Role of antithrombin in modulating hypercoagulability following trauma

Bryan A Cotton, MD, MPH
The John B Holmes Chair of Clinical Sciences
Department of Surgery and Center for Translational Injury Research
McGovern Medical School at
The University of Texas Health Science Center
Houston, Texas

UTHealth The University of Texas Health Science Center at Houston | McGovern Medical School

Red Duke Trauma Institute
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Disclosures

I have received research funds from and serve on the scientific advisory board for Grifols

Trauma and VTE

- Venous thromboembolism (VTE): 200,000 new cases per year and 1 in 5 sudden deaths, $1.5B in annual healthcare costs
- 50% of all VTEs occur surrounding hospitalization or surgery with incidence between 2-20% in trauma population
- 11% of potentially preventable trauma deaths from massive PE

Measuring thrombin generation as a tool for predicting hemostatic potential and transfusion requirements following trauma

Jessica C. Cardenas, PhD, Elaheh Rahbar, PhD, Matthew J. Pommerening, MD, Lisa A. Baer, MS, Nena Matijevic, PhD, Bryan A. Cotton, MD, John B. Holcomb, MD, *and* Charles E. Wade, PhD, *Houston, Texas*

Thrombin generation profiles as predictors of symptomatic venous thromboembolism after trauma: A prospective cohort study

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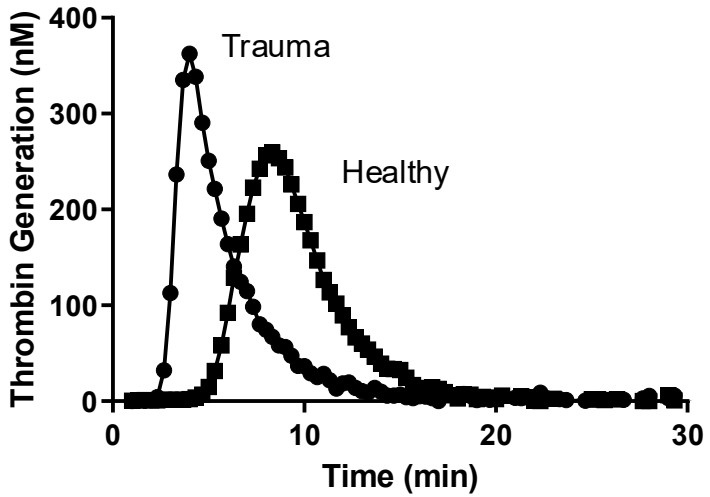

83% of patients have profoundly elevated TG

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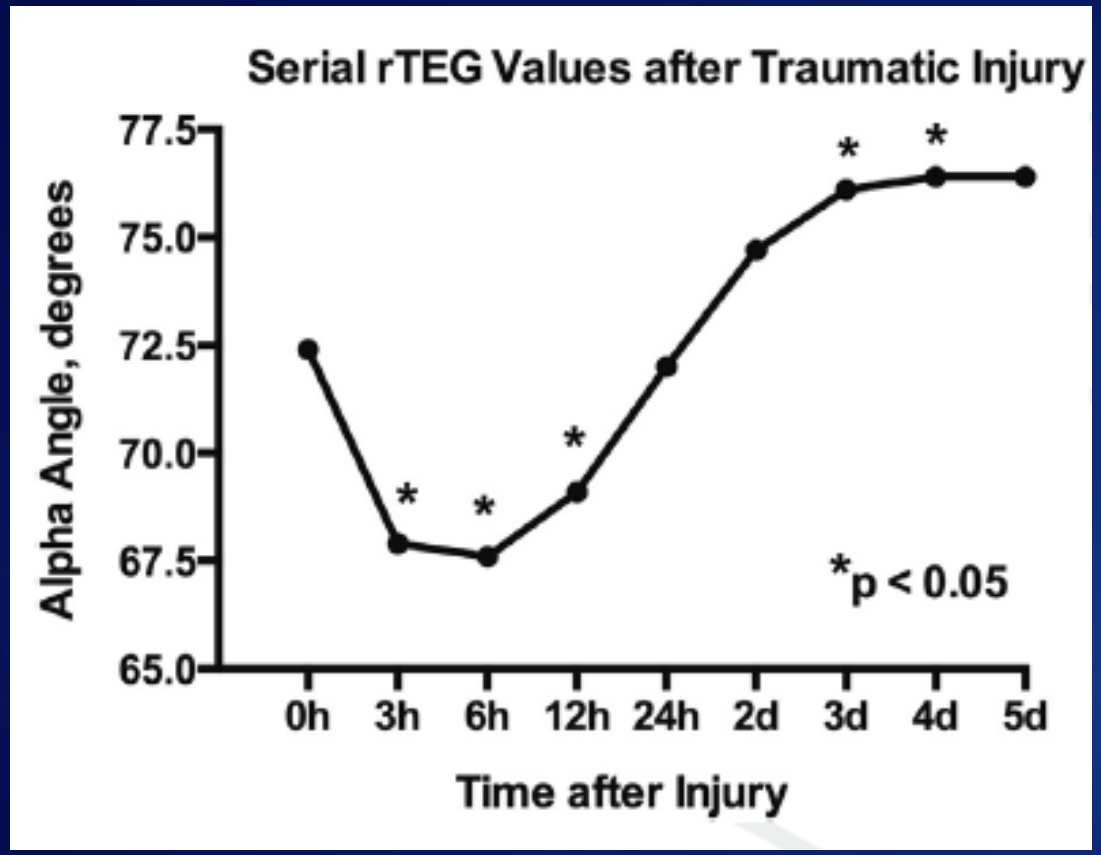
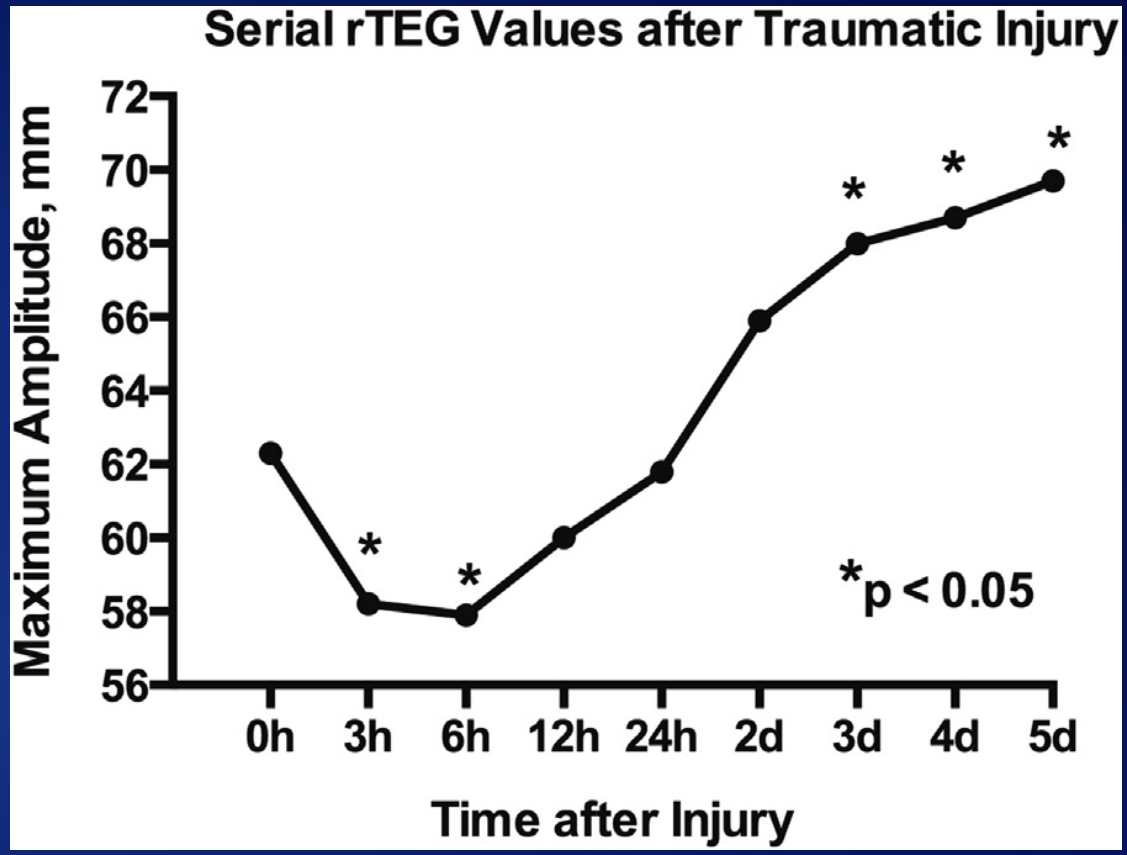
Increase in Hypercoagulability After Trauma

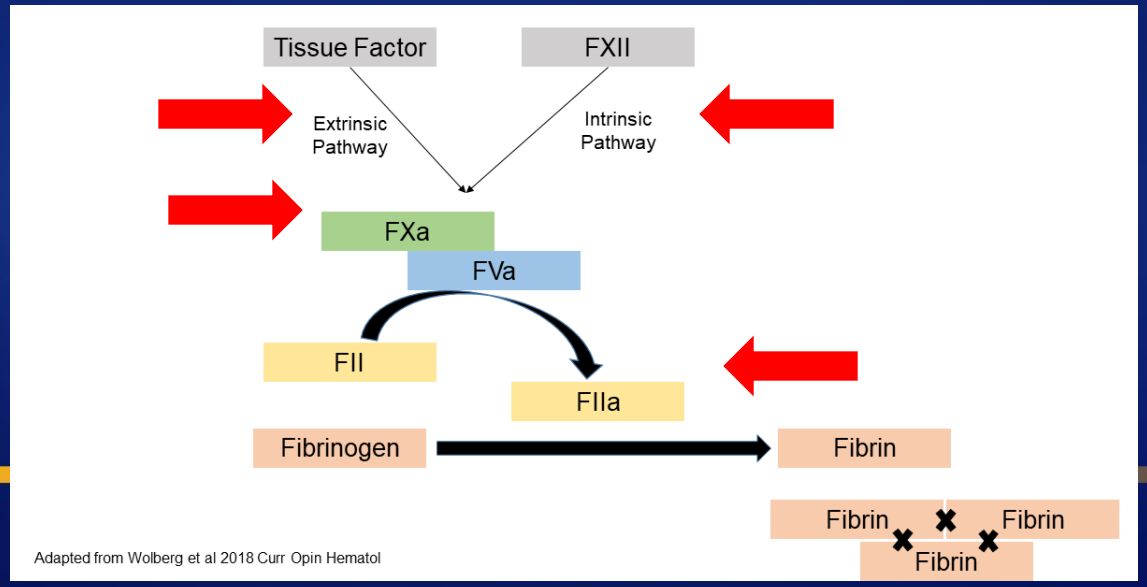




Regulation of TG by AT

- AT = Antithrombin, liver derived, circulates 120 ug/mL, normal range 80-120%

- AT is the primary circulating anticoagulant, working on VIIa, IXa, XIa, Xa, and IIa (thrombin)



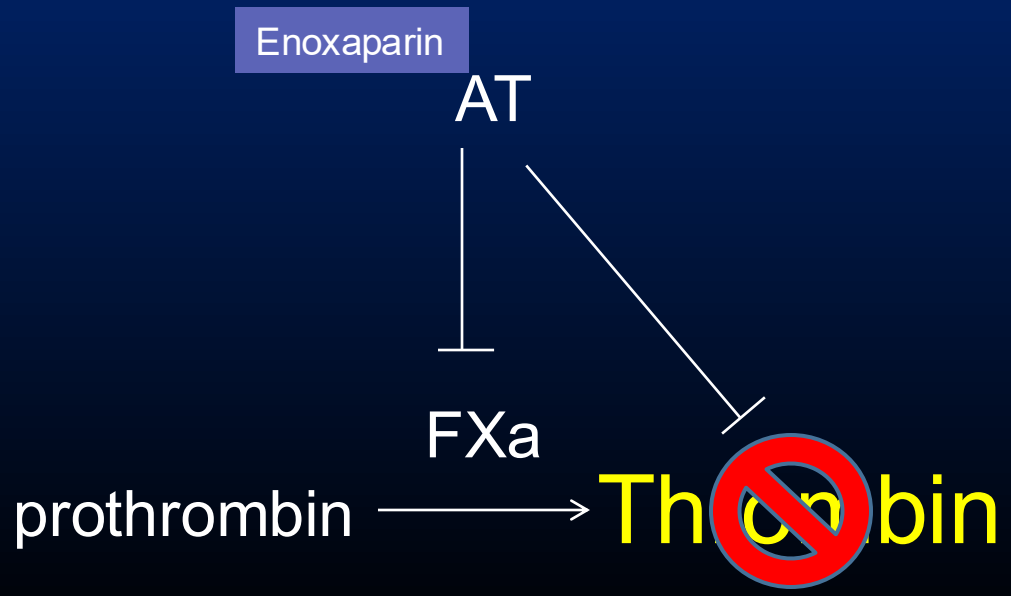
Regulation of TG by AT

AT = Antithrombin

AT is the primary circulating anticoagulant ⊣

FVIIa
FIXa
FXIa
Fxa
Thrombin

AT activity accelerated by heparinoids



Previous work on AT:

SHOCK, Vol. 45, No. 2, pp. 166–173, 2016

PLASMA RESUSCITATION PROMOTES COAGULATION HOMEOSTASIS FOLLOWING SHOCK-INDUCED HYPERCOAGULABILITY

Jessica C. Cardenas,[*†] Andrew P. Cap,[*‡] Michael D. Swartz,[†§] Maria del Pilar Huby,[*†] Lisa A. Baer,[*†] Nena Matijevic,[*†] Bryan A. Cotton,[*†] John B. Holcomb,[*†] and Charles E. Wade[*†]

[*]Department of Surgery; [†]The Center for Translational Injury Research, The University of Texas Health Science Center at Houston, Houston; [‡]U.S. Army Institute of Surgical Research, Fort Sam Houston; and [§]Department of Biostatistics, School of Public Health, The University of Texas Health Science Center at Houston, Houston, Texas

Trauma and HS associated with consumption of AT and AT can be restored through plasma resuscitation, which normalizes TG

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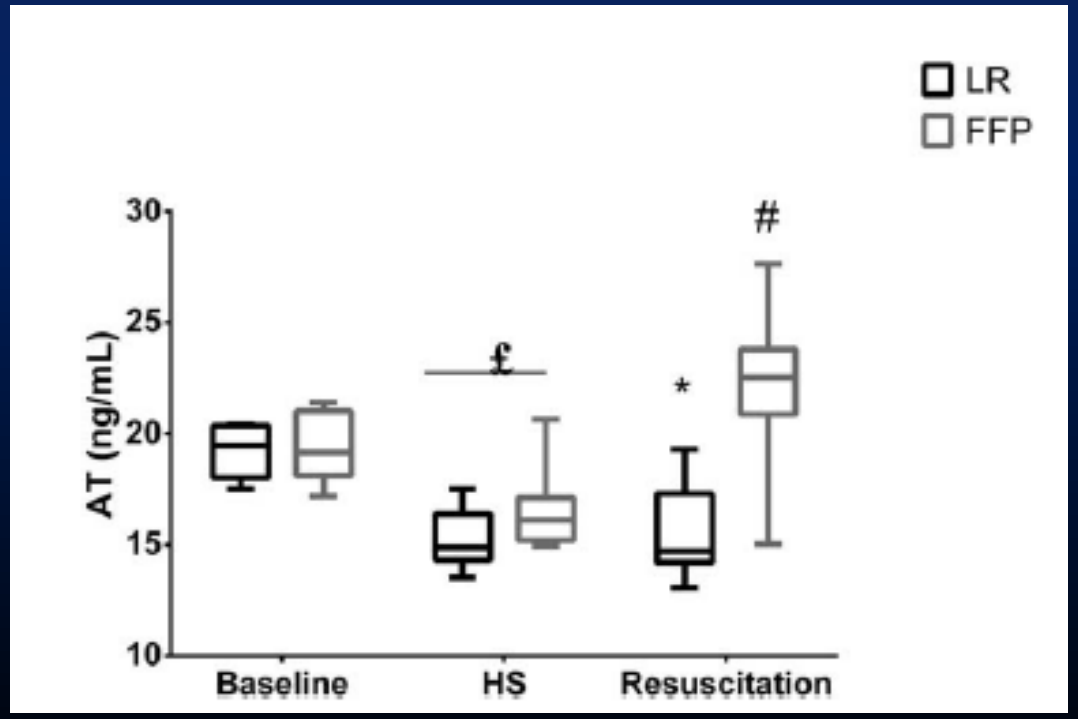

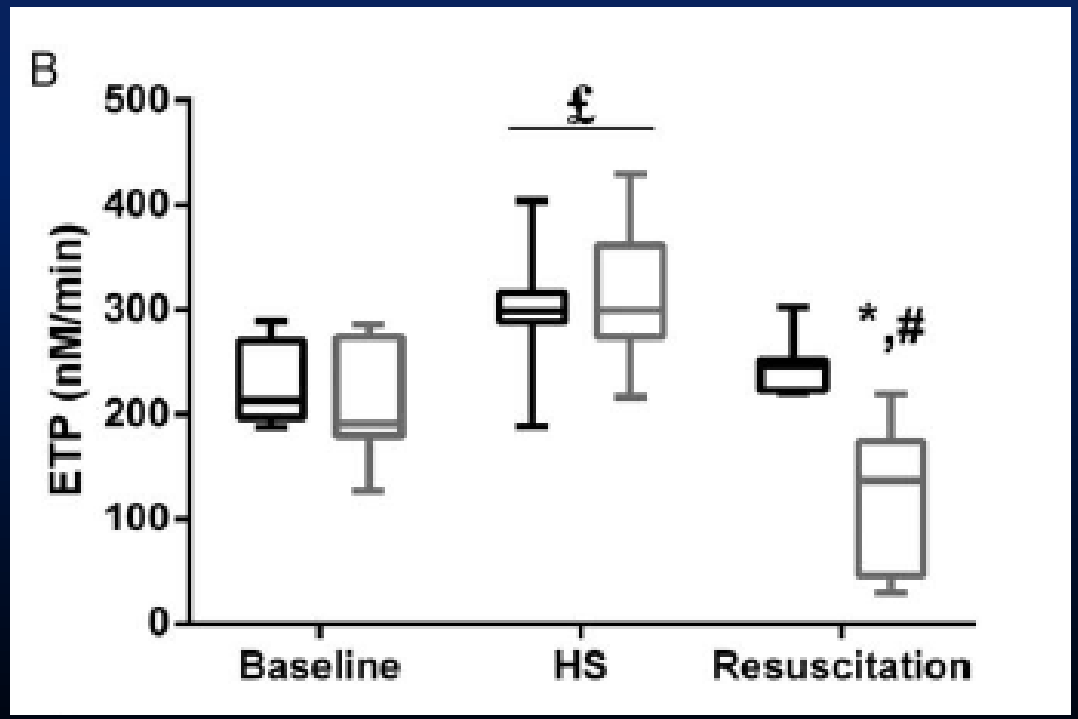

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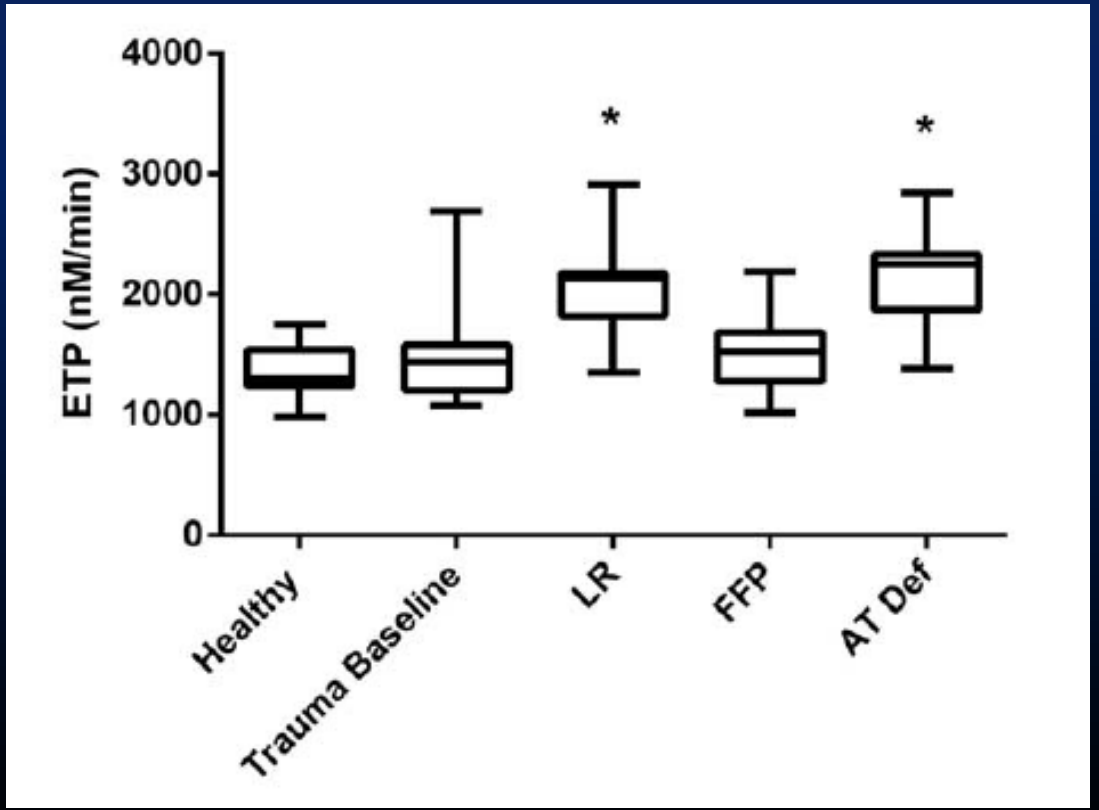

Previous work on AT:

ANTITHROMBIN III CONTRIBUTES TO THE PROTECTIVE EFFECTS OF FRESH FROZEN PLASMA FOLLOWING HEMORRHAGIC SHOCK BY PREVENTING SYNDECAN-1 SHEDDING AND ENDOTHELIAL BARRIER DISRUPTION

Ernesto Lopez,[*†] Zhanglong Peng,[*†] Rosemary A. Kozar,[‡] Yanna Cao,[§] Tien C. Ko,[§] Charles E. Wade,[*†] and Jessica C. Cardenas[*†]

[*]Division of Acute Care Surgery, Department of Surgery, The University of Texas Health Science Center and the McGovern School of Medicine, Houston, Texas; [†]Center for Translational Injury Research, Houston, Texas; [‡]Shock Trauma Center, University of Maryland School of Medicine, Baltimore, Maryland; and [§]Division of General Surgery, Department of Surgery, The University of Texas Health Science Center and the McGovern School of Medicine, Houston, Texas

If you resuscitate with plasma that's depleted of AT, you fail to normalize TG and worsen endothelial activation

ANTITHROMBIN III CONTRIBUTES TO THE PROTECTIVE EFFECTS OF FRESH FROZEN PLASMA FOLLOWING HEMORRHAGIC SHOCK BY PREVENTING SYNDECAN-1 SHEDDING AND ENDOTHELIAL BARRIER DISRUPTION

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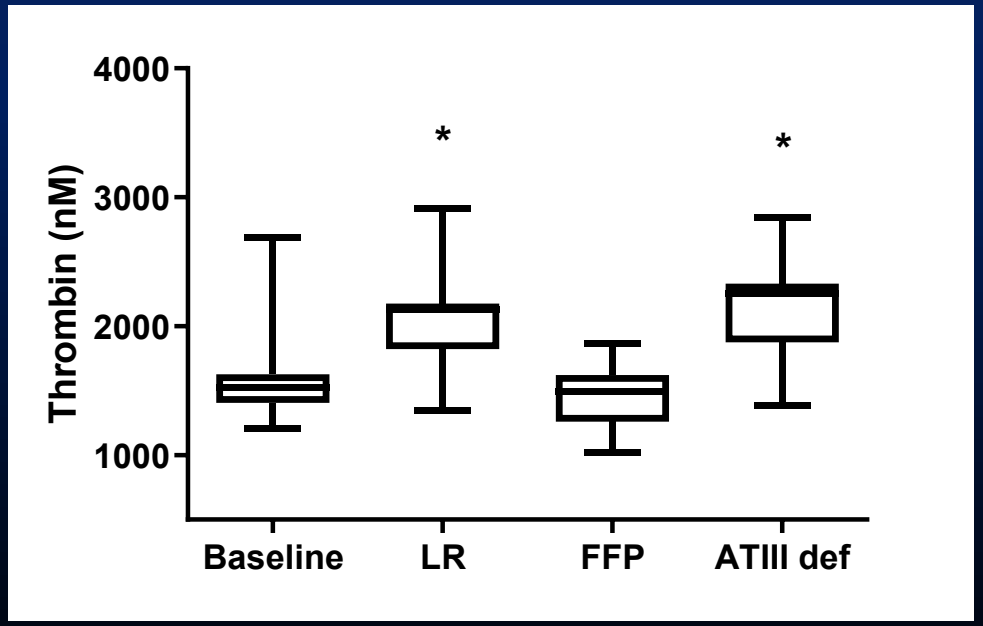
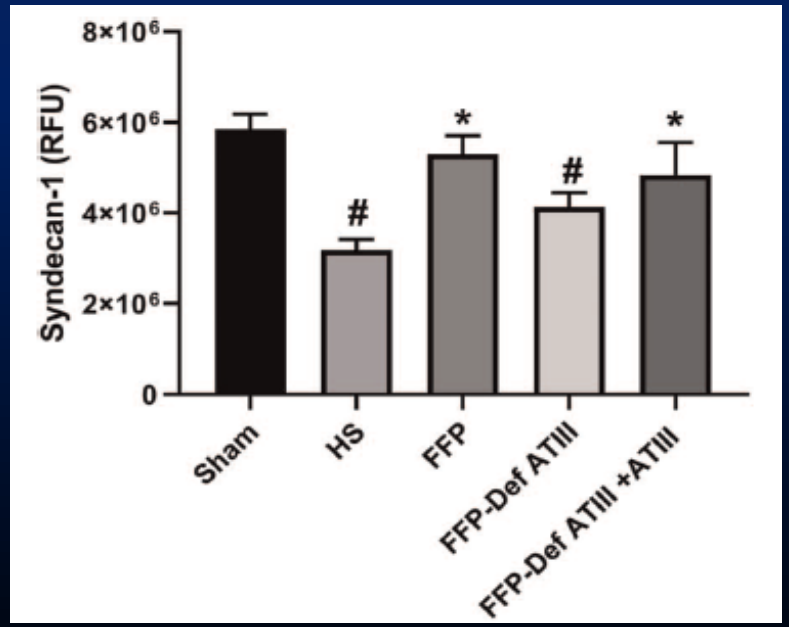
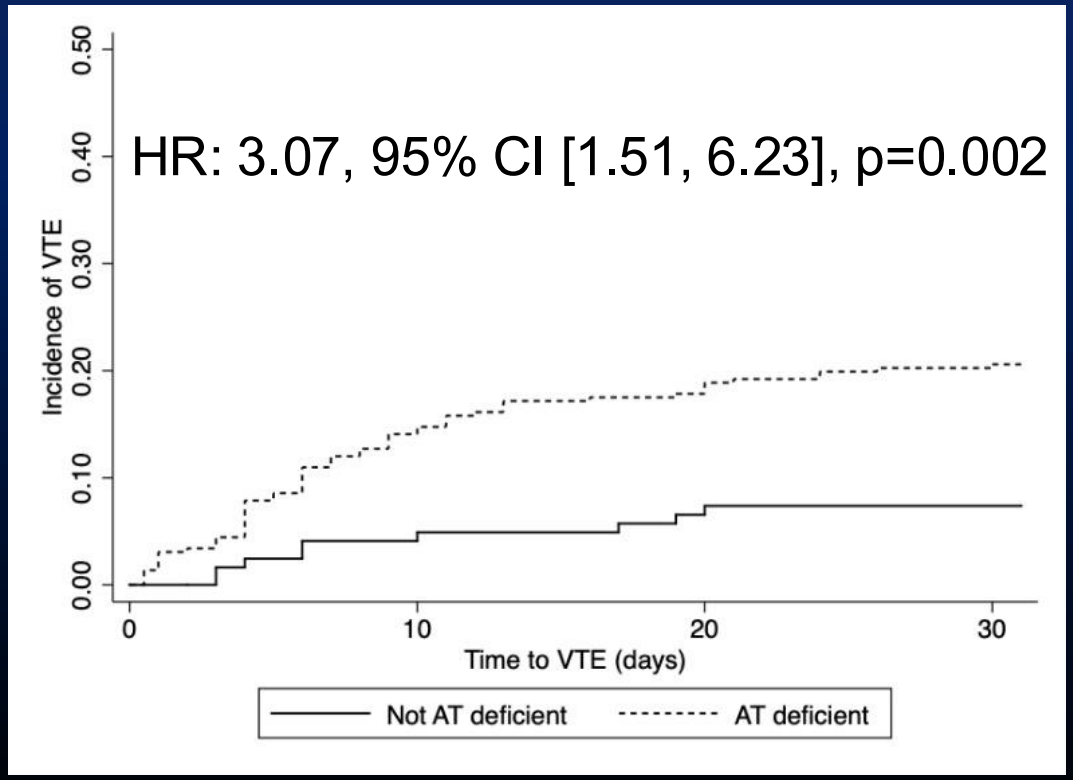
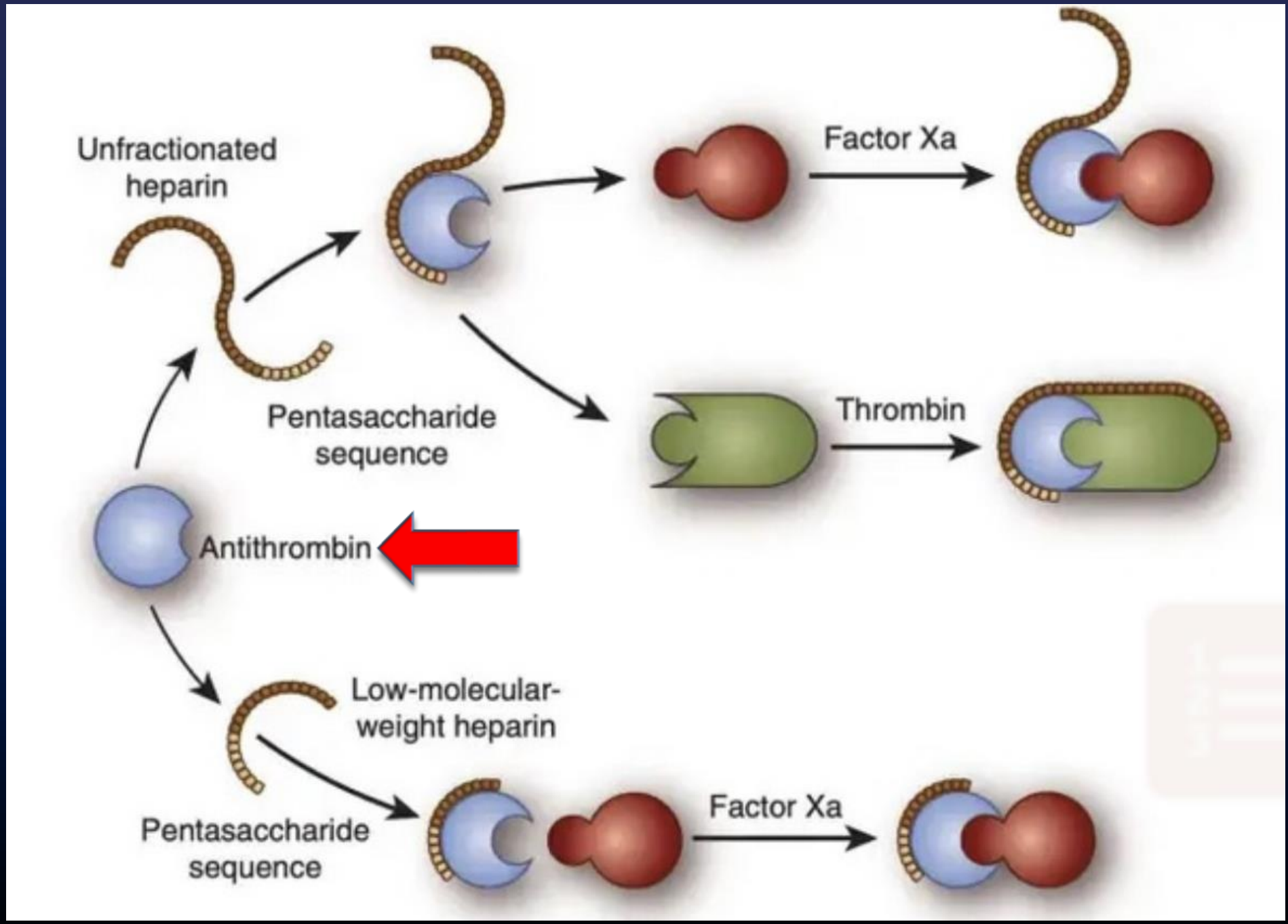




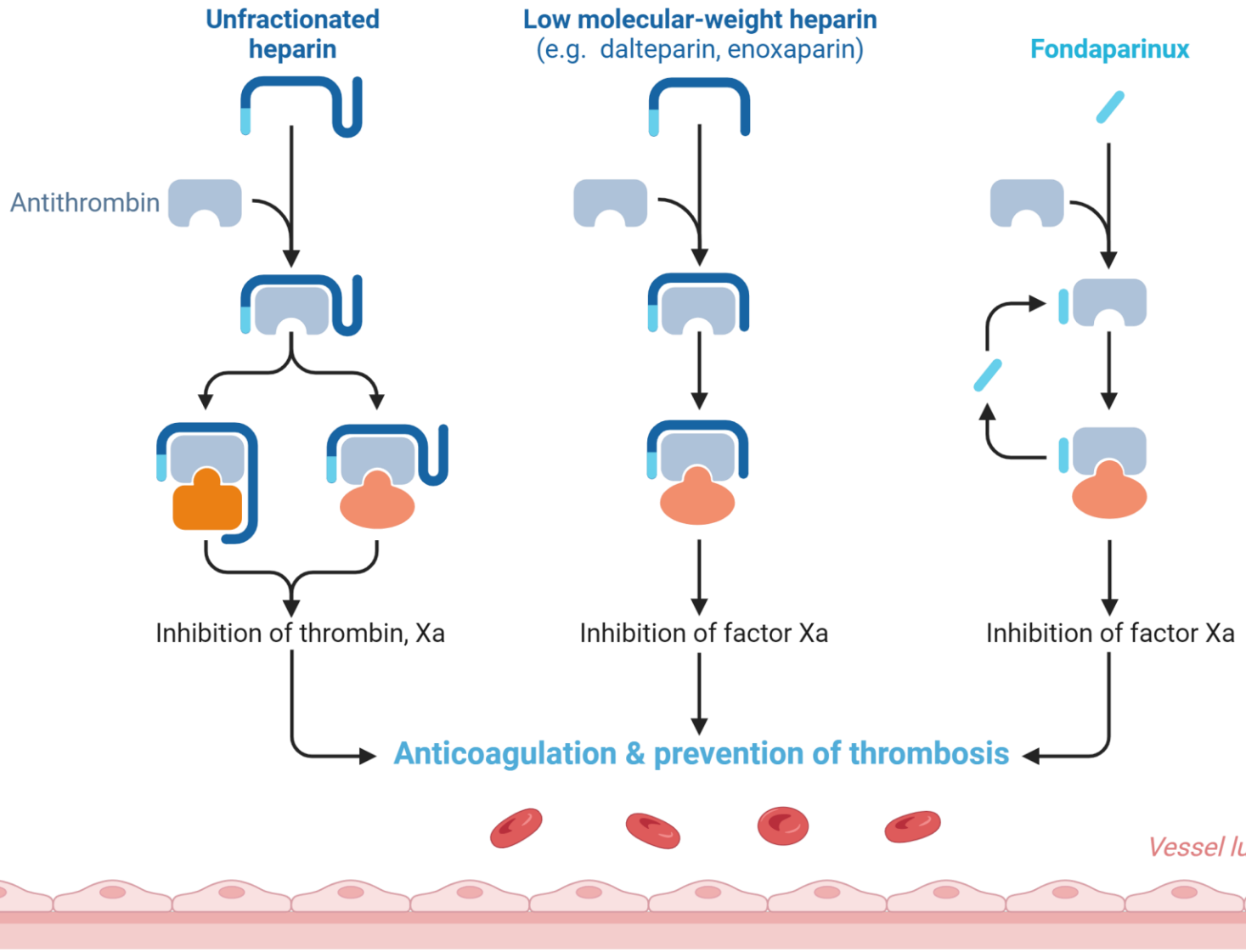
Previous work on AT:

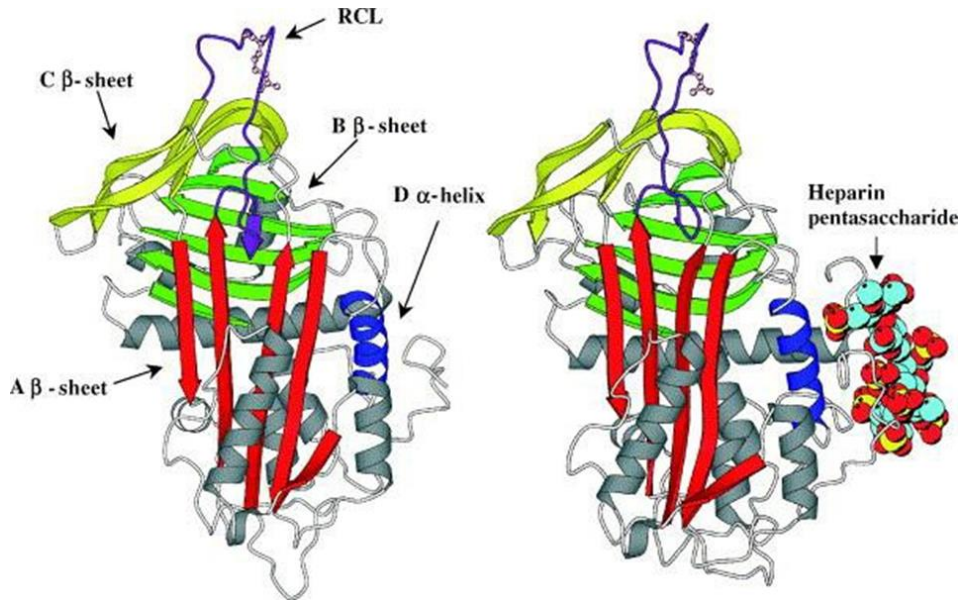
3. AT deficiency in T/HS patients is associated with a 3-fold increased risk of VTE after controlling for known risk factors
   - Thrombosis Research 2020




Unfractionated heparin
Factor Xa
Pentasaccharide sequence
Thrombin
Antithrombin
Low-molecular-weight heparin
Pentasaccharide sequence
Factor Xa

Mechanism of Action





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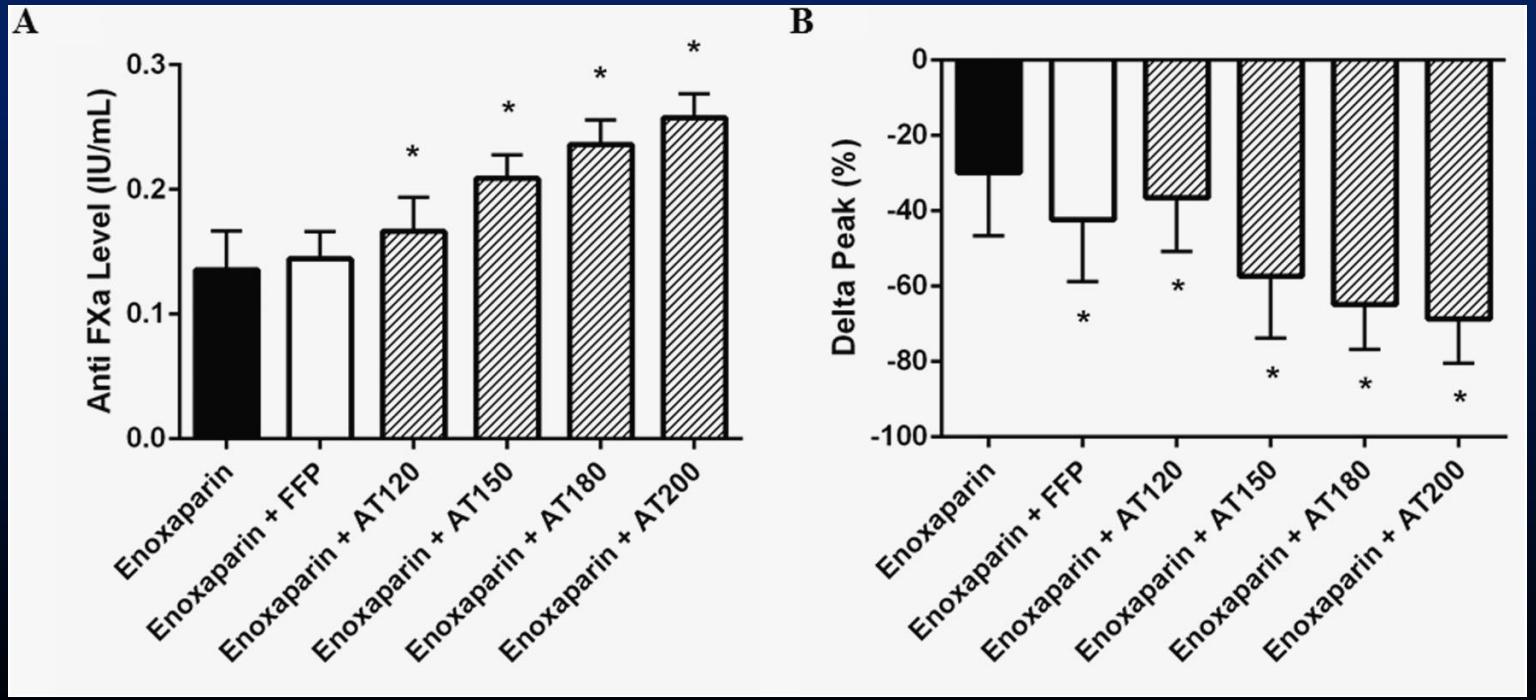
Full Length Article

Supplementation with antithrombin III *ex vivo* optimizes enoxaparin responses in critically injured patients

Jessica C. Cardenas[a,b,*], Yao-Wei Wang[b], Jay V. Karri[b], Seenya Vincent[b], Andrew P. Cap[a,c], Bryan A. Cotton[a,b], Charles E. Wade[a,b]



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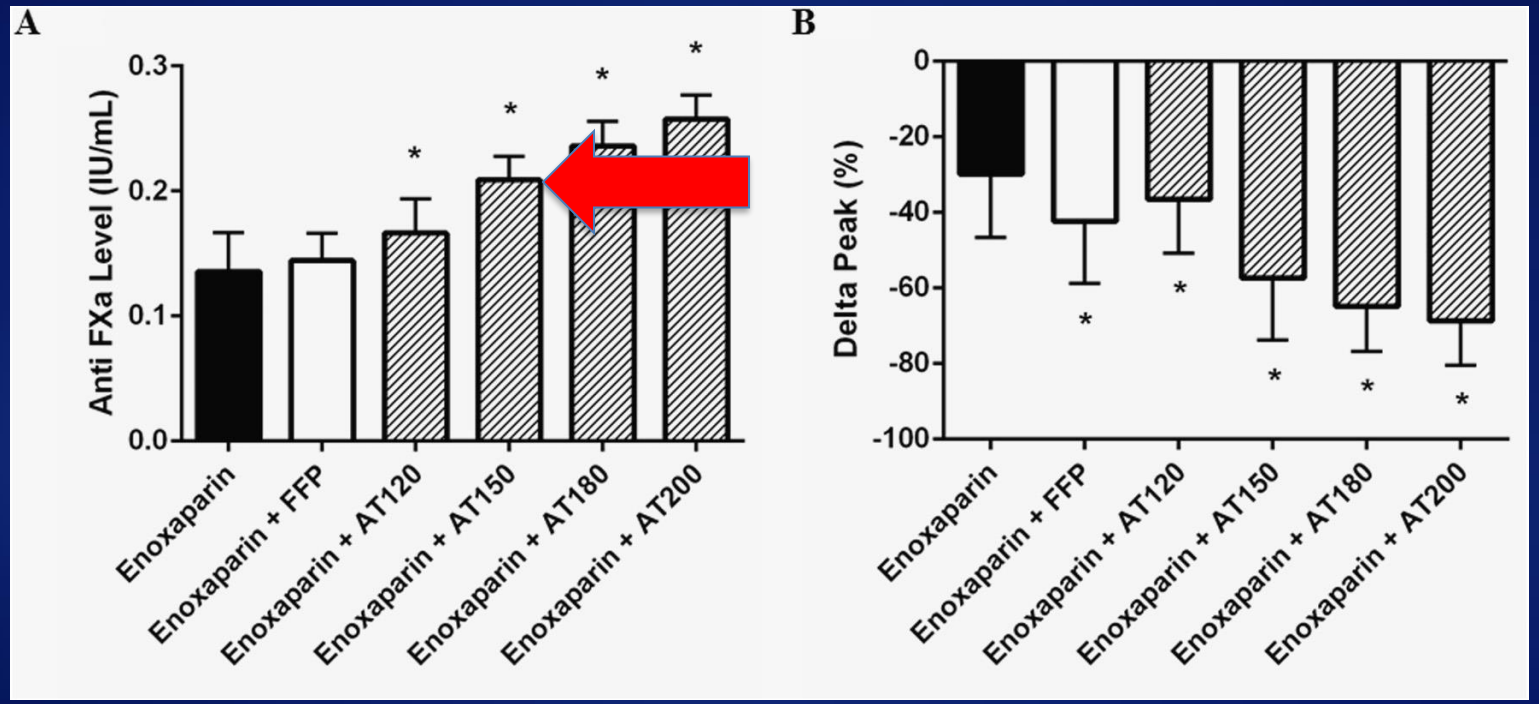


JAMA Surgery | Original Investigation

Association of Changes in Antithrombin Activity Over Time With Responsiveness to Enoxaparin Prophylaxis and Risk of Trauma-Related Venous Thromboembolism

Laura E. Vincent, MS, RN; Michael M. Talanker, BS; Dakota D. Butler, BS; Xu Zhang, PhD; Jeanette M. Podbielski, RN; Yao-Wei W. Wang, MD; Amber Chen-Goodspeed, BA; Selina L. Hernandez Gonzalez, BS; Erin E. Fox, PhD; Bryan A. Cotton, MD; Charles E. Wade, PhD; Jessica C. Cardenas, PhD

DESIGN, SETTING, AND PARTICIPANTS This single-center, prospective cohort study was performed at a level 1 trauma center between January 7, 2019, and February 28, 2020. Adult trauma patients admitted to the trauma service at high risk for VTE, based on injury pattern and severity, were screened and enrolled. Patients who were older than 70 years, were pregnant, had a known immunologic or coagulation disorder, or were receiving prehospital anticoagulants were excluded.

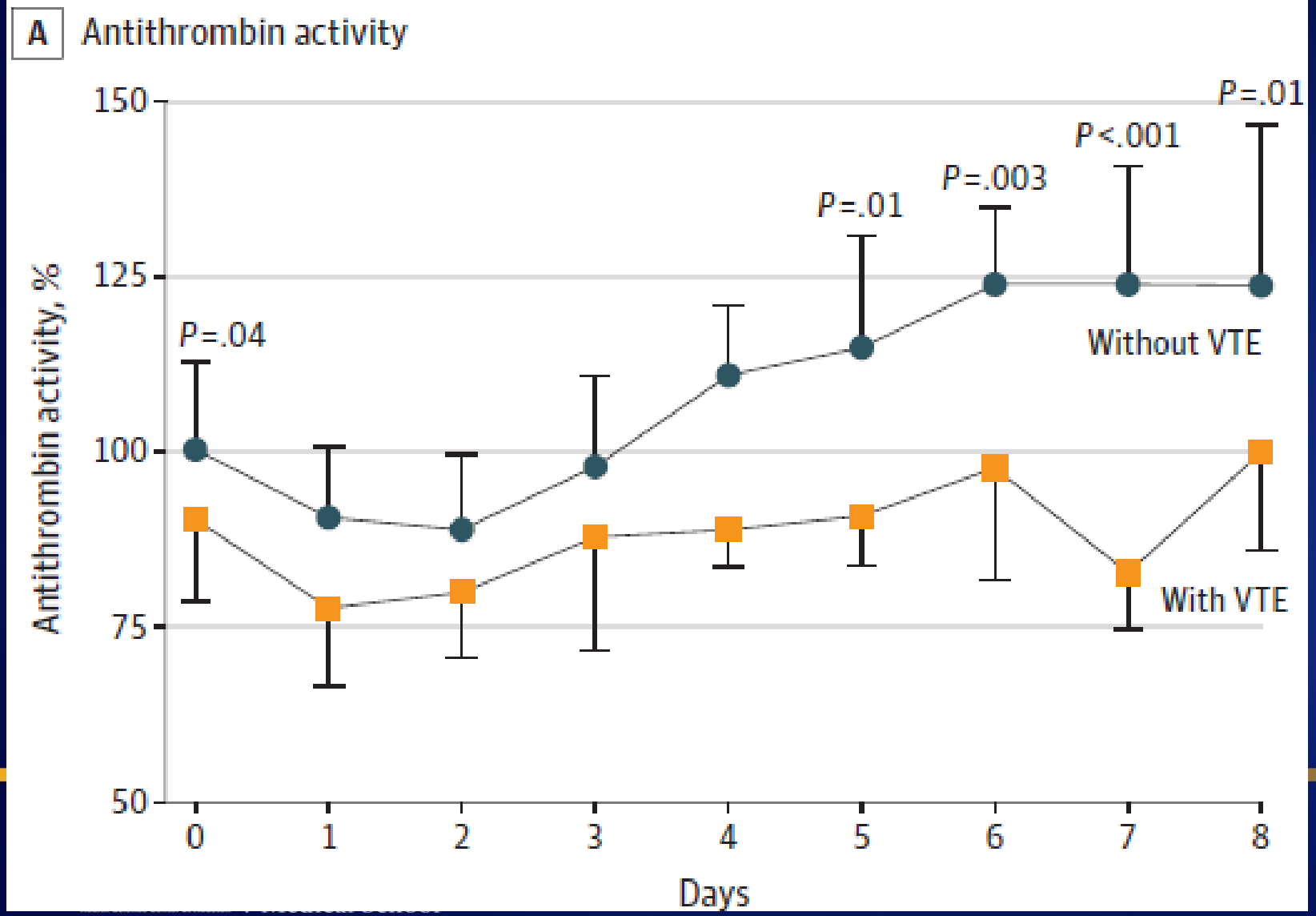
BLUF

All Responder – anti Fxa ≥ 0.2 for every dose after 3 doses of enoxaparin
Temporary Responder – anti Fxa ≥ 0.2 for at least 1 once after 3 doses
Never Responder – never achieved an anti Fxa ≥ 0.2 at any time

N=110	Incidence
All Responder	16.4%
Temporary Responder	60.0%
Never Responder	23.6%

	Incidence of VTE
All Responder	5.6%
Temporary Responder	6.1%
Never Responder	30.8%

Figure 1. Antithrombin Activity Levels Over Time After Severe Trauma



Lower ATIII levels during initial and later hospital days of hospitalization

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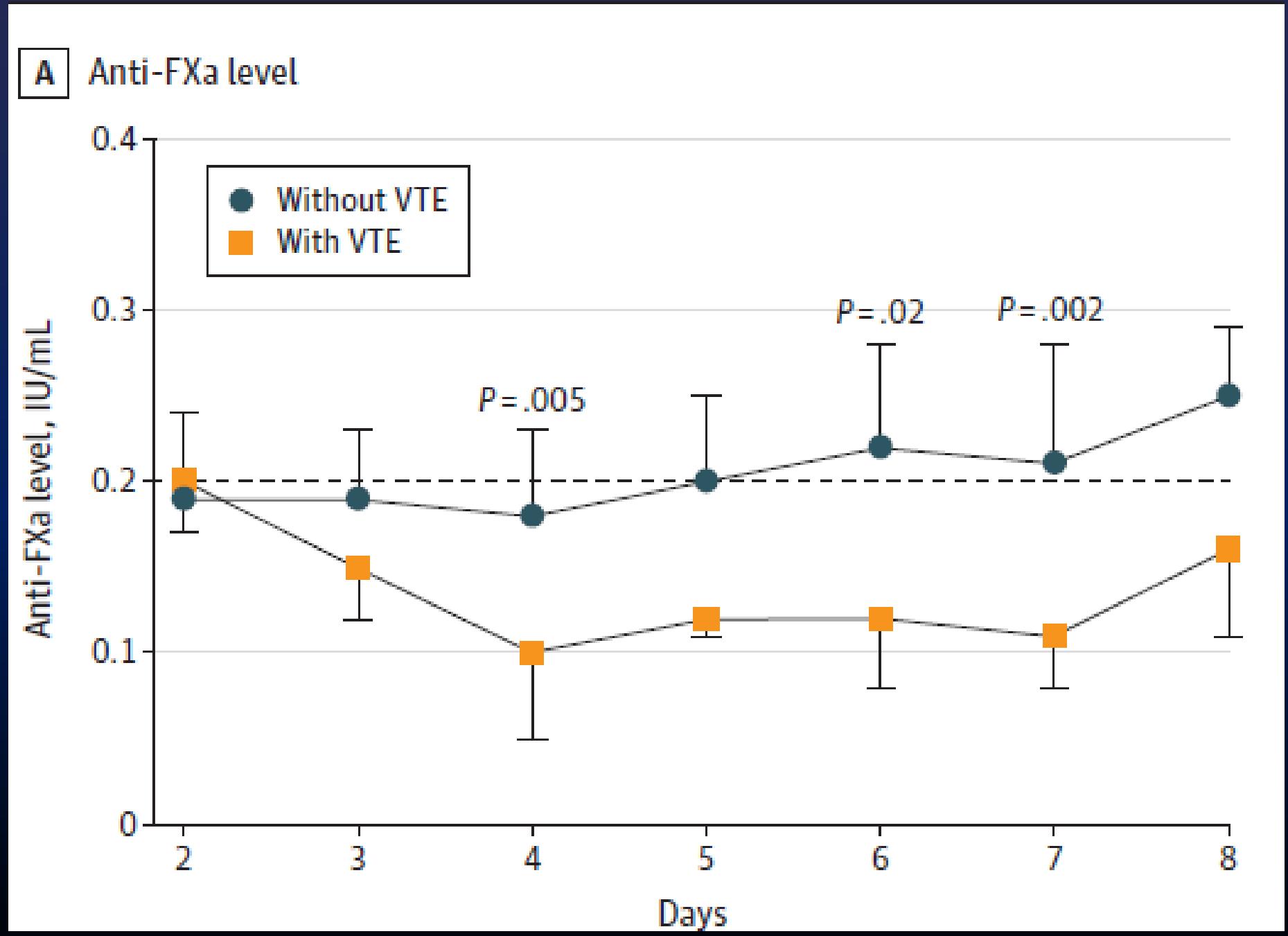
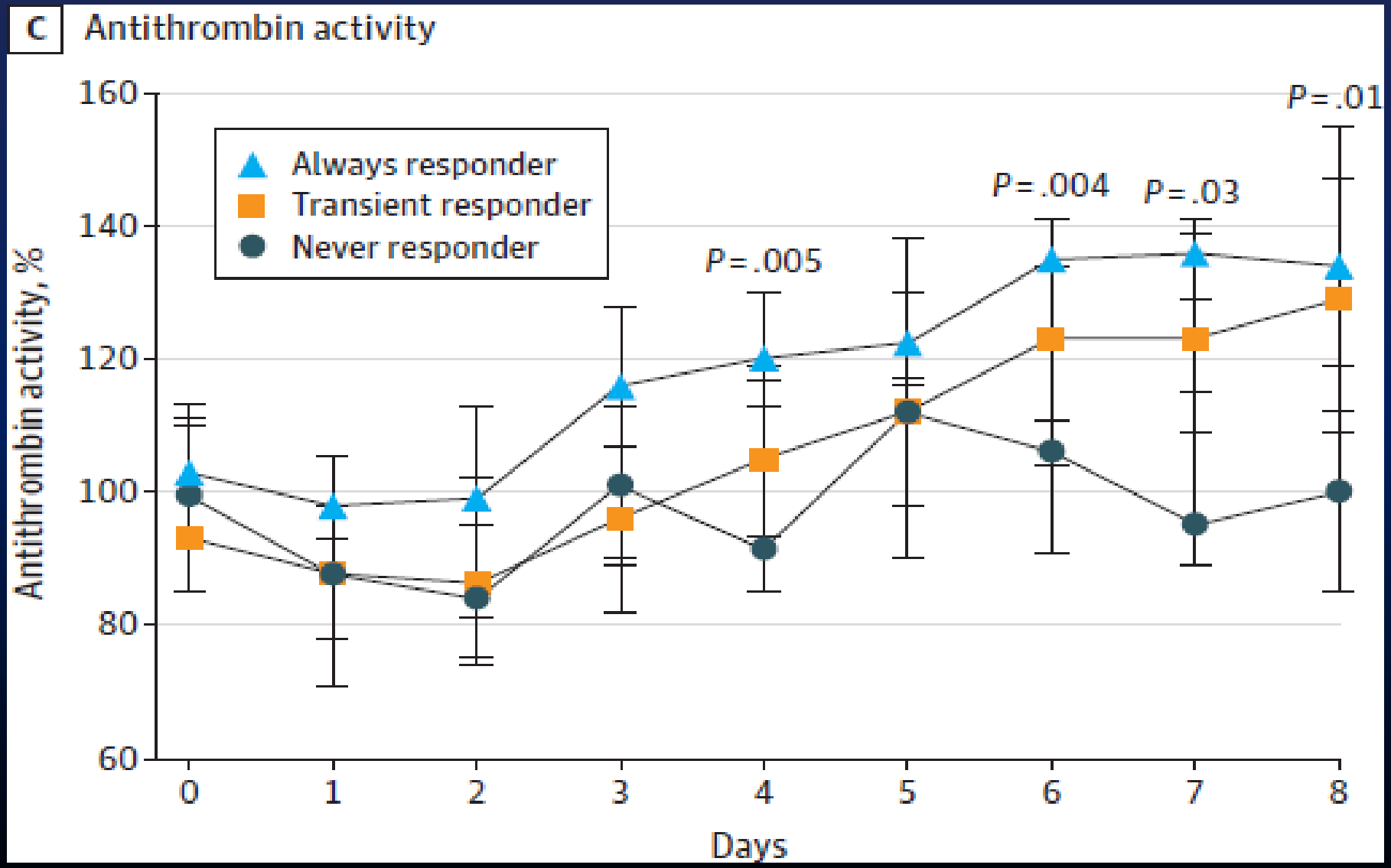
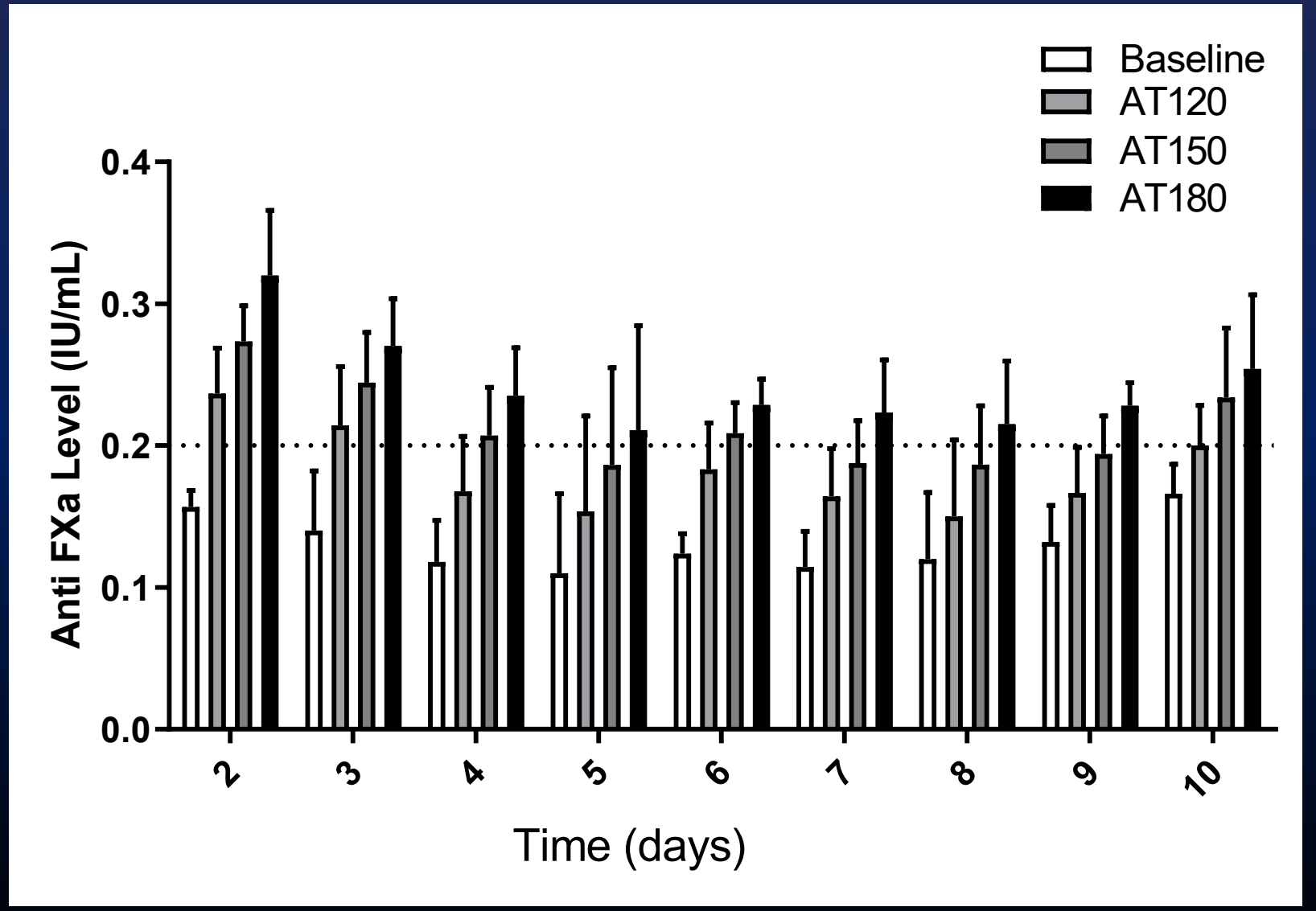

A
Anti-FXa level
Without VTE
With VTE
P = .005
P = .02
P = .002
Anti-FXa level, IU/mL
0.4
0.3
0.2
0.1
0
2
3
4
5
6
7
8
Days

Findings


C
Antithrombin activity
160
140
120
100
80
60
Antithrombin activity, %
Always responder
Transient responder
Never responder
P = .005
P = .004
P = .03
P = .01
0
1
2
3
4
5
6
7
8
Days

Findings


Baseline
AT120
AT150
AT180
Anti FXa Level (IU/mL)
0.4
0.3
0.2
0.1
0.0
2
3
4
5
6
7
8
9
10
Time (days)

TRAIT Trial:

Antithrombin to Improve Thromboprophylaxis and Reduce the Incidence of Trauma-Related Venous Thromboembolism

- $4.1 million dollar multicenter (UTH-CU-VANDY-MIAMI), randomized, double-blind interventional clinical trial to evaluate efficacy of early AT III administration in trauma patients at high risk for VTE.

- 314 subjects will be randomized to receive a bolus intravenous AT III to achieve antithrombin (AT) activity levels at 150% or placebo (saline).

- Incidence of VTE and prophylactic anti-FXa will be assessed as co-primary endpoints.

What we are looking to treat?

- Looking to evaluate the efficacy of early AT III administration in trauma patients at high risk for VTE.

- Hypothesis: Patients randomized to AT III infusion will have reduced incidence of VTE and accelerated time to achieve a therapeutic anti-FXa, and no adverse bleeding outcome.

Patient population

Inclusion Criteria

1. ≥ 18 years of age
2. Polytraumatic injuries OR pelvic/long bone fractures
3. Admission to STICU

Exclusion Criteria

1. Prisoners (defined as those directly admitted from correctional facility)
2. Known or suspected pregnancy
3. ≥20% total body surface area (TBSA) burn or Nonsurvivable head injuries
4. Known hematologic or immunologic disorders
5. Known prehospital anticoagulant use
6. Patients initially placed on unfractionated heparin for thromboprophylaxis
7. Known allergy to Antithrombin or it's components
8. Enrollment in another interventional study

Treatment

- Patients enrolled into the study will either be randomized to
  - **Interventional arm** (which consists of)
    - Thrombate infusion prior to 3rd dose of Enoxaparin to achieve antithrombin activity of 150%
  - **Placebo arm** (which consists of)
    - Normal saline infusion prior to 3rd dose of Enoxaparin

Study Product Preparation

- Thrombate dose is based on weight:

  Dose (in units) = (150-90) x (weight in kg)/1.4 = units

Weight (kg)	60	70	80	90	100
AT dose (IU)	2571	3000	3428	3857	4285
Thrombate vials	5	6	7	8	9

- Placebo (normal saline) in same volume according to subject's weight

Primary Outcomes

- Incidence of VTE in 14 days
- Incidence of anti-FXa of ≥0.2 IU/mL up to 14 days post hospital admission

Secondary Outcomes

- Time to achieve anti-FXa of ≥0.2 IU/mL up to 14 days post hospital admission
- Number of enoxaparin dose escalations up to hospital discharge or 14 days (whichever occurs first)
- Incidence of other thrombotic complications (arterial thrombosis, myocardial infarction, stroke) up to hospital discharge or 30 days (whichever occurs first)
- Incidence of bleeding events (interoperative bleeding, abdominal bleeding) up to hospital discharge or 30 days (whichever occurs first)
- Lengths of stay
- In-hospital mortality

Summary

- Thrombin generation is a risk factor for VTE and limiting thrombin generation is the tenet of thromboprophylaxis
- AT governs both endogenous thrombin generation and inhibition of thrombin generation by enoxaparin
- ATdeficiency is common and a risk factor for VTE and poor responsiveness to enoxaparin
- *Ex vivo* AT supplementation improves responsiveness to enoxaparin
- Whether this translates into reduction in VTE is still under investigation