Anticoagulants - a matter of heart!

Towards a bright future?

Clinical issues – which drug for which patient

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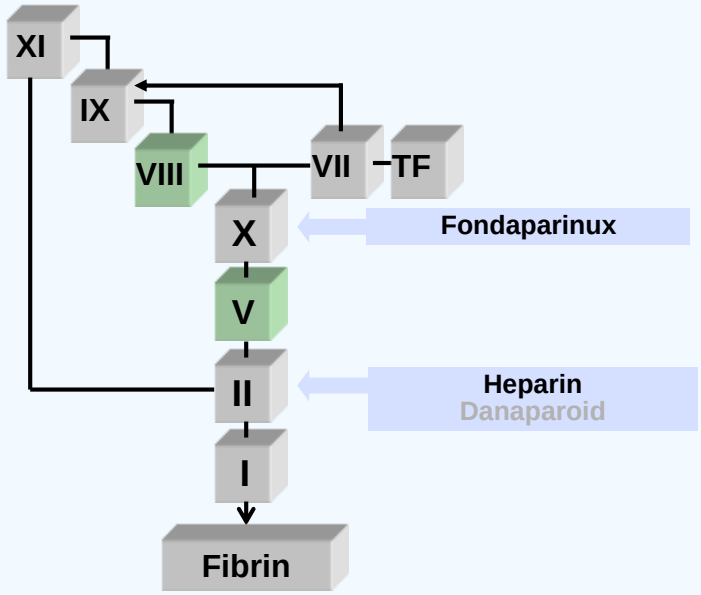
Conflicts of interest

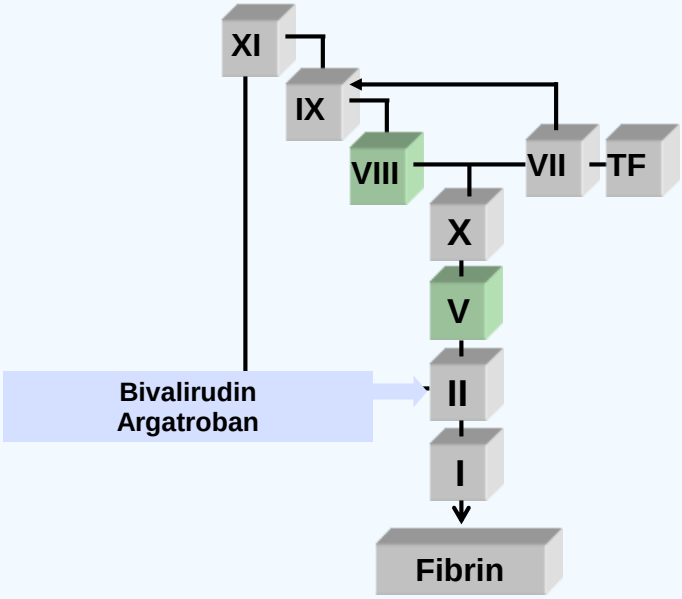
Consultancies, member of advisory boards:

Boehringer-Ingelheim
Bayer
Daiichi-Sankyo
Bristol Myers Squibb
Pfizer

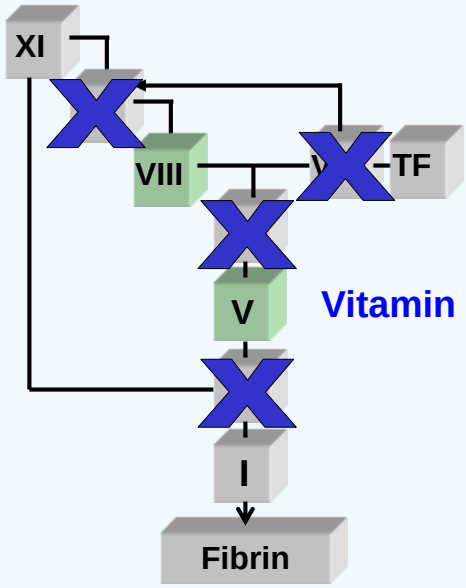
Indirect parenteral anticoagulants



Direct parenteral anticoagulants



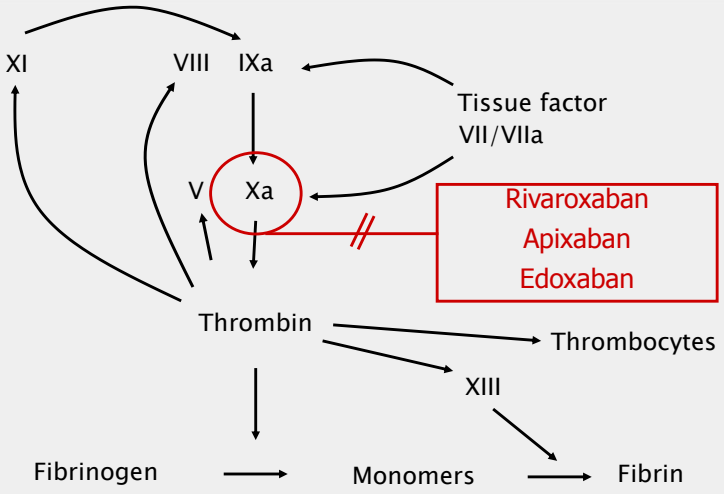
Indirect oral anticoagulants



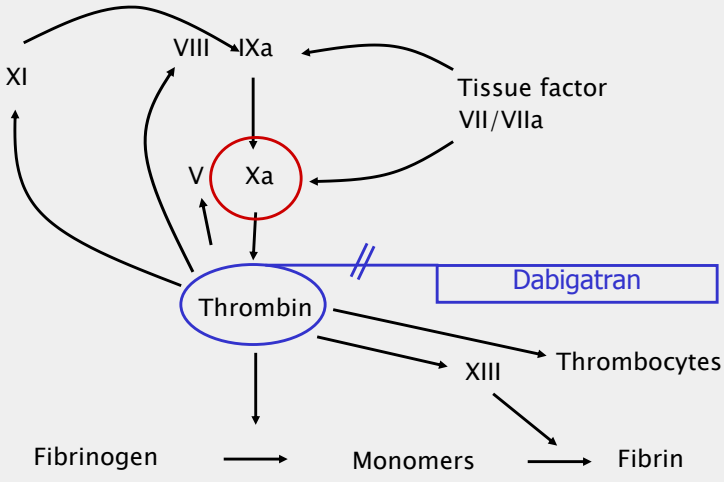
Disadvantages of VKA

- Slow onset and offset of action → heparin bridging
- Unpredictable dose response → monitoring
- Narrow therapeutic window → monitoring
- Food and drug interactions → monitoring
- Coumarin necrosis

Direct oral anticoagulants



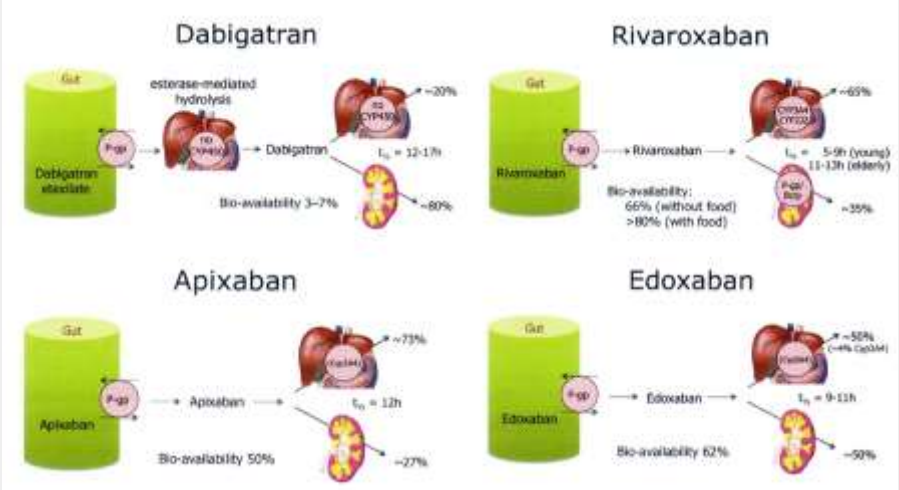
Direct oral anticoagulants



Direct oral anticoagulants

	Dabigatran **Pradaxa®**	**Rivaroxaban** **Xarelto®**	**Apixaban** **Eliquis®**	**Edoxaban** **Lixiana®**
Target	**IIa**	**Xa**	**Xa**	**Xa**
C max	**1.5-3 h**	**2-4 h**	**1-4 h**	**1-2 h**
T1/2	**12-17 h**	**5-13 h**	**9-14 h**	**8-10 h**
Monitoring	**no**	**no**	**no**	**no**

Absorption, metabolism and elimination



Direct oral anticoagulants

Renal function (Cockroft-Gault)

$$CCr = \frac{(140 - age) \times weight}{72 \times SCr} \times (0.85 \text{ if female}),$$

Direct oral anticoagulants

Renal function (Cockroft-Gault)

$$CCr = \frac{(140 - 86) \times 48 \text{ kg}}{72 \times 1.2} \times (0.85 \text{ if female}),$$

CrCl = 25.5 ml/min

Direct oral anticoagulants

Drug interactions

	Dabigatran Edoxaban	Rivaroxaban Apixaban
P-glycoprotein inhibitors (amiodarone, phenotiazin, carboxylic acid, azole antifungals, verapamil, antimalarial, cyclosporine, thioxanthenes)	Yes	Yes
P-glycoprotein inducers (dexamethasone, rifampicin, St. John's Wort)	Yes	Yes
CYP3A4 inhibitors (phenotiazin, carboxylic acid, azole antifungals, verapamil, erythromycin, telithromycin, nefazodone, antimalarial, cyclosporine, thioxanthenes)	No	Yes
CYP3A4 inducers (carbamazepine, efavirenz, nevirapine, phenytoin, phenobarbitone, rifabutin, rifapentine, rifampicin, St. John's Wort, alcohol, eucalyptol)	No	Yes
NSAIDS (aspirin, naproxen, diclofenac)	Yes	Yes
Antiplatelet agents (clopidogrel)	Yes	Yes

Pengo, Thromb Haemost 2011

EHRA guidelines, Heidbuchel, Eur Heart J 2013

Direct oral anticoagulants

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T1/2	**12-17 h**	**5-13 h**	**9-14 h**	**8-10 h**
Monitoring	**no**	**no**	**no**	**no**
Renal excretion	**80%**	**33%**	**27%**	**35%**
Drug interactions	**P-Gp Inhibitors**	**CYP3A4/ P-Gp Inhibitors**	**CYP3A4/ P-Gp Inhibitors**	**P-Gp Inhibitors**

Direct oral anticoagulants

Indications - Licensed

	Dabigatran Pradaxa®	**Rivaroxaban** Xarelto®	**Apixaban** Eliquis®	**Edoxaban** Lixiana®
Hip/knee-repl.	✓	✓	✓	✓
Atrial fibrillation	✓	✓	✓	
VTE		✓		
ACS		✓		

Direct oral anticoagulants

Venous thromboembolism: Phase III studies

Trial name	Patients, n	Design	Initially LMWH / fondap…	…tatus
Rivaroxaban				
EINSTEIN DVT	3449	O…		…ed 2010
EINSTEIN PE	4832			…d 2012
EINSTEIN EXT				… 2010
Dabigatr…				
RE-COVE…				Published 2009
RE-COVER…				bid Published 2013
RE-MEDY			--	bid Published 2013
RE-SONATE		…ind	--	bid Published 2013
Apixaban				
AMPLIFY	5395	Double blind	No	bid Published 2013
AMPLIFY-EXT	2482	Double blind	--	bid Published 2013
Edoxaban				
Hokusai-VTE	8240	Double blind	Yes	od Published 2013

- **At least as effective and safe as warfarin**
- **Only rivaroxaban currently licensed**

Direct oral anticoagulants

Atrial fibrillation: Phase III studies

Trial name	Patients, n	Design	Comparator	Dosing	Status
Rivaroxaban					
ROCKET-AF	14264	Double blind	Warfarin	od	Published 2011
Dabigatran					
RELY	18113	PROBE	Warfarin	bid	Published 2009
RELY-ABLE	5851	Open label	Warfarin	bid	Published 2013
Apixaban					
AVERROES	5599	Double blind	Aspirin	bid	Published 2011
ARISTOTLE	18201	Double blind	Warfarin	bid	Published 2011
Edoxaban					
ENGAGE-AF	21105	Double blind	Warfarin	od	Published 2013

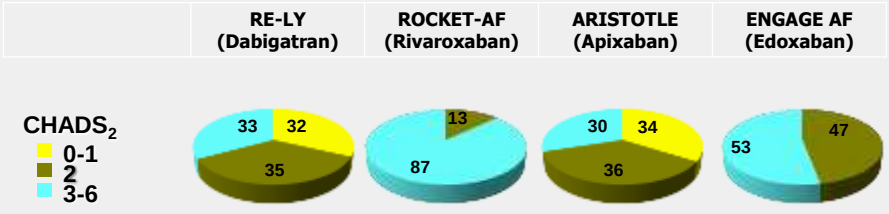
DOAC - atrial fibrillation

Phase III studies: patient characteristics

	RE-LY (Dabigatran)	ROCKET-AF (Rivaroxaban)	ARISTOTLE (Apixaban)	ENGAGE AF (Edoxaban)
Randomized, n	18,113	14,264	18,201	21,105
Age, years	72 ± 9	73 [65-78]	70 [63-76]	72 [64-78]
Female, %	37	40	35	38
$CHADS_2$ score ≥3, %	32	87	30	53
Paroxysmal AF, %	32	18	15	25
Prior stroke/TIA, %	20	55	19	28
VKA naïve, %	50	38	43	41
Aspirin use, %	40	36	31	29
Median follow-up, years	2.0	1.9	1.8	2.8
Median TTR, %	66	58	66	68

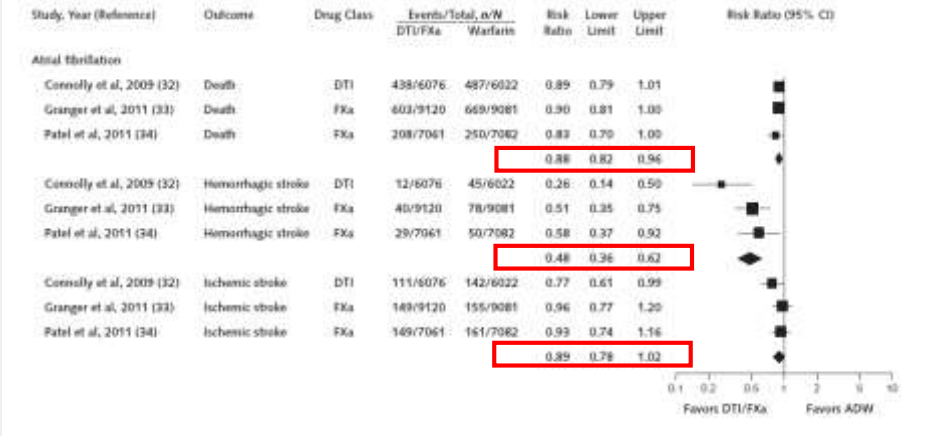
DOAC - atrial fibrillation

Phase III studies: patient characteristics



DOAC - atrial fibrillation

Meta-analysis



Adam, Ann Intern Med 2012

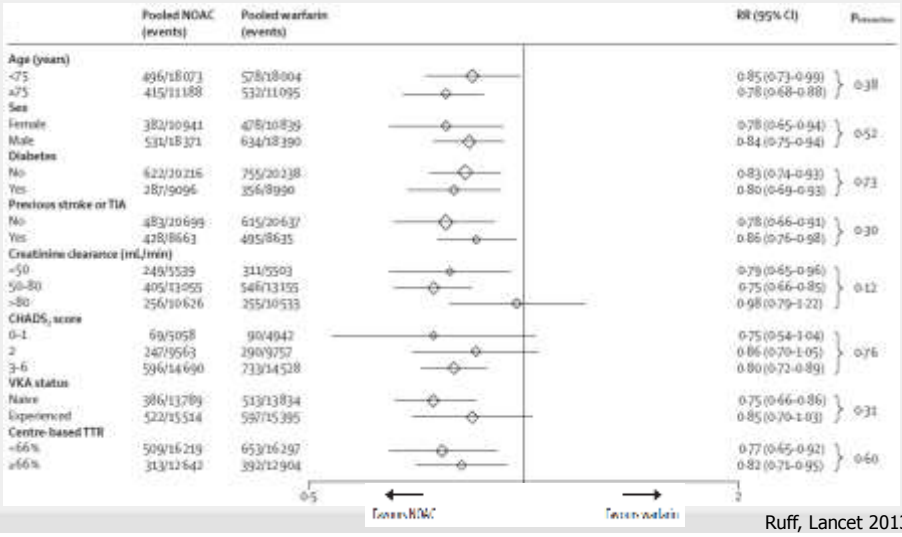
DOAC – atrial fibrillation

Intracranial bleeding

vs. Warfarin	HR (95% CI)	P-value
Dabigatran		
2 x 110 mg	0.31 (0.2 – 0.5)	< 0.001
2 x 150 mg	0.40 (0.3 – 0.6)	< 0.001
Rivaroxaban	0.67 (0.5 – 0.9)	0.02
Apixaban	0.42 (0.3 – 0.6)	<0.001
Edoxaban		
1 x 30 mg	0.30 (0.2 – 0.4)	< 0.001
1 x 60 mg	0.47 (0.3 – 0.6)	< 0.001

DOAC – atrial fibrillation

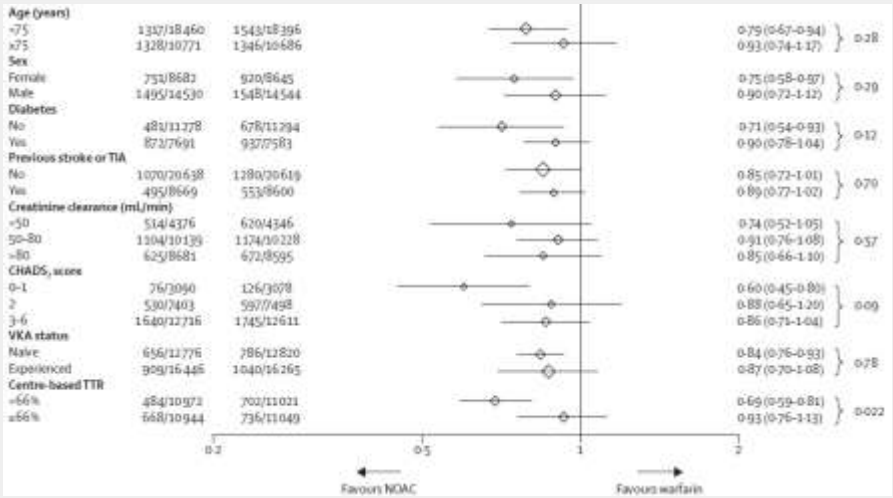
Stroke or systemic embolic events



Ruff, Lancet 2013

DOAC – atrial fibrillation

Major bleeding



Ruff, Lancet 2013

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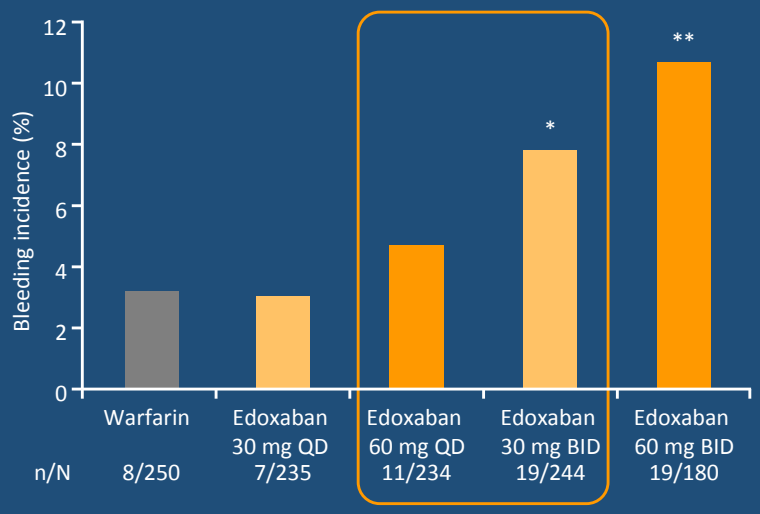
Renal excretion	80%	33%	27%	35%
Drug interactions	P-Gp Inhibitors	CYP3A4/ P-Gp Inhibitors	CYP3A4/ P-Gp Inhibitors	P-Gp Inhibitors
Dosing	**2x/d**	**1x/d**	**2x/d**	**1x/d**

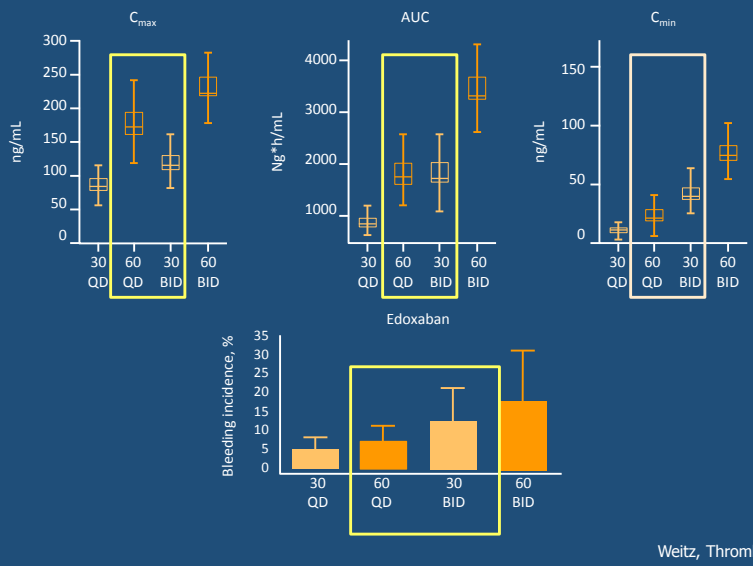
Edoxaban Phase II dose finding study in AFIB: major and clinically relevant non-major bleeding



*p<0.05, **p<0.01, vs warfarin

Weitz, Thromb Haemost 2010

Edoxaban Phase II dose finding study in AFIB: exposure and all bleeding events



Weitz, Thromb Haemost 2010

Atrial fibrillation

Pradaxa®: which dose?

- **2 x 150 mg/day** → standard dose
- **2 x 110 mg/day**

  Recommended
  - Age >80 years
  - Comedication with verapamil

  Consider
  - Age 75 - 80 years at increased bleeding risk and low thrombotic risk
  - High bleeding risk and impaired renal function (CrCl 30-50 ml/min)
  - Patients with gastritis, esophagitis oder gastro-esophageal reflux

Atrial fibrillation

Xarelto®: which dose?

- **1 x 20 mg/day** → standard dose
- **1 x 15 mg/day** → CrCl 15 - 49 ml/min

Eliquis®: which dose

- **2 x 5 mg/day** → standard dose
- **2 x 2.5 mg/day** in case of two of the following:
  - age >80 years
  - serum creatinine >1.5 mg/dl
  - body weight <60 kg

Direct oral anticoagulants

Contraindication

- Artificial heart valves
- Valvular atrial fibrillation
- Creatinine clearance
  - <30 ml/min Dabi
  - <15 ml/min Api, Riva
- Pregnancy, breastfeeding
- Severe hepatopathy
- Severe coagulopathy

Caution

- Creatinine clearance <30 ml/min Api, Riva
- Increased bleeding risk: thrombocytopenia, platelet function inhibitor, NSAR, recent GI beeding

Direct oral anticoagulants

Advantages

- TSOACs = „Target specific oral anticoagulants"
- Rapid offset of action
- Rapid onset of action
  → No need for injections
- Predictable dose-response
  → Fixed dose
  → No need for monitoring
- At least as effective and safe as compared with standard treatment in patients atrial fibrillation

Direct oral anticoagulants

(Potential) disadvantages and open questions

- Renal clearance
- No data on correlation between coagulation test results and clinical outcomes
- No antidot (yet)
- No need for monitoring
  - No methods to assess adherence
  - No clinical surveillance
  - Reduced awareness of the therapy
- Patients frequently (TTR > 80%) in INR target range
- Costs

Question 1

1. DOACs are licensed for
   1. General postoperative thromboprophylaxis
   2. Non-valvular atrial fibrillation
   3. Artificial heart valves
   4. Longterm treatment of pulmonary embolism

Answers:

a) All correct
b) None correct
c) 1,2,3 correct
d) 3 correct

Question 2

1. Which laboratory test is most important when using a direct oral anticoagulant

a) aPTT
b) Creatinine clearance
c) Liver function tests
d) Platelet count

Question 3

1. In contrast to vitamin K antagonists, direct oral anticoagulants do not interfere with other drugs and should therefore be preferred.

a) Strongly agree
b) Agree
c) Neither agree not disagree
d) Disagree
e) Strongly disagree