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CADTH OPTIMAL USE REPORT

Optimal Strategies for the Diagnosis of Acute Pulmonary Embolism: Recommendations

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Abbreviations

CPR	clinical prediction rules
CT	computed tomography
CTPA	computed tomography pulmonary angiography
DVT	deep vein thrombosis
HTA	health technology assessment
HTERP	Health Technology Expert Review Panel
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
PE	pulmonary embolism
PERC	pulmonary Embolism Rule-Out Criteria
PET-CT	positron emission tomography–CT
QALY	quality-adjusted life-year
SPECT	single-photon emission computed tomography
VQ	ventilation-perfusion
VQ SPECT	VQ single-photon emission computed tomography
VTE	venous thromboembolism
US	ultrasound

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Summary of Recommendations

Acute pulmonary embolism (PE) is the third most common acute cardiovascular disease, after myocardial infarction and stroke.[1] The optimal diagnostic strategy for suspected PE among experts remains controversial,[2,3] and it can differ based on factors related to the health care setting (i.e., urban, rural, or remote) that may impact access to diagnostic technologies. For instance, provision of timely diagnosis may be more challenging in rural and remote facilities due to lack of access to certain testing and imaging modalities and specialist expertise, as well as geographical barriers to care. Inability to access optimal diagnostic testing in a timely manner could increase the risk for missed diagnoses, as well as unnecessary anticoagulation due to either false-positives or long wait times to receive a final diagnosis for patients who were treated on suspicion of PE.[4]

Additionally, certain strategies may not be suitable for all patients such as patients with known allergy to contrast media or pregnant women. Exposure to radiation is another consideration when selecting a diagnostic imaging modality. Patient safety concerns associated with exposure to radiation and contrast media that accompanies several imaging studies also disproportionately affect specific patient groups, including pregnant women, and young women for whom the risk of radiation-associated breast cancer ishigher.[4]

To facilitate decision-making, CADTH conducted a health technology assessment (HTA) on the clinical effectiveness and cost-effectiveness of strategies for the diagnosis of acute PE in adults. Patient perspectives and experiences, implementation issues, the environmental impact, and ethical considerations related to the diagnosis of PE were also assessed, as these are also considerations for selecting the optimal diagnostic strategy.[5]

- For the general population with suspected pulmonary embolism, the Health Technology Expert Review Panel (HTERP) recommends the two-tier Wells followed by D-dimer testing followed by computed tomography pulmonary angiography (CTPA), as a diagnostic pathway.
- For the pregnant population, HTERP recommends the two-tier Wells followed by PERC and D-dimer testing followed by leg ultrasound and, if necessary, computed tomography pulmonary angiography as a diagnostic pathway. However, where there is a heightened concern about radiation exposure, and where the clinical situation allows, it would also be reasonable for the clinician and patient to undertake a shared decision making process to select between CTPA and VQ-SPECT as the final step in the diagnostic pathway.
- Among patients for whom computed tomography is strongly contraindicated, HTERP recommends two-tier Wells followed by D-dimer testing, followed by VQ-SPECT, and if necessary, leg ultrasound as a diagnostic pathway.

Technology

Diagnosis of PE is typically a multi-component approach involving initial clinical assessment of risk (i.e., risk stratification involving clinical prediction rules and ancillary tests) followed by confirmation with diagnostic imaging. The diagnosis of PE includes a wide range of options.[6]

Risk Stratification

A patient may initially undergo assessment to determine the probability of PE. Clinicians may use clinical gestalt in decision-making, though this process is less objective than a standardized approach and tends to vary with experience.[7] Clinical prediction rules (also called clinical decision rules) aim to determine risk profile and the necessity of undergoing diagnostic testing in a standardized way. Patients assessed to have a high probability of PE may proceed directly to imaging, while patients with low probability may undergo further testing such as Pulmonary Embolism Rule-Out Criteria (PERC) or D-dimer assessment to further identify the need for diagnostic imaging. This may be supplemented by additional biochemical or imaging studies to rule-out differential diagnoses or strengthen estimates of PE risk.

The Wells rule is a CPR based on an analysis of 40 clinical variables associated with PE. Typically patients with scores lower than or equal to four are deemed low risk for PE, although there is variation in the cut-offs applied. The Geneva score differs from Wells in that additional diagnostic testing may contribute to the score in addition to consideration of risk factors and clinical presentation.[8] A revised Geneva score has been developed that can be determined independently of the additional diagnostic tests.[9]

D-dimer testing is one of several lab-based or imaging studies used to increase confidence on the decision to forego testing by ruling out PE. A negative D-dimer test in a low-probability patient can support the decision to forego further investigation of PE. Conversely, a positive D-dimer test indicates that further imaging is necessary. Various quantitative, semi-quantitative, and qualitative D-dimer assays are available and range in their sensitivity.[10]

PERC is an additional tool that can be applied in patients with low pretest probability, following initial clinical assessment, to help assess whether D-dimer testing is necessary.[11] It is based on parameters that are available at initial emergency department assessment and uses an eight-factor decision rule. The clinician must answer “no” to all questions for a negative result, which can rule-out PE and defers the need for further testing.

The ancillary tests include, but are not limited to, lower-limb compression ultrasound (US), echocardiography, chest X-ray, capnography, and electrocardiography. Some modalities are used to rule-out PE or for prognostic assessment of confirmed PE.[12]

Diagnostic Imaging

Patients who are deemed at high risk of PE following risk stratification, or based on unstable presentation, usually undergo diagnostic imaging for confirmation of disease positivity. Conventional pulmonary angiography has been previously regarded as the gold standard, but due to its invasive nature, it has been overtaken by alternative modalities.[13,14] Less-invasive methods of diagnosing PE that are in routine use include computed tomography pulmonary angiography (CTPA), and ventilation-perfusion (VQ) modalities including VQ scanning planar scintigraphy, VQ single-photon emission computed tomography (SPECT). Thoracic ultrasound is used under special circumstances, and the use of magnetic resonance angiography (MRA) and the hybrid modality of VQ SPECT-CT are being actively investigated.

Computed tomography (CT) uses X-rays, radiation detectors, and computerized analysis to assemble cross-sectional images of the body.[15] It allows for rapid imaging and diagnosis, as well as the ability to visualize fine details of physical body structures, but is accompanied by exposure to radiation. CTPA is used to visualize clots within the arteries of the lung.[16-18]

Magnetic resonance imaging (MRI) uses electromagnetic and radiofrequency fields as well as computerized analysis to assemble cross-sectional images of the body. It does not use ionizing radiation, thus is preferred for patients with contraindications to CT, such as allergy to CT contrast agents, or in children and in pregnant women whose fetus is more sensitive to the effects of radiation. MRI enables visualization of soft-tissue details including segmental and subsegmental vessels, but the time to conduct an exam, requirement for the patient to be motionless within a small space and inability to conduct exams in those with pacemakers and other metallic implants are limitations. MRI is used to visualize clots within the arteries of the lung.[19-22]

Several modalities are used to measure ventilation-perfusion (VQ) mismatch, which indicates the presence of a blood clot based on mismatch between air-flow and blood-flow in the lung. In all cases, radiopharmaceuticals are injected intravenously and inhaled and detected by scintigraphy (2-dimensional), SPECT or SPECT-CT (both 3-dimensional).[23] VQ scintigraphy uses gamma photons to generate two-dimensional or planar images. VQ SPECT uses nuclear medicine cameras to detect gamma rays from the radiopharmaceuticals and generate cross-sectional images. Duration of the exam tends to vary, but is generally longer than CT. The scan quality may be lower anatomic resolution. These scans also require a supply of radiopharmaceuticals. VQ SPECT-CT combines SPECT and CT imaging to generate both anatomic and functional information and improve resolution of the scan. One drawback is the exposure to ionizing radiation involved with both scans.

Thoracic ultrasound involves the use of pulses high frequency sound to visualize structures within the body. Tissue interfaces reflect sound, and the time from pulse to reflection is used to determine depth. In practice, ultrasound is more likely to be used for the unstable patient who may not readily be transferred to diagnostic imaging.

Policy Question

What is the optimal diagnostic strategy for acute PE in urban, rural, and remote settings? For the purposes of this report, urban, rural and remote settings will be discussed in the context of availability of testing modalities, geographical barriers and other accessibility concerns, and types of institutions (i.e., primary care to tertiary care).

Methods

CADTH conducted a HTA to assess the clinical effectiveness, cost-effectiveness, patients' perspectives and experiences, implementation issues, environmental impact, and ethical considerations of strategies for the diagnosis of adults with suspected PE. The Health Technology Expert Review Panel (HTERP) (Appendix 1) developed recommendations about the diagnosis for acute PE in adults based on the evidence presented in the HTA report. HTERP members reviewed the evidence, discussed all elements of the HTERP deliberative framework,[24] and developed a consensus-based recommendation through discussion and deliberation. See Appendix 2 for details.

Additional information on the HTERP process is found on the HTERP page of the CADTH website: https://www.cadth.ca/collaboration-and-outreach/advisory-bodies/health-technology-expert-review-panel.

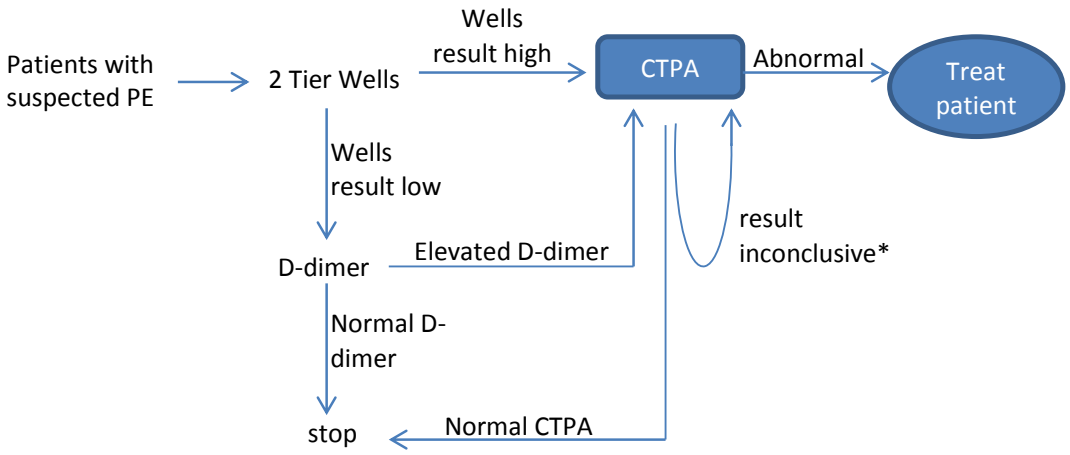
Detailed Recommendations

The objective of these recommendations is to provide advice for Canadian health care decision-makers about the optimal strategies for the diagnosis of acute PE in adults, in urban, rural, and remote health care settings. These recommendations are relevant for patients who are 18 years or older and are undergoing testing for acute PE in urban and rural settings. Although specific recommendations could not be made for the remote setting due to a lack of data, the use of point-of-care D-dimer tests may be an option to determine which patients to treat and transfer for a definitive diagnosis. The population excludes patients with recurrent VTE and patients with suspected DVT without suspicion for concurrent PE.

Shared decision-making, particularly related to radiation dose, may be important if clinical circumstances permit, to discuss the balance of benefit and harm.

- For the general population with suspected pulmonary embolism, HTERP recommends the two-tier Wells followed by D-dimer testing followed by computed tomography pulmonary angiography (CTPA), as a diagnostic pathway.
- For the pregnant population, HTERP recommends the two-tier Wells followed by PERC and D-dimer testing followed by leg ultrasound and, if necessary, computed tomography pulmonary angiography as a diagnostic pathway. However, where there is a heightened concern about radiation exposure, and where the clinical situation allows, it would also be reasonable for the clinician and patient to undertake a shared decision-making process to select between CTPA and VQ SPECT as the final step in the diagnostic pathway.
- Among patients for whom computed tomography is strongly contraindicated, HTERP recommends two-tier Wells followed by D-dimer testing, followed by VQ SPECT, and if necessary, leg ultrasound as a diagnostic pathway.

Figure 1: Recommendation 1 sequence of risk assessment and imaging for patients with suspected PE



*repeat computed tomography pulmonary angiography when results are not conclusive due to technical inadequacy such as patient movement

Figure 2: Recommendation 2 sequence of risk assessment and imaging for pregnant patients

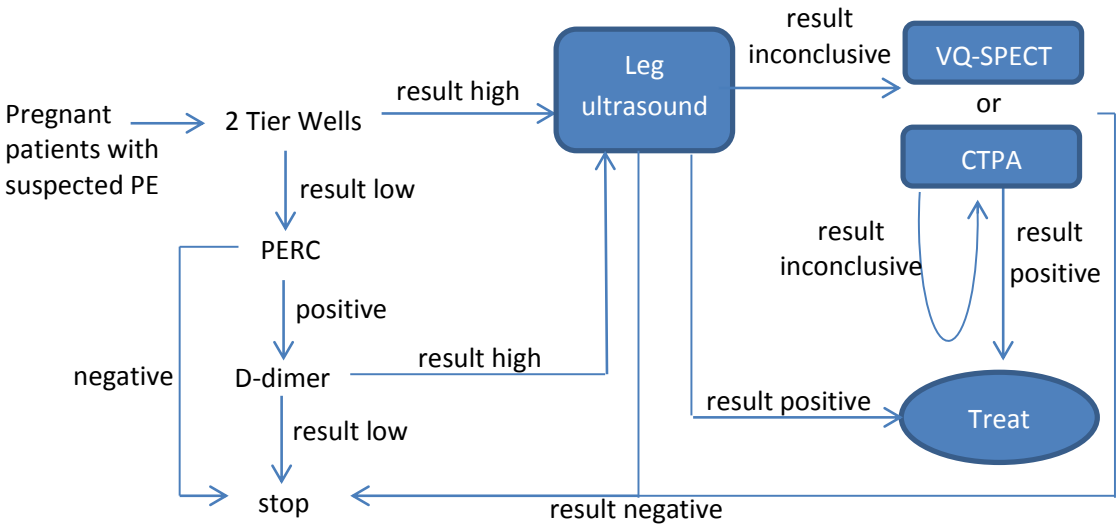
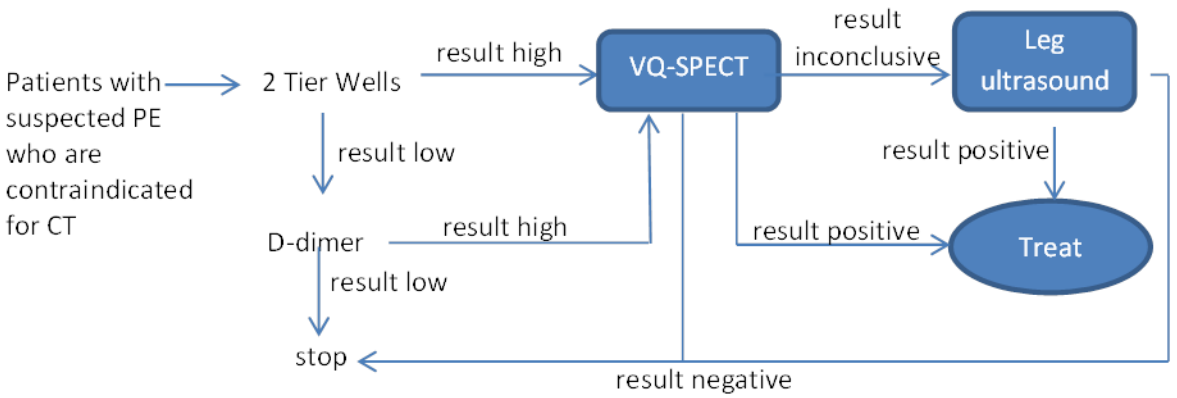


Figure 3: Recommendation 3 sequence of risk assessment and imaging for patients with CT contraindications



Rationale

The results of the overview of systematic reviews indicated that the Wells rule for predicting PE probability showed greater specificity than both the Geneva score and the revised Geneva score. The included SRs[25-27] in the clinical overview of reviews did not show a consistent diagnostic advantage of one CPR over the others with respect to the dichotomized Wells rule, the Geneva score or the revised Geneva score. Combining clinical prediction rules with D-dimer testing improves the ability to rule-out PE.

Individual meta-analyses for CT, MRI, US, VQ, and VQ SPECT, including an adjustment for the use of variable and imperfect reference standards were conducted. Overall, results indicated that CTPA had the highest estimates of sensitivity and specificity, and the least statistical heterogeneity. There was greater uncertainty in the estimates for modalities other than CTPA. CTPA and VQ SPECT both offer similarly high estimates for sensitivity and the lowest number of missed diagnoses when used for rule-out testing. VQ SPECT-CT had too few studies for meta-analysis.

The proportion of patients with test failure, defined as recurrent VTE after a negative test, was low for CTPA, MRI, Q-SPECT, VQ, and VQ SPECT. Except for MRI, all modalities were below the acceptable limit of 3% over three months.[14] Moreover, proportions with test failure from diagnostic pathways consisting of combinations of CPR, D-dimer, CTPA, and VQ, were below 3% for eight of ten pathways.

In patients with suspected PE, a diagnostic strategy involving risk stratification followed by CTPA was cost-effective if willingness-to-pay was under $57,097 per QALY, as long as there are no contraindications to CT. Specifically, the strategy of Wells (two-tier) > d-dimer

> CTPA was the most likely cost-effective diagnostic strategy if the willingness-to-pay threshold was between $13,556 to $57,097 per QALY. If patients have contraindications to CT, the economic analysis found that diagnostic strategies involving VQ SPECT, with leg US to resolve non-diagnostic findings, can be cost-effective.

Reducing radiation exposure is important for younger patients, women, and people who have undergone or will undergo repeated imaging. Dose profile (e.g., fetal or breast exposure) is another consideration. CT imaging results in higher overall doses than the other modalities, with lower exposure from VQ, VQ SPECT, and VQ SPECT-CT. However, CT technology continues to evolve to achieve progressively lower doses. Radiation exposure is of particular concern for pregnant patients. In pregnant patients, leg US introduced earlier in the diagnostic pathway as an ancillary test before diagnostic imaging can reduce the overall exposure to radiation and could be potentially cost-effective if the willingness-to-pay threshold was greater than $7,882 per QALY.

Several studies on the individual experiences of patients undergoing imaging spoke to the ways in which the power of these diagnostic technologies to map out both current and prospective health concerns helped to mitigate various levels of discomfort felt throughout their respective exam. Nonetheless, however powerful this prognostic potential “to know” may be, many participants still framed their experience in terms of their concerns with self-control, isolation and being unprepared. There remains a need to understand how surreal an experience diagnostic imaging can be for individuals unfamiliar with the technologies or settings. Patient factors, provider knowledge and choice may influence the initial assessment, and subsequent investigation, of suspected PE.

Findings of an ethical analysis suggest there is variation in the clinically and ethically appropriate diagnostic pathway for individual patients. In determining the optimal diagnostic pathway for diagnosing PE, clinicians, health care organizations and the relevant policy-makers must take the various stakeholder’s values or interests and the ethical considerations into account. Based on the clinical and economic evidence, the use of CTPA appears to be the most likely candidate for the ethical provision of PE diagnosis, unless contraindicated.

Choosing Wisely Canada states “Don’t order CT pulmonary angiograms or VQ scans in patients with suspected pulmonary embolism until risk stratification with decision rule has been applied and when indicated, D-dimer biomarker results are obtained.”[28] The HTERP recommendations align with Choosing Wisely Canada, with the recommendation to use two-tier Wells, followed by D-dimer tests before moving on to imaging with CTPA.

Considerations

The clinical review included all imaging modalities used for the diagnosis of PE. CTPA, VQ, and VQ SPECT have all been used as part of routine clinical practice, while US has limited use, and the optimal imaging conditions for MRI are still being investigated. In many studies there is a risk of bias due to the modality being assessed also forming part of the final diagnostic conclusion, which tends to result in overestimates of diagnostic test accuracy. Studies of CTPA had the least statistical heterogeneity, while studies of VQ SPECT had more variation in reference standards and interpretation criteria.

The low proportions with test failure of diagnostic algorithms that incorporate D-dimer help support current practice and argue for its inclusion in the work-up of patients who may even be at intermediate risk of PE.

The economic review evaluated 57 potential diagnostic strategies for acute PE. These strategies represented different permutations of clinical prediction rules, rule-out tests, diagnostic imaging modality (i.e., CT, VQ, VQ SPECT, and MRI) and additional testing for non-diagnostic results (i.e., CT or leg US). In total, six diagnostic strategies formed the efficiency frontier (i.e., the set of strategies that, for varying costs, produces the highest health benefits).

For additional testing of non-diagnostic results, CTPA was part of a cost-effective strategy. When CTPA was contraindicated, leg US was most likely to be part of a cost-effective strategy. In cases where DVT is suspected, use of leg US prior to VQ SPECT may be considered though this was not explored in the economic analysis.

The risk stratification tests have not been validated among pregnant patients and no studies were identified that assessed the diagnostic performance of imaging modalities in pregnant patients. Comparative utility data were only available for VQ and CT in this population. For pregnant patients, leg US may be a suitable ancillary test to avoid further diagnostic imaging and, thus, radiation exposure. In a cohort of pregnant patients 30 years of age, the economic model found that offering leg US as an ancillary test before CTPA may be cost-effective if one's willingness-to-pay was greater than $7,882 per QALY (Table 2). In this scenario, a subset of patients can be diagnosed with DVT and receive anti-coagulant therapy without proceeding to further diagnostic imaging.

Radiation exposure, frequency of incidental findings, and other contextual factors are important considerations in the selection of a diagnostic imaging modality. The long-term safety concerns of radiation exposure resulting from imaging for the diagnosis for PE were not assessed. Keeping radiation exposure as low as reasonably achievable is a general principal for radiology and important for reducing the risk due to radiation exposure.[29] While CT typically results in higher overall radiation exposure than VQ SPECT, the fetal and breast dose profiles differ between modalities and may be a consideration. The benefits and harms of radiation exposure has been addressed in the Bonn Call-for-Action.[30] Adhering to the principals and actions of the Bonn Call-for Action will help to ensure protection from radiation, including the appropriateness of imaging, the prioritization of patient safety, and increased awareness of risk and benefits.

To reduce the risks of unnecessary tests, it is important that patients understand the benefits and risks involved with PE imaging and how clinicians communicate this information with their patients. Clear communication will also help patients prepare for the imaging experience and know what to expect.

Although CT is the most geographically accessible imaging modality across Canada, less is known about the capacity for CT regarding the number of patients that access the technology for other conditions and how this might impact accessibility for patients with suspected PE. There was limited information identified specific to rural or remote communities. Data from the Canadian Medical Imaging Inventory indicates that CT is the most common imaging modality in rural and remote areas, so while the economic analysis did not explicitly explore the cost-effectiveness of diagnosis across different settings, the finding that CT was less costly and more clinically effective than other imaging techniques is likely to be consistent in rural and remote settings. Of note, the cost of transportation to a medical facility was not factored in the evaluation and may be significant in rural and remote settings.

Point of care (POC) D-dimer may be a consideration for use in remote settings. A CADTH Rapid Response report[31] suggested that a negative POC D-dimer test has good diagnostic accuracy, although the negative predictive value was lower in elderly patients. Although there is limited evidence on the use of POC D-dimer tests, the use of POC D-dimer in remote settings may identify patients at a high or intermediate possibility of PE who could then be treated and transferred for a definitive diagnosis.

In rural and remote settings, transportation costs for diagnostic imaging may have significant cost implications. PERC may be an option in these settings to provide additional information to inform treatment and decisions about transferring patients for a definitive diagnosis. Although the impact of transportation cost was not explored, economic modelling exercises suggest that the introduction of PERC before d-dimer into the recommended strategy (recommendation #1) would lead to one additional false-negative finding but seven fewer false-positive findings if 1,000 patients suspected of PE participated in the diagnostic pathway (prevalence = 15%). This approach would result in 70 fewer patients undergoing CT imaging, however may result in 10 patients with a false-negative finding who may not receive timely treatment. The mortality rate of untreated PE has been estimated as 30% but may be lower.[32-34]

There are differences in the patient populations, treating clinicians, health care organizations, and access to PE diagnostic tools and tests in Canada that must be considered. CT is the most widely available imaging modality in Canada.[15] While VQ SPECT has been recommended for patients for whom CT is strongly contraindicated or when there is heightened concern about radiation exposure, roughly two-thirds of Canadian centres have VQ SPECT technology.[35] When VQ SPECT is unavailable and CT cannot be used, VQ may be an appropriate alternative.

Background

An analysis of the clinical and cost-effectiveness and a review of patient perspectives and experiences, implementation issues, environmental impact, and ethical considerations were conducted to inform recommendations about the optimal strategies for the diagnosis of PE in adults. The findings are published in the CADTH HTA: *Optimal Strategies for the Diagnosis of Acute Pulmonary Embolism in Adults.*[36]

Research Questions

1. What are the A) diagnostic test accuracy, B) comparative clinical utility, and C) safety of Wells or Geneva clinical prediction rules for the risk stratification of adult patients presenting with PE symptoms in urban, rural, and remote settings:
    a. with or without the use of PERC
    b. with or without the use of D-dimer testing
    c. with or without the use of other biochemical or imaging risk stratification strategies?
2. What are the A) diagnostic test accuracy, B) comparative clinical utility, and C) safety of diagnostic pathways including imaging studies for the diagnosis of PE in adult patients in urban, rural, and remote settings?
3. What are the A) diagnostic test accuracy, B) comparative clinical utility, and C) safety of imaging studies for the diagnosis of PE in adult patients in urban, rural, and remote settings?

4. What is the cost-effectiveness of diagnostic pathways, including imaging studies, to test adult patients suspected of PE?
5. What are the experiences with the diagnostic process from the perspective of those who have undergone testing for acute PE, in any setting include the emergency room setting, from the perspective of patients and their family members and non-clinical caregivers?
6. What are the experiences with diagnostic imaging for any reason and in any setting including the emergency room, from the perspective of patients, their family members and their non-clinical caregivers?
7. What are the issues associated with implementing the optimal use of diagnostic strategies, including imaging, for acute PE in adults in urban, rural, and remote settings?
8. What are the environmental impacts associated with the use of diagnostic pathways, including imaging studies, for the diagnosis of PE in adults in urban, rural, and remote settings?
9. What are the key ethical considerations identified in the literature on strategies for diagnosing acute PE?

Summary of the Evidence

Clinical Evidence

An overview of systematic reviews was performed for the research question on risk stratification strategies, and a de novo systematic review and meta-analyses were conducted on diagnostic pathways and diagnostic imaging studies.

The results of the overview of systematic reviews indicated that the Wells rule for predicting PE probability, regardless of cut-off (<2 or ≤4), showed greater specificity than both the Geneva score and the revised Geneva score. There were not enough data or consistency in trend to allow a conclusive statement about which CPR had the best sensitivity. Strategies combining CPRs and D-dimer testing were effective and safe to rule-out PE in patients presenting with suspected PE symptoms.

Studies of defined diagnostic pathways included clinical prediction rules, D-dimer testing, and VQ and CT, but did not report diagnostic test accuracy data. Sufficient information was available for individual diagnostic test accuracy meta-analysis for CT, MRI, US, VQ, and VQ SPECT. The meta-analysis included an adjustment for the use of variable and imperfect reference standards in the pooled studies. With the exception of VQ (sensitivity 0.864), all imaging modalities had pooled sensitivity greater than 0.950, and with the exception of VQ SPECT (specificity 0.914), all imaging modalities had pooled specificity greater than 0.940, with CT having both the highest estimates of sensitivity and specificity, and the least statistical heterogeneity. CT and VQ SPECT both offer similar high estimates for sensitivity, and therefore the lowest number of missed diagnoses when used for rule-out testing. There was greater uncertainty in the estimates for US, VQ, and VQ SPECT, and the results for thoracic US, in particular, varied widely according to the choice of the statistical model. We were unable to explain the heterogeneity with the available patient and study covariate data, although for VQ and VQ SPECT, the differing interpretation criteria and handling of indeterminate (non-diagnostic) values may have contributed. CT, VQ, and VQ SPECT have all been used as part of routine clinical practice, while US has limited use, and MRI is still being investigated.

Safety data tended to be sparsely reported, and renal and allergic adverse events or procedural complications were few and generally not serious for all modalities. Few studies reported radiation doses, although most studies that used CT identified concerns about radiation exposure in the discussion. Most of the studies excluded patients with absolute or even relative contraindications for imaging potentially lowering the risk of adverse events, but, conversely, many drew from an inpatient population, potentially raising the risk. It is therefore difficult to anticipate how much the risk of adverse events in the study population might differ from the general clinical population.

At least one study reported proportion with test failure for each of CT, MRI, Q-SPECT, VQ, and VQ SPECT. For all but MRI (proportion with test failure 0.034) proportion with test failure was below the accepted threshold of 3% over 3 months. Moreover, proportions with test failure from diagnostic pathways consisting of combinations of CPR, D-dimer, CT, and VQ, were below 3% for eight of ten studies. There were no diagnostic test accuracy studies in pregnant patients, and comparative utility data only for CTPA and VQ. Proportions with test failure for both CT and VQ modalities in pregnant patients were well below the accepted threshold of 3% VTE risk over three months; however, there were more cases of VTE in patients negative for PE based on CT results than with VQ modalities.

Economics

A decision-analytic hybrid model was constructed to examine the clinical outcomes and costs associated with the diagnostic management of patients suspected of acute PE. It entailed an upfront decision tree that captured the short-term screening outcomes and a downstream Markov model to capture the long-term outcomes following a correct or incorrect diagnosis. The clinical pathway and decision-analytic model were developed by reviewing existing clinical and economic literature, and the conceptualization of the model and its structure was subsequently validated by clinical experts from different medical specialties involved at different stages of the diagnostic process and clinical management of PE (e.g., radiology, emergency medicine). The primary outcome was cost per QALYs gained, in 2017 Canadian dollars. As the clinical and cost consequences of a diagnosis of PE can persist indefinitely, a lifetime time horizon was adopted and a payer perspective was chosen. All analyses were probabilistic. The economic analysis was conducted in adherence to current Canadian guidelines in conducting the economic evaluation.[37]

In the results of the model, a trade-off was observed between false-positives and false-negatives as diagnostic strategies with higher incremental cost-utility ratios had fewer false-negatives but were associated with more false-positives findings. In general, a diagnostic strategy involving CT was most likely to be cost-effective so long as there are no contraindications to CT, as CT was found to have the highest diagnostic test accuracy, lowest proportion of non-diagnostic findings and was associated with the lowest costs to perform among diagnostic imaging modalities. The use of CPR to determine clinical pretest probability of PE and the application of rule-out test for patients with low-to-moderate risk of PE may be cost-effective while reducing the proportion of patients requiring CT and lowering radiation exposure. The economic analysis therefore observed that, at a willingness-to-pay value of $50,000 per QALY, a diagnostic strategy of Wells (two-tier)> d-dimer> CTPA > CTPA would most likely be considered cost-effective (probability = 72.3%) (Table 1). The economic model was robust to most sensitivity analyses including scenarios that explored alternative parameter inputs for diagnostic tests accuracy. Parameters with the greatest impact on the results included the analyzed time horizon (i.e., three months), the prevalence of PE and the management of patients with moderate pretest probability of PE based on the

Wells criteria. In terms of specific patient populations, separate analyses were conducted on patients contraindicated for CT or who are pregnant. In a setting in which only nuclear medicine imaging modalities exist and are appropriate (i.e., patients contraindicated for CT), diagnostic strategies involving VQ SPECT with leg US to resolve non-diagnostic findings could be cost-effective depending on one's willingness-to-pay threshold with the diagnostic strategy of Wells (2 tier)> d-dimer> VQ SPECT> Leg US most likely to be cost-effective at a willingness-to-pay threshold of $50,000 per QALY. In pregnant patients, offering leg US earlier in the diagnostic pathway as an ancillary test before diagnostic imaging would be cost-effective if the willingness-to-pay threshold was greater than $7,882 per QALY and could reduce overall radiation exposure. At a willingness-to-pay threshold of $50,000 per QALY, Wells (two-tier)> PERC>d-dimer> VQ SPECT> Leg US was found to be the most likely cost-effective diagnostic strategy in this patient subgroup.

Table 1: Base-Case Incremental Cost-Effectiveness Results for Diagnostic Strategies on the Efficiency Frontier (Probabilistic Results)

Strategy				Costs ($)	QALYs	ICUR ($/QALYs)
Risk Stratification		Dx Imaging	Test for Non-Dx Findings			
No Imaging or risk stratification				2,997	16.8286	-reference-
Revised Geneva	PERC > D-dimer	CT	CT	3,937	17.4632	1,481
Wells: three tier	PERC > D-dimer	CT	CT	3,945	17.4655	3,706
Wells: two tier	PERC > D-dimer	CT	CT	4,073	17.4822	7,661
Wells: two tier	D-dimer	CT	CT	4,183	17.4903	13,556
None		CT	CT[†]	4,571	17.4971	57,097[a]

Dx = diagnostic; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.
[a] It is suspected that the incremental cost-utility ratio for the "all CT" may in fact by higher given limitations to the economic evaluation. The analysis did not consider capacity constraints in terms of the potential clinical and economic impact if there was limited CT availability leading to delays in patient access to diagnosis.

Table 2: Findings From Sensitivity Analyses

Subgroup of Pregnant Patients					
Strategy					**ICUR ($/QALYs)**
Risk Stratification		**Rule-out Test**	**Dx Imaging**	**Test for non-Dx findings**	
No imaging					-reference-
Revised Geneva	PERC > D-dimer	None	CT	Leg US	2,162
Wells: three tier	PERC > D-dimer	None	CT	Leg US	5,892
Wells: three tier	PERC > D-dimer	Leg US	CT	CT	7,882
Wells: two tier	PERC > D-dimer	Leg US	CT	CT	14,859
None		Leg US	CT	CT	65,076
Subgroup of Patients Contraindicated for CT					
Strategy				**ICUR ($/QALYs)**	
Risk stratification		**Dx Imaging**	**Test for non-Dx findings**		
No imaging				-reference-	
Revised Geneva	PERC > D-dimer	VQ SPECT	Leg US	2,348	
Wells: three tier	PERC > D-dimer	VQ SPECT	Leg US	6,333	
Wells: two tier	PERC > D-dimer	VQ SPECT	Leg US	13,337	
Wells: two tier	d-Dimer	VQ SPECT	Leg US	23,438	
None		VQ SPECT	Leg US	113,187	

CT = computed tomography; Dx = diagnostic; ICUR = incremental cost-utility ratio; US = ultrasound; VQ SPECT = VQ single-photon emission computed tomography; QALY = quality-adjusted life-year.

Patients' Perspectives and Experiences

A review of the published qualitative literature was conducted to gain an understanding of patients,' family members,' and non-clinical caregivers' perspectives, and experiences of the process of undergoing diagnosis for acute PE.

The few available studies on the individual experiences spoke to the ways in which the power of these diagnostic technologies map out both current and prospective health concerns helped to mitigate various levels of discomfort felt throughout their respective exam. Nonetheless, however powerful this prognostic potential "to know" may be, many patients still framed their experience in terms of their concerns with self-control, isolation and being unprepared. In addition, self-control could be placed under threat at any point throughout the imaging process. Physical reminders of the presence of loved ones or more verbal or visual reminders of a radiographer's presence, however, could serve as anchors throughout the imaging process and help alleviate related concerns. Similarly, though potentially irrelevant to the emergency room diagnostic process for PE, clear lines of communication between individuals and clinicians prior to examination could help to alleviate these concerns.

Implementation Issues

A survey was developed to provide information and context on this topic, and conducted as part of a CADTH Environmental Scan. The objectives of the Environmental Scan were to: identify current practice related to diagnostic strategies for PE in Canada; identify which tests, scans, and tools are available across Canadian jurisdictions and settings (i.e., urban, rural, and remote health care centres) to diagnose PE; and identify challenges and enablers

to the diagnosis of PE, including relevant implementation issues in Canada. A targeted literature search was conducted to identify information on issues relevant to implementation of diagnostic strategies for PE in Canada. To supplement the findings of the survey and the literature search, an interview with a clinical expert in the field of emergency medicine was conducted. This interview centered on the expert views of the approach to diagnosing PE, including challenges to diagnosis and the Canadian context.

The results indicate that provider knowledge and choice, as well as patient factors, may influence the initial assessment, and subsequent investigation, of suspected PE, and policies and protocols can be used to support the diagnostic strategies for PE. Further, resources, including staffing, access to tests, scans, and imaging are differentially located across the country. As evidenced in the literature, and from the survey and interview, access to tools and tests used to diagnosis PE varies across Canada and differs depending on whether a site is located in an urban centre, is rural, or is remote.

Environmental Impact

Diagnostic imaging modalities differ in their use of radioisotopes, and the production and use of those isotopes may have an impact on the environment. Other ways that imaging modalities may differ in environmental impact include energy use and waste management, including the creation of waste contaminated with radioactive materials. The literature search did not find any studies or reports that evaluated the environmental impact of imaging modalities for PE. Future research can examine the most effective approaches and opportunities to decrease the environmental footprint and improve resource efficiencies of imaging modalities, such as energy savings, waste and toxicity reduction, and waste management, across various health care settings.[38]

Ethics

A review of the empirical and normative bioethics literature was conducted to identify and analyze of the potential ethical issues with diagnosing acute PE.

The findings suggest that there is variation on the clinically and ethically appropriate diagnostic pathway for individual patients, given their unique histories, location, and medical needs. The ethical considerations related to the diagnosis of PE will vary to some degree for clinicians across different specialties. There are likely to be similar ethical considerations for different health care organization, but the ways to address these ethical challenges may vary across organizations. At a systems level, there appears to be greater ethical difference between the various diagnostic pathways and imaging modalities for the diagnosis of PE. As technological advancements in the context of PE diagnosis and the broader health care and social environments change, the ethics of various PE diagnostic pathways will also evolve.

Patients and clinicians have an ethical interest in timely and accurate diagnosis of a potentially life-threatening condition (clinical beneficence); however, they also have an ethical concern to avoid exposure to the harms of diagnostic testing, both those intrinsic to the diagnostic test, such as radiation exposure and reactions to contrast media, and the over-treatment that can result from overdiagnosis (nonmaleficence). In addition, their interest in diagnostic confidence must be balanced with the economic and opportunity costs of achieving that confidence, and so resource allocation comes into play, as reflected in the economic analysis. One approach adopted by the Choosing Wisely campaign to improve the value of clinical care is greater transparency in informed choice, consistent with the value of

respect for patient autonomy; in the emergency department there is widespread reliance on implied consent for diagnostic procedures. Shared decision-making may be appropriate for particular subgroups that are at higher risk from overuse of imaging (pregnant women) or have a preference to avoid imaging. Shared decision-making may, however, have wider applicability where there is a desire to change practice. Fostering trust and educating patients on the limitations of diagnostic imaging may mitigate medicolegal risk concerns. There may be educational challenges specific to imaging (excessive confidence in results) and nuclear medicine (fear of radiation) that influence patient preferences both for and against imaging. The economic implications of overuse are not best addressed through informed choice; other measures for encouraging or ensuring that practitioners practice value-conscious care may be considered. A number of systems-level options exist to improve this situation (education, audit and feedback, controlled access to testing); their feasibility is discussed in the implementation section.

Research Gaps

Given the concern about exposure to radiation, particularly for certain susceptible patient populations, there are opportunities for development and study of reduced-dose protocols, more sensitive detectors, and imaging modalities that do not involve ionizing radiation. The use of imaging modalities capable of higher resolution leads to the identification of smaller and more peripheral emboli. Research is required to identify their clinical significance and determine the risk and benefit of treatment.

There are insufficient data to conduct formal subgroup analyses to evaluate whether the clinical utility differs between strategies and modalities for patients in rural or remote settings, the pregnant population, or patients with cancer. This may emerge to be an important issue if evidence suggests clinical heterogeneity in the clinical utility and safety of different diagnostic tests and imaging modalities between these subgroups. Although the economic analysis did look at pregnant populations given a different set of diagnostic strategies may be relevant to this subgroup, it is important to note that this analysis is limited. There was a paucity of clinical literature on the diagnostic test accuracy of these tests in a pregnant population and the analysis relied on the assumption that the diagnostic tests performed identically in a pregnant and non-pregnant population.

On a related note, the diagnostic test accuracy inputs for D-dimer were based on the pooled analyses from two different publications.[39,40] However, emerging data suggest differences may exist between the type of assay used for D-dimer tests and increasingly, there is interest in employing age-adjusted D-dimer given that D-dimer levels increase with age. Greater research in this area and appropriate meta-analyses would permit analysis to evaluate whether the clinical and cost-effectiveness differs according to the assay type or the patient's age for D-dimer testing. There was limited information identified in a Rapid Response report[31] to address the accuracy of POC D-dimer. Additional research would help to inform decisions about the use of POC D-dimer, particularly in remote settings.

The economic analysis did not evaluate all imaging modalities of interest to the clinical review as there was limited data on some clinical prediction rules and imaging tests. In particular, VQ SPECT/CT represents a potentially promising technology that could not be evaluated given the lack of clinical data to parameterize the economic model. A recent study undertaken from a US health plan payer perspective suggested that the total cost of a SPECT/CT diagnostic strategy could be lower than a CTPA-based diagnostic strategy and could result in more lives saved given improved diagnostic tests accuracy and lower non-

diagnostic rates over a six-month duration.[41] However, these findings should be interpreted with caution as, in their study, diagnostic test accuracy data were pooled by weighting the inputs according to the sample size and assumed perfect reference standards, regardless of the reference standard used. The clinical review in this HTA undertook a more sophisticated statistical approach to adjust for imperfect and composite reference standards in order to estimate sensitivity and specificity of VQ SPECT/CT and, despite using a nearly identical set of publications, found high instability in the pooled estimates.

The use of clinical decision support tools and computer assisted diagnosis was out of the scope for this HTA. As these tools may play a role in diagnosis and may influence the outcome of screening, additional research may be warranted. Moreover, the clinical review focused on patients suspected of acute PE. While it is acknowledged that PE is part of the spectrum of VTE, evidence that focused on patients suspected of having DVT or that focused on patients suspected of broader VTE without PE specific outcomes available was not included. Some of this evidence may be relevant to the general clinical area, so further research is required.

As little has been done to explore experiences or perspectives of individuals undergoing diagnostic imaging for PE, it would be interesting to see how PE specific experiences align with those included within this report. While there is value in understanding the perceived benefits, harms and experiences outlined in this report, a more diverse representation may be possible with further research. We were unable to fully explore the question of how patients perceive being assessed as low risk for PE and therefore ruled-out for further imaging, but the value patients placed on imaging technologies' capacity to help know what was going regardless of risks demonstrates further need to explore these types of questions. As all of these studies were conducted outside of Canada, to gain a greater understanding of PE imaging within the Canadian context and its range of urban, semi-urban and rural populations further research should be conducted in Canada. The Canadian Medical Imaging Inventory update will provide current information regarding where medical imaging units are located across the country. This report will provide updated information on access to imaging modalities in the provinces and territories, especially as it relates to type and placement of imaging units. It may also provide insight on access to these units for those in rural or remote settings. In addition to this, future research efforts could focus on hospital or provincial wide policies and procedures for the diagnosis of PE (e.g., travel policies for patients transported out of centre), and the supports and barriers to the implementation of these practices.

There is a need for more research concerning the impact of PE diagnostic pathways on both the environment and population health. There are also opportunities for deeper exploration of the ethical analyses related to certain patient populations and comparison of the implementation and provision of the various diagnostic pathways and imaging modalities within different jurisdictions in Canada.

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Appendix 1: HTERP

HTERP consists of up to seven core members appointed to serve for all topics under consideration during their term of office, and up to five expert members appointed to provide their expertise for a specific topic. For this project, two expert members were appointed; their expertise included radiology and thromboembolism. The core members include health care practitioners and other individuals with expertise and experience in evidence-based medicine, critical appraisal, health technology assessment, bioethics, and health economics. One public member is also appointed to the core panel to represent the broad public interest.

HTERP is an advisory body to CADTH and is convened to develop guidance or recommendations on non-drug health technologies to inform a range of stakeholders within the Canadian health care system. Further information regarding HTERP is available at https://www.cadth.ca/collaboration-and-outreach/advisory-bodies/health-technology-expert-review-panel.

HTERP Core Members

Dr. Hilary Jaeger (Chair)
Dr. Jenny Basran
Dr. Leslie Anne Campbell
Dr. Jeremy Petch
Dr. Lynette Reid
Ms. Tonya Somerton
Dr. Jean-Eric Tarride

Expert Members

Dr. Marc Carrier
Dr. Sandor Demeter

Past HTERP Members Who Contributed

Dr. Stirling Bryan
Dr. Lisa Schwartz

Conflict of Interest

No members declared any conflicts of interest. Conflict of Interest Guidelines are posted on the CADTH website.