Late Breaking Clinical Trials: 2018

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ACC Late Breaking Clinical Trials 2018

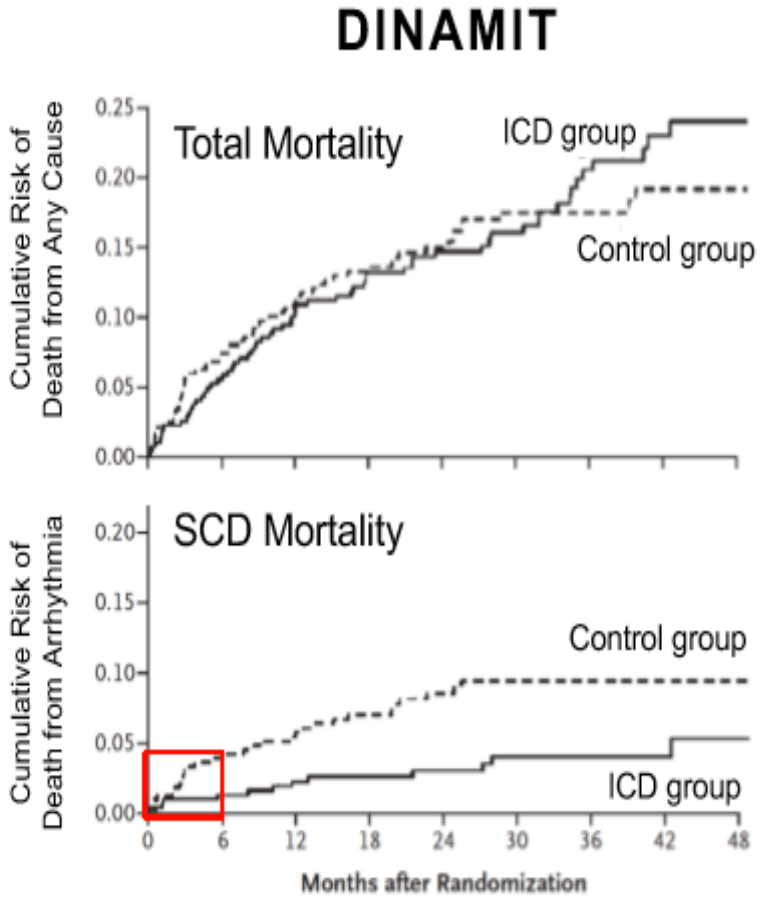
UCSF
University of California
San Francisco

Vest Prevention of Early Sudden Death Trial (VEST)

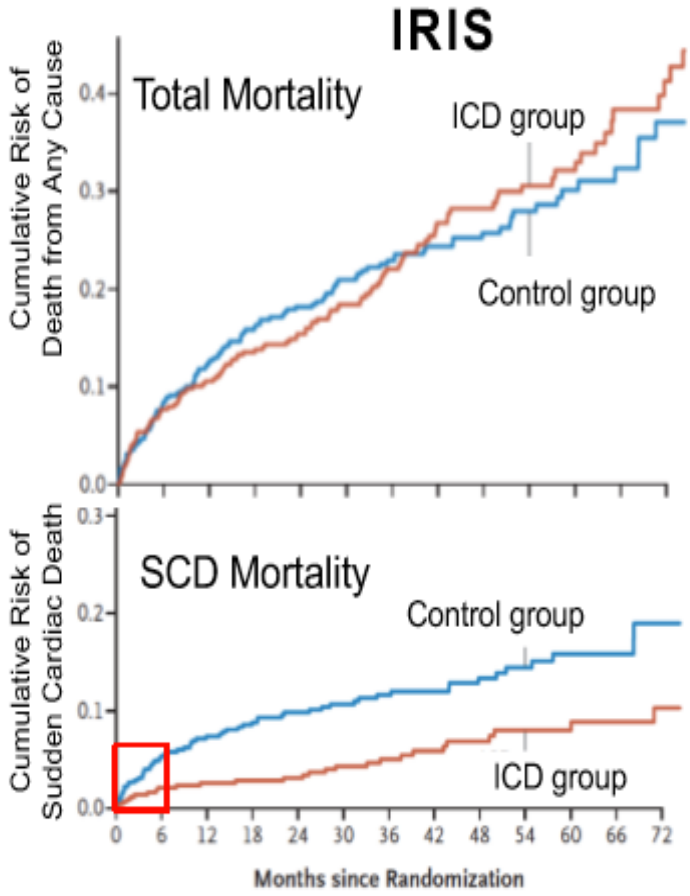
Jeffrey Olgin, MD, FACC
Division of Cardiology, UCSF
On behalf of the VEST Investigators

Oklahoma Heart Institute

Background: No benefit from early ICD



DINAMIT: Hohnloser, *et al.* NEJM 2004



IRIS: Steinbeck, *et al.* NEJM 2009

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Background: Guideline recommendations

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Al-Khatib SM, et al.
2017 VA/SCD Guidelines

6.1.2. Primary Prevention of SCD in Patients with Ischemic Heart Disease

Recommendations for Primary Prevention of SCD in Patients With Ischemic Heart Disease		
COR	LOE	Recommendations
I	A	1. In patients with LVEF of 35% or less that is due to ischemic heart disease who are at least 40 days post-MI and at least 90 days post revascularization, and with NYHA class II or III HF despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected (1,2).

2017 ACC/AHA/HRS Guideline for Management of Patients With Ventricular Arrhythmias. JACC 2017

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Background: VEST rationale

- ICD not indicated in immediate post-MI period
- Some early mortality not due to arrhythmias immediately post-MI, thus not preventable by ICD
- LVEF may recover over 3 months post-MI

Can a wearable cardioverter defibrillator (WCD) reduce SD mortality in the immediate post-MI period (<90 days) in patients with reduced LVEF, as a bridge to evaluation for ICD?

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Methods: Study design

- **Multi-center, randomized, open-label trial**
- **Participants enrolled within 7 days of hospital d/c with acute MI and EF≤35%**
- **Randomized 2:1 to receive:**
  - Wearable cardioverter defibrillator (WCD) + guideline-directed therapy **or**
  - Guideline-directed medical therapy alone

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Methods: Intervention-WCD

Washable-Interchangeable Garment

Self-Gelling Defibrillation Electrodes

Dry ECG Electrodes

Rechargeable Monitor & Battery Pack

Response Buttons

Monitors
- Wear-time
- Noise
- Device warning
- Asystole
- VT/VF

Treatment
- VT/VF

Investigators blinded to data

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Methods: Outcomes

- **Follow-up at 1 month & 3 months**
- **Search NDI at end of study**
- **Primary Outcome: SCD & death due to ventricular arrhythmias**
- **Secondary outcomes**
  - Total mortality & Non-sudden death
  - Cause-specific death
  - Non-fatal outcomes
    - CV Hospitalizations
    - WCD compliance
    - Adverse events

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Results: Participant characteristics

Characteristic	WCD Group (N=1524)	Control Group (N=778)
Age, mean ± SD	60.9 ± 12.6	61.4 ± 12.3
Men, n (%)	1107 (72.8%)	577 (74.7%)
Body mass index, Mean ± SD	28.4 ± 5.5	28.6 ± 6.6
Smoker, n(%)	561 (36.9%)	273 (35.5%)
Race n (%)		
White	1278 (84.1%)	636 (82.6%)
Black	143 (9.4%)	75 (9.7%)
Asian	23 (1.5%)	14 (1.8%)
Native American/Alaskan	25 (1.7%)	12 (1.6%)
Pacific Islander/Hawaiian	1 (0.1%)	0 (0%)
Mixed	20 (1.3%)	14 (1.8%)
Hispanic, n (%)	85 (5.6%)	34 (4.4%)

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Results: Characteristics of index MI

Characteristic	WCD Group (N=1524)	Control Group (N=778)
LVEF	28.2 ± 6.1%	28.2 ± 5.9%
PCI during MI hospitalization	1272 (84.2%)	650 (84.1%)
Thrombolytics during MI hospitalization	118 (7.8%)	71 (9.2%)
CABG during index hospitalization	14 (0.9%)	12 (1.5%)
Cardiac Arrest/VF	169 (11.2%)	70 (9.1%)
Pulmonary Edema requiring Intubation	162 (10. 7%)	88 (11.4%)
Intra-aortic Balloon Pump	173 (11.5%)	93 (12.0%)
Cardiogenic Shock	136 (9.0%)	79 (10.2%)

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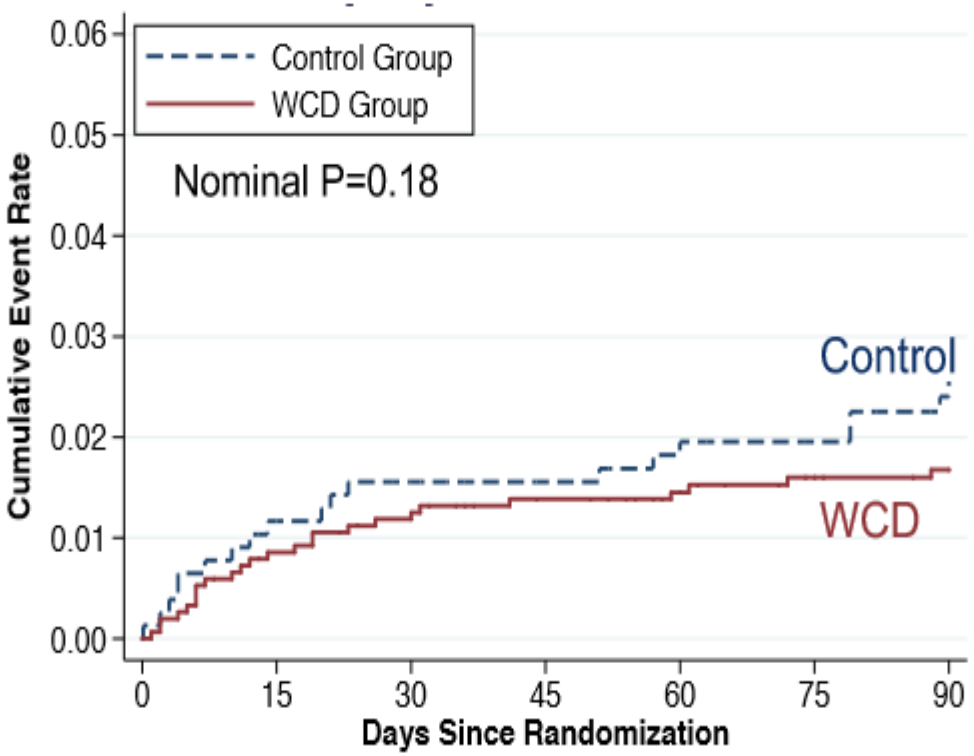
Results: Outcomes, intention-to-treat

A Sudden + Ventricular Tachyarrhythmia Death



No. at Risk							
Control Group	778	759	754	746	742	657	650
WCD Group	1524	1502	1495	1486	1479	1314	1309

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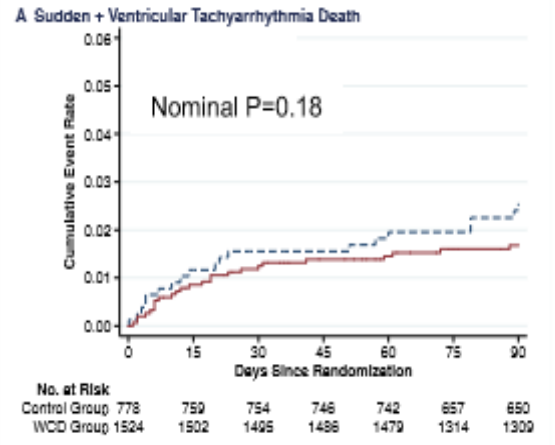
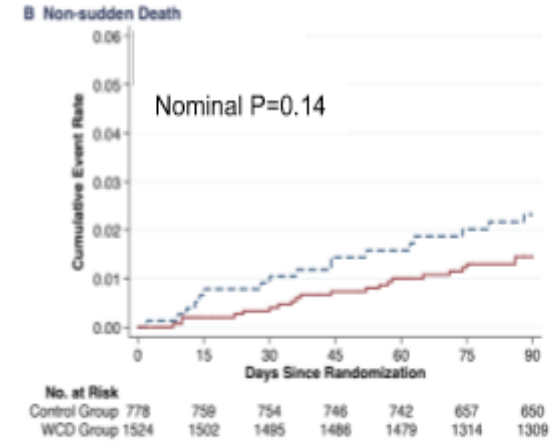
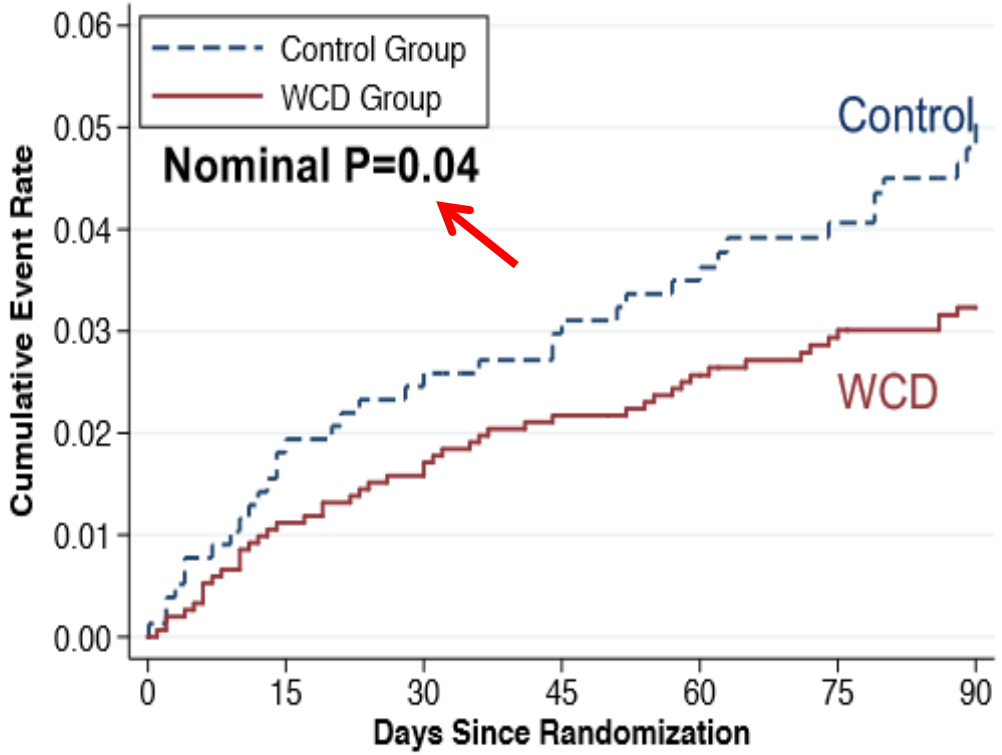
Results: Outcomes, intention-to-treat





C Death from Any Cause



No. at Risk

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Conclusions

- VEST represents the first randomized controlled trial of the WCD
- The WCD did not statistically significantly reduce sudden death mortality, our primary outcome
- The WCD was associated with lower total mortality in the first 90 days post-MI in patients with LVEF ≤35%
- Prescribing the WCD is reasonable to protect high-risk patients with a low LVEF post-MI until evaluation for an ICD at 40-90 days

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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

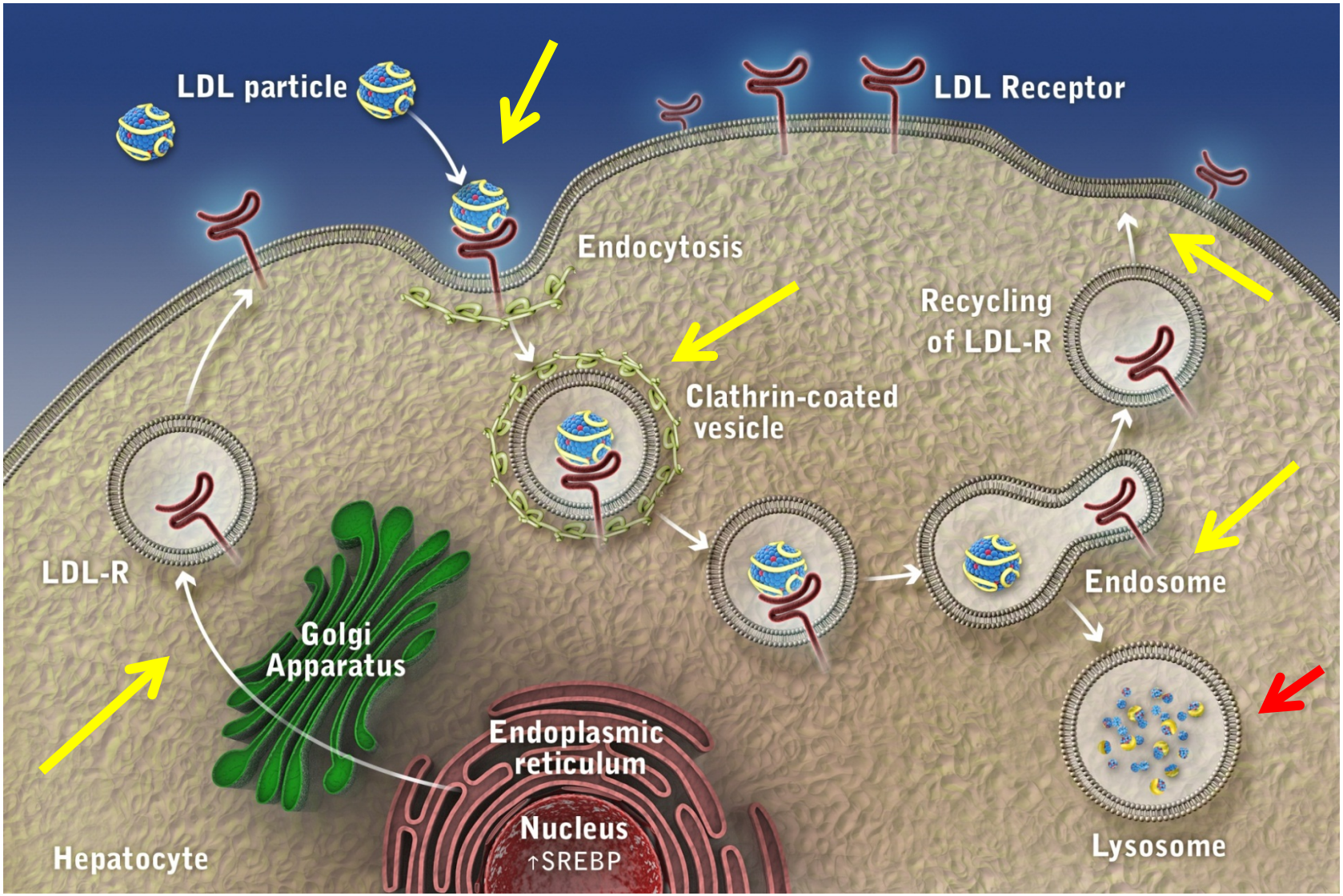
Residual Risk After Acute Coronary Syndrome

- Remains high despite evidence-based preventive therapies
- Is related, in part, to levels of low-density lipoprotein cholesterol (LDL-C)
- Is reduced when LDL-C is lowered by
  - Statin therapy, compared with placebo[1]
  - High-intensity, compared with moderate-intensity statin therapy[2]
  - Ezetimibe, compared with placebo, added to statin[3]

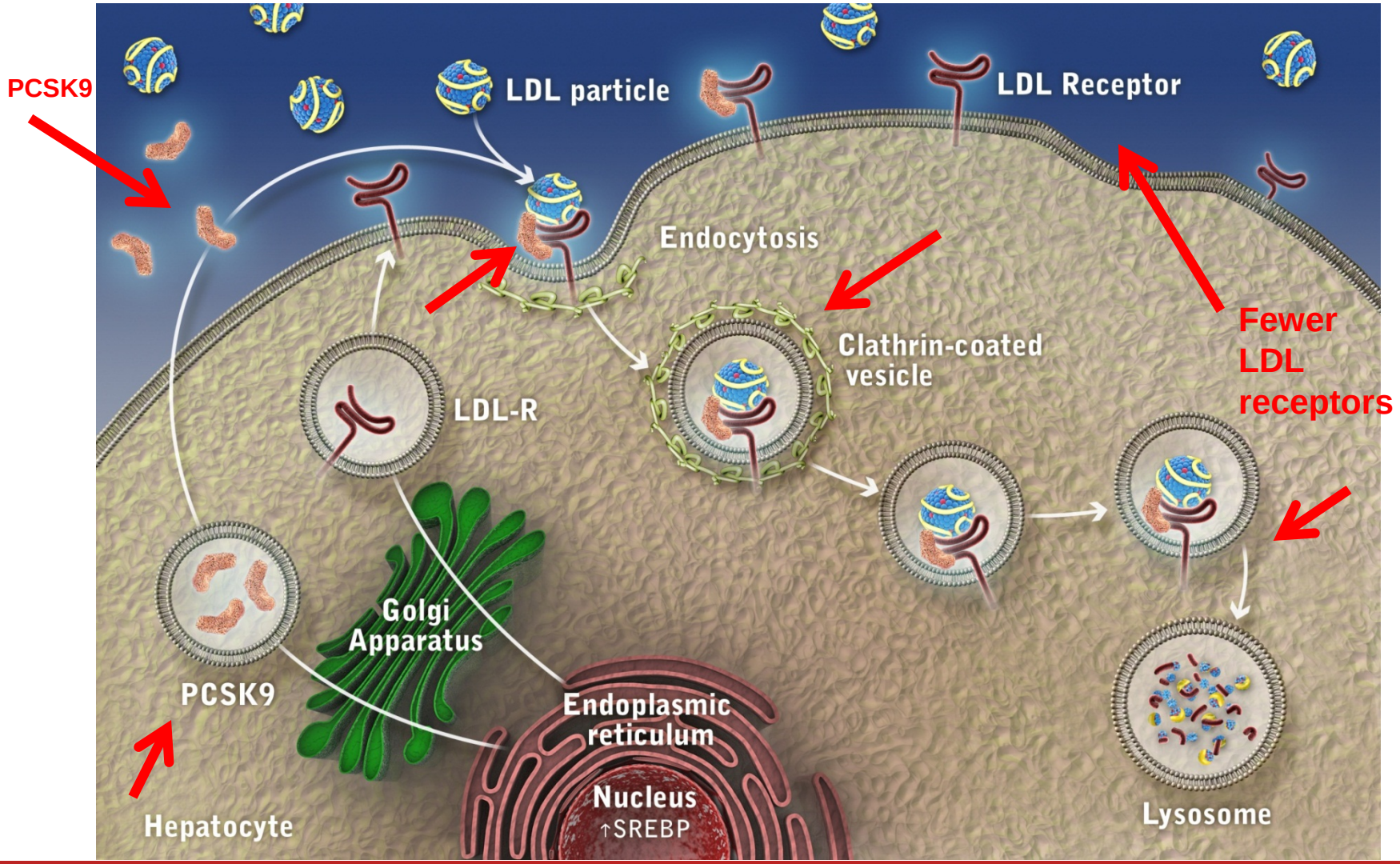
1. Schwartz GG, et al. JAMA 2001;285:1711-8. 2. Cannon CP, et al. NEJM 2004;350:1495-504.
3. Cannon CP, et al. NEJM 2015;372:2387-97.

ODYSSEY OUTCOMES

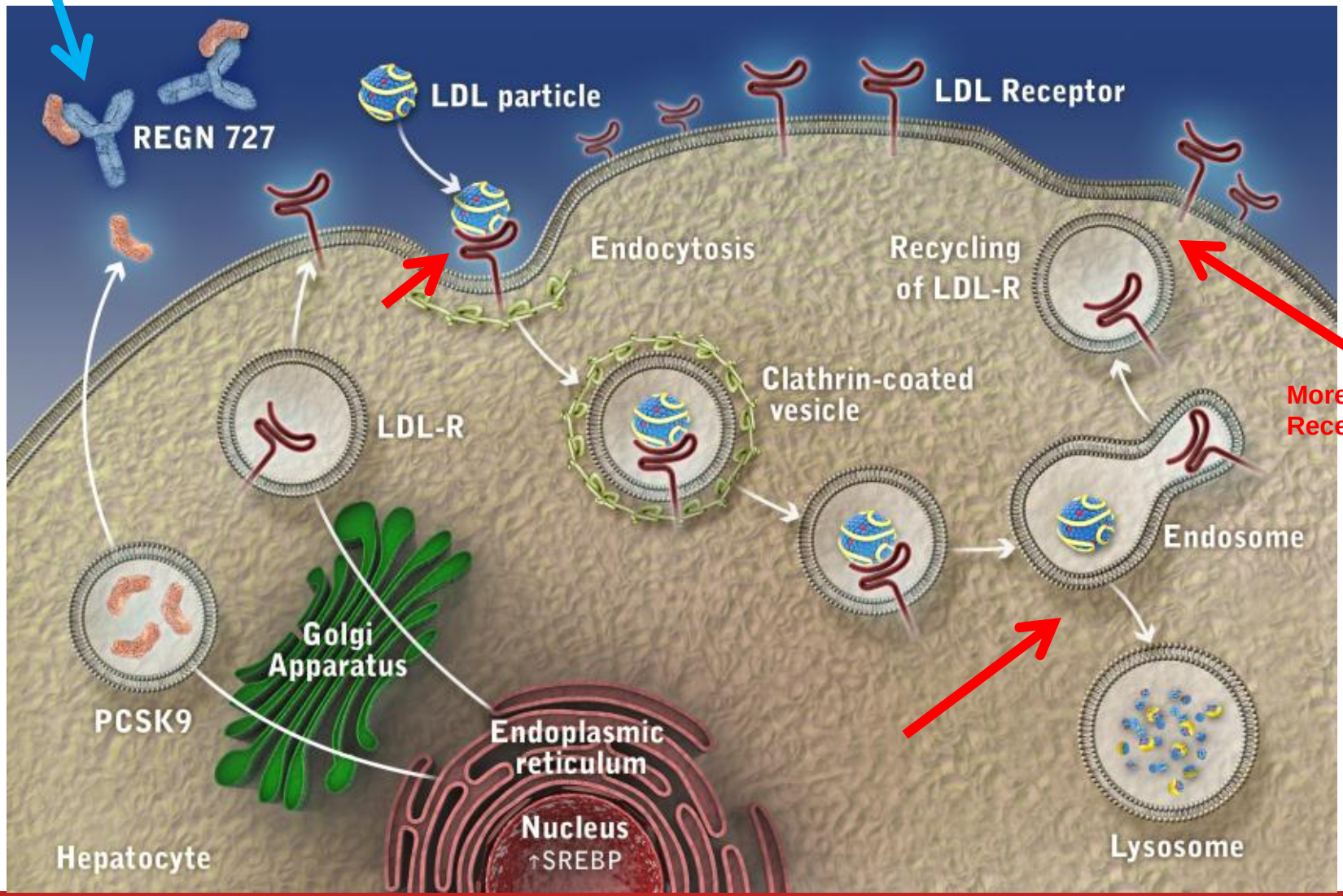
LDL Receptor Function and Life Cycle



The Role of PCSK9 in the Regulation of LDL Receptor Expression



Impact of an PCSK9 mAb on LDL Receptor Expression



Alirocumab

- PCSK9 is a validated target for risk reduction in stable atherosclerotic cardiovascular disease[1–3]
- A fully human monoclonal antibody against PCSK9
- Produces substantial and sustained reductions in LDL-C and other atherogenic lipoproteins[2]
- Has been safe and well-tolerated in studies to date[4]

PCSK9, proprotein convertase subtilisin/kexin type 9

1. Sabatine et al, NEJM 2017;376:713-22. 2. Robinson JG et al. NEJM 2015;372:1489-99.
3. Ridker PM et al. NEJM 2017;376:1527-39. 4. Robinson JG et al. JACC 2017;69:471-82.

ODYSSEY OUTCOMES

Study Hypothesis

Alirocumab, versus placebo, reduces cardiovascular (CV) morbidity and mortality after recent acute coronary syndrome (ACS) in patients with elevated levels of atherogenic lipoproteins despite intensive or maximum-tolerated statin therapy

Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

ODYSSEY OUTCOMES

Main Inclusion Criteria

- **Age** ≥40 years
- **ACS**
  - 1 to 12 months prior to randomization
  - Acute myocardial infarction (MI) or unstable angina
- **High-intensity statin therapy***
  - Atorvastatin 40 to 80 mg daily or
  - Rosuvastatin 20 to 40 mg daily or
  - Maximum tolerated dose of one of these agents for ≥2 weeks
- **Inadequate control of lipids**
  - LDL-C ≥70 mg/dL (1.8 mmol/L) or
  - Non-HDL-C ≥100 mg/dL (2.6 mmol/L) or
  - Apolipoprotein B ≥80 mg/dL

*Patients not on statins were authorized to participate if tolerability issues were present and documented

Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

Primary Efficacy Outcome

Time of first occurrence of:

- **Coronary heart disease (CHD) death, or**
- **Non-fatal MI, or**
- **Fatal or non-fatal ischemic stroke, or**
- **Unstable angina requiring hospitalization***

All outcomes adjudicated by the Clinical Events Committee, under the auspices of the Duke Clinical Research Institute (DCRI). Members were unaware of treatment assignment and lipid levels

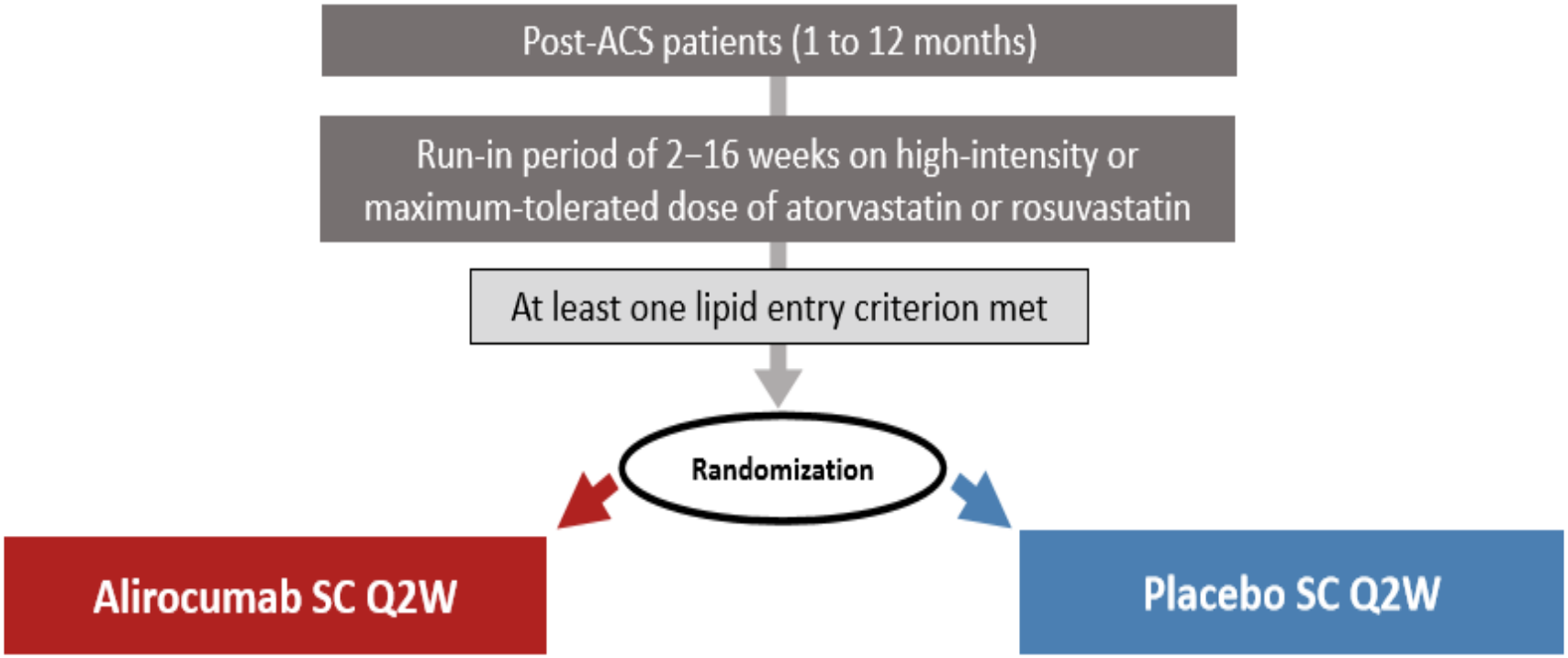
*Required all of the following:

1. Hospital admission >23 h for MI symptoms, ↑ tempo in prior 48 hours and/or ≥20 min of chest discomfort at rest
2. New ECG findings consistent with ischemia or infarction
3. Angiographically significant obstructive coronary disease

Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

ODYSSEY OUTCOMES

Treatment Assignment



Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

ODYSSEY OUTCOMES

Baseline Demographics

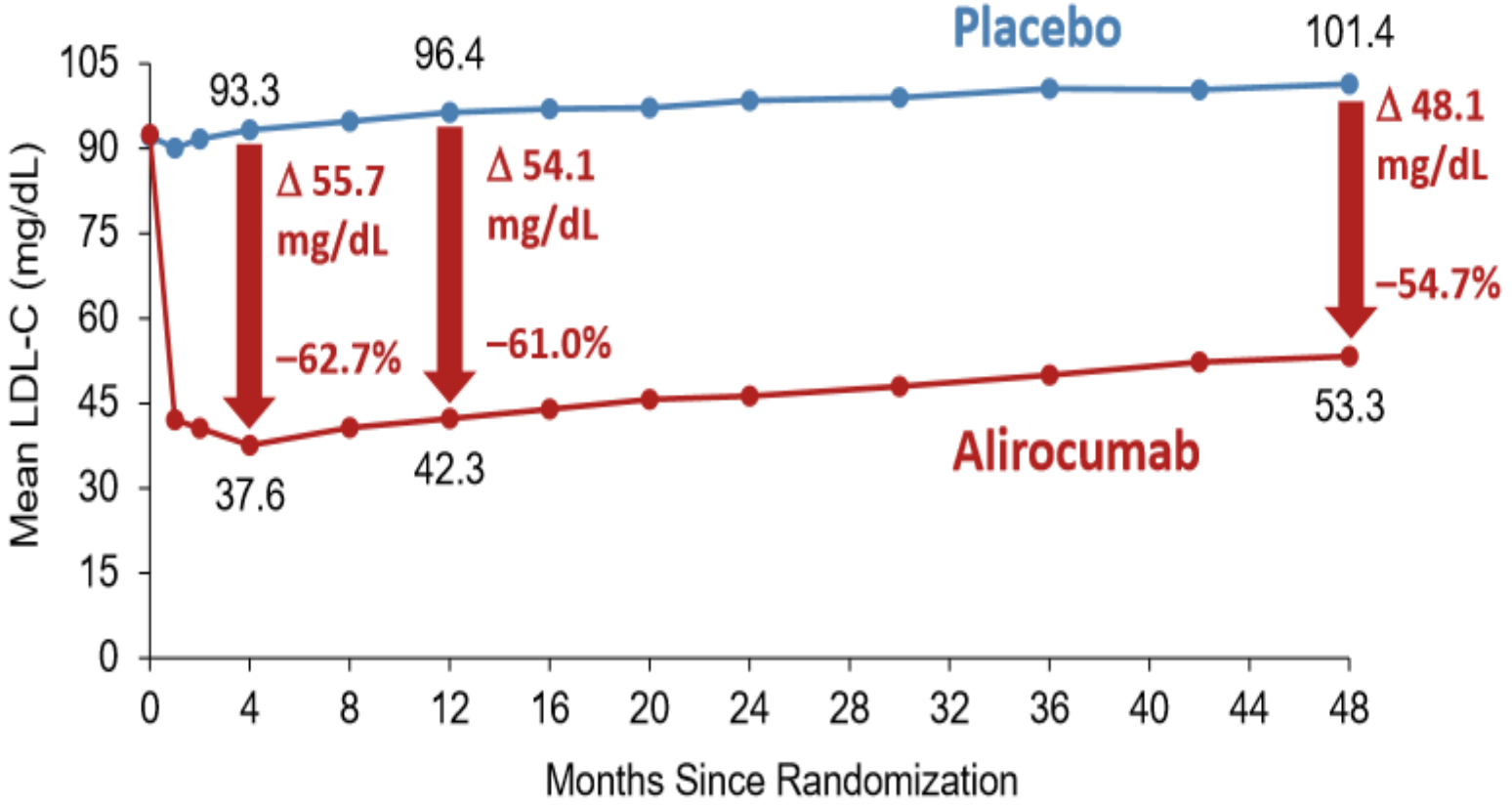
Characteristic	Alirocumab (N=9462)	Placebo (N=9462)
Age, years, median (Q1–Q3)	58 (52–65)	58 (52–65)
Female, n (%)	2390 (25.3)	2372 (25.1)
Medical history, n (%)		
Hypertension	6205 (65.6)	6044 (63.9)
Diabetes mellitus	2693 (28.5)	2751 (29.1)
Current tobacco smoker	2282 (24.1)	2278 (24.1)
Prior MI	1790 (18.9)	1843 (19.5)

Baseline Lipid Characteristics

Characteristic, mg/dL, median (Q1–Q3)	Alirocumab (N=9462)	Placebo (N=9462)
LDL-C	87 (73–104)	87 (73–104)
Non-HDL-C	115 (99–136)	115 (99–137)
Apolipoprotein B	79 (69–93)	80 (69–93)
HDL-C	43 (37–50)	42 (36–50)
Triglycerides	129 (94–181)	129 (95–183)
Lipoprotein(a)	21 (7–59)	22 (7–60)

92.5% of patients qualified on the basis of LDL-C ≥70 mg/dL

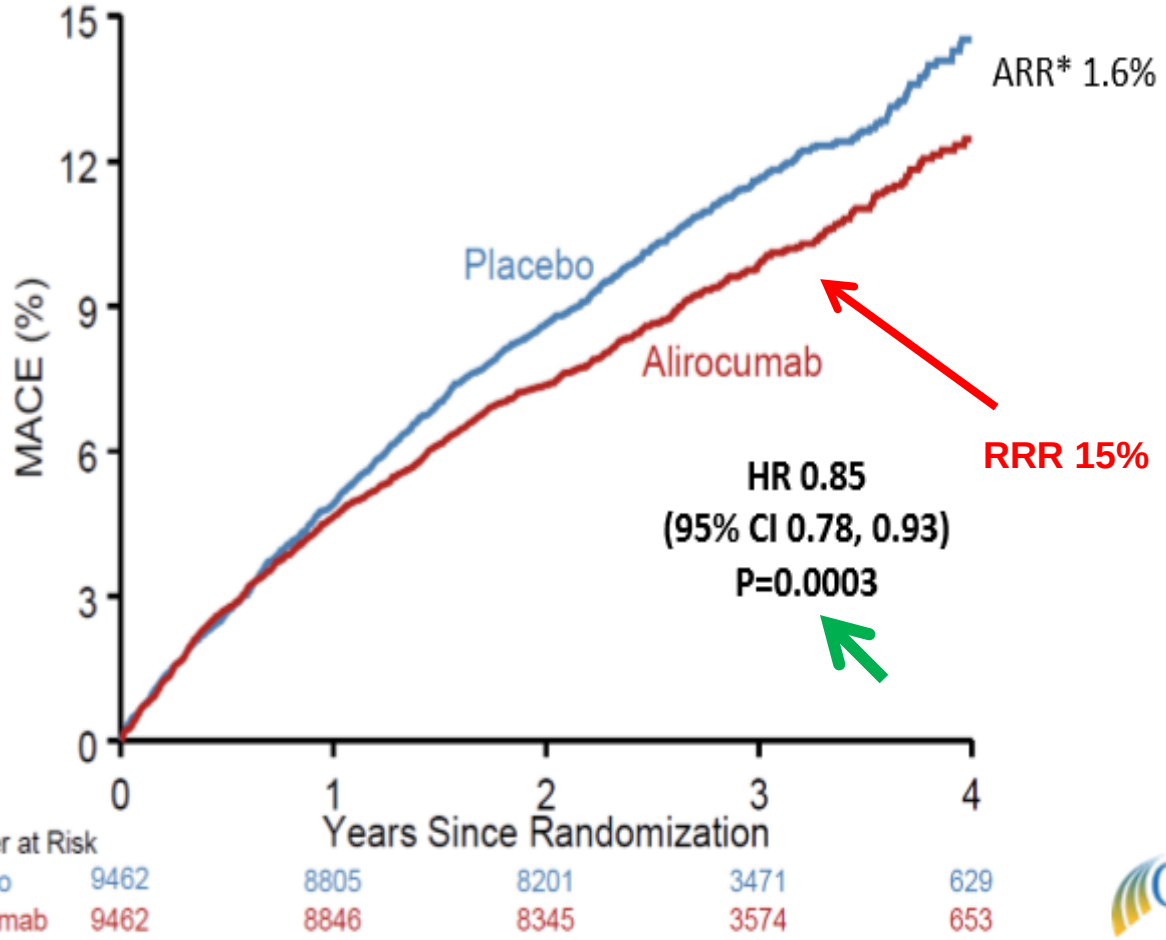
LDL-C: On-Treatment Analysis



Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
Approximately 75% of months of active treatment were at the 75 mg dose

ODYSSEY OUTCOMES

Primary Efficacy Endpoint: MACE

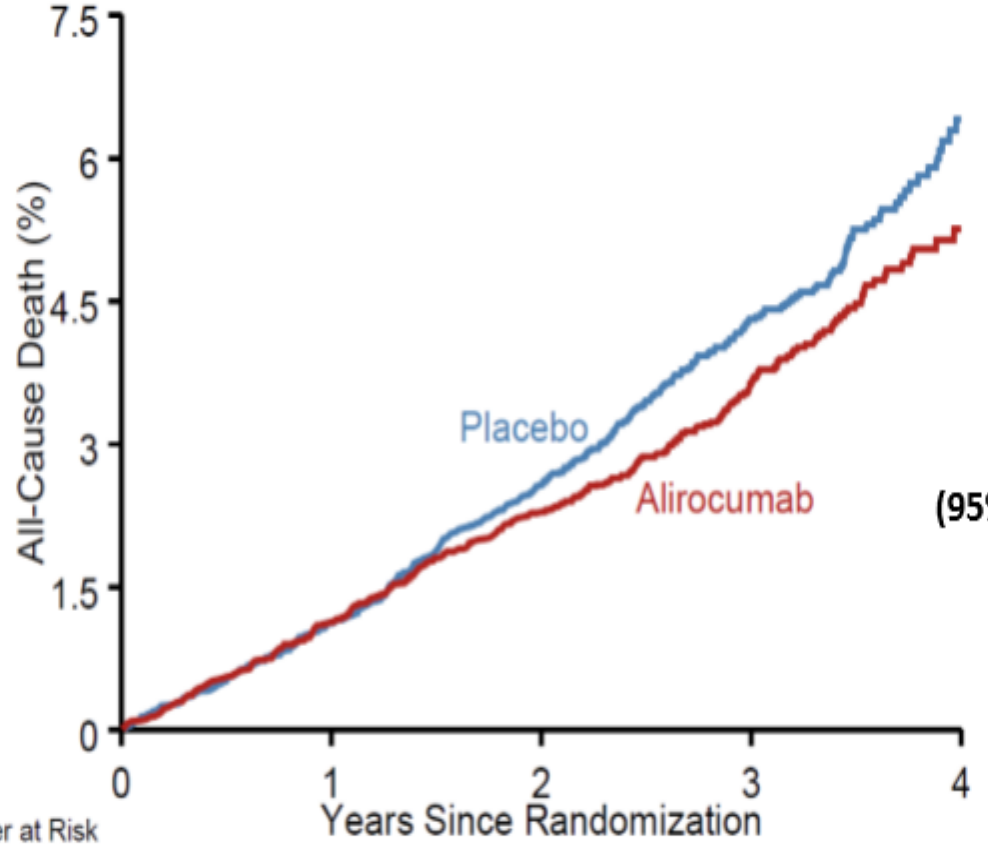


MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

*Based on cumulative incidence

ODYSSEY OUTCOMES

All-Cause Death



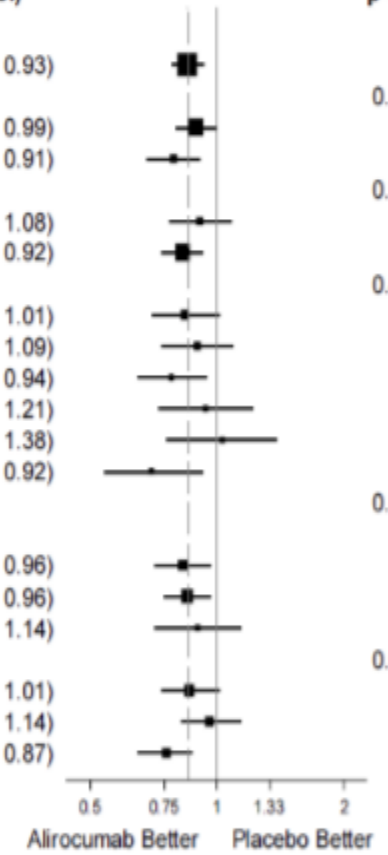
*Nominal P-value

†Based on cumulative incidence

ODYSSEY OUTCOMES

Primary Efficacy in Main Prespecified Subgroups

Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)	p-value*
Overall	18924	9.5	11.1	0.85 (0.78, 0.93)	
Age					0.19
< 65 Yr	13840	8.5	9.5	0.89 (0.80, 0.99)	
≥ 65 Yr	5084	12.4	15.5	0.79 (0.68, 0.91)	
Sex					0.35
Female	4762	10.7	11.8	0.91 (0.77, 1.08)	
Male	14162	9.2	10.9	0.83 (0.74, 0.92)	
Region					0.40
Eastern Europe	5437	7.9	9.3	0.84 (0.70, 1.01)	
Western Europe	4175	9.1	10.0	0.90 (0.74, 1.09)	
North America	2871	13.7	17.1	0.78 (0.65, 0.94)	
South America	2588	9.1	9.7	0.94 (0.73, 1.21)	
Asia	2293	7.7	7.6	1.03 (0.76, 1.38)	
Rest of World	1560	12.2	16.7	0.70 (0.54, 0.92)	
Time from Index Event to Randomization					0.85
<2 Months	6178	10.3	12.3	0.83 (0.71, 0.96)	
2 - <6 Months	9518	9.6	11.1	0.85 (0.75, 0.96)	
≥6 Months	3228	8.0	8.7	0.90 (0.71, 1.14)	
LDL (mg/dL)					0.09
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
80 - <100	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)	



*P-values for interaction

ODYSSEY OUTCOMES

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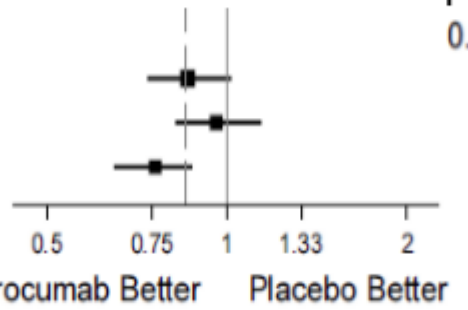
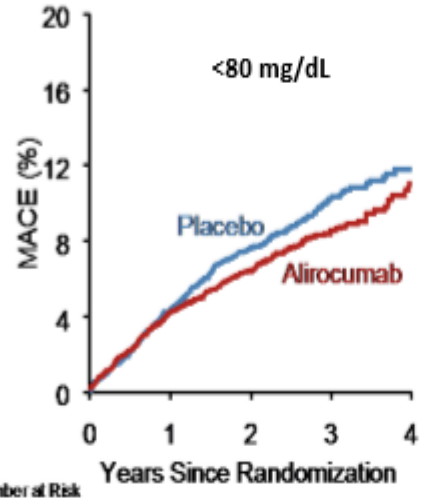
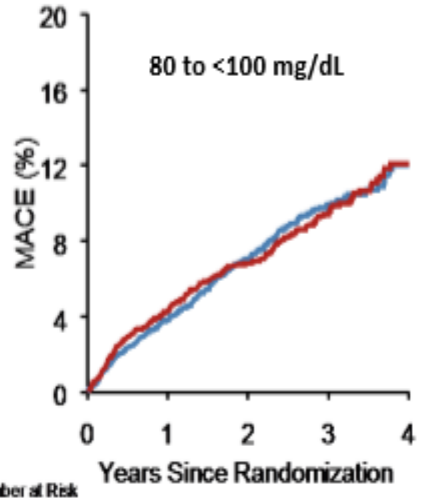
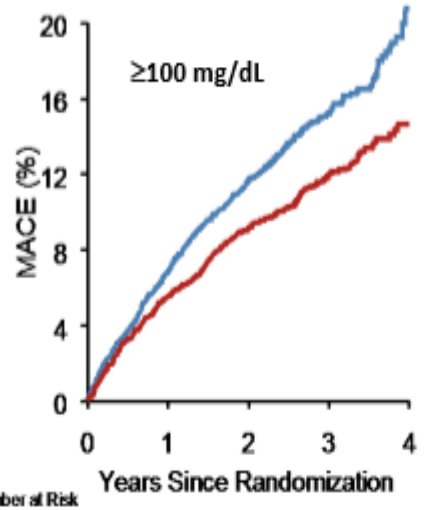


*P-values for interaction







ODYSSEY OUTCOMES

Safety (1)

Treatment-emergent adverse events, n (%)	Alirocumab (N=9451)	Placebo (N=9443)
Any	7165 (75.8)	7282 (77.1)
Serious	2202 (23.3)	2350 (24.9)

Laboratory value	Alirocumab	Placebo
ALT >3 × ULN, n/N (%)	212/9369 (2.3)	228/9341 (2.4)
Creatine kinase >10 × ULN, n/N (%)	46/9369 (0.5)	48/9338 (0.5)

Safety (2)

Event	Alirocumab (N=9451)	Placebo (N=9443)
Diabetes worsening or diabetic complications: *pts w/DM at baseline*, n/N (%)	506/2688 (18.8)	583/2747 (21.2)
New onset diabetes; *pts w/o DM at baseline*, n/N (%)	648/6763 (9.6)	676/6696 (10.1)
General allergic reaction, n (%)	748 (7.9)	736 (7.8)
Hepatic disorder, n (%)	500 (5.3)	534 (5.7)
Local injection site reaction, n (%)*	360 (3.8)	203 (2.1)
Neurocognitive disorder, n (%)	143 (1.5)	167 (1.8)
Cataracts, n (%)	120 (1.3)	134 (1.4)
Hemorrhagic stroke, n (%)	9 (<0.1)	16 (0.2)

*HR vs. placebo 1.82 (95% CI 1.54, 2.17)

ODYSSEY OUTCOMES

Conclusions

Compared with placebo in patients with recent ACS, alirocumab 75 or 150 mg subcutaneous Q2W targeting LDL-C levels 25–50 mg/dL, and allowing levels as low as 15 mg/dL:

1. Reduced MACE, MI, and ischemic stroke
2. Was associated with a lower rate of all-cause death
3. Was safe and well-tolerated over the duration of the trial

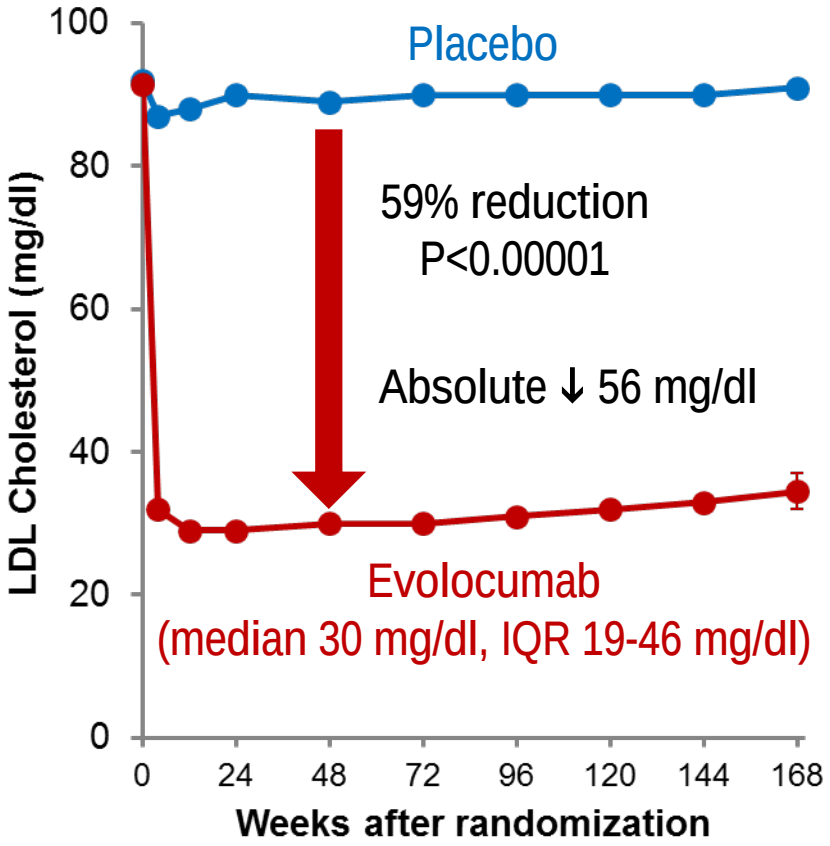
Clinical Perspective

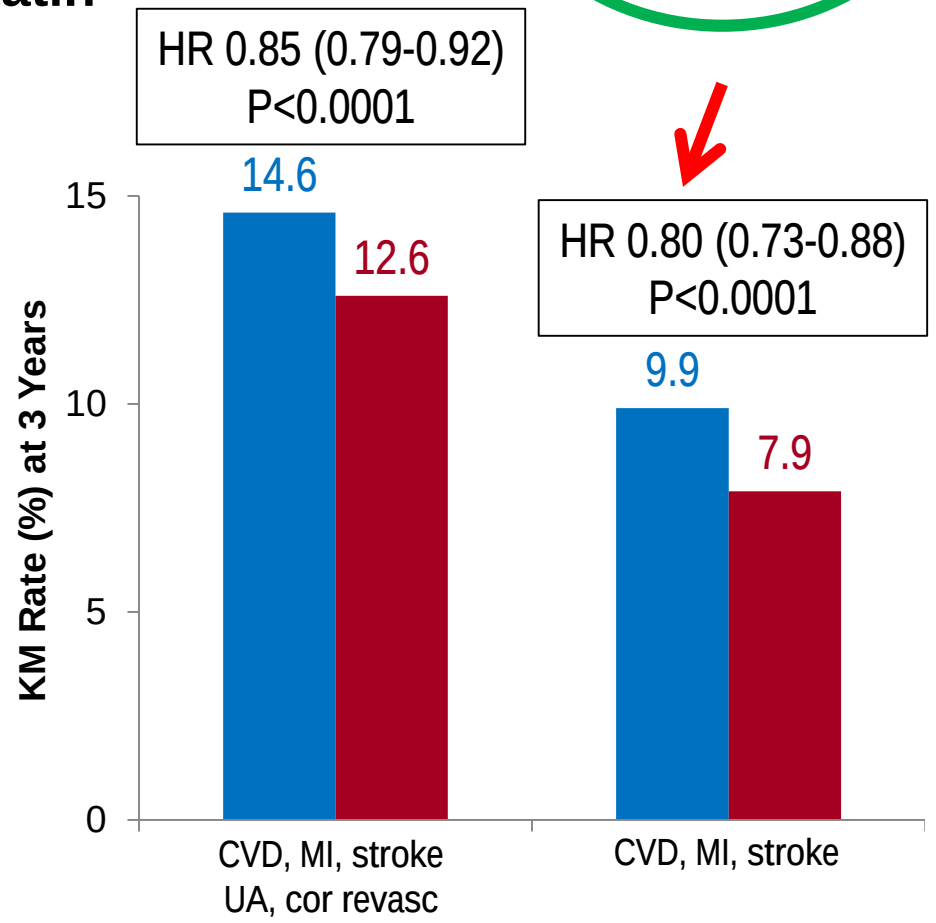
- In this nearly 19,000-patient placebo-controlled trial, including many patients treated for ≥3 years, there was no safety signal with alirocumab other than injection site reactions
- Among patients with ACS and baseline LDL-C ≥100 mg/dL, alirocumab reduced MACE by 24% (ARR 3.4%) and all-cause death by 29% (ARR 1.7%) compared with placebo
  - ➢These are the patients who may benefit most from treatment

ARR, absolute risk reduction

Summary of Effects of PCSK9i Evolocumab

- ↓ LDL-C by 59% to a median of 30 mg/dL
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated





Sabatine MS et al. *NEJM* 2017;376:1713-22

LDL Cholesterol Lowering with Evolocumab and Outcomes in Patients with Peripheral Artery Disease: Insights from the FOURIER Trial

Marc P. Bonaca, Patrice Nault, Robert P. Giugliano, Anthony C. Keech, Armando Lira Pineda, Estella Kanevsky, Julia Kuder, Sabina A. Murphy, J. Wouter Jukema, Basil S. Lewis, Lale Tokgozoglu, Ransi Somaratne, Peter S. Sever, Terje R. Pedersen, Marc S. Sabatine

for the FOURIER Steering Committee & Investigators

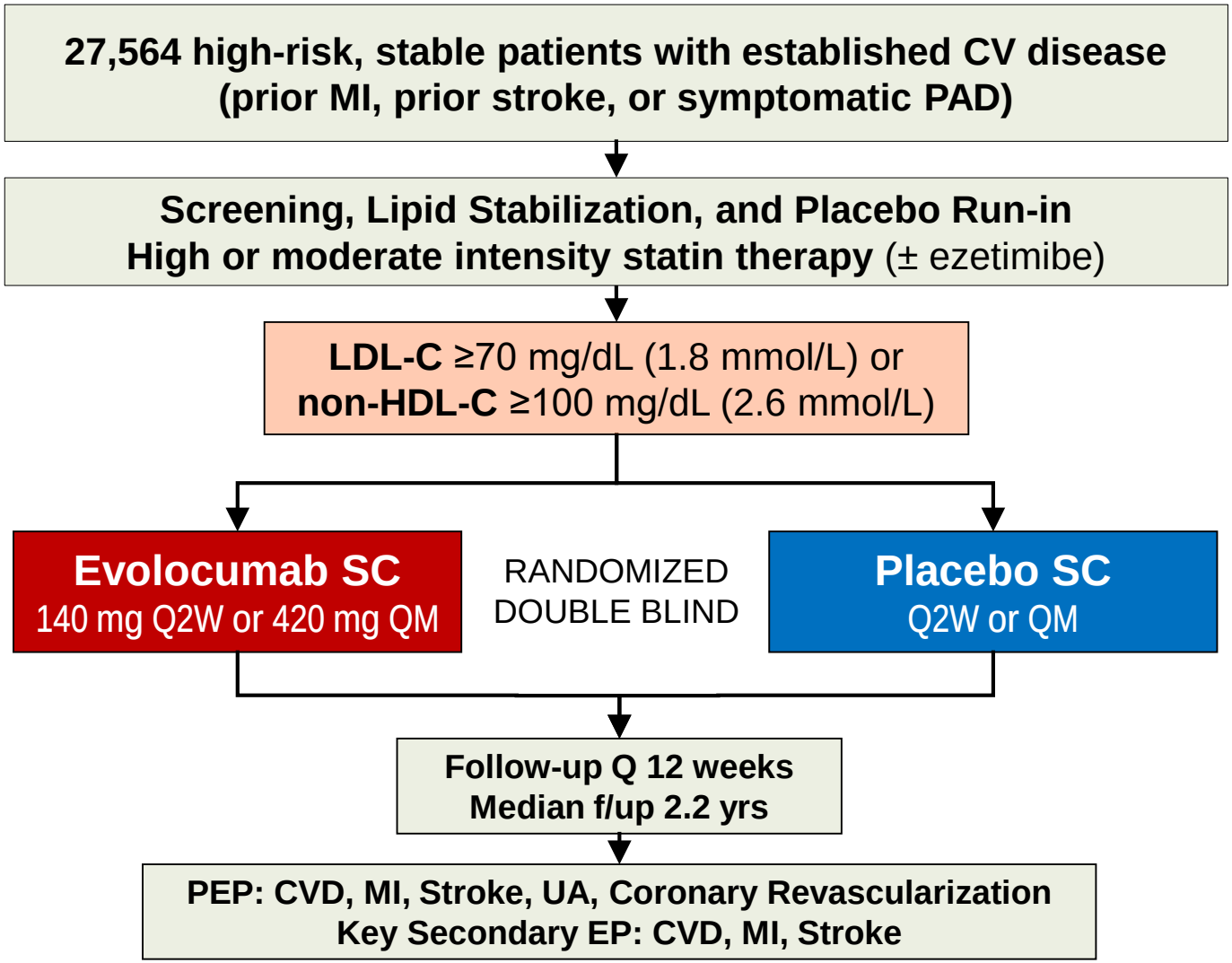
American Heart Association – Annual Scientific Session

Late-Breaking Science in Prevention

November 13, 2017

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

Trial Design



Sabatine MS et al. *Am Heart J* 2016;173:94-101

Background & Objectives

Patients with lower extremity PAD are at heightened risk of adverse cardiovascular (MACE) and limb events (MALE)

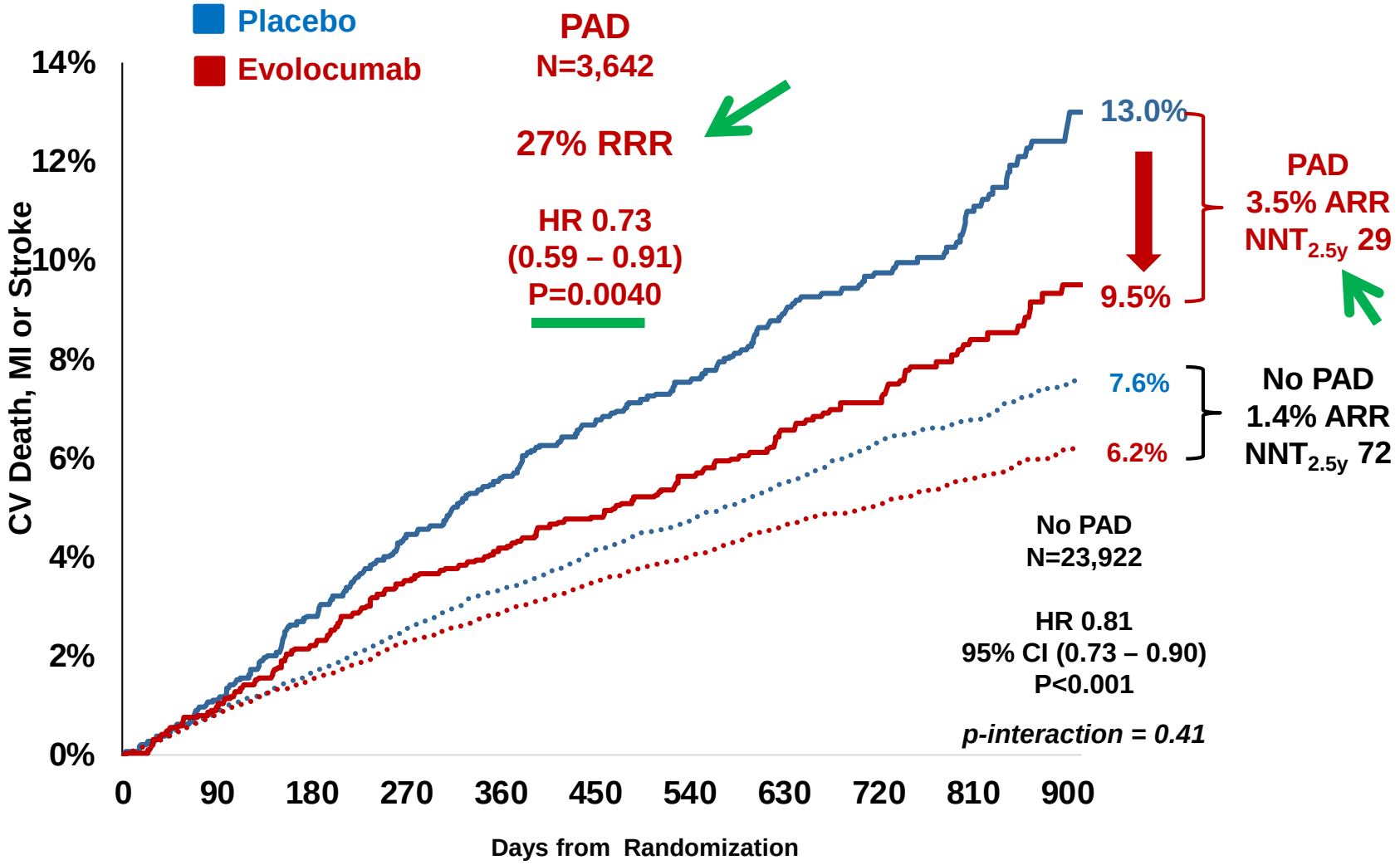
Statin vs. Placebo reduces CV risk and peripheral revascularization & observational studies suggest reductions in amputations

<u>In patients with PAD on statins:</u>

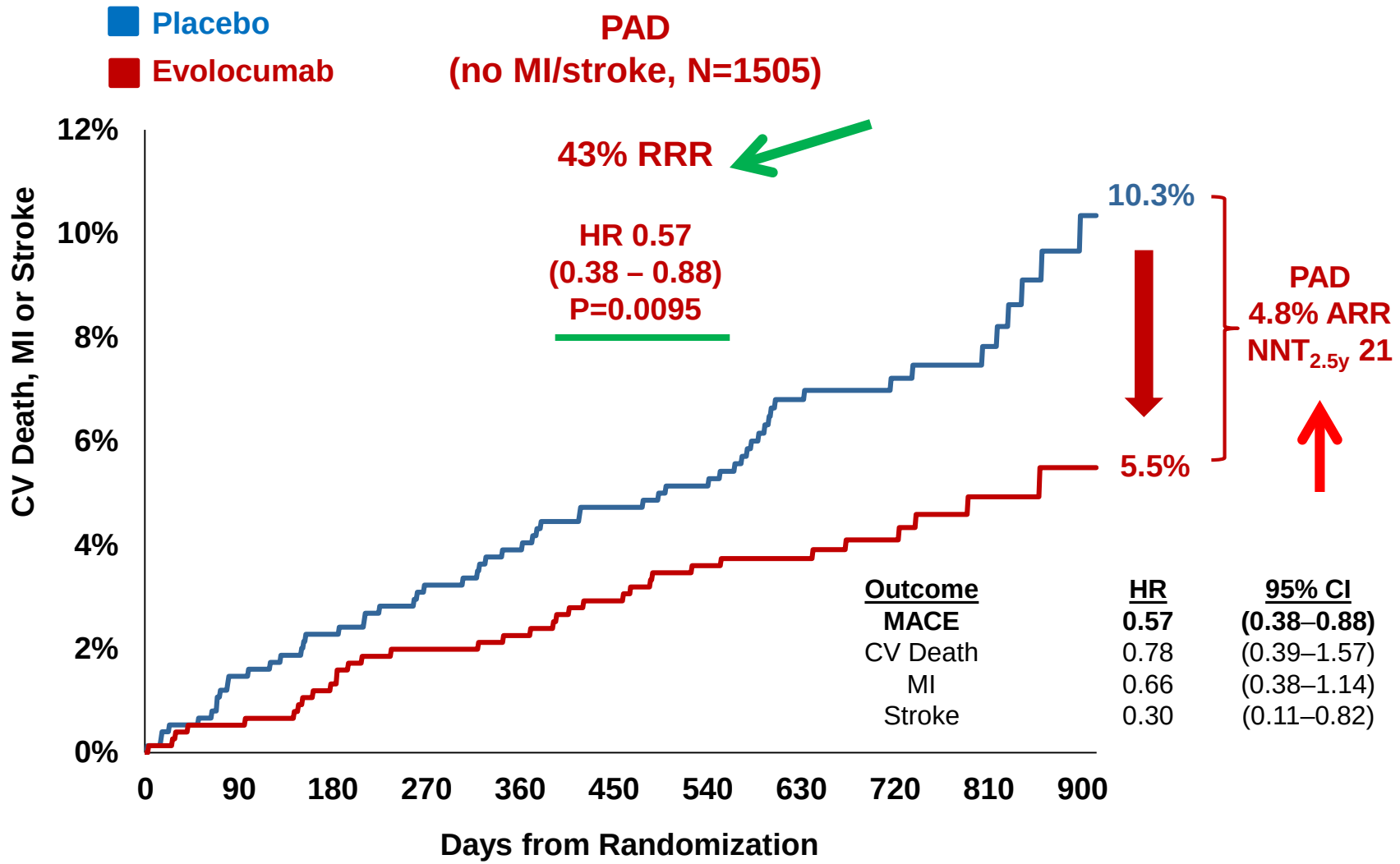
- ***Does further reducing LDL-C reduce CV risk?***
- ***Does lowering LDL-C reduce the risk of MALE?***

Heart Protection Study Collaborative Group J Vasc Surg 2007; Kumbhani DJ et al. EHJ 2014

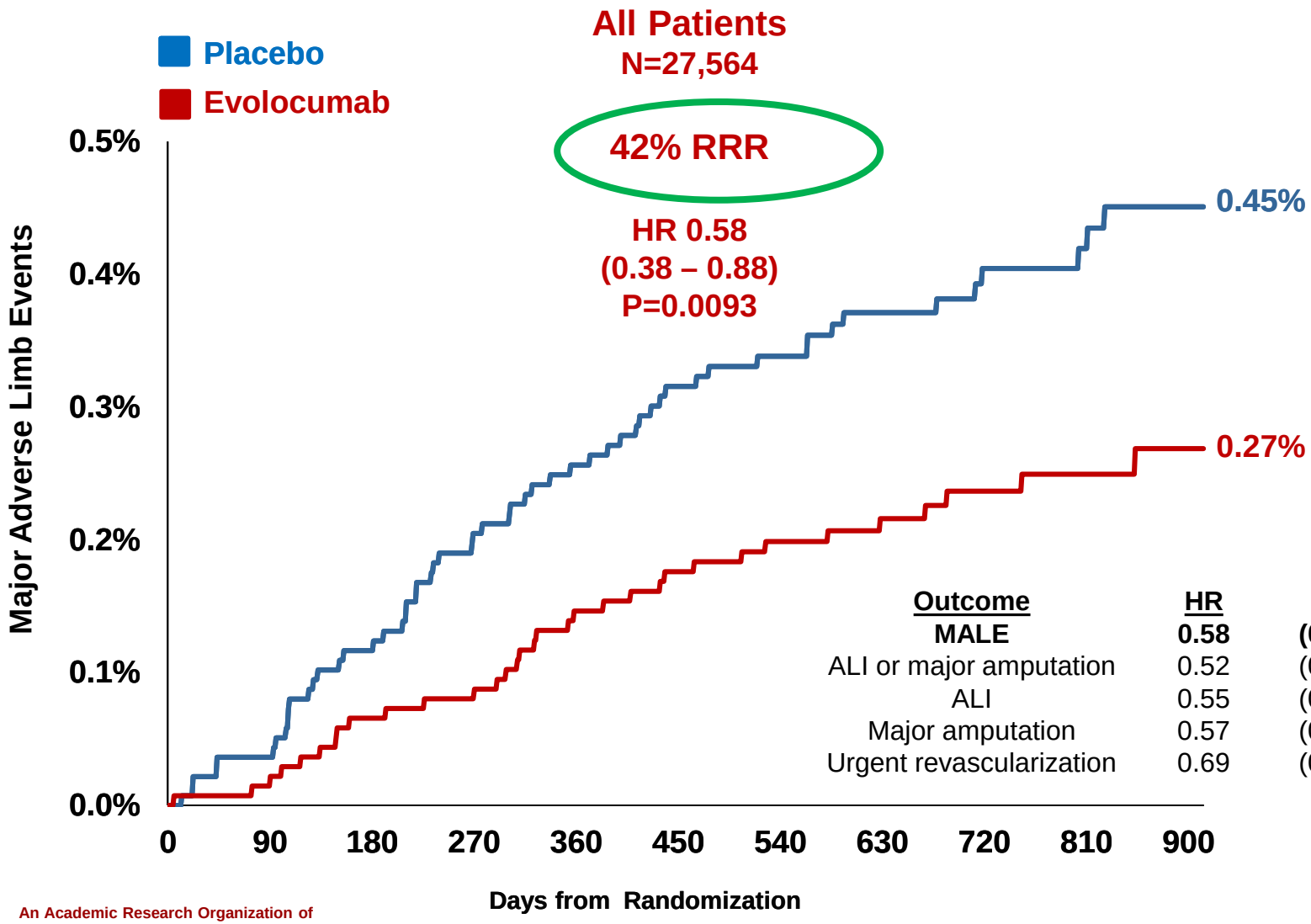
CV Death, MI or Stroke in Patients with and without Peripheral Artery Disease



CV Death, MI or Stroke in Patients with PAD and no MI or Stroke

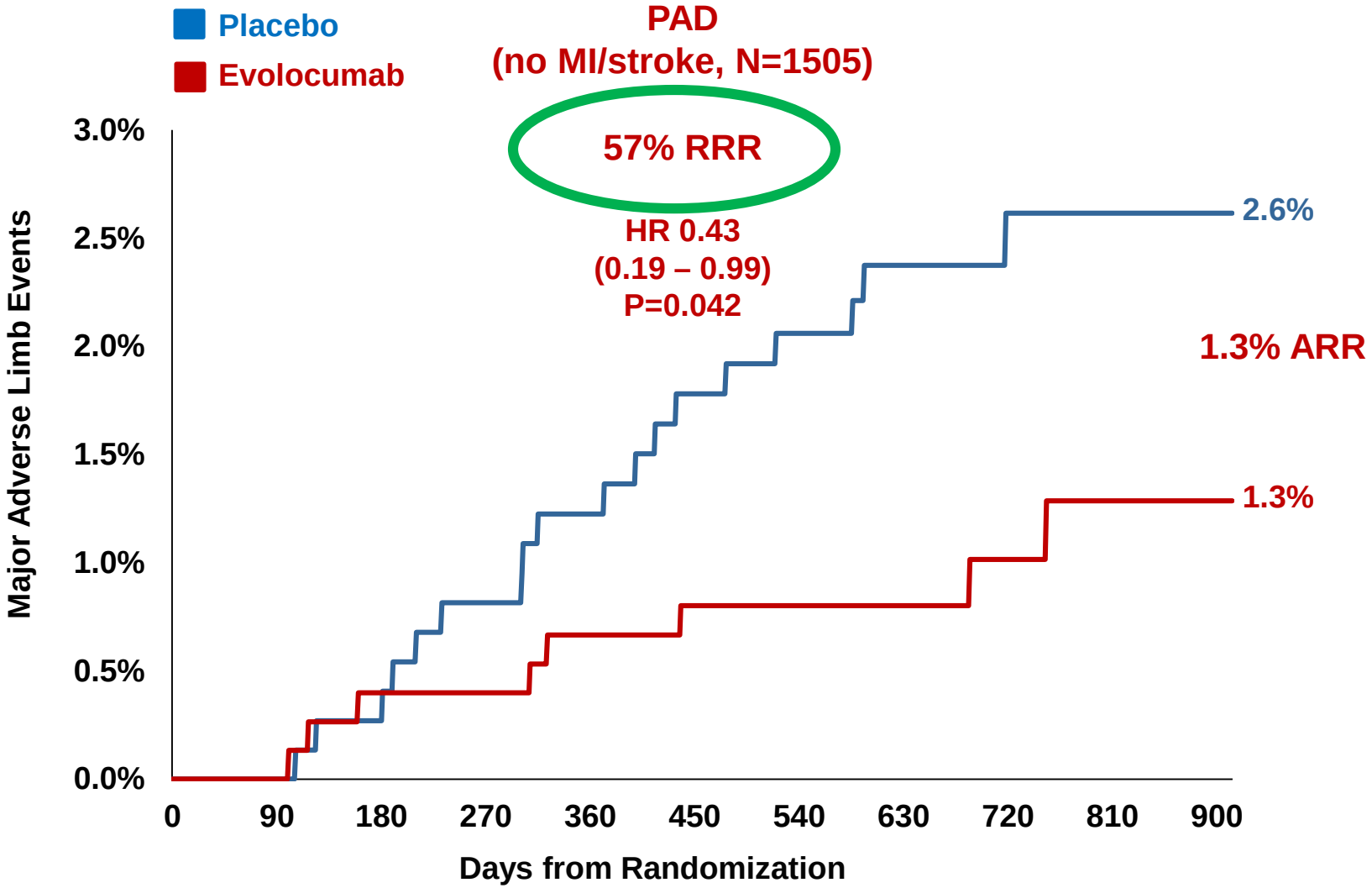


Major Adverse Limb Events

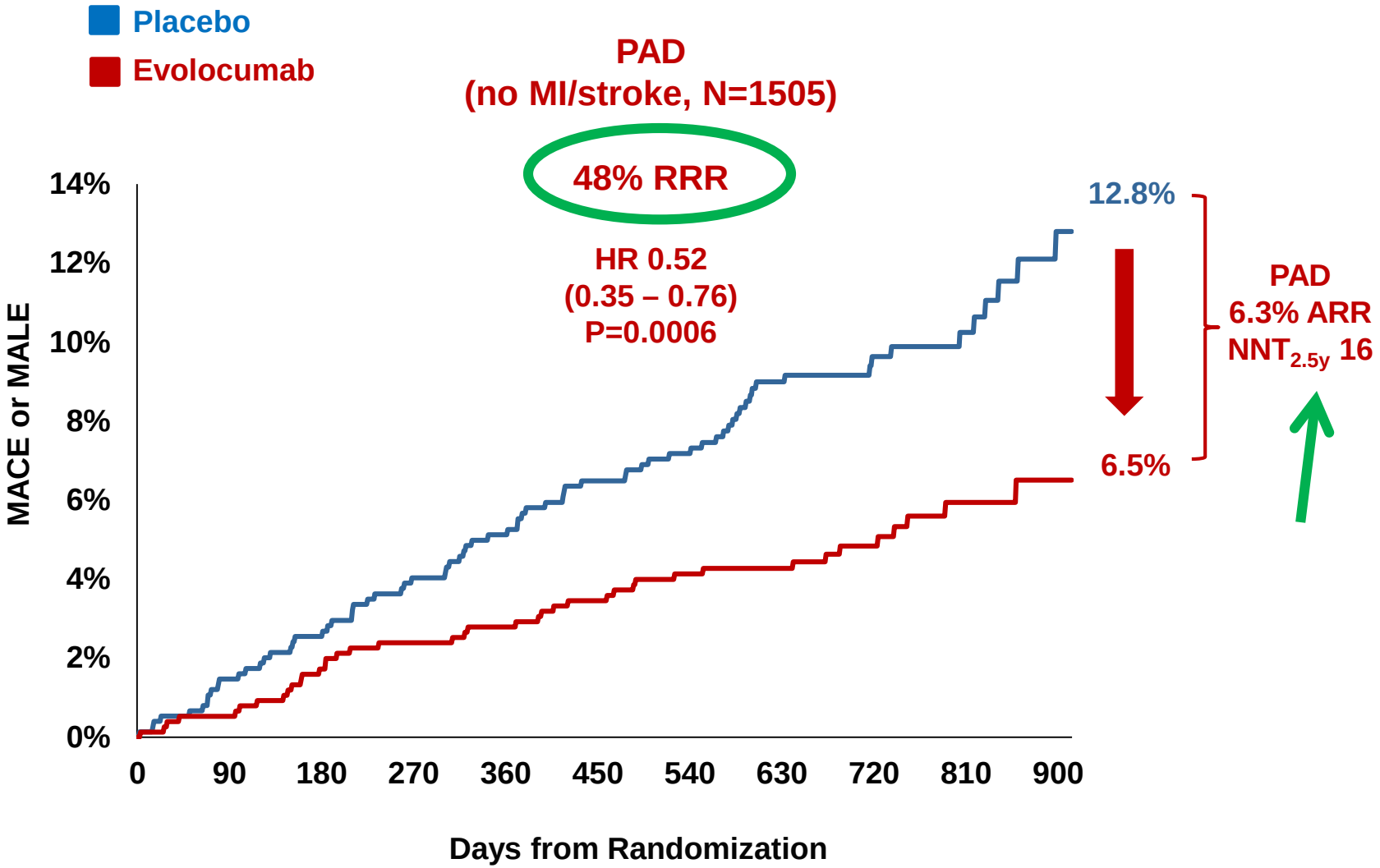


Outcome	HR	95% CI
MALE	**0.58**	**(0.38–0.88)**
ALI or major amputation	0.52	(0.31–0.89)
ALI	0.55	(0.31–0.97)
Major amputation	0.57	(0.17–1.95)
Urgent revascularization	0.69	(0.38–1.26)

Major Adverse Limb Events in Patients with PAD and no MI or Stroke



MACE or MALE
In Patients with PAD and no MI or Stroke



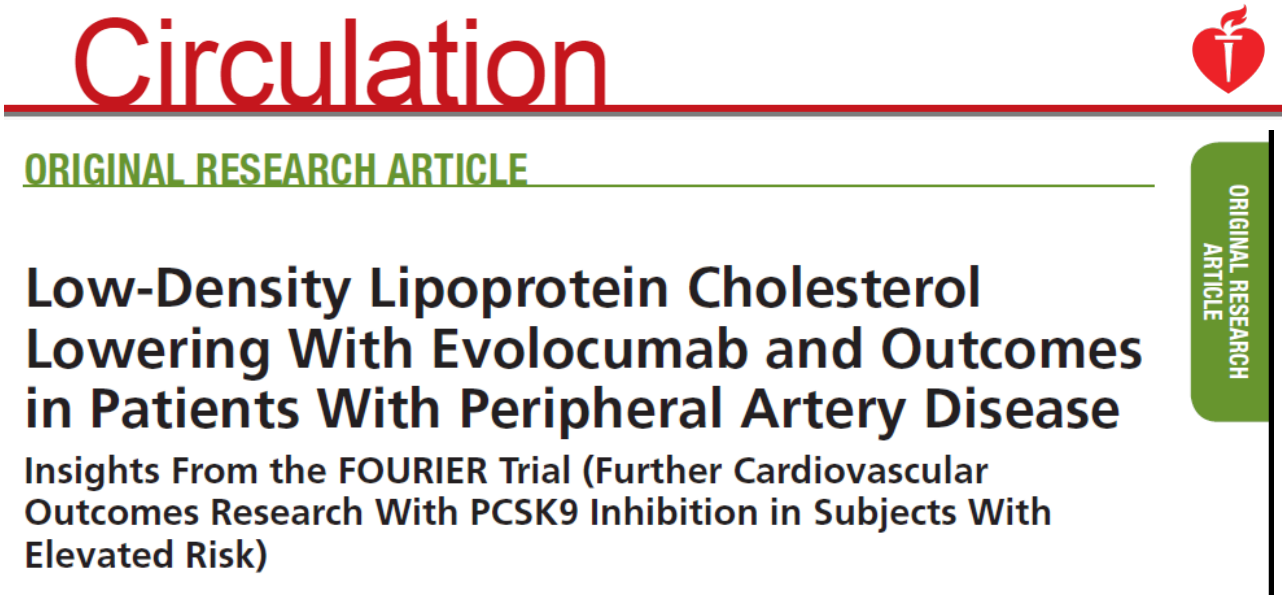
Summary

- **Patients with PAD are at heightened risk of MACE and MALE**
- **LDL-C lowering with evolocumab in patients with PAD:**
  - **Reduces major adverse CV events with robust ARR**
  - **Reduces major adverse limb events**
- **Benefits extend to PAD without prior MI or stroke with an ARR for MACE or MALE of 6.3% (NNT 16) at 2.5 years**

Conclusion

LDL-C reduction to very low levels should be considered in patients with PAD, regardless of history of MI or stroke, to reduce the risk of MACE and MALE

For more information see simultaneous publication in:



AHA 2017

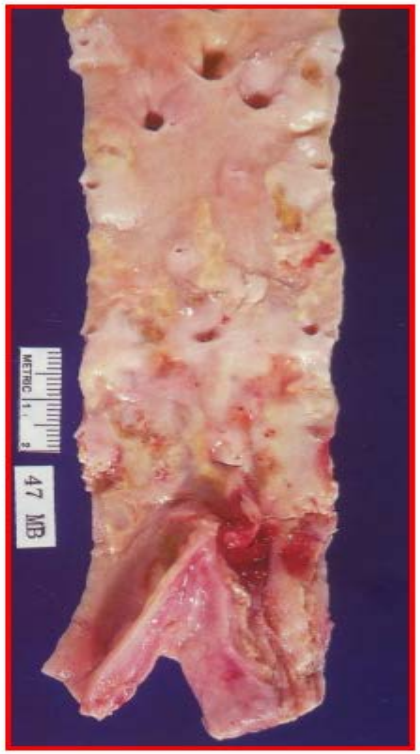
Residual Inflammatory Risk and Residual Cholesterol Risk: Critical Analysis from CANTOS

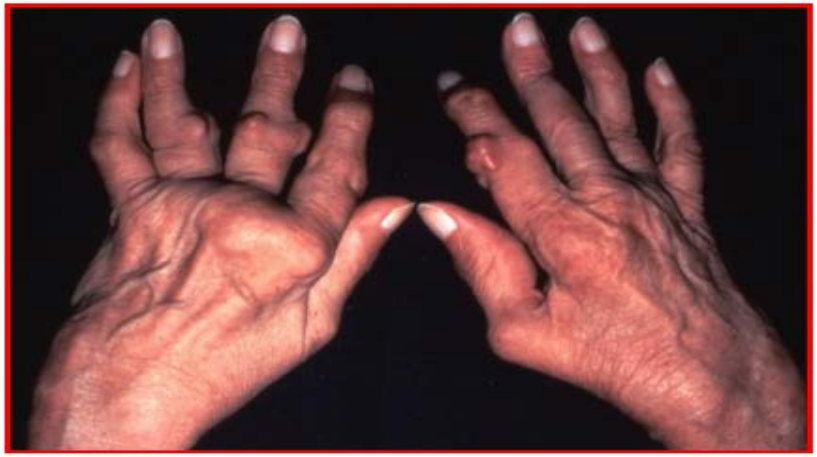
Relationship of CRP Reduction to Cardiovascular Event Reduction Following Treatment with Canakinumab

Paul M Ridker MD, Jean MacFadyen BS, Brendan Everett MD, Peter Libby MD, Tom Thuren MD, and Robert Glynn, PhD
on behalf of the worldwide investigators and participants in the
Canakinumab **An**ti-Inflammatory **T**hrombosis **O**utcomes **S**tudy (**CANTOS**)

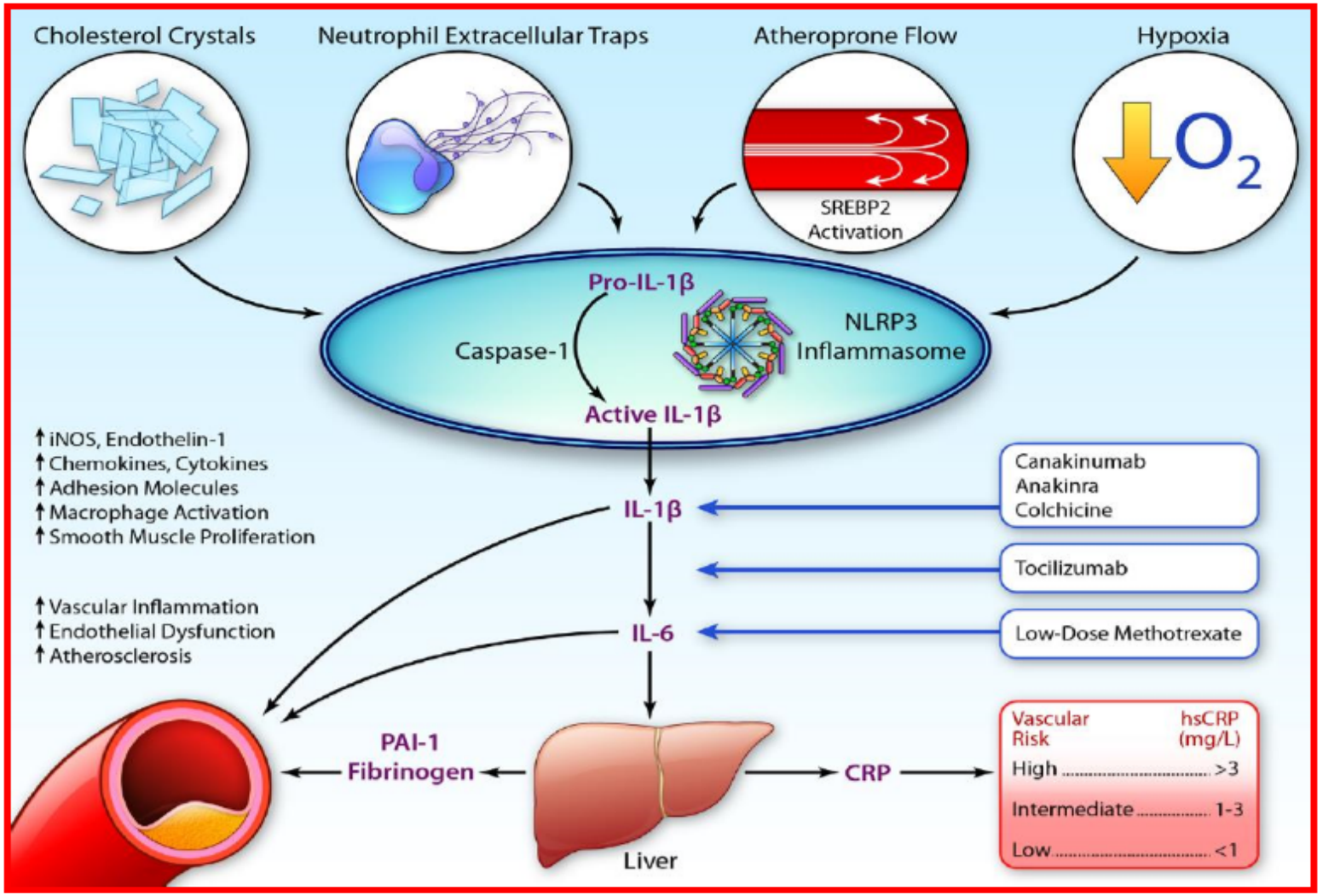
CANTOS TRIAL

Can Inflammation Reduction, in the Absence of Lipid Lowering, Reduce Cardiovascular Event Rates?

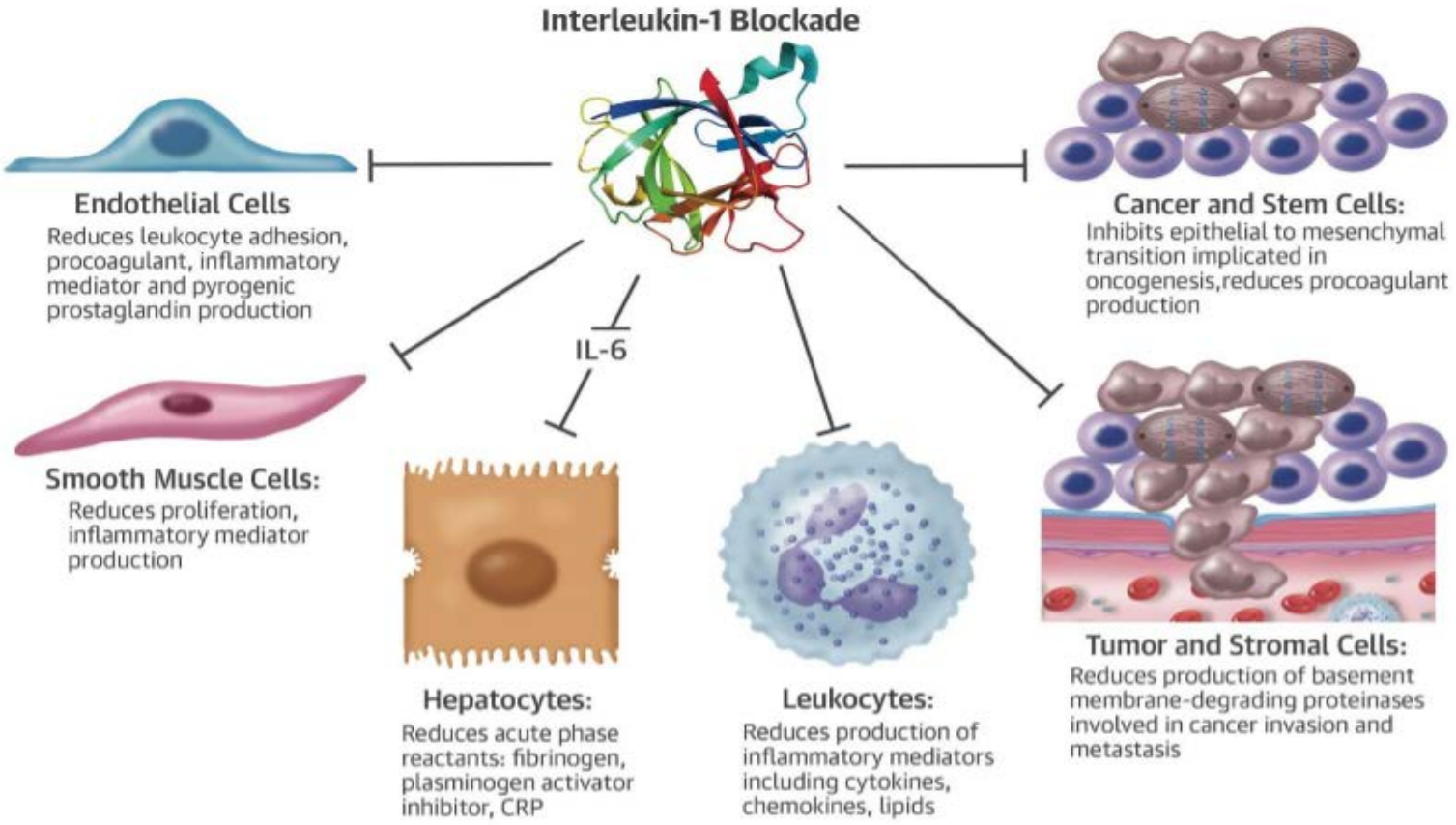




From CRP to IL-6 to IL-1: Moving Upstream to Identify novel Targets for Atheroprotection

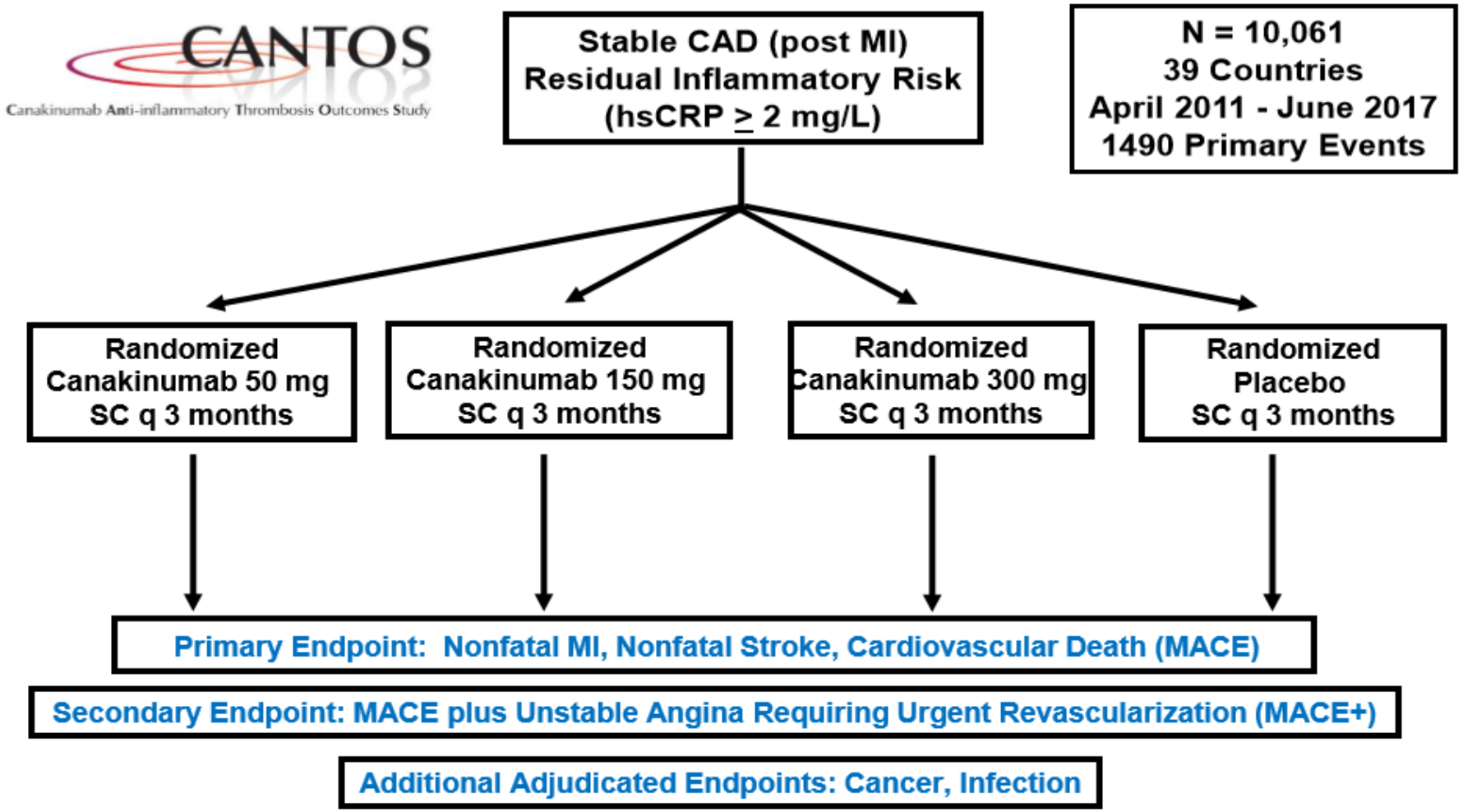


Ridker PM. Circ Res 2016;118:145-156.



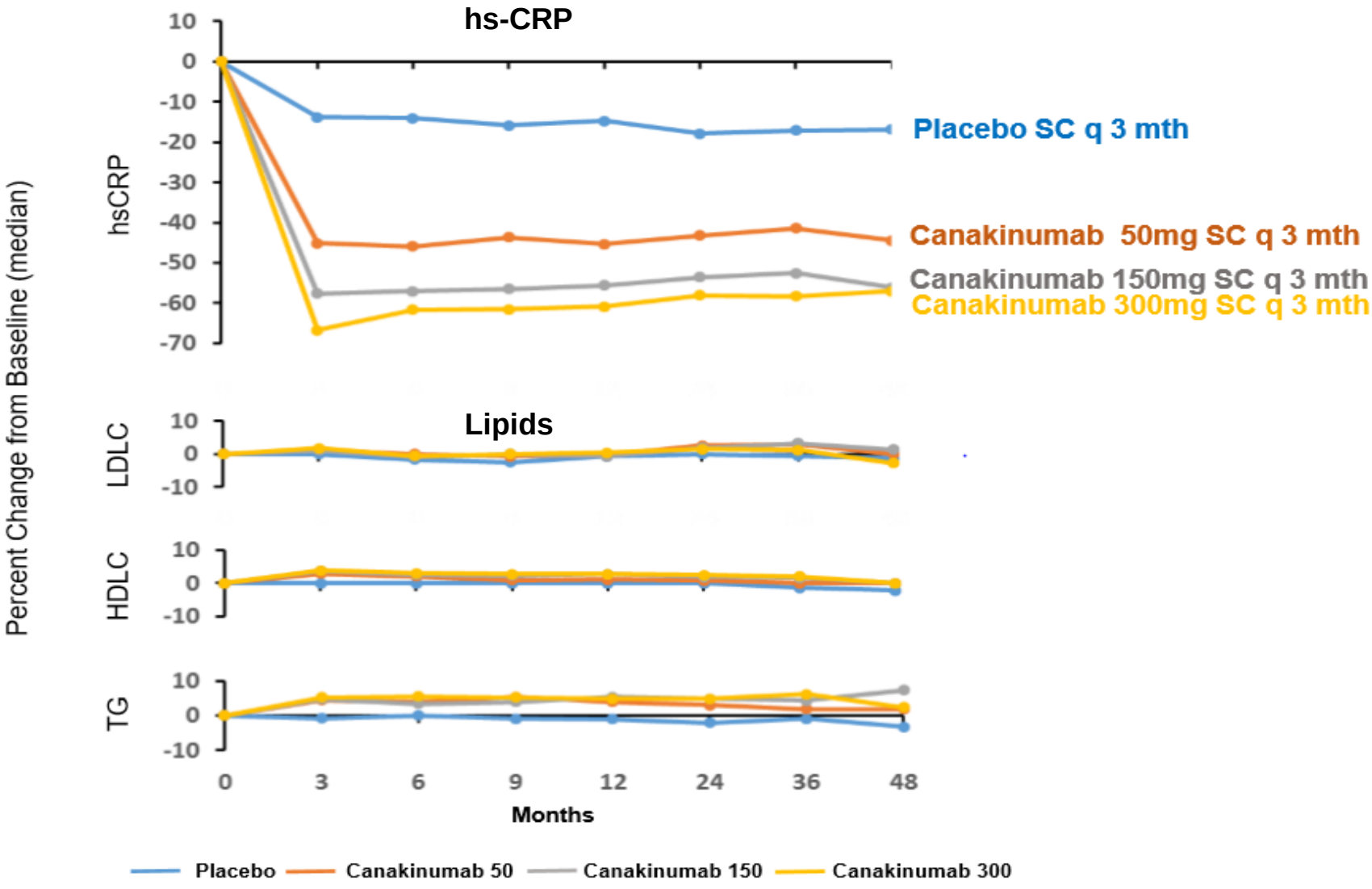
Libby P. Interleukin-1 Beta as a Target for Atherosclerosis: Biologic Basis for CANTOS and Beyond. JACC 2017 (October 31, 2017)

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)



Ridker PM et al. N Engl J Med. 2017;377:1119-31

CANTOS: Dose-Dependent Effects on Inflammatory Biomarkers and Lipids (48 Months)

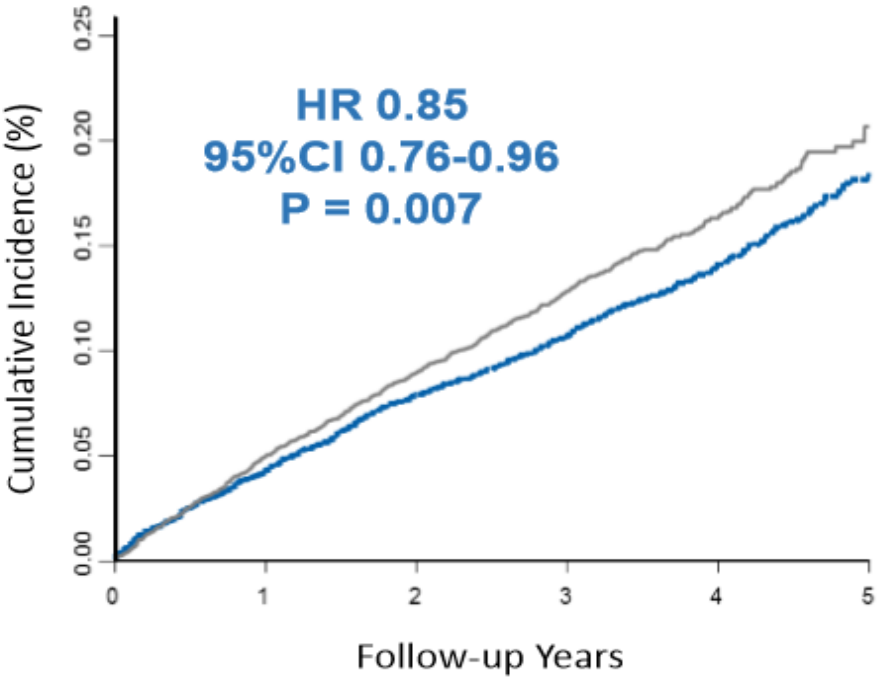


Ridker PM et al. N Engl J Med. 2017;377:1119-31

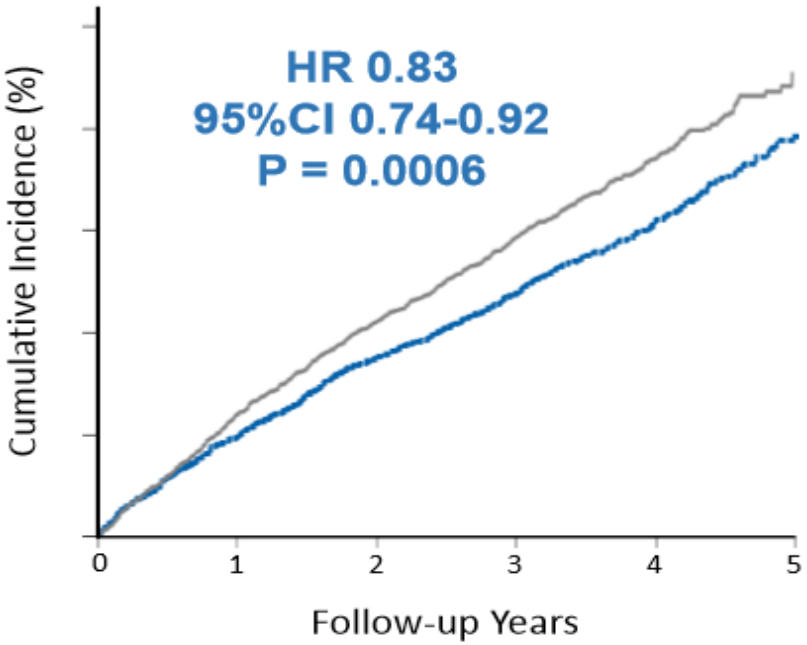
CANTOS: Primary Cardiovascular Endpoints

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

MACE



MACE - Plus

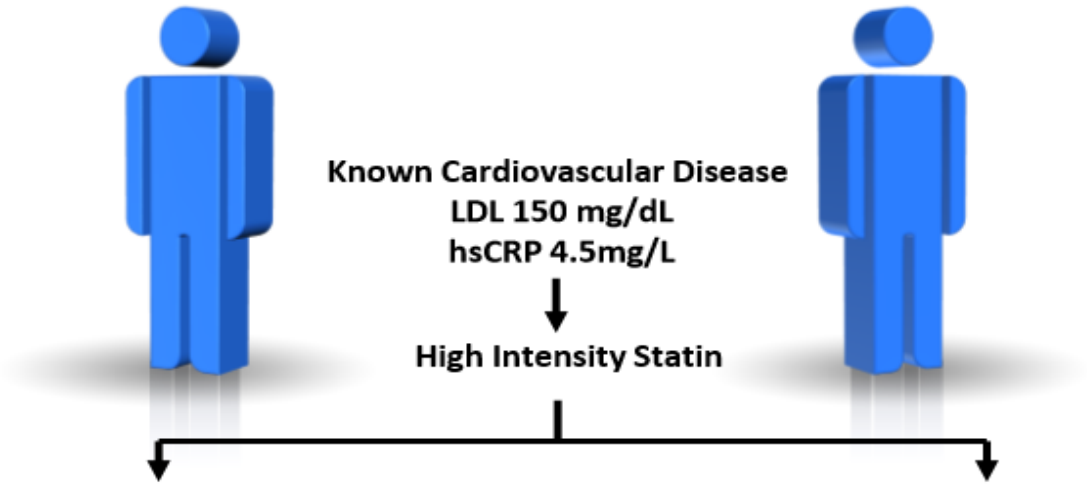


35 - 40% reductions in hsCRP and IL-6
No change in LDLC

Ridker PM et al. N Engl J Med. 2017;377:1119-31

Residual Inflammatory Risk:
Addressing the Obverse Side of the Atherosclerosis Prevention Coin

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



"Residual Cholesterol Risk"

LDL 110 mg/dL
hsCRP 1.8 mg/L

↓

Additional
LDL Reduction

Fourier / Odyssey

PCSK9 Inhibition SC q 2 weeks 15% RRR

"Residual Inflammatory Risk"

LDL 70 mg/dL
hsCRP 3.8 mg/L

↓

Additional
Inflammation Reduction

CANTOS

Canakinumab 150-300mg SC q 3 months 15%RRR

CANTOS: Critical Unanswered Clinical Questions

Monoclonal Antibodies and the Era of Personalized Medicine

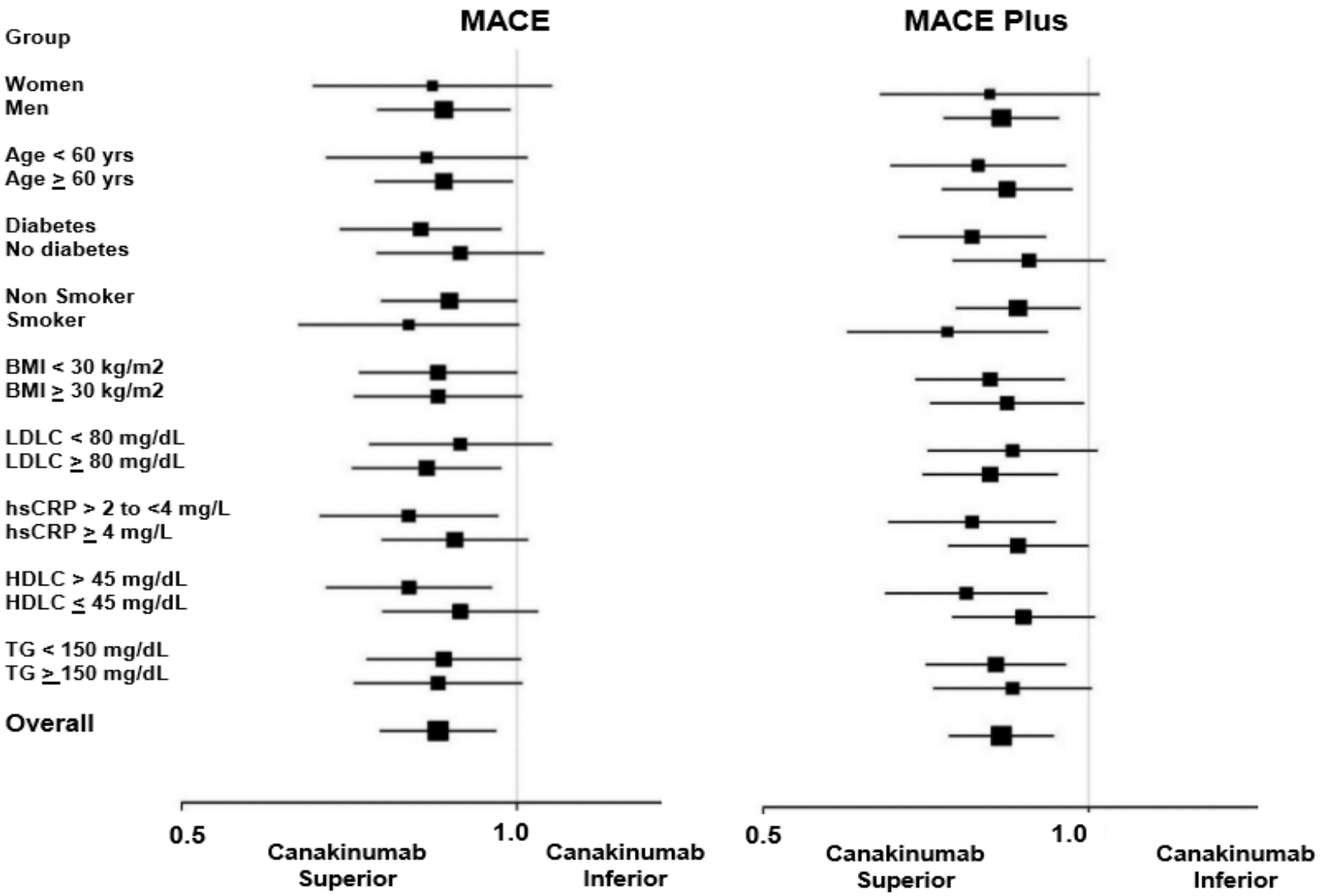
Can we predict who benefits the most from effective but expensive treatments?

Is there an easily identified clinical subgroup for whom benefits are large and might clearly outweigh hazards?

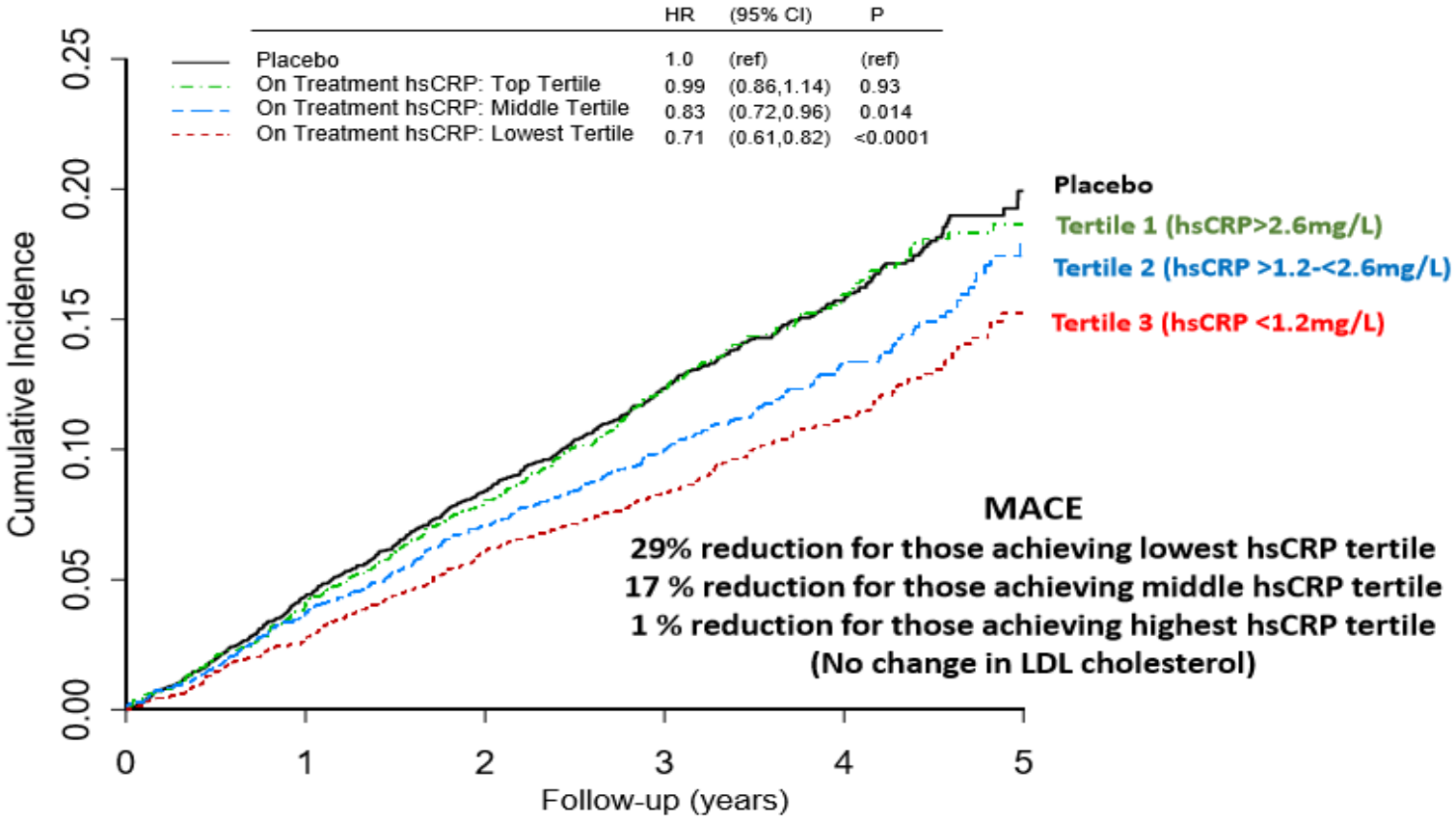
Is there an easily identifiable subgroup where there is evidence not only of reduced MACE, but also of reduced cardiovascular mortality and reduced all-cause mortality?

Is there an easily identified clinical subgroup for whom benefits are small and may not justify the hazards?

CANTOS : Consistency of Effect Across All patient Groups Defined By Baseline Clinical Characteristics



CANTOS Sensitivity Analysis III. Cardiovascular Outcomes According to On-treatment Tertiles of hsCRP Measured After the Initial dose of Canakinumab (MACE)

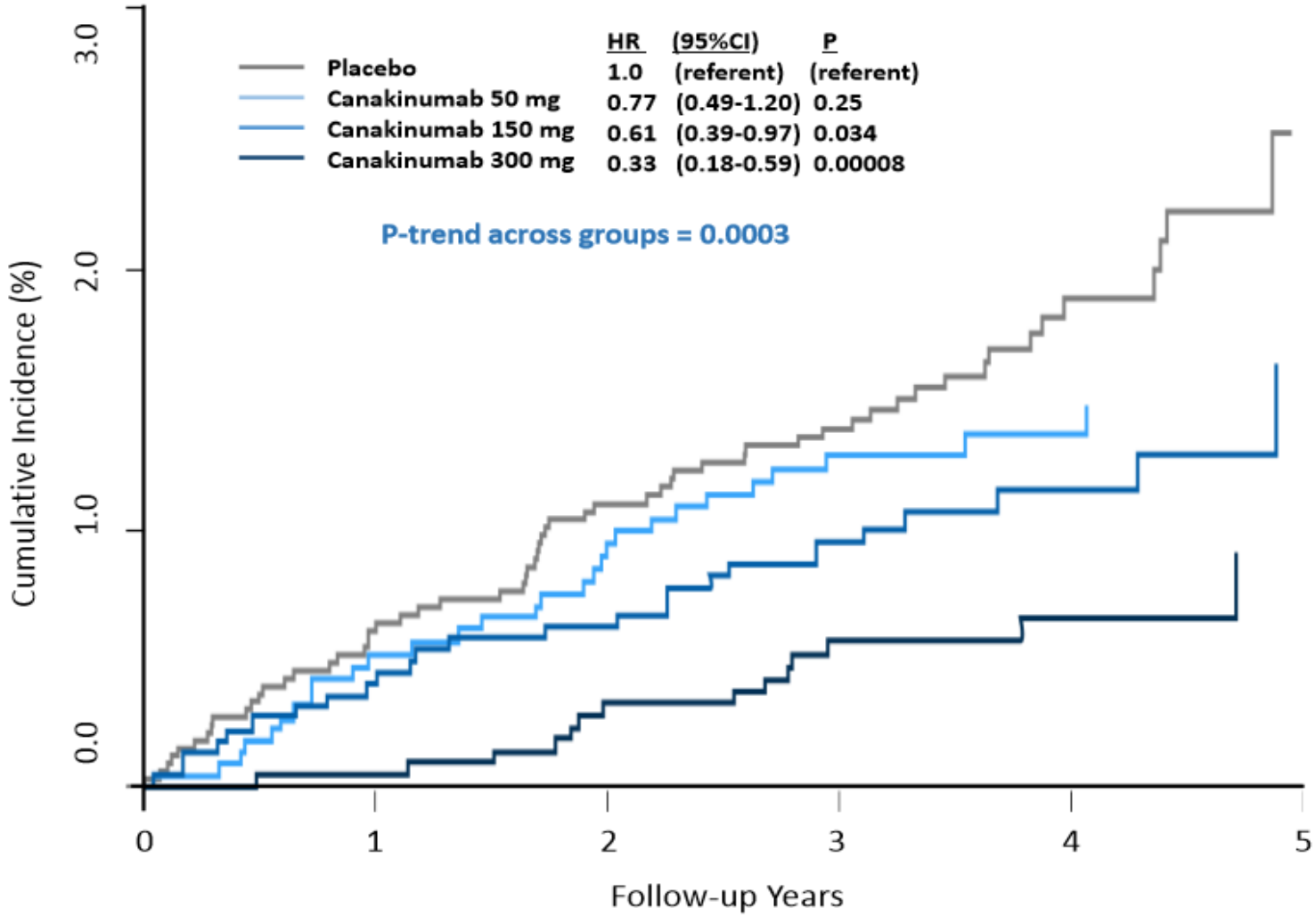


MACE

29% reduction for those achieving lowest hsCRP tertile
17 % reduction for those achieving middle hsCRP tertile
1 % reduction for those achieving highest hsCRP tertile
(No change in LDL cholesterol)

No. at risk:						
Placebo	3182	3014	2853	2525	1215	200
Canakinumab:						
Top Tertile	2090	1983	1866	1632	789	139
Middle Tertile	2044	1947	1866	1660	821	146
Lowest Tertile	2218	2147	2056	1856	888	153

CANTOS: Additional Non-Cardiovascular Clinical Benefits
Incident Lung Cancer



Ridker PM et al. Lancet. 2017;390:1833-1842

Conclusions:

The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

1. Overall, CANTOS demonstrates that targeting the IL-1b to IL-6 pathway of innate immunity with canakinumab reduces cardiovascular event rates and potentially reduces rates of incident lung cancer and lung cancer mortality.

2. CANTOS thus provides critical proof-of-concept that inflammation inhibition, in the absence of lipid lowering, can improve atherothrombotic outcomes. It has been uncertain, however, if there are patient groups where the benefits of treatment clearly outweigh potential hazards.

Conclusions:

The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

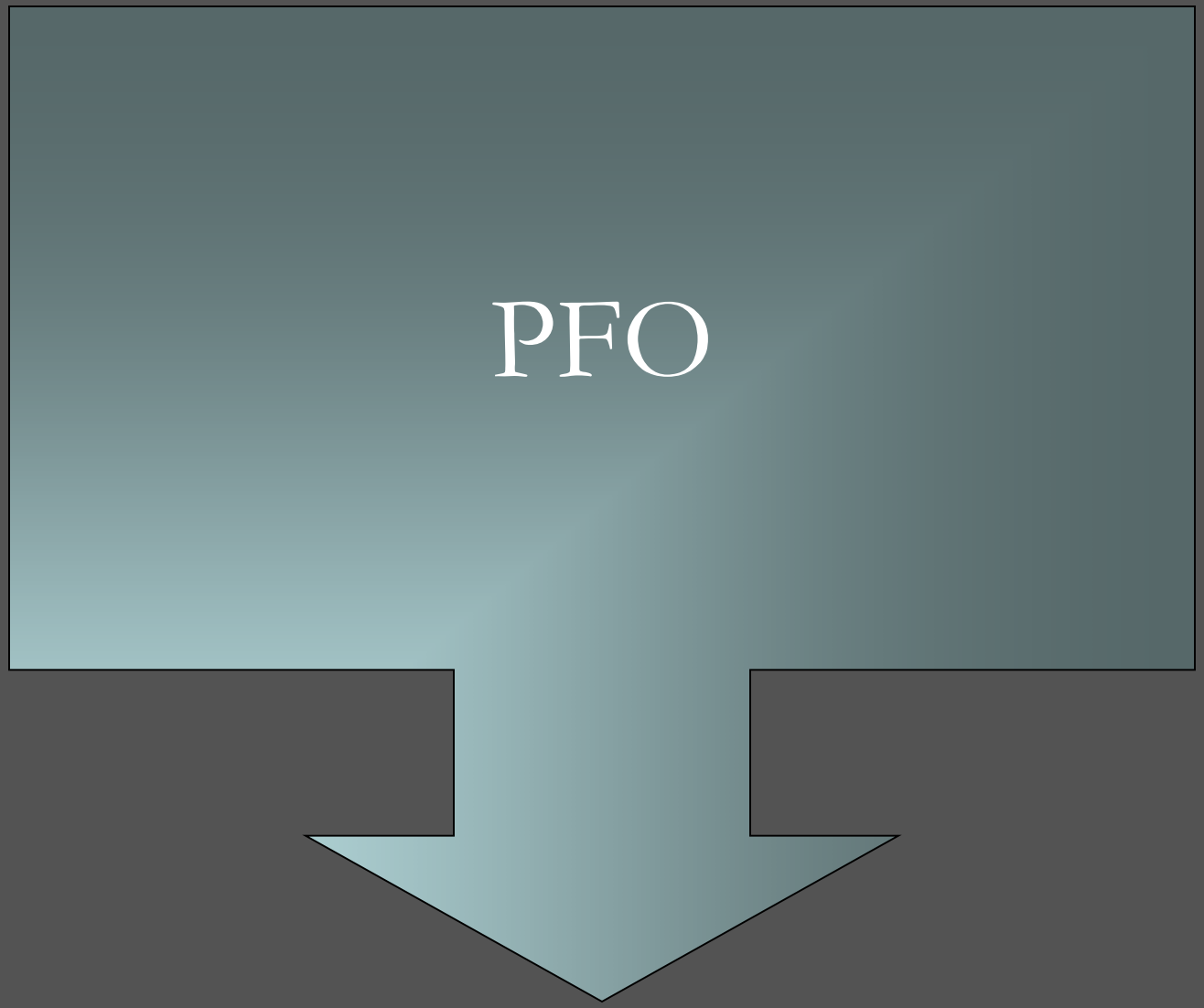
4. For example, among those who achieved levels of hsCRP <2mg/L after a single dose of canakinumab, continued long-term treatment was associated with a 25% reduction in MACE (P<0.0001), a 31% reduction in cardiovascular mortality (P=0.0004) and a 31% reduction in all-cause mortality (P<0.0001). By contrast, effects were smaller in magnitude and non-significant for all of these endpoints among those with a less profound inflammatory response.

Conclusions:

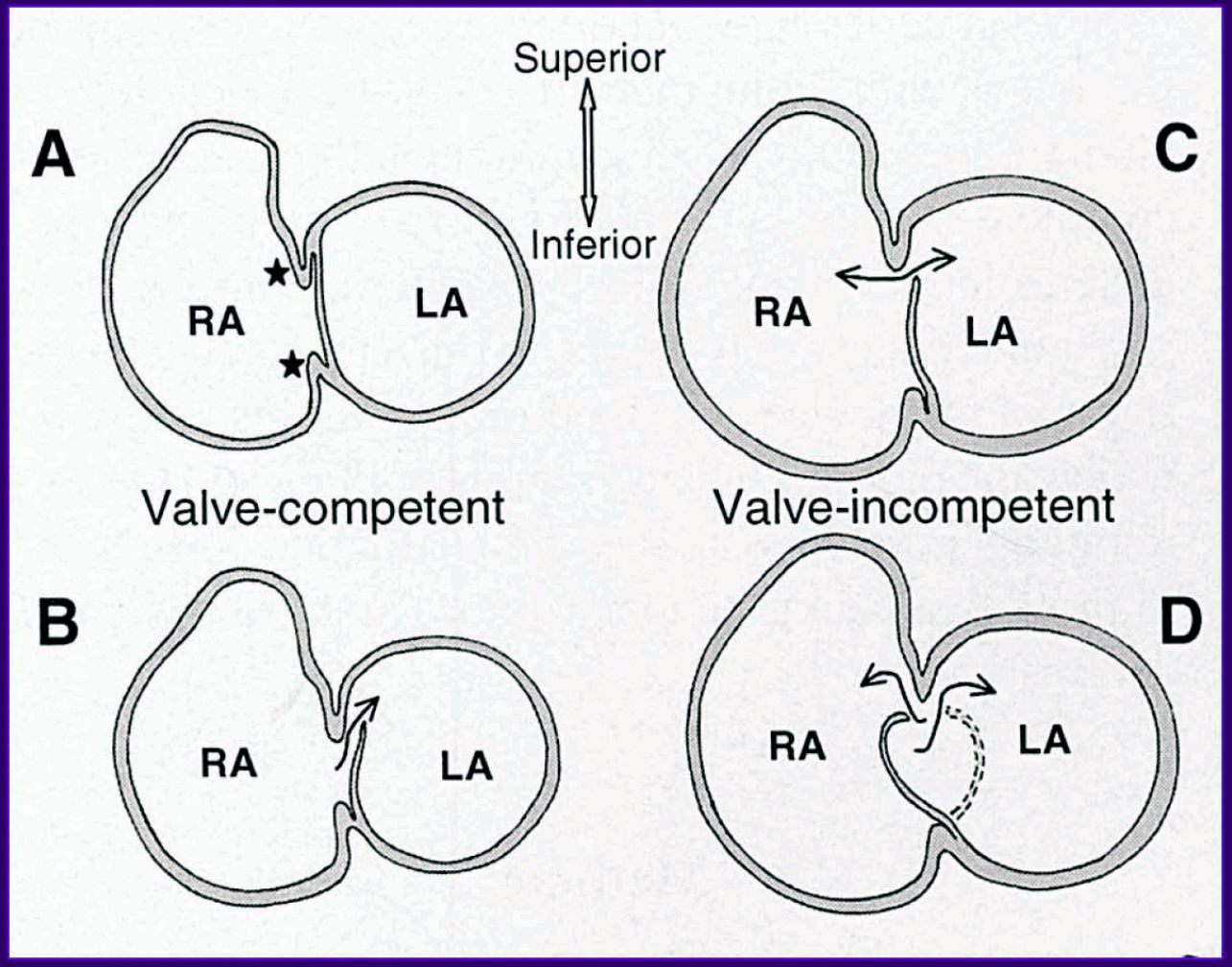
The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

For example, the 5-year number-needed-to-treat (NNT) for the endpoint of myocardial infarction, stroke, coronary revascularization, or death from any cause was 16 among those with on-treatment concentrations of hsCRP <2mg/L. By contrast, the 5-year NNT was 57 for those treated with canakinumab who did not achieve this inflammation threshold.

The main hazard of canakinumab – a small but statistically significant increase in fatal infection – was not related to on-treatment hsCRP levels. As such, the use of biologic response to canakinumab may also provide a simple selection tool to maximize benefit without increasing clinical hazard.

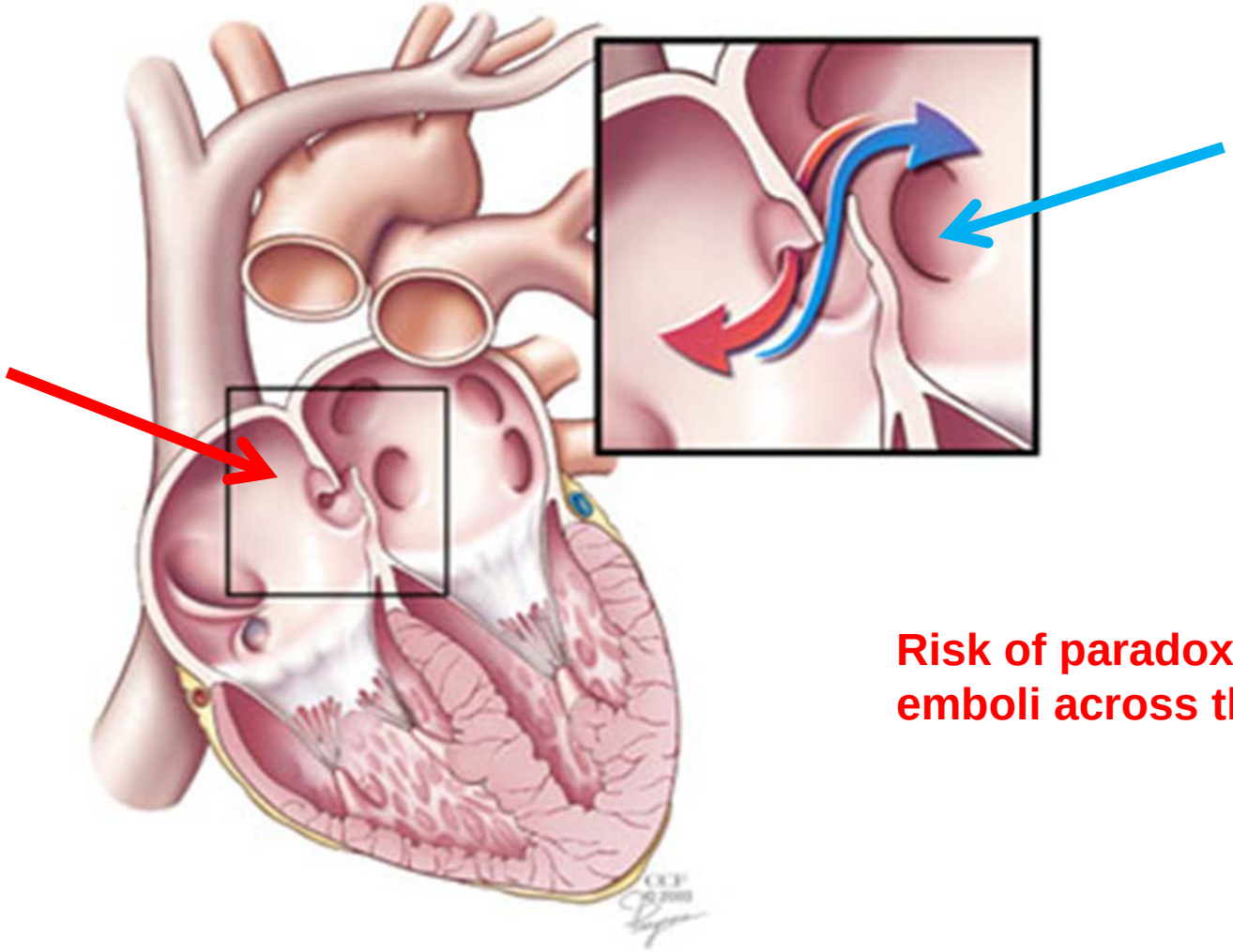

PFO

PFO MORPHOLOGY



JIC 2003;16:33

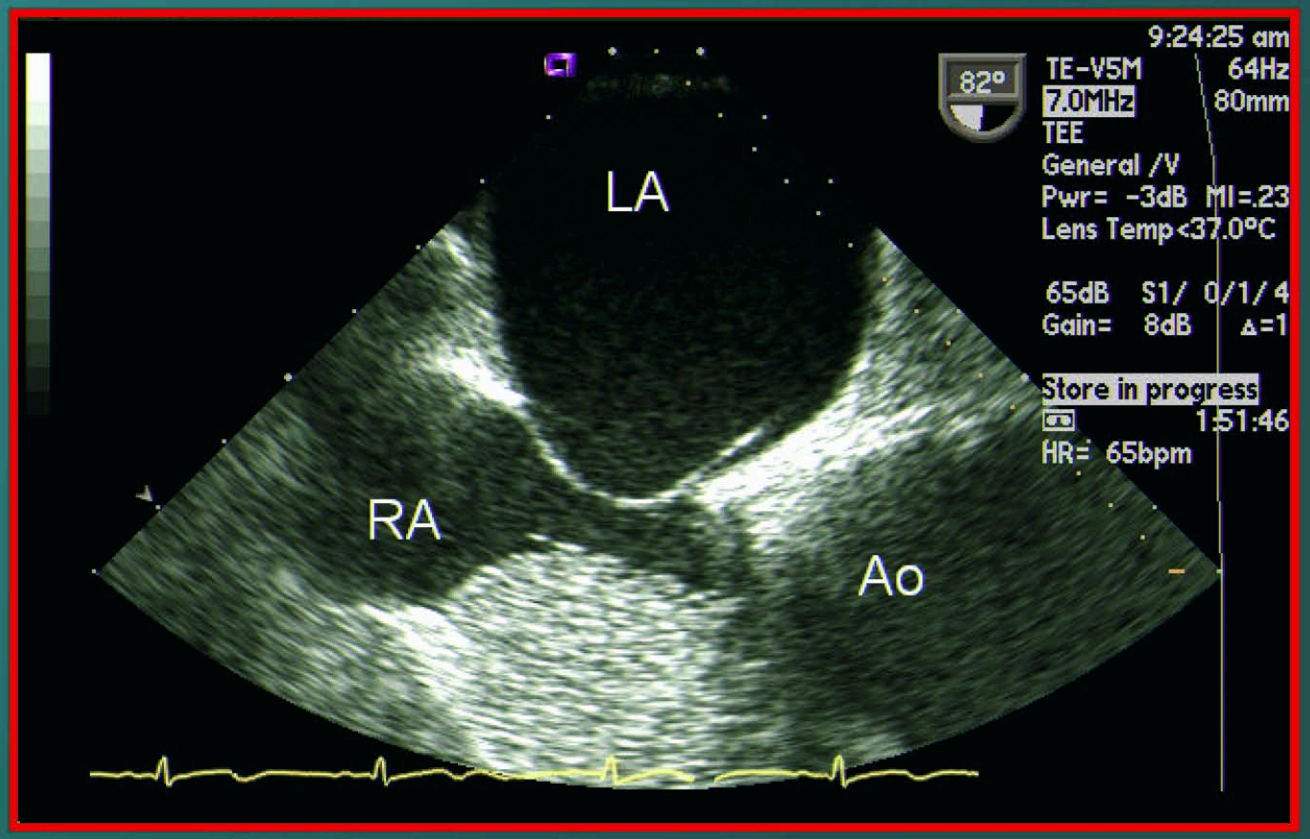
Patent Foramen Ovale (PFO)



Risk of paradoxical emboli across the defect

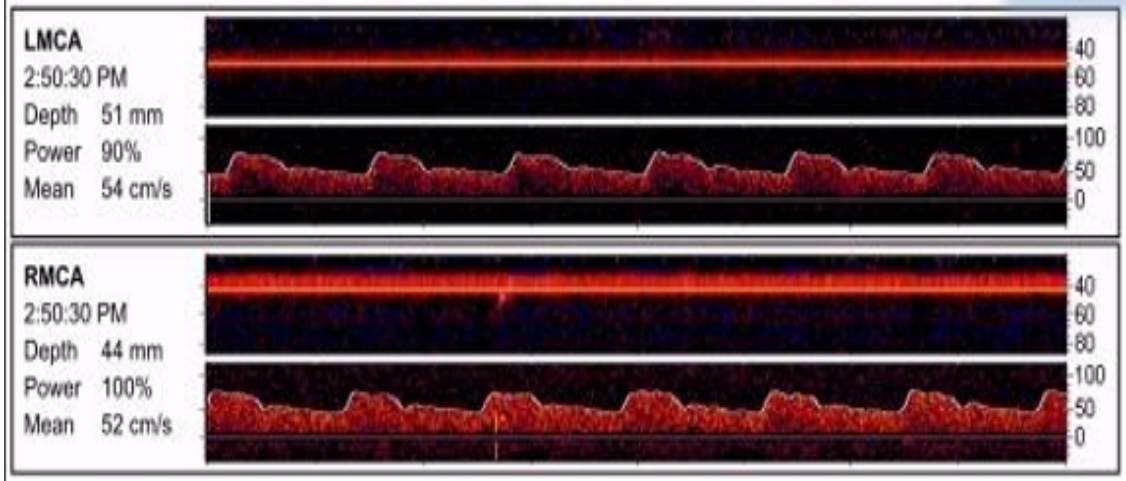
Patient Evaluation

✓ Transesophageal Echo Findings

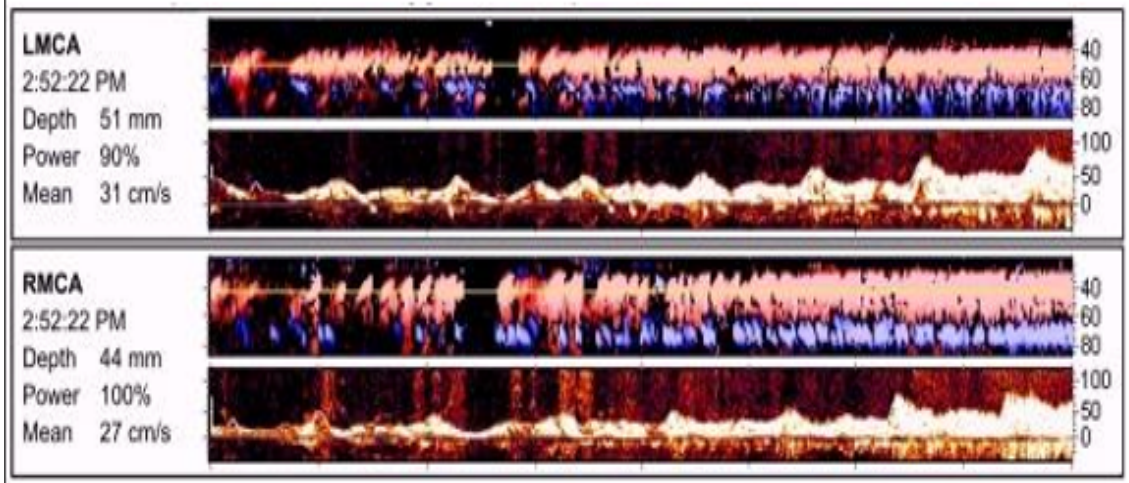


Transcranial Doppler

Rest



With valsalva and contrast



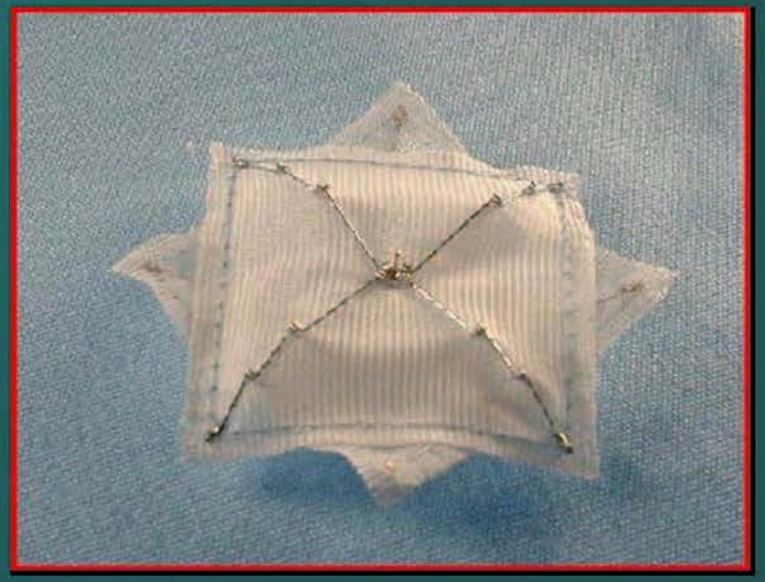
- Noninvasive alternative to TEE for detection of right-to-left shunt.
- Sensitivity 97%
- Specificity 93%
- Post-test probability of 93% to 94% when testing positive
- Post-test probability of 4% when testing negative

M. Khalid Mojadidi . J Am Coll Cardiol Img 2014;7:236–

Transcatheter Closure of PFO

Double Occluder Devices with HDE Approval in US

Amplatzer



NMT Medical

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

Jeffrey L. Saver, M.D., John D. Carroll, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

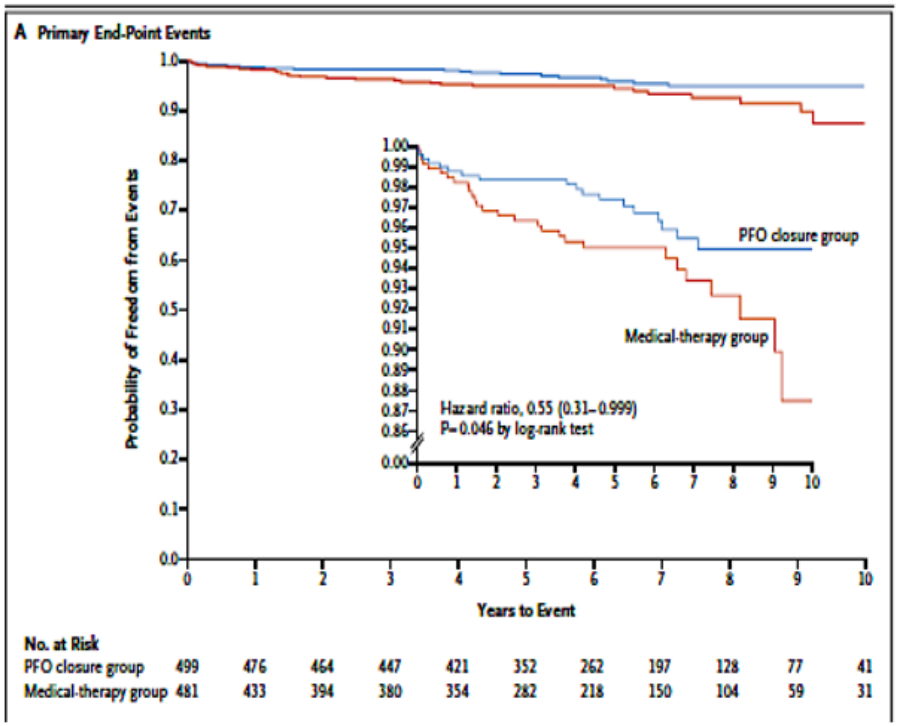
ABSTRACT

BACKGROUND

Whether closure of a patent foramen ovale reduces the risk of recurrence of ischemic stroke in patients who have had a cryptogenic ischemic stroke is unknown.

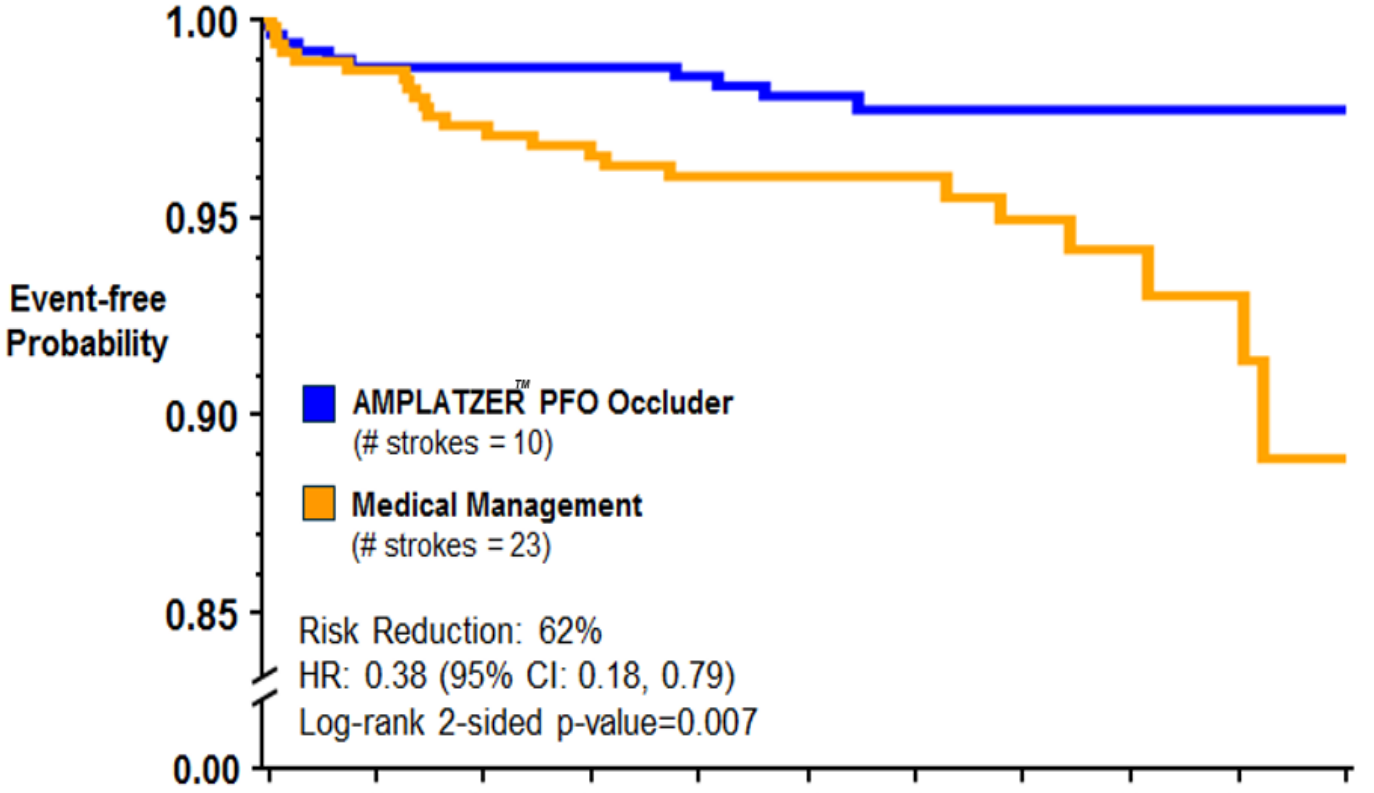
METHODS

In a multicenter, randomized, open-label trial, with blinded adjudication of endpoint events, we randomly assigned patients 18 to 60 years of age who had a patent foramen ovale (PFO) and had had a cryptogenic ischemic stroke to undergo closure of the PFO (PFO closure group) or to receive medical therapy alone (aspirin, warfarin, clopidogrel, or aspirin combined with extended-release dipyridamole; medical-therapy group). The primary efficacy end point was a composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization. The results of the analysis of the primary outcome from the original trial period have been reported previously; the current analysis of data from the extended follow-up period was considered to be exploratory.



N Engl J Med 2017;377:1022-32.

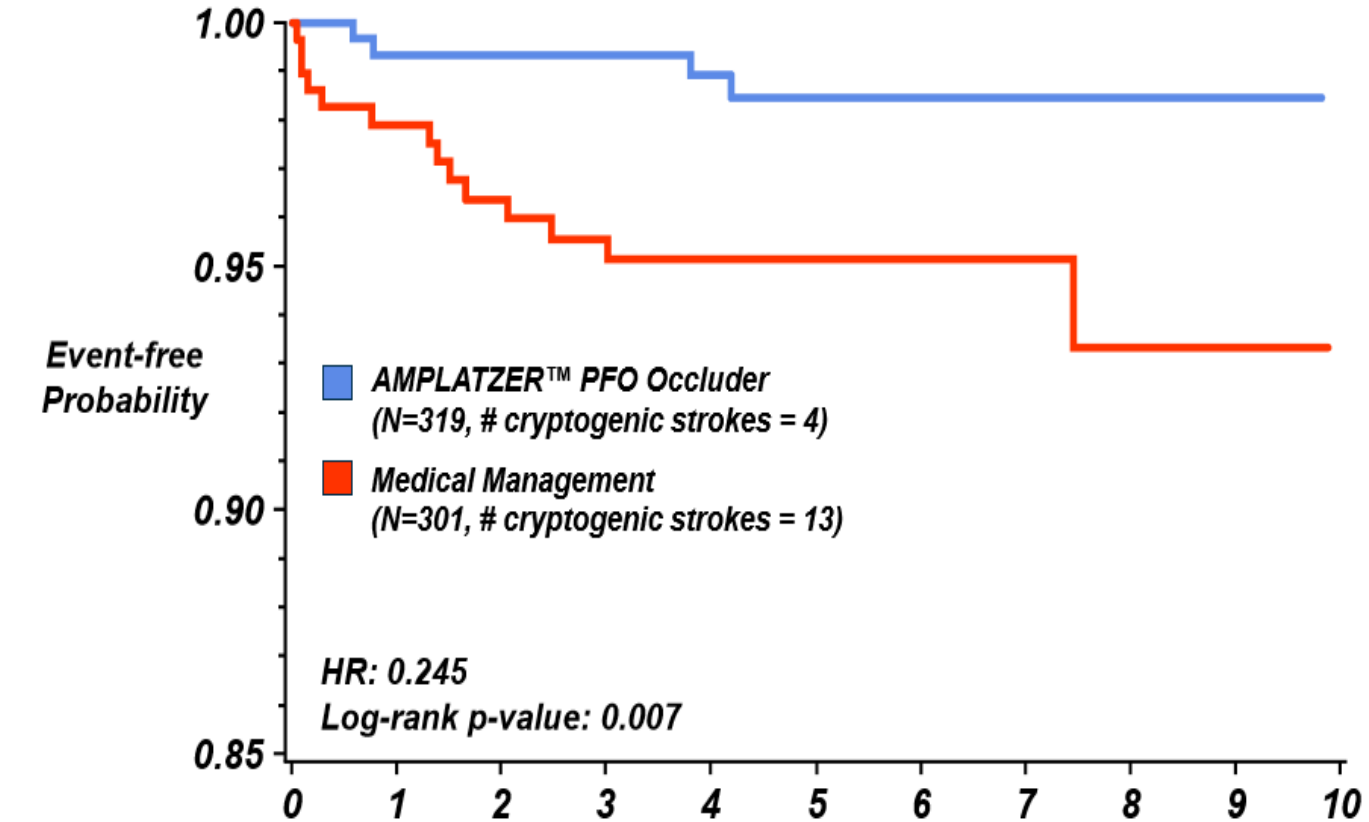
Freedom from Recurrent Ischemic Stroke of Unknown Mechanism (Intention to Treat)



# at Risk (KM Estimates)										
AMPLATZER	499 (0%)	476 (1.2%)	464 (1.2%)	447 (1.2%)	421 (1.5%)	352 (2.0%)	262 (2.3%)	197 (2.3%)	128 (2.3%)	77 (2.3%)	41 (2.3%)
MM	481 (0%)	433 (1.3%)	394 (2.7%)	380 (3.5%)	354 (4.0%)	282 (4.0%)	218 (4.0%)	150 (5.1%)	104 (5.8%)	59 (7.0%)	31 (11.1%)

Substantial Shunt or ASA Subgroup

75% Relative Risk Reduction in Recurrent Cryptogenic Stroke in ITT Population



# at Risk (KM Estimates)						
AMPLATZER	319 (0%)	299 (0.6%)	229 (1.0%)	134 (1.5%)	52 (1.5%)	11 (1.5%)
MM	301 (0%)	243 (3.6%)	186 (4.8%)	105 (4.8%)	45 (6.6%)	7 (6.6%)

Summary

- In the RESPECT trial, PFO closure with the AMPLATZER™ PFO Occluder was more beneficial than medical management alone
- Collaboration between a cardiologist and neurologist is important for proper patient selection
- For patients with cryptogenic stroke and PFO, closure with the AMPLATZER™ PFO Occluder is an appropriate treatment option that reduces the risk of recurrent stroke

The REDUCE trial

Aim:

Establish superiority of PFO closure in conjunction with antiplatelet therapy over antiplatelet therapy alone in reducing the risk of recurrent clinical ischemic stroke or new brain infarct

Design

- Randomized, controlled, open-label trial
- 664 subjects randomized in a 2:1 ratio to:

  Closure: PFO closure plus antiplatelet therapy

  Medical therapy: antiplatelet therapy alone

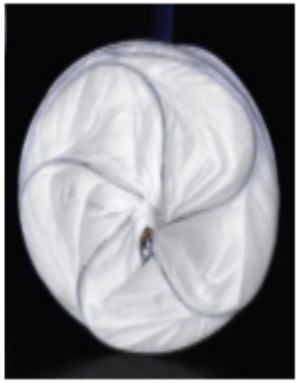
- 63 sites in 7 countries:

  Canada, Denmark, Finland, Norway, Sweden, UK, US

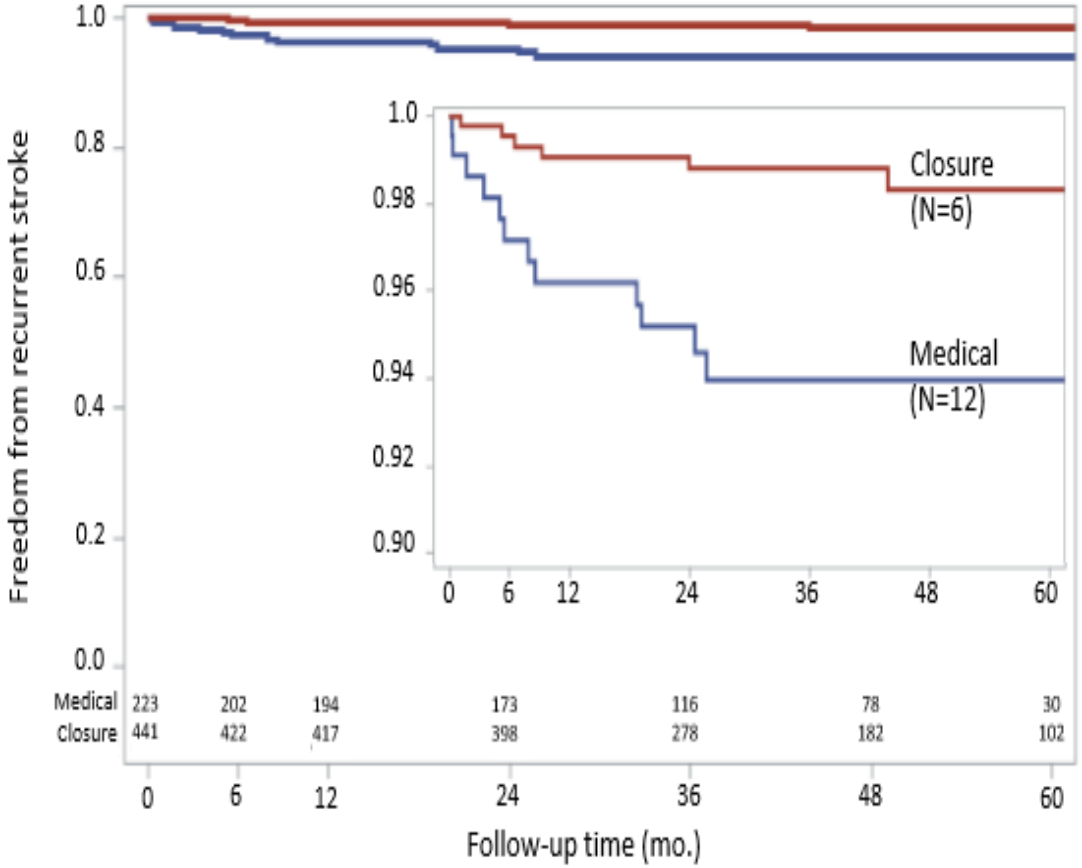
Gore Occluders

- GORE® HELEX® Septal Occluder (HELEX)
  - Used from 2008-2012, no longer available

- GORE® CARDIOFORM Septal Occluder (GSO)
  - Used from 2013-2015



Clinical stroke (ITT)



Annualized event rates

Closure: 0.39 per 100 person-years

Medical: 1.70 per 100 person-years

Hazard ratio, 0.23

95% CI, 0.09-0.62

Log-rank p=0.001

Adjusted for multiple testing

Conclusions

- In patients with cryptogenic stroke, PFO closure with the Gore Septal Occluders significantly reduced the risk of recurrent stroke (77%) and new brain infarct (49%) compared to antiplatelet therapy alone
- Most patients continued on aspirin (60%) or clopidogrel (30%)
- Approximately 8% of patients in both groups received anti-coagulation, but this did not affect trial outcome

2017 Canadian Stroke Best Practice Recommendations

Recurrent Stroke in Patients with PFO

Recommendations	LOE
Recent ischemic stroke or TIA attributed to a PFO should have an evaluation by clinicians with stroke and cardiovascular expertise	C
Recent ischemic stroke or TIA attributed to a PFO, closure device plus long-term antiplatelet therapy is recommended over long-term antithrombotic therapy alone provided all the following criteria are met: a. Age 18–60 years b. Diagnosis confirmed by imaging as a nonlacunar embolic ischemic stroke or a TIA c. Alternate stroke etiologies excluded by neurologist or clinician with stroke expertise	A
Patients requiring long-term anticoagulation, the decision regarding PFO closure remains unclear, and decisions should be based on individual patient characteristics and risk versus benefit profile	C
Recent ischemic stroke or TIA in pts who do no undergo PFO closure and are aged 60 years or younger, either antiplatelet or anticoagulant therapy is recommended for secondary stroke prevention	B

Wein T et al Int J Stroke 2017
https://doi.org/10.1177/1747493017743062

PRESERVE Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine

S.D. Weisbord, M. Gallagher, H. Jneid, S. Garcia, A. Cass, S.-S. Thwin, T.A. Conner, G.M. Chertow, D.L. Bhatt, K. Shunk, C.R. Parikh, E.O. McFalls, M. Brophy, R. Ferguson, H. Wu, M. Androsenko, J. Myles, J. Kaufman, and P.M. Palevsky, for the PRESERVE Trial Group*

PRESERVE Trial
n = 5177

Group		Primary Endpoint
Sodium Bicarb		4.4%
Sodium Chloride		4.7%
Acetylcysteine		4.6%
Placebo		4.5%

No Benefit Seen From Either Treatments

PRESERVE Trial

n = 5177

DISCUSSION

In this multinational, randomized, controlled trial in patients with chronic kidney disease who were undergoing angiography, we found no benefit of intravenous sodium bicarbonate over intravenous sodium chloride or of oral acetylcysteine over oral placebo for the prevention of death, need for dialysis, or persistent kidney impairment at 90 days or for the prevention of contrast-associated acute kidney injury or other secondary end points.

Efficacy and Safety of a Dual Ticagrelor plus Aspirin Antiplatelet Strategy after Coronary Artery Bypass Grafting: The DACAB Randomized Clinical Trial

Qiang Zhao[1] Yunpeng Zhu[1], Zhiyun Xu[2], Zhaoyun Cheng[3], Ju Mei[4], Xin Chen[5], Xiaowei Wang[6]

[1]**Ruijin Hospital Shanghai Jiao Tong University School of Medicine, Shanghai, China;**
[2]Changhai Hospital of Shanghai, Shanghai, China;
[3]Henan Provincial People's Hospital, Zhengzhou, China;
[4]Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China;
[5]Nanjing First Hospital, Nanjing, China;
[6]Jiangsu Province Hospital, Nanjing, China

Background

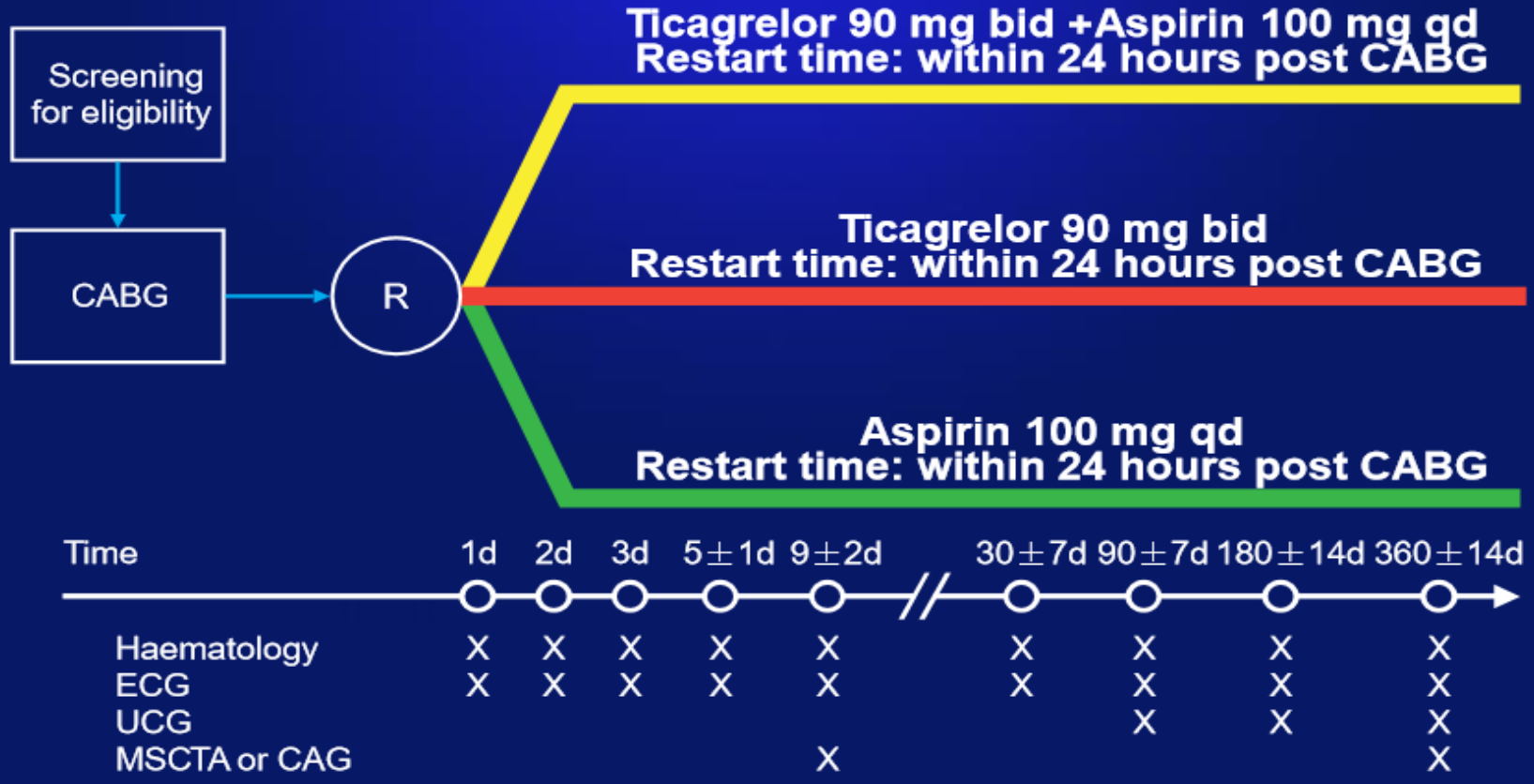
- Currently the saphenous vein graft (SVG) is sill the most commonly used in CABG
- However, the SVG failure rate is 10–25% at 1 year and 50% at 10 years post-CABG
- Dual antiplatelet therapy (DAPT) reduces MACE in patients with ACS who undergo CABG, but data regarding SVG patency is limited
- Effects of dual ticagrelor plus aspirin therapy on graft patency has been evaluated in a small pilot study that was terminated early because of low recruitment

Objective

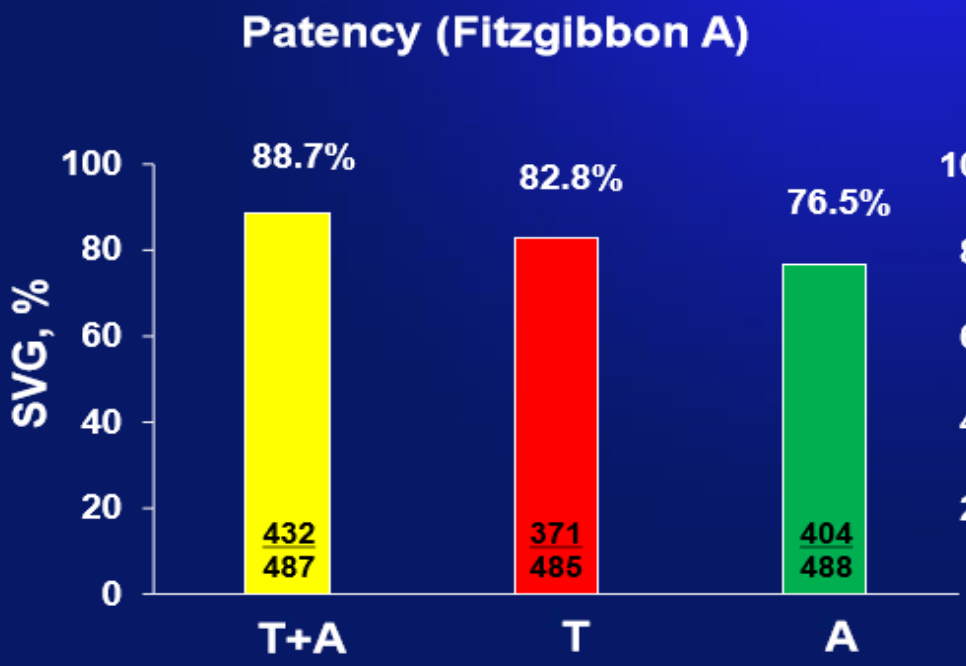
- Compare the efficacy and safety of combination ticagrelor plus aspirin therapy (T+A) or ticagrelor monotherapy (T) with aspirin monotherapy (A) on SVG patency 1 year after elective CABG

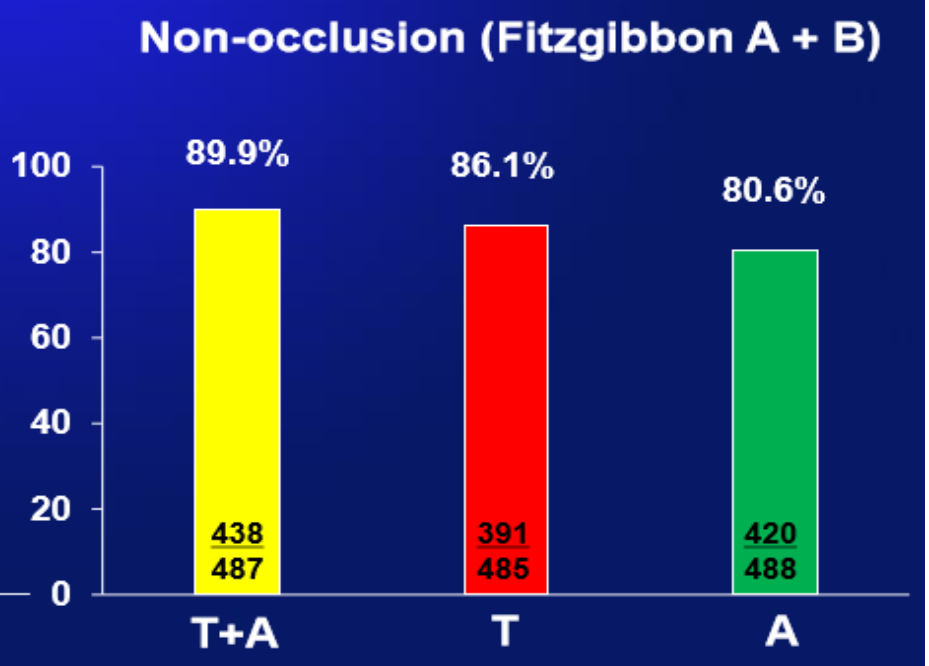
Study Design

- Randomized (1:1:1), multicentre, open-label



SVG Outcomes at 1 year (ITT)





T+A vs A: Δ = 12.2% (5.2, 19.2) *P* = .0006

T vs A: Δ = 6.3% (–1.1, 13.7) *P* = .0962

T+A vs A: Δ = 9.3% (2.7, 16.0) *P* = .0060

T vs A: Δ = 5.4% (–1.5, 12.4) *P* = .1264

Conclusions

- Ticagrelor plus aspirin combination therapy significantly improves SVG patency 1-year after CABG when compared with aspirin monotherapy without excess risk of major bleeding

Culprit vs Multivessel PCI

Culprit Vessel Versus Multivessel Versus In-Hospital Staged Intervention for Patients With ST-Segment Elevation Myocardial Infarction and Multivessel Disease

Stratified Analyses in High-Risk Patient Groups and Anatomic Subsets of Nonculprit Disease

M. Bilal Iqbal, MD, PHD,[a,b] Imad J. Nadra, MD, PHD,[a,b] Lillian Ding, MSc,[c] Anthony Fung, MD,[d] Eve Aymong, MD,[e] Albert W. Chan, MD,[f] Steven Hodge, MD,[g] Anthony Della Siega, MD,[a,b] Simon D. Robinson, MD,[a,b] on behalf of the British Columbia Cardiac Registry Investigators

Iqbal MB et al. J Am Coll Cardiol Intv 2017;10:11-23

Culprit vs Multivessel PCI

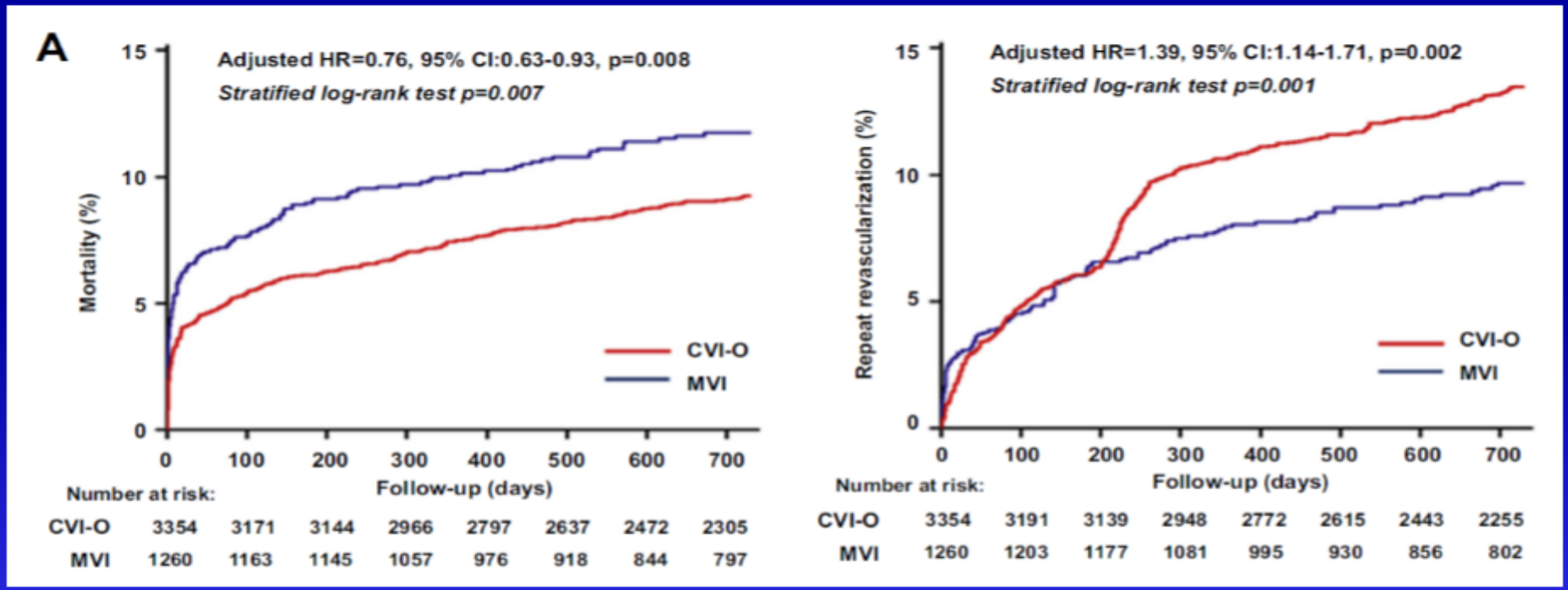
British Columbia Cardiac Registry (2008-2014)

- N = 12,105; then excluded SVD, shock, LMCAD
- 6,503 STEMI + MVD
- Revascularization Strategies
  - Multivessel PCI (all vessels treated during PPCI)
  - Culprit-only PCI (culprit only treated throughout)
  - Culprit-staged PCI (culprit during PPCI + other PCI later)
- 2-Year Outcome
  - All-cause mortality
  - Repeat revascularization

Iqbal MB et al. J Am Coll Cardiol Intv 2017;10:11-23

Culprit vs Multivessel PCI

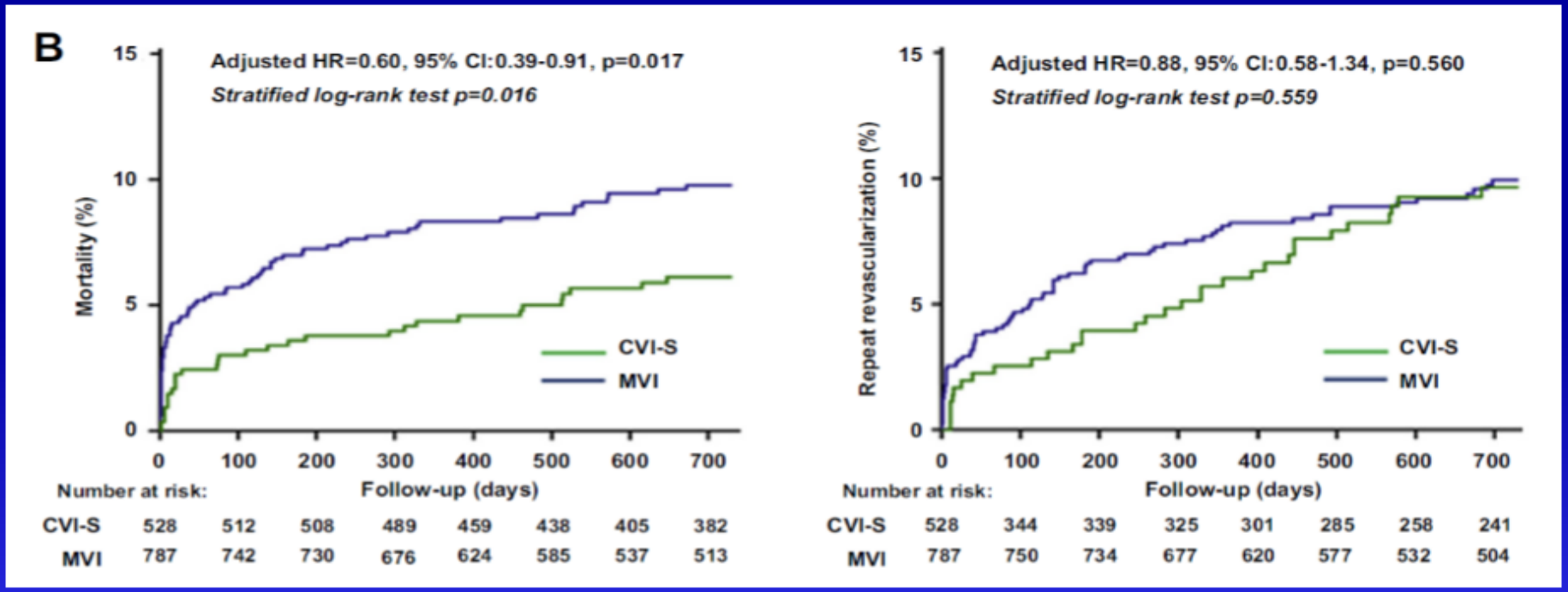
MVI vs CVI-O (propensity matched)



Iqbal MB et al. J Am Coll Cardiol Intv 2017;10:11-23

Culprit vs Multivessel PCI

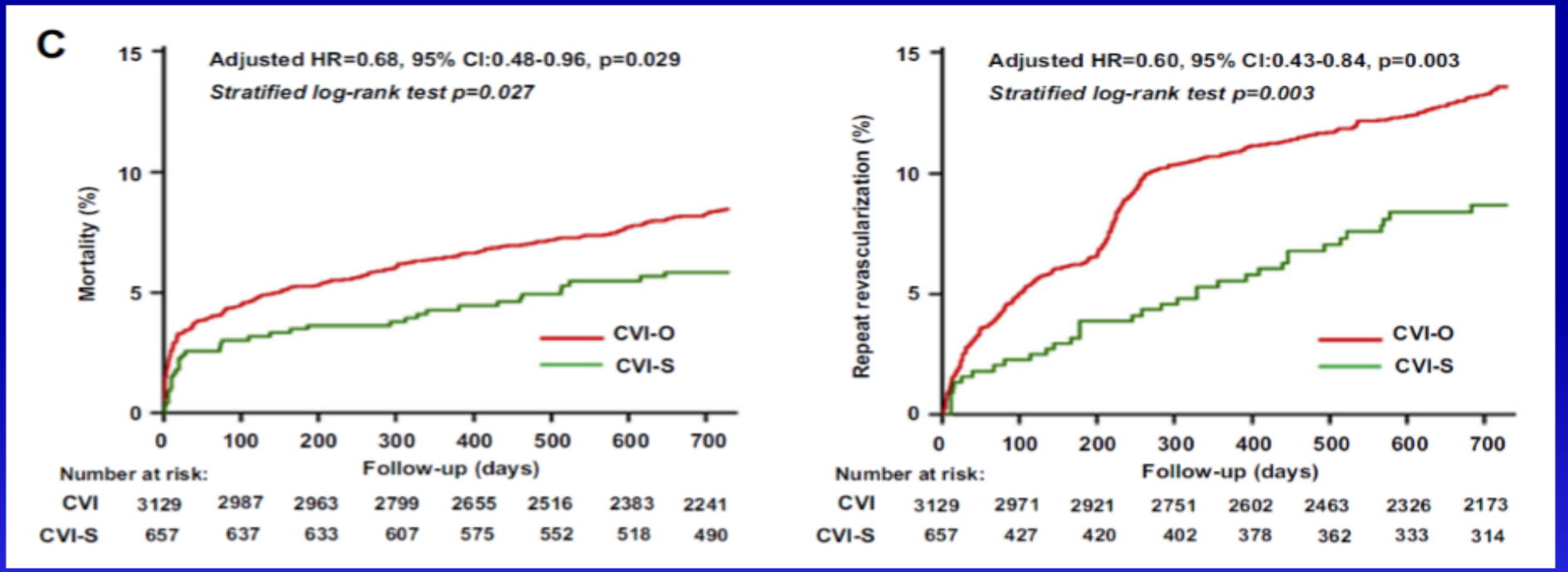
MVI vs CVI-S (propensity matched)



Iqbal MB et al. J Am Coll Cardiol Intv 2017;10:11-23

Culprit vs Multivessel PCI

CVI-O vs CVI-S (propensity matched)



Iqbal MB et al. J Am Coll Cardiol Intv 2017;10:11-23

Culprit Vs Multivessel Stenting For Acute MI

- **Culprit Lesion Stenting With;**

  Staged PCI Of Other Significant Stenoses Was Superior Option.

Igbal MB et al; JACC Int 2017

POISE

1-Year outcomes of perioperative beta-blockade in patients undergoing noncardiac surgery

Dr. PJ Devereaux on behalf of POISE Investigators
Population Health Research Institute, Hamilton, Canada

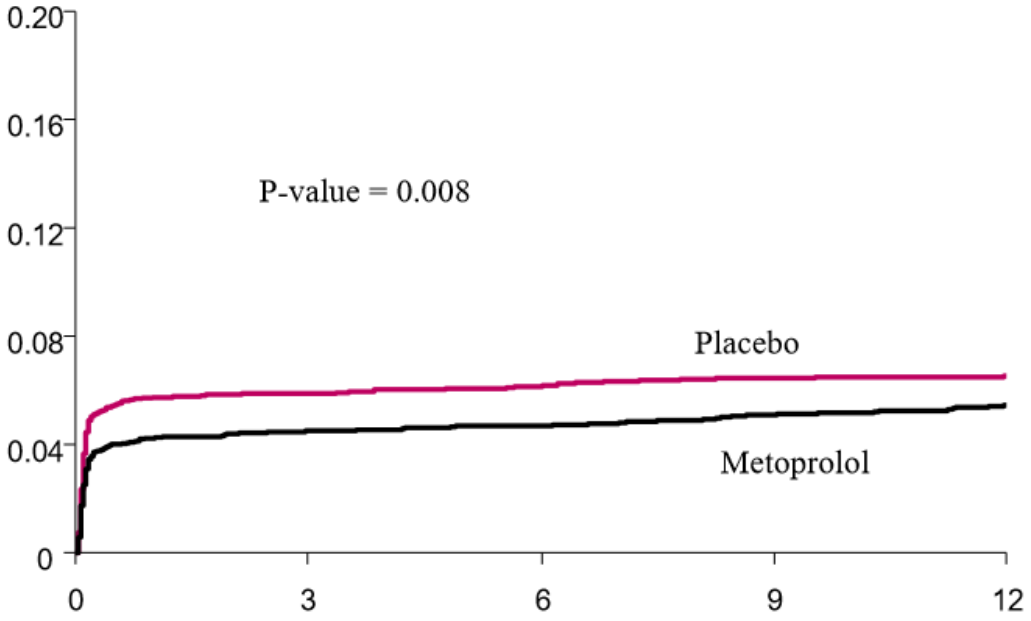
Main funding: Canadian Institutes of Health Research

Background

- 200 million adults globally undergo major noncardiac surgery annually
  - >3 million have periop MI
- We undertook POISE Trial, because beta-blockers attenuate effects of increased periop catecholamines
  - we hypothesized that perioperative beta-blockade would decrease risk of perioperative MI and its sequela

POISE Trial

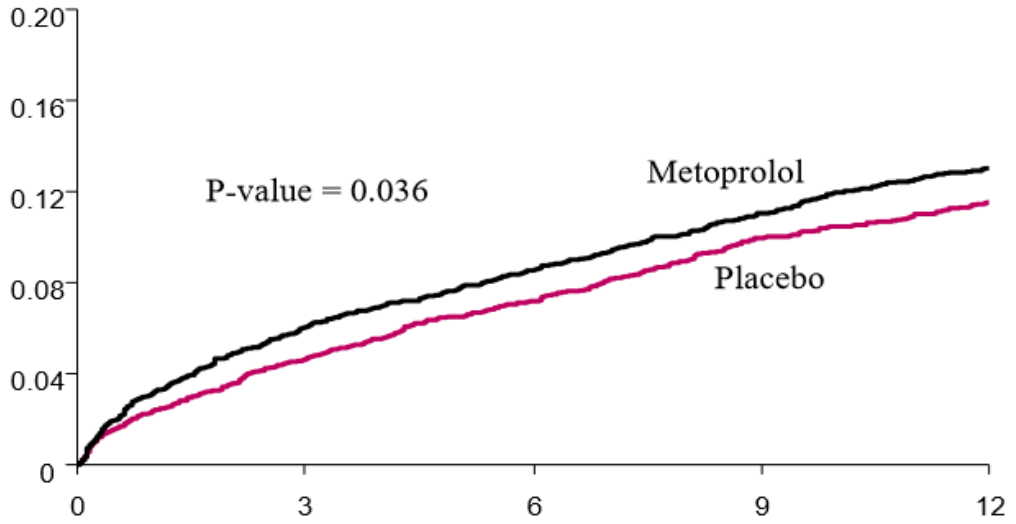
1-year myocardial infarction



No. at Risk					
Placebo	4177	2548	2450	2370	2308
Metoprolol	4174	2542	2445	2357	2264

POISE Trial

1-year all-cause mortality



No. at Risk					
Placebo	4177	2668	2559	2473	2408
Metoprolol	4174	2626	2522	2439	2347

POISE Trial

Conclusions

- Perioperative beta-blocker effects that occurred within 30-days persisted to 1-year after surgery
- Perioperative metoprolol CR at 1 year follow-up
  - decreased risk of MI and cardiac revasc but
  - increased risk of mortality and stroke

COMPASS

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

August 27, 2017

Rivaroxaban with or without aspirin in stable cardiovascular disease

John Eikelboom, on behalf of the
COMPASS Steering Committee and Investigators
Independently conducted by PHRI, Sponsored by Bayer AG

COMPASS Trial

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Background

- CV disease affects 4% of world population (300 million persons)
- Aspirin is the single most widely used preventive treatment but produces only a 19% RRR during the long term
- Warfarin with or without aspirin is more effective than aspirin but increases bleeding, including intracranial hemorrhage
- Rivaroxaban is safer than warfarin and reduces mortality in patients with recent acute coronary syndrome

COMPASS Trial

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Objectives

To determine in stable CV disease, whether:

- Rivaroxaban 2.5 mg bid + aspirin 100 mg od, or
- Rivaroxaban 5 mg bid

reduces CV death, stroke or myocardial infarction compared with aspirin 100 mg od

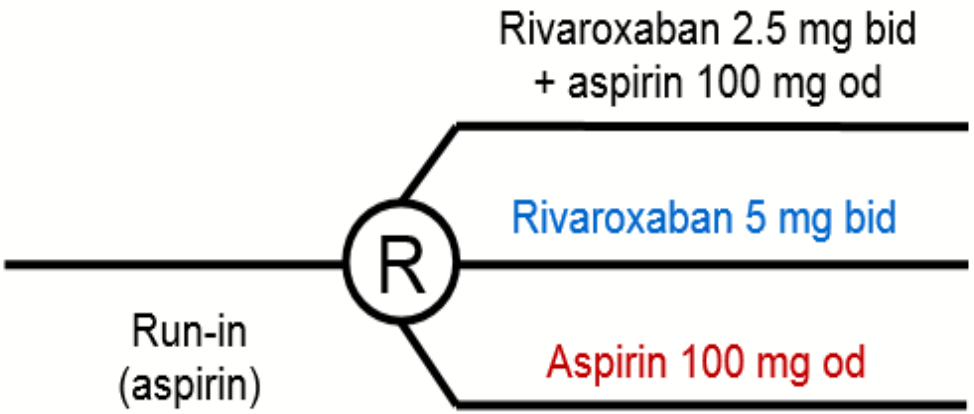
And whether:

- Pantoprazole compared with placebo reduces upper GI events (ongoing)

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

COMPASS design

Stable CAD or PAD
2,200 with a primary outcome event



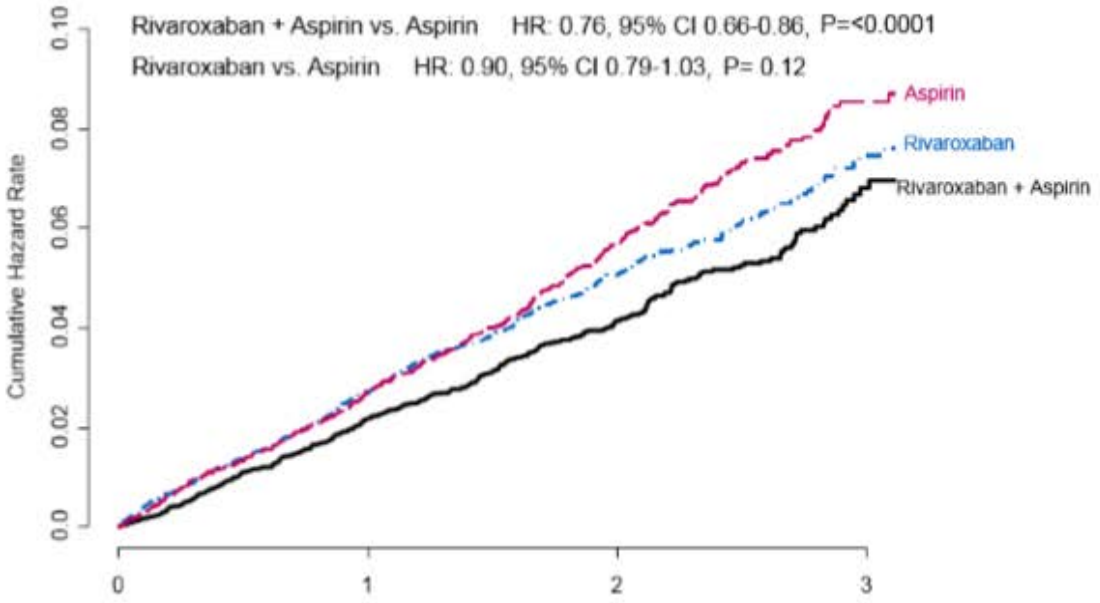
Expected follow up
3-4 years

Oklahoma Heart Institute

COMPASS Trial

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Primary: CV death, stroke, MI



Oklahoma Heart Institute

COMPASS Trial

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Conclusion

Rivaroxaban 2.5 mg bid plus aspirin 100 mg od:

- Reduces CV death, stroke, MI
- Increases major bleeding without a significant increase in fatal, intracranial or critical organ bleeding
- Provides a net clinical benefit

No significant benefit of rivaroxaban alone

COMPASS Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

J.W. Eikelboom, S.J. Connolly, J. Bosch, G.R. Dagenais, R.G. Hart, O. Shestakovska, R. Diaz, M. Alings, E.M. Lonn, S. Anand, P. Widimsky, M. Hori, A. Avezum, L.S. Piegas, K.R.H. Branch, J. Probstfield, D.L. Bhatt, J. Zhu, Y. Liang, A.P. Maggioni, P. Lopez-Jaramillo, M. O'Donnell, A. Kakkar, K.A.A. Fox, A.N. Parkhomenko, G. Ertl, S. Störk, M. Keltai, L. Ryden, N. Pogosova, A.L. Dans, F. Lanas, P.J. Commerford, C. Torp-Pedersen, T.J. Guzik, P.B. Verhamme, D. Vinereanu, J.-H. Kim, A.M. Tonkin, B.S. Lewis, C. Felix, K. Yusoff, P.G. Steg, K.P. Metsarinne, N. Cook Bruns, F. Misselwitz, E. Chen, D. Leong, and S. Yusuf

Diabetes Treatment

- SGLT-2 Inhibitors Associated with Lower Cardiovascular Events (All cause mortality and heart failure hospitalization, MI, Stroke).

Empagliflozin (Jardiance) & Canagliflozin (Ivokana)

(EMPA-REG Trial) **(CANVAS Trial)**

SGLT-2 Inhibitors For Diabetes Therapy

CVD Real 2 Study:

Medical Claims records and national registries from multiple countries.

235,064 SGLT-2 new users vs 235,064 new oGLD

Compared with the oGLD's, SGLT-2 inhibitors:

- **Reduced all cause death and HF Hospitalization by 40%**
- **Reduced all cause death by 49%**
- **Reduced HHF by 36%**
- **Reduced MI's by 19%**
- **Reduced stroke by 32%.**

Decreased Acute Kidney Injury With Impella In High Risk PCI

- 230 High Risk PCI patients
- 115 Unsupported matched controls
- Retrospective study

Decreased Acute Kidney Injury With Impella In High Risk PCI

5.2% AKI in Impella supported pts versus 27.8% AKI in unsupported pts.

Late Breaking Clinical Trials: 2018

Wayne N. Leimbach, Jr. MD, FACC,

Clinical Associate Professor of Medicine
University of Oklahoma College of Medicine - Tulsa

Director of the Cardiac Catheterization Laboratories
Oklahoma Heart Institute at Hillcrest Medical Center

Medical Director of Cardiology
Oklahoma Heart Institute