



Brigham and Women's Hospital

Founding Member, Mass General Brigham

Horizons in Cardiovascular Prevention

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Director, Center for Cardiovascular Disease Prevention

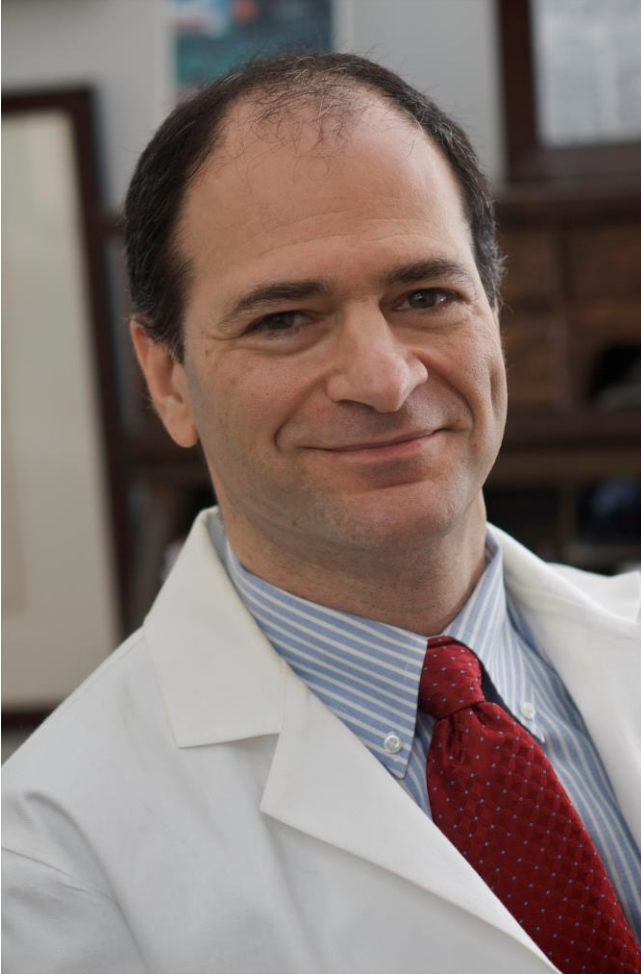
Brigham and Women's Hospital

Eugene Braunwald Professor of Medicine

Harvard Medical School



Paul Ridker, MD, MPH



Harvard Medical School, MD
Harvard School of Public Health, MPH

Residency and CV Fellowship, BWH

Director, Center for Cardiovascular Disease
Prevention, BWH

Eugene Braunwald Professor of Medicine
Harvard Medical School



Conflicts of Interest:

Dr. Ridker has received research grant support from Novartis, Kowa, Amarin, Pfizer, Esperion, and the NHLBI;

has served as a consultant to Novartis, Flame, Agepha, AstraZeneca, Janssen, Civi Biopharm, Glaxo Smith Kline, SOCAR, Novo Nordisk, Upton, Omeicos, Health Outlook, Montai Health, New Amsterdam, Boehringer-Ingelheim, Angiowave, RTI; Horizon Therapeutics, and Cardio Therapeutics;

and receives compensation for service on the Peter Munk Advisory Board (University of Toronto), the Leducq Foundation (Paris, FR), and the Baim Institute (Boston, MA).

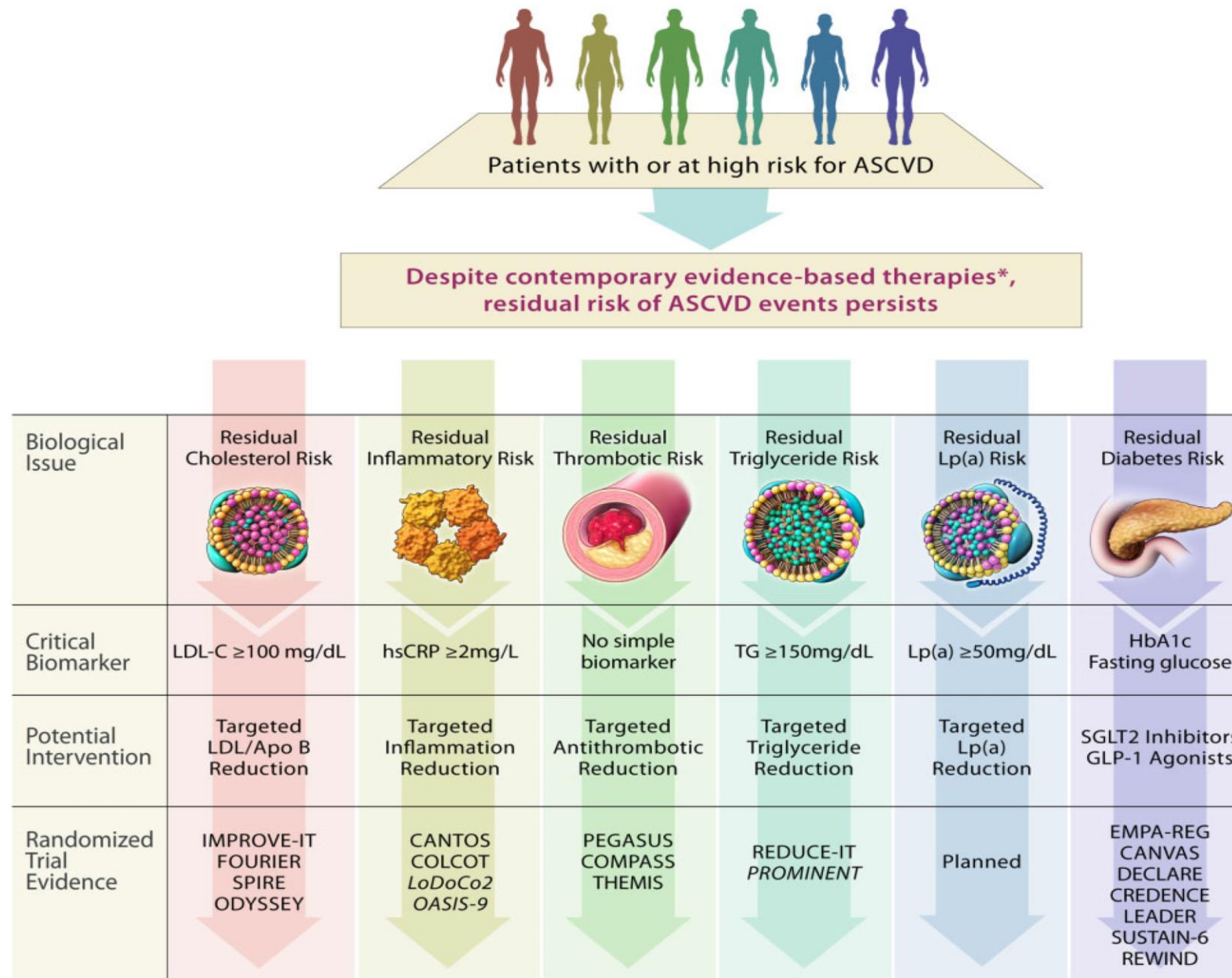


Key Learning Objectives: Horizons in Cardiovascular Prevention

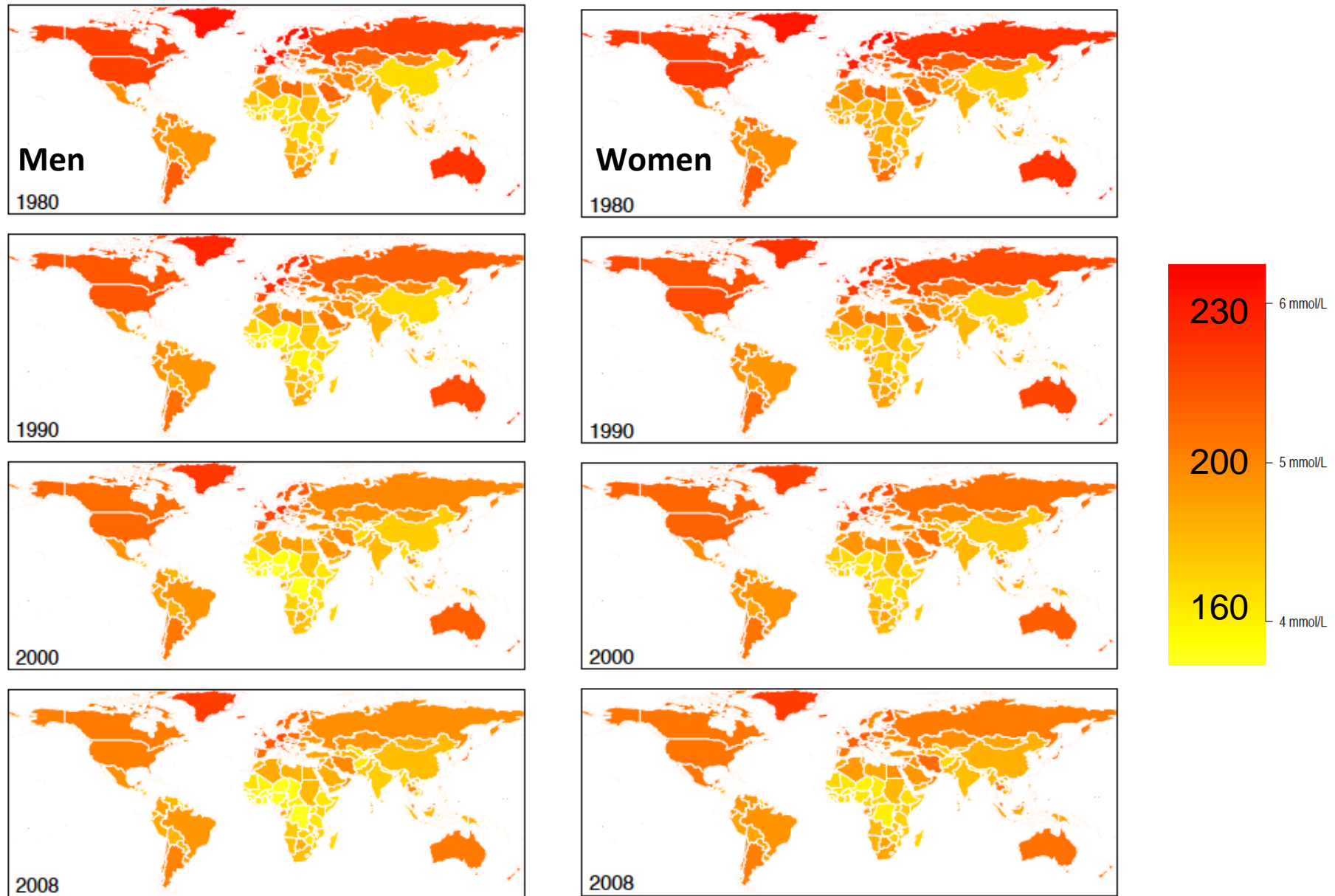
What is new in cardiovascular disease prevention?

How can I apply new data to my daily practice?

Residual Risk Pathways in the Contemporary Care of Atherosclerosis



Global Trends in Total Cholesterol 1980 - 2010



The NEW ENGLAND JOURNAL *of* MEDICINE

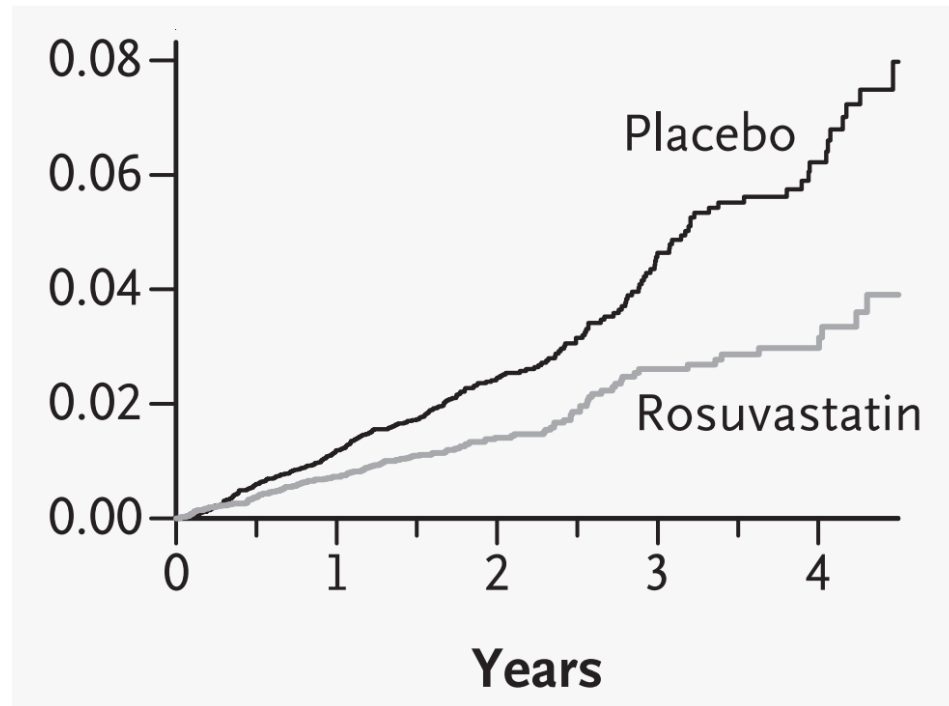
ESTABLISHED IN 1812

NOVEMBER 20, 2008

VOL. 359 NO. 21

High-intensity statin therapy
in primary prevention with
already low levels of LDLC

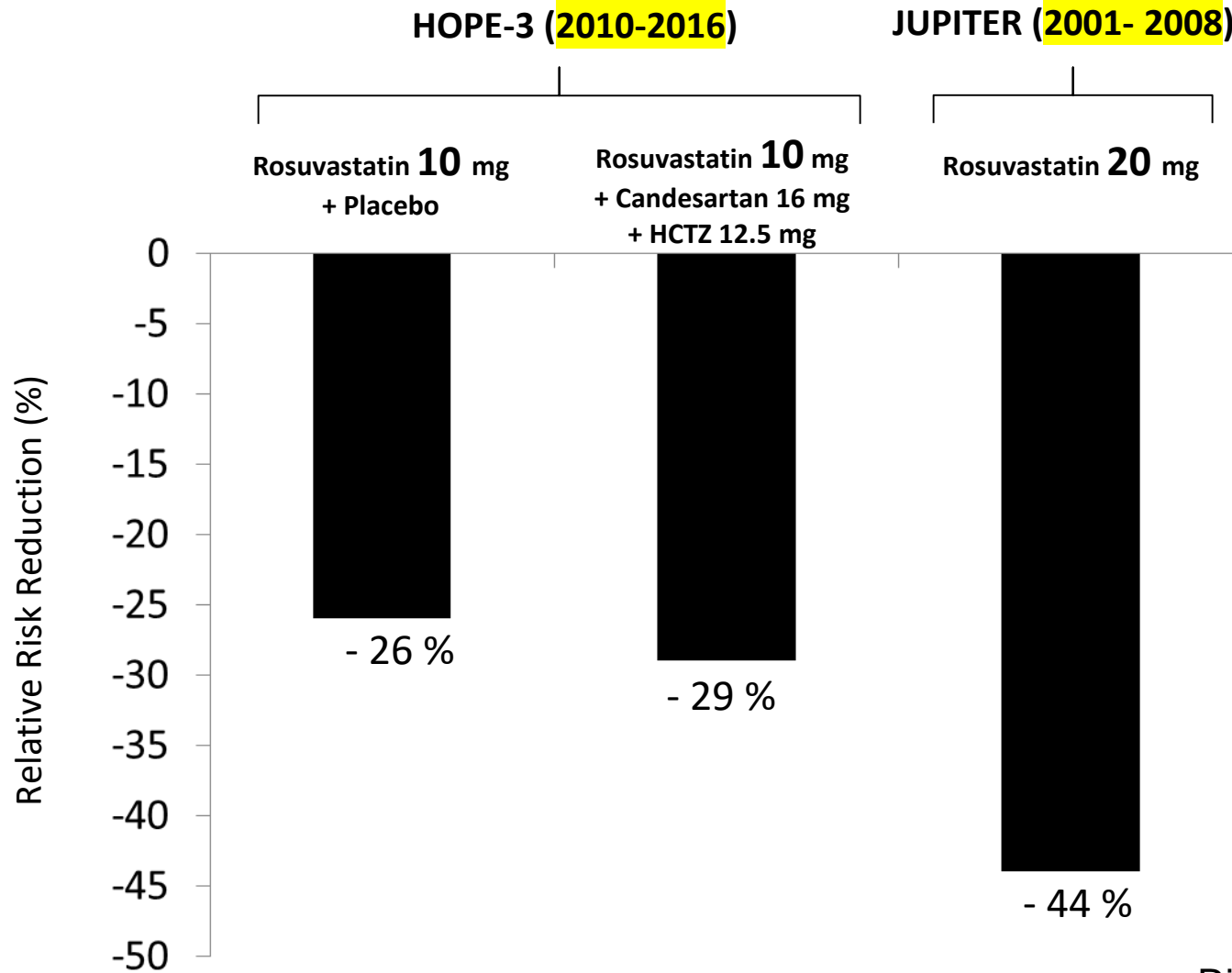
Rosuvastatin to Prevent Vascular Events in Men and Women
with Elevated C-Reactive Protein



JUPITER Trial Results

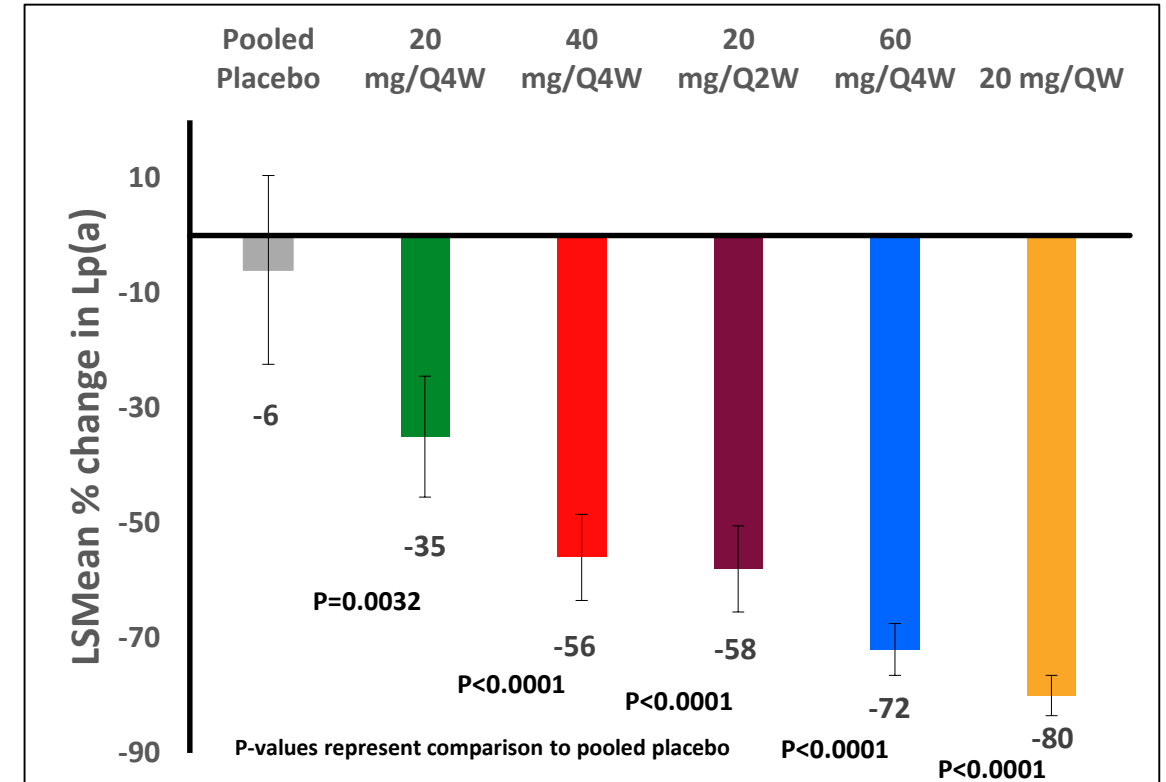
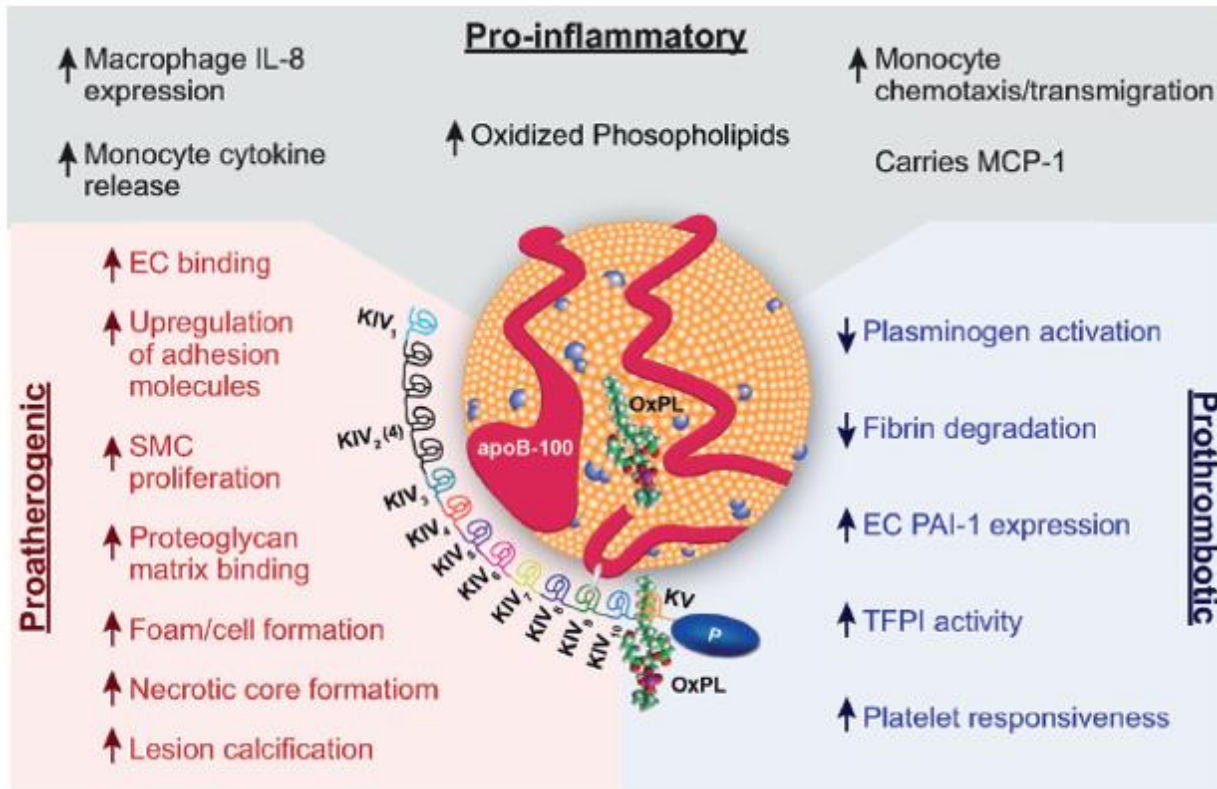
Endpoint	Relative Risk Reduction (%)	HR (95% CI)	P
Primary Endpoint	44	0.56 (0.46-0.69)	<0.00001
MI	63	0.37 (0.22-0.58)	<0.00001
Stroke	48	0.52 (0.34-0.79)	0.002
Revascularization	46	0.54 (0.41-0.72)	<0.0001
Death	20	0.80 (0.67-0.97)	0.02

Is Statin Monotherapy the Perfect Polypill?



Are we going backwards?

Lp(a), atherosclerosis, aortic stenosis, and dose-dependent effects of antisense oligonucleotides targeting Lp(a)



Tsimikas et al N Engl J Med. 2020;382:244-255

Novel Triglyceride Lowering Therapies In Development

Pemafibrate (Kowa)

selective peroxisome proliferator-activated receptor alpha modulator

Evinacumab (Regeneron)

human monoclonal antibody to ANGPTL3

Vupanorsen (Ionis/Pfizer)

antisense oligonucleotide targeting ANGPTL3

ARO-ANG3 (Arrowhead)

siRNA to ANGPTL3

AKCEA-APOCIII-Lrx (Akcea)

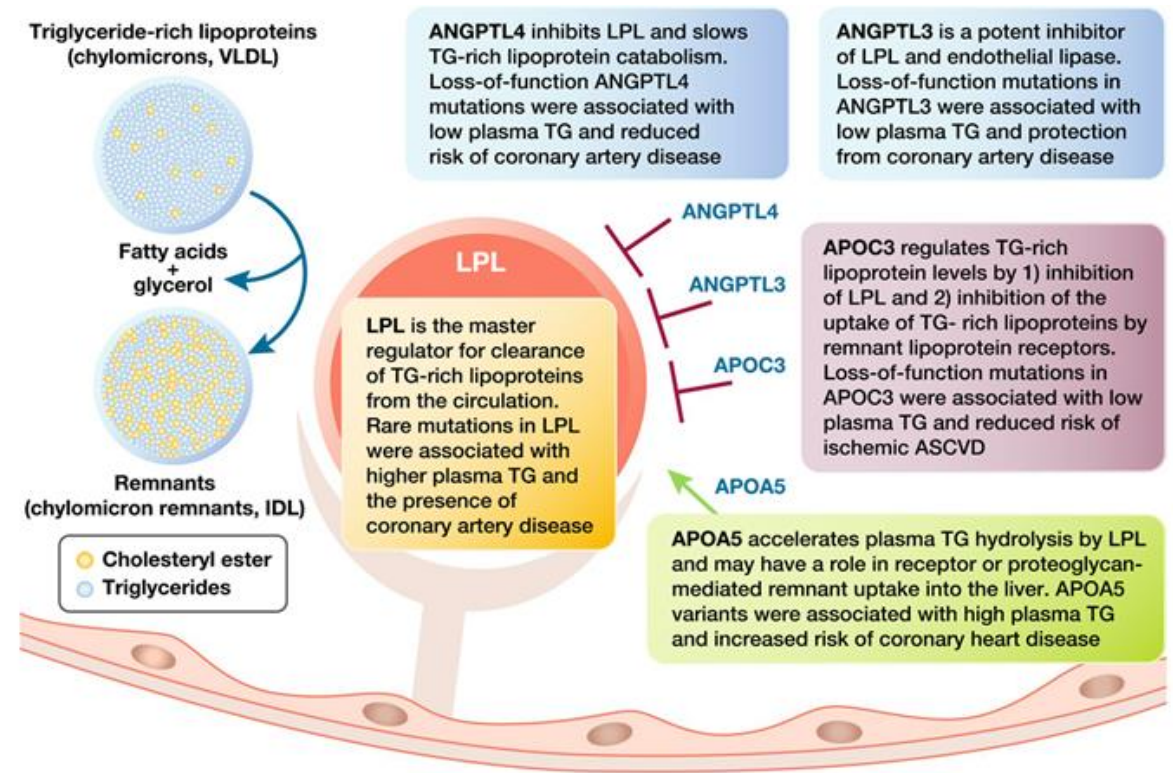
antisense oligonucleotide to apolipoprotein C-III

ARO-APOC3 (Arrowhead)

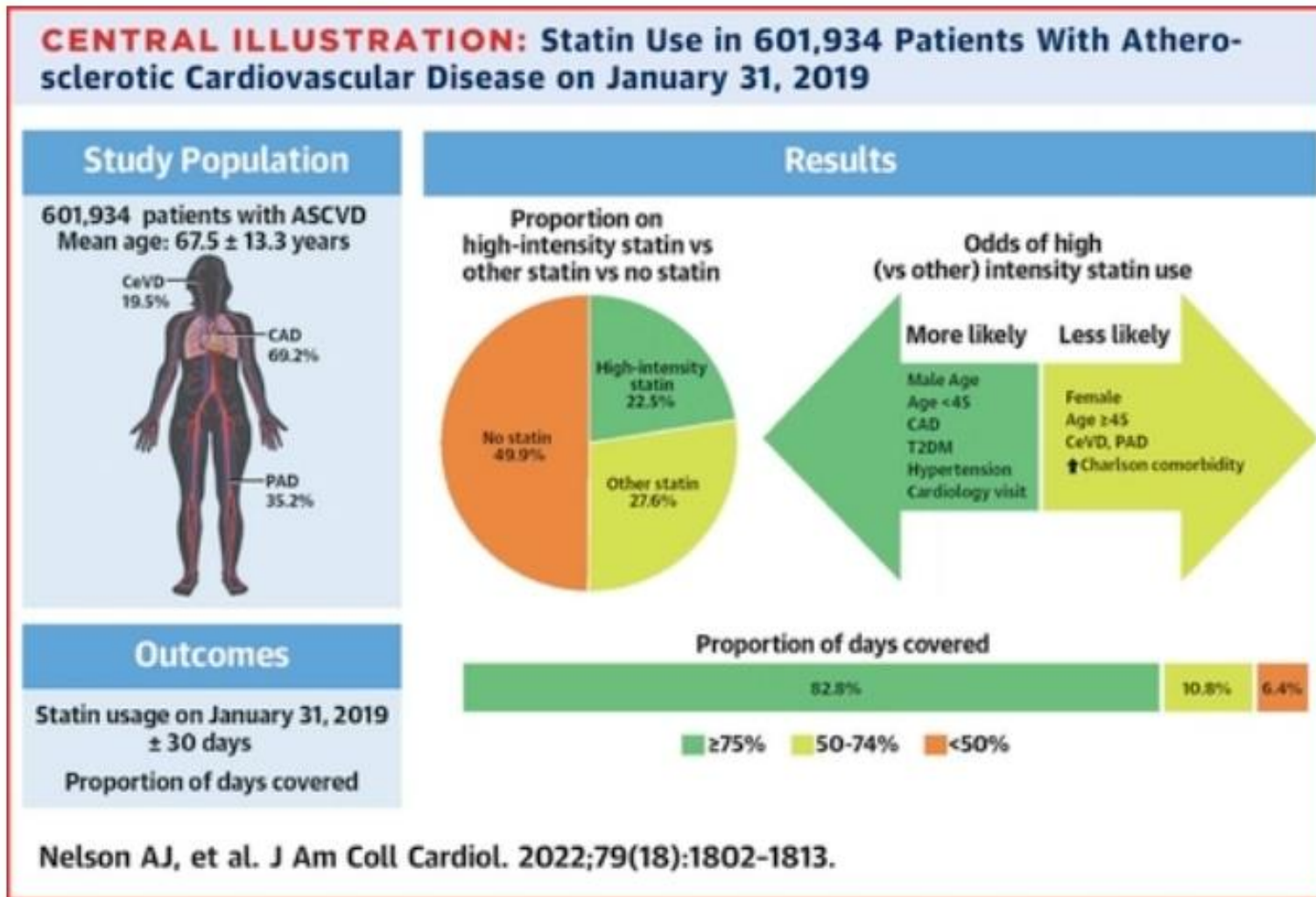
siRNA to apolipoprotein C-III

BIO89-100 (89 Biopharma)

glycoPEGalated analog of fibroblast growth factor 21



Has the clinic been disconnected to the biology?



Pharmaceutical Focus:

PCSK9i
Incliserin
siRNA
Antisense oligonucleotides
Ionis / Novartis Lp(a)
ApoC3
AngPTL3
sPPARM
OTC lipid lowering

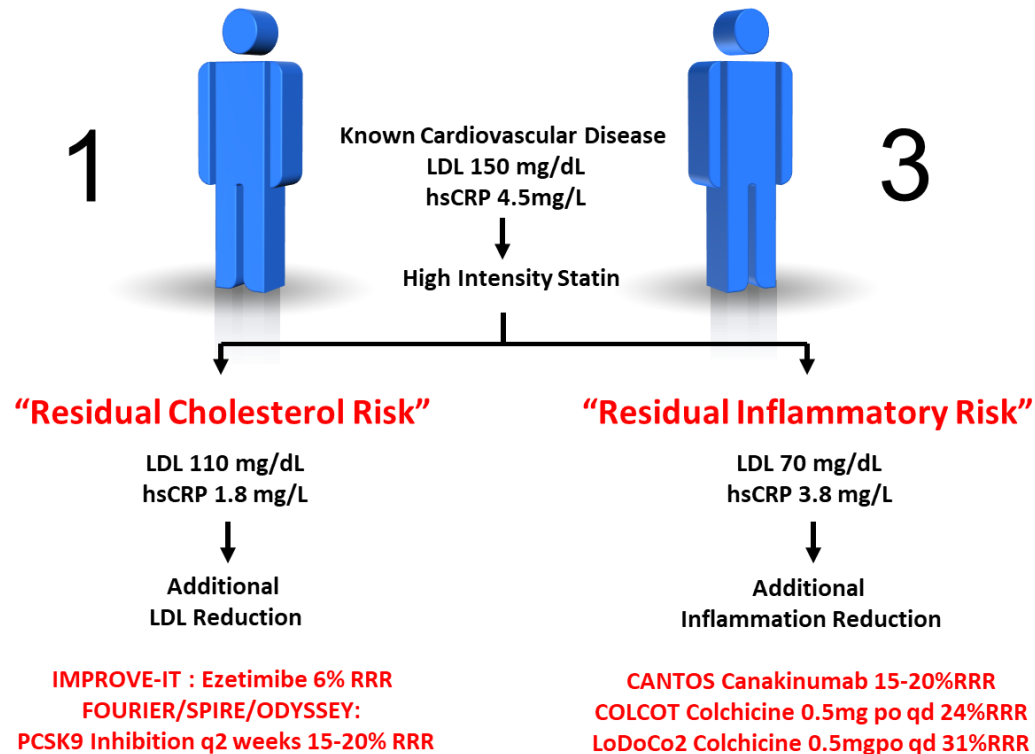
Provider – Patient Focus

Non-compliance
Mis-information

All participants have either private or public insurance

Residual Inflammatory Risk in the Contemporary Care of Atherosclerosis

**Residual Inflammatory Risk:
Addressing the Obverse Side of the Atherosclerosis Prevention Coin**
Eur Heart J 2016;37:1720-22



Ridker P. *Eur Heart J* 2016;37:1720-22

 **ESC**
European Society
of Cardiology
European Heart Journal (2021) 00, 1–111
doi:10.1093/eurheartj/ehab484

ESC GUIDELINES

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies

4.10. Anti-inflammatory therapy

Recommendation for anti-inflammatory therapy

Recommendation	Class ^a	Level ^b
Low-dose colchicine (0.5 mg o.d.) may be considered in secondary prevention of CVD, particularly if other risk factors are insufficiently controlled or if recurrent CVD events occur under optimal therapy. ^{85,86}	IIb	A

© ESC 2021

CVD = cardiovascular; o.d. = *omni die* (once a day).

^aClass of recommendation.

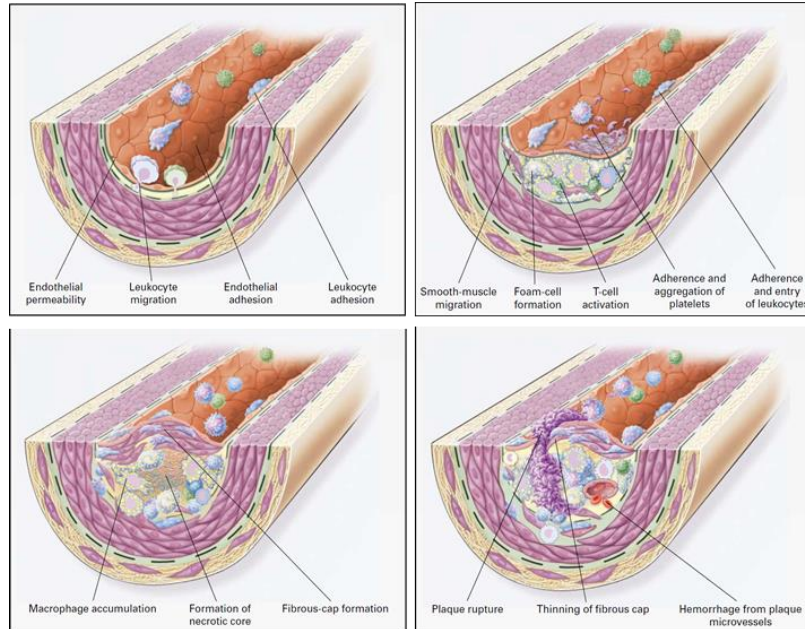
^bLevel of evidence.

Eur Heart J 2021 (September 1)

Inflammation in atherosclerosis: from pathophysiology to practice

ATHEROSCLEROSIS — AN INFLAMMATORY DISEASE

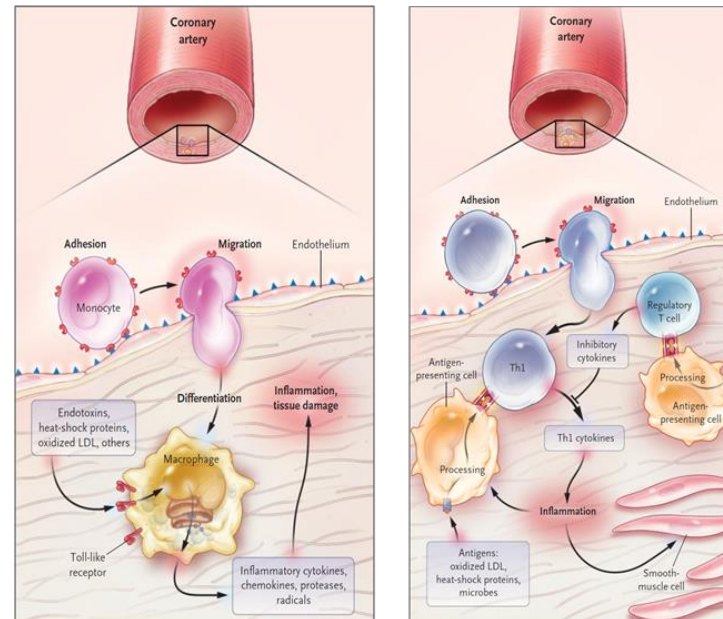
RUSSELL ROSS, PH.D.



1999

MECHANISMS OF DISEASE Inflammation, Atherosclerosis, and Coronary Artery Disease

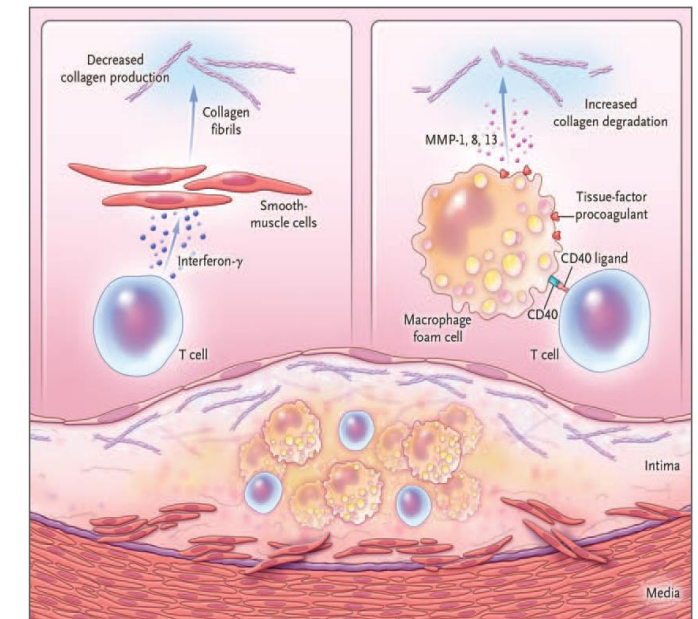
Göran K. Hansson, M.D., Ph.D.



2005

MECHANISMS OF DISEASE Mechanisms of Acute Coronary Syndromes and Their Implications for Therapy

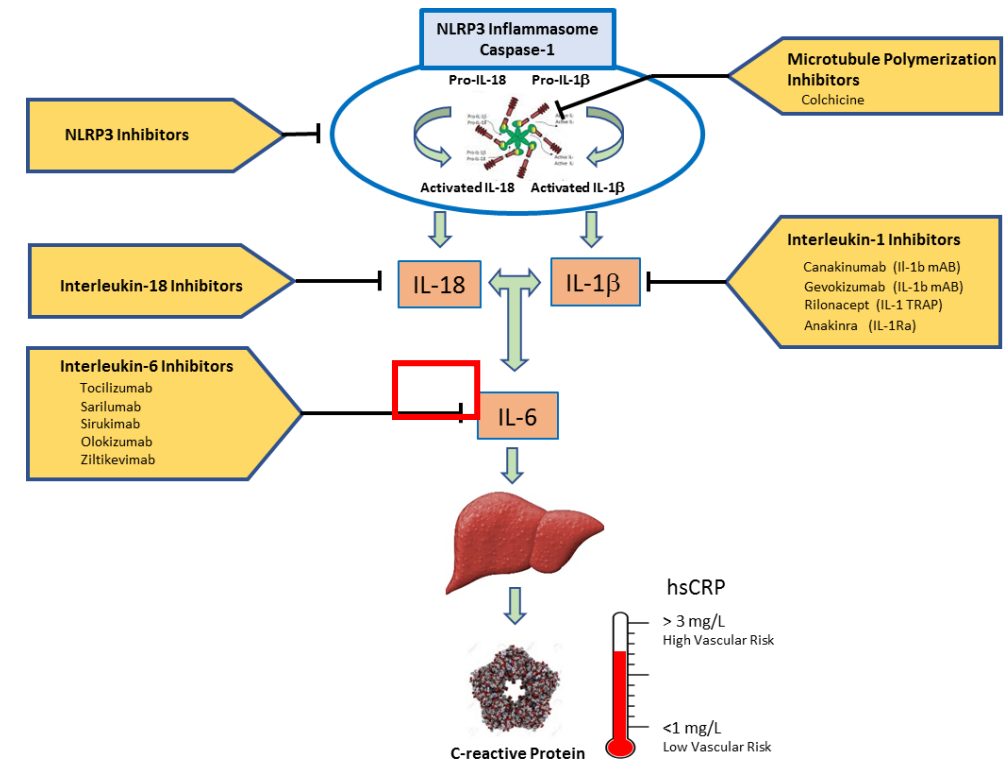
Peter Libby, M.D.



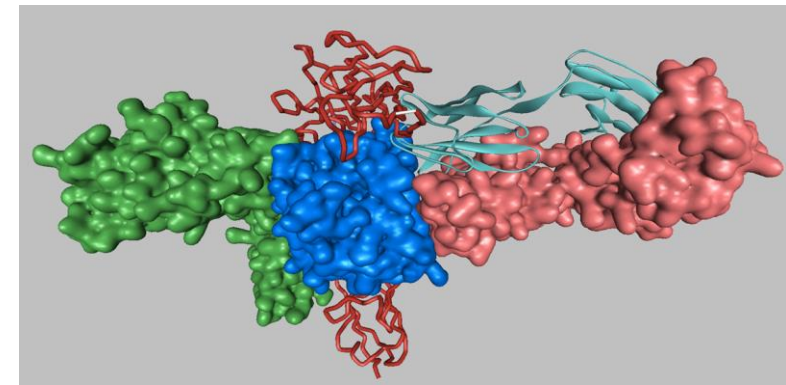
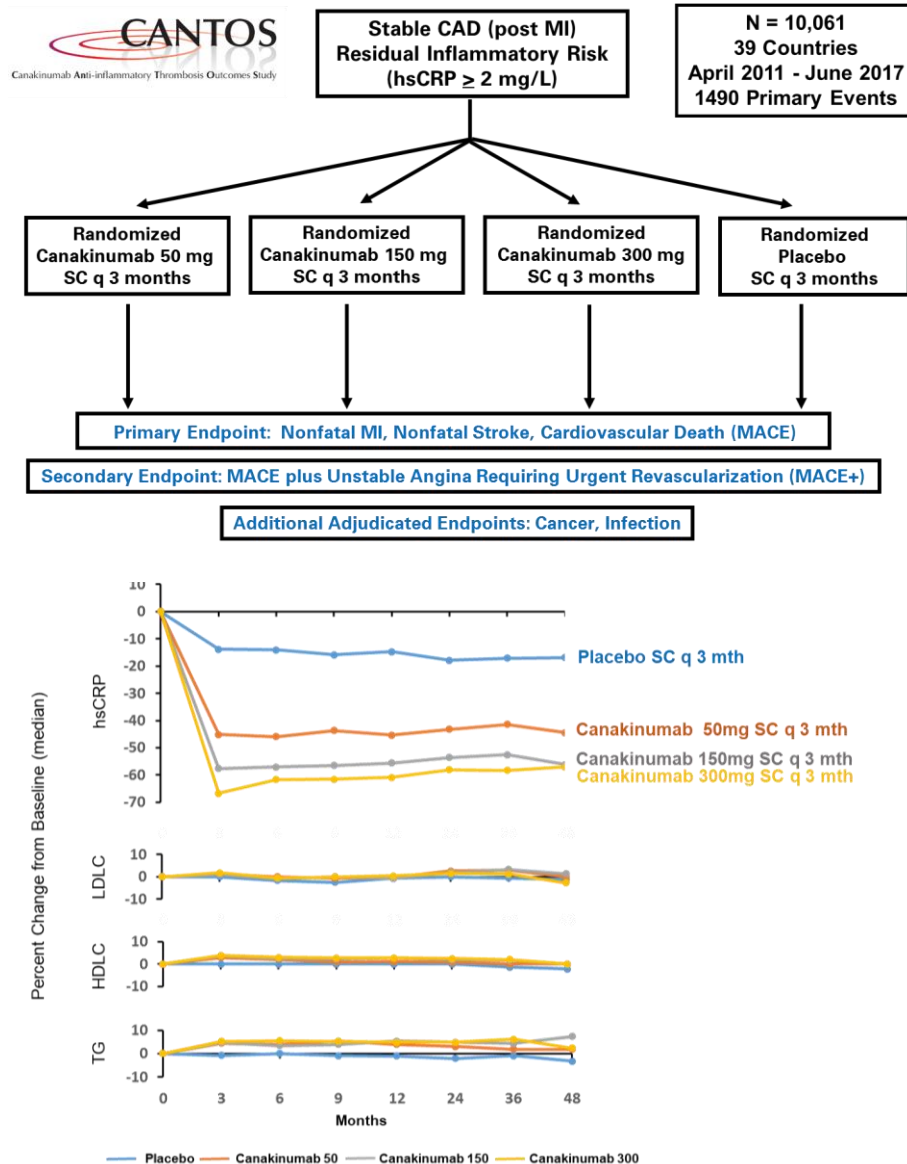
2013

Moving Beyond Cholesterol: Can Targeted Anti-Cytokine Therapy Reduce Cardiovascular Event Rates and Prolong Life?

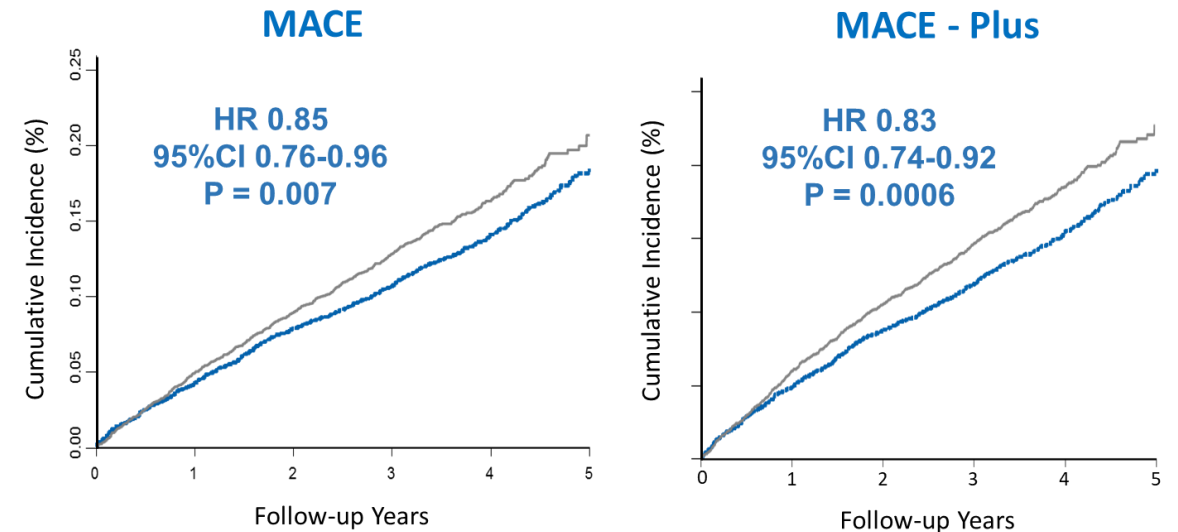
Focus on the Interleukin-1 (IL-1 β) to Interleukin-6 (IL-6) to CRP Pathway



Canakinumab, a Human Monoclonal Antibody Neutralizing IL-1 β



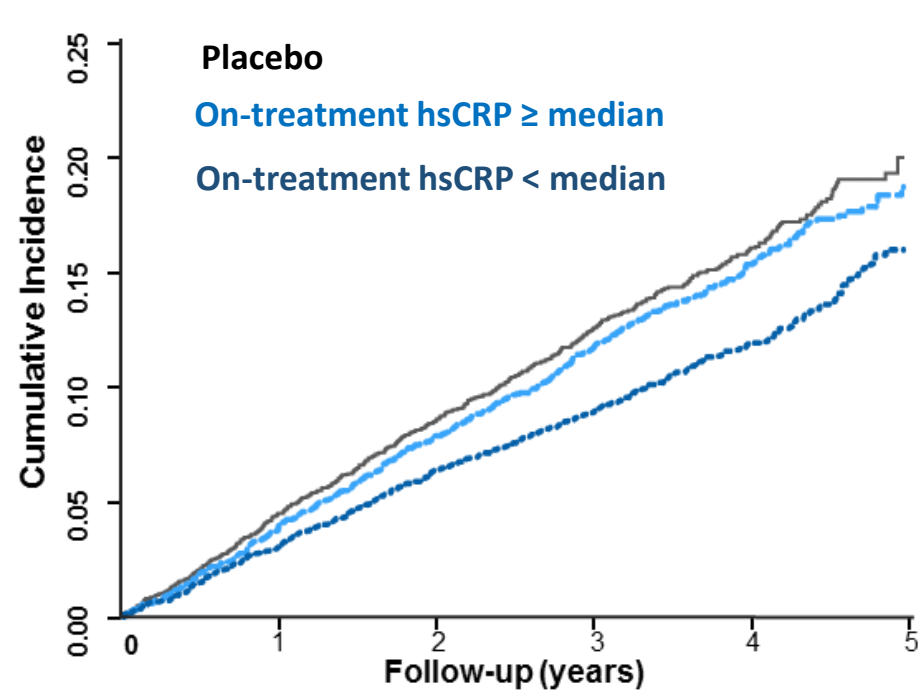
— Placebo SC q 3 months
— Canakinumab 150/300 mg SC q 3 months



35 - 40% reductions in hsCRP and IL-6
No change in LDLC
No change in BP

CANTOS: Greater Risk Reduction With Greater Cytokine Inhibition (MACE)

On-Treatment hsCRP

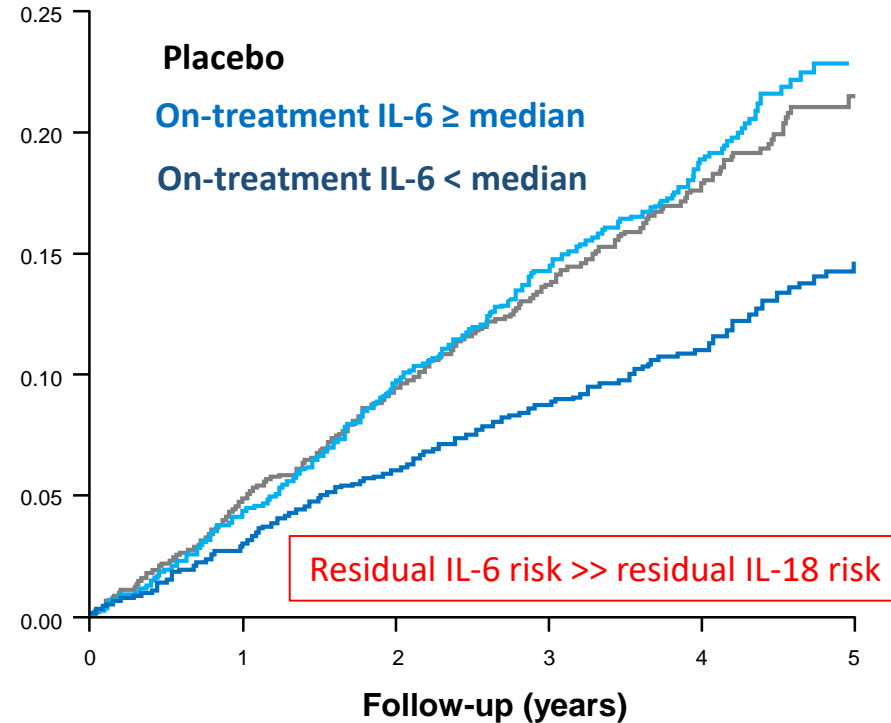


MACE

25% reduction in risk for those achieving hsCRP below median
5 % reduction in risk for those achieving hsCRP above median
(No change in LDL cholesterol)

Ridker et al Lancet 2018;391:319-328

On-Treatment IL-6



MACE

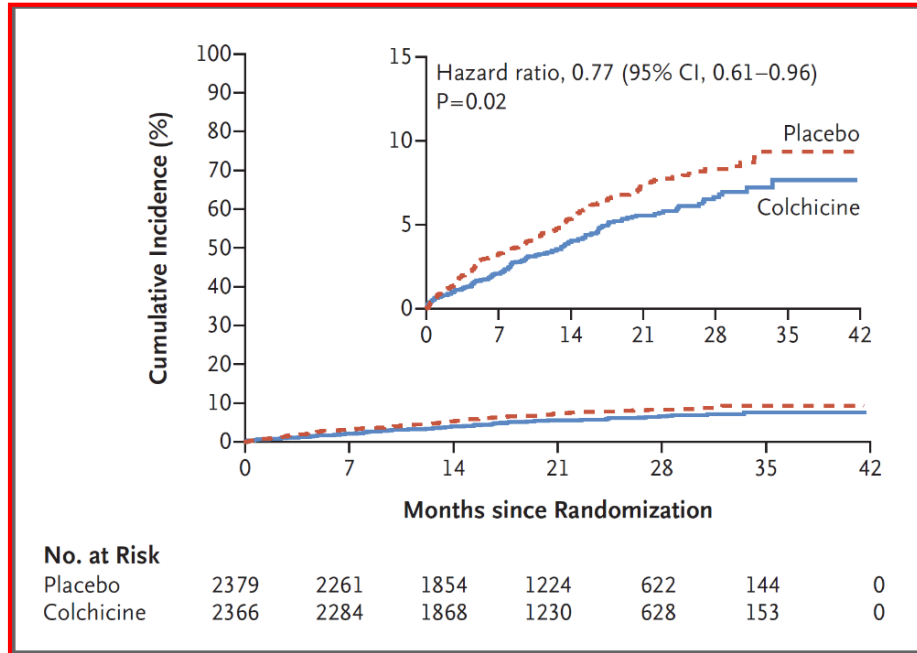
36% reduction for those achieving IL-6 below median
No benefit for those achieving IL-6 above median
(No change in LDL cholesterol)

Ridker et al Eur Heart J 2018;39:3499-3507

Colchicine 0.5 mg po qd for CVD Risk Reduction

COLCOT (N = 4,745 recent MI)

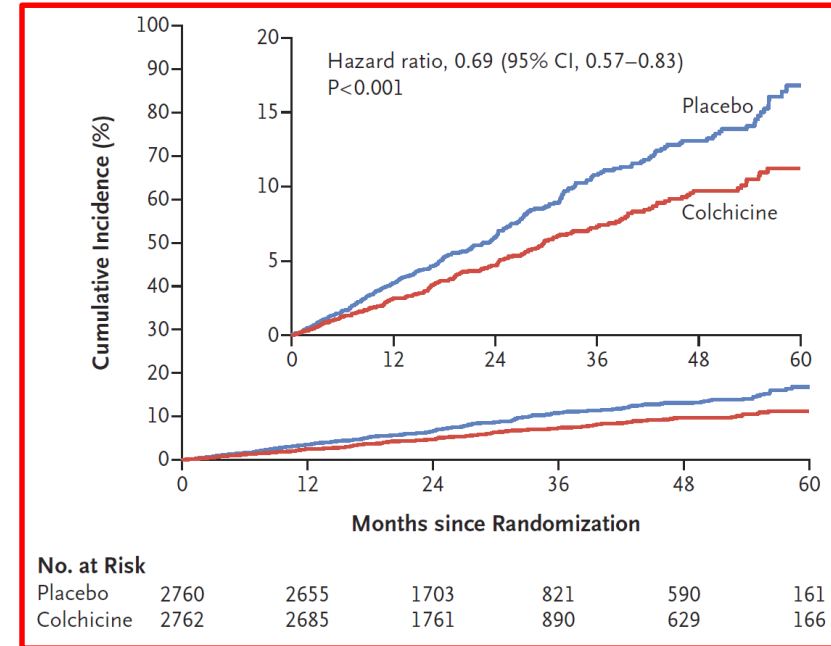
Tardif JC et al NEJM 2019;381:2497-2505



MACE+ HR 0.68 (0.54-0.81)
All Cause Mortality HR 1.04 (0.61-1.78)

LoDoCo2 (N = 5,522 stable CAD)

Nidorf SM et al NEJM 2021;384:776-779

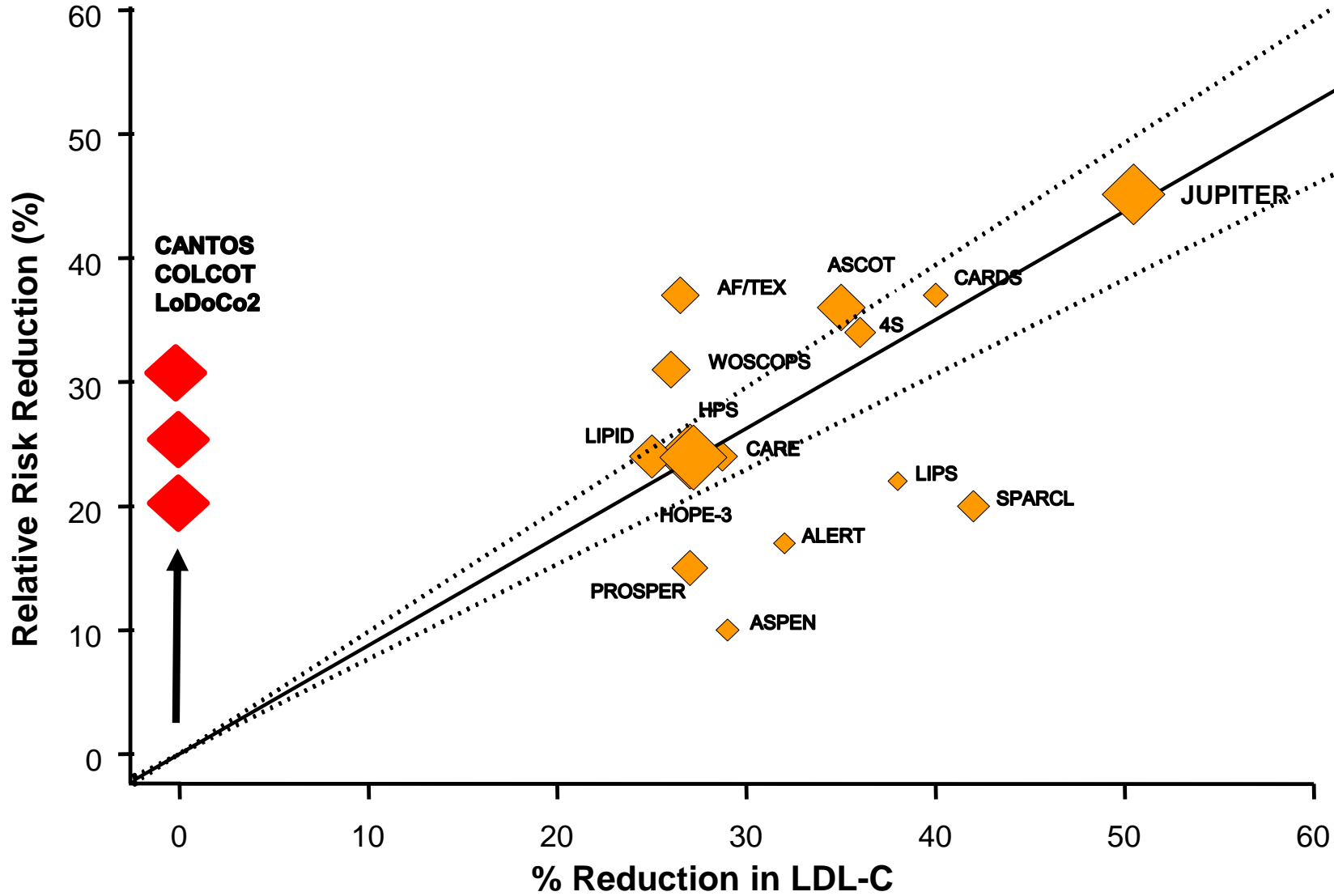


eGFR > 60 HR 0.66 (95%CI 0.54-0.80)
eGFR < 60 HR 1.19 (95% CI 0.53-2.65)

Guidelines should be poised to promote colchicine as an adjunct
to statin therapy in the setting of secondary prevention
BUT

Physicians should use caution in the setting of chronic kidney disease.

CANTOS, COLCOT, LoDoCo2: Adding a New Axis to the LDL Lowering Line



Non-Pharmacologic Approaches to Inflammation Inhibition

STATE-OF-THE-ART PAPER

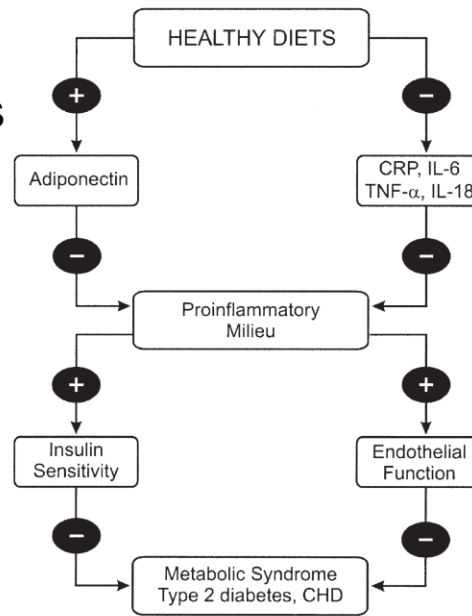
The Effects of Diet on Inflammation

Emphasis on the Metabolic Syndrome

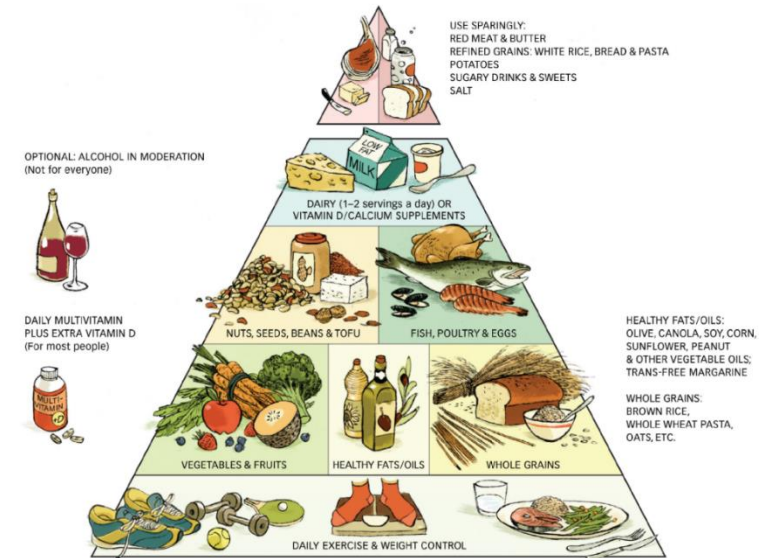
Dario Giugliano, MD, PhD,* Antonio Ceriello, MD,† Katherine Esposito, MD, PhD*

Naples, Italy; and Coventry, United Kingdom

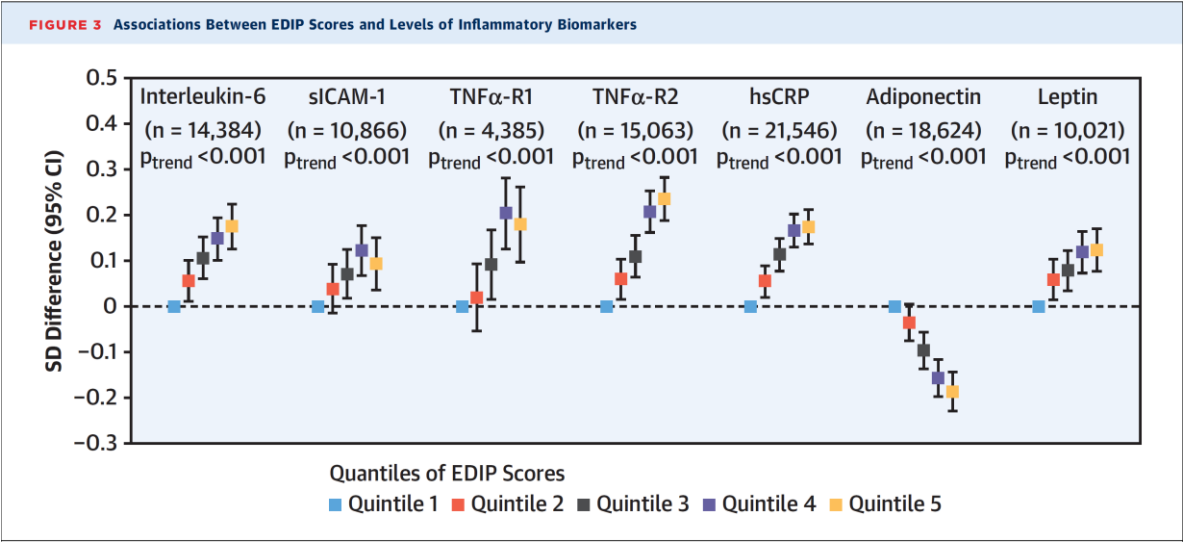
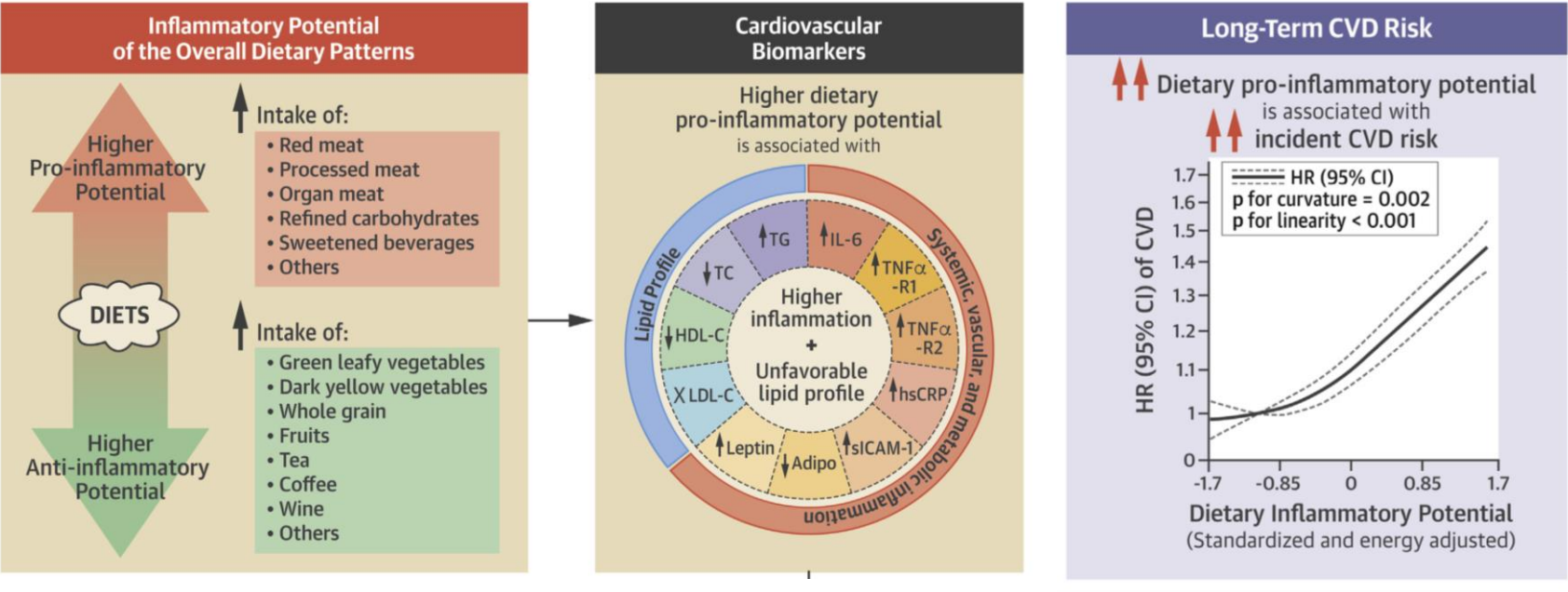
- ↑ omega-3, fish
- ↓ saturated and trans fats
- ↑ fruits, vegetables, nuts
- ↑ whole grains
- ↓ sugar
- ↑ exercise
- ↑ alcohol
- ↓ smoking



Diet, Exercise, Smoking Cessation AHA/ACC Simple Seven



Pro Inflammatory Diets and CVD Outcomes : Nurses Health Study



“The Western diet appears to be mistakenly recognized by the immune system as a threat to the organism”

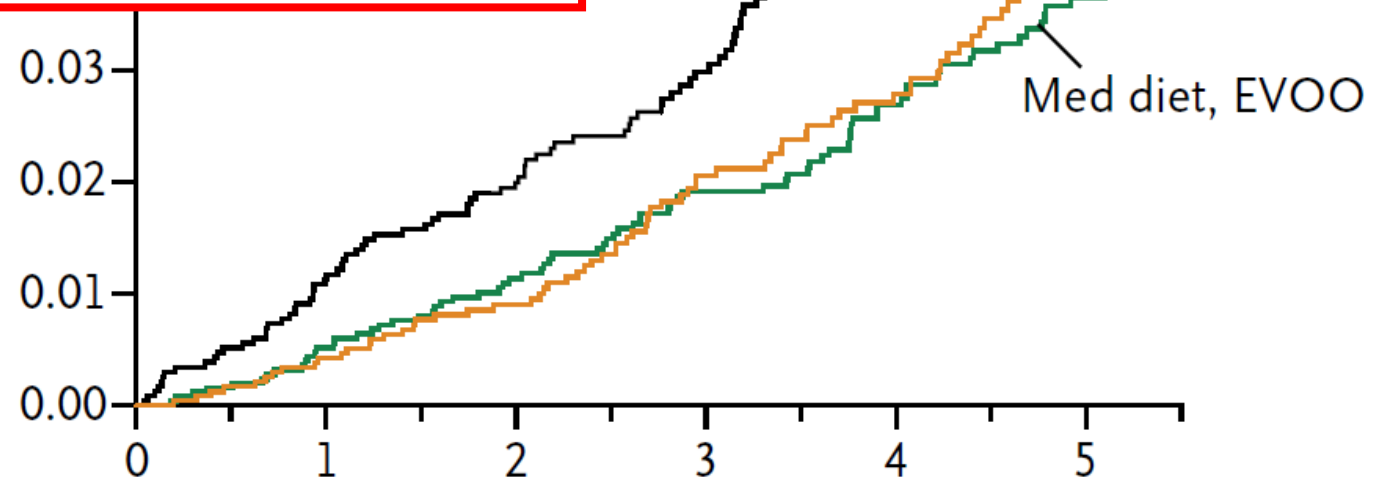
Anette Christ, Eicke Latz, Nature Rev Immunology 2019

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm., M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*



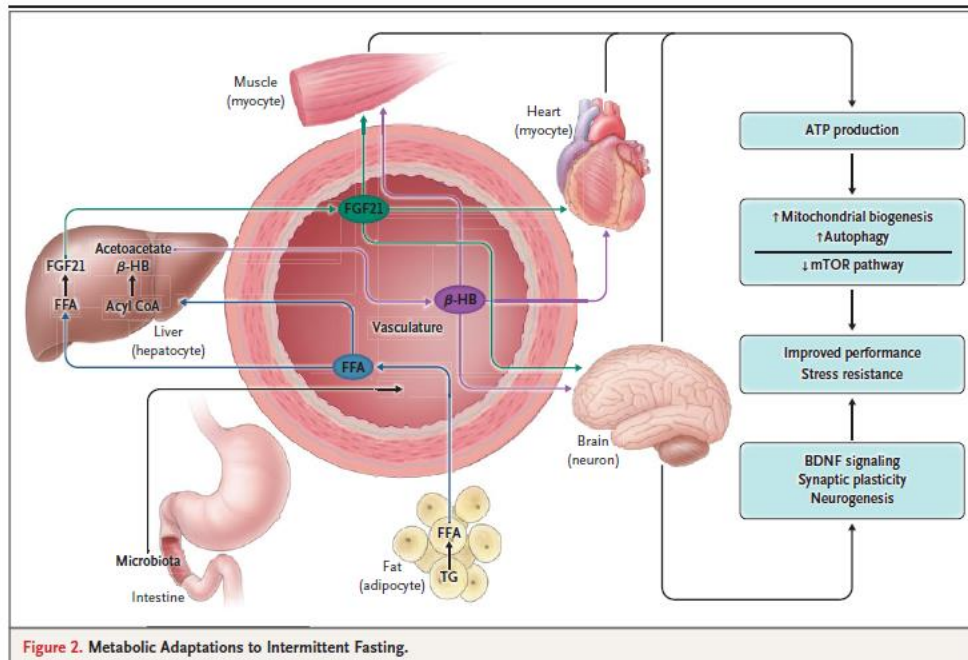
REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Effects of Intermittent Fasting on Health, Aging, and Disease

Rafael de Cabo, Ph.D., and Mark P. Mattson, Ph.D.

NEJM 2019;381:2541-2551



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

APRIL 21, 2022

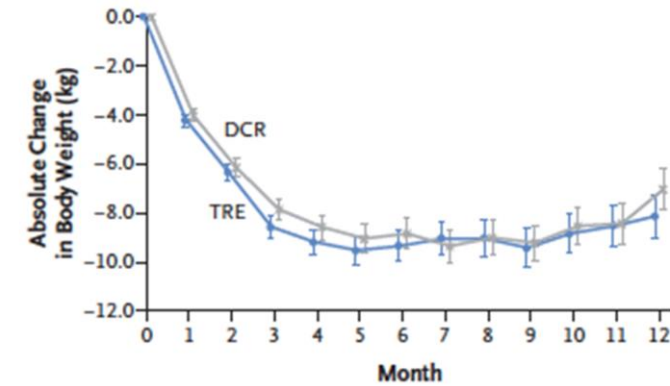
VOL. 386 NO. 16

Calorie Restriction with or without Time-Restricted Eating in Weight Loss

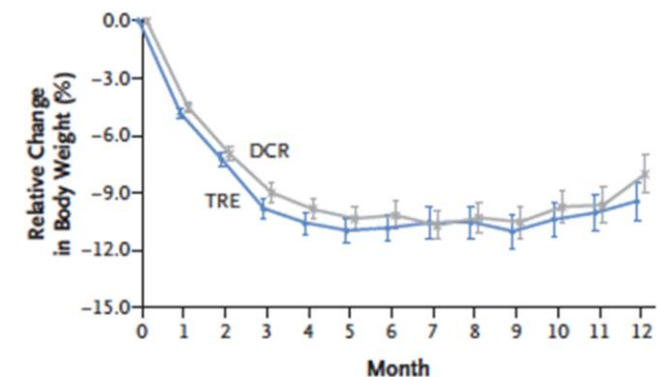
Deying Liu, M.D., Yan Huang, M.S., Chensihan Huang, M.D., Shunyu Yang, M.D., Xueyun Wei, M.D., Peizhen Zhang, M.D., Dan Guo, M.D., Jiayang Lin, M.D., Bingyan Xu, M.D., Changwei Li, Ph.D., Hua He, Ph.D., Jiang He, M.D., Ph.D., Shiqun Liu, M.D., Linna Shi, M.D., Yaoming Xue, M.D., and Huijie Zhang, M.D., Ph.D.

NEJM 2022 (April 21)

A



B



 Daily Mail

Intermittent fasting will NOT help you lose weight faster, scientists claim

Dr Ethan Weiss, a diet researcher at California University, San Francisco, told the New York Times there was 'no benefit to eating in a narrow...

2 horas atrás



The New York Times  @nytimes · Apr 21

In a one-year study, people who confined a low-calorie diet to certain hours lost no more weight than those who ate at any time.

"There is no benefit to eating in a narrow window," one diet researcher said.

 People

Intermittent Fasting Diets Are 'Not More Beneficial' to Increasing Weight Loss, Study Finds

A large study found that intermittent fasting was 'not more beneficial' to weight loss than dieting alone.

18 horas atrás



 The New York Times

Scientists Find No Benefit to Time-Restricted Eating

In a yearlong study, participants who confined meals to certain hours lost no more weight than those who ate at any time.

23 horas atrás



 Euronews

Intermittent fasting may not help you lose weight faster than a standard diet, a 1-year trial found

Intermittent fasting is one of the most popular dieting methods out there. Search for it on Instagram and you'll find nearly five million...

1 hora atrás



 Illustré

Dossier santé Jeûne intermittent: démêler le vrai du faux

De plus en plus plébiscité, le jeûne intermittent consiste à ne pas manger ni boire de boissons contenant des calories pendant des périodes prédéfinies sur...

23 horas atrás



 VEJA

Cientistas constataam que jejum intermitente não traz benefícios

A proposta de limitar os horários para alimentação e passar períodos sem comer, o jejum intermitente, logo se popularizou como uma forma de...

15 horas atrás



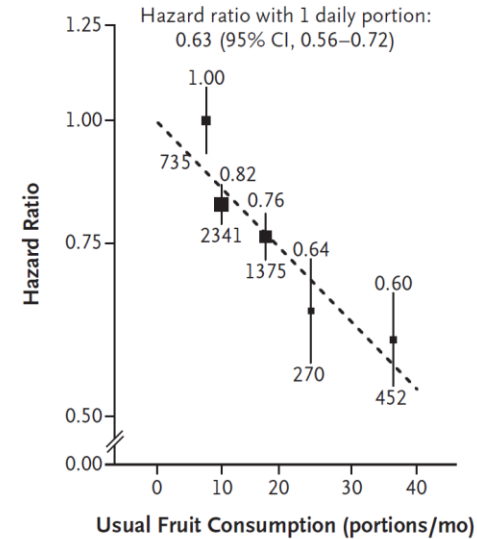
ORIGINAL ARTICLE

Fresh Fruit Consumption and Major Cardiovascular Disease in China

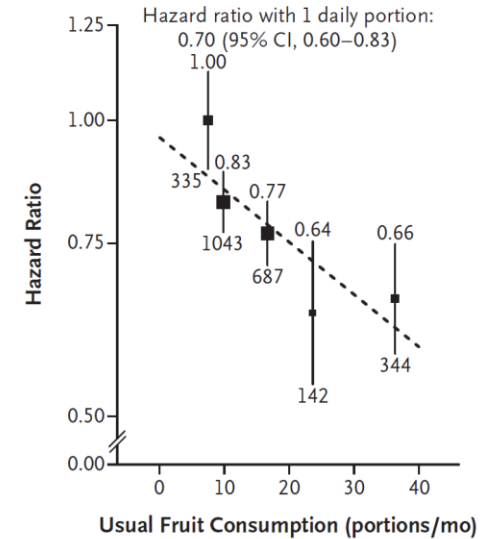
Huaidong Du, Ph.D., Liming Li, M.D., M.P.H., Derrick Bennett, Ph.D., Yu Guo, M.Sc., Timothy J. Key, D.Phil., Zheng Bian, M.Sc., Paul Sherliker, B.A., Haiyan Gao, Ph.D., Yiping Chen, D.Phil., Ling Yang, Ph.D., Junshi Chen, M.D., Shanqing Wang, Ph.D., Ranran Du, B.A., Hua Su, M.D., M.P.H., Rory Collins, F.Med.Sci., F.R.C.P.(E.), Richard Peto, F.R.S., and Zhengming Chen, D.Phil., for the China Kadoorie Biobank Study*

Du H, et al; N Engl J Med. 2016;374):1332-43.

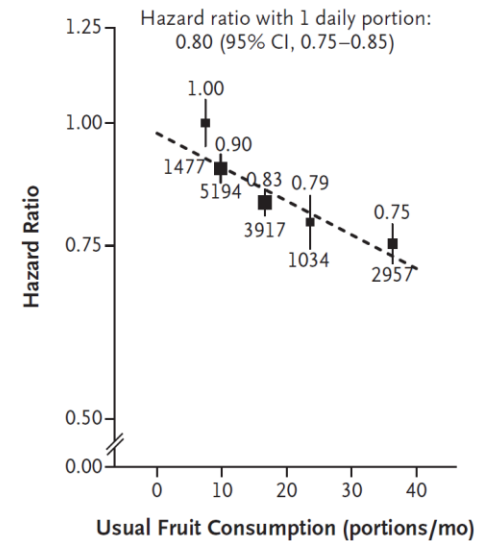
A Cardiovascular Death (N=5173)



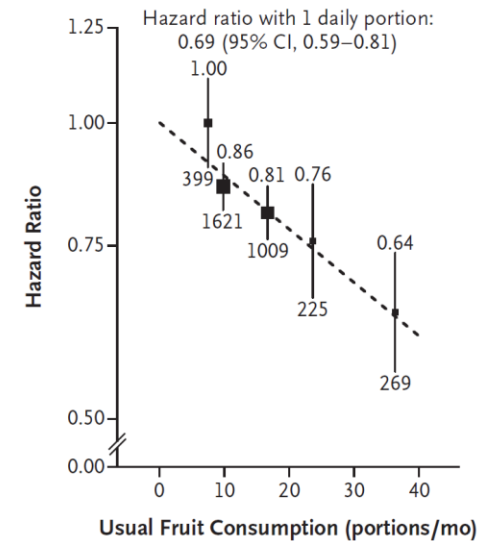
B Major Coronary Events (N=2551)




C Ischemic Stroke (N=14,579)



D Hemorrhagic Stroke (N=3523)

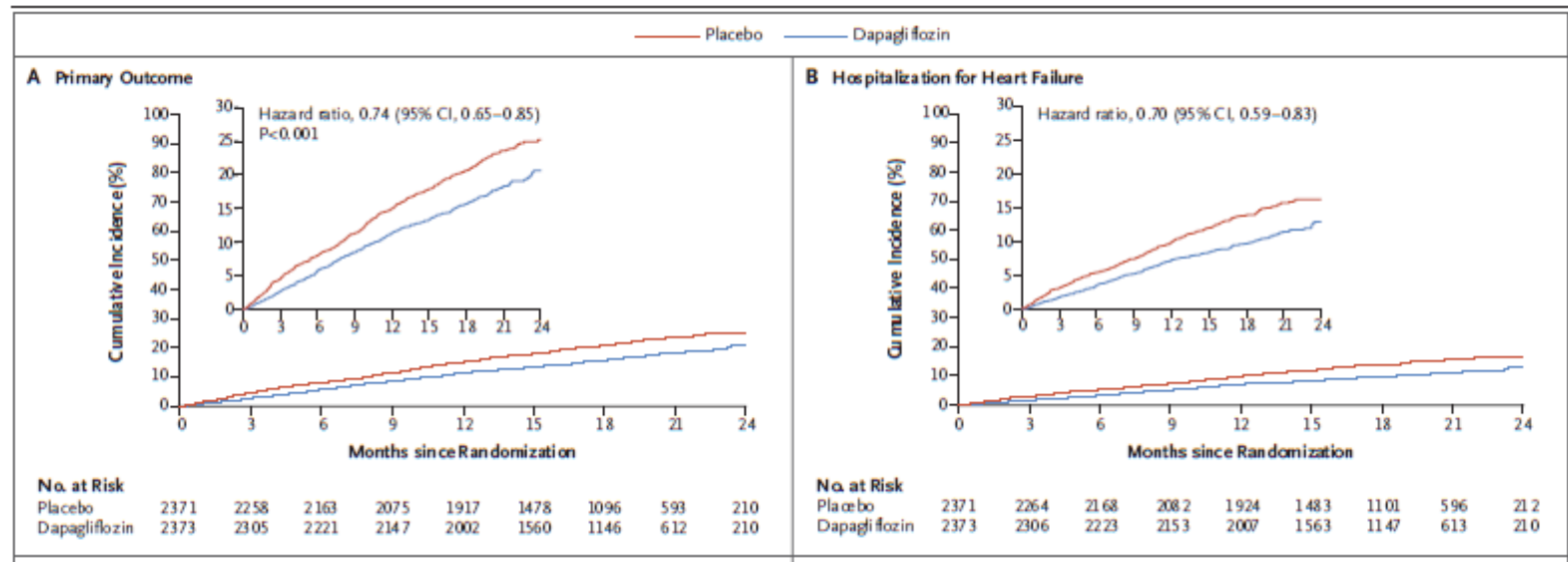
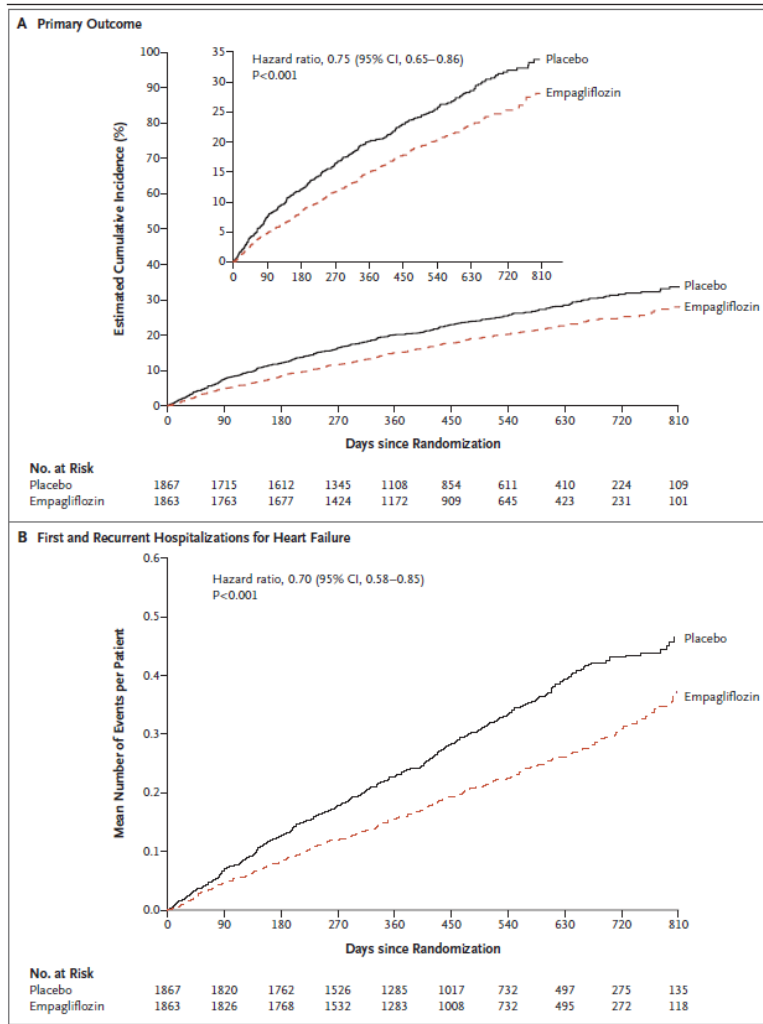


SGLT2 inhibitors: the statins of the 21st century

Eugene Braunwald  1,2*

¹TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Hale Building for Transformative Medicine, Suite 7022, 60 Fenwood Road, Boston, MA 02115, USA; and ²Department of Medicine, Harvard Medical School, Boston, MA, USA

A relatively small number of drugs have been responsible for major advances in medical practice. The discovery, development, and elucidation of the mechanisms of action of aspirin, penicillin, and statins are remarkable success stories, each with some surprises and each crowned by a Nobel Prize. The sodium glucose co-transporter inhibitors have been proven effective in the treatment of type 2 diabetes mellitus, various forms of heart failure, and kidney failure and represent *the, or one of the,* major pharmacological advances in cardiovascular medicine in the 21st century.



Packer NEJM 2020;383:1413-1424

McMurray NEJM 2019;381:1995-2008

Canagliflozin
Dapagliflozin
Empagliflozin

And what about GLPi1 analogues? (Exanatide, Liraglutide, Semaglutide, etc)

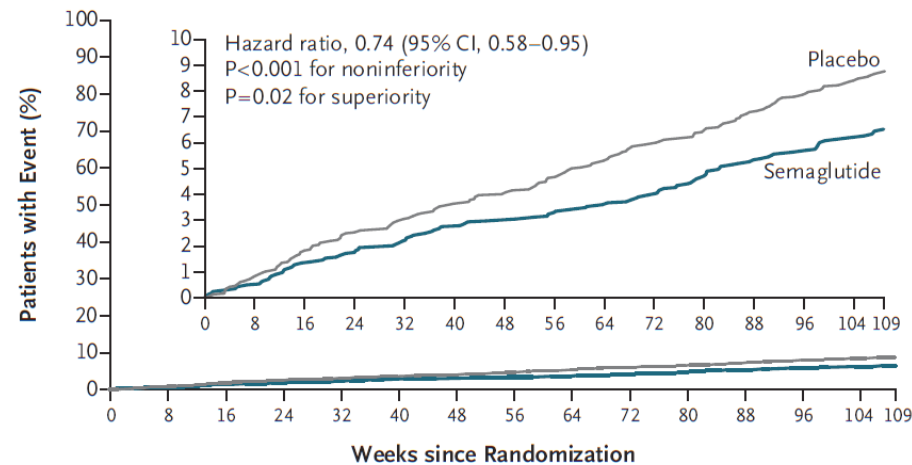
September 16, 2016

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaszewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

A Primary Outcome



No. at Risk

Placebo	1649	1616	1586	1567	1534	1508	1479
Semaglutide	1648	1619	1601	1584	1568	1543	1524

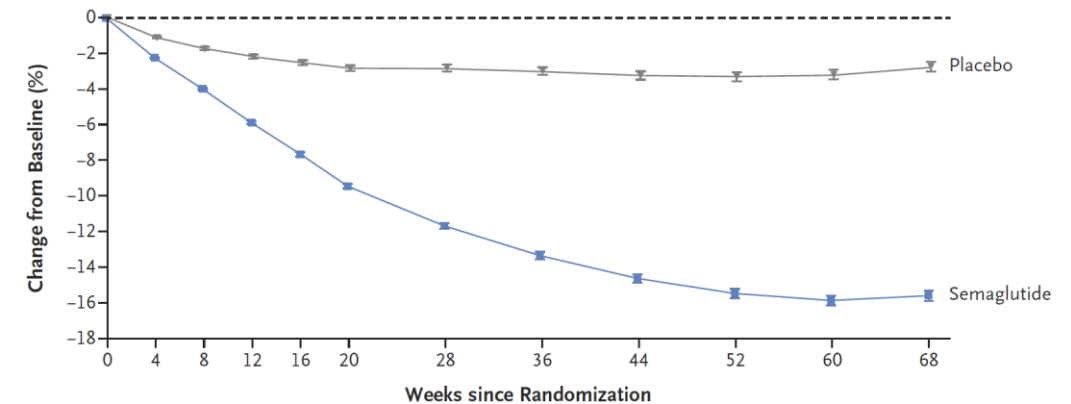
February 10 ,2021

ORIGINAL ARTICLE

Once-Weekly Semaglutide in Adults with Overweight or Obesity

John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D., Salvatore Calanna, Ph.D., Melanie Davies, M.D., Luc F. Van Gaal, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Barbara M. McGowan, M.D., Ph.D., Julio Rosenstock, M.D., Marie T.D. Tran, M.D., Ph.D., Thomas A. Wadden, Ph.D., Sean Wharton, M.D., Pharm.D., Koutaro Yokote, M.D., Ph.D., Niels Zeuthen, M.Sc., and Robert F. Kushner, M.D., for the STEP 1 Study Group*

A Body Weight Change from Baseline by Week, Observed In-Trial Data



No. at Risk

Placebo	655	649	641	619	615	603	592	571	554	549	540	577
Semaglutide	1306	1290	1281	1262	1252	1248	1232	1228	1207	1203	1190	1212

Prevention 10 Years From Now: My predictions and how to get yourself ready

Personalized Biology

Precision Medicine

Community Based Care

Individual Level Care

International Global Health

Government and Political Change

Some new technologies will be game changing



Suspend on low*

Suspends insulin delivery *when* sensor glucose (SG) reaches a pre-set low limit



Suspend before low*

Suspends insulin delivery *before* SG reaches a pre-set low limit



Auto Mode

Automatically adjusts basal insulin delivery based on SG

ORIGINAL ARTICLE

Closed-Loop Insulin Delivery for Glycemic Control in Noncritical Care

Lia Bally, Ph.D., Hood Thabit, Ph.D., Sara Hartnell, B.Sc.,
Eveline Andereggen, R.N., Yue Ruan, Ph.D., Malgorzata E. Wilinska, Ph.D.,
Mark L. Evans, M.D., Maria M. Wertli, Ph.D., Anthony P. Coll, M.D.,
Christoph Stettler, M.D., and Roman Hovorka, Ph.D.

Hospital Based Glucose Management

136 patients with type 2 diabetes requiring insulin

70 closed loop insulin delivery

66 conventional SC insulin delivery

Primary Endpoint : time (%) glucose in target range

65.8% closed-loop vs 41.5% conventional $P < 0.001$

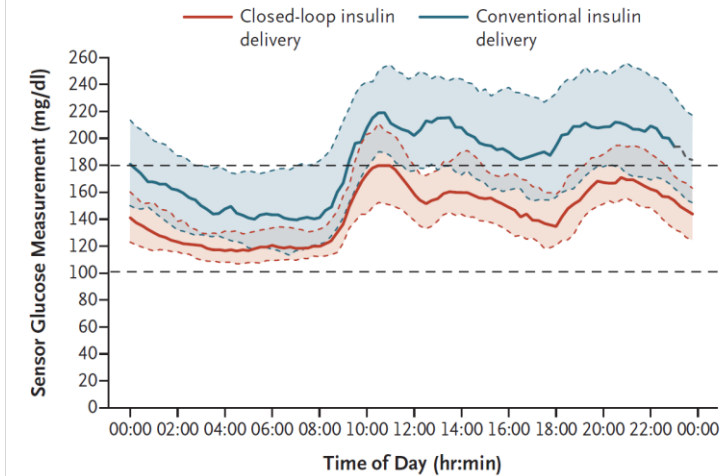
Reduced hyperglycemia episodes

No severe hypoglycemia

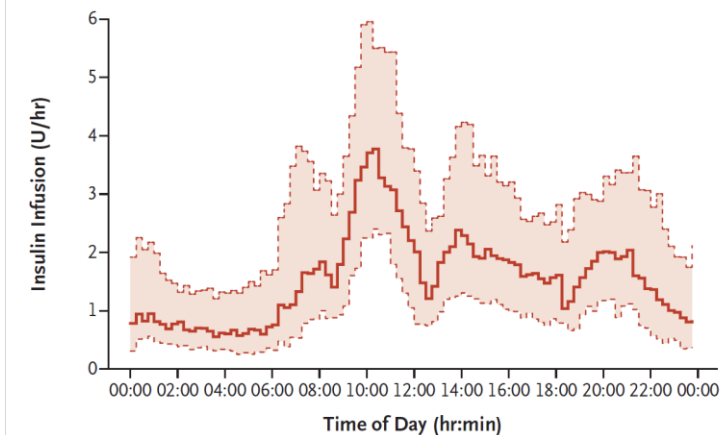
Mean glucose 154mg/dL vs 188mg/dL $P < 0.001$

Bally L et al, N Engl J Med. 2018 Jun 25. [Epub ahead of print]

A Sensor Glucose Measurement



B Closed-Loop Insulin Delivery



Other new technologies, maybe not...



iMessage
Today 12:40 PM

Waking is cheap. It can be done almost anywhere. All you need are comfortable shoes & clothing.

Text Med Trial (Chow et al, Circulation 2022;145:1443-1455)

1424 Post-ACS patients randomized to usual care or usual care plus once weekly supportive text messages addressing lifestyle choices, medication compliance, and motivation over a 12 month period.

No difference in medication adherence

No difference in LDL-C

No difference in blood pressure

Small improvements in daily servings of fruits and vegetables



Advertisement Campaigns

- \$635 million (McDonald's)
- \$298 million (Burger King)
- \$224 million (Coca Cola)

Photo courtesy of Randal Thomas



DOCTORS' ORDERS: **STOP MARKETING JUNK FOOD TO KIDS**

*An open letter to McDonald's
CEO Jim Skinner from more than
550 health professionals and
institutions in all 50 states.*

To join the growing movement
of health professionals, visit:

www.LetterToMcDonalds.org

Dear CEO Skinner,

As health professionals engaged directly in the largest preventable health crisis facing this country, we ask that you stop marketing junk food to children.

The rates of sick children are staggering. Ballooning health care costs and an overburdened health care system make treatment more difficult than ever. And we know that reducing junk food marketing can significantly improve the health of kids.

Our community is devoted to caring for sick children and preventing illness through public education. But our efforts cannot compete with the hundreds of millions of dollars you spend each year directly marketing to kids.

Indeed, as health professionals, we know that parents exercising responsibility for their children's diets and exercise is vital. We also know that no authoritative data indicates a breakdown in parental responsibility.

Obesity and disease levels among kids and parents continue to exercise us. So what has changed?

What has changed is the food children are

bombarded with. We know the contributors to today's obesity response is required. But marketing of this massive problem.

We ask that you heed our concern and stop the high in salt, fat, sugar, and calories to kids. Stop the Ronald McDonald to toy giveaways.

Our children and health care system

Sincerely* (View the full text and signatories)

(Affiliation is for ID purposes only)

> **INSTITUTIONS:**
American Academy of Child and Adolescent Psychiatry

American Medical Student Association

Arizona Center for Integrative Medicine, University of Arizona

Baltimore Medical System

Chicago Hispanic Health Coalition

Department of Family Medicine at Tufts University School of Medicine

Doctors for America

Family Practice and Counseling Network, Philadelphia, PA

Illinois Maternal & Child Health Coalition

Inpatient Diabetes Program, Boston University

Massachusetts Public Health Association

Mercy Hospital & Medical Center, Chicago, IL

National Council of Asian and Pacific Islander Physicians

New Mexico Public Health Association

Nutrition and Weight Management Center, Boston Medical Center

Oregon Academy of Family Physicians

Physicians Committee for Responsible Medicine

The Prevention Institute

Science and Environmental Health Network

The Vermont Nurse Practitioners Association

> **NATIONAL HEALTH LEADERS:**

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T. Colin Campbell

China Study

Biochemist

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Director, Yale

Editor-in-Chief

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Fmr. President, American Public Health

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Andrew Weil, MD, Author; Founder and

Director, Arizona Center for Integrative

Medicine, Prof. of Medicine and Public

Health, and Jones-Lovell Endowed Chair

for Integrative Rheumatology, University of

Arizona, Tucson, AZ



University of Illinois Chicago

Quentin Young, MD, National Coordinator, Physicians for a National Health Program; Doctor of Internal Medicine, Hyde Park Associates in Medicine

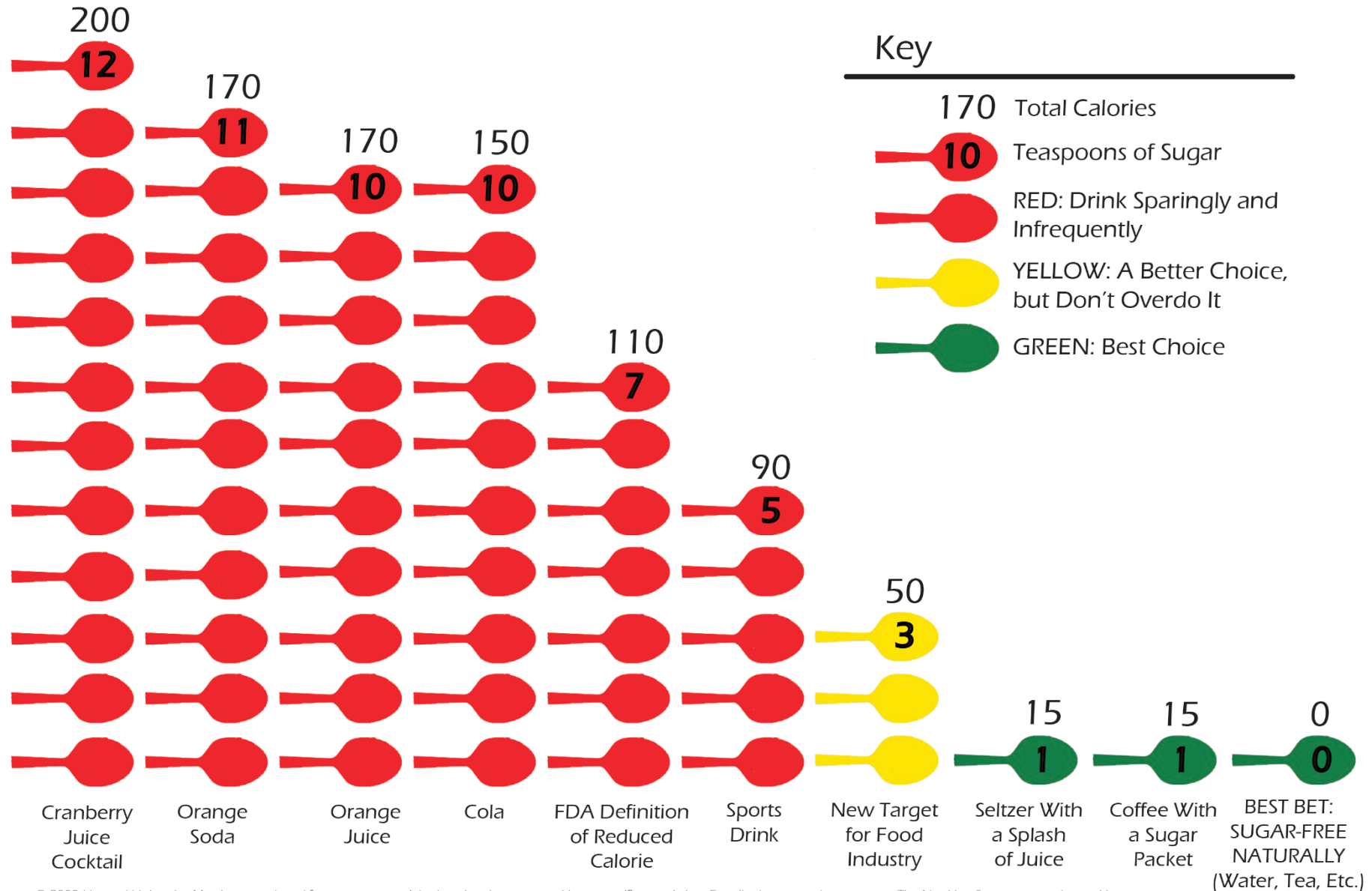
Donald W. Zeigler, PhD, Director, Prevention and Healthy Lifestyles, American Medical Association; Visiting Assistant Prof., Community Health Program and Dept. of Preventive Medicine, Rush University Medical Center

*PARTIAL LIST OF SIGNATURES

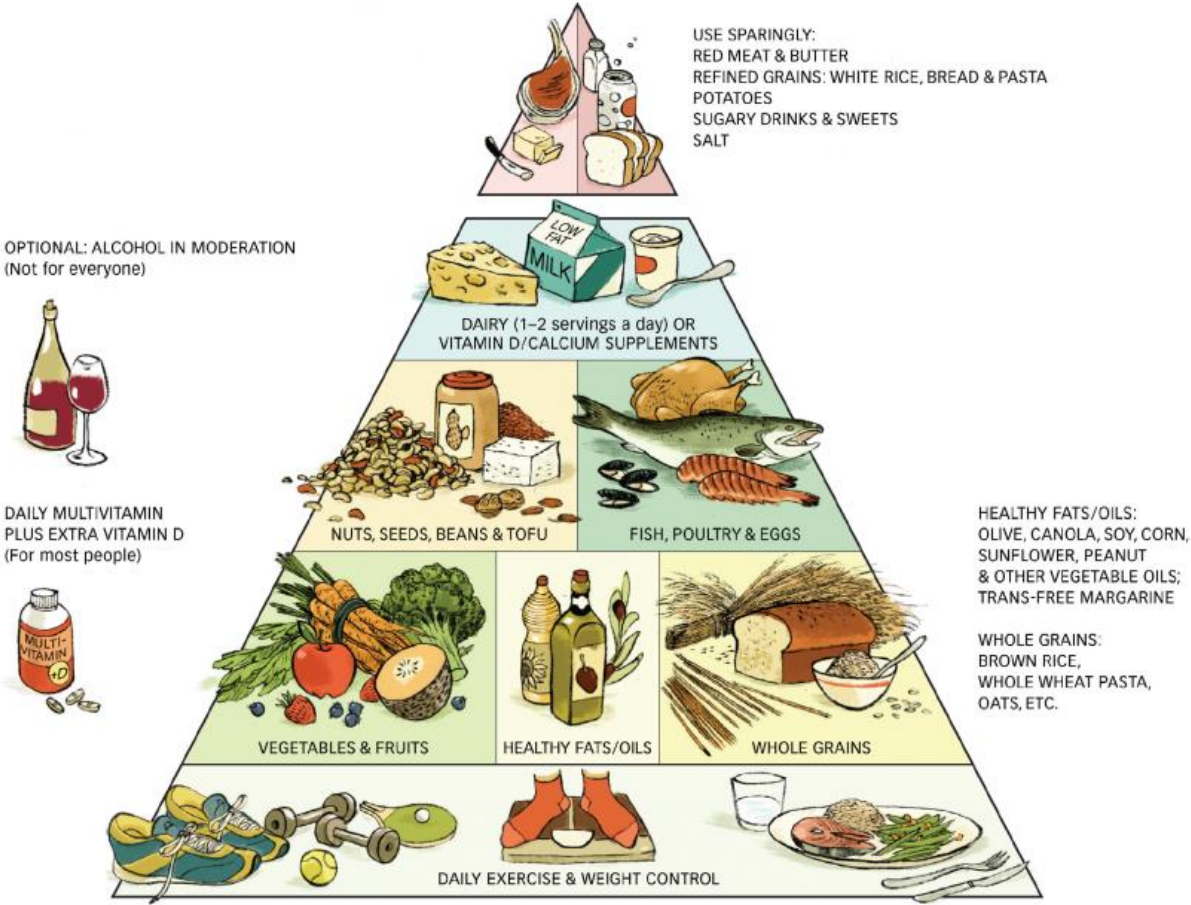
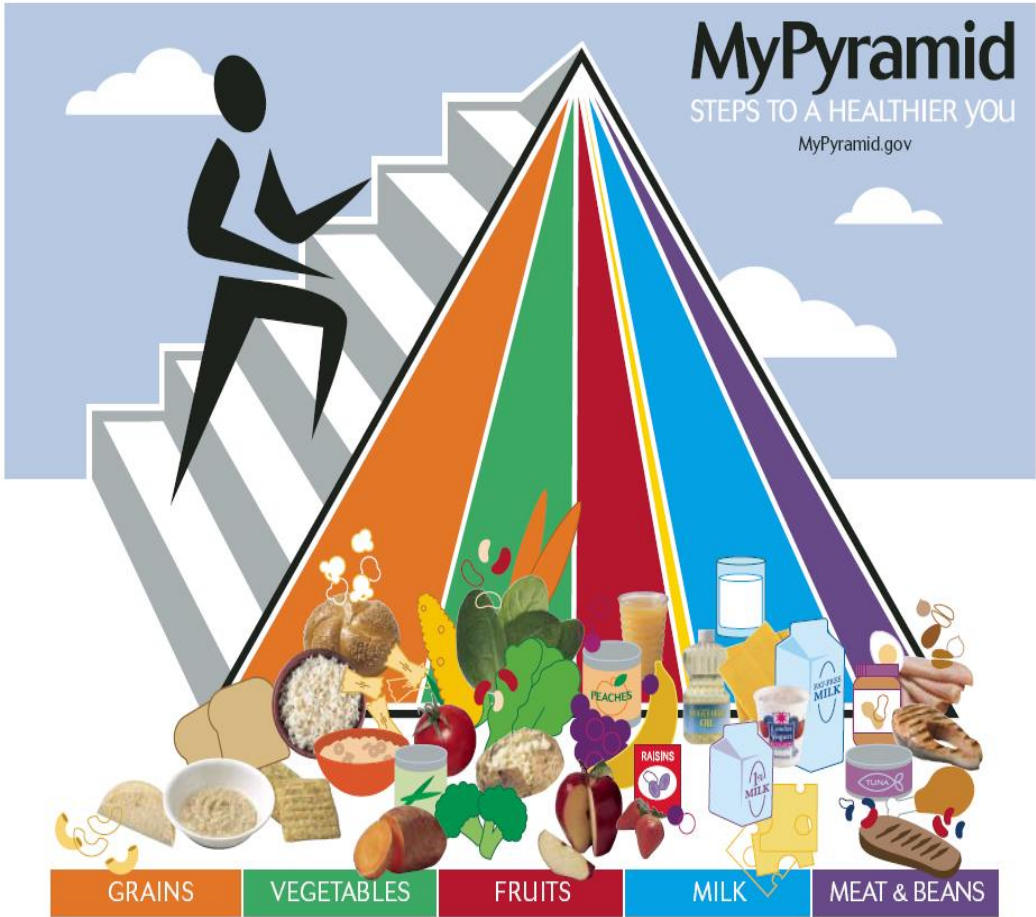
How Sweet Is It?

Calories and Teaspoons of Sugar in 12 Ounces of Each Beverage

For more information, see The Nutrition Source, www.hsph.harvard.edu/nutritionsource/healthy-drinks/



Two Radically Different Approaches to the Food Pyramid



Clarity of Medical Communication is a Public Health Problem



Global Warming and Consequent Human Migration are Medical Issues





Review Question 1.

Which of the following interventions has been proven to lower cardiovascular event rates?

- A. Lowering LDL-C
- B. Lowering triglycerides
- C. Lowering hsCRP
- D. Lowering Lp(a)
- E. Raising HDL-C



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“If you don’t measure it, you can’t treat it”



Review Question 2.

Among statin treated atherosclerosis patients, which of the two following groups is most common?

- A. Residual Cholesterol Risk (LDL-C > 70 mg/dL, hsCRP < 2 mg/L)
- B. Residual Inflammatory Risk (LDL-C < 70 mg/dL, hsCRP > 2 mg/L)

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In North America today, there are 3 patients with residual inflammatory risk for every one patient with residual cholesterol risk

“If you don’t measure it, you can’t treat it”