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Ah, Push It! Fibrinolysis in Cardiac Arrest

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Learning Objectives

Upon completion of this program, participants will be able to:

- Review the pathophysiology of post-cardiac arrest syndrome and describe common causes of thrombosis leading to cardiac arrest.
- Evaluate the available literature and indications for use of fibrinolysis and thrombolytics in cardiac arrest.
- Formulate a care plan for post-arrest care for patients receiving fibrinolytics.

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Disclosures

- Nicholas Cottrell has no real or apparent conflicts of interest to disclose

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Thrombosis in Cardiac Arrest

- Sudden cardiac arrest is the leading cause of death in adults
- More than 365,000 out-of-hospital cardiac arrests (OHCA) annually
  - Survival approximately 10%
- In hospital cardiac arrest occurs in over 290,000 adults annually
  - Survival approximately 25%
- About 70% of these cases have underlying myocardial infarction and/or pulmonary embolism
  - Myocardial infarction accounts for about 2-4% of all cardiac arrest
  - Pulmonary thromboembolism accounts for up to 8-13% of all cardiac arrest

Resuscitation. 2002;52(1):63-69.
Sci Rep. 2021;11(1):24095.
Circulation. 2014;129(23):2426-2435.
The Journal of Emergency Medicine. 2019;57(4):478-487.

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H's

- Hypovolemia
- Hypoxia
- Hydrogen ions (acidosis)
- Hypothermia
- Hyperkalemia/hypokalemia

T's

- Tension pneumothorax
- Tamponade, cardiac
- Toxins
- Thrombosis, pulmonary
- Thrombosis, coronary

Circulation. 2020;142(16suppl2):S366-S468.

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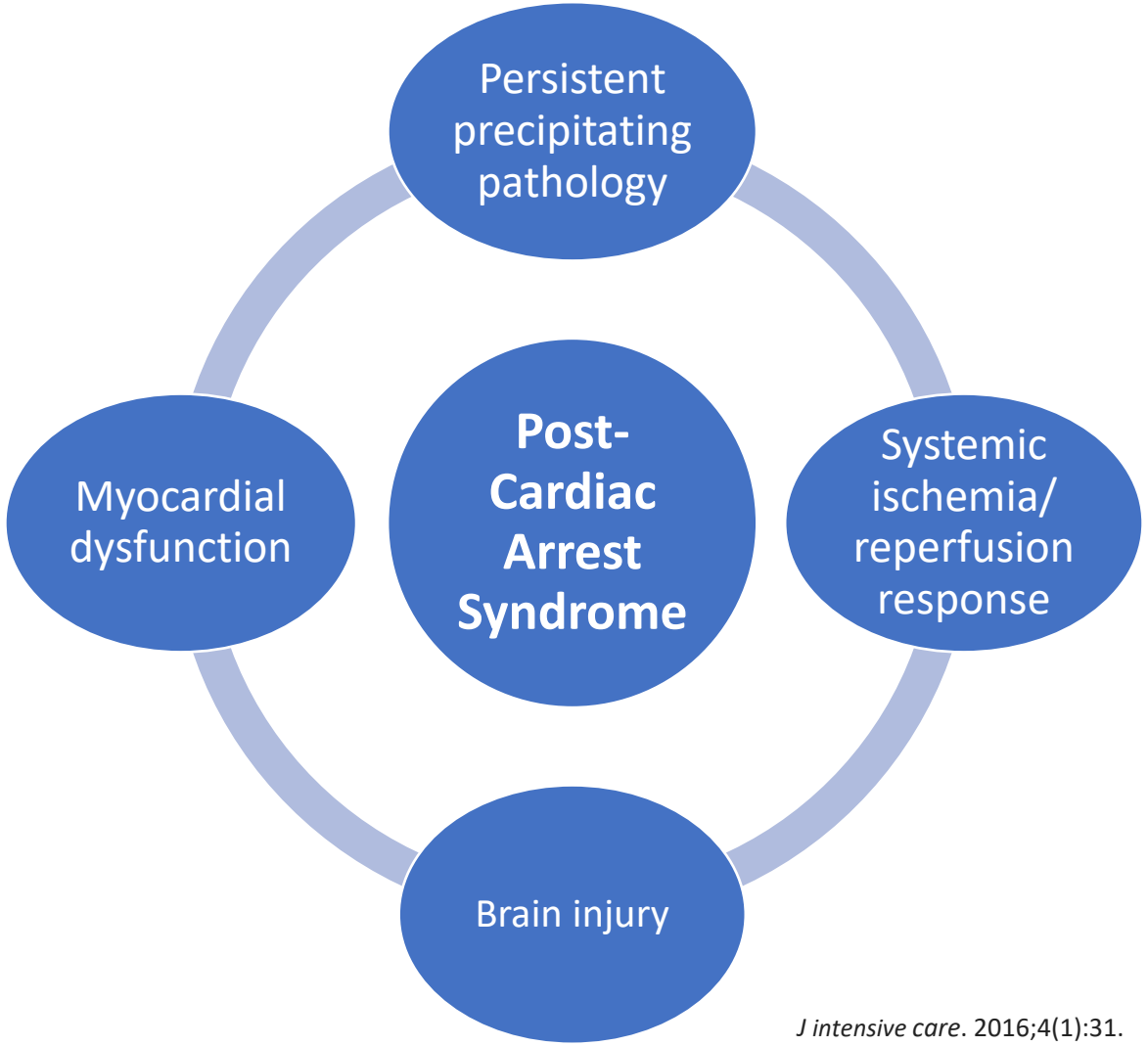
Reasons to Consider Tissue Plasminogen Activator

- Massive pulmonary embolism
- Myocardial infarction
- Aid in rehabilitation of post cardiac arrest syndrome



J intensive care. 2016;4(1):31.

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Differentiating Cause of Cardiac Arrest

- HISTORY IS KEY
  - Past medical history
  - Recent surgery history
  - Medication list/medication history
  - What was the circumstance around the arrest?
- Bedside testing
  - Point of care ultrasound (POCUS)
  - Point of care laboratory testing
  - Electrocardiogram (EKG)- rhythm analysis

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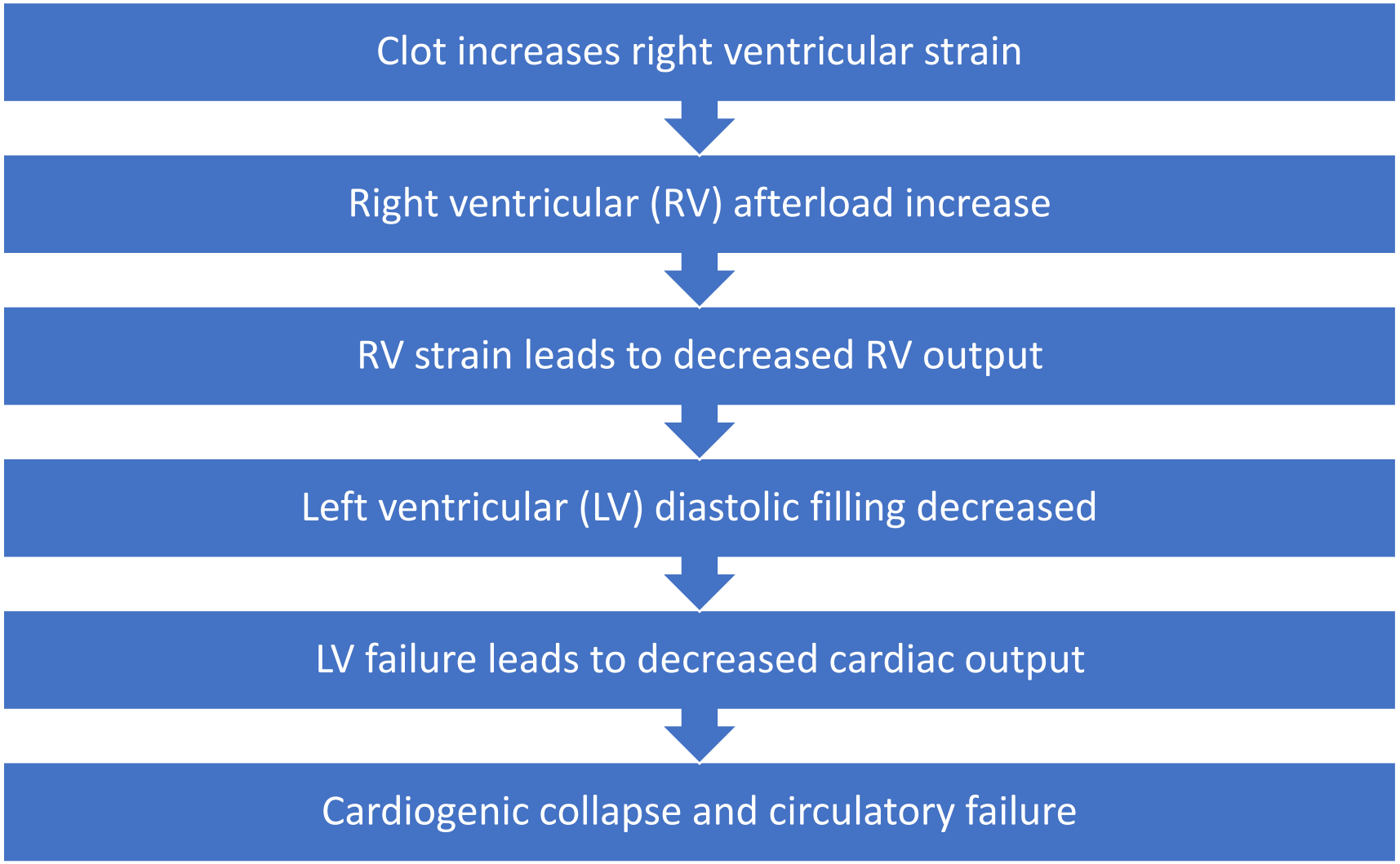
Pathophysiology- Pulmonary Embolism



Arch Intern Med. 2020;160:1529-1535.

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Considering PE as Cause of Cardiac Arrest

- History/Physical
  - PEA rhythm
  - Pre-arrest EKG (if applicable)
  - Unilateral swelling
  - Known history of PE or thromboembolic disorder
  - Pro-thrombotic medications
  - Known or suspected hypercoagulable state
  - Bystander report, EMS run sheet

Indian Heart J. 2018;70(5):731-735.
Consultant. 2021;61(5):e6-e8.
Arch Intern Med. 2020;160:1529-1535.

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Considering PE as Cause of Cardiac Arrest

- Point of Care Ultrasound (POCUS)
  - Lower extremity DVT
  - Intraventricular thrombi
  - Increased pulmonary artery or right ventricular pressures
  - Right ventricular dilatation (RV/LV >1:1)
  - Tricuspid regurgitation
  - Interventricular septal deviation
  - RV hypokinesis with normal apical contractility (McConnell sign)

J Am So Echocardiograph. 2017. 30: 714-23.e4.
SAEM Journal. 2019. 26(11). 1213-1220.
Ultrasound J. 2021;13(1):46.

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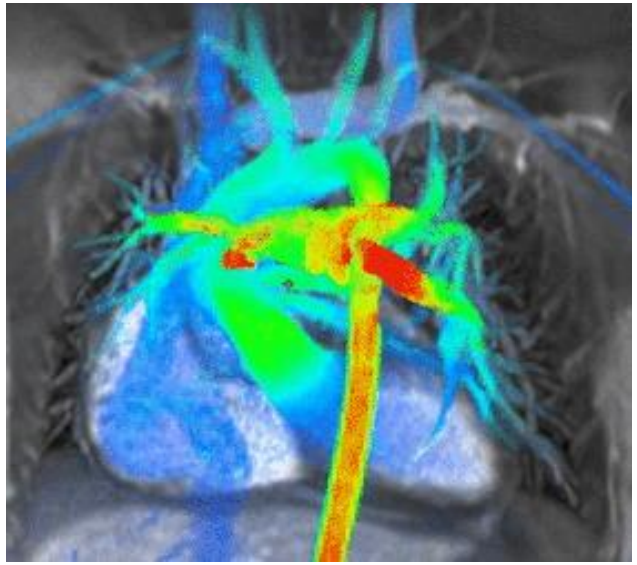
Pathophysiology- Myocardial Infarction/Ischemia

- Myocardial ischemia caused by clot in a coronary artery
- Ischemia can lead to ventricular tachyarrhythmias
- These can include the lethal ventricular arrhythmias ventricular tachycardia and ventricular fibrillation



J Am Heart Assoc. 2018;7:e010004
Image: Myocardial infarction. Physiopedia.

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Considering MI as Cause for Cardiac Arrest

- Usually shockable rhythm- ventricular tachycardia, ventricular fibrillation
- ST-elevation on EKG
- Cardiac enzyme elevation (troponin, CKMB, etc.)
- Bystander report, EMS run sheet
- Not easy to differentiate between specific types of MI in context of cardiac arrest

J Am Heart Assoc. 2018;7:e010004.
Circ: Cardiovascular Imaging. 2017;10(12).

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Knowledge Check #1

What is the most common presenting rhythm in cardiac arrest secondary to myocardial infarction/ischemia?

A. Pulseless electrical activity
B. Asystole
C. Ventricular fibrillation/tachycardia

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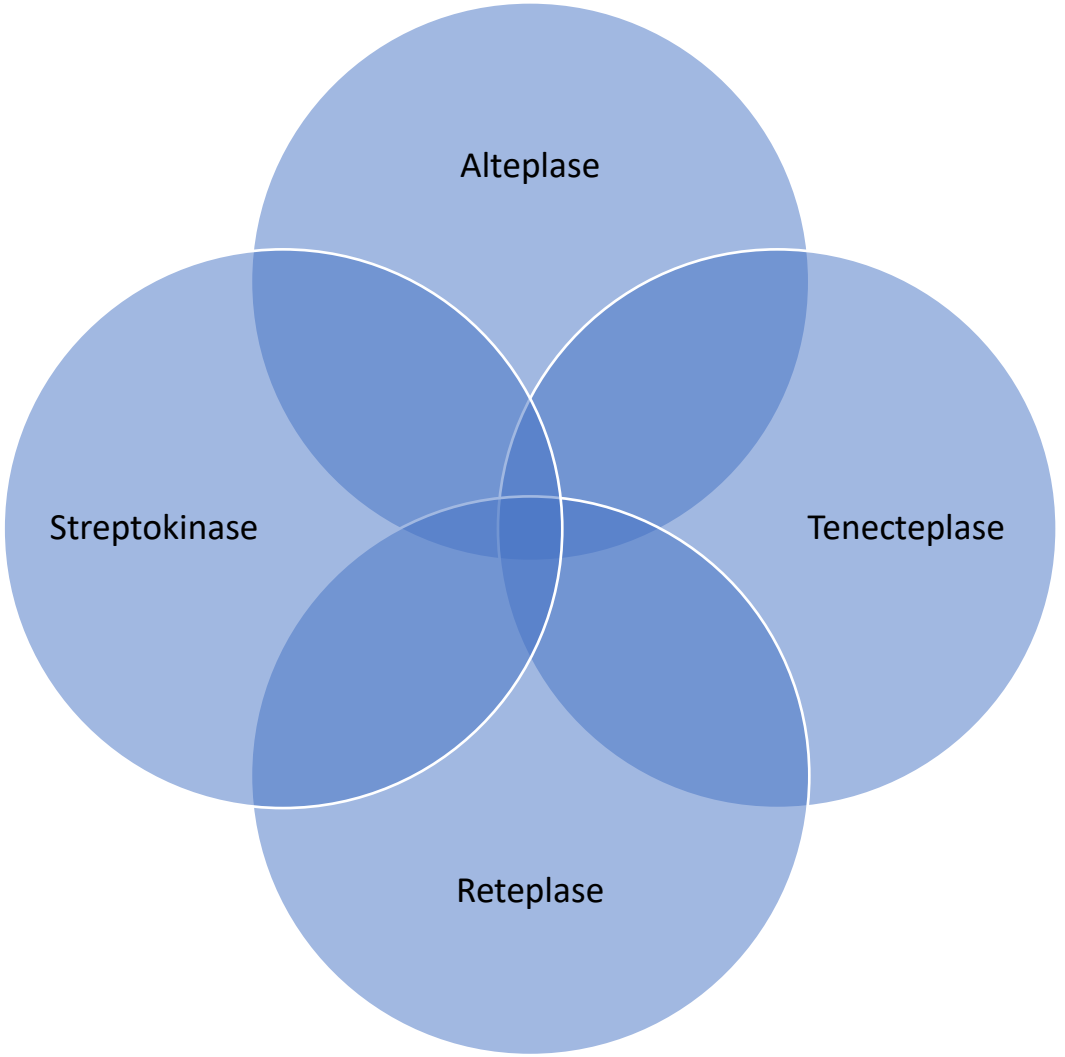
Choice of Thrombolytic Agent



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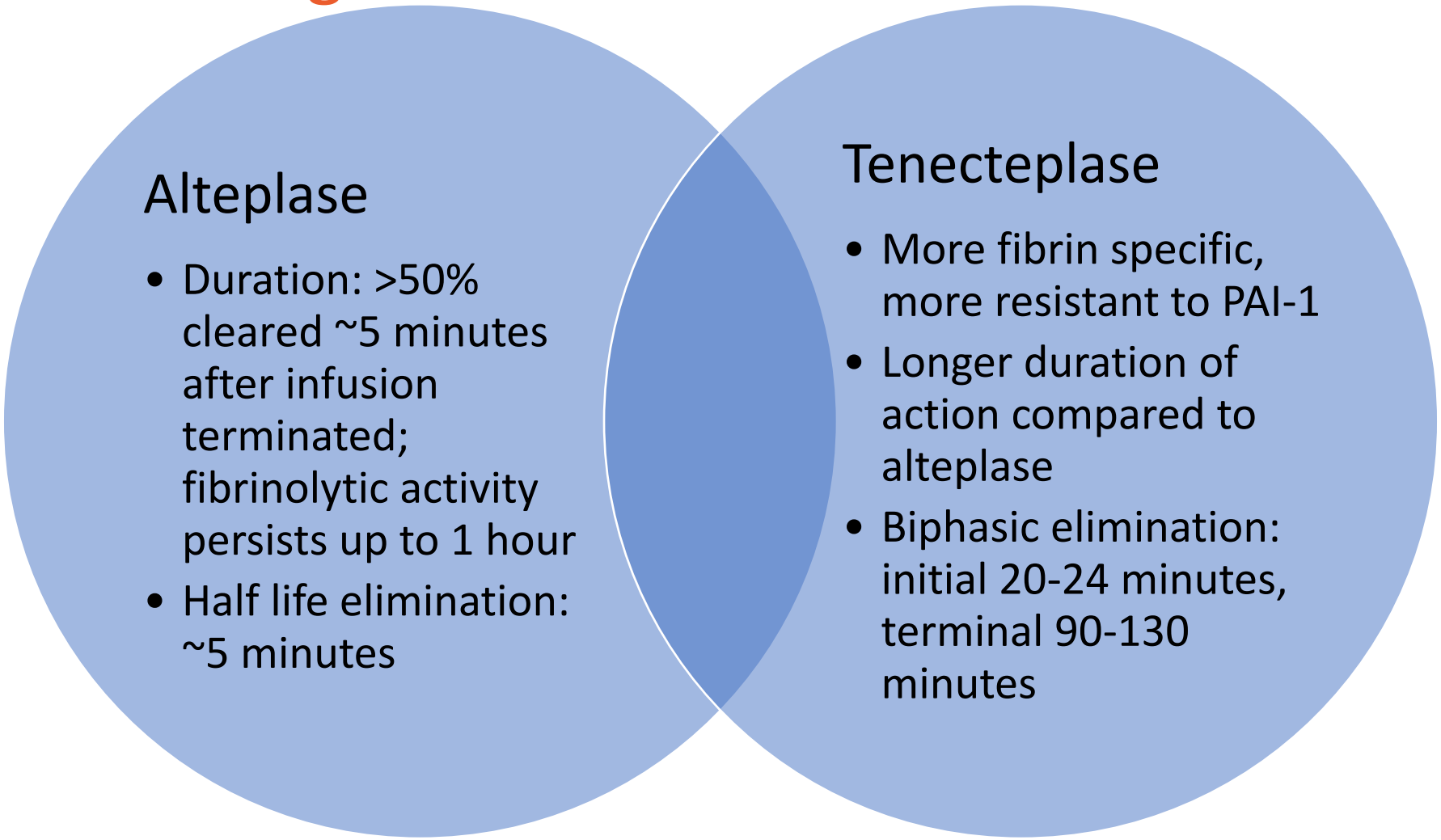
Tissue Plasminogen Activator



Activase (alteplase) [prescribing information] San Francisco, CA: Genentech; February 2018.
TNKase (tenecteplase) [prescribing information]. South San Francisco, CA: Genentech; March 2021.

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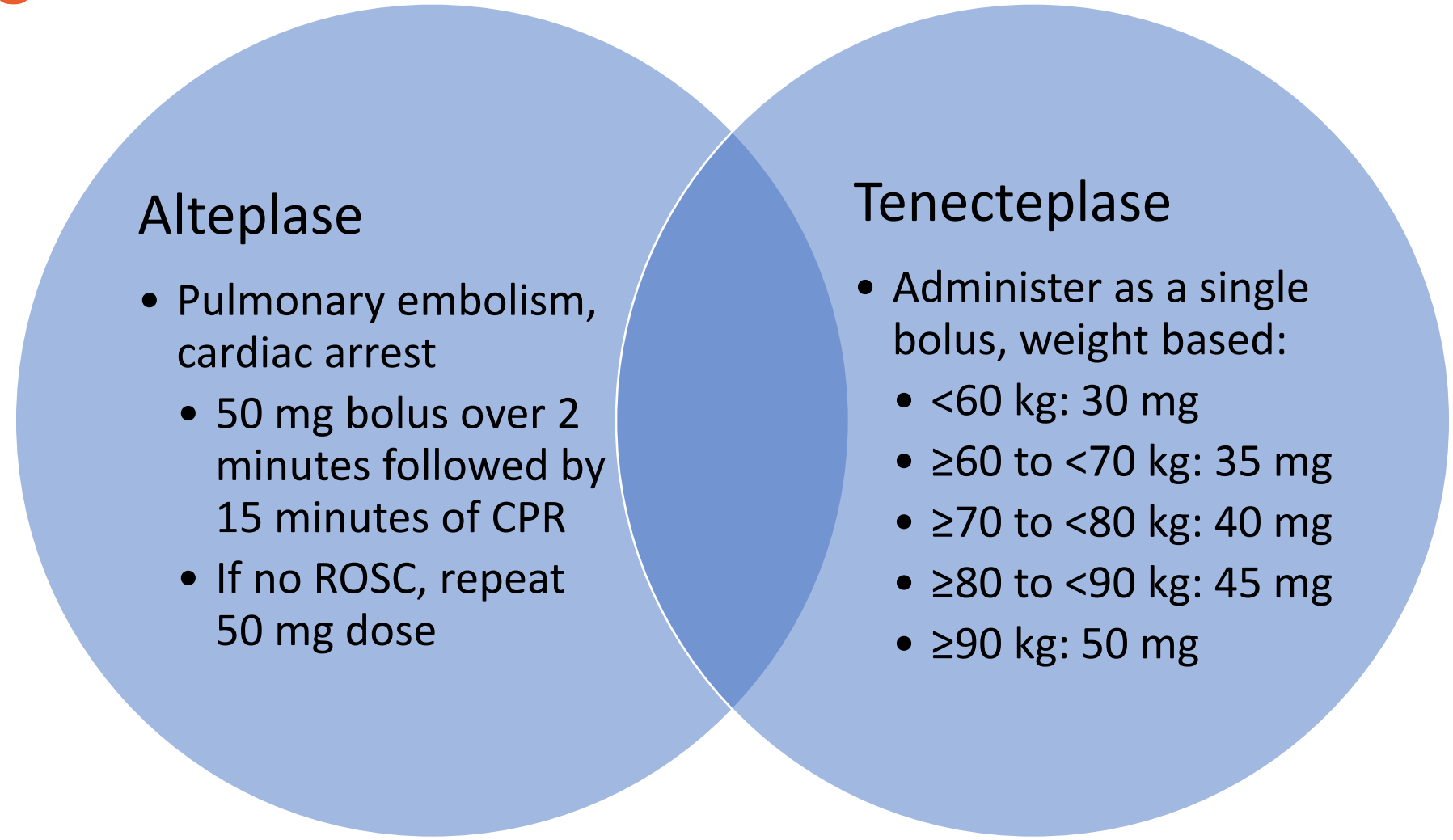
Dosing Patients WITHOUT a Pulse



Alteplase. Lexi-Drugs. Lexicomp. UpToDate, Inc.; 2022. Updated May 15, 2022. Accessed May 15, 2022.
Tenecteplase. Lexi-Drugs. Lexicomp. UpToDate, Inc.; 2022. Updated April 19, 2022. Accessed May 15, 2022.

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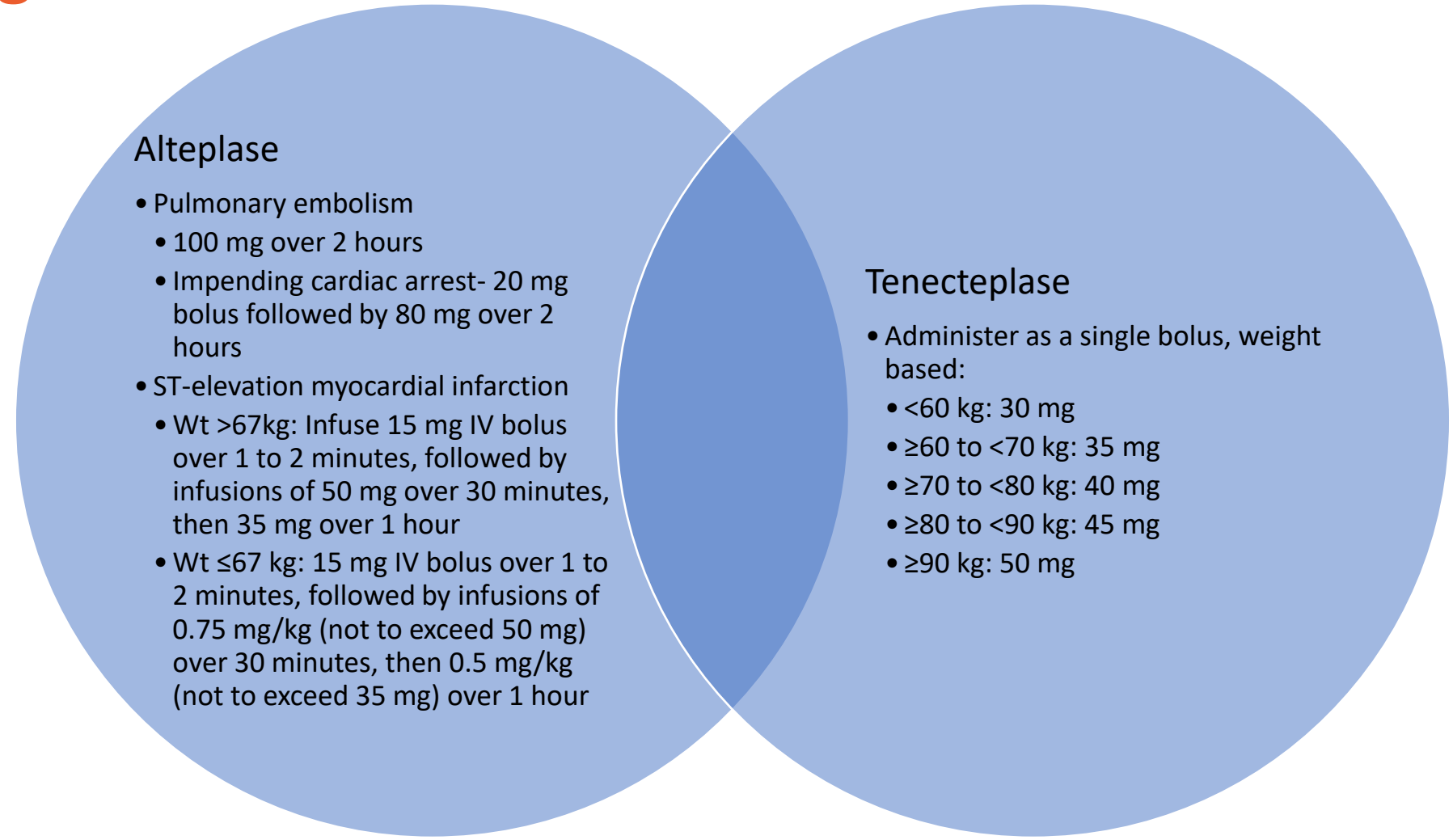
Dosing Patients with Pulse



Alteplase. Lexi-Drugs. Lexicomp. UpToDate, Inc.; 2022. Updated May 15, 2022. Accessed May 15, 2022.
Tenecteplase. Lexi-Drugs. Lexicomp. UpToDate, Inc.; 2022. Updated April 19, 2022. Accessed May 15, 2022.

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Warnings/Contraindications

Contraindications	Relative contraindications
• Active bleeding • Recent intracranial or intraspinal surgery or serious head trauma • Intracranial conditions that may increase the risk of bleeding • Bleeding diathesis • Current severe, uncontrolled hypertension • Ischemic stroke within 3 months • Significant closed head or facial trauma within 3 months	• Age greater than 75 years • Pregnancy • Current use of anticoagulant • Prolonged cardiopulmonary resuscitation • Recent bleeding • History of severe uncontrolled hypertension • Remote ischemic stroke (previous 3 months) • Major surgery within 3 weeks

- Warnings:
  - Bleeding- may cause significant and/or fatal bleeding which may occur 1 or more days after administration of alteplase
  - Thromboembolism- increased risk of thromboembolic events in patients with high likelihood of left heart thrombus and risk of re-embolization due to lysis of underlying deep vein thrombosis

Alteplase. Lexi-Drugs. Lexicomp. UpToDate, Inc.; 2022. Updated May 15, 2022. Accessed May 15, 2022.
Tenecteplase. Lexi-Drugs. Lexicomp. UpToDate, Inc.; 2022. Updated April 19, 2022. Accessed May 15, 2022.

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Summary- Dosing

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Massive Pulmonary Embolism	• 100 mg over 2 hours • Impending cardiac arrest- 20 mg bolus followed by 80 mg over 2 hours	Administer as a single bolus, weight based: <60 kg: 30 mg ≥60 to <70 kg: 35 mg ≥70 to <80 kg: 40 mg ≥80 to <90 kg: 45 mg ≥90 kg: 50 mg
ST-elevation myocardial infarction	• Wt >67kg: 15 mg IV bolus over 1 to 2 minutes, followed by infusions of 50 mg over 30 minutes, then 35 mg over 1 hour • Wt ≤67 kg: 15 mg IV bolus over 1 to 2 minutes, followed by infusions of 0.75 mg/kg (not to exceed 50 mg) over 30 minutes, then 0.5 mg/kg (not to exceed 35 mg) over 1 hour	
Patients WITHOUT a Pulse		
	Alteplase	**Tenecteplase**
Massive Pulmonary Embolism	50 mg bolus over 2 minutes followed by 15 minutes of CPR If no ROSC, repeat 50 mg dose	Administer as a single bolus, weight based: <60 kg: 30 mg ≥60 to <70 kg: 35 mg ≥70 to <80 kg: 40 mg ≥80 to <90 kg: 45 mg ≥90 kg: 50 mg
ST-elevation myocardial infarction		

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Knowledge Check #2

A 37 year-old female presents in cardiac arrest from a skilled nursing facility, initial rhythm interpreted as narrow-complex PEA. POCUS demonstrates a non-compressible L femoral vein and significant right heart strain. No past medical history is available per EMS. Upon quick examination, patient has reverse question mark incision over left temporal bone with sutures still in place.

With information presented above, this patient would be a candidate for thrombolysis.

A. True
B. False

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A. True
B. False

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2020 ACLS Guidelines

- Pulmonary embolism
  - In patients with confirmed pulmonary embolism as the precipitant of cardiac arrest, thrombolysis, surgical embolectomy, and mechanical thrombectomy are reasonable emergency treatment options (2a, C-LD)
  - Thrombolysis may be considered when cardiac arrest is suspected to be caused by pulmonary embolism (2b, C-LD)
- Myocardial ischemia/infarction
  - Only recommendations exist if return of spontaneous circulation(ROSC) is achieved
  - Insufficient evidence to make recommendation for role in cardiac arrest

Circulation. 2020;142(16):S366-S468.

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Timing with Resuscitation

- European Resuscitation Council (ERC) Guidelines recommend continuing CPR for at least 60 to 90 minutes after thrombolysis before terminating resuscitation
- No concrete recommendation explicitly stated in American guidelines
  - Alteplase data suggests CPR at least 15 minutes between doses
- Available literature varies on time to cessation
  - Shortest duration: 15 minutes
  - Longest duration: >90 minutes

Decision to terminate should be highly individualized based on case and discussed by all practitioners involved in care.

Resuscitation. 2015;95:148-201.
Circulation. 2020;142(16):S366-S468.
N Engl J Med. 2002;346(20):1522-1528.
Current Opinion in Critical Care. 2001;7(3):176-183.

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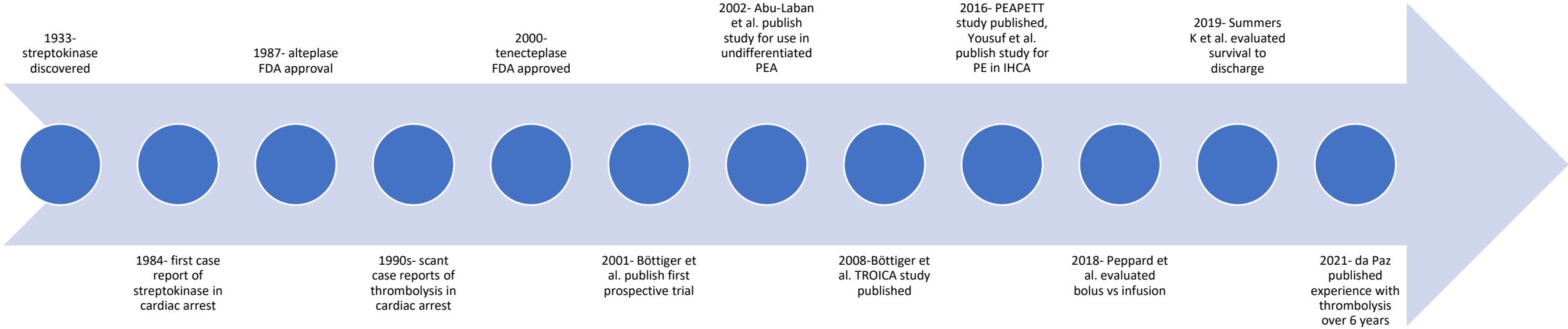
Evidence for Use in Cardiac Arrest



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Use in Undifferentiated Cardiac Arrest

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Tissue Plasminogen Activator in Cardiac Arrest with Pulseless Electrical Activity

Objective: Evaluate the effect of tissue plasminogen activator (tPA) in undifferentiated Pulseless Electrical Activity (PEA) arrest.

Methods: Blinded RCT of 233 patients. Before enrollment, patients with >1 minute of PEA arrest unresponsive to initial therapy underwent: endotracheal intubation, ventilation with 100% oxygen, bolus of normal saline and 1mg of epinephrine IV, then randomized to 100mg of tPA or placebo in a double-blind fashion. Resuscitation was continued for at least 15 minutes.

Results: Only one patient (in the tPA group) in the whole study survived to hospital discharge. There was no statistically significant difference in rate of return of spontaneous circulation (ROSC), length of hospital stay, and hemorrhage.

	tPA (n=117)	Placebo (n=116)	Absolute difference (95% CI)	P value
ROSC	25	27	-1.9 (-12.6 to +8.8)	0.85
Median length of stay	0.4	0.5	-0.1 (-0.4 to +2.5)	0.62
Major hemorrhage	2	0	+1.7 (-1.7 to +6.4)	0.50
Minor hemorrhage	1	1	0 (-4.1 to +4.1)	0.62
Survival to discharge	1	0	+0.9 (-2.6 to +4.8)	0.99

No evidence of beneficial effect of fibrinolysis in patients with cardiac arrest and Pulseless Electrical Activity (PEA) arrest of unknown cause.

N Engl J Med. 2002;346(20):1522-1528.

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Thrombolysis during Resuscitation for Out-of-Hospital Cardiac Arrest (TROICA)

Objective: Evaluate the effect of tenecteplase during out of hospital cardiac arrest (OHCA).

Methods: Randomized, double-blind placebo-controlled multicenter trial. Adult patients were randomly assigned to receive Tenecteplase or placebo during CPR and then CPR was continued for at least 30 minutes; no adjunctive antithrombotic therapy was used.

The primary endpoint was 30-day survival; the secondary endpoints were hospital admission, ROSC, 24-hour survival, survival to hospital discharge, and neurologic outcome.

Results: After blinded review of data from the first 443 patients, the data and safety monitoring board recommended discontinuation of enrollment of asystolic patients due to low survival. In a subsequent review after enrolling a total of 1050 patients, the study was discontinued due to futility.

	Tenecteplase (n=525)	Placebo (n=525)	Relative risk (95% CI)	P value
30-day survival	77	89	0.87 (0.65-1.15)	0.36

No difference in mortality. This RCT was stopped prematurely due to futility.

N Engl J Med. 2008;359(25):2651-2662.

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Use in Cardiac Arrest by Presumed Pulmonary Embolism

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PEA in pulmonary embolism treated with thrombolysis (from the "PEAPETT" study)

Objective: Evaluate the outcome of low-dose systemic thrombolysis with tPA in patients presenting with PEA due to PE.

Methods: Single center cohort of 23 patients with PEA and CA due to confirmed massive PE. This cohort was followed prospectively for clinical and echocardiographic outcomes. All patients received 50mg of tPA IV push over 1 minute, subsequently started on heparin. Outcomes studied included ROSC, survival to hospital discharge, major and minor bleeding. They also looked at certain ultrasound parameters such as RV/LV ratio and pulmonary artery systolic pressure.

Results: ROSC occurred in all but 1 patient. There was no minor or major bleeding. Of the 23 patients, only 2 died in the hospital and 20/23 were alive at 22 +/- 3 months of follow up. The echo parameters studied improved significantly within 48 hours (both parameters $p<0.01$).

	RV/LV ratio	PASP
Admission	1.79	58.1
Within 48h	1.16	40.25

Alteplase 50mg rapidly given in PEA arrest due to confirmed massive PE prior to arrest was effective in obtaining ROSC and led to enhanced survival and reduction in pulmonary artery pressures

Am J Emerg Med. 2016;34(10):1963-1967.

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Tissue Plasminogen Activator Use in Cardiac Arrest Secondary to Fulminant Pulmonary Embolism

Objective: Evaluate survival to hospital discharge for patients who had in-hospital cardiac arrest (IHCA) from suspected or confirmed PE who received IV tPA vs no thrombolytics.

Methods: Single center, retrospective review on 42 patients who had IHCAs previously diagnosed with PE via imaging (CTA or V/Q scan) or had signs of right heart strain on US. Patients either received 100mg IV alteplase (45%) or no thrombolytics (55%) based on provider preference.

Results: There was no significant difference in survival to hospital discharge (primary endpoint) or in ROSC, major bleeding, or minor bleeding (secondary endpoints).

	IV Alteplase (n=19)	No thrombolysis (n=23)	P value
ROSC	9 (47%)	11 (48%)	1.00
Survival to discharge	2 (11%)	2 (9%)	0.98

No significant difference in survival to hospital discharge, ROSC, or bleeding among patients with IHCA with confirmed or suspected pulmonary embolism who received IV tPA during cardiac arrest vs those who did not.

J Clin Med Res. 2016 Mar;8(3):190-5.

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Characterization of Alteplase Therapy for Presumed or Confirmed Pulmonary Embolism During Cardiac Arrest

Objective: Describe the dosing and administration of alteplase in cardiac arrest due to suspected or confirmed PE.

Methods: Retrospective, multi-center, cohort study of 35 patients which evaluated alteplase use characteristics in adults who received alteplase during PE-induced cardiac arrest.

Results: 46% of patients received bolus-only dosing strategy, and the most common dose was 50mg. Patients in the bolus-with-infusion group were more likely to survive CA compared with other dosing strategies, but no significant difference in survival to hospital discharge was found between the three groups.

	Bolus (n=16)	Infusion (n=8)	Bolus + infusion (n=11)
ROSC	1	0	2
Survival CA	0	0	2
Survival to discharge	0	0	1

No clear difference in survival to hospital discharge between alteplase dosing strategies. Most common alteplase dose for patients with presumed or confirmed PE during cardiac arrest was a single 50 mg bolus. Ideal dosing strategy cannot be identified

Am J Health Syst Pharm. 2018 Jun 15;75(12):870-875.

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Evaluation of Rescue Thrombolysis in Cardiac Arrest Secondary to Suspected or Confirmed Pulmonary Embolism

Objective: Evaluate baseline survival rate of patients with cardiac arrest presumed or confirmed to be due to PE who received IV thrombolytics during resuscitation.

Methods: Single center retrospective review of 22 patients who had IHCA (68%) or OHCA (32%) with clinical suspicion or confirmed PE by CT Angiography who received IV thrombolytics. The thrombolytic given was heterogenous and was mostly alteplase (both 100mg IV and 50mg IV doses) or less commonly tenecteplase 45mg IV.

Results: Primary outcome was survival to hospital discharge. Secondary outcomes included ROSC and ICU/Hospital Length of Stay. Hospital length of stay was >10 days in all three patients who survived to discharge.

	ROSC	Survival to hospital discharge
Thrombolytics given (n=22)	11	3

Very few patients who had cardiac arrest due to suspected or confirmed pulmonary embolism and received thrombolytics survived to hospital discharge.

Ann Pharmacother. 2019 Jul;53(7):711-715.

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Emergency Thrombolysis During Cardiac Arrest due to Pulmonary Embolism: Our Experience Over 6 Years

Objective: Examine the effect of alteplase in patients with cardiac arrest secondary to PE.

Methods: Retrospective, observational, single-center cohort of 16 patients with confirmed or highly suspected PE as cause of cardiac arrest who received CPR with or without emergency thrombolytic therapy using alteplase.

Results: There was no statistically significant difference in ROSC between the two groups, nor in secondary outcomes (24 hour mortality, survival to hospital discharge, survival with neurologic outcome).

	Alteplase, n=8 (%)	No thrombolytics, n=8 (%)	P value
ROSC	8 (100)	7 (87.5)	0.3
Death at 24h	2 (25)	4 (50)	0.3
Death at 30d	5 (62.5)	5 (62.5)	1.0

No difference in ROSC or 24-hr survival rate in adults with cardiac arrest due to pulmonary embolism between the groups. Limited by unclear treatment group allocation which may be a source of bias.

Open Access Emerg Med. 2021 Feb 22;13:67-73.

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The patient has a pulse! Now what?

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Post Arrest Care

- Initiate ACLS post arrest care algorithm
- Is there a specialist readily available?
- Obtain imaging/laboratory evidence to back diagnosis
- Systemic anticoagulation
  - Heparin over other agents
  - Highly patient specific, significant increase in intracranial hemorrhage (ICH)
  - For every 10 second increase of 12 hour activated patrial thromboplastin time (aPTT) above 70 increases ICH chance by 0.07%

Risk Factors for Major Bleeding following Thrombolytic
Demographic Characteristics
Advanced age (>75 years)
Female gender
African American race
Low body weight (risk inversely related with each 10 kg below 100 kg)
Medical History
Acute myocardial infarction
Hypertension (poorly controlled at baseline)
Aortic dissection
Acute pancreatitis
Dementia
Cardiopulmonary resuscitation exceeding 10 minutes
Major surgery within prior 3 weeks
Stool occult positive
Internal bleeding in previous 4 weeks
Gastrointestinal bleeding in prior 3 months
Invasive device
Elevated bilirubin (> 3 mg/dl)
Coagulopathy (defined as INR >1.7)
Presence of intra-aortic balloon pump
Femoral venous access

Circulation. 2020;142(16):S366-S468.
Heart. 2004;90(5):581-588.
Therapeutic Advances in Drug Safety. 2015;6(2):57-66.

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Knowledge Check #3

After ROSC is achieved after thrombolysis for presumed massive pulmonary embolism, which is the anticoagulant of choice?

A. Enoxaparin
B. Unfractionated heparin
C. Fondaparinux
D. Argatroban

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Summary- Dosing

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Massive Pulmonary Embolism	50 mg bolus over 2 minutes followed by 15 minutes of CPR If no ROSC, repeat 50 mg dose	Administer as a single bolus, weight based: <60 kg: 30 mg ≥60 to <70 kg: 35 mg ≥70 to <80 kg: 40 mg ≥80 to <90 kg: 45 mg ≥90 kg: 50 mg
ST-elevation myocardial infarction		

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Pro Tips

- Collect as much information as quickly as possible
- Quickly “examine” the patient yourself
- Know what fibrinolytics your institution has and where they are kept
- Bring up thrombolysis sooner than later with your team
- Discuss goals of care and therapy with team

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Take Home Points

- Few patients who suffer cardiac arrest from massive pulmonary embolism will survive to hospital discharge
- There have been no RCTs that have studied administration of thrombolytics in cardiac arrest due to pulmonary embolism/myocardial infarction
- RCTs utilizing thrombolysis in undifferentiated cardiac arrest have not shown survival benefit
- No clear mortality or functional outcome benefit to any thrombolytic
- Severe heterogeneity with alteplase dosing
- The risks and benefits of administering thrombolytics should be weighed heavily amongst all clinicians

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Future Directions

- Larger, more robust studies
- Increased access to thrombolytics
- Defining a fibrinolytic of choice
- Improving pre-test probability of disease
- Optimizing dosing regimen of medications
  - Optimal dosing for treatment of post-arrest syndrome
  - Optimal dosing for alteplase in pulmonary embolism- no “one size fits all” regimen


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