

A little learning is a dangerous thing – how little do we know about when to treat pulmonary embolism?

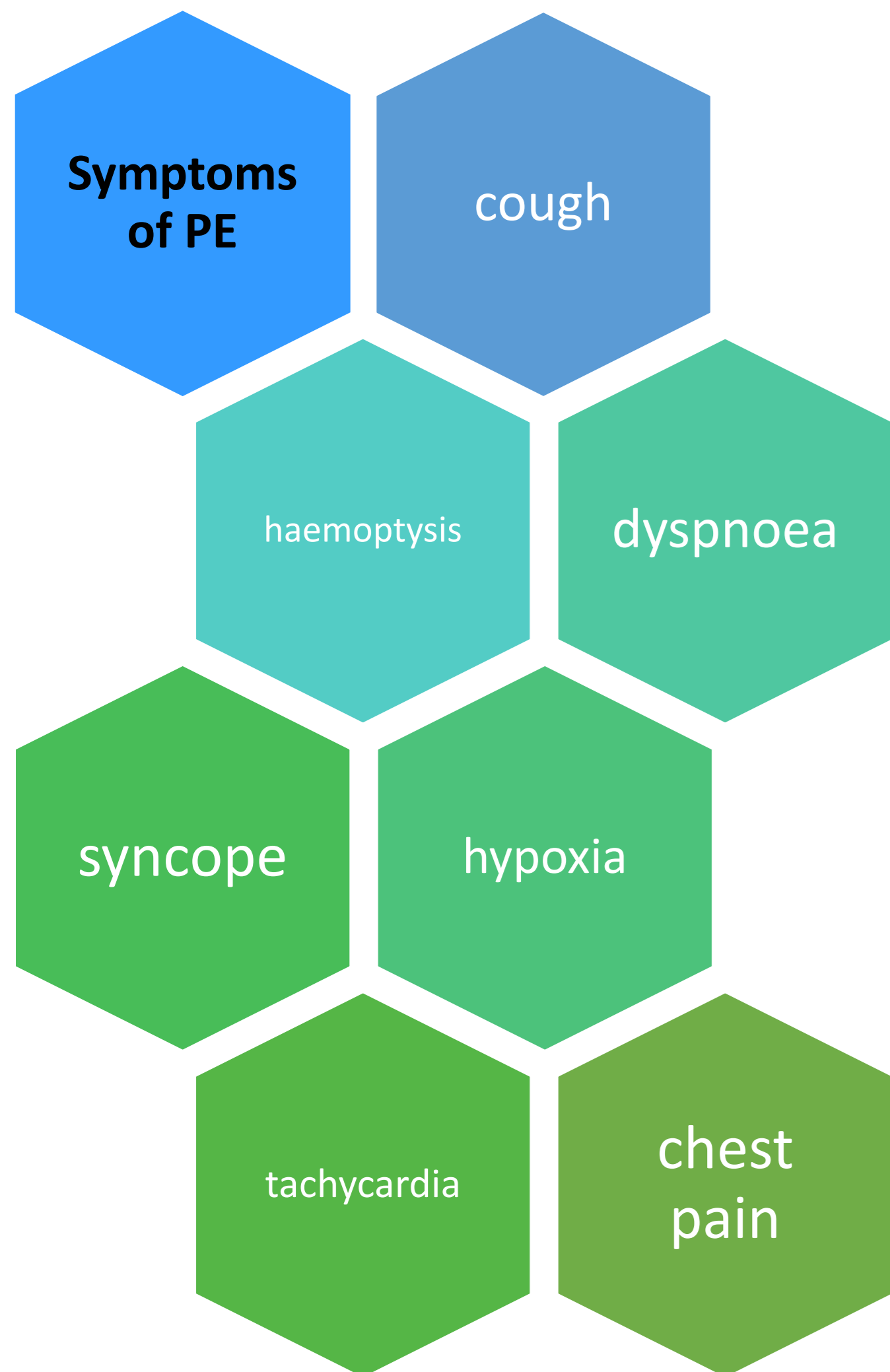
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Introduction

- Clinical guidelines written by National Institute for Health and Care Excellence (NICE) and professional societies make professional development easier for clinicians by making recommendations founded on the best available evidence.
- However, this can disincentivise clinicians from assessing primary evidence for themselves, and the quality of evidence (evaluated by GRADE criteria) is often not emphasised in guideline summary documents.
- Taking pulmonary embolism as an example, we discuss how guidelines and consensus mask the weaknesses in the evidence base for common interventions, such as anticoagulation.

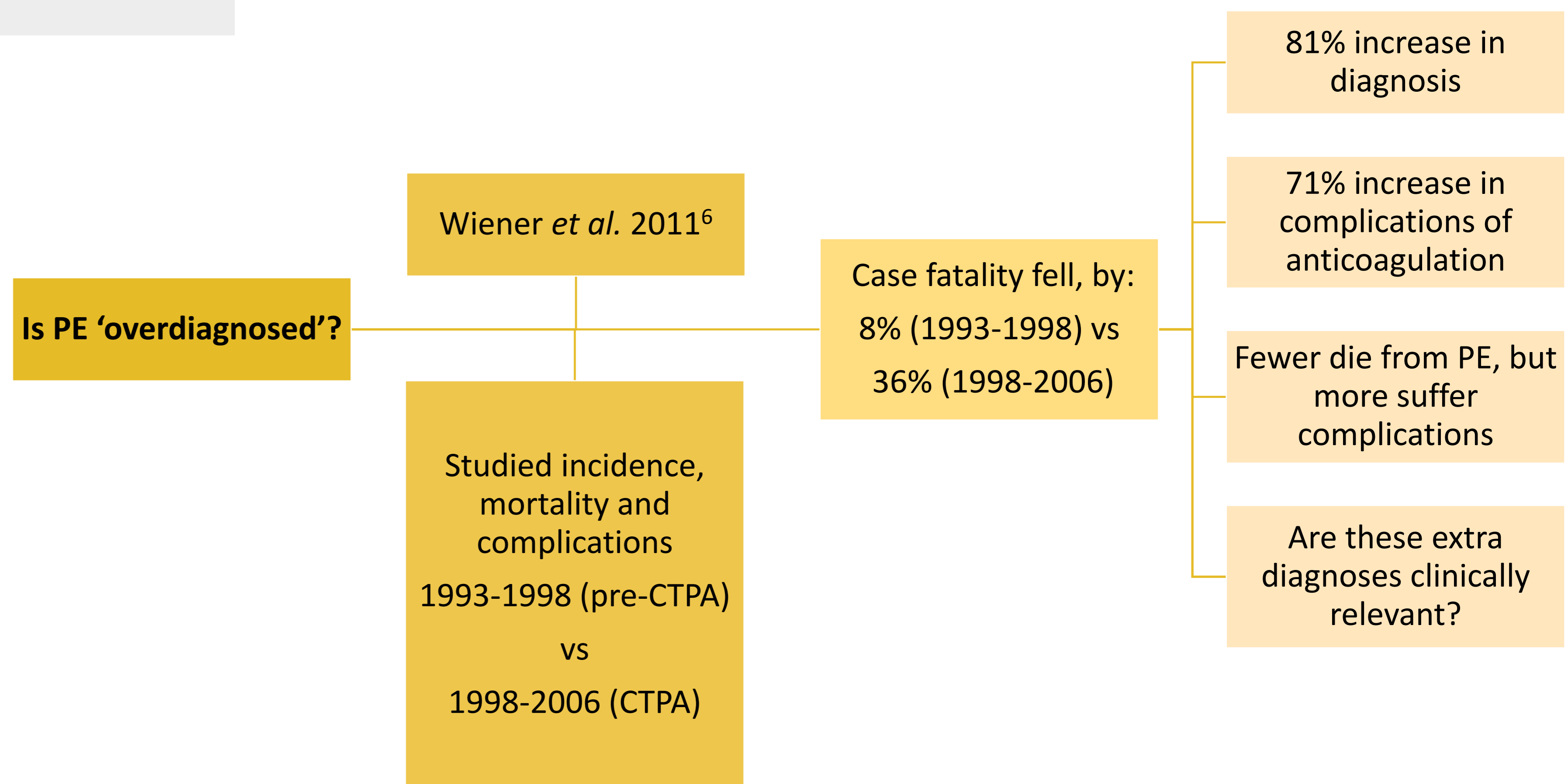
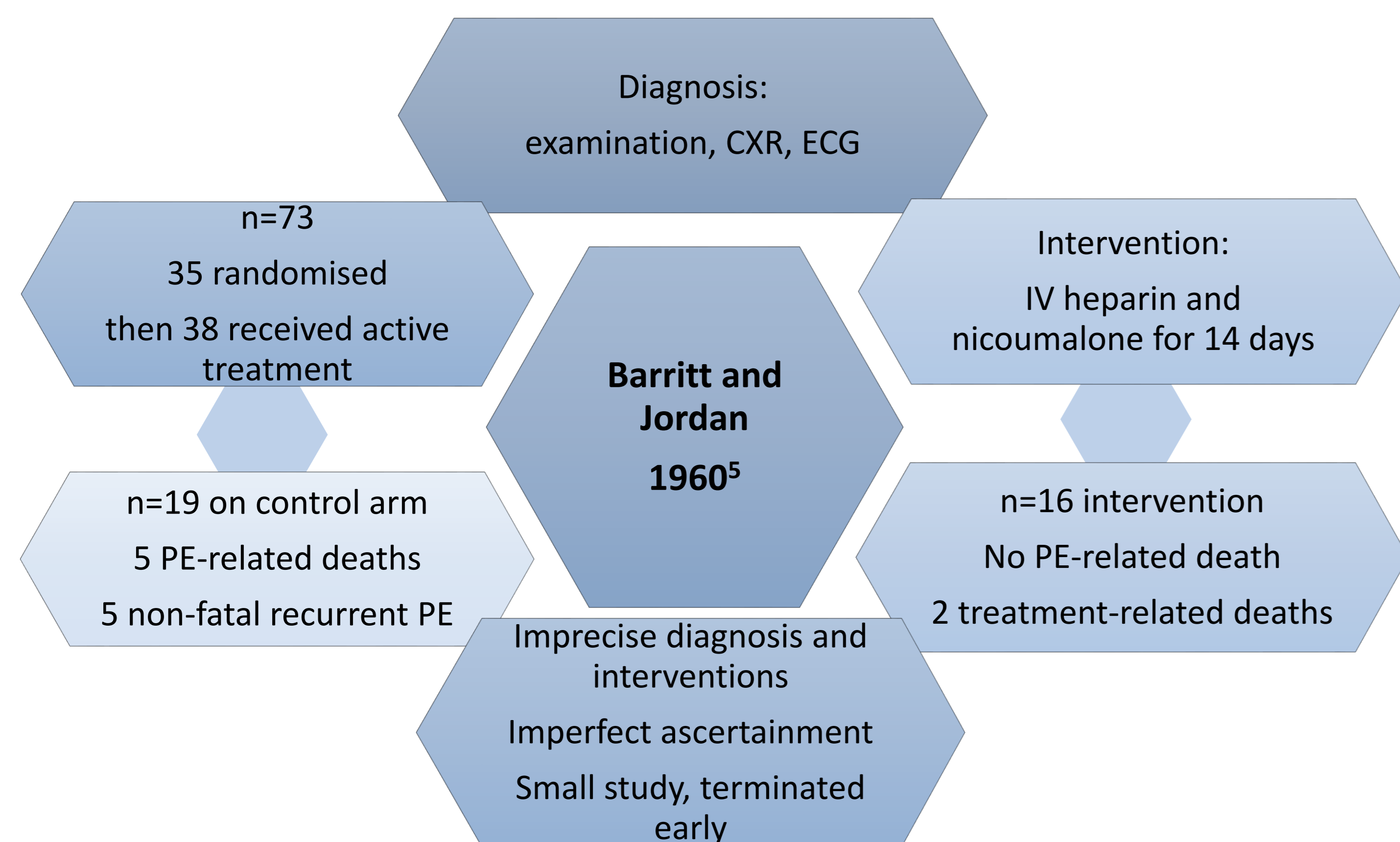
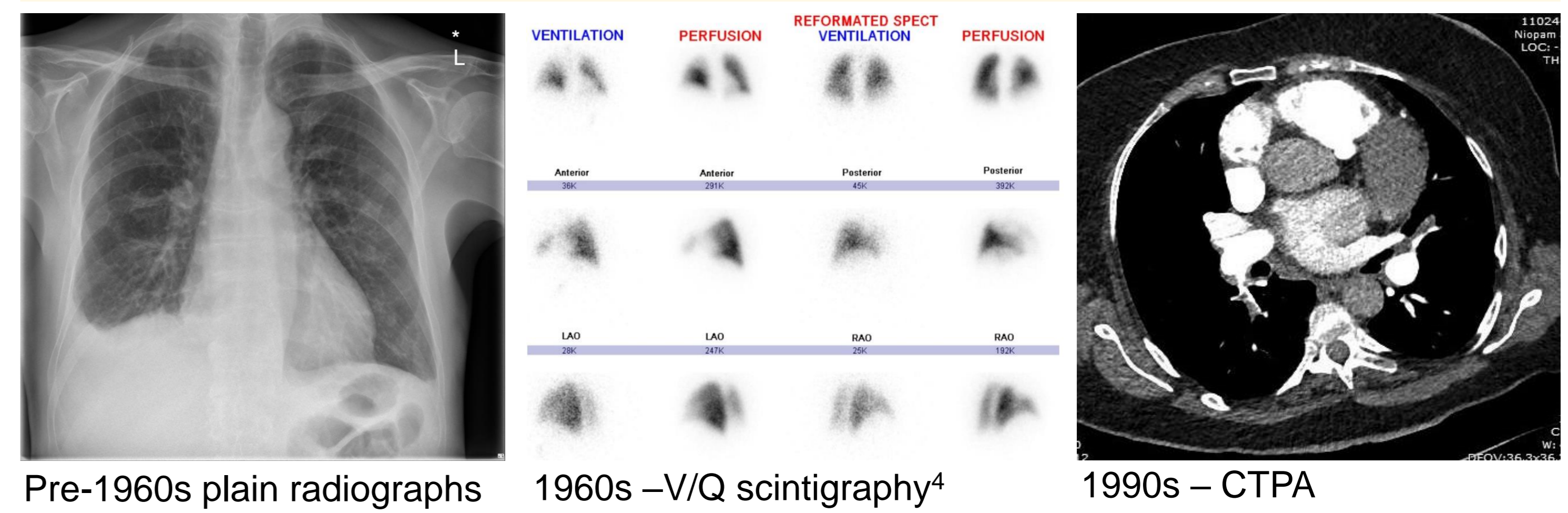
The History of Pulmonary Embolism and its Management



- The clinical presentation of pulmonary embolism (PE) is often non-specific, with highly variable symptoms.
- The clinical definition of a PE has changed with developments in diagnostic imaging. As imaging modalities have increased in sensitivity, PE diagnoses have become more common as smaller subsegmental thrombi were identified.

- For the first half of the 20th century, PE diagnosis relied on respiratory signs and symptoms, possibly in combination with signs and symptoms of deep venous thrombosis (DVT, coincident with PE in 45% of cases in one cohort³). Chest radiography was used but rarely identified specific findings.
- Ventilation/perfusion (V/Q) scintigraphy in the 1960s and then computed tomography pulmonary angiography (CTPA) in the early 1990s had higher sensitivity than clinical diagnosis.

- Treatment of PE in the early 20th century was speculative and variable.
- Published series in 1950¹ and 1954² described ambulatory therapy and anticoagulation using heparin.
- In Bauer's 1950 case series, mortality from PE among inpatients with DVT dropped from 18% to 0.4% after anticoagulation introduction.¹
- One randomised trial showed a benefit from anticoagulation:



The validity of historical evidence fades

The evidence for anticoagulation of PE:

- Several case series, and one small randomised trial, all performed prior to 1960
- Study inclusion was based on bedside assessment of diagnosis

The validity of this evidence in contemporary clinical populations is low:

- Major changes in diagnostic imaging with much higher sensitivity
- Widespread use of thromboprophylaxis in inpatients
- Higher use of concomitant antiplatelet drugs

Nonetheless the recommendation has not been re-examined, and the paucity of high quality evidence is not mentioned in NICE recommendations⁷

Anticoagulation treatment for confirmed DVT or PE

1.3.5 Offer anticoagulation treatment for at least 3 months to people with confirmed proximal DVT or PE. For recommendations on treatment after 3 months see the section on [long-term anticoagulation for secondary prevention](#). [2020]

The NICE guideline development group acknowledged that

- the quality of evidence from studies assessing the utility of CTPA in PE was very low
- there was no clinical evidence regarding anticoagulation while awaiting imaging in 'likely' cases of PE

When diagnostic or epidemiological changes redefine a disease entity, therapeutic interventions must be re-assessed. Barriers to repeating trials include:

- Repeated practices over time establish a perception of a 'gold standard'
- Clinicians prefer to 'do something'
- Limited public funding for research
- Pharmaceutical industry funding promotes new interventions in favour of re-testing old ones.

Since May 2020, one placebo-controlled randomized trial has started recruiting patients with subsegmental PE to test whether anticoagulation confers benefit (ClinicalTrials.gov identifier NCT04263038)

Conclusions and recommendations

- Anticoagulation for all cases of pulmonary embolism is not supported by moderate or high quality evidence, but has been near-universal practice for 50 years.
- Widespread use of 'meta-evidence' in guideline form can conceal flaws in the evidence base from clinicians.
- GRADE evaluation results should be included in guidance summaries, so clinicians can be fully informed when prescribing and recruiting to clinical trials.

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