Greetings from Lucknow

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Lets discuss:

Management of NOAC induced Bleeding

We are all familiar with the NOACs

- Dabigatran: Direct Thrombin Inhibitor(oral)

- Rivaroxiban
- Apixaban
- Edoxaban
- Betrixaban Direct Factor Xa Inhibitors(oral)

For:
Non Valvular AF
Venous thromboembolism

Bleeding on NOACS is of Special Concern because…

- Can be life threatening
- Specific antidotes : hard to get and expensive
- Routine Coagulation tests are not very helpful

While …all types of bleeding are important

- Very minor bleeding (echymosis) may not require anything
- Minor bleeding (Bleeding Piles, Menorrhagia, Epistaxis)
  - Local measures
  - Without Drug Interruption or Reversal

Bleeds that Require immediate attention

- Life threatening bleeds
  - Intracranial
  - Compartmental
  - Retro peritonial
  - Massive GI bleeding

- Major bleeds
- Requiring intervention
  - surgery, interventional radiology procedures, endoscopic treatments.
- Major bleeding has a significant risk of immediate morbidity.
- Some major bleeding may be life-threatening.

Both may be managed on the same guidelines

Start by assessing the coagulation Status

- This depends upon :
  - Agent used
  - Timing of Last dose
  - Renal and Hepatic functions
  - Other medications(Aspirin, Clopidogrel etc)
  - Co morbidities

Anticoagulation FULLY resolves after 5 Half Lives since last dose(normal Renal/Hepatic functions)

- Dabigatran 2.5-3.5 days

- Rivaroxiban 1-2 days
- Apixaban 1.5 -3 days
- Edoxaban 1.3-2 days
- Betrixaban 4-5.5 days

Impaired Renal Hepatic function prolongs anticoagulant effect

Renal Clearance

• Dabigatran	85%	Rest : hepatic
• Rivaroxiban	35%	“
• Apixaban	25%	“
• Edoxaban	35%	“
• Betrixaban	11%	“

Coagulation Testing

- Prolonged Coagulation times indicate Residual anticoagulant effect
- Normal values
  - Cannot be taken as evidence to eliminate aggressive intervention specially with continued bleeding.
    - Exception: Dabigatran
      - Normal TT means absence of residual anticoagulant effect

Tests

- PT
- aPTT
- TT
- In those on Dabigatran:
  - If available, a calibrated dilute TT is preferable

- Specialized Tests
  - Quantitative factor Xa inhibitor levels
  - Dabigatran levels
    - Limited availability
    - Need a rapid turnaround time from a laboratory that is familiar with such testing.

- OTHERS
  - Hb
  - Platelet count
  - Liver and renal functions

Coagulation Tests That May Be Useful In a Patient on NOACS

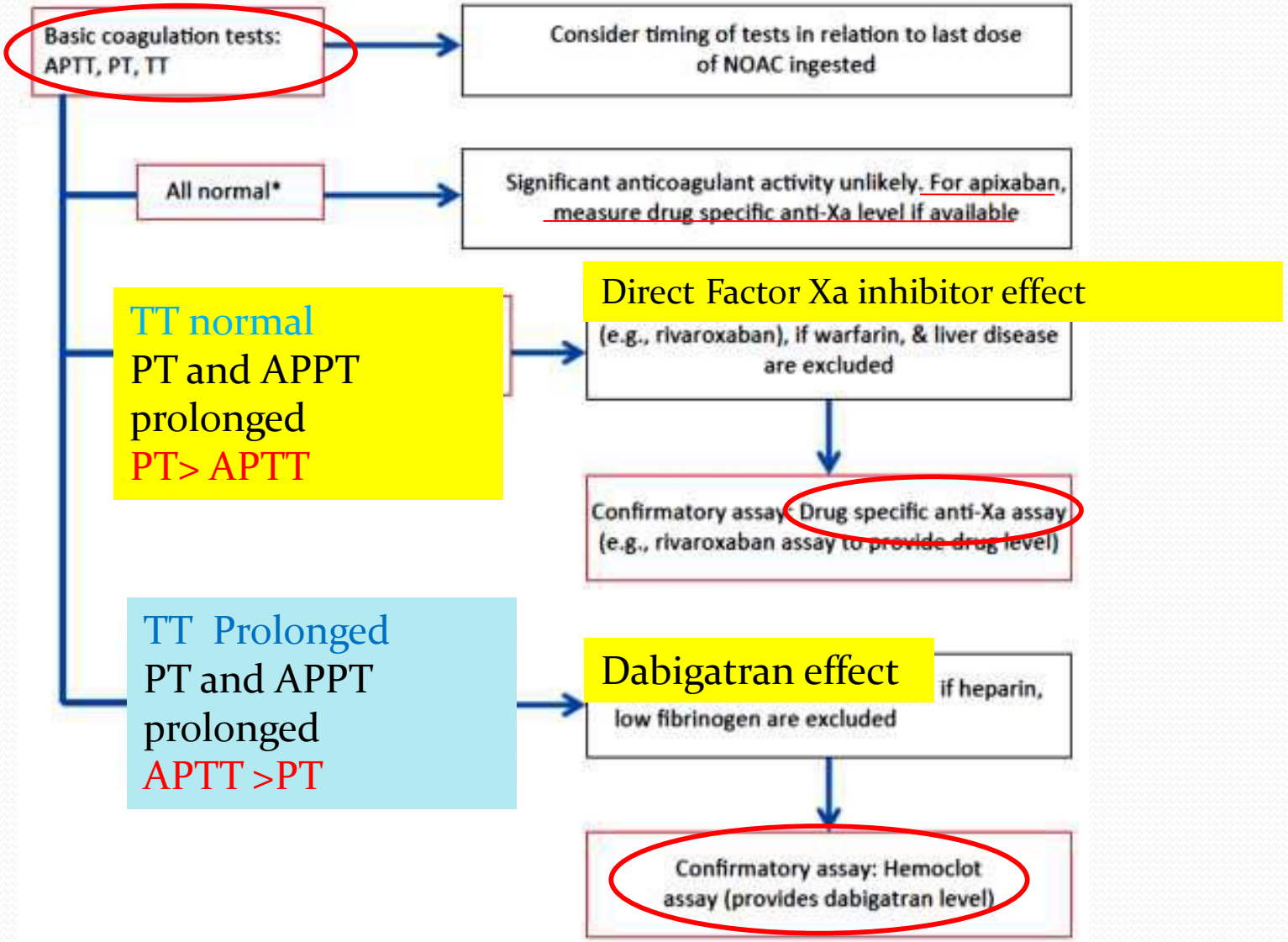
DOAC	PT	aPTT	TT	Ecarin clotting time	Hemoclot assay	Anti FXa activity	
						Clot based	chromogenic
Dabigatran	↑ or ↔	↑	↑	↑	↑*	---	---
Rivaroxaban	↑ or ↔	↑ or ↔	---	---	---	↑	↑*
apixaban	↑ or ↔	↑ or ↔	---	---	---	↑*	↑*

*** Preferred test ↑ increase ↔ no change --- not applicable**

The relationship between test results and bleeding risk is currently unknown

Siegal D. et al. Blood 2014;123;1152-1158

Evaluating a Patient on NOAC Presents with a Major Bleeding or Requires Urgent Surgery



Tran H. et al. Internal Med J 2014; 44;525-536

Life threatening/Major Bleeding

- ICCU admission
- Haemodynamic support
- Stop drug
- Drug Removal
  - Activated Charcoal
- Haemodylisis

Anticoagulant reversal

- CT /MR for ICH
- Contact Appropriate specialists for diagnostic and therapeutic support
- Management of Intra peritonial, Compartmental syndrome and massive GI bleeding

Strategies for Anticoagulant reversal

1. A specific reversal agent/antidote
    1. Dabigatran: Idaruzimab
    2. Factor Xa inhibitors: Andexanet

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2. Nonspecific agents such as prothrombin complex concentrates (PCCs)
3. Antifibrinolytic agents
4. Desmopressin(DDAVP)
5. Drug removal from the circulation and/or gastrointestinal tract depending on the time from ingestion

- Life threatening Bleeding …Including Uncontrolled bleeding
- or
- Urgent surgery is required
  - where there is high confidence that Anticoagulation effect is present

Specific Antidote

Specific Antidote
Not available or ineffective

- Activated or non activated Prothrombin complex
  - Not known to be effective in NOAC induced bleeding
  - Can cause thrombosis
- No Data on
  - Activated factor VII
  - Fresh frozen plasma
  - Cryoprecipitate
    - Can cause
      - Thrombosis
      - Volume load
      - Transfusion reaction

Specific Antidotes

Dabigatran Reversal: Idaruzimab

- Humanized anti Dabigatran monoclonal Antibody Fragment
- Given when there is convincing evidence of Significant Dabigatran levels
  - Time from Ingestion
  - Lab evidence
    - Prolonged TT
    - Levels

5gm(two vials) Bolus or Infusion

Do not Give Idaruzimab in those with NORMAL Thrombin Time

RE-VERSE AD study (2017)

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal — Full Cohort Analysis

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., Joanne van Ryn, Ph.D., John W. Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Chak-Wah Kam, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Gordon Royle, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., Peter Verhamme, M.D., Bushi Wang, Ph.D., Laura Young, M.D., and Jeffrey I. Weitz, M.D.

Idarizumab :Highly effective

- 503 patients on Dabigatran mostly for AF
- Bleeding :
  - 301
    - GI ,Intracerebral,or Traumatic
- Urgent procedure:
  - 202

- Bleeding cessation in 24 hr
  - 68%
    - 134/203 evaluated
  - Median time: 2.5 Hrs
- Haemostatsis
  - Normal 184/197: 93%
  - Mild Impaired: 10(5%)
  - Moderately Impaired: 3(2%)
  - **Severely Impaired: none**

RE-VERSE AD

- TT was abnormal in 92%
- Normalized within 15 minutes in almost all
- Effect Maintained at 24 hrs

- Antibodies that reacted with Idaruzimab present in
  - 19 before treatment
  - 9 more post treatment
- Did not interfere with reversal

If Idaruzimab is not available or inefective

- Pro coagulant reversal Agents
- aPCC
  - FEIBA(Factor Eight Inhibitor Bypassing Agent)
    - 50-80 units/Kg
  - If not available
  - Un activated 4-factor/3-factor PCC
    - 50 Units/kg
    - Do not Combine with Idaruzimab

Products to improve clotting:

contain clotting factors purified from human plasma

- 3 factor PCC
- II,IX and X
- 4 factor PCC
- II,IX and X and VII

- No proven benefit in DOAC induced bleeding

- Activated PCC have a higher chance of precipitating a thrombotic event

Non Life threatening Major bleeding

- Antifibrinolytic agents
  - Traneximic Acid
  - Epsilon AminoCaproic Acid
- May also be used in less serious but ongoing bleeding

- Oral Activated Charcoal
  - if the last dose of Dabigatran was given less than 2 hrs before
- Also be given in less severe Bleeding if an overdose of dabigatran has been taken
- Haemodylisis

- RBC transfusions if needed for anemia
- Platelet transfusions if needed for thrombocytopenia or impaired platelet function (eg, due to aspirin)
- Surgical/endoscopic intervention if appropriate

Direct Xa Inhibitors reversal

Andexanet Alpha

- Recombinantly produced ,Catalytically inactive form of Xa that acts as a decoy to bind and sequester the Anticoagulants

- FDA approval 2018 :for Reversal of Rivaroxaban and Apixaban
  - For Life threatening or uncontrolled bleeding
  - Evidence of significant factor Xa levels
    - Clinical history of recent ingestion
    - Lab tests

Andexanet dose

- **Low Dose**
- Rivaroxaban ≤10 mg
- Apixaban <5 mg
- ≥8 hrs post ingestion

- **High dose**
- Rivaroxaban ≥10 mg
- Apixaban ≥5 mg
- ≤ 8 hrs post ingestion

- 400 mg bolus at 30 mg/min
- 480 mg :2 Hr infusion at 4 mg/min

- 800 mg bolus at 30 mg/min
- 960 mg :2 Hr infusion at 8 mg/min

ANNEXA-4 (2019)

ORIGINAL ARTICLE

Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors

S.J. Connolly, M. Crowther, J.W. Eikelboom, C.M. Gibson, J.T. Curnutte, J.H. Lawrence, P. Yue, M.D. Bronson, G. Lu, P.B. Conley, P. Verhamme, J. Schmidt, S. Middeldorp, A.T. Cohen, J. Beyer-Westendorf, P. Albaladejo, J. Lopez-Sendon, A.M. Demchuk, D.J. Pallin, M. Concha, S. Goodman, J. Leeds, S. Souza, D.M. Siegal, E. Zotova, B. Meeks, S. Ahmad, J. Nakamya, and T.J. Milling, Jr., for the ANNEXA-4 Investigators*

N Engl J Med 2019;380:1326-35.

ANNEXA-4

- 352 patients with acute bleeding
- 80% for AF or venous Thromboembolism
- Majority on Rivaroxaban or Apixaban
- Arbitrary level to indicate high bleeding Risk
- High dose for <7 hrs post ingestion

Andexanet: Highly effective

- **Haemostasis:**
- Good to Excellent: 203/249 (82%)
- Subgroup Analysis
  - GI bleed 85%
  - Intracranial 80%
- Anticoagulant re started after control of bleeding in 62%

- **Anti Factor Xa activity reduction**
- Rivaroxaban 92%
- Apixaban 92%
- **Thrombosis**
  - Stroke, MI,DVT,PE
- 3% at 5 days
- 10% at 30 days
- **Mortality** 14% at 30 days

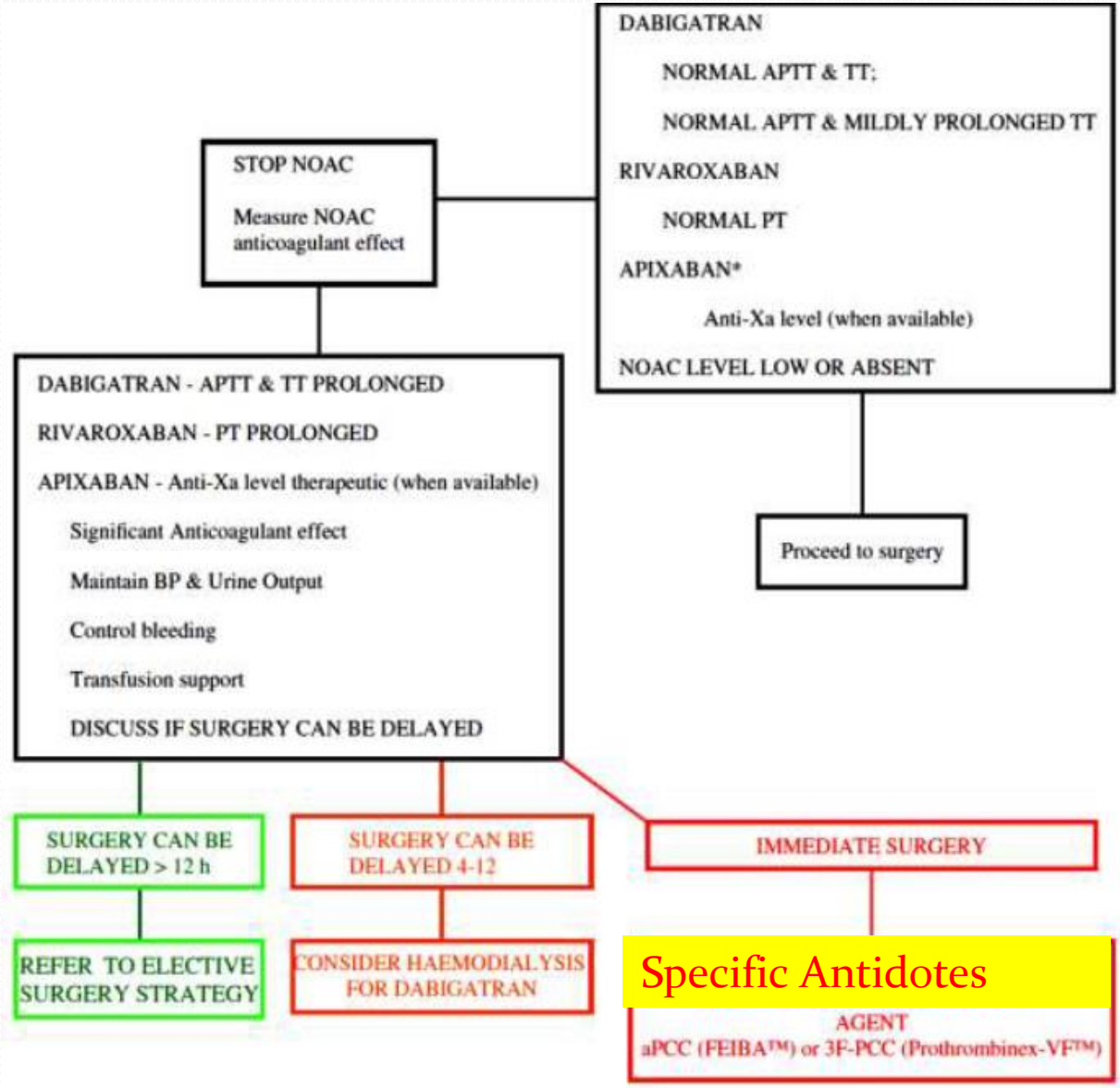
If Andexanet is not available or ineffective

Reversal agent	FXa Inhibitors
PCC	Reversal of coagulation tests in vivo No effect on bleeding in an animal model case reports
aPCC (FEIBA)	C… …nt effect in animal …el
	In vitro: corrects some clot-based coagulation tests, thromboelastometry parameters, and thrombin generation indices
rFVIIa	Partial reversal of clot test in vitro Favorable effect on lab in vivo
Hemodialysis/ hemoperfusion	No published data
Active charcoal /gastric lavage	For apixaban: up to 3h (entero-enteric recirculation)

None to limited data

Urgent Surgery ?

Suggested Management of Patients Receiving NOAC Requiring Urgent Surgery



Tran H. et al. Internal Med J 2014; 44;525-536

Timing for Elective Surgery

	Timing of last dose before surgery		
Calculated creatinine clearance, mL/min	T1/2, hours	Standard risk of bleeding	High risk of bleeding
Dabigatran			
>80	13 (11-22)	24h	2d
> 50 - ≤ 80	15 (12-34)	24h (24-48h)	2d (48-72h)
> 30 - ≤ 50	18 (13-23)	2d (48-72h)	4d (96h)
≤ 30	27 (22-35)	4d (2-5d)	6d (>5d)
Rivaroxaban			
> 30	12 (11-13)	24h	2d
< 30	unknown	2d	4d

Schulman S. Crowther MA Blood 2012;119;3016-3023

Thanks for the opportunity..