UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI FARMACIA

Nuovi meccanismi d'azione e target farmacologici

Prof. Alberto Corsini
Dipartimento di Scienze Farmacologiche

Lipoprotein Management in Patients With Cardiometabolic Risk: Consensus Conference Report From the American Diabetes Association and the American College of Cardiology Foundation

John D. Brunzell, Michael Davidson, Curt D. Furberg, Ronald B. Goldberg, Barbara V. Howard, James H. Stein, and Joseph L. Witztum

J. Am. Coll. Cardiol. 2008;51;1512-1524; originally published online Mar 27, 2008;

JACC
Journal of the American College of Cardiology

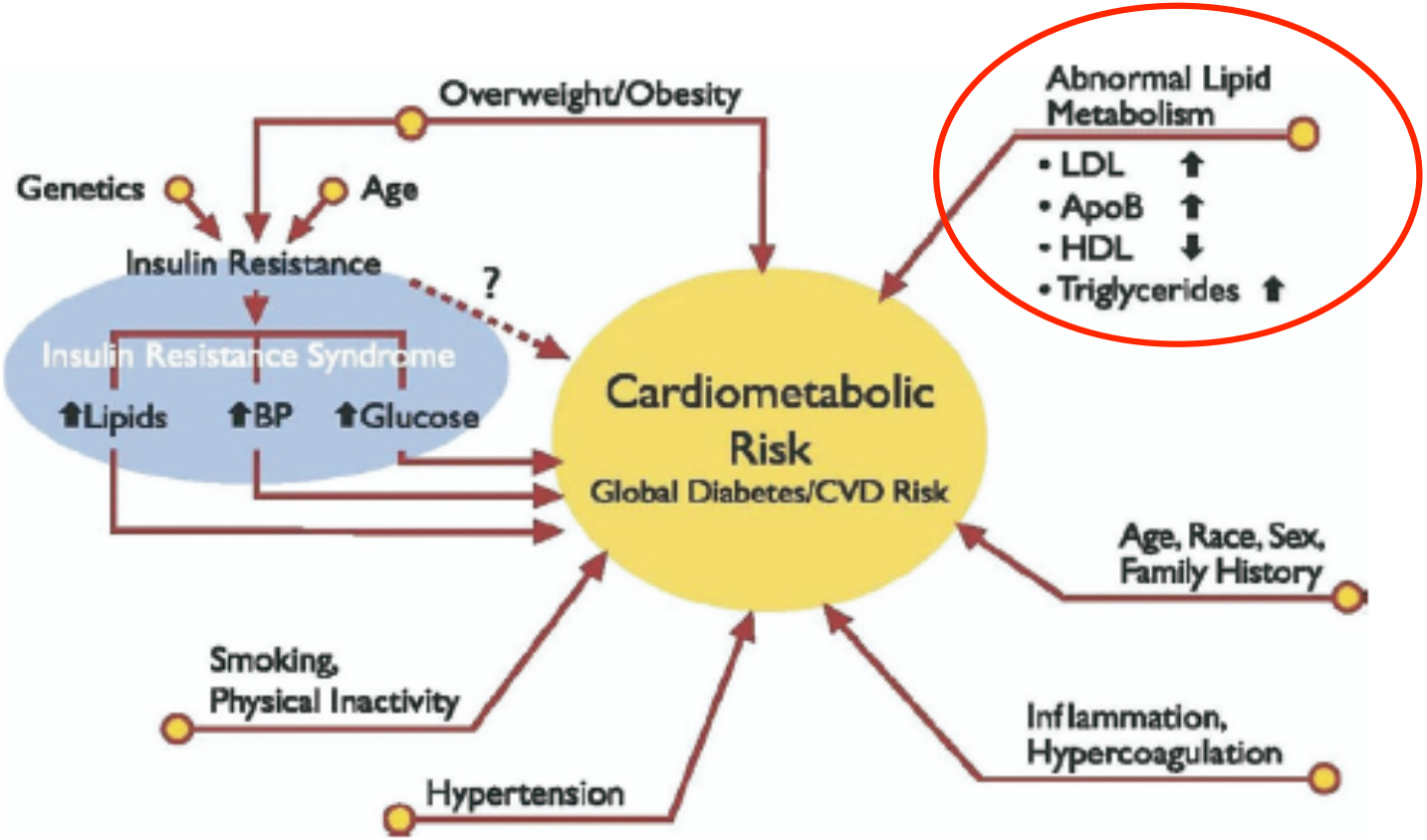
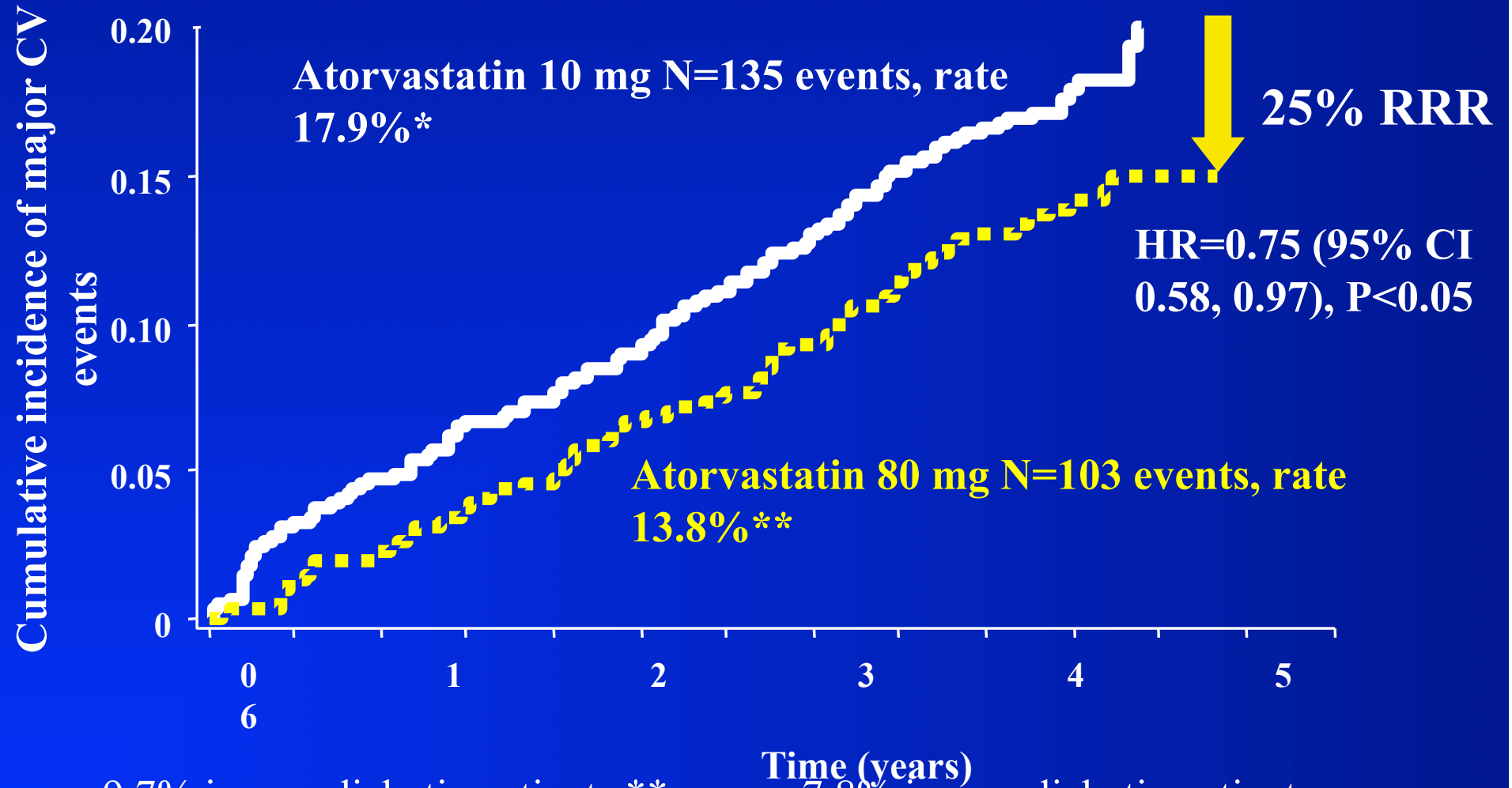


Figure 1. Factors Contributing to Cardiometabolic Risk

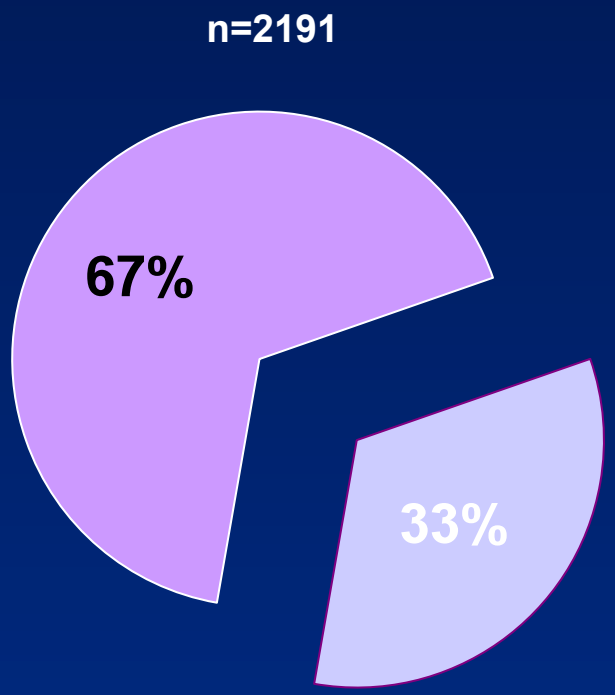
TNT: Time to First Major Cardiovascular Endpoint in Patients With Diabetes



*versus 9.7% in non-diabetic patients ** versus 7.8% in non-diabetic patients

Shepherd J et al. Diabetes Care 2006

Patients at or below LDL-C of 100 mg/dl had Vascular Events



Retrospective cohort study conducted in the UK of 19,882 patients >35 years of age

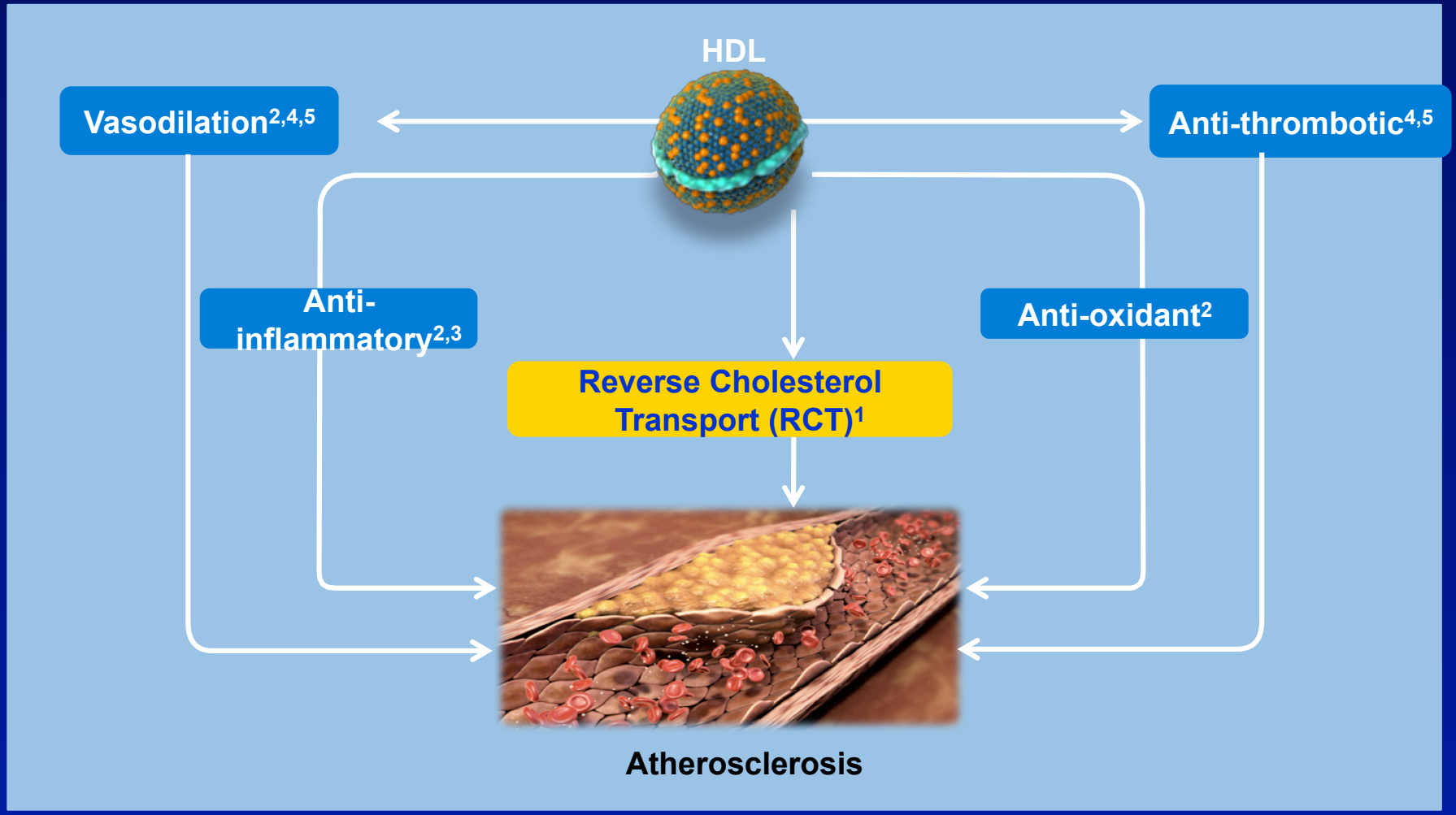
- Of 2191 statin-treated patients who experienced a CV/CB event, **67%** were at LDL-C of 100 mg/dl
  - **33%** of the 2191 patients who had a CV event were not at LDL-C of 100 mg/dl
- Among patients with a CV/CB event and
  - With LDL-C <100 mg/dl, **38.6%** had low HDL-C and/or elevated triglycerides
  - With LDL-C >100 mg/dl, **43.9%** had low HDL-C and/or elevated triglycerides

Patients were on statin therapy ≥6 weeks; >2 years pre- and post-statin history with laboratory data; no concomitant lipid-lowering drugs; and ≥1 complete lipid profile pre- and post-statin initiation. Patients were followed for up to 5 years

LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; CV=cardiovascular; CB=cerebrovascular

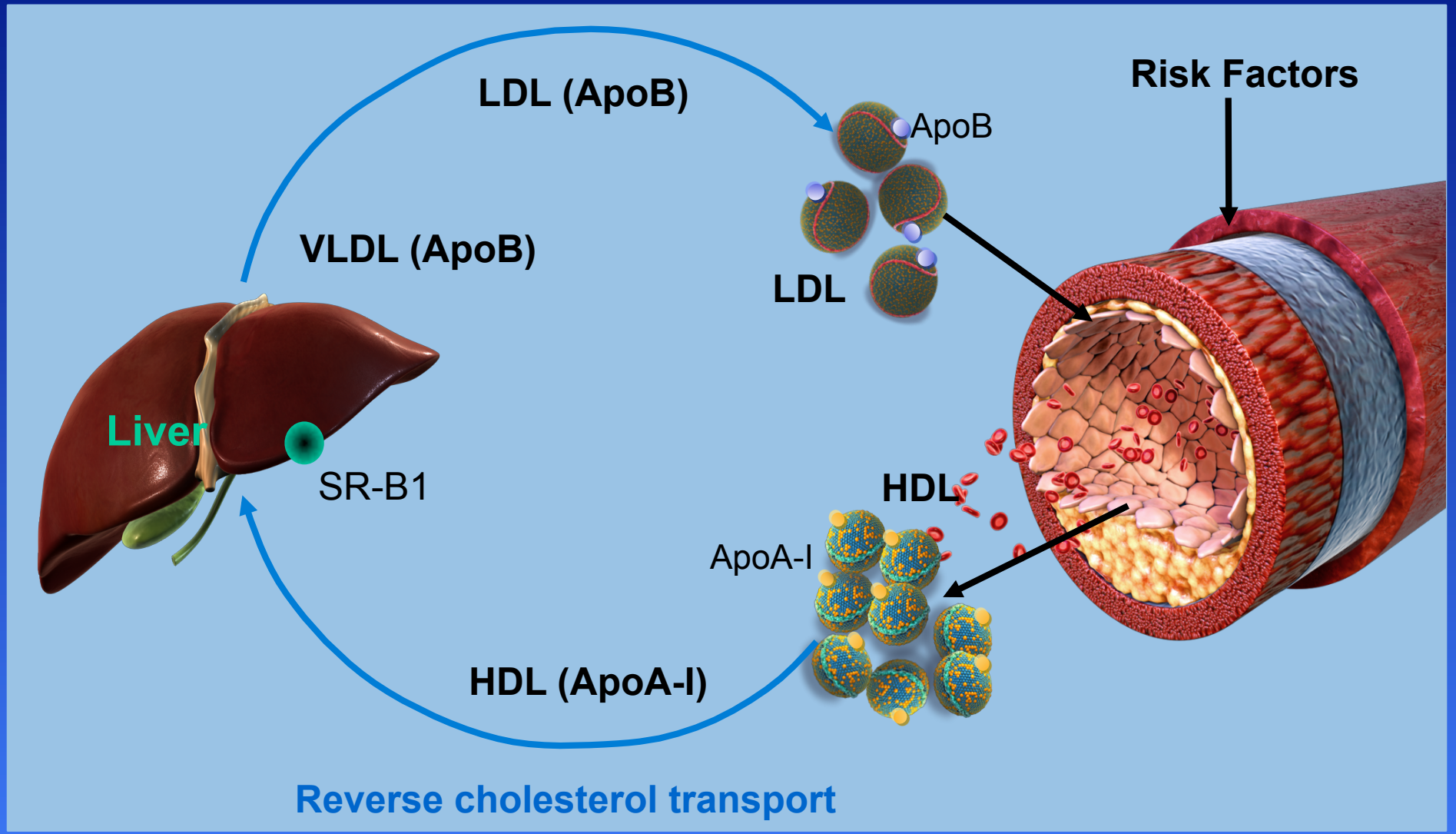
Phatak H et al. Poster presented at the European Atherosclerosis Society Congress; 10–13 June 2007: Helsinki, Finland. Poster P016-441.

HDL has multiple cardiovascular benefits



[1]Barter P. *Eur Heart J Suppl*. 2004;6(Suppl. A): A19–A22; [2]Tabet F, Rye KA. *Clin Sci* 2009;116:87-98; [3]Yvan-Charvet et al. *Arterioscler Thromb Vasc Biol* 2010;30;139-143; [4]O'Connell BJ, Genest J, Jr. *Circulation.* 2001;104:1978–1983; [5]Calabresi et al. *Arterioscler Thromb Vasc Biol*. 2003;23:1724–1731.

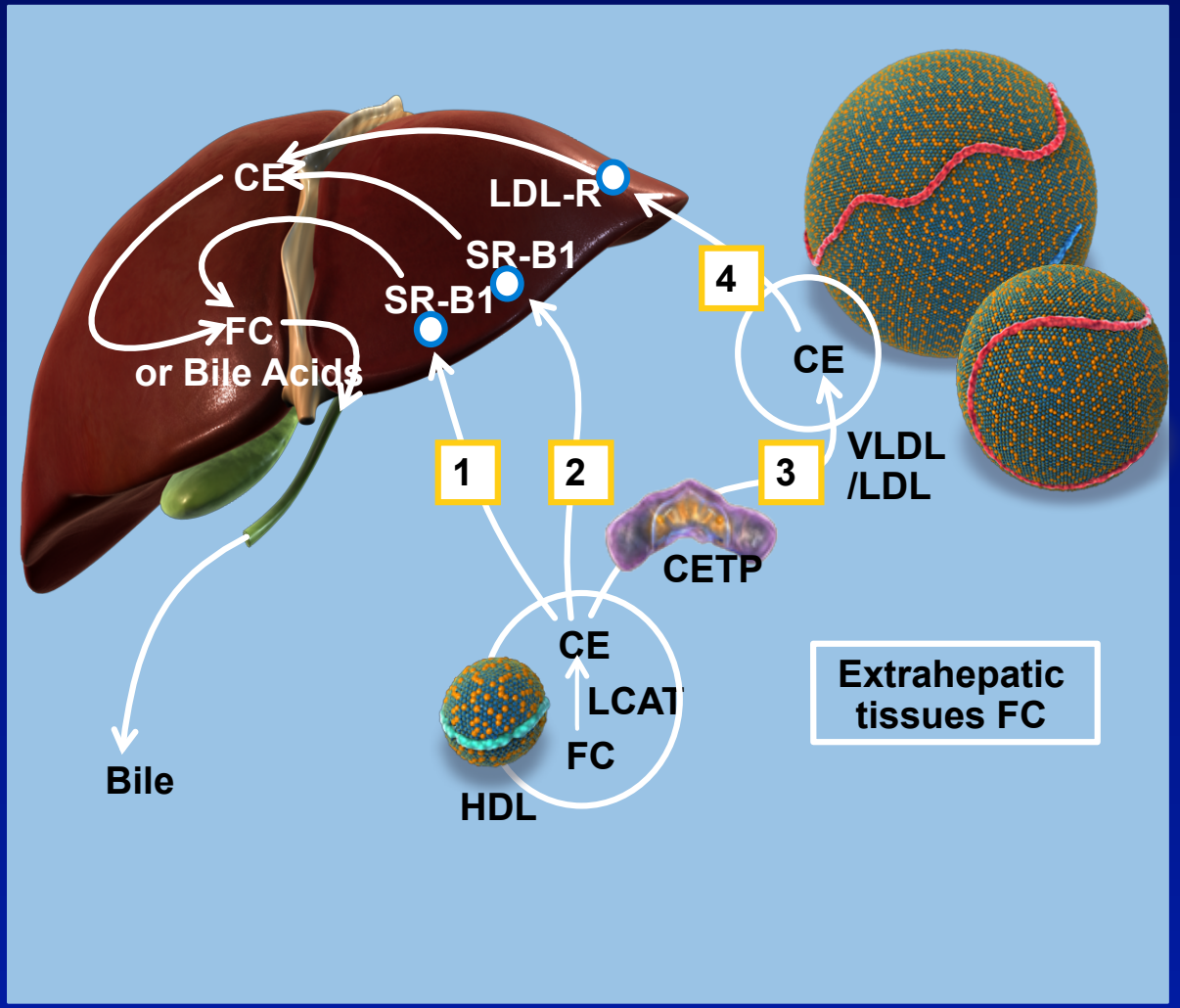
The simple good and the simple bad!



Adapted from Barter P. *Eur Heart J Suppl*. 2004;6(Suppl A): A19–A22.

HDL and reverse cholesterol transport

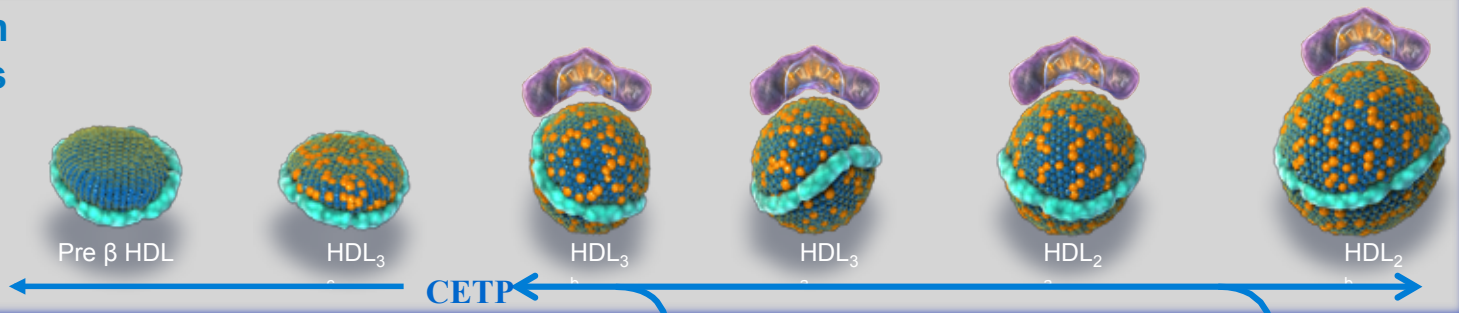
1. Direct uptake of FC from HDL by SR-B1
2. Esterification of FC by LCAT; CE taken up by SR-B1
3. CETP-mediated transfer of CE from HDL to VLDL in exchange for TG
4. Uptake of CE following binding to LDL-R



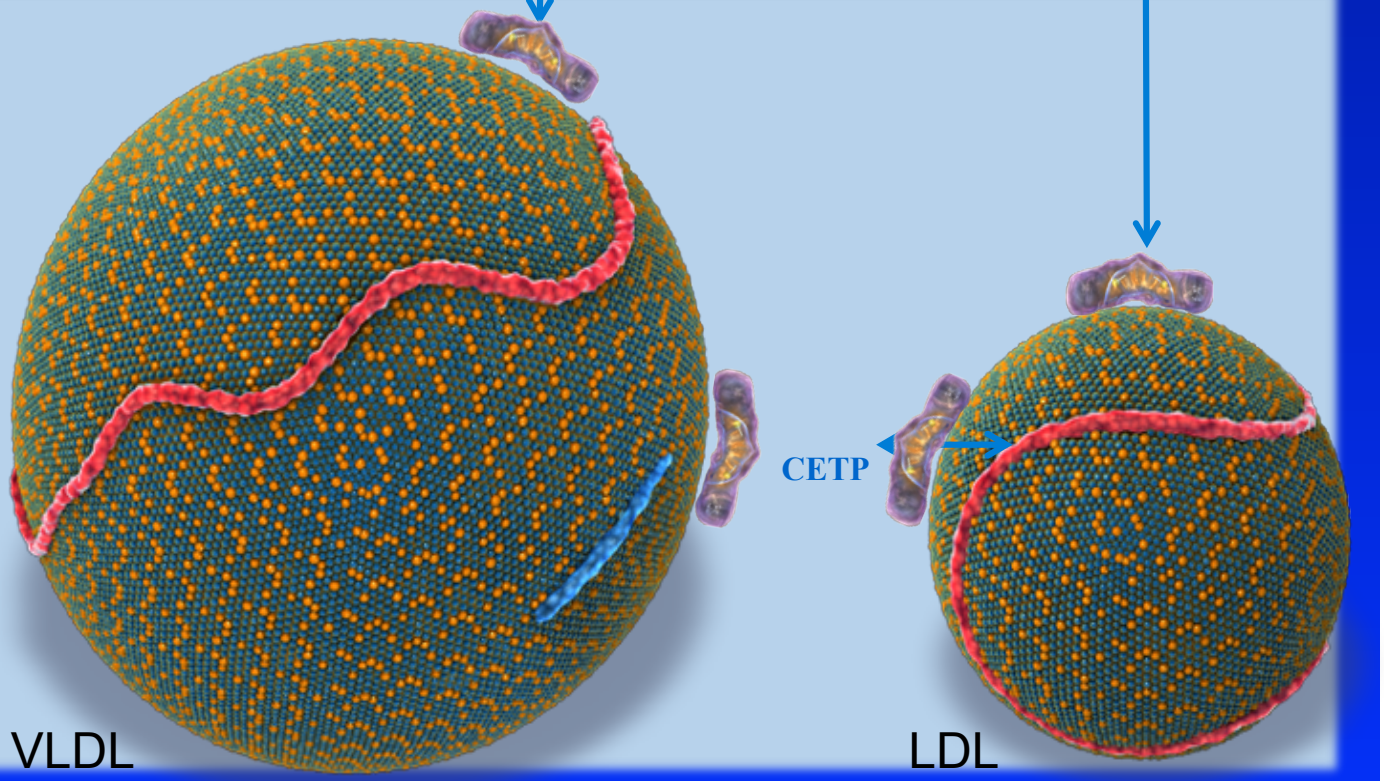
Adapted from Barter P, Rye KA. *A new therapeutic target: cholesteryl: ester transfer protein. Current status and future directions.* Birmingham, UK: Sherbourne Gibbs, 2008.

The Function of CETP: lipid transfer among all lipoproteins

CETP is involved in the natural process of HDL remodeling



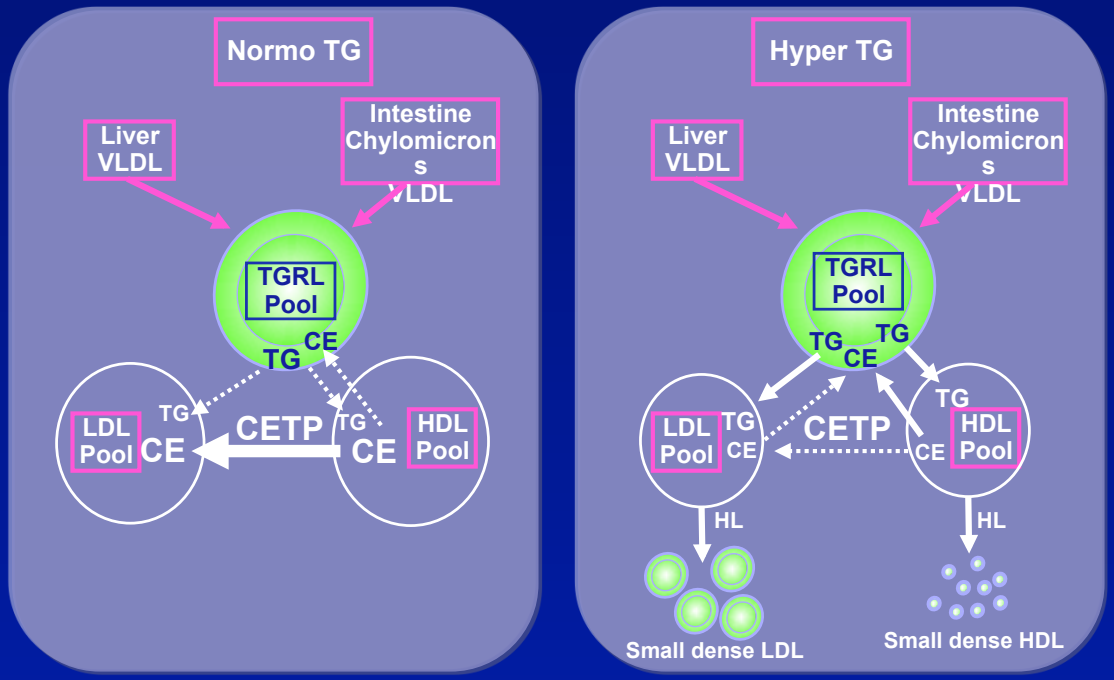
CETP is involved in the transfer of cholesterol from HDL to VLDL and LDL



Adapted from Niesor E., et al, .J Lipid Res. 2010 Dec;51(12):3443-54. Epub 2010 Sep 22.

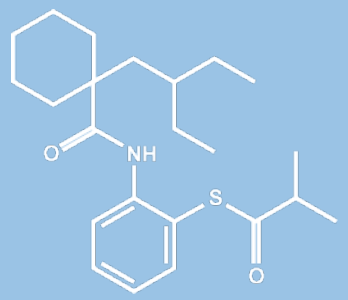
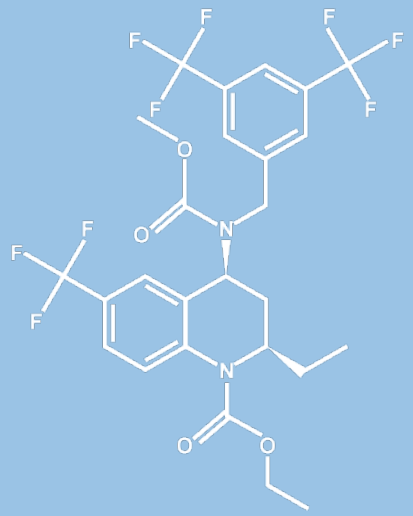
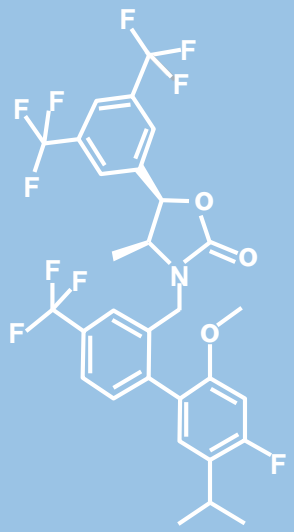
The Role of CETP in Atherogenesis

- CETP may promote or inhibit atherogenesis, depending on TG levels
- When TGs are normal CETP maintains an equilibrium of cholesteryl esters between HDL and LDL
- When TGs are elevated, CETP promotes transfer of cholesteryl esters to VLDL



Adapted from Barter et al. *Arterioscler Thromb Vasc Biol*. 2003;23:160–167.

CETP inhibitors: Differences in chemical structure and physicochemical properties

	Dalcetrapib[1]	Torcetrapib[2]	Anacetrapib[3]
			
Molecular weight	389.60	600.40	637.51
Lipophilicity	cLogP ~7	cLogP ~9	cLogP ~9

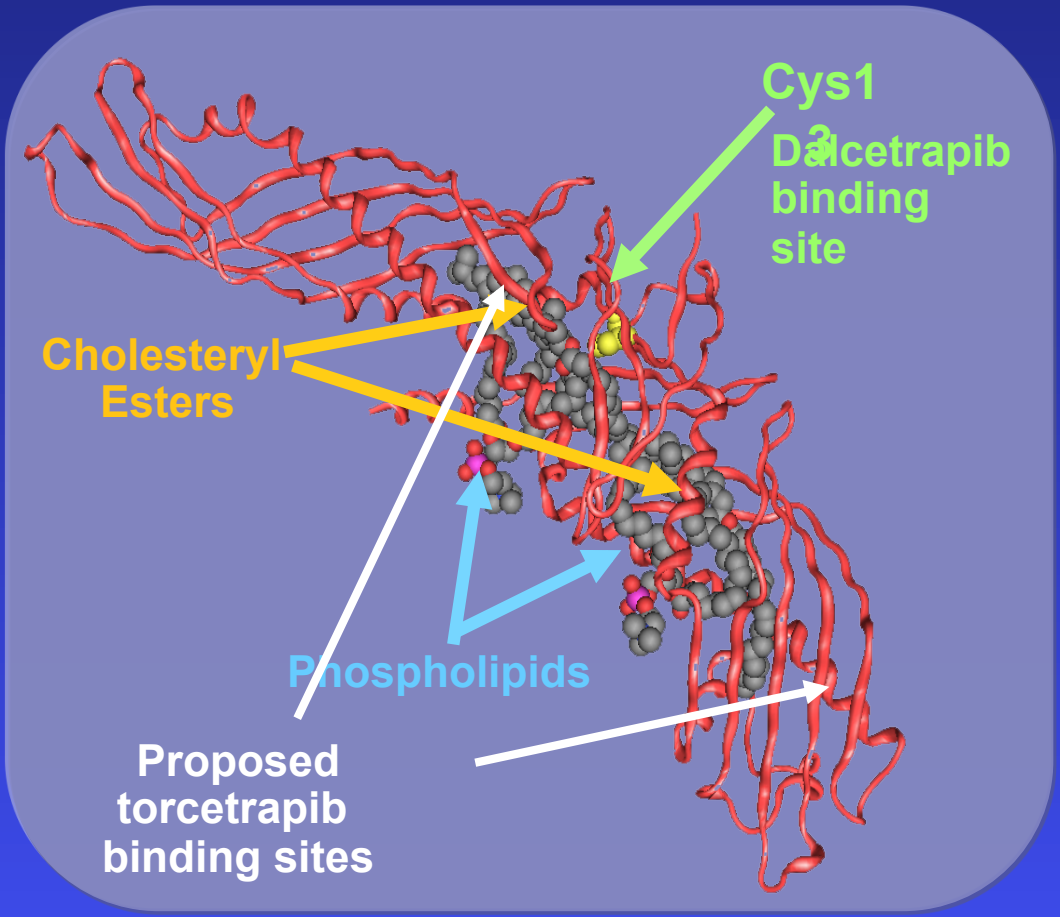
[1]http://www.ama-assn.org/ama1/pub/upload/mm/365/dalcetrapib.doc;
[2]http://www.ama-assn.org/ama1/pub/upload/mm/365/torcetrapib.doc;
[3]http:// www.ama-assn.org/ama1/pub/upload/mm/365/anacetrapib.pdf.

Clinical Pharmacology of Dalcetrapib

- Chemical structure and Mechanism of action
- Preclinical studies
- Pharmacokinetics
- Clinical trials

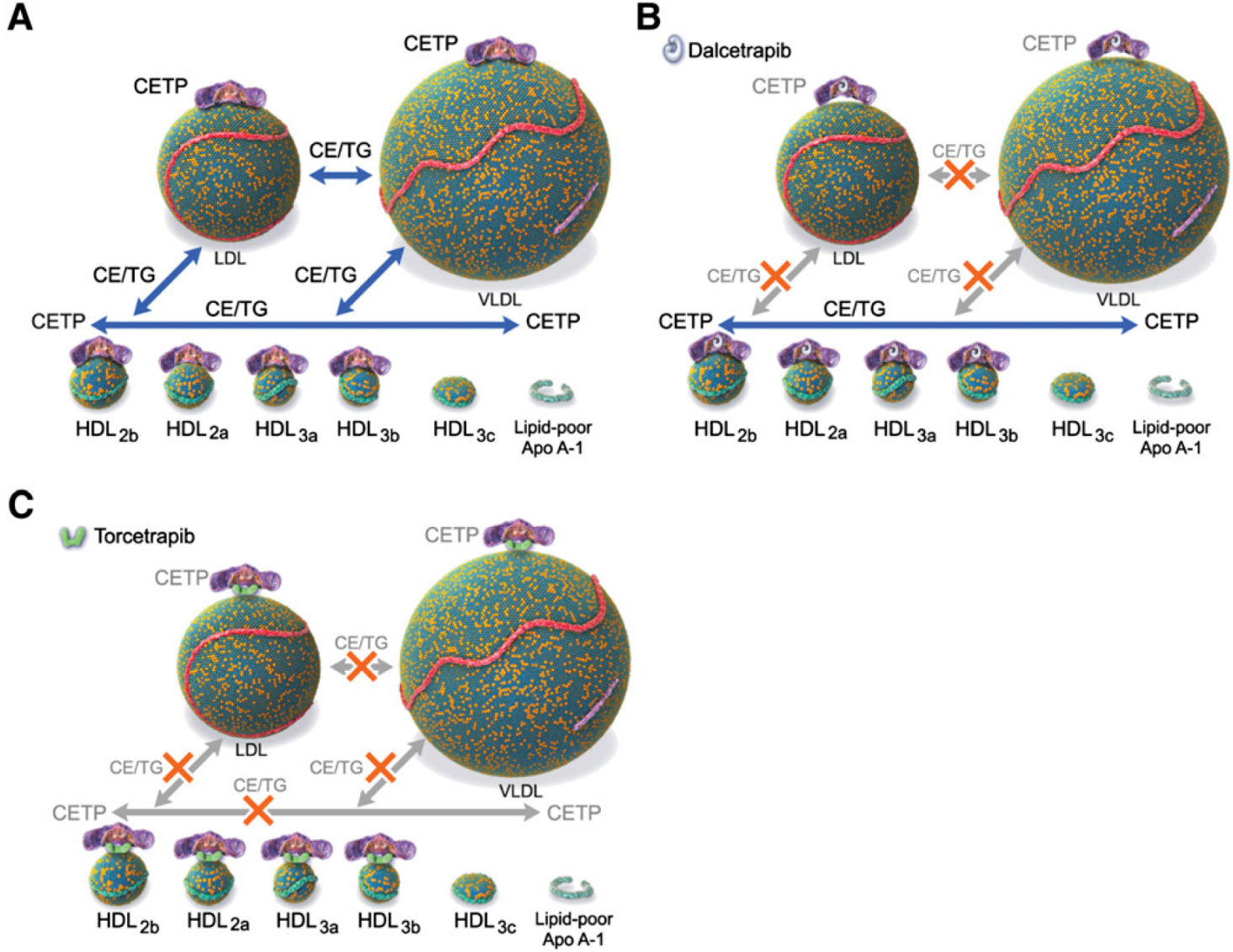
CETP Inhibitors: Mechanism of Action
Binding of Lipids and CETP Inhibitors to the CETP Molecule

- The cysteine at residue 13 of CETP seems to be essential for decreased CETP activity with dalcetrapib[1]
- Torcetrapib is believed to bind to the helices at the end of the C and N barrels of the CETP molecule[2]



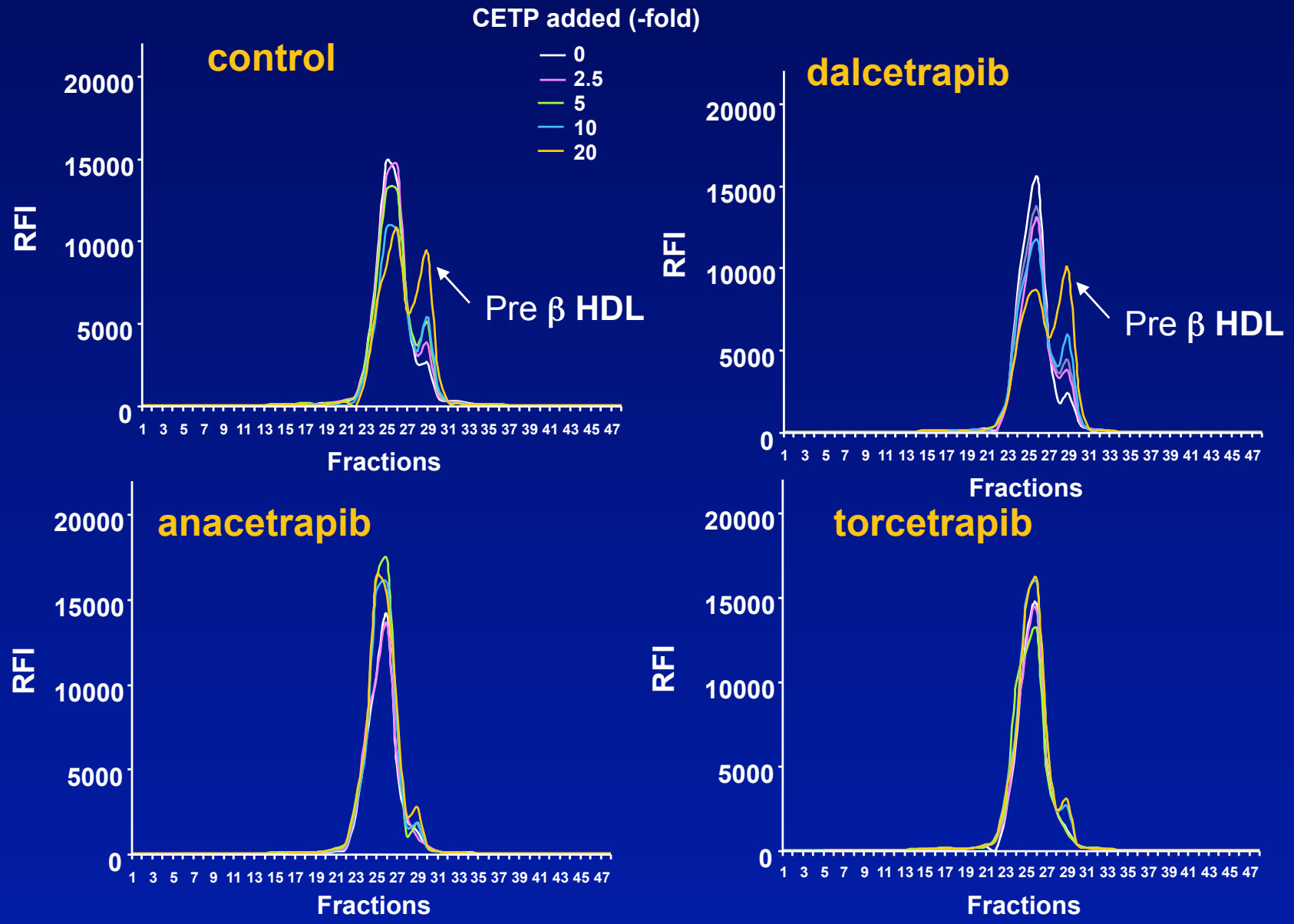
[1]Okamoto et al. *Nature.* 2000;406:203–207; [2]Clark et al. *J. Lipid Res.* 2006;47:537–552;
[3]Barter et al. *N Engl J Med*. 2007;357:2109–2122.

Dalcetrapib Differs from Anacetrapib and Torcetrpaib by not Preventing rhCETP induced pre-β-HDL formation



Niesor E., et al, .J Lipid Res. 2010 Dec;51(12):3443-54. Epub 2010 Sep 22.

Effect of compounds affecting CETP activity on CETP induced pre-β-HDL formation (in vitro)

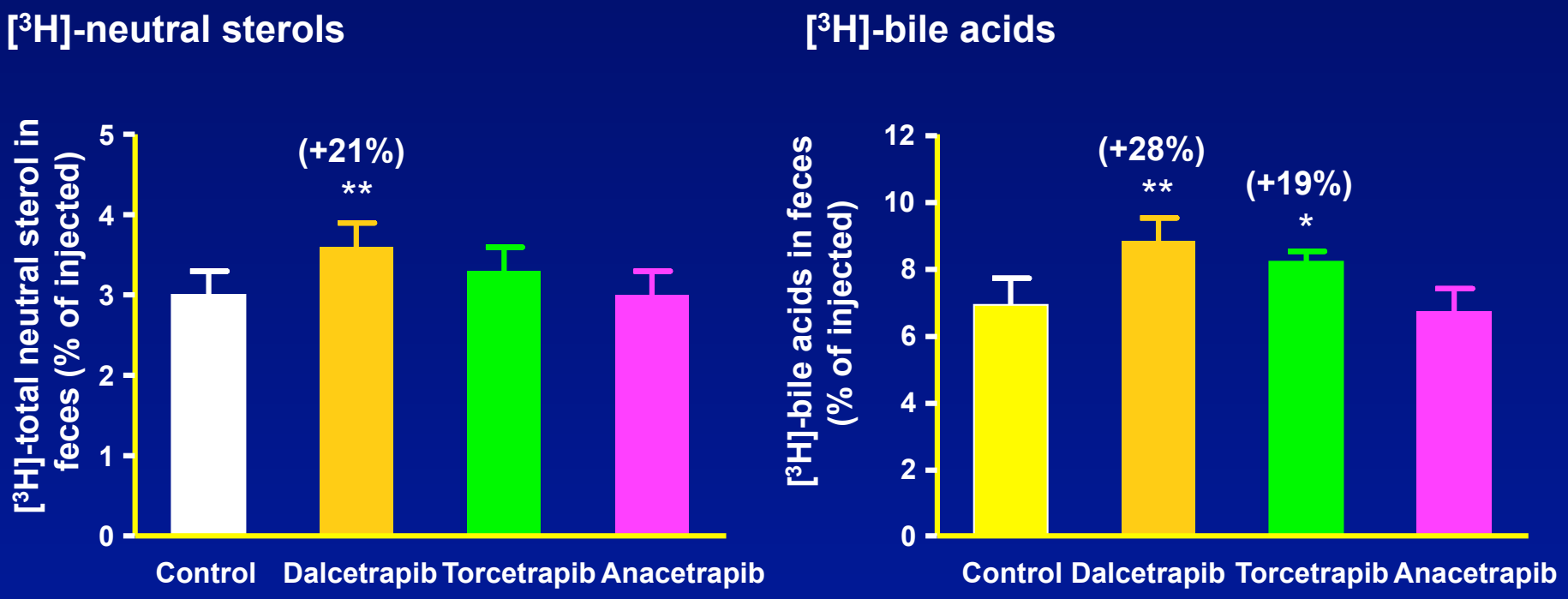


[1]Dernick et al. Poster presented at 6th IAS-Sponsored Workshop on HDL. May 17-20, 2010; Whistler, BC, Canada; [2]Barter et al. *N Engl J Med*. 2007;357:2109–2122.

Clinical Pharmacology of Dalcetrapib

- Chemical structure and Mechanism of action
- Preclinical studies
- Pharmacokinetics
- Clinical trials

Dalcetrapib increased fecal [3H]-bile acid and [3H]-neutral sterol radioactivity



Data shown are mean ±SD

*$P < .05$; **$P < .01$ vs. control (Dunnett test)

Dalcetrapib 100 mg/kg bid; torcetrapib 30 mg/kg qd; anacetrapib 30 mg/kg qd

Clinical Pharmacology of Dalcetrapib

- Chemical structure and Mechanism of action
- Preclinical studies
- Pharmacokinetics
- Pharmacodinamics
- Clinical trials

Comparison of CETP inhibitors: Clinical pharmacology

	Dalcetrapib	Torcetrapib	Anacetrapib
Clinical dosing regimen	600 mg o.d.[1]	60 mg o.d.[2]	100 mg o.d.[3]
Food effect*	~2x[4]	~20–30x[5]	~6–8x[6]
Terminal half-life	~30 h[7]	~200 h[8]	>100 h[9]
Accumulation	~20%[10]	?	85-280%[11]
Clearance route	Metabolism[7]	Metabolism[8]	Metabolism[9]
Metabolic pathways	Glucuronidation, methylation[7]	Decarbamoylation (CYP3A4)[8]	Demethylation (CYP3A4)[9]
Drug-drug interactions with cytochrome P450 inhibitors	None[12]	?	Ketoconazole: 4.6x[13] Diltiazem: 1.9x[14]

[1]Schwartz et al. *Am Heart J*. 2009;158:896-901; [2]Barter et al. *N Engl J Med*. 2007;357:2109–2122; [3]Cannon et al. *Am Heart J*. 2009;158:513-519; [4]Roche data on file;
[5]Perlman et al. *Int J Pharm*. 2008:351:15–22; [6]Krishna et al. *Br J Clin Pharmacol*. 2009;68:535-545; [7]Derks et al. *Clin Pharmacol Ther*. 2010;87 (suppl 1):S24;
[8]Dalvie et al. *Drug Metab Dispos*. 2008;36:2185-98; [9]Kumar et al. *Drug Metab Dispos*. 2010;38:474–483; [10]Derks et al. *Eur J Clin Pharmacol*. 2010; doi 10.1007/s00228-010-0841-2; [11]Krishna et al. *Clin Pharmacol Ther*. 2008;84:679-683; [12]Derks et al. *Clin Ther*. 2009;31:586–599;
[13]Krishna et al. *J Clin Pharmacol*. 2009;49:80-87; [14]Garg et al. *J Clin Pharmacol*. 2010; in press.

Clinical Pharmacology of Dalcetrapib

- Chemical structure and Mechanism of action
- Preclinical studies
- Pharmacokinetics
- Clinical trials

The dal-HEART Program dalcetrapib HDL Evaluation, Atherosclerosis & Reverse cholesterol Transport

Double blind, randomized, placebo-controlled studies

dal-OUTCOMES[1]

15,600 *patients recently hospitalized for ACS*

To evaluate the effect of dalcetrapib on CV outcomes

RECRUITING

dal-VESSEL[2]

450 *patients with CHD or CHD risk equivalent*

To evaluate the effect of dalcetrapib on endothelial function and blood pressure, measured by FMD and ABPM

RECRUITMENT COMPLETE

dal-PLAQUE[3]

130 *patients with CHD*

To evaluate the effect of dalcetrapib on plaque inflammation, plaque size and burden, measured by PET/CT and MRI

RECRUITMENT COMPLETE

dal-PLAQUE 2[4]

900 *patients with CAD*

To evaluate the effect of dalcetrapib on atherosclerotic disease progression, assessed by IVUS and carotid B-mode ultrasound

RECRUITING

[1]Schwartz et al. *Am Heart J.* 2009;158:896-901; [2]http://clinicaltrials.gov/ct2/show/NCT00655538 Accessed April 1st 2010;
[3]http://clinicaltrials.gov/ct2/show/NCT00655473 Accessed 1st April 2010; [4]http://clinicaltrials.gov/ct2/show/NCT01059682. Accessed April 1st 2010

JACC
JOURNAL of the AMERICAN COLLEGE of CARDIOLOGY

Lipoprotein Management in Patients With Cardiometabolic Risk: Consensus Conference Report From the American Diabetes Association and the American College of Cardiology Foundation

John D. Brunzell, Michael Davidson, Curt D. Furberg, Ronald B. Goldberg, Barbara V. Howard, James H. Stein, and Joseph L. Witztum

J. Am. Coll. Cardiol. 2008;51;1512-1524; originally published online Mar 27, 2008;

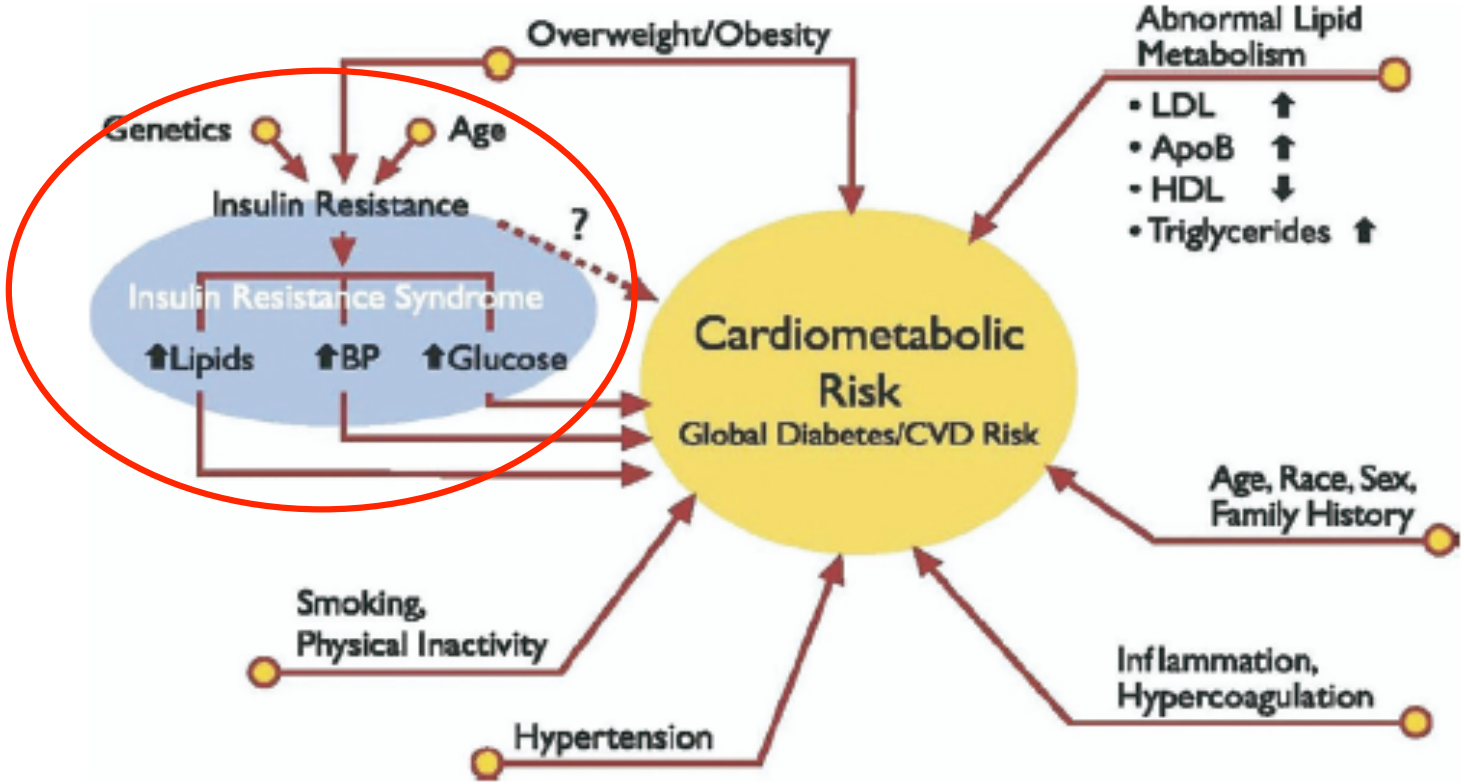
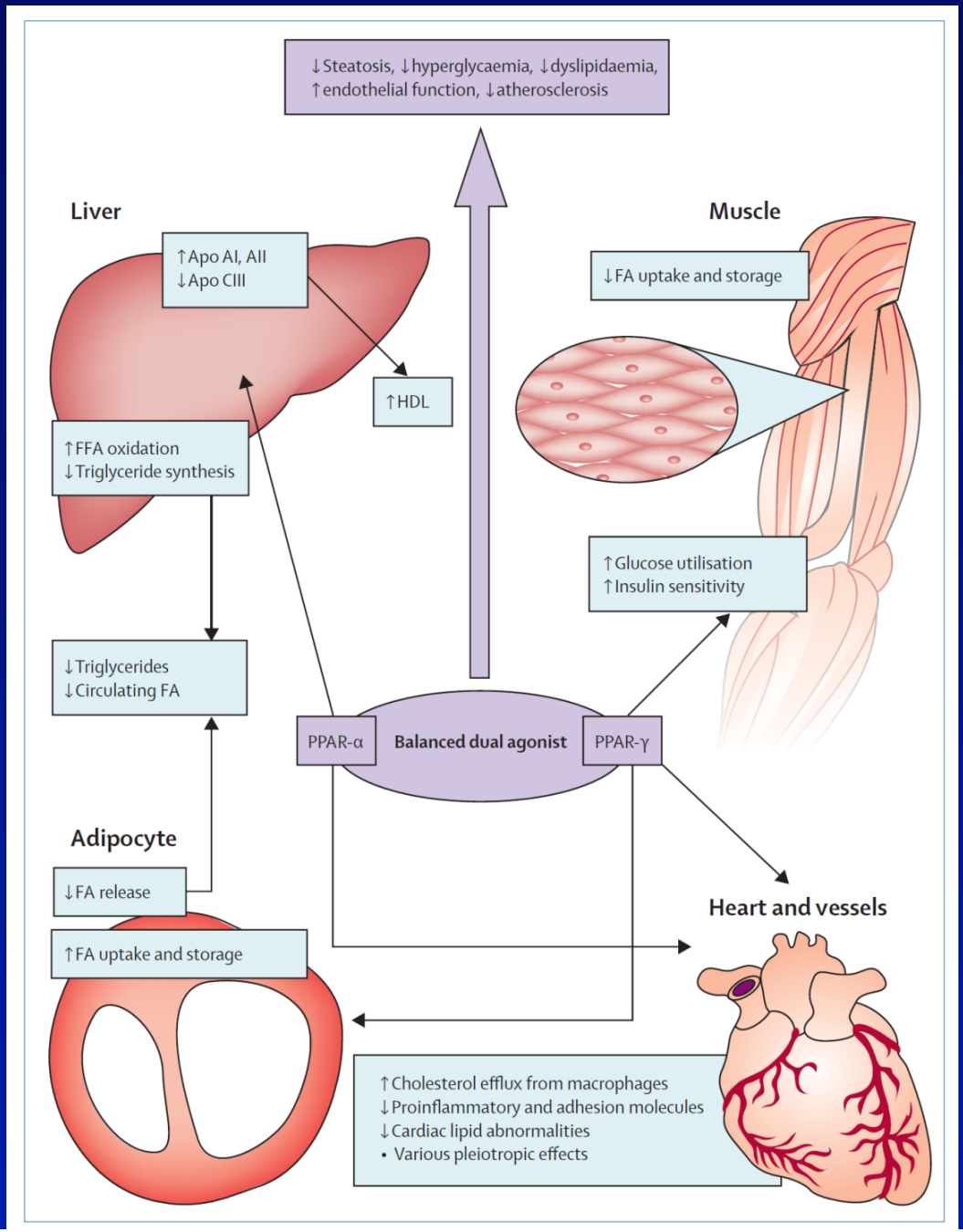


Figure 1. Factors Contributing to Cardiometabolic Risk

Synergistic beneficial actions of balanced PPAR-α/γ agonists

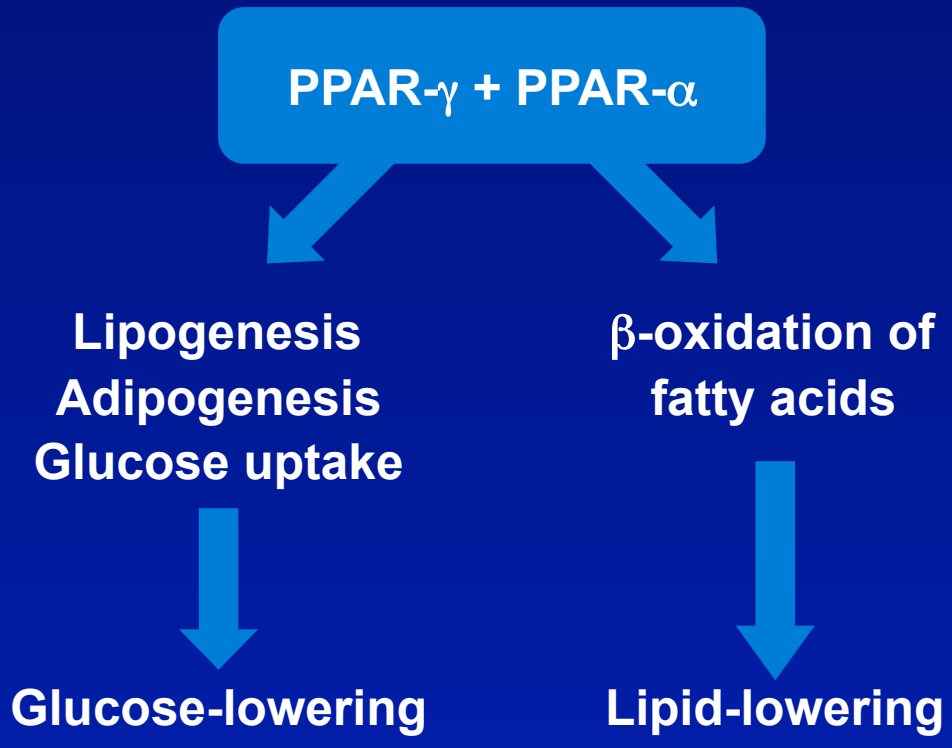


Charbonnel B, Lancet
374: 97-98; 2009

Dual PPAR agonists

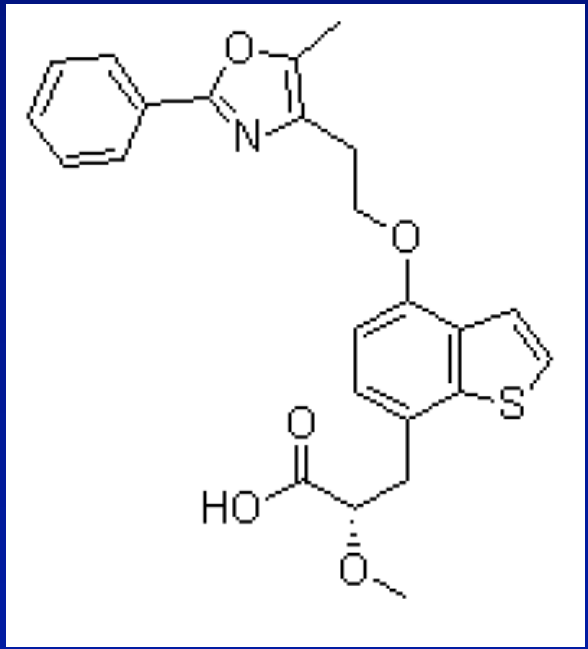
A Promising Approach

- ***B*oth dyslipidemia and insulin resistance appear to promote atherosclerosis in diabetics**
- **Likewise, improving lipid profile and insulin resistance both promise to improve clinical outcomes**



Aleglitazar

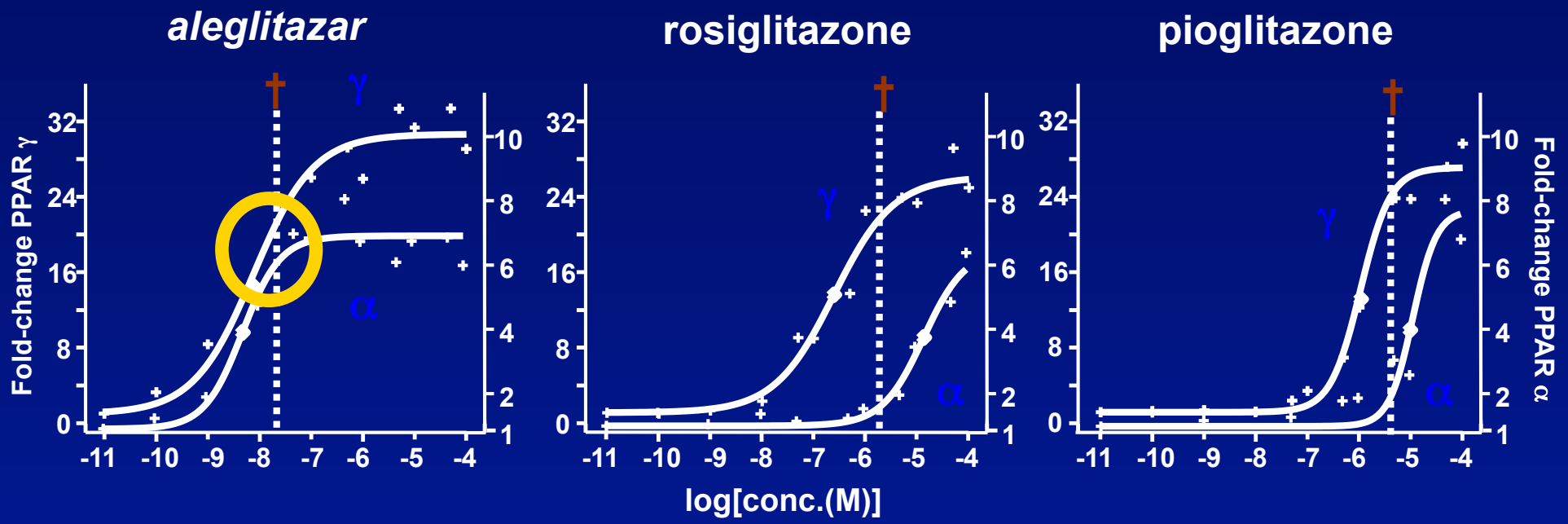
A novel dual α/γ PPAR activator



Development of dual PPAR agonists to date

	Reason for termination	Phase	Comments
Tesaglitazar	Impairment of renal function	III	Too much PPAR-α activity?
Muraglitazar	Excess CV events in pooled trials	III	Too much PPAR-γ activity?
Aleglitazar		III	Balanced PPAR effects?

Aleglitazar's balanced activation of both PPARα and PPARγ receptors in vitro compared to unbalanced profile of rosi and pio



	aleglitazar	rosiglitazone	pioglitazone
EC_{50} PPARg (nM)	**8**	**245**	**1060**
EC_{50} PPARa (nM)	**5**	**15000**	**11700**
Clinical Dose	**150 µg**	**8 mg**	**45 mg**

† maximum plasma concentration at clinical dose

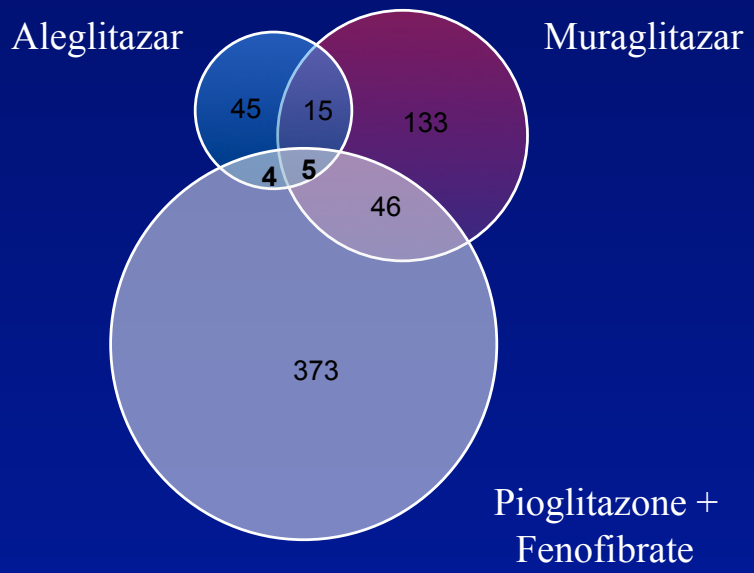
Source: RDR report 1038635

Aleglitazar: Gene Chip Microarray Analysis

Significant state changes between treatment and control

EC50 aligned dosage	Drug concentration	State changes
Aleglitazar		
- Low	0.013 mM	69
- Medium	0.064 mM	-
- High	0.32 mM	69
Muraglitazar		
- Low	0.13 mM	-
- Medium	0.64 mM	73
- High	3.2 mM	199
Pioglitazone + Fenofibric Acid		
- Low	0.11 mM + 6 mM	-
- Medium	0.56 mM + 30 mM	-
- High	2.8 mM + 155 mM	428

Shared state changes at high doses



- These data suggest that the gene activation/deactivation pattern of aleglitazar is distinct compared with muraglitazar and is distinct compared to a combination of pioglitazone + fenofibrate

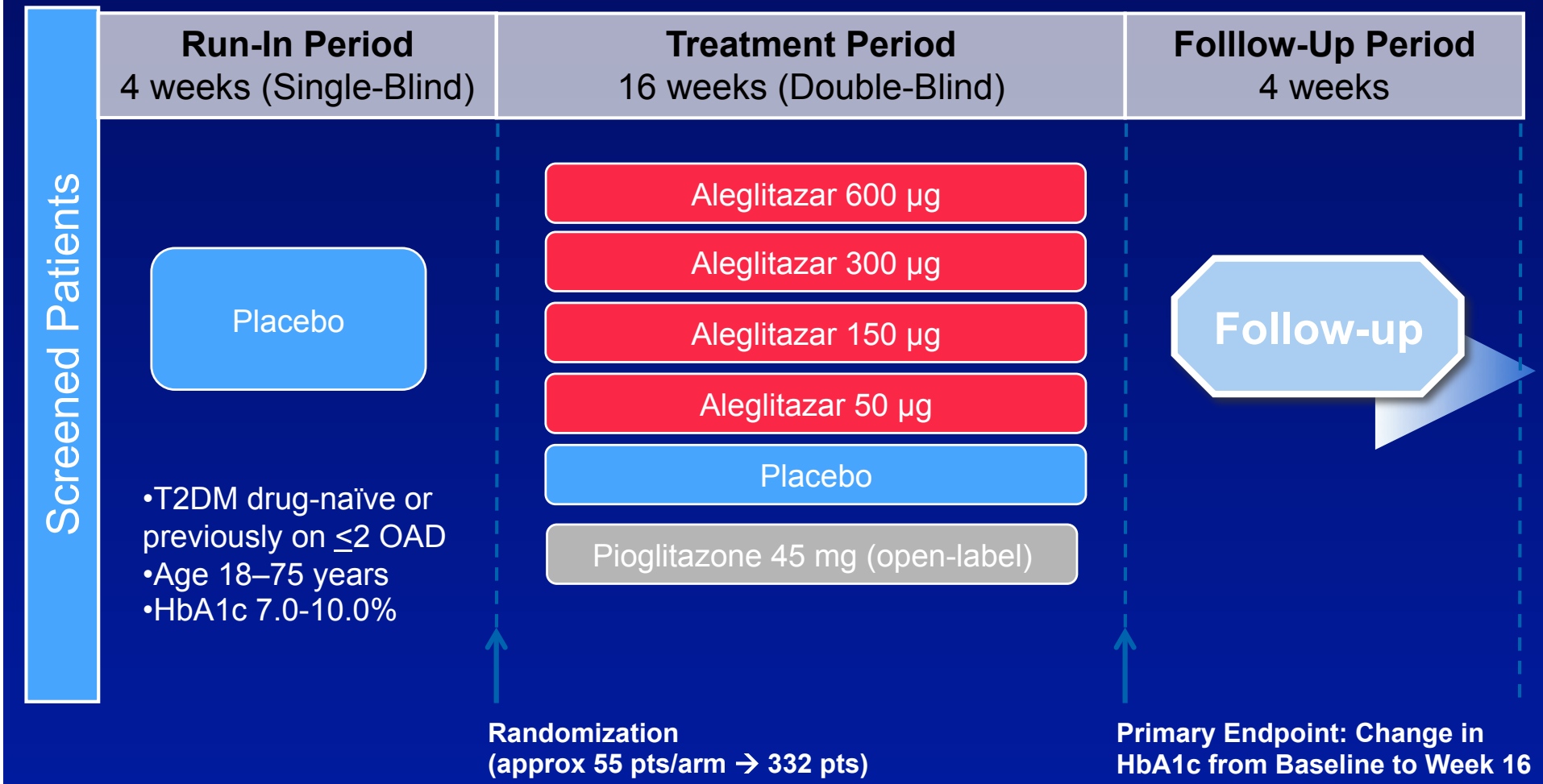
  Data on FIle

Aleglitazar Clinical Development Program

Study	Objectives
SYNCHRONY **trial**[1]	♦ **Dose finding, determine efficacy, safety, and tolerability** ♦ **Primary Endpoint: HbA1c change from baseline at week 16**
SESTA-R **trial**[2]	♦ **Evaluate effect (at 4x therapeutic dose, 600 μg) on GFR, renal plasma flow, and serum creatinine**
ALECARDIO **trial**[3]	♦ **To determine whether aleglitazar reduces CV mortality and morbidity in patients with a recent ACS event and T2DM** ♦ **Evaluate the effects of aleglitazar on other clinical endpoints of CV risk** ♦ **Evaluate the effects of aleglitazar on glycemic control, the lipoprotein profile, blood pressure, and biomarkers of CV risk** ♦ **Evaluate the tolerability and long-term safety profile of aleglitazar (e.g. fluid retention, heart failure, fractures, renal function, musculoskeletal adverse events and liver enzyme elevation)**
ALENEPHRO **trial**[4]	♦ **Long-term safety data (52-weeks) and reversibility (8-weeks) with aleglitazar at therapeutic dose (150 μg)**
Drug-drug interaction studies **(ACE-I, ARBs, ASA, NSAIDs)**	♦ **PK/PD effects of concomitant treatment of aleglitazar and another agent on renal function in controlled setting**
Renal Mechanistic Study	♦ **Examination of renal effects in comparison to fibrate and pioglitazone**

[1]Henry R et al. *Lancet* 2009;374:126; [2]ClinicalTrials.gov NCT00461006; [3]ClinicalTrials.gov NCT01042769; [4]ClinicalTrials.gov NCT01043029;

SYNCHRONY: Study Design

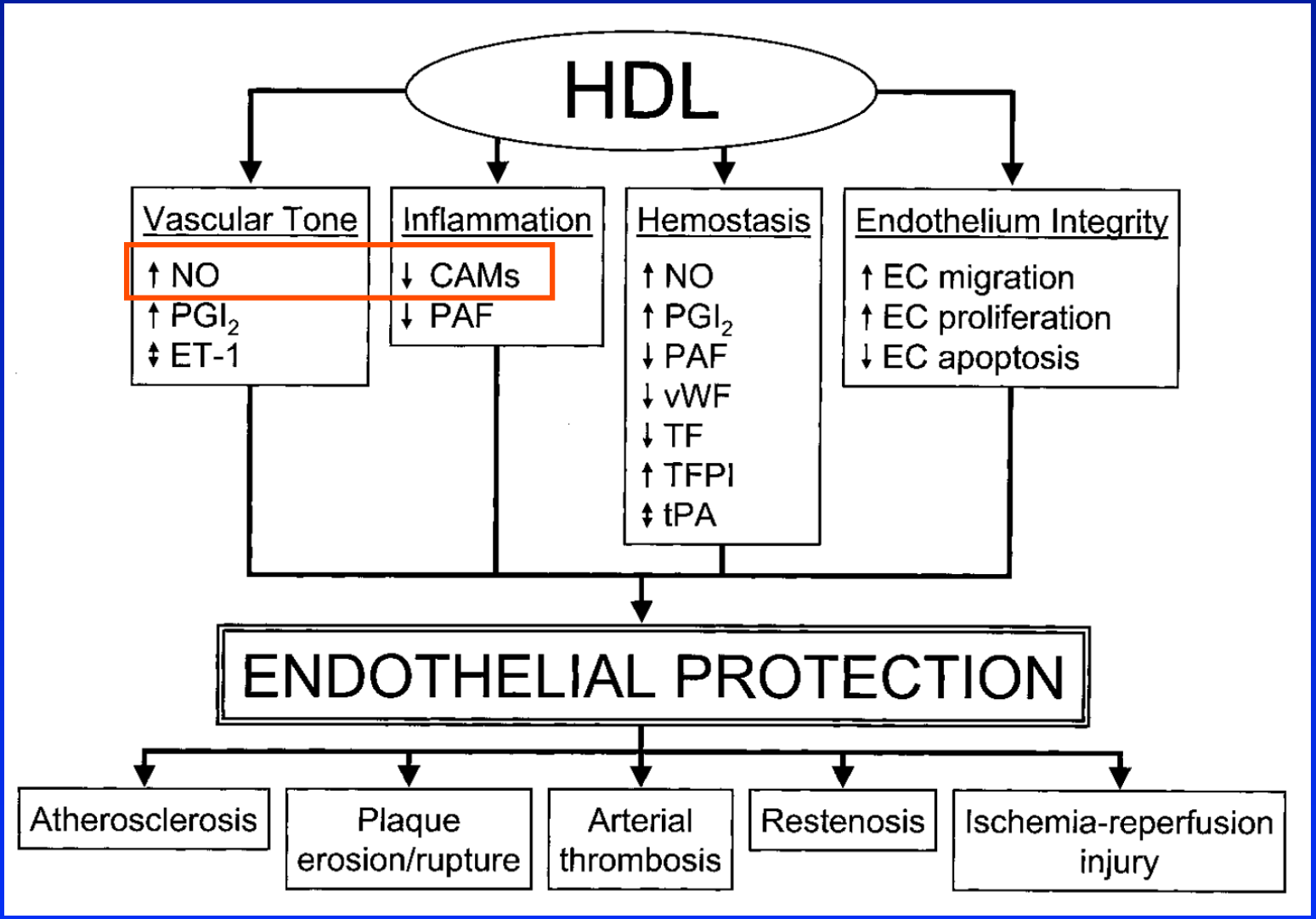


Henry R et al. Lancet 2009;374:126

UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI FARMACIA

Effect of aleglitazar on HDL functionality: ex-vivo study in non-human primates

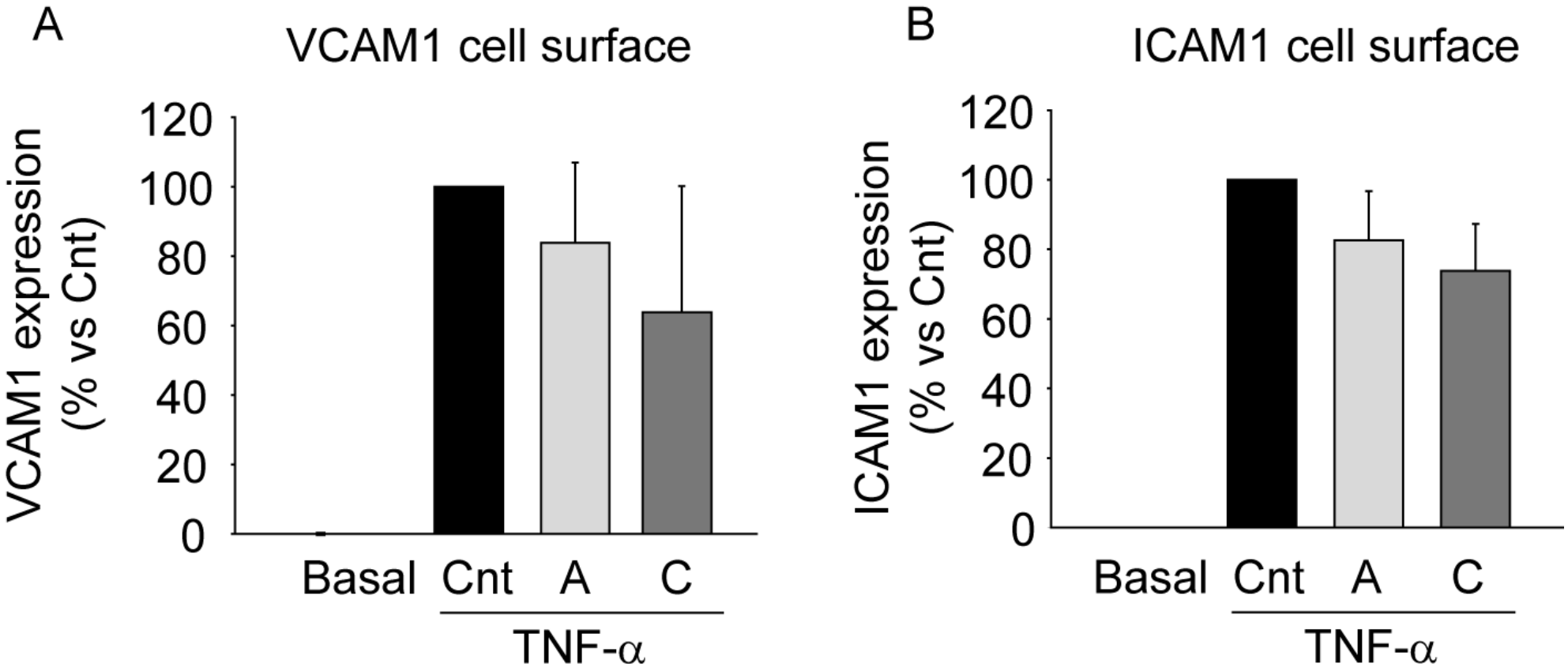
Multiple biological actions of HDL on vascular endothelium



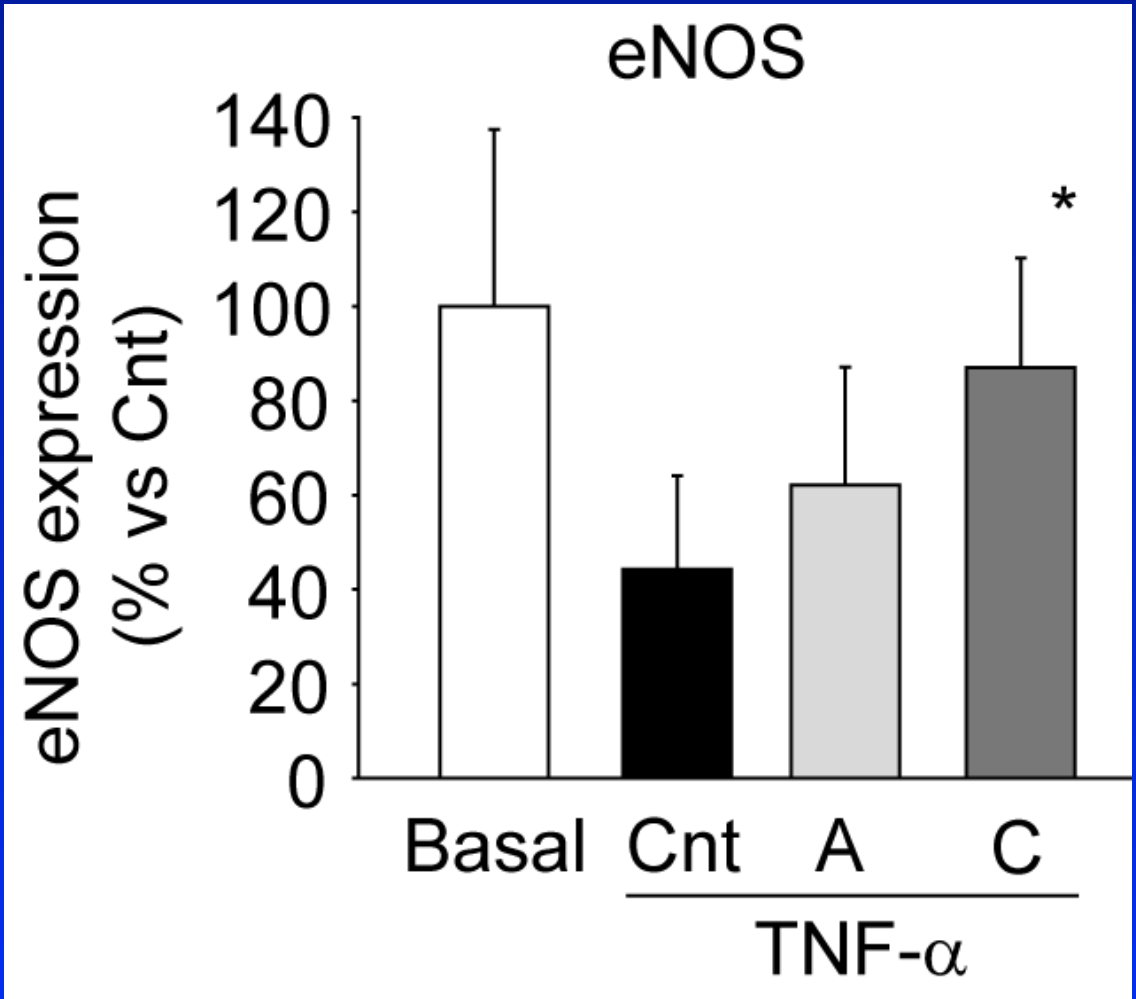
Calabresi L, ATVB. 2003;23(10):1724-31

Effect of HDL on cell surface expression levels of VCAM1 and ICAM1

FACS



Effect of HDL on eNOS expression levels



Lipid composition of HDL from monkeys treated or not with aleglitazar

Component	Human HDL*	Group A	Group C
FC + CE	48.4%	27.0%	34.1%
TG	6.3%	3.1%	1.7%
PL	45.3%	69.9%	64.2%

* Data from Ronald W.C. et *al*. ATVB (2004) 24:490-497

Atherosclerosis 204 (2009) 424–428

Contents lists available at ScienceDirect

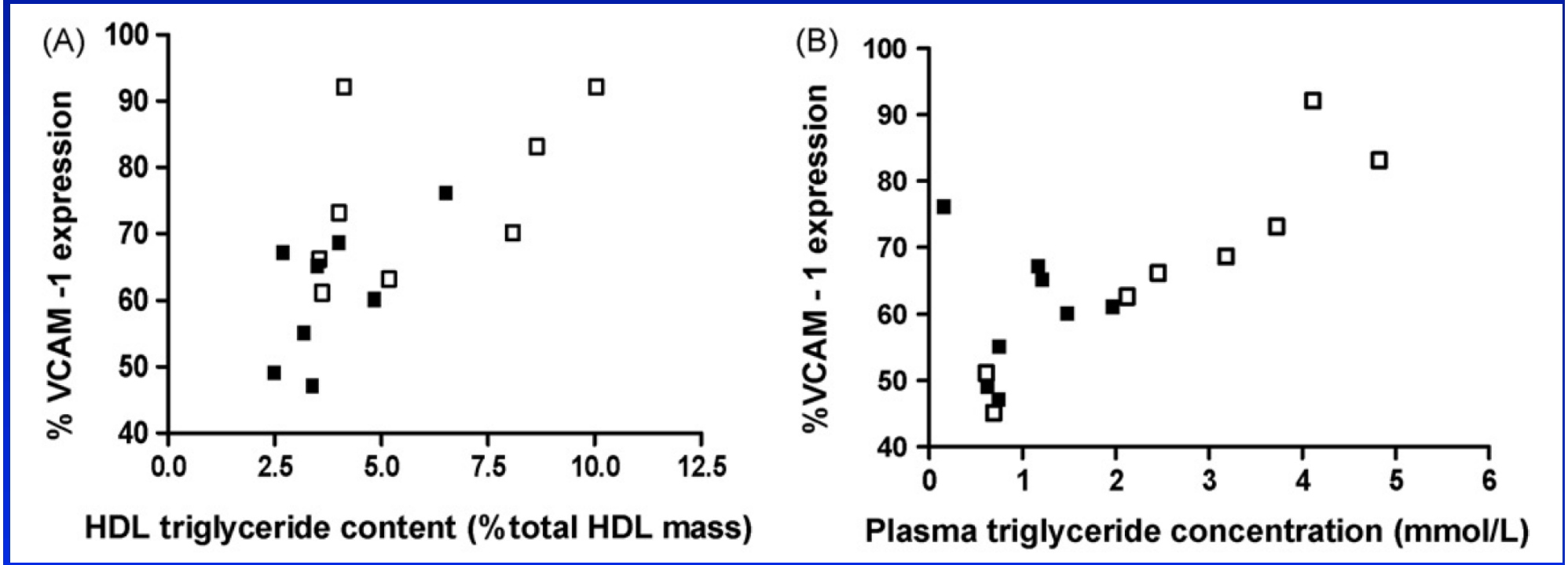
Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Acute hypertriglyceridaemia in humans increases the triglyceride content and decreases the anti-inflammatory capacity of high density lipoproteins

Sanjay Patel[a,b,c,*], Rajesh Puranik[a,b,c], Shirley Nakhla[a], Pia Lundman[d], Roland Stocker[e], Xiao S. Wang[e], Gilles Lambert[a], Kerry-Ann Rye[a,c], Philip J. Barter[a,c], Stephen J. Nicholls[f], David S. Celermajer[a,b,c]

Effects of triglyceride enrichment on the anti-inflammatory properties of HDL



Patel S et al. Atherosclerosis. 2009;204(2):424-8

Conclusions

HDLs isolated after treatment with aleglitazar seem to reduce the extent of VCAM1 and ICAM1 expression in response to 6h stimulation with TNF-α and to preserve the expression of eNOS after 24 h incubation with TNF-α.

Both changes may exert a positive effect on the HDL function and therefore can account for a potential atheroprotective effect of aleglitazar.

Aleglitazar significantly decreases HDL's TG concentrations and only marginally those of phospholipids. Notably, a compositional change in TG has also been evident.

Lipoprotein Management in Patients With Cardiometabolic Risk: Consensus Conference Report From the American Diabetes Association and the American College of Cardiology Foundation

John D. Brunzell, Michael Davidson, Curt D. Furberg, Ronald B. Goldberg, Barbara V. Howard, James H. Stein, and Joseph L. Witztum

J. Am. Coll. Cardiol. 2008;51;1512-1524; originally published online Mar 27, 2008;

JACC

Journal of the American College of Cardiology

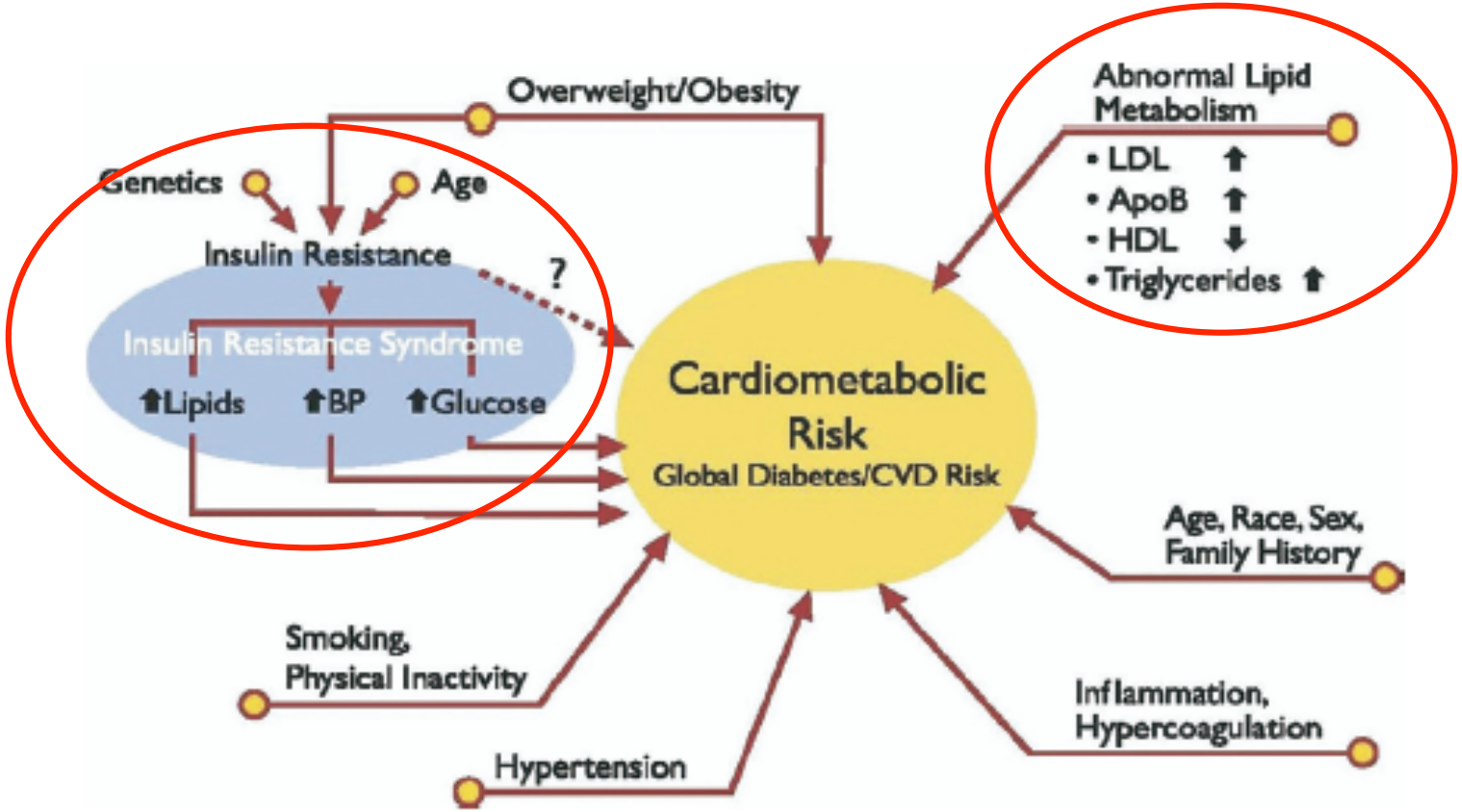


Figure 1. Factors Contributing to Cardiometabolic Risk