Symposium on Cardiometabolic Risk In Type 2 Diabetes

DYSLIPIDEMIA IN DIABETES

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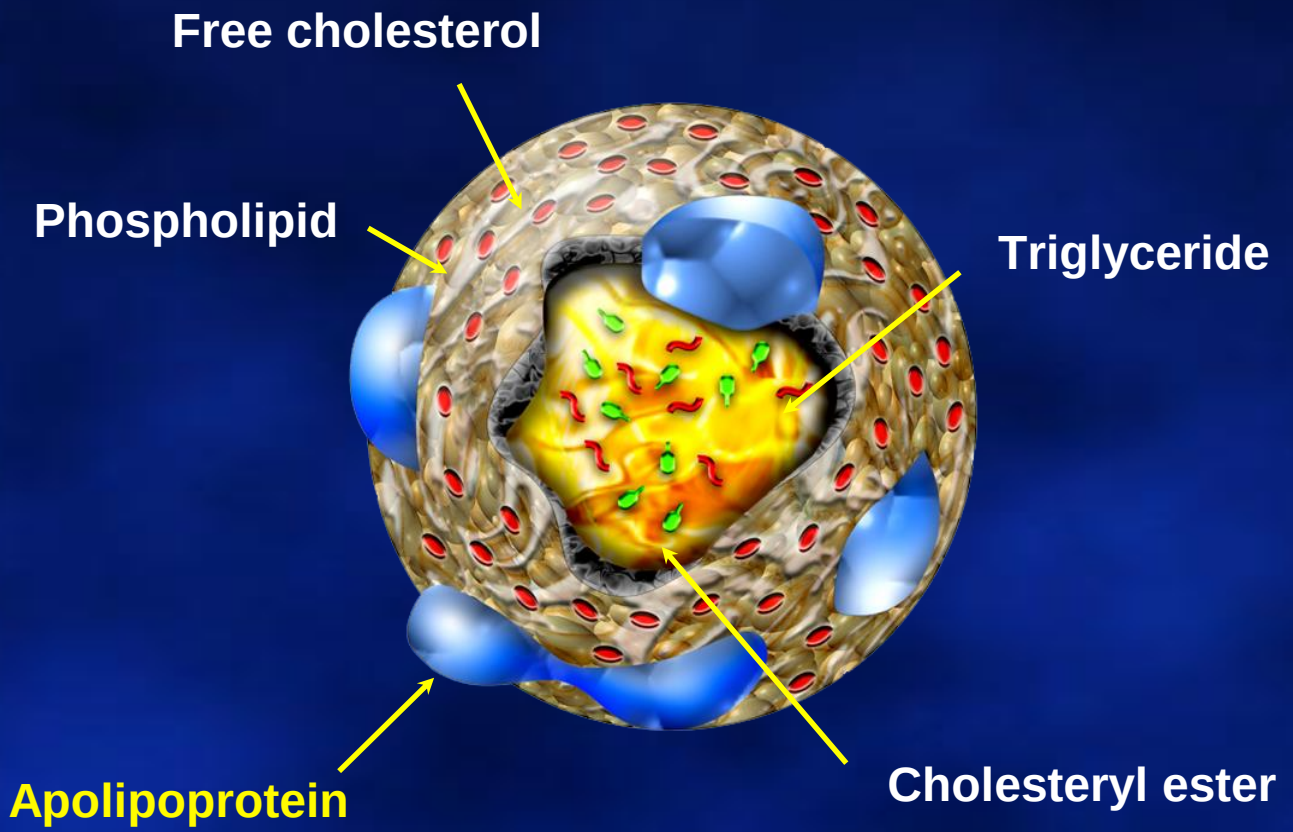
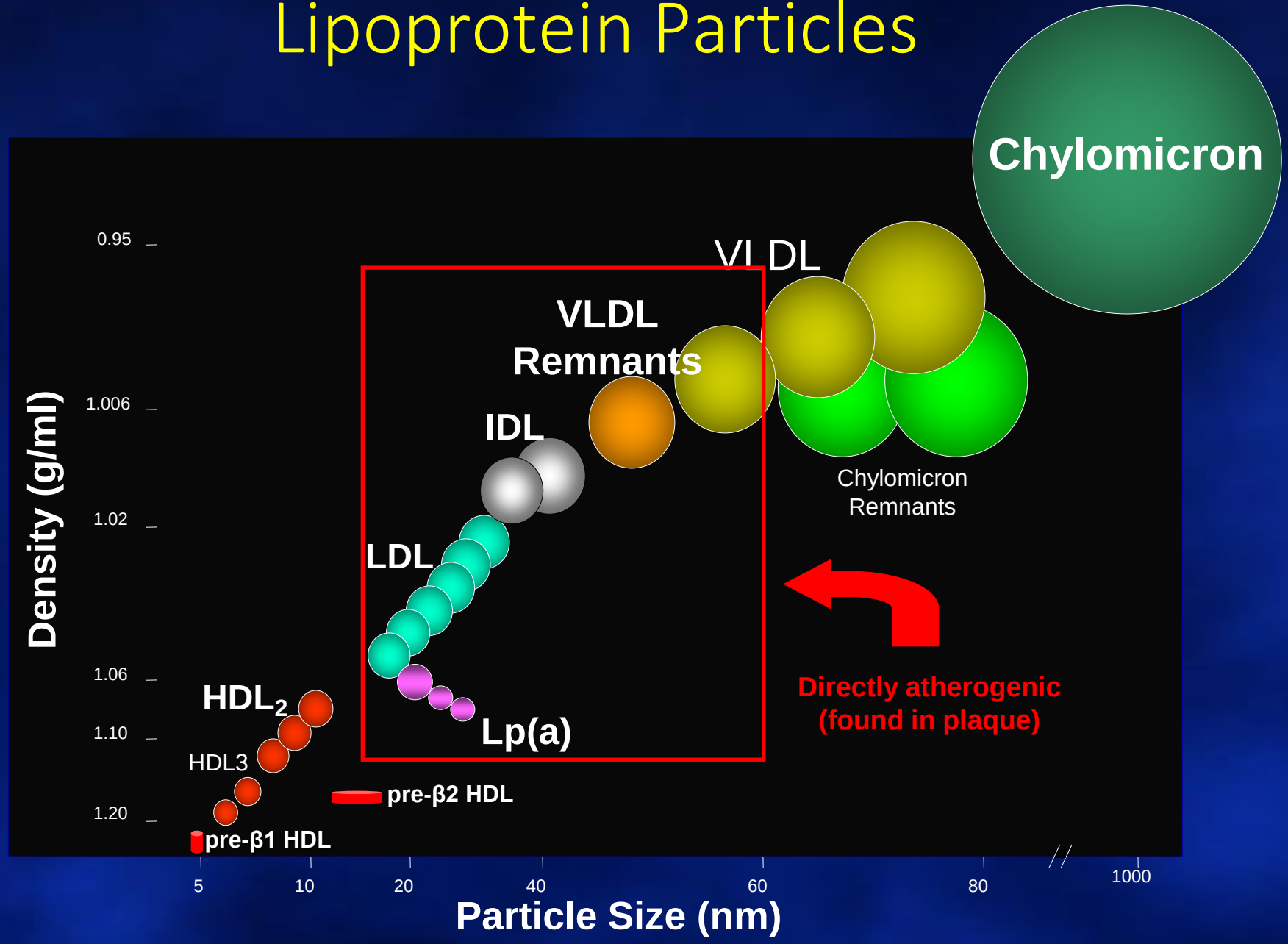
OUTLINE

- PATHOPHYSIOLOGY OF DYSLIPIDEMIA IN DIABETES
- ASSOCIATION BETWEEN LDL-C AND CARDIOVASCULAR DISEASE
- EVIDENCE OF STATIN TRIALS FOR CARDIOVASCULAR RISK REDUCTION IN DIABETES
- EVIDENCE OF NON-STATIN THERAPY TRIALS FOR CARDIOVASCULAR RISK REDUCTION IN DIABETES
  - NIACIN
  - EZETIMIBE
  - PCSK-9 INHIBITORS
  - FIBRATE
  - OMEGA-3 FATTY ACIDS
- BRIEF DISCUSSION OF NEW CHOLESTEROL GUIDELINES

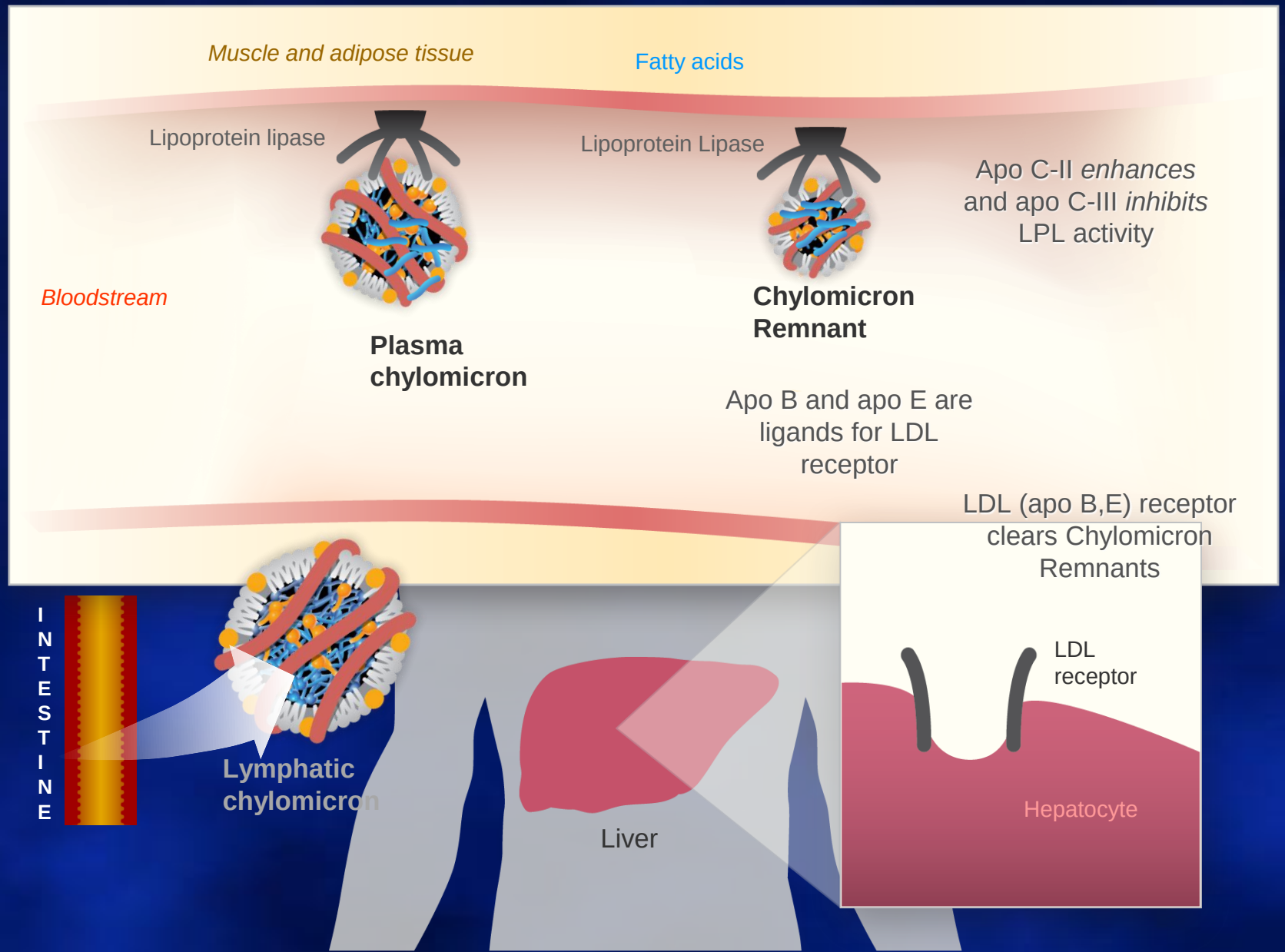
LIPOPROTEIN



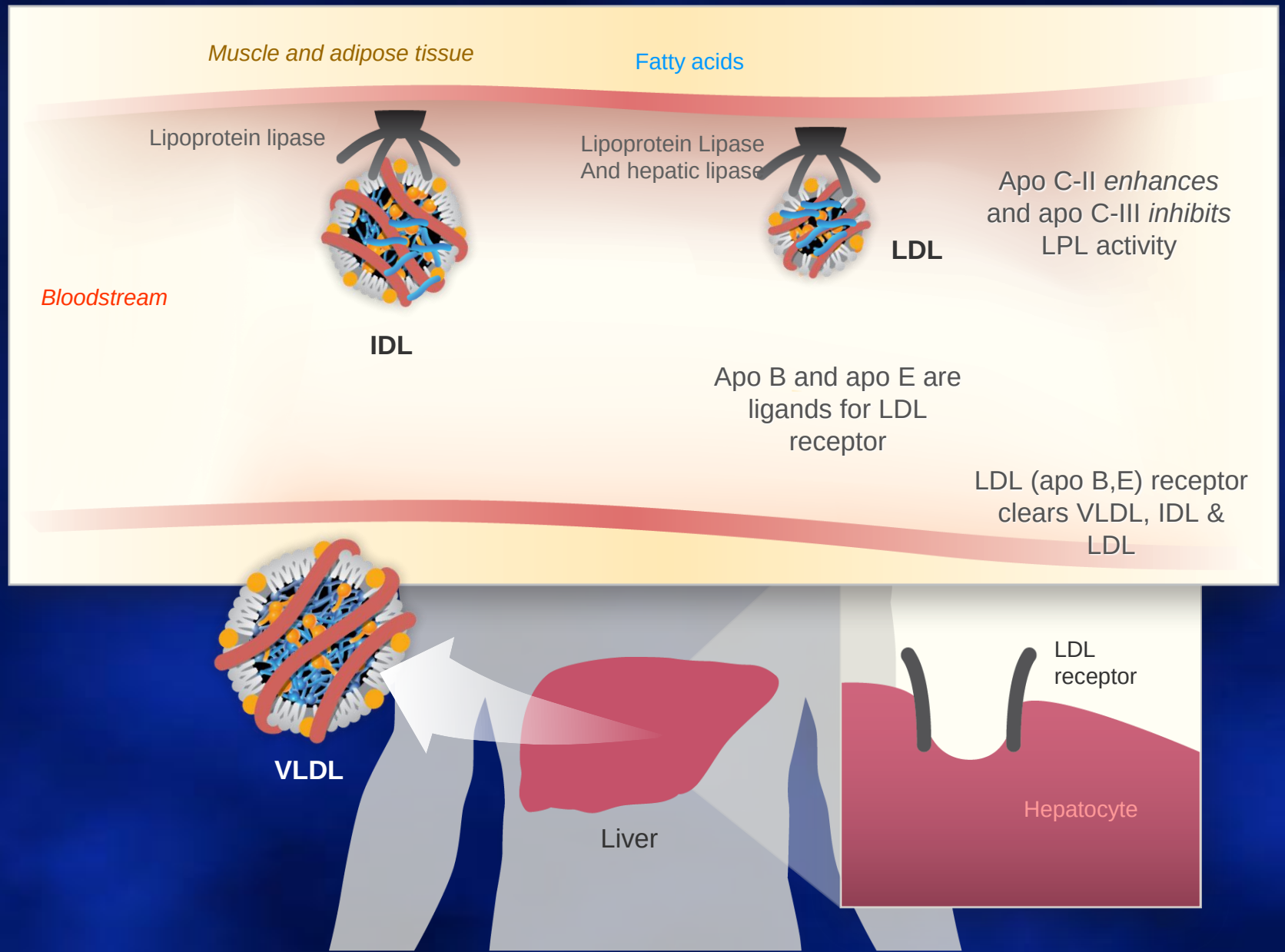
Lipoprotein Particles



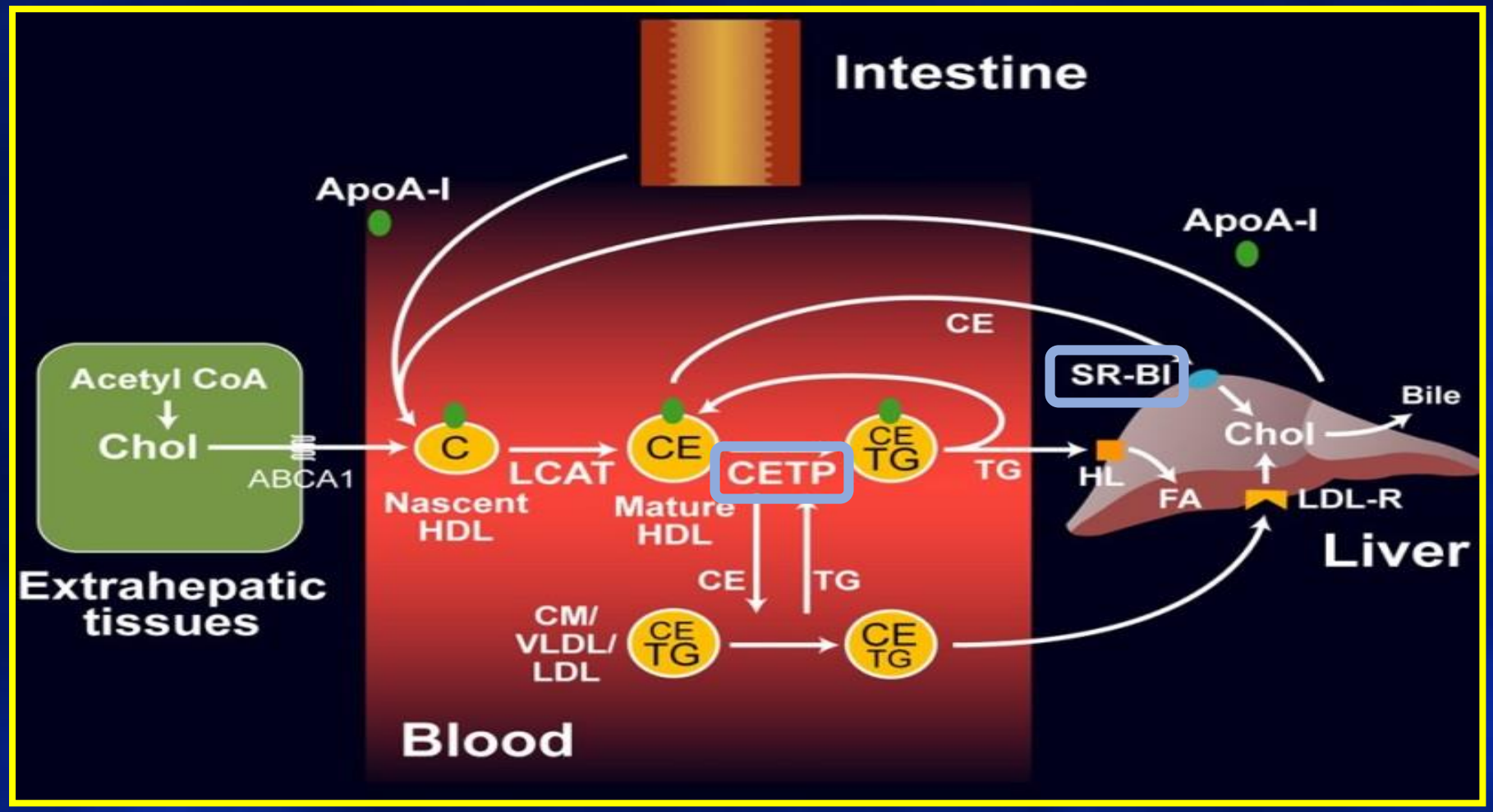
Exogenous (dietary) lipid metabolism

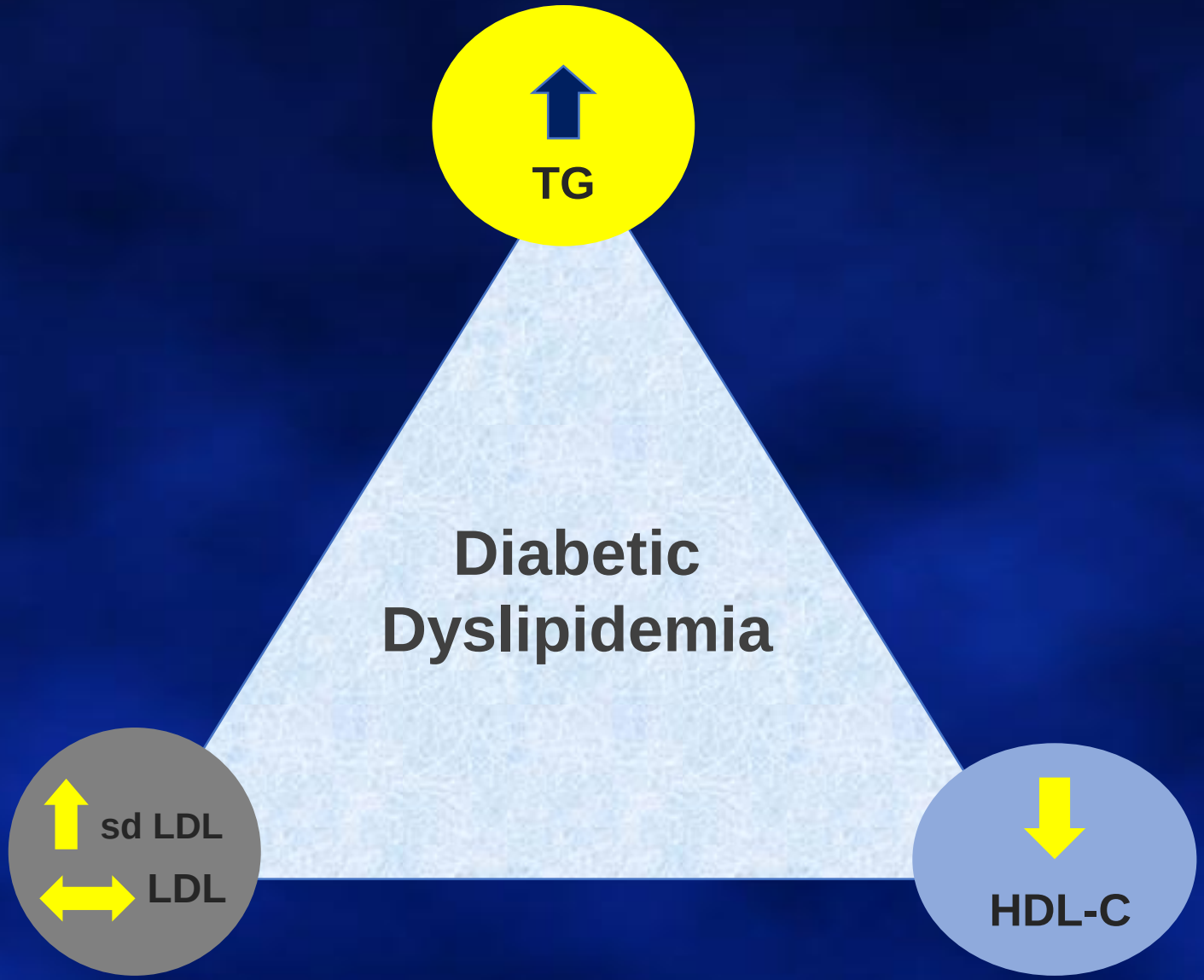


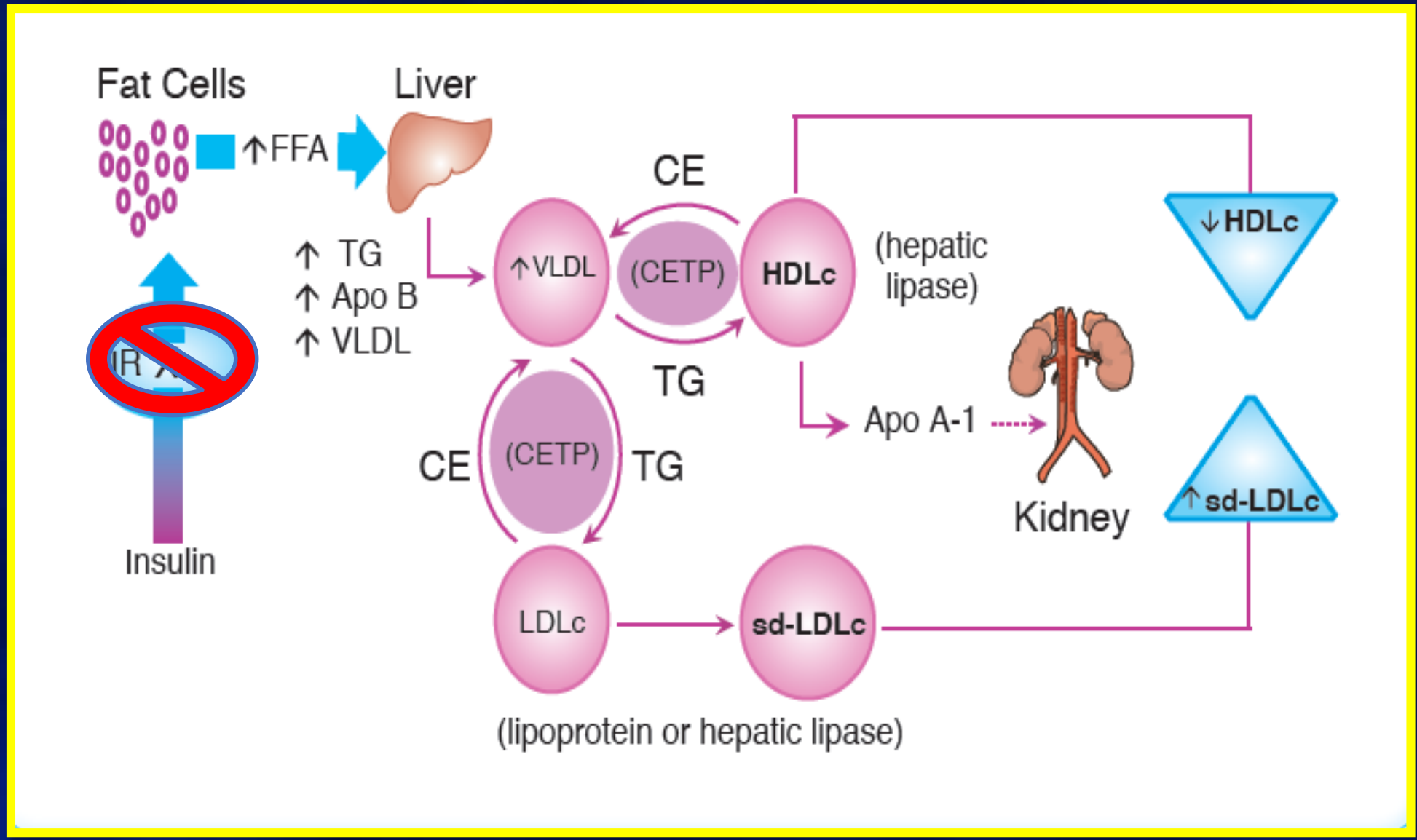
Endogenous lipid metabolism



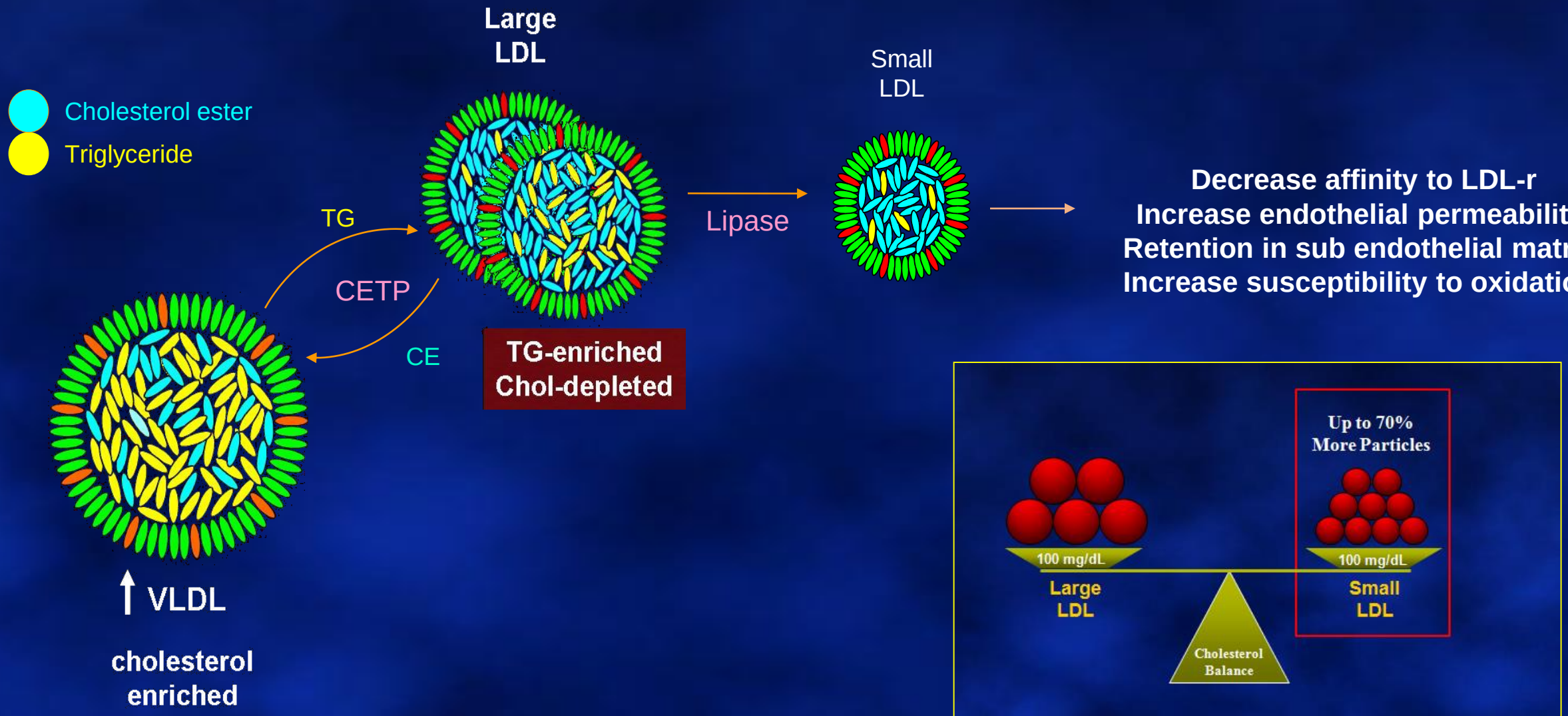
Reverse Cholesterol Transport




TG
Diabetic
Dyslipidemia
sd LDL
LDL
HDL-C


Fat Cells
Liver
↑FFA
↑ TG
↑ Apo B
↑ VLDL
IR ↑
Insulin
CE
↑VLDL
(CETP)
HDLc
(hepatic lipase)
TG
↓HDLc
Apo A-1
Kidney
CE
(CETP)
TG
↑sd-LDLc
LDLc
sd-LDLc
(lipoprotein or hepatic lipase)

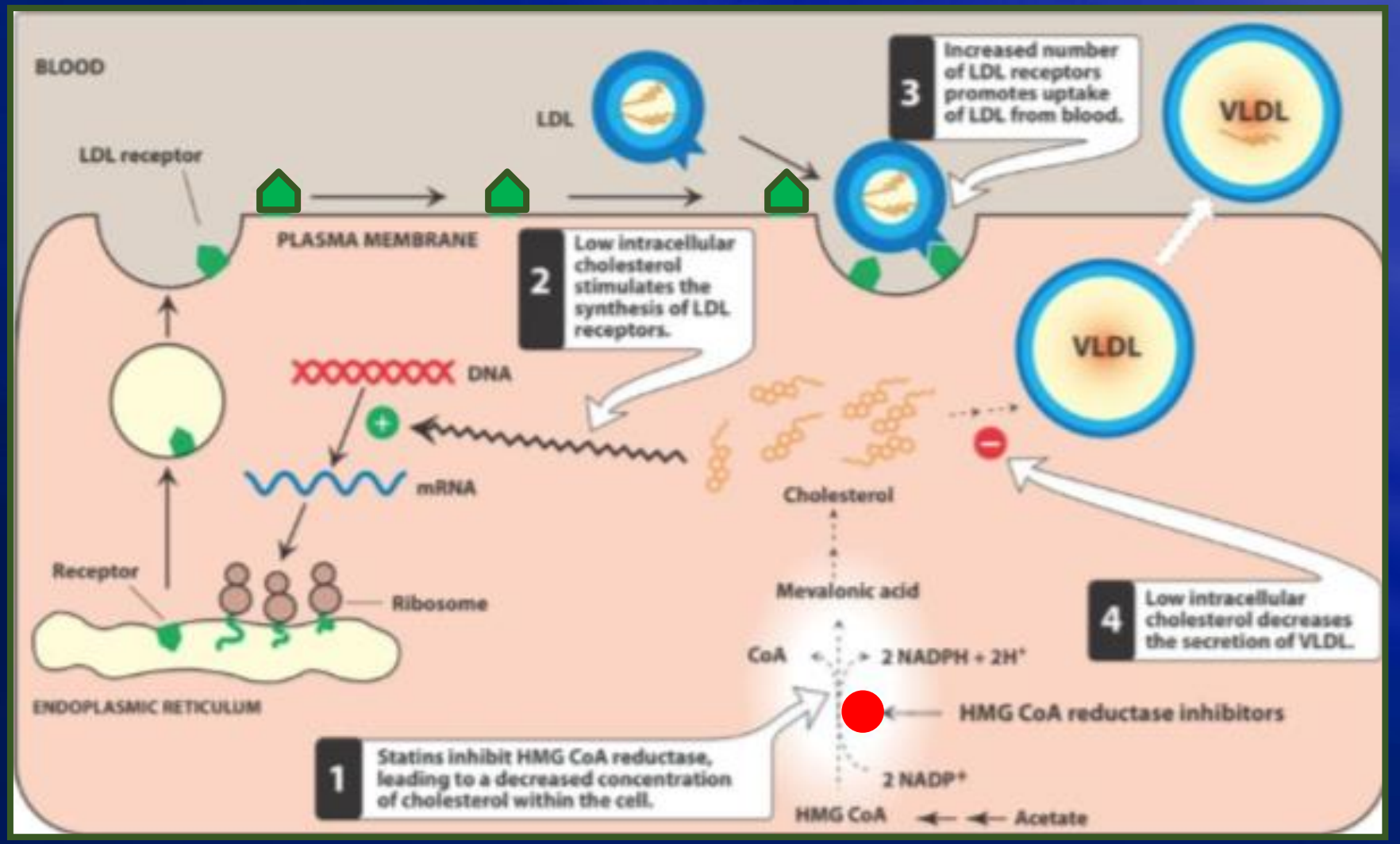
TG affects cholesterol content, and hence size, composition and density of lipoproteins



Otvos JD, et al. *AJC* 2002;90(8A):22i-29i

STATIN TRIALS FOR CARDIOVASCULAR RISK REDUCTION IN DIABETES

Statins mechanism of action



Statin Trials For Cardiovascular Risk Reduction in Diabetes

Primary Prevention

Study (year of primary publication)	Comparison	Subjects	Subjects with diabetes (%)	Diabetes results
CARDS (2004)	Atorvastatin 10 mg vs placebo	2,838	2,838 (100%)	Significant 37% reduction in primary endpoint
ASPEN (2006)	Atorvastatin 10 mg vs placebo	2,410	2,410 (100%), 1,905 primary prevention	No significant reduction in primary endpoint
HPS (2002)	Simvastatin 40 mg vs placebo	20,536	5,963 (28%), 2912 primary prevention	Significant 33% reduction in defined endpoint for subcategories
ALLHAT-LLT (2002)	Pravastatin 40 mg vs usual care	10,355	3,638 (35%)	No significant reduction in primary endpoint
ASCOT-LLA (2003)	Atorvastatin 10 mg vs placebo	10,305	2,532 (25%)	Significant 23% reduction in major cardiovascular events or procedures
MEGA (2006)	Pravastatin 10–20 mg vs usual care	7,832	1,632 (21%)	Significant 36% reduction in coronary heart disease events

Secondary Prevention

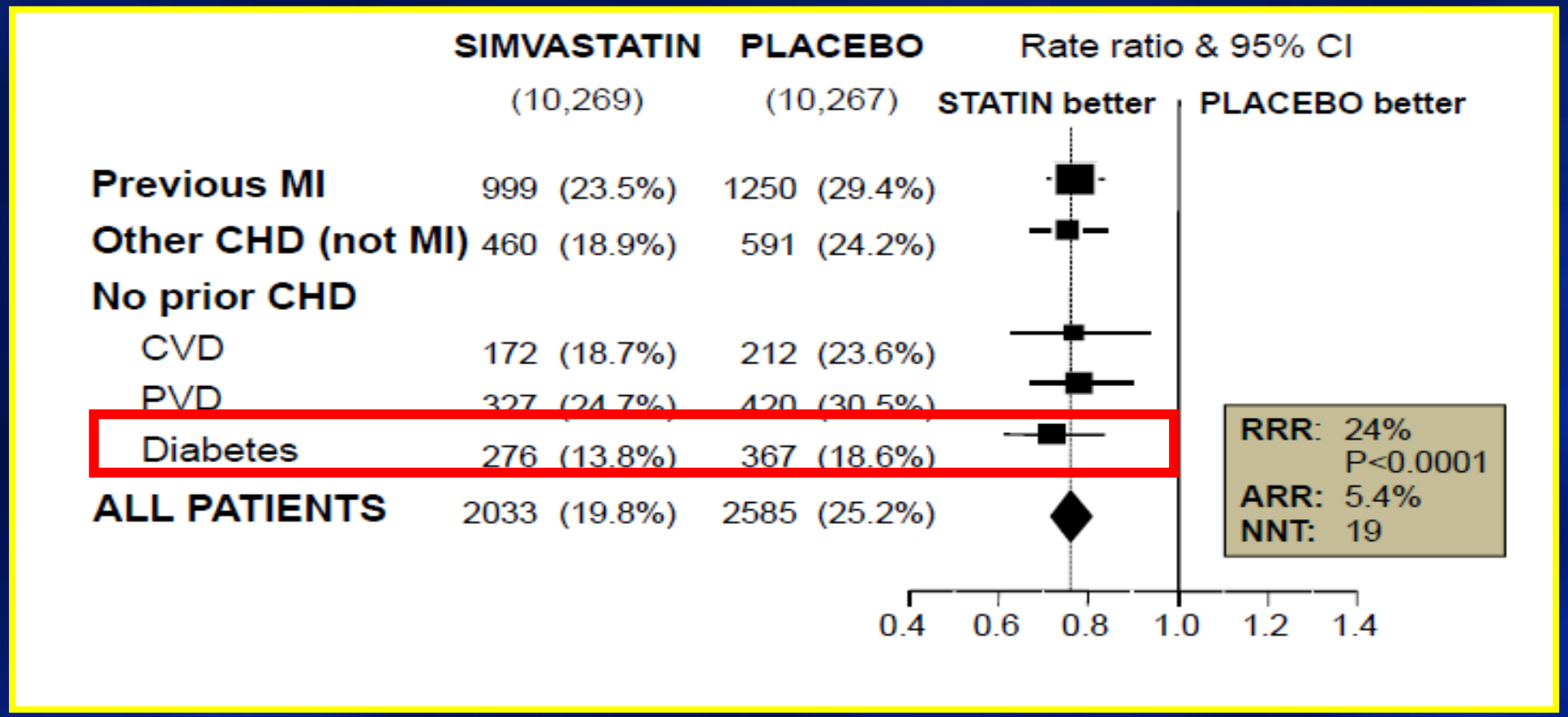
Study (year of primary publication)	Comparison	Subjects	Subjects with diabetes (%)	Diabetes results
4S (1994)	Simvastatin 20–40 mg vs placebo	4,444	202 (5%) 483 (11%)	No significant reduction in total mortality, significant 55% reduction in major coronary events
CARE (1996)	Pravastatin 40 mg vs placebo	4,159	586 (14%)	No significant reduction in major coronary events, significant 25% reduction in expanded coronary endpoint
LIPID (1998)	Pravastatin 40 mg vs placebo	9,014	1,077 (12%)	No significant reduction in major coronary events, significant 21% reduction in any cardiovascular event
HPS (2002)	Simvastatin 40 mg vs usual care	20,536	5,963 (28%), 3,051 secondary prevention	Significant reduction in defined endpoint for subcategories
4D (2005)	Atorvastatin 20 mg vs placebo	1,255	1,255 (100%)	No significant reduction in MACE
SPARCL (2006)	Atorvastatin 80 mg vs placebo	4,731	794 (17%)	No significant reduction in strokes, significant reduction in major coronary events and MACE

Heart Protection Study (HPS) of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo controlled trial (2002)

Treatment comparison	N	Target population	Entry lipid criteria	Primary Endpoint
Simvastatin 40mg vs. placebo	20,536 Diabetes subgroup 5,963	Patients at high risk for CVE (Hx. of MI, other atherosclerotic lesions, diabetes, hypertension)	Non-fasting TC ≥ 135mg/dl Baseline LDL: 127 mg/dL	All cause mortality and major cardiovascular events

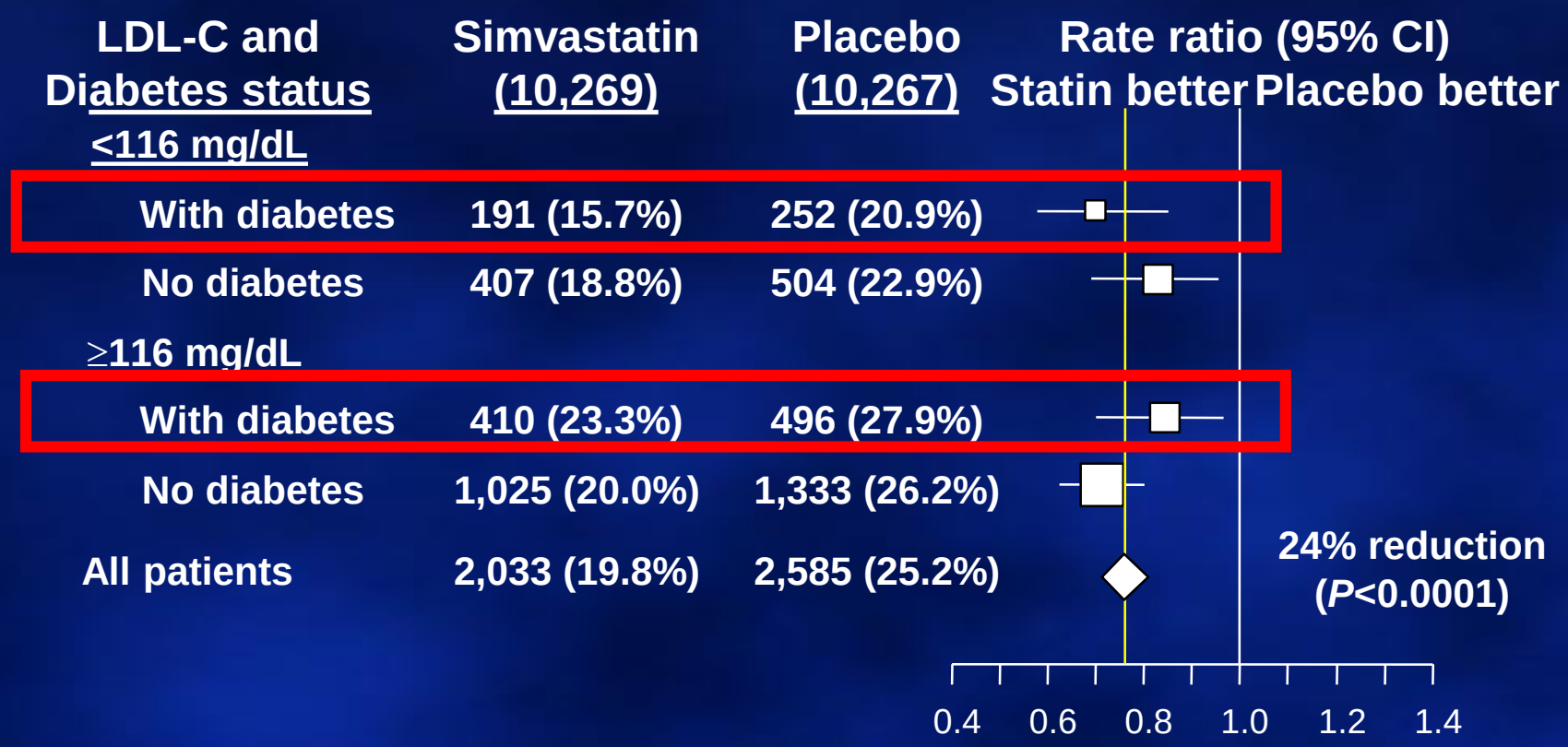
Heart Protection Study Collaborative Group. *Lancet* 2003;361:2005–2016.

HPS Primary Endpoint Results by Group



Heart Protection Study Collaborative Group. *Lancet* 2003;361:2005–2016.

HPS: Major Vascular Events by LDL-C and Prior Diabetes



A statin provides CV benefit in diabetics

In high risk patients with LDL < 100mg/dl statin therapy would result in benefit.

Heart Protection Study Collaborative Group. *Lancet* 2003;361:2005–2016.

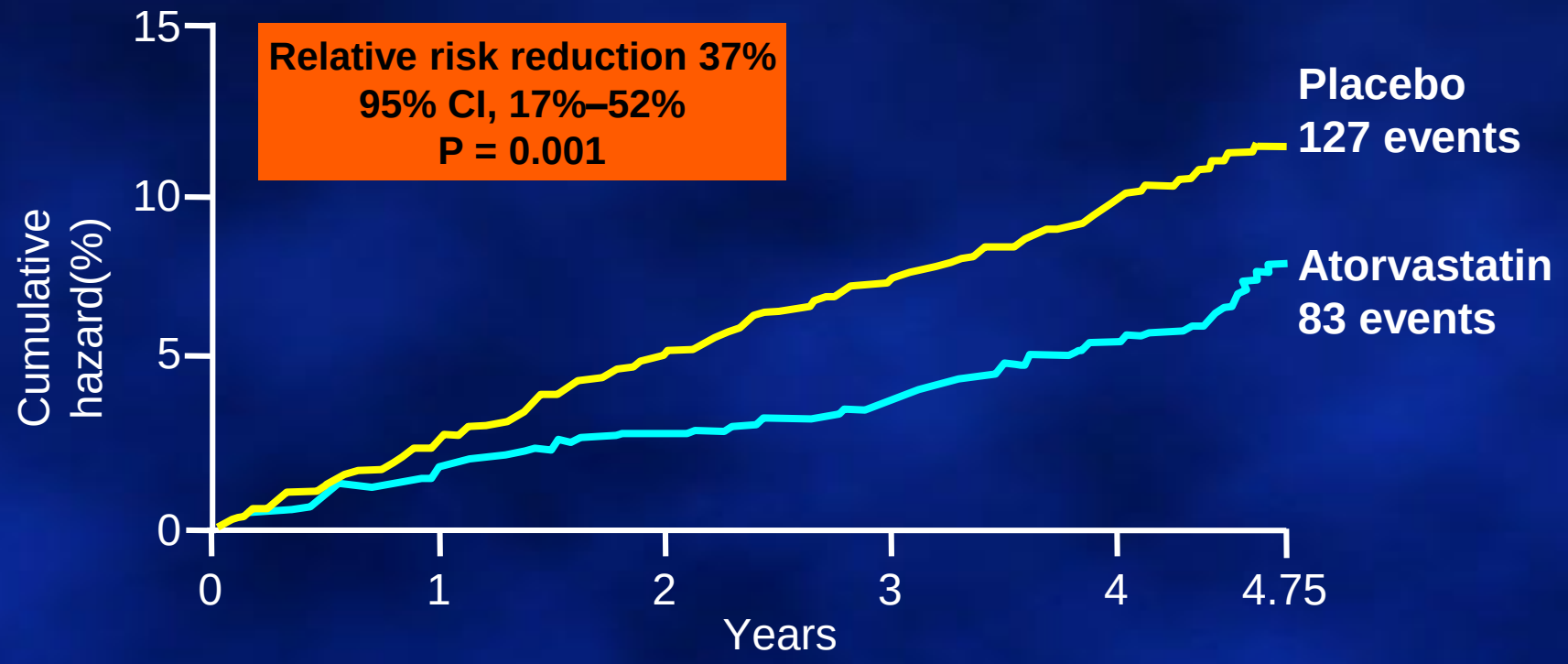
Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study: CARDS (2004)

Treatment comparison	N	Target population	Entry lipid criteria	Primary Endpoint
Atorvastatin 10mg vs. placebo	2,838	Patients at high risk of CVD (hypertension, retinopathy, renal disease, or smoking) No evidence of clinical atherosclerosis.	LDL-C ≤ 160 mg/dL TG < 600 mg/dL Baseline LDL: 120mg/dL	Time to first major CVD (CHD death, nonfatal MI, revascularization, stroke)

Colhoun, H.M., Betteridge, D.J., Durrington, P.N., Hitman, G.A., & investigators, C.B. (2004). CARDS: multicentre randomised placebo-controlled trial. *The Lancet, 364*, 685-696.

CARDS Primary Endpoint ResultsTime to first CV event

40% LDL-C reduction with 80% achieving LDL-C levels below 100 mg/dL



Placebo	1410	1351	1306	1022	651	305
Atorvastatin	1428	1392	1361	1074	694	328

Colhoun, H.M., Betteridge, D.J., Durrington, P.N., Hitman, G.A., & investigators, C.U.R. (2004). CARDS multicentre randomised placebo-controlled trial. *The Lancet, 364*, 685-696.

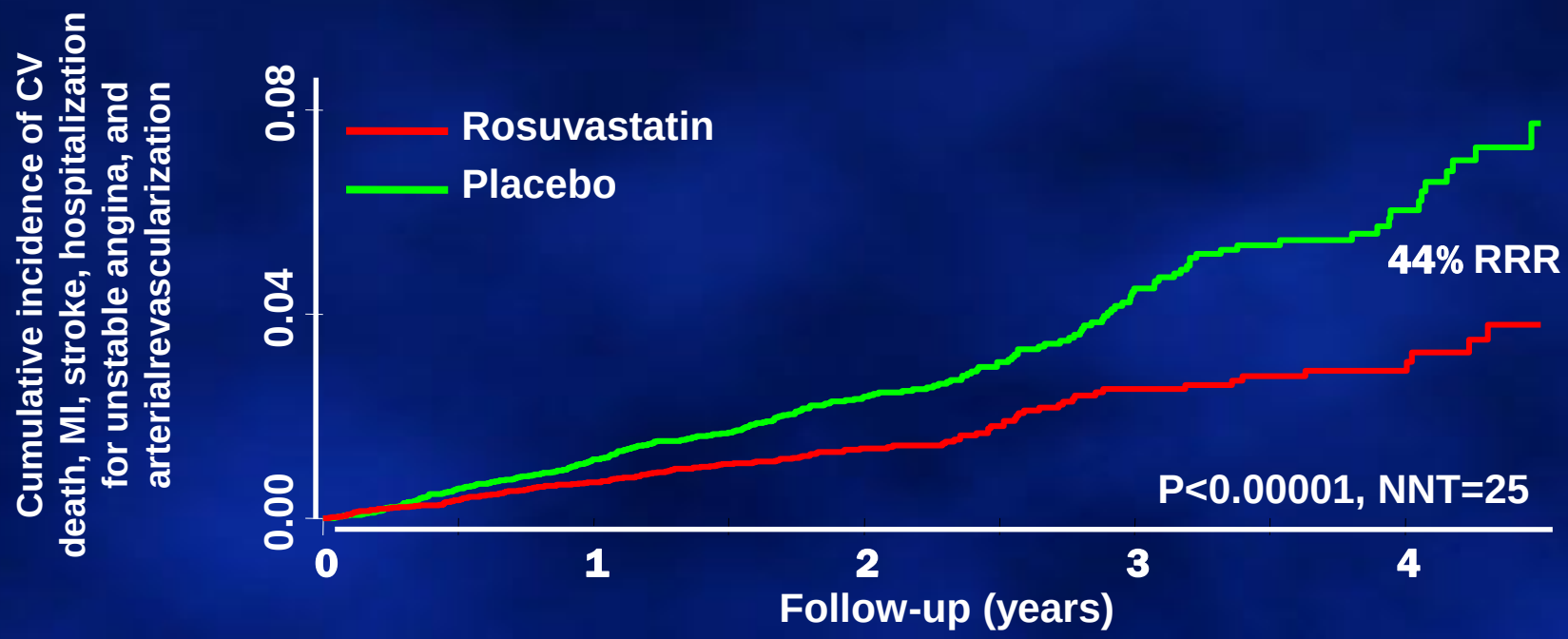
Justification for the Use of Statins in Prevention
An Intervention Trial Evaluating Rosuvastatin – JUPITER (2008)

Treatment comparison	N	Target population	Entry lipid criteria	Primary Endpoint
Rosuvastatin 20mg vs. placebo	17,802	No prior CVD or MI with elevated hs-CRP >2 mg/L	LDL-C ≤ 130 mg/dL Baseline LDL: 104mg/dL	MI, Stroke, UA/Revascularization, CV Death

Engl J Med 2008; 359:2195-2207, DOI: 10.1056/NEJMoa0807646

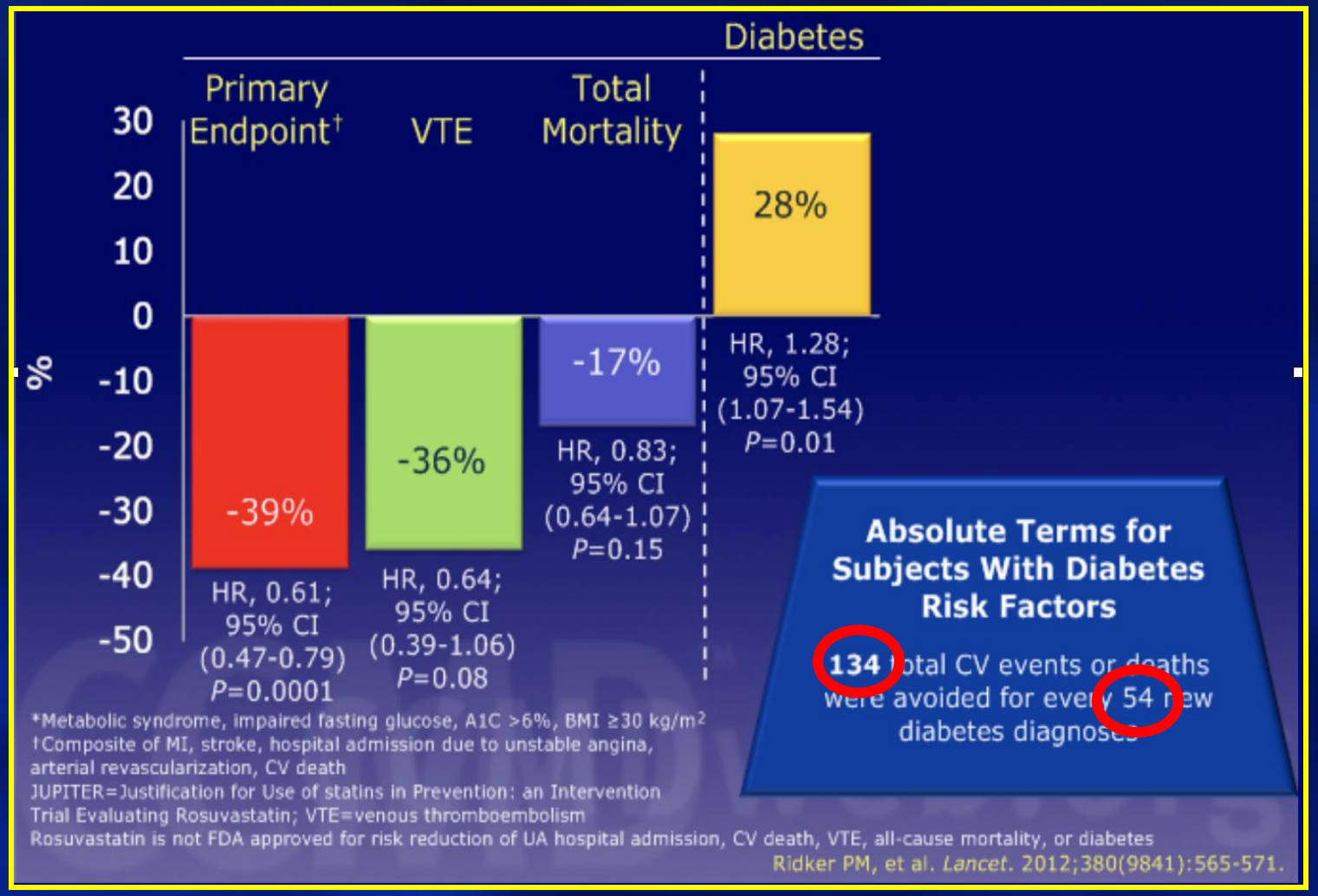
JUPITER

Primary Endpoint : MI, Stroke, UA/Revascularization, CV Death



Engl J Med 2008; 359:2195-2207, DOI: 10.1056/NEJMoa0807646

JUPITER
Risk reduction with rosuvastatin treatment for those with ≥1 diabetes risk factor



Patients with ≥1 diabetes risk factor (metabolic syndrome, IFG, A1C >6%, BMI ≥30 kg/m^2) CV and mortality benefit of statin therapy exceeded the risk of developing diabetes.

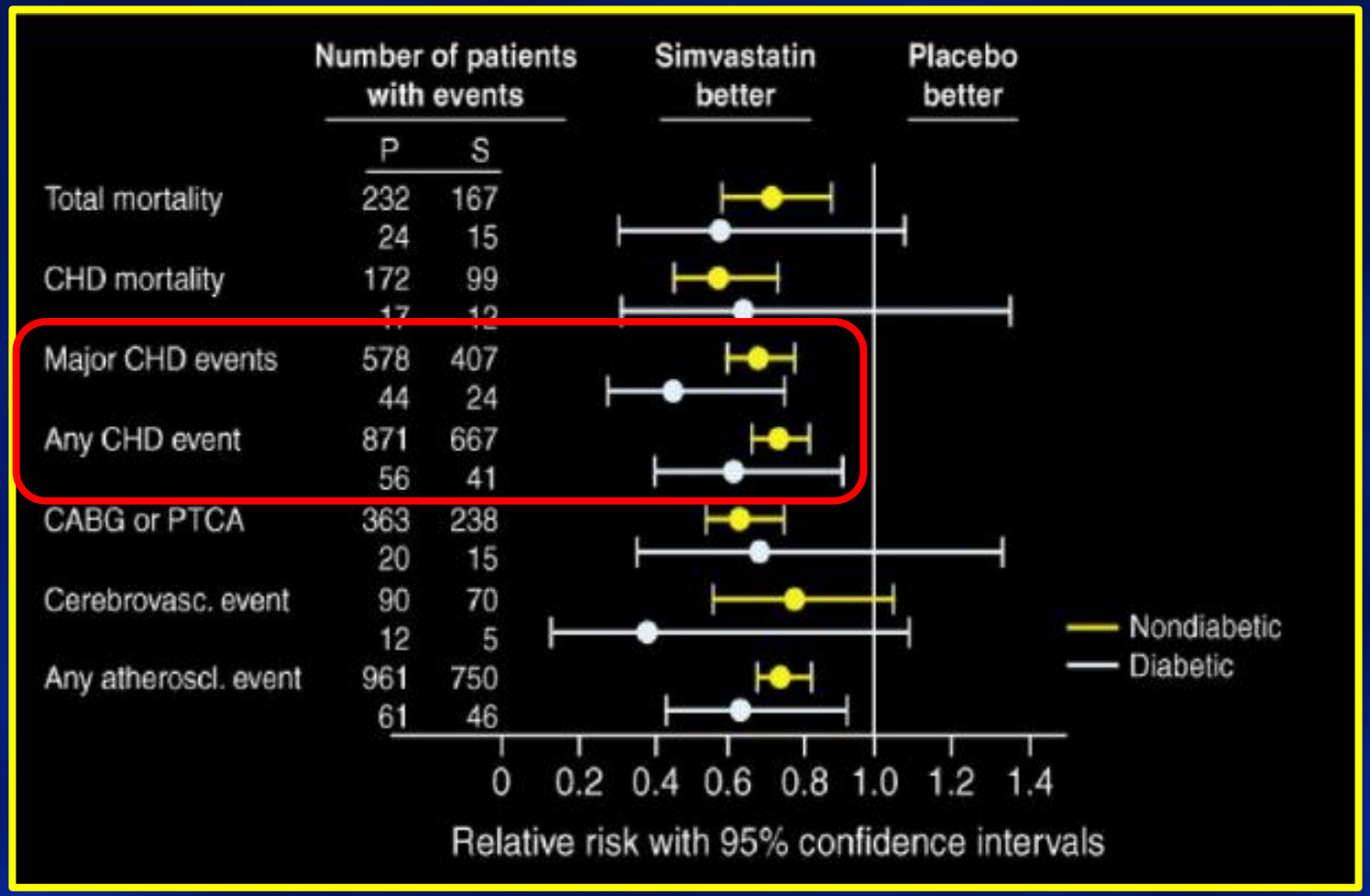
CV benefits came with hazard of diagnosis of new onset diabetes **5-6 weeks earlier** among statin allocated patients.

Scandinavian Simvastatin Survival Study 4S (1994)

Treatment comparison	N	Target population	Entry lipid criteria	Primary Endpoint
Simvstatin 20mg – 40mg vs. placebo	4,444 Diabetes subgroup 202	Patients with prior MI and/or angina	TC: 212-309 mg/dL Baseline LDL: 185mg/dL	All cause mortality

Diabetes Care 1997 Apr; 20(4): 614-620.https://doi.org/10.2337/diacare.20.4.614

Benefit of Lipid Lowering in Diabetic Subgroup with CHD 4S



Diabetes Care 1997 Apr; 20(4): 614-620.https://doi.org/10.2337/diacare.20.4.614

Low Dose vs. High Dose Statin Trials in Diabetes

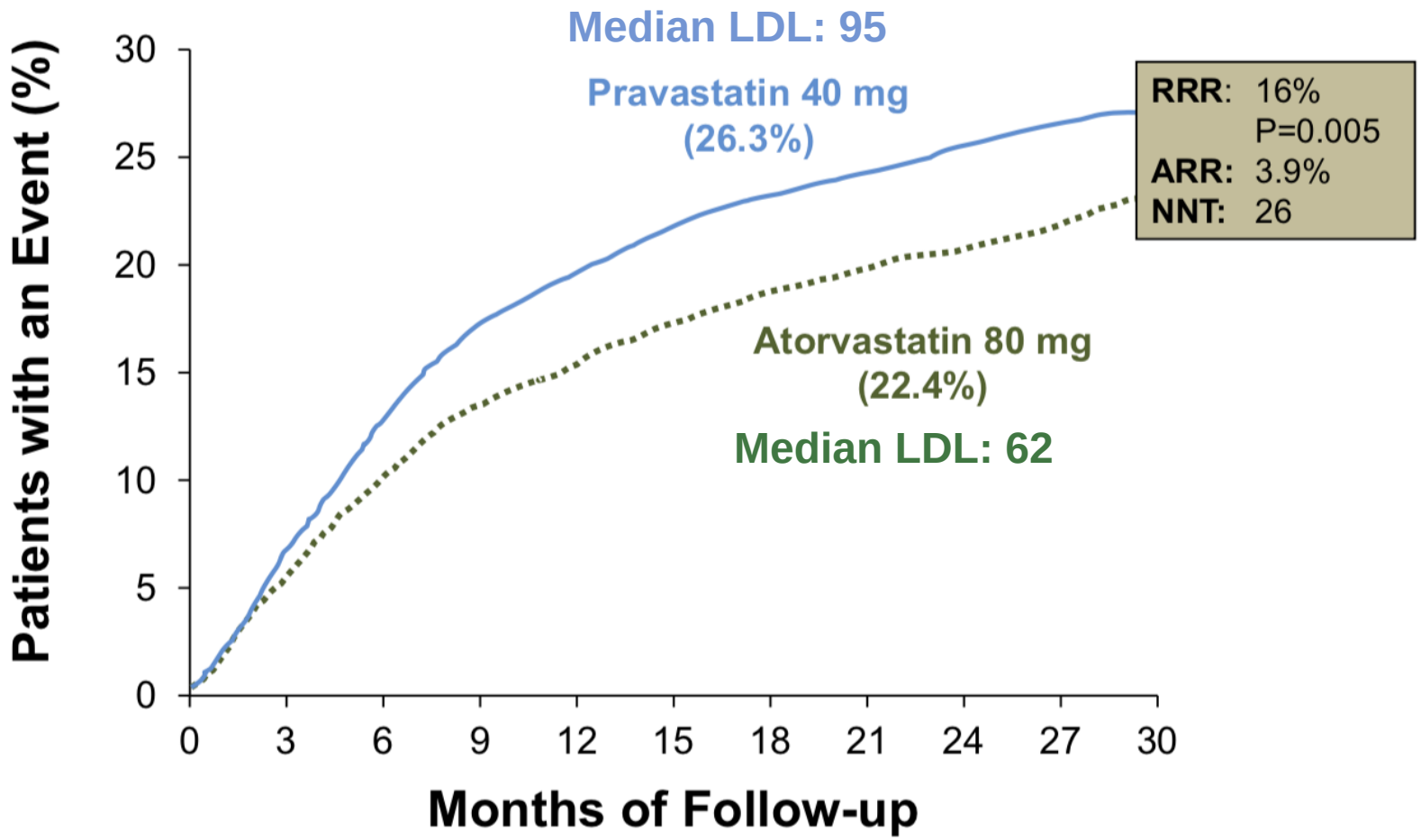
Study (year of primary publication)	Comparison	Subjects	Subjects with diabetes (%)	Diabetes results
PROVE IT (2004)	Atorvastatin 80 mg vs pravastatin 40 mg	4,162	978 (23%)	Significant 25% reduction in acute cardiac events
A to Z (2004)	Simvastatin 40 mg then 80 mg vs placebo then simvastatin 20 mg	4,497	1,059 (24%)	Insignificant reduction in primary endpoint
TNT (2005)	Atorvastatin 80 mg vs atorvastatin 10 mg	10,001	1,501 (15%)	Significant 25% reduction in major cardiovascular events
IDEAL (2005)	Atorvastatin 80 mg vs simvastatin 20–40 mg	8,888	1,069 (12%)	Overall no significant reduction in primary endpoint, diabetes subgroup not reported
SEARCH (2010)	Simvastatin 80 mg vs simvastatin 20 mg	12,064	1,267 (11%)	Overall no significant reduction in primary endpoint, diabetes subgroup not reported

Pravastatin or Atorvastatin Evaluation and Infection Therapy: PROVE-IT (2004)

Treatment comparison	N	Target population	Entry lipid criteria	Primary Endpoint
Atorvastatin 80 mg vs Pravastatin 40 mg	4,162 Diabetes subgroup: 734	Hospitalization for acute MI or high-risk unstable angina within 10 days of the event.	TC ≤240 mg/dL Baseline LDL: 106mg/dL	Death from any cause or a major cardiovascular event (MI, UA requiring rehospitalization, revascularization, or stroke).

Wiviott SD, Cannon CP, Morrow DA et al. for the PROVE-IT TIMI 22 Investigators. J Am Coll Cardiol. 2005;46:1411-1416.

PROVE- IT



Cannon C, et al. *N Engl J Med*. 2004;350:1495-1504.

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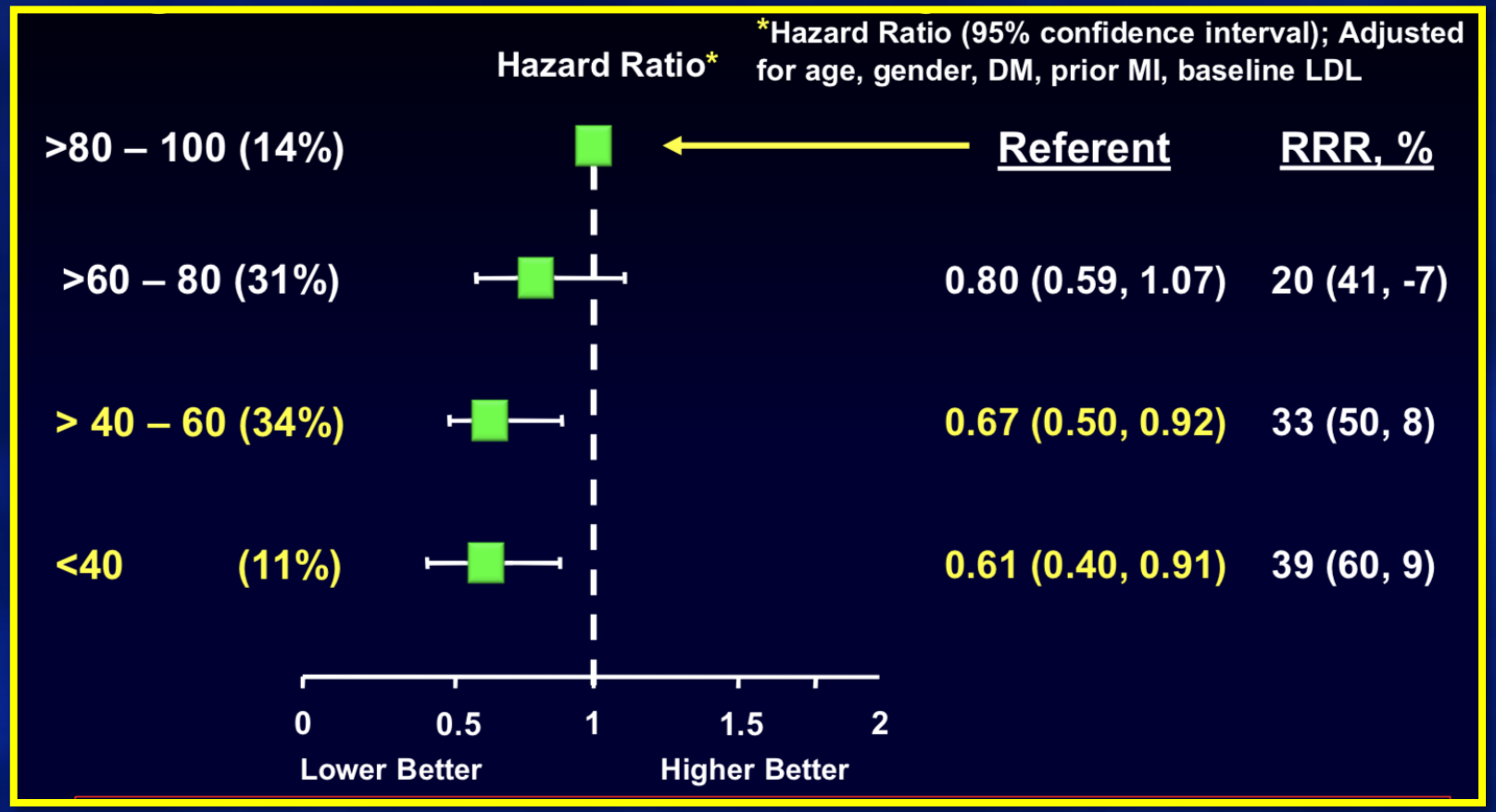
Among the relatively small proportion of subjects with diabetes, the risk reduction was **17%,** which did not reach statistical significance.

PROVE-IT: Long-Term Risk of Death or Major CV Event

Are Outcomes Better with Low Achieved LDL-C?



A lower rate of clinical events and no increase in adverse events in patients who achieved very low cholesterol levels (<60 mg/dL).

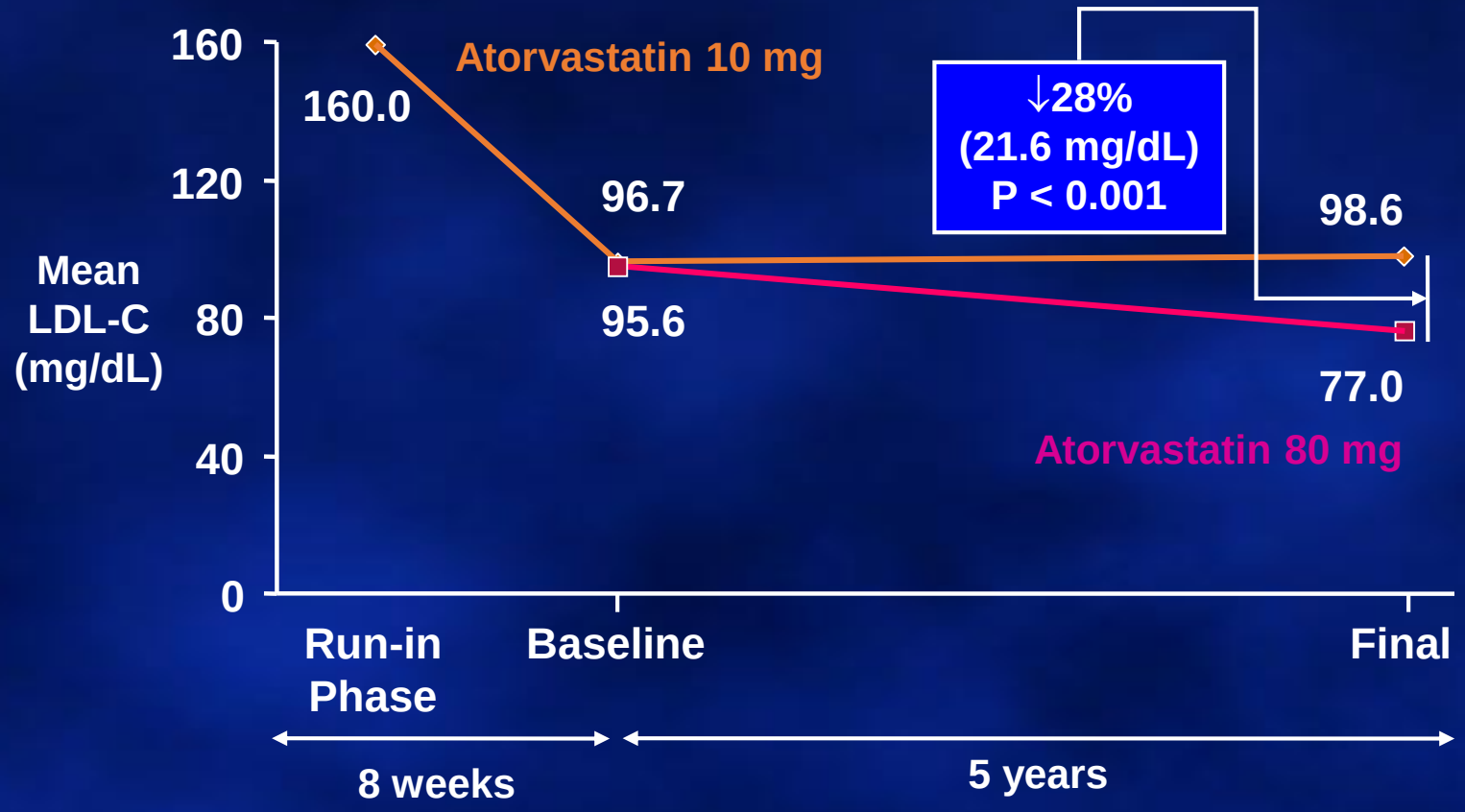
Wiviott SD, Cannon CP, Morrow DA et al. for the PROVE-IT TIMI 22 Investigators. J Am Coll Cardiol. 2005;46:1411-1416.

Treating to New Targets (TNT) Study Design (2005)

Treatment comparison	N	Target population	Entry lipid criteria	PrimaryEndpoint
Atorvastatin 80 mg vs Atorvastating 10 mg	10,001 Diabetes subgroup: 1,501	Patients with established CVD	LDL-C < 130 mg/dL Baseline LDL: 98mg/dL	Time to first CV event (CHD death, MI, resuscitation after cardiac arrest or stroke)

TNT diabetic analysis: Treatment effects on LDL-C

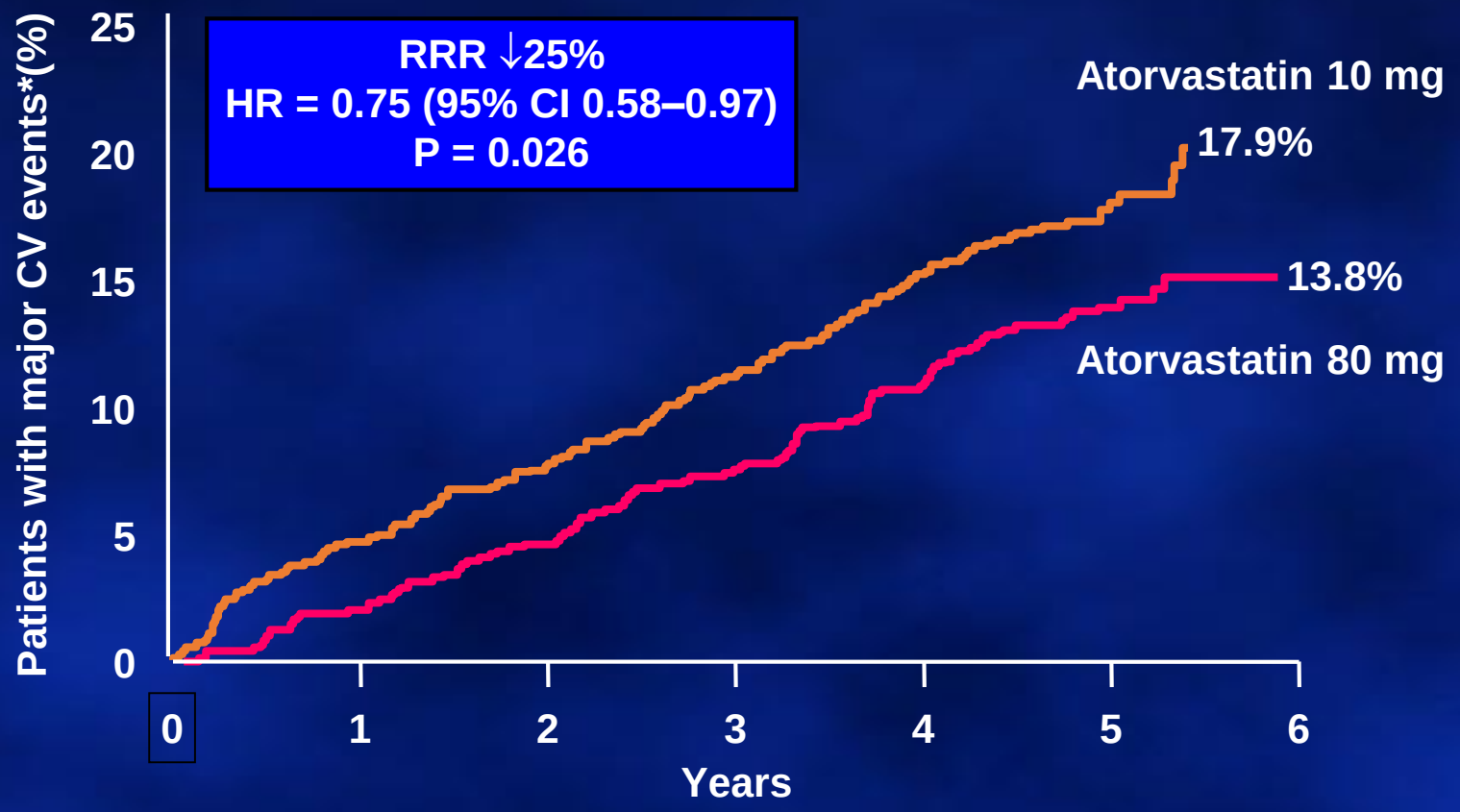
N = 1501 with CHD and diabetes



Shepherd J et al. *Diabetes Care*. 2006;29:1220-6.

TNT diabetic analysis: First major CV event

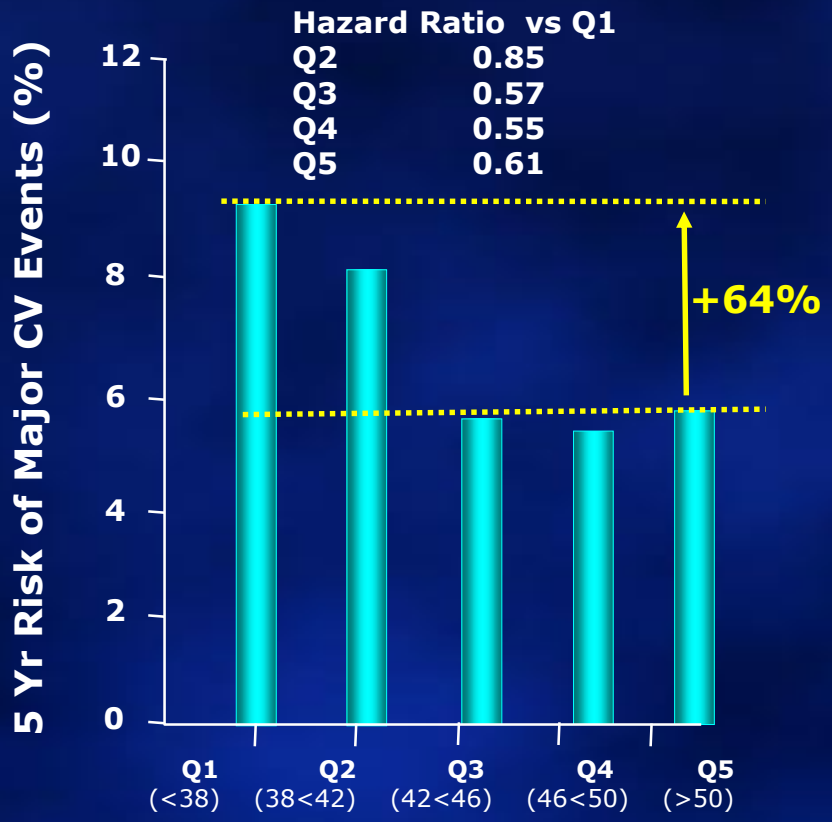
N = 1501 with CHD and diabetes



*CHD death, nonfatal non-procedural MI, resuscitated cardiac arrest, fatal/nonfatal stroke

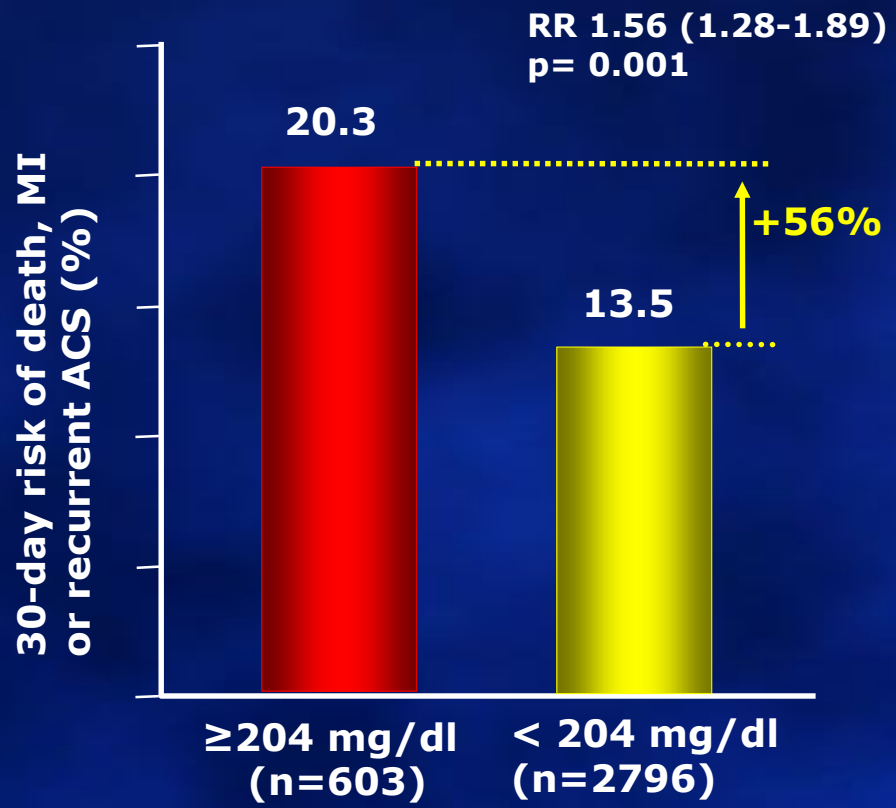
Shepherd J et al. *Diabetes Care*. 2006;29:1220-6.

HDL-C & TG remain predictive of CVD events even when LDL-C < 70 mg/dL: TNT & PROVE-IT



On-Treatment Quintile of HDL-C In Pts with LDL-C < 70 mg/dL

Barter P et al. NEJM 357:1301-10, 2007



On-Treatment TG In Pts with LDL-C < 70 mg/dL

Miller et al. 2008

Meta-analysis: Effects of Cholesterol Lowering on Major Vascular Events Among Patients with Diabetes in 14 Randomized Trials of Statins (CTT trials)

	Diabetes mellitus			No diabetes
	Type 1	Type 2*	Any type	
4S[15]	24 (0·5%)	178 (4·0%)	202 (4·5%)	4242 (95·5%)
WOSCOPS[16]	8 (0·1%)	68 (1·0%)	76 (1·2%)	6519 (98·8%)
CARE[17]	193 (4·6%)	393 (9·4%)	586 (14·1%)	3573 (85·9%)
Post-CABG[18]	27 (2·0%)	89 (6·6%)	116 (8·6%)	1235 (91·4%)
AFCAPS/TexCAPS[19]	0	155 (2·3%)	155 (2·3%)	6450 (97·7%)
LIPID[20]	106 (1·2%)	676 (7·5%)	782 (8·7%)	8232 (91·3%)
GISSI-P[21]	120 (2·8%)	462 (10·8%)	582 (13·6%)	3689 (86·4%)
LIPS[22]	39 (2·3%)	163 (9·7%)	202 (12·0%)	1475 (88·0%)
HPS[23]	615 (3·0%)	5348 (26·0%)	5963 (29·0%)	14 573 (71·0%)
PROSPER[24]	51 (0·9%)	572 (9·9%)	623 (10·7%)	5181 (89·3%)
ALLHAT – LLT[25]	0	3638 (35·1%)	3638 (35·1%)	6717 (64·9%)
ASCOT – LLA[26]	0	2527 (24·5%)	2527 (24·5%)	7778 (75·5%)
ALERT[27]	280 (13·3%)	116 (5·5%)	396 (18·8%)	1706 (81·2%)
CARDS[28]	3 (0·1%)	2835 (99·9%)	2838 (100%)	0
Total	1466 (1·6%)	17 220 (19·1%)	18 686 (20·7%)	71 370 (79·3%)

Data are number (%). *Includes 13 participants with diabetes of unknown type.

Table 1: **Number of participants with diabetes by trial**

CTT trials

In all cause mortality per mmol/L (39 mg/dL) reduction in LDL-C.

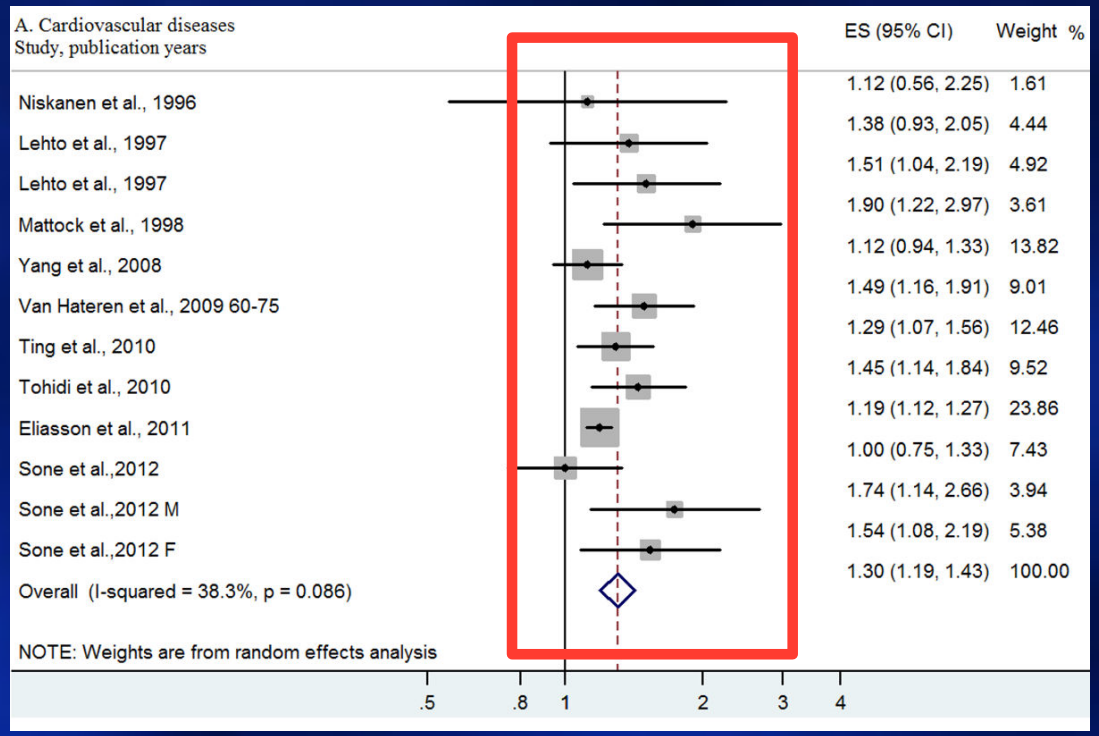
In major vascular events per mmol/L (39 mg/dL) reduction in LDL-C.

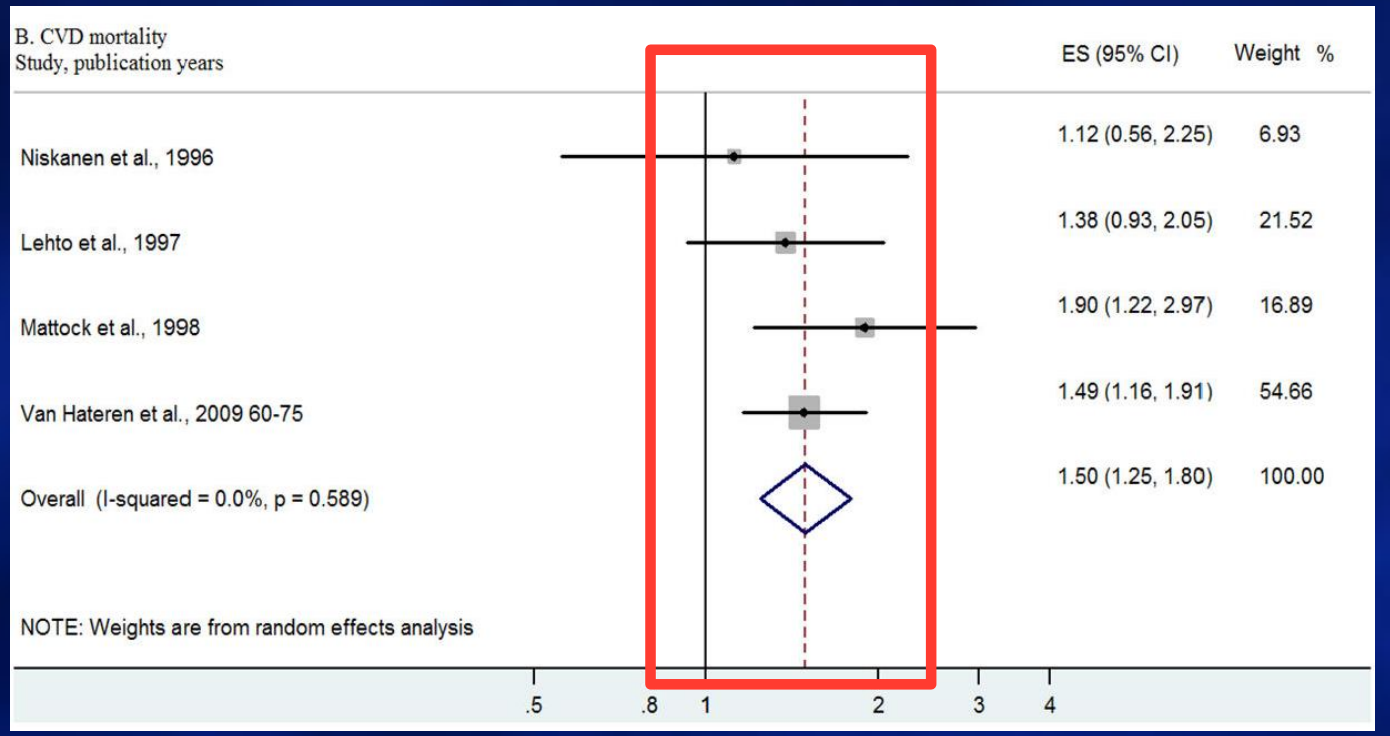
The beneficial effect of statin therapy was seen in primary and secondary prevention patients.

The benefit of statin therapy in people with diabetes was largely independent of pretreatment concentrations of LDL-C, HDL-C and triglycerides.

The benefits seemed to be linearly related to the absolute LDL reduction produced by statin therapy, without any lower threshold below which benefit was absent.

Impact of LDL-C on cardiovascular outcomes in people with type 2 diabetes: a meta-analysis of prospective cohort studies





The risk of **incident CVD increased 30%** and the **risk of CVD mortality increased 50%** along with **39 mg/dL increase in LDL** cholesterol.

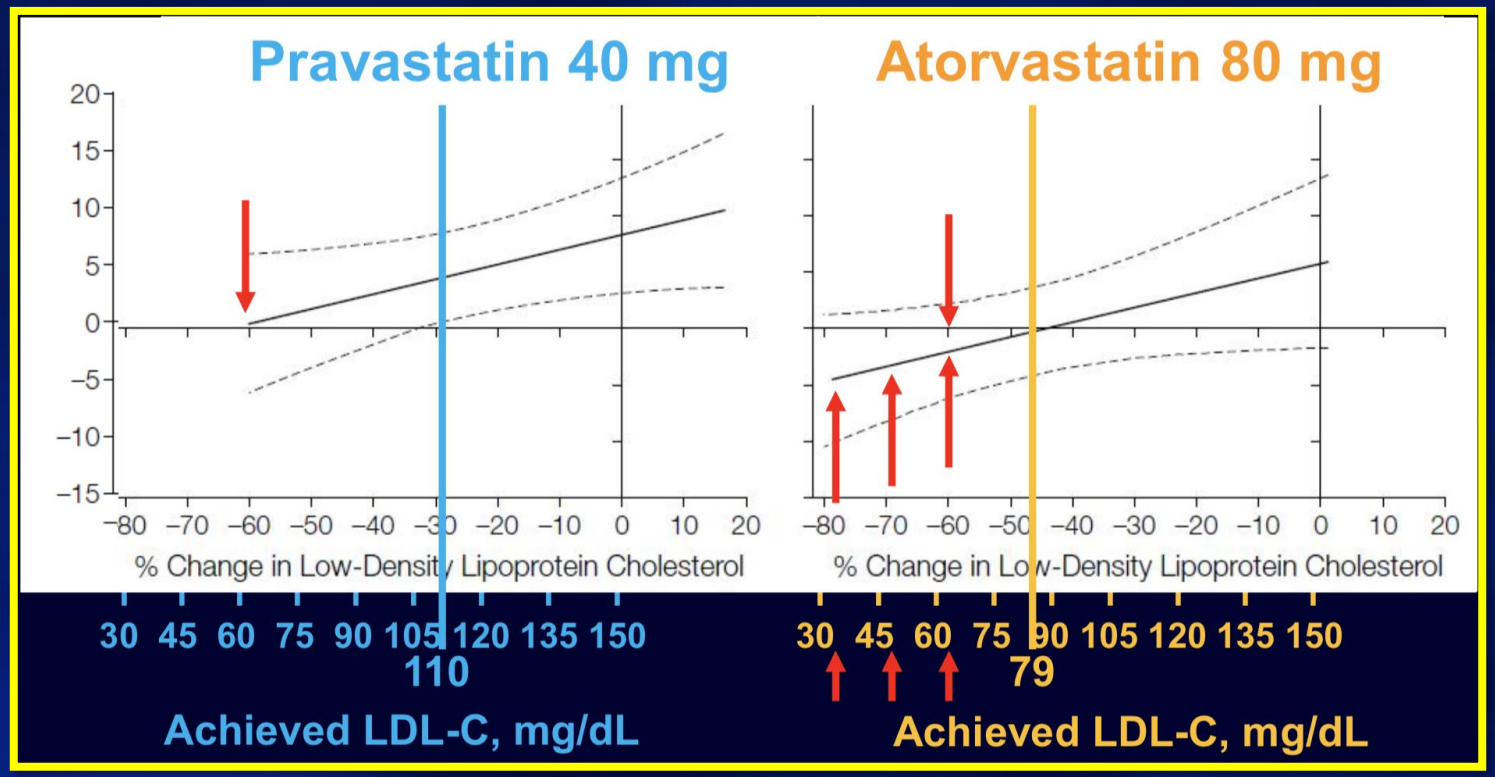
Diabetes Res Clin Pract. 2013 October ; 102(1): 65–75. doi:10.1016/j.diabres.2013.07.009.

Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL)

Treatment comparison	N	Target population	Entry lipid criteria	Primary Endpoint
Pravastatin 40 mg vs Atorvastatin 80 mg	502 Diabetes subgroup 95	Symptomatic CAD a 20% or greater stenosis by angiography, and elevated LDL	LDL-C 125 - 210 mg/dl	Percent change in atheroma volume on IVUS between baseline and 18 month follow-up

Nissen SE, et al. Effect of Intensive Compared With Moderate Lipid-Lowering Therapy on Progression of Coronary Atherosclerosis: JAMA.2004;291(9):1071–1080. doi:10.1001/jama.291.9.1071

Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL): Linear Regression Analysis of Change in Atheroma Volume.

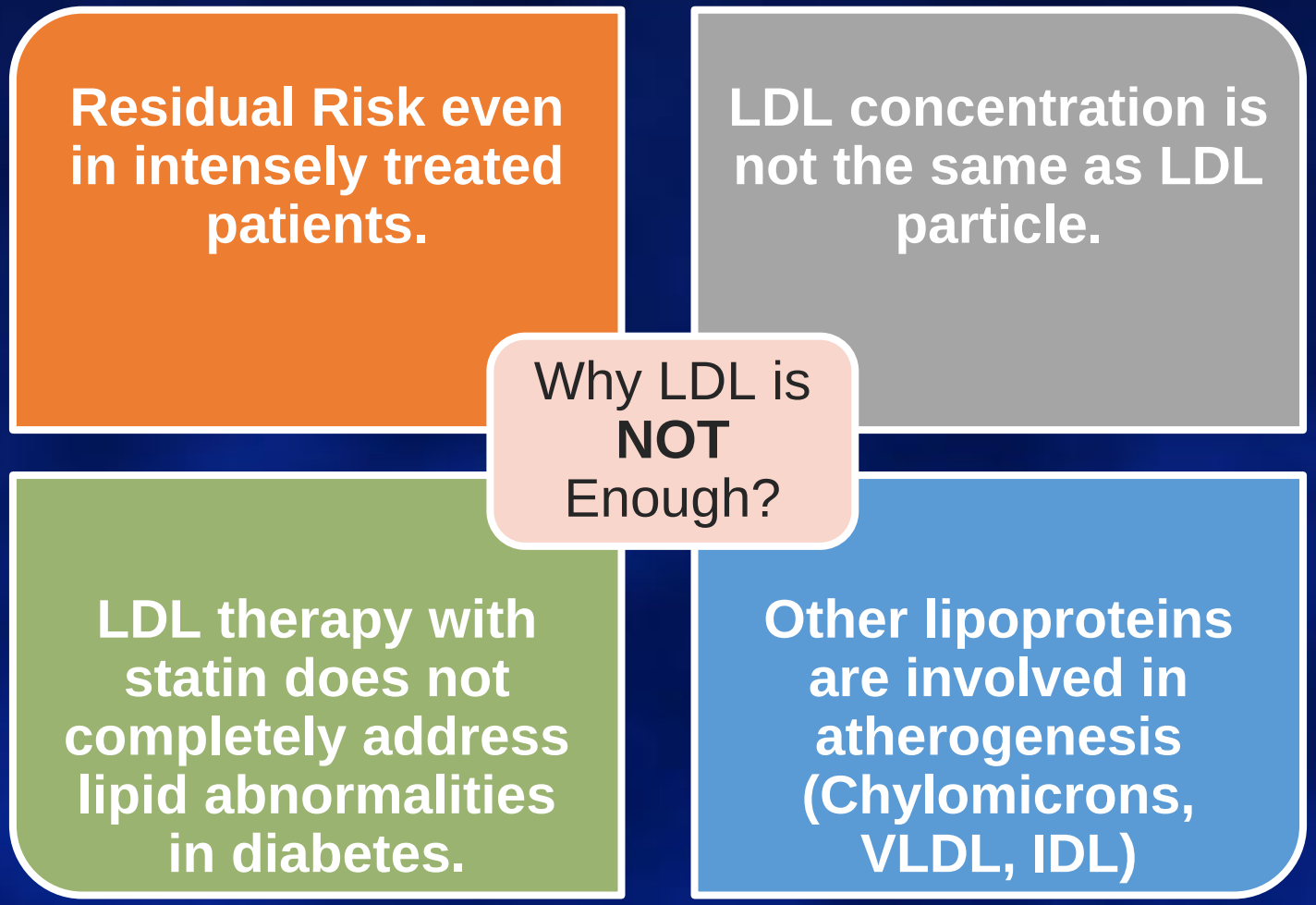


- Each 10% reduction in LDL-C level (15 mg/dL) yielded a 1% reduction in atheroma volume after 18 months.
- Progression occurs even below LDL-C <100 mg/dL.
- Regression occurs with >50% LDL-C reduction or at LDL-C levels well below 75 mg/dL.
- Regression occurs with high-intensity statin, but not with the moderate-intensity statin.

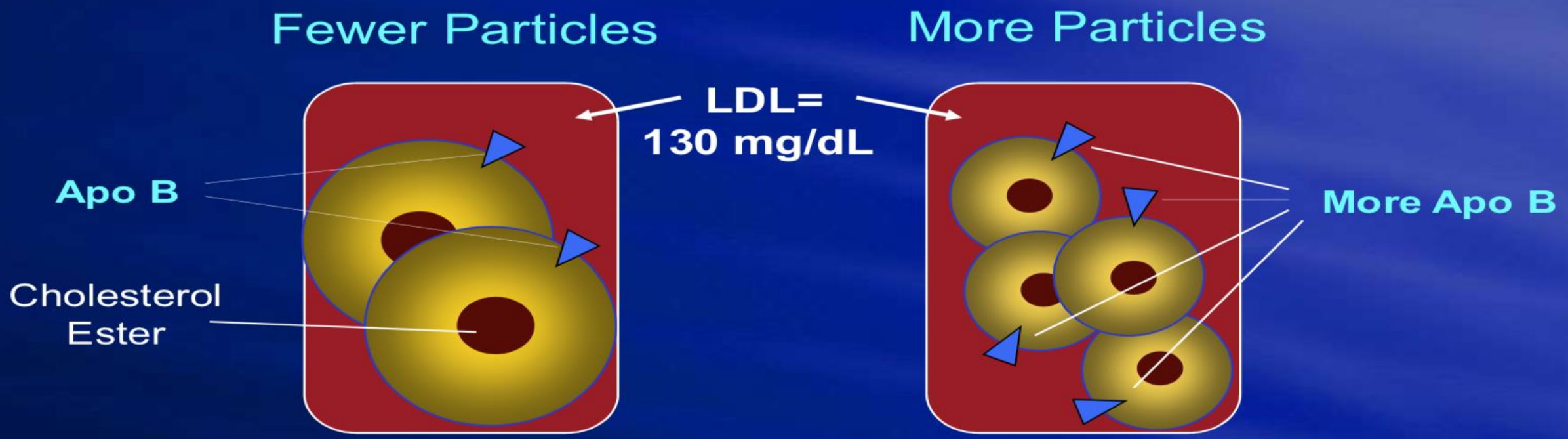
Nissen SE, et al. Effect of Intensive Compared With Moderate Lipid-Lowering Therapy on Progression of Coronary Atherosclerosis: JAMA 2004;291(9):1071-1080. doi:10.1001/jama.291.9.1071

LOWERING LDL IS NOT ENOUGH

The Unfinished Business in Cardiovascular Risk Reduction


Residual Risk even in intensely treated patients.
LDL concentration is not the same as LDL particle.
Why LDL is NOT Enough?
LDL therapy with statin does not completely address lipid abnormalities in diabetes.
Other lipoproteins are involved in atherogenesis (Chylomicrons, VLDL, IDL)

Same LDL-C Levels, Different Cardiovascular Risk



Correlates with:	
TC	198 mg/dL
LDL-C	130 mg/dL
TG	90 mg/dL
HDL-C	50 mg/dL
Non–HDL-C	148 mg/dL

Correlates with:	
TC	210 mg/dL
LDL-C	130 mg/dL
TG	250 mg/dL
HDL-C	30 mg/dL
Non–HDL-C	180 mg/dL

Otvos JD, et al. *Am J Cardiol*. 2002;90:22i-29i.

Are other lipid parameters better than LDL-C for identifying residual risk in statin treated patients? TNT and IDEAL

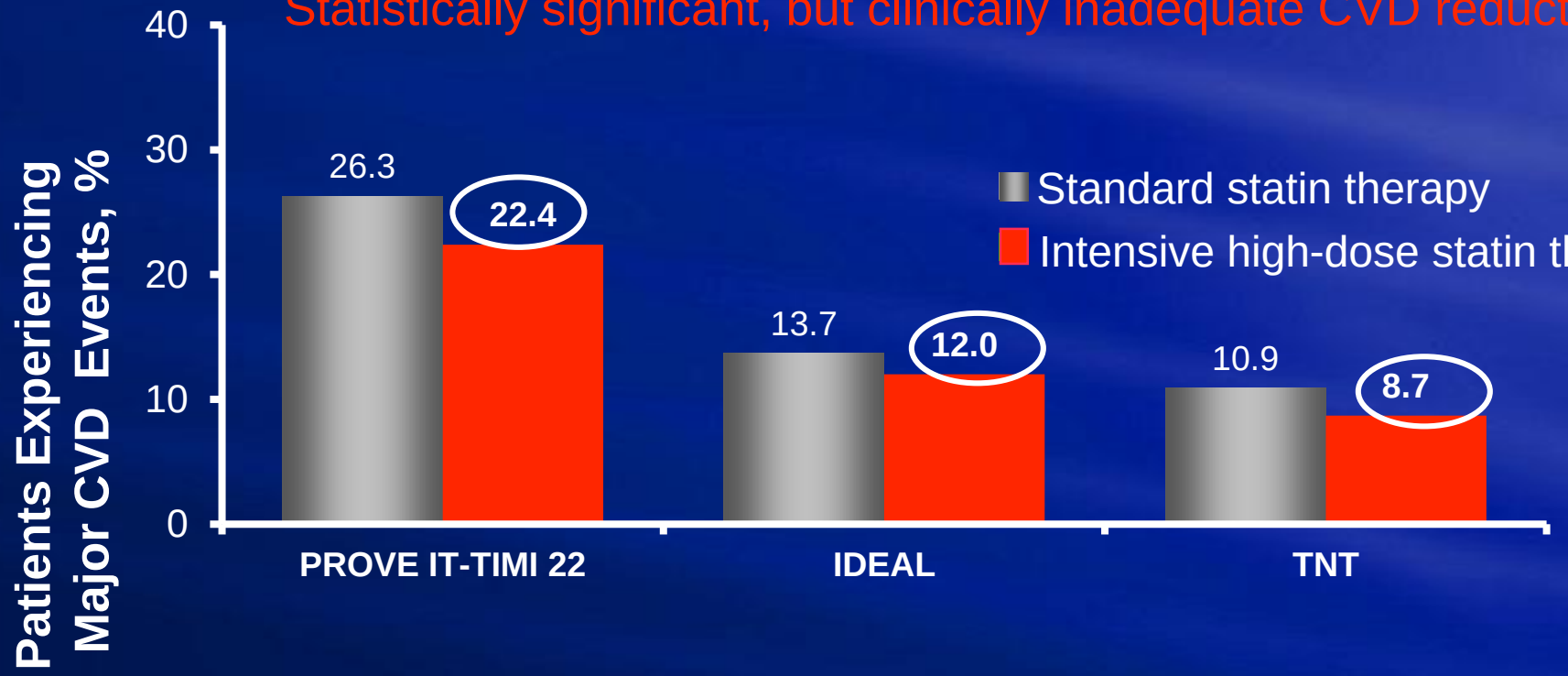
	HR for CVD	95% CI	P
ALL SUBJECTS (per standard unit change)			
LDL-c	1.15	1.10 – 1.20	<0.001
Non-HDL-c	1.19	1.14 – 1.25	<0.001
Apo B	1.19	1.14 – 1.24	<0.001
SUBGROUP ACHEIVING LDL-c ≤ 100 mg/dl			
LDL-c	1.08	0.97 – 1.20	0.16
Non-HDL-c	1.15	1.05 – 1.25	0.002
Apo B	1.15	1.05 – 1.25	0.002

In patients receiving statin therapy and achieving low LDL-c, on-treatment levels of non-HDL-c and apo B were more closely associated with cardiovascular outcomes than levels of LDL-c.

JJ Kastelein et al, Circulation 2008; 117:3002-2009

Residual Cardiovascular Risk in Major Statin Trials

Statistically significant, but clinically inadequate CVD reduction[1]



	PROVE IT-TIMI 22[2]		IDEAL[3]		TNT[4]	
N	4162		8888		10 001	
LDL-C,* mg/dL	95	62	104	81	101	77

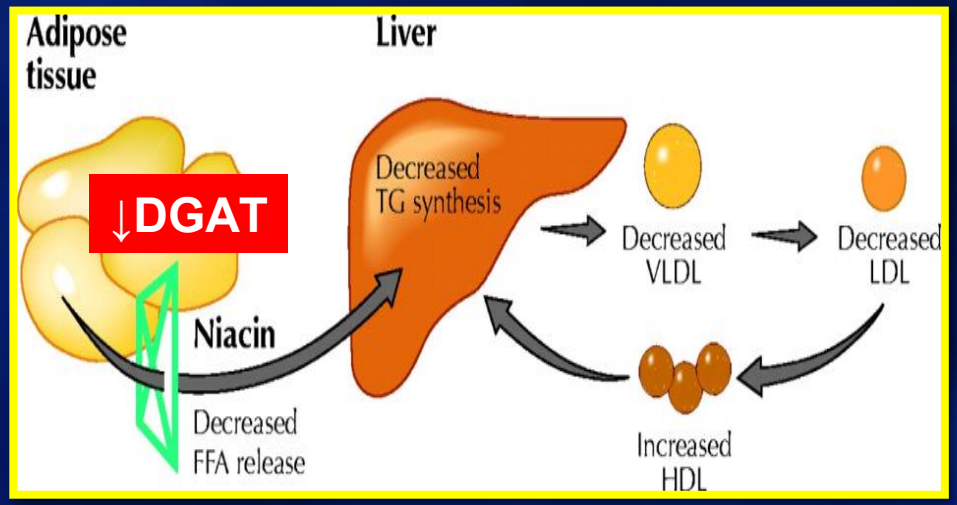
*Mean or median LDL-C after treatment

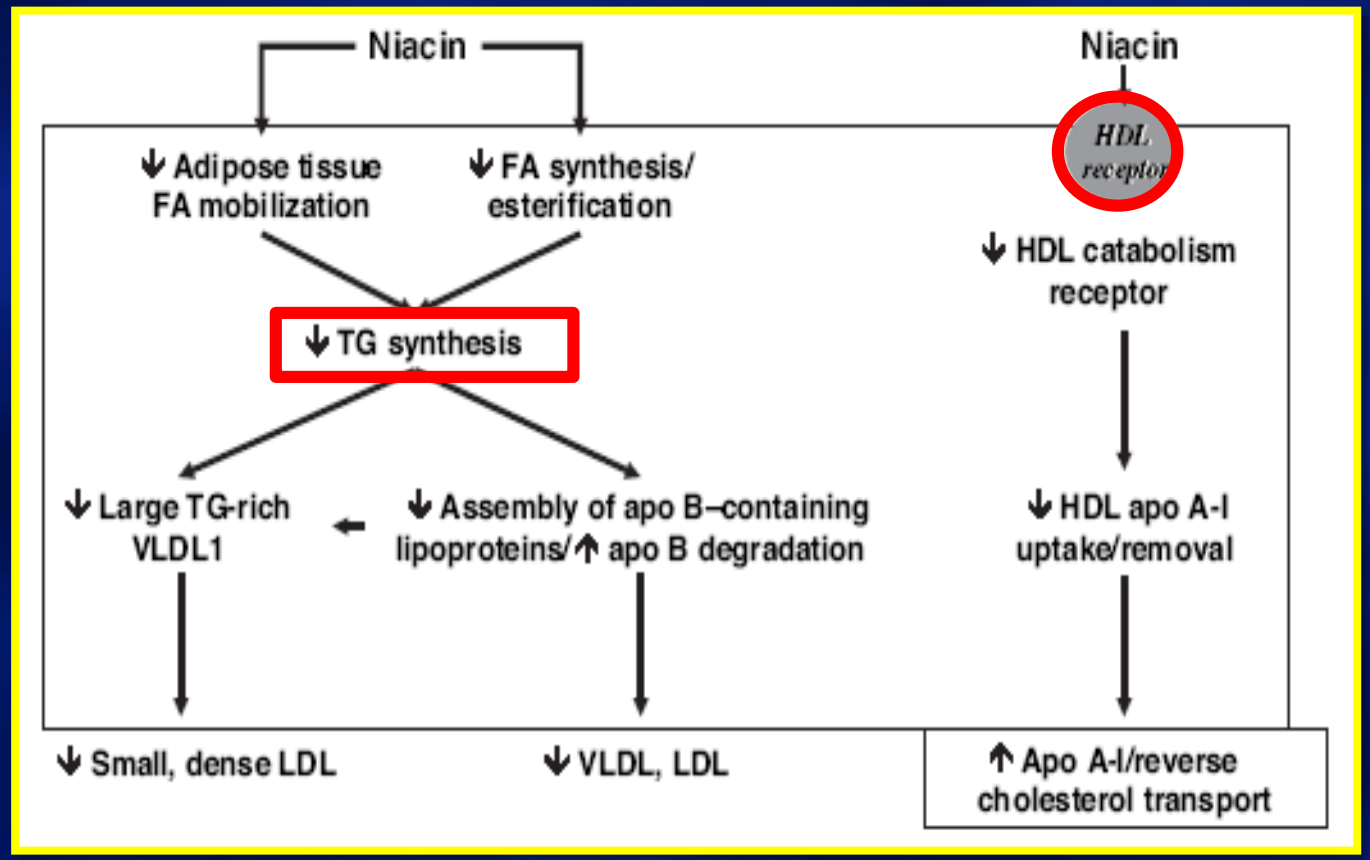
[1]Superko HR. *Br J Cardiol.* 2006;13:131-136.
[2]Cannon CP, et al. *N Engl J Med.* 2004;350:1495-1504.
[3]Pedersen TR, et al. *JAMA.* 2005;294:2437-2445.
[4]LaRosa JC, et al. *N Engl J Med.* 2005;352:1425-1435.

WHAT ELSE CAN WE DO?

NON-STATIN THERAPIES

NIACIN Mechanism of Action



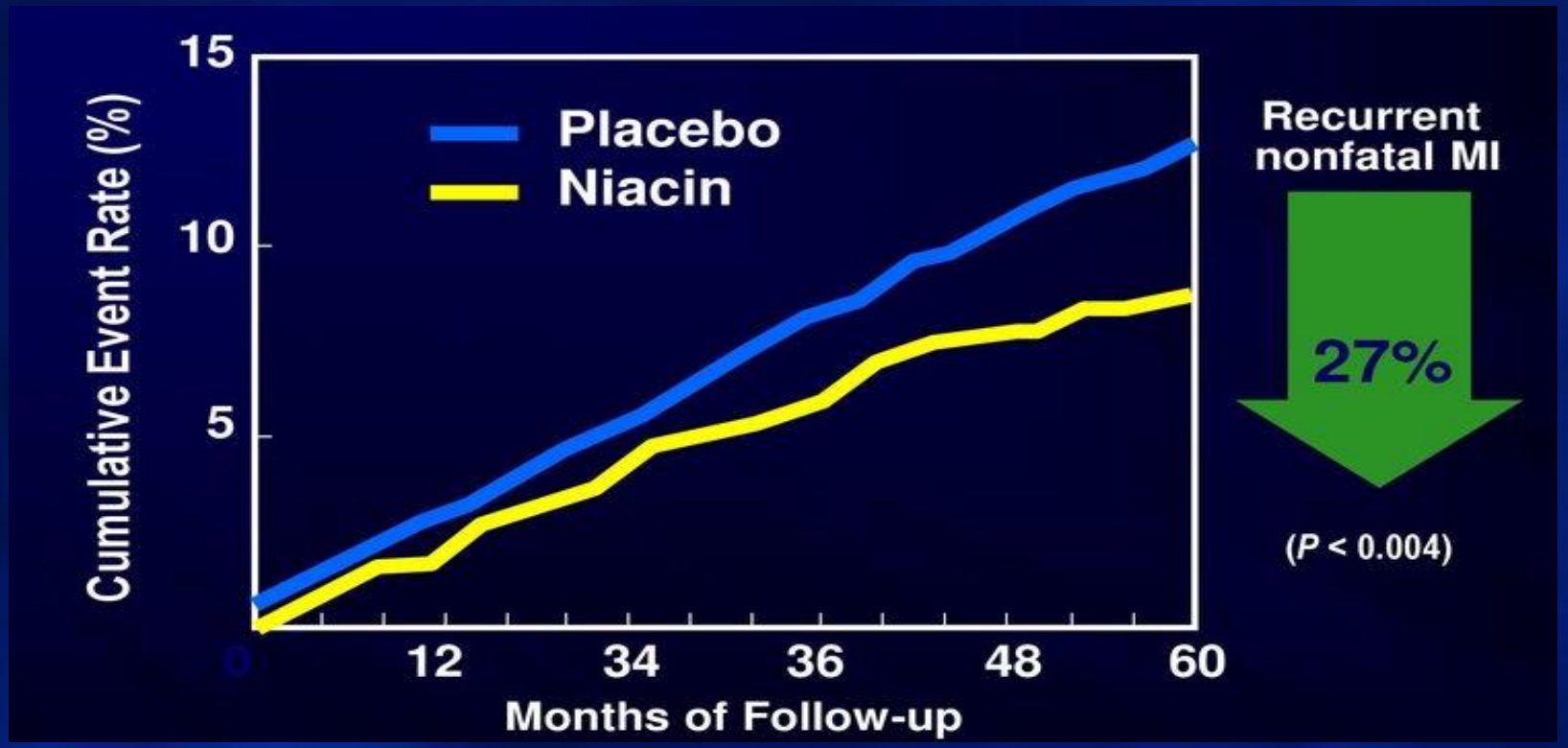


Adapted with permission from Curr Atheroscler Rep. 2000;2:36-46.[30]

Coronary Drug Project:
Effect of Niacin in Post MI patients treated with niacin or placebo

Cumulative Rate of Nonfatal MI in Post-MI Patients Treated with Niacin or Placebo

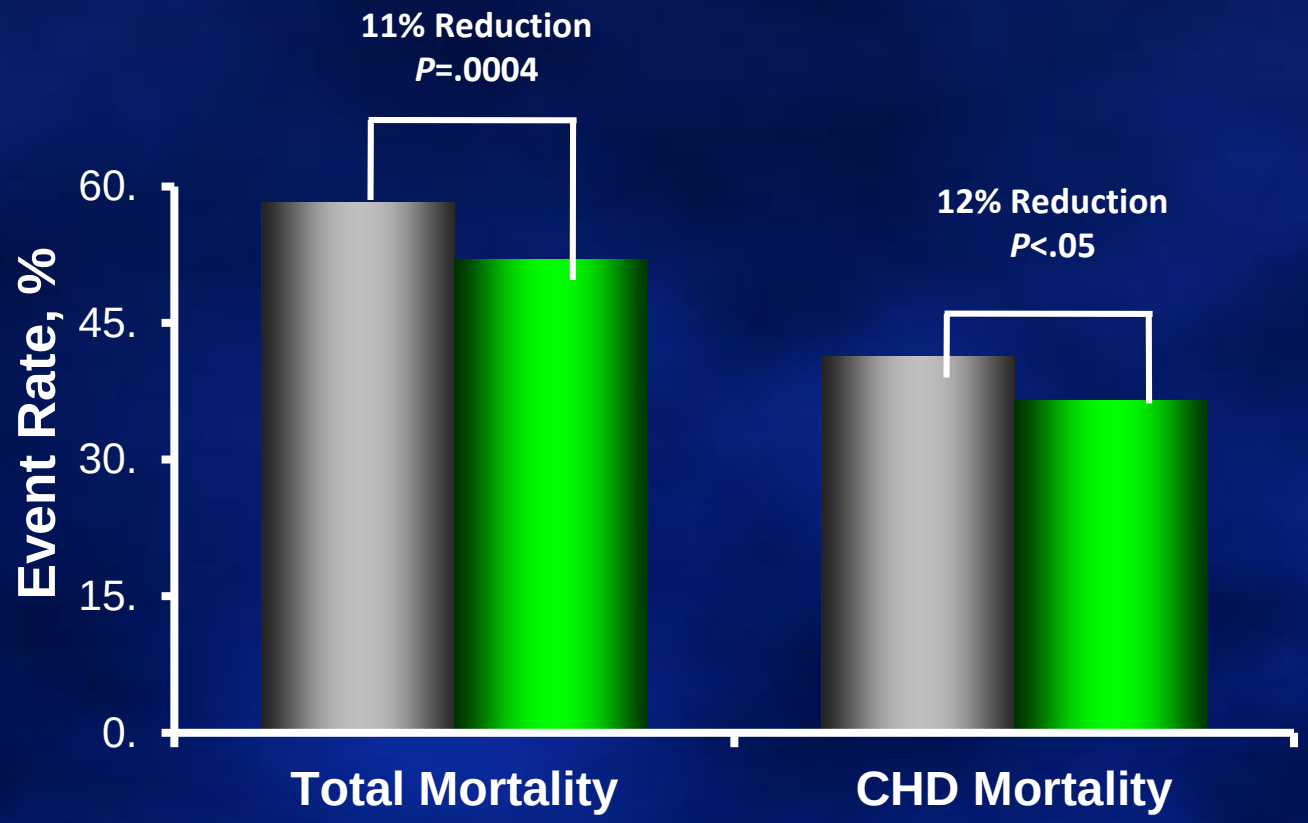
N: 8,341 men



Primary endpoint:
Total mortality: 24.4% with niacin, 25.4% with placebo; P=ns

JAMA. 1978;239(25):2655-2656. doi:10.1001/jama.1978.03280520027005

Coronary Drug Project: 15-Year Follow-Up



Placebo (n = 2008)

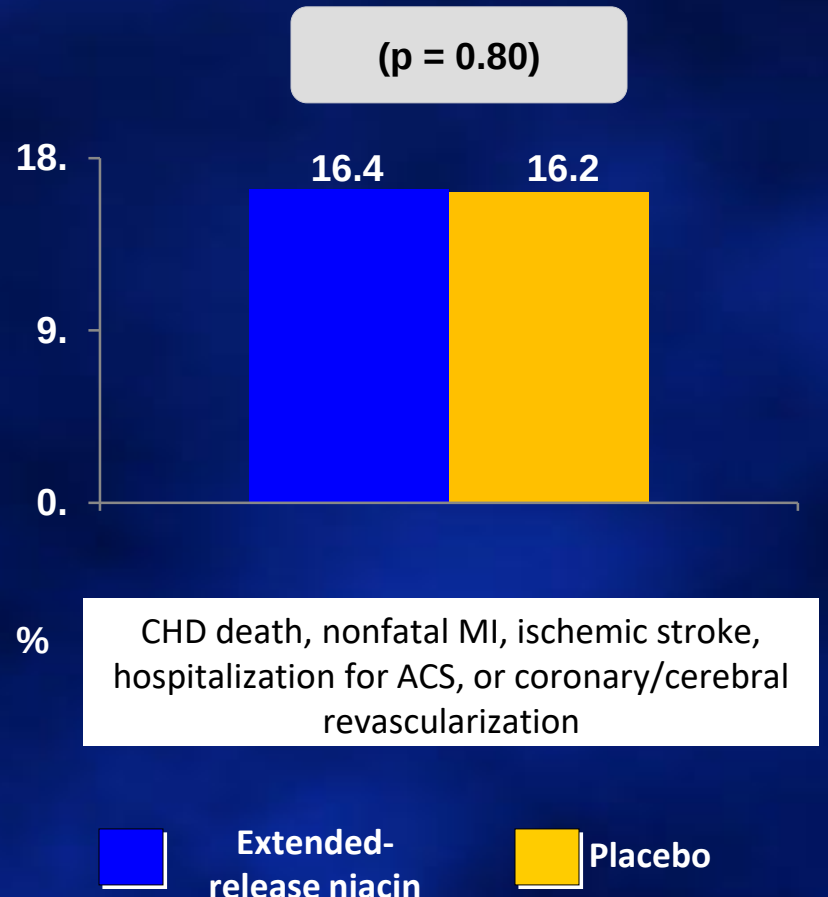
Niacin (n = 827)

Niacin monotherapy reduced cardiovascular and total mortality, both in normal subjects and patients with diabetes.

Canner PL, et al. *J Am Coll Cardiol.* 1986;8:1245-1255.

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes AIM-HIGH

Trial design: Statin-treated patients (optimally treated LDL cholesterol) with established vascular disease and low HDL cholesterol were randomized to extended-release niacin, 1500-2000 mg daily (n = 1,718) vs. placebo (n = 1,696).



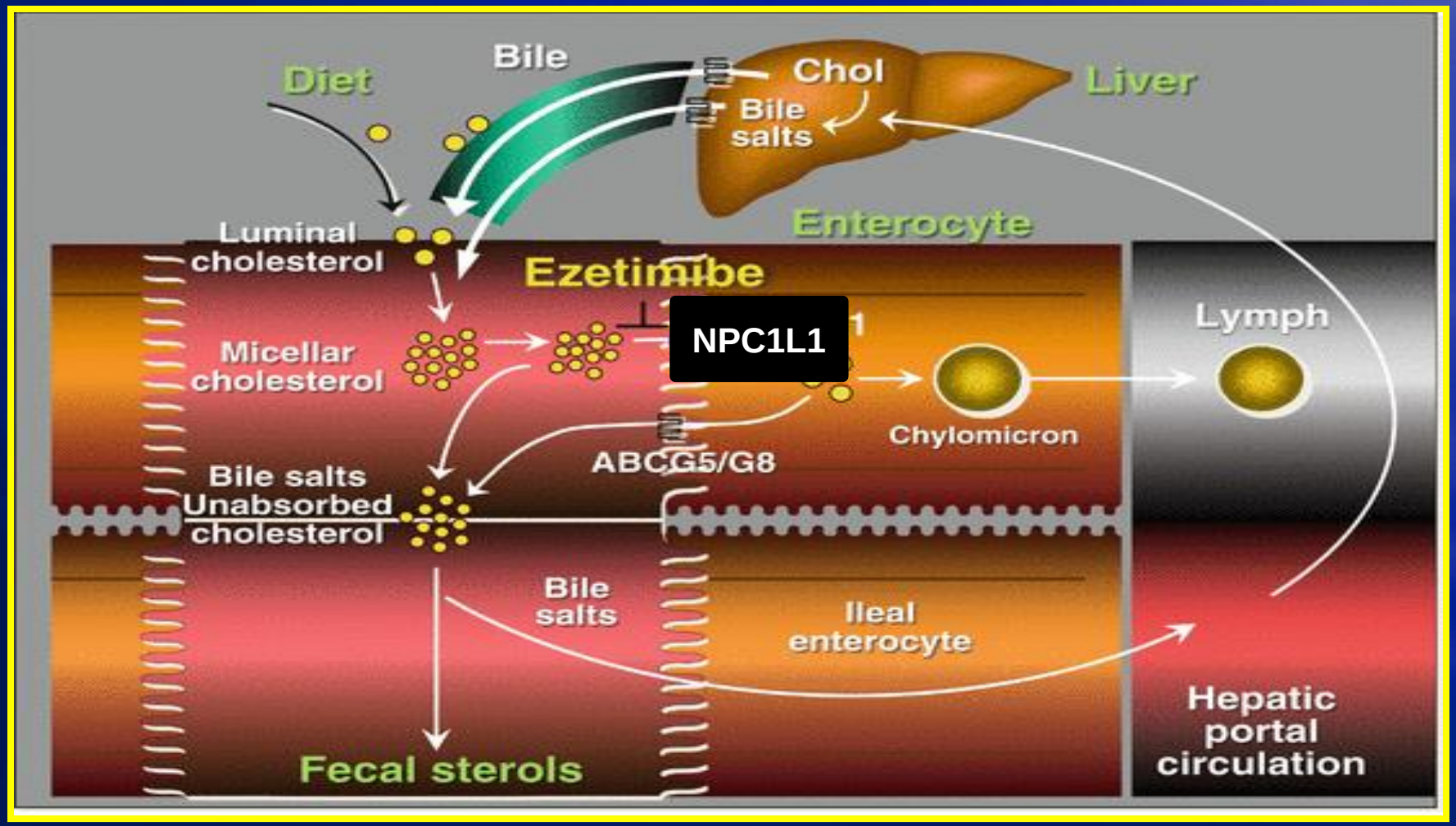
Primary and secondary end points

End points	Niacin (%)	Placebo (%)	Hazard ratio (95% CI)	p
Primary end point	16.4	16.2	1.02 (0.87–1.21)	0.80
CHD death/ nonfatal MI/ ischemic stroke/ high-risk ACS	9.3	10.0	1.08 (0.87–1.34)	0.49
CHD death/ nonfatal MI/ ischemic stroke	8.1	9.1	1.13 (0.90–1.42)	0.30

CONCLUSION

- Increase HDL-C levels 15%-30%
- Decrease TG levels 15%-50%
- Dose-dependent effects on LDL-C levels (up to 40%)
- Niacin did not reduce composite adverse events

EZETIMIBE Mechanism of Action



IMPROVE-IT

Improved Reduction of Outcomes, Ezetimibe Efficacy International Trial

Trial design: 18,144 individuals with a recent ACS (within 10 days) and LDL-C < 125 mg/dL or <100mg/dL if on prior lipid lowering therapy.
Simvastatin 40 mg + Ezetimibe 10 mg or Simvastatin 40 mg alone.

The **primary endpoint :** cardiovascular death, myocardial infarction, documented UA requiring hospitalization, coronary revascularization within 30 days of treatment, or stroke.
Mean follow-up was 7 years.

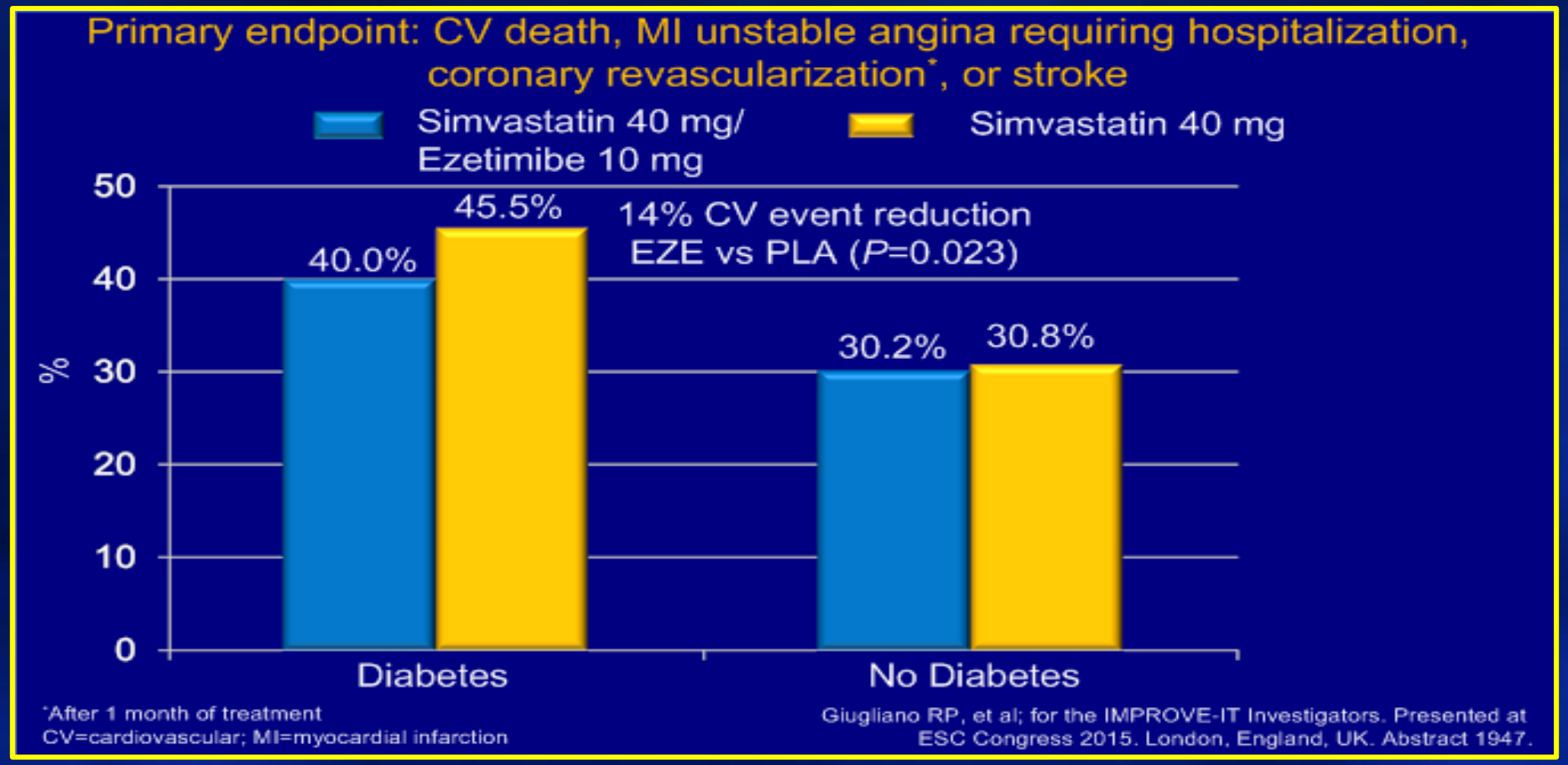
Primary endpoint was significantly reduced in the simvastatin-ezetimibe group: 32.7% vs 34.7% placebo—an absolute risk difference of 2.0 % points (HR=0.936; 95% CI: 0.89-0.99; *P*=0.016)

Correia LC. Ezetimibe: Clinical and Scientific Meaning of the IMPROVE-IT Study. Arq Bras Cardiol. 2016;106(3):247–249. doi:10.5935/abc.20160033

IMPROVE-IT Substudy: Diabetic Population.

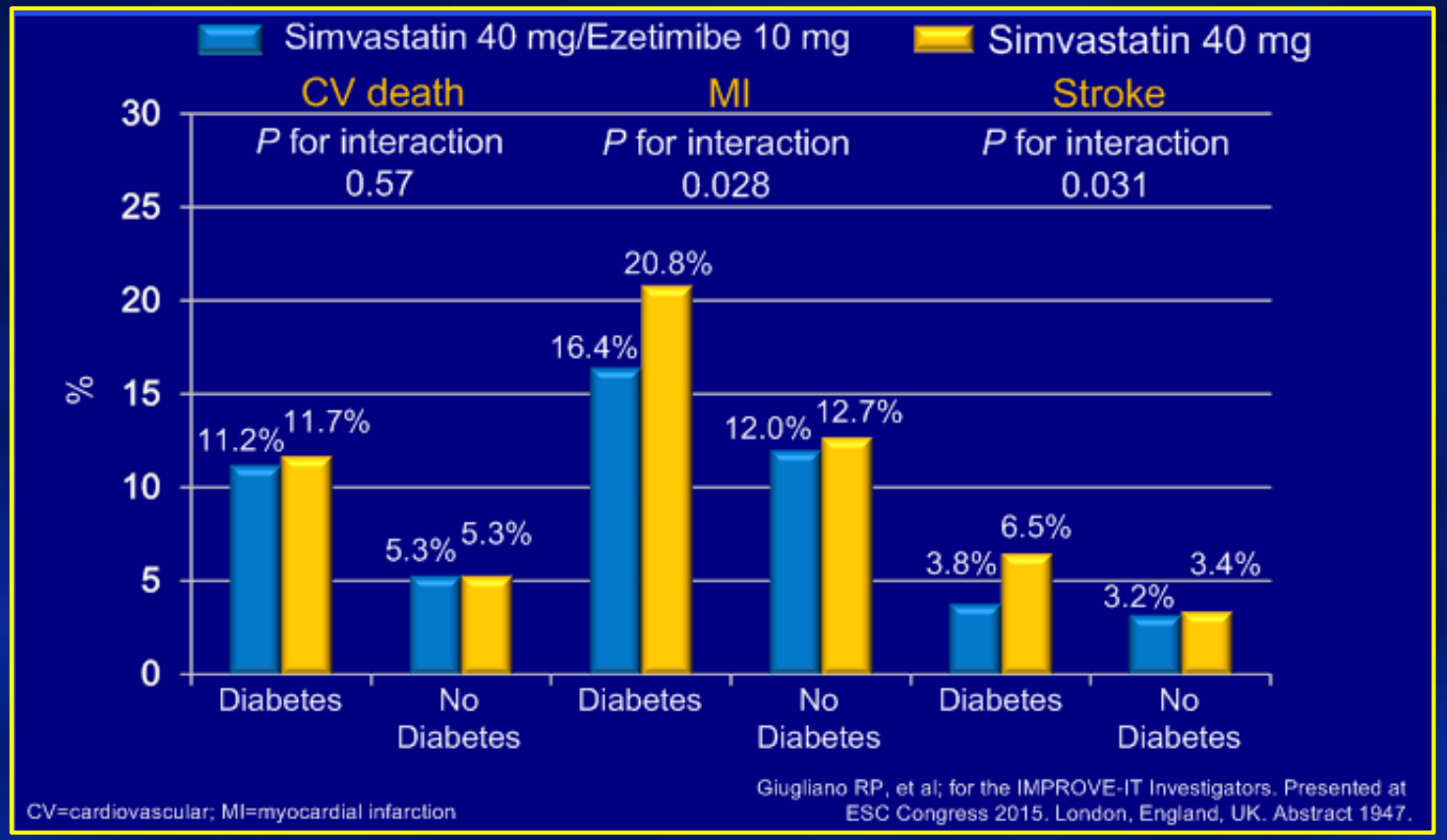
4,933 subjects with type 2 diabetes.
Diabetic cohort was older, had a higher BMI, and had more history of cardiovascular disease. These subjects also had lower LDL-C levels, as they were more likely to have been treated with statins.

IMPROVE-IT Substudy: Greater CV Event Reduction in Diabetic Subjects



Correia LC. Ezetimibe: Clinical and Scientific Meaning of the IMPROVE-IT Study. Arq Bras Cardiol. 2016;106(3):247–249. doi:10.5935/abc.20160033

IMPROVE-IT Substudy: Greater MI & Stroke Reduction in Diabetic Patients

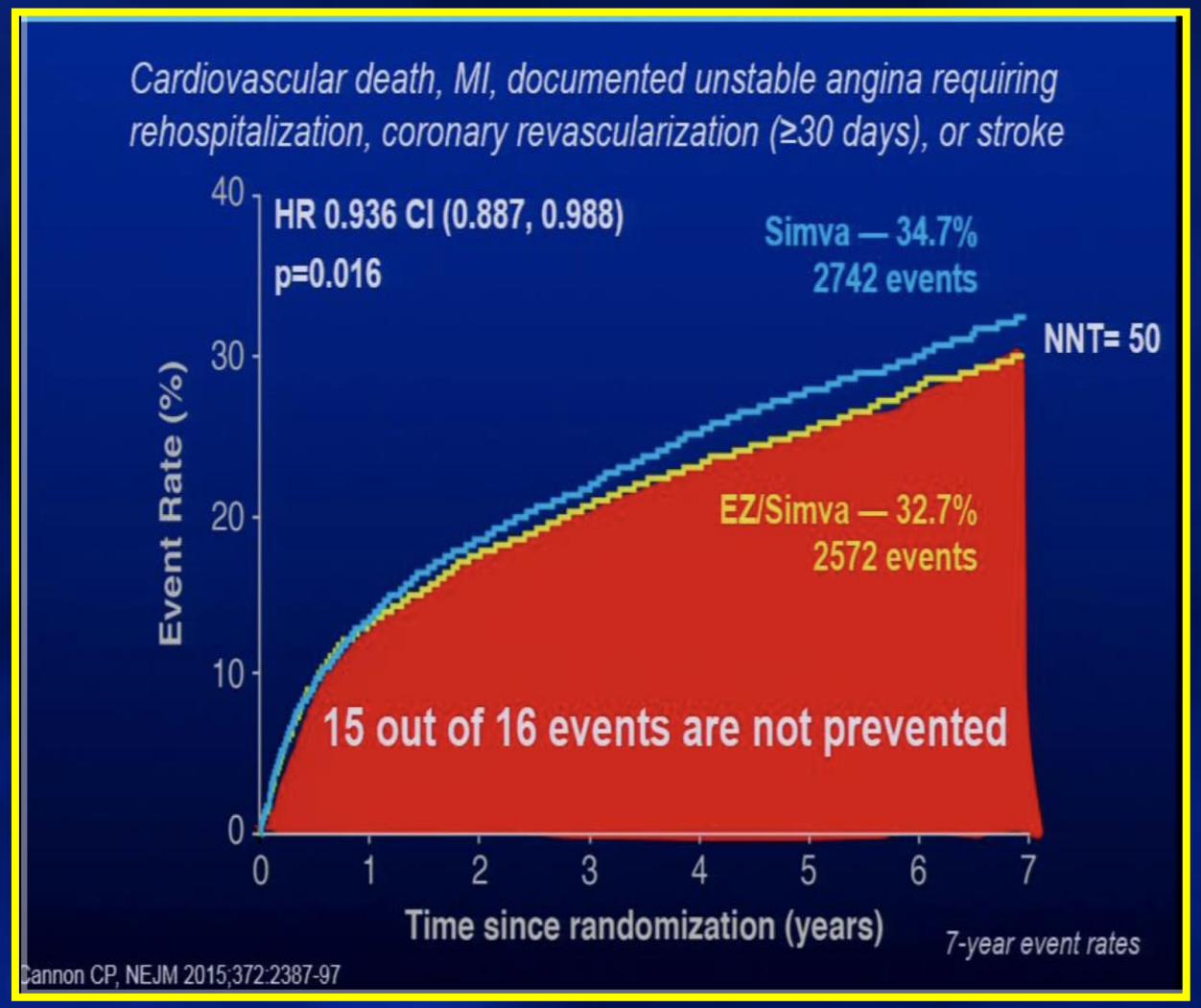


Correia LC. Ezetimibe: Clinical and Scientific Meaning of the IMPROVE-IT Study. Arq Bras Cardiol. 2016;106(3):247–249. doi:10.5935/abc.20160033

IMPROVE-IT Clinical Implications

In patients admitted with an ACS and LDL-C≥50 mg/dL, healthcare providers should consider adding ezetimibe to statin to reduce the risk of cardiovascular events.

IMPROVE-IT Clinical Implications

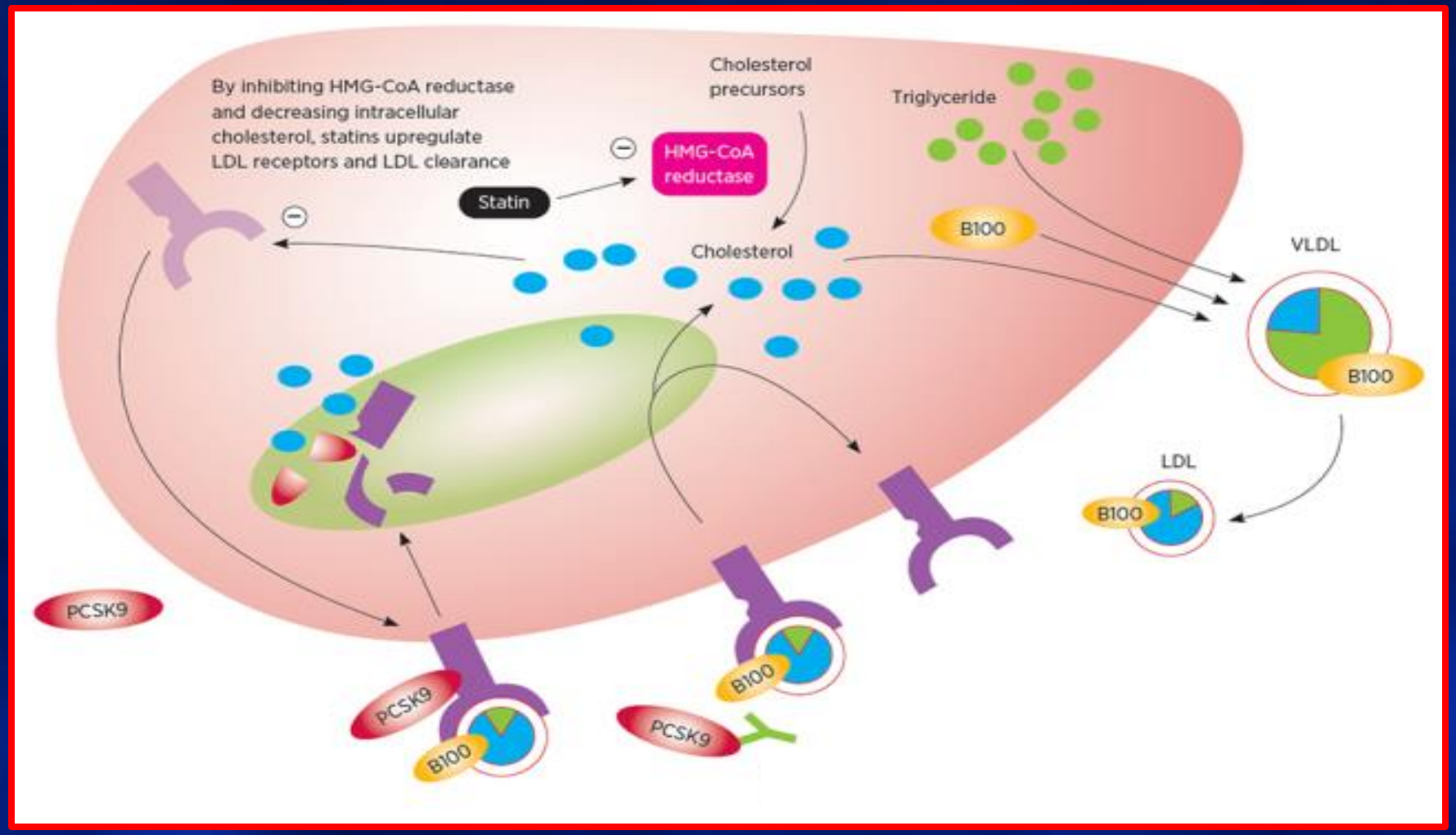


Of every 16 patients that will have an event with Simvastatin only one event is prevented with Ezetimibe

Can we do even better?

Correia LC. Ezetimibe: Clinical and Scientific Meaning of the IMPROVE-IT Study. Arq Bras Cardiol. 2016;106(3):247–249. doi:10.5935/abc.20160033

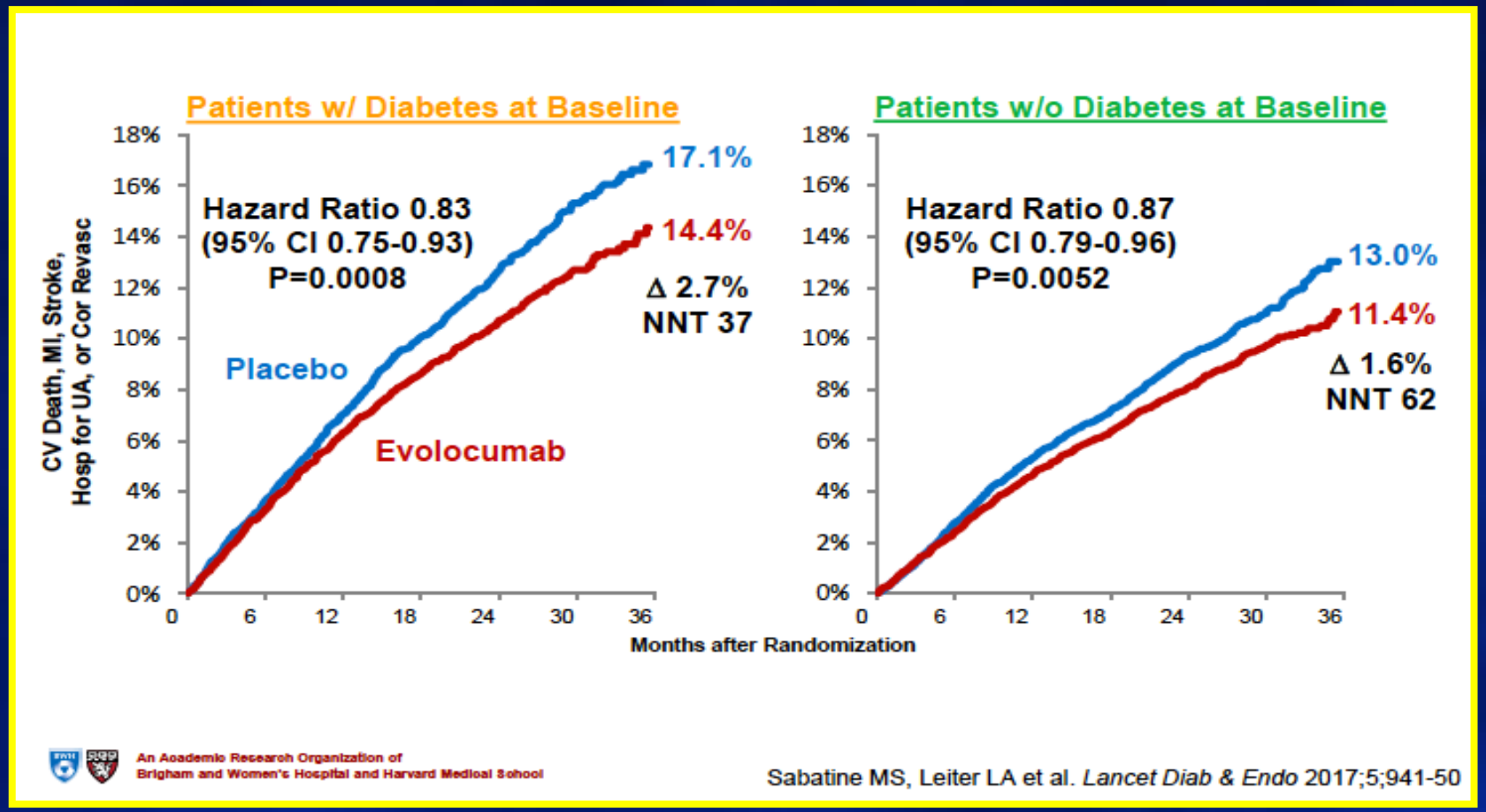
PCSK9 regulates the surface expression of LDLRs by targeting for lysosomal degradation



PCSK9 Inhibitor CVD Outcomes Trials

TRIALS	EVOLOCUMAB (FOURIER)	ALIROCUMAB (ODYSSEY)
Sample Size	27,500	18,000
Diabetic Population	**11,031**	**5,487**
Patients	MI, stroke or PAD	4-52 wks post-ACS
Baseline LDL-C	92 mg/dL	87 mg/dl
Endpoint	CV death, MI, stroke, revasc or hosp for UA.	Death, MI, ischemic stroke, hosp for UA
Completion	2017	2018

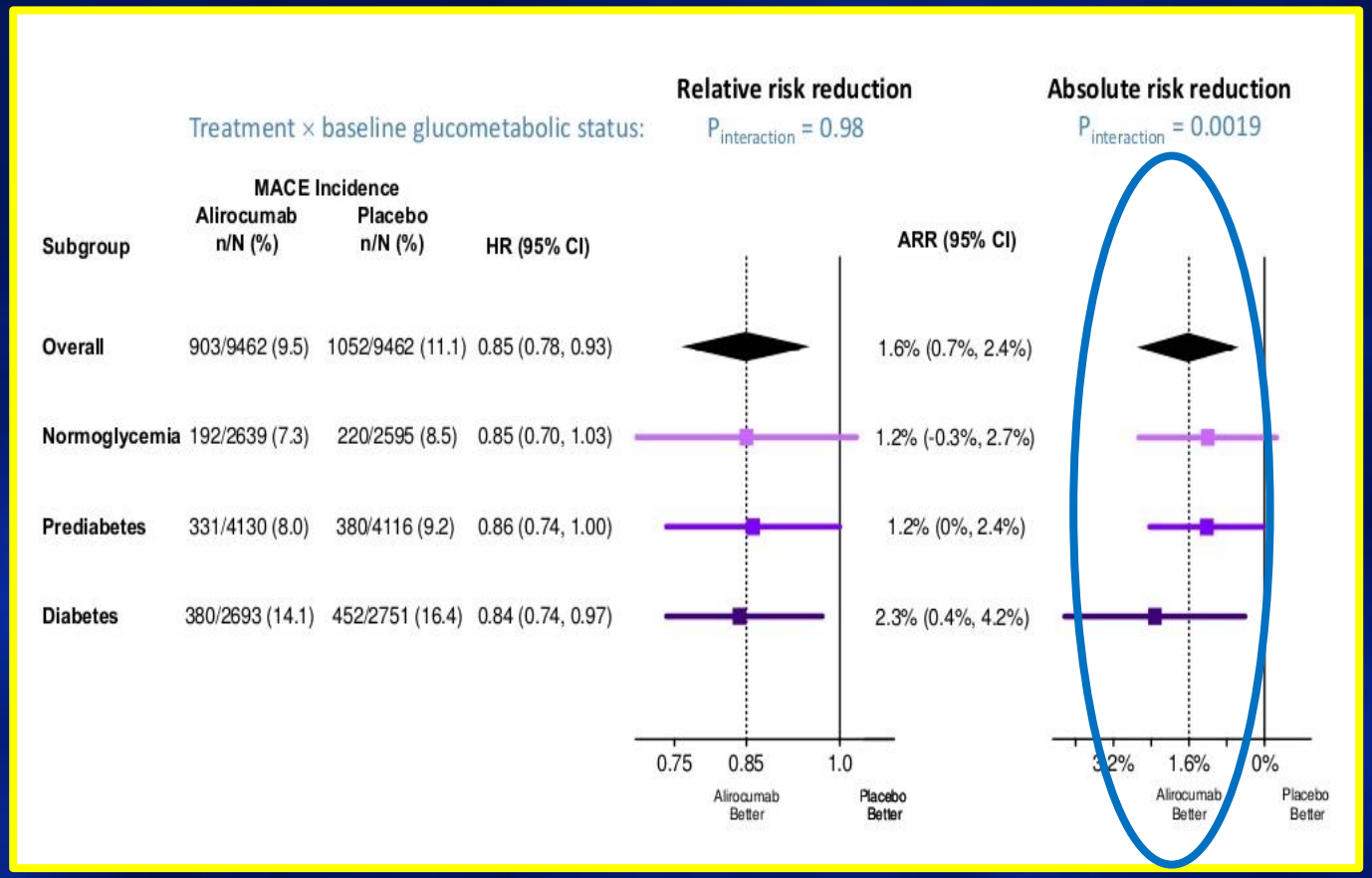
FOURIER in Patients With Diabetes



Median LDL-C levels were reduced by 57% in those with diabetes mellitus and by 60% in those without diabetes mellitus.

ODYSSEY DM-DYSLIPIDEMIA

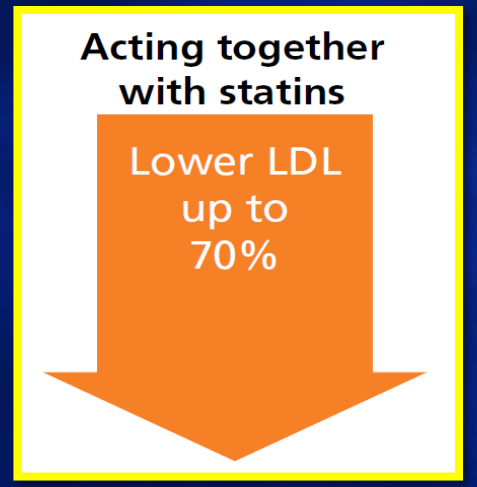
Prespecified analysis comparing CV efficacy and glucometabolic safety of alirocumab or placebo among patients with DM, prediabetes or normoglycemia.



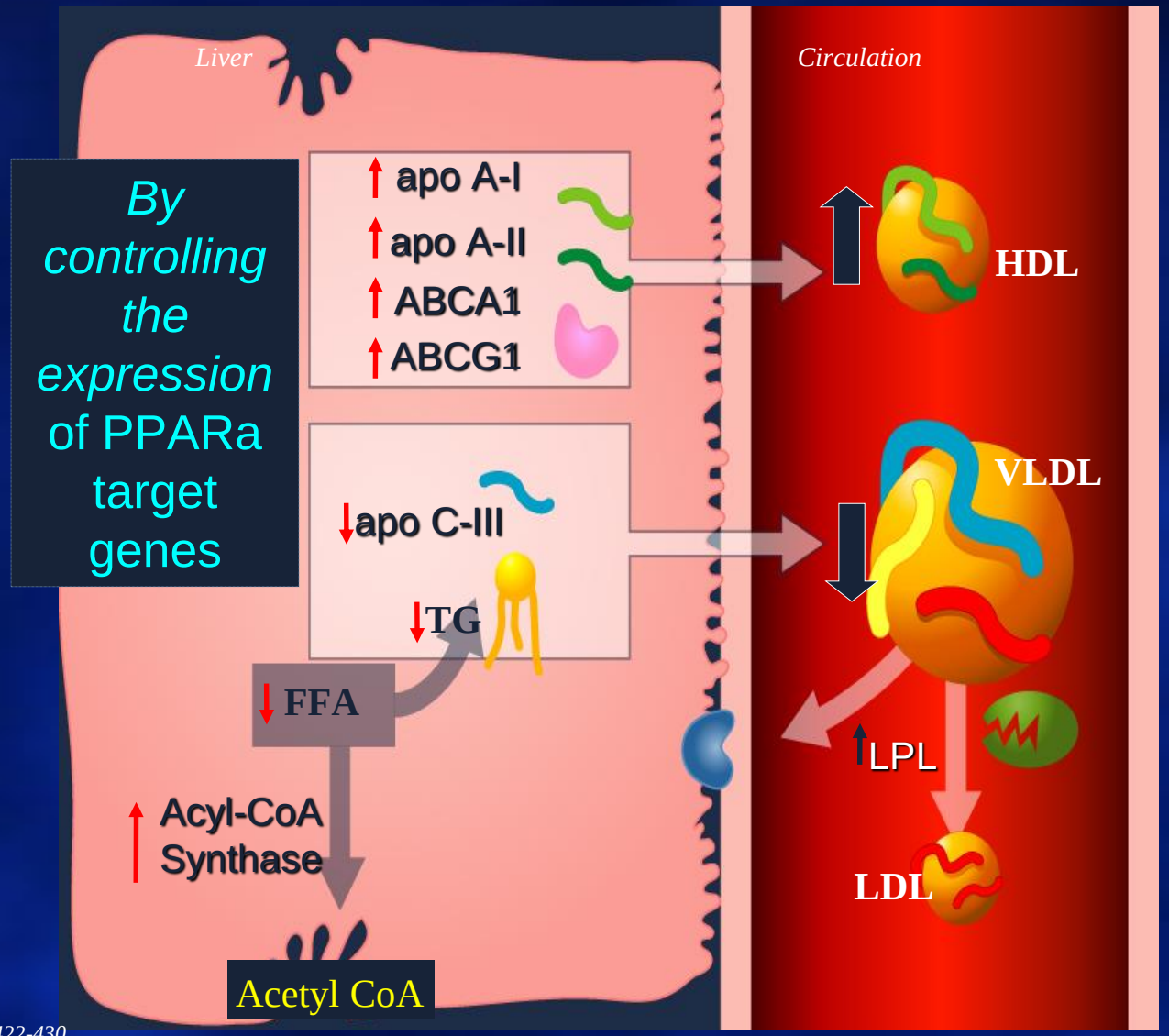
Chan, P., Shao, L., et. al2017). The ODYSSEY DM-DYSLIPIDEMIA trial: confirming the benefits of alirocumab in diabetic mixed dyslipidemia. *Annals of translational medicine*, *5*(23), 477. doi:10.21037/atm.2017.10.26

FOURIER VS ODYSSEY OUTCOMES

Outcomes relative risk reduction	EVOLOCUMAB (FOURIER)	ALIROCUMAB (ODYSSEY)
Primary Endpoint	15%	15%
MI	**27%**	**14%**
Stroke	21%	27%
CV death	+ 5% (NS)	12% (NS)
All cause death	+ 4% increase (NS)	15% (p=0.026)



Fibrates regulate lipid metabolism



Results

- Increased HDL Production
- Decreased VLDL Production
- Increased VLDL Clearance
- Decreased TG levels

Duval C, et al. Trends Mol Med. 2002;8:422-430.
Lee CH, et al. Endocrinology. 2003;144:2201-2207.

Fibrate Outcome Trials

Trial	HHS	VA-HIT	BIP	FIELD	ACCORD
Drug	Gemfibrozil	Gemfibrozil	Bezafibrate	Fenofibrate	Fenofibrate
Primary Endpoint	MI (fatal and nonfatal) cardiac death	Nonfatal and cardiac death	MI (fatal and nonfatal), sudden death		Non-fatal MI non-fatal stroke, or CVD death.
Diabetic population	292	769	1470		5518
Prevention	Primary	Secondary	Secondary		Primary
Lipid % change from baseline		LDL: 0 TC: -4 TG: -31 HDL: +6	LDL: -6.5 TC: -4.5 TG: -21 HDL: +18	LDL: -12 TC: -11 TG: -29 HDL: +5	LDL: -19 TC: -14 TG: -22 HDL: +8.4
Outcomes	**CHD ↓34%; nonfatal MI ↓37%;** Total mortality: no change	**CHD and nonfatal MI ↓22%**; total	Fatal, nonfatal MI and sudden death ↓9% (ns); total mortality: no change	Fatal and nonfatal MI ↓11%(ns), total mortality ↑19% (ns)	Nonfatal MI, stroke, CVD death ↓ 8% (ns) total mortality ↓9% (ns)

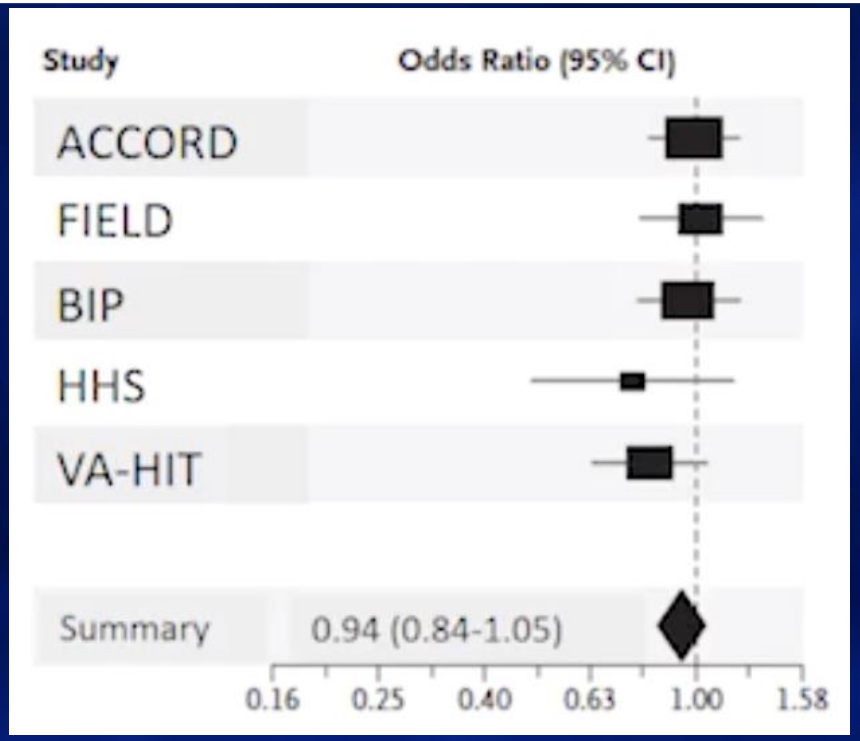
Diabetes: Decrease coronary events by 68% but small sample size.

Diabetes: no change in non fatal MI

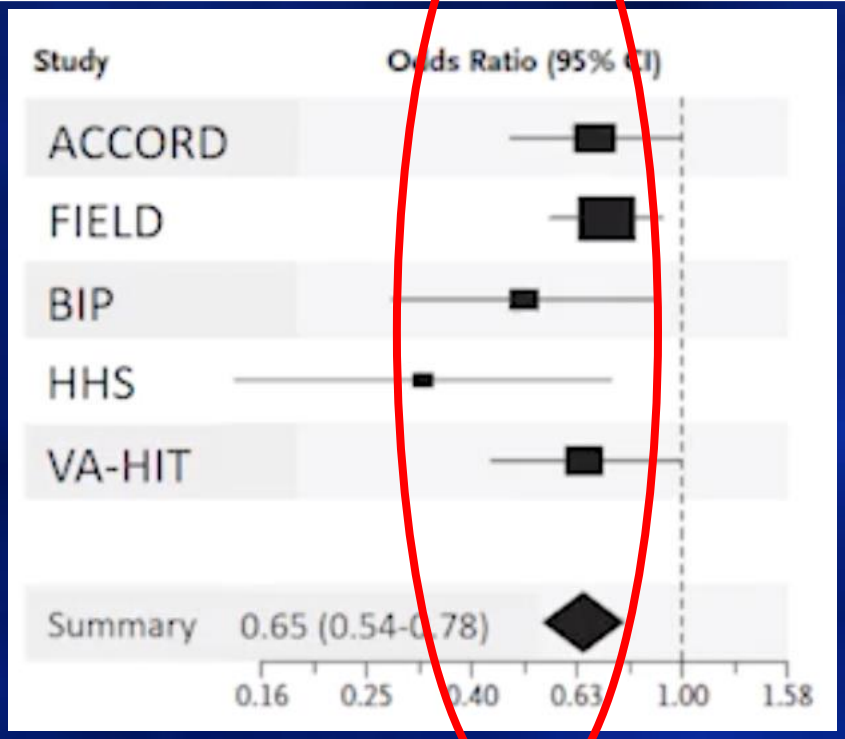
Diabetes: Reduced albuminuria and slowed GFR loss. Reduce retinopathy progression

Insights from Fibrate Trials: where we studying the right patients?

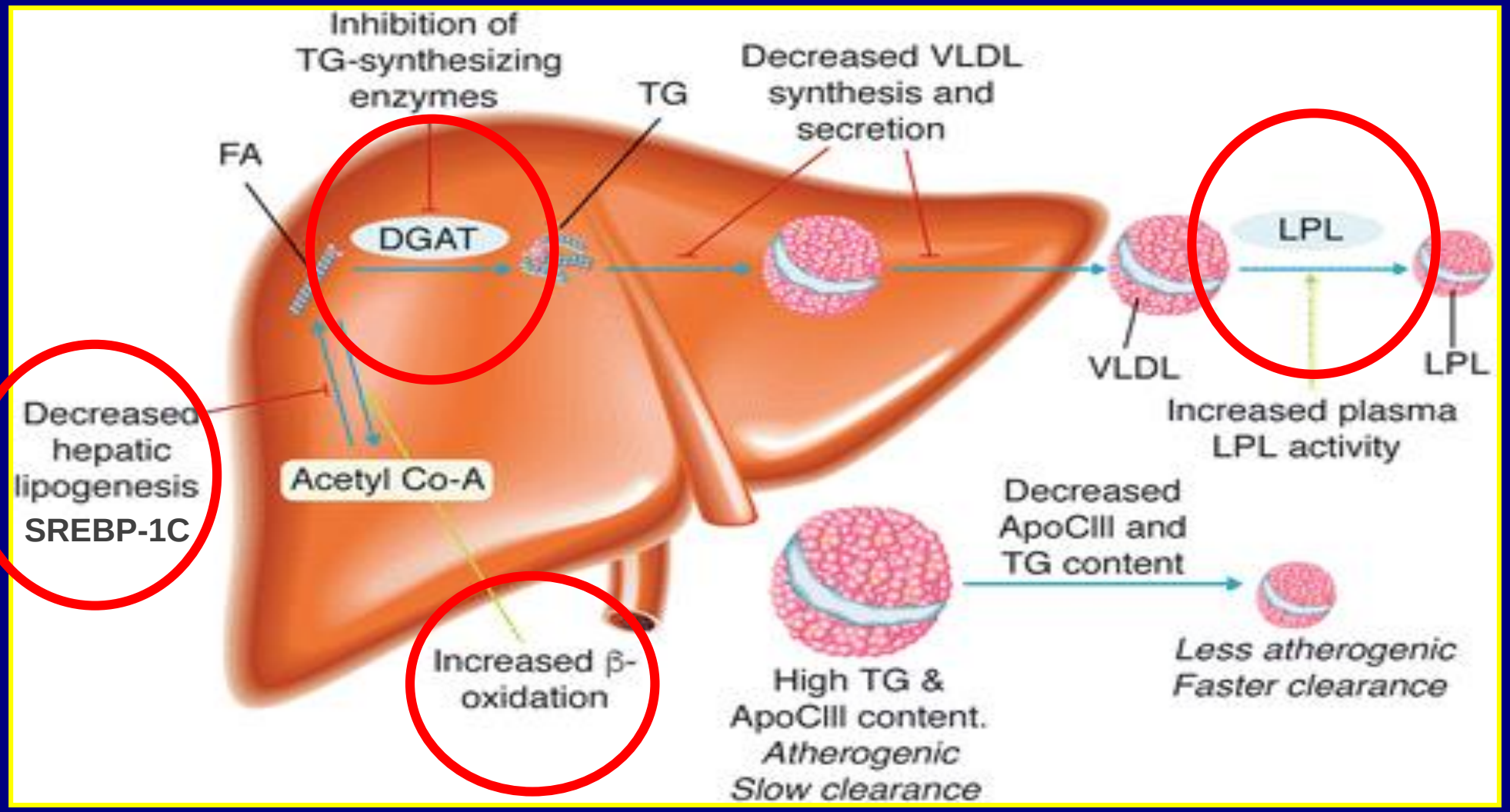
Subgroup without High TG, Low HDL



Subgroup with High TG, Low HDL



Omega-3 Fatty Acids
Proposed mechanisms of action



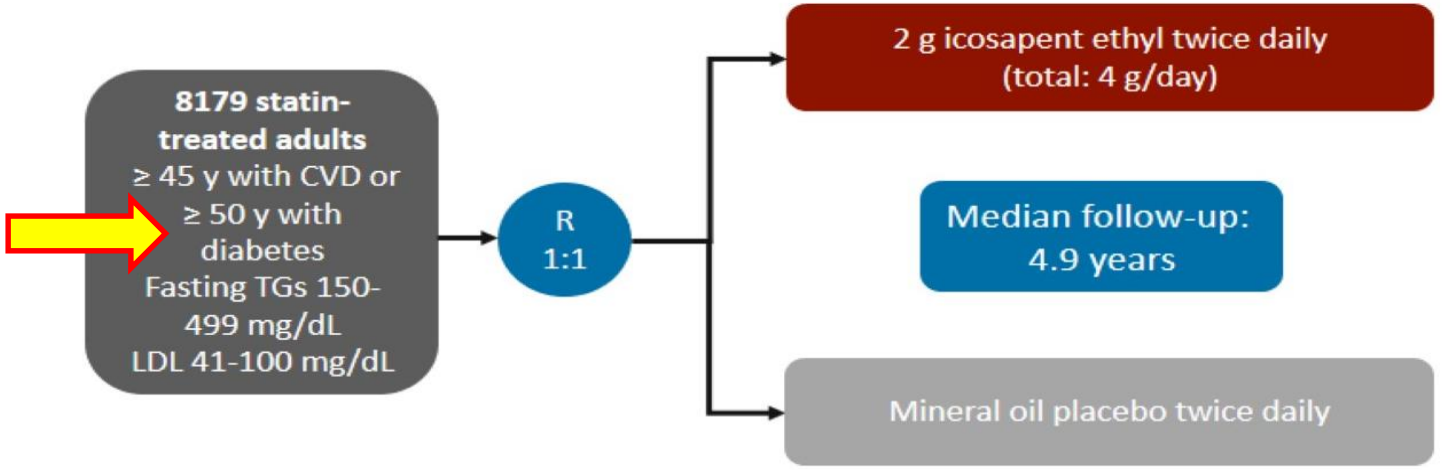
Backes et. Al *Lipids in Health and Disease*201615:118

Omega-3 Fatty Acids

Generic Name	Omega-3-ethyl-esters	Icosapent ethyl
Brand Name	Lovaza or Omacor	Vascepa
EPA/capsule	0.465 g	1 g
DHA/capusle	0.375 g	none
Daily Dose	4 capsules/day	4 capsules/day

Reduction of Cardiovascular Events with Icosapent Ethyl Intervention Trial: REDUCE-IT

Phase 3b, double-blind, multicenter, randomized, placebo-controlled trial in statin-treated patients with established CVD or with diabetes



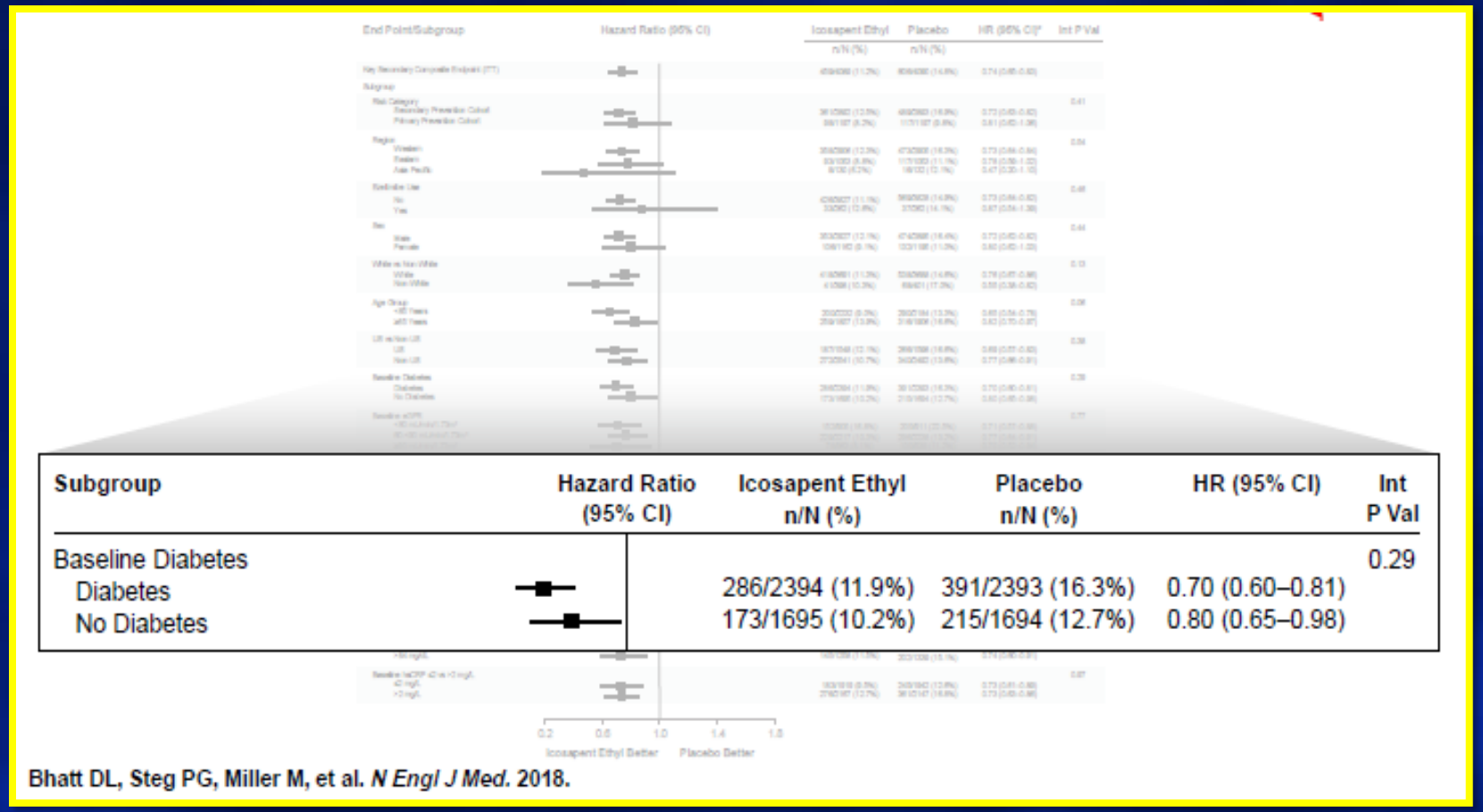
- Primary efficacy endpoint: composite of CV death, nonfatal MI,* nonfatal stroke, coronary revascularization, UA
- Key secondary endpoint: composite of CV death, nonfatal MI,* or nonfatal stroke

*Including silent MI.

Bhatt DL, et al. *N Engl J Med.* 2019;380:11-22.

REDUCE-IT: Key Secondary End Point in Subgroups

Composite of CV death, nonfatal MI, and nonfatal stroke in a time-to-event analysis.

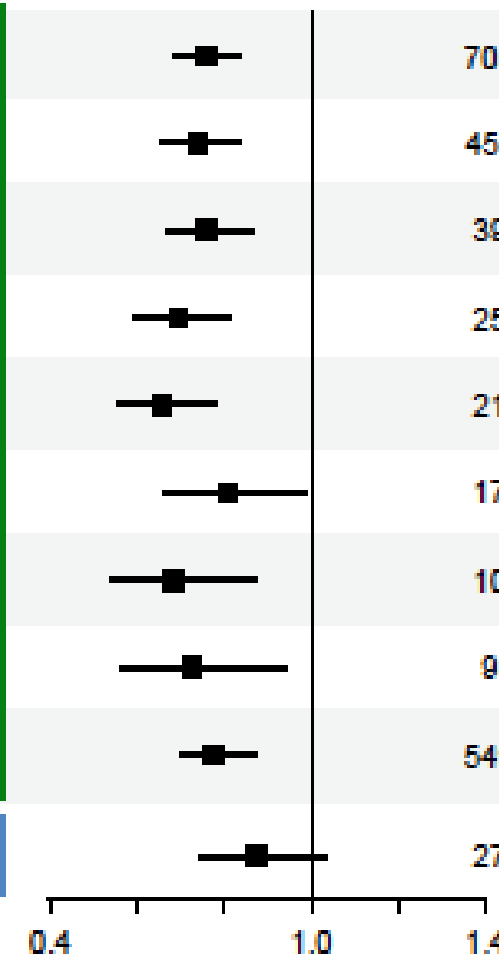


Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Diabetes					0.29
Diabetes		286/2394 (11.9%)	391/2393 (16.3%)	0.70 (0.60–0.81)	
No Diabetes		173/1695 (10.2%)	215/1694 (12.7%)	0.80 (0.65–0.98)	

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

REDUCE-IT: Prespecified Hierarchical Testing

Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%	<0.001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%	0.03
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%	0.002
Fatal or Nonfatal Stroke	98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%	<0.001
Total Mortality	274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%	0.09



RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2018.

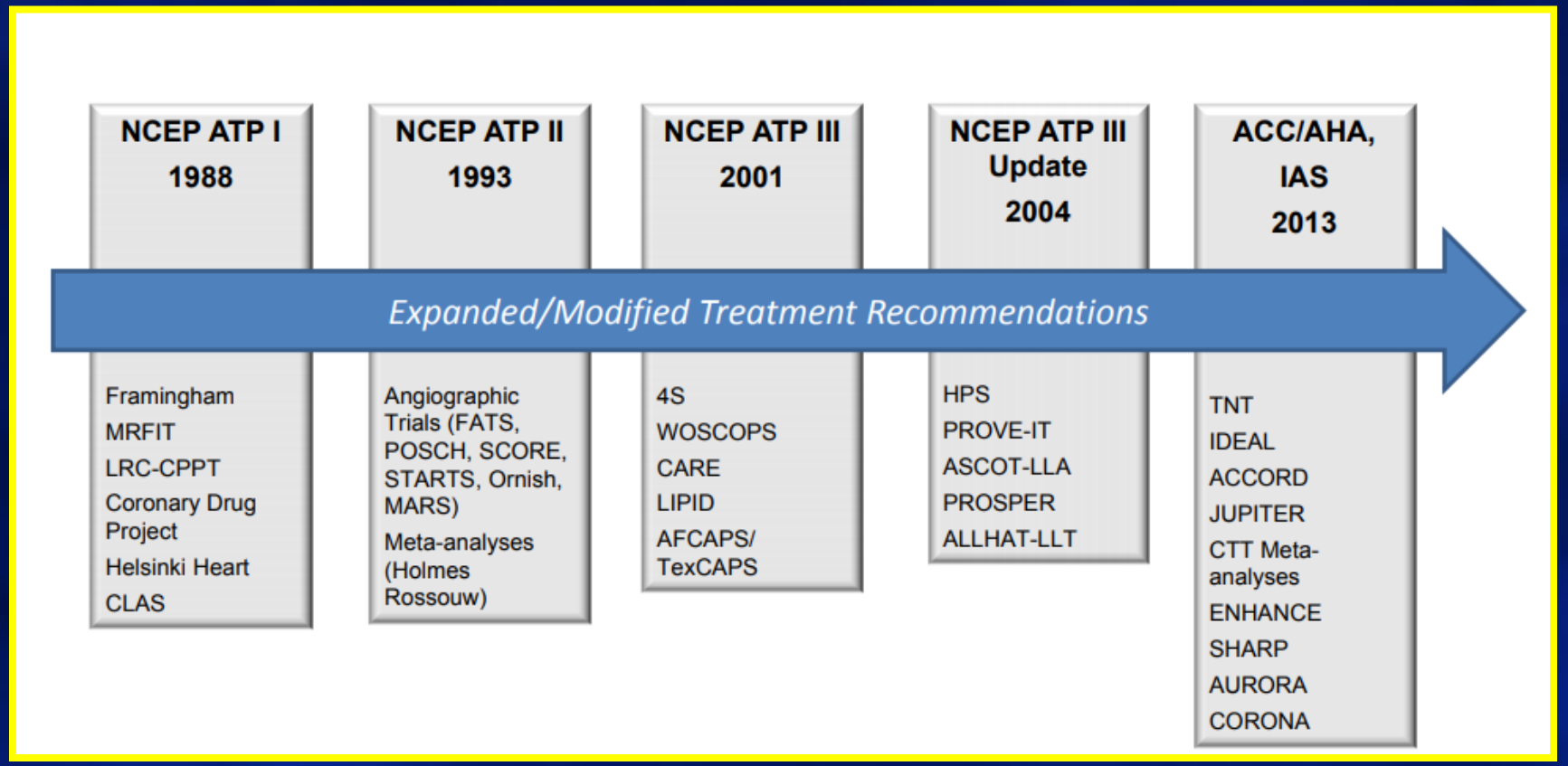
Cardiovascular Outcome Trials in Patients with Hypertriglyceridemia

	REDUCE – IT	STRENGTH	PROMINENT
Agent Dose	EPA (EE) 4 g/d	EPA+DHA (FFA) 4 g/d	SPPARMα – Pemafibrate 0.2 mg bid
Location	International	International	International
N	~8000	Estimated 13,000	Estimated 10,000
Age	≥ 45 years	≥ 18 years	≥ 18 years
Risk Profile	CVD (70%) or ↑ CVD risk (30%)	CVD (50%) or ↑ CVD risk (50%)	T2D only CVD (2/3) or ↑ CVD risk (1/3)
Follow-up	4–6 years (planned)	3–5 years (planned)	5 years (planned)
Statin Use	100% (at LDL-C goal)	100% (at LDL-C goal)	Moderate-/high-intensity or LDL-C < 70 mg/dL
Primary Endpoint	Expanded MACE	Expanded MACE	Expanded MACE
Statistical Power	Powered for 15% RRR	Powered for 15% RRR	Powered for 18% RRR
Entry TG Entry HDL-C	200–499 mg/dL N/A	200–499 mg/dL < 40 mg/dL M, < 45 mg/dL W	200–499 mg/dL ≤ 40 mg/dL

a. ClinicalTrials.gov. NCT01492361; b. ClinicalTrials.gov. NCT02104817; c. ClinicalTrials.gov. NCT03071692.

GUIDELINES DISCUSSION

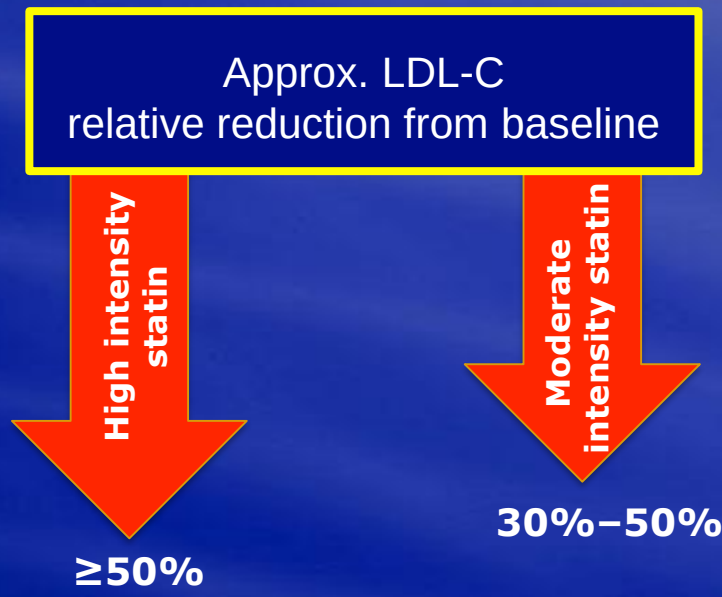
EVOLUTION OF GUIDELINES AND LANDMARK TRIALS



2017 2018

Major Statin Benefit Groups

	ASCVD	LDL mg/dL	DM (40-75 years)	10-year risk ASCVD ≥ 7.5%
1	YES	--	--	--
2	--	≥ 190	--	--
3	NO	70-189	YES	--
4	NO	70-189	NO	YES



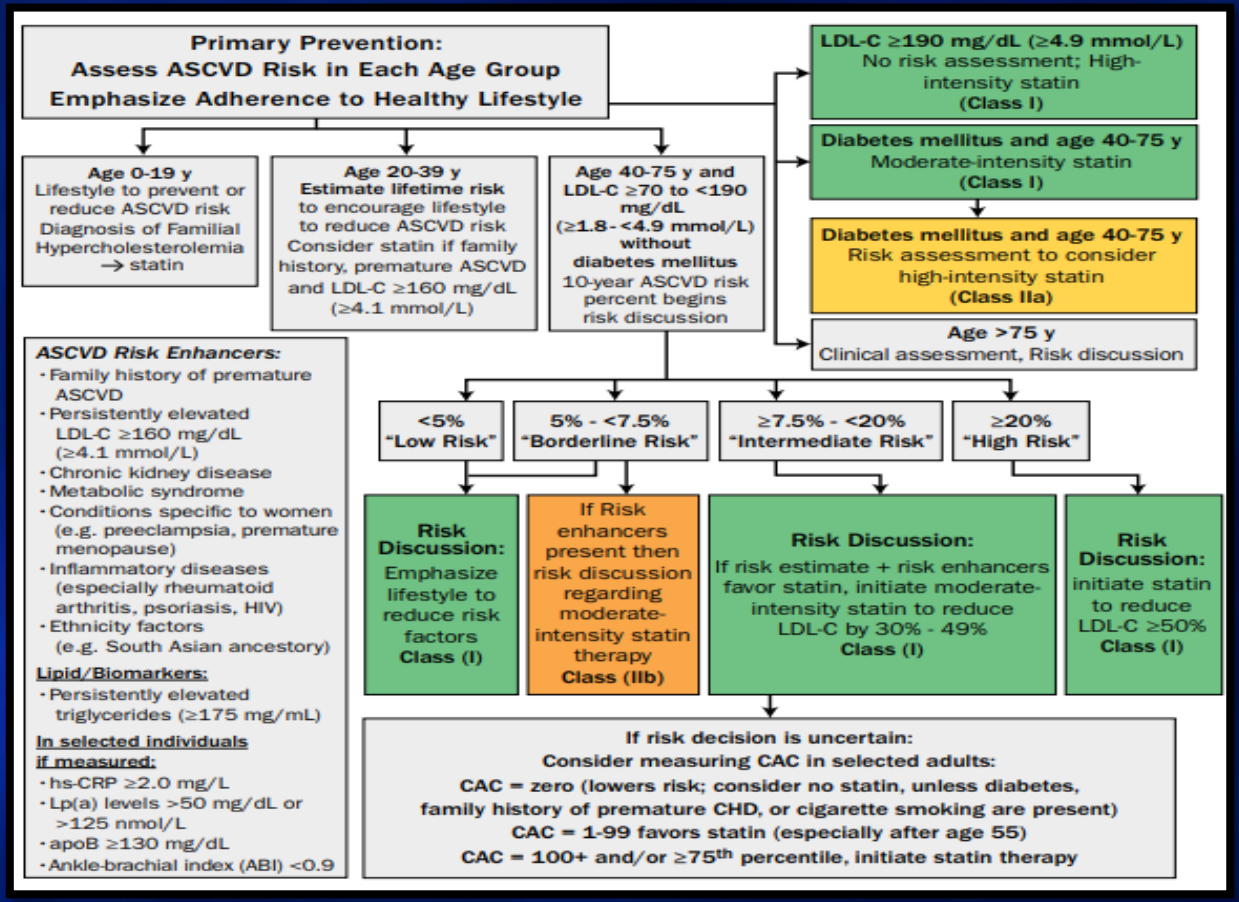
Statin therapy	Daily dose	
	High intensity* (mg)	Moderate intensity** (mg)
Atorvastatin	40–80	10 (20)
Rosuvastatin	20 (40)	(5) 10
Simvastatin	-	20–40
Pravastatin	-	40 (80)
Lovastatin	-	40
Fluvastatin	-	40
Pitavastatin	-	2–4

Atherosclerotic Cardiovascular Disease Risk Categories and LDL-C Treatment Goals. AACE 2017

Risk category	Risk factors[a]/10-year risk[b]	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – Diabetes or CKD 3/4 with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10-20% – Diabetes or CKD 3/4 with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Major independent risk factors:
- High LDL-C
- PCOS
- Cigarette smoking
- Hypertension
- Family history of CAD (male first-degree <55 yr; in female, first-degree <65 yr)
- CKD stage 3 and 4
- Evidence of coronary artery calcification and age (men ≥45; women ≥55 years)

ACC/AHA Guideline
Primary Prevention in Adults 40 to 75 Years of Age With Diabetes



Regardless of estimated 10-year ASCVD risk**, moderate-intensity statin** therapy is indicated.

Assess the 10-year risk of a first ASCVD event by using the PCE to help stratify ASCVD risk

Adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe **high-intensity statin** therapy with **the aim to reduce LDL-C levels by 50%.**

In adults with diabetes mellitus and 10-year ASCVD risk of ≥ 20%, it may be reasonable to add **ezetimibe** to maximally tolerated statin therapy to **reduce LDL-C levels by 50% or more**.

Journal of the American College of Cardiology Nov 2018, 25709; DOI:10.1016/j.jacc.2018.11.003

ACC/AHA Guideline
Primary Prevention in Adults 20 to 39 Years of Age With Diabetes

Consider initiating **moderate-intensity statin** therapy in adults who have had **type 2 diabetes mellitus for at least 10 years** or **type 1 diabetes mellitus for at least 20 years** and with patients with **1 or more major cardiovascular disease risk factors or complications**, such as:

- **Albuminuria (≥30 mcg of albumin/mg creatinine)**
- **GFR < 60 mL/min per 1.73 m2**
- **Retinopathy**
- **Ankle brachial index less than 0.9**
- **Neuropathy**

Journal of the American College of Cardiology Nov 2018, 25709; DOI:10.1016/j.jacc.2018.11.003

ACC/AHA Guideline
Primary Prevention in Adults Older Than 75 Years

Statin therapy may be considered after discussing the potential benefits and risks with your patient.

If the patient is already on statins, it is reasonable to continue on statin therapy.

Journal of the American College of Cardiology Nov 2018, 25709; DOI:10.1016/j.jacc.2018.11.003

Multiple Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS listed)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation)

High-Risk Conditions
Age ≥65 y
HeterozygousFam hypercholesterolemia
History of prior CABG surgery or pPCI outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (≥100 mg/dL) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

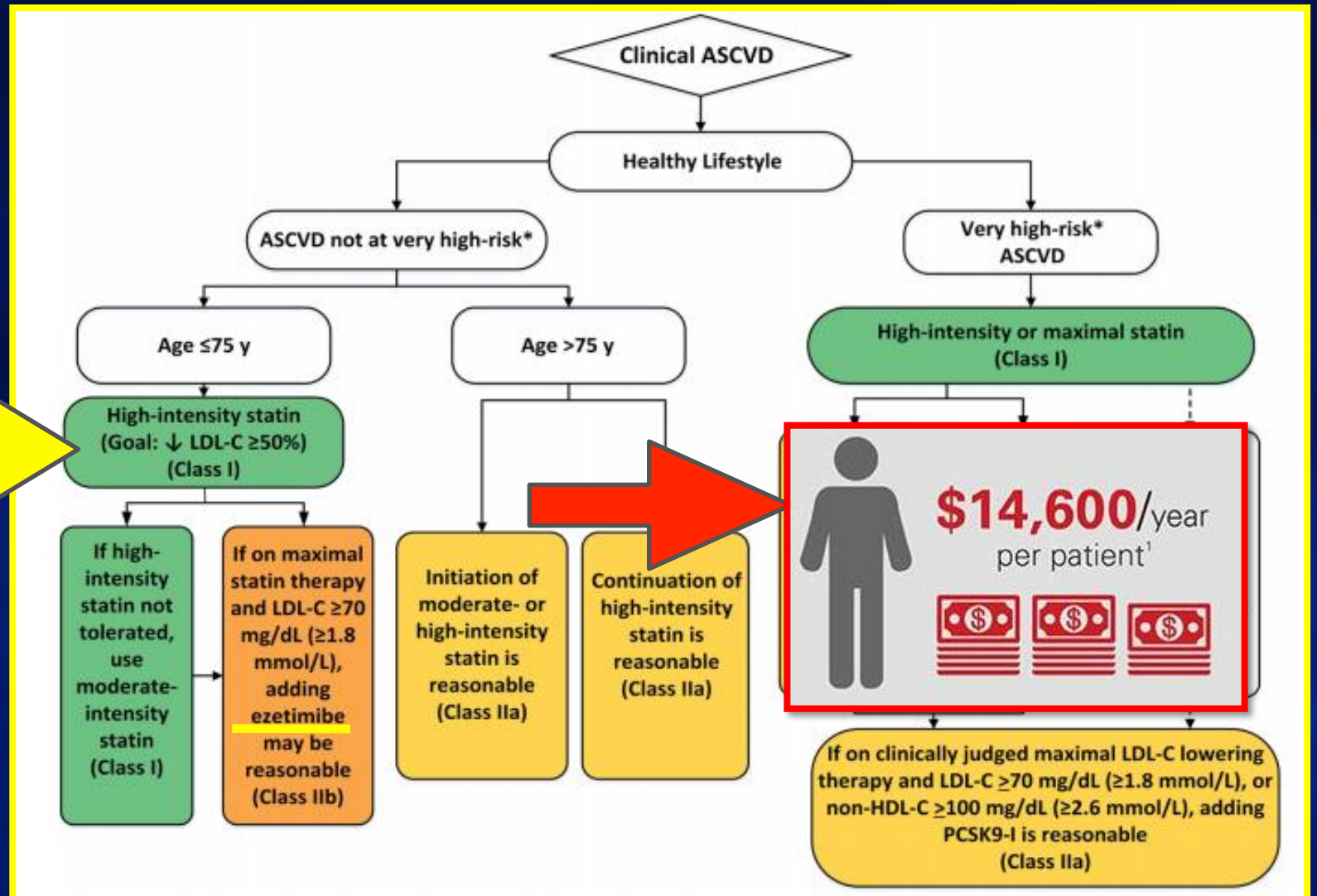
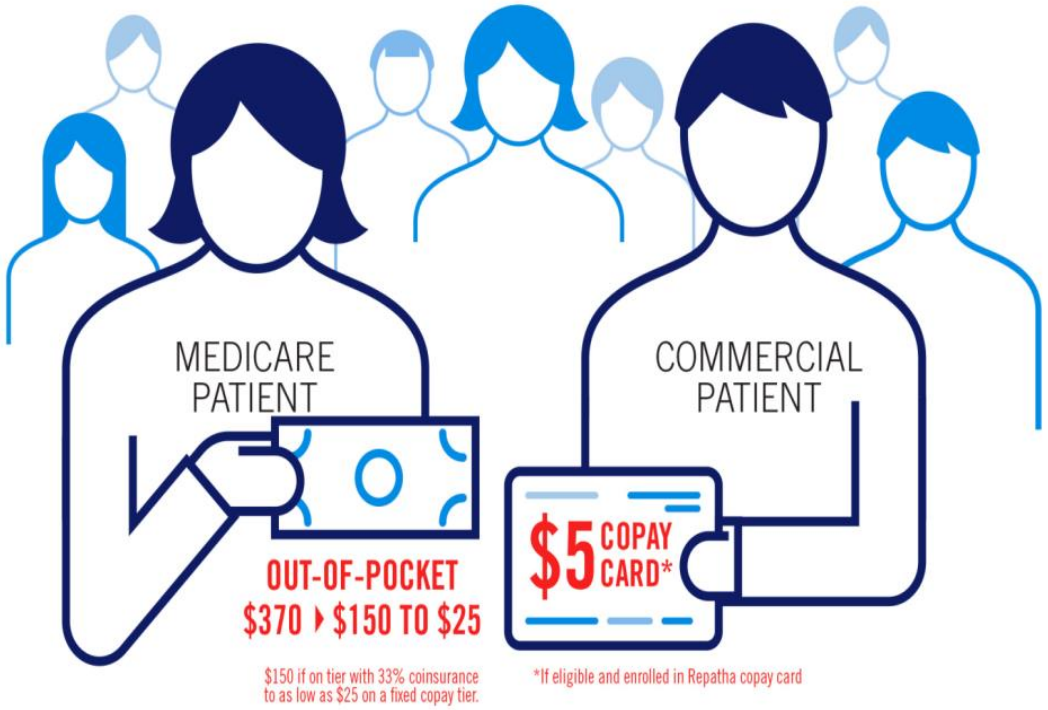


Figure 6. Secondary prevention.

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9-I, PCSK9 inhibitor. *Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

Journal of the American College of Cardiology Nov 2018, 25709; DOI:10.1016/j.jacc.2018.11.003

AMGEN MAKES REPATHA AVAILABLE AT LOWER LIST PRICE (ILLUSTRATIVE)



60% US LIST PRICE REDUCTION → TO **$5,850** NEW ANNUAL LIST PRICE ($450 PER RX)

Repatha (evolocumab) injection 140 mg/mL

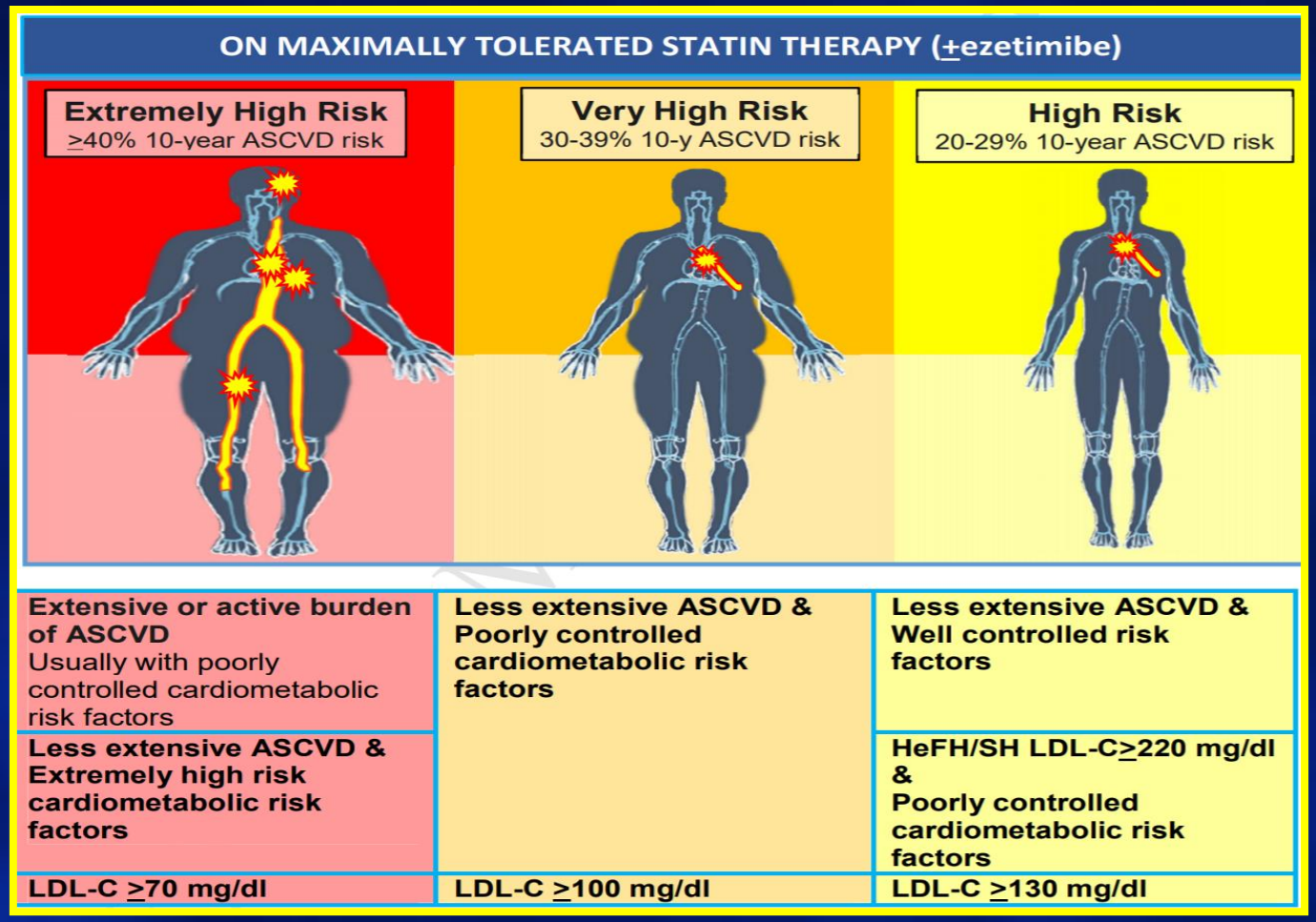
Questions? Contact our team at RepathaReady (1-844-REPATHA).

LOWER TOGETHER
LDL-C • RISK • HASSLE • COST

Alirocumab Price Cut Makes Second PCSK9 Inhibitor More Affordable

Regeneron/Sanofi have cut the cost of Praluent by 60%, mal it no more expensive than evolocumab, which saw its price tag slashed last year.

Enhancing the value of PCSK9 Ab by identifying patients most likely to benefit. *National Lipid Association*



Adapted from Robinson J, Watson K. Identifying patients for nonstatin therapy. Rev Cardiovasc Med 2018;19(suppl 1):S1-S8
1933-2874/ 2019 Published by Elsevier Inc. on behalf of National Lipid Association.

Building a Successful Treatment Plan

Asses patients risk of ASCVD	• Use ASCVD risk calculator for patients 40-75 yr • Assess patients risk enhancing factors.
Discuss patients lifestyle	• Diet, exercise, tobacco, BMI
Consider drug therapy benefits	• Statins first and consider combining with nonstatins for selected patients. • Discuss adverse drug effects.
Consider the cost of treatment	• Consider patient insurance and discuss prices.
Make treatment decisions together	• Ensure that patient understands and encourage treatment.

GRACIAS