ANTIHIPERTENSIVE

CLASIFICARE

1. **SIMPATOLITICE**

- centrale: agonisti alfa 2 presinaptici si agonisti ai rr imidazolici I1 presinaptici : **clonidina**, guanfacina, guanabenz, monoxidine, rilmenidina
- periferice: rezerpina, guanetidina, falsi mediatori
- alfa-blocante
- beta-blocante
- ganglioblocante

1.1 Centrale: Clonidina

-tp de ½ 8-12 h;
-cpr 0.1mg; 0.1-0.2mg/zi→0.6mg/zi in 2 doze
Efecte adverse: sedare, gura uscata, sedare, direct proportionale cu doza

Ex.
Dg: HTA
Rp/ clonidina 0.0001g
Cpr XXX
DS intern 1cpr/zi

*__Metildopa__

-analog al L-dopa→alfa-methyldopamina si alfa metilnorepinefrina→substituie NA in depozite→→fals neurotransmitator

--efect maxim in 4-6 ore, durata pana la 24h

Efecte adverse:
-sedare, cresterea secretiei de PRL, alterarea capacitatii de concentrare, vertij, anemie hemolitica, toxicitate hepatica, sindrom lupus-like
-cpr 250mg→250x2/zi→max 3g/zi

1.2: Periferice

-**Guanetidina**: substituie NA in veziculele de stocaj

- HTA 10mgx3/zi
-**Rezerpina:** cpr 0.25mg; inhiba recaptarea NA in veziculele de stocaj

1.3 Ganglioblocante-trimetarfan

-blocheaza receptorii nicotinici la nivel postganglionary, atat S cat si PS
-se administreaza supravegheat, intraspitalices
-in cursul interventiilor chirurgcale pentru a scadea TA
-administrat iv, in perfuzie

1.4 Blocante alfa 1

-**neselective**: fentolamina, fenoxibenzamina
-**selective:** prazosin, doxazosin, terazosin-bloc. rr alfa 1 arteriolari si venosi; risc< de tahicardie reflexa comparative cu cele neselective.
-**selective**- eficiente in asociere cu alte clase de antihipertensive
!
! TA este redusa I special in ortostatism

Prazosin: cpr 1;2 mg: 0.5mg/zi, 1 saptamana, crestere progresiva→3-30mg/zi in 2 administrari
Doxazosin: tp de ½ 22 h; 1mg/zi→4mg/zi
Terazosin: x2/zi, 5-20mg; tp de ½: 12 hours

1.5 Beta-blocante

CLASIFICARE:

-BETA 1: METOPROLOL BETAXOLOL, BISOPROLOL, NEBIVOLOL, ESOMOLOL, ATENOLOL

-BETA 1 SI BETA 2: PROPRANOLOL,

-BETA1, 2 SI ALPHA ADRENOLITICE: CARVEDILOL, LABETALOL

-EFECT CHINIDINIC, DE TIP ANESTEZIC LOCAL: PROPRANOLOL

INDICATII:

-HTA

-angina pectorala

--aritmii

**PROPRANOLOL-cpr* *10;40mg; fiole1mg*
****METOPROLOL cpr 25;50;100MG***
****CARVEDILOL cpr 6.25mg; 12.5; 25mg***
****BISOPROL cpr 2.5; 5; 10mg***

Exemple retete-semestrul 1

2. **Vasodilatatoare**

-directe/MUSCULOTROPE
-blocante ale canalelor de calciu

TABLE 11–3 Mechanisms of action of vasodilators.

Mechanism	Examples
Release of nitric oxide from drug or endothelium	Nitroprusside, hydralazine, nitrates,[1] histamine, acetylcholine
Reduction of calcium influx	Verapamil, diltiazem, nifedipine
Hyperpolarization of smooth muscle membrane through opening of potassium channels	Minoxidil, diazoxide
Activation of dopamine receptors	Fenoldopam

[1]See Chapter 12.

2.1 Vasodilatatoare-directe (musculotrope)

→arteriale: hydralazina, diazoxid, minoxidil
→venoase si arteriale: nitroprusiat

*** Hidralazina**

-vasodilatatie arteriolara→ scaderea rezistentei vasculare periferice→hTA
-↑prin mechanism reflex cresc secretia de renina
-tahicardie reflexa, cresterea debitului cardiac
-tp de ½: 1.5-3 h
Efecte adverse: tahicardie, palpitatii, edeme
-cefalee
-sindrom lupus like
-12.5x2/zi initial→50-200mg/zi in 2-4 administrari
-de obicei asociat cu un betablocant pentru reducerea tahicardiei

BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

2.1 Vasodilatatoare-directe (musculotrope)

***Nitroprusiat de sodiu 100mg in 1000ml glucoza pev**

-folosit in urgente hipertensive, EPAc datorat IVS

-vasodilatator arterial si venos→ reduce rezistenta vasculara periferica si intoarcerea venoasa

-activeaza guanilat-ciclaza fie prin eliberarea de NO fie prin stimulare directa→ creste cGMP intracelular→ relaxarea musculaturii netede

Farmacocinetica: scade rapid tensiunea arteriala dupa 1-10 minutes de la administrare

-administrat perfuzabil 100mg in 1000mg glucoza-o.5mcg/kg/min→ pana la 10mcg/kg/min;

BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

2.1 Vasodilatatoare-directe (musculotrope)

***Nitroprusiat de sodiu**

Efecte adverse:

-methomoglibinemie prin acumularea de tiocianat (la administrare peste 2-3 zile)
-colaps

2.1 Vasodilatatoare-directe (musculotrope)

***Diazoxid-fiole 50mg**

-arteriolodilatatie cu scaderea TA sistolice si diastolice
-tahicardie reflexa cu cresterea Qc
-creste activitatea reninei
-retentie hidrosalina
Hiperglicemie-prin diminuarea eliberarii insulinei pancreatice si utilizarii glucozei intracellular
-relaxarea musculaturii netede viscerale

2.1 Vasodilatatoare-directe (musculotrope)

***Diazoxid-fiole 50mg**

-iv 50-150mg repetat la nevoie, la 5-15 minute
Efect in 5 minute
-indicat de elective in tratametul de urgenta al HTA severe, urgente hipertensive

* **Nitroglicerina** (Trinitrosan 5/50mg)

2.2 **Blocante ale canalelor de calciu**: blocheaza influxul ionilor de claciu la nivelul canalelor voltaj dependente (L)

Clasificare

***in functie de structura chimica**:

→**dihidropiridine:** amlodipina, felodipina, nicardipina, nifedipina
→**benzotiazepine:** diltiazem
→**fenilalchilamine**: verapamil

BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

2.2 * **In functie de efect:**

- -**predominant vasodilatatoare artriale periferice:** dihidropiridine, folosite mai ales ca anti-HTA
- -**predominant coronarodilatatoare (antianginoase)**: diltiazem
- -**predominant deprimante cardiace, pe miocardul contractile si testutul excitoconductor (antiaritmice)**: verapamil

- !!**Affinity order**: Nifedipine: pheripheral arteries>coronaries>>contractile myocardic cells>conductor myocardic tissue
- D: coronaries>periperal arteries>>contractile m>>conductor m
- V: conductor m>contractile m>vessels

BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

2.2 BCCa

- !!**Ordinea afinitatii si intensitatii actiunii este urmatoarea**
- Nifedipina: arteriole periferice>coronare>>miocard contractile>>>>miocard excito-conductor
- Diltiazem: arteriole coronare>arteriole periferice>miocard contractile=tesut nodal
- Verapamil: tesut nodal>>miocard contractile=vase

2.2 BCCa

*__Nifedipina__
-absorbtie buna orala si sublinguala (aprox 90%)

-__Fd:__
-arteriolodilatatie periferica cu scaderea RVP si efect antihipertensiv
-coronarodilatatie
-efect deprimant cardiac redus→efect inotrop redus, nu deprima nodul sinusal si nodul AV
-tahicardie reflexa, consecutive hioptensiunii

Efecte adverse
-hTA ortostatica, cefalee, edeme-consecutive vasodilatatiei
-tahicardie, palpitatii
-depresiva, nevrozitate, greata

2.2 **BCCa:**

***Nifedipina**

Indicatii:
-antipertensiv HTA
-angina pectorala
-insuficienta cardiaca
-cpr 10mg; 1 cpr x3-4/zi
-sublingual 10mg, repetat dupa 30 minute, daca este necesar (in crize hypertensive)

BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

3. INHIBITORI AI SISTEMULUI RENINA ANGIOTENSINA ALDOSTERON (SRAA)

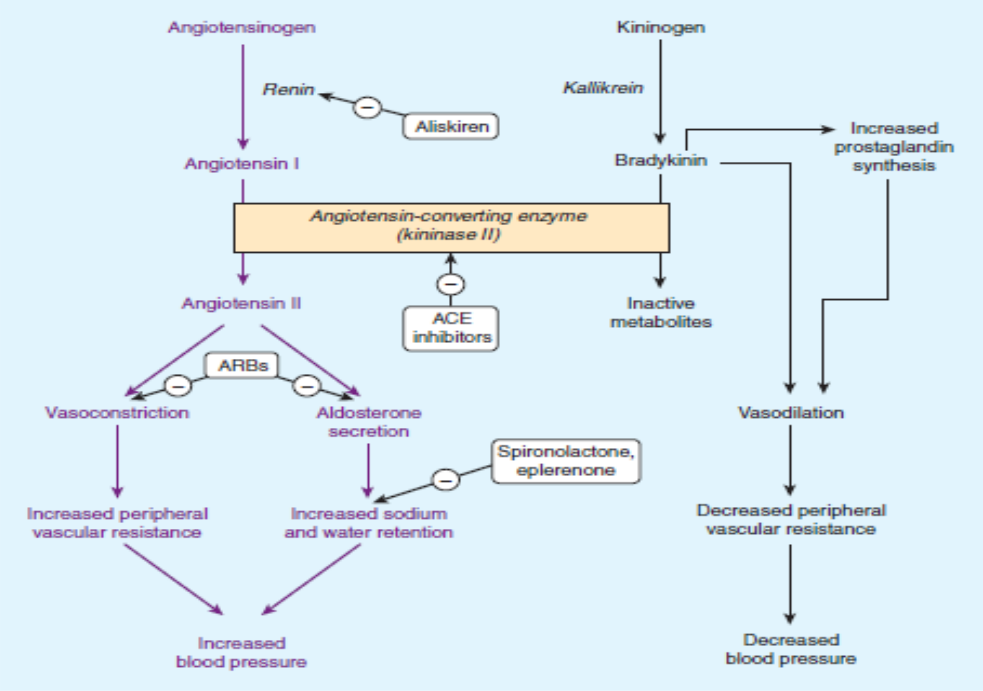


FIGURE 11–5 Sites of action of drugs that interfere with the renin-angiotensin-aldosterone system. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers.

3. INHIBITORI AI SRAA

3.1 INHIBITORI AI ENZIMEI DE CONVERSIE A ANGIOTENSINEI (IECA)

-SUBSTANTE ACTIVE: captopril, lisinopril

-PRODROGURI: benazepril, enalapril, fosinopril, moexipril, perindopril, ramipril, quinapril, trandolapril, zofenopril

3.2 **INHIBITORI AI RECEPTORILOR PENTRU ANGIOTENSINA**: sarlazina, candesartan, losartan, irbesartan

3. **INHIBITORI AI SRAA**

3.1 **IECA**

-↓ stimularea rr AT-1,↓stimularea S si eliberarea de CA→vasodilatatie arteriala si scaderea RVP

-↓secretia de aldosteron si retentia de sare si apa

-↑secretia de renina (mecansm de feed-back, consecutive scaderii conc. De angiotensina II)

-act. Si asupra SRAA paracrine de la nivelul vaselor si cordului; efect asupra remodelarii miocardice

-cresc secretia de bradikinina, consecutive similitudinii dintre bradikina si kinaza II→stimularea PG endogene (PGE2 si PGI2)→vasodilatatie (flush), alergii

3.1 **IECA**

Efecte adverse:

-gura uscata, obstructive nazala (datorita excesului de bradikina si PG)
-tulburari de gust
-angioedem
-insuficienta renala acuta, in special la pacientii cu stenoza bilaterala de artera renala sau rinichi unic
-hiperpotasemie, la pacientii cu insuf. renala sau diabet
-hipotensiune
-contraindicate in semestrul II sau III de sarcina, datorita riscului fetal sau hipotensiunii, anuriei, insuf. renale, datorita riscului de malformatii, morti fetale

3.1 **IECA**

Indicatii: HTA asociata cu insuf. Cardiaca, boala cronica renala-efect anti-proteinuric si stabilizarea functiei renale (ex. la pacientii cu diabet), dupa infarct miocardic.

3.1 IECA

REPREZENTANTI:

-Captopril cpr 25; 50; 12.5 mg: 12.5-300mg/zi
-Enalapril cpr 5; 2.5; 10; 20 mg; fiole 2.5mg/ml; 5-40mg/day (1-2 administrari)
-Fosinopril 10;20mg: 10-40mg/zi (1-2 administrari)
-Perindopril 4; 8mg cpr: 2-8mgx1/zi
-Ramipril cpr 2.5; 5; 10mg; 1.25-10mg/zi, 1 administrare

3.2 BLOCANTI AI RECEPTORILOR PENTRU ANGIOTENSINA

-bloc. RR AT-1 r→blocheaza efectele angiotensinei II (cv)
-AT-2 →efecte adverse
N: AT1: muschi netezi vasculari, miocard, SNC, renal.
AT2: medulosuprarenala, SNC, renal, placenta

Activarea rr AT1: inhibita secretia de renina, eliberarea de CA, vasoconstrictie, secretie de aldostero, retentive hidrosalina
Activarea AT2: anti-proliferativ, efect de reducere a cresterii

3.2 BLOCANTI AI RECEPTORILOR PENTRU ANGIOTENSINA

EFECTE ADVERSE:

- hTA,
- Hiperpotasemie
- scaderea functiei renale
- Stenoza bilaterala a arterei renale

-datorita activarii AT2:

- contraindicate in sarcina!
- Alterarea cresterii si dezvoltarii normale.

3.2 **BLOCANTI AI RECEPTORILOR PENTRU ANGIOTENSINA REPREZENTANTI:**

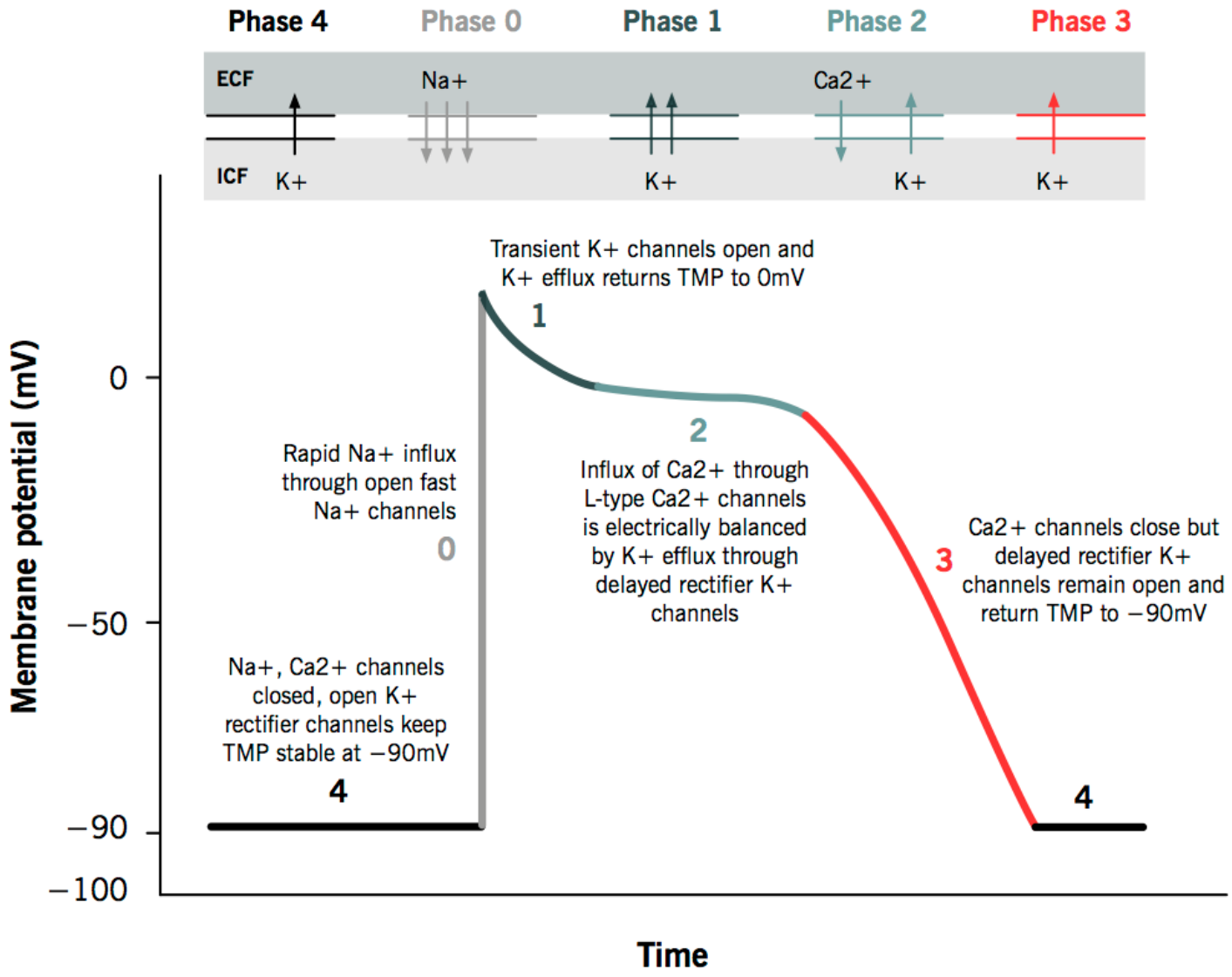
Candesartan (Atacand): CPR 8;16; 32 mg
Irbesartan (Aprovel) CPR 150-300mg
Telmisartan=CPR 20; 40mg; 80mg
Valsartan: CPR 80mg

4. DIURETICE

ANTIARITMICE

Action potential of cardiac muscles

Grigoriy Ikonnikov and Eric Wong



CLASA I-BLOCANTE ALE CANALELOR DE SODIU
-ACTIUNE ANESTEZICA LOCALA PRIN BLOC. CANALOR DE NA

CLASA IA-PROCAINAMIDA

-ACTIONEAZA PREDOMINANT ASUPRA CANALELOR DE NA ACTIVE (FAZA 0) SI ↓ AMPLITUDINEA PA, ↑ DURATA REPOLARIZARII→DIMINUA PERIOADA REFRACTARA

! ACTIONEAZA SPECIFIC PE ZONELE DEPOLARIZATE

-EFECT DEPRIMANT DIRECT ASUPRA NS SI NAV

-EFECTE EXTRACARDIACE: PROPIETATI GANGLIOBLOCANTE CU REDUCEREA REZISTENTEI VASCULARE PERIFERICE SI A TA, IN SPECIAL DUPA ADMIN. IV

CLASA I-BLOCANTE ALE CANALELOR DE SODIU
PROCAINAMIDA

EFECTE ADVERSE:

↑ADP→cresterea intervalului QT→risc de aritmii

-incetinirea excesiva a conductibilitatii

-sindrom lupus-like, la 1/3 din pacientii tratati pe termen lung

-greata, diaree

CLASA I-BLOCANTE ALE CANALELOR DE SODIU
PROCAINAMIDA

-

Indicatii: majoritatea aritmiilor atriale si ventriculare, dar cu limitarea administarii pe termen lung, consecutive efectelor adverse→ medicatie de linia a 2-a, a 3-a (dupa esecul altor clase), pentru tratamentul aritmiilor ventriculare associate IMA

CLASA I-BLOCANTE ALE CANALELOR DE SODIU
CHINIDINA-IA

-

-actiune similara procainamidei

-creste durata rapolarizarii, a perioadei refractare

-incetineste conducerea A-V

-actiune PS-litica directa→risc de tahicardie sinusala si aritmii

CLASA I-BLOCANTE ALE CANALELOR DE SODIU
CHINIDINA-IA

-EFECTE ADVERSE:
-greata, varsaturi, diaree
-aritmii
-dozele toxice induc fenomenul de toxic doses: cinconism: cefalee, ameteala2
-reactii imunologice: trombocitopenie, hepatita autoimuna, edem angineurotic, febra

-cps 200mg; 200-800 mg/zi

Indicatii: aritmii atriale sau ventriculare extrasistole ventriculare, mentinerea RS dupa conversia fibrilatiei sau flutter-ului atrial

CLASA I-BLOCANTE ALE CANALELOR DE SODIU
LIDOCAINA-IB

-efecte adverse reduse si eficacitate crescuta in aritmiile associate cu IMA
-utilizate exclusiv iv
-blocheaza atat canalele inactivtate, cat si cele activate, predominant prima categorie
-efect mai intens asupra celulelor cu potential de actiune de durata lunga (Purkinje, celule ventriculare)
-nu influenteaza actitatea normala
-scad automatismul in ariile ischemice

EFECTE ADVERSE:
-doze mari hTA
-frecvent neurologice: convulsii, tulburari de auz, tulburari de vorbire.

CLASA I-BLOCANTE ALE CANALELOR DE SODIU
LIDOCAINA-IB

-Solutie inj2mg/ml-fiole 2ml; solutie injectabila**1%-fiole** 5;10ml; 2%-2ml; 4%-2ml

Indicatii:
-tratamentul aritmiilor ventriculare care apar in infarctul miocardic
-Iv 1-2mg/kgc; bolus 50mg/min; repetat la fiecare 5 minute; perfuzie 20mg/min, 10 minute; apoi 1-4mg/minut, 24-30 h.

-Fenitoina-cpr 100mg; fiole 100mg
-Doar in aritmii induse de supradozajul digitalic.

IC-FLECAINIDA

Mecanism: blocant al canalelor de sodiu si potasiu
-inhiba faza 0 (depolarizarea sistolica) =>un PA slab, cu penetrabilitate redusa.

! Nu influenteaza perioada refractara si durata PA!
-utilizata pentru aritmiile ventriculare si supraventriculare; eficienta in extrasistolele ventriculare

-100-200mgx2/zi
-cpr 50; 100mg

IC-PROPAFENONA

Mecanism: blocheaza canalele de sodiu, similar flecainidei; efect beta-blocant slab
-metabolizata hepatic, tp. De ½ 5-7 ore.
-cpr 150mg; sol. Inj. 3.5mg/ml-20ml: 450-900mg/zi

-utilizata pentru tratamentul extrasistolelor atriale si ventriculare, TPSV, TV, aritmiile care apar la pacientii cu sindrom WPW

Efecte adverse:
-efect inotrop negative→poate precipita fenomene de insuficienta cardiaca
-bradicardie, consecutive ef. Inotrop negativ sau efectului inhibitor direct pe NS

CLASA AII-A-BETA-BLOCANTE

-deprima NS si scad frecventa cardiaca (eficace pentru scaderea frecventei cardiace la pacientii cu aritmii)
-deprima NAV, cu cresterea perioadei refractare
-deprima contractilitatea
-reduc efluxul ionilor de K in timpul depolarizarii diastolice

CLASA AIII-A
BLOCANTE ALE CANALELOR DE K

Mec: Block canalele de K →cresc durata repolarizarii, perioada refractara si durata intregului potential de actiune

Reprezentanti: amiodarona, sotalol, bretilium, ibutilide

AMIODARONA
--creste durata repolarizarii (faza a 3a)
-deprima NS→ scad automatismul si frecventa cardiaca
depressess sinusal node→decreases automatism and cardiac frequency
-cresc perioada refractara
-cornarodilatator
-vasodilalator sistemic
-blocheaza si canalele rapide de Na(faza0)→cresc durata PA

CLASA AIII-A
BLOCANTE ALE CANALELOR DE K

AMIODARONA
EFECTE ADVERSE
-bradicardie
-toxicitate pulmonara direct proportionala cu doza de acumulare→fibroza pulmonara
--depozite cutanate→fotodermatita si colorarea in gri/albastrui a zonelor expuse la soare
-depozite corneene, asimptomatice, la toti pacientii
-blocheaza conversia periferica a tiroxinei la triiodotironina→ alterarea functiei tiroidiene
Indicatii:
-aritmii atriale si ventriculare
-cpr 200mg; sol perfuzabila 50mg/ml

CLASA AIII-A
BLOCANTE ALE CANALELOR DE K

SOTALOL
-beta blocant cu efect de prelungire a potentialui de actiune
-administrat in aritmii severe si mentinerea ritmului sinusal la pacientii cu FIA

-Cel mai sever potential efect advers: torsade varfurilor

CLASA A IVA
BLOCANTE ALE CANALELOR DE Ca

-inhiba depolarizarea la nivelul tesuturilor excito-conductoare cu PA lent-NS si NAV

-Verapamil-cpr 40;80mg 180mg; 240mg; sol. injectabila-2.5mg/ml-2ml

SUMMARY Antiarrhythmic Drugs

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
CLASS 1A				
• Procainamide	I_{Na} (primary) and I_{Kr} (secondary) blockade	Slows conduction velocity and pacemaker rate • prolongs action potential duration and dissociates from I_{Na} channel with intermediate kinetics • direct depressant effects on sinoatrial (SA) and atrioventricular (AV) nodes	Most atrial and ventricular arrhythmias • drug of second choice for most sustained ventricular arrhythmias associated with acute myocardial infarction	Oral, IV, IM • eliminated by hepatic metabolism to *N*-acetylprocainamide (NAPA; see text) and renal elimination • NAPA implicated in torsades de pointes in patients with renal failure • *Toxicity:* Hypotension • long-term therapy produces reversible lupus-related symptoms
• *Quinidine: Similar to procainamide but more toxic (cinchonism, torsades); rarely used in arrhythmias; see Chapter 52 for malaria*				
• *Disopyramide: Similar to procainamide but significant antimuscarinic effects; may precipitate heart failure; not commonly used*				
CLASS 1B				
• Lidocaine	Sodium channel (I_{Na}) blockade	Blocks activated and inactivated channels with fast kinetics • does not prolong and may shorten action potential	Terminate ventricular tachycardias and prevent ventricular fibrillation after cardioversion	IV • first-pass hepatic metabolism • reduce dose in patients with heart failure or liver disease • *Toxicity:* Neurologic symptoms
• *Mexiletine: Orally active congener of lidocaine; used in ventricular arrhythmias, chronic pain syndromes*				
CLASS 1C				
• Flecainide	Sodium channel (I_{Na}) blockade	Dissociates from channel with slow kinetics • no change in action potential duration	Supraventricular arrhythmias in patients with normal heart • do not use in ischemic conditions (post-myocardial infarction)	Oral • hepatic and kidney metabolism • half life ~ 20 h • *Toxicity:* Proarrhythmic
• *Propafenone: Orally active, weak β-blocking activity; supraventricular arrhythmias; hepatic metabolism*				
• *Moricizine: Phenothiazine derivative, orally active; ventricular arrhythmias, proarrhythmic. Withdrawn in USA*				
CLASS 2				
• Propranolol	β-Adrenoceptor blockade	Direct membrane effects (sodium channel block) and prolongation of action potential duration • slows SA node automaticity and AV nodal conduction velocity	Atrial arrhythmias and prevention of recurrent infarction and sudden death	Oral, parenteral • duration 4–6 h • *Toxicity:* Asthma, AV blockade, acute heart failure • *Interactions:* With other cardiac depressants and hypotensive drugs
• *Esmolol: Short-acting, IV only; used for intraoperative and other acute arrhythmias*				
CLASS 3				
• Amiodarone	Blocks I_{Kr}, I_{Na}, I_{Ca-L} channels, β adrenoceptors	Prolongs action potential duration and QT interval • slows heart rate and AV node conduction • low incidence of torsades de pointes	Serious ventricular arrhythmias and supraventricular arrhythmias	Oral, IV • variable absorption and tissue accumulation • hepatic metabolism, elimination complex and slow • *Toxicity:* Bradycardia and heart block in diseased heart, peripheral vasodilation, pulmonary and hepatic toxicity • hyper- or hypothyroidism. • *Interactions:* Many, based on CYP metabolism
• Dofetilide	I_{Kr} block	Prolongs action potential, effective refractory period	Maintenance or restoration of sinus rhythm in atrial fibrillation	Oral • renal excretion • *Toxicity:* Torsades de pointes (initiate in hospital) • *Interactions:* Additive with other QT-prolonging drugs
• *Sotalol: β-Adrenergic and I_{Kr} blocker, direct action potential prolongation properties, use for ventricular arrhythmias, atrial fibrillation*				
• *Ibutilide: Potassium channel blocker, may activate inward current; IV use for conversion in atrial flutter and fibrillation*				
• *Dronedarone: Amiodarone derivative; multichannel actions, reduces mortality in patients with atrial fibrillation*				
• *Vernakalant: Investigational, multichannel actions in atria, prolongs atrial refractoriness, effective in atrial fibrillation*				

(continued)

ANTIANGINOASE

CLASIFICARE

→NITRATI ORGANICI

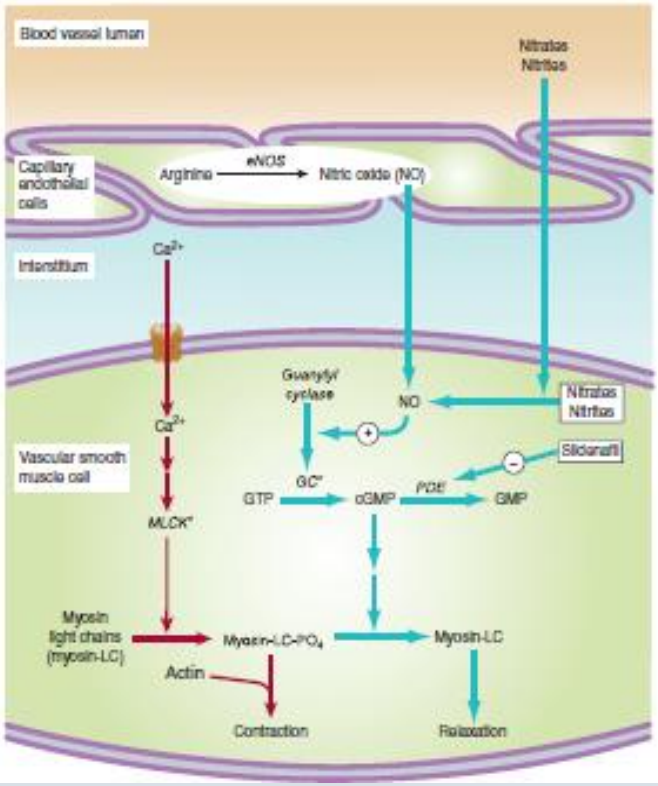
→BLOCANTE ALE CANALELOR DE Ca-BCCa

→BETA-BLOCANTE

-toate diminua consumul de oxigen prin inhibarea tuturor determinantilor necesarului de oxigen (frecventa cardiaca, volumul ventricular, TA, contractilitatea miocardica)

I. NITRATI ORGANICI

-vasodilatatie in toate teritoriile, in special veno
Vene de calibru mare, dar si arterial, prin
Intermediul oxidului nitric-NO
-vasodilatatia in special in jumatatea superioara
a corpului->cefalee, flush facial
-coronarodilatatie exclusive in teritoriile indemn
-efect antiagregant plachetar



Efecte adverse: cefalee, dureri oculare, flush,
Tahicardie, methemoglobinemia, aparitia fenomenului de toleranta

I. NITRATI ORGANICI

NITROGLICERINA

-cpr sublinguale, efect cu debut rapid (1-3 minute), durata scurta (20-30 minute); 0.5mg, repetat de maxim 2-3 ori;
-cpr retar (cu eliberare prelungita): 2.5; 5; 7.5; 2.6mg; x2-3/zi; efect in 30-45 minute, durata 4-8 ore
-unguent 2%x2-4/zi
-plasturi 10; 25; 50; 18; 36 mg
-inhalator-spray- 0.4mg/puff
-solutie perfuzabila 5mg/ml; latenta<1 minut

I. NITRATI ORGANICI

ISOSORBID DINITRAT (EX. ISODINIT)
-CPR 10; 20; 5mg; CPR RETARD 40mg
-CPS 20;40mg
-CPR SUBLINGUALE-latenta 5-10 minute; durata 1-2 ore
--inhalator-spray: 30mg/puff

PENTAERITRIL TETRANITRAT (EX. NITROPECTOR)

-CPR 20; 50mg; durata 4-8 ore

II. BETA-BLOCANTE

-scad frecv. Cardiaca, contractilitatea, TA → scad necesarul de oxygen atat in repaus, cat si in timpul efortului fizic
-reprezentanti: prezentati in capitolul antihipertensive si betablocante-semestrul I

III. BCCa

-deprima contractilitatea→ reduc necesarul de oxygen
-scad presiunea arteriala
-clasificare-laborator 5-antihipertensive

ALTE ANTIANGINOASE

TABLE 12–6 New drugs or drug groups under investigation for use in angina.

Drugs
Amiloride
Capsaicin
Direct bradycardic agents, eg, ivabradine
Inhibitors of slowly inactivating sodium current, eg, ranolazine
Metabolic modulators, eg, trimetazidine
Nitric oxide donors, eg, L-arginine
Potassium channel activators, eg, nicorandil
Protein kinase G facilitators, eg, detanonoate
Rho-kinase inhibitors, eg, fasudil
Sulfonylureas, eg, glibenclamide
Thiazolidinediones
Vasopeptidase inhibitors
Xanthine oxidase inhibitors, eg, allopurinol

-Trimetazidina-inhiba oxidarea acizilor grasi (modulatori metabolici)

-ivabradina-blocheaza selectiv canalele de sodiu If→ reduc frecventa cardiaca prin actiune DOAR la nivelul NS!!

SUMMARY Drugs Used in Angina Pectoris

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
NITRATES				
• Nitroglycerin	Releases nitric oxide in smooth muscle, which activates guanylyl cyclase and increases cGMP	Smooth muscle relaxation, especially in vessels • other smooth muscle is relaxed but not as markedly • vasodilation decreases venous return and heart size • may increase coronary flow in some areas and in variant angina	Angina: Sublingual form for acute episodes • oral and transdermal forms for prophylaxis • IV form for acute coronary syndrome	High first-pass effect, so sublingual dose is much smaller than oral • high lipid solubility ensures rapid absorption • *Toxicity:* Orthostatic hypotension, tachycardia, headache • *Interactions:* Synergistic hypotension with phosphodiesterase type 5 inhibitors (sildenafil, etc)
• *Isosorbide dinitrate: Very similar to nitroglycerin, slightly longer duration of action*				
• *Isosorbide mononitrate: Active metabolite of the dinitrate; used orally for prophylaxis*				
BETA BLOCKERS				
• Propranolol	Nonselective competitive antagonist at β adrenoceptors	Decreased heart rate, cardiac output, and blood pressure • decreases myocardial oxygen demand	Prophylaxis of angina • for other applications, see Chapters 10, 11, and 13	Oral and parenteral, 4–6 h duration of action • *Toxicity:* Asthma, atrioventricular block, acute heart failure, sedation • *Interactions:* Additive with all cardiac depressants
• *Atenolol, metoprolol, others: β_1-Selective blockers, less risk of bronchospasm, but still significant*				
• *See Chapters 10 and 11 for other β blockers and their applications*				
CALCIUM CHANNEL BLOCKERS				
• Verapamil, diltiazem	Nonselective block of L-type calcium channels in vessels and heart	Reduced vascular resistance, cardiac rate, and cardiac force results in decreased oxygen demand	Prophylaxis of angina, hypertension, others	Oral, IV, duration 4–8 h • *Toxicity:* Atrioventricular block, acute heart failure; constipation, edema • *Interactions:* Additive with other cardiac depressants and hypotensive drugs
• Nifedipine (a dihydropyridine)	Block of vascular L-type calcium channels > cardiac channels	Like verapamil and diltiazem; less cardiac effect	Prophylaxis of angina, hypertension	Oral, duration 4–6 h • *Toxicity:* Excessive hypotension, baroreceptor reflex tachycardia • *Interactions:* Additive with other vasodilators
• *Other dihydropyridines: Like nifedipine but slower onset and longer duration (up to 12 h or longer)*				
MISCELLANEOUS				
• Ranolazine	Inhibits late sodium current in heart • also may modify fatty acid oxidation	Reduces cardiac oxygen demand • fatty acid oxidation modification may improve efficiency of cardiac oxygen utilization	Prophylaxis of angina	Oral, duration 6–8 h • *Toxicity:* QT interval prolongation, nausea, constipation, dizziness • *Interactions:* Inhibitors of CYP3A increase ranolazine concentration and duration of action
• *Ivabradine: Investigational inhibitor of sinoatrial pacemaker; reduction of heart rate reduces oxygen demand*				

TONICARDIACE/GLICOZIZI CARDIOTONICI

AGENTI INOTROPI POZITIVI

-DIGITALICE
-INHIBITORI DE FOSFODIESTERAZA
-BETA1 ADRENOMIMETICE

DIGITALICE (GLICOZIZI CARDIOTONICI)

Mecanism de actiune:

1.

→Blocheaza AT-aza Na/K ATP prin legarea la situsul pentru K (fiziologic extrage Na din celula si introduce K -3Na, 2K)

→Blocarea pompei→↑ Nai si ↓K→ schimb Na/Ca →↑ Cai→ stimularea contractilitatii

2.

→ Stimuleaza eliberarea Ca prin stimularea canalelor membranare de Ca

DIGITALICE

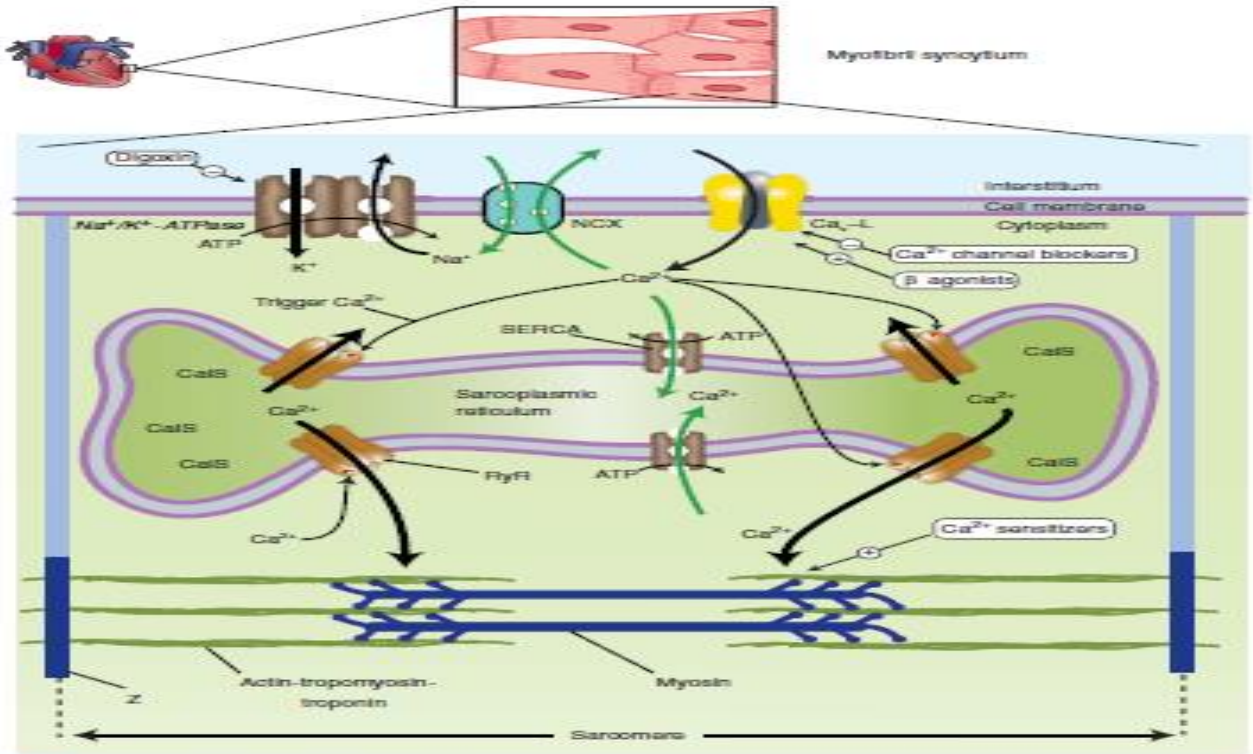


FIGURE 13–1 Schematic diagram of a cardiac muscle sarcomere, with sites of action of several drugs that alter contractility. Na^+/K^+-ATPase, the sodium pump, is the site of action of cardiac glycosides. NCX is the sodium-calcium exchanger. Ca_V-L is the voltage-gated, L-type calcium channel. SERCA (sarcoplasmic endoplasmic reticulum Ca^{2+}-ATPase) is a calcium transporter ATPase that pumps calcium into the sarcoplasmic reticulum (SR). CaIS is calcium bound to calsequestrin, a high-capacity Ca^{2+}-binding protein. RyR (ryanodine RyR2 receptor) is a calcium-activated calcium channel in the membrane of the SR that is triggered to release stored calcium. Calcium sensitizers act at the actin-troponin-tropomyosin complex where activator calcium brings about the contractile interaction of actin and myosin. Black arrows represent processes that initiate contraction or support basal tone. Green arrows represent processes that promote relaxation.

DIGITALICE

Efecte farmacodinamice:

A. Cardiace:

-stimuleaza miocardul contractil si il inhiba pe cel excitoconductor

-efect inotrop, tonotrop si batmotrop pozitiv

-efect cronotrop si tonotrop negativ

DIGITALICE

- ↑debitul cardiac

→↓ frecventa contractiilor

→↑ excitabilitatea prin scaderea perioadei refractare→ risc crescut de aritmii

→↓ conductibilitatea, in special la nivelul NAV, NS nu este influentat

DIGITALICE

-Alte efecte:

-stimuleaza toate tesuturile excitabile, incluzand musculature neteda si SNC, efectele digestive fiind cele mai frecvente (diaree, anorexie, greata, varsaturi)
-efecta SNC in special la varstnici
-perturbarea perceptiei culorilor

-

DIGITALICE

EKG:

-↑PR, ↓QT, ↑AMPLITUDINEA QRS, unde T negative, aplatizarea segmentului ST

TABLE 13-2 Effects of digoxin on electrical properties of cardiac tissues.

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

Digitalice

efecte adverse:

→digestive: greata, varsaturi, diaree, anorexie
→cardiace: aritmii-cel mai frecvent supraventriculare, bradiardie, BAV
→neurologice: astenie, somnolenta, cefalee, halucinatii
→vedere colorata in galben, verde.

DIGITALICE

Supradozajul digitalic: ↓↓↓K

-oprirea tratamentului
-administrarea de suplimente de potasiu (KCl)
-atropine in cazul bradicardiei
-antiaritmice in cazul tuburarilor de ritm
- Anticorpi anti-digoxina- fragmente Fab purificate (DIGIBIND).

DIGITALICE

Interactiuni:

Potasiu

→administrarea concomitenta de suplimente de potasiu actioneaz aprin mechanism competitive cu reducerea efectelor digitalicelor; hipo-potasemia amplifica efectul

-actiune sinergica pe functia cronotropa si dromotrope si antagonica pentru cea inotropa si batmotropa

DIGITALICE

Ca, Magneziu

→**Ca** potenteaza actiunea toxica a glicozizilor

→Mg actioneaza in sens opus

DIGITALICE

INDICATII

-Insuficienta cardiaca

-aritmii-pentru controlul frecventei ventriculare

DIGITALICE

CONTRAINDICATII

-bradicardie

-BAV

-tahicardia ventriculara

-miocardite, CMHO

Precautie la pacientii cu insuficienta hepatica, renala, hipopotasemie/hiperpotasemie, hipomagneziemie

DIGITALICE

CLASIFICARE

A. Grupul digitoxinei: absorbtie orala inalta, legarea in procent cerscut de proteinele plasmatice, durata si latenta lunga, risc crescut de toxicitate prin acumularea dozei

-metabolizare hepatica

DIGITALICE

B. Grupul digoxinei (digoxin, lanatozide C, deslanozid): absorbtie digestive medie

-eliminare renala

C. Grupul strofantinei: durata si latenta scurta

-eliminare rapida, renala

DIGITALICE

Digitoxina

-liposolubilitate inalta, timp de injumatatire de aproximativ 6-7 zile

-solutie alcoolica 1/1000-5picaturi (0.1mg) x3/zi, 3-5 zile→ 5pic/5 zi, 5zile/saptamana

-pulbere de digitala-cpr 100mg (contin 0.1mg digitoxina)

-1cprx3/zi, 3 zile, ulterior 1cpr/zi, 5 zile pe saptamana

DIGITALICE

LANATOZIDUL C

-drajee 0.25mg

-2 drajesx2/zi 5 zile, ulterior 1/zi

DIGITALICE

3. DIGOXIN CPR 0.25mg; FIOLE 0.5mg

-liposolubilitate medie→ abs. orala 65-75%, legare in procent redus de proteinele plasmatice

-metabolizare hepatica in proportie de 20-40%; eliminare renala, nemetabolizata (60-80%)

DIGITALICE

3. DIGOXIN

-tp de 1/2≈1.5days

-inj: latenta 5-30 minute, efect maxim in 1-3 ore

-**oral**: latenta 1-3h; efect maxim in ≈6 ore

-efectul se mentine 2-6 zile dupa intreruperea tratamentului

DIGITALICE

4.STROFANTINA (OUBAIN)-ADMINISTRARE EXCLUSIV IV

--eliminare renala

-latenta 5-10 minutee, efect maxim in aprox. 1 ora

-fiole 0.25mg; inj iv lent, dizolvata in 10ml ser fiziologic

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(GLICOZIZI CARDIOTONICI)

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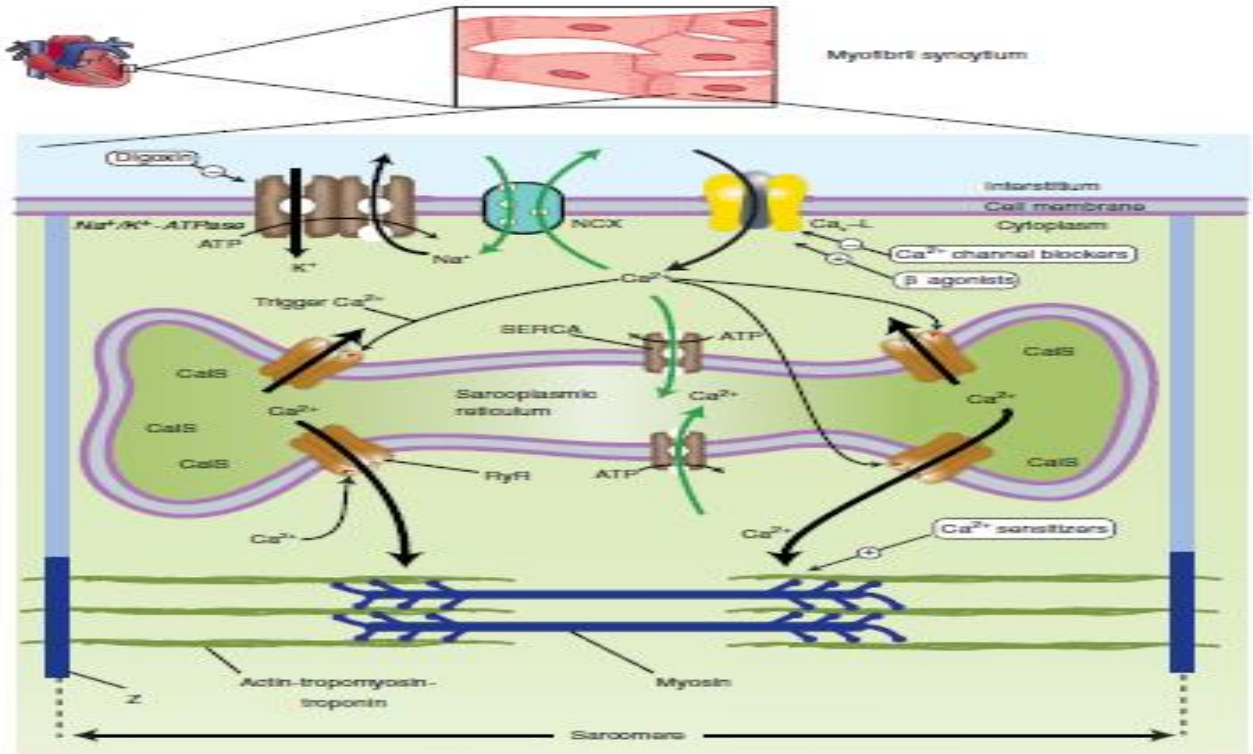

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