Literature review of unprovoked venous thromboembolism malignancy workup: extensive vs. risk-factor appropriate

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Abstract
Venous thromboembolism (VTE) is a life-threatening condition with known risk factors of venous stasis, vascular injury, and hypercoagulability. One cause of hypercoagulability is malignancy, and patients with unprovoked VTE are at increased risk for an underlying malignancy. The goal of this systematic literature review was to determine the appropriate malignancy workup in patients with unprovoked VTE. PubMed and the Cochrane Database of Systematic Review were searched and articles were assessed for inclusion criteria: meta-analyses, systematic reviews, cohort studies, and randomized control studies which compared extensive and limited screening for cancer in unprovoked VTE. Literature reviews and opinion articles were excluded. Seven articles were selected, including two randomized control studies, one cohort study, two systematic reviews, and two combined systematic reviews and meta-analyses. Studies were critically assessed using the Center for Evidence-Based Medicine's critical appraisal worksheets. Quality of the studies was hindered due to lack of blinding and variability in screening tests. Current research suggested advanced computerized tomography or positron emission tomography did not result in lower-staged cancer at the time of diagnosis or a decreased mortality rate. A detailed history was the most significant test leading to suspicion and ultimate diagnosis of cancer. Based on the findings of this systematic literature review the appropriate malignancy workup is a conservative approach: a detailed history and physical at VTE diagnosis, basic labs, age and gender appropriate cancer screening, and close follow-up for one year. More extensive screening should only be considered for patients with specific risk factors based on smoking and family history.

Introduction

Venous thromboembolism (VTE) in patients is a common disorder managed in internal medicine or family practice settings. It is the clinician's responsibility to monitor and adjust patients' anticoagulation treatment. Furthermore, the precipitating cause of the event must be evaluated. If no known risk factors were present, other reasons would need to be assessed – including coagulation disorders and underlying malignancy. Unless costly genetic testing was performed, testing for coagulation disorders was limited while a patient was on anticoagulation and not indicated unless there was a family history of clotting disorders.

Testing for malignancy can range from an extensive history and physical to full body positron emission testing (PET) or magnetic resonance imaging (MRI). Extensive scans and tests can be costly, result in false positives, and cause harm through increased radiation exposure or procedures. The primary goal of this research was to determine the appropriate malignancy workup for a patient with unprovoked VTE. Whether extensive screening for cancer would improve a patient's outcome was evaluated and compared to limited screening. The indications for computed tomography (CT) or MRI was determined, as well as when they should be avoided to prevent false positive or unnecessary health care costs. Finally, the role of serum cancer markers in screening for malignancy was investigated. While the debate to assess aggressively for malignancy will likely continue as cancer diagnosis and treatment improves, having a clear understanding of the current tests and benefits will allow providers to rapidly adjust as medicine advances.

Background

Venous thromboembolism (VTE) is a serious acute condition commonly seen in emergency departments, consisting of either pulmonary embolism (PE) or deep vein thrombosis (DVT). Undiagnosed VTE can result in heart failure, pulmonary hypertension, and death.[1] The estimated VTE incidence in people with European ancestry is 104 to183 per 100,000 person-years.[2]

The current theory of PE formation involves fragments of a DVT breaking off or dislodging and traveling through the venous system to the heart, where the embolus is pushed into the pulmonary artery and lodged in a smaller vessel in the lungs.[3] As a result, the pressure in the pulmonary arteries is increased and the right side of the heart is placed under strain.[3] Studies of the natural history of PE found eleven percent of patients died within one hour of onset.[1] Of the patients who survived past the first hour who were not accurately diagnosed, thirty percent died.[1] The high mortality of undiagnosed PE makes accurate identification and diagnosis of DVT or PE essential in the clinical setting.

Virchow's Triad consists of three factors known to increase the likelihood of thromboembolism: altered blood flow, vascular injury, and hypercoagulable states.[4] Altered blood flow primarily refers to stagnant or constricted flow, a condition invoked when a patient is sedentary or not moving for extended periods of time. Patients traveling for long periods or immobilized after surgery are at increased risk for VTE. Vascular injury increases the likelihood of VTE formation by promoting the body's immune system to repair the lesion and recruiting clotting factors to the site of injury. While mild injuries do not generally increase likelihood, major surgeries or injuries are associated with increased clot formation. Hypercoagulable states can be inherited or acquired. The most common inherited traits include factor V Leiden mutation, prothrombin G20210A mutation, antithrombin deficiency, protein C deficiency, and protein S deficiency.[4,5] Acquired hypercoagulable states may result from antiphospholipid syndrome, nephrotic syndrome, lupus anticoagulant, antiphospholipid antibodies, paroxysmal

nocturnal hemoglobinuria, or underlying malignancy.[5] The pathology of VTE in occult malignancy depends on the type and extent of underlying malignancy in addition to normal patient risk factors of age, obesity, tobacco use, inherited coagulopathies, pregnancy, and immobilzation.[6] Tumors can release factors increasing coagulopathy, such as cancer procoagulant, tissue factor, and tumor necrosis factor alpha.[6] Other tumors induce increased platelet or leukocyte numbers to increase coagulopathy.[6] Furthermore, patients who are undergoing treatment for malignancy have increased risk of VTE due to chemotherapy, surgical interventions, central venous catheters, and catheter associated infections.[6]

Current guidelines from the American Academy of Family Physicians and the American College of Physicians, as well as the United Kingdom's National Institute for Health and Clinical Excellence (NICE), provide clinical guidance for the assessment for VTE using Well's Criteria for VTE and PE, serum D-dimer, and appropriate imaging modalities.[7,8] Well's Criteria are clinical prediction tools which have been well validated and are regularly applied to calculate an estimated probability of VTE.[7] Well's Criteria for DVT has a sensitivity of seventy-seven to ninety-eight percent and scores a point for each of the following: active cancer, immobilization of lower extremities, bedridden or recent surgery, localized tenderness, calf swelling greater than three centimeters, unilateral pitting edema, visible collateral superficial veins, and unilateral swelling of the entire leg.[8] Two points are subtracted if there is an alternate diagnosis equally as likely, such as cellulitis or lymphedema. Any patient whose final score of one or more is recommended to have duplex ultrasound evaluation of their veins to assess for DVT.[7] The Revised Well's Criteria for PE has a sensitivity of eighty-four percent and scores points for each of the following: prior PE or DVT, tachycardia, recent surgery or immobilization, signs of DVT, hemoptysis, cancer, and alternative diagnosis being less likely.[8,9] Any patient with a total score greater than two is recommended for further imaging for PE.[7] Historically, a ventilation-perfusion (V/Q) scan was the best test for PE, but computed tomography pulmonary angiography (CTPA) scanning is more economical and preferred in most cases today.[8]

Well's Criteria directly apply Virchow's Triad but are not all inclusive and not 100 percent sensitive for VTE. Smoking, pregnancy, hormonal supplementation, known hypercoagulable states, and prolonged travel are also associated with increased rates of VTE but not included in Well's Criteria.[5] When a patient's Well's score is low but there are additional factors, such as travel or a known hypercoagulable state, a clinician can assess for VTE using an alternate clinical assessment tool or serum D-dimer testing. Serum D-dimer testing is a cost-effective test which is seventy-five to 100 percent sensitive for VTE.[8] When Well's score is low and serum D-dimer is negative, a clinician can be reasonably confident to rule out VTE.[7] The United Kingdom's National Institute for Health and Clinical Excellence estimates the combination of Revised Well's Criteria and D-dimer may miss zero to 1.33 percent of PE cases, suggesting a combined sensitivity of 98.7 to 100 percent.[8] Unfortunately, D-dimer alone is not specific and can be elevated in a large variety of conditions, including pregnancy and recent trauma. A positive D-dimer is only an indication that further assessment is necessary to rule out VTE. If the Well's Score is low and the D-dimer is positive, guidelines recommend an appropriate imaging test to assess for VTE.[8]

Upon diagnosis of VTE, current recommendation by the American Colleges of Chest Physicians (CHEST) recommend anticoagulant therapy in patients without a significant bleeding risk.[10] In patients without cancer, novel anticoagulants are the preferred therapy, including dabigatran, rivaroxaban, apixaban, or edoxaban for a minimum of three months.[10] If a novel anticoagulant is too expensive or the patient is unable to tolerate them, coumadin is preferred

over low-molecular weight heparin.[10] In contrast, the preferred treatment in patients with cancer is low-molecular weight heparin.[10] This difference is based on evidence-based outcomes of research trials; patients with cancer treated with low molecular weight heparin have fewer instances of recurrent VTE compared to coumadin or a novel anticoagulant.[10] The difference in treatment modalities is one argument for investigation of underlying cancer in patients with an unprovoked VTE.

While diagnosis of VTE is usually made in the emergency department, follow-up is generally carried out in an internal medicine or primary care clinic. If the patient does not have an obvious instigating factor, including recent surgery, prior VTE, extended immobilization, or known cancer, the VTE is considered unprovoked (idiopathic) and further investigation for the cause is indicated.[5] At times, several minor risk factors can be identified to explain the event – including use of hormonal contraceptive, increased age, smoking, and obesity. Other patients have disorders causing increased coagulation, such as Factor V Leiden, prothrombin mutation, or antiphospholipid antibodies. Unfortunately, no clear cause can be identified in up to twenty percent of patients with VTE, resulting in the diagnosis of unprovoked VTE.[4] Of those patients, up to ten percent will be diagnosed with an underlying malignancy within a year.[11]

Given the correlation between VTE and malignancy, the extent of malignancy workup in unprovoked VTE has been debated in medical literature for years. Some researchers argue for limited, age and risk factor appropriate workup for malignancy.[12–15] These recommendations focus on a detailed history, physical, and age appropriate screening including colonoscopy, pap smear (Papanicolaou test), or mammogram screening. Additionally, standard blood tests, including a complete blood count (CBC), comprehensive metabolic panel (CMP), and prostate specific antigen (PSA) are advocated.[12] A CBC may show abnormalities suggesting leukemia or hematologic cancer; an abnormal CMP may show altered liver or renal function suggesting further investigation of those systems, and an elevated PSA may indicate prostate cancer. Other researchers are investigating the benefit of extensive workups, with the addition of positron emission test (PET) or computed tomography (CT) scans to assess for cancerous masses.[16–18]

In addition to PSA as a cancer specific marker, the study of cancer has resulted in a growing number of cancer markers which can be assessed easily, often at a higher financial cost. Other cancer markers include cancer antigen 125 (CA-125) for ovarian cancer, cancer antigen 19-9 (CA19-9) for pancreatic cancer, CA15-3 for breast cancer, squamous-cell antigen for cervical and uterine cancer, β_2-microglobulin for lymphoproliferative cancers, ferritin for splenic and myelocytic cancer, and αFP for liver and germ cell cancers.[19] Carcinoembryonic antigen (CEA) and neuron-specific enolase can be elevated in lung, breast, gastrointestinal, thyroid, and reproductive tumors.[19] Serum protein electrophoresis can identify multiple myeloma or B-cell tumors.[19] These are just a few of a growing number of serum tumor marker tests available for clinicians. While testing for these may be easy, many are expensive, and a negative result is not conclusive. Not all prostate cancer is positive for PSA, and not all ovarian cancer results in elevated CA-125.[19] Therefore, blindly testing for tumor markers can result in a high financial burden without definitive results.

A clinician must assess the patient and order tests which are in the patient's best interest. Many patients will want aggressive scanning and testing, but there is no clear benefit unless earlier diagnosis can be made and mortality is reduced. A responsible clinician will use research-based evidence to guide the workup. If aggressive testing does not allow earlier diagnosis or decreased mortality, it may not be in the best interest of the patient. A clinician

needs a clear understanding of the benefit of these tests to provide responsible care for their patients.

The purpose of this research was to determine the appropriate cancer workup in a patient with unprovoked VTE, and what tests should be performed to assess for cancer without exposing a patient to unnecessary costs or procedures. Success of this study can be determined by clear clinical suggestions for testing based on evidence currently in the literature.

Methods

The purpose of this study was to determine the appropriate workup for cancer in unprovoked venous thromboembolism. The PubMed database and the Cochrane Database of Systematic Reviews were searched in May of 2018 using the following search string: ("Venous Thromboembolism" OR "Venous Thrombosis") AND "Early Detection of Cancer" OR ("Mass Screening" AND "Neoplasms"). A PubMed search yielded fifty-eight articles, and Cochrane yielded eight results, with a total of fifty-nine after removal of duplicates. Articles consisted primarily of randomized control studies, meta-analysis, systematic reviews, literature reviews, and expert opinion articles.

The fifty-nine articles identified were assessed for the primary inclusion criteria: systematic reviews, meta-analysis, retrospective studies, cohort studies, and RCT comparing limited and extensive malignancy screening following unprovoked VTE. These types of articles were considered because they included involved comparative analysis using data from multiple patients to develop evidence-based conclusions. They were more likely to result in conclusions which could be applied to larger populations and was less prone to bias. Abstracts and articles were reviewed for primary inclusion criteria, resulting in exclusion of sixteen studies which did not address or did not compare limited and extensive malignancy screening methods. Six articles were excluded because the abstract was not available in English and could not be assessed. Twenty-two articles were excluded because they were commentaries or brief reviews of the literature, resulting in high level of bias depending on the author's field of study.

Of the fifteen remaining articles, two systematic reviews and two combined systematic review and meta-analyses compared screening methods for cancer in unprovoked VTE were chosen for analysis.[11,20–22] One combined systematic review and meta-analysis had a published companion protocol paper which was included for analysis.[21,23] Eight of the remaining studies assessed were randomized control studies or retrospective studies. Two studies were excluded because the methods were not detailed enough for analysis. Two studies were chosen for analysis because they were landmark studies on this topic, cited repeatedly in the literature.[24,25] This allowed an analytical assessment of the major studies used as a basis for a large number of smaller studies and literature reviews. A final retrospective study was chosen because it assessed utilization of d-dimer values to determine which patients should have extensive screening.[26] This article is important because extensive testing is extremely expensive and exposing every patient to an extensive workup may be more harmful than not. Identifying and screening only higher risk patients for occult malignancy would allow both ethical and fiscally responsible practice of medicine. A total of seven articles were selected for the final review, consisting of: two combined systematic review/meta-analyses, two systematic reviews, two randomized control trials, and one retrospective study. Articles were critically appraised utilizing the Center for Evidence-Based Medicine's critical appraisal worksheets and conclusions were compiled from the results.

Review of the Literature

"Extensive screening for occult malignant disease in idiopathic venous thromboembolism: a prospective randomized clinical trial" was published in 2004 by Piccioli, Lensing, Prins et al. and the SOMIT investigator group.[24] The SOMIT trial was a multi-center randomized control trial comparing screening strategies for undiagnosed cancer in patients with unprovoked venous thromboembolism (VTE). VTE was considered unprovoked if there was no trauma, immobilization, or surgical procedure within six months of the event. Additional criteria included no thrombocytosis, personal or family history of VTE, known coagulopathy, estrogen use, or recent pregnancy or childbirth. Coagulopathies excluded from unprovoked VTE included antithrombin deficiency, lupus anticoagulant, or protein C or S deficiencies. All patients with unprovoked VTE were screened for underlying cancer using history, physical, CBC, Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), calcium, urinalysis, and chest x-ray.

Patients with unprovoked VTE and no identifiable signs of cancer were enrolled in the study, resulting in 201 participants. Randomization utilizing the Zelen design resulted in 102 patients allocated to the control group and ninety-nine patients allocated to the extensive screening group. The control group was allocated to receive no additional screening but twenty-three patients in the control group received additional screening tests resulting in zero malignancy diagnoses. Additional screening tests included abdominopelvic ultrasound, abdominopelvic CT, gastroscopy, barium swallow, colonoscopy, sigmoidoscopy, rectoscopy with barium enema, CEA, α-FP, CA125, fecal hemoccult, Pap smear, transabdominal prostate ultrasound, or PSA.

Patients in the extensive screening group were offered abdominopelvic ultrasound and CT, upper endoscopy or barium swallow, colonoscopy or sigmoidoscopy with barium enema. Laboratory tests included fecal hemoccult, sputum cytology, and serum tumor markers CEA, α-fetoprotein and CA125. Women were offered mammography and Pap smear while men were offered transabdominal ultrasound of the prostate and serum PSA. While colon cancer screening was deferred in twenty patients, eighty percent of the extensive group underwent a complete gender appropriate extensive work-up. Extensive screening resulted in thirteen cancer diagnoses, ten of which could be identified by abdominopelvic CT alone or the combination of abdominopelvic ultrasound and cancer marker screening.

Patients were followed for two years after VTE, with standardized screening performed at three, twelve, and twenty-four months. During this time period, malignancy was identified in one patient from the extensive screening group and ten patients from the control group, a difference of 8.8% (95% CI 0.8-19.1, p-value <0.01). Sensitivity of initial extensive screening for cancer was 93% (95% CI 66-100). Cancer staging found stage T1 or T2 in nine of fourteen patients from the extensive group and eight of ten patients from the control group, resulting in a p-value of 0.047 after comparison. Time to diagnosis was 11.6 months in the control group and 1.0 month in the extensive group; comparison of the two times resulted in a p-value of less than 0.001. Overall, two extensive group and four control group patients died from cancer-related mortality, an absolute difference of 1.9% (95% CI -5.5-10.9), p-value not reported.

"Screening for occult cancer in unprovoked venous thromboembolism" was published in 2015 by Carrier, Lazo-Langner, Shivakumar, Tagalakis, Zarychanski, Solymoss et al. and the SOME investigators group.[25] The SOME trial was a multicenter open-label RCT that compared limited and extensive screening for occult cancer in patients with unprovoked VTE. Selection following referral to thrombosis clinics for VTE resulted in 3186 prospective candidates. VTE was considered unprovoked if patients did not have known cancer, thrombophilia, prior VTE, or

immobilization or major surgery in the prior three months. Exclusion criteria included study refusal, age below eighteen years, claustrophobia, obesity, ulcerative colitis, glaucoma, or impaired kidney function. A total of 856 patients were randomized and included in the trial. Patients were grouped by age, above and below fifty years, prior to randomization due to differences in the rate of cancer, with randomization occurring within twenty-one days of VTE. In the course of the study, thirteen patients were lost to follow-up, eleven died, and eight withdrew consent prior to the completion. Limited screening of 423 patients included a history, physical, CBC, electrolytes, creatinine, LFT, chest x-ray. Age appropriate gender-specific tests of PSA, DRE, mammography, and pap smear were included if they had not been performed in the prior year. The extensive screening strategy assigned to 431 patients also included an abdominopelvic CT.

Patients in which no cancer was found at baseline were followed for one year for newly diagnosed cancer. Cancer incidence at one-year was 3.2% (95% CI 1.9-5.4) in the limited group and 4.5% (95% CI 2.9-6.9) in the extensive group, resulting in a p-value of 0.28. Of the 423 limited screening patients, ten occult cancers were diagnosed during baseline screening and four during the follow-up period. Of the 431 extensive screening patients, fourteen occult cancers were diagnosed during baseline screening and five during the follow-up period. Limited screening methods missed 29% (95% CI 8-58) of occult cancers and extensive screening missed 26% (95%C CI 9-51) of occult cancers. The average time from VTE to cancer diagnosis was 4.2 months in limited group and 4.0 months in the extensive group; comparison of these two groups resulted in a p-value of 0.88.

Secondary outcomes included the rate of recurrent VTE, overall mortality, cancer-related mortality, and early diagnosis of cancer. Recurrent VTE occurred at a rate of 3.3% in the limited group and 3.4% in the extensive group, with a p-value of 1.0 upon comparison. Overall mortality was 1.4% in the limited group and 1.2% in the extensive group, with a p-value of 1.0 upon comparison. Cancer related mortality was 1.4% in the limited group and 0.9% in the extensive group, with a p-value of 0.75 upon comparison. Early stage cancers were detected at a rate of 0.23% in the limited group and 0.71% in the extensive group, with a p-value of 0.37 upon comparison.

"Systemic Review: The Trousseau Syndrome Revisited: Should We Screen Extensively for Cancer in Patients with Venous Thromboembolism?" was published in 2008 by Carrier, Le Gal, Wells, Fergusson, Ramsay, Rodger.[11] The study attempted to determine the cancer incidence in patients with VTE and whether a cancer workup is indicated in idiopathic VTE. The study consisted of a systematic analysis of thirty-four studies, including retrospective cohorts, prospective cohorts, and randomized control trials.

Determination of cancer incidence utilized all thirty-four studies and 9516 patients with VTE, of which 3286 were considered unprovoked VTE and 2993 were considered provoked VTE. The remaining 3297 patients were not classified as either provoked or unprovoked, instead listed as 'unspecified' VTE. The study assessed the prevalence of previously undiagnosed cancer at time periods after VTE diagnosis, one month, two to six months, and seven to twelve months. Pooled analysis found an occult cancer prevalence of 10.0% (95% CI 8.6-11.3) at twelve months in patients with unprovoked VTE diagnosis and 2.6% (95% CI 2.6-3.6) in patients with provoked VTE diagnosis.

Having determined there was an increased incidence of cancer in unprovoked VTE, Carrier et al. narrowed the study's focus to the fifteen studies that directly compared limited screening and extensive screening. Limited screening included a detailed history, physical, and

lab work. Ten of the fifteen studies included a chest x-ray in the limited workup. Lab work was listed but not clearly defined in five of the articles. Of the ten remaining articles, all ten utilized a CBC, eight utilized liver function tests, seven utilized serum protein electrophoresis, six utilized erythrocyte sedimentation rate, four utilized urinalysis, three utilized lactate dehydrogenase, three utilized creatinine, and two utilized a blood smear. Tests included in only one study include unspecified electrolytes, calcium, fibrinogen, ferritin, iron, uric acid, antinuclear antibodies, unspecified hemostasis factors, cholesterol, and C reactive protein. Extensive screening included the limited screening tests with additional diagnostic screening. Abdominopelvic ultrasound was used in ten studies, while abdominopelvic CT was used in only six studies. Three studies included upper gastrointestinal endoscopy and one included colonoscopy, pap smear, and mammography. One study assessed only cancer markers, with no additional imaging in the extensive screening group. That study included CEA, CA19-9, squamous-cell antigen, neuron-specific enolase, CA15-3, CA125, αFP, PSA, β_2-microglobulin. Carcinoembryonic antigen was tested in six studies, PSA in four studies, αFP in two studies, and CA125 in two studies. One-hundred and ninety of the 1877 patients with unprovoked VTE had cancer diagnoses after twelve months. Of these, ninety-three cases were identified from the limited screening group and forty-one cases were identified from the extensive screening group. During the twelve months following initial VTE diagnosis and screening, an additional fifty-six patients were diagnosed with cancer. The screening allocation of these fifty-six patients whose cancer was missed on the initial limited or extensive screening was not indicated.

To compare the benefit of limited and extensive screening, Carrier et al. pooled data by abdominopelvic CT, abdominopelvic ultrasound, CEA, and PSA. Studies that used abdominopelvic CT in extensive screening found more cases of cancer at baseline compared to limited screening; extensive screening found 69.7% (95% CI 61.1-77.8) of cancer cases compared to 49.4% (95% CI 40.2-58.5) with limited screening. Studies which used abdominal/pelvic ultrasound, CEA, or PSA resulted in a higher proportion of cancer diagnosis among the extensive screening, but the confidence intervals overlapped with limited screening. Abdominopelvic ultrasound found 54.2% (95% CI 45.5-62.9) of cancer cases in limited screening and 63.5% (95% CI 54.9-72.1) of cancer cases in extensive screening; CEA found 66.7% (95% CI 28.9-100) of cancer cases in limited screening and 66.1% (95% CI 59.0-73.2) of cancer cases in extensive screening, and PSA found 51.0% (95% CI 40.0-62.0) of cancer cases in limited screening and 60.6% (95% CI 49.6-71.7) of cancer cases in extensive screening. Of the extensive tests assessed, the authors concluded the abdominopelvic CT had the highest benefit for diagnosis of undetected cancer when used in conjunction with a detailed history, physical, and basic labs.

"Screening for occult cancer in patients with unprovoked venous thromboembolism" was published by van Es, Gall, and Otten et al. in 2017.[21] The study was a combined systematic review and individual patient data meta-analysis of ten studies. It sought to address several research questions surrounding occult cancer workup in unprovoked VTE, with a goal to provide clinicians with a clear understanding of the cancer risk and useful screening tools for unprovoked VTE. The authors published a companion article, "Screening for cancer in patients with unprovoked venous thromboembolism: protocol for a systematic review and individual patient data meta-analysis," in *BMJ Open*, which described in detail the protocol used to address those questions.[23] Information from both articles are included in the following review and analysis. The inclusion criteria required studies which followed patients for at least twelve months after diagnosis of unprovoked VTE and clearly defined strategies for cancer workup. Studies with

patient enrollment prior to cancer screening were used in primary analysis while those with patient enrollment after initial negative cancer screening were utilized for secondary analysis.

Limited screening included history, physical, variable lab work, and age/gender appropriate screening tests. Lab work included CBC in six studies, liver function tests in four studies, LDH and creatinine in three studies, ESR and calcium in two studies, urinalysis and CRP in one, and unspecified blood work in one study. Gender specific pap smears and PSA were included in three studies' limited screening. Mammograms varied; three studies considered them limited, and two studies considered them extensive. Extensive screening included the limited screening tests with the addition of imaging. Four studies used abdominopelvic CT, three used full body PET/CT scans, and one used chest CT. Fecal occult blood test was included in one study under extensive screening. Two studies included additional tumor markers in the extensive screening; CEA and CA 125 were included in two studies, while CA19-9, CA15-3, and αFP were only included in one study.

Utilizing the seven studies that enrolled a total of 2001 patients prior to screening, cancer diagnoses in 101 patients within twelve months after unprovoked VTE resulted in cancer prevalence of 5.2% (95% CI 4.1-6.5) at one year post unprovoked VTE diagnosis. Of these 101 patients, seventy-one were diagnosed in the initial screening period, a cancer prevalence of 3.5% (95% CI 2.8-4.5) within one month of VTE diagnosis. The remaining thirty patients were diagnosed with cancer in the twelve-month follow-up, a 1.6 % prevalence (95% CI 1.0-2.6). The prevalence of new cancer diagnosis between twelve- and twenty-four-month time points was only 1.0% (95% CI 0.56-1.9). Further subgroup analysis of patients by age found the twelve-month cancer prevalence 6.8% (95% CI 5.6-8.3) in patients fifty or more years old, compared to 1.0% (95% CI 0.5-2.3) in patients below the age of fifty, significantly different with a p-value <0.001. Subgroup analysis based on estrogen use showed a twelve-month cancer prevalence of 1.3% (95% CI 0.3-5.1) with estrogen and 5.8% (95% CI 3.8-8.8) without estrogen use.

Three studies directly compared limited and extensive screening strategies. At the time of VTE diagnosis, limited screening of 885 patients resulted in a cancer prevalence of 2.4% (95% CI 1.6-3.6), twenty-one of 885 patients. An additional four studies were included in the meta-analysis of extensive screening for cancer. This resulted in fifty of 1116 patients diagnosed with cancer at the time of VTE diagnosis, a prevalence of 4.5% (95% CI 3.4-5.9). With data only taken from the three studies directly comparing screening strategies, an adjusted odds ratio of a 2.0 (95% CI 1.2-3.4, P = 0.012) higher probability of cancer diagnosis at baseline with extensive screening. Analysis of cancer types from the fifty diagnosed in the extensive screening, thirty-three of these patients could have diagnosed by a limited screen. Furthermore, a detailed history and physical elucidated enough information to guide focused testing and diagnosis in thirty-two of the seventy-one cancer cases.

Cancer staging within the seven studies which enrolled patients prior to screening found no statically significant difference between limited and extensive screening strategies. Of the seventy-one cancers, only sixty-three were stageable. Sixteen of forty-six cancers found through limited screening were early-stage and eight of seventeen cancers found through extensive screening were considered early-stage. There was no discussion or analysis of the cancer stages of the remaining thirty patients diagnosed in the twelve-month follow-up.

The index tests which led to the suspicion and diagnosis of cancer showed the value of an extensive history; the history provided clear suspicion in twelve of twenty-one cancers in the limited screening group and fourteen of the fifty cancers in the extensive screening group. Other index tests for the twenty-one cancers in the limited screening group included four cases with

CBC, three cases with LFT, three cases with PSA, three cases with chest x-ray, and one case in each of the following: physical exam, CT pulmonary angiography, mammography, and abdominal ultrasound. Other index tests for the fifty cancers in the extensive group included ten cases with abdominopelvic CT, three cases with PSA, four cases with mammography, one case with CT chest, one case with chest x-ray, one case with LFT, one case with compression ultrasonography, and five cases with each of the following: CBC, physical exam, CT pulmonary angiography, and PET/CT.

"Effect of testing for cancer on cancer- and venous thromboembolism (VTE)-related mortality and morbidity in people with unprovoked VTE" was published by Robertson, Yeoh, Stansby, and Agarwal in 2017.[20] The systematic review had a primary goal to determine the morbidity and mortality benefit of cancer workup in idiopathic VTE. Secondary goals included assessments of quality of life, adverse testing affects, timing of cancer diagnosis, and types of cancer. Inclusion criteria consisted of randomized controlled trials or quasi-randomized controlled trials. A total of four studies were used, totaling in 1648 patients with unprovoked VTE and no clinical signs of cancer. Patients in all four studies were allocated to either extensive or limited screening within three months of idiopathic VTE diagnosis. In two studies limited screening consisted of a history, physical, and additional testing by physician discretion. No list of tests was described in the review or the original papers. The other two studies included CBC, CMP, chest x-ray, PSA, mammography, and pap-smear in the limited screening tests. Extensive screening of testing included CT or PET scans of the abdomen/pelvis and chest in all four studies. PSA, mammography, and pap-smear were considered extensive screening in one study.

Data from the two studies comparing extensive and physician directed screening were pooled for further analysis. Out of 197 patients in the extensive testing pool, four patients died of cancer. Out of 199 patients in the physician directed or limited screening, eight patients died of cancer. These results suggested a decreased mortality with extensive screening, with an odds ratio of 0.49 (95% CI 0.15 to 1.67) and a statistically insignificant p-value of 0.26. Cancer stages 3 or 4 were found in extensive screening with an odds ratio of 0.25 (95% CI 0.03-2.28) and a p-value of 0.22.

Data was pooled from the two studies which compared PET/CT scanning to standard testing. The odds ratio for cancer diagnosis with extensive screening was 1.71 (95% CI 0.91-3.20) with a p-value of 0.09 when compared to standard testing. Nine of 628 patients died from the limited screening group and eleven of the 620 patients died from the extensive group with added CT. Calculation of the odds ratio, 1.22 (95% CI 0.49-3.04) suggested no difference in mortality between the groups with a p-value of 0.66. Further analysis found only six of the 620 patients in the extensive screening group died of cancer-related causes, while all eleven deaths in the limited group were cancer-related. Further comparisons of the types of cancer, stages of cancer, and frequency of cancer found no statistically significant difference.

Assessment of time from VTE to cancer diagnosis was not pooled because only two of the studies performed this assessment: one from the group utilizing PET/CT scanning and one from the group utilizing physician discretion. The SOMIT trial found the mean time to cancer diagnosis was 11.6 months with physician discretion, compared to 1.0 month with extensive testing, with a p-value < 0.001.[24] The SOME trial reported the average time from VTE to cancer diagnosis was 4.2 months in standard testing and 4.0 months in the CT group, a p-value of 0.88.[25]

"Screening for occult cancer in idiopathic venous thromboembolism - Systemic review and meta-analysis" was published in 2017 by Klein, Shepshelovich, and Spectre et al.[22] This combined systematic review and meta-analysis compared limited and extensive screening for cancer in idiopathic VTE. The primary outcome was all-cause mortality and secondary outcomes were cancer-related mortality, time to cancer diagnosis, cancer incidence, and staging at the time of diagnosis. A total of five trials with 2287 patients were included, four randomized-control trials and one open-label trial without randomization. Follow-up of patients varied from twelve to thirty months. The limited screening group received variable tests depending on the study, four clearly defined and one allowing any test at the physician discretion except CT. Excluding the study using physician discretion, limited screening included a detailed history, physical, blood tests, and chest x-ray. Blood tests included CBC in four studies, LFT in four studies, calcium in two studies, ALP in three studies, ESR in three studies, CRP in three studies, and electrolytes and creatinine in one study. Age and gender appropriate screening, including PSA, pap smear, mammogram, and colonoscopy were considered extensive screening in one study and limited screening in two studies. Extensive screening included the limited screening tests and abdominopelvic ultrasound in one study, abdominopelvic CT scans in all five studies, chest CT in one study, and full body PET/CT in one study.

Only four of the trials included the primary outcome, leading to an analysis of 2073 patients. Pooled assessment found no significant difference in all-cause mortality, with a relative risk ratio of 0.86 (95% CI 0.58-1.27). Pooled assessment of all five trials resulted in no significant difference in cancer-related mortality, with a relative risk of 0.93 (95% CI 0.54-1.58).

All five trials were analyzed for cancer incidence and diagnosis timing. Initial extensive screening of 1159 patients yielded sixty-six cancer diagnoses with twenty-one diagnosed during the follow-up. Initial limited screening of 1115 patients yielded twenty-nine cancer diagnoses, with thirty-nine diagnosed during the follow-up period. Fewer cancer diagnoses were missed in the initial screening with extensive testing compared to limited testing, a risk ratio of 0.5 (95% CI 0.29-85). Overall incidence of cancer at the end of follow-up was 7.5% of patients in the extensive group and 6.1% in the limited screening group, with a risk ratio of 1.22 (95% CI 0.9-1.65) suggesting no statistical difference in incidence rates.

Cancer staging was not found to be statistically different in the two patient groups, with a risk ratio of 1.49 (95% CI 0.86-2.56). Cancer types were assessed and found to be primarily solid-type tumors: 14% were colorectal cancer (RR 1.57, 95% CI 0.68-3.62), 11.6% were lung cancer (RR 1.13, 95% CI 0.45–2.84), 9.6% were prostate cancer(RR 0.85, 95% CI 0.28–2.53), 7% were gynecologic cancers (RR 0.64, 95% CI 0.23–1.79), and 5.8% were lymphomas (RR 1.19, 95% CI 0.33–4.32). Overall, cancer diagnosis was earlier with extensive screening, but the difference in all-cause mortality, cancer related mortality, overall incidence, and cancer stages was not statistically significant.

"Impact of D-dimer for prediction of incident occult cancer in patients with unprovoked venous thromboembolism" was published in 2016 by Han, ó Hartaigh, Lee, Cho, Shim, and Chang et al.[26] It retrospectively assessed data from patients with unprovoked VTE to determine if D-dimer could be utilized to predict occult cancer. VTE was considered unprovoked if there was no recent pregnancy or surgery, coagulopathy, hormone use, or known cancer. Out of 824 patients with VTE, 169 were classified as unprovoked and were included in the analysis. Patient records were reviewed for a median follow-up of 5.3 years (interquartile range 3.4-6.7), assessing for new cancer diagnosis. Out of 169 patients with unprovoked VTE, twenty-four patients (14.2%) were diagnosed with cancer during the follow-up period. The median time to

cancer diagnosis of 6.5 days (interquartile range 2-14 days) after VTE. Twenty-one of the twenty-four cancer diagnoses were made during the initial VTE hospitalization. Sixteen of the twenty-four patients had metastatic cancer at the time of diagnosis.

Patient records were grouped into those with cancer and those without cancer for further analysis. Groups were compared by age, gender, comorbidity (hypertension, coronary artery disease, diabetes), type of VTE, and D-dimer value. The p-value was greater than the defined threshold of 0.05 for all categories except the D-dimer. D-dimer levels were 2834.7 (± 5287.2) ng/mL for patients without cancer and 5313.9 (± 5533.2) ng/mL for patients with cancer, a p-value of 0.036. Comparison of the log D-dimer resulted in a p-value of 0.009.

D-dimer values were further grouped into three categories: below 2000 ng/mL, from 2000-4000 ng/mL, and greater than 4000 ng/mL. Thirty-two percent of patients with d-dimer >4000 ng/mL had an occult cancer, compared to 13.8% with a D-dimer from 2000-4000 ng/mL, and 9.3% with a D-dimer <2000 ng/mL. Screening for occult cancer in patients with a D-dimer >4000 ng/mL had a sensitivity of 33.3%, specificity of 88.3%, positive predictive value of 32%, and negative predictive value of 88.9%. Cox regression models of the log D-dimer associated values >4000 ng/mL with an occult cancer hazard ration of 4.12 (95% CI 1.54-11.04, p-value 0.005) and a metastatic hazard ratio of 9.55 (95%CI 2.46-37.17, p-value 0.001) when compared to patients with D-dimer values < 2000 ng/mL.

Discussion

"Extensive screening for occult malignant disease in idiopathic venous thromboembolism: a prospective randomized clinical trial" was a multicenter randomized control study to assess extensive and limited screening for occult malignancy in unprovoked VTE.[24] The definition of unprovoked VTE was consistent with most commonly accepted risk factors, specifically excluding the presence of lupus anticoagulant, protein C or S deficiency, and antithrombin deficiency. Both factor V and prothrombin mutations were discovered during the course of the study and the authors appropriately assessed enrolled patients retrospectively. Statistical comparison found these mutations to be 14.1% of extensive-group patients and 18.6% of patients in limited group, a difference considered not statistically significant though no p-value was reported. No statistically significant difference between the groups was found when compared for gender, age, smoking, alcohol, and obesity, though no p-value was reported for these either.

Patients were randomized at a central location using the Zelen design, which only obtained informed consent from the extensive arm patients. Patient in the limited group were not informed of the study and not asked to consent to the study. This study design was deemed unethical by many centers, limiting patient enrollment and numbers. While physicians were not discouraged from assessing for cancer in patients from the limited group, they were aware of cancer diagnoses found in the extensive screening group during the course of the study. Consequently, physicians began ordering more screening tests on patients in the limited group. This progressive increase in screening of the patients allocated to the limited group ultimately lead to study termination after enrollment of only 201 patients. Enrolled patients were followed for twenty-four months with visits at three, twelve, and twenty-four months. All patients received the same history assessing for signs of cancer with a standardized form at each visit, with the physician blinded to the method of initial screening. While this standardized follow-up controlled for bias, physician knowledge of early study results and early termination of the study created a large concern regarding the validity of the study.

Statistical analysis of the results included an intention-to-treat principle, with 95% confidence intervals calculated for the incidence of cancer, sensitivity of screening calculation, and Fisher's Exact test to compare the proportion of early stage cancer. While statistical calculations showed significant difference in the timing and staging of cancer diagnosis, the clinical applicability of the results was limited due to biased assessment and early termination.

"Screening for occult cancer in unprovoked venous thromboembolism" was a randomized control study of patients with first time unprovoked VTE referred to one of nine Canadian centers within twenty-one days of their VTE diagnosis.[25] Lists were generated using random-number tables in permuted blocks of two or four and stratified by center and age (greater than or less than fifty years old). Age stratification was necessary and appropriate since patients at older ages are at higher risk for cancer overall. Patients were assigned using a central Web-based randomization to ensure assignment concealment.

Groups were compared for baseline characteristics of age, gender, race, weight, hypertension, history of MI or stroke, heart failure, prior cancer, prior provoked VTE, current and former smoker, type of VTE, estrogen and antiplatelet use. Statistical analysis found no difference between the groups using a p-value of 0.05, except gender. Limited occult screening group was 64.1% male and extensive group was 70.7% male, considered significantly different at a p-value of 0.045. This is weakly significant but may have skewed the results since men are slightly more likely to get cancer.[27] The US Surveillance, Epidemiology, and End-Results Program (SEER) reported yearly cancer rate of 0.502% for men and 0.4206% for women.[27] Of the 431 patients assigned to the limited screening, four did not receive the assigned intervention. Of the 423 patients assigned to the extensive screening, thirty-five did not receive the assigned intervention. This difference is concerning for bias but was not discussed and cannot be explained medically since patients with poor renal function or claustrophobia were excluded from the study. Furthermore, authors did not distinguish between patients who received their intended screening and those who did not in the evaluation of cancers missed on initial screening. Thirty-five patients did not receive their assigned abdominopelvic CT. If a disproportionate number of these patients had a malignancy diagnosed in follow-up, it would create a faulty interpretation of the rate of missed occult cancers.

After initial screening, patient retention was consistent between the two groups; the limited group lost eight to follow-up, three to withdrawn consent, and six to death. The extensive group lost five to follow-up, five to withdrawn consent, and five to death. Despite central randomization, it was not feasible to blind the clinicians to the initial screening process, creating an opening for bias. Furthermore, it was unclear if clinicians conducting the follow-up screening were blinded, another key component in assessing clinician bias. Patients in each group received a one-year follow-up, with assessment at fixed intervals and a strict checklist protocol to assess for cancer, recurrent VTE, or other illness. Patients with abnormal findings on initial screening or follow-up received additional testing at the discretion of the physician. These tests were not described in the article beyond requiring biopsy confirmation of malignancy or objective confirmation of recurrent VTE. This allowed for the possibility of bias, since the amount of work-up for a subjective complaint, such as 'fatigue,' may vary greatly between clinicians. If a clinician knew a patient was in the limited screening group, the malignancy work-up may have been excessive for a subjective complaint or abnormality.

Statistical analysis of data was performed using an intention-to-treat basis. A two-sided, unadjusted Fisher's Exact test of proportions was used to compare the difference in cancer diagnoses, secondary VTE, and mortality. The Wilson method was utilized to calculate the 95%

confidence intervals. Finally, a Kaplan-Meier test assessed the time to diagnosis of cancer between the two groups. Analysis of occult cancer missed on initial screening resulted in an absolute difference of 0.25%, with a 95% CI -1.12 to 1.63. Using undefined lower confidence interval boundaries, the authors calculated the number needed to screen; ninety-one patients would need to receive an abdominopelvic CT to detect one missed cancer. The authors concluded there was no clinically significant benefit to extensive screening for malignancy with abdominopelvic CT. The validity of this conclusion was potentially biased by gender difference between the groups, patients not receiving the assigned screening, and lack of clear blinding of the clinicians.

"Systemic Review: The Trousseau Syndrome Revisited: Should We Screen Extensively for Cancer in Patients with Venous Thromboembolism?" clearly stated research goals of cancer incidence determination and comparison of limited and extensive malignancy screening in unprovoked VTE.[11] The authors followed a rigorous process to ensure all relevant studies were assessed through clearly defined search terms, search of major databases, and hand-searching of conference proceedings. The results of the search were outlined in a diagram, including number of articles assessed and excluded. It was unlikely that important, relevant studies were missed because the methodology included searches of multiple types of publications.

Articles were considered for inclusion based on use of patients with newly diagnosed venous thromboembolism and a measured incidence of cancer at VTE diagnosis, six months, and twelve months. Each study was assessed independently by two reviewers for inclusion, with a third reviewer to address discrepancies. The validity and quality of the studies were evaluated using Newcastle-Ottawa Quality Assessment, which was designed to examine comparability of nonrandomized studies. The quality assessment was published in a table to demonstrate the selection of study groups, outcome, follow-up length and quality. The validity of the Newcastle-Ottawa scale was not disclosed or discussed. While using a tool to assess data is appropriate, the tool is only appropriate for the use for which it was designed and validated. This review included retrospective cohorts, prospective cohorts, and randomized control trials, which do not all apply to the validated function of the Newcastle-Ottawa scale.

Inclusion criteria required observational or RCT studies including adult patients with newly diagnosed VTE, who were screened for cancer through limited or extensive means. Limited screening included history, physical, basic blood work, and chest x-ray. Extensive screening included abdominal ultrasound or CT and/or serum tumor markers. A clear definition of laboratory tests was neither required nor defined. Five studies generalized laboratory or blood work without defining any specific test. While many specific tests were listed, ten of the fifteen studies had at least one ambiguous laboratory assessment – including urinalysis, hemostasis factors, and electrolytes. The variability of laboratory tests created uncertainty regarding the quality of the original studies. Furthermore, clinical application of the meta-analysis was hindered because clinicians cannot use the data to determine the appropriate testing for patients with unprovoked VTE. Despite poorly defined laboratory testing in the limited screening strategy, extensive screening was clearly defined. Utilization of ultrasound or CT and testing for tumor markers was consistently considered extensive.

Patient enrollment varied greatly between the studies, ranging from forty-eight to 864 and complicating the comparison of homogeneity. Data for homogeneity was not assessed or discussed. Since patient age and exposure to tobacco or carcinogens play a large role in the development of cancer, lack of comparison between the studies limited clinical application.

The ideal workup was not clearly defined, and the sensitivity and specificity of the screening was not assessed due to lack of reported false positives and false negatives. The study did not categorize the original screening method used in the patients who developed cancer during the follow-up period. The allocation of those fifty-six people is essential for the assessment of the value of extensive and limited screening strategies. The authors concluded the abdominopelvic CT was the screening test most likely to identify occult cancer in patients with unprovoked VTE. The value and applicability of their conclusion is hindered by variable definitions of unprovoked VTE, variable workups, and statistical limitations.

"Screening for occult cancer in patients with unprovoked venous thromboembolism" sought to determine the appropriate screening for occult cancer in patients with unprovoked VTE through a combined systematic review and meta-analysis.[21] The purpose of the analysis was to guide clinician's discussion and decision making when a patient presented with unprovoked VTE. Major databases were searched with clearly stated criteria, and results were published in a protocol companion paper in *BMJ Open*.[23] Extensive detail in the protocol companion paper provided transparency to the study and allowed replication of the study. The detailed and expansive protocol makes it unlikely relevant studies were missed.

Inclusion criteria required clearly defined screening strategies, resulting in exclusion of many articles utilized in Carrier et al.[11] This exclusion was appropriate because it allowed pooling of patient data to complete a meta-analysis. In order to properly compare screening strategies, there must be clearly defined boundaries to ensure testing considered extensive in one study were not considered limited in others. While strategies were required to be clearly defined, the extensive screening strategies varied between studies, including either PET, CT, or tumor marker testing - three strategies with different sensitivities for occult cancer. Furthermore, gender-specific mammogram was considered extensive in two studies and limited in three studies. These variations complicated both analysis and interpretation, causing difficulty in clinical application of this study. The authors mitigated this by publishing a table listing the index test which led to cancer suspicion and diagnosis. This table provided a valuable tool for clinician use and determination of the appropriate screening using both data and individual patient risk factors.

Studies published prior to 2000 were excluded due to the evolution of cancer screening tools in this millennium. While setting the date to 2000 was somewhat arbitrary, it was appropriate given the advances in medicine – more tumor marker tests were available, and CT was a regular assessment in the last few decades. Studies that enrolled patients prior to initial cancer screening were used for the primary analysis, and studies that enrolled patients after negative cancer screening were utilized for limited data analysis. This minimized potential selection bias influencing the results of this meta-analysis. Studies were assessed by two independent reviewers and by using both the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool and Newcastle-Ottawa Scale. Using multiple quality assessment tools with similar results increased the validity of the research presented and allows a clinician to apply the data in practice.

Prevalence of cancer at different time points was published using forest plots in the supplemental material and described in the text. Heterogeneity existed when all studies were combined due to variability of enrollment timing before or after initial cancer screening. Separation of data into groups by timing of enrollment resolved heterogeneity and allowed comparison of data within each subgroup. Heterogeneity was further examined and ruled out

within subgroups of women with estrogen use, screening type, and time point. Researchers made conclusions based on groups with no heterogeneity and appropriately avoided comparing different subgroups when heterogeneity existed. All included studies were used to calculate the one-year cancer incidence, but only studies with similar enrollment periods were used to compare screening methods. This separation was appropriate but decreased the number of patients addressing the primary topic of this thesis. Since the heterogeneity was in timing of enrollment and not in the patient population, the data was still clinically applicable.

Prevalence of cancer in the first year of follow-up, at defined time points, and by age and subgroups, was published in the printed article. Additional results were described and published in the supplementary online material. Accessing supplementary material required subscription and online access, presenting potential problems for clinicians utilizing library or print resources. While extensive and complete results were available, they were difficult to access and may not be utilized. A clinically useful table was published in the supplementary material, which listed the indexed screening tests which led to a malignancy diagnosis. Knowing the tests most likely to identify an occult cancer is essential when a clinician attempts to determine the appropriate work up. Overall, this article was applicable and useful for a clinician when determining the appropriate cancer work-up following VTE, despite difficulties in accessing data due to publishing format.

"Effect of testing for cancer on cancer- and venous thromboembolism (VTE)-related mortality and morbidity in people with unprovoked VTE" studied the outcome of cancer screening for patients with unprovoked VTE.[20] The primary outcomes assessed the effect of malignancy testing on all-cause, cancer-related, and VTE-related mortality. The primary outcome was appropriately important for clinical application, since the benefit of extensive work-up must be assessed with clear understanding of the adverse effects and patient outcomes. Authors searched the Cochrane Register of Studies and the Specialized Register created by the Cochrane Vascular Information Specialist, and performed weekly searches of MEDLINE, EMBASE, CINAHL, and AMED. Furthermore, researchers searched multiple databases storing clinical trials and hematology conference proceedings. Utilization of multiple databases minimized the chance important studies were missed, particularly since there was no date or language restriction. Search results and the number of excluded articles were clearly published in a study flow diagram, providing transparency for clinician assessment.

Search criteria was broad and listed in the appendix, including MESH headings. Inclusion criteria was defined as randomized or quazi-randomized trials examining different malignancy testing strategies for patients with unprovoked VTE. Database searches resulted in 623 articles after removal of duplicates, of which 619 were recorded as not relevant, and only four articles were included in the analysis. While search and inclusion criteria may have varied, the authors explained 619 articles as not relevant because they only allowed randomized controlled studies. The quality and risk bias of the four studies was assessed with the Cochrane tool by two independent researchers. The study appropriately identified strong bias in the two studies which used physician discretion to drive screening strategies. Expansion to include cohort or retrospective studies could have provided less biased studies and more data from which interpretations could have been made.

This study concluded the data were not strong enough to declare extensive testing was or was not beneficial. The study asserted more research was needed to determine whether extensive cancer workup would result in decreased mortality in patients. Furthermore, additional

research was required to assess the adverse impacts of testing, VTE related mortality, and quality of life. The clinical application of this review was limited to understanding further research was needed to provide clear and evidence based clinical recommendations or guidelines.

"Screening for occult cancer in idiopathic venous thromboembolism - Systemic review and meta-analysis" examined the efficacy of malignancy screening strategies in patients with unprovoked VTE, with an ultimate goal to define the appropriate clinical workup.[22] Cochrane, PubMed, and conference proceedings for hematological societies were searched using clearly defined search criteria. Search results were published in a flow chart showing 461 search results and methods for narrowing articles down to the final five studies. Researchers included all RCT and prospective trials comparing limited and extensive malignancy screening strategies in patients with unprovoked VTE. Studies were not excluded by publication date or language. This extensive and exhaustive search for relevant articles suggested adequate search of the literature. It was unlikely articles or studies were missed based on reported search criteria.

Two reviewers independently assessed studies for bias using Cochrane Collaboration tool. Each RCT was measured for randomization, blinding, selection bias, selective reporting, and incomplete data using Higgins 2011 method. The single non-randomized study was assessed using the Newcastle Ottawa quality assessment. Researchers appropriately assigned a risk bias for randomization and selection bias in the Piccoli et al study which did not blind clinicians and ended the trial early.[24]

Data were analyzed using forest plots of the risk ratio, calculating chi-squared for heterogeneity, and determining I-squared for inconsistency. Heterogeneity was further assessed by grouping data by age, prior cancer, smoking status, randomization time, comorbidity, and hormone use. Forest plots were published showing overlapping confidence intervals, suggesting no significant difference between the groups. Analysis was complicated by variability in the follow-up between trials, ranging from twelve to thirty months. Results may have been interpreted differently if the follow-up was longer or consistent between studies.

"Impact of D-dimer for prediction of incident occult cancer in patients with unprovoked venous thromboembolism" was a retrospective analysis of patients with VTE, attempting to determine if D-dimer could be used as an occult screening tool in patients with unprovoked VTE.[26] As a retrospective analysis, it was not blinded and researchers knew which patients ultimately had a cancer diagnosis. This allowed research bias and limited the clinical application of this study. Patients were appropriately excluded from the study if the record showed diagnosis of cancer, immobilization, surgery, pregnancy, coagulopathy, or hormone use prior to diagnosis of VTE because these known risk factors would disqualify the classification of unprovoked. The researchers' definition of unprovoked VTE was consistent with other studies and current medical practice. This study was conducted at a single medical center and composed of patients with Korean-Asian ethnicity, which left some doubt regarding the applicability of the findings to a more diverse population.

Patient records were reviewed for diagnosis of cancer after the index VTE event. Patients diagnosed with unprovoked VTE between January 2007 and October 2012 were enrolled in the study and medical records were followed through February 2015. The length of follow-up varied depending on the date of presentation with VTE, with an interquartile range from 3.4-6.7 years. While this variability was concerning, the risk of occult cancer presenting more than one year after unprovoked VTE was 1.1%, so followup for greater than three years should have been sufficient to identify all occult cancers.[21] Of greater concern was the limitation to a single medical center. Many cancer diagnoses may have been missed due to care received at

a different medical center. The researchers did not contact patients to verify the lack of cancer diagnosis in the follow-up period. Therefore, there were possibly patients who were diagnosed with cancer but not recorded as such for this study, an implicit bias.

Statistical analysis included Student's t-test and Pearson's chi square test to compare patient groups. Patients were grouped by presence or absence of a cancer diagnosis, allowing comparison of age, gender, comorbidity, VTE type, and D-dimer. Comparison of comorbidities including hypertension, diabetes mellitus, and coronary artery disease demonstrated no significant difference in these common disease states, which was not unexpected since they do not correlate with increased cancer rates. A multivariable cox regression analysis of the hazard ratios assessed risk of cancer within D-dimer groups, with adjustment for VTE type, age and gender. The adjustments for gender and age were appropriate since the cancer incidence could have varied with both. The adjustment for VTE type was also appropriate since the proportion of patients presenting with DVT and PE varied. Cox regression analysis of D-dimer and log D-dimer calculated a 4.12 hazard ratio for occult cancer in patient with D-dimer greater than 4000, with a p-value 0.005. Despite the study limitations and bias, the p-value was highly significant and clinically applicable. While a clinician may be limited when applying these results to patients with low D-dimer, the index of suspicion for occult cancer should be higher with an extremely elevated D-dimer value.

Conclusion

The purpose of this literature review was to determine the appropriate malignancy workup in patients with unprovoked VTE. The PICO question investigated was: "In patients with unprovoked venous thromboembolism, does an extensive malignancy workup allow earlier diagnosis of cancer compared to a risk-factor appropriate workup?" Articles from PubMed and Cochrane were assessed and critically reviewed to determine the value of various malignancy screening strategies and the ideal assessment in the current medical climate. Seven articles were assessed in full and the resulting conclusions provided clinical guidance. This study did not determine if early diagnosis of cancer would improve prognosis or decrease mortality overall. Nor did it include assessment of the psychological toll a patient may experience with a possible unknown cancer. The study was focused on determining the clinically appropriate workup given the current research.

This review included the major landmark RCT studies which provided the groundwork for many of the reviews cited in the literature, both of which had flaws and bias which hindered their clinical application.[24,25] Piccioli et al. used ethically questionable methods and did not blind clinicians to the early results of extensive testing.[24] As a result, clinicians began performing more extensive testing in the patients from the limited group, leading to ultimate cessation of the trial.[24] The authors concluded the extensive screening missed fewer cases of cancer and advocated for extensive screening.[24] The RCT by Carrier et al. found no statistically significant difference between limited screening and extensive screening, as defined by addition of abdominopelvic CT.[25] It was also was less biased and used a rigorously followed protocol, resulting in higher quality data compared to the Piccioli et al. RCT. While the results of these studies were conflicting, the quality of the Carrier et al. study provided greater support for the conclusion that screening for cancer with an abdominopelvic CT would have provided no clear benefit for patients with unprovoked VTE.

Of the systematic reviews and meta-analysis articles, one concluded significant benefit with an abdominopelvic CT, one found benefit of extensive screening but determined an

extensive history and physical are best, one found extensive screening diagnosed more cancer but had no difference in mortality, and one made no conclusion either way. Of the two major trials, one found extensive screening beneficial and one found no improvement. Clearly, there was no agreement on the benefit of extensive screening. The small benefit seemed to be outweighed by potential harm of false positive and prohibitive costs. In a society with rapidly increasing medical costs, the balance between providing excellent care at an affordable cost was one of the largest struggles. If every patient with unprovoked VTE received a full extensive screening with advanced imaging, the cost of medical care would rise. Furthermore, CT and PET scans exposed patients to large amounts of radiation.

Identifying cost-effective methods for stratifying the cancer risk was one way of managing costs while providing patients at most risk the appropriate workup. Han et al. identified D-dimer as a potentially cost-effective way to stratify patient risk. Patients with D-dimer >4000 were more likely to have underlying malignancy.[26] While the study was flawed by being a retrospective trial at a single medical center composed of a homogenic ethnicity, it provided another measure for clinicians to use to stratify patient risk. If a patient is older, with a history of smoking, and an extremely high D-dimer, then a more extensive workup may identify an underlying malignancy. More research is needed to confirm this application of the D-dimer and identify other cost-effective strategies to determine the appropriate work up.

Currently, the benefit of an extensive work-up is unclear. A conscientious clinician must provide evidence-based medicine using known risk factors to guide care. When a patient presents with a recent unprovoked VTE, a detailed history and physical should be obtained (Figure 1). Lifestyle questions, including exposure to radiation or known carcinogens are indicated. Particular attention to family history of thrombosis and cancer may provide insight to patient risk factors. A detailed history and physical, and a head-to-toe assessment for signs and symptoms should be performed because a good H&P was consistently the best tool for identifying signs of cancer. Basic lab work including CBC and CMP may identify abnormalities; if they have not been assessed in the last year, they may provide important information at a reasonable cost. Age and gender appropriate screening should be performed if they are not up to date. Many patients may not have received the recommended colonoscopy due to psychological factors. This provides an opportunity to urge patients to receive the age appropriate care they may have been avoiding. New guidelines by the US Preventative Services Task Force recommend annual low-dose chest CT for persons between the age of fifty-five and eighty with a thirty pack-year smoking history who currently smoke or have quit in the last fifteen years.[28] The patient's smoking status and exposure should be considered and a low-dose CT should be included, if indicated.

If the family cancer history is strong, the patient has elevated risk factors, or the patient's D-dimer was >4000 ng/mL, a clinician should consider additional testing or an abdominopelvic CT. Otherwise, patients should have close follow-up, with a history and physical every three months for the year after their VTE because majority of cancers present with symptoms within one year of unprovoked VTE.[21] A clinician should meet with the patient to assess for present signs and symptoms and perform testing as indicated by their symptoms. However, medicine is an evolving landscape and the definition of limited screening will likely evolve as technology advances, costs change, and research progresses. A clinician must be conscientious of new studies which may provide insight into the appropriate work up of cancer in patients with unprovoked VTE.

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Figures and Tables

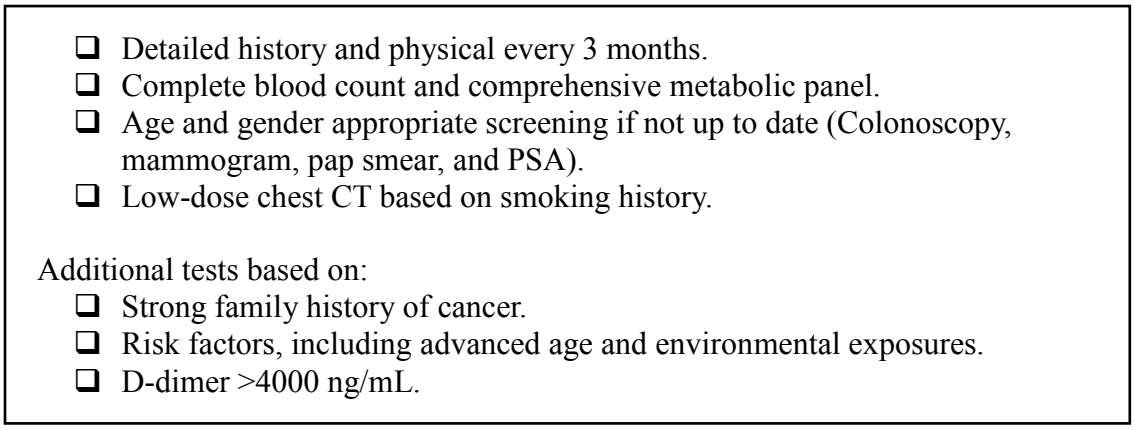

Figure 1. Recommended Cancer Screening Strategy for Patients with Unprovoked VTE.