Pulmonary embolism assessments in emergency departments Who and how, in light of recent consensus?

Joint position statement by the Association des médecins d'urgence du Québec (AMUQ) and the Association des spécialistes en médecine d'urgence du Québec (ASMUQ) adopted on October 8th, 2015 (Updated, August 31st, 2016)

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INTRODUCTION

Other than the problem of evoking a pulmonary embolism (PE) diagnosis, physicians must also make assessment choices that are, to some extent, arbitrary. Diagnostic tools have changed in recent years and new guidelines have been published by academic institutions[1]. These guidelines, incorporated into clinical protocols, may allow us to standardize and limit assessments and hence make better use of the available tests. This would benefit patients and would constitute a more economic approach to the issue. The American College of Emergency Physicians (ACEP) has targeted the use of the pulmonary angiogram as an intervention of choice for the *Choosing Wisely* campaign in the United States[2]. Physicians must also remember that it is advisable to involve their patients in the decision-making process, where several assessment options are available. In a cohort of patients who came to emergency rooms for dyspnea or chest pain, 37% said that, in a hypothetical situation, they would choose not to undergo rule-out tests for pulmonary embolism[3].

The Association des médecins d'urgence du Québec (AMUQ) and the Association des spécialistes en médecine d'urgence du Québec (ASMUQ) wish to take part in the knowledge transfer process, in line with the Canadian *Choosing Wisely* campaign, by publishing this position statement, which has been adapted to a large extent from the European consensus of 2014.

CLINICAL PRESENTATION

The typical characteristics of the disease are: pleuritic chest pain, dyspnea, quasi-syncope and hemoptysis (the latter two are rarer). Pulmonary embolism can also be identified during autopsy or assessment for other conditions, and may be completely asymptomatic. The lungs act as natural filters for embolisms generated by peripheral venous circulation, some of which probably occur within normal physiology. In contrast, pulmonary embolism may be present, although more rarely, in association with shock or even, in the case of a massive embolism, sudden death.

Although there are a number of predisposing factors, 30% of pulmonary embolisms occur in patients who present no such factors. It is important to distinguish between a **provoked pulmonary embolism**, i.e. one that occurs in a specific, reversible predisposing context, and an **unprovoked pulmonary embolism**, which does not occur in such circumstances. The distinction between provoked and unprovoked will have consequences for the choice and duration of treatment.

- **Provoked: presence in the preceeding 3 to 6 months of a post-operative state, a trauma, an immobilisation, a pregnancy or an hormonal therapy.**
- **Unprovoked: absence of the above (this category includes all cancers).**

Determination of pretest clinical probability of pulmonary embolism

Determining the pretest clinical probability of pulmonary embolism, either through clinical judgment or using one of the clinical decision rules[4-5], is an essential step in evaluating patients where the presence of the disease is suspected.

The Wells and Geneva rules have recently been simplified in order to separate patients into two categories: improbable or probable pulmonary embolism. These two simplified rules have been tested (see Tables 1 and 2)[6-7] and it was found that their discriminatory powers have been maintained, with very little impact on the percentage of low-risk patients. Pulmonary embolism was confirmed in 12% of patients classified as having low probability; it is therefore important for physicians to add other discriminatory elements in order to reduce this risk and be fully confident when completing their assessment. The two main elements used for this are the PERC rule and the D-dimer test (see below).

Table 1. Wells Rules

Wells Rule	Original	Simplified
History of thromboembolic disease	1.5	1
Heart rate > 100	1.5	1
Surgery or immobilization < four months prior to episode	1.5	1
Hemoptysis	1	1
Active cancer	1	1
Clinical signs of thrombophlebitis	3	1
Less probable alternate diagnosis	3	1
Three-level clinical probability		
Low probability	< 2/12.5	Doesn't apply
Two-level clinical probability		
Less probable	≤ 4/12.5	≤ 1/7
More probable	> 4/12.5	> 1

Table 2. Simplified Geneva Rule

History of thromboembolic disease	1
Heart rate = 75-94	1
Heart rate > 94	2
Surgery or fracture in the last month	1
Hemoptysis	1
Active cancer	1
Unilateral pain in one limb	1
Pain on palpation of the veinous pathway and unilateral oedema in one limb	1
Age > 65 years	1
Clinical probability	
Improbable pulmonary embolism	≤ 2
Probable pulmonary embolism	≥ 3

Once pretest probability has been determined, physicians can use the PERC (Pulmonary Embolism Rule-Out Criteria) rule to eliminate those patients with the lowest probability of pulmonary embolism based on purely clinical criteria, even without using the D-dimer test; the probability of thromboembolic disease is estimated as being < 2% for negative PERC patients (score of zero)[8-9] (see Diagnostic strategy, Figure 2). The pulmonary embolism diagnosis is therefore ruled out at this point and the physician can consider other diagnoses.

Table 3. PERC Rule	
Age > 50 years	1
Heart rate > 100	1
O_2 saturation < 95%	1
History of thromboembolic disease	1
Recent trauma or recent surgery	1
Hemoptysis	1
Estrogen use	1
Unilateral oedema in one limb	1
Negative PERC	**Score = 0**
Positive PERC	**Score > 0**

Investigations

D-dimers are present in serum during acute thrombosis following simultaneous activation of coagulation cascades and fibrinolysis. D-dimers dosage must be performed using an ELISA or turbidimetric (LIA) test, those tests having a negative likelihood ratio (LR-) below 0.15[11-13]. The negative predictive value of D-dimers is high, but its positive predictive value is low, especially in the presence of concomitant conditions such as cancer, inflammation, necrosis, trauma or hemorrhage[14].

Table 4. Factors associated with an increase in D-dimers
Age 60-69 years [OR = 2.6], 70-79 years [OR = 4.5], ≥ 80 years [OR = 10.5]
Cocaine [OR = 2.0]
Immobilization: general [OR = 2.3], lower limb [OR = 2.8], neurological [OR = 3.0]
Hemoptysis [OR = 2.0]
Active cancer [OR = 2.6]
Rheumatoid arthritis [OR = 2.8]
Lupus [OR = 2.1]
Sickle-cell anemia [OR = 24.2]
Pregnancy: 2nd trimester [OR = 7.3], 3rd trimester [OR = 51.3], post-partum [OR = 4.2]
Surgery in the last four weeks: abdominal [OR = 3.5], thoracic [OR = 2.7], orthopaedic [OR = 2.2], other [OR = 3.2]

However, a negative D-dimers result in the presence of conditions conducive to a high D-dimers score maintains its negative predictive value (e.g. a patient with cancer who obtains a negative D-dimers score is at lower risk of pulmonary embolism).

A patient investigated for pulmonary embolism who is found to have low pretest probability and a negative D-dimers score may be sent home with no further diagnostic assessment, since prospective studies have shown that the three-month thromboembolic risk for these patients is less than 1%[15]. This group accounts for 30% of all patients assessed for pulmonary embolism. D-dimers specificity declines with age (85% of tests are positive (> 500µg/L) at 80 years of age)[16]. A recent meta-analysis has shown that an age-adjusted D-dimer threshold (age x 10µg/L over 50 years of age) would increase the test's specificity while maintaining sensitivity at more than 97%[16-18].

Age-adjusted D-dimers:
Age of patient x 10 (µg/L) starting at age 50.

A **chest X-ray** is useful only to show other causes of chest pain or dyspnea.

An **ECG** is used to identify signs of right ventricle (RV) distress: T wave inversion in V1-V4, QR in V1, S1Q3T3, complete or incomplete right bundle-branch block[10]. Anomalies such as these on an ECG are associated with a poorer prognosis[19]. In cases where there is no right ventricular dysfunction, the only anomaly will be sinus tachycardia (40% of cases). De novo auricular fibrillation may also be associated with pulmonary embolism.

A **pulmonary CT-angiogram** is currently the most accessible form of imaging to assess pulmonary embolism. It has the advantage of describing significant findings such as lung tumors, infiltrations and vascular lesions. However, its accuracy is subject to discussion. In the PIOPED II study, its accuracy was measured at 83%, with a specificity of 96%[20]. This study is complex and difficult to apply to current clinical practice. On the other hand, the combined value of pulmonary CT angiogram, D-dimers and a low probability Wells score, as observed in the CHRISTOPHER study among others[21-22], offers excellent negative predictive value, in excess of 98%. Unfortunately, accuracy comes at a price: the number of false positives, in roughly 6% to 10% of cases[14], probably leading to overdiagnosis and needless anticoagulation[20, 23-25]. Some authors have estimated sensitivity and specificity at around 90%[14, 26]. Technical problems during CT, for example due to obesity, rapid breathing or injection quality, are encountered on a regular basis and make it difficult to read the image in a significant number of cases[27, 28]. For example, 6% of the PIOPED II exams and 0.9% of the CHRISTOPHER study exams had to be rejected. The new devices, which have more detector elements, also provide more accurate images that allow for diagnosis of subsegmental pulmonary embolisms.

A paper published in 2015 in the *Journal of the American Radiology Association* revealed a discrepancy in 25.9% of the positive interpretations of 937 pulmonary CT-angiograms when reviewed by specialized thoracic radiologists in a tertiary hospital. Moreover, 59.4% of the embolisms diagnosed at a sub segmental levels were false positives, mostly due to movement artifacts. Some 46.2% of the solitary embolisms were also false positives. This study therefore shows that the problem of overdiagnosing pulmonary embolisms with pulmonary CT-angiograms is very real[29]. Also, observers have not been able to agree on the clinical significance of sub segmental embolisms, and the subject remains a controversial one[24, 33-34].

For investigation of pulmonary embolism, the pulmonary CT-angiogram is also the form of imaging that exposes patients to the most radiation: between 10 and 20MSv[30] on average. Some patients react to the contrast products too. In addition, the technology is hard on kidney function, and there is a risk of irreversible injury[31-32]. However, protocols exist to limit allergic reactions and reduce the impact of the iodine load on kidney function.

CT-angiograms sometimes detect other nodules, the clinical signification of which has not yet been shown. The phenomenon, known as incidentaloma, can trigger a cascade of investigations, causing anxiety in patients and generating substantial costs.

There are two forms of the **lung ventilation/perfusion scan or V/Q scan**. The first of these, the planar method, which uses xenon, provides two-dimensional images. The PIOPED I study was carried out with this type of device, which is still used in the United States. In Canada, however, we use everywhere the newer form, SPECT, which uses Technegas and provides three-dimensional images[35, 47]. So far, this new technology has only been assessed in small-scale studies. Patients are exposed less to radiation, and the technology does not affect kidney function, making it an excellent choice for certain patient groups, including pregnant women and patients with renal insufficiency. Allergic reactions caused by the scan are rare, and always benign. However, the technology is more reliable when the lung anatomy is relatively normal, but this limitation is overcome to a large extent by the routine addition of a low-dose CT scan at the same time[36]. The small number of studies that have been carried out suggest that the addition of a low-dose CT scan to the V/Q scan improves specificity by reducing the false positive rate while maintaining the same sensitivity level[37-38]. The main obstacle to large-scale use of the nuclear imaging was the high rate of indeterminate results with the planar method. This problem has largely been eliminated by the use of new reading protocols and scintitomography (SPECT). Thanks to these developments, nuclear medicine specialists are now, in most cases, able to deliver a binary answer (presence or absence of pulmonary embolism). However, the technology is still not as widely available as the pulmonary CT-angiogram.

Table 5. Comparison: pulmonary angiogram and lung scan		
	Angiogram	**V/Q scan**
Advantages	• Gold-standard • Availability • Identifies suspect lesions from the lung X-ray (descending aortic aneurism, tumors of the lung or infiltrates)	• Very little radiation • Independent of kidney function • Ideal for pregnant women or young people • Diagnostic accuracy equivalent to the CT-angiogram if the lung X-ray is almost normal • Also diagnoses isolated sub segmental pulmonary embolisms
Disadvantages	• X-rays • Damages kidney function • High rate of incidentalomas • Identifies sub segmental lesions of undetermined significance • Reactions to contrast products • Slightly more complex procedure	• Not as easily available in some centers • Difficult to interpret if the lung X-ray is highly abnormal

Lower limb compression ultrasonography[39-41] offers excellent sensitivity (90%) and specificity (95%) for diagnosis of deep-vein thrombosis in the lower limbs. Most pulmonary embolisms originate in these limbs: this is the case for 30% to 50% of all diagnosed acute pulmonary embolisms[42]. Where pulmonary embolism is suspected, discovery of deep vein thrombosis is sufficient for a diagnosis. This method can be useful for pregnant women, since it avoids the need to expose the patient to radiation. It is possible to limit the assessment to the groin and popliteal fossa. Correlation with pulmonary embolism via CT-angiogram is very good: sensitivity of 39% and specificity of 99%. Therefore, if the compression ultrasound is positive, the pulmonary embolism assessment is terminated and the physician selects an appropriate treatment. Compression ultrasonography is one of the skills taught in advanced ultrasound training for emergency physicians.

Prognostic indicators

Biomarkers (NT-proBNP and troponin) can highlight right ventricular dysfunction. A abnormal value is not specific, but is sensitive enough to reassure physicians about the lack of hemodynamic repercussions from the pulmonary embolism in cases where dosage is normal[43-44]. Similarly, myocardial cell damage, signaled by an increase in the troponin dosage, is associated with a poorer prognosis in patients with pulmonary embolism[45]. Both markers also seem as effective as imaging, if not more so, for prognostic evaluation of pulmonary embolism[1].

Cardiac ultrasound is becoming more accessible, and has the advantage of being quick to administer, at the patient's bedside. Dilatation of the right ventricle (RV) compared to the left (LV) marks the embolism's impact on pulmonary circulatory resistance. The hemodynamic impact with RV dysfunction is gradual and can create pulmonary hypertension with short- or long-term repercussions ranging from reduced functional capacity to death. A RV/LV size ratio greater than 1, and perhaps greater than 0.9, is associated with a greater risk of 90-day mortality[46].

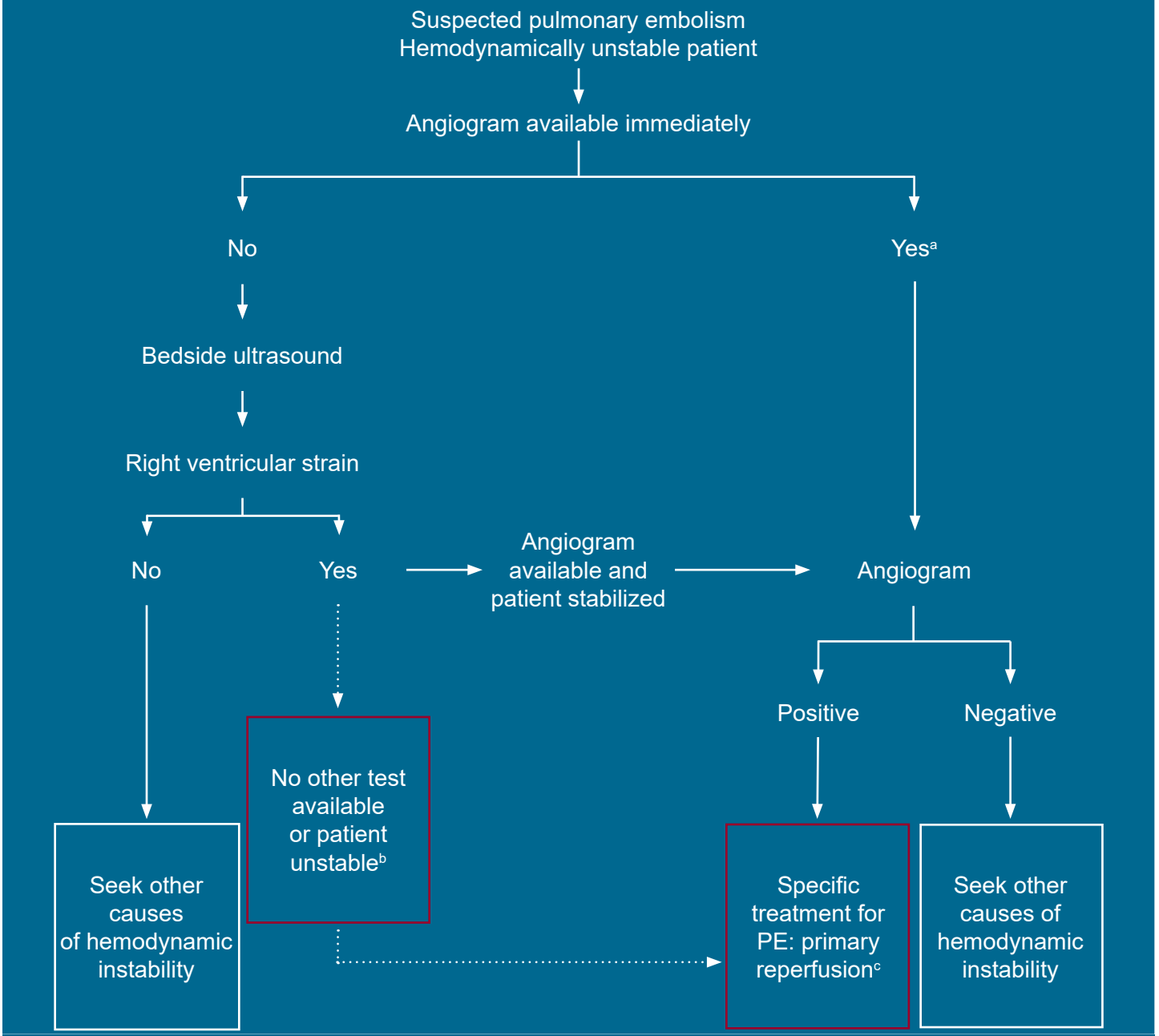
A cardiac ultrasound may become crucial in cases where pulmonary embolism is suspected and the patient is hemodynamically unstable. There is extensive support in the literature for the use of targeted ultrasound by emergency physicians in order to diagnose pulmonary embolism in unstable patients. The technology facilitates and speeds up the decision process with a view to performing rapid thrombolysis.

Diagnostic strategies

Suspected pulmonary embolism in hemodynamically unstable patients

The following algorithm, taken from the 2014 European consensus, can be used to simplify the decision process where the patient is hemodynamically unstable. Shock is defined as hypotension < 90mmHg persisting for more than 15 minutes after initial treatment. Note that we suggest a bedside cardiac ultrasound instead of an CT-angiogram if the patient remains unstable, even if the CT-angiogram is available.

Figure 1. Suspected pulmonary embolism in hemodynamically unstable patients

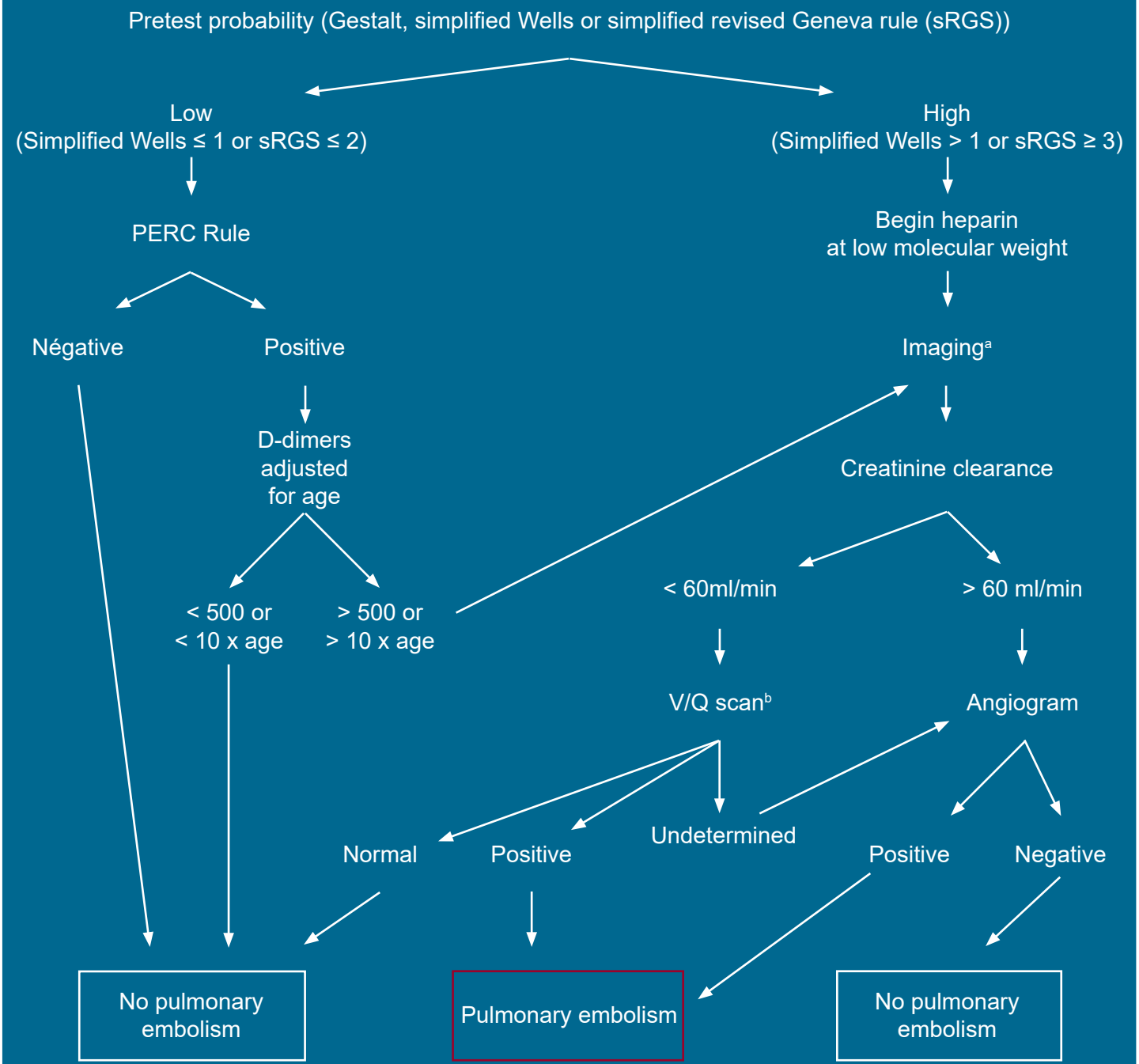


a. Unless the patient is too unstable to go to radiology.
b. In addition to diagnosing right ventricular dysfunction, bedside transthoracic echocardiogram can, in some cases, confirm pulmonary embolism directly by displaying a mobile thrombus in the right heart. Bedside ultrasound techniques also includes the transesophageal echocardiogram, which can identify embolisms in the pulmonary arteries and their main branches, and lower limb compression ultrasonography, which can confirm deep vein thrombosis and is useful in the decision-making process.
c. Thrombolysis or surgical embolectomy or intra-arterial therapy.

Suspected pulmonary embolism in hemodynamically stable patients

This section is inspired by a paper written by Dr. Jeffrey Kline[14], an American emergency physician. We propose a modified algorithm, based on that of Dr. Kline, in which we use a two-level approach to the application of pretest probability. Nuclear medicine investigation is better in Québec than in the United States, where Dr. Kline practices. We obtain binary results much more frequently. As a result, the number of non-diagnostic scintitomograms is much lower than in the United States, which is why we recommend this examination more strongly in the algorithm.

Figure 2. Suspected pulmonary embolism in hemodynamically stable patients.



a. The decision to anticoagulate the patient before imaging depends on the evaluation of the bleeding risk against the probalility of PE, and its severity. For example, it is suitable to anticoagulate a patient with a low bleeding probability if the investigation can't be done quickly: immediately for a patient with a high probability of PE, up to four hours for a patient with a moderate probability, and up to 24 hours for a patient with low probability.
b. Pregnant women or patients with severe iodine allergies may be included here. Compression ultrasound can be used for investigations carried out on pregnant women.

Risk stratification for confirmed pulmonary embolism

A short-term risk of complications (death, shock or recurrent embolism) before or after the pulmonary embolism diagnosis, even with proper treatment, still exists. Stratification of patients according to risk levels will help the physician and patient to choose the best diagnostic options (bedside resuscitation room assessment or use of normal technologies, possibly in an outpatient clinic) and treatment options (from thrombolysis for more unstable patients to outpatient treatment for the patients at least risk of complications).

Patients with cardiogenic shock or persistent hypotension run a high risk of quick death. For those who tolerate the embolism well, the risk arises mainly from the probability of recurrence if there are still clots that have not yet been dislodged, or others that continue to form. Anticoagulation simply prevents the formation or extension of thrombi. Lysis of existing clots takes place over the following days, using our own system or via medication.

Simplified PESI score or sPESI (Simplified Pulmonary Embolism Severity Index)

The sPESI is used to stratify the risk of complications in patients with confirmed embolisms, and guides them safely towards the best options[48-49]. Cardiac markers do not need to be measured in patients with a sPESI equal to zero[1]. A patient with a sPESI of zero can be considered for outpatient treatment. Note that roughly 50% of patients diagnosed with pulmonary embolism have sPESI scores of zero.

Table 6. sPESI variables	
Age > 80	1
Cardiac insufficiency	1
Cancer	1
Pulse > 110	1
Systolic BP < 100	1
Saturation < 90%	1
Low risk	**Score = 0**
Higher risk	**Score ≥ 1**

Bova score

For patients at intermediate risk (normal blood pressure and sPESI ≥ 1), it may be useful to refine the poor short-term prognosis risk calculation. This calculation has just been published by Bova et al[50-51]. It can be used in conjunction with imaging data and biomarkers to identify a category of high-risk patients with normal blood pressure, who would benefit from thrombolytic treatment.

Table 7. Bova score calculation	
Systolic BP 90-100mmHg	2
Increased troponin	2
Right ventricular dysfunction (echocardiogram or CT scan)	2
Pulse > 110/min	1

Points are assigned for each variable and the total score is obtained by adding them together (range from 0 to 7). The Bova score is used to subdivide intermediate-risk patients into three subcategories, as shown in the last algorithm (see Figure 3 and Table 9). High Bova scores (i.e. above 4) will be obtained by roughly 5% of intermediate-risk patients, and more aggressive treatment can be envisaged for this subgroup.

Table 8. Three-step strategy
Identify patients in shock: sustained hypotension (< 90mmHg) (≥ 15 min).
Identify low-risk patients: normal blood pressure, sPESI = 0.
Of the remaining patients (intermediate risk), stratify into three subcategories (Bova score) 0 to 7.

Areas of uncertainty

A randomized study directly comparing planar V/Q scans to CT-angiograms found a significant increase in pulmonary embolism detections, but no significant impact on mortality[52]. It may therefore be the case that overdiagnosis is a factor in the growing prevalence of pulmonary embolism.

The prognosis for isolated sub segmental pulmonary embolisms, which are currently on the increase, is under debate. Current data, based on retrospective research, are contradictory[24, 33-34]. A recent study confirmed the high rate of false positives from CT-angiograms reporting isolated or sub segmental embolisms[29].

Pulmonary embolisms discovered by chance are also a subject of debate. Some experts recommend treating patients with cancer, but there is, as yet, no solid clinical proof to support this[53-54].

The effectiveness of triple rule-out CT-angiograms (acute coronary syndrome, pulmonary embolism, aortic dissection) has not yet been proved in clinical studies, for lack of power. As an approach, it is costly and exposes patients to high levels of radiation[55].

CONCLUSION

In this position statement on pulmonary embolism assessment, we present an evaluation strategy that will help practitioners in Quebec to adopt a standard, safe, scientifically tested approach to a condition frequently encountered in emergency rooms.

Once the diagnosis has been established or excluded, emergency physicians can start treatment and direct their patients to those services that provide the necessary treatment and follow-up. The question of therapeutics has voluntarily been left aside here, given the many different options available and the rapid changes that occur in this field.

In view of the limitations of the various tests available to confirm a diagnosis of pulmonary embolism, it is vital that physicians be careful when selecting the patients they will investigate, and how. Some uncertainty must be tolerated, and patients will often accept this when the physician takes time to explain the consequences of overdiagnosis and the risk of bleeding.

ADDENDUM

As this position statement was going to press, the American College of Physicians had just published six guidelines for evaluation of pulmonary embolisms, all of which support the position we have taken here, except for the less important role of ventilation-perfusion scintigraphy, due to the differences in available technology, as mentioned in our text[58].

The authors have no conflict of interest to declare.

Figure 3. Clinical suspicion of pulmonary embolism

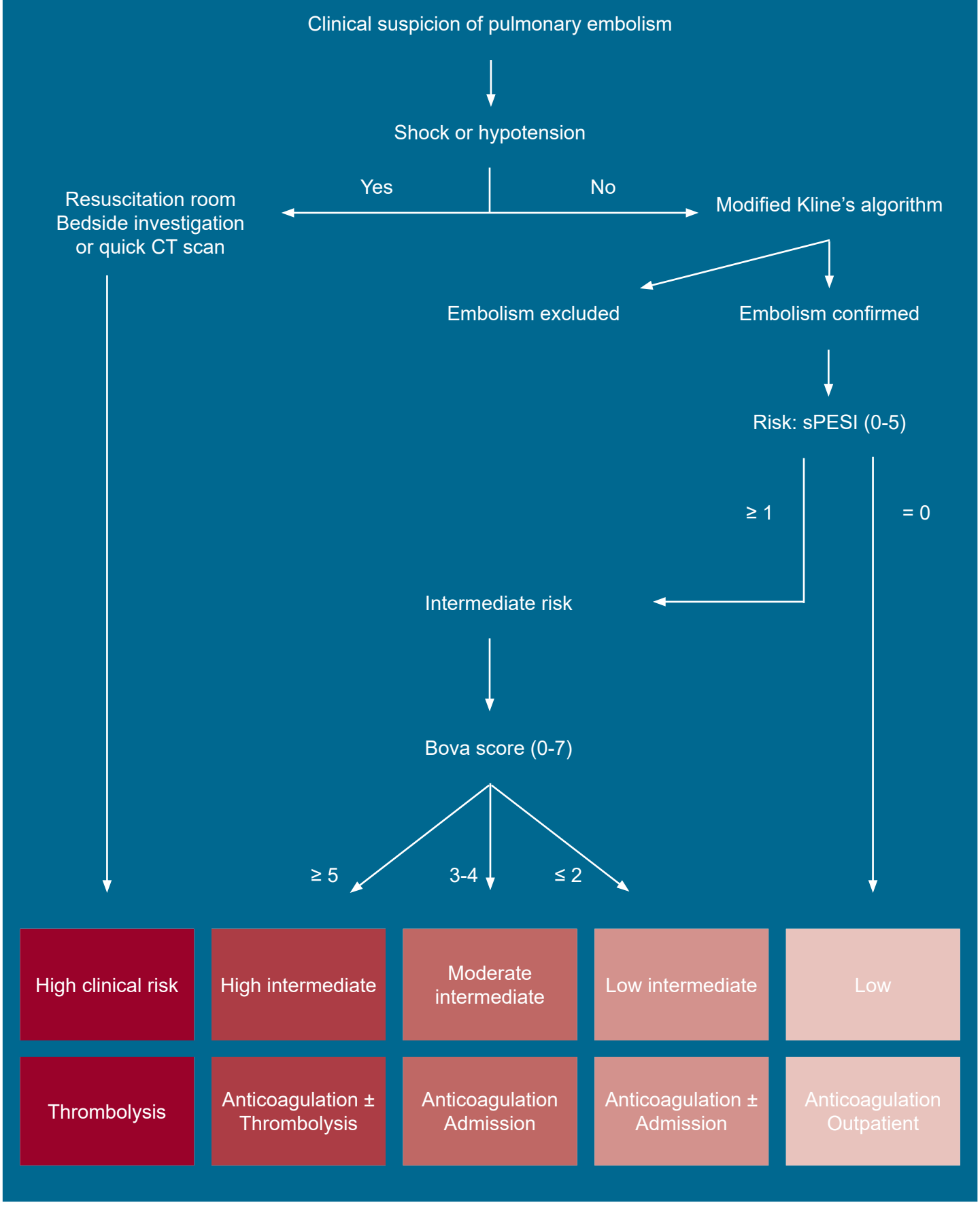


Table 9. Main risk categories

Stratification	Criteria	Presentation	Investigation	Treatment Place	Treatment Type	Risk of complications	Reference
Patient in shock Massive pulmonary embolism	BP < 90 for at least 15 minutes	Syncope Hypotension Diaphoresis Tachycardia	Bedside, in resuscitation room Angiogram if available immediately	Resuscitation room and intensive care	Thrombolysis	≥ 30%	Wood[56]
Intermediate risk Submassive pulmonary embolism	sPESI ≥ 1 Bova III	Variable	Standard algorithm	Hospital (at first)	Anticoagulation (thrombolysis for some patients)	29,2%	Bova[50]
	sPESI ≥ 1 Bova II				Anticoagulation and admission	10,8%	
	sPESI ≥ 1 Bova I				Anticoagulation (outpatient treatment for some patients)	4,2%	
Low risk	sPESI = 0	Variable	Outpatient treatment, with anticoagulants until diagnosis ruled out	Outpatient	Anticoagulation (outpatient treatment for many patients)	≤ 1%	Vinson et al[57]
Subsegmental pulmonary embolism	By scan	Variable	Already done	Individualized	Individualized		
Chance discovery, no symptoms	By scan, during examination for another reason	Asymptomatic	Already done	Individualized	Individualized		

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