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rpth research & practice in thrombosis & haemostasis

ILLUSTRATED REVIEW

Tranexamic acid evidence and controversies: An illustrated review

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Abstract

Tranexamic acid (TXA) is an antifibrinolytic agent commonly used for the treatment or prevention of bleeding. Indications for TXA are diverse, including heavy menstrual bleeding, trauma, postpartum hemorrhage, traumatic brain injury, and surgical site bleeding. Despite decades of use and a robust body of evidence, hesitancy using TXA persists in many clinical settings. This illustrated review describes the history, pharmacology, and practical considerations of TXA use. We also describe the major landmark randomized controlled trials of TXA and their implications. Finally, we review the evidence around common controversies surrounding TXA such as the risk of thrombosis, prescription along with combined hormonal contraceptives, and use in patients with gross hematuria.

KEYWORDS
antifibrinolytic agents, blood coagulation, contraceptive agents, thrombosis, tranexamic acid

Essentials

- Tranexamic acid (TXA) decreases the risk of bleeding and often the risk of death from bleeding.
- In general, TXA does not increase the risk of blood clots.
- Consider shared decision making in patients taking TXA and combined hormonal contraceptives.
- It is unknown if TXA causes harm in patients with blood in the urine.

History of Tranexamic acid

The Okamoto Legacy[1]

Left: Shosuke Okamoto, Right: Utako Okamoto

1940s

1945: Drs. Utako and Shosuke Okamoto, wife and husband team, were medical doctors and researchers at Kobe and Keio Medical School in Japan. After World War II, they directed their research towards hemostasis due to scare resources

"If there was not enough [resources], we could simply use our own [blood]"

1960s

1960s: Post-partum hemorrhage (PPH) was identified as the major cause of maternal death in Japan. Utako and Shosuke Okamoto began to develop new compounds that could reduce the risk of PPH

1960s: Studied anti-fibrinolytic ***epsilon-amino-caproic acid*** **(EACA)** ➔ Determined that a more potent agent was required

1962: Discovered ***1-(aminomethyl)-cyclohexane-4-carboxylic acid*** **(AMCHA)**[2], a chemical relative of EACA that is 27x more powerful. AMCHA was later renamed **tranexamic acid (TXA)**

After 1962: Utako and Shosuke Okamoto were unable to persuade obstetricians to conduct research studies on the use of TXA for PPH

2004

November 1, 2004: Shosuke Okamoto died

2010

2010: CRASH-2 trial showed TXA safely reduced the risk of death in bleeding trauma patients[3]

2011

2011: TXA added to WHO list of essential medicines[4]

2014

2014: Principle investigator of **WOMAN Trial** investigating TXA for PPH visits Utako in Japan. Utako said: "It is going to be effective"

2016

April 14, 2016: WOMAN Trial reached recruitment target of 20,000 patients

April 21, 2016: Utako Okamoto died in Kobe, Japan at 98 years of age

Did you know?

Earlier in her career, Utako worked long hours in the lab while also caring for her daughter. She was once asked to leave a conference because "events were not for women and children". Unfortunately, sexism in academia and in medicine remains prevalent today[6]

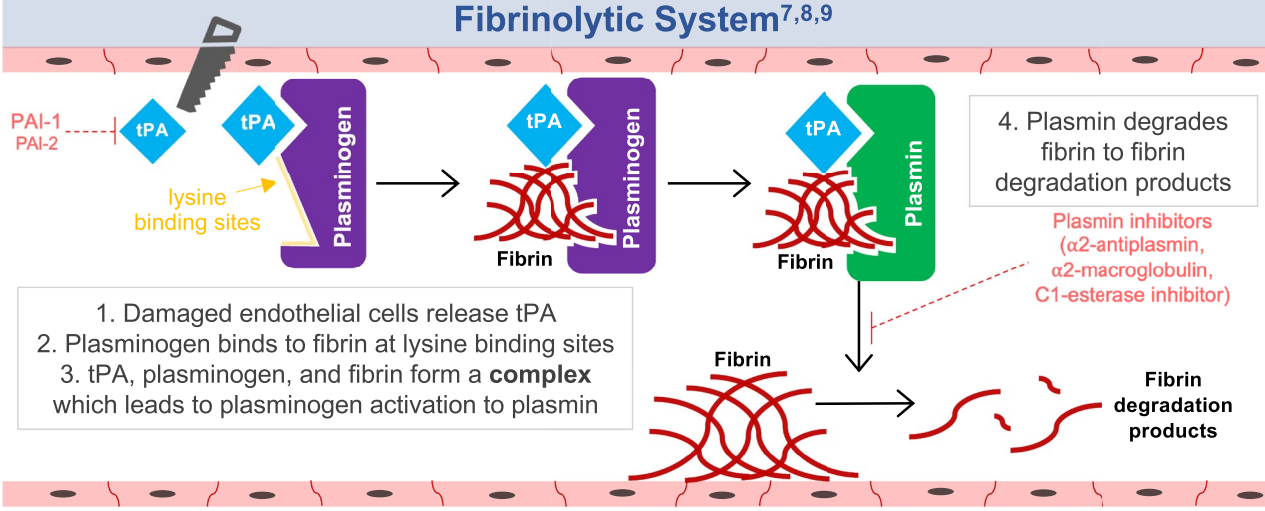
#SHERO

2017

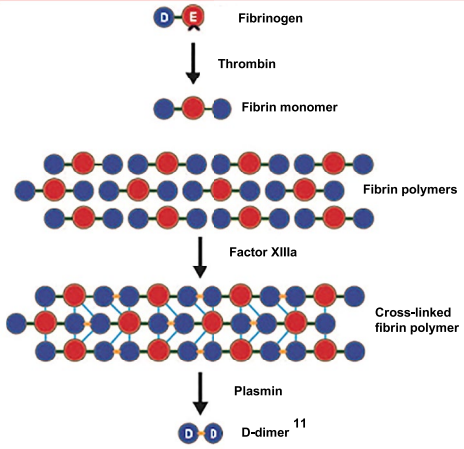
2017: WOMAN Trial showed that TXA safely decreased the risk of hemorrhagic death in women with PPH[5]

Results of the **WOMAN Trial** shown below!

Fibrinolytic System[7,8,9]



Difference between fibrin degradation products (FDPs) and D-dimer?



FDPs can be present in the absence of stable clot formation when plasmin cleaves circulating fibrinogen

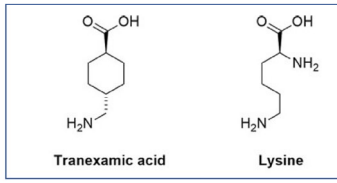
D-dimer is a FDP consisting of two D domains formed by degradation of crosslinked fibrin polymers
Indicates formation of a stable fibrin-rich clot crosslinked by **factor XIIIa** [10,11] and subsequent fibrinolysis

Caution ⚠

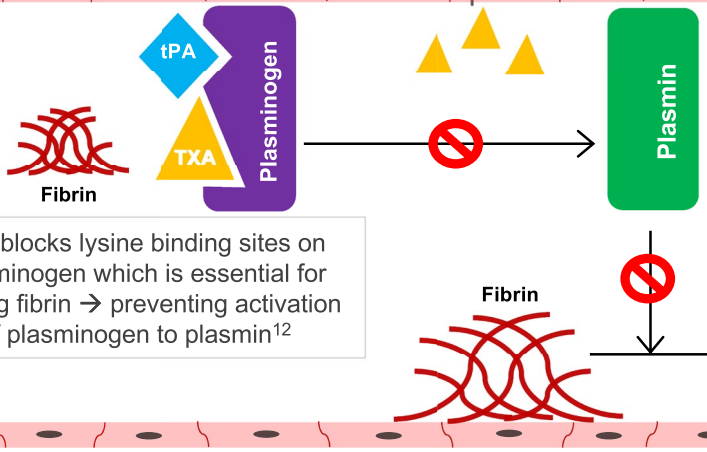
D-dimer can be elevated in thrombosis, infection (e.g. COVID-19), DIC, inflammation, malignancy, trauma, pregnancy, liver disease, older age, and recent surgery[11]

Tranexamic Acid: Mechanism of Action

TXA is an **anti-fibrinolytic**



TXA is a synthetic analog of the amino acid **lysine**



TXA blocks lysine binding sites on plasminogen which is essential for binding fibrin → preventing activation of plasminogen to plasmin[12]

TXA ultimately reduces fibrinolysis and stabilizes the fibrin-rich clot

TXA Indications

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system was used to classify quality of evidence as *high*, *moderate*, or *low*[13]

Green = High quality evidence
Yellow = Moderate quality evidence
Orange = Low quality evidence

Indication	TXA Regimen
Postpartum hemorrhage (PPH)[5,14] **WOMAN TRIAL**	1g IV over 10 min. If bleeding continues after 30 min or restarts within 24h a 2nd dose of 1g IV can be given
Trauma-associated hemorrhage[3] **CRASH-2 TRIAL**	1g IV over 10 min then 1g over the next 8 hours as a continuous infusion
Reducing transfusion in cardiac surgery[15]	50mg/kg IV over 30 min during the OR
Traumatic brain injury with GCS > 9[16] **CRASH-3 TRIAL**	1g IV over 10 min then 1g over the next 8 hours as a continuous infusion
Heavy Menstrual Bleeding[17,18,19]	1300mg PO 3 times daily (3900mg/day) for up to 5 days during each monthly menstruation
Intracerebral Hemorrhage (ICH)[20] **TICH-2 TRIAL**	1g IV over 10 min then 1g over the next 8 hours as a continuous infusion
Hemoptysis[21,22]	500-1000mg nebulized in 5-10mL 0.9% normal saline
Reducing transfusion during orthopedic surgery[23,24]	10mg/kg IV loading dose during the OR followed by 1mg/kg/hour maintenance infusion
Von Willebrand Disease (VWD) related bleeding[25,26]	Oral: TXA 20mg/kg PO TID Mouthwash: TXA 5% 10mL QID prn – Swish and spit
Topical surgical field blood loss reduction[27]	Variable doses; most commonly 1g TXA in 50 mL administered intraarticularly
Epistaxis[28,29]	Topical: Cotton gauze soaked with injectable form of TXA (500mg in 5mL)
Hereditary Hemorrhagic Telangiectasia related bleeding[30]	1g PO TID
Prophylaxis in Acute Myeloid Leukemia related bleeding[31]	1g IV q6h when platelet count <20 or falling trend <50, until platelets >20 on two counts
Prophylaxis in Acute Promyelocytic Leukemia related bleeding[31]	2g IV q8h for 6 days
Melasma[33]	250mg PO BID or 4mg/mL injected intradermal to melasma lesions
Hereditary angioedema[34]	Long-term prophylaxis: 0.5-1g PO BID-TID Short-term prophylaxis: 1g PO QID x48 before and after procedure

Did you know?

The **TRAAP study** showed that in women with **vaginal delivery** who received prophylactic oxytocin, **TXA did NOT result in significantly lower rates of measured PPH** compared to placebo[35]

Research In Progress

Does prophylactic TXA in women with **cesarean delivery** reduce the risk of PPH?
TRAAP2 study[36]: NCT03431805
MFMU Study: NCT03364491

WOMAN-2 → Does TXA prevent PPH in women with **vaginal delivery** and **moderate or severe anemia**?[37] NCT03475342

Research In Progress

Side Effects of Systemic TXA[38,39,40]

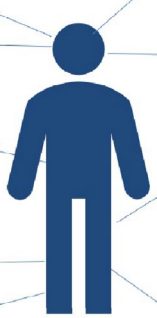
Nervous system: Headache (50%)

Respiratory: Nasal symptoms (25%)

Gastrointestinal: Nausea, vomiting, diarrhea, abdominal pain (20%)

Neuromuscular: Musculoskeletal pain, arthralgia, back pain (10%)

Other: Fatigue (5%)



Visual Disturbances (<1%)
Impaired vision, blurred vision, color vision impairment

Seizure (<1%)

Hypersensitivity Reaction (<1%)
Mild/moderate: Pruritis, urticaria
Severe: Anaphylaxis

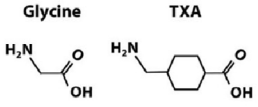
Thrombosis?

Blood Drop
Patients can **take oral TXA with meals** or **reduce the dose** to reduce GI side effects

Evidence for risk of thrombosis with TXA is discussed below

TXA Associated Seizure

TXA is a competitive antagonist of $GABA_A$ and glycine receptors[41]



TXA is a structural analogue of glycine

Did you know?
$GABA_A$ and glycine receptors are inhibitory receptors in the CNS

Glycine receptor **$GABA_A$ receptor**

↓ **Inhibitory Current** → ↑ **Excitability** →

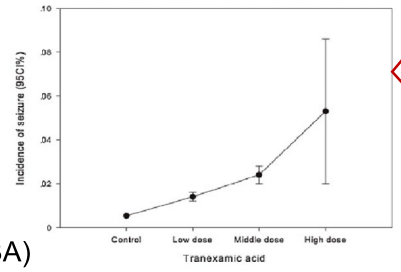
= TXA = Glycine / GABA

Risk factors[15,41-45]

- Open-chamber cardiac surgery
- Cardio-pulmonary bypass time >150min
- High dose TXA (>80-100mg/kg total)
- Renal dysfunction
- Age >75 years
- Poor overall health

Treatment: Anesthetics, Lorazepam (↑GABA)

Dose-effect response of TXA-associated seizure[45]



Cumulative incidence rate of TXA associated seizure[44]
~2.7%*
*(*cardiac surgery, pulmonary endarterectomy)*

Caution ⚠

Urinary excretion is the main route of elimination for TXA. Dose adjustment for renal impairment required!

Serum creatinine	Adjusted TXA Dose[38,39]
120-250 µmol/L	15mg/kg PO or 10mg/kg IV BID
250-500 µmol/L	15mg/kg PO or 10mg/kg IV daily
>500 µmol/L	15mg/kg PO or 10mg/kg q48h

TXA Contraindications

Canada[38]

Subarachnoid Hemorrhage

Antifibrinolytics in **aneurysmal SAH[46]:**

✔ **Reduced risk of rebleeding** by ~35%

✖ Increased risk of **cerebral ischemia**

↓

No net clinical benefit

TXA Hypersensitivity[47]

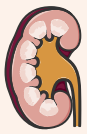
Mild/ Moderate: pruritis, urticaria

Severe: Anaphylaxis

Mechanism:

IgE mediated or Cellular mediated

Protocol exists for verification of TXA anaphylaxis[48]



Hematuria

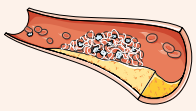
Controversy! The use of TXA for hematuria is discussed below

Disturbances of color vision

Visual impairment, blurred vision, impaired color vision can occur[38]

➔ **Discontinue TXA if these symptoms develop**

Consider regular ophthalmic check-up with **long-term uninterrupted TXA**



Thrombosis

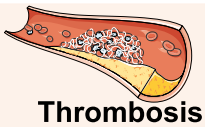
Active or history of thrombosis

Controversy! Is TXA associated with a risk of thrombosis? Discussed below

United States[39]

Subarachnoid Hemorrhage

TXA Hypersensitivity



Thrombosis

Active or history of thrombosis

Avoid use with medications that may be pro-thrombotic: Factor IX complex concentrates, **hormonal contraceptives**

Controversy! This is discussed below.

Did you know?

Despite the risk of cerebral infarction, 2012 AHA guidelines for the management of **aneurysmal SAH** recommend short term (<72h) TXA or aminocaproic acid to reduce the incidence of aneurysmal rebleeding when there is an unavoidable surgical delay ***(Class IIa, Level of Evidence B)***[49]

⚠ Off-label use of TXA ⚠

What does newer evidence say (2020)

ULTRA Trial[50]: In patients with **aneurysmal SAH** ➔ Ultra-early (<24h), short-term TXA did not improve clinical outcomes

✖ Based on new evidence, **routine use of TXA for aneurysmal SAH is not recommended**

Select Landmark TXA Randomized Controlled Trials

★ *primary outcome*

HMB[19]

ELIGIBILITY Adult women with **heavy menstrual bleeding** (mean menstrual blood loss (MBL) ≥80mL)

Exclusion: thromboembolic disease, ocular disease, **severe anemia**, pregnant, lactating, endometrial or cervical abnormalities

METHODS

n=187

Placebo n=72 ⟷ **TXA** n=115

TXA 1.3g PO TID x 5 days at the onset of HMB for six menstrual cycles

RESULTS

	TXA	Placebo	*P*
★ Average reduction MBL (mL)	**69.6**	12.6	<0.001
★ Reduction MBL >50mL	**56%**	19%	<0.001
★ % cycles with clinically meaningful reduction in MBL (>36mL)	**69%**	29%	<0.001

Improvements in **health-related quality of life (HR-QoL)** in TXA group compared to placebo (*P*<0.01)

Adverse events were mild/ moderate in severity (e.g. headache)

CONCLUSION TXA was **well tolerated**, and **significantly improved MBL** and **HR-QoL** in women with HMB

WOMAN[5]

ELIGIBILITY Woman >16 yo with **post partum hemorrhage**

METHODS

n=20060

TXA n=10051 ⟷ **Placebo** n=10009

TXA 1g IV Repeat if bleeding continues after 30min or rebleed within 24h

RESULTS

	TXA	Placebo	*P*
★ **Composite of all cause mortality or hysterectomy**	5.3%	5.5%	0.65
Death from bleeding	**1.5%**	1.9%	**0.045**

No difference between groups in adverse effects

CONCLUSION TXA had no effect on all cause mortality but safely **reduced risk of death due to bleeding** in women with post partum hemorrhage

Research In Progress

WOMAN-2 → Does TXA prevent PPH in women with **vaginal delivery** and **moderate or severe anemia**?[37] NCT03475342

What is Heavy Menstrual Bleeding (HMB)?[51,52]

Menstrual Blood Loss (MBL) >80mL

MBL that interferes with:

Physical Emotional Social

Quality of Life

More info at: **www.letstalkperiod.ca**

Management of HMB in women with VWD:[53]

Who do NOT wish to conceive

Hormonal therapy (CHC or levonorgestrel-releasing intrauterine system) or **TXA** recommended over desmopressin (DDAVP)

- TXA likely reduces MBL more than DDAVP[54]

Who do wish to conceive

TXA recommended over DDAVP

Select Landmark TXA Randomized Controlled Trials

★ *primary outcome*

2010

CRASH-2[3]

ELIGIBILITY Adult **trauma patients** within 8 hours of injury

METHODS

n=20211

TXA n=10067 | **Placebo** n=10060

TXA 1g IV over 10 min then: TXA 1g IV over 8 hrs

RESULTS

	TXA	Placebo	*P*
★Mortality	14.5%	16.0%	0.003
Death from bleeding	4.9%	5.7%	0.007

No difference between groups in adverse events

CONCLUSION Early TXA (<3h) safely **reduced risk of death from bleeding** in trauma patients

2017

Cardiac Surgery[15]

ELIGIBILITY Adult patients undergoing **cardiac surgery**

METHODS

n=4662

TXA n=2329 | **Placebo** n=2333

TXA 100mg/kg IV, protocol changed to 50mg/kg halfway through trial

RESULTS

	TXA	Placebo	*P*
★Death or Thrombosis	16.7%	18.1%	0.22
Transfusion	37.9%	54.7%	<0.001
Hemorrhage + reoperation	1.4%	2.8%	<0.001
✖ Seizure	0.7%	0.1%	0.002

CONCLUSION TXA **reduced risk of transfusion & reoperation for hemorrhage.** No increased risk of death or thrombosis. TXA increased risk of seizure

2018

TICH-2[20]

ELIGIBILITY Adults with primary **intracranial hemorrhage** within the last 8 hours

METHODS

n=2325

TXA n=1161 | **Placebo** n=1164

TXA 1g IV over 10 min then: TXA 1g IV over 8 hrs

RESULTS ★ **Functional status at 90 days** did not differ significantly between groups

	TXA	Placebo	*P*
Mortality at 7 days	9%	11%	0.04
Mortality at 90days	22%	21%	0.37

No difference between groups in adverse events

CONCLUSION TXA **did not affect functional status at 90 days.** Suggestion of decreased risk of early death

2019

CRASH-3[16]

ELIGIBILITY **Acute traumatic brain injury (TBI)** within 3 hours of injury

METHODS

n=9202

TXA n=4613 | **Placebo** n=4514

TXA 1g IV over 10 min then: TXA 1g IV over 8 hrs

RESULTS

	TXA	Placebo	RR
★ All head-injury related death (28d)	18.5%	19.8%	0.94
Severe (GCS 3-9)	39.6%	40.1%	0.99
GCS 9-15	5.8%	7.5%	0.78

No difference between groups in adverse events

CONCLUSION **Early TXA (<3h)** reduced risk of head injury related death. TXA appeared safe in TBI.

(see next page)

Select Landmark TXA Randomized Controlled Trials

★ *primary outcome*

2020

HALT-IT [55]

ELIGIBILITY Adult with significant **upper or lower gastrointestinal (GI) bleed**

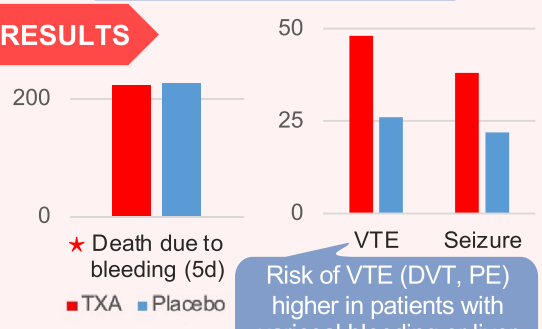
Including: patients with cirrhosis

METHODS

TXA n=5994 | n=12009 | **Placebo** n=6015

TXA 1g IV over 10 min then: TXA 3g IV over 24h

RESULTS



Risk of VTE (DVT, PE) higher in patients with variceal bleeding or liver disease (p=0.035)

CONCLUSION

TXA **did not reduce death** from GI bleeding

- Risk of **VTE** and **seizure** higher in the TXA group

Factors Potentially Increasing VTE in HALT-IT Trial [56]

↑ **Average Age** (58 yrs vs. 35 yrs in CRASH-2 trial)
↑ **Comorbidities** (7% malignancy)

Liver disease (40%): ↓ fibrinolysis in cirrhosis[57] may be associated with ↑VTE[58]

Higher dose *(may also explain increased risk of seizure)*

TXA not recommended for empiric treatment of GI bleeding at this time

a-TREAT [59]

ELIGIBILITY Patients w/ **hematologic malignancy** undergoing chemotherapy or hematopoietic stem cell transplantation with **platelets <30**

METHODS

TXA n=165 | n=327 | **Placebo** n=163

TXA 1g IV or TXA 1.3g PO q8h for platelets <30 until platelets >30

RESULTS

	TXA	Placebo	*P*
★ **Grade 2+ bleeding**	45.4%	48.8	0.74
Central line occlusion	**19.5%**	11.0%	N/A*

No increase in non-catheter thrombotic events

CONCLUSION **TXA had no effect** on the incidence of WHO Grade 2+ bleeding in this population. **Increased line occlusion** in the TXA arm but no other thrombotic events

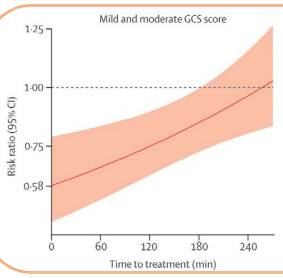
**Awaiting full text publication*

WHO bleeding scale [60]

Grade 0	No bleeding
Grade 1	Petechial bleed
Grade 2	Mild blood loss (clinically significant)
Grade 3	Gross blood loss requires transfusion (severe)
Grade 4	Debilitating blood loss, retinal/cerebral bleed (associated with fatality)

Did you know?

CRASH-2, **CRASH-3** and **WOMAN** trials showed that early tranexamic acid **(<3 hours)** is associated with optimal effect



CRASH-3 [16]

Early TXA (<3h)
+
Mild-moderate head injury
=
Greatest mortality benefit

Controversy #1: TXA and Thrombosis

Given the anti-fibrinolytic effects of TXA, concern exists regarding increased risk of **thromboembolic events**

Non-surgical Patients

Risk of arterial and venous thrombosis in **non-surgical patients** receiving systemic TXA[61]:

- Systematic review of 22 RCTs (including **CRASH-2** and **WOMAN**)

		DVT	PE	MI	Stroke
Number of trials (n)		8 (46630)	6 (43161)	3 (42470)	5 (42815)
Weighted event rates	**TXA**	0.28%	0.52%	0.27%	0.45%
	No TXA	0.29%	0.54%	0.30%	0.41%
RR (95% CI)		0.97 (0.69-1.37)	0.97 (0.75-1.26)	0.88 (0.43-1.84)	1.10 (0.68-1.78)

No increased risk of venous or arterial thrombosis in non-surgical patients receiving systemic TXA

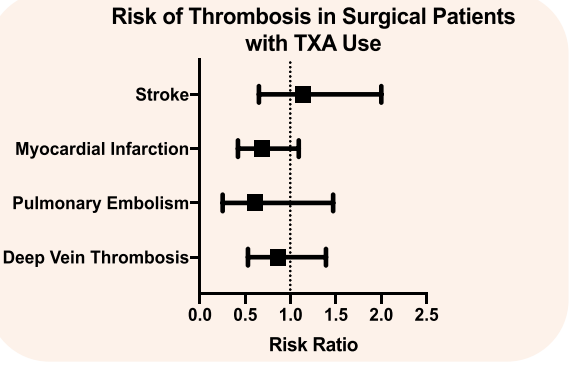
Patients with a known history of thrombosis were excluded from these studies. In the **WOMAN** trial, patients with a known thrombotic event during pregnancy were excluded

Surgical Patients

Studies of **surgical patients** have also not shown a significant increase in thrombotic events for any surgery type while reducing blood loss[62,63,64]

Did you know?

There was no dose response relationship for reducing surgical blood loss with TXA doses above 1g IV[64]



In the absence of patient specific factors (e.g. history of thrombosis or cirrhosis) **evidence suggests there is no reason to avoid TXA in medical or surgical patients for fear of thrombosis**

Controversy #2: TXA and Combined Hormonal Contraception

Can patients taking combined hormonal contraception for heavy menstrual bleeding use TXA?

Blood Drop
Combined hormonal contraception contains both **estrogen** and **progestin**

Caution ⚠
Combined hormonal contraception is listed as contraindication to TXA in the United States[38]

There is a theoretical concern that TXA will further increase VTE risk in patients taking combined hormonal contraception (CHC)[65]

Absolute risk of VTE in patients taking CHC

Nonpregnant, no hormonal contraception: **1-5/10,000 woman yrs**[66]

Nonpregnant + CHC **9-10/10,000 woman yrs**[67]

This means patients taking CHC are **~2x** more likely to develop VTE

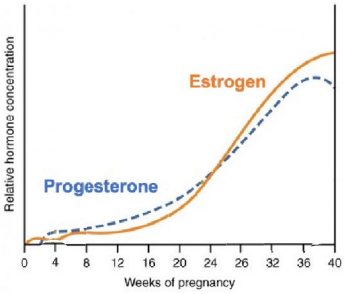
Nonpregnant + CHC **+ TXA**
Unknown

Only one published case reports **CHC + TXA** as a cause of thrombosis of a coronary vessel[68]
→ This could have occurred with CHC alone or perhaps even without CHC…

Evidence that *may* suggest that CHC + TXA is safe:

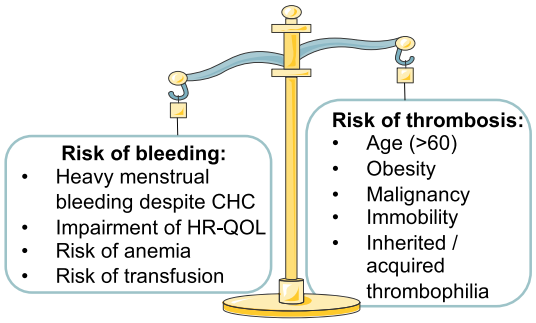
Post-partum VTE risk: **~300/10,000 woman yrs**[67] (due to hormonal effects similar to CHC)

WOMAN Trial[5]
In patients with PPH, there was **no increased risk of VTE with TXA**



Individualized care and shared decision making is required when considering TXA in combination with CHC for patients with heavy menstrual bleeding[65]

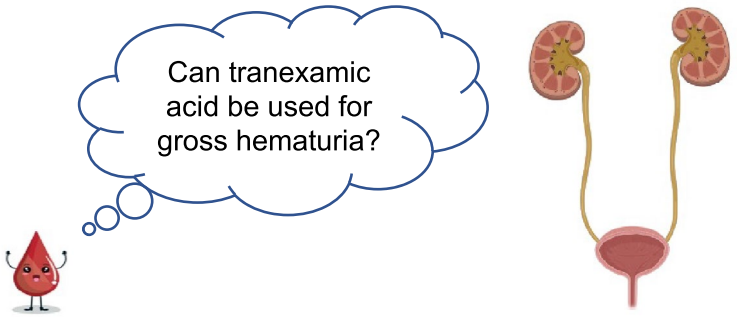
- Counselling on individual risks of VTE
- Weigh **benefits of therapy** against **potential risk of thrombosis**



Did you know?
CHC is **NOT** a risk factor for recurrent VTE while patients are anticoagulated[69]

Studies on the use of CHC + TXA are needed to determine combined efficacy & safety
A scoping review[70] and ISTH registry are ongoing to address this controversy

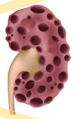
Controversy #3: Tranexamic Acid and Hematuria



Caution

Hematuria caused by diseases of renal parenchyma is listed as contraindication to TXA in Canada[37]

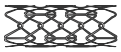
The concern is that TXA may encourage **clot formation in the ureter or renal pelvis** which many lead to **acute kidney injury**[37]



Evidence is **weak** and mostly in patients with **polycystic kidney disease (PCKD)**

One case report[71] in a patient with PCKD presenting with **life-threatening hematuria**

- ✓ Bilateral nephrectomy avoided
- ✗ Clot obstructing ureters requiring **J stents**



Case report[72] and case series[73] in patients with PCKD presenting with hematuria showed **evidence of benefit**

- ✓ Cessation of hematuria
- ✓ No acute kidney injury
- ✓ No thromboembolism

Research In Progress

Systematic review of hematuria and acute renal failure with cyclokapron (TXA)[74] **in progress** to better address this controversy

Larger studies likely needed to evaluate benefit and characterize risk of clot formation and acute kidney injury

TXA ILLUSTRATED REVIEW

Reference citations[1-74]

ACKNOWLEDGMENTS

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RELATIONSHIP DISCLOSURE

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

NR and MS conceived and designed the manuscript. NR, NLJC, and MS wrote the paper.

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