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| **Module** | Management of VKAs (HCP) |
| **Topic** | The adverse effects of warfarin |
| **Audience** | Healthcare professional |
| **Type** | Core content |
| **Version** | 5 |

**1. What should I learn from this topic?**

The aim of this topic is to give you a practical understanding of the adverse effects of warfarin

By the end of this topic you should be able to:

1. Identify the common adverse effects of warfarin
2. Describe the action to be taken if a patient reports signs or symptoms of bleeding
3. State if warfarin can be taken in pregnancy or whilst breast-feeding
4. Describe the advice to be given to those having surgery or a dental procedure
5. List the relative contraindications to warfarin treatment

**2. Check your understanding**

Before you start reading this topic check how much you already know by taking a short quiz. You will have an opportunity to take the quiz again at the end of the module, where we will reveal the correct answers.

a) Which of the following are adverse affects associated with warfarin? (Select all that apply)

1. **Nose bleed**
2. **Skin rash**
3. **Skin necrosis**
4. Dry eye
5. Actinic keratosis
6. **Alopecia**

b) Which of the following can be evidence of bleeding? (Select all that apply)

1. **Black, tarry stools**
2. **Severe headache**
3. **Pink or brown urine**
4. **Severe bruising**

c) You should advise patients that if they notice a little bit of blood whilst brushing your teeth they should go straight to their nearest Emergency Department

True / **False**

d) What should an anticoagulated patient do if they have had a severe headache over a few days? (Please select the response that best answers this question)

1. They do not need to do anything
2. They should take a pain killing medicine (e.g. paracetamol tablets)
3. They should discuss it with their anticoagulant practitioner at their next clinic appointment
4. **They should go straight to their nearest Emergency Department**

e) What should an anticoagulated patient do if they notice that they have black, tarry stools? (Please select the response that best answers this question)

1. They do not need to do anything
2. They should take a laxative (e.g. senna tablets)
3. They should discuss it with their anticoagulant practitioner at their next clinic appointment
4. **They should go straight to their nearest Emergency Department**

f) If a woman takes warfarin in early pregnancy, it can damage the unborn child

**True** / False

g) A woman who takes warfarin should not breast-feed her infant

True / **False**

h) Patients should stop warfarin 48hours before a dental extraction

True / **False**

i) Renal impairment is a contraindication to warfarin

True / **False**

**3. What are the adverse effects of warfarin?**

The side effects of warfarin fall into two broad groups:

* Bleeding side effects
* Non-bleeding side effects.

**4. What are the bleeding side effects of warfarin?**

Bleeding is the most serious complication of treatment with oral anticoagulants. It is most common in the first month of treatment.

It occurs most frequently in the nose, mouth and the soft tissues, followed by GI and urinary tracts (often caused by previously undiagnosed lesions). Although infrequent in occurrence, intracranial bleeding resulting in haemorrhagic stroke represents the most frequent cause of fatal bleeding associated with warfarin.

QUIZ

How common is fatal and major bleeding with warfarin? Please select the value you think comes closest to the reported incidence.

Fatal bleeding

1. 2%
2. 6%
3. 15%

Major bleeding

1. 4%
2. 10%
3. 18%

Feedback ->

Are you surprised at this answer?

Although numerous studies have demonstrated that the risk of bleeding is directly related to the INR, determining the true incidence of bleeding complications associated with vitamin K antagonists has been difficult. Definitions of the occurrence and severity of bleeding have differed between studies, and there has been a lack of consistency in anticoagulant initiation doses used.

A review of bleeding complications associated with oral anticoagulant treatment reported bleeding rates of 0 – 4.8% for fatal bleeding and 2.4 to 8.1% for major bleeding1. In another review of observational studies, the average annual rates of fatal and major bleeding were 0.8% and 4.9% respectively2. A meta-analysis of 33 studies involving patients receiving OAT for the treatment of venous thromboembolism with more than six months of follow-up reported a rate of fatal major bleeding as 13.4%3.

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**If you would like to take a look at these published reviews of bleeding complications with anticoagulants, here are the links:**

1. Levine MN, Hirsh J, Landefeld S, Raskob G. Hemorrhagic complications of anticoagulant treatment. *Chest* 1992;**102**:352S-363.

<http://journal.publications.chestnet.org/article.aspx?articleID=1065505>

2. Landefeld C,.Beyth RJ. Anticoagulant-related bleeding - clinical epidemiology, prediction and prevention. *Am J Med* 1993;**95**:315-28.

<http://www.amjmed.com/article/0002-9343(93)90285-W/pdf> (subscription required to view full text)

3. Linkins LA, Choi PT, Douketis JD. Clinical Impact of Bleeding in Patients Taking Oral Anticoagulant Therapy for Venous Thromboembolism: A Meta-Analysis. *Annals of Internal Medicine* 2003;**139**:893-900.

<http://annals.org/article.aspx?articleid=716961> (subscription required to view full text)

**5. What are the signs and symptoms of severe bleeding?**

**QUIZ**

Now try to list the signs and symptoms of severe bleeding. Then click below to see how many you were able to list.

*Reveal answer*

* Prolonged nosebleeds (more than 30 minutes)
* Haematemesis
* Haemoptysis
* Haematuria (pink or red urine)
* Malaena (Black ‘tar-like’ bowel movements that are foul-smelling)
* Severe or spontaneous bruising
* For women, unusually heavy bleeding during menstruation or any other vaginal bleeding
* Severe, unusual headache, dizziness, fatigue or weakness.
* Severe bleeding from gums
* Severe bleeding from a small cut (more than 30 minutes)

**Signs and symptoms of severe bleeding**

**6. What should I do if the patient reports bruising or nose bleeds?**

Bruising and nose bleeds are the types of bleeding most commonly reported to anticoagulant clinics. The recommended actions to take are summarised below.

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| **Sign** | **Recommended advice** |
| **Bruising** | If bruise is not spreading reassure patient. If low level of anticoagulation (i.e. Target INR of 2.5 or less), consider reducing dose slightly for a few days to allow bruising to subside.  If the bruise is spreading seek further medical advice if necessary |
| **Nose bleed** | If bleeding is sparse and related to a cold, reassure patient.  If bleeding is intermittent, reduce dose for a few days and recheck within a week. If the problem persists, refer patient back to GP.  Persistent nose bleeds, not as a result of a high INR may be put down to nasal capillary vessel weakness and vessel cauterisation may be required. |

**Recommended advice for patient reports of nose bleed and bruising**

*(this could be framed in a Q&A style / MCQ … i.e. If I the person was bleeding from a small cut they should …)*

**7. What is skin necrosis?**

*(image 17\_Coumarin-induced\_skin\_necrosis.jpg - Skin necrosis (Herbert L. Fred, MD and Hendrik A. van Dijk / CC-BY 2.0)*

* Skin necrosisis extremely rare (incidence 0.01 – 0.1%), but serious, adverse effect of warfarin.
* Skin necrosis occurs within **3 - 6 days after initiation** of warfarin therapy and associated with high loading doses.
* The condition presents as a **painful discoloration of breast, buttocks, thigh or penis**. The discoloration is associated with hypercoagulable conditions.
* It is associated with rapid depletion of Protein C and Protein S.

**7.1 How is skin necrosis managed?**

* Warfarin should be stopped and the patient referred to a medical practitioner.
* Amputation may be necessary in extreme cases.

**8. What is purple toes syndrome?**

*(image - 17\_article-g01\_400\_300.jpg. Purple toes syndrome. (From: R Shariat-Moharreri, M Khajavi, K Ghazisaidi, M Mojtahedzadeh. Purple Toes Syndrome Related to Warfarin Therapy: A Case Report. The Internet Journal of Anesthesiology. 2004 Volume 9 Number 1)*

* Purple toes syndrome is another extremely rare adverse effect of warfarin.
* It usually occurs within **3 – 10 weeks** after initiation of warfarin therapy
* The toes appear purplish or mottled with discoloration of plantar surfaces and sides, and blanches on pressure and fades with elevation of the legs.
* The condition may result from cholesterol embolisation in the small vessels of the toes, restricting blood flow to the extremeties

**8.1 How is purple toes syndrome managed?**

* Warfarin should be stopped and the patient referred to a medical practitioner.

**9. What are the other (non-bleeding) adverse effects of warfarin?**

Other adverse effects people have reported with warfarin are listed below:

* Gastro-intestinal disturbances (e.g. indigestion, nausea)
* Skin reactions
* Alopecia (hair thinning and loss)
* Tiredness
* Intolerance to cold

**Other side effects associated with warfarin**

**10. Can people be allergic to warfarin?**

Allergic reactions to warfarin are rare.

**11. Can pregnant women take warfarin?**

*(Image - 118\_MP900448533.JPG)*

* Warfarin crosses the placenta, and is not given in the initial stage of pregnancy because the drug is **teratogenic**. It is not given in the latter stage of pregnancy because of the **risk of bleeding** in the foetus.

* Between six and ten weeks gestation is the critical period for foetal development and if warfarin is taken, **foetal warfarin syndrome** (FWS) may result. The common characteristics of FWS include nasal hypoplasia, failure of development of the nasal septum results in an upturned appearance. Other features of FWS include low birth weights, eye defects, hypoplasia of the extremities (ranging from severe rhizomelic dwarfing to dystrophic nails and shortened fingers).
* Other problems associated with warfarin use during the first trimester include **central nervous system defects, spontaneous abortion, stillbirth, prematurity and haemorrhage**. In all cases, about 70% of pregnancies are expected to result in a normal infant.
* Administration of warfarin is contraindicated in the final stages of pregnancy because it can lead haemorrhagic complications for the mother and intracranial haemorrhage in the baby during delivery.
* Women taking warfarin are advised to discuss plans for future pregnancy with their doctor before trying to conceive. Should a woman taking warfarin become pregnant, it is important that they are referred to their GP for a change in management to a **low molecular weight heparin** (LMWH). There is no evidence of foetal growth abnormalities associated with LMWH u administration.
* The **NOACs** are not licensed in pregnancy

**12. Is warfarin safe when breast-feeding?**

*(image - 118\_MP900308946.JPG*)

Warfarin is considered **safe** in breast-feeding. Although warfarin is expressed in breast milk, there is little evidence that it affects neonatal growth/development.

**13. How should warfarin be managed if someone is to have minor surgery?**

*(image - 17\_US\_Navy\_041006-N-0184L-010\_Hospital\_Corpsman\_3rd\_Class\_Carlos\_Cordova\_conducts\_minor\_surgery\_on\_a\_patient\_aboard\_the\_Naval\_Hospital\_Corpus\_Christi.jpg)*

* If surgery is planned, the surgical team usually advises the patient on their anticoagulation. This is usually done at the pre-assessment appointment.
* Their advice will depend on how invasive the surgery will be, the risk of clotting and the person’s risk of bleeding. They may need to stop warfarin for a few days before the procedure. If there is a high risk of clotting, they may be asked to use heparin injections for a short period before and after the procedure.

**14. What about dental work?**

* Consensus guidance states that if the person’s **INR is less than 4.0**, they should not have to stop or reduce their dose of warfarin before a routine dental procedure. Although continuing warfarin may increase their risk of bleeding, this is felt to be less than the risk of developing a clot if they had stopped warfarin.
* Their INR should be checked no more than **72hours** before the planned dental procedure (ideally 24 hours before). After the dental procedure, their dental surgeon should give the patient clear instructions on how to manage the clot after surgery.

Patients may need to referred to a **specialist dental hospital** for treatment if they fall under any of the categories below:

1. They are kept at an INR > 4.0
2. They have very erratic INR control
3. They have a condition that affects blood clotting or bleeding (e.g. liver impairment)
4. They are taking cytotoxic medication

**15. What are the contraindications to warfarin?**

*(image - Stop sign. 115\_MP900448683.JPG)*

The UK’s Drug Regulatory Body, the MHRA, updated its list of contraindications to warfarin in 2009.

* Known hypersensitivity to warfarin or to any of the excipients
* Haemorrhagic stroke
* Clinically significant bleeding
* Within 72 hours of major surgery with risk of severe bleeding
* Within 48 hours postpartum
* Pregnancy
* Concomitant use of fibrinolytic drugs

**Contraindications to warfarin (MHRA, 2009)**

If you would like to learn more about the contraindications and cautions for warfarin please visit the [MHRA's website](http://www.mhra.gov.uk/).([www.mhra.gov.uk](http://www.mhra.gov.uk))

**DEMONSTRATE YOR UNDERSTANDING**

Finally, please try to answer the questions at the start of this topic again