Cost effectiveness of the addition of a comprehensive CT scan to the abdomen and pelvis for the detection of cancer after unprovoked venous thromboembolism

Short Title: Cost effectiveness of CT scan following VTE

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ABSTRACT

BACKGROUND: Although there is an established association between unprovoked venous thromboembolism (VTE) and cancer, it is unclear to what extent testing should be done in these circumstances to allow early detection of occult cancers. Using data from the SOME trial, this study compared the cost effectiveness of adding a comprehensive cancer screening strategy that included computed tomography (CT) of the abdomen/pelvis and virtual colonoscopy, with a more limited screening strategy.

METHODS: We assessed the health care related costs, number of missed cancer cases and health related utility values of the limited screening strategy with and without the addition of a comprehensive CT scan. Analysis was conducted with a one-year time horizon from a Canadian health care perspective using data from 854 patients enrolled in the SOME trial who had an unprovoked VTE. Primary analysis was based on complete cases, with sensitivity analysis using appropriate multiple imputation methods to account for missing data.

RESULTS: The addition of a comprehensive CT scan was associated with higher costs ($551 CDN) with no improvement in utility values or number of missed cancers. Results were consistent when adopting multiple imputation methods.

CONCLUSIONS: The addition of a comprehensive CT scan to screening patients with unprovoked VTE for occult cancer is not cost effective, as it is both more costly and not more effective in detecting occult cancer.

Introduction

Venous thromboembolism (VTE) can be classified as either provoked, when it is associated with a transient risk factor such as trauma or surgery, or unprovoked when it is associated with neither a strong transient risk factor nor overt cancer. Up to 10% of patients with unprovoked VTE are diagnosed with cancer within a year of their index VTE (Carrier, Le Gal et al. 2008). Thus, unprovoked VTE may be an early sign of cancer (White, Chew et al. 2005).

Although there is a known association between unprovoked VTE and cancer, it is unclear to what extent testing should be done in patients with unprovoked VTE to allow early detection of occult cancers. A current guidance statement recommends patients undergo limited screening, generally consisting of basic blood testing, chest radiography and age- and sex-appropriate screening for breast (a mammogram), cervical (Papanicolau smear) and prostate (PSA test) cancer (Khorana, Carrier et al. 2016).

A recent randomized controlled trial (Screening for Occult Cancer in Unprovoked Venous Thromboembolism Study (SOME)) studied whether a more extensive screening strategy that added comprehensive computed tomography (CT) of the abdomen and pelvis and virtual colonoscopy to a limited screening strategy would improve both detection of cancer and patient related outcomes (Carrier, Lazo-Langner et al. 2015). The trial found that an extensive screening strategy did not lead to fewer missed cancers compared to a limited screening strategy.

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There are clearly cost implications of additional comprehensive CT scan testing. Differences in the screening procedure may result in differential healthcare resource use during the follow up period, in that the addition of a CT scan may deter further diagnostic tests at a later date. Thus, a comprehensive analysis of the cost implications of the additional test is warranted. In addition, the impact of the implementation of additional screening tests on patient quality of life is unknown.

Within Canada, as in other countries with a comprehensive publicly provided health care system, the budget for health care is limited and the pressure placed on this budget is increasing (The Financial Accountability Office of Ontario 2016). Thus, it is necessary that decisions related to strategies which require increased use of health care resources should be taken carefully with due consideration of the opportunity costs of such funding decisions. Thus, the decision problem in this context is whether the funding of a comprehensive abdominal and pelvic CT scan in addition to limited occult cancer screening is a justified use of scarce health care resources.

Against this background, the objective of this analysis is to examine the cost effectiveness of an extensive occult cancer screening strategy that includes a comprehensive abdominal/pelvic CT scan and virtual colonoscopy to a limited cancer screening strategy.

METHODS

Clinical Trial

Details of the SOME trial have been provided elsewhere; therefore, only a summary is provided here (Carrier, Lazo-Langner et al. 2015). This multicentre, open-label, controlled trial randomized patients who presented with an unprovoked VTE to either limited occult-cancer screening or an extensive screening strategy which included ~~a~~ limited occult-cancer screening in combination with a comprehensive abdominal and pelvic CT scan. Included within the limited occult-cancer screening were basic blood testing, chest radiography and age- and sex-appropriate screening for breast, cervical and prostate cancer. A total of 854 patients were randomised, 423 to the limited screening and 431 to limited screening plus CT scan. The primary outcome was the confirmed diagnosis of cancer, which was missed by the screening strategy, but detected by the end of the 1 year follow up period. Information on adverse events was collected for both screening strategies.

Form of Analysis

We conducted a trial based cost effectiveness analysis to compare costs and outcomes of the extensive cancer screening (limited plus comprehensive CT scan) versus the limited cancer screening alone in patients with unprovoked VTE based on the results of the SOME clinical trial. Outcomes included both the primary clinical outcome from the clinical trial and health related utility values. Thus, if the extensive occult cancer strategy was found to be both more costly and more effective we would assess the incremental additional cancer detected at screening (cost effectiveness analysis) and the incremental cost per QALY gained (cost utility analysis).

The analysis was conducted from the perspective of the Canadian healthcare system, with a timeframe of one year, consistent with the trial duration.

Resource Utilization and Cost

The SOME trial was formally designed to collect information on healthcare resources. At three follow-up time points - 4, 8 and 12 months - information was collected with respect to physician visits, emergency room visits, hospitalizations, all additional investigations pursuant to the investigation of a cancer diagnosis and adverse events over the previous 4 months.

The cost for each patient was calculated by multiplying their resource use by the appropriate unit cost standardized to 2015. Unit costs for healthcare resources were sourced from published Canadian references – where costs are provide on a provincial basis Ontario was used as a proxy for Canada. The costs of medical procedures included both the physician and technician fees and the overhead costs, where applicable. These were sourced from the Ontario Schedule of Physician Fees, the Ontario Case Costing Initiative and the Canadian Institute for Health Information (CIHI) patient cost estimator (OCCI 2010-2011, CIHI 2016, Ontario Ministry of Health and Long Term Care 2016). The schedule of laboratory fees was used to estimate the cost of lab tests (Ontario Ministry of Health and Long Term Care 2015). In the case of emergency room visit costs and tests for diagnostic markers, the costs were sourced from the published literature (Ooi and M. 2002, Dawson and Zinck 2009, Prostate Cancer Canada 2015, Ontario Ministry of Health and Long Term Care 2016). All costs were inflated to 2015 prices based on the Bank of Canada inflation calculator. (Bank of Canada 2016).

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Utility Assessment

Patients completed a health questionnaire, the EQ-5D, upon entering into the study and at the 12 month follow up visit (The EuroQol Group 1990). This validated instrument allows estimation of the impact of each monitoring strategy on the quality of life of patients and the estimation of associated utility values. We used the value set for the United Kingdom in calculating an index score, as a Canadian value set is not currently available.

Missing Data

We conducted a systematic examination of missing data for both costs and utilities following established guidelines for the handling of missing data in cost effectiveness analysis of randomised clinical trials (Faria, Gomes et al. 2014). This included descriptive statistics to assess the quantity of missing data, an assessment of missing data patterns and an examination of the association between missing data and baseline variables and observed outcomes.

The base case analysis was conducted as a complete case analysis in which only data for those with complete resource and health questionnaire information, at each data point, were included within the analysis. A secondary analysis was conducted using multiple imputation methods to evaluate the impact of missing data on the cost effectiveness estimates. Multiple imputations was conducted with chained equations using predictive mean matching which is appropriate given the non-normal distribution of the cost and utility data to be imputed. We included all covariates thought to be associated with the potential for data to be missing within the prediction equation. These included age, race, gender, costs at each follow up time and baseline and 12 month EQ-5D scores.

Uncertainty

A bias-corrected non-parametric bootstrap procedure involving 5000 replications was used to assess uncertainty around the estimates of incremental cost effectiveness and produce a cost effectiveness acceptability curve (Campbell and Torgerson 1999).

Budget Impact Analysis

A budget impact analysis (BIA) was conducted from the perspective of the Canadian healthcare system in which we compared the implementation of extensive CT screening for all patients with unprovoked VTE in addition to limited screening versus limited screening alone. Full details are provided in the Online Appendix. The incidence rates for unprovoked VTE were estimated based on a Quebec study which was then applied to the Canadian population to estimate the annual total number of unprovoked VTE events (Tagalakis et al. 2013, Statistics Canada 2015). These were then weighted by the cost difference from the economic analysis to estimate the overall budget impact.

RESULTS

Complete Case Analysis

Of the 854 patients entering the study, 784 (92%) (391 within the limited screening group and 393 within the extensive screening group) provided resource data and health questionnaires at all follow up periods. This constitutes the completed case analysis population.

Resource use was comparable between the two arms of the study. There were no significant differences between the screening arms with respect to the number of healthcare contacts or number of days of hospitalization over the follow-up period (Table 1). The number of additional tests was higher within the limited occult screening group, primarily due to a greater number of ultrasounds and laboratory tests, specifically liver enzyme and lactose dehydrogenase tests. However, patients assigned to the extensive cancer screening group required significantly more mammograms and endoscopies.

Within the intent-to-treat population, 428 of the 431 patients assigned to the extensive ~~cancer~~ screening group underwent the comprehensive CT scan and 36 patients assigned to the limited screening arm also received a CT of the abdomen and pelvis. In the completed case population there were 388 of 391 patients who received the comprehensive CT scan in the extensive cancer screening group and 27 of 393 within the limited screening arm that also underwent a CT abdomen/pelvis. No patients within either arm of the trial experienced serious adverse events related to the interventions. Minor adverse events resolved without need for further intervention and did not incur additional resource use.

Based on the completed case analysis, in comparing the total costs within each arm of the trial, the costs were higher within the extensive screening arm with the average cost per patient of $2394 (95% CI $1566 - $3221) versus $1843 (95% CI $1137 - $2549): a difference of $550.69 (95% CI -535.79 to

1637.16, p=0.32). (Table 2) Even without the cost of the comprehensive CT scan, the costs within the extensive screening arm are $333 higher, at an average of $2174 (95% CI $1347 - $3002) per person versus $1841 (95% CI $1135 - $2547), although again, the difference is not significant.

Utility values were not balanced at baseline (Table 2). The mean utility value increased from 0.745 at baseline within the limited screening group to 0.838 at 12 months and from 0.780 within the extensive cancer screening group at baseline to 0.872 at 12 months follow up. Although the utility values at baseline and 12 months differed between the two treatment groups, the change from baseline to 12 months did not differ significantly between the two groups. The utility value improved by 0.092 (95% CI 0.067 – 0.116) within the extensive cancer screening group compared with 0.093 (95% CI 0.069 – 0.118) within the limited screening group; a mean difference in change of -0.001, (95% CI -0.036 to 0.033, p=0.93).

With respect to the cost effectiveness analysis, after standardizing the rate of cancers detected throughout the trial, the proportion of patients in each arm who had a cancer missed during the screening period were 1.0% with the comprehensive screening protocol and 1.1% with the limited screening protocol. Thus, the incremental cost per missed cancer diagnosis avoided with the more extensive cancer screening strategy is $631,803.

Thus, both the cost utility analysis and the cost effectiveness analysis found the limited screening alone strategy to be more cost effective. Based on these results within the cost utility analysis, the limited screening plus CT strategy was dominated by the limited screening alone strategy in that it was more costly and no more effective. For the cost effectiveness analysis, the limited screening plus CT strategy was more costly and unlikely to be cost effective given the high incremental cost per missed cancer diagnosis avoided.

Analysis with Multiple Imputation of Missing Data

Of the 854 patients studied, 70 (8%) had missing data on either costs or the health questionnaire for at least one time point. Resource use was complete for the original CT scan; however, it was missing in 2.8% of patients at 4 months, 4.7% of patients at 8 months and 3.0% of patients at 12 months. With respect to the health questionnaire, baseline data was missing in 0.7% of patients and 3.4% of patients at 12 months. Descriptive analysis revealed that if one resource element at a specific time point was missing, all resource data for that time point was missing. The pattern of missing data was not monotonic, in that if data was missing for an individual at one time point, it was present in some cases, at a later time point. Examination of the relationship between the pattern of missing variables and both baseline variables and data recorded at different time~~s~~ points, supported the assumption that data is missing at random, as opposed to completely at random.

Missing data on costs at each follow up period and EQ-5D scores at baseline and 12 months were imputed creating 200 imputed data sets. The validity of the multiple imputation process was confirmed through a comparison of the distribution of the imputed data to that of the completed case data which found the two to be similar. Additionally, the Monte Carlo errors were less than 15% of the coefficient and confidence interval estimates, indicating that the number of replications (200) wa~~s~~ere sufficient.

The results of the multiple imputation analysis did not differ significantly from the completed case analysis, although the difference in costs between the two arms was lower, as was the difference in utility values at 12 months. In the multiple imputation data set analysis, the costs of the extensive cancer screening group were higher at $2295.10 (95% CI $1052.47 to $3537.94) than with limited screening alone at $2097.35 (95% CI $135.74 to $4058.97), although the difference was not statistically significant (p=0.31) (Table 4). Within the multiple imputation analysis, the change in utility from baseline to 12 months also did not differ significantly between the two groups. The difference in the

change in utility values from baseline to 12 months between the extensive compared to the limited screening group was -0.006 (95% CI -0.042 to 0.030, p=0.75).

Based on the revised estimates of the incremental costs from the extensive screening protocol, the incremental cost per missed cancer diagnosis avoided with the extensive cancer screening strategy is $205,801.

Uncertainty

The bias corrected bootstrap found that the probability that a CT scan in combination with limited occult screening is cost effective versus limited occult screening alone is 28.3% for a willingness to pay for a $50,000 per QALY and 21.6% for a willingness to pay of $30,000 (Figure 1).

Budget Impact Analysis

Based on the current rates of unprovoked VTE in Canada and the cost differences from the completed case analysis, the budget impact of funding a comprehensive CT scan for patients with unprovoked VTEs was estimated to be $4.4 million per annum. Sensitivity analysis suggested the impact could range between $1.4 million and $8.6 million.

DISCUSSION

This analysis found that an extensive occult cancer screening strategy combining ~~a~~ limited occult screening with a comprehensive CT scan of the abdominal and pelvis in patients with unprovoked VTE was more costly than the strategy of limited occult screening alone. This may be expected due to the incremental usage of CT scans, though it was uncertain whether the use of CT may have deterred the use of further diagnostic tests. There was no difference between the groups with respect to the number of physician visits. However, our analysis did find that those receiving a limited cancer screening alone did undergo statistically significantly more investigations, although the mean cost of investigations per patient did not differ between the screening strategies.

The ability to assess the comparative cost utility of the two interventions was limited because information on patient quality-of-life was collected only at baseline and at 12 months follow-up. However, the conduct of extensive CT screening is expected to have very limited impact on patient quality-of-life. As there was no significant difference in the detection of occult cancer between the two strategies there is no reason to expect a difference in utility between the two strategies. This is supported by the comparable change from baseline in utility with both strategies.

The combination of limited occult screening with the comprehensive CT scan did not result in greater effectiveness in terms of changes in quality-of-life as expressed by utility values and had a negligible impact on the detection of cancers missed during the screening as compared with limited screening alone. The addition of the comprehensive CT scan will result in significant cost implications for the healthcare system, with an incremental cost of over 4 million dollars annually. Thus, given the higher costs and no improvement in either effectiveness or health related quality of life, we conclude that the addition of a comprehensive abdominal and pelvic CT scan to limited occult cancer screening in patients

who present with an unprovoked venous thromboembolism is not a cost effective use of scarce health care resources.

AUTHOR DISCLOSURE

The SOME clinical trial was supported by the Canadian Institutes of Health Research. The economic analysis was supported by the Canadian Institutes of Health Research.

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Table 1: ~~Comparative~~ Use of healthcare resources per 1000 patients, over the 12 month follow up period ~~utilization~~ (completed case analysis)*

	Limited occult-cancer screening ~~(n=391) Mean (SE)~~	Limited occult-cancer screening plus CT ~~(n=393) Mean (SE)~~	P value for difference between treatments
Screening tests			
CT scan	8 (4)~~0.008 (0.004)~~	931 (13)~~0.931 (0.013)~~	<0.01
Doctor visits			
Family physician visits	3302 (193)~~3.30 (0.19)~~	3272 (175)~~3.27 (0.18)~~	0.91
Walk-in clinic visits	223 (46)~~0.22 (0.05)~~	201 (36)~~0.20 (0.04)~~	0.71
Specialist physician visits	4488 (193)~~4.49 (0.19)~~	4695 (187)~~4.69 (0.19)~~	0.44
Emergency room visits	560 (61)~~0.56 (0.06)~~	646 (72)~~0.65 (0.07)~~	0.36
Hospital days	678 (251)~~0.68 (0.25)~~	939 (318)~~0.94 (0.32)~~	0.52
Additional investigations			
CT scans	322 (44)~~0.322 (0.044)~~	229 (32)~~0.229 (0.032)~~	0.09
Ultrasounds	299 (36)~~0.299 (0.036)~~	122 (20)~~0.122 (0.020)~~	<0.01
MRIs	31 (11)~~0.031 (0.011)~~	51 (12)~~0.051 (0.012)~~	0.21
X-rays	26 (9)~~0.026 (0.009)~~	20 (7)~~0.020 (0.007)~~	0.64
Colonoscopy, gastroscopy, endoscopy, cystoscopy, bronchoscopy	153 (28)~~0.153 (0.028)~~	267 (41)~~0.267 (0.041)~~	0.02
Biopsies	61 (14)~~0.061 (0.014)~~	46 (12)~~0.046 (0.012)~~	0.41
Nuclear medicine	23 (8)~~0.023 (0.008)~~	18 (7)~~0.018 (0.007)~~	0.61
Mammogram	10 (5)~~0.010 (0.005)~~	31 (9)~~0.031 (0.009)~~	0.04
PAP test	3 (3)~~0.003 (0.003)~~	0	0.32
Prostate specific antigen test~~SA~~	31 (13)~~0.031 (0.013)~~	25 (9)~~0.025 (0.009)~~	0.75
Other cancer markers	5 (4)~~0.005 (0.004)~~	5 (4)~~0.005 (0.004)~~	1.00
Other investigations~~#~~^	10 (5)~~0.010 (0.005)~~	5 (4)~~0.005 (0.004)~~	0.41
Additional Lab Tests			
Urinalysis	33 (13)~~0.033 (0.013)~~	10 (6)~~0.010 (0.006)~~	0.11
Complete Blood Count~~BC~~	8 (4)~~0.008 (0.004)~~	8 (4)~~0.008 (0.004)~~	0.99
Liver Function Tests~~FT~~	199 (23)~~0.199 (0.023)~~	130 (17)~~0.130 (0.017)~~	0.02
Lactate dehydrogenase test~~D~~	105 (17)~~0.105 (0.017)~~	43 (11)~~0.043 (0.011)~~	<0.01
Gamma glutamyl transferase test~~GT~~	8 (4)~~0.008 (0.004)~~	3 (3)~~0.003 (0.003)~~	0.31
Bilirubin	5 (4)~~0.005 (0.004)~~	3 (3)~~0.003 (0.003)~~	0.56
Stool occult blood	3 (3) ~~0.003 (0.003)~~	5 (4)~~0.005 (0.004)~~	0.57
Other lab tests^	5 (4)~~0.005 (0.004)~~	18 (12)~~0.018 (0.012)~~	0.30

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Total number of additional investigations	1340 (99)~~1.340 (0.099)~~	1038 (78)~~1.038 (0.078)~~	0.02

* Figures in parentheses are standard errors.

[#] Other investigations include angiogram, echocardiography, ovarian cystectomy, missed abortion, ileoinguinal resection bypass and thoracentesis.

^ Other laboratory tests include calcium, albumin, tsh, spe, creatinine, alphafetoprotein, hcg and protein.

Table 2: Comparative costs and utilities between groups (completed case analysis)

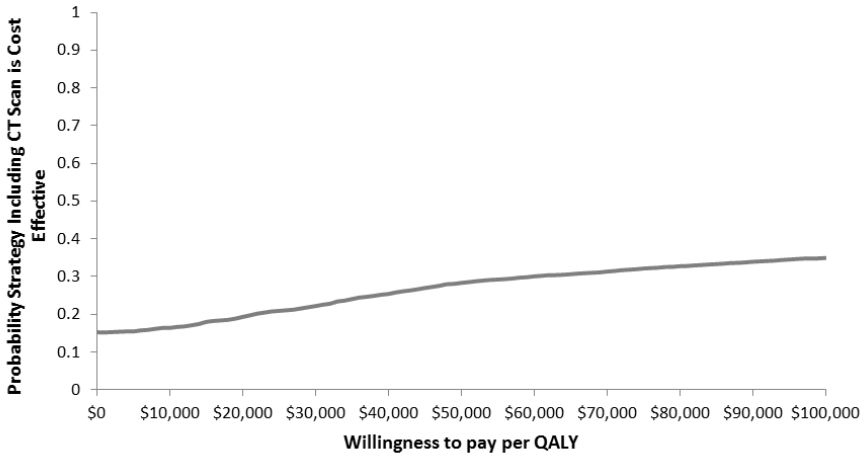
	Limited occult-cancer screening	Limited occult-cancer screening plus CT	Difference between groups (p value)
COSTS			
Screening costs			
CT scan	$1.81 (1.04)	$219.32 (3.01)	<0.01
Follow up costs			
Family physician visits	$126.62 (7.41)	$125.49 (6.72)	0.91
Walk in clinic visits	$17.78 (3.58)	$15.52 (2.79)	0.71
Specialist physician visits	$327.68 (13.72)	$344.19 (13.27)	0.39
Emergency room visits	$136.14 (14.92)	$157.1 (17.44)	0.36
Hospitalizations	$992.41 (341.62)	$1285.41 (404.7)	0.58
Additional Investigations	$241.25 (24.78)	$246.75 (34.7)	0.9
Total costs	$1843.1 (358.96)	$2393.79 (420.99)	0.32
Total costs without screening CT	$1841.29 (358.97)	$2174.47 (421.03)	0.55
UTILITIES			
Baseline utility	0.745 (0.012)	0.780 (0.011)	0.03
12 month utility	0.838 (0.012)	0.872 (0.010)	0.03
Change in utilities from baseline to 12 months	0.093 (0.013)	0.092 (0.012)	0.93

Figures are means with standard errors in parentheses.

Table 3: Incremental Analysis: Complete Case Analysis and Multiple Imputation

	Completed Case	Multiple Imputation
Incremental cost of limited screening plus CT scan versus limited screening alone	$550.69 (-535.79 to 1637.16)	$179.38 (-1048.77 to 1407.53)
Incremental change in utility values from baseline to twelve months for limited screening plus CT scan versus limited screening alone	-0.001 (-0.036 to 0.033)	-0.006 (-0.042 to 0.030)
Incremental costs effectiveness of limited screening plus CT scan versus limited screening alone	Dominated	Dominated

Figure 1: Cost effectiveness acceptability curve for CT scan plus limited occult screening versus limited occult screening using 5000 bootstrap replicates



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APPENDIX

EXHIBIT A: Unit costs for economic analysis ($Can, year 2015 values)

Parameter	Cost estimate		Source
Family physician visit (general re-assessment)	$38.35		(Ontario Ministry of Health and Long Term Care 2016)
Specialist MD visits			
Anesthesiologist	$47.50		(Ontario Ministry of Health and Long Term Care 2016)
Allergist	$79.85		
Audiologist	$41.10		
Cardiologist	$79.85		
Cardiac surgeon	$44.40		
Dermatologist	$38.70		
Diabetes specialist	$75.00		
Endocrinologist	$79.85		
Gastroenterologist	$79.85		
Geriatrician	$79.85		
General medicine specialist	$79.85		
General surgeon	$44.40		
Haematologist	$79.85		
Infectious disease specialist	$79.85		
Internal medicine specialist	$79.85		
Nephrologist	$79.85		
Neurologist	$78.80		
Obstetrician/gynecologist	$47.45		
Oncologist	$79.85		
Ophthalmologist	$57.70		
Orthopaedic surgeon	$42.55		
Otolaryngologist	$41.10		
Physical medicine and rehabilitation specialist	$74.00		
Plastic surgeon	$41.55		
Psychiatrist	$79.85		
Radiation oncologist	$77.55		
Respirologist	$79.85		
Rheumatologist	$79.85		
Thoracic surgeon	$44.40		
Urologist	$45.00		
Vascular surgeon	$44.40		
Emergency Room Visits			
Hospital cost	$186.77		(Dawson and Zinck 2009, Ontario Ministry of Health and Long Term Care 2016)
Physician cost	$56.30		
Total cost	$242.50		

Laboratory Tests			
ALP, ALT, AST, bilirubin, calcium, creatinine, GGT, protein, urinalysis	$2.585 per test		(Ontario Ministry of Health and Long Term Care 2015)
Albumin	$1.551 per test		
Alphafetoprotein	$23.265 per test		
CBC	$8.272 per test		
HCG	$15.51 per test		
LD	$5.17 per test		
Stool – occult blood	$1.551 per test		
TSH	$14.476 per test		
Urine cytology	$6.721 per test		
Lab collection fee	$7.755 per day		
Cancer Biomarker Tests			
PSA	$30 per test		(Prostate Cancer Canada 2015)
CA-125, CA15_3	$15 per test		(Ooi and M. 2002)
Diagnostic Tests	Physician and Technician Costs	Facilities Costs	
CT scans			
Abdomen	$86.60 no contrast	$181	
	$97.5 with contrast	$181	
Neck	$86.60 no contrast	$104	
	$97.5 with contrast	$104	
Pelvis	$86.60 no contrast	$161	
	$97.5 with contrast	$161	
Head	$43.25 no contrast	$97	
	$64.95 with contrast	$97	
Chest	$64.95 no contrast	$176	
	$75.85 with contrast	$176	
CT colonography	$235.30	$252	
Scopes/Biopsies/Aspirations			
Abdominal biopsy	$485.70	$619	
Bone marrow biopsy/aspiration	$78.35 - $202.06	$327-$1086	
Bronchoscopy	$250.41	$940	
Colonoscopy (with and without biopsy)	$127 - $258.84	$321-$561	
Cystoscopy	$264.36	$259	
Endometrial biopsy	$270.11	$623	
Endoscopy (with and without biopsy)	$128.29 - $233.79	$333-$529	
Gastroscopy (with and without biopsy)	$142.94 - $191.59	$347 - $463	
Liver biopsy (with and without ultrasound guide)	$296.07 - $380.22	$376	

Lung biopsy	$291.57	$1255	
Lymph node biopsy	$273.90	$485	
Mole removal biopsy	$230.95	$253	
Pancreatic endoscopy	$455.51	$566	
Pelvic biopsy / washing	$79.85 - $236.06	$293 - $1968	
Prostate biopsy	$254.51	$849	
Skin	$254.55 - $264.15	$231 - $279	
Thyroid biopsy	$117	$1039	
MRIs			
Abdomen	$73.35	$297	
Breast	$73.35	$149	
Head	$73.35	$247	
Pelvis	$73.35	$316	
Spine	$59.50	$222	
Ultrasounds			
Breast, neck, abdomen, pelvis, scrotum	$37.475 - $77.80		
X-Rays			
Chest, abdomen, pelvis, scapula	$21.30 - $36.95		
Skeletal survey	$21.50		
Bone scintigraphy (with and without SPECT)	$151.40 - $218.55		
Echocardiography	$208.80	$335	
Fluoroscopy – chest	$23.45	$228	
Inguinal resection bypass	$1124.80	$9054	
Liver and spleen scintigraphy	$118.80		
Mammography	$44.95		
Misses abortion	$202.46	$739	
Ovarian cystectomy	$484.16	$2081	
Parathyroid scintigraphy	$287.80		
PET	$237.50	$744	
Pulmonary angiogram	$211.46	$491	
Sigmoid polyp excision	$244.65	$571	
Small bowel radiology	$48.20		
Static renal imaging	$71.95		
Thoracentesis	$228.21	$636	
Thyroid scintigraphy	$102.85		

EXHIBIT B: Detailed Methods and Results of the Budget Impact Analysis

Base Case Analysis

A budget impact analysis (BIA) was conducted from the perspective of the Canadian healthcare system in which we compared the implementation of extensive CT screening for all patients with unprovoked VTE in addition to limited screening versus limited screening alone. The incidence of unprovoked VTE was estimated based on a Quebec study which used linked administrative databases to estimate the age and sex specific rate of VTE (Tagalakis et al. 2013). These incidence rates were applied to the Canadian population to estimate the annual total number of VTE events (n=35,686) (Exhibit C) (Statistics Canada 2015). An estimated 22.5% of these events were unprovoked (n=8039). Based on the cost estimate from the SOME analysis, the estimated incremental cost of implementing the CT screening strategy in addition to limited screening versus limited screening alone is $4.4 million per year. Although this cost is small in comparison with the budget for other cancer screening programs such as those for breast cancer and colorectal cancer, these population based programs have been shown to be cost effective. (Cancer Care Ontario. 2016) By not investing in extensive CT screening for patients with unprovoked VTE, these funds could go toward funding more cost effective heathcare interventions.

Sensitivity Analyses

Deterministic Analysis

The base case estimate is based on the definitive cases of VTE within the Quebec study; however, the study also provided an estimate of total VTE cases which included both definitive and probable cases within the linked administrative databases. The estimated rate of definitive and probable VTEs is 1.341 per 1000 person years, of which 32% are unprovoked (Exhibit C). Based on these estimates, the incremental cost of the extensive CT screening strategy with limited screening versus limited screening alone is $8.6 million per year.

Repeating the analysis using the cost difference identified from the multiple imputation analysis found a range in budget impact of between $1.4 million and $2.8 million per year.

Probabilistic Analysis

Using the uncertainty estimates from the source data, we fit probability distributions for each of the input parameters within the BIA (Exhibit C). Costs were assigned gamma distributions and probabilities and incidences were assigned beta distributions. We then conducted a Monte Carlo simulation to produce 5000 estimates of the total annual costs to the Canadian healthcare system of the two strategies.

Based on the estimated number of definitive unprovoked VTE events, the annual cost for the limited screening plus CT resulted in an annual cost of $19,267,442 (95% credible interval $13,195,199 to $26,435,209) versus $14,779,798 (95% credible interval $9,729,814 to $21,065,059) resulting in an incremental annual cost of $4,487,645 (95% credible interval -$4,132,103 to $13,224,886).

If the total events (definitive and probable) unprovoked VTEs are considered, the annual cost of the limited screening plus CT strategy is $37,211,346 (95% credible interval $25,498.476 to $51,041,128) versus $28,544,008 (95% credible interval $25,498,476 to $51,041,128) resulting in an incremental annual cost of $8,667,338 (95% credible interval -$7,984,786 to $25,503,236).

References

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Statistics Canada, CANSIM, table 051-0001. 2015 http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo10a-eng.htm Accessed: July 5, 2016.

EXHIBIT C: Input Data for Budget Impact Analysis

Variable	Value	Distribution
Costs		
limited screening strategy	$1494.33	gamma (26.36, 69.91)
limited screening and CT scan strategy	$2189.41	gamma (32.33, 74.04)
Definitive VTEs		
Incidence rates per 1000 person years by age:		
0-19 years	0.045	beta (770, 17300080)
20-29 years	0.220	beta (2070, 9389279)
30-39 years	0.327	beta (3383, 10357140)
40-49 years	0.503	beta (6249, 12415547)
50-59 years	0.954	beta (10096, 10575287)
60-69 years	1.910	beta (13440, 7021896)
70-79 years	3.553	beta (16702, 4683912)
80+ years	5.853	beta (14644, 2487269)
Percent of VTEs unprovoked	0.225	beta (15172, 52182)
Total (definitive and probable) VTEs		
Incidence rates per 1000 person years by age:		
0-19 years	0.069	beta (1201, 17299649)
20-29 years	0.366	beta (3440, 9387909)
30-39 years	0.563	beta (5828, 10354695)
40-49 years	0.827	beta (10274, 12411522)
50-59 years	1.421	beta (15047, 10570336)
60-69 years	2.574	beta (18110, 7017226)
70-79 years	4.407	beta (20714, 4679900)
80+ years	6.854	beta (17147, 2484766)
Percent of VTEs unprovoked	0.323	beta (29625, 62136)