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Austrian Institute for
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GmbH

Percutaneous aspiration thrombectomy for pulmonary embolism

Systematic Review

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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Content

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List of abbreviations

AHA ..... American Heart Association
BP ..... blood pressure
CDT ..... catheter-directed thrombolysis
CI..... confidence interval
CTPA ..... computed tomography pulmonary angiography
CTPH..... chronic thromboembolic pulmonary hypertension
CUS ..... compression ultrasonography
DF ..... Deanne Forel
DVT..... deep vein thrombosis
ERS ..... European Respiratory Society
ESC ..... European Society of Cardiology
EU ..... European Union
GG ..... Gregor Goetz
GRADE..... Grading of Recommendations, Assessment, Development and Evaluations
ICD ..... International Classification of Diseases
ICU..... intensive care unit
IHE..... Institute of Health Economics
LV..... left ventricular
MRA..... magnetic resonance angiography
MV..... Meegan Vandepeer
NM ..... Ning Ma
NRC ..... non-randomised comparative
PA..... pulmonary artery
PAP ..... pulmonary artery pressure
PAT ..... percutaneous aspiration thrombectomy
PE ..... pulmonary embolism
PESI ..... Pulmonary Embolism Severity Index
PICO ..... population, intervention, comparator, outcome
QoL ..... quality of life
RCT..... randomised controlled trial
RoB..... risk of bias
ROBINS-I ..... Risk Of Bias In Non-randomised Studies Of Interventions
RV..... right ventricular
SD..... standard deviation
SPECT ..... single-photon emission computed tomography
tPA..... tissue plasminogen activator
TTE ..... transthoracic echocardiogram
V/Q..... ventilation/perfusion
VTE ..... venous thromboembolism
WHO ..... World Health Organization
WHO-ICTRP ..... World Health Organization – International Clinical Trials Registry Platform

Executive Summary

Introduction

pulmonary embolism (PE) is one of the leading causes of cardiovascular death

Percutaneous aspiration thrombectomy is a minimally invasive procedure used to treat patients with pulmonary embolisms (blood clots in the lungs), one of the leading causes of cardiovascular death. It involves the insertion of specialised catheter into the femoral artery, through the right side of the heart, to the site of the clot and then removing it using suction. In this report the latest available evidence with regard to the comparative effectiveness and safety of percutaneous aspiration thrombectomy in patients with high-risk PE and intermediate risk PE that have developed haemodynamic instability and who are contraindicated or have failed systemic thrombolytics is summarised.

In Austria, a provisional XN code (XN050) has been available for the individual medical service since 2022.

Methods

systematic literature search in 4 databases

quality appraisal of literature

GRADE

A systematic search was conducted to evaluate the safety and efficacy of percutaneous aspiration thrombectomy compared with catheter-directed thrombolysis (CDT), catheter-directed mechanical thrombectomy (not involving aspiration) or surgical embolectomy. The following databases were searched: Medline, Embase, The Cochrane Library and the International Network of Agencies for Health Technology Assessment (INAHTA). The search was limited to articles published in English or German. Case series were only included for safety if they were prospective and included ≥ 20 patients. Two authors independently carried out study selection, data extraction and quality appraisal. The quality of the included studies was assessed using the ROBINS-I (Risk of Bias In Non-randomised Studies Of Interventions) tool (non-randomised comparative (NRC) studies) or the IHE (Institute of Health Economics) Quality Appraisal Checklist (single-arm studies) and the certainty of the evidence was rated according to Grading of Recommendations, Assessment, Development and Evaluations (GRADE).

Results

endpoints for relative efficacy: PE-related death, haemodynamic decompensation, pulmonary hypertension and recurrence

endpoints for safety: serious adverse events

One retrospective matched-control case series (n=52) and three prospective single-arm studies (n=1,023) were eligible for inclusion in this assessment.

Low certainty evidence from one small retrospective study in propensity matched high- and intermediate-risk PE patients comparing percutaneous aspiration thrombectomy to catheter directed thrombolysis (CDT) reported no statistically significant difference in 30-day all-cause mortality. Other outcomes considered crucial to derive a recommendation on the relative efficacy of percutaneous aspiration thrombectomy including haemodynamic decompensation, chronic thromboembolic pulmonary hypertension and PE recurrence were not reported.

retrospective comparative study: no stat. difference in critical endpoints

In the retrospective matched-control case series major bleeding and procedure-related deaths did not differ significantly between percutaneous aspiration thrombectomy and CDT. Other safety outcomes deemed crucial to derive a recommendation on the relative safety of percutaneous aspiration thrombectomy (treatment-related clinical deterioration, treatment-related pulmonary vascular injury and treatment-related cardiac injury) were not reported.

safety in single arm studies: major bleeding: 1.0-1.7% procedure related death: 0-0.8% treatment related injury: 0-0.1% clinical deterioration: 0.3-3.8%

The three prospective single-arm studies included to further inform safety included one large registry study of 800 high- and intermediate-risk PE patients and two studies of intermediate-risk PE patients. In these single-arm studies, major bleeding occurred in 1.0-1.7% of patients, procedure-related deaths occurred in 0.0-0.8%, treatment-related vascular injury occurred in 0.0-1.0%, treatment-related cardiac injury occurred in 0.0-0.1% and treatment-related clinical deterioration occurred in 0.3-3.8%. Of note, only one of the procedure-related deaths was reported as being due to the device. The certainty of the evidence informing the safety outcomes was deemed to be very low as assessed by GRADE.

two ongoing RCTs

Two ongoing randomised controlled trials on the use of percutaneous aspiration thrombectomy for PE were identified. One trial is comparing it to CDT, and the other to anticoagulants. Both trials are in haemodynamically stable intermediate-high-risk PE patients.

Discussion

main limitation of evidence: no reliable comparative studies,

The main limitation of the evidence is that it consists of only four studies, mostly single-arm, with the exception of one retrospective matched-control case series unlikely to be powered to detect a difference in safety or efficacy outcomes.

indirectness and …

Another major limitation is the indirectness of the evidence. The populations in all of the included studies did not match those defined in the PICO as they mostly included intermediate-risk PE patients who were not haemodynamically unstable and who generally were not contraindicated to or failed thrombolysis. This population is at much lower risk of death than patients who are categorised as high-risk PE or as intermediate-risk PE who become haemodynamically unstable. The lack of contraindication to thrombolysis could have possibly resulted in a bias against the intervention in the comparative study given the comparator was CDT. Whilst the amount of drug, and thus the risk of bleeding, is reduced with CDT compared with systemic thrombolysis, it is not obviated.

… aggregated reporting of outcomes relating to different risk groups and different specific utilized device generations

Another factor affecting the interpretation of the evidence includes the aggregated reporting of outcomes for high- and intermediate-risk patients, which occurred in two of the included studies. Safety data from the single-arm studies, particularly the large registry study, is further complicated by patients being on different anticoagulants, the use of thrombolytics in a small proportion of patients, updated (improved) versions of the device being used in a proportion of patients and data for some outcomes only being available for a subset of patients.

Conclusion

insufficient comparative evidence, re-evaluation in 2025

In the absence of robust comparative data, no conclusions can be drawn regarding the comparative effectiveness of aspiration thrombectomy compared with other procedures (such as catheter-based thrombolysis). Re-evaluation is recommended in 2025, when results from PEERLESS will be available.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Pulmonalembolie (PE) häufige Ursache für kardiovaskuläre Todesfälle

Die Lungenembolie (Pulmonalembolie/PE) ist eine der häufigsten Ursachen für kardiovaskuläre Todesfälle in Europa. Sie tritt auf, wenn sich ein Blutgerinnsel (Thrombus) – in der Regel aus dem tiefen Venensystem der unteren Extremitäten – löst und in einer Lungenarterie festsetzt, wodurch der Blutfluss zur Lunge blockiert wird. Dieses vom Entstehungsort losgelöste Blutgerinnsel wird auch Embolus genannt. Eine PE kann sehr unterschiedlich verlaufen: von asymptomatisch über Kreislaufkollaps bis hin zu plötzlichem Tod.

Unterteilung in 3 Risikogruppen: gering, intermediär und hoch

PE-Patient*innen können nach der Europäischen Gesellschaft für Kardiologie (ESC) in Risikogruppen mit geringem, intermediärem oder hohem Risiko frühzeitig zu sterben unterteilt werden. Die Risikostratifizierung basiert, unter anderem, auf Vitalparametern, Biomarker-Tests und Bildgebungsuntersuchungen der PE-Patient*innen.

Therapie: Überwachung, systemische Thrombolyse, unter Umständen auch Embolektomie bzw. kathetergestützte Behandlung möglich

Bei PE-Patient*innen mit hohem Risiko ist die unverzügliche Hemmung der Blutgerinnung (Antikoagulation) erforderlich. Zusätzlich empfiehlt die ESC-Leitlinie 2019 eine sofortige Therapie, die durch Gerinnsel aufgetretene Verschlüsse von Blutgefäßen auflöst, die systemische thrombolytische Therapie. Bei manchen Patient*innen ist die systemische Thrombolyse jedoch kontraindiziert, weshalb laut ESC-Leitlinie 2019 eine offene chirurgische Entfernung (Embolektomie) oder eine kathetergesteuerte Entfernung mit Thrombolyse (engl. Catheter-Directed Thrombolysis/CDT) in Betracht gezogen werden kann. Bei PE-Patient*innen mit intermediärem Risiko ist eine sorgfältige Überwachung und eine unverzügliche Antikoagulation indiziert. Bei diesen Patient*innen kann es trotz Antikoagulation zu einer hämodynamischen Verschlechterung kommen, wodurch die bereits beschriebenen Therapieoptionen einer Hochrisiko-PE indiziert sein können.

Beschreibung der Technologie

perkutane Aspirationsthrombektomie als neues minimalinvasives Verfahren zur Behandlung der PE

Die perkutane Aspirationsthrombektomie ist eine Form der mechanischen kathetergesteuerten Behandlung von PE. Bei diesem minimalinvasiven Verfahren wird ein spezieller Katheter (ein dünner, biegsamer Schlauch) durch die rechte Herzseite in die Lungenarterien bis zum Ort der Embolie geführt, die die Blockade verursacht. Zunächst wird versucht, den Embolus mit Hilfe einer Absaugtechnik zu entfernen. Bleibt die Absaugtechnik erfolglos, wird der Embolus mit Hilfe des Katheters mechanisch entfernt. Der perkutane Zugang erfolgt in der Regel über die Oberschenkelvene. Ziel des Verfahrens ist die rasche Wiederherstellung des Blutflusses (Revaskularisierung) und damit die Senkung der akuten PE-bedingten Sterblichkeit. Der Eingriff wird in der Regel unter Lokalanästhesie durchgeführt.

Geräte: FlowTriever® und Indigo®

Derzeit sind zwei Geräte für die perkutane Aspirationsthrombektomie bei PE-Patient*innen zugelassen: Das FlowTriever®-System (Inari Medical Inc.) und das Indigo®-System (Penumbra Inc.).

Fragestellung

Forschungsfrage

Ist die perkutane Aspirationsthrombektomie im Vergleich zur Standardbehandlung (insb. CDT oder chirurgische Embolektomie) bei der Behandlung von PE mit intermediärem und hohem Risiko wirksamer und gleich sicher in Bezug auf PE- und gerätebedingte Todesfälle und schwerwiegende unerwünschte Ereignisse, einschließlich schwerer Blutungen?

Methoden

systematische Suche in 4 Datenbanken

Die Forschungsfrage wurde mittels einer systematischen Übersichtsarbeit zur vergleichenden klinischen Wirksamkeit und Sicherheit der perkutanen Aspirationsthrombektomie adressiert. Dabei wurde eine systematische Literatursuche in folgenden vier Datenbanken durchgeführt: Medline via Ovid, Embase, The Cochrane Library, und die INAHTA Datenbank.

Studienauswahl, Extraktion & Qualitätsbeurteilung: von 2 Forscher*innen durchgeführt

Die Studienauswahl, die Datenextraktion, sowie die Qualitätsbeurteilung der eingeschlossenen Studien erfolgte unabhängig durch zwei Autor*innen. Für die Qualitätsbewertung der eingeschlossenen Studien wurde je nach Studiendesign das ROBINS-I-Tool (Risk of Bias In Non-randomised Studies Of Interventions) oder die IHE-20 (Institute of Health Economics) Checkliste verwendet. Die Vertrauenswürdigkeit der Evidenz wurde mit dem GRADE-System (Grading of Recommendations, Assessment, Development and Evaluations) bewertet.

Klinische Wirksamkeit

entscheidungs-relevante Endpunkte für klinische Wirksamkeit & Sicherheit

Zur Bewertung der komparativen klinischen Wirksamkeit der perkutanen Aspirationsthrombektomie wurden randomisierte Kontrollstudien und nicht randomisierte kontrollierte Studien eingeschlossen. Folgende Endpunkte wurden dabei als *entscheidend* definiert: PE-bedingter Tod, hämodynamische Dekompensation, chronische thromboembolische pulmonale Hypertonie und Wiederauftreten einer PE.

Sicherheit

Zur Bewertung der Sicherheit wurden – neben kontrollierten Studien – prospektive einarmige klinische Studien mit zumindest 20 Patient*innen für die Evidenzsynthese herangezogen. Dabei wurden folgende Endpunkte als *entscheidend* definiert: (schwerwiegende) unerwünschte Ereignisse.

Ergebnisse

Verfügbare Evidenz

insgesamt 4 Studien eingeschlossen: 3 Studien zu FlowTriever® 1 Studie zu Indigo®

Insgesamt wurden vier Studien in diese Literaturübersicht eingeschlossen: Eine retrospektive Fallserie (n=52) mit indirektem Vergleich (Propensity-Score-Matching) zwischen perkutaner Aspirationsthrombektomie mittels FlowTriever® und CDT bei Patient*innen mit intermediärem und hohem Risiko, sowie drei prospektive einarmige Studien (n=1.011). Unter letzteren befand sich eine prospektive Register-basierte einarmige klinische Studie (n=800), die vor allem die Sicherheit des FlowTriever® Systems bei PE-Patient*innen mit hohem (7,9 %) und intermediärem Risiko (92,1 %) analysierte. Die zwei anderen prospektiven einarmigen klinischen Studien untersuchten das FlowTriever® System (n=104) bzw. das Indigo® System (n=119) bei PE-Patient*innen mit intermediärem Risiko. Die Nachbeobachtungszeit betrug 30 Tage in allen eingeschlossenen Studien.

Vertrauenswürdigkeit der Evidenz

Die retrospektive Fallserie mit indirektem Vergleich wies ein hohes Verzerrungspotenzial auf. Ein ähnliches Bild zeigte sich bei den drei einarmigen klinischen Studien: Hier schwankte das Verzerrungspotential allerdings zwischen moderat bis hoch. Insgesamt wurde die Vertrauenswürdigkeit der gesamten Evidenz nach GRADE als sehr niedrig eingestuft. Die Evidenz zur vergleichenden Wirksamkeit war vor allem wegen erhöhtem Verzerrungspotenzial aufgrund ungleicher Zusammensetzung der Vergleichsgruppen (Selektionsbias) und unzureichender Präzision der Resultate eingeschränkt. Die Vertrauenswürdigkeit der Evidenz im Hinblick auf die Sicherheit der Intervention war – aufgrund von hohem Verzerrungspotential der einarmigen Studien und aggregierter Berichterstattung von PE-Patient*innen mit hohem und intermediärem Risiko – ebenfalls sehr niedrig.

Verzerrungspotenziel: moderat bis hoch

Vertrauenswürdigkeit der Evidenz: sehr niedrig

Klinische Wirksamkeit

In der retrospektiven Fallserie mit indirektem Vergleich wurde kein statistisch signifikanter Unterschied zwischen den beiden Behandlungen hinsichtlich der **30-Tage-Gesamtmortalität** oder der **Senkung des pulmonal-arteriellen Drucks** (chronische thromboembolische pulmonale Hypertonie) festgestellt. Weitere entscheidungsrelevante Wirksamkeitsendpunkte wie etwa das **Wiederauftreten von PE** oder die **hämodynamische Dekompensation** wurden in dieser Studie nicht berichtet.

Wirksamkeit: keine stat. signifikanten Unterschiede in 30-Tagen Mortalität und der Senkung des pulmonal-arteriellen Drucks in 1 retrospektiven Studie

Sicherheit

Über **schwere Blutungen** wurde in allen Studien berichtet: Die retrospektive Fallserie mit indirektem Vergleich zeigte keinen statistisch signifikanten Unterschied zwischen Patient*innen mit FlowTriever® System und Patient*innen mit CDT (4 % vs. 4 %; p>0,05). In den anderen drei Studien traten bei 1 % bis 1,7 % der Patient*innen schwere Blutungen auf.

Sicherheit: schwere Blutungen in 4 Studien berichtet: in 1 %-4 % der Patient*innen

Der Endpunkt verfahrensbedingte Todesfälle wurde in allen Studien berichtet: Während die retrospektive Fallserie mit indirektem Vergleich keinen statistisch signifikanten Unterschied zwischen Patient*innen mit FlowTriever® System und Patient*innen mit CDT feststellen konnte (8,3 % vs. 0 %; p>0,05), traten verfahrensbedingte Todesfälle lediglich bei einem der drei anderen einarmigen Studien auf (0,8 %). In den anderen zwei einarmigen Studien trat kein Todesfall auf (0 %). Es war nur einer der verfahrensbedingten Todesfälle auf das Gerät zurückzuführen.

verfahrensbedingte Todesfälle in 4 Studien berichtet: in 0 %-8,3 % der Patient*innen

In den einarmigen Studien wurden überdies **behandlungsbedingte Gefäßverletzungen** bei 0,0-1,0 % der Patient*innen, **behandlungsbedingte Herzverletzungen** bei 0,0-0,1 % und **behandlungsbedingte klinische Verschlechterungen** bei 0,3-3,8 % berichtet.

behandlungsbedingte Gefäß- bzw. Herzverletzungen bei 0,0-3,8 % der Patient*innen

Laufende Studien

laufende Studien:

Die Suche nach laufenden Studien ergab, dass es derzeit zwei laufende randomisierte Kontrollstudien gibt:

PEERLESS zu FlowTriever® (n=550): kombinierter primärer Endpunkt aus Mortalität und anderen klinischen Endpunkten

- PEERLESS (n=550) vergleicht das FlowTriever® System mit der CDT und definierte einen kombinierten primären Endpunkt bestehend aus Mortalität und anderen klinischen Endpunkten.

STORM-PE (n=100) zum Indigo System: Veränderung des RV/LV-Verhältnisses

- STORM-PE (n=100) vergleicht den Einsatz des Indigo® Systems mit der Antikoagulation (Heparin) und definierte eine Veränderung der rechtsventrikulären/linksventrikulären Ratio innerhalb der ersten 48 Stunden als primären Endpunkt.

Die Studienpopulation der beiden laufenden Studien sind hämodynamisch stabile PE-Patient*innen mit intermediärem bis hohem Risiko ohne Kontraindikation für Thrombolytika. Laut Informationen aus clinicaltrials.gov sollten diese Studien bis 2024 bzw. 2026 abgeschlossen sein.

Kostenerstattung

XN220 als neue Untersuchungs- und Behandlungsmethode

Die perkutane Aspirationsthrombektomie bei PE ist als neue Untersuchungs- und Behandlungsmethode (XN220) im österreichischen Krankenhausleistungskatalog abgebildet.

Diskussion

Evidenz: 1 retrospektive Studie mit indirektem Vergleich und 3 einarmige Studien

Die Evidenz zur Wirksamkeit der perkutanen Aspirationsthrombektomie beschränkt sich auf eine retrospektive Fallserie mit 52 Patient*innen, in der die Intervention indirekt mit CDT verglichen wurde. Weitere drei prospektive einarmige Studien wurden einbezogen, um Informationen über die Sicherheit der Intervention zu erhalten.

Einschränkung der Evidenz: keine robusten vergleichenden Daten

Die schwerwiegendste Einschränkung der Evidenz besteht darin, dass keine robusten vergleichenden Daten vorliegen. Die Aussagekraft der Daten aus der retrospektiven Studie mit indirektem Vergleich sind angesichts eines potentiellen Selektionsbias und fehlender statistischer Präzision erheblich eingeschränkt. In den einarmigen Beobachtungsstudien werden einerseits unterschiedliche Risikogruppen aggregiert analysiert und andererseits kommen unterschiedliche Antikoagulanzien zum Einsatz bzw. gibt es ebenfalls Unterschiede der verwendeten Versionen der Geräte.

Schlussfolgerung und Empfehlung

Evidenz unzureichend, Re-Evaluierung in 2025

In Ermangelung belastbarer vergleichender Daten sind keine Schlussfolgerungen zur komparativen klinischen Wirksamkeit der perkutanen Aspirationsthrombektomie im Vergleich zu anderen Verfahren (wie etwa der CDT oder katheterbasierten Thrombolyse) möglich. Aus diesem Grund wird die Aufnahme der Technologie in den Krankenhausleistungskatalog derzeit nicht empfohlen. Eine Re-Evaluierung wird 2025 angeraten, wenn Ergebnisse aus PEERLESS vorliegen.

1 Background

1.1 Overview of the disease, health condition and target population[1]

Overview of pulmonary embolism

perkutane Aspirationsthrombektomie als neue Behandlungsmodalität bei akuter Pulmonalembolie (PE):

Entfernung der Blutgerinnsel aus Lungenarterien

Percutaneous aspiration thrombectomy is used to treat pulmonary embolism (PE). A PE is a blood clot (thrombus) that has become stuck in the pulmonary arteries. It most commonly occurs when a deep vein thrombosis (DVT) from a lower extremity (usually a leg vein [1]) breaks free (becoming an embolus) and travels to the pulmonary arteries [2]. As the pulmonary arteries transfer blood from the heart to the lungs where it gets reoxygenated, if not enough blood is oxygenated due to the embolism blocking blood flow, oxygen levels in the body can drop dangerously low which could result in organs being damaged. In addition, as blood travels from the right side of the heart prior to entry into the pulmonary arteries, the blockage can increase pressure back onto that side of the heart, causing it to get stretched and work harder. As a result of the increase in pressure in the right side of the heart, the left side of the heart may get squeezed and not be able to pump enough blood, causing blood pressure (BP) to drop [3]. All of these effects can lead to death, either suddenly or a short time after the PE occurs if it is not treated [3]. Thrombosis (formation of a blood clot) may be triggered by plasma hypercoagulability, changes in blood flow and endothelial cell dysfunction [2].[2] The relevant International Classification of Diseases (ICD)-11 codes for PE are listed in Table 1-1.

Table 1-1: ICD-11 codes for PE

Pulmonary embolism	**BB00**
Acute pulmonary embolism	**BB00.0**
Specific anatomy	
Pulmonary artery	BB00/BB00.0&XA09J9
Pulmonary trunk	BB00/BB00.0&XA3713
Pulmonary vein	BB00/BB00.0&XA8FY4
Inferior pulmonary vein	BB00/BB00.0&XA2ZV2
Left pulmonary vein	BB00/BB00.0&XA1WN5
Superior pulmonary vein	BB00/BB00.0&XA9K75

Source: International Classification of Diseases 11th Revision [4]

bei Patient*innen mit hohem oder intermediärem Risiko und z. B. bei Kontraindikation für systemische Thrombolyse

This assessment is on patients with acute PE, meaning their embolus is situated centrally within the vascular lumen or it is blocking a vessel [5]. Specifically, this assessment is on patients with high-risk PE who are contraindicated for or have failed systemic thrombolysis and patients with intermediate-risk PE on anticoagulation treatment who develop signs of haemodynamic instability and who are contraindicated or have failed systemic thrombolysis [6].[3]

[1] This section addresses the EUnetHTA Core Model® domain CUR.

[2] **A0001** – For which health conditions, and for what purposes is the technology used?

[3] **A0002** – What is the disease or health condition in the scope of this assessment?

A list of relative and absolute contraindications for thrombolysis is presented in Table 1-2.

Definitions of high-risk and intermediate-risk PE are described below (see *Target population*).

Table 1-2: Relative and absolute contraindications to thrombolysis in high-risk PE.

Absolute	Relative
■ History of haemorrhagic stroke or stroke of unknown origin ■ Ischaemic stroke in previous 6 months ■ Central nervous system neoplasm ■ Major trauma, surgery or head injury in previous 3 weeks ■ Bleeding diathesis ■ Active bleeding	■ Transient ischaemic attack in previous 6 months ■ Oral anticoagulation ■ Pregnancy or first postpartum week ■ Non-compressible puncture sites ■ Traumatic resuscitation ■ Use of extracorporeal membrane oxygenation ■ Advanced liver disease ■ Infective endocarditis ■ Active peptic ulcer ■ Refractory hypertension (systolic blood pressure > 180 mmHg)

Source: Pruszczyk et al 2022 [7]

Risikofaktoren für PE u. a.: schwere Traumata, chirurgische Eingriffe, Frakturen der unteren Gliedmaßen …

Risk factors for PE may be environmental or genetic [6]. Known risk factors with a strong association with PE include major trauma, surgery (including hip or knee replacement), lower limb fractures, hospitalisation for previous heart failure or arterial fibrillation/flutter (within 3 months), previous myocardial infarction (within 3 months), previous venous thromboembolism (VTE), and spinal cord injury [6]. Prolonged immobilisation (due to paralysis, recovery from surgery/an injury, etc.) is also associated with PE risk [8].[4]

… aber auch einige Krebserkrankungen

Cancer, particularly in those receiving chemotherapy or radiation therapy, is also associated with PE, with different types of cancer having different levels of risk [6, 8]. Pancreatic, lung, gastric and brain cancer, and haematological malignancies are associated with the highest risk of PE [6].[4]

Inherited conditions, including thrombophilia (a condition where blood clots more easily due to deficiencies in various blood factors, such as antithrombin, protein C or S) is common in people who develop PE before the age of 50 [8].[4]

und östrogenhaltige orale Kontrazeptiva

In women of reproductive age, oestrogen-containing oral contraceptives are associated with an increased risk for PE [8]. Infection, blood transfusion and erythropoiesis-stimulating agents are all associated with an elevated risk of PE [6]. More common risk factors include cigarette smoking, obesity, hypercholesterolaemia, hypertension and diabetes mellitus [6]. According to cross-sectional data, incidence of VTE is close to eight times higher in individuals aged >80 years compared with individuals in their 50s, as such, advancing age may also be considered a risk factor for PE [6].[4]

PE ist ein lebensbedrohlicher Notfall

High-risk PE is a life-threatening medical emergency. Patients with this classification present with either cardiac arrest, obstructive shock or persistent hypotension are at a high risk of death. In those with obstructive shock, death usually occurs within the first few hours after presentation at the hospital if treatment is not given to restore blood flow [9].[5]

[4] **A0003** – What are the known risk factors for the disease or health condition?

[5] **A0004** – What is the natural course of the disease or health condition?

Ziel der Behandlung: Wiederherstellung des Blutflusses

Patients classified as intermediate-risk but who develop signs of haemodynamic instability despite being on anticoagulants (defined as the presence of cardiac arrest, obstructive shock or persistent hypotension) become high-risk and thus are also at risk of death unless treatment is provided to restore blood flow [6].[5]

Effects of pulmonary embolism on the individual and society

hohes Mortalitätsrisiko

PE is associated with high mortality and morbidity. It is the third most common cause of hospital-related death and the most common cause of preventable hospital-related death [10].[6]

hohes Nebenwirkunsrisiko

A recent meta-analysis of 40,363 consecutive patients with acute PE reported that 3.9% had high-risk PE. The short-term (up to 90 days after PE diagnosis) all-cause mortality rate in this cohort was 19% (95% confidence interval (CI): 17%, 21%) [11]. A German single-centre registry study including 784 consecutive PE patients, enrolled between September 2008 and March 2018, reported in-hospital adverse outcomes (PE-related death or cardiopulmonary resuscitation) and in-hospital all-cause mortality in high-risk PE patients. Deaths were deemed as PE-related if either confirmed by autopsy or following a clinically severe episode of acute PE in the absence of an alternative diagnosis. Of the 784 PE patients, 86 (11.0%) were classified as high-risk according to the European Society of Cardiology (ESC) 2019 guidelines risk stratification algorithm (described in *Target population*). In this high-risk population there were 32.6% in-hospital PE-related deaths and the in-hospital all-cause mortality was 34.9%. A total of 30 high-risk patients (34.9%) required cardiopulmonary resuscitation and 46 patients (53.5%) required reperfusion treatment (systemic thrombolysis 51.2%; surgical thrombectomy 4.7%). The one-year all-cause mortality in all high-risk patients was 51.2% and 25% in the 56 high-risk patients who were discharged alive [12].[6]

PE mit lebenslangen Folgen

For those patients who survive the immediate in-hospital treatment phase, PE has a potentially life-altering and lifelong effect. They may experience a range of adverse events including major bleeding, recurrent VTE, arterial cardiovascular disease and post-pulmonary embolism syndrome (defined as dyspnoea, exercise intolerance, and diminished quality of life [QoL]), particularly in the first year after diagnosis [1, 13].[6]

ökonomische Belastung für Gesellschaft

PE is associated with a substantial economic burden to society. A multicentre, 12-month, observational study on patients from seven European countries with first-time or recurrent PE, reported that 20.7% of employed patients with PE in DACH countries (Germany, Austria and Switzerland) did not return to work after one year. Further, amongst those who did return to work, 34.8% reported working reduced hours when they first returned, and 22.1% reported that they did not do the same type of work [14]. During the 12-month follow-up, 98.4% of patients had visited a physician and 24.1% of patients were re-hospitalised [14].[7]

Rückgang des Sterblichkeitsrisikos in den letzten 20 Jahren

Age-standardised PE mortality estimates for Austria based on registration data from the World Health Organization (WHO) Mortality Database showed a decrease from 11.1 to 6.1 deaths per 100,000 people between 2002 and 2015 [15].[7]

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[6] **A0005** – What is the burden of disease for patients with the disease or health condition?

[7] **A0006** – What are the consequences of the disease of health condition for the society?

Target population

Klassifizierung der PE: nach AHA und ESC

There are different schemes used to classify PE severity and a patient's risk of mortality. The most commonly used ones are those developed by the American Heart Association (AHA) [16] and the ESC [6].[8]

Hochrisiko-PE und PE mit indermediärem Risiko

The current assessment is on two target populations; high-risk PE and intermediate risk-PE (as defined by the 2019 ESC Guidelines detailed in Table 1-3).

Table 1-3: Definition of high-risk and intermediate-risk PE according to ESC guideline [6] who are eligible for percutaneous catheter-directed treatment.

People with high-risk PE defined by the presence of the following: ■ Haemodynamic instability[a] ■ Clinical parameters of PE severity and/or comorbidity[b] ■ Right ventricular (RV) dysfunction on transthoracic echocardiogram (TTE) or computed tomography pulmonary angiography (CTPA)[c] ■ Elevated cardiac troponin levels[d]
AND who are contraindicated for or failed systemic thrombolytics and/or anticoagulant treatment.
People with intermediate-risk[e] PE defined by the presence of the following: ■ Clinical parameters of PE severity and/or comorbidity[b,f] ■ RV dysfunction on TTE or CTPA[c] ■ Elevated cardiac troponin levels[d]
AND who experience haemodynamic deterioration despite anticoagulation (treatment failure) and who are contraindicated for systemic thrombolysis OR who have failed systemic thrombolysis.

Abbreviations: CTPA – computed tomography pulmonary angiography; PE – pulmonary embolism; RV – right ventricular; TTE – transthoracic echocardiogram.

Notes:

[a] *Including one of the following clinical presentations: cardiac arrest, obstructive shock (systolic blood pressure <90 mmHg or vasopressors required to achieve a blood pressure ≥90 mmHg despite an adequate filling status, in combination with end-organ hypoperfusion), or persistent hypotension (systolic blood pressure <90 mmHg or a systolic blood pressure drop ≥40 mmHg for >15 min, not caused by new-onset arrhythmia, hypovolaemia, or sepsis). Haemodynamic instability, combined with pulmonary embolism confirmation on computed tomography pulmonary angiography and/or evidence of right ventricular dysfunction on transthoracic echocardiogram, is sufficient to classify a patient into the high-risk category. In these cases, neither calculation of the Pulmonary Embolism Severity Index nor measurement of troponins or other cardiac biomarkers is necessary.*

[b] *Pulmonary Embolism Severity Index class III–V or simplified Pulmonary Embolism Severity Index ≥1. Details of these scoring systems can be found the 2019 European Society of Cardiology Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society [6].*

[c] *Prognostically relevant imaging (transthoracic echocardiogram or computed tomography pulmonary angiography) findings in patients with acute pulmonary embolism. Cut-offs and their prognostic value can be found in the 2019 European Society of Cardiology Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society [6].*

[d] *Elevation of further laboratory biomarkers, such as N-terminal pro B-type natriuretic peptide ≥600 ng/L, heart-type fatty acid-binding protein ≥6 ng/mL, or copeptin ≥24 pmol/L, may provide additional prognostic information.*

[e] *The intermediate-risk category is delineated as intermediate-high and intermediate-low. To fulfil the intermediate-high category patients must meet all 3 criteria. To fulfil the intermediate-low category patients must fulfil the first criteria and one or none of the remaining criteria.*

[f] *Signs of right ventricular dysfunction on transthoracic echocardiogram (or computed tomography pulmonary angiography) or elevated cardiac biomarker levels may be present, despite a calculated Pulmonary Embolism Severity Index of I-II or an s Pulmonary Embolism Severity Index of 0. Until the implications of such discrepancies for the management of pulmonary embolism are fully understood, these patients should be classified into the intermediate-risk category.*

[8] **A0007** – What is the target population in this assessment?

AHA Leitlinien verwenden andere Begriffe

leichte Unterschiede in der Definition

It should be noted that the AHA Guidelines use the term massive PE instead of high-risk PE and submassive PE instead of intermediate-risk PE. These terms are used interchangeably in the literature; however, there are slight differences in the definitions between the two [17]. The AHA criterion for submassive PE is right ventricular (RV) strain without hypotension whilst the ESC criteria are broader and include patients who have a simplified Pulmonary Embolism Severity Index (PESI) score ≥ 1, regardless of whether there is RV strain [18]. The ESC then subdivides intermediate-risk PE patients into two groups: 1) intermediate-risk high (patients with both RV dysfunction and RV injury) and 2) intermediate-risk low (patients with only one or neither of these findings) [18]. For the purposes of this report, we have used the terminology as reported in the included studies.[8]

PE Inzidenz: 39-115 pro 100.000 Personen jährlich

VTE presenting as PE or DVT is the third most common acute cardiovascular syndrome, following myocardial infarction and stroke, globally [6]. Epidemiology studies report annual incidence rates for PE between 39 and 115 per 100,000 population [6]. A recently published registry study on 885,806 patients diagnosed with PE in Germany between 2005 and 2015 reported that PE incidence rates increased from 84.3 PE events per 100,000 population in 2005 to 108.7 in 2015 [19].[9]

Anteil der Pts. mit Hochrisiko-PE variierte in den Studien zwischen 0 und 11 %

The PE populations of interest in this assessment are those presenting to hospital assessed as having either high-risk PE as well as being either contraindicated or having failed systemic thrombolysis, and those who have intermediate-risk PE and despite adequate anticoagulation, progress to a state of haemodynamic deterioration. With respect to the proportion of patients with PE who are classified as high-risk, in a recent meta-analysis that included 40,363 patients with acute symptomatic PE, 3.9% (95% CI: 3.7%, 4.1%) had high-risk PE [11]. In the German single-centre study (n=784) previously described, 11.0% of its cohort were classified as high-risk [12]. A retrospective analysis of acute PE patients admitted to the Medical University of Graz, Austria, emergency department during two time periods (March 16th to April 30th 2019, n=22; January 1st to February 15th 2020, n=26) reported the incidence of high-risk and intermediate-high-risk. The percentage of patients with high-risk PE was 0.0% and 3.8% and the percentage with intermediate-high-risk PE was 15.4% and 27.3%, for the two time periods respectively. It should be noted that this data is based on small sample sizes and short time periods [12].[9]

nach ESC und EAPC: derzeit nicht möglich präzise Definition über Thrombolyseversagen bei Hochrisiko-PE zu geben

Of those patients with high-risk PE who are contraindicated for systemic thrombolysis, data from a German multi-centre registry study enrolling 1,001 consecutive patients from 204 centres with high-risk PE reported that 47% of patients had a least one contraindication to thrombolytic treatment [20]. The proportion of high-risk PE patients who failed systemic thrombolysis was reported as 8.2% in one prospective, single-centre registry study of 488 PE patients. Failure to respond within the first 36 hours was prospectively defined as both persistent clinical instability and residual echocardiographic RV dysfunction [21]. However, a clinical consensus statement by the ESC working group and European Association of Percutaneous Cardiovascular Interventions states that "currently it is not possible to provide a precise, evidence-based definition of thrombolysis failure for patients with high-risk PE" [7, 20].[9]

[9] **A0023** – How many people belong to the target population?

20-25 % von akuten PE sind Intermediär-Risiko-PE

In comparison to high-risk PE, intermediate-risk PE is reported to account for 20 to 25% of all acute PE. Among those patients with intermediate-risk PE on anticoagulants alone, 5 to 6.5% deteriorate haemodynamically and progress to high-risk PE [22].[9]

durchschnittliche jährliche Inzidenzrate von 98,6 pro 100.000 in D zwischen 2005 und 2015

In the large registry study (n=885,806) previously described, a total of 450 (0.05%) percutaneous mechanical pulmonary embolectomies and 1,394 (0.2%) surgical embolectomies were performed. The number of percutaneous mechanical pulmonary embolectomy procedures increased from 0.04% in 2005 to 0.06% in 2015, whilst the number of surgical embolectomies remained largely unchanged [19]. In another publication of the same large registry (over a longer time period: 2005-2016; n= 978,094), 1,175 (0.1%) had catheter-directed thrombolysis (CDT) [23].[9]

ca. 100 Aspirationsthrombektomien pro Jahr in Ö

According to the applicant, the estimated annual frequency of utilisation of percutaneous aspiration thrombectomy for PE at their institute was 100 per year and the estimated annual frequency of utilisation in Austria was 100 per year [24].[9]

1.2 Current clinical practice[10]

Current clinical management of pulmonary embolism

Diagnosis

Empfehlungen für Diagnose und Behandlung von Patienten mit akuter PE in ESC/ERS Leitlinie aus 2019 enthalten

Recommendations for the diagnosis and management of patients suspected of having acute PE are provided in the 2019 guideline developed by ESC and the European Respiratory Society (ERS) [6]. Briefly, this guideline documents how patients with suspected PE in the presence or absence of haemodynamic instability should be assessed to confirm or reject a diagnosis of PE, with specific recommendations for various diagnostic tests. The classes of recommendations and levels of evidence used in the guidelines are summarised in Table 1-4.

Table 1-4: Definition of classes of recommendations and levels of evidence in the ESC guidelines

Class of recommendation	Definition
I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
IIb	Usefulness/efficacy is less well established by evidence/opinion
III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.
Levels of evidence	**Definition**
A	Data derived from multiple randomized clinical trials or meta-analyses
B	Data derived from a single randomized trial or large non-randomized studies
C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Source: ESC guidelines [6]

[10] This section addresses the EUnetHTA Core Model® domain CUR.

The specific diagnostic workup used is dependent on the patient's clinical probability of PE, assessed by either clinical judgment or a validated prediction rule (Class I; Level of evidence A).[11]

Messung von Plasma-D-Dimeren oder CTPA-Befund tlw. empfohlen

In an outpatient/emergency department setting, plasma D-dimer measurements are recommended in patients with a low or intermediate clinical probability of PE to exclude a diagnosis (Class IIa; Level of evidence B) and to reduce the need for unnecessary imaging (Class I; Level of evidence A). Normal computed tomography pulmonary angiography (CTPA) results are also sufficient to exclude a PE diagnosis in this (low–intermediate) patient group without further testing (Class I; Level of evidence A). A CTPA finding of segmental or more proximal filling defects in patients with intermediate or high clinical probability is recommended to accept a PE diagnosis without further testing (Class I; Level of evidence B).[11]

andere Tests wie V/Q oder CUS empfohlen

MRA zum Ausschluss einer PE nicht empfohlen

Other tests including ventilation/perfusion (V/Q) scintigraphy and lower-limb compression ultrasonography (CUS) are recommended to reject and accept a PE diagnosis, respectively. In the case of a normal perfusion lung scan (using V/Q scintigraphy) PE diagnosis is rejected (Class I; Level of evidence A) and in the case of demonstration of a proximal DVT (using CUS) PE diagnosis is accepted in patients showing clinical signs of PE (Class I; Level of evidence A). V/Q single-photon emission computed tomography (SPECT) may be considered for PE diagnosis (Class IIb; Level of evidence B) and magnetic resonance angiography (MRA) is not recommended for ruling out PE (Class III; Level of evidence A).[11] Imaging is not performed in pregnant patients (clinical expert, personal communication)

Management

2 Leitlinien identifiziert: ESC/ERS 2019 ESC/EAPC 2022

Two recent guidance documents were identified which provide recommendations on the management of patients diagnosed with PE. They are the 2019 guideline by ESC and ERS for the diagnosis and management of acute PE and the 2022 consensus statement on percutaneous treatment options for acute PE by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function and the European Association of Percutaneous Cardiovascular Interventions [6, 7].[12]

ESC 2019 empfiehlt unverzügliche Antikoagulation als ersten Behandlungsschritt bei hohem und mittlerem PE-Risiko; zahlreiche Kontraindikationen zu beachten; nur als "Rescue" Intervention in Erwägung zu ziehen

In summary, the 2019 ESC guidelines recommend anticoagulation without delay as the initial management step in both high and intermediate-risk PE patients (Class I; Level of evidence C). In addition, in high-risk PE patients for whom systemic thrombolysis is contraindicated or has failed then surgical embolectomy is recommended (Class I; Level of evidence C) whilst percutaneous catheter-directed techniques (e.g. aspiration thrombectomy, other mechanical thrombectomy techniques and thrombolysis) should be considered (Class IIa; Level of evidence C). In intermediate-risk PE patients who are contraindicated or who have failed thrombolysis, the guidelines note that both surgical embolectomy and catheter-directed therapies (as defined above) should be considered (Class IIa; Level of evidence C) [6].[12]

[11] **A0024** – How is the disease or health condition currently diagnosed according to published guidelines and in practice?

[12] **A0025** – How is the disease or health condition currently managed according to published guidelines and in practice?

Essentially, percutaneous catheter-directed techniques, such as aspiration thrombectomy, are considered rescue techniques for high-risk and intermediate-risk patients with haemodynamic instability who have contraindications or have failed systemic thrombolysis. Reasons for contraindications to systemic thrombolysis are listed above in Table 1-2.[12]

1.3 Features of the intervention[13]

perkutane Aspirationsthrombektomie: mechanische kathergestützte Behandlung der PE

The technology being assessed is percutaneous aspiration thrombectomy. This is a type of mechanical catheter-directed treatment for PE. Only those percutaneous aspiration thrombectomy devices with a CE mark that are indicated for treatment of PE were considered in this assessment. At the time of writing, these included the FlowTriever® System (Inari Medical Inc., California, United States of America) and the Indigo® System (Penumbra Inc., California, United States of America).[14] Features of the intervention are provided in Table 1-5.

Table 1-5: Features of the intervention and comparators

	Intervention/Technology	Comparator	Comparator	Comparator
Name	Percutaneous aspiration thrombectomy	Surgical embolectomy	Catheter-directed thrombolysis[a]	Catheter-directed mechanical thrombectomy (without aspiration)[b]
Proprietary name	FlowTriever® System Indigo® System	NA	EKOS™ (Ekosonic Endovascular System)	NA
Manufacturer	Inari Medical Inc., California, USA Penumbra Inc., California, USA	NA	Boston Scientific, Massachusetts, USA)	Numerous
Names in other countries	NA	NA	NA	NA
Device classification	*FlowTriever System* Embolectomy catheters and accesssories (class IIa); ClotTriever Thrombectomy System (class IIa); FlowTriever Retrieval/Aspiration System (class III)	NA	Class II	NA
	Indigo System Indigo Aspiration System (class III)			
UDI	*FlowTriever System* FlowTriever Catheter S=00850291007000; FlowTriever Catheter M=00850291007017; FlowTriever Catheter L=00850291007024; FlowTriever Catheter XL=00850291007055; Triever 20=00850291007079; Triever 24=00850291007185; Triever 16=00850291007130	NA	*Ekos System* 00191506015473; 00191506015466; 00191506015527; 00191506015510; 00191506015503; 00191506015497; 00191506015480; 00191506015459	NA
	Indigo System Aspiration catheters=081454801INDCAT5M; Separators=08145801INDSEP89; Aspiration catheter plus aspiration tubing=081454801INDKIT7M; Aspiration catheter plus Lightening Aspiration Tubing-KITs=081454801INDLITNGSL			

[13] This section addresses the EUnetHTA Core Model® Domain TEC.

[14] **B0001** – What is the technology and the comparator(s)?

Source: FlowTriever and Indigo Systems UDI and class information provided by the manufacturers. Ekos System UDI [25] and Class information [26] were sourced online.

Abbreviations: NA – not applicable; UDI – Unique Device Identification; USA – United States of America.

Notes:

[a] *There are several CDT devices on the market with CE certification. The only one that currently has an indication for use in the pulmonary arteries and that was used in the studies included in the assessment is ultrasound accelerated thrombolysis with EkoSonic Endovascular System catheters (Boston, Scientific) [27, 28].*

[b] *Currently there are several mechanical thrombectomy devices without aspiration that have a CE mark but none that are indicated for use in the pulmonary arteries [29].*

Komparatoren: Katheterbasierte Thrombolyse, chirurgische Thrombektomie etc.

The comparator technologies in this assessment include other catheter-directed treatments including CDT, with or without adjunct interventions such as ultrasound, other mechanical catheter-directed thrombectomy techniques (not involving aspiration) and surgical embolectomy (Table 1-5).[14]

Ziel aller Behandlungsmodalitäten ist die rasche Wiederherstellung des Blutflusses

In the two populations of interest in this assessment, the primary aim of percutaneous aspiration thrombectomy and the comparator procedures is to reduce acute PE-related mortality by rapidly restoring blood flow (referred to as reperfusion), thereby reversing haemodynamic compromise and gas exchange abnormalities [18]. Depending on its safety and efficacy, percutaneous aspiration thrombectomy could potentially replace other catheter-directed mechanical thrombectomy techniques and surgical embolectomy or be an alternative treatment in these two populations.[14]

Intervention

Percutaneous aspiration thrombectomy

2 Produkte mit CE Kennzeichnung:

FlowTriever System

Flowtriever®:

Katheter-Zugang über die Oberschenkelvene und Navigation durch die rechte Herzseite mit einem sogenannten Piqtail- oder Swan-Ganz Katheter

The FlowTriever Gen 1 Aspiration System consists of three parts: the flow restoration catheter, a long catheter which is made up of three self-expanding nitinol disks to mechanically disrupt the thrombus if necessary (available in small, medium, large and extra-large sizes); the aspiration guide catheter, which comes in 16, 20 or 24F and the retraction aspirator device. It also requires an introducer sheath [30]. The FlowSaver System, designed to be used with the FlowTriever System, reduces blood loss by filtering aspirated thrombi from blood for reinfusion back to the patient. It includes a 40 micron filtration system, clot reservoir and 60 cc collection syringe [31]. Inari Medical Inc. reports that advancements have been made to the Triever20 and Triever24 aspiration catheters to enhance trackability and support, aspiration flow rate and ease of use. The Triever24 is said to have –20cc/sec increased aspiration compared with the previous generation to maximise thrombus removal [31]. A FlowTriever 2 System exists but this is not indicated for the pulmonary arteries [31].[14]

Entfernung von Thromben aus Lungenarterie durch Aspiration und mithilfe mechanischer Komponenten unter örtlicher Betäubung

Percutaneous aspiration thrombectomy, irrespective of the device used, involves PA catheterisation, a procedure which involves guiding a catheter (thin flexible tube) through a blood vessel into the right side of the heart towards the PA [32]. It is usually performed under local anaesthesia [33]. The initial step in the procedure involves accessing the vein under ultrasound guidance. In the percutaneous aspiration thrombectomy procedure it is typically the femoral vein that is accessed [33]. A pigtail or balloon tipped catheter is then used to navigate through the right side of the heart. This is then exchanged for a more supportive wire (e.g. Amplatz). The access site is then dilated and

the FlowTriever catheter is placed over the wire so the distal tip is positioned just proximal to the thrombus where the nitinol disks are deployed if required. The disks and thrombus are then retracted and removed through the aspiration catheter by negative pressure from the 60 ml syringe. The resulting blood and thrombus mixture is filtered through the FlowSaver device for reinfusion back to the patient via the sidearm of the femoral venous sheath. When the thrombus has been removed the device and sheath are removed and the wound closed via a preclosure technique, figure-eight suture or manual compression haemostasis [34].[14]

Indigo System

Indigo Aspirationssystem: vgl. Zugang wie oben

The Indigo System consists of a flexible big lumen catheter, aspiration catheter (available in 7, 8 and 12F sizes) with a canister and a tubing set to connect the canister with the catheter [35]. The 12F catheter is reported to be the one most frequently used in the treatment of PE. The canister is mounted on the Penumbra ENGINE that generates a continuous vacuum at –741.68 mmHg. When needed, a separator is used to macerate the thrombus into smaller pieces to aid removal [34].[14]

ebenfalls u. a. mit einem Pigqtail-Katheter

Similar to the FlowTriever procedure, the femoral vein is accessed under ultrasound guidance and then the right heart is traversed using either a pigtail or Swan-Ganz catheter. The catheter is exchanged over a wire for a catheter that is used to select the branch of the PA that is to be treated. Following removal of the catheter and initial sheath a 12F long sheath is advanced into either the main or right/left PA. Through this sheath the aspiration catheter is advanced and aspiration activated. If required, the separator device is advanced through the catheter to macerate the thrombus into smaller pieces [34]. When the thrombus has been removed the device and sheath are removed and the wound closed via a preclosure technique, figure-eight suture or manual compression haemostasis [34].[14]

Entfernung der Thromben ebenfalls durch Aspiration und mechanische Komponente

A recent advancement in this device is the development of the Indigo Aspiration System with Lightning 7 and Lightning 12 mechanical thrombectomy technologies. This computer-aided clot detection technology, which is CE marked, is used in conjunction with the 7F CAT7 and 12F CAT12 aspiration catheters [36]. The microprocessor is said to monitor blood flow in real time through pressure sensors in the aspiration tubing. It is claimed the system can distinguish between a clot and blood by monitoring fluid characteristics through pressure differentials. When the system is in a patent blood vessel the computer shuts the aspiration valve within milliseconds, thereby reducing blood loss [37-39]. The new CAT12 aspiration catheter is reported to have significantly higher luminal area and improved torqueability, increasing aspiration efficiency [37].[14]

Comparators

Unterschied zu Komparatoren: Art, wie die Blutgerinnsel in der Lungenarterie entfernt werden:

The comparator procedures to percutaneous aspiration thrombectomy include CDT (with or without adjunct interventions), catheter-directed mechanical thrombectomy (not involving aspiration) and surgical embolectomy. It should be noted that as for percutaneous aspiration thrombectomy, CDT and catheter-directed mechanical thrombectomy not involving aspiration are minimally invasive techniques that have similar procedural details – they all require pulmonary artery catheterisation. The difference between these technologies is the type of catheter and the mechanism used to treat the embolism.[14]

CDT, with or without adjunct interventions

CDT is the delivery of thrombolytic drugs directly at the thrombus site by way of specialised catheters to break down thrombi and improve blood flow. It uses lower doses of thrombolytic agents compared to intravenous systemic administration and thus is proposed to reduce the risk of bleeding [40].[14]

etwa Katheterbasierte Thrombolyse (CDT): lokale Auflösung (Lyse) statt Entfernung

Ultrasound-facilitated thrombolysis, which is reported to be the most studied of catheter-thrombolysis techniques, uses high-frequency, low power ultrasound energy, designed to loosen the fibrin strands and enhance delivery of the thrombolytic drug into the thrombus [40].[14]

Catheter-directed mechanical thrombectomy not involving aspiration

Catheter-directed mechanical thrombectomy techniques unlike CDT, do not use drugs but a range of other techniques to restore blood flow. Aspiration, the focus of this assessment, is one of the techniques. Other, comparator mechanical techniques include using rotating catheters to break up the clot and arterial balloons that are inflated to extract the clot [41]. These are sometimes used in conjunction with thrombolysis.[14]

andere katheterbasierte mechanische Thrombektomien

Surgical thrombectomy

During a surgical thrombectomy patients undergo a median sternotomy and are placed on cardiopulmonary bypass. The pulmonary artery is opened longitudinally, distal to the pulmonic valve, to a length of approximately 5 cm. Sponge forceps are used to grasp and remove visible clots. If thrombi extend to the peripheral pulmonary arteries, an additional incision to the right main pulmonary artery is performed [42, 43].[14]

chirurgischen Thrombektomie mittels chirurgischer Durchtrennung des Brustbeins und kardiopulmonalem Bypass

CE Mark and market authorisation

At the time of writing this assessment the only CE marked percutaneous aspiration devices which are indicated for use in the pulmonary arteries, as noted by the manufacturers, were the FlowTriever System (approved December 2020) and the Indigo System (approved January 2022). Both devices have 510(k) approval with the United States Food and Drug Administration (FDA). The FlowTriever System received 510(k) approval (K180466) for use in the peripheral vasculature and for the treatment of pulmonary emboli in May 2018 [44], whilst the Indigo System received 510(k) approval (K192833) for use in removal of thrombi from vessels of the peripheral arterial and venous systems and for the treatment of pulmonary emboli in December 2019 [45].

CE-Kennzeichnung nur bei FlowTriever und Indigo

The claimed benefit of percutaneous aspiration thrombectomy for PE is that it is less invasive than a surgical thrombectomy which requires a sternotomy (where the surgeon cuts through the breastbone of a patient) and a cardiopulmonary bypass. Compared with CDT, it can relieve haemodynamic compromise without the need for thrombolytics, resulting in a potentially quicker clot removal and minimising the risk of serious bleeding [37]. It is also claimed that there is a reduction in time spent in the intensive care unit (ICU) with percutaneous aspiration thrombectomy [30]. It should be noted; however, that thrombectomy devices are uniformly larger than infusion catheters and the wires and catheters needed to deliver these devices are often stiffer than those used for infusion catheter placement; increasing the risk of trauma to the pulmonary vasculature or cardiac structures [18].[15]

vermeintliche Vorteile: weniger invasiv, schneller, geringeres Risiko schwerer Blutungen

allerdings größer und steifer als Infusionskatheter

Phase of development and implementation

Percutaneous aspiration thrombectomy

FlowTriever in 17 europäischen Ländern erhätlich

FlowTriever by Inari Medical Inc. is commercially available in the following European countries: Germany, the United Kingdom, Austria, Switzerland, the Netherlands, Belgium, Greece, Italy, Denmark, Sweden, Norway, Finland, Slovenia, Spain, Portugal, Ireland and France (information provided by the manufacturer).[15]

Indigo in 6 europäischen Ländern erhältlich

The Indigo System by Penumbra is commercially available in the following European countries: Ireland, Germany, Italy, Poland, Spain and France (information provided by the manufacturer).[15]

CDT

CDT: 2 andere Systeme für PE geeignet

There are several CDT systems on the market with a CE mark. Only two were identified that were indicated for PE (EkoSonic™ Endovascular System, Boston Scientific; Viper, Invamed) [29].[15]

Catheter-directed mechanical thrombectomy not involving aspiration

andere mechanische Geräte nicht für PE indiziert

There are several catheter-directed mechanical thrombectomy devices with a CE mark, none were identified that were indicated for PE, other than those involving aspiration [29]. However, it is possible these devices are being used off-label to treat PE.[15]

Surgical embolectomy

Not applicable.[15]

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

Catheter-directed technologies

Durchführung in Tertiärkliniken mit Katheterlabor und Bildgebungsgeräten

Percutaneous aspiration thrombectomy, catheter-directed mechanical thrombectomy (not involving aspiration) and CDT, are commonly referred to as catheter-directed technologies for the treatment of PE. Catheter-directed technologies are performed in tertiary hospitals that have a catheterisation laboratory equipped with specialised imaging equipment.[16]

durch v. a. interventionelle Radiolog*innen/ Kardiolog*innen

These procedures are usually administered by an Interventional radiologist or cardiologist. A range of other personnel are required including:

- Interventional neurosurgeon
- Interventional cardiologist
- Endovascular nurse and technician
- Anaesthesiologist [46].[17]

[15] **B0003** – What is the phase of development and implementation of the technology and the comparator(s)?

[16] **B0008** – What kind of special premises are needed to use the technology and the comparator(s)?

[17] **B0004** – Who administers the technology and the comparators and in what context and level of care are they provided?

Due to the risk of complications during CDT, close monitoring during thrombolytic infusion is required. Most hospitals require intensive care unit monitoring during infusion [47].[16]

Überwachung auf Intensivstation meistens notwendig

Equipment required for catheter-directed technologies include:

besondere Ausrüstung für kathetergeführte Technologie benötigt

- An introducer needle or sheath
- Multiple-sized guidewires (used to gain access to the vessel, insert sheaths and deliver therapeutic devices)
- Closure compression device
- For CDT an infusion system for the pharmacotherapies
- For catheter-directed mechanical thrombectomy the catheter device used to breakdown or remove the embolism [47].[18]

In addition, healthcare professionals should use proper sterile techniques, including sterile drapes, gloves and gowns [47].[18]

angemessene Steriltechniken notwendig

Surgical embolectomy

Surgical embolectomies are performed by Cardiothoracic Surgeons in conjunction with anaesthetists and specialised nursing staff in tertiary hospitals that perform cardiac surgery.[17]

Embolektomie von Herz-Thorax Chirurg*innen durchgeführt

For surgical embolectomy standard surgical equipment is required including scalpels, forceps, sutures, cannulae and clamps as well a machine for performing a cardiopulmonary bypass [48]. In addition, a balloon catheter and stent (to keep the blood vessel open) may be used [49].[18]

chirurgische Standardausrüstung erforderlich

Investments and tools required

The only investments required for this technology are the aspiration systems. Most large tertiary hospitals would have catheterisation laboratories with the associated imaging equipment required to perform this procedure.

As these devices have FDA approval in the United States of America, records of adverse events or incidents are required to be reported in the Manufacturer and User Facility Device Experience (MAUDE) database by manufacturers, importers and device user facilities.[19]

Regulatory & reimbursement status

Percutaneous aspiration thrombectomy for PE is currently included in the Austrian hospital benefit catalogue as new examination and treatment method (XN220) but is not a fully reimbursable service in the Austrian health care system.[20]

XN220 als neue Methode, aber nicht voll erstattungsfähig

[18] **B0009** – What supplies are needed to use the technology and the comparator(s)?

[19] **B0010** – What kind of data/records and/or registry is needed to monitor the use of percutaneous aspiration thrombectomy and catheter-directed thrombolysis, catheter-directed mechanical thrombectomy (not involving aspiration) or surgical embolectomy?

[20] **A0021** – What is the reimbursement status of the technology?

2 Objectives and Scope

2.1 PICO question

PIKO-Frage

Is percutaneous aspiration thrombectomy in comparison to CDT, catheter-directed mechanical thrombectomy (not involving aspiration) or surgical embolectomy more or as effective and safe in treating intermediate-risk and high-risk PE with regards to PE and device-related deaths and serious adverse events including major bleeding?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarised in Table 2-1.

Table 2-1: Inclusion criteria

Population	Patients with pulmonary embolism (PE) whose severity and risk of early (in-hospital or 30 day) death is either: 1. High-risk defined in the presence of the following: ■ Haemodynamic instability[a] ■ Clinical parameters of PE severity and/or comorbidity[b] ■ Right ventricular (RV) dysfunction on transthoracic echocardiogram (TTE) or computed tomography pulmonary angiography (CTPA)[c] ■ Elevated cardiac troponin levels[d] 2. Intermediate-risk[e] defined in the presence of the following: ■ Clinical parameters of PE severity and/or comorbidity[b,f] ■ RV dysfunction on TTE or CTPA[c] ■ Elevated cardiac troponin levels[d] And, Are contraindicated for or failed systemic thrombolytics and/or anticoagulant treatment. **ICD-11 Code:** BB00 Pulmonary thromboembolism (& specific anatomy codes: XA09J9 Pulmonary artery; XA3713 Pulmonary trunk; XA8FY4 Pulmonary vein; XA2ZV2 Inferior pulmonary vein; XA1WN5 Left pulmonary vein; XA9K75 Superior pulmonary vein) [4]. **Rationale:** Informed by information provided by the submitting hospital and clinical practice guideline [6].
Intervention	Percutaneous aspiration thrombectomy **Alternative terms:** aspiration embolectomy/thromboembolectomy; mechanical aspiration thrombectomy/embolectomy; thrombus aspiration; catheter-based aspiration **Product names:** ■ FlowTriever® System, Inari Medical, California, USA (CE mark) ■ Indigo® Aspiration System, Penumbra Inc., California, USA (CE mark)
Control	Guideline-directed standard care: ■ Catheter-directed thrombolysis (with or without adjunct interventions such as ultrasound (for acceleration of thrombolytic effects) ■ Catheter-directed mechanical thrombectomy not involving aspiration ■ Surgical embolectomy **Rationale:** Informed by clinical practice guideline [7].

Outcomes (not limited to)	
Efficacy	**Clinical end points** ■ PE-related deaths ■ Haemodynamic decompensation ■ Chronic thromboembolic pulmonary hypertension ■ PE recurrence **Patient-centric end points** ■ 6-minute walk distance ■ Generic quality of life (QoL) (Short Form-36 physical component score) ■ Disease-specific QoL (Pulmonary Embolism-QoL score) ■ New York Heart Association class >1 ■ Impaired cardiopulmonary exercise test (maximum oxygen consumption <80%) ■ Length of stay **Rationale:** Informed by American Heart Association Scientific Statement [18].
Safety	**Any major or minor adverse event including, but not limited to:** ■ Major bleeding ■ Device-related death ■ Treatment-related clinical deterioration ■ Treatment-related pulmonary vascular injury ■ Treatment-related cardiac injury **Rationale:** Informed by 510k clinical trial (FLARE – FlowTriever Pulmonary Embolectomy Clinical Study) [50].
Study design	
Efficacy	■ Well conducted systematic reviews ■ Randomised controlled trials (RCTs) ■ Non-randomised comparative (NRC) studies ■ Case series[g] A hierarchical approach to study selection will be taken, with recent, well constructed systematic reviews selected preferentially. If necessary, systematic reviews will be updated with primary studies published subsequent to the review search date. If no applicable systematic reviews are available, then RCTs will be included. If no RCTs are available, then NRC studies will be included. If no NRC studies are available, then case series will be included. **Excluded:** narrative reviews, letters to the editor and author responses, case reports, conference abstracts.
Safety	■ Well conducted systematic reviews ■ RCTs ■ NRC studies ■ Case series[g] A hierarchical approach to study selection will be taken, with recent, well constructed systematic reviews selected preferentially. If necessary, systematic reviews will be updated with primary studies published subsequent to the review search date. If no applicable systematic reviews are available, then RCTs will be included. If no RCTs are available, then NRC studies will be included. If no NRC studies are available, then case series will be included. **Excluded:** narrative reviews, letters to the editor and author responses, case reports, conference abstracts.

Abbreviations: BP – blood pressure; CTPA – computed tomography pulmonary angiography; ICD – International Classification of Diseases; NRC – non-randomised comparative; PE – pulmonary embolism; PESI – Pulmonary Embolism Severity Index; QoL – quality of life; RCT – randomised controlled trial; RV – right ventricular; sPESI – simplified Pulmonary Embolism Severity Index; TTE – transthoracic echocardiogram; USA – United States of America.

Notes:

[a] *Including one of the following clinical presentations: cardiac arrest, obstructive shock (systolic blood pressure <90 mmHg or vasopressors required to achieve a blood pressure ≥90 mmHg despite an adequate filling status, in combination with end-organ hypoperfusion), or persistent hypotension (systolic blood pressure <90 mmHg or a systolic blood pressure drop ≥40 mmHg for >15 min, not caused by new-onset arrhythmia, hypovolaemia, or sepsis).*
Haemodynamic instability, combined with pulmonary embolism confirmation on computed tomography pulmonary angiography and/or evidence of right ventricular dysfunction on transthoracic echocardiogram, is sufficient to classify a patient into the high-risk category. In these cases, neither calculation of the Pulmonary Embolism Severity Index nor measurement of troponins or other cardiac biomarkers is necessary.

[b] *Pulmonary Embolism Severity Index class III–V or simplified Pulmonary Embolism Severity Index ≥1. Details of these scoring systems can be found the 2019 European Society of Cardiology Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society [6].*

[c] *Prognostically relevant imaging (transthoracic echocardiogram or computed tomography pulmonary angiography) findings in patients with acute pulmonary embolism. Cut-offs and their prognostic value can be found in the 2019 European Society of Cardiology Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society [6].*

[d] *Elevation of further laboratory biomarkers, such as N-terminal pro B-type natriuretic peptide ≥600 ng/L, heart-type fatty acid-binding protein ≥6 ng/mL, or copeptin ≥24 pmol/L, may provide additional prognostic information.*

[e] *The intermediate-risk category is delineated as intermediate-high and intermediate-low. To fulfil the intermediate-high category patients must meet all three criteria. To fulfil the intermediate-low category patients must fulfil the first criteria and one or none of the remaining criteria.*

[f] *Signs of right ventricular dysfunction on transthoracic echocardiogram (or computed tomography pulmonary angiography) or elevated cardiac biomarker levels may be present, despite a calculated Pulmonary Embolism Severity Index of I-II or an s Pulmonary Embolism Severity Index of 0. Until the implications of such discrepancies for the management of pulmonary embolism are fully understood, these patients should be classified into the intermediate-risk category.*

[g] *The decision to include only prospective single-arm studies with greater than or equal to 20 patients was made a posteriori.*

3 Methods

3.1 Research questions

Assessment elements from the European Network for Health Technology Assessment (EUnetHTA) Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment.

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on the 09.12.2022 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- International Network of Agencies for Health Technology Assessment (INAHTA)

The systematic search was limited to articles published in English or German. After deduplication, overall 979 citations were included. The specific search strategy employed can be found in the Appendix.

Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 09.12.2022 resulting in 2 relevant hits (ongoing trials not included in evidence base, see Table A-7).

insgesamt 979 Publikationen identifiziert

Manufacturers of the two aspiration thrombectomy devices included in this assessment (FlowTriever and Indigo Systems) submitted 87 publications of which no new citations were identified.

By hand-search, no additional citations were found, resulting in a total of 979 hits.

3.2.2 Flow chart of study selection

Literaturauswahl

Overall 1,337 hits were identified. Title and abstract screen was undertaken by two independent researchers (DF and MV). Full text review was also undertaken by two independent researchers (DF or MV and GG) and in case of disagreement a third researcher (NM) was involved to resolve the differences.

No systematic reviews or RCTs meeting the PICO criteria were identified, limiting inclusion to lower levels of evidence. Due to the number of single-arm studies available, only those with a prospective study design and ≥20 patients were eligible for inclusion.

The selection process is displayed in Figure 3-1.

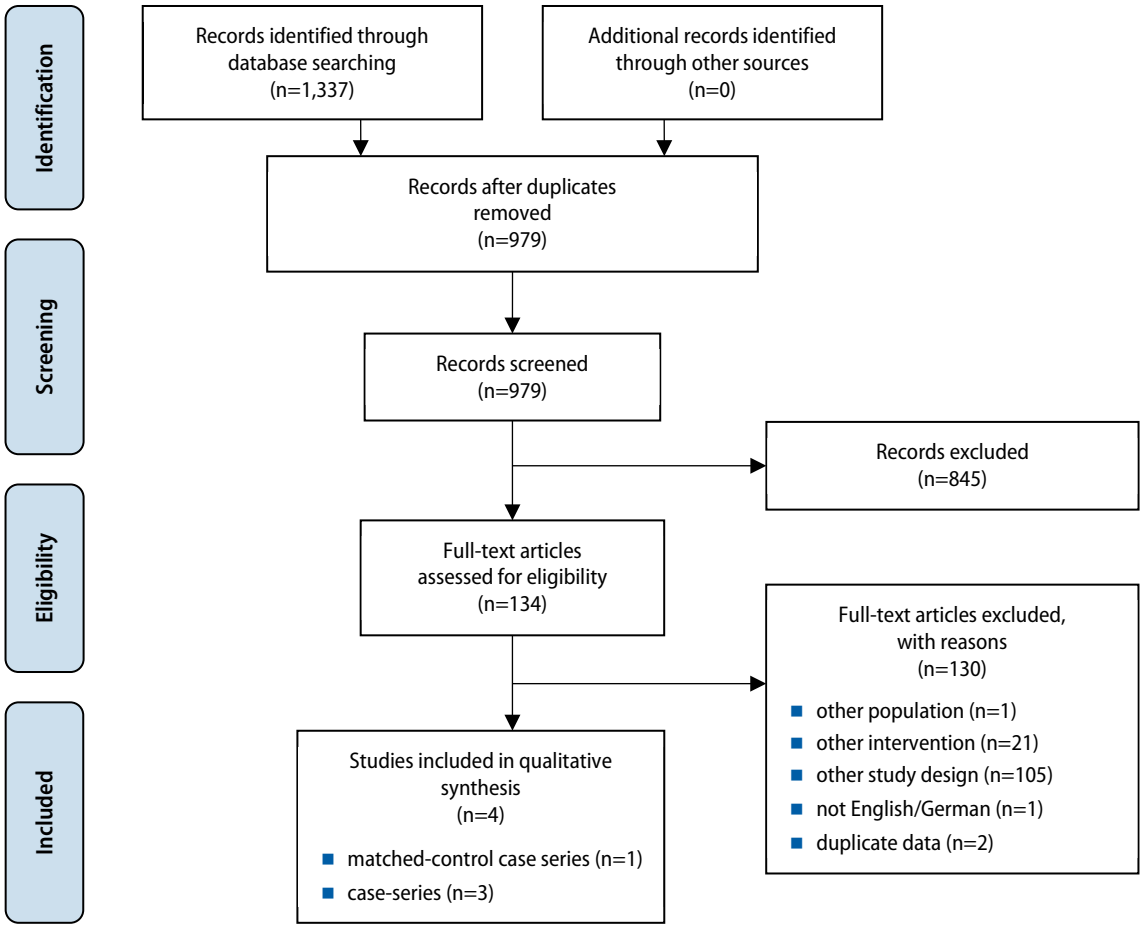

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

3.2.3 Analysis

Risk of Bias: ROBINS-I und IHE-20 Checkliste

Quality was assessed using the ROBINS-I (Risk Of Bias In Non-randomised Studies Of Interventions) tool (non-randomised comparative (NRC) studies) [51] or the IHE (Institute of Health Economics) Quality Appraisal Checklist (single-arm studies) [52]. Results of the appraisals are presented in Table A-3 and Table A-4 in the Appendix.

The following criteria was applied to determine the overall risk of bias (RoB) using the IHE Checklist: studies which fulfilled all of the criteria considered important for single-arm studies investigating percutaneous aspiration thrombectomy (by the report authors) were considered to be of low RoB, studies which failed to meet one of these criteria were considered to be of moderate RoB and studies which failed to meet two or more of the criteria were considered to be at high RoB. The important criteria were, consecutive recruitment (item 4 of the Checklist), similar disease at entry into the study (item 7) and clearly described interventions and co-interventions (items 8 and 9).

4-Augen-Prinzip bei allen Arbeitsschritten

One reviewer (DF or MV) systematically extracted relevant data from the included studies into data extraction tables. A second reviewer (GG) cross-checked the data extraction tables for accuracy. One reviewer (MV) analysed the certainty of the data using GRADE (Grading of Recommendations, Assessment, Development and Evaluations) [53], and two second reviewers (DF, GG) validated the analysis. GRADE assessment was unable to be undertaken for haemodynamic decompensation as it was not reported. GRADE assessments were undertaken for the following outcomes: all-cause mortality, mean change in pulmonary artery pressure (PAP), procedure-related deaths, major bleeding, treatment-related cardiac injury, treatment-related vascular injury and treatment-related clinical deterioration. Risk of bias (RoB) was conducted by two reviewers (DF and MV) and checked by another reviewer (GG); differences were settled via consensus.

3.2.4 Synthesis

qualitative Synthese der Evidenz

The research questions were answered in plain text format and tabular format, with reference to GRADE evidence tables (where applicable) that are included in Appendix.

Zusammenfassung der Ergebnisse mit GRADE

Unless otherwise stated results are reported as mean ± standard deviation (SD).

4 Results: Clinical effectiveness and Safety

4.1 Outcomes

4.1.1 Outcomes effectiveness

wesentliche Endpunkte:

PE-bezogener Tod, pulmonale Hypertonie, hämodynamische Dekompensation

The following outcomes were defined as *critical* to derive a recommendation:

- PE-related death (autopsy-confirmed PE in the absence of another more likely cause of death, objectively confirmed PE before death in the absence of another more likely cause of death or PE is not objectively confirmed, but is most likely the main cause of death) [54]
- Haemodynamic decompensation (sustained hypotension (i.e. systolic BP < 80-90 mmHg despite increasing doses of vasopressors and requiring mechanical haemodynamic support (i.e. intra-aortic balloon pump or left ventricular assist devices) [55].
- Chronic thromboembolic pulmonary hypertension (defined as mean PA pressure ≥25 mmHg with a pulmonary capillary wedge pressure <15 mmHg and at least one segmental perfusion defect detected by V/Q scan, computed tomography angiography or pulmonary angiography after 3 months of effective anticoagulation) [56].
- PE recurrence (diagnosis of a recurrent embolism anytime during the follow-up period)

Note: PE-related death was changed to all-cause mortality which included deaths due to any cause. If the authors noted that the deaths were PE-related this was reported.

4.1.2 Outcomes safety

und schwerwiegende Nebenwirkungen

schwere Blutungen

Behandlungs-induzierte Verletzungen

etc.

The following outcomes were defined as *critical* to derive a recommendation:

- Major bleeding (the AHA recommends the use of validated bleeding assessment tools for non-intracranial major bleeding including the Bleeding Academic Research Consortium (BARC), the International Society of Thrombosis and Haemostasis (ISTH) or the Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO)) [18]
- Device-related death
- Treatment-related clinical deterioration (no validated definition of clinical deterioration in a PE setting could be identified. Previously published studies define it as respiratory failure, cardiac arrest, new dysrhythmia, sustained hypotension and rescue reperfusion intervention) [57, 58]
- Treatment-related pulmonary vascular injury
- Treatment-related cardiac injury

Note: Device-related death was changed to procedure-related deaths which included any death reported by the authors to be device or procedure-related. Where the authors stated the death was caused by the device this was noted.

4.2 Included studies

4.2.1 Included studies effectiveness

Wirksamkeit:

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table A-5.

keine Evidenz zu Hochrisiko PE Pts.

Population 1 – People with high-risk PE and contraindications for or failed systemic thrombolysis.

No studies were identified that compared percutaneous aspiration thrombectomy to the comparator procedures in high-risk PE patients.

Patient*innen mit intermediärem Risiko

Population 2 – People with intermediate-risk PE experiencing haemodynamic instability despite being on anticoagulants and contraindicated for or failed systemic thrombolysis.

Study characteristics

1 retrospektive Vergleichsstudie

Vergleich mittels Propensity-Score-Matching, 52 Patient*innen

One small, single-centre, retrospective non-randomised study that compared 26 percutaneous aspiration thrombectomy patients with 26 CDT patients was identified [59]. The study included consecutive patients who underwent endovascular therapy for acute PE between December 2009 and May 2020 in a single community hospital system in the United States of America (USA). It includes a small proportion of high-risk PE patients (2/52 patients, 4%). Patients were excluded if they had received systemic thrombolysis before the procedure. It is not reported that the intermediate-risk patients experienced haemodynamic instability. In addition, none of the patients in CDT group and only 4/26 (15.4%) of patients in the percutaneous aspiration thrombectomy group had a contraindication to thrombolysis (p=0.100). The patients were propensity matched using the PESI [60] which encompasses multiple demographic, comorbidity and physiologic factors and PE severity before comparisons between the groups were made. No details were provided regarding the study sponsor; however, it is reported that one of the authors receives research grants from Inari Medical, the manufacturer of the FlowTriever System.

FlowTriever (n=26) vs. CDT (n=26)

Patients in the percutaneous aspiration thrombectomy group were treated with the FlowTriever System, mainly using the 20F aspiration catheter (22/26 patients, 85%). Several types of infusion catheters were used to treat the patients in the CDT group including a 5-F AP2 infusion angled pigtail catheter (Cook Medical), UniFuse multiple side-hole infusion catheters (AngioDynamics, Inc.) and ultrasound accelerated thrombolysis using the EkoSonic Endovascular System. At the time of diagnosis of PE, therapeutic dose anticoagulation was initiated according to physician preference in all but one patient. The type of anticoagulant used, which was not included in the propensity score matching, significantly differed between the treatments ($p < 0.001$). More of the percutaneous aspiration thrombectomy group were administered low-molecular weight heparin compared with the CDT group (73% vs 15.4%, respectively). Conversely, more unfractionated heparin was used in the CDT group than in the percutaneous aspiration thrombectomy group (85% vs 23%, respectively). The study's risk of bias was deemed as critical owing to concerns regarding bias of participants into the study (Table A-3).

Patient characteristics

Eligible patients were those presenting for treatmetnt within 14 days of symptom onset who were found of have acute massive or submassive PE according to the following: acute massive PE was defined by sustained hypotension, profound brachycardia or pulselessness and submassive PE was defined by a RV/left ventricle ratio >0.9 or biochemical marker evidence of myocardial necrosis. Mean patient age at baseline was not significantly different between the treatment groups. Patients treated with aspiration thrombectomy had a mean age of 60.2 years and patients treated with CDT had a mean age of 59.7 years. Males made up 46% of included patients in both treatment groups.

Patient*innen mit akuter massiver oder submassiver PE

Ø Alter: 60,2 vs. 59,7 J.

46 % männlich

4.2.2 Additional included studies safety

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table A-5.

Sicherheit:

Population 1 – People with high-risk PE and contraindications for or failed systemic thrombolysis.

No studies were identified on the use of percutaneous aspiration thrombectomy in high-risk PE patients.

Population 2 – People with intermediate-risk PE experiencing haemodynamic instability despite being on anticoagulants and contraindicated for or failed systemic thrombolysis.

Study characteristics

Three single-arm prospective studies (all multicentre) were included in the assessment for the evaluation of safety [33, 50, 61]. Of these, two used the FlowTriever System [50] [33] and one used the Indigo System [61]. All three studies were sponsored by the device manufacturers and all had a maximum follow-up of 30 days. One was a large FlowTriever registry of 800 patients undergoing percutaneous aspiration, including a small percentage of patients with high-risk PE (63/797, 7.9%), enrolled from 50 sites in the USA [33]. In the second study of 119 patients (Indigo System) enrolled from 22 sites in the USA, all but one patient had intermediate-risk PE [61], and in the third study of 104 patients (FlowTriever System) enrolled from 18 sites in the USA, all had intermediate-risk PE [50].

3 einarmige Beobachtungsstudien

104-800 Patient*innen

max. Nachbeobachtungszeit: 30 T.

In the two smaller studies consisting mostly of intermediate-risk patients, haemodynamic instability was an exclusion criterion in one [50] whilst the other did not mention it [61]. One study reported that none of the patients had previously failed thrombolysis [50]. Neither of the two studies reported whether the patients were contraindicated for thrombolysis. However, one reported that 1.7% of patients received intraprocedural tissue plasminogen activator (tPA) (thrombolytic drug) [61] and in the other study 1.9% of patients received thrombolytics immediately following the thrombectomy (type not reported). The use of anticoagulants pre-procedure was only reported by one study that noted 97% of patients were on anticoagulants [50]. The other study did not mention anticoagulant use [61]. Both studies were deemed to be at moderate risk of bias as it was unclear if patients were consecutively recruited and there was a lack of detail regarding co-interventions and the procedure.

mit vor allem intermediärem Risiko

hämodynamische Instabilität als Ausschlusskriterium in 2 Studien

bei 1/3 relative oder absolute Kontraindikation für Thrombolytika

Vielzahl von unterschiedlichen Antikoagulanzien

With respect to the large FlowTriever registry study containing mixed high- and intermediate-risk PE patients, some had failed prior PE therapy (40/771, 5.2%) (either anticoagulation, systemic thrombolysis, CDT or mechanical thrombectomy). Approximately one third of patients had either a relative or absolute contraindication to thrombolytics (256/797, 32.1%). A small percentage of patients received adjunctive PE therapy including either CDT (18/799, 2.3%) or other mechanical thrombectomy (1/799, 0.1%). A variety of different anticoagulants were prescribed at 48-hour follow-up including a new/direct anticoagulant in 55.3% of patients, a vitamin K antagonist in 5.3% of patients, low molecular weight heparin in 14.3% of patients, unfractionated heparin in 30.0% of patients and other anticoagulant agents in 2.1% of patients [33]. The study was deemed to have a high risk of bias owing to the lack of consecutive recruitment, patients having different levels of disease status and lack of details regarding the co-interventions.

Patient characteristics

Ø Alter: 55,6- 61,2

In one single-arm study using the FlowTriever System, included patients were aged 18-75 years with symptomatic proximal PE documented by computed tomography (CT). These patients presented within 14 days of symptom onset and were haemodynamically stable with no vasopressor requirement, heart rate <130 beats/minute, systolic blood pressure ≥90 mm Hg at baseline assessment, and site-reported RV/left ventricle ratio (on the basis of CT) of ≥0.9. Mean age was 55.6 years and 54% of patients were male.[50]

In the other single-arm study using the FlowTriever System, included patients were aged ≥18 years with acute intermediate- or high-risk PE (per ESC guidelines) who underwent mechanical thrombectomy at the discretion of the treating physician or local PE response team. Mean patient age was 61.2 years and 54% of patients were male.[33]

In the single-arm study using the Indigo System, included patients were aged ≥18 years with signs and symptoms of acute PE for a maximum of 14 days, CT angiography evidence of PE, systolic blood pressure ≥90 mmHg and evidence of a dilated RV (defined by a RV/left ventricle ratio > 0.9). Mean age was 59.0 years and 55% of patient were male.[61]

4.3 Results

Mortality

All-cause 30-day mortality

In the matched-control case series using the FlowTriever System, all-cause mortality at 30 days was 8% (2/26 patients) in the percutaneous aspiration thrombectomy treatment and 0% (0/26 patients) in the CDT treatment (p= 0.50) [59]. Both deaths were classified as procedure related.[21, 22]

Mortalität in 1 NRCT (n=52): kein stat. signifikanter Unterschied

Morbidity

Haemodynamic decompensation

No evidence was found on how percutaneous aspiration thrombectomy affects haemodynamic decompensation.

Chronic thromboembolic pulmonary hypertension

No evidence was found on how percutaneous aspiration thrombectomy affects chronic thromboembolic pulmonary hypertension.

Morbidität in 1 NRCT (n=52): keine stat. signifikanten Gruppenunterschiede in pulmonaler Hypertonie

PE recurrence

No evidence was found on how percutaneous aspiration thrombectomy affects progression (or recurrence) of pulmonary embolism.[23]

Pulmonary artery pressure (PAP)

There was a significant reduction in PAP in both treatments ($p < 0.001$) in the matched-control case series using the FlowTriever System. Both treatments reduced mean PAP to below 25 mmHg (≥ 25 mmHg is classified as pulmonary artery hypertension [62]). In the percutaneous aspiration thrombectomy treatment it reduced from a mean of 30.2 ± 8.3 mmHg to 22.4 ± 8.9 mmHg. In the CDT treatment it reduced from 29.2 ± 9.1 mmHg to 20.7 ± 6.4 mmHg. The reduction in mean PAP, which did not differ significantly different between treatments (p=0.60), was 7.8 ± 5.4 mmHg in the percutaneous aspiration thrombectomy treatment and 8.5 ± 7.4 in the CDT treatment [59].[24]

Change in heart rate

There was a significant reduction in heart rate in both treatments ($p < 0.048$) in the matched-control case series using the FlowTriever System. In the percutaneous aspiration thrombectomy treatment it reduced from a mean of 103 ± 17.5 to 97.5 ± 16.7 beats/min. In the CDT treatment it reduced from 94.6 ± 15.9 to 85. ± 14.6 beats/min. The reduction in mean heartrate, which

keine stat. signifikanten Gruppenunterschiede in Herzfrequenz

[21] **D0001** – What is the expected beneficial effect of percutaneous aspiration thrombectomy on mortality?

[22] **D0003** – What is the effect of percutaneous aspiration thrombectomy on the mortality due to causes other than pulmonary embolism?

[23] **D0006** – How does percutaneous aspiration thrombectomy affect progression (or recurrence) of pulmonary embolism?

[24] **D0005** – How does percutaneous aspiration thrombectomy affect symptoms and findings (severity, frequency) of pulmonary embolism?

did not differ significantly between treatments (p=0.4), was 5.4 ± 19.2 beats/min in the percutaneous aspiration thrombectomy treatment and 9.6 ± 15.8 in the CDT treatment [59].[24]

Change in pulmonary artery burden

stat. signifikanter Unterschied zugunsten der CDT in Pulmonalarterienbelastung

There was a significant reduction in pulmonary artery burden as measured by the Miller score in both treatments (p < 0.001) in the matched-control case series using the FlowTriever System. In the percutaneous aspiration thrombectomy treatment it reduced from a mean of 17.2 ± 4.9 to 9.8 ± 5.5. In the CDT treatment it reduced from 18.6 ± 4.2 to 8.5 ± 3.8. The reduction in mean Miller score, was significantly better in the CDT treatment (7.5 ± 3.8 in the percutaneous aspiration thrombectomy treatment and 10.1 ± 3.9 in the CDT treatment) (p=0.02) [59].[24]

Function

Funktion: keine Evidenz zum Wiederauftreten

No evidence was found to answer the research questions related to how percutaneous aspiration thrombectomy affects Function.[25,26] In particular, there was no evidence found for the following PICO outcomes: 6-minute walk distance, New York Heart Association class >1 and impaired cardiopulmonary exercise test (maximum oxygen consumption <80%).

Health-related quality of life

Lebensqualität: keine Evidenz

No evidence was found to answer the research questions related to how percutaneous aspiration thrombectomy affects health-related quality of life.[27,28] In particular, there was no evidence found for the following PICO outcomes: generic QoL (Short-Form-36 physical component score) and disease-specific QoL (Pulmonary Embolism-QoL score).

Patient satisfaction

Length of stay in hospital and ICU

kürzere Veweildauer im Spital in Flow Triever Gruppe im Vergleich zur CDT Gruppe

The length of hospital stay did not differ significantly between the percutaneous aspiration thrombectomy patients (5.4 ± 2.9 days) and the CDT patients (5.7 ± 3.4 days) (p=0.90) in the matched-control case series using the FlowTriever System. In comparison, the length of stay in ICU was significantly shorter for the percutaneous aspiration thrombectomy patients (0.8 ± 1.2 days) compared with the CDT patients (1.9 ± 1.9 days) (p < 0.001). In addition, it was reported that only 16/26 (62%) of the percutaneous aspiration thrombectomy patients were admitted to the ICU compared with all the patients in the CDT treatment (26/26, 100%) being admitted (p=0.004) [59].

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[25] **D0011** – What is the effect of percutaneous aspiration thrombectomy on patients' body functions?

[26] **D0016** – How does the use percutaneous aspiration thrombectomy affect activities of daily living?

[27] **D0012** – What is the effect of percutaneous aspiration thrombectomy on generic health-related quality of life?

[28] **D0013** – What is the effect of percutaneous aspiration thrombectomy on disease-specific quality of life?

Patient safety

Major bleeding

Bleeding complications were reported in all four included studies (Table 4-1) [33, 50, 59, 61]. In the matched-control case series, there was no significant difference in minor, moderate, or major bleeding events throughout the study period [59]. Major bleeding occurred in one patient in the CDT treatment (4%) and in no patients who received percutaneous aspiration thrombectomy [59]. Major bleeding occurred in 1.0-1.7% of patients receiving percutaneous aspiration thrombectomy across the three single-arm studies [33, 50, 61].[29]

Blutungskomplikation: kein stat. signifikanter Unterschied in NRCT und 1-1,7% in 3 Beobachtungsstudien

Table 4-1: Major bleeding

Study ID (Device)	Major bleeding
Graif et al 2020 [59] (FlowTriever System)	Major bleeding[a] – PAT: 0/26 (4%) vs CDT: 1/26 (4%) (p=1.0) Moderate bleeding – PAT: 0/26 (0%) vs CDT: 0/26 (0%) (p=NA) Minor bleeding – PAT: 1/26 (4%) vs CDT: 1/26 (4%) (p=1.0)
Toma et al 2022 [33] (FlowTriever System)	Major bleeding at 48 hours – 11/788 (1.4%)[b]
Tu et al 2019 [50] (FlowTriever System)	Major bleeding at 48 hours[c] – 1/104 (1%)
Sista et al 2021 [61] (Indigo System)	Major bleeding at 48 hours – 2/119 (1.7%)[a]

Abbreviations: CDT – catheter-directed thrombolysis; PAT – percutaneous aspiration thrombectomy.

Notes:

[a] *Bleeding outcomes were classified according to the Global Use of Strategies to Open Occluded Arteries (GUSTO) criteria.*

[b] *Major bleeding was defined as symptomatic bleeding in a critical area or organ, bleeding causing a haemoglobin drop of at least 5 g/dL, bleeding leading to transfusion of at least 2 units of blood products, or fatal bleeding, similar to Bleeding Academic Research Consortium (BARC) type 3b or greater.*

[c] *Bleeding events were classified according to the Valve Academic Research Consortium-2 Guidelines as 'major' if they met the criteria for life threatening, disabling or major bleeding.*

Procedure-related deaths

Procedure-related deaths were reported in all four included studies (Table 4-2) [33, 50, 59, 61]. Two single-arm studies (both using the FlowTriever System) reported no deaths related to percutaneous aspiration thrombectomy [33, 50] and one single-arm study (using the Indigo System) reported one device-related death at 48 hours follow-up due to sustained ventricular tachycardia approximately eleven hours post-venous puncture [61].[61]. There was no significant difference in the number of deaths that occurred in the two treatments in the matched-control case series, with 2/26 (8%) occurring in the percutaneous aspiration thrombectomy treatment and none in the CDT treatment [59]. One of the deaths occurred prior to the aspiration device being inserted into the patient's body and thus was not due to the device, the other occurred during the final steps of the procedure, after use of the aspiration device. The authors note it is unclear whether the second death was due to the procedure or natural progression of PE causing the cardiac arrest.[29]

Sicherheit: 1 NRCT und 3 Beobachtungsstudien: ein gerätebedingter Todesfall aufgrund ventrikulärer Tachykardie

zwei Todesfälle bei perkutaner Aspirations-thrombektomie in NRCT

[29] C0008 – How safe is percutaneous aspiration thrombectomy in comparison to catheter-directed thrombolysis, catheter-directed mechanical thrombectomy (not involving aspiration) or surgical embolectomy?

Table 4-2: Procedure-related deaths

Study ID (Device)	Procedure-related deaths, n/N (%)[a]
Graif et al 2020 [59] (FlowTriever System)	30 days: PAT: 2/26 (8.3%) vs CDT: 0/26 (0%) (p=0.5)[b] Both deaths were reported as procedure-related[c]
Toma et al 2022 [33] (FlowTriever System)	30 days: 0/788 (0%)
Tu et al 2019 [50] (FlowTriever System)	30 days: 0/104 (0%)
Sista et al 2021 [61] (Indigo System)	48 hours: 1/119 (0.8%) Death was reported as device-related

Abbreviations: CDT – catheter-directed thrombolysis; PAT – percutaneous aspiration thrombectomy.

Notes:

[a] *This also includes any deaths referred to as device-related.*

[b] *These deaths are also captured in the efficacy section under 'all-cause mortality'*

[c] *One death occurred prior to insertion of the device, the other occurred during the final steps of the procedure and the authors stated it was unclear whether it was the procedure or natural progression of PE which caused the cardiac arrest and subsequent death.*

Treatment-related clinical deterioration

klinische Verschlechterung in 3 Studien: 0,3-3,8 %

Three single-arm studies reported treatment-related clinical deterioration; their rates and definition for clinical deterioration can be found in Table 4-3 [33, 50, 61]. Treatment-related clinical deterioration occurred in 2 patients (0.3%) in the largest FlowTriever study (these patients were also reported in procedure-related adverse events) [33], in 4 patients (3.8%) in the other study using the FlowTriever System (these patients were also reported in procedure-related adverse events) [50] and in 1 patient (0.8%) in the study using the Indigo System (this patient was also reported in the 48 hour serious adverse event composite and in the 48 hours device-related adverse event composite) [61].

Table 4-3: Treatment-related clinical deterioration

Study ID (Device)	Treatment-related clinical deterioration
Toma et al 2022 [33] (FlowTriever System)	2/788 (0.3%)[a]
Tu et al 2019 [50] (FlowTriever System)	4/104 (3.8%)[b]
Sista et al 2021 [61] (Indigo System)	1/119 (0.8%)[c]

Notes:

[a] *Treatment-related clinical deterioration defined by haemodynamic or respiratory worsening meeting specific thresholds.*

[b] *Treatment-related clinical deterioration comprised treatment-related events such as unplanned requirement for mechanical ventilation, arterial hypotension (> 1h or requiring vasopressors), cardiopulmonary resuscitation, persistent worsening in oxygenation, ore emergency surgical embolectomy.*

[c] *Treatment-related clinical deterioration was defined as having one of the following: 1) the need for cardiopulmonary resuscitation, intubation, vasopressors, extracorporeal membrane oxygenation or extracorporeal life support; 2) systolic blood pressure <90mmHg for at least 15 min; 3) a drop of systolic blood pressure by at least 40 mmHg for at least 15 min with signs of end organ hypoperfusion (cold extremities or low urinary output <30 ml/h or altered mental status); or 4) the need for catecholamine administration to maintain adequate organ perfusion and a systolic blood pressure >90 mmHg.*

Treatment-related pulmonary vascular injury

Behandlungs-induzierte pulmonalvaskuläre Schädigung: 0-1 %

Three single-arm studies reported treatment-related pulmonary vascular injury (Table 4-4) [33, 50, 61]. One of these reported no treatment-related pulmonary vascular injuries [33] and the remaining two reported one injury each, in 1% [50] and 0.8% [61] of patients, respectively. [61] of patients, respectively.

Table 4-4: Treatment-related pulmonary vascular injury

Study ID (Device)	Treatment-related pulmonary vascular injury
Toma et al 2022 [33] (FlowTriever System)	0/788 (0%)
Tu et al 2019 [50] (FlowTriever System)	1/104 (1.0%)
Sista et al 2021 [61] (Indigo System)	1/119 (0.8%)

Notes:

[a] *Included in procedure-related adverse event composite*

[b] *Included in SAE at 48 hours composite and device-related adverse event at 48 hours composite*

Treatment-related cardiac injury

Behandlungs-induzierte Schädigung des Herzens in 3 Studien: 0-0,1 %

Three single-arm studies reported treatment-related cardiac injury (Table 4-5) [33, 50, 61]. Two of these reported no treatment-related cardiac injuries and one study reported one injury (which was also reported under procedure-related adverse events) [33].

Table 4-5: Treatment-related cardiac injury

Study ID (Device)	Treatment-related cardiac injury
Toma et al 2022 [33] (FlowTriever System)	1/788 (0.1%)
Tu et al 2019 [50] (FlowTriever System)	0/104 (0%)
Sista et al 2021 [61] (Indigo System)	0/119 (0%)

Serious adverse events

schwerwiegende unerwünschte Ereignisse: kein stat. signifikanter Unterschied in NRCT (n=52)

1,7-13,2 % in Beobachtungsstudien

All four included studies reported serious adverse events (Table 4-6) [33, 50, 59, 61]. The matched-control case series and one single-arm study reported serious adverse events as a composite of major bleeding and procedure-related deaths (reported individually above) [59, 61]. Similarly, the remaining single-arm studies provided serious adverse event rates which captured other safety outcomes reported by their authors. In the comparative study, there was no significant difference in serious adverse event rates between percutaneous aspiration thrombectomy and CDT (p=1.0) [59], and rates ranged from 1.7-13.2% in the single-arm studies [33, 50, 61].[29]

Table 4-6: Serious adverse events

Study ID (Device)	Serious adverse events
Graif et al 2020 [59] (FlowTriever System)	PAT: 2/26 (8%) vs CDT: 1/26 (4%) (p=1.0)[a] These include major bleeding and deaths.
Toma et al 2022 [33] (FlowTriever System)	48 hours: 35 events occurred in 34/791 (4.3%) This is likely to include procedure-related SAEs.
Tu et al 2019 [50] (FlowTriever System)	30 days: 26 events occurred in 14/104 (13.2%) This includes procedure-related SAEs.
Sista et al 2021 [61] (Indigo System)	48 hoursr: 2/119 (1.7%) This includes major bleeding and deaths.

Abbreviations: CDT – catheter-directed thrombolysis; PAT – percutaneous aspiration thrombectomy; SAEs – serious adverse events.

Note:

[a] *Major complications as classified according to the Society of Interventional Radiology (SIR) reporting standards*

No evidence was found on the susceptible patient groups that are more likely to be harmed through the use of percutaneous aspiration thrombectomy and on an association with user-dependent harms.[30,31]

[30] C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of percutaneous aspiration thrombectomy?

[31] C0007 – Are percutaneous aspiration thrombectomy and catheter-directed thrombolysis, catheter-directed mechanical thrombectomy (not involving aspiration) or surgical embolectomy associated with user-dependent harms?

5 Certainty of the evidence

RoB mit ROBINS-I und IHE-20

RoB for the matched-control case series was assessed using the ROBINS-I tool [51]. Single-arm studies were appraised using the IHE Quality Appraisal Checklist [52]. Results of the appraisals are presented in Table A-3 and Table A-4 in the Appendix.

kritisches Verzerrungspotenzial in retrospektivem NRCT

The overall RoB for the included retrospective matched-control case series, using the ROBINS-I tool, was critical [59]. This was mainly owing to the retrospective study design employed by the authors. Although propensity score matching was carried out to reduce bias somewhat, not every variable was matched.

Beobachtungsstudien: RoB moderat bis hoch

The overall RoB for the included single-arm studies was moderate for two studies [61] [50] and high for one study [33].

Stärke der Evidenz nach GRADE: sehr niedrig

The certainty of the evidence was rated according to GRADE [53] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [53].

GRADE bestehend aus 4 Kategorien: sehr niedrig bis hoch

GRADE uses four categories to rank the certainty of the evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

Zusammenfassung in Appendix

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and in the evidence profile in Appendix Table A-5.

Overall, the certainty of the evidence for the effectiveness and safety of percutaneous aspiration thrombectomy in comparison to CDT is very low. The certainty of the evidence for the additional safety data provided by single-arm studies is also very low.

kein Vergleich mit anderen Verfahren

No evidence is available comparing percutaneous aspiration thrombectomy to other mechanical thrombectomy procedures (not involving aspiration) or surgical embolectomy.

Table 5-1: Summary of findings table of percutaneous aspiration thrombectomy

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with comparison	Risk with intervention				
Efficacy – percutaneous aspiration thrombectomy vs CDT						
All-cause 30-day mortality	0 per 1000	0 per 1000	RR 4.7 (0.2, 92.6)	52 (1)	⨁◯◯◯ Very low	RR is greater with percutaneous aspiration thrombectomy RoB: retrospective study, concerns regarding patient selection Imprecision: one retrospective study Indirectness: wrong population
Haemodynamic decompensation						Not reported
Chronic thromboembolic pulmonary hypertension						Not reported
PE recurrence						Not reported
Safety– percutaneous aspiration thrombectomy vs CDT						
Major bleeding	38 per 1000	13 per 1000	RR 0.35 (0.0, 8.1)	52 (1)	⨁◯◯◯ Very low	RR is lower with percutaneous aspiration thrombectomy RoB: retrospective study, concerns regarding patient selection Imprecision: one retrospective study Indirectness: wrong population
Procedure-related deaths	0 per 1000	0 per 1000	RR 4.7 (0.2, 92.6)	52 (1)	⨁◯◯◯ Very low	RR is greater with percutaneous aspiration thrombectomy RoB: retrospective study, concerns regarding patient selection Imprecision: one retrospective study Indirectness: wrong population
Treatment-related clinical deterioration						Not reported
Treatment-related pulmonary vascular injury						Not reported
Treatment-related cardiac injury						Not reported
Outcome	**Number of participants (studies) Summary of findings**				**Quality**	**Comments**
Safety – single arm studies						
Major bleeding (48 hours)	1,011 (3) 14/1,011 (mean: 1.4%; range: 1%, 1.7%)				⨁◯◯◯ Very low	RoB: recruitment not consecutive or unclear, lack of detail regarding co-intervention, different disease status Indirectness: wrong population
Procedure-related deaths	1,011 (3) 1/1,011 (mean: 0.1%; range: 0%, 0.8%)				⨁◯◯◯ Very low	RoB: recruitment not consecutive or unclear, lack of detail regarding co-intervention, different disease status Indirectness: wrong population
Treatment-related clinical deterioration	1,011 (3) 7/1,011 (mean: 0.7%; range: 0.3%, 3.8%)				⨁◯◯◯ Very low	RoB: recruitment not consecutive or unclear, lack of detail regarding co-intervention, different disease status Indirectness: wrong population
Treatment-related pulmonary vascular injury	1,011 (3) 2/1,011 (mean: 0.2%; range: 0%, 1.0%)				⨁◯◯◯ Very low	RoB: recruitment not consecutive or unclear, lack of detail regarding co-intervention, different disease status Indirectness: wrong population
Treatment-related cardiac injury	1,011 (3) 1/1,011 (mean: 0.1%; range: 0%, 0.1%)				⨁◯◯◯ Very low	RoB: recruitment not consecutive or unclear, lack of detail regarding co-intervention, different disease status Indirectness: wrong population

Abbreviations: CDT – catheter-directed thrombolysis; CI – confidence interval; MD – mean difference; NA – not applicable; PAP – pulmonary artery pressure; PE – pulmonary embolism; RoB – risk of bias; RR – relative risk.

6 Discussion

The aim of this assessment was to compare the safety and effectiveness of percutaneous aspiration thrombectomy to CDT, other catheter-directed mechanical thrombectomy procedures (not involving aspiration) and surgical embolectomy in 1) high-risk PE patients who have either failed or are contraindicated to systemic thrombolysis and 2) intermediate-risk PE patients who despite being on anticoagulants, experience haemodynamic instability and who are also contraindicated or have failed systemic thrombolysis. These populations and comparator procedures were established based on the latest ESC guidelines on management of acute PE [6].

Vergleich perkutaner Aspirationsthrombektomie mit kathetergeführte Thrombolyse bei 2 Populationen

At the time of writing two percutaneous aspiration thrombectomy devices were CE marked and indicated for treated of PE. They were the FlowTriever System (approved December 2020) and the Indigo System (approved January 2022). Both devices have 510(k) FDA approval.

Summary of main findings

Only one comparative study was identified to inform the efficacy of percutaneous aspiration thrombectomy [59]. This small (total n=52), retrospective matched-control case series compared percutaneous aspiration thrombectomy to CDT in propensity-matched high- and intermediate-risk PE patients. Results were not separated for the two populations, although most patients had intermediate-risk PE (96%). The study reported no significant difference in 30-day all-cause mortality between the two treatments. This outcome was deemed by a clinical expert to be of critical importance for decision making. No data was available on the other efficacy outcomes deemed as critical for decision making (haemodynamic decompensation, chronic thromboembolic pulmonary hypertension and PE recurrence). The overall certainty of the evidence for all-cause mortality at 30 days was deemed to be very low as assessed by GRADE [59].

Zusammenfassung der Ergebnisse:

1 retrospektive Fallserie mit match-control (n=52) für die vergleichende Wirksamkeit

The same matched-control case series provided safety data [59]. Additional safety data was included from eligible prospective single-arm studies with ≥ 20 patients. Three single-arm studies were identified, including one large registry of 800 mixed high- (7.9%) and intermediate-risk (92.1%) PE patients (results were not separated for high- vs. intermediate-risk patients) [33]. The remaining single-arm studies included intermediate-risk PE patients [50, 61]. Major bleeding occurred in 1.0-1.7% of patients in the single-arm studies and there was no significant difference in its occurrence between treatment groups in the matched-control case series [59]. Procedure-related deaths occurred in 0.0-0.8% of patients in the single-arm studies and there was also no significant difference between the treatment groups in the matched-control case series [59]. Of note, across all four studies, only one death was reported as device related. Treatment-related cardiac injury, treatment-related pulmonary vascular injury and treatment-related clinical deterioration were only reported in the single-arm studies and ranged from 0.0-0.1%, 0.0-1.0% and 0.3-3.8% of patients, respectively. The overall certainty of the evidence for all safety outcomes (for both study types) was deemed to be very low as assessed by GRADE.

und zusätzlich 3 Beobachtungsstudien für die Sicherheitsbewertung

104-800 Patient*innen

sehr geringe Vertrauenswürdigkeit der Evidenz für alle Sicherheitsergebnisse

Interpretation of the findings

ähnliche Wirksamkeit und ähnliches Sicherheitsprofil

Based on the results from one retrospective matched-control case series, percutaneous aspiration thrombectomy appears to be similar in efficacy compared with CDT with respect to all-cause mortality. A similar safety profile was also observed for major bleeding and procedure-related deaths. Across all four included studies, critical safety events including major bleeding, treatment-related cardiac injury and treatment-related pulmonary injury occurred in less than 2% of patients. Only one death across all four studies was attributed to the device.

nur ein Todesfall auf Verfahren zurückzuführen

Evidence from published systematic reviews and Health Technology Assessment (HTA) agencies

Einbettung in bestehendes Wissen:

1 SR in 2022 v. a. zur Sicherheit

1 IQWIG-Report in Jänner 2023: keine belastbaren Daten für pulmonale Thrombektomie mittels Disc-Retriever

A systematic review and meta-analysis on mechanical aspiration thrombectomy was published in 2022 [63]. The review included three retrospective case series including only high-risk PE patients (n=188), two prospective case series including only intermediate-risk PE patients (n=223) and nine studies (seven retrospective case series and two prospective case series) including a combination of both PE risk groups. The main difference in the selection criteria for this review compared with the current assessment is that they allowed the inclusion of retrospective studies with fewer than 20 patients. The devices used were the FlowTriever System (6 studies), the Indigo System (5 studies), the Rotarex System (1 study) or the Aspirex System (2 studies). Four of the included studies allowed patients to receive thrombolytics. Of the outcomes reported in the current assessment, that were also reported in this review, findings fell within similar ranges. These outcomes were mortality (pooled estimate 3.6% (95% CI 0.7%, 7.9%)) and major bleeding (pooled estimate 0.5% (95% CI 0.0%, 1.8%)) [63]. The Institute for Quality and Efficiency in Health Care (IQWiG) published a review on aspiration thrombectomy in January 2023, and like the current assessment, concluded neither benefit nor harm or ineffectiveness of the intervention could be derived [64].

In January 2023, the National Authority for Health (HAS), via its National Commission for Evaluation of Medical Devices and Health Technologies, announced transitional coverage of the FlowTriever System for the "treatment of pulmonary embolism in combination with anticoagulant therapy for patients with severe pulmonary embolism, at high risk of premature death in failure or contraindicated to thrombolysis, or at high intermediate risk of premature death with hemodynamic deterioration despite well-conducted anticoagulant treatment, in failure or contraindicated to thrombolysis, when surgical embolectomy is not possible and after advice from a multidisciplinary team" [65]. This is the same patient population as in the current assessment.

Limitations of the report

Limitationen: Sprache als Einschlusskriterium

Although the present report followed a transparent and systematic methodology, including a systematic literature search according to the PICO scheme, it has limitations. These include an absence of extensive grey literature searches, such as specialty societies and the restriction of included articles to English and German language only, meaning studies published in other languages may have been missed. In addition, safety studies were limited to only prospective studies with ≥ 20 patients; however, it is unlikely the inclusion of retrospective, or smaller prospective case series studies would have changed

the findings of this assessment. This is supported by the similar results observed in the systematic review described above, which did not limit study inclusion as strictly.

Limitation of the evidence

Limitationen der Evidenz: keine randomisierten Kontrollstudien vorhanden

Owing to the small number of patients in the retrospective matched-control case series it is unlikely to be sufficiently powered to detect a difference between percutaneous aspiration thrombectomy and CDT [59]. Further, interpretation of the results is complicated for several reasons. The study had a mixture of high- and intermediate-risk PE patients and results were not separated. It is possible the inclusion of a small proportion of high-risk PE patients may have affected the results, given the small study numbers and that both patients were in the percutaneous aspiration thrombectomy treatment group. None of the patients in the CDT group and only four (15.4%) in the percutaneous aspiration thrombectomy were contraindicated to thrombolysis and thus the patients did not match the population defined in the PICO. The purported benefit of percutaneous aspiration thrombectomy compared with CDT is that it does not use thrombolytics and thus might reduce the risk of bleeding. This potential benefit may not be realised in patients without contraindications to thrombolytics, thus the study is biased against the intervention. In addition to the lack of contraindication to thrombolysis, it is not reported that any of the intermediate-risk PE patients experienced haemodynamic instability prior to the procedure. As such, mortality results are likely to be lower than would be expected than for intermediate-risk PE patients experiencing haemodynamic instability, although this would be the same for both treatments [59].

fehlende Kontraindikationen für Thrombolyse

Vorliegen hämodynamischer Instabilität nicht berichtet

Art des Antikoalulans und Lokalisation des Thrombus nicht in Propensity Score Matching einbezogen

In the matched-control case series, the type of anticoagulant that patients were on differed significantly between the treatments ($p < 0.001$) and was not included in the propensity score matching [59]. More of the percutaneous aspiration thrombectomy group were on low-molecular weight heparin compared with the CDT group (73% versus 15.4%, respectively). Conversely, more patients in the CDT group were on unfractionated heparin compared with the percutaneous aspiration thrombectomy group (85% versus 23%, respectively). The selection and influence of anticoagulation would have a significant impact, particularly on the translation into clinical practice. For example, the choice of a specific anticoagulant substance could affect the suitability of a patient for secondary systemic lysis, CDT, or percutaneous aspiration thrombectomy (clinical expert, personal communication). Also not included in the propensity score matching, as noted by the authors, was the configuration and distribution of thrombus in the pulmonary arteries (central versus peripheral location). The authors went on to suggest this was likely to have been a factor influencing the selection of what treatment was used and thus represents a source of bias [59].

mögliche Verzerrung

verschiedene Infusionstechniken

interventionelle Radiolog*innen mit unterscheidlich viel Erfahrung

Several types of infusion catheters were used to deliver the CDT, with one type using ultrasound acceleration. It is not known whether the different types of infusion catheters are equivalent in terms of their safety and efficacy. The study noted that one of nine interventional radiologists conducted the procedures, with experience ranging from 1 to 19 years. It is possible more experienced radiologists may have performed the intervention compared with the comparator procedure or vice versa, biasing the results. Also noted in the study was the fact that the percutaneous aspiration thrombectomy device had only recently become available at the study institution since 2018, whereas

CDT had been used since 2009. They suggest that as CDT is less technically demanding than percutaneous aspiration thrombectomy this may also present a confounding factor [59].

unterschiedliche Patient*innenpopulationen in großen Registerstudien

Hochrisikopatient*innen und Patient*innen mit mittlerem Risiko einbezogen ohne getrennte Ergebnisse

The PE populations in the single-arm studies included for safety also did not match those defined in the PICO [33, 50, 61]. The largest study, a multicentre registry, contained a very heterogenous mixture of patients [33]. Both high-risk and intermediate-risk patients were included, and the results were not reported separately. Of note, follow-up assessments were only available for a subset of the total registry (varying across outcomes); the authors attributed this to the effects of COVID-19 on clinical research. Additionally, only 32% of patients were determined to have either an absolute or relative contraindication to thrombolytic drugs, and around 5.2% (data not available for all patients) had failed a prior therapy for PE. As well as this, patients were put on different types of anticoagulants at 48 hours post-procedure which could have affected 30-day all-cause mortality. A small percentage of patients received adjunctive PE therapy including either CDT (2.3%) or other mechanical thrombectomy (0.1%). The study noted that several design iterations occurred with the percutaneous aspiration thrombectomy device during the later phase of enrolment, including a blood return system which became available and was used in 10.3% of patients [33].

Population aus 2 einarmigen Studien wich von PIKO ab

The other two single-arm studies contained intermediate-risk patients [50, 61]. In one study, haemodynamic deterioration was an exclusion criterion [50] and the other study did not report that any patients experienced haemodynamic deterioration [61]. Neither study reported whether the patients were contraindicated for thrombolysis; however, one reported that none of patients had previously failed thrombolysis [50]. Thus, they do not match the intermediate-risk PE population defined in the PICO. One study reported that 1.7% of patients received intraprocedural tPA (thrombolytic drug) [61] and in the other study 1.9% of patients received thrombolytics immediately following the thrombectomy (type not reported) [50].

standardisiertes Protokoll zu Erfolgsmessung und Verfahrensabbruch wäre hilfreich

One question that has been raised regarding embolectomy procedures, given that none lead to complete thrombus removal, is how should procedural success be measured and when should the procedure be stopped [66]. This is important given that with each pass of the aspiration catheter there is the risk of perforation. It is suggested this will differ depending on whether the patient is in shock. With aspiration thrombectomy, how much blood has been lost can also influence the length of the procedure, even when the desired anatomic or haemodynamic results have not been obtained [67]. A standardised protocol would help when comparing percutaneous aspiration thrombectomy to other procedures [66].

alle Studien nur auf kurzfristige Endpunkte bezogen

A major limitation of the evidence is that all of the included studies focussed on short-term endpoints [40]. Studies with longer follow-up are required that report on patient-relevant outcomes such as improvement in QoL, functional capacity and chronic thromboembolic pulmonary hypertension (CTPH). It is reported that much of the clinical burden for PE survivors (such as dyspnoea on exertion) is borne in the chronic PE phase and whether catheter-based treatments of acute PE such as percutaneous aspiration thrombectomy can impact the likelihood of CTPH or functional impairment is unknown, however it is critically important [68].

It should be noted that catheter-directed technologies for PE is a rapidly developing area within endovascular interventions, with new devices becoming available as well as modifications to first generation devices [69]. The companies that market the two percutaneous aspiration devices that were included in this assessment note that there have been improvements in these technologies, such as modifications to reduce blood loss. The large, single-arm registry study reported that a blood return system was introduced in 2021 and was utilised in a limited number of patients in the later phase of enrolment. In addition, several other FlowTriever System design iterations occurred during enrolment, including improvements to ergonomics, flexibility and tracking ability and the introduction of new devices into the toolkit [33]. It is not known how these modifications may have affected the results and whether these latest iterations would lead to better results than those observed in the included studies.

unklare Auswirkungen der Modifikationen an den Geräten auf Ergebnisse

mehrere Design-Iterationen des FlowTriever Systems

Evidence gaps and ongoing trials

A total of two ongoing RCTs were identified, one using the Indigo System and the other the FlowTriever System. The trial using the Indigo System is comparing it to anticoagulants. It has an estimated enrolment of 100 patients and completion date of July 2026. The trial using the FlowTriever System is comparing it to CDT. It has an estimated enrolment of 550 patients and completion date of March 2024. Both trials are in haemodynamically stable intermediate-high-risk PE patients. It has been noted in a consensus statement by the AHA that the low incidence (5%) of high-risk PE makes enrolment into clinical trials impractical and that enrolment of patients with life-threatening illnesses has challenges [18]. For this reason, it is unlikely that there will be any RCTs involving percutaneous aspiration thrombectomy in high-risk PE patients in the future.

zwei laufende RCTs:

PEERLESS zu FlowTriever® (n=550): Kombinierter primärer Endpunkt aus Mortalität und anderen klinischen Endpunkten

STORM-PE (n=100) zum Indigo System: Veränderung des RV/LV-Verhältnisses

Another unanswered question in the treatment of acute PE is the significance of reduced dose systemic thrombolytic therapy compared to interventional procedures. A recent systematic review concluded that compared with normal dose recombinant tissue-type plasminogen activator (rtPA), reduced dose rtPA had a lower rate of total bleeding events and similar efficacy regarding mortality and PE recurrence rate in the treatment of patients with acute PE [56].

Conclusion

In summary, in comparison to CDT, percutaneous aspiration thrombectomy had similar rates of all-cause 30-day mortality, procedure-related deaths and major bleeding events. These outcomes were deemed critical for decision making. No evidence was found comparing percutaneous aspiration thrombectomy to the other comparators considered in this assessment – surgical embolectomy and other mechanical percutaneous thrombectomy techniques not involving aspiration.

Schlussfolgerung: nur eine retrospektive Fallserie mit matched-control

26 Pts erhielten PAT, kurzes Follow-Up

The findings from this assessment should be considered with caution given that they were derived from one small retrospective matched-control case series and a few prospective single-arm studies, all with a maximum follow-up of 30 days. Interpretation of the evidence from these studies is complicated by numerous factors including the inclusion of intermediate- and high-risk PE patients without separation of the results, variable anticoagulant regimes, the use of adjunctive treatments, different iterations of devices being includ-

keine belastbaren vergleichenden Daten vorhanden

ed in the same studies and a lack of clarity regarding how completion of the procedure was determined. The included studies mostly reported outcomes for intermediate-risk PE patients without haemodynamic instability or contraindications to thrombolytics, which does not match those predefined in the PICO. It is not known whether the efficacy and safety of percutaneous aspiration thrombectomy in this population would be similar to that of high-risk PE patients or whether the treatment (due to its faster method of clot removal) would result in greater efficacy in the higher-risk PE population who require immediate treatment to restore blood flow.

7 Recommendation

In Table 7-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 7-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is **currently not recommended**.
	The **inclusion in** the catalogue of benefits is **not recommended**.

Reasoning:

Evidenz unzureichend: derzeit nicht empfohlen

The current evidence is not sufficient to prove, that the assessed technology, percutaneous aspiration thrombectomy (in the two populations of interest below) is equally effective and safe as the comparator procedures surgical embolectomy, CDT and other catheter based mechanical thrombectomy techniques not involving aspiration.

1) High-risk PE patients who are contraindicated or who have failed systemic thrombolysis, and
2) Intermediate-risk PE patients who develop haemodynamic instability despite being on anticoagulants and who are contraindicated or have failed systemic thrombolysis.

Re-Evaluierung in 2025, wenn Ergebnisse aus PEERLESS vorliegen

Two ongoing clinical trials investigating the safety and effectiveness of percutaneous aspiration thrombectomy in intermediate-high-risk PE are due for completion March 2024 and March 2026, respectively. Based on this, the re-evaluation of percutaneous aspiration thrombectomy for high-risk and intermediate risk PE is recommended at the end of 2025, when the result from PEERLESS will be available.

8 References

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Percutaneous aspiration thrombectomy: Results from matched-control case series

Author, year	Graif et al 2020 [59]
Country	United States
Sponsor	NA
Intervention/Product	Aspiration thrombectomy using FlowTriever
Comparator	CDT with recombinant tissue plasminogen
Study design	Retrospective non-randomised comparative study (propensity score matching was performed[a]) Single-centre
Number of pts	Total identified by retrospective review: 31 vs. 180 Total meeting study criteria: 27 vs. 141 Matched cases: 26 vs. 26
Inclusion criteria	Consecutive patients who underwent endovascular therapy for acute massive PE (defined by sustained hypotension, profound brachycardia or pulselessness) or submassive PE (defined by a right ventricle-to-left ventricle ratio >0.9 or biochemical marker evidence of myocardial necrosis) were identified by searching the medical records of a single hospital system. Patients were eligible for inclusion if they presented within 14 days of symptom onset and underwent large-bore aspiration thrombectomy or CDT.
Age of patients (yrs)	60.2 ± 17.1 vs. 59.7 ± 14.2 (p=0.7)
Male, n/N (%)	12 (46%) vs. 12 (46%)
ESC/AHA risk catergory, n/N (%)[b]	Massive PE: 2/26 (8%) vs. 0/26 (0%) Submassive PE: 24/26 (92%) vs. 26/26 (100%)
Were HR/massive patients contraindicated to/failed systemic thrombolytics?	Contraindicated to thrombolysis: 4/26 (15%) vs. 0/26 (0%) (Rates not reported per risk category) Failed thrombolysis: 0/2 (0%) vs. 0/0 (0%)
Did IR/submasive patients experience haemodynamic deterioration despite anticoagulants? n/N (%) Were patients contraindicated to/failed systemic thrombolytics? n/N (%)	Haemodynamic deterioration: NR Contraindicated to thrombolysis: See above Failed thrombolysis: 0/24 (0%) vs. 0/26 (0%)
History of PE or DVT, n/N (%)	History of PE: NR Lower extremity DVT: 23/25[c] (92%) vs. 23/26 (89%)
Co-intervention	None
Follow-up (days)	30
Loss to follow-up, n/N (%)	NR

Author, year	Graif et al 2020 [59]
Outcomes	
Procedural characteristics	
Access site	NR
PE location	Unilateral: 5/27 (19%) vs. NR Bilateral: 22/27 (81%) vs. NR
Procedural time (mins)	107.5 ± 27.5 vs. 62.2 ± 20.4d (p < 0.001)
Estmated blood loss, mls	NR
Number of passes attempted with device	NR
Efficacy	
PE-related deaths, n/N (%)	NR
All-cause mortality, n/N (%)	30 days: 2/26 (8%) vs. 0/26 (0%) (p=0.5) Both were reported as procedure-related
Haemodynamic decompensation, n/N (%)	NR
Chronic thrombolic pulmonary hypertension, n/N (%)	NR
PE recurrence, n/N (%)	NR
Patient-centric outcomes (i.e. QoL, LoS)	ICU stay required: 18/26 (69%) vs. 26/26 (100%)[e] (p=0.004) Duration of ICU stay (days): 0.8 ± 1.2 vs. 1.9 ± 1.9[f] (p < 0.001) Hospital stay (days): 5.4 ± 2.9 vs. 5.7 ± 3.4 (p=0.9)
PAP outcomes, mm Hg	Mean change in systolic PAP: -12 ± 6.4 vs. -11.9 ± 11.2 (p=0.6) Mean change in diastolic PAP: -5.7 ± 6.1 vs. -6.4 ± 7.8 (p=0.7) Change in mean PAP: -7.8 ± 5.4 vs. -8.5 ± 7.4 (p=0.6)
RV/LV ratio	NR
RV function	NR
Change in heart rate, beats/minute	-5.4 ± 19.2 vs. -9.6 ± 15.8 (p=0.4)
Change in PA thrombus burden	-7.5 ± 3.8 vs. -10.1 ± 3.9 (p=0.02)[g]
Oxygen saturation, %	NR
All-cause readmission, n/N (%)	30 days: 2/24 (8%) vs. 1/26 (4%) (p=0.1)
Safety	
Bleeding complications	Major bleeding: 0/26 (0%) vs. 1/26 (4%) (p=1.0)[h] Moderate bleeding: 0/26 (0%) vs. 0/26 (0%) (p=NA) Minor bleeding: 1/26 (4%) vs. 1/26 (4%) (p=1.0)
Procedure-related SAEs	NR

Author, year	Graif et al 2020 [59]
Procedure-related death	2/26 (8%) vs. 0/26 (0%) (p=0.5) These deaths are reported in all-cause mortality. Both are reported as procedure-related.
Procedure-related readmission	PE or procedure-related 30-day readmission: 1/2 (50%) vs. 0/1 (0%) (p=1.0)
Minor AEs	1/26 (4%) vs. 1/26 (4%) (p=1.0)[i]
Major AEs	2/26 (8%) vs. 1/26 (4%) (p=1.0)[i] It is likely these include major bleeding and deaths reported above.
Other safety outcomes	Cardiac arrest after initial procedure: 2/26 (8%) vs. 0/26 (0%) (p=0.5) Thrombocytopenia: 0/26 (0%) vs. 1/26 (4%) (p=1.0) There were no incidence of heparin-induced thrombocytopenia or acute kidney injury in either treatment group.

Abbreviations: AE – adverse event; AHA – American Heart Association; CDT – catheter-directed thrombolysis; DVT – deep vein thrombosis; ESC – European Society of Cardiology; ICU – intensive care unit; LoS – length of stay; LV – left ventricular; NA – not applicable; NR – not reported; PA – pulmonary artery; PAP – pulmonary artery pressure; PE – pulmonary embolism; QoL – quality of life; RV – right ventricular; SAE – serious adverse event.

Notes: Values are reported as mean ± standard deviation, unless otherwise reported and intervention vs. comparator.

[a] *Demographics and outcomes are reported for matched cases only. Of note, the type of anticoagulation received post-procedure was significantly different between the intervention and comparator group (more patients in the CDT group received unfractionated heparin infusion and more patients in the aspiration group received low-molecular-weight heparin ($p < 0.001$). Also, more patients in the CDT group had a body mass index > 30kg/m^2 compared with the aspiration group ($p=0.048$).*

[b] *Nomenclature and definitions for PE risk differ slightly between the ESC and AHA guidelines (i.e. high-risk PE – massive PE and intermediate-risk PE – submassive PE) [6, 16]. For the purpose of this extraction, we have used the terminology that was used in the study.*

[c] *There was no explanation for the missing patient.*

[d] *Total procedure time was measured from the time of administration of local anaesthetic (start) to application of dressing (end).*

[e] *All patients were monitored in the intensive care unit for the duration of the thrombolytic infusion.*

[f] *Calculated only for 16 patients who were admitted and discharged from the intensive care unit.*

[g] *Measured according to the Miller PE severity index, determined by a board-certified interventional radiologist.*

[h] *Bleeding outcomes were classified according to the Global Use of Strategies to Open Occluded Arteries (GUSTO) criteria.*

[i] *Complications were classified as major or minor according to the Society of Interventional Radiology (SIR) reporting standards.*

Table A-2: Percutaneous aspiration thrombectomy: Results from observational studies

Author, year	Tu et al 2019 [50]	Sista et al 2021 [61]	Toma et al 2022 [33]
Country	United States	United States	United States
Sponsor	Inari Medical Inc.	Penumbra Inc.	Inari Medical Inc.
Intervention/Product	Aspiration thrombectomy using FlowTriever	Aspiration thrombectomy using Indigo	Aspiration thrombectomy using FlowTriever
Study design	Prospective single-arm study Mutlicentre	Prospective single-arm study Mutlicentre	Prospective single-arm study Mutlicentre
Number of pts	104[a]	119	800[b]
Inclusion criteria	Patients 18 to 75 years of age with symptomatic, computed tomography–documented proximal PE of ≤14 days' duration, who were haemodynamically stable with no vasopressor requirement, heart rate <130 beats/min, systolic blood pressure ≥90 mm Hg at baseline assessment, and site-reported RV/LV ratio (on the basis of CT) of ≥0.9.	Patients with signs and symptoms of acute PE for ≤14 days, CTA evidence of PE, systolic blood pressure ≥90 mmHg with evidence of dilated RV (RV/LV ratio > 0.9) and ≥18 years of age.	Patients ≥18 years old with acute intermediate- or high-risk PE (per ESC guidelines) who underwent mechanical thrombectomy at the discretion of the treating physician or local PE response team.
Age of patients (yrs)	55.6 ± 13.7	59 ± 15.0	61.2 ± 14.6 (n=797)
Male, n/N (%)	56/104 (54%)	66/119 (55%)	431/798 (54%)
ESC/AHA risk catergory, n/N (%)c	Intermediate-risk PE: 104 (100%)	Massive PE: 1/119 (1%) Submassive PE: 118/119 (99%)	High-risk PE: 63/797 (7.9%) Intermediate-risk PE: 734/797 (92.1%)
Were HR/massive patients contraindicated to/failed systemic thrombolytics?	NA	NR	Not reported per PE risk stratification, only overall Absolute contraindication: 31/255 (12.2%) Relative contraindication: 224/255 (87.8%) Failed any prior therapy for current PE[d]: 40/771 (5.2%) Failed systemic thrombolysis: 4/40 (10%) Failed catheter directed thrombolysis: 2/40 (5.0%) Failed other mechanical thrombectomy: 3/40 (7.5%)
Did IR/submassive patients experience haemodynamic deterioration despite anticoagulants? n/N (%) **Were patients contraindicated to/failed systemic thrombolytics? n/N (%)**	Haemodynamic deterioration: No Contraindicated to thrombolysis: NR Failed thrombolysis: No	NR	
History of PE or DVT, n/N (%)	Prior DVT: 14 (13.5%) Prior PE: 10 (9.6%)	Prior DVT: 72 (60.5) Prior PE: 21 (17.6%)	Prior PE: 85/798 (10.7%) Prior DVT: 143/797 (17.9%)
Co-intervention	2 patients (1.9%) received thrombolytics immediately following thrombectomy	During the procedure: 2/119 (1.7%) of patients received intrapulmonary arterial tPA as an adjunctive treatment Post-procedure: 7/119 (6%) received tPA over the 48 h post-procedure	CDT: 18/799 (2.3%) Other mechanical thrombectomy: 1/799 (0.1%)
Follow-up (days)	30	30	30
Loss to follow-up, n/N (%)	2 (1.9%) Reason NR	1/119 (0.8%) This patient's procedure was aborted due to tortuous vessel anatomy	65/799 (8.1%) 46/65 (71%) withdrew from the study and 19/65 (29%) unknown status due to missing data

Author, year	Tu et al 2019 [50]	Sista et al 2021 [61]	Toma et al 2022 [33]
Outcomes			
Procedural characteristics			
Access site	Femoral: 104/104 (100%)	Femoral: 102/119 (85.7%) Jugular: 17/119 (14.3%)	Femorale: 794/798 (99.5%)
PE location	Unilateral, right: 4/104 (4%) Unilateral, left: 1/104 (1%) Central only: 5/104 (5%) Bilateral only: 53/104 (51%) Central + bilateral: 41/104 (39%)	Unilateral[f]: 8/119 (6.7%) Bilateral[f]:111/119 (93.3%) Right pulmonary artery: Upper 106/119 (89.1%); Mid 103/119 (86.6%); Lower 107/119 (89.9%) Left pulmonary artery: Upper 89/119 (74.8%); Mid 86/119 (72.3%); Lower 94/119 (79.0%)	PE location at screening: Saddle PE 319/798 (40.0%); Unilateral PE 68/798 (8.5%); Bilateral PE 411/798 (51.5%) Location of treated PE: Central only 234/798 (29.3%); Lobar only 100/798 (12.5%); Both 464/798 (58.1%)
Procedural time (mins)	93.8 ± 29.6 (reported for n=100)	37.0 (range: 23.5, 60.0)g	Total procedure time: median 66.0 (IQR: 51.0, 92.0) (n=757) Thrombectomy time: median 43.0 (IQR: 29.0, 62.0) (n=753)
Estmated blood loss, mls	NR	73.1% of patients had an estimated overall blood loss of < 400 ml	Overall: median 225.0 ml (IQR: 95.0, 400.0) (n=721) With FlowSaver blood return device: median 100.0 (IQR: 50.0, 200.0) (n=79/721) Without FlowSaver blood return: median 250.0 (IQR: 100.0, 400.0) (n=642/721)
Number of passes attempted with device	Number of passes attempted: 3.9 ± 1.7 (maximum 10) Number of passes with clot retrieved: 3.2 ± 1.6 Number with clot retrieved on no passes: 3 (2.9%) Number with clot retrieved on all passes: 66 (63.5%)	NR	NR
Efficacy			
PE-related deaths, n/N (%)	0/104 (0%)	0/119 (0%)	NR
All-cause mortality, n/N (%)	1/104 (1%) At 23 days from respiratory failure from undiagnosed breast cancer.	3/119 (2.5%) 95% CI: 0.0, 5.3 2 deaths occurred due to progression of existing diseases (cancer and ischemic stroke). 3rd death reported under Safety.	48 hours: 2/794 (0.3%) All reported as unrelated to the device[h] 30-days: 6/734 (0.8%) All reported as unrelated to the device[i]
Haemodynamic decompensation, n/N (%)	4/104 (4%)[j]	NR	NR
Chronic thrombolic pulmonary hypertension, n/N (%)	NR	NR	NR
PE recurrence, n/N (%)	0/104 (0%)	0/119 (0%)	NR
Patient-centric outcomes (i.e. QoL, LoS)	ICU stay required: NR Duration of ICU stay: 1.5 ± 2.1 Duration of hosital stay: 4.1 ± 3.5 (reported for n=103)	ICU stay required: 73/119 (61%) Duration of ICU stay: 1.0 (range: 1, 2)	ICU stay required (1 night)[k] : 153/756 (20.2%) (n=756) Duration of ICU stay: median 1 (IQR: 1, 2) (n=756)

Author, year	Tu et al 2019 [50]	Sista et al 2021 [61]	Toma et al 2022 [33]
PAP outcomes, mean mm Hg	Systolic PAP: baseline 135.7 ± 20.0; post-procedure 130.7 ± 21.1 (p=0.07); 48 hour 123.7 ± 16.4 (p < 0.0001 compared to baseline); 30 days 133.1 ± 14.7 (p=0.27 compared to baseline) Diastolic PAP: baseline 85.6 ± 12.0; post-procedure 83.7 ± 13.0 (p=0.27); 48 hour 74.0 ± 10.8 (p < 0.0001 compared to baseline); 30 days 79.5 ± 10.9 (p < 0.0001 compared to baseline) Mean PAP: baseline 29.8; post-procedure 27.8 (p=0.001)	Mean reduction in systolic PAP: Pre- to immediately post-aspiration 4.3 (95% CI 2.6, 5.9) 7.9% reduction (p < 0.0001)	Mean change in systolic PAP: -12.8 (23.4% decrease) n=769 (p < 0.0001) Mean change in right arterial pressure: -2.6 (16.9% decrease) n=657 (p < 0.0001) Change in mean PAP: -7.6 (23.0% decrease) n=767 (p < 0.0001)
RV/LV ratio	Mean baseline RV/LV ratio (n=104) 1.56 Mean 48-hour RV/LV ratio (n=101) 1.15 Mean 0.38 decrease (p < 0.0001) Equating to a mean 25.1% reduction post-procedure. Baseline variables or site did not significantly affect this outcome.	Mean RV/LV reduction from baseline to 48 hours: 0.43 (95% CI: 0.38, 0.47) (p < 0.0001) Equating to 27.3 ± 12.99% (95% CI: 24.83, 29.67) reduction.	Mean RV/LV change from baseline to 48 hours: 1.23 ± 0.36 to 0.98 ± 0.31 n=582 (p < 0.0001)
RV function	NR	NR	Mean RV systolic pressure change from baseline to 48 hours: 48 ± 14.9 to 38.8 ± 14.8 (22.9% decrease) n=130 (p < 0.0001) Decrease in severe RV function from baseline to 48 hours: 29.0% to 4.7% n=212 (p < 0.0001)
Change in heard rate, beats/minute	Baseline 89.5 ± 15.6; post-procedure 92.1 ± 16.5 (p=0.22); 48 hour 89.7 ± 15.6 (p=0.95 compared to baseline); 30 days 80.2 ± 13.6 (p < 0.0001 compared to baseline)	NR	Mean change from baseline to 48 hours: -12.0 (11.2% decrease) n= 778 (p < 0.0001)
Change in PA thrombus burden, mean score	Baseline 20.8 ± 2.4 Post-procedure 18.9 ± 2.9 p < 0.001[l]	Mean reduction at 48 hours: 11.3% (p < 0.0001)[m]	NR
Oxygen saturation, mean %	Baseline 95.7 ± 3.3; post-procedure 95.4 ± 4.1 (p=0.61); 48 hour 96.4 ± 2.1 (p=0.95 compared to baseline); 30 days 97.3 ± 1.9 (p < 0.0001 compared to baseline)	NR	NR
All-cause readmission, n/N (%)	NR	NR	30 days: 6.2%
Safety			
Bleeding complications	Major bleeding at 48 hours[n]: 1/104 (1%) Note: this patient is included in the 4 patients who experienced clinical deterioration (reported above under efficacy) and a procedure-related SAE (below)	Major bleeding at 48 hours[o]: 2/119 (1.7%) Note: these 2 patients are included in SAE composite (below)	Major bleeding at 48 hours[p]: 11/788 (1.4%) Note: no major bleed involved intracranial haemorrhage
Procedure-related AEs	48 hours: 4/104 (3.8%) experienced 6 SAEs Note 1: same 4 patients who experienced clinical deterioration (reported under efficacy above)	Device-related SAE composite at 48 hours[q]: 1/119 (0.8%)	3/788 (0.4%) (2 were clinical deterioration and 1 was a cardiac injury). Note 1: 0/788 pulmonary vascular injuries (0%) Note 2: 1/788 cardiac injuries (0.1%)

Author, year	Tu et al 2019 [50]	Sista et al 2021 [61]	Toma et al 2022 [33]
Procedure-related AEs *(continuation)*	Note 2: The authors reported that the events were procedure-related, not device-related. Note 3: 1 major bleeding event and 1 pulmonary vascular injury (the major bleeding event experienced by 1 patient was also classified as pulmonary vascular injury and clinical deterioration (1/104; 1.0%). Vascular injury was reported to be procedure-related.		Note 2: The authors reported that none of the events had a confirmed relationship with the study device.
Procedure-related death	0/104 (0%)	48 hours: 1/119 (0.8%) Note: this patient is included in SAE composite (below) and reported to be device-related	0/788 (0%) device-related deaths
Procedure-related readmission	NR	NR	30 days: 1.4%
Minor AEs	NR	NR	NR
Major AEs	30 days: 14/104 (13.2%) experienced 26 SAEs (inclusive of procedure-related SAEs). 5/14 (35.7%) experienced multiple SAEs	SAE composite 48 hours[r]: 2/119 (1.7%)	SAE at 48 hours: 35 events occurred in 34/791 (4.3%) of patients Note 1: It is likely the procedural-related AE reported above are included in this figure. Note 2: The authors reported that none were deemed as-related to the device.
Treatment-related cardiac injury	0/104 (0%)	0/119 (0%)	1/788 (0.1%)[w]
Treatment-related pulmonary vascular injury	1/104 (1.0%)[s]	1/119 (0.8%)[u]	0/788 (0%)
Treatment-related clinical deterioration	4/104 (3.8%)[st]	1/119 (0.8%)[uv]	2/788 (0.3%)[wx]
Other safety outcomes	Technical complications during index procedure: 2/104 (2%) Both consisted of kinking of the guide catheter	Aborted procedure: 1/119 (0.8%) Due to tortuous vessel anatomy	-

Abbreviations: AE – adverse event; AHA – American Heart Association; CDT – catheter-directed thrombolysis; CI – confidence interval; CT – computed tomography; CTA – computed tomography angiography; DVT – deep vein thrombosis; ESC – European Society of Cardiology; ICU – intensive care unit; IQR – interquartile range; LoS – length of stay; LV – left ventricular; NA – not applicable; NR – not reported; PA – pulmonary artery; PAP – pulmonary artery pressure; PE – pulmonary embolism; QoL – quality of life; RV – right ventricular; SAE – serious adverse event; tPA – tissue type plasminogen activator.

Notes: Values are reported as mean ± standard deviation, unless otherwise reported.

[a] *total of 106 patients were treated; however, 2 of these received adjunct thrombolytics and were analysed separately. Only the findings for the 104 patients who did not receive adjunct therapies have been extracted.*

[b] *800 patients were enrolled, one patient was excluded post-enrolment for meeting one of the exclusion criteria in effect at the time. Patient demographic data and results is not available for all patients. No reasons for this were provided by the study authors.*

[c] *Nomenclature and definitions for PE risk differ slightly between the ESC and AHA guidelines (i.e. high-risk PE – massive PE and intermediate-risk PE – submassive PE) [6, 16]. For the purpose of this extraction, we have used the terminology that was used in the study.*

[d] *In some patients more than one therapy was attempted.*

[e] *Access site sample size is the total number of access sites.*

[f] *Unilateral or bilateral classification: clots in the pulmonary arteries of one or both lungs, respectively, regardless of whether main pulmonary artery clots also occur.*

[g] *Time from first device insertion to last device removal.*

[h] *One intermediate-risk PE patient died due to cardiopulmonary arrest on day 2 post-thrombectomy.*
The second death occurred in an intermediate-risk PE patient who experienced a new PE, one day after thrombectomy.

[i] *Additional four deaths at 30 day follow-up were due to: 1) pre-existing cancer; 2) septic shock secondary to pneumonia; 3) septic shock secondary to ischemic bowel; and 4) deterioration during orthopaedic surgery that involved a new PE and cardiac arrest.*

[j] *Procedure-related clinical deterioration (defined as: unplanned requirement for mechanical ventilation, arterial hypotension (>1h or requiring vasopressors), cardiopulmonary resuscitation, persistent worsening in oxygenation, or emergency surgical embolectomy). These are the same four patients who experienced SAEs.*

[k] *It is reported that 62.6% required no overnight stay post-procedure and 20.2% required one overnight stay. The remaining 19.2% required more than one overnight stay.*

[l] *Measured according to the Miller PE severity index, determined by a board-certified interventional radiologist.*

[m] *Clot burden was measured using the Qanaldi computed tomography obstruction index.*

[n] *Bleeding events were classified according to the Valve Academic Research Consortium-2 Guidelines as 'major' if they met the criteria for life threatening, disabling or major bleeding.*

[o] *Bleeding outcomes were classified according to the Global Use of Strategies to Open Occluded Arteries (GUSTO) criteria.*

[p] *Major bleeding was defined as symptomatic bleeding in a critical area or organ, bleeding causing a haemoglobin drop of at least 5 g/dL, bleeding leading to transfusion of at least 2 units of blood products, or fatal bleeding, similar to Bleeding Academic Research Consortium (BARC) type 3b or greater*

[q] *Composite of device-related clinical deterioration (1/119; 0.8%), device-related pulmonary vascular injury (1/119; 0.8%) and device-related cardiac injury (0/119; 0%).*
Both events occurred in the same patient

[r] *Composite of major bleeding (2/119; 1.7%) and device-related death (1/119; 0.8%).*

[s] *Included in procedure-related adverse event composite*

[t] *Treatment-related clinical deterioration comprised treatment-related events such as unplanned requirement for mechanical ventilation, arterial hypotension (> 1h or requiring vasopressors), cardiopulmonary resuscitation, persistent worsening in oxygenation, ore emergency surgical embolectomy.*

[u] *Included in SAE at 48 hours composite and device-related adverse event at 48 hours composite*

[v] *Treatment-related clinical deterioration was defined as having one of the following: 1) the need for cardiopulmonary resuscitation, intubation, vasopressors, extracorporeal membrane oxygenation or extracorporeal life support; 2) systolic blood pressure <90mmHg for at least 15 min; 3) a drop of systolic blood pressure by at least 40 mmHg for at least 15 min with signs of end organ hypoperfusion (cold extremities or low urinary output <30 ml/h or altered mental status); or 4) the need for catecholamine administration to maintain adequate organ perfusion and a systolic blood pressure >90 mmHg.*

[w] *Included in procedure-related adverse events*

[x] *Treatment-related clinical deterioration defined by haemodynamic or respiratory worsening meeting specific thresholds.*

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA [70] and in the Guidelines of EUnetHTA [71].

Table A-3: Risk of bias of non –randomised studies comparing percutaneous aspiration thrombectomy versus CDT, see [71]

Study reference/ID	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of intervention	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Graif et al 2020 [59]	Moderate[a]	Critical[b]	Low	Low	Moderate[c]	Low	Moderate[d]	Critical	Most domains were scored poorly due to the retrospective nature of this study. It is unknown if this resulted in amendments to selection crtieria or outcomes reported. Propensity score matching was carried out which reduced bias somewhat but not all variables were matched

Notes:

[a] *Patients were selected retrospectively. Although propensity score matching was carried out to mitigate some of the bias associated with a retrospective study design, not all variables were propensity matched. In particular, the proportion of patients received unfractionated heparin or low molecular weight heparin post-intervention differed significantly between the treatment groups; the consequence of this on treatment effect is unknown. Additionally, the authors note that the configuration and distribution of thrombus in the pulmonary arteries (central versus peripheral) was not assessed in this study, and it was likely a factor in the selection between percutaneous aspiration thrombectomy and CDT.*

[b] *The retrospective nature of this study means it is possible selection criteria was amended to appoint certain patients into the study.*

[c] *The retrospective nature of this study means it is unknown if there were missing patients.*

[d] *The retrospective nature of this study means it is unknown if all the outcomes the authors intended on reported were reported, or if primary outcomes were modified.*

Table A-4: Risk of bias – study level (case series), see [52]

Study reference/ID	Sista et al 2021 [61]	Toma et al 2022 [33]	Tu et al 2019 [50]
Study objective			
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes
Study design			
2. Was the study conducted prospectively?	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	Yes	Yes	Yes
4. Were patients recruited consecutively?	Unclear	No[a]	Unclear
Study population			
5. Were the characteristics of the patients included in the study described?	Yes	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Yes	Yes
7. Did patients enter the study at a similar point in the disease?	Yes	No[b]	Yes
Intervention and co-intervention			
8. Was the intervention of interest clearly described?	Partial[c]	Yes	Partial[c]
9. Were additional interventions (co-interventions) clearly described?	Partial[d]	Partial[d]	Partial[d]
Outcome measures			
10. Were relevant outcome measures established a priori?	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes
Statistical Analysis			
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes
Results and Conclusions			
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes
16. Were losses to follow-up reported?	Yes	Yes	Yes
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes	Yes
18. Were the adverse events reported?	Yes	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes
Competing interests and sources of support			
20. Were both competing interests and sources of support for the study reported?	Yes	Yes	Yes
Overall risk of bias[e]	**Moderate**	**High**	**Moderate**

Notes:

[a] *Toma et al 2022 noted that recruitment of patients was, "all-comer, based on patients chosen by each treating physician to be good candidates for mechanical thrombectomy, which therefore may limit the applicability of the results to the general PE population".*

[b] *The point in the disease that patients entered the study was their PE risk status (i.e. intermediate-risk PE or high-risk PE). In studies which included a mix of intermediate-risk and high-risk patients, those who had at least 95% of patients with the same risk status were considered similar and awarded Yes for this checklist item.*

[c] *A partial score was given because a description of when the procedure was considered complete was not provided.*

[d] *This study indicated that adjunctive thrombolytics was administered in a proportion of its patient population. A partial score was given because the specific details of the thrombolytics given was not reported, i.e. drug type and/or dosage and timing of administration.*

[e] *Overall risk of bias was determined if a study fulfilled the three criteria deemed important by the report authors: 1) consecutive recruitment (item 4); 2) similar disease at entry into study (item 7); 3) clearly described intervention and co-interventions (items 8 and 9). If a study fulfilled all these criteria, they were considered to have low overall risk of bias. If they did not fulfil one or more of these criteria, they were considered to have moderate or high overall risk of bias, respectively.*

Table A-5: Evidence profile: efficacy and safety of percutaneous aspiration thrombectomy in intermediate- and high-risk PE patients

Quality assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparison	Relative (95% CI)	Absolute (95% CI)	
All cause 30-day mortality											
1 [59]	Matched-control CS	Serious[a]	None[b]	Serious[c]	Very serious[d]	None	2/26 (7.7%)	0/26 (0%)	RR 4.7 (0.2, 92.6)	0 fewer per 1,000	⨁◯◯◯ Very low
Major bleeding											
1 [59]	Matched-control CS	Serious[a]	None[b]	Serious[c]	Very serious[d]	None	0/26 (0.0%)	1/26 (3.8%)	RR 0.35 (0.01, 8.1)	25 fewer per 1,000 (38 fewer, 273 more)	⨁◯◯◯ Very low
Procedure-related mortality											
1 [59]	Matched-control CS	Serious[a]	None[b]	Serious[c]	Very serious[d]	None	2/26 (7.7%)	0/26 (0%)	RR 4.7 (0.2, 92.6)	0 fewer per 1,000	⨁◯◯◯ Very low
Major bleeding (48 hours)											
3 [33, 50, 61]	Single-arm	Serious[f]	Not serious	Serious[g]	Not serious	None	14/1,011 (mean: 1.4%; range: 1%, 1.7%)	NA	NA	NA	⨁◯◯◯ Very low
Procedure-related mortality											
3 [33, 50, 61]	Single-arm	Serious[f]	Not serious	Serious[g]	Not serious	None	1/1,011 (mean: 0.1%; range: 0%, 0.8%)	NA	NA	NA	⨁◯◯◯ Very low

Quality assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparison	Relative (95% CI)	Absolute (95% CI)	
Treatment-related clinical deterioration (48 hours)											
3 [33, 50, 61]	Single-arm	Serious[f]	Not serious	Serious[g]	Not serious	None	7/1,011 (mean: 0.7%; range: 0.3%, 3.8%)	NA	NA	NA	⨁◯◯◯ Very low
Treatment-related pulmonary vascular injury (48 hours)											
3 [33, 50, 61]	Single-arm	Serious[f]	Not serious	Serious[g]	Not serious	None	2/1,011 (mean: 0.2%; range: 0%, 1.0%)	NA	NA	NA	⨁◯◯◯ Very low
Treatment-related cardiac injury (48 hours)											
3 [33, 50, 61]	Single-arm	Serious[f]	Not serious	Serious[g]	Not serious	None	1/1,011 (mean: 0.1%; range: 0%, 0.1%)	NA	NA	NA	⨁◯◯◯ Very low

Sources: Graif et al 2020 [59]; Sista et al 2021 [61];Toma et al 2022 ; Tu et al 2019 [50]

Abbreviations: CI – confidence interval; CS – case series; MD – mean difference; NA – not applicable; RR – relative risk.

Notes:

[a] *Retrospective design with bias concerns due to baseline confounding owing to patients being on different anticoagulants and configuration and distribution of thrombus in the pulmonary being a likely factor for selection of use of either intervention or comparator device. Also, critical concerns regarding bias of selection criteria of participants into study given inclusion/exclusion was done retrospectively.*

[b] *Cochrane suggests when there is only one study that "none" should be stated for this outcome.*

[c] *Most of the patients (96%) had intermediate-risk PE; however only 8% were contraindicated to thrombolysis. In addition, there was no mention that they were haemodynamically unstable prior to the procedure. Thus, they do not match the population defined in the PICO. The remaining PICO domains (intervention, comparator, outcomes) do not contribute to indirectness.*

[d] *The study only had 52 patients total. It is unlikely it would be powered to detect a significant difference.*

[e] *The study only had 52 patients total. It is unlikely it would be powered to detect a significant difference. In addition, the standard deviations for the change in PAP were large.*

[f] *Studies marked down due to: one study noted patients weren't consecutively recruited and physician chose patients based on if they would be good candidates, in the other studies it was unclear if recruitment was consecutive. Co-interventions (thrombolysis) mentioned by all studies but not the quantity used. Two studies didn't state how it was determined procedure was finished. In one study patients had a different disease status.*

[g] *One study had a mixture of high- and intermediate-risk PE and the other two were intermediate-risk PE patients only. Intermediate-risk patients were not haemodynamically unstable. Only a portion of the patients in one study and no patients in the other two studies were reported to have either failed or be contraindicated to thrombolysis. Thus, they do not match the population defined in the PICO. The remaining PICO domains do not contribute to indirectness.*

Applicability table

Table A-6: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The included studies had a very heterogenous mixture of patients. In no study did all the patients match either of the two patient poulations defined in the PICO criteria (high-risk PE and failed or contrainidicated for systemic thrombolysis and intermediate-risk PE, with haemodynamic instability despite anticoagulation and failed or contraindicated for systemic thrombolysis). Two of the four studies, including the non randomised comparative study, had a mixture of high-risk and intermediate-risk patients, albeit mainly intermediate risk. In the comparative study only 8% of patients were contraindicated to thrombolytics and in the other large registry study contraindications to thrombolytics (either relative or absolute) were reported in only 32.1% of patients. There was no mention that intermediate-risk patients experienced haemodynamic instability prior to the procedure in either of these studies. The other two single-arm studies only included intermediate-risk PE patients, with the exception of one patient in one of the studies who had high-risk PE. Neither study reported that the patients were haemodynamically unstable prior to the procedure, one specifically noting this was an exclusion criteria. In addition, neither study reported whether the patients were either contraindicated to thrombolytics, although one noted no patients had failed thrombolysis. Complicating the interpretation and applicability of the three single-arm studies included for safety was the fact that a small percentage of patients received thrombolytics (≤ 6% in all three) either during the procedure or within the 48 hours post-procedure. In summary, most of the patients included in the studies in this assessment do not match either of the two PICO populations – they mainly included intermediate-risk PE patients without haemodynamic instability or contraindications to thrombolytics.The risk of short term mortality in this group is much lower than that observed for high-risk PE (or intermediate-risk PE that has progressed to become haemodynamically unstable) [18]. It is reported that anticoagulants alone prevents mortality for most patients with intermediate-risk PE [18]. As such, the applicability of data from these patients to those defined in the PICO is uncertain.
Intervention	Two different percutaneous aspiration thrombectomy devices were covered in the evidence base that informed this assessment – the FlowTriever System and the Indigo System. These two devices are CE marked and indicated for treatment of PE. It should be noted that since the first generation of these devices there have been several design iterations and improvements aimed at reducing blood loss. These include the Lightning 12 Aspiration System by Penumbra Inc., which includes computer-aided mechanical aspiration which reportedly differentiates between clot and blood and the FlowSaver device by Inari Medical, which filters aspirated thrombi and blood for reinfusion back to the patient. The large registry study included for safety notes that the FlowSaver device was used in a limited number of patients in the later phase of enrolment. It is not known whether the latest iterations of these devices would result in greater safety and efficacy than what was observed in the studies included in this assessment.
Comparators	Only one comparative study was identified and included in this assessment. This comparator procedure, CDT, was listed in the PICO. Advice from a clinical expert (radiologist) is that most large hospitals could perform this procedure.
Outcomes	The longest follow-up in the included studies was 30 days. The outcomes most commonly reported include PE or device-related deaths, all cause mortality, pulmonary arterial pressure, duration of hospital stay, number of patients requiring ICU stay, change in thrombus burden, bleeding complications and other serious adverse events. If the studies were on the populations of interest – high-risk patients or intermediate risk patients who become haemodynamically unstable, both groups with a contraindication or failure to systemic thrombolysis, then short-term mortality, as reported in the included studies, is noted by the AHA to be the best measure of clinical effectiveness because this group is at high risk of mortality. Although procedural safety should be monitored, the AHA note that tolerance for procedure-related complications is high given the high short-term mortality associated with anticoagulation alone in this population [18]. However, most of the patients in the included studies that informed this assessment had intermediate-risk PE without haemodynamic instability. In this population the AHA notes that clinical and patient centric outcomes should be reported over a longer term including PE-related mortality, chronic thromboemolic pulmonary hypertension and measures of functional status and QoL such as the 6-minute walk test, Pulmonary Embolism Quality of Life score, New York Heart Association Classification and Short-Form-36 scores [18].
Setting	Three of the four studies that informed this assessment were all conducted in the USA. The fourth, a large registry study included for safety, was conducted in multiple sites in the USA and throughout Europe (Austria, Belgium, France, Germany, Switzerland and the United Kingdom); however, the study only reports results from the full USA cohort. Thus, the results are likely to be applicable to the Austrian context. The type of clinical settings the procedures were performed in was not reported in the studies, with the exception of the single-centre, non randomised comparative study which stated that the records were retrieved from a community hospital system.

Abbreviations: AHA – American Heart Association; CDT – catheter-directed thrombolysis; ICU – intensive care unit; PE – pulmonary embolism; QoL – quality of life; USA – United States of America.

List of ongoing randomised controlled trials

Table A-7: List of ongoing RCTs of aspiration thrombectomy

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT05684796 STORM-PE	Patients with intermediate-high-risk acute PE Estimated enrolment = 100	Mechanical aspiration thrombectomy with the Indigo Aspiration System	Anticoagulation with unfractionated heparin or low molecular weight heparin	Change in RV/LV ratio at 48 hours on original therapy as assessed by CT pulmonary angiogram	March 2026	Penumbra Inc.
NCT05111613 PEERLESS	Patients with intermediate-high-risk acute PE Estimated enrolment = 550	Mechanical thrombectomy for PE using the FlowTriever System	CDT for PE (any commercially available system)	Composite clinical endpoint of the following: all-cause mortality, or intracranial haemorrhage, or major bleeding, or clinical deterioration defined by haemodynamic or respiratory worsening, and/or escalation to a bailout therapy, or ICU admission and ICU length-of-stay	March 2024	Inari Medical

Abbreviations: CDT – catheter-directed thrombolysis; CT – computed tomography; ICU – intensive care unit; LV – left ventricle; PE – pulmonary embolism; RV – right ventricle.

Search date: 09.12.2022

Literature search strategies

Search strategy for Cochrane

Search Name: Percutaneous Aspiration Thrombectomy	
Search date: 09.12.2022	
ID	Search
#1	MeSH descriptor: [Pulmonary Embolism] explode all trees
#2	((pulmon* OR lung* OR bronch* OR thromb*) NEAR (embol* OR thromboembol* OR thrombo-embol* OR clot*)) (Word variations have been searched)
#3	(PE):ti,ab,kw
#4	#1 OR #2 OR #3
#5	MeSH descriptor: [Thrombectomy] explode all trees
#6	(thrombectom*) (Word variations have been searched)
#7	((thrombus OR thrombi OR clot*) NEAR (remov* OR resect* OR extract* OR surg*)) (Word variations have been searched)
#8	#5 OR #6 OR #7
#9	(aspirat*) (Word variations have been searched)
#10	MeSH descriptor: [Suction] explode all trees
#11	(suction*) (Word variations have been searched)
#12	#9 OR #10 OR #11
#13	#8 AND #12
#14	(thromboaspirat*) (Word variations have been searched)
#15	(thrombo-aspirat*) (Word variations have been searched)
#16	(thrombosuction*) (Word variations have been searched)
#17	(thrombo-suction*) (Word variations have been searched)
#18	((aspirat* OR suction* OR vacuum*) NEAR (thrombectom* OR embolectom* OR thromboembolectom* OR thrombo-embolectom* OR thrombus OR thrombi)) (Word variations have been searched)
#19	(catheter-based aspirat*) (Word variations have been searched)
#20	(FlowTriever*) (Word variations have been searched)
#21	(Flow-Triever*) (Word variations have been searched)
#22	(indigo NEAR aspirat*) (Word variations have been searched)
#23	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#24	#4 AND #23
#25	(conference proceeding):pt
#26	(abstract):so
#27	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#28	#25 OR #26 OR #27
#29	#24 NOT #28
Total hits: 66	

Search strategy for Embase

Search Name: Percutaneous Aspiration Thrombectomy		
Search date: 09.12.2022		
No.	Query Results	Results
#1.	'lung embolism'/exp	118,567
#2.	(pulmon* OR lung* OR bronch* OR thromb*) NEAR/1 (embol* OR thromboembol* OR 'thrombo-embol*' OR clot*)	265,832
#3	pe:ti,ab	77,460
#4	#1 OR #2 OR #3	322,683
#5	'thrombus aspiration'/exp	5,303
#6	(aspirat* OR suction*) NEAR/1 (thrombectom* OR embolectom* OR thromboembolectom* OR 'thrombo-embolectom*' OR thrombus OR thrombi OR clot*)	6,330
#7	vacuum NEAR/2 (thrombectom* OR embolectom* OR thromboembolectom* OR 'thrombo-embolectom*' OR thrombus OR thrombi OR clot*)	80
#8	thromboaspirat*	575
#9	'thrombo-aspirat*'	94
#10	thrombosuction*	131
#11	'thrombo-suction*'	17
#12	'catheter-based aspirat*'	10
#13	flowtriever*	184
#14	'flow-triever*'	6
#15	indigo NEAR/1 aspirat*	33
#16	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	6,659
#17	#4 AND #16	1,156
#18	#4 AND #16 AND ([english]/lim OR [german]/lim)	1,121
#19	#18 AND 'Conference Abstract'/it	375
#20	#18 NOT #19	746
Total hits: 746		

Search strategy for Medline via Ovid

Search Name: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to December 06, 2022>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2018 to December 06, 2022>	
Search date: 09.12.2022	
ID	Search
#1	exp Pulmonary Embolism/
#2	((pulmon* or lung* or bronch* or thromb*) adj2 (embol* or thromboembol* or thrombo-embol* or clot*)).mp.
#3	PE.ti,ab.
#4	1 or 2 or 3
#5	exp Thrombectomy/
#6	thrombectom*.mp.
#7	((thrombus or thrombi or clot*) adj3 (remov* or resect* or extract* or surg*)).mp.
#8	5 or 6 or 7
#9	aspirat*.mp.
#10	exp Suction/
#11	suction*.mp.
#12	9 or 10 or 11
#13	8 and 12
#14	thromboaspirat*.mp.

#15	thrombo-aspirat*.mp.
#16	thrombosuction*.mp.
#17	thrombo-suction*.mp.
#18	((aspirat* or suction*) adj (thrombectom* or embolectom* or thromboembolectom* or thrombo-embolectom* or thrombus or thrombi)).mp.
#19	(vacuum* adj2 (thrombectom* or embolectom* or thromboembolectom* or thrombo-embolectom* or thrombus or thrombi)).mp.
#20	catheter-based aspirat*.mp.
#21	FlowTriever.mp.
#22	Flow-Triever.mp.
#23	(indigo adj aspirat*).mp.
#24	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
#25	4 and 24
#26	limit 25 to (english or german)
#27	remove duplicates from 26
Total hits: 525	

Search strategy for INATHTA

Search Name: Percutaneous Aspiration Thrombectomy	
Search date: 09.12.2022	
ID	Search
#1	"Thrombectomy"[mhe],"25","2022-12-09T13:06:09.000000Z"
#2	thrombectom*,"26","2022-12-09T13:06:27.000000Z"
#3	(thrombus OR thrombi OR clot*) AND (remov* OR resect* OR extract* OR surg*),"37","2022-12-09T13:07:05.000000Z"
#4	((thrombus OR thrombi OR clot*) AND (remov* OR resect* OR extract* OR surg*)) OR (thrombectom*) OR ("Thrombectomy"[mhe]),"62","2022-12-09T13:07:42.000000Z"
#5	aspirat*,"59","2022-12-09T13:08:13.000000Z"
#6	"Suction"[mhe],"8","2022-12-09T13:08:31.000000Z"
#7	suction*,"12","2022-12-09T13:08:54.000000Z"
#8	vacuum*,"26","2022-12-09T13:09:07.000000Z"
#9	(vacuum*) OR (suction*) OR ("Suction"[mhe]) OR (aspirat*),"95","2022-12-09T13:09:23.000000Z"
#10	((vacuum*) OR (suction*) OR ("Suction"[mhe]) OR (aspirat*)) AND (((thrombus OR thrombi OR clot*) AND (remov* OR resect* OR extract* OR surg*)) OR (thrombectom*) OR ("Thrombectomy"[mhe])),"0","2022-12-09T13:09:54.000000Z"
#11	thromboaspirat*,"0","2022-12-09T13:10:21.000000Z"
#12	thrombo-aspirat*,"0","2022-12-09T13:10:26.000000Z"
#13	thrombosuction*,"1","2022-12-09T13:10:34.000000Z"
#14	thrombo-suction*,"0","2022-12-09T13:11:10.000000Z"
#15	(aspirat* OR suction* OR vacuum*) AND (thrombectom* OR embolectom* OR thromboembolectom* OR thrombo-embolectom* OR thrombus OR thrombi),"0","2022-12-09T13:11:52.000000Z"
#16	(aspiration thrombectom*),"0","2022-12-09T13:12:37.000000Z"
#17	suction thrombectom*,"0","2022-12-09T13:13:09.000000Z"
#18	aspiration thromboembolectom*,"0","2022-12-09T13:14:18.000000Z"
#19	aspiration thrombo-embolectom*,"0","2022-12-09T13:14:22.000000Z"
#20	suction thromboembolectom*,"0","2022-12-09T13:14:49.000000Z"
#21	suction thrombo-embolectom*,"0","2022-12-09T13:15:03.000000Z"
#22	vacuum thrombectom*,"0","2022-12-09T13:16:04.000000Z"
#23	vacuum thromboembolectom*,"0","2022-12-09T13:16:40.000000Z"
#24	vacuum thrombo-embolectom*,"0","2022-12-09T13:16:44.000000Z"
#25	catheter-based aspirat*,"0","2022-12-09T13:18:51.000000Z"

#26	FlowTriever*,"0","2022-12-09T13:19:11.000000Z"
#27	Flow-Triever*,"0","2022-12-09T13:19:21.000000Z"
#28	indigo,"0","2022-12-09T13:19:56.000000Z"
#29	(indigo) OR (Flow-Triever*) OR (FlowTriever*) OR (catheter-based aspirat*) OR (vacuum thrombo-embolectom*) OR (vacuum thromboembolectom*) OR (vacuum thrombectom*) OR (suction thrombo-embolectom*) OR (suction thromboembolectom*) OR (aspiration thrombo-embolectom*) OR (aspiration thromboembolectom*) OR (suction thrombectom*) OR ((aspiration thrombectom*)) OR ((aspirat* OR suction* OR vacuum*) AND (thrombectom* OR embolectom* OR thromboembolectom* OR thrombo-embolectom* OR thrombus OR thrombi)) OR (thrombo-suction*) OR (thrombosuction*) OR (thrombo-aspirat*) OR (thromboaspirat*) OR (((vacuum*) OR (suction*) OR ("Suction"[mhe]) OR (aspirat*)) AND (((thrombus OR thrombi OR clot*) AND (remov* OR resect* OR extract* OR surg*)) OR (thrombectom*) OR ("Thrombectomy"[mhe]))),"1","2022-12-09T13:20:58.000000Z"
#30	((indigo) OR (Flow-Triever*) OR (FlowTriever*) OR (catheter-based aspirat*) OR (vacuum thrombo-embolectom*) OR (vacuum thromboembolectom*) OR (vacuum thrombectom*) OR (suction thrombo-embolectom*) OR (suction thromboembolectom*) OR (aspiration thrombo-embolectom*) OR (aspiration thromboembolectom*) OR (suction thrombectom*) OR ((aspiration thrombectom*)) OR ((aspirat* OR suction* OR vacuum*) AND (thrombectom* OR embolectom* OR thromboembolectom* OR thrombo-embolectom* OR thrombus OR thrombi)) OR (thrombo-suction*) OR (thrombosuction*) OR (thrombo-aspirat*) OR (thromboaspirat*) OR (((vacuum*) OR (suction*) OR ("Suction"[mhe]) OR (aspirat*)) AND (((thrombus OR thrombi OR clot*) AND (remov* OR resect* OR extract* OR surg*)) OR (thrombectom*) OR ("Thrombectomy"[mhe]))) AND (Engish OR German)[Language],"0","2022-12-09T13:21:33.000000Z"
Total hits: 0	

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