Thrombolytics in Cardiac Arrest: Life-Saving, Life-Changing, or Disappointing?

Heather D. Eppert, Pharm.D., BCPS
Alison M. Jennett, Pharm.D., BCPS
Renee Petzel, Pharm.D.

TOGETHER WE MAKE A GREAT TEAM

Poll Question 1

Which of the following best represents your practice setting:

1. Community Hospital, Less than 100 beds
2. Community Hospital, 100-200 beds
3. Community Hospital, Greater than 200 beds
4. Academic Hospital
5. Other

Poll Question 2

Please select the answer that best describes your practice setting:

1. Level 1 Emergency Department (ED)
2. All other ED
3. Intensive Care Unit
4. Internal Medicine
5. Other

Objectives

- Describe the most common attributable causes of cardiac arrest in the adult patient
- Describe the mechanism of action of thrombolytics in the setting of cardiac arrest
- Compare and contrast the evidence on the efficacy of thrombolytics in the setting of cardiac arrest
- Describe the evidence on the safety of thrombolytics in the setting of cardiac arrest

Poll Question 3

At the current time, I regularly respond to cardiac arrests in my institution.

1. True
2. False

Poll Question 4

What is your current professional opinion on the use of thrombolytics during cardiopulmonary resuscitation (cardiac arrest)?

1. Would not recommend nor consider
2. Would consider in selected patients
3. Would consider in all patients when “all else fails”
4. I don't have enough information to make this decision
5. I am currently undecided

Outcomes from Cardiac Arrest[1,2]

- Despite advances in knowledge and therapy, outcomes associated with cardiac arrest remain poor
- After cardiac arrest, survival rates range from 7% from out-of-hospital arrest, to 15% for in-hospital cardiac arrest
- If considering neurologic recovery, the statistics are even more dismal

Etiology of Cardiac Arrest[3]

- Acute myocardial infarction (MI) and massive pulmonary embolism (PE) are the most common causes of cardiac arrest
- At autopsy, approximately 70% of cases of cardiac arrest attributed to MI or massive PE

Pathophysiology of Cardiac Arrest[4—6]

- Cardiac arrest is associated with activation of the coagulation cascade, *without* compensatory activation of intrinsic fibrinolysis
- Imbalance leads to widespread development of microthrombi, even after 5—10 minutes of cardiopulmonary resuscitation (CPR)

Thrombolytics—The Theory[7,8]

- In a feline model of cardiac arrest, the "no-reflow" phenomenon was suggested to be responsible for poor outcomes
  - Areas of microthrombi throughout the brain responsible for poor neurologic outcomes
- In a follow-up study, administration of thrombolytics in a feline model *significantly* improved outcomes from cardiac arrest

Thrombolytics—The Problem[9,10]

- Thrombolytic therapy has been shown to be effective for both acute MI and PE in non-cardiac arrest patients
- While the theoretical basis has been introduced, CPR has been considered a relative *contraindication* to thrombolytic therapy

Testing the Theory

- The first case report:[11]
  - Authors: Renkes-Hegendörfer U, Hermann K.
  - Title: Successful treatment of a case of fulminant massive pulmonary embolism with streptokinase.
  - Citation: Anaesthesist 1974; 23: 500-501.
- The first prospective trial:[12]
  - Authors: Padosch SA, Motsch J, Böttiger BW.
  - Title: Hochdosierte Steptokinasetherapie bei fulminanter Lungenarterienembolie.
  - Citation: Anaestheist 1984; 33: 469.

The Use of Thrombolytics in Cardiac Arrest: The Evidence

TOGETHER WE MAKE A GREAT TEAM

Thrombolytics Utilized in Cardiac Arrest

- Alteplase
- Tenecteplase
- Reteplase
- Streptokinase

Articles Reviewed: Thrombolytic Use in Cardiac Arrest

Trial	Design	Patients (n)	Results	Discussion
Bottiger et al.[13], Lancet 2001	Prospective, non-randomized, observational	40 rt-PA and heparin 5000 unit bolus, repeated once vs. 50 controls	ROSC, ICU, and 24 hr survival significant; survival to d/c NS	No randomization or placebo; heparin given; possible bias
Abu-Laban et al.[14], NEJM 2002	Prospective, randomized double blind, placebo controlled	117 rt-PA infusion over 15 mins vs. 116 placebo; Continuation of CPR allowed	No difference in endpoints	Limited power; CPR for >35 mins prior to rt-PA; infusion protocol violations noted

ROSC = Return of spontaneous circulation
ICU = Intensive care unit admission
NS = No significant difference
d/c = discharge
CPR = cardiopulmonary resuscitation

Articles Reviewed: Thrombolytic Use in Cardiac Arrest

Trial	Design	Patients (n)	Results	Discussion
Janata et al.[15], Resuscitation 2003	Retrospective cohort	36 rt-PA vs. 30 control; weight based heparin given if ROSC	ROSC favored 24 hr survival; survival to d/c NS; major bleed	"Young" patients; selection bias; CPR continued for 2—120 min (average 40 min); administration time
Lederer et al.[16], Resuscitation 2001	Retrospective cohort	108 rt-PA	Favorable neurologic outcomes and quality of life	Focus quality of life and neurologic outcomes; follow-up; no controls; lack of data and power

ROSC = Return of spontaneous circulation
NS = No significant difference
d/c = discharge
CPR = cardiopulmonary resuscitation

Articles Reviewed: Thrombolytic Use in Cardiac Arrest

Trial	Design	Patients (n)	Results	Discussion
Fatovich et al.[17], TICA trial Resuscitation 2004	Prospective, randomized, double blind, placebo controlled	19 tenecteplase vs. 16 placebo; intervention first, followed by ACLS	ROSC significantly better; survival to admit and d/c alive NS	"Young" patients; v fib most common; 40 min for intervention; ROSC in 3 min
Bozeman et al.[18], Resuscitation 2006	Prospective, multicenter observational	50 tenecteplase; mean time to administration 30 min vs. 113 controls	ROSC and d/c alive significantly better; positive neurological outcomes in all survivors	ROSC in 7 min; no controls survived at 24 hours or d/c

ACLS = Advanced Cardiac Life Support
ROSC = Return of spontaneous circulation
NS = No significant difference
d/c = discharge
v fib = ventricular fibrillation

Articles Reviewed: Thrombolytic Use in Cardiac Arrest

Trial	Design	Patients (n)	Results	Discussion
Bottiger et al.[19], (TROICA) NEJM 2008	Double blind, placebo controlled, multicenter randomized	525 tenecteplase vs. 525 placebo; heparin not allowed	No difference in endpoints; ICH rate higher in tenecteplase group	Asystole; ended early due to futility; treatment of PE allowed open intervention within 18 min; ROSC in 8 min

ROSC = Return of spontaneous circulation
ICH = Intracranial hemorrhage
PE = Pulmonary embolism

Supporting Evidence

TOGETHER WE MAKE A GREAT TEAM

Pros—Reasons to Use Thrombolytics in Cardiac Arrest

- The use of thrombolytics in cardiac arrest is associated with a higher rate of return of spontaneous circulation (ROSC)
  - ROSC is *rapidly* achieved after administration (minutes)
  - Mean time to ROSC after TNK given[18]
    - 7 minutes (3-12 minutes)

Outcomes Associated with Thrombolytics after Cardiac Arrest

	ROSC n, (%)	Survival at 24 Hours n, (%)	Survival to Discharge n, (%)
Lederer et al.[16]			
TL (n = 108)	76 (70.4)*	52 (48.1)*	27 (25)
Control (n = 214)	110 (51)	71 (32.9)	33 (15.3)
Janata et al.[15]			
TL (n = 36)	24 (67)	19 (53)*	7 (19)
Control (n = 30)	13 (43)	7(23)	2 (7)
Bozeman et al.[18]			
TL (n = 50)	13 (26)*	2 (4)	2 (4)
Control (n = 113)	14 (12.4)	0	0
Bottiger et al.[13]			
TL (n = 40)	27 (68)	14 (35)	6(15)
Control (n = 50)	22 (40)	11 (22)	4(8)

* = statistically significant TL = thrombolytics
ROSC = Return of Spontaneous Circulation

Pros—Reasons to Use Thrombolytics in Cardiac Arrest

- In patients who survive to hospital discharge, neurologic recovery is complete at discharge, and at five year follow-up

Neurologic Status at Hospital Discharge

	Thrombolytic Group, n	Survival to Discharge, n (%)	CPC Score at Discharge
Bozeman et al.[18]	50 patients	2 (4%)	2
Lederer et al.[16]	108 patients	27 (25%)	22/27 = 1
Abu-Laban et al.[14]	117 patients	1 (1%)	MMME 91/100
Pedley et al.[20]*	87 patients	NA	67/87 = 1-2
Bottiger et al.[21]*	208 patients	68 (33%)	52/57 = 1
Newman et al.[22]*	67 patients	50 (75%)	47/50

*Review of case reports and case series combined

CPC = Cerebral Performance Category
MMME = Modified Mini-Mental State Examination
NA = not applicable

Pros—Reasons to Use Thrombolytics in Cardiac Arrest

- The use of thrombolytics in cardiac arrest generally appears to be safe
  - Not necessarily associated with increased risk of life-threatening bleeding
  - CPR does not appear to increase risk of bleeding

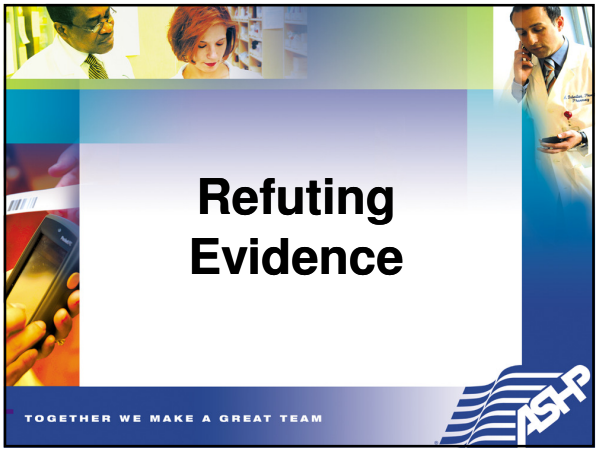
Bleeding Complications

	Major Bleeding, n (%)	Minor Bleeding, n (%)
Abu-Laban et al.[14]		
TL group (n = 117)	2 (1.7%)	1 (0.9%)
Placebo (n = 118)	0	1 (0.9%)
Bozeman et al.[18]		
TL group (n = 50)	1 (2%)	2 (4%)
Lederer et al.[16]		
TL group (n = 45)	6 (13%)	Not reported
Janata et al.[15]		
TL group (n = 36)	9 (25%)	9 (25%)
Placebo (n = 30)	3 (10%)	3 (10%)
TL & CPR ≤ 10 min (n = 8)	2 (25%)	Not reported
TL & CPR ≥ 10 min (n = 28)	7 (25%)	Not reported

TL = thrombolytic
CPR = cardiopulmonary resuscitation

Pros—Reasons to Use Thrombolytics in Cardiac Arrest

- Wide variability in results
  - Does not appear to be associated with devastating rate of fatal bleeding
  - Rate of bleeding does not differ based on duration of CPR
- GI bleeding was most commonly reported source of bleeding
  - Successfully managed by transfusion and/or surgery



Cons—Reasons NOT to Use Thrombolytics in Cardiac Arrest

- Rate of survival from cardiac arrest is low, despite use of medications and other interventions, including data for thrombolytics
- Thrombosis (MI and PE) account for ≈70% of cardiac arrests
- The remaining 30% are not likely to benefit, and may be *harmed*
- Ability to determine cause of arrest is challenging in the emergency situation

Additional Advanced Cardiac Life Support Measures

Trial	Thrombolytic Regimen	Other Medications Prior to Administration of Thrombolytic	Duration of CPR (minutes)
Bottiger, et al.[13]	50mg rt-PA + 5000 units heparin infused over 15 min, could be repeated.	Standard ACLS, 15 min CPR prior to administration of TL; other medications NR	Minimum 30; 40 TL 37 C; (NS)
Abu-Laban, et al.[14]	100 mg rt-PA infused over 15 min	500 mL Normal Saline, 1 mg EPI	Minimum 15; Mean 65 (NS)
Janata, et al.[15]	rt-PA used varied by physician, NR	NR	Median 40; (2-120 min)

ROSC = Return of spontaneous circulation
NS = No significant difference
C = Control/Placebo
TL = Thrombolytic
CPR = Cardiopulmonary resuscitation
EPI = Epinephrine
ACLS = Advanced Cardiac Life Support
NR = Not reported

Additional Advanced Cardiac Life Support Measures

Trial	Thrombolytic Regimen	Other Medications Prior to Administration of Thrombolytic	Duration of CPR (minutes)
Fatovich, et al.[17]	50 mg tenecteplase bolus	None prior—TL first medication administered; standard ACLS thereafter	43.5 TL 36 C (NS)
Bozeman, et al.[18]	Tenecteplase 30-50 mg	30 min CPR and 8 cycles of standard ACLS; specific medications NR	Mean 30; 43 TL 36 C (NS)
Bottiger, et al.[19]	Weight-based tenecteplase (30-50 mg)	Standard ACLS prior to and 30 min after TL; other medications NS	Minimum 30; NR

ROSC = Return of spontaneous circulation
NS = No significant difference
C = Control/Placebo
TL = Thrombolytic
CPR = Cardiopulmonary resuscitation
EPI = Epinephrine
ACLS = Advanced Cardiac Life Support
NR = Not reported

Initial Patient Presentation

Trial	Age, years (p-value)	Witnessed Arrest (p-value)	Initial Rhythm	Collapse to Start of CPR	Time to TL/Placebo Administration
Bottiger, et al.[13]	64 vs. 61; NS	NS	NS	NR	NR
Abu-Laban, et al.[14]	70 vs. 69; NS	NS	NS*	NS Mean 12 min	Mean 36 min (NS)
Janata, et al.[15]	50 vs. 70; NS*	NR	NR	NR	NR
Fatovich, et al.[17]	63 vs. 72; (0.04)	NS	NR	NS Mean 4/9 min	TL (3-73 min) C (12-105 min)
Bozeman, et al.[18]	58 vs. 65; NS	TL > C; (SD)	NS	NR	Mean 30 min TL; NR control
Bottiger, et al.[19]	64 NS	NS	NS	NS, 9 min	18 min (NS)

* = trend towards significance
C = Control/Placebo
NR = Not reported
NS = No significant difference
SD = Significantly different, p value not provided
TL = Thrombolytic

Rate of ROSC and Survival

Trial	ROSC (p-value)	Survival to ICU Admission (p-value)	Survival at 24 Hours (p-value)	Survival to Discharge
Prospective Trials				
Bottiger, et al.[13]	TL (0.026)	TL (0.009)	NS	NS
Abu-Laban, et al.[14]	NS	NS	NS	NS
Bozeman, et al.[18]	TL (0.04)	TL (0.0007)	NS	NS
Bottiger, et al.[19]	NS	NS	NS	NS
Fatovich, et al.[17]	NS	NS	NR	NS
Retrospective Trial				
Janata, et al.[15]	NS	NR*	TL (0.01)	NS

ROSC = Return of spontaneous circulation
NS = No significant difference
NR = Not reported
TL = Thrombolytic
* = trend towards significance

Cons—Reasons NOT to Use Thrombolytics in Cardiac Arrest

- Positive outcomes are from retrospective and observational cohorts and case reports
  - Significant selection bias
- Control group may have been difficult to compare
  - Differences in baseline characteristics, higher rates of mortality, or were not included at all
- The positive results seen in retrospective and observational trials have not been replicated in randomized, placebo-controlled trials

Cons—Reasons NOT to Use Thrombolytics in Cardiac Arrest

- Age of patients who benefit from thrombolytics are "young"
- Patients most likely to benefit if had "witnessed" arrest
  - Introduces bias towards drug efficacy
- Groups that received thrombolytics typically had longer resuscitation times

Cons—Reasons NOT to Use Thrombolytics in Cardiac Arrest

- Several studies have utilized out-of-hospital administration of thrombolytics
  - Out-of-hospital "ACLS Teams" comprised of MICU staff and physicians
- Inconsistent use of thrombolytics and doses utilized do not provide solid guidance for clinical practice
  - Between and even within reports

Cons—Reasons NOT to Use Thrombolytics in Cardiac Arrest

- Cost effectiveness
  - Cost likely to be prohibitive in many areas
  - Data lacking to suggest standard of care
  - Cost-benefit analysis not performed
- Physician acceptance of thrombolytics, particularly in this setting

Further Questions

- Which patient population is most likely to benefit, and how do we identify them early enough to administer therapy?
- How is consent handled? Is it considered implied?
- What drug and what dose should be used?

Further Questions

- If patient receives thrombolytics for arrest, should further anticoagulants (the standard of care) be withheld?
- How does administration of thrombolytics during arrest affect care "downstream"?

Poll Question 5

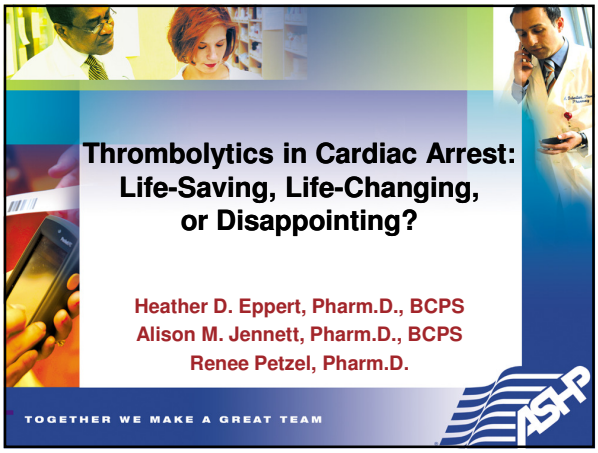
After today's presentation, do you feel that you have been given the information to prepare you *to discuss* thrombolytics as a potential treatment option for a patient in cardiac arrest?

1. Yes
2. No
3. Undecided
4. It would depend on the physician
5. Rather not answer

Poll Question 6

After today's presentation, do you feel that you would be more likely *to suggest* thrombolytics to your medical team during cardiac arrest?

1. Yes
2. No
3. Undecided
4. It would depend on the physician
5. Rather not answer



References

1. Bedell SE, Delbanco TL, Cook EF, et al. Survival after cardiopulmonary resuscitation in the hospital. N Engl J Med 1983; 309: 569-576.
2. Ballew KA, Philbrick JT, Caven DE, et al. Predictors of survival following in-hospital resuscitation: a moving target. Arch Intern Med 1994; 154: 2426-2432.
3. Silfvast T. Cause of death in unsuccessful prehospital resuscitation. J Intern Med 1991; 229: 331-335.
4. Li X, Fu QL, Jing WL, et al. A meta-analysis of cardiopulmonary resuscitation with and without the administration of thrombolytic agents. Resuscitation 2006; 70: 31-36.
5. Gando S, Kameue T, Nanzaki S, et al. Massive fibrin formation with consecutive impairment of fibrinolysis in patients with out-of-hospital cardiac arrest. Thromb Haemost 1997; 77: 278-282.
6. Böttiger BW, Motsch J, Böhrer H, et al. Activation of blood coagulation after cardiac arrest is not balanced adequately by activation of endogenous fibrinolysis. Circulation 1995; 92: 2572-2578.

References

7. Fisher M, Hossmann KA. No-reflow after cardiac arrest. Intens Care Med 1995; 21: 132-141.
8. Fisher M, Böttiger BW, Popov-Cenic S, et al. Thrombolysis using plasminogen activator and heparin reduces cerebral no-reflow after resuscitation from cardiac arrest: an experimental study in the cat. Intens Care Med 1996; 22: 1214-1223.
9. Van de Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. The Task Force on the management of ST-segment elevation actue myocardial infarction of the European Society of Cardiology. Eur Heart J 2008; 29: 2909-2945.
10. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction – executive summary: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the. Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation 2004 ;110:588–636.

References

11. Renkes-Hegendörfer U, Hermann K. Successful treatment of a case of fulminant massive pulmonary embolism with streptokinase. Anaesthesist 1974; 23: 500-501.
12. Padosch SA, Motsch J, Böttiger BW. Hochdosierte. Steptokinasetherapie bei fulminanter Lungenarterienembolie. Anaestheist 1984; 33: 469.
13. Bottiger BW, Bode C, Kern S, Gries A, et al. Efficacy and safety of thrombolytic therapy after initially unsuccessful cardiopulmonary resuscitation: a prospective clinical trial. Lancet. 2001; 357: 1583-1585.
14. Abu-Laban RB, Christenson JM, Innes GD, van Beek CA, et al. Tissue plasminogen activator in cardiac arrest with pulseless electrical activity. NEJM. 2002; 346: 1522-1528.
15. Janata K, Holzer M, Kurkciyan I, Losert H, et al. Major bleeding complications in cardiopulmonary resusciation: the place of thrombolytic therapy in cardiac arrest due to massive pulmonary embolism. Resuscitation. 2003; 57: 49-55.

References

16. Lederer W, Lichtenberger C, Pechlaner C, Kroesen G, et al. Recombinant tissue plasminogen activator during cardiopulmonary resuscitation in 108 patients with out-of-hospital cardiac arrest. Resuscitation. 2001; 50: 71-76
17. Fatovich DM, Dobb GJ, Clugston. A pilot randomized trial of Thrombolysis in cardiac arrest (The TICA trial). Resuscitation. 2004; 61: 309-313.
18. Bozeman WP, Kleiner DM, Ferguson KL. Empiric tenecteplase is associated with increased return of spontaneous circulation and short term survival in cardiac arrest patients unresponsive to standard interventions. Resuscitation. 2006; 69: 399-406.
19. Bottiger BW, Arntz H, Chamberlain DA, et al. Thrombolysis during resuscitation for out-of-hospital cardiac arrest. NEJM. 2008; 359: 2651-2662.
20. Pedley DK, Morrison WG. Role of thrombolytic agents in cardiac arrest. Emerg Med J. 2006; 23: 747-752.

References

21. Bottiger BW, Martin E. Thrombolytic therapy during cardiopulmonary resuscitation and the role of coagulation activation after cardiac arrest. Curr Opin Crit Care. 2001; 7: 176-183
22. Newman DH, Greenwald I, Callaway CW. Cardiac arrest and the role of thrombolytic agents. Ann Emerg Med. 2000; 35: 472-480.