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Drug-Drug Interactions in
CARDIOLOGY

first line

In hypertension

R

Telma®

(Telmisartan 20/ 40/ 80 mg tablets)

ON TARGET 20 hours + crucial last 4 hours



Cardiac Brand*

The 1st line Anti-hypertensive



**Only ARB Offering 24 hr BP control
with CV Risk Reduction¹**

1. Dezsi CA . Am J Cardiovasc Drugs. 2016 Mar 3

* Org Feb'16

Abbreviated Prescribing Information: Telma 20/40/80 mg

Active Ingredient: Telma 20/40/80 mg - Each uncoated tablet contains Telmisartan 20 mg or 40 mg or 80 mg. **Indications:** 1) For the treatment of mild to moderate hypertension and 2) cardiovascular risk reduction in patients unable to take angiotensin converting enzyme (ACE) inhibitor therapy. **Dosage and Administration:** Usual starting dose is 40 mg per day orally but some patients may benefit from 20 mg/day (Dose range: 20-80 mg/day). **Contraindications:** Known hypersensitivity to telmisartan or any of the components of the product, pregnant and lactating females. **Warning and Precautions:** Caution is needed in hepatic insufficiency. In cases of impaired renal function, progressive azotemia with acute renal failure is reported rarely. **Use in Pregnancy & Lactation:** For telmisartan, pregnancy category is C in first trimester and D in second and third trimester. Telmisartan should be discontinued immediately if the patient becomes pregnant. Excretion in human milk is unknown. **Adverse Drug Reactions:** Back pain, diarrhea, upper respiratory tract infection. Incidence of cough is lower as compared to ACE inhibitors and was similar to placebo in placebo-controlled trials.

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Drug-Drug Interactions in **Cardiology**

The drugs referred to in this booklet are discussed under following sections:

- Interacting Category/Drugs
- Effects of Interaction
- Consequences/Signs/Symptoms Subsequent to Interaction
- Severity of Interactions
- Time of Onset of Effects
- Section Excerpts and Recommendations

This booklet also includes tables & algorithms.

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The authors, editors and publisher have exerted every effort to ensure drug selection in accordance with the current recommendations and practice at the time of preparing/publishing this booklet. However, in view of ongoing research, changes in government regulations and constant flow of information relating to drug therapy and drug-drug interactions, the readers are urged to check the package insert for each drug for any change/modification in the information.

INTRODUCTION

Concurrent administration of two or more drugs may cause interaction between each other. This interaction may be potentiation or antagonism of the drugs concerned and may cause unexpected toxicity. As newer and more potent drugs become available, the number of serious drug-drug interactions is likely to increase.

Drug interaction series is a handy, pocket-sized book that presents a quick glance of the drug-drug interactions during administration of most used drugs in Cardiology,* through pictorial representation.

*Mentioned in ATC codes B01-B03, C01-C04, C07-C10, G04; also from the National List of Essential Medicine of India, 2011.

GUIDE TO READ

The heading on each page represents individual drug or the class of drugs commonly used in cardiology.*

The **first column** lists the commonly used category/drugs in cardiology.

The **second column** lists the category/drugs that interact with the given category/drugs used in cardiology.

The **third column** shows, in brief, the pharmacological effects of the interaction *in vivo*.

The **fourth column** shows the consequences/signs/symptoms of the patient due to the effects of drug-drug interaction. It is presented through the symbols and each symbol depicts a series of clinical signs/symptoms as mentioned in Table 1.

The **fifth column** defines the severity of interaction and these may be:

- 👉 **Major (!!!):** This defines potentially fatal effects of interaction that can cause permanent damage to the patient.
- 👉 **Moderate (!!):** The effects may cause a deterioration in patient's clinical condition, that may require hospitalization.
- 👉 **Minor (!):** The effects are mild and tolerable.

The **last column** is the pictorial representation of the time of onset of clinical effects, as shown below.

	Fast (occur within 24 hr)
	Slow (may occur in days to weeks)
-	Not known/not available

*Mentioned in ATC codes B01-B03, C01-C04, C07-C10, G04; also from the National List of Essential Medicine of India, 2011.

GUIDE TO READ

The symbols used may refer to the following consequences/signs/symptoms:

	Low blood pressure and resulting syncope, dizziness or fainting. Orthostatic hypotension.
	High blood pressure and resulting headache, dizziness and shortness of breath.
	Irregularity in rate and rhythm of the heart beat. May include tachycardia or bradycardia.
	Immunological disorders including fever/chills, hypersensitivity, allergy, skin rashes or infection in any part of the body.
	Respiratory disorders such as difficulty in breathing, cough, bronchospasm.
	Neurological disorders, may include confusion, impaired concentration, delirium and dizziness, lethargy, sedation, visual disturbances, headache, anxiety. Paralysis, muscle weakness, loss of sensation, ataxia and seizures.
	Diarrhea, stomach pain, nausea, vomiting, mild metabolic acidosis. GI ulceration.
	Electrolyte imbalance, may result in weakness, muscle pains or cramps, nausea, anorexia, visual disturbances, increased thirst, sweating, irritability.
	Hepatic disorders resulting in nausea, vomiting, abdominal pain, loss of appetite, diarrhea, weakness, pale skin and jaundice.
	Hemorrhage, easy bruising, prolonged bleeding from cuts. May include GI bleeding, vaginal bleeding, nosebleeds, bleeding of gums from brushing associated with pain.
	Blood clot resulting in chest pain, hemoptysis, shortness of breath, sudden loss of vision, pain, redness or swelling in extremity.
	Methemoglobinemia, causing slate-grey cyanosis in buccal mucous membranes, lips and nail beds.

GUIDE TO READ

	Increase in blood sugar level resulting in frequent urination, dry mouth, increased thirst.
	Decrease in blood sugar level causing headache, dizziness, drowsiness, hunger, tremor, weakness, sweating, palpitations.
	Ototoxicity causing partial or profound loss of hearing, tinnitus, vertigo.
	Myopathy causing muscle pain, fatigue, muscle tenderness and weakness, nocturnal cramping, tendon pain.
	Miscellaneous (patients may show any of the above mentioned signs/symptoms; may also include whole body).

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LIST OF ABBREVIATIONS

ACE	Angiotensin converting enzymes
ARB	Angiotensin receptor blocker
BP	Blood pressure
CAIs	Carbonic anhydrase inhibitors
CCBs	Calcium channel blockers
CHF	Congestive heart failure
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COX-2	Cyclooxygenase-2
CV	Cardiovascular
CVEs	Cardiovascular events
5-FU	5-Fluorouracil
GI	Gastrointestinal
GU	Genitourinary
HF	Heart failure
HMG-CoA	3-Hydroxy-3-methyl-glutaryl-CoA
INR	International normalized ratio
IV	Intravenous
LMWH	Low molecular weight heparin
MAO	Monoamine oxidase
MAOIs	Monoamine oxidase inhibitors
NAPA	N-Acetylprocainamide
NSAIDs	Non-steroidal anti-inflammatory drugs
PDE-5	Phosphodiesterase-5
PIs	Protease inhibitors
PPI	Proton pump inhibitor
RBC	Red blood cell
SNRIs	Serotonin norepinephrine reuptake inhibitors
SRIs	Serotonin reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
TCA s	Tricyclic antidepressants

ACE INHIBITORS

A

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
ACE INHIBITORS					
Captopril Enalapril Fosinopril Imidapril Lisinopril Moexipril Perindopril Quinapril Ramipril Trandolapril	Alpha agonist: Tizanidine Aliskiren	Increased risk of hypotension.* Risks of hypotension, hyperkalemia increases, and may cause acute renal failure, especially in patients with type 2 diabetes and renal impairment.		!!!	
	Allopurinol	Increased risk of severe hypersensitivity reactions, neutropenia, agranulocytosis, and serious infections.		!!!	-
	Antacids: Aluminum hydroxide/ Magnesium carbonate	Antacids may decrease the oral bioavailability of ACE inhibitors.		!	
	Capsaicin	Concomitant use may potentiate the cough associated with each of these agents individually.		!	
	Lithium	Coadministration may attenuate the vasodilator and hypotensive effects of ACE inhibitors.		!!	
	NSAIDs including COX-2 inhibitors: Celecoxib, Diclofenac, Flurbiprofen, Indomethacin, Mefenamic acid	NSAIDs may attenuate antihypertensive effects of ACE inhibitors. Deterioration of renal function in patients taking diuretics, or with compromised renal function.*		!!	

ACE INHIBITORS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Benazepril Captopril Enalapril Fosinopril Imidapril Lisinopril Moexipril Perindopril Quinapril Ramipril Trandolapril	Potassium sparing diuretics: Amiloride, Spironolactone, Triamterene Potassium salts: Potassium chloride	Increased risk of hyperkalemia.		!!	-
	Thiazide diuretics: Hydrochlorothiazide	Thiazide diuretics increases hypotensive effects of ACE inhibitors. ⁵		!!	-
	Vasodialators: Nitroglycerin or other nitrates	ACE inhibitors may increase vasodilatory and hypotensive effects of nitroglycerin.		!!	-
Captopril Enalapril Fosinopril Imidapril Lisinopril Perindopril Quinapril Ramipril	Phenothiazines: Chlorpromazine, Fluphenazine, Methotrime-prazine, Promethazine, Trifluoperazine	Phenothiazines may potentiate the hypotensive effect of given ACE inhibitors.		!!	
	Probenecid	Probenecid may prolong duration of action of ACE inhibitors.		!	
Enalapril Imidapril	Rifampin	Rifampin may decrease the antihypertensive effects of enalapril.		!	
Benazepril	Beta-blockers, Calcium channel blockers	Beta-blockers and calcium channel blockers may potentiate the antihypertensive effect of benazepril.	-	-	-
	Warfarin	Benazepril may decrease the anticoagulant effect of warfarin.	-	-	-

SECTION EXCERPTS AND RECOMMENDATIONS

High alert: ACE inhibitors majorly interact with aliskiren (a direct rennin inhibitor), potassium-sparing diuretics, potassium salts, allopurinol and tizanidine (an alpha agonist).

Recommendations:

* Tizanidine treatment should be initiated with 4 mg doses and gradually increase in 2-4 mg increments until optimum effect is achieved. The dose can be repeated at 6-8 hour intervals as required, up to a maximum of 3 doses in 24 hours and a total daily dosage of 36 mg.

The adverse effects may be reversed after the discontinuation of concurrent administration of drugs.

⁵ Discontinue diuretic or increase salt intake 1 week prior to start of ACE inhibitors or start therapy with ACE inhibitors in small doses (6.25 or 12.5 mg).

ALPHA AGONISTS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
ALPHA AGONISTS					
Clonidine	Beta-blockers (both cardio-selective and non-selective)	<p>Synergistic effects resulting in marked AV block, bradycardia, and hypotension.</p> <p>Life-threatening increase in BP with sudden withdrawal of clonidine or both clonidine and beta-blocker.[#]</p>		!!	
	Calcium channel blockers: Diltiazem, Verapamil	Synergistic pharmacological and toxic effects that may result in AV block and severe hypotension.		!!	
	Methyldopa	Sinus node dysfunction and AV block.		!!	
	Mirtazapine	Antihypertensive effect of clonidine may be reduced.		!!	
	Phenothiazines: Chlorpromazine, Fluphenazine	Antihypertensive effects of clonidine may be increased, while the antipsychotic effects of phenothiazines may be decreased.		!!	
	Prazosin	Prazosin decreases antihypertensive effects of clonidine. Sinus node dysfunction and AV block.		!!	
Clonidine	Tizanidine	Tizanidine may potentiate the hypotensive effects of clonidine.		!!!	
	Tricyclic anti-depressants: Amitriptyline, Amoxapine, Clomipramine, Desipramine, Doxepin and others	Potentially life-threatening elevations in blood pressure.		!!!	

ALPHA AGONISTS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Guanfacine	Barbiturates: Amobarbital, Pentobarbital, Phenobarbital, Primidone, Secobarbital	The antihypertensive effects of guanfacine may be decreased.		!!	-
	Tizanidine	Tizanidine may potentiate the hypotensive effects of guanfacine.		!!!	-
	Tricyclic anti-depressants: Amitriptyline, Imipramine	The antihypertensive effects of guanfacine may be decreased.		!!	

SECTION EXCERPTS AND RECOMMENDATIONS

High alert: Both clonidine and guanfacine should not be given with tizanidine. Concomitant administration of clonidine and tricyclic antidepressants is potentially life-threatening.

Recommendation:

- # Clonidine should never be discontinued abruptly, but should be weaned off over 2 to 4 days. The beta blocker should be discontinued a few days before gradually discontinuing the clonidine.

ALPHA BLOCKERS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
ALPHA BLOCKERS					
I. Alpha blockers					
Doxazosin Prazosin Terazosin	Beta-blockers	Additive hypotensive effects.			
Prazosin Terazosin	Calcium channel blocker: Verapamil	The hypotensive effects may be increased.			
Prazosin	Clonidine	Refer section 'Alpha agonists'.			
	NSAIDs: Indomethacin	NSAIDs may reduce the antihypertensive effects of prazosin.			
Terazosin	Sodium oxybate	CNS and respiratory-depressant effects of sodium oxybate may be potentiated.			-
	Tizanidine	Tizanidine may potentiate the hypotensive effect of terazosin. [#]			-
II. Non-selective alpha blockers					
Phenoxybenzamine Phentolamine	Tizanidine	Tizanidine may potentiate the hypotensive effect of both the alpha blockers. [#]			-

SECTION EXCERPTS AND RECOMMENDATIONS

High alert: Coadministration of alpha blockers, mainly terazosin, phenoxybenzamine and phentolamine should be avoided with sodium oxybate or tizanidine.

Recommendation:

- # Initiate tizanidine treatment with 4 mg doses and gradually increase in 2 to 4 mg increments until optimum effect is achieved. The dose can be repeated at 6 to 8 hour intervals as needed, up to a maximum of three doses in 24 hours and a total daily dosage of 36 mg.

AMIODARONE (ANTI-ARRHYTHMIC AGENT)

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
AMIODARONE					
Amiodarone	Azole antifungals: Clotrimazole, Fluconazole, Itraconazole, Ketoconazole	Increase in the plasma concentrations of amiodarone, increasing the risk of ventricular tachycardia, <i>torsade de pointes</i> , cardiac arrest and sudden death.		!!!	-
	Beta-blockers	Refer section 'anti-adrenergic drugs'.			
	Calcium channel blockers: Diltiazem, Verapamil	Sinus arrest, reduced myocardial contractility, and hypotension.		!!!	
	Digoxin, Digitoxin	Sharp increase in serum level of digoxin, resulting in clinical toxicity. ^a		!!!	
	Cimetidine	Increase in amiodarone and its active metabolite levels, resulting in greater therapeutic and adverse effects.		!!	
	Cyclosporine/ ciclosporine	Cyclosporine concentrations may be elevated, possibly increasing the risk of nephro and neuro toxicity.		!!	
	Fentanyl	The plasma concentrations of fentanyl may increase, prolonging adverse effects and may cause potentially fatal respiratory depression. Amiodarone may increase the risk of CV complications during or after general anesthesia with fentanyl.		!!!	

AMIODARONE (ANTI-ARRHYTHMIC AGENT)

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Amiodarone	Hydantoins: Phenytoin, Fosphenytoin, Mephenytoin	Amiodarone increases serum concentration of hydantoin, while hydantoin may decrease serum amiodarone concentrations, resulting in toxicity.		!!	
	Lidocaine	Amiodarone may increase serum concentration of lidocaine, increasing the risk of toxicity.		!!	
	Macrolide antibiotics: Azithromycin, Clarithromycin	Additive effects and increased risk of ventricular arrhythmias including <i>torsade de pointes</i> & sudden death.		!!!	-
	Procainamide	Amiodarone may increase the serum levels of procainamide, increasing the risk of additive effects such as hypotension, <i>torsade de pointes</i> and other arrhythmias.		!!	
	Propafenone	Coadministration may have additive effects on the QT interval, increasing the risk of ventricular arrhythmias including <i>torsade de pointes</i> and sudden death.		!!!	-
	Protease inhibitors: Indinavir, Lopinavir, Ritonavir	Plasma levels of amiodarone may be elevated leading to life-threatening reactions.		!!!	
	Quinidine	Amiodarone may increase serum level of quinidine and induce potentially fatal cardiac arrhythmias. [§]		!!!	

AMIODARONE (ANTI-ARRHYTHMIC AGENT)

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Amiodarone	Rifamycins: Rifabutin, Rifampin, Rifapentine	Rifamycins may decrease serum levels of amiodarone and its metabolites, reducing the therapeutic effects of amiodarone.	M	!!	
	Simvastatin, Lovastatin	Amiodarone may increase the plasma levels of simvastatin or lovastatin at higher dosages, thus increasing the risk of toxicity (such as myopathy and rhabdomyolysis)*		!!!	
	Sirolimus, Tacrolimus	Serum levels of both amiodarone and macrolide immunosuppressants may be elevated, increasing the risk of toxicity.	M	!!	
	Warfarin	Amiodarone may increase the pharmacologic effects of warfarin, resulting in significant hypoprothrombinemia and bleeding. ^y		!!!	

SECTION EXCERPTS AND RECOMMENDATIONS

High alert: Concomitant administration of amiodarone with azole antifungals, beta-blockers, calcium channel blockers (diltiazem and verapamil), cardiac glycosides, fentanyl, macrolide antibiotics, protease inhibitors, quinidine, simvastatin and lovastatin, and warfarin should be avoided.

Recommendations:

- ▲ After starting oral amiodarone, review the need for digitalis therapy and consider either for the empirical reduction of dose by approximately 50% or discontinuation of the therapy.
- § Quinidine and procainamide doses should be reduced by one-third when either is administered with amiodarone.
- # Dose of simvastatin in patients on amiodarone should not exceed 20 mg daily, and for lovastatin not to exceed 40 mg daily. The benefits of combination of simvastatin or lovastatin with amiodarone should be carefully weighed against the potentially increased risk of myopathy including rhabdomyolysis. The safer alternatives in patients receiving amiodarone are fluvastatin, pravastatin, and rosuvastatin.
- ¥ An empiric reduction of anticoagulant dosage to 30% to 50% along with frequent monitoring of the patient and the prothrombin time or International Normalized Ratio.

ANGIOTENSIN RECEPTOR BLOCKERS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
ANGIOTENSIN RECEPTOR BLOCKERS					
Candesartan Eprosartan Irbesartan Losartan Olmesartan Telmisartan Valsartan	Aliskiren	In patients with type 2 diabetes and renal impairment, increased risks of hypotension, hyperkalemia, including acute renal failure.	 	!!!	-
	Cetirizine, Levocetirizine	Additive impairment of mental alertness and performance.		!!	-
	Corticosteroids: Cortisone, Hydrocortisone, Prednisolone	Corticosteroids may antagonize the effects of antihypertensive medications by inducing sodium and fluid retention.	 	!!	-
	Lithium	May increase serum lithium levels, thus increase in therapeutic and adverse effects.		!!	
	NSAIDs including COX-2 Inhibitors: Acetaminophen, Aspirin, Ibuprofen, Indomethacin, Ketoprofen	Deterioration of renal function and acute renal failure in patients who are elderly, taking diuretics, or with compromised renal function. Antihypertensive effects of ARBs may be decreased by NSAIDs.	M	!!	
	Phenothiazines and neuroleptic agents: Aripiprazole, Promethazine	These agents may potentiate the hypotensive effect of ARBs.		!!	-

ANGIOTENSIN RECEPTOR BLOCKERS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Candesartan Eprosartan Irbesartan Losartan Olmesartan Telmisartan Valsartan	Potassium sparing diuretics: Amiloride, Spironolactone*, Triamterene	May increase the risk of hyperkalemia.			
	Potassium salts: Potassium phosphate, Potassium iodide, Potassium gluconate, Potassium bicarbonate			!!!	
	Ramipril	ARBs increase concentration of ramipril, thus may increase the risk of hyperkalemia, hypotension and renal dysfunction.	 	!!	-
Losartan	Azole antifungals: Fluconazole, Ketoconazole	Concomitant use may increase losartan concentration, thus increase antihypertensive and adverse effects of losartan.		!!	
	Hydantoins: Fosphenytoin, Phenytoin	Hydantoins may decrease the antihypertensive effects of losartan.		!!	
	Rifamycins: Rifampin	Serum levels of losartan may be reduced, thus decrease in the antihypertensive effects.		!!	
Telmisartan	Digoxin	Telmisartan may increase serum concentration of digoxin, thus risk of toxicity increases.		!!	

SECTION EXCERPTS AND RECOMMENDATIONS

High alert: ARBs should not be administered with aliskiren, potassium sparing diuretics and potassium salts.

Recommendation:

- # If spironolactone is prescribed with an ARB, its dosage should not exceed 25 mg/day in high-risk patients.

ANTICOAGULANTS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
ANTICOAGULANTS					
Direct thrombin inhibitors					
Argatroban Bivalirudin Dabigatran Lepirudin	Alteplase	Risk of bleeding complication increases.		!!!	-
	Aspirin	Aspirin may increase the risk of bleeding.		!!	-
	NSAIDs including COX-2 inhibitors: Ibuprofen, Ketoprofen, Naproxen, Diclofenac, Celecoxib	Anticoagulants may potentiate the risk of GI bleeding complications associated with NSAIDs.		!!	-
Heparin and Low molecular weight heparins					
Heparin	Aspirin	Coadministration may increase the risk of bleeding.		!!	
	Nitroglycerin	Concurrent administration of heparin and intravenous nitroglycerin may lead to a decreased anticoagulant effect.		!!	
	NSAIDs including COX-2 inhibitors: Ibuprofen, Ketoprofen, Naproxen, Diclofenac, Celecoxib	Coadministration may increase the risk of bleeding.		!!	-
Heparin Low molecular weight heparins: Dalteparin Enoxaparin Fondaparinux Tinzaparin	Alteplase	Alteplase may potentiate the risk of bleeding complications associated with the use of a low molecular weight heparin or its derivative. ¹²		!!!	-
	SSRIs: Fluoxetine, Fluvoxamine	Serotonin reuptake inhibitors on coadministration may potentiate the risk of bleeding.		!!	-

ANTICOAGULANTS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Low molecular weight heparins: Dalteparin Enoxaparin Fondaparinux Tinzaparin	Aspirin	Coadministration may increase the risk of bleeding. ^s		!!!	-
	NSAIDs including COX-2 inhibitors: Ibuprofen, Ketoprofen, Naproxen, Diclofenac, Celecoxib	NSAIDs may potentiate the risk of bleeding complications associated with LMWH, while NSAIDs dose-related gastrointestinal bleeding may be complicated by anticoagulant therapy. ^s	 	!!!	-
Warfarin					
Warfarin	Allopurinol	Allopurinol may inhibit warfarin metabolism, thus increasing its anticoagulant effects.		!!	
	Alteplase	Oral anticoagulants may increase the risk of serious bleeding when administered before, during, or after fibrinolytic agents. ^o		!!!	-
	Amiodarone	Refer section 'Amiodarone'.			
	Androgens and anabolic steroids: Danazol, Fluoxymesterone, Methyltestosterone, Testosterone	Androgens and anabolic steroids may potentiate the hypo-prothrombinemic response to warfarin and thus increase the risk of bleeding.		!!!	
	Anti-neoplastic agents: Capecitabine, Fluorouracil	Fluorouracil and its prodrug capecitabine may significantly potentiate the hypo-prothrombinemic effect of warfarin.		!!!	
	Aspirin	Aspirin, even in small doses, may increase the risk of bleeding in patients on oral anticoagulants.		!!!	
	Azole antifungals: Fluconazole, Miconazole, Voriconazole	Coadministration may significantly increase the hypo-prothrombinemic effect of warfarin.		!!!	

ANTICOAGULANTS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Warfarin	Barbiturates: Amobarbital, Butabarbital, Mephobarbital, Phenobarbital, Secobarbital	Barbiturates reduce the effects of oral anticoagulants. ^y		!!!	
	Fibric acid derivatives: Clofibrate, Fenofibrate, Gemfibrozil	Fibric acid derivatives may enhance the hypoprothrombinemic effect of warfarin. [#]		!!!	
	Lovastatin, Rosuvastatin	Rosuvastatin and lovastatin may enhance the hypoprothrombinemic effect of warfarin.		!!	
	Macrolide antibiotics: Clarithromycin, Erythromycin	Coadministration with interacting macrolides may infrequently but significantly increase the hypo- prothrombinemic effect of warfarin. ^x		!!!	
	Metronidazole	Coadministration may increase the plasma concentrations and hypoprothrombinemic effect of warfarin.		!!!	
	Nalidixic acid	Nalidixic acid potentiates the hypoprothrombinemic effect of warfarin.		!!!	
	NSAIDs including COX- 2 inhibitors: Diclofenac, Diflunisal, Ibuprofen, Indomethacin, Ketoprofen, Mefenamic acid, Naproxen, Piroxicam	NSAIDs may potentiate the hypoprothrombinemic effect and bleeding risk associated with oral anticoagulants.		!!!	
	Penicillins: Ampicillin, Penicillin G, Piperacillin, Ticarcillin	Penicillins may occasionally increase the risk of bleeding in patients on oral anticoagulants.		!!	
	Protease inhibitors: Indinavir	Coadministration may alter the plasma concentration/ pharmacological effects of warfarin.		!!	

ANTICOAGULANTS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Warfarin	Quinolones: Ciprofloxacin, Levofloxacin, Norfloxacin, Ofloxacin	Some quinolone antibiotics potentiate the hypoprothrombinemic effect of warfarin.		!!!	
	Rifamycins: Rifabutin, Rifampin, Rifapentine ^e	Rifampin may decrease the anticoagulant effect of warfarin.		!!!	
	Sulfonamides: Sulfamethizole, Sulfamethoxazole, Sulfasalazine, Sulfamethoxazole/ Trimethoprim	Coadministration with a sulfonamide may increase the plasma concentrations and hypoprothrombinemic effects of coumarin anticoagulants.		!!!	
	Tamoxifen	Tamoxifen may enhance the hypoprothrombinemic response to warfarin.		!!!	
	Tetracyclines	Tetracycline antibiotics may increase the action of oral anticoagulants.		!!	-

SECTION EXCERPTS AND RECOMMENDATIONS

High alert:

- Alteplase is contraindicated in patients with acute ischemic stroke who have received heparin within the last 48 hours and have an elevated activated partial thromboplastin time. It is also contraindicated in patients taking oral anticoagulants and having an INR greater than 1.7.
- In patients receiving neuraxial anesthesia or spinal puncture, the risk of developing an epidural or spinal hematoma during low molecular weight heparin therapy may be increased by the concomitant use of other drugs that affect coagulation, including NSAIDs. The development of epidural and spinal hematoma can lead to long-term or permanent paralysis.
- Excessive anticoagulation and bleeding may occur if the anticoagulant dose is not reduced after discontinuation of barbiturates.

Therefore, concomitant administration of oral anti-coagulants with alteplase, aspirin and NSAIDs should be avoided. High caution is recommended when warfarin is administered with amiodarone, androgens, anabolic steroids, antineoplastic agents, barbiturates, macrolides (especially clarithromycin and erythromycin), metronidazole and nalidixic acid, quinolones, rifamycins, sulfonamides and tamoxifen.

Recommendations:

- # Warfarin dose be reduced by approximately one-third to one-half initially, then gradually adjusted as necessary according to INR monitoring. Frequent prothrombin determinations are recommended till prothrombin level stabilizes.
- ♦ Interaction of warfarin with azithromycin is moderate in severity, thus it can be used as a substitute for clarithromycin and erythromycin.
- £ The interaction between warfarin and rifapentine is reported to be moderate in severity.

ANTIFIBRINOLYTIC AGENTS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
ANTIFIBRINOLYTIC AGENTS					
Amino- caproic acid Aprotinin Tranexamic acid	Fibrinolytic agents: Alteplase, Reteplase, Streptokinase, Tenecteplase, Urokinase	Coadministration may reduce the therapeutic effects of both drugs due to opposing pharmacodynamic actions.		!!	-
	Tretinoin	Coadministration may increase the risk of thrombosis. [#]		!!!	-
Amino- caproic acid Tranexamic acid	Ticagrelor	Antifibrinolytic agents may increase hemostasis and antagonize the effects of ticagrelor.		!	-
Tranexamic acid	Hormonal contraceptives: Ethynodiol- diacetate, Levonorgestrel, Norethindrone, Norgestrel	Coadministration may increase the risk of thrombotic events. ^{\$}		!!!	-

SECTION EXCERPTS AND RECOMMENDATIONS

High alert:

Tretinoin is associated with a risk of both venous and arterial thrombosis during the first month of treatment and may involve any organ system. Therefore, concomitant administration of antifibrinolytic agents such as aminocaproic acid, tranexamic acid and aprotinin should be avoided with tretinoin.

Recommendation:

\$ Tranexamic acid should not be used in women taking more than approved dose of a hormonal contraceptive.

ANTIPLATELET DRUGS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
ANTIPLATELET DRUGS					
Aspirin	Antacids: Aluminum carbonate, Aluminum hydroxide, Calcium carbonate, Magnesium carbonate	Chronic administration of antacids may reduce serum salicylate concentrations in patients receiving large doses of aspirin.			-
	Ibuprofen	The antiplatelet and cardioprotective effect of low-dose aspirin may be antagonized by ibuprofen. [#]			-
	Methotrexate	Aspirin may increase the pharmacologic effect and toxicity of methotrexate.			-
	SRIs: Fenfluramine, Fluoxetine TCA: Clomipramine	SRIs or clomipramine may potentiate the risk of bleeding in patients taking aspirin.			-
	Urinary alkalinizers: Potassium citrate, Sodium bicarbonate, Sodium citrate	Urinary alkalinizers can reduce serum salicylate concentrations in patients taking large doses of aspirin.			
	Valproic acid	Aspirin may increase the serum concentration of valproic acid. Large doses of aspirin may cause valproate toxicity and hepatotoxicity.			-
	Zafirlukast	Aspirin may increase the plasma concentrations of zafirlukast.			-

ANTIPLATELET DRUGS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Glycoprotein IIb/IIIa inhibitors: Abciximab Eptifibatide Tirofiban	Fibrinolytic agents: Alteplase, Reteplase, Tenecteplase, Streptokinase	Coadministration may increase frequency of major bleeding complications, including intracranial hemorrhage, retroperitoneal bleeding, spontaneous GI and GU bleeding.			-
	Heparin, Low molecular weight heparin, Warfarin	Coadministration increases risk of bleeding complications.			-
	NSAIDs: Ibuprofen, Ketoprofen	Risk of bleeding increases on coadministration.			-
Cilostazol	Macrolide antibiotics: Clarithromycin, Erythromycin	Coadministration may increase the plasma concentrations of cilostazol and or its pharmacologically active metabolites. ^s			
	Protease inhibitors: Ritonavir, Tipranavir	Coadministration may potentiate the risk of bleeding in patients.			-
	SRIs: Citalopram, Escitalopram	SRIs may potentiate the risk of bleeding in patients.			-
Cilostazol Clopidogrel Ticagrelor Ticlopidine	NSAIDs: Ibuprofen, Ketoprofen, Naproxen	Coadministration may increase the risk of bleeding.			-
Clopidogrel	Atorvastatin	Concomitant administration may reduce the metabolic activation of clopidogrel and its antiplatelet effects. ^x			-
	Azole antifungals: Fluconazole, Ketoconazole	Coadministration may reduce the efficacy of clopidogrel.			-
	Bupropion	Clopidogrel may increase the plasma concentrations of bupropion.			
	Cimetidine	Coadministration may reduce the efficacy of clopidogrel.			-

ANTIPLATELET DRUGS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Clopidogrel	Macrolide antibiotics: Clarithromycin, Erythromycin	Some macrolide antibiotics may reduce the metabolic activation of clopidogrel and its antiplatelet effects.		!!	-
	PPIs: Omeprazole, Rabeprazole	PPI may reduce the cardioprotective effects of clopidogrel. ^s		!!!	-
	Rifampin	Coadministration may increase the metabolic activation of clopidogrel.		!!	
Clopidogrel Prasugrel	SRIs: Venlafaxine, Fluoxetine, Fluvoxamine	SRIs may potentiate the risk of bleeding when used in patients treated with prasugrel and clopidogrel.			-
	Vitamin E	Vitamin E may potentiate the effects of platelet inhibitors. ^v		!!	-
Cilostazol Ticlopidine	Aspirin	The risk of bleeding may be increased.		!!	-
Dipyridamole	Low molecular weight heparins: Dalteparin, Enoxaparin, Tinzaparin	Dipyridamole may potentiate the risk of bleeding complications associated with LMWHs.		!!!	-
	Adenosine	Dipyridamole potentiates the effects of adenosine.		!!	
Prasugrel	NSAIDs: Ibuprofen, Ketoprofen, Naproxen	The risk of bleeding increases. ^e		!!!	-
Ticagrelor	Carbamazepine, Phenytoin, Fosphenytoin	Coadministration may significantly decrease the plasma concentrations of ticagrelor.		!!!	-
	Clarithromycin	Coadministration may significantly increase the plasma concentrations of ticagrelor.		!!!	-
	Dexamethasone	Coadministration may significantly decrease the plasma concentrations of ticagrelor.		!!!	-

ANTIPLATELET DRUGS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Ticlopidine	Cimetidine	Cimetidine may reduce the clearance of ticlopidine by up to 50%.		!!	-
	Theophylline	Ticlopidine interferes with theophylline metabolism, may cause theophylline toxicity.		!!	-

SECTION EXCERPTS AND RECOMMENDATIONS

High alert: Salicylates such as aspirin are reported to interact majorly with ibuprofen and methotrexate. Glycoprotein IIB/IIIA inhibitors such as abciximab, eptifibatide and tirofiban have major interactions with other fibrinolytics, and a few anticoagulants; while dipyridamole interacts strongly with LMWH.

* If vitamin E supplementation dosages greater than 400 units/day are initiated in patients stabilized on anticoagulant or antiplatelet therapy, hematological complications may occur and the patient should be monitored closely.

Recommendations:

- # For patients requiring routine NSAID therapy with concomitant low-dose aspirin, diclofenac may be considered as a suitable alternative.
- § Fifty percent dosage reduction of cilostazol (i.e., 50 mg twice a day) has been recommended in patients receiving erythromycin.
- ¤ Pravastatin, fluvastatin, and rosuvastatin are not metabolized by CYP450 3A4 and are theoretically not expected to interact with clopidogrel.
- ¤ PPIs should only be considered in high-risk patients such as those receiving dual antiplatelet therapy, those with a history of gastrointestinal bleeding or ulcers, and those receiving concomitant anticoagulant therapy.
- € Prasugrel may be used with aspirin, heparin, or glycoprotein IIb/IIIa inhibitors.

BETA-BLOCKERS

B

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
BETA-BLOCKERS					
Acebutolol Atenolol (S) Atenolol Betaxolol Bisoprolol Esmolol Metoprolol Nadolol	Aminophylline, Theophylline	High doses of beta-blockers may cause severe or fatal bronchospasm opposing the bronchodilator effects of the interacting drugs.		!!!	-
Nebivolol Penbutolol Pindolol Propranolol Sotalol Timolol	Calcium channel blocker: Nifedipine	Additive reductions in heart rate, cardiac conduction, and cardiac contractility, resulting in CHF, severe hypotension, and/or exacerbation of angina.		!!	
Carvedilol Labetalol	Calcium channel blockers: Diltiazem, Verapamil	Additive reductions in heart rate, cardiac conduction, and cardiac contractility, resulting in potentially serious CVE.		!!!	
	Clonidine	See category 'alpha agonist'.			
	Digoxin	Concomitant use may increase the risk of bradycardia.		!!	-
	Diphen- hydramine	Diphenhydramine may potentiate the hypotensive effect of beta blockers.		!!	
	Disopyramide	Coadministration may result in severe hypotension, syncope, severe bradycardia, asystole, and heart failure.		!!!	-
	H ₂ antagonist: Cimetidine	Cimetidine increases plasma concentrations of beta blockers.		!!	
	Lidocaine	Coadministration may result in lidocaine toxicity.		!!	

BETA-BLOCKERS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Acebutolol Atenolol (S) Atenolol Betaxolol Bisoprolol	NSAIDs: Ibuprofen, Indomethacin, Piroxicam	NSAIDs may decrease the antihypertensive effect of beta blockers.		!!	
Esmolol Metoprolol Nadolol Nebivolol Penbutolol Pindolol	Reserpine, Guanethidine, MAO inhibitors	Additive effect may result in hypotension, orthostasis, bradycardia and HF.		!!	
Propranolol Sotalol Timolol Carvedilol Labetalol	Sympatho- mimetics: Dobutamine, Dopamine, Metaraminol, Norepinephrine, Phenylephrine	Beta-blockers may antagonize the cardiotonulatory effects of pressor agents.		!!	-
	Tizanidine	Tizanidine may potentiate the hypotensive effect of beta blockers. [#]		!!!	-
Acebutolol Atenolol (S) Atenolol Betaxolol Bisoprolol Esmolol Metoprolol Nadolol Nebivolol Penbutolol Pindolol Propranolol Timolol Carvedilol Labetalol	Amiodarone	Additive effects of severe bradycardia, cardiac arrest, and ventricular fibrillation may occur.		!!	
Sotalol	Amiodarone, Disopyramide, Dofetilide, Haloperidol, Procainamide, Quinidine	Prolongation of the QT interval results in additive effects and increased risk of ventricular arrhythmias.		!!!	

BETA-BLOCKERS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Acebutolol Atenolol (S) Atenolol Betaxolol Bisoprolol Esmolol Metoprolol Nebivolol	Epinephrine	Beta-blockers may antagonize the cardiotonulatory effects of epinephrine.		!!	-
Nadolol Penbutolol Pindolol Propranolol Sotalol Timolol Carvedilol Labetalol	Epinephrine	Non-cardioselective beta-blockers can significantly enhance the pressor response to epinephrine. Concomitant administration may result in severe hypertension accompanied by bradycardia.	 	!!!	-
Acebutolol Atenolol (S) Atenolol Betaxolol Bisoprolol Esmolol Penbutolol Nadolol Nebivolol Carvedilol Labetalol	Phenothiazines: Chlorpromazine, Thioridazine	Phenothiazines may potentiate the hypotensive effect.		!!	
Pindolol Propranolol Sotalol	Phenothiazines: Chlorpromazine, Thioridazine	Coadministration may increase the plasma concentrations of thioridazine, increasing the risk of ventricular arrhythmias, cardiac arrest and sudden death.*		!!!	
Bisoprolol Penbutolol Propranolol Metoprolol Timolol Carvedilol Labetalol	Rifampin	Concurrent use of rifampin may decrease serum levels and effects of some oral beta-blockers.		!!	

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Metoprolol Propranolol	Sodium channel blockers: Flecainide, Propafenone	Serum levels and effects of some beta- blockers may increase significantly. Negative inotropic effects may also be potentiated.	 	!!	-

SECTION EXCERPTS AND RECOMMENDATIONS

High alert:

- Concomitant administration of almost all the cardioselective and non-selective beta-blockers with aminophylline and theophylline, calcium channel blockers (verapamil, diltiazem), sodium channel blocker (disopyramide), and tizanidine may prove to be fatal.
- Sotalol, if given along with drugs that prolong Q-T interval, such as amiodarone, quinidine, procainamide and disopyramide can result in severe adverse events including death.
- Severity of a few cardioselective and non-selective beta-blockers may vary with a hemostatic agent, epinephrine and phenothiazine derived drugs.

Recommendations:

- # Initiate tizanidine treatment with 4 mg doses and gradually increase in 2 to 4 mg increments until optimum effect is achieved. The dose can be repeated at 6 to 8 hour intervals as needed, up to a maximum of three doses in 24 hours and a total daily dosage of 36 mg.
- * Concurrent use is contraindicated.

CALCIUM CHANNEL BLOCKERS

C

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
CALCIUM CHANNEL BLOCKERS					
Amlodipine S-Amlodipine	Simvastatin	Coadministration may significantly increase the plasma concentrations of simvastatin and its active metabolite, simvastatin acid, and potentiate the risk of statin-induced myopathy. [#]		!!!	-
Amlodipine S-Amlodipine Felodipine Nicardipine Nifedipine Nimodipine Nisoldipine Diltiazem Verapamil	Azole antifungal: Itraconazole	Dose-related negative inotropic effects of itraconazole may be increased. ^{\$}		!!!	-
	Dolasetron	Coadministration may result in additive effects and increased risk of bradycardia and heart block.		!!!	-
	Nitroglycerin	Concurrent administration may cause symptomatic orthostatic hypotension.		!!	-
Amlodipine S-Amlodipine Felodipine Nicardipine Nifedipine Nisoldipine Diltiazem Verapamil	Protease inhibitors: Indinavir, Lopinavir/ Ritonavir	Coadministration may increase the plasma concentrations and pharmacologic effects of CCBs.		!!	
	Rifamycins: Rifabutin, Rifampin, Rifapentine	Rifamycins may decrease the bioavailability, plasma levels, and pharmacological effects of CCBs.		!!	-
	SRIs: Fluoxetine, Fluvoxamine	SRIs may increase the serum concentration of calcium channel blockers.		!!	-
Amlodipine S-Amlodipine Felodipine Nicardipine Nisoldipine	Barbiturates: Phenobarbital, Butabarbital, Amobarbital, Secobarbital	Coadministration may have additive effects on blood pressure and orthostasis.		!!	-

CALCIUM CHANNEL BLOCKERS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Diltiazem Verapamil	Dofetilide	Significant increase in dofetilide plasma concentrations and/or C_{max} .*			-
	Beta-blockers	Refer section 'beta-blockers'.			
	Benzo-diazepines: Midazolam, Triazolam	Both, diltiazem and verapamil increase peak plasma concentration and prolong the elimination half-life of midazolam.		!!	-
	Erythromycin	Coadministration may increase the plasma concentrations of erythromycin.		!!!	-
	Lovastatin, Simvastatin	Coadministration may significantly increase the plasma concentrations of simvastatin and lovastatin and potentiate the risk of statin-induced myopathy. ^s		!!!	-
Nifedipine	Cyclosporine/ ciclosporine	Cyclosporine may increase serum concentrations of some dihydropyridine CCBs.		!!	-
Nimodipine	Phenobarbital	Coadministration may significantly reduce the plasma concentrations and pharmacologic effects of oral nimodipine.		!!!	-

SECTION EXCERPTS AND RECOMMENDATIONS

High alert: Concurrent administration of CCBs with dolasetron and/or barbiturates should be avoided. Diltiazem and verapamil should not be given with beta-blockers, lovastatin, simvastatin and erythromycin.

- * Verapamil has shown severe interaction as compared to diltiazem with dofetilide.
- ^s Coadministration of CCBs and itraconazole may potentiate the risk of ventricular dysfunction, CHF, peripheral and pulmonary edema, particularly in patients with preexisting risk factors, such as patients having history of CHF, cardiac disease such as ischemic and valvular disease, significant pulmonary disease such as COPD, and edematous disorders such as renal failure.

Recommendations:

- # Simvastatin dosage should not exceed 20 mg daily when used in combination with amlodipine. Fluvastatin, pravastatin, and rosuvastatin are probably safer alternatives in patients receiving amlodipine, since they are not metabolized by CYP450 3A4.
- ^s Simvastatin dosage should not exceed 10 mg daily and lovastatin dosage not to exceed 20 mg daily when used in combination with diltiazem/verapamil.

DIGOXIN (ANTI-ARRHYTHMIC AGENT)

D

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
DIGOXIN					
Digoxin	Adenosine	Coadministration may increase the risk of ventricular fibrillation.		!!!	-
	Amiodarone	Refer section 'amiodarone'.		!!!	
	Antineo-plastic agents: Bleomycin, Carmustine, Cyclo-phosphamide, Doxorubicin, Methotrexate, Vincristine	Some antineoplastic agents decrease GI absorption of digoxin.		!!	
	Azole antifungals: Itraconazole, Ketoconazole	Coadministration may result in increased plasma concentrations of digoxin.		!!	
	Benzodiazepines: Alprazolam, Clonazepam, Diazepam, Triazolam	Benzodiazepines may increase serum levels of digoxin.		!!	
	Beta-blockers	Refer section 'beta-blockers'.			
	Calcium preparations: Calcium chloride, Calcium gluconate	Rapid IV injection of calcium preparations may precipitate serious cardiac arrhythmias in digitalized patients.#		!!!	-
	Cyclosporine/ciclosporine	Cyclosporine may increase both serum levels and pharmacologic effects of digoxin.		!!	-
	Diuretics: Acetazolamide, Chlorothiazide, Furosemide, Hydrochlorothiazide, Indapamide, Torsemide	Diuretic-induced hypokalemia and hypomagnesemia may predispose patients on digitalis to arrhythmias.		!!	-

DIGOXIN (ANTI-ARRHYTHMIC AGENT)

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Digoxin	Dolasetron	Coadministration may result in additive effects and increased risk of bradycardia and heart block.		!!!	-
	Macrolide antibiotics: Erythromycin, Clarithromycin	Macrolide antibiotics may increase plasma concentrations of orally administered digoxin.		!!	
	NSAIDs: Ibuprofen, Indomethacin	NSAIDs may increase plasma digoxin concentrations and half-life.		!!	
	Protease inhibitor: Atazanavir	Coadministration may increase the risk of conduction disturbances and atrioventricular block.		!!!	-
	Rifamycins: Rifampin, Rifabutin	Rifamycins may decrease the plasma concentration of digoxin.		!!	-
	Sodium channel blockers: Propafenone, Quinidine	Some sodium channel blockers significantly increase serum digoxin levels.		!!	
	Tetracyclines: Demeclocycline, Doxycycline, Minocycline, Tetracycline	Tetracyclines may increase serum levels of orally administered digoxin.		!!	

SECTION EXCERPTS AND RECOMMENDATIONS

High alert: Cardiac glycoside, digoxin when given with adenosine, amiodarone, dolasetron and protease inhibitors can result in serious drug interactions.

Recommendation:

- # Intravenous calcium preparations should not be administered to patients on digoxin therapy.

DIURETICS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
DIURETICS					
Carbonic anhydrase inhibitors: Aceta- zolamide Metha- zolamide	Aspirin	Large doses of aspirin with CAIs may result in severe metabolic acidosis and/or salicylate toxicity.	 	!!!	-
	Quinidine	Coadministration may decrease the urinary excretion of quinidine, resulting in quinidine toxicity.		!!	
Carbonic anhydrase inhibitors: Aceta- zolamide Metha- zolamide	Amiodarone	Coadministration may increase QT interval.		!!!	-
Loop diuretics: Bumetanide Furosemide Torsemide	Dofetilide	Coadministration may increase the plasma concentrations and pharmacodynamic effects of dofetilide.		!!!	-
Thiazide diuretics: Chloro- thiazide Chlor- thalidone Hydrochlo- rothiazide Indapamide Metolazone	Droperidol	Concurrent administration may increase the QT interval.		!!!	-
	Sulfonylureas: Glimepiride, Glipizide, Glyburide, Tolazamide, Tolbutamide	The efficacy of oral hypoglycemic agents may be decreased by diuretics.		!!	-

DIURETICS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Carbonic anhydrase inhibitors: Aceta- zolamide Metha- zolamide	Calcium salts: Calcium acetate, Calcium carbonate, Calcium citrate, Calcium gluconate, Calcium lactate And/or Vitamin D supplements	Coadministration may result in hypercalcemia.		!!	-
Thiazide diuretics: Chloro- thiazide Chlor- thalidone Hydrochlo- rothiazide Indapamide Metolazone	Corticosteroids: Hydrocortisone, Prednisolone	Coadministration may result in increased risk of hypokalemia.		!!	-
	SNRIs: Desvenlafaxine, Sibutramine, Venlafaxine SSRIs: Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Sertraline	Coadministration may potentiate the risk of hyponatremia, especially in elderly. Diuretics may potentiate the orthostatic effects of SSRIs and SNRIs.		!!	-
Loop diuretics: Bumetanide Furosemide Torsemide	Aminoglycoside antibiotics: Amikacin, Gentamicin, Streptomycin (parenteral preparations), Tobramycin, Neomycin (oral)	Coadministration may potentiate the risk of oto- and nephro- toxicity due to their additive or synergistic pharmacologic effects.	 	!!!	
	Digoxin, Digitoxin	Refer section 'cardiac glycosides'.			
	Skeletal muscle relaxant: Atracurium, Pancuronium, Tubocurarine	Loop diuretics may enhance or decrease the effect of nondepolarizing neuromuscular blockers.		!!	-

DIURETICS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Loop diuretics: Bumetanide Furosemide Torsemide Potassium sparing diuretics: Amiodarone Spirono- lactone Triamterene	Lithium	Coadministration may cause a rapid increase in serum lithium levels and potentiate the risk of lithium toxicity.		!!!	-
Thiazide diuretics: Chloro- thiazide Chlor- thalidone Hydrochlo- rothiazide Indapamide Metolazone	NSAIDs: Ibuprofen, Ketoprofen	Concomitant administration may adversely affect renal function. Hypotensive effect of the diuretics may be reduced. NSAIDs may also increase the risk of hyperkalemia.		!!	-
Loop diuretics: Bumetanide Furosemide Torsemide Thiazide diuretics: Chloro- thiazide Chlor- thalidone Hydrochlo- rothiazide Indapamide Metolazone	Dolasetron	Coadministration may increase the risk of arrhythmia.		!!!	-
Potassium sparing diuretics: Amiodarone Eplerenone Spirono- lactone Triamterene	ACE inhibitors ARBs	Refer section 'ACE inhibitors'. Refer section 'ARBs'.			
	Potassium preparations: Potassium bicarbonate, Potassium chloride, Potassium citrate, Potassium guaiacol- sulfonate	Concurrent administration may result in hyperkalemia.		!!!	-

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Thiazide diuretics: Chlorothiazide Chlor-thalidone Hydrochlorothiazide Indapamide Metolazone	ACE inhibitors	Refer section 'ACE inhibitors'.			
Thiazide diuretics: Chlorothiazide Chlor-thalidone Hydrochlorothiazide Indapamide Metolazone	Allopurinol	Thiazide diuretics may increase the risk of allopurinol-induced hypersensitivity reactions, especially in patients with renal insufficiency.			-
	Antineoplastic agents: Cyclophosphamide, Fluorouracil, Methotrexate	Antineoplastic-induced bone marrow suppression may be prolonged with concomitant thiazide administration.			
	Diazoxide	Coadministration may result in profound and prolonged hyperglycemia.			
	Skeletal muscle relaxant: Atracurium, Pancuronium, Tubocurarine	Thiazide diuretics may induce hypokalemia and prolong the neuromuscular blocking effects of nondepolarizing muscle relaxants.			
	Warfarin	Concurrent administration may decrease the anticoagulant effect.			

SECTION EXCERPTS AND RECOMMENDATIONS

High alert:

- Concurrent administration of CAs with aspirin, amiodarone, dofetilide and droperidol should be avoided.
- Loop diuretics interact majorly with amiodarone, dofetilide, droperidol, aminoglycoside antibiotics, lithium and dolasetron.
- Potassium sparing diuretics should not be given with lithium, ACE inhibitors, ARBs and potassium preparations.
- Coadministration of thiazide diuretics with dofetilide is contraindicated. Thiazide diuretics should also be avoided in patients taking amiodarone, droperidol, dolasetron and lithium.

Recommendation: Dosage reduction or discontinuation of drugs is recommended in patients experiencing severe adverse reactions.

FIBRINOLYTIC AGENTS

F

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
FIBRINOLYTIC AGENTS					
Alteplase Reteplase Streptokinase Tenecteplase	Antiplatelet drugs: Aspirin, Cilostazol, Clopidogrel, Dipyridamole	Antiplatelet drugs may increase the risk of bleeding when administered prior to, during, or after thrombolytic therapy.		!!	-
	Glycoprotein IIb/IIIa inhibitors: Abciximab, Eptifibatide	Refer section 'antiplatelet drugs'.			
	NSAIDs including COX-2 inhibitors: Ibuprofen, Ketoprofen, Diclofenac	Systemic and topical administration of NSAIDs with fibrinolysis may potentiate the risk of bleeding.		!!	-
	SSRIs: Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Sertraline SNRIs: Desvenlafaxine, Venlafaxine, Sibutramine	SRRIs may potentiate the risk of bleeding in patients treated with fibrinolytic agents.		!!	-
	Warfarin, Heparin and LMWH, Direct thrombin inhibitors	Refer section 'anticogulants'.			

SECTION EXCERPTS AND RECOMMENDATIONS

High alert: Fibrinolitics when used with glycoprotein IIb/IIIa inhibitors, can cause serious drug interactions.

Recommendation: When fibrinolitics are used concurrently with the given interacting drugs, hematologic complications, particularly at arterial puncture wounds should be closely monitored.

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
FOLIC ACID					
Folic acid	Anti-convulsants: Phenytoin, Phenobarbital, and Primidone	Folate therapy may reduce the anticonvulsant effects on concurrent administration.		!!	-
	Chemo-therapeutic agents: Fluorouracil and prodrugs, Capecitabine, Tegafur	Folate therapy may potentiate the pharmacologic effects of 5-FU or any of its prodrugs.	  	!!!	-

SECTION EXCERPTS AND RECOMMENDATIONS

Folic acid should be used with caution when given in patients on chemotherapy with 5-FU or any of its prodrugs.

GUANETHIDINE

G

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
GUANETHIDINE					
Guanethidine	Barbiturates: Amobarbital, Butabarbital, Phenobarbital, Secobarbital	Coadministration of barbiturates may result in additive effects.		!!	-
	CNS stimulants: Amphetamine, Methylphenidate, Phentermine	CNS stimulants may decrease the hypotensive effect of guanethidine.		!!	-
	Minoxidil	Guanethidine blocks the reflex sympathetic response to minoxidil-induced hypotension, resulting in profound hypotension or syncope. [#]		!!!	-
	Phenothiazines: Chlorpromazine, Fluphenazine, Mesoridazine, Thioridazine	Phenothiazines may inhibit the antihypertensive effect of guanethidine.		!!	
	Sympathomimetic amines: <i>Direct acting:</i> Dobutamine, Epinephrine, Norepinephrine, Pseudoephedrine; <i>Indirect acting:</i> Mephentermine	Sympathomimetic amines may decrease the hypotensive effect of guanethidine. Guanethidine may potentiate the pharmacologic effects of direct-acting sympathomimetic amines while inhibits indirect-acting sympathomimetic amines.		!!	
Guanethidine	TCAs: Amitriptyline, Clomipramine, Desipramine, Imipramine, Trimipramine	TCAs may reduce the antihypertensive effects of guanethidine. ^{\$}		!!	

GUANETHIDINE

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Guanethidi- dine	Thiazide diuretics: Chlorthalidone, Chlorothiazide, Hydrochloro- thiazide, Indapamide	The hypotensive effects of thiazide diuretics and guanethidine may be additive.		!!	-

SECTION EXCERPTS AND RECOMMENDATIONS

High alert:

Coadministration of guanethidine and minoxidil is contraindicated.

Recommendations:

Guanethidine should be discontinued, at least a week before minoxidil is started.

§ Either a different antidepressant or a different antihypertensive agent (such as an ACE inhibitor or beta-blocker) should be considered.

HMG-CoA REDUCTASE INHIBITORS

H

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
HMG-CoA REDUCTASE INHIBITORS					
Atorvastatin Fluvastatin Lovastatin Pravastatin Rosuvastatin Simvastatin	Colchicine	Coadministration may increase the risk of myopathy due to a combination of pharmacodynamic and pharmacokinetic effects. [#]		!!!	
Atorvastatin Lovastatin Pravastatin Rosuvastatin Simvastatin	Fibric acid derivative: Gemfibrozil	Gemfibrozil significantly increases the plasma concentrations of some statins and/or their active metabolites; may result in myopathy and rhabdomyolysis. [€]		!!!	
Atorvastatin Lovastatin Rosuvastatin Simvastatin	Cyclosporine/ ciclosporine	Significant increase in the plasma concentrations of some HMG-CoA reductase inhibitors and/or their pharmacologically active metabolites. [¥]		!!!	
	Niacin	Coadministration may result in severe myopathy and rhabdomyolysis. [§]		!!!	
	Protease inhibitors: Ritonavir, Saquinavir	PIs may significantly increase the plasma concentrations of given statins, increasing risk of myopathy including rhabdomyolysis. [§]		!!!	
Atorvastatin Lovastatin Simvastatin	Azole antifungals: Fluconazole, Itraconazole, Ketoconazole	Significant increase in the plasma concentrations of HMG-CoA reductase inhibitors resulting in increased risk of musculoskeletal toxicity. [¤]		!!!	
	Danazol	Use of danazol with higher doses of certain HMG-CoA reductase inhibitors may increase the risk of myopathy. [^]		!!!	-

HMG-CoA REDUCTASE INHIBITORS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Atorvastatin Lovastatin Simvastatin	Macrolide antibiotics: Clarithromycin, Erythromycin	Some macrolide antibiotics may elevate the plasma concentrations of HMG-CoA reductase inhibitors.*		!!!	
Fluvastatin	Glyburide	Coadministration may result in increased plasma concentrations of both drugs.		!!	
Lovastatin Rosuvastatin	Warfarin	Refer section 'anticoagulants'.			

SECTION EXCERPTS AND RECOMMENDATIONS

High alert: Concurrent administration of statins with colchicine should be avoided. Most of the statins should be used with caution when prescribed along with azole antifungals, cyclosporine, fibric acid derivatives, macrolides, protease inhibitors or niacin.

Recommendations:

- # Discontinuation of drugs is recommended, if creatine kinase is markedly elevated in the absence of strenuous exercise or if myopathy is suspected or diagnosed.
- € If the combination is prescribed, a fibrate other than gemfibrozil may be preferable, along with lower initial dosages of the HMG-CoA reductase inhibitor. If gemfibrozil is used, rosuvastatin daily dosage should not exceed 10 mg, while lovastatin should not be given more than 20 mg daily.
- ¥ Fluvastatin, pravastatin, and rosuvastatin are probably safer alternatives in patients receiving cyclosporine, since they are not metabolized by CYP450 3A4; but daily dosage of rosuvastatin should not exceed 5 mg when used in combination with cyclosporine.
- § Concurrent use of statins and lipid-modifying dosages of niacin (≥ 1 g/day) should generally be avoided. If co-prescribed, lovastatin and simvastatin dosages should not exceed 20 mg daily.
- § Atorvastatin dosage not to exceed 20 mg/day when used in combination with fosamprenavir or with dual protease inhibitor therapy consisting of ritonavir plus darunavir, saquinavir, or fosamprenavir. The dosage should not exceed 40 mg/day when used with nelfinavir. The dosage of rosuvastatin should be limited to 10 mg once a day when used in combination with lopinavir-ritonavir or atazanavir-ritonavir. Fluvastatin, pitavastatin, and pravastatin may be safer alternatives, since they are not metabolized by CYP450 3A4.
- ♀ Atorvastatin dose should not exceed 20 mg/day when prescribed with itraconazole. Fluvastatin, pravastatin, and rosuvastatin may be safer alternatives, since they are not metabolized by CYP450 3A4.
- ^ Fluvastatin, pitavastatin, and pravastatin are considered as safer alternatives in patients receiving danazol.
- * Atorvastatin dosage should not exceed 20 mg/day when used in combination with clarithromycin. Fluvastatin, pitavastatin, and rosuvastatin may be safer alternatives, since they are not metabolized by CYP450 3A4.

IRON SALTS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
IRON SALTS					
Ferrous fumarate Ferrous gluconate Ferrous sulfate	Antacids: Calcium carbonate, Magnesium hydroxide, Aluminum hydroxide	The bioavailability of orally administered iron may be reduced by concomitant administration of antacids. [#]		!!	-
	Methyldopa, Levodopa, Carbidopa	Iron salts may decrease the oral bioavailability and pharmacologic effects of methyldopa.		!!	-
	Dimercaprol	Dimercaprol can form nephrotoxic chelates with iron salts.*		!!!	-
	Tetracyclines: Doxycycline, Tetracycline	Concurrent administration may decrease the bioavailability of oral tetracyclines and iron salts.		!!	-
Ferrous fumarate Ferrous gluconate Ferrous sulfate Iron dextran	Vitamin E	Vitamin E may diminish the therapeutic response to iron therapy in patients with iron deficiency anemia.		!!	-
Iron dextran	ACE inhibitors: Benazepril, Captopril, Enalapril, Perindopril, Quinapril, Ramipril	ACE inhibitors may increase the risk of systemic adverse effects associated with the use of iron dextran. Anaphylactic-type reactions may occur on parenteral administration.		!!!	
Iron dextran	Chloramphenicol	Chloramphenicol can cause bone marrow depression and inhibit RBC maturation, which may interfere with the therapeutic effects of iron preparation in the treatment of anemia. ^{\$}		!!	-

SECTION EXCERPTS AND RECOMMENDATIONS

High alert: Concomitant administration of parenteral administration of iron dextran and ACE inhibitors can cause serious adverse reactions. Iron salts can cause major interaction with dimercaprol.

Recommendations:

- # Oral iron preparations should be administered at least two hours apart from antacids or other agents with acid-neutralizing effects.
- * Iron preparations should not be administered during chelation therapy with dimercaprol and also before 24 hours of the last dose of dimercaprol.
- § Chloramphenicol should not be given in patients with preexisting anemia due to the drug's depressive effect on bone marrow and reticulocytes.

MECAMYLAMINE

M

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
MECAMYLAMINE					
Mecamyl-amine	Phenothiazines: Chlorpromazine, Fluphenazine, Mesoridazine, Thioridazine, Trimeprazine	Phenothiazines may potentiate the hypotensive effects of mecamylamine.			-
	Urinary alkalizers: Potassium citrate, Sodium acetate, Sodium bicarbonate, Sodium citrate, Sodium lactate	Urinary alkalinizers may decrease renal elimination of mecamylamine, resulting in prolonged antihypertensive action.			

SECTION EXCERPTS AND RECOMMENDATIONS

Blood pressure of the patients on antihypertensive medication, mecamylamine should be closely monitored when they are coprescribed phenothiazines, neuroleptic agents or urinary alkalinizers.

METHYLDOPA

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
METHYLDOPA					
Methyldopa	Ferrous salts: Ferrous fumarate, Ferrous gluconate, Ferrous sulfate	Refer section 'iron salts'.			
	Lithium	Methyldopa may increase the effect of lithium with or without altering serum lithium levels.			-
	MAO inhibitor: Selegiline	Coadministration may result in loss of blood pressure control and/or signs of central stimulation such as hyperexcitability and hallucinations.#			-
	Nonselective beta-blockers: Carvedilol, Labetalol, Penbutolol, Pindolol, Propranolol, Sotalol, Timolol	The combination of nonselective beta-blockers (NSBB) and methyldopa show pharmacodynamic synergy; however, NSBB administration during withdrawal from methyldopa may lead to rebound hypertension.			-
	Sympathomimetics: Epinephrine, Dopamine, Norepinephrine, Phenylephrine, Phenylepin-ephrine	Methyldopa and other sympatholytics may increase or prolong the pressor effect of sympathomimetics.			-

SECTION EXCERPTS AND RECOMMENDATIONS

High alert: Methyldopa is used with caution with MAOIs and non-selective beta blockers. Concurrent use of methyldopa with MAOIs or other agents that possess MAOI activity (e.g., furazolidone, linezolid, procarbazine) is contraindicated.

Recommendations:

- # It is suggested that there should be a minimum of 14 days of elapse between discontinuation of MAOI therapy and initiation of treatment with methyldopa.

NITRATES (ANTI-ANGINAL DRUG)

N

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
NITRATES					
Amyl nitrite Isosorbide dinitrate Isosorbide mononitrate Nitroglycerin	Ergot alkaloids: Dihydro-ergotamine, Ergotamine	Ergot alkaloids may antagonize the effects of nitrates by causing vasoconstriction. Nitrates may increase the bioavailability of dihydroergotamine. [#]		!!	
	Lidocaine, Prilocaine	Coadministration may have additive effects and thus, may increase the risk of drug-induced methemoglobinemia. ^{\$}		!!!	-
	PDE-5 inhibitors: Avanafil, Sildenafil, Tadalafil	PDE-5 inhibitors may potentiate the hypotensive effect of organic nitrates. ^{\$}		!!!	
Isosorbide dinitrate Isosorbide mononitrate Nitroglycerin	ACE inhibitors: Captopril, Quinapril	Refer section 'ACE inhibitors'.			
Nitroglycerin	Calcium channel blockers: Amlodipine, Felodipine, Nicardipine, Nifedipine, Nimodipine, Nisoldipine Diltiazem, Verapamil	Refer section 'calcium channel blockers'.			
	Heparin	Refer section 'anticoagulants'.			

SECTION EXCERPTS AND RECOMMENDATIONS

High alert:

Ergot alkaloids are contraindicated in patients with ischemic heart disease.

\$ Concomitant use of PDE-5 inhibitors and organic nitrates is contraindicated.

\$ The concurrent use of topical lidocaine-prilocaine formulations with other methemoglobinemia-inducing medications should be avoided in infants younger than 12 months of age, and should be used with caution in other patients. Injectable prilocaine-containing formulations should be used with caution in the presence of other methemoglobin-inducing drugs.

Recommendations:

\$ If the concomitant use with avanafil or tadalafil is unavoidable, and is necessary in life-threatening situation, at least 12 hours gap after the last dose of avanafil and 48 hours gap after the last dose of tadalafil has been recommended before nitrate administration. (A suitable time interval following sildenafil or vardenafil use for the safe administration of nitrates has not been determined.)

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
PENTOXIFYLLINE					
Pentoxifylline	Anticoagulants: Warfarin, Heparin and LMWHs, Direct thrombin inhibitors	The risk of bleeding may be increased by concomitant treatment.*			-
	ACE inhibitors, ARBs, Beta- blockers, nonselective alpha blockers	Pentoxifylline may potentiate the action of hypotensive agents.			-
	Sulfonylureas: Glimepiride, Glipizide	Hypoglycemic effect of sulfonylureas may be increased.			-
	Theophylline	Coadministration may increase the serum concentrations of theophylline.			-

SECTION EXCERPTS AND RECOMMENDATIONS

Recommendation:

- # Frequent monitoring of INR should be done in patients on vitamin K antagonists such as warfarin following initiation or dosage change of pentoxifylline.

PYRIDOXINE

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
PYRIDOXINE (VITAMIN B₆)					
Pyridoxine	Anti-epileptics: Phenytoin, Phenobarbital	Large doses of pyridoxine (> 200 mg/day) may decrease the concentration of certain antiepileptic medications. [#]			
	Levodopa	Pyridoxine doses of ≥ 5 mg/day antagonize the effects of levodopa. ^{\$}			

SECTION EXCERPTS AND RECOMMENDATIONS

High alert:

^{\$} The concomitant use of pyridoxine and levodopa without dopa-decarboxylase inhibitors should be avoided.

Recommendation:

[#] If concomitant use of large doses of pyridoxine and phenytoin or phenobarbital is unavoidable, altered anticonvulsant effects should be observed carefully.

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
RANOLAZINE					
Ranolazine	Anti-convulsants: Carbamazepine, Phenytoin	Coadministration may decrease the plasma concentrations of ranolazine.		!!!	
	Aprepitant	Plasma concentrations of ranolazine increases significantly, thus increasing the risk of ventricular arrhythmias, including ventricular fibrillation and <i>torsade de pointes</i> .		!!!	-
	Azole antifungals: Fluconazole, Itraconazole, Ketoconazole, Nefazodone	Significant increase in the plasma concentrations of ranolazine, increasing the risk of ventricular arrhythmias, including ventricular fibrillation and <i>torsade de pointes</i> .		!!!	
	Barbiturates: Amobarbital, Butabarbital, Pentobarbital, Phenobarbital, Secobarbital	The plasma concentrations of ranolazine may reduce on coadministration.		!!!	
	Cyclosporine/ ciclosporine	Plasma concentrations of both drugs may increase. Cyclosporine toxicity or /and increase in the risk of ventricular arrhythmias including ventricular fibrillation and <i>torsade de pointes</i> may occur.	 	!!	
	Digoxin	The plasma concentrations of digoxin may increase, causing digoxin toxicity.		!!	
	Diltiazem, Verapamil	Plasma concentrations of ranolazine may increase significantly, thus increasing the risk of ventricular arrhythmias.		!!!	

RANOLAZINE

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Ranolazine	Lovastatin, Simvastatin	Increase in plasma concentrations of lovastatin/simvastatin and their active metabolites may occur, that potentiate the risk of statin-induced myopathy.*		!!!	
	Macrolide antibiotics: Clarithromycin, Erythromycin	Significant increase in plasma concentrations of ranolazine, increasing the risk of ventricular arrhythmias.		!!!	
	Protease inhibitors: Indinavir, Ritonavir, Saquinavir	Coadministration may significantly increase the plasma concentrations of ranolazine.		!!!	
	Rifamycins: Rifampin, Rifabutin, Rifapentine	Plasma concentrations of ranolazine may decrease on concurrent administration.		!!!	
	St. John's wort	Coadministration may decrease the plasma concentrations of ranolazine.		!!!	

SECTION EXCERPTS AND RECOMMENDATIONS

High alert: Concurrent administration of ranolazine with anticonvulsants, azole antifungals, barbiturates, macrolide antibiotics, protease inhibitors and rifamycins should be avoided. Ranolazine may have severe interaction with an antiemetic- aprepitant, calcium channel blockers-diltiazem and verapamil, statins-lovastatin and simvastatin, and St. John's wort.

Recommendation:

- # Fluvastatin, pitavastatin, pravastatin, and rosuvastatin may be safer alternatives in patients receiving ranolazine, since they are not substrates of P-glycoprotein or CYP450 3A4.

RESERPINE

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
RESERPINE					
Reserpine	Beta-blockers	Refer section 'beta blockers'.			
	Sympatho-mimetic amines: Dobutamine, Dopamine, Ephedrine, Epinephrine, Metaraminol, Methoxamine, Norepinephrine, Phenylephrine	Sympathomimetic amines may decrease the hypotensive effect of reserpine, while reserpine may potentiate the pharmacologic effects of direct-acting sympathomimetic amines but inhibit those that are primarily indirect-acting.	M	!!	
	Tetrabenazine	Coadministration of both monoamine depleters may have additive effect, increasing the risk of tardive dyskinesia. [#]		!!!	

SECTION EXCERPTS AND RECOMMENDATIONS

High alert:

If reserpine is not cleared from the body before starting tetrabenazine, overdosage and severe monoamine depletion in the CNS may occur. The risk of parkinsonism, dysphagia, akathisia, and other extrapyramidal symptoms may also be increased. Overdepletion of serotonin and norepinephrine may increase the risk of depression and suicidality. Therefore coadministration of reserpine and tetrabenazine is contraindicated.

Recommendation:

An elapse of 20 days has been recommended after stopping reserpine and before initiating therapy with tetrabenazine. It is advisable to wait for chorea to reemerge before administering tetrabenazine to avoid monoamine overdepletion in the central nervous system.

SODIUM CHANNEL BLOCKERS

S

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
SODIUM CHANNEL BLOCKERS					
Disopyramide	Beta-blockers: Atenolol, Metoprolol, Propranolol	Negative inotropic and chronotropic effects of disopyramide may increase.		!!!	
	Hydantoins: Phenytoin, Fosphenytoin	Hydantoins may decrease plasma levels and therapeutic effects of disopyramide.		!!	
	Rifamycins: Rifampin, Rifabutin	Rifampin may significantly decrease the plasma concentrations of disopyramide and increase concentrations of its metabolites, thus decreasing antiarrhythmic effect and increased anticholinergic effects.		!!	
	Verapamil	Disopyramide and verapamil may produce additive negative inotropic effects, especially in patients with conduction defects.*		!!	-
Disopyramide Procainamide	Amiodarone	Coadministration may increase the risk of additive effects such as hypotension, arrhythmias, <i>torsade de pointes</i> . ^s		!!	-
	Macrolide antibiotics: Clarithromycin, Erythromycin	Coadministration may result in additive effects and increased risk of ventricular arrhythmias including <i>torsade de pointes</i> and sudden death.		!!!	-
	Quinolones: Ciprofloxacin, Gemifloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Norfloxacin, Ofloxacin and Sparfloxacin	There may be dose-related prolongation of the QT interval, resulting in elevated risk of ventricular arrhythmias, including ventricular tachycardia and <i>torsade de pointes</i> .		!!!	-

SODIUM CHANNEL BLOCKERS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Disopyramide Procainamide Quinidine	Haloperidol	Coadministration may result in additive effects and increased risk of ventricular arrhythmias including <i>torsade de pointes</i> and sudden death.		!!!	-
	Sodium biphosphate/ Sodium phosphate	Bowel-cleansing phosphate and sulfate preparations may increase the risk of ventricular arrhythmia, particularly <i>torsade de pointes</i> . ^e		!!!	-
Flecainide Propafenone	Beta-blockers: Metoprolol, Propranolol, Sotalol	Refer section 'beta blockers'.			
	Cimetidine	Cimetidine may inhibit the hepatic metabolism of sodium channel blocker, increasing their plasma levels and a significantly increased QRS duration may result. ^x		!!	-
	Rifampin	Rifampin may significantly decrease plasma concentrations of given sodium channel blockers.		!!	-
Flecainide Mexiletine Propafenone	SSRIs: Fluoxetine, Fluvoxamine, Paroxetine	Coadministration may increase the serum concentrations of the given antiarrhythmic agents.		!!	-
Lidocaine	Beta-blockers	Refer section 'beta blockers'.			
	Cimetidine	Cimetidine may decrease the clearance of lidocaine, increasing serum lidocaine concentrations and risk of toxicity. ^s		!!	-

SODIUM CHANNEL BLOCKERS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Lidocaine Propafenone Mexiletine	Neuromuscular blocking agents: Pancuronium, Succinyl choline, Tubocurarine	Lidocaine may enhance the effect of neuromuscular blocking agents.		!!	-
	Protease inhibitors: Ritonavir, Saquinavir	Significant increase in the plasma concentrations of given antiarrhythmic agents may occur.		!!!	-
	Hydantoins: Fosphenytoin, Phenytoin	Hydantoins may induce the hepatic metabolism of mexiletine, decreasing plasma levels and effectiveness of mexiletine.		!!	-
	Rifampin	Rifampin may decrease the plasma concentrations of mexiletine		!!	-
	Theophyllines: Aminophylline, Theophylline	Mexiletine may inhibit the hepatic metabolism of theophyllines, increasing serum levels and risk of theophylline toxicity.		!!	-
	Urinary alkalinizers: Sodium bicarbonate, Sodium citrate	Urinary alkalinizers reduce the plasma clearance of mexiletine, increasing plasma levels and possible toxicity.		!!	-
Procainamide	Cimetidine	Cimetidine may increase plasma concentrations of procainamide and its active metabolite, NAPA, resulting in QRS widening or prolonged QT interval and increased risk of arrhythmias such as <i>torsades de pointes</i> . ^Ω		!!	-
Propafenone	Amiodarone	Refer section 'amiodarone'.			
	Digoxin	Refer section 'cardiac glycosides'.			

SODIUM CHANNEL BLOCKERS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Propafenone	Other sodium channel blockers: Disopyramide, Quinidine, Procainamide	Coadministration may have additive effects on the QT interval, increasing the risk of ventricular arrhythmias including <i>torsade de pointes</i> and sudden death.		!!!	-
Quinidine	Amiodarone	Refer section 'amiodarone'.			
	Antacids: Calcium carbonate, Magnesium hydroxide; Aluminum hydroxide/Magnesium carbonate	Antacids may decrease the urinary excretion of quinidine.		!!	
	Azole antifungals: Itraconazole, Ketoconazole	Azole antifungal agents may significantly increase the plasma concentrations of quinidine, causing prolongation of the QT interval.		!!!	
	Barbiturates: Phenobarbital, Pentobarbital	Some barbiturates may significantly decrease serum quinidine concentrations and half-life.		!!	
	Carbonic anhydrase inhibitors	Refer section 'diuretics'.			
	Cimetidine	Cimetidine may increase serum quinidine levels and the risk of toxicity.		!!	
	Diltiazem, Verapamil	Concurrent administration may increase plasma quinidine concentrations, causing quinidine toxicity.		!!	
	Hydantoins: Phenytoin, Fosphenytoin	Hydantoins may increase hepatic metabolism of quinidine, thus serum quinidine levels and quinidine effectiveness may be decreased.		!!	

SODIUM CHANNEL BLOCKERS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
Quinidine	Muscle relaxants: Pancuronium, Tubocurarine	The pharmacologic effects of nondepolarizing muscle relaxants and quinidine may be additive. ^A		!!	-
	Nifedipine	Some dihydropyridine CCBs may increase or decrease serum quinidine concentrations. quinidine may increase CCB levels.		!!	
	Rifamycins: Rifampin	Rifamycins may increase the hepatic metabolism of quinidine, decreasing serum quinidine levels and effects.		!!	-
	Urinary alkalinizers: Sodium bicarbonate, Sodium citrate	Drugs that can increase urinary pH may decrease the urinary excretion of quinidine.		!!	
	Warfarin	Refer section 'anticoagulants'.			

SECTION EXCERPTS AND RECOMMENDATIONS

High alert: Sodium channel blockers interact with most of the commonly used medications in clinical practice, thus caution is recommended.

Recommendations:

- # Disopyramide not to be administered less than 48 hours before or 24 hours after verapamil.
- \$ Concurrent use of amiodarone with other antiarrhythmic agents should only be given in patients with life-threatening ventricular arrhythmias, who are not completely responsive to a single agent or to amiodarone alone. If patients are coprescribed amiodarone, it is recommended that the dosages of previously administered agents should be reduced by 30% to 50% several days after the addition of amiodarone, when onset of arrhythmia suppression occur. If the combination is continued, patients should be monitored for adverse effects including conduction disturbances and exacerbation of tachyarrhythmias.
- € Plenty of clear liquids should be given to patients before, during, and after the bowel preparation process. Consumption of 36 to 48 fluid ounces of a carbohydrate-electrolyte solution has been recommended in 6 hours before the first dose.
- ¥ An alternative H2-antagonist (such as famotidine, nizatidine, ranitidine) should be considered.
- § Nizatidine and famotidine may be considered as alternatives, as they are not expected to interact with lidocaine.
- ¤ Famotidine and nizatidine do not appear to interact in this manner and may be considered as alternatives.
- △ Quinidine should not be administered immediately after surgery. Concurrent administration may require mechanical ventilatory support.

SYMPATHOMIMETICS

Category/ Drug	Interacting Category/Drugs	Effects of Interaction	Consequences/ Signs/Symptoms	Levels of Effects	Onset
SYMPATHOMIMETICS					
Dobutamine Dopamine Ephedrine Epinephrine Metaraminol Norepinephrine Phenylephrine	Digoxin	The concomitant use of sympathomimetic agents and cardiac glycosides may increase the risk of cardiac arrhythmias.			-
Dopamine Dobutamine Ephedrine Epinephrine Norepinephrine Phenylephrine	Ergot alkaloids: Ergotamine, Dihydro- ergotamine	Additive or synergistic increases in BP and/or ischemic response may occur when ergot alkaloids are combined with peripheral or central vasoconstrictors. ^a	 		-
Dopamine	Hydantoins: Phenytoin, Fosphenytoin	Coadministration of dopamine and hydantoin derivatives may result in profound hypotension.			-
Dopamine Ephedrine Epinephrine	Haloperidol	Phenothiazines and other neuroleptics may inhibit or reverse the pressor effect of sympathomimetics. ^s			-
Dobutamine Dopamine Epinephrine Metaraminol Norepinephrine	TCAs: Amitriptyline, Amoxapine, Imipramine, Doxepin, Nortriptylline	TCAs may markedly enhance the pressor response to parenteral direct-acting sympathomimetic agents. ^s	 		-
Dobutamine Dopamine Metaraminol Norepinephrine Phenylephrine	Beta-blockers	Refer section 'beta-blockers'.			
Dopamine Ephedrine Metaraminol Phenylephrine	MAO inhibitors: Furazolidone, Phenelzine, Procarbazine, Selegiline	Indirect- or mixed-acting sympathomimetic amines may cause severe hypertensive reactions and hyperpyrexia in patients treated with MAOIs. [#]			-

SYMPATHOMIMETICS

SECTION EXCERPTS AND RECOMMENDATIONS

High alert: Concomitant administration of sympathomimetic agents with MAOIs and/or TCAs is potentially risky.

Recommendations:

- Ω Intravenous forms of any ergot alkaloid should generally not be administered in combination with other vasoconstrictive agents.
- § Adrenaline, dopamine, and similar vasoconstrictors should not be used to treat drug-induced hypotension and circulatory collapse in patients taking phenothiazines or other neuroleptic agents. Alternative vasoconstrictor agents such as metaraminol, noradrenaline (norepinephrine), or phenylephrine should be considered.
- § Parenteral administration of direct-acting sympathomimetic agents should preferably be avoided during therapy with tricyclic antidepressants except in cases of emergency (e.g., treatment of anaphylaxis).
- # At least 14 days should elapse between discontinuation of MAOI therapy and initiation of treatment with sympathomimetic agents.

TABLES & ALGORITHMS

Table 1 Intravenous antihypertensive agents available for management of hypertensive emergencies

Arterial vasodilators	Hydralazine, fenoldopam, nicardipine, clevidipine, and enalaprilat
Venous vasodilators	Nitroglycerin
Mixed venous and arterial vasodilators	Sodium nitroprusside
Negative inotropic/chronotropic agents with vasodilator properties	Labetalol
Negative inotropic/chronotropic agents without vasodilator properties	Esmolol
α -adrenergic receptor blockers (for increased sympathetic activity)	Phentolamine

Based on information from: Awad AS, Goldberg ME. Role of clevidipine butyrate in the treatment of acute hypertension in the critical care setting: a review. *Vasc Health Risk Manag.* 2010 Aug 9;6:457-64.

Table 2 Antihypertensive agents for hypertensive emergencies: based on the organ damage present

Acute pulmonary edema/systolic dysfunction	Nicardipine/fenoldopam/nitroprusside + nitroglycerin + loop diuretic
Acute pulmonary edema/diastolic dysfunction	Esmolol/labetalol/metoprolol/verapamil + low-dose nitroglycerin + loop diuretic
Hypertensive encephalopathy	Labetalol/nicardipine/fenoldopam
Acute myocardial ischemia	Labetalol/esmolol + nitroglycerin
Acute aortic dissection	Labetalol/nicardipine + esmolol/nitroprusside + esmolol or IV metoprolol
Pre-eclampsia/eclampsia	Hydralazine/labetalol/nicardipine
Acute ischemic stroke	Nicardipine/labetalol/fenoldopam
Acute renal failure	Labetalol/nitroprusside/nicardipine/urapidil/fenoldopam

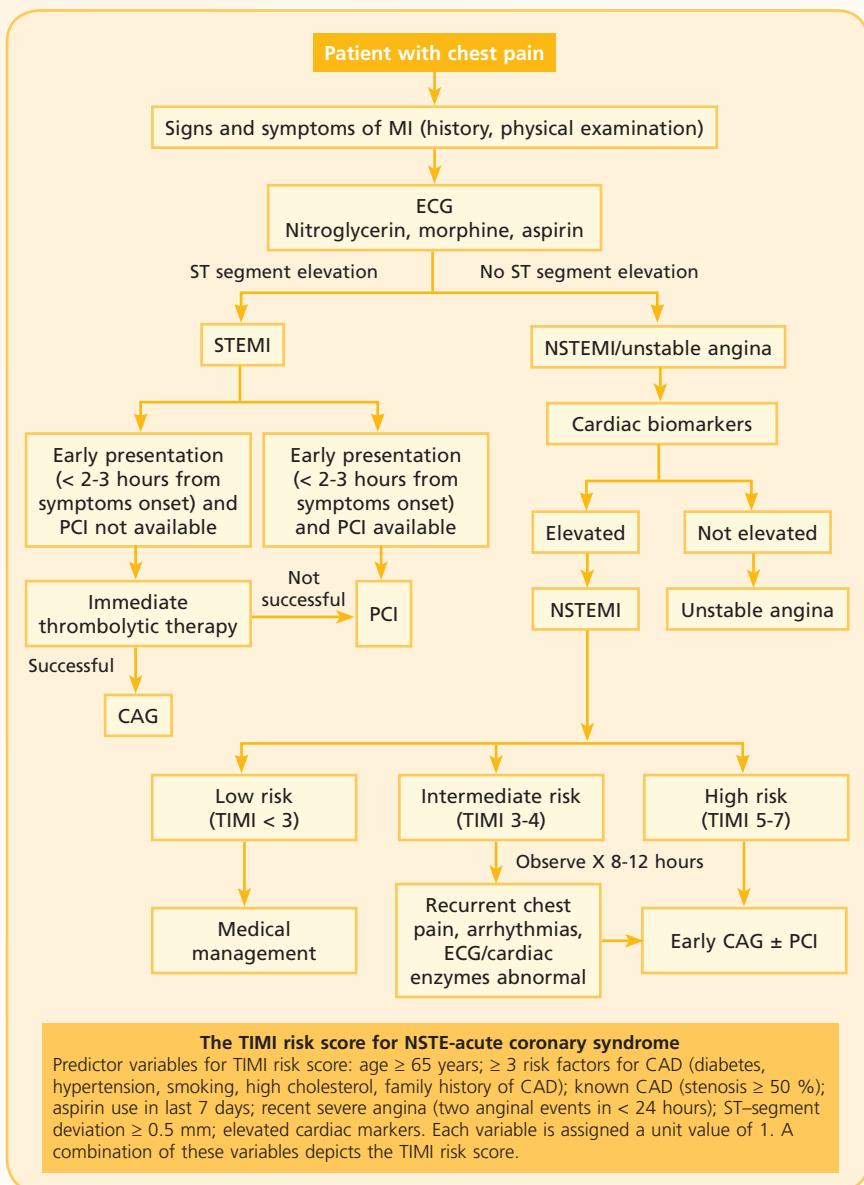
Abbreviation: IV, intravenous

Based on information from:

1. Marik PE, Varon J. Hypertensive Crises. Challenges and Management. *CHEST* 2007;131:1949–1962.
2. Van den Born BJH, Beutler JJ, Gaillard CAJM, et al. Dutch guideline for the management of hypertensive crisis – 2010 revision. *The Journal of Medicine*; 2011;69(5):248-255.

ALGORITHMS

Algorithm 1 Management algorithm for myocardial infarction



Continued on next page ...

Contraindications to thrombolytic therapy

Absolute contraindications	Relative contraindications
<ul style="list-style-type: none"> Prior intracranial hemorrhage Structural cerebral vascular lesion Ischemic stroke in past 3 months (except acute ischemic stroke in past 3 hours) Malignant intracranial neoplasm Suspected aortic dissection Active bleeding (except menses) or bleeding diathesis Significant closed head or facial trauma in last 3 months 	<ul style="list-style-type: none"> History of chronic, severe, poorly controlled hypertension Systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg on presentation History of ischemic stroke in past 3 months Dementia or known intracranial pathology Traumatic or prolonged resuscitation (>10 minutes) Major surgery in past 3 weeks Noncompressible vascular punctures Internal bleeding in past 2-4 weeks Prior allergic reaction or prior exposure (> 5 days ago) to streptokinase or anistreplase Pregnancy Active peptic ulcer Current use of anticoagulants [higher international normalized ratio (INR) correlates with higher risk of bleeding]

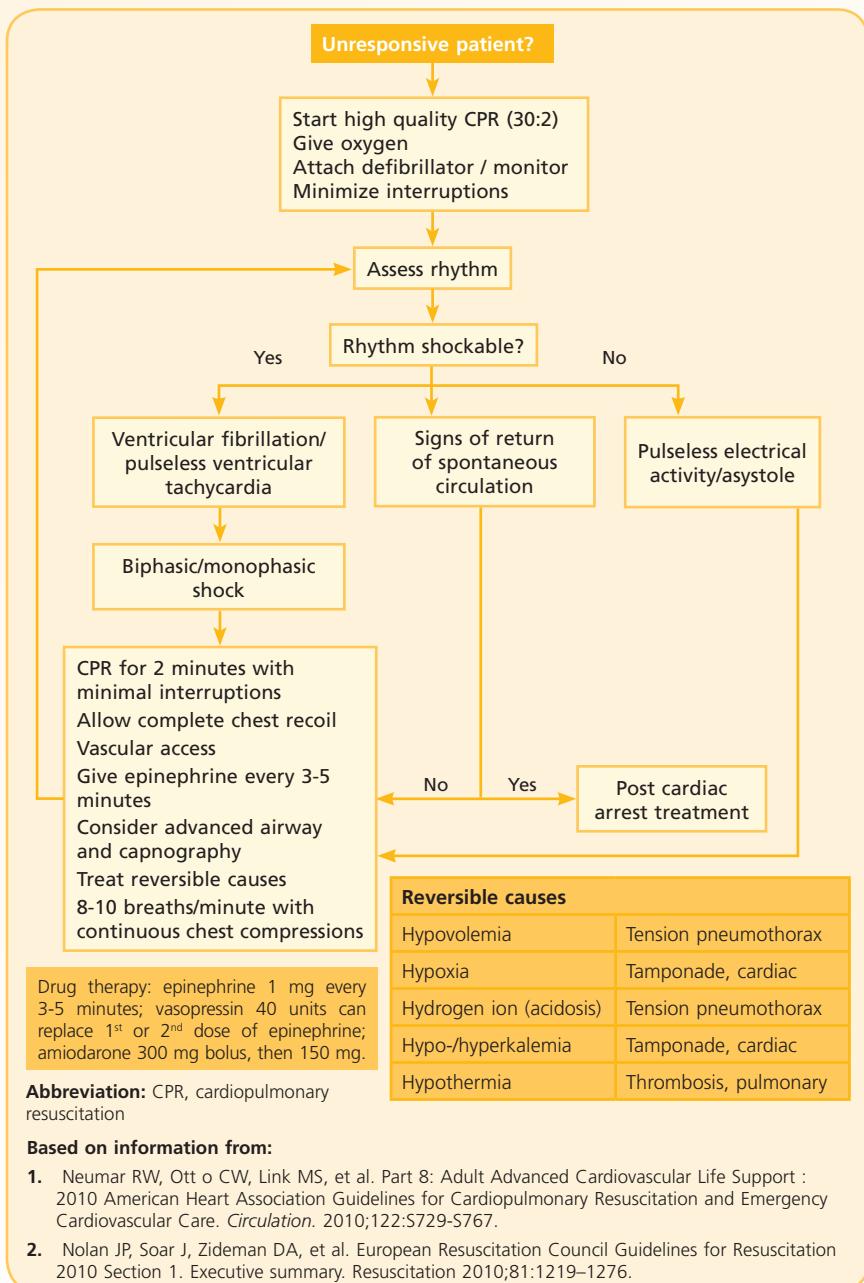
Abbreviations: MI, myocardial infarction; ECG, electrocardiogram; STEMI, ST-elevation MI; NSTEMI, non ST-elevation MI; PCI, percutaneous coronary intervention; CAG, coronary angiography; CAD, coronary artery disease; TIMI, thrombolysis in MI

Based on information from:

- Campbell-scherer DL, Green LA. ACC/AHA Guideline Update for the Management of ST-Segment Elevation Myocardial Infarction. *Am Fam Physician*. 2009;79(12):1080-1086.
- The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *European Heart Journal*. 2012;33:2569–2619.
- O'Connor RE, Brady W, Brooks SC, et al. Part 10: Acute Coronary Syndromes: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122:S787-S817.

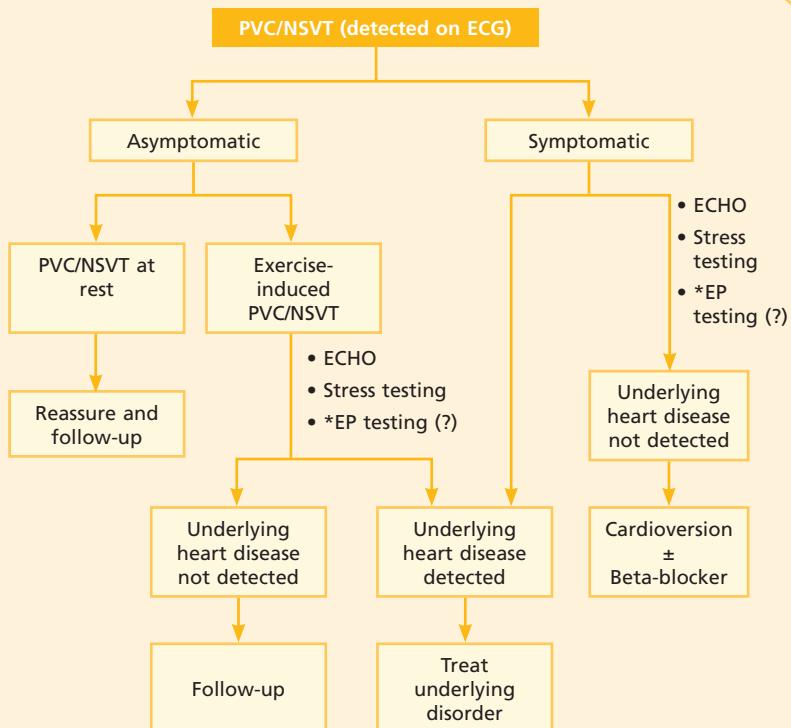
ALGORITHMS

Algorithm 2 Algorithm for cardiopulmonary resuscitation



Algorithm 3

Management approach in patients with premature ventricular complex or non-sustained ventricular tachyarrhythmias



*EP = electrophysiological testing (required in some patients)

Abbreviations: PVC, premature ventricular complex; NSVT, non-sustained ventricular tachyarrhythmias; ECG, electrocardiogram

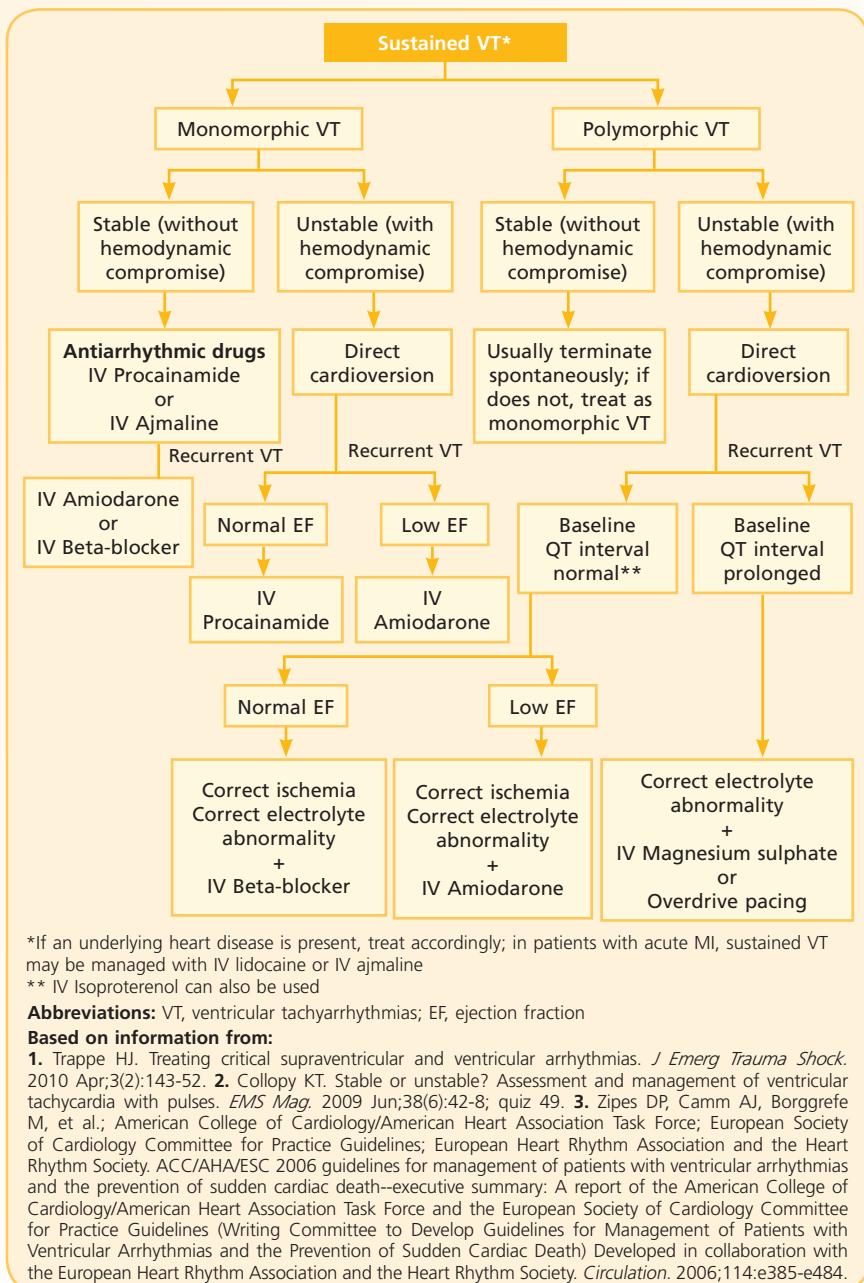
Based on information from:

1. Sheldon SH, Gard JJ, Asirvatham SJ. Premature Ventricular Contractions and Non-sustained Ventricular Tachycardia: Association with Sudden Cardiac Death, Risk Stratification, and Management Strategies. *Indian Pacing Electrophysiol J.* 2010 Aug;10(8):357-71.
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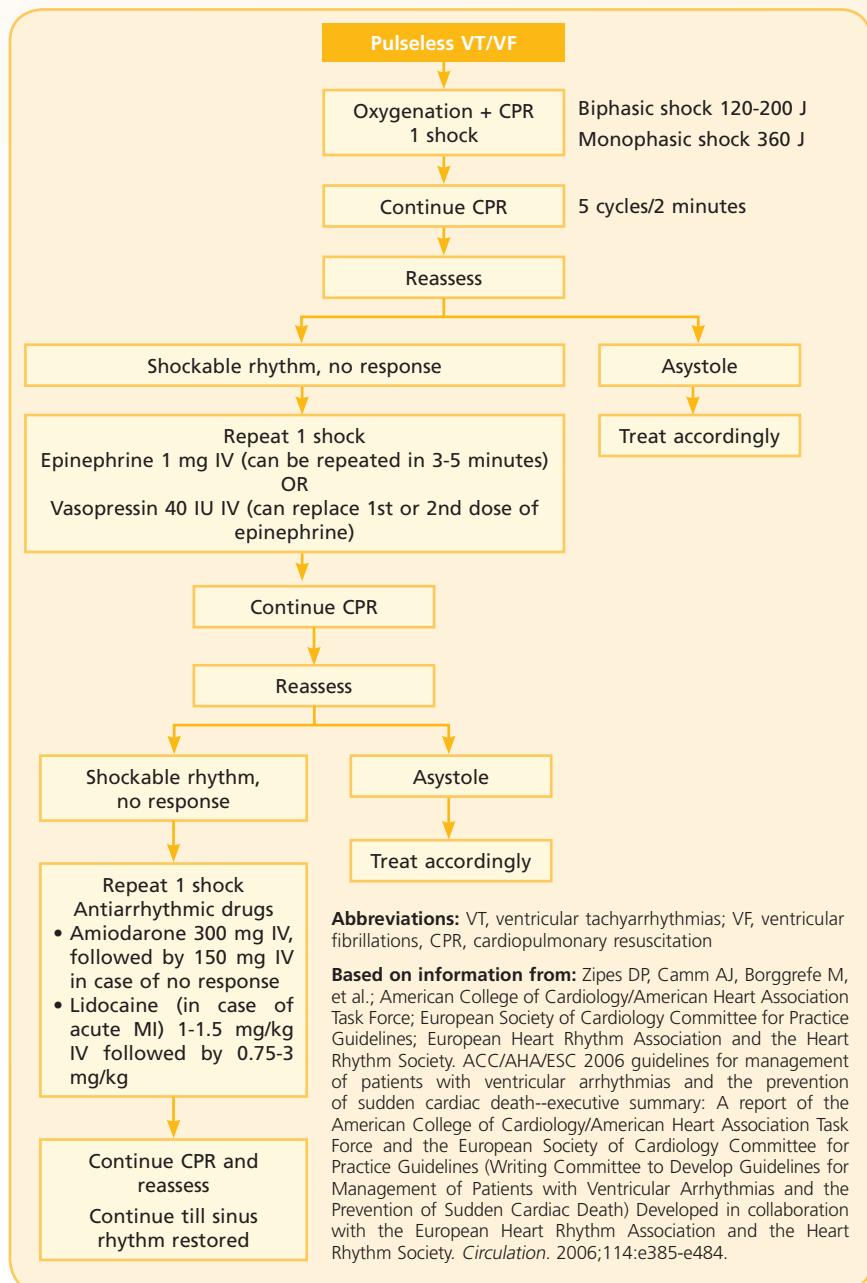
Algorithm 4

Management approach in patients with sustained ventricular tachyarrhythmias



Algorithm 5

Emergency management approach in patients with pulseless ventricular tachyarrhythmias/ventricular fibrillations



ALGORITHMS

Algorithm 6

Diagnostic and management approach in high-risk patients for reducing risk of sudden cardiac death

Patients with ischemic or non-ischemic cardiomyopathy having a low ejection fraction ($EF \leq 35\%$)

- First step is to see if ICD is indicated for secondary prevention of SCD; ideal candidates would be:
 - » Patients who had an unexplained syncope
 - » Cardiac arrest survivors from VT/VF
 - » Patients who had unstable sustained VT
 - » Patients who survive cardiac arrest due to rare arrhythmogenic cardiac disorders, such as long QT syndrome, hypertrophic cardiomyopathy and Brugada syndrome
- Also see if ICD is contraindicated; these candidates include:
 - » Patients with NYHA class IV heart failure
 - » Patients suffering from diseases associated with < 1 year of survival
 - » Patients with cardiogenic shock or hypotension
- In patients who are not ideal candidates for secondary prevention with ICD and in whom ICD is NOT contraindicated, go to the next box

In these patients evaluate for class of heart failure (NYHA I-IV) and also note for presence or absence of previous MI episode or if PCI/CABG has been recently performed; now identify candidates who require ICD for primary prevention

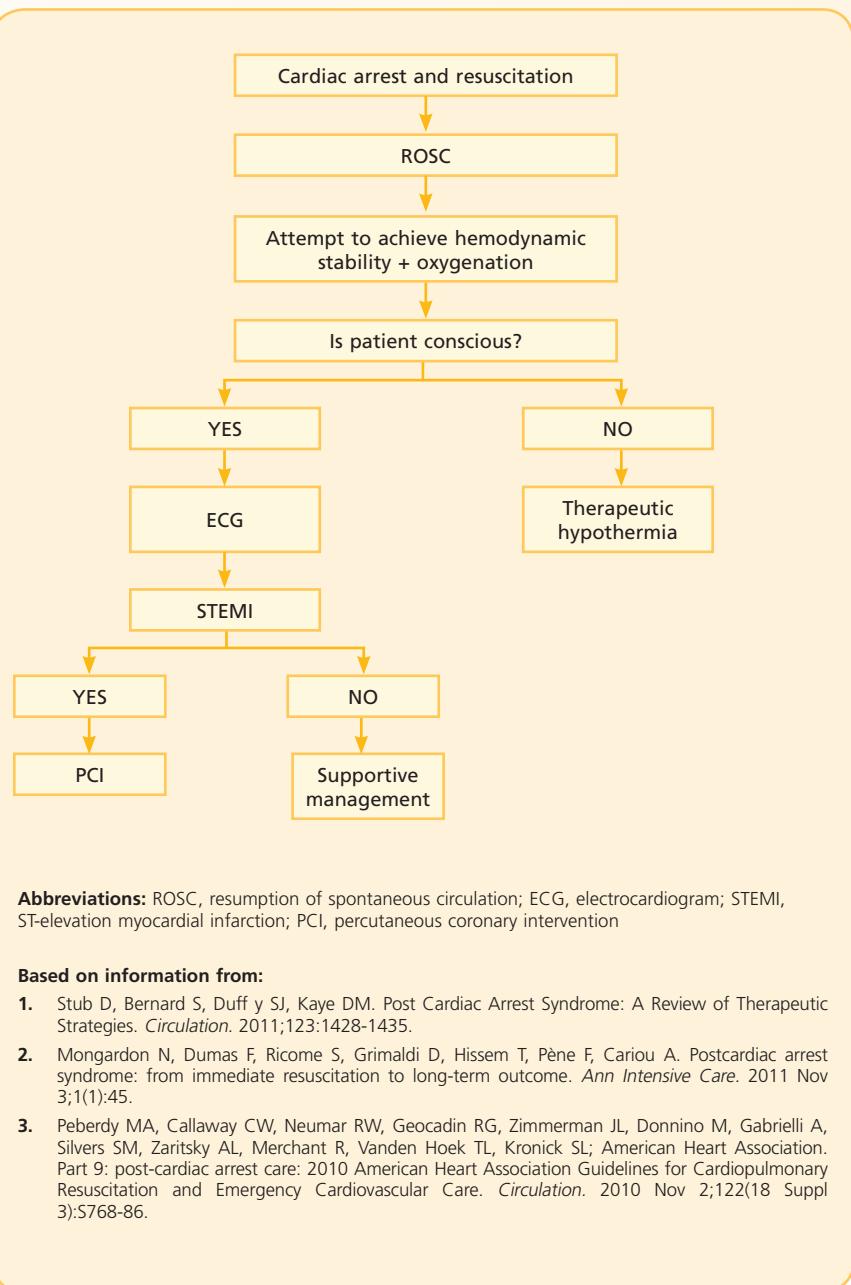
Patients who should receive ICD for primary prevention

- Patients who had MI episode ≥ 40 days back and are having $EF \leq 30\%$ with NYHA class I heart failure
- Patients in whom PCI/CABG was performed > 3 months back and are having $EF \leq 30\%$ with NYHA class I heart failure
- Patients who had MI episode within 40 days or in whom PCI/CABG was performed within previous 3 months, and these patients continue to have low EF and are in NYHA class I heart failure → medical management followed by reevaluation → EF remains $\leq 30\%$ (or $\leq 35\%$ with NYHA class II or III heart failure)
- Patients with ischemic and non-ischemic cardiomyopathy with low EF and who are having $EF \leq 35\%$ despite receiving optimal medical therapy for minimum 3 months
- Patients in advanced heart failure (NYHA class III and IV) with low EF and having $QRS \geq 120$ msec, cardiac resynchronization with defibrillation should be done (with or without ICD)

Abbreviations: SCD, sudden cardiac death; EF, ejection fraction; ICD, implantable cardioverter-defibrillator; VT, ventricular tachyarrhythmias; VF, ventricular fibrillation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; MI, myocardial infarction

Based on information from:

1. Herzog E, Aziz EF, Kukin M, Steinberg JS, Mittal S. Novel pathway for sudden cardiac death prevention. *Crit Pathw Cardiol.* 2009; 8:1–6.
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Algorithm 7**Practical diagnostic and management approach to post-cardiac arrest syndrome**

Abbreviations: ROSC, resumption of spontaneous circulation; ECG, electrocardiogram; STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention

Based on information from:

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2. Mongardon N, Dumas F, Ricome S, Grimaldi D, Hissem T, Pène F, Cariou A. Postcardiac arrest syndrome: from immediate resuscitation to long-term outcome. *Ann Intensive Care*. 2011 Nov 3;1(1):45.
3. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, Gabrielli A, Silvers SM, Zaritsky AL, Merchant R, Vanden Hoek TL, Kronick SL; American Heart Association. Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010 Nov 2;122(18 Suppl 3):S768-86.

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1. Redon et al. *Bld Press.* 2013, Dec; 22 (6); 377-85; # ORG May MAT'15.
2. Sværre Kjeldsen et al. *Expert Rev. Cardiovasc. Ther.* 11(6), 673-682 (2013)

* As compared to Chlorthalidone



Abbreviated Prescribing Information: Telma H

Active Ingredients: Telma H 40/12.5 and 80/12.5 mg - Each uncoated tablet contains: Telmisartan 40 mg or 80 mg and hydrochlorothiazide 12.5 mg. **Indication:** For the treatment of essential hypertension. Telma H can be used as initial therapy in patients likely to need multiple antihypertensive agents. **Dosage and Administration:** Patient with no adequate control of blood pressure either with telmisartan or hydrochlorothiazide monotherapy can be shifted to Telma-H. Dosages need to be individualized. **Contraindications:** Known hypersensitivity to either telmisartan or hydrochlorothiazide or other sulfonamide derivative products, patients with anuria, pregnant and lactating females. **Warning and Precautions:** Caution required in hepatic impairment, and in volume depleted patients. **Use in Pregnancy & Lactation:** For telmisartan pregnancy category is C for first trimester and D for second and third trimester. Excretion in human milk is unknown. With hydrochlorothiazide, there is risk of fetal and neonatal jaundice, and thrombocytopenia. Telma H should be discontinued immediately if the patient becomes pregnant. **Adverse Drug reactions:** Back pain, diarrhea, and upper respiratory tract infection, fatigue, dizziness, nausea. Cough - Incidence of cough with telmisartan is lower as compared to ACE inhibitors and was similar to placebo in placebo controlled trials.

ABPI Ref.: Telma H /03-Feb-2016



For further product related query, contact at
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For any Adverse Event or Product Quality Complaint related to Glenmark marketed products, contact on ae@glenmarkpharma.com



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