

Management of Anticoagulation in Hip Fracture

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Issues in Hip Fracture

- Thromboprophylaxis
- Management of patients taking antithrombotic medication who require hip fracture surgery

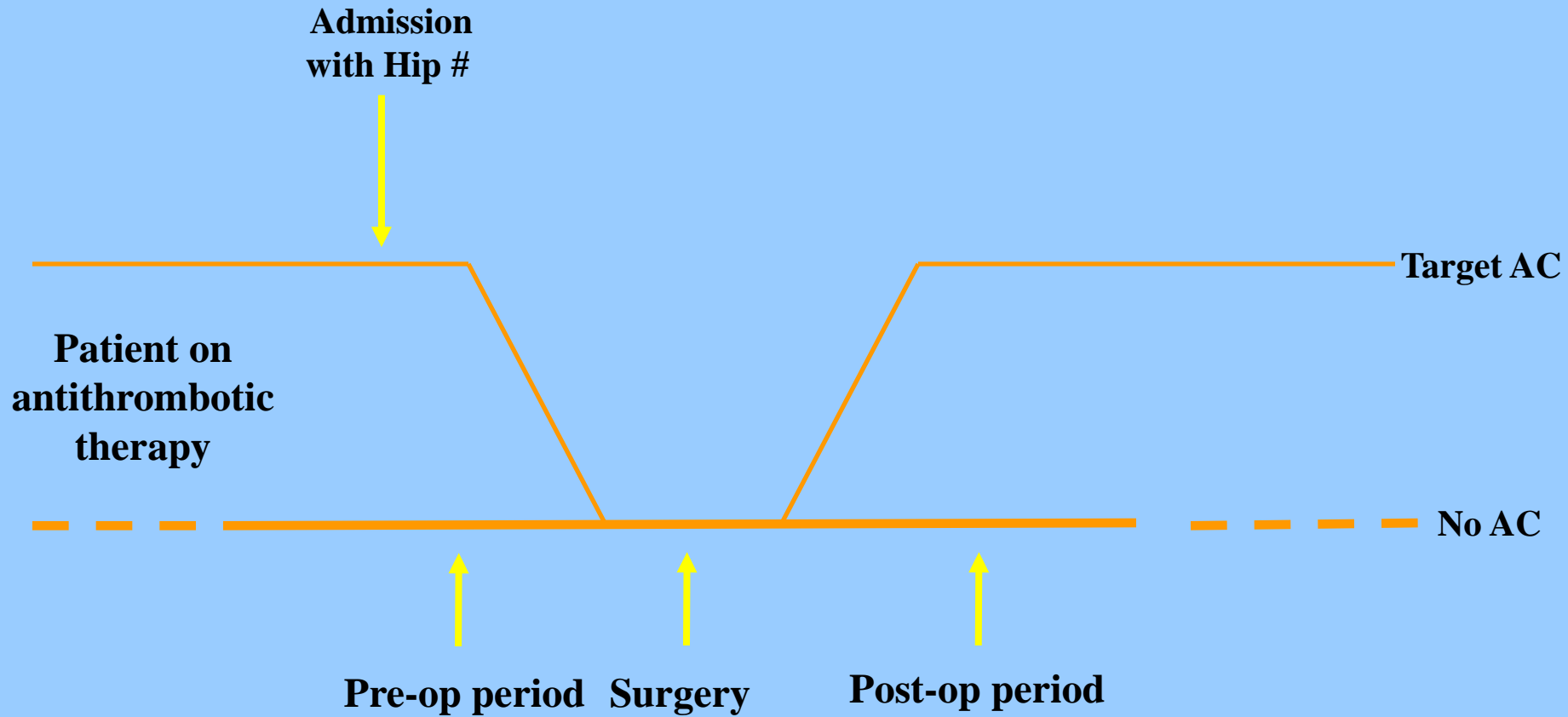
Thromboprophylaxis in Hip

- Hip Fracture patients are at high risk of thromboembolism
- Some patients with hip # are at **very high risk** due to co-morbidities
 - Active cancer
 - Prior history of VTE
 - Chronic venous insufficiency/VV
 - Obesity
 - Other conditions leading to poor post-operative mobility

Thromboprophylaxis is routine in Hip

- Optimal agent
 - LMWH, fondaparinux, DOACs
- Optimal timing
 - pre-operative and re-commence 8-12 hours post-operatively
- Duration
 - Most guidelines recommend extended TP to 35 days post-operatively
- Mechanical TP
 - IPC intra-operatively and whilst immobile
- Very high risk patients
 - Need anticoagulant + mechanical TP and consider therapeutic anticoagulation post-operatively

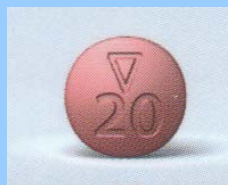
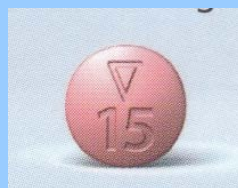
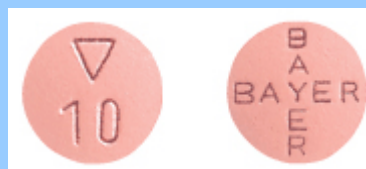
Bridging Therapy



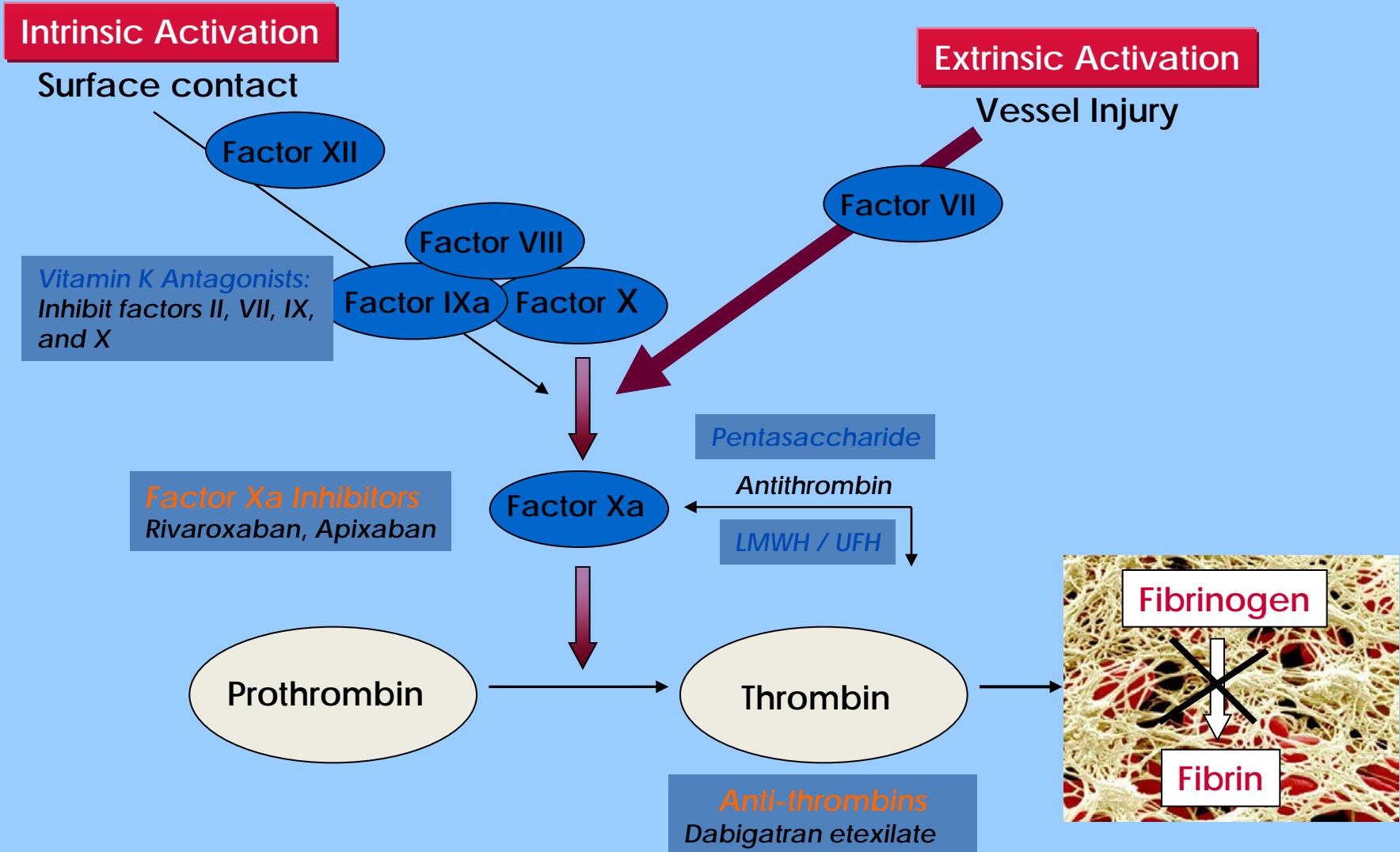
Warfarin and acute Surgery

- Identify indication for warfarin and need to peri-operative anticoagulation
- Measure INR
- <1.5 fit for surgery
- >1.5 need reversal prior to surgery
 - Immediate reversal with FFP or prothrombinex
 - Vitamin K 1-2mg if OT 24 hrs
- Need to plan post-operative anticoagulation before surgery

Direct Oral Anticoagulant Drugs (DOACs)



Anticoagulant Drugs – mechanism action



New Oral Direct Anticoagulants (1)

Generic	Rivaroxaban	Apixaban	Dabigatran Etexilate
Trade	Xarelto®	Eliquis®	Pradaxa®
Target	Activated Factor X	Activated Factor X	Thrombin (IIa)
Prevention VTE Arthroplasty	Authority	Authority	Authority
Stroke Prevention - NVAf + ≥ 1 RF	Streamline authority	Streamline authority	Streamline authority
Acute DVT/PE	Streamline authority	Streamline authority	TGA indication
Prevention VTE	Streamline authority	Streamline authority	TGA indication

Oral Direct Anticoagulants (4)

Generic	Rivaroxaban	Apixaban	Dabigatran Etexilate
Rapidly acting	Onset action at ~ 30 mins with time to Tmax 2.5-4 hrs with Rv & Ap, 0.5-2hrs with DE		
Half-life	5-9 hrs (11-13 hrs elderly)	9-14 hrs	7-9 hrs (12-14 hrs elderly)
Excretion	33% Renal	25% Renal	80% Renal
Hepatic metabolism	66% – CYP3A4, 2J2 and CYP-independent	75% - CP3A4/5	No
Drug Interactions	Potent CYP3A4 & P-glycoprotein inhibitors/inducers		PPI ↓absorption PGI 2-fold ↑AUC
Contra-Indications	Severe renal or hepatic disease	Severe renal or hepatic disease	Severe renal or hepatic disease
Antidote	In development	In development	Idarucizumab

DOACs and Acute Surgery

- Identify indication for DOAC and requirements for peri-operative anticoagulation
- Need to know
 - Dose and schedule, time last dose, weight & serum creatinine (and calculate Cl_{CR})
- Need to measure
 - APTT, TT, and Haemoclot if dabigatran
 - APTT PT and anti-Xa assay for rivaroxaban or apixaban
- Prolongation clotting times (APTT/ PT) are variable with each DOAC and with varying reagents/analysers
- Drug assays take 24 hrs or longer

Dabigatran and Acute Surgery

- Need to know
 - Dose and schedule, time last dose, weight & creatinine (calculate Cl_{CR})
- Need to measure
 - APTT, TT, and Haemoclot if dabigatran
- Prolongation PT/APTT variable between reagents
 - TT is very sensitive to dabigatran
 - Abnormal APTT ~25-50ng/ml and PT ~100ng/ml
 - APPT ratio 1.5 and 2.0 at ~100ng/ml and ~300ng/ml respectively
 - INR 2.0 at ~500 ng/ml
- Normal TT = no drug = surgery can proceed
- AbN TT & Normal APTT = low level drug so surgery can proceed (or delay 24 hours)
- Abn TT & APTT = significant drug level so either
 - Delay surgery pending drug assay
 - Surgery with reversal with Idarucizumab (Praxbind)

Pre-operative approach to NOACs

Spyropoulos AC, Douketis JD BLOOD 2012;120(15):2945-2962

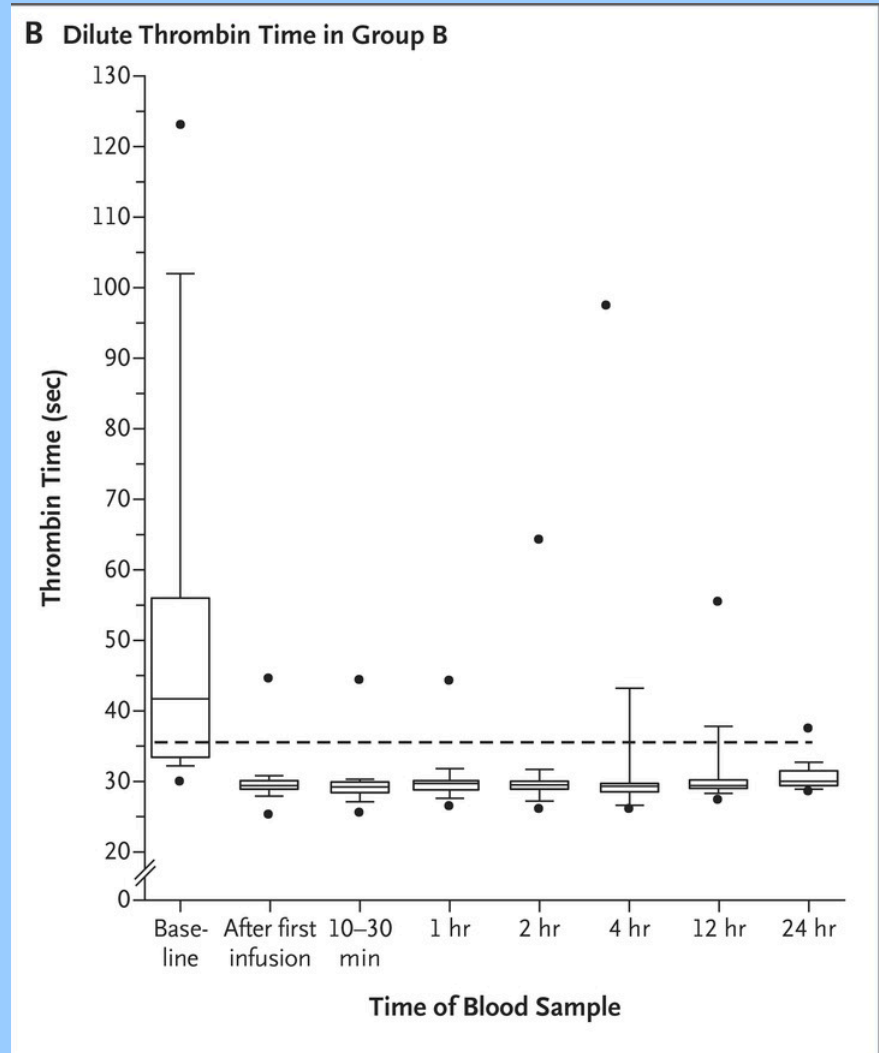
Drug	Renal Function	Low bleeding risk ¶	High bleeding risk §
Dabigatran 150mg twice daily (t½ ~ 12-17 hrs)	Cl _{CR} ≥50 mls/min	4 doses	6 doses
	Cl _{CR} 30-49 mls/min	6 doses	8-10 doses
Rivaroxaban 20mg once daily (t½ ~ 5-13 hrs)	Cl _{CR} ≥50 mls/min	1 dose	3 dose
	Cl _{CR} 30-49 mls/min	1 dose	3 doses
Apixaban 5mg twice daily (t½ ~ 8-15 hrs)	Cl _{CR} ≥50 mls/min	2 doses	4 doses
	Cl _{CR} 30-49 mls/min	4 doses	6 doses

¶ Interval last dose and surgery 2-3 half lives

§ Interval last dose and surgery 4-5 half lives

Reversal with Idarucizumab (Praxbind)

Figure 1 Time Course of the Dilute Thrombin Time before and after the Administration of Idarucizumab. The analyses included 39 who required urgent surgery or intervention. Idarucizumab was administered in two infusions. Blood samples were obtained at baseline, after the first infusion, at 10 to 30 minutes after the administration of the second infusion, and at 1, 2, 4, 12, and 24 hours.



Rivaroxaban and Acute surgery

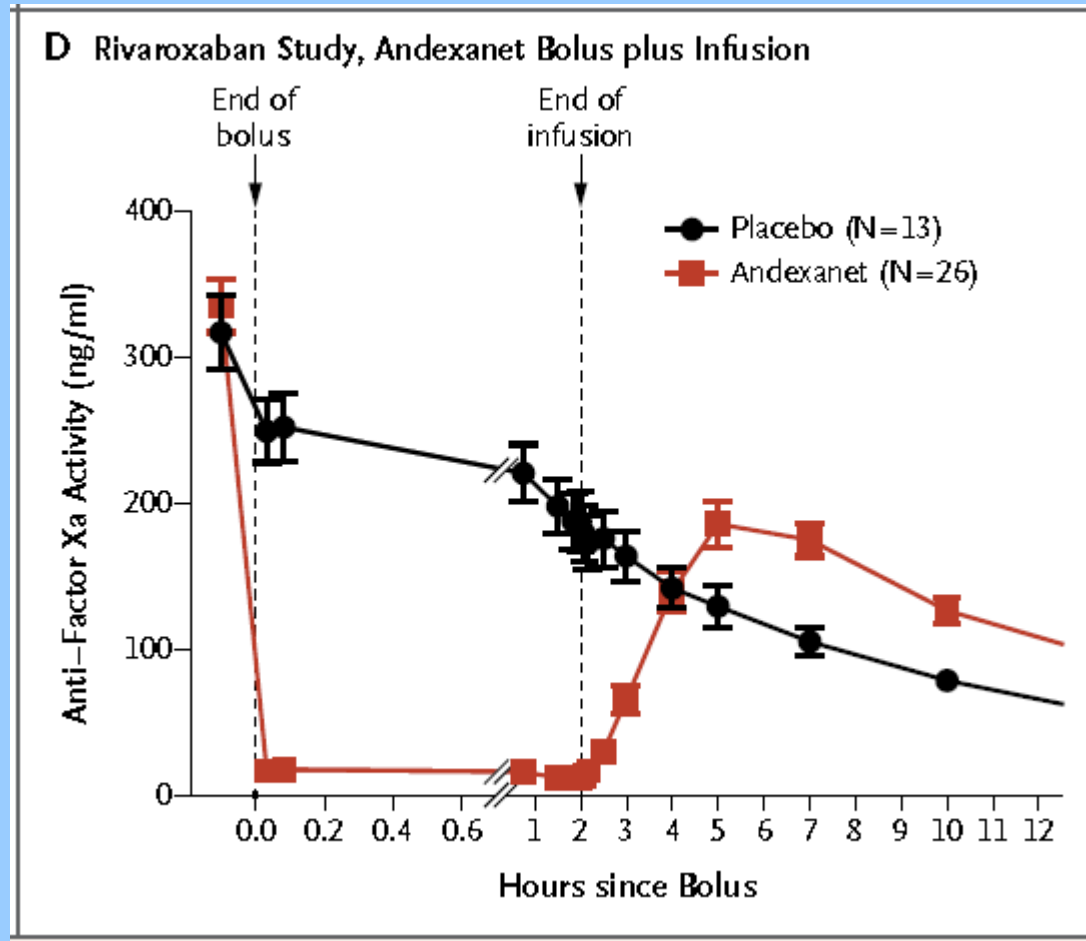
- Need to know
 - Dose and schedule, time last dose, weight & creatinine (calculate Cl_{CR})
- Need to measure
 - PT, APTT, and specific a-FXa assays
 - Prolongation PT > APTT
 - PT doubled at ~100ng/ml
 - APTT doubled at ~300ng/ml
- Normal PT & APTT = Low level drug (<50ng/ml) = most surgery can proceed
- Abnormal PT & Normal APTT = delay surgery if possible pending drug assay
- Abnormal PT & APTT = higher drug level so delay surgery if possible pending drug assay otherwise expect bleeding

Apixaban and acute surgery

- Need to know
 - Dose and schedule, time last dose, weight & creatinine (calculate Cl_{CR})
- Need to measure
 - PT, APTT, and specific a-FXa assays
- Clotting times minimally prolonged even at therapeutic apixaban levels so APTT/PT unhelpful and reliant on specific drug assay.
- Empiric delay in surgery according to expected/measured drug concentration
- No reversal strategy available
- Surgery often can be done with supportive management

Reversal Direct anti-Xa AC in development

Siegel DM et al NEJM 2015;373:2413-2424



Thank-you Questions

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