**Question 1**

Which of the following drugs does not interact with warfarin?

A Benzodiazepines

B Cephalosporins

C Phenobarbitone

D Loop diuretics

Explanation A

**Drugs that decrease INR**

Decrease due to changes in pharmacodynamics

Vitamin k (increase synthesis in clotting factors)

Diuretics (increase synthesis in clotting factors)

Hereditary resistance to clotting factors

Hypothyroidism (decrease turnover rate of clotting factors)

Decrease due to changes in pharmacokinetics

Barbiturates (increase metabolism)

Rifampicin (increase metabolism)

Cholestyramine (decrease gut absorption of warfarin)

**Drugs that increase INR**

Increase due to changes in pharmacodynamics

 Aspirin (increase turnover of clotting factors and platelets)

Third gen cephalosporins (eliminate bacteria that produce Vit K)

Heparin

Hyperthyroidism

 Increase due to changes in pharmacokinetics

Amiodarone, cimetidine, disulfiram, metronidazole, fluconazole and Bactrim (decrease metabolism)

**Question 2**

Which if the following clotting factor proteases does Heparin not inhibit?

A IXa

B Xa

C Va

D IIa

Explanation D

Heparin is a heterogenous mixture of sulphated mucopolysaccarides extracted from porcine or bovine intestine. It must be given IV or in the cleaxane form, subcutaneously. Protamine sulphate neutralizes heparin directly. Heparin is of animal origin and should be used with caution in patients with allergy. Increased loss of hair and transient alopecia has been reported. Long term heparin is associated with osteoporosis and spontaneous fractures. Mineral corticoid deficiency is also associated with long term heparin usage. Heparin accelerates antithrombin protease inhibitory reaction against clotting factors IIa, IXa, and Xa by forming equimolar stable complexes with them

In the current textbook it states that Warfarin should never be administered during pregnancy.

Note: warfarin has place in pregnancy albeit a small one. Women who have prosthetic heart valves and are at high risk of thromboembolism. Counselling and considerations (a team approach) need to be made regarding risk vs benefit. The recommendation would be to use LMWH in the first trimester and warfarin in the second and third trimester until week 36 of pregnancy.

For the purposes of the exam, follow the statement: Warfarin should never be administered during pregnancy.

LMWH is favoured over UFH during pregnancy; LMWH does not cross the placenta and has several advantages over UFH: It has a more predictable attainment of therapeutic levels of anticoagulation, appears to have less effect on bone, and is associated with less bleeding and thrombocytopenia

**Question 3**

Which statement is not true of warfarin?

A It affects the function of vit K

B Half life is 6 hours

C It has 100% bioavailability

D It is 99% protein bound

Explanation B

Warfarin’s half-life is 36hrs.

Warfarin decreases blood coagulation by inhibiting vitamin K epoxidereducatse that recycles oxidised vitamin K1 to its reduced form after it has participated in the carboxylation of several blood coagulation proteins, mainly prothrombin and factor VII. Warfarin does not antagonize the action of vitamin K, but rather antagonizes vitamin Krecycling, depleting active vitamin K. Thus, the pharmacologic action may always be reversed by administrating new vitamin K

**Question 4**

Which of the following statements regarding streptokinase is true?

A It binds to the endogenous plasminogen

B It activates the plasminogen that is bound to fibrin

C It is a complex lipopolysaccharide.

D It is synthesised by the human kidney

Explanation A

Streptokinase is a protein (but not an enzyme in itself) synthesized by streptococci. It combines with the proactivator plasminogen.

The kidney synthesizes urokinase.

tPA peferentially activate plasminogen that is bound to fibrin

**Question 5**

Heparin induced mild thrombocytopenia is caused by?

A Thrombosis

B Anti-platelet antibodies

C Release of lipoprotein lipase

D Platelet aggregation.

Explanation D

Heparin induced thrombocytopenia is transient and occurs 5-14 days after therapy. It may occur sooner if the patient is already sensitised to heparin. HIT occurs in 5% of patients receiving heparin. A smaller subset of patients may develop an antibody-mediated cause of thrombocytopenia that is associated with thrombosis. In this instance, the heparin-induced antibody is directed against the heparin platelet factor 4 complex. These antigen-antibody complexes bind to the Fc receptor on adjacent platelets, causing aggregation and paradoxical thromboembolism. The risk of HIT is lowered but not eliminated by the use of LMWH preparations. Once severe HIT occurs it will be exacerbated by the use of LMWH as well and must be avoided. Treatment involves cessation of the heparin and the use of other NON-heparin based anticoagulants must be started

**Question 6**

Regarding warfarin, which of the following statements is correct?

A It decreases thromboplastins

B It is 75% protein bound

C It is broken down in the GIT

D It has a half life of 6 hours

Explanation A

Warfarin has a bioavailability of 100%. Over 99% of warfarin is bound to plasma albumin, which may contribute to its small volume of distribution, its long half-life of 36hrs and it lack of urinary excretion of unchanged drug. The traditional term “thromboplastin” refers to a phospholipid-protein extract of tissue (usually lung, brain, or placenta) that contains both the tissue factor and phospholipid necessary to promote activation of factor X by factor VII. Warfarin’s anticoagulant effect results from a balance between partially inhibited synthesis and unaltered degradation of the four vitamin K dependant clotting factors- 2, 7, 9, 10.

Note: warfarin has an 8-12hr delayed onset of action. Doses >0.75mg/kg of warfarin do not hasten the anticoagulant effect of warfarin further.

**Question 7**

Which of the following drugs does not increase the action of warfarin?

A Disulfiram

B Phenobarbitone

C Metronidazole

D Amiodarone

Explanation B

See Q1

**Question 8**

In which condition is Low molecular weight heparin levels in plasma not necessary to measure?

A Pregnancy

B Obesity

C Liver insufficiency

D Renal insufficiency

Explanation C

Weight based dosing of LMWH results in predictable pharmakokinetics and plasma levels in patients with normal renal function. Therefore, LMWH levels are not generally measured except in the setting or renal insufficiency, obesity (body wt >150kg) and pregnancy

**Question 9**

What drug does not affect the metabolism of warfarin?

A Rifampicin

B Phenobarbiton

C Benzodiazepines

D Cimetidine

Explanation C

See Q1

**Question 10**

Which statement is correct regarding fibrinolytics?

A Gastrointestinal bleed within the previous 12 months is a contraindication

B TIMI trial shows that GI haemorrhage is the most common adverse effect

C Streptokinase is a human product

D Aminocaproic acid is an inhibitor of fibrinolysis

Explanation D

Streptokinase is a streptococcal bacterial protein.

A GIT bleed in the last 2-4 weeks or an active peptic ulcer is a contraindication to fibrinolysis.

TIMI trial showed that haemorrhagic stroke is the most common side effect.

Urokinase is a cheap human enzyme.

REMEMBER: tranexamic acid an analog of aminocaproic acid is an inhibitor of fibrinolysis. It competitively inhibits plasminogen activation. It is administered orally with a 15mg/kg loading dose followed by 30mg/kg every 6hrs. An IVI preparation is also available. 1000mg infusion over about 5min

**Question 11**

Regarding fibrinolytics, select the correct answer.

A APSAC lack the streptococcal antigen

B tPA does not occur naturally

C All thrombolytics act to convert active plasminogen to plasmin.

D Urokinase is a human product

Explanation D

Fibrinolytics act by converting inactive plasminogen to plasmin. Plasmin itself cannot be used because naturally occurring inhibitors in plasma prevent its effects. Plasmin formed inside a thrombus by these activators are protected form plasma antiplasmins, which allow it to lyse the thrombus from within.

Urokinase is a human enzyme synthesized by the kidney. APSAC- anisoylated plasminogen streptokinase activator complex- consists of a complex of purified human plasminogen and bacterial streptokinase that has been acylated to protect the enzyme’s active site. tPA occurs on the endothelial cells of vessels.

REMEMBER: tranexamic acid an analog of aminocaproic acid is an inhibitor of fibrinolysis. It competitively inhibits plasminogen activation. It is administered orally with a 15mg/kg loading dose followed by 30mg/kg every 6hrs. An IVI preparation is also available. 1000mg infusion over about 5min

Anistreplase is antigenic and promotes antibody formation

Fibrinolytics is the correct description of the drugs, but the term thrombolytic is sometimes used

**Question 12**

If a patient is on warfarin, which of the following drugs cause an increased INR?

A Barbituates

B Cholestyramine

C Amiodorone

D Rifampicin

Explanation C.

See Q1

**Question 13**

Regarding heparin, which of the following statements is correct?

A It inhibits antithrombin III

B Protamine is a competitive antagonist of heparin

C LMW fractions have more effect on thrombin than HMW fractions

D It may cause alopecia

Explanation D

LMW heparin inhibits activated factor X but has less effect on antithrombin - and on the coagulation in general - than HMW heparin. Heparin’s biological activity is dependant upon the plasma potease inhibitor antithrombin III. In the presence of heparin the antithrombin-clotting factor complex (which inhibits clot formation) is accelerated 1000 fold. Heparin accelerates this antithrombin protease inhibitory reaction against clotting factors IIa, IXa, and Xa by forming equimolar stable complexes with them Protamin binds to heparin and forms a complexes devoid of anticoagulant activity

**Question 14**

Which of the following statements regarding ticlopidine is correct?

A It inhibits prostaglandin metabolism

B Leukopenia is a common side effect

C It reduces platelet aggregation by the irreversible inhibition of the ADP-receptor

D It has no GI side effects

Explanation C

Ticlopidine, unlike aspirin, has no effect on prostaglandin metabolism.

GIT symptoms do occur: 20% may suffer dyspepsia, nausea and diarrhea. 5% GIT haemorrhage.

Only 1% of patients develop leucopenia. TTP may also occur.

**Question 15**

Which of the following fibrinolytics can be given as a PUSH BOLUS?

A Anistreplase

B Alteplase

C Streptokinase

D Tenecteplase

Explanation D

Streptokinase: Loading dose and infusion

Urokinase: Loading dose and infusion

Alteplase: Infusion

Tenecteplase: Push bolus

Anistreplase: Single bolus over 3-5min

**Question 16**

Which of the following is not a DIRECT ACTING anticoagulant?

A Argatroban

B Dabigatran

C Heparin

D Rivaroxaban

Explanation C

Heparin requires the presence of antithrombin III. It facilitates the a conformational change of ATIII that exposes its active site for the more rapid interaction with the activated clotting factor (proteases) II, IXa, Xa, Xia, XIIa. This results in the required anticoagulant effect

Rivaroxaban binds directly to factor Xa

Argatroban binds directly to factor IIa (thrombin)

Digabatron binds directly to factor IIa (thrombin)

**Question 17**

Which of the following is FALSE regarding Dabigatran?

A It has a slow onset and requires additional overlapping of other anticoagulants

B Dabigatron casuses more GIT bleeding than warfarin

C Dabigatron is the first oral direct thrombin inhibitor

D It does not interact with the P450 system

Explanation A

Dabigatron is the first oral direct thrombin inhibitor. It has predictable pharmacokinetics, bioavailability of 3-7%, half-life of 12-17hrs. It does not interact with the P450 system. Renal impairment results in decreased drug clearance and the dose should be reduced (150mg bd to 75mg bd). No monitoring is required. It has a rapid on and offset and does not require additional overlapping of other anticoagulants. It is prescribed for the prevention of systemic embolism and stroke in patients with non-valvular AF. It is also prescribed for patient post TKR and THR. Trails have shown a superior action to warfarin, however, there is an increase in GIT haemorrhage.

Note: in older textbook editions, ximelagatron was the first oral direct thrombin inhibitor approved, however it was withdrawn form the market due to hepatotoxicity. In the newer editions, this drug (and quote) is not mentioned. The text writes that Dabigatron is the first direct oral inhibitor approved by the FDA.