Lipid Lowering in Patients at High Risk for Cardiovascular Disease

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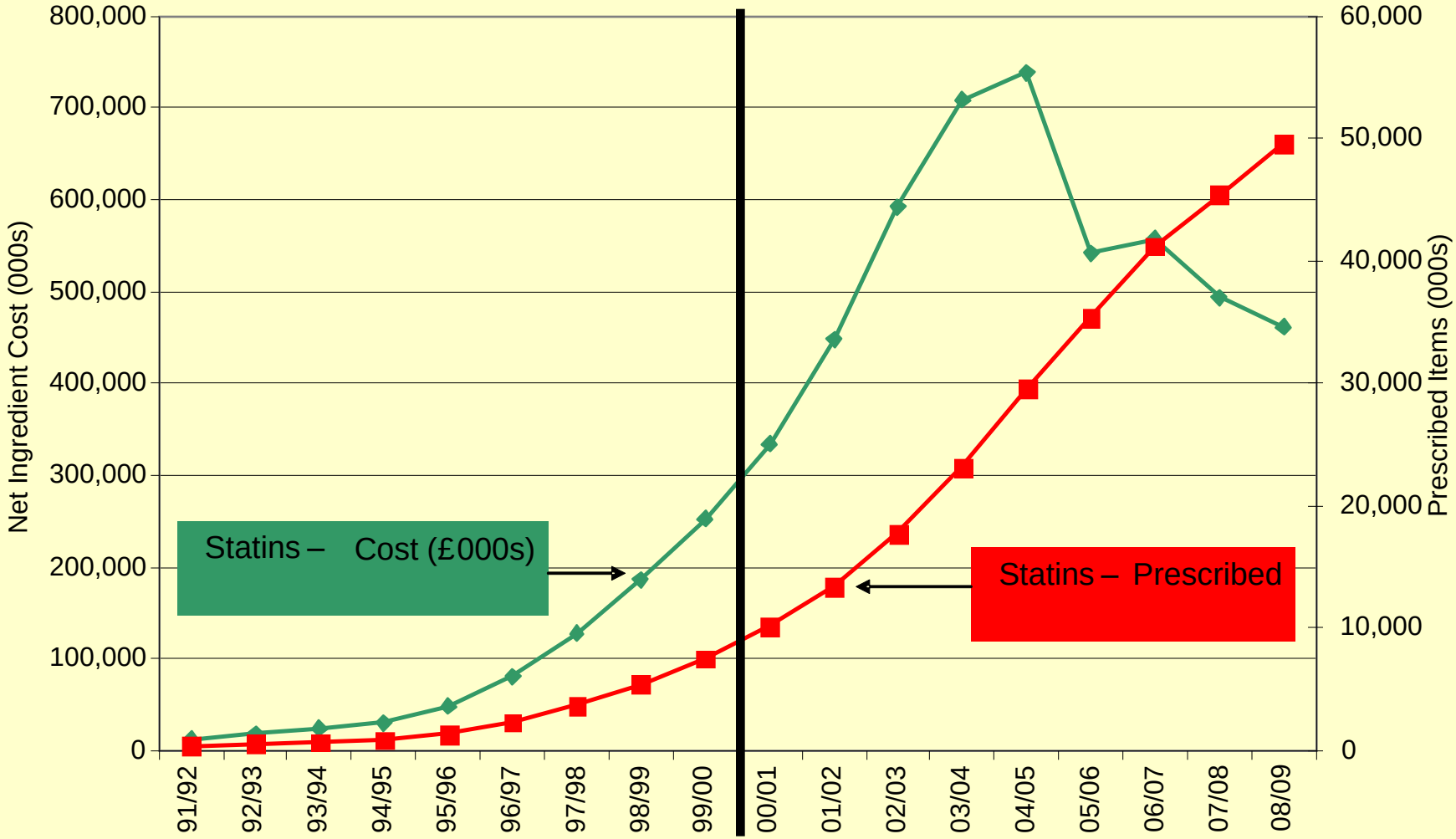
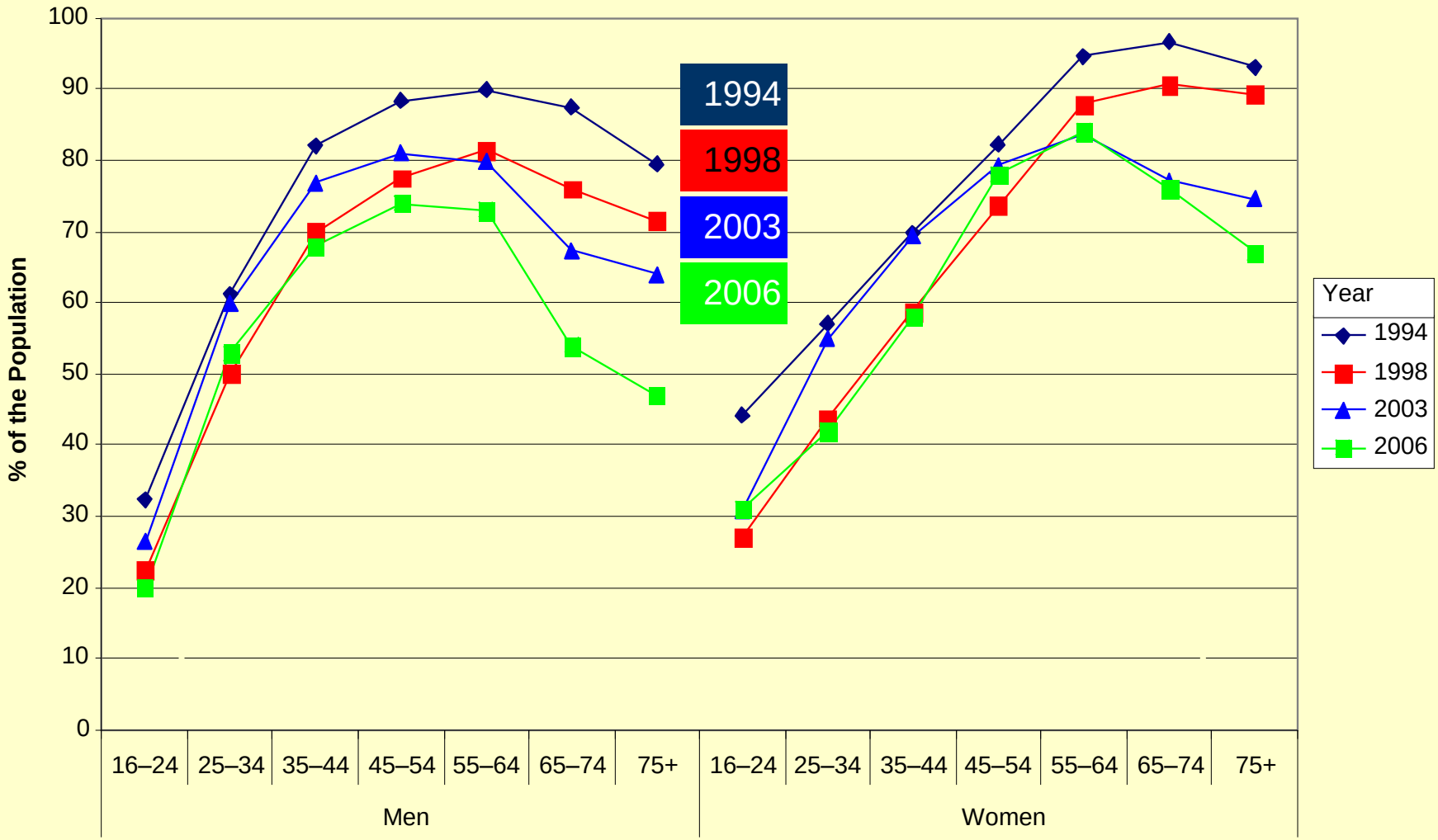
Novel Approaches to Modify Lipids and Lipoproteins

- Low Density Lipoprotein
- High Density Lipoprotein
- Triglyceride Rich Lipoproteins
- Inflammation
- Lipoprotein a

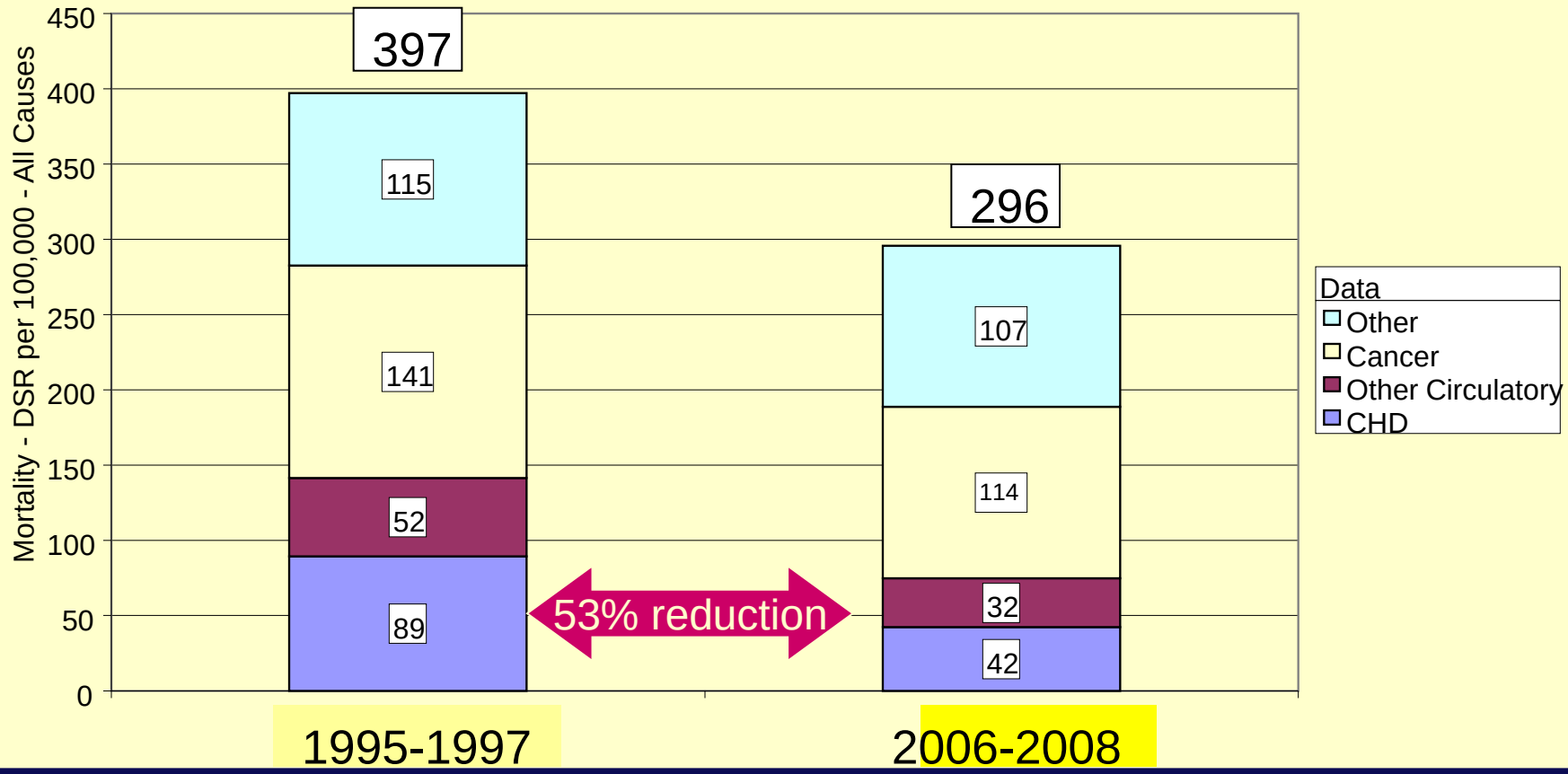
Statin Prescription in the UK



Percentage of the UK-population with TC > 5 mmol/l



All-Cause Mortality in the UK in those < 75 Years



New Approaches to LDL Reduction

What is in development?

- Cholesterol Absorption Inhibitors
- Squalene Synthase (SSI) inhibitors
- Thyroxin Receptor Agonists
- Apo B mRNA antisense drugs
- Microsomal Triglyceride Transfer Protein (MTP) inhibitors
- PCSK9 Inhibitors

New Approaches to LDL Reduction

- Ezetimibe is and will be the only cholesterol absorption inhibitor in clinical use
  - The SEAS tertiles analyses and the SHARP data are supportive for the combination of Eze and statins and aligned with the CTT regression line
  - Ezetimibe is currently the reference drug in several outcome studies for novel compounds such as CETP inhibitors and PCSK9 monoclonals
- Squalene synthase inhibitor development was discontinued because of liver toxicity
- The thyroxine receptor agonist Eprotirome study in FH (Akka) was halted for toxicity in animals

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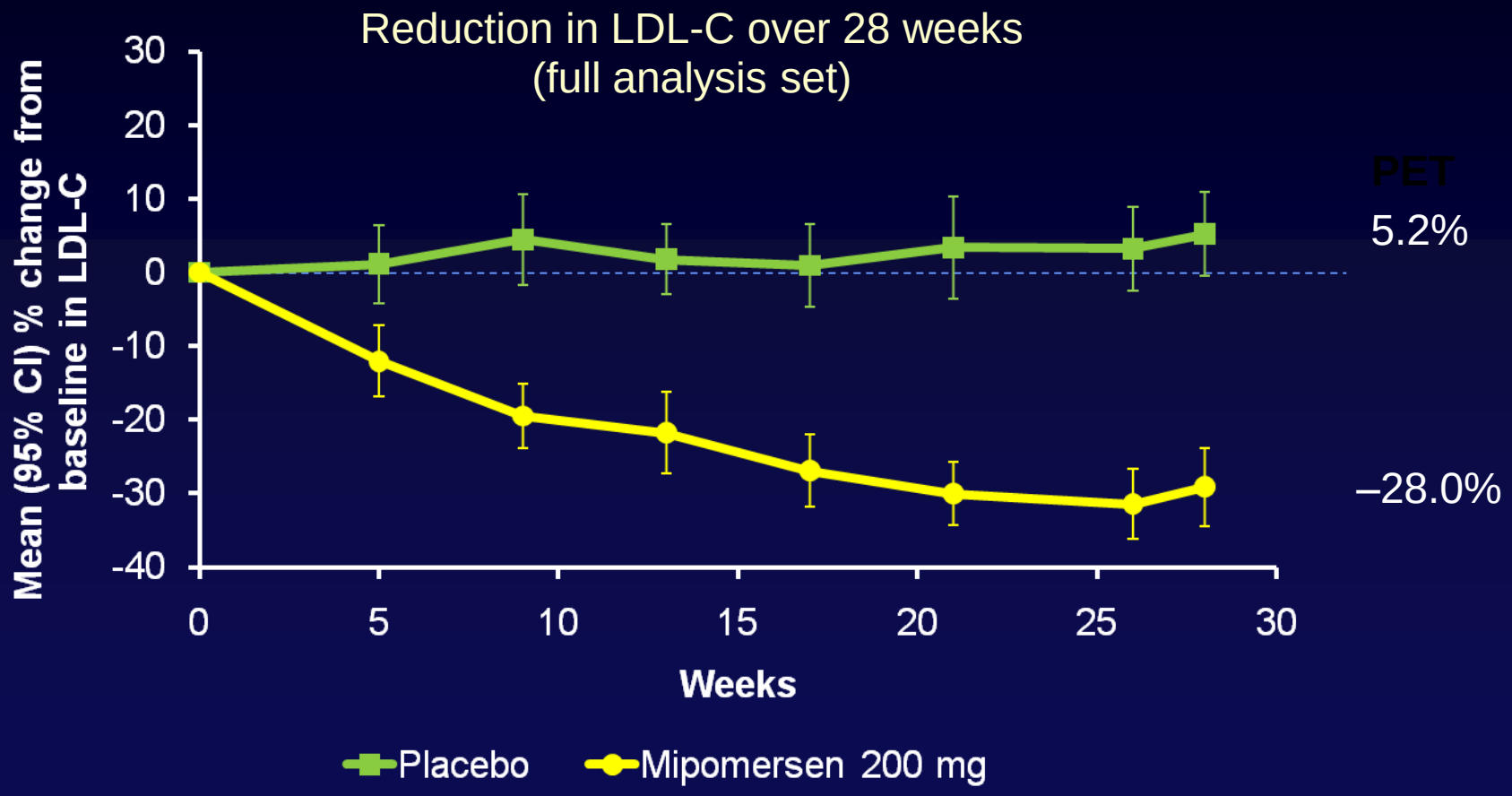
Heterozygous Familial Hypercholesterolemia Study Design

- Patients were randomized 2:1 to receive weekly subcutaneous injections of mipomersen 200 mg or placebo for 26 weeks

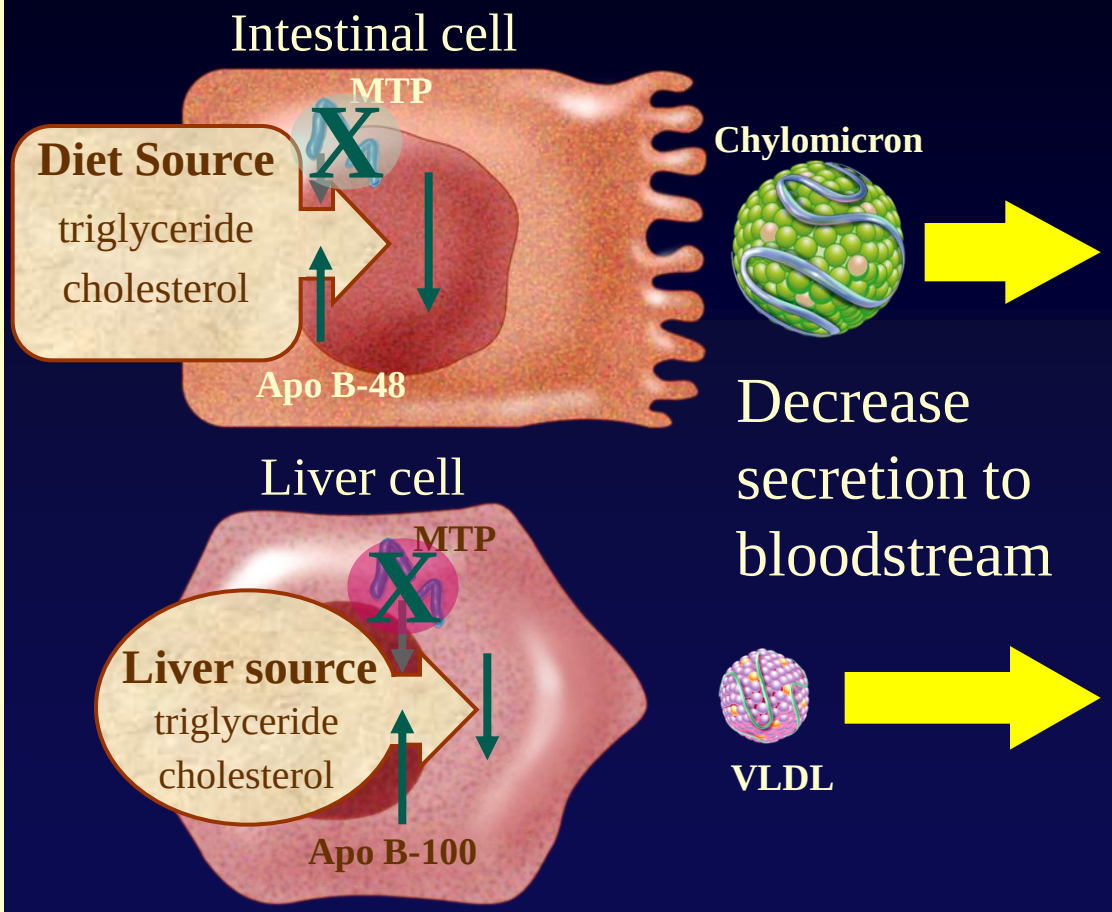
Cromwell W, et all, [poster]. American Heart Association Scientific Sessions; Nov 14-18; Orlando, FL; 2009

Mipomersen Significantly Reduced LDL-C



MTPIs – Efficacy comes from its dual mechanism of action

MTP inhibition will limit secretion of cholesterol and triglycerides from the intestine and liver



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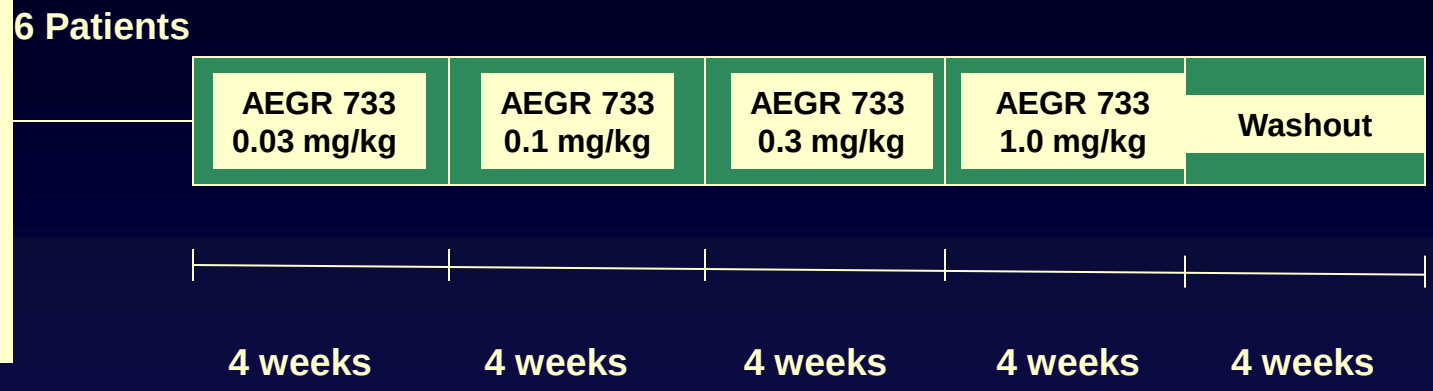
AEGR 733
HoFH Phase II Study Design

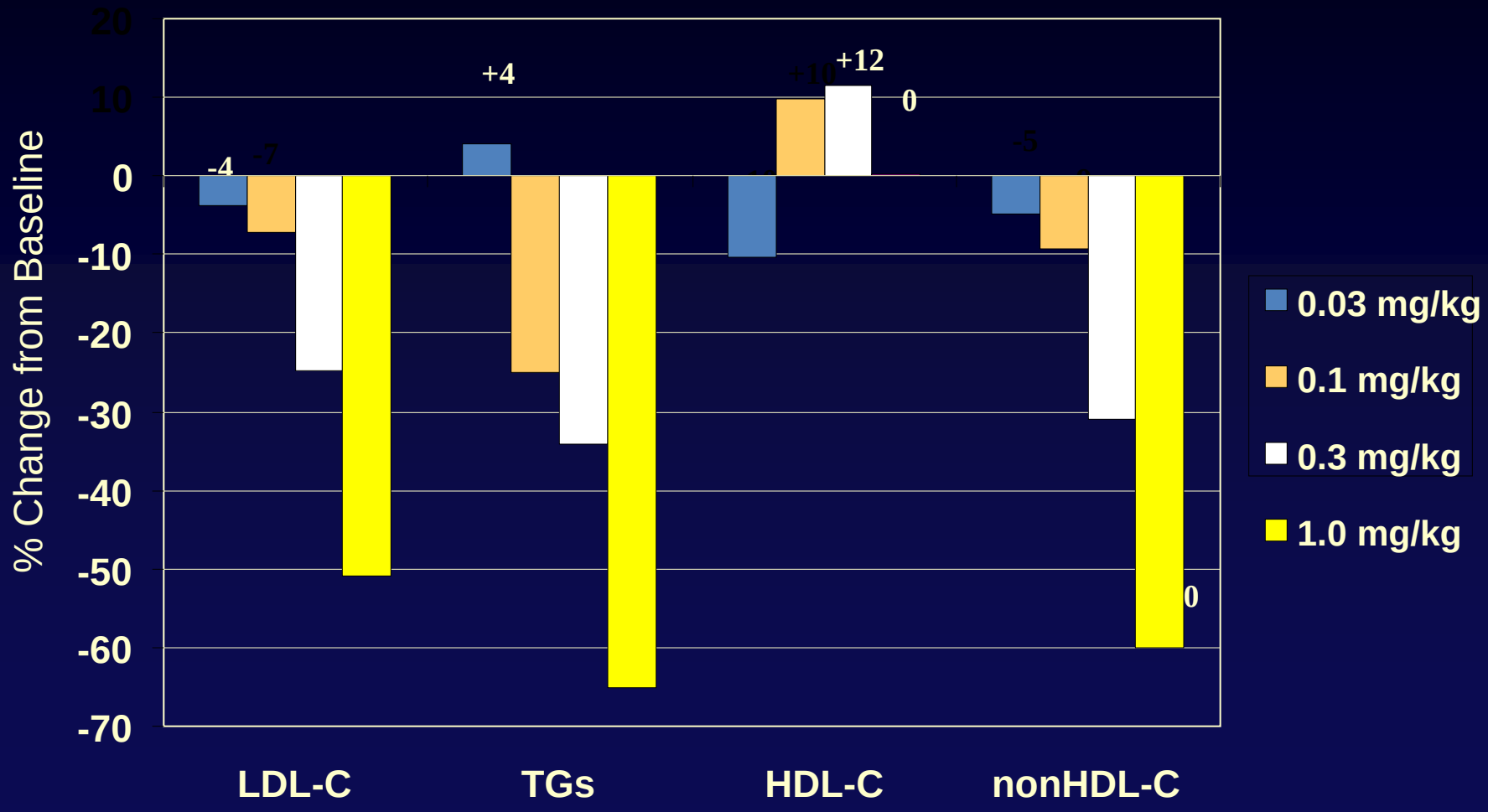
Patients:
- **Men/women aged 18-40**
- **HoFH confirmed by genetic analysis**
- **Mean Baseline LDL = 614 mg/dl**



- Open label, ascending dose trial
- Very low fat diet
- Visits: Screen, baseline, every 1, 2, and 4 weeks after each new dose, end of washout period

Cuchel, M. et al. NEJM 2007; 356:148-56.

Change in Lipids Using Lomitapide with no Background Therapy



Cuchel, M. et al. NEJM 2007; 356:148-56.

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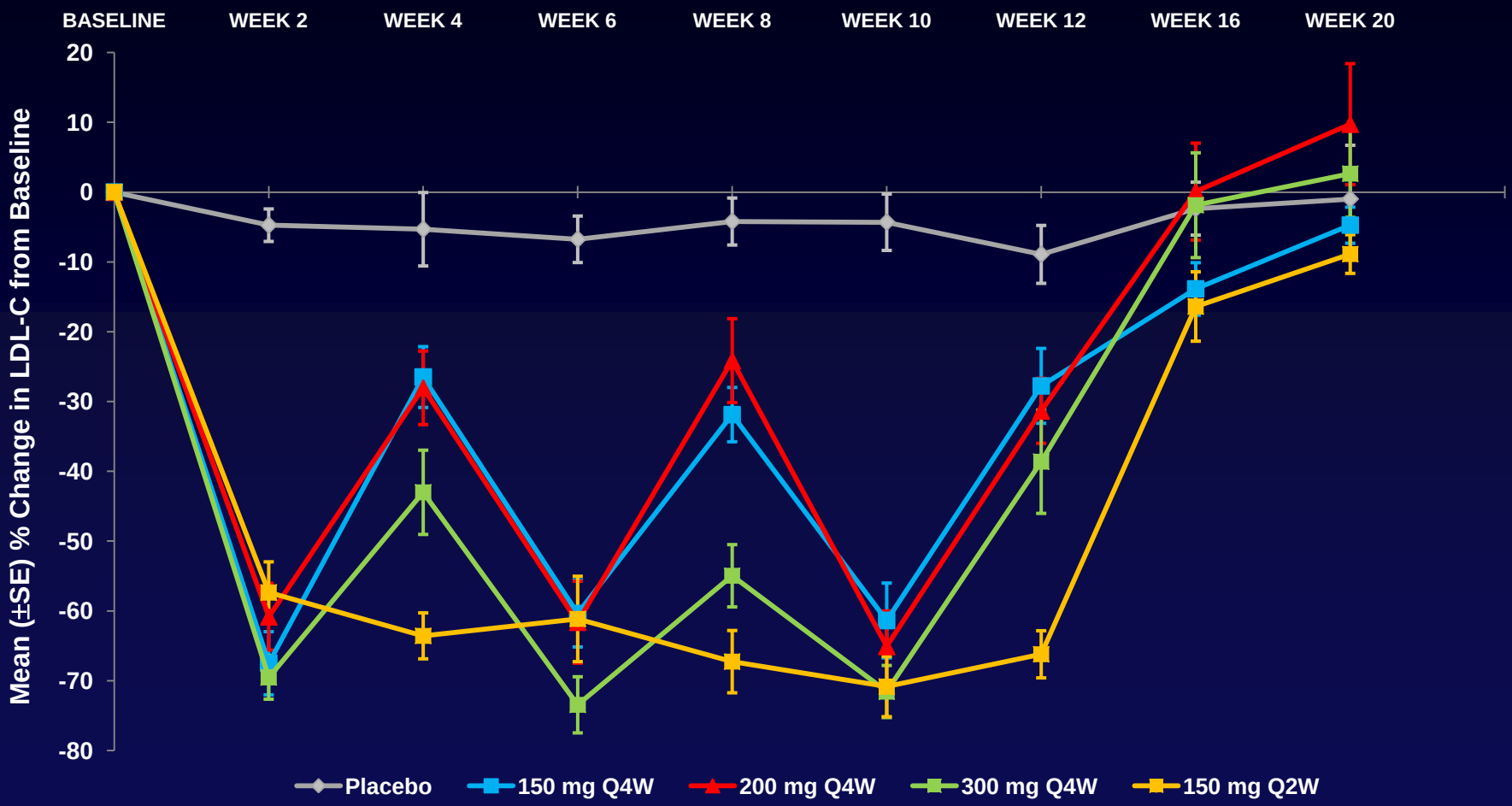
Change in Calculated LDL-C at 2 Weekly Intervals From Baseline to Week 20 REGN727



Stein EA et al. Lancet on-line May 26, 2012

Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, 12 , 16 and 20 in the modified intent-to-treat (mITT) population, by treatment group.

Novel Approaches to Modify Lipids and Lipoproteins

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- Triglyceride Rich Lipoproteins
- Inflammation
- Lipoprotein a

New Approaches for Raising HDL

What is in development?

- Cholesterol Ester Transfer Protein (CETP) inhibitors
- ER-Niacin / Laropiprant combination
- ApoA1 based strategies
- LCAT replacement strategies
- ABCA1 agonists / miR-33 inhibition

*The **Dal**-HEART Program*

***dal**cetrapib **H**DL **E**valuation, **A**therosclerosis & **R**everse cholesterol **T**ransport*

The **dal**-HEART Program tests a novel hypothesis: enhancing HDL efficacy through CETP modulation treats the underlying disease of atherosclerosis and will attenuate CV risk

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

RECRUITMENT COMPLETE

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 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

Anacetrapib

- Anacetrapib is a top priority in the cardiovascular area.
- Robust clinical development including REVEAL and other trials
- Serious investment into pre-clinical and basic science such as the CETP reaction, HDL function as well as reverse cholesterol transport.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety of Anacetrapib in Patients with or at High Risk for Coronary Heart Disease

Christopher P. Cannon, M.D., Sukrut Shah, Ph.D., R.Ph., Hayes M. Dansky, M.D., Michael Davidson, M.D., Eliot A. Brinton, M.D., Antonio M. Gotto, Jr., M.D., D.Phil., Michael Stepanavage, M.S., Sherry Xueyu Liu, M.S., Patrice Gibbons, M.S., Tanya B. Ashraf, B.A., Jennifer Zafarino, M.S., Yale Mitchel, M.D., and Philip Barter, M.D., Ph.D., for the DEFINE Investigators*

ABSTRACT

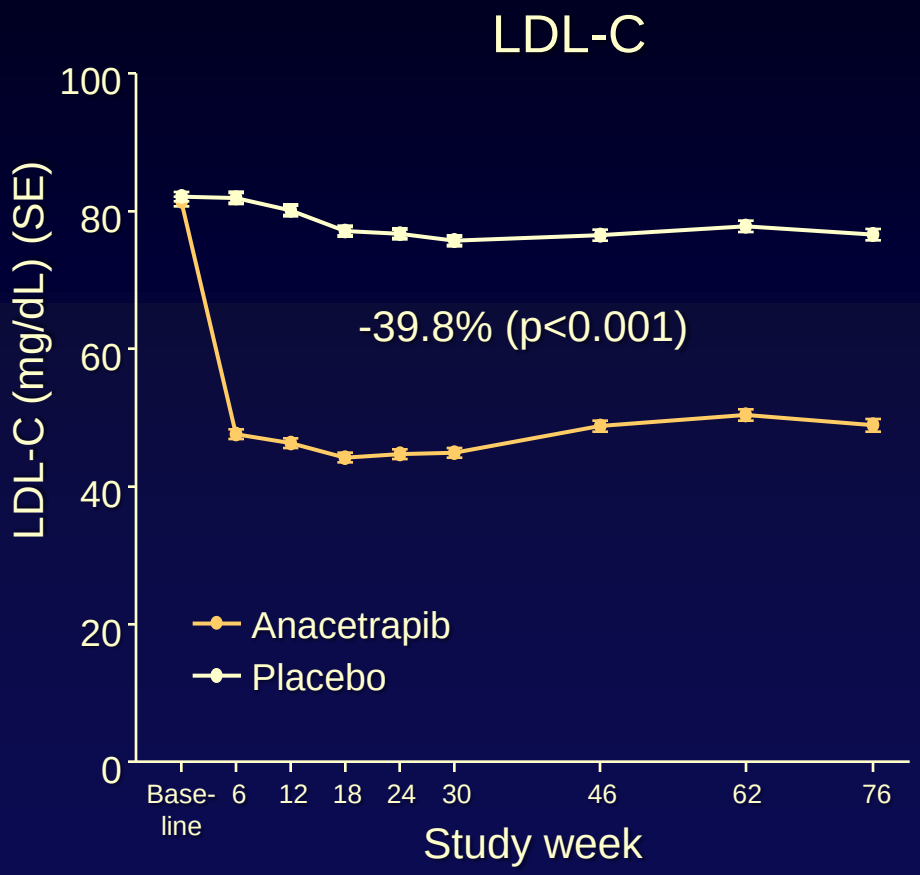
BACKGROUND

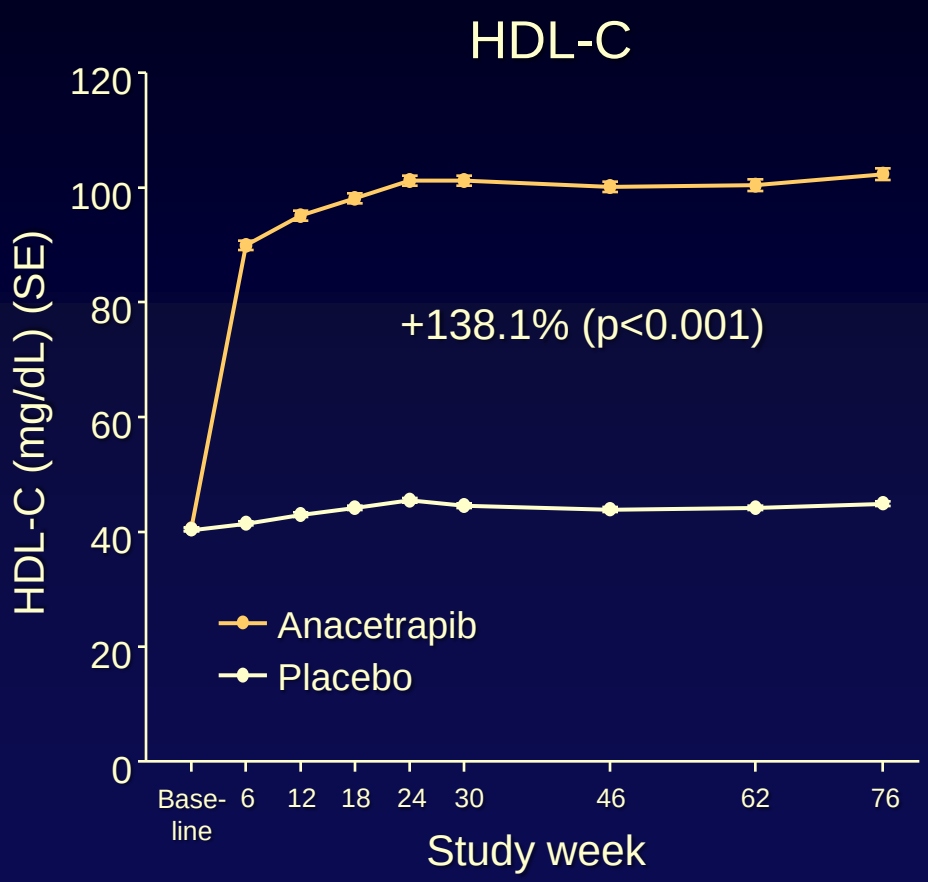
Anacetrapib is a cholesteryl ester transfer protein inhibitor that raises high-density lipoprotein (HDL) cholesterol and reduces low-density lipoprotein (LDL) cholesterol.

CONCLUSIONS

Treatment with anacetrapib had robust effects on LDL and HDL cholesterol, had an acceptable side-effect profile, and, within the limits of the power of this study, did not result in the adverse cardiovascular effects observed with torcetrapib. (Funded by Merck Research Laboratories; ClinicalTrials.gov number, NCT00685776.)

Effects on LDL-C and HDL-C





Future

- 30,000 patients with occlusive arterial disease in North America, Europe and Asia
- Background LDL-lowering with atorvastatin
- Randomized to anacetrapib 100 mg vs. placebo
- Primary outcome: Coronary death, myocardial infarction or coronary revascularization

www.revealtrial.org.

ORIGINAL CONTRIBUTION

Scan for Author Video Interview

Effects of the CETP Inhibitor Evacetrapib Administered as Monotherapy or in Combination With Statins on HDL and LDL Cholesterol

A Randomized Controlled Trial

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H. Bryan Brewer, MD, PhD
John J. P. Kastelein, MD, PhD
Kathryn A. Krueger, MD
Ming-Dauh Wang, PhD
Mingyuan Shao, MS
Bo Hu, PhD
Ellen McErlean, MSN
Steven E. Nissen, MD

Context Interest remains high in cholesteryl ester transfer protein (CETP) inhibitors as cardioprotective agents. Few studies have documented the efficacy and safety of CETP inhibitors in combination with commonly used statins.

Objective To examine the biochemical effects, safety, and tolerability of evacetrapib, as monotherapy and in combination with statins, in patients with dyslipidemia.

Design, Setting, and Participants Randomized controlled trial conducted among 398 patients with elevated low-density lipoprotein cholesterol (LDL-C) or low high-density lipoprotein cholesterol (HDL-C) levels from April 2010 to January 2011 at community and academic centers in the United States and Europe.

Interventions Following dietary lead-in, patients were randomly assigned to receive placebo (n=38); evacetrapib monotherapy, 30 mg/d (n=40), 100 mg/d (n=39), or 500 mg/d (n=42); or statin therapy (n=239) (simvastatin, 40 mg/d; atorvastatin, 20 mg/d; or rosuvastatin, 10 mg/d) with or without evacetrapib, 100 mg/d, for 12 weeks.

Main Outcome Measures The co–primary end points were percentage changes from baseline in HDL-C and LDL-C after 12 weeks of treatment.

Results The mean baseline HDL-C level was 55.1 (SD, 15.3) mg/dL and the mean baseline LDL-C level was 144.3 (SD, 26.6) mg/dL. As monotherapy, evacetrapib produced dose-dependent increases in HDL-C of 30.0 to 66.0 mg/dL (53.6% to 128.8%) compared with a decrease with placebo of –0.7 mg/dL (–3.0%; $P<.001$ for all compared with placebo) and decreases in LDL-C of –20.5 to –51.4 mg/dL (–13.6% to –35.9%) compared with an increase with placebo of 7.2 mg/dL (3.9%; $P<.001$ for all compared with placebo). In combination with statin therapy, evacetrapib, 100 mg/d, produced increases in HDL-C of 42.1 to 50.5 mg/dL (78.5% to 88.5%; $P<.001$ for all compared with statin monotherapy) and decreases in LDL-C of –67.1 to –75.8 mg/dL (–11.2% to –13.9%; $P<.001$ for all compared with statin monotherapy). Compared with evacetrapib monotherapy, the combination of statins and evacetrapib resulted in greater reductions in LDL-C ($P<.001$) but no greater increase in HDL-C ($P=.39$). Although the study was underpowered, no adverse effects were observed.

Conclusions Compared with placebo or statin monotherapy, evacetrapib as monotherapy or in combination with statins increased HDL-C levels and decreased LDL-C levels. The effects on cardiovascular outcomes require further investigation.

Trial Registration clinicaltrials.gov Identifier: NCT01105975

JAMA. 2011;306(19):2099-2109 www.jama.com

THE DEVELOPMENT OF STATINS for reducing low-density lipoprotein cholesterol (LDL-C) has revolutionized cardiovascular disease prevention.[1-6] Nonetheless, cardiovascular disease remains the number one cause of death.[7] Accordingly, considerable efforts have focused on development of novel therapeutic agents designed to address residual cardiovascular risk. Because individuals from the general population with elevations of high-density lipoprotein cholesterol (HDL-C) have a reduced incidence of coronary heart disease,[8] it has been assumed that finding an appropriate therapy to increase HDL-C levels would yield substantial clinical benefit.

However, development of drugs that increase HDL-C levels has been challenging and fraught with failures, including the premature termination of

For editorial comment see p 2153.

Author Video Interview available at www.jama.com.

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Corresponding Author: Stephen J. Nicholls, MBBS, PhD, Department of Cardiovascular Medicine, Mail Code JJ-65, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195 (nichols1@ccf.org).

New Approaches for LDL Reduction and HDL Raising

- The real battle in the future will be between PCSK9 Mab's and CETP inhibitors

* oral versus sc
* every day versus bi-weekly or once monthly
* atherogenic lipoproteins with or without HDL increase
* time to efficacy
* cost

New Approaches for Raising HDL

What is in development?

- Cholesterol Ester Transfer Protein (CETP) inhibitors
- ER-Niacin / Laropiprant combination
- ApoA1 based strategies
- LCAT replacement strategies
- ABCA1 agonists / miR-33 inhibition

ApoA1 Based Therapies

- ApoA1 Mimetics, such as APL-180 Novartis
- Full-length ApoA1, such as ApoA1 Cerenis Therapeutics
- Pre-Beta HDL, as generated by delipidation, HDL Therapeutics Inc.
- Reconstituted HDL, CSL Ltd.
- ApoA1 Milano, The Medicines Company
- Trimeric ApoA1, Borean Pharma and now Roche
- RVX-208, as developed by Resverlogix

Delipidation

IVUS clinical trial using selective delipidated HDL

Step 1

Collected~1 litre of plasma

Step 2

Plasma enriched through process

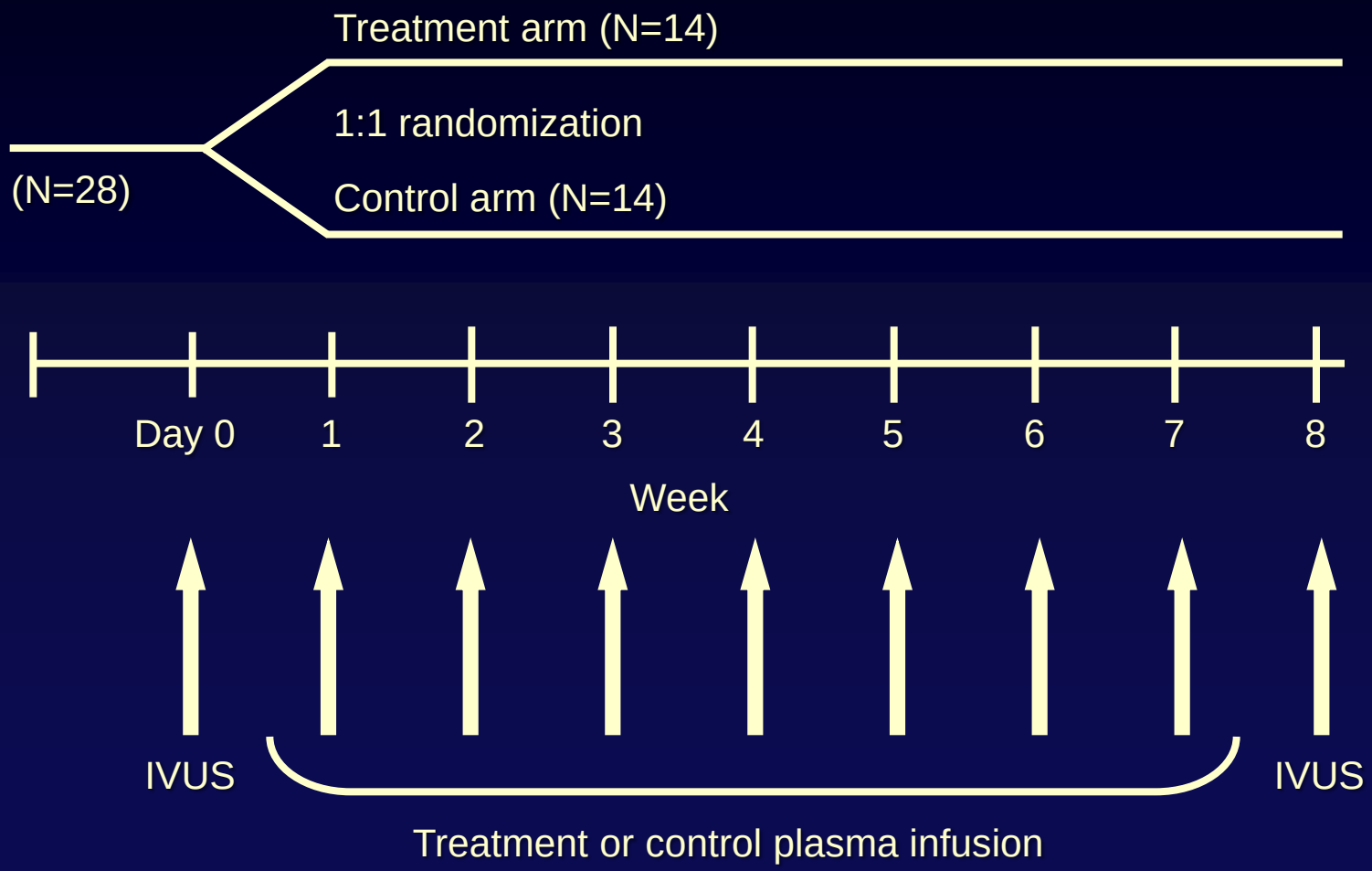
Step 3

Re-infused preβ enriched plasma

- Used patients own HDL
- Cholesterol removed from αHDL to yield preβ-HDL
- Preβ enriched plasma is re-infused into patient

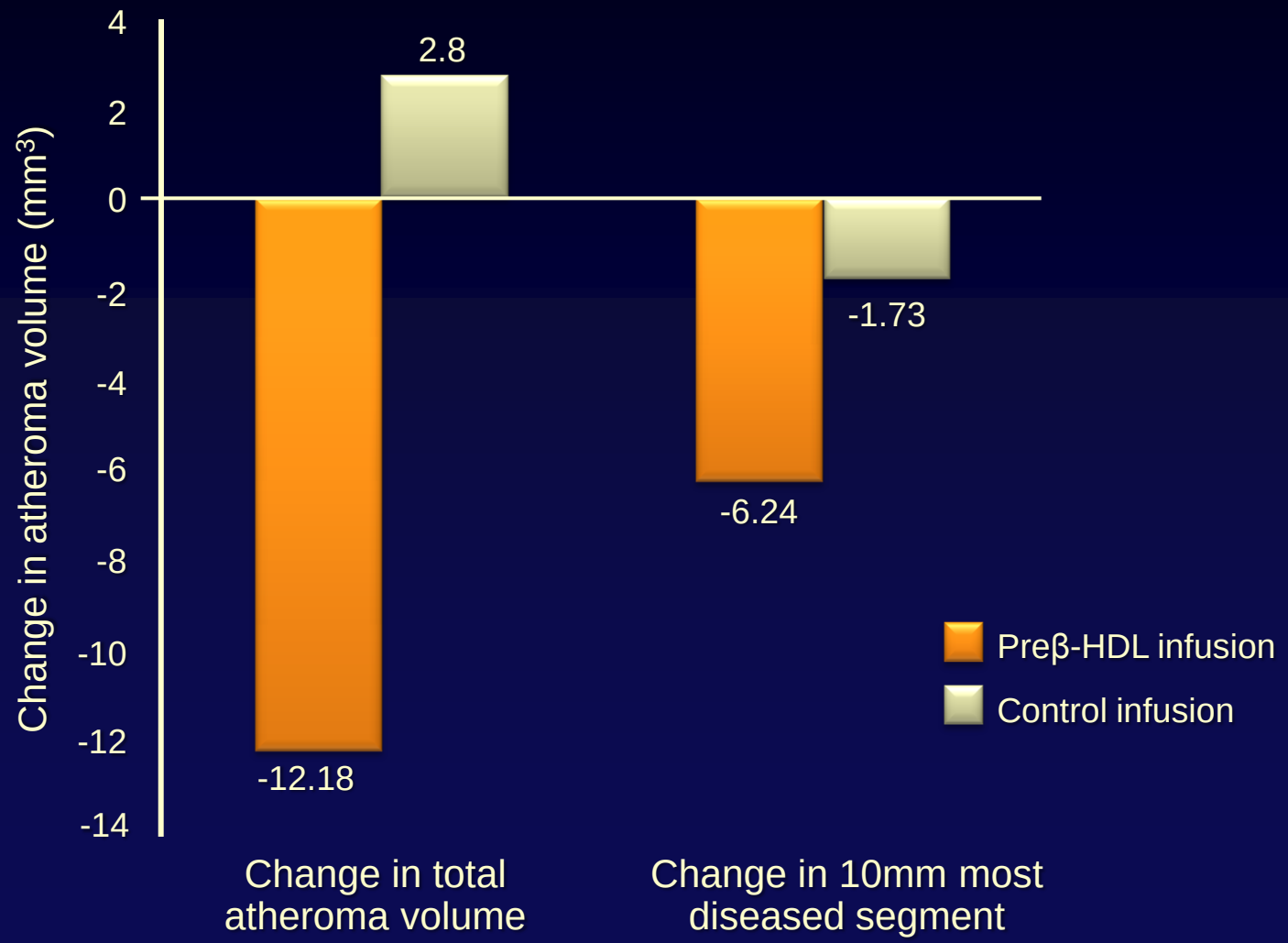
Walksman R, *et al. J Am Coll Cardiol* 2010; 55 : 2727-35.

IVUS Clinical Trial Using Selective Delipidated HDL



Walksman R, *et al. J Am Coll Cardiol* 2010; 55 : 2727-35.

Results of the IVUS Clinical Trial Using Selective Delipidated HDL



Waksman R, *et al. J Am Coll Cardiol* 2010; 55 : 2727-35.

New Approaches for Reduction of TG rich Lipoproteins

What is in development?

- Microsomal Triglyceride Transfer Protein (MTP) inhibitors
- DiacylGlycerol AcylTransferase (DGAT) inhibitors
- Marine Omega 3 Fatty Acids
- ApoCIII mRNA antisense drugs
- Lipoprotein lipase gene therapy

Conclusion

In the next five years, we will prove or disprove that additional LDL lowering with other agents than statins is effective

and

we will show or not show that the HDL hypothesis is true.