KARDIOVASKULÁRNÍ PREVENCE

Dyslipidemie a Ateroskleroza

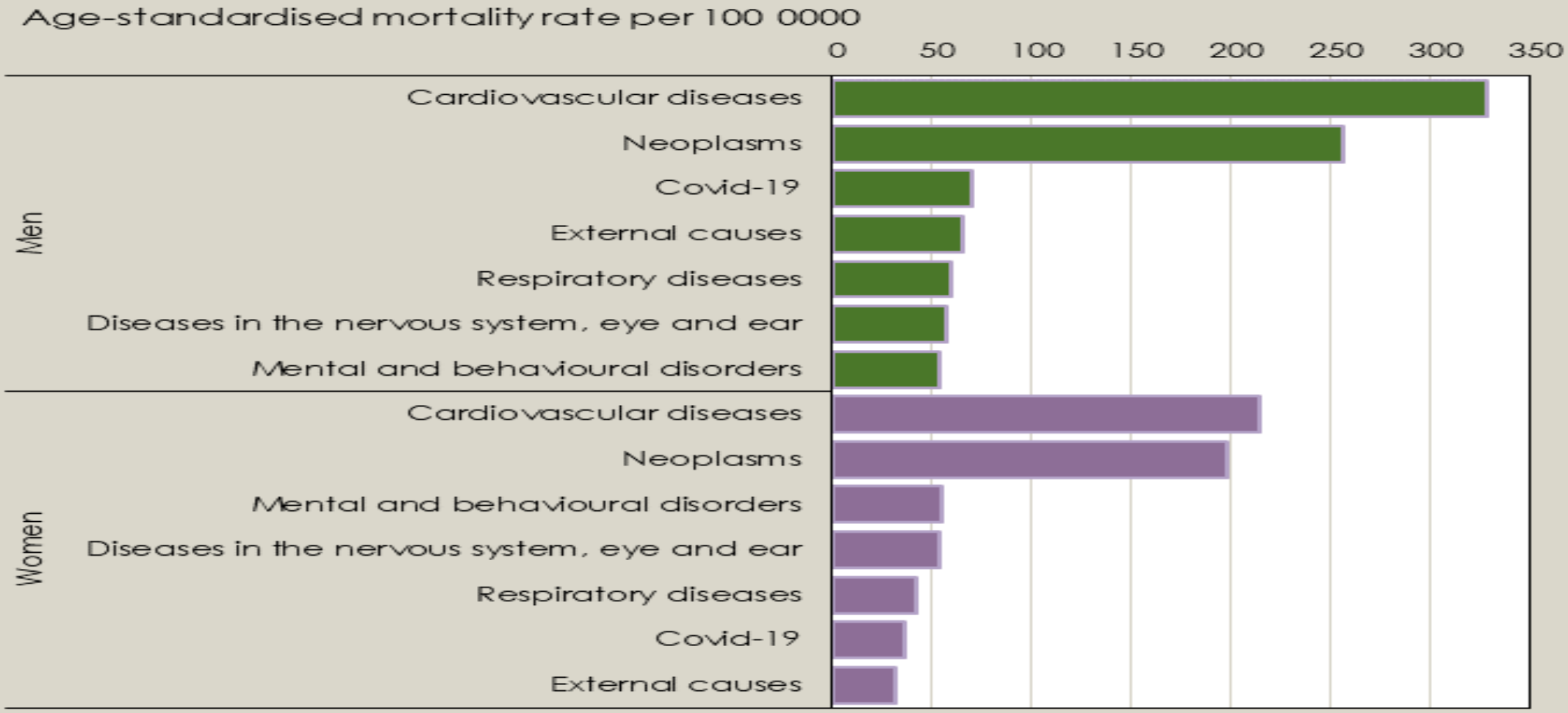
Richard Češka
Centrum preventivní kardiologie
III.Interní klinika 1.LF UK a VFN
Praha

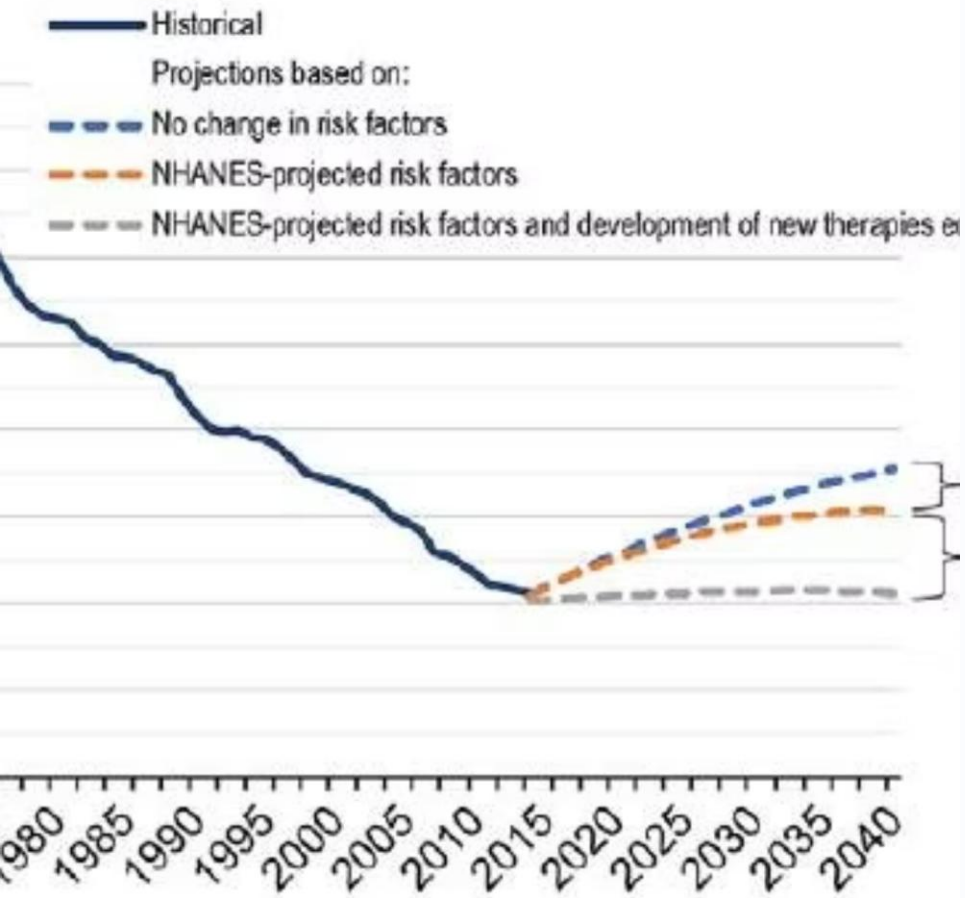


Illustrative arterial histology

CVD – leading cause of death worldwide

Figure 2. Mortality rate leading causes of death 2021





Mortality projections for three scenarios. CVD,
ar disease; NHANES, national health and nutri
survey. Figure depicts the historical rates of C
d the projected rates under three scenarios. H
n publication by Ma et al.[25] Future increases v
driven by a rapidly increasing CVD prevalence

Mortality Projections Through 2040

Clinical Cardiology. 2019;42:47–55.

Three projection scenarios illustrate CVD mortality through 2040. Without innovation equivalent to statins, rising risk factor prevalence will drive rates higher. New therapies — and better risk factor control — are both essential to bending the curve downward.

Atherosclerosis is the leading cause of cardiovascular death

A chronic inflammatory disease of the arterial wall, often silent for decades.

CORONARY ARTERIES

Myocardial infarction

Plaque complications can abruptly interrupt myocardial perfusion.

CEREBRAL CIRCULATION

Ischemic stroke

Atherothrombosis and embolization threaten brain perfusion.

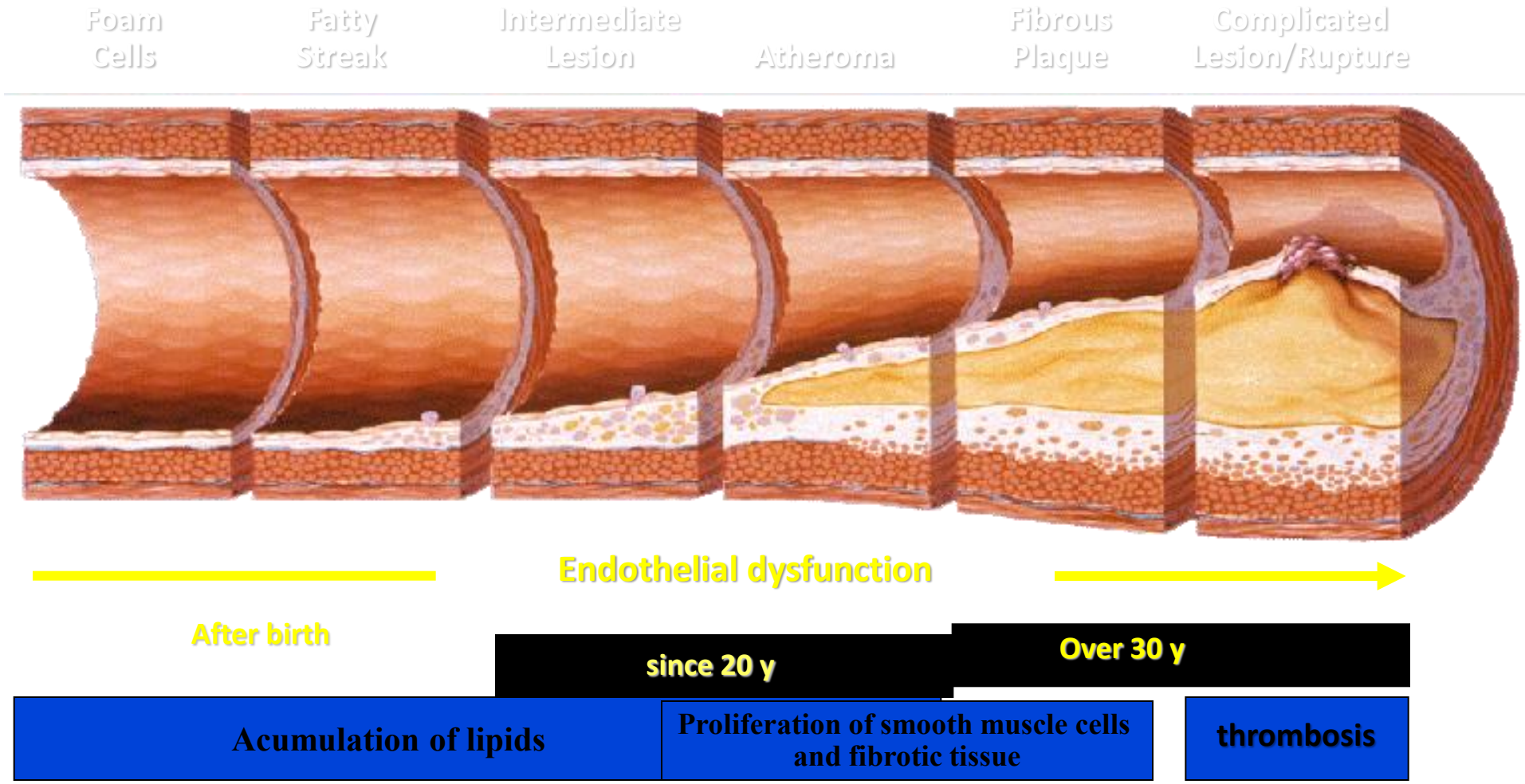
PERIPHERAL ARTERIES

Peripheral artery disease

Chronic obstruction or acute thrombosis compromises limb perfusion.

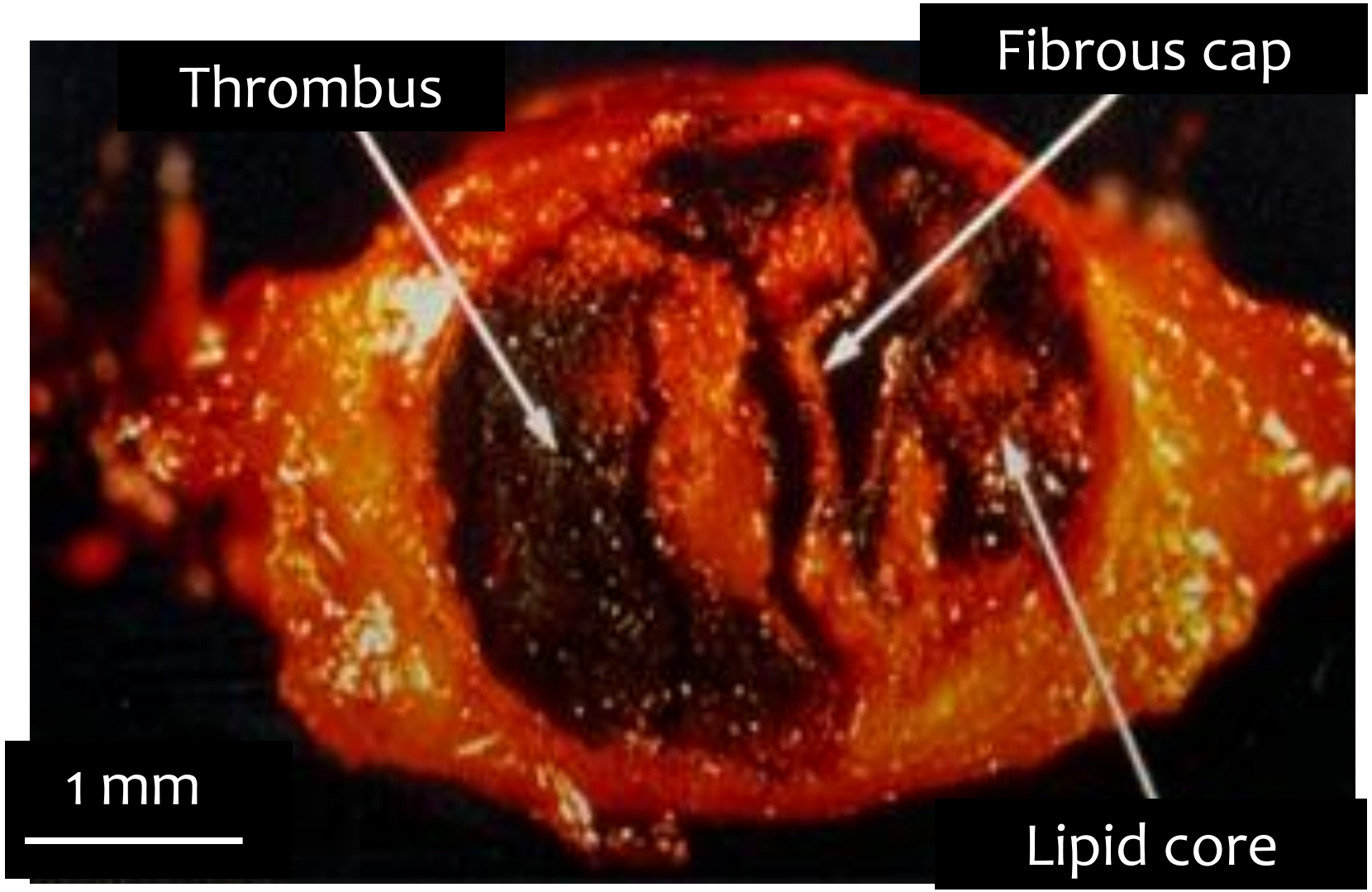
Plaque biology, not just stenosis, drives clinical events.

ATHEROGENESIS



Adapted from Stary HC et al. *Circulation* 1995;92:1355-1374.

Rupture of atherosclerotic plaque and thrombosis



Mummy of pharaohs - atherosclerosis



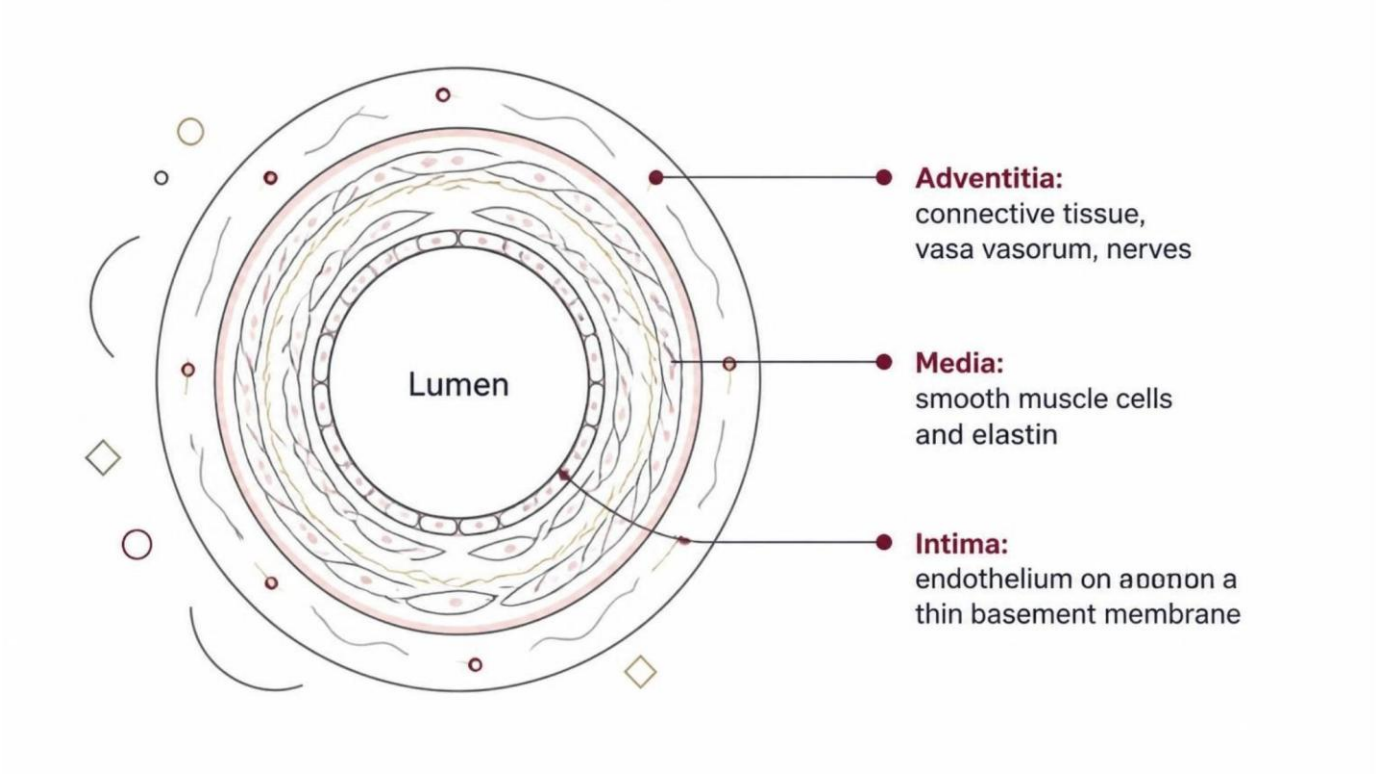
CT scans of ancient mummies have revealed arterial calcification, showing atherosclerosis is not only a modern disease.

Mummy of pharaohs - CVD



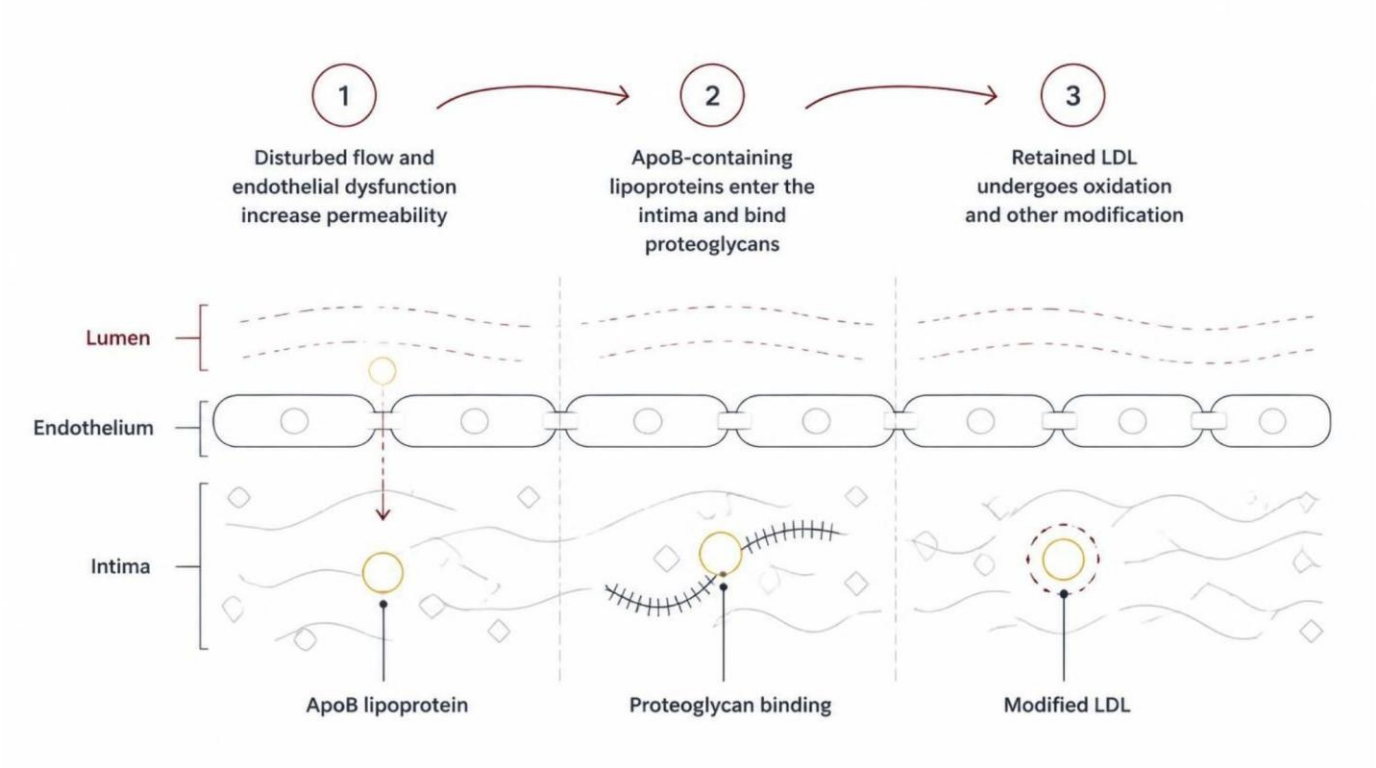
CT reconstruction shows calcified coronary, aortic and iliac arteries in an ancient mummy.

The healthy artery has three layers



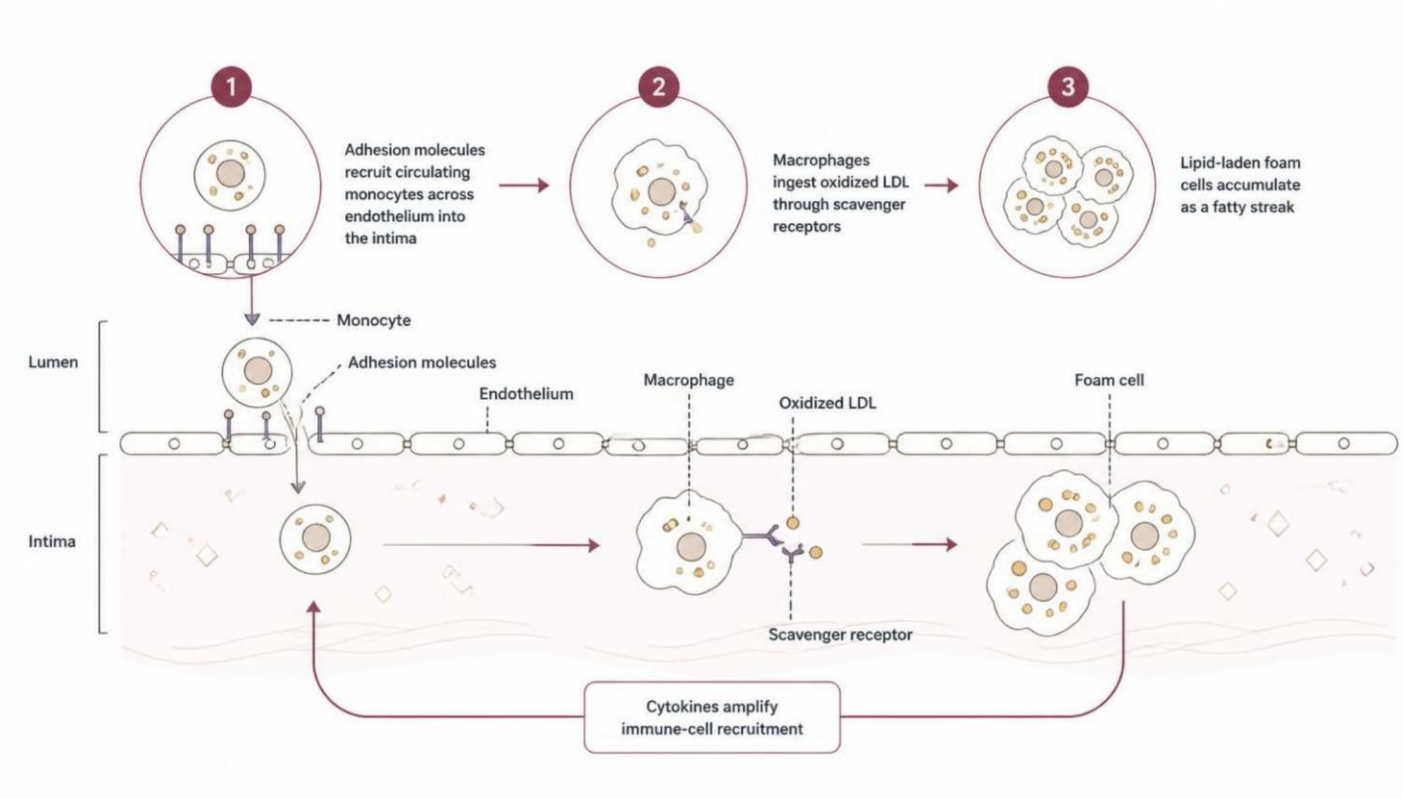
Intact endothelium maintains an anti-inflammatory, anti-thrombotic surface.

Injury starts with LDL retention in the intima



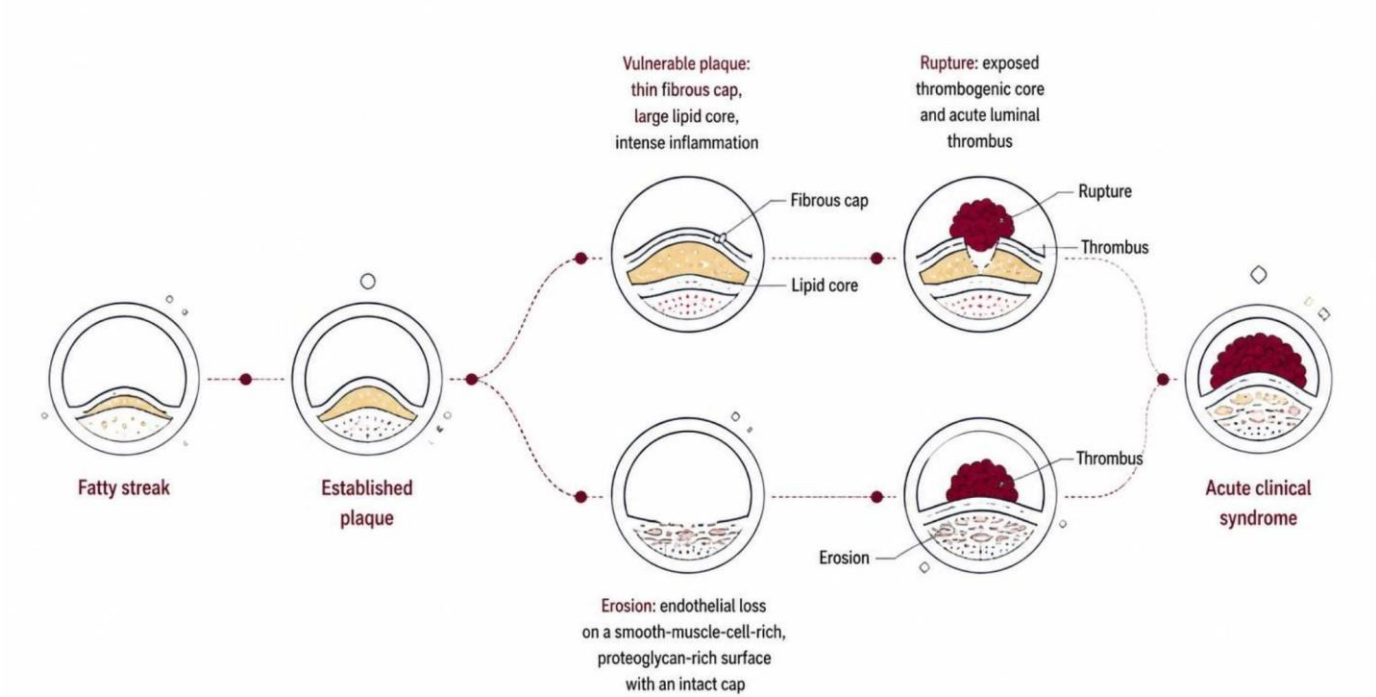
Retention of lipoproteins is the initiating step (response-to-retention hypothesis).

Inflammation turns macrophages into foam cells



Lipid retention and immune recruitment reinforce one another.

Rupture or erosion triggers the clinical event



Stable flow-limiting plaques often cause angina; plaque disruption and thrombosis can cause acute syndromes.

A risk factor raises probability, and causation needs more

Epidemiology, notably the Framingham Heart Study, established the major cardiovascular risk factors.

PREDICTION

Risk factor or marker

Identifies a higher probability of disease.

A risk marker may predict events without causing the disease.

CAUSATION

Causal factor

Acts through a biological mechanism.

Genetic evidence and intervention effects strengthen the causal inference.

Risk is multiplicative: factors compound one another.

Modifiable and non-modifiable risk factors

BASELINE SUSCEPTIBILITY

Non-modifiable

- Age and male sex
- Family history and genetics

MAJOR TREATMENT PRIORITIES

Modifiable

- Dyslipidemia and hypertension
- Diabetes and smoking

BEHAVIORAL CONTRIBUTORS

Also modifiable

- Obesity and inactivity
- Unhealthy diet

ADDITIONAL CONTRIBUTORS

Emerging factors

- Chronic kidney disease
- Chronic inflammation and air pollution

RISK

Clinical assessment

DECISION PATHWAY

Total risk guides how hard we treat

Treat the patient's overall cardiovascular risk, not a single lipid value.

1

Estimate

Use a validated, population-appropriate score such as SCORE2 or the pooled cohort equations.

2

Enhance

Consider family history, Lp(a), CKD, and inflammatory disease.

3

Refine

Coronary calcium scoring can clarify an uncertain decision at intermediate risk.

Established ASCVD and other high-risk conditions may determine treatment without a primary-prevention risk score.

LDL-C is a causal factor, supported by multiple lines of evidence

≈22%

relative event reduction

Per 1 mmol/L LDL-C lowered in meta-analyses of statin trials.

Genetics

Lifelong low LDL, including PCSK9 loss-of-function, confers much lower risk.

Familial hypercholesterolemia

Very high LDL produces premature atherosclerotic disease.

Randomized trials

Lowering LDL reduces cardiovascular events.

Relative benefit is distinct from absolute benefit, which depends on baseline risk.

Dyslipidemia has several clinical phenotypes

PHENOTYPE	TYPICAL PATTERN	CLINICAL IMPLICATION
High LDL-C	Polygenic or familial hypercholesterolemia	FH affects about 1 in 250-300 people
Atherogenic dyslipidemia	High triglycerides, low HDL-C, small dense LDL	Typical of insulin resistance
Elevated lipoprotein(a)	Predominantly genetically determined	Atherogenic and prothrombotic
Severe hypertriglyceridemia	Marked triglyceride elevation	Pancreatitis risk, especially above 500 mg/dL

Phenotypes can coexist; LDL-C alone does not describe the entire atherogenic burden.

Diagnosis: who to test and what to measure

1 Measure the lipid profile

Fasting or non-fasting total cholesterol, LDL-C, HDL-C, and triglycerides. Assess adults undergoing cardiovascular risk evaluation.

2 Capture particle burden and inherited risk

Non-HDL-C and apoB reflect total atherogenic burden. Measure Lp(a) at least once in every adult.

3 Exclude secondary causes

Hypothyroidism, nephrotic syndrome, cholestasis, drugs, and alcohol.

4 Look for familial hypercholesterolemia

Suspect FH with LDL-C above 190 mg/dL, tendon xanthomas, or a suggestive family history.

A stepwise approach and the triglyceride question

1

High-intensity statin

Start with the maximally tolerated regimen.

2

Add ezetimibe

If LDL-C remains above the risk-based goal.

3

Add a PCSK9 inhibitor

If still above target despite combination therapy.

TG above 150 mg/dL

Address lifestyle and secondary causes first. Icosapent ethyl reduced events in selected high-risk, statin-treated patients with elevated TG in REDUCE-IT.

TG above 500 mg/dL

Consider fibrates or prescription omega-3s to reduce triglycerides and pancreatitis risk.

CLINICAL PRACTICE

Atherosclerosis and dyslipidemia

KEY TAKEAWAYS

Key takeaways for practice

MECHANISM

Retention precedes disease

Atherosclerosis begins with LDL retention and inflammation, building over decades.

RISK

Treat the whole patient

Assess total cardiovascular risk and align LDL-C targets with the risk category.

DETECTION

Find inherited risk

Measure Lp(a) once and screen for familial hypercholesterolemia.

TREATMENT

Lower for longer

Lower LDL-C early and intensively; escalate treatment when the goal remains unmet.

Treatment targets scale with risk

RISK CATEGORY	LDL-C TARGET	REDUCTION REQUIREMENT
Very high risk	<1,4	At least a 50% reduction
High risk	<1,8	Also aim for at least a 50% reduction
Moderate risk	<2,6	Reach the risk-based goal
Low risk	<3,0	Reach the risk-based goal

ESC/EAS 2019 targets. US guidelines use treatment thresholds and percent reduction; apply the relevant local guideline.

Nonpharmacological Treatment

Lifestyle modification remains the essential foundation of LDL-C management. Dietary optimization — reducing saturated and trans fats, increasing fiber and plant sterols — combined with regular physical activity can achieve meaningful LDL-C reductions and should precede or accompany any pharmacological intervention.



Lifestyle is the foundation, and drugs do the heavy lifting

FOR EVERY PATIENT

Improve the metabolic profile

- Less saturated and trans fat; more fiber, fish, and nuts
- Weight loss and physical activity
- Smoking cessation and limited alcohol

FOR LDL-C GOAL ATTAINMENT

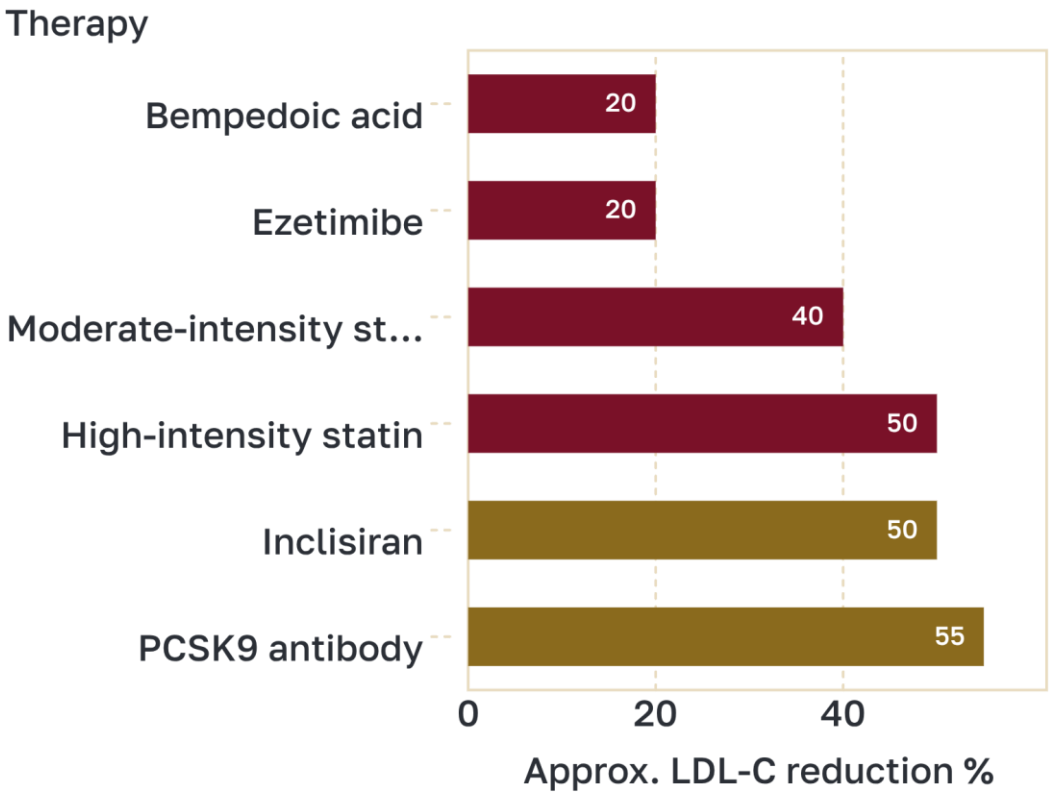
10–15%

Typical LDL-C lowering with lifestyle.

Usually insufficient alone in high-risk patients; add effective drug therapy rather than delaying escalation.

Lifestyle remains essential for triglycerides, HDL-C, and overall metabolic health.

Lipid-lowering drugs and what they achieve



- Statins are first line; about 30-55% lowering.
- Ezetimibe adds about 20% further lowering.
- Evolocumab or alirocumab lowers LDL-C about 50-60%.
- Inclisiran siRNA gives about 50% lowering with twice-yearly maintenance dosing.
- Bempedoic acid lowers LDL-C about 15-25%; useful in statin intolerance.

Typical approximate effects, not a head-to-head comparison. Added reductions act on the LDL-C remaining, not by simple addition.

A stepwise approach and the triglyceride question

1

High-intensity statin

Start with the maximally tolerated regimen.

2

Add ezetimibe

If LDL-C remains above the risk-based goal.

3

Add a PCSK9 inhibitor

If still above target despite combination therapy.

TG above 150 mg/dL

Address lifestyle and secondary causes first. Icosapent ethyl reduced events in selected high-risk, statin-treated patients with elevated TG in REDUCE-IT.

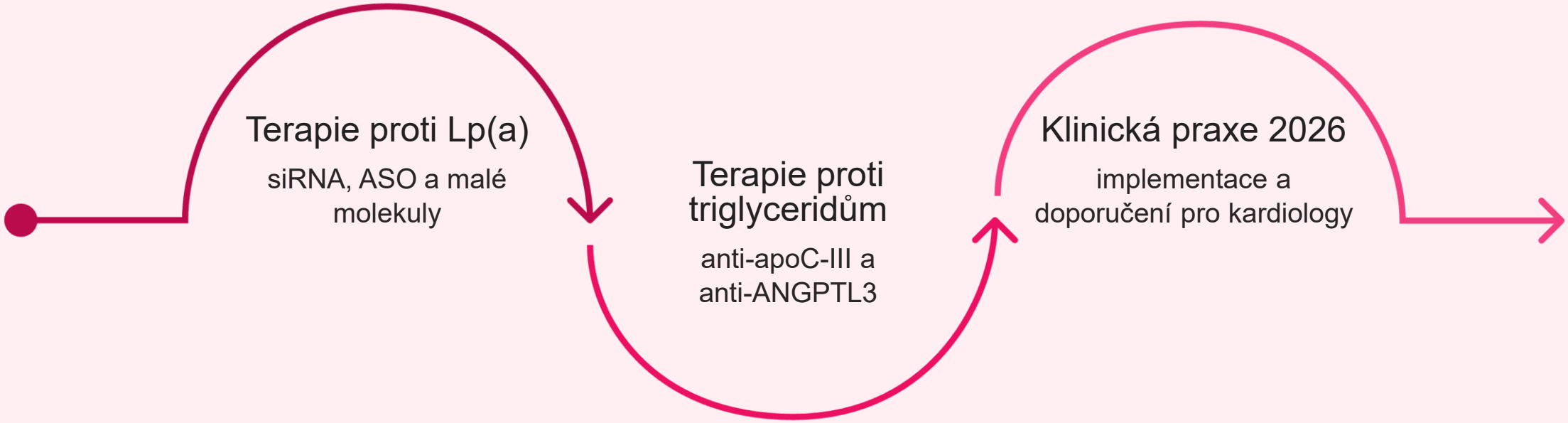
TG above 500 mg/dL

Consider fibrates or prescription omega-3s to reduce triglycerides and pancreatitis risk.

LIPIDOLOGIE 2026

Moderní farmakoterapie dyslipidemií: Lp(a) a triglyceridy

Přehled nejnovějších léků a molekul ovlivňujících lipoprotein(a) a triglyceridy — od RNA-cílených terapií po první perorální inhibitory. Určeno pro kardiology, lipidology a specialisty v oblasti kardiovaskulární medicíny.



LP(A) TERAPIE

RNA-cílené terapie: Nová éra léčby vysokého Lp(a)

Největší průlom v léčbě elevace Lp(a) představují **siRNA a antisense oligonukleotidy (ASO)**, které dosahují snížení Lp(a) o **80–98 %** — účinnost dosud nedosažitelná konvenčními hypolipidemikami. Všechny jsou určeny primárně pro pacienty s vysokým Lp(a) a prokázaným ASCVD. Většina molekul již vstoupila do fáze III nebo dokončila rozsáhlé fáze II s výsledky očekávanými v horizontu 2025–2027.

80–98%	20–30%	4
siRNA / ASO	PCSK9i	Fáze III
Snížení Lp(a) RNA-terapiemi	Snížení Lp(a) inhibitory PCSK9	Molekuly v pokročilých klinických zkouškách

LP(A) — SIRNA

Olpasiran (Amgen) — Nejvyšší účinnost třídy

Klíčová data

Snížení Lp(a): **~90–98 %**

Mechanismus: siRNA — cílení hepatální syntézy apo(a)

Studie fáze III: **OCEAN(a)** — probíhá

Sekundárně: zlepšení LDL-C a apoB

Klinický kontext

Olpasiran představuje momentálně **nejúčinnější molekulu** ve své třídě. Podává se subkutánně, typicky každé 3 měsíce. Studie OCEAN(a) zkoumá přínos na kardiovaskulární outcome u pacientů s ASCVD a Lp(a) ≥150 nmol/l. Výsledky budou klíčové pro regulatorní schválení a klinické guidelines.

Olpasiran je považován za „first-in-class" z hlediska hloubky snížení Lp(a) — téměř úplná suprese syntézy apo(a).

LP(A) — ASO & SIRNA

Pelacarsen, Zerlasiran & Lepodisiran

Pelacarsen (ASO, Novartis)

Snížení Lp(a): **~80 %**

Fáze III: **Lp(a)HORIZON** — výsledky **neprokazují ovlivnění KVO**. Jedná se o antisense oligonukleotid cílený na jaterní mRNA pro apo(a).

Zerlasiran (siRNA, Silence Therapeutics)

Snížení Lp(a): **~78 %**

Vedle Lp(a) zlepšuje LDL-C a apoB. Zaznamenány častější lokální reakce v místě vpichu v porovnání s jinými siRNA. Potenciálně vhodná alternativa pro specifické skupiny pacientů.

Lepodisiran (siRNA, Eli Lilly)

Snížení Lp(a): **~70–80 %**

Vyznačuje se **výjimečně dlouhým biologickým poločasem** — potenciálně umožňuje dávkování **1× ročně**, což by mohlo dramaticky zlepšit adherenci pacientů k terapii.

LP(A) — INOVACE

Muvalaplin — První perorální lék cílený na Lp(a)

Mechanismus účinku

Muvalaplin je **perorální small-molecule inhibitor** sestavení Lp(a) — blokuje nekovalentní interakci mezi apo(a) a apoB-100, čímž brání tvorbě kompletní Lp(a) partikule. Jedná se o zcela nový mechanismus — první neinjekční přístup k cílené inhibici Lp(a).

Klinická fáze

Aktuálně ve fázi II. Snížení Lp(a): **~65–70 %**. Výsledky jsou považovány za průlomové pro přijatelnost terapie v širší populaci.

Strategický přínos

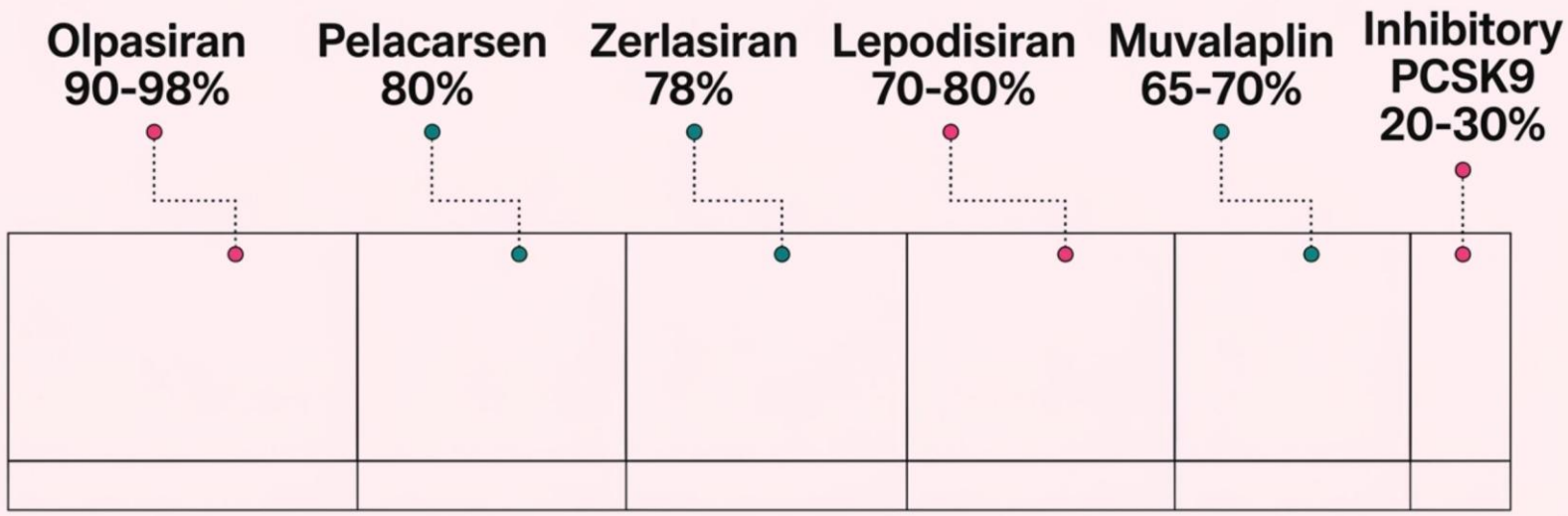
Perorální podávání eliminuje bariéru injekční aplikace a má potenciál oslovit miliony pacientů, kteří by jinak k léčbě nebyli indikováni nebo by ji odmítali. Pokud fáze III potvrdí bezpečnost a účinnost, muvalaplin by se mohl stát **zlatým standardem první linie** pro pacienty s mírně až středně zvýšeným Lp(a).

Muvalaplin je jediný lék cílený na Lp(a), který by mohl být podáván per os — zásadní výhoda pro dlouhodobou adherenci.

LP(A) — PCSK9I

PCSK9 Inhibitory a Lp(a): Limitovaný, avšak klinicky relevantní efekt

Inhibitory PCSK9 — evolocumab, alirocumab a inclisiran — snižují Lp(a) pouze o 20–30 %, což je výrazně méně než RNA-cílené terapie. Jejich primární indikací zůstává snížení LDL-C, kde dosahují redukce o 50–60 %. Přesto mohou být u pacientů se současnou elevací LDL-C a Lp(a) racionální volbou jako součást kombinované terapie — zvláště v současnosti, kdy specifické Lp(a)-cílené léky čekají na regulatorní schválení.



TRIGLYCERIDY — RNA TERAPIE

Průlom v léčbě hypertriglyceridémie: Anti-apoC-III a Anti-ANGPTL3

Největší pokrok v oblasti snižování triglyceridů přinášejí **RNA-cílené terapie namířené proti apoC-III a ANGPTL3** — klíčovým regulátorům lipoproteinové lipázy a clearance triglyceridů. Tyto molekuly dosahují snížení TG o **60–90 %** a jsou primárně určeny pro pacienty s těžkou hypertriglyceridémií, familiární chylomikronémií (FCS) nebo kombinovanou dyslipidemií.



Anti-apoC-III

apoC-III inhibuje lipoproteinovou lipázu → blokáda apoC-III zvyšuje clearance VLDL a chylomikronů. Klíčová molekula: **Olezarsen**.



Anti-ANGPTL3

ANGPTL3 inhibuje LPL a EL → blokáda snižuje TG, LDL-C i non-HDL-C. Klíčové molekuly: **Zodasiran, Plozasiran**.



Klinický potenciál

Snížení TG o 60–90 % s paralelním benefitem na apoB, LDL-C a non-HDL-C — potenciálně ovlivňující reziduální kardiovaskulární riziko.

TRIGLYCERIDY — KLÍČOVÉ MOLEKULY

Olezarsen, Zodasiran & Plozasiran

Olezarsen (ASO, Ionis)

Snížení TG: **~70–90 %**

Mechanismus: ASO proti apoC-III. Fáze III pro FCS dokončena — **schválení FDA/EMA očekáváno**. Výrazné snížení apoC-III, non-HDL-C a VLDL. Nejblíže ke klinické dostupnosti z celé třídy.

Zodasiran (siRNA, ANGPTL3)

Snížení TG: **~60 %**

Novinka roku 2026 — publikováno v *Nature Medicine*. Fáze I basket trial prokázal snížení TG, LDL-C i non-HDL-C. Vstup do fáze II/III se očekává v blízké budoucnosti. Nejnovější molekula s velmi slibným profilem.

Plozasiran (siRNA, ANGPTL3)

Snížení TG: **~60–80 %**

Fáze II s robustními výsledky — silný a trvalý efekt na TG i na LDL-C a apoB. Široký lipidový efekt jej předurčuje k léčbě kombinovaných dyslipidemií, kde je žádoucí simultánní ovlivnění více lipidových parametrů.

TRIGLYCERIDY — DOSTUPNÁ LÉČBA

Konvenční terapie triglyceridů: Současné možnosti v klinické praxi

Dostupné léky (2026)

Fibráty

Fenofibrát, bezafibrát: snížení TG o **30–50 %**. Dlouhodobě v praxi, pleiotropní efekty.

Icosapent ethyl (EPA)

Snížení TG o **20–30 %** + prokázaný CV benefit (studie REDUCE-IT). Standard péče u hypertriglyceridémie s vysokým rizikem.

GLP-1 agonisté

Mírné snížení TG (**10–20 %**) — přídatný metabolický efekt, primárně indikováni pro diabetes a obezitu.

SGLT2 inhibitory

Malé snížení TG, primarily kardiometabolický přínos přesahující lipidové účinky.

Zastaven vývoj: Vupanorsen

Vupanorsen (ASO proti ANGPTL3, Pfizer/Ionis) dosahoval účinného snížení TG (~50 %), avšak **program byl zastaven** kvůli závažným jaterním nežádoucím účinkům ve fázi II. Tato zkušenost zdůrazňuje důležitost jaterní bezpečnosti při vývoji ASO terapií namířených na hepatální cíle.

⚠ Vupanorsen: příklad, kdy příznivý lipidový profil nestačí — jaterní toxicita vedla k ukončení programu. Poučení pro vývoj dalších ASO molekul.

SHRNUTÍ 2026

Klinické Shrnutí: Nejperspektivnější Molekuly pro Praxi

🎯 Lp(a) — Top molekuly

01

Olpasiran

~90–98 % snížení Lp(a), fáze III (OCEAN(a))

02

Pelacarsen

~80 %, nejpokročilejší outcome studie Lp(a)HORIZON

03

Zerlasiran / Lepodisiran

~70–80 %, silné siRNA alternativy

04

Muvalaplin

~65–70 %, první perorální lék na Lp(a)

📉 Triglyceridy — Top molekuly

01

Olezarsen

~70–90 % snížení TG, nejblíže schválení

02

Zodasiran

~60 %, novinka 2026 (Nature Medicine), efekt i na LDL-C

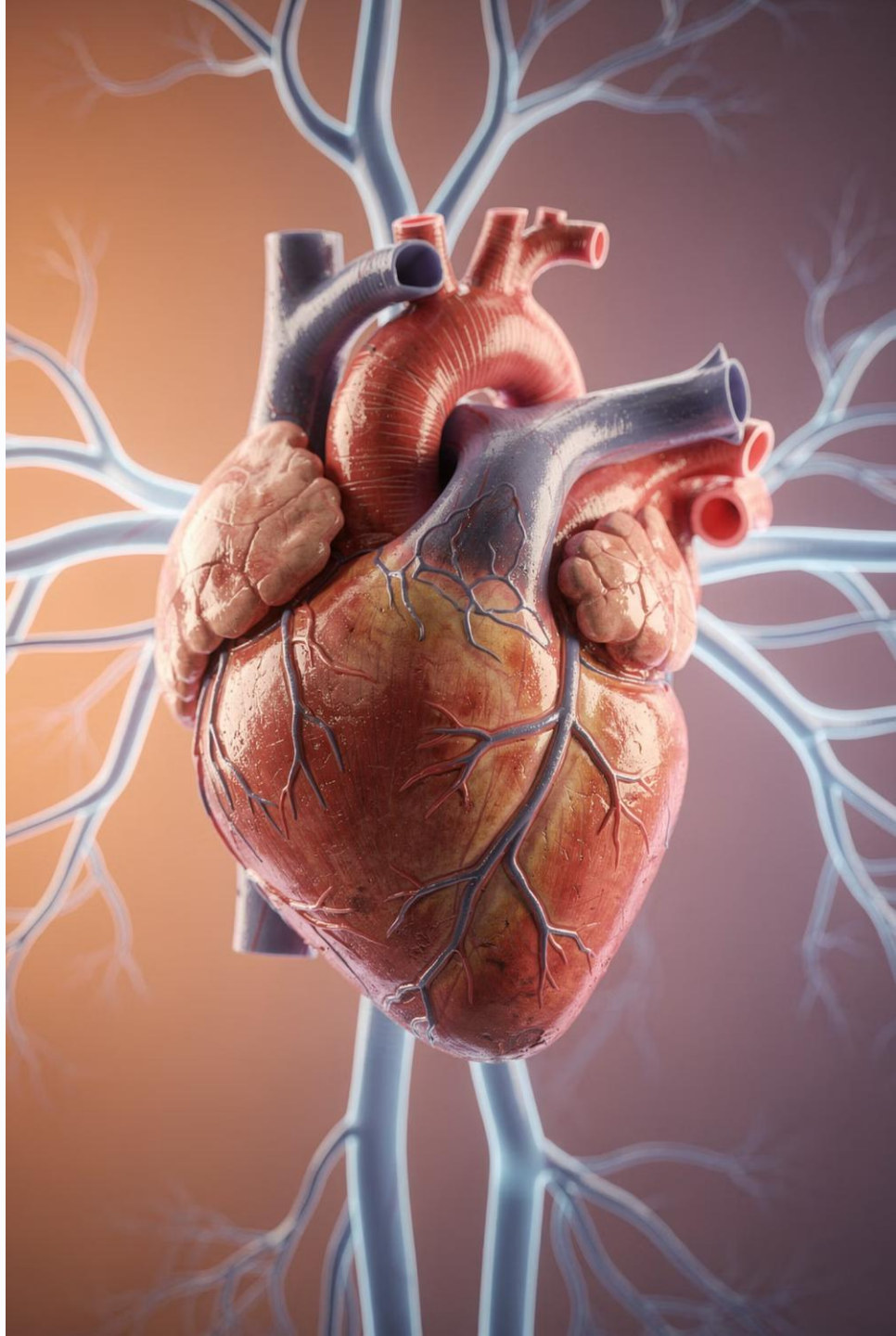
03

Plozasiran

~60–80 %, široký lipidový efekt, robustní fáze II

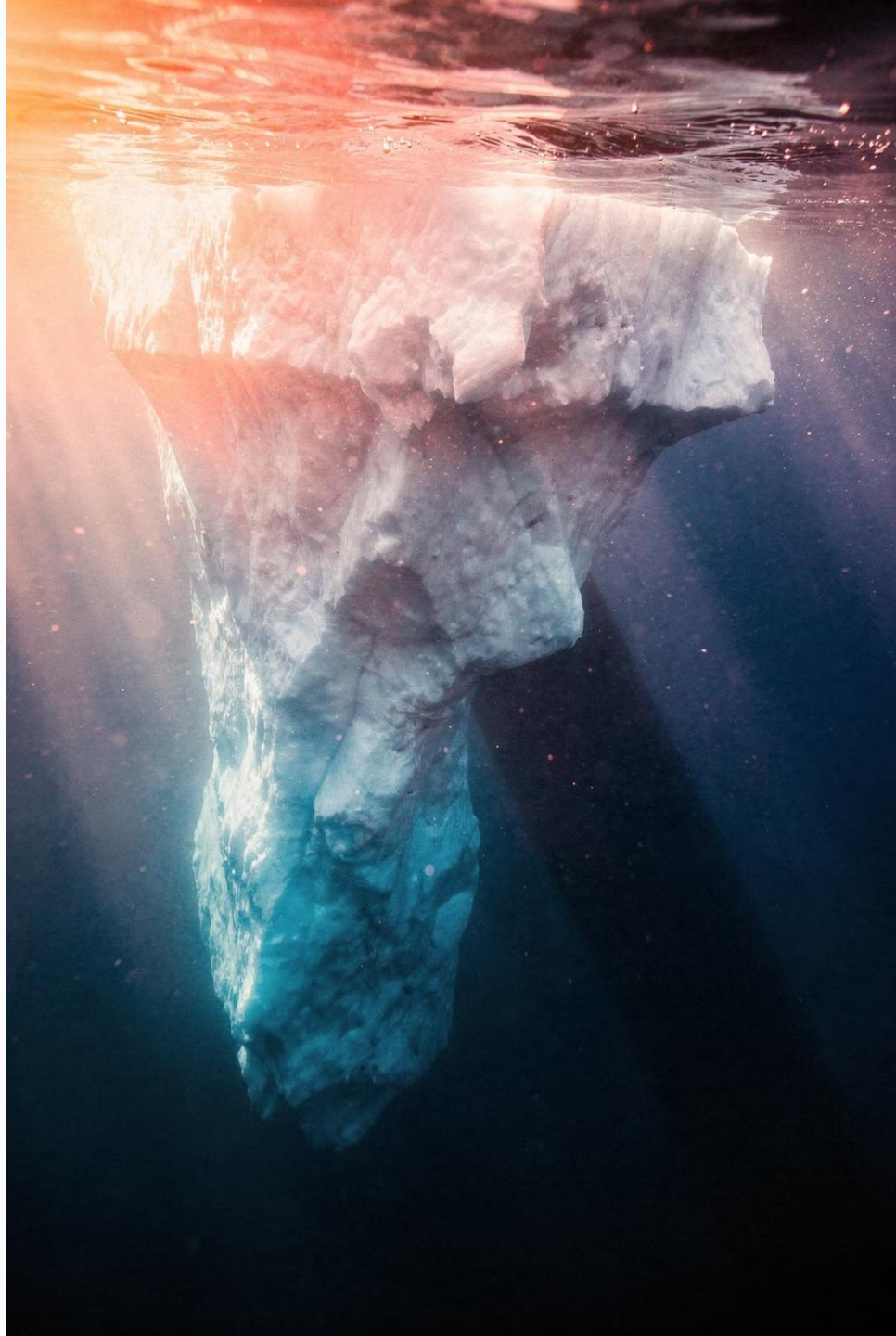
RNA-cílené terapie (siRNA a ASO) představují novou paradigmu léčby reziduálního kardiovaskulárního rizika spojeného s Lp(a) a těžkou hypertriglyceridémií.

LDL-C Lowering in 2026



LDL-C:
Killer No. 1

LDL cholesterol acts silently — no symptoms, no warning signs — progressively building plaque over decades before manifesting as a fatal cardiovascular event. Its silence is precisely what makes it so dangerous.



Atherosclerosis Risk Factors: A New Conceptual Framework

LDL-C — Proven Causal Factor

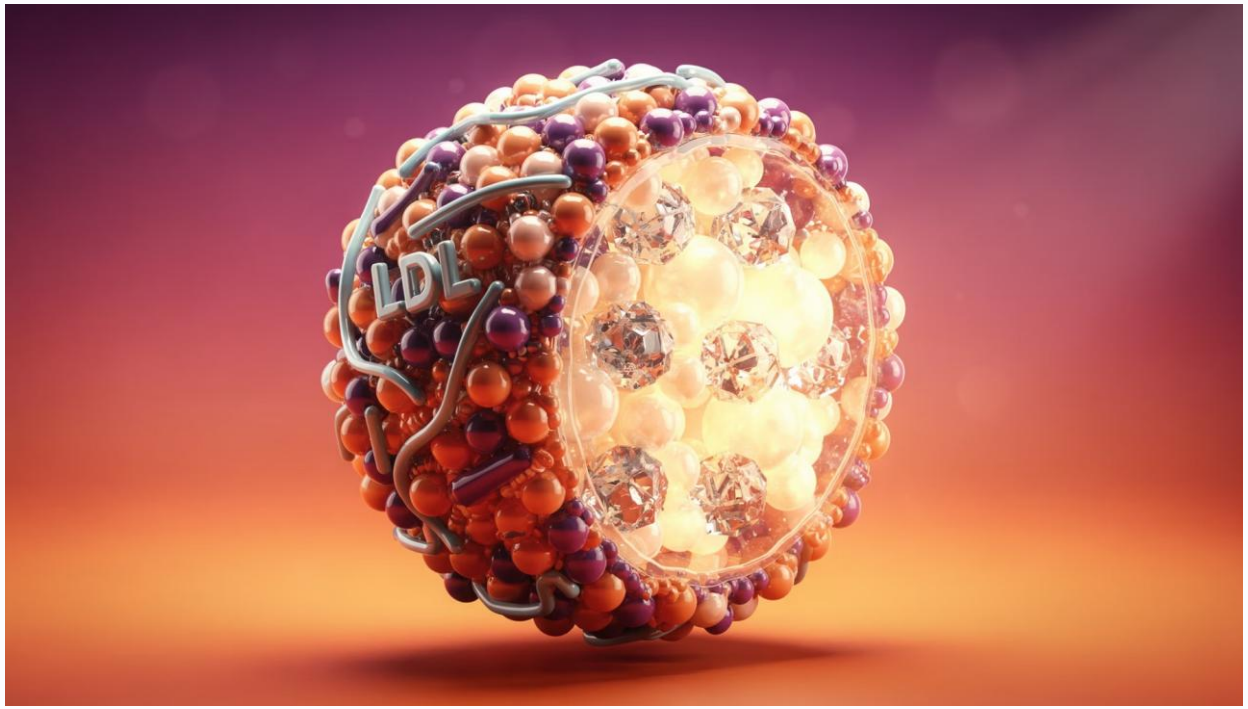
Genetic, epidemiologic, and clinical trial evidence establishes LDL-C as a direct cause of atherosclerotic CVD.

Accelerators

Smoking, diabetes, and hypertension amplify atherogenesis driven by LDL-C.

Biomarkers

Homocysteine and CRP are markers of risk — not independent causal drivers.



The LDL-C Treatment Landscape: A Historical Overview

Bile Acid Era

1970s: cholestyramine introduced

Enzyme Discovery

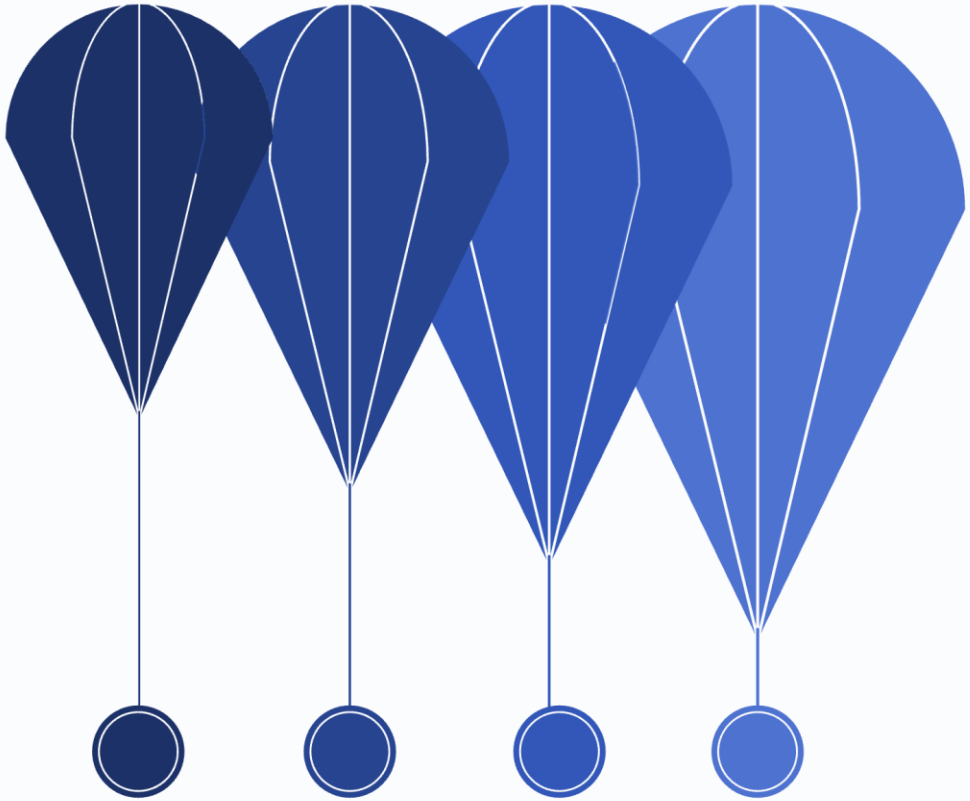
1976: HMG-CoA reductase identified

First Outcome Trial

1984: LRC-CPPT showed CV benefit

Statin Standard

1994: 4S trial established statins



From the first lipid-lowering trial in 1984 to the statin era and beyond — each decade has added a new layer of evidence, expanding the therapeutic armamentarium and refining our understanding of LDL-C as a causal driver of ASCVD.

1984: LRC–CPPT — The Cholestyramine Trial

The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) was the pivotal first proof-of-concept: lowering LDL-C with cholestyramine (a bile acid sequestrant) significantly reduced the incidence of coronary heart disease. This landmark trial established the causal relationship between LDL-C reduction and CV event prevention — laying the scientific foundation for the statin era.





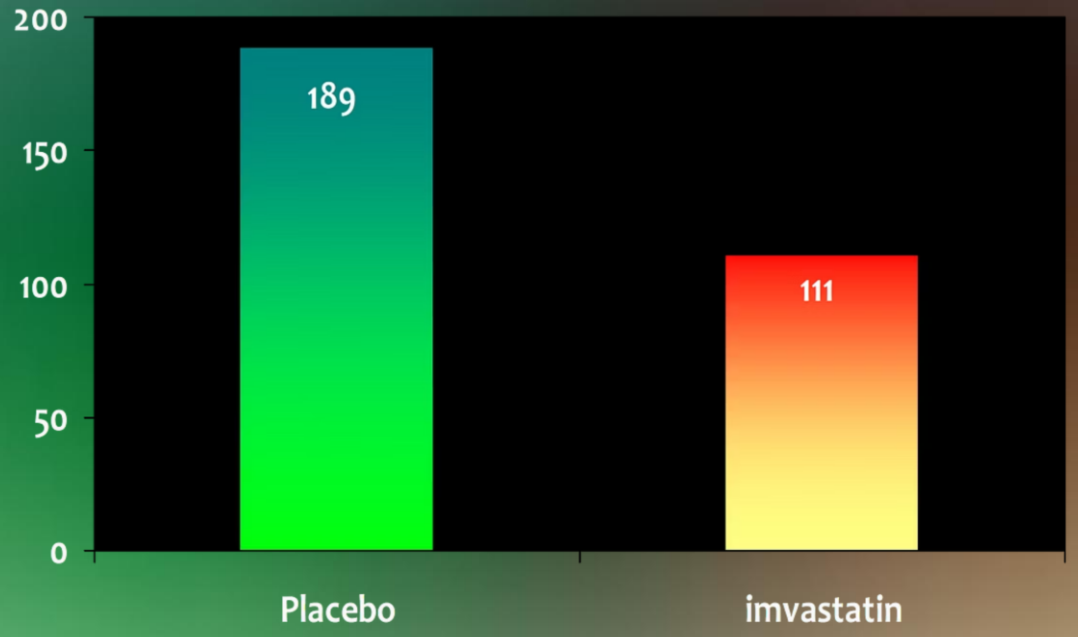
Discovery of HMG-CoA Reductase Inhibition

In 1976, **Akira Endo, Ph.D.** demonstrated that compactin (mevastatin), derived from *Penicillium citrinum*, competitively inhibits HMG-CoA reductase — the rate-limiting enzyme in cholesterol biosynthesis. This Nobel-worthy discovery initiated the statin revolution and transformed cardiovascular prevention globally.

Endo's work at Biopharm Research Laboratories remains one of the most consequential discoveries in modern medicine. *Image: Lasker Foundation, laskerfoundation.org*

1994: The 4S Trial — Simvastatin Reduces CV Mortality by 42%

The Scandinavian Simvastatin Survival Study (4S) was the first large-scale trial to demonstrate that statin therapy reduces total mortality in patients with established coronary heart disease — a paradigm-defining result that cemented LDL-C lowering as a cornerstone of secondary prevention.



4S Trial: Secondary Prevention Evidence

Study Design

4,444 patients with angina pectoris or prior MI randomized to simvastatin 20–40 mg vs. placebo over 5.4 years.

Key Finding

Significant reduction in total mortality with simvastatin, even in patients with average LDL-C levels — establishing the "lower is better" principle.

Source: 4S Group. Lancet 1994;344:1383–1389.

−42%

CV mortality reduction

−30%

Total mortality reduction (RRR)

5.4 yrs

Median follow-up duration

The Pyramid of Statin Evidence



The statin evidence base spans every risk stratum — from high-risk secondary prevention patients to lower-risk primary prevention populations. Twelve landmark trials collectively demonstrate consistent, proportional reductions in MACE across diverse populations, establishing statins as the most extensively validated lipid-lowering intervention in history.

CHAPTER 2

Beyond Statins: Expanding the Armamentarium

While statins remain foundational, a substantial proportion of high-risk patients fail to achieve guideline-recommended LDL-C targets on statin monotherapy. Ezetimibe, PCSK9 inhibitors, bempedoic acid, and emerging agents now offer a comprehensive, combinatorial approach to residual cardiovascular risk.



IMPROVE-IT: Ezetimibe Added to Simvastatin

The IMPROVE-IT trial demonstrated that adding ezetimibe to simvastatin produced a statistically significant reduction in the primary composite endpoint versus simvastatin alone across all major subgroups — validating the "lower is better" hypothesis with a non-statin agent.

- Benefit was most pronounced in diabetic patients (–5.5 pp) and those aged ≥65, supporting the concept of intensified LDL-C lowering in higher-risk subpopulations.

EZ/Simva vs Simva

LDL-C: 31.0 vs 34.0 mmol/l (women)
LDL-C: 33.3 vs 34.9 mmol/l (men)

Diabetic Patients

40.0% vs 45.5% primary endpoint — greatest absolute benefit

Age ≥65

36.4% vs 39.9% — consistent benefit in elderly



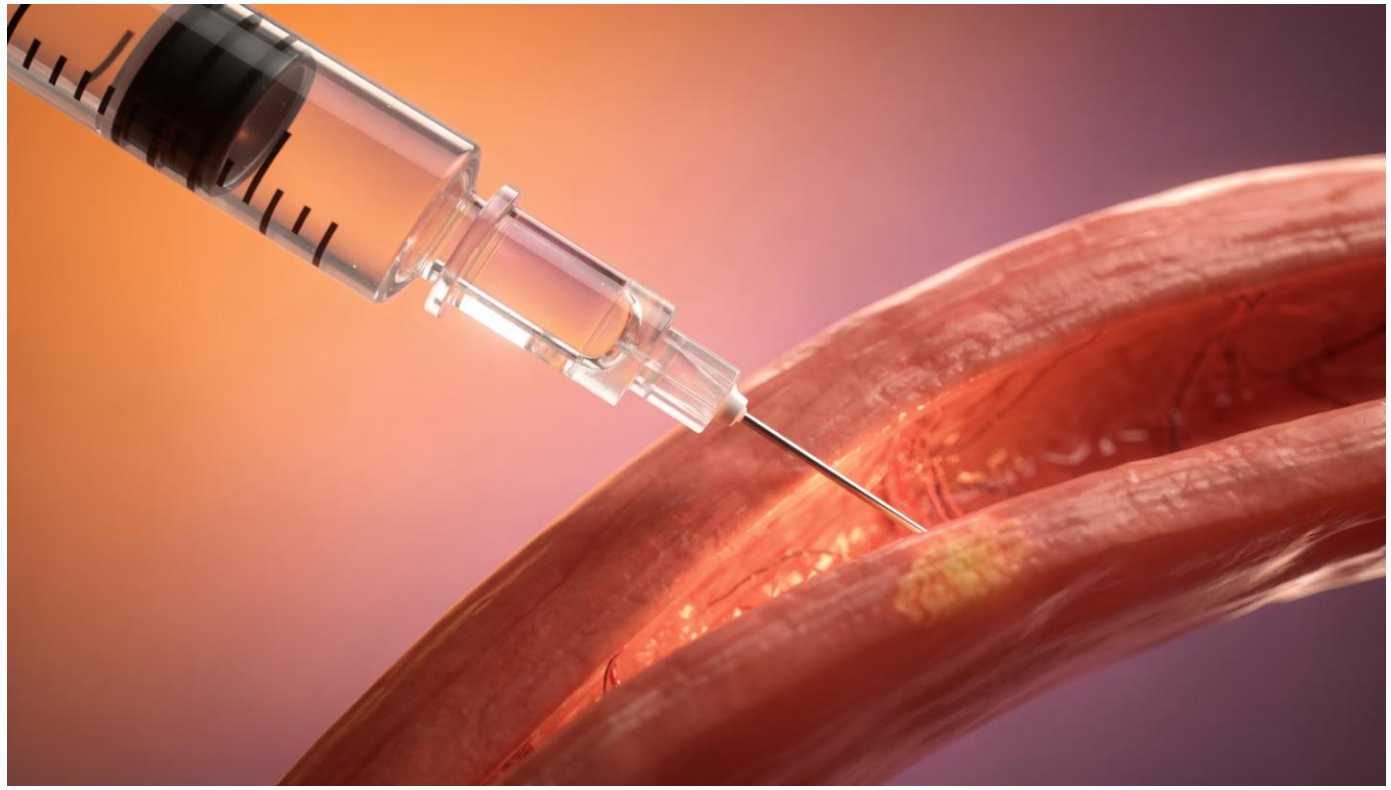
PCSK9 INHIBITION

PCSK9 Inhibitors: The Biological Breakthrough

PCSK9 inhibitors — monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 — prevent LDL receptor degradation, dramatically increasing hepatic LDL-C uptake. Evolocumab and alirocumab reduce LDL-C by 50–60% on top of maximally tolerated statin therapy, with robust outcomes data in both primary and secondary prevention.

RNA THERAPY

Inclisiran: A New Era of Twice-Yearly Dosing



Mechanism

Inclisiran is a small interfering RNA (siRNA) that silences PCSK9 mRNA in hepatocytes, durably reducing PCSK9 protein production — and LDL-C — with just **two subcutaneous injections per year**.

Clinical Advantage

The extended dosing interval addresses the critical barrier of adherence in long-term lipid-lowering therapy, offering a compliance-friendly alternative to monthly PCSK9 monoclonal antibodies.

PCSK9 Inhibition in Our Center of Preventive Cardiology

One subcutaneous injection every two weeks. Applied in both primary and secondary prevention settings, PCSK9 inhibitors deliver consistent, substantial LDL-C reductions — on average 50–60% below baseline — across the full spectrum of cardiovascular risk.



Dosing

1 subcutaneous injection every 2 weeks (evolocumab/alirocumab)



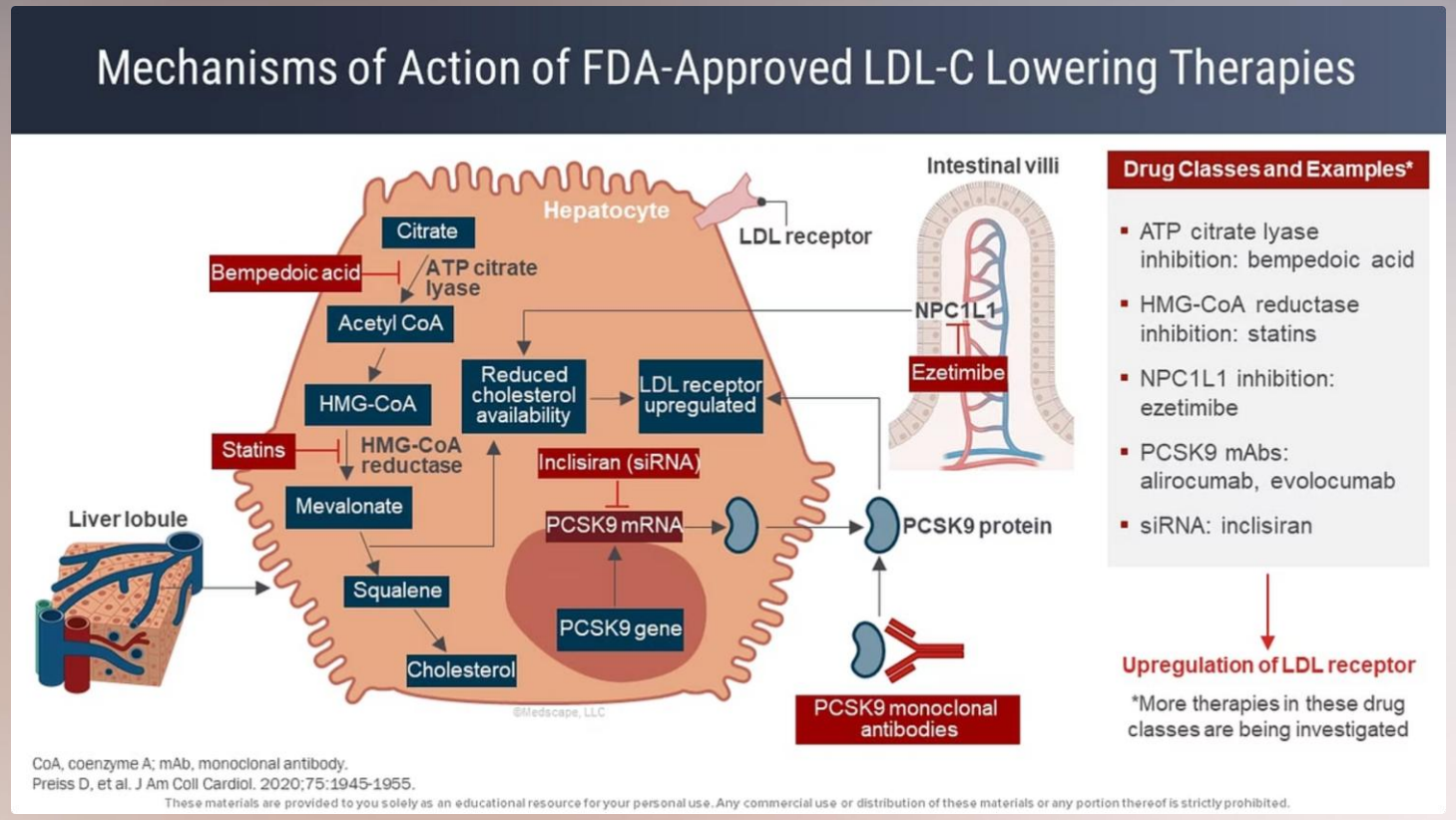
Indication

Primary and secondary prevention; FH and very high-risk patients



LDL-C Reduction

~50–60% reduction on top of maximally tolerated statin therapy



All FDA-approved LDL-C lowering therapies converge on a single mechanism: upregulation of the hepatic LDL receptor — achieved via distinct upstream targets including HMG-CoA reductase (statins), ACL (bempedoic acid), NPC1L1 (ezetimibe), and PCSK9 inhibition (mAbs and siRNA).

LDL-C: We Have Everything We Need

Measurement

LDL-C is routinely measured — we have abundant population-level data on risk and treatment response.

Evidence

Decades of RCTs and meta-analyses confirm that lowering LDL-C reduces MACE proportionally.

Therapies

Multiple drug classes, oral and injectable, are available with established safety profiles.

Guidelines

ESC/EAS 2019 and 2021 guidelines provide clear, risk-stratified LDL-C targets.



And Yet —
We Are Still Failing

Despite having the tools, the evidence, and the guidelines, a large majority of high-risk patients remain above recommended LDL-C targets. The gap between what we know and what we achieve in practice is one of the most urgent challenges in preventive cardiology.



Why LDL-C Management Underperforms: The Real-World Barriers



Low Awareness

LDL-C lacks visible symptoms — patients and even clinicians may underestimate urgency.



Intervention Bias

Clinical culture often favors procedural intervention over sustained pharmacological prevention.



Misinformation

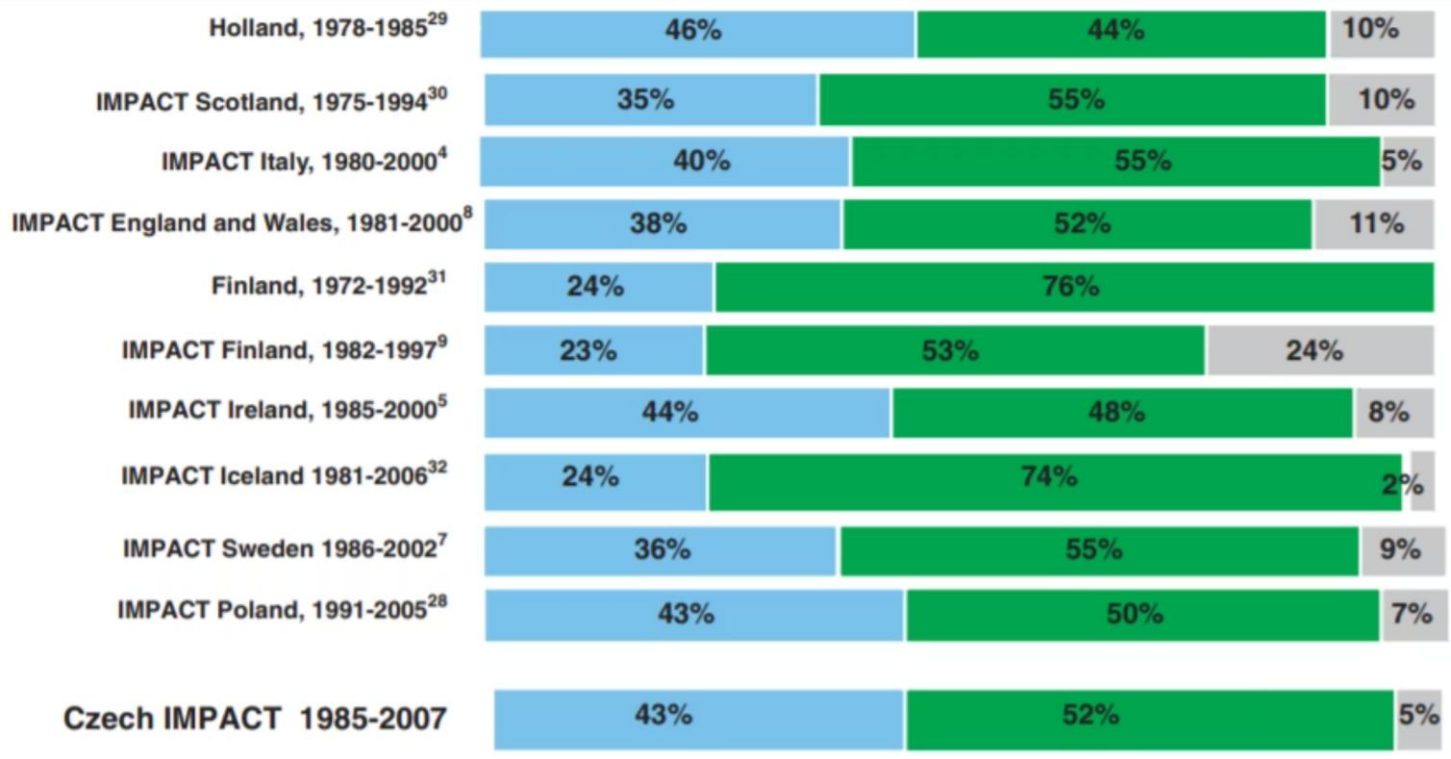
Widely circulated "statin skeptic" narratives undermine patient and physician confidence in therapy.



Competing Priorities

The diabetes and obesity pandemic diverts clinical attention from lipid management.

Prevention vs. Intervention: Where Does the Benefit Come From?



Czech population data (Bruthans et al., *Eur J Prev Cardiol* 2014;21:829–39) decompose the reduction in IHD mortality into contributions from pharmacological treatment versus modifiable risk factor changes. A meaningful proportion remains unexplained — underscoring the need for comprehensive, population-level primary prevention strategies.

Why We Fail in Treatment: The Physician Side



Knowledge Gap

Insufficient familiarity with current LDL-C targets and evidence-based intensification strategies.

Clinical Error

Incorrect risk classification, inappropriate drug selection, or subtherapeutic dosing.

Therapeutic Inertia

Failure to escalate therapy despite uncontrolled LDL-C — the most prevalent and correctible failure mode.

Why We Fail in Treatment: The Patient Side



Lack of Interest

Asymptomatic LDL-C elevation fails to motivate sustained behavioral change or treatment engagement.

Poor Compliance

Patients discontinue therapy due to perceived side effects, cost, or inconvenience.

Non-Adherence

Long-term adherence to statin and non-statin therapy remains below 50% in many real-world settings.

Problem 1 - Inaccurate Individualized Assessment of Cardiovascular Risk

WHO HAS HIGHER CARDIOVASCULAR RISK BASED ONLY ON RISK FACTORS?



Jim Fixx
Famous US Marathoner

- Not Overweight
- Very Fit
- Non-Smoker

DIED OF A MASSIVE HEART ATTACK AT AGE 52

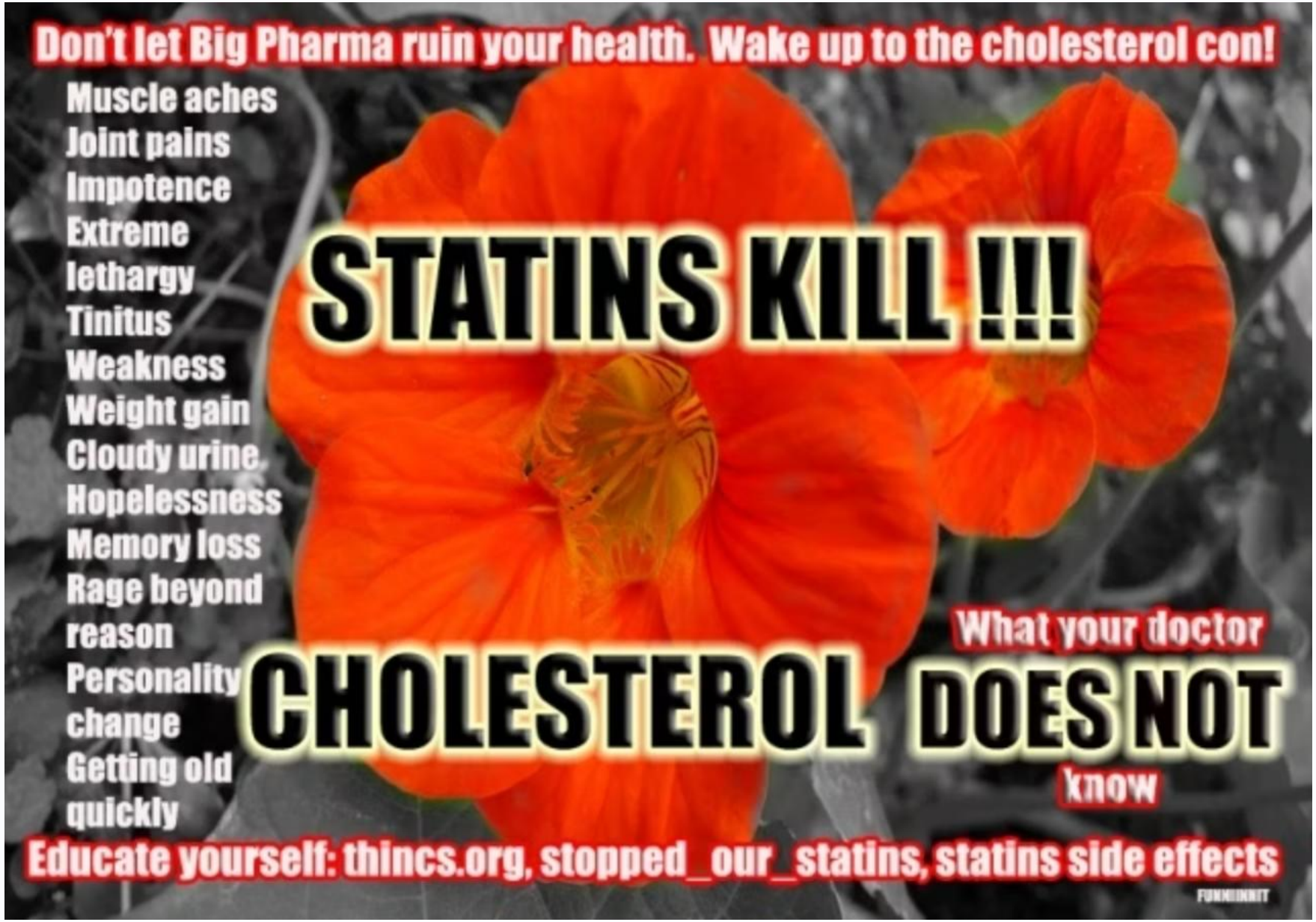


Winston Churchill
Prime Minister during WWII

- Overweight
- Not Fit
- Heavy Smoker

LIVED TO AGE 89

Endothelix, Inc. Tel: 713.529.2599 Fax: 832.201.9192 Web: www.endothelix.com


Don't let Big Pharma ruin your health. Wake up to the cholesterol con!
Muscle aches
Joint pains
Impotence
Extreme lethargy
Tinitus
Weakness
Weight gain
Cloudy urine
Hopelessness
Memory loss
Rage beyond reason
Personality change
Getting old quickly
STATINS KILL !!!
CHOLESTEROL
What your doctor
DOES NOT
know
Educate yourself: thincs.org, stopped_our_statins, statins side effects
FUNNIKNIT

Real-World Evidence: The Statin Adherence Crisis



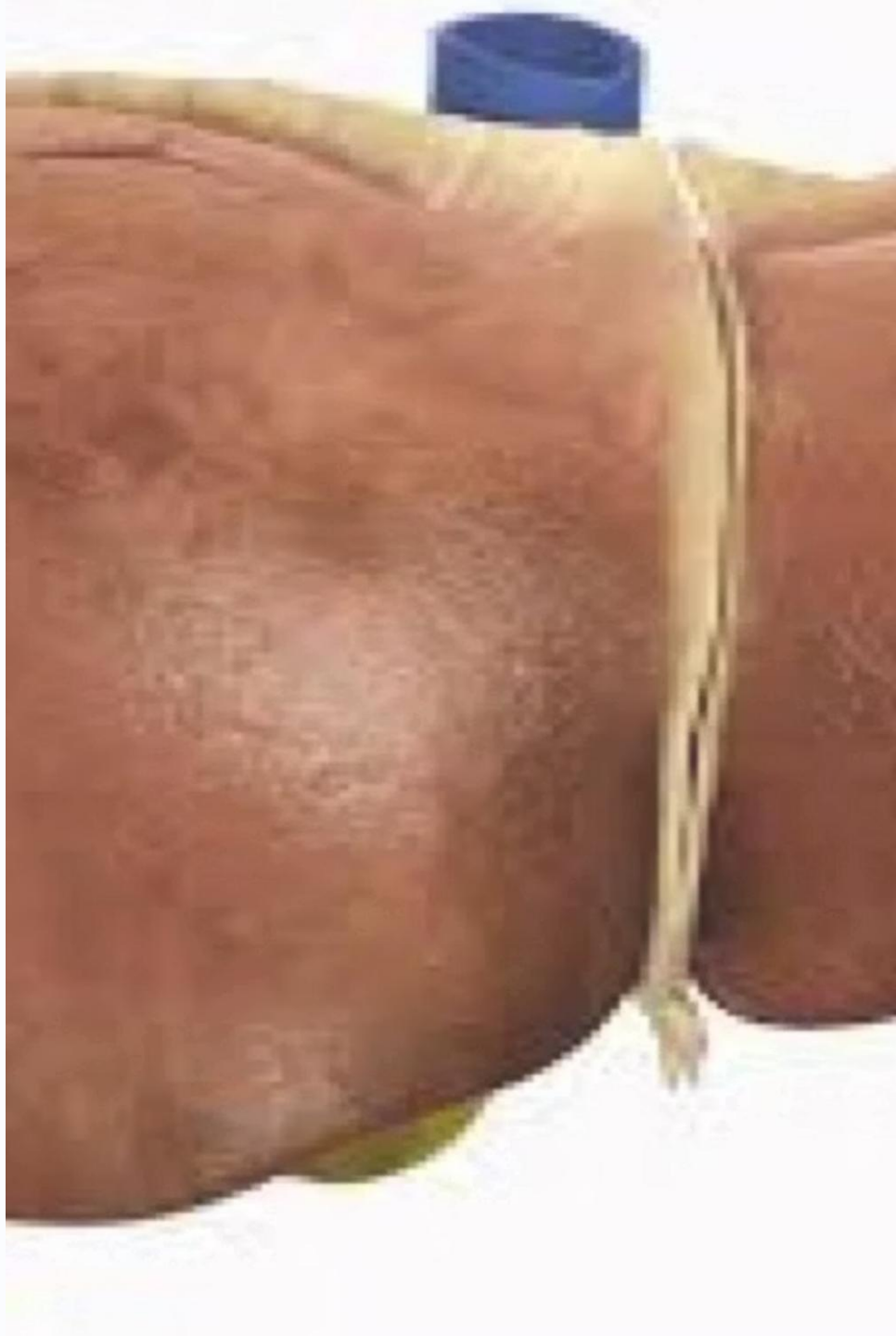
Statin Safety in Perspective: Comparison with Aspirin

The absolute risk of serious adverse events with statins is orders of magnitude lower than with aspirin — a drug widely accepted as safe.

Event	Aspirin (NNtH/year)	Statins (NNtH/year)
GI bleeding (severe)	248	—
GI bleeding (fatal)	2,066	—
Rhabdomyolysis	—	100,000
Death from rhabdomyolysis	—	1,000,000

Derry S, Loke YK. BMJ 2000;321:1183–7. Thompson PD et al. JAMA 2003;289:1681–1690.

Statins and the Liver: Reassessing the Risk



Statins and Liver Transaminases

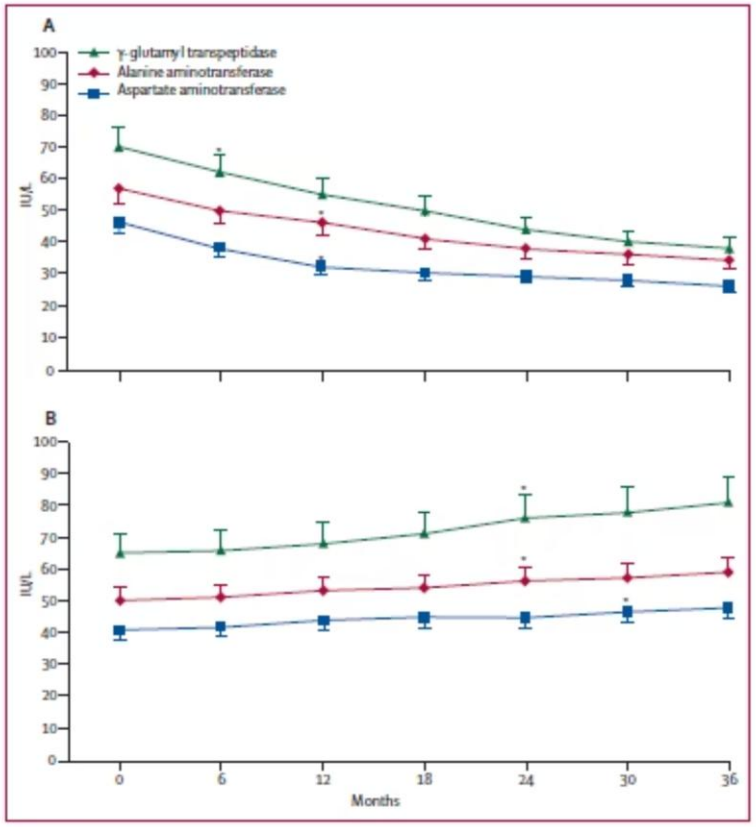


Figure 2: **Enzyme activity during 3-year follow-up in patients with raised liver enzymes**
(A) Patients on statin treatment (n=227). (B) Patients not on statin treatment (n=210). ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT=γ-glutamyl transpeptidase. *Time when differences became significant (p<0·05) compared with baseline. By the end of the study, all differences were p<0·0001 in patients on statins. In patients not on statin treatment, differences compared with baseline were 0·001, 0·003, and 0·01 for GGT, ALT, and AST, respectively.

Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis

Vasilios G Athyros, Konstantinos Tziomalos, Thomas D Gossios, Theodora Griva, Panagiotis Anagnostis, Konstantinos Kargiotis, Efstathios D Pagourelias, Eleni Theocharidou, Asterios Karagiannis, Dimitri P Mikhailidis, for the GREACE Study Collaborative Group*

Paradoxical finding: Higher baseline liver transaminases are associated with *greater* cardiovascular event reduction during atorvastatin treatment — not with increased harm. Routine monitoring requirements have been substantially relaxed in current guidelines.

Statins and Liver Transaminases

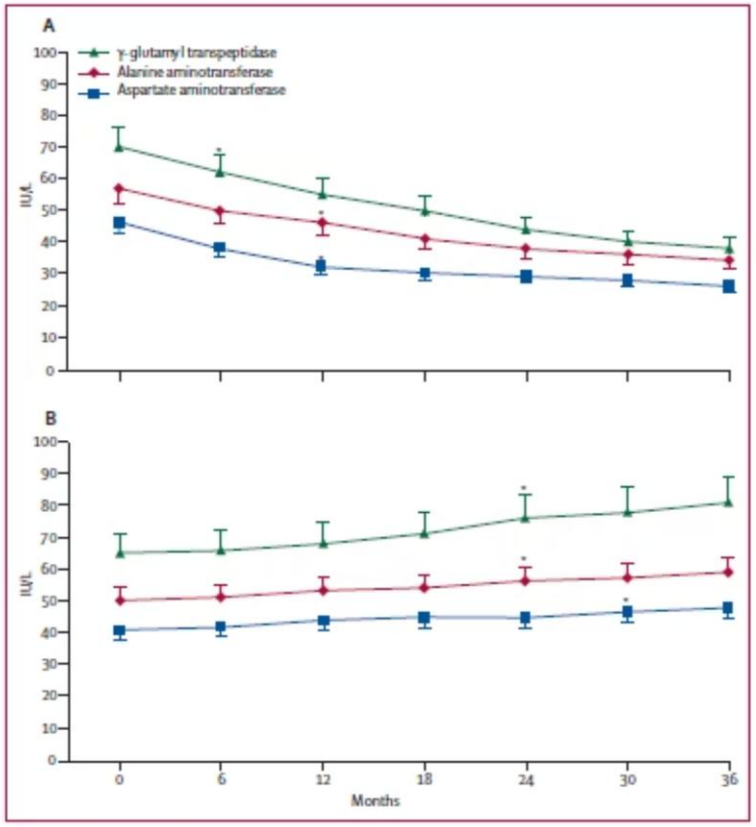


Figure 2: **Enzyme activity during 3-year follow-up in patients with raised liver enzymes**
(A) Patients on statin treatment (n=227). (B) Patients not on statin treatment (n=210). ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT=γ-glutamyl transpeptidase. *Time when differences became significant (p<0·05) compared with baseline. By the end of the study, all differences were p<0·0001 in patients on statins. In patients not on statin treatment, differences compared with baseline were 0·001, 0·003, and 0·01 for GGT, ALT, and AST, respectively.

Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis

Vasilios G Athyros, Konstantinos Tziomalos, Thomas D Gossios, Theodora Griva, Panagiotis Anagnostis, Konstantinos Kargiotis, Efstathios D Pagourelias, Eleni Theocharidou, Asterios Karagiannis, Dimitri P Mikhailidis, for the GREACE Study Collaborative Group*

Paradoxical finding: Higher baseline liver transaminases are associated with *greater* cardiovascular event reduction during atorvastatin treatment — not with increased harm. Routine monitoring requirements have been substantially relaxed in current guidelines.

Statins and New-Onset Diabetes: Context Matters

+9%

Relative risk increase for new-onset diabetes with statin use

Age >60

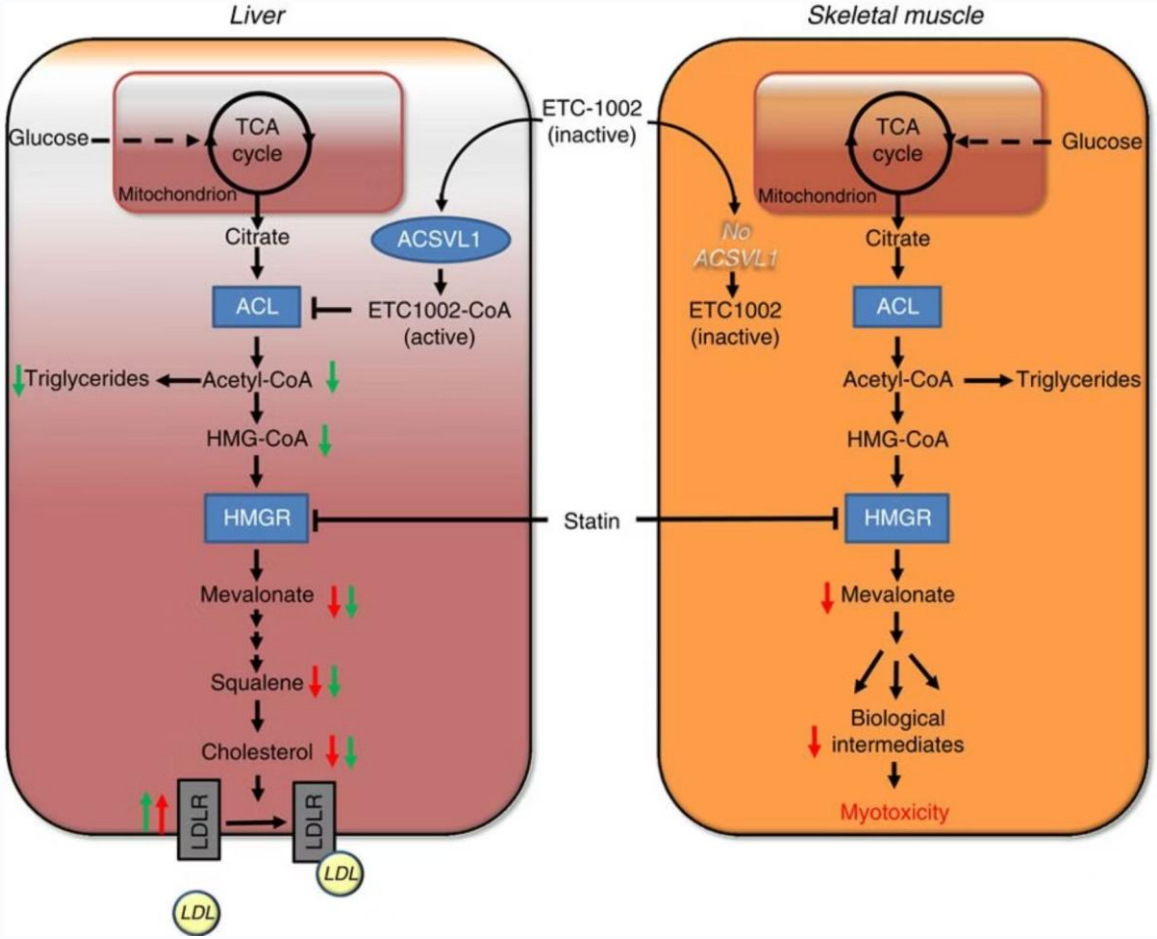
Risk is concentrated in older patients with pre-existing metabolic risk factors

1 : 9

Risk/benefit ratio — for every 1 new diabetes case, ~9 major CV events prevented

The diabetogenic risk of statins is modest, dose-dependent, and concentrated in patients who are already metabolically vulnerable (elevated BMI, components of metabolic syndrome). The absolute cardiovascular benefit far outweighs this risk across all major risk strata. Statin therapy should not be withheld due to diabetes concern.

Bempedoic Acid: A Muscle-Safe ACL Inhibitor



Mechanism

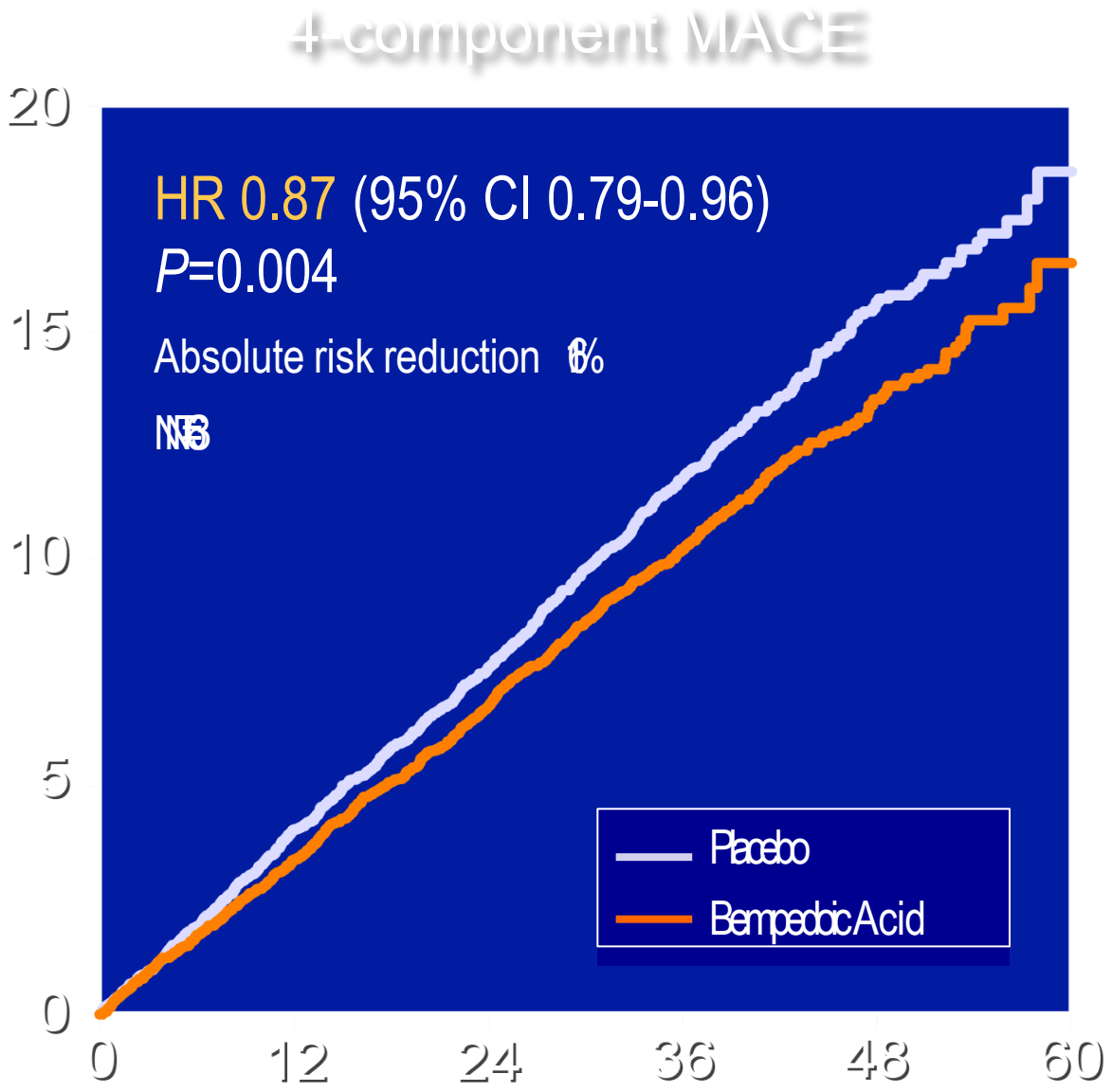
Bempedoic acid inhibits ATP citrate lyase (ACL) in the liver — upstream of the statin target — reducing cholesterol synthesis and upregulating LDL receptors.

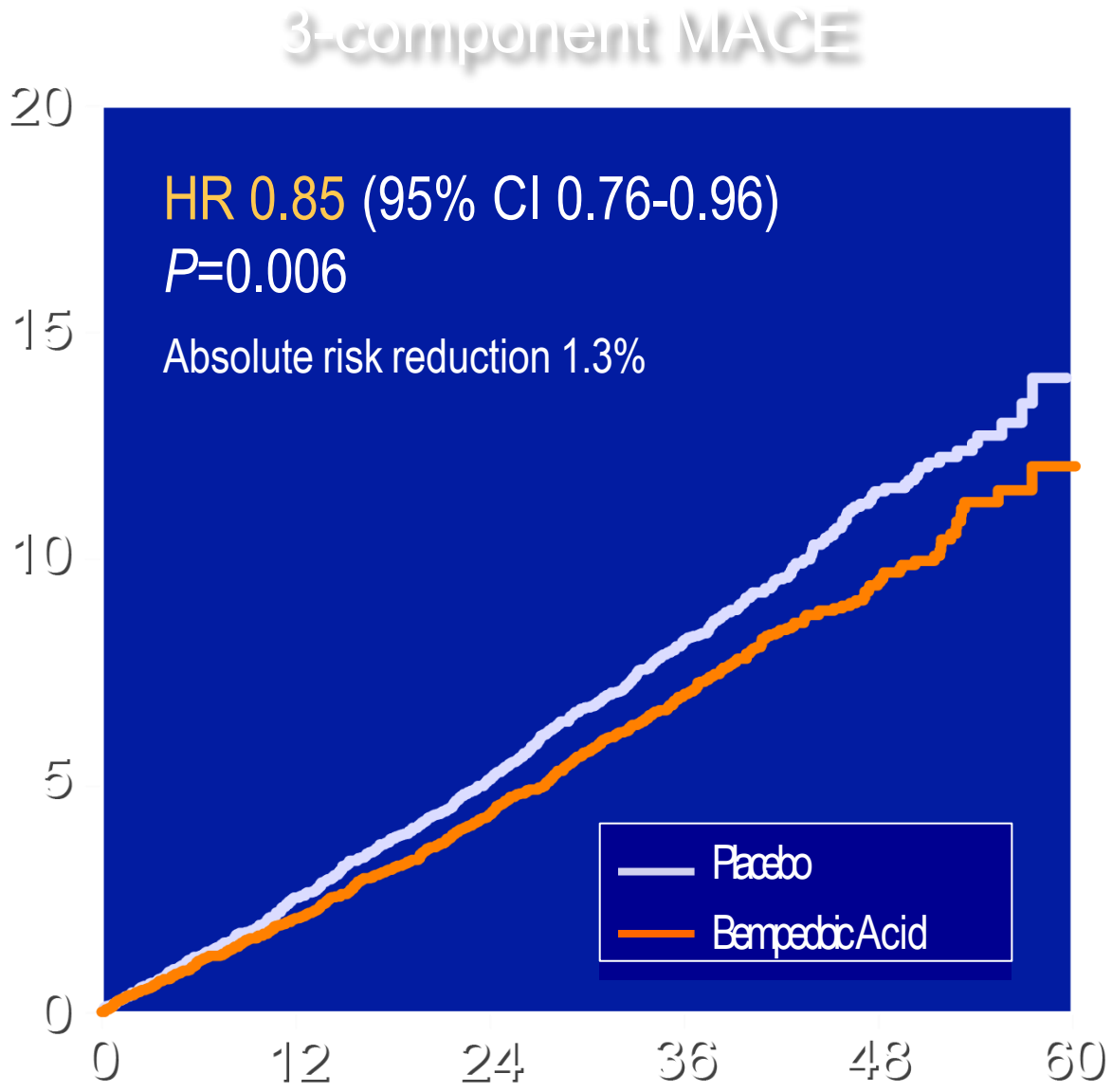
Key Differentiator

The drug is **not activated in skeletal muscle**, avoiding the myopathy risk associated with statins. This makes it particularly valuable in statin-intolerant patients.

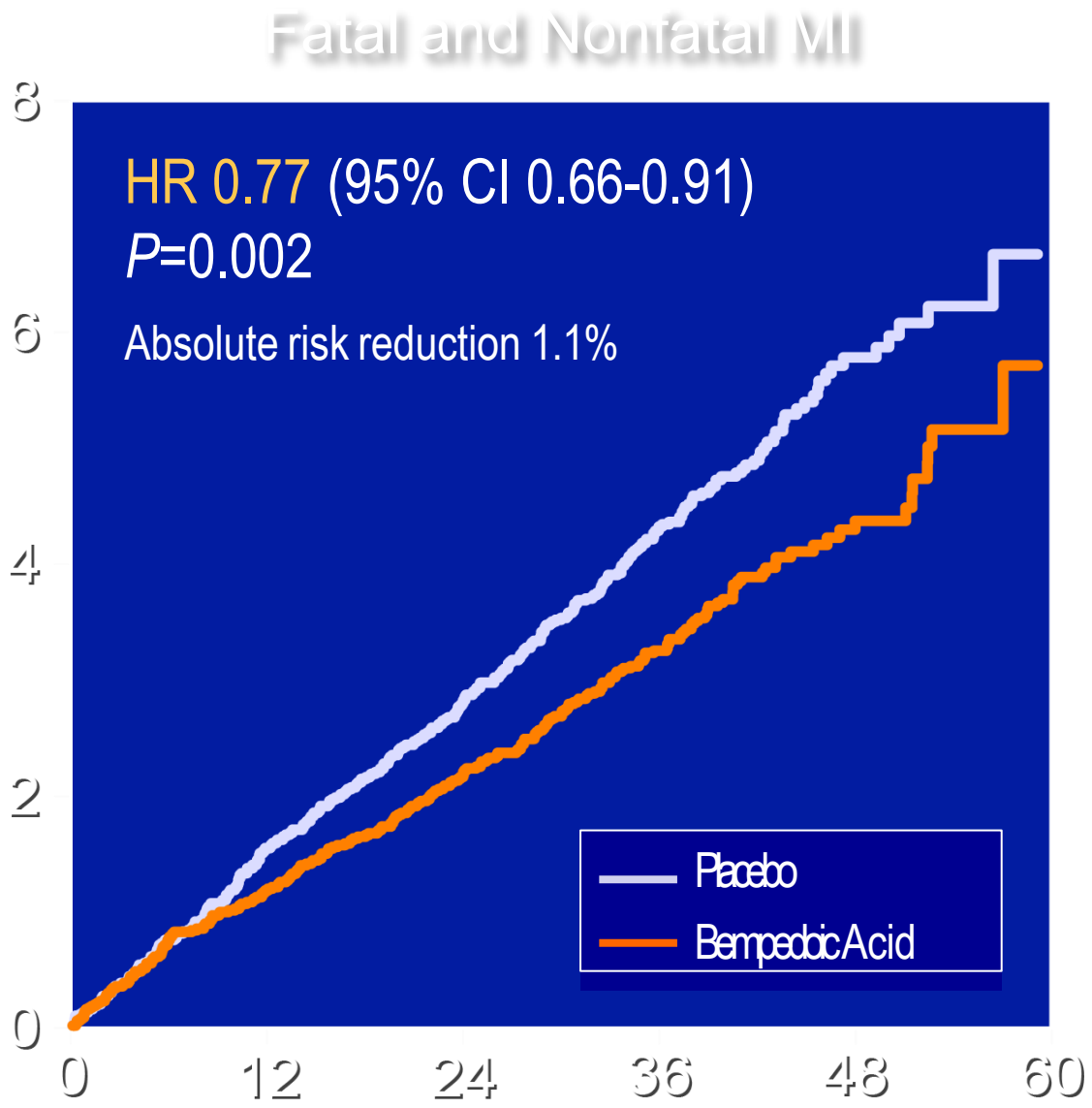
Pinkosky S et al. Nat Commun. 2016;7:13457.

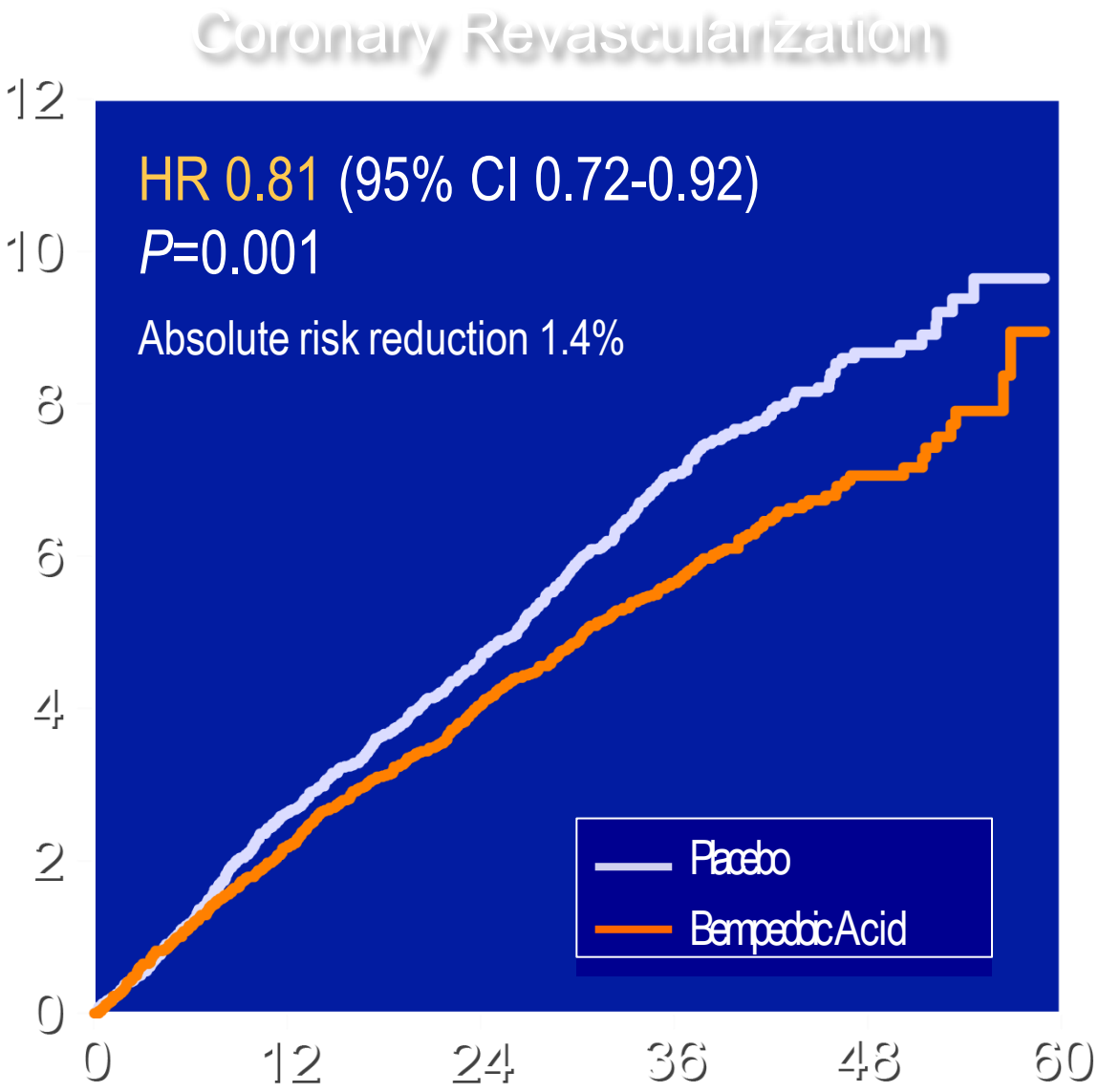
Primary and First Key Secondary Cardiovascular End Points



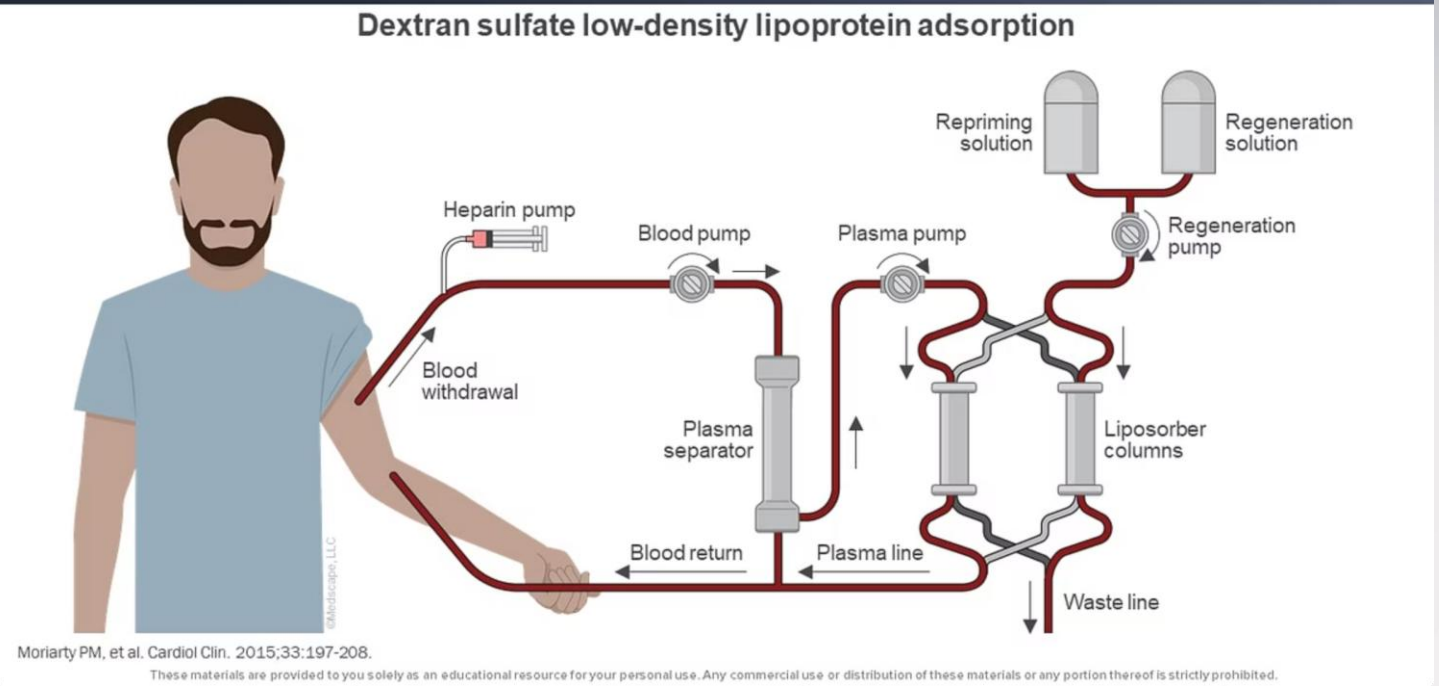


Key Secondary End Point: MI and Coronary Revascularization





LDL Apheresis



Moriarty PM, et al. Cardiol Clin. 2015;33:197-208.

These materials are provided to you solely as an educational resource for your personal use. Any commercial use or distribution of these materials or any portion thereof is strictly prohibited.

GENOVÁ TERAPIE

CRISPR-Cas9 jako jednorázová hypolipidemická léčba

Permanentní in vivo editace hepatocytů s cílem trvale vypnout gen regulující metabolismus lipidů — bez nutnosti opakované léčby.

Proč ANGPTL3?

ANGPTL3 je ideální první klinický cíl: silný a dobře ověřený lipidový efekt, přičemž jedinci s přirozenou ztrátou funkce tohoto genu nevykazují žádné závažné klinické fenotypy.

Mechanismus účinku

→ **Doručení**

Jednorázová i.v. infuze lipidových nanočástic nesoucích CRISPR-Cas9 mRNA + gRNA

→ **Editace**

Přesný knock-out cílového lokusu ANGPTL3 v hepatocytech

→ **Efekt**

↓ LDL-C · ↓ triglyceridy · ↓ non-HDL-C — trvalý výsledek

PHASE 1 — KLINICKÁ DATA

CTX310 (ANGPTL3 CRISPR): První výsledky u lidí

15 pacientů, jediná intravenózní infuze — výsledky překonaly očekávání ve všech sledovaných parametrech.

↓89%

ANGPTL3

Redukce proteinu dosažená u nejlépe reagujících pacientů (rozsah 79–89 %)

↓87%

LDL-C

Maximální pokles LDL cholesterolu; průměrná redukce 50–87 %

↓84%

Triglyceridy

Rozsah redukce 55–84 %; efekt nastupuje již do 2 týdnů

≥12M

Trvání efektu

Přetrvávající účinek po dobu nejméně 12 měsíců po jediné aplikaci

Bez závažných toxicit — zaznamenány pouze mírné infuzní reakce a přechodné elevace ALT u jednoho pacienta.

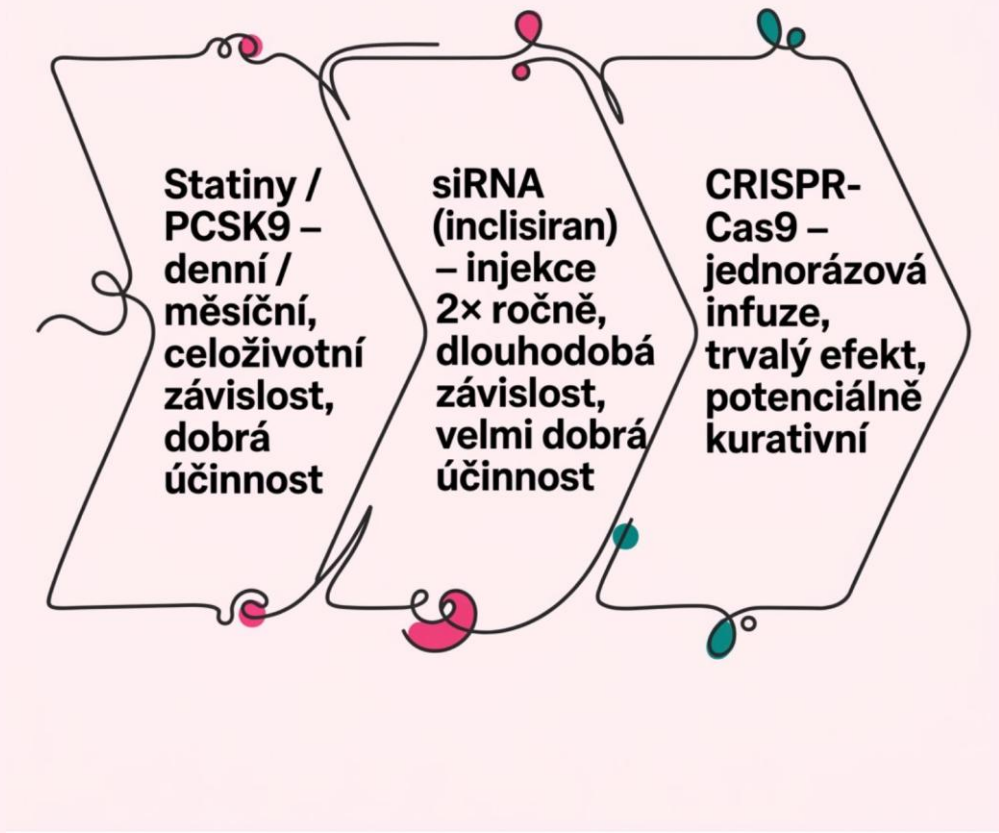
KLINICKÝ KONTEXT

Kam CRISPR zapadá do budoucnosti léčby dyslipidemií?

Od celoživotní terapie k jednorázovému zásahu

Současný standard — statiny, PCSK9 inhibitory a siRNA — vyžaduje kontinuální podávání. CRISPR-Cas9 nabízí zásadně odlišný model: **jedna infuze, trvalý efekt**.

Při potvrzení výsledků ve fázích 2 a 3 by se jednalo o **největší revoluci v lipidologii od příchodu PCSK9 inhibitorů**.



Klíčová otázka pro fáze 2/3: dlouhodobá bezpečnost off-target editací a trvání efektu nad horizont 12 měsíců.

The Future Is Great

From gene silencing to base editing and oral PCSK9 inhibitors, the next generation of LDL-C lowering therapies promises deeper, more durable reductions with fewer injections — fundamentally reshaping the landscape of cardiovascular prevention for decades to come.



Currently Available Non-Statin Agents

Drug	Dosing/Administration	Percent LDL-C Lowering	Adverse Effects	Indications
Alirocumab	75-150 mg Q2 weekly or 300 mg subcutaneously Q4 weekly	50-60	Injection-site reactions, hypersensitivity reactions	HeFH, ASCVD, **HoFH**
Evolocumab	140 mg Q2 weeks or 420 mg subcutaneously Q2-Q4 weekly			
Inclisiran	284 mg subcutaneously single injection, again at 3 months, Q6 monthly thereafter	50	Antibody development, injection-site reactions	HeFH, ASCVD
Ezetimibe	10 mg daily	18-25	URI, diarrhea, arthralgias	HeFH, **HoFH,** HLD, Sitosterolemia
Bempedoic acid	180 mg oral daily	17-25	Hyperuricemia/gout, possibly tendon rupture	HeFH, ASCVD
Bempedoic acid/ezetimibe	180 mg oral daily/10 mg oral daily	36	Hyperuricemia/gout, possibly tendon rupture	HeFH, ASCVD
Lomitapide	Initiate treatment at 5 mg once daily. Titrate dose based on acceptable safety/tolerability: increase to 10 mg daily after at least 2 weeks; and then at a minimum of 4-week intervals to 20 mg, 40 mg, and up to maximum recommended dose of 60 mg daily	40	Diarrhea, nausea, vomiting, dyspepsia, and abdominal pain	**HoFH**
Evinacumab	15 mg/kg intravenous Q4 weekly	50	Injection-site reactions, hypersensitivity reactions, nasopharyngitis	**HoFH**

Adapted from Gaine SP, et al. Curr Cardiovasc Risk Rep. 2022;16:69-78.

These materials are provided to you solely as an educational resource for your personal use. Any commercial use or distribution of these materials or any portion thereof is strictly prohibited.