NEW DRUGS IN MEDICINE

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Drugs used in hyperlipidemia:

1. **HMG-CoA Reductase Inhibitors (statins)**
2. **Niacin (vit B3)**
3. **Bile Acid sequestrants (cholestyramine)**
4. **Fibrates (fenofibrate)**
5. **Cholesterol absorption inhibitors (Ezetimibe)**
6. **Omega 3 fatty acids**

PCSK9 inhibitors

Who Are The Patients Whose Needs are Not Being Met by Current Therapies?

Patients whose LDL-C cannot be controlled with intensive statin ± other current therapies

- High-risk patients in whom we cannot get the LDL-C low enough
- Most patients with heterozygous familial hyperchol. (prevalence 1 in 200-500)
- Almost all patients with homozygous FH

Patients who cannot take a statin, or an effective dose

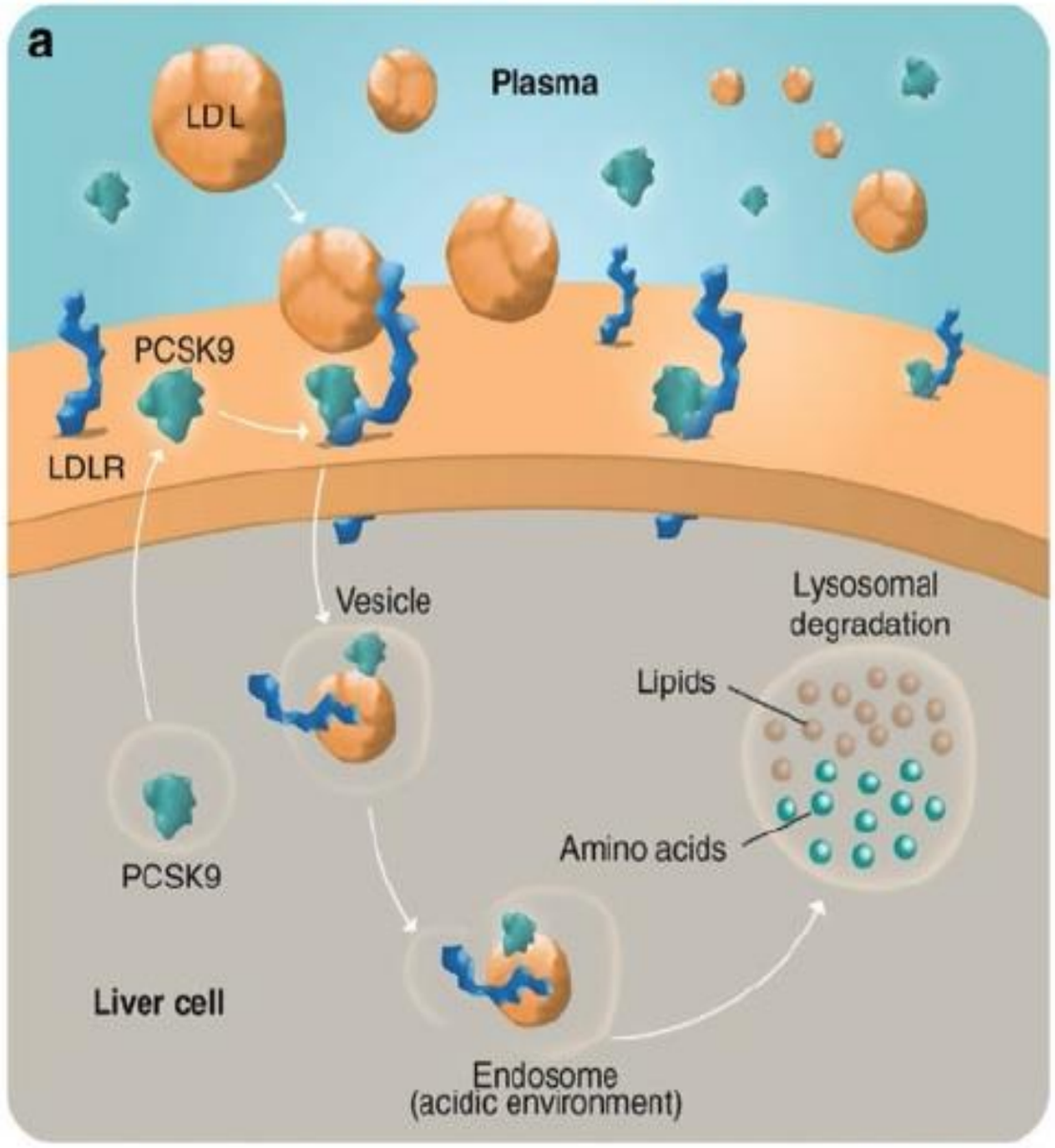
- Statin intolerance or statins are not clinically appropriate (eg, drug-drug interactions)

Item	Check
Indication and documentation of medical conditions (ASCVD or FH)	
Statin use history	
Failure to achieve LDL-C goal despite maximally tolerated statin therapy	
Documentation of adjunctive lipid-lowing therapy	
A recent lipid panel (<30 days old)	

PCSK9: Proprotein convertase subtilisin/kexin type 9

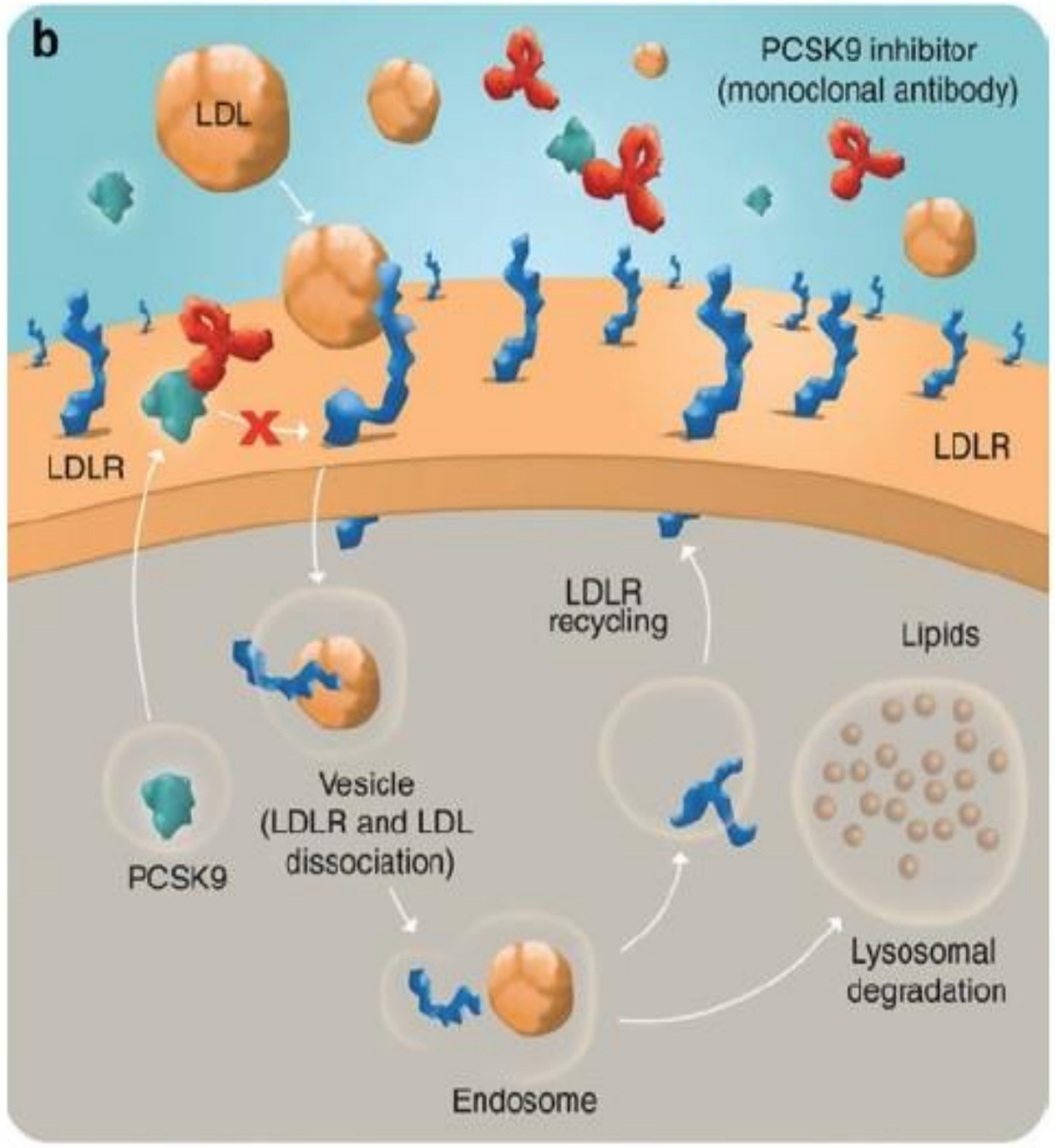
- **An enzyme, is predominantly produced in the liver.**
- **Normally, low-density lipoprotein receptors (LDL-R) in hepatocytes bind to LDL particles and remove them from circulation.**
- **PCSK9 bind to the LDL-R and promote their degradation.**
- **By blocking PCSK9, there will be increase in availability of LDL-R to remove LDL-C from the circulation**

How does PCSK9 work?



a) Secreted PCSK9 binds to LDLR on the liver cell surface and mediates the lysosomal degradation of the complex formed by PCSK9 - LDLR - LDL.

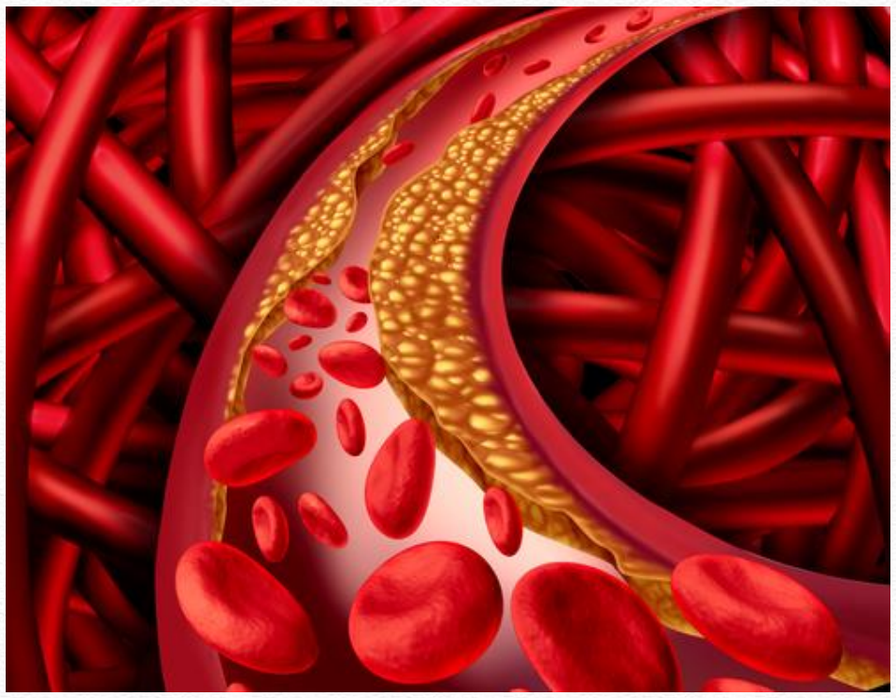
How does Inhibitors work?



b) In the presence of a monoclonal antibody that binds to PCSK9, the PCSK9-mediated degradation of LDLR is inhibited, resulting in an increased uptake of LDL-cholesterol by LDLR as more LDLR are recycled at the cell surface.

- Other mechanisms, besides LDL-C lowering, by which PCSK9 antibodies **might improve cardiovascular outcomes have been postulated.**

- These include a **reduction** in **inflammation and oxidative stress** within atherosclerotic plaques and inhibition of prothrombotic pathways.



PCSK9 inhibitor benefits:

- A reduction in LDL-C (70%)
- A reduction in lipoprotein(a) levels by (18 to 36) %
- Reduction triglyceride levels by (12 to 31) %
- increase in HDL-C by (5 to 9) %
- A decrease in present atheroma volume
- Reduction in cardiovascular event (50%)

PCSK9 inhibitor :

Evolocumab And Alirocumab

- The onset of inactivation of PCSK9 enzyme occurs within **four to eight hours** following the first subcutaneous injection of PCSK9 monoclonal antibodies

- Rote of administration: **Subcutaneous**. It can be injected in the upper arm or leg or in the abdomen.

- They have already been approved for use in primary hyperlipidemia, homozygous FH, statin intolerance, to achieve LDL-C goals and prevention of cardiovascular event(decrease risk of MI and stroke).

- High cost of therapy remains an issue. (600-700$)

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

- Current treatments for type 2 diabetes have centered on increasing insulin availability (either through direct insulin administration or through agents that promote insulin secretion), improving sensitivity to insulin, delaying the delivery and absorption of carbohydrate from the gastrointestinal tract, or increasing urinary glucose excretion.

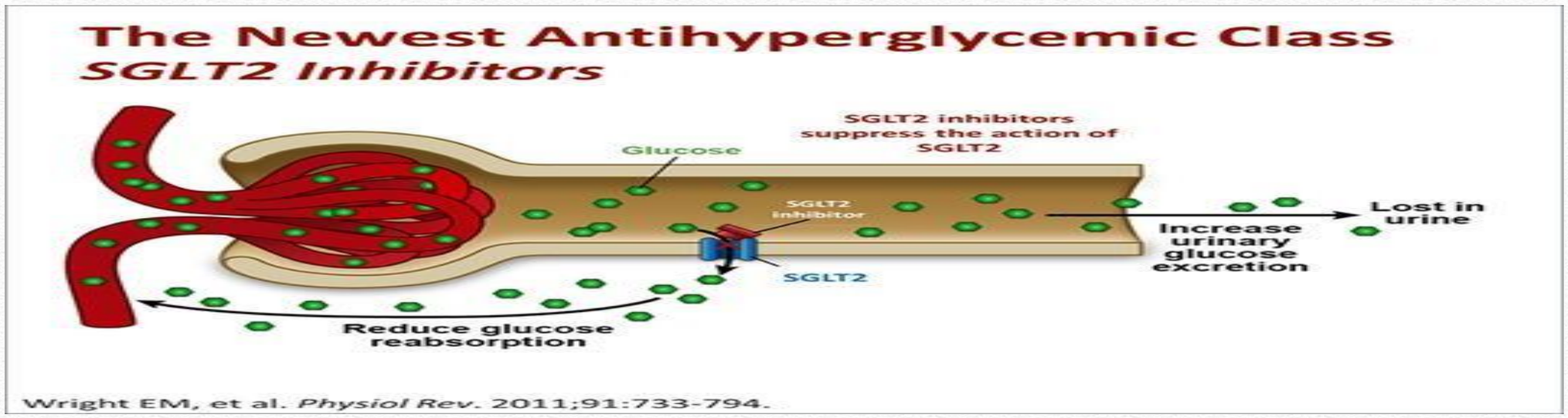
- Sodium-glucose co-transporter 2 (SGLT2) inhibitors reduce blood glucose by increasing urinary glucose excretion.

- The SGLT2 protein responsible of reabsorption of the filtered glucose in tubular lumen of kidney (mainly at PCT).

- SGLT2 inhibitors block these proteins which means less glucose gets reabsorbed back into the blood and gets passed out of the body via the urine

- IT decreases absorption of sodium, causes osmotic diuresis. May reduces systolic blood pressure and weight.

- Should be avoided in patient with renal dysfunction



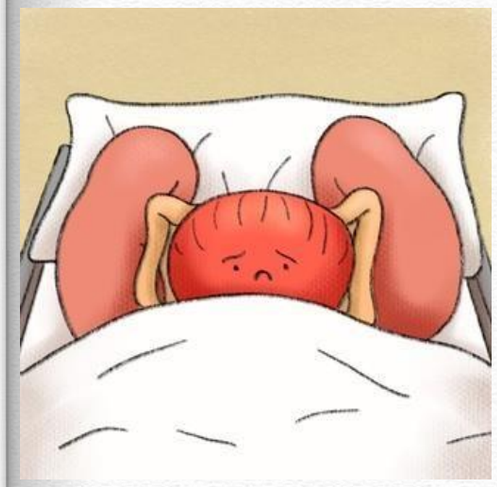
SGLT2 inhibitors may play a role in the following settings:

- **Empagliflozin:** decreasing the risk of cardiovascular death in adult with type 2DM and CVD

As a third-line agent in patients with inadequate glycemic control on two oral agents (eg, metformin and sulfonylurea) if for some reason combination metformin and insulin is not a therapeutic option

As a third-line agent in patients not adequately controlled on metformin and insulin therapy, in whom glucagon-like peptide-1 receptor agonists are contraindicated and increasing insulin dosing would lead to weight gain

As a second agent in patients with inadequate control on metformin who are unwilling or unable to consider injection therapy and in whom weight gain is a significant issue



Adverse Effects

1. Vulvovaginal candidal infections
2. Hypotension and dehydration
3. Acute kidney injury
4. Urinary tract infections
5. Euglycemic diabetic ketoacidosis
6. Increased risk of lower extremity amputation and bone fractures have also been reported

Choice of Therapy

When a decision has been made to use an SGLT2 inhibitor, available options are:

Canagliflozin

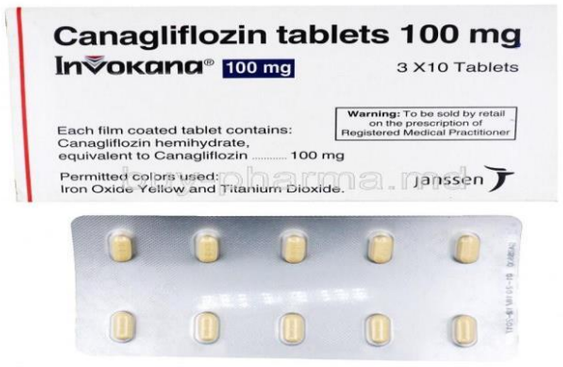
Dapagliflozin

Empagliflozin

Ertugliflozin

Often choice of agent is dictated by cost and insurer formulary preference, as the published trials have not revealed any substantial differences with regard to A1C lowering, weight reduction, or risk for mycotic infections.

Canagliflozin



-It should be taken orally before the first meal of the day
The initial dose is 100 mg once daily

Canaglifozin is contraindicated in:

- Type 1 diabetes
- Diabetic ketoacidosis
- Severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m2), end-stage renal disease
- Patients on dialysis

Canagliflozin (300 mg) reduced A1C to a slightly greater extent than Dapagliflozin (10 mg) or Empagliflozin (25 mg)

there was an increase in the risk of lower limb amputations and fractures.

Dapagliflozin

- 10 mg once daily can be taken any time of day with or without food.

It is not recommended for use in patients with GFR<60 mL/min or in patients with active bladder cancer.

- ✓ For patients with severely reduced liver function, a starting dose of 5 mg is recommended.

Empagliflozin

A prior history of <u>myocardial infarction or stroke</u> might favor choosing Empagliflozin

It should be taken orally once daily in the morning with or without food

Should not be initiated in patients with GFR <45 mL/min.

- should be discontinued In patients who are taking Empagliflozin and have a persistent fall in GFR below 45 mL/min
- May be used in patients with hepatic impairment.

Ertugliflozin

- It should be taken once daily in the morning with or without food.

- Contraindicated in patients with an GFR <30 mL/min and is not recommended in patients with GFR of 30 to <60 mL/min

- In patients taking ertugliflozin who have a persistent fall in eGFR below 60 mL/min, it should be discontinued

Monitoring

- In addition to glycemic indices (A1C, fasting blood sugar), renal function and volume status (blood pressure) should be monitored during SGLT2 treatment.

- **Renal function:**

eGFR >60 mL/min – We measure serum creatinine after three months and, if stable, then annually or as clinically indicated.

eGFR between 45 and 60 mL/min (canagliflozin and empagliflozin)

We measure serum creatinine every three months or as clinically indicated

NTRAL ILLUSTRATION: Stepwise Approach to Prescription of SGLT2
ibitors by Cardiologists

Candidates for Initiation

Selection of Drug and Dose

Pre-Initiation Safety Screen

Prescription of SGLT2i

Long-Term Continuatio

s with T2DM with or at High Risk Disease, Already on Metformin

ndividualized HbA1c Target:

non-metformin oral therapies (e.g. lureas) to a SGLT2i

ndividualized HbA1c Target:

er SGLT2i initiation

Drug Type

Canagliflozin, dapagliflozin, & empagliflozin with similar efficacy profile in reducing HF events

Starting Dose (once daily in AM)

- Canagliflozin (100mg)
- Dapagliflozin (5mg)
- Empagliflozin (10mg)
- Ertugliflozin (5mg)

Metformin+SGLT2i Combination Therapies

Consider to limit non-adherence and pill burden

Stable Hemodynamic and Clinical Status

Pre-Initiation eGFR must be above:

- 60 mL/min/1.73 m^2 (dapagliflozin, ertugliflozin)
- 45 mL/min/1.73 m^2 (canagliflozin, empagliflozin)

Anticipatory Guidance

Consider diuretic dose reduction

Patient Counseling

- Genital/perineal hygiene
- Orthostatic hypotension
- Regular foot exams
- Symptoms of DKA
- Avoid excessive alcohol

Multidisciplinary Care

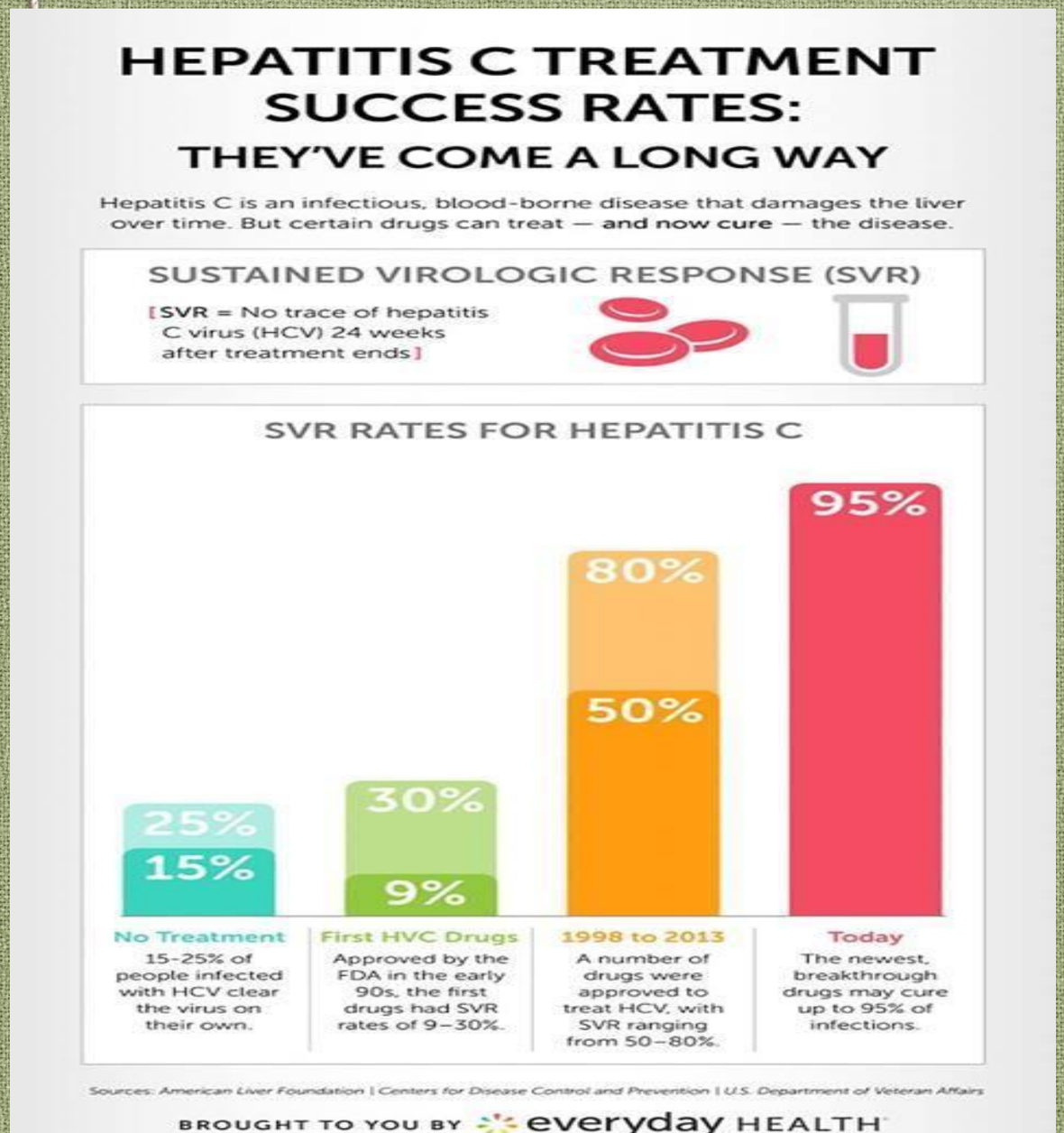
Close communication with other providers, including PCPs and endocrinologists

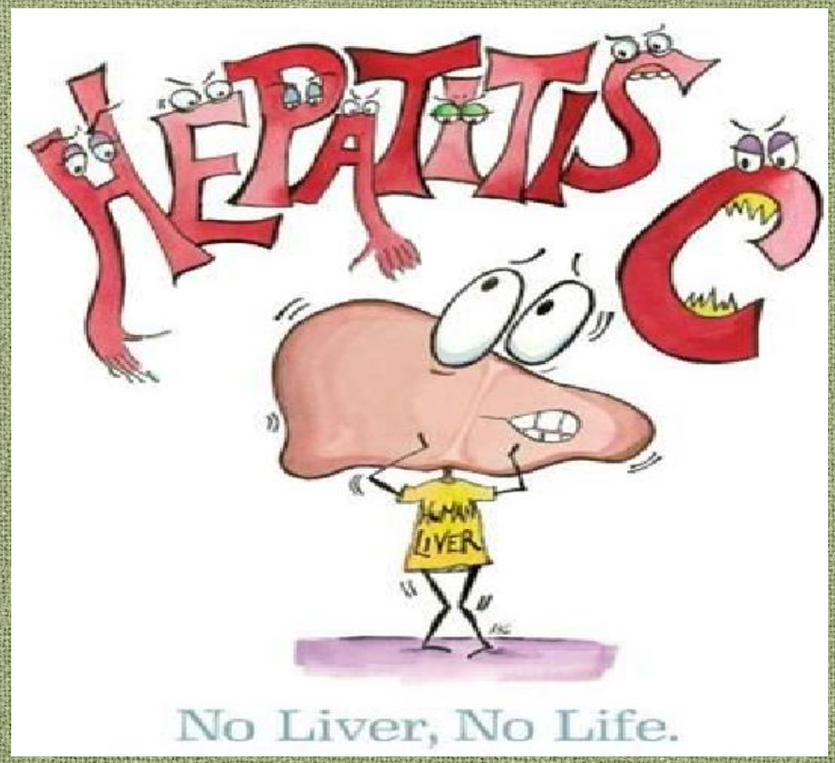
Follow-up and Monitoring

- Serial assessment of function, body weight pressure, and sympto
- Dose uptitration guide need for glycemic con
- Ensure adherence to other therapies, and therapeutic lifestyle
- Multidisciplinary care follow-up

leny, O. et al. J Am Coll Cardiol HF. 2019;7(2):169-72.

New Medications for Hepatitis C





- In the past the treatment for chronic hepatitis C virus (HCV) infection regardless of genotype was a combination therapy with injectable interferon-alfa and ribavirin.

- New generation of drug was found known as Direct-acting Antiviral agents (DDAs) that target specific steps in HCV life cycle include:

1-NS3/4A protease inhibitors

2-NS5A inhibitors

3-NS5B RNA-dependent RNA polymerase inhibitors

NS3/4A PROTEASE INHIBITORS

a serine protease, an enzyme involved in post-translational processing and replication of HCV. The inhibitor blocks catalytic site interaction. Ex. Glecaprevir, Paritaprevir & Grazoprevir

Simmerer 2nd Gen. in combo with peginterferon and ribavirin for chronic genotype 1 infection

S/E Itching, Upset stomach, Muscle pain, Diarrhea, Dizziness, Headache and Feeling tired or weakness

NS5A INHIBITORS

- Act on viral replication and the assembly of the hepatitis C virus. They are **generally quite potent and are effective across all genotypes,** but they have a low barrier to resistance and variable toxicity profiles. Can be **given in conjunction with peginterferon and ribavirin**. Ex. Daclatasvir, Elbasvir

s/e headache, fatigue, and nausea were the most commonly reported adverse effects . These were mild to moderate in severity

NS5B RNA-dependent RNA polymerase inhibitors

There are two classes:

A-nucleoside/nucleotide analogues (NPIs)

moderate to high efficacy across all six genotypes and have a very high barrier to resistance ex. Sofosbuvir (not to be used without other antiviral agents) - **Renal clearance**

B-non-nucleoside analogues (NNPIs)

less potent, and more genotype specific (type 1), given as adjunct to more potent compounds. Ex. Dasabuvir is administered and packaged with ombitasvir- paritaprevir-ritonavir

novel oral anticoagulants (NOACs)

New anticoagulants :

1. **Direct factor Xa inhibitor.**
2. **Direct thrombin inhibitor.**

1. Direct factor Xa inhibitor:

- Direct factor Xa inhibitors prevent factor Xa from cleaving prothrombin to thrombin.

- There are **no parenteral** direct factor Xa inhibitors in clinical use.

- Several oral agents are available, including rivaroxaban, apixaban, edoxaban, and betrixaban.

- Metabolized in the kidney (25 to 35 percent) and liver,

- Severe hepatic impairment could result in accumulation of these agents.

- However, direct factor Xa inhibitors **do not appear to cause hepatotoxicity.**

- A reversal agent for the direct factor Xa inhibitors → andexanet alfa.

Rivaroxaban

- Used in :

1. **Nonvalvular atrial fibrillation.**

2. prevention and treatment of **venous thromboembolic (VTE).**

3. Heparin-induced thrombocytopenia (Off-Label).

- Rivaroxaban crosses the placenta → Bleeding may occur in the fetus.

- Rivaroxaban is present in breast milk →Use of alternative anticoagulants is preferred

- **Rivaroxaban** is generally given at a fixed dose without monitoring, (15-20)mg tablets taken with food.

- The drug should not be used in individuals with a **creatinine clearance** <15 mL/minute, as well as in those with significant hepatic impairment .

- **Monitoring** is best done by measuring anti-factor Xa activity.

- Premature discontinuation of any oral anticoagulant, increases the risk of thrombotic events

Apixaban:

- Deep vein thrombosis.
- Nonvalvular atrial fibrillation.
- Pulmonary embolism.
- **Apixaban crosses the placenta → Bleeding may occur in the fetus.**
- **Apixaban is present in breast milk →Use of alternative anticoagulants is preferred**

Edoxaban:

- **Not recommended in patients with prosthetic heart valves or significant rheumatic heart disease.**

Pharmacologic Profiles of Approved and Investigational Oral Anticoagulants

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Vitamin K epaxide	Thrombin	Xa	Xa	Xa
Administration	Once daily	Twice daily	Once daily	Twice daily	Once daily
Prodrug	No	Yes	No	No	No
Half-life	40 hrs	12-14 hours	9-13 hours	8-15 hours	6-11 hours
Bioavailability	>95%	6.5%	80%	~66%	50%
Renal excretion	Minor	80%	30-60%	25%	35-39%
Time to Peak Plasma	72-96 hours	2 hours	2.5-4 hours	3 hours	1-2 hours
Metabolized by CYP3A4	Yes	No	Yes	Yes	Yes

Uchiyama S, et al. *J Stroke Cerebrovasc Dis*. 2012;21:165-173; Eriksson BI, et al. *Annu Rev Med*. 2011;62:41-57

2. Direct thrombin inhibitor

- **Inactivate circulating and clot-bound thrombin (factor IIa)**

- **Parenteral direct thrombin inhibitors:**

  - ***Percutaneous coronary intervention (PCI).***

  - ***Heparin-induced thrombocytopenia (HIT).***

- **Oral direct thrombin inhibitor:**

  - ***Dabigatran***

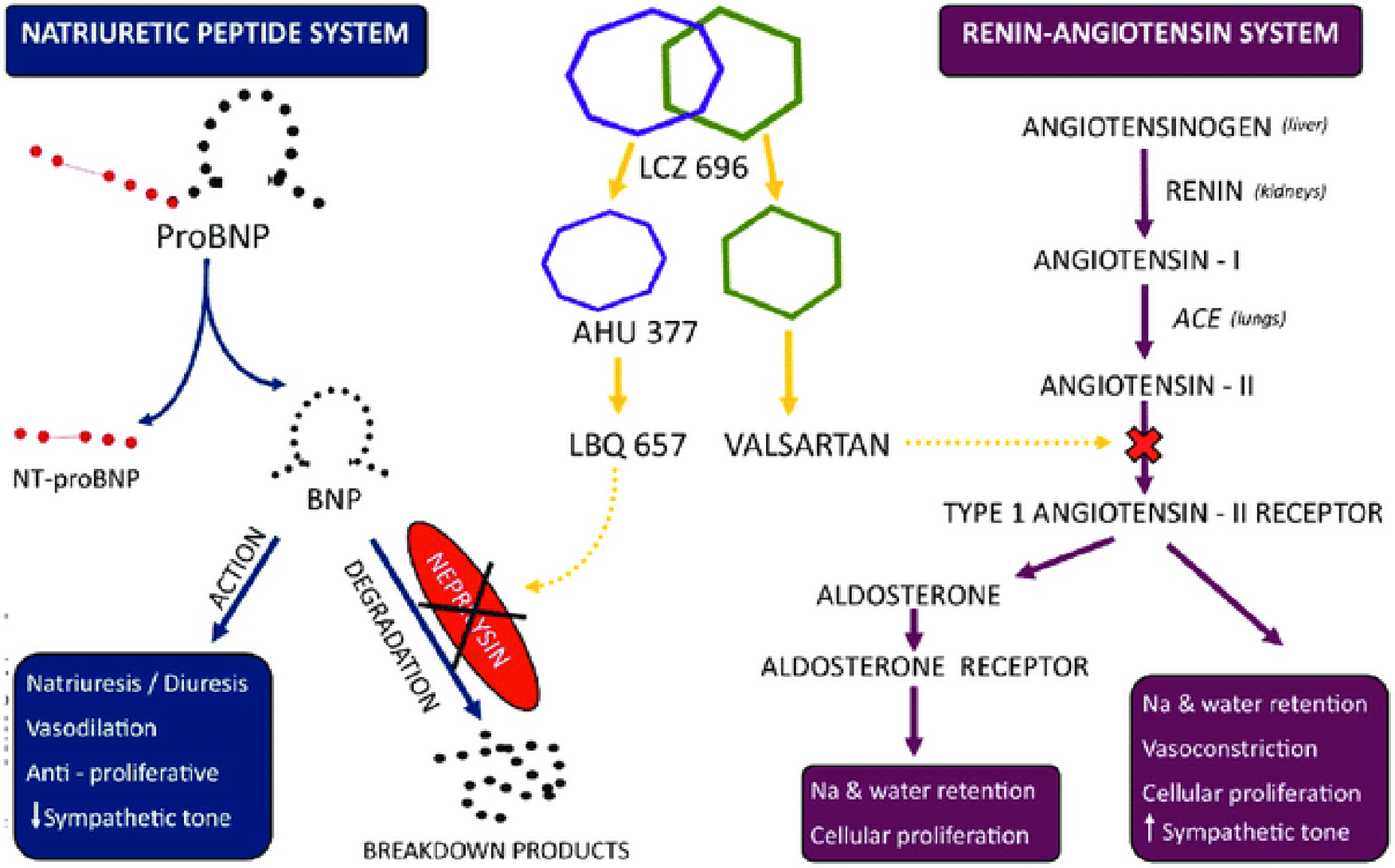
Dabigatran:

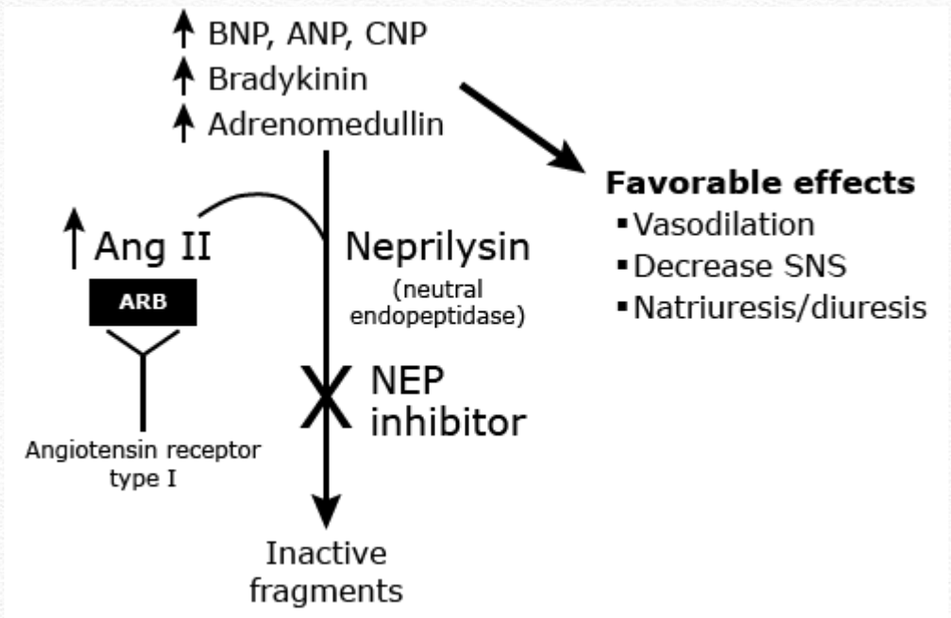
- **Used in:**
  - **DVT and Pulmonary embolism (treatment and prophylaxis).**
  - **Nonvalvular atrial fibrillation.**
  - **dabigatran capsules should only be dispensed and stored in the original bottle (with desiccant) or blister package in which they came, due to the potential for product breakdown from moisture and resulting loss of potency.**
  - **There does not appear to be an increased risk of serious liver injury.**
  - **As with all anticoagulants Dabigatran increase risk of bleeding, however the antidote → idarucizumab.**

Settings in which a heparin or vitamin K antagonist may be preferable:

1. **Prosthetic heart valves.**
2. **Pregnancy.**
3. **Renal impairment.**
4. **Severe liver disease.**
5. **Gastrointestinal disease.**
6. **Compliance and Cost.**

Sacubitril and valsartan


NATRIURETIC PEPTIDE SYSTEM
ProBNP
NT-proBNP
BNP
ACTION
Natriuresis / Diuresis
Vasodilation
Anti - proliferative
Sympathetic tone
DEGRADATION
NEPRILYSIN
BREAKDOWN PRODUCTS
LCZ 696
AHU 377
LBQ 657
VALSARTAN
RENIN-ANGIOTENSIN SYSTEM
ANGIOTENSINOGEN (liver)
RENIN (kidneys)
ANGIOTENSIN - I
ACE (lungs)
ANGIOTENSIN - II
TYPE 1 ANGIOTENSIN - II RECEPTOR
ALDOSTERONE
ALDOSTERONE RECEPTOR
Na & water retention
Cellular proliferation
Na & water retention
Vasoconstriction
Cellular proliferation
Sympathetic tone


BNP, ANP, CNP
Bradykinin
Adrenomedullin
Favorable effects
Vasodilation
Decrease SNS
Natriuresis/diuresis
Ang II
ARB
Angiotensin receptor type I
Neprilysin
(neutral endopeptidase)
NEP inhibitor
Inactive fragments

- Brand Names: US Entresto
- Brand Names: Canada Entresto
- Pharmacologic Category Angiotensin II Receptor Blocker; Neprilysin Inhibitor

Use

- Heart failure: Reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction; usually administered in conjunction with other heart failure therapies, in place of an angiotensin-converting enzyme (ACE) inhibitor or other angiotensin II receptor blocker (ARB)
- Note: According to the ACC/AHA/HFSA heart failure guidelines, in patients with chronic symptomatic heart failure with reduced ejection fraction (HFrEF) NYHA Class II or III who tolerate an ACE inhibitor or ARB, replacement with sacubitril/valsartan is recommended

- – Blockade of the renin-angiotensin-aldosterone system is a key component of treatment of patients with heart failure with reduced ejection fraction (HFrEF, also known as systolic HF or HF due to systolic dysfunction) .

Augmentation of beneficial counter-regulatory systems such as natriuretic peptides is an additional strategy to treat HF . Inhibition of neprilysin raises levels of several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. The combination of neprilysin inhibitor plus angiotensin II receptor blocker (ARB) therapy is used as an alternative to angiotensin converting enzyme (ACE) inhibitor (or single agent ARB) therapy

The following recommendations for use of sacubitril-valsartan

- **For patients with new diagnosis of NYHA class II to IV HFrEF (left ventricular ejection fraction [LVEF] ≤40 percent), we suggest use of an ACE inhibitor (or single agent ARB) rather than sacubitril-valsartan as a component of initial medical therapy.**
- **Some experts have suggested use of sacubitril-valsartan as a component of initial therapy for HFrEF, but we feel that at this time there is insufficient clinical experience to recommend its use as initial therapy.**

Criteria for patient selection

- are an elevated natriuretic peptide level defined as a brain natriuretic peptide [BNP] level ≥150 pg/mL or NT-proBNP ≥600 pg/mL;
- or if the patient was been hospitalized for HF within the previous 12 months, a BNP ≥100 pg/mL or an NT-proBNP ≥400 pg/mL),
- a systolic blood pressure ≥100 mmHg, an estimated glomerular filtration rate ≥30 mL/min/1.73 m^2, and tolerance of ACE inhibitor or ARB therapy in doses equivalent to at least enalapril 10 mg twice daily for ≥4 weeks.
- Patients should have no history of angioedema.

Initial evaluation for contraindications

- **In patients with hypersensitivity to any component.**
- **In patients with a history of angioedema (whether resulting from angiotensin converting enzyme [ACE] inhibition or not).**
- **In patients who are pregnant given risk of fetal toxicity including fetal death.**

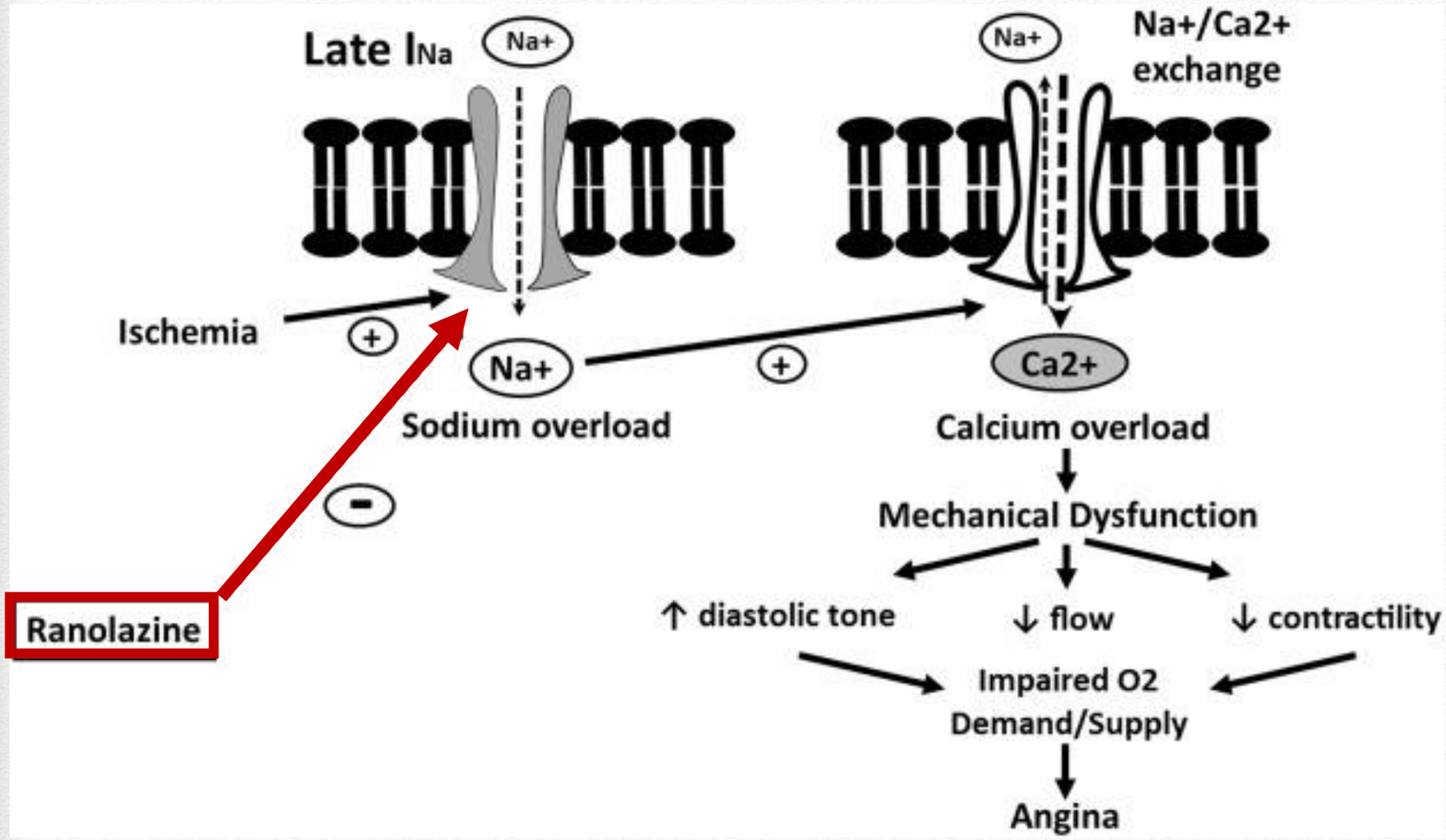
Monitoring Parameters Baseline and periodic serum potassium, renal function, BP.

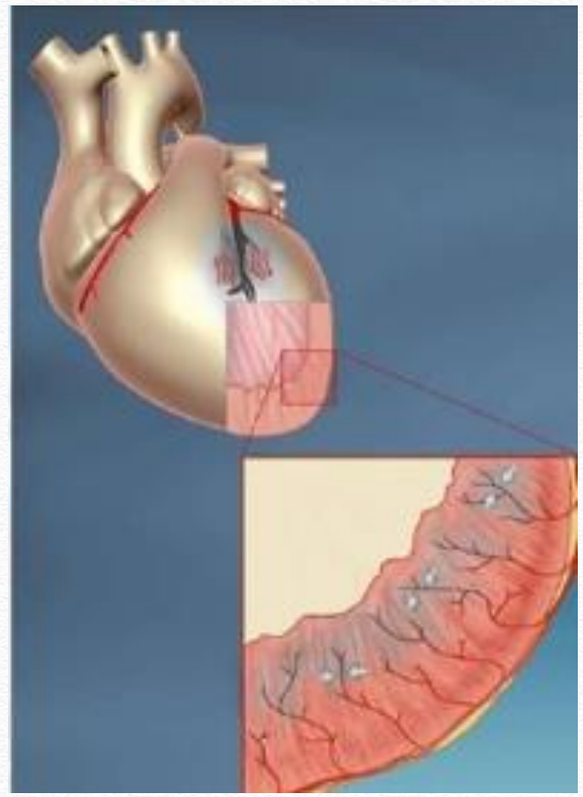
2013 ACCF/AHA Heart Failure guideline recommendations: Within 1 to 2 weeks after initiation of an ARB, reassess blood pressure (including postural blood pressure changes), renal function, and serum potassium; follow closely after dose changes.

RANOLAZINE

Brand Names: US Ranexa

Pharmacologic Category Antianginal Agent; Cardiovascular Agent


Late I_{Na}
Na+
Na+
Na+/Ca2+
exchange
Ischemia
+
Na+
+
Ca2+
Sodium overload
Calcium overload
Mechanical Dysfunction
↑ diastolic tone
↓ flow
↓ contractility
Impaired O2
Demand/Supply
Angina
Ranolazine
-



use

- Chronic angina: Treatment of chronic angina
- Note: ranolazine may be useful when prescribed as a substitute for beta blockers for relief of symptoms if initial treatment with beta blockers leads to unacceptable side effects, is less effective, or if initial treatment with beta- blockers is contraindicated. May also be used in combination with beta- blockers, for relief of symptoms when initial treatment with beta-blockers is not successful .
- Off-label Use: Ventricular tachycardia

INTRODUCTION/ treatment of chronic angina:

- ▶Medical therapy to prevent MI and death:
- ▶Anti platelet therapy: aspirin (clopidogrel if aspirin is contraindicated)
- ▶High-dose statin
- ▶Beta-blockers (if left ventricular ejection fraction [LVEF] < 40% or prior MI)
- ▶ACE inhibitors (ifLVEF < 40%, DM, HTN, or CKD)

- ▶ Medical therapy for relief of symptoms:
- ▶ Beta-blockers as initial therapy.
- ▶ Prescribe calcium channel blockers or long-acting nitrates when beta- blockers cannot be used, or in combination with beta-blockers when beta- blockers are not sufficient.
- ▶ Ranolazine in combination with maximally tolerated beta-blockers.

Mechanism of Action

- **Ranolazine exerts antianginal and anti-ischemic effects without changing hemodynamic parameters (heart rate or blood pressure). At therapeutic levels, ranolazine inhibits the late phase of the inward sodium channel (late I_{Na}) in ischemic cardiac myocytes during cardiac repolarization reducing intracellular sodium concentrations and thereby reducing calcium influx via Na^{+}-Ca^{2+} exchange. Decreased intracellular calcium reduces ventricular tension and myocardial oxygen consumption. It is thought that ranolazine produces myocardial relaxation and reduces anginal symptoms through this mechanism although this is uncertain. At higher concentrations, ranolazine inhibits the rapid delayed rectifier potassium current (I_{Kr}) thus prolonging the ventricular action potential duration and subsequent prolongation of the QT interval.**

Ranolazine - summary

Ranolazine:
Inhibits the late inward Na current

Ischaemia

↓

↑ Late I_{Na}

↓

Na^+ Overload

↓

Ca^{++} Overload

↓

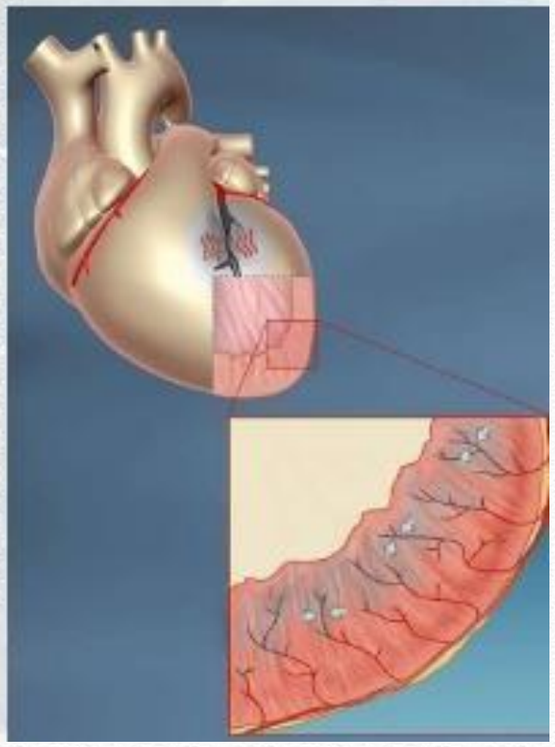
Diastolic relaxation failure (Increased diastolic tension) Extravascular compression

Intramural small vessel compression (↓ O2 supply) and ↑ O2 demand

Ranolazine

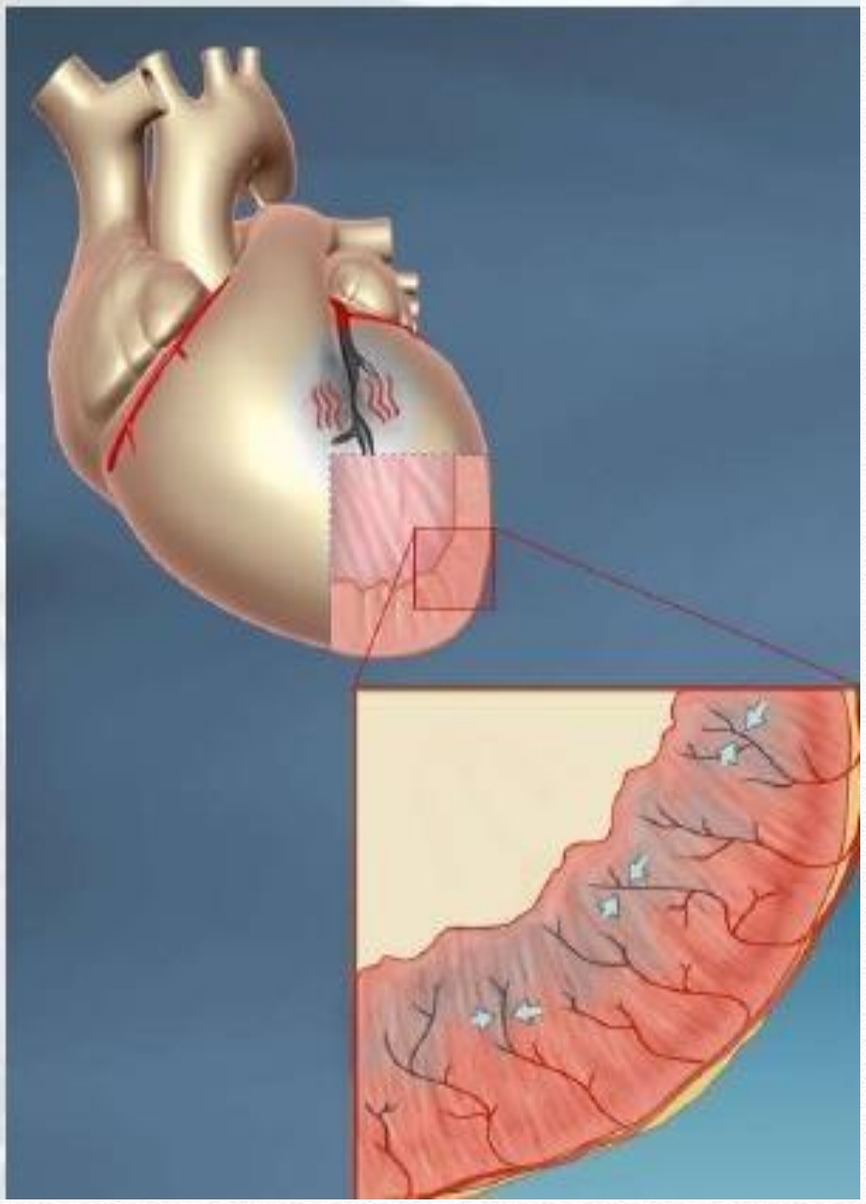
1-piperazineacetamide, *N*-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, (±)-; $C_{24}H_{33}N_3O_4$; M_r = 427.5; CAS number: 95635-55-5

Ranolazine prevents the diastolic stiffness and thereby preserves myocardial blood flow



Outcome of diastolic stiffness

- End result
  - Impaired coronary blood collection during diastole due to the diastolic stiffness
  - Increased ventricular diastolic wall stress and end-diastolic pressure.
  - Mechanical compression of the microcirculation within the wall of the ventricle,
  - Worsening of ischaemia, particularly in the sub-endocardial regions.



Adverse Reactions >0.5% to 10%:

- Cardiovascular: Bradycardia (≤4%), hypotension (≤4%), orthostatic hypotension (≤4%), palpitation (≤4%), peripheral edema (≤4%), prolonged QT interval on ECG (>500 msec: ≤1%)
- Central nervous system: Dizziness (6%; may be dose-related), headache (≤6%), confusion (≤4%), syncope (≤4%), vertigo (≤4%)
- Dermatologic: Hyperhidrosis (≤4%)
- Gastrointestinal: Constipation (5%), abdominal pain (≤4%), anorexia (≤4%), dyspepsia (≤4%), nausea (≤4%; dose-related), vomiting (≤4%), xerostomia (≤4%)
- Genitourinary: Hematuria (≤4%)
- Neuromuscular: Weakness (≤4%)
- Ophthalmic: Blurred vision (≤4%)
- Otic: Tinnitus (≤4%)
- Respiratory: Dyspnea (≤4%)

Ranolazine also inhibits pathways involved in the metabolism of digoxin and simvastatin, and dose reduction may be required.

Ranolazine – Drug interactions

- Inhibitors of CYP3A
- Increase ranolazine plasma levels and QTc prolongation and should not be coadministered with ranolazine:
  - Ketoconazole and other azole antifungals
  - Diltiazem
  - Verapamil
  - Macrolide antibiotics
  - HIV protease inhibitors
  - Grapefruit juice or grapefruit-containing products

- Inducers of CYP3A
- Reduce the plasma concentration of ranolazine to subtherapeutic levels and thus should not be given together:
  - Rifampin, Rifabutin, Rifapentin
  - Phenytoin
  - Phenobarbital
  - Carbamazepine
  - St. John's wort

ivabradine


Coralan® 5 mg
ivabradine
Film-coated tablet
56 film-coated tablets
SERVIER
Oral route
Coralan 7.5 mg
ivabradine
Film-coated tablet
56 film-coated tablets
SERVIER
Oral route

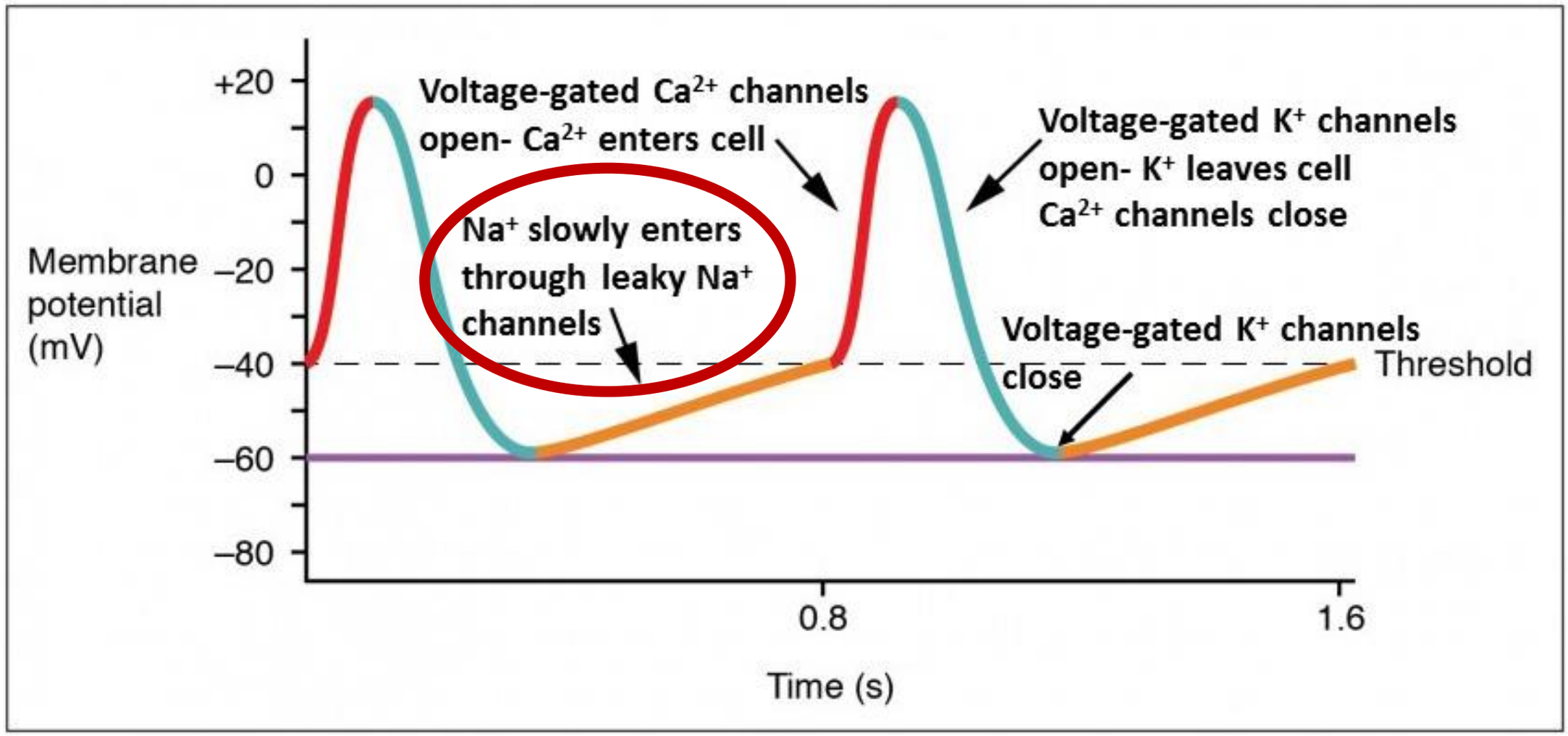
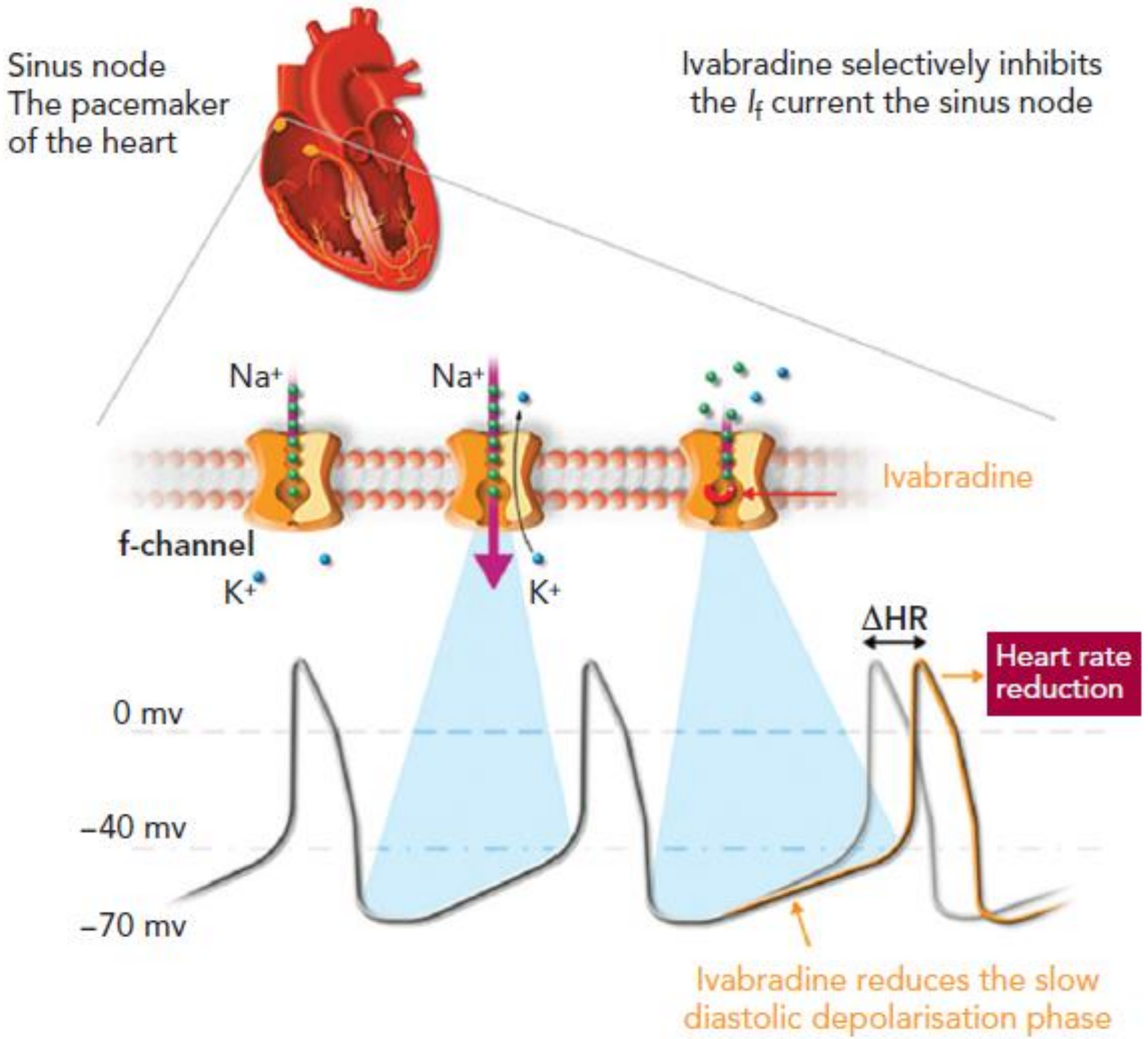

+20
0
–20
–40
–60
–80
Membrane potential (mV)
Voltage-gated Ca2+ channels open- Ca2+ enters cell
Na+ slowly enters through leaky Na+ channels
Voltage-gated K+ channels open- K+ leaves cell Ca2+ channels close
Voltage-gated K+ channels close
Threshold
0.8
1.6
Time (s)

Figure 1: Mechanism of Action of Ivabradine



Source: http://www.shift-study.com/ivrabradine/mode-of-action/ Reproduced with the permission of Servier © 2016.

- Brand Names: US Corlanor
- Brand Names: Canada Lancora
- Pharmacologic Category Cardiovascular Agent, Miscellaneous

USE

- Heart failure: To reduce the risk of hospitalization for worsening heart failure in patients with
- stable, symptomatic (NYHA class II to III according to the ACC/AHA/HFSA heart failure guidelines [Yancy 2016]) chronic heart failure with left ventricular ejection fraction ≤35%,
- who are in sinus rhythm with resting heart rate ≥70 beats per minute (bpm) and either are on maximally tolerated doses of beta blockers or have a contraindication to beta-blocker use.
- Use: Off-Label Inappropriate sinus tachycardia; Stable angina

mechanism of Action

- **Selective and specific inhibition of the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (f-channels) within the sinoatrial (SA) node of cardiac tissue resulting in disruption of If ion current flow prolonging diastolic depolarization, slowing firing in the SA node, and ultimately reducing heart rate. Has not demonstrated effects on myocardial contractility or relaxation, ventricular repolarization, or conduction apart from the sinus node effects. Partial inhibition of the retinal I_h current (similar to the cardiac I_f current) may explain visual disturbances (eg, phosphenes) (Nawarskas 2015).**

Adverse Reactions 1% to 10%:

- **Cardiovascular: Bradycardia (6% to 10%), hypertension (9%), atrial fibrillation (5% to 8%)**
- **Central nervous system: Phosphene (3%)**
- **Frequency not defined: Cardiovascular: Heart block, sinoatrial arrest**

Contraindications

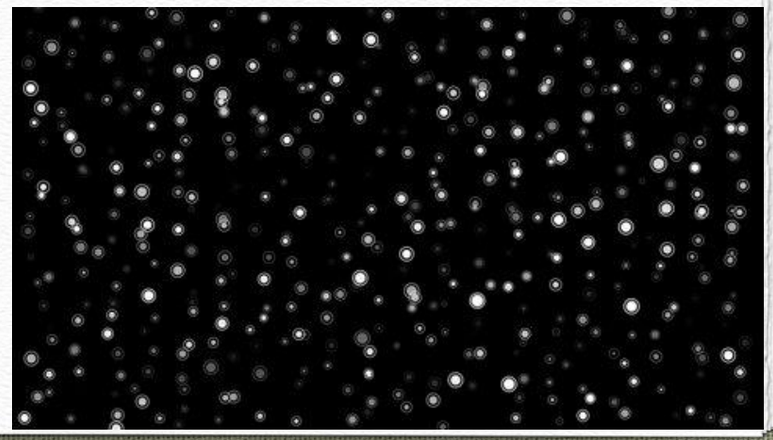
- Acute decompensated heart failure;
- blood pressure <90/50 mm Hg;
- sick sinus syndrome
- or third-degree AV block;
- resting heart rate <60 bpm prior to treatment;
- severe hepatic impairment;
- pacemaker dependence (heart rate maintained exclusively by the pacemaker).

Warnings/Precautions

Atrial fibrillation: increases the risk of atrial fibrillation; monitor cardiac rhythm. Discontinue if atrial fibrillation develops.

Avoid concurrent use with verapamil and diltiazem.

Visual function: Phosphenes – luminous phenomena (described as transient enhanced brightness in a limited area of the visual field, halos, image decomposition, colored bright lights, or multiple images) may occur with use. Onset is generally within the first 2 months of therapy and is reported to be of mild to moderate intensity; most cases resolve during or after treatment discontinuation.



Monitoring Parameters

- **Heart rate (prior to initiation, prior to increasing dose, or after decreasing dose); monitor heart rate more closely if receiving other negative chronotropes (eg, amiodarone, beta-blockers, digoxin)**
- **blood pressure**
- **cardiac rhythm (assessing for atrial fibrillation)**