Bradycardia and tachycardia drugs

Dr shima Jafari
Pharm D, BCPS
Assistant professor of clinical pharmacy

CLINICAL PRACTICE GUIDELINE

2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay

TABLE 4 Medications That Can Induce/Exacerbate Bradycardia or Conduction Disorders

Antihypertensive	Antiarrhythmic	Psychoactive	Other
■ Beta-adrenergic receptor blockers (including beta-adrenergic blocking eye drops used for glaucoma) ■ Clonidine ■ Methyldopa ■ Non-dihydropyridine calcium channel blockers ■ Reserpine	■ Adenosine ■ Amiodarone ■ Dronedarone ■ Flecainide ■ Procainamide ■ Propafenone ■ Quinidine ■ Sotalol	■ Donepezil ■ Lithium ■ Opioid analgesics ■ Phenothiazine antiemetics and antipsychotics ■ Phenytoin ■ Selective serotonin reuptake inhibitors ■ Tricyclic antidepressants	■ Anesthetic drugs (propofol) ■ Cannabis ■ Digoxin ■ Ivabradine ■ Muscle relaxants (e.g., succinylcholine)

TABLE 8 Acute Medical Management of Bradycardia Attributable to SND or Atrioventricular Block

Medication	Dosage	Comments
Symptomatic sinus bradycardia or atrioventricular block		
Atropine	0.5-1 mg IV (may be repeated every 3-5 min to a maximum dose of 3 mg) (S5.3.2.4-20–S5.3.2.4-24)	
Dopamine	5 to 20 mcg/kg/min IV, starting at 5 mcg/kg/min and increasing by 5 mcg/kg/min every 2 min (S5.3.2.4-25)	Dosages of >20 mcg/kg/min may result in vasoconstriction or arrhythmias
Isoproterenol	20-60 mcg IV bolus followed doses of 10-20 mcg, or infusion of 1-20 mcg/min based on heart rate response (S5.3.2.4-26–S5.3.2.4-32)	Monitor for potential development of ischemic chest pain
Epinephrine	2-10 mcg/min IV or 0.1-0.5 mcg/kg/min IV titrated to desired effect (S5.3.2.4-17, S5.3.2.4-31, S5.3.2.4-33)	
Second- or third-degree atrioventricular block associated with acute inferior MI		
Aminophylline	250-mg IV bolus	
Calcium channel blocker overdose		
10% calcium chloride	1-2 g IV every 10-20 min or an infusion of 0.2-0.4 mL/kg/h (S5.3.2.4-34–S5.3.2.4-36)	
10% calcium gluconate	3-6 g IV every 10-20 min or an infusion at 0.6-1.2 mL/kg/h (S5.3.2.4-34–S5.3.2.4-36)	
Beta-blocker or calcium channel blocker overdose		
Glucagon	3-10 mg IV with infusion of 3-5 mg/h (S5.3.2.4-37, S5.3.2.4-38)	
High dose insulin therapy	IV bolus of 1 unit/kg followed by an infusion of 0.5 units/kg/h (S5.3.2.4-36, S5.3.2.4-39, S5.3.2.4-40).	Follow glucose and potassium levels
Digoxin overdose		

Cont…

Digoxin overdose		
Digoxin antibody fragment	Dosage is dependent on amount ingested or known digoxin concentration (S5.3.2.4-41–S5.3.2.4-48)	■ One vial binds approximately 0.5 mg of digoxin ■ Administer over at least 30 min ■ May be repeated
Post-heart transplant		
Aminophylline	6 mg/kg in 100-200 mL of IV fluid over 20-30 min	
Theophylline	300 mg IV, followed by oral dose of 5-10 mg/kg/d titrated to effect	■ Therapeutic serum levels range from 10-20 mcg/mL ■ Usual posttransplant dosages average 450 mg±100 mg/d
Spinal cord injury		
Aminophylline	6 mg/kg in 100-200 mL of IV fluid over 20-30 min (S5.3.2.4-7)	
Theophylline	Oral dose of 5-10 mg/kg/d titrated to effect (S5.3.2.4-6)	Effective dosages often result in serum levels below the usual effective range of 10-20 mcg/mL

Atropine

Dosage form

Inj: 0/5 mg/mL

Inj: 10mg/mL (2mL)

Pharmacologic Category:

Anticholinergic Agent

0.5-1 mg IV (may be repeated every 3-5 min to a maximum dose of 3 mg)

- IV doses <0.5 mg have been associated with paradoxical bradycardia
- Restrict total dose to 0.03 to 0.04 mg/kg in patients with ischemic heart disease

Bradycardia, symptomatic

- **IV, IM:** 0.5 to 1 mg every 3 to 5 minutes; 1 mg is preferred for severe bradyarrhythmias (eg, hypotension/shock, altered mental status, acute heart failure); maximum total dose: 3 mg

- Atropine is ineffective in heart transplant patients due to lack of vagal innervation and likely not effective for type II second-degree or third degree atrioventricular node block

- Atropine may inhibit sweating and possibly lead to heat-related injury or hyperthermia in patients exposed to warm environments or exercise.

Use with caution in patients with

- Myocardial ischemia
- Heart failure
- Tachyarrhythmias
- Hypertension

- Use with caution in patients with severe narrow-angle glaucoma; may precipitate acute glaucoma.

- Use with extreme caution when used to treat side effects of acetylcholinesterase inhibition or avoid; may precipitate a myasthenic crisis.

Pharmacodynamics and pharmacokinetics

Onset of action:

Increased heart rate:

IM: Within 15 to 30 minutes maximum effect: 45 to 60 minutes

IV: Immediate; maximum effect: 0.7 to 4 minutes

Absorption:

Rapid and well absorbed from all dosage forms

Distribution:

Widely throughout the body; crosses blood-brain barrier

DOPAMINE

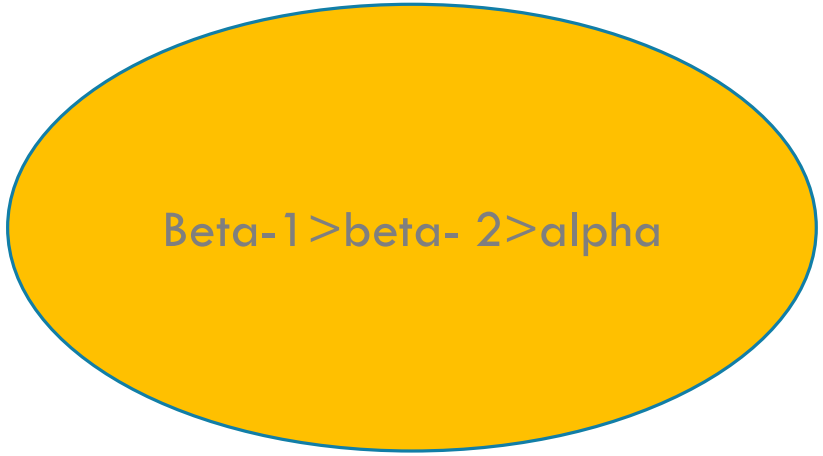
INJ: 40mg/mL (5mL)

Dose:

5 to 20 mcg/kg/min IV, starting at 5 mcg/kg/min and increasing by 5 mcg/kg/min every 2 min

DOPAMINE

- Endogenous catecholamine
- Dose-dependent effects on the cardiovascular system
- Interaction with four different receptors:
  - Dopaminergic type 1 and type 2
  - Adrenergic alpha-1
  - Beta-1



Dose	Effect
2.5 μg/kg/min	vasodilation of the splanchnic, coronary and renal vasculature
3–5 μg/kg/min	❖ Stimulating sarcolemmal **beta-1** receptors in cardiomyocytes ❖ Increases PCWP ❖ Significant chronotropic and inotropic effects
more than 5 μg/kg/min	potent vasoconstriction (via its effect on **alpha-1** adrenergic receptors of the vasculature)

Doses >20 mcg/kg/minute may not have a beneficial effect on blood pressure and may increase the risk of tachyarrhythmias

Hemodynamic effects of dopamine are dose dependent (however, this is relative and there is overlap of clinical effects between dosing ranges):

- Low-dose: 1 to 5 mcg/kg/minute, results in increased renal blood flow and urine output.

- Intermediate-dose: 5 to 10 mcg/kg/minute, results in increased renal blood flow, heart rate, cardiac contractility, and cardiac output

- High-dose: >10 mcg/kg/minute, alpha-adrenergic effects begin to predominate, resulting in vasoconstriction, increased blood pressure, in addition to increased heart rate, cardiac contractility, and cardiac output due to beta-adrenergica

CONTRAINDICATIONS

- Hypersensitivity to sulfites
- Pheochromocytoma
- Uncorrected tachyarrhythmias
- Ventricular fibrillation

- May cause increases in heart rate, increasing the risk of tachycardia and other tachyarrhythmias including ventricular arrhythmias
- Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy to minimize the risk of arrhythmias
- Use with extreme caution in patients taking MAO inhibitors; prolong hypertension may result from concurrent use

EPINEPHRINE

Amp: 1mg/mL

Amp: 0.1mg/ml (10mL)

Dose:

2-10 mcg/min IV or 0.1-0.5 mcg/kg/min IV titrated to desired effect

- Endogenous catecholamine
- Exhibits dose-dependent effects.
- When administered at lower doses of up to 0.01 μg/kg/min, it primarily acts on beta-2 peripheral adrenergic receptors thereby causing vasodilation.
- when administered at an increased rate of >0.2 μg/kg/min, its effect on beta-1 and alpha- 1 receptors predominates, resulting in overall positive inotropy and vasoconstriction.

SIDE-EFFECTS

Tachyarrhythmias

Headache

Anxiety

Cold extremities

Pulmonary edema

Cerebral haemorrhage

SIDE-EFFECTS

Tachyarrhythmias

Headache

Anxiety

Cold extremities

Pulmonary edema

Cerebral haemorrhage

Isoproterenol

Inj: 0.2 mg/mL

Pharmacologic Category

Beta1/Beta2 Agonist

Dose:

20-60 mcg IV bolus followed doses of 10-20 mcg, or infusion of 1-20 mcg/min based on heart rate response

Monitor for potential development of ischemic chest pain

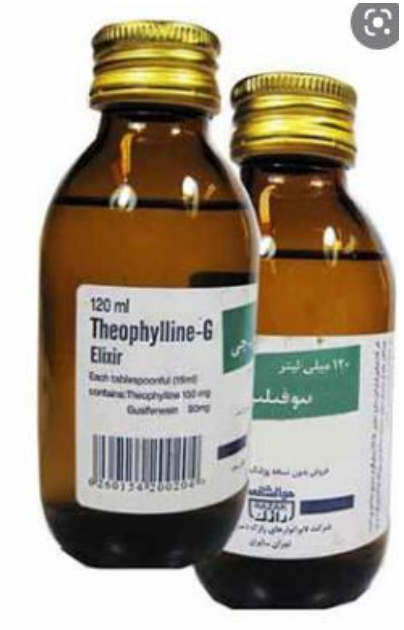
Use with caution in patients with:

- Cardiovascular disease (CAD); may increase myocardial oxygen demand resulting in ischemia
- Diabetes mellitus; may transiently increase blood glucose levels
- Hyperthyroidism; may induce thyroid storm in susceptible individuals

Pharmacodynamics and pharmacokinetics

- Onset of action: IV: Immediate
- Duration: IV: 10-15 minutes
- Metabolism: Via conjugation in many tissues including hepatic and pulmonary
- Half-life elimination: 2.5-5 minutes
- Excretion: Urine (primarily as sulfate conjugates)

Theophylline



Tab: 200 mg

Elixir

Pharmacologic Category

PDEI, Nonselective

Post-heart transplant

300 mg IV, followed by oral dose of 5-10 mg/kg/d titrated to effect

Renal Impairment

No dosage adjustment necessary

Hepatic Impairment

Oral:

Dose reduction and frequent monitoring of serum theophylline concentration are required; risk of severe and potentially fatal toxicity may occur.

Maximum dose: 400 mg/day

Theophylline toxicity:

- May occur if reduced theophylline clearance occurs.

Theophylline clearance may be decreased in patients with

- Acute pulmonary edema
- Heart failure
- Fever (≥102°F for ≥24 hours or lesser temperature elevations for longer periods)
- Hepatic disease
- Acute hepatitis
- Cirrhosis
- Hypothyroidism
- Sepsis with multiorgan failure, shock
- Patients following cessation of smoking.

If a patient develops signs and symptoms of theophylline toxicity (eg, nausea or persistent, repetitive vomiting), a serum theophylline level should be measured immediately and subsequent doses withheld

Use with caution in patients with

- Cardiac arrhythmias (excluding bradyarrhythmias); use may exacerbate arrhythmias.
- Cystic fibrosis; increased theophylline clearance may occur
- Hyperthyroidism; increased theophylline clearance may occur
- Active peptic ulcer disease; use may exacerbate peptic ulcer
- Seizure disorders; use may exacerbate seizure disorder.

Therapeutic levels:

Adults: 10 to 20 mcg/mL Toxic concentration: >20 mcg/mL

Pharmacodynamics and pharmacokinetics

- Absorption: Oral (solution and IR): Rapid and complete
- Metabolism: Hepatic via demethylation (CYP 1A2) and hydroxylation (CYP 2E1 and 3A4)
- Half-life elimination :Highly variable and dependent upon age, hepatic function, cardiac function, lung disease, and smoking history
- Time to peak, serum: Oral (solution and immediate release): 1 to 2 hours

- Increased theophylline clearance: Hyperthyroidism; cystic fibrosis; smoking

Aminophylline

Amp: 250 mg

Second- or third-degree atrioventricular block associated with acute inferior MI

- 250-mg IV bolus

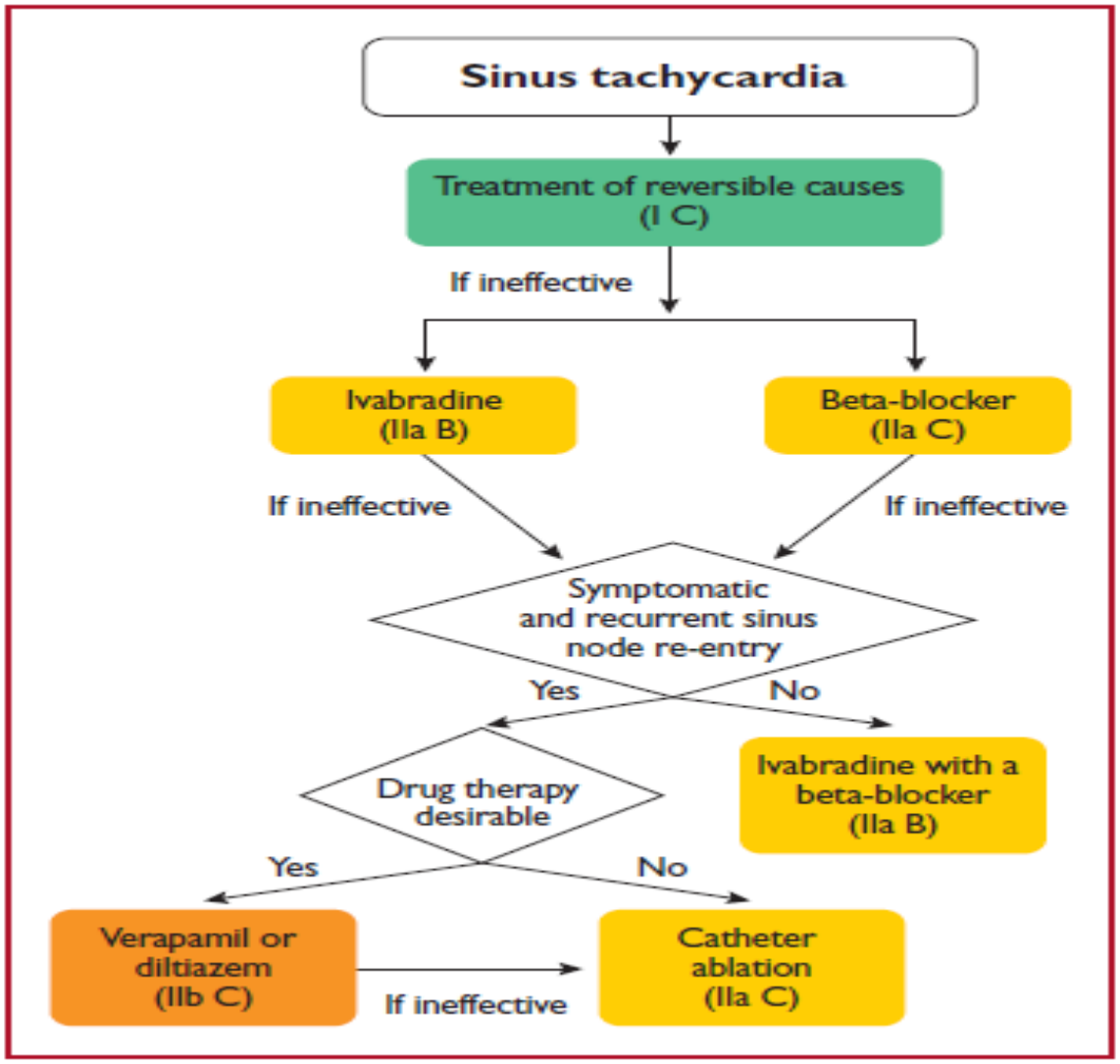
Post-heart transplant

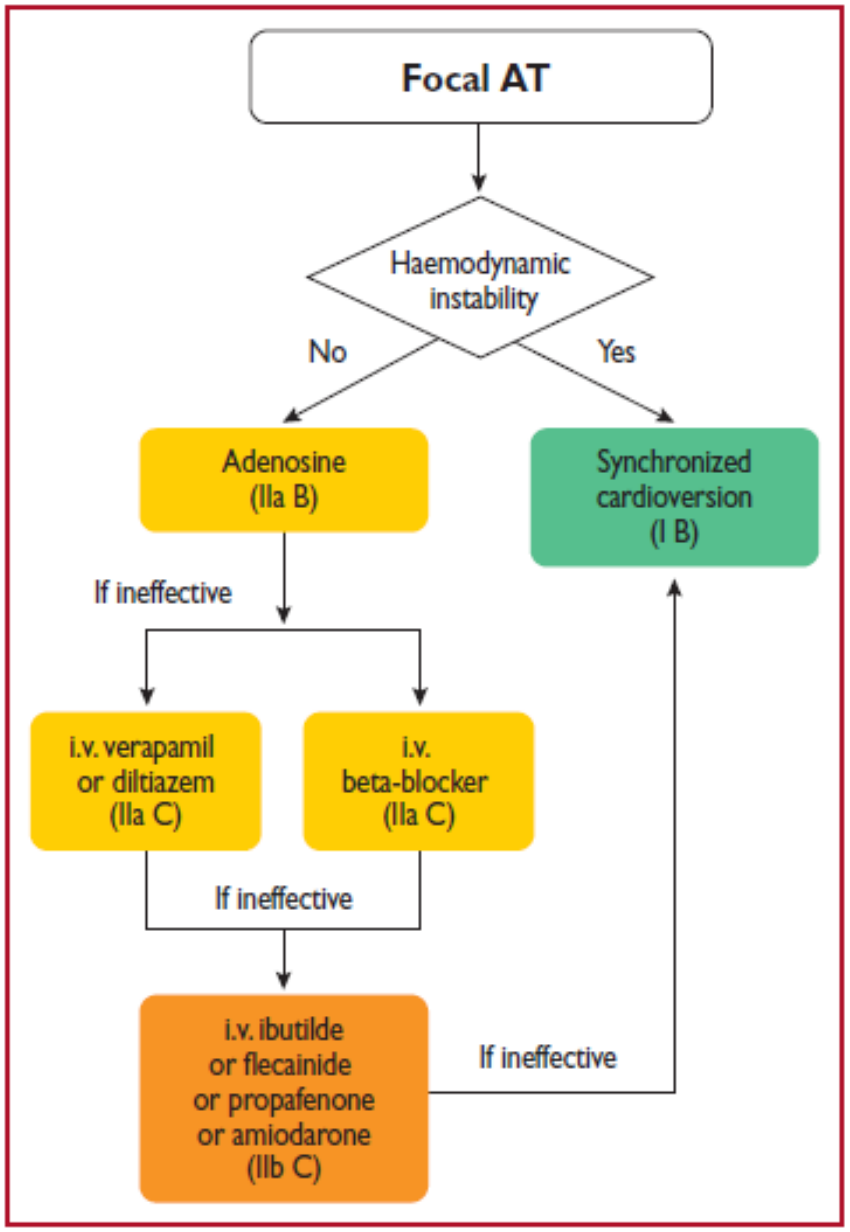
- 6 mg/kg in 100-200 mL of IV fluid over 20-30 min

Causes of physiological sinus tachycardiaa

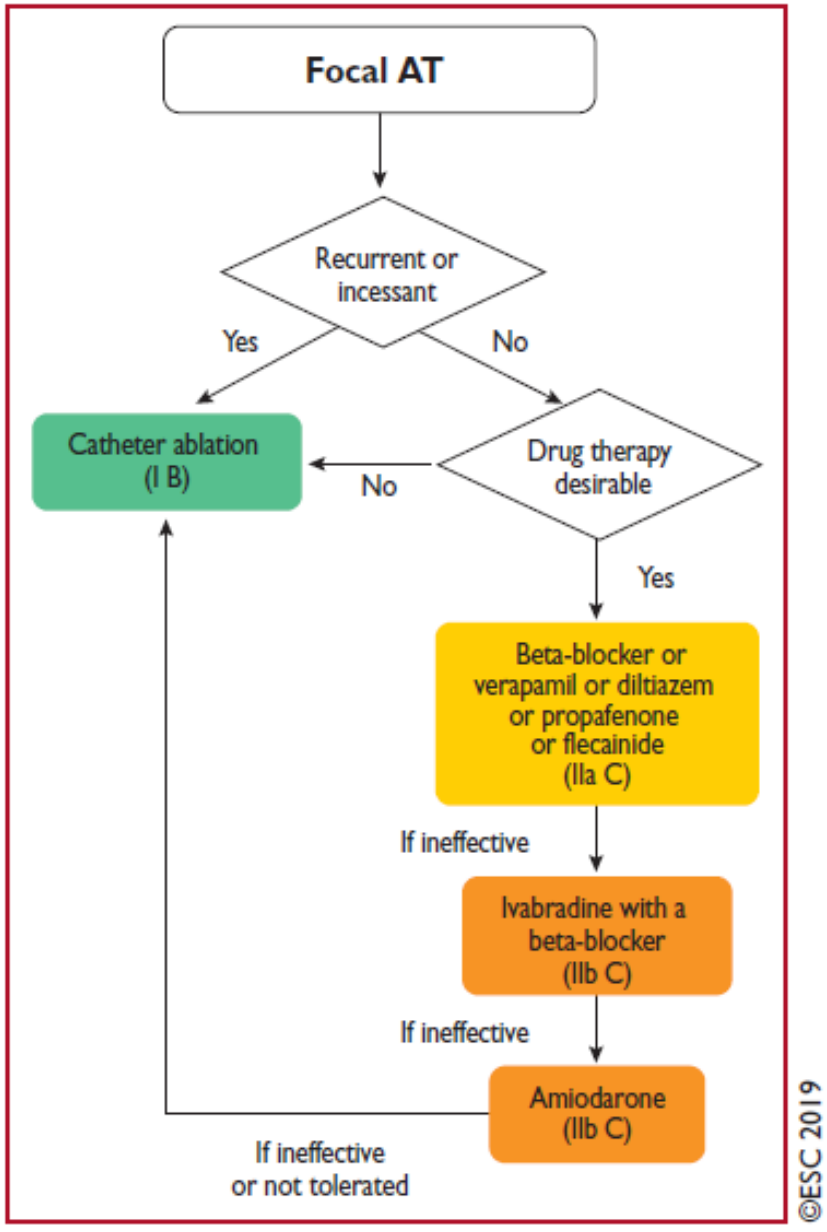
Drugs	Epinephrine, norepinephrine, dopamine, dobutamine, atropine, beta-2 adrenergic receptor agonists (salbutamol), methylxanthines, doxorubicin, daunorubicin, beta-blocker withdrawal
Illicit drugs	Amphetamines, cocaine, lysergic acid diethylamide, psilocybin, ecstasy, crack, cocaine
Other	Caffeine, alcohol

Sinus tachycardia

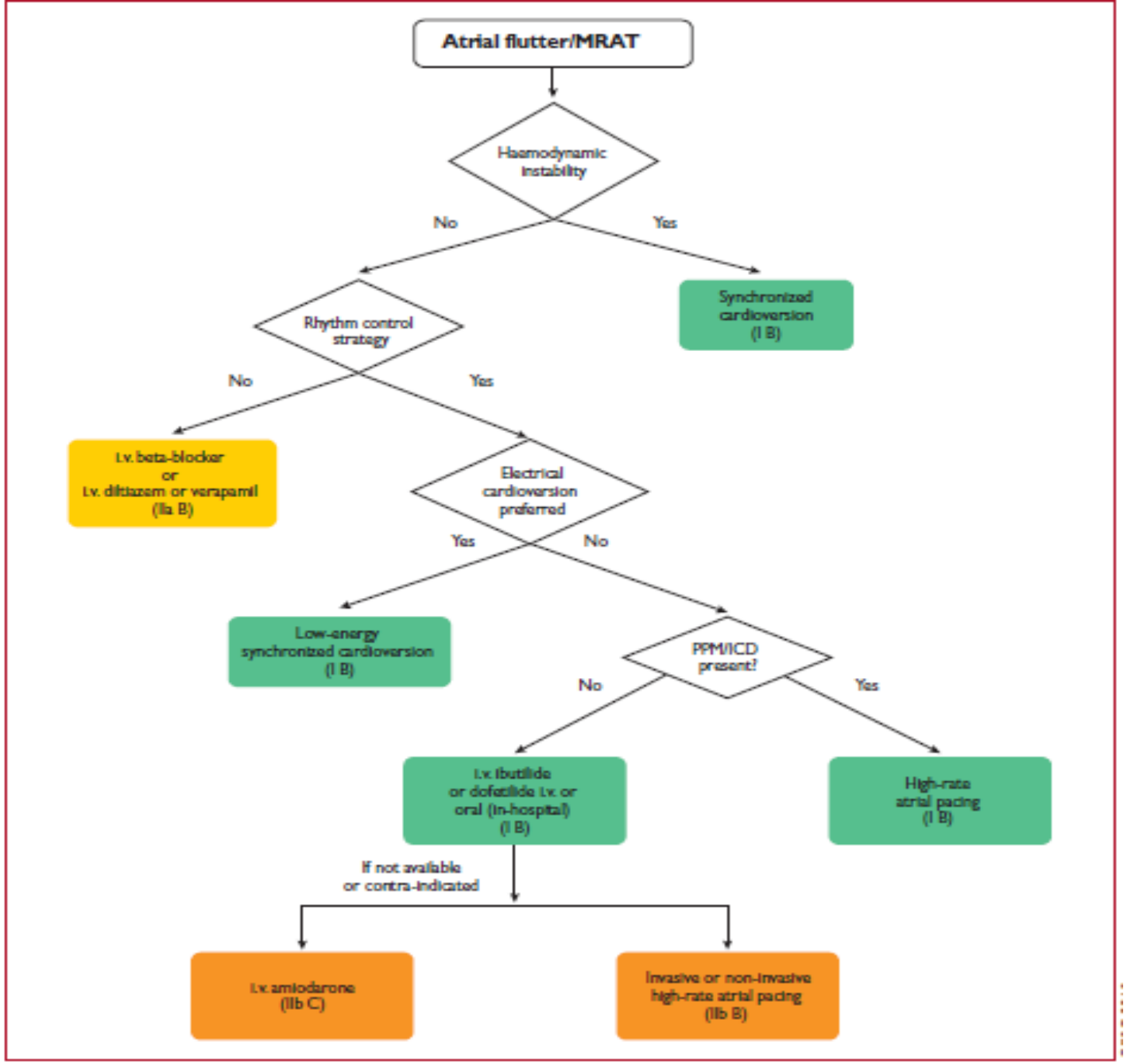




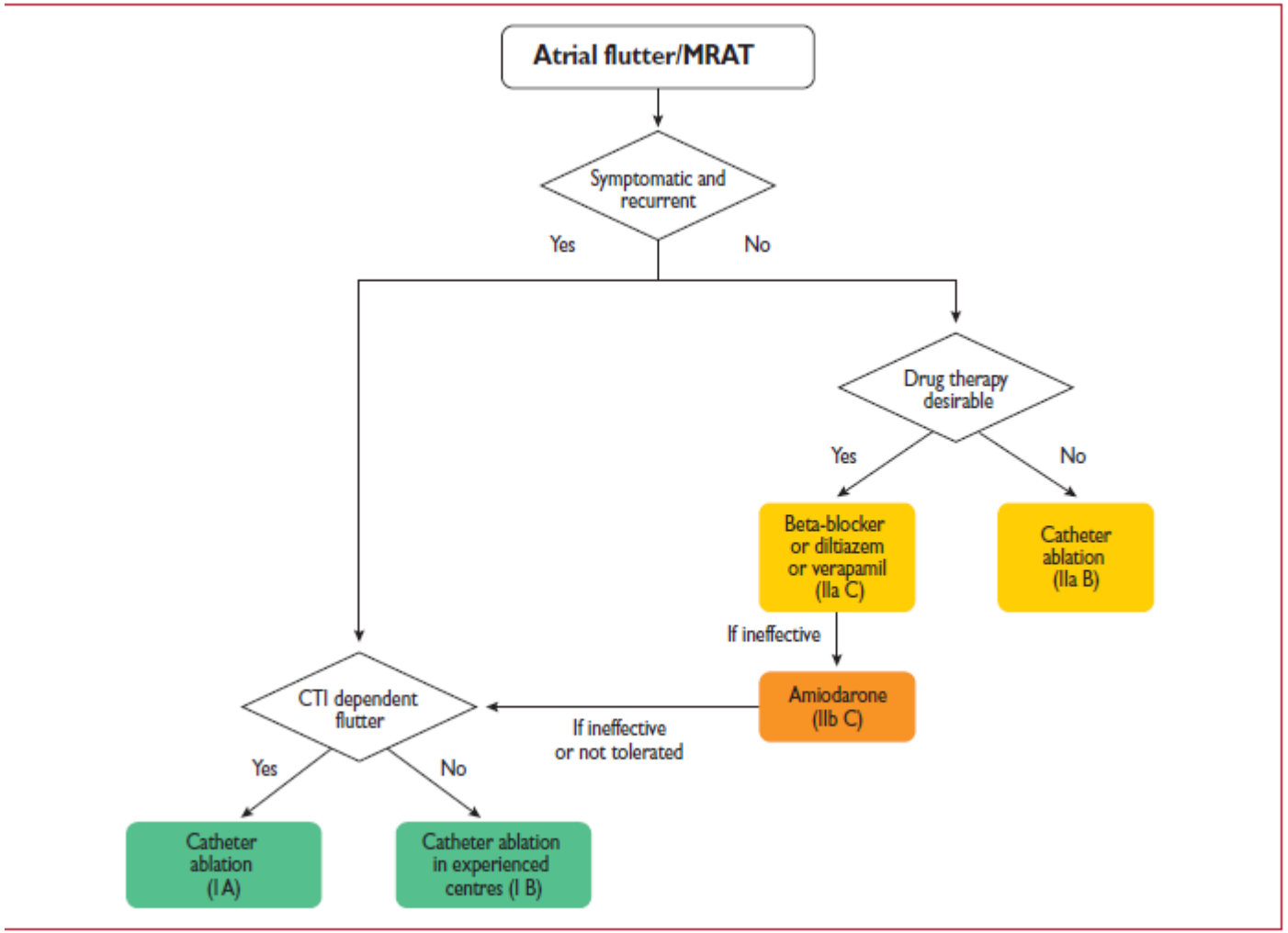
Acute therapy



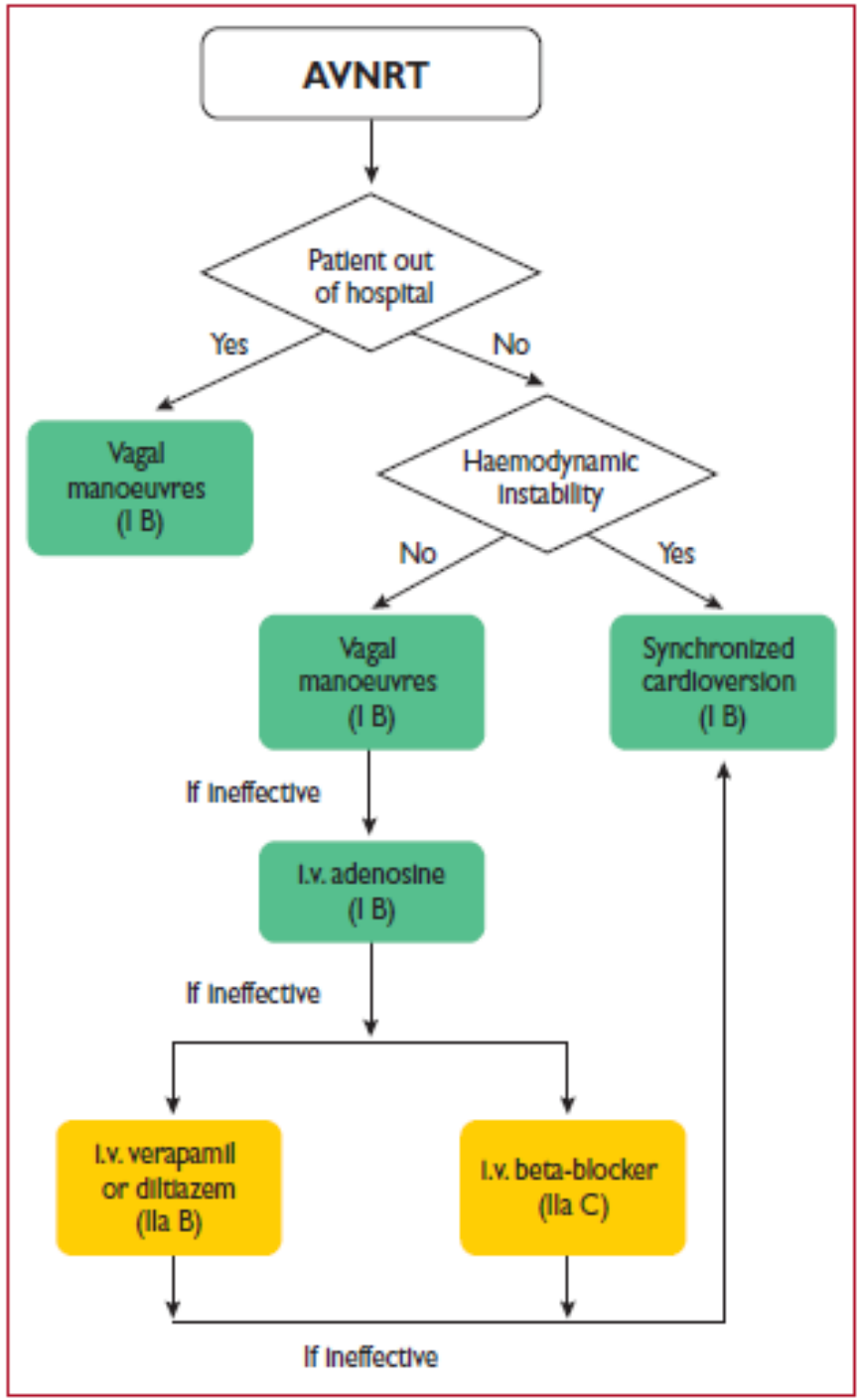
Chronic therapy

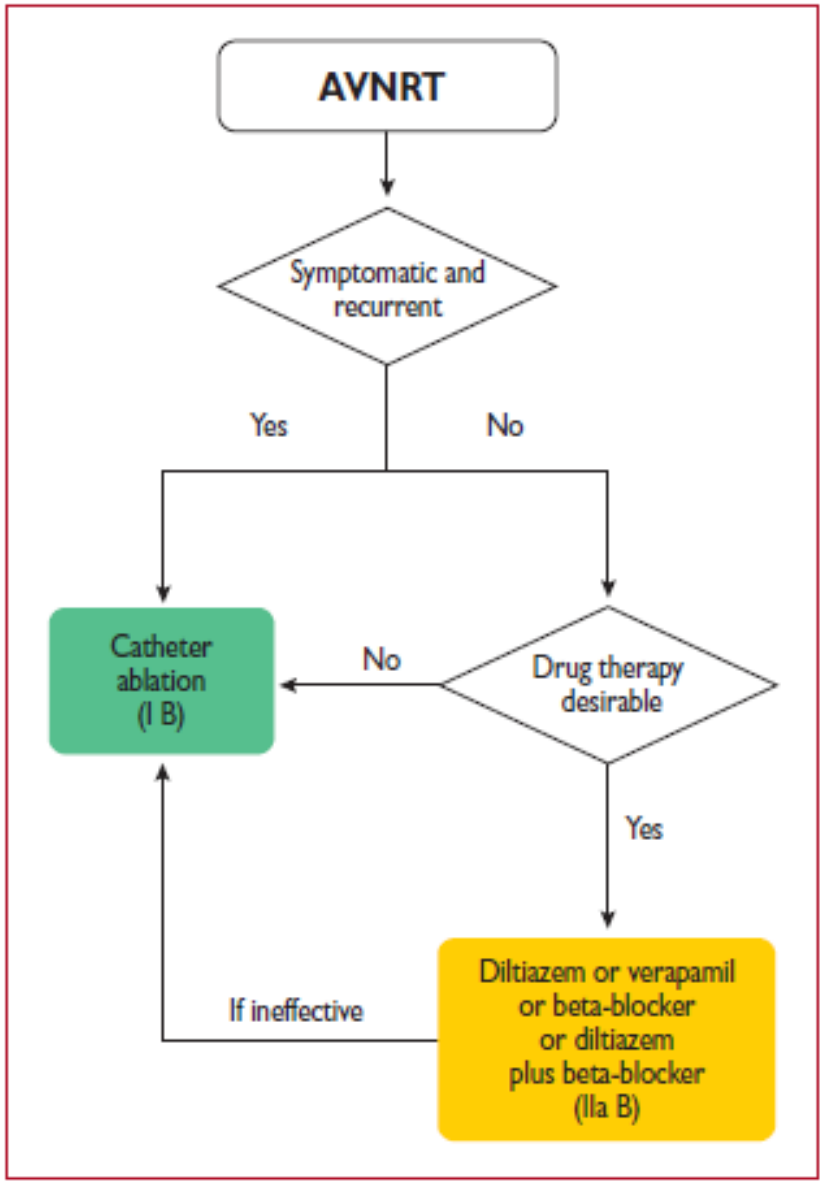


Acute therapy of stable atrial flutter ormacro-re-entrant atrial tachycardia



Chronic therapy of atrial flutter/macro-re-entrant atrial tachycardia


AVNRT
Patient out of hospital
Yes
No
Vagal manoeuvres (I B)
Haemodynamic instability
No
Yes
Vagal manoeuvres (I B)
Synchronized cardioversion (I B)
If ineffective
I.v. adenosine (I B)
If ineffective
I.v. verapamil or diltiazem (IIa B)
I.v. beta-blocker (IIa C)
If ineffective
©ESC 2019


AVNRT
Symptomatic and recurrent
Yes
No
Catheter ablation (I B)
No
Drug therapy desirable
Yes
If ineffective
Diltiazem or verapamil or beta-blocker or diltiazem plus beta-blocker (IIa B)
©ESC 2019

CALCIUM CHANNEL BLOCKERS

Antiarrhythmic Agent, Class IV

Non- dihydropyridine (non-DHP)

- Diltiazem

  Tab:60-120 mg

- Verapamil

  Tab:40-80mg

  Tab ER:240 mg

  Intravenous solution: 2.5 mg/mL

Adverse effects

- AV block
- Bradycardia
- HF exacerbation
- Hypotension
- Constipation (oral verapamil)

Drug Interaction

Diltiazem

CYP3A4 inhibitors may ↑ concentrations

Inhibits CYP3A4: ↑ cyclosporine and statin (some) concentrations

Drug Interaction

Verapamil

CYP3A4 inhibitors may ↑ concentrations

Inhibits P-gp: ↑ digoxin concentrations

Inhibits CYP3A4: ↑ cyclosporine and statin (some) concentrations

↑ dofetilide concentrations by competition for renal tubular secretion

Diltiazem

Avoid in patients

- Taking a beta-blocker
- HFrEF
- Sinus node dysfunction
- Second- or third-degree atrioventricular block unless a functioning pacemaker has been placed.

Diltiazem

Indication

- Atrial fibrillation or atrial flutter, rate control
- Nonsustained ventricular tachycardia or ventricular premature beats, symptomatic (alternative agent) (off-label use)
- Supraventricular tachycardia (alternative agent)

Diltiazem

Conversion from immediate-release to extended-release formulations:

Patients stabilized on a maintenance regimen between 120 and 360 mg of immediate-release tablets may be switched to an extended-release formulation at the same daily dose administered in 1 or 2 divided doses depending on formulation.

Conduction abnormalities

Diltiazem may cause

- first-degree atrioventricular (AV) block
- Second-degree atrioventricular block
- Complete atrioventricular block
- Sinus bradycardia

Risk increases with addition of other agents known to slow cardiac conduction

Mechanism:

Related to pharmacologic action and may occur at clinical doses

Onset:

Varied; conduction abnormalities may occur at any time during therapy

Risk factors:

- Concomitant use of beta-blockers or digitalis
- Older adults
- Chronic kidney failure
- Underlying AV conduction abnormalities are at increased risk of bradycardia

Cutaneous hypersensitivity reactions

- Maculopapular rash is the most common cutaneous adverse reaction reported
- Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis (AGEP), have occurred rarely
- Hyperpigmentation, often in a photodistributed pattern, has also been associated with diltiazem

Mechanism:

- Non-dose-related; immunologic Delayed hypersensitivity reactions (including SCARs): Type IV immune-mediated (T-cell mediated) hypersensitivity reactions
- Hyperpigmentation: The pathogenesis of diltiazem-induced hyperpigmentation is unknown
- Maculopapular rashes: Usually occur within 10 days after initiating diltiazem
- SCARs: Onset usually occurs between 1 to 8 weeks of treatment with the implicated drug although some cases of SJS/TEN may have a more rapid onset
- AGEP: Usually occurs 1 to 2 weeks after initiation of diltiazem
- In general, improvement is observed 1 to 2 weeks after discontinuation of diltiazem

- Hyperpigmentation: Onset averages 25 months after starting diltiazem, ranging from 1.5 months to 12.5 years (Ref). Gradual improvement is observed with discontinuation of diltiazem
- Risk factors: • Hyperpigmentation: Patients with dark skin, especially Black patients or patients of Asian descent (Ref) • Prior hypersensitivity reaction to diltiazem

ADR

>10%: Cardiovascular: Peripheral edema (5% to 15%; dose-related)

1% to 10%:

Cardiovascular: Bradycardia (3% to 4%), bundle branch block (<2%), cardiac arrhythmia (1%), cardiac failure (<2%), complete atrioventricular block (<2%), ECG abnormality (<2%), edema (2% to 3%), extrasystoles (2%), first-degree atrioventricular block (3% to 4%), hypotension (3% to 4%), lower extremity edema (5% to 8%), palpitations (1% to 2%), second degree atrioventricular block (<2%), syncope (<2%), vasodilation (2% to 3%)

Contraindications

sick sinus syndrome (except in patients with a functioning artificial pacemaker); second- or third-degree AV block (except in patients with a functioning artificial pacemaker); hypotension (systolic <90 mmHg) acute MI and pulmonary congestion

Canadian labeling:

Pregnancy; use in women of childbearing potential; concurrent use with IV dantrolene; concurrent use with ivabradine; severe bradycardia

- Onset of action: Oral: Immediate release tablet: 30 to 60 minutes
- Duration: IV: Bolus: 1 to 3 hours; Continuous infusion (after discontinuation): 0.5 to 10 hours
- Half-life elimination: Immediate release tablet: 3 to 4.5 hours; Extended release tablet: 6 to 9 hours
- Time to peak, serum: Immediate release tablet: 2 to 4 hours; Extended release tablet: 11 to 18 hours; Extended release capsule: 10 to 14 hours

VERAPAMIL

Indication

- Atrial fibrillation or atrial flutter, rate control
- Nonsustained ventricular tachycardia or ventricular premature beats, symptomatic (alternative agent) (off-label use)
- Supraventricular tachycardia (alternative agent)

Conversion between oral formulations:

When switching from IR to ER formulations, the total daily dose remains the same unless formulation strength does not allow for equal conversion. At higher doses, some ER products are recommended to be given twice daily.

Acute decompensated heart failure

- In patients with left ventricular systolic dysfunction, use of verapamil may result in acute decompensation and deterioration with development of pulmonary edema and/or hypotension
- Acute cardiac failure associated with verapamil in patients with no prior history of chronic heart failure have also been reported
- Decompensated state should return to baseline after discontinuation

Mechanism:

Dose-related; related to the pharmacologic action. Exhibits significant negative inotropic and vasodilator properties. Patients with left ventricular dysfunction may not be able to compensate or tolerate these hemodynamic effects

Onset: Rapid; typically within 4 to 5 days of therapy initiation

Risk factors:

Severe left ventricular dysfunction

Older patients

Cardiac amyloidosis

Bradyarrhythmias

Verapamil may cause first-, second-, or third-degree atrioventricular (AV) block or sinus bradycardia

Although reversal is possible after discontinuation, some patients continue to have symptoms

in patients whose symptoms resolve after discontinuation, permanent pacemaker (PPM) therapy will likely not be necessary; however, cases with recurrent or unresolved symptoms after discontinuation may warrant PPM placement

Mechanism:

Dose-related; related to the pharmacologic action.

Onset: Varied; in one study, bradycardia occurred 5 minutes after administration with a peak effect at 30 to 60 minutes

Risk factors:

- Concurrent use with other AV nodal-blocking agents (eg, beta-blockers)
- Sick sinus syndrome
- Underlying AV node dysfunction

Hepatic effects

- Mild-to-moderate increased serum transaminases, increased serum alkaline phosphatase, and increased serum bilirubin have been reported, including self-limited jaundice
- Complete recovery is generally expected within 2 to 6 weeks of discontinuation and may resolve with continuation of therapy
- Rechallenge may result in rapid recurrence of hepatocellular injury

Mechanism: Non–dose-related; immunologic or idiosyncratic

Onset: Varied; symptoms such as jaundice, fatigue, or weakness usually occur 2 to 8 weeks after initiation of therapy, although the onset may be 5 to 6 months

ADR

>10%: Nervous system: Headache (IV, oral: 1% to 12%)

1% to 10%:

Cardiovascular: Acute myocardial infarction (≤1%), angina pectoris (≤1%), ankle edema (1%), atrioventricular block (IV, oral: ≤1%), atrioventricular dissociation (≤1%), bradycardia (IV, oral: ≤1%), cardiac failure (≤2%), cerebrovascular accident (≤1%), chest pain (≤1%),

BETA BLOCKERS

Bisoprolol(concor)
- Tab=2.5,5,10 mg

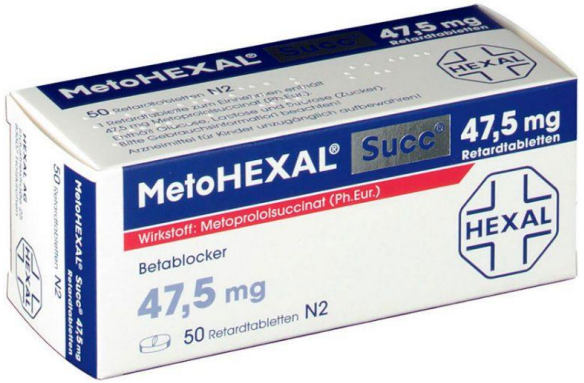
Metoprolol tartrate
- Tab=50-100

Metoprolol succinate
- Tab=23.75,47.5,95 mg

Propranolol
- Tab=10-20-40 mg

Carvedilol
- Tab=3.125,6.25,12.5 mg

Esmolol
- Vial: 10,100 mg
- Amp: 250mg/mL (10mL)



BETA BLOCKERS

Drugs (Ventricular Rate Control)	Loading Dose	Maintenance Dose
Esmolol	500 mcg/kg IV over 1 min	50–300 mcg/ kg/min continuous IV infusion (administer repeat bolus doses between each dose increase)
Propranolol:	1 mg IV over 1 min; may repeat 1 mg IV at 2-min intervals, up to three doses	(oral): 30–160 mg/day in divided doses
Metoprolol	2.5–5 mg IV over 2 min; may repeat 2.5–5 mg IV every 10 min, up to three doses	Metoprolol tartrate (oral): 25–100 mg twice daily Metoprolol succinate (oral): 50–400 mg once daily

ADR

Bradycardia

Increased airways resistance

Exacerbation of peripheral artery disease

Facilitation of hypoglycemia

Hyperkalemia

Sexual dysfunction

Depression

Fatigue

Alteration of serum TG and HDL-C

Drug Interaction

CYP2D6 inhibitors may ↑ concentrations

May ↑ lidocaine concentrations

Avoid abrupt cessation

DIGOXIN

Tab: 0.25 mg

Amp: 0.25mg/mL (1mL) (2mL)

Elixir: 0.05 mg/mL (60mL)

Drug interactions:

Digoxin concentrations are increased with concomitant:

- Clarithromycin, erythromycin
- Amiodarone (reduce digoxin dose by 30%–50% or reduce dosing frequency)
- Itraconazole, posaconazole
- Cyclosporine, tacrolimus
- Verapamil

MONITORING

- Minimizes the risk of adverse effects and ventricular arrhythmias associated with increased concentrations.
- Risk of toxicity increases with age and renal impairment.
- Risk of toxicity increases in the presence of hypokalemia, hypomagnesemia, or hypercalcemia.
- Signs of toxicity generally include nausea, vomiting, vision changes.

SCr should be monitored because the drug is primarily cleared renally.

Amiodarone

Tab:200mg

Amp: 50mg/ml (3ml)

Pharmacologic Category

Antiarrhythmic Agent, Class III

ADR

- AV block
- Bradycardia
- Blue-gray skin discoloration
- Corneal microdeposits
- Hepatotoxicity
- Hyperthyroidism
- Hypotension (IV)
- Hypothyroidism
- Peripheral neuropathy
- Photosensitivity
- Pulmonary fibrosis

Bradycardia/hypotension

Mechanism:

- Dose-related; related to pharmacologic action
- Acute hypotension with rapid IV administration has been attributed in part to polysorbate 80

Onset:

- Acute hypotension during IV administration: Rapid; generally has an onset within 90 minutes but may occur up to 12 hours after initiation

Other hypotensive adverse reactions: Intermediate; generally reported in the first 12 months of therapy, while bradycardia may develop over months to years

Risk factors:

Acute hypotension:

- Age >65 years with history of myocardial infarction
- Pediatric patients: Age <3 months; baseline blood pressure below the third percentile for age and height; rapid IV bolus administration (≤20 minutes)
- Formulations containing polysorbate 80

Hepatotoxicity

Mechanism:

Acute toxicity: Idiosyncratic, immunologic, and formulation-related (ie, polysorbate 80) mechanisms have been proposed

Chronic toxicity: Idiosyncratic; may be related to mitochondrial dysfunction and free-radical induced injury

Onset:

Acute toxicity following IV administration: Rapid; may occur within 24 hours of initiation

Chronic toxicity: Delayed; most cases occur after at least a year of therapy

Risk factors:

Acute toxicity:

- High doses
- IV administration
- Older adults
- Frailty

Chronic toxicity:

- Cumulative dose (potential risk factor)

Proarrhythmic effects

Amiodarone may exacerbate arrhythmias; also associated with new-onset ventricular tachycardia, and polymorphic ventricular tachycardia associated with prolonged QT interval on ECG and torsades de pointes (TdP). However, relative to other agents in this class, amiodarone is associated with relatively low rates of proarrhythmia (specifically a low rate of TdP

Pulmonary toxicity

Onset: Acute toxicity: Intermediate; may occur as early as 2 days to 2 weeks

Chronic toxicity: Delayed; pulmonary fibrosis is usually identified after months to years of therapy

Risk factors:

Acute toxicity:

Cardiothoracic surgery

Exposure to a high inspiratory fraction of inhaled oxygen (FiO2)

Pulmonary angiography (Ref)

Chronic toxicity:

- Daily and cumulative doses
- Chronic kidney disease
- Older adults (particularly >60 years of age)
- Preexisting lung disease/chronic obstructive pulmonary disease

CYP3A4 inhibitors may ↑ concentrations

Inhibits CYP1A2, CYP2C9, CYP2D6, and CYP3A4: ↑ warfarin and statin (some) concentrations

Inhibits P-gp: ↑ digoxin concentrations

- LFTs – Baseline and every 6 mo
- TFTs (T4 and thyroidstimulating hormone)– Baseline and every 6 mo
- Chest radiography – Baseline and annually
- ECG – Baseline and at least every 6 mo
- Ophthalmologic evaluation – At baseline if visual impairment or for symptoms
- PFTs – Baseline and for unexplained dyspnea, especially if underlying lung disease and if chest radiography abnormalities are suggested

Adenosine

Inj:3mg/ml (1ml)(2ml)(4ml)

Pharmacologic Category

Antiarrhythmic Agent, Miscellaneous; Diagnostic Agent

Dose

6-mg IV rapid bolus, injected into IV as proximal or as close to the heart as possible over 1–2 s, followed by rapid saline flush

If no response in 1–2 min, 12-mg IV rapid bolus, followed by rapid saline flush

Can repeat the 12-mg IV dose once

ADR

Transient AV block

Chest pain

Flushing

Dyspnea

Sinus pauses

Bronchospasm (rare)

AF can be provoked or can cause decompensation in the presence of preexcitation

Adverse effects are usually of very short duration because of adenosine's short half-life of ~10 s

ADR

>10%:

Cardiovascular: Cardiac arrhythmia (transient and new arrhythmia after cardioversion; eg, atrial premature contractions, atrial fibrillation, premature ventricular contractions; 55%), chest pressure (and discomfort; 7% to 40%)

Central nervous system: Headache (2% to 18%), dizziness (≤12%)

Dermatologic: Facial flushing (18% to 44%)

Gastrointestinal: Gastrointestinal distress (13%)

Neuromuscular & skeletal: Neck discomfort (includes throat, jaw; <1% to 15%)

Respiratory: Dyspnea (12% to 28%)

CONTRAINDICATIONS

- Second- or third-degree AV block
- Sick sinus syndrome
- Symptomatic bradycardia(except in patients with a functioning artificial pacemaker)

Drug interaction

Dipyridamole and carbamazepine accentuate response to adenosine: ↓ adenosine dose by 50%

Magnesium sulfate

INJ: 10%,20%,50%

Torsades de pointes (off-label use):

Polymorphic ventricular tachycardia (with pulse) associated with QT prolongation (torsades de pointes):

IV: 1 to 2 g (diluted in 50 to 100 mL D5W) over 15 minutes (range: 5 to 60 minutes). If no response or torsades de pointes recurs, may repeat dose up to a total of 4 g in 1 hour; may follow with a continuous IV infusion of 0.5 to 1 g/hour

ADR

Cardiovascular: Flushing (IV; dose related), hypotension (IV; rate related), vasodilation (IV; rate related)

Endocrine & metabolic: Hypermagnesemia

Ivabradine

Tab: 5, 7.5 mg

For patients with persistently symptomatic inappropriate sinus tachycardia, we suggest using ivabradine (5 mg to 7.5 mg twice daily) with or without a beta adrenergic receptor blocker

Ivabradine is labeled by the FDA for use in patients with systolic heart failure (ejection fraction

Maximum dose: 7.5 mg twice daily

Contraindications:

- ADHF
- BP <90/50 mm Hg
- resting HR <60 beats/min
- sinoatrial block
- concomitant use with strong CYP3A4 inhibitors

Monitoring

- Assess HR and rhythm for bradycardia (6%–10%) and AF (5%–8%) after 2 weeks of therapy initiation or modification and periodically thereafter
- Phosphenes (3%): transient rings or spots of light in the visual field

LIDOCAINE

Inj: 2% (5ml)

Indication:

Ventricular Tachycardia

ADR

Slurred speech

Diminished consciousness

Seizures

Bradycardia

β-Blockers ↓ lidocaine clearance by reduced hepatic blood flow

Rifampin ↑ lidocaine clearance by induction of CYP1A2

Antiarrhythmic Medications

Vaughan-Williams Classification	Indications[a]	Drugs	Mechanism of Action
Ia	AF, atrial flutter, paroxysmal supraventricular tachycardia, ventricular arrhythmias Disopyramide[a] – Only paroxysmal supraventricular tachycardia	Quinidine	Channel blocked: Na (intermediate association and dissociation), K, Ach, α ECG manifestations: May ↑ sinus rate; ↑ QT (not dose related); ↑ QRS high dose
		Disopyramide	Channel blocked: Na (intermediate association and dissociation), K, Ach ECG manifestations: May ↑ sinus rate; ↑ QT (not dose related); ↑ QRS high dose

Drug	MOA, PK, Contraindications, AEs, DIs	Dosing
Class Ia – Na channel blockers		
Quinidine (Quinidex, Quinaglute)	MOA: Strong vagolytic and anticholinergic properties, Na^+ and K^+ channel blockage PK: Half-life 5–9 hr Substrate CYP3A4 Inhibitor CYP2D6 AEs: Nausea/vomiting/diarrhea (30%) TdP (first 72 hr, not dose related) "Cinchonism": CNS symptoms, tinnitus Thrombocytopenia, rash, pruritus DIs: Warfarin, digoxin	Sulfate (extended release): 300 mg PO every 8–12 hr Gluconate (extended release): 324–648 mg PO every 8–12 hr
Disopyramide (Norpace, Norpace CR, Rythmodan, Rythmodan-LA)	MOA: Potent Na^+ and m^2 blockade, Ach; strong negative inotrope PK: Half-life 4–8 hr Substrate CYP3A4 CIs: Glaucoma AEs: Anticholinergic AEs TdP ADHF	Initial dose 400–800 mg/day in divided doses; IR every 6 hr, CR every 12 hr Maximum 1200–1600 mg/day Dose adjustment required for renal insufficiency

Ib	Ventricular arrhythmias Used most commonly as add-on to amiodarone and not as sole agent[a]	Mexiletine	Channel blocked: Na (fast association and dissociation) ECG manifestations: May ↓ sinus rate, generally do not affect QRS or QT

Drug	MOA, PK, Contraindications, AEs, DIs	Dosing
Class Ib – Na channel blockers		
Mexiletine (Mexitil)	MOA: Inactive Na^+ channel blocker	<u>VT maintenance:</u> 200–300 mg every 8 hr Maximum of 1200 mg/day
	PK: Half-life 12–20 hr Substrate CYP2D6, CYP1A2 Inhibitor CYP1A2	
	CIs: Third-degree AV heart block	
	AEs: GI upset (administer with food); CNS: Tremor, dizziness, ataxia, nystagmus	

Ic	AF and atrial flutter, paroxysmal supraventricular tachycardia, ventricular arrhythmias May precipitate atrial flutter in patients with AF if no rate-controlling agent coadministered[a]	Propafenone	Channel blocked: Na (slow association and dissociation), β ECG manifestations: May ↓ sinus rate; ↑ PR, ↑ QRS
		Flecainide	Channel blocked: Na (slow association and dissociation) ECG manifestations: May ↓ sinus rate; ↑ PR, ↑ QRS

Class Ic – Na channel blockers (***avoid with HF or post MI)		
Propafenone (Rythmol)	MOA: Na^+ and $Ca2^+$ channel blocker; ß-blocker	AF conversion: 600 mg (IR) PO × 1 (efficacy 45% in 3 hr) AF maintenance: IR: 150–300 mg PO every 8 hr SR: 225–425 mg PO every 12 hr
	PK: Half-life 10–25 hr Substrate CYP2D6, CYP1A2 Inhibitor CYP2D6	
	CIs: HF NYHA III–IV, liver disease, valvular disease (TdP), CAD, VT	
	AEs: Metallic taste, dizziness	
	DIs: Propafenone may ↑ digoxin concentrations, may decrease warfarin metabolism, has β-blocker properties and PK interaction increasing β-blocker concentrations – Need to monitor heart rate and reduce β-blocker dose, if necessary, to prevent symptoms/heart block	
Flecainide (Tambocor)	MOA: Strong Na^+ channel blockade; vagolytic, anticholinergic, and negative inotrope	AF conversion: 300 mg PO × 1 (efficacy 50% in 3 hr) AF maintenance: 50–200 mg PO BID
	PK: Half-life 10–20 hr Substrate CYP2D6 Inhibitor CYP2D6	
	CIs: HF, CAD, valvular/LV hypertrophy (TdP)	
	AEs: Dizziness, tremor, HF exacerbation, VT, atrial flutter (in patients with AF)	
	DI: May increase digoxin concentrations; flecainide concentrations increased by haloperidol, cimetidine, and fluoxetine	

II	AF, atrial flutter, paroxysmal supraventricular tachycardia, ventricular arrhythmias	ß-Blockers (i.e., metoprolol)	Channel blocked: β, indirect Ca ECG manifestations: ↓ Sinus rate
III	Amiodarone: Supraventricular and ventricular arrhythmias Dronedarone: Paroxysmal or persistent AF and atrial flutter Sotalol: Ventricular arrhythmias; maintenance of AF and flutter Dofetilide: Supraventricular arrhythmias; atrial flutter and fibrillation conversion	Amiodarone	Channel blocked: K, Na, Ca, β, α, Ach ECG manifestations: ↓ Sinus rate, ↑ PR, ↑ QRS, ↑ QT
		Dronedarone	Channel blocked: K, Na, Ca, β, α, Ach ECG manifestations: ↓ Sinus rate, ↑ PR
		Sotalol	Channel blocked: K, β ECG manifestations: ↓ Sinus rate, may ↑ PR, ↑ QT (dose related)
		Dofetilide	Channel blocked: K ECG manifestations: ↑ QT (dose related)
IV	AF, atrial flutter, paroxysmal supraventricular tachycardia	Diltiazem Verapamil	Channel blocked: Ca ECG manifestations: ↓ Sinus rate

Drug	MOA, PK, Contraindications, AEs, DIs	Dosing
Class III – K channel blockers *(continued)*		
Sotalol (Betapace)	MOA: K^+ channels, blocks β_1- and β_2-receptors PK: Renally eliminated Half-life 30–40 hr CIs: Baseline QTc > 0.45 s or CrCl < 40 mL/min/1.73 m^2 in atrial arrhythmias only AEs: HF exacerbation, bradycardia, AV heart block, bronchospasm, TdP 3%–8% within 3 days of initiation ***Ideally, initiated in hospital, because of proarrhythmia. DIs: Has β-blocker properties, so the dose of concomitant β-blockers may need tapering after sotalol initiation; monitor heart rate	AF conversion: No effect! AF maintenance: Dose 80–160 mg BID; CrCl > 60 mL/min/1.73 m^2 Daily; CrCl 40–60 mL/min/1.73 m^2 Contraindicated; CrCl < 40 mL/min/1.73 m^2 VT maintenance: Dose 80–160 mg BID; CrCl > 60 mL/min/1.73 m^2 Daily; CrCl 30–60 mL/min/1.73 m^2 Every 48 hr; CrCl 10–30 mL/min/1.73 m^2 Every 72 hr; CrCl > 10 mL/min/1.73 m^2