Management of Bleeding In the Medical Patient:

Anti-Coagulants and Anti-Platelet Drugs

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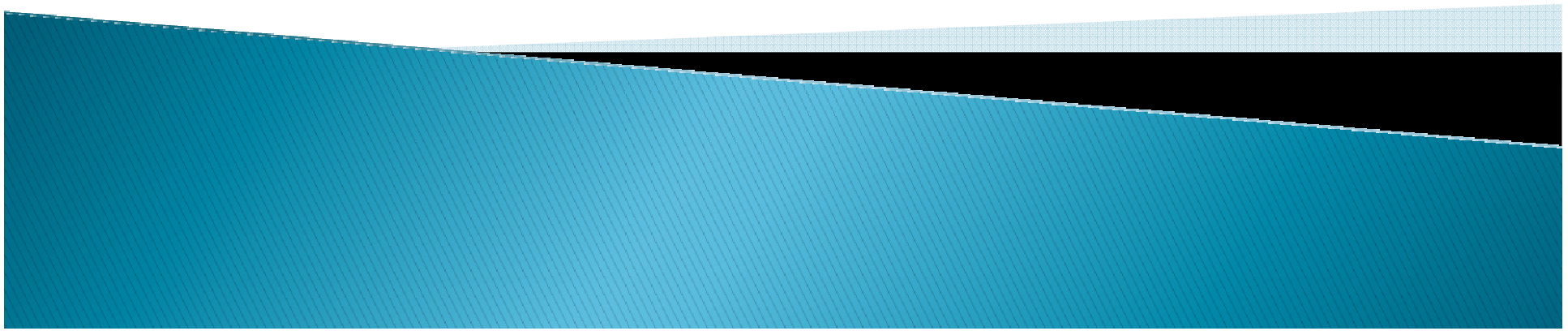
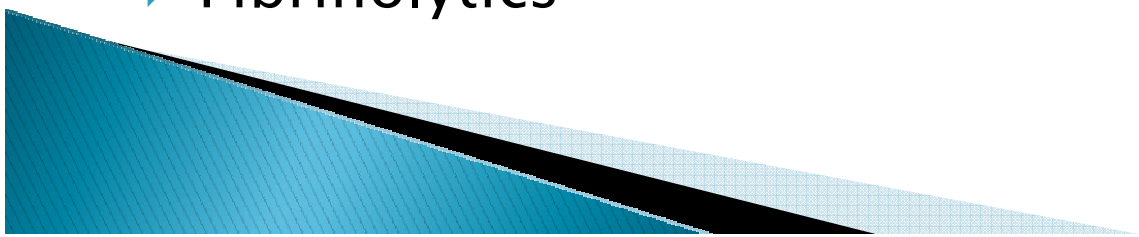
11th of May 2016



- AntiCoagulants
  - Heparin
    - Unfractionated Heparin
    - Low Molecular Weight Heparin
    - Fondaparinux
  - Vitamin K Antagonists (Warfarin)
  - NOACs/DOACs
    - Apixaban
    - Dabigatran
    - Edoxaban
    - Rivaroxaban
- AntiPlatelets
  - Aspirin
  - Clopidogrel
- Fibrinolytics



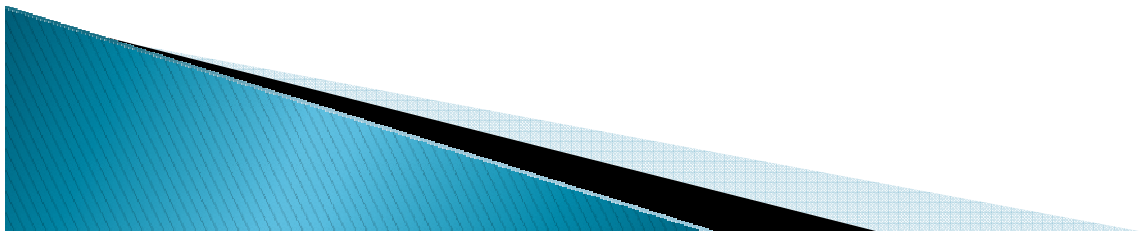
bjh guideline

Guideline on the management of bleeding in patients on antithrombotic agents

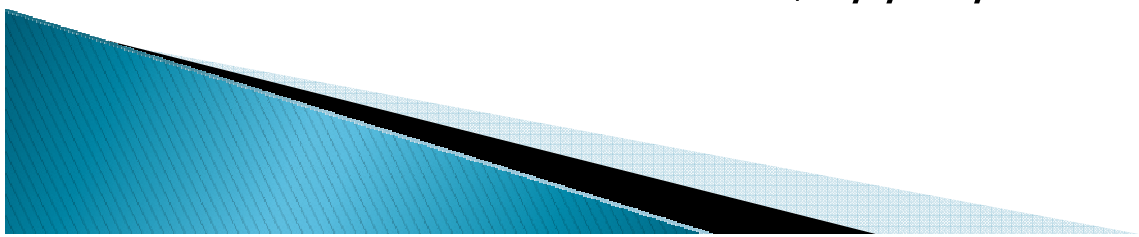
Mike Makris,[1,2] Joost J. Van Veen,[2] Campbell R. Tait,[3] Andrew D. Mumford[4] and Mike Laffan[5] on behalf of the British Committee for Standards in Haematology

British Journal of Haematology, 2012, **160**, 35–46

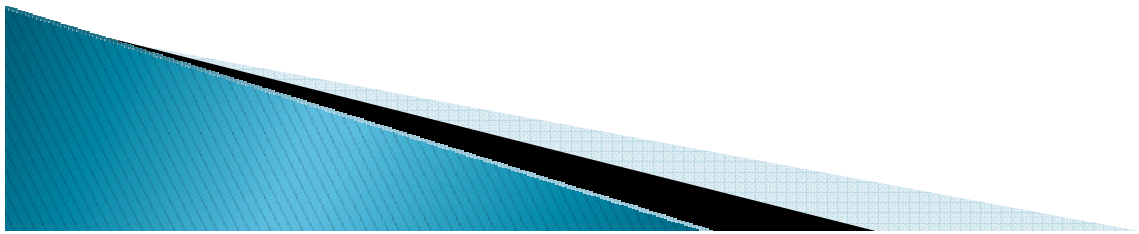
- General Non-Pharmacological Measures
  - Stop the Anti-Thrombotic Drug
  - Document
    - Dose & Timing of the last drug dose
    - Pre Existing Renal Impairment
    - Pre Existing Hepatic Impairment
  - Estimate the Half Life and length of functional defect induced by the drug
  - Assess the source of bleeding



- General Non-Pharmacological Measures Cont.
  - Request lab tests
    - FBC
    - PT/INR
    - aPTT
    - Fibrinogen
    - U&E's
    - LFT's
  - *Consider* specific laboratory test to assess the effect of the drug *if available/appropriate*
  - Correct haemodynamic compromise with IV fluids &/or RBC transfusion
  - Apply mechanical pressure *if possible/appropriate*
  - Consider using endoscopic, radiological or surgical measures *if available/appropriate*



- Unfractionated Heparin
  - Mechanism of Action
    - Binds to anti-thrombin causing a conformational change
      - Inactivates Thrombin
      - Inactivates Fxa
      - Also inhibits thrombin-induced activation of platelets, FV and FVIII.
  - T ½
    - 45-90 minutes at therapeutic IV doses
  - Elimination
    - Binds to Macrophages
      - Internalised and depolymerised
    - Binds to endothelial cells
      - Precludes anti-thrombin binding
    - At Higher doses these mechanisms become saturated and thus elimination is more reliant on renal function
  - Monitor with the aPTT



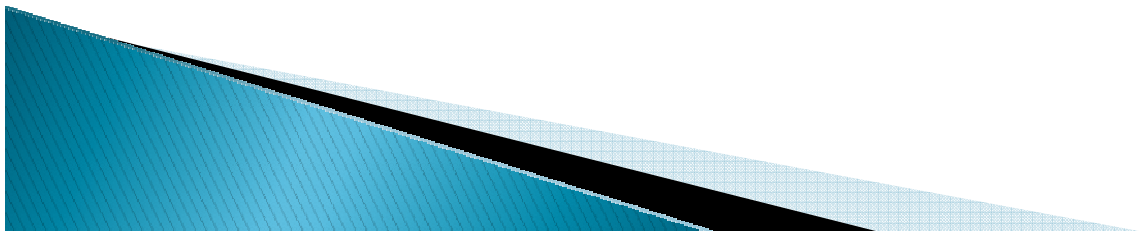
- Treatment or Prevention of Bleeding Associated with Unfractionated Heparin

  - **Majority of Circumstances**
    - Stopping infusion
    - General measures

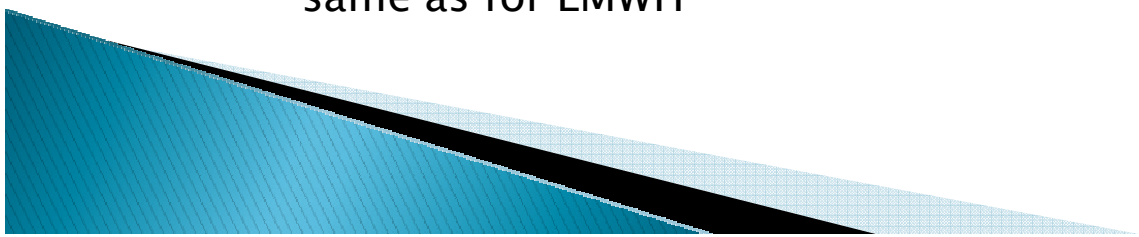
  - **If above measures insufficient and critical/ongoing bleeding Protamine Sulphate can be administered**

    - Forms a stable inactive salt with heparin
    - **Protamine dose may be calculated from the quantity of UFH administered in the 2 h prior to reversal using the assumption that 1 mg protamine neutralizes 80–100 units of UFH**
      - Eg Bleeding after a bolus dose of UFH of 5,000IU requires 50mg of Protamine (Maximum Dose)
    - The half-life of protamine is 7 min (shorter than UFH) thus, prolonged protamine administration may be necessary if UFH has been administered subcutaneously, causing entry into the circulation to be delayed
    - Can cause severe allergic reactions in ~10% of patients (give slowly over >5mins)
    - At higher doses may have significant anti-platelet & anticoagulant effect – Maximum dose 50mg

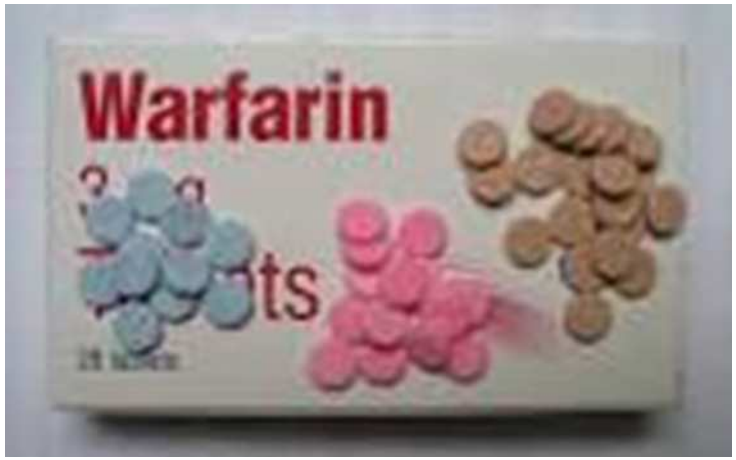
- Low Molecular Weight Heparin
  - Low molecular weight heparins (LMWH) are derived from UFH through chemical or enzymatic depolymerization
  - Mechanism of action
    - Binding leads to a conformational change of AT which accelerates its inhibition of activated factor X
  - T ½
    - Approximately 4hours
    - Dependent on renal function
    - Can be monitored with Anti-Xa level (not recommended as routine) – aPTT cannot be reliably used to monitor
    - Consider TEG in extremis



- Treatment or Prevention of Bleeding associated with LMWH
  - Majority of Circumstances
    - Stopping infusion
    - General measures
- If above measures insufficient and critical/ongoing bleeding/correction of anticoagulation required
- **If within 8 hr of LMWH administration** :
- Protamine Sulphate can be administered
  - Reverses ~60% of LMWH
  - Give 1mg of Protamine per 100 iu of LMWH
  - Maximum dose of 50mg
  - >8hr post administration of LMWH consider smaller doses of Protamine
  - *Consider (& discuss with local haematologist)* rFVIIa if
    - Continued life-threatening bleeding despite protamine sulphate
    - + time frame suggests there is residual effect from the LMWH contributing to bleeding
  - Management of bleeding of patients on Fondaparinux is essentially the same as for LMWH

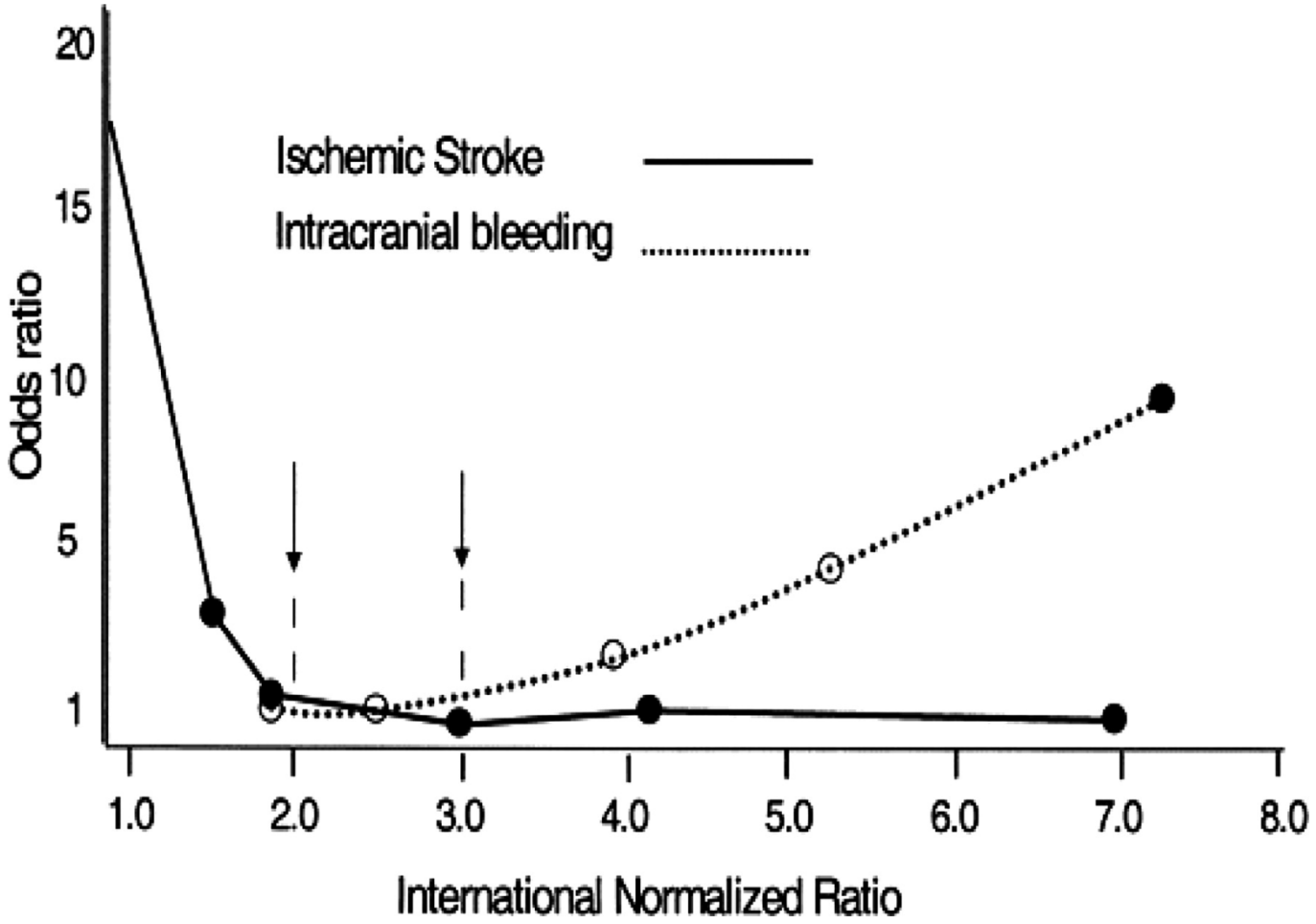


- Vitamin K Antagonists/Warfarin



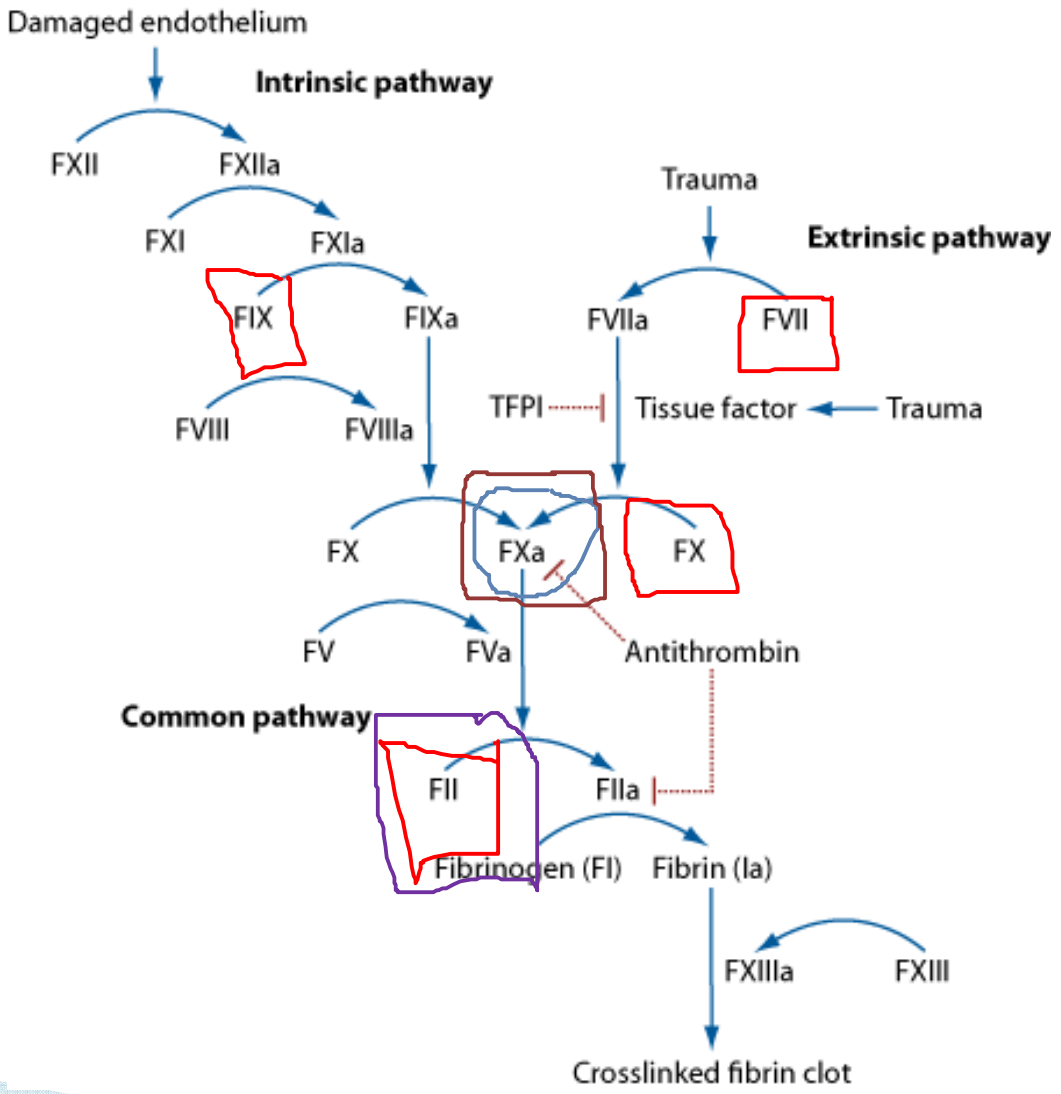
- Warfarin is an effective drug…

… But Only When In Therapeutic Range

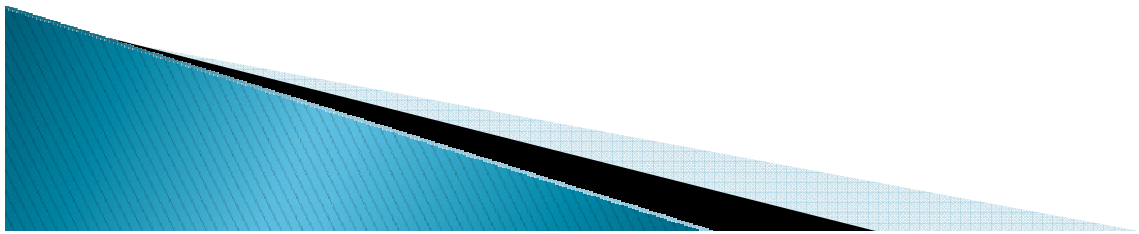


Ann Intern Med 1994;**120**:897–902

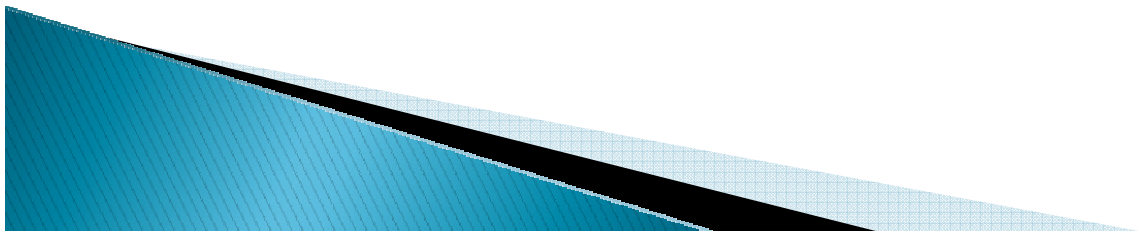
Mean T ½ is 40 hrs (20–60hrs)



- Major Life threatening/Ongoing Bleeding on Warfarin
  - 4 Factor PCC (F II, VII, IX, X) Octaplex (or Beriplex)
    - 25-50 iu per Kg
    - Administered urgently/promptly
      - Especially in setting of intracranial haemorrhage
  - *In Addition*
    - 5-10mg of Vitamin K IV to be administered promptly
      - rFVIIa is NOT recommended

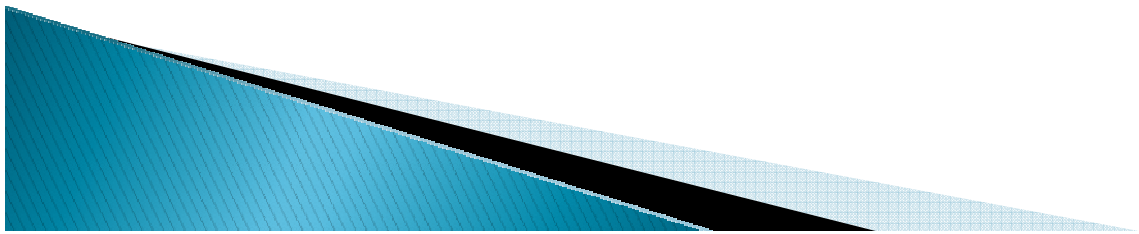


- For Non-Major Bleeding
  - General measures
  - Mechanical compression
  - 1-3 mg intravenous vitamin K IV or oral



- Patients with an international normalized ratio (INR) > 5.0 but who are not bleeding
  - Withold 1-2 doses of warfarin
  - Reduce maintenance dose
  - The cause of the elevated INR should be investigated

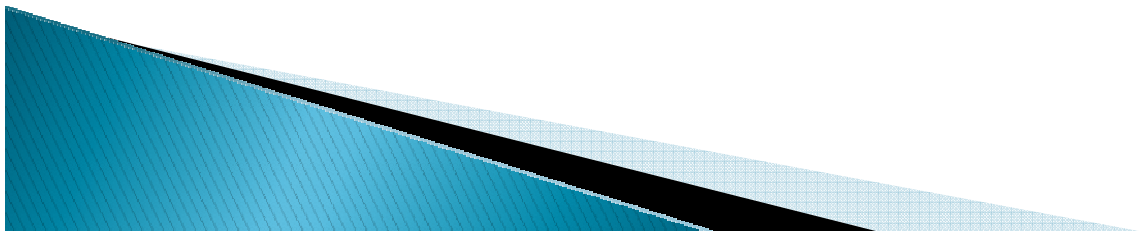
- Asymptomatic patients with an INR of >8.0 but who are not bleeding
  - Receive 1-5 mg of oral vitamin K orally
  - The INR should be rechecked the following day in case an additional dose of vitamin K is required
  - Again the cause of the elevated INR should be investigated



- For surgery/procedures that requires reversal of warfarin and that can be delayed 6–12 h
  - Correct the INR by giving intravenous vitamin K.

- For surgery/procedures that requires reversal of warfarin and which cannot be delayed for vitamin K to have time to take effect, the
  - Correct the INR by giving
    - PCC
    - *And* intravenous vitamin K

  - PCC should Not be used to enable elective or non-urgent surgery/procedures



- The ‘DOACs’
  - Dabigatran – *Pradaxa*
  - Rivaroxaban – *Xarelto*
  - Apixaban – *Eliquis*
  - Edoxaban – *Lixiana*

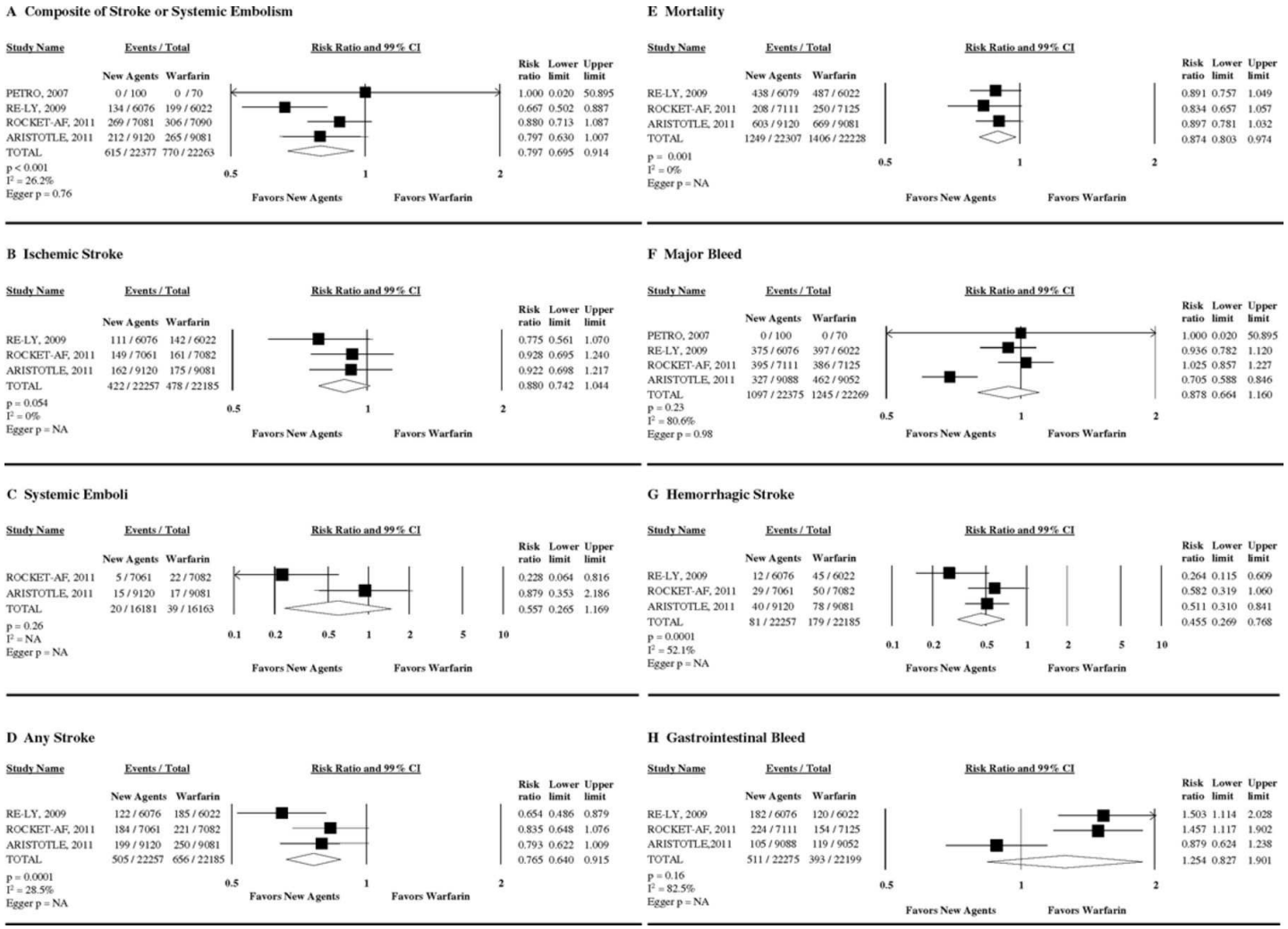
Feature	Warfarin	New agents
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food effect	Yes	No
Interactions	Many	Few
Monitoring	Yes	No
Offset	Long	Shorter

- Note All the NOACs have *Only been compared to Warfarin* in the landmark Registration studies

- Comparison between studies is difficult due to inherent differences in study design including, blinding status, control group parameters, inclusion and exclusion criteria

- There have been no large head to head studies

Forest plots comparing newer agents vs warfarin - AF studies.



Baker W L , and Phung O J Circ Cardiovasc Qual Outcomes. 2012;5:711-719