Cholesterol Summit
CCS Dyslipidemia Guidelines
- 2016 and beyond -

George Thanassoulis MD MSc FRCPC
Director, Preventive and Genomic Cardiology
McGill University Health Center

McGill

Centre universitaire de santé McGill
McGill University Health Centre

Disclosures

- **Research grants**: Ionis Pharma, Servier Canada, NIH, CIHR, HSFC
- **Industry relations**: Sanofi, Amgen, Ionis, Servier, Boehringer-Ingelheim

Disclosures

- **Research grants**: Ionis Pharma, Servier Canada, NIH, CIHR, HSFC
- **Industry relations**: Sanofi, Amgen, Ionis, Servier, Boehringer-Ingelheim

Learning Objectives

1. To provide an overview of the 2016 CCS dyslipidemia guidelines

2. To understand the utility of lipoprotein measurement in preventive care

3. To highlight the evidence that (1) earlier treatment may be better and (2) that lower LDL-C is better

Outline

- 2016 Dyslipidemia Guidelines – overview
- Primary prevention in 2019 – what's new
  - Earlier is better!
  - Risk modifiers -> apoB, Lp(a), CAC
- Secondary prevention
  - Lower is better!
- Future guidelines??
- Questions/Discussion

Canadian Journal of Cardiology 32 (2016) 1263–1282

Society Guidelines

2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult

Todd J. Anderson, MD,[a,*] Jean Grégoire, MD,[b,*] Glen J. Pearson, PharmD,[c,*] Arden R. Barry, PharmD,[d] Patrick Couture, MD,[e] Martin Dawes, MD,[f] Gordon A. Francis, MD,[g] Jacques Genest, Jr, MD,[h] Steven Grover, MD,[i] Milan Gupta, MD,[j,k] Robert A. Hegele, MD,[l] David C. Lau, MD, PhD,[m] Lawrence A. Leiter, MD,[k] Eva Lonn, MD,[n] G.B. John Mancini, MD,[f] Ruth McPherson, MD, PhD,[o] Daniel Ngui, MD,[f] Paul Poirier, MD, PhD,[p] John L. Sievenpiper, MD, PhD,[k] James A. Stone, MD, PhD,[a] George Thanassoulis, MD,[h] and Richard Ward, MD[q]

Who should I screen for dyslipidemia?

Which of the following is false:

(a) All men and women starting at 40 years of age

(b) Screening should start earlier in Native Canadians and inidividuals of South Asian descent

(c) Screening at any age with atherosclerosis

(d) Screening at any age with inflammatory conditions

(e) Screening is not required in women with prior pre-eclampsia

Who should I screen for dyslipidemia?

Which of the following is false:

(a) All men and women starting at 40 years of age

(b) Screening should start earlier in Native Canadians and inidividuals of South Asian descent

(c) Screening at any age with atherosclerosis

(d) Screening at any age with inflammatory conditions

(e) Screening is not required in women with prior pre-eclampsia

Who should I screen?

WHO TO SCREEN

Men ≥40 years of age; women ≥40 years of age (or postmenopausal)

Consider earlier in ethnic groups at increased risk such as South Asian or First Nations individuals

All patients with the following conditions regardless of age:

- Clinical evidence of atherosclerosis
- Abdominal aortic aneurysm
- Diabetes
- Arterial hypertension
- Current cigarette smoking
- Stigmata of dyslipidemia (arcus cornea, xanthelasma or xanthoma)
- Family history of premature CVD*
- Family history of dyslipidemia
- Chronic kidney disease
- Obesity (BMI ≥30 kg/m^2)
- Inflammatory bowel disease
- HIV infection
- Erectile dysfuntion
- Chronic obstructive pulmonary disease
- Hypertensive diseases of pregnancy

What tests do I need?

When performing a CV risk assessment what are the standard tests required?

(a) Fasting Standard lipid panel (± apoB)

(b) Glucose

(c) eGFR (± urine albumin/Cr ratio)

(d) All of the above

(e) None of the above

What tests do I need?

When performing a CV risk assessment what are the standard tests required?

(a) Fasting Standard lipid panel (± apoB)

(b) Glucose

(c) eGFR (± urine albumin/Cr ratio)

(d) All of the above

(e) None of the above

How to screen?

HOW TO SCREEN

For all:

- History and physical examination
- Standard lipid panel (TC, LDL-C, HDL-C, TG)
- Non-HDL-C (will be calculated from profile)
- Glucose
- eGFR

Optional:

- ApoB
- Urine albumin:creatinine ratio
  (if eGFR <60 mL/min/1.73m^2, hypertension or diabetes)

NON-FASTING LIPID TESTING IS ACCEPTABLE

Who requires treatment?

In which of the following patients is statin treatment generally recommended?

(a) 47 M with prior MI

(b) 54 M with incidental abdominal aorta measuring 3.2 cm

(c) 62 F with diabetes

(d) 52 F with moderate chronic kidney disease (eGFR < 60 ml/min/1.73 m^2

(e) 28 F with LDL-C 6.1 mmol/L and 2 first degree relatives with premature MI

(f) All of the above

Who requires treatment?

In which of the following patients is statin treatment generally recommended:

(a) 47 M with prior MI

(b) 54 M with incidental abdominal aorta measuring 3.2 cm

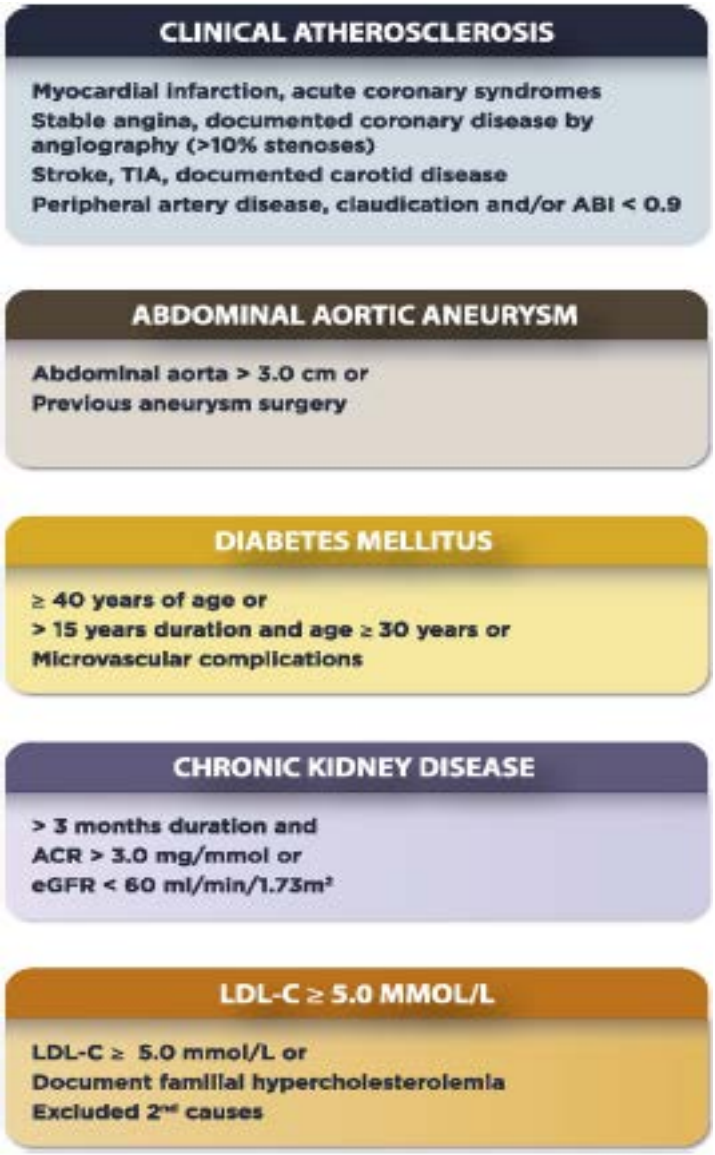
(c) 62 F with diabetes

(d) 52 F with moderate chronic kidney disease (eGFR < 60 ml/min/1.73 m^2

(e) 28 F with LDL-C 6.1 mmol/L and 2 first degree relatives with premature MI

(f) All of the above

Statin-indicated conditions



What LDL-C should I aim for?

Adequacy of statin therapy is determined by:

(a) LDL-C < 2.0 mmol/L

(b) apoB < 0.8 mg/L

(c) Non-HDL-C < 2.6 mmol/L

(d) LDL-C decrease by > 50%

(e) Any of the above

What LDL-C should I aim for?

Adequacy of statin therapy is determined by:

(a) LDL-C < 2.0 mmol/L

(b) apoB < 0.8 mg/L

(c) Non-HDL-C < 2.6 mmol/L

(d) LDL-C decrease by > 50%

(e) Any of the above

Treatment targets

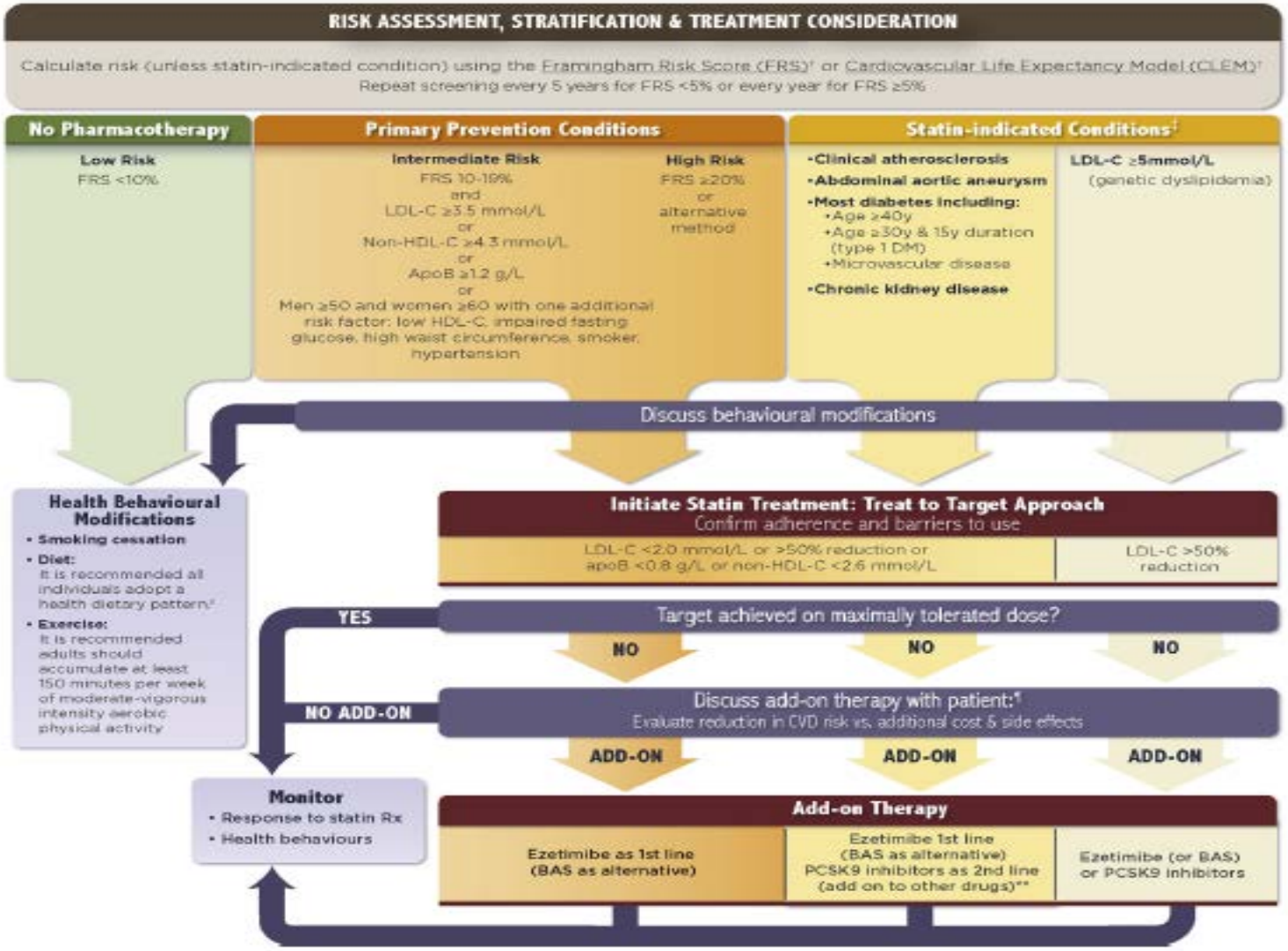
Category	Consider initiating pharmacotherapy if	Target	NNT
Primary prevention	High FRS (≥ 20%) All	LDL-C < 2.0 mmol/L or > 50% ↓ Or	35
	Intermediate FRS (10%-19%) LDL-C ≥ 3.5 mmol/L or non-HDL-C ≥ 4.3 mmol/L or ApoB ≥ 1.2 g/L or men ≥ 50 and women ≥ 60 years and 1 additional CVD RF	ApoB < 0.8 g/L Or non-HDL-C < 2.6 mmol/L	40
Statin-indicated conditions*	Clinical atherosclerosis†		20
	Abdominal aortic aneurysm		
	Diabetes mellitus Age ≥ 40 years 15-Year duration for age ≥ 30 years (DM 1) Microvascular disease		
	Chronic kidney disease (age ≥ 50 years) eGFR < 60 mL/min/1.73 m^2 or ACR > 3 mg/mmol		
	LDL-C ≥ 5.0 mmol/L	> 50% ↓ in LDL-C	

ACR, albumin:creatinine ratio; ACS, acute coronary syndrome; apoB, apolipoprotein B; CVD, cardiovascular disease; DM 1, type 1 diabetes mellitus; eGFR, estimated glomerular filtration rate; FRS, modified Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NNT, number needed to treat; RF, risk factor.

* Statins indicated as initial therapy.

† Consider LDL-C < 1.8 mmol/L for subjects with ACS within past 3 months.

2016 CCS dyslipidemia summary



What’s new in 2019 and beyond?

Case 1: Mr. Hy Risc

Mr. Hy. Risc

44 years old, non-smoker

- BMI = 26 kg/m^2
- BP 135/80 mm Hg
- No diabetes
- Total cholesterol = 5.9 mmol/L
- HDL cholesterol = 1.0 mmol/L
- TG = 1.7
- LDL-C = 4.1

New for 2019

Earlier LDL treatment is better

Mr. Hy Risc

Estimation of 10-year risk of total cardiovascular disease in men (Framingham Heart Study)

POINTS	Age	HDL-C	Total Cholesterol	SBP Not Treated	SBP Treated	Smoker	Diabetic	
–2		>1.6		<120				
–1		1.3-1.6						
0	30-34	1.2-1.3	<4.1	120-129	<120	NO	NO	
1		0.9-1.2	4.1-5.2	130-139				
2	35-39	<0.9	5.2-6.2	140-159	120-129			
3			6.2-7.2	160+	130-139		YES	
4			>7.2		140-159	YES		
5	40-44				160+			
6								
7	45-49							
8	50-54							
9								
10	55-59							
11	60-64							
12								
13	65-69							
14	70-74							
15	75+							TOTAL POINTS
Points Allotted								

Adapted from reference 33. HDL-C High-density lipoprotein cholesterol; SBP Systolic blood pressure

Cardiovascular disease risk for men

Points	Risk, %	Points	Risk, %	Points	Risk, %
–3 or less	<1	5	3.9	13	15.6
–2	1.1	6	4.7	14	18.4
–1	1.4	7	5.6	15	21.6
0	1.6	8	6.7	16	25.3
1	1.9	9	7.9	17	29.4
2	2.3	10	9.4	18+	>30
3	2.8	11	11.2		
4	3.3	12	13.3		

44 M

BMI = 26 kg/m^2
BP 135/80 mm Hg
No diabetes

Total cholesterol = 5.9 mmol/L
HDL cholesterol = 1.0 mmol/L
TG = 1.7

What's his risk?

Mr. Hy Risc

Estimation of 10-year risk of total cardiovascular disease in men (Framingham Heart Study)

POINTS	Age	HDL-C	Total Cholesterol	SBP Not Treated	SBP Treated	Smoker	Diabetic	
–2		>1.6		<120				
–1		1.3-1.6						
0	30-34	1.2-1.3	<4.1	120-129	<120	NO	NO	
1		0.9-1.2	4.1-5.2	130-139				
2	35-39	<0.9	5.2-6.2	140-159	120-129			
3			6.2-7.2	160+	130-139		YES	
4			>7.2		140-159	YES		
5	40-44				160+			
6								
7	45-49							
8	50-54							
9								
10	55-59							
11	60-64							
12								
13	65-69							
14	70-74							
15	75+							TOTAL POINTS
Points Allotted								

Adapted from reference 33. HDL-C High-density lipoprotein cholesterol; SBP Systolic blood pressure

Cardiovascular disease risk for men

Points	Risk, %	Points	Risk, %	Points	Risk, %
–3 or less	<1	5	3.9	13	15.6
–2	1.1	6	4.7	14	18.4
–1	1.4	7	5.6	15	21.6
0	1.6	8	6.7	16	25.3
1	1.9	9	7.9	17	29.4
2	2.3	10	9.4	18+	>30
3	2.8	11	11.2		
4	3.3	12	13.3		

44 M

BMI = 26 kg/m^2
BP 135/80 mm Hg
No diabetes

Total cholesterol = 5.9 mmol/L
HDL cholesterol = 1.0 mmol/L
TG = 1.7

What's his risk?

10 pts = 9% risk of CV event in 10 years (low risk)

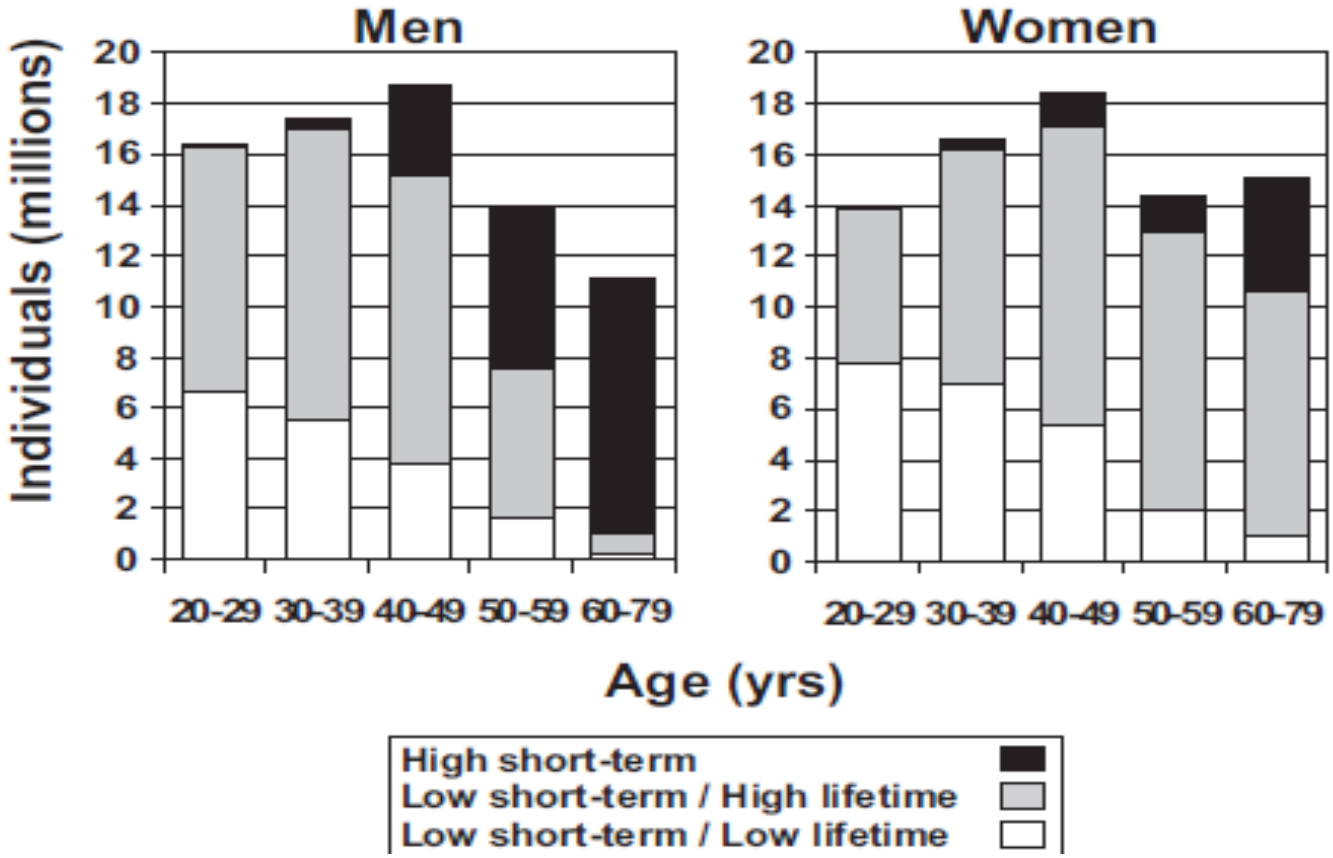
What would you do?

a) Congratulations! You're at low risk.
b) You need to work on your lifestyle
c) You need to start on ECASA
d) You need to start on statins
e) You need to start on blood pressure medications

What would you do?

a) Congratulations! You're at low risk.
b) You need to work on your lifestyle
c) You need to start on ECASA
d) You need to start on statins
e) You need to start on blood pressure medications

Low Short-term but High Lifetime Risk



What to do?

- A large proportion have low short-term BUT high lifetime risk
  - Counselling
  - Focus on lifestyle change
    - Target optimal risk factors
  - Consider EARLY preventative treatment?

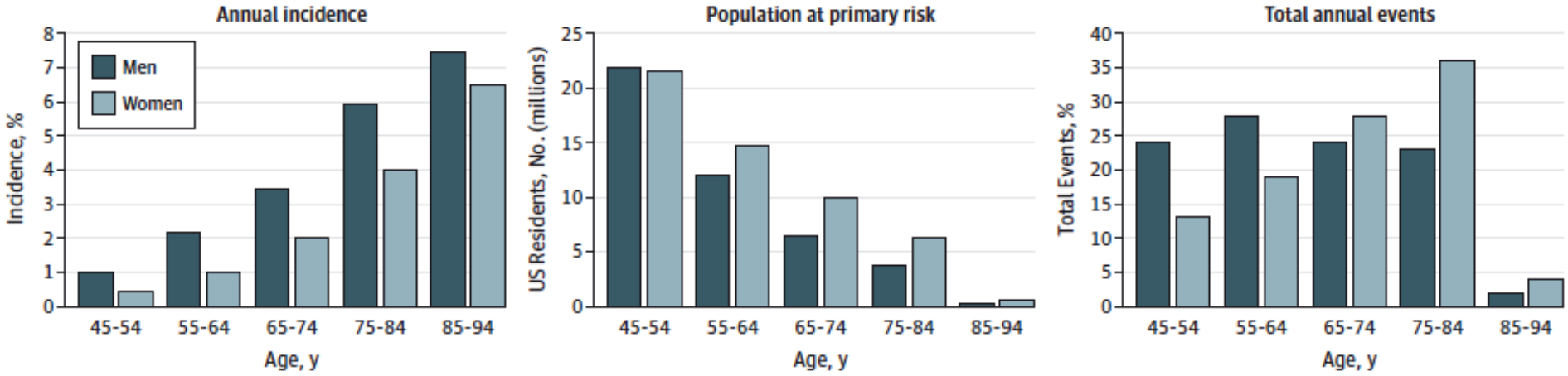
Earlier is better

What % of myocardial infarctions occur before the age of 65 years?

a) 65% in men and 50% in women
b) 50% in men and 33% in women
c) 33% in men and 20% in women
d) 15% in men and 10% in women
e) 5% in men and 2% in women

Earlier is better

Figure. Event Rates, Population at Risk, and Event Numbers by Sex and Age Groups



A, Average primary annual incidence rates of coronary heart disease, heart failure, stroke, or intermittent claudication. B, Numbers of US residents without clinical atherosclerotic cardiovascular disease represented in the 2005-2010 National Health and Nutrition Examination Survey. C, Percentage of the expected total of 930 621 annual primary events in men and 702 105 in women by age group.

Sniderman et al JAMA-Cardiology 2017

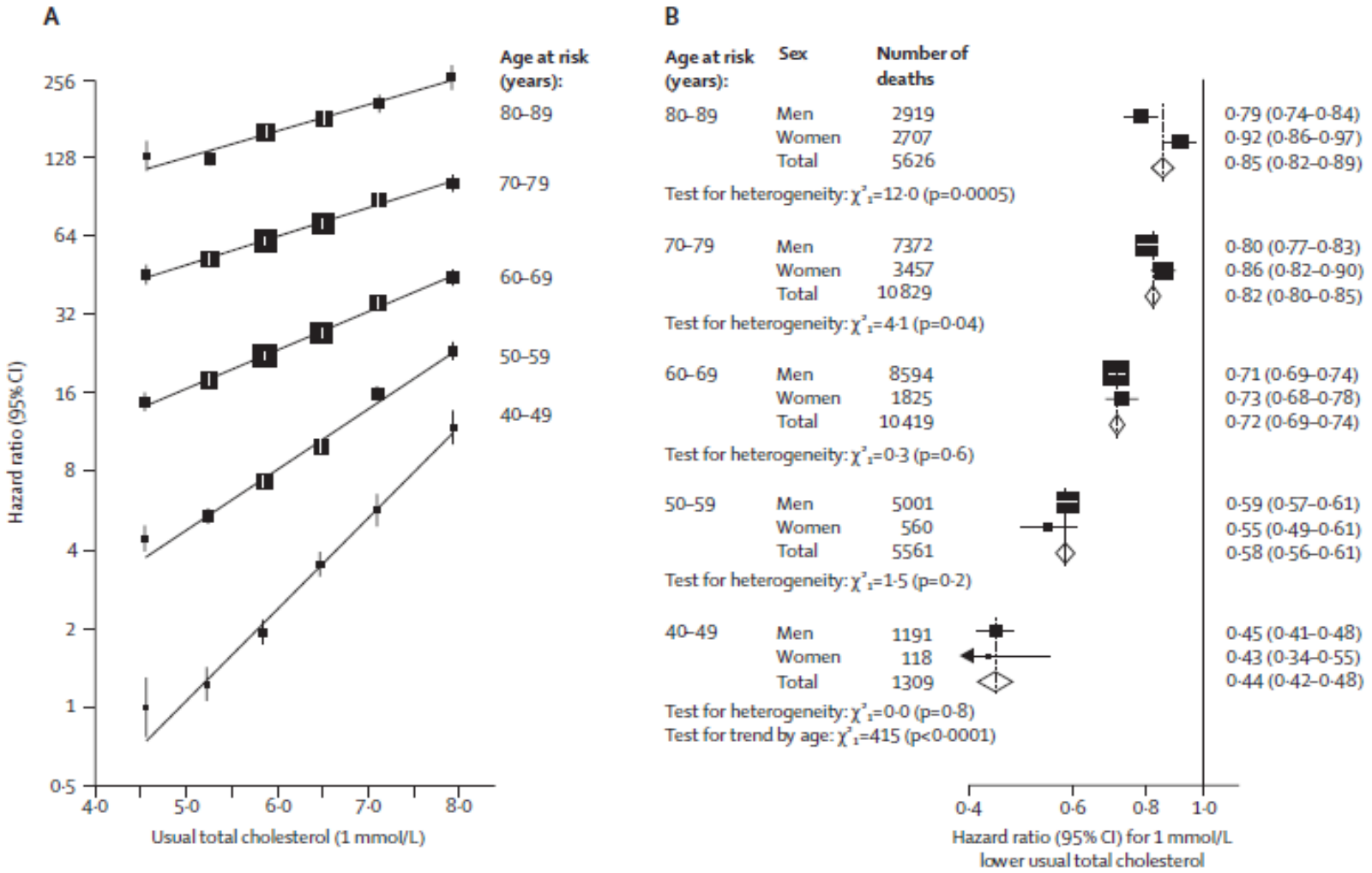
Earlier is better

What % of myocardial infarctions occur before the age of 65 years?

a) 65% in men and 50% in women
b) 50% in men and 33% in women
c) 33% in men and 20% in women
d) 15% in men and 10% in women
e) 5% in men and 2% in women

Earlier is better: Epidemiologic evidence

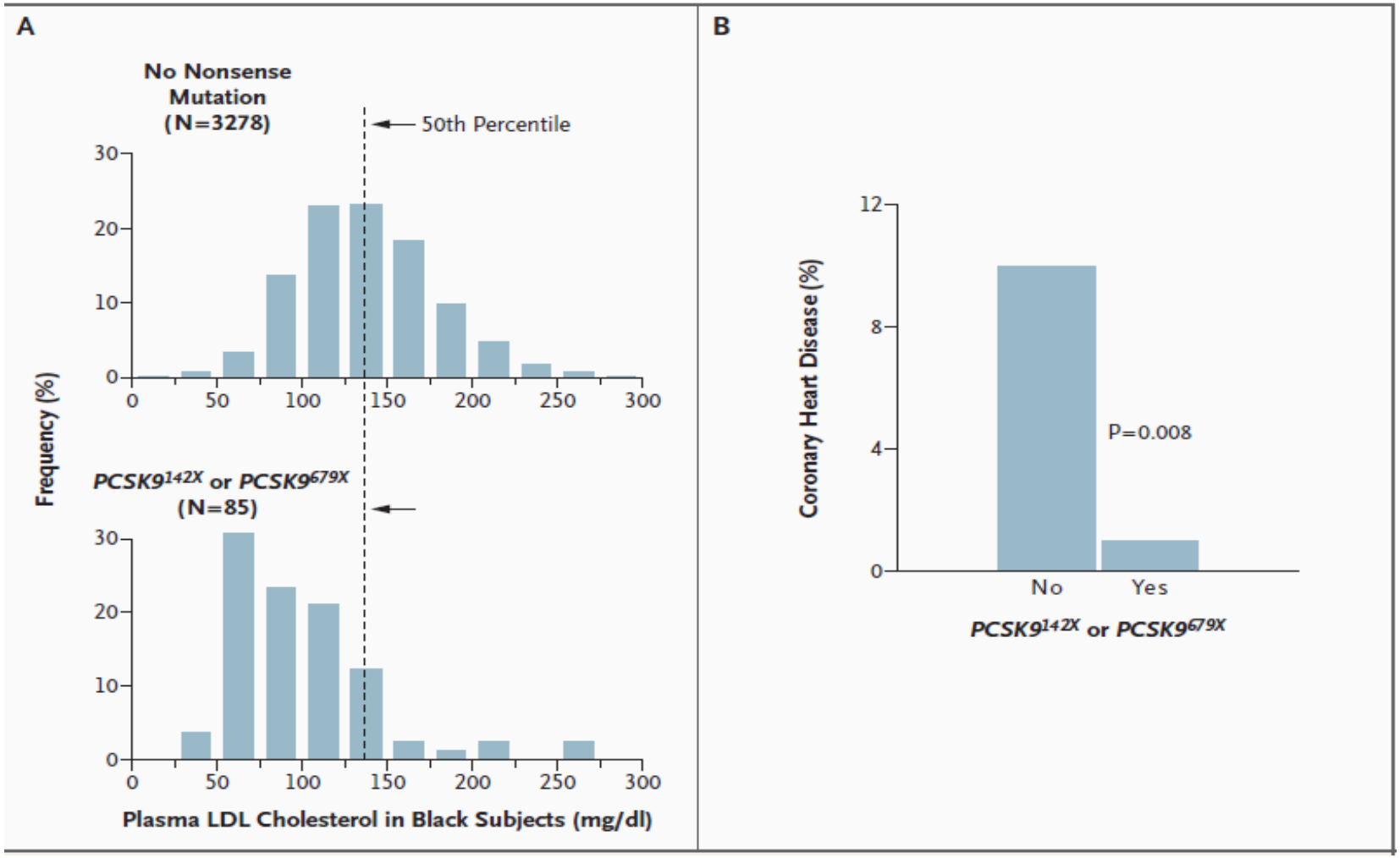
LDL is worse when young



Prospective Studies Collaboration Lancet 2007

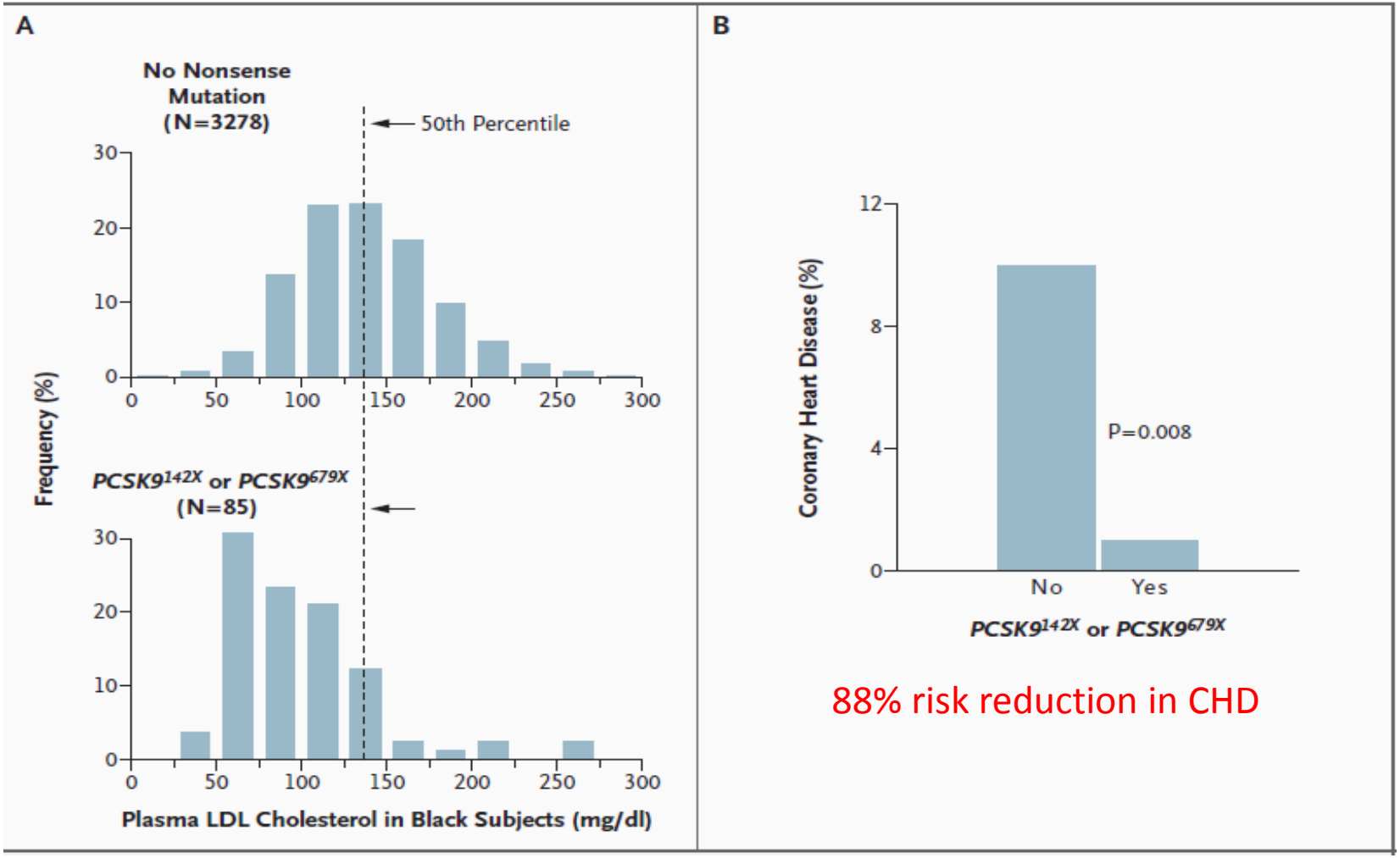
Earlier is better: Genetic evidence

Life-long lipids and Risk of CHD



Cohen JC *et al*, *NEJM* 2008

Life-long lipids and Risk of CHD

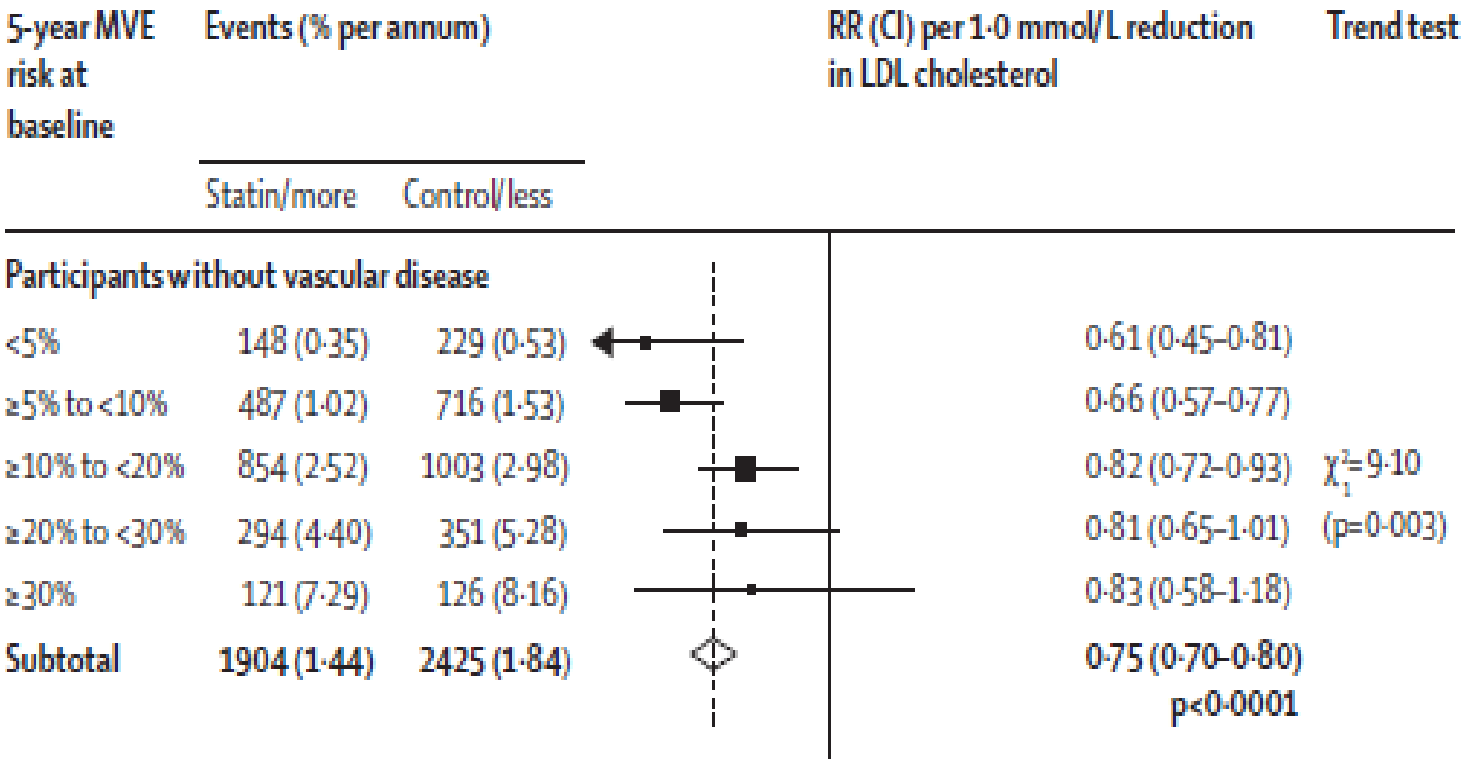


88% risk reduction in CHD

Cohen JC *et al*, NEJM 2008

Earlier is better: RCT evidence

Cholesterol Treatment Trialists



CTT collaboration *Lancet* 2010

How much benefit?

Epidemiology and Prevention

Individualized Statin Benefit for Determining Statin Eligibility in the Primary Prevention of Cardiovascular Disease

George Thanassoulis, MD, MSc; Ken Williams, MSc, PStat; Kathleen Kimler Altobelli, MS; Michael J. Pencina, PhD; Christopher P. Cannon, MD; Allan D. Sniderman, MD

Circulation 2016

How much benefit?

Epidemiology and Prevention

Individualized Statin Benefit for Determining Statin Eligibility in the Primary Prevention of Cardiovascular Disease

George Thanassoulis, MD, MSc; Ken Williams, MSc, PStat; Kathleen Kimler Altobelli, MS; Michael J. Pencina, PhD; Christopher P. Cannon, MD; Allan D. Sniderman, MD

- 9% risk at 10-year
- Atorvastatin 40 mg -> LDL-C from 4.1 to 2.5 mmol/L
- ARR = 9% x $(0.66)^{1.6}$ = 4.6%
- NNT = 1/ARR = 21.7

Circulation 2016

How much benefit?

MUHC-Duke Statin Benefit Calculator

version française

Age

50

Ethnicity

--- Select ---

Sex

Male Female

Blood Pressure

120 / 80

Are you currently being treated for hypertension?

Yes No

Do you currently smoke?

Yes No

Are you diabetic?

Yes No

Cholesterol:

Total

LDL-C

HDL-C

Units

mmol/L

Are you currently taking statins?

Yes No

https://github.com/tgetgood/statin-benefit

How much benefit?

- What is the NNT for 30 years?

How much benefit?

Research

JAMA Cardiology | Original Investigation

A Long-term Benefit Approach vs Standard Risk-Based Approaches for Statin Eligibility in Primary Prevention

George Thanassoulis, MD, MSc, FRCPC; Allan D. Sniderman, MD; Michael J. Pencina, PhD

CONCLUSIONS AND RELEVANCE A long-term benefit approach to statin eligibility identifies nearly 1 in 6 individuals as having a high degree of expected long-term benefit of statins, with a number needed to treat of less than 7. This approach identifies younger individuals with higher LDL-C levels who would not be currently recommended for treatment and may provide a more optimal approach for determining statin eligibility in primary prevention.

What about apolipoprotein B?

ApoB

Which of the following is true?

a) Each atherogenic particle contains 1 apoB molecule
b) Risk tracks apoB more closely than LDL-C
c) Differences in apoB and LDL-C occur in ~15% of individuals
d) Benefit of therapy is best predicted by change in apoB
e) All of the above

ApoB

Which of the following is true?

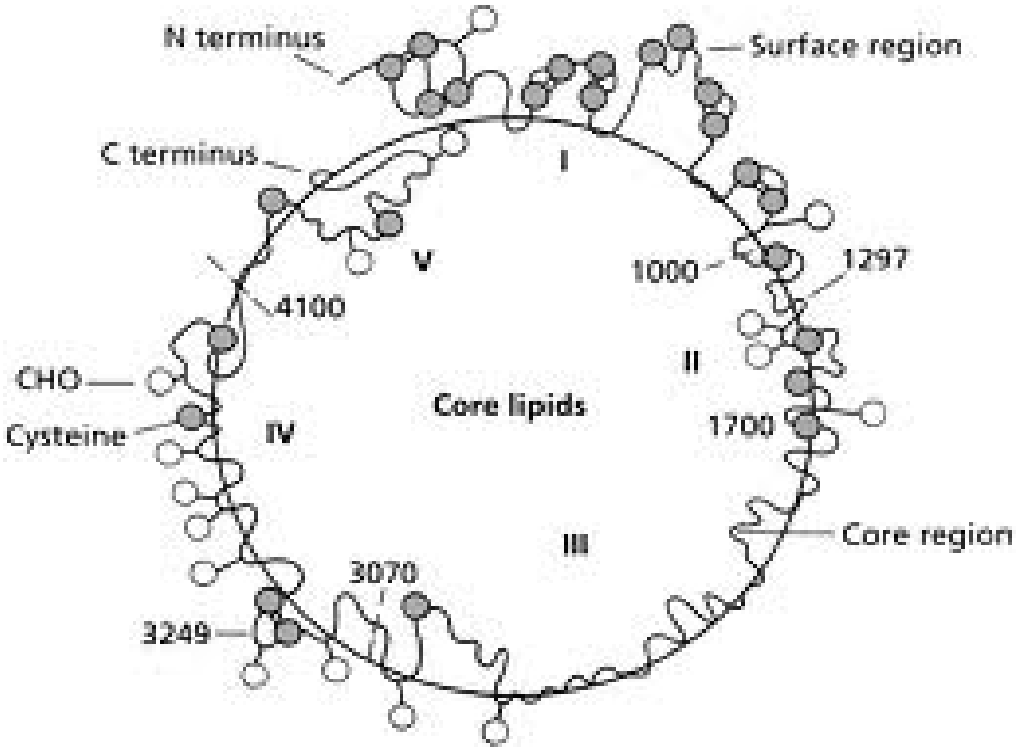
a) Each atherogenic particle contains 1 apoB molecule
b) Risk tracks apoB more closely than LDL-C
c) Differences in apoB and LDL-C occur in ~15% of individuals
d) Benefit of therapy is best predicted by change in apoB
e) All of the above

ApoB

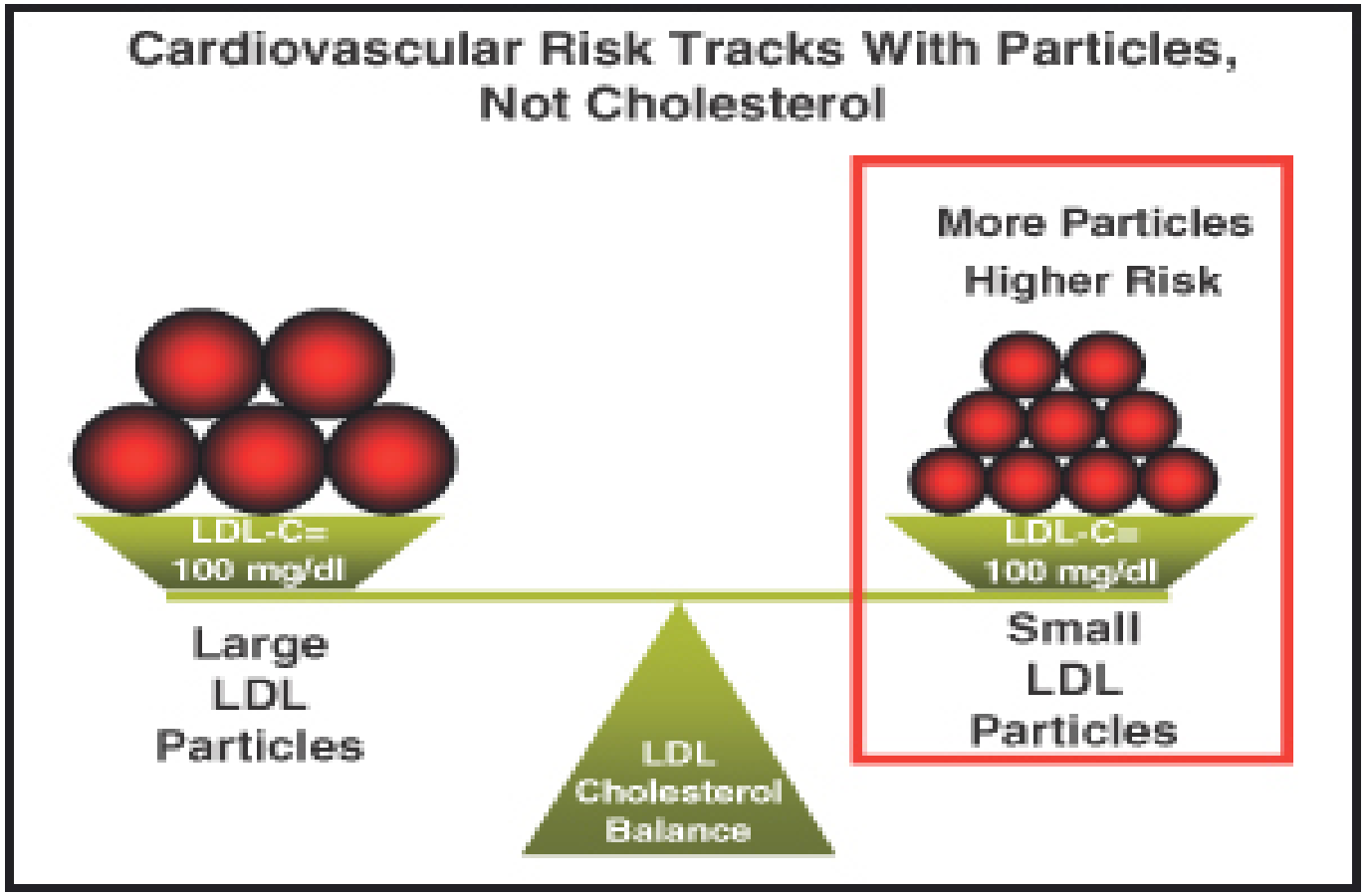
Which of the following is true?

a) Each atherogenic particle contains 1 apoB molecule
b) Risk tracks apoB more closely than LDL-C
c) Differences in apoB and LDL-C occur in ~15% of individuals
d) Benefit of therapy is best predicted by change in apoB
e) All of the above

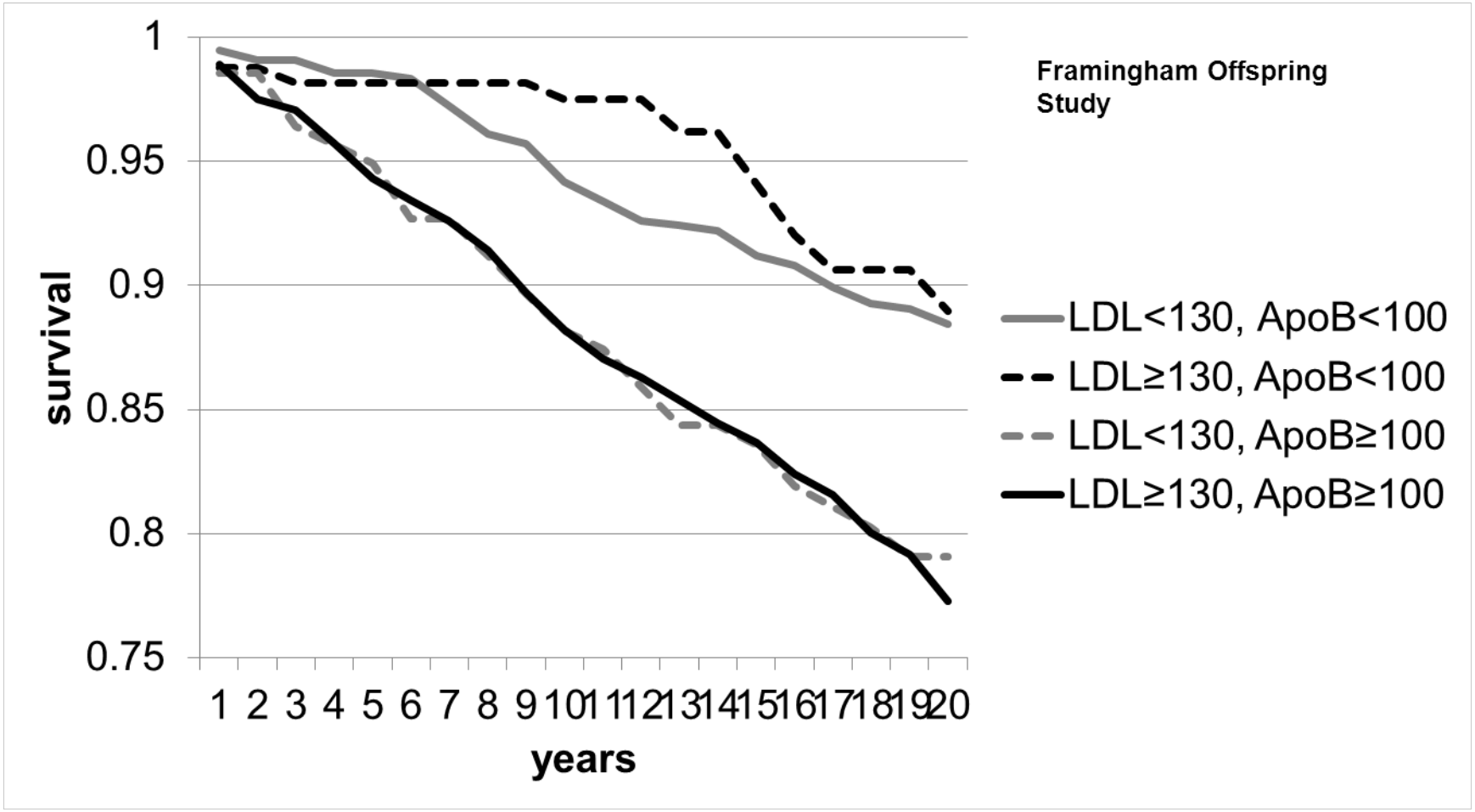
Apolipoprotein B



High apoB = danger



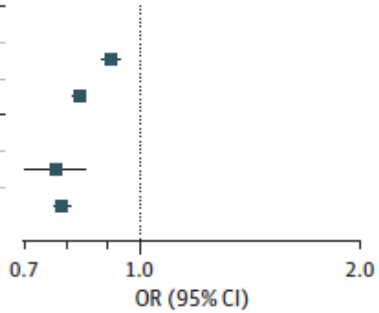
Risk tracks ApoB - always



Benefit also tracks ApoB - always

Figure 4. Association of Genetic Variants With Naturally Occurring Discordance Between Changes in Concentrations of LDL-C and apoB and the Risk of CHD Among CARDIoGRAMplusC4D Consortium Participants

	OR (95% CI)	*P* Value for Difference	MR-Egger OR (95% CI)
Effect per 10-mg/dL lower LDL-C			
Discordant variants score (21 variants)	0.916 (0.890-0.943)	2.9×10^{-8}	0.909 (0.826-0.992)
LDL-C score (36 variants)	0.831 (0.816-0.847)		0.839 (0.811-0.867)
Effect per 10-mg/dL lower apoB			
Discordant variants score (21 variants)	0.772 (0.701-0.844)	.68	0.747 (0.585-0.967)
LDL-C score (36 variants)	0.788 (0.769-0.807)		0.785 (0.751-0.821)



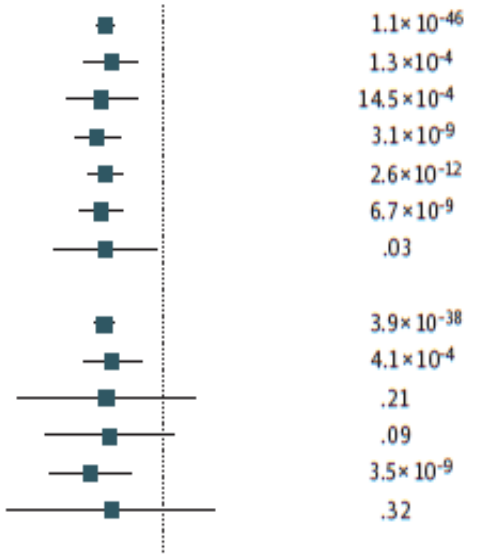
Analyses are based on summary data from up to 62 240 participants with coronary heart disease (CHD) and 127 299 control participants from the Coronary Artery Disease Genome Wide Replication and Meta-analysis plus the Coronary Artery Disease Genetics (CARDIoGRAMplusC4D) Consortium. Effect sizes are standardized per 10-mg/dL lower level of low-density lipoprotein cholesterol (LDL-C) or 10-mg/dL lower level of apolipoprotein B (apoB). MR-Egger regression estimates are presented for sensitivity analyses. Data markers indicate point estimates of effect; error bars, 95% confidence intervals.

Ference BA et al *JAMA* 2017

Benefit also tracks ApoB - always

/ith Triglycerides, Low-Density Lipoprotein Cholesterol (LDL-C), and Risk of Coronary Heart Disease (CHD) per 10-mg/dL Lower Concentration

Therapy	Δ Triglycerides (95% CI)	Δ Low-Density Lipoprotein Cholesterol (95% CI)	Odds Ratio (95% CI)	*P* Value
Therapeutic target	-1.9 (-3.9 to -0.1)	-14.2 (-14.8 to -13.6)	0.773 (0.746 to 0.801)	1.1×10^{-46}
Statin	-2.4 (-5.9 to 1.0)	-15.6 (-16.8 to -14.3)	0.795 (0.706 to 0.894)	1.3×10^{-4}
Ezetimibe	-7.6 (-14.8 to -0.5)	-14.6 (-17.6 to -11.6)	0.762 (0.654 to 0.887)	14.5×10^{-4}
PCSK9 inhibitor	-4.2 (-7.1 to -1.3)	-10.9 (-12.0 to -9.8)	0.748 (0.679 to 0.823)	3.1×10^{-9}
PCSK9 inhibitor	-0.5 (-2.7 to 1.7)	-18.0 (-18.8 to -17.2)	0.774 (0.721 to 0.832)	2.6×10^{-12}
Bile resin	-9.0 (-11.8 to -6.2)	-12.6 (-13.7 to -11.6)	0.761 (0.693 to 0.834)	6.7×10^{-9}
CETP inhibitor	-24.4 (-32.6 to -16.2)	-4.1 (-7.3 to -0.8)	0.774 (0.618 to 0.967)	.03
Therapeutic target	-69.9 (-71.6 to -68.1)	0.7 (0.0 to 1.4)	0.771 (0.741 to 0.802)	3.9×10^{-38}
LPL enhancer	-70.7 (-73.9 to -67.5)	-6.0 (-7.4 to -4.6)	0.798 (0.704 to 0.904)	4.1×10^{-4}
APOC3 inhibitor	-92.3 (-103.8 to -80.3)	-5.7 (-9.7 to -1.8)	0.778 (0.527 to 1.149)	.21
ANGPTL3 inhibitor	-30.9 (-69.7 to 7.8)	-8.9 (-20.3 to 2.4)	0.788 (0.598 to 1.040)	.09
ANGPTL4 inhibitor	-69.4 (-74.3 to -64.5)	-0.4 (-2.2 to 1.5)	0.726 (0.609 to 0.865)	3.5×10^{-9}
Fibrate	-25.0 (-38.7 to -11.3)	-16.4 (-21.5 to -11.3)	0.795 (0.506 to 1.248)	.32



Ference BA et al *JAMA* 2018

Mr. Hy. Risc

- 44 years old, non-smoker

- BMI = 26 kg/m^2
- BP 135/80 mm Hg
- No diabetes
- Total cholesterol = 5.9 mmol/L
- HDL cholesterol = 1.2 mmol/L
- TG = 1.7
- LDL-C = 4.1

Mr. Hy. Risc

- 44 years old, non-smoker

- BMI = 26 kg/m^2
- BP 135/80 mm Hg
- No diabetes
- Total cholesterol = 5.9 mmol/L
- HDL cholesterol = 1.2 mmol/L
- TG = 1.7
- LDL-C = 4.1
- Apo B 1.4

What about Lipoprotein(a)?

Lp(a)

Elevated Lp(a) is a likely cause of the following:

a) Myocardial infarction (frequently premature)
b) Stroke (including in children)
c) Aortic stenosis
d) Recurrent ACS
e) All of the above

Lp(a)

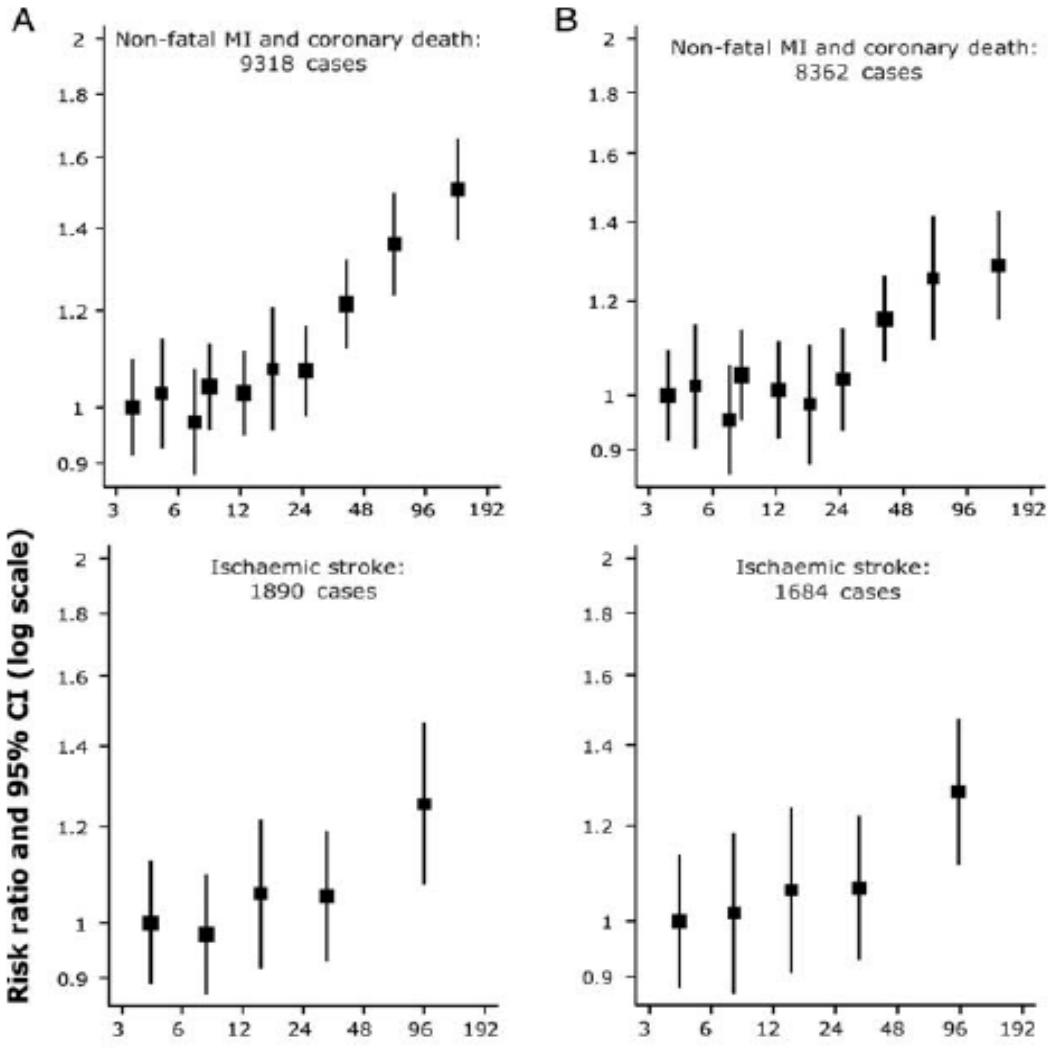
Elevated Lp(a) is a likely cause of the following:

a) Myocardial infarction (frequently premature)
b) Stroke (including in children)
c) Aortic stenosis
d) Recurrent ACS
e) All of the above

What is Lp(a)?

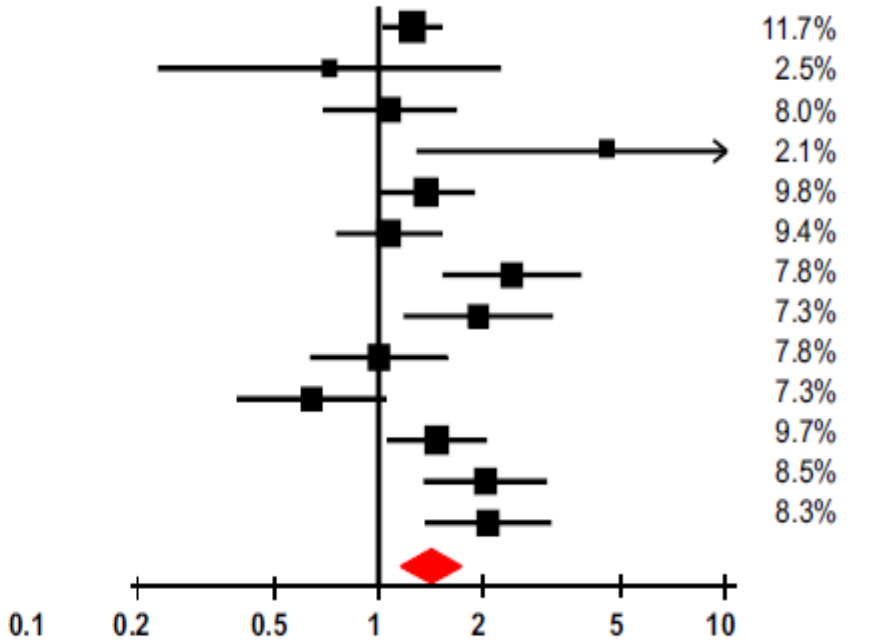
- ApoB+apo(a) → Lp(a)
- Lp(a) levels are almost entirely mediated by genetics
- Highly atherogenic, pro-calcific
- Most common genetic dyslipidemia
  - 6 million Canadians have high Lp(a)

Lp(a) is atherogenic



Lp(a) and recurrent events

Study name	Odds Ratio (95% CI)	P Value	Relative Weight
4S	1.25 (1.02-1.53)	0.03	11.7%
Skinner et al.	0.72 (0.23-2.26)	0.57	2.5%
CARE	1.08 (0.69-1.68)	0.75	8.0%
FATS	4.55 (1.28-16.18)	0.02	2.1%
HERS	1.37 (0.99-1.90)	0.06	9.8%
PEACE	1.07 (0.75-1.53)	0.71	9.4%
GENERATION	2.42 (1.52-3.85)	<0.001	7.8%
Stubbs et al.	1.94 (1.18-3.20)	0.009	7.3%
PROVE IT-TIMI 22	1.00 (0.63-1.59)	0.99	7.8%
Saely et al. - diabetic subjects	0.64 (0.39-1.06)	0.08	7.3%
Saely et al. - non-diabetic subjects	1.47 (1.05-2.05)	0.02	9.7%
AIM HIGH - niacin arm	2.03 (1.34-3.07)	0.001	8.5%
AIM HIGH - placebo arm	2.07 (1.35-3.16)	0.001	8.3%
OVERALL	**1.40 (1.15-1.71)**	**0.001**	



Heterogeneity: Q_{df12}=34.0; P=0.001, I^2=65%

Figure 3 Meta-Analysis of Published Studies of Lp(a) in Secondary Prevention

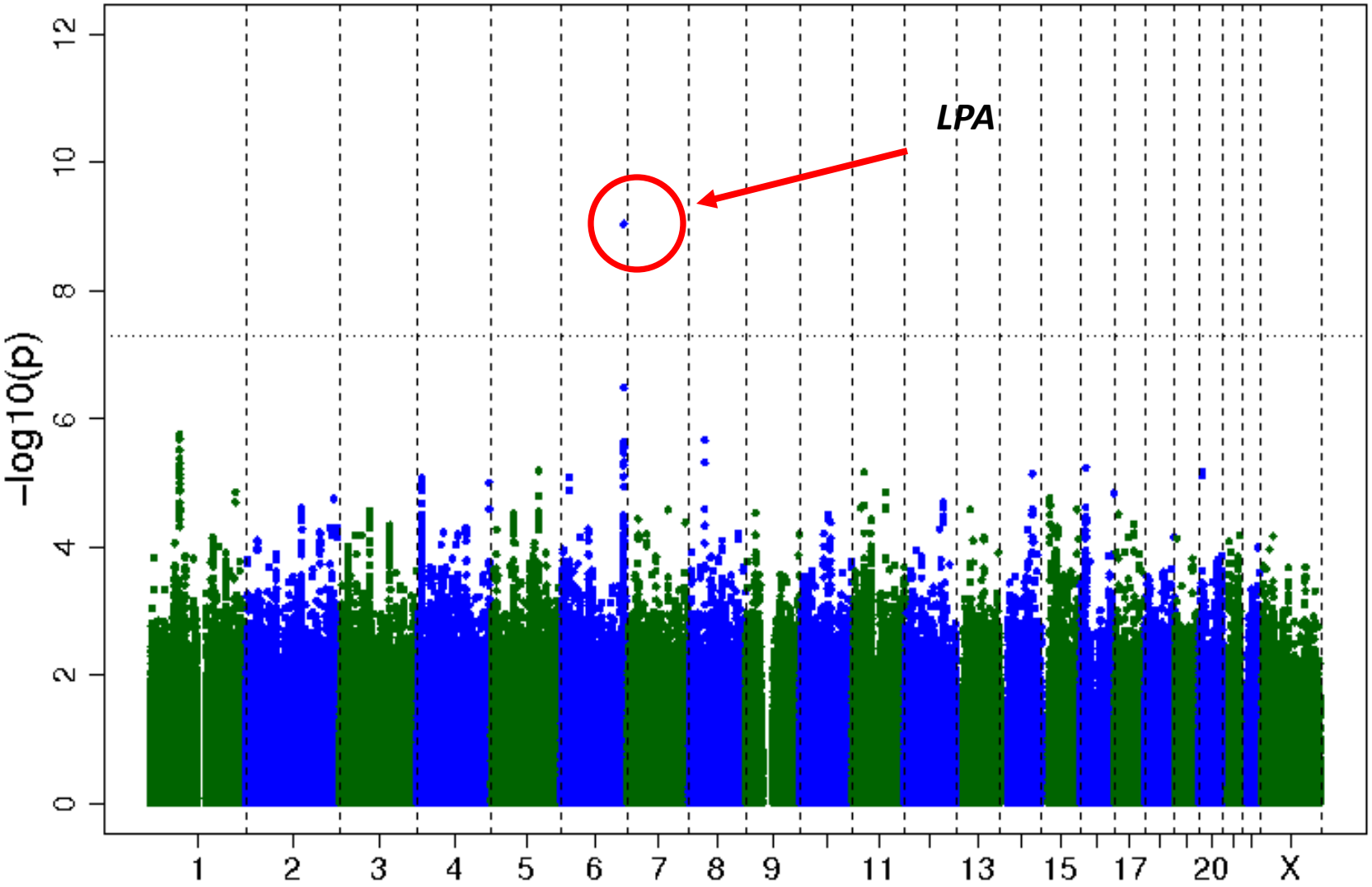
Lp(a) and aortic stenosis

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 7, 2013 VOL. 368 NO. 6

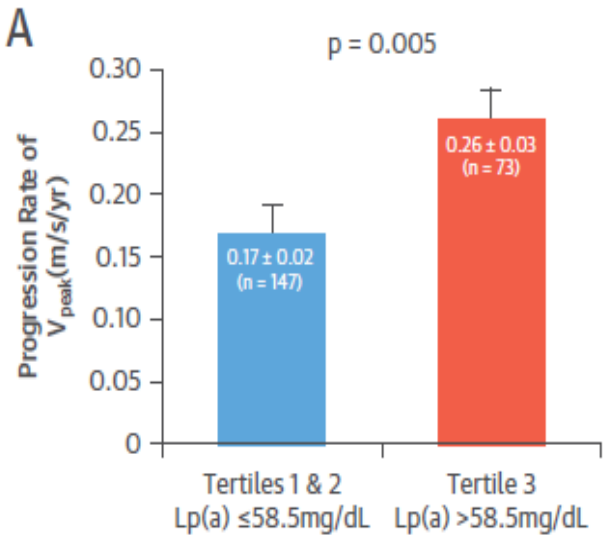
Genetic Associations with Valvular Calcification and Aortic Stenosis

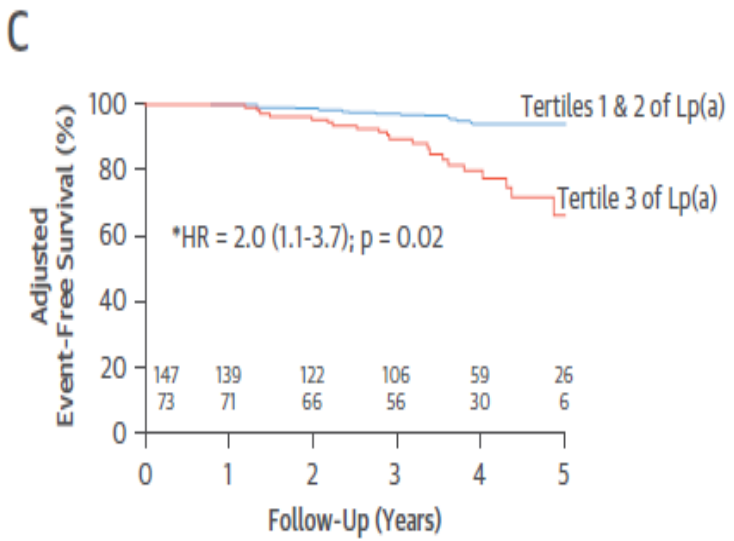
George Thanassoulis, M.D., Catherine Y. Campbell, M.D., David S. Owens, M.D., J. Gustav Smith, M.D., Ph.D., Albert V. Smith, Ph.D., Gina M. Peloso, Ph.D., Kathleen F. Kerr, Ph.D., Sonali Pechlivanis, Ph.D., Matthew J. Budoff, M.D., Tamara B. Harris, M.D., Rajeev Malhotra, M.D., Kevin D. O'Brien, M.D., Pia R. Kamstrup, M.D., Ph.D., Børge G. Nordestgaard, M.D., D.M.Sc., Anne Tybjaerg-Hansen, M.D., D.M.Sc., Matthew A. Allison, M.D., M.P.H., Thor Aspelund, Ph.D., Michael H. Criqui, M.D., M.P.H., Susan R. Heckbert, M.D., Ph.D., Shih-Jen Hwang, Ph.D., Yongmei Liu, Ph.D., Marketa Sjogren, Ph.D., Jesper van der Pals, M.D., Ph.D., Hagen Kälsch, M.D., Thomas W. Mühleisen, Ph.D., Markus M. Nöthen, M.D., L. Adrienne Cupples, Ph.D., Muriel Caslake, Ph.D., Emanuele Di Angelantonio, M.D., Ph.D., John Danesh, F.R.C.P., Jerome I. Rotter, M.D., Sigurdur Sigurdsson, M.Sc., Quenna Wong, M.S., Raimund Erbel, M.D., Sekar Kathiresan, M.D., Olle Melander, M.D., Ph.D., Vilmundur Gudnason, M.D., Ph.D., Christopher J. O'Donnell, M.D., M.P.H., and Wendy S. Post, M.D., for the CHARGE Extracoronary Calcium Working Group



Thanassoulis G et al. *NEJM* 2013

Lp(a) and AS progression





High Lp(a) associated with faster disease progression and increased incidence of AVR

Capoulade R *J Am Coll Cardiol*. 2015

Who should I screen for Lp(a)?

(i) premature CVD,
(ii) familial hypercholesterolaemia,
(iii) a family history of premature CVD and/or elevated Lp(a),
(iv) recurrent CVD despite statin treatment,
(v) ≥3% 10-year risk of fatal CVD according to the European guidelines,[35] and
(vi) ≥10% 10-year risk of fatal and/or non-fatal CHD according to the US guidelines[36]

Who should I screen for Lp(a)?

(i) premature CVD,
(ii) familial hypercholesterolaemia,
(iii) a family history of premature CVD and/or elevated Lp(a),
(iv) recurrent CVD despite statin treatment,
(v) ≥3% 10-year risk of fatal CVD according to the European guidelines,[35] and
(vi) ≥10% 10-year risk of fatal and/or non-fatal CHD according to the US guidelines[36]

vii. Premature aortic valve calcification or aortic stenosis

Management

- Individuals with high Lp(a)
  - Lifestyle change
  - Treat LDL-C (and all risk factors) much more aggressively
  - Consider ECASA
  - Consider extended-release niacin

Future therapy

Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study

Sotirios Tsimikas, Nicholas J Viney, Steven G Hughes, Walter Singleton, Mark J Graham, Brenda F Baker, Jennifer L Burkey, Qingqing Yang, Santica M Marcovina, Richard S Geary, Rosanne M Crooke, Joseph L Witztum

Case 2: Mr. Tremblay

Case: Mr. Tremblay

- 54 yrs old, non-smoker, 1 month post-ACS, stented pLAD and pCirc

- BMI = 27 kg/m^2
- BP 130/80
- No diabetes
- TC = 4.2 mmol/L
- HDL-C = 1.2 mmol/L
- TG = 1.7 mmol/L
- LDL-C = 2.2 mmol/L (on atorvastatin 80 mg daily)

Question

What % of post-ACS patients achieve CCS guideline based LDL-C targets in Canada?

a) 60-80%
b) 40-60%
c) 20-40%
d) 0-20%

Question

What % of post-ACS patients achieve CCS guideline based LDL-C targets in Canada?

a) 60-80%
b) 40-60%
c) 20-40%
d) 0-20%

Case: Mr. Tremblay

What would you do?

a) Cardiac rehabilitation for improvement in lifestyle and exercise
b) Switch atorvastatin 80 mg to rosuvastatin 40 mg
c) Add ezetimibe
d) Add niacin
e) Add PCSK9i

Lifestyle, diet and exercise

Canadian Cardiovascular Society
Leadership. Knowledge. Community.

Mediteranean diet	↓ 28-30 % CVE (ARR 0,6-1 % [NNT = 100-167)	
Portfolio diet	↓ 11 % CVE	Ideal efficacy ↓ LDL-C by 21-29 % (comparable to lovastatine 20 mg) Real-world efficacy : ↓ LDL-C 8-14 %
DASH diet (*Dietary Approaches to Stop Hypertension*)[97,98]	↓ 20 % CVE	↓ LDL-C by 3 %

Weight loss and reduction in abdominal obesity 5-10 % reduction in BMI	↓ CVE by 6 % for a ~5 unit change in BMI ↓ CVE by 9% for a 12,6 cm reduction in WC	↓ LDL-C by 11 % ↑ HDL-C by 3-12 % ↓ TG by 32 %
Physical exercise 30-60 min/d moderate to high intensity	↓ CVE 20-30 %	↑ HDL-C by 5-10 %
Smoking cessation	↓ CVE by 52 %	↑ HDL-C by 7-12 %
Combined lifestyle changes	↓ CVE (and mortality) by 75 %	

Lifestyle, diet and exercise

Canadian Cardiovascular Society
Leadership. Knowledge. Community.

Mediteranean diet	↓ 28-30 % CVE (ARR 0,6-1 % [NNT = 100-167)	
Portfolio diet	↓ 11 % CVE	Ideal efficacy ↓ LDL-C by 21-29 % (comparable to lovastatine 20 mg) Real-world efficacy : ↓ LDL-C 8-14 %
DASH diet (*Dietary Approaches to Stop Hypertension*)[97,98]	↓ 20 % CVE	↓ LDL-C by 3 %

Refer all patients to Cardiac Rehabilitiation Programs!!!

	reduction in WC	
Physical exercise 30-60 min/d moderate to high intensity	↓ CVE 20-30 %	↑ HDL-C by 5-10 %
Smoking cessation	↓ CVE by 52 %	↑ HDL-C by 7-12 %
Combined lifestyle changes	↓ CVE (and mortality) by 75 %	

Lipid-lowering post-ACS

	LDL lowering	Other effects	Results	Side effects
Niacin	**20 %**	↑ HDL 30 % ↓ TG 40 %	No benefit	Vasomotor symptoms, itchiness, nausea
Fibrates	**5-20 %**	↑ HDL (10-50 %) ↓ TG (20-50 %)	No benefit	Nausea, muscle pains
Bile acid sequestrants	**15-20 %**		Limited data	GI intolerance, myalgias
ezetimibe	**15-25 %**		**IMPROVE-IT** **MACE reduction 6,5 %**	**Muscle pains**

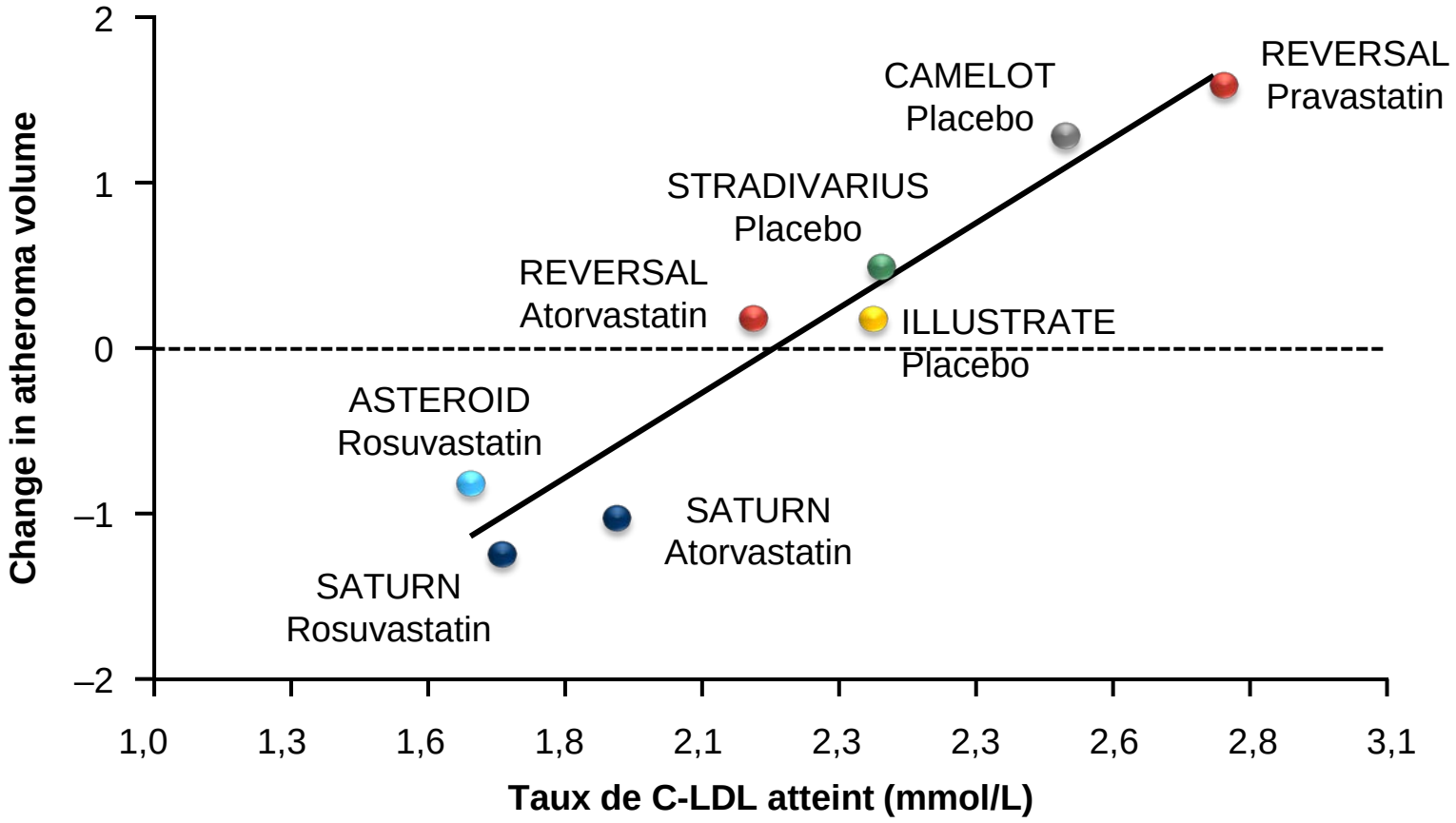
Case: Mr. Tremblay

What would you do?

a) Cardiac rehabilitation for improvement in lifestyle and exercise
b) Switch atorvastatin 80 mg to rosuvastatin 40 mg
c) Add ezetimibe
d) Add niacin
e) Add PCSK9i

Very low LDL-C: Is there a benefit?

Very low LDL-C: Is there a benefit?



Very low LDL-C: Is there a benefit?

JAMA Cardiology | Original Investigation

Efficacy and Safety of Further Lowering of Low-Density Lipoprotein Cholesterol in Patients Starting With Very Low Levels

A Meta-analysis

Marc S. Sabatine, MD, MPH; Stephen D. Wiviott, MD; KyungAh Im, PhD; Sabina A. Murphy, MPH; Robert P. Giugliano, MD, SM

Very low LDL-C: Is there a benefit?

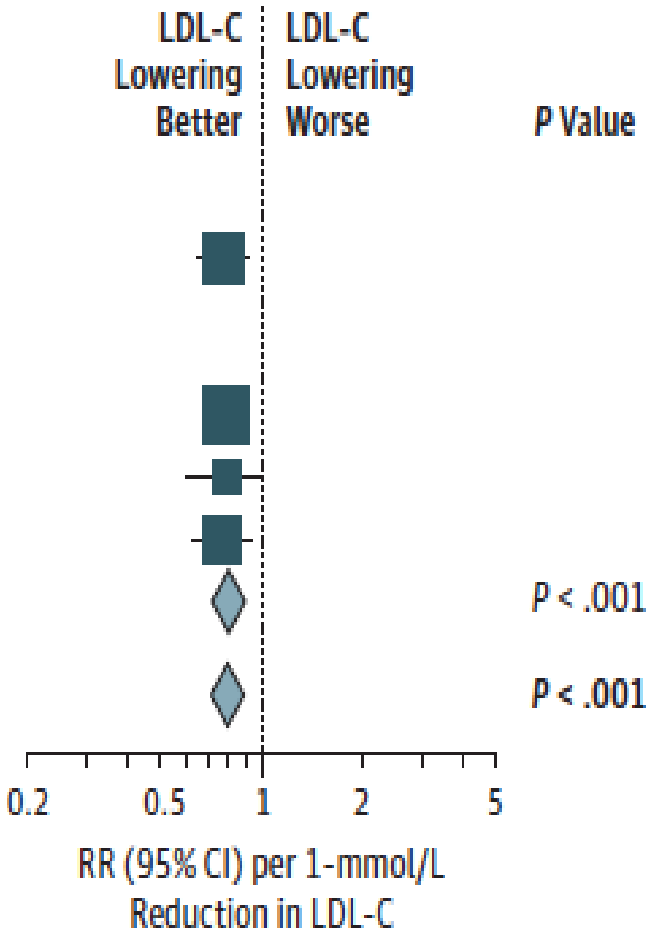
Table 1. Trial Characteristics

Trial	No. of Participants	Type of Intervention	Drug	Achieved LDL-C, mmol/L		Median Duration of Follow-up, y	Overall No. of Major Vascular Events
				Control Arm	Experimental Arm		
CTTC (<2 mmol/L)	NR	HMGCR inhibitor (statin)	Various	1.7[a]	NR	4.9[b]	1922
IMPROVE-IT	18 144	NPC1L1 inhibitor	Ezetimibe	1.8[c]	1.4	6.0	5104
FOURIER (<1.8 mmol/L)	2034	PCSK9 inhibitor	Evolocumab	1.7[d]	0.5	2.1	184
REVEAL	30 449	CETP inhibitor	Anacetrapib	1.6[e]	1.4	4.1	4282

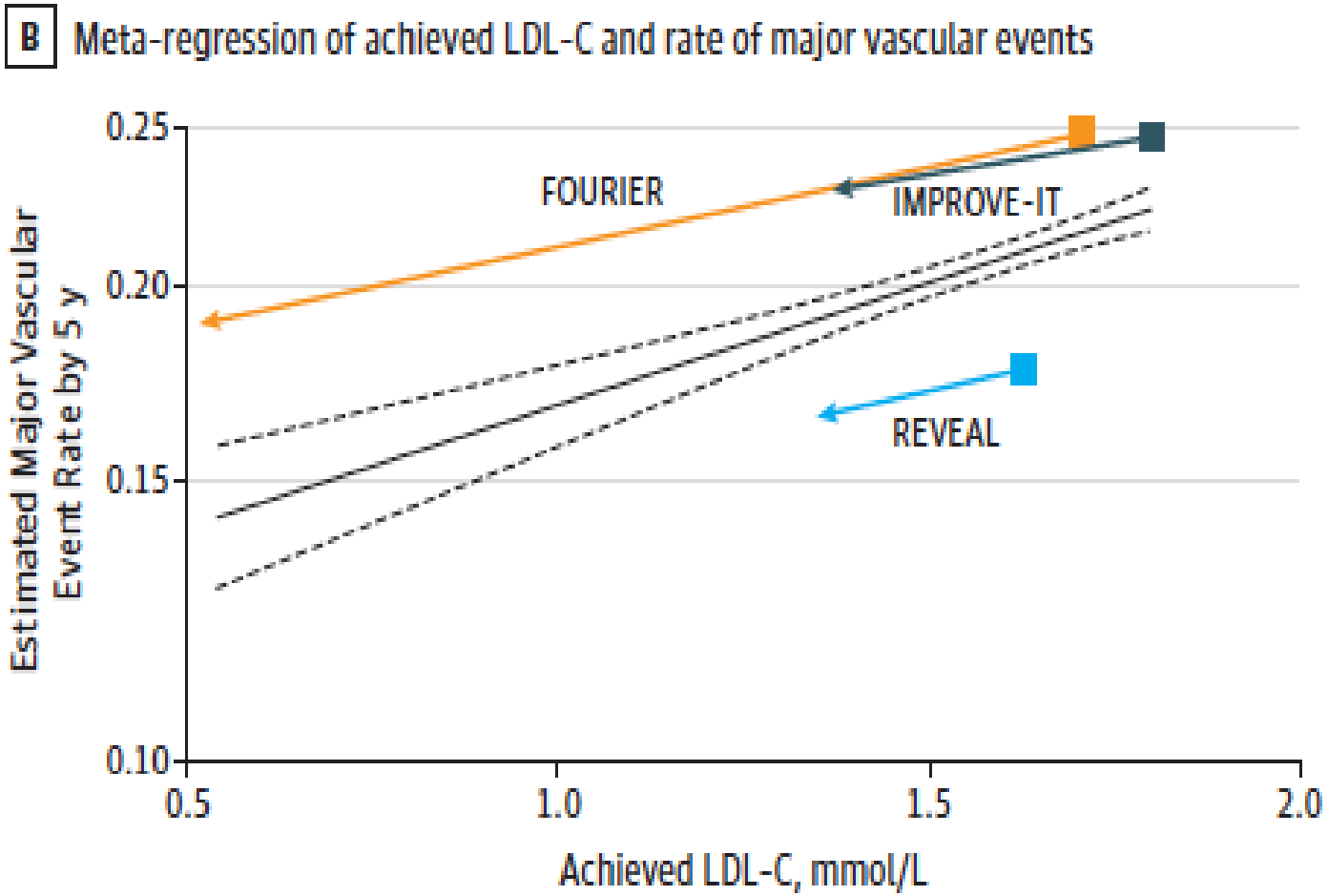
Very low LDL-C: Is there a benefit?

A Meta-analysis of effect of 1-mmol/L LDL-C lowering on the risk of major vascular events

Trial	Events, % per annum: Experimental Arm	Events, % per annum: Control Arm	RR (95% CI)	P Value
Statins				
CTTC <2 mmol/L subgroup	910 (4.1)	1012 (4.6)	0.78 (0.65-0.94)	
Nonstatin LDL-C lowering				
IMPROVE-IT	2455 (4.5)	2649 (4.9)	0.79 (0.67-0.93)	
FOURIER <1.8 mmol/L subgroup	81 (3.7)	103 (4.9)	0.80 (0.61-1.04)	
REVEAL	2068 (3.3)	2214 (3.5)	0.77 (0.63-0.96)	
Summary	4604	4966	0.79 (0.70-0.88)	P < .001
Overall summary	**5514**	**5978**	**0.79 (0.71-0.87)**	**P < .001**



Very low LDL-C: Is there a benefit?



Very low LDL-C: Is there HARM?

Very low LDL-C: Is there HARM?

Table 2. Safety Outcomes in Trials of Nonstatin Therapy

	Patients With Event, No.		Meta-analysis Data	
Safety Outcome	Experimental Arm	Control Arm	Risk Ratio (95% CI)	*P* Value
Any serious adverse event	12 809	12 836	1.00 (0.98-1.02)	.89
Myalgias or myopathy	116	135	0.85 (0.66-1.08)	.19
Aminotransferase elevation	488	510	0.96 (0.85-1.08)	.48
New-onset diabetes	1272	1320	0.97 (0.90-1.05)	.46
Hemorrhagic stroke	132	118	1.11 (0.87-1.43)	.40
Cancer	1747	1715	1.02 (0.96-1.09)	.55

Case: Mr. Tremblay

- 54 yrs old, non-smoker, 1 month post-ACS, stented pLAD + pCIRC

- BMI = 27 kg/m^2
- BP 130/80
- No diabetes
- TC = 4.0 mmol/L
- HDL-C = 1.2 mmol/L
- TG = 1.7 mmol/L
- LDL-C = 2.0 mmol/L (on atorvastatin 80 mg + ezetimibe daily)

Case: Mr. Tremblay

- What do you do?

a) Nothing
b) Add niacin
c) Add fibrate
d) Add PCSK9i
e) Add omega-3 fatty acids

Case: Mr. Tremblay

- What do you do?

a) Nothing
b) Add niacin
c) Add fibrate
d) Add PCSK9i
e) Add omega-3 fatty acids

FOURIER

Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

MS Sabatine, RP Giugliano, AC Keech, N Honarpour,
SM Wasserman, PS Sever, and TR Pedersen,
for the FOURIER Steering Committee & Investigators

An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

The ODYSSEY OUTCOMES Trial: Topline Results

Alirocumab in Patients After Acute Coronary Syndrome

Gregory G. Schwartz, Michael Szarek, Deepak L. Bhatt, Vera Bittner, Rafael Diaz, Jay Edelberg,
Shaun G. Goodman, Corinne Hanotin, Robert Harrington, J. Wouter Jukema, Guillaume Lecorps, Angèle Moryusef, Robert Pordy, Matthew Roe, Harvey D. White, Andreas Zeiher,
Ph. Gabriel Steg
On behalf of the ODYSSEY OUTCOMES Investigators and Committees

American College of Cardiology – 67th Scientific Sessions
March 10, 2018

ODYSSEY OUTCOMES

ClinicalTrials.gov: NCT01663402

Conclusions

- In primary prevention:
  - Earlier is better, especially when LDL-C is high
  - Consider using risk modifiers: apoB, Lp(a)

- In secondary prevention:
  - Lower is better, especially in high risk patients → **< 1.8 mmol/L**
  - Aggressive lowering of LDL-C (and/or apoB) is recommended often requiring ezetimibe ± PCSK9i

- Future guidelines:
  - Benefit vs risk-based approach
  - Treatment targets vs intensification thresholds?
  - How low should we go?

Questions

Types de résultats CV

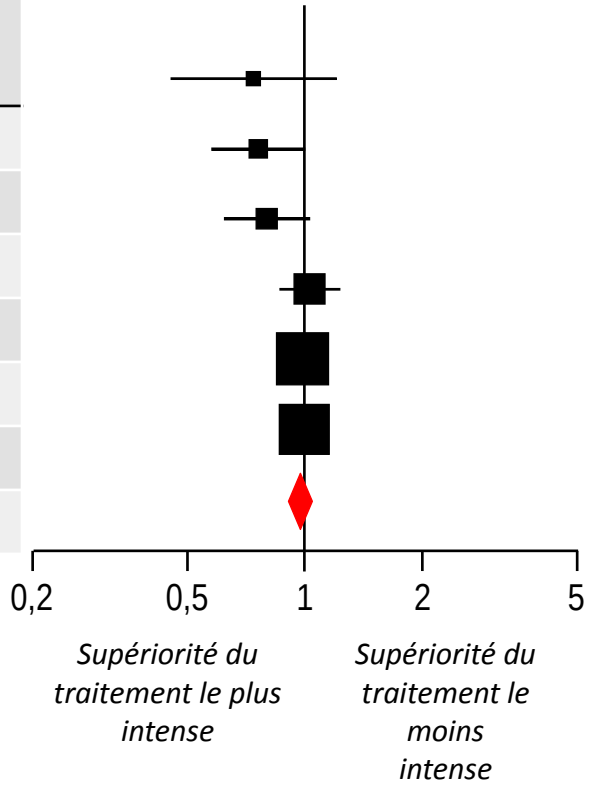
Paramètre d'évaluation	Évolocumab (N = 13 784)	Placebo (N = 13 780)	RRI (IC à 95 %)
	Taux de Kaplan-Meier après 3 ans		
Décès CV, IM ou AVC	**7,9**	**9,9**	0,80 (0,73-0,88)
Décès CV	**2,5**	**2,4**	1,05 (0,88-1,25)
Décès causé par un IM aigü	0,26	0,32	0,84 (0,49-1,42)
Décès causé par un AVC	0,29	0,30	0,94 (0,58-1,54)
Autre décès CV	1,9	1,8	1,10 (0,90-1,35)
IM	**4,4**	**6,3**	0,73 (0,65-0,82)
AVC	**2,2**	**2,6**	0,79 (0,66-0,95)

Réduction plus importante du C-LDL et décès CV

Aucun avantage manifeste sur les décès CV

		Nombre de décès CV		
Essai	Année	Groupe recevant le traitement le plus intense	Groupe recevant le traitement le moins intense	RRI (IC à 95 %)
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)
Résumé		1 540	1601	0,96 (0,90-1,03)

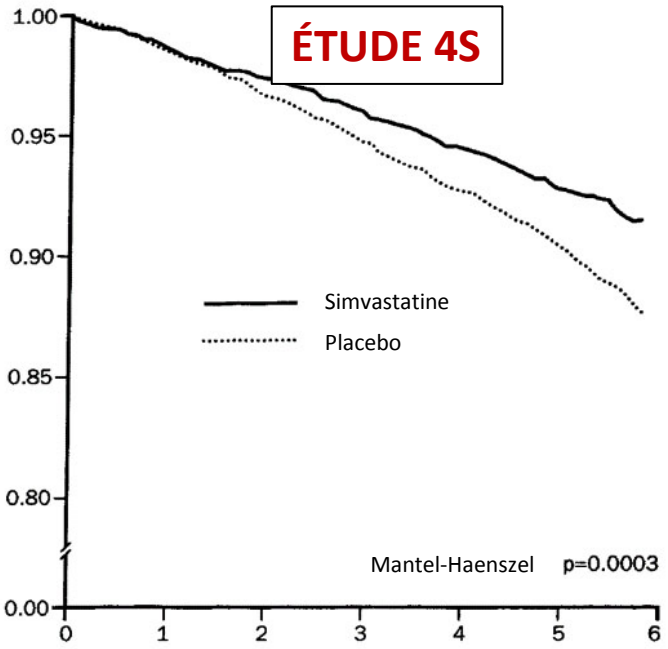
NEJM 2004;350:1495-504
JAMA 2004;292:1307-16
NEJM 2005;352:1425-35
JAMA 2005;294:2437-45
Lancet 2010;376:1658-69
NEJM 2015;372:2387-97



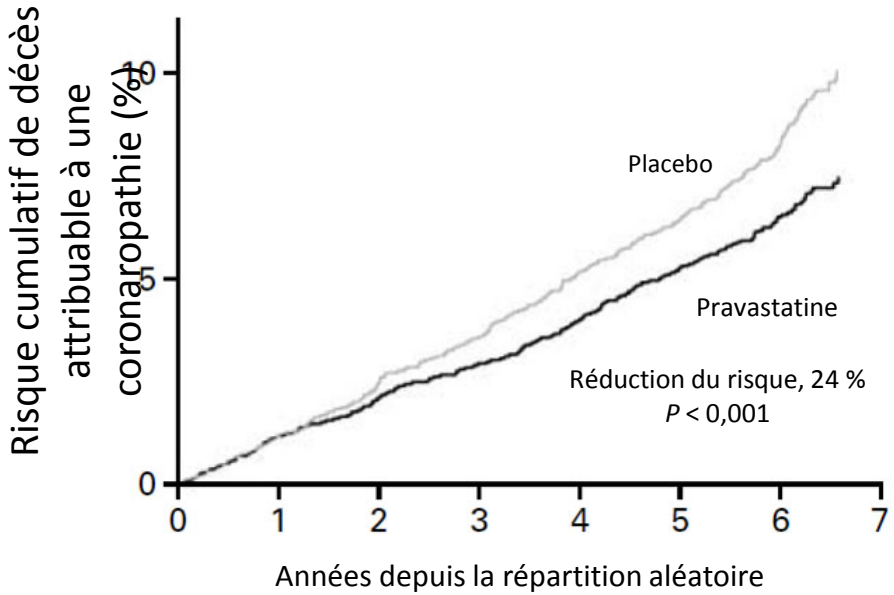
Réduction du C-LDL et des décès CV

Les bienfaits sur la mortalité n'étaient pas manifestes tôt dans l'essai même dans les essais pour lesquels il s'agissait du paramètre d'évaluation principal

ÉTUDE 4S



ÉTUDE LIPID

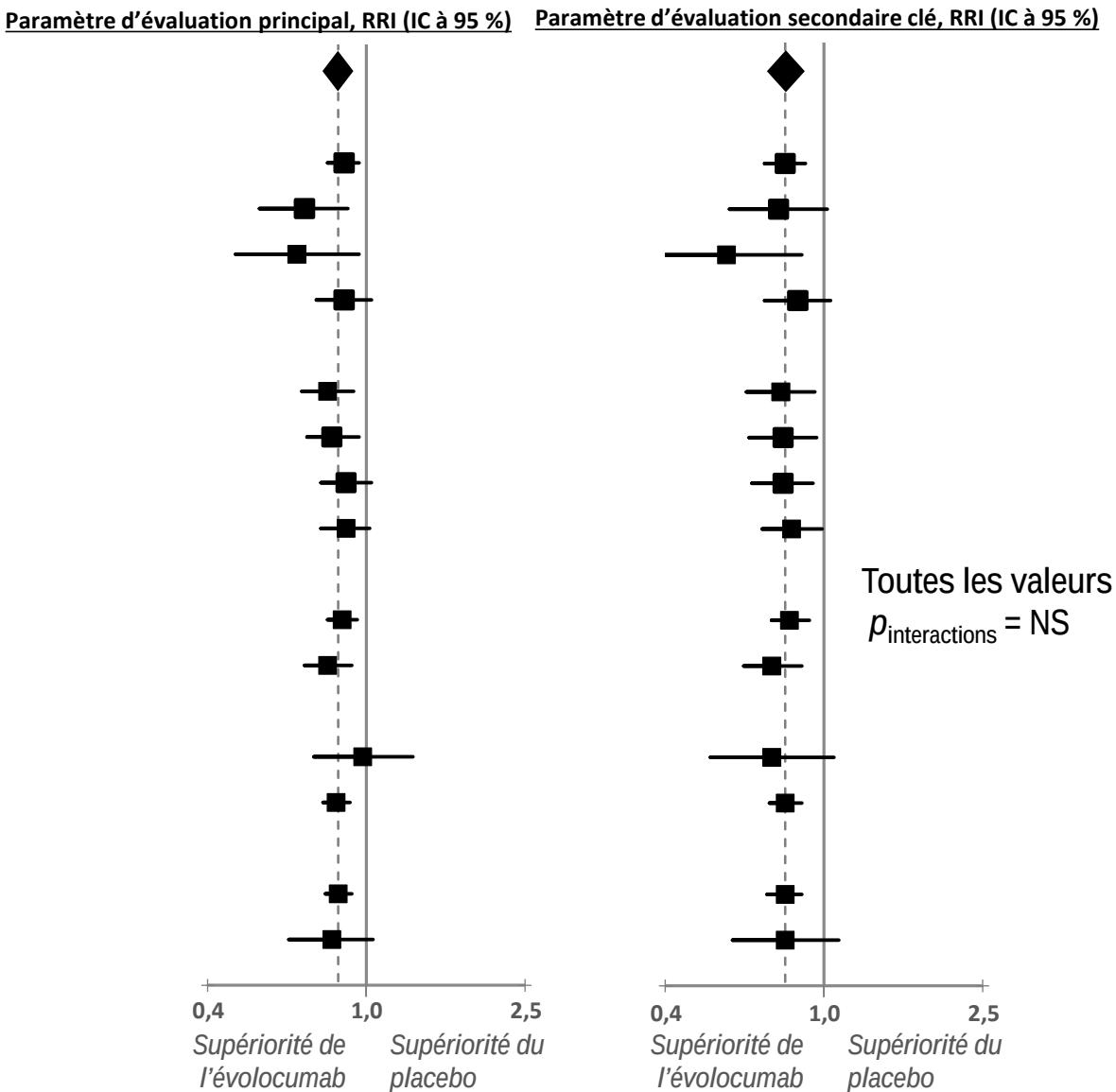


- Environ 2 ans pour une séparation des courbes
- **4S et LIPID**: 20% de fatality rate
- **FOURIER**: 5% de fatality rate

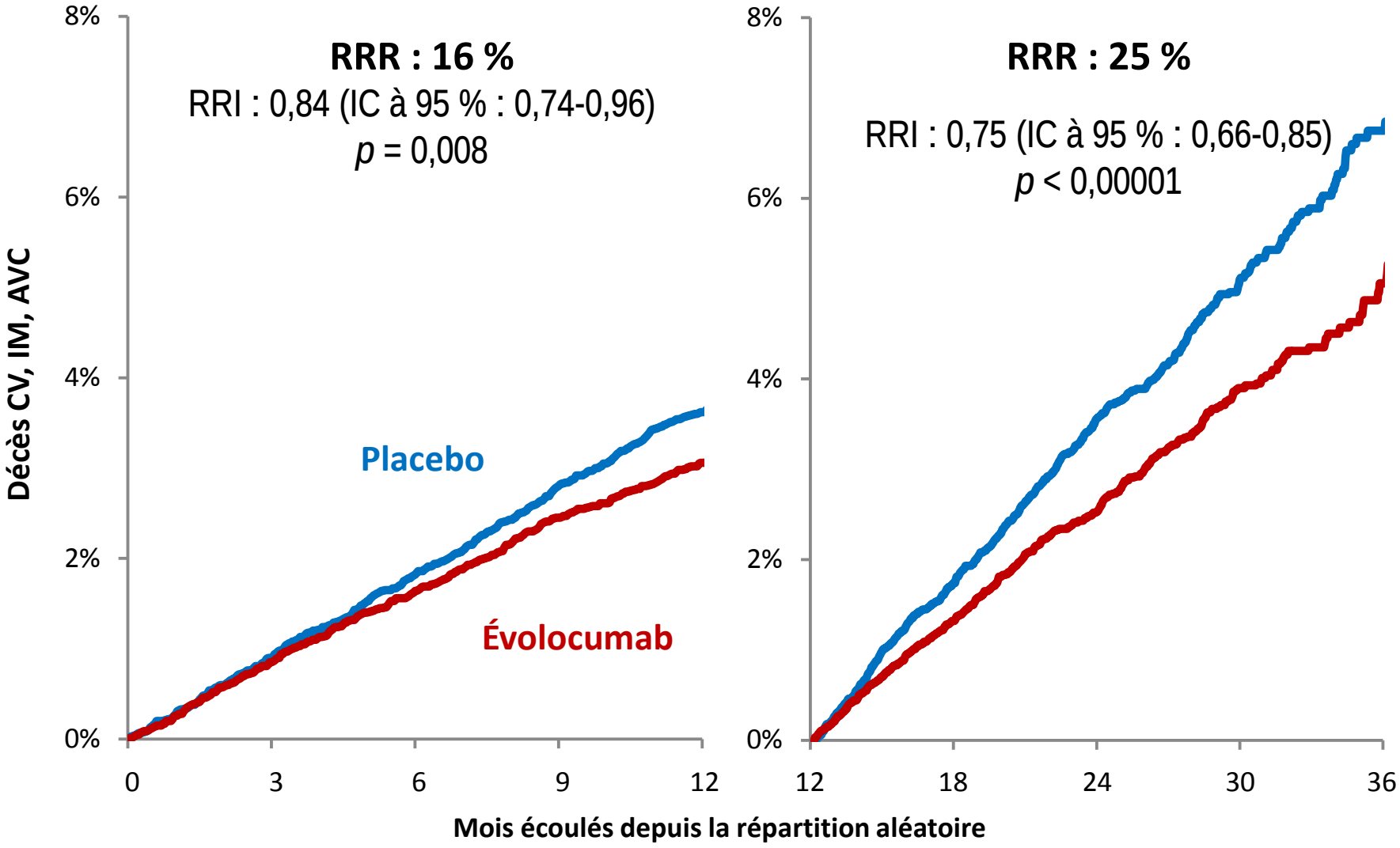
Lancet 1994;344:1383-89
NEJM 1998;339:1349-57

Sous-groupes clés

Sous-groupe	Patients
Total	*27 564*
Type de maladie	
IM seul	19 113
AVC seul	3 366
MAP seule	1 505
Maladie polyvasculaire	3 563
C-LDL au départ	
Q1 (< 2,07 mmol/L)	6 961
Q2 (2,07-< 2,38 mmol/L)	6 886
Q3 (2,38-2,82 mmol/L)	6 887
Q4 (> 2,82 mmol/L)	6 829
Intensité du traitement par statines au départ	
Élevée	19 103
Non élevée	8 461
Ézétimibe	
Oui	1 440
Non	26 124
Schéma posologique au départ	
Toutes les 2 semaines	24 774
Une fois par mois	2 790



Analyse déterminante



Réductions absolues du risque

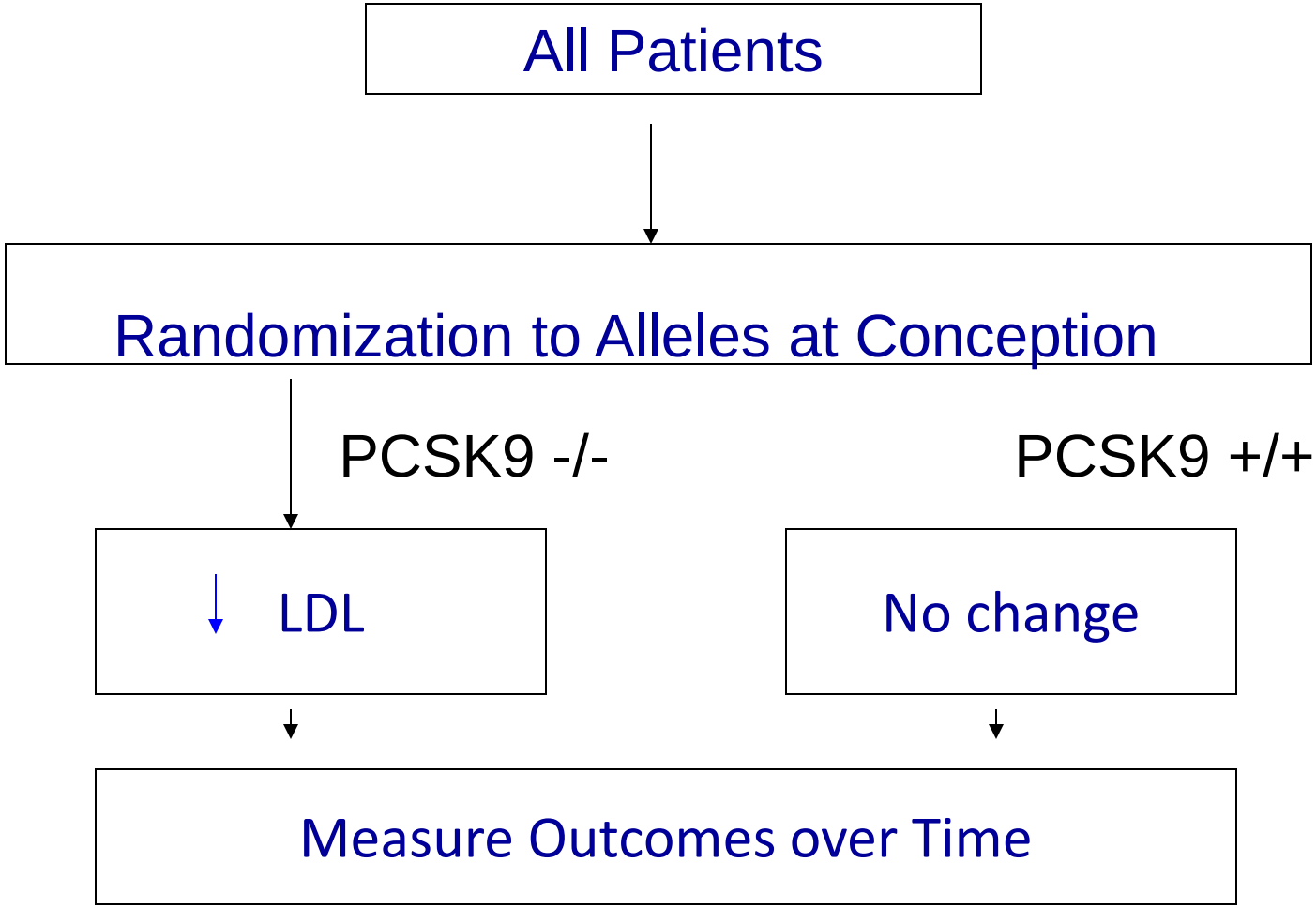
Dans le contexte de la prévention secondaire d'une maladie stable

Essai	Contexte de l'essai	↓ absolue selon les EICVM	Suivi	NNT sur 5 ans
CARE	Statine c. placebo chez des patients dont le C-LDL est moyen	3,0-4,2%	5,0 ans	24-34
LIPID	Statine c. placebo chez des patients dont le C-LDL est moyen	3,6-4,4%	6,1 ans	28-34
TNT	Ordonnance de doses de statines fortes c. modérées	2,2 %	4,9 ans	45
FOURIER	**iPCSK9 c. placebo chez des patients ayant reçu une ordonnance de statines**	**2,0 %**	**3,0 ans**	**25-30**

EICVM défini comme une combinaison du décès d'origine coronarienne ou CV, un IM ou un AVC.
Fourchette fournie lorsque les essais n'ont pas signalé une triple combinaison.
Dans le cas de l'essai FOURIER, la fourchette inférieure du NNT est fondée sur l'extrapolation du RRR des EICVM après la première année et les années subséquentes.

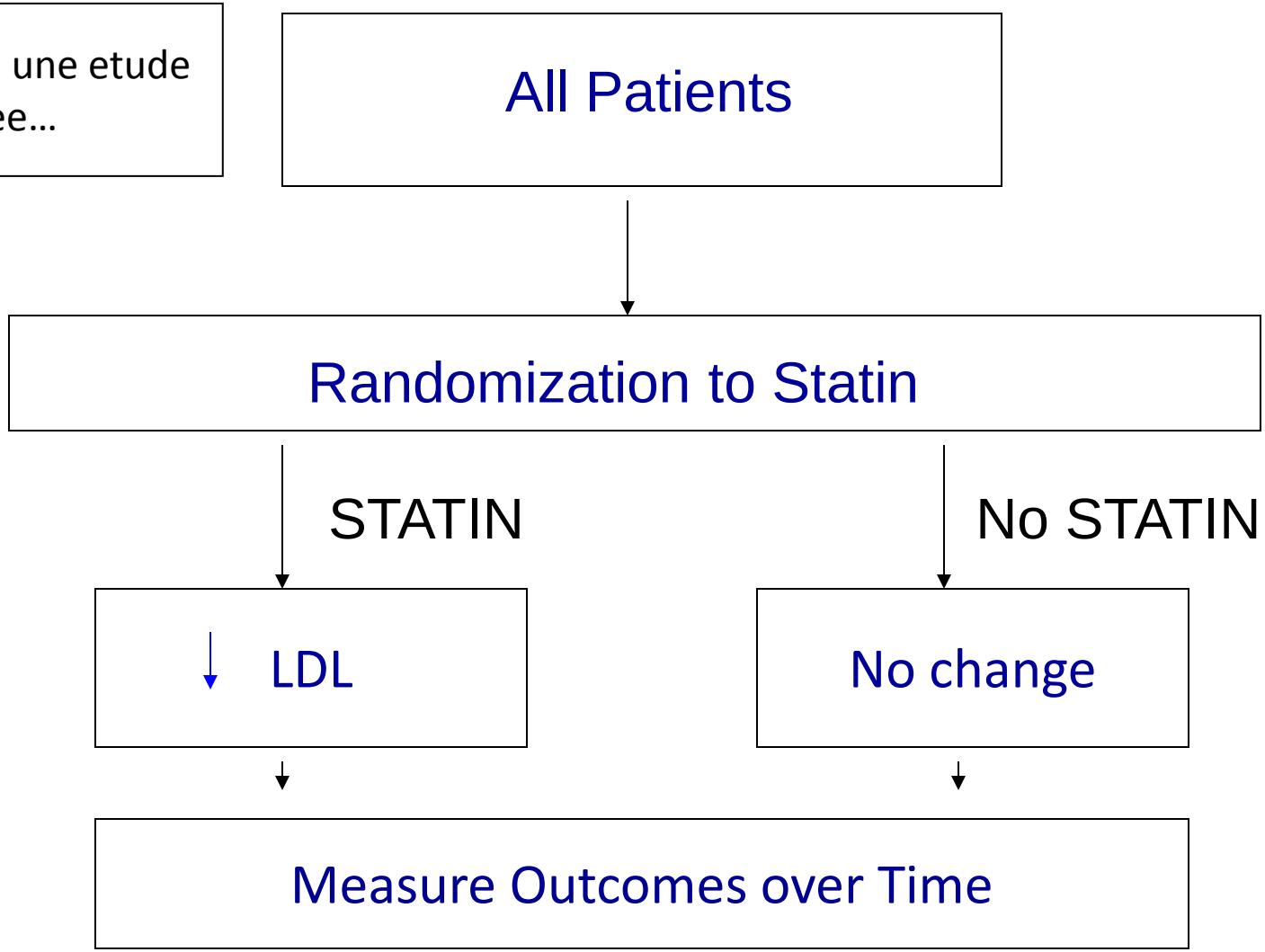
NEJM 1996;335:1001-9; *NEJM* 1998;339:1349-57; *NEJM* 2005;352:1425-35; *NEJM* 2017; publié en ligne avant l'impression.

#2. Variations génétiques



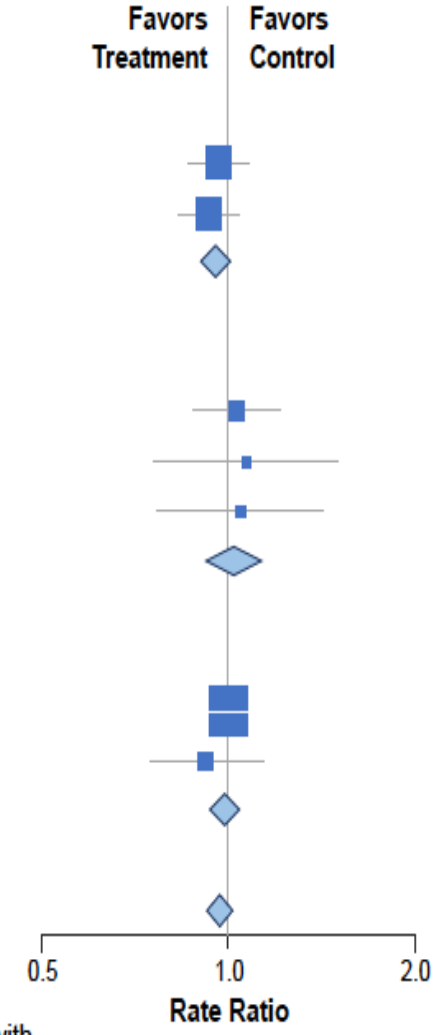
#2. Variations génétiques

Similaire a une etude randomisee…



Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

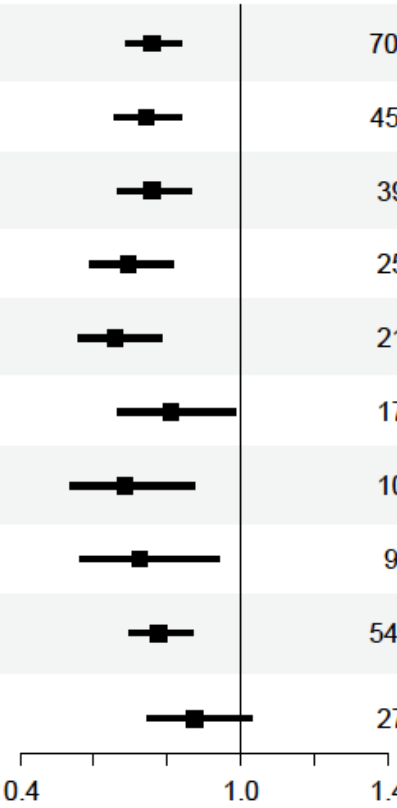
Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
Coronary heart disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87–1.08)
Coronary heart disease	1301 (3.3)	1394 (3.6)	0.93 (0.83–1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90–1.01)
			P=.12
Stroke			
Ischemic	574 (1.9)	554 (1.8)	1.03 (0.88–1.21)
Hemorrhagic	117 (0.4)	109 (0.4)	1.07 (0.76–1.51)
Unclassified/other	142 (0.4)	135 (0.3)	1.05 (0.77–1.43)
Any	870 (2.2)	843 (2.2)	1.03 (0.93–1.13)
			P=.60
Revascularization			
Coronary	3044 (9.3)	3040 (9.3)	1.00 (0.93–1.07)
Noncoronary	305 (2.7)	330 (2.9)	0.92 (0.75–1.13)
Any	3290 (10.0)	3313 (10.2)	0.99 (0.94–1.04)
			P=.60
Any major vascular event	5930 (15.2)	6071 (15.6)	0.97 (0.93–1.01)
			P=.10



Adapted with permission‡ from Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: Meta-analysis of 10 trials involving 77917 individuals. *JAMA Cardiol*. 2018;3:225-234. [‡https://creativecommons.org/licenses.org/by-nc/4.0/]

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.

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.

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.