- All DOACs are cleared to some extent by the kidneys

  - Dabigatran 80%
  - Rivaroxaban 33%
  - Apixaban 25%

  - Potential for drug accumulation in patients with severe renal impairment especially below eGFRs <30

- Rivaroxaban & Apixaban are both oral direct inhibitor of factor Xa.
- Rivaroxaban doses recommended for clinical use are 15mg od and 20 mg od (15 mg bd for first 3 weeks of treatment of DVT).
- Apixaban 5mg bd or 2.5mg bd
- Rivaroxaban peak plasma levels are reached 2 to 3 h after ingestion
- Apixaban peak plasma levels are reached ~3hrs after ingestion
- Rivaroxaban is taken with food – Apixaban without food
- Rivaroxaban is 33% renaly excreted and has a half-life of 9 h in patients with normal renal function.

- There is an analogy with Therapeutic LMWH
- We very rarely ask for an anti-Xa assay
  - And what is the clinical significance of a Xa assay ? (Cut off values are largely arbitrary)
- Fixed doses
- Importance of **When the last dose was taken ?**
- Importance of **What is the renal function ?**
- If bleeding
  - **What is the nature of the bleeding ?**
  - In extremis we can give protamine sulphate (? Efficacy)

- How to manage bleeding on a DOAC?

  –How severe is the bleeding ?

  –When was the last dose of medication ?

  –What is the renal function ? – Recheck

  –If ***minor*** bleeding; epistaxis, gingival, bruising, menorrhagia

    - **Withhold the NOAC** (when was the last dose taken?)
    - Recheck renal function
    - Check FBC
    - Local measures

    - Unlikely to require further intervention

      – Re-challenge
      – ? Switch NOAC
      – ? Switch to warfarin
      – ? Cease all anticoagulation

– If ***Major*** bleeding; GU, GI, Intracranial

- Withhold the DOAC (when was the last dose taken)
- Urgently refer to secondary care
  - If ***Ongoing AND Life Threatening*** bleeding we recommend flat dose PCC (Octaplex) to be given at a dose of 25 iu/kg
- Please note little clinical data to support the use of PCC or any other blood product to reverse the effects of DOACs, though an emerging consensus regarding PCC
  - BCSH guidelines do state APCC (FIBA) or rFVIIa administration can be considered
  - In addition for dabigatran
    - » If bleeding within 2 hrs of last dose activated charcoal can be given
    - » If rapidly deployable dialysis can be considered !!

- If normal PT/INR with Apixaban & Rivaroxaban *Cannot say there is No anticoagulation* – though *intensity* of anticoagulation is equivalent to no more than *prophylactic* LMWH

- Similar for Dabigatran and the aPTT/aPTT Ratio

- If elevated PT/INR – *Cannot* interpret the intensity of Anticogulation

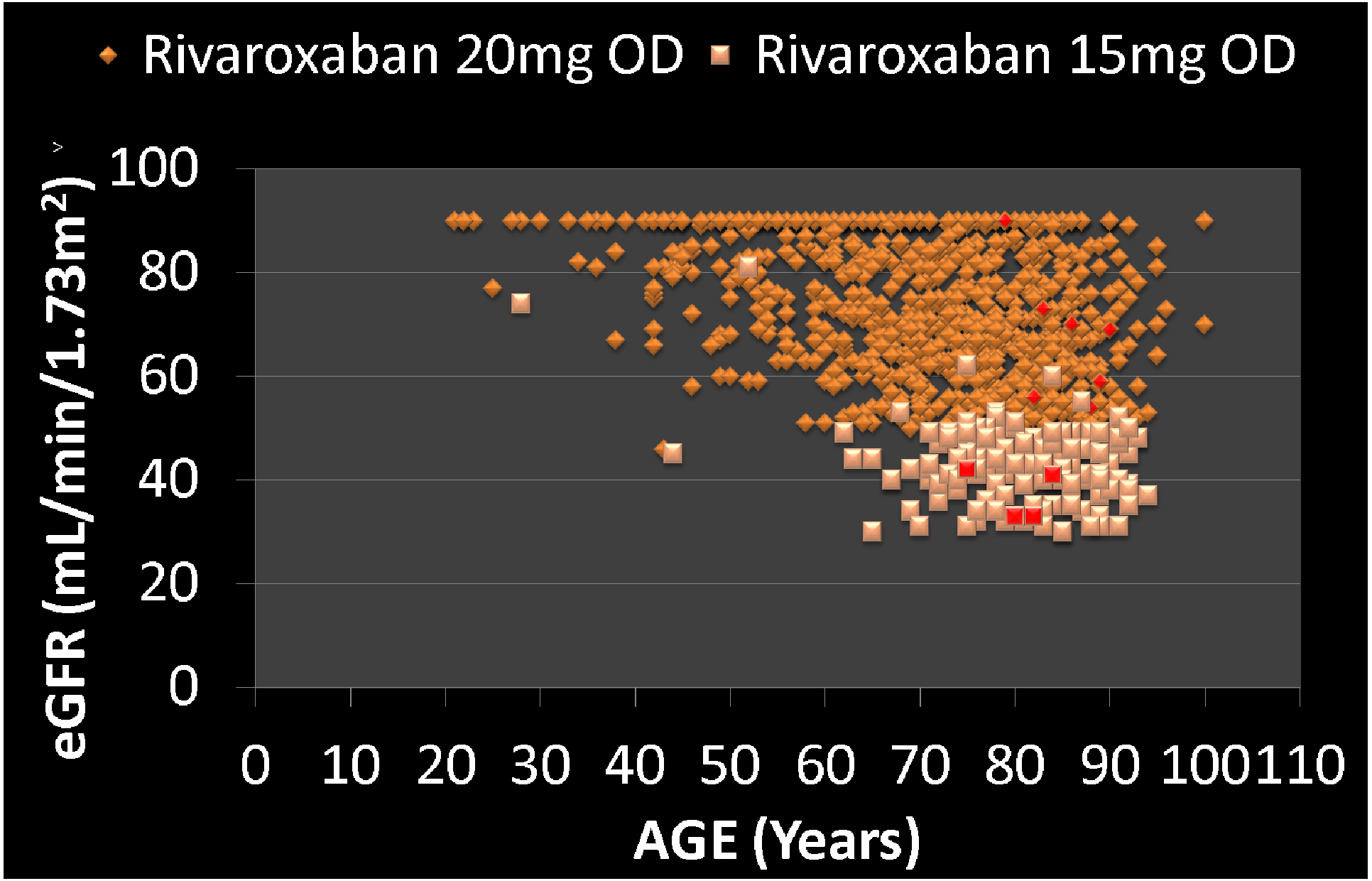
- TEG useful if urgent intervention required

- At RHH we have audited and continue to audit our use and outcomes with the NOACs

- EHA Poster

- **A SINGLE-CENTRE RETROSPECTIVE ANALYSIS OF THE INCIDENCE OF MAJOR BLEEDING IN OVER 1000 PATIENTS COMMENCED ON RIVAROXABAN FOR NON-VALVULAR ATRIAL FIBRILLATION AND VENOUS THROMBOEMBOLISM**
  - **498 patient years equivalent analysed**

Distribution by Age and eGFR of Rivaroxaban Patient Group



- Monoclonal antibody with very high affinity for Dabigatran

- Licensed for the specific reversal agent for dabigatran and is indicated in adult patients treated with Pradaxa (dabigatran) when rapid reversal of its anticoagulant effects is required:
  - For emergency surgery/urgent procedures
  - In life-threatening or uncontrolled bleeding

  - 2x 2.5g doses – consecutive infusions over 5-10 mins each
  - Can be repeated after 24 hours

  - Undergoing a NICE technology appraisal


The Future

Andexanet: Designed to Reverse Activity of Factor Xa Inhibitors Through a Well-Defined Mechanism of Action

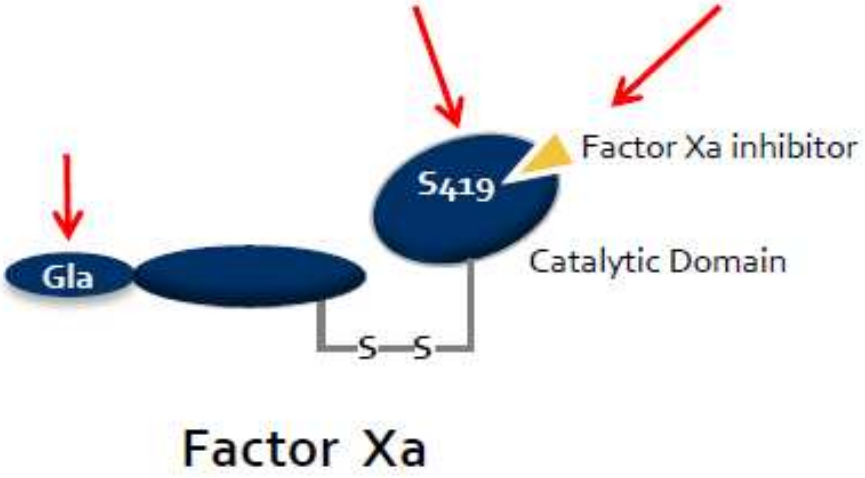
- NOT currently licensed
- Phase III trials are ongoing

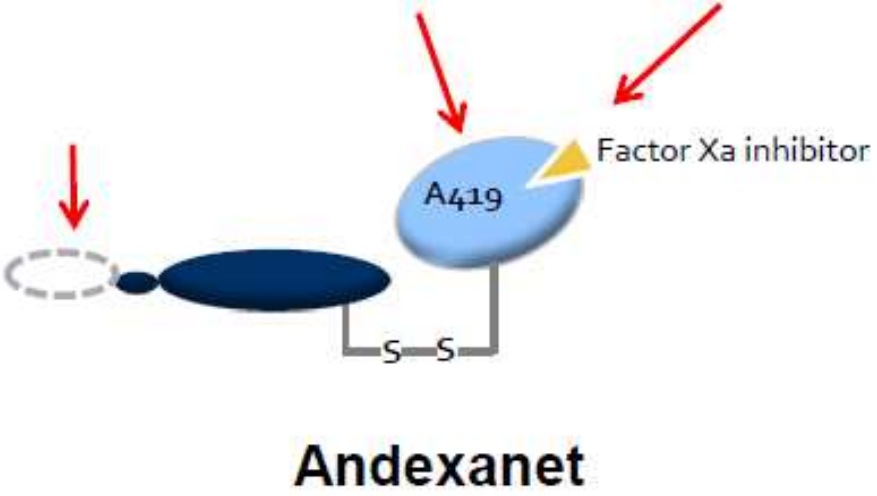
Recombinant engineered version of human factor Xa produced in CHO cells

- Acts as a fXa decoy and retains high affinity for all fXa inhibitors
- Change of Serine to Alanine to eliminate catalytic activity and prevent prothrombin cleavage
- GLA domain removed to prevent anticoagulant effect

- No known interaction with other coagulation factors

ɔment program to date





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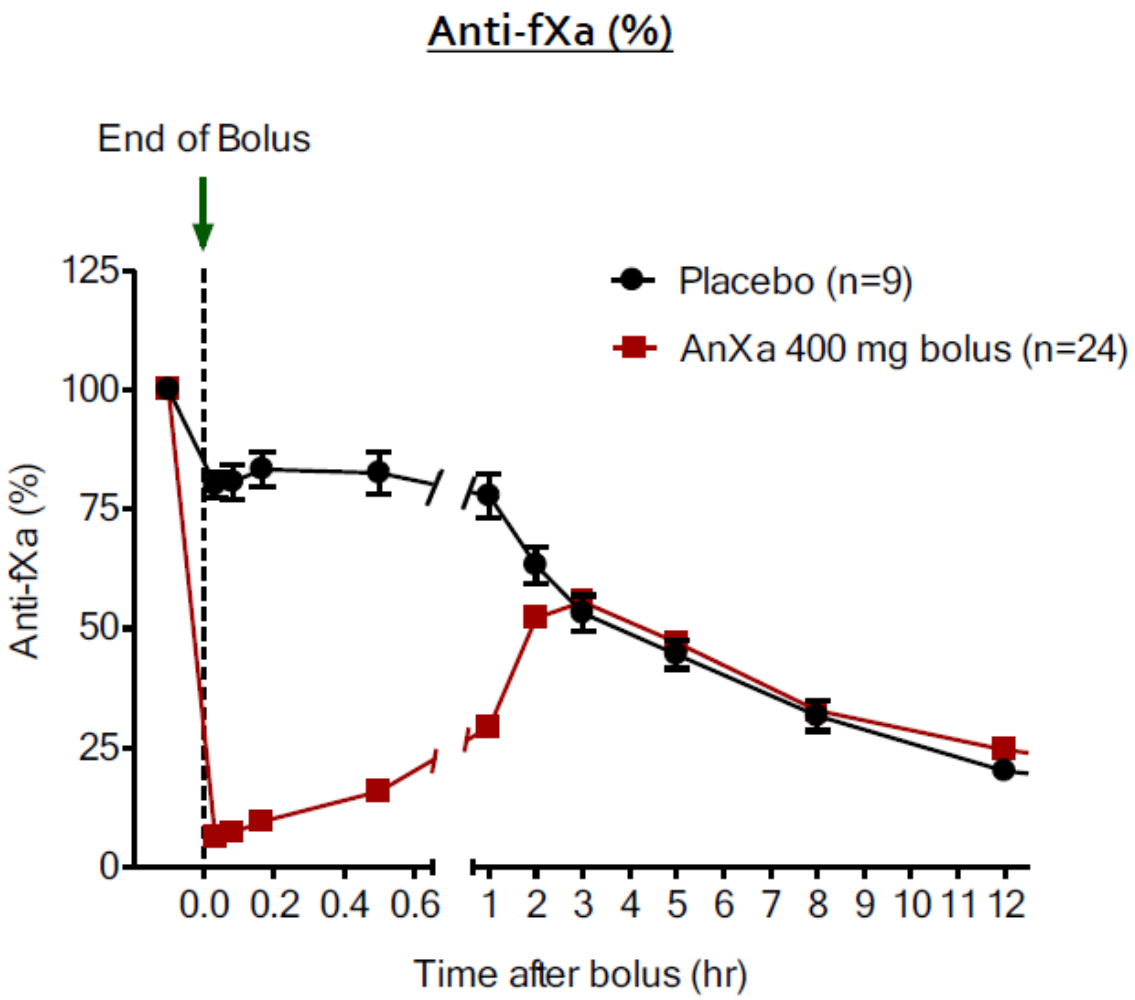
ANNEXA™-A (Apixaban, Part 1): Primary Endpoint Anti-FXa



- Met primary endpoint:
  - Percent change anti-FXa from baseline to nadir (94%)
    - $P<0.0001$
  - Met first secondary endpoint:
  - Number of subjects with >80% reversal: andexanet alfa (100%) vs. placebo (0%)
    - $P<0.0001$
  - All andexanet alfa subjects achieved ≥90% reversal

Data plotted as mean ± SEM.
fXa = factor Xa.

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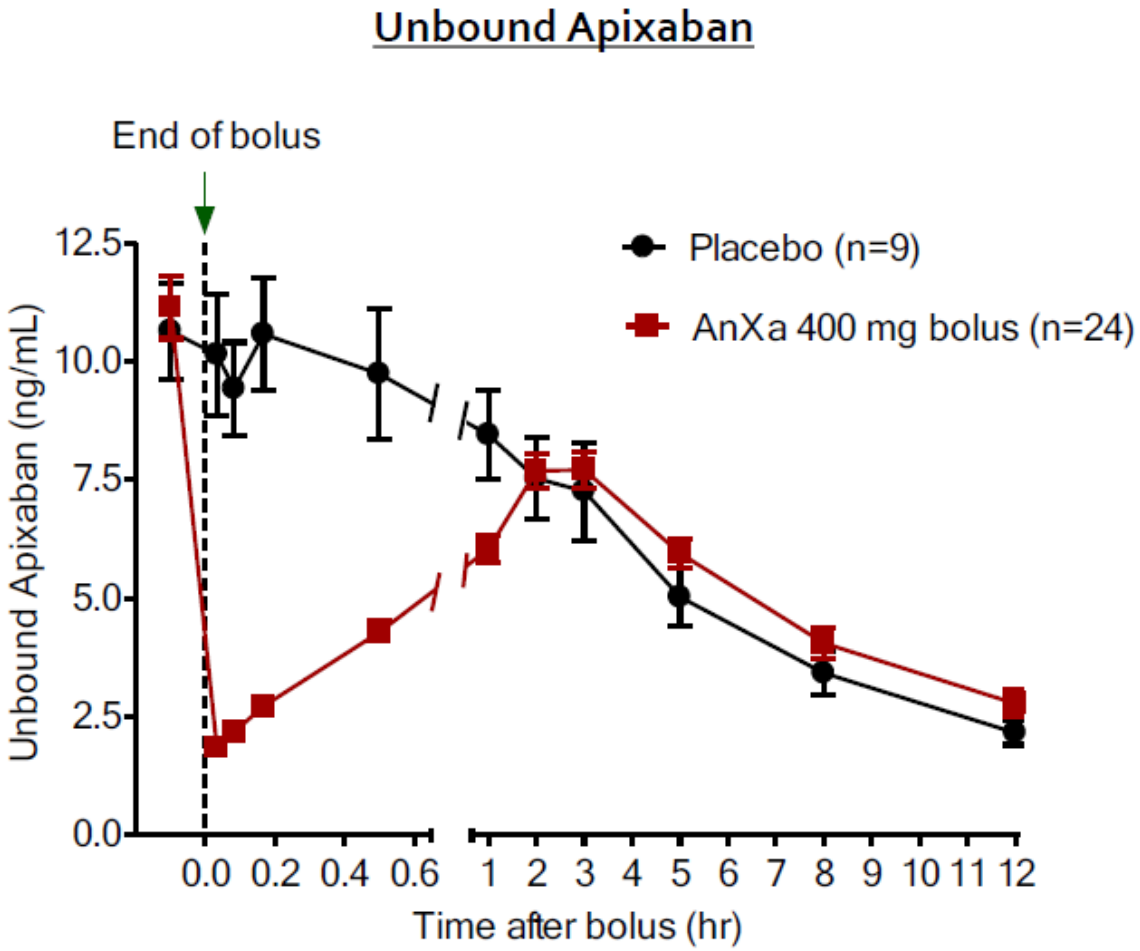
ANNEXA™-A (Apixaban, Part 1): Secondary Endpoint: Unbound Apixaban



- Met secondary endpoint:
  - Change in free apixaban concentration from baseline to nadir (1.8 ng/mL)
    - $P<0.0001$
- Consistent with Phase 2 data

Data plotted as mean ± SEM

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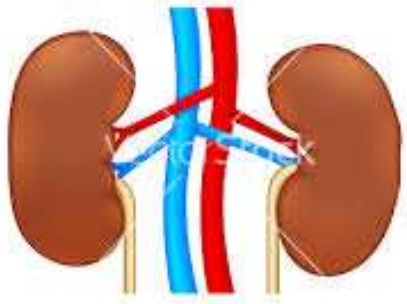
- **Elective Procedures**

  – If the patient is taking either Rivaroxaban, Dabigatran or Apixaban *exclusively* for AF there is no need to specifically bridge the short period of interruption for elective procedures with low molecular weight heparin

  – In patients with *normal renal function* who are to undergo a procedure with a low risk of bleeding (i.e. those procedures that would be safe w
  1.5), Rivaroxaban, Dabigatran and Api
  be interrupted for 24 hours



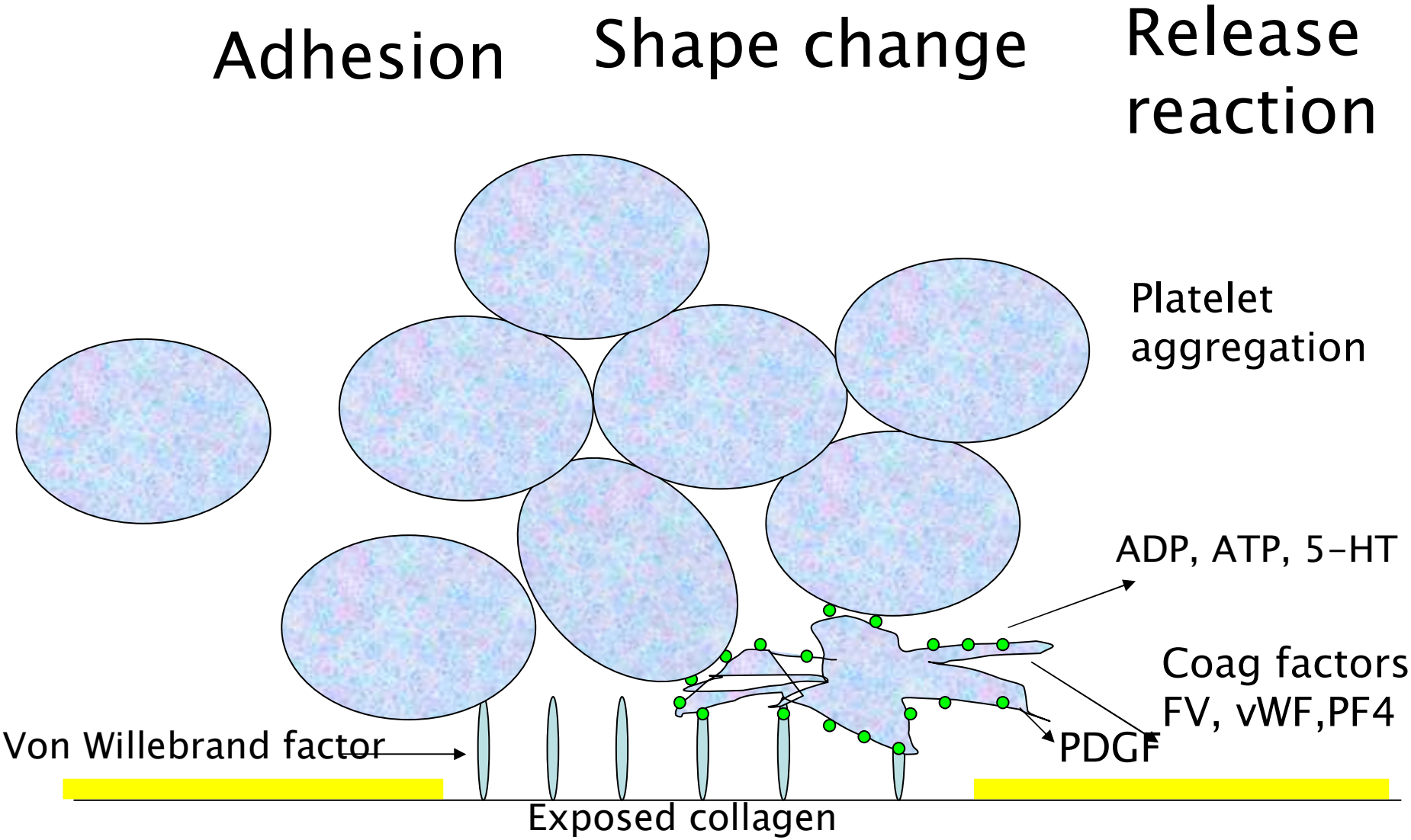
DABIGATRAN		
>80	24 hours	2 days
51-80	24 hours	2 days
31-50	2 days	4 days
<31	4 days	6 days

Apixaban SPC recommends similar management to Rivaroxaban as above

At RHH we request that Renal Function is checked within 1 month of an elective procedure

We do NOT recommend routinely checking clotting parameters prior to elective procedures

The role of platelets in coagulation



- Antiplatelets
  - Aspirin
    - Rapid onset of action <1hr
      - 3-4 hrs with enteric coated preperations
    - T ½ 20mins
    - Laboratory evidence of platelet inhibition
      - Persists for up to 4 days
      - Due to effect on individual platelets is irreversible
    - If minor bleeding
      - Withhold aspirin
      - Local measures
    - If major bleeding
      - *Consider* 1-2 units of platelets on discussion with haematology

– $P2Y_{12}$ antagonists /Clopidogrel

- A pro-drug
- 2 stage hepatic metabolisation
- Thus delayed onset of platelet inhibition of 4-8hrs
- T½ of active metabolite is ~30mins
- Irreversible $P2Y_{12}$ antagonists
- Thus platelet inhibition of 5-7 days
- No specific antagonist for clopidogrel

- If minor bleeding
  - Withhold clopidogrel
  - Local measures
- If major bleeding
  - *Consider* 1-2 units of platelets on discussion with haematology

- Fibrinolytic drugs
  - Alteplase
  - Tenecteplase
  - Reteplase
  - Urokinase
  - Streptokinase

    - All five agents function indirectly by promoting generation of plasmin, which then mediates clot lysis

    - Although the half-lives of the fibrinolytic drugs are themselves relatively short, their effect on coagulation parameters is much longer
      - eg After alteplase for stroke or myocardial infarction, fibrinogen was lowest at 2–3 h, remained low at 24 h and returned to normal at 48 h

– Thus for major bleeding (e.g. intracerebral) within 48 h of administration of a fibrinolytic
  - Stop infusion of fibrinolytic drugs and other antithrombotic drugs
  - Consider administration of FFP 12 ml/kg
  - Consider administration of intravenous tranexamic acid 1 g tds
  - If there is depletion of fibrinogen, administer cryoprecipitate or fibrinogen concentrate
  - Further therapy should be guided by results of coagulation tests

- Please Note Prevention is Better than Cure

  - This Applies to Anti-Thrombotic Related Bleeding too

  - Thus...

…Compliance with Warfarin & Especially DOACs is Very Important

- No regular monitoring with DOACs
  - Thus no reminder re clinical importance of anticoagulation and consequences of poor compliance

- More litigation surrounds warfarin than any other medication
  - Likely to be similar for the DOACs
- Usually related to poor communication
  - Indication for anticoagulation
  - Duration of anticoagulation
  - Consequences of poor compliance
  - Interactions

- **‘Events’ occur with patients on anticoagulation – *Any Anticoagulant* – However well managed**

Thank You

- Any Questions