S.I.Te.C.S.
Società Italiana di Terapia Clinica e Sperimentale

EAS

INTERNATIONAL WORKSHOP

THE ROLE OF DYSLIPIDAEMIAS IN DETERMINING CARDIOVASCULAR RISK: FROM LIFESTYLE TO PHARMACOLOGICAL INTERVENTION

Naples - 2018, November 17-18 - Hotel Royal Continental

Chairs
A.L. Catapano, P. Perrone Filardi and L. Tokgözoğlu

This meeting is endorsed by the European Atherosclerosis Society EAS

ATHEROGENIC DYSLIPIDAEMIAS

Addressing Residual CV Risk

Alberto Zambon
University of Padova
Italy

DISCLOSURE

Prof. A. Zambon reports having received grants, consulting fees and/or honoraria and delivering lectures for:

- Abbott
- AstraZeneca
- Merck Sharp & Dohme
- Amgen
- Sanofi
- Lilly
- Mylan
- Chiesi

ATHEROGENIC DYSLIPIDEMIAS: Addressing Residual CV Risk

Mr. Green

Known CV Disease
LDL-C 160 mg/dl
TG 125 mg/dl; HDL-C 45 mg/dl
hsCRP 4,5 mg/dl

High Intensity **Statin** Therapy*

Target LDL-C <70 mg/dl

Mr. Green

! LDL-C 110 mg/dl
✓ hsCRP 1,8 mg/dl

«Residual LDL-C Risk»
Additional LDL-C Reduction

IMPROVE-IT: **EZETIMIBE 6% CV event RRR**
FOURIER/SPIRE: **PCSK9 INHIBITION 15% CV event RRR**

LDL-C<70 mg/dl (1.8 mmol/L- **>80% of pts)**

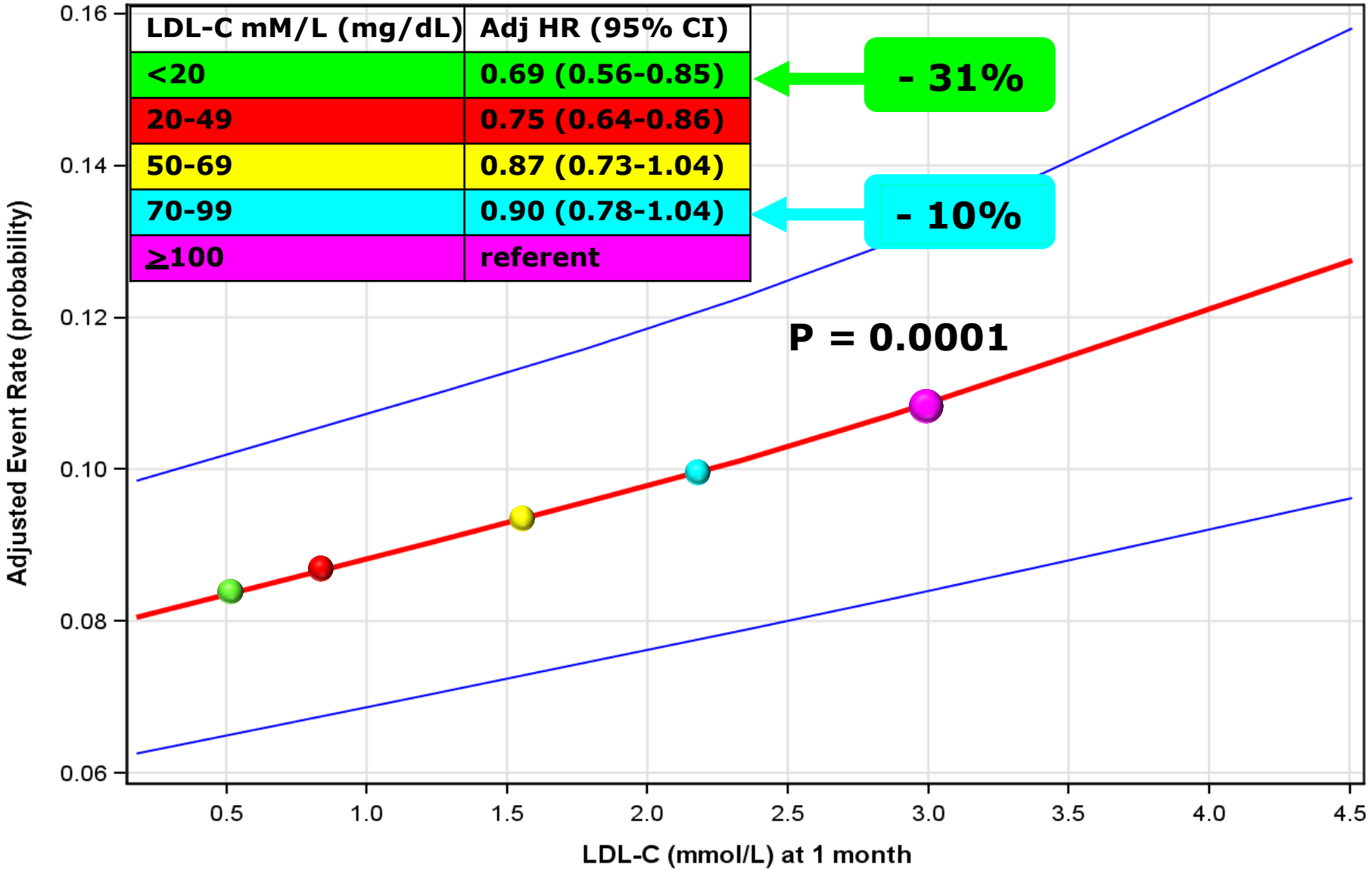
*Atorvastatin ≥40 mg/day; Rosuvastatin ≥20 mg/day

Pharmacological Treatment of Hypercholesterolemia

Recommendations	Class [a]	Level [b]	Ref [c]	
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A	62, 64, 68	→ **Choice #1 Statin high dose**
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C	239, 256, 257	
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B	63	→ **LDL-C NOT AT GOAL Statin-Ezetimibe ↓LDL-C by 20%**
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIb	C	115, 116	→ **PCSK9 INHIBITORS + Statin-Ezetimibe ↓LDL-C 55-70%**

European Heart Journal 2016 - doi:10.1093/eurheartj/ehv272

FOURIER: CV DEATH, MI, or STROKE



Giugliano RP et al. Lancet 2017;390;18;1962-1971

ATHEROGENIC DYSLIPIDEMIAS: Addressing Residual CV Risk

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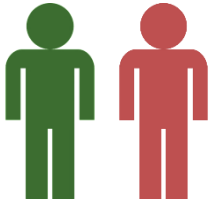
Patients With Diabetes Have Particularly High Residual CVD Risk After Statin Treatment

	Event Rate (No Diabetes)		Event Rate (Diabetes)	
	On Statin	On Placebo	On Statin	On Placebo
HPS[1]* (CHD patients)	19.8%	25.7%	**33.4%**	37.8%
CARE[2]†	19.4%	24.6%	**28.7%**	36.8%
LIPID[3]‡	11.7%	15.2%	**19.2%**	22.8%
PROSPER[4]§	13.1%	16.0%	**23.1%**	18.4%
ASCOT-LLA[5]‡	4.9%	8.7%	**9.6%**	11.4%
TNT[6]|	7.8%	9.7%	**13.8%**	17.9%

*CHD death, nonfatal MI, stroke, revascularizations
†CHD death, nonfatal MI, CABG, PTCA
‡CHD death and nonfatal MI
§CHD death, nonfatal MI, stroke
|CHD death, nonfatal MI, resuscitated cardiac arrest, stroke (80 mg versus 10mg atorvastatin)

[1]HPS Collaborative Group. *Lancet*. 2003;361:2005-2016.
[2]Sacks FM, et al. *N Engl J Med.* 1996;335:1001-1009.
[3]LIPID Study Group. *N Engl J Med.* 1998;339:1349-1357.
[4]Shepherd J, et al. *Lancet.* 2002;360:1623-1630.
[5]Sever PS, et al. *Lancet.* 2003;361:1149-1158.
[6]Shepherd J, et al. *Diabetes Care.* 2006;29:1220-1226.

ATHEROGENIC DYSLIPIDEMIAS: Addressing Residual CV Risk



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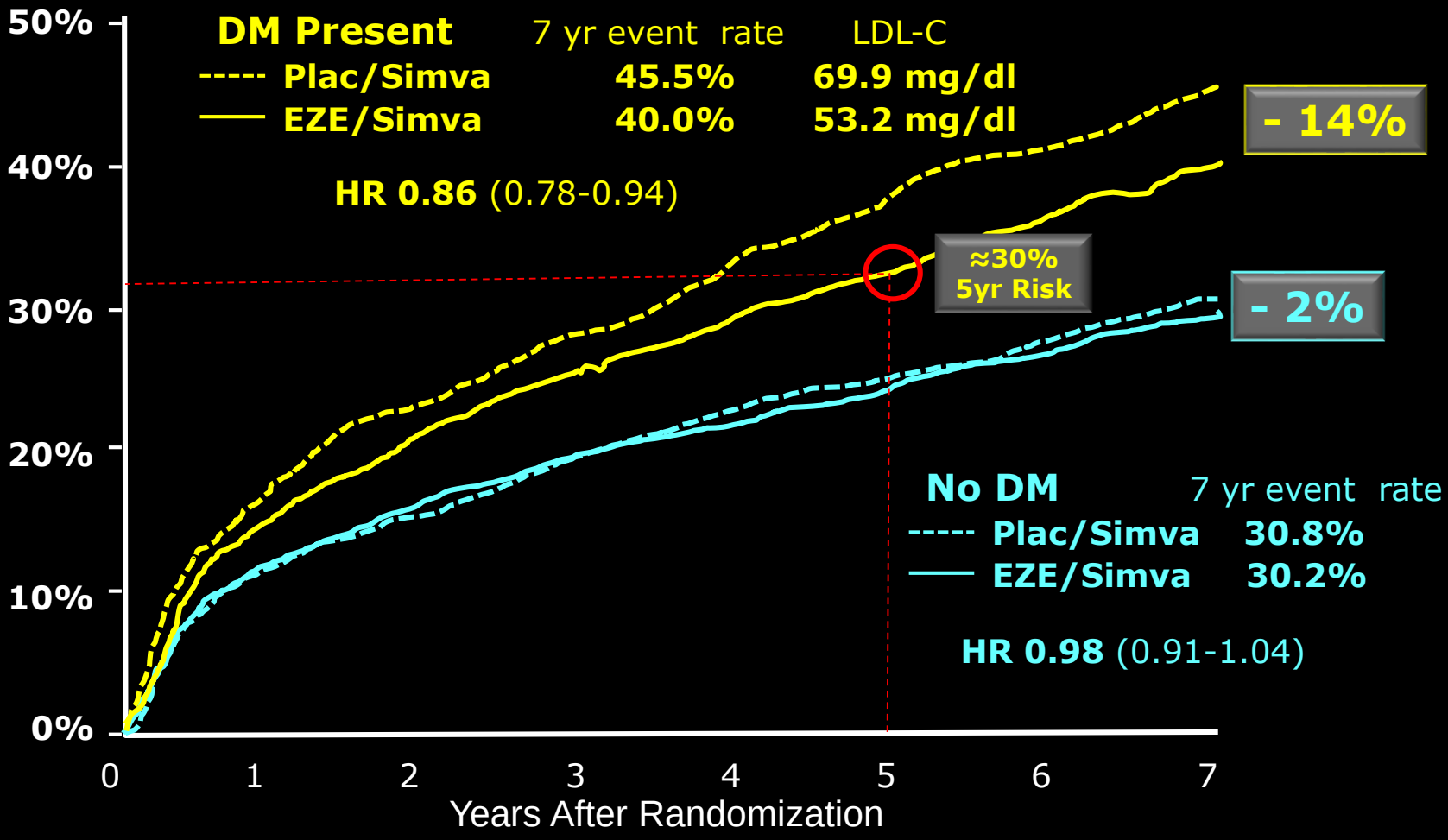
Option #1
Further LDL-C reduction

*Atorvastatin ≥40 mg/day; Rosuvastatin ≥20 mg/day; **Similar results from sub-groups, fibrate monotherapy, in HHS, BIP, VA-HIT, FIELD

IMPROVE-IT: Primary Endpoint

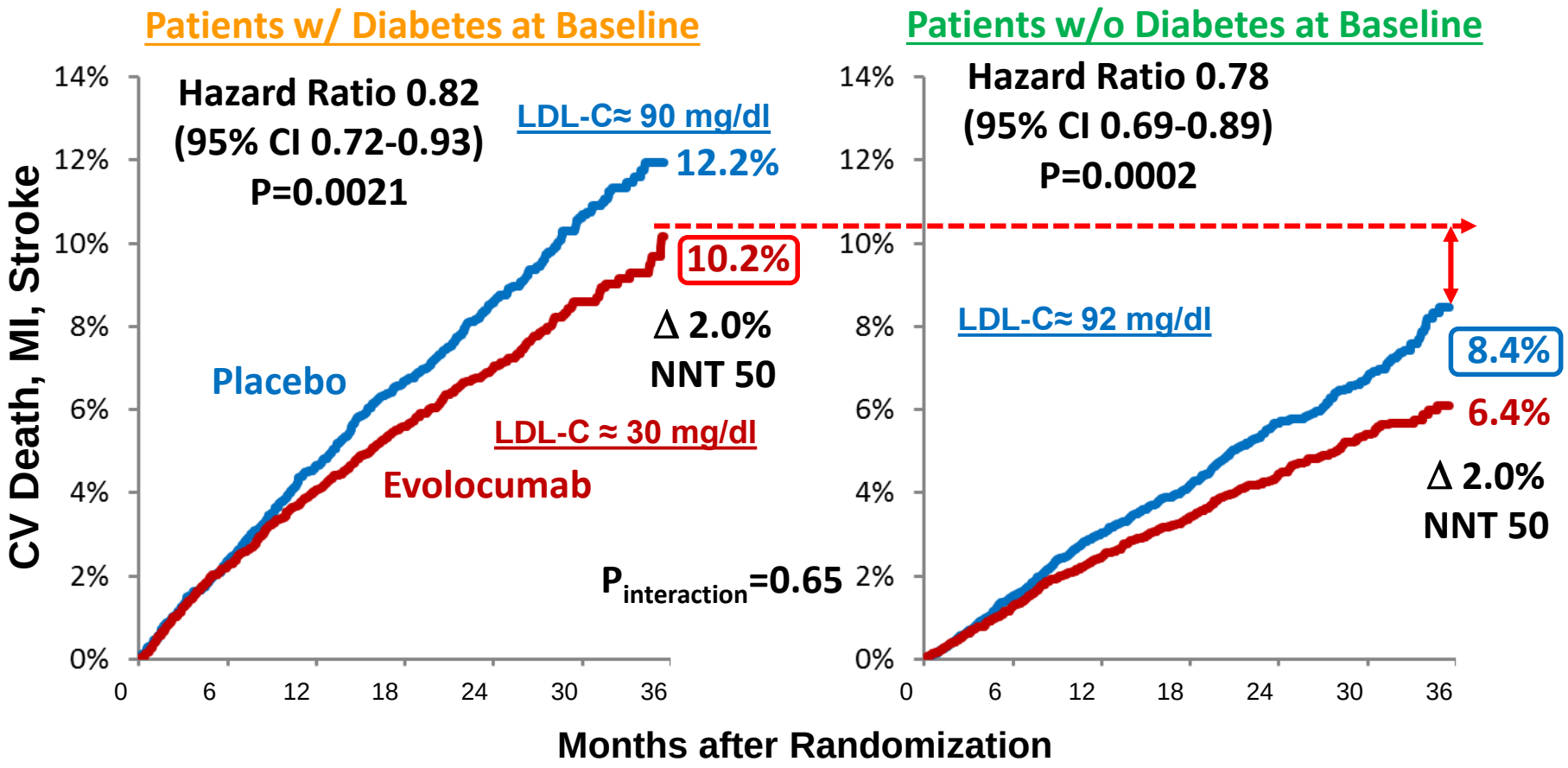
Diabetes YES vs Diabetes NO

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary rivascularization (≥30 days), stroke

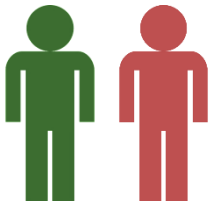


Giugliano RP et al Circulation, published online December 20, 2017

Effect of Evolocumab on Key Secondary Endpoint



ATHEROGENIC DYSLIPIDEMIAS: Addressing Residual CV Risk



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Option #1 Further LDL-C reduction

-14% (ezetimibe) to -18 % (PCSK9i)
Max CV event RRR
High Residual CV Risk

*Atorvastatin ≥40 mg/day; Rosuvastatin ≥20 mg/day; **Similar results from sub-groups, fibrate monotherapy, in HHS, BIP, VA-HIT, FIELD

ATHEROGENIC DYSLIPIDEMIAS: Addressing Residual CV Risk

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Option #2 Focus on Non HDL-C (TG-rich Lipoproteins)

LDL-C 69 mg/dl
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Non HDL-C 108 mg/dl -hsCRP 1,8 mg/l

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Lipid analyses as treatment targets

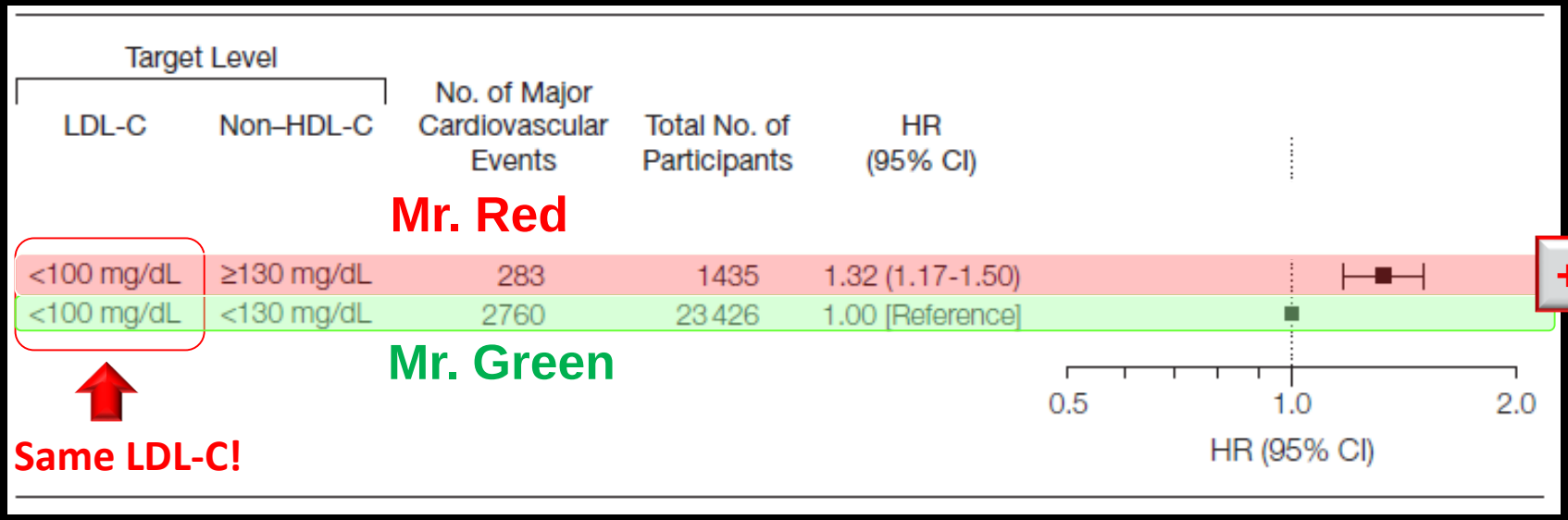
Recommendations	Class	Level
LDL-C is recommended as the primary target for treatment.	I	A
TC should be considered as a treatment target if other analyses are not available.	IIa	A
Non-HDL-C should be considered as a secondary treatment target.	IIa	B

Association of LDL-C, Non–HDL cholesterol, and Apo B with risk of cardiovascular events among patients treated with statins

A meta-analysis

62 154 patients enrolled in 8 trials published between 1994 and 2008

Risk of major cardiovascular events by LDL and non-HDL cholesterol categories



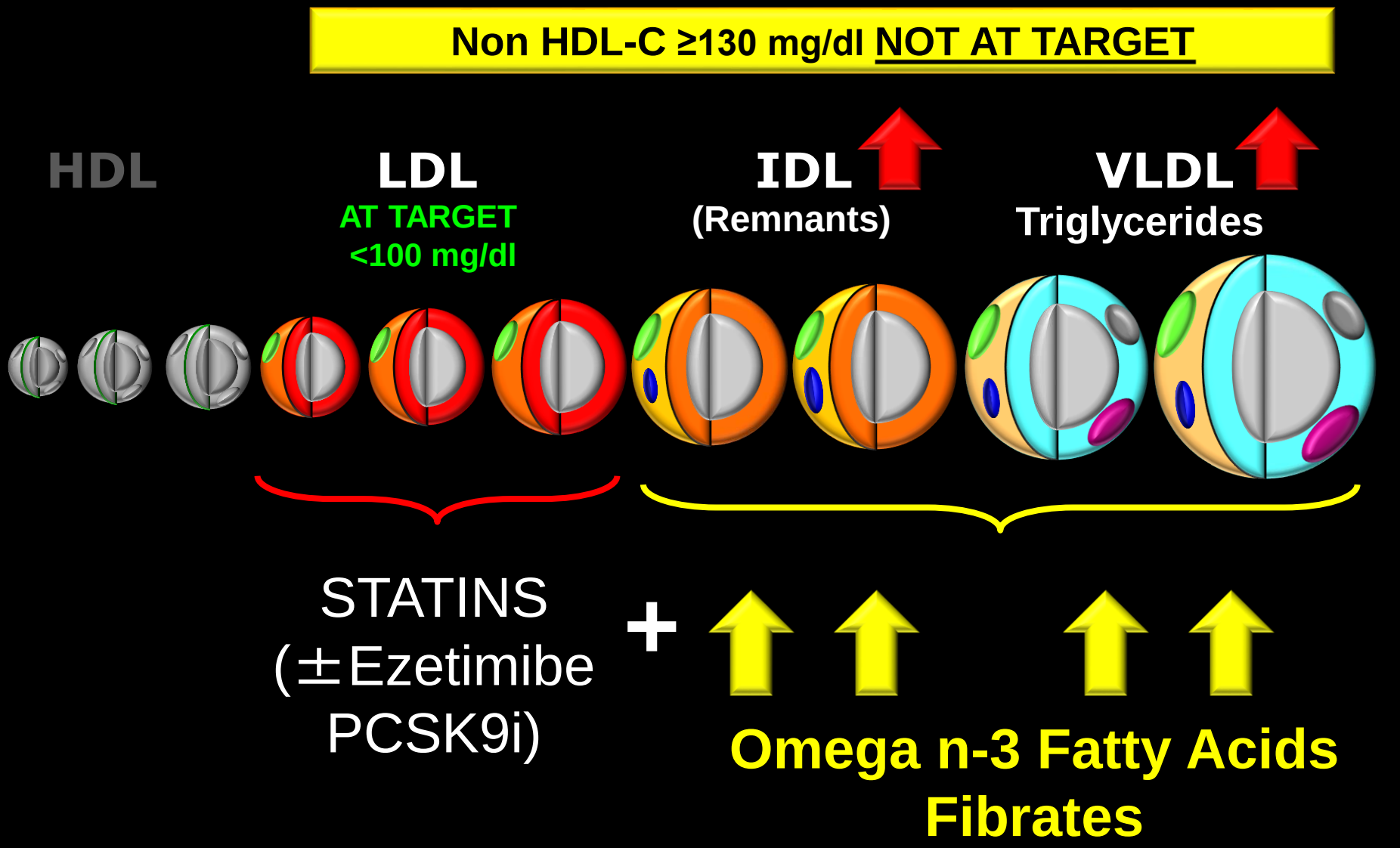
Data markers indicate hazard ratios (HRs) and 95% CIs for risk of major cardiovascular events. Results are shown for 4 categories of statin-treated patients based on whether or not they reached the LDL-c target of 100 mg/dL (2.6 mmol/L) and the non–HDL-C target of 130 mg/dL (3.4 mmol/L). HRs were adjusted for sex, age, smoking, diabetes, systolic blood pressure and trial

Boekholdt et al. JAMA 2012;307(12):1302–1309

Non-HDL Cholesterol

Mr. Red's Lipoprotein Profile

How to target Non-HDL Cholesterol



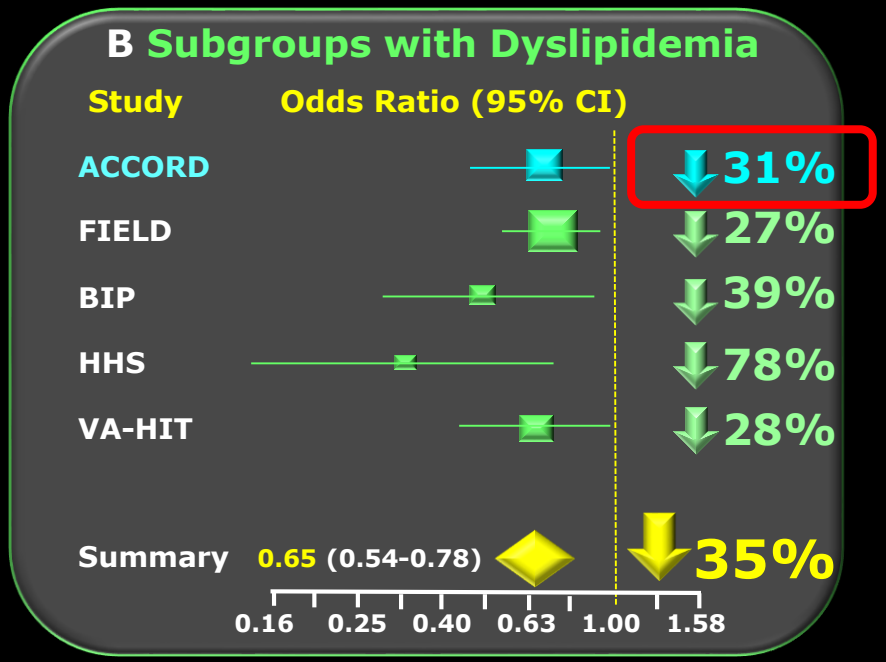
Pharmacological Therapy of Atherogenic Dyslipidemias

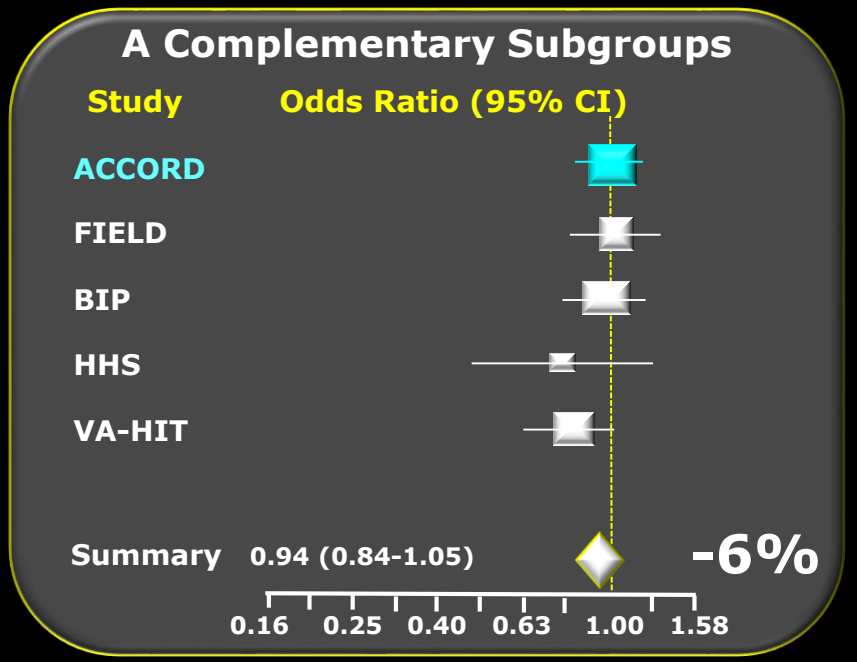
Class	Main Lipid Target	Outcome data on CVD events	Incident Diabetes	Other Adverse Events
Statins	**LDL-C**	**YES** (regardless of baseline lipid profile or clinical phenotype)	**YES**	Muscle-related intolerance 7-8% (Myalgia, Myopathy), Rabdomyolisis (extremely uncommon), elevation liver enzymes
Ezetimibe	**LDL-C**	**YES** (in combination with statin therapy, SHARP, IMPROVE-IT)	**NO**	Elevation liver enzymes, myalgia, myopathy (very rare)
PCSK9i Evolocumab Alirocumab	**LDL-C**	**YES** (FOURIER Evolocumab)	**NO**	No serious adverse events as monotherapy when combined with best available therapy
FIBRATES	**TG**	**SUBGROUPS** (low HDL-C- high TG) ACCORD, FIELD, VA-HIT, BIP, HHS)	**NO**	Gastrointestinal complaints most common Myopathy (Gemfibrozil), increased serum creatinine
Omega-n-3	**TG**	**YES** REDUCE-IT	**NO**	No major safety concerns Eructation, dyspepsia and disrupted ability to taste (dysgeusia) are most common

Chapman MJ et al for the EASociety Consensus Panel. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. Eur Heart J 2011; 32: 1345–1361 and Brunzell J. N Engl J Med 2007;357:1009-1017

Effect of fibrates in subgroups without (A) and with (B) dyslipidemia

A total of 2428 fibrate-treated subjects (302 events) and 2298 placebo-treated subjects (408 events) with dyslipidemia were included in the analysis





LIPID CRITERIA FOR DYSLIPIDEMIA

Trial	Triglycerides cut-off (mg/dL)	HDL cholesterol cut-off (mg/dL)
FIELD	≥204 (2.2 mmol/L)	<40 in men (1.0) ; <50 in women (1.3)
BIP	≥200	<35
Helsinki Heart Study	>204	<42
VA-HIT	>180	<40

Bruckert E et al J Cardiovasc PharmacolT 57:267, 2011

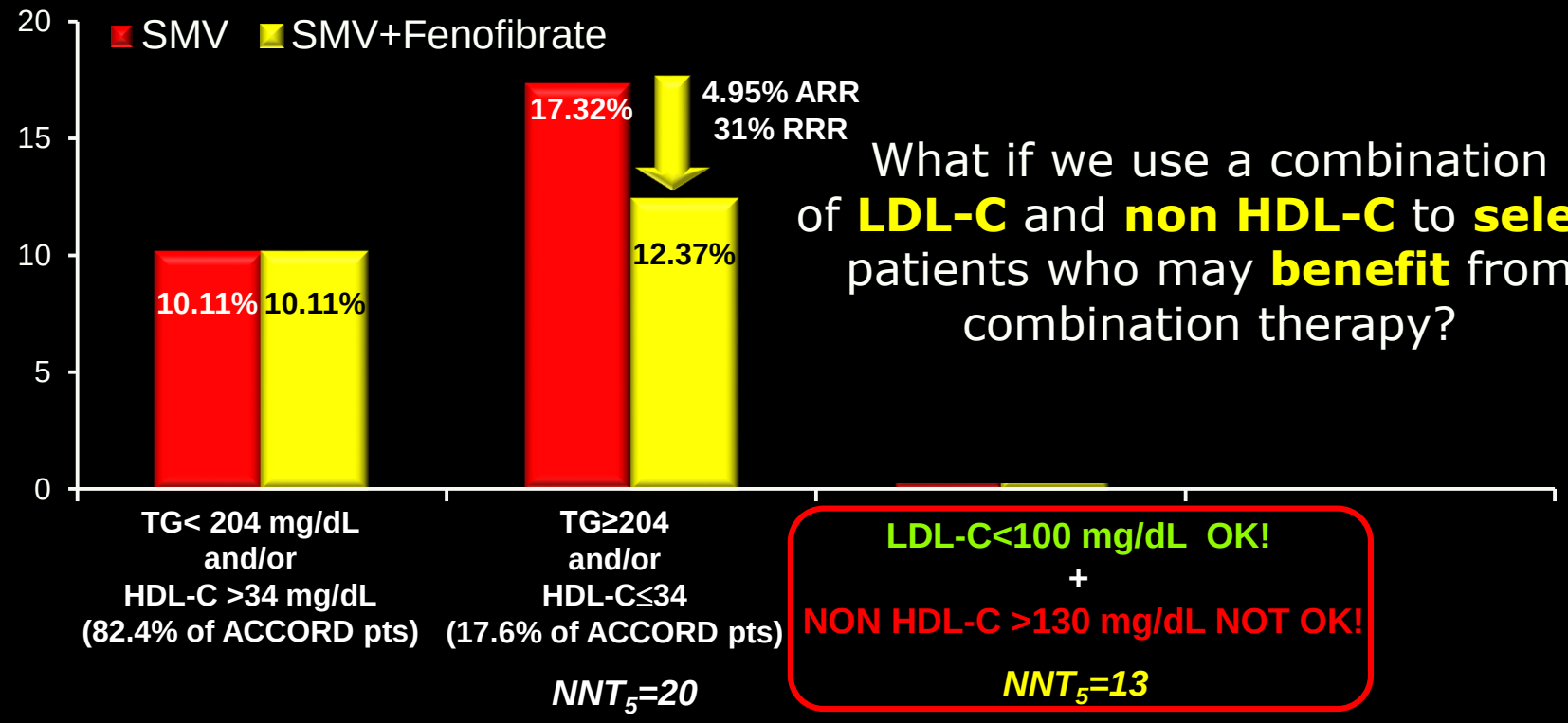
Lee M et al Atherosclerosis (2011), doi:10.1016/j.atherosclerosis

Sacks FM et al. N Engl J Med 2010

ACCORD

Optimizing Outcomes in Patients with Type 2 Diabetes

ACCORD-LIPID: Atherogenic dyslipidaemia ↑ 70% risk of major CV events



Major CV event (1º endpoint): CV death, nonfatal MI or nonfatal stroke

Modified form ACCORD Study Group. *N Engl J Med* **2010**; 362: 1563. FDA EMDAC Meeting 19 May 2011.

Overview: Significant reduction in TG and VLDL levels with omega-3 at 4 g daily dose

Study medications (daily dose)	Study duration	Triglycerides*	
		Placebo	Omega-3
Omega-3 at 4 g or placebo (Harris et al.)	16 weeks	↑15%	↓45%
Omega-3–statin combinations		Statin alone	Omega-3 + statin
Atorvastatin 40 mg + Omega-3 at 4 g or placebo (Chan et al.)	6 weeks	↓26%	↓40%
Simvastatin 10–40 mg + Omega-3 at 4 g or placebo (Durrington et al.)	24 weeks 48 weeks	↑3% –	↓24% ↓35%
Simvastatin 40 mg + Omega-3 at 4 g or placebo (Davidson et al.)	8 weeks	↓4%	↓28%

*Mean change from baseline

TG, triglycerides; VLDL, very low-density lipoproteins

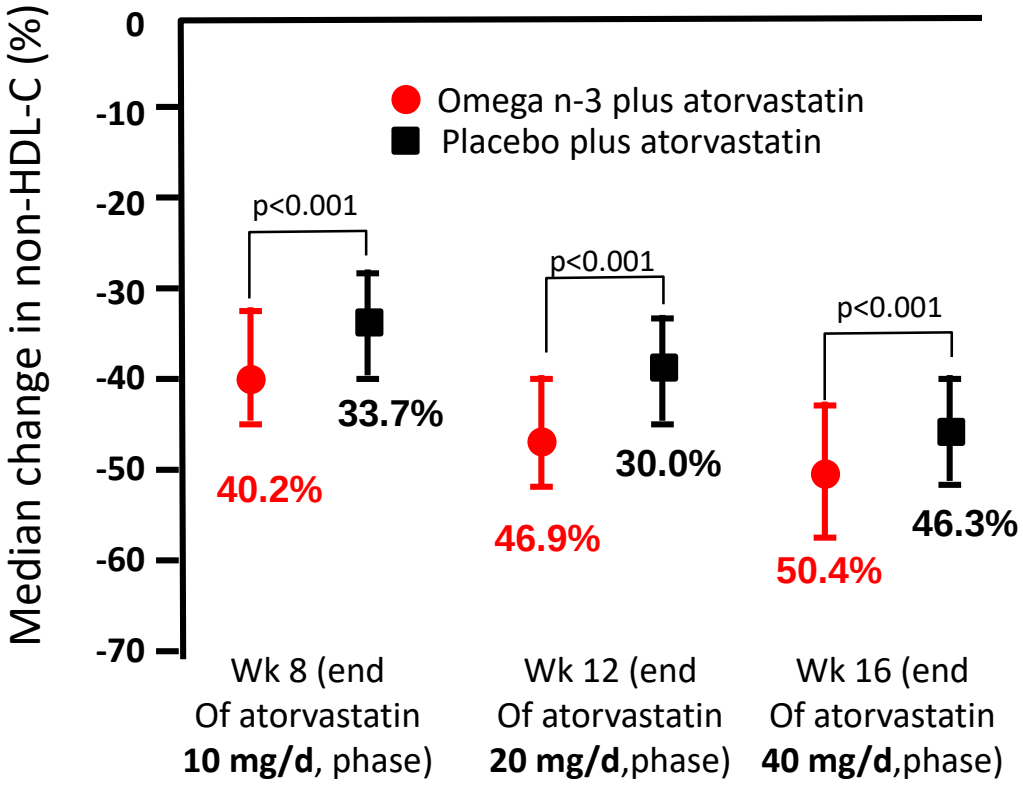
Harris WS, Ginsberg HN, Arunakul N, et al. Safety and efficacy of Omacor in severe hypertriglyceridemia. J Cardiovasc Risk 1997; 4: 385-391

Chan DC, Watts GF, Barrett PHR, et al. Regulatory effects of HMG CoA reductase inhibitor and fish oils on apolipoprotein B-100 kinetics in insulin-resistant obese male subjects with dyslipidemia. Diabetes 2002; 51: 2377-2386

Durrington PN, Bhatnagar D, Mackness MI, et al. An omega-3 polyunsaturated fatty acid concentrate administered for one year decreased triglycerides in simvastatin treated patients with coronary heart disease and persisting hypertriglyceridaemia. Heart 2001; 85: 544-548

Davidson MH, Stein EA, Bays HE, et al. COMBination of prescription Omega-3 with Simvastatin (COMBOS) Investigators. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther 2007; 29: 1354-1367

Effects of Prescription Omega-3-Acid Ethyl Esters on Non–High-Density Lipoprotein Cholesterol When Co-administered With Escalating Doses of Atorvastatin



Prescription omega-3-acid ethyl esters plus atorvastatin, 10, 20, and 40 mg/d, reduced median **non–HDL-C levels by 40.2% vs 33.7% (*P*<.001), 46.9% vs 39.0% (*P*<.001), and 50.4% vs 46.3% (*P*<.001)** compared with placebo plus the same doses of atorvastatin at the end of 8, 12, and 16 weeks, respectively

Bays HE et al. Mayo Clin Proc. 2010;85(2):122-128

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

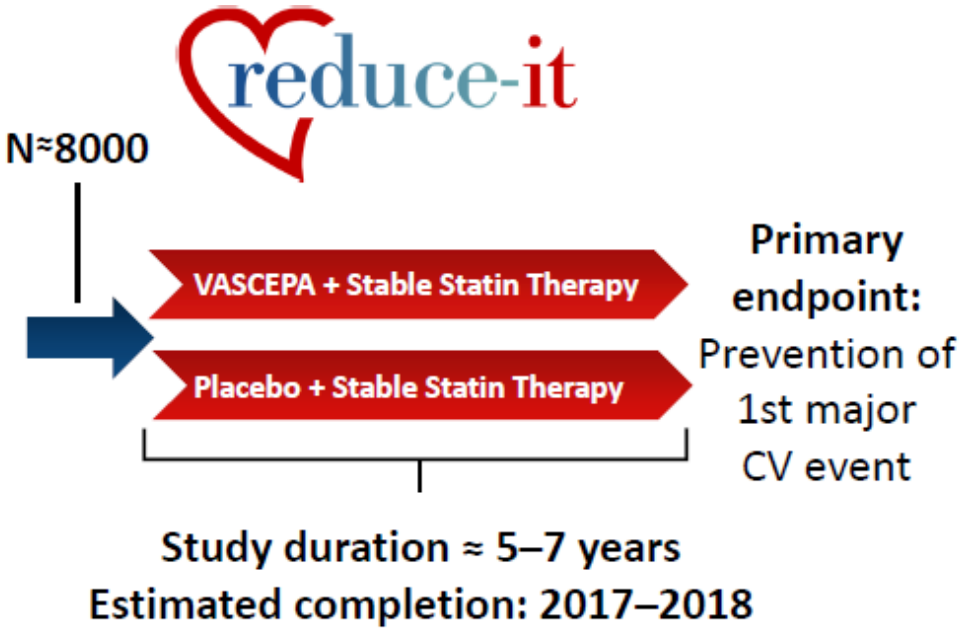
Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

Article available at https://www.nejm.org
Slides available for download at https://professional.heart.org
or at https://www.ACC.org

Reduction of CV Events with Icosapent Ethyl-Intervention Trial

- Men and women ≥45 years of age
- Established CHD or at high risk for CHD (diabetes + ≥1 risk factor)
- Atherogenic dyslipidemia
  - All patients required to be on stable statin therapy for at least 4 weeks
  - LDL-C >40 mg/dL and ≤100 mg/dL prior to randomization into the study
  - TG ≥200 to <500 mg/dL



- Randomized, double-blind, parallel-group design
- International trial; first patient enrolled: November 2011
- Other outcome measures: Incidence of additional CV events, lipid and lipoprotein levels, etc.
- Pre-defined subgroup analyses such as patients with diabetes
- Interim analysis planned for 967th event: Sept–Oct 2016; study expected to continue as planned

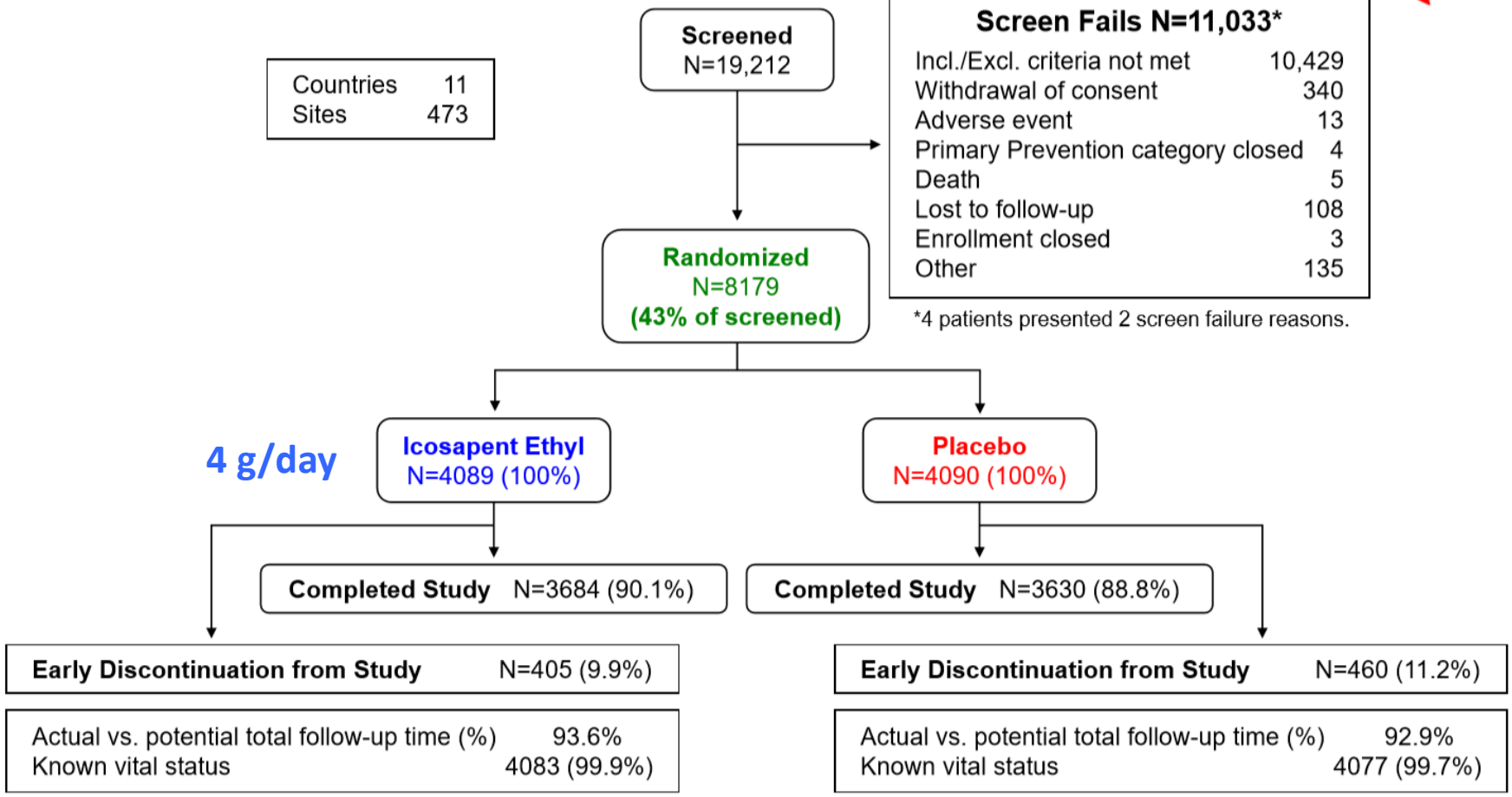
Primary Endpoint

Time from randomization to the first occurrence of composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina

VASCEPA: 96% pure ethyl aster of EPA

Bhatt DL, Ballantyne CM et al. Clinical Cardiology. 2017;**40:**138–148.

CONSORT Diagram



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

Median trial follow up duration was 4.9 years.

Key Baseline Characteristics

reduce-it

	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Age (years), Median (Q1-Q3)	64.0 (57.0 - 69.0)	64.0 (57.0 - 69.0)
Female, n (%)	1162 (28.4%)	1195 (29.2%)
Non-White, n (%)	398 (9.7%)	401 (9.8%)
Westernized Region, n (%)	2906 (71.1%)	2905 (71.0%)
CV Risk Category, n (%)		
Secondary Prevention Cohort	2892 (70.7%)	2893 (70.7%)
Primary Prevention Cohort	1197 (29.3%)	1197 (29.3%)
Ezetimibe Use, n (%)	262 (6.4%)	262 (6.4%)
Statin Intensity, n (%)		
Low	254 (6.2%)	267 (6.5%)
Moderate	2533 (61.9%)	2575 (63.0%)
High	1290 (31.5%)	1226 (30.0%)
Type 2 Diabetes, n (%)	2367 (57.9%)	2363 (57.8%)
Triglycerides (mg/dL), Median (Q1-Q3)	216.5 (176.5 - 272.0)	216.0 (175.5 - 274.0)
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (34.5 - 46.0)	40.0 (35.0 - 46.0)
LDL-C (mg/dL), Median (Q1-Q3)	74.0 (61.5 - 88.0)	76.0 (63.0 - 89.0)
Triglycerides Category		
<150 mg/dL	412 (10.1%)	429 (10.5%)
150 to <200 mg/dL	1193 (29.2%)	1191 (29.1%)
≥200 mg/dL	2481 (60.7%)	2469 (60.4%)

TG 216 mg/dl

LDL-C 74 mg/dl

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

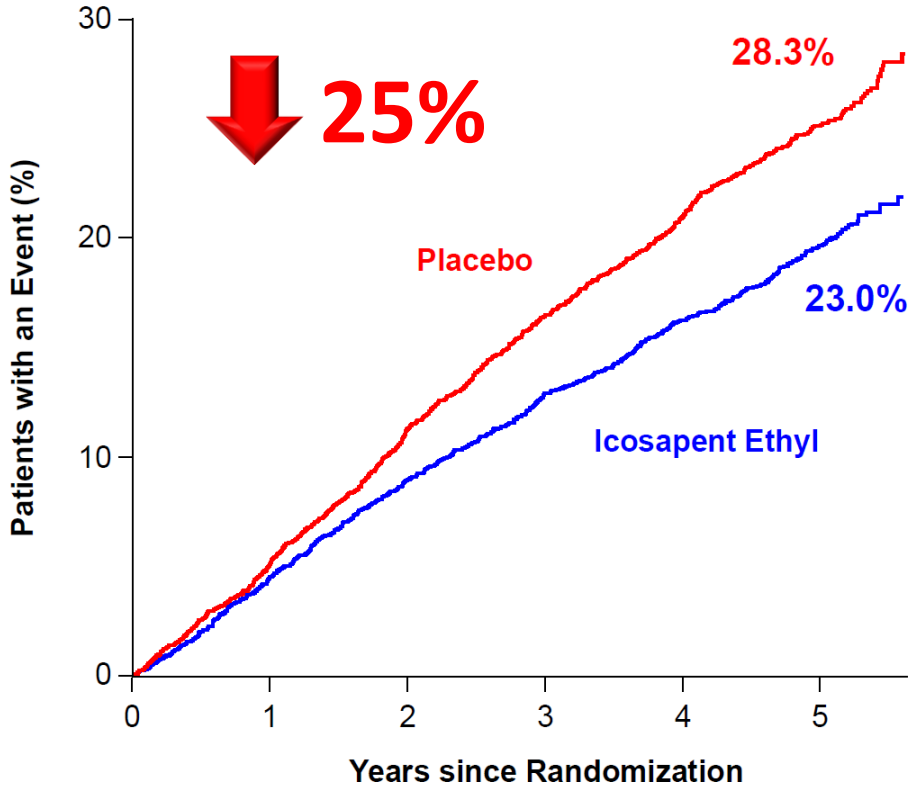
Effects on Biomarkers from Baseline to Year 1

	Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
Biomarker*	**Baseline**	**Year 1**	**Baseline**	**Year 1**	**Absolute Change from Baseline**	**% Change from Baseline**	**% Change P-value**
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	<0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	<0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	+358.8	<0.0001

*Apo B and hsCRP were measured at Year 2.

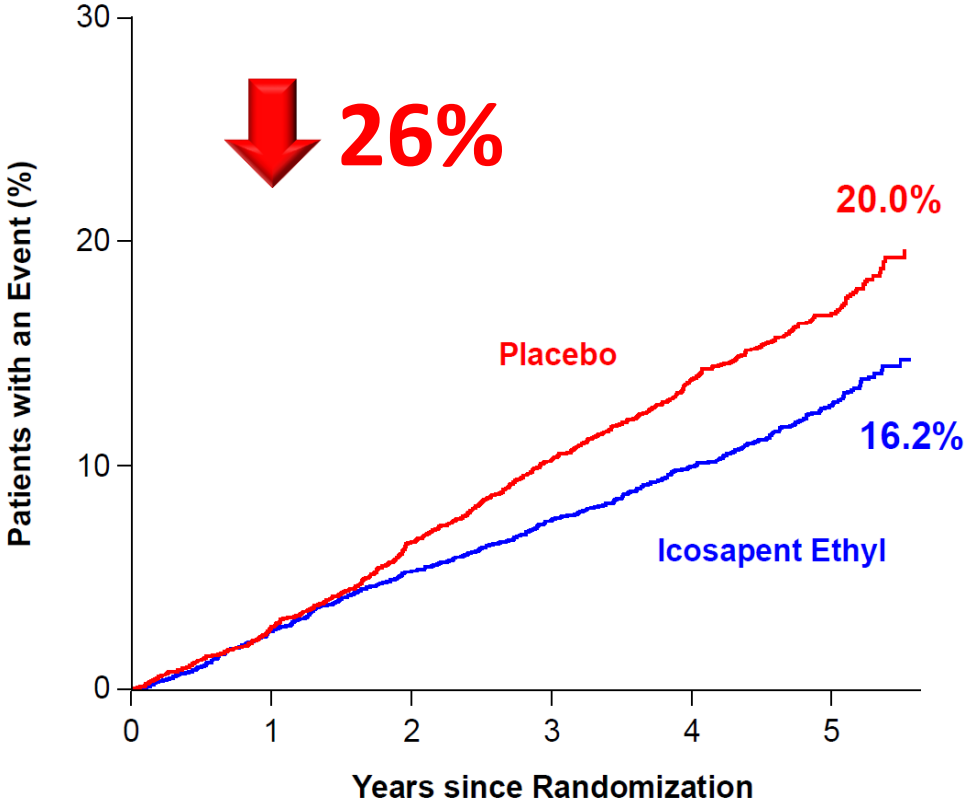
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Primary End Point:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



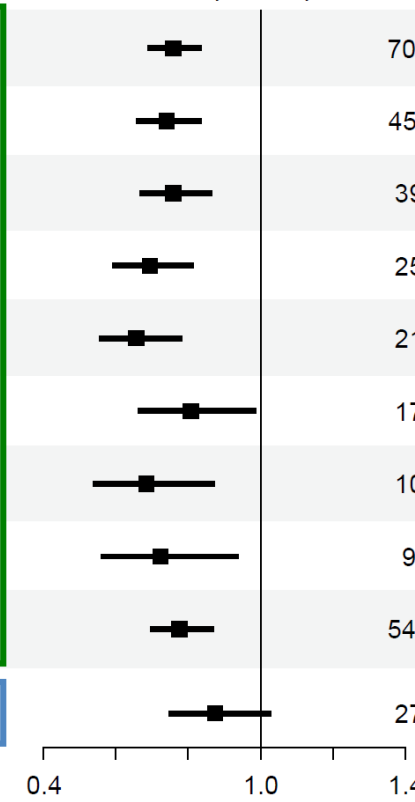
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.

Key Secondary End Point:
CV Death, MI, Stroke



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

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.

Treatment-Emergent Adverse Event of Interest: Serious Bleeding

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Bleeding related disorders	111 (2.7%)	85 (2.1%)	0.06
Gastrointestinal bleeding	62 (1.5%)	47 (1.1%)	0.15
Central nervous system bleeding	14 (0.3%)	10 (0.2%)	0.42
Other bleeding	41 (1.0%)	30 (0.7%)	0.19

- No fatal bleeding events in either group
- Adjudicated hemorrhagic stroke - no significant difference between treatments (13 icosapent ethyl versus 10 placebo; P=0.55)

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

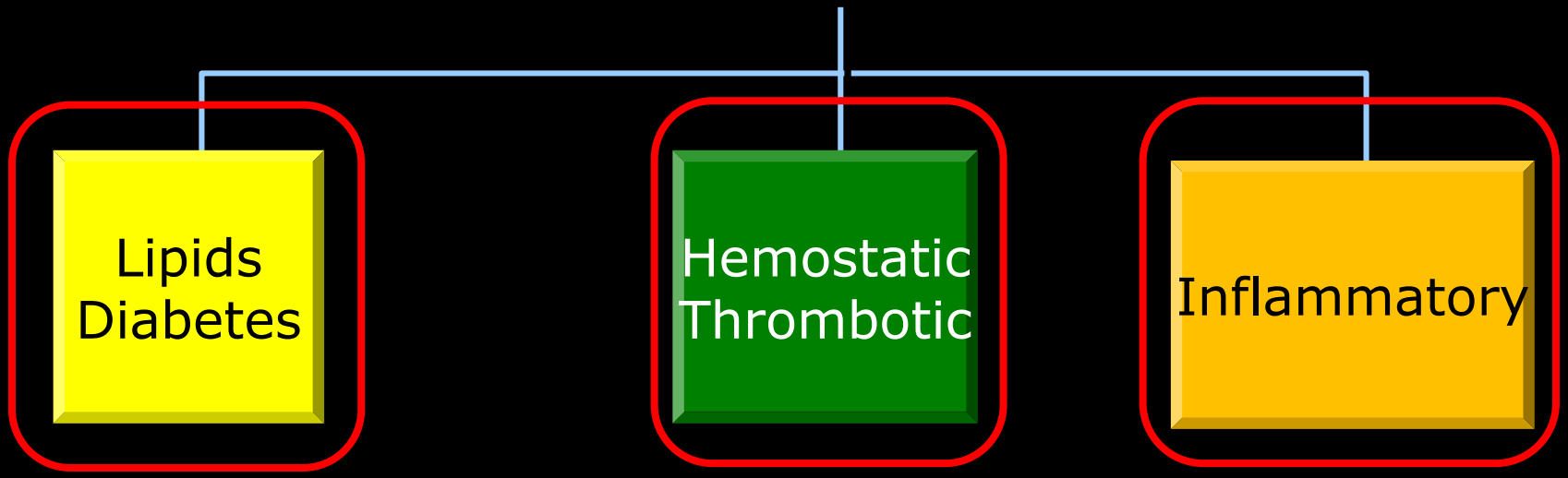
Most Frequent Treatment-Emergent Adverse Events: ≥5% in Either Treatment Group and Significantly Different

Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Diarrhea	367 (9.0%)	453 (11.1%)	0.002
Peripheral edema	267 (6.5%)	203 (5.0%)	0.002
Constipation	221 (5.4%)	149 (3.6%)	<0.001
Atrial fibrillation	215 (5.3%)	159 (3.9%)	0.003
Anemia	191 (4.7%)	236 (5.8%)	0.03

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

WHAT'S BEHIND THE CV BENEFITS in REDUCE-IT?

Reduction CV Death, MI and Stroke **by 24%**



- ↓ **TG 19.7% (45 mg/dl)**
- LDL-C 6.6% (5.0 mg/dl)
- ↓ Non HDL-C 13% (15.5 mg/dl)
- Apo B 9.7% (8.0 mg/dl)

Antithrombotic
Inhibition of Platelet Aggregation

Antinflammatory
- ↓ **hsCRP 40% (0.9 mg/L)**

ATHEROGENIC DYSLIPIDEMIAS: Addressing Residual CV Risk

Known CV Disease
LDL-C 160 mg/dl
TG 125 mg/dl;
HDL-C 45 mg/dl
hsCRP 4,5 mg/dl

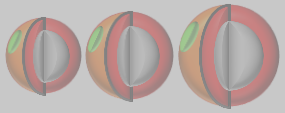
Mr. Green

Mr. Red

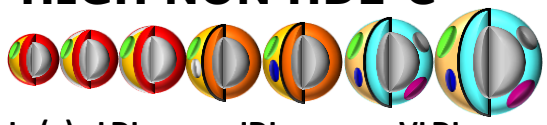
Known CV Disease, diabetes
Cholesterol 212 - LDL-C 128 mg/dl
HDL-C 42
TG 210 mg/dl
hsCRP 4,5 mg/L

High Intensity **Statin** Therapy*

HIGH LDL-C



HIGH NON HDL-C



Lp(a) LDL IDL VLDL

Mr. Green

«Residual LDL Cholesterol Risk»
LDL-C 110 mg/dl

Additional LDL-C Reduction

STATIN+ EZETIMIBE and STATIN+EZE+PCSK9 Inhibitors^

IMPROVE-IT: **EZETIMIBE 6% CV RRR**
FOURIER-ODYSSEY OUTCOMES
PCSK9 INHIBITION ≈15% CV RRR

#1 LDL-C

Mr. Red

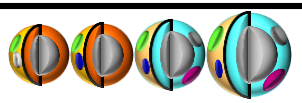
«Residual Non-HDL Cholesterol Risk»
✓ **LDL-C 69 mg/dl**
Non HDL-C 108 mg/dl

Additional LDL-C Reduction

STATIN+ EZETIMIBE
STATIN+EZE+PCSK9i

IMPROVE-IT: **EZE 6-14% CV RRR**
FOURIER-ODYSSEY OUTCOMES
PCSK9 INHIBITION 15-18% CV RRR
SIGNIFICANT CV Risk at LDL-C <30 mg/dl!!!

#2



IDL VLDL

↑ **TG Rich Lipoproteins**

Mr. Red

«Residual Non-HDL C Risk»
✓ LDL-C 69 mg/dl
✓ **Non HDL-C 108 mg/dl**

Target Non HDL-C Reduction (TG)

STATIN+ EPA (omega-3)
STATIN+FENOFIBRATE

REDUCE IT: STATIN-EPA: 25% CV RRR
FIBRATES:Sub-groups analysis pre-specified:
ACCORD: STATIN-FENOFIBRATE: ≈30% RRR

#3

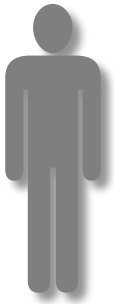
Mr. Red

«Residual Inflammatory Risk»
✓ LDL-C <70 mg/dl
✓ Non HDL-C<100
✓ **hsCRP 4,5 mg/L**

STATIN ± 2°LLD
+Canakinumab
or + Methotrexate?

CANTOS:
Statin**+ Canakinumab**
RRR 15%

PRECISION MEDICINE
The roadmap to Residual CV Risk (RR) Reduction



High CV Risk Patients

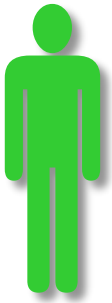
High Intensity Statin Therapy±Ezetimibe

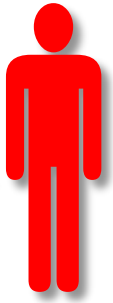
RESIDUAL CV RISK (RR)

LDL-C related RR

LDL-C not at goal
Normal TG

+ PCSK9 inhibitors ($$$$)





TG-Rich Lipoproteins Related RR
LDL-C at goal
Non HDL-C not at goal

+ EPA ($)
+Fenofibrate ($)

Inflammation related RR (selected patients*)

LDL-C and Non HDL-C at goal
BUT elevated hsPCR
+ Ac anti PCSK9 or EPA/Fenofibrate + antinflammatory agents (Canakinumab ?? Methotrexate?? ……)

* Rapidly progressive CVD, Recurrent ACS, Diabetes and CVD or PAD etc; $ Expensive