Late Breaking Clinical Trials: 2017

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From Gene Discovery to Clinical Trials

N ENGL JMED 366;12 NEJM.ORG MARCH 22, 2012

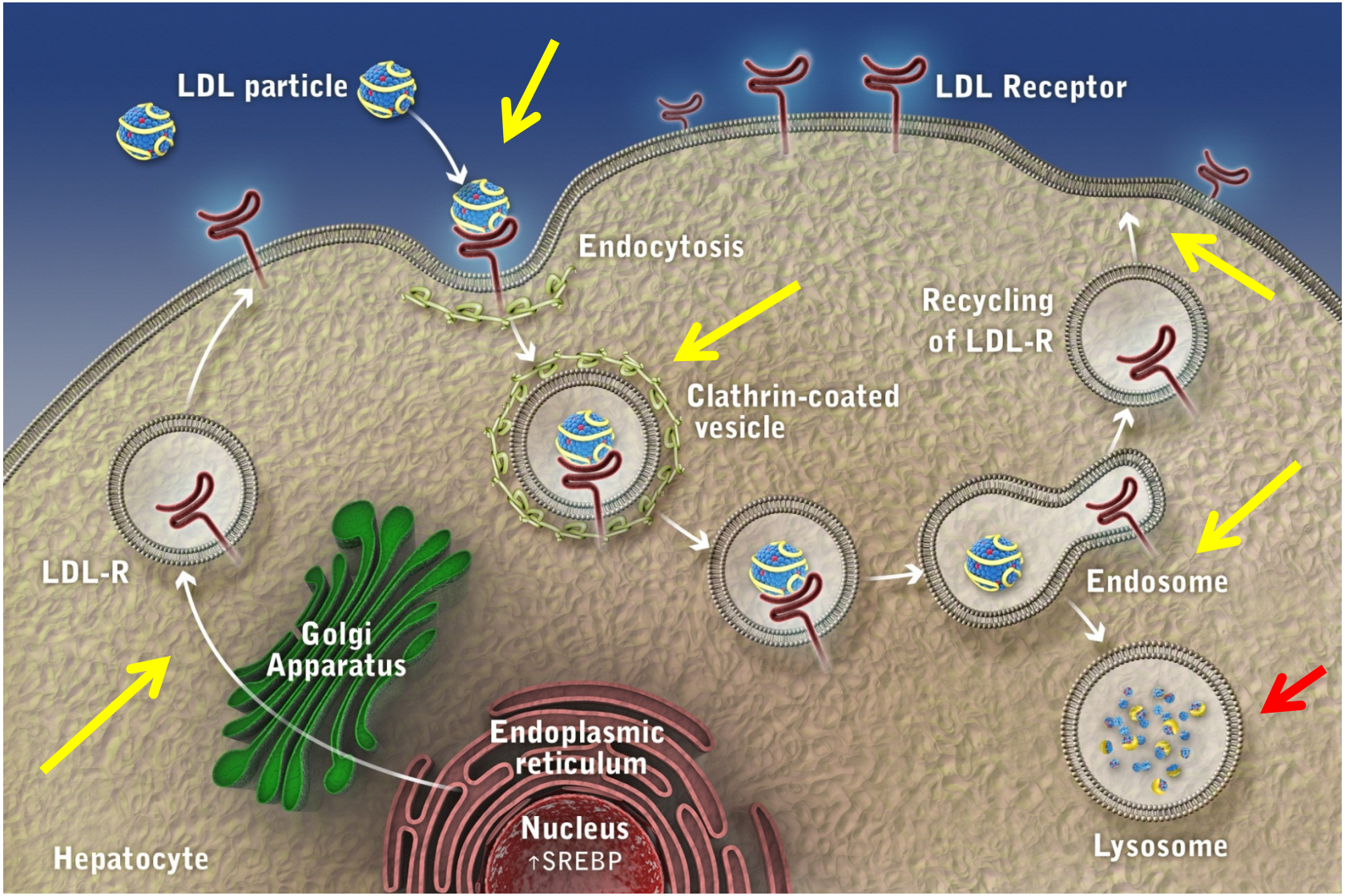
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

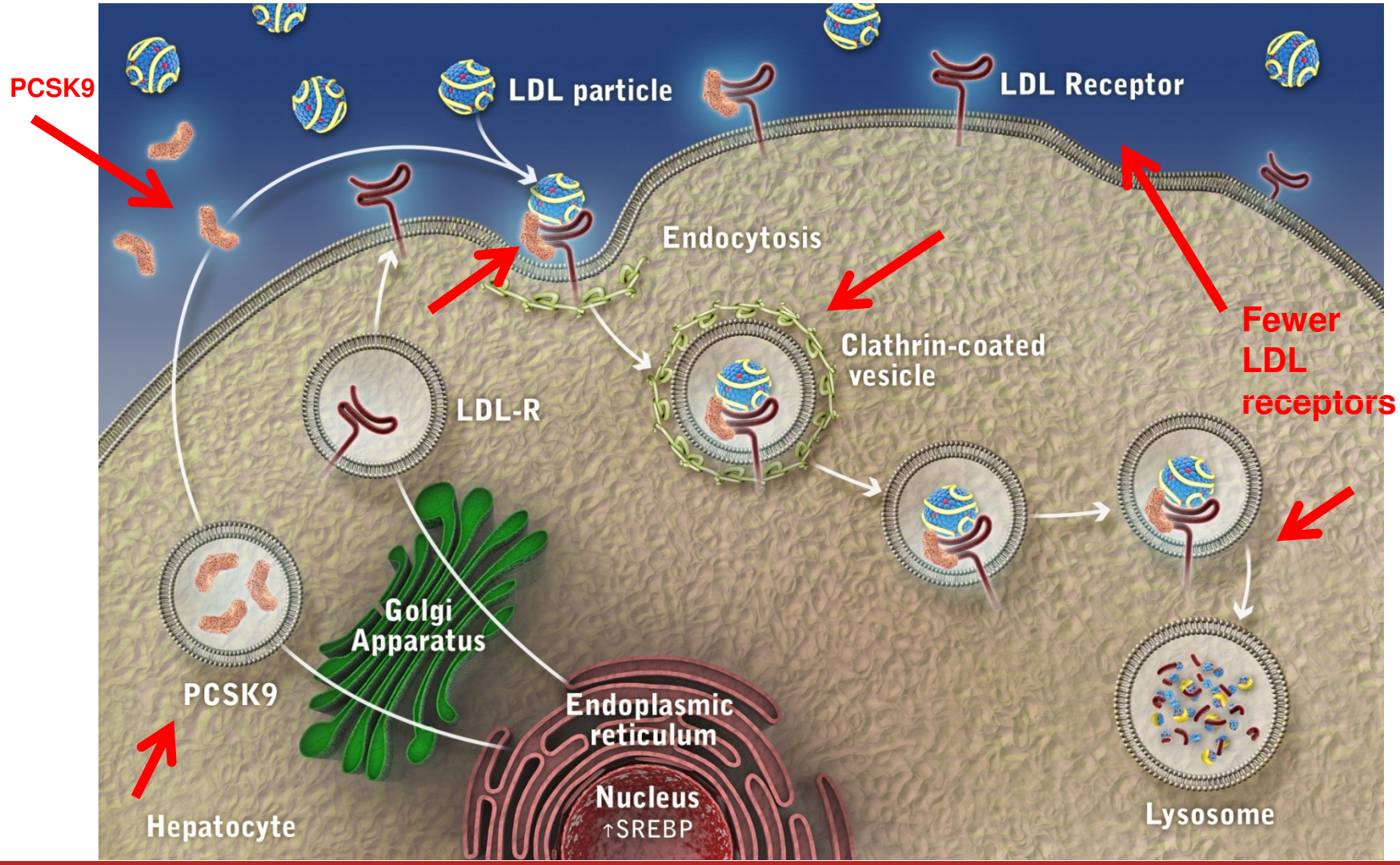
Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol

Evan A. Stein, M.D., Ph.D., Scott Mellis, M.D., Ph.D.,
George D. Yancopoulos, M.D., Ph.D., Neil Stahl, Ph.D., Douglas Logan, M.D.,
William B. Smith, M.D., Eleanor Lisbon, M.D., M.P.H., Maria Gutierrez, M.D.,
Cheryle Webb, M.D., Richard Wu, Ph.D., Yunling Du, Ph.D.,
Therese Kranz, R.N., M.B.A., Evelyn Gasparino, B.S.,
and Gary D. Swergold, M.D., Ph.D.

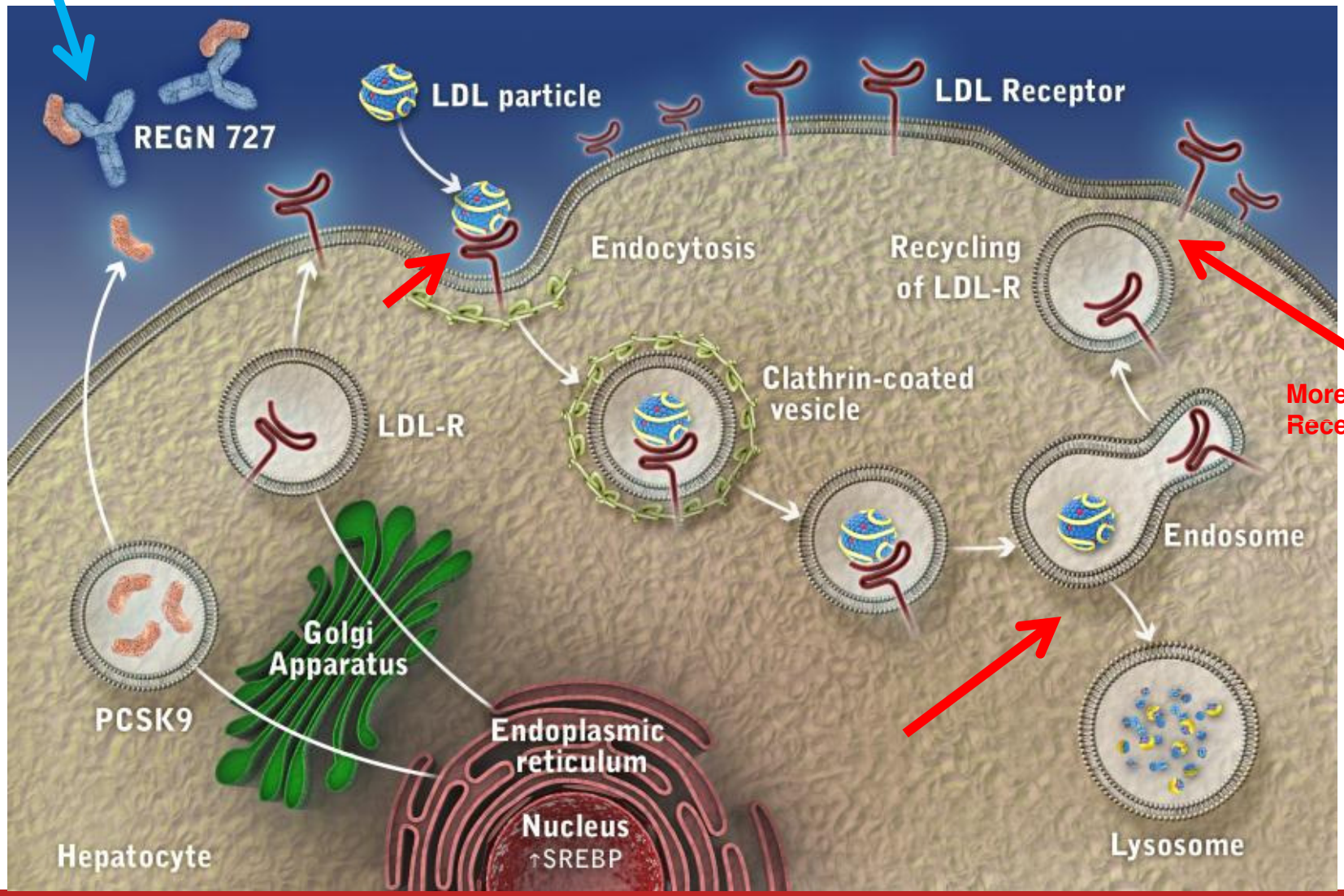
LDL Receptor Function and Life Cycle



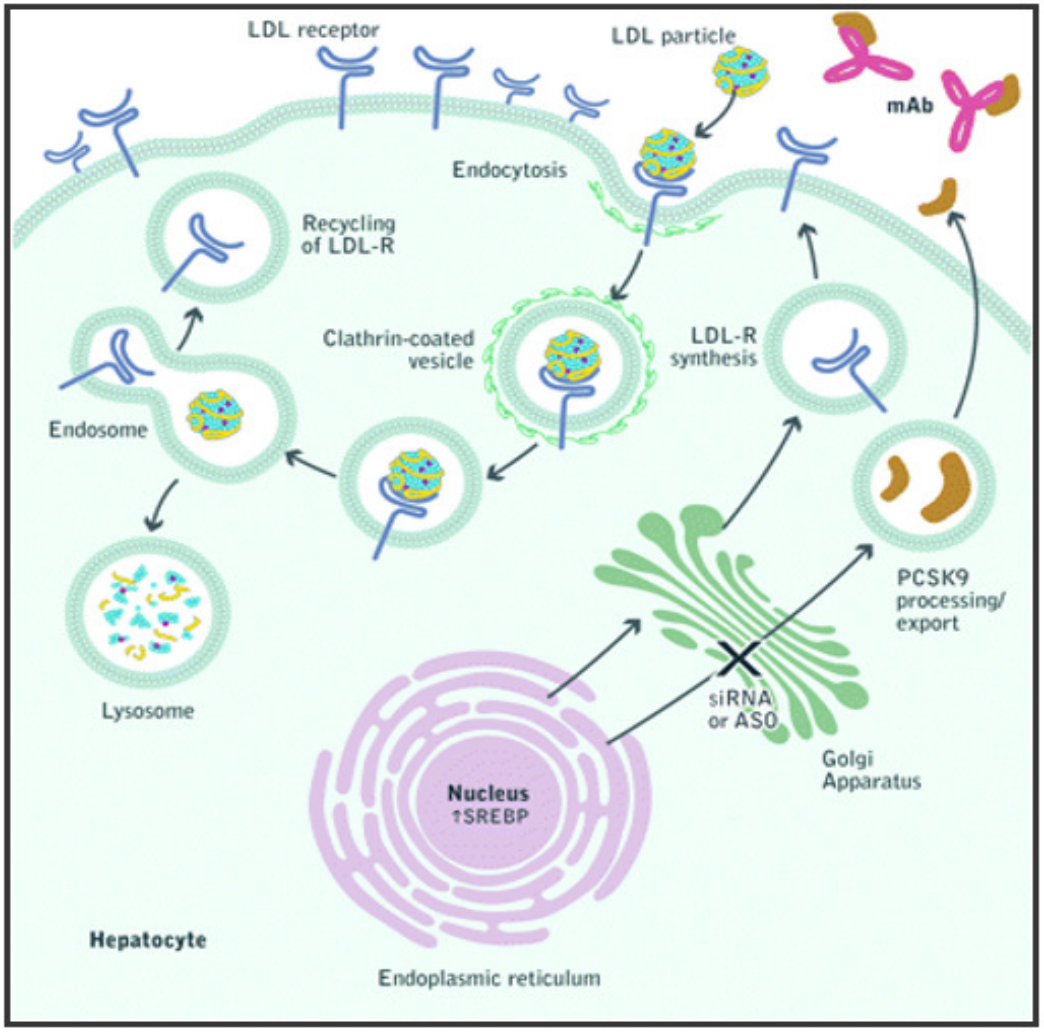
The Role of PCSK9 in the Regulation of LDL Receptor Expression



Impact of an PCSK9 mAb on LDL Receptor Expression



Monoclonal Antibodies to PCSK9 and Recycling of the LDL Receptor: Cardiovascular Outcomes Trials



Evolocumab (Amgen)
FOURIER
NCT 01764633

Alirocumab (Sanofi/Regeneron)
ODYSSEY
NCT 01663402

Bococizumab (Pfizer)
SPIRE-1, SPIRE-2
NCT 01975376
NCT 01975389

Ridker ACC 2017

FOURIER Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

ABSTRACT

BACKGROUND

Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9) and lowers low-density lipoprotein (LDL) cholesterol levels by approximately 60%. Whether it prevents cardiovascular events is uncertain.

From the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston (M.S.S., R.P.G., S.D.W.

FOURIER TRIAL

- Randomized trial of 27,564 patients with preexisting high risk cardiovascular disease.
- Double blind therapy with subcutaneous Evolocumab (Repatha) either 140 mg q 2 weeks or 420 mg q month versus placebo injections

FOURIER TRIAL

- Patients had baseline LDL-C levels of at least 70 mg/dl while on statin therapy which was continued throughout the study
- 69% on high – intensity statin therapy
- The rest were on moderate – intensity statin therapy.

FOURIER TRIAL

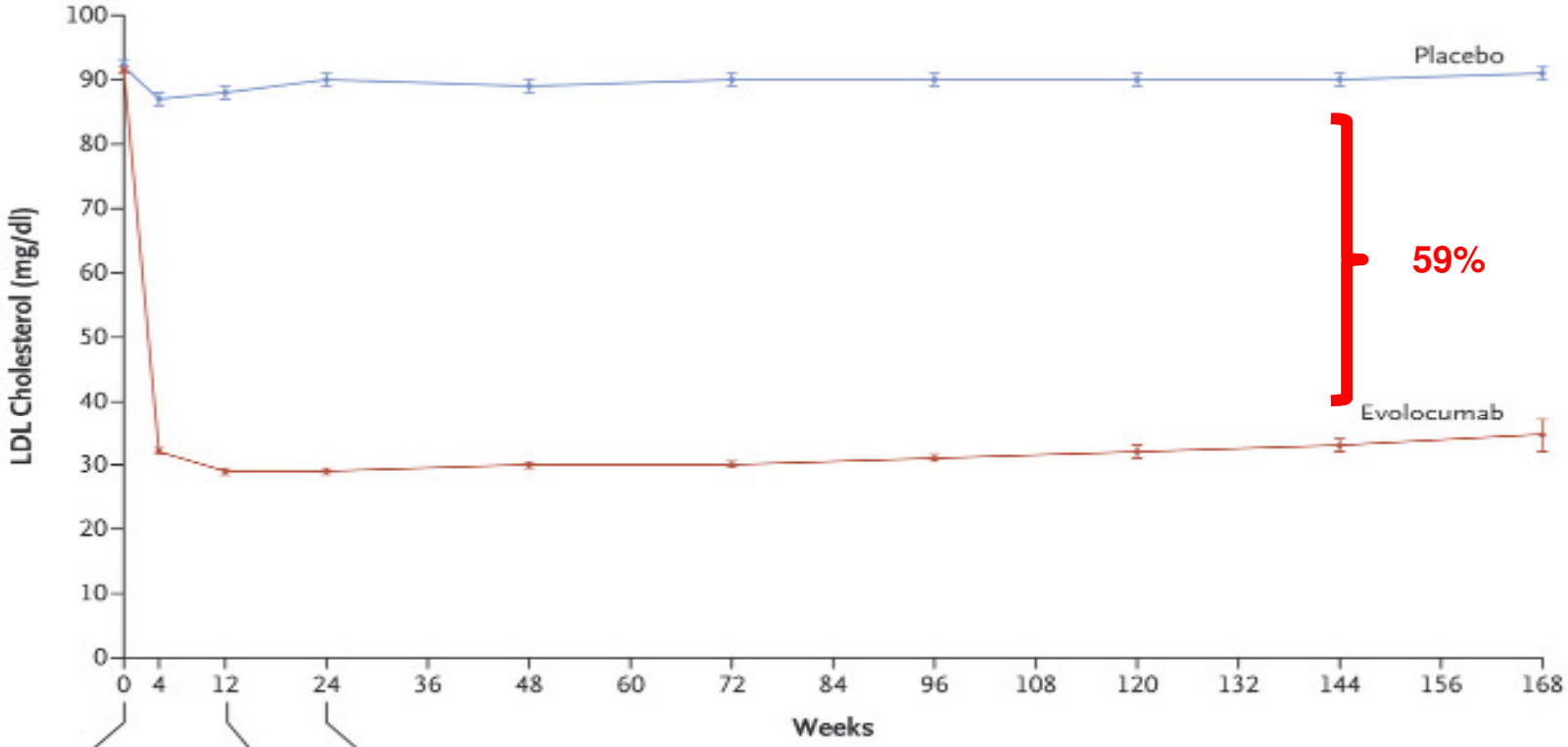
Median LDL-C level plunged from

92 mg/dl to 30 mg/dl in Evolocumab group **(59% reduction)**

One quarter of patients had LDL-C less than 20 mg/dl

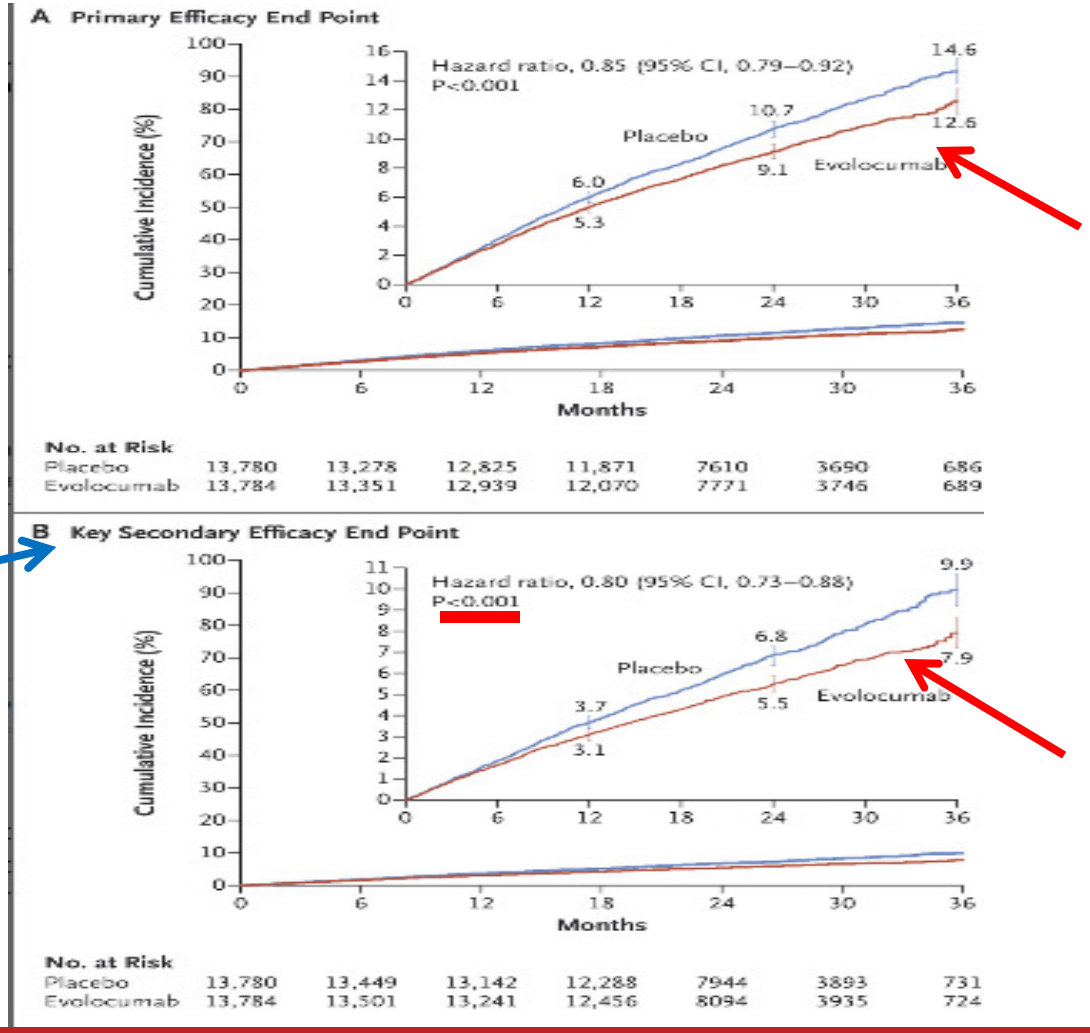
LDL-C reductions remained durable over median of 26 months follow-up

Reduction In LDL-C
Fourier Trial



No. at Risk										
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768
Absolute difference (mg/dl)		54	58	57	56	55	54	52	53	50
Percentage difference		57	61	61	59	58	57	55	56	54
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Reduction In Events With PCSK9 Inhibitor Fourier Trial



CV Death, MI, CVA

FOURIER TRIAL: Results

- **15%** relative risk reduction in primary endpoint of CV death, MI, CVA, Hosp for USA or coronary revascularization;

  (11.3% control vs 9.8% drug; p<0.001)

- **20%** relative risk reduction in secondary endpoint of CV death, MI, CVA;

  (p<0.001 for 7.4% control vs 5.9% drug)

FOURIER TRIAL: Results

- **19%** reduction of fatal and nonfatal MI or CVA in first 12 months
- **33%** reduction of fatal and nonfatal MI or CVA in the subsequent months of follow up

Table 3. Adverse Events and Laboratory Test Results.

Outcome	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Adverse events — no. of patients (%)		
Any	10,664 (77.4)	10,644 (77.4)
Serious	3410 (24.8)	3404 (24.7)
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)
Injection-site reaction*	296 (2.1)	219 (1.6)
Allergic reaction	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	228 (1.7)	242 (1.8)
Adjudicated case of new-onset diabetes†	677 (8.1)	644 (7.7)
Neurocognitive event	217 (1.6)	202 (1.5)
Laboratory results — no. of patients/total no. (%)		
Aminotransferase level >3 times the upper limit of the normal range	240/13,543 (1.8)	242/13,523 (1.8)
Creatine kinase level >5 times the upper limit of the normal range	95/13,543 (0.7)	99/13,523 (0.7)

* The between-group difference was nominally significant (P<0.001).
† The total numbers of patients were 8337 in the evolocumab group and 8339 in the placebo group, because patients with prevalent diabetes at the start of the trial were excluded.

FOURIER TRIAL

Conclusion

CONCLUSIONS

In our trial, inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events. These findings show that patients with atherosclerotic cardiovascular disease benefit from lowering of LDL cholesterol levels below current targets. (Funded by Amgen; FOURIER ClinicalTrials.gov number, NCT01764633.)

EBBINGHAUS:

- *A Cognitive Study of Patients Enrolled in the FOURIER Trial*

RP Giugliano, F Mach, K Zavitz, AC Keech, TR Pedersen,
MS Sabatine, P Sever, C Kurtz, N Honarpour, BR Ott,
on behalf of the EBBINGHAUS Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 18, 2017

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

Oklahoma Heart Institute

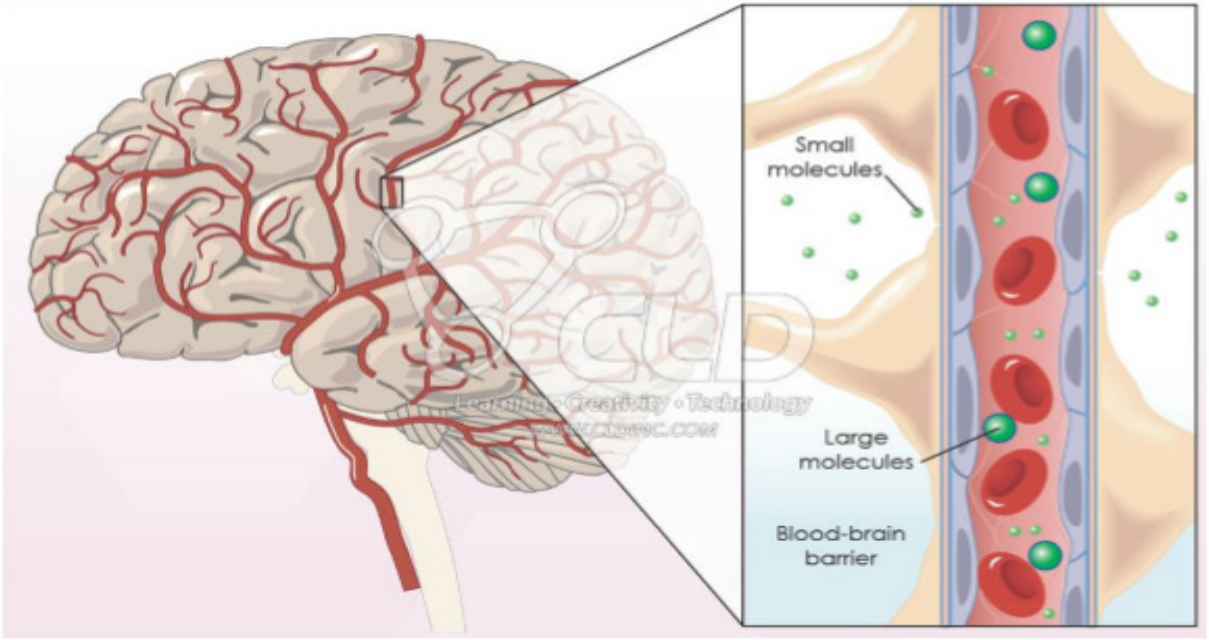
Cognition and Statins

- Case series and 2 small, 6-month RCTs with statins raised concern regarding cognitive deficits
- In 2012 FDA added risk of adverse cognitive effects to label of all statins
- However analyses from large scale RCTs do not support these findings and 2014 Statin Cognitive Safety Task Force* concluded that statins are not associated with cognitive side effects.

*The National Lipid Association
Rojas-Fernandez CH, et al. *J Clin.Lipidol.* 2014;8(3 Suppl):S5-16.

Cognition and PCSK9 Inhibitors

Brain synthesizes cholesterol locally

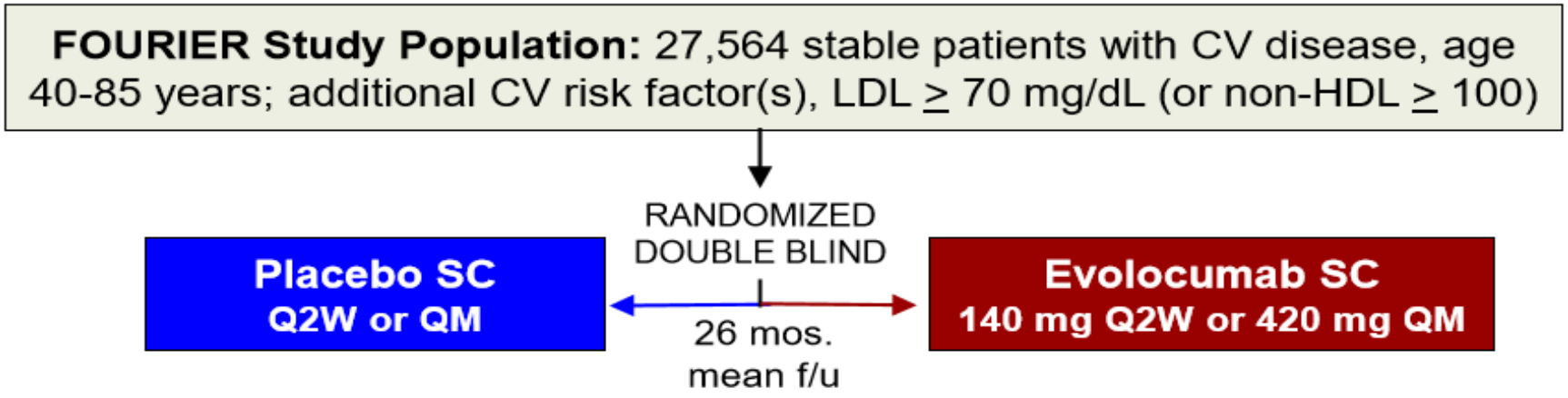


mAb (e.g., evolocumab) are too large to cross the intact blood-brain barrier

The question is whether significant lowering of the LDL-Cholesterol levels would affect Cholesterol levels in the brain and produce cognitive side effects.

*Lipinski MJ, et al. *Eur Heart J.* 2016;37(6):536-54

FOURIER: Summary Results

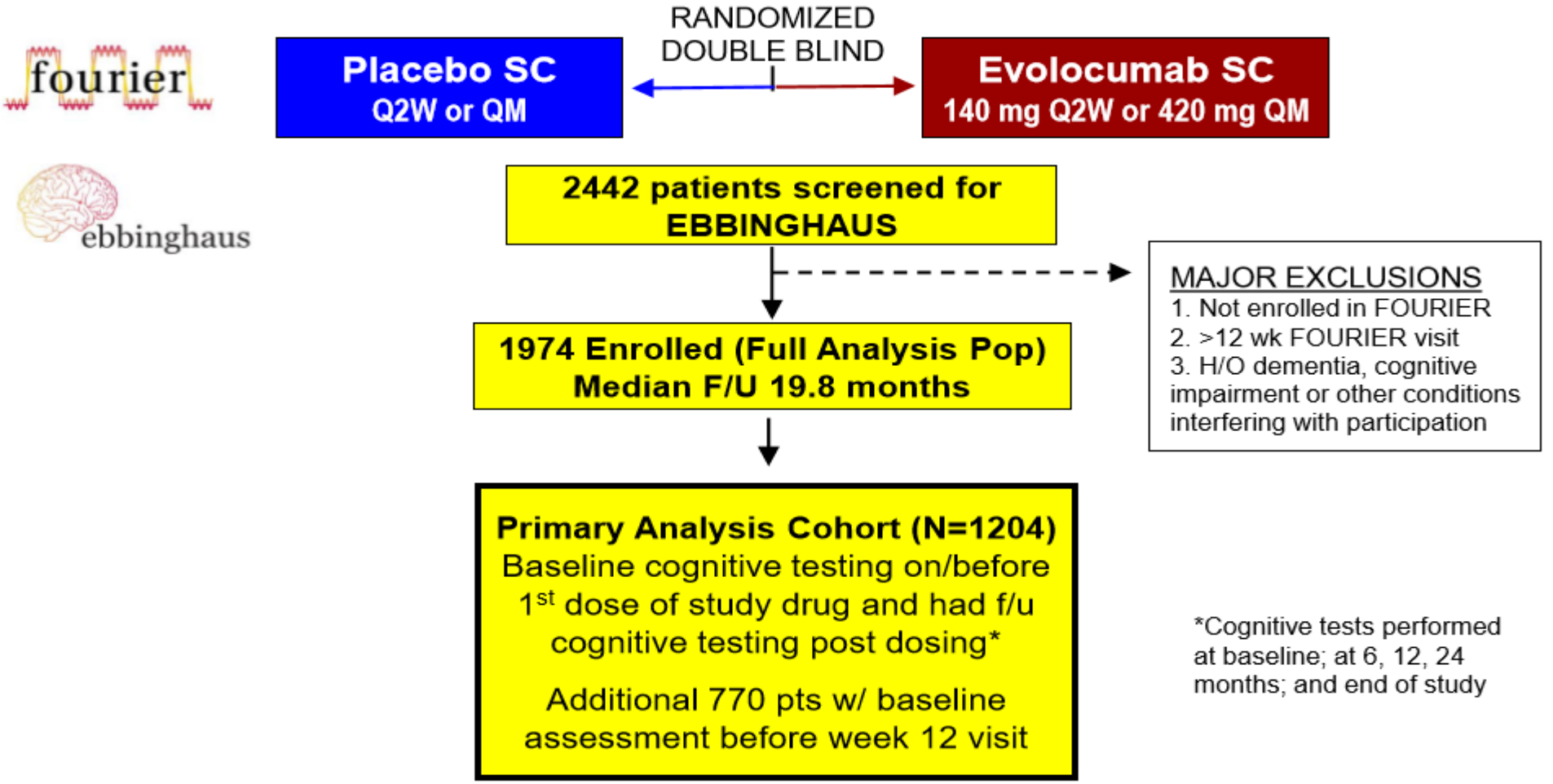


Evolocumab on background of statin c/w placebo:

- ↓ LDL-C by 59%
- ↓ CV outcomes on background of statin therapy
- Safe and well-tolerated

Sabatine, MS et al. *New Eng J Med*.2017.DOI: 10.1056/NEJMoa1615664 (on line March 17, 2017)

Trial Design



*Cognitive tests performed at baseline; at 6, 12, 24 months; and end of study

Giugliano RP et al. *Clin Card* 2017;40:59–65

Endpoints

1. **Cambridge Neuropsychological Test Automated Battery (CANTAB) Assessments, a standardized, well-validated computer tablet-based testing platform.**
   Assessed at baseline, 6, 12, 24, 48 mos and study end.
   - **Primary:** **Spatial working memory strategy index of executive function**
   - Secondary: Spatial working memory between errors
     Paired associates learning
     Reaction time
   - Exploratory: Global score (combines above 4 tests)
2. **Patient survey of everyday cognition* at study end**
3. **Investigator report of cognitive AEs**

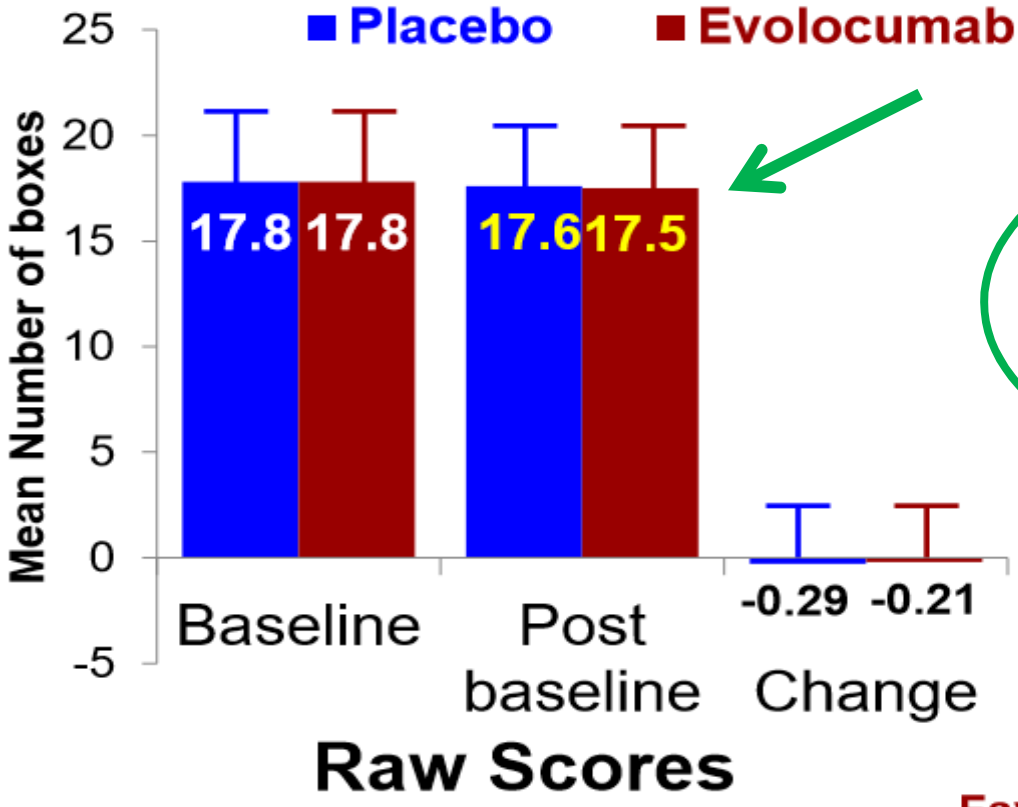
*Memory and executive function domains

Owen 1990 PMID: 2267054; Sahakian 1988, PMID: 3382917; Owen 1996 PMID: 8714706; Kollins PMID: 21476931

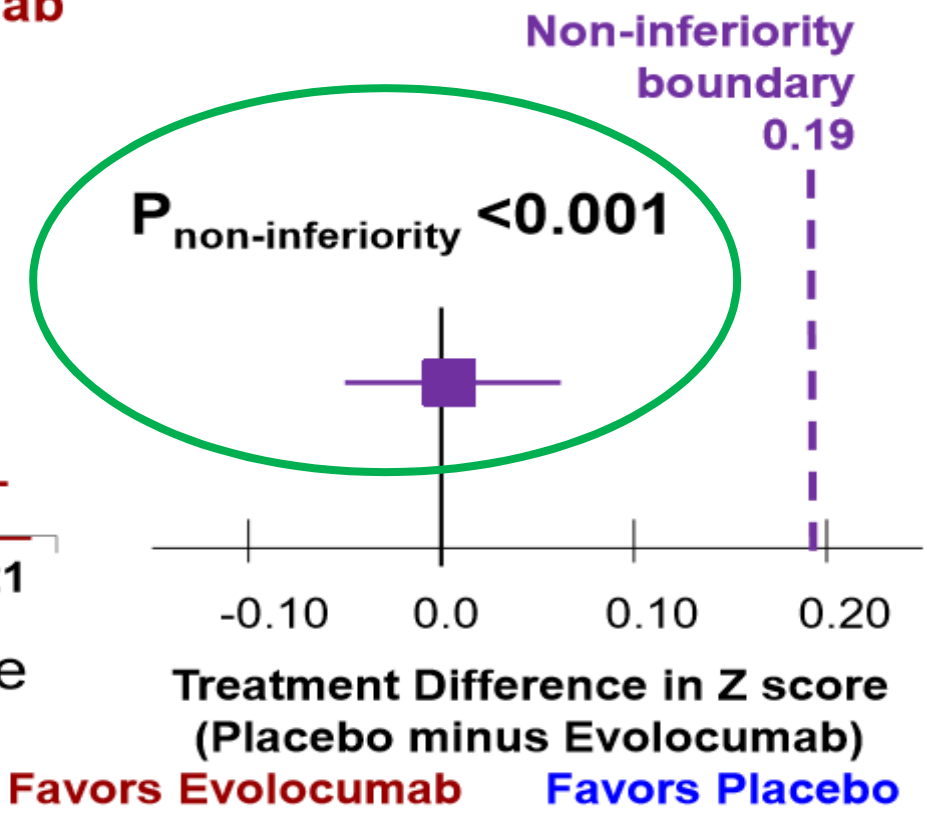
Giugliano RP et al. *Clin Card* 2017;40:59-65

Primary Endpoint

Spatial Working Memory Strategy Index



Raw Scores



Secondary Endpoints

Test Name	Task description	Scoring
Spatial Working Memory Between Errors Score	Find the hidden blue token	# times a box is re-visited in which a blue token had already been found
Paired Associates Learning	Memory matching game (Concentration)	# times errors made in finding a match
Reaction Time	Touch yellow dot quickly after it appears on screen	Time in milliseconds until dot touched

Lower scores (fewer errors, faster time) are better

Secondary Endpoint Results

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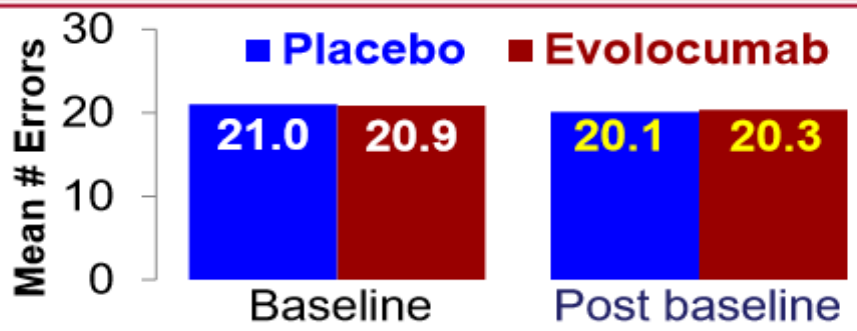
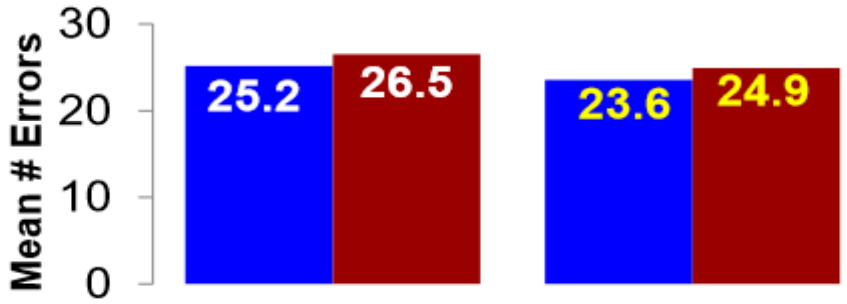
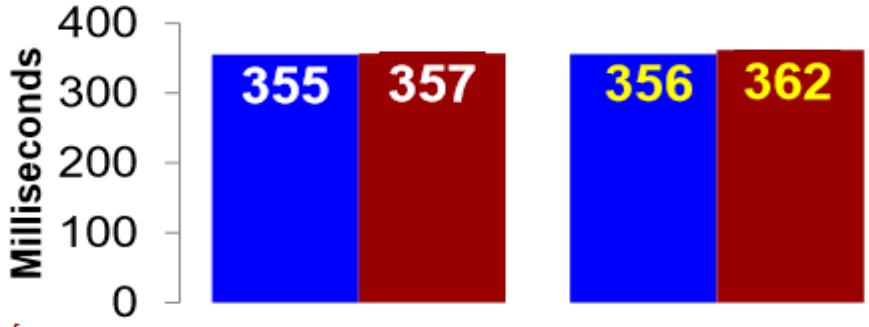
Spatial Working Memory Between Errors Score



Paired Associates Learning



Median 5-Choice Reaction Time



	Trt diff of Δ in Z-scores	$P_{superiority}$
Spatial Working Memory Between Errors Score	0.033	**0.36**
Paired Associates Learning	0.023	**0.49**
Median 5-Choice Reaction Time	0.073	**0.06**

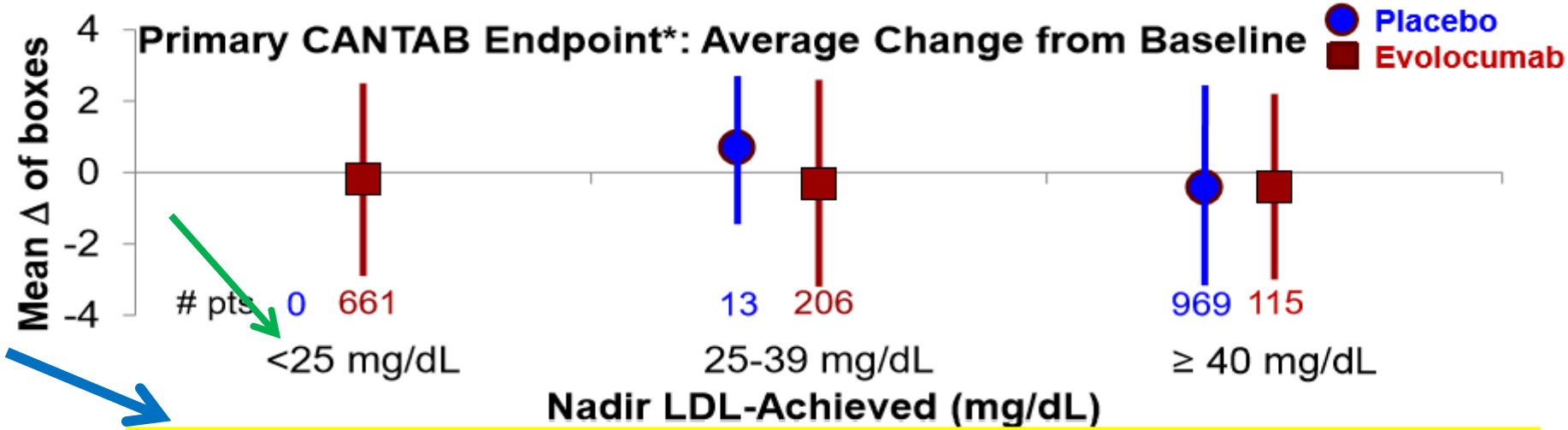
No Differences

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

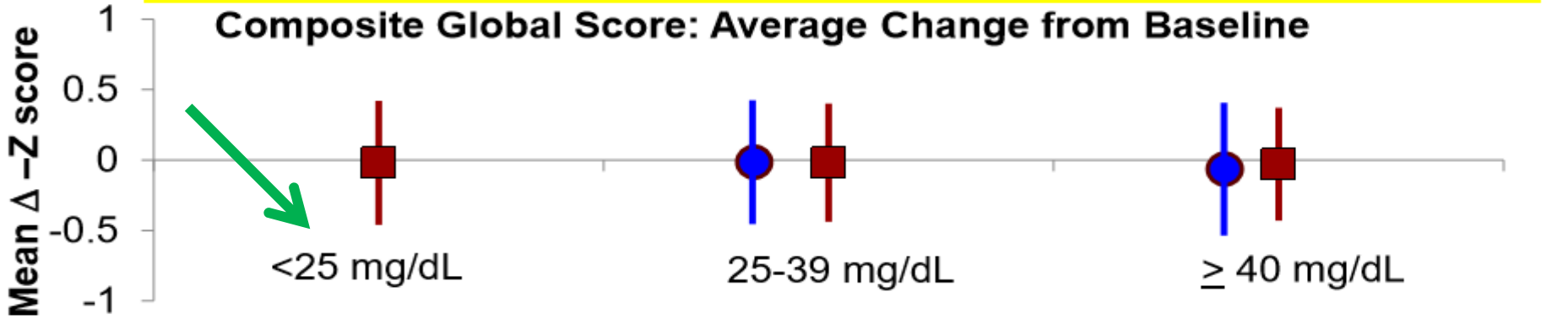
Lower raw scores (fewer errors, faster time) are better

Oklahoma Heart Institute

Cognitive Assessments by Nadir Achieved LDL-C and Treatment (Full Pop)



P=NS across LDL values achieved and also between treatments



Negative score -> improvement
Lower scores are better

*Spatial working memory strategy index of executive function, raw score

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Patient Self-Report: 23 Questions Regarding Everyday Cognition

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No Differences

All Patients	Placebo (N=781) Mean (SD)	Evolocumab (N=800) Mean (SD)	P-Value
Memory	1.16 (0.39)	1.17 (0.39)	0.81
Executive functioning total score	1.11 (0.32)	1.12 (0.32)	0.28
Planning	1.08 (0.31)	1.10 (0.32)	0.20
Organization	1.09 (0.32)	1.10 (0.33)	0.57
Divided attention	1.15 (0.42)	1.16 (0.41)	0.54
Total Score	1.13 (0.33)	1.14 (0.33)	0.42

Patient self-report at end of study as compared to randomization, graded as

1. *Better or no change*
2. *Questionable / occasionally worse*
3. *Consistently a little worse*
4. *Consistently much worse*

Lower scores represent better cognition

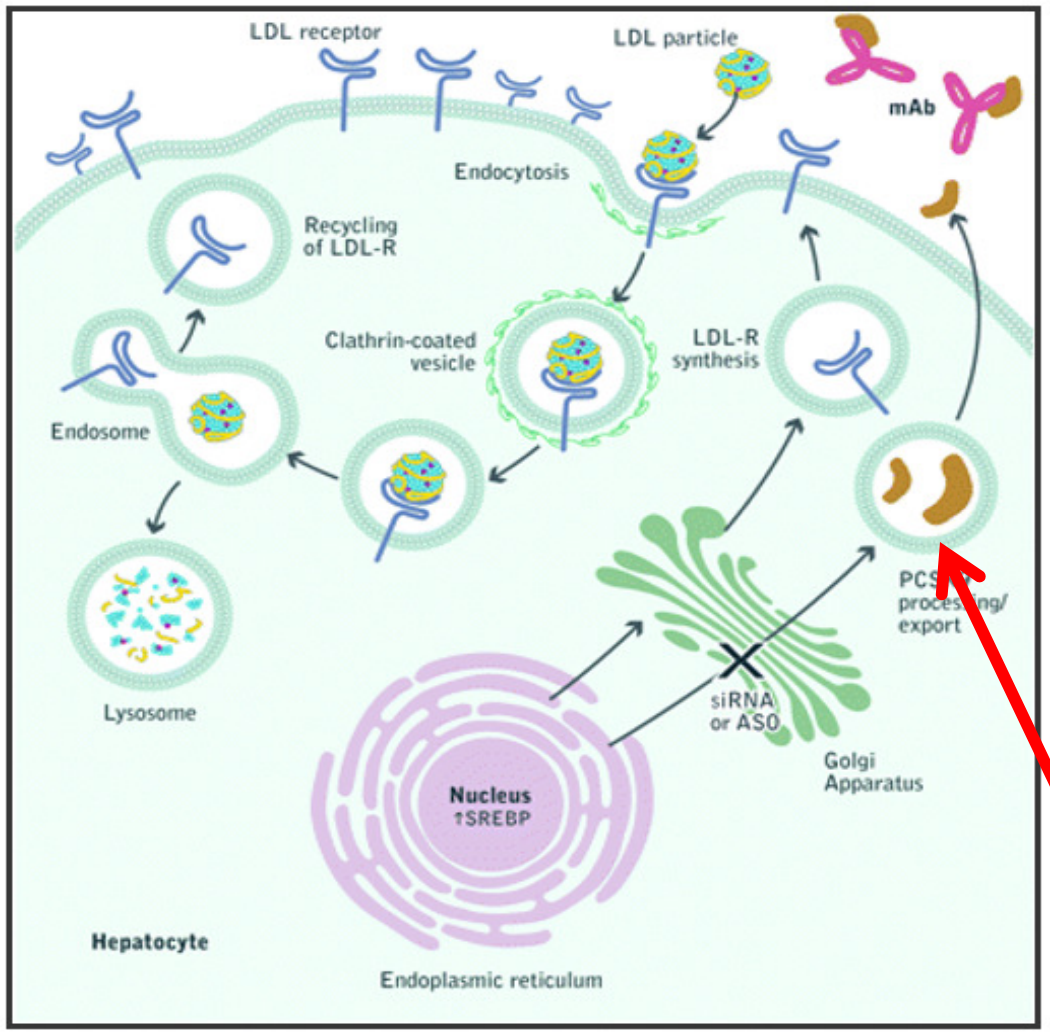
Conclusions

In patients with known cardiovascular disease on background statin followed for 20 months

1. **No differences btw evolocumab vs placebo**
   A. A battery of cognitive tests
   B. Patient-reported everyday cognition
   C. Adverse cognitive events reported by MD

2. **No evidence of differences in cognitive tests by achieved nadir LDL-C, even <25 mg/dL**

Monoclonal Antibodies to PCSK9 and Recycling of the LDL Receptor: Cardiovascular Outcomes Trials



Evolocumab (Amgen)
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ODYSSEY
NCT 01663402

~~Bococizumab (Pfizer)~~
~~SPIRE-1, SPIRE-2~~
~~NCT 01975376~~
~~NCT 01975389~~

Don't Make PCSK9 Option

Ridker ACC 2017

Original Article

Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol

Kausik K. Ray, M.D., Ulf Landmesser, M.D., Lawrence A. Leiter, M.D., David Kallend, M.D., Robert Dufour, M.D., Mahir Karakas, M.D., Tim Hall, M.D., Roland P.T. Troquay, M.D., Traci Turner, M.D., Frank L.J. Visseren, M.D., Peter Wijngaard, Ph.D., R. Scott Wright, M.D., and John J.P. Kastelein, M.D., Ph.D.

N Engl J Med
Volume 376(15):1430-1440
April 13, 2017

The NEW ENGLAND JOURNAL of MEDICINE

Study Overview

- Inclisiran, is a small interfering RNA that targets *PCSK9* mRNA. It was given as a single injection at baseline or in two doses at baseline and 90 days.

- At 180 days, LDL cholesterol was significantly lowered among persons at high cardiovascular risk who had elevated levels at baseline.

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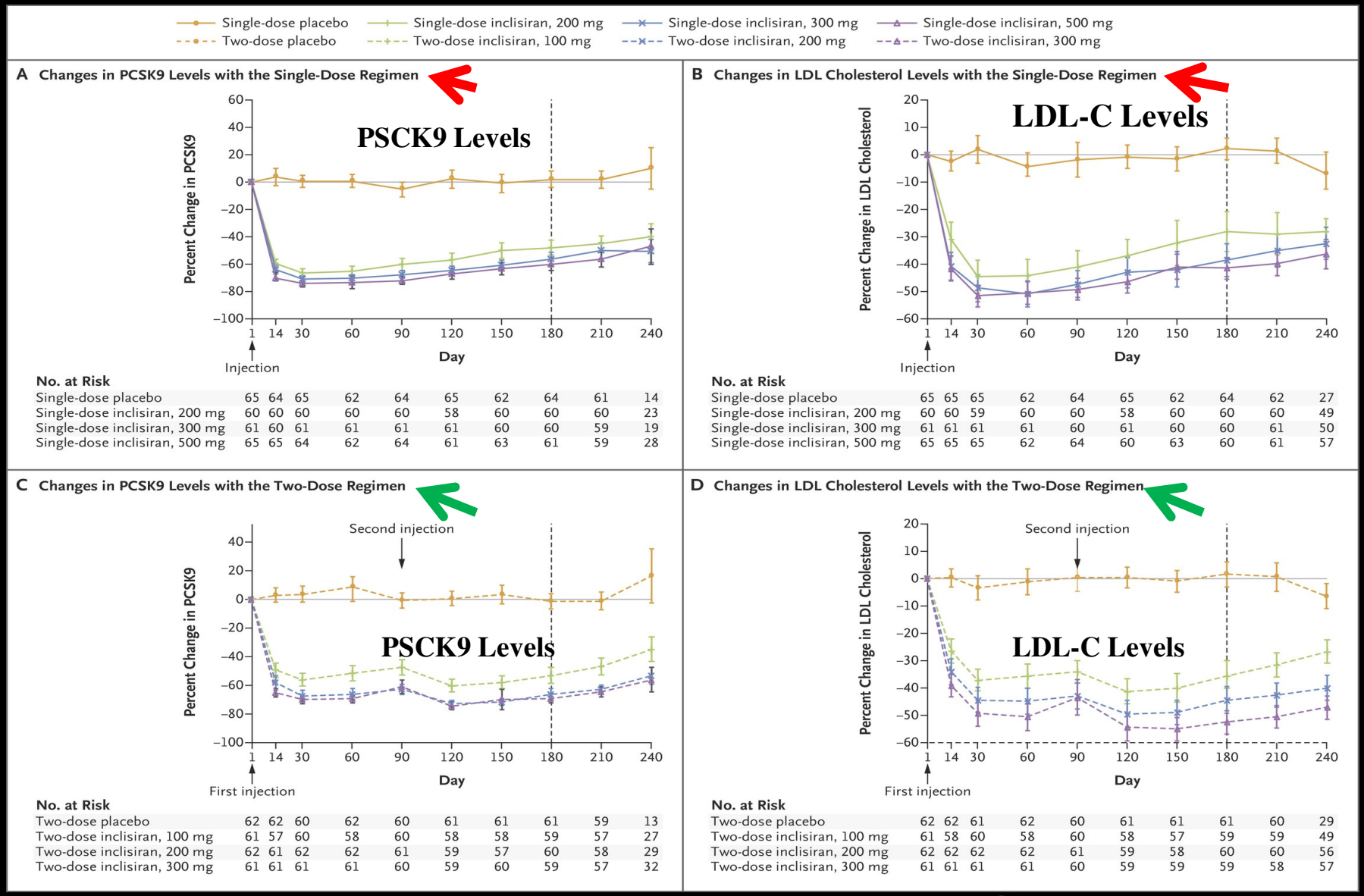
Effect of Inclisiran on PCSK9 and Low-Density Lipoprotein (LDL) Cholesterol Levels.



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Adverse Events That Occurred during Treatment through Day 210.

Table 3. Adverse Events That Occurred during Treatment through Day 210.*

Event	Single-Dose Regimen				Two-Dose Regimen			
	Placebo (N=65)	200 mg Inclisiran (N=60)	300 mg Inclisiran (N=61)	500 mg Inclisiran (N=65)	Placebo (N=62)	100 mg Inclisiran (N=61)	200 mg Inclisiran (N=62)	300 mg Inclisiran (N=61)
	number of patients (percent)							
Any event that occurred during treatment	46 (71)	47 (78)	44 (72)	49 (75)	50 (81)	48 (79)	47 (76)	47 (77)
Serious events	3 (5)	6 (10)	5 (8)	6 (9)	6 (10)	11 (18)	6 (10)	7 (11)
Severe events	2 (3)	2 (3)	4 (7)	5 (8)	7 (11)	5 (8)	6 (10)	8 (13)
Death	0	0	0	1 (2)†	0	0	1 (2)‡	0
Injection-site reaction§								4 (7)
ALT level >3 times the upper limit of the normal range								1 (2)
AST level >3 times the upper limit of the normal range	1							0
ALP level >2 times the upper limit of the normal range								0
Bilirubin level >2 times the upper limit of the normal range	1 (2)	0	0	0	0	1 (2)	0	0
Creatine kinase level >5 times the upper limit of the normal range	1 (2)‖	0	3 (5)**	0	0	0	2 (3)††	0
Myalgia	3 (5)	2 (3)	5 (8)	3 (5)	3 (5)	7 (11)	5 (8)	5 (8)
	percentage change from baseline							
Glycated hemoglobin‡‡	−0.2±7.0	−0.1±6.1	−0.1±3.3	0±6.9	0.3±13.7	0.6±10.4	0.5±5.4	−1.0±6.4
Platelets§§	1.7±12.0	4.8±12.6	0.7±12.5	1.4±15.6	5.6±20.3	−0.1±10.9	4.3±17.5	0.7±15.6

No Significant Differences Seen with Small Numbers

* Plus–minus values are means ±SD. The numbers of patients completing follow-up to day 210 in each group were as follows: in the single-dose cohort: 63 patients in the placebo group, 60 in the 200-mg inclisiran group, 61 in the 300-mg inclisiran group, and 61 in the 500-mg inclisiran group; in the two-dose cohort: 60 in the placebo group, 59 in the 100-mg inclisiran group, 60 in the 200-mg inclisiran group, and 59 in the 300-mg inclisiran group. ALP denotes alkaline phosphatase, ALT alanine aminotransferase, and AST aspartate aminotransferase.

† The death was due to a myocardial infarction.

‡ The death was due to sepsis and pneumonia after complications of surgery for aortic disease.

§ This category included rash, erythema, and pruritus.

¶ The elevated ALT and AST levels were in the same patient.

‖ The creatine kinase level in this patient was more than 73 times the upper limit of the normal range at baseline.

** One patient had a creatine kinase level that was more than 8 times the upper limit of the normal range at baseline.

†† One patient had a creatine kinase level that was more than 4 times the upper limit of the normal range at baseline.

‡‡ Glycated hemoglobin was measured in plasma and was assessed at day 180.

§§ Platelet count was measured in whole blood.

Conclusions

- In this trial, **inclisiran** was found to lower PCSK9 and LDL cholesterol levels among patients at high cardiovascular risk who had elevated LDL cholesterol levels.
- Injections could be given **once or twice** a year.

The NEW ENGLAND JOURNAL of MEDICINE

Original Article

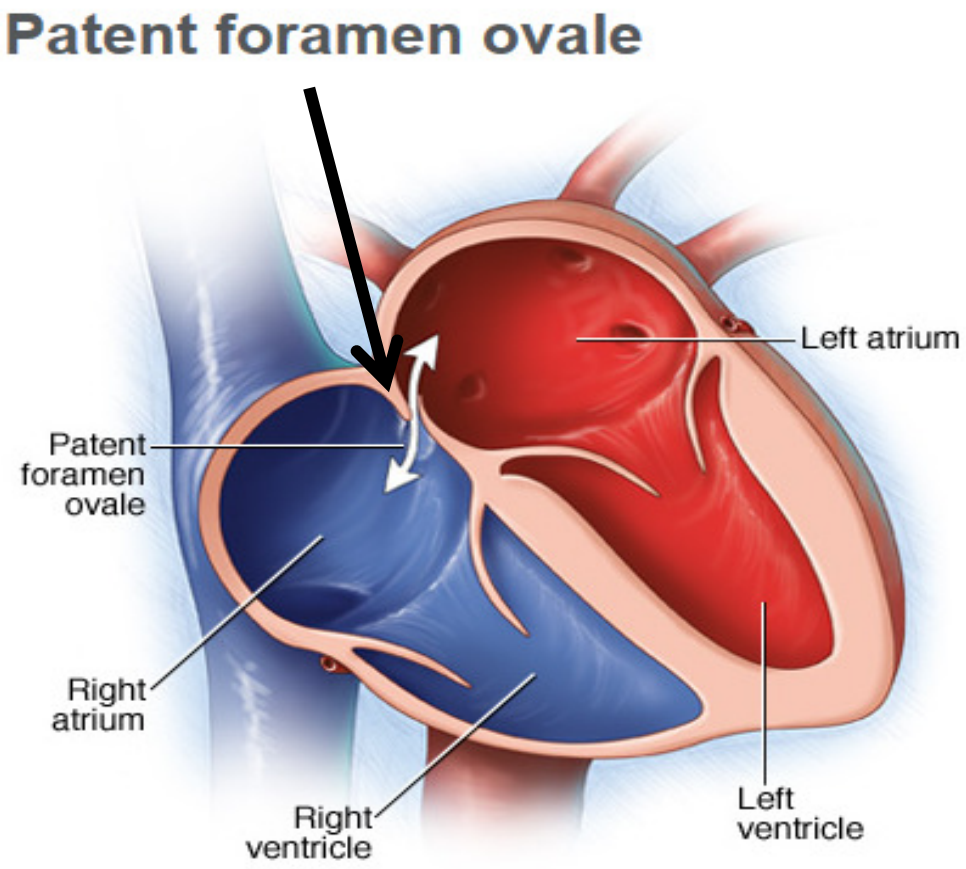
Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

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

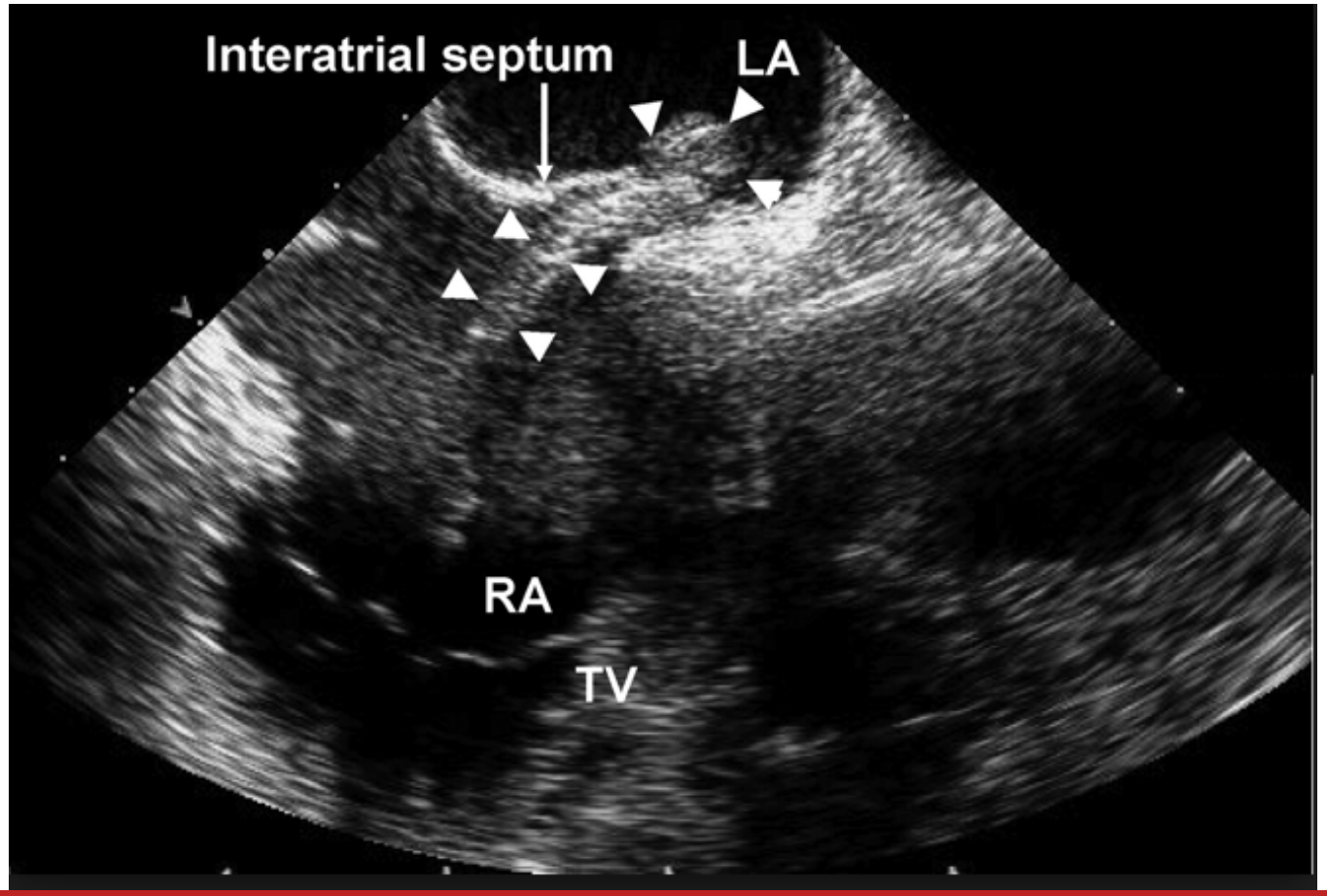
N Engl J Med
Volume 368(12):1092-1100
March 21, 2013

The NEW ENGLAND JOURNAL of MEDICINE

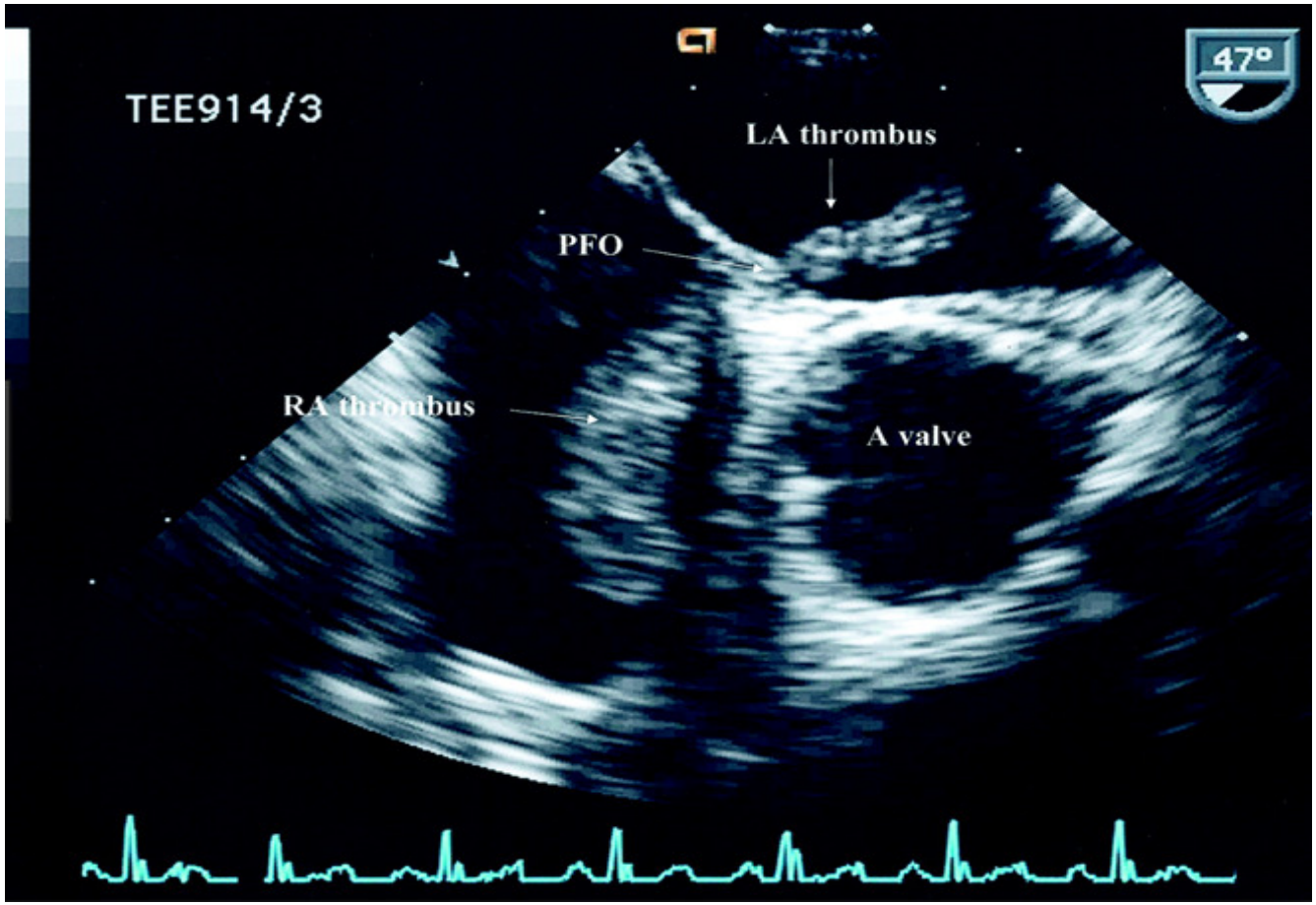
Patent Foramen Ovale:
The Risk Of Paradoxical Emboli



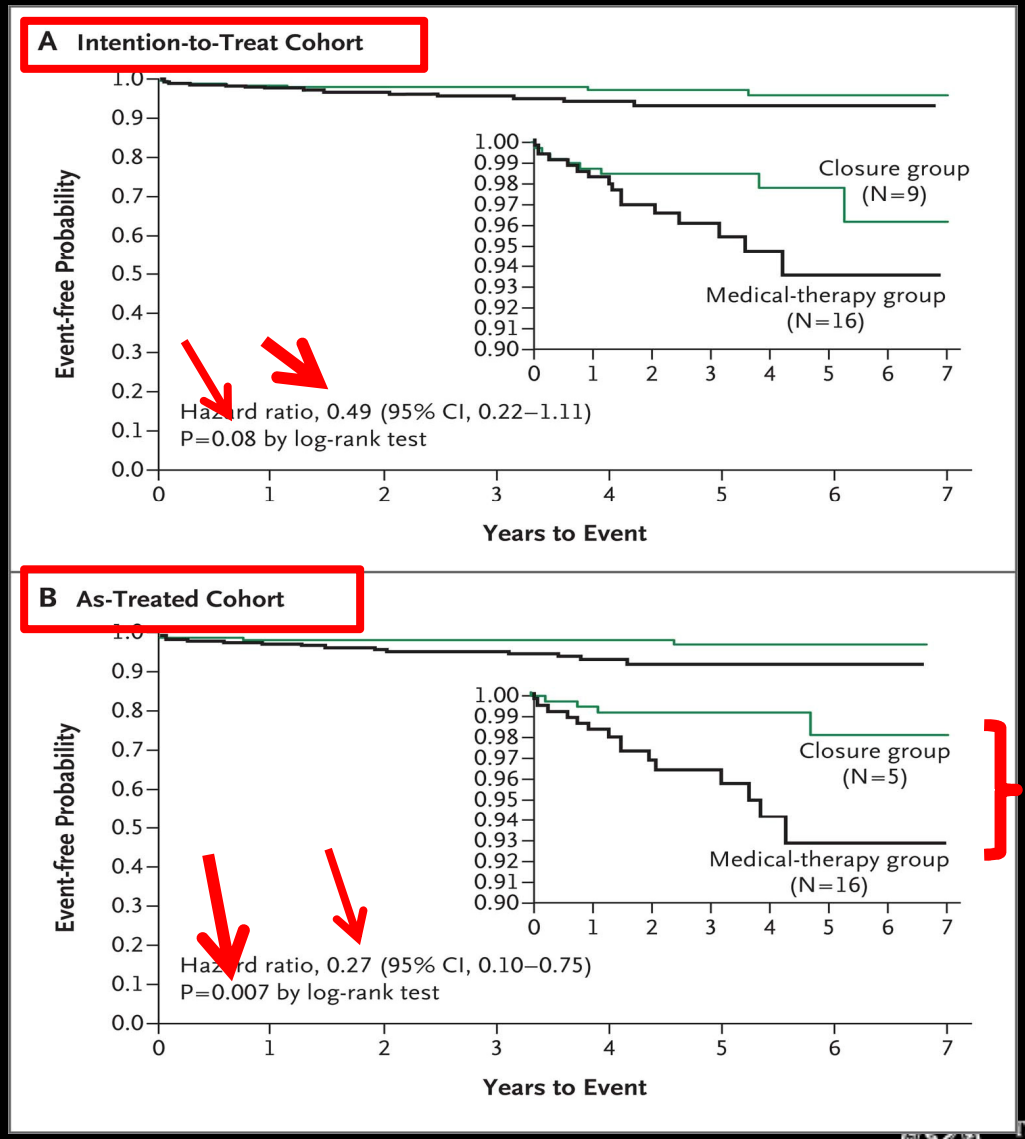
PFO With Thrombus In The Defect



The Risk Of Paradoxical Emboli: Large Thrombus In A PFO



Primary End-Point Events in the Intention-to-Treat and As-Treated Cohorts.



73 %

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Conclusions

- In the primary intention-to-treat analysis, there was no significant benefit associated with closure of a patent foramen ovale in adults who had had a cryptogenic ischemic stroke.
- However, closure was superior to medical therapy alone in the prespecified per-protocol and as-treated analyses, with a low rate of associated risks.

Now 3 Years Later

Long-term Comparison of Patent Foramen Ovale (PFO) Closure versus Medical Therapy after Cryptogenic Stroke:

Final Results of the RESPECT Trial

David E. Thaler, M.D., Ph.D.
Chairman of Neurology, Tufts University School of Medicine

On Behalf of RESPECT Investigators

Background

- ~25% of all ischemic strokes are “cryptogenic”[1]
- 34-46% of ischemic strokes occur between 18-60 years[2,3]
- PFO present in 40-50% of cryptogenic stroke patients[4,5]
- Young and middle aged patients have continued exposure to PFO-related recurrence risk
- No RCT has reported long-term outcomes of PFO closure

[1] Hart et al. *Lancet Neurology* 2014;13:429-436.
[2] Putaala et al. *Stroke* 2009;40:1195-1203.
[3] Wolf et al. *Cerebrovascular Dis* 2015;40:129-135.
[4] Lechat et al. NEJM 1988;318:1148-1152.
[5] Webster et al. Lancet 1988;332:11-12.

RESPECT Trial

- Randomized, event-driven, open-label trial with blinded endpoint adjudication
- Patients randomized 1:1 to AMPLATZER PFO Occluder (device) vs. guideline-directed medical management (MM)
- 980 subjects enrolled from 2003 to 2011
- 69 sites in U.S. and Canada

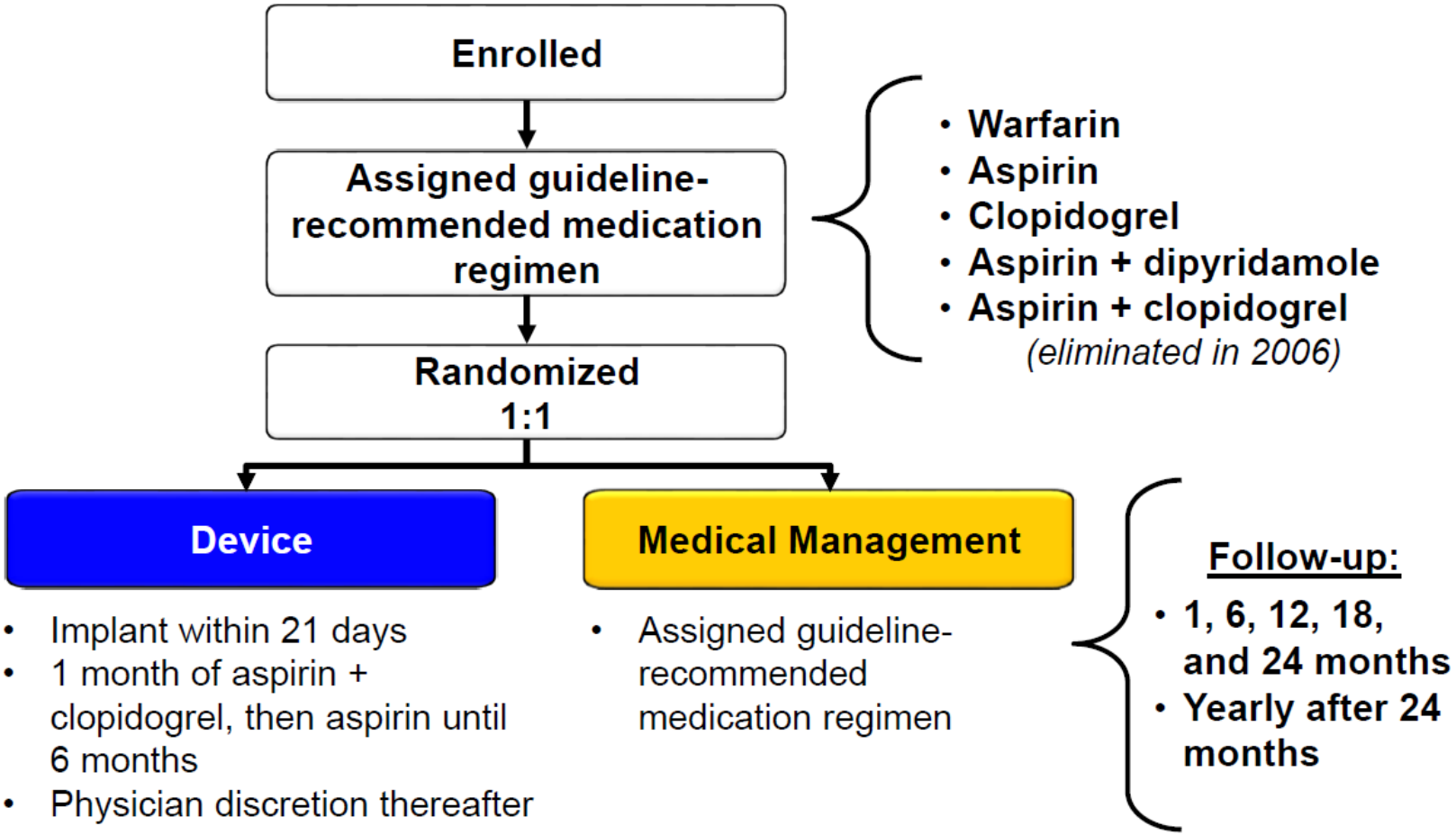
Primary Endpoint

- **Composite of:**
  - Recurrent nonfatal ischemic stroke
  - Fatal ischemic stroke
  - Early post-randomization death (within 45 days)
- **Stroke definition:**
  - Acute focal neurological deficit due to cerebral ischemia with:
    - Neuroanatomically relevant infarct on imaging

      or

    - Symptoms >24 hours

Patient Flow



Baseline Characteristics Balanced Between Groups

Characteristic	AMPLATZER™ PFO Occluder (N=499)	Medical Management (N=481)
Age (yr), mean ± SD	48 ± 10	46 ± 10
Male	54%	56%
Hypercholesterolemia	39%	41%
Family h/o CAD	33%	33%
Hypertension	32%	32%
COPD	0.8%	1.5%
Congestive heart failure	0.6%	0%
History of DVT	4.0%	3.1%
Atrial septal aneurysm	36%	35%
Substantial shunt	50%	48%

Procedural Results and Follow-up

- **Technical Success*** **99.1%**
- **Procedural Success**** **96.1%**
- **Mean Follow-up:** **5.9 years (0-12 years)**
  - Device
    - Mean 6.3 years; Total 3141 patient-years
  - Medical Management
    - Mean 5.5 years; Total 2669 patient-years

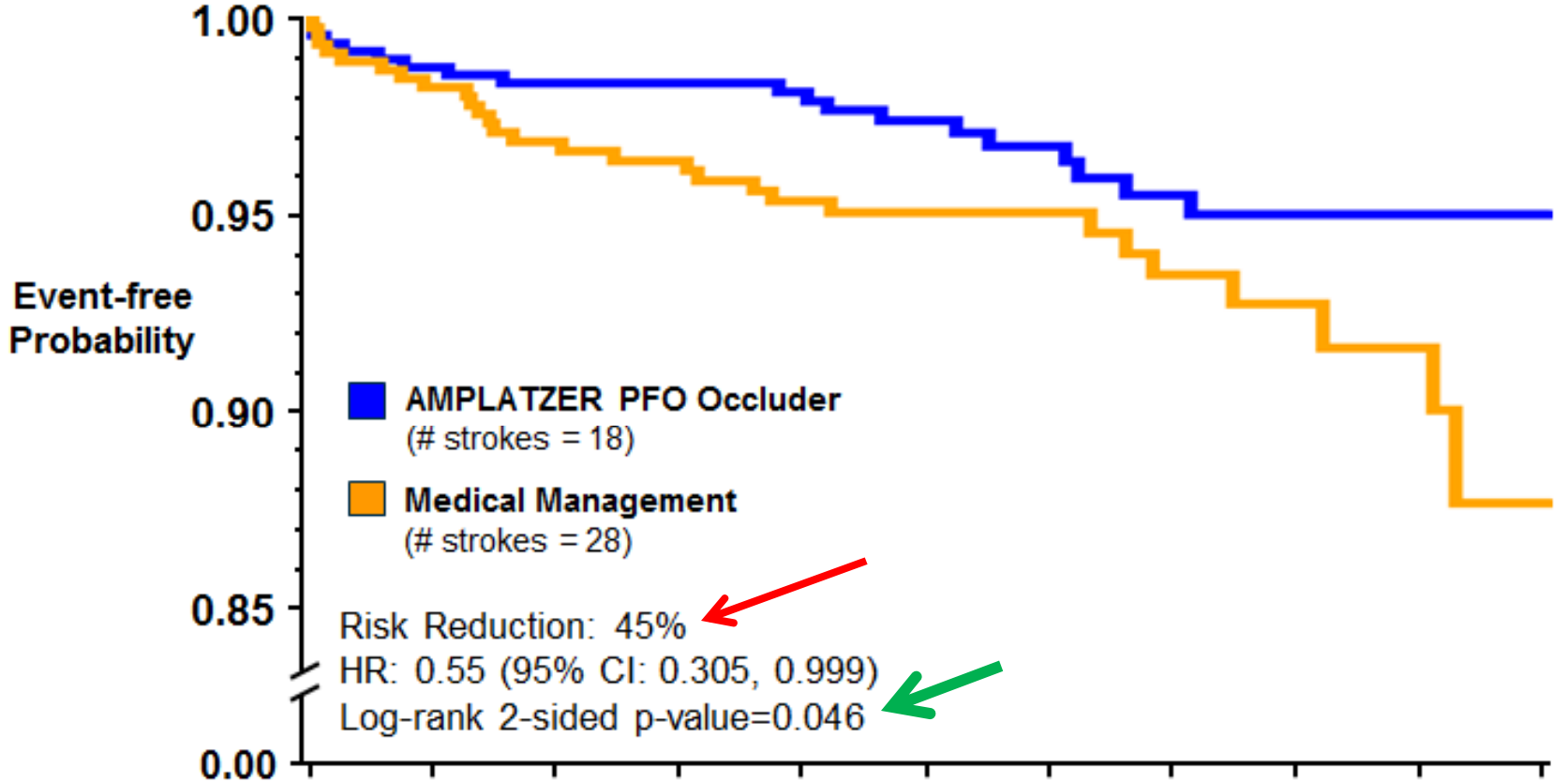
*Delivery and release of the device

**Implantation without in-hospital SAE

RESULTS

RESPECT Final Results

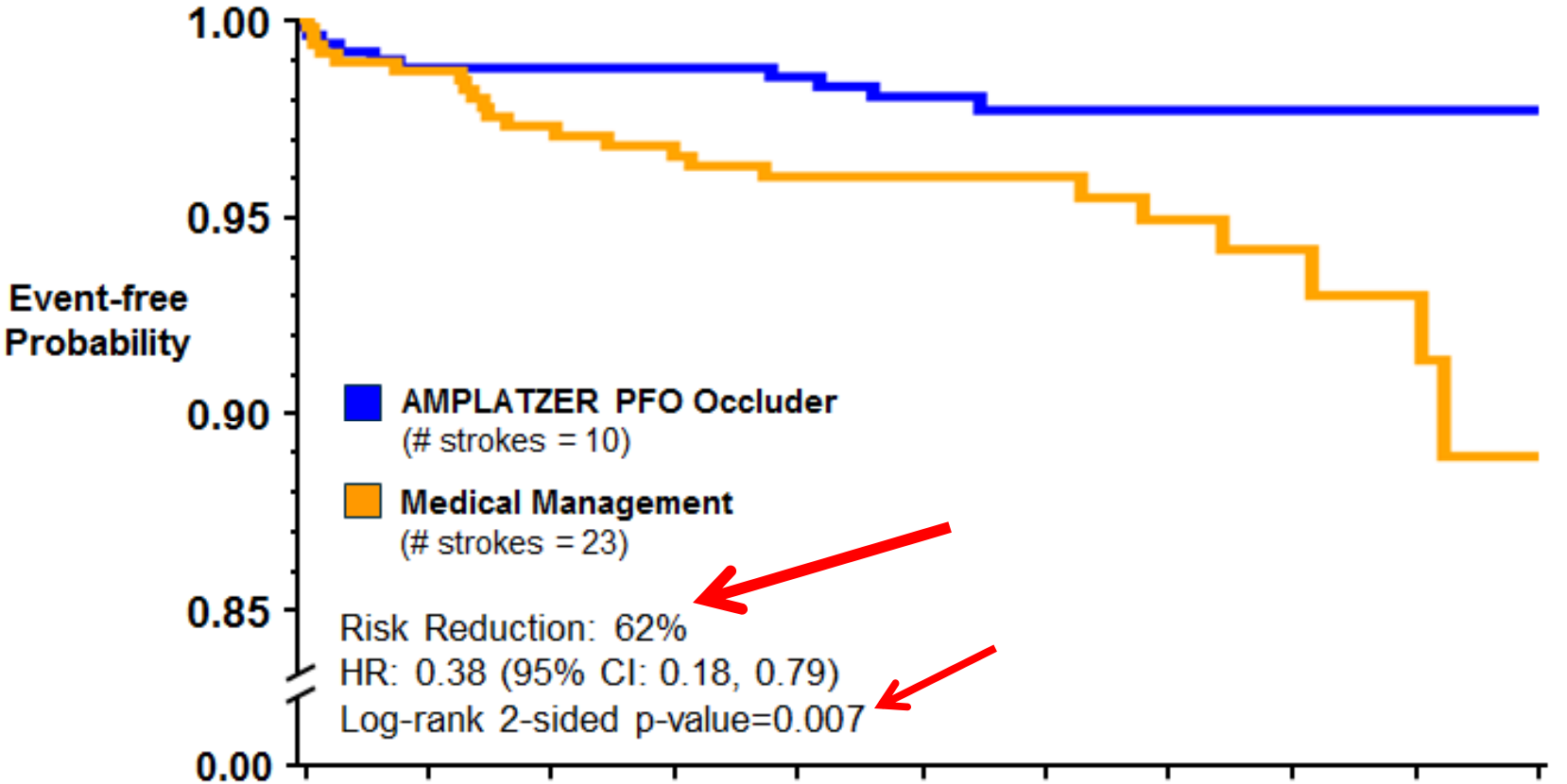
Freedom from Recurrent Ischemic Stroke (Intention to Treat)



# at Risk (KM Estimates)											
AMPLATZER	499 (0%)	476 (1.4%)	464 (1.6%)	447 (1.6%)	421 (1.9%)	352 (2.6%)	262 (3.3%)	197 (4.5%)	128 (5.0%)	77 (5.0%)	41 (5.0%)
MM	481 (0%)	433 (1.8%)	394 (3.2%)	380 (3.7%)	354 (4.7%)	282 (5.0%)	218 (5.0%)	150 (6.6%)	104 (7.3%)	59 (8.5%)	31 (12.5%)

RESPECT Final Results

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



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DSMB Adjudicated Procedure or Device Related SAEs

- No intra-procedural strokes
- No device embolization
- No device thrombosis
- No device erosion
- Major vascular complications (0.9%) and device explants (0.4%)

Adjudicated SAEs of Interest

Event Type	AMPLATZER™ PFO Occluder (N=499) [3141 Pt-Yrs]		Medical Management (N=481) [2669 Pt-Yrs]		P-value**
	Events	Rate*	Events	Rate*	
Atrial fibrillation	8	0.25	4	0.15	0.37
Major bleeding	18	0.57	15	0.56	0.96
Death from any cause	7	0.22	11	0.41	0.21
DVT/PE	18	0.57	4	0.15	0.006

* Rate expressed as number of events per 100 patient-years
**Based on the normal approximation to a difference in Poisson rates

Conclusions

- 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

FDA Approval 10/28/16

The AMPLATZER™ PFO Occluder is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.

SURTAVI

Transcather Aortic Valve Replacement (TAVR)

Versus

Surgical Aortic Valve Replacement (SAVR)

In Intermediate Risk Patients

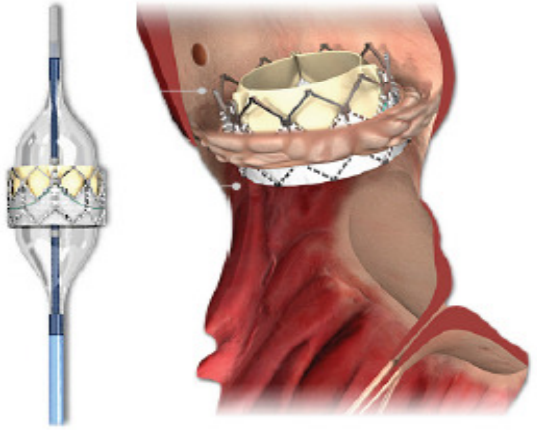
STS Score ≥ 3

Transcatheter Aortic Valve Replacement: TAVR

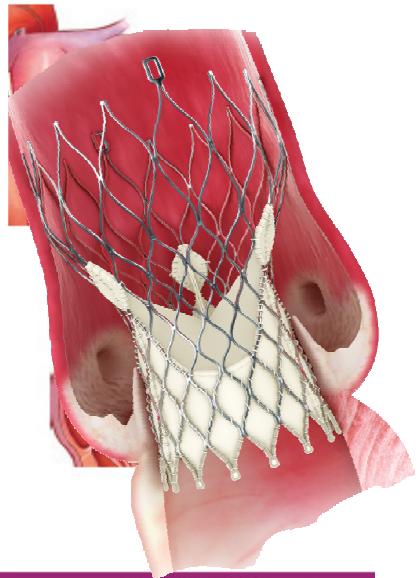
Background (II)

CHOICE

Balloon-expandable THV
Edwards Sapien XT
(Cobalt chromium stent frame, bovine pericardium)



Self-expandable THV
Medtronic CoreValve
(Nitinol stent frame, porcine pericardium)



SURTAVI Trial
TAVR vs SAVR

- 1,746 patients at 87 centers randomized
- STS Mortality scores of ≥ 3 and < 15 %
- Mean age = 80 years old
- 56% male

SURTAVI Trial: Results
TAVR vs SAVR

At Two Years Primary Endpoint of All-Cause Mortality or Disabling CVA:

***12.6% TAVR vs 14.0% SAVR**

P < 0.005 for non-inferiority

The disabling Stroke Rates were:

*** 2.6% TAVR vs 4.5% SAVR**

P = NS

TAVR vs SAVR: Issues

- **Two trials showing non-inferiority of TAVR to SAVR in intermediate risk patients**
- **(Edwards Sapien Balloon Expandable Valve and Medtronic Self - Expanding Core Valve)**
- **AVA consistently better for TAVR**
- **Still do not know the longevity/ durability data on TAVR for patient's living longer than 5 to 7 years**

RESOLVE Trial

- Subclinical leaflet thrombosis of bioprosthetic valves (TAVR and SAVR)
- 4% to 12% incidence seen
- DAPT not effective in preventing
- Oral anticoagulation was effective in preventing and treating

TAVR New Guidelines

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http://dx.doi.org/10.1016/j.jacc.2016.12.006

ACC CLINICAL DOCUMENT

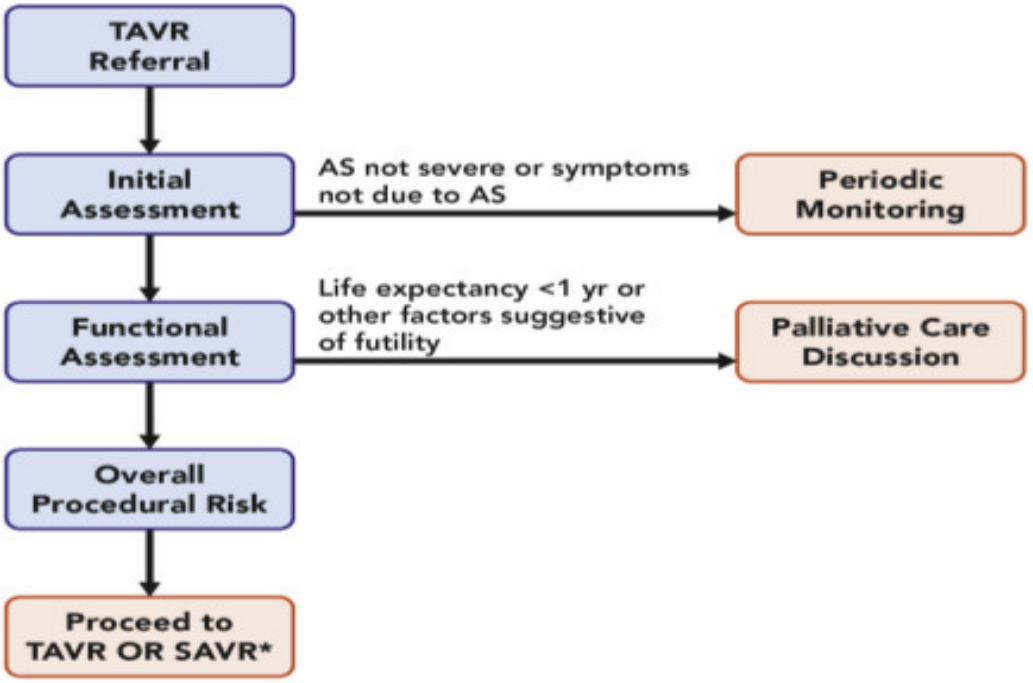
2017 ACC Expert Consensus Decision Pathway for Transcatheter Aortic Valve Replacement in the Management of Adults With Aortic Stenosis

A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents

Oklahoma Heart Institute

TAVR Referral Evaluation: 2017

FIGURE 2 Pre-TAVR Considerations by the Heart Valve Team



Abbreviations:
AS = aortic stenosis, AVR = aortic valve replacement, TAVR = transcatheter aortic valve replacement

*per current AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

EINSTEIN CHOICE

Dr. Phil Wells
on behalf of the EINSTEIN CHOICE Steering Committee and Investigators

Weitz JI et al. N Engl J Med 2017 (DOI: 10.1056/NEJMoa1700518)

NCT02064439

Oklahoma Heart Institute

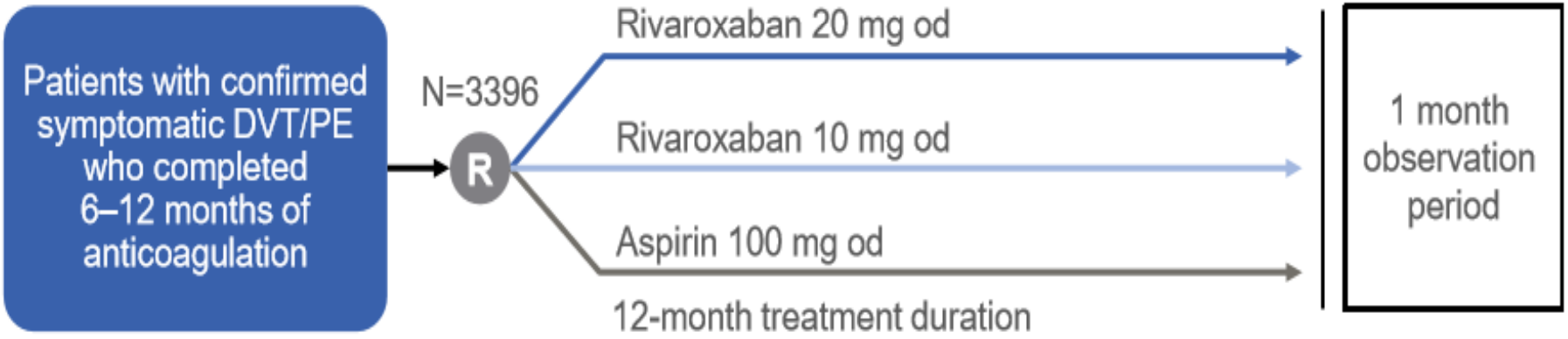
EINSTEIN CHOICE: Trial

Background

- In patients without reversible risk factors, the risk of recurrent venous thromboembolism is up to 10% in the first year if anticoagulation therapy is stopped
- Although extended anticoagulation therapy prevents recurrent venous thromboembolism, concerns about bleeding often lead to reluctance to continue treatment beyond 6 to 12 months
- Lower dose anticoagulant therapy, or aspirin instead of an anticoagulant may reduce this bleeding risk
- Head-to-head comparison is necessary to determine the relative efficacy and safety of these approaches

Study Design

- Aim: Compare the efficacy and safety of once daily rivaroxaban (20 or 10 mg) with aspirin (100 mg) in VTE patients who completed 6 to 12 months of treatment and with equipoise regarding the need for extended anticoagulation
- Randomized, double-blind, active-comparator, event-driven, superiority study



Weitz JI *et al. Thromb Haemost* 2015;114:645–50

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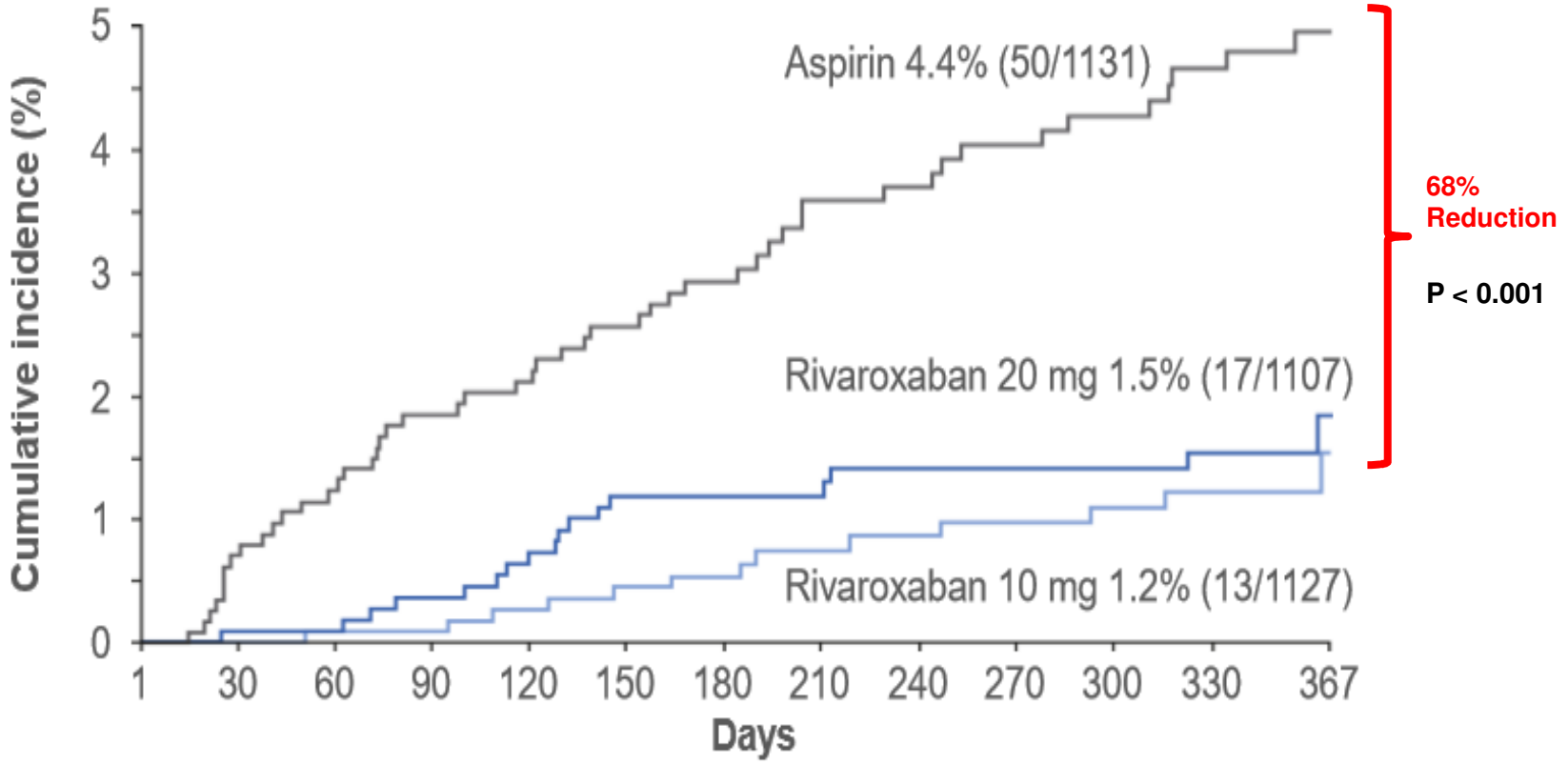
Oklahoma Heart Institute

Recurrent VTE – Cumulative Incidence



Number of patients at risk													
Rivaroxaban 20 mg	1107	1102	1095	1090	1084	1079	997	876	872	860	794	718	0
Rivaroxaban 10 mg	1126	1124	1119	1118	1111	1109	1029	890	886	867	812	723	0
Aspirin	1131	1121	1111	1103	1094	1088	1010	859	857	839	776	707	0

VTE, Venous thromboembolism; HR, hazard ratio

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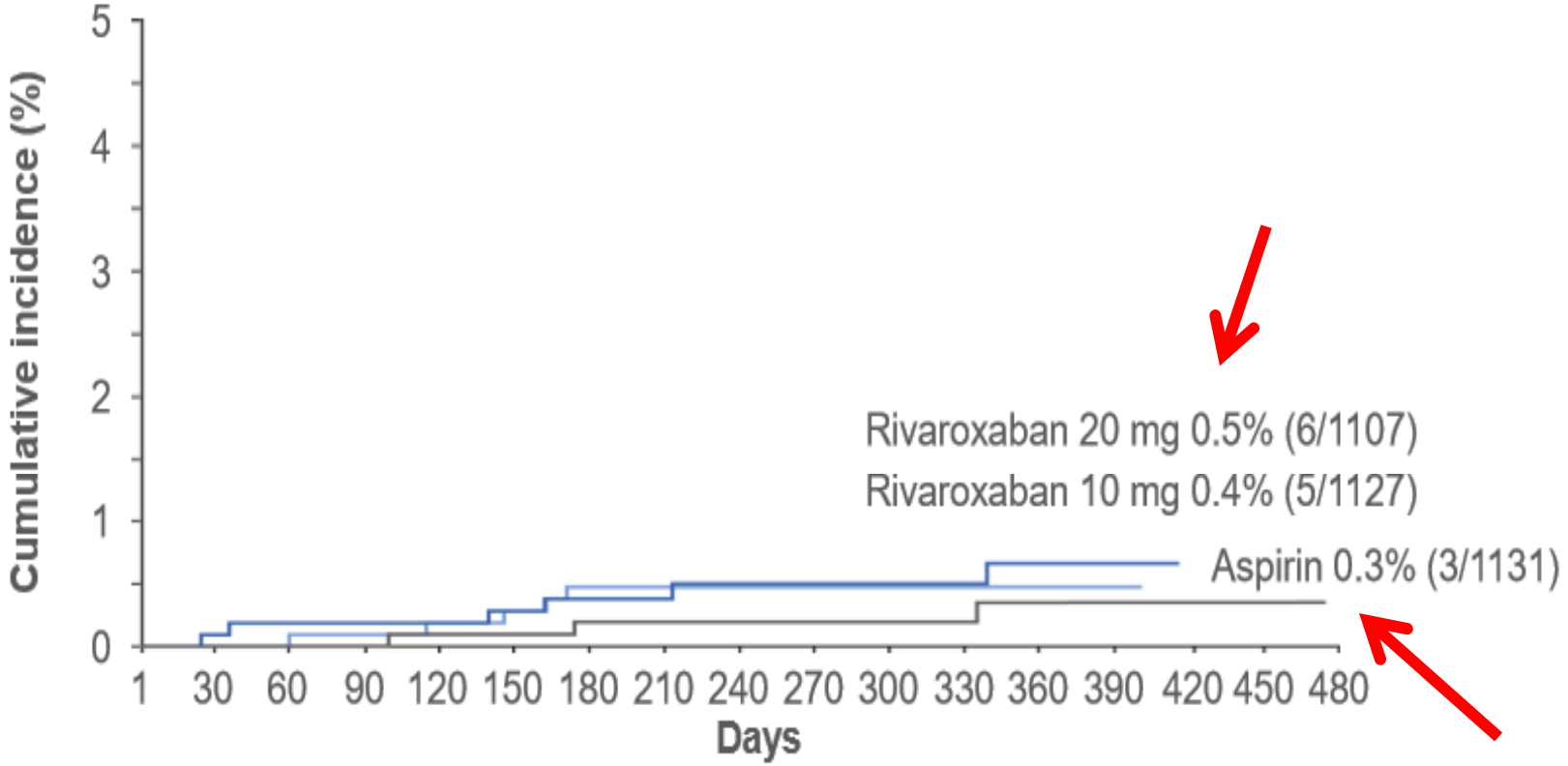
Major Bleeding – Cumulative Incidence



Number of patients at risk																	
Rivaroxaban 20 mg	1107	1081	1063	1048	1036	1024	963	818	801	780	712	642	449	10	0	0	0
Rivaroxaban 10 mg	1126	1103	1080	1070	1058	1046	988	823	812	790	733	653	469	8	0	0	0
Aspirin	1131	1096	1075	1058	1040	1023	970	800	791	768	709	645	445	5	2	2	0

Treatment-emergent major bleeding: onset during study treatment up to 2 days after stop of study treatment

EINSTEIN CHOICE

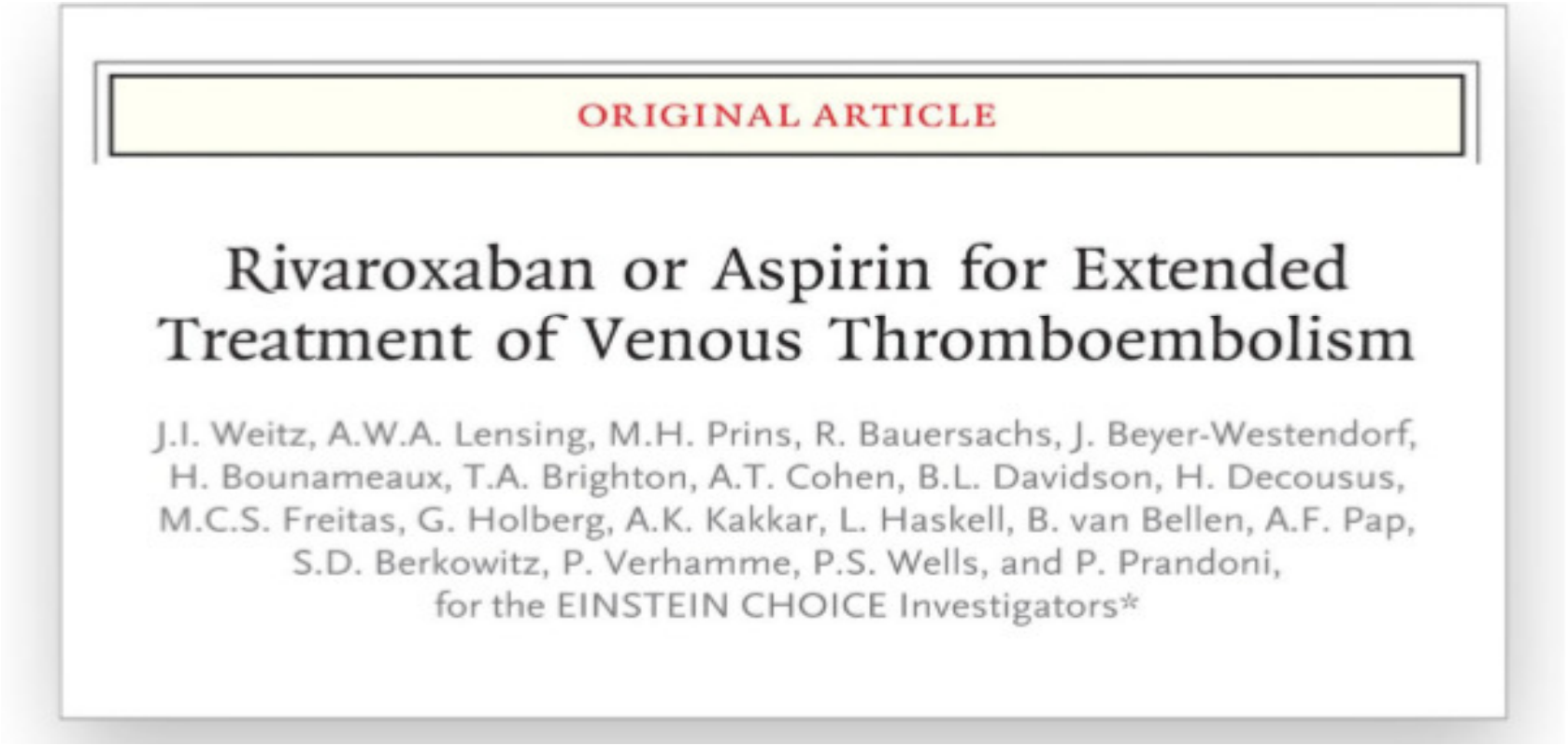
Summary and Conclusions

- In patients with symptomatic VTE who completed 6 to 12 months of treatment and with equipoise regarding the need for extended anticoagulation
  - Both rivaroxaban regimens (20 or 10 mg once daily) are superior to aspirin for the primary and other efficacy outcomes and are associated with similar rates of bleeding
  - Compared with aspirin, numbers needed to treat with rivaroxaban 20 or 10 mg for one year to prevent one VTE without an increase in bleeding are 33 and 30, respectively
  - Consistent results in subgroups of patients

- Rivaroxaban 10 mg once daily provides an additional option for extended VTE treatment
  - Patients requiring full-dose anticoagulant therapy were excluded and may need extended treatment with the 20 mg once daily rivaroxaban regimen

*Number needed to treat (NNT) compared with aspirin for primary efficacy outcome up to 1 year

EINSTEIN CHOICE Trial



ORIGINAL ARTICLE

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

J.I. Weitz, A.W.A. Lensing, M.H. Prins, R. Bauersachs, J. Beyer-Westendorf, H. Bounameaux, T.A. Brighton, A.T. Cohen, B.L. Davidson, H. Decousus, M.C.S. Freitas, G. Holberg, A.K. Kakkar, L. Haskell, B. van Bellen, A.F. Pap, S.D. Berkowitz, P. Verhamme, P.S. Wells, and P. Prandoni, for the EINSTEIN CHOICE Investigators*

ARISTOTLE

ACC.17
66th Annual Scientific Session & Expo

Digoxin And Mortality in Patients With Atrial Fibrillation With and Without Heart Failure: Does Serum Digoxin Concentration Matter?

Renato D. Lopes, MD, PhD, FACC
on behalf of the ARISTOTLE Investigators

Duke Clinical Research Institute

UCR
Uppsala Clinical Research Center

Background

- Digoxin is used in ≈ 30% of patients with atrial fibrillation (AF) worldwide, despite the lack of randomized clinical trials to assess its efficacy and safety in this setting.[1–3]
- Current AF guidelines recommend digoxin for rate control in patients with AF with and without heart failure (HF).[4,5]
- There are no specific recommendations about serum digoxin concentration monitoring in the AF guidelines.

[1]Allen LA, et al. J Am Coll Cardiol 2015;65:2691-8. [2]Washam JB, et al. Lancet 2015;385:2363-70. [3]Granger CB, et al. N Engl J Med 2011;365:981-92. [4]January CT, et al. Circulation 2014;130:2071-104. [5]Kirchof P, et al. Eur Heart J 2016;37:2893-962.

Research Context: ''A Controversial Topic''

European Heart Journal
doi:10.1093/eurheartj/ehv143

CLINICAL RESEARCH

Atrial fibrillation

Digoxin-associated mortality: a systematic review and meta-analysis of the literature

J Am Coll Cardiol. 2015 June 30; 65(25): 2691–2698. doi:10.1016/j.jacc.2015.04.045.

Digoxin use and subsequent outcomes among patients in a contemporary atrial fibrillation cohort

Larry A. Allen, MD, MHS*, Gregg C. Fonarow, MD†, DaJuanicia N. Simon, MS‡, Laine E. Thomas, PhD‡, Lucas N. Marzec, MD*, Sean D. Pokorney, MD, MBA‡, Bernard J. Gersh, MB

Digoxin use in patients with atrial fibrillation and adverse cardiovascular outcomes: a retrospective analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)

Jeffrey B Washam, Susanna R Stevens, Yuliya Lokhnygina, Jonathan L Halperin, Günter Breithardt, Daniel E Singer, Kenneth W Mahaffey, Graeme J Hankey, Scott D Berkowitz, Christopher C Nessel, Keith A A Fox, Robert M Califf, Jonathan P Piccini, Manesh R Patel, for the ROCKET AF Steering Committee and Investigators

European Heart Journal (2013) **34**, 1481–1488

Increased mortality among patients taking digoxin—analysis from the AFFIRM study

European Heart Journal (2013) **34**, 1489–1497

Lack of evidence of increased mortality among patients with atrial fibrillation taking digoxin: findings from *post hoc* propensity-matched analysis of the AFFIRM trial

European Heart Journal (2013) **34**, 1468–1470

Digoxin for patients with atrial fibrillation and heart failure: paradise lost or not?†

European Heart Journal (2013) **34**, 1465–1467

When 'digoxin use' is not the same as 'digoxin use': lessons from the AFFIRM trial

(*Circ Cardiovasc Qual Outcomes*. 2013;6:511-513.)

Editorial

Digitalis, Yesterday and Today, But Not Forever

Lionel H. Opie, MD, DSc

Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

ARISTOTLE

Inclusion risk factors
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Randomize
double blind, double dummy
(n = 18,201)

Exclusion
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

Apixaban 5 mg oral twice daily (2.5 mg BID in selected patients)

Warfarin (target INR 2–3)

Biomarker substudy
(n=14,892)
- Blood samples at baseline
- Plasma aliquots stored at -70°C

Warfarin/warfarin placebo adjusted by INR/sham INR based on encrypted point-of-care testing device

Primary outcome: stroke or systemic embolism

Lopes RD, et al. Am Heart J 2010;159:331–9.
Granger CB, et al. N Engl J Med 2011;365:981–92.

Duke Clinical Research Institute

UCR Uppsala Clinical Research Center

Objectives

Using data from the ARISTOTLE trial, we aimed to:

- Explore the association between digoxin use and mortality
  - According to serum digoxin concentration
  - In patients with and without HF
- Assess the efficacy and safety of apixaban versus warfarin in patients taking and not taking digoxin.

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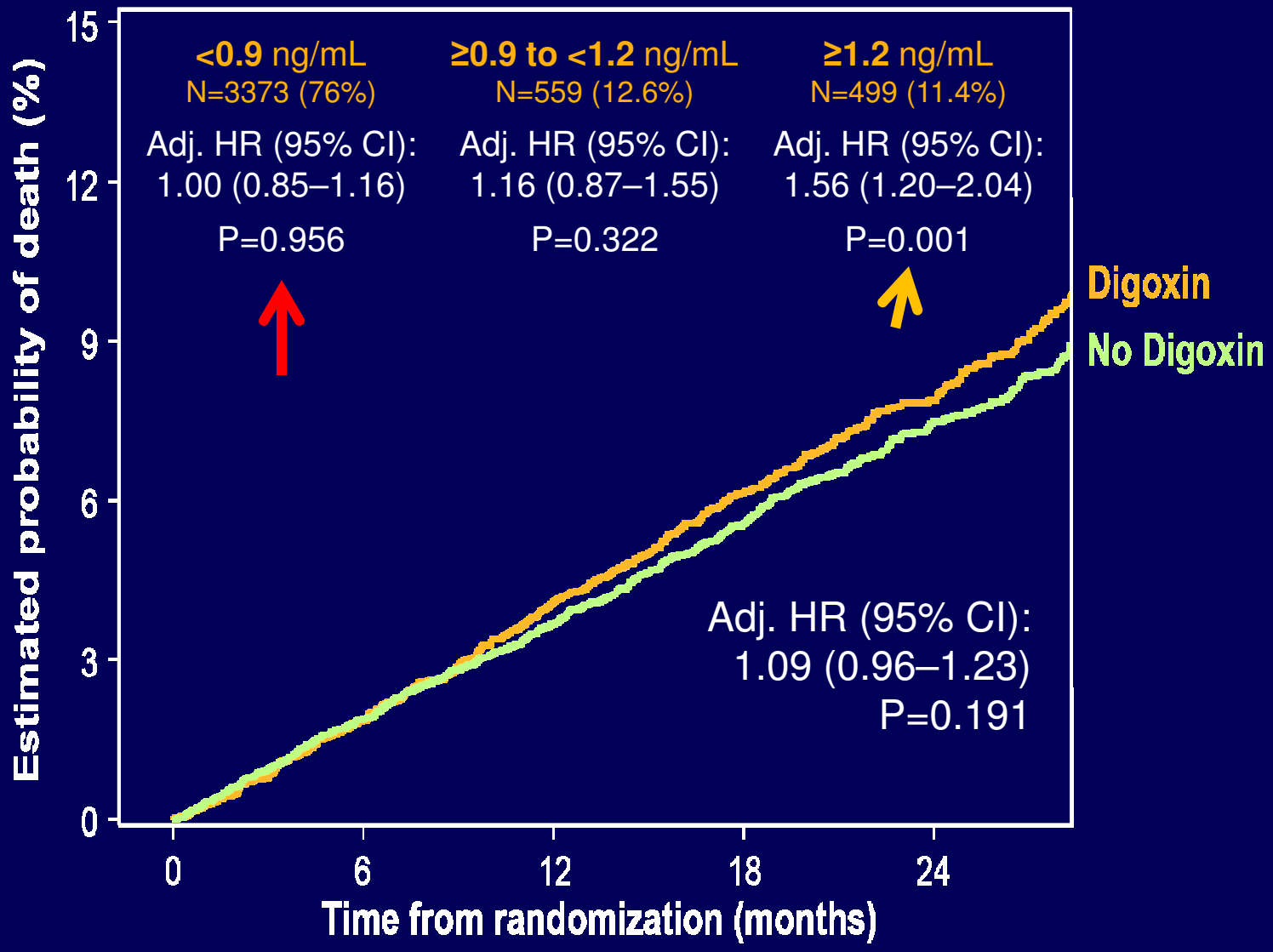
Digoxin and Mortality

MAIN RESULTS

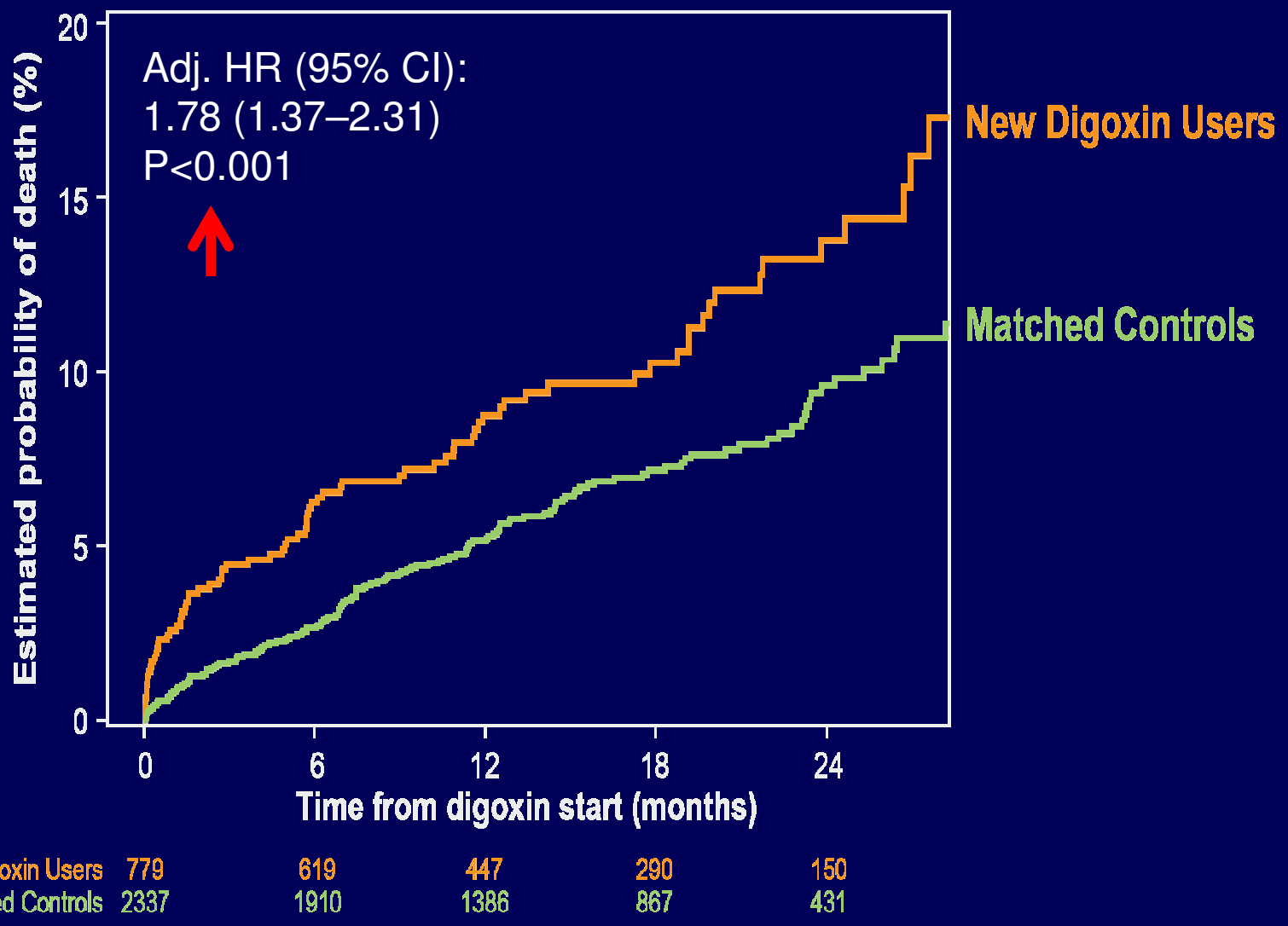
Duke Clinical Research Institute

UCR
Uppsala Clinical Research Center

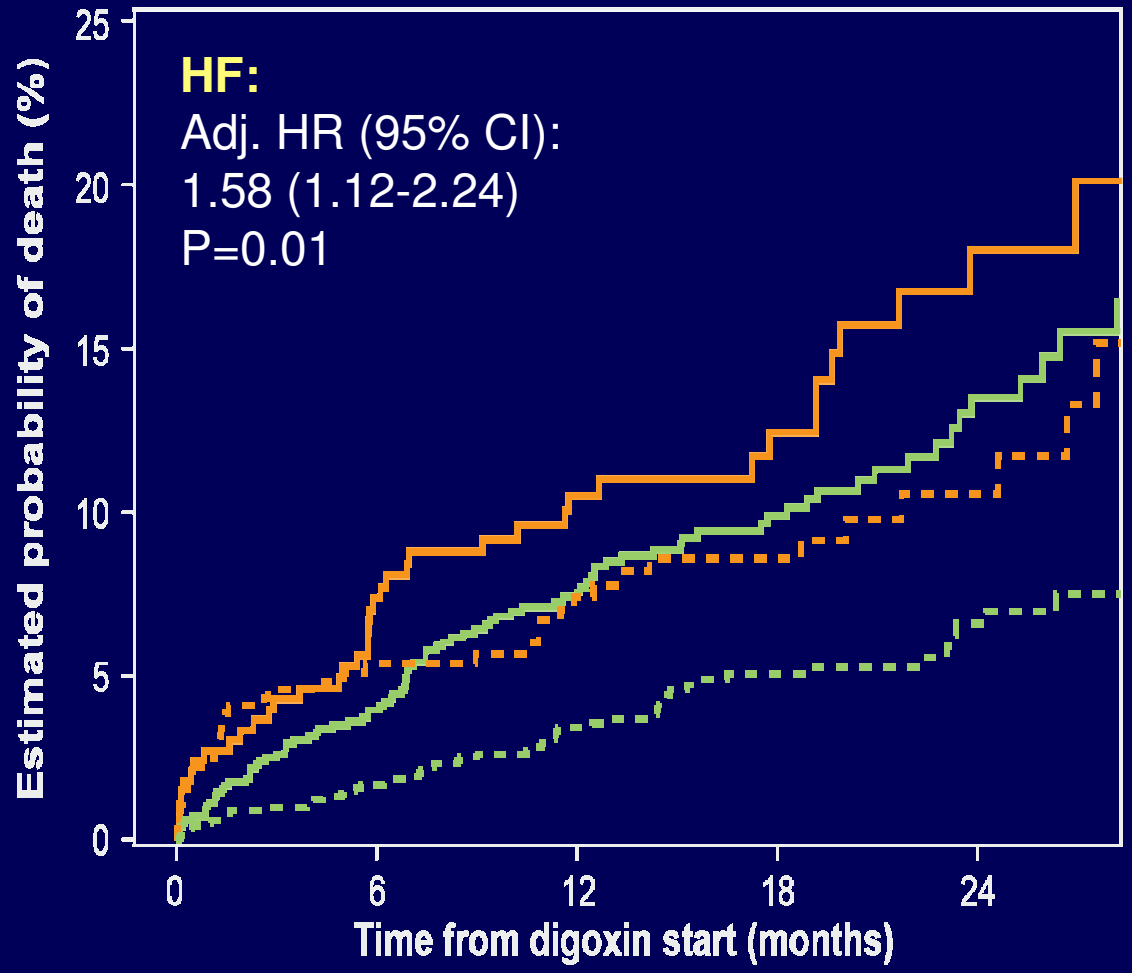
Baseline Serum Digoxin Concentration and Adjusted Mortality



Adjusted Mortality in New Digoxin Users versus Matched Controls



Adjusted Mortality in New Digoxin Users versus Matched Controls With and Without Heart Failure



New Digoxin Users / HF

Matched Controls / HF

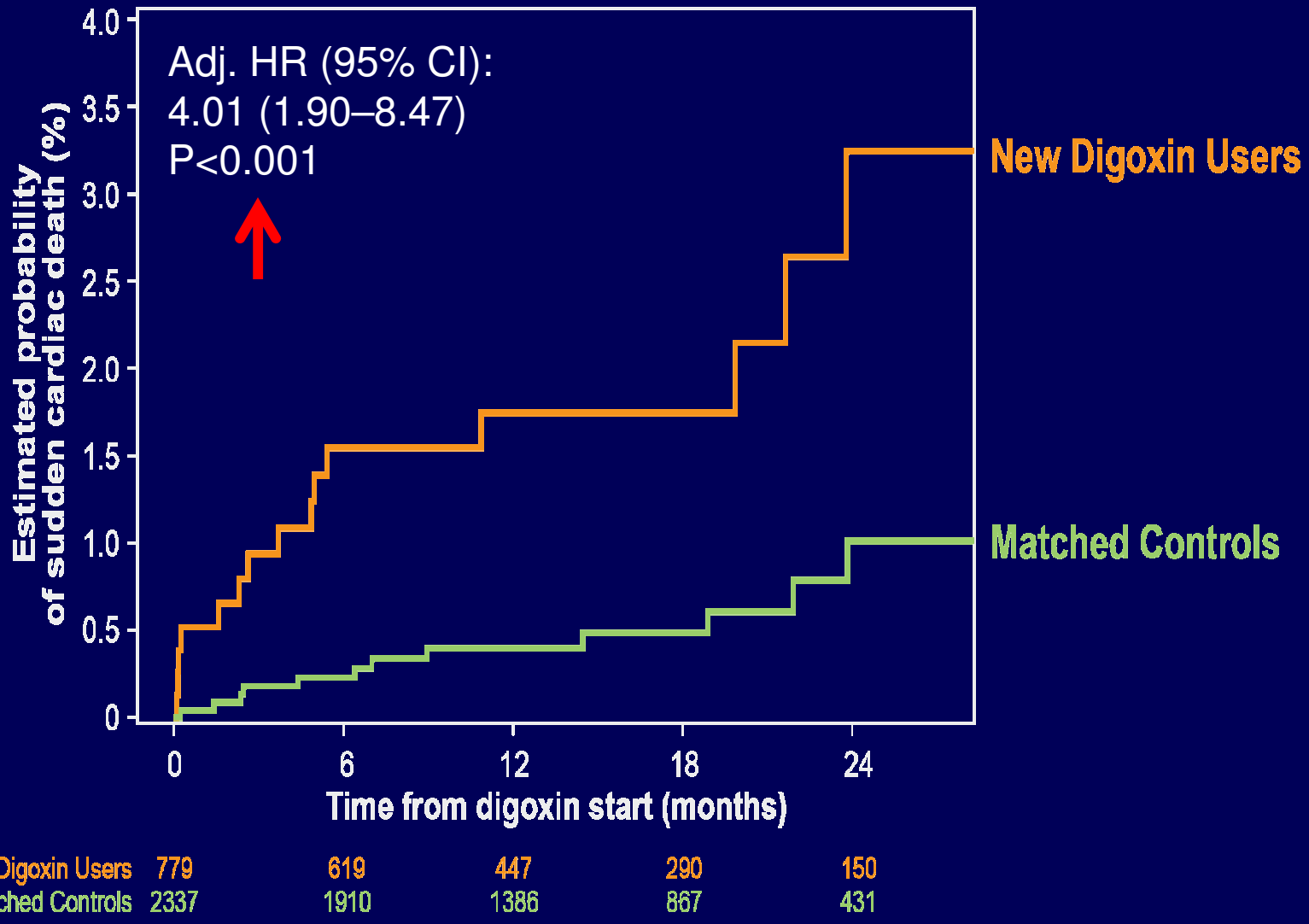
New Digoxin Users / Non-HF

Matched Controls / Non-HF

Non-HF:
Adj. HR (95% CI):
2.07 (1.39-3.08)
P=0.0003

New Digoxin Users / HF	333	266	191	120	62
New Digoxin Users / Non-HF	446	353	256	170	88
Matched Controls / HF	999	810	606	378	179
Matched Controls / Non-HF	1338	1100	780	489	252

Adjusted Sudden Death in New Digoxin Users versus Matched Controls



Conclusions

- In patients with AF currently taking digoxin, the risk of death is independently related to digoxin serum concentration and is highest in patients with concentrations ≥1.2 ng/mL.
- Initiating digoxin is independently associated with higher mortality in patients with AF, regardless of HF.
- The benefits of apixaban over warfarin are consistent in digoxin users and non-users.

Clinical Implication

- In the absence of randomized trial data showing its safety and efficacy, digoxin should not be prescribed for patients with AF, particularly if symptoms can be alleviated with other treatments.
- In patients with AF already taking digoxin, monitoring its serum concentration may be important, targeting blood levels <1.2 ng/mL.

COMPARE-ACUTE

ACC.17

Randomised trial of FFR-guided complete revascularization *versus* infarct artery only treatment in multivessel STEMI patients

On behalf of all COMPARE-ACUTE investigators

Pieter Smits

Maasstad Hospital

Rotterdam, The Netherlands

Compare Acute

MAASSTAD ZIEKENHUIS

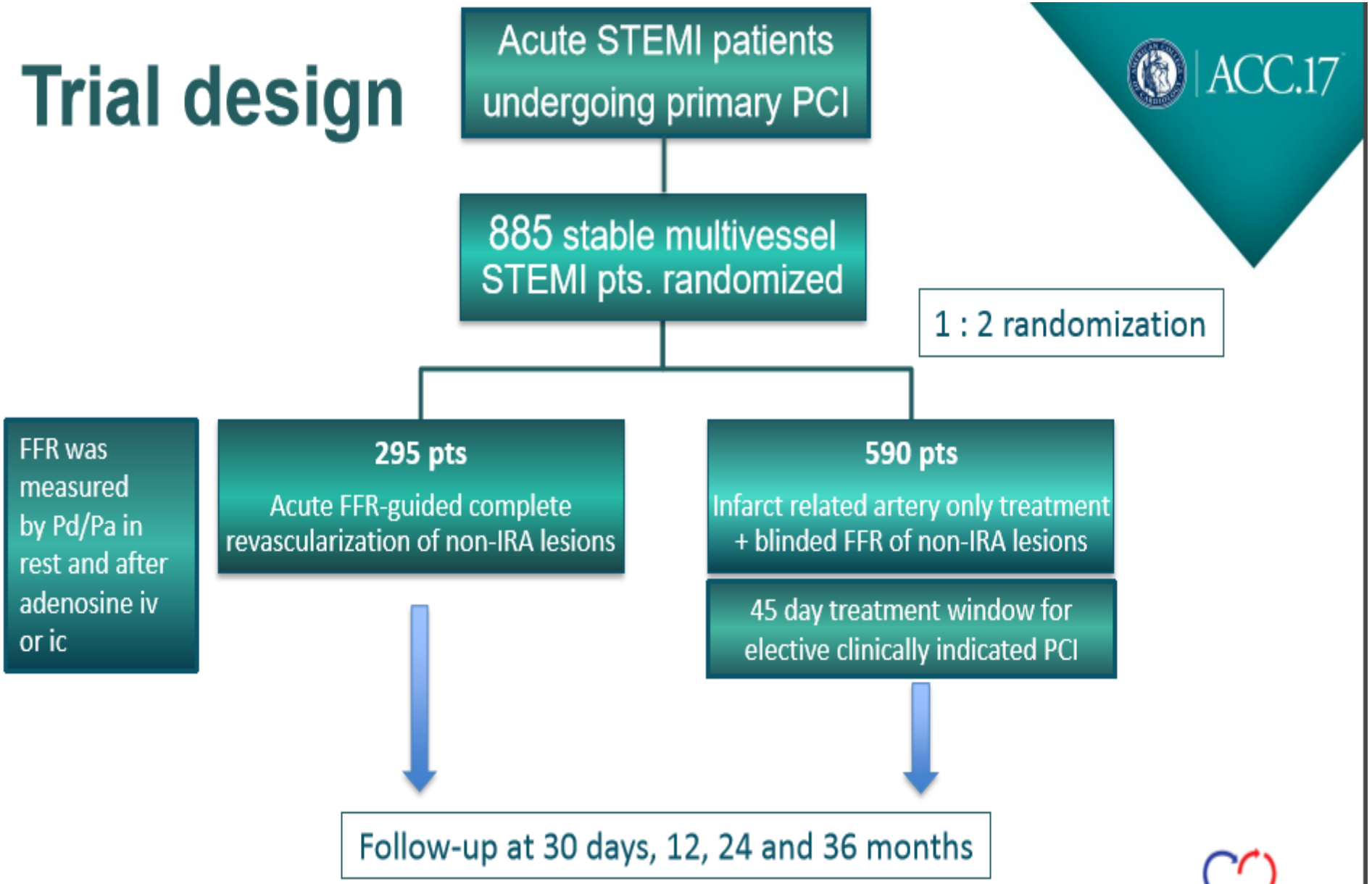
Oklahoma Heart Institute

Introduction

- Approximately 50% of the STEMI patients have multivessel disease at presentation; meaning 50% or more diameter stenosis in one or more non-infarct-related arteries (non-IRAs)

- What and when to do with these non-infarct-related artery (non-IRA) lesions remains a unresolved clinical dilemma

Trial design



ACC.17

Compare Acute

Oklahoma Heart Institute

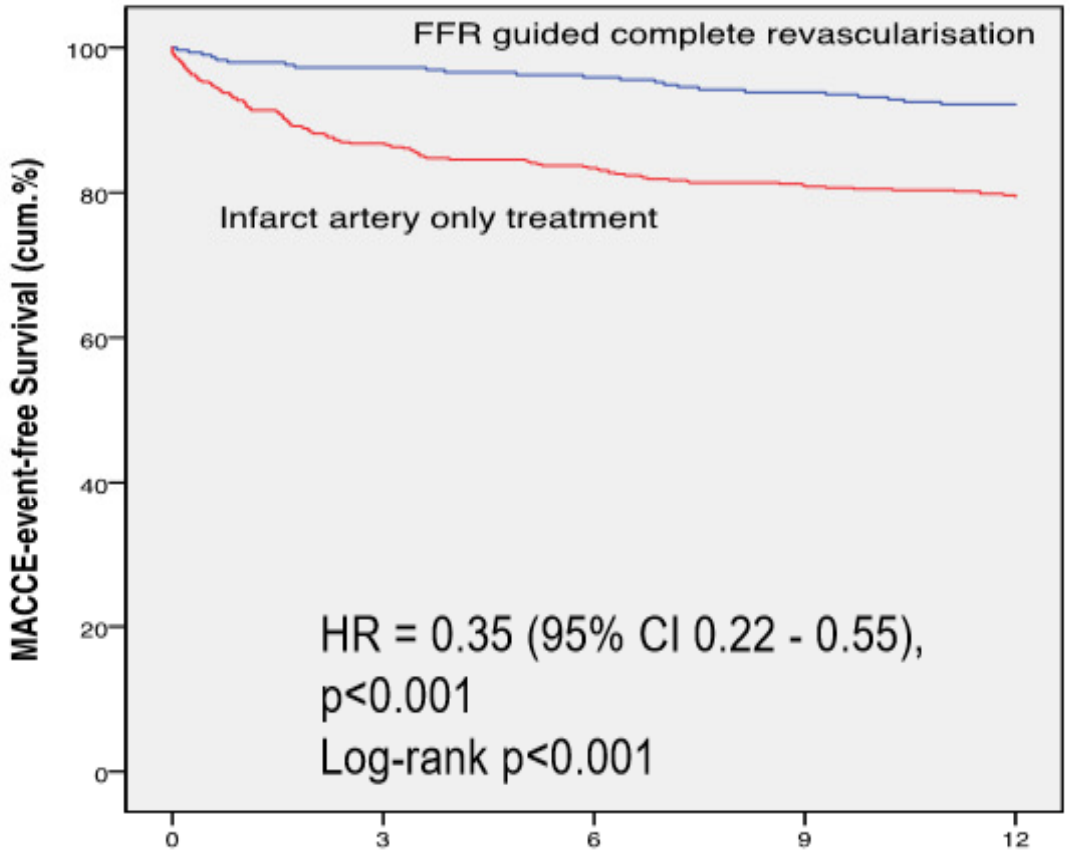
COMPARE ACUTE Trial

Endpoints

Primary endpoint:

The composite of all-cause death, recurrent myocardial infarction, recurrent revascularization and cerebrovascular event (MACCE) at 12 months follow-up

Primary outcome



7.8%

20.5%

No. at risk					
FFR guided complete	295	286	281	264	215
Culprit lesion only	590	512	492	457	371

Compare Acute

Oklahoma Heart Institute

Conclusions

- In multivessel STEMI patients, FFR-guided complete revascularization of non-infarct-related lesions in the acute phase of primary PCI significantly reduced the risk of the composite MACCE outcome as compared with a strategy of treatment of the infarct-related artery only

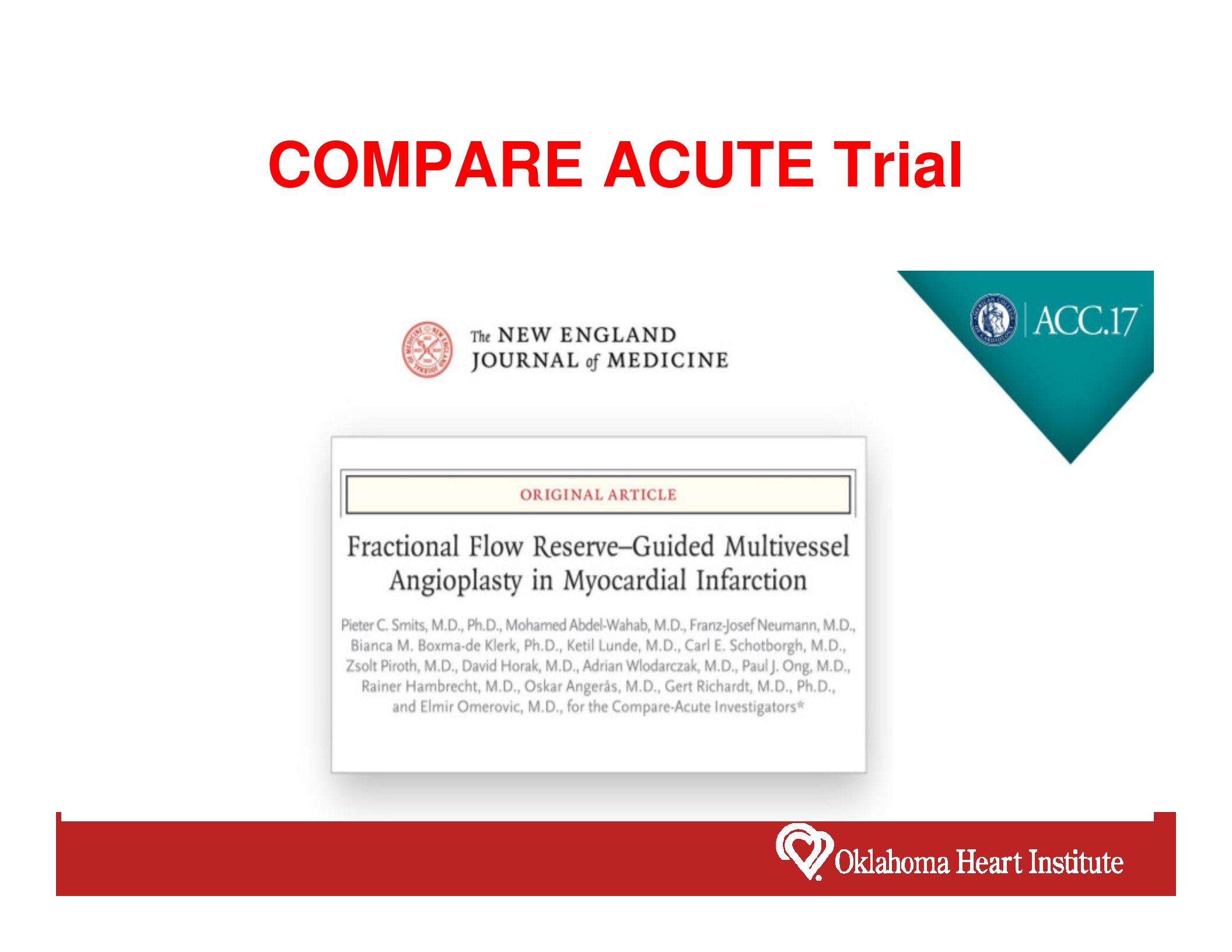
- This reduction was mainly driven by the decreased need for subsequent revascularization

Conclusions

- Approximately half of the lesions in non infarct-related arteries considered significant on coronary angiograms had an FFR value >0.8 and were therefore not physiologically significant

- Deferring treatment of angiographically significant coronary lesions in non-infarct related arteries with an FFR > 0.8 is safe and efficient

COMPARE ACUTE Trial



Late Breaking Clinical Trials: 2017

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