

## LESS IS MORE

# Time Trends in Pulmonary Embolism in the United States

## Evidence of Overdiagnosis

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**Background:** Computed tomographic pulmonary angiography (CTPA) may improve detection of life-threatening pulmonary embolism (PE), but this sensitive test may have a downside: overdiagnosis and overtreatment (finding clinically unimportant emboli and exposing patients to harms from unnecessary treatment).

**Methods:** To assess the impact of CTPA on national PE incidence, mortality, and treatment complications, we conducted a time trend analysis using the Nationwide Inpatient Sample and Multiple Cause-of-Death databases. We compared age-adjusted incidence, mortality, and treatment complications (in-hospital gastrointestinal tract or intracranial hemorrhage or secondary thrombocytopenia) of PE among US adults before (1993-1998) and after (1998-2006) CTPA was introduced.

**Results:** Pulmonary embolism incidence was unchanged before CTPA ( $P = .64$ ) but increased substantially after CTPA (81% increase, from 62.1 to 112.3 per 100 000;  $P < .001$ ). Pulmonary embolism mortality de-

creased during both periods: more so before CTPA (8% reduction, from 13.4 to 12.3 per 100 000;  $P < .001$ ) than after (3% reduction, from 12.3 to 11.9 per 100 000;  $P = .02$ ). Case fatality improved slightly before (8% decrease, from 13.2% to 12.1%;  $P = .02$ ) and substantially after CTPA (36% decrease, from 12.1% to 7.8%;  $P < .001$ ). Meanwhile, CTPA was associated with an increase in presumed complications of anticoagulation for PE: before CTPA, the complication rate was stable ( $P = .24$ ), but after it increased by 71% (from 3.1 to 5.3 per 100 000;  $P < .001$ ).

**Conclusions:** The introduction of CTPA was associated with changes consistent with overdiagnosis: rising incidence, minimal change in mortality, and lower case fatality. Better technology allows us to diagnose more emboli, but to minimize harms of overdiagnosis we must learn which ones matter.

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**T**HE INTRODUCTION IN 1998 of multidetector row computed tomographic pulmonary angiography (CTPA) revolutionized the way physicians approach pulmonary embolism (PE). Many assumed this highly sensitive test would improve outcomes of this

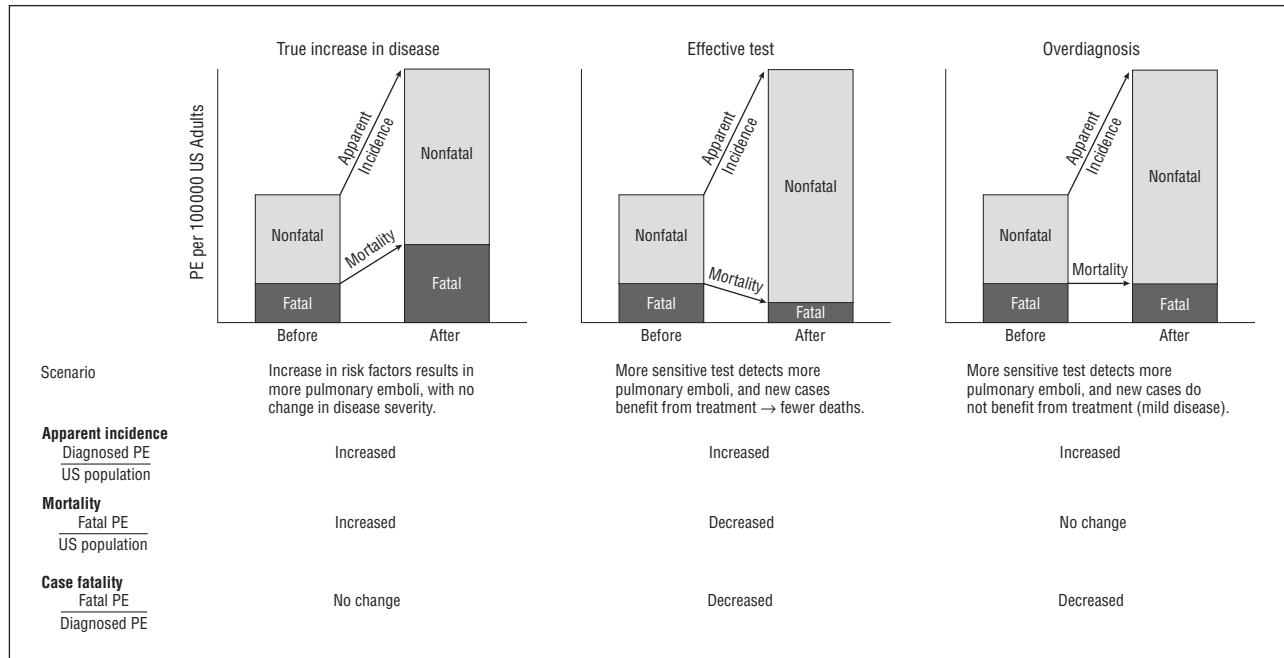
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deadly disease by detecting and allowing treatment of emboli that were previously missed. Computed tomographic pulmonary angiography rapidly spread into practice, largely replacing other tests for PE such as ventilation-perfusion scans and invasive pulmonary angiography.<sup>1</sup> Several institutions reported a 7- to 13-fold increase in use of CTPA by 2006,<sup>1-4</sup> and nationally there was an 11-fold rise in chest

CT angiography from 2001 to 2006 in the Medicare fee-for-service population (written communication, Daniel J. Gottlieb, MS, 2010). In 2007, 2.6 million chest CT angiography scans were performed in the United States.<sup>5</sup> Computed tomographic pulmonary angiography is now preferred as the first-line test for PE by both professional societies<sup>6</sup> and practicing physicians.<sup>7</sup>

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However, the increased sensitivity of CTPA may have a downside: the detection of emboli that are so small as to be clinically insignificant.<sup>8,9</sup> This phenomenon has been called “overdiagnosis,” defined as the detection of an abnormality that will never cause symptoms or death.<sup>10</sup>



**Figure 1.** Expected change in mortality and case fatality in various scenarios of rising apparent incidence. PE indicates pulmonary embolism.

Overdiagnosis matters because it can lead to iatrogenic harm. While a clinically insignificant PE is by definition not harmful, treating such an embolism can cause harm (eg, bleeding from anticoagulation, which can in the worst case be fatal). Many are aware of overdiagnosis from the recent controversy over prostate and breast cancer screening,<sup>11,12</sup> but there has been limited consideration of this possibility in other contexts such as PE.<sup>13,14</sup> Typically, as in a recent study reporting a national increase in the incidence of PE, the possibility of overdiagnosis is not seriously addressed.<sup>15</sup>

In the present article, we investigate whether CTPA has resulted in overdiagnosis of PE in the United States. Because there is no direct way to prove that a PE has been “overdiagnosed” (unless patients are observed without treatment until they die from an unrelated cause), we looked for indirect evidence by comparing trends in PE incidence and mortality before and after the introduction of CTPA. On the one hand, as shown in **Figure 1**, if increasing use of CTPA was improving our ability to find and successfully treat clinically important pulmonary emboli, we would expect to see an increase in incidence (since highly sensitive CTPA finds pulmonary emboli that were previously missed) and a reduction in mortality (because of successful treatment of the “new” pulmonary emboli). On the other hand, if CTPA primarily improves our ability to find pulmonary emboli of minimal clinical significance, we would expect to see rising incidence, but little change in mortality.

## METHODS

### DESIGN OVERVIEW

We conducted a time trend analysis of PE incidence, mortality, and treatment complications in US adults (age ≥18 years) from 1993 to 2006. This time frame encompasses the 5 years prior to

the introduction of CTPA (1993-1998) and the available years of data following its introduction (1998-2006). Studies using de-identified, publicly available data are exempt from institutional board review at Boston University and Dartmouth College.

## DATA SOURCES

We used the Nationwide Inpatient Sample<sup>16</sup> (NIS) to determine national estimates of hospitalization for PE. The NIS includes all discharges from a 20% stratified sample of nonfederal hospitals in the United States. Strata are based on geographic region, public or private status, urban or rural designation, teaching status, and hospital bed size. Hospitals included in the NIS may vary from year to year. Each record contains patient demographics, up to 15 *International Classification of Diseases, Ninth Revision (ICD-9)* procedure and diagnosis codes, vital status at hospital discharge, and a discharge weight to allow national estimates. Although the first year of available data in the NIS is 1988, Healthcare Cost & Utilization Project (HCUP) recommends conducting time trend analyses beginning in 1993 because of the small number of participating states prior to 1993.

We used the Multiple Cause-of-Death files<sup>17</sup> to determine national mortality from PE. This comprehensive database compiled by the National Center for Health Statistics contains data from all death certificates filed in the United States each year. Each record includes information on the decedent's demographics and up to 20 contributing causes of death recorded as *ICD-9* (1993-1998) or *International Statistical Classification of Diseases, 10th Revision (ICD-10)* (1999-2006) codes.

## PRIMARY OUTCOMES: PE INCIDENCE AND MORTALITY

### Incidence

We calculated the annual number of hospital discharges with a diagnosis of PE per 100 000 US adults as our measure of incidence. The numerator for the incidence rate includes all adults with a PE based on *ICD-9* codes for acute (415.11 and 415.19)

or obstetric (673.2) PE in any of the 15 diagnosis fields on the hospital discharge record. Because the specificity of these codes (eg, for distinguishing current vs historic embolism) has been questioned,<sup>18</sup> we also reported the incidence of PE among patients for whom this was the primary discharge diagnosis, which should have accuracy approaching 95%.<sup>19</sup> The denominator for the incidence rate (and all other population rates) is the corresponding mid-year US estimated adult population from the US Census survey.

## Mortality

Pulmonary embolism mortality was defined as the annual number of deaths in which PE was listed as a contributing cause per 100 000 US adults. Pulmonary embolism deaths were identified by the presence of the same acute or obstetric PE ICD-9 or ICD-10 (I26 and O88.2) codes in any of the 20 diagnosis fields on the death certificate.

The standard calculation of PE mortality includes all deaths in which PE is listed as a contributing cause of death rather than only cases in which it is reported as the underlying cause of death.<sup>20</sup> We followed this precedent for 2 reasons. First, relying only on the underlying cause of death reported on death certificates to determine deaths related to PE results in a sensitivity as low as 27%.<sup>21</sup> Second, the US Department of Health & Human Services' instructions on completing the death certificate direct that PE should not be coded as the underlying cause of death if there is a more specific cause that precipitated the embolism (eg, cancer, recent surgery).<sup>22</sup> In these cases PE is listed as a contributing cause, even if it is the immediate cause of death.

## SECONDARY OUTCOMES: CASE FATALITY AND TREATMENT COMPLICATIONS

We used the NIS to capture all secondary outcomes. Case fatality was defined as the proportion of hospital deaths among patients with a PE. We recorded potential in-hospital complications of anticoagulation for PE if these ICD-9 codes appeared in any of the 14 secondary diagnosis fields: gastrointestinal tract hemorrhage (65 codes given in the eTable; <http://www.archinternmed.com>),<sup>23</sup> intracranial hemorrhage (codes 430-432), and secondary (eg, drug-induced) thrombocytopenia (code 287.4). While these codes may overestimate in-hospital complications related to anticoagulation, trends over time should not be affected.

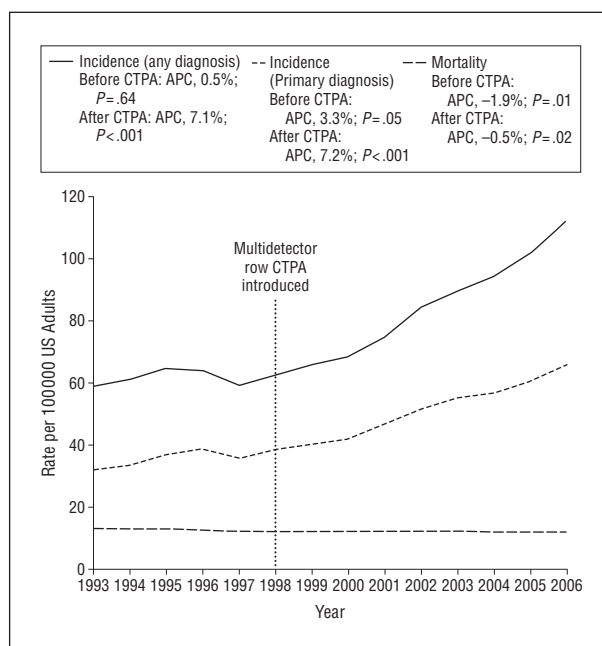
## STATISTICAL ANALYSIS

We derived national estimates from the NIS by applying each record's discharge weight using the SVY commands in Stata, release 10.1 (StataCorp, College Station, Texas). We calculated annual percentage change (APC) using the Joinpoint Regression Program, version 3.4.2 (Statistical Research and Applications Branch, National Cancer Institute). We standardized all rates by age to account for changing demographics. Outcomes reported per 100 000 US adults were standardized using the 2000 US Census as the standard population; outcomes reported as a percentage of patients with PE (eg, case fatality) were standardized using all patients with PE in the study period as the standard population.

## RESULTS

### INCIDENCE AND MORTALITY

As shown in **Figure 2**, overall age-adjusted incidence of PE did not significantly change in the period before



**Figure 2.** Incidence and mortality of pulmonary embolism in the United States, 1993-2006. APC indicates annual percentage change; and CTPA, computed tomographic pulmonary angiography.

CTPA (58.8 to 62.3 per 100 000; APC, 0.5%;  $P = .64$ ), but increased by 81% after CTPA was introduced, rising from 62.3 to 112.3 per 100 000 US adults (APC, 7.1%;  $P < .001$ ). In the subset of patients with a primary diagnosis of PE, incidence rose 19% before CTPA (32.3 to 38.3 per 100 000; APC, 3.3%;  $P = .05$ ), but showed a more dramatic rise of 72% after CTPA was introduced, increasing from 38.3 to 65.8 per 100 000; (APC, 7.2%;  $P < .001$ ). The pattern of stable PE incidence before CTPA and a large rise after the introduction of CTPA was consistent for all admission types. Specifically, after the introduction of CTPA, incidence rose by 86% among medical admissions (45.9 to 85.5 per 100 000; APC, 8.1%;  $P < .001$ ); by 60% among surgical admissions (16.0 to 25.6 per 100 000; APC, 6.5%;  $P < .001$ ), and increased 2.7-fold among obstetric admissions (0.7 to 1.9 per 100 000; APC, 13.6%;  $P < .001$ ).

As shown in Figure 2, age-adjusted PE mortality decreased throughout the study period. The decrease was more pronounced before CTPA (13.4 to 12.3 per 100 000; 8% decrease; APC, -1.9%;  $P = .01$ ) than afterwards, when mortality fell by 3% from 12.3 to 11.9 per 100 000; (APC, -0.5%;  $P = .02$ ).

## CASE FATALITY

As given in the **Table**, age-adjusted PE case fatality improved slightly before (8% decrease, from 13.2% to 12.1%;  $P = .02$ ) and substantially after CTPA was introduced (36% decrease, from 12.1% to 7.8%;  $P < .001$ ). For context, the APC in case fatality among patients with PE was similar to that among all medical admissions before CTPA (roughly -2.0%). But after CTPA was introduced, case fatality decreased by a third for all patients with PE and

**Table. Characteristics and Case Fatality of US Adults With PE**

Characteristics and Case Fatality	Year			Before CTPA (1993-1998)		After CTPA (1998-2006)	
	1993	1998	2006	APC	P Value	APC	P Value
PE (any diagnosis)	(n=110 726)	(n=126 887)	(n=258 602)				
Characteristics							
Age, mean (SE), y	64.8 (0.3)	64.9 (0.2)	63.6 (0.2)	...	...	...	...
Female, %	53.7	57.4	55.0	...	...	...	...
Admission type, %							
Medical	74.9	73.7	76.1	...	...	...	...
Surgical	24.2	25.5	22.9	...	...	...	...
Obstetric	0.8	0.8	1.0	...	...	...	...
Case fatality (ie, hospital mortality), %	13.2	12.1	7.8	-2.0	.02	-5.5	<.001
PE (primary diagnosis)	(n=60 849)	(n=77 990)	(n=151 345)				
Characteristics							
Age, mean (SE), y	64.6 (0.3)	64.2 (0.2)	62.5 (0.2)	...	...	...	...
Female, %	55.8	58.8	55.9	...	...	...	...
Admission type, %							
Medical	87.6	84.8	84.2	...	...	...	...
Surgical	11.7	14.5	14.9	...	...	...	...
Obstetric	0.7	0.7	0.8	...	...	...	...
Case fatality (ie, hospital mortality), %	7.1	6.7	3.7	-2.1	.14	-7.7	<.001
All medical admissions							
Hospital mortality, %	3.7	3.4	2.7	-1.6	<.001	-3.0	<.001

Abbreviations: APC, annual percentage change; CTPA, computed tomographic pulmonary angiography; PE, pulmonary embolism.

by half for patients with a primary diagnosis of PE, while falling only 20% among all medical admissions.

### TREATMENT COMPLICATIONS

As shown in **Figure 3**, the introduction of CTPA was associated with an increase in presumed in-hospital complications of anticoagulation for PE. Before CTPA, the age-adjusted complication incidence rate did not significantly change (2.7 to 3.1 per 100 000;  $P = .24$ ), but after CTPA was introduced, it increased by 71% from 3.1 to 5.3 per 100 000 (APC, 7.0%;  $P < .001$ ). Among patients with a primary diagnosis of PE, we observed the same pattern: stable complication rates before CTPA (1.2 to 1.5 per 100 000;  $P = .07$ ) and increasing rates after CTPA was introduced, when complications rose by 47% from 1.5 to 2.2 per 100 000 (APC, 5.2%;  $P < .001$ ).

### COMMENT

The epidemiologic patterns of PE have changed since CTPA was introduced. Compared with the pre-CTPA era, PE incidence rose, mortality changed little, and case fatality decreased.

What explains these findings (Figure 1)? At first glance, the rapid increase in incidence seems alarming—an apparent epidemic of PE. But the epidemic is unusual because it has only occurred among nonfatal emboli: despite increased incidence, population mortality from PE has not shown a parallel increase. Moreover, an epidemic (or true increase in disease incidence) is unlikely without a corresponding increase in risk factors. Risk of PE may actually be decreasing: in the past several years, quality improvement efforts have focused on increasing prophylaxis against venous thromboembolism in hospi-

talized patients. Despite the fact that most surgical patients now receive prophylaxis, PE incidence has risen substantially in the surgical population. Incidence has risen even more dramatically among obstetric patients, nearly tripling in the 8 years after CTPA was introduced. Although the major underlying risk factor (pregnancy) has remained constant, use of CT in the obstetric population has risen by 25% per year.<sup>24</sup>

The widespread adoption of CTPA points to an alternative explanation. Rather than an epidemic of disease, we think the increased incidence of PE reflects an epidemic of diagnostic testing that has created overdiagnosis. In this scenario, much of the increased incidence in PE consists of cases that are clinically unimportant, cases that would not have been fatal even if left undiagnosed and untreated.

Overdiagnosis explains the increased incidence, decreased case fatality, and minimal change in mortality we observed (Figure 1). If the extra emboli diagnosed were clinically important and benefited from treatment, mortality (ie, number of fatal pulmonary emboli/population at risk) would show a parallel decrease. This is exactly what happened in the 20 years prior to the introduction of CTPA: with improved prevention and treatment, PE mortality in the United States fell 50%, decreasing by 970 deaths per 100 000.<sup>20</sup> By contrast, in the 8 years since CTPA was introduced, despite the large increase in new cases, mortality decreased by only another 0.4 deaths per 100 000. Mortality changed little because many of the extra emboli may not have needed treatment at all.

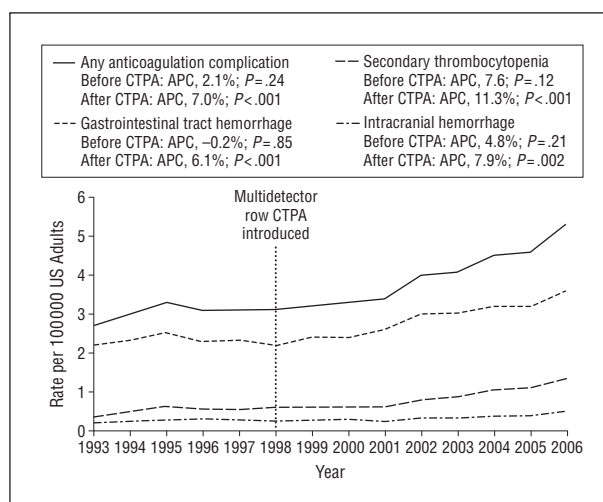
The concomitant improvement in case fatality is also explained by overdiagnosis. Case fatality (ie, number of deaths/people diagnosed) decreases because the denominator has been inflated with clinically insignificant cases that are only identifiable by highly sensitive tests (cor-

responding mortality statistic is not distorted, since the denominator includes all people at risk, not just those diagnosed). A recent time trend analysis of Pennsylvania residents hospitalized with PE confirms that patients admitted in recent years have a lower disease severity than patients admitted in the past.<sup>13</sup>

The discussion of overdiagnosis has been largely restricted to the cancer screening literature.<sup>11,12</sup> But the concept is relevant whenever there is a large reservoir of undiagnosed cases and a new, sensitive test to detect them. In the case of PE, both conditions exist. First, there appears to be a large reservoir of unsuspected emboli. Signs of recent or prior PE can be identified in more than half of autopsies if the pulmonary arteries are meticulously examined.<sup>9</sup> Moreover, among consecutive patients undergoing contrast chest CT for unrelated reasons (eg, cancer staging), unsuspected emboli are found in 4% overall,<sup>25</sup> in 17% of patients older than 80 years,<sup>26</sup> and in 24% of asymptomatic trauma patients.<sup>27</sup> Second, evidence of overdiagnosis of PE initially arose in the randomized trial comparing CTPA with ventilation-perfusion scan: while the CTPA arm detected more patients with PE, there was no apparent improvement in outcomes.<sup>8</sup> A recent meta-analysis confirms that many of the additional emboli identified by multidetector row CTPA are subsegmental emboli that do not lead to adverse outcomes even if left untreated.<sup>28</sup> In the present article, we demonstrate that it was not until after the introduction and rapid adoption of a highly sensitive test (CTPA) that the dramatic rise in PE incidence occurred.

Like any study relying on administrative databases, our study has limitations. While some factors inherent to administrative data may overestimate incidence, others cause an underestimate. Trends may be confounded by “up-coding,” an artifact whereby discharge records in later years contain more thorough ICD-9 coding in an effort to maximize reimbursement.<sup>29</sup> While such upcoding could lead to an overestimate of the increase in incidence over time, it is unlikely to explain the magnitude of change we noted (ie, nearly doubling in incidence). Because the NIS does not have identifiers to track individuals after hospital discharge, patients who are readmitted may be erroneously counted as 2 unique individuals with PE. There are reasons, however, to suspect that incidence is actually underestimated. Pulmonary embolism is considered to be one of the most common missed diagnoses; thus, our estimate of PE incidence is likely to be falsely low. Furthermore, the NIS did not allow us to capture emboli diagnosed and treated solely as an outpatient. However, more than 90% of patients with PE seen in US emergency departments in 2006 were admitted to the hospital.<sup>30</sup> This proportion was likely even higher early in the study period, when outpatient management of PE with low-molecular-weight heparin was unusual.<sup>31</sup> Hence, the overall rise in PE incidence may be even greater than what we captured among inpatients.

A second limitation is that death certificates undercount PE mortality. Since there is no national autopsy database, the Multiple Cause-of-Death database contains the most comprehensive data available on deaths in the US population. Studies have found that death certificates have a sensitivity less than 40% compared with



**Figure 3.** Rates of potential complications of anticoagulation treatment among US adults hospitalized with a pulmonary embolism, 1993-2006. APC indicates annual percentage change; and CTPA, computed tomographic pulmonary angiography.

autopsy results for identifying deaths related to PE.<sup>32</sup> To minimize this problem, we counted any diagnosis of PE listed on the death certificate (whether listed as the immediate or a contributing cause of death) as a PE death—a standard strategy in this area of research.<sup>20</sup> Although death certificate data may underestimate PE mortality, it can accurately estimate time trends and is routinely used for this purpose.<sup>20,33,34</sup>

While our findings suggest there may be substantial overdiagnosis of PE, we cannot conclude that overdiagnosis explains the entire increase. Some of these “emboli” may represent false-positive results; the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) trial found the positive predictive value of CTPA to be less than 60% in cases of low clinical suspicion for PE.<sup>35</sup> Increasing indiscriminate use of both CTPA itself and D-dimer testing prompting follow-up CTPA<sup>4,36</sup> may have led over time to more false-positive CTPA results in patients with low clinical pre-test probability of PE. Patients treated for a false-positive PE—just like those treated for a clinically unimportant one—can only be harmed. Among true-positive emboli detected by CTPA, there may be both clinically relevant and irrelevant emboli. The small decrease in population mortality may indicate that there has been some increase in the detection and successful treatment of clinically meaningful embolism. In the “best-case scenario” (ie, assuming decreased deaths are from increased detection alone), there appear to be 128 extra patients diagnosed as having a PE for every death avoided. Computed tomography pulmonary angiography, however, may have nothing to do with better outcomes; efforts at improved prevention and treatment of PE may be the explanation. Even if the increased diagnosis and treatment of the “new” pulmonary emboli detected by CTPA did not reduce death, it might reduce morbidity (eg, hemodynamic compromise at presentation or subsequent complications like recurrent embolism or chronic thromboembolic pulmonary hypertension). However, we believe that the increased incidence following introduction of CTPA is

unlikely to be attributable to increased detection of massive pulmonary emboli with hemodynamic compromise; these massive emboli could easily be detected in the pre-CTPA era by less-sensitive tests like ventilation-perfusion scanning. While it is possible that recognition and treatment of some pulmonary emboli may have prevented subsequent nonfatal complications (eg, pulmonary hypertension), which we could not detect using our databases, many patients will have received unnecessary treatment without any obvious benefit.

Overdiagnosis of these extra patients matters because treatment of PE can cause real harm. Anticoagulation, the current standard of care for all pulmonary emboli, is not benign. Even in the short-term context of the hospital stay, we found significant increases in presumed complications of anticoagulation for PE. The true danger of anticoagulation, however, lies in its longer-term use: 12% of patients anticoagulated for 3 to 6 months experience clinically significant bleeding.<sup>31</sup> A recent study suggested that patients with subsegmental emboli detected by multidetector row CTPA are far more likely to experience complications of anticoagulation than adverse outcomes from the embolism itself.<sup>37</sup> While newer treatments for PE, such as dabigatran, may be as effective but somewhat safer than warfarin,<sup>38</sup> these agents are not yet standard of care. In addition to the harms of anticoagulation, inferior vena cava filters, which are increasingly used in the management of PE,<sup>39</sup> can cause substantial morbidity, both during insertion (eg, bleeding) and while in place (eg, clotting of filter, fracture and migration of filter, increased incidence of subsequent deep vein thrombosis).<sup>40,41</sup>

As use of CT scans continues to rise,<sup>5</sup> the problem of overdiagnosis and overtreatment of PE will likely continue to grow. Because the harms of treatment can be substantial, including in the worst case death, it is imperative that we do not turn the problem of underdiagnosis into one of overdiagnosis. It is time to strengthen the evidence base: a trial randomizing stable patients with small emboli to observation vs anticoagulation would help determine whether all patients with PE require treatment.

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## INVITED COMMENTARY

# Acute Pulmonary Embolism

## *Underdiagnosed and Overdiagnosed*

**W**iener and colleagues have characterized time trends in PE in the United States in the pre- and post-CTPA angiography (CTA) eras. Using the NIS and Multiple Causes-of-Death databases, they have determined that the introduction of this diagnostic technology has been associated with a substantially increased incidence of acute PE, but with minimal change in PE mortality and a substantially improved case fatality rate. Their findings suggest the phenomenon of overdiagnosis, ie, the detection of an abnormality that will “never” cause symptoms or death. Furthermore, there was an increase in presumed complications resulting from anticoagulation. The authors have done a thorough job of outlining the potential limitations of using these databases, as well as limitations of death certificate diagnoses, how trends may be con-

founded, and how such issues were addressed. While the data are compelling, the authors are not trying to say that *all* small and/or asymptomatic pulmonary emboli are necessarily clinically insignificant, nor should they. The incidence of fatal PE recurrence without treatment has been suggested to be as high as 5%<sup>1</sup> to 35%<sup>2</sup>, although these data come from small studies with methodologic flaws and a different era. Smaller and/or asymptomatic emboli would logically appear to be associated with low mortality, but the catch remains in identifying the patients at high risk for recurrent PE or propagation of residual deep venous thrombosis (DVT) or more long-term sequelae including chronic thromboembolic pulmonary hypertension or post-thrombotic syndrome. Such long-term complications may be more difficult to track.