Overdiagnosis of pulmonary embolism

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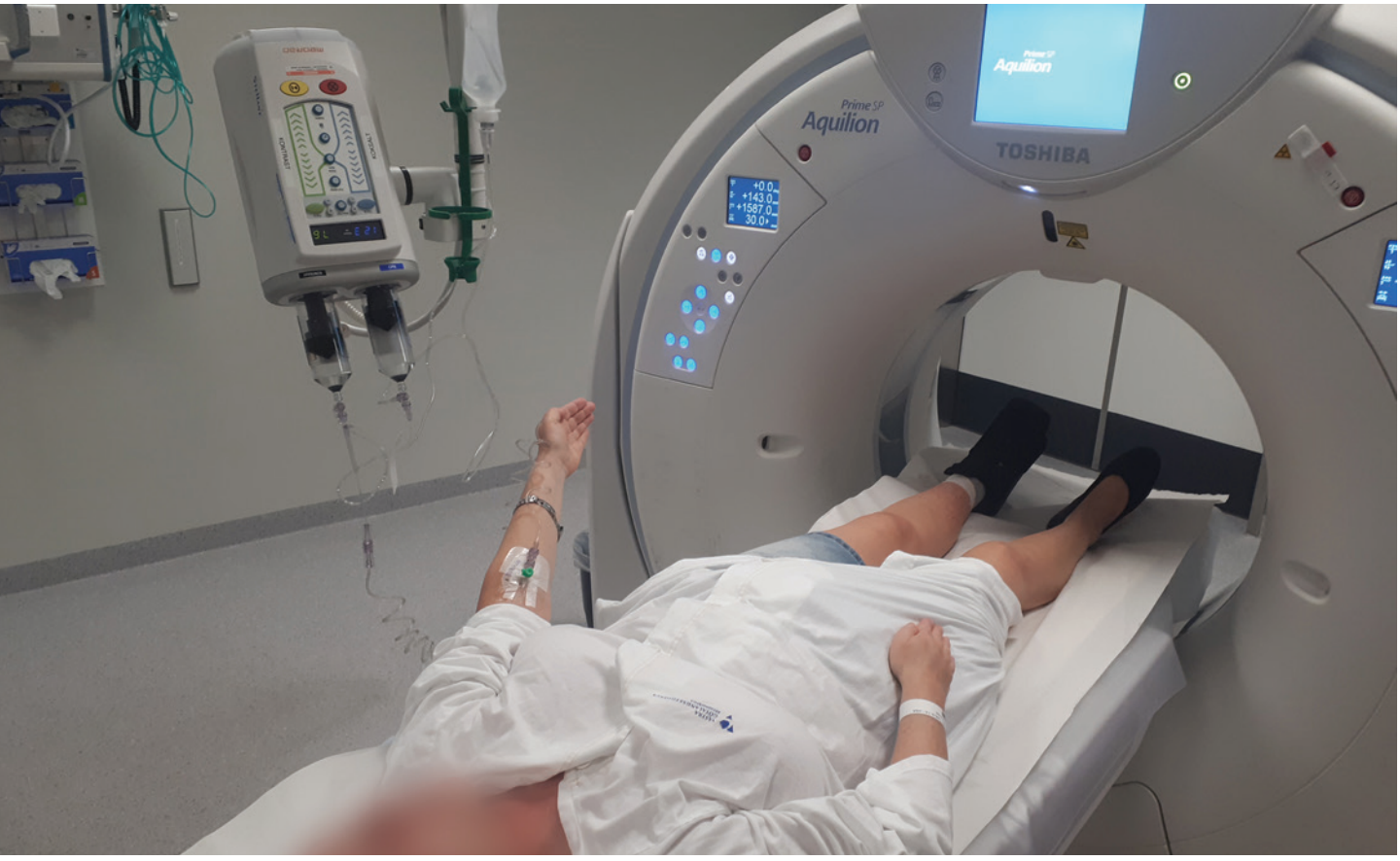

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Key points

- Since the introduction of computed tomography pulmonary angiography in 1998, there has been a steep increase in the diagnosis of pulmonary embolism (PE).
- An increased incidence of PE diagnoses, but an almost stable mortality from PE in the population, together with a decreased case fatality, point towards overdiagnosis (in the absence of more effective treatment).
- Whether PE is diagnosed as an incidental finding or following an investigation for suspected PE does not appear to influence the need for anticoagulation therapy.
- An isolated subsegmental PE may not require anticoagulation therapy, and treatment decisions should be made case by case, taking into account the patient's situation and preference.
- A suggested definition of overdiagnosis of PE: a diagnosis of PE that, if left untreated, would not lead to more harm than if it were treated with anticoagulation therapy, independent of symptoms.

Educational aims

- To understand the term "overdiagnosis" based on its narrow definition and be able to apply it to PE.
- To outline the diagnostic approach to PE.
- To summarise what is known about the treatment of incidentally detected PE.
- To summarise what is known about the treatment of subsegmental PE.
- To understand in which situations anticoagulation therapy for PE may not be beneficial.

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Review

Overdiagnosis of pulmonary embolism: definition, causes and implications

Overuse of computed tomography pulmonary angiography to diagnose pulmonary embolism in people who have only a low pre-test probability of pulmonary embolism has received significant attention in the past. The issue of overdiagnosis of pulmonary embolism, a potential consequence of overtesting, has been less explored. The term "overdiagnosis", used in a narrow sense, describes a correct (true positive) diagnosis in a person but without any associated harm. The aim of this review is to summarise literature on the topic of overdiagnosis of pulmonary embolism and translate this epidemiological concept into the clinical practice of respiratory professionals. The review concludes that the location of pulmonary embolism at a subsegmental level, rather than whether a diagnosis was made incidentally or following an investigation for suspected pulmonary embolism, is the best predictor for situations in which anticoagulation may not be necessary. In the absence of strong evidence of the optimal management of subsegmental pulmonary embolism, treatment decisions should be made case by case, taking into account the patient's situation and preference.

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Diagnostic approach to patients with suspected pulmonary embolism

Pulmonary embolism (PE) is a common disease and is responsible for an estimated 300000 deaths annually in Europe [1] and 100000 deaths annually in the USA [2].

Typical symptoms of PE, such as chest pain and shortness of breath, are nonspecific as they can also occur in other pulmonary or cardiac diseases including, for example, pneumonia or acute coronary syndrome. Diagnostic algorithms for PE typically involve assessment of a clinical risk score (*e.g.* Wells score, modified Wells score, revised Geneva score, or clinical gestalt) in conjunction with D-dimer levels, to determine the probability of PE [3–5]. In patients with a risk score above a certain threshold (*e.g.* Wells score >6), a diagnosis of PE is considered likely and further testing with computed tomography pulmonary angiography (CTPA) is indicated. In patients with an intermediate risk score (*e.g.* Wells score 2–6), no further testing is generally necessary if D-dimer is negative (D-dimer level ≤500 μg·L^{-1}) [4]. In low-risk patients with suspected PE (*e.g.* Wells score <2), a negative D-dimer has traditionally also been recommended to rule out PE. However, a multicentre randomised controlled trial published in 2018 demonstrated that in patients with very low clinical probability of PE, using PE rule-out criteria (PERC), an eight-item list of clinical

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criteria, to rule out a PE is not inferior compared with a traditional strategy including D-dimer testing, based on the outcome of thromboembolic events at 3 months [6]. All of the following eight criteria need to be fulfilled for the PERC-based strategy to rule out PE in very low-risk patients: arterial oxygen saturation measured by pulse oximetry of ≥95%, heart rate <100 beats·min^{-1}, patient age <50 years, no unilateral leg swelling, no haemoptysis, no recent trauma or surgery, no prior PE or deep venous thrombosis, and no exogenous oestrogen use. New diagnostic algorithms integrate the use of PERC to determine whether D-dimer testing is indicated in patients with a low pre-test probability of PE. If one or more criteria are not fulfilled, further testing with D-dimer is recommended; otherwise, no further testing is necessary.

Overtesting for PE

Despite numerous guidelines and algorithms that aim to prevent overtesting with CTPA in patients at low risk of PE, there is ample evidence that CTPA is frequently inappropriately ordered (*e.g.* without using pre-test clinical probability scores or ignoring evidence of low pre-test probability and/or negative D-dimer tests) [7–10]. There appear to be large variations in overtesting practices between clinicians [11]. In recent years, the "Choosing Wisely" initiative has drawn attention to overtesting with CTPA, with one of their recommendations emphasising that CTPA in emergency department patients with a low pre-test probability of PE and either negative PERC or a negative D-dimer should be avoided [12].

D-dimer, designed to rule out PE and thus reduce the inappropriate use of CTPA, has become a facilitator of overtesting [13]. The D-dimer test has a high sensitivity (a high negative predictive value) at the expense of specificity. When the D-dimer test is negative, the clinician can be confident that the patient does not have a PE. A positive D-dimer test, however, is unspecific. D-dimer testing should therefore not be indiscriminately used in patients with a very low clinical probability of PE. Recent evidence that it is safe to use a PERC-based strategy in this situation, without any further tests, will hopefully lead to a decrease in D-dimer testing and fewer unwarranted CTPA investigations.

Several studies have assessed interventions to reduce overuse of CTPA and other imaging for PE such as ventilation/perfusion (*V′/Q′*) scans. A systematic review of 17 such studies found evidence that clinical decision support can reduce imaging use (reduction ranging from 8.3% to 25.4%) and increase the diagnostic yield [14].

Overtesting for PE with CTPA can result in overdiagnosis and subsequent overtreatment of PE, and is associated with increased detection of incidental findings of unclear significance. About one in four CTPA tests detects an unexpected abnormality, such as a pulmonary nodule, thyroid nodule or adenopathy, which leads to further scans or invasive testing but usually turns out to be harmless [15].

Underdiagnosis of PE

Clinicians are mainly aware of the potential dangers of missing a diagnosis of PE, and for good reason, as PE is one of the most commonly missed or delayed diagnoses in clinical practice [16]. Of an estimated 370012 deaths attributed to venous thromboembolism in six European countries (France, Germany, Italy, Spain, Sweden and the UK) in 2004, 59% (217394) probably resulted from PE-related deaths following undiagnosed venous thromboembolism [17]. With evidence that PE is an underdiagnosed condition in a substantial number of people, could it at the same time be overdiagnosed in other people?

Overdiagnosis of PE

Definition of overdiagnosis

Distinct from the epidemiological concept of overtesting (also referred to as overuse or overutilisation) is the concept of overdiagnosis. Overdiagnosis is an epidemiological concept with variable definitions and interpretations. The definition of overdiagnosis has recently received a lot of attention, at least partially driven by efforts to reduce low-value care through initiatives such as "Choosing Wisely" [18]. The term overdiagnosis is often used as an umbrella term for different concepts, such as a false positive diagnosis (*e.g.* a test indicates that a condition is present, when in fact it is not) or a misdiagnosis (signs and symptoms in a person are attributed to an incorrect diagnosis) [19]. More recently, the term overdiagnosis has been used in a narrow sense to describe a correct (true positive) diagnosis in an asymptomatic person that does not produce a net benefit for that person [19]. An example is the diagnosis of a non-progressive prostate cancer detected through prostate-specific antigen screening when the cancer will not cause any symptoms and will not be the cause of death in this person.

The narrow definition of overdiagnosis that originated in the context of population-based cancer screening (where asymptomatic patients might be diagnosed with a cancer that will never cause any morbidity or mortality) might have to be adjusted in the context of PE, for which there is no population-based screening but rather targeted investigations for suspected PE as well as incidental findings of PE. As will be described further in this article, some patients with "overdiagnosed" PE might have symptoms consistent with PE.

Different imaging tests for PE

Before the introduction of CTPA in 1998, *V′/Q′* scans were the first-line test for PE [20]. While pulmonary angiography was the gold standard for the diagnosis of PE, allowing direct visualisation of filling defects in the pulmonary arteries [21], the threshold to order an invasive pulmonary angiography was high, given the potential harms from an invasive procedure and the technically difficult-to-perform procedure.

V′/Q′ scans do not provide direct visualisation of PE. Instead, a diagnosis of PE is inferred on the basis of areas of the lung that have significant "mismatches", *i.e.* good ventilation but poor perfusion. The likelihood of PE is graded as "high", "intermediate", or "low" probability, based on criteria from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study [22]. The findings on *V′/Q′* scan are combined with the pre-test probability of PE, resulting in a context-dependent interpretation [23]. Despite this evidence-based approach, *V′/Q′* scans often do not provide a clear answer about the presence of PE to clinicians, as "intermediate" probability of PE is common: 35% of patients with suspected PE in the PIOPED study had an "intermediate" probability *V′/Q′* scan, of which only one third had PE confirmed on pulmonary angiography [22].

CTPA can be accessed relatively easily (usually around-the-clock availability in tertiary hospitals), can provide direct visualisation of filling defects in the pulmonary arteries (and thus yes/no answers to the question about the presence of PE), and allows investigation of potential differential diagnoses of respiratory symptoms. It therefore comes as no surprise that the investigation is very popular with clinicians.

Evidence of overdiagnosis

After the introduction of CTPA, the incidence of PE diagnoses in the USA increased by 81%, from 62.1 per 100000 to 112.3 per 100000, between 1998 and 2006 [24]. Despite the substantial increase in PE diagnoses, the age-adjusted mortality from PE remained almost unchanged (12.3 and 11.9 deaths per 100000 in 1998 and 2006, respectively) [24].

While it is theoretically possible that the increase in PE diagnoses reflects a true change in the rate of PE in the population, this seems unlikely, as the major risk factors for PE have not shown a similar increase [25] and venous thromboembolism prophylaxis for hospital patients has been promoted as a quality-improvement initiative during the same time period [24]. If the underlying rate of PE had truly increased, one would also expect an increased mortality from PE in the population (in the absence of more effective treatment of PE), which was not the case.

If the underlying rate of PE in the population has not changed, additional PE cases represent previously undiagnosed PE, detected with a new, more sensitive test (CTPA). One would expect a substantial decrease in mortality from PE in the population if the large number of newly detected cases benefit from treatment. The fact that there was only a small change in mortality between 1998 and 2006 suggests that most of the additionally diagnosed cases did not benefit from treatment in terms of reducing the risk of death, indicating low-risk PE.

Additionally, the case fatality (deaths due to PE among people with a diagnosis of PE) decreased from 12.1% to 7.8%, suggesting that the additionally diagnosed PE cases are less fatal. If the decrease in case fatality was due to more effective treatment, a similar decrease in mortality from PE in the general population would be expected, but this was not demonstrated.

Additional evidence of overdiagnosis comes from a randomised controlled trial in which 1417 acutely symptomatic patients with an intermediate to high probability of PE (Wells score ≥4.5 or a positive D-dimer) underwent either a *V′/Q′* scan or CTPA [26]. Although more people in the CTPA group were diagnosed as having PE than in the *V′/Q′* scan group (19.2% *versus* 14.2%; p=0.01) and were treated with anticoagulation therapy, there was no difference in death from PE, sudden death or cardiopulmonary compromise (0.3% *versus* 0.3%). There was also no statistically significant difference in venous thromboembolism between groups during the 3-month follow-up period in those who did not have diagnosis of PE at the initial evaluation (0.4% *versus* 1.0% of patients in the CTPA and *V′/Q′* scan group, respectively; difference –0.6%, 95% CI –1.6–0.3%).

A systematic review and meta-analysis of 20 prospective cohort studies and two randomised controlled trials showed that multi-row-detector CTPA increases the proportion of patients diagnosed with subsegmental PE that is not associated with an increased thromboembolic risk at 3 months compared with single-row-detector CTPA [27].

Incidental PE

In addition to CTPA for PE, there has been explosion in the use of computed tomography (CT) for various reasons [28]. Incidental PE is a frequent finding on CT scans conducted for indications other than suspected PE: in 5.7% of hospital patients (16.7% in those aged >80 years) [29], in 24% of moderately to severely injured trauma patients [30], in 3.6% of oncological patients [31] and in 1.1% of coronary CT scans [31].

Although regular CT scans are not performed with a dedicated PE protocol and have suboptimal contrast enhancement, diagnosis of incidental PE has been demonstrated to be reliable up to the segmental and subsegmental arteries [31]. A confirmatory CTPA is not necessary unless the radiologist voices concerns about the quality of the CT scan (*e.g.* breathing artefacts) [31]. Inter-observer

agreement for incidental PE on regular CT scans is generally high [32, 33].

Importantly, an incidental PE diagnosis does not necessarily indicate that the patient is asymptomatic for PE. While an incidental PE is an unexpected finding on a CT scan performed for an indication other than suspected PE, studies have found that in retrospect up to 75% of patients reported at least one symptom that could be associated with acute PE [33, 34].

It is not clear whether an incidental PE is more commonly located at the subsegmental level compared to a suspected PE, although there is limited evidence from pooled estimates that this may be the case on multi-detector CT scans [31]. Comparative estimates of the relative prevalence of subsegmental PE are complicated by different study designs and variable sensitivity of the CT scanners used (*e.g.* CT with four-row technology *versus* multi-row-detector CT) [31]. Of patients with suspected PE confirmed on CTPA, 9.4% (95% CI 5.5–14.2%) have been reported to have subsegmental PE on multi-row-detector CTPA in a systematic review and meta-analysis (including 15 studies on single- and 11 studies on multiple-row-detector CTPA) [27]. The highest proportion was 15.0% (95% CI 7.7–24.1%) with 64- slice multi-row-detector CT scans. This was compared to a proportion of subsegmental PE of 4.7% (95% CI 2.5–7.6%) on single-row-detector CTPA in patients with suspected PE confirmed on CTPA. For incidental PE, a pooled estimate of 0% (95% CI 0–6.0%) for subsegmental PE on CT scan with four-row technology or less and a pooled estimate of 23% (95% CI 6.7–40%) for subsegmental PE on multi-row-detector CT has been described [31]. The pooled estimates for subsegmental incidental PE were based on four studies, but not a systematic review, significantly limiting the strength of the evidence.

A question of interest to clinicians is whether incidental PE should be treated in the same way as PE that was clinically suspected. The prognosis in regard to the risk of recurrent venous thrombotic disease and mortality appears to be similar for incidental PE and PE that had been clinically suspected, if left untreated [31]. No randomised clinical trials have been conducted to compare treatment *versus* no treatment in incidental PE. Data on incidental PE from 11 cohort studies in patients with cancer showed a pooled 6-month risk of recurrent venous thromboembolism of 6.2% (95% CI 3.5–12%) in patients treated with low molecular weight heparin, 6.4% (95% CI 2.2–12%) in those who received a vitamin K antagonist and 12% (95% CI 4.7–23%) in those who did not receive any anticoagulation therapy [35]. All-cause mortality was high in all groups: 37% (95% CI 29–44%) in patients treated with low molecular weight heparin, 28% (95% CI 18–40%) in those treated with a vitamin K antagonist and 47% (95% CI 28–66%) in those who did not receive any treatment. These data emphasise the substantial risk of recurrent venous thromboembolism in cancer patients with incidental PE, which was significantly increased in patients who did not receive anticoagulation therapy. Importantly, the patient characteristics of untreated patients did not differ greatly from those of treated patients.

Guidelines of the American College of Chest Physicians and the American Society of Clinical Oncology give a weak or moderate strength recommendation, respectively, to use the same treatment strategy in patients with incidental PE and in those with PE that had been clinically suspected [36, 37].

Subsegmental PE

Isolated subsegmental PE has a better prognosis than central PE and there is evidence to support that the potential benefits of treatment of subsegmental PE may not always outweigh potential harms.

A Cochrane systematic review on anticoagulation treatment for subsegmental PE (current until December 2015) found no randomised controlled trial evidence for the effectiveness and safety of anticoagulation therapy *versus* no intervention in patients with isolated (incidental or non-incidental) subsegmental PE [38].

In a cohort of 93 patients with isolated subsegmental PE on CTPA for suspected PE (of which 22 (24%) were not treated), the risk of a major haemorrhage was 5.4% (five out of 93) and the risk of recurrent PE was 1.08% (one out of 93, in the treatment group) [39]. There were no fatalities from either PE or haemorrhage. Thus, in a cohort of 1000 patients, 54 patients will have major bleeding to prevent 11 patients from having recurrent PE. Given this trade-off, consideration seems warranted about whether subsegmental PE should be treated.

Treatment with a novel oral anticoagulant (*e.g.* apixaban, rivaroxaban) should be considered if anticoagulation is initiated, as novel oral anticoagulants have been found to be non-inferior to conventional therapy for the treatment of acute venous thromboembolism and have a significantly reduced risk of bleeding [40, 41].

Summary outcomes of four studies including 192 patients with isolated subsegmental PE on CTPA showed that among the 65 patients who did not receive anticoagulation therapy (at the clinician's discretion) none had PE or died at 3 months [39]. Only one patient who received anticoagulation therapy had a recurrent (non-fatal) PE during the 3-month follow-up period (one out of 127; 0.8%), which was markedly lower than the typical PE recurrence rate with larger PE (6%) [42].

Further evidence that not all subsegmental PE findings are clinically significant comes from a study that compared two cohorts of patients undergoing CT for suspected PE with either single-row-detector CTPA or multi-row-detector

CTPA [43]. Better visualisation of smaller, more peripheral arteries afforded by multi-row-detector CTPA did not have an impact on clinical outcomes. There was no significant difference in subsequent thromboembolic events during the 6-month follow-up period and no significant difference in unrelated deaths.

Based on the data described here, it has been suggested that it is reasonable to not give anticoagulation therapy for subsegmental PE in certain circumstances, *e.g.* if 1) pulmonary-respiratory reserve is good; 2) there is no evidence of deep venous thrombosis on serial testing; 3) a major risk factor for PE was transient and no longer present; 4) there is no history of central venous catheterisation or atrial fibrillation; and 5) the patient is willing to return for serial venous ultrasound examinations [44]. Goodman [45] suggested that in subsets of patients with subsegmental PE, the risks associated with anticoagulation may outweigh the benefits, including symptomatic or asymptomatic patients with PE limited to the subsegmental level, no deep venous thrombosis, and adequate cardiopulmonary reserve; and including patients with contraindications to anticoagulation (*e.g.* intracranial haemorrhage, recent surgery, or trauma), isolated subsegmental PE, and no deep venous thrombosis.

In patients with cancer, anticoagulation therapy is generally recommended in any PE (including isolated subsegmental PE) because of the ongoing increased risk of recurrent venous thromboembolism.

Definition of overdiagnosis of PE

As outlined, overdiagnosis of PE describes cases of PE that do not necessarily require treatment based on the outcomes of recurrent venous thromboembolism or death caused by PE. It has also been used to describe cases of PE in which the harms of anticoagulation therapy likely outweigh the benefits. Several studies that point towards overdiagnosis of PE were conducted in symptomatic patients investigated for PE. Having symptoms from a diagnosis is not consistent with the narrow definition of overdiagnosis, originating in the context of cancer screening [19]. It is likely that in select patients with subsegmental PE and milder symptoms who do not receive anticoagulation therapy, symptoms will respond well to symptomatic treatment and will resolve as the small PE gets reabsorbed by the body.

Overdiagnosis of PE should therefore refer to the diagnosis of PE that, left untreated, would not lead to more harm than if it were treated with anticoagulation therapy, independent of symptoms or, in other words, "pulmonary emboli that do not need to be found" [20].

Self-evaluation questions

1. All patients with suspected PE but low clinical probability of PE (*e.g.* based on Wells score) must have a D-dimer test to determine whether they should undergo CTPA testing.
   a) True
   b) False
2. Which one of the following is the best definition of overdiagnosis of PE?
   a) Incorrect diagnosis of PE in a symptomatic patient
   b) Correct and clinically relevant diagnosis of PE
   c) False positive diagnosis of PE in an asymptomatic patient
   d) Correct diagnosis of PE with no net benefit of treatment
3. Which one of the following, at a population level, is indicative of overdiagnosis of PE?
   a) Increased incidence of PE, lower case fatality of PE, unchanged mortality from PE in the population
   b) Increased incidence of PE, unchanged case fatality of PE, increased mortality from PE in the population
   c) Increased incidence of PE, increased case fatality of PE, decreased mortality from PE in the population
   d) Unchanged incidence of PE, lower case fatality rate of PE, lower mortality from PE in the population
4. Whether a PE is incidentally detected or detected in a patient with suspected PE is the most important factor to determine whether treatment might not be necessary.
   a) True
   b) False
5. On which type(s) of studies is the evidence for overdiagnosis of PE based? Select all answers that apply.
   a) Randomised controlled trials comparing outcomes in patients with isolated subsegmental PE who did or did not receive anticoagulation therapy
   b) Administrative population data measuring incidence of PE, case fatality and mortality from PE
   c) Observational studies comparing outcomes in patients with isolated subsegmental PE who did or did not receive anticoagulation therapy
   d) Randomised controlled trials comparing outcomes in symptomatic patients with PE diagnosed on *V'/Q'* scan *versus* PE diagnosed on CTPA
6. In which scenario(s) do the harms of anticoagulation treatment potentially outweigh the risks of leaving the PE untreated? Select all answers that apply.
   a) In a patient with isolated subsegmental PE and surgery 10 days ago, with no evidence of deep vein thrombosis
   b) In a symptomatic patient aged >80 years with a central PE on CTPA, with no evidence of deep vein thrombosis
   c) In an asymptomatic patient with breast cancer and a segmental incidental PE on follow-up CT scan, with no evidence of deep vein thrombosis
   d) In a patient with an incidental isolated subsegmental PE on whole-body CT for trauma, deep vein thrombosis of the left leg, and normal CT of the brain

Conclusion

While there is compelling evidence for overdiagnosis of PE at a population level, the evidence to inform clinical decision making about which cases of PE can safely be left untreated is less clear. Whether PE is diagnosed as an incidental finding or following an investigation for suspected PE does not appear to influence prognosis and thus the need for anticoagulation therapy. An isolated subsegmental location in either incidental PE or PE that had been clinically suspected seems to be the best predictor of the likelihood that PE will not result in any significant harm if left untreated. Not giving anticoagulation therapy can be considered in isolated subsegmental PE that is not causing significant symptoms (or where temporary symptoms can be controlled with symptomatic treatment such as pain medication), there is no evidence of deep venous thrombosis, and the patient has adequate cardiopulmonary reserve; or patients with contraindications to anticoagulation (*e.g.* intracranial haemorrhage, recent surgery, or trauma), isolated subsegmental PE, and no deep venous thrombosis. Importantly, there is no definitive answer to the question about optimal management of subsegmental PE based on current evidence, and case-by-case decision making is therefore indicated.

The decision for or against anticoagulation therapy should be discussed with the patient in the same way that shared decision making would be applied in other situations where the balance of potential benefits and harms (including the treatment burden) of a healthcare intervention is not immediately apparent [46, 47].

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Conflict of interest

C.C. Dobler has nothing to disclose.

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Suggested answers

1. b.
2. d.
3. a.
4. b.
5. b, c, d.
6. a.