WPI

Social and Technical Issues in Ischemic Vascular Disease Prevention

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Executive Summary

Background and Pathophysiology

Cholesterol accumulation in the blood can result in blockages called plaques that cause larger issues such as heart attack or stroke. Cholesterol is made by the liver as a byproduct, which comes from food that an individual consumes. Current screening methods for high cholesterol primarily rely on blood lipid profiles. Physicians will also use lifestyle profiles to predict severity of cholesterol associated diseases, and in severe cases, ultrasound can locate plaques. The methods to clear plaques include atherectomies, which use a catheter to remove cholesterol; statins, which are a category of drug that can cease the production of cholesterol by the liver; apheresis, which is an extracorporeal device that can remove blood cholesterol; and dialysis, which is a generic extracorporeal blood cleaning method that uses a room-sized device that takes multiple hours to clean the blood.

Methods

Research databases were used to find articles for the literature review, which was used to source a majority of information on the existing disease state. Interviews were conducted to get both a patient's and doctor's perspective on issues, and a calculator was made to prove a correlation between relative geographical income and likelihood of cardiac mortality.

Social Determinants of Health

Social Determinants of Health can be defined as "The conditions and environments in which people are born, live, work, play, worship, and age", and include factors such as nutrition and exercise, which can influence the serum cholesterol levels; income, which can influence access to healthcare and healthy food; geography, which can influence healthcare and diet; and socioeconomics, which can influence factors such as diet and exercise. A calculator was made that proved correlation between relative geographical income and mortality due to cardiac illness.

Value Proposition

The problem of cardiac illness affects many industrialized nations and is a leading cause of death in a majority of these, including the United States, which has a prevalence rate of 73.5 million people total. Other solutions on the market exist, such as aforementioned apheresis, atherectomy, and dialysis. There was a US patent that was filed for a Wearable Artificial Kidney under the patent number 10,933,183, which has since expired. Our proposition is to have a drug that is injected into the veins that can dissolve existing plaques.

Proposed Solution

The proposed solution is to develop a drug based on the enzyme cholesterol esterase to break down cholesterol ester plaques that have already formed. This step would be between the point of taking statins and having an apheresis or atherectomy.

Social and Technical Issues in Ischemic Vascular Disease Prevention

Abstract

Cardiovascular disease is the leading cause of death in the United States and other major developed countries. Within the United States, one in three people will be diagnosed with high cholesterol, and 20% of deaths annually will be due to cardiac illness. Millions of Americans are diagnosed with high cholesterol each year, and live with it for most of the rest of their lives. High cholesterol has been associated with poor diet, lack of exercise, lower than average income, geography, and genetic predispositions. Cholesterol buildup in vasculature is called a plaque, which can cause narrowing of the arteries, ischemia, and eventually lead to major cardiac events such as heart attack or stroke.

In preparation for an injection based treatment for high cholesterol, this report was developed to research the anatomy, physiology, and pathophysiology of cholesterol based cardiovascular disease; current screening methods for hypercholesterolemia; the social determinants of health that influence cardiovascular disease; current treatment methods; the value proposition of an alternative treatment; and a technical proposal for the future project.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the United States as well as other major developed countries. Within the United States, one in three people will be diagnosed with high cholesterol, which is a significant risk factor for CVD, and 20% of deaths will be due to cardiac illness annually. Millions of Americans are diagnosed with high cholesterol each year, and live with it for most of the rest of their lives. Throughout the world, cholesterol is a major risk for CVD and early death or disability in developed countries such as Canada, Britain, Russia, China, and Scandinavia. High cholesterol has been associated with poor diet, lack of exercise, lower than average income, geography, and genetic predispositions. Cholesterol buildup in vasculature is called a plaque, which can cause narrowing of the arteries and full occlusions resulting in major ischemic events such as heart attack or stroke.

In preparation for an injection based treatment for high cholesterol, this report was developed to research the anatomy, physiology, and pathophysiology of cholesterol-based cardiovascular disease; current screening methods for hypercholesterolemia; the social determinants of health that influence cardiovascular disease; current treatment methods; the value proposition of an alternative treatment; and a technical proposal for the future project.

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Background and Pathophysiology

Anatomy and physiology of plaque buildup:

This section presents the anatomical and physiological processes that lead from food consumption to plaque buildup in arteries

Process of food to fats

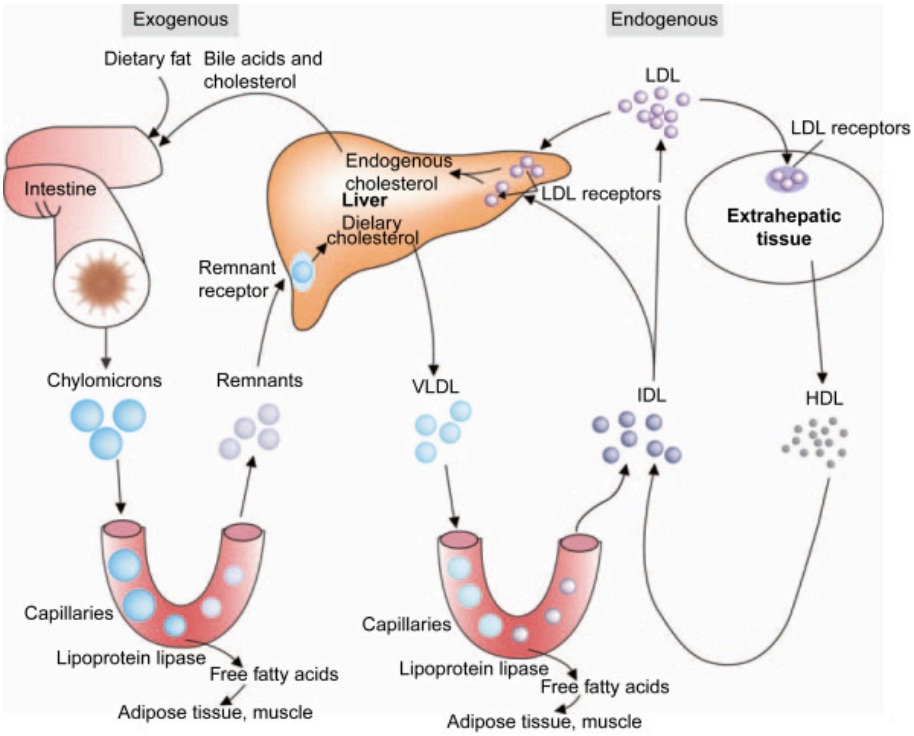


Figure 1 shows the pathway through which food is processed and turns into fats in the blood (Penny M et. al., 2023)

As shown in Figure 1, the process by which food is turned into plaque follows the the pathway: Food dietary cholesterol & saturated fats → Stomach → Digestion (Not broken down in Stomach) → Intestines → Converted to Chylomicrons → Lipoprotein Lipase in blood breaks down into free fatty acids → Remnants go to liver → Remnants converted to VLDL → VLDL goes to capillaries → Lipoprotein Lipase in blood breaks down into further free fatty acids → HDL, LDL, or Triglycerides.

HDL, or high density lipoprotein, is generally used for transportation of cholesterol while LDL, or low density lipoprotein, is also used for transportation of cholesterol but is not as efficient at this process. Cholesterol is used for injury repair, as it is found in the cell membrane between the phospholipid bilayer. It also helps with production of hormones and Vitamin D from sunlight (Shey Martin, 2024). Free fatty acids can build up in arteries. Foods from which cholesterol can initiate include fatty meats, baked goods (specifically sweets), oils, food, and full-fat dairy (such as whole milk). Free fatty acids turn into plaque buildup in arteries through cyclical processes. These cycles occur when endogenous cholesterol, or cholesterol that is not fully broken down, is returned to the intestines (Figure 2). Alternatively, when the LDL is free, it can return to the liver. There are some studies that suggest that plaque may build up in the

liver, this research has shown that plaque buildup can affect the liver but the plaque was not found directly in the liver (Harvard, 2015).

Figure 1 shows that the fatty acids are deposited in the body, but it does not show what happens after this point. There are multiple ways in which arteries can become blocked by plaques. Once source notes that plaque deposits can come from each of the subsequent sources (anonymous, Mount Sinai Health)

In addition to excess dietary plaque deposits, arterial plaque buildup can be caused by inflammatory immune responses, higher blood pressure, complications from diabetes, and vascular injury (NIH). Inflammation typically occurs in response to injury or to a foreign pathogen. The inflamed site can eventually turn into a bulge or indentation in the blood vessel or a fibrous deposit (scar). This serves as a catch point for the plaque to get caught and start the cascade of plaque buildup in the arteries.

High blood pressure (hypertension) can lead to muscular thickening of arterial walls and subsequent narrowing of the arteries. This thickening and narrowing can trap circulating plaques, a condition known as atherosclerosis. The chronic hypertension can also erode and release the plaque deposits that have aggregated on the inside layer of blood vessels, or within the inner lining.

High blood pressure has also been associated with turbulent blood flow, which then can cause potential plaques to get caught in eddies that form in the blood flow, which then can cascade into a plaque buildup.

Diabetes, a deficiency in blood sugar caused by pancreatic deficiency leading to insulin dysregulation, can cause a buildup in plaque by causing excess solute in blood. One study says that the excess solute in blood can result in clogged arteries. This is because it can obstruct blood flow and even reduce blood pressure, which then can result in plaques forming in the arteries (Branon, 2022). High cholesterol has been found in as many as 70% of patients diagnosed with diabetes

The last major source of plaque buildup is when there is an injury. Injuries generally involve cellular damage or death. As stated before, cholesterol is found in the cell membrane. Hence, when cellular repair is necessary, the body sends cholesterol to the area to be put into the new cell membranes. However, a physiological excess of cholesterol can contribute to plaque formation of plaques

Once there is a small inflammation or other bulge in the vessel wall, it creates the ability for plaques to form. How this happens is that the fats and cholesterol traveling

through the blood catch on the bulge. This starts a cascade where they adsorb to other similar molecules, such that the fats and cholesterol turn into a deposit of plaque. When caused due to injury, there frequently is a layer of endothelium that covers the plaque, as mentioned earlier. This makes it difficult for vascular immunogens to be able to identify and target the plaque. Figure 2 shows the formation of plaque.

Plaque formation in arteries

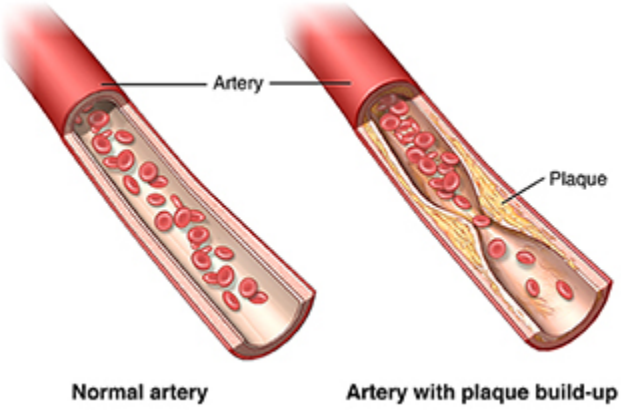


Figure 2 shows that some plaques may have a cellular surface between the plaque and the blood (Johns Hopkins Medicine)

Screening methods:

Current screening methods for CVD include ultrasound, lipid testing, calcium testing, genetic testing and algorithms that combine physiological tests with patient history (ASCVD testing)

Ultrasound is a non-invasive method that can be used to view the vasculature within and around the heart and in other areas that might have plaque buildup. An ultrasound works with a transducer that can, with the help of a gel, send and receive its own sound waves at varying frequencies. These frequencies, inaudible to the human ear, can be varied such that they have different penetration depths. The receiver then translates the sound into an image, where it is a plane parallel to the transducer.

Plaque buildup may be located in different areas of the body that might not be screened. The other limitation to ultrasound imaging for CVD is that depending on the depth, the ultrasound may not be able to get a very clear view of what each artery around the heart looks like, as there may be obstructions in and around the area. These obstructions could include other vasculature, organs, tissue, and bones. If the area is deeper in the chest, it may be more difficult to tell what could potentially be plaque

buildup. While ultrasound may detect narrowing and a potential blockage, it is not sensitive enough to determine the nature of the occlusion (cholesterol, blood clot, inflammation, tumor, normal physiology, or foreign body).

Assuming that it can work, ultrasound would be examined depending on what view of the artery there is. If it is a side view, then a bulge that makes the artery non-linear and creates a hump in the artery would be indicative of a buildup in that location. If there is a view of the cross section, then it would be easier to look for a buildup of plaque. In this case, the discriminator would be if there is a visible bulbous object in the vein but again, the ultrasound can not determine the cause of the suspected pathology.

To travel through the vein, the frequency of the ultrasound may be changed to observe the cross section at different depths so as to be able to view the entirety of the vein. However, as stated before, it is not easy to view all of the vasculature and there is the potential that some veins may be overlooked. Despite this, ultrasound seems to be one of the best options for non-invasive assessments and relatively cost effective screenings, although it does make it difficult for areas that are less developed to be able to screen effectively if they do not have access to ultrasound technology.

One potential workaround for ultrasound inability, in the case of not having electricity, is to deliver the ultrasound device with batteries and solar equipment to charge the batteries. This would allow for places that do not have electricity to screen for plaque buildup in arteries. In less developed areas, it would require training on how to use the device and what to look for specifically.

Lipid testing is a method through which a sample of blood is taken and analyzed for specific types of cholesterol. This type of examination looks for lipids in the blood in the form of fats. The way it detects and quantifies lipids is by centrifuging a blood sample, which would separate the blood into layers. This would leave a layer of fats, which are then extracted and weighed. Once the weight is obtained, it is converted to total body by using the ratio of blood drawn to total blood in body.

Calcium testing is another common method for testing for plaques, as calcium deposits are a concern in the blood. It works similarly to a lipid blood test, except that the calcium is turned into $CaCl_2$, which is a salt that can be quantified. Once the $CaCl_2$ has been obtained, it also is weighed, with the weight of the chlorine subtracted and then made proportional to the entire body.

There have been attempts at making calculators for risk based on health information and personal data. Two widely used tests in clinical practice are the ASCVD score calculator and PREVENT™ calculator. To test the validity of these calculators, interviews were done with people with high cholesterol or who were at risk for high cholesterol and their laboratory values were entered into the calculator. Results are discussed later in this report.

Calculating risk without actual physiological samples has benefits but also carries risk. These calculators generally take into account blood pressure, cholesterol levels, history of certain illnesses, and status on things such as statins. These calculators would normally give a 10 year risk percentage. From research done with actual numbers, different calculators with similar inputs gave drastically different answers. One such calculator gave an 8.8% chance for the conditions entered (see appendix G). For the same conditions, another calculator gave a risk factor of 3.5%. The two possible conclusions that can be drawn are either that the risk was too low to be accurately calculated, or the calculators are not reliable. A third calculator that was income-based calculated 9.6%, offering another data point. Future developments should include testing with different numbers to observe the data points.
The ASCVD testing calculator can be found at: https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/

Plaque Clearing methods:

Current methods for removing pathological plaques include both pharmacological and surgical approaches. A major concern for both approaches is that cleaning plaque from arteries by targeting cholesterol is getting rid of the ‘good cholesterol’. This is a concern because some types of cholesterol are physiologically useful, so by targeting cholesterol we may be targeting the good cholesterol as well.

The leading method of clearing cholesterol with medication is through statins. Statins are oral drugs that are consumed, metabolized by CYP_{450} isoenzymes, “and prevent gastrointestinal and hepatic first-pass metabolism”, (Cid-Conde and Lopez-Castro, 2019) This means that when first consumed, the statins are not metabolized in the body and the drug component remains in the same form as it was when it was consumed. Another means of clearing plaque is through prescription medications. Medications can reduce cholesterol by : inhibiting cholesterol production of cholesterol by the liver through disabling enzymes; limiting production of blood fats in liver; and bile acid sequestrants, which attach to bile acids so that they are removed from the body.

Atherectomy

An atherectomy involves a physician using an X-ray machine to pinpoint the location of the blockage or buildup of plaque. The modern ‘minimally’ invasive treatment deploys a laser or a blade on a catheter that is then inserted into the patient, typically through a femoral or radial vein or artery and directed to where the buildup or blockage is, and then used to cut out the blockage.

Atherectomies can result in insertion site infections, cellulitis, bleeding, or bruising. The catheter is inserted but there is little that is done to clean the residual plaque from the blood after the occlusion has been cleared. A suction catheter is typically deployed alongside the blade to catch debris. However, debris that is not captured may occlude in other locations.

Atherectomy graphic

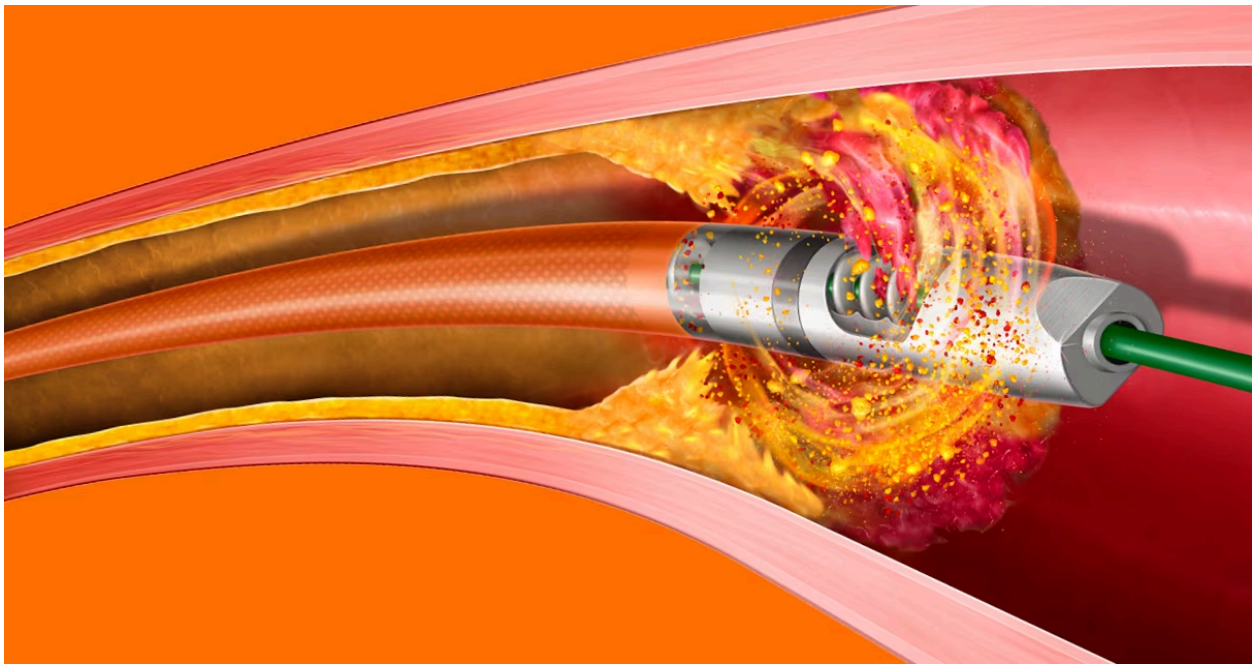


Figure 3 shows an atherectomy catheter graphic that demonstrates one of the numerous ways of clearing plaque from arteries (Rotarex, 2024)

Pharmaceutical treatments for arterial plaque buildup generally are used for reduction of cholesterol, but are limited in their ability to remove existing plaque buildup. The closest medication that can remove plaque is bile sequestrants, but even those are limited in their abilities. Generally, if someone needs bile sequestrants and those are not sufficient for reducing cholesterol levels, then they are referred to physical operations, as discussed in the previous paragraph. (American Heart Association, 2024).

As shown in Figure 4, statins work by competitive inhibition of HMG-CoA reductase, which is an enzyme that catalyzes the conversion of HMG-CoA into a substance called mevalonate. Mevalonate is a pathway that produces mevalonic acid (Tricario et. al 2015),. Mevalonic acid is then converted into Mevalonate 5-P and then 5-PP. During the steps between HMG-CoA and Mevalonate 5-P, Cholesterol is produced as a waste product.

The way statins work is that they use competitive inhibition to prevent the reductase from being able to function, hence shutting down the mevalonate pathway and preventing further production of cholesterol. However, statins only work to prevent further production of cholesterol and cannot function to actively reduce the amount of cholesterol that has already built up. (CDC, 2020)

Mevalonate pathway and its inhibition by statins

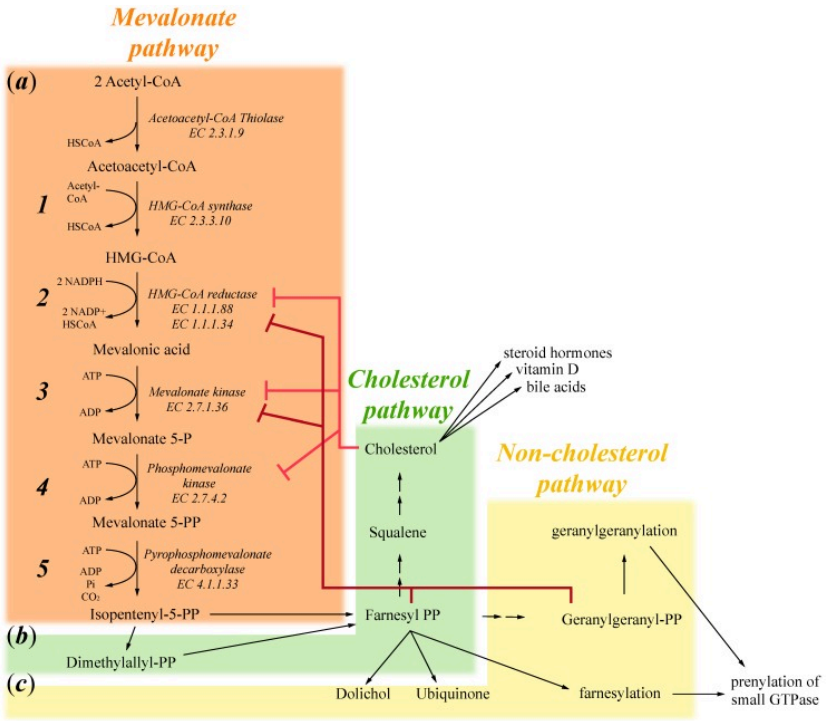


Figure 4 shows how the mevalonate pathway produces cholesterol. Statins work by inhibiting the process from steps 1 to 2 in the orange box. (Olson et al., 2015)

Blood Cleaning methods:

The primary method for cleaning blood is through dialysis. Dialysis is usually required when a patient has kidneys that become ineffective at removing contaminants in blood. This is usually done by a large machine with an intake and a return, which are two IV leads that go from an artery through the dialysis machine and back into the vein. The process can generally take a few hours and can be performed up to multiple (three

or less) times a week, which can be very uncomfortable for patients. Dialysis generally removes waste products that the kidneys would have removed, such as lactic acid from anaerobic respiration, and some elements such as Sodium, Calcium, Phosphorus, and Potassium. (NIDDK, 2018)

While dialysis can be life-saving for patients with kidney failure, the technology may not be easily accessible to a large demographic and requires a large amount of machinery to be able to perform the cleaning. It also takes a few hours to complete the full intake and a return cycle, which can be uncomfortable for patients.

There are two proposed methods by which hydrolyzed cholesterol can be removed via a dialysis-type process. Process one would require two filters, one being 50 nm and the other being 10 nm. The process would require an intake that removes the blood from the body, runs the blood through the filter, and then returns the blood through the return tube. The 50 nm section will remove the larger part of hydrolyzed cholesterol, and the 10 nm section will remove the smaller part. The length is the diameter of the pore sizes in the cleaning filter.

The blood will be blocked at the first filter and returned to the body through the return tube, and the hydrolyzed cholesterol molecules will be caught in the two removable chambers. When the chambers are removed, the valve will close, which would open a different valve that would allow all fluids taken out to return to the body. Two sections would then be cleaned and replaced, and the mechanism can continue to filter the blood.

There are some problems with this first proposed dialysis-type solution. Anything that is between 10 nm and 50 nm in size will get caught in the filter, which may not be desirable as some things that may be critical can get caught in the filter.

A second proposed option for a dialysis-type solution is an active filter. The hydrolyzed cholesterol ester would break down into two parts; the cholesterol itself and a fatty acid. The targeted cholesterol being mentioned is actually the ester thereof, meaning that the final product would be cholesterol and a fatty acid.

The active filter would have one section that chemically bonds to and removes the cholesterol, and one that binds to the fatty acid and removes that. These substances were researched to discover what substances the filters should be made of to bind to the cholesterol.

The section that removes cholesterol should be a soluble fiber. This would bind to and remove the cholesterol from the system. The structure would have pores that are large enough for the adsorbed soluble fibers to bind to cholesterol, but not too big that it would start leaking.

The second stage would have a structure similar to the first stage, but using something that binds to fatty acids instead. Fatty Acid-Binding Proteins (FABPs) are capable of binding to fatty acids. The structure of the second stage would contain FABPs that would adsorb to a mesh that would allow for the fatty acids to be caught in the mesh with the FABPs. Once full, the same valve mechanism would be in place as the passive filter, where the blood would be returned to the body if the filters have been removed. The filters can then be replaced and continue to absorb hydrolyzed cholesterol.

Custom diagram of proposed way to clean blood

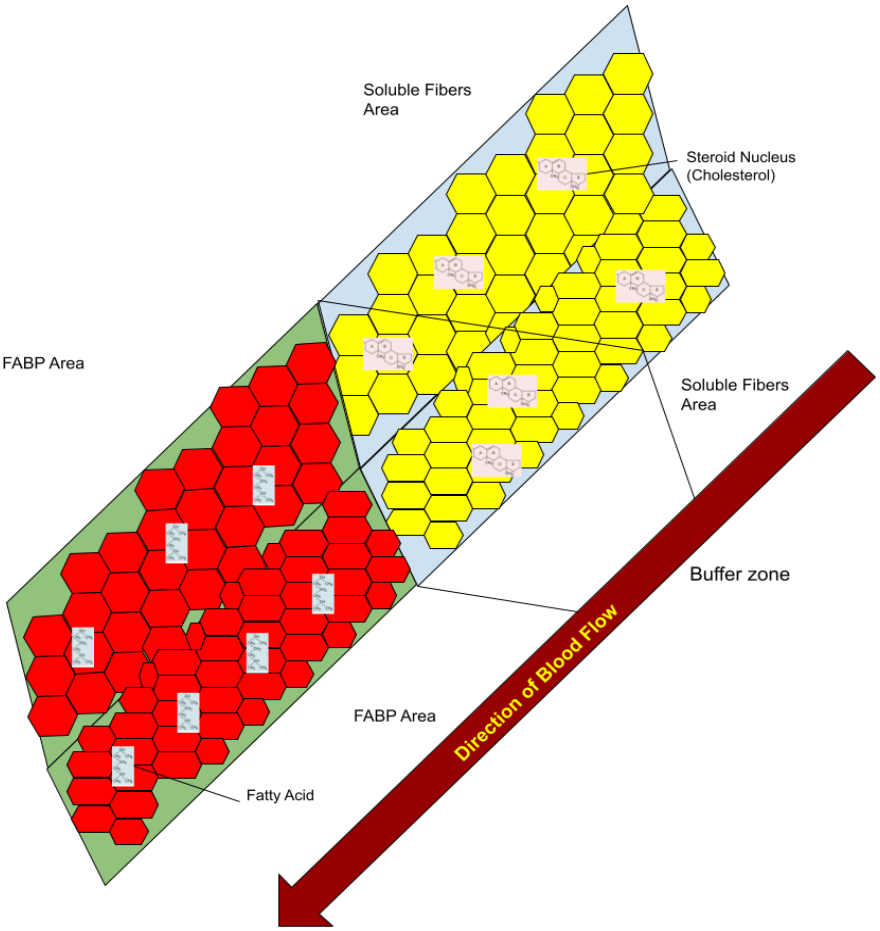


Figure 5 is a diagram of how an active filter would work, which was drawn specifically for this study by Christopher Libby. The Hexagons represent the pores in the material that would serve as a buffer area between the soluble fibers or FABP (depending on section) and the molecules themselves. The red molecules are the steroid nucleus or cholesterol and the chartreuse molecules are the fatty acids. The yellow hexagons are where the soluble fibers would be and the red hexagons are where the FABPs would be.

The above diagram shows that the hydrolyzed cholesterol ester molecules should stick to the filter where the fibers or FABPs have adsorbed to. This is a side view of what it would be, indicating that this would be cylindrical with this pattern going all the way around it. The active filter would have an inner tube and outer tube, where between these tubes will be the fiber or FABP areas, and inside the inner tube is where blood will flow, and the outside of the outer tube is the outermost layer, touching the atmosphere.

Apheresis

One of the options on the market is an Apheresis. An Apheresis works similarly to dialysis. It has an extracorporeal system that takes blood from the patient, runs it through a filter, and then returns the blood to the patient, as seen in figure 6.

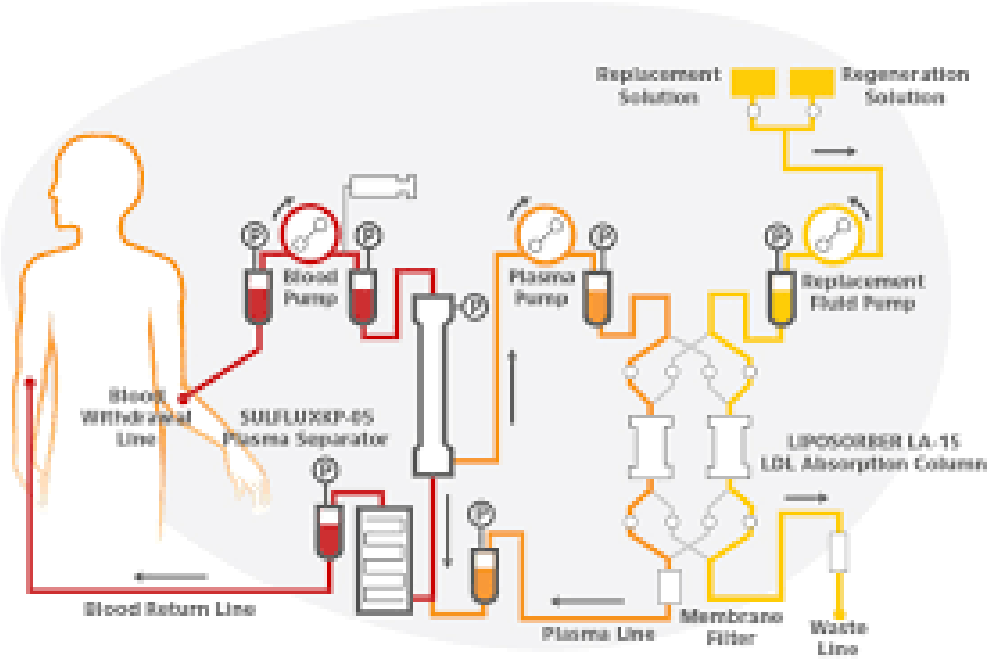


Figure 6 shows the process through which an apheresis machine works. (Metabolic Leader)

An Apheresis is used to target serum cholesterol for removal. As described in the article that sourced Figure 6, Apheresis is used as a last resort mechanism for people who did not respond to any other cholesterol lowering methods. Apheresis lasts for 3 to 4 hours and is repeated every two weeks.

The mechanism works by separating the red blood cells from the plasma. The plasma then travels through a cellulose-coated column that attracts LDL particles and removes them from the blood. After the LDL has been removed, the plasma is recombined with the red blood cells and returned to the body. An Apheresis can cost up to $2500 per treatment, resulting in $5000 per month, which results in $60,000 per year, which is above the median income for the United States.

Methods for Project Research

The project started by using existing literature. Cholesterol is known to be a major risk factor for Cardiovascular Disease (CVD), so there is significant

documentation. CVD itself is also well documented. This project consulted research reports and existing literature through databases such as Pubmed, NIH, and Medscape, as well as using tools such as gapminder for insight on mortality.

Beyond online research, multiple interviews were conducted. One was with a patient, and one with a practitioner; both of whom can be found in the acknowledgements.

Interviews

Below is the disclaimer and interview script used in the interviews with a patient (Interview 1) and a physician who specializes in cardiac care (Interview 2).

Disclaimer for participants

This interview is for research purposes only. You have the right and freedom to not answer a question that you do not wish to answer, and if you find it necessary, you may end the interview at any time.

Interview 1: John B. Libby, patient

Below can be found a summary of the conversation with the patient John B. Libby.

Q: What is your Sex, Age, Total Cholesterol, HDL cholesterol, BMI, eGFR, SBP, And your statuses on the following: Diabetes, smoking, anti-hypertensive medication, lipid-lowering medication, UACR, HbA1C, and your zip code?

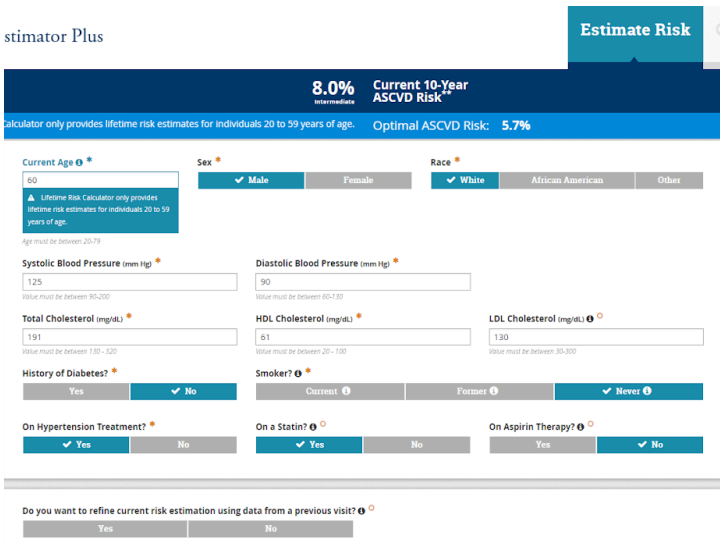
A: The answers are as follows

1. Male
2. 60
3. Total cholesterol is 191
4. HDL cholesterol is 61
5. BMI is 27.4
6. eGFR is 90
7. SBP is 125
8. DBP is 85
9. Not diabetic
10. Non-smoker
11. Yes, currently taking anti-hypertensive medication
12. Yes, taking lipid lowering medication
13. No, No UACR
14. No, No HbA1c
15. Zip code is 03909

Q: The calculator estimated 3.3% in the next 10 years. Do you feel this is accurate?

A: “Not bad odds. Probably fair.”
Q: Another calculator returned a chance of 8.0% for the same data.
A: ‘This feels as though the calculators are not precise as they returned drastically different numbers. What did your calculator return?’
Q: The calculator is percent deaths of all deaths per 100,000, so it is not the most reliable. I will run the numbers anyway. The calculator said 9% based on an estimated income.
A: This indicates that the second calculator was closer, or the real number is closer to 8%-10% rather than as low as 3%.
Q: This makes sense, as the first calculator did not request as much information.
A: “Ok. Calculators have a hard time accounting for the many factors. More a figure of merit”

ASCVD Calculator with Given Values



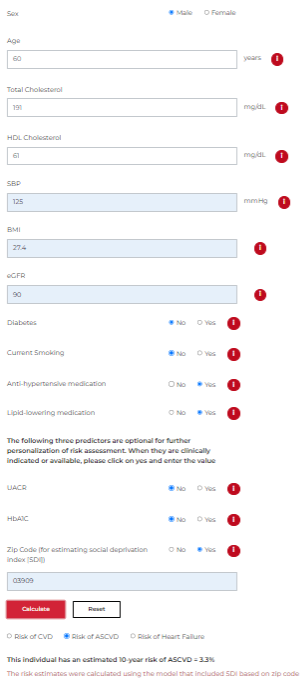


Figure 7 ASCVD Calculator with values from interview and results. Patient data used with permission.

Interview 2: Dr. Bill Dietz, medical practitioner

Section 1: Preliminary questions developed before the interview

1. How frequently do you diagnose a patient with high cholesterol; what percent of your patients have high cholesterol
2. What is the prevalence of heart disease and heart disease and high cholesterol in Southern Maine? Are we similar to national rates or different?
3. How do you screen for high cholesterol?
4. What symptoms do you normally see with high cholesterol? Are there patterns or other issues you generally see with patients with high cholesterol? What symptoms are most concerning?
    a. Can generally be asymptomatic
        i. Based on research, not actual answer to the question
5. How much of a risk would you say high cholesterol poses to your average patient who has high cholesterol?
6. How do you treat patients who have high cholesterol? What factors affect your determination as to what a patient with high cholesterol should do?

Section 2: Summary of the conversation

Q: How frequently do you test for high cholesterol in patients, and of those that you do test, how many would you say are in the at-risk range?

A: Test everyone, biggest risk factor for CVD. Screen almost all of the adult patients at least once every few years.
Q: Of the patients tested in southern Maine, would you say there is a high prevalence of high cholesterol in patients?
A: In York County and southern New Hampshire and some from inland, get referred people who have cardiac issues and prevalence of lipid problem is pretty high.
Q: Would you say 22% of deaths due to CVD is accurate
A: We get referred cardiac patients and your information is generalized so it's not really a good comparison. A more interesting statistic is deaths by age group.
Q: How do you screen for high cholesterol
A: Just do a standard lipid profile; standard profile, calculate LDL, HDL, total, and triglycerides.
Q: Are there any symptoms or diseases that are correlated with high cholesterol?
A: Hyperlipidemia is a risk for many other diseases. People can get other things, usually look at history and see if anything is modifiable, generally there is no symptom that is corresponding to high cholesterol. It can also be easily modifiable and treat it and help with risks for other heart issues.
Q: If someone has high cholesterol, how frequently would you say they are at risk?
A: It has to be put in the framing of the patient and the profile of the patient. Diabetes is a huge risk for cholesterol.
Q: We used multiple calculators and got different results, what do you make of this?
A: Nobody fits into a mold perfectly; some people have different risk factors.
Q: So if you had someone who had different scores, which would you use?
A: Personally don't look at risk scores, rather what absolute numbers look like. Sometimes look at calcification in arteries. Someone who is asymptomatic with high cholesterol and patient is hesitant, calcium scoring ct would be used to determine the necessity of treatment. A lot of times, it is patient driven and what their desire is to reduce their cholesterol.
Q: What factors determine if you treat high cholesterol
A: Profile the patient, doing primary prevention with the patients. If a patient has high cholesterol but no event before, then it comes to preference. Secondary prevention is they have already had a cardiac event and they get treated much more aggressively.
Q: How do you treat patients with high cholesterol?
A: Generally going to statins and use those frequently, and give the high-dose statin for treatment for secondary prevention. For primary prevention, many factors such as risk factors and their numbers and preferences come into play.

Reviews of Current Research

Reviews of current research included:

Research reports

Published Interviews
Pubmed
NIH database
Medscape

Keywords used in these searches included …..

Databases

Databases consulted for CVD morbidity and mortality included Gapminder and United States Government databases. These databases were used to develop a calculator (detailed below) that predicts CVD deaths based on national or regional income)

Social Determinants of Health

According to an NIH study on hypercholesterolemia, it was determined that it can affect 73.5 million adults in the United States, which equates to about 31.7% of this population (Ibrahim et al., 2023). The study also says that hypercholesterolemia and ischemic heart disease have been associated with nutrition and exercise, income, and geography. These factors are components of what are called the social determinants of health. Social determinants of health can be defined by the NIH as “The conditions and environments in which people are born, live, work, play, worship, and age” (NIH, 2023).

Two categories of measurement of disease are incidents and prevalence. Incidents are defined as the number of new cases per a period of time, and prevalence is total cases at a given point in time. If a disease or pathogen has low prevalence, it may either be sparse or uncommon, easily curable, or highly deadly. If something has a high incident count, then it is highly contagious.

Nutrition and Exercise

Nutrition and exercise are causal factors leading to hypercholesterolemia and cardiovascular disease. Availability of food and choices regarding foods consumed may lead to ischemic heart disease through increased cholesterol intake, while exercise can decrease LDL and increase HDL by exerting energy. Fats can be used as medium term energy, so if the patient is exercising, they can more easily burn energy in the form of fat. If the patient does not have easy access or capability to exercise, then they will build up fats to store energy but not wind up using them. Income can affect nutrition, and geography can affect exercise.

Another factor that affects how people may be able to exercise is disabilities. If someone has a disability, they may not be able to exercise normally, which can result in less energy exertion, which would then result in the buildup of fats. Even good nutrition can be limited if the person is unable to exercise. Allergies can be viewed as a disability from this perspective, as it can prevent good nutrition if the individual is allergic to certain foods that may be considered healthy. These two limitations may also affect how a person is able to monitor and control their cholesterol levels.

Income

Income is a significant determinant of health, as it dictates what people have access to, both in healthcare and nutrition availability. Lower income groups in industrialized regions tend to consume high convenience and lower priced foods (Khatabeh et al., 2022). These foods typically have fewer nutrients and higher saturated fats and cholesterol. Lower-income diets in these regions have also been shown to include fewer fruits, vegetables, and “heart protective” foods. Eating fast food at least twice a day has been shown to lead to higher chances of high cholesterol. Hence, the cheapest foods are generally not as healthy as foods designed for a proper diet. Moreover, lower income families may not have access to preventative healthcare that can be applicable to their needs.

Those who have low incomes are more predisposed to medical conditions (Zhang & Xiang, 2019). This is because lower-income individuals may not have access to medications that they need, or may not have access to preventative primary care. Figure 8 compares cardiovascular mortality by income groups. As shown in the figure, the risk of cardiovascular events was lower in low-income countries but these countries had a higher mortality rate than higher income countries. Higher income countries had a higher risk of cardiovascular disease but a lower disease burden.

Cardiovascular Mortality variants by income

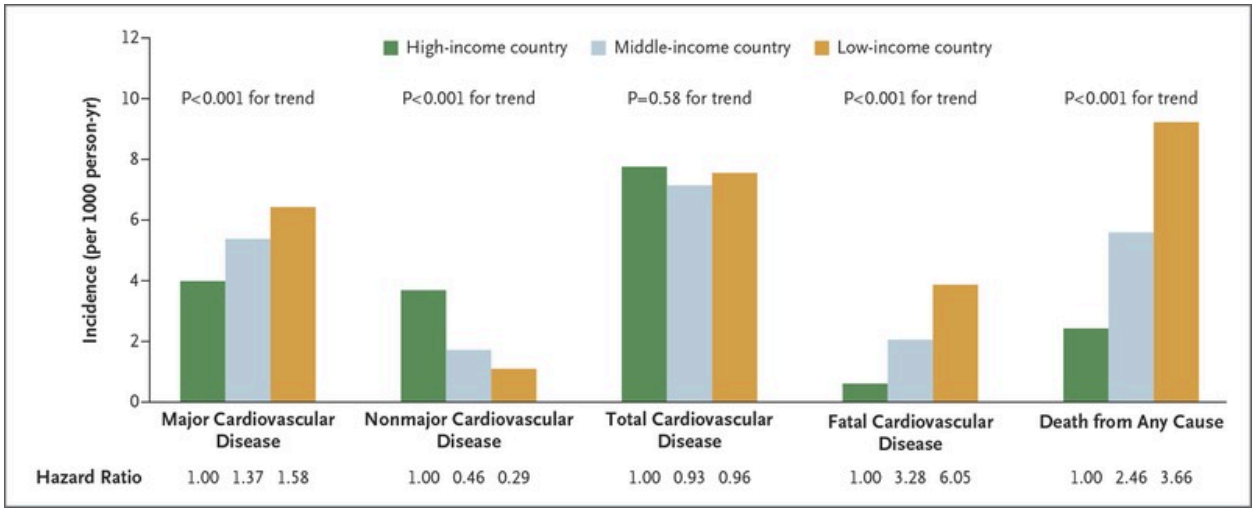


Figure 8. Cardiovascular diseases vary by income level depending on what type of cardiovascular disease . Major cardiovascular diseases are found in lower income groups generally due to access to healthcare, but nonmajor ones are found in higher income groups due to poor lifestyle choices. Source: (Yusuf et al., 2014).

As shown in Figure 8, Yusuf et al. categorized cardiovascular disease (CVD) into major and nonmajor cases. The authors concluded that major CVD generally occurs in lower income populations because lower-income populations have less access to cardiac care, preventative medicine, medications, and post-illness rehabilitation. Residents in higher-income groups generally experience fewer heart attacks and strokes, which are caused by plaque buildup in arteries. This is more prevalent in high income areas because they have access to fast food and convenience of access to food, and they generally do not follow nutrition and exercise guidelines. (Duffey et al., 2009).

Lower income populations can potentially be consuming less cholesterol, as they generally live in non-industrialized areas. Non-industrialized areas generally do not have fast food, which is a major source of cholesterol in higher income areas. Non-industrialized areas tend to have local food that they can access easily, which can generally be healthier.

Geography

An aspect that can dictate exercise is geography. One way to reduce ‘bad’ cholesterol is to exercise, as it burns the fat that would be stored as energy. However, those who live in dense areas may not have access to exercise easily. On the other hand, those who live in sparse areas may not have easy access to a medical facility. Geography plays a role in both physical capabilities of the potential patient as well as

their access to medical facilities. These are important factors to keep in mind, as they can affect what kind of symptoms and physiological situations they may have in their body.

Prevalence of High Cholesterol throughout the World

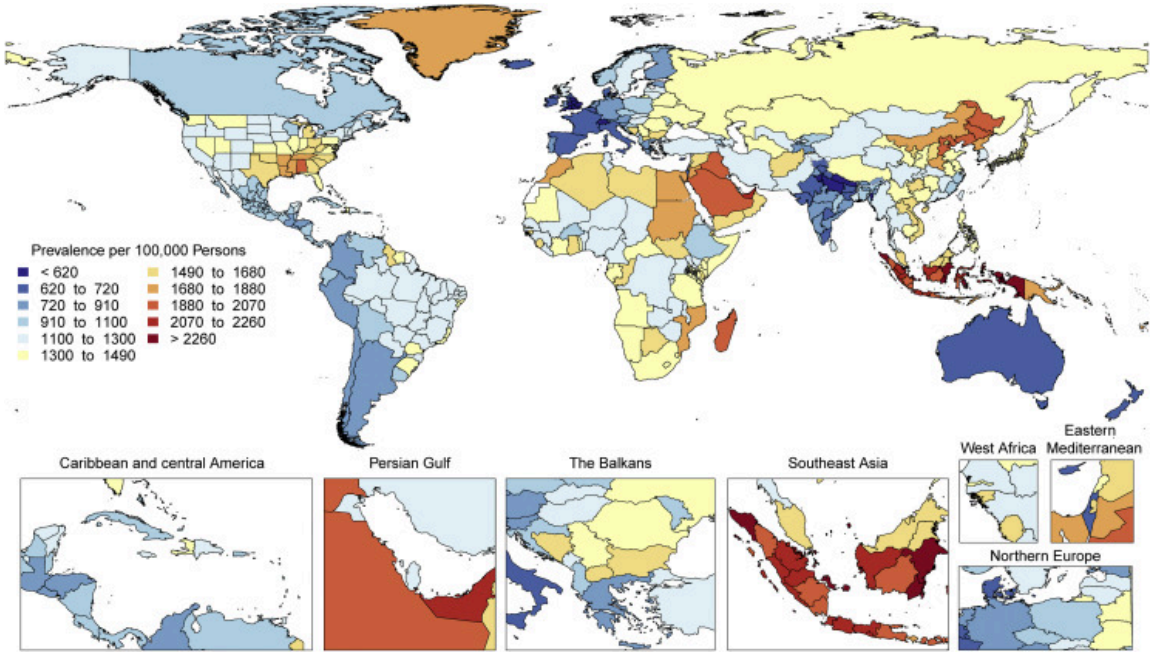


Figure 9 Prevalence of cholesterol per 100,000 people throughout the world, with focus areas. Many cultural centers, such as Southeast Asia, have higher cholesterol in their diet, whereas other cultural centers such as sub-saharan Africa have only moderate levels (Roth et al., 2020).

As shown in Figure 9, another aspect of geography impacting health is that the region and culture can affect diet, and locally found pathogens and other contaminants can cause people to experience different health issues. With culture, food and diet can greatly affect the people's physiology based on what they are consuming. If a culture was heavily predicated on a select group of foods, then they may have some issues; for example if that culture consumes high-cholesterol foods.

The other, more significant geographical factor is that locally found species and contaminants may affect how individuals experience health issues. For example, if the patient is in Sub-saharan Africa, then malaria-carrying mosquitoes are a concern, and malaria may affect heart rate, which can in turn affect blood pressure, which was determined to be a factor in plaque deposits. Geography can also play a role in contaminants. If the patient is located in an industrial district of a country like China, then they are exposed to air pollution on a daily basis. This can affect the person's lungs and their blood oxygen levels, which then in turn can affect their cardiovascular system which may have an impact on cholesterol deposits.

Two aspects of geography are the prevalence of high cholesterol in the region, and the number of deaths due to cholesterol. Figure 10 shows the number of deaths due to cardiovascular disease.

Deaths Due to Cardiovascular Disease

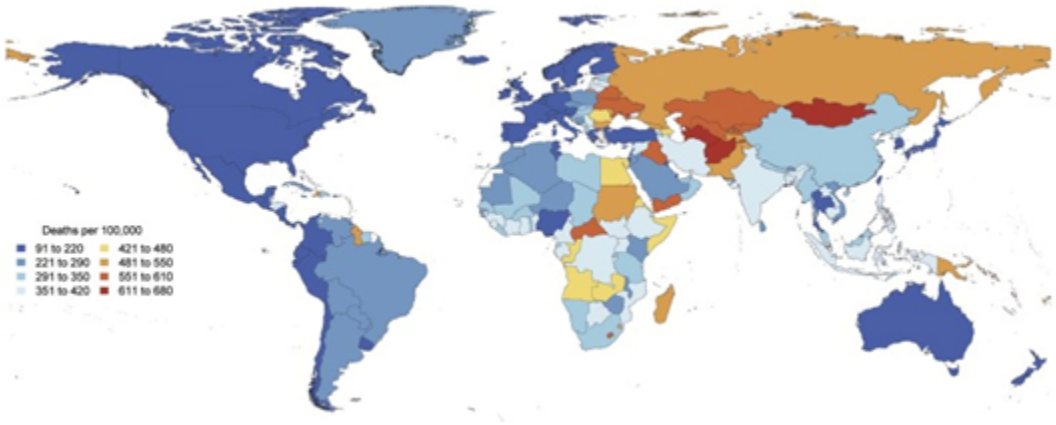


Figure 10 Deaths due to cardiovascular disease. Slavic countries have the highest rate of cholesterol-related deaths, (Majumder and Chetty, 2018).

Based on the information in Figures 9 and 10 regions with higher dietary cholesterol, tend to have more deaths due to circulatory and cardiac diseases. This can be attributed to either high-cholesterol foods in industrialized countries and fewer treatment options in non-industrialized countries.

Socioeconomics

Socioeconomics play a major role in the determination of medical conditions. These conditions, as shown in Figure 10, prove that moderation is best for medical conditions. Those who live in lower income areas but have little to no industrialization generally have better nutrition because they do not consume large quantities of fast food.

In other circumstances, those who are low income in highly industrialized areas are more prone to eating poorly, as fast food is what is primarily available. Again with highly industrialized areas, those who are wealthy tend to spend extravagantly on food and do not worry about nutrition or exercise. However, once they are in the prevalence section after being an incident, they have easy access to good healthcare.

In another circumstance, someone who has a high income in an non-industrialized area may have access to good nutrition, but does not have access to

nearby healthcare may be generally more inclined to have good health, but can transport themselves to healthcare should they need it.

From Figure 9, it can be inferred that people in moderate income regions are generally the healthiest on average. Although they are only the healthiest in one of five categories, the average of all the bars is mostly lowest on middle income. This is generally because people who are middle income have good food choices and have the disposable income to spend on healthy foods, have the capacity to exercise, and also are conscientious with their money. Given these factors, the middle income is the most average, and when it comes to all heart diseases they are the lowest.

Since the Framingham Heart study, knowledge gained about CVD risk has been disproportionately applied to higher resource groups, whereas lower resource groups have not been able to take advantage of the same information. (Abdalla et. al., 2020)

Delivery

An important aspect of turning this into a Worcester Polytechnic Institute Interactive Qualifying Project (WPI IQP) would be the social aspect. The social aspect that we can focus on is socioeconomic conditions that can affect access to a future product that would clean cholesterol from the blood. The enzyme itself may be difficult to transport but would also be difficult to produce. Hence, it should be investigated on how to transport the enzymes without needing intense electrical support such as refrigeration or incubation. However, research shows that an enzymatic solution does not appear to be easily used without refrigeration.

Another important aspect of the project will be how to make the artificial kidney more easily accessible. However, if the enzymatic solution is not easy to transport, then the transportation of the artificial kidney, whose job is to remove hydrolyzed cholesterol, would not be necessary, as it would be ineffective at removing anything if there is no enzymatic solution to go with it.

A primary concern for the social determinants of health is that the locations to which we would want to transport products in an equitable way so that it is available without income constraints. Hence, the solution would be to transport to the places that cannot produce the solutions themselves. Therefore, we need to create capacity to transport the products, including the enzymatic solution and the artificial kidney filtration pump. This indicates that the priority lies in being able to transport the products to lesser developed areas.

In order to transport these products, we will attempt to produce sustainable packaging in the sense that the packaging can be used to hold the enzymatic solution for long periods of time without relying on electrical sustenance. One option that might be available is that, independent of the type of transportation, there might be a portable fridge that can be plugged into a vehicle that is powered off of the engine, in which case the mode of transportation doesn't matter as much and the device can be transferred between vehicles without exposing it to the environment.

One important thing to take into consideration is the time period and quantity. However, the time period should not matter as much because it is not an emergency medical solution. Hence, the quantity is what matters most. Moreover, the quantity generally should not be that high, as it is not a very common problem encountered by many people.

The preferred solution to the transportation problem would likely be airlifting. The portable refrigerator option is preferable, as there is not as high quantity needed and the time period is not the most important. Although ground transportation might be cheaper, the accessibility of the product is important, and some areas are not as easily accessible by road. Using an air service may make it easier and more consistent to deliver to any area of the world without having to change methods of transportation.

The refrigeration device that is powered off of the vehicle may require some battery capacity to be able to transfer from one vehicle to another. Another important aspect is that the enzyme and filtration pump should be able to be mass-producible and distributable throughout the world.

To better understand what demographics might need our solution we could make use of maps of places that might need but do not have dialysis centers and what places have a higher rate of cholesterol buildup. Demographic mapping would be very useful in terms of being able to determine where and how much of our solution should be distributed.

Epicenters may be very useful to determine where distribution centers should be once they have been deployed to the location. Epicenters will be where the shipment arrives and then distributed out from there. These epicenters should be easily accessible both by air and by the population such that the people can get there and receive their portion of the products.

Our solution may be able to work as a dialysis machine that is wearable, potentially even at all or most times. To achieve this, we would have to provide the

means through which it can be installed in areas that do not have highly advanced medical capabilities. To make installation of the filtration pump or artificial kidney easier, we may provide the equipment with it that is needed to allow for the installation, as it requires an intake and a return. Investigations will be required as to what equipment is appropriate to allow for local technicians to be able to implant the device without highly advanced equipment. This may be achievable through miniature IV's (Intravenous) needles that can go into the artificial kidney and then return back through the other end of the artificial kidney.

The implantation device would require something that can keep the IV's in place as well as keep the artificial kidney in place. The other issue would be that there would have to be replacement filters delivered, which would require a longevity estimate to be created to determine how long until the next delivery of replacement filters, or if a certain number of replacement filters are provided with each delivery of artificial kidney or miniature dialysis machines.

Each shipment should have estimates of how many patients there are, and therefore how many artificial kidneys and replacement filters would be required to satisfy the demand. There should be an additional supply so that if something fails or new patients arise, that they can have a solution easily accessible. For example, if there are 10 patients that require a total of 24 replacement filters, then maybe 12-15 devices and 30-40 replacement filters delivered such that when new patients arise or failure of equipment or potentially shorter lifespans of equipment or longer lifespans of patients, there is not a shortage of supplies that requires a new delivery.

Investigation into implant requirements is necessary, as it needs to be determined what would need to be delivered with the devices. If we just deliver the devices, they would not necessarily be able to do anything with them if they cannot implant them. Demographics should also be taken into account such as access to electricity. If they do not have access to electricity, then they may need to have deliveries including non-electrical equipment that gets used to implant the devices. However, if they do have access to electricity, then what equipment may be useful that relies on electricity is a good question to ask to be able to deliver with the devices.

However, the least common denominator may be used, as it would make packaging and distribution easier. So, some assumptions may be made such as that they might not have access to electricity and do not have medical facilities. It would be easier to deliver supplies throughout the world that do not require location specific properties. It would also be easier to have something they don't need than to leave

them needing something that they don't have. These factors would be crucial to being able to make the solution as widespread and distributable as possible.

Calculating Risk

When trying to determine who is at risk for cardiovascular disease, one attempt that was made was to determine if making a calculator that corresponded income to cardiovascular disease risk for death was feasible. There was found to be a correlation between averages of income and likelihood of cardiac death. This equation was found to be that if $-100e^{-0.00625*\frac{a^2}{p}}+100$, where A is the regional average and P is the population subset income, it would return the percentage of the population subset that would be expected to die from cardiac illness. A was determined to be $36,000 USD for the United States, which corresponds to a 36 on the A, as orders of magnitude do matter in this equation since there is a squared function.

Income is not the only factor that can affect an individual's likelihood of death, though; as that is predetermined by lifestyle choices and genetics, so to get a personal score, P can be used in the equation as personal income, and this percentage should be taken in average with the ASCVD test percentage, where that would give a more relatively accurate percentage chance of death for an individual to die of cardiac disease.

The calculator has proven to be effective within 5% of the actual percentage of deaths due to cardiac illness, meaning that if it predicts 21%, then the real number is between 16% and 26%; under which circumstances 5% is added to each answer for an unknown region.

The purpose of the calculator not only shows that there is a strong correlation between income compared to the regional average, but also gives guidance on distribution. The calculator can be used for determining how many kits are needed in different areas. For example, the region of China containing Henan, Hunan, Hebei, and Anhui was determined to need roughly 1.4 million kits. This information can be useful for determining how many kits should be sent where, and where epicenters of cardiac illness are to thwart the problem as quickly as possible.

There were two other primary calculators that were found that could potentially calculate a 10 year risk. One was the American Heart Association, and the other was the American College of Cardiology. The AHA gave a patient that was interviewed a score of 3.3%. The ACC gave the same patient with the same information at the same

point in time a score of 8%. The income based calculator returned a score of roughly 10%; although the income based one is meant for populations and does not take into account personal data points.

However, the takeaway was that these calculators are likely not accurate, as they do not agree with each other. The other possible conclusion is that the patient that was used was at such low risk that it was hard to predict.

Distribution Centers

One primary use of the calculator would be to determine distribution centers and areas. The original thought was to have large distribution centers that service a large area. However, this would make commuting difficult for many patients and would cause congestion in the distribution center. It would imply that more people would spend time commuting, resulting in more person-hours spent in vehicles. This has environmental and other bigger implications that are beyond the purview of this project.

However, if there are more and smaller distribution centers and distribution areas, then it would be more local for more people, result in less congestion for refills and supplies as well as resupplies, and result in fewer person-hours spent in a vehicle. This does imply, however, that there would be more driving done by delivery drivers. Although this is inconvenient, it can save hundreds of hours that people would spend in a vehicle for transportation to the nearest distribution center. Hence, the smaller distribution centers and areas would be a better decision for the logistics of distribution.

Value Proposition

There are many solutions on the market to help with high cholesterol, but this one functions in a drastically different way. The main types of competition that we will face includes statins, atherectomy, and apheresis. The solution proposed is intended to reverse plaque buildup that has already occurred and potentially prevent other plaques from forming without using surgical methods. This solution could also work in conjunction with an external filter to remove hydrolyzed cholesterol.

Other products on the market

The other products to help mitigate risk of cardiovascular events due to cholesterol include solutions such as statins, apheresis, and atherectomy; each of which help mitigate cholesterol risks, but do not non-surgically remove plaques.

The first competitor is a statin. As noted above, statins work by inhibiting the liver's ability to produce more LDL cholesterol. These help with patients who have high cholesterol from getting higher levels of cholesterol, but do not directly lower these levels. The correlation between statins and lower cholesterol is that the body is able to naturally lower its cholesterol levels since more cannot be directly introduced into the bloodstream.

Another primary competitor is apheresis. This is most comparable to our extracorporeal filter that removes hydrolyzed cholesterol from the body. An apheresis is similar to dialysis in the way that it removes cholesterol in the blood through an extracorporeal filter that removes cholesterol that is freely flowing through the veins. A primary inhibition of it is that it cannot remove plaques that have already formed.

The last primary competitor listed is an atherectomy, which fills in where apheresis falls short. An Atherectomy is a process that targets large plaques that have already formed through a catheter that has a head that can physically degrade plaques and remove the debris through the catheter. This does require a surgical style method and can cost more than $15,000 USD. This is generally used as a last ditch effort to prevent or recover from a major cardiac event.

Patents and related Information

One concern of producing a new product is patent infringements. The closest patent that resembles a filtration enzyme pump was a Wearable Kidney, which was patented around 2021, meaning that at the time of 2024, the patent is still effective. However, it is not easily determinable if the proposed filter would impede on this patent.

Despite this shortcoming, it was determined that there is a patent for a wearable artificial kidney that functions as a 10 lb wearable dialysis device. The patent does not seem to be able to restrict the idea of a membrane to clean blood, moreover that our solution would use intermolecular attractions to filter only hydrolyzed cholesterol esters in the blood. Hence, the conclusion can be drawn that the device listed in Figure 1c would not be infringing on US patent 10,933,183.

Our Solution

The proposed solution is something that works similarly to an apheresis but achieves the same as an atherectomy. The proposition uses cholesterol esterase that is injected into the blood that would potentially break down plaques that have already formed by hydrolyzing the cholesterol esters that form it.

The hydrolysis results in a cholesterol body and a fatty acid tail, both of which can be removed through an extracorporeal filter if the body is not able to clear it out itself. The filter would have two stages, one to remove the cholesterol and the other to remove the resultant fatty acids. It would be similar to an apheresis in functionality as well as size, as the proposed filter would only remove cholesterol and resultant fatty acids and is not designed to be a replacement for dialysis.

Potential Candidates

This product and potential solution would be for people who already have plaques building up in their vasculature, which could be indicated by high serum cholesterol as well as high blood pressure. The general stage at which they would use our solution is after statins can no longer help reduce cholesterol and after an apheresis would be done, but before or instead of getting an atherectomy. The solution would be an injection that would break down plaques that have built up. It would cost more than a statin, but would be less than an apheresis, which can cost between $2,000 and $3,000 USD.

The projected cost would be around $100 to $300 per patient, as it could be done over an extended period of time due to the fact that cholesterol esterase would not immediately break down a plaque. The product would be able to gradually reverse plaque buildup by directly breaking it down. However, this would take longer than an atherectomy but would cost a small fraction of that of an atherectomy. However, the product may be able to work in concert with an atherectomy or with an apheresis, or potentially both; as it would not directly remove cholesterol from the blood like an apheresis, and would not break down the plaques as quickly as an atherectomy.

Cost - Benefit analysis

Our solution would be good for patients who are between the stages of having taken statins and needing an apheresis. The product would cost significantly more than a statin, which can be less than $20 and over-the-counter in some cases. However, an apheresis and atherectomy can cost $1,500 and $15,000 respectively.

The proposed solution would cost a patient around a few hundred dollars. The solution also would not require a surgery such as an atherectomy, but can directly break down plaques like one, while acting like an apheresis, which does not require any intrusive procedures but cannot directly break down a plaque. The solution would combine the functionality of both of these while working at a fraction of the cost. However, it would not be as efficient as either.

An atherectomy would be able to break down a plaque much quicker, and an apheresis can remove plaques at a faster rate. These procedures would both be quicker at doing one of the two objectives without being able to do the other, which our solution would be able to do both but not as quickly. The main benefit of our solution will be that it is significantly cheaper than apheresis or atherectomies, while being able to do both of the jobs that each try to do individually.

Proposed solution

At the moment, the best solution is either statins or an atherectomy, so an alternative to this is that we can provide a cholesterol injection that can be given after the cleaning to replace the good cholesterol. However, if the body does not naturally remove the enzyme, or the enzyme stays in the body, then the replacement of good cholesterol would simply get hydrolyzed and not be effective. Hence, it should be observed what happens with the plaque and interactions with the cholesterol as it interacts with the enzymatic solution and see what potential outcomes there may be. As of March 10, 2024, there is not a clear alternative as to what other methods may be used to clean the plaque from arteries.

An idea that was developed for this project is a wearable dialysis machine or something that can be used to clean the hydrolyzed cholesterol from the blood. This device may also be able to clean the entirety of the blood like a dialysis machine, but should start with cleaning the hydrolyzed cholesterol from the blood.

The state of the art is a 10 pound device that the patient can wear. Although a great leap forward in the technology, it is still clunky and difficult to use. However, it may be capable of being turned into an at-home device that the patient can use with plugs that may be able to stay in their body, and they can ‘plug in’ to the machine when they need to perform dialysis.

The proposed device that this project would use is a two stage active filter that would remove the two parts of hydrolyzed cholesterol, one in each stage. This device could be permanently wearable and may even be able to be turned into a pump that can inject more enzymatic solution if it is deemed that this is necessary.

Potential screenings could involve a hypothetical chemical screener. The way it would work is that it would be injected into the veins, travel throughout the body, and then a sample taken upstream from the injection point would be taken. The indicator may change color or have some other chemical property that changes when it contacts cholesterol. This is a more invasive method and would be more expensive to develop,

but may be easier for less developed areas to use as it doesn't necessarily require electricity and it has the ability to scan the entire vascular system. However, despite its ability to scan the entire body and lack of a need for electricity, it is more invasive and does not pinpoint the location of the plaque; it simply tells whether or not it is present.

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