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Role of omega-3 fatty acids and digoxin in cardiovascular diseases – A comprehensive review

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Abstract

Digoxin and omega-3 fatty acids are two different agents that have been studied for their potential roles in managing cardiovascular diseases. Cardiovascular diseases (CVDs) continue to be a global health concern, with their prevention and management being of paramount importance. Omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have garnered substantial attention for their potential therapeutic role in mitigating CVD risk factors and improving cardiovascular health. This comprehensive review aims to summarize the current state of knowledge regarding the impact of omega-3 fatty acids on cardiovascular diseases. The review encompasses a wide range of studies, including epidemiological investigations, and experimental research, to provide a holistic understanding of the mechanisms through which omega-3 fatty acids influence CVD. Key

areas of focus include their effects on lipid profiles, inflammation, endothelial function, blood pressure regulation, and arrhythmia prevention. Additionally, their potential roles in secondary prevention, such as reducing the risk of recurrent myocardial infarction and sudden cardiac death, are explored. The review also discusses the challenges and controversies surrounding omega-3 supplementation, including dosing, sources, and patient selection. Furthermore, it addresses emerging areas of research, such as the interplay between omega-3 fatty acids and gut microbiota, genetics, and personalized medicine. This comprehensive review underscores the multifaceted role of omega-3 fatty acids in cardiovascular diseases. While evidence suggests their potential benefits, further research is needed to refine recommendations and identify optimal strategies for integrating omega-3 fatty acids into cardiovascular disease prevention and management. Understanding the complexities of omega-3's effects on CVD will contribute to more effective and personalized approaches to improve cardiovascular health.

Keywords: *Omega-3 fatty, Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA), polyunsaturated fatty acids (PUFAs), Arrhythmia, Myocardial Infarction*

1. INTRODUCTION

Digoxin and omega-3 fatty acids are two distinct substances whose ability to treat cardiovascular disorders has been researched. Digoxin is a drug that is made from the foxglove plant (Digitalis purpurea) and is used to treat a variety of cardiac problems, most notably atrial fibrillation and heart failure. In comparison to omega-3 fatty acids, it operates through a different method. Atrial fibrillation is a frequent arrhythmia that is treated with digoxin to regulate the heart rate. It aids in lowering heart rate, resulting in a more effective heartbeat. Digoxin can improve the heart's ability to pump blood when a patient has heart failure [1][2]. It makes the heart muscle contract more forcefully, which some heart failure patients may find helpful. Digoxin's narrow therapeutic window, which results in a very tiny difference between a therapeutic dose and a hazardous dose, presents one difficulty. To prevent toxicity, blood levels must be regularly monitored. The ability of omega-3 fatty acids to lower triglycerides, inflammation, and the risk of arrhythmias makes them generally regarded as being advantageous for cardiovascular health. However, they may have different impacts on various cardiovascular outcomes, and not all studies have consistently demonstrated their advantages. On the other hand, digoxin is a drug that is mostly used to control heart rhythm and enhance heart function in specific cardiac disorders. Healthcare professionals should carefully weigh the risks and advantages of these procedures when choosing a treatment for cardiovascular illnesses based on the unique patient variables [3][4][5].

People are becoming more and more aware of how regularly consuming fish or fish oils rich in omega-3 fatty acids with long chains (n-3 PUFAs) reduces the risk of coronary heart disease (CHD) and guards against cardiac arrest. He suggested that the rise in Western illnesses like CHD may be due to a fatty acid deficit [6][7]. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), two types of omega-3 fatty acids (n3-FAs), have recently been studied to determine if they might reduce the risk of cardiovascular disease (CVD) in people who have taken statins. High triglyceride (TG)-rich lipoproteins (TGRLs), a dyslipidemia more common in people with diabetes and metabolic syndrome, are to blame for CV risk despite low-density lipoproteins (LDL) being effectively treated with oral and non-oral drugs [8][9]. An elevated CV risk is associated with the companion proteins Apo lipoprotein C3 (ApoC3) and angiopoietin-like 3 (ANGPTL3), which restrict lipoprotein lipase (LPL) function and increase TGRL levels. Human Mendelian randomization studies cannot establish the independence of TGs as a risk factor on their own since variations frequently have pleiotropic effects that might change the aetiology of disease. The alternative is to demonstrate the connection between TGRL and atherosclerotic events [10][11].

In individuals with well-controlled LDL-C levels and high TGs, randomised CV studies have evaluated n3-FAs for residual risk reduction. Although the TG reductions in this research were similar and effective, the results were wildly different. Studies have shown the advantages of the ethyl ester version of EPA called icosapent ethyl (IPE), but not those of more conventional mixed n3-FA preparations or other TG-lowering drugs [12][13]. Omega-3 fatty acids may lower blood pressure, particularly in people who already have hypertension. The risk of stroke and coronary artery disease can be decreased by lowering blood pressure.

The American Heart Association/American College of Cardiology, national cardiac societies, and the European Society for Cardiology have recently endorsed the utilization of the aquatic omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the treatment of cardiac infarction after it has occurred, in avoidance of fatal sudden cardiac events, and in secondary prevention [14]. Blood triglyceride levels can be lowered by omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are present in fatty fish and fish oil supplements. Reduced triglycerides can help reduce the risk of heart disease because they are a risk factor for the condition. Anti-inflammatory effects are a property of omega-3s. One of the main causes of cardiovascular disease is chronic inflammation in the body. The risk of CVD can be decreased by using omega-3 fatty acids to help decrease inflammation [15].

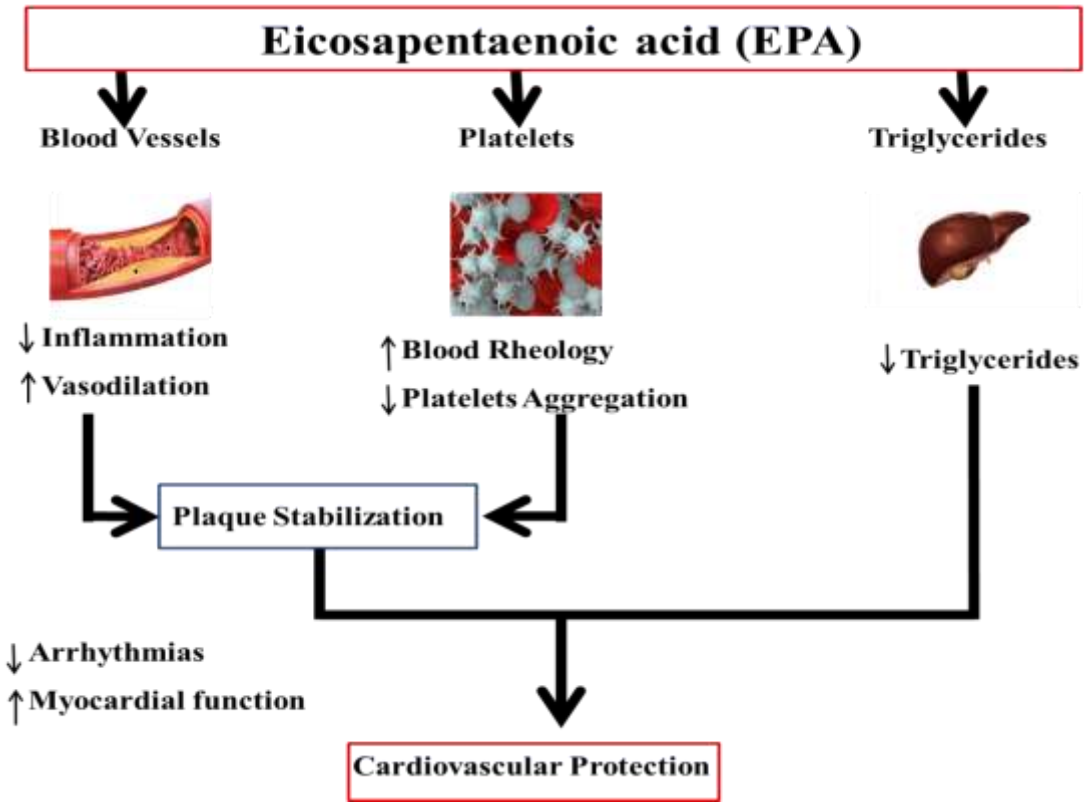

Fig. 1. Beneficial effects of omega 3 fatty acids

2. Prevalence studies of digoxin and omega 3 fatty acids

It's vital to note that prevalence studies are frequently carried out to educate politicians and healthcare professionals on the use and effects of these treatments in the actual world. The results of these researches can direct clinical practice and public health initiatives involving digoxin and omega-3 fatty acids. According on the area, healthcare system, and patient group under study, the prevalence of these agents might, however, differ greatly. For instance, they could look at whether specific comorbidities, demographics, or concurrent drugs are more likely to be linked to the prescription of digoxin [16][17]. It's vital to note that prevalence studies are frequently carried out to educate politicians and healthcare professionals on the use and effects of these treatments in the actual world. The results of these researches can direct clinical practice and public health initiatives involving digoxin and omega-3 fatty acids. According on the area, healthcare system, and patient group under study, the prevalence of these agents might, however, differ greatly [18][19].

Fish eaters frequently had decreased incidences of heart disease and unexpected cardiac death. Studies that adjust for the omega-3 fatty acid composition of the fish ingested show that this association is frequently greater [20]. It is clear that significant concentration-risk dependence exists for omega-3 fatty acid biomarkers: 90% fewer people are at risk of sudden cardiac death when their red blood cell membranes contain 6.5% more omega-3 fatty acids than when they have 3.3% more. These figures are from a case-control study of matched controls and those who had suffered sudden cardiac arrest in Seattle. Inferences from the Physicians' Health Study were

similar: After adjusting for confounders, doctors with whole blood omega-3 fatty acid levels of 6.87% had a 90% lower risk of sudden cardiac death than doctors with whole blood levels of 3.58% [21][22][23]. In the following areas of the vasculature, omega-3 fatty acids have also been associated with reduced risk: Women who ate fish five or more times per week had a 0.48 (95% confidence interval 0.21-1.06) lower risk of stroke compared to those who ate fish less frequently (less than once per month) [24]. The primary factor in these benefits seems to be the DHA and EPA richness of membrane phospholipids, which improves artery and endothelial function, reduces platelet aggregation, improves autonomic tone, boosts arrhythmic limitations, and decreases blood pressure [25][26]. Additionally, the presence of omega 3 fatty acids prevents the production of pro-inflammatory cytokines such as interleukin 6, interleukin 1, and tumor necrosis factor. Patients with heart failure should ingest 8g or more of omega 3 fatty acids per day since they reduce inflammation and improve body composition. The DHA recommends consuming 2-4 g of DHA and EPA per day for patients with excessive triglyceride levels since omega 3 fatty acids are good for lipid profiles [27][28].

Recent extensive research examined how omega 3 fatty acid supplementation affected the risk of CHD. 850 mg of DHA and EPA were given daily to 11,323 individuals who had a myocardial infarction within the preceding three months. Additionally, dietary modifications and pharmacological therapies were used to provide the optimum care for each patient. Those who received omega 3 treatment had a 21% reduced relative risk of mortality from any cause and a 45% lower relative risk of sudden cardiac death at the conclusion of the 3.5-year study [29].

Omega 3 fatty acids have not yet been the subject of a randomized control study that would examine their advantages in the main avoidance of heart attack and stroke mortality. A comparable relative risk decrease (18% vs. 19%) was seen in the secondary avoidance cohort of the Jells (n = 3,664) and the main prevention cohort (n = 14,981 hypercholesterolemia, statin treatment patients), but the latter group's reduction was statistically significant (P=0.048) while the former group's was not. The consistency of effect sizes shows that the primary prevention cohort's lack of statistically significant benefits was due to sample size rather than a difference in efficacy [30]. Fish, as well as fish oils, as well as fish oils, are recognized for their health benefits, mostly because of their substantial omega-3 fatty acid concentration. Omega-3 fatty acids are abundant in seafood, specifically fatty species like salmon, mackerel, sardines, and trout. Human health depends on omega-3 fatty acids, which also have a number of positive health effects. Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA) are the three major omega-3 fatty acid kinds that exist in fish. Omega-3 fatty acids help lower arterial pressure, cut triglyceride levels, and improve cholesterol profiles, which can all minimize the risk of heart disease. DHA is a vital part of brain tissue and is crucial for proper cognitive function. Additionally, omega-3s may lessen the chance of cognitive impairment. Omega-3s may aid in reducing inflammation and easing the signs and symptoms of illnesses like rheumatoid arthritis. DHA is critical for preserving clear eyesight and is present in high amounts in the retina [31][32]. Particularly for pregnant women and younger kids, consuming too much of certain fish might be dangerous since it may contain pollutants like

mercury. Choose seafood with lower mercury levels, such as salmon, and limit your intake of high-mercury species, including shark and swordfish, to reduce these hazards [33].

Selenium is additionally believed to possess antioxidant properties, the ability to minimize the detrimental effects of methyl mercury, and to be good for the cardiovascular system. It is present in fish in varying levels. Selenium reduces lipid peroxidation, the severity of myocardial infarctions, and ischemia-induced ventricular arrhythmias in addition to having antithrombotic properties. It also protects against free radicals and speeds up the healing of injuries brought on by ischemia or reperfusion [34][35]. Several different fish oil supplements are several different fish oil supplements on the market, including liquid and tablet versions. They are frequently used, especially for people who don't routinely eat fish, to guarantee a proper dose of omega-3s. However, speaking with a medical expert before beginning any supplements is crucial to speak with a medical expert before beginning any supplements [36].

3. Beneficial effects of digoxin and omega 3 fatty acids

Digoxin is a medication derived from the foxglove plant (Digitalis purpurea) and has been used for many years to treat specific heart conditions. Its primary beneficial effects are as follows:

- **Heart Rate Control in Atrial Fibrillation (AF):** Patients with atrial fibrillation (AF), an abnormal heart rhythm, are frequently administered digoxin. It assists by reducing the heart's electrical impulses, which can successfully regulate heart rate. Because uncontrolled fast heart rates in AF can induce symptoms like palpitations, shortness of breath, and a higher risk of problems, this is particularly crucial [37].
- **Enhanced Contractility:** Digoxin can be used to increase the power of the heart's contractions in conditions when the heart's capacity to pump blood adequately is impaired. This improved cardiac output and improved contractility might make it simpler for the heart to pump blood throughout the body. Patients with heart failure may therefore enjoy alleviation from symptoms including decreased edoema and increased capacity for activity [38].
- **Symptom Relief in Heart Failure:** Digoxin is renowned for relieving heart failure patients' symptoms. It can assist in reducing fluid accumulation in the lungs and extremities, which can help relieve symptoms including shortness of breath and edoema [39].
- **Narrow Therapeutic Window:** Although digoxin's limited therapeutic window may be a possible disadvantage, in other circumstances, it may also be advantageous. It's critical to regularly check blood levels to make sure patients get the right amount and don't experience toxicity [40].

Humans require fatty acids such as omega-3 (n-3) and omega-6 (n-6), which are further split into PUFAs based on where their initial double bonds are located in the carbon molecule. N-3 PUFAs have their first double bond at the third carbon atom, as opposed to n-6 PUFAs, which have their primary double bond at the sixth carbon atom. Arachidonic acid is created when linoleic acid, the main n-6 PUFA in humans, is prolonged and wanted. The longer-chain EPA PUFA can be produced by lengthening alpha-linoleic acid and raising DE saturation. Omega-3 and omega-6 polyunsaturated fatty acids (PUFAs) are not equivalent, despite the fact that they are both

necessary fatty acids and crucial parts of almost all cell membranes. Due to the biological effects of their metabolites, the decomposition of the n-3 and n-6 groups of fatty acids (Arachidonic acids) is of special interest. The decomposition of the n-3 and n-6 families of fatty acids (Arachidonic acid) is of special biological relevance due to the effects that its intermediates have on the body [41].

Example: n-3 PUFA-derived eicosanoids often suppress the accumulation of platelets and are anti-inflammatory in nature in contrast to eicosanoids generated from arachidonic acid, which serve as pro-inflammatory and pro-aggregator agonists [42].

The importance of omega-3 fatty acids in maintaining human health cannot be overstated. They are a kind of polyunsaturated lipid that has several advantages. Plant-based foods including flaxseeds, chia seeds, walnuts, and hemp seeds are good sources of alpha-linolenic acid. While this transformation is not very effective, the body converts ALA into the other two types of omega-3 fatty acids (EPA and DHA). Salmon, mackerel, and sardines are some examples of fatty fish that contain eicosapentaenoic acid (EPA). Additionally, it can be found in fish oil supplements. EPA is good for cardiovascular wellness and has anti-inflammatory qualities. Additionally, supplements made from fish oil and fatty fish include docosahexaenoic acid (DHA). It is necessary for the well-being of the brain, particularly throughout pregnancy and early childhood when it is essential for the nervous system's development [43].

Numerous biological processes are impacted by the lipid structure of the cell membrane. Adding omega-3 fatty acids to the cell membrane has been demonstrated in animal experiments to change how the cell functions by affecting the pathways and proteins that make up the outermost layer as well as changing the physiochemical properties of the cell membrane. When absorbed into membranes, omega-3 fatty acids may be able to change how membrane protein signals. In animal studies, the H-Ras signaling protein was also changed by the uptake of omega-3 fatty acids into cell membranes, and protein kinase levels were lowered. Message from C-theta [44]. Numerous mechanisms are involved in how omega-3 fatty acids exert their anti-inflammatory benefits. Based on certain animal research, omega-3 fatty acids may inhibit inflammation brought on by lipopolysaccharide and reduce the generation of interleukin-2. Rapid transcriptional regulation could affect inflammatory processes right away. Omega-3 fatty acids also protect against acute phase reactions [45]. The idea that omega-3 fatty acids alleviate inflammation has been refuted by a number of researches. Treatment with EPA and DHA did not reduce the hepatic inflammatory reaction brought on by laminectomy or spinal cord injury in a rat model of the disorder. According to the study, DHA exhibited anti-inflammatory qualities but EPA did not [46]. By encouraging endothelial cell synthesis of nitric oxide, omega-3 fatty acids may also enhance endothelial function [47].

Omega-3 fatty acids may also have anti-thrombotic qualities at extremely high levels, which may reduce the time that blood clots remain stable [48]. This may be explained by omega-3 fatty acids' ability to inhibit platelets. Arachidonic acid levels in tissues can be decreased by EPA and DHA, and they can be regenerated in cell membranes. Eicosanoids produced from EPA demonstrated less of a vasoconstrictive and platelet aggregating impact than eicosanoids derived

from Arachidonic acid [49]. Thromboxane A3, which is generated by the metabolism of omega-3 fatty acids, is less efficient than thromboxane A2 at activating platelets and inducing vasoconstriction. On the other hand, Arachidonic acid is converted via a metabolic process into thromboxane A2 [48]. At least not at doses that are generally advised, human studies have not consistently demonstrated a link between consumption of omega-3 fatty acids and coagulation factors or platelet aggregation [44].

Omega-3 fatty acids have the ability to block myocyte voltage-gated sodium channels and extend the relative refractory time, both of which may have a direct impact on heart rate. Higher voltages will consequently be required to depolarize the cell membrane, slowing the heart rate [47]. Omega-3 fatty acids are well known to decrease blood triglyceride levels by, among other things, lowering the amount of very low-density lipoprotein the liver produces, promoting fatty acid oxidation, and hastening the removal of triglycerides from plasma [50]. Randomized controlled studies on lipoproteins have produced a range of findings. Fewer studies have used EPA than have DHA to show an increase in low-density lipoprotein in general. Although there has been some variability in the response to EPA supplementation, high-density lipoprotein levels are frequently elevated in individuals who get DHA supplements.

Eating fish has a significant impact on reducing the risk of ischemia, heart attack, heart rate, and systemic vascular resistance, according to extensive population-based research [51][52]. Dietary guidelines from the American Heart Association advise eating fish at least twice a week, preferably oily fish like salmon, herring, and mackerel [53]. The Mediterranean diet has a lot of fish and other seafood. Along with abundance of fruits, vegetables, nuts, and grains, this diet also contains a moderate quantity of chicken [54]. A Mediterranean diet may assist to lower CVD risk factors, according to studies. The risk of significant cardiovascular events, such as cardiac infarction, stroke, and death from cardiovascular causes, can be reduced by using extra virgin olive oil or almonds in the Mediterranean diet. According to a recent large preventive randomized study with around 7000 persons at high risk of vascular issues, this is particularly true [54].

Essential fats known as omega-3 fatty acids have many positive health effects, especially for the heart and brain. They are found in foods like fatty fish (salmon, mackerel, and sardines), flaxseeds, chia seeds, walnuts, and some plant oils (canola oil, for example). However, some people might not get enough of these items in their diets, or they can suffer from illnesses that call for a larger intake of omega-3 fatty acids. Omega-3 supplements may be a practical solution in certain circumstances. One of the most well-liked forms of omega-3s is fish oil pills. Both liquid and pill versions are available. The two most advantageous omega-3 fatty acids for health are EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid), which are both found in fish oil [55][56][57][58][59].

4. Digoxin and amino-3 fatty acid's part in different cardiovascular disease

4.1. Myocardial ischemia (reduced blood supply to the heart muscle)

Elevated heart rates might make the heart work harder to get the oxygen it needs in cases of myocardial ischemia. Digoxin can be used to regulate the heart rate in those with myocardial

ischemia who also experience arrhythmias like atrial fibrillation. Digoxin may be able to decrease the heart's need for oxygen while also increasing the myocardial perfusion, or the flow of oxygen and nutrients to the heart muscle. Digoxin administration is not a recommended or first-line course of therapy for myocardial ischemia (reduced blood supply to the heart muscle). Digoxin helps regulate heart rhythm and improves cardiac contractility, making it mostly used to treat disorders including atrial fibrillation, atrial flutter, and heart failure.

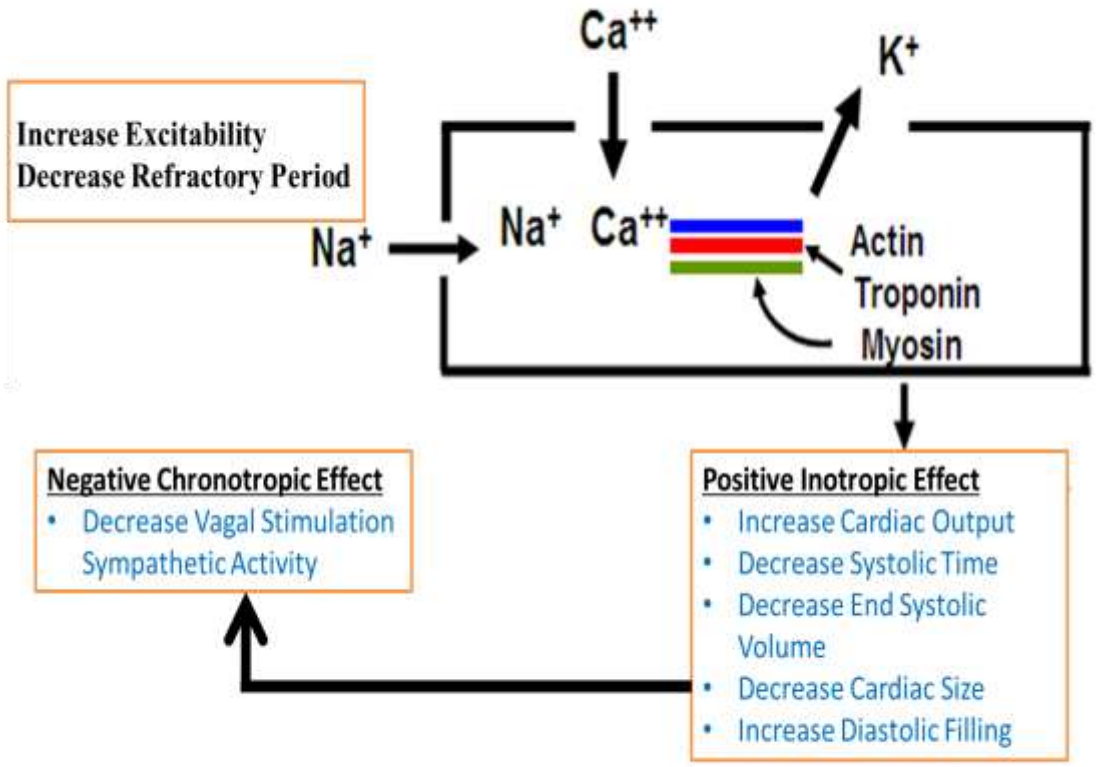

Fig. 2. Digoxin mechanism of action in myocardial ischemia

Atrial fibrillation (AF), an abnormal heart beat, is frequently treated with digoxin. It assists by reducing the electrical impulses that the heart sends out, which can successfully regulate the heart rate. This is crucial since unchecked AF-related fast heart rates can induce symptoms including palpitations, shortness of breath, and a higher risk of problems. Digoxin can be used to increase the force of the heart's contractions when a patient has heart failure, a condition in which the heart's capacity to pump blood properly is impaired. The heart may be able to pump blood more easily throughout the body because to this improved cardiac output from enhanced contractility. Patients with heart failure may therefore notice a reduction in symptoms such decreased edoema and increased exercise tolerance. The usage of digoxin is unique to particular cardiac problems, therefore not all people may benefit from it. This is a crucial point to keep in

mind[2][5][60]. Digoxin is prescribed in accordance with the unique characteristics of the patient, the existence of certain arrhythmias or heart failure, and the evaluation of possible risks and advantages by medical specialists. Digoxin use has also decreased over time as a result of worries about its limited therapeutic window and the accessibility of substitute therapies. For those with atrial fibrillation (AF), a disorder marked by irregular and frequently fast heartbeats, digoxin is frequently administered. The heart's upper chambers (atria), which fibrillate or tremble in AF, may cause an ineffective blood pump. By slowing down the electrical impulses that pass via the atrioventricular (AV) node, digoxin helps patients with AF manage their heart rate. This can be especially helpful when other rate-controlling drugs or therapies are ineffective or inappropriate[61][62]. Digoxin helps treat congestive heart failure, especially when there is systolic dysfunction. The heart's capacity to adequately pump blood is weakened in heart failure. Digoxin increases the force with which the heart contracts, improving cardiac output and reducing symptoms including weariness, fluid retention, and shortness of breath. Although it can ease symptoms, it does not enhance long-term survival[60].

Both laboratory research on isolated newborn rat cardiac myocyte and experimental examinations using canine models have been used to investigate the purported anti-arrhythmic capabilities of n-3 PUFAs, particularly EPA and DHA. For example, In order to lessen ischemia-induced cardiac arrest unexpectedly in exercising conscious dogs with previous surgically induced, large myocardial infarctions, an intravenous injection of fish oil and free fatty acid emulsion was given. This was done with an inflatable cuff around the left circumflex artery. Similar outcomes were obtained with a range of intravenous doses of pure free EPA, DHA, and -LNA [63][64][65]. Neonatal rat cardiac myocytes obtained spontaneously contracting in culture were used to further explore the mechanism(s) behind the antiarrhythmic benefits of n-3 PUFAs. By separately adding harmful substances to the bathing superfast, such as toxic Ca2+ concentrations, get, and beta-adrenergic agonist, these myocytes were made to fibrillate. It's odd that low dose n-3 PUFAs [66].

4.2. Coronary heart disease

Omega-3 fatty acids greatly reduce the incidence of coronary heart disease (CHD), a disorder in which the blood vessels nourishing the cardiac muscle constrict or become blocked, along with the creation of lipids and other substances [67]. The omega-3 fatty acids found in fatty fish and fish oil dietary supplements, particularly eicosapentaenoic acid, or and docosahexaenoic acid (DHA), help lower blood triglyceride levels. High triglyceride levels are associated with an increased risk of CHD [68]. Omega-3 fatty acids could assist in reducing blood pressure because it's a risk factor for CHD. They can improve endothelial activity and vasodilation (blood capillary expansion), leading to improved blood pressure control [69]. Elevated blood pressure is a risk factor for CHD that omega-3 fatty acids may assist in reducing. They can encourage vasodilation (blood vessel widening) and enhance endothelial function, resulting in improved blood pressure management. High-density lipoprotein or "good" cholesterol levels can be increased by omega-3 fatty acids, while low-density lipoprotein or "bad" cholesterol levels can

be decreased. The risk of CHD is decreased as a result of this advantageous change in lipid profile [70].

4.3. Cerebral blood flow

The necrosis of the brain tissue brought on by ischemia is referred to as a cerebral infarction. The cerebral blood flow (CBF) rate in a healthy person is 50 10 mL/100 g/min. Brain waves and the cerebral cortex evoked potential entirely vanish when CBF falls to 15 mL/100 g/min, yet cerebral cells continue to function. Additionally, when CBF falls even lower, to 8–10 mL/100 g/min, the ion pumps in neuronal membrane start to malfunction, causing sodium inflow and potassium efflux, which leads to the death of brain cells and cerebral infarction. Traditional definitions of TIA included bouts of neurologic impairment brought on by localized cerebral ischemia that resolve entirely in 24 hours [71]. In 2009, the American Heart Association updated the terminology, switching it from a time-based definition to a tissue-based definition [72]. Currently, the diagnosis of TIA primarily depends on the results of CT or MRI scansWhen an ischemic stroke damages brain cells, it is referred to as cerebral ischemia/reperfusion (I/R) injury, and the ischemic injury even worsens once hemoperfusion is restored. N-3 PUFAs can reduce the size of cerebral infarction by dietary supplementation in part by altering the activity of antioxidant enzymes and in part by acting directly as an antioxidant [73]. By improving the antioxidative ability, decreasing the induction of chaperon molecules, stabilizing membrane integrity, and decreasing lipid peroxidation, n-3 PUFA supplementation and chronic administration can alleviate the symptoms of cerebral I/R [74]. DHA can raise the expression of Nrf2 and HO-1 in glial cell cultures, but it is insufficient to promote their expression in living organisms. Actually, DHA therapy after an ischemic stroke can only act as a catalyst for Nrf2 and HO-1 promotion [75]. Ischemic stroke will result in complicated cellular reactions that include the activation of glial cells and the recruitment of inflammatory cells in terms of inflammation [76]. By increasing the expression of chemo attractant receptors, EPA and DHA can have neuroprotective benefits by preventing the activation of macrophages and microglia as well as the migration of neutrophils and monocytes. The production of ant apoptotic proteins like Bcl-xL and Bcl-2, which block the inflammatory response mediated by microglial cells, can also be increased by DHA [77].

4.4. Peripheral artery disease

The disorder known as peripheral artery disease (PAD) has a major effect on health in modern society. According to population-based research, more than 12% of people over 65 and more than 20% of people over 75 are considered to have PAD [78]. A more recent study found that more than one-third of patients in primary care who were over 70 had PAD [79]. In general, there are major information gaps in the public's awareness of PAD, including the disease's definition, risk factors, symptoms, and risks of amputation or mortality [80]. According to research from the International Reduction of Atherothrombosis for Continued Health (REACH) Registry, the cost of hospitalization and medication for treating PAD was greater than the cost of treating either coronary artery disease (CAD) or cerebrovascular disease (CVD) [81]. Affordable treatment is desperately needed to both prevent and treat PAD.

The HMG-CoA reductase and ACE enzymes are thought to be naturally suppressed by n-3 FAs, which are also thought to have anti-arrhythmic, anti-hypertensive, anti-atherosclerotic, anti-inflammatory, cytoprotective, and cardio protective characteristics [82].

4.5. Aortic disease

The most frequent reason for interventional therapy of the heart valves is aortic valve stenosis (AVS) [83], impacting 10% or more of those over the age of 80 [84]. Aortic valve leaflets that are fibro calcific and have a smaller valve aperture are symptoms of AVS [85]. Significant cardiac outflow blockage arises when AVS is bad enough. The only currently accessible and efficient therapeutic option for AVS is aortic valve replacement because there is no pharmaceutical therapy for the condition. The aortic valve allows blood to flow across the left chamber towards the aorta when it synchronizes its opening and shutting movements [85]. Inflammation, which is systemically shown by higher levels of C-reactive protein (CRP), has been linked in several studies to AVS [86][87]. AVS mouse models that exhibit enhanced lipoprotein infiltration, endothelial damage, inflammatory cell infiltration, and calcification of the aortic valve may offer more proof of the critical function that inflammation plays in the condition [88]. phagocytes and other cells that are inflammatory up regulate ECM-degrading enzymes and pro-inflammatory cytokines [87].

4.6. Myocardial infarction

Omega-3 fatty acids have a major impact on the treatment and prevention of cardiac infarction (MI), often known as cardiac arrest. Myocardial infarction happens when a portion of the heart muscle's blood supply is cut off, frequently as a result of the development of a blood clot in a coronary artery. Two forms of omega-3 fatty acids may be found in fatty fish and certain supplements: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The anti-inflammatory effects of omega-3 fatty acids help reduce atherosclerosis-related inflammation and stabilise atherosclerotic plaques. Atherosclerosis is the buildup of plaque in arteries. It is more probable that an unstable plaque will attack. Triglyceride levels in the blood can be decreased by omega-3 fatty acids. Cardiovascular disease, particularly MI, is at risk due to elevated triglyceride levels. The risk of atherosclerosis may be decreased and general heart health may be improved by lowering triglycerides [89][90][91].

5. Conclusion

The body of evidence strongly suggests that omega-3 fatty acids, particularly EPA and DHA, have a beneficial impact on cardiovascular health. These fatty acids have been associated with improved lipid profiles, reduced inflammation, enhanced endothelial function, and potential blood pressure regulation. Omega-3 supplementation may play a crucial role in secondary prevention, reducing the risk of recurrent cardiovascular events such as myocardial infarction and sudden cardiac death. This highlights their potential as a complementary therapy for individuals with established cardiovascular diseases. There are ongoing controversies and challenges in the field of omega-3 research. These include variations in study designs, populations, and the need for long-term studies to ascertain the sustained effects of omega-3

supplementation. Additionally, understanding the interactions with genetics, gut microbiota, and personalized medicine is a complex but promising avenue of investigation. The future of omega-3 fatty acid recommendations for cardiovascular health may involve personalized approaches. Factors such as genetics, baseline health status, and individual response to supplementation should be considered when determining the most effective strategies. Omega-3 fatty acids hold promise as a valuable addition to the armamentarium for cardiovascular disease prevention and management. While further research is needed to address remaining questions and refine recommendations, the existing body of evidence supports their inclusion in a comprehensive approach to cardiovascular health. Tailoring omega-3 strategies to individual patient needs and considering them within the context of overall cardiovascular care will likely yield the greatest benefits.

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