Medicaţia antitrombotică

MEDICATIA ANTITROMBOTICA

Această grupă cuprinde medicamente utile pentru tratamentul şi profilaxia afecţiunilor tromboembolice.

Medicamentele antitrombotice intervin la nivelul **plachetelor**, al **proteinelor coagulării** sau al **sistemului fibrinolitic**, fiind indicate diferenţiat în trombozele arteriale, trombozele venoase, trombozele intracardiace sau coronariene, în funcţie de mecanismul fiziopatologic al procesului trombogen.

Medicamentele inhibitoare ale funcţiilor plachetare - antiagregantele plachetare

- Antiagregantele plachetare sunt medicamente capabile să inhibe agregarea şi alte funcţii ale plachetelor, responsabile de formarea trombusului alb sau care intervin în coagulare.

Inhibarea funcţiilor plachetare se manifestă prin:

- prelungirea timpului de sângerare
- împiedicarea adeziunii şi agregării plachetelor
- prelungirea vieţii acestora (scurtată în bolile tromboembolice).

Antiagregantele plachetare sunt indicate mai ales pentru profilaxia trombozelor arteriale, caracterizate prin formarea trombusului plachetar la nivelul endoteliului vascular lezat.

Antiplatelet Drugs

Antiplatelet drugs, also known as antiaggregants, are drugs that decrease platelet aggregation and thereby inhibit thrombus formation.

Antiplatelet drugs are effective in the **arterial circulation** and are widely deployed in the prevention of thrombotic cardiovascular and cerebrovascular disease.

Class	Examples	Mechanism
COX inhibitors	**Aspirin**	Irreversibly inhibits COX-1, thereby blocking formation of thromboxane A2.
Phosphodiesterase inhibitors	**Dipyridamole**	Inhibition of the enzyme phosphodiesterase type 5
ADP receptor antagonists	**Clopidogrel** **Prasugrel** **Ticagrelor**	Irreversible binding to purinergic P2 receptors for ADP on platelet surface. Ticagrelor exhibits reversible binding.
Glycoprotein IIb/IIIa receptor antagonists	**Abciximab** **Tirofiban** **Eptifibatide**	Abciximab irreversibly binds these receptors – blocking binding of fibrinogen. Tirofiban reversibly blocks this receptor.
Prostacyclin	**Epoprostenol**	Increases platelet cAMP which, at low concentrations, inhibits platelet aggregation.

ASPIRINA

- **Aspirina (Aspenter tb. 75 mg, Aspirin cardio tb. 100 mg)**
- Determină inactivarea ireversibilă, prin acetilare, a ciclooxigenazei, enzimă care catalizează sinteza unor substanțe endogene de tip prostaglandinic; este importantă impiedecarea formării în plachete a tromboxanului A2 care favorizează agregarea plachetară.

Indicaţii:

- boala coronariană ischemică: angina stabilă, infarct miocardic acut;
- bolnavi ce au avut un accident vascular ischemic
- purtători de valve, altele decât metalice (anticoagulante)

Reacţiile adverse şi contraindicaţii

- iritaţie gastrică
- reacţii alergice
- hemoragii (mai ales în asociere cu anticoagulante)

Doza : 75 – 325 mg/zi

TICLOPIDINA

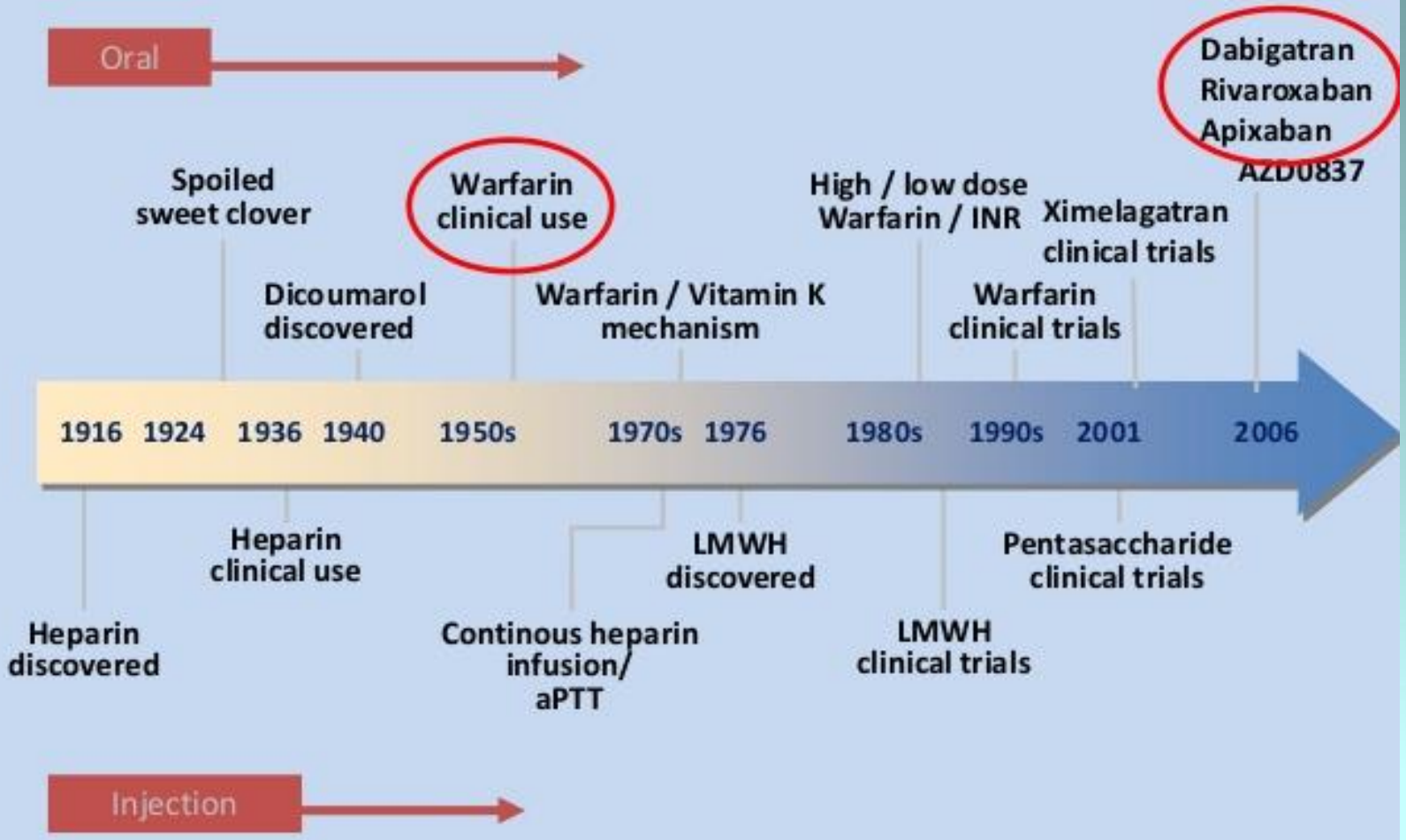
- **Ticlopidina (Ticlid)**
  - **Acțiune :**
    - împiedică adeziunea şi agregarea plachetară
    - nu permite retracția cheagului
    - prelungeşte timpul de sângerare
  - **Indicații:**
    - prevenirea complicațiilor tromboembolice arteriale(AVC, IMA)
    - prevenția trombozelor la nivelul protezelor coronariene
  - **Doza**: 250 mg de 2 ori/zi(la mese)
  - **Efecte secundare**:
    - tulburări gastrointestinale (microhemoragii digestive, rareori ulcer, fenomenele fiind mai uşoare decât la administrarea de aspirina),
    - neutropenie reversibilă care apare în primele 3 luni de la începutul tratamentului

CLOPIDOGREL

Clopidogrel (Plavix) cp. 75 mg

- **Acțiune :**
  - are acelaşi mecanism de acţiune ca şi ticlopidina
- **Indicații:**
  - prevenirea complicațiilor tromboembolice arteriale la bolnavii cu AVC, IMA
  - prevenirea complicațiilor tromboembolice la bolnavii cu arteriopatie obliterantă
- **Reacţii adverse**:
  - tulburări gastro-intestinale de tip hemoragic
  - neutropenia apare mai rar.
- Doze: 75 mg o dată /zi.

Anticoagulants – historical development



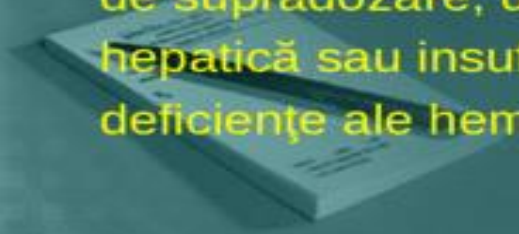
ANTICOAGULANTE

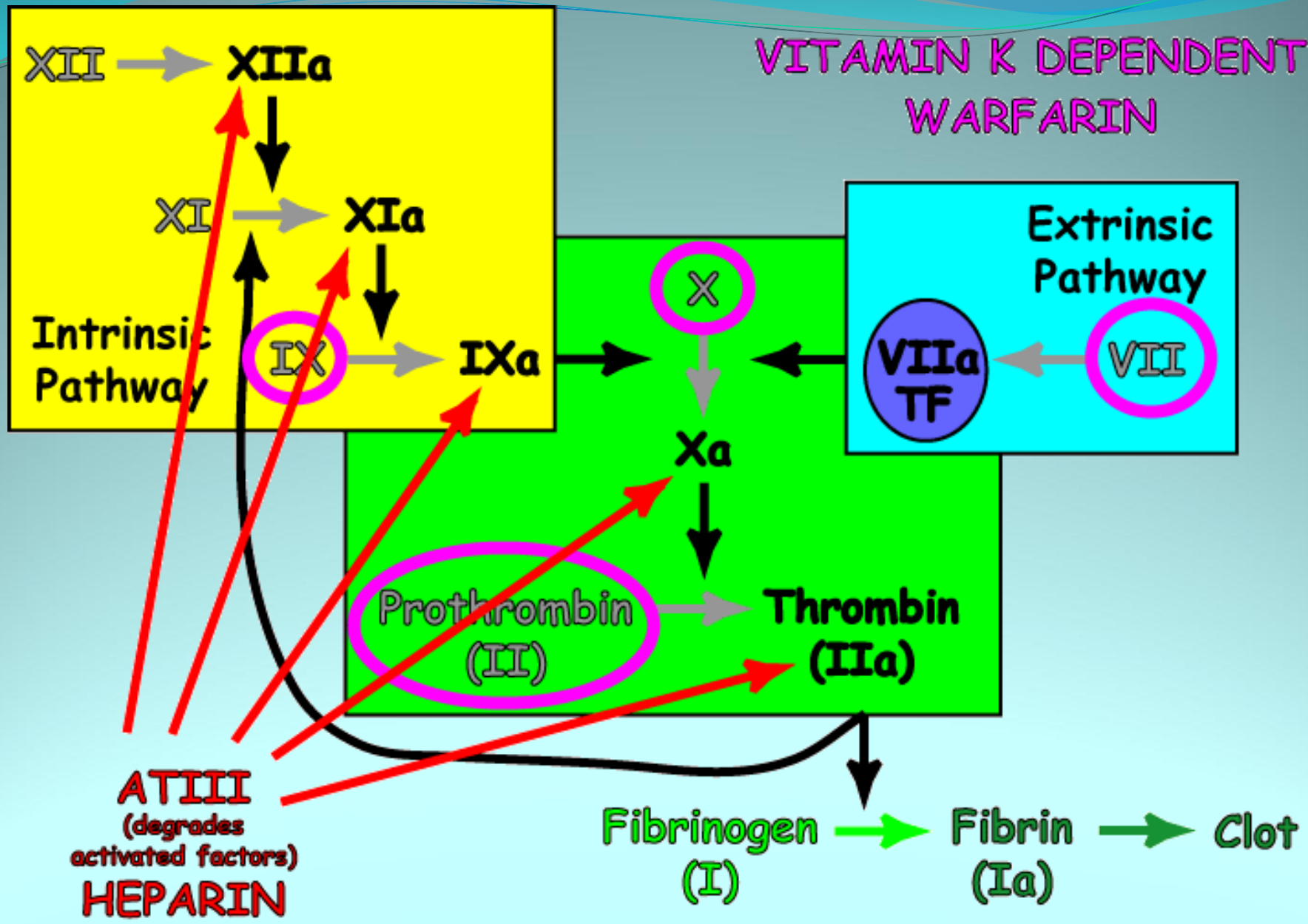
Anticoagulante

- Anticoagulantele sunt medicamente care împiedică procesul coagulării, acţionând la nivelul sistemului plasmatic responsabil de gelificarea sângelui. Ele sunt utile îndeosebi în *tromboza venoasă*, unde fenomenul principal este formarea trombusului de fibrină.
- Sunt indicate atât pentru profilaxia primară, oprind generarea trombozei,

cât şi pentru profilaxia secundară, oprind extinderea cheagului şi evitând accidentele embolice.

- De asemenea se folosesc la purtătorii de valve cardiace protetice (de preferinţă în asociere cu antiagregantele plachetare).
- Complicaţia majoră este reprezentată de *hemoragiile,* care survin în caz de supradozare, dar şi la dozele obişnuite, la bolnavii cu insuficienţă hepatică sau insuficienţă renală. Riscul este mult crescut în prezenţa unor deficienţe ale hemostazei.




VITAMIN K DEPENDENT
WARFARIN
XII
XIIa
XI
XIa
Intrinsic
Pathway
IX
IXa
X
Extrinsic
Pathway
VIIa
TF
VII
Xa
Prothrombin
(II)
Thrombin
(IIa)
ATIII
(degrades
activated factors)
HEPARIN
Fibrinogen
(I)
Fibrin
(Ia)
Clot

HEPARINA

a. Anticoagulante acute

Heparina f. 5000 u.i

- Se cuplează cu o globulină plasmatică – *antitrombina III* – grăbind acțiunea acesteia de inactivare a trombinei, factorului X şi altor factori ai coagulării
- Are structură polară, de aceea nu se absoarbe şi e distrusă de sucurile gastrice, nu traversează bariera hematoencefalică şi nici placenta, putându-se administra gravidelor care fac tromboflebite profunde.
- Are efect antitrombocitar prin inhibarea agregării plachetelor, indusă de trombină.
- Clarifică plasma lipemica prin activarea lipoproteinlipazei.
- Se leagă de endoteliu, proteine plasmatice şi macrofage, apoi se elimină renal. De aceea nu se administrează în insuficienţele renale.

HEPARINA

Mod de administrare

- intravenos: perfuzie continuă sau intermitentă → heparina sodică
- subcutanat → heparina calcică.
- administrarea subcutanată e foarte dureroasă

- Doza administrată subcutanat 5.000 u.i la 8 – 12 ore
- Dozele pentru administrare intravenoasă: în perfuzie continuă : 1000 u.i/ oră sau i.v inițial 10 000 u.i, apoi 5 000 – 10 000 u.i la 4 -6 ore

- Efectul heparinei trebuie supravegheat clinic şi biologic.

- Pentru testarea eficacității, se măsoară timpul de coagulare, iar pentru testarea securității timpul de trombină, a căror valoare trebuie să fie de 2 – 3 ori mai mare decât cea normală

Initial Dose:

Bolus:

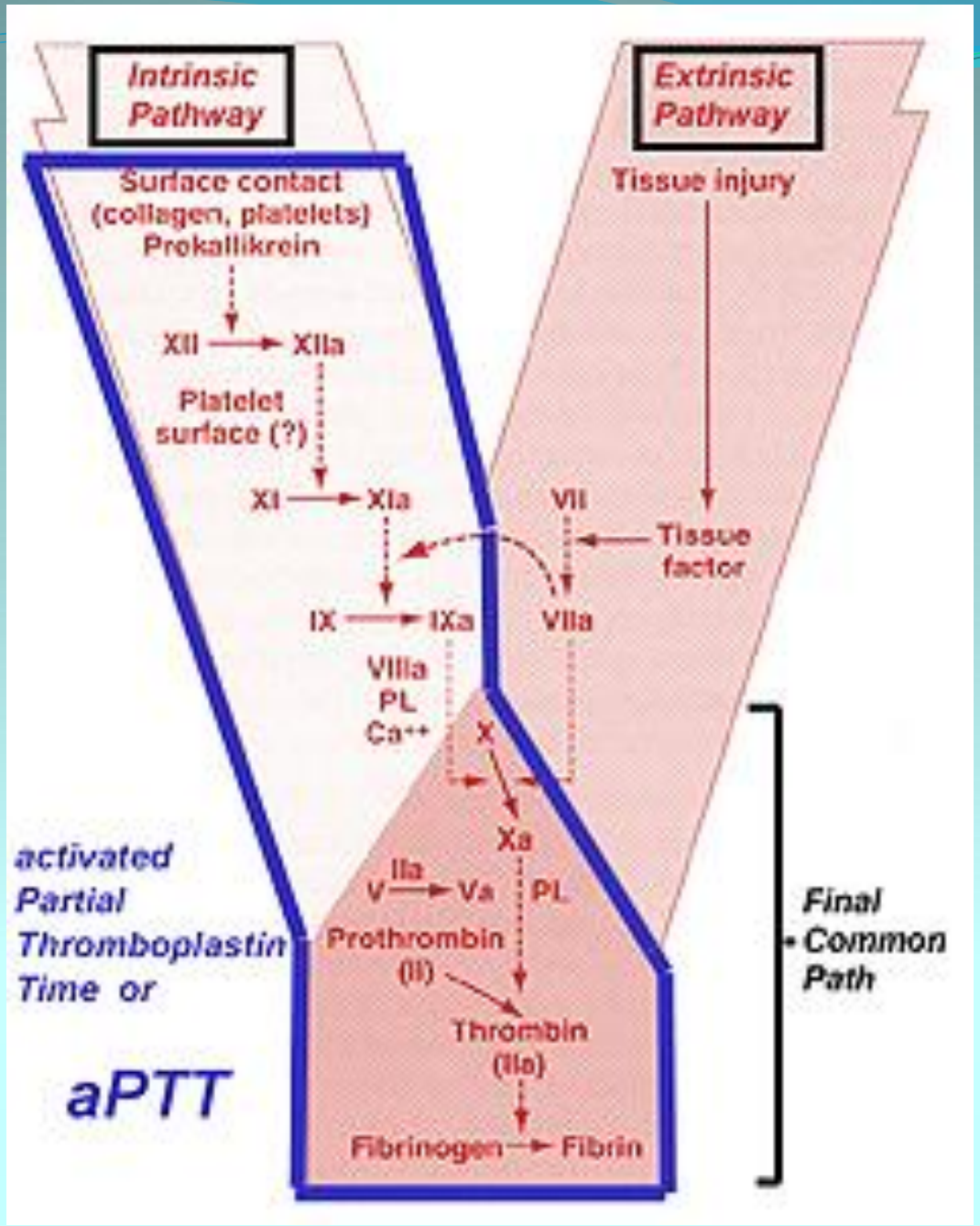
60 U/kg bolus to a maximum of 4000 U (i.e., 4000 U bolus dose should be used for any patient who weighs >67 kg)

Infusion:

12 U/kg/h infusion to a maximum of 1000 U/h (i.e., 1000 U/h infusion dose should be used for any patient who weighs >83 kg)

Weight-Based Adjustments Based on 6-Hour PTT:

PTT <1x control: re-bolus 60 U/kg (max 4000 U) and increase infusion rate by 2 U/kg/h
PTT 1 to 1.5x control: increase infusion rate by 2 U/kg/h
PTT 1.5 to 2x control: no change (therapeutic range)
PTT 2 to 3x control: decrease infusion rate by 2 U/kg/h
PTT >3x control: stop infusion, recheck PTT in 1 hour, follow algorithm based on repeat PTT


Intrinsic Pathway
Extrinsic Pathway
Surface contact
(collagen, platelets)
Prekallikrein
Tissue injury
XII
XIIa
Platelet surface (?)
XI
XIa
VII
Tissue factor
IX
IXa
VIIa
VIIIa
PL
Ca++
X
Xa
activated Partial Thromboplastin Time or
aPTT
IIa
V
Va
PL
Prothrombin (II)
Thrombin (IIa)
Fibrinogen
Fibrin
Final Common Path

HEPARINA

Indicaţii:

- tromboza venoasă profundă
- infarctul miocardic acut
- angină instabilă
- tromboembolia pulmonară

Reacţii adverse:

- hemoragii → se foloseşte ca antidot sulfatul de protamină, în perfuzie lentă
- trombocitopenie → la administrarea peste 5 zile
- alergie
- osteoporoză, mai ales administrată timp îndelungat

Contraindicaţii:

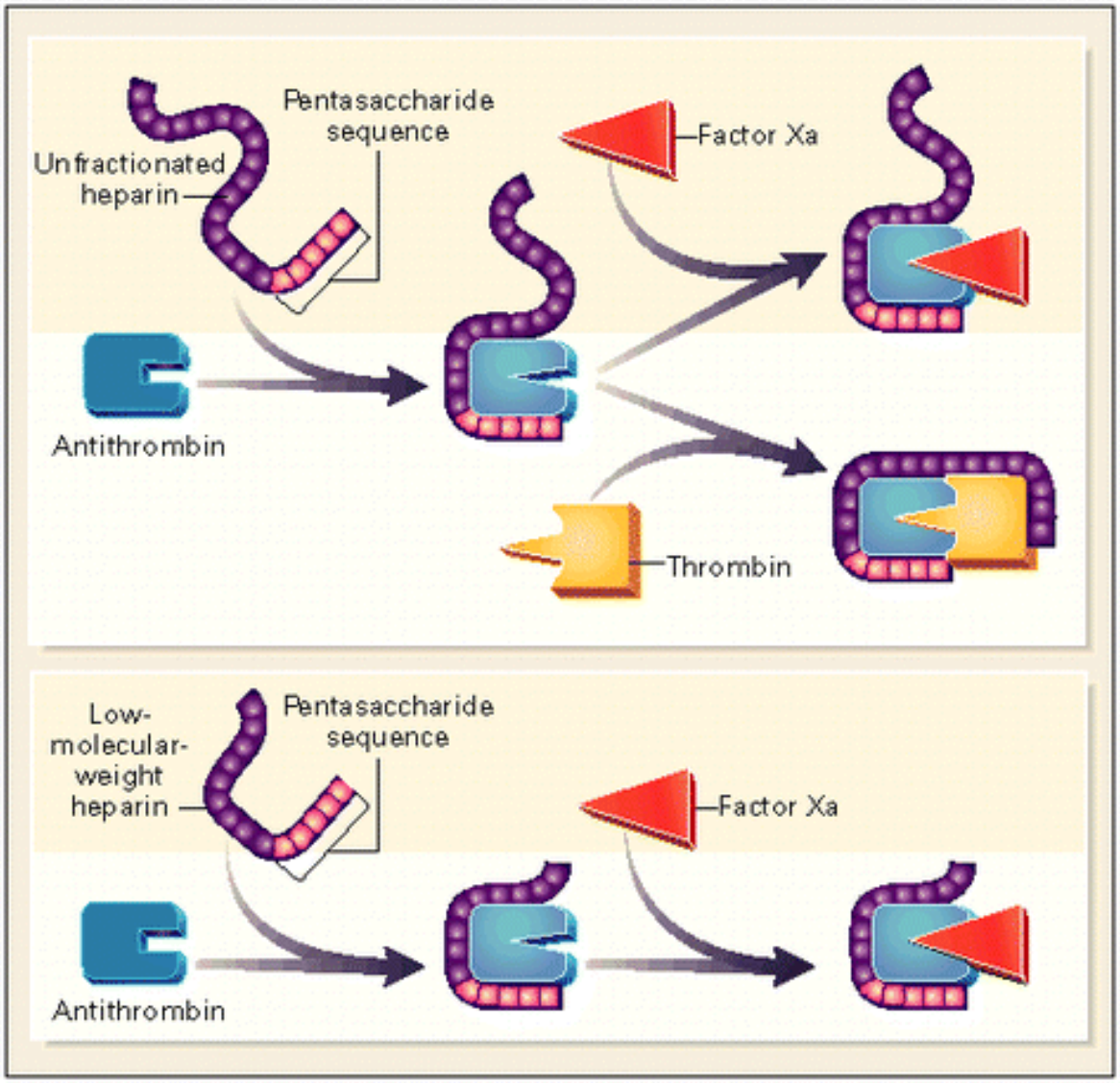
- hemoragie cerebrală
- HTA severă

HEPARINE CU MASA MOLECULARA MICA

Heparine cu masa moleculara mică

- **Dalteparina (Fragmin)**
- **Enoxaparina (Clexane)**
- **Nadroparina (Fraxiparina)**
- **Reviparina (Clivarin)**

- Se administrează subcutanat de 1-2 ori pe zi
- Are mecanism de acţiune ca heparina clasică, dar direcţionat mai mult pe factorul X.
- Se folosesc pentru profilaxia trombozelor venoase şi emboliilor.


Pentasaccharide sequence
Unfractionated heparin
Factor Xa
Antithrombin
Thrombin
Low-molecular-weight heparin
Pentasaccharide sequence
Factor Xa
Antithrombin

Limitations of UFH

Unpredictable anticoagulant effect

- Significant protein binding
- Saturable clearance mechanism
- Inactivation by platelet factor 4
- < 25% of patients in therapeutic range 12 hours after beginning Rx (TIMI 9B)
- Inaccessibility to clot-bound thrombin

Monitoring required

IV administration

Platelet activation

Risk of HIT

Advantages of LMWH

More predictable anticoagulant response

- Reduced protein binding
- Less inactivation by PF 4

No monitoring required

SQ dosing

Reduced platelet activation

Less risk of HIT

ANTICOAGULANTE CUMARINICE
ANTIVITAMINA K

b. Anticoagulante cronice

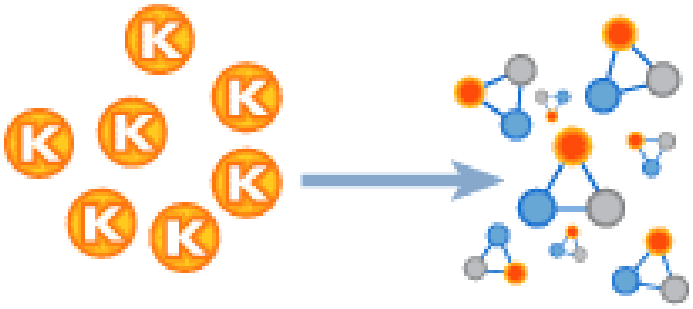
Se mai numesc şi **anticoagulante cumarinice** sau **antivitamine K.**

- Ele împiedecă sinteza hepatică a factorilor coagulării dependentă de vitamina K(II, VII, V, X)

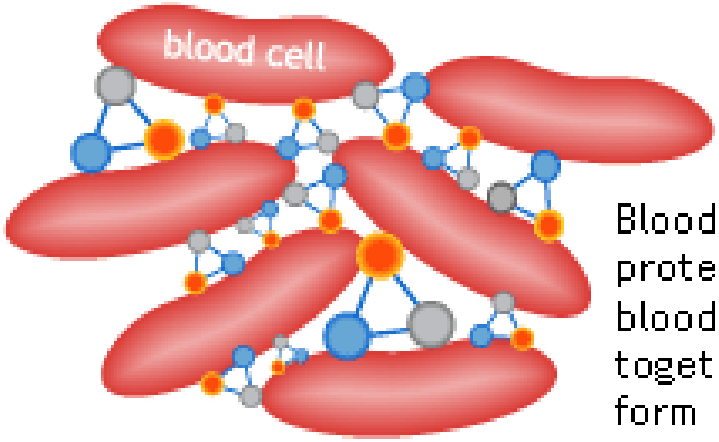
  Acenocumarolum → Trombostop cp. 2 mg
  Sintrom cp. 4 mg

  Warfarina (mai ales in SUA)
- Traversează bariera hematoencefalică şi placenta (contraindicate gravidelor).
- Se leagă procentual mai mult de proteinele plasmatice.
- Au timp de latenţă mai mare (timpul de latenţă este egal cu timpul de viaţă al factorilor coagulării deja activaţi)
- Au durată de acţiune prelungită
- Dozarea trebuie riguros controlată prin:
  - timpul Quick
  - INR *(International Normalized Ratio)* această metodă compară TQ al pacientului cu TQ mediu al unui grup de indivizi consideraţi normali. Valoarea normală **0,8-1,2.**

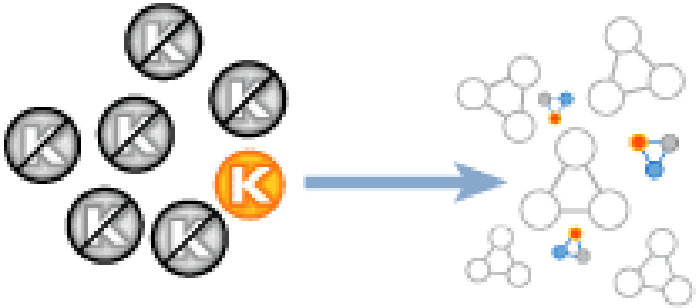
How Warfarin Affects Blood Clotting



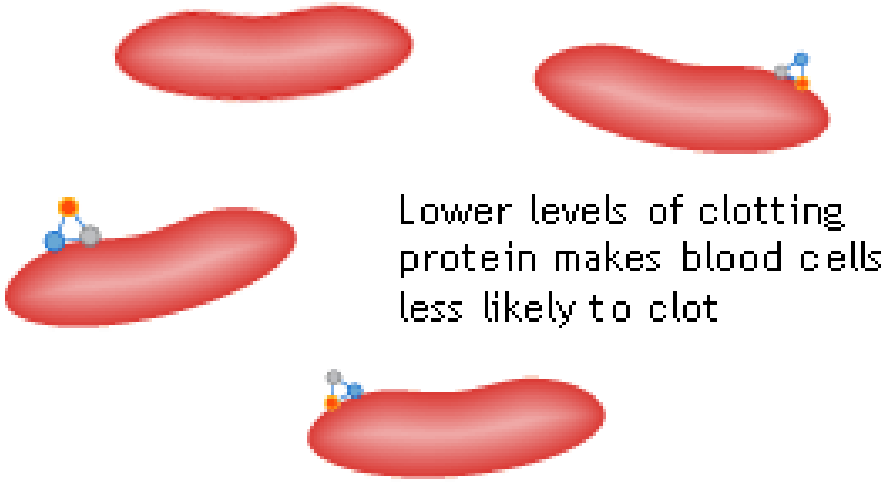
Vitamin K, produced by the body, helps form blood-clotting proteins



Blood-clotting proteins hold blood cells together to form clots



Warfarin reduces the body's ability to make Vitamin K which interferes with protein creation



Lower levels of clotting protein makes blood cells less likely to clot

ANTICOAGULANTE CUMARINICE
ANTIVITAMINA K

Indicaţii:

- tromboza venelor profunde
- infarct miocardic acut
- trombembolism pulmonar (6 luni)

Reacţii adverse:

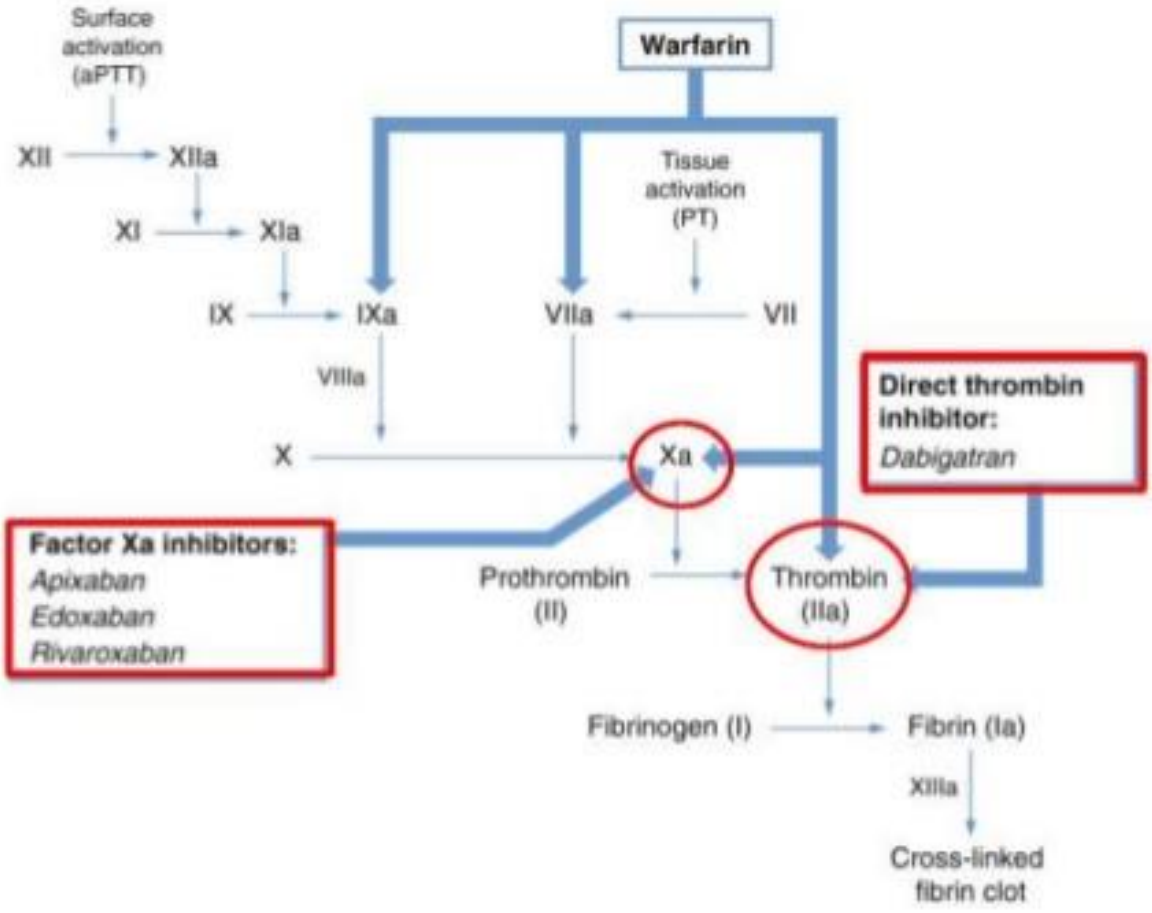
- Sângerare: ca antidot se administrează vitamina K fiola de 10 mg injectată intravenos lent (pentru că poate determina moarte subită.
- Se mai administrează plasma proaspată congelată şi crioprecipitat.
- Necroza ţesutului gras din zona perfuziei
- La făt, în primul trimestru, medicamentul e teratogen, afectează mai ales oasele iar în ultimul trimestru, există risc hemoragic.

- **Contraindicaţii**: sarcină, ulcer, alăptare, diateze hemoragice.

Novel Oral Anticoagulants (NOACs)

Direct Xa Inhibitor

Direct IIa Inhibitor



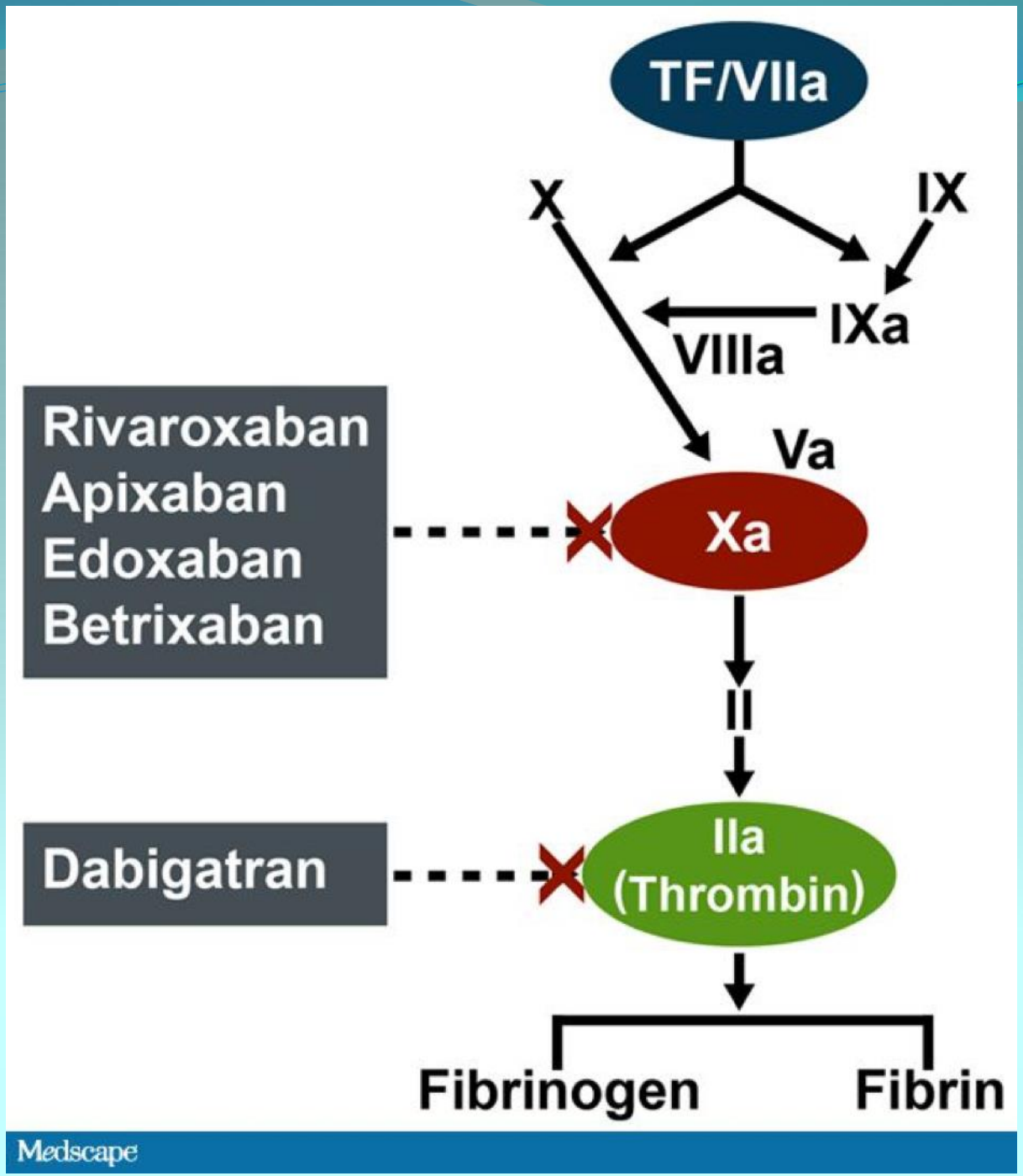

TF/VIIa
X
IX
IXa
VIIIa
Va
Xa
Rivaroxaban
Apixaban
Edoxaban
Betrixaban
II
IIa
(Thrombin)
Dabigatran
Fibrinogen
Fibrin
Medscape

Table 1. Properties of warfarin and oral inhibitors of thrombin and factor Xa inhibitors approved for use in the United States

	Warfarin	Dabigatran etexilate	Rivaroxaban	Apixaban
Target	Vitamin K epoxide reductase (VKORC1) lowers levels of vitamin K–dependent coagulation factors	Thrombin	Factor Xa	Factor Xa
Prodrug	No	Yes	No	No
Bioavailability	> 95%	6.5%	80%	~ 66%
Tmax		2 h	2.5-4 h	3 h
Half-life	40 h	12-14 h	7-13 h	8-13 h
Routine coagulation monitoring	Yes	No	No	No
Dosing	Once daily (INR-adjusted)	Fixed, BID	Fixed, BID	Fixed, BID
Elimination	Hepatically metabolized	80% renal	67% renal (half is inactive drug), 33% fecal	25% renal, 75% fecal
Potential drug interactions	CYP 2C9, 3A4, and 1A2	Potent P-gp inhibitors and P-gp inducers	Strong dual CYP 3A4 and P-gp inhibitors/inducers	Strong dual CYP 3A4 and P-gp inhibitors/inducers

Adapted from Bauer[2] and Ansell.[4]

Tmax indicates time to peak plasma levels; and P-gp, P-glycoprotein.

NOACs: Indications and Dosing

	Dabigatran	Rivaroxaban	Apixaban
Class	**Direct Thrombin Inhibitor**	**Factor Xa Inhibitor**	**Factor Xa Inhibitor**
Indications	• Reduction of risk of stroke and systemic embolism in nonvalvular AF	• Reduction of stroke and systemic embolism in nonvalvular AF • Treatment of DVT & PE • Reduction of recurrence of DVT & PE • Prophylaxis of DVT following hip or knee replacement surgery	• Reduction of stroke and systemic embolism in nonvalvular AF
Recommended Dosing for AF	150 mg BID	20 mg QD	5 mg BID
Renal Dosage Adjustments	CrCl 15-30 mL/min: 75 mg BID	CrCl 15-50 mL/min: 15 mg QD	≥2 present: ≥80 years, body weight ≤60 kg, or serum creatinine 1.5 mg/dL: 2.5 mg BID

Dabigatran Prescribing Information, 2012; Rivaroxaban Prescribing Information, 2012; Apixaban Prescribing Information, 2012.

Novel Oral Anticoagulants (NOACs)

Generic name	Brand name	Enzyme target	Renal clearance	Half-life (h)
Dabigatran	*Pradaxa*	Thrombin	85%	12 -17
Rivaroxaban	*Xarelto*	Factor Xa	30%	7 - 11
Apixaban	*Eliquis*	Factor Xa	25%	12
Edoxaban	*Lixiana*	Factor Xa	35%	10 - 14

Table 1

Agent with the largest relative risk reduction of ischemic stroke	Dabigatran
Agents with the largest renal elimination	Dabigatran (80%)
	Edoxaban (50%)
Agent to avoid in patients w/ CrCl>95ml/min	Edoxaban
Once daily dosing	Edoxaban
	Rivaroxaban
Established dosing for high-risk patients w/ modest renal function	Rivaroxaban
	Apixaban

Anticoagulation - NOACs

Recommendations for prevention of thromboembolism in non-valvular AF - NOACs		
Recommendations	Class	Level
When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)[d] … is recommended.	I	B
Where OAC is recommended, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban)[d] … should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.	IIa	A

Camm AJ, et al. *Europace*. 2012 ;14:1385-1413.[22]

Dose Recommendations Vary Across Different NOACs*

	VTE prevention after elective hip or knee replacement	Acute VTE treatment	Cont'd VTE treatment and prevention of VTE recurrence	Stroke prevention in NVAF	Secondary prevention of ACS
Dabigatran[1]	2 caps 110 mg od	Parenteral AC for at least 5 days followed by 1 caps 150 mg bid	1 caps 150 mg bid	1 caps 150 mg bid	n.a.
Apixaban[2]	1 tab 2.5 mg bid	2 tabs 5 mg bid for 7 days followed by 1 tab 5 mg bid	1 tab 5 mg bid for 6 months followed by 1 tab 2,5 mg bid	1 tab 5 mg bid	n.a.
Edoxaban[3]	n.a., except Japan	Parenteral AC for at least 5 days followed by 1 tab 60 mg od	1 tab 60 mg od	1 tab 60 mg od	n.a.
Rivaroxaban[4]	1 tab 10 mg od	1 tab 15 mg bid for 21 days	1 tab 20 mg od from day 22 onwards	1 tab 20 mg od	1 tab 2.5 mg bid on top of single or dual AP therapy

*Different dosing recommendations may exist for special patient populations or other certain conditions. The SmPC recommendations for each NOAC need to be followed. AP=Antiplatelet.

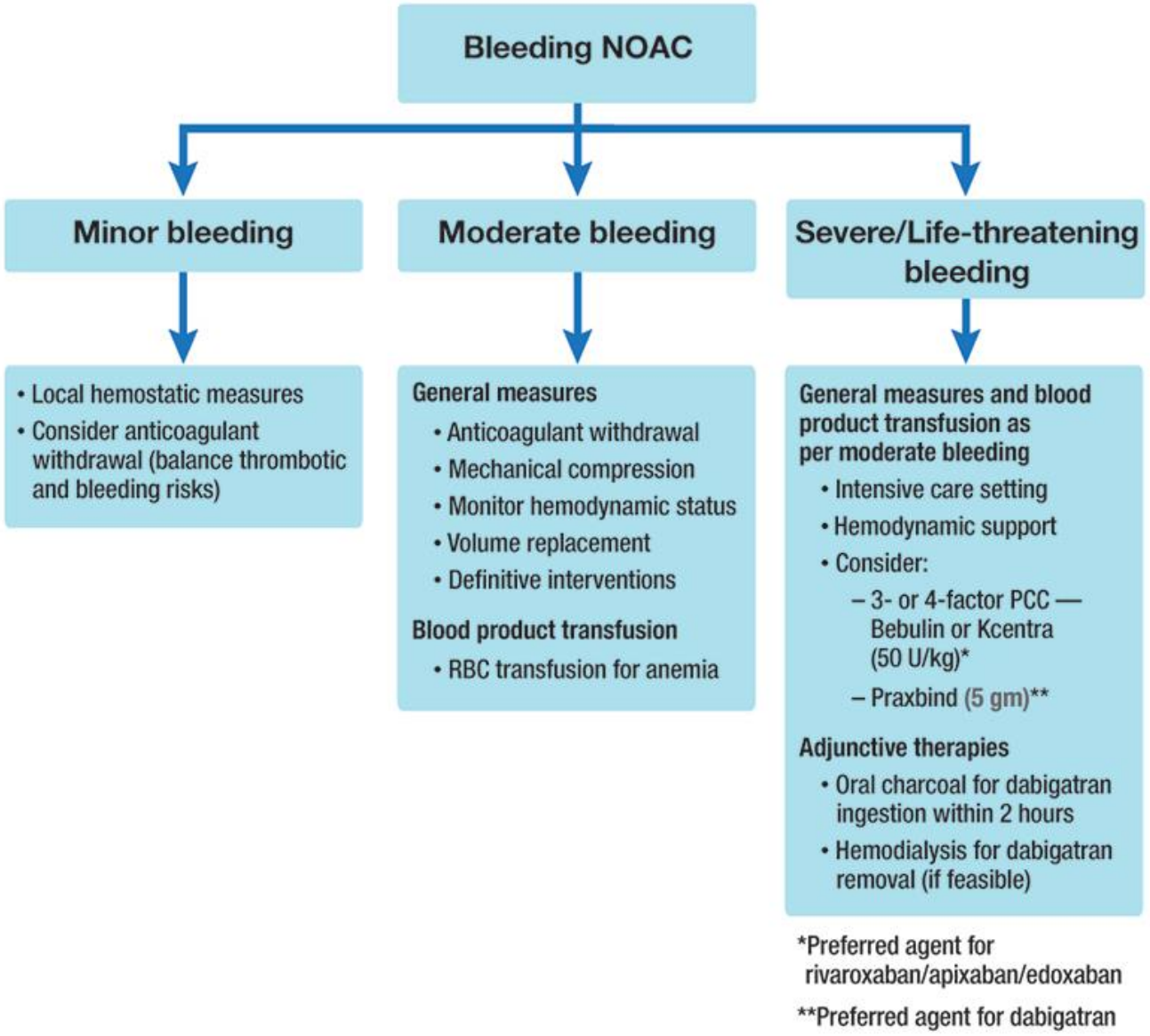
1. Dabigatran Summary of Product Characteristics; 2. Apixaban Summary of Product Characteristics;
3. Edoxaban Summary of Product Characteristics; 4. Rivaroxaban Summary of Product Characteristics.

NOACs in liver disease – is there a problem?

Because **all NOACs are dependent on the liver for metabolism to some degree**, patients with hepatic dysfunction are not ideal candidates for these agents, especially if there is pre-existent evidence of coagulopathy (an elevated INR).

Restrictions for the use of NOACs in patients with liver disease are based on the **Child-Pugh classification system** and exclusion criteria applied in pivotal trials.

Guidelines For Management Of Bleeding Associated With NOAC



NOACs in renal dysfunction – Practical recommendations for dosing in chronic kidney disease

Dabigatran	Apixaban	Edoxaban *	Rivaroxaban
When CrCl 30-49 ml/min, 150 mg BID is possible (SmPC) but 110 mg BID if 'high risk of bleeding' (SmPC) or 'recommended' (GL update)[1] Note: 75 mg BID approved in US only ** -if CrCl 15-30 ml/min - if CrCl 30-49 ml/min -and other orange factor (e.g. verapamil)	CrCl 15-29 ml/min: 2.5 mg BID is possible Serum creatinine ≥ 1.5 mg/dl in combination with age ≥80 years or weight ≤60 kg (SmPC) or with other yellow' factor: 2.5 mg BID	not available	15 mg OD when CrCl 15-49 ml/min

* No EMA approval yet. Needs update after finalisation of SmPC ** No EMA indication. FDA recommendation based on pharmacokinetics. Carefully consider benefits and risks of this approach Note that 75 mg capsules are not available in Europe for AF indication.

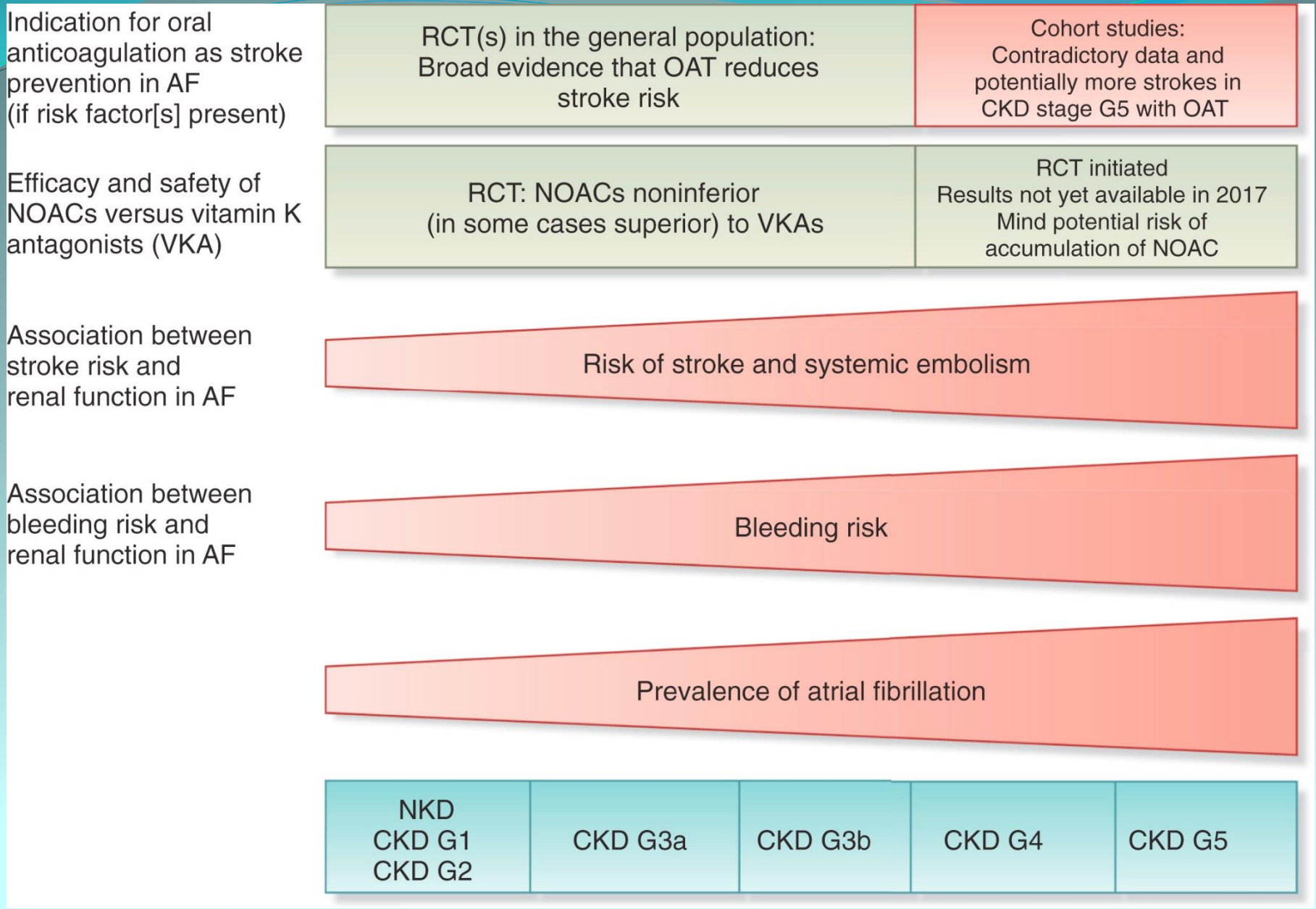
1. Camm et al, Eur Heart J 2012;33:2719-47

CCS 2012 Update to AF Guidelines: Renal Function

GFR	Warfarin	Dabigatran	Rivoraxaban	Apixaban
GFR >50 mL/min	Dose adjusted for INR 2.0–3.0	150 mg BID or 110 mg BID	20 mg daily	5 mg BID
GFR 30–49 mL/min	Dose adjusted for INR 2.0–3.0	150 mg BID or 110 mg BID	15 mg daily	5 mg BID (for GFR >25 ml/min only) Consider 2.5 mg BID
GFR <30 mL/min	No RCT data	Contraindicated	No RCT data	No RCT data

†Consider Apixaban 2.5 mg po bid if GFR ≤ 25 mL/min, especially if age > 80 or body weight < 60 kg
‡Dose adjusted warfarin has been used, but observational data regarding safety and efficacy is conflicting
¶No published studies support a dose for this level of renal function; product monographs suggest the drug is not recommended for this level of renal function

The patient's eGFR should be regularly reassessed in order to ensure that changes in the NOAC drug or dose correspond to changes in the eGFR.


Indication for oral anticoagulation as stroke prevention in AF (if risk factor[s] present)
RCT(s) in the general population: Broad evidence that OAT reduces stroke risk
Cohort studies: Contradictory data and potentially more strokes in CKD stage G5 with OAT
Efficacy and safety of NOACs versus vitamin K antagonists (VKA)
RCT: NOACs noninferior (in some cases superior) to VKAs
RCT initiated
Results not yet available in 2017
Mind potential risk of accumulation of NOAC
Association between stroke risk and renal function in AF
Risk of stroke and systemic embolism
Association between bleeding risk and renal function in AF
Bleeding risk
Prevalence of atrial fibrillation
NKD
CKD G1
CKD G2
CKD G3a
CKD G3b
CKD G4
CKD G5

FIBRINOLITICE

Fibrinoliticele

- Medicamentele fibrinolitice sunt capabile să lizeze cheagul de sânge.
- Ele favorezează formarea plasminei, fiind active îndeosebi în interiorul cheagului, care protejează plasmina de antiplasminele circulante.
- Sunt indicate în cazuri selecţionate de infarct miocardic acut, embolie pulmonară gravă, tromboze venoase profunde severe, tromboze arteriale la nivelul membrelor (atunci când intervenţia chirurgicală nu este posibilă).
- Trebuie administrate precoce deoarece cheagurile vechi sunt puţin influenţate.

  - **Alteplaza**
  - **Streptokinaza**
  - **Urokinaza**
- Toate acestea determină liza cheagului de fibrină prin activarea sau stimularea plasminei.

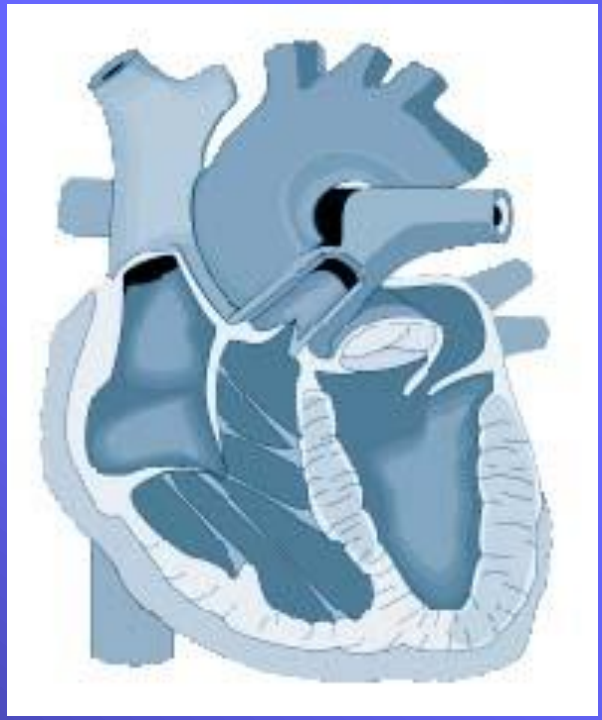
FIBRINOLITICE

- **Alteplaza** este o enzimă naturală ce se leagă de fibrină, la suprafaţa trombului şi determină transformarea plasminogenului în plasmină. E tromboselectivă.
  - Indicaţiile ateplazei sunt trombus arterial recent (infarct miocardic acut, trombembolism pulmonar) adică la maxim 6 – 8 ore după apariţia lui.
  - Contraindicaţii :traumatisme recente, intervenţii chirurgicale recente, accident vascular recent, HTA severă, ulcer, 30 minute după masajul cardiac, intoleranţa la glucoză.

- **Streptokinaza** nu are efect direct pe plasminogen dar îl activează.
  - Contraindicaţii: infecţie recentă streptococică
  - Reacţii adverse: alergie, hta severă.

- **Urokinaza** se obţine din culturi celulare renale umane; activează direct plasminogenul. Reacţiile adverse sunt mai uşoare.

MEDICAMENTE INOTROP POZITIVE



- **DIGITALICE (TONICARDIACE, GLICOZIZI CARDIACI)**
- **INHIBITORII FOSFODIESTERAZEI**
- **SIMPATICOMIMETICE (ADRENERGICE SI DOPAMINERGICE):**

Adrenalina	**Isoprenalina**
Dopamina	**Prenalterol**
Dobutamina	**Pirbuterol**

DIGITALICE

ORIGINE:

200 ani

- DIGITOXINA <= Digitalis purpureea
- DIGOXIN si LANATOSID C <= Digitalis lanata
- STROFANTINA <= Strofantus gratus
- B-METIL-DIGOXIN <= semisinteza

FARMACOCINETICA

- DIGITOXINA – foarte liposolubil
- DIGOXIN – uşor liposolubil
- STROFANTINA - hidrosolubil

FARMACOCINETICA

Absorbţia:

- DIGITOXINA: 90 – 100%
- DIGOXIN: 55 – 75%
- STROFANTINA: 1 – 3%

FARMACOCINETICA

Distribuţia:

Fixarea pe proteinele plasmatice:

- DIGITOXINA – 95%
- DIGOXIN – 25%
- STROFANTINA – 0,5%

FARMACOCINETICA

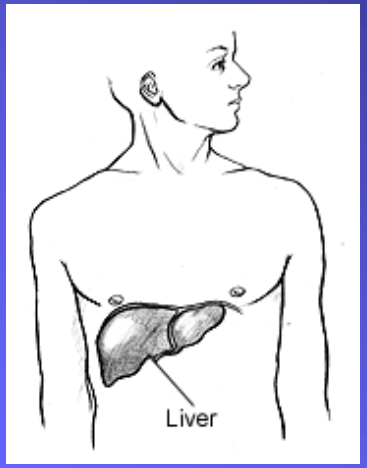
Timpul de injumatatire:

- DIGITOXINA = 6 zile 
- DIGOXIN = 40 ore 
- STROFANTINA = 21 ore 

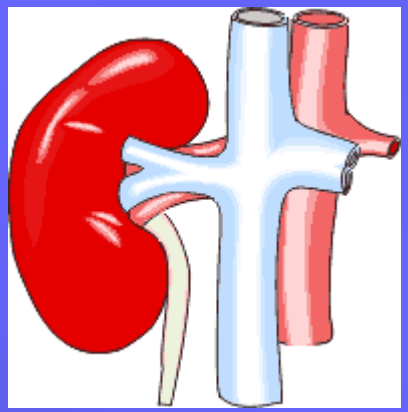
FARMACOCINETICA

Eliminarea:

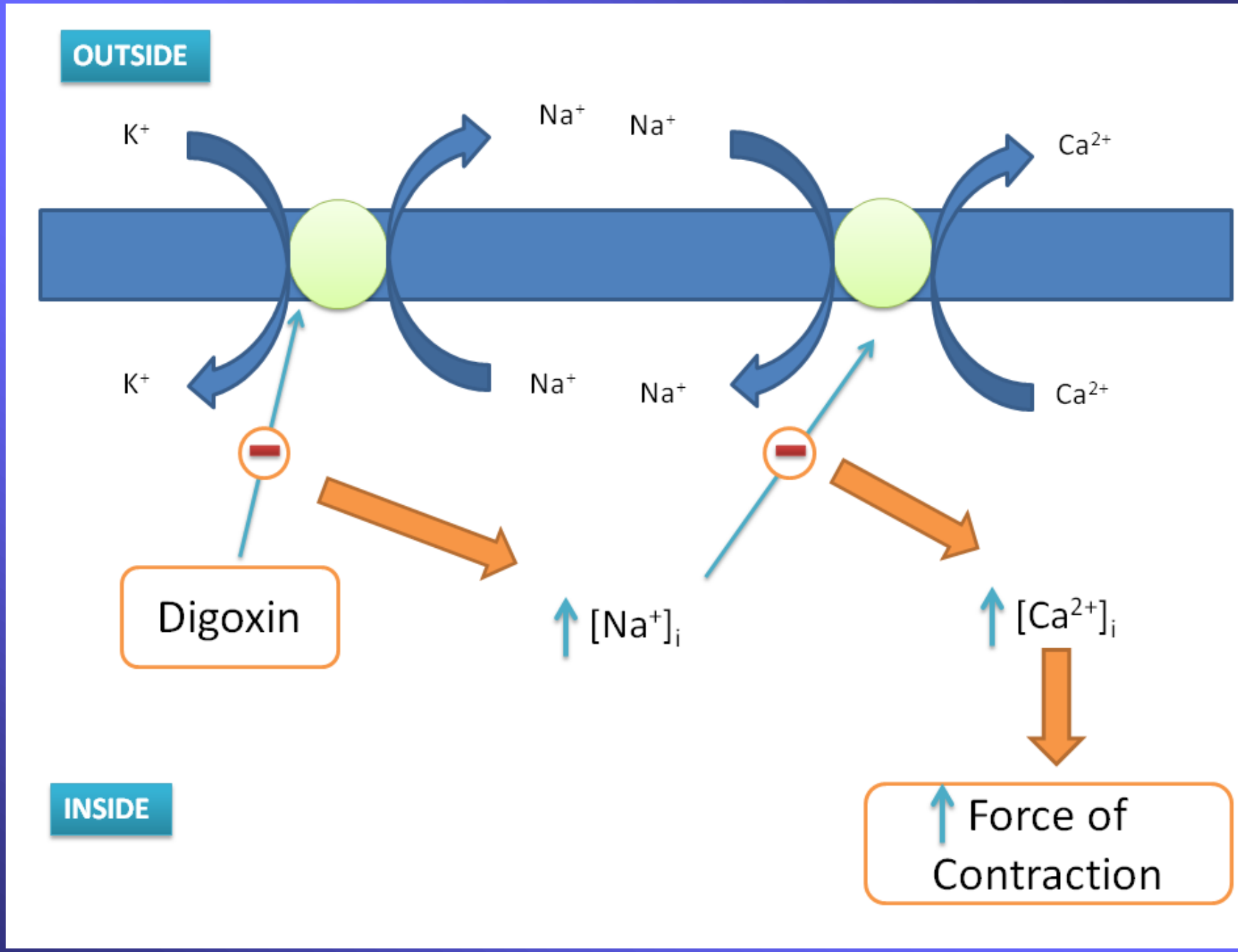
- DIGITOXINA – metabolizat hepatic 90%



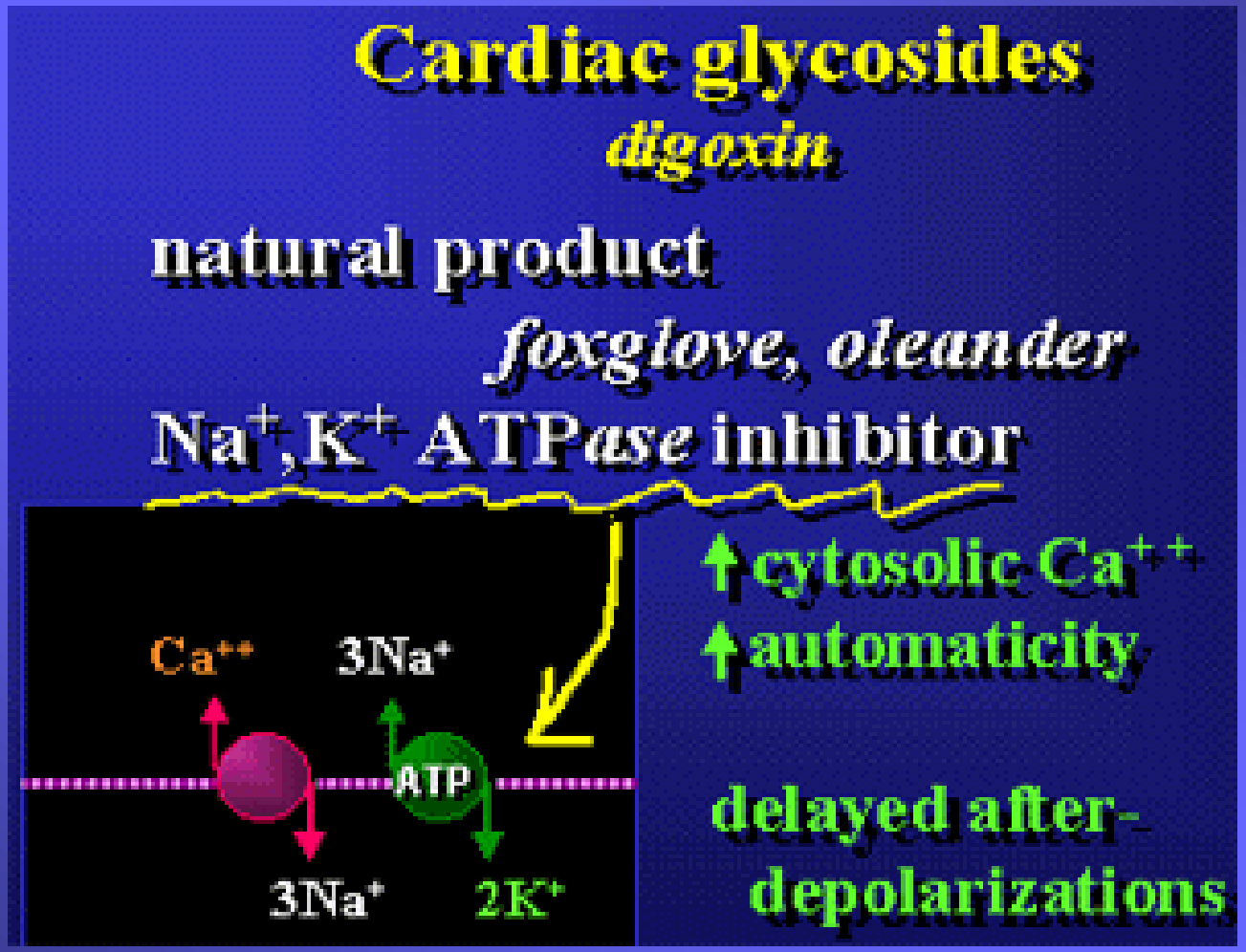
- DIGOXIN – eliminat renal



- STROFANTINA – eliminat renal


OUTSIDE
K+
Na+
Na+
Ca2+
K+
Na+
Na+
Ca2+
Digoxin
↑ [Na+]i
↑ [Ca2+]i
INSIDE
↑ Force of Contraction

MECANISM DE ACTIUNE



MECANISM DE ACTIUNE

Na^+K^+ATP aza

↓

Pompa Na^+K^+

↓

Na^+ intracelular

↓

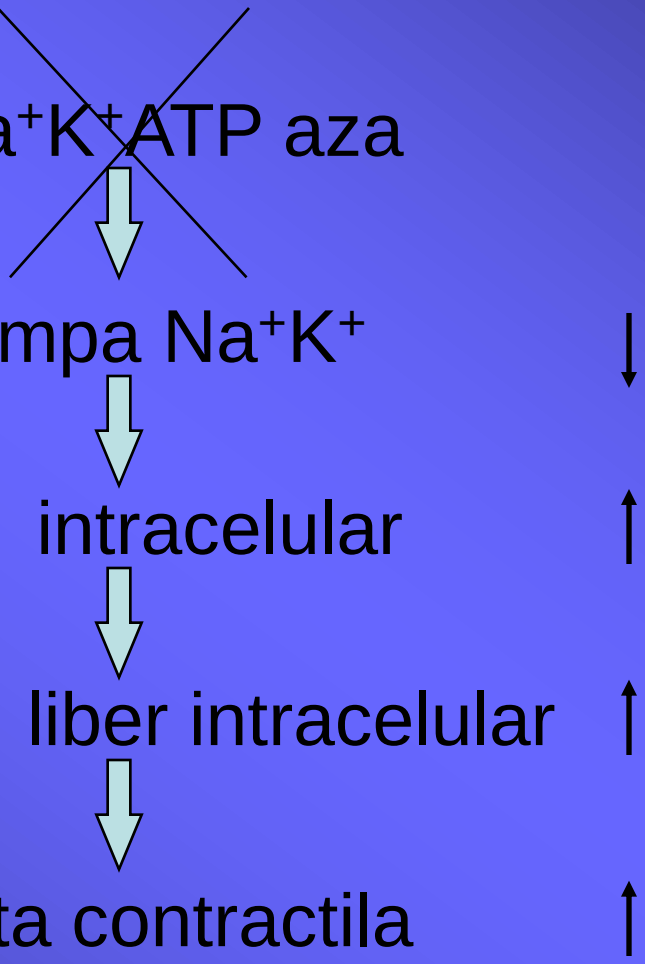
Ca^{2+} liber intracelular

↓

forta contractila

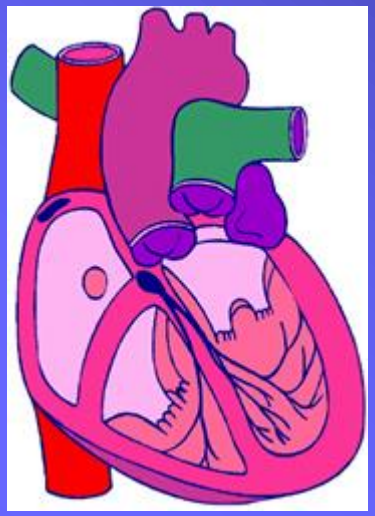
MECANISM DE ACTIUNE

DIGOXIN



ACTIUNE FARMACODINAMICA

- Efecte cardiace



- Efecte extracardiace:
  - Asupra rinichiului
  - Asupra vaselor
  - Asupra SNC

EFECTE CARDIACE

- Inotrop +
- Cronotrop –
- Dromotrop –
- Batmotrop –

EFECTE CARDIACE

Inotrop +

– Forta si viteza de contractie a miocardului normal si insuficient

↓ durata ejectiei ventriculare

↑ volumul de ejectie ventricular

↑ timpul de umplere diastolica

EFECTE CARDIACE

Cronotrop –

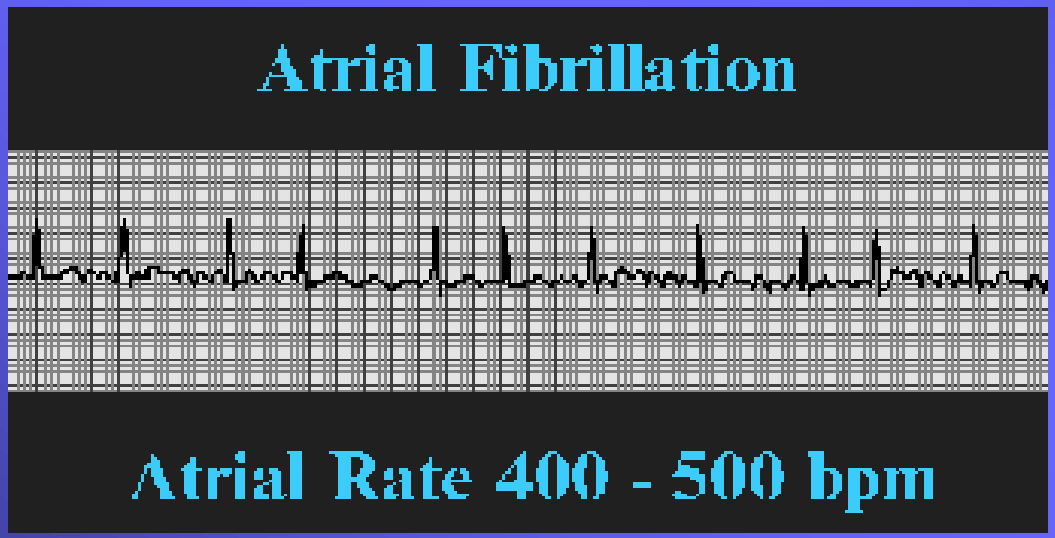
= efect bradicardizant

- Stimularea directa a centrilor vagali
- Activare baroreceptori din sinus carotidian si crosa aortei

EFECTE CARDIACE

Dromotrop –

- Incetinirea vitezei de conducere atrio-ventriculara => efect in fibrilatia atriala cu ritm rapid



EFECTE CARDIACE

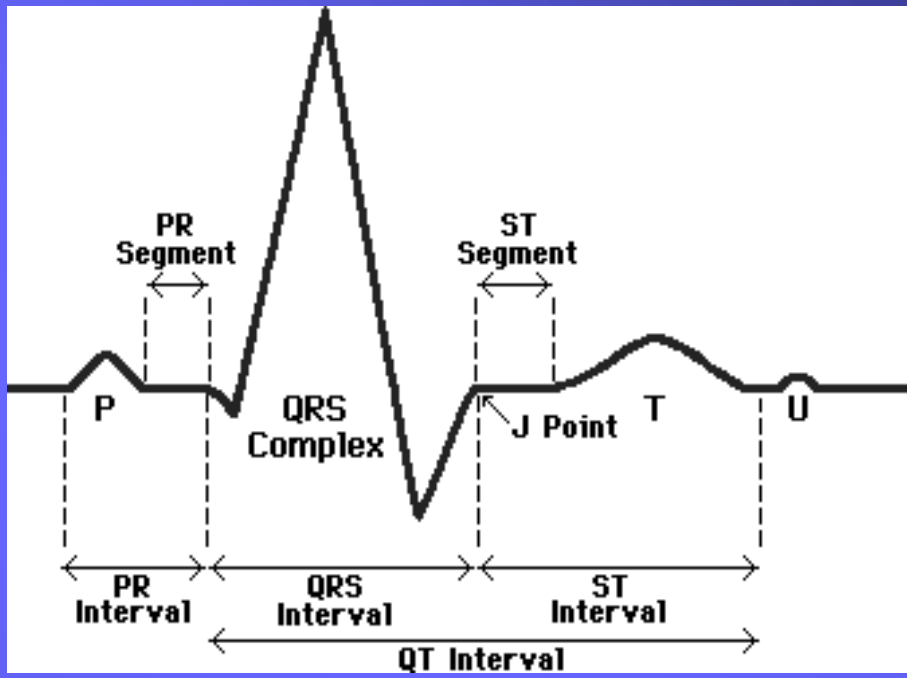
Batmotrop

= efect proaritmic

- miocard indemn, doze terapeutice–>efect neglijabil
- miocard lezat, doze mari sau terapeutice –> efect proaritmic (prin ↑ PRE si ↑ excitabilitatii miocardului ventricular)

EFECTE EKG

- ↓ frecventei cardiace
- ↑ PR
- ↓ QT
- Subdenivelare ST, uneori cu concavitatea in sus
- Aplatizarea sau inversarea undei T

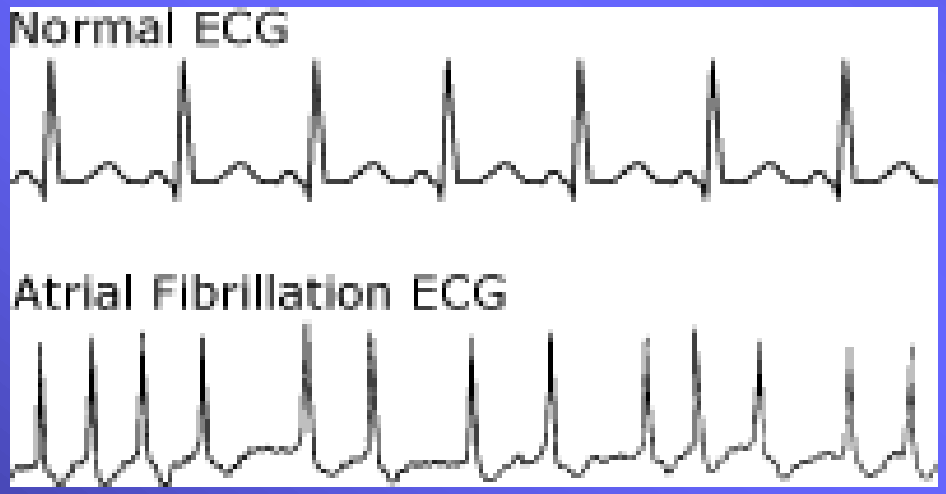


EFECTE EXTRACARDIACE

- Pe rinichi: efect diuretic
- Pe vase:
  - Vasoconstrictie arteriolara => ↑ RPT
  - ↑ tonusul venos => ↑ presarcina
- SNC: activare tonus vagal

UTILIZARI TERAPEUTICE

- Insuficienta cardiaca acuta (EPA)
- Insuficienta cardiaca cronica cu FiA rapida
- Tulburari de ritm supraventricular:
  - Fi A
  - Fl A
  - TPSV



CONTRAINDICATII

- Intoxicatia digitalica
- Bradicardie
- Bloc AV
- Aritmii ventriculare grave: TV, ExV
- IC prin disfunctie diastolica (SA sau HTA):
  - Tonicardiacele cresc rigiditatea miocardului

EFECTE ADVERSE
INTOXICATIA DIGITALICA

- IT mic = 2 – 3
- Frecventa reactiilor adverse: 2% - 10-20%
- Factori favorizanti:
  - Doze inadecvate
  - Cardiopatie veche: Doze terapeutice –> D toxice
  - Varsta inaintata: ↓ FG
  - Hipokaliemia

INTOXICATIA DIGITALICA

Simptomatologie:

- Manifestari extracardiace: anorexie, greata, voma, tulburari de tranzit, dureri abdominale, tulb. neuro-senzoriale, vedere monocromatica 
- Manifestari cardiace: bradicardie sinusala, tulb. de conducere AV, tulb. de ritm atrial/ventricular, bigeminism ventricular

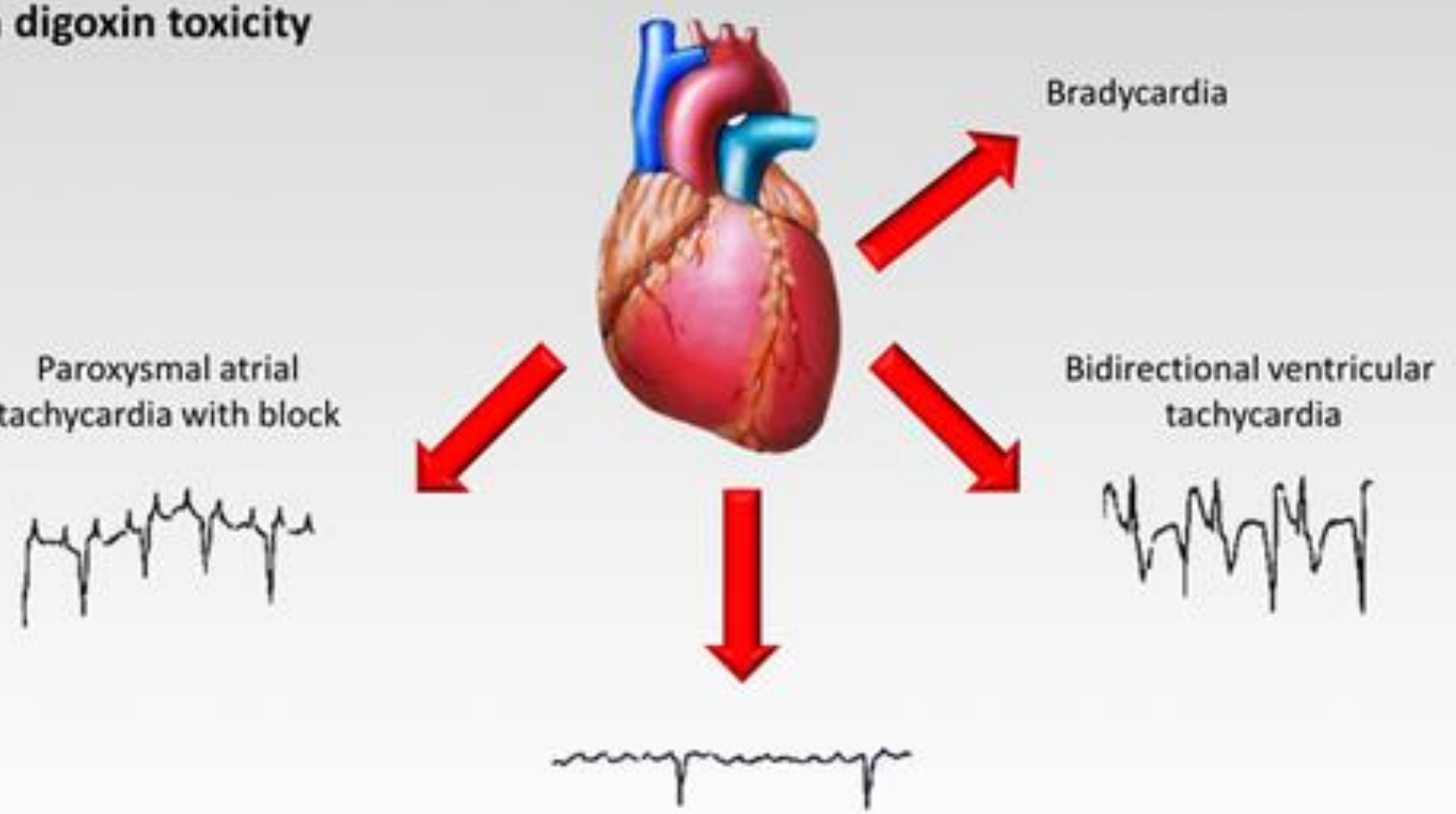
How to Recognize Digoxin Toxicity: Common Symptoms and Signs

Digestive	Vomiting, nausea, anorexia, diarrhea
Neurologic	Fatigue, headache, disorientation, delirium, confusion
Visual	Blurred or double vision, altered color perception, greenish-yellow halos around images or lights
Cardiac arrhythmia	Paroxysmal atrial tachycardia with AV block, PVCs, regularized atrial fibrillation *(regular R-R intervals)*, bidirectional VT *(QRS complexes from 2 different ectopic foci)*, *bradycardia (due to markedly enhanced vagal effect)*

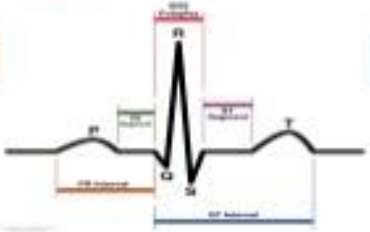
Mann DL. Management of heart failure patients with reduced ejection fraction. In: Libby P, Bonow RO, Mann DL, Zipes DP, Braunwald E, eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. Philadelphia, PA: Saunders Elsevier; 2008:611-640.

How to Recognize Digoxin Toxicity: Common Symptoms and Signs

Common arrhythmias associated with digoxin toxicity



Digitalis – EKG Changes



Tissue or Variable	Effects at Therapeutic Dosage	Effects at Toxic Dosage
Sinus node	↓ Rate	↓ Rate
Atrial muscle	↓ Refractory period	↓ Refractory period, arrhythmias
Atrioventricular node	↓ Conduction velocity, ↑ refractory period	↑ Refractory period, arrhythmias
Purkinje system, ventricular muscle	Slight ↓ refractory period	Extrasystoles, tachycardia, fibrillation
Electrocardiogram	↑ PR interval, ↓ QT interval	Tachycardia, fibrillation, arrest at extremely high dosage

ADMINISTRAREA DIGITALICELOR

DOZA DE INCARCARE = DOZA DE SATURARE = STOC DIGITALIC (DS)

- Prima doza = 1/3 DS
- Restul dozei:
  - 24 h: digitalizare rapida
  - 2-3 zile: digitalizare medie
  - 6-7 zile: digitalizare lenta
- Eficienta: ↓ FC, ↓ edemelor, ↓ hepatomegaliei, turg. jugularelor, amelior. dispneei, ↑ diurezei

ADMINISTRAREA DIGITALICELOR

DOZA DE INTRETINERE (DI)

= doza / zi care mentine o concentratie plasmatica eficienta

= cantitatea de digitalice inactivate si eliminate pe zi

ADMINISTRAREA DIGITALICELOR

DIGOXIN

cp. 0,25 mg, f. 0,5 mg,

sol. 0,5mg/ml=30pic

DS pt. i.v.: 0,5 – 1,5 mg

ex. 2f.: ora 0 – 1f.

ora 12 – ½ f.

ora 24 – ½ f.

DS pt. oral: 1 – 1,5 mg

ex. 6 cp.: ziua I: 2x1cp.

ziua II: 2x1cp.

ziua III: 2x1cp.

ADMINISTRAREA DIGITALICELOR

DI / zi – se adm. oral:

0,25 mg / zi

= 1 cp. / zi la adulti

0,125 mg/zi

= ½ cp / zi peste 70 ani

Table 1. Brief Summary of Digoxin

Dosing	Dosage Adjustment	Target Serum Concentration	Bioavailability	Pharmacokinetics
Heart Failure				
LD: not recommended; MD: 0.125-0.25 mg daily	MD: CrCl >120 mL/min—0.25 mg once daily; CrCl 80-120 mL/min—0.25 mg alternating with 0.125 mg once daily; CrCl 30-80 mL/min—0.125 mg once daily; CrCl <30 mL/min—0.125 mg q48h. Patients >70 y should receive 0.125 mg daily or every other day. Reduce by 50% in ESRD	0.5-0.9 ng/mL	Oral: 70%; capsule: 90%; elixir: 80%; IV: 100%	Onset of action: IV—15-30 min; po—30-120 min Peak effect: IV—1-3 h; po—2-6 h
Atrial Fibrillation				
LD: 0.25 mg po/IV q2h (max 1.5 mg/24 h); MD: 0.125-0.375 mg po/IV daily	MD: CrCl >50 mL/min—no adjustment necessary; CrCl 10-50 mL/min—25%-75% of normal daily dosage q36h; CrCl <10 mL/min—10%-25% of normal daily dosage q48h. Continuous RRT: 25%-75% of normal daily dosage q36h	0.8-1.2 ng/mL	NA	NA

CrCl: creatinine clearance; ESRD: end-stage renal disease; LD: loading dose; max: maximum; MD: maintenance dose; min: minute; NA: not applicable; RRT: renal replacement therapy.
Source: References 2, 3, 5, 6.

MEDICAŢIA ANTIANGINOASĂ

- NITRATII ORGANICI si MOLSIDOMINA
- BETA-BLOCANTELE
- BLOCANTELE CANALELOR DE Ca

DERIVATII NITRATI

DERIVATII NITRATI CLASIFICARE

- **Derivati nitrati cu latenta si durata scurta de actiune**

  NITROGLICERINA, ISOSORBID DINITRAT - compr. sublinguale, spray sublingual

- **Derivati nitrati cu durata lunga de actiune**

NITROGLICERINA - compr. retard adm. oral; unguent-extern; sistem transdermic (plasture)

ISOSORBID DINITRAT – compr.

ISOSORBID MONONITRAT– compr.

PENTAERITRIL TETRANITRAT– compr.

DERIVATII NITRATI
MECANISM DE ACTIUNE

Derivati nitrati

↓

– Tionitriti si ↑ NO

↓

– GMPc

↓

↓ Ca++ intracelular

↓

Relaxarea musculaturii netede vasculare

DERIVATII NITRATI
ACTIUNE FARMACODINAMICA

- *vasodilatatie venoasa:*

↓ întoarcerea venoasa → ↓ presarcina → ↓ travaliul cardiac si ↓ consumul de O_2

- *vasodilatatia arterelor coronare:*

↑ debitul coronarian cu favorizarea redistribuirii sângelui spre zonele ischemiate

- accesoriu, *la doze mari vasodilatatia arteriolara* cu reducerea rezistentei periferice =>

↓ postsarcina

DERIVATII NITRATI
UTILIZARI TERAPEUTICE

- boala coronariana

  - angina pectorala de efort stabila sau angina instabila (tratament profilactic şi curativ)

  - infarctul miocardic acut: trat. cu nitroglicerina i.v.;

- insuficienţa cardiaca congestiva (secundara cardiopatiei ischemice) alaturi de tratamentul cu digitalice şi diuretice

DERIVATII NITRATI
EFECTE ADVERSE

-cefalee pulsatila dependenta de doza, mai ales la începutul terapiei; este secundara vasodilataţiei cerebrale cu ↑ presiunii intracraniene;

-hipoTA ortostatica, mai frecventa la vârstnici;

-tahicardie reflexa (la doze mari);

-toleranta medicamentoasa (după tratament continuu) determină disparitia actiunii antianginoase.

Pt. **evitarea tolerantei**:

- administrarea discontinua 10 - 12 ore/zi NTG + 12 ore blocanţi de calciu sau betablocante