

Meta-Analysis: Outcomes in Patients with Suspected Pulmonary Embolism Managed with Computed Tomographic Pulmonary Angiography

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Background: Spiral computed tomographic pulmonary angiography (CTPA) is increasingly being used in the evaluation of patients with clinically suspected pulmonary embolism (PE). However, CTPA as a definitive diagnostic test may be limited by inadequate sensitivity, especially in instances of isolated subsegmental emboli.

Purpose: To assess the safety of withholding anticoagulation in patients with suspected PE and negative results on CTPA.

Data Sources: All relevant studies identified in MEDLINE (1966 to March 2004) and EMBASE (1974 to 2004) and in bibliographies of key articles. The search was not limited to the English language.

Study Selection: The authors selected all published studies that used CTPA to evaluate suspected PE and reported at least 3 months of follow-up in patients not receiving anticoagulation on the basis of a negative CTPA result.

Data Extraction: Two reviewers independently rated study quality on the basis of predetermined criteria. Data were extracted

on participants, CTPA technique, diagnostic studies performed, prevalence of PE, number of patients with negative or indeterminate CTPA results who were followed, and subsequent rates of venous thromboembolism and fatal PE.

Data Synthesis: Twenty-three studies reported on 4657 patients with negative CTPA results who did not receive anticoagulation. The 3-month rate of subsequent venous thromboembolic events was 1.4% (95% CI, 1.1% to 1.8%), and the 3-month rate of fatal PE was 0.51% (CI, 0.33% to 0.76%).

Limitations: The CTPA technology used varied across studies and was not applied uniformly in the same step of diagnostic algorithms. Only 1 study used CTPA as the sole diagnostic test.

Conclusion: The rate of subsequent venous thromboembolism after negative results on CTPA is similar to that seen after negative results on conventional pulmonary angiography. It appears to be safe to withhold anticoagulation after negative CTPA results.

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Pulmonary embolism (PE) remains a major cause of morbidity and mortality (1). The limitations of clinical examination in establishing a diagnosis of PE, as well as the perils of unnecessary anticoagulation and untreated clots, mandate use of judicious objective diagnostic testing in the evaluation of this disorder. Spiral computed tomographic pulmonary angiography (CTPA) has become an integral part of the diagnostic evaluation for suspected PE, given its widespread availability, ease of acquisition, favorable performance characteristics (2), and utility in revealing alternative diagnoses (3, 4). Researchers have been cautiously optimistic that CTPA may be useful as a definitive study to exclude PE (5).

However, CTPA is often applied as part of an algorithmic screening approach that includes other diagnostic tests, including pretest prediction models, D-dimer testing, lower-extremity compression ultrasonography, and lung scintigraphy (3, 6–13). Many of these algorithms recommend conventional pulmonary angiography (CPA) as the gold standard (14). Although screening algorithms are reported to have good efficacy, they remain cumbersome to apply (15) and may be considerably underused in clinical practice (16). Some recent investigations suggest that CTPA merits consideration as a definitive diagnostic study (17–19). However, many authors remain unconvinced that negative CTPA results alone can reliably exclude clinically significant pulmonary emboli (20, 21).

Bates and Ginsberg (20) have proposed that accep-

tance of CTPA as a definitive study would require establishment of its interobserver and intraobserver variability and study characteristics, determination of its accuracy, and an assessment of outcomes after anticoagulation is withheld because of a negative test result. The first 2 criteria have been evaluated (21, 22). In the current study, we performed a systematic review of the literature and conducted a meta-analysis of eligible studies to determine the safety and efficacy of withholding systemic anticoagulation after negative results on CTPA for PE.

METHODS

We searched MEDLINE (1966 to March 2004) and EMBASE (1974 to 2004) using the terms *pulmonary embolism, computed x-ray tomography, CTPA, angiography, sensitivity and specificity, prognosis, and recurrence*. We augmented our search by reviewing the reference lists of retrieved articles and review articles, our personal files, and reference lists of related articles in our files. Our medical librarian performed an independent search to ensure completeness. The search was not limited to the English language, but only published reports were included (Figure 1).

Study Identification and Eligibility

We attempted to identify all published studies that examined the rate of subsequent symptomatic venous thromboembolism (VTE) in patients who did not receive anticoagulation after negative or indeterminate CTPA re-

sults. To be included in the analysis, studies had to 1) have a consecutive sample or a well-defined reason for a selected sample (for example, inclusion of only patients with underlying cardiopulmonary disease or those referred to specialty centers); 2) define the diagnostic strategy used to confirm or exclude VTE; 3) withhold anticoagulation or clearly state the reason for administering anticoagulation when VTE was excluded (patients who received anticoagulation were excluded from the final analysis); 4) have a minimum of 3 months of follow-up; and 5) report subsequent symptomatic VTE events and the means of confirmation.

Study Quality

Two reviewers independently rated each study’s quality. Because there are no validated tools for quality assessment of outcome studies, we adapted the McMaster criteria for evaluating the validity of studies about prognosis (23). Studies were assessed for presence of 9 features: description of patient sample characteristics, description of inclusion and exclusion criteria, potential selection bias, length of follow-up, completeness of follow-up, description of patients lost to follow-up, description of reasons for incomplete follow-up, definition of outcomes at the start of the study, and objectivity of outcomes. The intraclass correlation coefficient for agreement between the 2 raters on overall quality rating for all included studies was 0.85 ($P < 0.001$). Disagreements were resolved by consensus. In addition to abstracted data on patients, CTPA performance, and outcomes, we recorded the number of patients who had initial nondiagnostic CTPA results and follow-up of these patients if reported. Patients who received antico-

Context

Is it safe to withhold anticoagulation in adults with suspected pulmonary embolism (PE) and negative results on spiral computed tomographic pulmonary angiography (CTPA)?

Contribution

This meta-analysis summarized data from 23 studies that reported rates of thromboembolism among patients with suspected PE who did not receive anticoagulation after negative results on CTPA. Among 4657 patients, the 3-month risks for a thromboembolic event and fatal PE were 1.4% and 0.51%, respectively.

Cautions

Studies used early-generation CT technology and different diagnostic algorithms for thromboembolism.

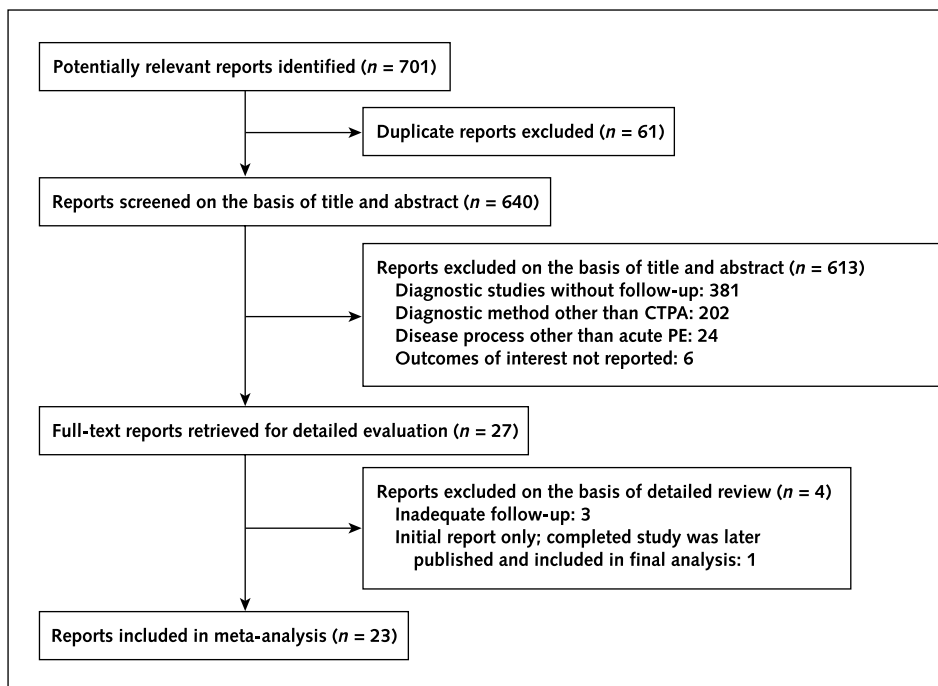
Implications

Withholding anticoagulation from patients with low to moderate probability of PE and negative results on CTPA appears reasonable.

—The Editors

agulation despite initial negative results on CTPA were excluded from the final analysis. Although some studies included a longer follow-up period, we limited our analysis to the first 3 months after negative results on CTPA be-

Figure 1. Flow diagram of study selection.



CTPA = computed tomographic pulmonary angiography; PE = pulmonary embolism.

Table. Data Extracted from Individual Studies*

Study, Year (Reference)	Study Type	Patient Sample	CT Slice Thickness, mm	Caudocranial Image Acquisition	Read on a View Box Station	Patients, n	Inpatients, n	Other Studies Performed
Blachere et al., 2000 (32)	Prospective	Consecutive	2 and 3	False	True	179	151	V/Q, US
Bourriot et al., 2003 (33)	Prospective	Selected	2 or 3	False	True	175	117	US, D-dimer
Donato et al., 2003 (17)	Retrospective	Consecutive	3	True	True	433	59	V/Q (n= 50)
Ferretti et al., 1997 (31)	Prospective	Consecutive	5	True	True	164	58	V/Q, US
Garg et al., 1999 (34)	Retrospective	Consecutive	3	False	False	256	NS	
Garg et al., 1998 (35)	Prospective	Selected	1.5–2.0	False	True	54	NS	V/Q
Goodman et al., 2000 (36)	Prospective	Consecutive	3	True	True	548	274	US
Götsäter et al., 2001 (15)	Retrospective	Consecutive	5	True	True	305	82	
Kavanagh et al., 2004 (37)	Prospective	Selected	1.25	False	True	108	NS	
Krestan et al., 2004 (19)	Retrospective	Consecutive	5	True	False	485	316	V/Q, US
Lombard et al., 2003 (18)	Retrospective	Consecutive	5	True	True	62	NS	V/Q (n= 27)
Lomis et al., 1999 (38)	Retrospective	Consecutive	3	True	True	143	NS	V/Q, US
Lorut et al., 2000 (11)	Prospective	Consecutive	2.7	False	False	228	44	D-dimer, V/Q, US
Musset et al., 2002 (13)	Prospective	Consecutive	2–3	False	True	1041	240	US, V/Q in some
Nilsson et al., 2002 (39)	Retrospective	Consecutive	3	False	True	739	276	
Ost et al., 2001 (12)	Prospective	Selected	3	True	True	103	103	V/Q
Perrier et al., 2004 (40)§	Prospective	Consecutive	3	False	False	965	0	D-dimer, US
Perrier et al., 2001 (6)§	Prospective	Consecutive	3	False	True	299	0	V/Q, US, CPA
Remy-Jardin et al., 2000 (41)	Prospective	Selected	2 and 3	False	False	370	NS	V/Q, US
Remy-Jardin et al., 2002 (42)	Prospective	Consecutive		False	False	259	211	
Swensen et al., 2002 (43)	Retrospective	Consecutive	3	False	False	1512	NS	Not stated
Tillie-Leblond et al., 2002 (44)	Prospective	Selected	2 or 3	False	False	334	58	V/Q or US in some
van Strijen et al., 2003 (3)	Prospective	Consecutive	5	True	True	512	236	US
Total								

* CPA = conventional pulmonary angiography; CT = computed tomography; CTPA = computed tomographic pulmonary angiography; DVT = deep venous thrombosis; NS = not significant; PE = pulmonary embolism; US = ultrasonography; V/Q = ventilation–perfusion scanning; VTE = venous thromboembolism.

† Excluded before CTPA.

‡ Excluded from analysis.

§ These studies eventually had no eligible patients because outcome could not be assessed on the basis of CTPA results.

cause events after 3 months are likely to be new rather than recurrences.

Statistical Analysis

The rates of subsequent VTE events and fatal PE were calculated from the abstracted numbers for each study. Extracted outcomes were the proportion of individuals with negative results on CTPA who subsequently experienced pulmonary emboli, fatal or otherwise. These data were combined by using an approximation to the inverse variance approach, effectively weighting each study according to its sample size (24). The 95% CI for each study and for the overall effect was calculated by using exact binomial methods. Heterogeneity was assessed visually with Galbraith plots (25). Publication bias was assessed visually by using funnel plots and by statistically using the method of Egger and colleagues (26). The sensitivity of our results to potential publication bias was assessed by using the methods of Duval and Tweedie (27). We performed sensitivity analyses, assessing the effects of type of study (prospective vs. retrospective), year of study, whether patients were consecutive or selected, generation of computed tomography (CT) scanner, the thickness of CT cuts, caudocranial image acquisition, view box interpretation, and the prevalence of PE.

Role of the Funding Source

No funding was received in support of this review.

RESULTS

We identified 640 abstracts in our search. Most were excluded because they did not include outcome data on patients not treated with anticoagulants (Figure 1). Among the 27 remaining articles, 4 were excluded: 3 had insufficient follow-up data (4, 28, 29) and 1 reported duplicate data (30) that were presented as part of the final report of a prospective study (31). Therefore, 23 articles were included in our analysis (3, 6, 11–13, 15, 17–19, 31–44). One of these (33) included 35 patients from another study (32).

Qualitative Review

The 23 studies included 15 prospective and 8 retrospective trials (Table). Study samples ranged from 54 to 1512, averaging 403 patients. Seventeen of the included studies examined consecutive patients, and 6 included selected patient samples. Overall, the mean prevalence of PE was 19.8% (range, 13% to 42%). Three studies (34, 37, 38) enrolled only patients in whom PE had been excluded and therefore did not report on prevalence in the sample.

Table—Continued

Prevalence of PE, %	CTPA				Anti-coagulation Received, <i>n</i>	Lost to Follow-up, <i>n</i>	Eligible for Outcomes Assessments, <i>n</i>	Recurrent VTE, <i>n</i>	Confirmation of Recurrent VTE?	Fatal PE	Confirmation of Fatal PE?
	Patients, <i>n</i>	PE Present, <i>n</i>	Non-diagnostic Results, <i>n</i>	PE Absent, <i>n</i>							
38	179	67	5	107†	24‡	13‡	100	3	NS	0	NS
33	171	54	0	117	46	5	112	2	Imaging studies	3	Clinical
28	433	119	14	300	57	4	239	3	US and CTPA	1	Clinical
15	164	39	0	125	14	0	111	2	High-probability V/Q	1	Clinical
0	132	48	2	82	3	1	78	0	NS	1	Autopsy
13	28	7	0	21	3	0	18	0	NS	0	NS
20	393	108	0	285	63	24	198	2	Autopsy, CTPA	0	NS
20	305	61	17	227	16	0	215	2	Autopsy, CTPA	1	Autopsy
0	108	23	0	85	6	0	79	1	CTPA, V/Q	0	NS
28	485	134	26	325	49	56	220	1	Autopsy	0	NS
18	62	11	0	51	3	7	41	1	Autopsy	1	Autopsy
0	143	22	8	113	12	13	88	0	NS	0	NS
42	201	70	11	120	0	19	0‡	0	NS	0	NS
35	987	290	96	601	18	10	497	4	Adjudication	5	Adjudication
21	751	158	12	581	88	45	441	2	CTPA	2	Autopsy
21	103	22	10	71	0	0	43	1	DVT on US	0	NS
23	593	124	11	458	44	1	406	5	NS	2	NS
40	299	96	12	191	34	0	0‡	0	NS	0	NS
29	370	104	49	217	20	0	71	2	CTPA	0	NS
20	259	51	20	188	13	12	163	0	NS	1	NS
33	1512	502	0	1010	17	19	974	8	CTPA, CPA, questionnaire	3	Clinical
24	334	81	38	215	0	14	185	0	NS	2	Clinical
24	510	124	8	378	0	0	378	2	US and CTPA	1	Adjudication
								41		24	

Nine of the studies included images obtained in the caudocranial direction, and 15 interpreted images on view box stations. The average CT scanner thickness was 2.1 mm (range, 2 to 5 mm). Ten prospective studies used CTPA with other diagnostic methods as part of a predetermined algorithm (3, 6, 11–13, 31–33, 35, 40). Pretest probability was used in 6 studies (6, 12, 13, 31, 32, 35), lung scintigraphy in 5 (11, 12, 31, 32, 35), lower-extremity compression ultrasonography in 6 (3, 13, 31–33, 40), and D-dimer testing in 4 (6, 11, 33, 40). Fourteen studies (3, 12, 13, 15, 17–19, 31, 33, 36, 37, 39, 41, 43) used objective imaging to confirm subsequent VTE events, while only 6 (3, 13, 15, 18, 34, 39) used autopsy confirmation or central adjudication to confirm fatal events.

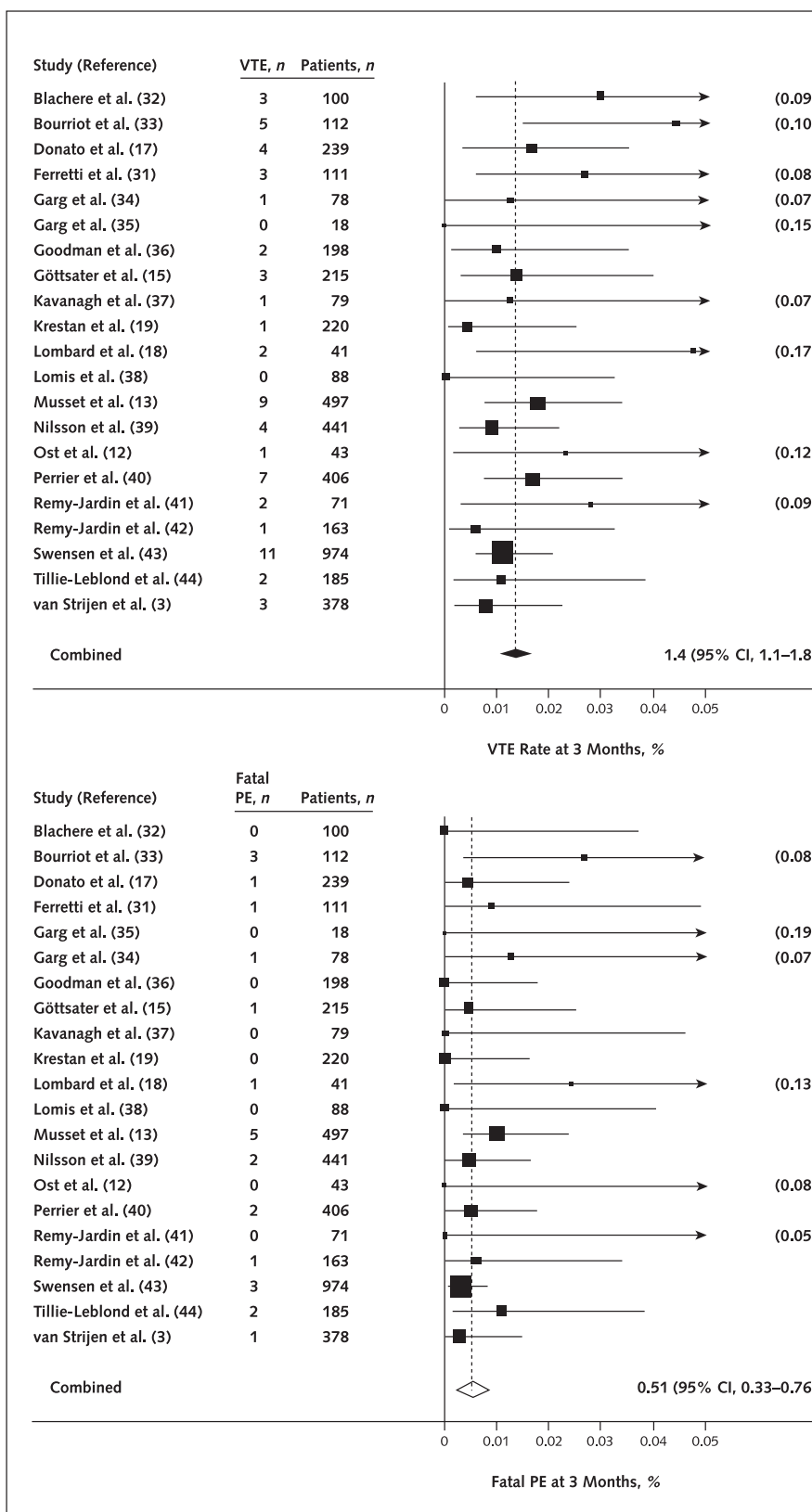
Twenty-one of the studies included a small proportion of patients (*n* = 492) who received anticoagulation despite negative results on CTPA. The reasons for anticoagulation included presence of deep venous thrombosis on concomitant ultrasonography (*n* = 70), chronic VTE (*n* = 68), and cardiac arrhythmias or other cardiac abnormalities (*n* = 204). Four patients had positive results on another test (ventilation–perfusion scanning or CPA) that suggested PE, while 65 patients (13%) were listed as having nonthromboembolic disorders. The reason for anticoagulation was not stated in 63 patients. Only 18 patients received anticoagulation because of persistent high clinical

suspicion of PE despite negative results on CTPA. These patients were not included in our analysis of outcomes.

Overall quality ratings ranged from 3 to 9 (Appendix Table, available at www.annals.org). Common quality problems included inadequately clear inclusion and exclusion criteria in 6 studies, potential selection bias in 16 studies, incomplete follow-up in 13 studies, inadequate description of the patients lost to follow-up in 14 studies, inadequate description of the reason for incomplete follow-up in 7 studies, and problems with the objectivity of outcome assessment in 9 studies.

Three studies (3, 6, 12) met all 9 criteria assessing methodologic quality. In an observational study, Perrier and colleagues (6) performed CTPA in 299 consecutive outpatients who had suspected PE and plasma D-dimer levels greater than 500 µg/L; PE was diagnosed by using a previously validated strategy (10) that did not include CTPA results. Thirty-four patients with negative CTPA results initially received a diagnosis of PE by ventilation–perfusion scanning, lower-extremity compression ultrasonography, or CPA; these patients received anticoagulation. At 3-month follow-up, none of the 157 patients who did not have PE on CTPA and did not receive anticoagulation had experienced recurrent or fatal PE. Of note, despite its strengths, this study was not included in our pooled event rate because CTPA results did not influence

Figure 2. Forest plots of total venous thromboembolism (VTE) events (top) and fatal pulmonary embolism (PE) events (bottom).



The number of patients for each study is the number of patients eligible for outcome assessment, and the event rates are a combination of recurrent VTE and fatal PE (see Table). Values in parentheses on the right-hand side of the figure are the upper bound of the CI unless otherwise indicated.

patient management and subsequent VTE events could not be assigned to CTPA results.

Ost and colleagues (12) performed CTPA in 103 patients with high pretest clinical suspicion for PE and nondiagnostic results on ventilation–perfusion scanning. Three of 71 patients with negative CTPA results subsequently developed nonfatal VTE at 6-month follow-up, with a negative predictive value of 96% when clinical outcome was used as the reference standard. Van Strijen and associates (3) studied 510 consecutive patients with suspected PE by using sequential single-detector CTPA and lower-extremity compression ultrasonography. Two of 248 patients with negative results on CTPA and no alternative diagnosis had positive results on lower-extremity compression ultrasonography. Of the 376 patients who had negative results on diagnostic studies and did not receive anticoagulation, 3 subsequently developed VTE during 3-month follow-up (VTE rate, 0.8% [CI, 0.2% to 2.3%]).

Quantitative Review

When all extracted data were pooled, 4657 patients were eligible for analysis. The rate of subsequent VTE (both nonfatal and fatal) among these studies ranged from 0% to 4.9%, with no evidence of heterogeneity. Over all studies, the pooled rate of VTE during 3-month follow-up among patients with negative CTPA results was 1.4% (CI, 1.1% to 1.8%) (Figure 2, top). Fatal PE occurred in 24 patients (pooled risk, 0.51% [CI, 0.33% to 0.76%]) (Figure 2, bottom).

Among the 15 prospective studies, 2361 patients were eligible for analysis. Subsequent VTE events occurred in 39 patients (pooled risk, 1.2% [CI, 0.6% to 1.8]), and fatal PE occurred in 15, yielding a pooled rate of 0.26% (CI, –0.5% to 52.5%). Of the 9 studies that followed patients for longer than 3 months, 8 studies, 5 of them prospective, recorded at least a mean of 6 months of follow-up. Only 1 subsequent PE was documented beyond the 3-month follow-up period (44).

Sensitivity Analysis

Our reported study outcomes for both total VTE and fatal PE rates were not affected by year of study, study type (prospective vs. retrospective), patient sample (consecutive vs. selected), the generation of the scanner, the thickness of scanner cuts, caudocranial image acquisition, image reading (view box vs. no view box), performance of other studies as part of the study protocol, or the prevalence of PE ($P > 0.2$ for all comparisons).

Publication Bias

We found no evidence of publication bias by examining funnel plots (data not shown) or by performing the Egger test (26) (overall VTE rate, $P = 0.07$; fatal PE, $P > 0.2$). Because tests for publication bias are relatively insensitive, we corrected for potential unpublished data by using the Duval and Tweedie (27) meta-trim method, which produced an adjusted overall PE rate of 1.1% (CI, 0.8% to 1.5%) and no change in the fatal PE rate.

Outcomes after Inconclusive, Nondiagnostic, or Suboptimal CTPA Results

Sixteen studies (3, 6, 11–13, 15, 17, 19, 32, 34, 38–42, 44) explicitly reported that 327 patients had CTPA results described as inconclusive, indeterminate, uninterpretable, nondiagnostic, or suboptimal. Seventy-four of these 327 patients, from 8 studies (3, 6, 12, 15, 32, 38, 40, 41), were classified separately. They were not excluded from the final analysis, did not receive anticoagulation empirically, and either underwent additional diagnostic evaluation or were followed clinically. Twelve patients (16.2%) subsequently received a diagnosis of VTE.

DISCUSSION

Our data suggest that it is safe to withhold anticoagulation in patients with negative results on CTPA. Our literature review and meta-analysis of 23 studies revealed that the 3-month rate of subsequent VTE after negative results on CTPA is very low (VTE, 1.4% [CI, 1.1% to 1.8%]; fatal PE, 0.51% [CI, 0.33% to 0.76%]). This low rate of recurrent VTE is similar to that seen after negative results on CPA (45, 46). In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study (45), the largest pre-CTPA study with outcome data, rates of subsequent VTE and fatal PE were 1.6% (CI, 0.3% to 2.9%) and 0.53% (CI, 0.16% to 1.9%), respectively. Van Beek and coworkers (46) performed a systematic review of all prospective trials (including PIOPED) that included outcome data on patients who did not receive anticoagulation after negative results on CPA. They reported summary rates of 1.7% (CI, 1.7% to 2.7%) for VTE and 0.30% (CI, 0.02% to 0.70%) for fatal PE.

Although CTPA for diagnosis of PE was first assessed in 1992 (47), recent literature reviews have concluded that sufficient evaluation of this method is still lacking (21, 22). The important missing piece of information is whether it is safe to withhold anticoagulation after negative CTPA results. Our findings suggest that rates of subsequent events in patients with negative CTPA results are similar to rates observed after negative results on CPA. Although CTPA has not been proven to be accurate as CPA, much of the literature on CTPA has used early-generation CT scanners with a limited number of detectors. More recent literature has shown that the use of multidetector CT scanners and more sophisticated reconstruction algorithms allows better identification of higher-generation pulmonary arteries and improved diagnostic yield (48–52). In addition, multidetector scanners can perform image acquisition approximately twice as quickly as single-detector scanners and may reduce the number of technically inadequate studies (48). Nonetheless, our results suggest that even early-generation CTPA is safe for management of patients with suspected acute PE.

Two of the most methodologically robust prospective studies we reviewed combined CTPA with lower-extremity

compression ultrasonography (3, 6). One of these studies reported, however, that the 3-month VTE recurrence rate would have been 1.3% if anticoagulation had been withheld only because of normal CTPA results (that is, if no lower-extremity compression ultrasonography had been performed) (3). Our sensitivity analysis did not show that the way CTPA was performed—alone or in combination—had any significant effect on the pooled rates of VTE and fatal PE. However, we did find that among patients who received anticoagulation despite negative CTPA results, 14% were treated because venous ultrasonography had revealed acute DVT. Had these patients been left untreated because of negative CTPA results, the subsequent VTE rate may have been slightly higher. Therefore, the role of CTPA without concomitant lower-extremity imaging is still undefined. Computed tomographic venography has shown promise as an adjunctive study when added to CTPA and may increase the diagnostic yield (53–55); recent studies (53, 54) suggest that this test may be more sensitive at detecting DVT than concomitant lower-extremity ultrasonography.

Only 6 studies combined an assessment of clinical probability with imaging. Although the PIOPED study (45) demonstrated that a pretest clinical estimate of PE was very valuable in dictating management after lung scintigraphy, and although clinical prediction scoring systems for PE have been devised and validated (9, 56, 57), the influence of clinical pretest probability on dictating diagnostic strategy after negative results on “screening” CTPA is unknown. Furthermore, if CTPA were applied as a definitive study (a step our meta-analysis would support), any influence of pretest probability would not be important. Pretest probability assessments should be used to select patients for CTPA, since recent publications support the exclusion of PE based on a low pretest probability and negative results on D-dimer testing (7–11, 13).

Some of the included studies documented a high rate of subsequent VTE after inconclusive results on CTPA, although not all allowed extraction of these data. Criteria for nondiagnostic CTPA results, which varied among studies, were arguably subjective but were generally defined by a combination of insufficient contrast enhancement (for example, inadequate vessel clarity past the central pulmonary arteries), inter-reader variability, and technical considerations (for example, significant motion or imaging artifact). Nondiagnostic results after CTPA are not uncommon (13, 41, 44) and occur with frequency similar to that of nondiagnostic results on CPA (58, 59). However, CTPA results that are inconclusive for PE do not modify the prior probability of disease (6). It would be important to know whether the subsequent rate of VTE in this population correlated with the number of inconclusive studies, but we could not extract these data from the information provided by the primary authors. In our review, the cumulative rate of subsequent VTE among patients who had inconclusive CTPA results but did not receive

anticoagulation was high (16.2%). This finding supports the recommendation that when a viable alternative diagnosis is not revealed incidentally, additional testing is indicated (6, 12). Improvements in technical quality (37, 60) and interpretation (61) of CTPA results may decrease the frequency of nondiagnostic results, but until such improvements are realized, CPA, repeated CTPA, or serial lower-extremity ultrasonography should be performed to confirm or exclude PE. Local resources and expertise should dictate study selection.

Studies included in our review had several important limitations. Our search was not limited to the English language but included only published studies. However, we could find no evidence of publication bias. Prospective studies used a variety of diagnostic algorithms, as detailed earlier. No two management strategies were identical, although we found no evidence of heterogeneity in outcomes between studies. Although a majority of studies (16) enrolled consecutive patients, there were some differences in patient selection. Autopsy or objective diagnostic testing was usually used to confirm recurrent VTE; however, clinical suspicion or adjudication committee opinion was used on occasion. Rarely, means of confirmation were not described. Follow-up was not complete in most studies.

In addition, CTPA techniques varied both across and within studies. Moreover, all studies used early-generation CT technology, and none of the studies used reconstruction algorithms for interpretation. Thus, our findings may not be directly applicable to patients imaged with variable-thickness scanning, although advances in data acquisition would probably improve outcomes after negative results on CTPA.

In sum, the rate of subsequent VTE after negative results on CTPA appears to be very low. We found that CTPA compares favorably with CPA as a definitive study to confirm or exclude PE. Ideally, a trial that randomly assigns patients to evaluation with CTPA versus CPA as the definitive diagnostic study, withholds anticoagulation in all patients with negative imaging results, and rigorously documents subsequent VTE events would provide clear guidance on the management of patients with suspected PE. However, given the very low rates of subsequent VTE previously documented in patients managed according to CPA results, as well as in patients managed with CTPA as we have shown here, such a trial would require the enrollment of more than 10 000 patients to detect a clinically significant difference in subsequent VTE rates. Therefore, it is unlikely to be performed. In the absence of such a trial or prospective trials examining clinical outcomes when CTPA is used as the sole diagnostic examination, imaging of the lower extremities (either lower-extremity ultrasonography or CT venography) should be performed concurrently. Withholding anticoagulation seems to be safe in patients managed in this way.

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Appendix Table. Quality Ratings of Included Studies*

Study, Year (Reference)	Sample	Inclusion/ Exclusion	Selection Bias	3-Month Follow-up	Complete Follow-up	Patients Lost Similar	Reasons Stated	Outcomes Defined	Objectively Defined	Total
Blachere et al., 2000 (34)	1	1	1	1	0	0	0	1	1	6
Bourriot et al., 2000 (35)	1	0	0	1	0	0	0	1	0	3
Donato et al., 2003 (17)	1	0	1	1	0	0	1	1	0	5
Ferretti et al., 1997 (33)	1	1	1	1	0	0	0	1	0	5
Garg et al., 1999 (37)	1	1	0	0	1	1	1	1	0	6
Garg et al., 1998 (36)	1	0	1	1	0	0	0	1	0	4
Goodman et al., 2000 (38)	1	1	1	1	0	1	0	1	1	7
Götsäter et al., 2001 (15)	1	1	1	1	0	0	1	0	0	5
Kavanagh et al., 2004 (39)	0	0	0	1	1	1	1	1	1	6
Krestan et al., 2004 (19)	1	0	1	1	0	1	1	1	1	7
Lombard et al., 2003 (18)	1	0	1	1	0	0	0	1	0	4
Lomis et al., 1999 (40)	1	1	0	1	0	0	0	1	0	4
Lorut et al., 2000 (11)	1	0	1	1	0	0	1	1	1	6
Musset et al., 2002 (13)	1	1	1	1	0	0	1	1	1	7
Nilsson et al., 2002 (41)	1	1	1	1	0	0	1	1	1	7
Ost et al., 2001 (12)	1	1	1	1	1	1	1	1	1	9
Perrier et al., 2004 (6)	1	1	1	1	1	1	1	1	1	9
Perrier et al., 2001 (42)	1	1	1	1	0	1	1	1	1	8
Remy-Jardin et al., 2000 (44)	1	0	0	1	0	0	1	1	1	5
Remy-Jardin et al., 2002 (43)	1	0	1	1	0	0	0	1	0	4
Swensen et al., 2002 (45)	1	0	1	1	0	0	1	1	1	6
Tillie-Leblond et al., 2002 (46)	1	1	0	1	0	0	0	1	0	4
van Strijen et al., 2003 (3)	1	1	1	1	1	1	1	1	1	9

* A rating of 1 means that the study met the quality indicator; a rating of 0 indicates that it did not. The ratings for each study reflect the consensus of the 2 reviewers after discussion of any disagreement.

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