Dyslipidemia & Atherosclerosis

BCH 130 — Advanced Human Biochemistry · Dr. Radi

By the end of this unit, you can…

- Interpret a lipid panel (LDL-C, HDL-C, triglycerides, non-HDL, apoB) in terms of the underlying lipoprotein metabolism.
- Explain familial hypercholesterolemia (LDL-receptor / apoB / PCSK9 defects) and its dominant biochemistry, and the major hypertriglyceridemias (LPL/apoC-II).
- Walk the biochemistry of atherogenesis
- Explain lipid-lowering pharmacology by target

Today's route

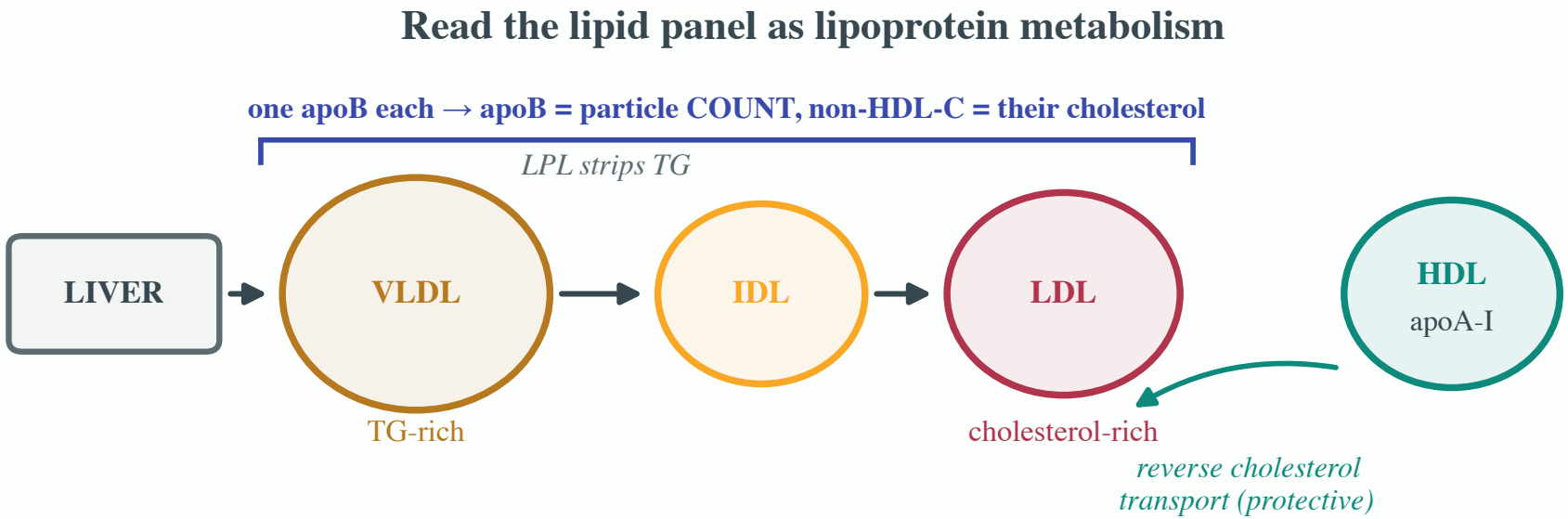
1. **Dyslipidemias — Reading the Lipid Panel**
2. **Atherosclerosis — Pathogenesis & Drugs**

1 · Dyslipidemias — Reading the Lipid Panel

"That lipid panel on the screen isn't five random numbers — it's a readout of lipoprotein metabolism in motion. Learn to see the particles behind the numbers, and the inherited disorders that make them go haywire, and the panel starts telling you a story."

The panel is lipoprotein metabolism

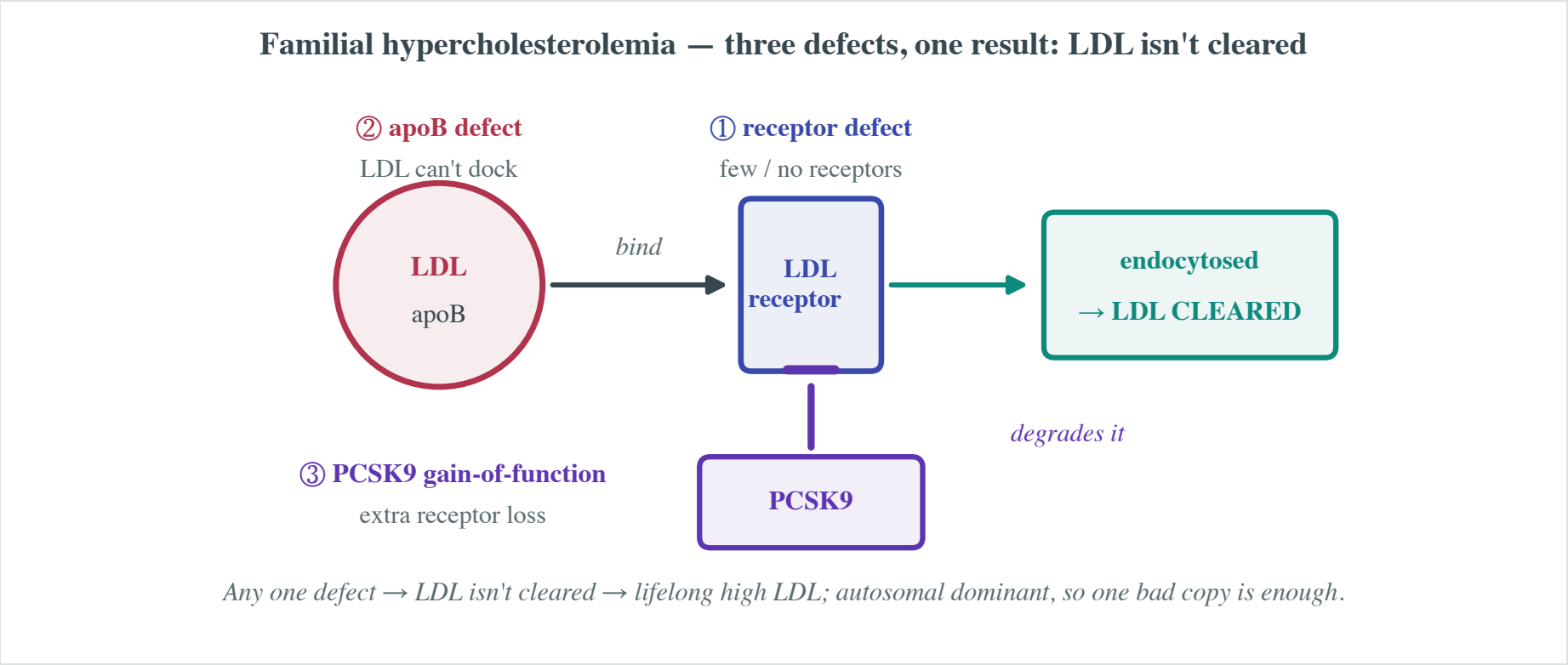
Don't read the lipid panel as five numbers — read it as **particles**. The liver ships **VLDL**; lipase strips its triglyceride down to cholesterol-rich **LDL**. Every one of those atherogenic particles carries exactly **one apoB** — so **apoB** counts them and **non-HDL-C** measures their cholesterol. **LDL-C** is only part of the story; **HDL** runs cholesterol back the other way.



LDL-C is just the cholesterol in LDL — apoB and non-HDL-C capture EVERY atherogenic particle.

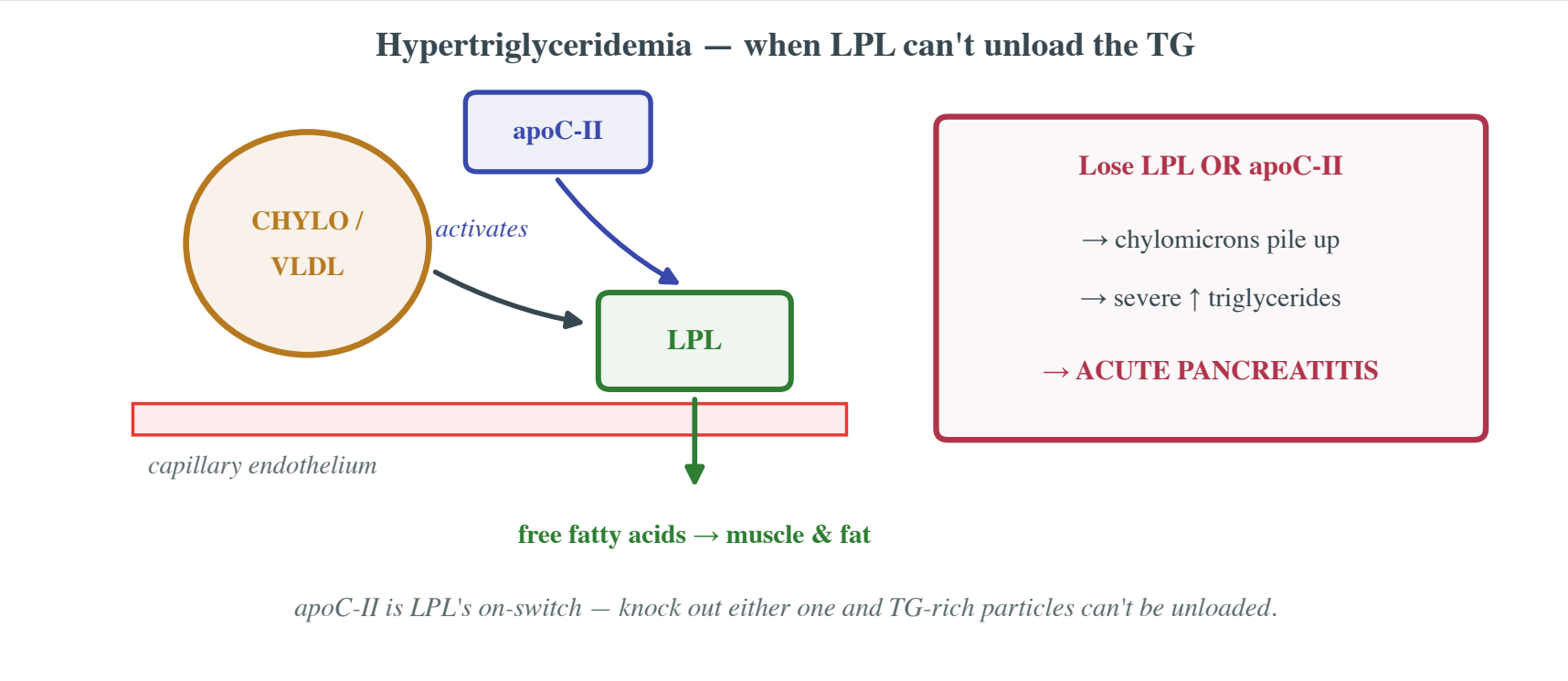
Familial hypercholesterolemia

Here's a disease of a single broken step: LDL just won't leave the blood. The hepatic **LDL receptor** normally grabs LDL by its **apoB** and pulls it in. Break the **receptor**, break the **apoB** ligand, or make **PCSK9** hyperactive (it degrades the receptor) — and clearance fails. It's **autosomal dominant**, so even one bad copy means sky-high LDL from birth.



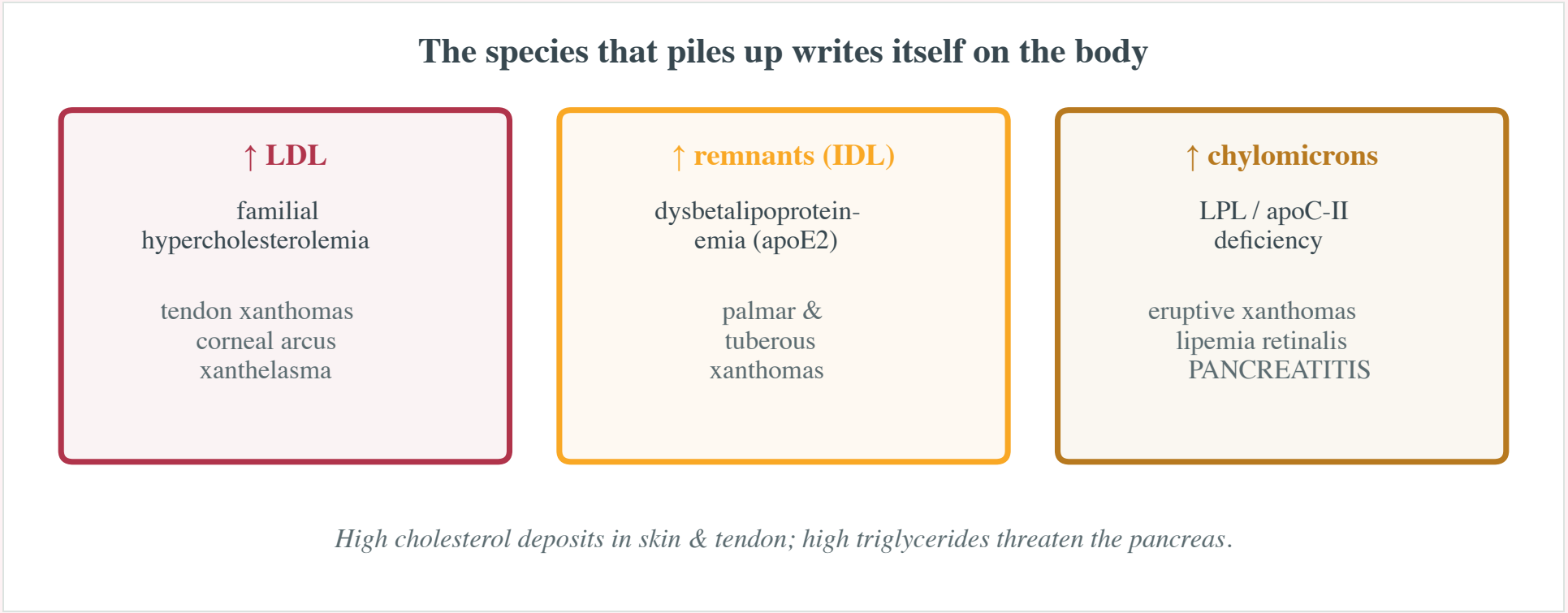
When triglycerides run wild

Now the other pole. **Lipoprotein lipase (LPL)**, anchored on the capillary wall, unloads triglyceride from chylomicrons and VLDL — and **apoC-II** is its essential **on-switch**. Lose either one and those fat-stuffed particles have nowhere to go: **triglycerides skyrocket**, and the real danger is **acute pancreatitis**.



The body wears its dyslipidemia

The species that accumulates literally shows up on the exam — the physical one! **High LDL** parks cholesterol in tendons and skin: **tendon xanthomas**, **corneal arcus**, **xanthelasma**. Stalled **remnants** give palmar and tuberous xanthomas. Sky-high **chylomicrons** bring **eruptive xanthomas**, milky **lipemia retinalis**, and pancreatitis. Read the skin, predict the particle.



2 · Atherosclerosis — Pathogenesis & Drugs

"This is where the numbers become a heart attack. Atherosclerosis is a slow, decades-long inflammatory response to lipid trapped in an artery wall — and once you see it built step by step, every lipid-lowering drug we reach for lands on an obvious target. Then we watch a plaque decide to kill."

Building a plaque, step by step

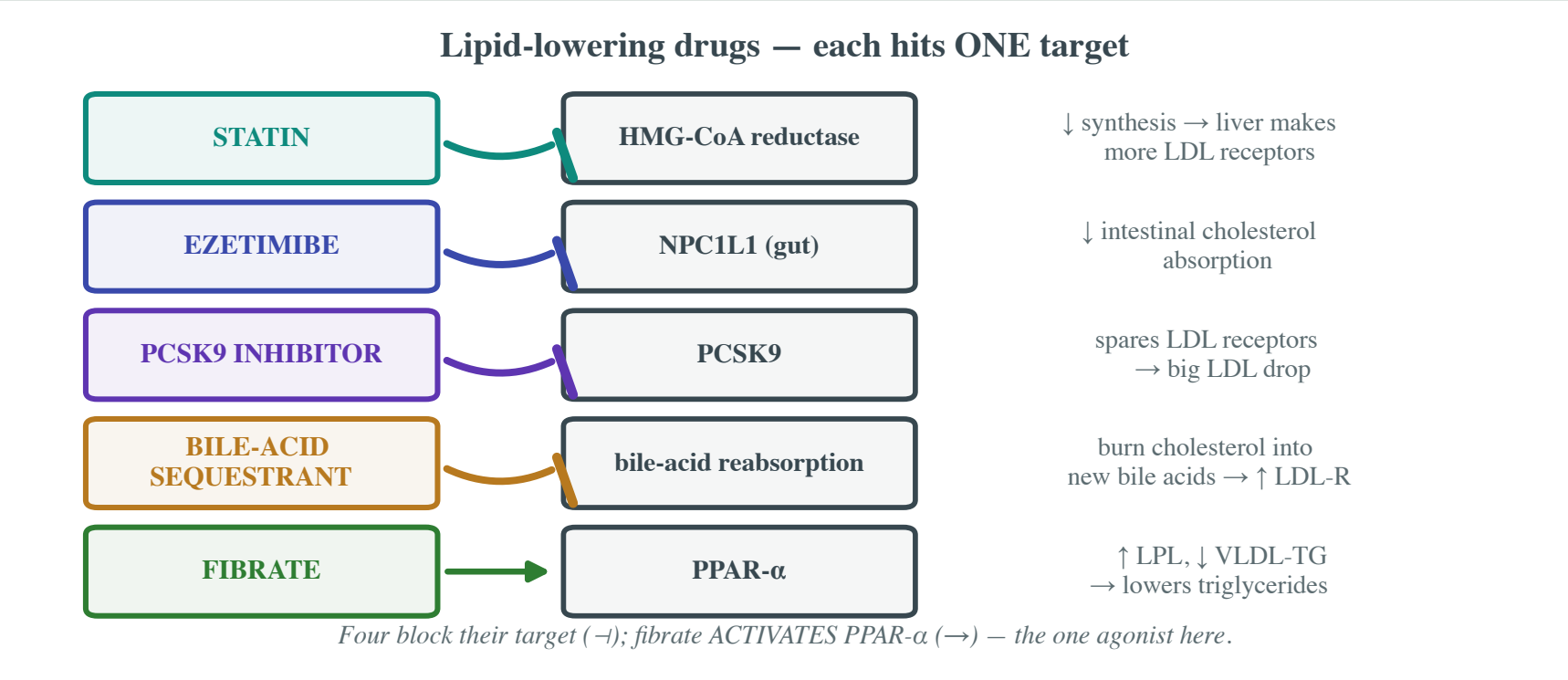
Atherosclerosis is an **inflammatory response to trapped lipid**. First the **endothelium** is injured – by LDL, smoking, glucose, high pressure. **LDL slips into the intima**, gets **oxidized**, and sounds the alarm. **Monocytes** pour in, become macrophages, and their **scavenger receptors** gorge on oxLDL into **foam cells**. Smooth muscle throws a **fibrous cap** over the mess.

Atherogenesis: five steps from a healthy artery to a plaque

Retained, oxidized LDL is the spark — the immune response to it builds the plaque.

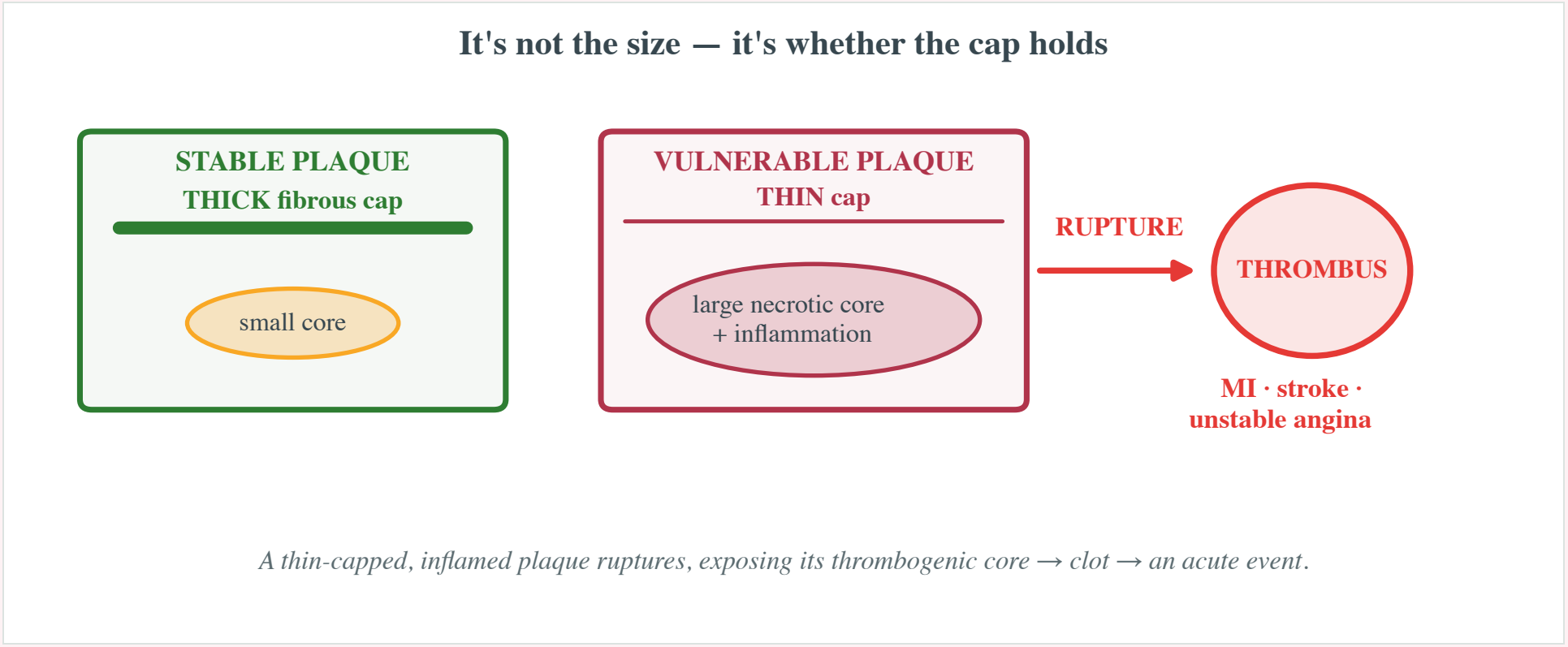
Every drug hits one target

Watch how cleanly this maps. **Statins** block **HMG-CoA reductase**, so the liver makes more LDL receptors. **Ezetimibe** blocks **NPC1L1** in the gut. **PCSK9 inhibitors** spare the receptor for a huge LDL drop. **Bile-acid sequestrants** make the liver burn cholesterol into new bile acids. **Fibrates activate PPAR-α** to clear triglycerides.



The plaque that kills

Here's the twist that surprises everyone: the plaque that stops your heart usually **wasn't the biggest one**. A **stable** plaque has a **thick fibrous cap** over a small core. A **vulnerable** plaque has a **thin, inflamed cap** over a big necrotic core — and when it **ruptures**, the thrombogenic core hits blood, a **clot** forms, and you get an **MI or stroke** in minutes.



A thin-capped, inflamed plaque ruptures, exposing its thrombogenic core → clot → an acute event.

Can you…?

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If any box stays empty, the practice site has a drill for it.
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