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Atherosclerotic Disease: Pathogenesis & Approaches to Management

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Background

Defining Atherosclerotic Disease

Atherosclerosis refers to the process of fibrofatty plaque formation within arterial walls. This process may lead to hemodynamically significant narrowing and disruption of arterial flow to end-organs, manifesting as atherosclerotic disease.[1] Atherosclerosis may develop in any arterial segment and commonly leads to disease states in the coronary, carotid, cerebral, mesenteric, renal, and lower extremity arterial beds. Clinically, atherosclerosis in these distributions leads to important entities such as stroke, myocardial infarction (MI), coronary artery disease (CAD), mesenteric ischemia or ischemic colitis, and lower extremity peripheral artery disease (PAD). The risk of developing atherosclerotic disease is influenced by comorbidities, including dyslipidemia, hypertension, obesity, and diabetes. Management of these diseases may vary based on the clinical scenario and is aimed at mitigating or disrupting common pathways for the development of atherosclerosis. This chapter will review the pathogenesis of atherosclerotic disease as well as current approaches to managing patients with clinically stable atherosclerotic disease.

Impact of Atherosclerotic Disease

Collectively, atherosclerotic diseases represent the leading causes of death worldwide.[2] Stroke leads to 1 in 6 deaths, while the prevalence of CAD among adult Americans is estimated at 7.1%, or around 20 million people. The prevalence of PAD is increasing and is now estimated to affect more than 236 million people worldwide.[3] An increasingly

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recognized clinical entity is polyvascular disease, or atherosclerosis affecting multiple arterial beds, which is increases risk of future heart attack, stroke, or death.[4]

Pathogenesis of Plaque Formation and Progression

Mechanism of Plaque Formation

Arterial walls consist of three distinct layers, each having a unique role in maintaining vessel wall integrity and function. The adventitia is the outermost layer and contains the small blood vessels that feed the arterial wall (vasa vasorum), while smooth muscle cells and extracellular matrix proteins make up the media, or middle layer.[5] The intima represents the innermost layer of the arterial wall and is lined with endothelial cells; the sub-endothelial space is the primary site of plaque formation. Plaque development occurs due to an interplay between endothelial cells, smooth muscle cells, and immune cells, including monocytes and macrophages (Table 1).[6] Vulnerable sections of endothelium develop in areas of turbulent or disrupted blood flow, commonly at sites of bifurcation, due to excessive hemodynamic stress.[7] This leads to increased endothelial permeability and activation of signaling molecules, including inflammatory mediators and cell adhesion molecules. Circulating lipoproteins, including low-density lipoprotein (LDL) particles, can traverse the endothelial layer and become trapped in the sub-endothelial space, where they undergo oxidative changes that reinforce the local inflammatory response.[8] Reactive monocytes mature into macrophages as they are recruited to the intimal layer via attractant chemokines, and activated platelets aggregate and adhere to the endothelium.[6] Foam cells form as mature macrophages attempt to clear oxidized lipoproteins via phagocytosis, and ultimately undergo necrosis. The resulting cycle of localized chronic inflammation leads to the deposition of cell-breakdown products as well as fibrinous material deposited by smooth muscle cells attracted from the media into the intimal layer, which may propagate and extend into the vessel lumen as plaque.[5]

Plaque Histology

Plaque formation begins as fatty streaks, or xanthomas, which are the result of lipid-rich foam cell aggregation within the intimal layer.[7] In response, smooth muscle cells proliferate and migrate from the media to intima, leading to intimal hyperplasia.[1] As this process continues, the smooth muscle cells organize and deposit extracellular matrix, forming a fibrous cap.[9] If this process is uninterrupted, the plaque continues to proliferate and enlarge, ultimately producing a hemodynamically significant stenosis. Erosion or rupture of the fibrous cap can lead to thrombotic occlusion or distal embolism due to exposure of bloodstream coagulation factors with thrombogenic plaque material, causing platelet aggregation, obstruction of blood flow, and resultant end-organ ischemia.[10,11] Several features have historically defined plaque vulnerability or propensity to rupture (Table 2). Lesions with these findings are at greater risk of causing a future vascular event.[9]

Risk Factors for Atherosclerosis Development

Smoking

Cigarette smoking remains one of the leading preventable risk factors for the development of atherosclerotic disease. The prevalence of cigarette smoking daily or some days for adults in the United States is estimated at 14%.[2] Overall rates of cigarette smoking have declined significantly in recent decades, but former smokers remain at excess risk for atherosclerotic disease.[2] Cigarette smoking likely perpetuates the cycle of local inflammation, endothelial damage, and pro-thrombotic conditions that lead to atherosclerosis, but these mechanisms are incompletely understood.[12]

Diet

Dietary patterns contribute to the development of atherosclerosis through alterations in blood pressure, circulating lipoprotein concentrations, insulin resistance, inflammation, and oxidative stress.[13] Emerging evidence suggests that overall diet quality, rather than specific food groups, leads to changes in the gut microbiome, hepatic lipogenesis, and metabolism.[13] Poor dietary quality, especially when combined with a sedentary lifestyle, predisposes patients to higher rates of obesity and metabolic syndrome and subsequent increased atherosclerotic risk.[2]

Obesity

Obesity is associated with the development of atherosclerotic disease and is linked to increases in circulating lipoproteins, including LDL and triglycerides.[2,14] Excess adipose tissue releases signaling molecules that increase systemic inflammation, enhance hypercoagulability, worsen insulin resistance, and promote endothelial dysfunction.[15]

Dyslipidemia

Elevated blood concentration of LDL cholesterol (LDL-C) in humans is causally linked to atherosclerotic disease.[16] Pro-inflammatory and pro-immunogenic properties of oxidized LDL underlie this relationship, though more recent studies have questioned the role of oxidized LDL.[11,17] In recent years, there has been increasing interest in triglyceride-rich lipoproteins (TGRLs), which are proatherogenic and proinflammatory,[18] as well as blood elevations in lipoprotein (a) (Lp(a)).[19]

Hypertension

Elevated blood pressure is associated with increased atherosclerotic disease risk, primarily driven by increases in shear stress along the vascular endothelial surface, arteriolar remodeling, vascular stiffness, and dysregulated cellular sodium processing.[20] Lymphocytes and monocyte/macrophages accumulate within perivascular renal arterioles in response to chronically elevated blood pressure and release cytokines that enhance oxidative stress, immune activation, and vascular dysfunction.[21]

Diabetes

Diabetes and insulin resistance have well-documented associations with atherosclerosis and cardiovascular risk.[22] Hyperinsulinemia causes increases in circulating fatty acids, which are proinflammatory and proatherogenic.[18] Excess circulating glucose leads to glycosylation of enzymes which may increase oxidative stress and enhance pro-inflammatory pathways.[23] These factors collectively lead to modification of the micro- and macrovascular structure and promote the formation and progression of plaque.[21,23]

Inflammation

Local inflammation drives plaque propagation, erosion, and rupture and may be the common pathway by which many traditional risk factors lead to atherosclerosis. Systemic inflammation can be initiated by excess circulating fatty acid intermediates, glycosylated lipoprotein products, or hypertension, ultimately leading to alterations in circulating immune cells and increases in oxidative stress.[23] Inflammasomes, or large intracellular multimeric protein complexes activated in response to local tissue damage, are thought to drive this inflammatory response by controlling the release of inflammatory cytokines, including interleukin (IL)-1β and IL-18.[21,24] These cytokines are elevated in disease states including CAD and lead to downstream expression of systemic inflammatory mediators including tumor necrosis factor (TNF) and IL-6.[24] The role of novel anti-inflammatory therapies, including those targeting IL-1β and IL-6, in mitigating future cardiovascular risk remains an area of active research.[25]

Thrombosis

Arterial thrombosis is the eventual mechanism by which obstruction of blood flow occurs in atherosclerotic disease. Local thrombosis occurs due to rupture or erosion of plaque and exposure of necrotic or lipid-rich core components to the systemic circulation, which results in platelet aggregation, platelet activation, and induction of the coagulation cascade via tissue factor release.[26] Platelet-rich thrombi form and ultimately lead to vessel occlusion if uninhibited.[26] In addition to lipid-lowering therapies, pharmacotherapy to interrupt or prevent the thrombotic process is a mainstay of management.

Management of Stable Atherosclerotic Disease

Atherosclerosis requires a multi-faceted management approach that needs to be tailored to the individual patient risk profile. The astute clinician must identify opportunities for risk reduction and dynamically tailor therapies throughout years of management.

Smoking Cessation

In heavy smokers, cessation is associated with a nearly 40% reduction in cardiovascular risk within 5 years, but the cardiovascular risk remains elevated compared to never-smokers for up to 25 years after cessation.[27] Many patients struggle with tobacco cessation, and fewer than 10% of patients who attempt to quit are successful. Referral to a multidisciplinary smoking cessation program that includes pharmacotherapy and behavioral intervention increases the likelihood of achieving abstinence 3-fold and should be the cornerstone

of management.[28] Varenicline, nicotine replacement therapy (NRT), and bupropion are well-established therapies recommended for cessation by multiple societal guidelines and consensus statements.[29] Varenicline is superior to both NRT and bupropion in 6-month tobacco abstinence and has even greater efficacy when combined with long and short acting NRT.[30] NRT is most effective when prescribed in both long- and short-acting formulations to provide both basal and bolus coverage.

Diet and Exercise

A healthy diet and physical activity are key components of atherosclerotic prevention, particularly as obesity rates rise across the United States.[31] Societal guidelines recommend counseling patients at every visit on the importance of a diet rich in vegetables, fruits, nuts, whole grains, lean animal protein, and fish while minimizing *trans* fats, red and processed meats, refined carbohydrates, and sweetened beverages.[32] While not directly linked to atherosclerosis, diets high in sodium (>2000 mg daily) have been linked to increased blood pressure and increased risk of cardiovascular events.[33] Though large-scale randomized controlled trials with hard cardiovascular endpoints are limited, multiple observational studies have demonstrated an association between poor dietary habits and cardiovascular mortality.[32]

Physical activity offers several beneficial cardiovascular effects, including improved physical functioning, weight reduction, and glycemic and blood pressure control.[32] There is a strong, inverse, dose-response relationship between physical activity and cardiovascular events, and current guidelines recommend at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes per week of vigorous-intensity physical activity.[33] Patients should be regularly counseled on the benefits of an active lifestyle, especially those with established atherosclerotic disease, obesity, or diabetes mellitus who are at greatest cardiovascular risk.[34]

Blood Pressure Control

Nearly 50% of Americans meet the criteria for hypertension and approximately 25% are on antihypertensive medications.[35] Each 20 mmHg rise in systolic blood pressure (SBP) above 115 mmHg and 10 mmHg rise in diastolic blood pressure (DBP) above 75 mmHg is associated with a 2-fold increase in risk of death from stroke, heart disease, or other atherosclerotic vascular diseases.[36] Patients with atherosclerotic disease should be treated to blood pressure (BP) targets of SBP <130 mmHg and DBP <80 mmHg, as intensive BP control is associated with significant reductions in cardiovascular events, even in elderly patients.[37] All patients with atherosclerosis should be started on pharmacologic therapy if not at goal. American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend combination therapy for Black patients and for adults with more severe hypertension (SBP≥140 mm Hg or DBP ≥90 mm Hg and an average SBP/DBP >20/10 mm Hg above their target BP).[37] Calcium channel blockers, thiazide diuretics, angiotensin-converting-enzyme inhibitors (ACEi), or angiotensin receptor blockers (ARBs) should be used as initial pharmacologic agents and selected based on the patient profile (Table 3).[37]

Glycemic Control

Lifestyle modification (as described above) should be discussed at every preventative health visit to reduce the risk of developing metabolic syndrome and T2DM. When this has failed, the American Diabetes Association recommends a hemoglobin A1c target of <7% for most nonpregnant adults, <6.5% for young patients, and <8% for those with limited life expectancy.[38] Intensification of lifestyle modification remains first line therapy to improve glycemic control. This includes dietary modification, such as adhering to a Mediterranean, DASH, or vegetarian/vegan diet, institution of an exercise program, and weight loss.[32] Metformin is the first-line choice once pharmacologic therapy is needed and has beneficial effects on hyperglycemia, weight loss, and atherosclerotic risk.[32] In those with additional risk factors for atherosclerotic disease, sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor (GLP-1R) agonists have been shown to significantly reduce cardiovascular events and can be added to metformin if additional glycemic control is needed.[39,40] SGLT-2 inhibitors should be preferentially selected for patients with atherosclerosis and T2DM who also have concurrent heart failure or albuminuria.[41]

Lipid Lowering Therapies

Statins reduce LDL-C levels and risk of cardiovascular disease in those with atherosclerotic disease and are the preferred initial therapy for hyperlipidemia (Table 4).[42,43] Goal LDL-C reduction is ≥ 50% or to a target of ≤ 70 mg/dL for those at high risk, which includes all patients with prior atherosclerotic cardiovascular events.[44] Those patients with established atherosclerotic disease but without prior cardiovascular events should be stratified by atherosclerotic cardiovascular disease (ASCVD) risk score, and any recommendation for moderate- versus high-intensity statin should be based on those results.[44] For patients not at goal with high-intensity statin therapy alone, ezetimibe is the most commonly utilized non-statin therapy and lowers LDL-C by an additional 13–20%.[44] Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are powerful LDL-lowing drugs that reduce LDL-C levels by 43–64% and have been shown to reduce atherosclerotic risk in patients not achieving LDL-C goal with maximally tolerated statin therapy and ezetimibe. Ongoing studies are testing the efficacy of small interfering RNA (siRNA) molecules to achieve long-term LDL or Lp(a) reduction.[45]

Antiplatelet Therapy

Aspirin has been widely used for the prevention of atherosclerotic events. In patients who have had a prior MI, transient ischemic attack (TIA), or stroke, aspirin is a mainstay of secondary prevention, and extensive data support its use to reduce atherosclerotic events.[46]

$P2Y_{12}$ inhibitors, such as clopidogrel, ticagrelor, and prasugrel, are more potent and efficacious antiplatelet agents.[47] These agents are commonly used in combination with aspirin (termed dual antiplatelet therapy, or DAPT) for the prevention of ischemic events following acute coronary syndrome, percutaneous coronary intervention, and TIA/stroke.[48,49] Duration of therapy following an acute event depends on the clinical syndrome and patient profile. Antiplatelet regimens should be tailored to the individual patient's bleeding and ischemic risk while also considering the location of atherosclerosis and prior procedural characteristics that may increase the risk of future cardiovascular events. In

patients with stable atherosclerotic disease, there is evidence that chronic $P2Y_{12}$ inhibitor monotherapy may be more efficacious than aspirin without incurring a higher risk of bleeding.[50]

Antithrombotic Therapy

Antithrombotic therapy plays an important role in reducing long-term cardiovascular risk in individuals with atherosclerotic disease, particularly those with polyvascular disease. The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial found that rivaroxaban 2.5 mg daily in combination with aspirin reduced the composite event of cardiovascular death, MI, and stroke compared to aspirin alone in patients with CAD and PAD.[51] Similar results were seen in subgroup analyses of patients with PAD with additional reductions in major adverse limb events.[52] A subsequent trial also demonstrated a reduction in acute limb ischemia, major amputation, myocardial infarction, ischemic stroke, and cardiovascular death with rivaroxaban 2.5 mg twice daily and aspirin compared to aspirin alone in patients undergoing lower extremity revascularization.[53] Rivaroxaban 2.5mg twice daily with low-dose aspirin should be considered in all patients with stable atherosclerotic disease in ≥ 2 vascular beds and acceptable bleeding risk.

Clinics Care Points: Antiplatelet and Antithrombotic Therapy in Polyvascular Disease

- Pearls
  - Identification of polyvascular disease is the first step in determining appropriate management.
  - Common definitions:
    - CAD: stenosis ≥50%, prior percutaneous coronary intervention, or prior coronary artery bypass graft surgery
    - PAD: ABI <0.9 or ≥ 50% stenosis of lower extremity artery
    - Cerebrovascular disease (CVD): prior stroke, TIA, or ≥50% stenosis of carotid artery
  - Once individuals with polyvascular disease are identified, medical management varies by affected vascular bed.
- Pitfalls
  - Polyvascular disease is often overlooked, and clinicians may presume treatment of atherosclerosis does not vary by arterial distribution.
  - Even patients with atherosclerotic obstruction in an arterial bed but without obvious symptoms remain at heightened risk of cardiovascular events.
- Recommendations[50,54]

- In patients with stable CAD, CVD, or PAD, aspirin is first line for risk reduction. Clopidogrel can be utilized as monotherapy in select patients, particularly those with PAD.
- In patients with stable CAD and either CVD and/or PAD, aspirin should be combined with low dose rivaroxaban.
- Following any revascularization, DAPT is typically indicated, with the exception of lower extremity revascularization where aspirin, low dose rivaroxaban, +/− clopidogrel should be utilized.
- De-escalation of therapy after an acute event should be tailored to the individual patient's bleeding and ischemic risk.

Conclusions & Future Directions

Despite a better understanding of risk factors and disease-modifying interventions, atherosclerosis continues to affect millions of people with significant ramification for the healthcare system. There are numerous ongoing efforts to identify novel risk factors, better calculate individual risk, and develop unique therapeutic interventions with the ultimate goal of further mitigating atherosclerotic disease burden. Newly appreciated risk factors, such as clonal hematopoiesis of indeterminate potential (CHIP) and air pollution, are linked to excess cardiovascular risk through pro-inflammatory or pro-thrombotic properties.[11,55] Advances in genomics are bringing personalized genetic risk assessment closer to a reality along with the possibility of genome editing as a therapeutic intervention.[56] Novel therapeutic drugs, namely siRNAs, have been developed that can dramatically reduce LDL-C or Lp(a) concentrations with only a few doses each year, and phase III trials of these drugs are ongoing.[57,58] Collectively, these areas of active research will dramatically impact our strategies for prevention and treatment of atherosclerosis in the near future.

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Synopsis:

Atherosclerotic disease, including stroke and myocardial infarction, is the leading cause of morbidity and mortality worldwide. Atherosclerotic plaque formation occurs in the setting of excess oxidative and hemodynamic stress, and is perpetuated by smoking, poor diet, dyslipidemia, hypertension, and diabetes. Plaque may rupture, resulting in acute thrombotic events. Smoking cessation, lifestyle modification, risk factor optimization, and antithrombotic therapies are the mainstays of atherosclerotic disease management and are the cornerstones to reducing morbidity and mortality in this high-risk patient population. Novel therapeutics are in development and will add to the growing armamentarium available to physicians who manage atherosclerotic disease.

Key Points

- Atherosclerosis is a complex, multi-faceted process that is impacted by behavior, environment, genetics, and comorbid disease states.
- Inflammation represents a key pathophysiologic mechanism in the development and propagation of plaque formation.
- Management of atherosclerotic disease is multifaceted. Optimizing lifestyle through smoking cessation, diet, and exercise while concurrently optimizing medical therapies for hypertension, diabetes, and dyslipidemia is the cornerstone of mitigating cardiovascular risk.

Table 1:

Key contributors in atherosclerotic plaque formation.

Key Players	Role in Plaque Formation
Endothelial cells	Activation under conditions of inflammation or stress, expression of adhesion molecules
Smooth muscle cells	Migration to the intimal layer, accumulation of extracellular matrix
Leukocyte adhesion molecules	Adherence of circulating monocytes and lymphocytes
Monocytes	Development of foam cells due to lipid uptake
Lymphocytes	Expression of pro-inflammatory mediators
Cytokines	Cell-cell communication; attract monocytes and macrophages
Platelet-derived growth factor (PDGF)	Promotes smooth muscle cell migration and proliferation, enhances extracellular matrix production
Interleukins (IL-1, IL-6)	Lymphocyte activation, innate immunity
Tumor necrosis factor (TNF)	Leukocyte activation, cytokine release, production of reactive oxidative species
Colony-stimulating factor (CSF)	Macrophage proliferation and survival
Interferon (IFN-γ)	Activation of monocytes, promotes formation of foam cells

Adapted from Libby P. The changing landscape of atherosclerosis. *Nature*. 2021;592(7855):524–533.

Table 2:

Histopathologic features of stable and vulnerable plaques

Vulnerable Plaque	Stable Plaque
Thin fibrous cap	Thick fibrous cap
Large lipid-rich and/or necrotic core	Small lipid core without necrosis
Intraplaque hemorrhage	Plaque calcification
Plaque ulceration	Smooth plaque
Local inflammation	Absence of significant inflammation

Risk of plaque rupture increases in the setting of vulnerable plaque.[10]

Table 3:

Anti-Hypertensive Therapy

Therapy	Dose	Prescribing Considerations
ACEi or ARB *	Usual Dosing Range- ACEi: Benazepril 10–40mg/d (1–2 doses) Captopril 12.5–150mg/d (2–3 doses) Enalapril 5–40mg/d (1–2 doses) Lisinopril 10–40mg/d (1 dose) Usual Dosing Range- ARB: Candesartan 8–32mg/d (1 dose) Irbesartan 150–300mg/d (1 dose) Losartan 50–100mg/d(1–2 doses) Valsartan 80–320mg/d (1 doses)	Utilize in patients with DM, HF, microalbuminuria Consider combination use with thiazide diuretic or CCB Monitor eGFR and potassium after initiation Avoid monotherapy in black patients unless additional indication Avoid combination of ACEi/ARB/direct renin inhibitors
CCB *	Usual Dosing Range: Amlodipine 2.5–10mg/d (1 dose) Nifedipine SR 60–120mg/d (2 doses) Nifedipine LA 30–90mg/d (1 dose)	Avoid in HF Monitor for lower extremity edema Thiazide diuretic or CCB preferred first-line in black adults without HF or CKD (even if DM present).
Thiazide Diuretic *	Usual Dosing Range: Chlorthalidone 12.5–25 mg/d (1 dose) Hydrochlorothiazide 25–50 mg/d (1 dose)	Monitor for hyponatremia and hypokalemia, and calcium levels.
MRAs	Usual Dosing Range: Eplerenone 50–100mg/d (1–2 doses) Spironolactone 25–100mg/d (1 dose)	Fourth line agent Monitor for hyperkalemia

* First line

ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; CCB: calcium channel blocker; d: day; CKD: chronic kidney disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HF: heart failure; mg: milligram; MRA: mineralocorticoid receptor antagonist

Table 4:

Lipid Lowering Therapy

Therapy	Dose	Prescribing Considerations
Statin	Usual Dosing Range- High Intensity: Atorvastatin 40–80mg/d Rosuvastatin 20–40mg/d Usual Dosing Range- Moderate Intensity: Atorvastatin 10–20 mg/d Rosuvastatin 5–10 mg/d Simvastatin 20–40 mg/d Pravastatin 40–80 mg/d Lovastatin 40–80 mg/d Fluvastatin 80 mg/d	Monitor for subjective myalgias (5–20% of patients) Rhabdomyolysis and hepatotoxicity rare but serious complications
Ezetimibe[59]	Usual Dosing Range: Ezetimibe 10mg/d	Up to 20% LDL-C reduction Generally well tolerated
PCSK9 inhibitors	Usual Dosing Range- PCSK9 antibodies: Alirocumab[60] Initial: 75 mg/2 weeks or 300 mg/4 weeks Max: 150mg/2 weeks Evolucumab[61] 140 mg/2 weeks or 420 mg/month	Subcutaneous administration Side effects: flu-like symptoms, injection site reactions, muscle aches

d: day; LDL-C: low-density lipoprotein cholesterol; mg: milligram; PCSK9: proprotein convertase subtilisin/kexin type 9