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Review Article

**AN OVERVIEW ON CARDIOVASCULAR DRUGS: DIGOXIN,
EPINEPHRINE, ATENOLOL & ISOPRENALINE AND RECENT
DEVELOPMENTS CARRIED OUT IN THE FIELD OF
MEDICAL HEALTH SCIENCES**

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Abstract:

There are various cardiovascular drugs which are being utilized in the treatment of various threatening cardiovascular diseases in modern times. In this review article we would be able to get to know the various problems in relation to administration of digoxin which may result in increase in mortality rates. The influence of congestive heart failure and myocardial infarction on change in mortality rate caused due to the administration of digoxin was also discussed. The importance of Atenolol as an antihypertensive drug was also discussed. The formulation of Gastroretentive floating tablets in order to increase the bioavailability of atenolol was also briefed. This review also discusses the pharmacological actions of Epinephrine and the combination effect of this drug with Vasopressin in treatment of cardiovascular resuscitation(CVR) and spontaneous circulation (ROSC) along with the mechanisms involved in the alteration of cardiac rhythmicity and response to the sympathomimetic amines at varied pH levels .

Keywords: Digoxin; Atenolol; Epinephrine; Cardiovascular diseases; Vasopressin***Corresponding author:****Syed Tazib Rahaman***

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1. INTRODUCTION:

Cardiovascular diseases are said to be the most dangerous diseases of the world. According to the reports they are responsible for causing most number of deaths in countries like U.S. Diseases like cardiac arrest, myocardial infarction, coronary heart disease, atrial fibrillation are commonly caused cardiovascular diseases. Coronary heart diseases are said to be causing lot of death both in males and females though it is preventable because of it causing symptoms like Angina pectoris which is said to be a chest pain due to insufficient oxygen supply. Cholesterol is also said to be one of the major causes in recent times which is leading to chronic heart diseases even in younger aged patients. LDL cholesterol when present in larger concentrations leads to diseases related to arteries and thus LDL cholesterol is considered as Bad cholesterol. There are many lipid regulating drugs such as statin which help in reducing the LDL levels. Statins are said to act as a Lipid regulating agents by blocking the production of LDL's from the liver which helps in preventing cardiovascular diseases caused due to Bad cholesterol. The condition in which two upper chambers beat chaotically and irregularly is called Atrial fibrillation. Digoxin is the drug which is extracted from fox glove plant i.e Digitalis which is used in treatment for atrial fibrillation, atrial flutter and congestive heart failure. Verapamil is also cardiovascular drugs which are also known as calcium blockers. These drugs are advised to not to be given to the patients who consume excess of alcohol as it may produce adverse reactions in the body of the patient. Sotalol is a type of cardiovascular

drug which is used to slow the heart rate in some of the cases of arrhythmias. This drug is also used to suppress ventricular ectopics. Amiodarone is also a cardiovascular drug which helps in correcting abnormal rhythms of the heart. Though it is said to have many side effects it is successful in treatment of arrhythmias while other Anti arrhythmias drugs have failed in producing an effective drug action. Flecainide is also a cardiovascular drug which is helpful in regulating the rate and rhythm of the heart by decreasing the sensitivity of heart muscle cells to electrical impulses. This slows down the electrical conduction and leads to restoration of disturbances in heart rhythms. Adrenaline is said to be a natural cardiovascular drug produced by adrenal gland which is helpful in preventing Cardiac arrest. Adrenaline is repeatedly given in the case of cardiac arrest till it is suppressed.

The drugs which help in prevention of such heinous cardiovascular diseases are known as cardiovascular drugs. These drugs are said to be of many types on the basis of their mechanism of action they follow and the type of disease they prevent from attacking our body. Cardiovascular drugs like Digoxin, Atenolol, Epinephrine and Isoprenaline are discussed in this review article which briefs about their pharmacological action and problems associated with them if any. Various cardiovascular drugs which are being used in treatment for heart diseases are Digoxin, Atenolol, Isoprenaline and Epinephrine. The chemical structures of those drugs are given in Figure1.

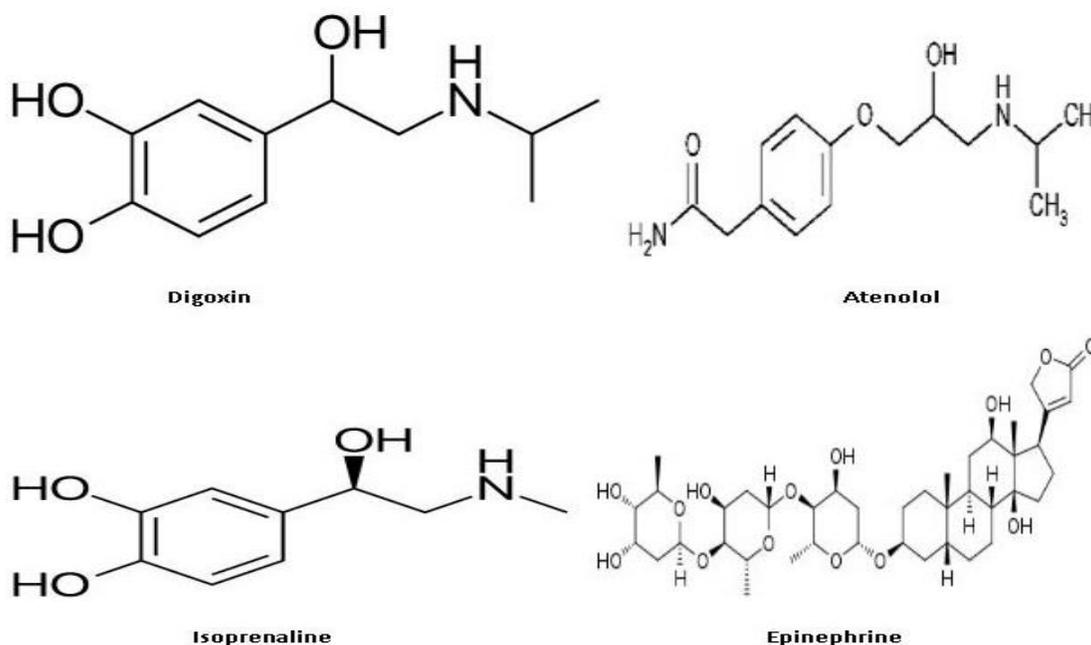
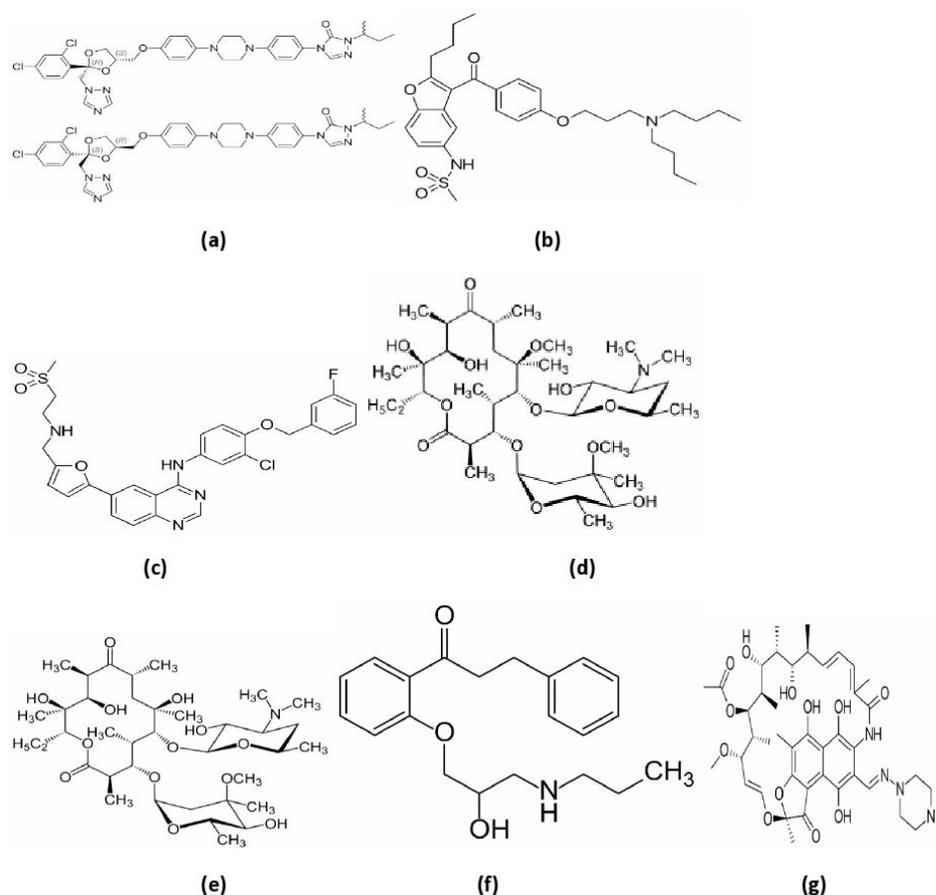


Fig1: Structures of Cardiovascular Drugs

2.1 Digoxin:

Since the discovery of digoxin on 1785, there have been many ambiguities and doubts arising in renowned research scholars which lead to the discovery of its function in acting as a cardiovascular agent. Initially it was used as a positive inotrope in treatment for cardiac failure and also used the negative chronotropic activity for atrial fibrillation. Recently this drug's usage started to decline as this led to an increase in mortality of patients who were treated with this drug. In order to clarify the impact of this drug on mortality a study was done by Oliver J. Ziff et al [1] by conducting randomized and observational trials which proved that digoxin had a neutral effect on mortality in randomized and lower rate of admissions to hospitals were recorded. This study also reported that meta analysis was

suitable for five outcomes such as mortality, cardiovascular mortality, all cause hospital admissions, cardiovascular hospital admissions, and heart failure hospital admissions. This study has been very much beneficial in knowing the accurate mortality effect which is being caused due to digoxin. Though the reduction rate of cardiovascular diseases due to digoxin is substantially increasing the risk of mortality of the patient is a crucial factor to be considered. The analysis done also proved that baseline characteristics of patients such as age, effected by Diabetes, Atrial fibrillation and Cardiac failure showed large bias (P value <0.001) which would lead to an increase in mortality in patients. There are a lot of drug interactions with digoxin which cause adverse effects to the human body [Fig2].



Drug Interactions with Digoxin

- (a) Itraconazole (b) Dronedarone (c) Lapatinib (d) Clarithromycin (e) Erythromycin (f) Propafenone
(g) Rifampicin

Fig 2: Drug interactions with Digoxin

One more factor which is influencing the effect of digoxin on mortality is Heart failure. A study done by Alon Eisen et;al [2] reported the impact of Heart failure(HF) is causing sudden cardiac death. Patients without HF when analysed it was observed that 20% caused sudden cardiac death without any significant interaction with age and sex. This created a new source of analysis which may lead to many more worst outcomes if analysed further. Heart failure is said to be a very common disease in relation to the patients suffering with cardiac problems thus, we can consider that majority of deaths would be caused due to usage of digoxin in cardiovascular treatment. Thus there is definitely an alarming need to analyse this drug properly and should carry out an alternate drug combinations with digoxin in order to inhibit the cardiovascular deaths caused due to it.

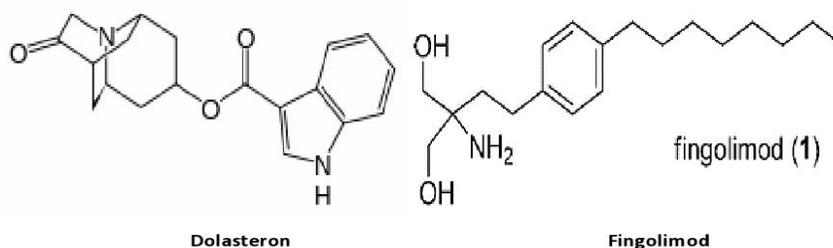
Another study was carried out by Claude S Elayiet;al [3] which analysed the effect of systolic congestive heart failure, Atrial fibrillation and after Myocardial infraction on mortality rate of patients treated with digoxin. The study reported that patients with congestive heart failure showed neutral effect on mortality rate mostly in the cases where digoxin was closely monitored. However, patients suffering with atrial fibrillation but without being attacked of congestive heart failure showed higher rate of increase in mortality due to intake of digoxin. This proved that patients suffering with atrial fibrillation showed higher mortality rate due to use of digoxin. Thus, this factor further strengthens the limited use of digoxin in cardiovascular treatments.

2.2 Atenolol:

Hypertension is considered to be the most dangerous symptom which is said to be the major risk factor for cardiovascular and cerebrovascular diseases. Beta blockers are one of the most commonly used drugs to treat hypertension which would decrease chances of the patients to get effected with cardio vascular diseases and also extends the lifetime of patients. The use of beta blockers in combination with diuretics to

treat hypertension lead to causing of diabetes in patients which lead to decline in the use of beta blockers as the first line therapy in treatment for hypertension. This resulted in search of an alternative which finally lead to introduction of atenolol which is also a type of beta blockers which helped in prevention of hypertension and Coronary heart disease[4]. Atenolol is said to lower systolic and diastolic pressures when this drug is administered in lower dose.

Atenolol is considered to be an antihypertensive drug which showed poor bioavailability of just 50% which would decrease it's efficiency of curing hypertension in patients. There are loads of drug interactions which occur with Atenolol which cause adverse reactions [Fig3] Thus in order to increase its bioavailability a study was performed by Harshal Ashok Pawaret;al [5] which included the formulation of a floating tablet which increased the gastric retention of this drug which further lead to enhancing of it's bioavailability. The floating tablet was formulated using hydrophilic polymers such as Hydroxy propyl methyl cellulose (HPMC), Hydrophobic retardants like Hydrogenated cotton seed oil(HCSO) and sodium bicarbonate as gas generating agent which would increase the floating lag time. The quality control tests on weight variation, hardness, friability, swelling index, floating lag time, and total floating time were also carried out in this study which helped in improving the efficacy of the drug. HPMC is said to be hydrophilic and also act as a retardant thus this study showed increase in retardation effect when HPMC was used in combination with HCSO. These regenerative floating tablets improved Gastro retention of the drug molecules which would show qualitative decrease of hypertension in patients. The study reported that floating tablets showed good compressibility and the Hausner's ratio was said to be in the range of 1.13-1.22. This study also proved that this kind of change in dosage form in some of the drugs would help in showing a wide range of change in the efficiency of drug action on the body of the patient.



Drug interactions with Atenolol

Fig 3: Drug Interactions with Atenolol

Atenolol is a highly polar hydrophilic drug with good water solubility rate. It is also a lipid insoluble drug molecule which is excreted in kidneys and has very low brain penetration. Atenolol gets ionized in stomach and intestine and thus it is said to show very low oral bioavailability. The study done by Rafik Karaman et al [6] proposed an alternative prodrugs of atenolol which were designed on the basis of acid catalysed reaction [Fig 4] of N-alkyl maleamic acids. The presence of amide moiety in place of amine group in the prodrug helped in showing better stability which is very much beneficial in showing effective drug action. This study also compared the stability of atenolol-ester derivatives with ester

derivatives which showed that ester derivatives have better bioavailability than that of atenolol-ester derivatives. This was said to be the source which showed that the addition of atenolol played a major role in decreasing the stability. This study also performed kinetic studies of atenolol and propranolol which showed that increase in lipophilicity would definitely lead to increase in stability of aqueous solutions. Thus, this helped in showing that prodrugs which were proposed in this study would be stable and resistant to heat. This study also stated that when the proposed prodrug is said to be exposed to stomach the carboxylate ion would be in a dominant form.

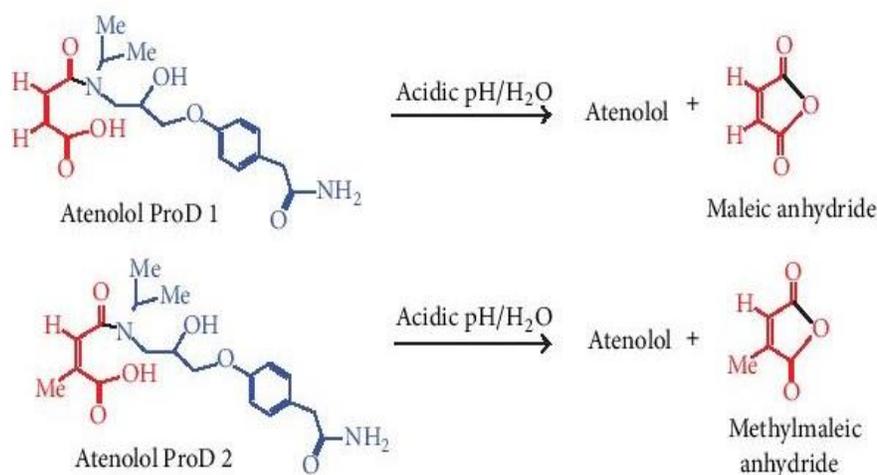
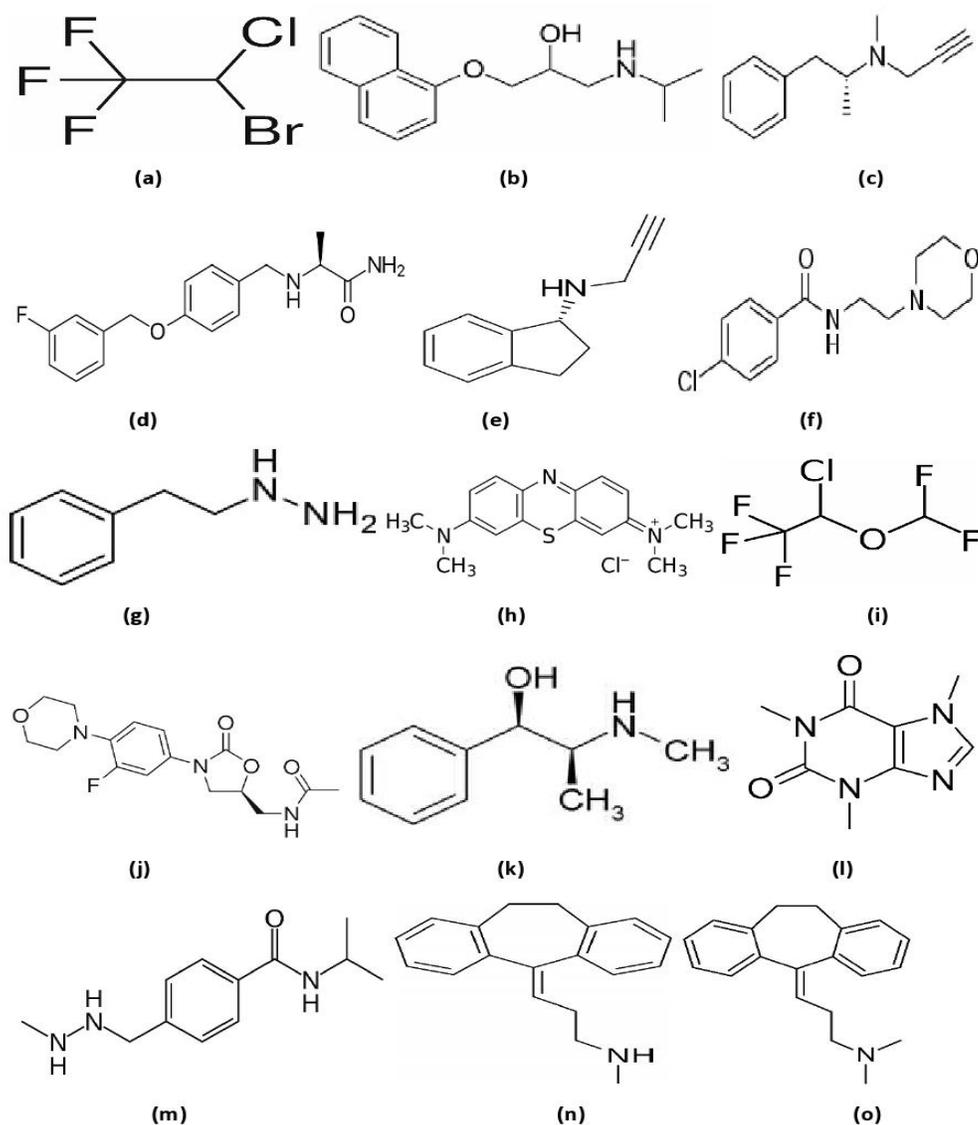


Fig 4: Acid catalysed hydrolysis for Atenolol ProD 1 and ProD 2 [6]

2.3 Epinephrine & Isoprenaline:

Epinephrine is considered to play a major role in causing allergic diseases such as Anaphylaxis. This disease is an acute lethal and multi system allergic reaction. The beta-adrenergic properties of epinephrine would cause bronchodilation, increase myocardial output and contractility, and suppress further mediator release from mast cells and basophils. According to the study done by Kemp et al [7] when Epinephrine was administered in low

concentrations paradoxically it produced vasodilation, hypotension, and increased release of inflammatory mediators. This study also stated that administration of epinephrine enhances coronary blood flow. Epinephrine is said to have a narrow therapeutic window. This Epinephrine also causes adverse reactions due to varied Drug interactions with it [Fig 5]. According to this study over dosage of I.V infusion with epinephrine lead to myocardial infraction and pulmonary edema in rare cases.



Drug interactions with Epinephrine

(a) Halothane (b) Propranolol (c) Selegiline (d) Sildenafil (e) Rasagiline (f) Moclobemide
 (g) Phenelzine (h) Methylene Blue (i) Isoflurane (j) Linezolid (k) Ephedrine (l) Caffeine
 (m) Procarbazine (n) Nortriptyline (o) Amitriptyline

Fig 5: Drug Interactions with Epinephrine

Another study performed by Xiao-li Jing et al [8] showed the beneficial effect of administration of Vasopressin in combination with Epinephrine in treatment of cardiopulmonary resuscitation (CPR). This study involved the comparison of results of patients treated with only epinephrine and that in combination with vasopressin which showed that combination of epinephrine with vasopressin helped in increasing the survival rate of the patients and thus we can say that vasopressin increased the drug action

of epinephrine in preventing CPR. This study also analysed other diseases such as spontaneous circulation (ROSC) in sub groups of patients who represented different cardiac rhythms such as asystole, pulseless electrical activity (PEA) and ventricular fibrillation (VF). The results from this study also showed that the combined effect of vasopressin and epinephrine also lead to effective prevention of ROSC. Hence this study suggests that addition of another drug which is helpful in

enhancing the pharmacological action of the actual drug is very much useful in treatment of various diseases. Thus, this process is needed to be adopted for giving an effective treatment to a patient suffering with a disease.

Epinephrine, norepinephrine and Isoproterenol showed effective restoration of cardiac activity during cardiac arrests. According to this molar sodium lactate helped in increasing the heart rate in the cases of partial and complete A-V Heart block. Thus, studies were done by Santlago V. Guzmanet;al [9] which elucidated the mechanisms involved in the alteration of cardiac rhythmicity and response to the sympathomimetic amines at varied pH levels. According to this study, the response given by each animal to various intravenous doses of the different sympathomimetic amines was determined before acidosis (metabolic or respiratory) was induced. Isoproterenol, levarterenol and epinephrine were the drug concentrations which lead to increase in idioventricular rate by 30 to 40 percent. This study also showed that acute hyperkalaemia induced in three dogs used for the experiment showed decrease in both idioventricular and atrial rates as the serum level raised where as the response sympathomimetic amines did not change due to alteration of pH. The study also showed that when a small amount of alkylating agent such as molar sodium lactate was administered in the left circumflex coronary artery it leads to a transient change in pH which was followed by increase in idioventricular rate. Intra coronary injections which were administered on the same site did not cause in any change idioventricular rate.

A study was carried out by M. Silvermanet; al [10] which showed the effect of Isoprenaline in the cardiac activity and respiratory activity of humans. The results showed that by I.V administration of isoprenaline there was no significant change in the respiratory activity whereas there was an effective increase in Heart rate in all the subjects on which the experiment was performed. In 90% of the subjects used in the experiment there was increase in cardiac output. This study was very much beneficial in finding out a new source to prevent cardiovascular diseases. Though there was no change in oxygen consumption recorded during this study but according to previous studies done by Cobbold et al [11] 1960 there was increase in oxygen consumption of resting subjects.

3. Recent Developments in Health Sciences:

A novel non invasive test for heart disease was proposed by Rabbatet;al [12] which is also known as FFR-CT. This test helps in calculating the blood flow

through coronary arteries. This Fractional Flow Reserve Computed Tomography helps in detecting coronary heart disease which is attacking millions of people all over the world. There is no need of any invasive test for detecting this disease as this single test is enough. This game changing test which is economically cheaper would definitely help the patients suffering with heart diseases.

Shannon Laughlin et;al [13] reported that Hysterectomy in women lead to causing of cardiovascular disorders. When surveyed among women who have undergone hysterectomy this study reported that 33% of total are suffering with coronary heart disease. Hysterectomies also lead to lipid abnormalities in women. This study also suggests women to not to undergo hysterectomy which is causing such life threatening diseases.

Yanbin Dong et;al [14] reported that high doses of vitamin D causes increase in arterial stiffness which further leads to increase in pulse wave velocity and thus, causes cardiometabolic diseases. Though Vitamin D is helpful in reducing inflammation and can suppress vascular smooth muscle proliferation it may also lead heart diseases. This new development has raised many more questions on the magnitude of impact high dose of Vit D is causing which would be answered in near future after larger scale of survey.

Proteasome inhibitor carfilzomib has been playing a major role in treatment of multiple myeloma disease. Brendan et;al [15] performed a survey which showed that 13% of patients who were treated with carfilzomib had symptoms such as hypertension, Heart failure, Heart attacks and more than 8% of the total patients experience Cardiovascular adverse events (CVAE). By this study we could understand the alarming need of limiting the use of carfilzomib in the treatment of multiple myeloma.

Varenicline is a kind of drug which is helpful for men in quitting smoking. The recent study which was done in Canada [16] reported that this drug causes increase of chances to get attacked by cardiovascular diseases. The cardio vascular events which were caused in the people who used this drug which were reported are heart attack, stroke, arrhythmias, unstable angina and peripheral vascular diseases. This study confirms the fact that this drug has adverse effects of causing heart diseases thus there is an alarming need of limiting the usage of this drug by heart patients and a larger survey is needed to be done in order to know more dangerous effects caused due to this drug.

4. CONCLUSION:

From the above studies done by various research scholars we can conclude that there are loads of amendments which are need to be done in the methodology of treatment given to patients suffering cardiovascular diseases. Digoxin has proved to very much fatal to the patients as it is leading to increase in mortality which is creating an alarming need for limiting the utilization of this drug. The change in dosage form of the drug is very much needed most importantly in Atenolol in which we observed to have more bioavailability in Floating tablets rather than that of the originally being used form. Thus, this change in the form of drug administration in some of the lifesaving drugs would definitely help in improving the efficiency of drug action. Though it is a Prodrug of Atenolol we observed that it showed effective bioavailability and stability than that of the active form of Atenolol. Epinephrine when combined with vasopressin helped in producing effective drug action on diseases like cardiovascular resuscitation (CVR) and spontaneous circulation (ROSC). This proved that the addition of a drug to the active drug molecule in order to increase the efficacy of the active drug molecule helps in providing effective treatment to the patients suffering with several life-threatening diseases. The mechanisms involved in the alteration of cardiac rhythmicity and response to the sympathomimetic amines at varied pH levels of epinephrine, norepinephrine and isoprenaline were also studied. The effect of Isoprenaline in cardiovascular and respiratory activity resulted in knowing the effective drug action of which resulted in increasing the heart rate and cardiac output of patients. All of these studies help us in understanding that certain modifications in the active drug molecule will make a large difference in efficiency of drug action. Thus, certain changes in the drug are needed to be analysed carefully of every lifesaving drug during its formulation.

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Conflicts of interest

There are no conflicts of interest.

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