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ADVERSE DRUG REACTIONS ASSOCIATED WITH DRUGS USED IN THE TREATMENT OF CARDIOVASCULAR SYSTEM

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ABSTRACTS:

Adverse drug reactions (ADRs) occur frequently in modern medical practice, increasing morbidity and mortality and inflating the cost of care. Patients with cardiovascular disease are particularly vulnerable to ADRs due to their advanced age, polypharmacy, and the influence of heart disease on drug metabolism. The ADR potential for a particular cardiovascular drug varies with the individual, the disease being treated, and the extent of exposure to other drugs. Knowledge of this complex interplay between patient, drug, and disease is a critical component of safe and effective cardiovascular disease management. The majority of significant ADRs involving cardiovascular drugs are predictable and therefore preventable. Better patient education, avoidance of polypharmacy, and clear communication between physicians, pharmacists, and patients, particularly during the transition between the inpatient to outpatient settings, can substantially reduce ADR risk.

Keywords: Adverse drug effects, Cardiovascular Disease, Drug , Metabolism

INTRODUCTION

Adverse drug reactions are unintended and undesired effects of drugs used for prevention, diagnosis, or treatment of disease.In light of the ever-increasing number of medications available, it should come as no surprise that such reactions are extremely common. The incidence statistics vary considerably depending upon the method by which the data are derived and the nature of the population under study.Estimates, however, range from 2% to 7% of hospital inpatients. Although most reactions are mild, they are sometimes severe and a source of considerable morbidity and occasional [1,2,3]

Adverse drug reactions (ADRs) may be more frequent in patients who present some diseases. By means of an intensive prospective drug surveillance work, 492 patients with heart diseases, hospitalized at the Department of Medicine of the Clinical Hospital of the University of Chile,

were studied in order to determine the frequency and characteristics of ADRs. ADRs were significantly more frequent in patients with heart failure (HF) (30.0%) than in those without HF (22.7%)(p less than 0.05). Patients presenting HF developed more metabolic disturbances than patients not presenting HF (p less than 0.001). Furosemide was the most frequently used drug in both groups, but treatment with it was longer in patients with HF who presented a significantly higher frequency of adverse reactions to this diuretic (p less than 0.05). 89.9% of ADRs in patients without HF and 93.8% of ADRs in those with HF, were dose-related effects. Analyses of some predisposing factors to ADRs, such as age, number of drugs administered, duration of hospitalization, ADR or allergy histories and presence of a renal failure, did not explain differences found between ADRs in patientswithout and with HF. These findings suggest that heart failure may be a determinant of frequency and characteristics of ADRs [4,5,6].

The diagnosis of an adverse drug reaction is frequently problematical, the clinical appearances often being similar, if not identical, to a number of primary dermatoses and infectious conditions (particularly viral exanthems) and, in the context of transplantation patients, graft-versus-host disease (GVHD). The histologic diagnosis can also be extremely difficult, as drug reactions can demonstrate several inflammatory histologic patterns that mimic other dermatoses (i.e., spongiotic, psoriasiform, lichenoid, pityriasiform).10 The problem is exacerbated in the immunologically compromised patient. Frequently, the diagnostic difficulties are worsened by the multitude of drugs prescribed. The problem is further compounded by the multiplicity of different eruptions that any one particular drug may induce. Contrariwise, a given clinical appearance may be caused by a large number ofunrelated drug [7,8,9].

The prevalence of agents responsible for adverse drug reactions reflects the prescribing tendencies for any given population as much as the relative risks ascribed to any particular drug. It should come as no surprise, therefore, that – in a hospital environment – antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and psychotropic drugs are commonly reported as being the most frequently incriminated.Oral anticoagulants, low-dose aspirin, and digoxin are also frequent causes. In a large hospital survey, penicillin and sulfonamides accounted for over 80% of all adverse drug reactions. Experience in general practice has been much less often documented. In a survey from the Netherlands, sulfonamide- trimethoprim combinations, fluoroquinolones, and penicillin were the most common antibacterials causing drug-related eruptions.In the series of approximately 150 000 patients, 1% developed a reaction.

Adverse drug reactions are mostly no immunologically mediated. They develop either as a result of an unwanted but known property of the drug (and hence are entirely predictable) or as a consequence of drug intolerance/idiosyncrasy (and are completely unpredictable). The former are by far the more common, accounting for approximately 80% of all adverse drug reactions. Less often, adverse drug reactions represent a manifestation of an immunological phenomenon, so-called allergic drug reactions. Although in theory the above subdivisions are sharply defined, in many patients the underlying pathogenetic mechanisms are far from clear [10,11,12].

Cardiovascular diseases are prevalent in developing countries like India. Patients with cardiovascular diseases are prescribed multiple drugs, hence polypharmacy may attribute to higher incidence of adverse drug reactions in these patients. To monitor and to analyze the pattern of occurrence of adverse drug reactions reported with cardiovascular drugs in intensive cardiac care unit of a tertiary care hospital, Chennai. This was a prospective surveillance study carried out for a period of 6 months. Analysis of various adverse drug reactions reported were done using various assessment scales. Descriptive statistics was used and values were expressed in numbers and percentage. During the study period, 282 adverse reactions were reported from 389 patientsat includes 232 males and 157 females. The average age of the patients included in this study was 58.1± 16.8 years . The most common ADRs observed were electrolyte imbalance (14.89%), headache (13.12%) and gastritis (12.41%). Assessment using WHO Causality assessment scale revealed 60.28% were possible, 18.43% probable, 12.76% certain and 8.51% unlikely. According to Schumock and Thornton scale 65.9% of ADRs were preventable and 34% non preventable. Analysis with Hartwig and Seigel's scale 62.05% of ADRs were moderate in severity, 27.95% mild and 10.99% severe. Drugs attributing to highest ADRs were Digoxin and Furosemide. The common ADRs due to cardiovascular drugs can be reduced by improvingthe prescription pattern. Intense monitoring and reporting of ADRs could help in minimizing the preventable ADRs, among the health care professionals [13,14].

Adverse drug reactions (ADR) are far more commonplace than one would think. It is estimated that ADRs represent the fourth leading cause of death in the United States and Canada behind heart disease, cancer, and stroke. Further, it is estimated that ADRs are the sixth leading cause of death worldwide. Recent meta-analysis of prospective ADR studies estimates that over 180,000 Americans will die from ADRs and over one million will be injured from ADRs in 2008. Although these data are controversial and the actual incidenceof ADRs is impossible to assess, there is no doubt that ADRs have a significant impact onboth the healthcare delivery and the drug development industries. The monetary costs to society due to these ADRs are equally hard to assess accurately, but recent studies have estimated the costs to range from $75 to $180 billion each year for adults alone. When compared to the costs of treating diseases such as diabetes ($45 billion), cardiovascular disease ($120–150 billion), or cancer ($130–195 billion) we begin to truly realize the impact of this aspect of pharmacology on healthcare delivery. Yet another way to demonstrate the impact of ADRs is to realize that approximately 5% of all hospital admissions are a direct result of ADRs, and unfortunately incidence has not changed over the past 30 years. If ADRs are such a drain on our healthcare delivery system, what are ADRs? The World Health Organization has put forth the definition of ADR as “any response to a drug which is noxious and unintended, and which occurs at doses used in manfor prophylaxis, diagnosis or treatment.” In other words, an ADR could be an unexpected or unwanted effect that is a direct extension of the mechanism of drug action; in an organ system that is not the target of drug therapy; an allergic response; a hypersensitive response;an idiosyncratic response (one totally unpredictable); or a drug interaction with unexpectedresults. In each case the ADR represents an unwanted toxic effect as a result of taking a given drug or set of drugs. The purpose of this chapter is discuss in detail the various types of ADRs using specific examples to demonstrate the types of ADRs that can be encounteredwhen drugs are administered as well as factors that may affect the incidence or severity ofa given ADR [15,16].

CLASSIFICATION OF ADVERSE DRUG REACTIONS

Adverse drug reactions are classified into six types (with mnemonics): dose-related (Augmented), non-dose-related (Bizarre), dose-related and time-related (Chronic), time- related (Delayed), withdrawal (End of use), and failure of therapy (Failure).07-Oct-2000

An adverse drug reaction (ADR) is a harmful, unintended result caused by taking medication. ADRs may occur following a single dose or prolonged administration of a drug or result from the combination of two or more drugs. The meaning of this term differs from the term "side effect" because side effects can be beneficial as well as detrimental. The study of ADRs is the concern of the field known as pharmacovigilance. An adverse drug event (ADE) refers to any unexpected and inappropriate occurrence at thetime a drug is used, whether or not associated with the administration of the drug. An ADRis a special type of ADE in which a causative relationship can be shown. ADRs are only one type of medication-related harm, as harm can also be caused by omitting to take indicated medications.[17]

Types of ADRs……..

Type	Type of effect	characteristics	example
A	Augmented	Dose dependent predicted from the known pharmacology of the drug	Hypoglycaemia-insulin
B	Bizarre	Unpredictable Dose independent Rare,fatal	Anaphylaxis to penicillin
C	Chronic	Prolong treatment	Analgesic neuropathy
D	Delayed	After years of treatment	Antipsycotic –turdive dyskinesia
E	End of use	Withdrawal effect	GC withdrawal→ adrenocortical

Basics of adverse drug reactions

An adverse drug reaction (ADR) can be defined as 'an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product. Since 2012, the definition has included reactions occurring as a result of error, misuse or abuse, and to suspected reactions to medicines that are unlicensed or being used off-label in addition to the authorised use of a medicinal product in normal doses. While this change potentially alters the reporting and surveillance carried out by manufactures and medicinesregulators, in clinical practice it should not affect our approach to managing ADRs.

Seminal research undertaken in the late 20th and early 21st century in the USA and the UK demonstrated that ADRs are a common manifestation in clinical practice, including as a cause of unscheduled hospital admissions, occurring during hospital admission and manifesting after discharge. The incidence of ADRs has remained relatively unchanged over time, with research suggesting that between 5% and 10% of patients may suffer from an ADR at admission, during admission or at discharge, despite various preventative efforts. Inevitably, the event frequency is associated with the method used to identify such events and the majority of ADRs do not cause

serious systemic manifestations. Nevertheless, this frequency of potential harm needs to be considered carefully because it has associated morbidity and mortality, can be financially costly and has a potentially negative effect on the prescriber-patient relationship.

Medicines that have been particularly implicated in ADR-related hospital admissions include antiplatelets, anticoagulants, cytotoxics, immunosuppressants, diuretics, antidiabetics and antibiotics. Fatal ADRs, when they occur, are often attributable tohaemorrhage, the most common suspected cause being an antithrombotic/anticoagulant co-administered with a non-steroidal anti-inflammatory drug (NSAID) [18,19,20].

Methodology for detection and classification of ADR

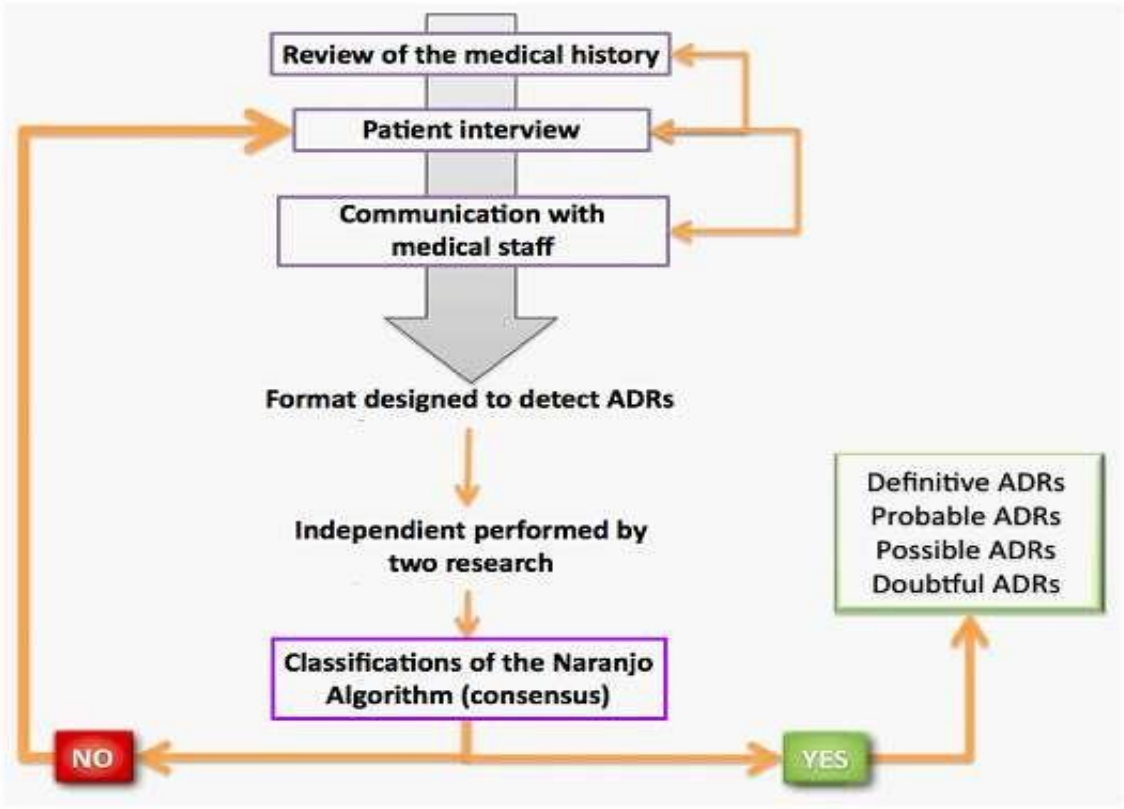


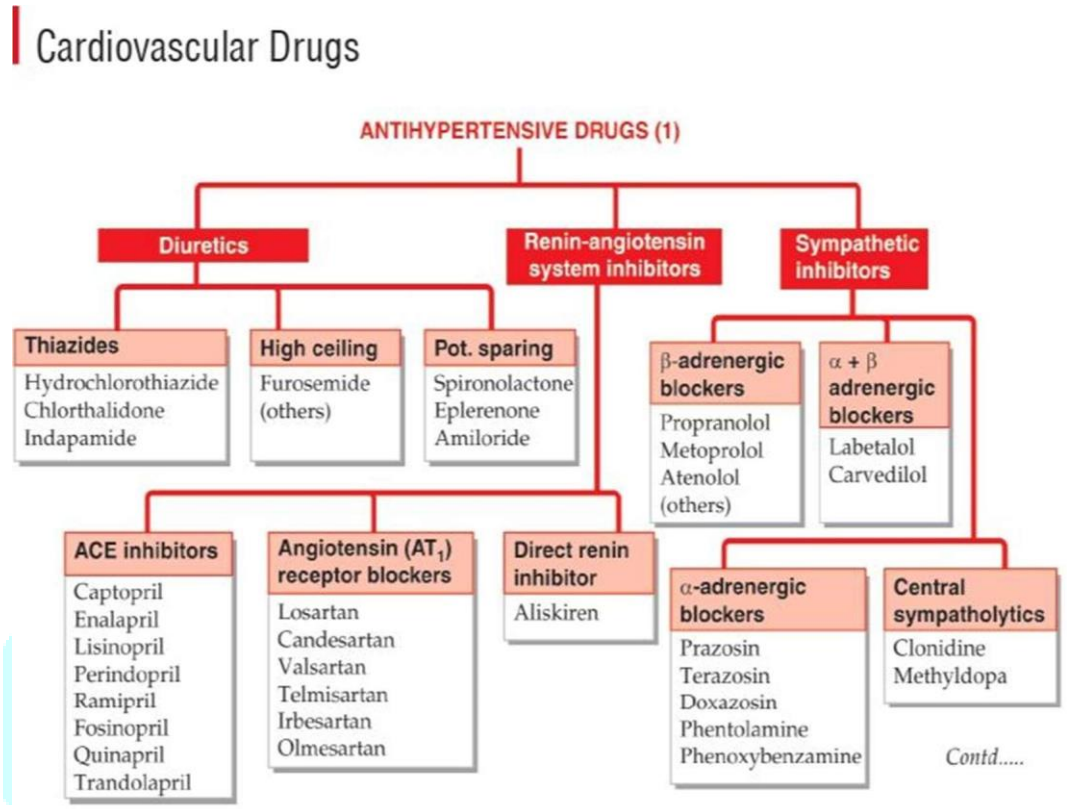
Figure 1. Methodology for detection and classification of ADRs

CLASSIFICATION OF ANTI HYPERTENSIVE DRUG

The four major classes of antihypertensive drugs—diuretics, β-blockers, calcium channel blockers, and renin-angiotensin system inhibitors (including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers)—have significant qualitative and quantitative differences in the adverse effects they cause.

Antihypertensives are a class of drugs that are used to treat hypertension (high blood pressure). Antihypertensive therapy seeks to prevent the complications of high blood pressure, such as stroke and myocardial infarction. Evidence suggests that reduction of theblood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischaemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease. There are many classes of antihypertensives, which lower blood pressure by different means. Among the most important and

most widely used medications are thiazide diuretics, calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists (ARBs), and beta blockers.



CLASSIFICATION OF ANTIARRHYTHMIC DRUGS

Antiarrhythmic agents, also known as cardiac dysrhythmia medications, are a group of pharmaceuticals that are used to suppress abnormal rhythms of the heart (cardiac arrhythmias), such as atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation.

Many attempts have been made to classify antiarrhythmic agents. The problem arises fromthe fact that many of the antiarrhythmic agents have multiple modes of action, making any classification imprecise.

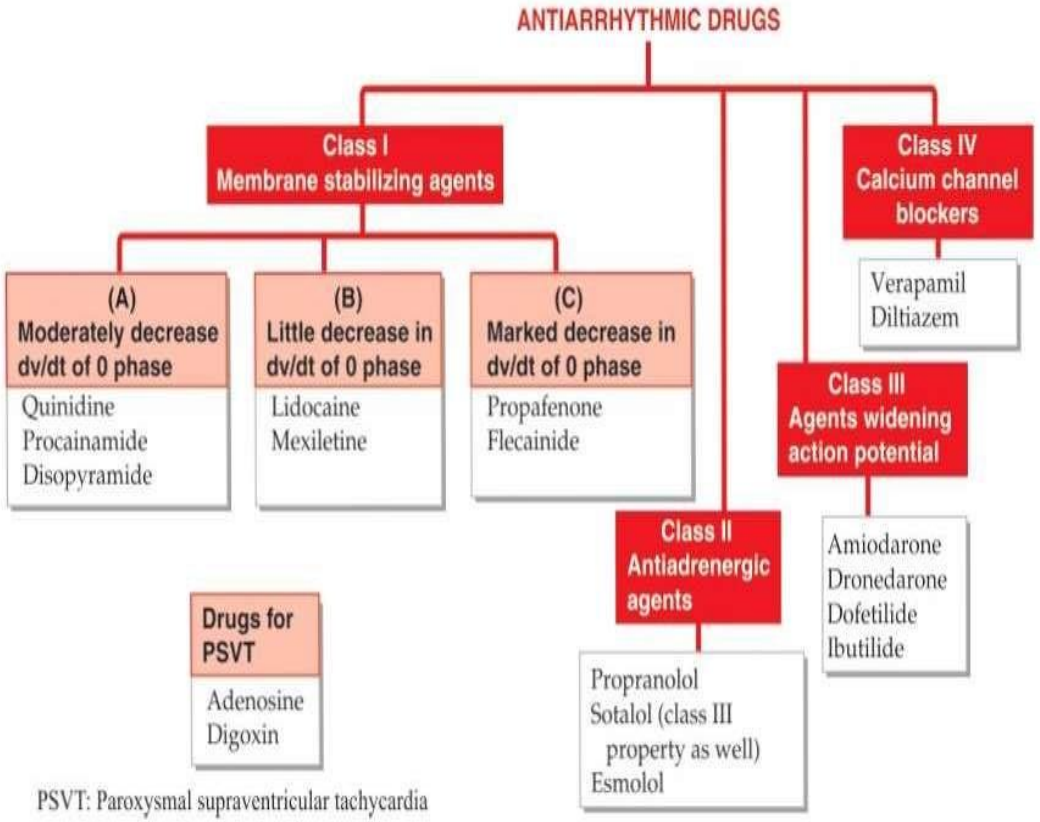
The Vaughan Williams classification was introduced in 1970 by Miles Vaughan Williams.

Vaughan Williams was a pharmacology tutor at Hertford College, Oxford. One of his students, Bramah N. Singh, contributed to the development of the classification system. The system is therefore sometimes known as the Singh-Vaughan Williams classification.

The five main classes in the Vaughan Williams classification of antiarrhythmic agents are:

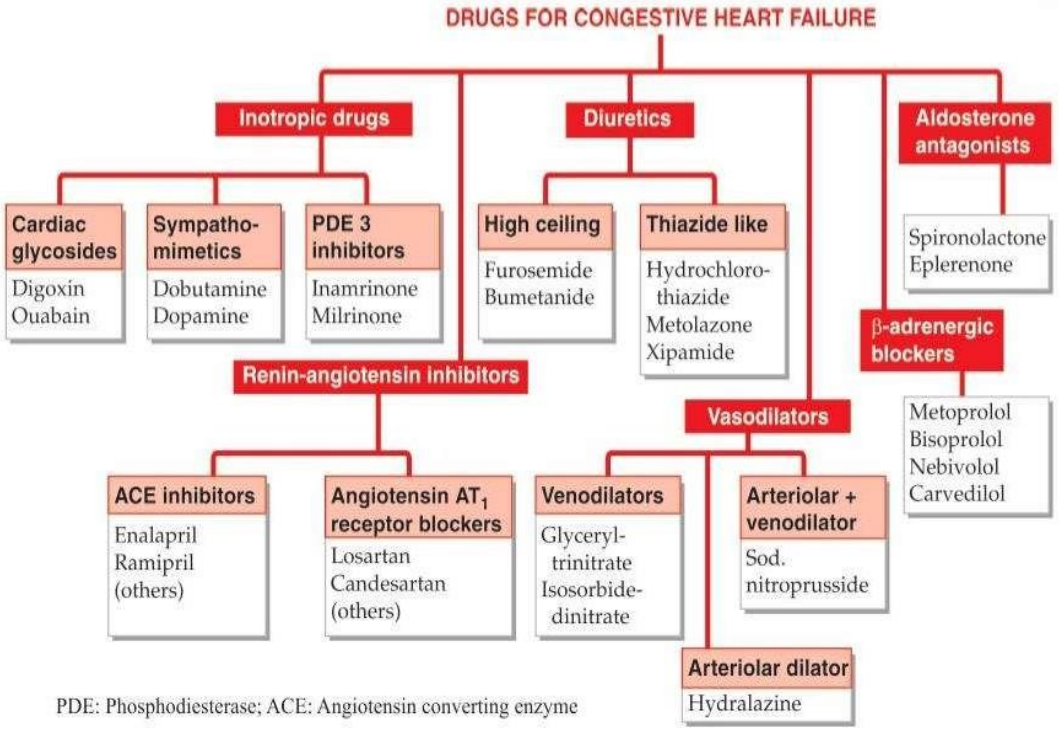
- **Class I** agents interfere with the sodium (Na+) channel.
- **Class II** agents are anti-sympathetic nervous system agents. Most agents in thisclass are beta blockers.
- **Class III** agents affect potassium (K^+) efflux.

- **Class IV** agents affect calcium channels and the AV node.
- **Class V** agents work by other or unknown mechanisms.



CLASSIFICATION OF CONGESTIVE HEART FAILURE DRUGS

The various classes of pharmacological agents that are currently used for patients suffering from CHF include angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), aldosterone antagonists, beta-blockers, calcium channel blockers (CCBs), digitalis drugs, diuretics, inotropic agents, nitrates, and vasodilators. While these agents are all important therapeutic tools in the treatment of CHF, the prognosis for patientswith CHF remains poor.



MECHANISMS OF ANTIHYPERTENSIVE DRUGS

Centrally-acting antihypertensives decrease blood pressure by diminishing sympathetic outflow from the vasomotor centre. Peripherally-acting antihypertensives act by depletingor inhibiting the release of catecholamines from the peripheral nerve ending or altering theresponse at alpha 1- and alpha 2-receptor sites [21,22].

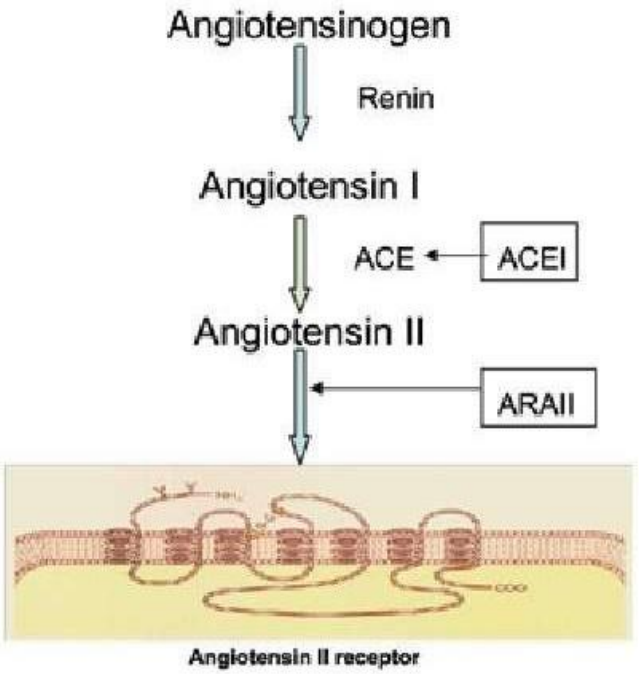


Fig. Mechanisms Of Antihypertensive Drugs

MECHANISMS OF ANTIARRHYTHMIC DRUGS

Antiarrhythmic agents act by blocking the membrane sodium, potassium, and calcium channels, but no agent has exclusive action on a given type of channel. Arrhythmias resulting from reentry form the largest group of clinically significant arrhythmias. Most arrhythmias result from depressed sodium channel function [23,24].

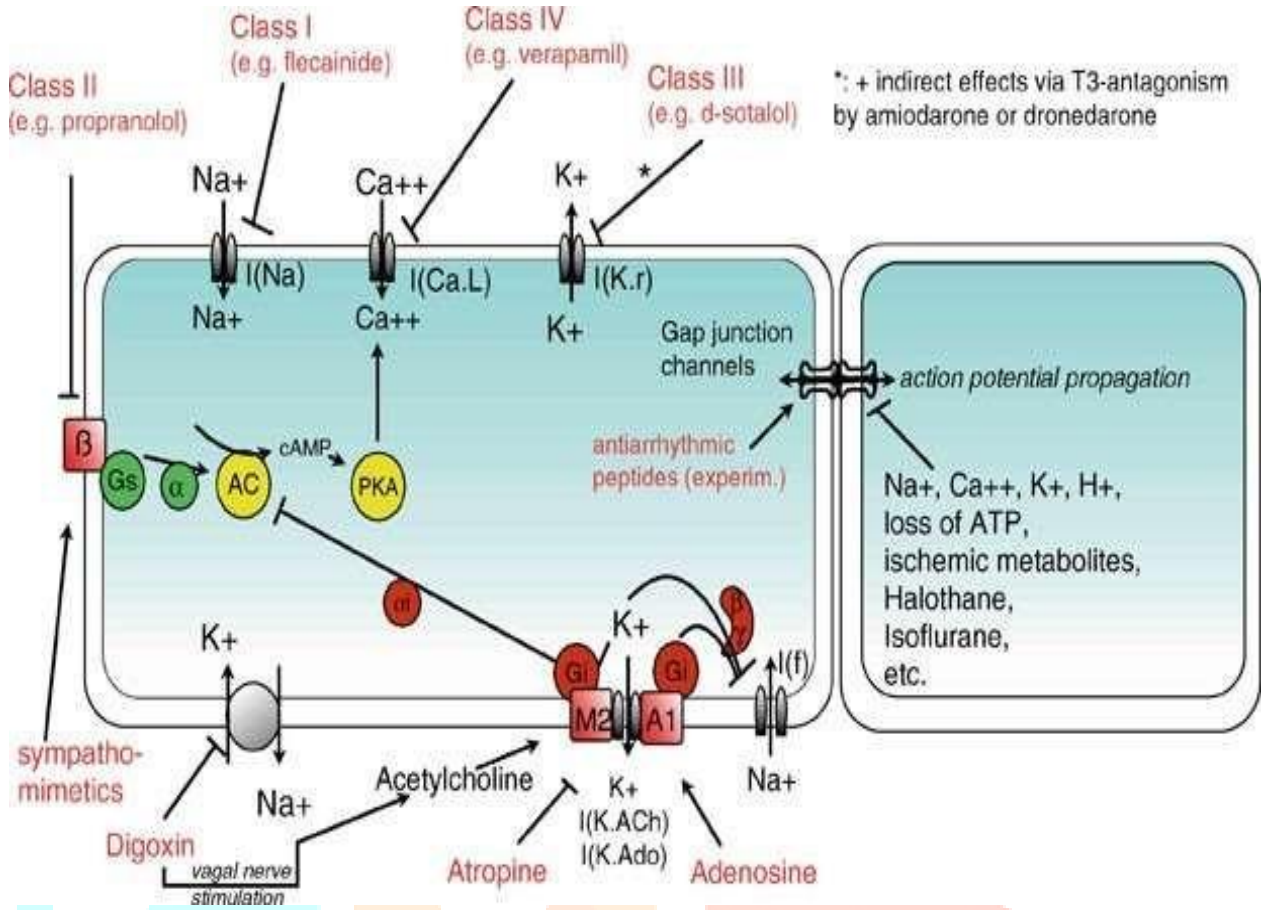


Fig. Mechanisms Of Antiarrhythmic Drugs

MECHANISMS OF CONGESTIVE HEART FAILURE DRUGS

Congestive heart failure is a syndrome that can be caused by a variety of abnormalities, including pressure and volume overload, loss of muscle, primary muscle disease or excessive peripheral demands such as high output failure. In the usual form of heart failure,the heart muscle has reduced contractility [25,26].

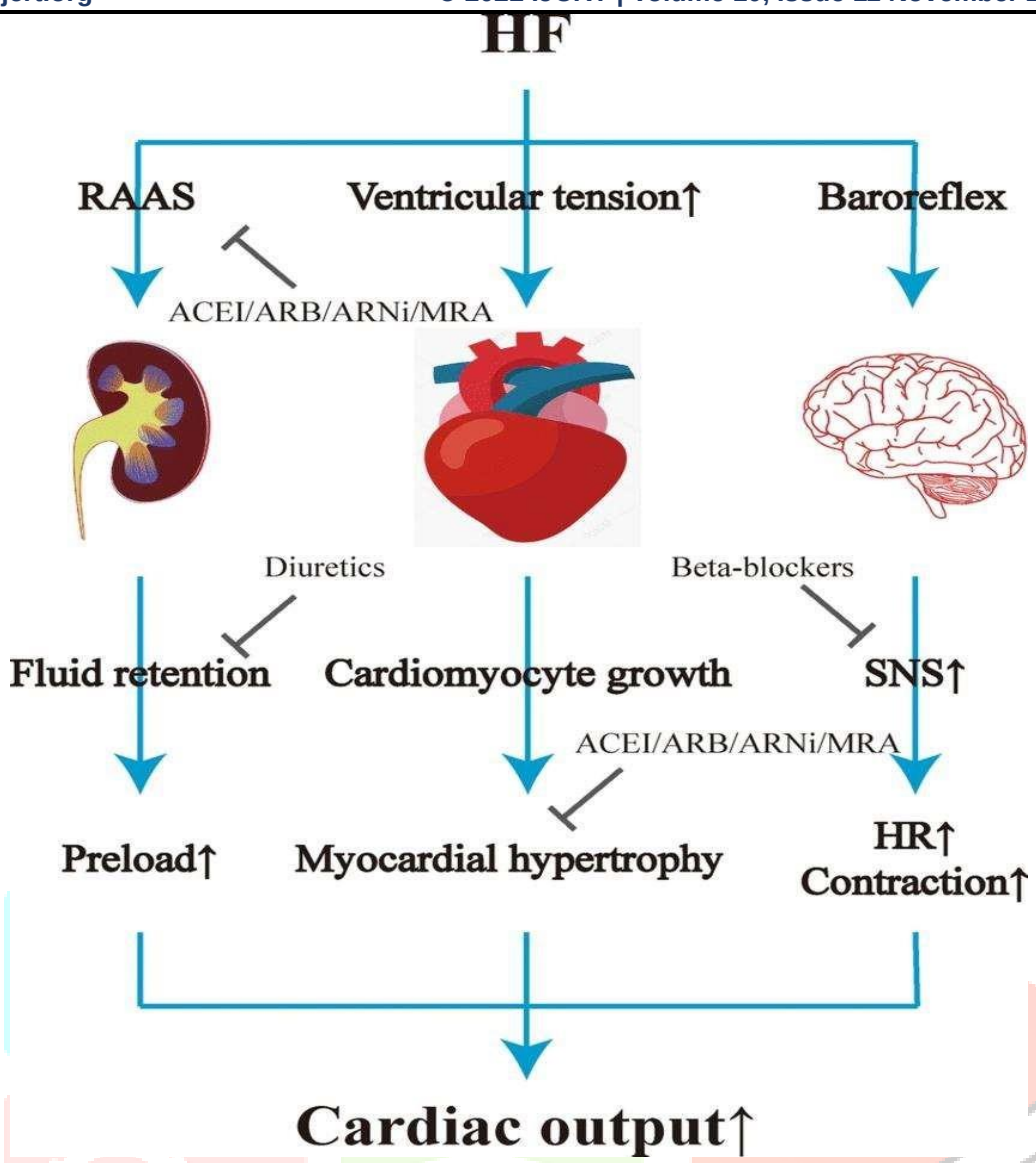


Fig. Mechanisms Of Congestive Heart Failure Drugs

COMMAN DRUGS USED IN CARDIOVASCULAR DISEASE

There are many drugs prescribed for heart disease. It's important for people with heart disease and those who care for them to understand the meds, follow the labels, and recognize possible side effects [26,27,28].

❖ **The ones most people with heart disease are given by their doctor include:**

i. **ACE inhibitors**: These widen arteries to lower your blood pressure and make it easier for your heart to pump blood.

ii. **Aldosterone inhibitors**: Eplerenone (Inspra) and spironolactone (Aldactone) are part of a class of medicine called potassium-sparing diuretics. They can ease the swelling and water buildup heart disease can cause. They help the kidneys send unneeded water and salt from your tissues and blood into your urine to be released.

iii. **Angiotensin II receptor blockers (ARBs):** These are used to lower blood pressure for people with heart failure. They help keep your blood vessels as wide as possible so blood can flow through your body more easily. They also lessen salt and fluid buildup in your body.

iv. **Beta-blockers:** They block the effects of adrenaline (epinephrine). This helps your heart work better. These meds also drop production of harmful substances your body makes in response to heart failure. And they cause your heart to beat slower and with less force. Those both lower your blood pressure.

v. **Calcium channel blockers:** These treat chest pain (your doctor may say "angina")and high blood pressure. They relax blood vessels and increase blood and oxygen to your heart. That eases its workload. They're used only when other medicines to lower blood pressure don't work. Ask your doctor if one is right for you.

vi. **Cholesterol-lowering drugs:** Cholesterol helps your body build new cells, insulatenerves, and make hormones. But inflammation may force cholesterol to build up inthe walls of your arteries. That buildup increases your chance of having a heart attack or stroke.

vii. **Digoxin:** It helps an injured or weakened heart to send blood through the body andwork more efficiently. It strengthens the force of the heart muscle's contractions. Itmay improve blood circulation. You may be prescribed this if you have an irregularheartbeat (your doctor may call this atrial fibrillation, or AFib). It may help slow down your heart rate

viii. **Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors:** You may getthis new class of cholesterol-lowering drugs if diet and statin treatments aren't helping. They block a liver protein called PCSK9. That protein hinders your liver'sability to get rid of LDL (bad) cholesterol

ix. **Vasodilators**: These relax your blood vessels so blood can flow more easily through your body. You'll get these if you can't take ACE inhibitors.

x. **Warfarin**: This helps prevent clots from forming in your blood. You'll get it if yourbody is making blood clots, or if you have a condition that helps cause them.

LATEST DRUGS WIDELY USED IN CARDIOVASCULAR DISORDER

i. **CARDIOVASCULAR DRUG PIPELINE, 2009:** The cardiovascular drug market isseverely impacted by the scarcity of new agents and the loss of patent protection by 2012 for major statins (Lipitor; Pfizer, USA), angiotensin receptor blockers (ARBs) (Diovan; Novartis, Switzerland) and antiplatelet agents (Plavix; Bristol Myers Squibb Sanofi Pharmaceuticals Partnership, USA) (Table 1).

ii. **Upcoming patent expirations for cardiovascular drugs:** The movement to generics is expected to change the complexion of the market. The anticholesterol pipeline is devoid of new agents due to the success of statins. The hypertension market is expectedto slow after the ARBs lose patent protection beginning in 2010. An additional concern is the current United States (US) Food and Drug Administration (FDA) review (1) of studies indicating an association between ARBs and malignancy. The outcome of this review is still uncertain, but may hasten switches to drugs other than ARBs if the findings are determined to be accurate. However, the biggest impact is expected to be in the antiplatelet and antithrombotic market, which is

expected to overtake anticholesterol agents as the sales leader [29].

iii. **NEW APPROVALS, 2009:** The current pipeline has produced two agents marketed in 2009; namely, prasugrel and dronedarone. Prasugrel is an ADP receptor blocker that competes with clopidogrel for maintenance of open arteries following percutaneous coronary intervention (PCI). The target patient populations have acute coronary syndrome (ACS) and PCI, are younger than 75 years of age, weigh more than 60 kg, and have not had a transient ischemic attack or stroke. Dronedarone is a treatment for atrial fibrillation (AF) similar to amiodarone; each will be discussed separately under their respective therapeutic models.

iv. **CURRENT PIPELINE:** The current drug pipeline is focused on two main categories: antidyslipidemic agents and antiplatelet/antithrombotic agents. The American Heart Association estimates that there are 34 million Americans with mixed dyslipidemia. Hence, emphasis has been placed on this category [30,31,32].

The most promising antidyslipidemics are the following:

i. **Certriad (rosuvastatin [Crestor; AstraZeneca, UK] and fenofibric acid [Trilipix; Abbott Laboratories, USA] combination):** The new drug application (NDA) was submitted on June 4, 2009, for management of mixed dyslipidemia. The product is a combination of two marketed agents and was submitted in three dosage combinations
– 5 mg, 10 mg and 20 mg of rosuvastatin combined with fenofibric acid.

ii. **Darapladib (GlaxoSmithKline Inc, UK)**: Darapladib is a lipoprotein-associated phospholipase A2 inhibitor that promotes plaque stabilization by blocking the phospholipase A2 enzyme. The emphasis on targeting plaques versus treating laboratory cholesterol values is hoped to be a major shift in management. The agent began phase III trials in December 2008; the NDA filing will depend on the rate of cardiovascular events observed in the phase III Stabilization of Atherosclerotic Plaqueby Initiation of Darapladib Therapy (STABILITY) trial.

The most promising of the antiplatelet/antithrombotic agents are the following:

i. **Ticagrelor (AZD6140, Brilinta; AstraZeneca):** Ticagrelor is a reversible ADP receptor blocker. The PLATelet inhibition and patient Outcomes (PLATO) phase III trial (5) demonstrated superior effectiveness to clopidogrel (Plavix) for ACS. The bleeding risk was greater than clopidogrel (Plavix), but similar to prasugrel (Effient; Daiichi Sankyo, Japan, and Eli Lilly, USA). The NDA for ticagrelor was submitted in November 2009, and is still pending approval by the FDA.

ii. **SCH530348 (Schering-Plough, USA**): This agent is a thrombin receptor antagonist that is initially being studied as potential treatment for ACS, but is ultimately expected to target secondary prevention. The Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRA*CER) phase III trial (6) is currently being investigated with

a sample size of approximately 31,000 subjects, with an NDA possible in 2010.

iii. **Rivaroxaban (Xarelto; Bayer Schering Pharma AG, Germany)**: Rivaroxaban is on the market in Europe, but has not been approved in the US. It is first in the class of factor Xa inhibitors and is being submitted for prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery. The Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosisand Pulmonary Embolism (RECORD) studies demonstrated superiority of rivaroxabanto enoxaparin (Lovenox; sanofi-aventis, France). A 'complete response' letter was issued by the US FDA in May 2009, but final US approval is not likely until 2010. Dabigatran (Pradaxa; Boehringer Ingelheim, USA): Dabigatran is a direct thrombin inhibitor for treatment of venous thromboembolism (VTE) and prevention of stroke associated with AF. The drug is currently in phase III trials (9) investigating the oral, direct thrombin inhibitor dabigatran etexilate twice daily in the long-term prevention ofrecurrent, symptomatic VTE. Comparisons of dabigatran to warfarin for AF indicated similar to better efficacy and equal to lower bleeding risks. The dearth of new products is not reflective of the many options that are being pursued. While there are no guarantees of product approvals, there are a number of therapeutic models that are of interest. These models will be discussed under each targeted disease category.

MOST COMMON ADVERSE EFFECTS OF DRUGS USED IN TREATMENT OF CARDIOVASCULAR DISORDERS

Heart disease drugs that relax narrow blood vessels might make you dizzy. If that happens when you stand or get out of bed, then sit or lie down for a few minutes. This helps raise your blood pressure. When you're ready, get up more slowly.

- Heavy bleeding during your period
- Red or brown pee
- Tar-like stools
- Bleeding from your gums or nose that doesn't stop right away
- Red things you cough up
- Severe headache or stomachache
- Unusual bruising
- Cuts that won't stop bleeding
- A bump on the head or serious fall [32].

SUMMARY

- Adverse drug reactions are unintended and undesired effect of drug used in normal therapeutic dose
- Cardiovascular disorders affect the heart and blood vessels, in which chest pain and shortness of breath occur resulting Cardiac arrest
- Depending on the condition, a Healthcare provider may also seek to stabilize heart rhythms,reduce blockages and relax the arteries to enable a better flow of blood
- Antihypertensive are a class of drugs that are used to treat hypertension and this therapy prevent the complication of high blood pressure such as stroke and myocardial infraction
- Antihypertensive are agents are also known as cardiac dysrythmia medication, thatare used to supress abnormal rhythm of heart
- Congestive heart failure - occurs when the pump heart muscle doesn't pump blood as well as it should when this happens blood often backsup and fluid can build in the lungs causing shortness of breath.
- Risk factor includes high level of cholesterol and triglycerides in the blood
- Latest drugs used in the treatment of cardiovascular disorders such as Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril etc.
- These drugs show various adverse effects such as heavy bleeding during periods, bleeding from gums or nose, itching, swelling of hands, face and trouble inswallowing.

CONCLUSION

In this review article studies the information about cardiovascular system Drugs, classification Mechanisms and also about Adverse drug reactions. And Adverse drug reactions (ADRs) occur frequently in modern medical practice, increasing morbidity and mortality and inflating the cost of care. Patients with cardiovascular disease are particularlyvulnerable to ADRs due to their advanced age, polypharmacy, and the influence of heart disease on drug metabolism

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