

Constitutional Risk Factors

Atherosclerosis: inherited predisposition, aging and biological sex

Pathology • mechanisms and clinicopathologic interpretation

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What this lecture should establish

- Distinguish constitutional susceptibility from potentially modifiable vascular risk.
- Explain monogenic and polygenic genetic contributions to atherosclerosis.
- Trace age-associated vascular injury and innate immune changes, including CHIP.
- Interpret sex- and menopause-associated patterns without inferring hormone-therapy benefit.

Three constitutional axes of vascular risk

GENETICS

Inherited liability and family clustering

AGE

Cumulative injury plus immunobiologic change

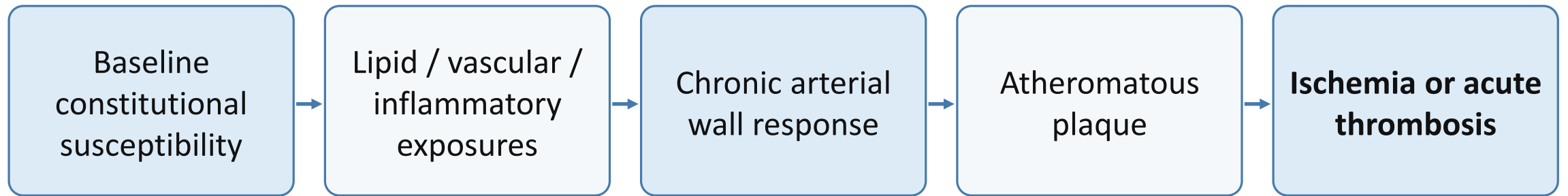
BIOLOGICAL SEX

Different population patterns across life stages

Atherosclerosis is the disease framework

- Atheromas are intimal plaques with lipid-rich cores and fibrous caps.
- Progressive lesions can compromise arterial flow or become thrombogenic after plaque rupture.
- Constitutional determinants modify the probability of developing disease; They are not themselves plaques.

From susceptibility to clinical disease



Schematic sequence: Source-supported causal / pathological relations

Risk factors are not all equally modifiable

Constitutional

- Genetic variation / family history
- Increasing age
- Male sex risk-factor table

Potentially modifiable

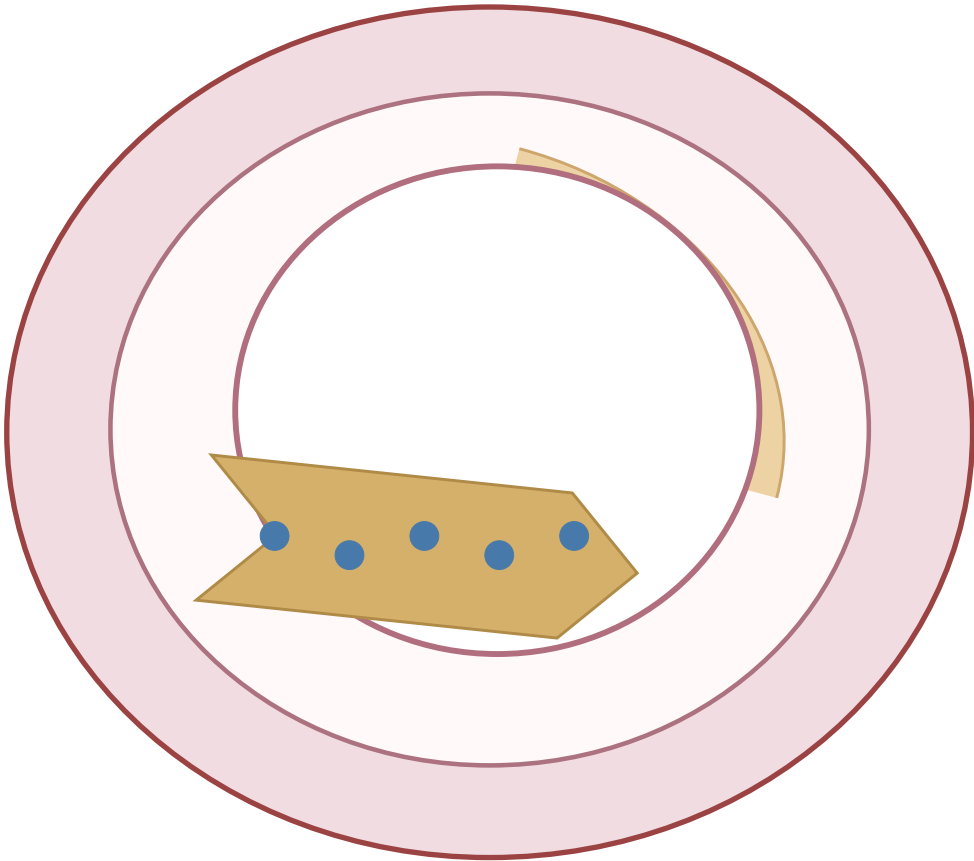
- Hyperlipidemia
- Hypertension and diabetes
- Cigarette smoking / inflammation

A constitutional predisposition does not eliminate the value of modifying acquired risk.

Risk factors act together

- Prospective studies link multiple risk characteristics to atherosclerotic burden and ischemic events.
- Concurrent risk factors can have greater-than-additive effects.
- Reducing acquired risk can mitigate overall risk even when baseline susceptibility remains.

What makes an atheroma clinically important



1. Fibrous cap over lipid-rich core

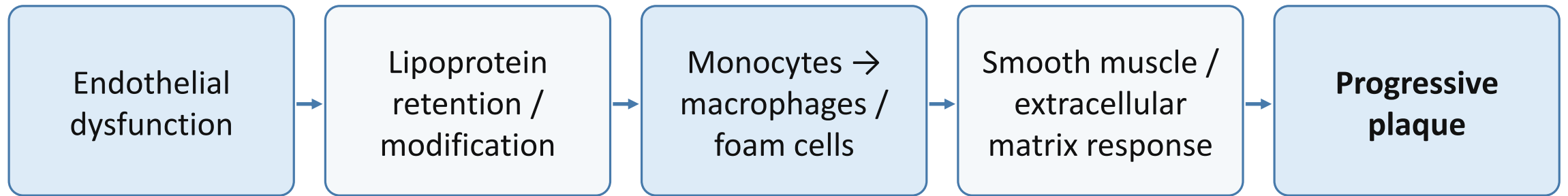
2. Plaque encroaches on arterial lumen

3. Rupture can trigger thrombosis

4. Media weakening contributes to aneurysm risk

Schematic artery cross-section — not a histologic specimen

Atherosclerosis as a response to injury



Schematic sequence: Source-supported causal / pathological relations

Read constitutional factors as susceptibility modifiers

- Genetic background can alter lipid handling and vascular response.
- Age reflects both accumulated lesions and changes in innate immunity.
- Sex-associated population patterns vary with menopausal status and coexist with major acquired risk factors.

Genetics: The family-history signal

Family history

Family history as the most important independent risk factor for atherosclerosis.

Familial clustering does not imply a single disease-causing allele.

Assessment must distinguish rare Mendelian disorders from common polygenic predisposition.

Familial clustering has more than one explanation

Inherited variants

- Rare high-impact disease-causing variants
- Numerous common variants with small effects
- Shared background susceptibility

Shared context

- Dietary and behavioral exposures
- Smoking patterns and activity
- Household/cultural environment

Shared environment is an interpretive consideration, not a substitute for the textbook's genetic emphasis.

Genetic risk has distinct architectures

MONOGENIC

Single pathogenic genetic defect; Often large phenotype

POLYGENIC

Many common inherited alleles with small individual effects

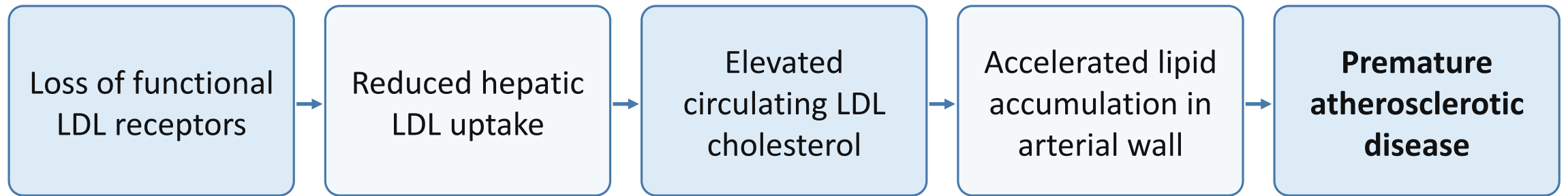
FAMILIAL HISTORY

Clinical indicator encompassing inherited and shared influences

Rare Mendelian disorders are consequential

- Familial hypercholesterolemia is a prominent atherosclerosis-associated Mendelian condition.
- Such disorders may markedly accelerate arterial disease in individual patients.
- They explain only a small proportion of atherosclerosis cases at the population level.

Familial hypercholesterolemia: Causal sequence



Schematic sequence: Source-supported causal / pathological relations

LDL receptor dysfunction changes cholesterol clearance

- The LDL receptor normally permits hepatic uptake and catabolism of circulating LDL.
- Loss-of-function mutations reduce this clearance pathway.
- Sustained elevated LDL exposure promotes initiation and progression of atherosclerotic lesions.

Severe inherited LDL-receptor dysfunction

Early disease

Homozygous familial hypercholesterolemia can cause myocardial infarction before age 20.

This illustrates an extreme monogenic phenotype—not the typical age distribution.

Do not generalize the severity of homozygous disease to all familial risk.

Monogenic disease versus common familial susceptibility

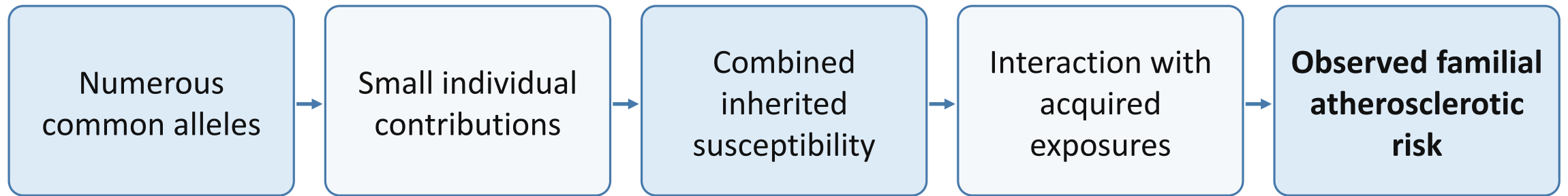
Mendelian

- Single major inherited defect
- Can produce strong clinical phenotype
- Relatively uncommon explanation for all cases

Polygenic

- Many susceptibility alleles
- Small effects accumulate across loci
- Typical basis of familial predisposition

Polygenic susceptibility accumulates small effects



Schematic sequence: Source-supported causal / pathological relations

Why polygenic risk is common

- Relatives share portions of many genetic variants.
- Individual variants often have modest effects but can combine to influence susceptibility.
- A family history is compatible with many alleles rather than one Mendelian mutation.

What family history can and cannot establish

Can indicate

- Clustering of vascular events within relatives
- A reason to consider inherited vulnerability
- A clinical cue to scrutinize acquired risk

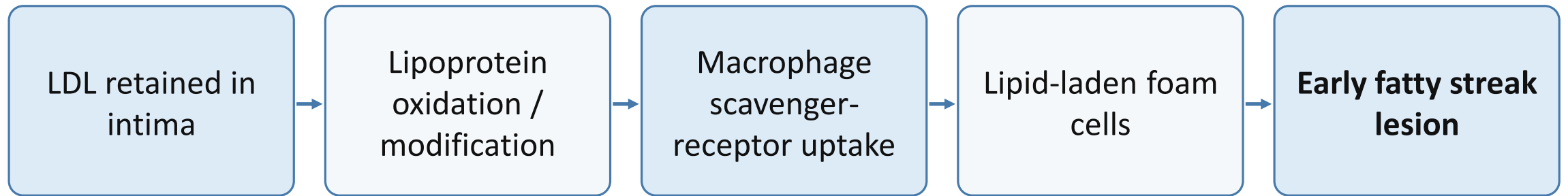
Cannot by itself establish

- A specific causal gene or variant
- A molecular diagnosis of hypercholesterolemia
- The timing or certainty of an individual event

Genetic predisposition can act through lipoproteins

- Genetic changes in lipoprotein uptake or metabolism may elevate LDL.
- Circulating LDL enters and accumulates in arterial intima.
- Intimal LDL modification facilitates foam-cell development and inflammatory activation.

From excess LDL to fatty streak



Schematic sequence: Source-supported causal / pathological relations

Risk genotype and plaque phenotype are distinct

- A pathogenic allele is an inherited exposure; It is not a microscopic diagnosis of plaque.
- The arterial lesion reflects cumulative lipid, inflammatory, and smooth-muscle responses.
- Atherosclerosis becomes clinically relevant through stenosis, plaque change, and downstream ischemia.

Case 1 — striking familial susceptibility

An adolescent has markedly elevated LDL cholesterol and a strong family history of premature myocardial infarction.

Discussion prompts

1. Which constitutional axis dominates the history?
2. Which high-impact mechanism should be considered?
3. Why is the age of presentation significant?

Case 1 — mechanistic interpretation

- Inherited susceptibility is prominent; Evaluate a possible Mendelian lipid disorder.
- Familial hypercholesterolemia illustrates impaired LDL-receptor–mediated clearance.
- Premature disease is consistent with severe sustained LDL exposure; The vignette alone does not prove genotype.

Genetics: Synthesis

- A positive family history is an important independent risk signal.
- Rare monogenic disorders can produce dramatic disease; Most familial predisposition is polygenic.
- The proximate arterial injury still involves lipoprotein accumulation, inflammation, and plaque remodeling.

Age is a dominant influence

Time + biology

Plaque progression typically becomes clinically manifest in middle age or later.

Aging permits prolonged accumulation of vascular injury.

Robbins also emphasizes acquired changes in innate immunity.

Age gradient in myocardial infarction

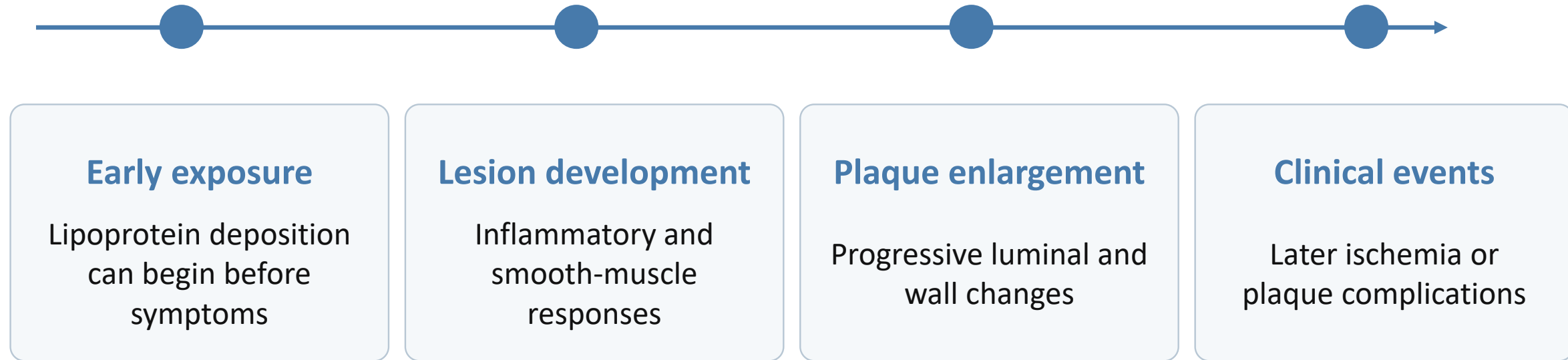
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**Myocardial infarction incidence rises
fivefold between ages 40 and 60.**

This textbook comparison describes a
population age association.

It is not a prediction for a particular individual
and should not be applied as a personalized
multiplier.

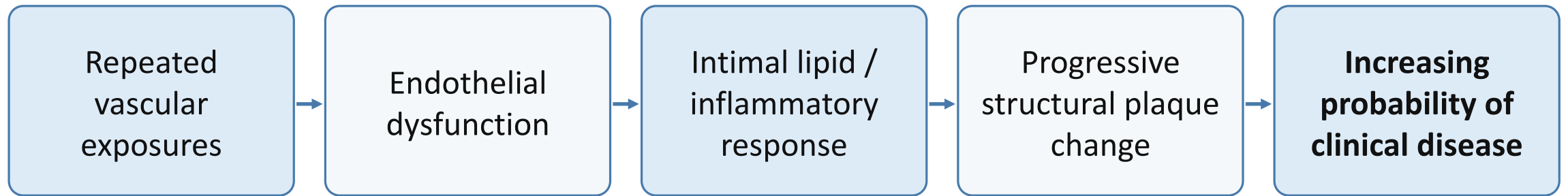
Atherosclerosis accumulates across decades



Clinical silence does not imply absent disease

- Atherosclerotic lesions develop progressively.
- A patient may remain asymptomatic before flow limitation or acute plaque complications.
- Later clinical presentation therefore reflects a prolonged pathological process.

One component of aging: Cumulative arterial injury



Schematic sequence: Source-supported causal / pathological relations

Aging is not simply more years of exposure

- Advancing age to alterations in the innate immune system.
- These alterations may modify inflammatory behavior during atherogenesis.
- The age association therefore combines cumulative lesion development with acquired biology.

Two complementary aging pathways

CUMULATIVE INJURY

Long-term exposure to
endothelial / lipid insults

IMMUNE AGING

Acquired alteration of
innate immune-cell biology

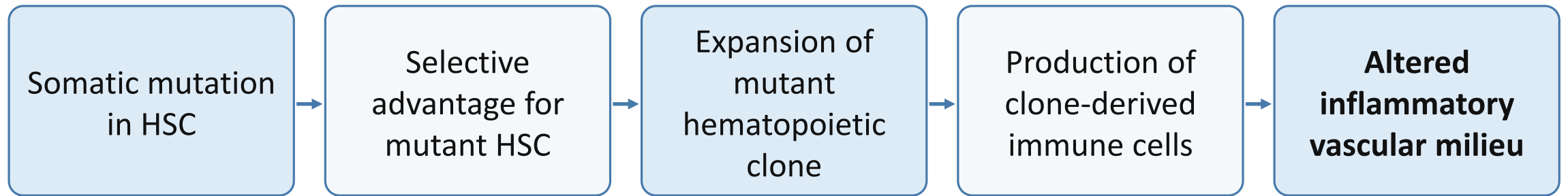
CLINICAL EXPRESSION

Greater burden and
consequences of arterial
plaques

Clonal hematopoiesis: The defining observation

- Some hematopoietic stem-cell clones acquire somatic mutations.
- Specific mutations can confer a growth or survival advantage over other stem-cell clones.
- The mutant clone expands and contributes circulating blood cells.

CHIP develops through clonal selection



Schematic sequence: Source-supported causal / pathological relations

CHIP is not a diagnosis of leukemia

CHIP

- Clonal hematopoiesis without defined hematologic malignancy
- May be identified in otherwise apparently well adults
- Associated with future hematologic risk

Atherosclerotic relevance

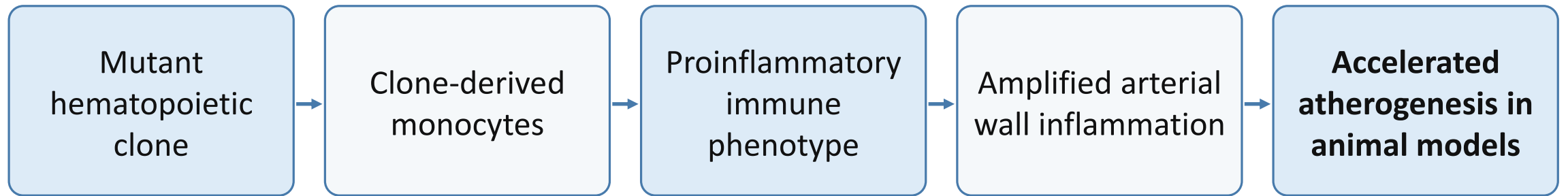
- Clone-derived myeloid cells may be proinflammatory
- Linked with cardiovascular mortality
- Potential amplifier of existing lesion biology

A clonal mutation does not establish a hematologic cancer or atherosclerotic event.

CHIP has two distinct clinical associations

- CHIP is associated with increased risk of hematopoietic malignancy.
- The textbook also describes a strong association with cardiovascular mortality.
- These are separate outcomes; An association alone is not proof of mechanism in humans.

Proposed inflammatory route from CHIP to plaque

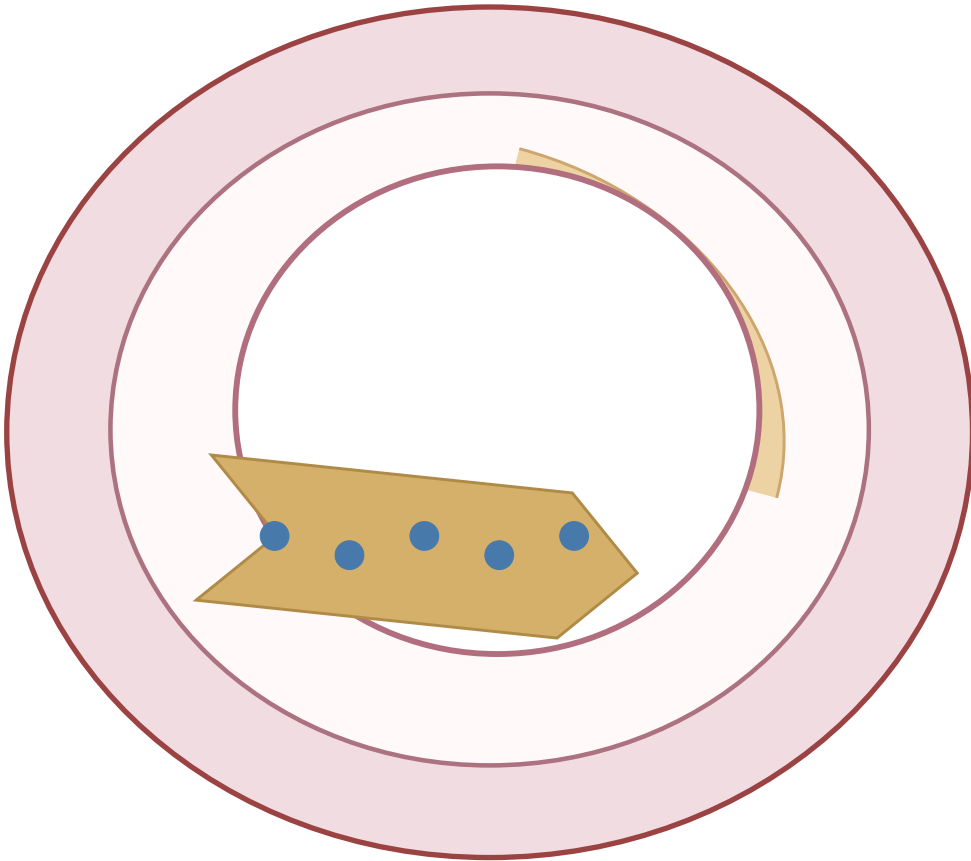


Schematic sequence: Source-supported causal / pathological relations

Why monocytes matter

- Monocytes adhere to activated endothelium and migrate into the intima.
- Intimal monocytes differentiate into macrophages.
- Macrophages ingest modified lipoproteins and release inflammatory mediators.
- This positions myeloid behavior at the intersection of CHIP and atherosclerosis.

Inflammation links blood cells with arterial plaque



1. Endothelial activation recruits monocytes

2. Macrophages accumulate in intima

3. Lipid-filled foam cells populate lesions

4. Chronic inflammation sustains plaque remodeling

Schematic artery cross-section — not a histologic specimen

What is established versus mechanistically inferred

Human association

- CHIP is associated with cardiovascular mortality
- CHIP is linked with hematologic malignancy risk
- Association does not define an individual prognosis

Animal-model inference

- Clone-derived monocytes can be proinflammatory
- Inflammatory phenotype can worsen lesions
- Mechanistic evidence should not be overstated as human proof

An age-related vascular-risk model

- Years of exposure permit plaque accumulation.
- Age-associated hematopoietic clones may further influence myeloid inflammation.
- Together these processes help explain why aging tracks strongly with ischemic disease.

Case 2 — vascular risk in later life

An older adult has progressive coronary atherosclerosis without a recognized Mendelian lipid disorder.

Discussion prompts

1. What age-related mechanisms are relevant?
2. Why is cumulative injury not the sole explanation?
3. How should an incidental CHIP finding be interpreted?

Case 2 — interpretation

- Progressive vascular injury can accumulate over many years.
- Innate immune alterations are an additional aging-associated mechanism.
- CHIP supports an association with cardiovascular risk but does not prove that the clone caused this individual's lesion.

Age: Synthesis

- Risk rises with age because atherosclerosis is progressive.
- Innate immune changes provide a complementary biological explanation.
- CHIP connects somatic clonal selection with proinflammatory myeloid responses and cardiovascular association.

Biological sex influences atherosclerotic risk

**Life stage
matters**

The Robbins population-level comparison changes substantially before and after menopause.

Risk patterns are group-level observations, not disease exclusion rules.

Severe acquired risk factors can override apparent premenopausal protection.

Premenopausal sex-associated pattern

Premenopausal females

- Relatively lower atherosclerotic complication frequency
- MI generally uncommon without other strong predisposition
- Risk is never zero

Age-matched males

- Higher frequency of atherosclerosis and consequences comparison
- Population contrast, not an individual prediction
- Other risk factors still modify risk

Premenopausal protection is relative

- Lower atherosclerotic burden and consequences before menopause.
- This comparison is with age-matched males, not with all older or younger populations.
- The relationship should not be interpreted as immunity to coronary disease.

When premenopausal complications do occur

DIABETES

Major acquired risk can counter baseline protection

HYPERLIPIDEMIA

High lipid exposure can accelerate lesions

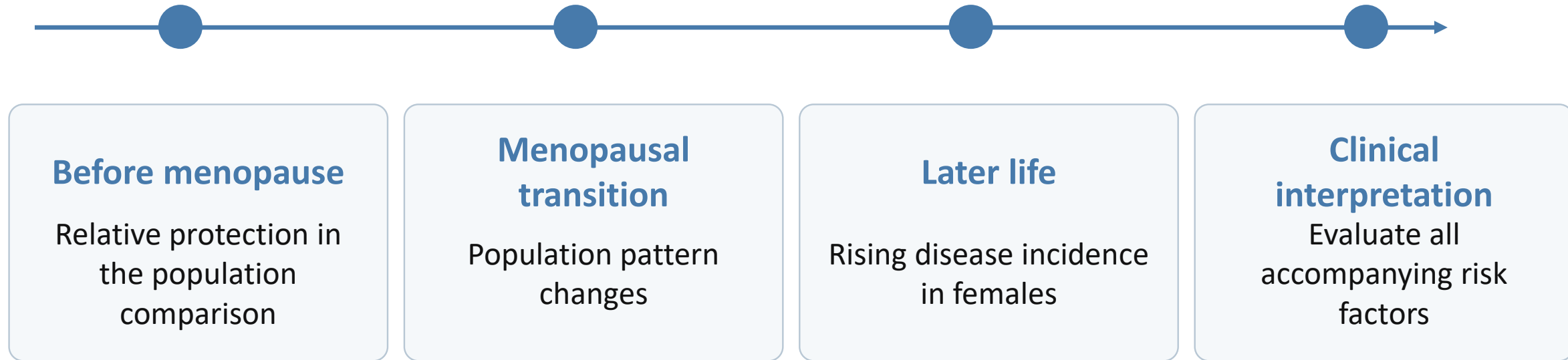
SEVERE HYPERTENSION

Sustained hemodynamic stress increases vascular risk

Menopause alters the epidemiologic pattern

- Following menopause, the incidence of atherosclerosis-related disease rises in females.
- An eventual incidence exceeding that in males.
- The comparison is time- and population-dependent; Do not infer an exact crossover age from this source.

Sex-associated risk varies with life stage



Estrogen protection was a hypothesis

- A favorable vascular influence of estrogen was proposed to explain premenopausal patterns.
- Such a biological hypothesis does not establish that prescribing estrogen prevents events.
- Intervention trials are required to test clinical benefit and harm.

Physiological association versus treatment effect

Observation

- Premenopausal females have lower event rates
- Temporal association suggests possible mechanisms
- Multiple biological and acquired factors coexist

Intervention

- Postmenopausal estrogen replacement was tested
- Trials did not demonstrate cardiovascular benefit
- Some older recipients experienced higher cardiovascular risk

Menopausal hormone therapy is not vascular prevention

**No prevention
benefit**

No cardiovascular benefit from estrogen replacement trials and increased risk in some older females.

Do not infer treatment efficacy from the premenopausal epidemiologic pattern.

Hormone therapy has separate indications and risks not evaluated in this focused lecture.

Sex-associated risk must be interpreted conditionally

- Premenopausal status modifies baseline probability but cannot rule out disease.
- Diabetes, major lipid abnormalities, and severe hypertension remain important.
- After menopause, the epidemiologic pattern changes; Clinical assessment remains multifactorial.

Case 3 — challenge the protection assumption

A premenopausal adult presents with an ischemic event and has severe hyperlipidemia and diabetes.

Discussion prompts

1. Is this incompatible with Robbins' sex-risk description?
2. Which factors undermine relative premenopausal protection?
3. Would this case support estrogen prophylaxis?

Case 3 — interpretation

- Relative, not absolute, protection.
- Coexisting hyperlipidemia and diabetes can confer substantial atherosclerotic risk.
- The clinical event does not establish any preventive role for postmenopausal estrogen replacement.

Biological sex: Synthesis

- Sex-associated atherosclerosis patterns depend on age and menopausal status.
- Premenopausal risk remains clinically important with major acquired exposures.
- Trials refute the assumption that postmenopausal estrogen therapy prevents cardiovascular events.

Integrate the constitutional axes

GENOTYPE

Monogenic disease or
distributed polygenic
liability

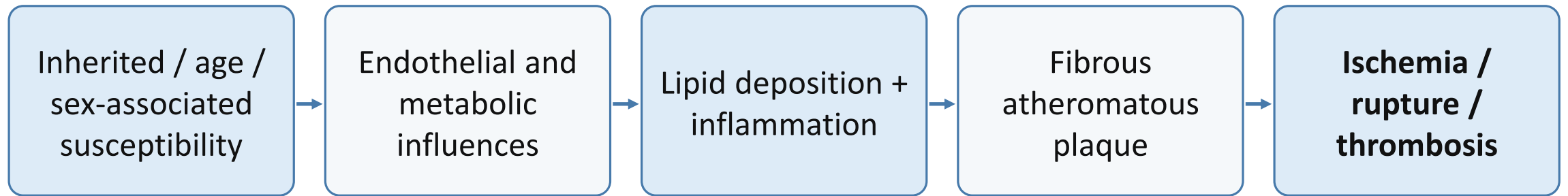
AGING

Cumulative injury and
immunobiological
remodeling

SEX / LIFE STAGE

Population-level shifts
before and after
menopause

A single downstream pathological pathway



Schematic sequence: Source-supported causal / pathological relations

Predisposition and event are different outcomes

Susceptibility

- Inherited alleles
- Age-related processes
- Sex / menopausal profile

Clinical event

- Arterial plaque burden / location
- Plaque disruption or critical narrowing
- Thrombosis and downstream tissue injury

Why modifiable factors remain relevant

- Constitutional factors cannot simply be removed, but acquired exposures remain tractable.
- That risk factors interact and interventions can mitigate total risk.
- A risk assessment should not mistake fixed determinants for inevitable disease.

A clinically useful contrast

Constitutional determinant	Principal interpretation	Potential pitfall
Family history	Inherited susceptibility; often polygenic	Assuming a unique Mendelian variant
Increasing age	Cumulative vascular injury plus immune change	Equating age with time alone
Biological sex	Life-stage-dependent epidemiologic pattern	Assuming absolute premenopausal protection
CHIP (age-linked)	Cardiovascular association; possible inflammatory mechanism	Treating association as proven individual cause

Integrated case — interpret layered risk

A 62-year-old postmenopausal adult with a family history of premature coronary disease and long-standing hypertension develops angina.

Discussion prompts

1. Which factors are constitutional?

2. Which factor is potentially modifiable?

3. What arterial lesion could underlie angina?

Integrated case — answer

- Age, sex/life stage, and family history are constitutional determinants.
- Hypertension is a major potentially modifiable co-exposure.
- An atheromatous plaque causing coronary flow limitation is one plausible substrate; Clinical findings alone do not prove plaque morphology.

Five conclusions to retain

- Familial history is an important independent marker of atherosclerotic susceptibility.
- Rare monogenic disease contrasts with the more usual polygenic predisposition.
- Aging links lesion accumulation with acquired innate immune changes.
- CHIP is cardiovascular-risk-associated; Proposed inflammation is supported particularly by animal experiments.
- Menopause modifies population risk, but estrogen replacement has not prevented cardiovascular events.

Primary source and scope

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026).
- Blood Vessels: Atherosclerosis — constitutional risk factors.
- Parent context: atherosclerosis, major risk factors, and mechanisms of atherogenesis.
- Textbook-derived epidemiologic statements reflect the edition; no external guideline claims were added.