

Seminar:

Cardiovascular system II. - anticoagulants

Pharmacist's role in providing pharmaceutical care to patients with anticoagulants

Patients with warfarin

Patients with new oral anticoagulants (NOACs)

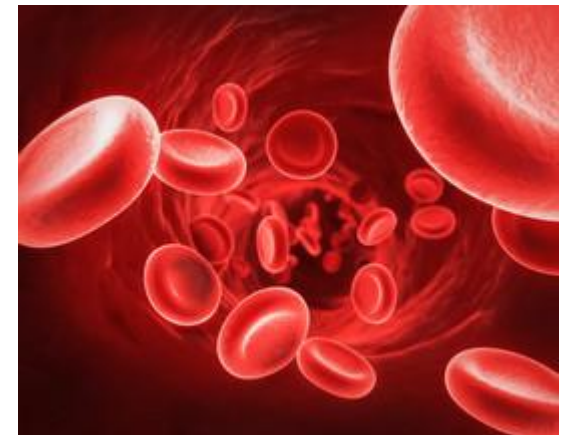
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ANTICOAGULANT TREATMENT

- **Warfarin**
- **Low Molecular Weight Heparins (LMWHs)**
- **New Oral AntiCoagulants - NOACs**
 - **Dabigatran**
 - **Rivaroxaban**
 - **Apixaban**



Warfarin

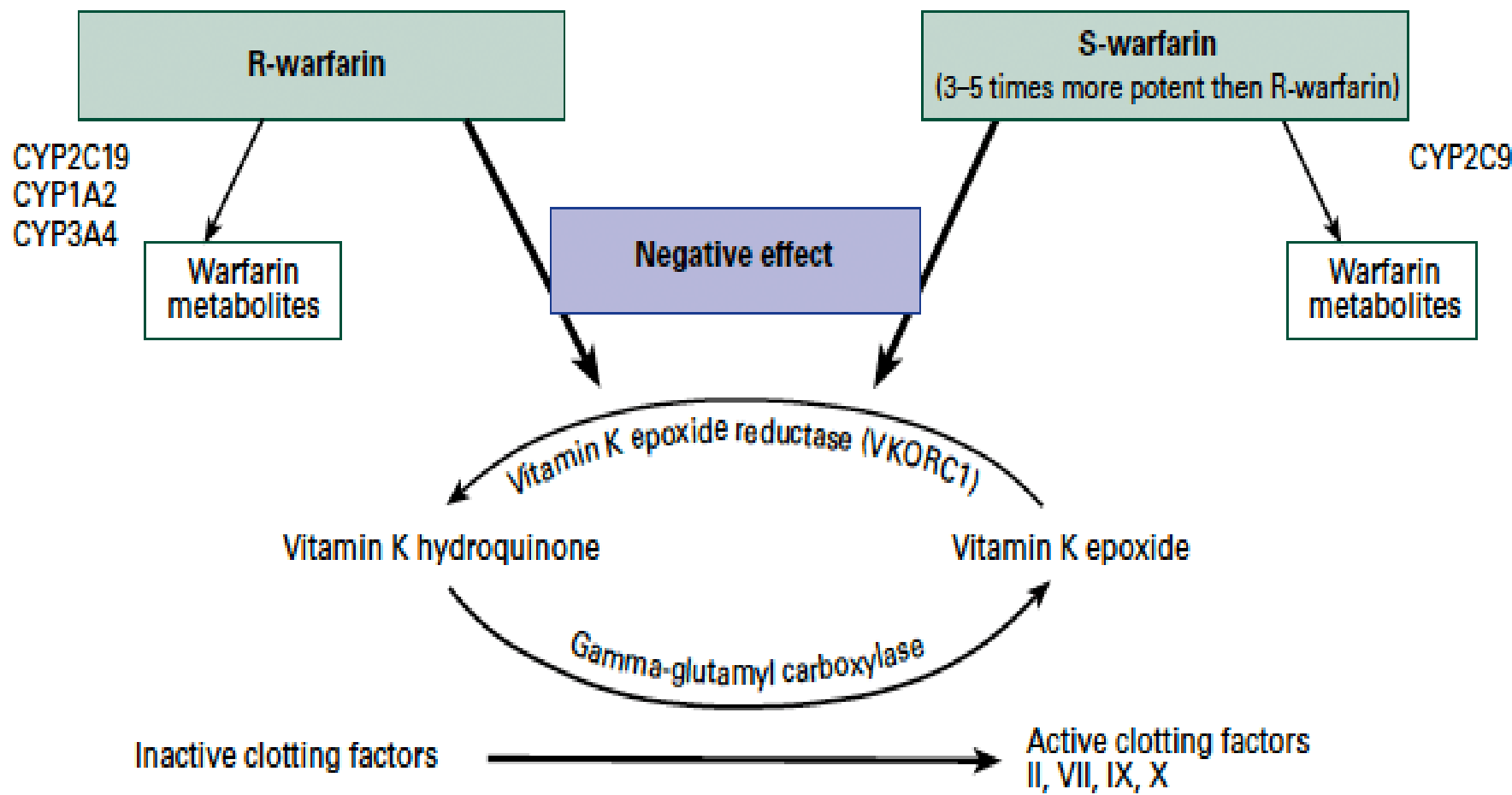
- vitamin K antagonist
- anticoagulant effect by decreasing of activity of: protrombin, factors VII, IX, X
- racemic mixture of 2 enantiomers:
 - **S-warfarin** is 2-5 times more potent than **R-warfarin**

Warfarin pharmacokinetic

- immediate and complete absorption from GI tract - oral administration
- nearly completely bound to plasma proteins (albumin): 99 %
- the maximum plasma concentration: til 90 min.
- T1/2: 34 - 45 h.
- anticoagulant effect begins: til 60 h.
 - → **latency of warfarin effect**
- anticoagulant effect persists: 72 h.
 - → **long persisting effect after warfarin withdrawals**



- liver metabolism : til 120 h.
- S- and R-warfarin are metabolized differently in the liver:
 - S is metabolized primarily by **CYP 2C9**
 - R is metabolized by **CYP 1A2, CYP 2C19, CYP 3A4**



Warfarin indications

Myocardial infarction

Pulmonary embolism

Trombophilia

Deep vein thrombosis

Prevention of thromboembolism in atrial fibrillation

Thromboembolic stroke prophylaxis



Pharmacist's role in providing pharmaceutical care to patients with warfarin

Warfarin side effects

Any signs of an allergic reaction to warfarin:

- **urticaria, difficult breathing, swelling of your face, lips, tongue, or throat**

Warfarin increases patient's risk of bleeding, any signs of bleeding:

- **petechia**
- **unusual headache, feeling very weak or dizzy**
- **swelling (edema), pain**
- **bleeding gums, nosebleeds**
- **bleeding from needle injections that will not stop**
- **heavy menstrual periods or abnormal vaginal bleeding**
- **blood in your urine, bloody or tarry stools**
- **coughing up blood or vomit that looks like coffee grounds**

Group of patients with increased risk of bleeding

- high BP or serious heart disease
- kidney disease
- cancer or low blood cell counts
- an accident or surgery
- stomach bleeding, intestines bleeding
- a stroke
- age of 65 or older

Side effects always consult your doctor or pharmacist.

Recommend seeking emergency help if patient have any bleeding that will not stop!

Teratogenicity

- warfarin readily **crosses placenta**

- information for women patients:

If you are not pregnant, use effective birth control to prevent pregnancy while taking warfarin and for at least 1 month after your last dose.

Tell your doctor right if you become pregnant.

Breast-feeding a baby

- it is not known whether warfarin passes into breast milk

Dosage of warfarin

- take warfarin at the same time every day, with or without food – once a day, in the morning
- **never take a double dose**
- initial dose: **2 to 5 mg orally once a day**
- maintenance dose: **2 to 10 mg orally once a day**
- dosage should not be the same in various days
- necessity of daily dose oscillates individually

Missing a dose of warfarin

- information for patients
 - *take the missed dose as soon as you remember*
 - *if you usually take warfarin in the morning and forget to take it at your normal time, take it as soon as you remember and continue as normal*
 - *if you forget to take your dose of warfarin in the evening but remember before midnight on the same day, take the missed dose*
 - *skip the missed dose if it is almost time for your next scheduled dose*

Color coding of warfarin tablets - US

- in the United States, manufacturers of both brand and generic warfarin have agreed to make each strength a consistent color

Helpful Mnemonics:

„Please Let **G**ranny **B**rown **B**ring **P**eaches **T**o **Y**our **W**edding“

Tablet strength	Tablet color
1 mg	Pink
2 mg	Lavender (light purple)
2.5 mg	Green
3 mg	Tan
4 mg	Blue
5 mg	Peach (light orange)
6 mg	Teal (blue-green)
7.5 mg	Yellow
10 mg	White

Warfarin overdosing

- immediate warfarin withdrawal
- **carbo medicinalis**
- elimination of warfarin effect :
 - **concentrate of protrombin complex**
 - warfarin antidote: **vitamin K (phytomenadiol)**

Factors influencing stability of anticoagulant therapy

I. Patient's compliance

II. Warfarin interactions

III. Non-pharmacological influence

I. Patient's compliance

- adherence to terms of INR monitoring
 - beginning of warfarin treatment: INR control **2 – 3x a week**
 - ongoing warfarin treatment: INR control **once a 4 - 6 weeks**
 - long-term ongoing warfarin treatment: INR control **once a 12 weeks**

INR monitoring

INR values:

- healthy person who is not taking a blood thinner: **INR 0,8 – 1,2**
- people taking blood thinners: **INR 2 – 3**

Information for patient:

If your value of INR is too high, it may increase your risk for uncontrollable bleeding.

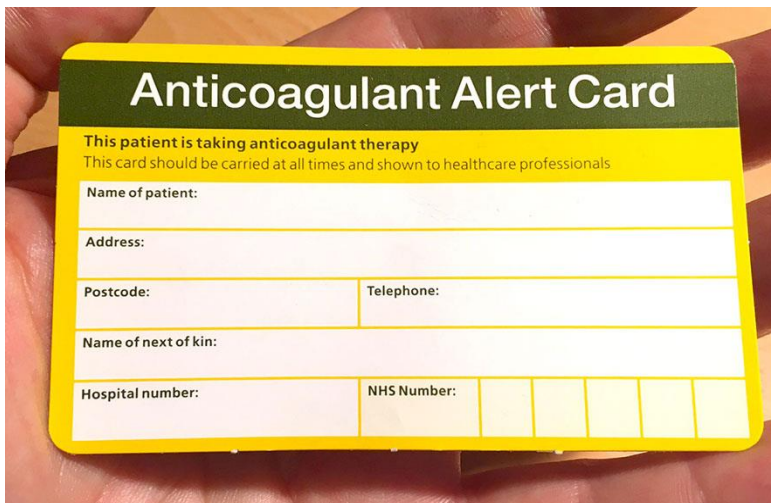
If your value of INR is too low may put you at risk for a blood clot or stroke.

Quality of INR control

- efficacy of warfarin is limited by quality of INR control:
 - multiple food and drug interactions
 - variable pharmacodynamic / pharmacokinetic
 - narrow therapeutic window (INR 2 – 3)
 - regular monitoring and dose adjustment

- proper drug using

- patient receive „warfarin / anticoagulant alert card“
- right instruction for warfarin using (from physician, from pharmacist)



- adherence to diet limitation
- inform also other physicians, that patient use warfarin
- avoid cutting yourself while taking anticoagulant medication because of the risk of excessive bleeding
- take care when shaving and brushing your teeth
- wear protective clothing when gardening, sewing or playing contact sports
- use insect repellent to avoid insect bites

- because of the risk of bleeding, dose of warfarin may need to be lowered or stopped a few days before having an operation or dental work
- BEWARE: random using of other various drugs
- BEWARE: alcohol excess



**Most people
take
Warfarin
for life**



**Tell people
you are on
warfarin**

II. Warfarin interactions

- **S-warfarin** metabolized primarily by **CYP 2C9**
- **R-warfarin** metabolized primarily by **CYP 3A4, CYP 1A2, CYP 2C19**

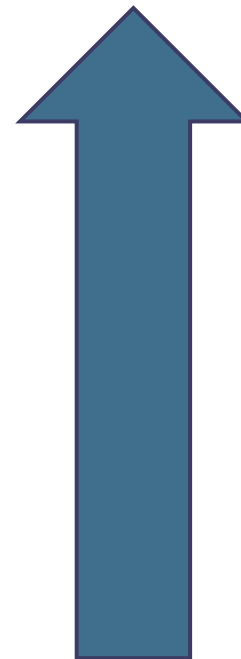
- aspect of isomer effectiveness:
 - high-risk are drugs from group of **inhibitors CYP 2C9**

- aspect of high of plasmatic concentration:
 - higher plasmatic concentrations have **R-warfarin**

Drug – drug interactions

Drugs, that can increase anticoagulant effect or risk of bleeding:

- Amiodaron
- Cimetidine
- Levothyroxine
- Omeprazole (PPI)
- Laxatives (senna concentrates)
- Phenytoin
- Quinidine
- Quinine
- Ibuprofen



**Anticoagulant
effect**

Safe pharmacotherapy in patients with warfarin

Analgetic drugs

- **metamizol**
- **paracetamol**
- **opiates**
- **tramadol**
- in the case of necessity of NSAIDs: **diclofenac**
 - **pantoprazol**

Antipyretic drugs

- **metamizol**
- **paracetamol**

Antibiotics

- **azitromycin, spiramycin**
- **penicillins**
- **cefalosporins**
- **ciprofloxacin, ofloxacin**
- **nitrofurantoin**

Proton pump inhibitors (PPI)

- **pantoprazol**

III. Non-pharmacological influence

Herbal drugs and other aspects, that can increase anticoagulant effect or risk of bleeding

- alcohol excess
- Koenzym Q10
- **Herbal products**
 - Chamomilla recutita
 - Allium sativum - garlic
 - Ginkgo biloba
 - Panax ginseng
 - Salvia officinalis
 - cranberry
- Fever
- Inappetence, malnutrition
- Diarrhea
- Hyperthyreosis
- Liver insufficiency

III. Non-pharmacological influence

Herbal drugs and other aspects, that can decrease anticoagulant effect or risk of blood clot

- **foods that are rich in vit. K**
- **Smoking**
- **Herbal products**
 - **Hypericum perforatum**
 - **Thea sinensis**
- **Hypothyreosis**

Low Molecular Weight Heparins (LMWHs)

- predictable level of anticoagulation
- monitoring: routine measurement of anti-Xa levels is **not indicated**
 - except in the setting of:
 1. renal failure
 2. obesity
 3. gravidity
 4. children therapy

LMWH indication

Venous Thromboembolism (deep vein thrombosis)

Deep vein thrombosis prophylaxis

Switching from warfarin

Anticoagulant treatment in gravidity

LMWH side effects

- Increased bleeding
- antidotum:
 - Protamin
 - Recombinant factor VII a
- Heparin induced trombocytopeny

After beginning with LMWH therapy always control of blood count!!!

LMWH subcutaneous self-application



New Oral AntiCoagulants - NOACs

Direct trombin inhibitor (DTIs)

- **dabigatran** (Pradaxa tbl)
 - twice daily

Oral direct factor Xa inhibitors (Anti-Xa inhibitors)

- **rivaroxaban** (Xarelto)
 - once daily
- **apixaban** (Eliquis)
 - twice daily
- **edoxaban** (Lixiana tbl)
 - once daily

NOACs indication

Stroke prevention in atrial fibrillation

Venous Thromboembolism (deep vein thrombosis)

Prevention of VTE (deep vein thrombosis) after total hip or knee replacement surgery

Pharmacological properties of NOACs

Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inh.
Pro-drug	Yes	No	No	No
Bioavailability, %	6%	66% without food up to 100% with food	50%	62%
Half-life, h	12–17 h	5–9 h (young) 11–13 h (elderly)	12 h	9–11 h
Time to maximum plasma concentration	0.5–2	2–4 h	1–4 h	1–2 h
Renal excretion	80%	35%	25%	50%
Liver metabolism	No	Yes	Yes	Minimal
Gastrointestinal tolerability	Dyspepsia	No problem	No problem	No problem
Absorption with food	No effect	+39% more	No effect	6–22% more
Intake with food?	No	Mandatory	No	No official recommendation
Dosing	Twice daily	Once daily	Twice daily	Once daily

NOACs - pros

- oral tablets
- uses of fixed-dosing
- wider therapeutic window
- absence of drug interactions
 - vs. apixaban
- no laboratory monitoring
- rapid onset of action

NOACs - cons

- miss a dose – risk of clot
- no agent for anti-Xa inhibitors
- reservations in patients with kidney disease
- high cost
- *Patient Alert Cards*

Patient Alert Card

Eliquis[®]
(apixaban)

Carry this card with
you at all times

Show this card to your pharmacist, dentist and
any other healthcare professionals that treat you.

Information for patients

- Take Eliquis[®] regularly as instructed. If you miss a dose, take it as soon as you remember and continue to follow your dosing schedule.
- Do not stop taking Eliquis[®] without talking to your doctor, as you are at risk of suffering from a stroke or other complications.
- Eliquis[®] helps to thin your blood. However, this may increase your risk of bleeding.
- Signs and symptoms of bleeding include bruising or bleeding under the skin, tar-coloured stools, blood in urine, nose-bleed, dizziness, tiredness, paleness or weakness, sudden severe headache, coughing up blood or vomiting blood.
- If the bleeding does not stop on its own, **seek medical attention immediately.**
- If you need surgery, inform your doctor that you are taking Eliquis[®].

I am under anticoagulation treatment
with Eliquis[®] (apixaban)
to prevent blood clots

Information for healthcare professionals

- Eliquis[®] (apixaban) is an oral anticoagulant acting by direct selective inhibition of factor Xa.
- Eliquis[®] may increase the risk of bleeding. In case of major bleeding events, it should be stopped immediately.
- Treatment with Eliquis[®] does not require routine monitoring of exposure. A calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations, e.g., overdose and emergency surgery (prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT) clotting tests are not recommended) – see SmPC.

Please complete this section or ask your doctor to do it

Name: _____

Birth Date: _____

Indication: _____

Dose: _____ mg twice daily

Doctor's Name: _____

Doctor's telephone: _____

PATIENT ALERT CARD

Pradaxa® Dabigatran etexilate

- Keep this card with you at all times
- Make sure to use the latest version

April 2014



Dear Patient,

Your doctor has initiated treatment with Pradaxa® (dabigatran etexilate). In order to use Pradaxa® safely, please consider the important information inside.

As this patient alert card contains important information about your treatment, please carry this card with you at all times to inform healthcare professionals about your intake of Pradaxa®.



Pradaxa®: Information for Patients

- Follow your doctor's instructions when taking Pradaxa®.
- Pradaxa® prevents clots by making your blood less "sticky". However, this may increase the risk of bleeding.
- In case of a bleeding event which does not stop spontaneously, immediately inform your doctor.
- If you fall or injure yourself during treatment, especially if you hit your head, please seek urgent medical attention. You may need to be checked by a doctor, as you may be at increased risk of bleeding.
- As Pradaxa® acts on the blood clotting system, most side effects are related to signs of bruising or bleeding. Signs and symptoms of bleeding events might be haematoma of the skin, tar stools, blood in urine, nose bleed, etc.
- If surgical or invasive procedures need to be performed, inform the treating physician about your intake of Pradaxa®.
- Do not stop the intake of Pradaxa® without talking to your doctor, as you are at risk of suffering from a stroke or other complications due to blood clot formation.
- In the case of bleeding, please contact your doctor before stopping the intake of Pradaxa®.
- Take Pradaxa® regularly as instructed and do not miss a dose.
- Inform your doctor about all medicines you are currently taking.

- Pradaxa® can be taken with or without food. The capsule should be swallowed whole with a glass of water, to ensure delivery to the stomach. Do not break, chew, or empty the pellets from the capsule since this may increase the risk of bleeding.

Pradaxa® Information for Healthcare Professionals

- Pradaxa® is an oral anticoagulant acting by direct thrombin inhibition and is eliminated predominantly via the kidney.
- In case of surgical or other invasive procedure, Pradaxa® needs to be stopped in advance (for details, see Summary of Product Characteristics).
- In case of major bleeding events, Pradaxa® must be stopped immediately.

- Since Pradaxa® is eliminated predominantly by the kidneys, adequate diuresis must be maintained. Pradaxa® is dialyzable, but there is limited clinical experience (for details and more advice to antagonize the anticoagulant effect of Pradaxa®, see Summary of Product Characteristics).

Please complete this section or ask your doctor to do it.

Patient Information

(Name of the patient)

(Date of birth)

(Indication for anticoagulation)

(Dosage of Pradaxa®)