Cardiovascular Diseases and Drug Therapy - A Review

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ABSTRACT

Cardiovascular drugs are drugs which are used to treat diseases relating to the heart and blood vessels structure and function. Most common diseases includes: heart failure, coronary artery disease, high cholesterol, blood clots, circulation disorders etc.

As we know the varieties and extent of cardiovascular drugs have increased rapidly in past decades. An effective oral diuretic which was approved in 1950s has outstanding effect on treatment of heart failure and hypertension. Beta blockers agents in 1960s brought major changes for treatment of hypertension or angina pectoris patients. In 1980s Calcium channel blockers and ACE inhibitors were used widely and given effective treatment to patients with coronary artery disease, hypertension and heart failure. Major transform was invention of clotting factors which have saved thousands of patients from heart attack.

INTRODUCTION

Cardiovascular diseases are major cause of illness and death worldwide and it is also estimated by scientists that morality rate of disease and death will be more in future. Five major cardiovascular diseases are Heart attack, stroke, hypertension, inflammatory heart disease, rheumatic heart disease and these diseases cause 16 million deaths per year all over world [1-7]. According to World health Organization, cardiovascular disease prevalence and incidence vary according to gender also and number of females getting affected is more than number of males. Different types of cardiovascular drugs are used for treatment of these diseases [8-16]. As we know that genetics plays an important role in treating patients likewise it also plays an important role in treatment of patients with particular drugs. In this review article we have discuss briefly on the effect of cardiovascular drugs on genetics [17-23].

The effect of drug is varying from patient to patient and it can result in adverse reaction, toxic effects or ineffectiveness of drugs in their normal doses. As per estimation genetic factors affect 20-95% of variations in the effects of the used drugs for treatment. Along with non-genetic factors there are several other factors which effects response of drugs therapy. These factors include [24-31]: Sequence variants in the genes encoding drug-metabolizing enzymes, drug transporters, trans-membrane receptors, intracellular enzymes and molecular targets. Drug response on genetic basis can be determined by the patient genes approach. Pharmacogenetics is the study of the effect of variation in a single gene on drug response which includes efficacy and toxicity. Pharmacogenomics is the study of multiple genes to variability in drug response [32-37].

Pharmacogenetic variation sources can be divided into three categories [38-42]

a) Pharmacokinetic
b) Pharmacodynamic
c) Variability in disease being treated

Cardiovascular drugs are classified into 7 different categories [43-57]

1) Anti-anginals: A disease of coronary arteries named angina pectoris is treated with pharmaceutical agents called anti-anginals.
2) Anti-arrhythmics: These agents are used for treatment of Arrhythmia in which the rhythmic contraction of the heart is interrupted.

3) Anti-hypertensives: Hypertension which is the most common of all cardiovascular diseases and it has affected nearly 40 million people in the US. It is the major cause of stroke and heart attack.

4) Anticoagulants: These drugs are used to inhibit the blood clotting in blood vessels. Anticoagulants are also used in myocardial infarction, venous thrombosis, peripheral arterial emboli, pulmonary embolism, blood transfusions, extracorporeal blood circulations and dialysis procedures.

5) Anti-hyperlipidemic agents: These drugs are also known as lipid lowering drugs. These drugs are used for the treatment of lipids (cholesterol) in blood.

6) Hypo-glycemic agents: These drugs are used for lowering glucose level in blood.

7) Anti-thyroid drugs and thyroid hormones: Antithyroid drugs are used to treat an overactive thyroid (hyperthyroidism) which is caused by Graves' disease.

To diagnose people with heart disease along with medicine there are many other points which are useful for controlling risk associated with disease as first action \[48-53\]:
- Cutting down on cholesterol and fat
- Regular exercise
- Smoking cessation

Most common FDA approved drugs to treat cardiovascular diseases (Table 1) \[54-60\]:

**Table 1: Drugs for treatment of Cardiovascular Diseases.**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradaxa (dabigatran etexilate mesylate)</td>
<td>For the risk reduction of stroke and embolism due to atrial fibrillation</td>
</tr>
<tr>
<td>Eliquis (apixaban)</td>
<td>For the prevention of stroke and systemic embolism resulting from nonvalvular atrial fibrillation</td>
</tr>
<tr>
<td>Xarelto (rivaroxaban)</td>
<td>For the reduction in the risk of stroke and systemic embolism resulting from atrial fibrillation</td>
</tr>
<tr>
<td>Xarelto (rivaroxaban)</td>
<td>In treatment of prophylaxis of deep vein thrombosis during knee or hip replacement surgery</td>
</tr>
<tr>
<td>Adcirca (tadalafil)</td>
<td>In treatment of pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Adempas (riociguat)</td>
<td>In treatment of Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension</td>
</tr>
<tr>
<td>Advicor (extended-release niacin/lovastatin)</td>
<td>In treatment of cholesterol disorders</td>
</tr>
</tbody>
</table>

**CARDIOVASCULAR DRUGS AND THERAPY**

As we are aware of the fact that cardiovascular disease is the main cause of death all over world. Using drugs that inhibit coagulation, disrupt platelet function, reduce cholesterol levels, control blood pressure levels, etc. can reduce mortality in patients. In recent studies it is found that there are 17 different types of drugs which are used to treat cardiovascular diseases \[51-73\].

Recent researches are carried out in defining DNA sequence variations which balance patient’s response to drug administration. Most of the information related to this has been collected with respect to warfarin (anticoagulant) and clopidogrel (antiplatelet agent) \[74-82\]. These studies includes identification of single nucleotide polymorphisms (SNPs) which affect drug metabolism, it is also an analysis to enable prediction of clinical outcomes in possible settings and it also gives illustration on how frequency of drug-related adverse events can be decreased with the help of genotype-directed prescription.

**SOME COMMONLY USED THERAPIES WITH DIFFERENT DRUGS ARE DISCUSSED BELOW**

**Antiplatelet Therapy**

Some commonly use antiplatelet drugs are: Aspirin, clopidogrel, prasugrel, ticagrelor.
These drugs are used to decrease atherothrombotic disease adverse effects in patients. But due to genetic variations after using medication also patients are suffering from atherothrombotic disease \(^{[83-89]}\).

Aspirin is the commonly used antithrombotic agent. Aspirin irreversibly acetylates the cyclooxygenase (COX)-1 enzyme, which leads to the suppression of thromboxane A2 and related metabolites. There is possibility with almost 40\% of aspirin using patients which can suffer from serious vascular problems due to aspirin resistance. There are different types of genetic polymorphisms which are supposed to affect aspirin response and lead to unacceptable situation \(^{[90-93]}\).

Clopidogrel is widely used for antiplatelet treatment. Active clopidogrel metabolite irreversibly binds to the platelet ADP P2Y12 receptors. It is found that almost 21\% of patients receiving PCI exhibit there is none clopidogrel response and which leads to 8 times increase in risk of adverse effects of cardiovascular disease \(^{[94-96]}\).

For example: Primary isoform which is responsible for activation of clopidogrel is CYP2C19. CYP2C9*2 and CYP2C9*3 carriers will lose their ability to metabolize clopidogrel. This results in reducing platelet aggregation and increases cardiovascular risks.

Antiplatelet therapy can be used for the patients for whom the genotype causes future risk for reduced antiplatelet efficacy. Genotyping cannot be prescribed for patients at lower risk. If a patient has poor drug metabolism then clopidogrel can be replaced with other medicines such as prasugrel or ticagrelor.

**Oral Anticoagulants**

**Coumarin derivates**

Such as warfarin which are used for the treatment of thrombotic disorders. Adjustment of dose and routine monitoring is very important in use of warfarin for a patient's international normalized ratio (INR) and careful adjustment of the dose of particular patient. Warfarin levels can be affected by diet of patients, alcohol use or any other drug use. Many adverse effects like the risk of bleeding in patients which can be fatal can also be noticed \(^{[97-100]}\). A low dose can induce thromboembolism, and a high dose can induce bleeding. In studies it I found that patient response to anticoagulant therapy is also affected by genetic factors.

The variability of 50\% in coumarin derivates maintenance dose can be described with genetic polymorphisms in some genes. They are:

a) CYP2C9 – the principal metabolizing enzyme of all coumarines;

b) VKORC1 (vitamin K epoxide reductase complex subunit 1)–the pharmacologic target of coumarins;

c) CYP4F2 (vitamin K1 oxidase).

Genetic variation in some other genes like apo-lipo protein E, glutamyl carboxylase, calumenin, epoxide hydrolase 1, and factor VII are also affecting warfarin dose requirement.

**Beta-blockers**

Beta-blockers are cardiovascular drugs which are used for clinical utility of pharmacogenetics. Variations in the genes involved in the synthesis of proteins for the beta-1 and beta-2 adrenergic receptors (ADRB1, ADRB2), and the gene that codes for associated regulatory proteins such as G protein-coupled receptor kinase 4 and 5 involved in signal transduction (GRK4, GRK5) could influence the treatment outcome.

Many beta-blockers are metabolized predominantly by hepatic CYP2D6. Polymorphisms in the gene coding for the CYP2D6 isoenzyme may also affect beta-blocker response.

Some commonly used beta blockers are:

- Bisoprolol (Zebeta)
- Metoprolol succinate (Toprol XL)
- Carvedilol (Coreg)
- Carvedilol CR (Coreg CR) Toprol XL
CONCLUSION

Based on the available data, it could be expected that in the future genome-tailored drug prescription and use of defined algorithm will help in giving successful drug action by reducing the frequency of unfavorable results and it will also have significant clinical relevance.

Discovery and validation of Gene variants which will be clinically validated and modulate the effectiveness of cardiovascular drugs will be continued.

A complete inventory of the genetic variation can responsible for the efficacy of drug action and the frequency of adverse events can provide data which will be more effective and will give greater clinical relevance.

REFERENCES


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