

CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Thrombolytics for Patients with Acute or Massive Pulmonary Embolisms: Clinical Effectiveness and Guidelines

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Research Questions

1. What is the clinical effectiveness of thrombolytics for the treatment of adults with acute or emergent massive pulmonary embolism?
2. What are the evidence-based guidelines regarding thrombolytics in managing adult patients with acute or emergent massive pulmonary embolism?

Key Findings

Three systematic reviews with meta-analyses, seven meta-analyses, five randomized controlled trials, and one non-randomized study were identified regarding the clinical effectiveness of thrombolytics for the treatment of adults with acute or emergent massive pulmonary embolism. Three evidenced-based guidelines were identified regarding thrombolytics in managing adult patients with acute or emergent massive pulmonary embolism.

Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were thrombolytics and pulmonary embolism. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, randomized controlled trials, controlled clinical trials, or any other type of clinical trial, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and August 14, 2019.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with acute and/or emergent massive pulmonary embolism (PE) in a hospital setting
Intervention	Q1-Q2: Thrombolytics, including tissue plasminogen activator (t-PA) (e.g., alteplase)
Comparator	Q1: Usual care or standard care Q2: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., length of hospital stay, neurologic recovery), safety or harms/benefits (e.g., neurologic deterioration, bleeding complications, reperfusion) Q2: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

Three systematic reviews with meta-analyses¹⁻³, seven meta-analyses⁴⁻¹⁰, five randomized controlled trials¹¹⁻¹⁵, and one non-randomized study¹⁶ were identified regarding the clinical effectiveness of thrombolytics for the treatment of adults with acute or emergent massive pulmonary embolism. Three evidenced-based guidelines¹⁷⁻¹⁹ were identified regarding thrombolytics in managing adult patients with acute or emergent massive pulmonary embolism. No relevant health technology assessments were identified

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Three systematic reviews with meta-analyses¹⁻³, seven meta-analyses⁴⁻¹⁰, five randomized controlled trials¹¹⁻¹⁵, and one non-randomized study¹⁶ were identified regarding the clinical effectiveness of thrombolytics for the treatment of adults with acute or emergent massive pulmonary embolism.

The identified systematic reviews with meta-analyses¹⁻³ differed with their conclusions when comparing thrombolytic therapy to anticoagulation for a variety of outcomes. Overall, two systematic reviews with meta-analyses^{1,2} suggested that thrombolytic therapy decreased the risk of mortality while another study³ suggested there was no statistically significant difference in the risk of mortality between thrombolytic therapy and anticoagulation alone in patients with acute pulmonary embolism.

Similarly, the identified meta-analyses⁴⁻¹⁰ measured a variety of outcomes and had differing conclusions with regards to thrombolytic therapy compared to anticoagulation. Three meta-analyses^{4,6,7} suggested thrombolytic therapy decreased the risk of mortality whereas another three meta-analyses^{5,8,10} suggested there was no statistically significant difference in the risk of mortality between thrombolytic therapy compared to anticoagulation alone in patients with acute pulmonary embolism.

The identified randomized controlled trials¹¹⁻¹⁵ also differed in their conclusions with regards to thrombolytic therapy compared to anticoagulation in patients with acute pulmonary embolism. For instance, three of the randomized controlled trials¹¹⁻¹³ showed no difference in mortality between thrombolytic therapy and anticoagulation alone.

Lastly, the identified non-randomized study¹⁶, a small retrospective trial in patients with acute pulmonary embolism, suggested that there was no difference between thrombolytic therapy and anticoagulation in terms of the clinical cure rate.

Three evidenced-based guidelines¹⁷⁻¹⁹ were identified regarding thrombolytics in managing adult patients with acute or emergent massive pulmonary embolism. The American College of Chest Physicians CHEST guideline¹⁷ suggests that systemic thrombolytic therapy be administered to low bleeding risk patients with an acute pulmonary embolism and hypotension (blood pressure < 90 mmHg) or to low bleeding risk patients with an acute pulmonary embolism who deteriorate after starting anticoagulant therapy regardless of hypotension being present. However, the guideline¹⁷ also recommends against

administering systemic thrombolytic therapy in patients with an acute pulmonary embolism not associated with hypotension. The Royal College of Obstetricians & Gynaecologists guideline¹⁸ recommends that pregnant women or women in the puerperium period who experience a massive, life-threatening pulmonary embolism should be managed on an individual basis with either intravenous unfractionated heparin, thrombolytic therapy or surgical embolectomy. The guideline¹⁸ also states thrombolytic therapy should be considered, in combination with intravenous unfractionated heparin, for the treatment of massive, life-threatening pulmonary embolisms with hemodynamic compromise. Lastly, the European Society of Cardiology guideline¹⁹ recommends thrombolytic therapy be administered to patients with high-risk pulmonary embolisms and hypotension/shock. Furthermore, the guideline¹⁹ recommends considering thrombolytic therapy administration to patients with intermediate to high-risk pulmonary embolisms without the presence of hypotension or shock.

Detailed study characteristics are included in Table 2.

Table 2: Study and Patient Characteristics of Included Studies

First Author, Year	Study Characteristics	Population	Intervention vs Comparator	Relevant Outcomes Assessed	Conclusions
Systematic Reviews and Meta-Analyses					
Hao, 2018 ¹	<ul style="list-style-type: none"> • SR and MA • 18 RCTs • N= 2,197 	<ul style="list-style-type: none"> • Patients with acute PE 	<ul style="list-style-type: none"> • Thrombolytic therapy plus heparin vs heparin alone or heparin plus placebo 	<ul style="list-style-type: none"> • Mortality • Recurrence of PE • Minor hemorrhagic events • Major hemorrhagic events • Length of hospital stay • Quality of life 	<ul style="list-style-type: none"> • Thrombolytic therapy plus heparin reduced the risk of mortality and recurrence of PE compared to control group • Thrombolytic therapy plus heparin increased the risk of major and minor hemorrhagic events compared to control group • No statistically significant differences in length of hospital stay and quality of life between thrombolytic therapy plus heparin and control group
Marti, 2015 ²	<ul style="list-style-type: none"> • SR and MA • 15 RCTs • N= 2,057 	<ul style="list-style-type: none"> • Patients with acute PE 	<ul style="list-style-type: none"> • Thrombolytic therapy plus anticoagulant vs anticoagulant alone 	<ul style="list-style-type: none"> • Overall mortality • Combined death or treatment escalation • PE related mortality • PE recurrence • Major hemorrhage • Fatal or intracranial bleeding 	<ul style="list-style-type: none"> • Thrombolytic therapy plus anticoagulant reduced the risk of overall mortality, combined death or treatment escalation, PE related mortality, and PE recurrence compared to heparin alone • Thrombolytic therapy plus anticoagulant increased the risk of major hemorrhage and fatal or intracranial bleeding compared to heparin alone

First Author, Year	Study Characteristics	Population	Intervention vs Comparator	Relevant Outcomes Assessed	Conclusions
Cao 2014 ³	<ul style="list-style-type: none"> • SR and MA • Seven RCTs • N= 594 	<ul style="list-style-type: none"> • Patients with acute, submassive PE 	<ul style="list-style-type: none"> • Thrombolytic therapy vs heparin alone 	<ul style="list-style-type: none"> • Mortality • PE recurrence • Major hemorrhage • Minor hemorrhage 	<ul style="list-style-type: none"> • No statistically significant differences in mortality, PE recurrence, or incidence of major hemorrhage between thrombolytic therapy and heparin alone • Thrombolytic therapy increased the risk of minor hemorrhage compared to heparin alone
Meta-Analyses					
Gao, 2015 ⁴	<ul style="list-style-type: none"> • MA • Eight RCTs • N= 1,755 	<ul style="list-style-type: none"> • Patients with acute, intermediate-risk PE 	<ul style="list-style-type: none"> • Thrombolytic therapy vs anticoagulation 	<ul style="list-style-type: none"> • Mortality • Major bleeding • Minor bleeding • PE recurrence 	<ul style="list-style-type: none"> • Thrombolytic therapy decreased the risk of mortality and PE recurrence compared to anticoagulation treatment • Thrombolytic therapy increased the risk of major and minor bleeding compared to anticoagulation treatment
Xu, 2015 ⁵	<ul style="list-style-type: none"> • MA • Seven RCTs • N= 1,631 	<ul style="list-style-type: none"> • Patients with acute, intermediate-risk PE 	<ul style="list-style-type: none"> • Thrombolytic therapy vs anticoagulation 	<ul style="list-style-type: none"> • 30-day, all-cause mortality • Clinical deterioration • PE recurrence • Minor bleeding • Major bleeding 	<ul style="list-style-type: none"> • No statistically significant differences in 30-day, all-cause mortality and major bleeding between thrombolytic therapy and anticoagulation • Thrombolytic therapy decreased the risk of clinical deterioration and PE recurrence compared to anticoagulation treatment • Thrombolytic therapy increased the risk of minor bleeding compared to anticoagulation treatment
Chatterjee, 2014 ⁶	<ul style="list-style-type: none"> • MA • 16 RCTs • N= 2,115 • Subanalysis • Eight RCTs • N= 1,775 	<ul style="list-style-type: none"> • Patients with acute PE • Subanalyses in hemodynamically stable patients with RVD 	<ul style="list-style-type: none"> • Thrombolytic therapy vs anticoagulant therapy 	<ul style="list-style-type: none"> • All-cause mortality • Major bleeding • PE recurrence 	<ul style="list-style-type: none"> • Thrombolytic therapy decreased all-cause mortality and PE recurrence compared to anticoagulant therapy • Thrombolytic therapy increased the risk of major bleeding compared to anticoagulant therapy • Thrombolytic therapy in patients with RVD decreased mortality and

First Author, Year	Study Characteristics	Population	Intervention vs Comparator	Relevant Outcomes Assessed	Conclusions
					increased major bleeding compared to anticoagulant therapy
Chen, 2014 ⁷	<ul style="list-style-type: none"> • MA • 15 RCTs • N= 1,247 	<ul style="list-style-type: none"> • Patients with moderate PE 	<ul style="list-style-type: none"> • Thrombolytic therapy vs heparin therapy 	<ul style="list-style-type: none"> • Mortality • PE recurrence • Major bleeding • Non-major bleeding 	<ul style="list-style-type: none"> • Thrombolytic therapy decreased the risk of death and PE recurrence compared to heparin therapy • No statistically significant difference in major bleeding between thrombolytic therapy and heparin therapy • Thrombolytic therapy increased the risk of non-major bleeding compared to heparin therapy
Liu, 2014 ⁸	<ul style="list-style-type: none"> • MA • Seven RCTs • N= 594 	<ul style="list-style-type: none"> • Hemodynamically stable patients with acute PE 	<ul style="list-style-type: none"> • Alteplase vs heparin 	<ul style="list-style-type: none"> • Mortality • PE recurrence • Major bleeding • Escalation of care 	<ul style="list-style-type: none"> • No statistically significant differences in mortality, PE recurrence, and major bleeding between alteplase and heparin • Alteplase decreased the incidence of the escalation of care in patients compared to heparin
Nakamura, 2014 ⁹	<ul style="list-style-type: none"> • MA • N= 1,510 	<ul style="list-style-type: none"> • Patients with acute, submassive PE 	<ul style="list-style-type: none"> • Adjunctive thrombolytic therapy vs heparin alone 	<ul style="list-style-type: none"> • Composite endpoint of all-cause death or recurrent PE • Composite endpoint of all-cause death or clinical deterioration • Major bleeding 	<ul style="list-style-type: none"> • No statistically significant differences in the incidence of the composite endpoint of all-cause death or recurrent PE and major bleeding between adjunctive thrombolytic therapy and heparin alone • Adjunctive thrombolytic therapy decreased the risk of the composite endpoint of all-cause death or clinical deterioration compared to heparin alone
Riera-Mestre, 2014 ¹⁰	<ul style="list-style-type: none"> • MA • 11 RCTs • N= 1,833 	<ul style="list-style-type: none"> • Hemodynamically stable patients with acute PE 	<ul style="list-style-type: none"> • Thrombolytic therapy (alteplase, tenecteplase, and urokinase) vs heparin therapy 	<ul style="list-style-type: none"> • Major bleeding • Intracranial hemorrhage • Fatal bleeding • All-cause death • PE recurrence 	<ul style="list-style-type: none"> • Thrombolytic therapy increased the risk of major bleeding compared to heparin therapy • No statistically significant differences in intracranial hemorrhage, fatal bleeding and all-cause death between thrombolytic therapy and heparin therapy

First Author, Year	Study Characteristics	Population	Intervention vs Comparator	Relevant Outcomes Assessed	Conclusions
					<ul style="list-style-type: none"> Thrombolytic therapy decreased the incidence of PE recurrence compared to heparin therapy
Randomized Controlled Trials					
Zhang, 2018 ¹¹	<ul style="list-style-type: none"> RCT N= 66 	<ul style="list-style-type: none"> Patients with acute, intermediate-risk PE 	<ul style="list-style-type: none"> Alteplase vs LMWH 	<ul style="list-style-type: none"> Mortality VTE recurrence Major bleeding Minor bleeding Hemodynamic decompensation 	<ul style="list-style-type: none"> <i>"At 90 days, there was no difference in mortality, recurrent venous thromboembolism and major bleeding as a safety outcome, but increased minor bleeding and decreased hemodynamic decompensation occurred in the rt-PA group."</i>¹¹
Konstantinides, 2017 ¹²	<ul style="list-style-type: none"> RCT N= 1,006 	<ul style="list-style-type: none"> Patients with acute PE 	<ul style="list-style-type: none"> Tenecteplase plus anticoagulation vs placebo plus anticoagulation 	<ul style="list-style-type: none"> Overall mortality 	<ul style="list-style-type: none"> No statistically significant difference in overall mortality between tenecteplase plus anticoagulation and placebo plus anticoagulation
Sinha, 2017 ¹³	<ul style="list-style-type: none"> RCT N= 86 	<ul style="list-style-type: none"> Patients with acute, submassive PE 	<ul style="list-style-type: none"> Tenecteplase plus heparin vs placebo plus heparin 	<ul style="list-style-type: none"> Hemodynamic decompensation Mean hospital stay Mortality Major bleeding Minor bleeding 	<ul style="list-style-type: none"> Tenecteplase plus heparin decreased hemodynamic decompensation and mean hospital stay compared to placebo plus heparin No statistically significant differences in mortality and major bleeding between tenecteplase plus heparin and placebo plus heparin Tenecteplase plus heparin increased minor bleeding compared to placebo plus heparin
Kline, 2014 ¹⁴	<ul style="list-style-type: none"> RCT N= 83 	<ul style="list-style-type: none"> Patients with submassive PE 	<ul style="list-style-type: none"> Tenecteplase plus LMWH vs placebo plus LMWH 	<ul style="list-style-type: none"> Composite patient-oriented outcome 	<ul style="list-style-type: none"> Trial terminated prematurely <i>"Treatment of patients with submassive pulmonary embolism with tenecteplase was associated with increased probability of a favorable composite outcome."</i>¹⁴
Taherkhani, 2014 ¹⁵	<ul style="list-style-type: none"> RCT N= 50 	<ul style="list-style-type: none"> Patients with acute, submassive PE 	<ul style="list-style-type: none"> Alteplase or streptokinase plus enoxaparin vs 	<ul style="list-style-type: none"> Composite of in-hospital death or 	<ul style="list-style-type: none"> Thrombolytic therapy decreased the incidence of the composite of in-hospital death or clinical

First Author, Year	Study Characteristics	Population	Intervention vs Comparator	Relevant Outcomes Assessed	Conclusions
			enoxaparin alone	clinical deterioration • Major bleeding	deterioration compared to enoxaparin alone • No fatal bleeding or cerebral bleeding reported with thrombolytic therapy
Non-Randomized Studies					
Fei, 2014 ¹⁶	• Retrospective trial • N= 50	• Patients with acute, submassive PE	• Thrombolytic therapy vs anticoagulation	• Clinical cure • Hemorrhage	• No statistically significant difference in clinical cure rates between thrombolytic therapy and anticoagulant therapy • Thrombolytic therapy increased the incidence of hemorrhage compared to anticoagulant therapy

LMWH= low-molecular weight heparin; MA= meta-analysis; PE= pulmonary embolism; RCT= randomized controlled trial; rt-PA= recombinant tissue-type plasminogen activator; RVD= right ventricular dysfunction; SR= systematic review; VTE= venous thromboembolism

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

Systematic Reviews with Meta-analyses

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See Sections 5.3- Thrombolytic Treatment and 5.8- Therapeutic Strategies

Appendix — Further Information

Systematic Review

No Abstract Available

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