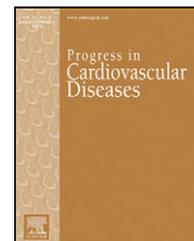


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Special Article

Coronary Atherosclerosis: Pathophysiologic Basis for Diagnosis and Management



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ABSTRACT

Coronary atherosclerosis is a long lasting and continuously evolving disease with multiple clinical manifestations ranging from asymptomatic to stable angina, acute coronary syndrome (ACS), heart failure (HF) and sudden cardiac death (SCD). Genetic and environmental factors contribute to the development and progression of coronary atherosclerosis. In this review, current knowledge related to the diagnosis and management of coronary atherosclerosis based on pathophysiologic mechanisms will be discussed. In addition to providing state-of-the-art concepts related to coronary atherosclerosis, special consideration will be given on how to apply data from epidemiologic studies and randomized clinical trials to the individual patient. The greatest challenge for the clinician in the twenty-first century is not in absorbing the fast accumulating new knowledge, but rather in applying this knowledge to the individual patient.

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“TA PANTA REI”... “Everything is changing”
[Heraclitus 540-480 B.C.]

Introduction

In the middle of the last century, it was almost impossible to imagine the progress that would be made over the next several decades for the diagnosis and management of

coronary atherosclerosis. Compared to the remarkable technology at present, the electrocardiogram and chest x-ray were the only available diagnostic tools for coronary atherosclerosis. Likewise, compared to multiple sophisticated therapeutic modalities available today, only nitroglycerin, morphine and bed rest were used for the management of coronary atherosclerosis at that time.¹

Coronary atherosclerosis is a complex, long lasting and continuously evolving inflammatory disease characterized by remodeling of the coronary arteries, which supply oxygen

Statement of Conflict of Interest: see page 689.

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Abbreviations and Acronyms

ACS = acute coronary syndrome
CABG = coronary artery bypass grafting
CKD = chronic kidney disease
CRP = C-reactive protein
CVD = cardiovascular disease
DAPT = dual antiplatelet therapy
DM = diabetes mellitus
HDL-C = high density lipoprotein cholesterol
HF = heart failure
HTN = hypertension
LDL-C = low density lipoprotein cholesterol
LV = left ventricular
MI = myocardial infarction
OMT = optimal medical therapy
PCI = percutaneous coronary intervention
SCD = sudden cardiac death
STEMI = ST elevation myocardial infarction

to the myocardium. It has various clinical manifestations ranging from asymptomatic to stable angina, acute coronary syndromes (ACS), sudden cardiac death (SCD) or heart failure (HF). Development and progression of coronary atherosclerosis is related to genetic and environmental factors that modulate disease risk individually and through different interactions. Due to the nature of the disease, the majority of the patients may live with coronary atherosclerosis for many years and often decades.^{2–5} In this brief review, current knowledge related to the diagnosis and management of coronary atherosclerosis based on pathophysiologic mechanisms will be discussed. In addition

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function; it appears that this genetic variant increases the risk of a first coronary heart disease event, but not subsequent events. Of interest, this variant is associated with periodontitis and gout, both conditions that are associated with increase inflammation, but not with C-reactive protein (CRP).^{9,10}

For years it has been known that the incidence of myocardial infarction (MI) is related to the ABO blood type; having alleles for blood type A or B is associated with a greater risk for MI compared to blood type O. Group A or B are also associated with higher levels of von Willebrand factor complex.^{9,10}

Evidence that LDL-C plays an important role in the development and progression of coronary atherosclerosis has been known for decades. One of the major observations that demonstrated the genetic link between LDL-C and coronary atherosclerosis was by Brown and Goldstein discovering a mutation in the LDL-C receptor in patients with familial hypercholesterolemia, premature coronary atherosclerosis and early death.¹¹ This observation was crucial for the development of statins, a pharmacologic agent that has been widely used in primary and secondary prevention of atherosclerosis, resulting in a significant decrease in cardiovascular disease (CVD) events and CVD death. Another significant discovery with a genetic link is the enzyme PCSK9 and its effects on LDL-C and coronary atherosclerosis. The enzyme PCSK9 (chromosome 1p32.3) increases the degradation of LDL-C receptors. Mutations that increase the function of PCSK9 are associated with high levels of LDL-C and increase incidence of coronary atherosclerosis. In contrast, mutations that result in loss of function of PCSK9 are associated with low levels of LDL-C and decrease incidence of coronary atherosclerosis. These observations resulted in the development of monoclonal antibodies that inhibit the function of the PCSK9 enzyme¹² (see later). Administration of these agents to patients with hypercholesterolemia who were treated with a statin produced a dramatic decrease in LDL-C (this decrease was in addition to that obtained with statins) and to a significant decrease in CVD events. More recently, a mutation in ANGPL4 has been identified. ANGPL4 is known to inhibit lipoprotein lipase increasing triglyceride levels; carriers with a loss of function mutation were shown to have lower blood levels of triglycerides and lower incidence of coronary atherosclerosis compared to non-carriers. The data suggest that lipoprotein lipase pathway plays an important role in the development of coronary atherosclerosis; it follows that new drugs modulating these pathways can be developed in the near future potentially decreasing the incidence of coronary atherosclerosis.¹³ Although low levels of HDL-C are associated with coronary atherosclerosis, therapeutic interventions that increase HDL-C currently have not demonstrated any effect on survival or reduction in CVD events.^{9,13–15}

tion to general concepts related to coronary atherosclerosis, special considerations will be given on how to approach the individual patient.

Development of coronary atherosclerosis

Genetic and environmental factors that contribute to the development of the atherosclerotic lesion and progression of the disease are shown schematically in Fig 1.

Genetic factors

Genome-wide association studies have shown that more than 55 loci are related to coronary atherosclerosis. Each individual inherits genetic variants (i.e., minor alleles, polymorphisms, mutations), but only individuals who inherit a combination of multiple variants are at the greatest risk for the development of the disease.^{6–10} It should be mentioned that most of these genetic variants related to coronary atherosclerosis are located at DNA sequences that do not code proteins. Only 15 of the genetic variants are related to known risk factors [7 to low density lipoprotein cholesterol (LDL-C), 4 to arterial hypertension (HTN), 2 to triglycerides, 1 to high density lipoprotein cholesterol (HDL-C) and 1 to thrombosis]. The first described genetic variant found to be associated with coronary atherosclerosis is located on the short arm of chromosome 9 (chromosome 9p21) with yet unknown

Environmental factors

In addition to cholesterol, other risk factors for coronary atherosclerosis are shown in Fig 1. HTN and diabetes mellitus (DM) are major risk factors contributing to the development of coronary atherosclerosis. Even isolated systolic HTN in young and middle age adults has been shown to be associated with a higher incidence of coronary atherosclerosis. It follows that optimal medical management of HTN and DM, as recent data

Genetic and Environmental Risk Factors

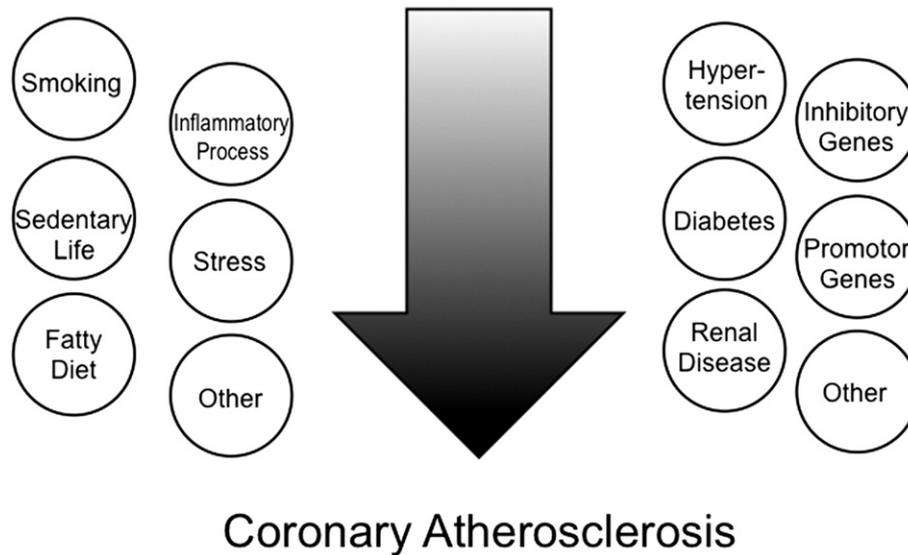


Fig 1 – Genetic and environmental risk factors that promote the development and progression of coronary atherosclerosis are shown.

have shown, is of great clinical significance. A sedentary lifestyle may predispose to obesity and DM, which are associated with hyperlipidemia and an inflammatory process. Thus, moderate exercise and a balance diet, particularly a Mediterranean diet, are recommended. It is important at this point to emphasize the major risk of second and third-hand smoking that is associated with inflammation and continues to be a serious problem in several countries including “developed” countries.^{16–23}

Progression of coronary atherosclerosis

“The whole is greater than the some of its parts”

[–Aristotelis]

When an atherosclerotic plaque develops in the wall of a coronary artery, the artery undergoes remodeling in which the luminal area of the vessel is enlarged.²⁴ Thus, although an atherosclerotic plaque is present, the luminal area of the artery may not be diminished. The degree of luminal stenosis, therefore, may not be directly related to the size of the atherosclerotic plaque and for this reason a large atherosclerotic plaque may produce a small degree of stenosis (Fig 2A). Atherosclerotic plaques could be stable or unstable. An unstable atherosclerotic plaque is characterized by a large lipid pool, high concentrations of macrophages that suggest an inflammatory process, small amount of collagen, and a thin cap that covers the plaque.³ In contrast, a stable atherosclerotic plaque is characterized by a small lipid pool, large amount of collagen, low density of macrophages suggesting a minimal or no inflammatory process, and a thick cap that covers the plaque. A stable atherosclerotic plaque at any time may become unstable, while an unstable plaque may be stabilized. An unstable plaque may rupture,

however, plaque rupture more often results in disease progression and less often to intravascular thrombosis and vascular occlusion (Fig 2B).^{24,25} A ruptured plaque in which thrombus formation does not produce complete occlusion of the artery may result in unstable angina or a non-ST elevation MI. An acute complete occlusion of the artery results in a ST elevation MI (STEMI). Acute MI and myocardial necrosis results in left ventricular (LV) dysfunction, LV remodeling, and ischemic cardiomyopathy with or without symptoms of HF. Often a varying degree of mitral regurgitation is present. One clinical picture of the disease may lead to another. Occasionally during superficial plaque rupture (i.e., erosion), chest pain lasting more than 20 min may occur without myocardial necrosis; this episode essentially is an acute ischemic syndrome, however, since the pain usually is not related to exertion and often disappears for an extended period of time it may be characterized as “atypical” chest pain. It should be emphasized that several unstable plaques may be present at the same time in the same patient with varying degrees of instability and progression. At present, diagnostic invasive or non-invasive techniques are of limited value to define plaques that are likely to progress and cause an ACS. Overall prognosis is not just related to one atherosclerotic lesion, but to the total atherosclerotic burden, LV function and co-existence of mitral regurgitation (Fig 3).^{26–34}

Diagnostic considerations

“We had the experience but missed the meaning”

[–T.S. Eliot]

Early diagnosis of coronary atherosclerosis is essential, particularly prior to plaque rupture that may result in an acute

MI or SCD. Unfortunately, a plaque producing a smaller degree of stenosis (50% to 60%) may rupture.^{35,36} A stenosis of less than 70% typically is not associated with symptoms and cannot induce ischemia on stress testing (Fig 4). Thus, the diagnosis of coronary atherosclerosis based on stress-induced ischemia may be too late (i.e., after plaque rupture and an acute ischemic syndrome). Multiple sliced computed tomography provides important information related to the presence of atherosclerotic plaques in the coronary arteries; however, recent studies suggest that multiple sliced computed tomography in symptomatic patients with suspected coronary atherosclerosis who required non-invasive stress testing did not improve clinical outcomes over a median follow up of two years compared to just performing a stress test. Further, multiple sliced computed tomography does not define precisely the degree of stenosis. Coronary calcium score also is not very useful for the individual patient since significant coronary atherosclerosis may be present even in patients with a calcium score of zero; however, it should be mentioned that a high calcium score is associated with more adverse outcomes

compared to patients with a low calcium score. Further, a calcium score cannot define the severity of lumen stenosis or the coronary arteries with significant luminal obstruction. Identification of atherosclerotic plaques in other arteries (e.g., carotid arteries, femoral arteries, aorta) that can be achieved non-invasively increases the possibility for the presence of coronary atherosclerosis, but does not prove its presence and obviously does not provide information in regards to coronary anatomy. For these reasons, coronary arteriography should be considered in almost all patients with suspected coronary atherosclerosis.³²⁻³⁴ Fractional flow reserve, intravascular ultrasound and optical coherence tomography may provide additional information in certain cases. Molecular imaging that will be available in the near future for clinical use will also provide additional important information.^{34,37} Despite all these advantages, unfortunately early diagnosis of coronary atherosclerosis is currently not feasible in the general population. Given the fact that approximately one third of patients with coronary atherosclerosis die suddenly, prevention should be emphasized.

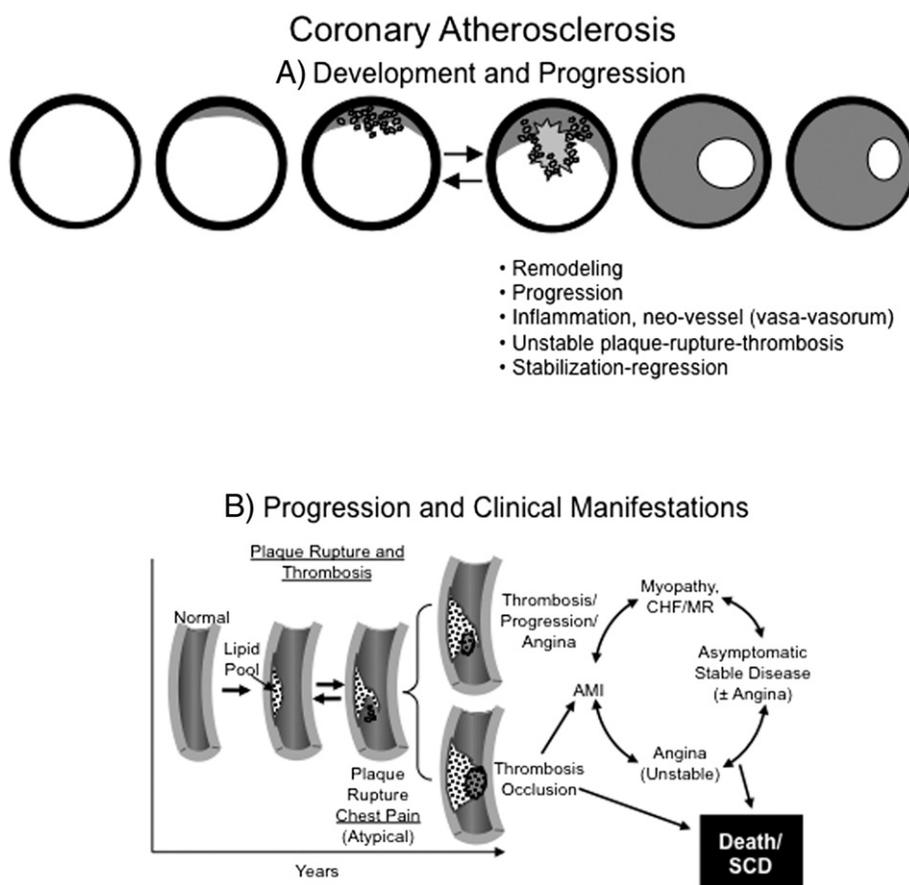


Fig 2 – A: Coronary atherosclerosis is a dynamic disease process. When an atherosclerotic plaque develops in the wall of a coronary artery, the artery undergoes remodeling in which the luminal area of the artery and the plaque area are not linearly related. Inflammatory process and neo-vessel (vasa-vasorum) may be present in the plaque. After rupture of an atherosclerotic plaque, thrombosis may occur that leads to progression of the disease (more often) and/or to an acute coronary syndrome. A stable plaque may become unstable and an unstable plaque may be stabilized (bi-directional arrows). B: Progression of coronary atherosclerosis and clinical manifestations are shown. An atherosclerotic plaque (lipid pool) may become unstable. An unstable plaque may rupture leading to intravascular thrombosis resulting in an acute coronary syndrome, sudden cardiac death (SCD) or progression of the disease (most often). One clinical picture of coronary atherosclerosis may lead to another. An unstable plaque may be stabilized. Abbreviations: AMI = acute myocardial infarction, CHF = congestive heart failure, MR = mitral regurgitation.

Coronary Artery Disease: Prognosis is Related to Overall Disease and Status of LV Function

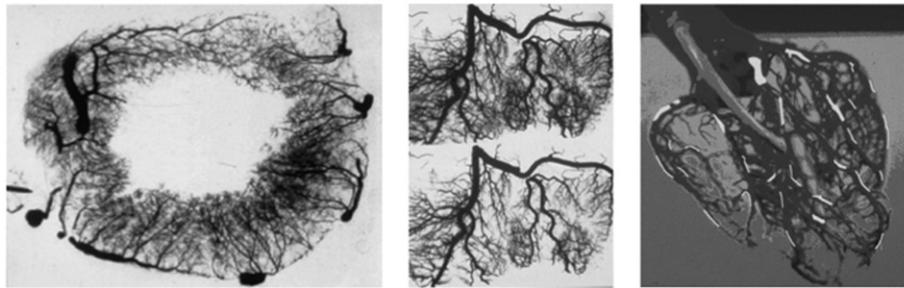


Fig 3 – Pathologic specimen of a coronary artery tree (left and middle images); atherosclerotic lesions are shown schematically in white and a vein graft to a coronary artery is also shown (right image). The prognosis of coronary artery disease is related to overall disease and status of left ventricular (LV) function and not to a single lesion.

Management

An atherosclerotic plaque that compromises coronary blood flow may lead to myocardial ischemia or necrosis, LV remodeling, ischemic cardiomyopathy and HF. Further, coronary atherosclerosis may be associated with angina pectoris. Unfortunately, coronary atherosclerosis often may result in SCD. Management of coronary atherosclerosis, therefore, should include therapy to prevent progression or rupture of the atherosclerotic plaque and to facilitate regression. In addition, attention should be made to preserve and/or to improve LV function, alleviate angina pectoris and provide therapy to prevent SCD (Fig 5). Certain vaccinations and the treatment of other underlying diseases should be taken into consideration.

Therapy for the plaque

Patients with coronary atherosclerosis should be treated aggressively to prevent plaque progression, potentially facilitate plaque regression, stabilize the unstable plaque, and prevent plaque rupture.³ Considering the complex relationship between plaque rupture and the development of an ACS, managing patients at risk mandates a greater focus on the atherosclerotic disease burden than on the feature of an individual plaque (Fig 3). Further, antiplatelet therapy with aspirin 75 mg to 150 mg daily is recommended to prevent thrombosis, especially when plaque rupture occurs. After stent placement or after an ACS, a thienopyridine in combination with aspirin is indicated to prevent thrombosis (see later). Smoking cessation and aggressive cholesterol reduction are the first most important steps to prevent

The Shortcomings of Diagnosing Coronary Atherosclerosis Based on Stress-Induced Ischemia

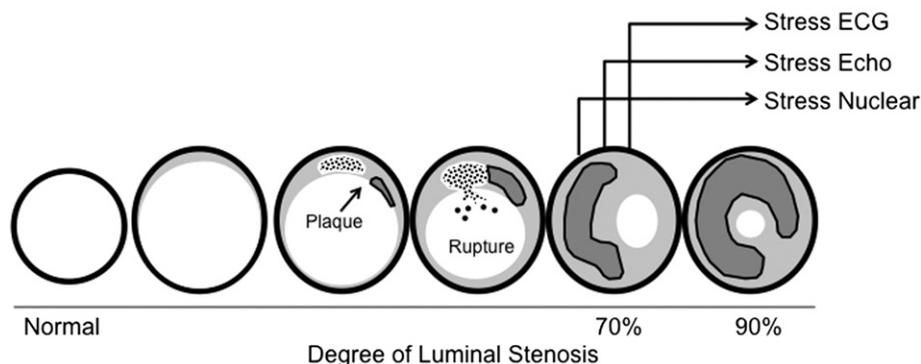


Fig 4 – Diagnosis of coronary atherosclerosis with non-invasive methods currently is based mostly on stress-induced ischemia. As a general rule, ischemia cannot be induced if the degree of stenosis is less than 70%; plaque rupture, however, may occur in plaques producing a less severe stenosis. Thus, diagnosis of coronary atherosclerosis by stress-induced ischemia, in certain cases, may be too late. Abbreviations: ECG = electrocardiogram, Echo = echocardiogram.

Coronary Atherosclerosis: Management

Goal	D/C Smoking	↓ Cholesterol	Anti-Platelet	β-Blockers	ACEI	Revascularization	Thrombolysis	Cell Therapy	Nitrates	Ca ⁺⁺ Blockers	ICD
Stabilize Plaque Prevent Progression	+	+		+							
Prevent Plaque Rupture	+	+		+							
Prevent Thrombosis	+		+								
Prevent MI	+	+	+			?					
Decrease MI Size				+		+	+	+			
Improve LV Function				+	+	+	+	+			
Treat Ischemia/Angina	+	+		+		+			+	+	
Prevent Death	+	+	+	+	+	+	+	?			+

Fig 5 – Management of coronary atherosclerosis. Abbreviations: ACEI = angiotensin converting enzyme inhibitor, Ca = calcium, D/C = discontinue, ICD = implantable cardioverter defibrillator, MI = myocardial infarction, LV = left ventricle, + indicates positive effect, down arrow indicates decrease.

progression and plaque rupture. Diet low in saturated fat, preferably following the Mediterranean diet, and statin therapy is recommended in all patients. LDL-C should be less than 70 mg/dl. Therapy with statins has contributed significantly to LDL-C reduction and to a decrease in the incidence of CVD events and death. More recently, monoclonal antibodies that inhibit the enzyme PCSK9 (e.g., alirocumab, evolocumab) have proved to be very effective in reducing LDL-C and CVD events. In certain cases, ezetimibe in combination with a statin may also be used. All these pharmacologic agents that decrease cholesterol have proved beyond any doubt that LDL-C is a key player in the development and progression of coronary atherosclerosis. It also has been suggested that statins in addition to their action on cholesterol may have other important pleiotropic effects (i.e., anti-inflammatory, effect on the endothelial and arterial wall function, other). Therapy with niacin or cholesterol ester transfer protein inhibitors (CEPT) may increase HDL-C cholesterol, but studies have shown that this therapy did not decrease or may increase the incidence of CVD events in patients already treated with a statin.^{38–47}

Inflammation plays an important role in the development and progression of atherosclerosis; specific therapeutic interventions to address this issue are underway (see later). All these interventions related to management of atherosclerotic plaque may prevent progression, facilitate regression, prevent rupture, and decrease CVD events and mortality. In certain instances, genetic analysis (pharmacogenetics) and functional studies can be used to define the effect of antiplatelet or statin therapy.

This type of testing is not ready for routine use in daily clinical practice.^{48,49}

Management to preserve or improve LV function

MI produces myocardial necrosis and LV dysfunction. LV systolic function is a stronger prognostic indicator compared to the number of diseased coronary arteries. Thus, therapy to preserve or improve LV function is of great clinical significance. Prevention of MI by stabilizing the atherosclerotic plaque obviously will preserve LV function. Triggers of MI such as high emotional stress or heavy physical activity, especially in cold or hot weather, should be avoided. Emergent percutaneous coronary intervention (PCI) or thrombolytic therapy (PCI is superior to thrombolysis) in patients with an acute STEMI results in decrease in the infarct size and preservation of LV function (Fig 5). Revascularization in chronic coronary artery disease also preserves LV function, especially when viable myocardium is present and when there is a large area of myocardium at risk (see later). Delayed recovery of hibernating myocardium after revascularization may occur. The STICH (Surgical Treatment of Ischemic Heart Failure) study, however, suggested that revascularization did not improve survival in patients with viable myocardium at 5-year follow-up, but viable myocardium was associated with a better prognosis compared to patients with no viable myocardium. The STICH study at 10-year follow-up, however, did show that the outcome of patients with an ischemic cardiomyopathy was better

in those who had coronary artery bypass grafting (CABG) surgery plus medical therapy compared to medical management alone. Therapy with β -blockers, renin-angiotensin-aldosterone axis inhibitors or other pharmacologic agents may preserve or improve LV function. Cell therapy has been used in experimental animal models and in clinical research studies. Data suggest that cell therapy may improve LV performance, but it is still at the research level and not for use in routine clinical practice. Adding surgical ventricular reconstruction to CABG was associated with a reduction of LV volume, as compared to CABG alone; however, this anatomical change was not associated with an improvement in exercise tolerance, improved symptom relief, or reduction in the rate of cardiac death or hospitalization.^{50–60}

Management to prevent ischemia and angina

In patients with angina pectoris, therapy to control symptoms should be provided. β -Blockers, calcium channel blockers, nitroglycerin or revascularization are effective in controlling symptoms. β -Blockers decrease myocardial oxygen demand by decreasing heart rate and myocardial contractility. The reduction of heart rate is associated with an increase in diastolic time (myocardial perfusion time) and thus, an increase in myocardial blood flow. β -Blockers along with relieving chest pain prolong life, particularly in post-MI patients and in patients with LV systolic dysfunction. In the era of PCI, however, is not clear if β -blockers increase survival in post-MI patients with normal LV systolic function. Calcium channel blockers mostly produce arteriolar dilatation, decrease myocardial oxygen consumption and may increase myocardial oxygen supply. In certain cases, calcium channel blockers resulting in arteriolar dilatation may result in a steal phenomenon (pro-ischemic effect). Nitroglycerin decreases venous return (mostly venous dilatation), LV filing pressure and myocardial oxygen supply. In addition, nitroglycerin may decrease myocardial oxygen demand. Calcium channel blockers and nitroglycerin improve symptoms, but do not

improve survival^{38,61–67} (Fig 5). Ivabradine should be considered in patients with a heart rate greater than 70 beats per minute while on β -blockers; it is our experience, however, that a heart rate greater than 70 beats per minute in patients who are treated with adequate amounts of β -blockers is extremely unusual. In the study SIGNIFY (Study Assessing the Mortality Benefits of the If Inhibitor Ivabradine in Patients with Coronary Artery Disease), the administration of ivabradine in patients with coronary atherosclerosis who had a heart rate greater than 70 beats per minute and were treated with a β -blocker did not demonstrate a significant difference in the incidence of cardiovascular events compared to placebo; however, patients who had a significant degree of exertional angina who were treated with ivabradine had more CVD events compared to placebo. Patients in the ivabradine group had more often bradycardia and atrial fibrillation compared to placebo.⁶⁸ In certain cases, ranolazine may be used in patients with persistent symptoms when other therapeutic modalities have not provided symptomatic relief. Ranolazine exerts its anti-anginal effects via voltage (frequency and concentration dependent) inhibition of the late sodium current in the ischemic myocytes. Either surgical or percutaneous revascularization increases myocardial blood flow without any effect on myocardial oxygen consumption. Revascularization is a very effective therapy as it reduces symptoms and, in certain cases, increases survival (see later). Studies also suggested that smoking cessation and therapy with statins improves exercise capacity; this effect is independent of their other beneficial effects related to the development and progression of atherosclerosis. In rare cases where symptoms cannot be controlled with the interventions mentioned, other devices such as coronary sinus narrowing or external counter-pulsation may be used.^{69,70}

Therapy to prevent SCD

“I look for the resurrection of the dead”

[– Greek Orthodox Liturgical 381 A.D.]

As it was mentioned earlier, SCD is common in patients with coronary atherosclerosis. Factors contributing to SCD are shown in Fig 6. Therapies to prevent progression of atherosclerosis will prevent SCD. Administration of β -adrenergic blocking agents and angiotensin converting enzyme inhibitors improve LV function, increase survival and decrease the incidence of SCD in patients with LV systolic dysfunction (Fig 5). The autonomic nervous system plays an important role in the pathogenesis of cardiac arrhythmias. Studies have suggested that altered sympathetic innervation of the LV myocardium that may occur after a MI is associated with higher incidence of ventricular arrhythmias and SCD. Regular moderate aerobic exercise, 30 to 45 min a day, among other effects improves autonomic nervous system function and may decrease the incidence of ventricular arrhythmias. In certain cases, implantation of an automatic defibrillator may be required to convert ventricular tachycardia or ventricular fibrillation and prevent SCD; in this case, the patient essentially is “resurrected from the dead”. In the early post-MI period, a wearable

Coronary Atherosclerosis: Factor Contributing to Sudden Cardiac Death

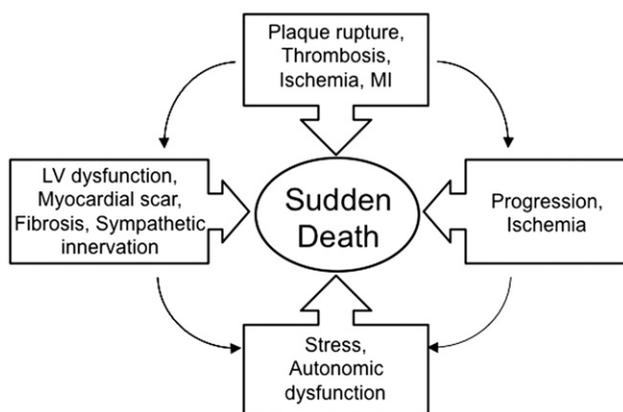


Fig 6 – Factors that may contribute to sudden cardiac death. Abbreviations: LV = left ventricle, MI = myocardial infarction.

Coronary Atherosclerosis: The Role of the Aorta and the Kidneys

- Stiff aorta:
 - ↓ Myocardial perfusion, ↑ MVO_2
- Chest pain of aortic origin
- Atherosclerosis → stroke during coronary bypass
- Renal disease is associated with higher cardiovascular morbidity and mortality



Fig 7 – A stiff aorta may result in a decrease in myocardial blood flow and an increase in myocardial oxygen consumption (MVO_2). In coronary atherosclerosis, pulse wave velocity and reflected wave velocity (shown schematically) are increased. Increased pulse wave velocity may result in target organ damage particularly the kidneys and the brain. Increase reflected wave velocity may result in an increase in central aortic pressure and the disappearance of diastolic wave that will result in an imbalance between myocardial oxygen consumption and supply. Atherosclerotic plaques or calcium in the aorta when present may result in stroke during revascularization therapy, especially during coronary artery bypass graft surgery. Chronic kidney disease in general and in patients with coronary atherosclerosis is associated with greater incidence of cardiovascular events. Up arrow indicates increase, down arrow indicates decrease (modified from reference 90).

defibrillator may be suggested in certain patients, however, there is not enough experience with this type of therapy at present.^{17,27,71–74}

Other issues to consider

Vaccinations

Influenza vaccination should be performed annually in all patients with coronary atherosclerosis regardless of age. Use of influenza vaccine was associated with lower risk of major CVD events. The greatest effect was seen among the highest risk patients with more active coronary atherosclerosis. Vaccination for pneumonia is recommended every 10 years. MI may be an early complication of pneumonia that it is associated with *in vivo* platelet activation.^{75,76}

Coffee, alcohol, other

An intake of two to three cups of coffee a day appears to be safe, if not beneficial, in most patients. Likewise, small to moderate amounts of alcohol intake is safe and may be beneficial in preventing atherosclerosis. Available data, however,

on coffee and alcohol use are based on observational studies.¹⁹ Low levels of vitamin D have been reported to be associated with higher incidence of CVD events. At present, however, it is not known if vitamin D administration to all patients would be beneficial.^{19,23}

Elective general surgery

Special care is required in patients with coronary atherosclerosis who will undergo general surgery. Among other issues, antiplatelet therapy and administration of β -blockers should be carefully evaluated. One cannot define rules that apply to all patients and thus, management should be individualized.

Antiplatelet therapy

If the patient has chronic stable coronary atherosclerosis without previous PCI and stent placement, therapy with aspirin can be discontinued safely for several days. Administration of aspirin in such patients before surgery and through the early post-surgical period increases the incidence of bleeding and has been shown to have no significant effect on the composite rate of death or non-fatal MI. In patients

who had stent(s) placement, elective surgery should be postponed for at least six months after stent implantation. At the time of surgery, aspirin cannot be discontinued in order to avoid stent thrombosis regardless of how long ago the stent was implanted. The thienopyridine can be discontinued after consultation with the interventional cardiologist who performed the procedure, and in general can be discontinued six to twelve months after drug eluting stent placement. The newer generation coronary artery stents may require a shorter duration of dual antiplatelet therapy (DAPT) compared to the older generation stents; however, this remains to be defined. In certain cases, surgery can be performed while the patient is on DAPT; risk of bleeding related to the surgery should be considered and obviously should be discussed with the surgeon who will be performing the procedure. The longer the interval from stent placement, the lower the risk of stent thrombosis. Data, however, suggest that discontinuation of thienopyridine even thirty months after stent placement may be associated with adverse CVD events. Careful evaluation is required to provide risk stratification for the purpose of safe discontinuation of DAPT beyond thirty months of treatment. Data also suggest that patients can safely undergo CABG while on clopidogrel; experience in this area is growing. All these issues should be discussed in advance with the cardiologist, surgeon and anesthesiologist.^{64,77–83}

β-Blockers

Therapy with β -blockers should be individualized for each patient undergoing surgery. If the patient is stable and is not taking β -blockade therapy, the patient can undergo surgery without initiating such therapy. If the patient is taking a β -blocker, continuation of therapy may be appropriate. Perioperative β -blockade therapy has been associated with lower rates of death mostly in high-risk patients. If for some reason the decision is made to discontinue β -blockade therapy, this should be done one week to ten days prior to surgery in order to avoid the so called β -blockade withdrawal phenomenon that is related to adrenergic hypersensitivity that can be seen for several days after β -blockade withdrawal. In cases where the patient appears to have a high adrenergic tone (tachycardia, anxiety), therapy with β -blockers may be appropriate. Perioperative β -blockers started within one day or less before non-cardiac surgery prevent non-fatal MI, but increase the risk of bradycardia, hypotension, stroke and death. There is insufficient information on β -blockade therapy that is started two or more days prior to surgery.^{84–86}

Oral anticoagulation

Another group of patients who requires special consideration are those who need oral anticoagulation therapy (e.g., atrial fibrillation, mechanical prosthetic valve) in addition to antiplatelet therapy after stent placement. Multiple studies have demonstrated a very high risk of bleeding among these patients. Information available suggests that oral anti-coagulation and clopidogrel without aspirin was associated with significant reduction of bleeding with no increase in the rate of thrombotic events, as compared to anti-coagulation with clopidogrel plus aspirin. Perhaps, this may be the optimal regimen for patients

who require oral anticoagulation therapy after PCI with stent placement.^{87,88}

Non-steroidal anti-inflammatory

Non-steroidal anti-inflammatory medications in post-MI patients receiving antithrombotic therapy are associated with increased risk of bleeding. In addition, use of non-steroidal anti-inflammatory medications may increase the incidence of CVD events. Therefore, non-steroidal anti-inflammatory medication use in patients with coronary atherosclerosis should be avoided whenever possible. Obviously many patients require these agents due to severe osteoarthritis, and when required, proton pump inhibitors may be needed to reduce upper gastrointestinal symptoms, ulceration and bleeding; these agents should generally be given 1 h after the aspirin dose to avoid inhibiting aspirin's potent antiplatelet effects, although one agent (celecoxib) does not seem to have antiplatelet activity or to interact with aspirin's antiplatelet effects.⁸⁹

Proton pump inhibitors

Proton pump inhibitors often are given simultaneously with antiplatelet therapy to prevent gastrointestinal bleeding. Previous studies suggested that proton pump inhibitors may interfere with metabolism of thienopyridine, thus may decrease its antiplatelet effect. It appears, however, that this is not a major risk. It is suggested that proton pump inhibitors should be given ten to twelve hours after thienopyridine administration in order to avoid a drug-drug interaction, that is if it does exist. More recent studies suggest that proton pump inhibitors may interfere with endothelial function and decrease nitric oxide levels; presently there is not sufficient information to make a meaningful recommendation.^{48,49}

Co-existent disorders and diseases

Underlying diseases if present (e.g., DM, HTN, other) should be treated aggressively.²²

The role of the aorta and the kidneys

The aorta plays an important role regulating LV performance, arterial function, myocardial oxygen consumption and coronary blood flow (Fig 7). Several studies have shown that a stiff aorta is associated with a worse prognosis in patients with coronary atherosclerosis and other CVD. It should also be mentioned that the presence of calcium or atherosclerotic plaques in the aorta might be associated with a higher risk of stroke during revascularization, especially during CABG. Chronic kidney disease (CKD) also is associated with a higher risk for adverse CVD events in patients with coronary atherosclerosis, regardless of the type of therapy.⁹⁰

Medical therapy versus revascularization

Medical therapy and revascularization improve symptoms and increase survival. Aggressive medical management in most patients with stable coronary atherosclerosis may be

non-inferior to revascularization. A stress test may be necessary to document myocardial ischemia while the patient is on optimal medical therapy (OMT). Patients with a large area of myocardial ischemia (>10%) as defined by stress imaging techniques may benefit from revascularization. Stress tests can be used to follow the effect of therapy and fractional flow reserve is a complimentary tool that helps to define the pathophysiologic significance of a stenosis. In certain cases, intravascular ultrasound or optical coherence tomography may be necessary to better define the atherosclerotic plaque and quantitate the degree of stenosis.^{64,91,92}

Medical therapy

As medical therapy is getting better, revascularization therapies look better as well (are getting a “free ride”) since all patients with coronary atherosclerosis regardless of revascularization receive OMT. Many studies suggest that OMT for most patients with coronary atherosclerosis should be the initial approach. Revascularization should be reserved for patients with persistent symptoms despite OMT or those with a large area of myocardium at risk (i.e., large area of myocardial ischemia seen on stress testing). The greater the severity of ischemia, extent of disease and LV systolic dysfunction, the greater the survival benefit from revascularization compared to OMT. PCI in stable patients with a total occluded infarct-related artery and without severe inducible ischemia in the sub-acute phase after MI did not reduce the incidence of CVD events.^{93–95} Silent ischemia that can be detected by 24 h ambulatory monitoring or by a stress test occurs often in patients with coronary

atherosclerosis. Presence of significant silent ischemia in patients on OMT, especially in those with DM, might identify a subgroup with increased risk of CVD events. Repeat revascularization, however, in patients with silent ischemia who had revascularization previously, was not associated with better outcomes. It should be noted, however, that patients with silent ischemia often have ischemic episodes that are associated with chest pain. Thus, episodes with only silent ischemia are extremely rare. Silent myocardial ischemia is common in patients who had cardiac transplantation and denervated hearts when vasculopathy and/or atherosclerosis are present.^{96–98}

Differences between CABG and PCI

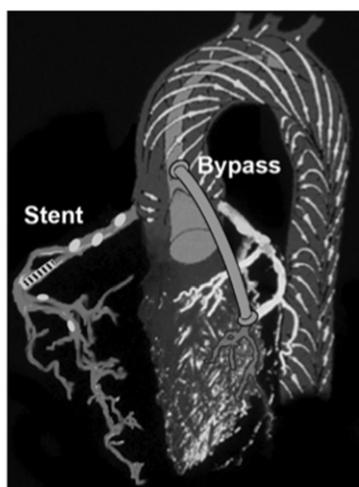
CABG and PCI are complimentary. Each approach has advantages and limitations. PCI may be associated with a lower procedural morbidity and mortality compared to CABG. Long-term antiplatelet therapy (twelve months or longer) after placement of a drug eluting stent in order to decrease the risk of stent thrombosis, however, may constitute a problem in certain patients. With the development of newer generation stents with biocompatible polymers and faster drug eluting characteristics, it may be discovered that shorter duration of DAPT will be needed.

PCI does not protect from lesions that may develop in the future proximal to stent placement (Fig 8). In contrast, CABG may protect against future CVD events if a lesion proximal to a bypass graft anastomosis develops or ruptures. PCI has been shown to be inferior to CABG in patients with DM and CKD.

Coronary Atherosclerosis: Differences Between PCI and CABG

PCI

- Minimal invasive with lower procedural morbidity/mortality as compared to CABG
- Does not protect from lesions that may develop proximal to the site of the stent
- Distal embolization
- Restenosis
- Need for long term dual antiplatelet therapy
- Suboptimal results in diabetes, chronic kidney disease, vein grafts



CABG

- Protects from future cardiovascular events if lesions proximal to anastomosis develop or rupture
- More complete revascularization compared to PCI
- LIMA or bilateral IMA excellent long term results
- Surgical mortality
- Problems related to vein grafts
- Stroke/brain damage

Fig 8 – Differences between percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG). Abbreviations: LIMA = left internal mammary (thoracic) artery, IMA = internal mammary artery.

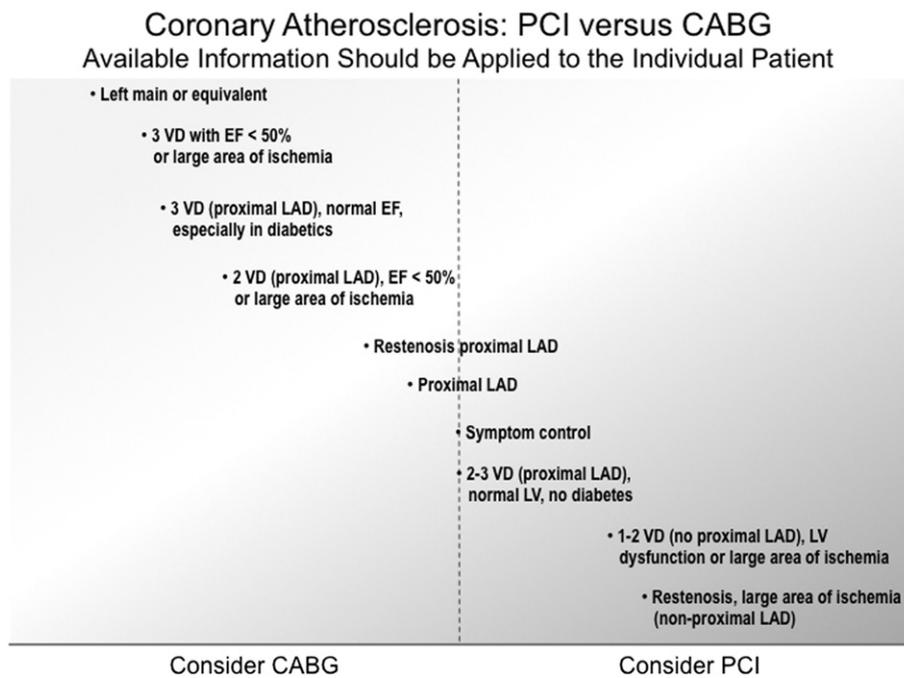


Fig 9 – Revascularization therapy in coronary atherosclerosis. Patients with characteristics shown on the left of the perpendicular line may benefit more from coronary artery bypass graft surgery (CABG), while patients with characteristics shown on the right may benefit more from percutaneous coronary intervention (PCI). Abbreviations: EF = ejection fraction, LAD = left anterior descending coronary artery, LV = left ventricle, VD = vessel disease.

CABG provides a more complete revascularization associated with survival benefit compared to PCI especially in high SYNTAX score patients. It should be emphasized that the use of the left internal mammary (thoracic) artery anastomosis to the left anterior descending coronary artery provides excellent long term results; this may be the single most important factor in the superior survival seen with CABG compared to PCI, since the long-term patency of saphenous vein graphs is suboptimal. In certain patients, a hybrid approach (i.e., left internal mammary artery to the left anterior descending coronary artery and PCI to the remaining vessels) may be used; CABG can be performed prior to, at the same time using a hybrid operating room, or after PCI. Left internal mammary artery to left anterior descending coronary artery can be performed off pump; this may be associated with a decrease in the incidence of stroke, especially in the elderly. Elderly patients (80 years old or older) have shown a significant improvement in symptoms following CABG allowing them to have a quality of life comparable to age-matched general population.^{99–106}

The SYNTAX score can be used to define artery lesions and stratify patients into various angiographic risk groups to determine the optimal revascularization strategy whether PCI or CABG; the outcome of a patient, however is not only related to angiographic coronary disease, but also to other factors such as status of LV function and associated co-morbidities (e.g., DM, CKD, chronic obstructive pulmonary disease, other). Although most recently some clinical information has been incorporated into the SYNTAX score, it does not take into consideration the full clinical picture of the patient, which obviously is a significant limitation.

Patients most likely to benefit from PCI or CABG are shown in Fig 9. As a general rule, patients with LV systolic dysfunction and extensive coronary artery disease that includes the proximal left anterior descending artery benefit more from CABG compared to PCI. Newer generation stents do show promising results as compared to CABG; PCI, however, is associated with higher incidence of repeat revascularization mostly in patients with incomplete revascularization. When PCI is performed, drug eluting stents should be used rather than bare metal stents due to better clinical outcomes.

In patients with left main coronary artery stenosis, PCI can be performed. The short and mid-term results are comparable to CABG; however, there is a lack of long-term follow-up data. Further, many patients with left main coronary artery disease often have other diseased vessels; these patients will benefit more from a complete revascularization that can be better achieved with CABG. Finally, very long-term DAPT (potentially lifelong) may be required, until more data becomes available.^{107–115}

Coronary atherosclerosis associated with valvular heart disease

As the population ages, many patients with significant coronary atherosclerosis requiring revascularization also have aortic stenosis (common etiology with atherosclerosis) or functional mitral regurgitation due to ischemic cardiomyopathy. Simultaneous CABG plus valve surgery may increase the surgical risk. In this case, a hybrid approach may be used (i.e., staged valve surgery plus PCI). In the very elderly and high-risk patients, transcatheter aortic valve replacement or transcatheter mitral valve repair using the MitraClip may be used.^{116–118}

Coronary Atherosclerosis: Available information should be applied to the individual patient



Fig 10 – Coronary atherosclerosis: evolution of atherosclerotic plaque is shown on the top of the figure while therapeutic approaches are shown schematically in the middle. The challenge of the physician is to apply the multiple diagnostic and therapeutic modalities to the individual patient (modified from reference 119).

Individual patient analysis

“It is more important to know what sort of a person has a disease than to know what sort of disease a person has”
[-Hippocratis]

This manuscript is not intended to be a comprehensive review related to coronary atherosclerosis. It addresses, however, several issues that should be taken into consideration for the diagnosis and management of patients with coronary atherosclerosis and to help the physician apply the knowledge to the individual patient. Coronary atherosclerosis is a dynamic disease process and our understanding of atherosclerosis is evolving continuously. Diagnostic and therapeutic modalities related to coronary atherosclerosis are changing constantly. Data from epidemiologic and randomized clinical trials should be applied to the individual patient (Fig 10).¹¹⁹ Patient’s characteristics and preferences, physician’s experience for each procedure, and importantly outcomes for each procedure in each particular hospital should be taken into consideration. The physician who is taking care of patients with coronary atherosclerosis, in addition to knowledge, should have clinical wisdom and clinical experience in order to apply the fast accumulating knowledge to the individual patient. Clinical wisdom and clinical experience are acquired only by following patients over a long period of time on a daily basis. Montaigne

once wrote that, “we can be knowledgeable with other men’s knowledge, but we can’t be wise with other men’s wisdom”. The greatest challenge for the clinician in the twenty-first century is not in absorbing the fast accumulating new knowledge, but rather in applying this knowledge to the individual patient.

Halfway Technology and Cost of Medicine

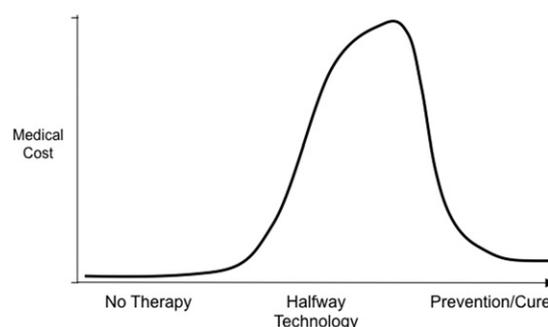


Fig 11 – In most chronic diseases, three phases of medical cost can typically be defined. In the first phase, when there is no therapy available the medical cost of the disease is relatively low. In the second phase, when “halfway technology” (i.e., technology that does not provide curative therapy) is present and there is no cure, the medical cost increases substantially. In the third phase, when prevention and/or cure is available, the cost declines significantly.

Future considerations: Cure of atherosclerosis

“Time present and time past. Are both perhaps present in time future, And time future contained in time past”

[–T.S Eliot]

The mortality rate of coronary atherosclerosis has declined over the last several decades. Data suggest that long-term mortality after PCI is mostly due to non-cardiac causes and a significant decline of CVD mortality from 1991 to 2008 in such patients was observed.¹²⁰ Despite that, however, coronary atherosclerosis cannot be cured today. Several years ago, Lewis Thomas proposed a concept that he called “halfway technology” (i.e., technology that does not provide curative therapy). Diseases cannot be cured with today’s mostly “halfway technology”. In addition, halfway technology substantially increases medical cost (Fig 11). This technology, however, may provide new insight into basic pathophysiology, provide a better understanding of basic mechanisms of diseases, and eventually result in the prevention and cure of the diseases of time present, as was the case with diseases of time past. For example, rheumatic fever, rheumatic valve disease, syphilis with all of its cardiovascular involvements, poliomyelitis and peptic ulcer disease are rarely seen today in developed countries. This is the ultimate goal of medicine.¹²¹

Atherosclerosis in general, particularly coronary atherosclerosis, is considered a chronic inflammatory process. Several anti-inflammatory agents are being studied to determine their

effects on coronary atherosclerosis. Large phase III trials are now underway with agents that decrease interleukin, like canakinumab, in order to determine the effect of anti-inflammatory therapy on the “natural” history of the disease. Canakinumab is a monoclonal antibody that particularly targets interleukin 1 and 6, which have been linked to atherosclerosis. Further, methotrexate that has a more broad anti-inflammatory response and typically used to treat rheumatoid arthritis, psoriasis, and in larger doses cancer, is also being investigated. Patients with a previous MI and associated inflammatory process such as high CRP levels, type 2 DM, or other metabolic disorders associated with inflammation will be included in these studies. Other therapeutic modalities may also prove to be effective. In a small number of patients, studies suggest that therapy with colchicine in patients with stable coronary atherosclerosis may provide additional protection to that of standard therapy.^{122–127}

Vaccines that have been used for almost one hundred years have eradicated several infectious diseases. Thus, the idea to develop a vaccine for a very common chronic disease such as atherosclerosis it is not unreasonable. The strong association between LDL-C and atherosclerosis makes LDL-C and apoB-100 logical targets for this purpose. Preclinical studies using LDL-C or apoB-100 peptides as candidate antigens in a vaccine formulation support this hypothesis. Obviously, the ultimate goal would be prevention.^{128–130}

Studies in experimental animal models and in humans suggest that atherosclerosis regression and normalization of arterial function may occur when LDL-C levels decrease significantly early in the course of the disease. Newer monoclonal antibodies affecting the function of PCSK9 enzyme, which have resulted in a dramatic decrease of LDL-C, and improvements in imaging technology including

Coronary Atherosclerosis: Early Treatment May Prevent the Clinical Manifestations of the Disease

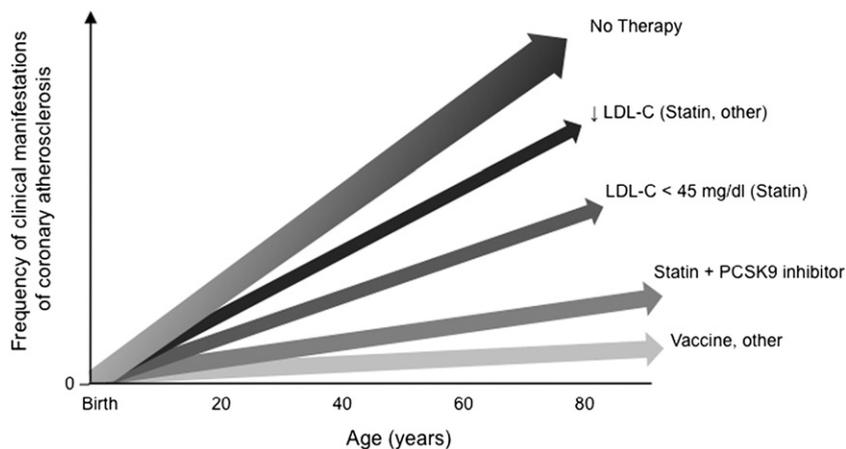


Fig 12 – Reduction of low density lipoprotein cholesterol (LDL-C) with statin therapy and treatment with β -blockers, angiotensin converting enzyme inhibitors and other therapeutic interventions has resulted in a substantial decrease in the clinical manifestations of coronary atherosclerosis; the lower the LDL-C (<45), the lower the incidence of cardiovascular events. The introduction in clinical practice of PCSK9 inhibitors is expected to further decrease the clinical manifestations of coronary atherosclerosis. In addition, a vaccine for atherosclerosis along with novel therapies that will be used in the near future will result in prevention and/or cure of coronary atherosclerosis.

molecular imaging will contribute significantly in this exiting area in the near future.¹³¹ Further, development of new drugs that mimic the natural success of the human genome along with medications like PCSK9 inhibitors and the development of a vaccine for atherosclerosis in the near future may result in the elimination of coronary atherosclerosis^{129,132} (Fig 12).

Conclusion

Coronary atherosclerosis is a complex, long lasting and continuously evolving inflammatory disease characterized by remodeling of the coronary arteries, which supply blood to the myocardium. Development and progression of coronary atherosclerosis is related to genetic and environmental factors that modulate disease risk individually and through multiple interactions. Coronary atherosclerosis has various clinical manifestations ranging from asymptomatic to stable angina, ACS, HF and SCD. The overall prognosis of the disease is related to the total atherosclerotic burden and status of LV function and not just to one atherosclerotic lesion and/or to a symptom. Management of coronary atherosclerosis should include therapy for the atherosclerotic plaque to prevent progression or rupture and to facilitate regression, preserve and/or improve LV function, prevent ischemia, alleviate angina pectoris, and prevent SCD.

The mortality rate from coronary atherosclerosis has declined significantly over the last several decades. Coronary atherosclerosis cannot be cured with the “halfway technology” of today. This technology, however, does provide new insights into the pathophysiology of disease and gives a better understanding of the basic mechanisms of disease; eventually this will result in the prevention and cure of atherosclerosis, as it was the case with diseases of the past (e.g., rheumatic fever). In the near future, development of new drugs that mimic the natural success of the human genome along with medications like PCSK9 inhibitors and the development of a vaccine for atherosclerosis will result in the elimination of the disease.

Our understanding of coronary atherosclerosis, until prevention or cure is achieved, will evolve continuously with diagnostic and therapeutic modalities changing constantly. Data from epidemiologic and randomized clinical trials should be applied to the individual patient. The greater challenge for the physician in the twenty-first century is not in absorbing the fast accumulating new knowledge, but rather in applying this knowledge to the individual patient.

Disclosures and conflict of interest

None of the authors have any conflicts of interests with regard to this publication.

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