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# Rapid Review in Cardiology

*(For DM/DNB Cardiology, FNB Interventional Cardiology, Pediatric Cardiology, and MD/DNB Medicine Students)*



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SECTION 3

# Atherosclerosis

## 3.1 COMPLICATION OF ATHEROSCLEROSIS

### ARTERIAL STENOSIS AND CLINICAL IMPLICATION

After the plaque burden exceeds the capacity of artery to remodel outward
↓
Encroachment on arterial lumen begins
↓
Eventually it impedes blood flow
↓
Lesion of >60% stenosis causes limitation of flow under increased demand
↓
Produce chronic stable angina pectoris or intermittent claudication
↓
Can progress to critical stenosis
↓
Myocardial infarction

- Even small atheromatous lesion can lead to MI when they rupture – form thrombus and occludes artery

### THROMBOSIS AND COMPLICATIONS

Modes of plaque disruption

(2/3rd) (1) Fracture of plaque's fibrous cap (Plaque rupture)

(1/3rd) (2) Superficial erosion
More common in females

#### Plaque Rupture

Due to imbalance between

- Forces that impinge on plaque's cap
- Mechanical strength of CAP

*Factors Responsible*

- Factors that decrease collagen synthesis
  T-cell derived cytokine INFY
  ↓
  Decreased collagen content of plaque cap
  ↓
  Prone to rupture
- Increased catabolism of ESM macromolecules that forms the fibrous cap of plaque
  - MMP enzymes
  - Elastolytic cathepsin
    ↓
    Breakdown collagen and elastin
    ↓
    Thinning of fibrous cap
    ↓
    Prone to rupture
- *Relative lack of SMC*
  Inflammatory mediators ↓ T-cell ↓
  Induce programmed cell death of SMC
  ↓
  Weakening of plaque cap
  ↓
  Prone to rupture
- Prominent accumulation of macrophage with large lipid pool

| | |
|---|---|
| Large lipid pool | Activated macrophage |
| ↓ | ↓ |
| Increased biomechanical force | Cytokines and matrix degrading enzymes |
| ↓ | ↓ |
| On shoulder region of plaque | Degradation of collagen and SMC |
| ↓ | ↓ |
| Fracture of plaque | Plaque prone for rupture |

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### Superficial Erosion

More likely to cause MI in women and in patients with hypertriglyceridemia and DM

- Underlying molecular mechanism is obscure

*Possible mechanisms:*

- Apoptosis of EGs → desquamation of EGs in areas of superficial erosion
- MMPs (such as certain gelatinases) degrade nonfibrillar collagen (Type-4) in BM
  - Tethering of EG to subjacent basal lamina → promote their desquamation

↓

Mural platelet thrombi can complicate plaque erosion without causing arterial occlusion → Most plaque erosion do not give rise to clinically evident coronary events

↓

Repetitive cycles of plaque disruption, mural thrombosis in sites and healing contributes to lesion evolution and plaque growth

↓

This nonocclusive thrombi precedes the fatal event more frequently

*Healing*

- By PDGF and TGF-B released from platelet granules at the site of thrombosis

↓

Stimulate migration of SMC and increase collagen synthesis

(and)

- Thrombin generated at site of mural thrombi

↓

Stimulate SMC proliferation

This burnt-out fibrous and calcific atheroma represents late stage of plaque that previously uses lipid rich with characteristic association with plaque rupture but has become fibrous and hypocellular because of wound healing response.

## PLAQUE SUSCEPTIBILITY TO RUPTURE AND INFLAMMATION IN ATHEROGENESIS

"Vulnerable Plaque"

CAG, OCT, IVUS, MRI, and CT all have shed light on morphology of plaques that causes Acs

Inflammatory markers (e.g., CRP) also increased in patients with MI)

Imaging + Inflammatory markers suggest widespread, diffuse and systemic nature of instability of atheromas in individual with or at risk of ACS.

## THROMBOSIS DEPENDS ON

- *Solid state of plaque:* That may rupture or erode to trigger, thrombosis
- *Fluid state of blood:* That determine consequences of a given plaque disruption
  - i. Amt of tissue factor in lipid core of a plaque
    - Control degree of clot formation
  - ii. Level of fibrinogen in fluid determine whether plaque rupture leads to occlusive thrombus or mural thrombi
  - iii. Elevated level of inhibitor of fibrinolysis (e.g., PAI)
    - Impede the ability of endogenous thrombolytic enzyme to limit thrombus growth

- Inflammation limits both thrombotic vs fibrinolytic
- Balance in both solid state and fluid state
- PAI-1 and fibrinogen both are acute phase reactants
- As well as inflammation mediator CD40 ligand induces tissue factor expression

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## 3.2 SPECIAL CASES OF ATHEROSCLEROSIS

### RESTENOSIS AFTER PCI

#### After Balloon Angioplasty

- SML prolification in intimal thickening (relatively less important)
- *Negative remodeling:* Due to advential inflammation caused by balloon-scar formation-wound contraction by healing process – arterial constriction-narrowing of lumen.

#### After Stent

Depends on intimal thickening rather than negativity remodeling stents prevent constriction from adventitia.

### ACCELERATED ATHEROSCLEROSIS AFTER TRANSPLANT

- Limitation to long term survival
- Difficult to diagnose
  - No angina (denervated heart)
  - Diffuse and concentric disease/difficult to diagnose by CAG
- Selective environment of AN-grafted vessel with sparing of host's native arteries suggest-accelerated arteriopathy does not necessarily resulted from immunosuppressive therapy or other systemic factors in transplantation recipient
- Immunologic difference between host and recipient vessel might contribute to pathogenesis of disease
- Homozygous familial hypercholesterolemia—can detect fatal ath in 1st decade of life due to elevation in LDL
- EC in engrafted coronaries express MHC antigen-activate T cell-secrete INF—increasing adhesion molecule-increases leukocyte accumulate-enhance plaque formation (diffuse)

  ↓

  So graft arteriosclerosis represents extreme case of immunologically derived arterial hyperplasia

### ANEURYSMAL DISEASE

- Dorsal surface of infrarenal aorta is prone to develop fatty streaks
- Because of absence of vasa vasorum the relative lack of blood supply to tunica media in this portion of abdominal aorta can explain susceptibility of these portions to develop aneurysm
- Additionally lumbar lordosis may alter the hemodynamics of blood flow-flow disturbance may promote lesion formation

| ***Atherosclerosis*** | ***Aneurysm*** |
|---|---|
| ▪ Expansion of intimal lesion produces stenotic lesion<br>▪ Tunica media underlying the lesion is thinned but with well preserved structure | ▪ Transmural destruction of arterial structure |

### INFECTION AND ATHEROSCLEROSIS

- Infection may cause atherosclerosis
- Certain bacteria (e.g., *Chlamydia pneumonia*) and certain virus (e.g., *Cytomegalovirus*) has been shown to be responsible in seroepidemiological studies
- Multiple clinical trials have not shown benefit of antibiotic therapy in 2° prevention of atherosclerosis events

#### Confounding Factors

*C. Pneumoniae:* High incidence of bronchitis in smoker occurs due to *C pneumonia*

This *C pneumonia* infection is merely a marker for tobacco use, which is in turn a risk factor for ath events

*Theories*: Infection may potentiate the action of conventional risk factor, e.g., hypercholesterolemia

1. Cells within the plaque itself may harbor the infection (macrophage in plaque harboring infection with a pneumoniae)
   This can activate and accelerate inflammatory pathway
2. Specific microbial product (e.g., lipopolysaccharide or HSP) may act locally at level of arterial wall to potentiate atherosclerosis)
3. Minor breach in intestinal epithelium—breach by endotoxin—vascular reactivity and inflammation in adipose tissue – Insulin resistance and other factors of metabolic syndrome – CV death
4. Extravascular lesion also potentiate ath lesions, e.g., circulating endotoxin or cytokines produced in response to remote infection can act locally at level of artery wall to promote activation of vascular cells and lenocytes in preexisting lesion
5. Acute phase reactants also affect vascular inflammation and leucocyte activation
6. Acute infection can produce H.D alteration that can provoke coronary events (e.g., Tachycardia and hypotension)

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## 3.3 NOVEL RISK MARKERS

### INTRODUCTION

Basic requirement for risk marker

- There should be standardized and reproductive assay method
- Series of prospective study should have demonstrated predictive risk status of positive marker
- There should be evidence that novel marker adds to risk stratification by lipids
- It should add to global risk prediction score
- It should have proven intervention to reduce risk

### hs-CRP

- Inflammation characterize all phases of atherosclerosis (including plaque formation, rupture and thrombus formation, occlusion, infarction)
- Various inflammatory markers associated

  ↓

  Most studied and most easily applied is acute phase reactant-CRP

#### CRP

- 5(23 k-Da) subunits
- Circulating member of penetration family
- Function in human innate immune response
- Primary derived from lives
- Cells in coro circulation can also elaborate CRP
- Whether CRP simply marks the risk or has direct role in atherothrombotic risk is controversial
- CRP measured with high sensitive (hs-CRP) independently predict risk of MI, stroke, PAD, SCD, among apparent healthy person (even when LDL cholesterol level are low)

  Patients with high hs-CRP but low LDL → higher risk
  Patients with low hs-CRP but high LDL → lower than above subgroup
  ] Absolute risk

#### AHA Guidelines Cut-off

- Low risk ≤1 mg/L
  Intermediate = 1–3 mg/L
  High risk ≥3 mg/L
- Screening of hs-CRP should be done as a part of global risk and not as a replacement for LDL and HDL cholesterol
  - Greatest used in patients with intermediate risk (anticipated risk between 5 to 20%)
- hs-CRP evaluation recommended by CSS 2009 guidelines and 2011 guidelines from National Leopard Association USA
- hs-CRP >8 mg/dL ≥ represents acute phase response caused by underlying inflammatory disease are intercurrent infection

  ↓

  Repeat testing in 2 to 3 weeks
- hs-CRP: Minimal circadian Variation
  Do not depend on prandial state
- hs-CRP Incorporated into Reynolds risk score
- hs-CRP >3 → Predict recurrent coronary events
  Thrombotic complications after angioplasty
  Poor outcome in sitting of UF
  Vascular complication after CABG

#### AMT-additionally High hs-CRP Acute MI Suggest Enhanced

Inflammatory response at the time of hospital admission (even without troponin elevation) can determine subsequent M. rupture

↓

Patient with high hs-CRP likely to be benefited more with aggressive (early) intervention

#### Synd X

hs-CRP level also increased in syndrome X suggesting role of inflammation in coronary micro vascular function

#### AMI

hs-CRP elevation are more common in patients with frankly ruptured plate than those with plaque erosion

#### Prognosis

In patient with CRF and dialysis allograft vasculopathy ] High CRP suggest pov short term prognosis

*hs-CRP also predict onset of T2 DM
*hs-CRP also adds prognostic info at all level of Met synd

#### Intervention

- Diet
- Exercise
- Smoking cessation

] First line intervention

- *Use of statin therapy:* To reduce vascular risk among patients with elevated hs-CRP (even with low LDL)

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### JUPITER Trial

Healthy male and female with high hs-CRP (>2 mg/L) with low LDL (<130 mg/dL)

↓

Use of rosuvastatin resulted in 44% reduction in 1° endpoint of all vascular event 54% reduction in MI; 4% reduction in stroke; 46% reduction in arterial revasc; 20% reduction in all-cause mortality

↓

All subgroup significantly benefited with statin therapy "Low risk" group (women, nonsmoker, those without ms, those with Framingham score <10%)

- Jupiter trial also demonstrated significant reduction of hs-CRP and LDL level by rosuvastatin

### PROVE IT-TIMI 22

Acs created with statin, achieving hs-CRP <2 mg/L conferred long term event free survival as achieving LDL cholesterol <70 mg/d. Those who net both this goal → greater benefit

#### *Drawbacks*

- With chronic inflammatory disease such as RA, IBD, psoriasis—Have elevated hs-CRP and on average are somewhat at higher vascular risk
- Low grade infection (gingivitis) are those with chronic carriers of *chlamydia pneumoniae*, *H. pylori*, herpes simplex, cytomegalovirus, also may have high CRP level and height and risk of CV disorder due to chronic inflammatory response.

## OTHER BIOMARKERS OF INFLAMMATION

- Cytokines such as IL-1 and IL-6
- Soluble intercellular adhesion molecule (SICAM-1)
- p selectin
- CD 40 ligand
- Marker of leukocyte activation (myeloperoxidase)
- Preg. associated plasma protein A (PLAP-A)
- IL-1 receptor family member (ST-2)

↓

  - Some have analytic limitation
  - Some have too short half life
  - Some have limited ability to predict risk
  - No large scale trials
- Soluble CD40 provide insight into efficacy of specific antithrombotic agents
- Myeloperoxidase provide prognostic information in case of acute ischemia
- ST2 is novel association in HF and ischemia

8. Fibrinogen
   - Positive association with age, obesity, smoking, DM and LDL cholesterol level and negative association with HDL cholesterol level, alcohol use, physical activity, and exercise level
   - Fibrinogen was among the front "novel" risk factor evaluated
   - Linear association was seen between usual fibrinogen level and the risk of CAD and stroke
   - hs-CRP and fibrinogen showed addictive ability to predict risk
   - Fibrinogen has highest predictive usefulness in patients with other concomitant elevation of Lp(a) or homocysteine

### Anti-inflammatory Modulators

- Broad based
  Aspirin, statin, colchicine, methotrexate
- Anti-pro-inflammatory cytokines
  IL-1: canakinumab, anakinra
  IL-6: tocilizumab
  INF: infliximab, etanercept, adalimumab, golimumab, certolizumab
- Delivery of anti-inflammatory cytokines (TGF-β, IL-10, IL-19)
- Treg cell induction
- In vivo transfection
- Lp-PLA2
  - Only other marker available commercially
  - Positive relation between Lp-PLA2 and vascular risk
  - LP-PLA2 bound to apo B100 (So its level closely related to LDL cholesterol)
  - 2 large scale clinical trial
    Lp-PLA2, no longer predicted residual risk after aggressive LDL cholesterol reduction with statin

### Interventions

4 clinical trials → Disappointing result

- Bezafibrate → No reduction in risk
- Hormone replacement therapy → lower fibrinogen but not improve clinical outcome

Therapies under evaluation

- Darapladib (inhibitor of Lp PLA2)
- Canakinumab (monoclonal ab against IL-1β)
- Generic anti-inflammatory agent low dose methotrexate (already in use for methotrexate)

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## LIPOPROTEIN (A)

- Consist of LDL particle with its apo B100 component link bi disulfide bridge to apolipoprotein(a)
- Lp(a) level varies inversely with apo(a) isoform
- >25 forms available
  1. Homology between lp(a) and plasminogen → raised possibility that it Lp may inhibit endogenous fibrinolysis by completing with plasminogen binding site
  2. Lp(a) binds and inactivate tissue factor pathway inhibitor and augment expression of plasminogen activator inhibitor for the linking Lp and thrombosis
  3. Lp(a) also colocalizes with ath lesion and may have local action through oxidized phospholipids pathway

*Lp(a):*

- Prognostic information to overall risk in 1 prevention remains uncertain
- In most studies lp(a) has proven to be e credit to for person already known to have high risk because of elevated LDL levels
- Predicts risk non-linearly
- At present laboratories lp(a) in a manner independent of apo(a) isoform size

*Interventions*

1. High dose niacin
2. LDL chol reduction markedly reduce hazard associated with Lp(a)
3. New agents: PCSK9 inhibitors
   Anacetrapib
   Mipomersen

## HOMOCYSTEINE

In patient with inherited defect of methionine metabolism severe hypercholesterolemia can develop

↓

Elevated risk of premature atherosclerosis as well as venous thromboembolism.

### Mechanism

Endothelial dysfunction, accelerated oxidation of LDL cholesterol, impairment of flow mediated endothelial derived relaxing factor, platelet activation, and oxidative stress.

### Cause

1. Mild-mod elevations (1.5 mmol/L) are more common in gen pop because of insufficient dietary intake of folic acid
2. Patients receiving folate antagonist-methotrexate, carbazine
3. Impaired homocysteine metabolism due to hypothyroidism or renal insufficiency
4. Mutation in MTHFR (methylenetetrahydrofolate reductase)-can elevate homocysteine level

Recent guidelines has not advocated its use

### Intervention

*Trials:* None of trials has shown substance benefit

1. *VISP:* High dose and low dose regimes containing folate and pyridoxine → no diff between 2 regimes
2. *NORVIT:* In patient with acute MI: Harmful effect with combined vit B supplement
3. *HOPE2:* 5 years of therapy with folate, vit B6 and vit B12 resulted in no benefit

Subgroups who can't get benefited with treatment

1. Those taking traditional risk factors
2. With renal failure
3. With markedly premature atherosclerosis or family h/o, MI or stroke at young age

## DIRECT PLAQUE IMAGING

1. Ultrasound measure of carotid—IMT
2. Coronary art calcium scoring (CAC)
   - Recent meta-analysis—IMT is of doubtful prognostic importance
   - MESA-CAC, ADI, hs-CRP and family history (not IMT) can independently predicts vascular event among persons at intermediate risk

*Drawback:*

1. However CAC has high false positive rate
2. Radiation exposure
3. CT detect place with least likely to rupture and does not detect noncalcified thin capped lesion
4. Absence of CAC does not preclude ath risk

New-functional imaging

Potential targets for function imaging

- Measure of glucose uptake, specific adhesion molecule, biomarker of apoptosis and protein degradation (proteinases, MMPs, cathepsins)
- MRI, PET and contrast enhanced ultrasound all are under evaluation
- Function measure of vascular reactivity also decreases evaluation

### Intervention

- No trials showed benefit of treatment based on imaging
- DIAD trial underscores the importance of performing such trials
- EISNAR trial did not show any beneficial effect as estimating CAC

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## GENETIC MARKERS

- 95 genetic loci association with normal lipid variation and extreme lipid phenotypes
- Most loci appears to act on process of atherosclerosis independent of traditional risk factors
- Magnitude of risk associated with any one genetic variant tends to be small
- Individual SNP (single nucleotide polymorphism) or multiple genetic panels to predict CV risk has proved to be disappointing
- Reynolds risk score which included F/H and traditional risk factors highlights the importance of F/H as a variable of shared genetic and environmental factors

### Intervention

[Pharmogenetic study of inherited and acquired genetic variation in drug response that can affect both individual and selected population]

E.g., Statin induced myopathy
Clopidogrel resistance
Warfarin dosing

1. *SEARCH trial:* Common variant in (SLCOIBI) found strong association with increased risk of simvastatin induced myopathy
   Encodes organic anionic transporting protein known to regulate hepatic uptake of statin
2. TIMI group found genetic variation in cytochrome p450 system responsible for clopidogrel resistance

### Newer Biomarkers

1. Plaque instability markers
   - Preg associated plasma protein
   - Myeloperoxidase
   - MMPG, MMP-2, TIMP-1
   - Myeloid related Port 8/14
   - Interleukin 6 and 18
   - Soluble lectin like oxidized LDL
2. Inflammatory markers
   - hs-CRP
   - Homocysteine
   - Pentraxin -3
   - Serum Amyloid-A
   - Fibrinogen
   - Lipoprotein associated phospholipase A2
3. Endothelial markers
   - ET1/CT pro ET1
   - Mid regional pro adrenomedullin
4. Biomarkers of cardiac necrosis
   - Hs Tnl assay
   - Heart FA binding prot
   - Ischemia modified albumin
5. Markers of biomechanical stress
   - BNP
   - Copeptin
   - Mid—regional pro-ANP
   - GDF-15 and ST 2
3. Several genetic polymorphisms has been found to be related with warfarin dosing
   *So to conclude:* Family history can be considered important to know and predict CV disease related risk

## ENVIRONMENTAL FACTORS

- Depression and mental stress
  Depression
  Chronic stress
  Anxiety
  Chronic hostility and anger
  Social isolation
  } Risk of CAD
- Depression doubles the risk of CVD (INTERHEART)
- Effect of depression:
  - Effect on inflammation
  - Endothelial dysfunction
  - Increased platelet activity
  - Increase whole blood serotonin
  - Enhanced activity of HP-A axis
  - Alteration in cardiac autonomic tone
  - Adverse lifestyle factors (poor diet, smoking, lack of exercise, nonadherence to medication)
- Mental stress adrenergic stimulation—Increased myocardial oxygen requirement and aggravate myocardial ischemia; coronary vasc constrictions platelets and endothelial dysfunction; metabolic syndrome and induction of vent arrhythmias

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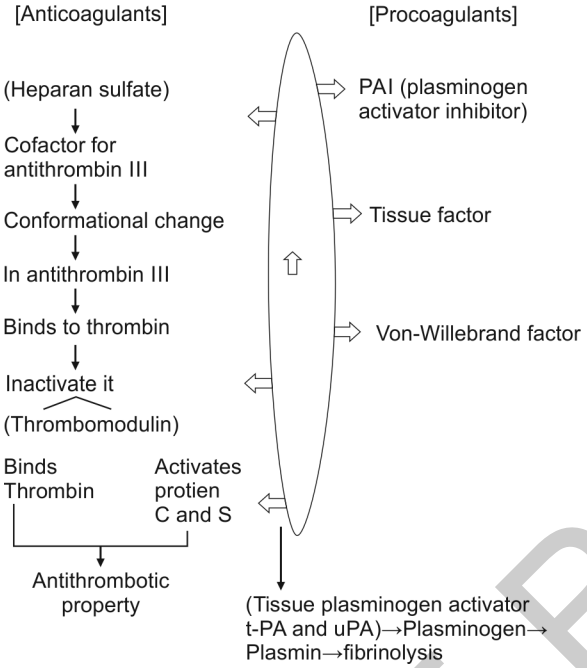
## 3.4 VASCULAR BIOLOGY AND ATHEROSCLEROSIS

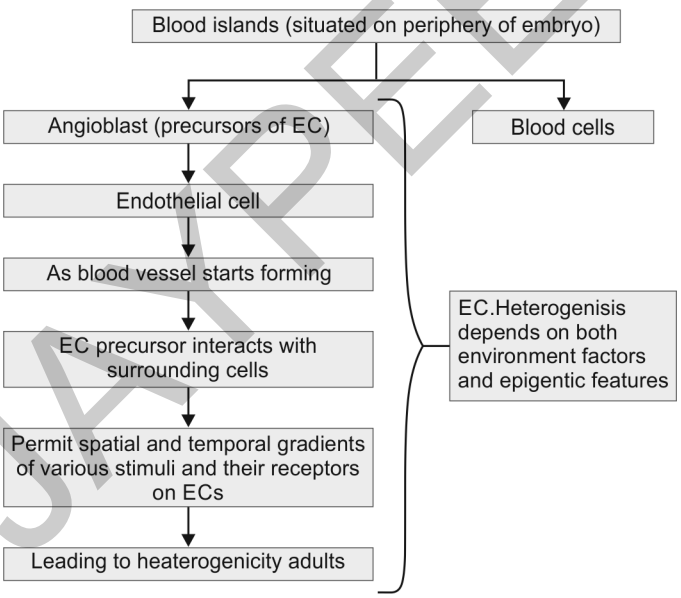
### STRUCTURE OF NORMAL ARTERY

#### Cells of Normal Artery

1. Endothelial cells:
   - Directly in contact with blood
   - Maintain blood in liquid state




*Embryology*




*Postnatal Life*

Cells that make various components of arterial wall originate

From bone marrow
↓
Peripheral blood contains endothelial precursor cells
↓
Helps repair areas of endothelial desquamation

2. *Arterial smooth muscle cells*
   - Second major cell type
   - Function
     1. Contract and relax → control blood flow through various arterial beds (especially muscular arterioles) → abnormal SMC contraction → vasospasm
     2. Synthesize bulk of complex ECM → plays key role in normal vascular homeostasis → formation and complication of atherosclerosis
     3. Migrate and proliferate → formation of intimal hyperplastic lesions (atherosclerosis and restenosis) (e.g., restenosis after PCI and anastomatic hyperplasia complicating vein grafts)
     4. Death of SMC → destabilization of atheromatous plaque ecstatic remodeling and ultimately aneurysm formation

*Embryologically:* Arise from many sources

- Neural crest
- 2nd heart field
- Somites
- Various stem cells
- Mesoangioblasts
- Proepicardium
- Splanchnic mesoderm
- Mesothelium

After ECS form tubes (rudimentary blood vessels)
↓
ES, recruit SMC and pericytes
↓

- Descending aorta and its branches from regional mesoderm
- Distal aorta and its branches from somites
- Arteries and carotids from neuroectoderm
- Asc aorta and carotids from proepicardial mesoderm
- Coronary artery from proepicardial mesoderm

} Various SMC arise from

↓
Heterogenicity of SMC
↓
Decide about capacity of certain arteries or regions to develop atherosclerosis of heightened response to injury or its medial degeneration (e.g., marfan)

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Small population of precursor cells may reside in tunica media of normal arteries → gives rise to SMC that accumulate in injured atherosclerotic arteries

*Layers of normal arteries:*

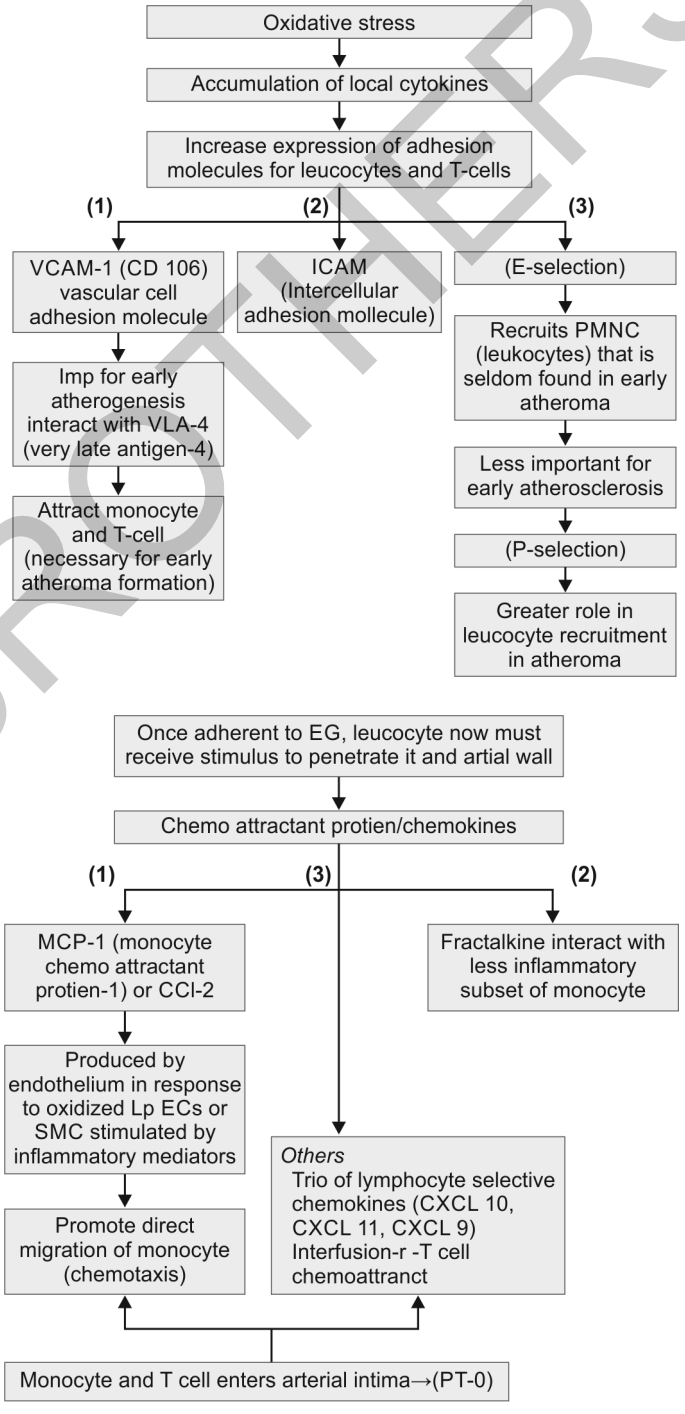
1. *Intima:* Innermost layer
   - Thin at birth (monolayer)
   - Resides on basement membrane containing non fibrillar collagen (such as Type IV)
   - With aging human arteries develop complex intima containing arterial SMC and fibrillan form of collagen type I and III. SMC produce ECM of arterial intima
   - Precursor of complex adult intima is diffuse intimal thickening (characterize most adult human arteries)
   - Some region develop thicker intima even in absence of atherosclerosis (e.g., Prox LAD)
   - Internal elastic memb bound turned intima abluminally and serve as border between intima and media
2. *Media:*
   *Elast Art*—Contains well developed concentric layer of SMCs interlaced with layers of elastin rich ECM.
   *Modular Art.*
   - SMCs embedded in surrounding matrix in more continuous than lamelle array
   - SMCs seldom proliferate
   - SMCs rate of division and cell death is low
     CSM—Neither accumulates nor atrophies matrix synthesis and dissolution balances each other
   - Tunica media bounded by EEL
3. *Adventitia:*
   Contains:
   1. Collagen fibrils (loose than intima)
   2. Vasa vasorum and nerve endings
   3. Fibroblast and mast cells
      (Evidences suggested role of mast cells in atherosclerosis but human importance is still speculative)

## INITIATION OF ATHEROSCLEROSIS

A. *Extracellular*
*Lipid accumulation*

Diet rich in cholesterol and saturated fat
↓
Small lipoprotein particles accumulate in Intima
↓
Lp decorates the proteoglycan in intima and tends to coalesce into aggregate
↓
[Lp + proteoglycan] retained by intima for prolonged time
↓
Increase susceptibility of oxidative or other chemical modification
↓

B. *Leucocyte recruitment and retention*




C. *Focality of lesion formation:*
Why atheroma is focal?

1. *Multicenter origin hypothesis:*
   - Atheroma arise as benign leiomyomas of arterial wall

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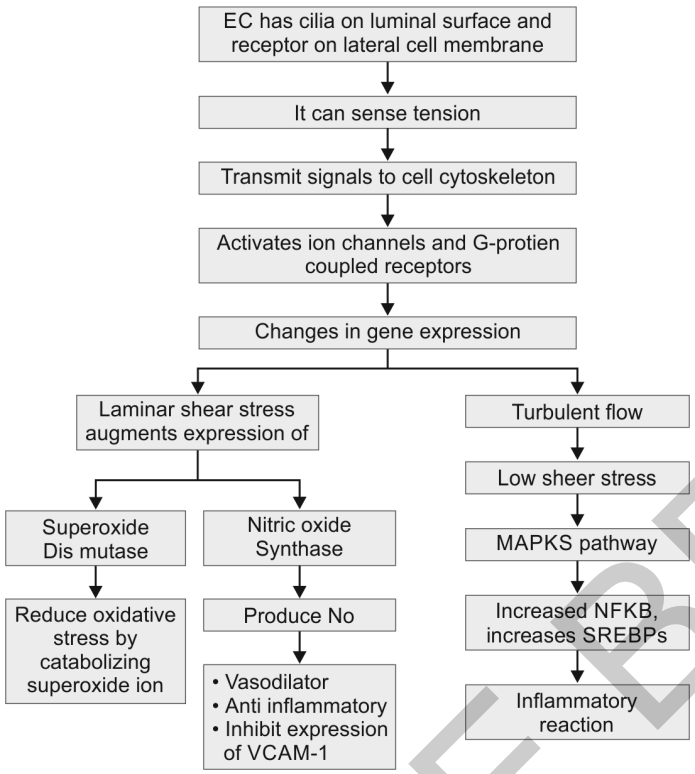
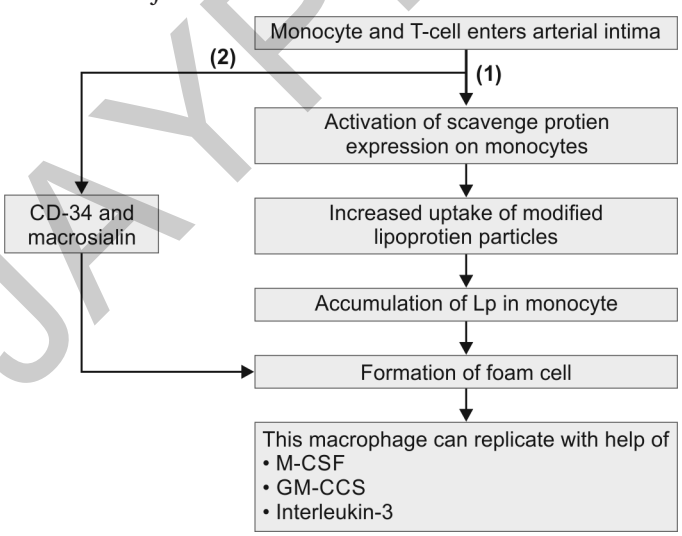
2. *Hydrodynamic basis hypothesis:*
   - Prediction of proximal portion of arteries after branch point or bifurcation at flow dividers
   - Arteries without many branches (e.g., IMA and radial tend not to develop atherosclerosis

- *Laminar flow:* Antiatherogenic
- Decreases sheer stress at branching → atherogenic




[Transcription factor KLF-2 –(Kruppel-like factors 2) Regulate anti-inflammatory activity of EC]
[KLF2 enhance no synthase expression and inhibit NFK-β function]

D. *Foam cell formation*




*Fatty streak:* Lesion consists primarily of lipid engorged macrophages. No thrombosis, No calcification

- Its precursor lesion of atheroma
- Can regress to some extent

E. *Fatty streak to atheroma*

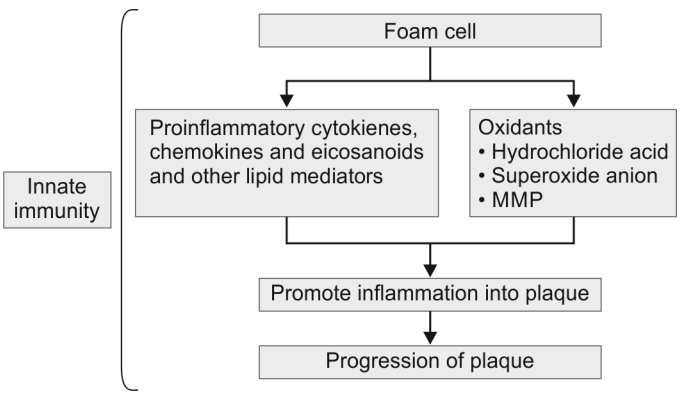
Foam cell
↓
Produce additional cytokines
- Hypochloric acid
- Superoxide anion ($O_2$)
- MMP

↓
Stimulate migration of SMC
↓
From media to intima
↓
SMC can divide and elaborate ECM
↓
ECM accumulate in growing atherosclerotic plaque
↓
Fatty streak evolve into fibrofatty lesion
↓
$Ca^{++}$ accumulation can occur

Sometimes SMC death (apoptosis) leads to relatively acellular
Fibrous capsule surrounding lipid rich core that may also contain
Dying or dead cells and their debris

## EVOLUTION OF ATHEROMA

A. Role of innate and adaptive immunity: Mechanism of inflammation:

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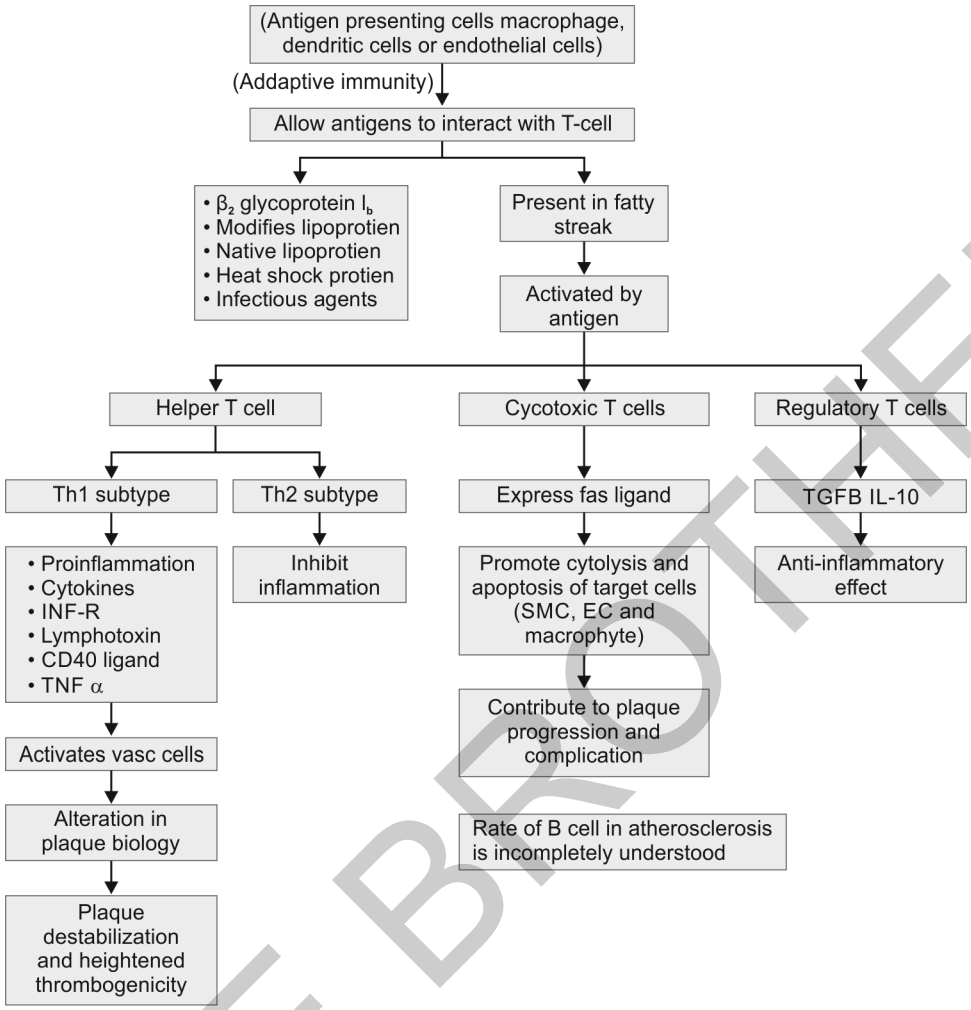



B. SMC migration and proliferation

- SMC in intima is less mature than that in arterial medial layer
- Intimal SMC has higher embryonic isoform of myosin
- So SMC in intima is of embryonic type and it can recapitulate
- It contain more ER and fewer contractile fibers

How intimal SMC differ from medial SMC

Burst of SMC replication may occur during life history of a given atheromatous lesion

*Note:* Accumulation of SMC and growth of intima may not occur in linear pattern

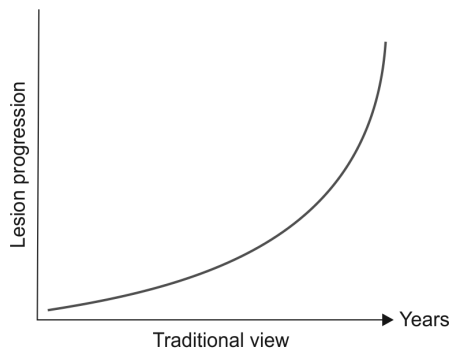
C. *Smooth muscle cell death during atherogenesis*

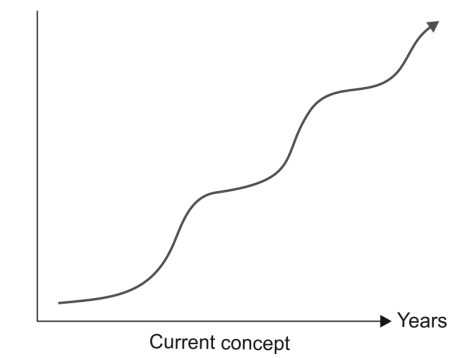
- Apoptosis/programmed cell death
  - Due to inflammatory cytokines or
  - Due to T-cell in atheroma

  (Fas ligand on T cell birds to Fas on SMC → SMC death)

So SMC accumulation in plaque depends on

1. SMC replication
2. SMC death

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*Arterial ECM*:

- ECM makes up much of plaque
- ECM macromolecules that accumulates in atheroma
  1. Collagen (Type I and III)
  2. Proteoglycans (versican, biglycan, aggrecan, decorin)
  3. Elastin fibers
     - Stimuli for excessive ECM production by SMC: PDGF and TGF-β
     - MMP dissolution of ECM by MMP contributes to migration of SMC from media to intima

↓

Leads to arterial remodeling

↓

Initial plaque growth occur outwards in an abluminal fashion (increasing the caliber of entire artery) (positive remodeling)

↓

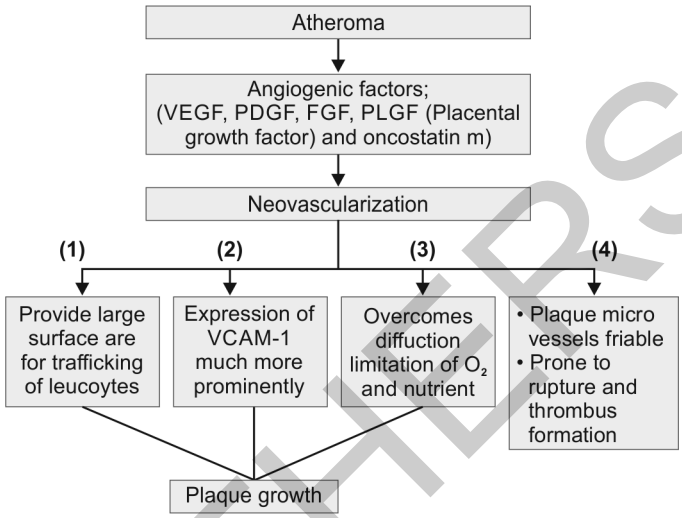
Must involve tumor of ECM to accommodate circumferential growth of artery

↓

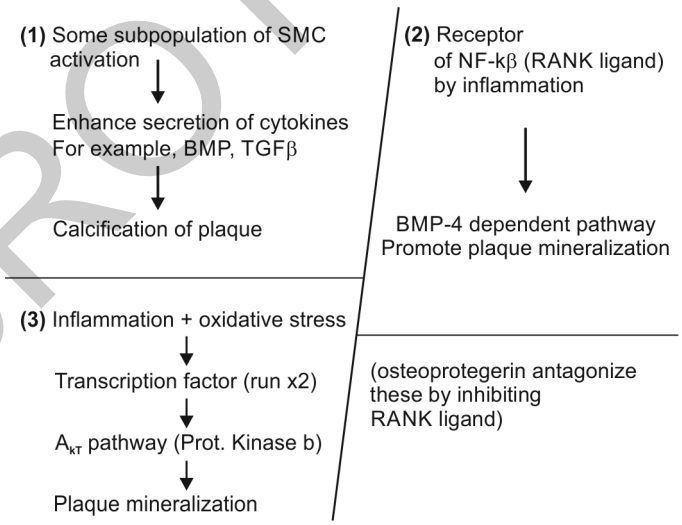
Luminal stenosis tends to occur only after the plaque burden exceeds approx 40% of cross sectional area of artery

D. *Angiogenesis in plaque:*

Ath. Pl. develop their own microcirculation as they grow because of endothelial migration and replication




E. *Plaque mineralization:*




*Micro particles elaborated by macrophage provides nidus for plaque calcification (link between inflammatory cell and CV disease)

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# 3.5 RISK MARKERS AND PRIMARY PREVENTION OF CARDIOVASCULAR DISEASES

## INTRODUCTION

*Core approach to 1° prevention (historically)*
Global risk estimating algorithm
1. Framingham risk score
2. Reynolds risk score
3. European risk evaluation (SCORE)

*Stratified patients into B group*
- Low risk
- Intermediate risk
- High risk
- Lifestyle intervention for low and intermediate risk
- Pharmacological intervention for higher risk

*Current concept*
- 1° prevention strategy should be based on RCT and not on epidemiological data
- This scoring system themselves are not tested in a random manner.

## CONTROVERSY WITH STATIN

Multiple RCTs do not support statin therapy
1. CORONA (Controlled rosuvastatin multinational trial in HF)
2. AURORA (A study to evaluate use of rosuvastatin in subjects on regular hemodialysis)
3. 4D (Gorman analysis and diabetes study)
4. GISSI-HF

↓

All enrolled high absolute risk patients who achieved large LD4 chol reduction with statin but none showed significant clinical benefit
5. JUPITER (Justification for use of statin in prevention: and international trial evaluating rosuvastatin)
6. AFCAPS/Tex CAPS (Air force/texas coro ath. prev prog)
7. MEGA (Management of elevated cholesterol in adult Japanese)

↓

32621 1° prevention patients

↓

Enrolled low risk patients (most of whom will not qualify for statin treatment due to current guidelines)

↓

- All 3 showed marked benefit with statin therapy
- Greatest relative risk reduction ever achieved with statin therapy

↓

Interference from above 7 trials

1. Not used statin in patients with
   - Heart failure (CORONA, GISSI-HF)
   - Renal failure (AURORA, 4G)
2. Used statin aggressively as 1 prevention in
   - In elevated LD2 cholesterol (MEGA)
   - Low HDL cholesterol (AFCAPS/Tex CAPS)
   - Elevated CRP (JUPITER)

↓

Cardiologist in US or Canada and Europe has suggested following five recommendations
1. Adjunct to diet, exercise and smoking cessation for 2° prevention in patients with prev. HIO MI, smoker clinically apparent ath.
   (Trials: 4S, HPS, CARPs, LIPID)
2. Can be considered as adjunct to diet exercise and smoking cessation in setting of 1° prevention for those age >50 years and with either diabetes (CAEDS)
   - Elevated LDL chol. (WOSCOPS) (MEGA)
   - Low HDL (AFCAPS)
   - High hs-CRP (JUPITER)

   Physician may limit statin prescription to above group who also has at least one additional risk factor (HTN/smoking)
3. Physician should maximize intensity of treatment and then focus on compliance and long-term adherence
   (Trials: PROVEIT, TNT)
   Dose should not be selected close to or at higher level the individual patient can tolerate without S/E
4. Non-statin lipid lowering agent for monotherapy or combination with statin should be limited during the wait for evidence that such an approach further reduces CV event rates in specific patient group.
   (Trial: AIM-HIGH, HPS2 THRIVE, ACCORD, FIELD)
5. Guidelines based on trial (what works) and trial entry criteria (in whom) is simply practical and consistent with evidence based principles.

## CONVENTIONAL RISK FACTORS

### Smoking

- Important risk factor
- Second hand smoke exposure too
- Smokes lose 1 decade of life expectancy compared to nonsmoker
- Increased risks are now equal for male and female
- Increased risk of CAD and stroke both
- Smoking → vasoconstriction → greater risk of developing PVD and Abd Ao. Aneurysm

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- CTO Interventions
- Peripheral Interventions
- Coronary Angiograms, Peripheral Angiograms and Cardiac Catheterization
- Angioplasties (including single, double, triple vessels)
- Pacemakers, AICD, CRT, Pulse Generator Replacement
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