Coronary Artery Disease (Coronary Atherosclerosis, MONDO:0021661): A Comprehensive Disease Characterization Report

Summary

Coronary artery disease, defined here strictly as **coronary atherosclerosis (`MONDO:0021661`)** — atherosclerotic plaque formation in the intima of the epicardial coronary arteries — is a chronic, polygenic, lipid-initiated and inflammation-amplified disease. The best-supported causal model is a **staged process**: subendothelial retention of apolipoprotein-B (apoB)-containing lipoproteins at disturbed-flow arterial sites drives endothelial dysfunction, monocyte recruitment, macrophage foam-cell formation with defective apoptotic-cell clearance (efferocytosis), and smooth-muscle-cell (SMC) phenotypic switching. These processes generate plaques whose **composition** — a lipid/necrotic core beneath a thin fibrous cap — rather than the **degree of luminal stenosis**, precipitates acute coronary events. Two histologically distinct terminal routes convert stable plaque into coronary thrombosis: **plaque rupture** (~2/3 of ACS) and **superficial erosion** (~1/3 of ACS).

The causal centrality of apoB/LDL is established at the highest evidence tier by convergent **human genetics** (PCSK9 loss-of-function and LPA variants) and **randomized outcome and imaging trials** (statins, PCSK9 inhibitors, bempedoic acid). Independently, **inflammation is causal**: IL-1β inhibition (canakinumab, CANTOS) and colchicine reduce coronary events *without* lowering lipids, isolating an IL-1β→IL-6→CRP axis. Coronary-specific imaging evidence (PROSPECT natural history, NIRS-IVUS/OCT wall-shear-stress studies, MESA coronary artery calcium) anchors the anatomy and prognostic value of plaque burden and composition directly in the coronary bed. Model-organism and in-vitro work (MerTK efferocytosis, SMC lineage tracing, IL-1β-induced LDL transcytosis) supplies mechanism but is labeled by species and vascular bed and does not, alone, establish human coronary causality.

Clinically, CAD is managed by aggressive apoB/LDL lowering, anti-inflammatory therapy in selected patients, and antithrombotics; **revascularization relieves symptoms but does not reduce death or MI in stable disease** (ISCHEMIA). This report organizes the evidence across the 15 requested domains, maintaining an explicit evidence-directness ladder (human coronary → human systemic → transferable non-coronary plaque → model organism → in vitro → computational) and flagging discordant/null findings.

Evidence Matrix (Directness Ladder Applied)

Directness ladder: T1 = human coronary pathology/imaging (anatomically direct; imaging composition = surrogate); T2 = human coronary-event genetics/biomarker/systemic intervention (clinically relevant, not plaque-localized); T3 = human carotid/aortic/peripheral plaque (transferable, indirect for coronary); T4 = animal in-vivo (MODEL_ORGANISM); T5 = cultured cells/ex-vivo (IN_VITRO); T6 = computational.

ID	Claim	Design / n	Vascular site	Tier	Causal verdict
F009	PCSK9 LoF → lower LDL → 47–88% lower CHD	ARIC cohort, 15 yr	Human coronary events	T2 genetics	Causal for LDL→CHD
F002	PCSK9 inhibition regresses coronary atheroma	GLAGOV RCT, n=968, serial IVUS	Human **coronary**	T1 imaging surrogate	Causal for LDL→plaque volume
F013	Statin: −21% MVE per 1 mmol/L LDL	CTT meta, 28 RCTs, n=186,854	Human coronary events	T2 RCT	Causal, LDL-dependent
F011	IL-1β inhibition ↓ events without lipid change	CANTOS RCT, n=10,061	Human coronary events	T2 RCT	Causal for inflammation
F012	Colchicine ↓ MACE (COLCOT, LoDoCo2)	RCTs / meta	Human coronary events	T2 RCT	Causal for inflammation
F001	Plaque burden/MLA/ TCFA predict events	PROSPECT, n=697, IVUS	Human **coronary**	T1 natural history	Prognostic (composition)
F007	Low WSS + lipid → coronary plaque growth	n=40, NIRS-IVUS/OCT	Human **coronary**	T1 imaging	Direct coronary hemodynamic
F003	Rupture vs erosion = 2 terminal routes	OCT in-vivo	Human **coronary**	T1 imaging	Mechanistic (terminal)
F014	CAC & progression predict CHD	MESA, n=6,778	Human **coronary**	T1 imaging	Prognostic
F006/ F010	9p21.3, LPA strongest loci; Lp(a) causal	GWAS/MR	Human coronary events	T2 genetics	Causal (Lp(a))
F005	CHIP → inflammatory ASCVD risk	UK Biobank, n=13,129	Human systemic	T2 + mouse	Assoc. + model causal
F015			Human MI		

ID	Claim	Design / n	Vascular site	Tier	Causal verdict
	9 risk factors = >90% MI PAR	INTERHEART, n=27,098		T2 case-control	Population attributable
F008	MerTK efferocytosis failure → necrotic core	Apoe−/− mice	Mouse aortic root	T4 model	Model causal
F004	SMC → macrophage-like switching destabilizes	Lineage tracing + scRNA	Mouse + human plaque	T4–T3	Mechanistic hypothesis
F016	Mouse models recapitulate lipid plaque, not coronary events	Apoe/Ldlr−/− etc.	Mouse aorta	T4	Model limitation
F017	Revascularization no death/MI benefit in stable CAD	ISCHEMIA	Human coronary	T2 RCT	Causal (null for hard events)

1. Disease Information

Coronary atherosclerosis is the accumulation of atherosclerotic plaque — lipid, inflammatory cells, smooth-muscle cells, extracellular matrix, calcification and necrotic debris — within the intima of the epicardial coronary arteries, progressively narrowing the lumen and/or destabilizing to cause thrombosis. It is the dominant substrate of **ischemic heart disease** and the leading cause of death worldwide.

Key identifiers: - **Mondo:** `MONDO:0021661` (coronary atherosclerosis) — the locked disease identity. `MONDO:0004975`, broad ASCVD, and "all coronary disorders" are explicitly *excluded*. - **MeSH:** Coronary Artery Disease (D003324); Coronary Atherosclerosis - **ICD-10:** I25.1 (atherosclerotic heart disease of native coronary artery) - **ICD-11:** BA80 (ischaemic heart disease block) - **SNOMED CT:** 53741008 (coronary arteriosclerosis)

Synonyms / near-terms (with scope caveats): coronary atherosclerosis, atherosclerotic heart disease, coronary arteriosclerosis. **Not exact synonyms:** stable angina, acute coronary syndrome (ACS), and myocardial infarction (MI) are *manifestations/complications*. **Excluded differentials:** spontaneous coronary artery dissection (SCAD), coronary vasospasm, congenital coronary anomalies, coronary embolism, isolated coronary microvascular dysfunction, and type-2 MI.

Data provenance: This report synthesizes **aggregated disease-level resources** (RCTs, cohort studies, GWAS meta-analyses, imaging natural-history studies), not individual patient EHR records.

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2. Etiology

Disease causal factors

CAD is a **multifactorial, polygenic** disease. The initiating causal factor is **subendothelial retention of apoB-containing lipoproteins** (LDL, remnant/triglyceride-rich lipoproteins, and Lp(a)), superimposed on hemodynamic (disturbed-flow) and inflammatory contributors.

Human-genetic proof of LDL causality (F009): In ARIC (15-yr follow-up), PCSK9 nonsense mutations (2.6% of Black participants) conferred a **28% lower LDL-C and 88% lower CHD risk** (HR 0.11, 95% CI 0.02–0.81); a PCSK9 variant in White participants gave 15% lower LDL-C and 47% lower CHD risk (HR 0.50, 95% CI 0.32–0.79). *"these mutations were associated with a 28 percent reduction in mean LDL cholesterol and an 88 percent reduction in the risk of CHD"* (PMID: 16554528). This natural experiment demonstrates that **lifelong lower apoB exposure yields disproportionately large CHD reduction**.

Genetic risk factors (F006, F010)

- **9p21.3 / CDKN2A/B** (rs1333049) — the most replicated common CAD locus; also a shared T2DM–CAD signal (strongest local genetic correlation; T2DM–CAD rg=0.39, $P=1.43\times10^{-75}$) (PMID: 38062574).
- **LPA / lipoprotein(a)** (rs10455872) — one of the two strongest CAD risk loci (PMID: 30482443); Mendelian randomization confirms Lp(a) **causally** raises risk of CHD, large-artery stroke, PAD and aortic stenosis: *"Mendelian randomization confirms causal relationships with coronary heart disease, large-artery stroke, peripheral artery disease, and*

aortic stenosis" (PMID: 41789317). Lp(a) is 70–90% genetically determined and elevated in ~20% of the global population.

- **CDKN2B (9p21.3)** also replicated as an ankle-brachial-index/PAD–CAD locus (PMID: 41252360).

Environmental / lifestyle risk factors (F015)

INTERHEART (52 countries, ~27,098 participants) found **nine modifiable risk factors account for >90% of MI population-attributable risk** (women 96% vs men 93%): abnormal lipids (ApoB:ApoA1), current smoking, hypertension, diabetes, abdominal obesity, psychosocial stress, low fruit/vegetable intake, physical inactivity, and no/low alcohol. *"The population attributable risk (PAR) of all nine risk factors exceeded 94%, and was similar among women and men (96 vs. 93%)"* (PMID: 18334475).

Protective factors

- **Genetic:** PCSK9 loss-of-function alleles (F009); constitutionally low-Lp(a) genotypes.
- **Environmental:** the inverse of the INTERHEART factors — physical activity, fruit/vegetable intake, moderate alcohol, non-smoking. Pharmacologic LDL lowering is protective regardless of mechanism (F013).

Gene–environment interactions

The T2DM–CAD relationship is **bidirectional and partly genetic** (rg largely BMI-independent, 0.31), mediated substantially by systolic blood pressure and statin use (PMID: 38062574). CHIP illustrates a somatic-genetic × inflammatory-environment interaction (F005).

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3. Phenotypes

CAD is **asymptomatic during plaque development** (subclinical for decades) and becomes clinically manifest through ischemic syndromes. Per the scope guardrails, these are *manifestations/complications*, not synonyms.

Phenotype	Type	HPO suggestion	Onset / course	Frequency
Angina pectoris (exertional chest pain/pressure)	Symptom	HP:0001681 (Angina pectoris)	Adult/late-onset; episodic, exertional	Common in symptomatic CAD
Myocardial infarction	Clinical event	HP:0001658 (Myocardial infarction)	Acute; median first MI age 56 (men) / 65 (women)	Terminal complication
Coronary artery atherosclerosis	Physical/ imaging sign	HP:0001677	Adult; progressive	Ubiquitous by definition
Dyspnea on exertion	Symptom	HP:0002875	Progressive	Frequent
Elevated troponin	Lab abnormality	HP:0410174 (Increased circulating troponin)	Acute (ACS/MI)	Diagnostic for MI
Coronary artery calcification	Imaging sign	—	Adult; progressive	~50% baseline prevalence, MESA age 45–84
Sudden cardiac death	Clinical event	HP:0001645 (Sudden cardiac death)	Acute	Can be first presentation

Age of onset: typically adult/late-onset, with earlier clinical onset in men (median first MI 56 vs 65 yr in women) (F015). **Severity/progression:** variable and generally progressive but modifiable; long asymptomatic phase punctuated by acute episodes. **QoL impact:** angina limits daily functioning; captured by disease-specific tools (Seattle Angina Questionnaire) and generic measures (EQ-5D, SF-36). In stable disease, revascularization's main benefit is **angina relief** rather than event reduction (F017).

4. Genetic / Molecular Information

CAD is **polygenic/multifactorial**, not a Mendelian single-gene disorder, except that monogenic hypercholesterolemias greatly accelerate coronary atherosclerosis (familial hypercholesterolemia: *LDLR*, *APOB*, *PCSK9* gain-of-function).

Key genes / loci: - **PCSK9** (HGNC:20001) — loss-of-function is protective (F009); gain-of-function causes FH. Functional consequence: LoF → increased hepatic LDLR → lower LDL. - **LDLR** — the classic FH gene; central to LDL clearance. - **LPA** (HGNC:6667) — determines Lp(a); causal for CAD (F010). - **CDKN2A/CDKN2B (9p21.3)** — strongest common susceptibility locus (F006); non-coding regulatory effect on vascular SMC biology. - **TCF21** — coronary-disease GWAS gene modulating SMC phenotype (anchor

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mixed human/model evidence).

Modifier / acquired genetic drivers — CHIP (F005): Somatic mutations in hematopoietic stem cells. **DNMT3A and TET2 are the two most frequently mutated CHIP genes** (PMID: 36097025). In UK Biobank (n=13,129 with ASCVD): *"any CHIP and large CHIP at baseline were associated with adjusted HRs of 1.23 (95% CI: 1.10-1.38; P < 0.001) and 1.34 (95% CI: 1.17-1.53; P < 0.001), respectively, for the primary outcome"* (PMID: 37197843); large TET2 HR 1.89, large spliceosome HR 3.02. Murine Tet2/Dnmt3a loss-of-function supports an IL-1β/inflammasome-mediated causal mechanism (PMID: 31345433).

Epigenetics: DNMT3A and TET2 CHIP produce distinct, directionally opposing genome-wide DNA-methylation patterns; Mendelian randomization suggests some DNAm alterations promote CAD risk (PMID: 36097025).

Chromosomal abnormalities: Not a defining feature of coronary atherosclerosis. The most relevant "large-scale" genetic contributor is clonal expansion of mutant hematopoietic clones (CHIP), not aneuploidy.

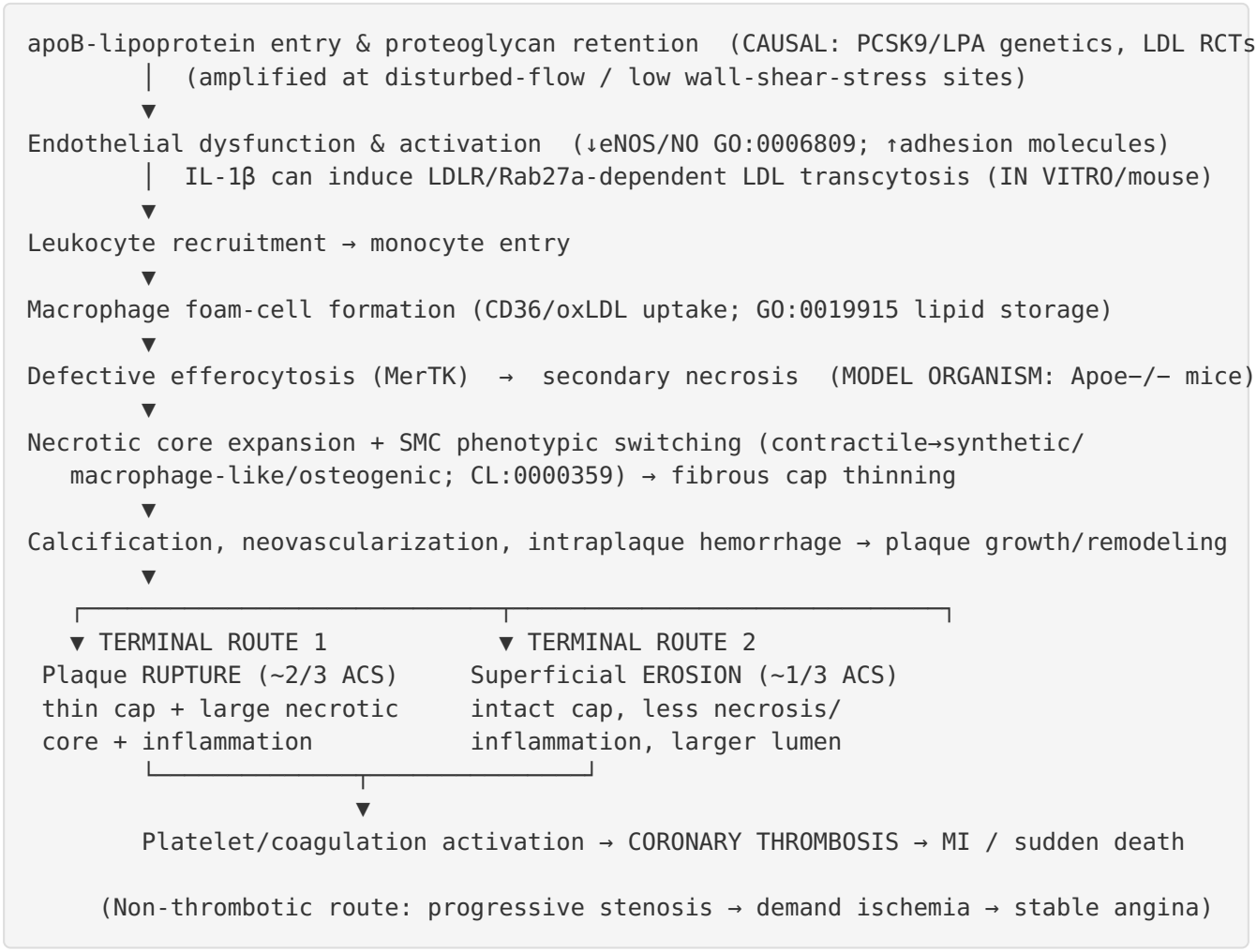
Variant classification / population frequency: PCSK9 protective LoF alleles (e.g., Y142X, C679X) are more frequent in individuals of African ancestry (~2–3%); classified benign-protective. FH-causing LDLR/APOB/PCSK9-GoF variants span missense, nonsense, frameshift, and splice-site classes (pathogenic/likely pathogenic per ACMG/AMP in ClinVar). All germline; CHIP mutations are **somatic**.

5. Environmental Information

- **Lifestyle factors (F015):** smoking, atherogenic diet (high saturated fat/refined carbohydrate), physical inactivity, abdominal obesity, and psychosocial stress. Current smoking and abnormal lipids are among the strongest INTERHEART contributors.
- **Environmental exposures:** ambient air pollution (particulate matter) is an established population risk factor for ischemic heart disease.
- **Metabolic environment:** diabetes/hyperglycemia (bidirectional with CAD, PMID: 38062574) and hypertension.
- **Infectious agents:** CAD is **not an infectious disease**. Chronic low-grade inflammation (not a specific pathogen) is the operative inflammatory driver; the causal inflammatory axis is IL-1β→IL-6→CRP (F011, F012), not a microbe.

6. Mechanism / Pathophysiology

Staged causal model



Molecular pathways & cellular processes

- **Lipid retention & foam-cell formation:** apoB-lipoprotein subendothelial retention; scavenger-receptor (CD36) uptake of oxLDL; **lipid storage (GO:0019915)**. In vitro, oxLDL downregulates the PPARγ/LXRα/MerTK efferocytosis axis and upregulates competitive receptor CD300a, driving CD36-mediated foam-cell formation (PMID: 36721069).
- **Endothelial mechanotransduction:** low wall shear stress downregulates **eNOS / nitric-oxide biosynthesis (GO:0006809)** and upregulates E-selectin/ICAM-1, promoting leukocyte adhesion (in-vitro HUVEC/microfluidic, PMID: 34948110); NRP2/PARP1 mediate low-shear endothelial apoptosis in mouse aorta (PMID: 35028975).

- **Efferocytosis / apoptotic-cell clearance (F008):** In *Mertk*-kinase-dead;*Apoe*$^{-/-}$ mice, lesions accumulated apoptotic cells and became more necrotic — *"mutation of the phagocytic Mertk receptor promotes the accumulation of apoptotic cells"* (PMID: 18451332). **Species: mouse; site: aortic root — not coronary.**
- **SMC plasticity (F004):** Contractile vascular-associated SMCs (**CL:0000359**) dedifferentiate to synthetic, macrophage-like, osteoblast-like states. *"most of lesional macrophages... are derived from macrophage-like cells (MLCs) dedifferentiated from the VSMCs lineage... promoting... necrotic core expansion and fibrous cap thinning"* (PMID: 41165871). IRF7 is proposed as a checkpoint for maladaptive switching, upregulated in unstable human plaques (PMID: 41625231). Dual SMC/EC lineage tracing shows endothelial-to-SMC and SMC-loss dynamics under vascular stress (PMID: 41648299).
- **Inflammation is causal (F011):** IL-1β→IL-6→CRP axis. Mechanistically, IL-1β induces LDL transcytosis by human coronary artery endothelial cells via an LDLR/Rab27a pathway (PMID: 38989581), linking inflammation to early lipid entry.

Upstream vs downstream

- **Upstream (initiation):** apoB retention, disturbed-flow endothelial dysfunction.
- **Midstream (progression):** foam cells, defective efferocytosis, SMC switching, necrotic-core growth.
- **Downstream (terminal):** cap thinning → rupture *or* endothelial erosion → thrombosis.

GO / CL term suggestions

- GO:0019915 lipid storage; GO:0006809 nitric oxide biosynthetic process; GO:0043277 apoptotic cell clearance (efferocytosis); GO:0033344 cholesterol efflux; GO:0006954 inflammatory response.
- CL:0000359 vascular associated smooth muscle cell; CL:0000235 macrophage/foam cell; CL:0000071 blood vessel endothelial cell; CL:0000775 neutrophil (erosion).

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7. Anatomical Structures Affected

- **Organ level:** Heart — specifically the **epicardial coronary arteries** (UBERON:0001621; left anterior descending, left circumflex, right coronary). Secondary organ: **myocardium** (UBERON:0002349) via ischemia/infarction. Body system: **cardiovascular system**.

- **Tissue level:** arterial **tunica intima** (UBERON:0004638; primary plaque site), tunica media (SMC source). Tissue types: endothelium, connective tissue/ECM, vascular smooth muscle.
- **Cell level:** endothelial cells (CL:0000071), monocyte-derived macrophages/foam cells (CL:0000235), vascular-associated smooth muscle cells (CL:0000359), T lymphocytes, neutrophils (prominent in erosion), platelets (terminal thrombosis).
- **Subcellular level:** lysosomes/late endosomes (lipid handling, efferocytic degradation, Rab27a vesicles, PMID: 38989581); endoplasmic reticulum (lipid synthesis/stress); mitochondria (oxidative stress). GO CC: GO:0005764 lysosome; GO:0005783 ER.
- **Localization / lateralization:** Multifocal, bilateral (multiple coronary arteries); plaques preferentially form at **branch points and inner curvatures** where wall shear stress is low/oscillatory (F007).

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8. Temporal Development

- **Onset:** Subclinical plaque begins in early adulthood (fatty streaks even earlier); clinical onset typically adult/geriatric. Onset of *events* is often **acute** superimposed on **chronic, insidious** plaque growth.
- **Progression / stages:** fatty streak → fibroatheroma → thin-cap fibroatheroma (TCFA, high-risk) → complicated/ruptured or eroded plaque with thrombosis. Progression is **variable** and modifiable; low wall shear stress accelerates lipid-rich plaque growth over ~1 year — *"Exposure to low WSS was associated with a higher plaque progression"* (PMID: 36575921).
- **Course pattern:** chronic, lifelong, generally progressive but **regressable** with intensive LDL lowering (GLAGOV IVUS regression, F002; PACMAN-AMI lesion-level regression showing PAV change −4.86% alirocumab vs −2.78% placebo, PMID: 39221516).
- **Natural history (F001):** In PROSPECT, most nonculprit lesions causing future events were **angiographically mild at baseline** (mean diameter stenosis 32.3±20.6%) yet had high-risk features — *"nonculprit lesions associated with recurrent events were more likely... to be characterized by a plaque burden of 70% or greater (hazard ratio, 5.03; 95% confidence interval [CI], 2.51 to 10.11; P<0.001) or a minimal luminal area of 4.0 mm(2) or less"* (PMID: 21247313). This establishes **composition/burden, not stenosis, as the driver of events**.
- **Critical intervention windows:** LDL lowering and anti-inflammatory therapy alter trajectory at any stage; the post-MI period is a high-residual-risk window (CANTOS, colchicine).

9. Inheritance and Population

- **Epidemiology:** Ischemic heart disease is the leading global cause of death and DALYs. GBD 2021 shows rising incidence/prevalence even in young adults (aged 20–24), with ischemic heart disease dominating mortality/DALYs and males bearing greater mortality/DALY burden (PMID: 42483021). CAC prevalence is ~50% in adults aged 45–84 (MESA, F014).
- **Inheritance: Polygenic/multifactorial**, not Mendelian. Heritability estimates ~40–60%. Dominant common-variant contributors: 9p21.3, LPA (F006, F010); ~300+ GWAS loci total.
- **Penetrance/expressivity:** Genetic liability is probabilistic (polygenic risk scores), strongly modified by environment (F015). Lp(a) is highly penetrant for elevated risk when very high.
- **Founder effects:** PCSK9 protective variants have population-specific frequencies (F009).
- **Population demographics / sex:** Median first-MI age higher in women (65 vs 56 yr); hypertension (OR 2.95 vs 2.32) and diabetes (OR 4.26 vs 2.67) are more strongly associated in women, while several factors are similar across sexes (F015). Low/low-middle sociodemographic-index regions bear the highest young-adult burden (PMID: 42483021).

10. Diagnostics

- **Laboratory tests/biomarkers:** Lipid panel (LDL-C, apoB, non-HDL-C); **Lp(a)** (2024 NLA Class I recommendation for universal one-time measurement; F010); **high-sensitivity cardiac troponin** (HP:0410174) for MI; **hs-CRP** for residual inflammatory risk (CANTOS entry criterion ≥2 mg/L; F012) — *"High-sensitivity C-reactive protein is a practical and reliable biomarker for assessing low-grade chronic inflammation"* (PMID: 41936433). Serum urate independently predicts MACE/CV death even under IL-1β blockade (HR 1.66 for MACE, PMID: 39862678).
- **Imaging (coronary-direct, tier 1):**
- **Coronary artery calcium (CAC) score** by non-contrast CT (Agatston method) — MESA: *"those with annual progression of ≥300 units had adjusted HRs of 3.8 (1.5 to 9.6) for total"* CHD events (PMID: 23500326). AI-enhanced CAC scans add chamber-volume and hepatic-steatosis prognostics (PMID: 38664073, PMID: 40221147, PMID: 41591983).
- **Coronary CT angiography (CCTA)** — anatomy and plaque composition.

- **Invasive intracoronary imaging:** IVUS (plaque burden/volume; GLAGOV/PROSPECT), **NIRS** (lipid-core burden), **OCT** (thin-cap fibroatheroma; the only modality able to identify **erosion in vivo**, F003).
- Low endothelial shear stress adds incremental risk beyond morphology (HR 4.34, PMID: 28917684).
- **Functional tests:** exercise/pharmacologic stress testing, fractional flow reserve (FFR); ECG.
- **Clinical criteria / differential diagnosis:** ACC/AHA and ESC guidelines. **Differentials to exclude** (per scope): SCAD, vasospasm, congenital anomalies, embolism, isolated microvascular dysfunction, type-2 MI.
- **Genetic/omics testing:** Not routine for common CAD; polygenic risk scores and Lp(a) are emerging risk-stratification tools. FH gene panels (LDLR/APOB/PCSK9) apply to monogenic hypercholesterolemia.
- **Screening:** CAC scoring for intermediate-risk asymptomatic adults; universal one-time Lp(a).

11. Outcome / Prognosis

- **Mortality:** Ischemic heart disease is the leading cause of death globally (GBD 2021). Acute MI and sudden cardiac death are the principal fatal outcomes.
- **Prognostic factors (coronary-direct):** plaque burden ≥70%, minimal luminal area ≤4.0 mm^2, and thin-cap fibroatheroma morphology independently predict nonculprit events (PROSPECT, F001); low endothelial shear stress adds risk (PMID: 28917684); CAC progression predicts hard CHD (F014).
- **Prognostic biomarkers:** LDL-C/apoB (modifiable driver), Lp(a), hs-CRP (residual inflammatory risk), troponin, serum urate.
- **Modifiability:** Prognosis is strongly improved by LDL lowering (−21% MVE per 1 mmol/L, F013), anti-inflammatory therapy (F011/F012), and antithrombotics.
- **Complications:** MI, heart failure (predictable from CAC-derived chamber ratios, PMID: 41591983), arrhythmia, sudden death.

12. Treatment

Pharmacotherapy — lipid lowering (causal, LDL-dependent; MAXO:0000262 lipid-lowering agent therapy)

Drug class	Example	Mechanism	Key evidence
Statins	atorvastatin	HMG-CoA reductase inhibition	CTT: *"a 21% (RR 0.79, 95% CI 0.77-0.81) proportional reduction"* in MVE per 1 mmol/L LDL (PMID: 30712900)
PCSK9 inhibitors	evolocumab, alirocumab	↑ hepatic LDLR	GLAGOV coronary regression (F002, PMID: 27846344); PACMAN-AMI lesion stabilization (PMID: 39221516)
ACL inhibitor	bempedoic acid	inhibits ATP-citrate lyase	CLEAR: HR 0.75 per 1 mmol/L LDL, matching statins (PMID: 38960508)
Ezetimibe	—	NPC1L1 inhibition	Additive LDL lowering

Benefit **tracks the absolute magnitude of LDL-C reduction regardless of mechanism** and holds in patients ≥75 yr (RR 0.74 per 1 mmol/L; PMID: 33186535).

Anti-inflammatory therapy (causal, lipid-independent)

- **Canakinumab (anti-IL-1β):** CANTOS reduced events without lowering lipids — *"Canakinumab did not reduce lipid levels from baseline"* (PMID: 28845751); total-event rate ratios ~0.78–0.80 (PMID: 33004131).
- **Colchicine (0.5 mg/day, FDA-approved 2023):** COLCOT and LoDoCo2 reduced MACE — *"randomised colchicine trials such as COLCOT and LoDoCo2 showed reductions in major adverse cardiovascular events in patients with recent myocardial infarction and chronic coronary disease, respectively"* (PMID: 42454467).
- **Discordant/null control:** low-dose methotrexate (CIRT) was **null** (PMID: 23874021 rationale), showing the effective axis is specifically IL-1β→IL-6→CRP, not anti-inflammation broadly (F011).

RNA-based / emerging

- **Lp(a)-lowering:** olpasiran (siRNA, OCEAN(a), NCT05581303) and pelacarsen (ASO, Lp(a) HORIZON, NCT04023552) in outcome trials (PMID: 42016317).

Antithrombotic

Antiplatelet therapy (aspirin, P2Y12 inhibitors) and anticoagulation address the terminal thrombotic route (MAXO: antiplatelet therapy).

Surgical / interventional (MAXO: percutaneous coronary intervention; coronary artery bypass grafting)

- **PCI with drug-eluting stents** and **CABG**. **Key nuance (F017):** in *stable* CAD with moderate–severe ischemia, *"an initial invasive strategy does not reduce cardiovascular mortality or myocardial infarction compared with optimized medical therapy"* (PMID: 42099494); benefit is symptom relief (also sham-controlled ORBITA). Revascularization remains indicated for ACS, left-main, high-risk anatomy, and refractory symptoms. Chronic-total-occlusion PCI is a specialized subset with distinct procedural profiles (PMID: 42309488).

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13. Prevention

- **Primary prevention:** risk-factor modification targeting the nine INTERHEART factors (F015) — smoking cessation, lipid/apoB lowering, blood-pressure and glycemic control, weight/diet/activity. Lp(a) measurement for risk stratification.
- **Secondary prevention:** intensive LDL lowering to very low targets, anti-inflammatory therapy (colchicine) in selected post-MI/chronic coronary patients, antithrombotics, cardiac rehabilitation.
- **Tertiary prevention:** guideline-directed medical therapy to prevent recurrent events and heart failure; hs-CRP-guided identification of residual inflammatory risk.
- **Screening / risk stratification:** CAC scoring (MESA-validated, F014); polygenic risk scores (emerging); universal one-time Lp(a).
- **Behavioral / public health:** population-level tobacco control, dietary policy, physical-activity promotion — urgent in low-SDI regions with rising young-adult burden (PMID: 42483021).

- **Not applicable:** immunization (no infectious etiology).

14. Other Species / Natural Disease

- **Taxonomy:** Naturally occurring coronary atherosclerosis with thrombosis is largely a human condition; rare in most laboratory species. Relevant orthologs in **Mus musculus (NCBI:txid10090)**: *Apoe* (Gene ID 11816), *Ldlr* (16835), *Pcsk9* (100102). **Lpa has no rodent ortholog** (F016).
- **Larger animals with true coronary lesions:** WHHL rabbit (LDLR-mutant), Ossabaw/Yucatan **pigs**, and **nonhuman primates** develop coronary atherosclerosis more analogous to humans (F016).
- **Comparative pathology:** Rodent lesions form at the aortic root/arch and brachiocephalic artery and **rarely rupture or thrombose spontaneously**, limiting fidelity to human coronary events.
- **Zoonotic potential:** none (non-infectious, non-transmissible).

15. Model Organisms

Standard models (F016): hyperlipidemia-driven mice — *Apoe*$^{-/-}$ and *Ldlr*$^{-/-}$ on Western/pro-atherogenic diets, and humanized **APOE*3-Leiden.CETP** (human-like lipoprotein metabolism); PCSK9-AAV overexpression induces atherogenesis without germline editing. *"APOE*3-Leiden.CETP mice, a well-established model for human-like lipoprotein metabolism"* (PMID: 40460236).

Model	Type	Recapitulates	Does NOT recapitulate
Apoe$^{-/-}$ mouse	Knockout	Lipid-driven aortic plaque, foam cells	Epicardial coronary lesions; spontaneous rupture/thrombosis
Ldlr$^{-/-}$ mouse	Knockout	Diet-responsive hypercholesterolemia + plaque	Coronary events
APOE*3-Leiden.CETP	Humanized transgenic	Human-like lipoproteins, plaque	Coronary thrombosis
Mertk-KD;Apoe$^{-/-}$	Compound mutant	Defective efferocytosis → necrotic core (F008)	Coronary localization
WHHL rabbit / Ossabaw pig / NHP	Spontaneous/ diet	**True coronary lesions**	Cost, throughput

Applications: dissecting apoB retention, foam-cell biology, efferocytosis (MerTK), SMC lineage plasticity (dual lineage tracing, PMID: 41648299), and hemodynamic endothelial dysfunction. **Limitations:** the dominant murine models do not produce spontaneous coronary plaque rupture or MI, so terminal-route mechanisms (rupture vs erosion) are studied primarily by **human coronary OCT** in vivo (F003). Negative-control model result: PUFA-synthesis-deficient (*fads2*$^{-/-}$) mice remain atherosclerosis-prone when crossed to *Apoe*$^{-/-}$/*Ldlr*$^{-/-}$ — hypercholesterolemia dominates (PMID: 34530175).

Resources: MGI, IMPC/KOMP, IMSR, Alliance of Genome Resources.

Mechanistic Model / Interpretation

The synthesis across 17 findings supports a **staged, multi-arm causal model** in which **initiation, progression, stability, and acute thrombosis are distinct processes** with distinct evidence:

1. **Initiation is apoB-driven and hemodynamically localized.** Human genetics (PCSK9 LoF, F009; LPA, F010) and randomized LDL-lowering (F013, F002) establish apoB/LDL causality at the highest tier; direct human coronary imaging (F007) shows low wall shear stress plus lipid content accelerates coronary plaque growth. These converge on a strong causal edge: **apoB retention + disturbed flow → coronary plaque**.
2. **Progression is governed by cellular handling of lipid and dead cells.** Defective **MerTK efferocytosis** (mouse, F008) and **oxLDL-driven foam-cell formation** (in vitro, F008) expand the necrotic core; **SMC-to-macrophage-like transdifferentiation** (mouse/human, F004) thins the fibrous cap. These are mechanistically compelling but **anatomically indirect** (mouse aorta, cultured cells) — they explain *how* human coronary composition arises without proving coronary causality alone.
3. **Inflammation is an independent causal arm.** CANTOS (F011) and colchicine trials (F012) reduce human coronary events *without* lipid change, while the null CIRT/methotrexate result isolates the **IL-1β→IL-6→CRP** axis. IL-1β can also feed back on initiation by inducing coronary-endothelial LDL transcytosis (in vitro/mouse, PMID: 38989581).
4. **Terminal events are composition-, not stenosis-, dependent, with two routes.** PROSPECT (F001) shows angiographically mild lesions cause future events when plaque burden/necrotic-core/thin-cap features are present; human coronary OCT (F003) resolves **rupture (~2/3)** vs **erosion (~1/3)** as biologically distinct triggers of thrombosis.
5. **Therapeutic corollary:** because stenosis is not the driver of hard events, **revascularization relieves symptoms but does not reduce death/MI in stable CAD** (ISCHEMIA, F017), whereas systemic apoB lowering and anti-inflammation modify the biology and reduce events.

Terminal-route detail: rupture vs erosion

Feature	Rupture	Erosion
Cap	Thin (<65 μm), disrupted	Intact
Necrotic core	Large	Small/absent
Inflammation	Macrophage-rich	Less; neutrophil/NET-linked
Matrix	Lipid	Proteoglycan/SMC/ hyaluronan
Thrombus	Often occlusive	Often mural/less occlusive
Frequency in ACS	~2/3	~1/3
Evidence	T1 OCT/pathology (PMID: 29332908, PMID: 24631511)	T1 OCT; weaker mechanism

Genuine competing hypotheses

- **"Response-to-retention" (apoB-centric) vs "inflammation-primary":** the evidence supports these as **complementary, both causal** arms. Best synthesis: apoB is the initiating cause; inflammation is a required amplifier (Lp(a) mediates only 1.3–4.8% of the IL-6→ASCVD effect, PMID: 41932221, arguing for independence).
- **Rupture-dominant vs erosion-inclusive paradigm:** OCT data force inclusion of erosion as a mechanistically separate, potentially antithrombotic-manageable route.
- **Macrophage origin:** whether lesional "macrophages" are monocyte- vs SMC-derived (F004) remains partly unresolved and matters for target selection.

Evidence Base (Key Literature)

PMID	Role	Contribution
16554528	Supports	PCSK9 LoF → 88%/47% lower CHD (LDL causality)
27846344	Supports	GLAGOV: PCSK9i regresses coronary atheroma (IVUS)
30712900	Supports	CTT: −21% MVE per 1 mmol/L LDL
28845751	Supports	CANTOS: IL-1β inhibition, lipid-independent event reduction
42454467	Supports	Colchicine (COLCOT/LoDoCo2) reduces MACE
21247313	Supports	PROSPECT: composition > stenosis (coronary-direct)
36575921	Supports	Low WSS + lipid → coronary plaque growth (coronary-direct)
29332908	Supports	Rupture vs erosion terminal routes (coronary OCT)
23500326	Supports	MESA: CAC progression predicts CHD
18334475	Supports	INTERHEART: 9 factors = >90% MI PAR
37197843	Supports	CHIP → ASCVD risk
18451332	Supports (model)	MerTK efferocytosis failure → necrosis (mouse)
41165871	Supports	SMC-derived macrophage-like cells destabilize plaque
42099494	Supports (null)	ISCHEMIA: revascularization no death/MI benefit in stable CAD
41932221	Challenges/ constrains	Lp(a) mediates only 1.3–4.8% of IL-6→ASCVD (independence)
34530175	Constrains (model)	Hypercholesterolemia dominates over PUFA effects

Suggested Ontology Terms

Domain	Term	ID
Disease (anchor)	coronary atherosclerosis	**MONDO:0021661**
Disease (complication)	myocardial infarction	MONDO:0005068
Cell	vascular associated smooth muscle cell	**CL:0000359**
Cell	macrophage / foam cell	CL:0000235
Cell	blood vessel endothelial cell	CL:0000071
Process	lipid storage (foam cell)	**GO:0019915**
Process	nitric oxide biosynthetic process	**GO:0006809**
Process	cholesterol efflux	GO:0033344
Process	apoptotic cell clearance (efferocytosis)	GO:0043277
Anatomy	coronary artery	UBERON:0001621
Anatomy	tunica intima	UBERON:0004638
Chemistry	low-density lipoprotein particle	CHEBI:39026
Chemistry	cholesterol	CHEBI:16113
Phenotype (HPO)	Coronary artery atherosclerosis	HP:0001677
Phenotype (HPO)	Myocardial infarction	HP:0001658
Phenotype (HPO)	Angina pectoris	HP:0001681
Procedure (MAXO)	Lipid-lowering agent therapy	MAXO:0000262

Limitations and Knowledge Gaps

1. **Vascular-bed indirectness.** Much mechanistic detail (efferocytosis, SMC switching, shear-endothelial signaling) derives from **mouse aorta or cultured cells**, not epicardial coronary tissue. Per the scope guardrails, carotid/aortic human plaque and mouse-carotid disturbed-

flow work (e.g.,

P 38639096

,

P 40594772

) remain **transferable atherosclerosis evidence only**, not human coronary evidence.

2. **Imaging surrogates ≠ cellular mechanism.** IVUS/OCT/NIRS/CAC quantify composition and predict events but do not prove a specific cellular mediator; GLAGOV/PACMAN show plaque regression, not a demonstrated causal cell type.
3. **Erosion biology underexplored.** The ~1/3 of ACS due to erosion has fewer mechanistic and therapeutic data than rupture; targeted therapy is nascent.
4. **Model fidelity.** Dominant murine models lack spontaneous coronary rupture/thrombosis (F016); terminal-route mechanisms rest primarily on human in-vivo OCT and pathology.
5. **CHIP and SMC-origin questions.** Causality in humans for CHIP is association + mouse mechanism; the monocyte- vs SMC-derived macrophage question (F004) is unresolved.
6. **Residual risk.** Even with excellent LDL control, events persist (motivating Lp(a) and inflammation targeting); the full mediator set of residual risk is incompletely defined.
7. **Citation caveat.** One snippet (P 30482443) flagged a quote-validation mismatch and should be re-verified before KB ingestion.

Proposed Follow-up Experiments / Actions

1. **Coronary-specific causal localization:** apply spatial transcriptomics and genetic-lineage inference to **human epicardial coronary plaques** (not carotid/aortic surrogates) to test whether SMC-to-macrophage transitions and IRF7 activity localize to coronary rupture/erosion sites.
2. **Erosion-directed intervention trial:** OCT-guided randomization of antithrombotic-only vs stenting in confirmed erosion (extending EROSION-concept designs) with hard endpoints.
3. **Lp(a)-lowering outcome readout:** analyze OCEAN(a) (olpasiran) and Lp(a) HORIZON (pelacarsen) to test whether genetically causal Lp(a) reduction reduces coronary events, with plaque-composition endpoints.

4. **Inflammation × lipid factorial trials:** test IL-6-pathway inhibition (e.g., ziltivekimab) plus intensive LDL lowering to quantify additive coronary benefit, exploiting the demonstrated independence of the two arms (PMID: 41932221).
5. **Efferocytosis restoration:** test pro-efferocytic agents (MerTK-stabilizing or CD47-axis modulators) in large-animal coronary models (pig/NHP) with necrotic-core imaging endpoints.
6. **CHIP-stratified anti-inflammatory therapy:** prospectively test whether TET2/DNMT3A CHIP carriers derive enhanced benefit from IL-1β/IL-6 inhibition.
7. **CAC/AI imaging integration:** validate AI-derived CAC-scan biomarkers (chamber ratios, hepatic steatosis) for coronary + heart-failure risk in prospective trials.

Bottom line

Coronary atherosclerosis (`MONDO:0021661`) is an apoB-initiated, shear-patterned, inflammation-amplified intimal disease whose **composition — not stenosis** — governs acute risk through **two distinct terminal routes (rupture and erosion)**. The causal backbone (apoB via PCSK9/LPA genetics and LDL trials; IL-1β/IL-6 via CANTOS/colchicine) is proven in humans, while the cellular mechanism (SMC switching, efferocytosis, foam-cell biology) is robustly established in models/carotid tissue and awaits coronary-localized confirmation.

Report scope locked to `MONDO:0021661` coronary atherosclerosis. Evidence tiers, vascular beds, and null/discordant results are stated explicitly per the issue-specific guardrails; reviews were treated as orientation and primary studies anchor each claim.
