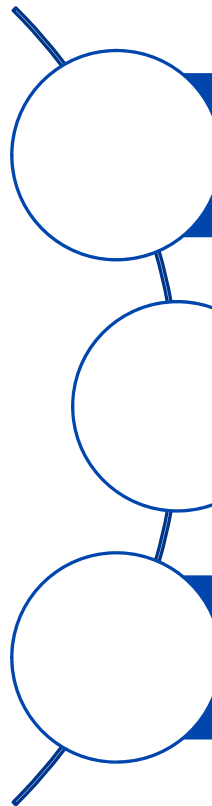




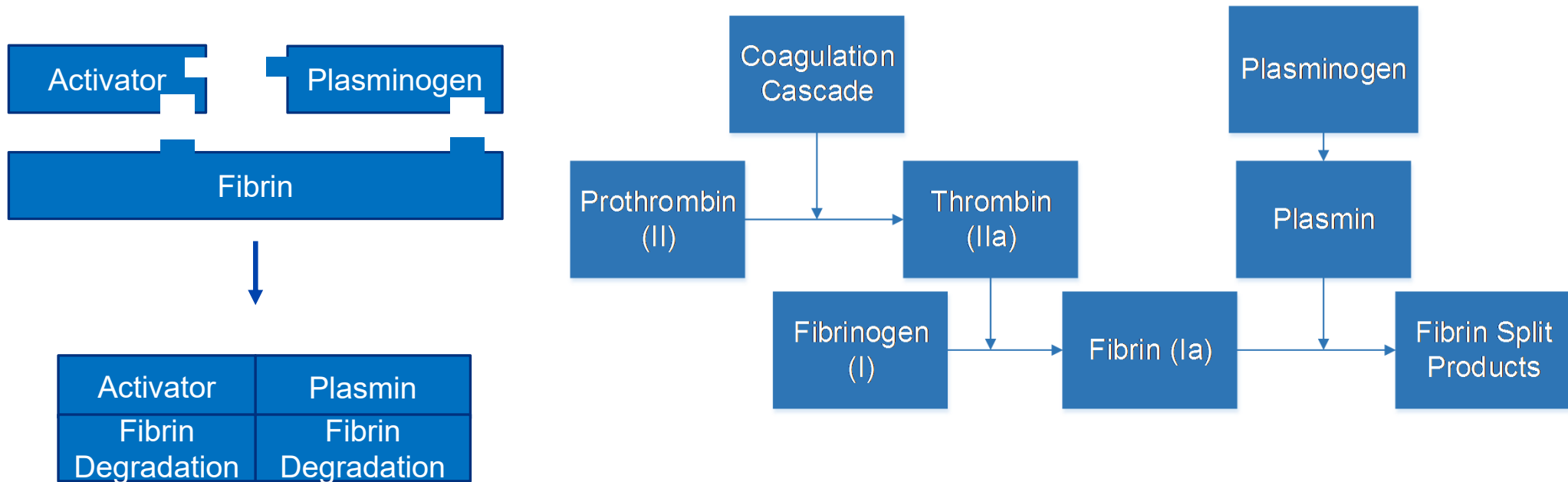
# The tXa Files: Bleeding Management with Tranexamic Acid

Nicholas Vollmer, PharmD  
PGY-1 Pharmacy Resident

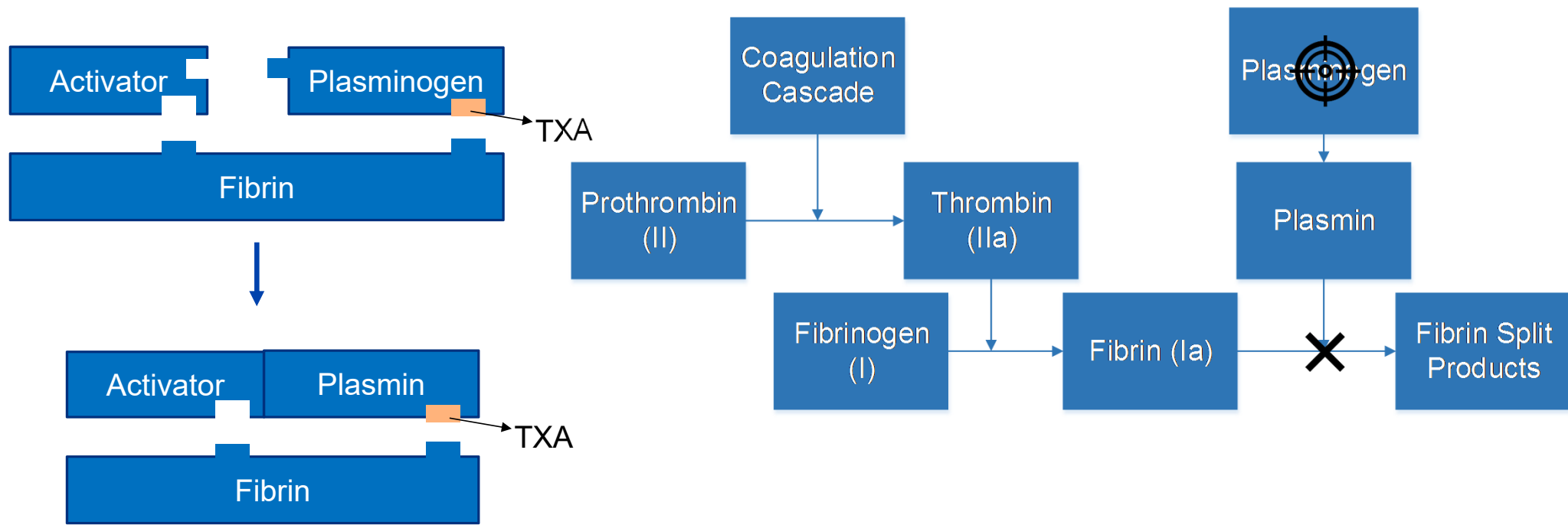
## Objectives

- 
- 1 Discuss pharmacological characteristics of tranexamic acid
  - 2 Compare and contrast primary literature for proposed tranexamic acid indications
  - 3 Identify pharmacotherapy pearls related to tranexamic acid

# Clotting Mechanism



# TXA Mechanism of Action



TXA = Tranexamic acid

## Which of the following regarding the mechanism of action of TXA is true?

- It binds directly to fibrinogen preventing its conversion to fibrin thus stabilizing the clot
- It is an analog of thrombin causing increased conversion of fibrinogen to fibrin thus stabilizing the clot
- It binds to plasminogen preventing its active form, plasmin, from destabilizing the clot
- It binds to plasmin directly preventing the degradation of the fibrin clot

## Which of the following regarding the mechanism of action of TXA is true?

- It binds directly to fibrinogen preventing its conversion to fibrin thus stabilizing the clot
- It is an analog of thrombin causing increased conversion of fibrinogen to fibrin thus stabilizing the clot
- **It binds to plasminogen preventing its active form, plasmin, from destabilizing the clot**
- It binds to plasmin directly preventing the degradation of the fibrin clot

# Overview

|                                                                                     | TXA Indications        | Benefit? |
|-------------------------------------------------------------------------------------|------------------------|----------|
|    | Perioperative Bleeding | ?        |
|    | PPH                    | ?        |
|    | Trauma                 | ?        |
|    | ICH                    | ?        |
|   | Epistaxis              | ?        |
|  | Hemoptysis             | ?        |
|  | GiB                    | ?        |

## Perioperative Bleeding



| Trial                                                                                                                                                                                                | Design                                                                       | Major Outcomes (TXA vs placebo)                                                                                                                                                                                                                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ker 2012                                                                                                                                                                                             | Systematic Review and Meta-Analysis of 129 trials of 10,488 surgery patients | <ul style="list-style-type: none"> <li>Probability of receiving blood transfusion: RR 0.62 (0.58-0.65; <math>p &lt; 0.001</math>)</li> <li>Death: RR 0.61 (0.39-0.98; <math>p = 0.04</math>)</li> <li>No associated with MI, stroke, or PE</li> </ul> |
| <p>Reduced blood loss and blood product use with no increase in thromboembolism</p> <p>Increased risk for seizures?</p> <p>Ongoing research evaluating its use in various perioperative settings</p> |                                                                              |                                                                                                                                                                                                                                                       |
| Dastrup 2018                                                                                                                                                                                         | Outcomes including 10,200 THA patients                                       | <ul style="list-style-type: none"> <li>All-cause mortality: HR 0.73 (0.41-1.28)</li> </ul>                                                                                                                                                            |
| Jaszczek 2015                                                                                                                                                                                        | RCT of 124 THA patients                                                      | <ul style="list-style-type: none"> <li>Percentage of patients requiring transfusion: 3.27% vs 22.22% (<math>p = 0.002</math>)</li> </ul>                                                                                                              |
| Zirk 2018                                                                                                                                                                                            | Retrospective cohort of 542 patients with post-surgical oral bleeding        | <ul style="list-style-type: none"> <li>Cessation of bleeding: 4.8% (TXA soaked gauze) vs 36.7% (gauze compression)</li> </ul>                                                                                                                         |



# Overview

|                                                                                     | TXA Indications        | Benefit? |
|-------------------------------------------------------------------------------------|------------------------|----------|
|    | Perioperative Bleeding | ✓        |
|    | PPH                    | ?        |
|    | Trauma                 | ?        |
|    | ICH                    | ?        |
|   | Epistaxis              | ?        |
|  | Hemoptysis             | ?        |
|  | GiB                    | ?        |



## Postpartum hemorrhage

| Trial | Design                                                                                                                                                                                                                                                                 | Major Outcomes (TXA vs placebo)                                                                       |
|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| WOMAN | <ul style="list-style-type: none"><li>• Primary outcome changed mid study</li><li>• Clinician unsure of potential benefit was an exclusion criteria</li><li>• PPH diagnosis was made clinically</li><li>• Delayed administration showed inconsistent benefit</li></ul> | 3 hours:                                                                                              |
| TR    | <ul style="list-style-type: none"><li>• PPH defined as more than 500cc of blood collected via collector bag</li><li>• What is the value of provider-assessed clinically significant bleeding?</li></ul>                                                                | <ul style="list-style-type: none"><li>• PPH incidence:</li><li>• 7.2% vs 9.7% (p=0.006)</li></ul> ng: |

# Overview

|                                                                                     | TXA Indications        | Benefit? |
|-------------------------------------------------------------------------------------|------------------------|----------|
|    | Perioperative Bleeding | ✓        |
|    | PPH                    | ✓*       |
|    | Trauma                 | ?        |
|    | ICH                    | ?        |
|   | Epistaxis              | ?        |
|  | Hemoptysis             | ?        |
|  | GiB                    | ?        |

\*=Treatment, not prophylaxis



## Trauma - CRASH-2

Multicenter, double-blind, placebo-controlled trial in 274 hospitals in 40 countries

↓  
Inclusion

- Adult trauma patients
- Significant Hemorrhage (SBP<90 mmHg, HR >110 BPM, or both)
- At risk for significant hemorrhage
- Within 8 hours of injury

↓  
N=20,211 patients

↓  
TXA – 1g over 10 minutes, then 1g  
infusion over 8 hours  
N=10,060 (49.8)

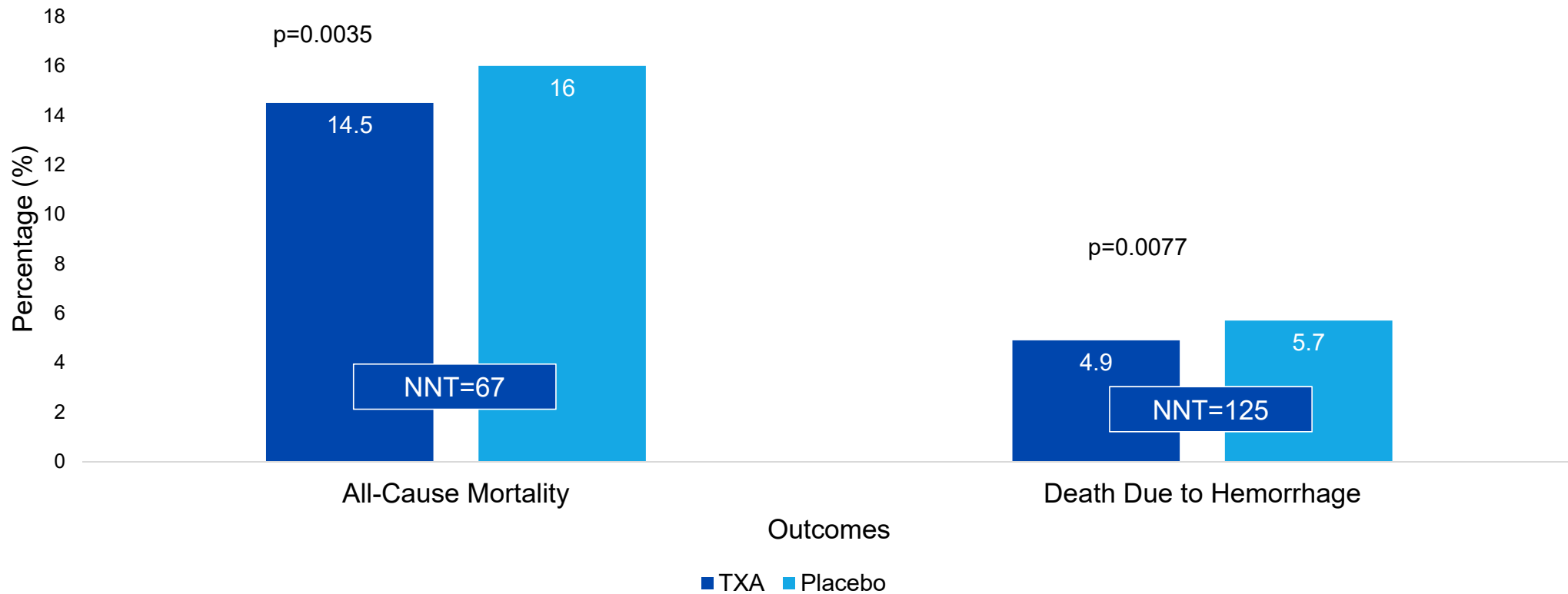
↓  
Placebo – 0.9% NS  
N=10,067 (49.8)

Ollidashi et al. *Lancet*. 2010;376(9734):23-32.

SBP = Systolic blood pressure  
HR = Heart rate  
BPM = Beats per minute  
TXA = Tranexamic acid  
NS = Normal saline



## Trauma - CRASH-2

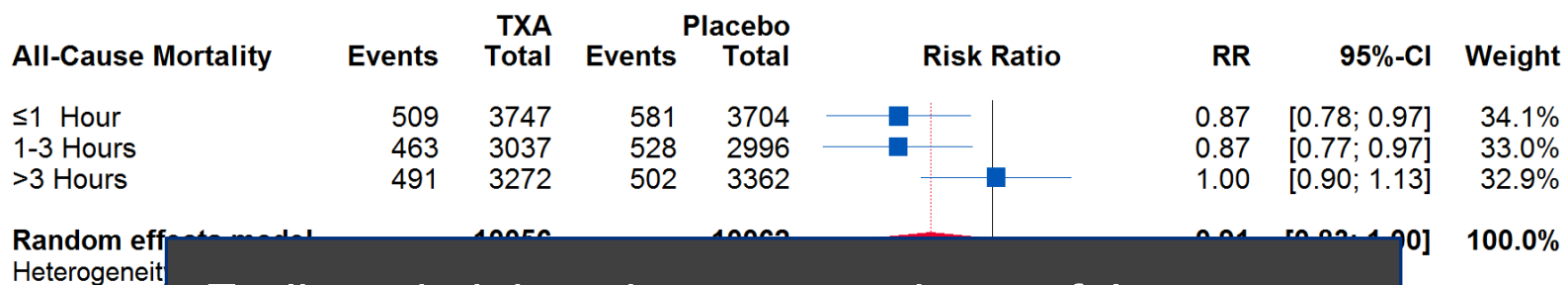


Ollidashi et al. *Lancet*. 2010;376(9734):23-32.

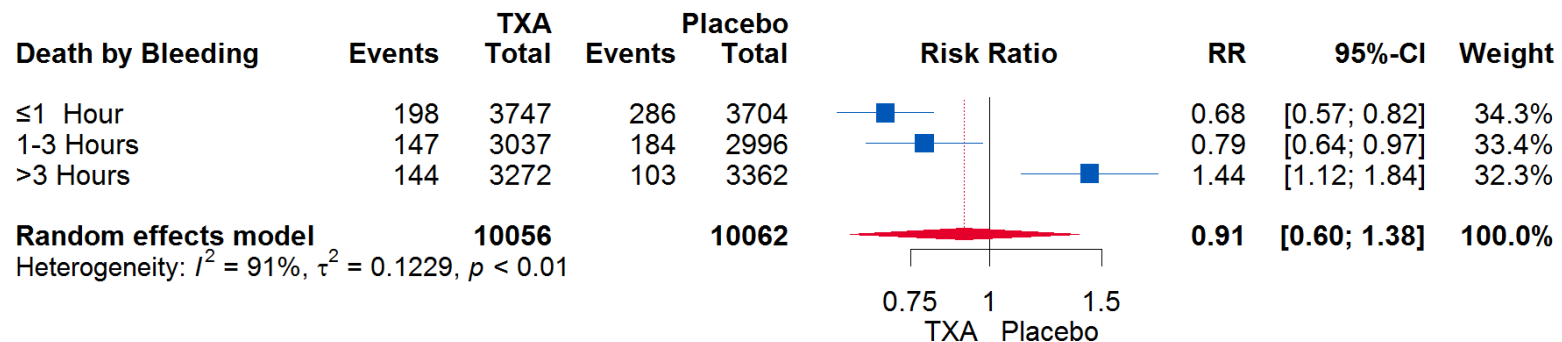
NNT = Number needed to treat  
TXA = Tranexamic acid



## Trauma - CRASH-2



Earlier administrations = more impactful outcomes



Ollidashi et al. *Lancet*. 2010;376(9734):23-32.

TXA = Tranexamic acid  
RR = Relative risk  
CI = Confidence interval



## Trauma - MATTERs

Single Center, retrospective, observational study at a Southern Afghanistan regional hospital

896 consecutive trauma admission secondary to combat injuries requiring a transfusion within 24 hours

1g TXA within 1 hour of injury  
N=293 (32.7)

Massive transfusion activated  
N=125 (42.7)

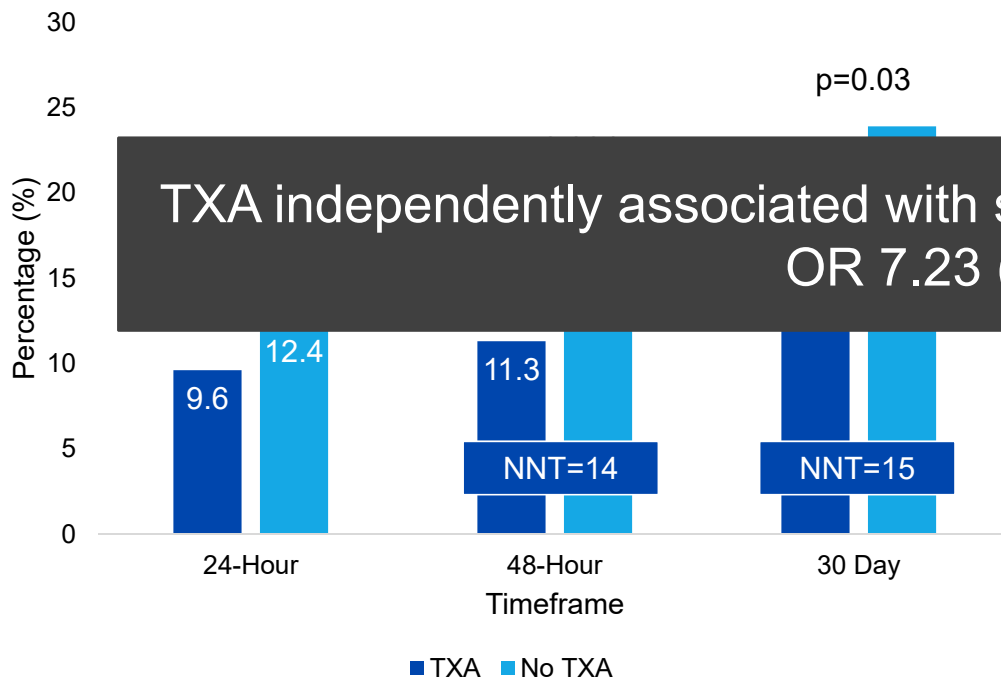
Standard Care  
N=603 (67.3)

Massive transfusion activated  
N=196 (32.5)

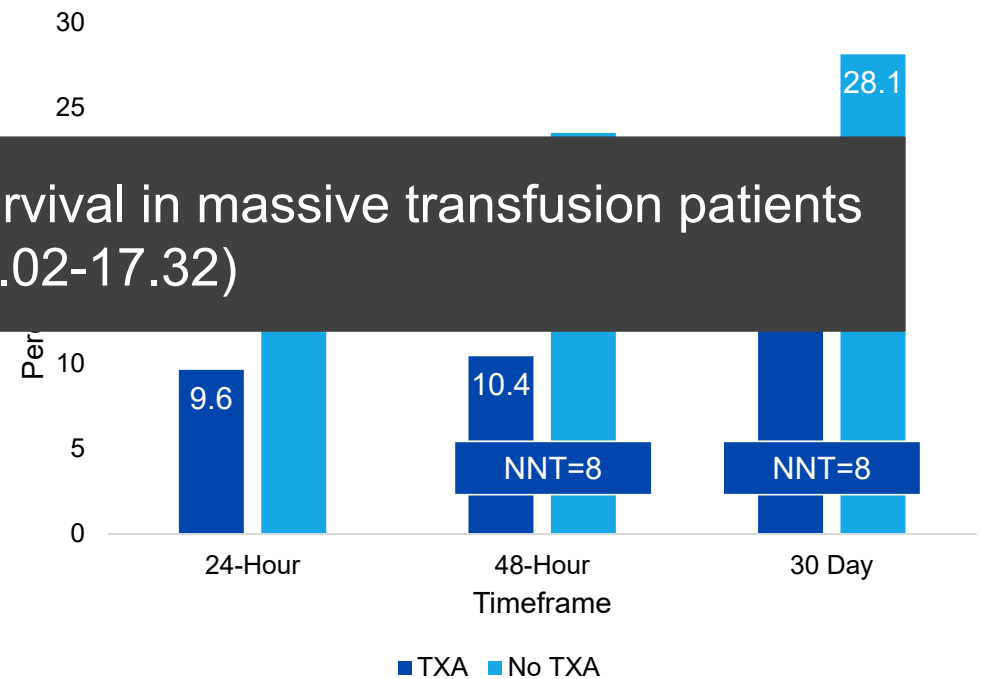


# Trauma - MATTERS

Overall Mortality



Massive Transfusion Mortality



TXA independently associated with survival in massive transfusion patients  
OR 7.23 (3.02-17.32)

Morrison et al. *Arch Surg.* 2012;147(2):113-119

NNT = Number needed to treat  
TXA = Tranexamic acid  
OR = Odds ratio





# Overview

|                                                                                     | TXA Indications        | Benefit? |
|-------------------------------------------------------------------------------------|------------------------|----------|
|    | Perioperative Bleeding | ✓        |
|    | PPH                    | ✓*       |
|    | Trauma                 | ✓        |
|    | ICH                    | ?        |
|   | Epistaxis              | ?        |
|  | Hemoptysis             | ?        |
|  | GiB                    | ?        |

\*=Treatment, not prophylaxis



## ICH: TICH-2

International, randomized, double-blind, placebo-controlled, parallel group, phase 3 trial in 124 hospitals in 12 countries

### Inclusion

- Adults with ICH
- With 8 hours of stroke symptom onset or last seen well

### Exclusion

- ICH secondary to antcoagulation, thrombolysis, trauma, or structural abnormality
- mRS > 4 at baseline
- Life expectancy <3 months
- GCS score <5

N=2,325 patients

TXA – 1g over 10 minutes, then 1g infusion over 8 hours  
N=1,161 (49.9)

Placebo – 0.9% NS  
N=1,150 (49.5)

Sprigg et al. *Lancet*. 2018;391(10135):2107-2115.

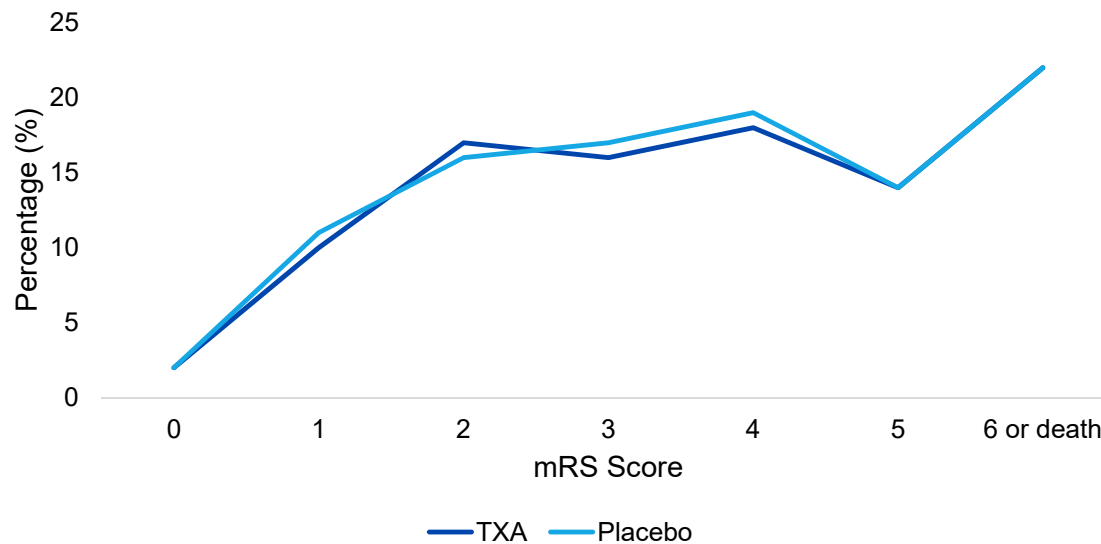
ICH = Intracranial hemorrhage  
TXA = Tranexamic acid  
mRS = Modified rankin scale  
GCS = Glasgow coma scale

NS = Normal saline

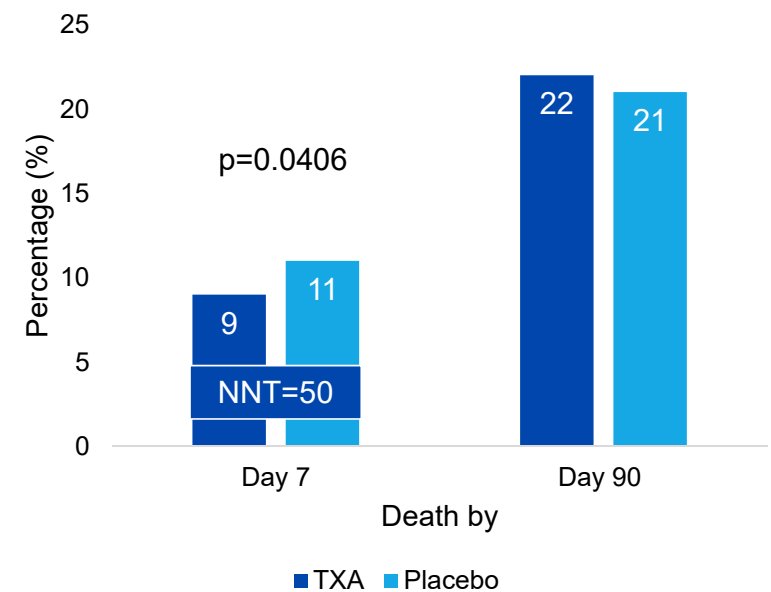


# ICH: TICH-2

Participants with mRS Outcome at Day 90



Mortality



Sprigg et al. *Lancet*. 2018;391(10135):2107-2115.

ICH = Intracranial hemorrhage  
mRS = Modified rankin scale  
TXA = tranexamic acid  
NNT = Number needed to treat



## ICH: TICH-2

### Hematoma Expansion

Reduces death within 7 days, but no difference in death at 90 days or in mRs

Rate of hematoma expansion and mean volume is decreased

### Limitations

Most patients enrolled >3 hours after ICH

Broad inclusion criteria

At Day 2  
Timeframe

■ TXA ■ Placebo

At Day 2  
Timeframe

■ TXA ■ Placebo

Sprigg et al. *Lancet*. 2018;391(10135):2107-2115.

ICH = Intracranial hemorrhage  
NNT = Number needed to treat  
TXA = Tranexamic acid  
mRS = Modified rankin scale



# ICH: CRASH-3

Multicenter, double-blind, parallel-group, randomized-controlled trial in 175 hospitals in 29 countries

## Inclusion

- Adult with TBI who were within 3 hours of injury
- GCS score  $\leq 12$
- Any intracranial bleeding on CT scan

## Exclusion

- Major extracranial bleeding

N=12,737 patients

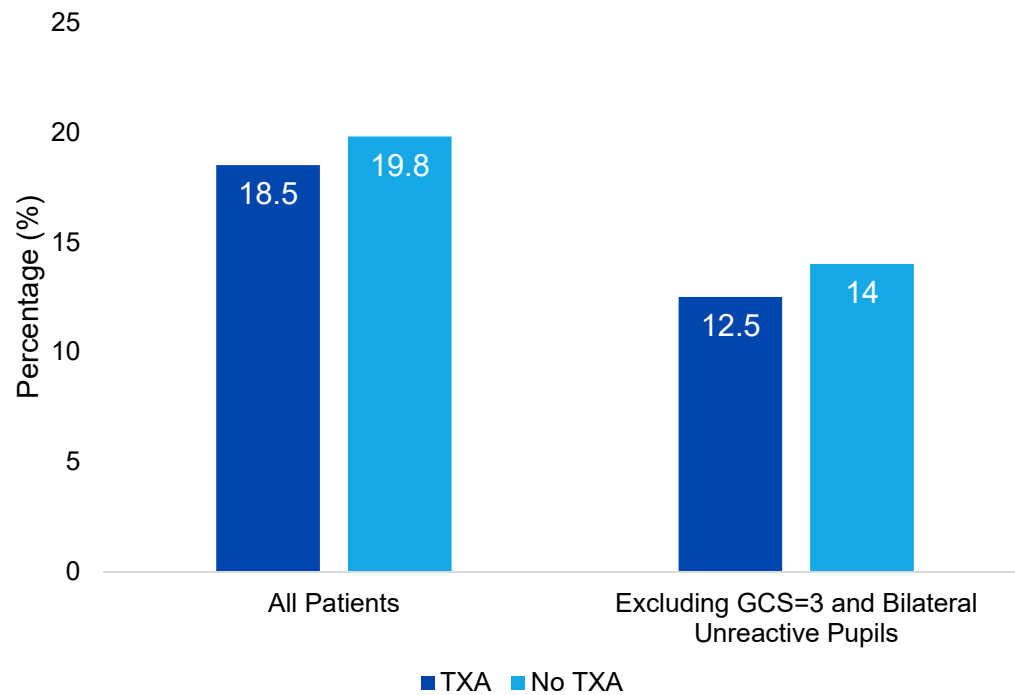
TXA – 1g over 10 minutes, then 1g infusion over 8 hours  
N=6,406 (50.3)

Placebo – 0.9% NS  
N=6331 (49.7)



# ICH: CRASH-3

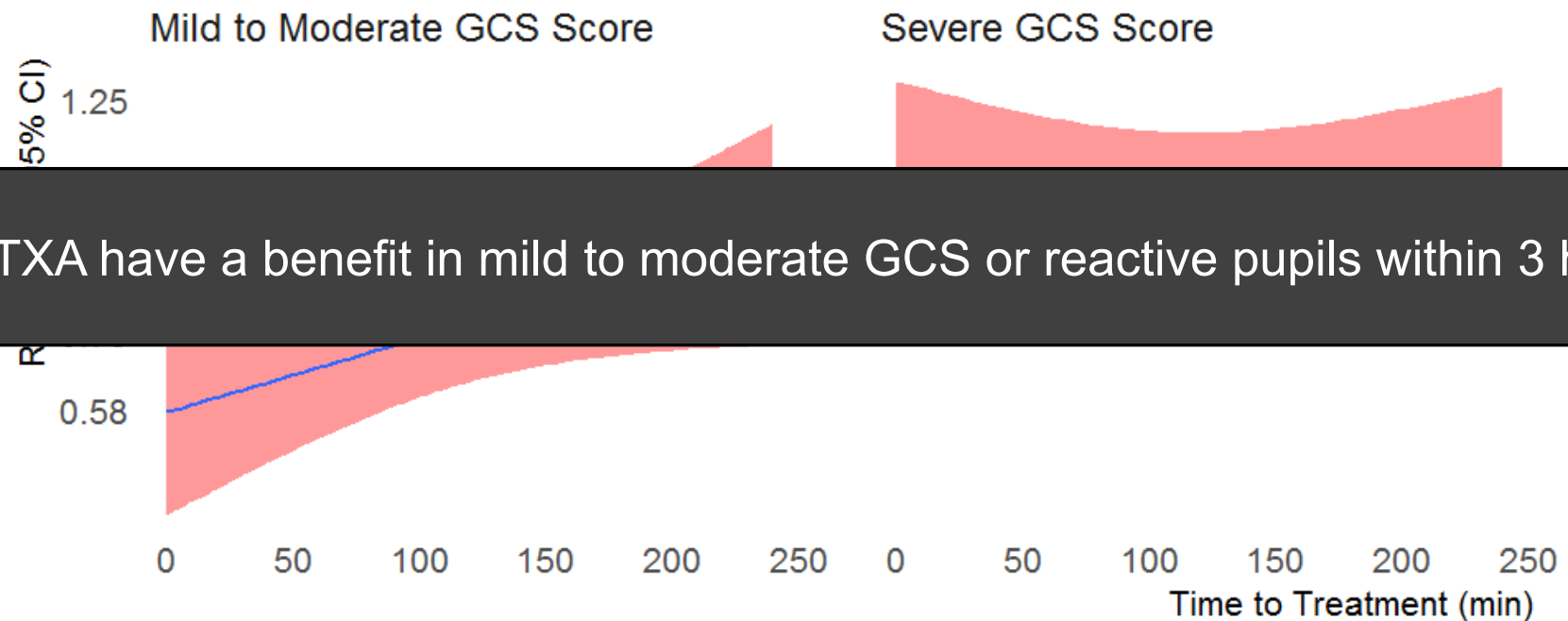
## Head Injury-Related Death within 28 Days



| Head-Injury Related Death                        | Relative Risk (TXA vs placebo) | 95% CI    |
|--------------------------------------------------|--------------------------------|-----------|
| All Patients                                     | 0.94                           | 0.86-1.02 |
| Excluding GCS =3 and Bilateral Unreactive Pupils | 0.89                           | 0.80-1.00 |



## Effect of TXA on Head-Injury Related Death



Does TXA have a benefit in mild to moderate GCS or reactive pupils within 3 hours?

CRASH-3 trial collaborators. *Lancet*. 2019;394(10210):1713-1723.

TXA = Tranexamic acid  
GCS = Glasgow coma scale  
CI = Confidence interval



## ICH: CRASH-3

| Baseline Characteristic | Events | TXA<br>Total | Placebo<br>Events | Placebo<br>Total | Risk Ratio | RR | 95%-CI | Weight |
|-------------------------|--------|--------------|-------------------|------------------|------------|----|--------|--------|
|-------------------------|--------|--------------|-------------------|------------------|------------|----|--------|--------|

Reduced head-injury related death in mild-to-moderate head injury or reactive pupils

All patients saw a reduction of head-injury related death at 24 hours, but the benefit was not sustained at 28 days

| Head-Injury Related Death within 24 hours           |                                   |                         |
|-----------------------------------------------------|-----------------------------------|-------------------------|
|                                                     | Relative Risk<br>(TXA vs placebo) | 95% Confidence Interval |
| Head-Injury Related Death                           | 0.87                              | 0.69-0.95               |
| Excluding GCS =3 and Bilateral<br>Unreactive Pupils | 0.72                              | 0.56-0.92               |

CRASH-3 trial collaborators. *Lancet*. 2019;394(10210):1713-1723.

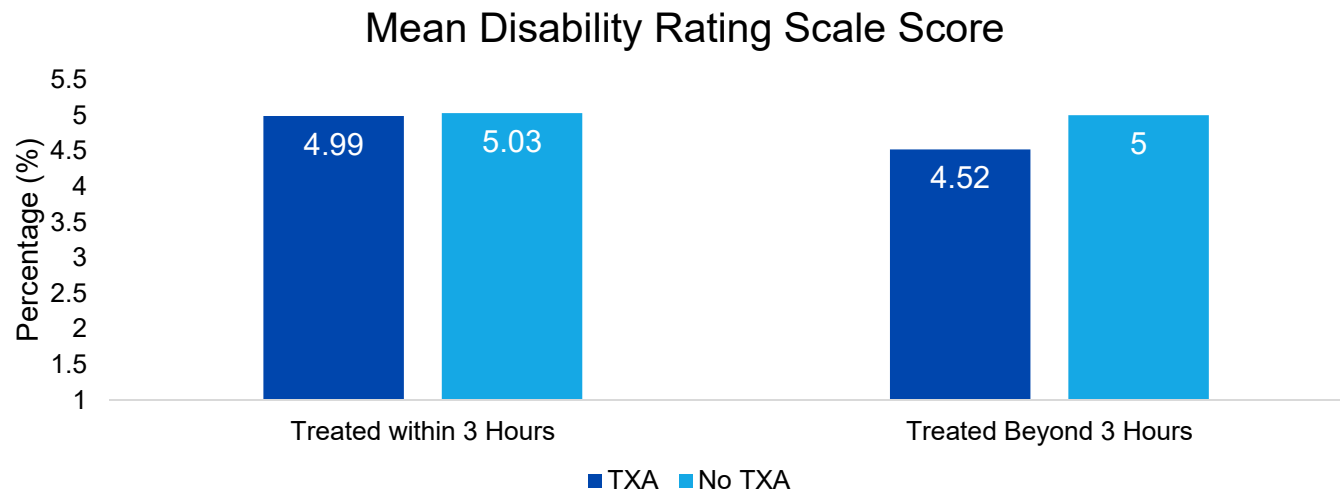
ICH = Intracranial hemorrhage  
GCS = Glasgow coma scale  
RR = Relative risk  
CI = Confidence interval





## ICH: CRASH-3

| Head-Injury Related Death Stratified by: | Relative Risk<br>(TXA vs placebo) | 95% CI    | P-Value |
|------------------------------------------|-----------------------------------|-----------|---------|
| High-Income Countries                    | 0.76                              | 0.55-1.04 | 0.26    |
| Low-Income and Middle-Income Countries   | 0.92                              | 0.81-1.04 |         |



# Overview

|                                                                                     | TXA Indications        | Benefit? |
|-------------------------------------------------------------------------------------|------------------------|----------|
|    | Perioperative Bleeding | ✓        |
|    | PPH                    | ✓*       |
|    | Trauma                 | ✓        |
|    | ICH                    | ?        |
|   | Epistaxis              | ?        |
|  | Hemoptysis             | ?        |
|  | GiB                    | ?        |

\*=Treatment, not prophylaxis



# Epistaxis - Zahed

Single Center, randomized, parallel-group clinical study

## Inclusion

- Presented to ED with acute, new, or recurrent, ongoing anterior epistaxis
- Currently taking antiplatelet (aspirin, clopidogrel, or both)
- Persistent bleeding despite 20 minutes of compression with finger and thumb

## Exclusion

- Traumatic epistaxis
- Current anticoagulant drug use
- Inherited bleeding disorders
- Inherited platelet disorder
- INR > 1.5
- Visible bleeding vessel

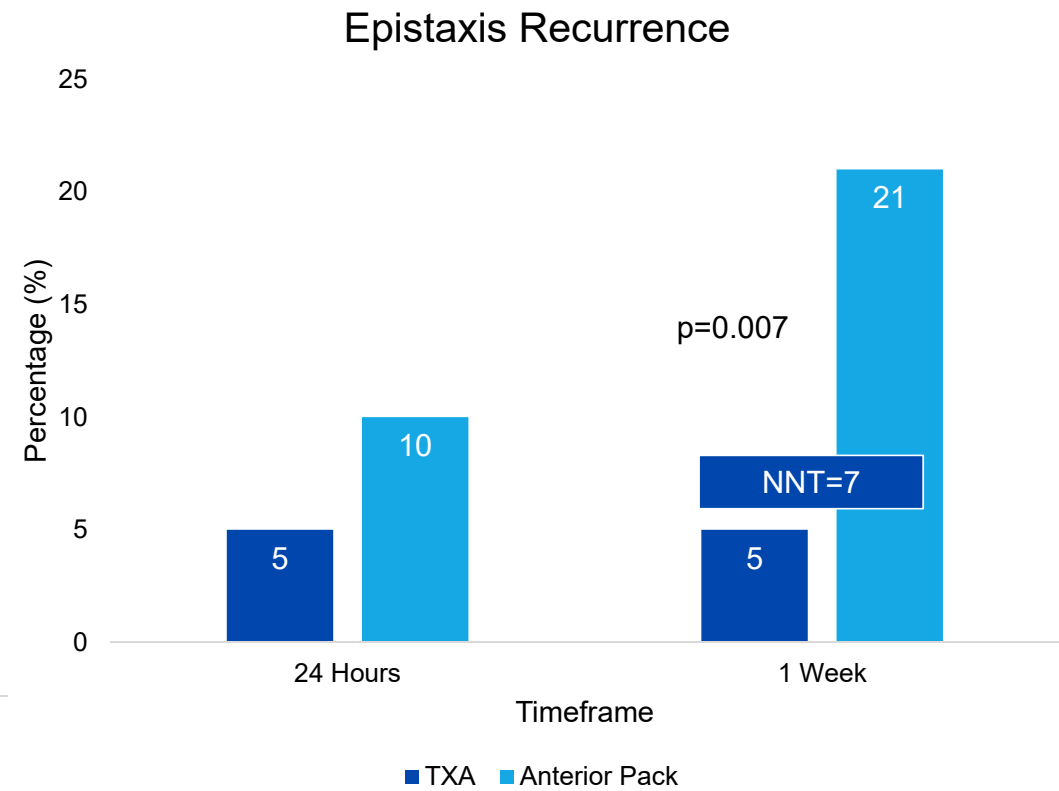
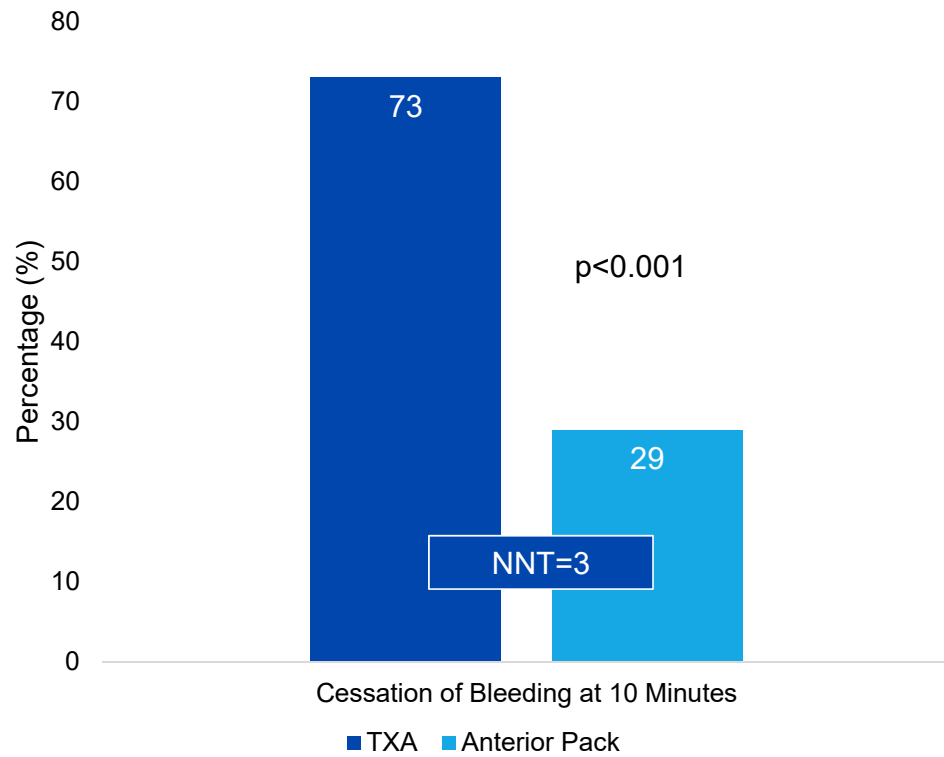
N=124 patients

Topical TXA 500mg in 5cc  
N=62 (50)

Anterior packing with epinephrine and lidocaine  
N=62 (50)



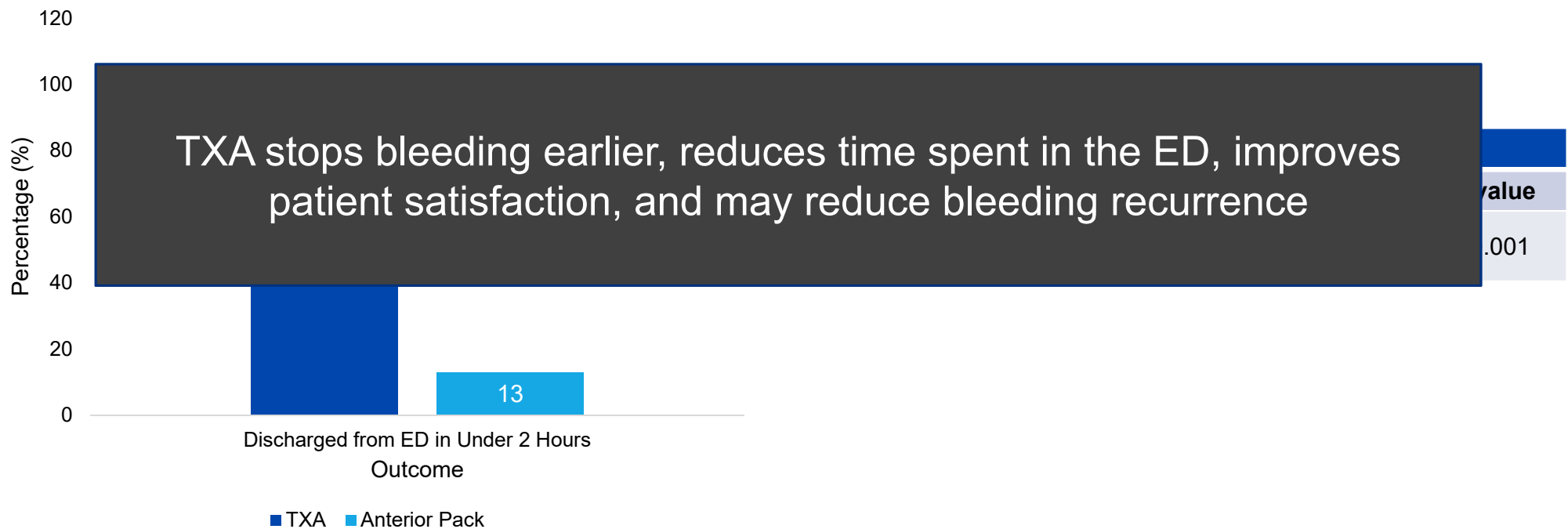
# Epistaxis - Zahed





# Epistaxis - Zahed

## Discharge Speed



Zahed et al. *Acad Emerg Med*. 2018;25(3):261-266.

NNT = Number needed to treat  
ED = Emergency department  
TXA = Tranexamic acid  
IQR = Interquartile range

# Overview

|                                                                                     | TXA Indications        | Benefit? |
|-------------------------------------------------------------------------------------|------------------------|----------|
|    | Perioperative Bleeding | ✓        |
|    | PPH                    | ✓*       |
|    | Trauma                 | ✓        |
|    | ICH                    | ?        |
|   | Epistaxis              | ✓        |
|  | Hemoptysis             | ?        |
|  | GiB                    | ?        |

\*=Treatment, not prophylaxis



# Hemoptysis - Wand

Single-center, double-blind, randomized, controlled trial

Inclusion

- $\geq 18$  years of age
- Hemoptysis in previous 24 hours

Exclusion

- Massive hemoptysis ( $>200\text{cc}$  within 24 hours)
- Respiratory or hemodynamic instability
- Coagulopathy (INR  $>2$ )
- Treatment with TXA prior to screening

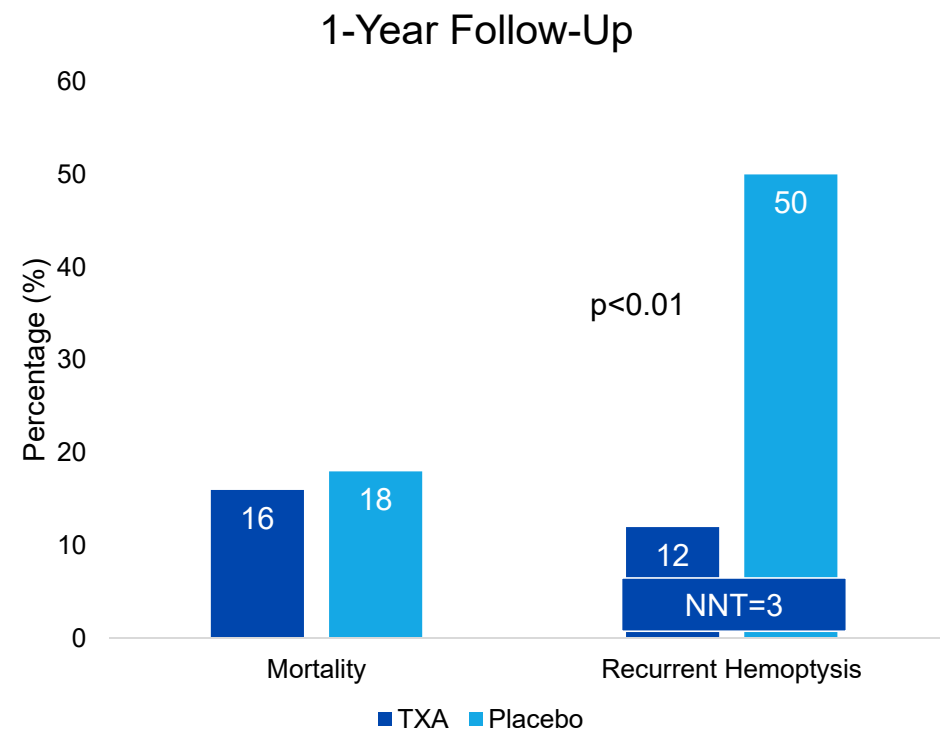
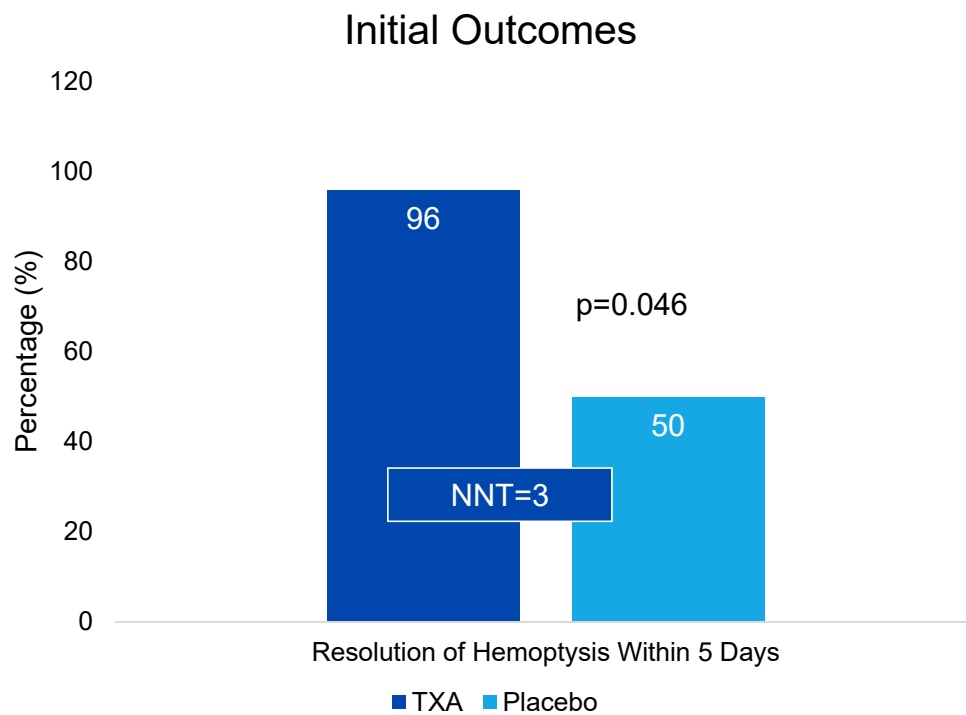
N=47 patients

Nebulized TXA 500mg 3x per day  
N=25 (53.2)

Placebo – 0.9% NS  
N=22 (46.8)



# Hemoptysis - Wand



Wand et al. *Chest*. 2018;154(6):1379-1384.

NNT = Number needed to treat  
TXA = Tranexamic acid



# Overview

|                                                                                     | TXA Indications        | Benefit? |
|-------------------------------------------------------------------------------------|------------------------|----------|
|    | Perioperative Bleeding | ✓        |
|    | PPH                    | ✓*       |
|    | Trauma                 | ✓        |
|    | ICH                    | ?        |
|   | Epistaxis              | ✓        |
|  | Hemoptysis             | ?        |
|  | GiB                    | ?        |

\*=Treatment, not prophylaxis

# Overview



| TXA Indications        | Benefit? | Overall Summary                                                     |
|------------------------|----------|---------------------------------------------------------------------|
| Perioperative Bleeding | ✓        | ↓ rate of blood transfusion, ↓ amount of blood transfused           |
| PPH                    | ✓*       | ↓ death due to PPH, ↔ in outcomes related to ppx                    |
| Trauma                 | ✓        | ↓ mortality (all-cause, death due to hemorrhage), ↑ thrombosis?     |
| ICH                    | ?        | ↔ mortality, ↓ hematoma expansion rates and volume                  |
| Epistaxis              | ✓        | ↓ time in ED, ↑ patient satisfaction, ↑ early cessation of bleeding |
| Hemoptysis             | ?        | ↔ mortality, ↑ hemoptysis resolution, ↓ hemoptysis recurrence       |
| GiB                    | ?        | More to come...                                                     |

Based on the presented studies, which of the following regarding TXA is true?

- Decreases mortality in hemoptysis patients
- Reduces the incidence of PPH when used for prevention
- Decreases mortality in trauma patients
- It does not affect hematoma expansion rates in ICH

Based on the presented studies, which of the following regarding TXA is true?

- Decreases mortality in hemoptysis patients
- Reduces the incidence of PPH when used for prevention
- **Decreases mortality in trauma patients**
- It does not affect hematoma expansion rates in ICH

## Is TXA Prothrombotic?

| VTE Risk |                       |                       |      |           |                |           |
|----------|-----------------------|-----------------------|------|-----------|----------------|-----------|
|          | TXA (%)               | Placebo (%)           | RR   | 95% CI    | P-value        | VTE Risk? |
| CRASH-2  | 1.7                   | 2                     | 0.84 | 0.68-1.02 | 0.084          | No        |
| MATTERs  | 2.7 (PE)<br>2.4 (DVT) | 0.3 (PE)<br>0.2 (DVT) | -    | -         | 0.001<br>0.001 | Yes       |
| CRASH-3  | 1.6                   | 1.6                   | 0.98 | 0.74-1.08 | -              | No        |
| TICH-2   | 3.4                   | 3.2                   | -    | -         | 0.98           | No        |
| WOMAN    | 0.3                   | 0.3                   | 0.88 | 0.54-1.43 | 0.603          | No        |
| TRAAP    | 0.1                   | 0.2                   | 0.25 | 0.03-2.24 | 0.37           | No        |

Olldashi et al. *Lancet*. 2010;376(9734):23-32.

Morrison et al. *Arch Surg*. 2012;147(2):113-119

CRASH-3 trial collaborators. *Lancet (London, England)*. 2019;394(10210):1713-1723.

Sprigg et al. *Lancet*. 2018;391(10135):2107-2115.

Shakur et al. *Lancet*. 2017;389(10084):2105-2116.

Sentilhes et al. *N Engl J Med*. 2018;379(8):731-742.

VTE = Venous thromboembolism

TXA = Tranexamic acid

RR = Relative risk

CI = Confidence interval

## Is TXA Associated with Seizures?

- Doses > 100mg/kg have been associated with seizures

| Seizures |                 |             |      |          |         |               |
|----------|-----------------|-------------|------|----------|---------|---------------|
|          | TXA (%)         | Placebo (%) | RR   | 95% CI   | P-value | Seizure Risk? |
| ATACAS   | 0.7             | 0.1         | 7.6  | 1.8-68.7 | 0.002   | Yes           |
| CRASH-2  | Didn't evaluate |             |      |          |         |               |
| MATTERs  | Didn't evaluate |             |      |          |         |               |
| CRASH-3  | 3.2             | 3.0         | 1.09 | 0.9-1.33 | -       | No            |
| TICH-2   | 6.6             | 7.3         | -    | -        | 0.44    | No            |
| WOMAN    | 0.3             | 0.4         | 0.76 | 0.49-1.2 | 0.242   | No            |
| TRAAP    | 0.1             | 0           | -    | -        | -       | No            |

Myles et al. *N Engl J Med.* 2017;376(2):136-148.  
 Ollidashi et al. *Lancet.* 2010;376(9734):23-32.  
 Morrison et al. *Arch Surg.* 2012;147(2):113-119  
 CRASH-3 trial collaborators. *Lancet (London, England).* 2019;394(10210):1713-1723.  
 Sprigg et al. *Lancet.* 2018;391(10135):2107-2115.

Shakur et al. *Lancet.* 2017;389(10084):2105-2116.  
 Sentilhes et al. *N Engl J Med.* 2018;379(8):731-742.

VTE = Venous thromboembolism  
 TXA = Tranexamic acid  
 RR = Relative risk  
 CI = Confidence interval



## DOSING

| Dosage form | Trial      | Bolus                                                      | Maintenance dose                                                               |
|-------------|------------|------------------------------------------------------------|--------------------------------------------------------------------------------|
| IV          | ATACAS     | 100 mg/kg (was changed to 50 mg/kg due to seizure reports) | Aimed to maintain effective plasma concentration for 6-8 hours                 |
|             | CRASH-2    | 1g over 10 minutes                                         | 1g over 8 hours                                                                |
|             | TICH-2     | 1g over 10 minutes                                         | 1g over 8 hours                                                                |
|             | CRASH-3    | 1g over 10 minutes                                         | 1g over 8 hours                                                                |
|             | MATTERs    | 1g                                                         | Repeated per clinician                                                         |
|             | WOMAN      | 1g over 10 minutes                                         | 1g if bleeding continued after 30 min or stopped and restarted within 24 hours |
|             | TRAAP      | 1g over 30-60 seconds                                      | -                                                                              |
| Topical     | Zahed 2018 | 500mg (5cc) soaked cotton pledget                          | -                                                                              |
|             | Akkan 2019 | 500mg (5cc) atomized and sprayed into both nostrils        | -                                                                              |
| Inhaled     | Wand 2018  | -                                                          | 500mg (5cc) nebulized 3x per day                                               |

## Topical and Inhaled TXA



Compression device



Cotton pledget



Atomizer



Nebulizer

TXA = Tranexamic acid



## Which of the following regarding TXA is true?

- TXA has been shown to consistently increase VTE risk
- A barrier to use of TXA is cost
- TXA currently has a defined role in GiB
- TXA reduces time spent in the ED due to epistaxis

## Which of the following regarding TXA is true?

- TXA has been shown to consistently increase VTE risk
- A barrier to use of TXA is cost
- TXA currently has a defined role in GiB
- **TXA reduces time spent in the ED due to epistaxis**

# Pipeline



HALT-IT Trial (NCT01658124)  
TXA in GiB  
Estimated completion 10/2020

TRANSACT Trial (NCT03044184)  
TXA in Spontaneous Acute Cerebral Hemorrhage  
Recruiting

TARAA Trial (NCT02125890)  
TXA in Ruptured AAA  
Recruiting

TXA for Hemorrhage Prevention in Cesarean  
Delivery (NCT03856164)  
Recruiting

## Summary

- Unclear impact in developed countries
- TxA has not been shown consistently in the studies to be either prothrombotic or seizure-provoking
- TxA has shown potential benefits in multiple indications with many more indications being further evaluated



## Questions & Comments

Nicholas Vollmer, PharmD  
PGY-1 Pharmacy Resident