Placebos" 8,357 S36 MH "Clinical Trials" 93,009 S35 TX "multi-centre study" OR "multi-center study" OR "multicentre study" OR "multicenter study" OR "multi-site study" 4,493 S34 TX crossover OR "cross-over" 14,582 S33 AB placebo* 28,376 S32 TX random* 219,464 S31 TX trial* 250,950 S30 TX "latin square" 142 S29 S12 AND S20 AND S28 4,143 S28 S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 1,385,201 S27 TX testing 80,806 S26 TX test 534,812 S25 TX investigat* 247,601 S24 TX assess* 571,672 S23 TX diagnos* 564,639 S22 TX screen* 112,837 S21 (MH "Early Diagnosis+") 5,934 S20 S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 360,362 S19 TX Trousseau 334 S18 TX tumour* or tumor* 67,488 S17 TX carcinoma* or adenocarcinoma* 38,313 S16 TX cancer* 244,456 S15 TX neoplas* 211,854	April 2019: 140 May 2021: 309

(Continued)

	S14 TX malignan* 25,785 S13 (MH "Neoplasms+") 245,346 S12 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 44,954 S11 TX lung n3 clot* 22 S10 TX pulmonary n3 clot* 29 S9 TX blood n3 clot* 913 S8 TX (vein* or ven*) N thromb* 121 S7 TX PE or DVT or VTE 11,031 S6 (MH "Pulmonary Embolism") 4,771http://web.b.ebscohost.com/Legacy/Views/UserControls/Ehost/ S5 TX thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol* 36,269 S4 (MH "Venous Thrombosis+") 6,363 S3 (MH "Venous Thromboembolism") 3,091 S2 (MH "Thromboembolism") 3,239 S1 (MH "Thrombosis") 4,638	
AMED	1 thrombosis/ 199 2 thromboembolism/ 72 3 (thrombus* or thrombotic* or thrombolic* or thromboemboli* or thrombos* or embol*).ti,ab. 640 4 (PE or DVT or VTE).ti,ab. 245 5 ((vein* or ven*) adj thromb*).ti,ab. 310 6 (blood adj3 clot*).ti,ab. 34 7 (pulmonary adj3 clot*).ti,ab. 0 8 (lung adj3 clot*).ti,ab. 0 9 or/1-8 866 10 exp Neoplasms/ 14356 11 malignan*.ti,ab. 1398 12 neoplas*.ti,ab. 359 13 cancer*.ti,ab. 12116 14 (carcinoma* or adenocarcinoma*).ti,ab. 1443 15 (tumour* or tumor*).ti,ab. 3725 16 or/10-15 19252 17 9 and 16 119 18 exp Mass screening/ 642	April 2019: 0 May 2021: 1

(Continued)

19 screen*.ti,ab. 4769	
20 diagnos*.ti,ab. 15264	
21 assess*.ti,ab. 38696	
22 investigat*.ti,ab. 26974	
23 test.ti,ab. 18151	
24 testing.ti,ab. 6475	
25 or/18-24 82460	
26 17 and 25 45	
27 exp CLINICAL TRIALS/ 3749	
28 RANDOM ALLOCATION/ 314	
29 DOUBLE BLIND METHOD/ 657	
30 Clinical trial.pt. 1211	
31 (clinic* adj trial*).tw. 5381	
32 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw. 2833	
33 PLACEBOS/ 586	
34 placebo*.tw. 3102	
35 random*.tw. 17520	
36 PROSPECTIVE STUDIES/ 1097	
37 or/27-36 22515	
38 26 and 37 3	
39 ("2017" or "2018").yr. 2075	
40 38 and 39 0	
TOTAL before de-duplication	9463
TOTAL after de-duplication	7509

Appendix 2. Extensive tests versus tests at the physician's discretion

Extensive tests versus tests at the physician's discretion					
Patient or population: people with unprovoked VTE **Setting:** hospital **Intervention:** extensive tests **Comparison:** tests at physician's discretion					
Outcomes	**Anticipated absolute effects* (95% CI)**	**Relative effect (95% CI)**	**No of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**

(Continued)

	Risk with tests at physician's discretion	Risk with extensive tests				
Characteristics of diagnosed cancer: type of cancer - lung	Study population		OR 2.08 (0.19 to 23.34)	201 (1 RCT)	⊕⊕⊖⊖ **Low** [1]	-
	10 per 1000	20 per 1000 (2 to 188)				
Characteristics of diagnosed cancer: type of cancer - bladder	Study population		OR 2.08 (0.19 to 23.34)	201 (1 RCT)	⊕⊕⊖⊖ **Low** [1]	-
	10 per 1000	20 per 1000 (2 to 188)				
Characteristics of diagnosed cancer: type of cancer - stomach	Study population		OR 1.03 (0.06 to 16.71)	201 (1 RCT)	⊕⊕⊖⊖ **Low** [1]	-
	10 per 1000	10 per 1000 (1 to 142)				
Characteristics of diagnosed cancer: type of cancer - kidney	Study population		OR 3.12 (0.13 to 77.55)	201 (1 RCT)	⊕⊕⊖⊖ **Low** [1]	-
	0 per 1000	0 per 1000 (0 to 0)				
Characteristics of diagnosed cancer: type of cancer - adrenal gland	Study population		OR 3.12 (0.13 to 77.55)	201 (1 RCT)	⊕⊕⊖⊖ **Low** [1]	-
	0 per 1000	0 per 1000 (0 to 0)				
Characteristics of diagnosed cancer: type of cancer - liver	Study population		OR 3.12 (0.13 to 77.55)	201 (1 RCT)	⊕⊕⊖⊖ **Low** [1]	-
	0 per 1000	0 per 1000 (0 to 0)				
Characteristics of diagnosed cancer: type of cancer - uterus	Study population		OR 3.12 (0.13 to 77.55)	201 (1 RCT)	⊕⊕⊖⊖ **Low** [1]	-
	0 per 1000	0 per 1000 (0 to 0)				
Characteristics of diagnosed cancer: type of cancer - breast	Study population		OR 1.03 (0.06 to 16.71)	201 (1 RCT)	⊕⊕⊖⊖ **Low** [1]	-
	10 per 1000	10 per 1000 (1 to 142)				
Characteristics of diagnosed cancer: type of cancer - ovary	Study population		OR 3.12 (0.13 to 77.55)	201 (1 RCT)	⊕⊕⊖⊖ **Low** [1]	-
	0 per 1000	0 per 1000 (0 to 0)				
Characteristics of diagnosed cancer: type of cancer - colon	Study population		OR 0.51 (0.05 to 5.72)	201 (1 RCT)	⊕⊕⊖⊖ **Low** [1]	-
	20 per 1000	10 per 1000 (1 to 103)				
	Study population		OR 0.51 (0.05 to 5.72)	201 (1 RCT)	⊕⊕⊖⊖ **Low** [1]	-

(Continued)

Characteristics of diagnosed cancer: type of cancer - prostate	20 per 1000	10 per 1000 (1 to 103)				
Characteristics of diagnosed cancer: type of cancer - pancreas	Study population		OR 0.20 (0.01 to 4.26)	201 (1 RCT)	⊕⊕⊖⊖ **Low** [1]	-
	20 per 1000	4 per 1000 (0 to 79)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **RCT:** randomised controlled trial; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate, the true effect is likely to be substantially different from the estimate of effect.

[1] Certainty of evidence downgraded for imprecision due to low number of events. Downgraded further as risk of bias high in study by Piccioli 2004b. Study terminated early after inclusion of only 201 participants after 5 years for several reasons. First, only five of more than 40 potential participating centres could contribute participants to study. Second, some medical ethics committees rejected the protocol because of absence of screening for occult cancer in the control group, other centres could not start because the proposed extensive screening was judged unethical. Finally, identification of cancer at an apparent early stage in extensive screening group led to an increasing tendency among physicians in participating hospitals to initiate screening for cancer in control participants.

Appendix 3. Standard testing plus PET/CT scanning versus standard testing alone

Standard testing plus PET/CT scanning versus standard testing alone

Patient or population: people with unprovoked VTE
Setting: hospital
Intervention: standard testing + PET/CT scanning
Comparison: standard testing alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard testing alone	Risk with standard testing + PET/CT scanning				
Characteristics of diagnosed cancer: type of cancer - acute leukaemia	Study population		OR 1.62 (0.20 to 13.22)	1248 (2 RCTs)	⊕⊕⊖⊖ **Low** [1,2]	-
	2 per 1000	3 per 1000 (0 to 21)				
Characteristics of diagnosed cancer: type of cancer - gynaecological	Study population		OR 2.39 (0.43 to 13.36)	1248 (2 RCTs)	⊕⊕⊖⊖ **Low** [1,2]	-
	3 per 1000	8 per 1000				

(Continued)

		(1 to 41)			
Characteristics of diagnosed cancer: type of cancer - skin: melanoma	Study population 2 per 1000	2 per 1000 (0 to 37)	OR 1.02 (0.06 to 16.34)	854 (1 RCT)	⊕⊕⊕⊖ **Moderate** [2]	-
Characteristics of diagnosed cancer: type of cancer - colorectal	Study population 8 per 1000	3 per 1000 (1 to 19)	OR 0.43 (0.08 to 2.40)	1248 (2 RCTs)	⊕⊕⊖⊖ **Low** [1,2]	-
Characteristics of diagnosed cancer: type of cancer - prostate	Study population 3 per 1000	8 per 1000 (2 to 40)	OR 2.52 (0.48 to 13.12)	1248 (2 RCTs)	⊕⊕⊖⊖ **Low** [1,2]	-
Characteristics of diagnosed cancer: type of cancer - pancreatic	Study population 0 per 1000	0 per 1000 (0 to 0)	OR 4.81 (0.55 to 42.48)	1248 (2 RCTs)	⊕⊕⊖⊖ **Low** [1,2]	-
Characteristics of diagnosed cancer: type of cancer - cholangiocarcinoma	Study population 5 per 1000	2 per 1000 (0 to 26)	OR 0.51 (0.05 to 5.63)	854 (1 RCT)	⊕⊕⊕⊖ **Moderate** [2]	-
Characteristics of diagnosed cancer: type of cancer - lymphoma	Study population 5 per 1000	4 per 1000 (0 to 27)	OR 0.74 (0.09 to 5.83)	1248 (2 RCTs)	⊕⊕⊖⊖ **Low** [1,2]	-
Characteristics of diagnosed cancer: type of cancer - breast	Study population 5 per 1000	1 per 1000 (0 to 19)	OR 0.20 (0.01 to 4.24)	854 (1 RCT)	⊕⊕⊕⊖ **Moderate** [2]	-
Characteristics of diagnosed cancer: type of cancer - urological	Study population 5 per 1000	3 per 1000 (0 to 56)	OR 0.62 (0.03 to 12.32)	1248 (2 RCTs)	⊕⊕⊖⊖ **Low** [1,2]	-
Characteristics of diagnosed cancer: type of cancer - liver	Study population 5 per 1000	2 per 1000 (0 to 40)	OR 0.33 (0.01 to 8.19)	394 (1 RCT)	⊕⊕⊖⊖ **Low** [1,2]	-
Characteristics of diagnosed cancer: type of cancer - head and neck	Study population 0 per 1000	0 per 1000 (0 to 0)	OR 3.02 (0.12 to 74.47)	394 (1 RCT)	⊕⊕⊖⊖ **Low** [1,2]	-
Characteristics of diagnosed cancer: type of cancer - lung	Study population 0 per 1000	0 per 1000 (0 to 0)	OR 3.02 (0.12 to 74.47)	394 (1 RCT)	⊕⊕⊖⊖ **Low** [1,2]	-

(Continued)

Characteristics of diagnosed cancer: type of cancer - unknown primary	Study population		OR 0.34 (0.01 to 8.34)	854 (1 RCT)	⊕⊕⊕⊖ **Moderate** [2]	-
	5 per 1000	8 per 1000 (1 to 41)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **PET/CT:** positron emission tomography/computed tomography;**RCT:** randomised controlled trial; **VTE:** venous thromboembolism.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1] Certainty of evidence downgraded as risk of detection bias high for one study as outcome assessors not blinded to treatment (Robin 2016).
[2] Certainty of evidence downgraded for imprecision due to low number of events.

WHAT'S NEW

Date	Event	Description
16 September 2021	New search has been performed	New search run. No new included studies. One new excluded study. Two new ongoing studies identified. Additional references to previously included studies added
16 September 2021	New citation required but conclusions have not changed	New search run. No new included studies. One new excluded study. Two new ongoing studies identified. Additional references to previously included studies added. No change to conclusions.

HISTORY

Protocol first published: Issue 11, 2013
Review first published: Issue 2, 2015

Date	Event	Description
11 July 2018	New search has been performed	Search updated. No new studies included or excluded.
11 July 2018	New citation required but conclusions have not changed	Search updated. No new studies included or excluded. Additional references to previously included studies added. No change to conclusions.
6 November 2017	Amended	Error in assumed control risk for outcome cancer-related mortality in Summary of findings table 'Extensive tests versus tests at the physician's discretion' corrected and inconsistencies be-

Date	Event	Description
		tween quality of evidence reported in text and Summary of findings table corrected.
20 July 2017	New search has been performed	Searches rerun, two new included studies added
20 July 2017	New citation required but conclusions have not changed	Searches rerun, two new included studies added, Summary of Findings table added. No change to conclusions

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.
CB: assessed studies for inclusion, revised text for update.
SEY: selected studies for inclusion, assessed the quality of the studies and carried out data extraction.
GS: provided clinical input into the review.

DECLARATIONS OF INTEREST

LR: none known.
CB: none known. As CB is based within Cochrane Vascular, editorial tasks for this review update were carried out by other members of the Cochrane Vascular editorial team.
SEY: none known.
GS: none known.

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- No sources of support provided

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2018 version

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

INDEX TERMS

Medical Subject Headings (MeSH)

Cause of Death; Early Detection of Cancer; Neoplasms [*complications] [*diagnosis] [diagnostic imaging] [mortality]; Positron Emission Tomography Computed Tomography; Pulmonary Embolism [diagnostic imaging] [*etiology] [mortality]; Randomized Controlled Trials as Topic; Risk Factors; Venous Thromboembolism [diagnostic imaging] [*etiology] [mortality]; Venous Thrombosis [diagnostic imaging] [*etiology] [mortality]

MeSH check words

Humans