

2017 MID-ATLANTIC
CONFERENCE

7th *ANNUAL* CURRENT CONCEPTS IN
VASCULAR THERAPIES

2017



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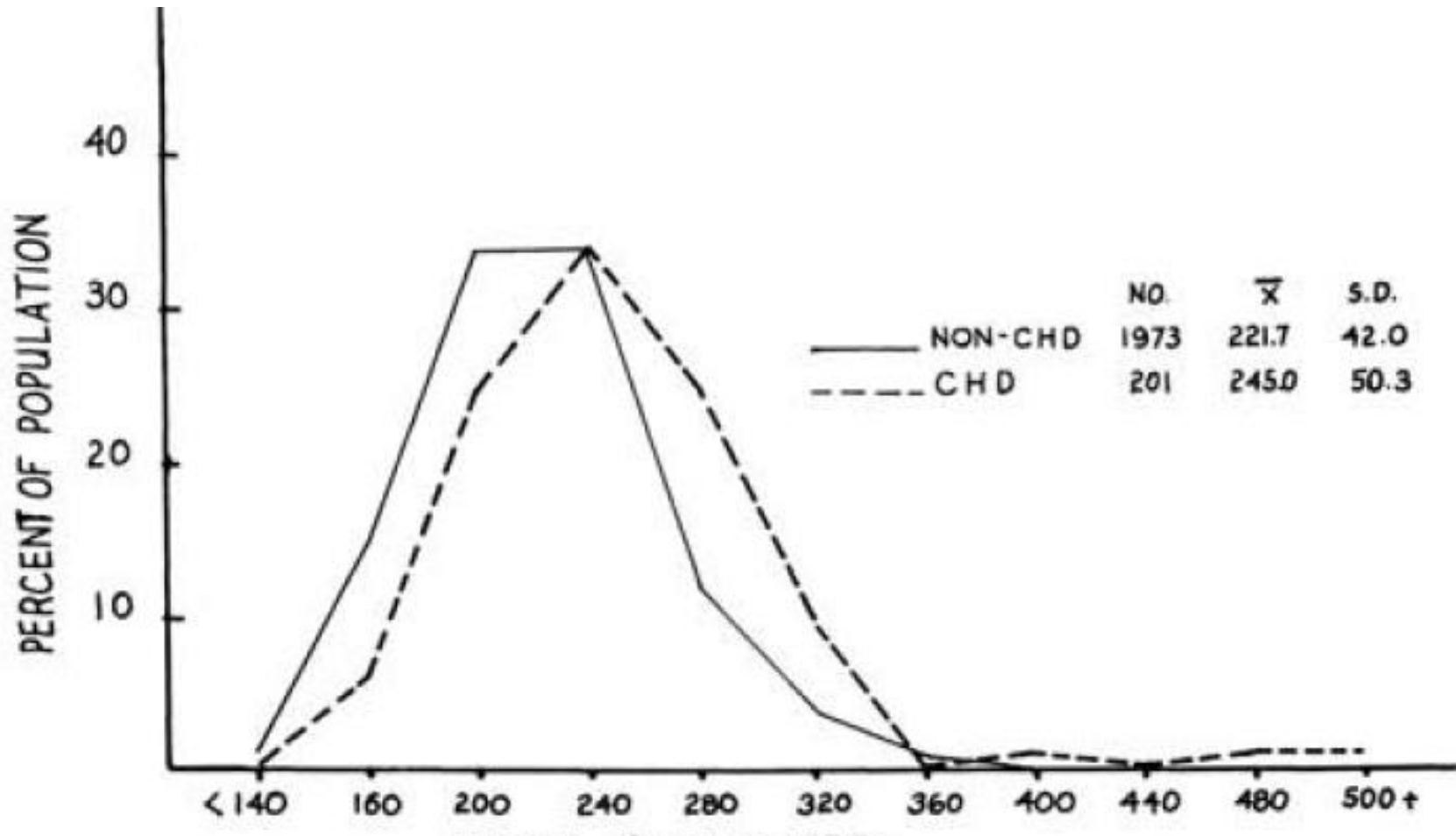
April 21.2017

All Vascular Patients Should Be on
High Dose Statin Therapy

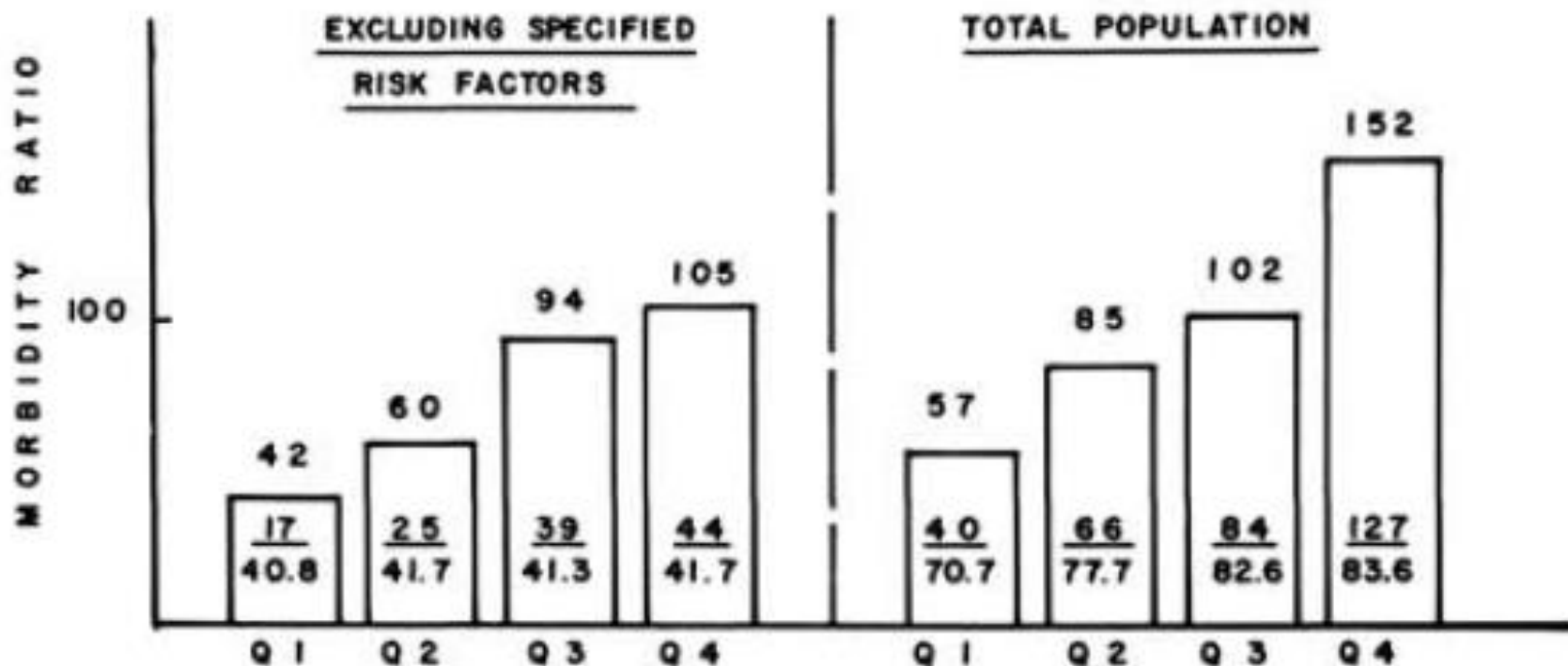
Disclosures

- None

Cholesterol and Coronary Artery Disease Framingham Study



Risk of CAD, Framingham

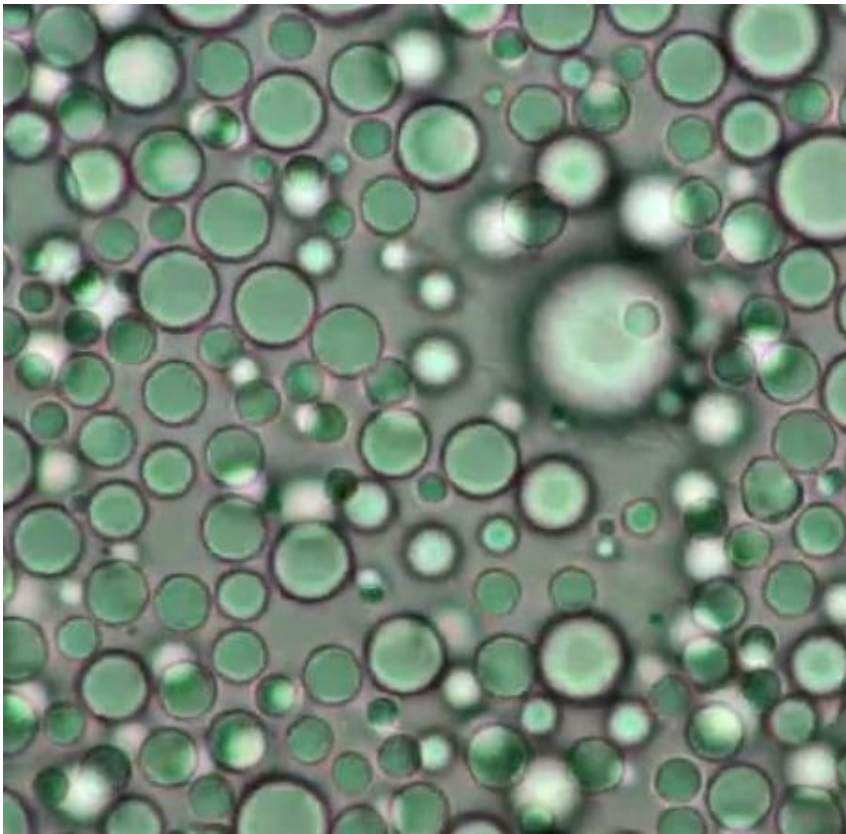


SERUM CHOLESTEROL CONCENTRATION - QUARTILES, INITIAL EXAMINATION

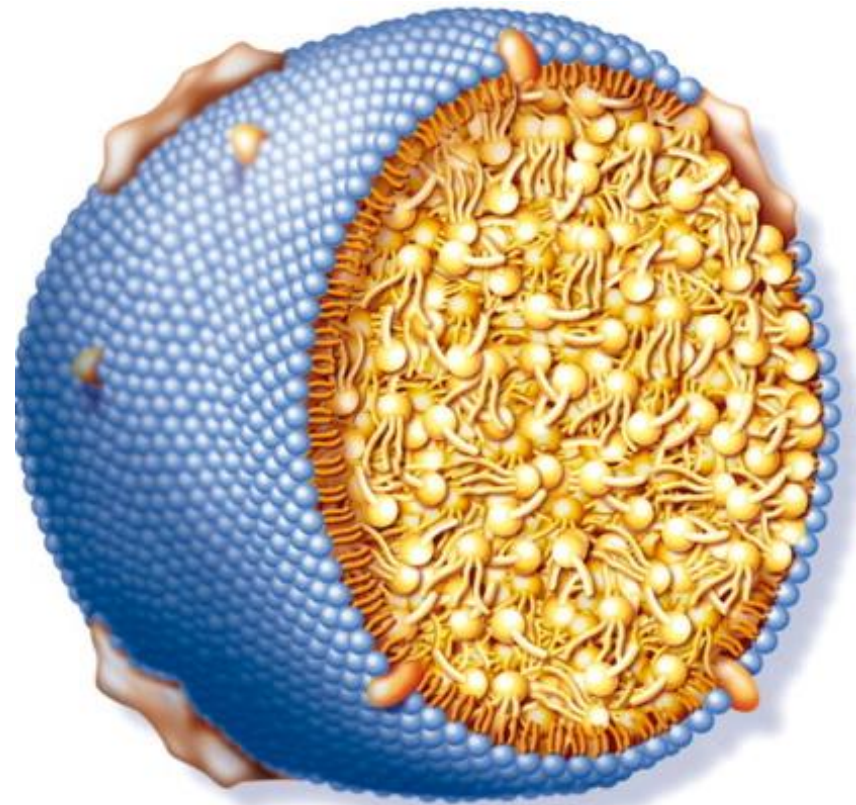
*OTHER RISK FACTORS EXCLUDED: - ECG ABNORMALITY, DIABETES, HIGH BLOOD PRESSURE, CIGARETTES > 1 PKG.
55 PERSONS WITH UNKNOWN ATTRIBUTES NOT INCLUDED

Cholesterol

Fat Globules

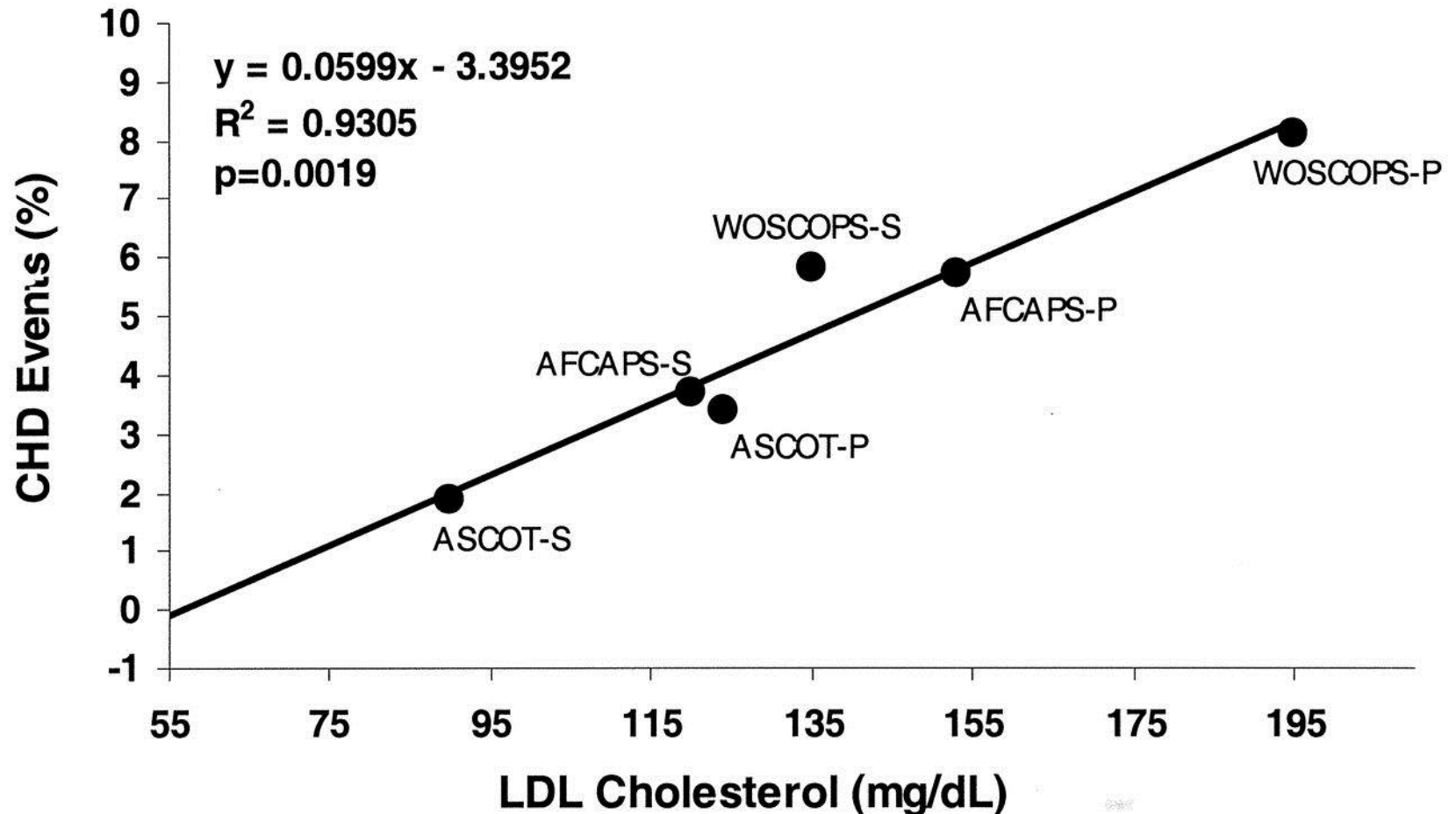


LDL



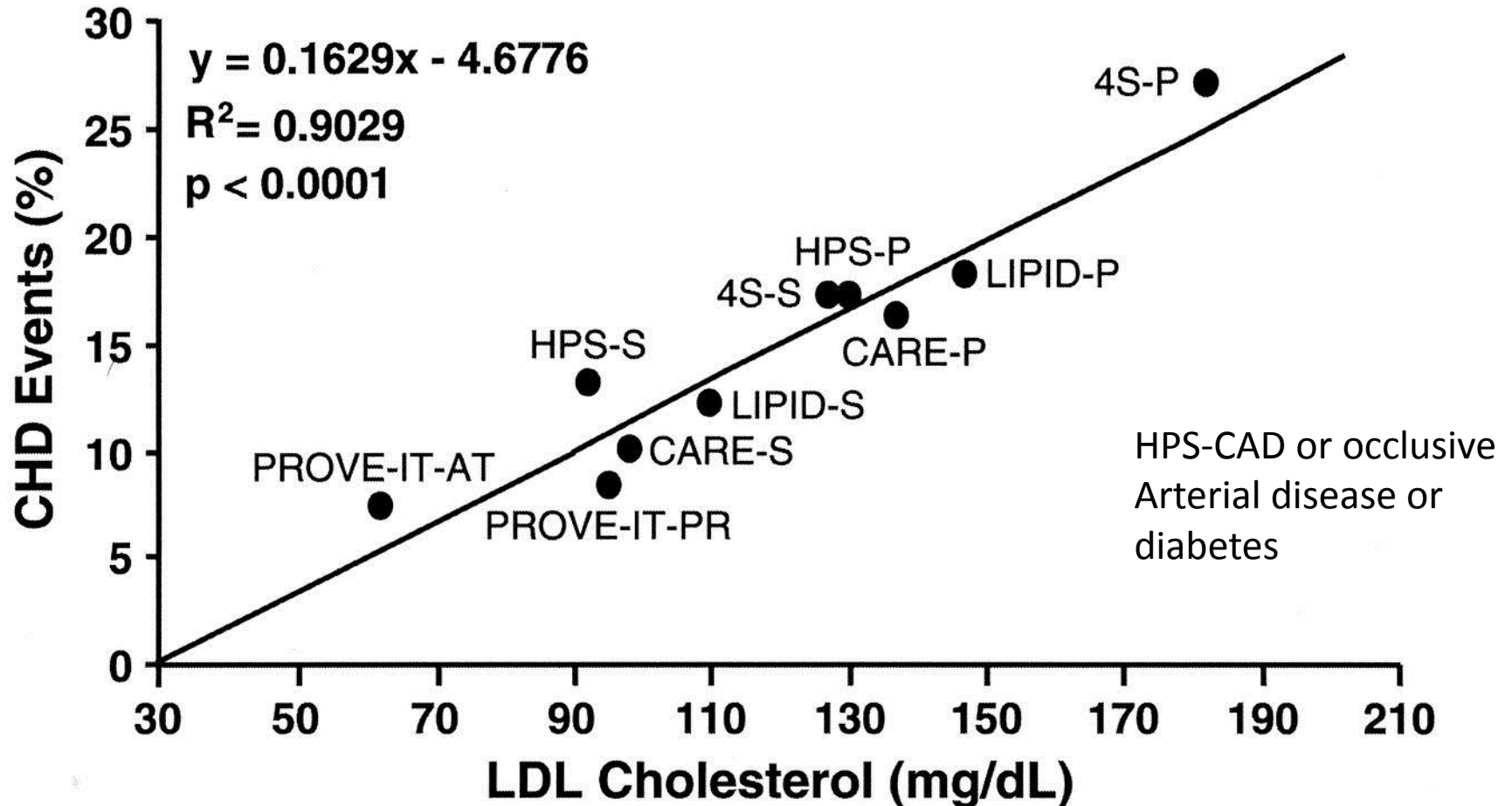
Phospholipid membrane (blue), cholesterol (yellow), apolipoproteins (beige).

Primary Prevention Trials



James H O'Keefe, Jr et al. JACC 2004;43:2142-2146

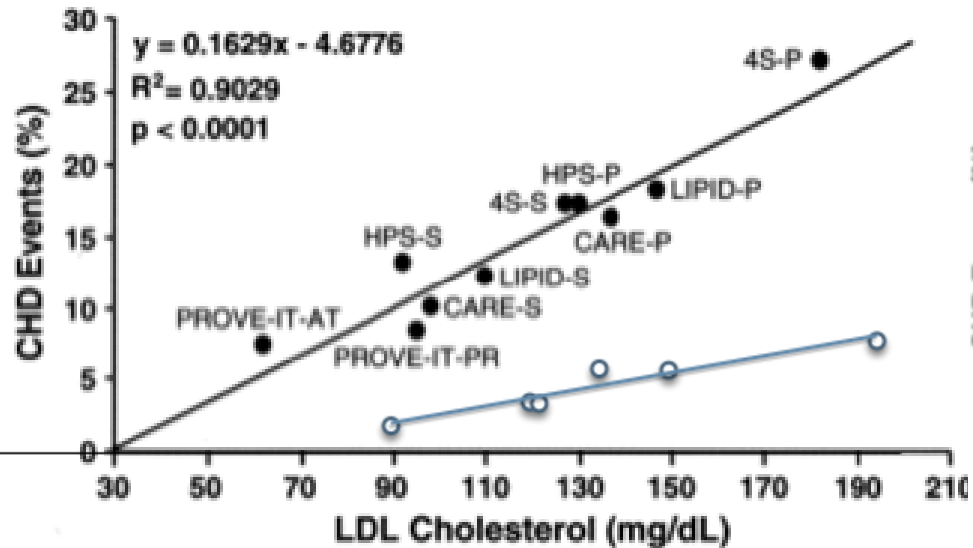
Secondary Prevention Trials



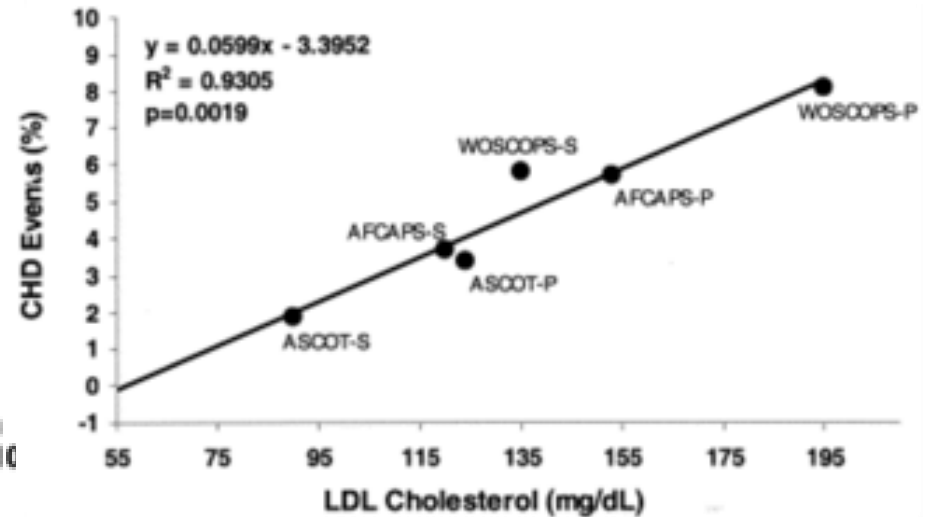
James H O'Keefe, Jr et al. JACC 2004;43:2142-2146

LDL and CHD Events

Secondary Prevention Trials



Primary Prevention Trials

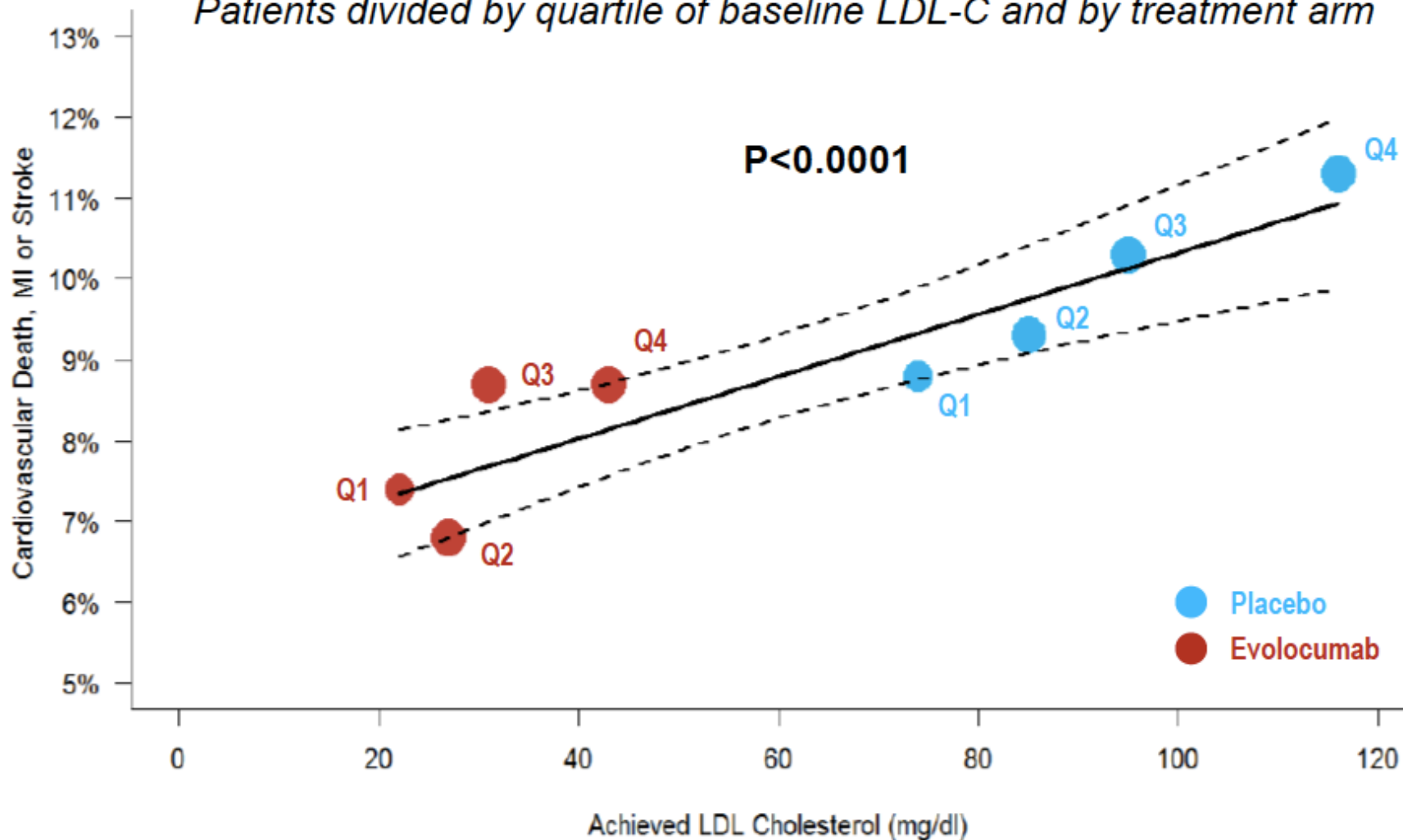




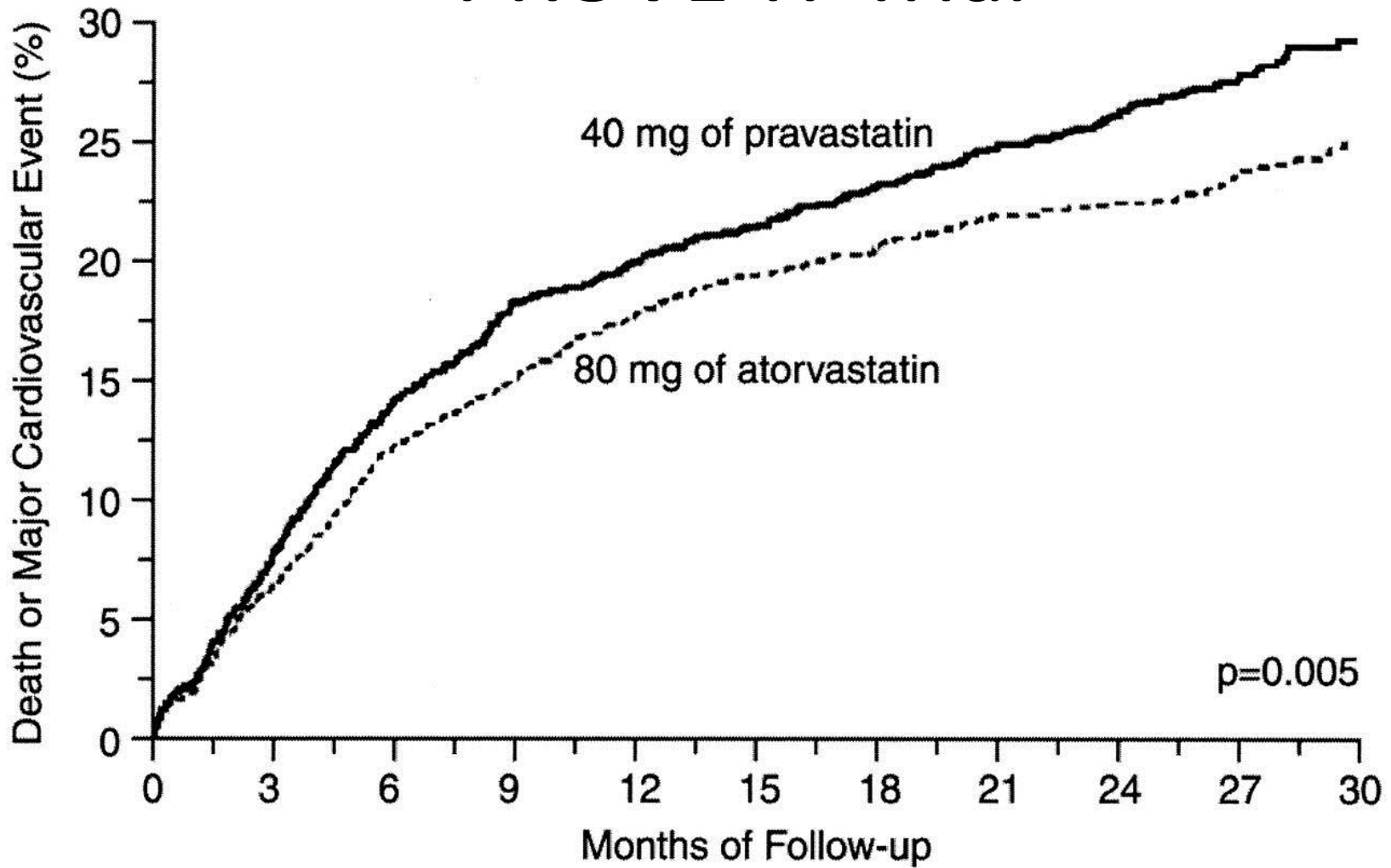
Lower LDL-C Is Better



Patients divided by quartile of baseline LDL-C and by treatment arm



PROVE-IT Trial



Cannon, et al. NEJM 2004: 350:1495-1505

LDL-C reduction (mmol/L)

Events (% per annum)

Unweighted RR (CI)

RR (CI) per 1 mmol/L reduction in LDL-C

Statin/more Control/less

More vs less statin

PROVE-IT	0.65	406 (11.3%)	458 (13.1%)
TNT	0.62	889 (4.0%)	1164 (5.4%)
IDEAL	0.55	938 (5.2%)	1106 (6.3%)
SEARCH	0.39	1347 (3.6%)	1406 (3.8%)
A to Z	0.30	257 (7.2%)	282 (8.1%)

Subtotal (5 trials)

0.51	3837/19829	4416/19783
	(4.5%)	(5.3%)

Statin vs control

SSSS	1.77	555 (5.4%)	796 (8.2%)
HPS	1.29	1511 (3.1%)	2043 (4.3%)
ALLIANCE	1.16	254 (5.4%)	293 (6.4%)
CARDS	1.14	81 (1.5%)	123 (2.4%)
JUPITER	1.09	105 (0.5%)	194 (1.0%)
ASCOT-LLA	1.07	217 (1.3%)	307 (1.9%)
Post-CABG	1.07	79 (3.0%)	100 (3.8%)
WOSCOPS	1.07	232 (1.5%)	318 (2.1%)
PROSPER	1.04	431 (4.9%)	495 (5.6%)
CARE	1.03	433 (4.8%)	553 (6.3%)
LIPID	1.03	936 (4.1%)	1153 (5.2%)
ASPEN	0.99	114 (2.7%)	136 (3.3%)
AURORA	0.99	362 (8.1%)	368 (8.3%)
AFCAPS/TexCAPS	0.94	143 (0.8%)	201 (1.2%)
LIPS	0.92	164 (6.9%)	195 (9.0%)
GISSI-HF	0.92	172 (2.2%)	174 (2.2%)
4D	0.89	144 (9.0%)	162 (10.1%)
ALERT	0.84	135 (2.7%)	140 (2.7%)
MEGA	0.67	102 (0.5%)	140 (0.7%)
ALLHAT-LLT	0.54	758 (3.3%)	812 (3.5%)
GISSI-P	0.35	208 (5.4%)	231 (6.1%)

Subtotal (21 trials)

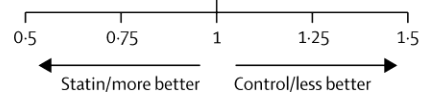
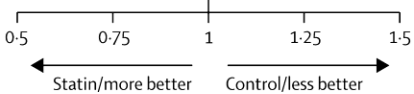
1.07	7136/64744	8934/64782
	(2.8%)	(3.6%)

Overall (26 trials)

10973/84573	13350/84565
(3.2%)	(4.0%)

Heterogeneity between statin vs control and more vs less:
 - before taking account of LDL differences: $\chi^2=10.7$ (p=0.001)
 - after taking account of LDL differences: $\chi^2=4.5$ (p=0.03)

■ 99% or
 ◇ 95% CI



Trend: $\chi^2=12.4$
(p=0.0004)

Trend: $\chi^2=3.7$
(p=0.05)

0.85 (0.82-0.89)
p<0.0001

0.72 (0.66-0.78)
p<0.0001

Trend: $\chi^2=32.3$
(p<0.0001)

Trend: $\chi^2=0.6$
(p=0.4)

0.78 (0.76-0.81)
p<0.0001

0.79 (0.77-0.81)
p<0.0001

0.78 (0.76-0.80)
p<0.0001

0.78 (0.76-0.80)
p<0.0001

Cholesterol Treatment Trialist Collaboration

The Lancet 2010 376, 1670-1681 DOI: (10.1016/S0140-6736(10)61350-5)

Historical Perspective on Prevention Guidelines

- 1977- First NIH Guidelines
 - National High Blood Pressure Education Program
 - Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7), published in 2003.
 - National Cholesterol Education Program
 - Expert Panel on Prevention, Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, (Adult Treatment Panel III), published in 2002, updated in 2004
- 2008 - NHLBI commissioned 5 guideline writing committees to rewrite prevention guidelines.
- 2011- IOM report on Guidelines
- 2013 - NHLBI announced that they will produce evidentiary reviews, but will rely on partnering organizations to produce guidelines.
- April, 2013 - NHLBI approached ACC/AHA (as well as ACP and AAFP)
- November, 2013 - ACC/AHA released 4 of 5 prevention guidelines

Revised ATP-III Goals, 2004

Risk category	LDL cholesterol goal	Initiate therapeutic lifestyle changes	Consider drug therapy
High risk: CHD or CHD risk equivalents (10-year risk >20%)	<100 mg/dL (with an optional goal of <70 mg/dL)	>100 mg/dL	>100 mg/dL (consider drug options if LDL-C <100 mg/dL)
Moderately high risk: two or more risk factors (10-year risk 10%-20%)	<130 mg/dL (with an optional goal of <100 mg/dL)	>130 mg/dL	>130 mg/dL (consider drug options if LDL-C 100-129 mg/dL)
Moderate risk: two or more risk factors (10-year risk <10%)	<130 mg/dL	>130 mg/dL	>160 mg/dL
Low risk: <1 risk factor	<160 mg/dL	>160 mg/dL	>190 mg/dL (consider drug options if LDL-C 160-189 mg/dL)

Cholesterol Guidelines Critical Questions

1. What is the evidence for LDL and non-HDL goals for secondary prevention?
2. What is the evidence for LDL and non-HDL goals for primary prevention?
3. What is the role for drugs in general and in specific sub-groups?

Cholesterol Guidelines

- No evidence for specific cholesterol targets. No recommendation for or against.
- Cholesterol is like an environmental exposure where there is a linear relationship between level and risk.
- Non-statin drugs have no proven benefit for ASCVD risk reduction.
- Statins are recommended based on overall ASCVD risk.

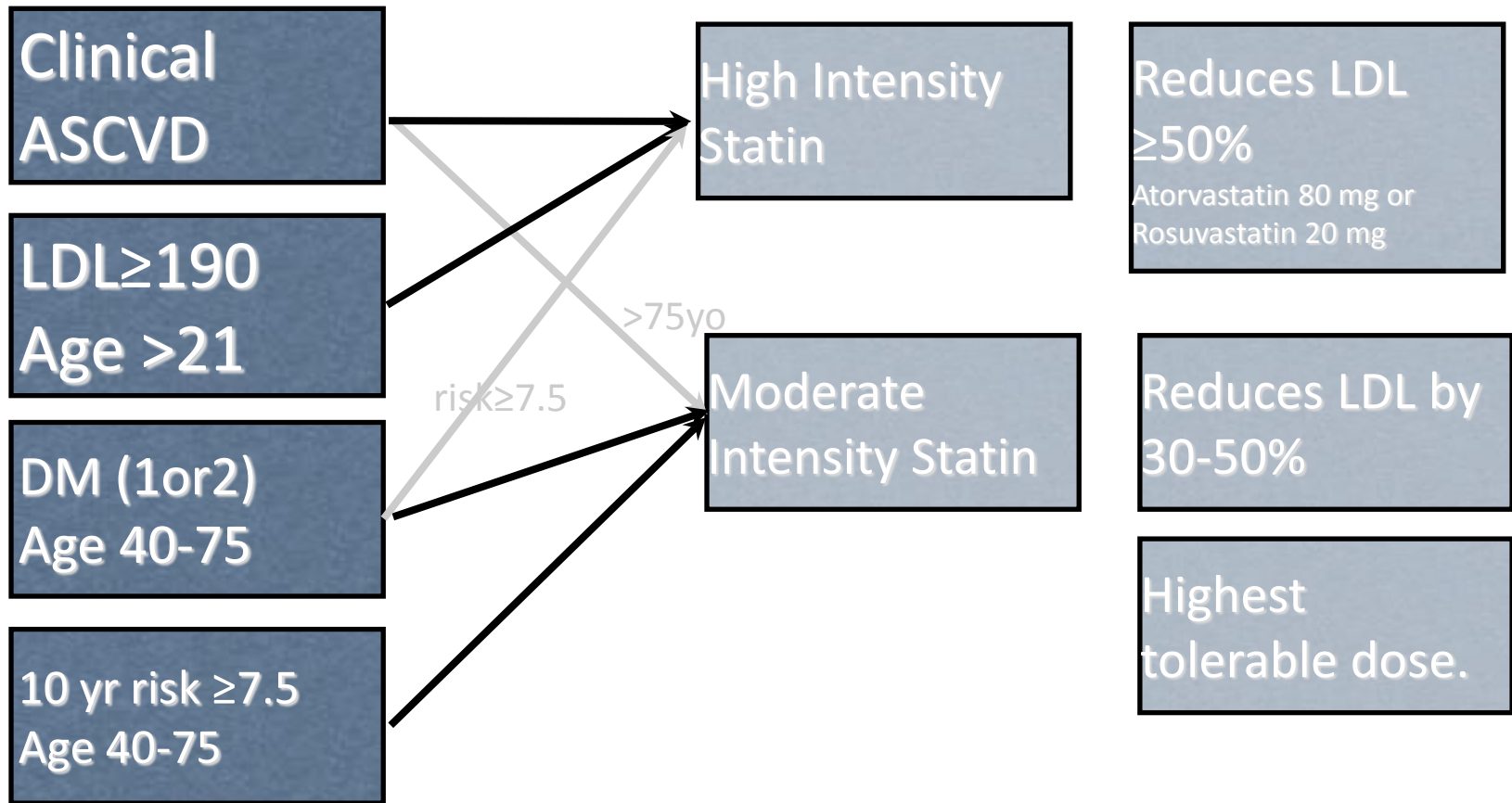
Cholesterol Guidelines

Treatment Groups

1. Secondary prevention for patients with clinical ASCVD*
2. Patients with Diabetes
3. Patients with $LDL \geq 190$
4. Patients with a calculated 10 risk of MI, CVA, or CV death of $\geq 7.5\%$

*Clinical ASCVD includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or **peripheral arterial disease presumed to be of atherosclerotic origin.**

Treatment Groups and Statin Dosing



Non-statins?

- Ezetimide
 - Enhance Trial - reduced LDL by 17%, yet no effect on CIMT in FH patients
 - ARBITER 6-HALTS Trial - Niacin versus ezetimide on CIMT, no effect.
 - CIMT is surrogate endpoint, ?lack of power?
 - IMPROVE-IT Trial - ezetimibe/simvastatin 10/40 mg compared with simvastatin 40 mg in 18,144 patients with ACS, over 7 years: 34.7% vs. 32.7% (CV death, MI, CVA, UA hosp, revas.)

Non-statins?

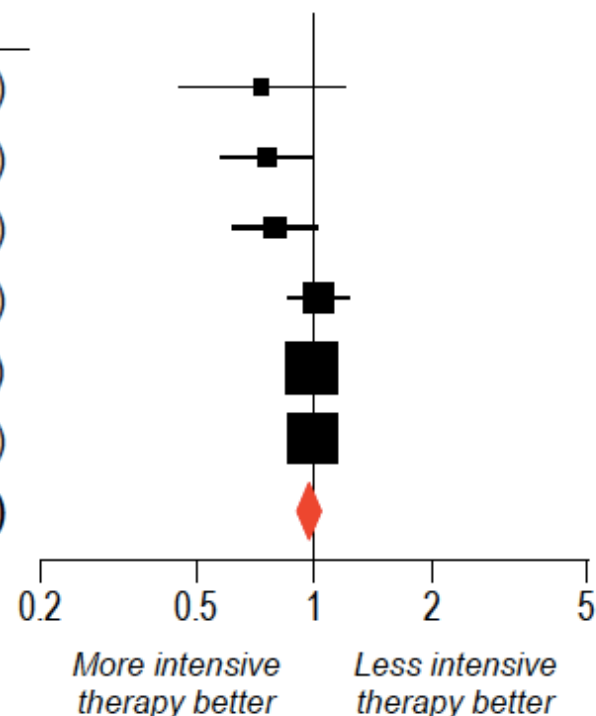
- Niacin - avoid if elevated transaminases, or cutaneous side-effects, or new-onset Afib or weight loss occurs. (AIM-HIGH Trial showed no benefit when added to statin in CAD pts)
- Fibrates - contraindicated if taking statins. Can be considered if severely elevated TG
- Omega - 3-fatty acids (several meta-analyses show no benefit for secondary prevention)
- Bile-acid Sequestrants - avoid if fasting TG ≥ 300 mg/dl
- PCSK9 Inhibitors-very effective, very expensive.



More Intensive LDL-C Lowering & CV Death

No clear benefit on CV mortality

Trial	Year	# of CV Deaths		HR (95% CI)
		More Intensive Rx Arm	Less Intensive Rx Arm	
PROVE-IT TIMI 22	2004	27	36	0.74 (0.45-1.22)
A2Z	2004	86	111	0.76 (0.57-1.01)
TNT	2005	101	127	0.80 (0.61-1.03)
IDEAL	2005	223	218	1.03 (0.85-1.24)
SEARCH	2010	565	572	0.99 (0.88-1.11)
IMPROVE-IT	2015	538	537	1.00 (0.89-1.13)
Summary		1540	1601	0.96 (0.90-1.03)



NEJM 2004;350:1495-504

JAMA 2004;292:1307-16

NEJM 2005;352:1425-35

JAMA 2005;294:2437-45

Lancet 2010;376:1658-69

NEJM 2015;372:2387-97



All Vascular Patients Should Be on High Dose Statin Therapy

- It's supported by 5 clinical trials.
- It's supported by the guidelines.
- It's well tolerated.
- It's affordable.
- It seems to make sense.

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