# Reversal of Warfarin-Induced Hemorrhage in practice.

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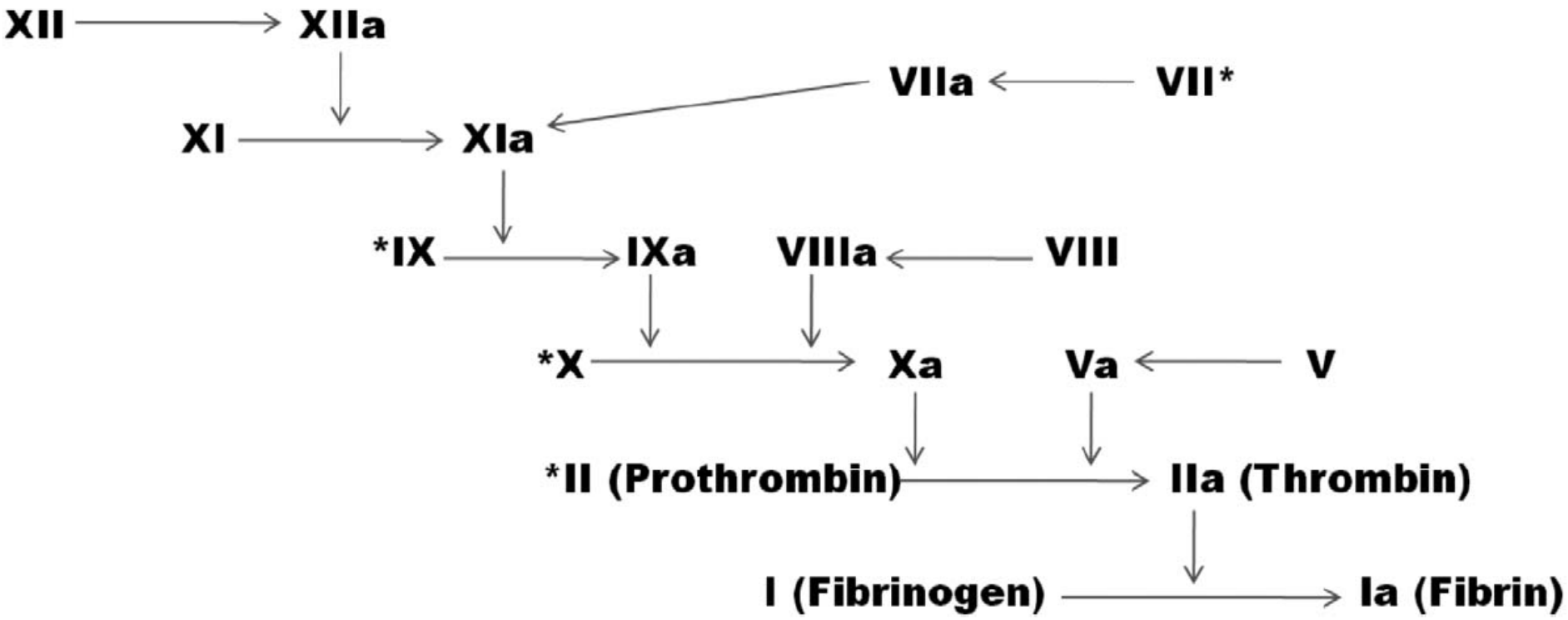
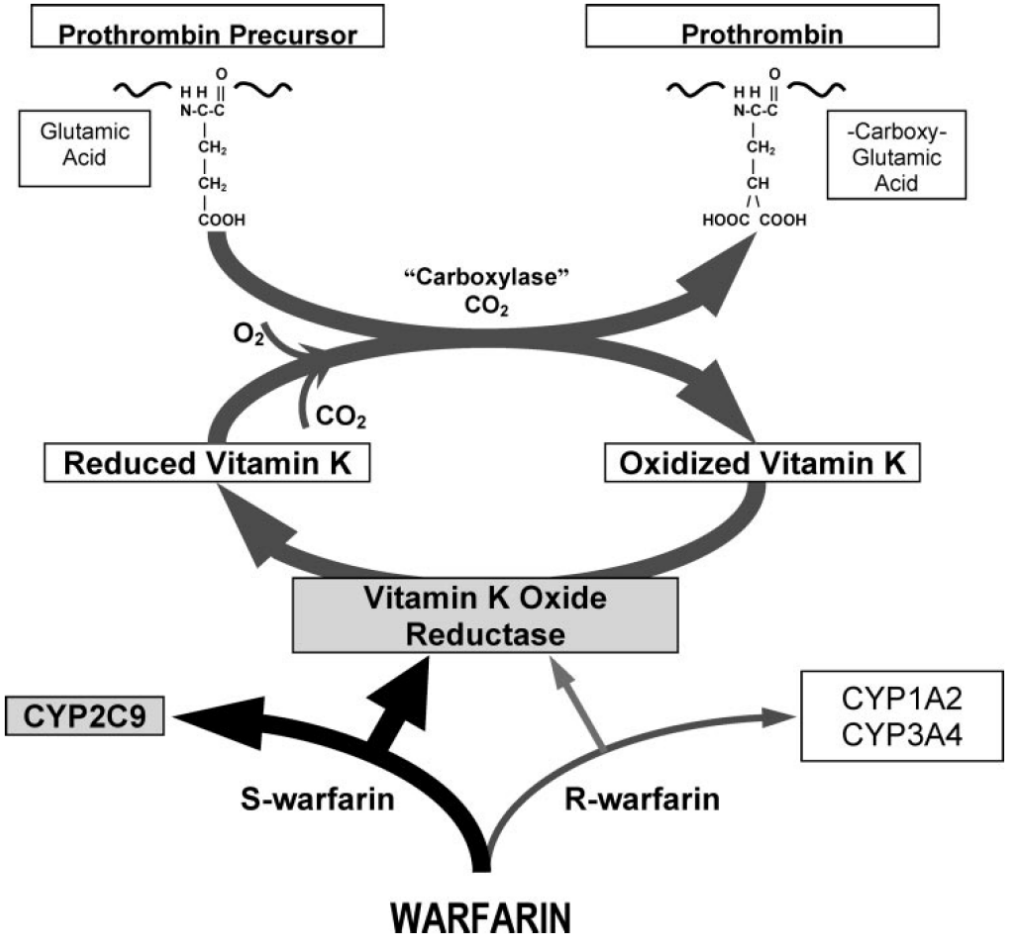
Action mechanism of Warfarin (Coumadin): **Vitamin K** dependant coagulation factors (II, VII, IX, X, protein C, S, Z)



# Action mechanism of Warfarin (Coumadin): Inhibition of **Vitamin K** dependant coagulation factors.



# Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (**ISCOAT**)

| | |
|---|---|
| **Venous thromboembolism** | 892 (32·5%) |
| **Non-ischaemic heart disease** | 661 (24·1%) |
| Dilated cardiomyopathy | 136 |
| Atrial fibrillation | 462 |
| Endocavitary thrombosis | 24 |
| Other | 39 |
| **Ischaemic heart disease** | 403 (14·7%) |
| Post-myocardial infarction | 144 |
| After ACBP or PTCA | 135 |
| Other | 124 |
| **Atrial vascular disease** | 281 (10·2%) |
| Peripheral | 48 |
| Cerebral | 93 |
| After vascular surgery | 80 |
| After peripheral emboli | 44 |
| Other | 16 |
| **Heart-valve prosthesis** | 296 (10·8%) |
| Biological | 34 |
| Mechanical | 262 |
| **Heart-valve disease** | 183 (6·7%) |
| **Other diagnoses** | 29 (1·1%) |
| **Total** | 2745 |

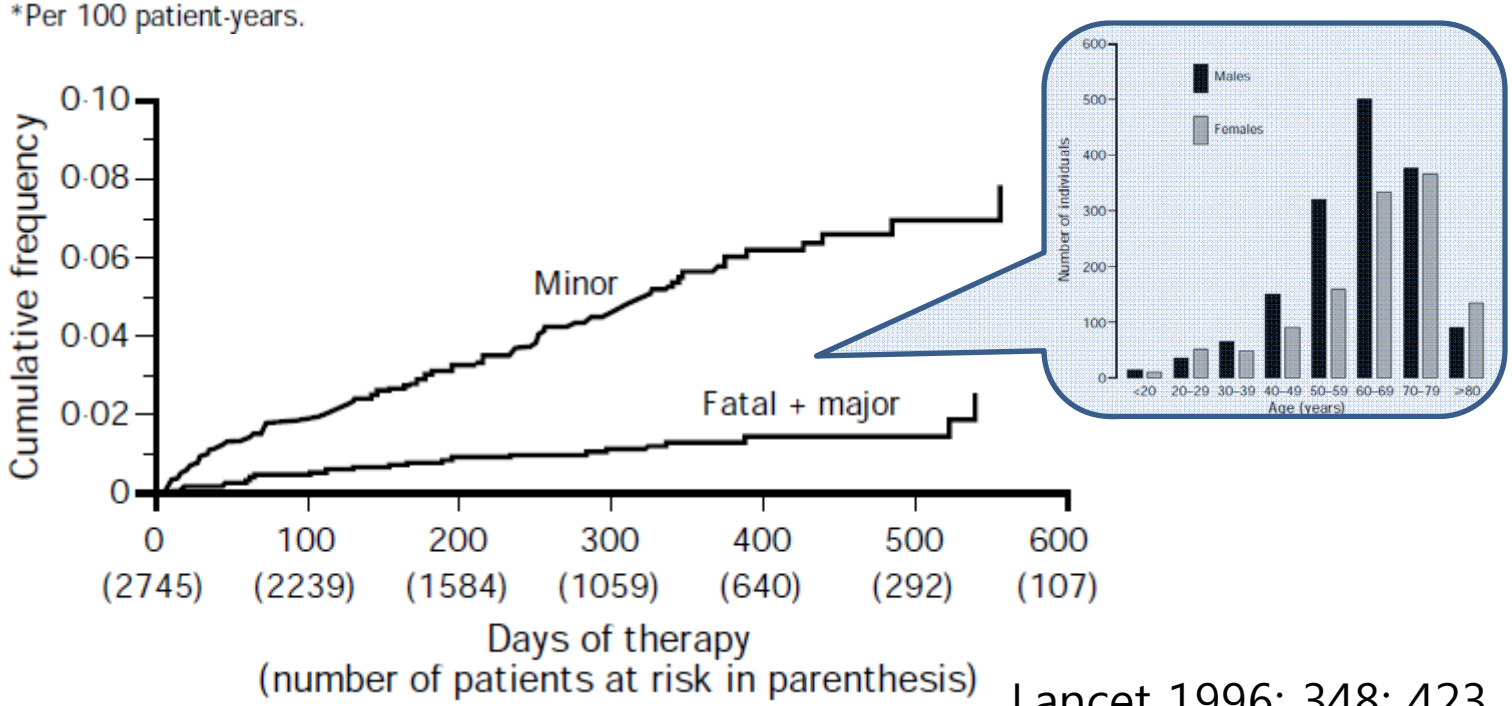
ACBP=aorto-coronary bypass, PTCA=percutaneous transluminal coronary angioplasty.

Lancet 1996; 348: 423

# ISCOAT

| | | | |
|---|---|---|---|
| **All** | 153 (7·6)* | **Minor** | 125 (6·2) |
| **Fatal (all cerebral, 4 women)** | 5 (0·25) | 32 haematuria<br>25 proctorrhagia<br>16 uterine bleeding<br>14 gastrointestinal bleeding<br>14 haematoma<br>13 large bruising<br>2 epistaxis<br>9 other or multiple sites<br>6 with two minor bleeding episodes<br>4 with three minor bleeding episodes | |
| **Major** | 23 (1·1) | | |
| 7 digestive | | | |
| 5 ocular (2 with diabetic retinopathy) | | | |
| 4 cerebral | | | |
| 3 haemarthrosis | | | |
| 2 haemoptysis | | | |
| 1 retroperitoneal | | | |
| 1 haematuria | | | |

*Per 100 patient-years.




Lancet 1996; 348: 423

# Reversal methods against warfarin.
# -depended on the level of INR and severity of bleeding-

1. Omission of a dose of warfarin.
   begin to correct within 24~36 hr, fully effect after 3~5 d.
2. Oral administration of Vitamin K.
   directly activate Vitamin K dependant factors within 24 hr.
3. IV administration of Vitamin K.
   more rapid action (within 5~6 hr).
4. Fresh frozen plasma (FFP).
   immediate action.
5. PCC (Prothrombin Complex Concenturation)
   3 factor or 4 factor PCC.
   immediate action.

# Reversal methods against warfarin.
# -Side effects of vitamin K, FFP and PCC-

1. IV administration of Vitamin K.
   **severe anaphylactoid reaction** when administered IV.
   AHA/ACC, ACCP recommend the use of IV Vitamin K be limited to life-threatening bleeding.
2. Fresh frozen plasma (FFP).
   factor II, VII, X: but it lacks factor IX.
   not concentrated (have to use a large volume).
   ABO matching, thawing… (in real field, it takes 5~6 hr).
   various viral infection, transfusion related acute lung injury.
3. PCC (Prothrombin Complex Concenturation)
   3 factor or 4 factor PCC: II, IX, X with/out VII.
   no need to thawing and ABO matching.
   applicable to quantified amount for warfarin reversal.
   thromboembolic event.

# Reversal methods against warfarin.
# -FFP *Vs.* PCC-

| | FFP | PCC |
|---|---|---|
| concentration | 4% of PCC<br>(eg. 2~4 L of FFP Vs.<br>20~50 U/kg of 4F PCC) | As small amount as 1/25 of FFP[1]. |
| Onset time (INR normalization) | Within 15 min (mean INR=1.3) when PCC was administered. | 4~5 times more rapid than those of treated with FFP[2]. |
| Safety for viral infections. | | More safe[3]. |


1) Thromb Haemost. 1997;77:477–480.
2) Clin Lab Haematol. 1998;20:363–367.
3) Thromb Haemost. 2007;98:790–797.

# Reversal methods against warfarin. New therapeutic options for bleeding. -rFVIIa *Vs.* FEIBA-

| | Recombinant factor VIIa | Factor eight inhibitor bypass activity |
|---|---|---|
| components | Pure factor VII | Activated PCC, mainly VIIa. small amount of factor II, IX, X. |
| cost | Expensive. | Not expensive. |
| usage | 10~90 mg/kg, combined with FFP, vitamin K IV. | Combined with 10mg vitamin K IV.<br>12 times faster than FFP. |
| Action duration | 2.5~3 Hr. | |

# Peri-operative anticoagulation.

## Recommendation

- For some invasive procedures, such as joint injections (Thumboo & O'Duffy, 1998), cataracts (Dunn & Turpie, 2003) and certain endoscopic procedures (including mucosal biopsy) (Eisen et al, 2002), warfarin does not need to be stopped.
- If bridging therapy is given it is now usually with LMWH. This is effective in VTE prevention but there are fewer data for using LMWH in patients with AF or a mechanical heart valve (MHV) and it appears to be less effective than warfarin in MHV patients (Chan et al, 2000).

Logistically, warfarin should not be taken for 5 d before surgery and, if possible, the INR should be determined the day before surgery to allow the administration of oral vitamin K if the INR is ‡1.5, so reducing the risk of cancellation. In patients who are receiving pre-operative bridging with LMWH the last dose should be at least 24 h before surgery and some recommend that the last dose is halved for high risk surgery (Douketis et al, 2008). The INR should be checked on the day of surgery and warfarin can be resumed, at the normal maintenance dose, the evening of surgery or the next day if there is adequate haemostasis (Douketis et al, 2008).

# Peri-operative anticoagulation.

## Recommendation

- Pre-operative bridging carries a low risk of bleeding but the use of post-operative bridging requires careful consideration due to the high risk of bleeding. We recommend that post-operative bridging should not be started until at least 48 h after high bleeding risk surgery (1C).
- Patients with VTE more than 3 months earlier can be given prophylactic dose LMWH (or a suitable alternative) rather than bridging therapy (2C).
- Patients with low risk AF (no prior stroke or TIA) do not require bridging therapy (2C).
- Patients with a bileaflet aortic MHV with no other risk factors do not require bridging (2C).
- Patients with a VTE within the previous 3 months, patients with AF and previous stoke or TIA or multiple other risk factors, and patients with a mitral MHV should be considered for bridging therapy (2C).

# INRs > 5.0 and > 8.0 (or 9.0) in Non-bleeding patients.

## Recommendation

- Patients with an INR >5.0 but who are not bleeding should have 1–2 doses of warfarin withheld and their maintenance dose should be reduced (1B). The cause of the elevated INR should be investigated (1C).
- Patients with an INR >8.0 (or 9.0) should receive 1–5 mg of oral vitamin K (1B).

There is an almost exponential increase in the risk of bleeding with increasing INR.

Older age, uncontrolled hypertension, diabetes, renal or liver failure, previous GIT or cerebral bleed and use of anti-platelet medication, are associated with a higher risk of bleeding.

In the non-bleeding patient, oral administration of vitamin K is preferred over the intravenous route as equal correction is achieved at 24 h.

Baker et al (2006) observed good correction with 2.5 mg of oral vitamin K for patients with INR of 8.0~12.0 and 5 mg for those with INR >12.0.

The decision to give vitamin K to patients with an INR of <8.0 is more controversial.

# Emergency surgery for patients on warfarin.

## Recommendation

- For surgery that requires reversal of warfarin and that can be delayed for 6–12 h, the INR can be corrected by giving intravenous vitamin K.
- For surgery that requires reversal of warfarin and which cannot be delayed, for vitamin K to have time to take effect the INR can be corrected by giving PCC and intravenous vitamin K. PCC should not be used to enable elective or non-urgent surgery (2C).

# Major bleeding.

## Recommendation

- All hospitals managing patients on warfarin should stock a licensed four-factor prothrombin complex concentrate (1C).
- Emergency anticoagulation reversal in patients with major bleeding should be with 25–50 u/kg four-factor prothrombin complex concentrate and 5 mg intravenous vitamin K (1B).
- Recombinant factor VIIa is not recommended for emergency anticoagulation reversal (1B).
- Fresh frozen plasma produces suboptimal anticoagulation reversal and should only be used if prothrombin complex concentrate is not available (1C).

Major bleeding, in terms of anticoagulation reversal, can be defined as limb or life-threatening bleeding that requires complete reversal within 6–8 h.

Although all PCCs contain factors II, IX and X, there is significant variability in their factor VII (FVII) content. PCCs with little FVII (the so called 3-factor PCCs) produce poor correction of the INR and are not recommended (Holland et al, 2009).

# Non-major bleeding.

## Recommendation

- Anticoagulation reversal for non-major bleeding should be with 1–3 mg intravenous vitamin K (1B).

Intravenous vitamin K produces a more rapid correction of the INR than oral vitamin K and should be used in preference in the bleeding patient. Significant correction of the INR is seen within 6–8 h after intravenous vitamin K use (Watson et al, 2001).

Vitamin K should not be given subcutaneously due to inconsistent correction and intramuscular administration should be avoided due to the risk of intramuscular haematoma in the anticoagulated patient.

Anaphylactoid reactions following intravenous vitamin K have been reported following the rapid administration of the older formulation, which contained polyethoxylated castor oil, but this risk is lower with the currently used micelle formulation (Makris et al, 2010).

Patients bleeding at therapeutic levels of anticoagulation should be investigated for the source of bleeding.

# Head injury in patients on warfarin.

## Recommendation

- All patients on warfarin presenting to Accident and Emergency departments with head injury should have their INR measured as soon as possible (1C).
- A lower threshold for performing a head CT scan should be used for patients on warfarin (2C).
- Patients on warfarin presenting with a strong suspicion of intracerebral bleed should have their anticoagulation reversed before the results of any investigations (2C).

Delayed intracranial bleeding can occur in patients on warfarin even when the initial CT scan is normal (Cohen et al, 2006). In view of this, patients with a supra-therapeutic INR should have this corrected into the therapeutic range with oral vitamin K. It is suggested that the INR is maintained as close to 2.0 as possible for the 4 weeks after a significant head injury and a normal CT scan.

경청해주셔서
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