

#FSHP2018

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A New Era Of Bleeding: Navigating Strategies To Achieve Control And Resuscitation

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Disclosure

I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation

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Objectives

- Review current anticoagulant reversal options
- Evaluate the place in therapy for andexanet alfa
- Describe the use of thromboelastography (TEG) to aid in selection of pharmacologic reversal agents
- Summarize the risks associated with massive transfusion
- Discuss the potential of oxygen carriers as a therapeutic alternative for life threatening anemia

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Oral Anticoagulation

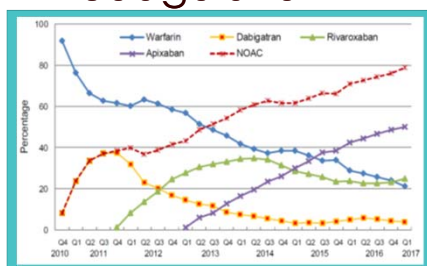
- National trends significantly increased
 - More frequent utilization & longer durations
 - 2.05 million to 2.83 million office visits quarterly
- Steady increase in oral anticoagulation (OAC) presenting to the ED
 - Rates of admissions on OAC have doubled
- Shift towards direct oral anticoagulants (DOAC)

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Oral Anticoagulation



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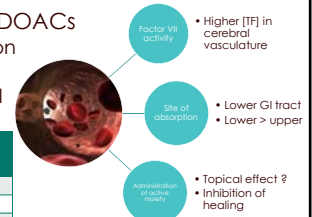
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Oral Anticoagulation Bleeding

- Greater safety margin with DOACs
 - Directed mechanism of action
 - Lower incidence of ICH
 - Higher rate of gastrointestinal bleeding

	Intracranial Hemorrhage (%/yr)	Gastrointestinal Bleed (%/yr)
Dabigatran	0.3	1.51
Rivaroxaban	0.5	2
Apixaban	0.3	0.76
Warfarin	0.8	1.02



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Bleeding Outcomes

DOAC

Less blood products
Shorter ICU LOS
Lower risk of severe bleeding
Less immediate elaborate interventions
Lower hospital mortality

Warfarin

Reversal available
Higher rate of ICH
More blood product utilization
Greater in-hospital mortality

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Oral Anticoagulation

- Complicates bleeding populations
- Standard resuscitation approaches
- Requirement of reversal agents
- 1940s – 2008 VKAs only available oral agent
- Complex pharmacokinetics/pharmacodynamics
- Reliable reversal

Class	1930s	1940s	1980s	1990s	2000s	2008
Target	ATII + Xa + IIa (1:1 ratio)	II, VII, IX, X (Protein, C, S)	ATII + Xa + IIa (Xa + IIa)	Thrombin	ATII + Xa	Oral direct factor Xa inhibitors
Route	Parenteral (Injectable)	Oral	Parenteral (Injectable)	Parenteral (Injectable)	Parenteral (Injectable)	Oral

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Factor products

- Fresh frozen plasma (FFP)
- Prothrombin complex concentrate (PCC)
- Recombinant factor VII (rFVIIa)
- Factor eight inhibitor bypassing agent (FEIBA)

Inhibitors of fibrinolysis

- Tranexamic acid (TXA)
- ϵ -aminocaproic acid

Direct reversal

- Protamine
- Idarucizumab
- Andexanet alfa
- Ciraparantag

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VKA reversal

- Vitamin K supplementation
- Rapid and prolonged reversal

FFP

Novel factor products

- PCC
- rFVIIa
- FEIBA

- 3 vs. 4 factor
- Fixed dose

Reversal approaches have trended towards a unified approach...

Variance in strategies

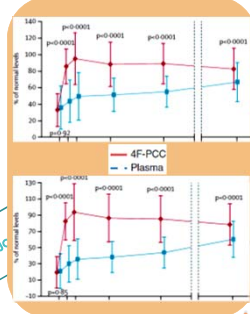
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VKA reversal

- Studies supporting PCC in VKA associated bleeding
 - 3 factor vs. 4 factor
 - Fixed vs. variable dose
- Products containing adequate II & X
 - rFVIIa failed to restore coagulation
 - FEIBA & PCC similar efficacy



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DOAC reversal

- Introduction of DOACs preceded reversal options
 - Factor product supported by animal models
- 3 retrospective clinical studies

Schulman et al. Acute bleeding

- 25 IU/kg 4-factor PCC
- Rivaroxaban or apixaban
- 16.9 hrs from previous dose
- Good hemostasis 65%
- Thromboembolism 8%
- Death 14%

Piran et al. Surgery/invasive procedures

- 26 IU/kg 4-factor PCC
- Rivaroxaban or apixaban
- Good hemostasis 85%
- No thromboembolic events

Majeed et al. Acute bleeding

- 26.7 IU/kg 4-factor PCC
- Rivaroxaban or apixaban
- Effective 69.1%
- Thromboembolism 5%
- Death 32%

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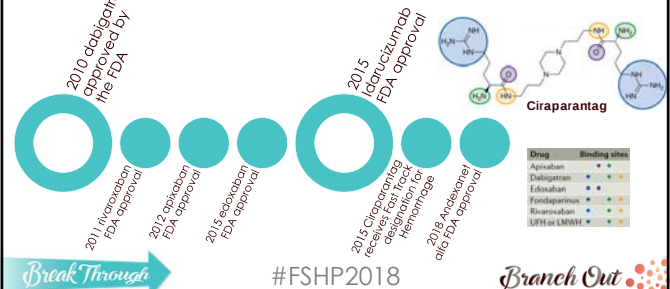
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DOAC reversal



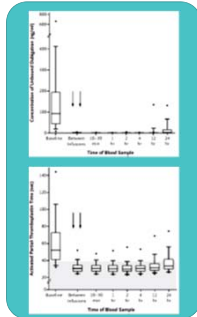
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REVERSE-AD

- 2 arm prospective trial (n=503)
 - Actively bleeding
 - Emergency surgery
- 100% reversal within 4 hrs
 - Time to bleeding cessation 2.5 hrs
 - Time to surgery 1.6 hours
- Median pre-dose 110 ng/mL
 - Post dose < 20 ng/mL
 - 23% rebound after 12 hours
- 4.8% thrombosis at 30 days



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Andexanet Alfa

- Factor X decoy via alanine substitution at 419
 - Universal Xa inhibitor reversal
 - Dose dependent
 - Prothrombotic? → tissue factor pathway inhibitor
- Infusion duration chosen based on coagulation
 - Rebound effect 2 hrs post infusion
- May 3, 2018 FDA approved

Apixaban

400 mg bolus
4 mg/min for 120 min
Total 880 mg

Rivaroxaban or edoxaban

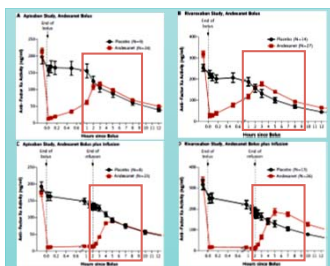
800 mg bolus
8 mg/min for 120 min
Total 1,760 mg

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ANNEXA Trials



Apixaban 5mg BID for 3 days
Rivaroxaban 20 mg daily for 4 days

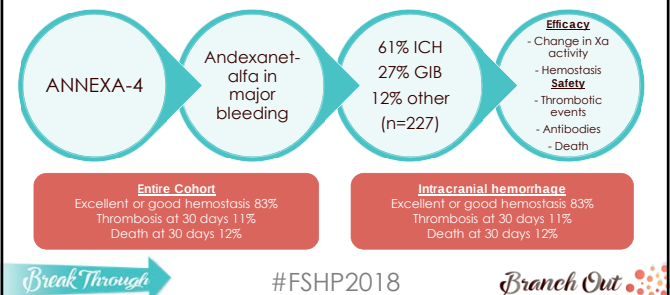
Part 1 bolus only
Part 2 bolus + infusion

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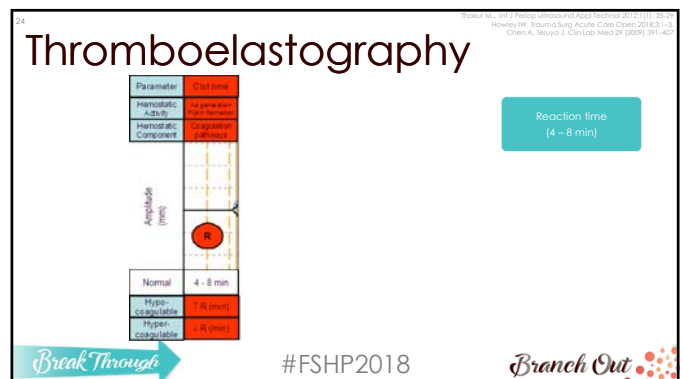
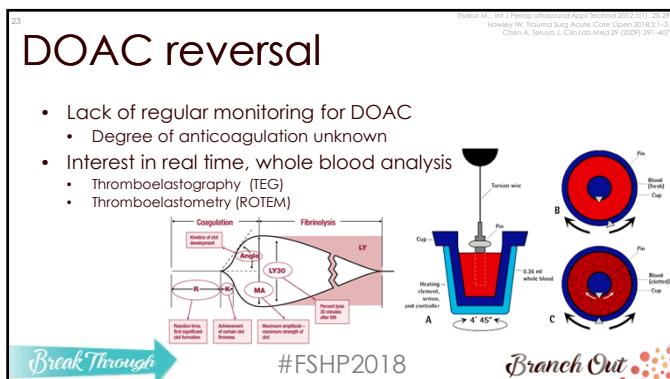
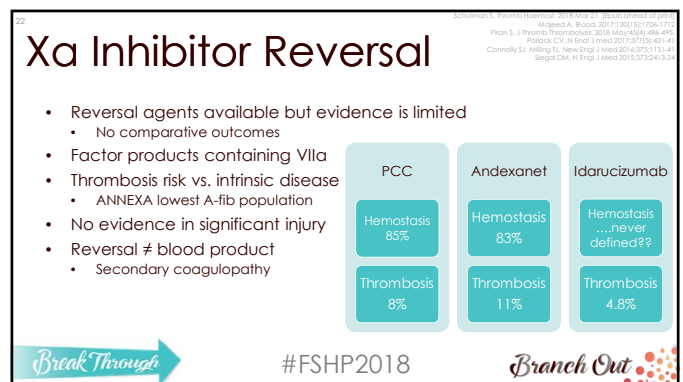
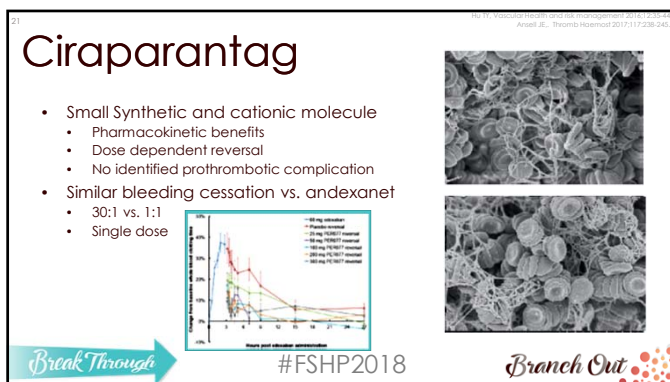
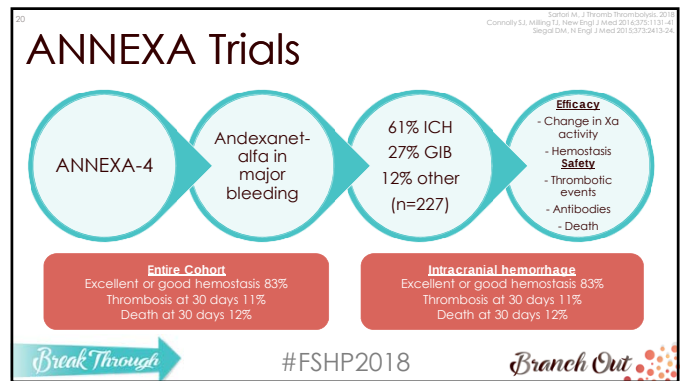
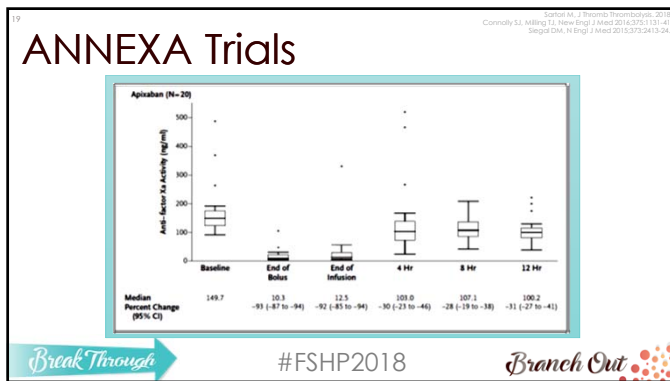
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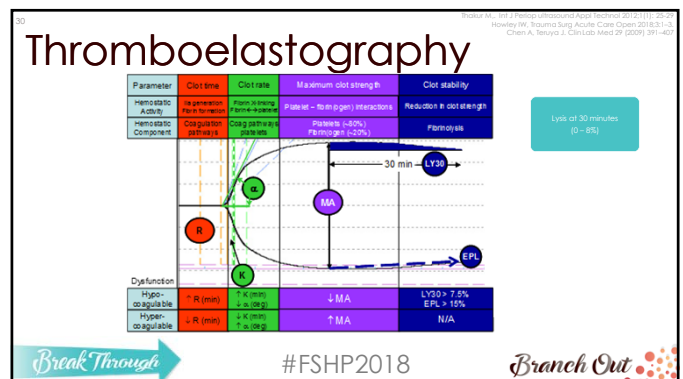
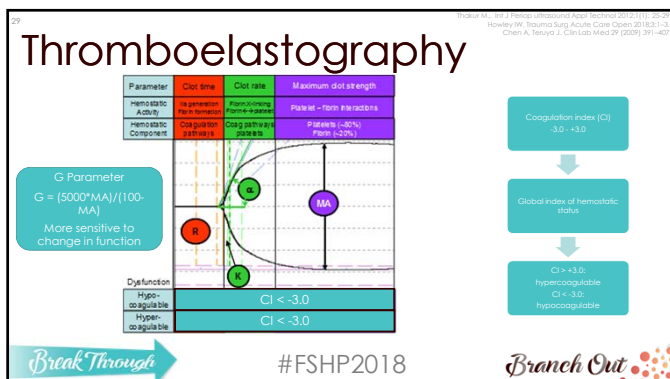
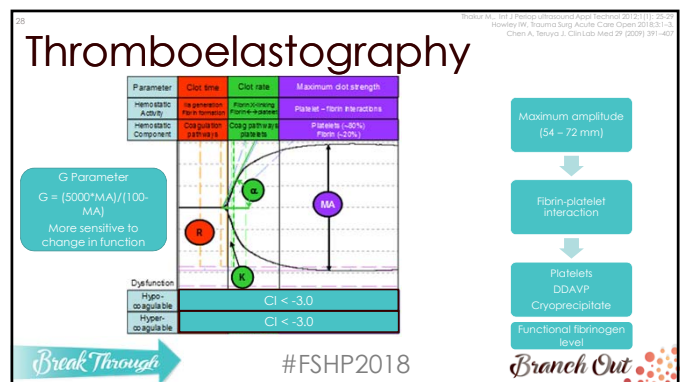
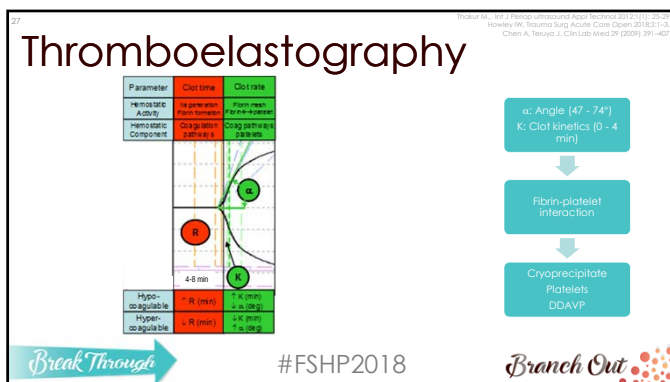
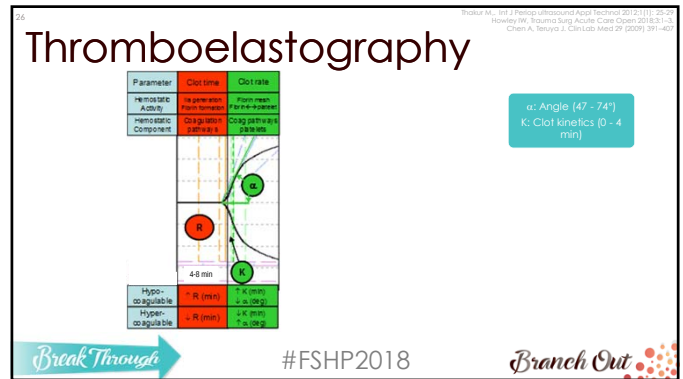
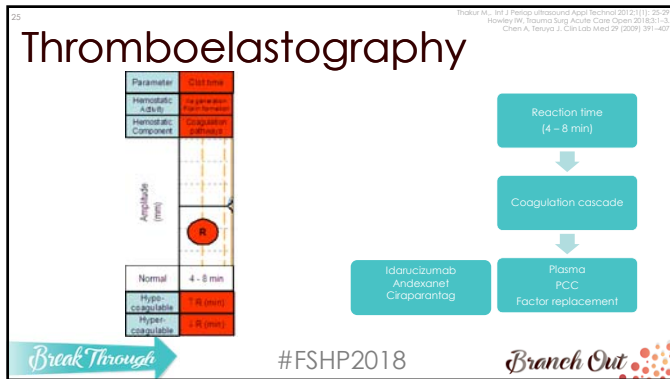


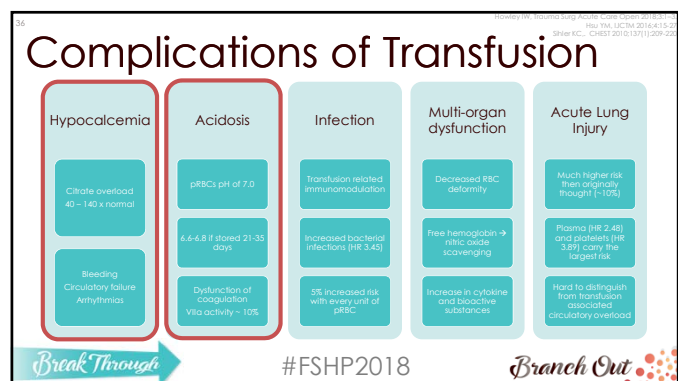
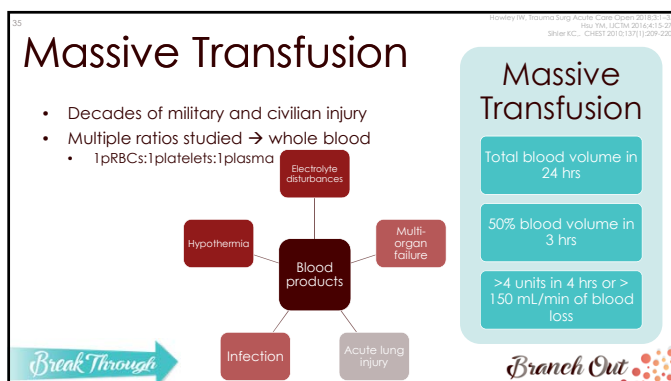
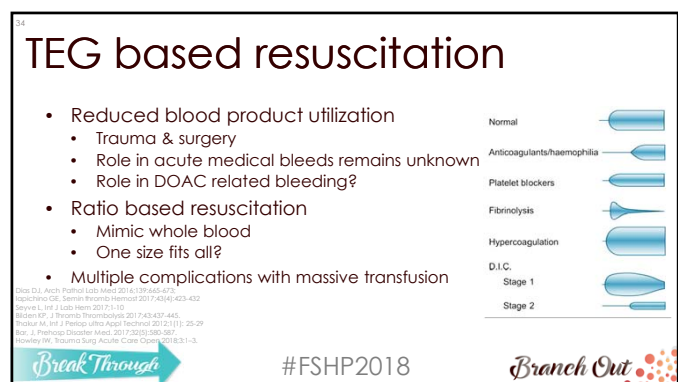
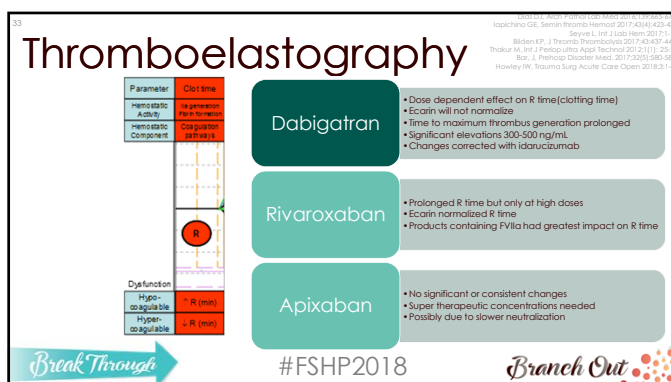
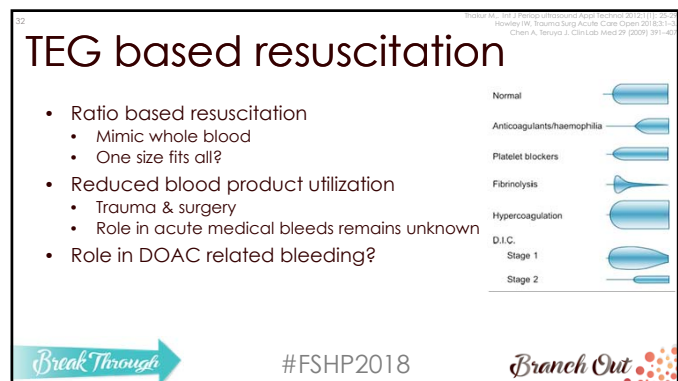
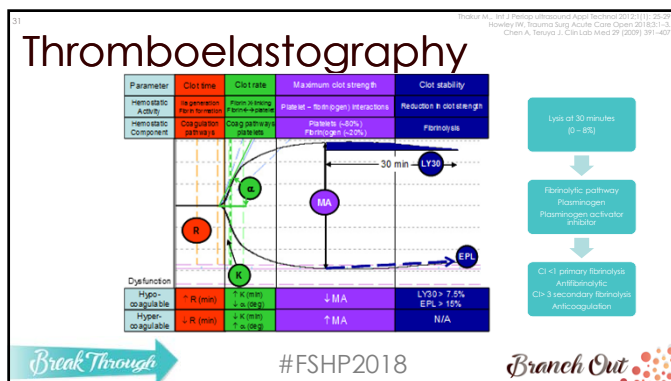
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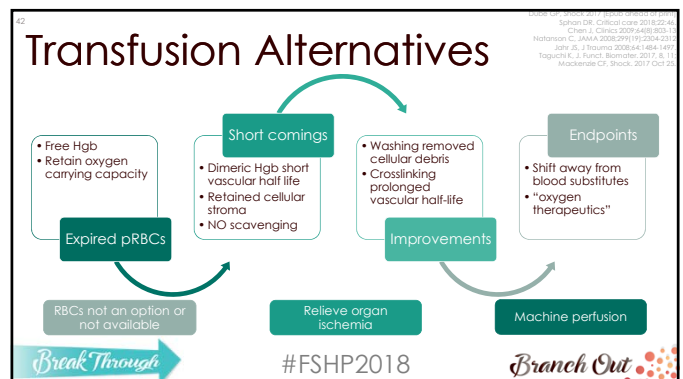
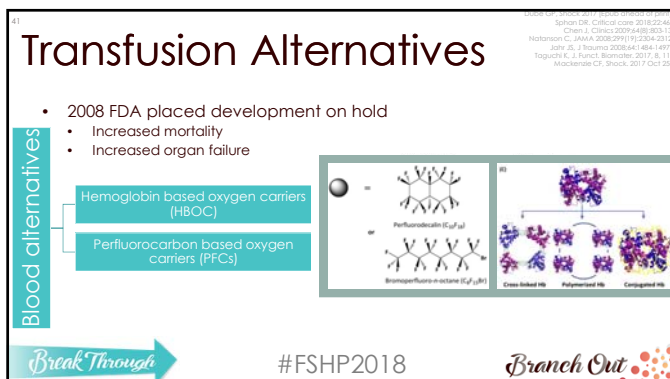
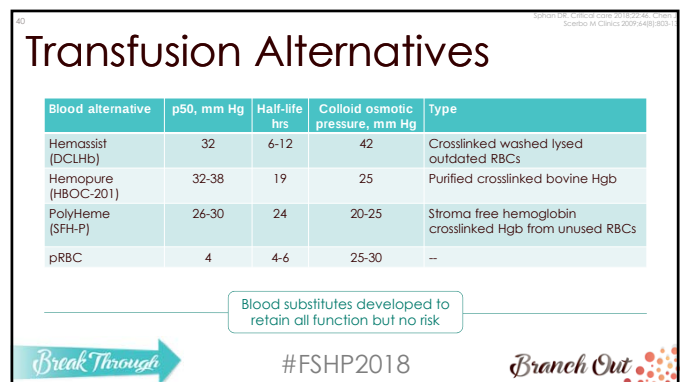
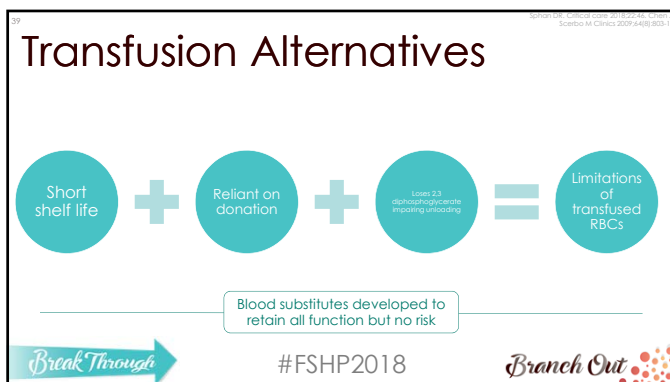
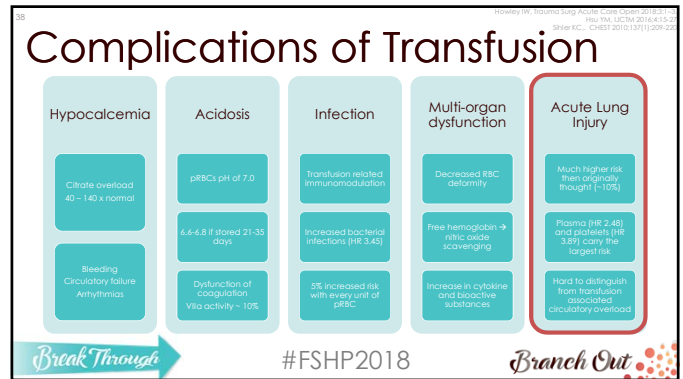
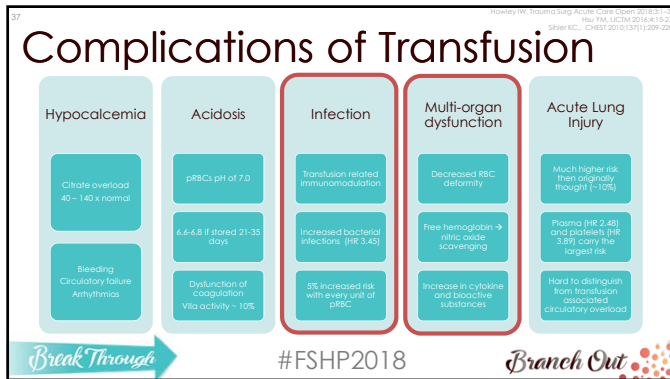
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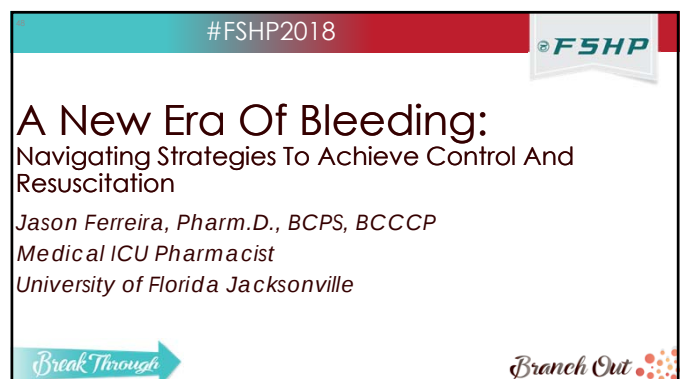
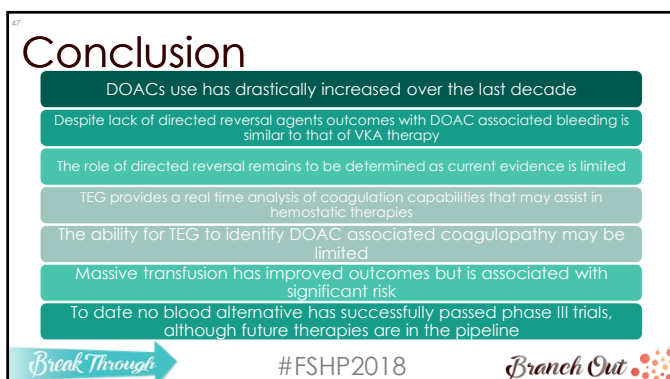
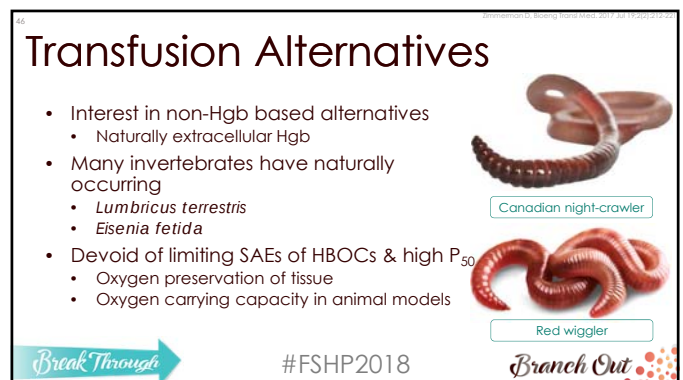
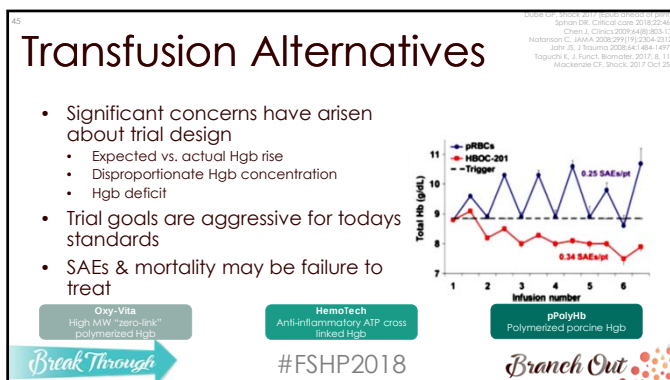
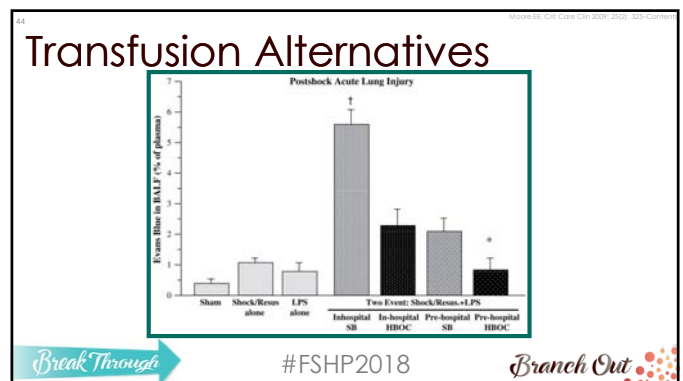
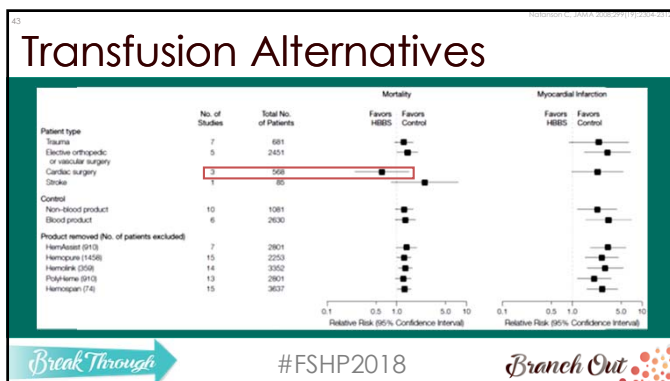
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Break Through

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