Research on Drug Therapy of Atherosclerosis

Yu Cao[1,*,†a] and Xiangrui Chen[2,†b]
[1]Southland Christian Schools CA, U.S.A.
[2]Chengdu Foreign Languages School the International Department, Chengdu, Sichuan, China

[†]These authors contributed equally

Keywords: Atherosclerosis, PCSK-9 Inhibitors, Marine Omega-3 Fatty Acids, Statin, Bio-Nanomedicines, Berberine.

Abstract: Atherosclerosis is a chronic inflammatory disease in which atherosclerotic plaque accumulated on the walls of blood vessels and causes narrowing of the arteries. Atherosclerosis usually is asymptomatic in its early stages, and may causes coronary artery disease, stroke, peripheral artery disease and renal failure in severe cases. In general, the symptoms associated with atherosclerosis do not appear until after middle age. Most elderly people who over 65-years-old have atherosclerosis of varying degrees, atherosclerosis is the leading cause of death and disability in developed countries. The atherosclerotic process is very complex, to participate in the cells and tissues, including epithelial cells, smooth muscle, monocytes, macrophage, platelets, lipoprotein, growth hormone, cholesterol, fat and cytokines, etc. Based on these participated mediators, cells and tissues, scientist developed many drugs to relief atherosclerosis. Prevention of atherosclerosis generally includes a healthy diet, exercise, quitting smoking, and maintaining a healthy weight. The drugs include Statins, aspirin, berberine and antiplatelet drugs. In addition to drugs, percutaneous coronary intervention, coronary bypass surgery can also be used to treat atherosclerosis. Recently, scientists focused on the "Bio-Nano" which provide more efficient approach to treat atherosclerosis. The advantages of Nanomedicines are obvious and show its effective function in the clinically experiments, Nanomedicine possess targeted positing systems and enter capillaries and flow freely in the blood circulation system. The Nanomedicine with high future expectation worth showing to more people who suffer atherosclerosis. The review article introduces several distinctive drugs which relief atherosclerosis based on the disease's pathogenesis, including their functions, detailed mechanism, how to play its function in human body.

1 INTRODUCTION

According to the global survey, one people has a stroke among 12 people in China, there are about 2.7 million new cerebrovascular diseases every year, and trend is increasing year by year, especially in rural areas (Deright, Jorgensen, & Cabral, 2015). In the United States, one person has a stroke among forty people, the ischemic stroke accounts for 87%. The recurrence rate of ischemic stroke is high, previous report of Western stroke registries showed that the cumulative recurrence rate within 5 years after stroke was 17%-30%. (Carpenter, Ford, & Lee, 2010). Although ischemic stroke has many etiologies or risk factors, atherosclerosis is the main pathogenic factor, especially in people over 5o years of age (Sanne, Zinkstok, Ludo, & Beenen, et al. 2014). Atherosclerosis, driven by the chronic inflammation of the arteries caused by early endothelial dysfunction and monocyte recruitment leading to the platelet aggregation, gradually the plaque was formed with the accumulation of cholesterol, lipid, or other blood substance on the blood vessel wall, is the primary cause of heart disease and stroke (Greenstein, Sun, Calderon, Kim, Berman. 2000). In fact, Atherosclerosis took place in people since adolescent because of the transportation of oxygen and other material to the rest of body make the arteries thicken and harder, Healthy arteries are flexible and elastic (Schreiber, Greenstein, Kim, Calderon, Berman, 1998), but over time, the walls in your arteries can harden, a condition commonly called hardening of the arteries. In westernized societies, it is the underlying cause of about 50% of all deaths (Kim, Kang, Kwon,

[a] https://orcid.org/0000-0003-0479-5544
[b] https://orcid.org/0000-0003-0855-6727

Cao, Y. and Chen, X.
Research on Drug Therapy of Atherosclerosis.
DOI: 10.5220/0011214500003443
In *Proceedings of the 4th International Conference on Biomedical Engineering and Bioinformatics (ICBEB 2022)*, pages 440-447
ISBN: 978-989-758-595-1

2005). To eliminates the patient's conditions, researcher developed several efficient drugs to relief the Atherosclerosis, including statins, which lower bad cholesterol as low-density lipoproteins, several drugs such as PCSK-9 inhibition and Marine Omega-3 Fatty Acids that promoting the cleanness of cholesterol and the protection for fragile fibrous cap, antiplatelet drug, and vasodilation drug, which all researched and developed by the pathogenesis of the atherosclerosis. These drugs matured during the long period of applying and studying, But the bio-Nanomedicine was still in the researching stage and had profound meaning for atherosclerosis, with high future expectations. Nowadays, many scientists, especially Chung Hang Jonathan Choi research interests include "Bio-Nano " interactions, and bio-nanomaterials, drug delivery (Davis, Mark, Zuckerman, Jonathan, & E, 2010). The Bio-Nano medicine provided a new perspective for scientists to study the atherosclerosis, which was a more effective approaches to help patients relieve. One more important thing was that atherosclerosis was not a disease that only affected human's heart, it also had subsequent impact on other organs, such as brain, kidney, liver. Therefore, the information about medicine that treated atherosclerosis was vital and necessary for many people who had atherosclerosis or not. The purpose of the review article was to summarize different types of medicine and advanced techniques around the world (Mulder, Jaffer, Fayad, & Nahrendorf, 2014), because many European countries, the amount of people who suffer atherosclerosis increased by a dramatic rate. People could get more advanced information about these medicine from the article and know the basic knowledge about the atherosclerosis, and how to prevent the formation of atherosclerosis.

1.1 Atherosclerosis

Atherosclerosis is known as Arteriosclerotic Vascular Disease (ASVD) which is considered an inflammatory disease of the artery, which can thicken and harden the arterial wall, and gradually lose elasticity and narrow lumen in the artery. Injury to endothelial cells in the artery provokes a series of inflammatory responses (Nilsson, 2019). The endothelial cells start to produce cell surface adhesion molecules like VCAM-1, which can cause monocytes and T-lymphocytes to adhere to the endothelial cells, and let endothelial cells move downstream through squeezing. The endothelial cells also change shape, and elasticity, which increase the permeability to fluid, lipids and leukocytes, especially the LDL (Kang, Martinez, HJ Müller, & E Angléscano. 1997). When these factors migrate into the intima, monocytes differentiate into macrophages, which begin to take up LDL. Macrophages retain the lipid they take up, and as they become more lipid-laden, they are referred to as foam cells. Finally, foam cells will undergo apoptosis and die, but the lipid will accumulate in the intima (Munro, 1988). That's why the fatty streak forms in the artery wall beneath the endothelium. Over time, the fatty streak can evolve into atherosclerotic plaques, or they can remain stable or even regress. Slowly growing plaques expand gradually due to accumulation of lipid in foam cells and migration and proliferation of smooth muscle cells, these slowly growing plaques are matured and called fibrin caps, which are not prone to rupture. But other plaque grows more rapidly as a result of more rapid lipid ruptures, it can trigger an acute thrombosis by activating platelets and the clotting cascade (Cunningham, Gotlieb, 2005).

In detail, atherosclerosis can be divided into three diseases, including arteriosclerosis of small arteries, arteriosclerosis in the middle layer and atherosclerosis. The atherosclerosis appears with the growth of age, and its rule usually occurs in the adolescent periods and aggravates and comes on in the middle and old age. and atherosclerosis is usually asymptomatic in its early stages, but when it becomes serious, may cause coronary artery disease, stroke, peripheral artery disease and renal failure in several cases (Kutikhin, Brusina, & Yuzhalin, 2013). The pathogenesis of atherosclerosis is complex and has not been fully elucidated, the main risk factors are included hypertension, hyperlipidemia, smoking, diabetes and genetic factors, the treatment plan for various risk factors consist of appropriate physical activity, intervention of lifestyle and food, as well as drug and surgical treatment. Among them, the drug therapy is the most effective and quick treatment for atherosclerosis.

2 DRUG TYPES

Currently there are three kinds of medications that have been put into use in order to treat atherosclerosis, which are antiplatelet drugs, anticoagulants, and cholesterol-lowering drugs.

2.1 Antiplatelet Drugs

Firstly are the antiplatelet drugs, medicines used to reduce the aggregation of platelets in the blood therefore preventing the formation of blood clots. After the vascular endothelial injury, collagen is exposed, and stationary platelets, platelet membrane glycoprotein (GPlb), and von Willebrand factor (vWF) is influenced, then blood platelets are activated and show adhesive property. With the effect of platelet activator, such as ADP, TXA 2, 5-HT and Adr, platelet membrane receptors GPIIb/IIIa bind to fibrinogen to form early thrombosis. During the adhesion, a series of reactions take place, including the metabolism of arachidonic acid (AA), with production of TXA2. As the platelets absorb fibrin network, the blood clot gradually develop into strong platelet-fibrin mesh.

Aspirin, as one familiar name for a large number of people, is considered as the most commonly used oral antiplatelet drug. It works by irreversibly inhibiting the cyclooxygenase enzyme (COX) activity in the prostaglandin synthesis pathway (PGH2). This prostaglandin is a precursor of thromboxane A2 (TXA2) and PGI2. (Warner, Nylander, & Whatling, 2011) Also being an epoxide inhibitor, the inhibition on COX-1 is reversible using Indobufen. As mentioned, TXA2, a synthetase, is produced during the activation of platelets, which can be controlled by a kind of thromboxane synthase inhibitor called Ozagrel. Another medicine, tirofiban, works by reversibly combining with platelet receptor GPIIb/IIIa, preventing receptors and fibrinogen coming together, therefore resisting platelet aggregation. Tirofiban is very effective and highly selective. In antithrombotic therapy, sometimes a combination of drugs is required as different drugs taking effects at different stages may be more efficient.

2.2 Anticoagulants

Anticoagulants play an important role in restricting clot formation at the injured site. Anticoagulants mainly focus on thrombin, an important enzyme that causes the final path of coagulation process, and coagulation factor X, known as the intersection of endogenous and exogenous coagulation systems. They can be divided into thrombin direct (bivalirudin, argatroban) and indirect (heparin) inhibitors, vitamin K antagonists and factor Xa inhibitors (rivaroxaban, apixaban). Direct thrombin inhibitors can inhibit both fibrin-binding thrombin and free thrombin, while indirect thrombin inhibitors can only work on free thrombin. Xa factor, a kind of vitamin K - dependent serine protease, is the speed-limiting factor in the formation of thrombin. The inhibitors have a strong inhibitory effect on both Xa factors and prothrombinase complex. As the role of factor Xa infers, the inhibition on factor Xa is thought to be more effective than the effect of thrombin inhibitors. (Viladrich, E Daudén Tello, Solano-López, FJ López Longo, Samso, & P Sánchez Martínez, et al. 2016)

2.3 Cholesterol-lowering Drugs

There are also cholesterol-lowering medicines, which are used to lower lipid level in the blood, particularly the low density lipid (LDL) cholesterol. Statins is one of the cholesterol-lowering medicines， including simvastatin, atorvastatin, and pravastatin. Bile acid sequestrants—colesevelam, cholestyramine and colestipol—and nicotinic acid are other types of medicine that may be used to reduce cholesterol levels.

Among those, the statins are the first choice of lipid-lowering drugs. HMG-CoA reductase is a rate-limiting enzyme in the cholesterol synthase system. By inhibiting it, statins can reduce cholesterol synthesis, reduce cholesterol concentration in plasma and tissue cells, promote the activity of concentration-dependent LDL receptors, and accelerate the catabolism of LDL. It can also reduce the synthesis of very low density lipoprotein, which is VLDL, and convert VLDL into LDL reduction. Therefore, it is proven that statins can significantly decrease TC and LDL levels, reducing TC levels by 30%-40% and LDL-C levels by 35%-45%.

3 PROVE TO CLEAR SUBSTANCE

3.1 PCSK9 Inhibitor

Proprotein convertase subtilisin/kexin type-9 (PCSK-9) is a key player in plasma cholesterol metabolism that can bind to LDL-R at the liver and stimulates the absorption and degradation of these receptors, eventually lowering the receptors levels (Cameron, Ranheim, Kulseth, Leren, & Berge, 2008). PCSK-9 is a 72-kd protease, expressed highly in the liver with three recognizable domains, an N-terminal pro domain, a catalytic domain, and a carboxyl-terminal domain of unknown function, and these can bind to the LDL receptor on the surface of cells, when the nuclear environment reach the acidic level, the

affinity of PCSK-9 for the LDL receptor increases by nearly 150-fold, and PCSK-9 binds to the epidermal growth factor (EPG) repeat A of the LDL receptor, which known as a crucial for recycling of the LDL receptor from endosome to the cell surface (Mabus, Palmer, Prouty, Hornby, & Wade, 2010). Overall, PCSK-9 disrupts the route of the LDL receptor, making it miss the way to reach the cell surface.

So, the drug called PCSK-9 inhibitors can play its function through inhibition of PCSK-9, the degradation of LDL-R is prevented thereby improving the absorption by the liver of LDL cholesterol particles, which consequently leads to lower LDL cholesterol plasma concentration (Norata, Garlaschelli, Grigore, Raselli, Tramontana, & Meneghetti, et al. 2010). For now, the PCSK-9 therapy is suitable in a wide range of patients provided that they express LDL-R.

3.2 Marine Omega-3 Fatty Acids

Marine Omega-3 Fatty Acids are nutrients people get from food or supplements that help build and maintain a healthy body. They're key to the structure of every cell wall people have, also an energy source and help keep heart, lungs, blood vessels and immune system working the way they should. Based on the function of Marine Omega-3 Fatty Acids, researcher found the potentially possibility to relief Atherosclerosis (Calder, 2012). Marine Omega-3 Fatty Acids can make the fibrous cap or plaque become more stable, the patients who ingest Marine Omega-3 Fatty Acids in a long time, the plaque from patients are more likely to be type IV, which possess well-formed necrotic core with an overlapping thick fibrous cap, IV plaque can be considered a good fibrous cap (Kühnast, van der Hoorn, JoséVan, Havekes, Liau, & Jukema, et al. 2012). Marine Omega-3 Fatty Acid also lowers the level of these immune cells surrounding the plaque. Rupture of plaque is an extremely acute occurrence that exposes the plaque contents to the high prothrombotic environment of the vessel lumen, which can lead to myocardial infarction, stroke or another vascular event. Also, inflammatory cells, including macrophages, T cells, mast cells, are typically abundant at such locations within thin and tender fibrous cap that easier to rupture, and these cells can produce a range of medicator and enzymes that can thin and weaken the fibrous cap making the plaque vulnerable and unstable (Eschen, Christensen, Toft, & Schmidt, 2005). So essentially Atherosclerosis is an inflammatory event called plaque that can rupture and lead to a series of dangerous consequences. Marine Omega-3 Fatty Acids can stabilize atherosclerotic plaque by decreasing infiltration of inflammation and immune cells, like monocyte/macrophages and lymphocytes, into the plaques or by decreasing the activity of these cells once in the plaque to lower the possibility of rupture of plaque. There are two crucial ones- EPA and DHA which are primarily found in certain fish, ALA (Alpha-Linolenic Acid), another Omega-3 Fatty Acids, is found in plant sources such as nuts and seeds (Calder, 2012). EPA and DHA give rise to resolving which are anti-inflammatory and inflammation resolving, and also affect production of peptide mediators of inflammation.

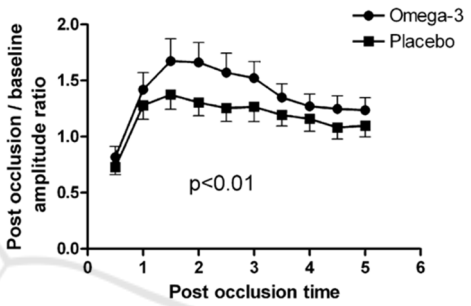

Figure 1: Vasodilatory response to reactive hyperemia after omega-3 or placebo treatment. Pair-wise compared curves using global fitting are shown (p = 0.01). Data points represent mean ± SD. (Dangardt, Osika, Chen, & et al. 2010).

4 NEWTYPE DRUGS

4.1 Target Medications

Several nanomedicines are exemplified by the US Food and Drug Administration's approval for various conditions. The main idea about nanomedicine is about targeting specific substances in the blood, like nonspecific targeting, specific targeting of the vasculature, etc. Nanoparticle-facilitated therapeutics can potentially be applied to target the liver and change lipid levels systemically, or they can directly inject the high density of lipoprotein nanoparticles to enhance the transport of cholesterol in plaque to the liver for excretion. And nanomedicine can deplete the recruitment of monocytes or decrease plaque inflammation and neovascularization (Tian, Lu, Feng, & Melancon, 2018). Nanomedicine is a new type and still developing medication. Nanomedicine's delivery systems can solubilize drugs, improve drug half-life, improve drug distribution in vivo and reduce toxic and side effects.

Bio-Nanomaterials is considered as a new strategy to curing Atherosclerosis and the application of the strategy to promote the specific delivery of therapeutic molecules to atherosclerotic plaques is under active investigation. A classic example is the doxorubicin-containing liposome, the first Bio-Nanomedicine approved by the United States Food and Drug Administration for treating cancer in 1995 (Maranh, Tavares, AF Padoveze, Valduga, Oliveira, & Rodrigues, 2006). Because Bio-Nanomedicine contains partially or completely of biomolecules, such as lipids, sugars and nucleic acid and proteins, which is easier to control or develop the methods to change the dimensional structure or the number of biomolecules. An efficient approach to apply bio-nanomedicine is to let the drug be injected into a lipid which acts as a vector, and the drug-encapsulated lipid could target the atherosclerotic plaques. In 2016, Scientists (Kim, Rutka, & Chan, 2010) loaded carmustine, a lipophilic chemotherapeutic, into lipid NPs for targeting atherosclerosis plaques. They set a series of experiments which inject the bio-Nanomedicine into the atherosclerotic New Zealand rabbits, and the drug-encapsulated NPs can reduce the plaque size. But the method still was in the experiment stage. Actually, all Bio-Nanomedicine was applied based on the pathogenesis of Atherosclerosis. The migration and death of monocyte and macrophage can destroy local tissue of architecture by secreting proteases and inflicting oxidative stress on the vessel wall. And some enzymes would digest the fibrous cap, thereby initiating plaque rupture. So, the macrophage was readily ingested nanomaterial and could be the prime of target for novel therapeutics. Lobato et al. (Lobatto, Fayad, Silvera, Vucic, Calcagno, & Mani, et al. 2010) develop the methods of using bio-nanomedicine to inhibit plaque macrophage inflammation directly, they observed marked and persistent plaque inflammation inhibition using a liposomal nanoparticle containing glucocorticoids in the atherosclerotic mouse.

One new study of Bio-Nanomedicine is using a “camouflage” to inhibit the atherosclerotic plaque. Because when strangers enter into the bloodstream in a human's body, the immune system would start to attack the drug and make it fail (Yamawaki, & Iwai, 2006). The methods used the methods that cover the drug with the common cell membrane that the immune system recognized and familied, and then inject it into blood, the immune system still would attack the drug but less than without the “camouflage”. The Biomimetics nanometer therapy (Rienzo, Jacchetti, F Cardarelli, Bizzarri, F Beltram, & Cecchini, 2013) in the study is to read cell membrane packages on the surface of nanodrugs, implementation of nanodrugs “camouflage”, which can effectively reduce the possibility that the body system removes the nanodrugs, so that nanodrugs can make long-term-nanodrug efficiency in the blood circulation, thereby promoting nanodrugs targeting to the pathological changes of atherosclerosis.

4.2 Berberine as an Antiatherosclerosis Drug

Scientists have been also working on new type drugs for higher effectiveness as atherosclerosis is still a serious disease today. One of the existing drugs that mainly works on digestive system has been found to behave as a lipid-lowering drug. Berberine, which a lot of studies have been done on, has antibacterial effect on hemolytic streptococcus, Staphylococcus aureus, Neisseria gonorrhoeae and Shigella dysentery, etc., and can enhance leukocytophagocytosis. It has varying degrees of inhibitory effect on tuberculosis bacillus and yersinia pestis, and also has inhibitory effect on amoeba in rats. With the strong support of the National Natural Science Foundation of China, the research team led by Dr. Jiang Jiandong, director of the Institute of Medical Biotechnology of the Chinese Academy of Medical Sciences, has made breakthroughs in gene sequence, cell, animal experiments and clinical treatment. The pharmacodynamics, pharmacodynamics and molecular mechanism of berberine in reducing blood cholesterol and triglyceride were systematically studied. They found that berberine lowers blood lipids at the post-transcriptional level by acting on mRNA (messenger RNA) that stabilizes LDL receptors in the 3'UTR region, a mechanism completely different from that of statins currently used to reduce blood lipids. This provides a new molecular target for finding new hypolipidemic drugs in theory. Clinical studies have shown that oral berberine (1 gram per day for 3 months) can reduce cholesterol, low density lipoprotein and triglyceride by 20% ~ 35% in patients with hyperlipidemia, which has been further confirmed by hyperlipidemia golden hamster model animal experiments. Dr. Jing Wei from Nanjing First Hospital and Dr. Jingwen Liu from Veterans Hospital paralto, California, USA, both indicated that berberine may be a substitute for statins, and is expected to be used in combination with statins in the treatment of cardiovascular diseases.

4.2.1 BBR Protect the Cardiac Muscles by Raising the Concentration of Protein Kinase of Ischemic Myocardia

The activated adenosine 5'-monophosphate-activated protein kinase (AMPK), as the key particles in the regulation of biological energy metabolism, can restrain the consuming of adenosine triphosphate (ATP). On the other hand, it can stimulate cells to produce more ATP, therefore prolonging ATP supply time within the cells, which plays a protective effect to ischemic cardiac muscle cells.

Calcium ions are vital to the human body, because they participate in the clotting process, muscle contractions, neurotransmitter synthesis and release, hormone synthesis and secretion, plus they are the important elements in bone formation. When BBR reduces the number of alpha-adrenergic receptors on the membranes of the cardiac muscles, calcium influx is inhibited, and cell apoptosis is blocked in order to protect myocardial cells. (Cheng-Yi, H. U., & Zhi-Xian, M. O)

4.2.2 Trials of Patients with Related Diseases

According to a series of trials involving 874 patients who had type 2 diabetes, hyperlipidemia, hypercholesterolemia and related diseases. Ten experiments were single-center experiments, and one study was multi-center experiments. Patients with type 2 diabetes were included in four studies. One study recruited hyperlipidemia patients with type 2 diabetes. And there was a study of patients with impaired glucose tolerance and hyperlipidemia. Patients with hyperlipidemia were included in two other studies. And another two studies included patients with hypercholesterolemia. Besides, one of the research projects included recruited patients with polycystic ovary syndrome and insulin resistance.

Six studies randomly assigned participants to take berberine under lifestyle changes and without changes, and placebo with or without intervention. According to experiment description, two trials showed combined effects of berberine and oral hypoglycemic agent with a controlled hypoglycemic agent. Two others compared the combination action of berberine and simvastatin with a simvastatin control. One trial compared a combined intervention of berberine and cyproterone acetate with placebo plus cyproterone acetate. Two berberine preparations were used in the inclusion trials, berberine chloride tablets (used in 10 trials) and berberine chloride liposome capsules (used in only 1 trial). Different doses of berberine were used in these trials. The intake of berberine is generally between 0.5-1.5 g per day. Daily intake of berberine is divided into two or three doses. The dose of berberine did not change during the 8 trial periods. Three trials reduced the dose of berberine when gastrointestinal discomfort occurred during the study period.

A comprehensive estimate of the effect of treatment on lipid concentration is summarized in Figure 3. There was significant statistical heterogeneity in blood TC and TG results among different studies (P <0.10). The results showed that there was significant difference between the berberine treatment group and the control group. Berberine was significantly better than the control group in improving blood TC (P < 0.00001;Md-0.61 easier/L;95% CI-0.83 ~ 0.39) and TG (P <0.00001;Md-0.50 mmol/L: 95% CI-0.69 ~ 0.31).There were no statistically significant differences in LDL-C and HDL-C among tests (P > 0.10).Compared with the control group, the level of LDL-C was significantly increased in patients taking berberine (P <0.00001; Md-0.65 easier/L; 95% CI -0.76 -- 0.54) and HDL-C (P =0.001;MD 0.05 easier/L; 95% CI 0.02 to 0.09).(Dong, H., Zhao, Y., Zhao, L., & Lu, F.. (2013)

Figure 2: Meta-analyse of the effects of berberine on total cholesterol levels.

5 CONCLUSIONS

In conclusion, atherosclerosis is a chronic vascular disease that usually occurs in the aorta and muscular arteries, such as the coronary, cerebral, renal, and carotid arteries (Stary, Blankenhorn, Chandler, Glagov, Insull, & Richardson, et al. 1992). These disease with high death rate were caused by atherosclerosis, so the medication for reliving atherosclerosis was more vital. Clinically, there are many drugs used for the pathogenesis of atherosclerosis, such as dyslipidemia and hypertension, and their action pathways and targets

are different. Based on the dyslipidemia, which was a basic pathogenesis of atherosclerosis, scientists developed the drug called PCSK-9 inhibitor, which inhibits the PCSK-9 that prevents the LDL receptor bind with cholesterol. And statin was the most common drug that was used in relieving atherosclerosis, statin could lower cholesterol level, its working process to block a specific substance that participated in process making cholesterol. Drugs, like statin, PCSK-9 inhibitor, antiplatelet medication, were tested and already used for a long time (Taleb, Witztum, & Tsimikas, 2011). They possessed high stability and took advantage in the drug market. In addition, different drugs can be used in combination according to different mechanisms of action to achieve better efficacy. Nowadays, some kinds of bio-nanomedicine are undergoing development. They achieve progress in the experimental stage, which motivates people to study further and persist. Scientists indicated the bio-Nanomedicine with "camouflage" might potentially become the most expectable drug (Stenosis, 1995), which reduces the rejection phenomenon. Within the potentiality of bio-nanomedicine, it would become the mainstream of atherosclerosis, it is more precise and readily but still undergoes experiment clinically. In the future, Bio-nanomedicine may would be the mainstream to cure or treat some diseases, which could provide more efficient treatment for patients and more precise to target its pathological position. Scientists might should pay more attention on the accuracy of target with the bio-nanomedicine and how to use magnetic field to kill cancer cells.

REFERENCES

Carpenter, D. A., Ford, A. L., & Lee, J. M. . (2010). Patent foramen ovale and stroke: should pfos be closed in otherwise cryptogenic stroke. Current Atherosclerosis Reports, 12(4), 251-258.

Cunningham, K. S., & Gotlieb, A. I.. (2005). Erratum: the role of shear stress in the pathogenesis of atherosclerosis. Laboratory Investigation.

Cameron, J., Ranheim, T., Kulseth, M. A. , Leren, T. P. , & Berge, K. E. . (2008). Berberine decreases pcsk9 expression in hepg2 cells. Atherosclerosis, 201(2), 266-273.

Calder, P. C. (2012). The role of marine omega-3 (n-3) fatty acids in inflammatory processes, atherosclerosis and plaque stability. Molecular Nutrition & Food Research, 56(7).

Calder, P. C. (2012). The role of marine omega-3 (n-3) fatty acids in inflammatory processes, atherosclerosis and plaque stability. Molecular Nutrition & Food Research, 56(7).

Cheng-Yi, H. U., & Zhi-Xian, M. O.. Research progress on pharmacological actions and mechanism of berberine. Chinese Journal of Experimental Traditional Medical Formulae.

Deright, J., Jorgensen, R. S., & Cabral, M. J. . (2015). Composite cardiovascular risk scores and neuropsychological functioning: a meta-analytic review. Annals of Behavioral Medicine, 49(3), 344-357.

Davis, Mark, E., Zuckerman, Jonathan, & E., et al. (2010). Evidence of rnai in humans from systemically administered sirna via targeted nanoparticles. Nature, 464(7291), 1067-1070.

Dong, H., Zhao, Y., Zhao, L., & Lu, F.. (2013). The effects of berberine on blood lipids: a systemic review and meta-analysis of randomized controlled trials. Planta Medica, 79(06), 437-446.

Dangardt, F., Osika, W., Chen, & Y., et al. (2010). Omega-3 fatty acid supplementation improves vascular function and reduces inflammation in obese adolescents. ATHEROSCLEROSIS -AMSTERDAM-.

Eschen, O., Christensen, J. H., Toft, E. , & Schmidt, E. B. . (2005). Soluble adhesion molecules and marine n-3 fatty acids in patients referred for coronary angiography. Atherosclerosis, 180(2), 327-331.

Greenstein, S. M. , Sun, S. , Calderon, T. M. , Kim, D. Y. , & Berman, J. W. . (2000). Mycophenolate mofetil treatment reduces atherosclerosis in the cholesterol-fed rabbit. Journal of Surgical Research, 91(2), 123-129.

S Kühnast, van der Hoorn, José W.A., Van, d. H. A. M. , Havekes, L. M. , Liau, G. , & Jukema, J. W. , et al. (2012). Aliskiren inhibits atherosclerosis development and improves plaque stability in apoe*3leiden.cetp transgenic mice with or without treatment with atorvastatin. Journal of Hypertension, 30.

Kim, J. S., Kang, D. W. , & Kwon, S. U. . (2005). Intracranial atherosclerosis: incidence, diagnosis and treatment. *Journal of Clinical Neurology,* 1(1), 1-7.

Kang, C. , Martinez, C. , HJ Müller, & E Angléscano. (1997). 2.p.121 binding of apo(a) isoforms to fibrin is modified by their incorporation into an ldl lipoparticle. Atherosclerosis, 134(1), 142-142.

Kutikhin, A. , Brusina, E. , & Yuzhalin, A. E. . (2013). A Hypothesis of Virus-Driven Atherosclerosis. Springer New York.

Kim, B. , Rutka, J. T. , & Chan, W. . (2010). Nanomedicine — NEJM.

Kunde, S. S., & Wairkar, S. . (2021). Platelet membrane camouflaged nanoparticles: biomimetic architecture for targeted therapy. International Journal of Pharmaceutics, 598, 120395.

Lobatto, M. E., Fayad, Z. A. , Silvera, S. , Vucic, E., Calcagno, C. , & Mani, V. , et al. (2010). Multimodal clinical imaging to longitudinally assess a nanomedical anti-inflammatory treatment in experimental atherosclerosis. other, 7(6).

Mulder, W. J. M., Jaffer, F. A. , Fayad, Z. A. , & Nahrendorf, M.. (2014). Imaging and nanomedicine in inflammatory atherosclerosis. Science Translational Medicine, 6(239), 239sr1.

Munro, J.. (1988). The pathogenesis of atherosclerosis: atherogenesis and inflammation. Lab Invest, 58.

Maranh O, R. C. , Tavares, E. R. , AF Padoveze, Valduga, C. J. , Oliveira, T. V. , & Rodrigues, D. G. . (2006). Wh-w49:7 paclitaxel associated with a lipidic nanoemulsion (lde) promotes atherosclerosis regression in the rabbit. Atherosclerosis Supplements, 7(3), 466-466.

Mabus, J. R. , Palmer, J. M. , Prouty, S. M. , Hornby, P. J. , & Wade, P. R. . (2010). Methods of modulating intestine epithelial functions. Janssen Pharmaceutica.

Norata, G. D. , Garlaschelli, K. , Grigore, L. , Raselli, S. , Tramontana, S. , & Meneghetti, F. , et al. (2010). Effects of pcsk9 variants on common carotid artery intima media thickness and relation to apoe alleles. Atherosclerosis, 208(1), 177-182.

Nilsson, J. ,. . (2019). Cytokines and smooth muscle cells in atherosclerosis.

Poston R . TREATMENT OF ATHEROSCLEROSIS: US, WO2006032905 A1[P]. 2006.

Rienzo, C. D. , Jacchetti, E. , F Cardarelli, Bizzarri, R. , F Beltram, & Cecchini, M. . (2013). Unveiling lox-1 receptor interplay with nanotopography: mechanotransduction and atherosclerosis onset. Scientific Reports, 3, 1141.

Sanne, M., Zinkstok, Ludo, F., & Beenen, et al. (2014). Early deterioration after thrombolysis plus aspirin in acute stroke. Stroke, 45(10).

Schreiber, T. C. , Greenstein, S. M. , Kim, D. Y. , Calderon, T. M., & Berman, J. W.. (1998). Effect of mycophenolate mofetil on atherosclerosis in a rabbit model: initial histologic and immunohistochemical analyses. Transplantation Proceedings, 30(4), 961-962.

Stary, H. C., Blankenhorn, D. H., Chandler, A. B., Glagov, S., Insull, W., & Richardson, M. , et al. (1992). A definition of the intima of human arteries and of its atherosclerosis-prone regions. a report from the committee on vascular lesions of the council on arteriosclerosis, american heart association. Circulation, 85(1), 391-405.

Stenosis, E.. (1995). Executive committee for the asymptomatic carotid atherosclerosis study. jama.

Tian, L., Lu, L. , Feng, J. , & Melancon, M. P. . (2018). Radiopaque nano and polymeric materials for atherosclerosis imaging, embolization and other catheterization procedures. Acta Pharmaceutica Sinica B, 8(003), 360-370.

Taleb, A., Witztum, J. L., & Tsimikas, S.. (2011). Oxidized phospholipids on apob-100-containing lipoproteins: a biomarker predicting cardiovascular disease and cardiovascular events. Biomarkers in Medicine, 5(5), 673-694.

Viladrich, I. M., E Daudén Tello, G Solano-López, FJ López Longo, Samso, C. T., & P Sánchez Martínez, et al. (2016). Consensus document on prevention and treatment of tuberculosis in patients for biological treatment. Archivos De Bronconeumologia, 52(1), 36-45.

Warner, T. D., Nylander, S., & Whatling, C.. (2011). Anti-platelet therapy: cyclo-oxygenase inhibition and the use of aspirin with particular regard to dual anti-platelet therapy. British Journal of Clinical Pharmacology, 72(4), 619-633.

Yamawaki, H., & Iwai, N. (2006). Mechanisms underlying nano-sized air-pollution-mediated progression of atherosclerosis. Circulation Journal, 70(1), 129-140.

Zhang, L., & Nichol, M. B. (2007). Ao1 medication compliance to statin therapy and its impact on disease outcomes in type 2 diabetes. Value in Health, 10(3), A6-A6.