

# Treatment Options for High Cardiometabolic Risk Patients with Atherosclerosis

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## ABSTRACT

In 2020, coronary artery disease (CAD) affected over 20 million people and resulted in 382,820 deaths in the United States. Heart disease such as CAD and its precursor atherosclerosis have severe consequences such as limiting the amount of blood flow and reducing the flow of vital elements like oxygen to vital tissues and organs like the heart. Elderly adults, obese patients, patients with diabetes, and those with a genetic predisposition of increased Low-Density Lipids (LDLs), are at higher risk of developing atherosclerosis. This paper examines treatment options for atherosclerosis in people with high cardiometabolic risk and discusses their efficacy as well as their associated risks and benefits. First-line therapy includes medication such as statins, ACE Inhibitors, or diuretics along with appropriate lifestyle adjustments. If unsuccessful, second-line interventions offer increased risk reduction in patients with established coronary vascular disease and reduce the probability of recurrence of an acute cardiac event. This calls for the use of medication with higher risks such as beta blockers and anti-thrombotics and even surgical procedures such as bypass and angioplasties. Regardless of the patient's condition, the first recommendation for preventing and managing atherosclerosis is lifestyle adjustment. Medications offer benefits but with varying levels of side effects. Thus, it is important to look at the specific conditions of each patient to find the most suitable medication. This paper looked at the existing magnitude of treatments for atherosclerosis and summarised which ones are best for patients with different conditions that put them at high risk for developing atherosclerosis.

## Introduction

In 2020, coronary artery disease (CAD) affected over 20 million people and led to 382,820 deaths in the United States (Ryan). This highlights the seriousness of heart disease, and CAD in particular. Atherosclerosis, which leads to CAD, is a disease in which plaque from cholesterol deposits builds up in blood vessels. This narrows the vessel, limiting the amount of blood flow and reducing the flow of vital elements like oxygen to vital tissues and organs like the heart. This can result in fatal blockages (Goldman and Kohli).

There are many factors that can lead to the development of atherosclerosis. These include high levels of cholesterol and triglycerides, high blood pressure, smoking, diabetes, obesity, physical inactivity and poor diet ("Atherosclerosis"). The onset of disease begins when there is damage to the inner lining of the blood vessel, and lipids start to deposit in the subendothelial space. The buildup attracts macrophages to the site, which ingest the lipids and clump together to form foam cells. As the foam cells accumulate, smooth muscle cells are recruited to build a lining over them, forming a fibrous cap that protects the foam cells from erosion. The artery is narrowed by the atherosclerotic plaque limiting blood flow through the body. In some instances, the plaque ruptures and travels through the blood vessels to deposit in various smaller vessels. If this happens in the coronary arteries, it can cause an acute myocardial infarction commonly known as a 'heart attack' (LaMorte). This paper will examine the risk factors associated with atherosclerotic buildup and explore the ways in which it can be treated. Patients at a high risk of developing atherosclerosis are those with obesity, diabetes, elderly, or those with genetic risk for dyslipidaemia. This

paper will also investigate treatment options for atherosclerosis in people with high cardiometabolic risk and discuss their efficacy, associated benefits, risks, and risk management.

## Treatment Options

It is important to first provide an overview of interventions that may be taken to prevent further consequences of atherosclerosis (e.g., acute myocardial ischemia, stroke). Primary prevention consists of first-line therapy, which is a standard set of treatments regarded as the best initial way to treat a patient (HIV.gov). If this does not achieve the desired result, second-line therapies, which have additional impact but may have more side effects or be more costly, will be used. Secondary prevention, defined as an intervention or therapy that is used in patients with a disease to prevent further harm from disease progression, can be used for patients with a history of acute myocardial infarction (Institute for Work & Health). Surgery may be required in emergency cases or if a higher level of care not provided by first or second line therapies is required. Surgical options are riskier due to the level of invasiveness that is required, making the patient more susceptible to complications, such as haemorrhage, infection, and hypoxia.

## Primary Prevention

First-line therapies include adjustments to the patient's lifestyle. Lifestyle changes include increasing exercise to improve cardiovascular endurance and decreasing blood pressure, making dietary changes to reduce the amount of lipids in circulation, and overall decreasing weight to healthier standards. This will improve blood pressure and lipid profiles, delay type 2 diabetes, and improve glycemic levels in patients with type 2 diabetes (LeBlanc et al.). There are several medications that can be used to treat patients with atherosclerosis, and each have different mechanisms of action but can achieve the same results. It includes prescribing medication that has been shown to provide significant benefit without severe side effects such as statins, Angiotensin Converting Enzyme (ACE) inhibitors, or diuretics. One of the most effective options are statins, which lower LDL levels by approximately 30% and up to 50% in high doses. Statins block the enzyme HMG-CoA-Reductase, which is responsible for LDL production in the liver ("Statins and Cholesterol Medicine - HEART UK"). Lower LDL levels reduce atherosclerotic plaque buildup, and statins also lower blood vessel inflammation which reduces blood pressure and mitigates some of the side effects of atherosclerosis (Amarengo et al.). However, statins have several negative side effects, such as muscle pain, increase in blood sugar, and very rarely, liver damage (Mayo Clinic Staff).

Along with statins, ACE inhibitors may also lessen a major consequence of atherosclerosis: hypertension, which is when the patient a higher-than-normal blood pressure. ACE is responsible for activating the hormone angiotensin II, which regulates blood pressure. Angiotensin II, once activated by ACE, causes blood vessels to constrict, increasing blood pressure and leading to hypertension. ACE inhibitors block the function of ACE, leading to vessel relaxation, reducing blood pressure and thus improving hypertension. This makes living with atherosclerotic buildup in the blood vessels much easier. There are not many side effects of ACE inhibitors, but it is possible to have an allergic reaction or a dry irritating cough. In such cases, patients should consult their general physician who may advise an alternative medication (Mayo Clinic). ACE inhibitors are often prescribed with a diuretic, a medication which brings more sodium into the kidneys, thus removing water from the blood and reducing blood pressure. Much like ACE inhibitors, diuretics are used to treat the high blood pressure from hypertension and are generally safe to use, but can have side effects such as dizziness, headaches, dehydration, muscle cramps, impotence, and very rarely, cause low potassium levels (Ogbru and Marks).

## Secondary Prevention and Emergency Treatment

Methods used in secondary prevention are much like primary prevention methods but are focused on intense risk reduction in patients with established coronary vascular disease. This is because the patient is experiencing or has experienced an incidence of chest pain from a blocked artery or even a myocardial infarction. In cases of emergency, surgical methods would be needed to achieve revascularization so that a fatality does not occur (Smith Jr. et al.). This would mainly be angioplasty, in which a balloon is inflated to reopen the vessel and a stent is placed to keep the vessel open and allow normal blood flow. Once the emergency has passed, bypass grafting is likely performed, during which the blood flow is redirected from the channel with the plaque buildup towards an alternative unblocked path. There is also an option for endarterectomy, which involves surgically removing the plaque from the walls of the blocked vessel. It is usually only done to increase the success of an angioplasty. Additionally, a thrombolysis can be performed to dissolve blood clots and improve blood flow (“Catheter-directed Thrombolysis”). Beta blockers block beta receptors to lower blood pressure and treat hypertension. It also helps with angina (a squeezing chest pain felt from lack of oxygen to the heart muscle), and this commonly occurs with patients diagnosed with atherosclerosis. However, there are many side effects of beta blockers such as slowed heart rate, hypotension, irregular heart rhythms, fatigue, dizziness, nausea, insomnia, and dry mouth, which makes it more of a secondary option to other medications and are typically prescribed only after an event such as cardiac arrest or myocardial infarction. Beta blockers cause the heart to beat slower and with less force, and this makes it optimal for helping in the recovery of patients after a procedure because of the lightened strain from the myocardial contractions (“Beta-blockers: Types, Uses and Side Effects”). During and after a surgical procedure, it is recommended to use antithrombotics such as antiplatelet medications that prevent the formation of blood clots. This makes it easier for blood to flow by reducing blood pressure and decreasing blockages from blood clots. However, it is important to note that using thrombotics is risky because it can cause excessive bleeding which can be dangerous and potentially fatal (“Antiplatelet Drugs: Types, Uses & Side Effects”). Additionally, any patient that has had a myocardial infarction (heart attack), must be on dual antiplatelet therapy (DAPT) for at least 12 months. Treatment with low-dose aspirin is then continued long-term. Following 12 months, the risk of bleeding versus thrombosis should be reassessed and the decision to stop or continue antiplatelet therapy can be discussed between the patient and their doctor (Kumbhani).

The next section describes those at high risk for atherosclerosis and the therapies most commonly used to manage atherosclerosis in such high-risk patients.

## Elderly Patients

Elderly patients, specifically those who aged 60 years and above, have a higher incidence of atherosclerosis. As we age, different mechanisms related to age-induced elevations in circulating and intracellular IL-6 levels promote the development and progression of atherosclerosis. IL-6 is an inflammatory cytokine and its signalling increases bone marrow adipocytes during aging. This is thought to cause haematopoietic stem cells to differentiate into myeloid cells and may increase the risk of mutations in genes encoding transcriptional regulators, such as TET2. Myeloid cell clones with mutated TET2 show an increased IL-6 production, which can lead to atherosclerosis through chronic inflammation (Tyrrel and Goldstein).

When treating atherosclerosis in the elderly, one has to be very cautious because of the vulnerabilities elderly people have. The best primary treatment for the elderly would be changing lifestyle routines with low intensity exercise along with a diet low in saturated and trans fats. Exercise reduces the effects of atherosclerosis and strengthens patients, improving their cardiovascular health and allowing them to endure other treatments while saving them from illnesses that are more common with age. Recommended exercises could include light aerobic exercises and strength training (Nied and Franklin).

Alongside improvements in lifestyle, there are some medications that should be taken in tandem to relieve pressure in the vascular system. Cholesterol medication such as statins are often more prescribed

since their benefits in reducing LDLs and plaque buildup significantly outweigh the minimal risks (Bittencourt and Cerci) and side effects, i.e., of intermittent muscle pain and weakness (Williams and Aungst). A 10-year Atherosclerotic Cardiovascular Disease (ASCVD) risk estimator can be used to guide the patient-provider discussion on the benefits of initiating a statin in patients aged 40 - 75 (“ASCVD Risk Estimator”). Patients older than 75 years should discuss the risks and benefits with their provider, based on their healthcare goals. Elderly patients can also be given antiplatelet medicine to prevent coagulation around the plaque buildup which may block blood flow (Rosa et al.). However, elderly patients are also prone to bleeding so antiplatelet therapy is recommended only as a secondary prevention method. The current recommendation for antithrombotic medications such as prasugrel is a reduced daily dose of 5 mg for patients greater than 75 years following percutaneous coronary intervention (PCI) i.e., angioplasty and stent placement, so that the risk of bleeding is minimized (Barnes).

Comorbidities such as hypertension and diabetes should be addressed. Both ACE inhibitors and diuretics are effective and highly recommended, but doctors should be careful when prescribing diuretics because they can cause syncope (fainting) in the elderly (O'Brien and Kenny). They should be started at the lowest dose and adjusted accordingly. Beta blockers are not first-line for hypertension but are used in patients with heart failure and as secondary prevention due to their ability to support positive structural changes in the heart (“Managing Hypertension in the Elderly: A Common Chronic Disease with Increasing Age”). The best treatment in the case of an acute coronary syndrome would be a surgical procedure, namely, angioplasty, endarterectomy, bypass grafting, and/or thrombolysis. Fortunately, in most patients aged 60 and above, the progression of atherosclerosis is slow which means that surgical procedures are not required. However, in emergency cases or exceptions, angioplasty is the procedure (DeBakey).

## Obese Patients

Not only is the link between obesity and atherosclerosis similar in their incidence and cardiovascular risk, but they also have related pathophysiological pathways. We categorise obese people as those with a body mass index (BMI) of 30 or above, and the higher the BMI, the more likely a person is to develop atherosclerosis. The high lipid concentrations in obese people directly affect atherosclerotic buildup due to oxidized LDLs and free fatty acids triggering inflammation and subsequent disease. Both diseases also consist of high rates of cell death, T-cell activation, accumulation of macrophages, and cytokine release (Rocha and Libby). These various factors come together during obesity, and they greatly increase the chances of high plaque buildup and result in severe atherosclerotic complications such as plaque rupture. To address this, the first recommendation for obese individuals is a change in lifestyle and weight loss. Losing just 5% of total body weight can lower LDL and triglycerides levels, as well as prevent or delay type 2 diabetes (Ratini). To minimize the risk of the adverse effects of atherosclerosis and decrease plaque buildup, these risk factors can play a large influence.

Medications, starting with statins, also play a role in disease management. Statins are beneficial for both primary and secondary prevention because they reduce the mortality in those who have an acute myocardial infarction (AMI). However, there is also an obesity paradox where statins have been shown to be more effective in obese patients who had an incident of AMI, than those who have not (Won et al.). Studies have shown that even with optimized statin therapy, there is still progression of atherosclerosis in obese patients as well as a chance of weight gain (Sandfort et al.). However, the decision to initiate a statin should still be a discussion between the patient and their medical provider, using a ten-year ASCVD risk calculator to understand the risks and benefits. ACE inhibitors and diuretics are often the first medicine prescribed, either together or separately since they help relieve hypertension (Henning). Beta blockers can decrease metabolic rate by 10%, resulting in weight gain, making it an undesirable option for obese patients. However, it may be given as a second line treatment for hypertension (Sharma) or if required for other reasons. Additionally, obese patients may be more sensitive to platelet medications, which means they will benefit more from anti-platelet medication in smaller doses (Puccini and Rauch). Surgery is used in acute, emergent situations or in patients with unstable angina. As is true for all patients, clinicians need to evaluate

whether the obese patient going into surgery is at high perioperative risk or not. A thorough examination should be done before the surgery to see if the patient can survive the surgery or not, using aids such as an Obesity Surgery Mortality Risk Score (OS-MRS), which can give us an estimate of how likely a fatality is if the patient goes through surgery (Poirier and Alpert).

## Patients with Diabetes

Patients with diabetes also have a high risk because of the already present factors. Glucose takes part in forming chemically reversible products of early glycosylation, whose reactive amino groups rearrange to form more stable products. Some early glycosylation products on proteins such as vessel wall collagen go through more complex forms of rearrangement to form advanced glycosylation end products (AGEs). These can accelerate the process by the diverse mechanisms of non-receptor dependent and receptor mediated pathways and induce further acceleration of plaque buildup (Aronson and Rayfield).

This group can benefit from lifestyle changes such as decreasing intake of simple carbs such as sugar, soda, cakes, candies, etc. Maintaining a healthy weight will also help maximize their health profile ("Living Healthy with Diabetes"). Statins can be taken, although they have a small risk of raising blood glucose levels. The positive effects of taking statins outweigh the drawbacks and they can be taken along with glucose management medications so that there are minimal adverse side effects (Poulson). Patients with diabetes have demonstrated higher sensitivity to antiplatelet therapy, which means there is increased likelihood of bleeding. Careful consideration must be taken on whether or not to take antiplatelet medicine and only take it as a secondary prevention therapy (Capodanno and Angiolillo). Beta blockers are controversial for diabetics because of their effects on insulin sensitivity and the potential for weight gain. But they can help control blood pressure and help with the effects of atherosclerosis, making it a fitting secondary prevention treatment. It can also be used side by side with ACE inhibitors (McGill). ACE inhibitors are effective in reducing cardiovascular events and can be an appropriate first-line treatment for hypertension (Rubenfire). This is also true for diuretics, which are just as effective as ACE inhibitors at lowering blood pressure but have side effects such as dizziness (DTN Staff). Much like all other patients, surgical procedures should strictly be the final choice of treatment. Bypass surgeries such as coronary artery bypass grafting (CABG) are usually preferred over stents and angioplasty due to their effectiveness in increasing lifespan. However, angioplasty may be the safest and most expedient choice in cases of emergency. Endarterectomy is only useful to increase the chances of the stent succeeding and is not often recommended because of its low effectiveness (Hoffman).

## Patients with Genetic Predispositions

It has been seen that there are genetic factors that have increased the chance of atherogenesis. These genes can be inherited by the children of carriers of the mutated genes. One identified genetic mutation is in the ApoAII gene. This gene codes for apolipoprotein A-II, which is a vital component of HDLs. These A-II rich HDLs have decreased antioxidant potential which may be the reason that A-II rich HDLs promote atherogenesis. This link can also be tied to another disease: autosomal dominant hypercholesterolemia. Some specific genes for this disease are LDL-R, ApoB, and PCSK9, and they affect proteins in the body. These cause the patient to have lifelong elevated levels of LDL-C and lead to the formation of atherosclerotic buildup in early years (Mcgowan et al.).

The ability to affect atherosclerotic buildup through genetic predisposition to atherosclerotic buildup can be frightening as patients could have it and not know. Fortunately, because the underlying cause of atherosclerosis in these patients is influenced by genes, they could still be relatively healthy and not have much difficulty in being treated. This means the first treatment done should be improving lifestyles through exercise and diet changes. Maintaining a healthy weight and building cardiovascular endurance are examples of ways to improve health. It also means patients will be able to more safely take medications such as statins, diuretics, and ACE inhibitors. This is only true if they do not have any other conditions that prevent

them from taking these medications without serious side effects such as the risk factors previously mentioned. There are also some specific inhibitors which can be used for those with familial hypercholesterolemia. These inhibitors block the working of proteins made from the genetic code of the affected sequences. These include pcsk9 inhibitors such as Alirocumab and Evolocumab ("PCSK9 Inhibitors: How They Manage Cholesterol and Side Effects") and mipomersen, an ApoB inhibitor (Akdin et al.). These medications have been shown to be effective in lowering LDL-C levels, but their safety is still questionable. Beta blockers and antiplatelet medications should still be taken as second-line treatments since they have greater potential side effects. Surgical procedures should only be done in cases of emergency because of the risks that arise during surgery, as well as the recovery period. It is also important to note the use of gene therapy as a possible future treatment. While it is not yet approved for use clinically, it has promising features that would be ideal in treating atherosclerosis in patients who inherited genes that caused the atherosclerotic buildup. Some examples of this are the ability to reverse the cholesterol transport and cause an anti-atherogenic effect, as well as its anti-inflammatory and immuno-modulatory effects (Chyu and Shah).

## Summary: Recommendations for Treating Atherosclerosis

### Lifestyle

The first advice any physician should give to any patient with atherosclerosis is to make changes in their lifestyle. A balanced and nutritious diet can help improve a patient's comorbid diseases such as hypertension and diabetes. Changes in diet include eating less fats and more proteins, as well as more fibrous sources of carbs such as fruits and vegetables. This is recommended for all patients regardless of their condition and is most effective in its long-term benefits. Exercise tolerance may depend on the condition of the patient, but even light aerobic exercises and physical motion can serve to reinforce the patient's cardiovascular health. Much like improving the diet, exercise is highly beneficial in the long run and maintaining both exercise and a nutritious diet would put the patient in the best condition for medications and surgical interventions if and when needed. Weight loss in obese patients can improve cardiovascular and overall health status.

### Medications

There are varying levels of side effects for the medications described here; it is important to look at the specific conditions of a patient to find the optimal regimen. Statins are highly recommended as first-line treatments for atherosclerosis unless they have a contraindication such as patients with liver disease. There is a risk of weight gain from taking statins, which means appropriate nutrition counselling and countermeasures must be taken for obese patients (Sandfort et al.). Diuretics can cause low blood pressure and syncope in elderly patients, so they should be prescribed with caution and appropriate counselling. ACE inhibitors treat hypertension, which is a major comorbidity of atherosclerosis. While some of their side effects require frequent laboratory testing, ACE inhibitors are recommended as a first-line treatment for patients with high blood pressure and diabetes.

Beta blockers are crucial medications for patients with structural heart conditions, hypertension, and arrhythmias. However, patients with diabetes and obesity may be more sensitive to these medications, which can increase their weight and alter their insulin sensitivities. These side effects can lead to worsening of risk factors if not taken into consideration. Beta blockers are currently recommended as a secondary preventative treatment for patients with an acute cardiovascular event or heart failure. Antiplatelet are not indicated as a primary prevention therapy because of the dangers of low platelet levels. They should generally only be taken after a cardiac event occurs and/or following an operation during recovery. Secondary prevention treatments are given after a surgical procedure or following an emergency such as a cardiac event. Following surgery, medications such as antithrombotics or beta blockers are prescribed as necessary (Smith Jr et al.). Not only is DAPT used in those who have experienced a heart attack, but shorter duration

of DAPT may be used in patients with stable ischemic heart disease after a PCI to reduce the risk of bleeding. This is regardless of predisposition and any risk factors in order to make sure that the patient has the best ease of recovery.

### Surgical Procedures

When looking at surgical procedures, angioplasty and bypass surgeries are the most effective choices for revascularization. Angioplasties are often the safest choice because they are minimally invasive and relatively quick; depending on the patient’s condition, this procedure can take as little as 30 minutes up to a few hours (Kohli). However, it has been found that a CABG was able to increase one’s lifespan more than an angioplasty (Hoffman). In cases where a surgery is needed but it is not immediately, then it is often best to choose a CABG. In elderly patients, going through an invasive operation such as CABG is very risky because they may be too frail for the perioperative effects, which is why angioplasty is often the better choice. However, a recent study suggested that some elderly patients may benefit from bypass surgery over angioplasty because of the increased lifespan. The decision should be made jointly with the patient, their family, and the care team (Shah et al.).

Bypass surgery is recommended for revascularization in obese patients as studies have shown improved long-term outcomes following bypass compared to angioplasty, although these improved outcomes may not hold for severely obese patients (Terada et al.). Patients genetically predisposed to atherosclerosis can go through either procedure since they tend to be relatively healthy and younger. There are two other procedures one can opt for. One is an endarterectomy, which wouldn’t be as beneficial because it would mainly serve to improve the effectiveness of an angioplasty. The second alternative is thrombolysis, which addresses blockages by dissolving the blood clot, and is only as effective as other blood flow improving medications which tend to be much safer, less expensive, and more beneficial overall.

**Table 1.** Recommended cardiovascular disease treatment options and management for patients with atherosclerosis in four high risk groups

		Elderly patients	Obese Patients	Patients with diabetes	Patients with high genetic risk
Lifestyle Changes	Diet And Exercise	✓	✓	✓	✓
Medications**	Statin	✓	✓X*	✓	✓
	Ace-Inhibitors	✓	✓	✓	✓
	Beta Blockers	✓X*	X	X	✓X*
	Antiplatelet Therapy	X	X	X	X
	Diuretics	✓X*	✓	✓	✓
	Bypass Surgery	X	X	X	X

Surgical Options	Angioplasty	X	X	X	X
	Thrombolysis	X	X	X	X
	Endarterectomy	X	X	X	X

✓ - Indicated

X- Not Indicated

✓X- Can be given, but comes with an increased risk of certain adverse effects.

\*Explanation on benefits and risks can be found in the paper above.

\*\*Ace inhibitors, beta blockers, and diuretics are often prescribed for hypertension, a common comorbidity of atherosclerosis. While beta blockers are not first line medications for hypertension, they may be first line therapeutics for other heart diseases which are often present with atherosclerosis.

**Table 2.** Recommended treatment options for cardiovascular disease and management of atherosclerosis in four high risk groups after the occurrence of a cardiac incident

		Age	Obesity	Diabetic	Genetic
Lifestyle Changes	Diet And Exercise	✓	✓	✓	✓
Medications	Statin	✓	✓	✓	✓
	Ace-Inhibitors	✓	✓	✓	✓
	Beta Blockers	✓	✓	✓	✓
	Antiplatelet Therapy	✓	✓	✓	✓
	Diuretics	✓	✓	✓	✓
Surgical Options	Bypass Surgery	✓X*	✓	✓	✓
	Angioplasty	✓	✓X*	✓X*	✓
	Thrombolysis	✓X*	✓X*	✓X*	✓X*
	Endarterectomy	✓X*	✓X*	✓X*	✓X*

✓ - Indicated

X- Not Indicated

✓X- Can be given, but comes with an increased risk of certain adverse effects

\*Explanation on benefits and risks can be found in the paper above.



\*\*Ace inhibitors, beta blockers, and diuretics are often prescribed for hypertension, a common comorbidity of atherosclerosis. While beta blockers are not first line medications for hypertension, they may be first line therapeutics for other heart diseases which are often present with atherosclerosis.

## Conclusion

The goal of this paper was to provide an overview of existing treatment options for atherosclerosis and comment on which might be optimal for patients at high-risk of atherosclerosis. While there are multiple options available, individual factors such as age, past medical history and family history, must be considered when selecting the optimal treatment regimen. Both patients and providers should be well informed about the treatment options and decide as a team what is best for the patient to receive the most ideal treatment plan and avoid any further complications. Further research into alternative methods, such as gene therapy, and medical innovations that are not available to patients today will be invaluable to improve the recovery of patients from atherosclerosis.

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