Cardiovascular precision medicine

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MONTREAL HEART INSTITUTE

J-C Tardif - Presenter Disclosures

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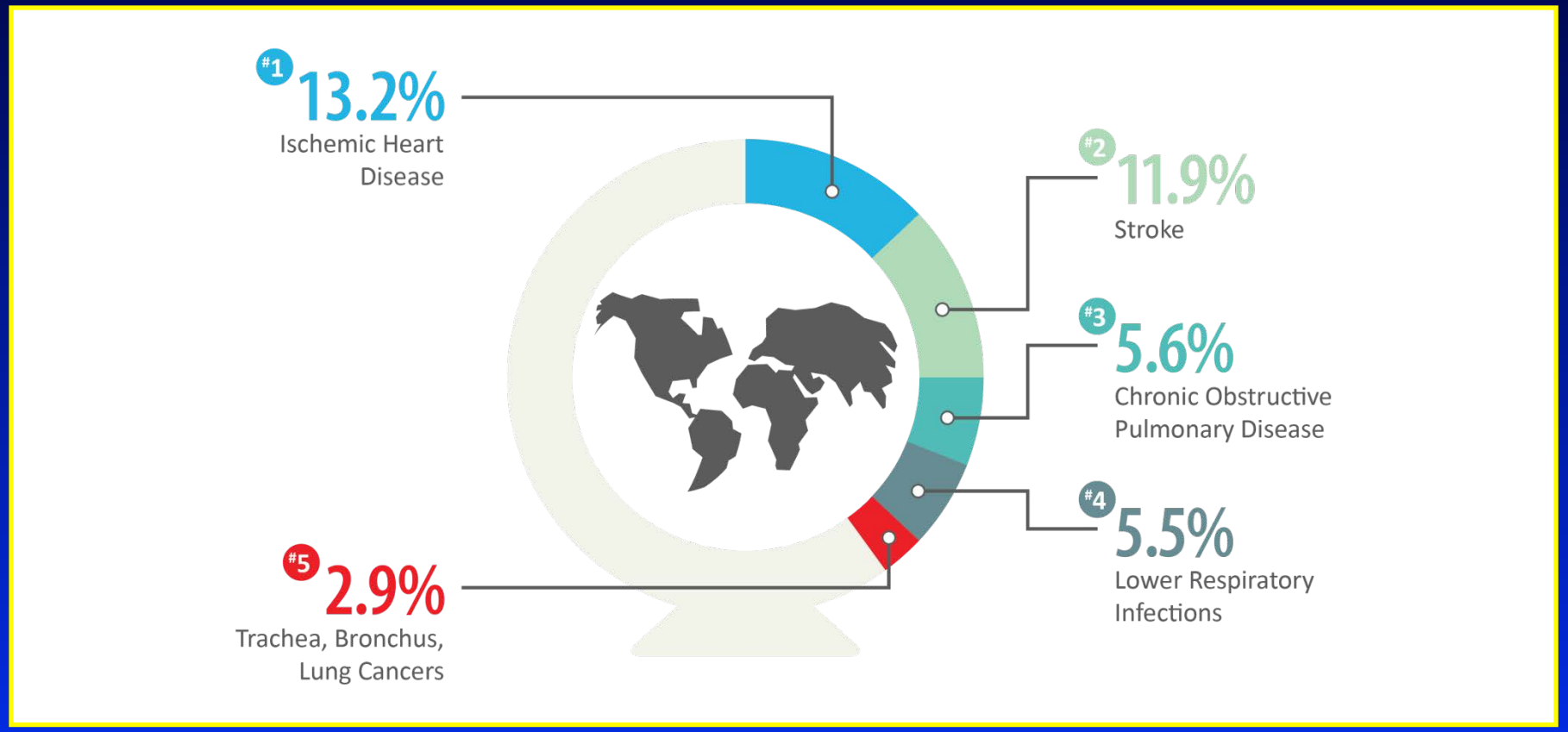
Consulting Fees: DalCor, Pfizer, Servier

Equity: DalCor

Cardiovascular diseases are the leading global cause of death

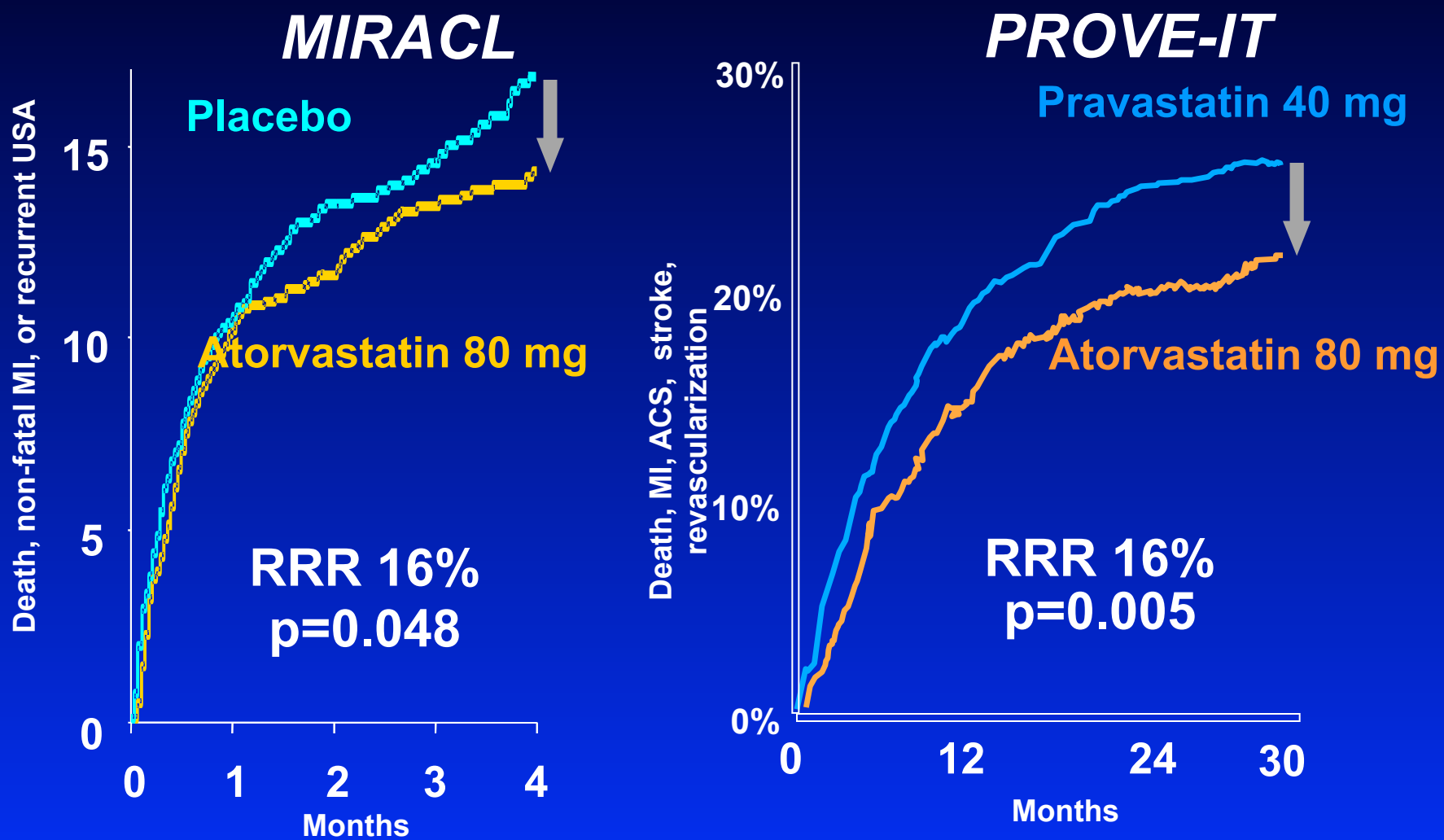
Top 5 Global Causes of Death in 2012



CVD includes ischemic heart disease and stroke.

World Health Organization. Cause-specific Mortality. Accessed at: http://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html.

Statins after ACS: Residual risk remains high despite intensive treatment



JAMA 2001;285:1411

N Engl J Med 2004;350:1495

Curbing atherosclerosis

- Multifaceted approach, multiple targets including:

  - LDL-cholesterol
  - High-density lipoprotein (HDL) function
  - Inflammation
  - Diabetes

- Precision medicine

  - Genetic markers
  - Plasma biomarkers
  - Imaging (molecular)
  - Personalized therapies

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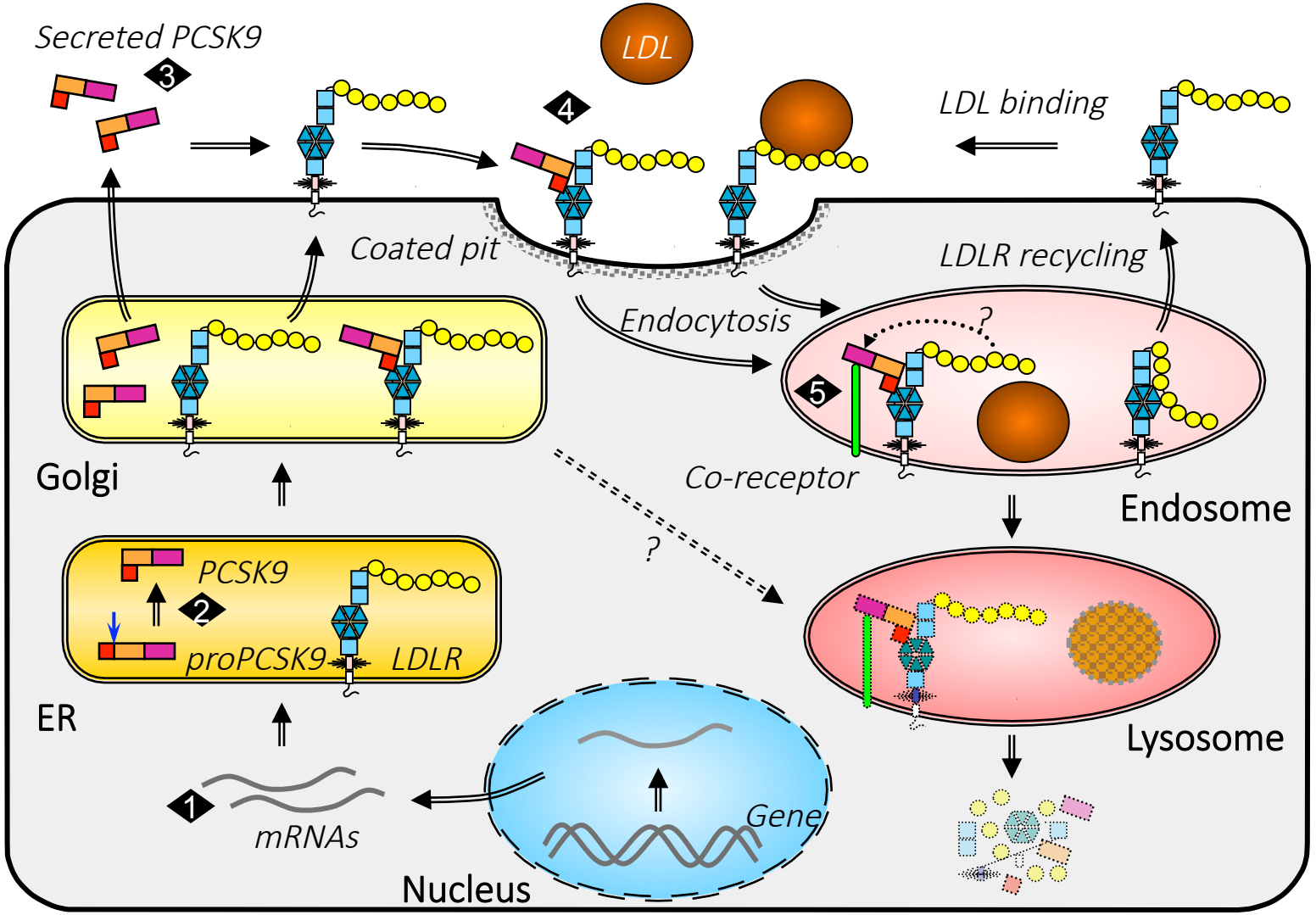
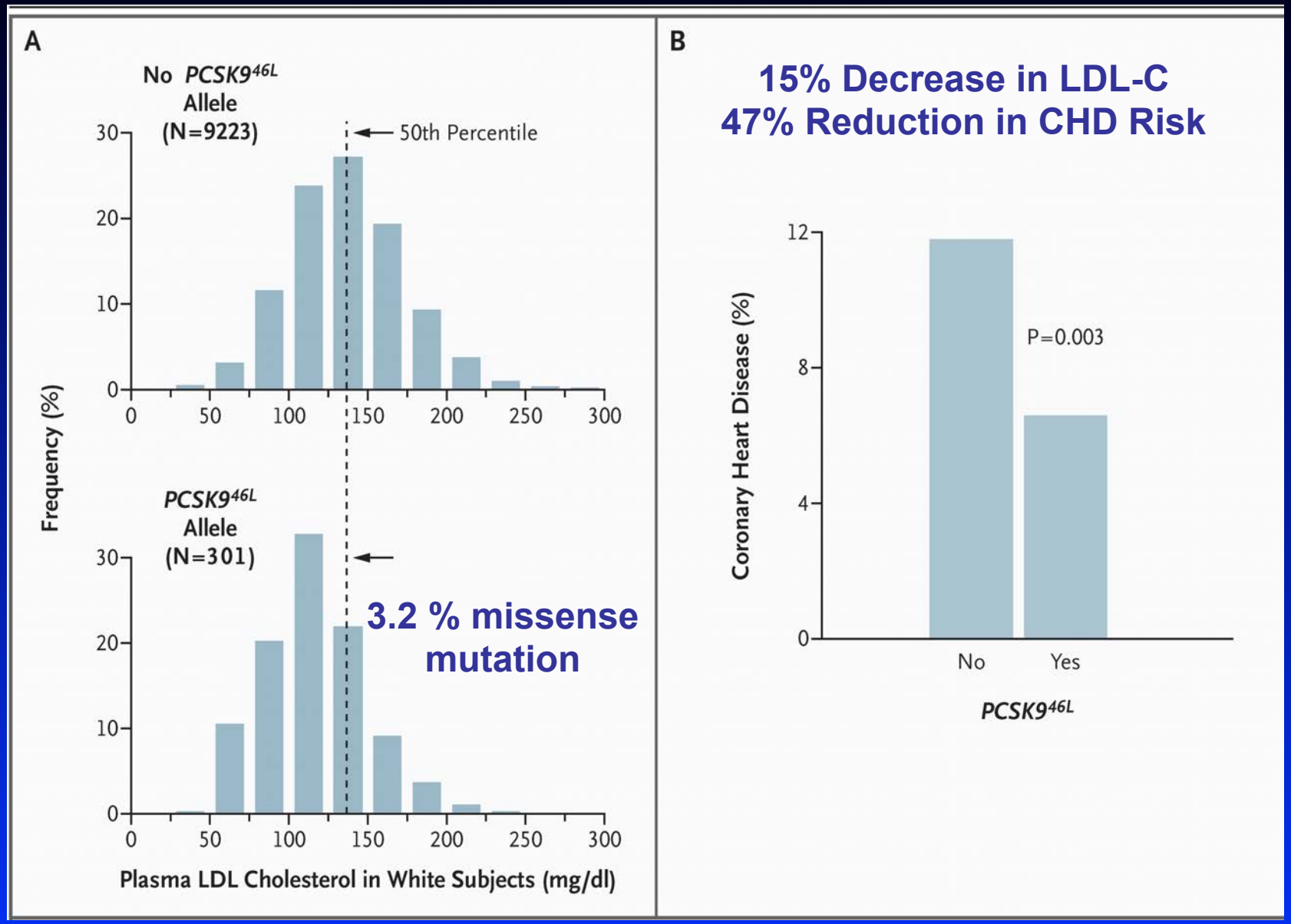
PCSK9 Causes Degradation of the LDLR



Rhainds D, Arsenault B and Tardif JC. Clin Lipidol 2012;7:621-640.

PCSK9 Mutations, LDL-C Reduction, and Vascular Events – White Subjects



Cohen NEJM 2006;354:1264-72

Monoclonal Antibodies to PCSK9 in Phase II studies

Effective as monotherapy
Koren Lancet 2012;380:1995-06
Sullivan JAMA 2012;308:2497-06

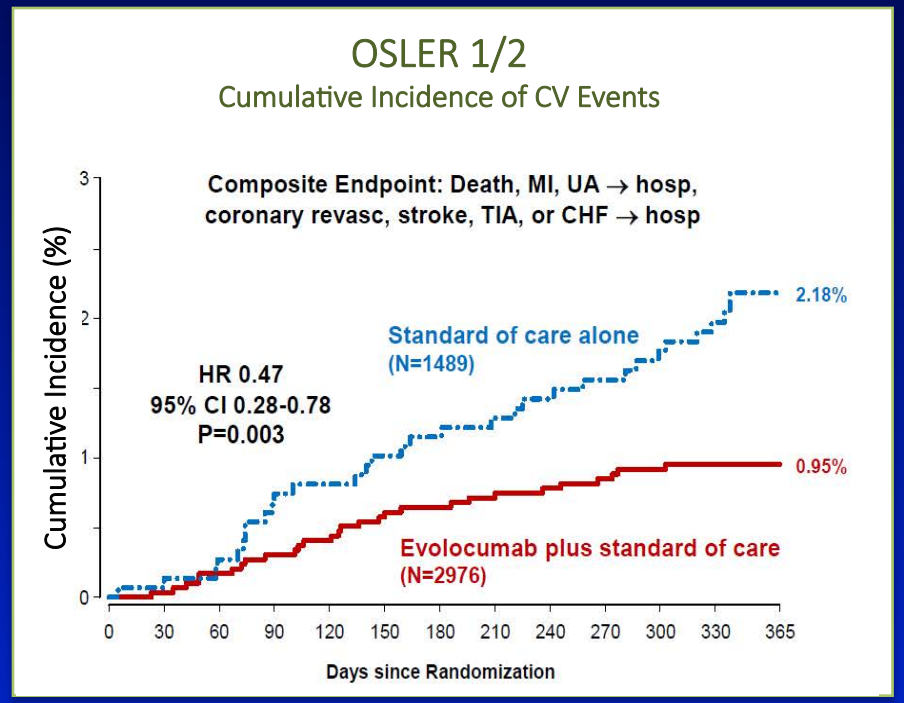
Effective as add-on to statin
Stein Lancet 2012;380:29-36
Stein NEJM 2012;366:1108-18
McKenney JACC 2012;59:1108-18
Guigliano Lancet 2012;380:2007-17
Stein Circulation 2013;128:2113-20
Roth NEJM 2012;367:1891-900
Blom NEJM 2014;370:1809-19

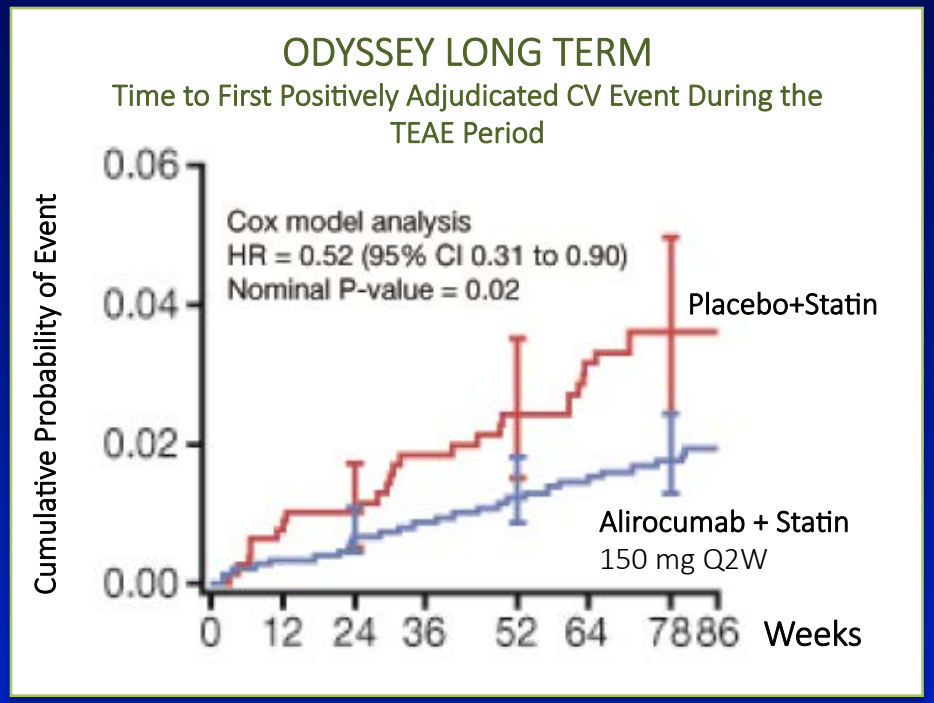
Effective in statin intolerance
Stroes JACC 2014;63:2541-8

Effective in heterozygous FH
(reduced LDLr activity)
Raal Circulation 2012;126:2408-17

Effective in homozygous FH
(LDLr defective)
Stein Circulation 2013;128:2113-20

Exploratory and Post Hoc Analyses Suggest Outcomes Benefit With PCSK9 Inhibition



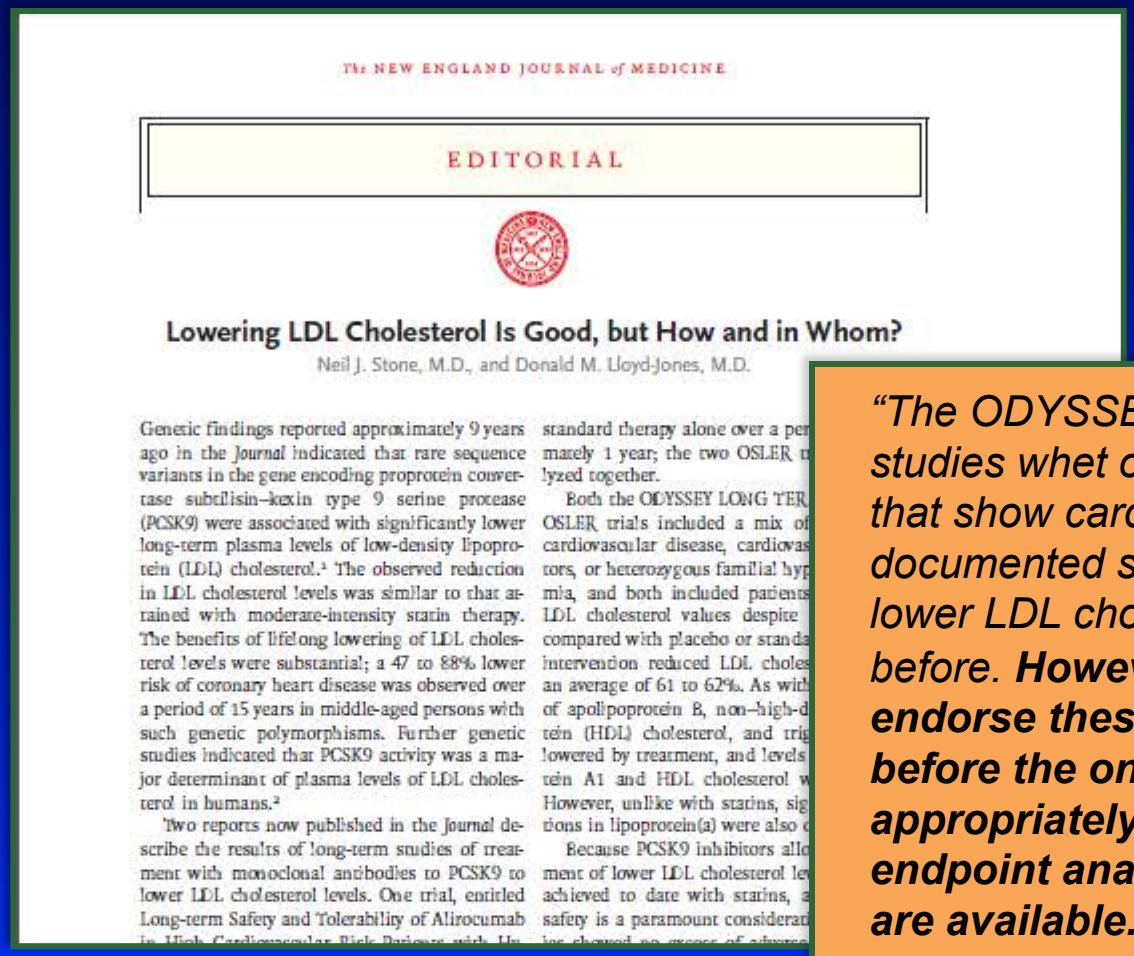


- CV outcomes declined by 53% over 1 year
  - Prespecified exploratory outcome with relatively few events

- In a post hoc analysis, the rate of death from CHD, nonfatal MI, ischemic stroke, or unstable angina requiring hospitalization was 3.3% in the placebo group and 1.7% in the intervention group
  - Low number of CV events limits ability to draw conclusions on outcomes

Sabatine et al. *N Engl J Med*. 2015;372(16):1500-9.
Robinson J et al. *N Engl J Med*. 2015;372(16):1489-99.

Despite Initial Findings, Data from Ongoing CVOTs Are Needed To Confirm Outcomes Benefit With PCSK9 Inhibition



The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Lowering LDL Cholesterol Is Good, but How and in Whom?

Neil J. Stone, M.D., and Donald M. Lloyd-Jones, M.D.

Genetic findings reported approximately 9 years ago in the *Journal* indicated that rare sequence variants in the gene encoding proprotein convertase subtilisin–kexin type 9 serine protease (*PCSK9*) were associated with significantly lower long-term plasma levels of low-density lipoprotein (LDL) cholesterol.[1] The observed reduction in LDL cholesterol levels was similar to that attained with moderate-intensity statin therapy. The benefits of lifelong lowering of LDL cholesterol levels were substantial; a 47 to 88% lower risk of coronary heart disease was observed over a period of 15 years in middle-aged persons with such genetic polymorphisms. Further genetic studies indicated that PCSK9 activity was a major determinant of plasma levels of LDL cholesterol in humans.[2]

Two reports now published in the *Journal* describe the results of long-term studies of treatment with monoclonal antibodies to PCSK9 to lower LDL cholesterol levels. One trial, entitled Long-term Safety and Tolerability of Alirocumab

standard therapy alone over a per
mately 1 year; the two OSLER
lyzed together.

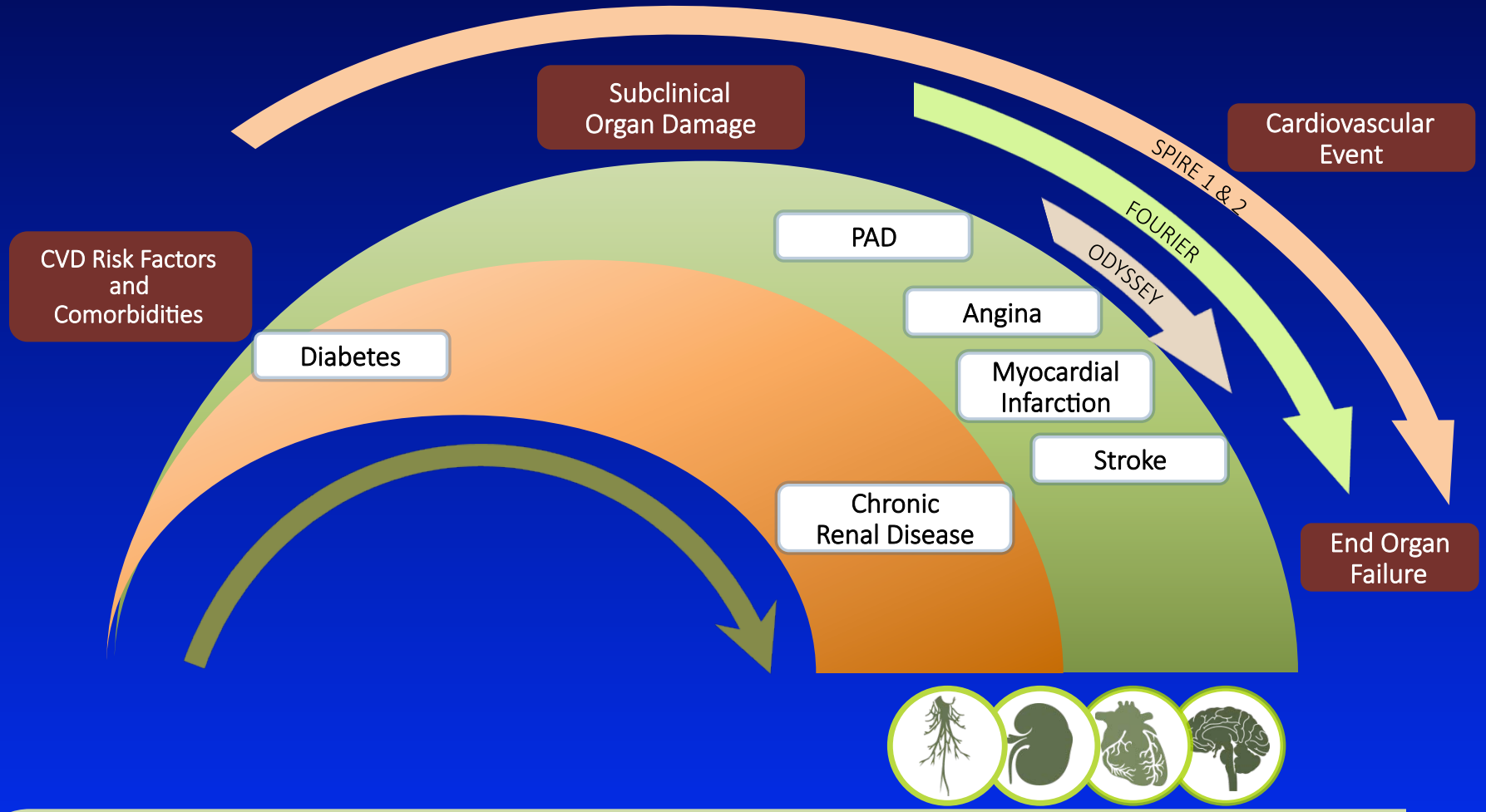
Both the ODYSSEY LONG TER
OSLER trials included a mix of
cardiovascular disease, cardiovas
tors, or heterozygous familial hyp
mia, and both included patients
LDL cholesterol values despite
compared with placebo or standa
intervention reduced LDL choles
an average of 61 to 62%. As with
of apolipoprotein B, non–high-d
tein (HDL) cholesterol, and trig
lowered by treatment, and levels
tein A1 and HDL cholesterol w
However, unlike with statins, sig
tions in lipoprotein(a) were also

Because PCSK9 inhibitors allo
ment of lower LDL cholesterol le
achieved to date with statins,
safety is a paramount considerat

"The ODYSSEY LONG TERM and OSLER studies whet our appetites for further results that show cardiovascular benefit and documented safety, even at substantially lower LDL cholesterol ranges than achieved before. ***However, it would be premature to endorse these drugs for widespread use before the ongoing randomized trials, appropriately powered for primary endpoint analysis and safety assessment, are available.*** *Reports from several lipid treatment trials provide important object lessons in this regard…"*

Stone NJ, Lloyd-Jones DM. *N Engl J Med.* 2015 Mar 15.

Ongoing CVOTs Will Evaluate the Impact of PCSK9 Inhibition on CV Events in Distinct Populations Throughout the CV Risk Continuum

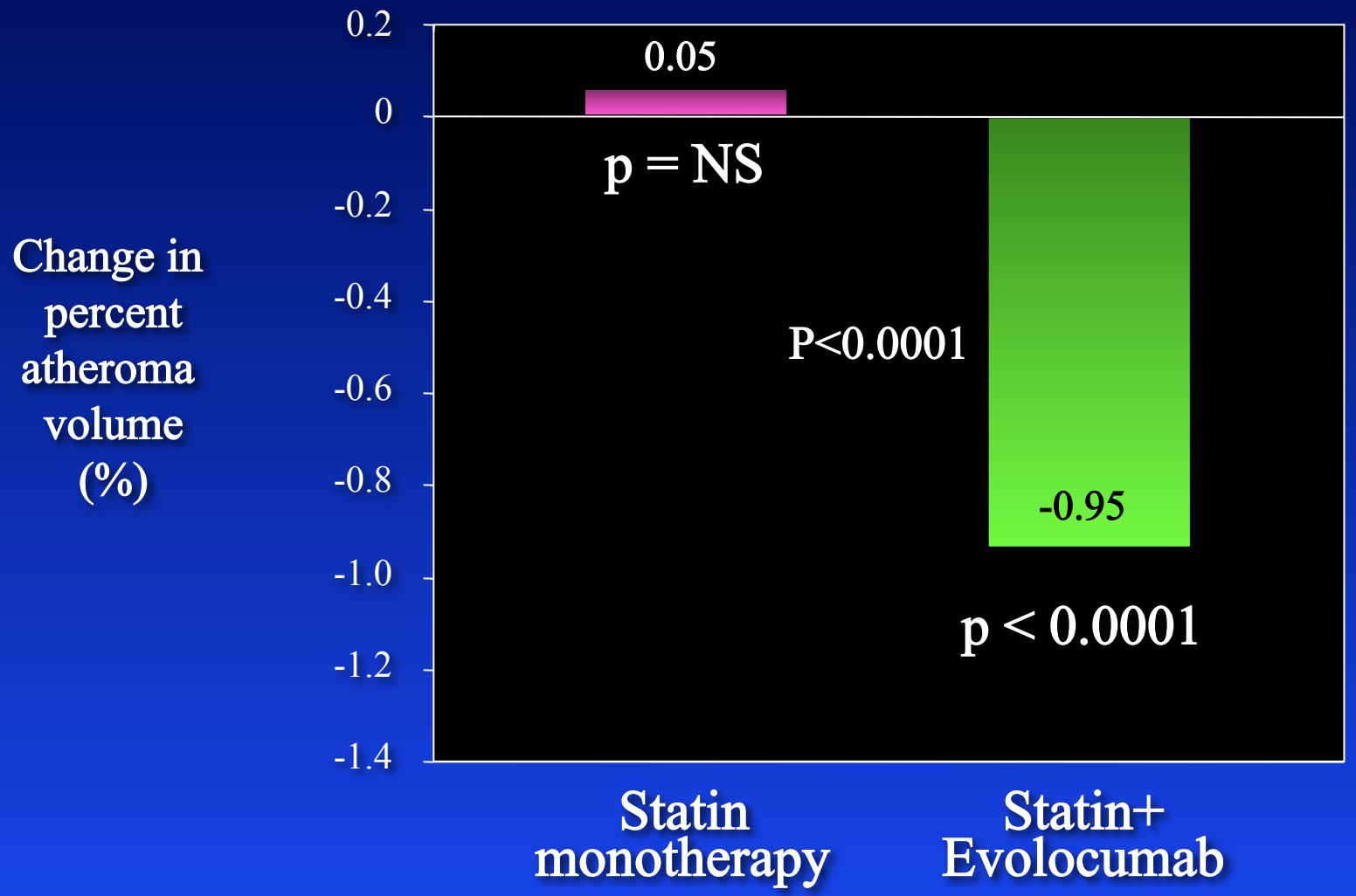


SPIRE 1 and 2 were designed to evaluate CV outcomes in patients on lipid-lowering therapy that have combinations of CVD comorbidities and risk factors that create a high risk of a first CV event OR have had a prior CV event or related procedure*

Dzau VJ, et al. *Circulation*. 2006;114:2850-70; Dzau VJ, et al. *Circulation*. 2006;114:2871-91.

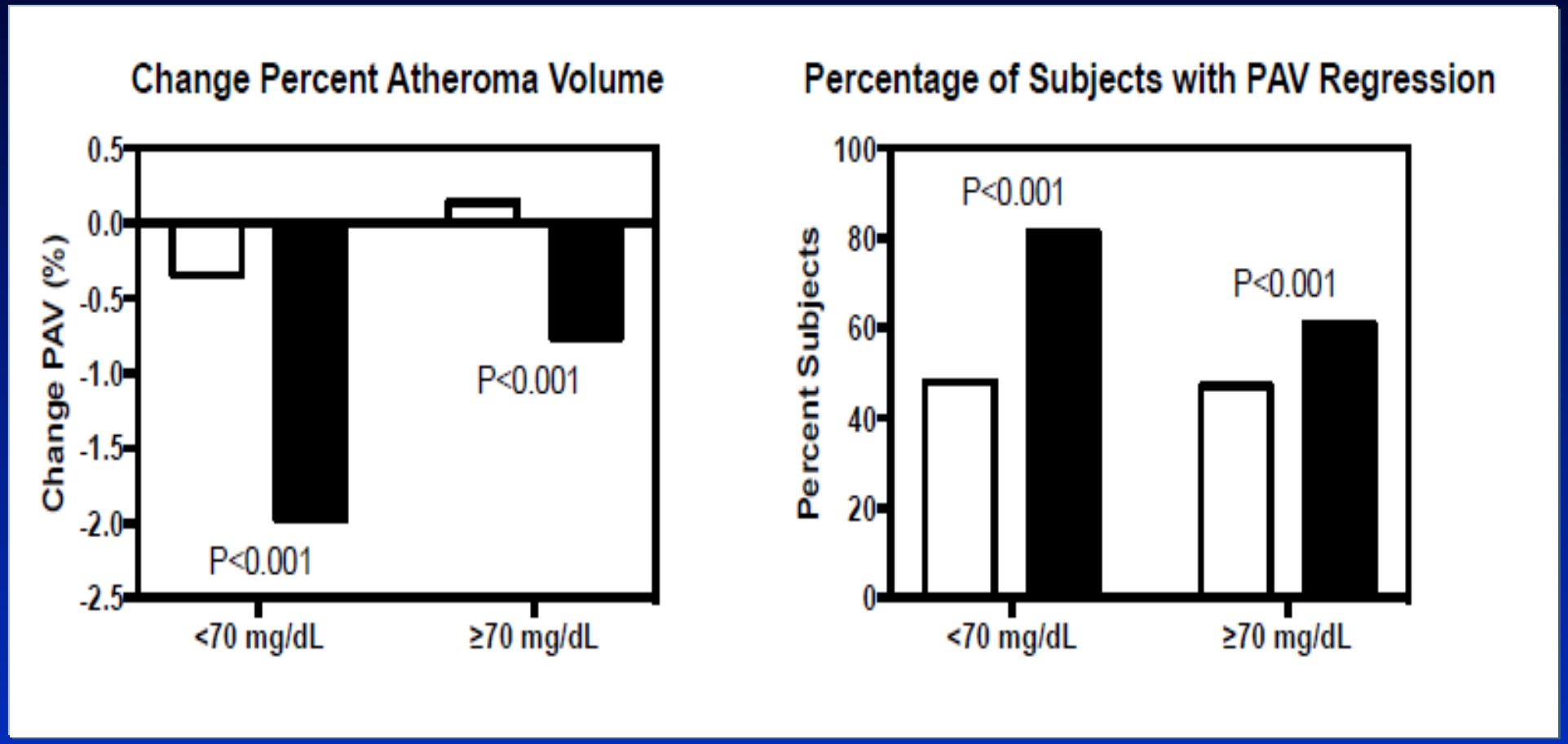
*Includes highly effective statins unless statin intolerant.

Primary endpoint: Percent atheroma volume



Nicholls SJ, et al. *JAMA* 2016 Nov 15.

Changes on IVUS according to baseline LDL-C



Nicholls SJ, et al. *JAMA* 2016 Nov 15.

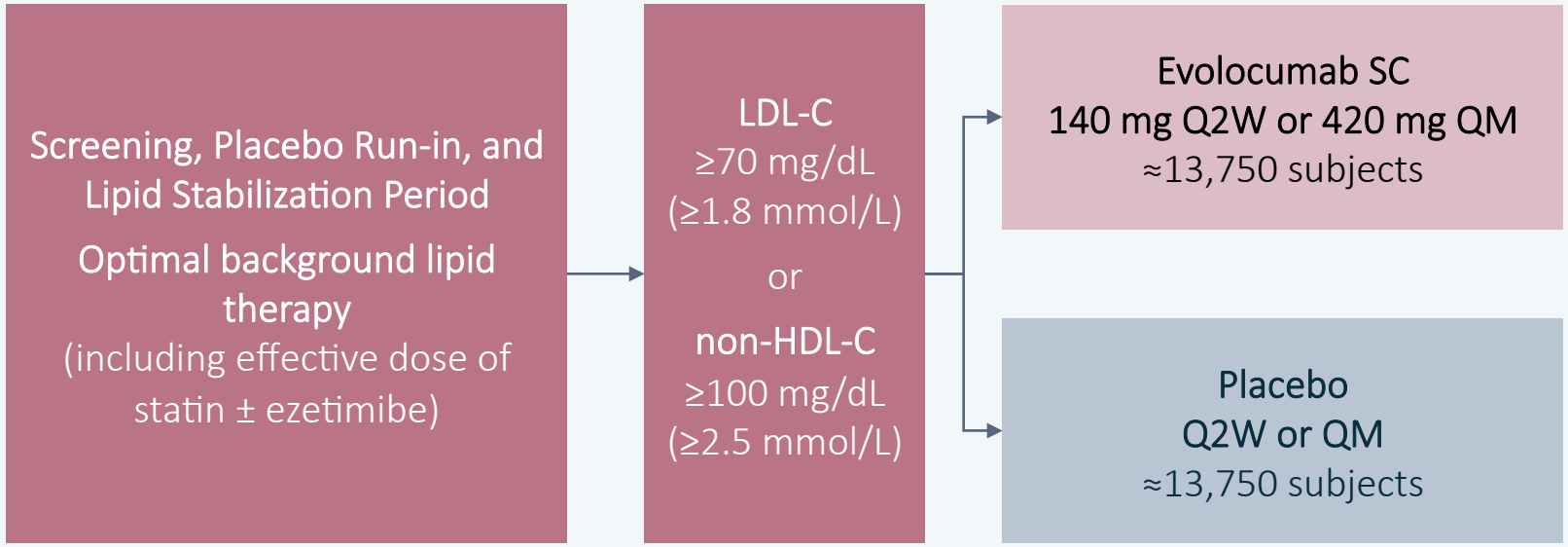
The Evolocumab FOURIER Study Assesses CV Outcomes in a Secondary Prevention Population With Prior CVD

Patient Population

- 27,564 patients with CVD (prior MI, non-hemorrhagic stroke, or symptomatic PAD)
- Age 40 to 85 years
- Additional risk factors (1 major or 2 minor)

Primary Endpoint

- CV death
- MI
- Hospitalization for unstable angina
- Stroke
- Coronary revascularization



CV=cardiovascular; CVD=cardiovascular disease; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; non-HDL-C=non-high-density lipoprotein cholesterol; PAD=peripheral arterial disease; Q2W=every two weeks; QM=monthly; SC=subcutaneous.

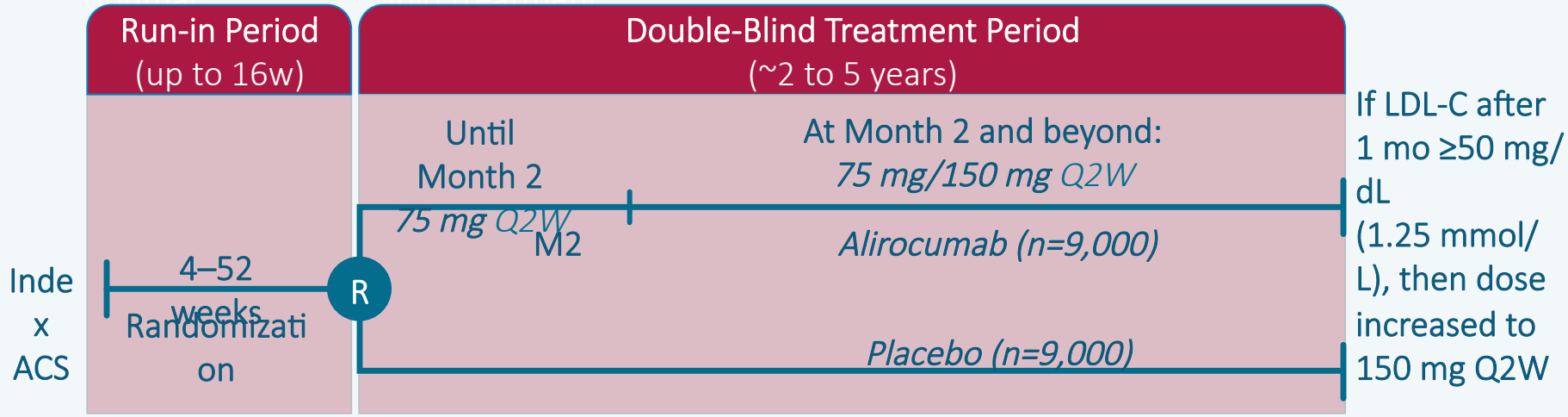
Repatha™ (evolocumab) has been approved for use by the U.S. FDA and EC.

Sabatine MS. *AHJ American Heart Journal.* 2016;173:94-101.

The Alirocumab ODYSSEY Outcomes Study Focuses on a Secondary Prevention Population Post ACS

Patient Population
- ACS event 4 to 52 weeks prior to randomization
- Age >40 years
- LDL-C ≥70 mg/dL (1.8 mmol/L) despite optimal lipid treatment

Primary Endpoint: Composite of
- CHD death
- Non-fatal MI
- Ischemic stroke
- Unstable angina requiring hospitalization



Background lipid treatment: Atorvastatin 40/80 mg, or rosuvastatin 20/40 mg, or atorvastatin/rosuvastatin at maximal tolerated dose, with or without nonstatin lipid treatments, throughout study

Diet: NCEP-ATPIII Therapeutic Lifestyle Changes or equivalent throughout study

ACS=acute coronary syndrome; CHD=coronary heart disease; LDL=low-density lipoprotein; MI=myocardial infarction; Q2W=every two weeks.
Praluent® (alirocumab) has been approved for use by the US FDA and EC.
Schwartz GG et al. *Am Heart J.* 2014;168(5):682-689.

SPIRE Phase 3 Bococizumab Clinical Program:

Recently terminated

J-C Tardif, Executive committee co-chairman

SPIRE (Studies of PCSK9 Inhibition and the Reduction of Vascular Events) N=~30,000

SPIRE Lipid Lowering Studies

SPIRE HR (n = 600)
On statin
High risk of CV event
LDL-C ≥70 or ≥100 mg/dL

SPIRE LDL (n = 1,932)
On statin
High risk of CV event
LDL-C ≥70 mg/dL

SPIRE FH (n = 300)
HeFH (genetic diagnosis or Simon Broome Criteria),
LDL ≥70 mg/dl

SPIRE LL (n = 690)
On statin High / very high risk of CV event
LDL-C ≥100 mg/dL

SPIRE SI (n = 150)
Statin intolerant
LDL-C ≥70 mg/dL

SPIRE CV Outcomes Studies

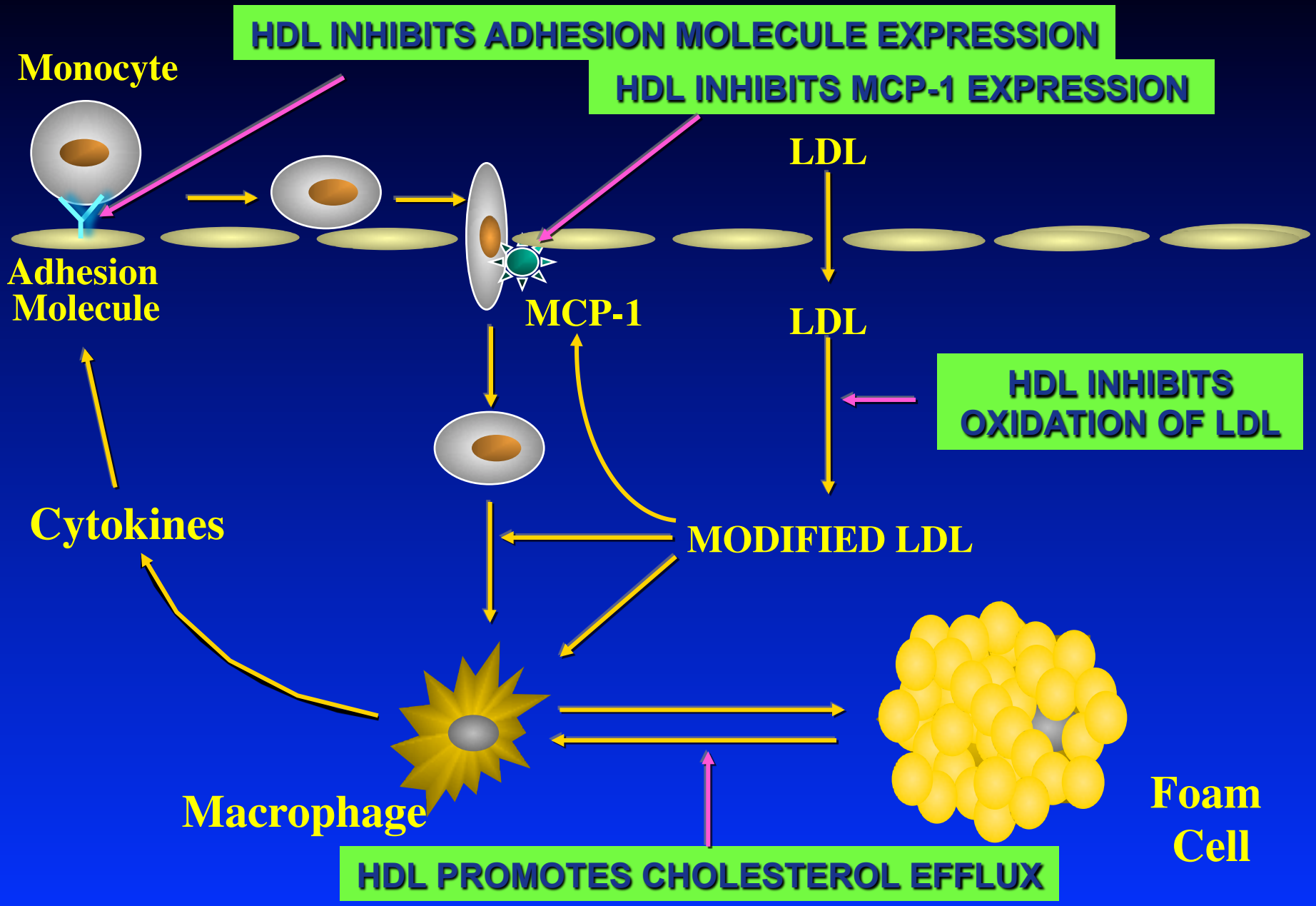
SPIRE-1 (n = 17,000)
High Risk Primary and Secondary Prevention
LDL-C ≥70 to <100 mg/dL on statins (or statin intolerant)

SPIRE-2 (n = 11,000)
High Risk Primary and Secondary Prevention
LDL-C ≥100 mg/dL on statins (or statin intolerant)

SPIRE
Studies on PCSK9 Inhibition and the Reduction of vascular Events

NCT#: https://clinicaltrials.gov
SPIRE HR: NCT01968954
SPIRE LDL: NCT01968967
SPIRE HF: NCT01968980
SPIRE-LL: NCT02100514
SPIRE-SI: NCT02135029
SPIRE-1: NCT01975376
SPIRE-2: NCT01975389

INHIBITION OF ATHEROSCLEROSIS BY HDL



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

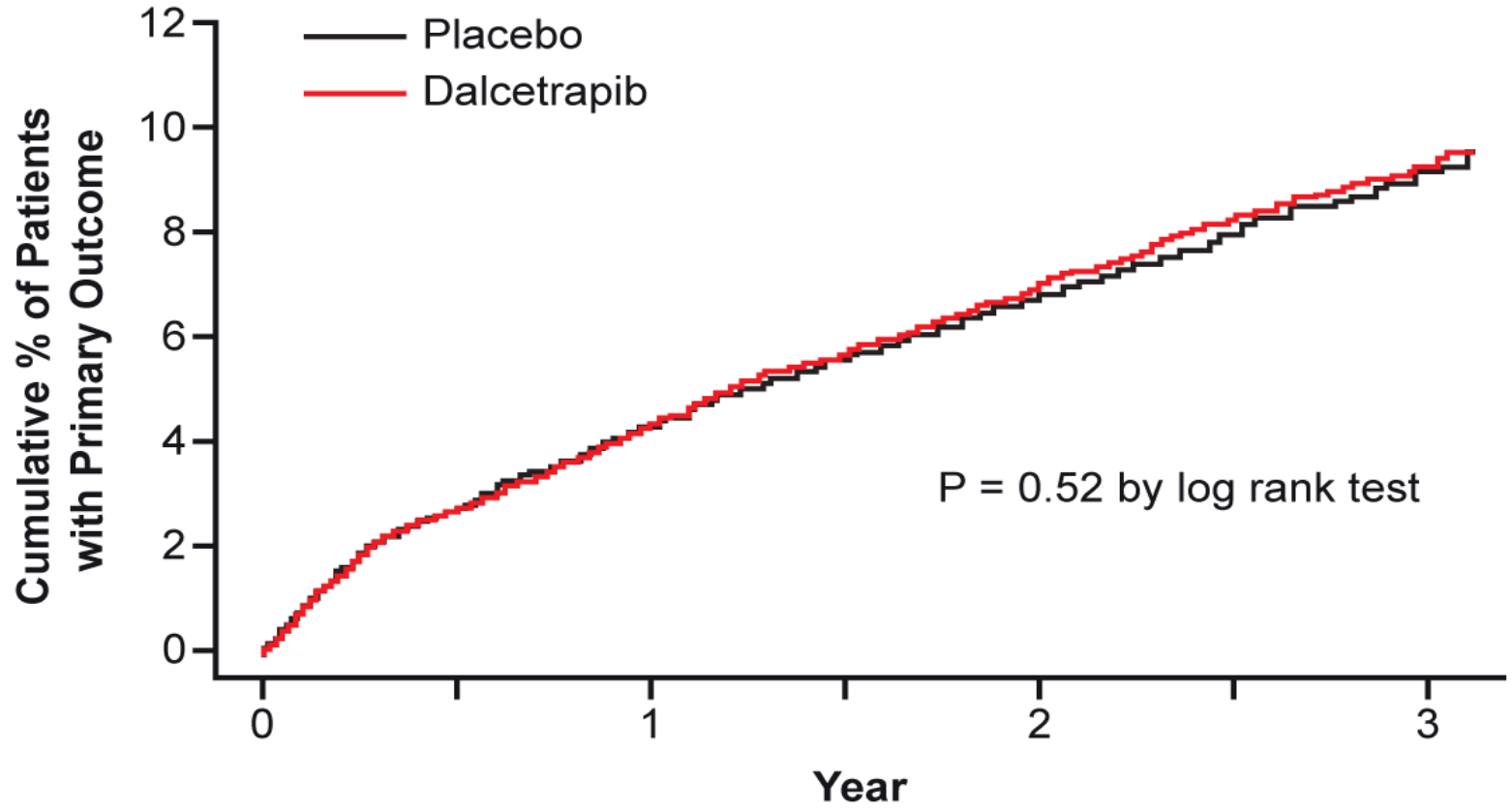
Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome

Gregory G. Schwartz, M.D., Ph.D., Anders G. Olsson, M.D., Ph.D., Markus Abt, Ph.D., Christie M. Ballantyne, M.D., Philip J. Barter, M.D., Ph.D., Jochen Brumm, Ph.D., Bernard R. Chaitman, M.D., Ingar M. Holme, Ph.D., David Kallend, M.B., B.S., Lawrence A. Leiter, M.D., Eran Leitersdorf, M.D., John J.V. McMurray, M.D., Hardi Mundl, M.D., Stephen J. Nicholls, M.B., B.S., Ph.D., Prediman K. Shah, M.D., Jean-Claude Tardif, M.D., and R. Scott Wright, M.D., for the dal-OUTCOMES Investigators*

Quintiles (a clinical research organization), Montreal Heart Institute Coordinating Center, and Cleveland Clinic Coordinating Center for Clinical Research managed the study and collected the data. An independent data and safety monitoring

NEJM 2012;367:2089-2099

Main dal-Outcomes Trial Results



No. at Risk				
Placebo	7933	7386	6551	1743
Dalcetrapib	7938	7372	6495	1736

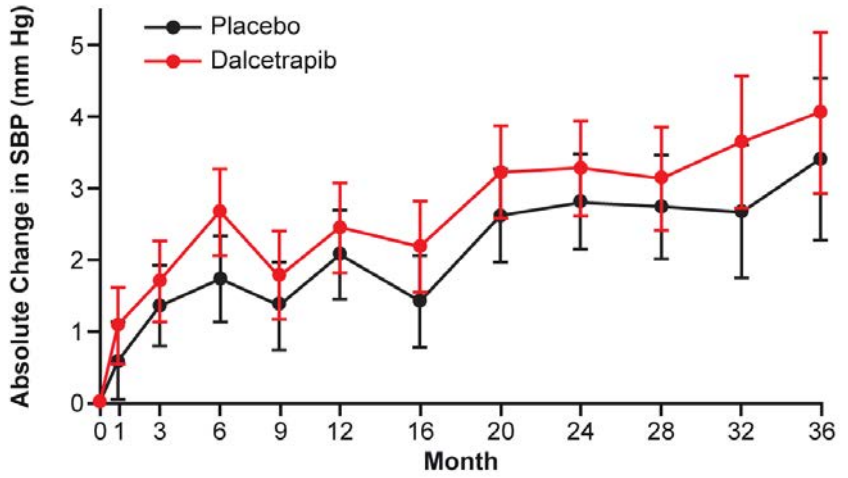
NEJM 2012;367:2089-2099

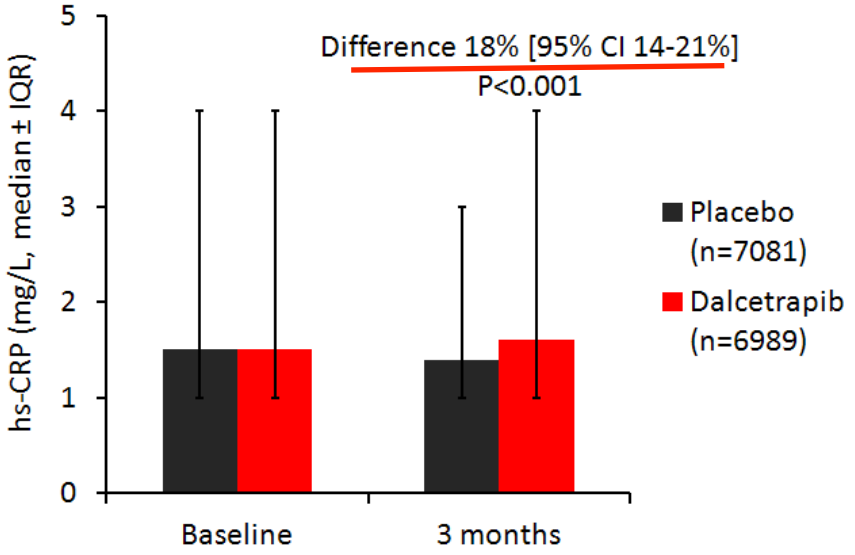
hs-CRP was higher with dalcetrapib than placebo

With dalcetrapib, versus placebo:

- Mean *systolic blood pressure* was 0.6 mm Hg higher (P<0.001)
- More AE/SAE related to hypertension
- No effect on plasma aldo-sterone, bicarbonate, or K+
- No difference in number of anti-hypertensive medications

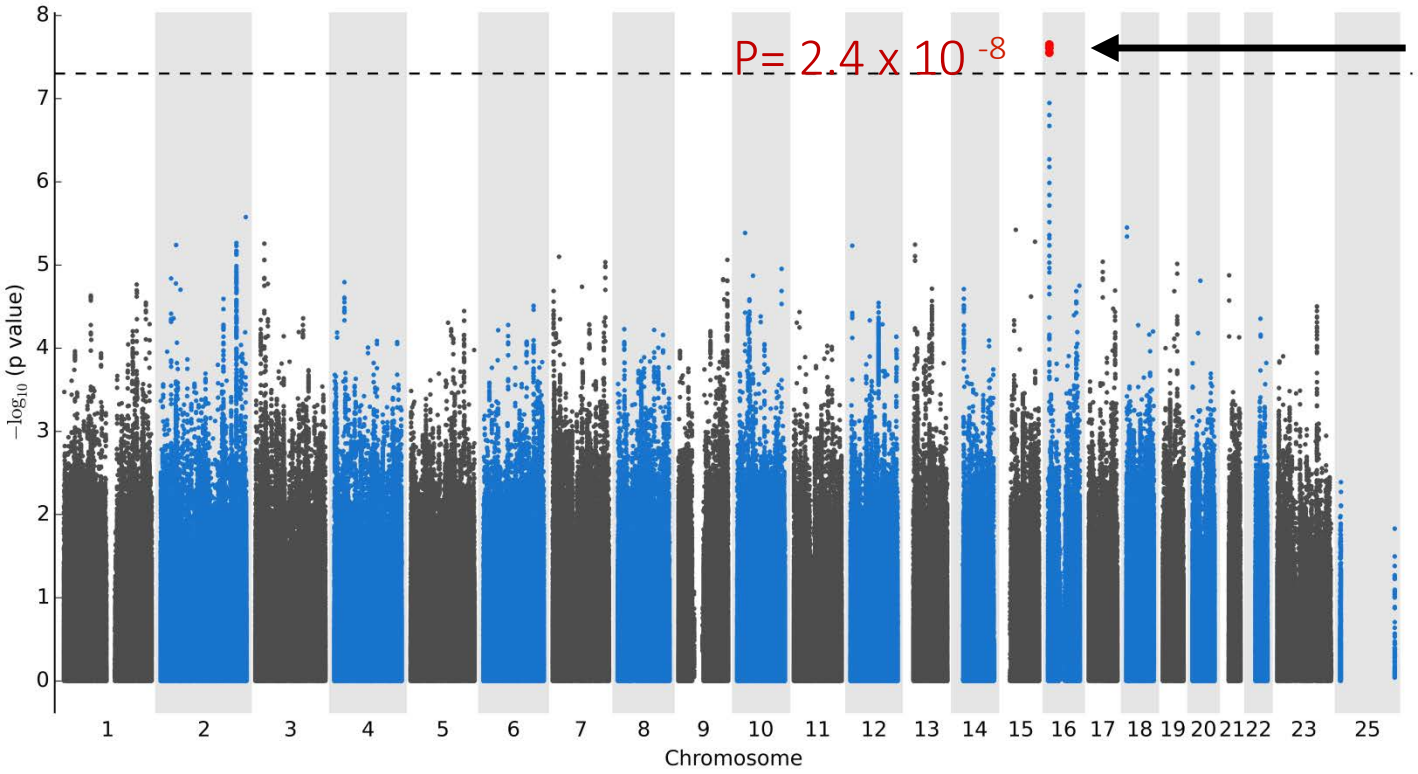
- At 3 months, *hs-CRP* was higher with dalcetrapib (P<0.001, ANOVA after log transformation)



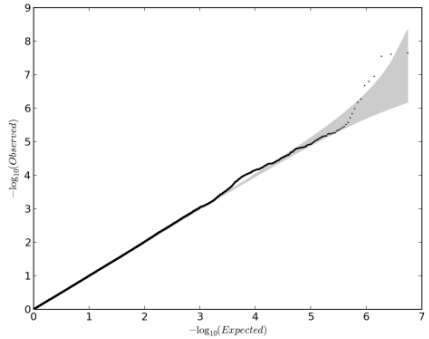


Discovery GWAS results in dal-Outcomes

Manhattan plot of 5,543,264 SNPs with MAF ≥ 0.05 in the dalcetrapib arm



Q-Q plot



Cox proportional hazards model for CV events adjusted for sex and 5 principal components

Note: Chr 23 is the non-pseudoautosomal region of the X chr and 25 is for the pseudoautosomal regions

Tardif et al. Circulation Cardiovasc Genet. 2015;8:372-382

Discovery GWAS results

Table 2. Results with $P<5X10^{-8}$ in the dal-OUTCOMES discovery genome-wide association study (GWAS)

a. Cox proportional-hazards results in the dal-OUTCOMES dalcetrapib arm (n=2845)

SNP	Genotype group	Patients with events	Patients without events	β_g[1]	β_g P value[2]	HR (95% CI)
rs1967309	AA	38	447	-0.429	2.41×10^{-8}	0.651 (0.560, 0.757)
	AG	176	1203			
	GG	176	802			

b. Cox proportional-hazards results in the dal-OUTCOMES placebo arm (n=2904)

SNP	Genotype group	Patients with events	Patients without events	β_g[1]	β_g P value[2]	HR (95% CI)
rs1967309	AA	59	417	-0.085	0.248	0.916 (0.793, 1.06)
	AG	192	1225			
	GG	146	860			

1. Estimate of the regression parameter for the additive genetic effect adjusted for gender and 5 principal components for genetic ancestry, and where homozygotes for the common allele are coded 0, heterozygotes 1, and homozygotes for the rare allele are coded 2; ***2.*** Likelihood ratio test of the genotype effect, where H_0: $\beta_g=0$; HR: hazard ratio; SNP: single nucleotide polymorphism.

Genome-wide significant finding

Effect absent with placebo

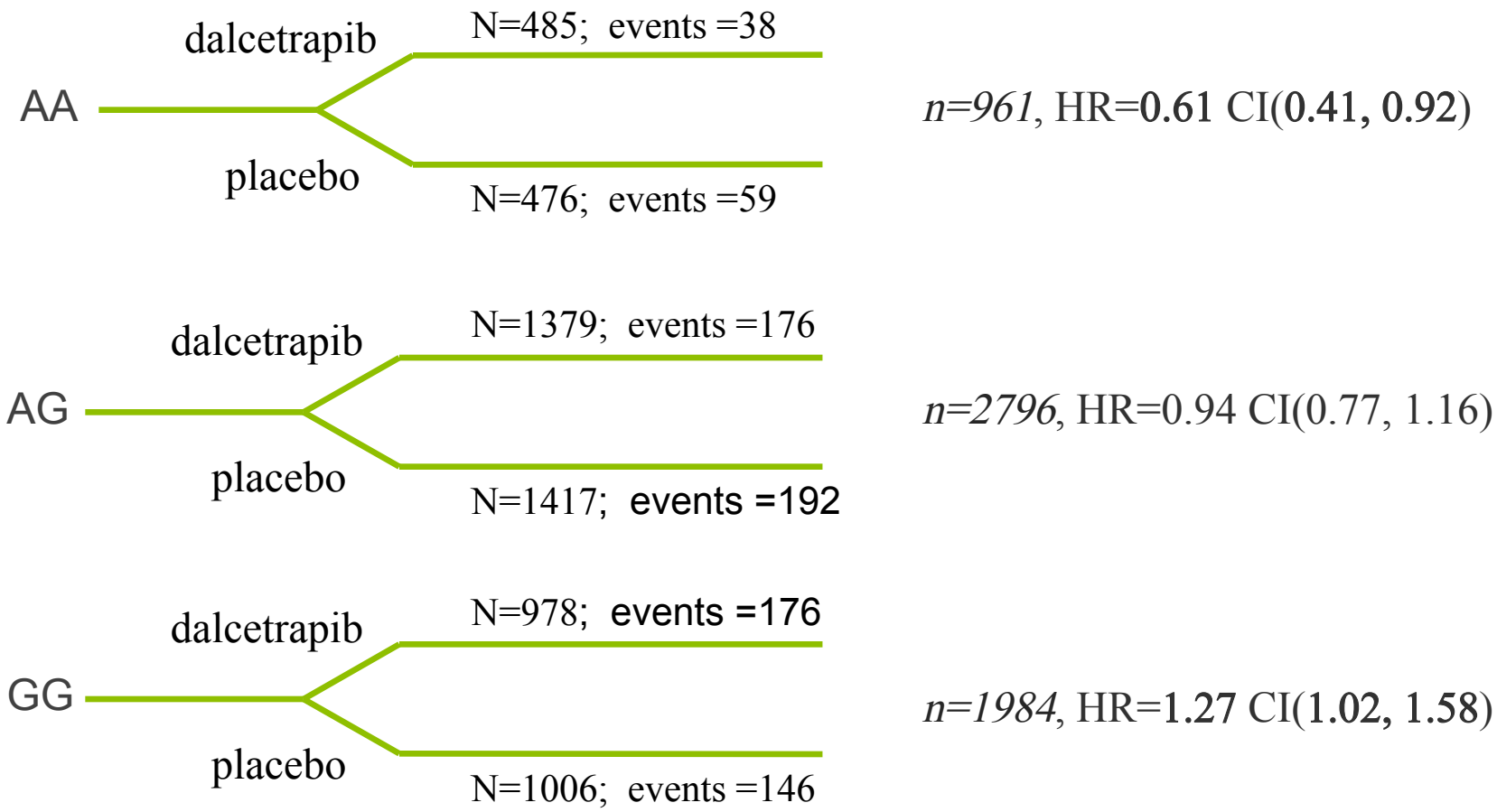
The gene-by-treatment arm interaction term is indicative of a statistical interaction (P=0.0014; beta: -0.340)

Tardif et al. Circulation Cardiovasc Genet. 2015;8:372-382

Treatment effect stratified by genotypes

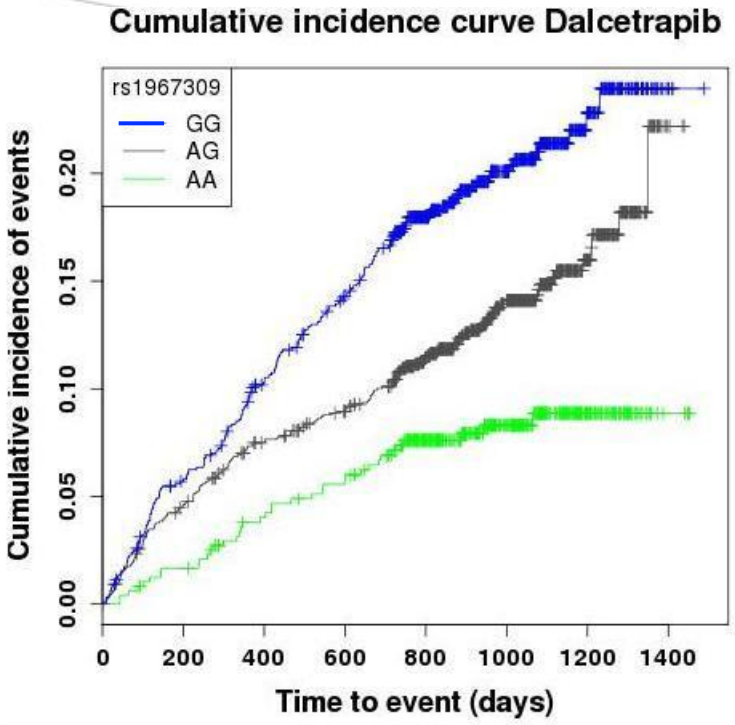
ADCY9 rs1967309

Tested for main study primary outcome adding unanticipated coronary revascularization (Primary PGx)

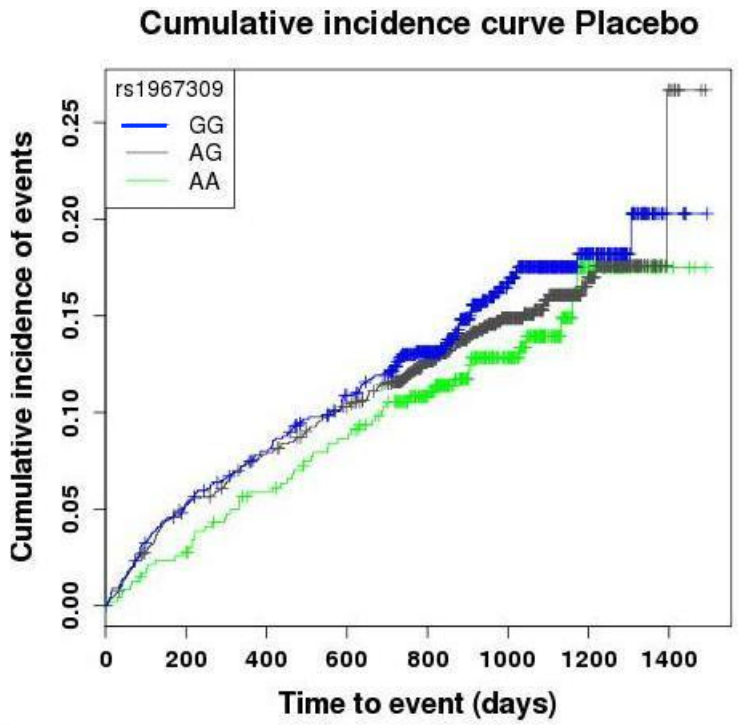


Tardif et al. Circulation Cardiovasc Genet. 2015;8:372-382

Treatment effect by genotypes



No. at risk								
GG	978	915	866	825	720	421	89	89
AG	1379	1309	1260	1227	1012	572	204	171
AA	485	476	459	450	419	270	178	178



No. at risk								
GG	1006	949	919	883	760	393	148	48
AG	1417	1329	1287	1247	1048	610	204	11
AA	476	462	442	427	387	268	74	74

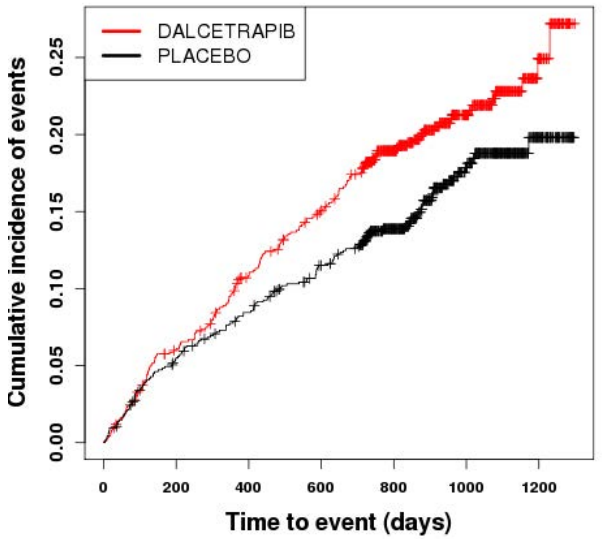
Tested for main study primary outcome *or* unanticipated coronary revascularization (Primary PGx endpoint)

Tardif et al. Circulation Cardiovasc Genet. 2015;8:372-382

Treatment effect by genotypes: A different picture emerges

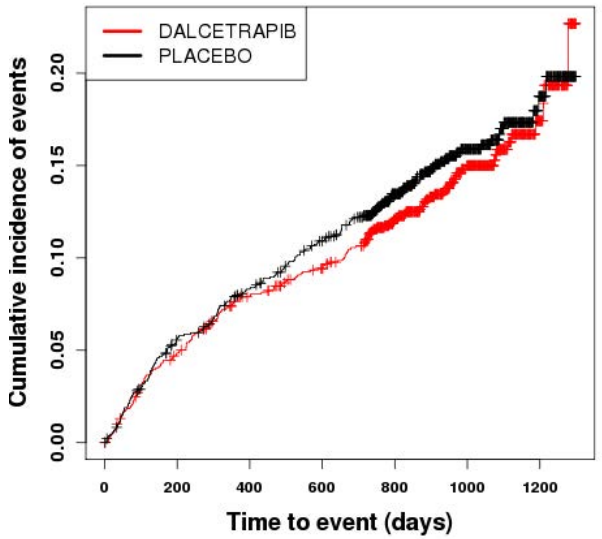
ADCY9 rs1967309

GG



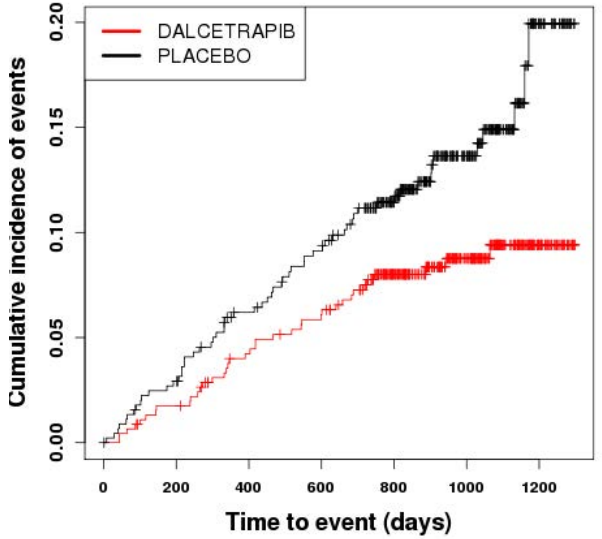
N at risk/days	*0*	*200*	*400*	*600*	*800*	*1000*	*1200*
Dalcetrapib	933	870	820	778	604	329	74
Placebo	956	898	867	831	649	339	75

AG



	0	*200*	*400*	*600*	*800*	*1000*	*1200*
	1313	1242	1189	1159	937	504	120
	1342	1253	1211	1170	946	504	119

AA



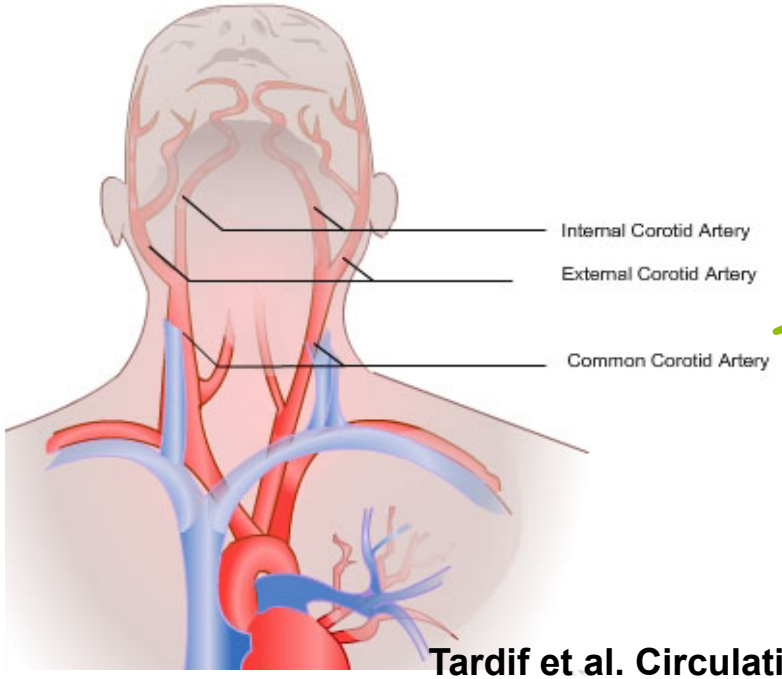
	0	*200*	*400*	*600*	*800*	*1000*	*1200*
	462	452	435	426	355	200	51
	452	437	416	402	331	186	33

Events:
main study primary outcome or unanticipated coronary revascularization

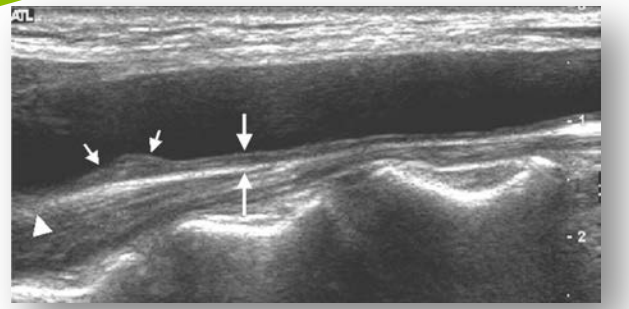
Tardif et al. Circulation Cardiovasc Genet. 2015;8:372-382

Supporting evidence
dal-PLAQUE-2 trial

- Among the 411 patients, 386 have imaging measures at baseline, 6 months, and 12 months
  - 194 patients are in the dalcetrapib treatment arm
  - 192 in the placebo arm



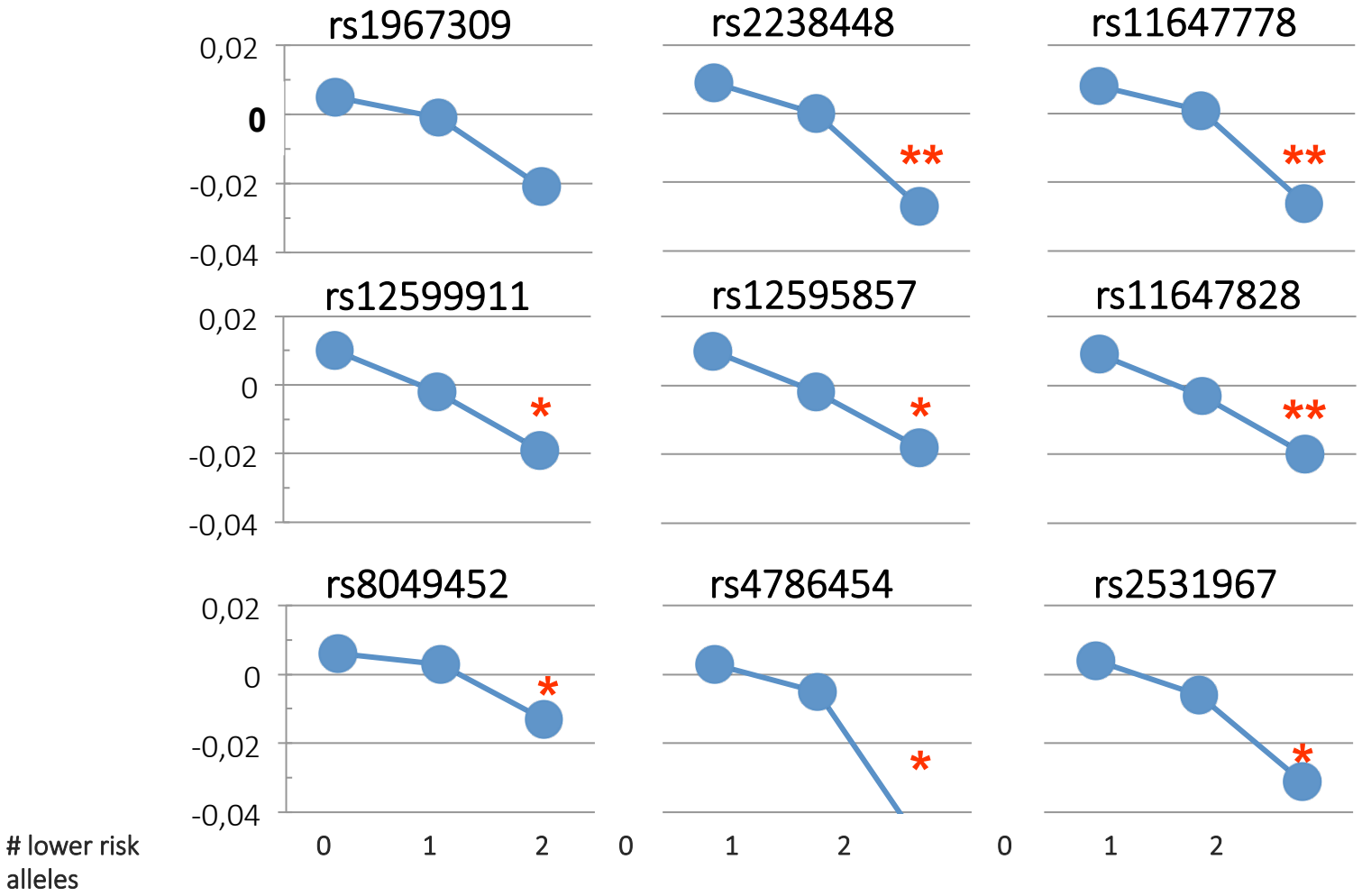
The common carotid artery measures were used as supporting evidence



Tardif et al. Circulation Cardiovasc Genet. 2015;8:372-382

Supporting evidence dal-PLAQUE-2 trial

Mean change from baseline in cIMT after 12 months of dalcetrapib treatment



Tardif et al. Circulation Cardiovasc Genet. 2015;8:372-382

Chasing—and Catching—the Wild Goose

Hypothesis-Free Post-Hoc Stratification Studies as a New Paradigm for Drug Development

Klaus Lindpaintner, MD, MPH

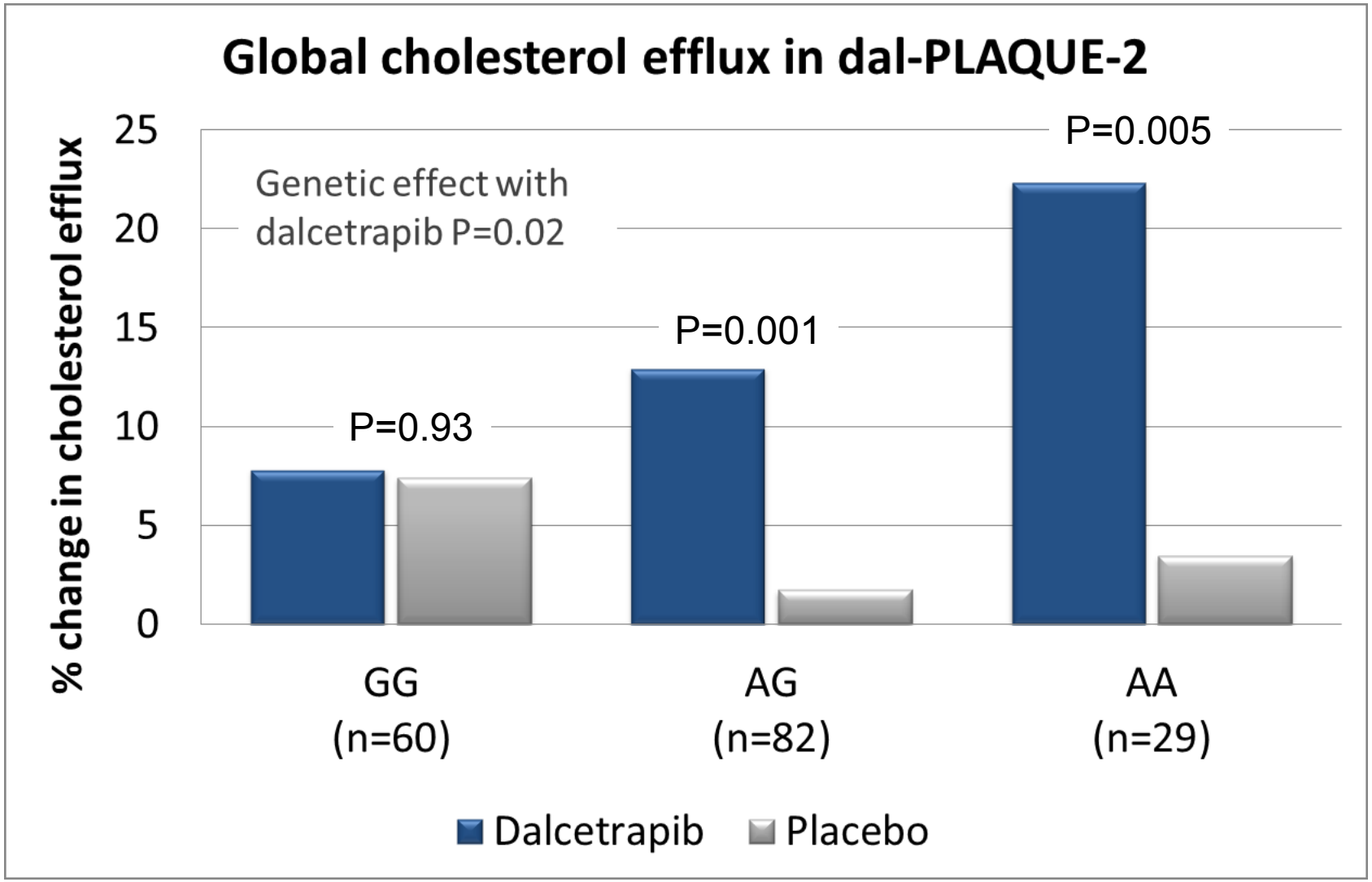
In this issue, Tardif et al[1] report on the results of a retrospective analysis of 2 phase III trials of the cholesteryl ester transfer protein inhibitor, dalcetrabip, dal-OUTCOMES, and dal-PLAQUE-2. Using a hypothesis-free whole genome screening process that could be likened to a wild-goose-chase, they identified genetically distinct subpopulations among the probands, which demonstrated markedly different clinical outcomes when treated with dalcetrabip as a secondary prevention strategy. If substantiated prospectively, the effect of this finding will be paradigm changing.

Outlook

The brave new world of drug development research that includes the hypothesis-free retrospective investigations that Tardif et al's[1] work heralds may be daunting, but it also offers a glimpse of hope that we may be at the brink of fundamentally improving medical care. Improving the failure-littered track record of clinical studies is certainly a prospect that sponsors should embrace. However, advocating for this approach as a universally applied principle of drug development offers an even more compelling vista for society by allowing new medicines that may be highly effective in addressing unmet medical needs to reach the specific patient subgroups who will benefit, instead of being prescribed in a shotgun manner to all comers or being abandoned because of lack of differentiated targeting.

Lindpaintner K. Circulation Cardiovascular Genetics 2015

dal-PLAQUE-2: Change in global cholesterol efflux from baseline to 12 months



Tardif JC et al. Circ Cardiovasc Genetics 2016;9:340-348

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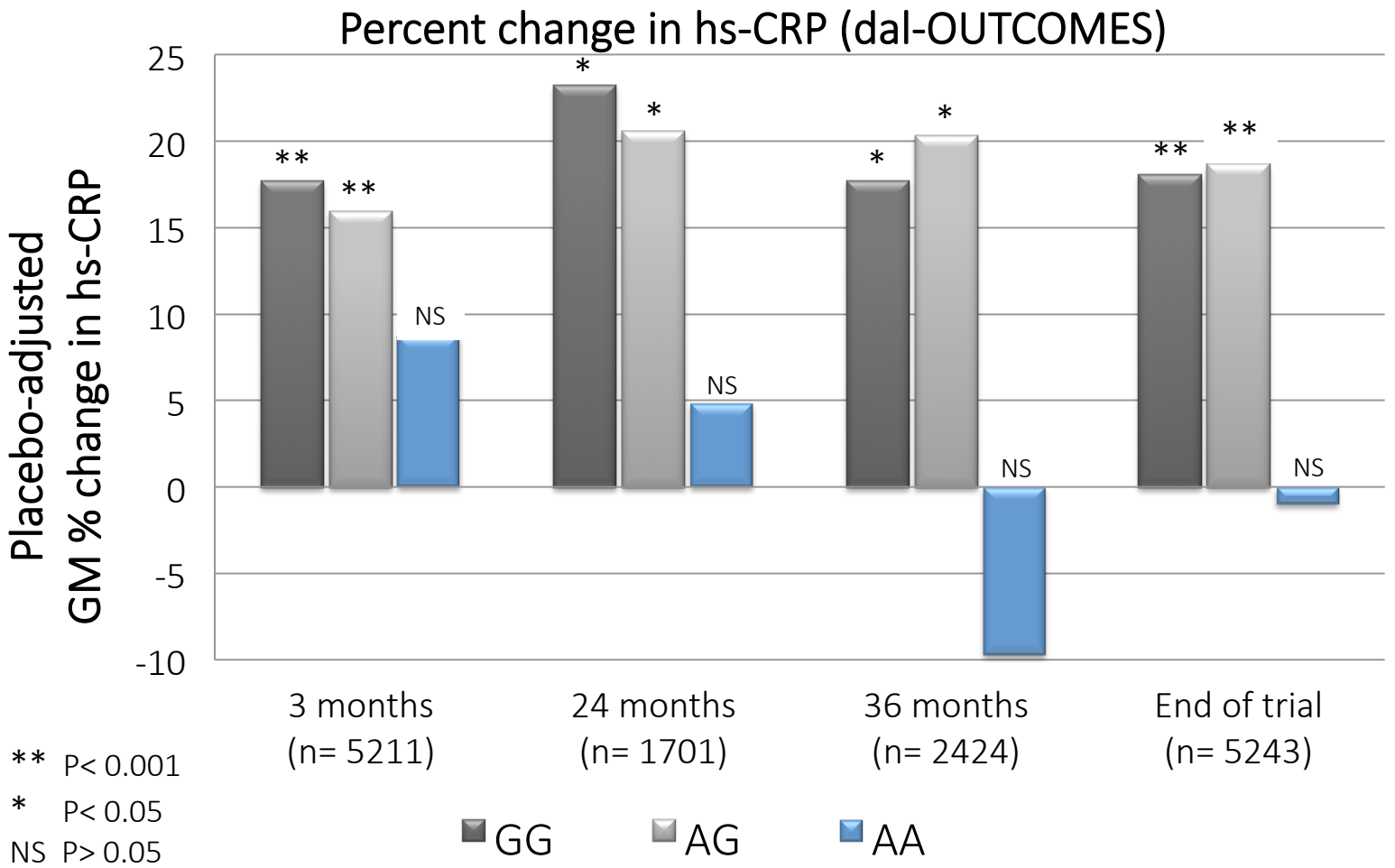
dal-OUTCOMES : Placebo-adjusted GM percent change in hs-CRP



Tardif JC et al. Circ Cardiovasc Genetics 2016;9:340-348

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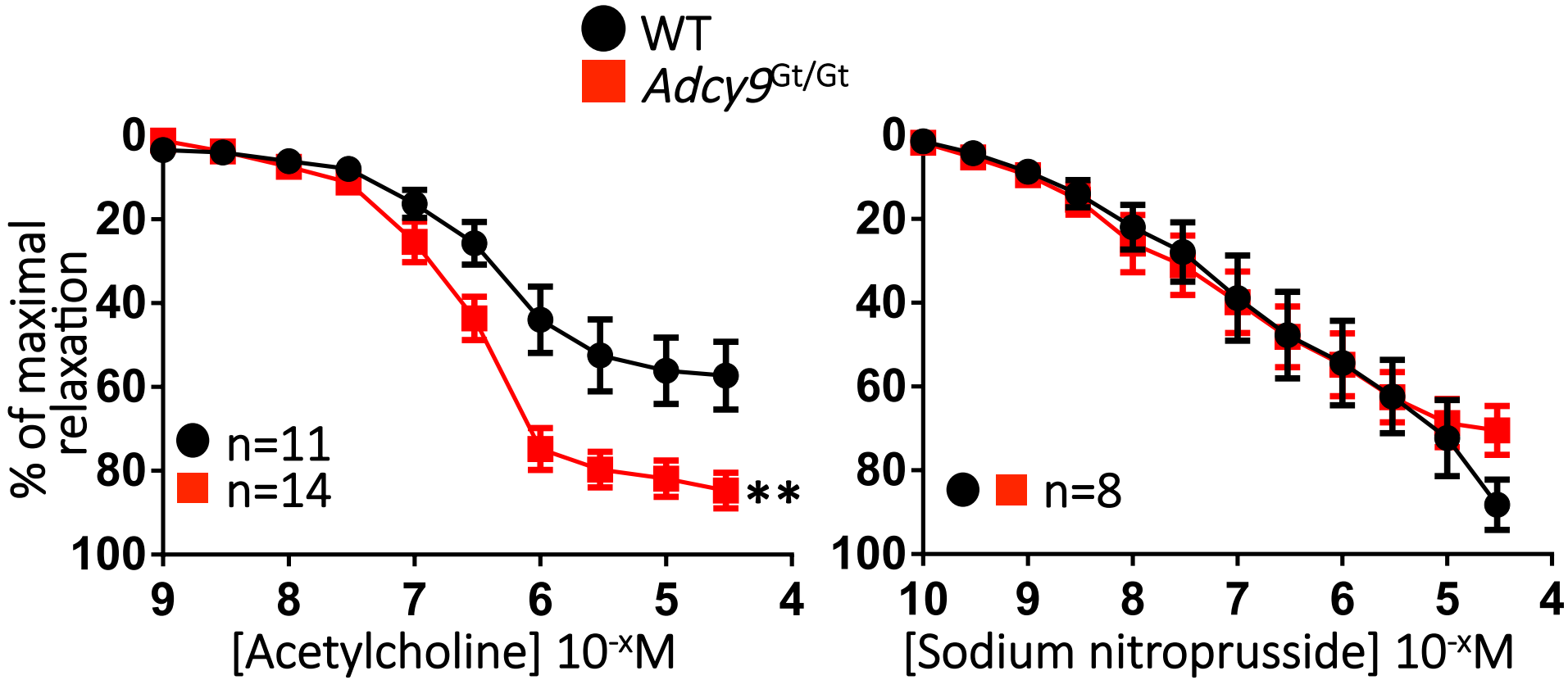
Adcy9 inactivation potentiates endothelial-dependent vasodilation in mouse femoral arteries



** *P*<0.01 versus WT

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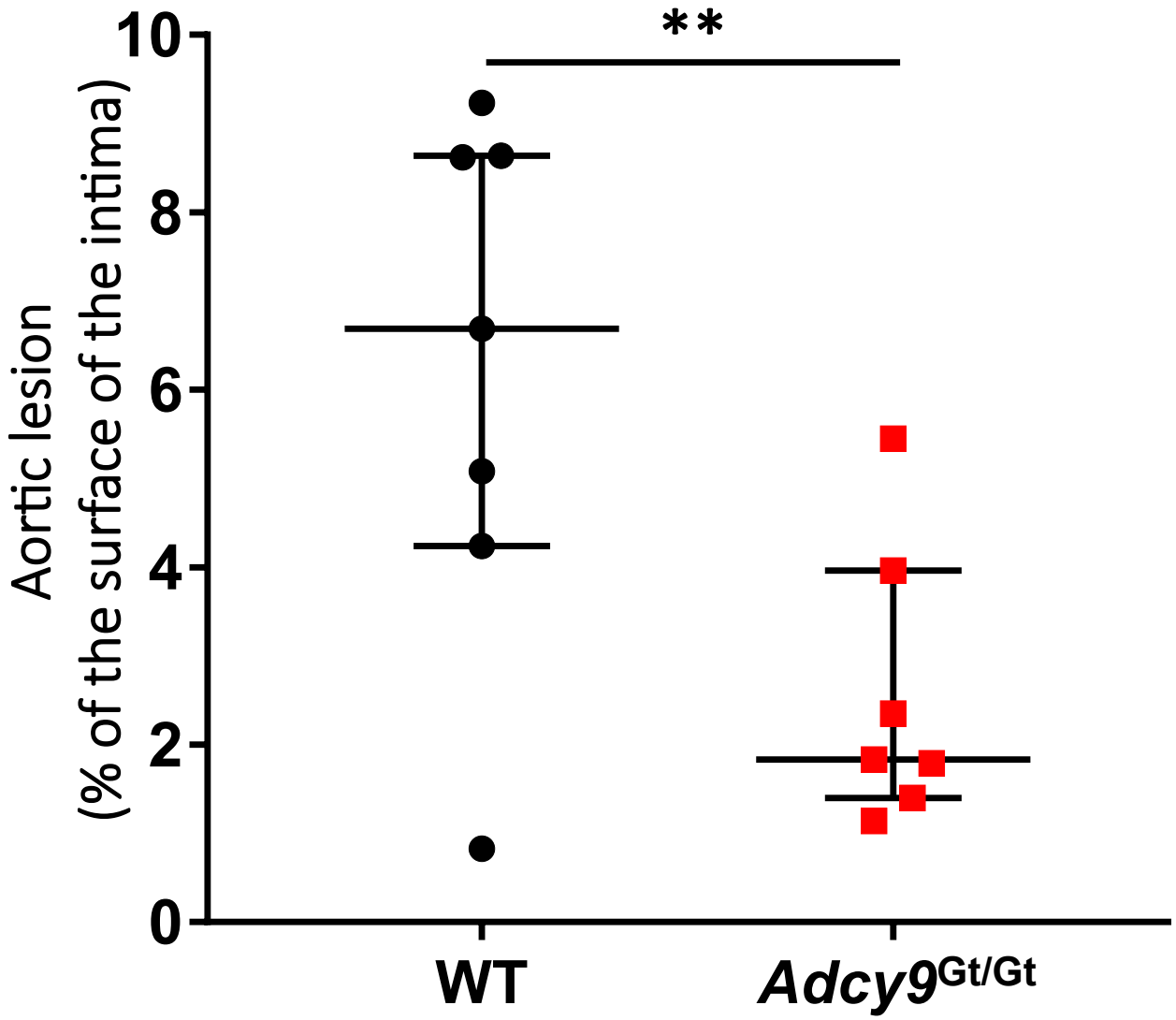
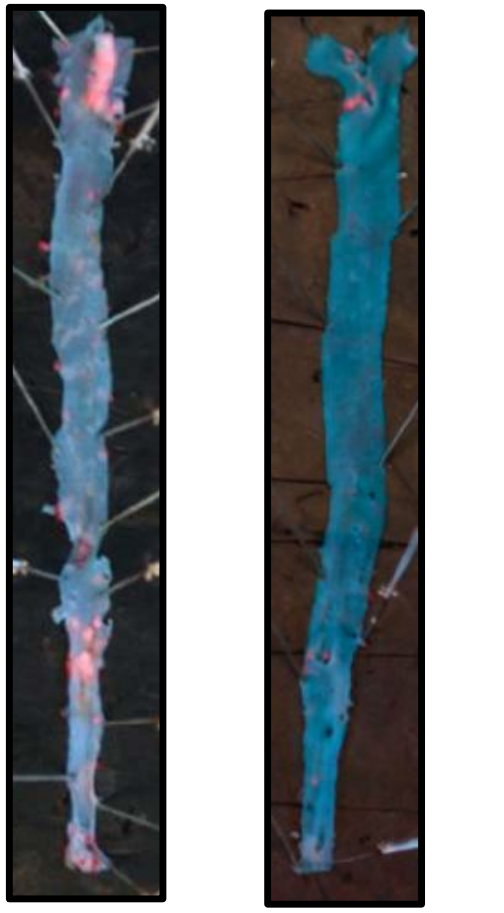
Adcy9 inactivation protects from atherosclerosis in mice infected with AAV8-Pcsk9_D377Y fed a high-cholesterol diet





** *P*<0.01

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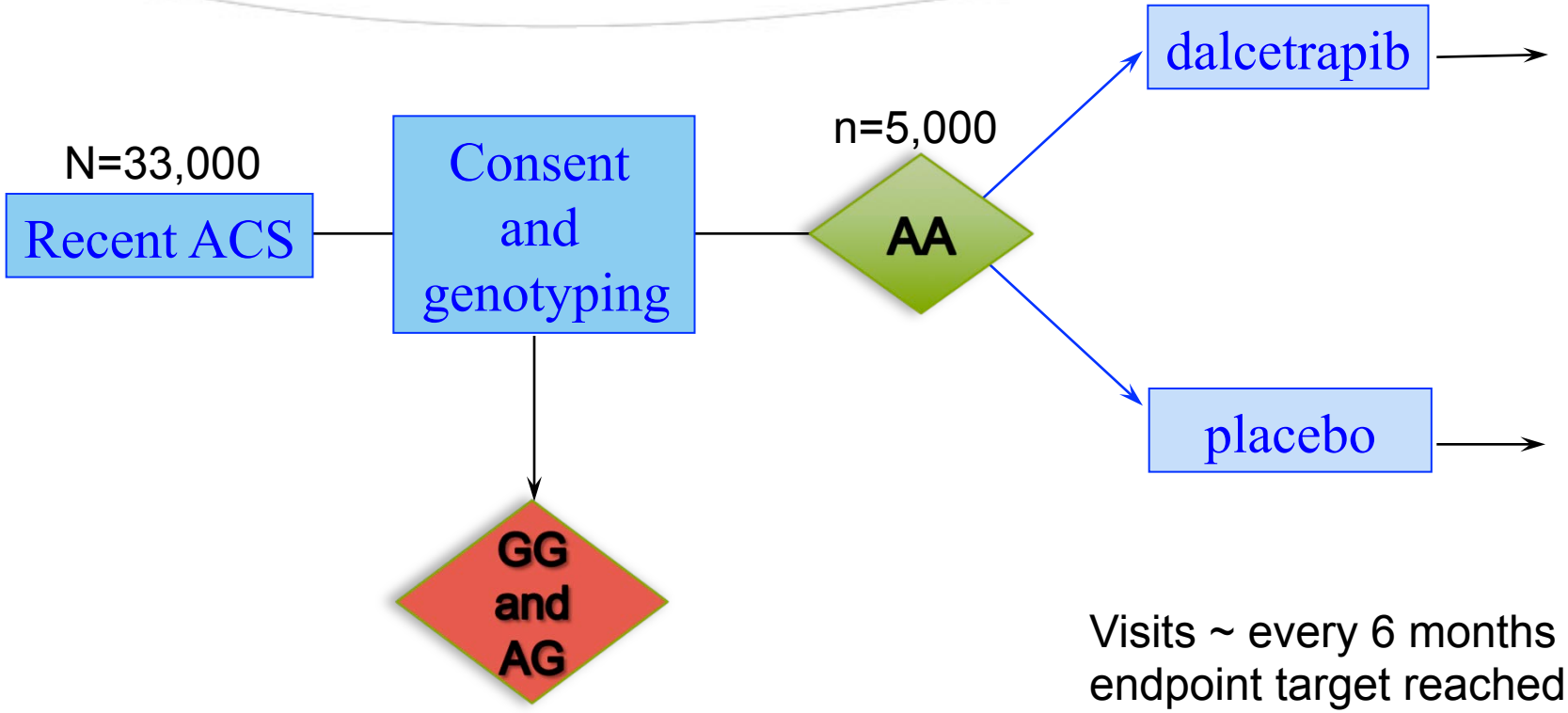
DaI-GenE Study Design



Visits ~ every 6 months until endpoint target reached

Primary Objective: To **prospectively** evaluate the potential of dalcetrapib to reduce cardiovascular morbidity and mortality in patients with a documented recent ACS and the AA genotype at rs1967309 in ADCY9 gene

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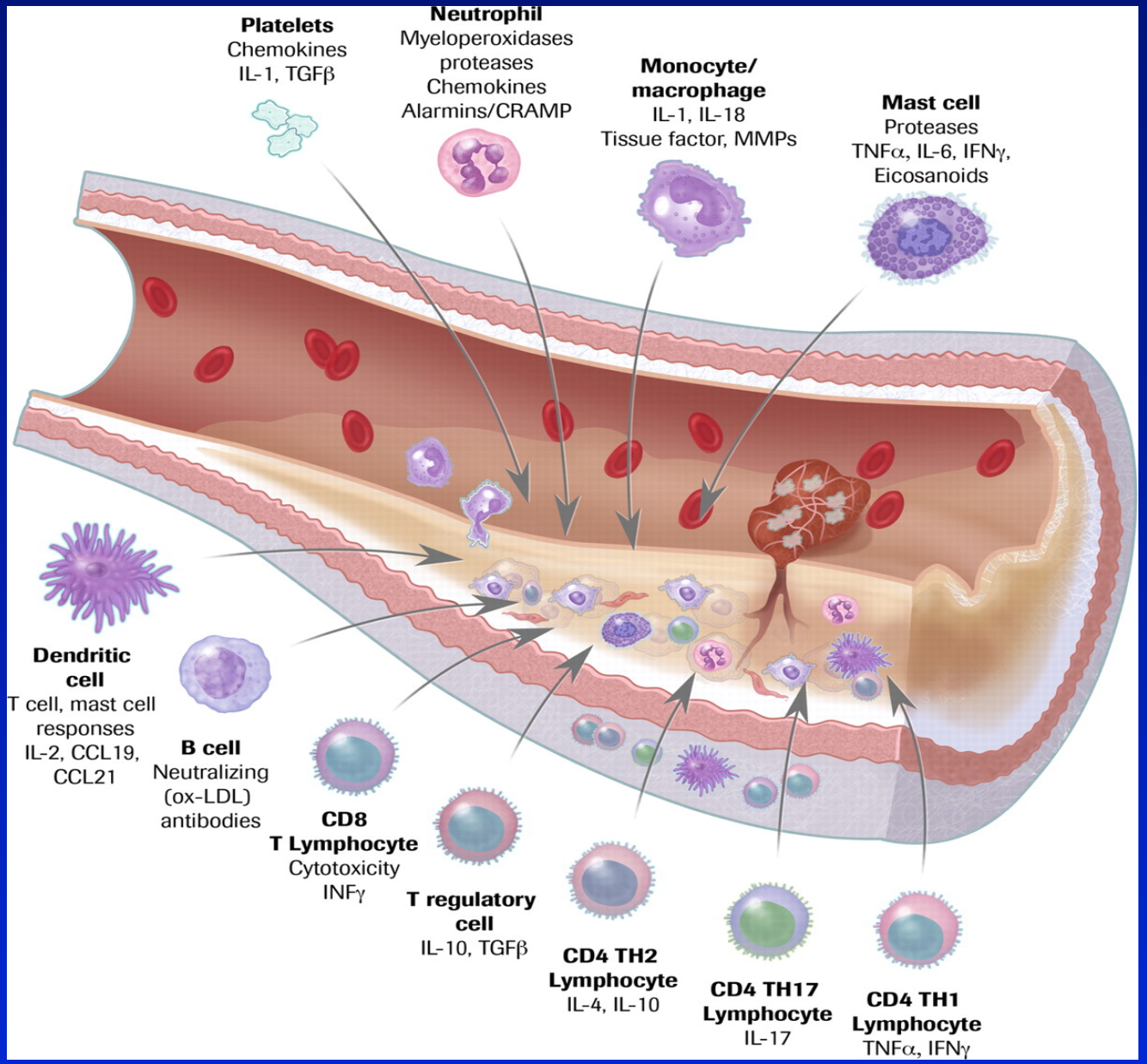
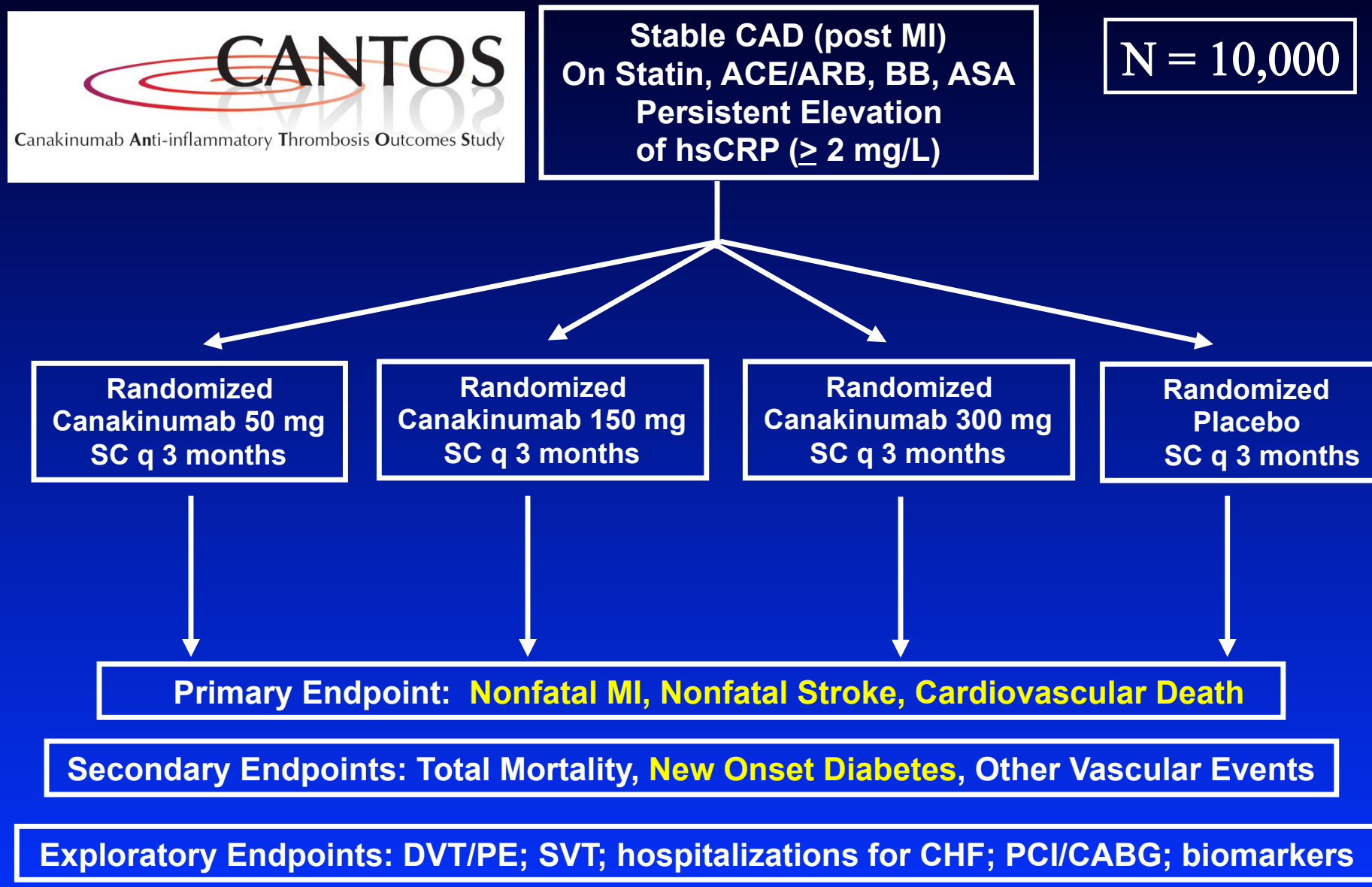
Inflammation and immunity in atherosclerosis



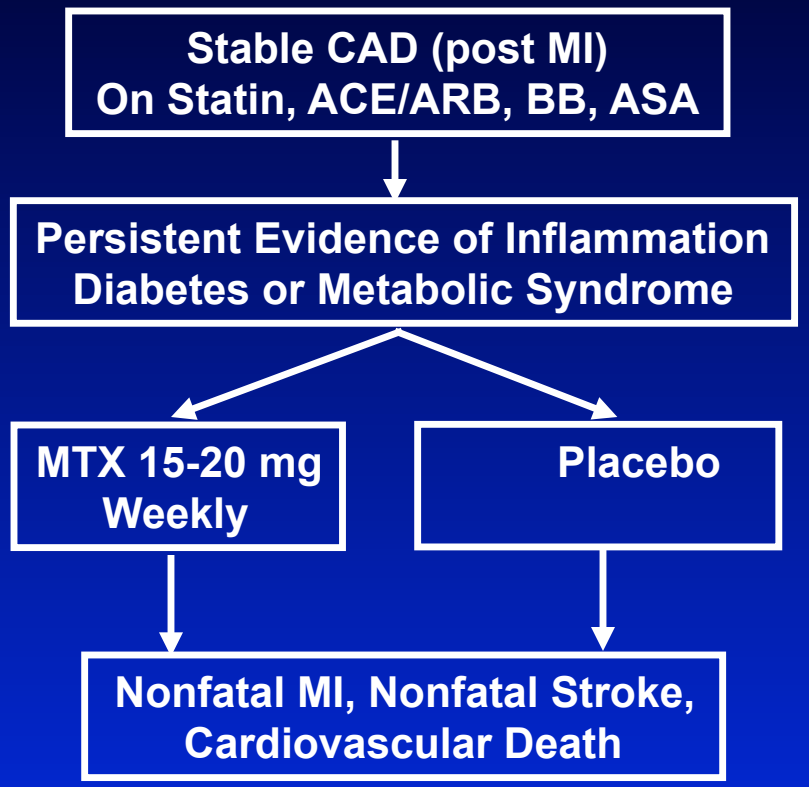
circres.ahajournals.org

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)



Cardiovascular Inflammation Reduction Trial (CIRT)

Primary Aims



- To directly test the inflammatory hypothesis of atherothrombosis
- To evaluate in a randomized, double-blind, placebo-controlled trial whether MTX given at a target dose of 20 mg po weekly over a three year period will reduce rates of recurrent myocardial infarction, stroke, or cardiovascular death among patients with a prior history of myocardial infarction and either type 2 diabetes or metabolic syndrome.

CIRT
CARDIOVASCULAR INFLAMMATION REDUCTION TRIAL

N = 7,000 NHLBI-Sponsored
Enrollment Started June 2013
350 US and Canadian Sites

The LODOCO study

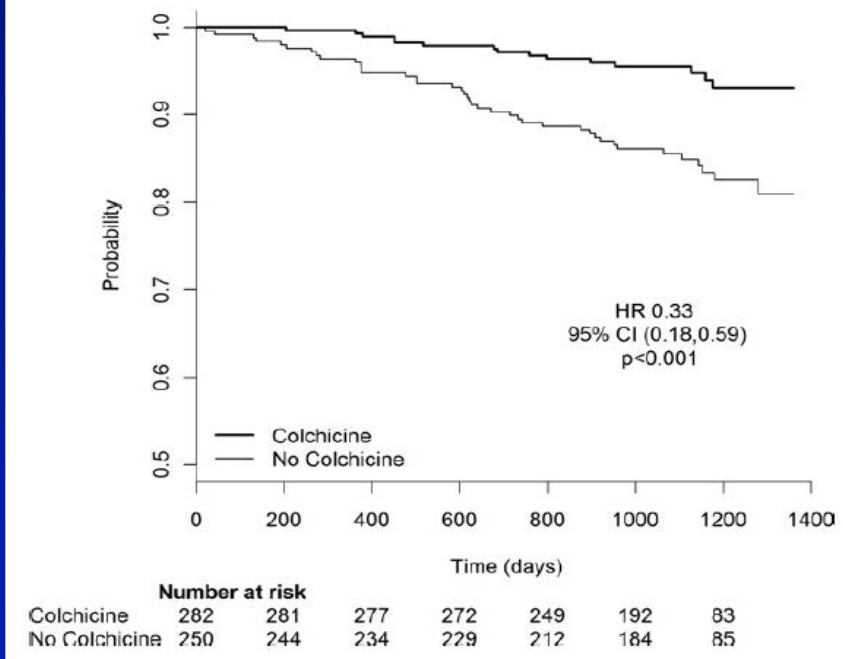


Figure 2 Freedom From the Primary Outcome

Freedom from the primary outcome (acute coronary syndrome, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke) by treatment. CI = confidence interval; HR = hazard ratio.

Table 3 Primary Outcome and Its Components

	Control (n = 250)	Treatment (n = 282)	HR (95% CI)	p Value
Primary outcome	40 (16)	15 (5.3)	0.33 (0.18-0.59)	<0.001
Components of primary outcome				
Acute coronary syndrome	34 (13.6)	13 (4.6)	0.33 (0.18-0.63)	<0.001
OOH cardiac arrest	2 (0.8)	1 (0.35)*	0.47 (0.04-5.15)	0.534
Noncardioembolic stroke	4 (1.6)	1 (0.35)	0.23 (0.03-2.03)	0.184
Components of ACS				
Stent-related	4 (1.6)	4 (1.4)		NS
Nonstent-related	30 (12)	9 (3.2)	0.26 (0.12-0.55)	<0.001
Nonstent-related AMI	14 (5.6)	4 (1.6)	0.25 (0.08-0.76)	0.014
Nonstent-related UA	16 (12)	5 (2.4)	0.27 (0.10-0.75)	0.011

Values are n (%). *Nonfatal.
ACS = acute coronary syndrome; NS = nonsignificant; OOH = out of hospital; other abbreviations as in Table 1.

The effect of adding colchicine became evident early, continued to accrue over time, and was largely driven by a reduction in ACS unrelated to stent disease.

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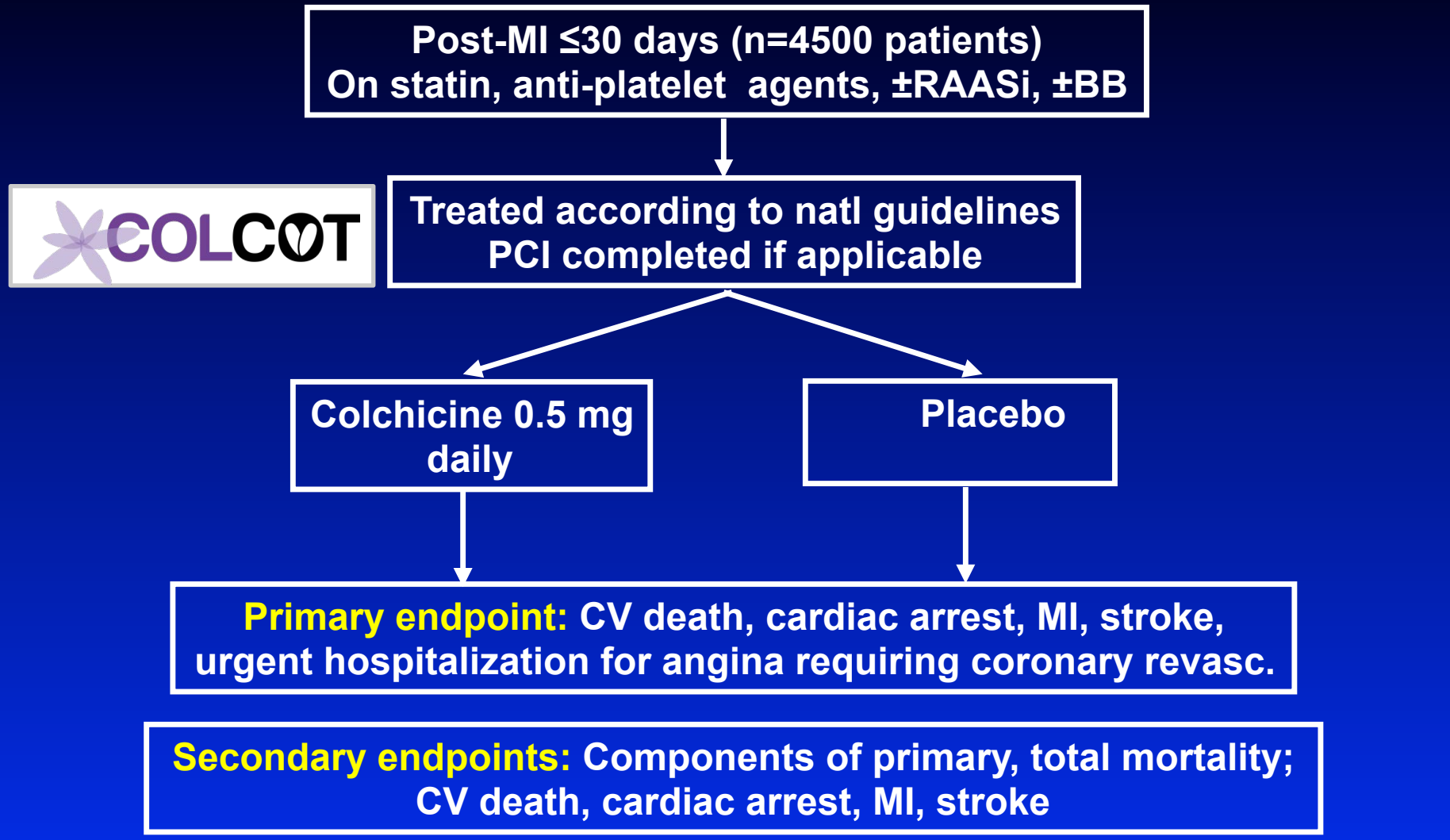
Nidorf SM et al. J Am Coll Cardiol 2013;61:404-410

Colchicine Cardiovascular Outcomes Trial (COLCOT)



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