Systemic Thrombolysis for Acute Pulmonary Embolism: Alteplase vs. Tenecteplase, Full-Dose vs. Half-Dose

Introduction

1. Acute pulmonary embolism (PE) carries a 30-day mortality of ~2% (low-risk) to >25% (high-risk / massive). The 2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN multi-society guideline (Creager et al.) stratifies PE by risk: **high-risk** (sustained hypotension or arrest), **intermediate-high-risk** (RV dysfunction + elevated troponin + hemodynamically stable), **intermediate-low-risk** (RV dysfunction OR troponin), and **low-risk**.
2. Systemic IV thrombolysis is a Class I recommendation for high-risk (massive) PE per the 2026 multi-society guideline. The standard regimen is alteplase 100 mg IV over 2 hours (or 0.6 mg/kg up to 50 mg over 15 min in cardiac arrest).
3. For intermediate-high-risk PE (formerly "submassive"), the role of systemic thrombolysis remains controversial. PEITHO (Meyer 2014, n = 1,005) showed tenecteplase reduced hemodynamic decompensation (RR 0.30) but at the cost of major bleeding (11.5% vs. 2.4%) and intracranial hemorrhage (2.0% vs. 0.2%) — without mortality benefit at 7 days or 2 years (Sanchez 2022 long-term).
4. Reduced-dose / "safe-dose" thrombolysis (MOPETT 50 mg alteplase, ultra-low-dose 20 mg, viscoelastometry-guided individualized dosing) and catheter-directed thrombolysis (CDT, ULTIMA, OPTALYSE-PE) have emerged as bleeding-mitigation strategies. **Two 2026 RCTs** — Kjaergaard (Cardiovasc Res, n = 210, 20 mg alteplase USAT vs. IV vs. heparin) and Kállai (Intensive Care Med Exp, viscoelastometry-guided median 32 mg rtPA over 8.5 hr) — represent the most recent evidence on dose individualization. The 2026 multi-society guideline recommends CDT for intermediate-high-risk PE in centers with PE response team (PERT) capability when bleeding risk is elevated.
5. Tenecteplase (single-bolus, fibrin-specific) and alteplase (2-hour infusion) are the most-studied agents. Direct head-to-head comparative data in PE are limited; the choice typically reflects institutional formulary, vial size, and operator familiarity. **PEITHO-3 (Sanchez 2025) is the awaited definitive trial** of reduced-dose tenecteplase, designed to address the bleeding signal of full-dose tenecteplase in PEITHO.
6. This pearl synthesizes the available randomized evidence — 9 landmark RCTs (including 2 published in 2026 on low-dose strategies) and 1 large meta-analysis (n >2,500 patients combined) — focused on systemic thrombolysis for acute PE. Catheter-directed thrombolysis is mentioned as adjunct context but is a separate clinical workflow with its own pharmacology profile.

Pharmacology

Pharmacology — Systemic Thrombolytics for Acute PE		
	Alteplase (Activase®)	**Tenecteplase (TNKase®)**
Mechanism of Action	Recombinant tissue plasminogen activator (tPA); converts plasminogen to plasmin, lyses fibrin within the embolus.	Genetically modified tPA variant (T103N, N117Q, KHRR 296-299AAAA mutations) — increased fibrin specificity (~14×), decreased PAI-1 inhibition (~80×), longer half-life (~17 vs.

		5 min).
FDA-approved PE dose	**100 mg IV over 2 hours** (full dose, FDA-approved for PE) **Cardiac arrest from PE:** 0.6 mg/kg (max 50 mg) IV over 15 min, then heparin **Off-label half-dose (MOPETT):** 50 mg total (10 mg bolus + 40 mg over 2 hr)	**NOT FDA-approved for PE** (FDA approval limited to AMI; PE use is off-label) **PEITHO regimen:** weight-based single bolus over 5–10 sec — 30 mg (<60 kg), 35 mg (60–69), 40 mg (70–79), 45 mg (80–89), 50 mg (≥90 kg) **PEITHO-3 reduced-dose:** 50% of standard dose (under investigation)
Administration	Reconstitute 100 mg vial with sterile water → 1 mg/mL Bolus 10 mg IV over 1 min, then 90 mg over 2 hr via dedicated peripheral line **Heparin:** HOLD during infusion; resume when aPTT <2× upper normal limit	Reconstitute 50 mg vial with 10 mL sterile water → 5 mg/mL Single IV bolus over 5–10 sec — major logistical advantage **Heparin:** hold during bolus; resume when aPTT <2× upper normal limit
PK/PD	Half-life: ~5 min (initial) Hepatic metabolism Fibrin specificity: moderate PAI-1 sensitive	Half-life: ~17–20 min (initial) Hepatic metabolism Fibrin specificity: 14× higher PAI-1 resistant (~80× reduction in inhibition)
Adverse Effects	• **Major bleeding**: ~11–13% (full-dose 100 mg); ~3% (half-dose MOPETT 50 mg); numerically increased but reduced vs. full-dose with low-dose 20 mg (Kjaergaard 2026) • **Intracranial hemorrhage**: 1.5–2% (full-dose); 0% in MOPETT (n = 121); 0% in Kállai 2026 viscoelastometry-guided cohort (n = 12) • Allergic / anaphylactoid reactions (rare) • Site bleeding, hypotension during infusion	• **Major bleeding**: 11.5% (PEITHO full-dose) vs. 2.4% placebo • **Intracranial hemorrhage**: 2.0% (PEITHO) vs. 0.2% placebo (RR 9.8) • Higher ICH risk in patients age >75 (PEITHO subgroup) • PEITHO-3 (Sanchez/Klok 2025) — reduced dose to mitigate bleeding signal
Drug Interactions and Warnings	**Anticoagulants:** DOACs, warfarin, heparin — bleeding synergy **Antiplatelets:** aspirin/P2Y12 — bleeding synergy **Absolute CIs:** active major bleeding, recent intracranial pathology (<3 mo CVA, CNS neoplasm), recent surgery (<10 days), suspected aortic dissection	Same anticoagulant/antiplatelet warnings as alteplase **Age >75:** ICH risk substantially elevated — consider half-dose or CDT alternative Standard absolute and relative CIs apply equally
Compatibility	Reconstitute with sterile water (NO bacteriostatic — inactivates) Compatible with NS post-reconstitution; D5W can be used	Reconstitute with sterile water; compatible with NS post-reconstitution

Comments	**Only thrombolytic FDA-approved for PE.** Standard of care for high-risk (massive) PE. Reduced-dose strategies expanding: MOPETT 50 mg (n = 121), Kjaergaard 2026 ultra-low 20 mg over 6 hr (n = 210), and Kállai 2026 viscoelastometry-guided individualized dosing (median 32 mg over 8.5 hr) all show favorable safety profiles.	**Off-label for PE but heavily used** — single-bolus logistics make it preferred in some centers. PEITHO (full-dose) showed reduced hemodynamic decompensation but at major bleeding cost. Reduced-dose tenecteplase under definitive evaluation in PEITHO-3 (Sanchez 2025).

Overview of Evidence — Systemic Thrombolysis for Acute PE

Author, year	Design / sample size	Intervention & comparison	Outcome
Konstantinides S, 2002 (MAPPET-3)	Multicenter double-blind RCT (n = 256 adults with intermediate-risk PE: RV dysfunction, normotensive)	Alteplase 100 mg IV over 2 hr + heparin vs. placebo + heparin	Primary composite (death or treatment escalation): 11.0% (alteplase) vs. 24.6% (heparin alone) — p = 0.006 NO significant mortality difference at 30 days (3.4% vs. 2.2%) NO major bleeding requiring transfusion in alteplase group Established benefit of thrombolysis in intermediate-risk PE for preventing decompensation
Sharifi M, 2013 (MOPETT)	Single-center RCT (n = 121 adults with moderate PE: RV strain or hemodynamic concern, stable)	Half-dose alteplase 50 mg total (10 mg bolus + 40 mg over 2 hr) vs. anticoagulation alone Both groups received anticoagulation	Pulmonary HTN at 28 mo: 16% (half-dose) vs. 57% (control) — p < 0.001 Recurrent PE: 0% vs. 5% (NS) Major bleeding or ICH: 0% in BOTH groups Established proof-of-concept for reduced-dose thrombolysis with markedly improved safety profile
Meyer G, 2014 (PEITHO)	Multicenter, double-blind, placebo-controlled RCT (n = 1,005 adults with intermediate-high-risk PE: RV dysfunction + positive troponin)	Tenecteplase weight-based single bolus + heparin vs. placebo + heparin	Primary composite (death or hemodynamic decompensation at 7 days): 2.6% vs. 5.6% — OR 0.44; p = 0.02 All-cause mortality at 7 days: 1.2% vs. 1.8% (NS) Major extracranial bleeding: 6.3% vs. 1.2% (p < 0.001) Hemorrhagic stroke / ICH: 2.0% vs. 0.2% (p = 0.003) — particularly elevated in patients age >75 Established the trade-off: prevented decompensation BUT bleeding cost
Kline JA, 2014 (TOPCOAT)	Multicenter, double-blind RCT (n = 83 adults with intermediate-risk	Tenecteplase weight-based bolus + LMWH vs. placebo + LMWH	Primary composite (90-day functional capacity, dyspnea, mortality): favored tenecteplase (p = 0.017 in completed cohort)

	PE — early termination due to slow enrollment)		37% reduction in poor outcomes with tenecteplase Limited by underpowering (target n = 200) Supported PEITHO findings for symptomatic / functional benefit
Chatterjee S, 2014 (meta)	Meta-analysis of 16 RCTs (n = 2,115 adults — high + intermediate-risk PE)	Thrombolysis (alteplase, tenecteplase, urokinase, streptokinase) vs. anticoagulation alone	All-cause mortality: 2.17% (thrombolysis) vs. 3.89% (anticoag) — OR 0.53; NNT = 59 Recurrent PE: OR 0.40; NNT = 54 Major bleeding: 9.24% vs. 3.42% — OR 2.73; NNH = 18 ICH: 1.46% vs. 0.19% — OR 4.63; NNH = 78 Established population-level mortality benefit BUT clear bleeding signal in intermediate-risk subgroup
Sanchez O, 2022 (PEITHO long-term)	5-year long-term follow-up of PEITHO trial (n = 709 of 1,005 enrolled)	Tenecteplase + heparin vs. placebo + heparin — extended outcomes	All-cause mortality at 2 years: 20.3% (tenecteplase) vs. 18.0% (placebo) — NS Persistent dyspnea: 36% vs. 30% (NS) Persistent RV dysfunction: 11% vs. 13% (NS) Chronic thromboembolic pulmonary hypertension (CTEPH): 2.1% vs. 3.2% (NS) Confirmed: NO long-term mortality benefit OR durable functional improvement to offset acute bleeding cost
Klok FA, 2024 (PEITHO-3 protocol)	Ongoing/recent multicenter RCT (n target = 650 adults with intermediate-high-risk PE)	Reduced-dose tenecteplase (~50% of weight-based dose) + heparin vs. placebo + heparin	Primary composite at day 30: PE-related death, hemodynamic decompensation, or recurrent symptomatic PE Designed to test whether reduced-dose maintains efficacy benefit while mitigating bleeding cost Awaited definitive evidence — may redefine intermediate-risk thrombolysis pathway
Kjaergaard J, 2026	Multicenter open-label RCT (n = 210 adults with intermediate-high-risk PE, Denmark)	3-arm: ultra-low-dose alteplase (20 mg over 6 hr) by USAT vs. by IV vs. heparin alone	Low-dose thrombolysis reduced thrombus burden (refined Modified Miller Score) by 3.6 points vs. heparin (95% CI 2.2–5.0; $p < 0.001$) USAT vs. IV route: NO difference in thrombus reduction (mean diff −0.1; $p = 0.88$) — catheter route adds no efficacy Bleeding complications numerically more frequent with low-dose thrombolysis (NS) Establishes 20 mg alteplase IV as effective thrombus-reducing dose; questions added value of ultrasound-assisted catheter

			delivery
Kállai A, 2026	Single-center RCT feasibility trial (n = 19 analyzed, Hungary)	Viscoelastometry-guided individualized rtPA dosing (VGG, median 32 mg over 8.5 hr) vs. ESC-recommended 100 mg/2 hr (CG)	VGG received SIGNIFICANTLY LOWER total rtPA dose (median 32 mg vs. 100 mg) over LONGER duration RV dysfunction resolved in ALL VGG patients; persisted in 2/7 control patients Major bleeding: 1/12 (VGG) vs. 2/7 (CG) — numerically lower with individualized dosing Establishes feasibility of personalized, viscoelastometry-guided low-dose thrombolysis
Creager MA, 2026 (multi-society guideline)	AHA/ACC/ACCP/ ACEP/CHEST/ SCAI/SHM/SIR/ SVM/SVN multi-society guideline	Comprehensive evaluation and management recommendations for acute PE in adults	High-risk PE: systemic thrombolysis Class I (full-dose alteplase 100 mg) Intermediate-high-risk PE: thrombolysis or CDT "may be considered" in centers with PERT — individualized risk-benefit Reduced-dose alteplase (MOPETT) and tenecteplase reasonable alternatives in selected patients Patients age >75, recent surgery, or high bleeding risk: prefer CDT over systemic

Conclusions

- **Systemic thrombolysis is Class I for high-risk (massive) PE** — full-dose alteplase 100 mg IV over 2 hr (or 0.6 mg/kg up to 50 mg over 15 min in cardiac arrest) per the 2026 multi-society guideline (Creager et al.).
- **For intermediate-high-risk PE: PEITHO trade-off (Meyer 2014)** — tenecteplase reduced hemodynamic decompensation (OR 0.44) but caused 5× more major bleeding and 10× more intracranial hemorrhage. PEITHO long-term (Sanchez 2022) confirmed NO mortality OR functional benefit at 2 years.
- **Reduced-dose alteplase strategies are accumulating evidence:** MOPETT 50 mg (0% major bleeding/ICH at n = 121, sustained PH reduction at 28 months); Kjaergaard 2026 ultra-low 20 mg (n = 210, IV route as effective as USAT for thrombus reduction); Kállai 2026 viscoelastometry-guided individualized dosing (median 32 mg, complete RV recovery, n = 19 feasibility). PEITHO-3 (Sanchez 2025) is the awaited definitive reduced-dose tenecteplase trial. 2026 guideline labels reduced-dose "reasonable."
- **Catheter-directed thrombolysis (CDT) does not appear to add efficacy over equivalent low-dose IV thrombolysis** — the 2026 Kjaergaard RCT (n = 210, 20 mg alteplase USAT vs. IV) found ZERO difference in thrombus burden reduction between routes (mean diff −0.1; p = 0.88). CDT remains preferred per 2026 guideline in PERT centers when bleeding risk is elevated, but the case for ultrasound-assisted catheter delivery as an efficacy advantage is now substantially weaker.
- **Tenecteplase is off-label for PE but increasingly used** — single-bolus administration, fibrin specificity, and PAI-1 resistance offer logistical and pharmacologic advantages. Lack of FDA approval is the only formal barrier.
- **Age >75 substantially elevates ICH risk** — PEITHO subgroup analysis showed disproportionate hemorrhagic stroke in this group. Strongly consider CDT or reduced-dose thrombolysis instead of full-dose systemic.
- **Anticoagulation is co-administered with thrombolysis** — HOLD heparin during the infusion/bolus, resume when aPTT <2× upper normal limit. Switch to DOAC after 5–10 days per standard PE management.

- **PEITHO-3 (Klok 2024) is the highest-priority trial to watch** — if reduced-dose tenecteplase preserves efficacy while eliminating the bleeding signal, it may become the new intermediate-risk standard. Awaited results.

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