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Should we Screen Patients with Venous Thromboembolism for Previously Undiagnosed Malignancy? A Systematic Review and Pilot Trial

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SHOULD WE SCREEN PATIENTS WITH VENOUS THROMBOEMBOLISM FOR PREVIOUSLY UNDIAGNOSED MALIGNANCY? A SYSTEMATIC REVIEW AND PILOT TRIAL

MARC CARRIER

Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in Partial fulfillment of the requirements for the MSc degree in Epidemiology

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ABSTRACT

Statement of the problem:

Malignancy screening for patients with venous thromboembolism (VTE) is controversial.

Methods of investigation:

A systematic review was performed to quantify the additional value of an extensive malignancy screening strategy compared to a more limited screen. A pilot study assessing the utility of a comprehensive computed tomography as a malignancy screening tool was performed

Results:

The systematic review demonstrated that an extensive malignancy screening strategy increases the proportion of previously undiagnosed malignancy detected from 49.5% (95% CI: 40.5-58.5) (limited screening alone) to 67.4% (95% CI: 59.0-75.6) (limited screen + CT).

The pilot study showed that approximately 6 eligible consenting patients can be recruited per month.

Conclusion:

Previously undiagnosed malignancies are common in patients with unprovoked VTE. These malignancies are more likely to be detected by an extensive screening strategy (limited screen and CT). A clinical trial in that particular clinical setting is feasible.

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Finalement, je voudrais dédier ma thèse à ma petite fille Rose, née le 13 janvier 2008, qui, de son berceau, me regardait écrire.

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1.0 INTRODUCTION

1.1 Overall Aim

To determine if previously undiagnosed malignancy detection is a frequent finding in patients with newly diagnosed venous thromboembolim (VTE). If it is found to be common and problematic in the specific population, is a study assessing different screening strategy needed? If so, which trial design should be performed? Finally is that trial feasible in patients with newly diagnosed VTE?

1.2 Venous Thomboembolism Epidemiology

Venous thromboembolism is the third leading cause of cardiovascular mortality in North America and has an incidence of 100-150 per 100,000 of the general population [1-3]. VTE can present as deep vein thrombosis (DVT), a vein blood clot, usually in the legs, or pulmonary embolism (PE), a blood clot in the lungs. VTE are commonly subdivided into two categories: provoked and unprovoked VTE. Over half of VTE occur without a provoking risk factor (unprovoked VTE) with the remainder being associated with a clear external precipitant (provoked VTE) or known malignancy (malignancy associated VTE). External VTE precipitants include: 1) recent surgery; 2) recent cast; or 3) prolonged immobilization. Of patients with unprovoked VTE, many will have previously undiagnosed malignancy.

1.3 Statement of the Problem

VTE can be the earliest sign of malignancy [4-7]. Published literature suggests that approximately 4 to 10% of patients with unprovoked VTE will be newly diagnosed with malignancy within the first year following unprovoked VTE diagnosis [8].

Identifying previously undiagnosed malignancy in patients with VTE may be important for several reasons: 1) the malignancy may be at a curable stage, and if detected at a later date, may no longer be curable, 2) treating malignancy earlier may prevent malignancy associated morbidity (e.g. pathologic fractures, compression syndromes) and 3) malignancy associated VTE is now initially treated with low molecular weight heparin (LMWH) for 6 months rather than vitamin K antagonists [9], to reduce the heightened risk of recurrent VTE with malignancy associated thrombosis [10] and potentially increase survival in patients without metastatic disease [11].

While retrospective studies suggested that a limited malignancy screen including a careful medical history, physical examination and basic blood work was adequate to detect most undiagnosed malignancies in patients with VTE [12-13], two recent prospective studies suggest that a more extensive screening strategy can increase the rate of detection of cancer [14-15]. However, extensive malignancy screening may cause anxiety, lead to test complications and unnecessary further testing for false positives, and is invasive and expensive.

Therefore, screening for previously undiagnosed malignancy in patients with unprovoked VTE is controversial [16]. There is presently no agreed consensus as well as great diversity in opinions and practices [16].

In order to counsel VTE patients on the risks and benefits of malignancy screening clinicians require: 1) estimates of the absolute risks of previously undiagnosed malignancy in VTE patients and VTE patient subgroups (provoked and unprovoked), 2) estimates of the additional cancers detected by extensive malignancy screening strategies compared to more limited screening strategies and 3) estimates of the potential additional risks and benefits (morbidity, mortality) of an extensive screening strategy. To address these knowledge gaps, A systematic review of the literature was performed to summarize period prevalences of previously undiagnosed malignancy at baseline and during different intervals of follow up, and the additional yield and complications of extensive malignancy screening strategies. Based on the results of the systematic review, a pilot study was also performed to assess the *feasibility* of a clinical trial comparing a limited malignancy strategy to a more extensive strategy. If a clinical trial is needed and feasible on screening for previously undiagnosed malignancy in patients with VTE, future work should focus on determining if malignancy screening is efficacious, effective, safe and cost effective.

2.0 BACKGROUND

2.1 Association between Venous Thromboembolism and Previously Undiagnosed Malignancies

Venous thromboembolism can be the earliest sign of malignancy. Malignancy induces a hypercoagulable state. This hypercoagulable state promotes tumor growth, angiogenesis and metastasis [17]. Tumor cells can interact with platelets, clotting and fibrinolytic proteins which contribute to the development of VTE [16]. The best-characterized cancer pro-coagulant is tissue factor. Tissue factor is a trans-membrane protein that initiates coagulation by binding to the activated coagulation factor VII [16]. Sequential downstream activation of clotting enzyme complexes leads to thrombin generation and ultimately thrombosis formation. Tissue factor is normally expressed on fibroblasts of the vascular adventitia and other stromal cells but it can also be found on the surfaces of almost all solid tumor cells and acute mylelogenous leukemia cells [18]. Tissue factor is also likely an important mediator between activation of coagulation and tumor growth [16]. Tissue factor is a critical promoter of angiogenesis and thereby contributes to a positive cycle of tumor growth and thrombus formation. Furthermore, cytokine release, acute phase reaction and other host responses stimulated by tumor cell interactions with endothelial cells and tumor-associated macrophages further promote clotting activation [16]. It is therefore biologically plausible that VTE might be the first clinical sign of an underlying undiagnosed malignancy.

Previous epidemiological studies have suggested an association between thrombosis and previously undiagnosed malignancies. A case control study demonstrated that the odds ratio for undiagnosed malignancy in patients with VTE is 3.2 compared with those who had VTE excluded [6]. Furthermore, the incidence of malignancy in patients with unprovoked VTE appeared higher than in patients with transient external precipitants [19]. Two hundred and sixty patients with symptomatic DVT were followed during a two-year period. The incidence of previously undiagnosed malignancy was 3.3% in patients with unprovoked VTE and 0% in patient with a well-recognized risk factor other than malignancy [19].

Accurate estimates of the prevalence of previously undiagnosed malignancy detection in patients with provoked and unprovoked VTE are required. A wide range of prevalence of underlying cancer has been reported in the literature, ranging from 0.9 to 13.3% [8]. The largest study is a population-based case series using the Swedish Inpatient Register and linkage to the national wide Cancer Registry. The reported standardized incidence ratio for all malignancies was 4.4 (95% CI: 4.2-4.6%) in patients with VTE [4]. A dichotomous pattern of risk with time was found with the highest risk reported to be within the first 6 months following the VTE diagnosis. The overall risk of malignancy detection in the first year after the VTE was greater than 4-fold compared to the general population with particularly high relative risk for malignancy of the liver, pancreas, ovaries and Hodgkin's lymphoma [4]. Although the analysis had the strength of being a large, population-based case series with virtually no losses to long-term follow-up, the investigators relied on recorded diagnoses which on may have been erroneous.

This could tend to minimize the strength of the associations. Furthermore, the authors could not obtain the information to confirm that malignancies detected were actually previously undiagnosed. Therefore, the true prevalence or incidence of previously undiagnosed malignancy detection in patients with VTE remains unclear.

2.1.1 Malignancy Screening Strategies

Caregivers screening patients with new VTE for previously undiagnosed malignancy can use a limited (medical history, physical examination and basic blood work) or a more extensive strategy (limited screen + ultrasound (U/S) of the abdomen/pelvis, computed tomography (CT) of the abdomen/pelvis and/or serum tumor makers).

2.1.2 Limited Screening Strategies for Previously Undiagnosed Malignancies Detection

Retrospective studies suggest that a limited malignancy screening strategy is adequate to detect most previously undiagnosed malignancies in patients with VTE [12-13]. Nordstrom M *et al* retrospectively followed 1389 patients with confirmed DVT diagnosed between 1984 and 1988 in one Swedish hospital [12]. Investigators used the southern Swedish tumor registry to identify new diagnosis of malignancy. Follow-up was continued until January 1991 [12]. Of the 1389 patients with DVT (unprovoked and provoked), 150 developed malignancy. Sixty-six (44%) patients had their diagnosis of malignancy within 6 months. Of these,

55 (83%) were easily detected by a combination of a medical history, physical examination, and routine blood tests. Another retrospective cohort study examined a limited malignancy screening strategy consisting of a comprehensive medical history physical examination, basic blood work and a chest X-ray (CXR), suggested this was enough to detect most of the previously undiagnosed malignancies in patients with unprovoked VTE [13]. In this retrospective cohort study, 142 patients with DVT were followed for a median of 34 months. 16/136 (12%) of patients with unprovoked VTE were diagnosed with a malignancy during hospitalization. All 16 patients had at least one or more abnormalities on at least one of the four components of the clinical examination. Three patients (2.1%) were diagnosed with malignancy during follow-up.

These two studies have several limitations. They were both conducted in only one hospital, which limits the generalizability of the results. The retrospective collection designs resulted in missing data. The retrospective design of the study also means that the intensity and scrutiny with which the patients were investigated at the time of admission might have varied. Finally, they could not reliably assess the yield of some potential limited malignancy screening tools such as breast examination and digital rectal examination because these tests were often not recorded.

Based on these two retrospective studies, a limited screening strategy may detect as high as 85% of previously undiagnosed malignancies. However, as detailed below prospective studies suggest otherwise (See 2.1.3).

2.1.3 Extensive Screening Strategies for Previously Undiagnosed Malignancy Detection

A large prospective cohort study (n=864) using a two-step screening strategy for previously undiagnosed malignancy in patients with VTE (40% unprovoked and 60% provoked) was recently published [14]. The initial screening step consisted of a limited malignancy screening strategy including a thorough history and physical examination, blood work [complete blood count (CBC), liver and renal function, sedimentation rate (ESR) and serum electrophoresis], a urinalysis and a CXR. Subsequent investigations to confirm a suspected malignancy were performed if the initial limited malignancy screen was abnormal. 167/864 (20%) patients had an abnormal limited malignancy screen. 34/167 (20%) of these patients had a confirmed diagnosis of malignancy (i.e. true positive limited malignancy screen) with the rest having false positive limited malignancy screen (133/167). The remaining 830 patients (normal or false positive limited malignancy screening strategy) underwent further investigations including: an US abdomen/pelvis and serum tumor markers (Carcinoembryonic antigen (CEA), Prostate specific antigens (PSA) for men and cancer antigen-125 (CA-125) for women). 54/830 (6.5%) patients had abnormal findings in the extensive malignancy screen and 13/54 (24%) patients subsequently had a confirmed diagnosis of malignancy. During the 1-year follow-up, 14/830 (1.7%) additional malignancies were diagnosed. Thus a total of 61/834 (7.3%) patients were diagnosed; 34/61 (56%) malignancies were found with limited malignancy screen, 13/27 (48%) diagnosed following the extensive malignancy screen only and 14/61 (23%) were missed by

both screens. The limited malignancy screen had a sensitivity of 56% (34/61) and adding the second had a sensitivity of 77% (47/61). This study suggests that limited malignancy screen alone is insufficient to detect all previously undiagnosed malignancies. However, this study's major limitation is that it could not demonstrate a positive effect of the screening program on the prognosis (i.e. morbidity, mortality) of patients with unprovoked VTE.

The SOMIT investigators group recently published a study randomizing patients with negative limited malignancy screen to either the strategy of extensive occult malignancy screening strategy or to no further testing using a Zelen randomization [15]. Zelen randomization implies that only the experimental group received complete information about the study after randomization. A total of 56 patients were diagnosed with malignancy. 32/56 (57%) were diagnosed by the limited malignancy screening strategy. The limited malignancy screening strategy consisted of: clinical history, physical examination, CBC, liver function tests (Alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT)), calcium, urinalysis and CXR. These patients were excluded from the study. Two hundred and one eligible patients with unprovoked VTE and negative limited malignancy screening strategy were included into the study and randomized. The extensive screening battery included U/S and CT of the abdomen/pelvis, gastroscopy or double-contrast barium swallowing, colonoscopy or sigmoidoscopy followed by barium enema, fecal occult blood, sputum cytology, CEA, CA-125, alpha-fetoprotein (α-FP), PSA and trans-

abdominal US of prostate for men, Papanilacou smear and mammography for women. 13/99 (13%) patients in the extensive screening arm were diagnosed with a malignancy. Only one patient was missed and became symptomatic in the two-year follow-up period in the extensive screen group. The sensitivity of the extensive screening strategy was 93% hence 13/14 patients. Furthermore, the extensive malignancy screening strategy diagnosed significantly more earlier-stage cancers (T_{1-2},N_0) as compared to the control group (64% versus 20%, $p=0.047$) and the diagnosis was made significantly earlier (median 1.0 month versus 11.6 months, $p<0.001$). Although the absolute risk reduction of malignancy-related mortality was 1.9% during the 2-year follow-up period, this difference was not statistically significant. The study was not adequately powered to detect important difference in malignancy-related mortality. The trend of the SOMIT study favors the extensive malignancy screening strategy for patients with unprovoked VTE. The SOMIT investigators were only able to recruit 20% of the expected number of patients and the study was conducted in only 5 of the 40 centers approached. The limited recruitment of participants and centers raises concerns about selection bias and the generalizability of these findings. The 95% confidence interval (CI) around the 92.9% (13/14) additional cases detected by the extensive work-up is wide 66%-100% undermining confidence in this finding.

Overall, limited malignancy screening strategy seems to be insufficient because it misses numerous previously undiagnosed malignancies. On the other hand, current evidence does not support improvements in malignancy-related mortality,

morbidity or quality of life with an extensive malignancy screening strategy in VTE patients. Based on this apparent clinical equipoise, a systematic review of the literature was performed to ensure that a trial assessing an extensive malignancy screening strategy in patients with VTE is needed. The results of the systematic review then led to a pilot study to determine the feasibility of a trial comparing a limited malignancy screening strategy to a more extensive screening combining the tests performed in a limited screen to a comprehensive CT (cCT) of the abdomen/pelvis.

3.0 SYSTEMATIC REVIEW

3.1 Rationale for the Systematic Review

As detailed above, accurate estimates of the prevalence of previously undiagnosed malignancies detection in patients with VTE (provoked and unprovoked) are unknown. These estimates are required for physician to appropriately counsel patients on the underlying malignancy risk and the need for further testing. If the prevalence of previously undiagnosed malignancy is low, it is probably unnecessary to utilize scarce health care resources or expose patient to potential complications of screening (e.g. radiation exposure during CT scans). On the other hand, if the prevalence is high, it might be appealing for physicians to screen patients for a potential underlying malignancy. Furthermore, prevalence of previously undiagnosed malignancy detection might be different in certain subgroups of patients (provoked Vs unprovoked) and previously undiagnosed

malignancy detection might only be warranted in subgroups with high prevalence of underlying malignancies. If prevalence of previously undiagnosed malignancy is high and further testing is needed, it is currently unknown if an extensive malignancy screening strategy provides any significant benefits (increase proportions of malignancy detected, increase survival, etc) over a more limited malignancy screening. Risks (complication from investigations (e.g. biopsy), anxiety, high costs) and benefits (increase proportion of previously undiagnosed malignancy detection, earlier cancer diagnosis, survival) of extensive malignancy screening strategies are unknown. Finally, if an extensive screening strategy is shown to have potential benefit over a more limited strategy, the ideal components (e.g. U/S or CT of the abdomen/pelvis or serum tumor markers) of that extensive malignancy screening are still unknown.

3.2 Systematic Review Methods

3.2.1 PICOS Question and Objectives

3.2.1.1 PICOS Questions

a) Prevalence of Previously Undiagnosed Malignancy:

Population: Patients with newly diagnosed VTE

Intervention: n/a

Comparator: n/a

Outcome: Previously undiagnosed malignancy detection at baseline, 6 and/or 12 months

Study: Observational studies and clinical trials (Randomized-controlled or quasi-experimental).

b) Extensive versus limited extensive malignancy screening

Population: Patients with newly diagnosed VTE

Intervention: Extensive malignancy screening (limited malignancy screening in combination with U/S or CT abdomen/pelvis or serum tumor markers)

Comparator: Limited malignancy screening (History, physical examination, basic blood work and CXR)

Outcome: Previously undiagnosed malignancy detection

Study: Observational studies and clinical trials (Randomized-controlled or quasi-experimental).

3.2.1.2 Objectives

3.2.1.2.1 The Primary Objectives:

1) To summarize the period prevalence of previously undiagnosed malignancy at baseline (within 1 month of VTE diagnosis), 6 and 12 months following VTE.
2) To quantify the additional value of an extensive malignancy screening strategy at baseline compared to a more limited screen (history, physical exam and simple widely available tests) at baseline.

3.2.1.2.1 The Secondary Objectives:

1) To quantify the additional value of an extensive malignancy screening strategy at baseline on:
    a. Early cancer detection
        i. Local cancer without nodal or metastatic spread as per TNM classification
            1. $T_{1-2}N_0M_0$
    b. Malignancy-related mortality
2) Quantify the number of prevalent and incident cases of previously undiagnosed malignancy detection following VTE diagnosis.
3) Determine the frequency of various types of cancers following VTE diagnosis.

3.2.2 Data Sources and Searches

A systematic literature search strategy was conducted to identify potential trials on MEDLINE (1950 to November week 1 2007), EMBASE (1980 to 2007 week 45), the Cochrane Register of Controlled Trials (4th quarter 2007) and all EBM Reviews (4th quarter of 2007) using the OVID interface. Publications were also sought through a hand-search of the International Society of Thrombosis and Haemostasis (ISTH) conference proceedings for the past 5 years (2003-2007). In addition, a manual search by reviewing the reference lists of original and narrative review articles was conducted. Investigators were also contacted to ensure that we were not missing any other known or ongoing trials. Finally, a "grey literature" search using SIGLE was also performed. The systematic search strategy is documented in Table 1. The search was restricted to humans. There was no restriction on language, publication year or type of publication.

3.2.3 Study Selection

Using a structured question format to aid our literature search strategy, we reviewed abstracts of observational studies or clinical trials reporting the prevalence or incidence of previously undiagnosed malignancy following VTE.

To determine the period prevalence of previously undiagnosed malignancy at baseline and during different intervals of follow up, we reviewed potentially relevant articles that satisfied all of the following criteria: 1) adult patients with newly diagnosed VTE (DVT and/or PE); 2) prevalence and/or incidence of

malignancy detection reported at diagnosis and at 6 months and/or 12 months; 3) observational studies and clinical trials (Randomized-controlled or quasi-experimental)..

In order to assess the efficacy of limited and extensive occult malignancy screening, we reviewed potentially relevant studies that satisfied all of the following criteria: 1) adult patients with newly diagnosed VTE (DVT and/or PE); 2) patients were screened for malignancy using: history, physical examination, basic blood work, and CXR (limited malignancy screen) and at least one of the following: serum tumor markers, U/S or CT of abdomen/pelvis (extensive malignancy screen); 3) Observational studies and clinical trials (Randomized-controlled or quasi-experimental).; 4) one or more primary or secondary outcome measures was reported.

Table 1: Systematic Literature Search Strategy

1. exp Thrombosis/
2. exp Venous Thrombosis/
3. Thromb$.ti,ab.
4. phlebothrombosis.mp.
5. Deep vein thrombosis.mp.
6. pulmonary emboli.mp.
7. venous thromboembolic event$.mp.
8. or/1-7
9. exp Neoplasms/
10. cancer.mp.
11. neopl$.ti,ab.
12. tumor$.ti,ab.
13. cancer$.ti,ab.
14. exp Medical Oncology/
15. onco$.ti,ab.
16. exp Hematologic Neoplasms/
17. or/9-16
18. exp Early Diagnosis/
19. exp Mass Screening/
20. screening.mp.
21. or/18-20
22. 8 and 17 and 21

3.2.4 Outcome Measure

The primary outcome measure was detection of a previously undiagnosed malignancy. Previously undiagnosed malignancy was defined as any new malignancy detected after the index VTE diagnosis until the end of follow up in patients with no known history of malignancy. Prevalent cases at baseline of previously undiagnosed malignancy were defined as a malignancy detected at, or shortly after ($\leq$ month), the index VTE diagnosis in patients with no known history of malignancy. Newly diagnosed malignancies after the baseline period were defined as a new diagnosis diagnosed between the index visit of VTE (> 1 month) and the end of follow-up. Limited malignancy screening was defined as a combination of medical history taking, physical examination, routine laboratory blood tests and a chest-X ray. Extensive malignancy screening was defined as a combination of the limited malignancy screen and one of the following: 1) U/S of the abdomen/pelvis 2) CT of the abdomen/pelvis and/or 3) serum tumor markers. We followed the "provoked VTE" definitions provided in the original studies. Unprovoked VTE was defined as patients with VTE and no predisposing factor. We excluded patients with previous diagnosis of malignancy from the present analysis.

Secondary outcome measures included: proportion of early stage malignancy, malignancy-related mortality and screening complications. Early stage malignancy was defined using the Tumor/Nodes/Metastasis classification as T_{1-2} N_0 M_0. Screening complication was defined as any complication arising directly

from the screening (e.g. biopsy) or from any other subsequent investigations to confirm/refute malignancy.

3.2.5 Data Extraction and Quality Assessment

Two reviewers (MC and GL) independently applied the two sets of inclusion criteria to the identified articles from the initial search strategy. Articles for potential full review were discussed between the two reviewers. Reviewers independently extracted baseline characteristics, number of cases of previously undiagnosed malignancy, time period of diagnosis (baseline, 2 to 6 months, 7 to12 months), type and stage of malignancy and diagnostic modality used for diagnosis. Data was extracted for all patients with any, unprovoked or provoked VTE. Discrepancies were noted and adjudicated by a third party (MR).

A priori, the methodological quality of observational studies was planned to be evaluated using the validated Newcastle – Ottawa Quality Assessment scales and the evaluation of RCT using the Jadad score [20-21]. Trial quality of RCT was further assessed by examining allocation concealment [22].

The Newcastle – Ottawa quality score was designed to assess the quality of non-randomized studies in meta-analyses [21]. The scale assesses cohort and case-control studies using three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest or the exposure for cohort studies and case-control studies respectively. The Jadad score for RCT provides scoring for randomisation (0-2 points), double-

blinding (0-2 points) and account for withdrawals (1 point), with scores ranging from 0 to 5. A score of 3 or more was considered high quality [20].

Post-hoc, the Newcastle – Ottawa scale was also used to assess the RCT quality since there was only one RCT and that we used the two arms of the RCT as two cohorts without comparing outcomes between them. Quality of RCT was further assessed by examining allocation concealment [22].

For all eligible studies, 2 reviewers (MC and GL) independently assessed trial/study quality and extracted the data using a standardized data abstraction form. Likewise, any discrepancies were documented and adjudicated by a third reviewer (MR).

3.2.5 Data Synthesis and Analysis

Period prevalence was defined as the proportion of the VTE population with previously undiagnosed malignancy detected over a specific period of time. In order to estimate the period prevalence at baseline and after different intervals of follow-up periods, data was extracted from the individual studies (including the two arms of the RCT [15]) to form a cohort of patients followed over time. The cohort was defined as a group of patients without a previously known cancer at the time of the VTE diagnosis. The period prevalence at baseline includes all prevalent cases of previously undiagnosed malignancy from the time of VTE diagnosis to 1 month. The period prevalences from baseline to 6 and baseline to

12 months combine all cases of previously undiagnosed malignancy over the specific time periods. Ninety-five percent confidence intervals (CI) were calculated for each period prevalences using averaged, inverse variance-weighted estimates from each study. The Freeman-Tukey arcsine transformation was used to stabilize variances. Fixed effect modeling was used to perform the analysis. Pooled period prevalences were determined for all patients with VTE and in subgroups based on VTE etiology (provoked and unprovoked). The I^2 statistic was used to estimate total variation across studies [23]. An I^2 of < 25% was considered as low-level heterogeneity, 25% to 50% was moderate level and higher than 50% was considered as high level [24].

Since malignancy screening was performed shortly after the index VTE, we used a cross-sectional design to assess if extensive screening provided any additional benefits in cancer detection. We estimated the pooled probability of identifying a previously undiagnosed malignancy using a limited or extensive screening strategy. We also determined the proportions of previously undiagnosed malignancies detected using different diagnostic modalities (ultrasonography, computed tomography and tumor markers) within the different extensive screening strategies. The proportions represent the number of previously undiagnosed malignancies detected by the specified screening tool over the total number of malignancies (prevalent and incident) detected in the population at the end of follow-up. Again, ninety five percent confidence intervals were calculated using averaged, inverse variance-weighted estimates from each study. The

Freeman-Tukey arcsine transformation was used to stabilize variances. Fixed effect modeling was used to perform the analysis. The I^2 statistic was calculated to assess the heterogeneity among studies [23].

3.3 Results of Systematic Review

3.3.1 Baseline Characteristics of Included Studies

A total of 939 citations were identified by our literature search and 35 articles (1 abstract, 34 full articles) were deemed potentially eligible (Figure 1) [12-15, 25-55]. Two studies were not written in English, French or Spanish and had to be excluded because not enough information could be extracted from the English abstract [54-55].

3.3.2 Period Prevalence:

A total of 9,516 patients with VTE (3,286 unprovoked; 3,297 provoked and 2933 not specified) from 33 studies were included in the assessment of the period prevalence of previously undiagnosed malignancy detection (Table 2) [12-15, 25-53]. The period prevalence at baseline and during different intervals of follow up of previously undiagnosed malignancy following VTE is shown in Table 3. The period prevalence of previously undiagnosed malignancy detection from baseline to 12 months was 7.7% (95% CI: 6.9 to 8.4) in all patients with VTE. The baseline to 12 month period prevalence of previously undiagnosed malignancy

was higher in patients with unprovoked VTE (12.1%; 95% CI: 10.6 to 13.7) compared to those with provoked VTE (3.1%; 95% CI: 2.1 to 4.3). The period prevalences of newly diagnosed malignancy were similar within the first and second 6 months of follow-up after presentation with VTE. The Forest plots of the different pooled estimate are shown are found on Figure 2, 3 and APPENDIX 1.

3.3.2.1. Sensitivity Analyses

The Forest plots allow to qualitatively assess for any outlying results among the studies. The result from the study by Sannella and colleagues seem to be different than the others in patients with any VTE (Figure 2). Similarly, the results form the studies by Sannella and Psitorius are significantly higher than the other studies (Figure 3). Sensitivity analyses were performed by excluding these studies from the calculations and the results are depicted in APPENDIX 2. Removing these studies did not significantly alter the results (APPENDIX 2).

Figure 1: Flow Diagram Summarizing the Identification Process of Relevant Articles

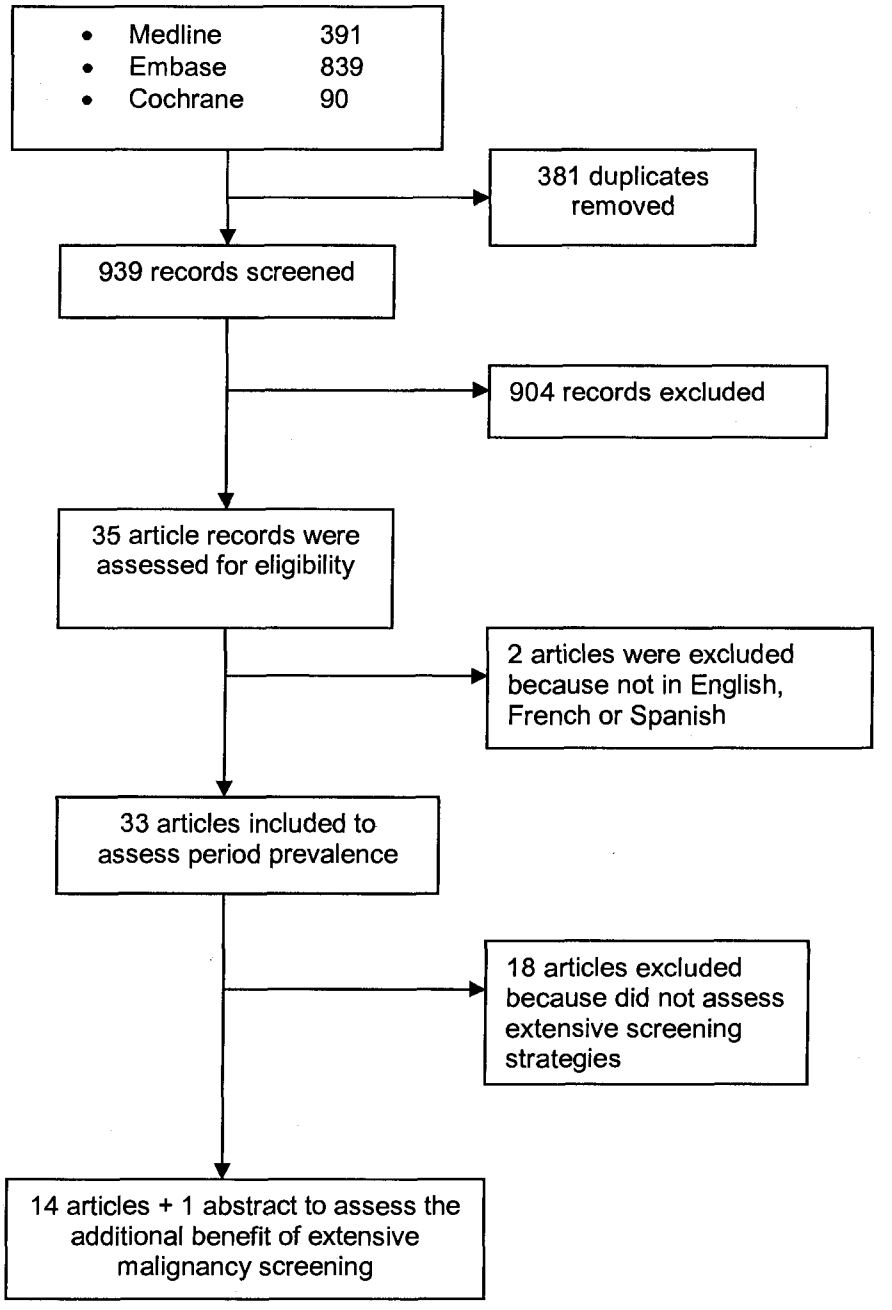


Table 2: Breakdown of Patients Included in the Period Prevalence Analysis

Studies	Year	Total # VTE	# Unprovoked VTE	# Provoked VTE
Gore [32]	1982	113	23	90
Minar [40]	1982	279	Not specified	Not specified
O'Connor [35]	1984	127	17	110
Aderka [27]	1986	83	35	48
Goldberg [36]	1987	370	Not specified	Not specified
Griffin [37]	1987	113	Not specified	Not specified
Monreal [34]	1988	94	21	73
Monreal [42]	1991	113	31	82
Sannella [43]	1991	228	21	207
Ranft [39]	1991	200	Not specified	Not specified
Barrellier [44]	1992	128	Not specified	Not specified
Prandoni [28]	1992	260	153	107
Monreal [45]	1993	78	27	51
Nordstrom [12]	1994	1383	Not specified	Not specified
Pistorius [46]	1994	53	17	36
Ahmed Z [30]	1996	196	113	83
Cornuz [13]	1996	142	Not specified	Not specified
Bastounis [47]	1996	293	86	207
Cailleux [48]	1997	148	36	112
Monreal [25]	1997	685	112	573
Rajan [29]	1997	264	152	112
Rance [38]	1997	809	279	530
Fahrig [49]	1998	318	Not specified	Not specified
Netzer [50]	1998	135	135	0
Hettiarachchi [26]	1998	326	137	189
Girolami [33]	1999	305	305	0

Subira [31]	1999	40	10	30
Enguinos [53]	2002	48	48	0
Ronsdorf [51]	2003	485	236	249
Saba [41]	2003	183	127	56
Monreal [14]	2004	864	345	519
Piccioli [15]	2004	339	339	0
van doomal [52]	2007	444	444	0

Table 3: Period Prevalence at Baseline and Over Different Time Periods of Follow-Up of Previously Undiagnosed Malignancy in Patients with Venous Thromboembolism

Period Prevalence at Baseline (≤1 month)	(%, 95% CI)
Overall	4.8 (4.3-5.4)
Unprovoked	7.4 (6.4-8.5)
Provoked	1.8 (1.3-2.3)
Period Prevalence Baseline to 6 months (0 to ≤6 months)	
Overall	6.2 (5.5-6.8)
Unprovoked	10.7 (9.1-12.4)
Provoked	2.2 (1.4-3.1)
Period Prevalence Baseline to 12 months (0 to ≤12 months)	
Overall	7.7 (6.9-8.4)
Unprovoked	12.1 (10.6-13.7)
Provoked	3.1 (2.1-4.3)

Figure 2: Forest Plot of the Pooled Period Prevalence from Baseline to 12 Months in Patients with any Venous Thromboembolism

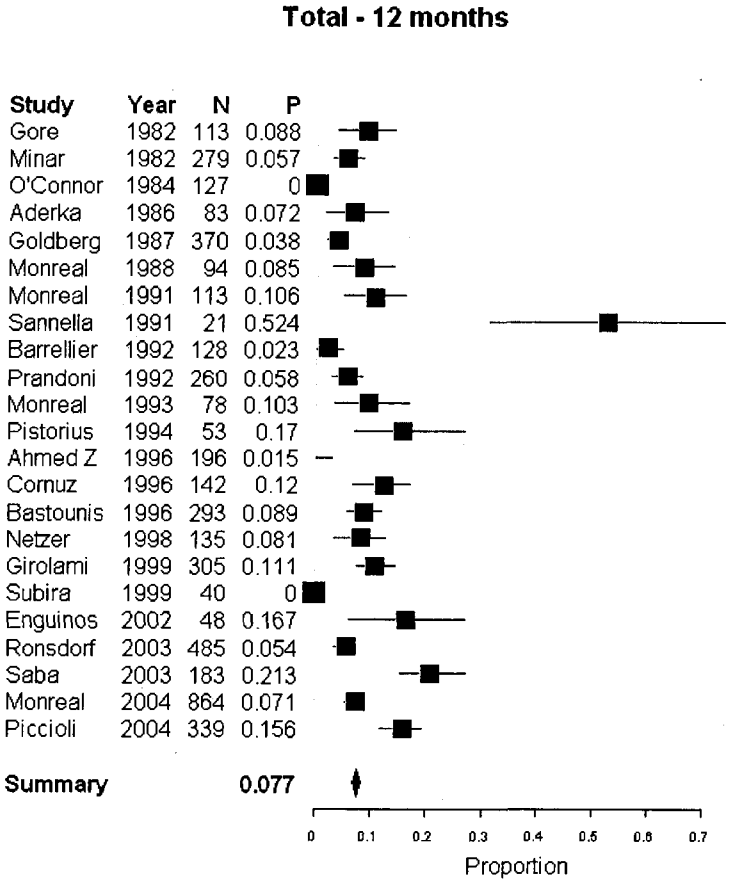
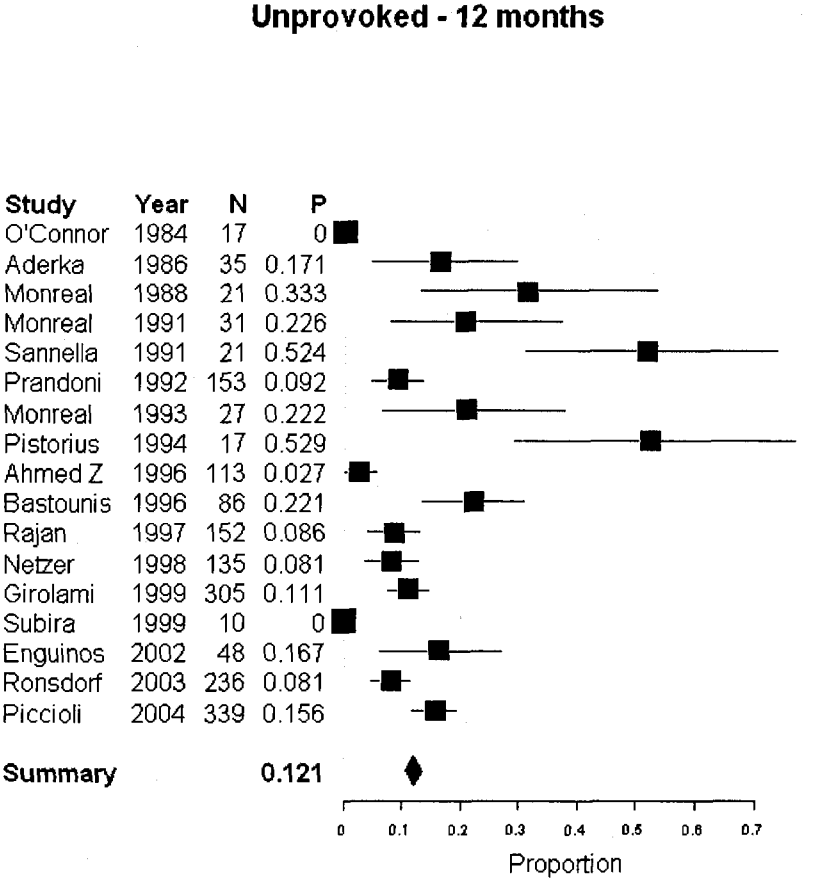


Figure 3: Forest Plot of the Pooled Period Prevalence from Baseline to 12 Months in Patients with Unprovoked Venous Thromboembolism



3.3.2.2. Heterogeneity

The I^2 statistic was performed to assess all pooled prevalence. The results are reported in Table 4. The I^2 statistic was consistent with a high level of heterogeneity for the pooled period prevalence of patients with any and unprovoked VTE.

Table 4: Assessment of the Heterogeneity for Each Pooled Period Prevalence

	I^2 Results
Overall VTE	
Baseline	85.9
6 months	86.3
12 months	84.5
Unprovoked VTE	
Baseline	87.2
6 months	80.3
12 months	78.5
Provoked VTE	
Baseline	0%
6 months	0%
12 months	25.6%

3.3.2.2 Quality Assessment

Thirty-two studies were cohort studies. Fifteen were retrospective studies and 17 were prospective. One study compared an exposed and a non-exposed cohort (different centers) prospectively [52] and one was a RCT [15]. Quality assessment was done using the Newcastle – Ottawa quality assessment scale (Appendix 4) [14]. Twenty-five cohort studies did not have an exposed (diagnosis of VTE) and non exposed cohort (no diagnosis of VTE) and therefore, comparability of cohorts could not be assessed (Appendix 4). The quality of the RCT was also evaluated using the same quality scale since the two arms of the RCT were used as cohorts without comparing outcomes between them.

3.3.3 Extensive Versus Limited Malignancy Screening Strategy

Of the 33 articles used for period prevalence assessment, 14 articles and one abstract also met the second set of inclusion criteria for the efficacy assessment of extensive versus limited malignancy screening (Figure 1). There were no discrepancies between the 2 reviewers with regards to study eligibility [14-15, 25, 42-53]. Limited malignancy screening in most studies was defined as a combination of careful medical history taking, physical examination, laboratory blood testing and chest X-ray. Extensive malignancy screening included U/S or CT of the abdomen/pelvis and/or tumor markers (prostate specific antigen, carcinoembryonic antigen and/or cancer antigen-125 levels). One study also included gastroscopy or barium swallow, colonoscopy or barium enema, mammography and sputum cytology [15]. Most studies did not report the performance (sensitivity and specificity) of the individual diagnostic modalities (e.g. CT abdomen/pelvis) used in malignancy screening. The limited and extensive malignancy screening were completed within 2 to 4 weeks of the index VTE in a majority of studies. No studies performed regular testing during follow-up. New malignancy diagnoses were reported if a patient sought medical attention and/or on chart review.

3.3.3.1 Baseline Characteristics of the Included Studies

A total of 4,378 patients from all 15 studies were included. Sample size ranged from 21 to 864 patients. Baseline characteristics were similar among the trials (Table 4). Thirteen studies were cohort studies. Four were retrospective studies and nine were prospective. One study compared an exposed and a non-exposed cohort (different centers) prospectively [52] and the last one was a RCT [15]. Seven studies (713 patients) reported the rate of malignancy detection in patients with unprovoked VTE [15, 25, 42, 43, 45, 50, 53]. Four studies reported the TNM staging of the malignancies detected [14, 42, 45, 51]. One study reported overall and malignancy related mortality [15]. Although sensitivity and subgroup analyses were planned, the small number of studies precluded a number of analyses.

Table 5: Characteristics of Included Studies in the Comparison Analysis between Extensive and Limited Occult Malignancy Screening Strategies

Study	Purpose of the study	Criteria for inclusion	Limited screening (# of patients tested)	Extensive screening (# of patients tested)	Testing per protocol	F/U methods	Length of F/U	Lost to F/U	Outcome Assessment
Retrospective cohort studies									
Sannella, 1991 [43]	Assess CT as a malignancy screening modality in patients with unprovoked DVT	Patients with DVT. Only unprovoked DVT evaluated (n=21)	Hx, PE, CBC, CXR (21)	CT abdo/pelvis (17)	Not specified	Chart review	Over 8 years	0	Not specified
Fahrig, 1998 [49]	Assess the incidence of malignancy in patients with DVT	Patients with DVT and no known cancer	Laboratory investigations, CXR (?)	U/S abdo/pelvis (?)	Not specified	Not specified	Not specified	0	Not specified
Netzer, 1999 [50]	Assess U/S abdo/pelvis in patients with unprovoked DVT	Consecutive patients with unprovoked DVT	Other means during Hospitalization (?)	U/S abdo/pelvis (135)	No	Chart reviews, telephone interviews, autopsy reports	Mean 30 months	5	Histology
Ronsdorf, 2003 [51]	Assess the prevalence of malignancy in patients with provoked and unprovoked DVT	Patients with new DVT	Hx, PE, CBC, electrolytes, ESR, creat, U/A (?) CXR (479)	U/S abdo/pelvis (385)	Yes	Mailed questionnaires, chart reviews, death certificates.	Mean 33 months	51	Not specified
Prospective cohort studies									
Monreal, 1991 [42]	Validate extensive malignancy screening on all patients with DVT	Consecutive patients with DVT and no known cancer	Hx, PE, CBC, LFTs, ESR, LDH, SPEP, CXR, blood smear (113)	CEA (113) U/S abdo/pelvis (113) CT abdo/pelvis (69) Upper endoscopy (83)	Yes	Clinic visits	Mean 12-15 months	9	Not specified
Barrelier, 1992 [44]	Assess diagnostic testing to determine the etiology of an unprovoked VTE	Patients with unprovoked DVT no known cancer	Hx, PE, CBC, iron, ferritin, uric acid, SPEP, cholesterol, LFTs, ANA, hemostasis factors (?)	U/S abdo/pelvis (?)	Yes	Not specified	12 months	0	Not specified
Monreal, 1993 [45]	Validate extensive malignancy screening on all patients with pulmonary embolism	Consecutive patients with pulmonary embolism and no known cancer	Hx, PE, CBC, LFTs, ESR, LDH, SPEP, CXR, blood smear (78)	CEA (78) U/S abdo/pelvis (78) UGI endoscopy (55)	Yes	Clinic visits	Mean 9-21 months	11	Not specified

Pistorius, 1994 [46]	Assess diagnostic testing to determine the etiology of DVT	Patients with DVT	Hx, PE, CBC, LFTs, ESR, CRP, fibrinogen, SPEP, CXR (53)	U/S abdo/pelvis (53)	Yes	Clinic visits	1 year	4	Not specified
Bastounis, 1996 [47]	Assess the incidence of malignancy in patients with DVT	Consecutive patients with first episode of DVT and no known cancers	Hx, PE, CBC, ESR, LFTS, Creat, SPEP, U/A, CXR (293)	CEA (293) CT abdo/pelvis (222)	Yes	Clinic visits	2 years	7	Not specified
Cailleux, 1997 [41]	Assess U/S as a malignancy screening modality in hospitalized patients with VTE	Consecutive patients with VTE and no known cancer	Hx, PE, basic blood work, CXR (?)	U/S abdo/pelvis (143)	No	Clinic visit	3 to 6 months	27	Not specified
Monreal, 1997 [25]	Assess malignancy screening diagnostic tests in patients with VTE	Consecutive patients with DVT and no known cancer	Hx, PE, CBC, LFTs, ESR, LDH, SPEP, CXR, blood smear (674)	CEA (674) PSA (?) U/S abdo (569) CT abdo/pelvis (105)	Yes	Clinic visit	1-3 years	Not specified	Not specified
Equidanos, 2002 [53]	Assess tumor markers as a malignancy screening modality in patients with unprovoked DVT	Consecutive patients with unprovoked DVT	Hx, PE, lab assessment (48)	CEA, CA 19-9, SCC, NSE, CA 15-3 α-FP, β-2-microglobulin (48) PSA (33) CA 125 (15)	Yes	Clinic visits	Median 10 months	0	Histology (6/8)
Monreal, 2004 [14]	Assess malignancy screening diagnostic tests in patients with VTE	Consecutive patients with new VTE and no known cancer	Hx, PE, CBC, LFTs, Creat, ESR, SPEP, U/A, CXR (864)	CEA, U/S abdo-pelvis (830) PSA (?) CA-125 (?)	Yes	Clinic visits	12 months	28	Histology
Van Doormaal, 2007 [52] *	Assess CT as an malignancy screening modality in patients with unprovoked VTE	Patients with unprovoked VTE	Hx, PE, Basic laboratory examination and CXR (444)	CT thorax, abdo/pelvis (214)	Yes	Not specified	Median 12 months	Not specified	Histology
Randomized controlled trial									
Piccioli A, 2004 [15] **	Assess extensive malignancy screening in patients with unprovoked VTE and normal limited screen	Consecutive patients with unprovoked VTE and no known cancer	Hx, PE, CBC, AST, ALT, ALP, calcium and U/A CXR (339)	U/S abdo/pelvis (114) CT abdo/pelvis (95) UGI endoscopy or barium swallow (84) Colonoscopy, barium enema or	Yes	Clinic visits	24 months	0	Histology

	sigmoidoscopy (84) CEA, α-FP, CA 125 (119) Hemoccult (110) Sputum cytology (97) Pap smear (59) Mammography (38) PSA (65) Prostate U/S (65)

Abdo: abdomen; Hx: history; PE: physical exam; DVT: deep vein thrombosis; VTE: venous thromboembolism event; CBC: complete blood count; LFT: liver function tests; ESR: erythrocytes sedimentation rate; Creat: creatinine; SPEP: serum protein electrophoresis; CRP: C-reactive protein; U/A: urine analysis; CXR: Chest X-ray; U/S: ultrasonography; CT: computed tomography; CEA: carcinoembryonic antigen; α-FP: alpha fetoprotein; PSA: prostate specific antigen; SCC: squamous cell antigen; NSE: neuron-specific enolase; ANA: anti-nuclear antibodies.

* Prospective cohort study with concurrent controls.
** Randomized controlled trial assessing the clinical outcome in patients with unprovoked VTE in who limited clinical examination did not reveal malignancy (extensive screening *Vs* control).

3.3.3.2 Primary and Secondary Outcomes Measures

The additional value of extensive malignancy screening to detect previously undiagnosed malignancies is depicted in Table 6. The Forest plots of all pooled estimates are reported in Figure 4-5 and APPENDIX 3). Extensive malignancy screening increased the proportion of previously undiagnosed malignancy. Computed tomography of the abdomen/pelvis statistically significantly increased the proportion of undiagnosed malignancy detected from 47.8% (95% CI: 40.2 to 55.4) with limited malignancy screening alone to 64.2% (95% CI: 56.7 to 71.3) in all patients with VTE, and from 49.5% (95% CI: 40.5 to 58.5) to 67.4% (95% CI: 59.0-75.6) in the sub-group of patients with unprovoked VTE (Table 6, Figure 4-5). Although U/S of the abdomen/pelvis, CEA and PSA increased the frequency of malignancy detection, their 95% CI overlap with those from the limited malignancy screening alone (Table 6, APPENDIX 3).

The I^2 square statistic was computed to assess the heterogeneity of each proportion (Table 7). The variation between trials ranges from minimal to high depending on the test assessed and the number of studies included in the pooled estimate.

Table 6: Proportion of Previously Undiagnosed Malignancies Detected at Baseline by Limited Malignancy Screening Alone or in Combination with Specific Other Tests

Proportion of previously undiagnosed malignancy detected by:	Limited malignancy screening alone without any other tests*	Limited malignancy screening in combination with specific other test*
	% (95% CI)	% (95% CI)
CT abdomen/pelvis		
All VTE	47.8 (40.2-55.4)	64.2 (56.7-71.3)
Unprovoked VTE	49.5 (40.5-58.5)	67.4 (59.0-75.6)
Ultrasonography of abdomen/pelvis		
All VTE	53.6 (46.9-60.3)	63.1 (56.4-69.5)
Unprovoked VTE	53.4 (44.5-62.1)	63.5 (55.5-72.5)
Tumor Markers CEA		
All VTE	46.9 (39.0-54.9)	51.7 (43.8-59.7)
Unprovoked VTE	60.1 (35.1-82.6)	73.8 (49.5-92.1)
Tumor Markers PSA		
All VTE	50.9 (43.1-58.8)	62.1 (54.3-69.5)
Unprovoked VTE	51.2 (40.2-62.2)	60.2 (49.3-70.7)

CT: computed tomography; CEA: carcinoembryonic antigen; CI: confidence intervals; PSA: protate specific antigen; VTE: venous thromboembolism.

*The denominator represents the total number of malignancies (prevalent and incident) detected in the population at the completion of follow-up for the specified studies.

Figure 4: Forest Plot of the Pooled Proportion of Malignancies Detected by Limited or Extensive (Limited + Computed Tomography Abdomen/Pelvis) Malignancy Screening in Patients with All Venous Thromboembolism.

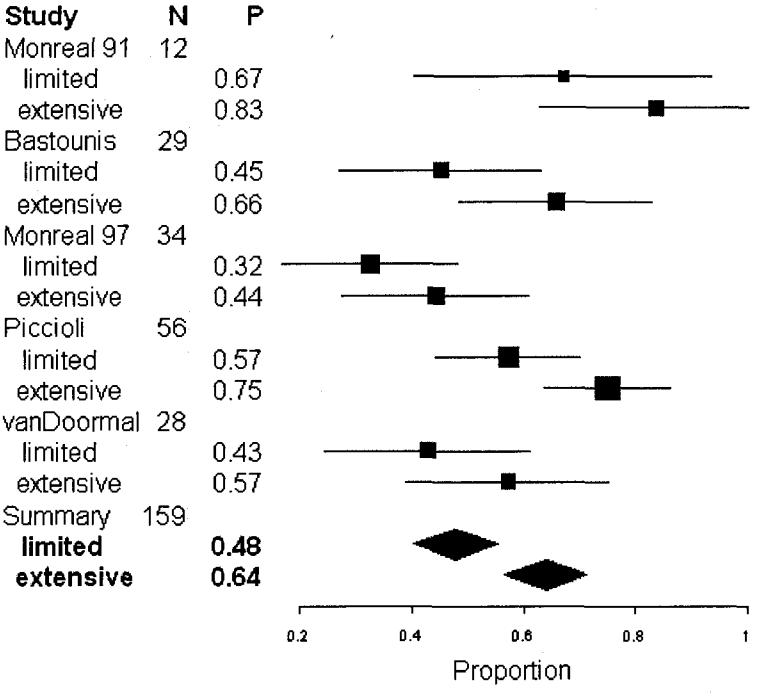


Figure 5: Forest Plot of the Pooled Proportion of Malignancies Detected by Limited or Extensive (Limited + Computed Tomography Abdomen/Pelvis) Malignancy Screening in Patients with Unprovoked Venous Thromboembolism

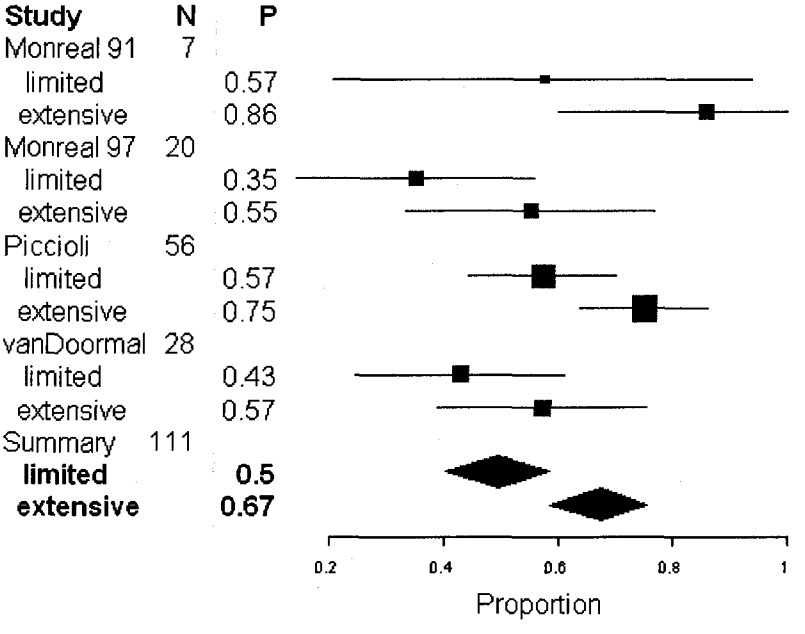


Table 7: Assessment of the Heterogeneity for Each Pooled Period Prevalence

	I2 Statistic (%)	
	Limited malignancy screening alone without any other tests	Limited malignancy screening in combination with specific other test*
CT abdomen/pelvis		
All VTE	44.8	63.9
Unprovoked VTE	16.0	41.0
Ultrasonography of abdomen/pelvis		
All VTE	0	0
Unprovoked VTE	0	0
Tumor Markers CEA		
All VTE	0	23.4
Unprovoked VTE	0	0
Tumor Markers PSA		
All VTE	58.4	0
Unprovoked VTE	64.0	0

Period prevalences of previously undiagnosed malignancy detected by screening and new cases of newly diagnosed malignancy (i.e. missed by screening) are reported in Table 8. Frequencies of the various types of cancer detected by malignancy screening are shown in Table 9.

Four studies compared the rate of detection of early-stage previously undiagnosed malignancies ($T_{1-2}N_0M_0$) between the limited and extensive screening strategy [14, 42, 45, 51]. Two studies showed a benefit in early cancer

detection with extensive malignancy screening [14, 42] whereas the other two did not [45, 51]. A total of 123 cancers were detected in these four studies. Extensive malignancy screening (pooled data across the different diagnostic modalities) increased the number of early-stage previously undiagnosed cancer detection from 17 cases (13.8% (95% CI: 8.8 to 21.0) (limited malignancy screening only) to 27 cases (22.0% (95% CI: 15.6 to 30.1) [12, 35, 38, 44]. Only one study reported the rate of cancer-related mortality according to the screening strategy used [15]. An absolute difference in cancer related mortality of 1.9% (95% CI: -5.5 to 10.9%) was detected favoring the extensive screening strategy. No studies reported screening complications.

3.3.3.3 Quality Assessment

Thirteen studies were cohort studies. Four were retrospective studies and nine were prospective. One study compared an exposed and a non-exposed cohort (different centers) prospectively [52] and the last one was a RCT [15]. Quality assessment was done using the Newcastle – Ottawa quality assessment scale (Appendix 5) [21]. Thirteen cohort studies did not have an exposed (malignancy screening) and non exposed cohort (non malignancy screening) and therefore, comparability of cohorts could not be assessed (Appendix 5). The quality of the RCT was also evaluated using the same quality scale since the two arms of the RCT were used as cohorts without comparing outcomes between them. The RCT did not report on allocation concealment [22].

Table 8: Prevalent and Incident Cases of Previously Undiagnosed Malignancy

Studies	Total # of patients with VTE	Total number of previously undiagnosed malignancy	Prevalent cases diagnosed by limited screening alone	Prevalent cases diagnosed by extensive screening **	Incident cases diagnosed during follow-up	# of patients without new diagnosis of malignancy
Monreal 1991 [35]	All: 113 Unprovoked: 31	All: 12 Unprovoked: 7	All: 8 Unprovoked: 4	All: 11 Unprovoked: 7	All: 1 Unprovoked: 0	All: 101 Unprovoked: 24
Sannella 1991 [36]	All: 228 (Only 21 followed) Unprovoked: 21	All: 11 Unprovoked: 11	All: 3 Unprovoked: 3	All: 10 Unprovoked: 10	All: 1 Unprovoked: 1	All: 217 (only 10 followed) Unprovoked: 10
Barrelier 1992 [37]	All:125 Unprovoked: n/a	All: 3 Unprovoked: n/a	All: 2 Unprovoked: n/a	All: 3 Unprovoked: n/a	All: 0 Unprovoked: n/a	All: 122 Unprovoked: n/a
Monreal 1993 [38]	All: 78 Unprovoked: 27	All: 9 Unprovoked: 7	All: 6 Unprovoked: 4	All: 7 Unprovoked: 5	All: 2 Unprovoked: 2	All: 69 Unprovoked: 20
Pistorius 1994 [39]	All: 53 Unprovoked: 17	All: 9 Unprovoked: 9	All: 8 Unprovoked: 8	All: 8 Unprovoked: 8	All: 1 Unprovoked: 1	All: 44 Unprovoked: 8
Bastounis 1996 [40]	All: 293 Unprovoked: 86*	All: 29 Unprovoked: n/a	All: 13 Unprovoked: n/a	All: 24 Unprovoked: n/a	All: 7 Unprovoked: n/a	All: 264 Unprovoked: 86*
Cailleux 1997 [41]	All: 148 Unprovoked: 36*	All: 6 Unprovoked: n/a	All: 5 Unprovoked: n/a	All: 6 Unprovoked: n/a	All: 0 Unprovoked: n/a	All: 142 Unprovoked: 36*
Monreal 1997 [18]	All: 685 Unprovoked: 112	All: 34 Unprovoked: 23	All: 11 Unprovoked: 7	All: 26 Provoked: 16	All: 8 Unprovoked: 7	All: 651 Unprovoked: 89
Fahrig 1998 [42]	All: 318 Unprovoked: n/a	All: 24 Unprovoked: n/a	All: 20 Unprovoked: n/a	All: 24 Unprovoked: n/a	All: 0 Unprovoked: n/a	All: 294 Unprovoked: n/a
Netzer 1998 [43]	All: 135 Unprovoked: 135	All: 14 Unprovoked: 14	All: 8 Unprovoked: 8	All: 10 Unprovoked: 10	All: 4 Unprovoked: 4	All: 121 Unprovoked: 121
Equidanos 2002 [46]	All: 48 Unprovoked: 48	All: 8 Unprovoked: 8	All: 5 Unprovoked: 5	All: 6 Unprovoked: 6	All: 0 Unprovoked: 2	All: 40 Unprovoked: 40
Ronsdorf 2003 [44]	All: 485 Unprovoked: 236	All: 42 Unprovoked: 27	All: 14 Unprovoked: 10	All: 16 Unprovoked: 11	All: 26 Unprovoked: 16	All: 443 Unprovoked: 209
Monreal 2004 [12]	All: 864 Unprovoked: 345*	All: 61 Unprovoked: n/a	All: 34 Unprovoked: n/a	All: 47 Unprovoked: n/a	All: 14 Unprovoked: n/a	All: 803 Unprovoked: 345*

Piccioli 2004 [13]	All: 339 Unprovoked: 339	All: 56 Unprovoked: 56	All: 32 Unprovoked: 32	All: 45 Unprovoked: 45	All: 11 Unprovoked: 11	All: 283 Unprovoked: 283
Van Doormal 2007 [45]	All: 444 Unprovoked: 444	All: 28 Unprovoked: 28	All: 12 Unprovoked: 12	All: 16 Unprovoked: 16	All: 12 Unprovoked: 12	All: 416 Unprovoked: 416
Total	All: 4356	All: 346/4356	All: 181/346	All: 259/346	All: 87/346	All: 4010/4356
	Unprovoked: 1877	Unprovoked: 190/1877	Unprovoked: 93/190	Unprovoked: 134/190	Unprovoked: 56/190	Unprovoked: 1687/1877

*Number of provoked venous thromboembolic events diagnosed by limited and extensive occult malignancy screening not reported
** Pooled data across the different extensive screening strategies.

Table 9: Frequency of Various Types of Cancers Following Venous Thromboembolism Diagnosis

Cancer	Monreal [35]	Sannella [36]	Barrelier [37]	Monreal [38]	Pistorius [39]	Bastounis [40]	Cailleux [41]	Monreal [18]	Fahrig [42]	Netzer [43]	Enguidamos [46]	Ronsdorf [44]	Monreal [12]	Piccioli [13]	Van Doormaal [45]
Gastric (n=17)	2	0	0	0	0	2	0	3	1	0	0	1	6	2	n/a
Pancreas (n=25)	1	2	0	0	0	5	1	2	2	2	1	3	3	3	n/a
Colon/rectal (n=49)	2	1	0	3	2	10	1	6	3	3	1	7	7	3	n/a
Esophageal (n=1)	0	0	0	1	0	0	0	0	0	0	0	0	0	0	n/a
Liver/Biliary tree (n=7)	0	1	0	1	0	0	1	1	0	0	0	0	2	1	n/a
Lung (n=32)	1	1	0	0	0	2	0	1	4	0	4	8	7	4	n/a
Bladder (n=14)	2	0	0	0	0	1	1	2	1	2	0	0	2	3	n/a
Kidney (n=12)	0	1	0	0	0	1	0	1	3	0	0	2	3	1	n/a
Ovarian (n =13)	0	3	0	1	0	1	0	2	1	0	0	1	3	1	n/a
Uterus/cervix (n=10)	0	1	0	0	1	1	1	1	1	0	0	0	3	1	n/a
Prostate (n=36)	0	0	0	2	2	3	0	9	2	1	0	5	10	2	n/a
Testicular (n=1)	0	0	0	0	0	1	0	0	0	0	0	0	0	0	n/a
Breast (n=14)	0	0	0	1	1	1	0	1	1	2	0	3	2	2	n/a
CLL (n=3)	2	0	0	0	0	0	0	0	1	0	0	0	0	0	n/a
Multiple Myeloma (n=1)	0	0	0	0	0	0	0	0	0	0	1	0	0	0	n/a
Lymphoma (n=10)	0	1	0	0	0	0	0	2	2	1	0	3	1	0	n/a
MPD (n=6)	0	0	2	0	1	0	0	0	0	0	0	2	1	0	n/a
Acute leukemia (n=6)	0	0	0	0	0	1	0	0	1	0	0	1	3	0	n/a
Sarcoma (n=2)	0	0	0	0	0	0	1	0	0	0	0	0	1	0	n/a
ENT (n=7)	0	0	0	0	0	0	0	2	0	0	0	3	2	0	n/a
Hemamgioendothelioma (n=1)	0	0	0	0	0	0	0	0	1	0	0	0	0	0	n/a
Brain (n=1)	0	0	0	0	0	0	0	0	0	0	1	0	0	0	n/a
Adrenal (n=1)	0	0	0	0	0	0	0	0	0	0	0	0	0	1	n/a
Skin (n=3)	1	0	0	0	1	0	0	0	0	0	0	1	0	0	n/a
Unknown (n=14)	1	0	1	0	1	0	0	1	0	3	0	2	5	0	n/a
Not defined (n=60)	0	0	0	0	0	0	0	0	0	0	0	0	0	32	28

CI: Confidence intervals; CLL: Chronic lymphocytic leukemia; ENT: Ear nose and throat; MPD: Myeloproliferative disorder.

3.4 Discussion of the Systematic Review

The systematic review demonstrates that previously undiagnosed malignancies are frequent in patients with unprovoked VTE. The period prevalence of previously undiagnosed malignancy in patients with unprovoked VTE is 7.4% (95% CI: 6.4 to 8.5) at baseline and 12.1% (95% CI: 10.6 to13.7) from the time of VTE diagnosis to 12 months. Therefore, one in ten to one in fourteen patients with unprovoked VTE will be diagnosed with malignancy in the year following a diagnosis of unprovoked VTE. This highlights that previously undiagnosed malignancy detection in patients with unprovoked VTE is an important area of research. On the other hand, it appears that occult malignancy screening in patients with provoked VTE is less important and should not be considered in clinical practice or future research. This review adds to the literature by reporting pooled estimates of the period prevalence of previously undiagnosed malignancy at baseline and during subsequent follow-up up to 1 year.

This systematic review is also the largest and most comprehensive assessment of the incremental value of an extensive compared to a more limited malignancy screening. It showed that using an extensive screening strategy, in particular adding a CT abdomen/pelvis to a limited screen, detects more malignancies compared to a limited screening strategy alone, without reported complications. However, due to the lack of reporting in the studies, it is still unclear if an increase in previously undiagnosed malignancy detection will result in a

significant change in the detection rate of early stage cancers, or a decrease in malignancy related morbidity, malignancy related mortality or overall mortality. It is important to assess if extensive screening strategy will not only result in lead time or length time biases. Lead-time bias suggests that the natural history of the disease is not truly affected by screening. For example, a patient with new unprovoked VTE may be diagnosed with prostate cancer at 50 years of age through tumor makers during extensive screening strategy. He then undergoes treatment but ultimately progresses and dies at 60 years of age. Accordingly, the same patient without extensive malignancy screening develops symptomatic bony metastases at age 58, undergoes treatment and dies at age 60. Although the diagnosis was made 8 years earlier in the first scenario through extensive malignancy screening, his death was not affected by screening or early detection. Length-time bias is slightly different but also suggests no benefit to screening. Length-time bias suggests that extensive malignancy screening would be more likely to detect slow-growing tumors and not the fast-growing and potentially more lethal tumors. Ensuring that extensive malignancy screening does not lead to lead-time and length-time biases is before recommending screening to all patients with unprovoked VTE. Finally, as discussed below, important consequences of extensive malignancy screening including anxiety, complication (including radiation exposure), discomfort from extensive screening procedures, burden of additional tests for false positives and cost effectiveness, could not be assessed.

These previously undiagnosed malignancies may be important to diagnose for a variety of reasons. First, patients with malignancy are at higher risk of recurrent VTE and bleeding despite adequate anticoagulation with vitamin K antagonists [19]. The overall incidence of recurrent VTE in patients with malignancy is 30.0 per 100 patient-years as compared with 12.8 per 100 patient-years in those without malignancy, while the incidence for major bleeding is 15.7 and 8.6 per 100 patient-years respectively [19]. Therefore, malignancy-related VTE are preferably treated with at least six months of low molecular weight heparin to prevent recurrent VTE [9]. Secondary prophylaxis using LMWH was shown to decrease the rate of recurrent VTE by 52% at 6 months [10] and potentially increase survival in patients without metastatic disease [11] when compared to vitamin K antagonists. Second, detecting undiagnosed malignancy earlier might lead to an increase in the rate of "curable" malignancies and potentially result in increased survival. Population registry studies have suggested that approximately 40% of the previously undiagnosed malignancies diagnosed during follow-up were already metastatic at the time of diagnosis [4-5]. Unfortunately only 4 studies reported the frequency of detection of early-stage previously undiagnosed malignancies using extensive compared to limited occult malignancy screening [14, 42, 45, 51]. Combining the prevalence of these four studies showed that an extensive malignancy screening (pooled results from all diagnostic modalities) detected more early stage previously undiagnosed malignancies compared to the limited malignancy screen. However, the small numbers of early malignancies detected in each individual trial limit the interpretation of the pooled result. One study evaluated

the impact of extensive malignancy screening on cancer prognosis [15]. The investigators found an absolute 1.9% (95% CI: -5.5 to 10.9) reduction in malignancy related mortality but the study was underpowered to find a statistically significant difference. Only 201 of the projected 1000 patients deemed required by the sample size calculation were enrolled in the study [15]. Physicians favoring extensive malignancy screening and the use of a Zelen randomization procedure were major obstacles to successful completion of the study. Finally, detecting malignancies earlier may prevent malignancy associated morbidity potentially leading to an increase in quality of life. Further research is urgently required to evaluate the impact of previously undiagnosed malignancy detection on mortality and quality of life.

The SOMIT trial has demonstrated that a RCT is not possible in the context of this clinical question [15]. The SOMIT investigators attempted a RCT design, but were only able to recruit 20% of the expected number of patients due to "patient and physician's unwillingness to participate" and were thus underpowered to evaluate important clinical endpoints [15]. This unwillingness to randomize or be randomized appears to be due to the substantial risk of previously undiagnosed malignancy in patients with unprovoked VTE (as previously detailed, approximately 10%). Patients are therefore understandably reluctant to enter a study that promises an even chance of receiving less aggressive investigations for underlying undiagnosed malignancy. The SOMIT investigators used a Zelen randomization (only the experimental group received complete information about

the study after randomization) to avoid having to disclose the underlying risk to the participants in the control arm. Several ethics committees at potential participating centers felt that Zelen randomization was unethical making it impossible for the study to recruit sufficient centers and hence patients to reach their original target sample size. Furthermore, physicians at participating centers favored extensive malignancy screening for their patients. Given that all investigations included within the extensive malignancy screening strategy (e.g. U/S, tumor markers) were available to physicians and patients outside of the clinical trial, many physicians with patients enrolled into the control arm conducted most, if not, all of the "extensive" investigations. Fifteen percent of patients in the control group underwent abdominal U/S and 20% had tumor maker testing done. Therefore, in order to evaluate the impact of extensive malignancy screening on mortality and quality of life years, investigators will have to: 1) use an alternative trial design where patients are not asked to accept (what they or their physicians perceive as) a chance of receiving less than adequate care; and 2) Assess a new technology not available outside of a clinical trial.

The components of an ideal extensive malignancy screening are still unknown. The meta-analysis favors a strategy combining a limited screen to a CT abdomen/pelvis. A decision analysis using the SOMIT trial reported similar findings [56]. A screening strategy combining limited screen and CT abdomen/pelvis has a number needed to screen (NNS) of 10 [56]. Di Nisio and colleagues have demonstrated that the accuracy that particular strategy could be

improved by the addition of a colonoscopy (NNS of 9) [56]. In other words, nine patients with unprovoked VTE need to be screened with limited screen and CT abdomen/pelvis in combination with a colonoscopy to find one previously undiagnosed malignancy. Limited screen in combination with U/S of the abdomen alone, U/S of the abdomen and colonoscopy or U/S abdomen and tumor markers have a NNS of 19.8, 16.5 and 16.5 respectively. Therefore, a screening strategy that combines limited screen, CT abdomen/pelvis and colonoscopy might represent the ideal extensive malignancy screening regimen. However, before recommending an extensive screening strategy to all patients with unprovoked VTE, a number of factors must be considered including: 1) morbidity and cost of extensive screening; 2) risks of invasive diagnostic procedure to confirm the presence of malignancy; 3) incidental findings and their associated morbidity and 4) psychological burden associated with new diagnosis of malignancy or false-positives. Furthermore, the recent advances in diagnostic imaging modalities (three-dimensional CT display, FDG-positron emission tomography, etc) may help also to improve the rate of detection of previously undiagnosed malignancies in patients with VTE.

3.5 Limitations

First, the sensitivity and specificity of both malignancy screening strategies could not be calculated. Ideally we would have reported the sensitivities and specificities for each malignancy strategies and their component individual modalities, however, false positive results (positive diagnostic test results without

ultimately malignancy diagnosis) were not reported in a large majority of studies making calculations of sensitivities and specificities impossible. Second, the cost of extensive malignancy screening can be substantial and this was not accounted for in the present analysis. Cost-effectiveness analysis should be performed alongside of any future trial done regarding this clinical question. Third, results from retrospective and prospective studies were pooled which may lead to an overestimation of the overall effect. Fourth, the variation between the studies was elevated in the analyses assessing the pooled estimates of the period prevalence. A number of factors might have lead to the significant heterogeneity among the trials results. Some studies have a retrospective horizon while others are prospective. Retrospective studies may not be able to capture all the previously undiagnosed malignancies and therefore may bias the estimate towards the null effect. Furthermore, the definitions of "provoked" VTE was heterogeneous among studies. Some investigators included weaker provoking factors such as known thrombophilia, legs varices, previous VTE, congestive heart failure and peripheral vascular disease. Individual patient data on predisposing factors of VTE and study outcomes were not reported in a large majority of studies making it difficult to apply a uniform definition of provoked and unprovoked VTE. This may have led to an ascertainment bias with some patients with "unprovoked" VTE, as defined by more accepted definitions, being categorized in our study as patients with provoked VTE. This would have biased towards a null effect in some studies when comparing the period prevalence of newly diagnosed malignancy in provoked to unprovoked VTE patients, likely led

to lower estimates of period prevalence in unprovoked VTE patients and higher estimates of period prevalence in provoked VTE. Fifth, the additional benefit of an extensive malignancy screening strategy could have been evaluated by pooling the absolute difference in proportion between the two screening strategies for all the individual studies. This could have permitted assessment of the pooled absolute difference in the proportion detected by an extensive screening strategy. However, given that all but one of the studies were non-randomized these differences in proportions likely would have been biased. Hence, we chose the more descriptive approach of pooling the proportion and analyzing confidence intervals around the proportions for the thesis. Sixth, formal publication bias assessment could not be performed. Funnel plots could be used to plot the standard error over the odds ratio, relative risk or risk difference of each individual study. Unfortunately, period prevalence or proportion of additional previously undiagnosed malignancy detected cannot be plotted in a funnel plot. Although we might have captured an unbiased sample of the studies published on previously undiagnosed malignancy in patient with VTE, our pooled estimates might be biased by publication bias. Seventh, the proportions of previously undiagnosed malignancies detected in Table 5 are biased to short term follow-up and might be different in longer term follow-up as more previously undiagnosed malignancies may become evident. Eight, most studies did not report all important components required by the Newcastle-Ottawa Quality assessment scale limiting the interpretation of the quality assessment. However, as reported in Appendix 4 and 5, the studies were reasonably homogeneous regarding the

quality. Ninth, the assessment of the agreement between reviewers (selection of article, data extraction, quality assessment) using the kappa statistics was not performed. Finally, we were unable to review all non-English publications.

3.6 Conclusion

The incidence of previously undiagnosed malignancy is high in patients with unprovoked VTE. An extensive malignancy screening strategy including a CT of the abdomen/pelvis seems to be the most promising and detect statistically significantly more malignancies when compared to a more limited screening strategy but research performed to date is scarce especially regarding the impact of previously undiagnosed malignancy detection on mortality and quality of life years. A decision analysis using the data from the only RCT on the topic showed that a CT abdomen/pelvis in combination with colonoscopy has the smallest number needed to screen to find one occult malignancy (NNS = 9).

Although there are still many unanswered clinical questions justifying an intervention trial on extensive malignancy screening in patients with unprovoked VTE, it might be a difficult task to initiate and conduct a trial based on previously published experience [15]. The SOMIT trial has demonstrated that a straight RCT is not possible in this context. Therefore, an alternative trial design might be a possible solution. Nonetheless, a trial assessing the benefits of an extensive malignancy screening strategy is needed.

4.0 TRIAL PROTOCOL

4.1 Rationale for the Comprehensive Computed Tomography

The previous systematic review suggests that the highest yield for an extensive screening intervention might include the combination of a limited malignancy screen to a CT of the abdomen/pelvis. As discussed above, a decision analysis also showed that the addition of a colonoscopy to this extensive screening strategy might increase the accuracy [56]. A comprehensive CT (cCT) includes a CT abdomen/pelvis and a virtual colonoscopy. It also provides value beyond a CT abdomen/pelvis because it will assess other organs frequently associated with thrombosis (pancreas, ovaries, and stomach) [4-5]. A cCT includes a virtual colonoscopy and gastroscopy, a biphasic enhanced CT for hepatoma and renal cell carcinoma, parenchymal pancreatogram with minimum intensity projection (MinIP) reformation for pancreatic carcinoma, and finally uniphasic enhanced CT of distended bladder for bladder and ovarian carcinomas. A screening strategy combining a limited malignancy screen and a cCT could have potentially detected all the malignancies diagnosed in the extensive screening group of the SOMIT RCT [15].

Three-dimensional CT displays including virtual colonoscopy (VC) and virtual gastroscopy (VG) are becoming an increasingly popular screening tool for malignancy. Three-dimensional CT displays are less invasive than optical

endoscopy but immediate intervention (polyp removal or biopsy) cannot be performed. At this time, three multi-center trials of VC compared to optical colonoscopy (OC) have been published [57-59]. They demonstrated that VC is comparable to OC for screening of colon cancer [57-59] in symptomatic and asymptomatic patients. A recent meta-analysis of 2610 patients, mostly from single-center studies, demonstrated that virtual colonoscopy had a sensitivity of 95.5% (95% CI 91.4-98.5%) in the detection of symptomatic malignancy [60]. VC as a diagnostic tool on a per-patient basis has a high average sensitivity (93%, 95%CI 73-98%) and average specificity (97%, 95% CI 95%-99%) for larger (> 1cm) colorectal polyps [60]. VC seems sufficiently sensitive and specific in the detection of colon cancer and large and medium polyps. Virtual gastroscopy is a new evolving technology. A recent report of a prospective pilot study demonstrated the feasibility and safety of performing virtual gastroscopy [61]. The gastric lumen from the cardia to the pylorus was well visualized in all patients. Prospective studies comparing VG to endoscopy are currently ongoing.

4.2 Rationale for the Current Study

An extensive malignancy screening strategy that combines a limited screen to a CT abdomen/pelvis seems to detect more previously undiagnosed malignancies than limited screen alone in patients with unprovoked VTE. Early detection of previously undiagnosed malignancies can potentially decrease malignancy-related morbidity, mortality and VTE recurrence. The cCT is potentially a non-invasive, sensitive occult malignancy screening tool.

Although a trial assessing the accuracy and usefulness of using a cCT as an extensive malignancy screening strategy tool is needed, it is unclear what study design would be optimal to address this important clinical question. As discussed above, the SOMIT investigators attempted a straight RCT design, but were only able to recruit 20% of the expected number of patients due to "patient and physician's unwillingness to participate" and were thus underpowered to evaluate important clinical endpoints [15]. Many patients found it unacceptable not to have all available screening tests conducted to search for malignancy given that they have a one in ten chance of having an previously undiagnosed malignancy. A prospective cohort study, where all participants have a limited screen and cCT (i.e. no control group), could have significant performance and measurements biases. A performance bias would result in systematic differences in care provided apart from the intervention being evaluated. Without standardization of care protocol and blinding of clinicians, health care provider might respond differently for abnormal results seen on the extensive compared to the limited occult malignancy screening. For example, a patient with an occult renal cell carcinoma would present with high hemoglobin on limited malignancy screen and a renal mass seen on the cCT. The care would obviously differ between both results. The increased hemoglobin might be repeated for confirmation before requesting further tests whereas the renal mass will be immediately referred for biopsy.

A measurement bias would lead to differences between comparison groups in how outcomes are ascertained. In the previous example, the previously

undiagnosed malignancy detected might be attributed to the extensive screening strategy (renal mass on CT abdomen/pelvis) even if the limited screen was initially abnormal (increased hemoglobin). Standardization of care protocol, a comparator group without the intervention (i.e. control), and blinding the outcome assessors should minimize performance and measurement biases.

A matched clustered randomized controlled trial randomizing time periods to the intervention or to a comparator group instead of individual would potentially be a desirable study design. Although a this type of design could not completely control selection bias as a RCT would, generating a random sequence of time periods for allocating participants would offer better control than a prospective cohort study. Such methods fail to conceal the allocation sequence from caregivers but could potentially increase patient and physician's willingness to participate since the allocation assignment is known upon enrolment. An informal survey of thrombosis expert at the Ottawa hospital showed that basic blood work, CXR, breast and prostate malignancy screening are perceived as standard of care for patients with newly diagnosed unprovoked VTE. Using these tests as the comparator group would make patients and physicians avoid accepting what they perceived as an inferior screening. Instead they would be asked to participate in an intervention study assessing a new technology (i.e. cCT) not yet available outside of clinical trials.

4.3 Study Protocol

4.3.1 Objectives of the Study

4.3.1.1 Primary Objectives:

- To determine if a screening strategy using cCT in addition to limited malignancy screen detects more previously undiagnosed malignancies than a limited malignancy screen alone in patients with unprovoked VTE.

4.3.1.2 Secondary Objectives:

- To determine the difference in overall mortality between the two screening strategies at two-years.
- To determine the difference in recurrent VTE between the two screening strategies at two years
- To determine if cCT independently detects more early ($T_{1\text{-}2}N_0M_0$) previously undiagnosed malignancies than a limited malignancy screen
- To conduct a cost-utility analysis comparing the screening strategy combining limited malignancy screen and cCT to limited malignancy screen alone.

4.3.2 Hypothesis of the Study

4.3.2.1 Primary:

- A screening strategy using a limited malignancy screen in combination with cCT detects more previously undiagnosed malignancies than a limited malignancy screen alone in patients with unprovoked VTE.

4.3.2.2 Secondary:

- Patients undergoing an extensive screening strategy including cCT in combination to limited screen will have less VTE recurrence compared to patients undergoing limited screen alone.
- Patients undergoing an extensive screening strategy including cCT in combination to limited occult malignancy screen will have decrease overall mortality compared to those undergoing a limited screen alone.
- The screening strategy using limited occult malignancy screen + cCT detects significantly more early ($T_{1\text{-}2}N_0M_0$) previously undiagnosed malignancies than a limited malignancy screen alone.
- The screening strategy using cCT in addition to limited malignancy screen is cost-effective.

4.3.3 Methods

4.3.3.1 Study Design

Consecutive patients diagnosed with unprovoked VTE at The Ottawa Hospital (TOH) Thrombosis Unit will be approached to participate into the study. Blocks of 16 weeks will be divided in two consecutive 8-week intervention time-periods (A or B). Time-periods will be randomly assigned to two different malignancy screening strategies (Figure 6 and 7). Within each block, one 8-week time period will be randomly allocated to the limited malignancy screen and the other will be allocated to the limited malignancy screen and cCT screening strategy. Participants providing informed consent will be assigned to either strategy based on the date of the participant's radiological diagnosis of VTE. All abnormal findings on limited malignancy screen and/or cCT will be followed by documented

investigations to confirm or refute suspected previously undiagnosed malignancy (i.e. presence or absence of tissue proven malignancy). The radiologist analyzing the cCTs will be blinded to the results of the limited malignancy screen. Following this period of initial investigations all the participants will be followed for two years.

Figure 6: Randomization of Time Periods

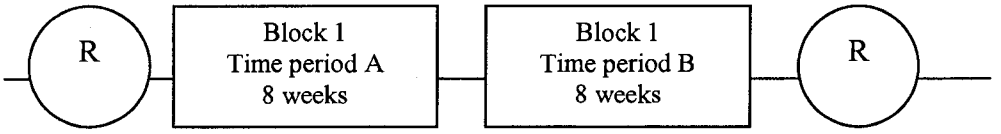
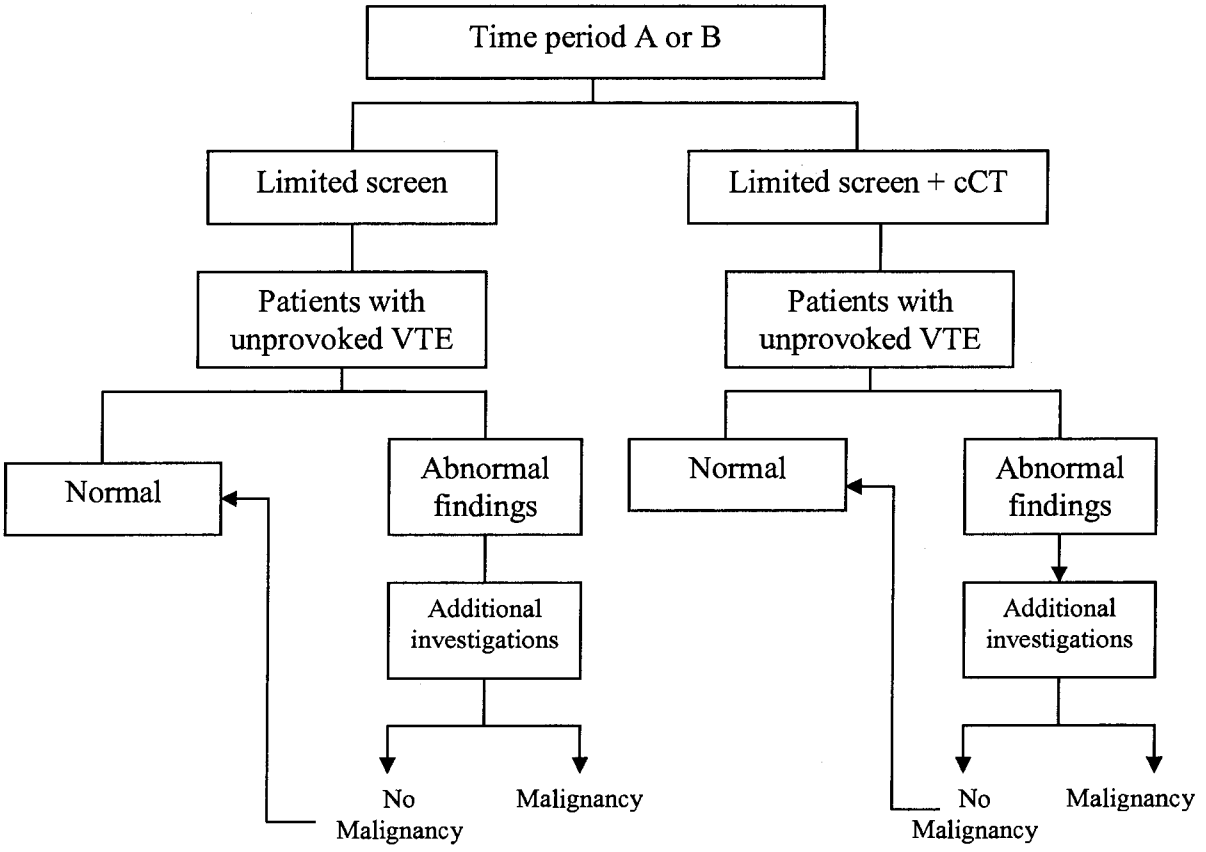


Figure 7: Study Design



4.3.3.2 Study Participants

4.3.3.2.1 Study Participants

At their 1 week (2 days to 4 weeks) follow-up visit after a diagnosis of unprovoked VTE, patients at the Thrombosis Unit of the TOH will be approached for participation in the study.

4.3.3.2.2 Inclusion Criteria:

New diagnosis of unprovoked*** proximal deep vein thrombosis (DVT)* or pulmonary embolism (PE) **

* DVT: Proximal DVT on venous compression U/S or venogram.

** PE: i) Patients with a high/intermediate pre-test probability (Wells' model > 4) + high probability V/Q scan

ii)) Positive pulmonary angiogram

iii) Spiral CT demonstrating intraluminal filling defect in a vessel larger than a segmental artery;

*** Unprovoked: no known risk factors for thrombosis including:

i) Known active cancer;

ii) Recent (less than 3 months) paralysis, paresis or plaster immobilization of the lower extremities

iii) Recently bedridden for period of 3 or more days, or major surgery, within the previous 12 weeks requiring general or regional anaesthesia

iv) Previous unprovoked VTE

v) Known thrombophilia (hereditary or acquired)

vi) Current pregnancy

4.3.3.2.3. Exclusion Criteria:

(i) Age < 18 years-old;

(ii) Refusal or inability to provide informed consent;

(iii) Allergy to contrast media;

(iv) Creatinine clearance < 60 ml/min;

(v) Claustrophobia or agoraphobia;

(vi) Weight > 130 kg;

(vii) Ulcerative colitis: Increased risk of perforation during the colon dilatation for cCT

(viii) Glaucoma: Absolute contraindication for treatment with hyoscine butylbromide which is requested for cCT

4.3.4 Interventions

4.3.4.1 Limited Malignancy Screening

A complete history including a complete review of symptoms of all body systems and a complete physical examination on all study patients will be performed by the referring physician. History, physical examination findings and baseline characteristics including patient's demographics, VTE risk factors and qualifying episode of VTE will be collected (See Appendix 6).

The limited malignancy screening test included:

- Blood testing:
    - Complete blood count and electrolytes
    - Liver and renal function tests

- Calcium
- Chest X-ray

As per Canadian Task Force on Preventive Health Care and the US Preventive Services Task Force [62-63]:

- In women:
  - Breast examination
  - Pap smear
  - Pelvic examination
  - Mammogram (> 50 years old) if not conducted in last year
- In men:
  - Prostate examination +/- a prostate-specific antigen testing (>40 years old)

If the mammogram, pap test, prostate examination or PSA were performed within the last year, they will not be repeated but final report or documentation of findings will be collected from family physicians.

4.3.4.2 Limited Malignancy Screening + Comprehensive Computed Tomography

Participants allocated to the limited malignancy screen + cCT will have all the investigation described above in combination with a cCT. The cCT protocol is described in Appendix 7. The cCT should be performed within 6 weeks of

enrolment into the study. It is a reasonable delay since it corresponds to the waiting time for a non-urgent CT abdomen/pelvis at the Ottawa Hospital.

Any other subsequent investigations to confirm/refute malignancy will be performed as appropriate.

4.3.5 Study Visits

4.3.5.1 *Enrolment* Visit (Visit 1)

Consent will be obtained and signed. Baseline characteristics including patient's demographics, thrombotic risk factors and qualifying episode of VTE will be obtained (See Appendix 6). Limited malignancy screen including history, physical examination, basic blood work and routine diagnostic imaging will be performed. Preference-based EQ-5D questionnaire will be completed by the study participants.

4.3.5.2 Visit 2 (For Patients assigned to a Limited Malignancy Screen + Comprehensive Computed Tomography): Day 7-42:

If time period at the time of their VTE diagnosis (time of VTE diagnosis defined as date of imaging procedure confirming VTE) is assigned to limited malignancy screen + cCT, then a cCT will be performed within 6 weeks (see protocol in Appendix 7). Any other subsequent investigations to confirm/refute malignancy will be performed as appropriate.

4.3.5.3 Follow-up:

Telephone Interviews (Follow-up for Cost-Utility Analysis):

Telephone interviews will be conducted every 3 months to collect the resource utilization for each patient (See Cost-Utility analysis protocol below).

In-person Interview (Follow-up for malignancy development):

Visit 3: Day 150-190, Visit 4 Day 340-370, Visit 5 Day 520-550, Visit 6 Day 700 to 730

The interviews will determine if the participant was diagnosed with an previously undiagnosed malignancy during the follow-up period. If a new malignancy was diagnosed, chart review will be conducted to document the localization of the primary malignancy, the TNM classification, the treatment and the prognosis of the malignancy. Patients will complete the preference-based EQ-5D questionnaire at the last interview (Visit 6).

4.3.6 Outcome Measures

4.3.6.1 Primary Outcome:

- Previously undiagnosed malignancy after unprovoked VTE: Biopsy proven tissue diagnosis of malignancy diagnosed from the time of VTE diagnosis to completion of the malignancy screening strategy.

4.3.6.2 Secondary Outcomes:

- Recurrent VTE

- Two year overall mortality
- Early previously undiagnosed malignancy: $T_{1\text{-}2}N_0M_0$ as per the World Health Organization TNM classification system.
- QALYs gained: Calculated by multiplying the number of "life-years saved" (additional previously undiagnosed malignancy detected by adding the cCT screening strategy) by a standard weight that reflects the Health Related Quality of Life (HRQL) during that time. Systematic reviews will be conducted to define "life-years saved" by long term-cure rates and prognosis of common malignancies after treatment. Preference-based scores will be measured indirectly using the EQ-5D instrument.
- Incremental cost-effectiveness ratio (ICER) at two-year
- Adverse events with cCT: Any adverse events with cCT will be described and documented

4.3.7 Sample Size

A total of 11.6% (32/274) of the patients (provoked VTE only) in the SOMIT RCT were diagnosed with cancer after the limited malignancy screen [15]. An additional 13% (13/99 in extensive screening arm) were diagnosed following extensive occult malignancy screening [15]. A cCT would have potentially detected all the malignancies in the extensive screening group of the SOMIT RCT. Based on expert opinions, the minimal clinical significant difference (MCID) was felt to be 6%. That is, we feel that conducting greater than 13 cCT to detect one malignancy (Some of which will be incurable) is unlikely to be more acceptable

than alternate strategies (e.g. using abdominal ultrasonography and colonoscopy; NNS of 16) especially when one considers radiation exposure, the risks of IV contrast agents (risk of anaphylaxis and renal failure) and the downsides of false positives (anxiety, additional tests (cost, invasiveness, discomfort). We have designed our study to have 80% power to detect the MCID. This will require a sample size of 558 (279 per group). Since we expect to conservatively recruit 12 participants per month, a study period of 4 years will provide us with approximately 580 and yield to at least 80% power.

4.3.8 Statistical Analysis

4.3.8.1. Primary Analysis:

The primary analysis will compare the number of additional previously undiagnosed malignancies detected by the screening strategy of limited malignancy screen + cCT to the number of previously undiagnosed malignancies detected by the limited occult malignancy screen alone.

The one-sided null hypothesis that the number of previously undiagnosed malignancies detected per 100 patients is identical under the two screening strategies will be tested using the standard normal test for a proportion. Rejecting the null hypothesis will be evidence that cCT detects previously undiagnosed malignancies that are missed by the limited malignancy screen alone. We will also compute a 95% confidence interval for the number of additional cases of previously undiagnosed malignancies detected. Kaplan Meier analysis to

examine time to previously undiagnosed malignancy detection will be conducted over the 2 years follow-up period for both groups.

4.3.8.2. Secondary Analysis:

For secondary analysis a number of analysis will be performed: (1) Kaplan Meier analysis to examine survival between both groups; 2) Difference in proportion between the two groups for number of recurrent VTE; 3) Difference in proportion between the two groups for the number of early previously undiagnosed malignancies ($T_{1\text{-}2}N_0M_0$) detected; 4) Similar analysis for the number of QALYs gained between the two groups; 5) Descriptive statistics will be used to determine proportions of study participants experiencing adverse reactions to cCT.

4.3.9 Cost-Utility Analysis Design:

A prospective cost-utility analysis (CUA) within the framework of a decision analytic model will be conducted using data collected prospectively alongside the trial. The result of the CUA will be expressed as an incremental cost-effectiveness ratio: the incremental cost per QALY gained.

4.3.9.1 Perspective:

The principal perspective will be of the public payer in Canada. The related costs associated with this perspective include the direct costs to publicly funded health care system and direct costs to publicly funded services other than health care. As sensitivity analysis we will adopt a quasi societal perspective by including direct costs to patients and their families. Productivity costs will not be included in

the analysis since their magnitude and impact is likely to be insignificant on the result of the analysis.

4.3.9.2 Effectiveness and Time Horizon

Effectiveness will be defined in terms of gain in QALYs associated with additional previously undiagnosed malignancies detected by cCT during the trial. Data and parameters used to define the effectiveness will be extracted from the trial.

Primary analysis will have a time horizon for both costs and outcomes of two years. Secondary analysis will involve modeling over a longer term horizon (ten years) based on assumptions relating to long term disease incidence.

4.3.9.3 Modeling:

Appendix 10 represents the structure of the decision analysis tree. Patients will be assumed to experience two types of outcomes following screening: 1) normal tests, or 2) abnormal tests. The model tries to simulate real life situations, with patients cycling through the different cancer status following screening. Patients can be diagnosed with a new malignancy following screening or later on during follow up (i.e. missed by the screening strategy).

4.3.9.4 Input parameters:

Transition probabilities

Transition probabilities to populate the decision model will be obtained directly from the trial.

Utilities

Utility values will be obtained for each patient at three month intervals throughout the trial. Values will be obtained by the patients completing the EQ5D a validated indirect utility measurement tool which has been successfully adopted in a number of clinical trials in a variety of settings. This will allow measurement of utilities with and without the incidence of VTE.

Resource use

Resource use will be obtained directly from the trial. Resource used will be collected at baseline and every 3 months thereafter. Information on the following items will be collected: initial screening strategy and further investigations; baseline and routine monitoring of patients; and treatment of the newly diagnosed malignancy including physician fees and hospitalization (if required).

Costs

Costs are the only input parameter which will not be directly obtained from the trial. Costs for the cCT, the limited malignancy screen and any other outpatient diagnostic investigations will be based on the OHIP Schedule of Fees (2005). Costs for laboratory tests will be derived from the Ontario Schedule of Benefits for Laboratory Services (2005). Physician's services for the medical consultations and interpretations of the diagnostic investigations will also be based on the OHIP Schedule of Fees (2005).

The case-costing data for hospital resources will be obtained from an on-line resource-utilization-based-patient-specific cost accounting system (TI 1985). This system measures the resources by each patient (with a certain diagnosis) and assigns a fully allocated cost to those resources (e.g. nursing time units [direct and indirect costs]). Chemotherapy medication given to patients diagnosed with new malignancy will be based on hospital pharmacy acquisition costs. Costs of new medications taken by the patients will be based on Canadian market prices. Unrelated costs that are incurred during normal life-years will be excluded from the evaluation. Unrelated costs that are incurred during life-years gained from cCT will be included in the sensitivity analysis

4.3.9.5 Economical Analysis

For both screening strategies, the total cost and QALYs up to two years will be measured. This will facilitate measurement of the incremental cost per QALY gained for the more effective treatment option. In addition, stratified analysis will be performed to account for variability within the study population. Analysis will be stratified by age group and gender.

Deterministic sensitivity analysis using simple sensitivity analysis, threshold and analysis of the extremes will be executed for all model inputs. In addition, probabilistic sensitivity analysis using Monte Carlo simulations will be conducted using the Crystal Ball ® simulation software by employing probability distributions for transition probabilities, utility and costs derived from the study. Analysis will be conducted by replicating the model 5000 times to estimate a set of 5000 outcomes. The results from the Monte Carlo simulation will be presented by 95% certainty intervals for costs and QALYs and by a cost-effectiveness acceptability curve.

4.3.10 Feasibility

The TOH Thrombosis Unit will evolve into a Regional Thrombosis Program in the next year and expects approximately 3-4 additional new cases of patients with unprovoked VTE per week to be managed by our unit (i.e. double our current volumes). With a conservative accrual rate of 12 patients per month, 558 patients can be recruited within 4 years.

4.3.11 Ethical Issues

The Ottawa Hospital Research Ethics Board has approved all aspects of the current protocol. Strict patient confidentiality will be maintained for the patients enrolled in the study. Patients will only be identified by their initials, date of birth and hospital chart number in the database. Patients will not be identified in any publication or presentation resulting from this project.

4.3.12 Safety

Patients will be carefully assessed prior to enrolment to ensure that patients satisfy the inclusion/exclusion criteria. Given the study's hypothesis and trial design, it is anticipated and likely that patients undergoing the screening strategy using limited malignancy screen and cCT will have more incidental findings detected and hence, more additional investigations than the limited malignancy screen alone group. The number of patients requiring further investigations for abnormal cCT and/or limited occult malignancy screen and the complete battery of testing done will be recorded. Any complications associated with additional investigation will be captured and reported.

The total radiation dose required for a cCT is approximately 15 to20 mSv which is comparable to a regular contrast-enhanced abdomen/pelvis CT.

4.3.13 Research Team

Dr Carrier will be the Principal Investigator. Dr Rodger will be the nominal Principal Investigator and will supervise Dr Carrier in this role. Dr Carrier is currently a CIHR Fellow, a thrombosis clinical fellow, a Clinical Investigator

Program fellow and an MSc in Epidemiology candidate. Drs Rodger and Wells are Senior Scientists with the Clinical Epidemiology Program of the Ottawa Health Research Institute, hematologists and clinical epidemiologists. They have extensive experience in the conduct and analysis of case control, cohort and randomized trials in the area of venous thrombosis. Dr Coyle is a professor with the department of Epidemiology and Community Medicine at the University of Ottawa. Dr Coyle has extensive experience in the conduct and analysis of cost-utility studies. Dr Le Gal is an associate professor of Medicine in Brest, France and a Thrombosis fellow at the University of Ottawa. He has a PhD in clinical epidemiology and will contribute to the study as a content and methodological expert for the study. Dr Tao is an associate professor in Radiology at the University of Ottawa. Dr Tao will provide both content expertise and interpretation of all cCT.

5.0 PILOT STUDY

As described above, the cCT is potentially a non-invasive, sensitive occult malignancy screening tool. However, before performing a large study examining cCT as an extensive occult malignancy screening strategy, a pilot study assessing the feasibility of such a study needed to be undertaken especially given the experiences of the only RCT evaluating malignancy screening in patients with unprovoked VTE which demonstrated that a straight RCT was not feasible [15].

5.1 Objectives of the Pilot Study

1. Obtain an estimate of the recruitment rate

   Goal:

   - Recruitment of 12 patients per month in the time periods allocated to limited screen alone and limited screen in combination with cCT

2. Obtain an estimate of previously undiagnosed malignancy event rate using a limited malignancy screening strategy alone and in combination with cCT.

   Goal:

   - Detection of a higher rate of previously undiagnosed malignancy detection in patients undergoing a limited screen + cCT as compared to limited screen alone.

3. Determine the feasibility of obtaining local cCT and their interpretation

   Goals:

   - Waiting time to cCT < 6 weeks
   - The cCT findings are correlating with histological diagnosis (gold standard)

5.2 Patients and Methods

5.2.1 Study Design

Consecutive patients with unprovoked VTE treated at the THO Thrombosis Unit were approach to participate in a matched cluster randomized controlled trial comparing two different malignancy screening strategy. The trial design randomized time periods to intervention (i.e. extensive occult malignancy screening strategy) or a comparator (limited occult malignancy screening strategy) (Figure 6 and 7). Patients were approached at their 1 week (up to 3 months) follow-up appointment to participate into the study. Therefore, calendar year was divided in blocks of 16 weeks starting at July 1st 2007 (Table 10). Each block consisted of two consecutive 8-week intervention time periods. Within each block, one 8-week time period was randomly allocated either to the limited malignancy screening strategy alone (comparator) or to the extensive malignancy screening strategy (intervention). The extensive occult malignancy strategy consisted of the limited malignancy screen in combination with cCT. The other time period within the same block was allocated to the alternative allocation

(comparator or intervention) (Table 10). Computer-based randomization of each block was performed by Dr Tim Ramsay (Statistician) before starting enrolment into the pilot study. Participants were assigned to the appropriate time period based on the date of the participant's radiological diagnosis of VTE to minimize selection bias or tampering by delaying enrolment of patients into a "preferred" time period. All abnormal findings on limited malignancy screen and/or cCT were followed by documented investigations to confirm or refute suspected malignancy (i.e. presence or absence of tissue proven malignancy). Dr Hardy Tao (radiologist) interpreted all cCTs.

Table 10: Time Period Randomization

Block	Time Period A	Start	End	Time Period B	Start	End
1	**C**	1/7/2007	25/08/2007	**T**	26/082007	20/10/2007
2	**T**	21/10/2007	15/12/2007	**C**	16/12/2007	9/2/2008
3	**T**	10/2/2008	5/4/2008	**C**	6/4/2008	31/05/2008

C: Control = Limited occult malignancy screening strategy alone;
T: Intervention = cCT + limited occult malignancy screening strategy

5.2.2 Outcome Measure

The primary outcome measure was recruitment rate. Secondary outcome measures included: Diagnosis of new previously undiagnosed malignancy after

VTE (i.e. primary outcome event rate for the full trial), refusal rate and adverse events with cCT. Data analysis was done using descriptive statistics and univariate comparisons.

5.2.3 Sample Size

A pilot study length of 16 weeks was originally decided a priori based on financial and convenient reasons. The original start date was July 1st 2007. However a number of factors have lead to the delay of starting recruitment. Delay in the final Ethics approval and financial constraints (average cost per patient for the study is 399.70$) were the major ones. Furthermore, other revenue generating competitive trials (i.e. enrolling patients with newly unprovoked VTE) limited the length of study. Nonetheless, all eligible patients diagnosed with unprovoked VTE were approached over an 18-weeks period starting on October 1st. The length of the study was prolonged by two weeks to account for the clinic's slow downs during the holiday season.

5.3 Results

5.3.1 Primary Outcome: Recruitment Rate

From October 1st 2007 to January 31st 2008, consecutive patients with unprovoked VTE were approached at their 1 week (up to 3 months) follow-up appointment to participate into the study. Forty-two consecutive patients with unprovoked VTE were approached over a 18-week period to participate into the pilot study. A total of 11 weeks were assigned to the limited screening in

combination to the cCT and 7 weeks to the limited screening alone (See Table 10). Thirteen (31.0%; 95% CI: 19.1 to 46.0) patients refused consent, 3/42 (7.1%; 95% CI: 2.5 to 19.0) were not eligible and 26/42 (61.9%; 95% CI: 46.8 to 75.0) were eligible and consented. Most patients (10/13 (76.9%; 95% CI: 49.7 to 91.8)) who chose not to participate were not interested in knowing if they had an underlying malignancy. The rate of refusal was similar between the two malignancy screening strategies. Three patients (37.5%; 95% CI: 13.7 to 69.4) refused to participate in the limited screen alone time period and 10 (32.3%; 95% CI: 18.6 to 49.9) refused to participate in the limited screen in combination with cCT time period (Table 11). The most common reason for exclusion of participants was the presence of abnormal renal function (n=3). Of the three patients ineligible for the study, two were aproached during the October 21st-December15th time period (Limited screen + cCT) and the other one was approach during the December16th-January 31st time period (limited screen only)

Of the 26 patients enrolled, 21 were enrolled into the limited screening and cCT group whereas 5 were enrolled into the limited screening only group (Table 11). The recruitment rate eligible consenting patient is 6 per month (4 weeks).

Table 11: Number of Refusing and Eligible Consenting Patients

Time periods	Allocation	Number of patients recruited	Number of patients refusing
October 1st-October 20th 2007	Limited screen + cCT	2	1
October 21st -December 15th 2007	Limited screen + cCT	19	9
December 16th – January 31st 2007	Limited screen only	5	3

5.3.2 Baseline Characteristics

Baseline characteristics of enrolled patients are depicted in Table 12. All patients were Caucasians. Patients in the limited screen only group were more likely to have a significant family history of cancer. Patients in the limited screen and cCT group were more likely to have a previous history of heavy smoking or to have a pulmonary embolus as qualifying event. Otherwise, the patients in both groups had generally similar baseline characteristics. Baseline characteristics of the three patients ineligible for the study are also reported in Table 12.

5.3.3 Secondary Outcome: Previously Undiagnosed Malignancy Detection

5.3.3.1 Limited Malignancy Screening Strategy

All patients had a complete limited occult malignancy screen. Results of the limited screen are reported in Table 13 for both groups. A total of 7 (33.3% 95% CI: 17.2-54.6) patients in the limited screen and cCT group had clinical signs and

symptoms suspicious for malignancy. Two patients described more than one clinical symptom on history. Only one patient with symptoms suspicious for malignancy (back pain) was diagnosed with cancer. No patient in the limited screening alone group reported any symptoms. Physical examination was normal for all patients. No patients in the limited screen alone group had abnormalities in the limited screen, no further investigations were requested in that group and therefore no malignancies were diagnosed. Four patients in the limited screen and cCT group had abnormalities on basic blood work: 1) abnormality on liver function tests; 2) thrombocytosis with abnormality on liver function test; 3) decrease albumin and abnormality on liver function test; and 4) decrease albumin. Only one patient with abnormalities on limited screen was be diagnosed with malignancy (see below). Other than the cCT, one patient underwent additional investigation (i.e. outside of protocol) in that group. The patient with a new cough underwent a CT thorax which was normal.

Table 12: Baseline Characteristics of Study Population

Characteristics	Limited occult malignancy screening + cCT group N=21	Limited occult malignancy screening only group N=5	Patients excluded from the study N=3
Age (years old), median (range)	57 (27-84)	50 (40-80)	55 (46-70)
Sex N, (%; 95% CI)	14 (66.7; 37.1-76.2)	3 (60; 23.1-88.2)	2 (66.7; 2.8-93.9)
Weight (kg), median (range)	92 (57-137)	100 (84-128)	83 (77-110)
Other medications, N (%)			
ASA	0	1 (20; 3.6-62.5)	0
Clopidogrel	0	0	0
ASA/Dipyridamole	0	0	0
Smoking Status, N (%)			
Current smoker	6 (28.6; 13.8-50.0)	1 (20; 3.6-62.5)	1(33.3; 6.2-79.2)
Previous smoker	7 (33.3; 17.2-54.6)	1 (20; 3.6-62.5)	1 (33.3; 6.2-79.2)
Alcohol use, N (%)			
Mild (<2 / week)	11 (52.4; 32.4-71.7)	2 (40; 11.8-76.9)	2 (66.7; 2.8-93.9)
Heavy (>7 / week)	2 (9.5; 2.7-28.9)	0	0
Family history of cancer (first degree relatives), N (%)	7 (33.3; 17.2-54.6)	3 (60; 23.1-88.2)	1 (33.3; 6.2-79.2)
Qualifying VTE event, n (%)			
DVT:	13 (61.9; 40.9-79.3)	5 (100)	2 (66.7; 2.8-93.9)
Right leg	3 (14.3)	2 (40)	0
Left leg	6 (28.6)	3 (60)	2(100)
Upper extremity	2 (9.5)	0	0
Bilateral	2(9.5)	0	0
Pulmonary embolism:	8 (38.1; 20.8-59.1)	0	1 (33.3; 6.2-79.2)

Table 13: Limited Screen Results in Both Malignancy Screening Strategies

Characteristics Median (range)	Limited occult malignancy screening + cCT group N=21	Limited occult malignancy screening only group N=5
History, N (%; 95% CI):		
Weight loss:	4 (19.0; 7.7-40.0)	0
Fever/Chills:	0	0
Change in bowel habits:	3 (14.3; 5.0-34.6)	0
Bleeding:	0	0
Other:		
Back pain	1 (4.8; 0.9-22.7)	0
Cough	1 (4.8; 0.9-22.7)	0
White blood cell count	7.9 (5.7-16.8)	8.3 (5.5-9.2)
Hemoglobin	146 (92-168)	144 (133-153)
Platelets	275 (174-910)	248 (119-436)
AST	25 (15-106)	22 (12-71)
ALT	29 (16-157)	25 (14-97)
ALP	71 (50-262)	89 (70-101)
Total bilirubin	13 (7-210)	12 (10-18)
LD	159 (143-314)	187 (166-269)
Creatinine	81 (64-98)	88 (70-160)
Calcium (total)	2.37 (2.17-2.49)	2.37 (2.34-2.47)
CXR abnormality	0	0
Mammogram abnormality	0	0
Pap smear	0	0
Prostate (DRE or PSA)	0	0

DRE: digital rectal examination; PSA: prostate specific antigen; LD: lactate dehydrogenase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

4.5.2.2. Comprehensive Computed Tomography

Twenty of the 21 (95.2%; 95% CI: 77.3 to 99.2) patients assigned to the limited screen and cCT screening strategy had a cCT done. One patient was admitted repetitively for acute ischemic leg and could not undergo the cCT. All cCT were performed within 30 days of enrolled into the study. Five patients (25%; 95% CI: 11.2 to 46.9) had abnormalities on cCT that were suspicious for malignancy and required further investigations: 1) Three patients had lesions suspicious for pancreatic cancer; 2) one patient had colonic polyps and rectal thickening; and finally 3) one patient had mild prostate enlargement. Four patients underwent a biopsy (2 adenocarcinoma of pancreas, 1 chronic pancreatitis, 1 adenomatous colonic polyp). One of the patients with pancreatic adenocarcinoma was diagnosed early ($T_{1\text{-}2}N_0M_0$) and is awaiting a surgical consultation. Of note, the patient with early adenocarcinoma of the pancreas had a normal limited screen including history and physical examination. The other patient with adenocarcinoma of the pancreas was diagnosed late (metastatic – M_1) and died on January 13th 2008. The patient with mild prostatic enlargement had a normal PSA and no further investigations were ordered.

5.4 Discussion

The pilot study demonstrates that a study design randomizing time periods instead of individual patients to allocate participant to two different malignancy screening strategy was feasible but did not achieve the expected recruitment targets. The recruitment rate was of approximately 6 eligible consenting patients

per month. The expected recruitment was of 12 participants per month in order to be able to recruit 580 patients over 4 years (See full trial protocol).

The pilot study suggests that previously undiagnosed malignancies are frequent in patients with unprovoked VTE. Although the numbers are small and have to be interpreted carefully, 7.7% (95% CI: 2.1 to 24.1) of patients with unprovoked VTE were diagnosed with previously undiagnosed VTE. An extensive screening strategy combining a limited screen and a cCT also seemed to detect more malignancies (10%; 95% 2.8 to 30.1) compared to a limited screening strategy alone (0%), without any complications. However, these results are only hypothesis generating and larger trials need to be conducted to confirm these estimates.

All cCT were performed within 30 days of enrollment into the study suggesting that cCT was locally easily accessible. Seventy-five percent (75.0%; 95% CI: 30.0 to 95.4) of the findings suspicious for malignancy detected by the cCT were confirmed by histology.

5.4.1 Estimate of the Primary Outcome (Recruitment Rate)

A total of twenty-six patients were enrolled into the study, averaging approximately 6 patients per month. The length of the study was prolonged by two weeks to 18 weeks from the original 16 weeks study period to account for the

Thrombosis Unit slow downs during the holiday season. Recruitment rates during the time periods assigned to the limited screen and cCT, and to the limited screen screening strategies averaged 7 and 3 enrolment per month, respectively. A number of factors may have accounted for the discrepancy reported in the recruitment rates between the two groups. First, the time period assigned to the limited screen alone overlapped with the Holiday season. The Thrombosis Unit was functioning with minimal staff (i.e. similar as week-end coverage) for 2 weeks and research nurses were not available. No patients were enrolled during that period of time leading to a decrease recruitment rate in the limited screen alone group. Therefore, a total of 5 patients were enrolled during 4 weeks of active recruitment which is comparable to recruitment in cCT time periods. However, since the number of patients recruited in the limited screen alone group is very small and over a short period of time, we cannot conclude than the recruitment between the two groups is not different. Second, the recruitment rate was higher during the first 4 weeks, enrolling about 10 patients. The first few time periods of the study were randomized to the cCT screening strategy (See Table 10). Since patients, up to the 3-month follow-up period, were approached into the study, patients with unprovoked VTE diagnosed as early as July 1st 2007 were enrolled during the first month of recruitment leading to an disproportionably high recruitment rate cCT screening strategy group. Third, it is possible that the enthusiasms for the study by the different recruiting clinicians decreased over time. Busy clinicians often forget to approach eligible patients for participation

into clinical studies. Furthermore, enrolling patients into studies require time commitment from the patient and physician.

Ideally, the length of the study would have included at least two blocks (4 Time periods). This would have provided more experience switching between the comparator and intervention and give more insight into physician/patient behavior regarding enrollment into the comparator group. This would also have provided with higher sample size on which to base the analysis. Numerous factors have contributed to the length and timing of the pilot study. The original start date was July 1st 2007. Delay in the final Ethics approval and financial constraints (Dr. Rodger only able to fund 16 weeks of 0.5 nursing time for a Master's student project at a cost of $21,000) contributed to the short length and timing of the study. Furthermore, other revenue generating competitive trials (i.e. enrolling patients with newly unprovoked VTE) limited the length of study. Nonetheless, these are all learning points which will need to be strongly considered upon starting the full trial.

The next step will be to seek financial assistance in order to conduct a second pilot study overlapping over at least two blocks.

The expected recruitment rate was of 12 participants per month in order to be able to conduct the complete trial over for years. The pilot study did not achieve the expected recruitment target. The TOH Thrombosis Unit will evolve into a Regional Thrombosis Program in the next year and expects approximately 3-4 additional new cases of patients with unprovoked VTE per week to be managed

by our unit (i.e. double our current volumes). Although the creation of a regional program may facilitate recruitment, a contingency plan is required. A contingency plan could include: 1) reviewing and analyzing the logs of screened patients (including reasons for ineligibility and source of study referral) and logs of refusers (including reasons and source of study referral); 2) Contacting thrombosis physicians, emergency physicians and family physicians every 6 months to remind them of the study; 3) Approach other centers to participate into the study. The London Health Science Center and Montreal Jewish General Hospital have previously shown an interest in participating into the study by a larger multicenter pilot study would be required to assess the feasibility of a multi-centered trial.

Although the pilot study did not meet the expected recruitment rate, it showed that a matched cluster randomized controlled trial design randomizing time periods to the intervention or comparator is achievable. A few factors might be contributing to the success of that particular design over a straight RCT. First, the limited malignancy screen in our study consisted of basic blood work and basic malignancy screening investigations (breast, prostate, cervix) and, hence, patients were not asked to accept (what they or their physicians perceive as) a chance of receiving less than adequate care. Second, screening strategy allocation was already determined upon approaching patients to participate in our study, removing the perception of having a chance to be randomized to a lesser

screening strategy. Finally, the cCT is not available to physicians outside of this clinical study.

5.4.2 Secondary Outcome: Diagnosis of Previously Undiagnosed Malignancy after Venous Thromboembolism

The overall estimate of the incidence of previously undiagnosed malignancy in patient with unprovoked VTE in the pilot study was 7.7% (95%CI: 2.1 to 24.1) and it is consistent with the pooled cumulative incidence reported in our systematic review of the literature (Table 3). All cancers were diagnosed by the extensive screening strategy (limited screen + cCT) group. As previously mentioned these results are hypothesis generating (very small numbers, wide 95% CI, etc) and need confirmation in larger prospective trials. Interestingly, the incidence of previously undiagnosed malignancy in the extensive screening strategy group is 9.5% (95% CI: 2.7 to 28.9) at VTE diagnosis which is approximately the estimated cumulative incidence expected at 12 months (See Table 3). Therefore, one possible hypothesis is that the extensive screening strategy diagnosed all previously undiagnosed malignancy in that group. Long term follow studies are required to confirm these findings (i.e. ensure that no other previously undiagnosed malignancies are detected on follow-up).

As previously mentioned, these two previously undiagnosed malignancies were important to diagnose. First, the VTE of the two patients with adenocarcinoma of

the pancreas were treated with LMWH instead of vitamin K antagonists to prevent recurrent VTE [9]. Previous studies have also suggested that treatment with LMWH may increase survival in patients with non-metastatic malignancies. None of these patients had a recurrent VTE or major bleeding episode. Recurrent VTE, major bleeding episode and death will be secondary endpoint of the complete trial. Second, one of the adenocarcinoma of the pancreas was localized in the head of the pancreas ($T_1N_0M_0$) and is potentially curable by surgical resection or chemotherapy. This patient had a normal history, physical and limited malignancy screen. Detecting this malignancy early might increase the survival of this particular patient. At larger scale, extensive screening using a combination of limited screen and cCT may potentially increase survival in patients with unprovoked VTE diagnosed with previously undiagnosed malignancy. Finally, detecting occult malignancies earlier may have prevented cancer-related morbidity. Patients with metastatic malignancies may also potentially benefit from earlier detection. Palliative procedure (e.g. stent in pancreatic cancer), radiation and chemotherapy alleviate malignancy-related symptoms and may potentially increase quality of life (QALY). As previously mention in the study protocol, QALYs gained using a preference-based score (using the EQ-5D instrument) will be captured in the complete trial.

Unfortunately, these results are only hypothesis generating and no firm conclusion can be drawn due to the small number of patients. Furthermore, the short length of the study recruitment has lead to an imbalance in the number of patients allocated to each group leading to difference in baseline characteristics

between both groups that could explain the results reported in the study. Further research with a larger number of patients is urgently required to evaluate the impact of previously undiagnosed malignancy detection using an extensive screening strategy on mortality, early cancer detection, recurrent VTE, bleeding, and quality of life years.

5.4.3 Feasibility and Accuracy of Comprehensive Computed Tomography

A waiting time of 6 weeks was considered to be reasonable since it corresponds to the waiting time for a non-urgent CT abdomen/pelvis at the TOH. All cCT in the pilot study were performed within 30 days following recruitment. This suggests that cCT is readily available and feasible at the TOH.

Four abnormalities suspicious for malignancy were detected on cCT required further investigations and biopsies. The cCT findings were corresponding to the confirmatory biopsy in three (75%; 95% CI: 30.0 to 95.4) cases (1 colonic polyp, 2 adenocarcinoma of the pancreas). One patient with a suspicious lesion on cCT was found to have severe chronic pancreatitis. This patient had no complications of the confirmatory procedure (*i.e.* biopsy). These results suggest that cCT, including its virtual components (e.g. virtual colonoscopy), is potentially an accurate diagnostic modality. However, accuracy studies comparing cCT components to gold standard are required to confirm these findings. Furthermore, in order to improve the generalizability of the results, the cCT should be

interpreted by two blinded radiologists. Discrepancies between the final reports will be documented and the findings adjudicated by a third party. Finally, a screening strategy combining limited screen to cCT is potentially highly sensitive and likely to have numerous false positive. Suspicious findings may frequently turn out to be false positives. Only one patient in the pilot study had a false positive cCT result but again, the numbers are small. Additional investigations done to pursue abnormal findings and any associated complication will be recorded and reported during the complete trial. Specificity and false positive rate for both screening strategies will be calculated and compared.

5.4.4 Study Design

The current study design was originally described as a quasi-experimental design but some aspect of the design closely aligns to a matched cluster randomized controlled trial.

The sample size calculation may need to be adjusted in a matched clustered randomized controlled trial. The observations collected on participants from the same cluster could be correlated (non-independent) and therefore, the effective sample size may be less than the total number of participants in the study [64-65]. The reduction in effective sample size depends on average cluster size and the degree of correlation within clusters [64]. However, there is no intra-class correlation expected in the current trial. It is very unlikely that the probability of having a previously undiagnosed malignancy detected varies between time

periods of 8 weeks. Therefore, the sample size does not need any further adjustment. Other methodological issues need to be considered in a matched clustered randomized controlled trial. For example, all clustered are randomized at once which can lead to post-randomization bias (individually approaching participants within the cluster) and possibly also raising ethical issues.

6.0 FUTURE DIRECTIONS

Although a study randomizing time period allocated to a limited malignancy screen alone or in combination with cCT is feasible at the TOH, it did not achieve the recruitment targets. Combining the previously discussed contingency plan to a multicenter trial design could potentially increase the recruitment rate. The next step is to seek financial assistance to conduct a multi-centered pilot study of a duration of at least two blocks that includes the TOH, the Montreal General Hospital and the London Health Center. This second pilot study would allow the assessment of the feasibility of a complete trial. If feasible, a multi-center trial using the same design will be undertaken. This trial should definitively be able to determine whether a screening strategy using limited malignancy screen and cCT is a valid and cost-effective screening tool to detect previously undiagnosed malignancy associated with unprovoked VTE.

Trial design terminology will also have to be discussed among the co-investigator. Sample size and planned analysis may require further work.

7.0 CONCLUSION

In conclusion, previously undiagnosed malignancies are common in patients with unprovoked VTE. There is currently no consensus regarding malignancy screening in patients with unprovoked VTE as well as great diversity in opinions and practices. Previously undiagnosed malignancies are more likely to be detected with a more extensive malignancy screening strategy compared to limited screen alone. Specifically, CT abdomen/pelvis should be considered in the diagnostic work up of previously undiagnosed malignancy in patients with unprovoked VTE. Early detection of previously undiagnosed malignancies can potentially decrease malignancy-related morbidity, mortality and VTE recurrence. However, before recommending an extensive screening strategy to all patients with unprovoked VTE, a number of factors must be considered including: 1) morbidity and cost of extensive screening; 2) risks of invasive diagnostic procedure to confirm the presence of malignancy; 3) incidental findings and their associated morbidity and 4) psychological burden associated with new diagnosis of cancer or false-positives.

The cCT is potentially a safe, accurate and sensitive screening tool but it is unknown if the cCT will be sufficient as the only test beyond the limited malignancy screen. Safety and cost-effectiveness of cCT also need to be evaluated. Our pilot study demonstrated that a trial randomizing time period to limited screen alone or in combination to cCT is feasible at the TOH but is not

meeting the recruitment targets to complete a full trial within reasonable delay. A second multi-centered pilot study is required to assess the feasibility of the trial in multiple center before pursuing to the complete trial/

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APPENDIX1

Figure 8: Forest Plot of the Pooled Period Prevalence at Baseline in Patients with Any Venous Thromboembolism

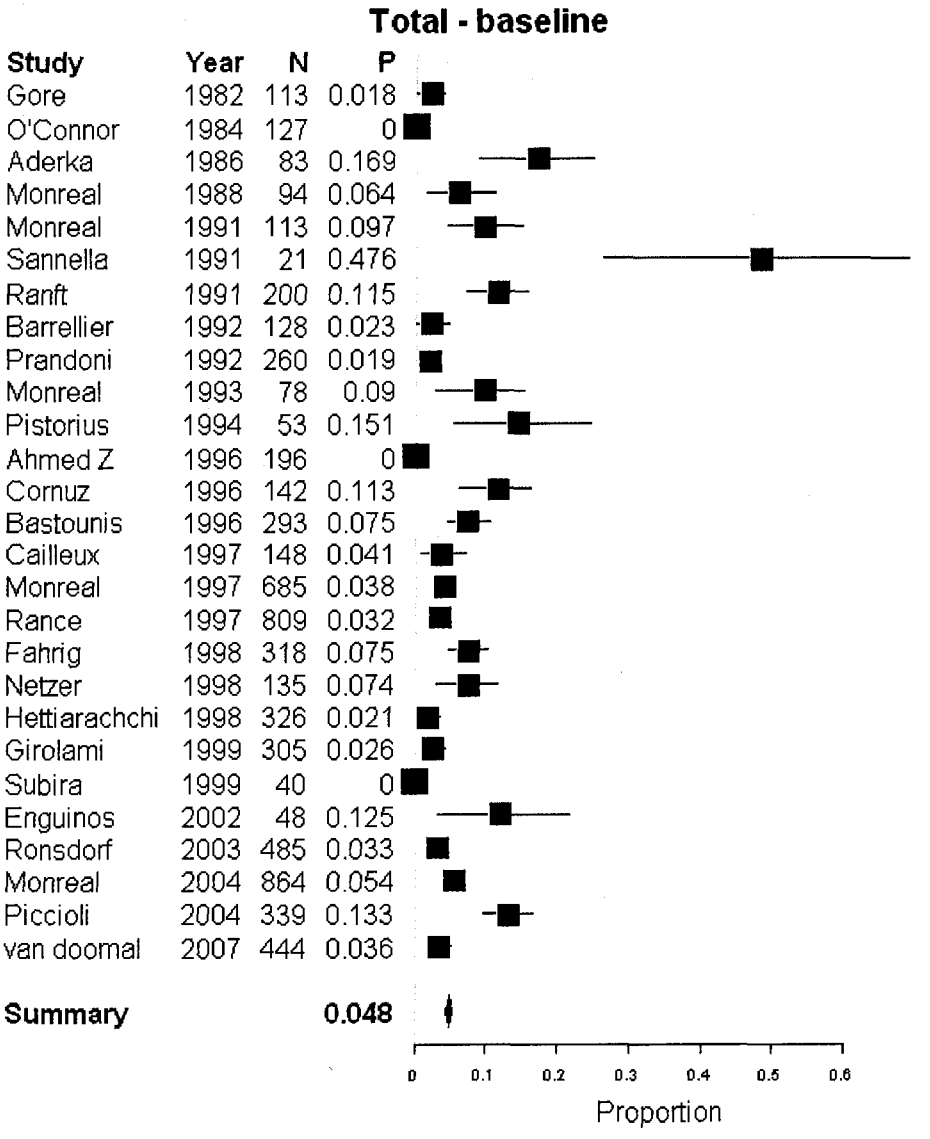


Figure 9: Forest Plot of the Pooled Period Prevalence from Baseline to 6 Months in Patients with Any Venous Thromboemblism

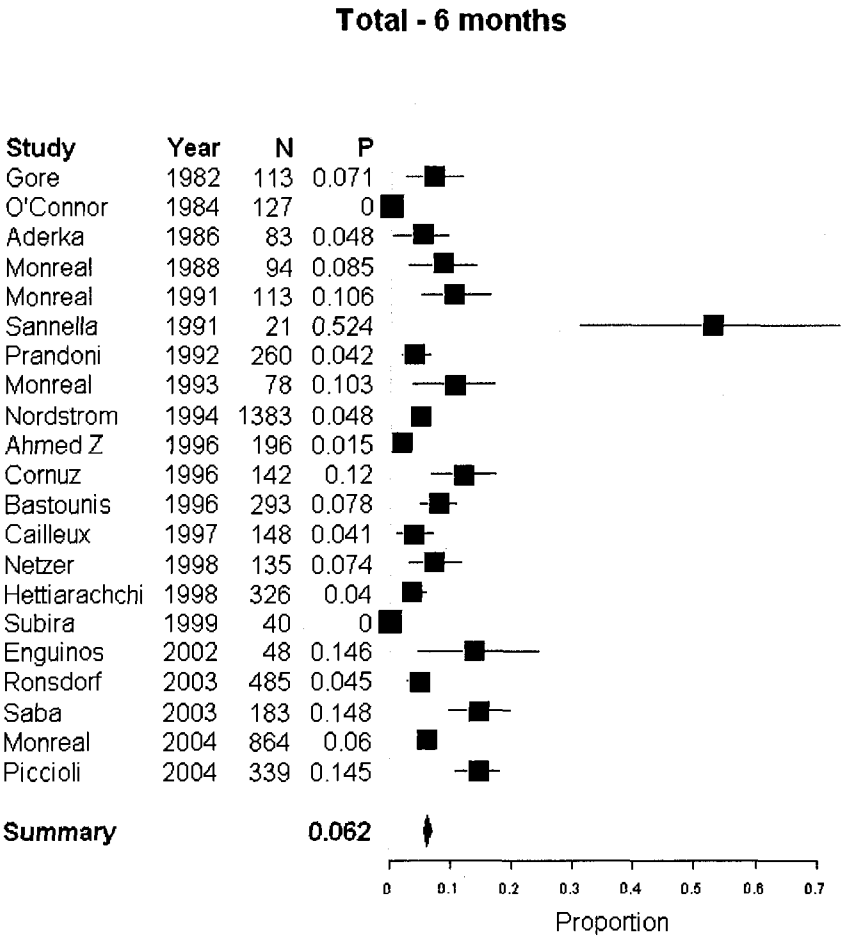


Figure 10: Forest Plot of the Pooled Period Prevalence at Baseline in Patients with Unprovoked Venous Thromboemblism

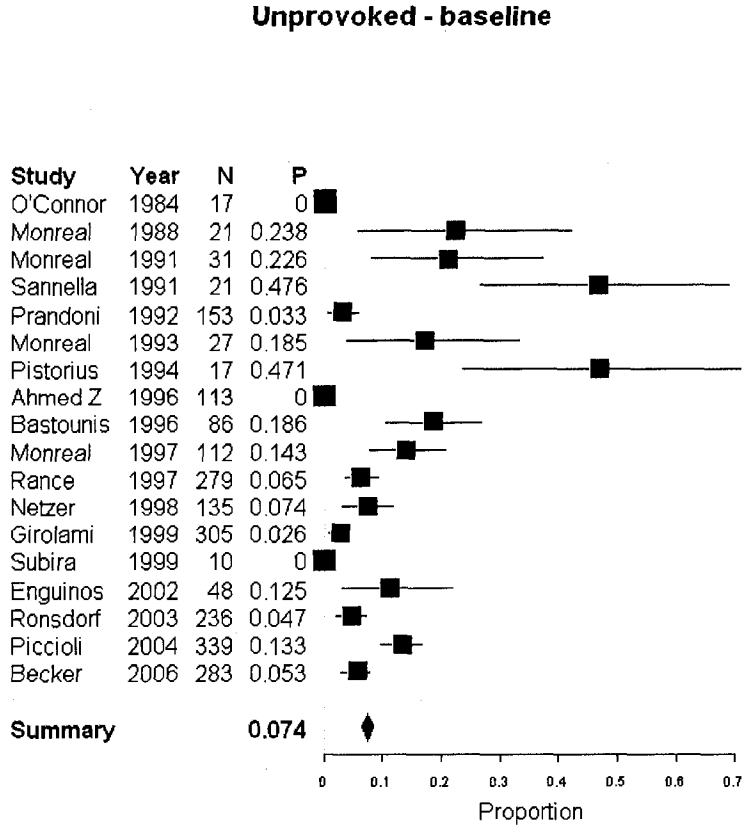


Figure 11: Forest Plot of the Pooled Period Prevalence from Baseline to 6 Months in Patients with Unprovoked Venous Thromboemblism

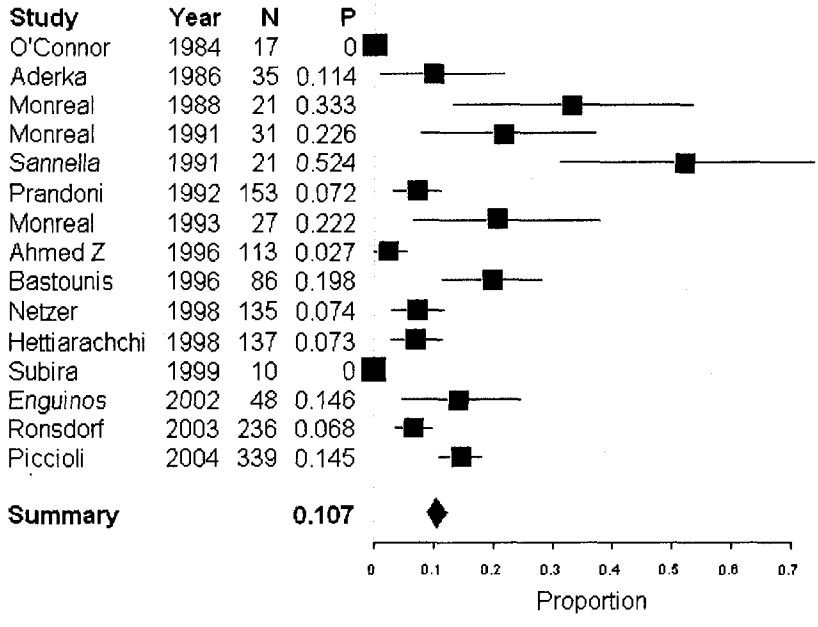


Figure 12: Forest Plot of the Pooled Period Prevalence at Baseline in Patients with Provoked Venous Thromboemblism

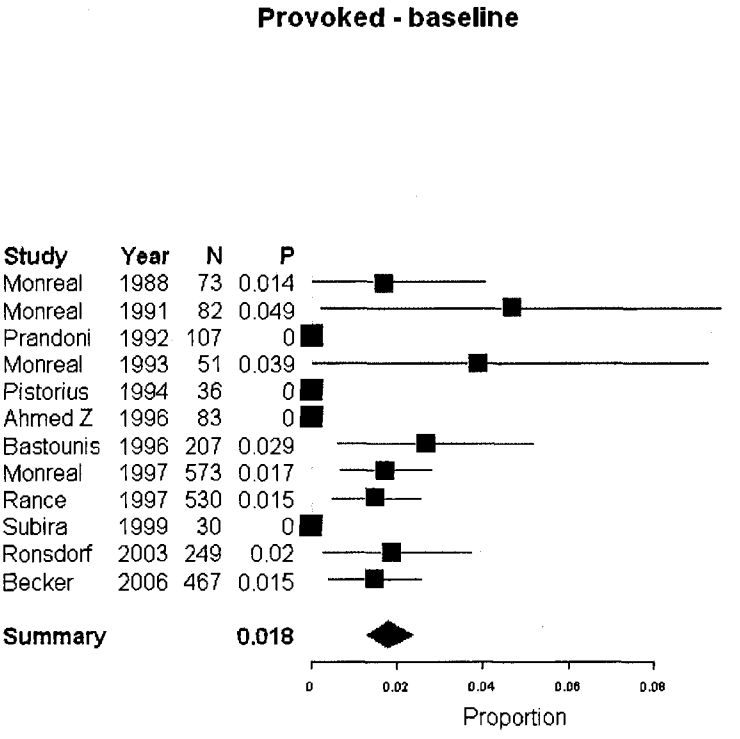


Figure 13: Forest Plot of the Pooled Period Prevalence from Baseline to 6 Months in Patients with Provoked Venous Thromboemblism

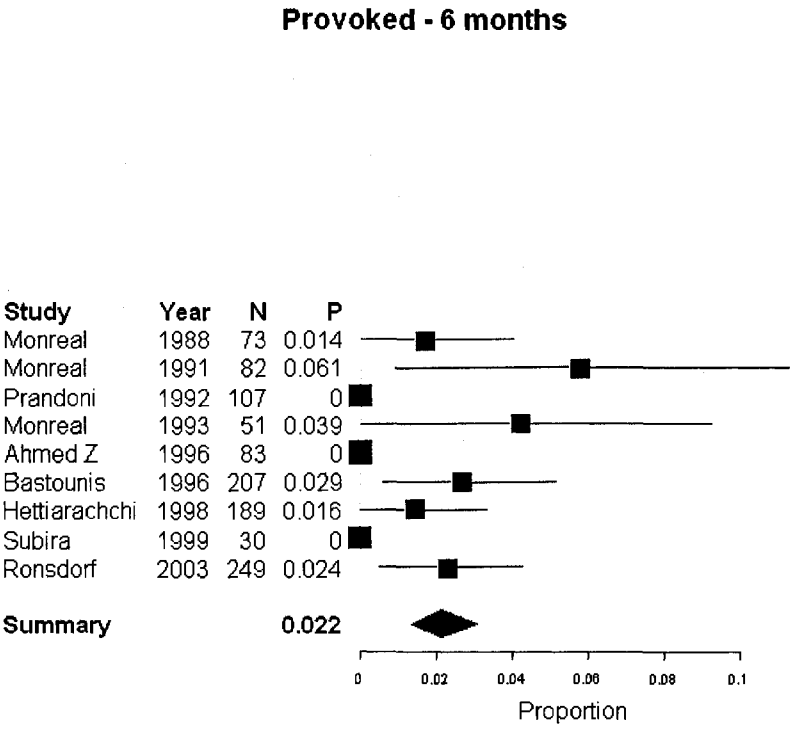
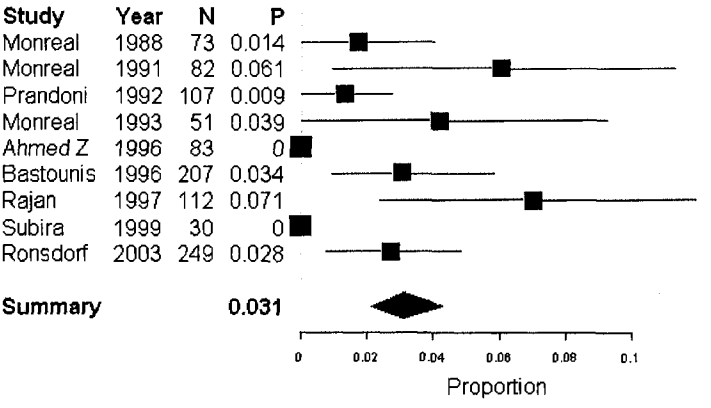


Figure 14: Forest Plot of the Pooled Period Prevalence from Baseline to 12 Months in Patients with Provoked Venous Thromboemblism



APPENDIX2

Sensitivity Analysis

Table 14: Period Prevalence at Baseline and Over Different Time Periods of Follow-up of Previously Undiagnosed Malignancy in Patients with Any Venous Thromboemblism Without Including the Study From Sannella

Period Prevalence	**(%, 95% CI)**
Baseline (≤1 month)	4.7 (4.3-5.3)
Baseline to 6 months (0 to ≤6 months)	6.1 (5.4-6.7)
Baseline to 12 months (0 to ≤12 months)	7.5 (6.8-8.3)

Table 15: Period Prevalence at Baseline and Over Different Time Periods of Follow-up of Previously Undiagnosed Malignancy in Patients with Unprovoked Venous Thromboemblism Without Including the Study From Sannella and Pistorius

Period Prevalence	**(%, 95% CI)**
Baseline (≤1 month)	6.9 (5.9-8.0)
Baseline to 6 months (0 to ≤6 months)	10.2 (8.7-11.9)
Baseline to 12 months (0 to ≤12 months)	11.4 (9.9-13.0)

APPENDIX3

Figure 15: Forest Plot of the Pooled Proportion of Malignancies Detected by Limited or Extensive (Limited + Ultrasonography Abdomen/Pelvis) Malignancy Screening in Patients with All Venous Thromboembolism

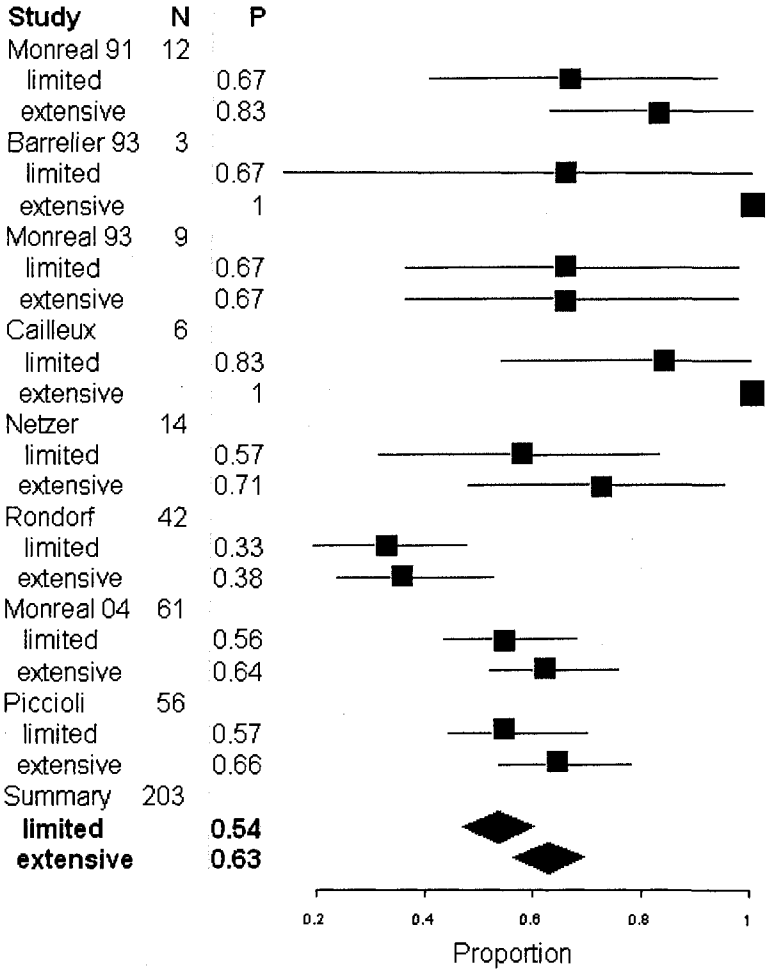


Figure 16: Forest Plot of the Pooled Proportion of Malignancies Detected by Limited or Extensive (Limited + Ultrasonography Abdomen/Pelvis) Malignancy Screening in Patients with Unprovoked Venous Thromboembolism

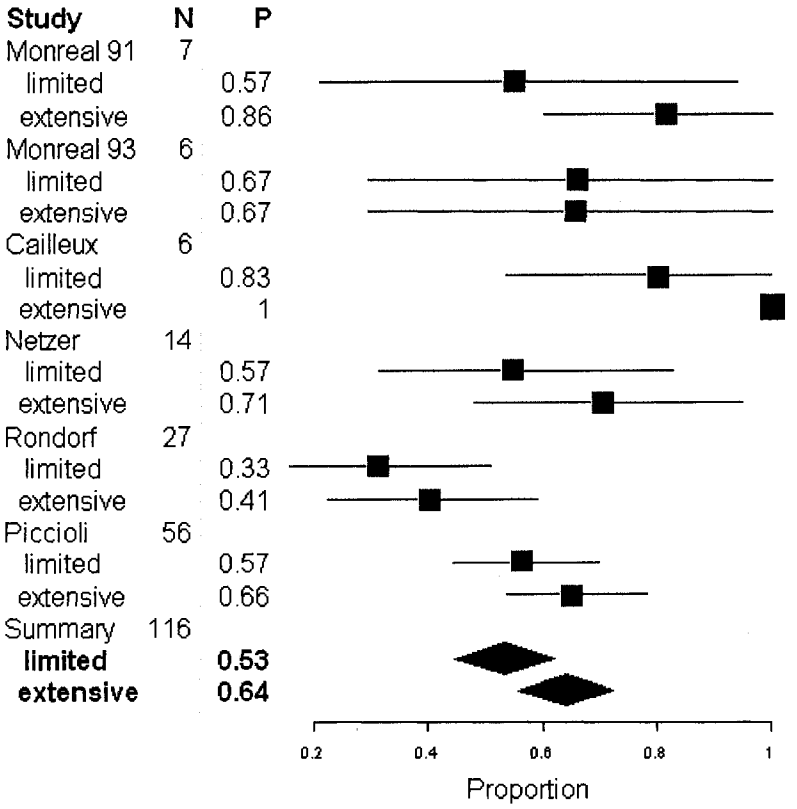


Figure 17: Forest Plot of the Pooled Proportion of Malignancies Detected by Limited or Extensive (Limited + Prostate Specific Antigen) Malignancy Screening in Patients with All Venous Thromboembolism

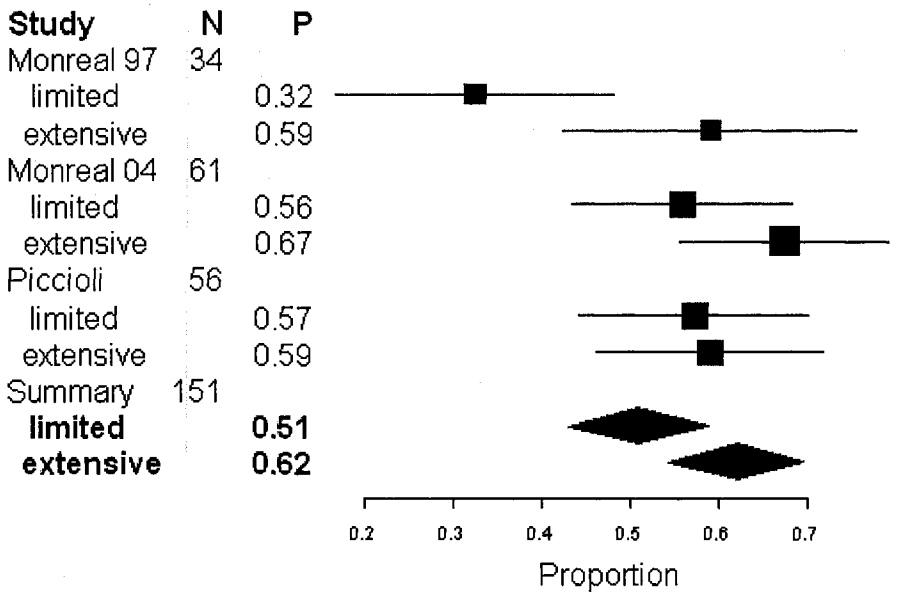


Figure 18: Forest Plot of the Pooled Proportion of Malignancies Detected by Limited or Extensive (Limited + Prostate Specific Antigen) Malignancy Screening in Patients with Unprovoked Venous Thromboembolism

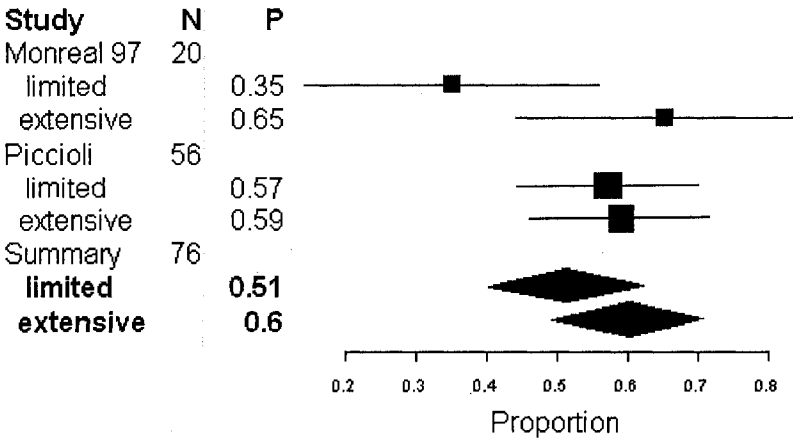


Figure 19: Forest Plot of the Pooled Proportion of Malignancies Detected by Limited or Extensive (Limited + Carcinoembryogenic Antigen) Malignancy Screening in Patients with All Venous Thromboembolism

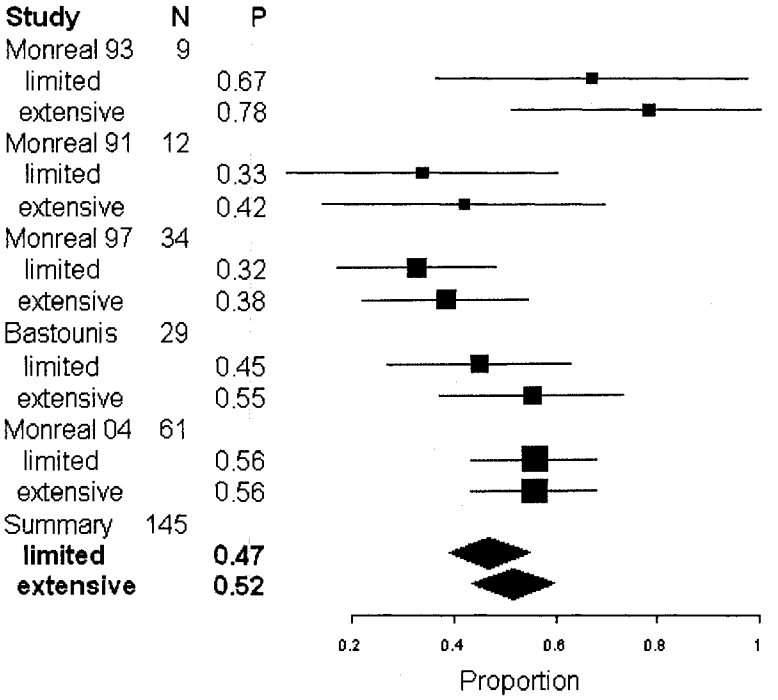
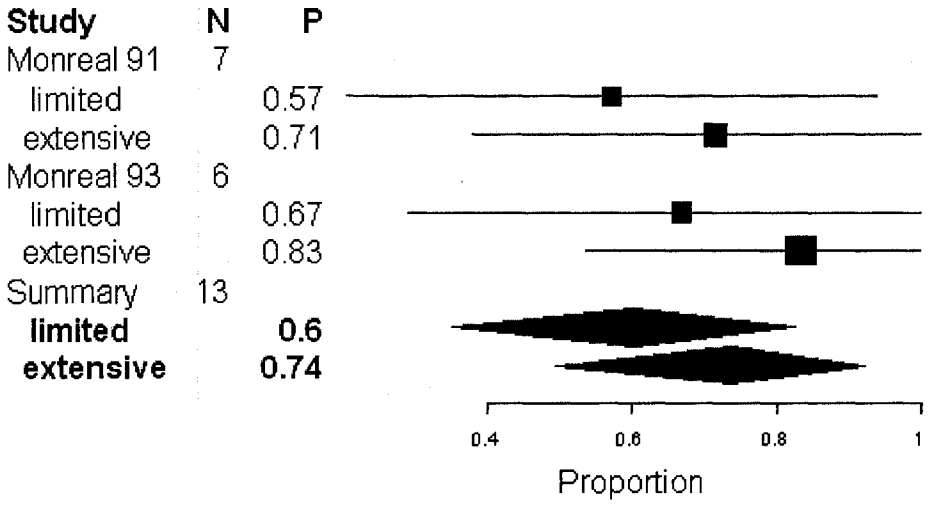


Figure 20: Forest Plot of the Pooled Proportion of Malignancies Detected by Limited or Extensive (Limited + Carcinoembryogenic Antigen) Malignancy Screening in Patients with Unprovoked Venous Thromboembolism



APPENDIX 4

Table 16: Quality of Included Studies in the "Period Prevalence" Systematic Review Using the Newcastle – Ottawa Quality Scale for Cohort Studies

Study	Selection				Comparability		Outcome	
	Representativeness of exposed cohort	Representativeness of non exposed cohort	Ascertainment of exposure	Outcome not present at beginning of study	Comparability of cohorts	Assessment of Outcome	Was follow-up long enough?	Adequacy of follow-up
Retrospective Cohort Studies								
Gore, 1982 [32]	*	*	*	*	**	*	*	-
Goldberg, 1987 [36]	*	*	*	*	*	-	*	*
Sannella, 1991 [43]	*	n/a	*	*	n/a	-	*	*
Ranft, 1991 [39]	*	n/a	-	*	n/a	-	-	-
Nordstrom, 1994 [12]	*	-	*	*	**	*	*	*
Ahmed, 1996 [30]	*	n/a	-	*	n/a	*	-	-
Cornuz, 1996 [13]	*	*	*	*	**	*	*	*
Rajan, 1997 [29]	*	n/a	*	*	n/a	*	*	*
Rance, 1997 [38]	*	n/a	*	*	n/a	-	*	-
Fahrig, 1998 [49]	*	n/a	*	*	n/a	-	-	*
Hettiarachchi, 1998 [26]	*	n/a	*	*	n/a	-	-	*
Netzer, 1999 [50]	*	n/a	*	*	n/a	*	*	*
Subira, 1999 [31]	*	n/a	*	*	n/a	*	*	*
Ronsdorf, 2003 [51]	*	n/a	*	*	n/a	-	*	*
Saba, 2003 [41]	*	*	*	*	**	-	*	-
Prospective Cohort studies								
Minar, 1982	+	n/a	+	+	n/a	-	+	-

[40] O'Connor, 1984 [35]	*	n/a	*	-	n/a	*	*	*
Aderka, 1986 [27]	+	n/a	+	+	n/a	-	+	+
Griffin, 1987 [37]	*	-	*	*	*	*	*	*
Monreal, 1988 [34]	*	n/a	-	*	n/a	-	*	*
Monreal, 1991 [42]	*	n/a	*	*	n/a	-	*	*
Barrelier, 1992 [44]	*	n/a	*	*	n/a	-	*	*
Prandoni, 1992 [28]	*	n/a	*	*	n/a	*	*	*
Monreal, 1993 [45]	*	n/a	*	*	n/a	-	*	*
Pistorius, 1994 [39]	*	n/a	*	*	n/a	-	*	*
Bastounis, 1996 [47]	*	n/a	*	*	n/a	-	*	*
Cailleux, 1997 [48]	*	n/a	*	*	n/a	-	-	*
Monreal, 1997 [25]	*	n/a	*	*	n/a	-	*	-
Girolami, 1999 [33]	*	n/a	-	*	n/a	-	*	-
Equidanos, 2002 [53]	*	n/a	*	*	n/a	*	-	*
Monreal, 2004 [14]	*	n/a	*	*	n/a	*	*	*
Van Doormaal, 2007 [52] *	*	-	*	*	*	*	*	-
Randomized Controlled Trial								
Piccioli, 2004 [15] **	*	*	*	*	* *	*	*	*

* A study can be awarded a maximum of one star for each numbered item within the "Selection" and "Outcome" categories. A maximum of two stars can be given for "Comparability".

APPENDIX 5

Table 17: Quality of Included Studies in the "Extensive Vs Limited Malignancy Screening" Using the Newcastle – Ottawa Quality Scale for Cohort Studies

Study	Selection				Comparability	Outcome		
	Representativeness of exposed cohort	Representativeness of non exposed cohort	Ascertainment of exposure	Outcome not present at beginning of study	Comparability of cohorts	Assessment of Outcome	Was follow-up long enough?	Adequacy of follow-up
Sannella, 1991 [36]	*	n/a	*	*	n/a	-	*	*
Fahrig, 1998 [42]	*	n/a	*	*	n/a	-	-	*
Netzer, 1999 [43]	*	n/a	*	*	n/a	*	*	*
Ronsdorf, 2003 [44]	*	n/a	*	*	n/a	-	*	*
Monreal, 1991 [35]	*	n/a	*	*	n/a	-	*	*
Barrelier, 1992 [37]	*	n/a	*	*	n/a	-	*	*
Monreal, 1993 [38]	*	n/a	*	*	n/a	-	*	*
Pistorius, 1994 [39]	*	n/a	*	*	n/a	-	*	*
Bastounis, 1996 [40]	*	n/a	*	*	n/a	-	*	*
Cailleux, 1997 [41]	*	n/a	*	*	n/a	-	-	*
Monreal, 1997 [18]	*	n/a	*	*	n/a	-	*	-
Equidanos, 2002 [46]	*	n/a	*	*	n/a	*	-	*
Monreal, 2004 [12]	*	n/a	*	*	n/a	*	*	*
Van Doormaal, 2007 [45] *	*	-	*	*	*	*	*	-
Piccioli A, 2004 [13] **	*	*	*	*	**	*	*	*

* A study can be awarded a maximum of one star for each numbered item within the "Selection" and "Outcome" categories. A maximum of two stars can be given for "Comparability"

APPENDIX 6

SOME: Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism

BASELINE ASSESSMENT

Date of Assessment (yyy/mm/dd): _____

1 Patient demographics

Patient initials	
Date of birth (yyy-mm-dd)	
Family MD (name + phone number)	Name: Phone number:
Hospital ID number	
Race	□ Caucasian □ Black □ Asian □ Other: _____
Gender	□ M □ F
Weight/height	kg Cm
Known allergies to contrast dyes	□yes □no
Other allergies to medications (please list)	1. 2. 3. 4.
Hospital status at diagnosis	□ Outpatient □ Inpatient
Relevant Medical History (please list)	1. 2. 3. 4. 5. 6. 7.

Known renal dysfunction? □yes □no

Creatinine level: _____

Date: _____

Previous cancer:

Location of cancer:

Date of diagnosis (YYYY-mm-dd)

Known metastasis:

Any surgical treatment required:

1) Type of surgery:

2) Date of surgery (YYYY-mm-dd):

Any chemotherapy required:

1) Type of chemo:

2) Number of cycles:

3) Date of treatment (yyyy-mm-dd)

Any radiotherapy required:

1) Date of treatments:

Prognosis:

□ Remission

□ Cured

□ Ongoing

List of all active medications

1.
2.
3.
4.
5.
6.
7.
8.
9.

Smoking History

□ Current
Cigarettes/day:_____
How many years:_____
□ Former
How many years ago:_____
□ non-smoker

Alcohol History □ yes □ no

If yes,

How may drinks per week _____
(1 beer/3 onces of wine/1 once of liquor)

Any Alcohol previous abuse □ yes □ no

Family history of cancer □ yes □ no

□ First degree
(parents, siblings or children)
Location of cancer: _____
Age at diagnosis:_____
□ Second degree
(grandparents, aunts, cousins)
Location of cancer: _____
Age at diagnosis:_____

Is the VTE symptomatic? □ yes □ no

Duration of Treatment _____Days

2 Thrombotic Risk Factors:

Prior Thrombosis □yes □no

If yes,

Number of previous episodes _____

Type:
□ DVT
□PE
□Other _____

DVT location:
□ Left
□ Right
□ Bilateral

Known Thrombophilia □yes □no

If yes:

Type of thrombophilia _____

Current use of hormone replacement therapy or oral contraceptives □yes □no

Family history of thrombosis □yes □no
□First degree
(parents, siblings or children)
how many events: _____
□ Second degree
(grandparents, aunts, cousins)
How many events: _____

(SOME): Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism

Inclusion Criteria	Yes	No
1)Objectively confirmed DVT or PE (compression ultrasound of legs, VQ scan or CT scan of the chest	□	□
2) Idiopathic VTE event, defined as :		
-absence of known malignant disease	□	□
-absence of trauma of the leg, surgical procedures, general anesthesia or immobilization greater than 3 days within previous 3 months	□	□
-absence of previous idiopathic VTE (but previous secondary DVT for which anticoagulation has been discontinued for greater than 1 year is accepted)	□	□
-absence of known thrombophilia (hereditary or acquired)	□	□
-absence of current pregnancy or puerperium	□	□

Exclusion Criteria	Yes	No
1) Age < 18 years-old	□	
2) Refusal or inability to provide informed consent;	□	
3) Allergy to contrast media	□	
4) creatinine clearance < 80cc/min	□	
5) Claustrophobia or agoraphobia	□	
6) Weight > 130 kg	□	
7) Ulcerative colitis	□	
8) Glaucoma	□	

Eligibility Status

Date of eligibility determined (yyyy-mm-dd) _____

Patient is (check one):

Not eligible □

Eligible, non-consenting □

Eligible consenting □

_____ _____

Research Coordinator's signature Date

Qualifying Episode of VTE

Date of documented VTE (yyy-mm-dd) _____

1 VTE

Type of VTE	□ Leg DVT □ PE □ Other _____	
Location:	□Right □Left	□ Bilateral □Other: _____
Please attach diagnostic report(s)	□ Attached	□ Not attached
2 Method of diagnosis		
Compression U/S If yes, Date performed (yyyy-mm-dd)	□yes	□no
Please attach diagnostic report	□ Attached	□ Not attached
Venography: If yes, Date performed (yyyy-mm-dd)	□yes	□no
Please attach diagnostic report	□ Attached	□ Not attached

Spiral CT: If yes, Date performed (yyyy-mm-dd)	□yes	□no
Please attach diagnostic report	□ Attached	□ Not attached
Pulmonary angiography: If yes, Date performed (yyyy-mm-dd)	□yes	□no
Please attach diagnostic report	□ Attached	□ Not attached
Echo: If yes, Date performed (yyyy-mm-dd)	□yes	□no
Please attach diagnostic report	□ Attached	□ Not attached
Other diagnostic information	_____	
Date performed (yyyy-mm-dd)	_____	
Please attach diagnostic report		

Limited occult malignancy screen

1) Baseline History and Physical Examination:

Clinical Symptoms suspicious of malignancy

1) Bleeding	□yes	□no
2) Epigastric pain	□yes	□no
3) Change in bowel Habits	□yes	□no
4) Weight Loss	□yes	□no
5) Other:	□yes	□no

Specify_____

Investigations requested by thrombosis physician:

Please attach diagnostic report or laboratory result □ Attached □ N/A

Abnormal Physical Examination Please specify:

_____

Investigations requested by thrombosis physician:

Please attach diagnostic report or laboratory result □ Attached

2) Baseline Laboratory measurements

	Date collected	Value
1 Hematology		
WBC		10^9/L
Hemoglobin		g/L
Platelet count		10^9/L
2 Chemistry		
ASL		U/L
ALT		U/L
ALP		U/L
Tot Bili		Umol/L
LD		U/L
creatinine		mMol/l
Calcium		Mmol/L
Albumin		g/L
4 Imaging		
CXR in last 12 months		
If yes, Date performed (yyyy-mm-dd)		
Please attach diagnostic report	□ Attached	
mammogram in last 12 months		
If yes, Date performed (yyyy-mm-dd)		

Please attach diagnostic report ☐ Attached

Pap smear (women) in last 3 months
If yes,
Date performed (yyyy-mm-dd)

Please attach diagnostic report ☐ Attached

If not, referral to CTU gynecology ☐ Consult Sent

(SOME): Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism

Post comprehensive CT

Date of Comprehensive CT abdo/pelvis (yyyy-mm-dd):_____

Any abnormal findings?

If yes,
Please
describe:_____

Primary thrombosis physician aware of results: □yes □no

If yes,

Name of physician _____

Date contacted (yyyy-mm-dd) _____

Please attach diagnostic report □ attached

SOME): Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism

Additional investigations post limited occult malignancy screen and cCT to pursue diagnosis of cancer

Any additional investigations	1)_____ 2)_____ 3)_____ 4)_____
Please attach diagnostic report	□ Attached
Any complications from the additional investigations If yes, please list	1)_____ 2)_____ 3)_____
Diagnosis of cancer from the additional investigations?	□yes □no
If yes, please attach diagnostic report	□ Attached

APPENDIX 7

Comprehensive Abdomen/Pelvis CT Protocol

Preparation at home:
1- Bowel preparation with ROYVAC® (Waymar Pharmaceuticals Inc, Oshawa, ON) the day before the procedure
2- Patient is allowed to have clear fluid for breakfast and their usual medications.
3- Patient should empty the bladder one hour before leaving home and not void afterwards.

Pre-imaging:
1- Intravenous access by an iv nurse in the department.
2- Patient will be given gas granules and water to swallow.
3- A small tube will be inserted in the patient's rectum.
4- Intravenous hyoscine butylbromide (Buscopan) 20mg will be administered.
5- Room air insufflations into colon (via rectal tube) until proper distension.

Imaging:
Patient in prone position. Scout views and first scanning:
120 kV, 50 effective mAs, pitch of 1.3-1.5, 3.75 mm-1.6 mm, abdomen and pelvis.
Patient in supine position
Intravenous contrast injection of Omnipaque 300®
130 ml at a rate of 4 ml/sec
Scan at 35 seconds.
For this second scanning: 120 kV, 200 effective mAs, pitch of 1.3-1.5, 2.5 mm-1.2 mm, abdomen and pelvis
Third scanning at 70 seconds: same parameters but liver and kidneys only.
Anterior-posterior scout view at 5 minutes.

Post-imaging:
1- Removal of rectal tube and intravenous route.
2- Patient observation for 10 minutes before leaving the department.

Technical Summary
Colon preparation on the day before the procedure.
No voiding for at least 1 hour before the test.
Gas granules by mouth for stomach distension.
Air by rectum for colon distension.
Enhanced abdomen/pelvis in late arterial phase.
Enhanced abdomen CT in portal venous phase.

APPENDIX 8

Patient Information Sheet and Consent Form

Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism: a Prospective Cohort Study using Comprehensive Abdomen/Pelvis Computed Tomography. The SOME study.

Principal Investigator: **Dr. Marc Rodger**

Sub-investigator: **Dr. Marc Carrier**

1. Background of Study

Up to 10% of patients with unprovoked vein blood clots (meaning blood clots for no apparent reason) in a deep vein of a leg, arm, or lung will be diagnosed with cancer in the few years after the diagnosis of their unprovoked vein blood clot. This risk of cancer is 3 to 4-fold higher than in the general population followed for the same time. Cancer causes a state in which the blood can clot more easily and it is well known that blood clots can be the earliest sign of cancer.

It is unclear how extensively we should screen patients with an unprovoked vein blood clot for cancer. Some studies have shown benefit in using an extensive cancer screening approach whereas others have not.

2. Purpose and Design of Study

The usual screening strategy includes: blood work, urinalysis and basic diagnostic imaging. We think that a more extensive cancer screening strategy, which will give us the most information possible, with the least discomfort possible, should be considered. We have chosen to study a special test called a comprehensive abdomen/pelvis computed tomography (cCT scan). A cCT is designed to find as many cancer types all at once in one test. It includes looking at the stomach, the large bowel, the bladder, the pancreas and the liver. The highly sensitive CT scan used in our hospital is ideal to evaluate the usefulness of cCT for finding cancer in patients with unprovoked vein blood clots. However, the cCT may be somewhat uncomfortable, may result in some side effects (see below), is expensive, involves some radiation (see below), we do not yet know whether it is effective at finding cancers in patients with unprovoked blood clots and we do not know that doing the cCT will result in many unnecessary further tests (in other words it finds changes that are not important but other tests are needed to confirm this).

We hope to recruit 558 patients over 4 years with unprovoked vein blood clots in the Thrombosis Clinic.

3. Study Procedures

You are being approached today to participate in a cancer screening study to determine if an extensive cancer screening approach including cCT is as effective and safe as the usual approach.

This study is divided into time periods of 2 months (Time period A and B). Each time period will be assigned to one of the cancer screening strategies randomly (like flipping a coin) and will be pre-assigned (in other words before the study begins and for the whole study period). Time period A will comprise of basic malignancy screen (outlined below) and Time period B will comprise the usual screen and a comprehensive CT (outlined below). The date of diagnosis of your unexplained clot will be used to determine which time period you fall under.

Time period A

If your blood clot was diagnosed during a 2 month block assigned to Time A period, you will have the following tests completed:

A routine examination, including history taking and physical examination by the physician in the Thrombosis clinic; for women, your gynecologist or your family practitioner will perform a routine pelvic examination and Pap smear; for men a routine prostate exam will be performed; blood tests (blood count, liver and renal functions, calcium) drawn in 2 tubes for a total of 7.5 mls or 1 ½ teaspoons); urine analysis, chest x-ray and mammogram.

You may skip any questions or any part of the physical examination if you do not feel comfortable answering or having the examination performed.

Time Period B

If your blood clot was diagnosed during a 2 month block assigned to Time B period, you will have the tests outlined in Time Period A and a comprehensive abdomen/pelvis CT (cCT) will be performed.

Description of the comprehensive abdomen/pelvis CT (cCT)
The cCT is more sophisticated than a regular CT and the test is completed within 10 to 15 minutes. Here are the steps for the cCT:

1) A bowel preparation, taken by mouth, <u>starting at noon the day before</u> the cCT with liquid diet, using RoyVac® (Waymar Pharmaceuticals Inc, Oshawa, ON). This preparation will be provided to you and instructions are included in the kit. The morning of the cCT, you are allowed to have clear fluids and you should take

your routine medication. You should empty your bladder one hour before leaving home and not void thereafter.

2) In the radiology department, a nurse will put an intravenous (IV) line in your arm. You will be given medication (gas granules) and water to swallow so that your stomach will inflate a little. A small flexible rubber tube (3-4 mm wide) will be inserted in your rectum for 5-10 minutes. A muscle relaxant, Buscopan®, will be given intravenously to reduce your discomfort while room air is placed into your colon so that it can become properly inflated. Images (cCT pictures) will be taken before and after intravenous dye is injected, while you are lying on your back and then on your stomach

3) You will be closely watched for 10 minutes after the cCT before you can leave the department. Your pulse and blood pressure will be checked before and after the test

4. Length of Study

The overall study will continue for 4 years but your participation will be for 2 years. The study will continue for 2 years. You must attend follow-up visits which will be done at the same time as your regular follow-up in the Thrombosis clinic. These visits are usually done at 1 week, 1 month, 6 months, 1 year and 2 years after the unproved blood clot. Our study nurse will also call you every three months to collect information on health care utilization.

5. What could happen to me if I am in the group that gets a cCT?

1) Bowel preparation can cause discomfort. Loose bowel movements or diarrhea are expected in the late afternoon on the day of preparation. Whether patients are able to work or not on the afternoon of the preparation depends on the individual.

2) An intravenous muscle relaxant, Buscopan®, will improve your comfort during the test. It should not make you feel tired and no side effects are expected. (For reference, Buscopan is administered safely as a routine procedure for patients having a large bowel examination called barium enema).

3) A small red rubber tube of 12 F or 14F (3-4 mm wide) will be inserted a few cms in your rectum. It is small and flexible and you might feel a slight discomfort but you might not even feel it. The tube is not likely to perforate the rectal wall. There are rare previous reported cases of perforation with rectal tubes using a large rigid rectal tube.

4) Colon inflation with room air is likely to cause some discomfort. Colon perforation from air is a very rare complication and is usually seen in patients with extensive inflammation of the colon. We don't know of any cases of colon perforation because of CT colonography test.

5) Intravenous dye can cause allergic reactions. Mild allergic reaction, such as itching and hives, sometimes occur. These reactions may improve with medication and sometimes even improve without any medication. Very rarely, more severe allergic reactions can occur. These can include a drop in blood pressure and irregularities of heart beat. In extremely rare cases, stroke or death can occur. The doctors in charge of your case are aware of these risks and possible complications associated with the test that has been requested. In their opinion, the information to be gained about your condition outweighs these risks.

6) Intravenous dye can cause kidney failure in patients with some level of kidney problems. We will check if your kidney function is adequate prior to the test (cCT).

7) The amount of radiation you will receive from participating in this research study is about the
same amount a person would receive naturally, while living in Ontario for 7.4 years. This is considered to be **minimal** and there are no expected consequences associated with this exposure.

6. Benefits of the Study

If cancer is diagnosed, it could possibly be detected at an earlier stage and possibly increase your chances of being cured.

7. Voluntary Participation

You are under no obligation to participate in this study. You may choose not to participate in the study or to withdraw from the study at any time without providing the investigator with a reason. Your decision to withdraw will not affect your present and future care by the Thrombosis clinic.

8. Withdrawal from the Study

You may withdraw from the study at any time without any impact to your care for blood clots (VTE). If you withdraw, you will be given the choice of having your data withdrawn from the study completely.

9. Compensation

In the event of a research-related injury, you will be provided with appropriate medical treatment. You are not waiving your legal rights by agreeing to participate in this study. The study doctor and the hospital still have their legal and professional responsibilities.

10. Costs

You will be reimbursed for the cost of parking for your study visits.

11. Confidentiality

Information gained in this study will be accessible to members of the study groups coordinating this trial. All records identifying you will be kept confidential to the extent permitted by law. Your records will not be made publicly available, for example if the results are published your name or any information that would identify you will not be revealed. All personal communication will remain confidential, and in any report an assigned number, not your name, will be used. The members of the study group and the Ottawa Hospital Research Ethics Board (OHREB) may examine your clinical record under confidentiality. Regulatory authorities (e.g. Health Canada) will also have direct access to your original medical records to verify trial procedures and/or date to the extent permitted by the applicable laws and regulations, however your confidentiality will be maintained. By signing this consent form, you are allowing access to these documents. No records bearing your name will leave the Ottawa Hospital.

12. Questions about the Study and Contact Information

The study staff is available to answer any questions you may have regarding the treatment or study procedure. If you desire or want more information on this study, or this research, or in the event of a research related injury, please contact:

Dr. Marc Carrier

Study coordinator: Angèle Levac, RN
613-798-5555 ext.

Dr. Marc Rodger
613-798-5555 ext. 74641

If you have unusual side effects or symptoms after regular business hours (especially after the cCT), please call our 24-hour phone number 613-722-7000 and ask to speak with the thrombosis doctor on call.

If you have any questions about your rights as a research subject, you may contact:

The Chairperson of the Ottawa Hospital Research Ethics Board at 613-798-5555, extension 14902.

14. Consent

I have read this Patient Information Sheet and Consent Form (or have had this document read to me) and have had an opportunity to ask my study doctor or research nurse any questions I had about the study.

My questions and/or concerns have been answered to my satisfaction and I agree to participate in this study. If I decide at a later stage in the study that I would like to withdraw my consent, I may do so at any time.

A copy of the Patient Information Sheet and Consent Form will be provided to me should I want to review the information at a later date, if I need to contact someone about the study or my participation in the study, or simply for my records.

15. Signatures

_____	_____	
Participant's name	Participant's signature	Date
_____	_____	
Investigator/Delegate's name	Investigator/Delegate's signature	Date

(Valid until April 2008)

APPENDIX 9

Feuille d'information et formulaire de consentement à l'intention du patient

Dépistage de cancers occultes chez des patients atteints de thrombo-embolie veineuse idiopathique : Étude de cohorte prospective faisant appel à la tomographie par ordinateur complète de l'abdomen/pelvis. L'étude SOME.

Chercheur principal : **D[r] Marc Rodger**

Collaborateurs : **D[r] Marc Carrier**

1. Contexte de l'étude

Jusqu'à 10 % des patients qui présentent des caillots de sang veineux non provoqués (c'est-à-dire une coagulation sanguine sans raison apparente) dans une veine profonde de la jambe, du bras ou des poumons reçoivent un diagnostic de cancer dans les quelques années suivant le diagnostic d'un caillot sanguin veineux non provoqué. Ce risque de cancer s'avère de 3 à 4 fois plus élevé que chez une population générale suivie pour une durée de temps similaire. Le cancer provoque un état qui facilite la formation de caillots sanguins et il est bien connu que les caillots sanguins peuvent représenter un des premiers signes précurseurs de cancer.

L'importance du dépistage pour le cancer chez les patients aux prises avec un caillot sanguin veineux non provoqué demeure incertaine. Certaines études ont démontré les avantages de faire appel à un dépistage exhaustif pour le cancer, alors que ce n'est pas le cas pour d'autres études.

2. But et plan de l'étude

La stratégie de dépistage habituelle comprend : analyse sanguine, analyse d'urine et imagerie diagnostique de base. Nous croyons qu'une stratégie de dépistage du cancer plus exhaustive, qui nous offrirait le plus d'informations possible, avec un minimum d'inconfort, devrait être considérée. Nous avons choisi d'entreprendre l'étude d'un test spécial appelé tomographie par ordinateur complète de l'abdomen/pelvis (imagerie TOc). Une TOc est conçue pour repérer le plus de types de cancer à l'aide d'un seul test. Il permet l'examen de l'estomac, du gros intestin, de la vessie, du pancréas et du foie. Le tomodensitogramme à haute sensibilité qui se trouve dans notre hôpital est idéal pour évaluer l'utilité de la TOc dans le dépistage du cancer chez des patients présentant des caillots sanguins veineux non provoqués. Cependant, la TOc peut s'avérer plus ou moins confortable, peut occasionner des effets secondaires (voir ci-dessous), est dispendieuse, comporte des radiations (voir ci-dessous) et nous ignorons toujours

son efficacité à déceler des cancers chez des patients présentant des caillots sanguins non provoqués et nous ignorons également si la TOc donnera lieu à plusieurs autres tests moins utiles (en d'autres mots, il permet de dépister des changements moins importants, mais d'autres tests devront servir à confirmer ces faits).

À la clinique de thrombose, nous espérons recruter 558 patients qui présentent des caillots sanguins veineux non provoqués au cours des 4 prochaines années.

3. Méthodologie de l'étude

Nous sollicitons votre participation à une étude sur le dépistage du cancer afin de déterminer si une approche comprenant un dépistage complet pour le cancer, y compris une TOc, comporte le même niveau d'efficacité et d'innocuité que l'approche habituelle.

Cette étude est divisée en 2 périodes de 2 mois (Période A et B). Chaque période sera assignée au hasard à l'une des stratégies de dépistage du cancer (comme tirer à pile ou face) et sera assignée au préalable (en d'autres mots, avant que l'étude soit entreprise et pour toute la durée de la période d'étude). La période A inclura un dépistage de malignité de base (décrit ci-dessous) et la période B comportera les méthodes de dépistages habituelles et la TO complet (décrit ci-dessous). Nous ferons appel à la date du diagnostic de votre caillot inexpliqué afin de déterminer à quelle période vous serez affectée.

Période A

Si votre caillot sanguin a été diagnostiqué pendant la période de 2 mois assignée à la période A, vous devrez vous soumettre aux tests suivants :

Un examen de routine, y compris antécédents médicaux et examen physique effectué par le médecin à la clinique de thrombose; pour les femmes, votre gynécologue ou votre médecin de famille effectuera un examen pelvien de routine et un test de PAP; pour les hommes, un examen de routine de la prostate sera effectué; analyses sanguines (numération globulaire, fonctions rénales et hépatiques, calcium) prélevées dans 2 tubes, pour un total de 7.5 ml ou 1 ½ cuillère à thé); analyse d'urine, radiographies du thorax et mammographie.

Vous pouvez omettre de répondre à toutes questions ou sauter toute partie de l'examen physique avec lesquelles vous n'êtes pas à l'aise.

Période B

Si votre caillot sanguin a été diagnostiqué pendant la période de 2 mois assignée à la période B, vous devrez vous soumettre aux tests décrits pour la période A ainsi qu'à une TO complète de l'abdomen/pelvis (TOc).

Description de la TO complète de l'abdomen/pelvis (TOc)
La TOc est plus sophistiquée qu'une TO normale et le test prend de 10 à 15 minutes à compléter. Voici les étapes de la TOc :

4) Une préparation de l'intestin, prise oralement, commençant à midi le jour précédent la TOc et une diète liquide, utilisant Roy Vac® (*Waymar Pharmaceuticals Inc*, Oshawa, ON). Cette préparation vous sera fournie et des instructions seront incluses dans la trousse. Le matin de la TOc, vous pourrez consommer des liquides clairs et vous devriez prendre vos médicaments comme d'habitude. Vous viderez votre vessie une heure avant de partir de la maison et vous ne devrez plus uriner par la suite.

5) Au département de radiologie, une infirmière insérera une intraveineuse (i.v.) dans votre bras. Vous recevrez des médicaments (granules de gaz) et de l'eau afin que votre estomac se gonfle légèrement. Un petit tube de caoutchouc flexible (3-4mm de large) sera inséré dans votre rectum pour 5 à 10 minutes. Un relaxant musculaire (Buscopan ®) vous sera injecté par intraveineuse afin de limiter votre inconfort tandis que de l'air ambiant sera injecté dans votre côlon afin de gonfler de façon convenable. Des images (photos TOc) seront captées avant et après l'injection d'un agent de contraste pendant que vous êtes étendu sur le dos et ensuite sur le ventre.

6) Nous effectuerons une supervision étroite pendant 10 minutes après la TOc avant que vous quittiez le département. Nous vérifierons votre pouls et votre pression artérielle avant et après chaque test.

4. Durée de l'étude

L'étude au complet s'étendra sur 4 ans, mais votre participation ne sera requise que pour une période de 2 ans. L'étude continuera pendant 2 ans. Vous devrez vous présenter à des visites de suivi qui seront effectuées au même moment que vos visites de suivi régulières à la clinique de thrombose. Ces visites sont normalement prévues après une semaine, un mois, six mois, un an et deux ans après le diagnostic de caillot sanguin non provoqué. Notre infirmière de l'étude vous appellera également tous les trois mois afin de recueillir des informations sur votre utilisation de soins de santé.

5. Qu'est-ce qui pourrait se produire si je faisais partie du groupe de TOc?

8) La préparation de l'intestin pourrait s'avérer inconfortable. Il est normal de présenter des selles molles ou une diarrhée plus tard en après-midi le jour de la préparation. Le fait que la personne puisse travailler ou non ce jour-là dépend de chaque individu.

9) Un relaxant musculaire intraveineux (Bucospan ®) améliorera votre confort au cours du test. Il ne devrait pas occasionner aucune fatigue et aucun effet secondaire n'est prévu. (Aux fins de référence, le bucospan est administré de façon sécuritaire à titre

de procédure habituelle chez des patients devant se soumettre à un examen du gros intestin appelé lavement baryté).

10) Un petit tube rouge de 12F ou 14F (largeur de 3-4 mm) sera inséré quelques centimètres à l'intérieur de votre rectum. Le tube est petit et flexible et vous pourriez ressentir un léger malaise, mais il est possible que vous ne ressentiez rien du tout. Il y a peu de risque que le tube perfore les parois rectales. Les rares cas rapportés de perforation rectale étaient dus à l'utilisation d'un tube rectal large et rigide.

11) Le gonflement du colon à l'air ambiant pourrait entraîner certains malaises. La perforation du côlon due à l'air est une complication très rare et habituellement rapportée chez les patients présentant une inflammation étendue du côlon. Nous ne sommes pas au courant d'aucun cas de perforation du côlon due à un test de colonoscopie par TO.

12) L'agent de contraste intraveineux pourrait entraîner des réactions allergiques. Des réactions allergiques légères, telles que les démangeaisons et l'urticaire, ont parfois lieu. Ces réactions pourraient s'améliorer avec l'usage de médicaments et parfois même s'améliorer sans médicaments. Dans de rares cas, des réactions allergiques graves peuvent se manifester. Celles-ci peuvent inclure une baisse de pression artérielle et un pouls irrégulier. Dans des cas extrêmement rares, un ACV ou la mort peuvent s'en suivre. Les médecins chargés de votre cas sont au courant de ces risques et des complications possibles reliées au test qui a été demandé. Selon ces derniers, l'importance de l'information obtenue à propos de votre condition à l'aide de ce test l'emporte sur l'importance de ces risques.

13) Les agents de contraste peuvent entraîner une insuffisance rénale chez des patients atteints d'un certain niveau de problème rénal. Nous vérifierons si votre fonction rénale est adéquate avant d'effectuer le test (TOc).

14) La quantité de radiation à laquelle vous serez exposée en prenant part à cette étude est comparable à la quantité qu'une personne recevrait naturelle si elle vivait en Ontario pour 7.4 années. Le risque est donc **minimal** et nous ne prévoyons aucune conséquence reliée à ce degré d'exposition.

6. Avantages reliés à l'étude

Si un cancer est diagnostiqué, il est possible qu'il soit décelé plus tôt et que cela améliore vos chances de guérison.

7. Participation volontaire

Vous n'êtes pas obligé de participer à cette étude. Vous pouvez choisir de ne pas y prendre part ou de vous retirer de l'étude en tout temps sans fournir de raison au chercheur. Votre décision de vous retirer n'aura aucune conséquence sur la qualité de vos soins actuels ou futurs à la clinique de thrombose.

8. Retrait de l'étude

Vous pouvez vous retirer de l'étude en tout temps sans que cela n'influe sur les soins dispensés pour vos caillots sanguins (TEV). Si vous vous retirez, vous pourrez décider que retirer complètement vos données de l'étude.

9. Indemnisation

En cas de blessure reliée à la recherche, vous obtiendrez les soins médicaux appropriés. Vous ne renoncez pas à vos droits légaux en acceptant de prendre part à cette étude. Le médecin de l'étude et l'hôpital sont toujours tenus de respecter leurs responsabilités légales et professionnelles.

10. Coûts

Les frais de stationnement encourus lors de vos visites vous seront remboursés.

11. Confidentialité

L'information recueillie dans le cadre de cette étude sera accessible à tous les membres des groupes d'étude qui coordonne cet essai. Tout dossier vous identifiant sera gardé confidentiel dans les mesures permises par la loi. Vos dossiers ne seront pas divulgués publiquement, par exemple si les résultats étaient publiés, votre nom, ou toute information qui pourrait servir à vous identifier, demeurera confidentiel. Toute communication personnelle demeurera confidentielle et nous ferons appel à un numéro d'étude plutôt que votre nom pour tous les rapports. Les membres du groupe d'étude et du Conseil d'éthique en recherches de L'Hôpital d'Ottawa (CERHO) pourraient examiner votre dossier médical, toujours soumis aux mêmes règles de confidentialité. Des autorités réglementaires (ex. Santé Canada) auront également un accès direct à vos dossiers médicaux originaux afin de vérifier les procédures ou les dates de l'essai dans les mesures permises par les lois et la réglementation en vigueur toutefois, toujours en assurant que votre confidentialité sera maintenue. En signant ce formulaire de consentement, vous permettez l'accès à ces documents. Aucun dossier portant votre nom ne quittera l'Hôpital d'Ottawa.

12. Questions au sujet de l'étude et personnes-ressources

Le personnel de l'étude est disponible pour répondre à toutes les questions que vous pourriez avoir au sujet du traitement ou des procédures de l'étude. Si vous désirez obtenir de plus amples informations au sujet de l'étude ou de cette recherche ou en cas de blessure reliée à cette étude, nous vous invitons à communiquer avec :

D[r] Marc Carrier

Coordonnatrice de l'étude : Angèle Levac, inf. aut.

613-798-5555,

D[r] Marc Rodger

613-798-5555, poste 74641

Si vous remarquez des effets secondaires ou des symptômes inhabituels après les heures de bureau (surtout après la TOc), nous vous prions d'appeler le service téléphonique 24 heures au 613-722-7000 et de demander à parler avec le médecin spécialiste des thromboses qui est de garde.

Si vous avez des questions au sujet de vos droits à titre de sujet de recherche, vous pouvez communiquer avec :

Le président du Conseil d'éthique en recherches de L'Hôpital d'Ottawa, au 613-798-5555, poste 14902.

14. Consentement

J'ai lu cette feuille d'information et ce formulaire de consentement à l'intention du patient (ou quelqu'un me les a lus) et j'ai eu l'occasion de poser toutes mes questions au sujet de l'étude au médecin de l'étude ou à l'infirmière de recherche.

On a répondu à mes questions ou mes préoccupations de manière satisfaisante et j'accepte de participer à cette étude. Si je décidais plus tard de retirer mon consentement, il me sera possible de le faire en tout temps.

Un exemplaire de la feuille d'information et du formulaire de consentement me sera remis advenant que je veuille le consulter à nouveau, que je désire communiquer avec quelqu'un au sujet de l'étude ou de ma participation à l'étude, ou simplement pour mes dossiers.

15. Signatures

_____	_____	
Nom du participant	Signature du participant	Date
_____	_____	
Nom du chercheur/délégué	Signature du chercheur/délégué	Date

(Valide jusqu'en avril 2008)

APPENDIX 10

Decision analysis tree representing the outcomes related to occult malignancy screening