QUESTION

Should thrombolytics vs. no thrombolytics be used for cardiac arrest (adults or children)?	
POPULATION:	Cardiac arrest (adults or children)
INTERVENTION:	Thrombolytics
COMPARISON:	No thrombolytics
MAIN OUTCOMES:	Survival to hospital discharge; Return of spontaneous circulation (ROSC); Any intracranial hemorrhage; Favourable Neurological Outcome at hospital discharge;
SETTING:	Any setting
PERSPECTIVE:	Individual Patient
BACKGROUND:	Pulmonary embolism and acute coronary syndrome are not uncommon etiologies of cardiac arrest. Thrombolytics are treatment options for these conditions for patients not in cardiac arrest. Some have questioned whether thrombolytics should be added to the routine / standard management algorithm for cardiac arrest.
CONFLICT OF INTERESTS:	One member was the lead author on the TROICA trial.

ASSESSMENT

Problem
Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	It is estimated that there are over 4 million cardiac arrests that occur per year globally. Acute coronary occlusion (ACS) and pulmonary embolisms (PE) are both common etiologies of cardiac arrest, for which treatment options may include thrombolytic medications. Although the etiology of cardiac arrest is rarely known at the time of treatment, given that ACS and PE are common etiologies, it has been suggested that intra-arrest thrombolysis may be an appropriate empiric treatment option for undifferentiated cardiac arrest.	

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	There have been three randomized clinical trials performed (one pilot trial and two clinical-effectiveness trials), randomizing individuals with cardiac arrest (primarily out-of-hospital cardiac arrest, but a small number of in-hospital cardiac arrest patients) to intra-arrest thrombolytics vs placebo. No trial reported a significant improvement of survival to hospital discharge or survival to hospital discharge with favourable neurological outcome. When examining subgroup analyses, among those with bystander CPR, treatment with thrombolysis (vs. placebo) resulted in a lower proportion with 30-day survival (RR 0.55, 95% CI 0.35, 0.87). Among those with initial shockable rhythms, data was suggestive that thrombolysis (vs. placebo) may lead to worse outcomes (RR 0.80, 95% CI 0.60, 1.06) however this was not statistically significant.	

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The primary risk of thrombolysis is of bleeding complications. Two studies reported bleeding complications, which were consistently numerically higher for those treated with thrombolysis. However, the only bleeding complication that was statistically different between groups was "any intracranial hemorrhage" (RR 6.96, 95% CI 1.59, 30.41).

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	The research investigating thrombolysis for undifferentiated includes three randomized clinical trials. One trial was judged to have a high risk of bias, however was small and contributed a very small weight to the meta-analysis. Further, the results were not inconsistent with other data. Thus, we have not down-graded the overall certainty of evidence based on this single study. All data are consistent, with no evidence demonstrating a benefit of thrombolysis. However, the confidence intervals of the results are wide, and thus there may still be benefit or harm within these bounds.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Previous data indicate that patients prioritize survival with intact neurological function, but also value survival.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The available randomized clinical evidence did not detect a benefit of thrombolysis for undifferentiated out-of-hospital cardiac arrest. Among those with bystander CPR, a harmful effect was detected. Further, thrombolysis resulted in a higher proportion of cases with intracranial hemorrhage. Also worth considering is the task-saturated nature of cardiac arrest resuscitations, and that the deployment of additional interventions may interfere with or worsen the quality of standard resuscitation management. Overall, the balance between desirable and undesirable effects favour not administering thrombolytics. (See Appendix A "Evidence Table" below).

Resources required

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Thrombolytics are expensive, often costing over $1000 USD per dose. The drugs typically need to be refrigerated (at 2-8 degrees C), which adds to the expense of storing on ambulances in the out-of-hospital setting. The drugs have a typical shelf-life of 3 years. Overall, the costs and logistical challenges of providing this therapy are not negligible.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There are no studies evaluating the resources required for this intervention.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	There are no studies which have examined cost-effectiveness. However given the cost of the intervention and lack of evidence of effectiveness, it is unlikely that the intervention would be cost-effective.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Given there was no benefit seen with thrombolytics, there is no expected impact on equity. If there was a benefit seen, monitoring efforts for inequitable access to this expensive treatment option would have been appropriate.	

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The available research did not include any assessments of acceptability. However, given that survival with favourable neurological outcomes is a prioritized outcome of patients, and that thrombolytic medications are administered while patients are unconscious, it is likely that the eventual neurological outcome data would govern acceptability. Overall, it is likely that this intervention would be acceptable to patients if it demonstrated effectiveness.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The cost for thrombolytics is not negligible, often costing over $1000 USD per dose. Thrombolytics require refrigerated storage (at 2–8 °C) and need to be reconstituted prior to administration. Overall, thrombolytic use is potentially feasible, but does add to healthcare costs, as well as resulting in additional tasks to perform during cardiac arrest resuscitations.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
●	○	○	○	○

CONCLUSIONS

Recommendation

We recommend against the routine administration of thrombolytics during cardiopulmonary resuscitation for the treatment of cardiac arrest (strong recommendation, moderate certainty of evidence).

Justification

· There were three RCT's which examined the benefit of thrombolytics (vs. no thrombolytics) for cardiac arrest. Overall, available data did not demonstrate a benefit of thrombolytics for any clinical outcome, however data indicated a risk of harm due to an increased risk of intracranial bleeding.

· Although studies had specific inclusion criteria (presumed cardiac origin [i.e. no obvious non-cardiac cause], witnessed arrest, or PEA), these categories were still broadly undifferentiated.

· Risk of bias was judged to be low for two large RCT's, and high for a small pilot study. However, we elected not to downgrade the certainty of evidence based on the high risk of bias for the single study, given that: (1) in the meta-analysis the small study had minimal impact on the overall results; (2) results were consistent after removal of the small study; and (3) the results of the small study were consistent with the two larger studies.

· All safety outcomes examining bleeding were suggestive of an increased risk of bleeding from thrombolytic therapy. A single outcome of "any intracranial hemorrhage" showed a statistically significant harm. We classified safety outcomes at a high risk of bias (specifically verification bias), given that all cases were not evaluated for the outcome of interest. For example, patients that died early in the course of treatment did not survive long enough to be evaluated. Even those that survived initial treatment did were not all evaluated for bleeding complications. It is likely that bleeding (even life-threatening bleeding) was missed given that all patients were critically ill and did not all undergo evaluation for bleeding. However, the direction of bias would likely be in underestimating the harms of thrombolytics, and thus a comprehensive evaluation of bleeding would likely only increase the current findings which already suggest a risk of increased bleeding.

Subgroup considerations

· Although analyses examining subgroups should be considered exploratory and at risk of type I error given multiple comparisons, it is notable that among cases with bystander CPR, thrombolytic therapy (in comparison to no thrombolytic therapy) resulted in an lower proportion of survivors. The subgroup of cases with initial shockable rhythms was also suggestive of harm.

Implementation considerations

· We considered the resource implications of administering this therapy, which were not negligible. The therapy often costs >$1000 USD, require refrigerated storage, and need to be reconstituted prior to administration.

Monitoring and evaluation

· Not applicable

Research priorities

· Our review examined cases of undifferentiated cardiac arrest, which were largely out-of-hospital cardiac arrests

· Future research may be warranted to examine the benefit of thrombolytics among: (1) those with an increased risk of PE; (2) in-hospital cardiac arrest.

Appendix A: Evidence Table

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no thrombolytics	With thrombolytics		Risk with no thrombolytics	Risk difference with thrombolytics
Survival to hospital discharge											
1299 (3 RCTs)	not serious[a]	not serious	not serious	serious[b]	none	⨁⨁⨁◯ Moderate[a,b]	91/646 (14.1%)	79/653 (12.1%)	**RR 0.86** (0.65 to 1.14)	91/646 (14.1%)	**20 fewer per 1,000** (from 49 fewer to 20 more)
Return of spontaneous circulation (ROSC)											
1294 (3 RCTs)	not serious[a]	not serious	not serious	serious[b]	none	⨁⨁⨁◯ Moderate[a,b]	307/643 (47.7%)	316/651 (48.5%)	**RR 1.04** (0.72 to 1.51)	307/643 (47.7%)	**19 more per 1,000** (from 134 fewer to 243 more)
Any intracranial hemorrhage											
1032 (1 RCT)	serious[c]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low[b,c]	2/514 (0.4%)	14/518 (2.7%)	**RR 6.95** (1.59 to 30.41)	2/514 (0.4%)	**22 more per 1,000** (from 2 more to 111 more)
Favourable Neurological Outcome at hospital discharge											
1299 (3 RCTs)	not serious[a]	not serious	not serious	serious[b]	none	⨁⨁⨁◯ Moderate[a,b]	55/653 (8.4%)	55/646 (8.5%)	**RR 1.00** (0.70 to 1.41)	55/653 (8.4%)	**0 fewer per 1,000** (from 25 fewer to 35 more)

CI: confidence interval; **RR:** risk ratio

Explanations

a. Risk of bias for Fatovich 2024 was judged to be high, however given the small sample size and low weight on the results, we did not downgrade the overall certainty of evidence based on this single study.

b. Confidence interval are wide, including both clinically important potential benefit and harm.

c. Bleeding outcomes were not consistent across studies. Verification bias was a concern