WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 3, 1040-1055. Review Article ISSN 2277– 7105

RECENT ADVANCEMNET OF NDDS IN CARDIOVASCULAR DISEASES

Sonawane A. R.*, Waghmare S. A., Kamble H. V., Wagh R. T., Shelke M. M. and Andhale A. K.

Student at Loknete, Shri Dadapatil Pharate College of Pharmacy Mandavgan Pharata, Tal – Shirur, Dist – Pune.

Article Received on
07 January 2022,

Revised on 27 January 2022,
Accepted on 17 Feb. 2022

DOI: 10.20959/wjpr20223-23321

***Corresponding Author**
Sonawane A. R.
Student at Loknete, Shri Dadapatil Pharate College of Pharmacy Mandavgan Pharata, Tal – Shirur, Dist – Pune.

ABSTRACT

The need for novel approaches to cardiovascular drug development served as the impetus to convene an open meeting of experts from the pharmaceutical industry and academia to assess the challenges and develop solutions for drug discovery in cardiovascular disease Cardiovascular diseases like atherosclerosis, angina pectoris, acute myocardial infraction, are a major cause of mortality in the whole world owing to the present day hectic lifestyle .In this review we will concentrate on the various novel drug delivery systems like micelles, liposomes that are being used over the years & in the present day for the treatment of these diseases. Certainly, many of these medication models will not lead to the development of important drugs. Nonetheless, we can hope that these models will provoke intellectual discussion, lead to the discovery of new clinical information or provide direction for future research.

KEYWORD: - Novel approaches, Cardiovascular diseases, Mortality, Hectic lifestyle, Intellectual discussion, Discovery of new clinical information.

INTRODUCTION

Drug therapy is a major treatment modality in cardiovascular disease, but there have been few new medications approved for treatment. However, the number of new agents does not indicate that the field is bereft of new ideas. The present review explores the newer, more promising models for medication treatments in each of the major cardiovascular conditions, indicating the most promising of those agents being investigated. Cardiovascular diseases (CVDs) were responsible for the highest number of deaths in 2019.

According to the World Health Organization (WHO)

1) Increasing and aging populations further complicate the situation, and 22.2 million CVD-related deaths are expected to occur in 2030
2) There is an important link between complex oxidation reactions and the development of atherosclerosis
3) Increasing levels of oxidative stress contribute to the subsequent formation and progression of atherosclerotic plaques
4) A lack of endogenous antioxidants is another important cause of coronary heart disease
5) The use of traditional medicinal plants has rapidly expanded in recent years. Medical plant research is no longer limited to chemical composition and pharmacology and now encompasses the study of metabolomics and underlying mechanisms of action.

Novel drug delivery system

Definition

NDDS are defined as the systems which are capable of controlling the rate of drug delivery sustaining the duration of therapeutic activity or targeting the delivery of a drug to tissue.

Types of NDDS

1. Oral drug delivery systems
2. Nasal/Pulmonary drug delivery systems
3. Parenteral drug delivery systems
4. Topical drug delivery systems
5. Transdermal drug delivery systems

1. Micelles

Micelles are polymer (or) lipid-based amphiphilic molecules with hydrophobic cores and hydrophilic shells. They act as carrier vehicles to overcome the solubility problems by enclosing the hydrophobic portion of a drug by creating an aqueous environment in the drug. An example of micelle drug delivery is chlorine loaded polymeric micelles.

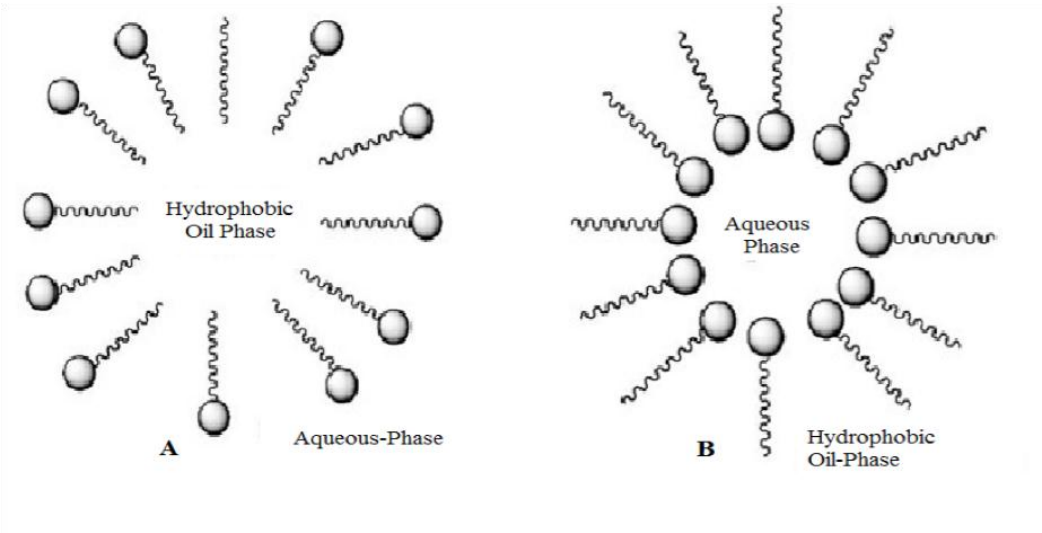

Fig. 1: Micells structure.

2. Liposomes

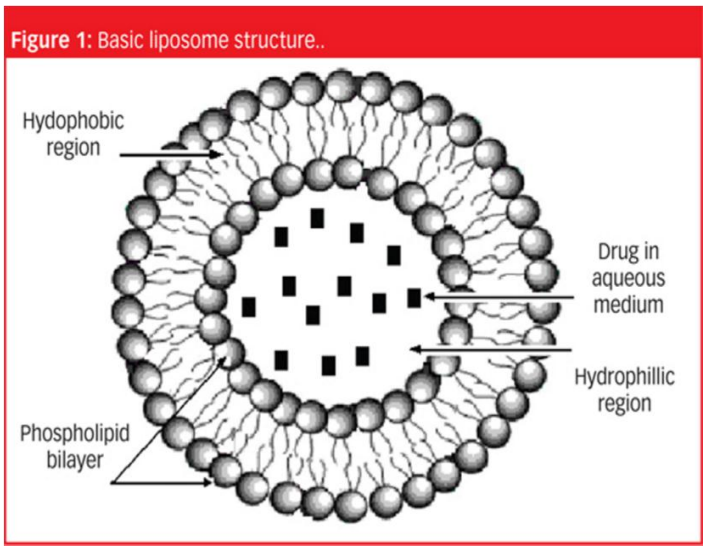

Fig. 2: Liposomes.

1. There are many different types of drug delivery vehicles, like polymeric micelles, liposomes, dendrimers, lipoprotein based drug carriers, nanoparticle drug carriers etc.
2. An ideal drug delivery vehicle should be biocompatible, non-toxic, non-immunogenic, and biodegradable and should avoid recognition by the host's defense mechanisms.
3. Liposomes are made up of phospholipids and may comprise small amounts of other molecules.
4. Liposomes can vary in the size from a low micrometer range to tens of micrometers in range.

5. Unilamellar liposomes are in the lower size range with various other targeting ligands to their surface, which allows for their surface-attachments and accumulation in pathological areas for treatment of disease.
6. Liposomes are non-hemolytic, non-toxic, non-immunogenic, biocompatible and biodegradable in nature and could be designed to avoid clearance mechanisms such as chemical or enzymatic inactivation, renal clearance etc.
7. Liposomes supply both a lipophilic environment and aqueous environment in one system and are therefore suitable for the delivery of hydrophobic, amphipathic and hydrophilic drugs.
8. Liposomes have the ability to protect their encapsulated drug from the external environment.
9. Liposomes can be formulated as a suspension, or in a semisolid form such as cream, gel and lotion, or they can be administered through most routes of administration including ocular, pulmonary, nasal, oral, intramuscular, or through the vein.
10. Liposomes are helpful in reducing the exposure of sensitive tissues to toxic drugs.
11. Liposomes alter the pharmacokinetic and pharmacodynamics property of the drugs

Advantages of liposomal drug delivery systems

1. It is suitable for potent drugs.
2. It mainly improves the therapeutic efficacy of a drug.
3. It provides stabilization of entrapped drug.

Disadvantages of liposomal drug delivery systems

The major disadvantage Structure of liposomes is when the parenteral route administers these liposomes, they show rapid clearance by reticuloendothelial system.

3. Nano particles

Nanoparticles are the Nano-sized particles used in the targeted drug delivery through the encapsulation process. Even though these nanoparticles show some toxic effects the polymeric nanoparticles are used in the treatment of acute myocardial infraction, which is caused due to atherosclerotic platue destabilization and rupture by inflamed monocytes and macrophages. Some other examples of Nano drug delivery systems are PEG gold Nanoparticles, and Nanoparticles containing pitavastatin reduces the inflammation.

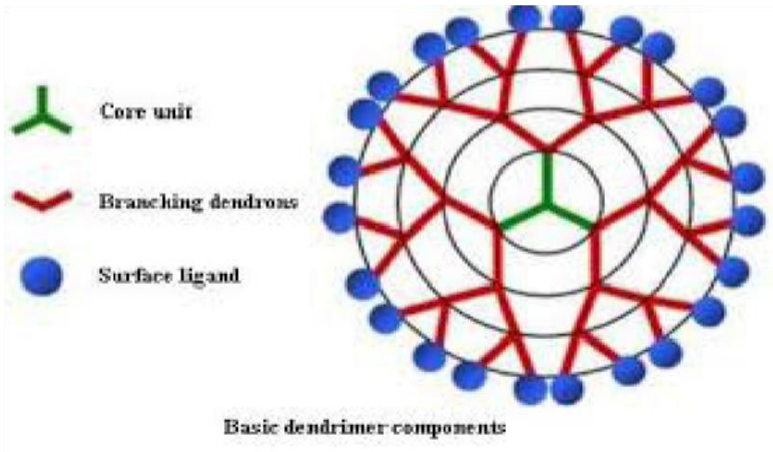

Fig. 3: Nanoparticles.

4. Dendrimers

A dendrimers is nanoparticle consisting of continuous branched molecules that posse's molecular uniformity and low disparity. The other name of dendrimers is Cascade molecules.

Mechanism of action

The drug particle is embedded in cavities of the core structure and folding of branches that form cages and channels, i.e., simple entrapment process.

Examples of dendrimers

Starburst dendrimers are the name for a subclass of PAMAM dendrimers based on tris amino ethylene imine core, which regulates the gene transfer in vivo and invitro environment. The dendrimers complexes increase the gene transfer in murine cardiac grafts.

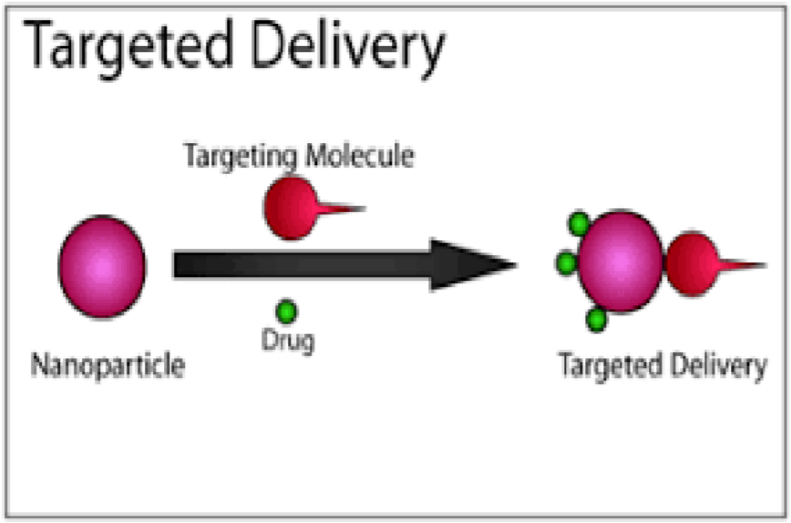

Fig. 4: Dendrimers.

5. Micro bubbles

1. Micro bubbles are the gas bubbles consisting of phospholipids and biodegradable polymers administered through the intravenous route.
2. These are spherical and small in size as that of red blood cells.
3. The techniques used for encapsulation is coating and surface binding.
4. They are also used in the treatment of vascular thrombosis by son thrombolysis.

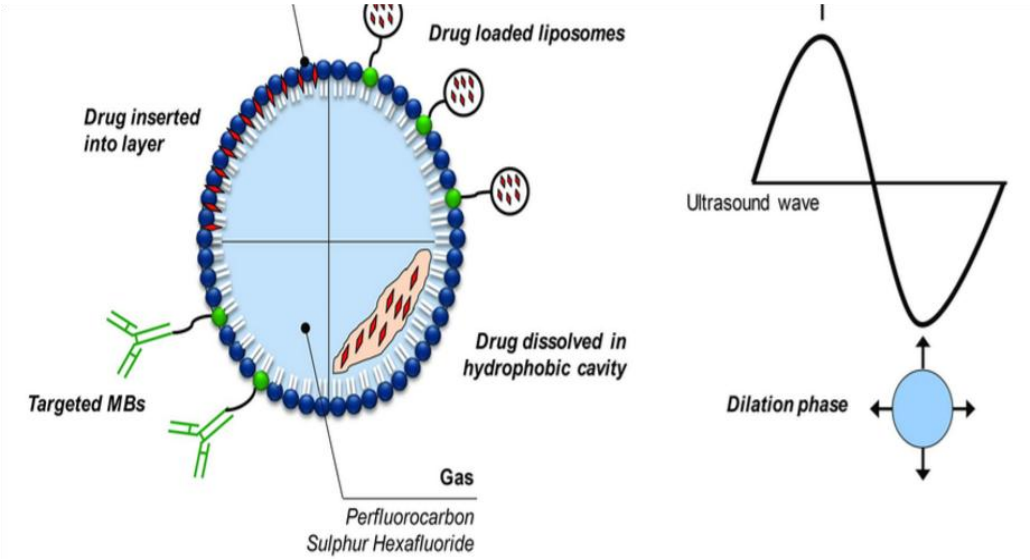

Fig. 5: Micro bubbles.

6. Drug-eluting stents

1. In older days, the metal stents were used in the treatment of atherosclerotic vascular disease.
2. Still, now the use of metal stents was limited because of its inflammatory response, thrombosis, and restenosis.
3. So, a new technique was developed, i.e., drug-eluting stents, which reduces the restenosis less than 10% due to the polymeric layer disruption at the site of injury.
4. To overcome the problem, the biodegradable polymer stents were developed. Some of the examples of biodegradable stents are poly L lactide stent, bioresorbable stent.

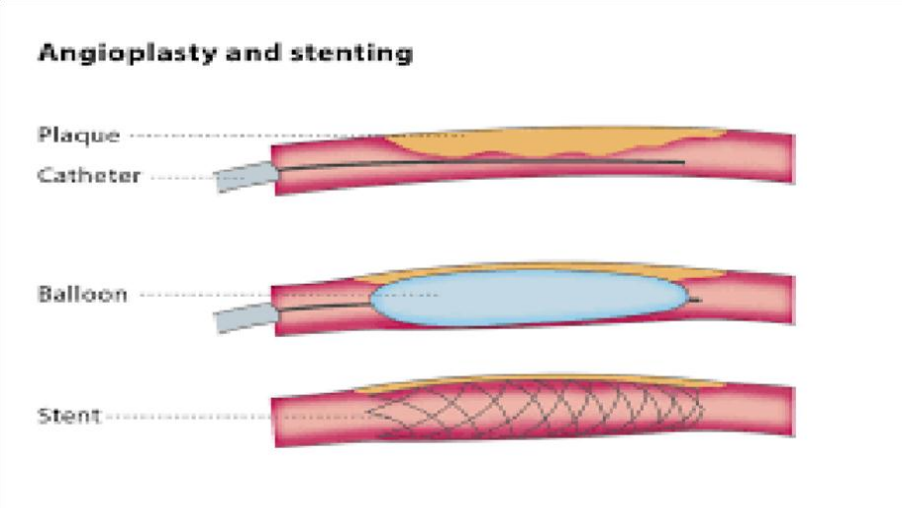

Fig. 6: Drug-eluting stents.

7. Drug-eluting balloons

1. Drug-eluting balloons are used in the treatment of coronary restenosis, subsequent revascularization.
2. The paclitaxel drug-eluting balloon is an important device that is used to deliver the antirestenostic drug paclitaxel into a coronary vessel.
3. These eluting drug balloons are used as an alternative to eluting drug stents affected coronary artery drug-eluting balloon in the artery treated coronary artery by DEB

Therapeutic models: Angina

1. Drug therapy models to treat angina have not been productive with regard to producing new therapies.
2. Angina is caused by the imbalance of oxygen supply versus demand to the myocardium, leading to myocardial hypoxemia.
3. Supply-side models directed toward treating coronary artery vasospasm, fixed stenotic lesions or thrombus have been addressed over the past decade with anticoagulants and antithrombotic that are now generally mature, with few new options.
4. Similarly, demand-side models are focused on oxygen consumption regulated by heart rate, inotrope, afterload and preload.
5. Increased oxygen demand has been treated with beta-blockers, Ca^{2+} channel blockers and nitrates, which are now mature drug categories with conceptually few novel approaches.
6. The greatest interest has been directed toward the dysfunctional or diseased vascular endothelium that affects both oxygen supply and demand.

7. The healthy vascular endothelium produces a protective mechanism through the production of nitric oxide (NO) and prostacyclin, which dilate coronary arteries and prohibit clot formation.
8. A dysfunctional vascular endothelium cannot produce adequate supplies of NO and prostacyclin, leading to vasoconstriction, platelet aggregation and clot formation.
9. The models focus on the activity of NO to protect tissues from ischemia in low doses, but sustained levels of NO lead to tissue toxicity and vascular collapse.
10. Therapies being studied include nitrates, an NO synthase transcription enhancer, Ca^{2+} channel blockers (particularly diltiazem) and a cardiac metabolic modifier (ranolazine).

Therapeutic models

Coronary artery disease

1. Treatments for coronary artery disease have taken very different approaches that focus on models attacking atherosclerosis and restenosis, and gene therapy.
2. Atherosclerosis models combine extended-release niacin formulations with statins.
3. The emphasis on extended-release niacin is to decrease flushing, while the statin component is usually simvastatin, available as a generic, put into a combination drug to allow for branded patent extension.
4. Restenosis models are targeted to the cell damage caused by angioplasty for narrowed blood vessels using drug-eluting stents.
5. The first stage of restenosis after surgery is targeted with the use of antiplatelet IIa/IIIb inhibitors - e.g., tirofiban, eptifibatide and abciximab – to prevent thrombosis.
6. The second stage of restenosis is targeted with medications eluted from the stents that inhibit intimal tissue growth from scar tissue and cell proliferation produced by the stent.
7. Gene therapy is also being evaluated to prevent coronary artery disease.
8. Current interest is in hypoxia-inducible factor-1alpha, which is being developed by BioCardia, USA.

Therapeutic models: Arrhythmia – AF

1. AF is the most common symptomatic tachyarrhythmia and is expected to grow as the population ages.
2. The expectation is that the AF population will grow from 2.1 million in 1995 to 5.6 million in 2050.

3. Drug treatment models for AF have addressed the problem from several directions including rate control, rhythm control, and agents altering the atrial substrate, anticoagulation and ablation.
4. At this time, only rhythm control studies have produced an approvable agent in dronedarone, which is similar to amiodarone.
5. K^+ channels in the heart determine heart rate, resting membrane potential, action potential shape and duration.
6. These channels are classified as either voltage gated (i.e., dependent on inflow/outflow of K^+) or ligand gated (i.e., ligands expand the channel, allowing ions to flow into the myocardium).
7. Voltage gated channels are further classified into transient outward current, delayed rectifier current and inward rectifier current.
8. The delayed rectifier current channel is divided into ultra-rapid, rapid and slow.
9. These distinctions are not just physiological because the atrium has a greater density of repolarizing K^+ currents that are relatively insensitive to class III agents including amiodarone, sotalol and dofetilide.
10. Ligand gated channels are distinguished by whether they are dependent on ATP or acetylcholine as their transport substrate.
11. Research has targeted K^+ channels for atrial-specific arrhythmias using either voltage-gated channel blockers or combinations of voltage- and ligand-gated channel blockers.
12. While there are no recently approved agents, there is still promise.

Therapeutic models: CHF

1. CHF is being studied from several vantage points – diuretics, renin/aldosterone inhibitors to improve kidney function and produce vasodilation, inhibitors of progressive myocardial remodeling, activation of cardiac myosin, myocardial rescue and myoblast transplantation.
2. There are also preliminary studies at Washington University (USA) to study the use of nuclear receptor proteins (peroxisome proliferator-activated receptors) to modulate myocardial energy metabolism.
3. Diuretics and renin-aldosterone inhibitors in development aim to expand on already mature franchises.
4. These are generally targeted toward preserving kidney function through aldosterone inhibition (e.g. carperitide).

5. An alternative approach to preserving kidney function is to produce synthetic forms of naturally occurring peptides that regulate fluid balance and Na^+ homeostasis.
6. These approaches are in the early stages of phase II trials and will not be available, if at all, for many years.
7. Antidiuretic hormone receptor antagonists continue to attract interest, with the latest being lixivaptan, a selective antidiuretic hormone receptor antagonist.
8. Vasopressin continues to be a target of interest with tolvaptan, a vasopressin V2 receptor antagonist.
9. A totally unique model is opioid receptor like-1 receptor.
10. This is a randomized, multicenter, double-blinded, placebo-controlled, parallel group study to assess the efficacy and safety of intravenous Adentri dosed according to body weight for up to five days in acute decompensated heart failure patients with impaired renal function. The trial is evaluating Adentri against placebo and against standard care in 900 patients in 21 countries.
11. Acute heart failure is being attacked by pharmacological and nonpharmacological means.
12. Immune modulation using Cascade, a nonpharmacological therapy, is being developed by Vasogen, a Canadian-based biotechnology company.
13. Early development of pharmacological treatments for heart failure involve enzyme inhibitors, which binds to DNA and regulates gene expression.
14. These treatments are being studied in animal models and require extensive review in humans.

Applications of novel drug delivery systems

Novel drug delivery systems have been used in a broad range of pharmaceutical applications like

1. **In drug targeting:** - Controlled release of drug or encapsulated bioactive could be achieved using NDDS. Desired release pattern will definitely improve the pharmacokinetics and hence pharma- codynamics of drug. Drug from implants avoids regular administration of drug hence ensures patients compliance.
2. **Studying immune response:**- Immunotherapy is one of the most upcoming therapeutics approaches explored presently for the management of various diseases & disorders.
3. **Delivery of peptide drugs:** - Deport formulations of short -acting peptides have been successfully developed using micro particle technology. Such peptides include leuprorelin acetate and triptoreline, both luteinizing hormone releasing hormone agonist.peptides

formulated as sustained release micro particles include the angiotensin receptors-antagonist for the treatment of hypertension, thyrotrophic releasing hormone for central nervous system stimulation, salmon calcitonin for the treatment of hyperkalemia or postmenopausal osteoporosis and the immunosuppressant drug cyclosporine A.

4. **Tissue engineering:-** The field of tissue engineering has witnessed great progress over the past few decades is that the dissociated cells have the ability to reassemble onto structure that resemble the original tissue .both natural as well as synthetic materials have been evaluated as scaffolds for tissue engineering .
5. **In cancer therapy:-** Leuprorelin polylactided acid co-glycolide microspheres may be used as a monthly and three monthly dosage forms in the treatment of advancement prostate cancer, endometriosis and other hormone responsive conditions. These microspheres effectively halt the progression of prostate cancer or endometriosis in patients and are currently marketed as prostap SR
6. **Anti-microbial activity:** - The controlled delivery of antibiotics in the treatment of H. Pylori via NDDS is an effective process compared to conventional one.

Recent therapeutic strategies for cardiovascular diseases

Despite all the advancement in pharmacological and clinical treatment, heart failure is a leading cause of morbidity and mortality worldwide. Many new and advanced therapeutic strategies, including cell transplantation, gene delivery or therapy, and cytokines or other small molecules have been researched to treat heart failure (HF) (Arora et al. 2012b). Recent advancement in the study of those molecules that regulate the cardiac functions shows that they are key molecules to treating heart failure.

Lifestyle modifications

1. **Exercise**

Exercise is universally recognized as having a positive impact on the majority of health outcomes and its effect on CVD is no different. Mortality and morbidity directly due to exercise remains minimal even up to very intense levels of exercise and in the overwhelming majority the benefits outweigh the risks.

2. **Diet**

Diet is thought to play a significant role in CVD risk but the body of evidence regarding its use is not clear, nor are the guidelines overwhelmingly consensual.

The AHA recommend the Dietary Approaches to Stop Hypertension (DASH) diet which is low in sugars and saturated fats, high in vegetables, fruits and whole grains. This has been shown to as a method to lower blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) which are independent risk factors for CVD, but they do not attempt to show a direct reduction in CVD risk.

3. Smoking

Smoking has long been known as the major risk factor for CVD. European data indicate that smoking doubles the 10 year CVD mortality rate[3] whilst 30% of US CVD mortality is attributable to smoking. Not only is it deleterious but this effect is dose related with no safe lower limit seen. Passive smoking is similarly harmful as workplace exposure increases CVD risk by 30% and UK public health initiatives including smoking bans are associated with a significant fall in CVD events.

4. Weight

Having a body mass index (BMI) > 25 is a risk factor for CVD with lowest all-cause mortality seen at BMI 20–25 but, due to increased all-cause mortality with BMI < 20, reductions below this level are not routinely recommended. No guidelines recommend specific intervention regarding weight, but advise maintenance of a healthy weight for reduction of CVD risk. BMI is a good predictor of CVD risk, particularly at higher levels, but there is good evidence that, at all levels of BMI, visceral adiposity and liver fat are significant drivers of risk. This helps to explain the heterogeneity in the CVD risk profile seen in the overweight as it varies depending on the location of adipose deposition. There are moves to suggest that, alongside reduction in BMI, reduction in waist circumference as a proxy for reductions in visceral fat should become an important target for amelioration of CVD risk.

5. Alcohol

Alcohol consumption is a controversial subject given the known sequelae of regular and excess alcohol use. The difficulty exists as historically the evidence suggested a J-shaped curve when it comes to risk, where abstinence is associated with an increase in CVD compared to light drinkers, with low levels of alcohol consumption associated with a lower level of CHD. Besides the understood physiological effects of alcohol, interfering with platelet aggregation, evidence from the interheart study would appear to substantiate these claims, showing reductions in risk for those with moderate and light use of alcohol.. This would suggest that reductions in alcohol intake, even for moderate drinkers, are associated

with a reduction in CVD risk. It is on this basis that the ESC guidelines recommend no safe level of alcohol intake.

Medical treatment

1. Lipid-lowering therapy

Interventions to ameliorate lipid levels have long been used in primary prevention and sub-fractions of serum lipids have been studied to differentiate their individual effects on CVD risk profile.

LDL-C is the best understood atherogenic sub-fraction with a strong correlation between LDL-C levels and CVD risk: reducing LDL-C by 1.0 mmol/L causes a corresponding 20–25% risk reduction in CVD mortality and non-fatal MI. It has been hypothesized that raised high-density lipoprotein cholesterol (HDL-C) levels are cardio protective but the causal link remains unproven.

2. Anti-hypertensive therapies

Hypertension is an independent risk factor for the development of CVD. The effect of increasing BP > 115/75 mmHg is consistent and exponential, where each 20 mmHg increase in systolic blood pressure (SBP) or a 10 mmHg increase in diastolic BP doubles the risk of a cardiovascular event.

Previous meta-analyses have shown a reduction in CVD risk over a wider range of BPs suggesting that there is no lower limit to the benefit of BP reduction, and no obvious cut-off at which further reductions become harmful.

3. Blood glucose

Glucose control is pertinent in the diabetic populations but is non-significantly associated with CVD risk in non-diabetics. On average diabetes mellitus (DM) risk of CVD, whilst those with impaired fasting glucose (IFG) are known to be at significant risk of CVD as well as progression to DM. In DM serum glucose reduction is shown to reduce CVD, with lowest risk at normal blood sugars. More intense glucose reductions were deleterious, with particular CVD risk from certain thiazolidinedione and dipeptidyl peptidase-4 inhibitors. Recent trials from the sodium/glucose transporter 2 inhibitor class of oral hypoglycemic such as empagliflozin have been shown to significantly reduce all-cause mortality by 32%, as well as CVD death by 28% and HF by 35% in comparison with standard care. It appears that these

effects were not mediated by reduction in glucose, rather cardio-renal hemodynamic effects, but the substantial benefits demonstrated would recommend its early use in diabetic patients.

4. Anti-platelet therapy

Anti-platelet therapy is a significant contributor to secondary prevention but should be avoided in primary prevention in those without comorbidities due to increased bleeding risk with no evidence of CVD risk reduction. In patients with DM the advice is conflicting: ESC guidelines maintain that the bleeding risk exceeds the benefits of aspiring therapy, whilst the American College of Chest Physicians recommend aspirin therapy in patients with DM and 10-year CVD event risk of $\geq$ 10%.

CONCLUSION

Nano carriers and their advancement are a promising and innovative drug delivery system that can play a vital role. Nano carriers are improving molecular imaging to help improve diagnosis and treatment of cardiovascular disease. The various novel drug delivery systems used for the treatment of cardiovascular diseases are discussed above, and these systems provide targeted drug delivery and improve the lives of various cardiovascular disorder patients by increasing patient compliance and therapeutic activity.

REFERENCES

1. S.Gousia Begum, D.Mustafa Various Novel Drug Delivery Systems in Treatment of Cardiovascular Diseases Indian Journal of Pharmaceutical and Biological Research (IJPBR) ISSN: 2320-9267.
2. Xing Chang, [1, 2] Tian Zhang, [3] Wenjin Zhang, [1] Zhenyu Zhao, and Jiahui Sun[1] Natural Drugs as a Treatment Strategy for Cardiovascular Disease through the Regulation of Oxidative Stress Oxidative Medicine and Cellular Longevity, 2020, Article ID 5430407.
3. mohd. gayoor khan the novel drug delivery system world journal of pharmacy & pharmaceutical science, 6(7): 477-487. 2278 – 4357.
4. Abrams J; Transdermal nitroglycerin in angina pectoris; European Heart, 1989; 10: 11-19.
5. Xingyan L, Hong L, Zhaowu Z, Weihua Z, Jianqiang L, Zhiwei H; Pharmacokinetics of Ligustrazine ethosome Patch in rats and anti-myocarcial and anti-ischemic reperfusion injury effect; Int J Nanomed, 2011; 6: 1391-1398.

6. Y, Bai Y, Price C, Boros P, Qin L, Bielinska AU, Kukowska-Latallo JF, Baker JR, JS: Combination of electroporation and DNA/dendrimer complexes gene transfer into murine cardiac transplants; Am. J. Transplantation, 2001; 1(4): 334-338.
7. Matoba T, Koga JI, Nakano K, Egashira K, Tsutsui H; Nanoparticle- mediated drug delivery system for atherosclerotic cardiovascular disease; J., 2017; 70(3): 206-211.
8. Paulis LE, Geelen T, Kuhlmann MT, Coolen BF, Schafer's M, Nicolay strijkers;"Distribution of lipidbased nanoparticles to infarcted myocardium with application for MRI monitored drug delivery"J Con. Rel, 2012; 162 (2): 276-285.
9. Rosenschein U, Roth A, Rassin T, Basan S, Laniado S, Miller HI; "Analysis of Coronary ultrasoun Rosenschein U, Roth A, Rassin T, Basan S, Laniado S, Miller HI; "Analysis of Coronary ultrasound thrombolysis endpoints in acute myocardial infarction (ACUTE trial) results of the feasibility phase"; Circulation, 1997; 95(6): 1411-1416.
10. Y. Mamani-Ortiz, M. San Sebastián, A. X. Armaza et al., "Prevalence and determinants of cardiovascular disease risk factors using the WHO STEPS approach in Cochabamba, Bolivia," *Bmc Public Health*, 2019; 19: 1 - 786.
11. Virmani R, Farb A, Guagliumi G, Kolodgie FD; "Drug eluting Stents: Caution and Concerns for long-term Outcome"; Coron. Artery Dis, 2004; 15(6): 313-318.
12. Belkacemi A, Agostoni P, Voskuil M, Doevendans 14. Waksman R and Pakala R;"Drug-Eluting Balloon: The P, Stella P; Drug-eluting in Coronary Artery Disease Comeback ?"; Circ Interv, 2009; 2(4): 352-358.
13. Xingyan L, Hong L, Zhaowu Z, Weihua Z, Jianqiang L, Zhiwei H; Pharmacokinetics of Ligustrazine ethosome Patch in rats and anti-myocarcial and anti-ischemic reperfusion injury effect; Int J Nanomed, 2011; 6: 1391-1398.
14. Y, Bai Y, Price C, Boros P, Qin L, Bielinska AU, Kukowska-Latallo JF, Baker JR, JS: Combination of electroporation and DNA/dendrimer complexes gene transfer into murine cardiac transplants; Am. J. Transplantation, 2001; 1(4): 334-338.
15. Matoba T, Koga JI, Nakano K, Egashira K, Tsutsui H; Nanoparticle- mediated drug delivery system for atherosclerotic cardiovascular disease; J., 2017; 70(3): 206-211.
16. Khar RK, Jain NK. Solid lipid nanoparticle as Novel Nanoparticle system in Targeted and controlled drug delivery. *IJPR*, 102-103.
17. Chaturvedi M, Kumar M, Sinhal A, Alimuddin Saifi. Recent development in novel drug delivery systems of herbal drugs.
18. Jain NK. Controlled and Novel drug delivery, New Delhi: CBS Publishers and Distributers, 2002; 4: 236- 237.

19. Amin T, Bhat SV. A Review on Phytosome Technology as a Novel Approach to Improve the Bioavailability of Nutraceuticals. *International Journal of Advancements in Research and Technology*, 2012; 1(3): 1-15.