Late-Breaking Clinical Trials and FDA Update

Moderator & Presenter

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Presenters & Discussants

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Late-Breaking Clinical Trials & FDA Update

Obesity

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 3-Year Outcomes

Philip R. Schauer, M.D., Deepak L. Bhatt, M.D., M.P.H., John P. Kirwan, Ph.D., Kathy Wolski, M.P.H., Stacy A. Brethauer, M.D., Sankar D. Navaneethan, M.D., M.P.H., Ali Aminian, M.D., Claire E. Pothier, M.P.H., Esther S.H. Kim, M.D., M.P.H., Steven E. Nissen, M.D., and Sangeeta R. Kashyap, M.D., for the STAMPEDE Investigators*

ABSTRACT

BACKGROUND

In short-term randomized trials (duration, 1 to 2 years), bariatric surgery has been associated with improvement in type 2 diabetes mellitus.

METHODS

We assessed outcomes 3 years after the randomization of 150 obese patients with uncontrolled type 2 diabetes to receive either intensive medical therapy alone or intensive medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy. The primary end point was a glycated hemoglobin level of 6.0% or less.

RESULTS

The mean (±SD) age of the patients at baseline was 48±8 years, 68% were women, the mean baseline glycated hemoglobin level was 9.3±1.5%, and the mean baseline body-mass index (the weight in kilograms divided by the square of the height in meters) was 36.0±3.5. A total of 91% of the patients completed 36 months of follow-up.

From the Bariatric and Metabolic Institute (P.R.S., S.A.B., A.A.), Lerner Research Institute (J.P.K.), Heart and Vascular Institute (K.W., C.E.P., E.S.H.K., S.E.N.), Urological and Kidney Institute (S.D.N.), and Endocrinology Institute (S.R.K.), Cleveland Clinic, Cleveland; and Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School — both in Boston (D.L.B.). Address reprint requests to Dr. Schauer at the Bariatric and Metabolic Institute, Cleveland Clinic, M61, 9500 Euclid Ave., Cleveland, OH 44195, or at schauep@ccf.org.

*The contributions of the authors and committee members in the Surgical Treatment and Medications Potentially Eradi-

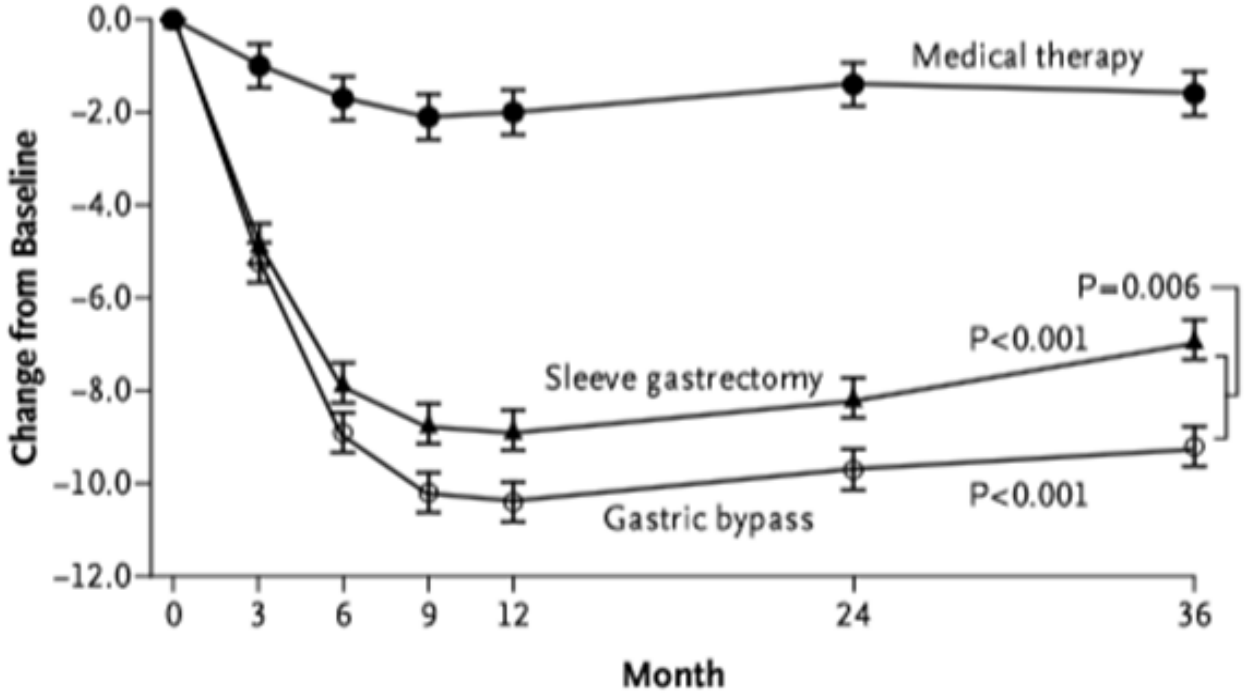
Schauer et al. NEJM 2014;370:2002-13.

STAMPEDE: Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently

- **Primary Objective – To assess outcomes 3 years after the randomization of patients with uncontrolled T2DM (*A1c 9.3 ± 1.5%)* to either intensive medical therapy alone or intensive medical therapy + Roux-en-Y gastric bypass or sleeve gastrectomy.**
  - n = 150 men (34%) and women (66%) at the Cleveland Clinic
  - Age: 48 ± 8 years
  - BMI: 36.0 ± 3.0 kg/m2
  - Primary endpoint: A1c of ≤ 6.0%
  - Secondary outcomes – many

Schauer et al. NEJM 2014;370:2002-13.

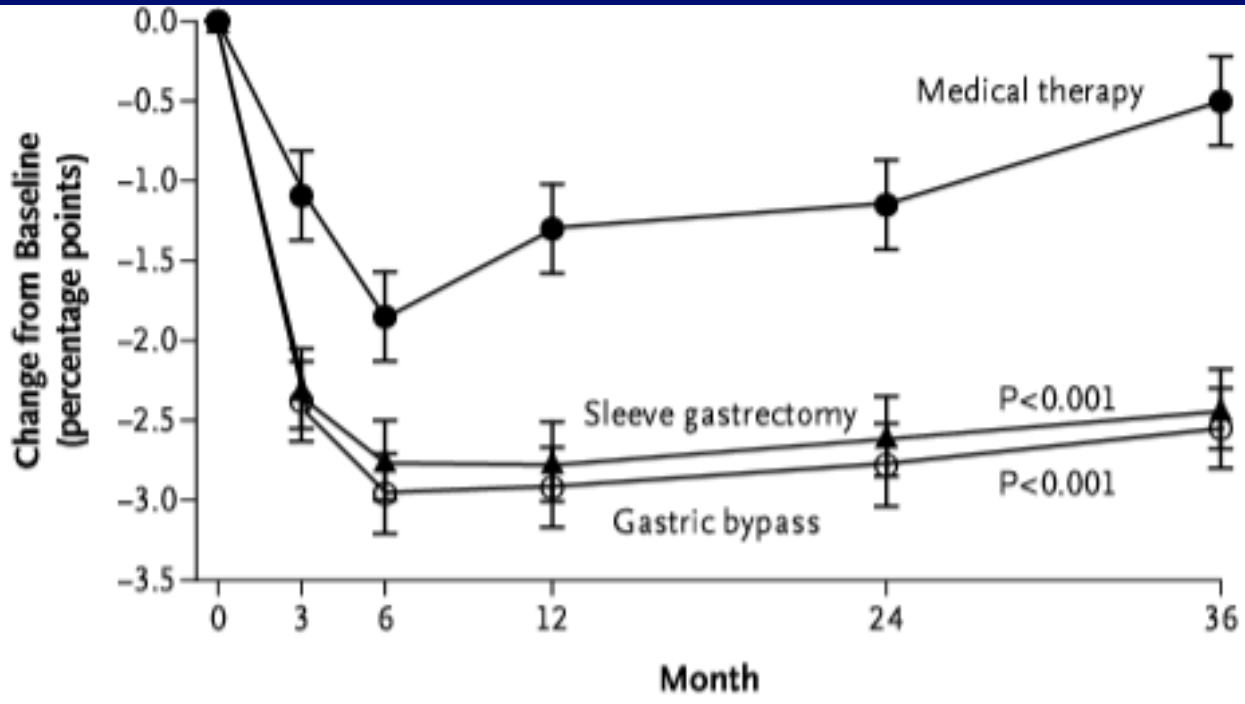
STAMPEDE: Effect of Surgery vs. Medical Management of T2DM on BMI



Value at Visit					
Medical therapy	36.4	34.6	34.2	35.0	34.8
Sleeve gastrectomy	36.1	28.3	27.1	27.9	29.2
Gastric bypass	37.1	28.2	26.7	27.3	27.9

Schauer et al. NEJM 2014;370:2002-13.

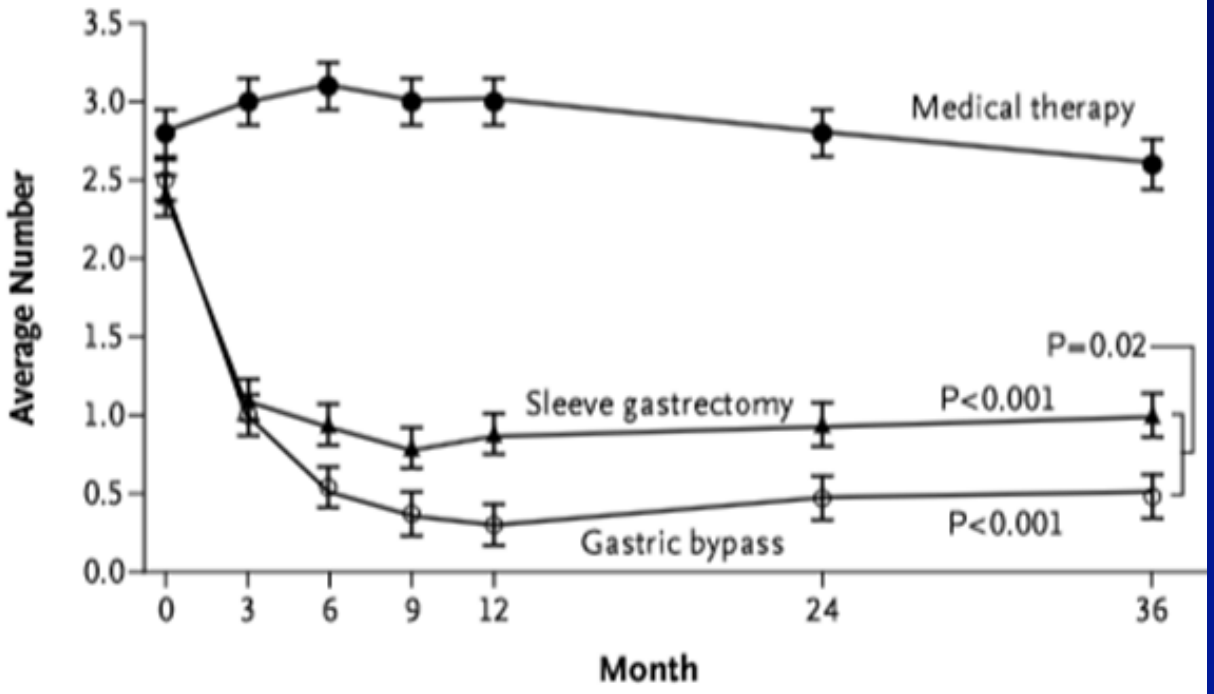
STAMPEDE: Effect of Surgery vs. Medical Management of T2DM on A1c



Value at Visit					
Medical therapy	9.0 (8.5)	7.1 (6.8)	7.5 (6.9)	7.7 (7.3)	8.4 (7.6)
Sleeve gastrectomy	9.5 (8.9)	6.7 (6.4)	6.6 (6.4)	6.8 (6.8)	7.0 (6.6)
Gastric bypass	9.3 (9.2)	6.3 (6.2)	6.3 (6.1)	6.5 (6.4)	6.7 (6.6)

Schauer et al. NEJM 2014;370:2002-13.

STAMPEDE: Effect of Surgery vs. Medical Management of T2DM on Medications



Value at Visit					
Medical therapy	2.8	3.1	3.0	2.8	2.6
Sleeve gastrectomy	2.4	0.94	0.88	0.94	1.0
Gastric bypass	2.5	0.54	0.3	0.47	0.48

Schauer et al. NEJM 2014;370:2002-13.

Anti-Obesity Drugs Currently Approved and Pending Approval

FDA-Approved Drug	Company	Mechanism of Action	Comments
Phentermine (Adipex, Suprenza)	Gates, Alpex	Noradrenaline/dopamine releasing stimulator	Schedule IV drug, approved 1973 for short-term use
Orlistat (Xenical) (Alli -OTC)	Roche, GSK	Pancreatic lipase inhibitor	Approved for long-term use in 1999
Phentermine/Topiramate (Qysmia) *(formerly Qnexa)*	Vivus	Noradrenaline releasing + modulator of ɣ aminobutyric acid (GABA)/ carbonic anhydrase inhibition	Approved July 2012
Lorcaserin (Belviq)	Arena Pharma	Selective 5-HT_{2C} receptor agonist	Approved June 2012
Bupropion/Naltrexone (Contrave) New!	Orexigen	Inhibitor of dopamine and noradrenaline reuptake + μ opiate antagonist	Approved September 2014
Anti-obesity Drug Pending Final Approval			
Liraglutide PENDING	Novo Nordisk	GLP-1 agonist	Approved January 2010 for treatment of Type 2 DM; phase III for anti-obesity at higher doses Recommended for FDA Approval September 2014. Final decision is expected by Oct. 20

Modified from Zhang, Wang. Acta Pharmacologica Sinica. 2012;33:145-7.

Novel Approaches to Weight Loss

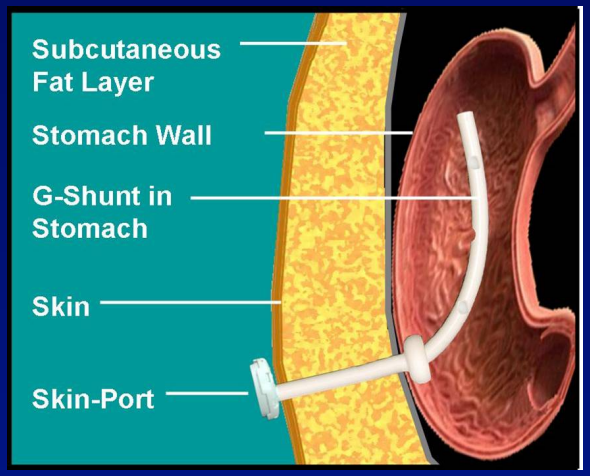
- Gastric aspiration
- Endoluminal barrier
- Gastric balloon
- Transoral gastric suturing

Novel Approaches to Weight Loss

- Gastric aspiration

Aspiration Therapy Overview

- A-shunt® implantation-outpatient 15-min endoscopic procedure, no general anesthesia
- 30 years experience with PEG tubes; 250,000/yr
- Provides "portion control" at the stomach
- Easy, aspirate stomach contents ~20-min after meal-takes ~ 5-10 minutes
- Removes 25%-30% of consumed calories
- **Lowers threshold for achieving successful weight loss, which empowers patients**
- Provides safe, gradual, and controlled weight loss, with the patient "in control"
- Counting device has limited number of aspiration cycles (115), forcing patient back to physician
- Reversible; does not preclude bariatric surgery



Clinical Experience Overview

- Three trials to date, total of 24 obese patients (BMI 35.5-48.6 kg/m2) treated with Aspiration Therapy:
  - 3 in proof-of-principle trial in the US
  - 10 in pilot trial in Mexico
  - 11 in ongoing randomized controlled feasibility trial in the US
- Safety confirmed by all three trials
  - Careful monitoring for electrolytes, kidney and liver function, vitamins, etc.
  - Only serious adverse event reported: buried bumper
- Efficacy confirmed by all three trials
  - Percent of patients** losing ≥25% excess weight loss (EWL*) at 52 wks = 94% (50% is FDA guideline)
  - Mean** %EWL* at 52 wks = 49.8% (25% is FDA guideline)
  - Mean** %WL at 52 weeks = 18.6%

US Pilot Study

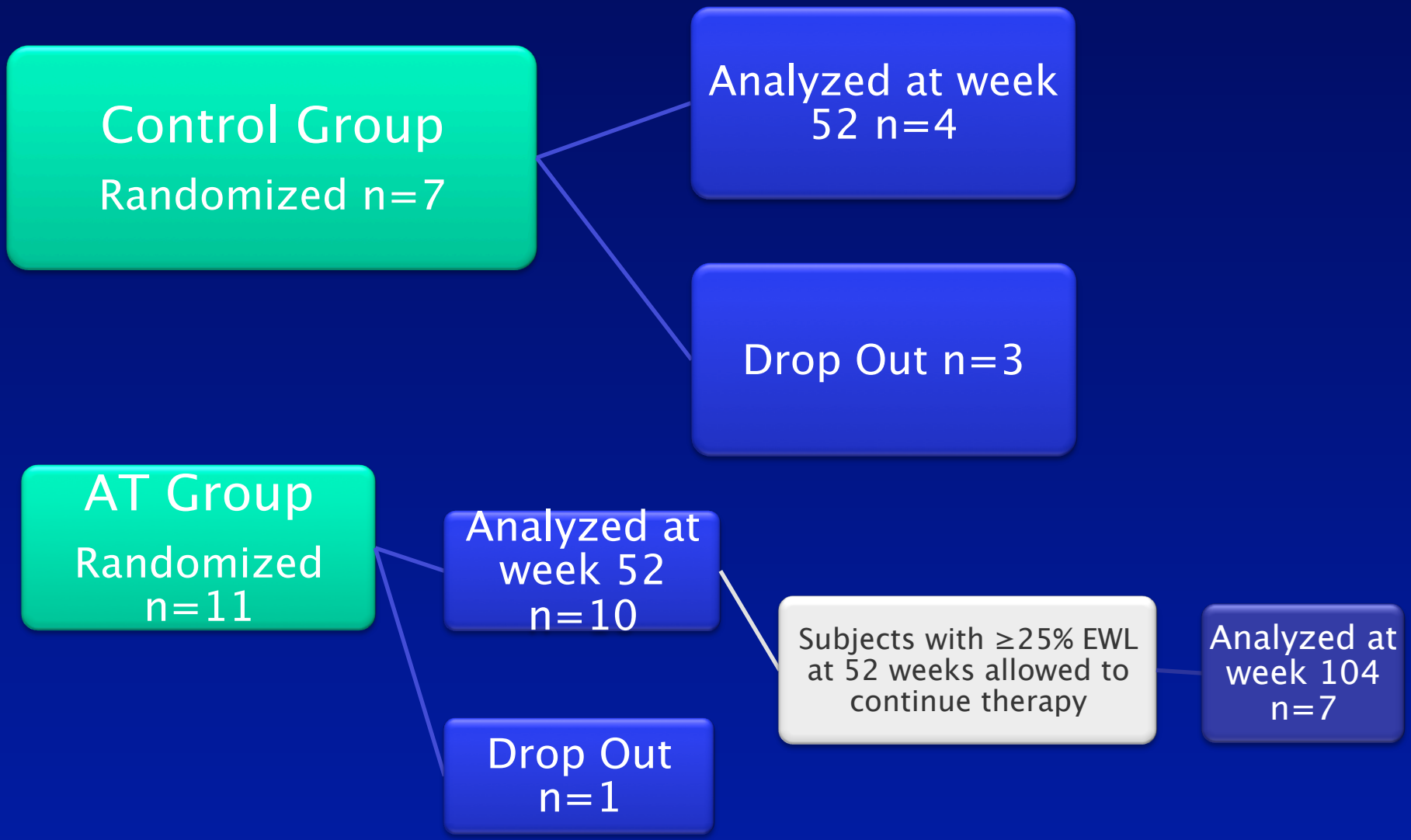
Control Group (12 months)

- 15-session diet and behavioral weight loss program
- Two Town Hall Meetings
- Multivitamin & mineral supplement

AT Group

- A-Tube placed endoscopically
- Tube conversion at 10-14 days post placement
- Subjects instructed on aspiration procedure
- Proton pump inhibitor & potassium
- 15-session diet and behavioral weight loss program
- Two Town Hall meetings
- Multivitamin & mineral supplement

US Pilot Study



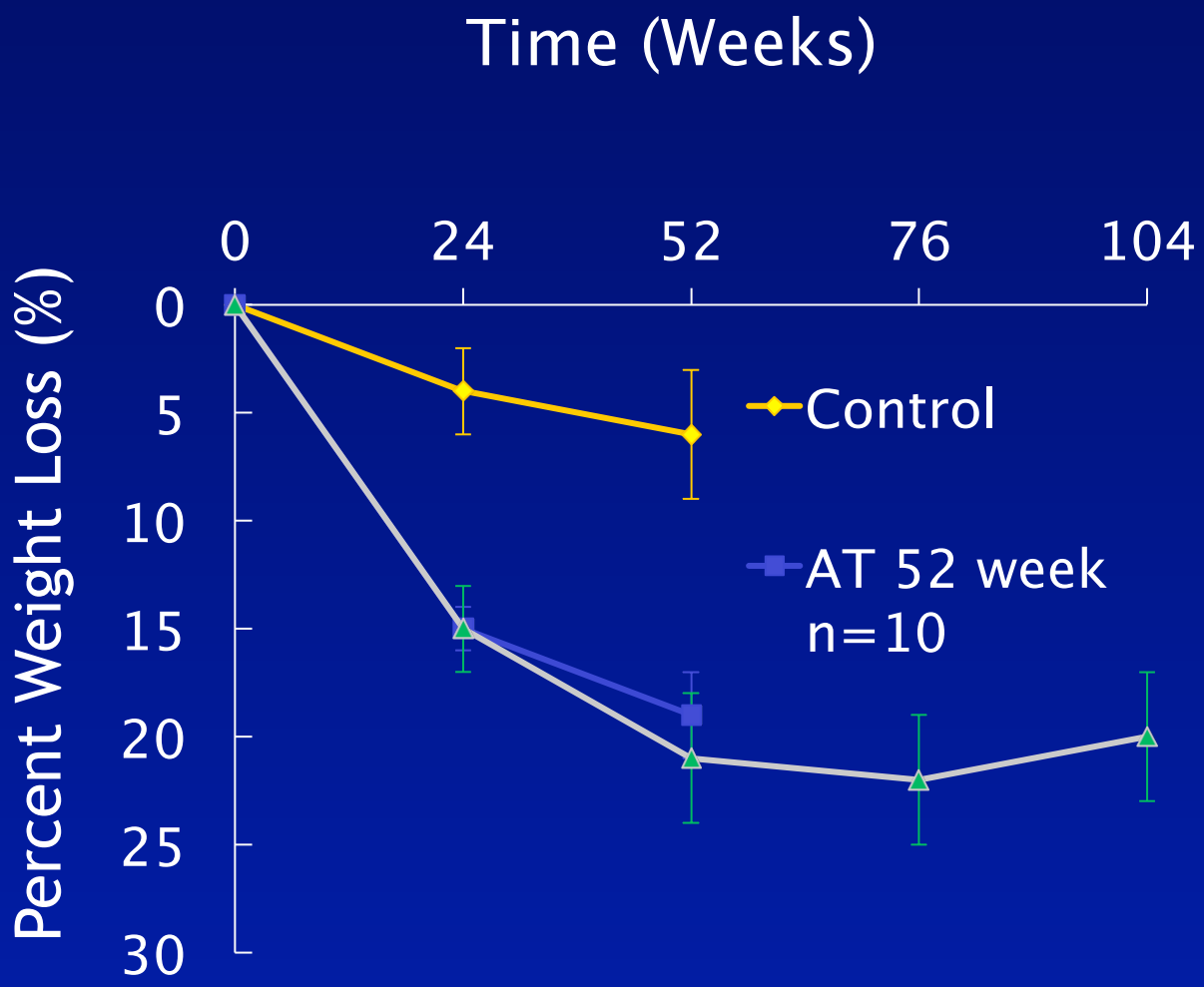
Baseline Characteristics

	Control Group	AT Group
Number (M/F)	4 (1/3)	10 (0/10)
Age (years)	45.3 ± 2.8	38.7 ± 2.3
Weight (kg)	105.3 ± 2.5	112.2 ± 4.6
BMI (kg/m^2)	39.3 ± 1.1	42.0 ± 1.4
Glucose (mg/dL)	86.8 ± 3.4	83.9 ± 1.9
HDL-C (mg/dL)	48.5 ± 4.1	53.6 ± 2.9
LDL-C (mg/dL)	116.0 ± 13.0	112.8 ± 6.9
Triglycerides (mg/dL)	139.3 ± 12.8	113.4 ± 18.8
ALT (IU/L)	26.8 ± 7.3	20.6 ± 2.6
Systolic BP (mmHg)	121.8 ± 6.4	125.8 ± 3.5
Diastolic BP (mmHg)	80.5 ± 3.4	82.6 ± 1.2

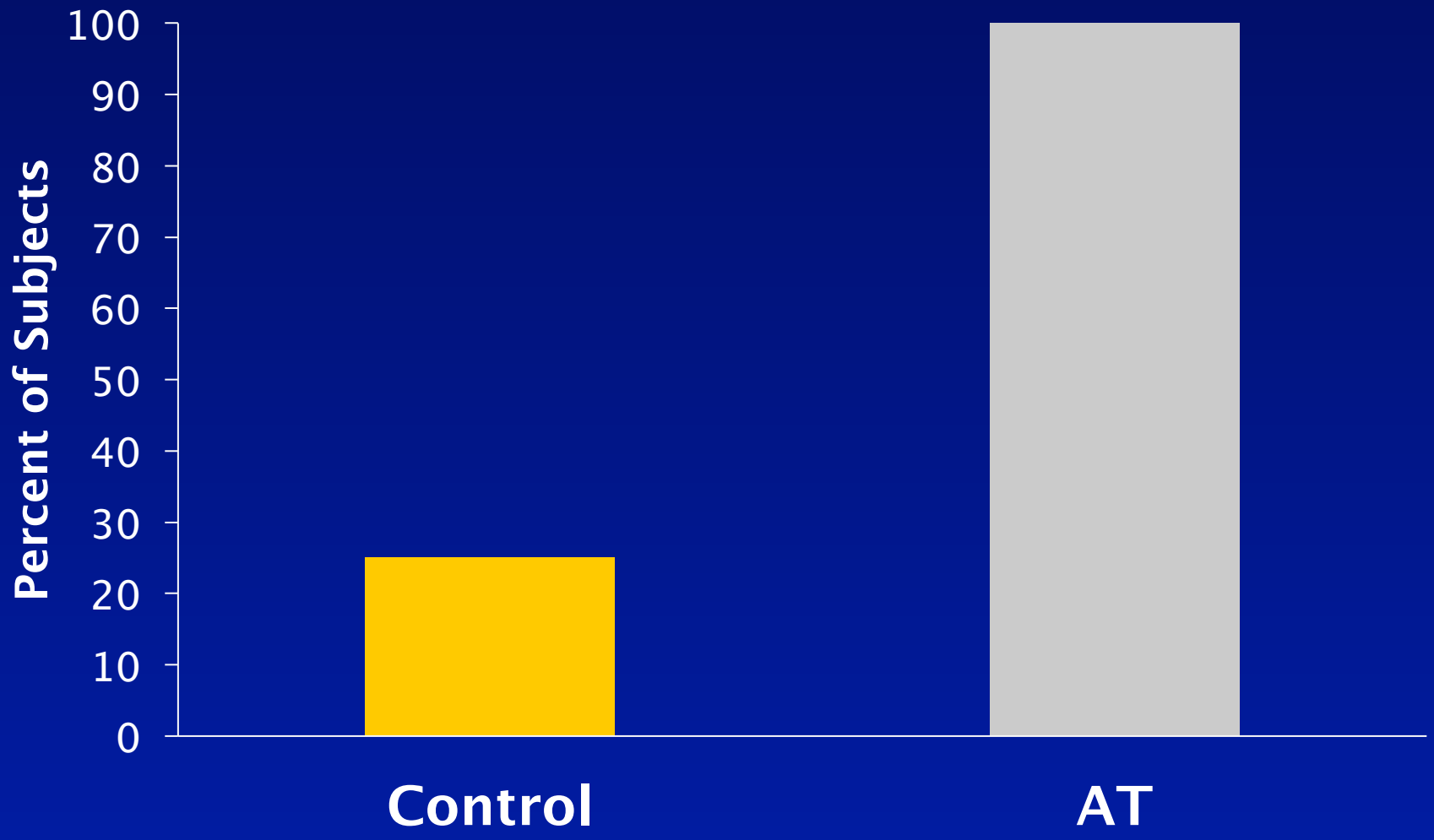
Aspiration Characteristics

Meal	Number of tests	Gastric Aspirate (gm)	Percent of Ingested Calories Aspirated	Aspiration Time (min)
450 kcal, 20 minute wait	6	1747 ± 186	29 ± 4	10.1 ± 1.1
450 kcal, 60 min wait	6	1761 ± 196	18 ± 3	8.5 ± 1.2
800 kcal, 20 min wait	7	2080 ± 240	28 ± 4	9.9 ± 1.1
800 kcal, 60 min wait	7	2034 ± 200	27 ± 5	8.4 ± 1.1

Effect of Aspiration Therapy on Body Weight

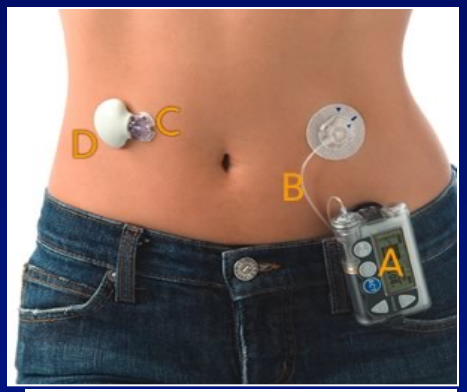


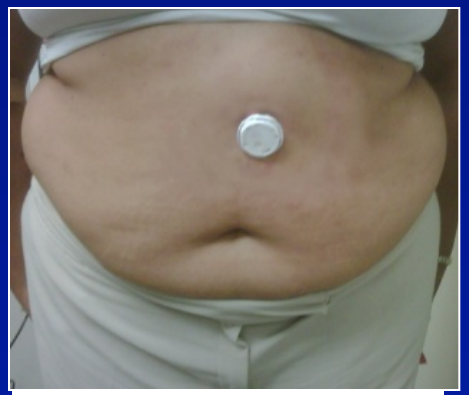
Percent of Subjects Who Achieved ≥25% EWL at Week 52



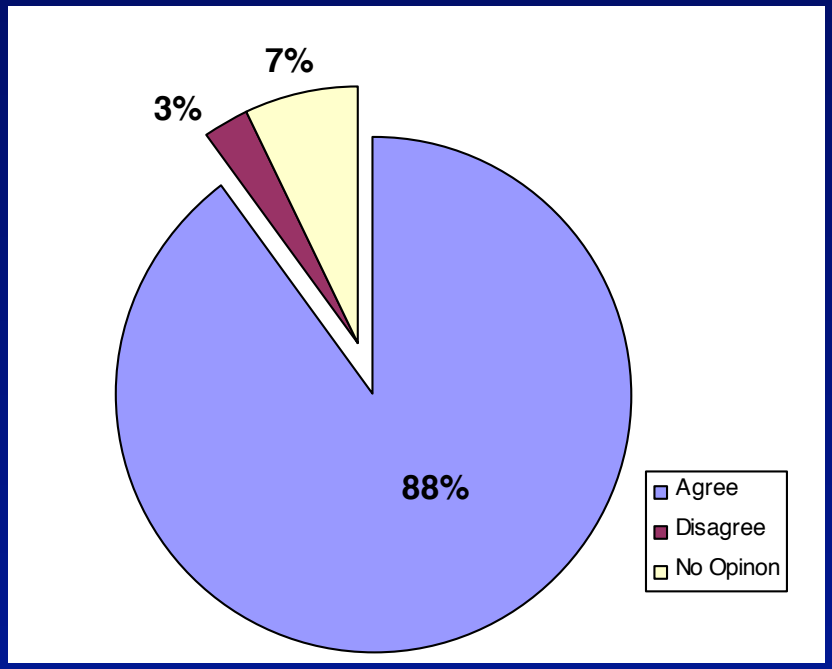
Patient Acceptance

- **AT overwhelmingly accepted by patients**
  - Able to eat normally
  - Minimal invasiveness
  - Reversibility and no anatomical rearrangement
  - No general anesthesia
  - Discreet/Private
  - Clear mechanism of action
- **Some people dislike having an object attached to their abdomen**
- **Some people fear criticism of therapy**
- **Family acceptance increased over time after weight loss was achieved**

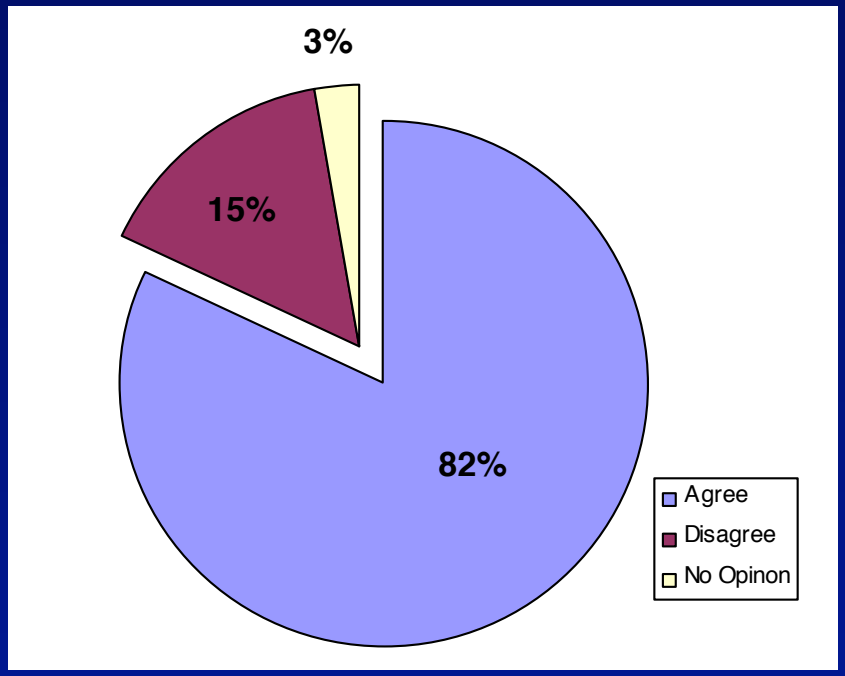




Acceptability of AspireAssist™



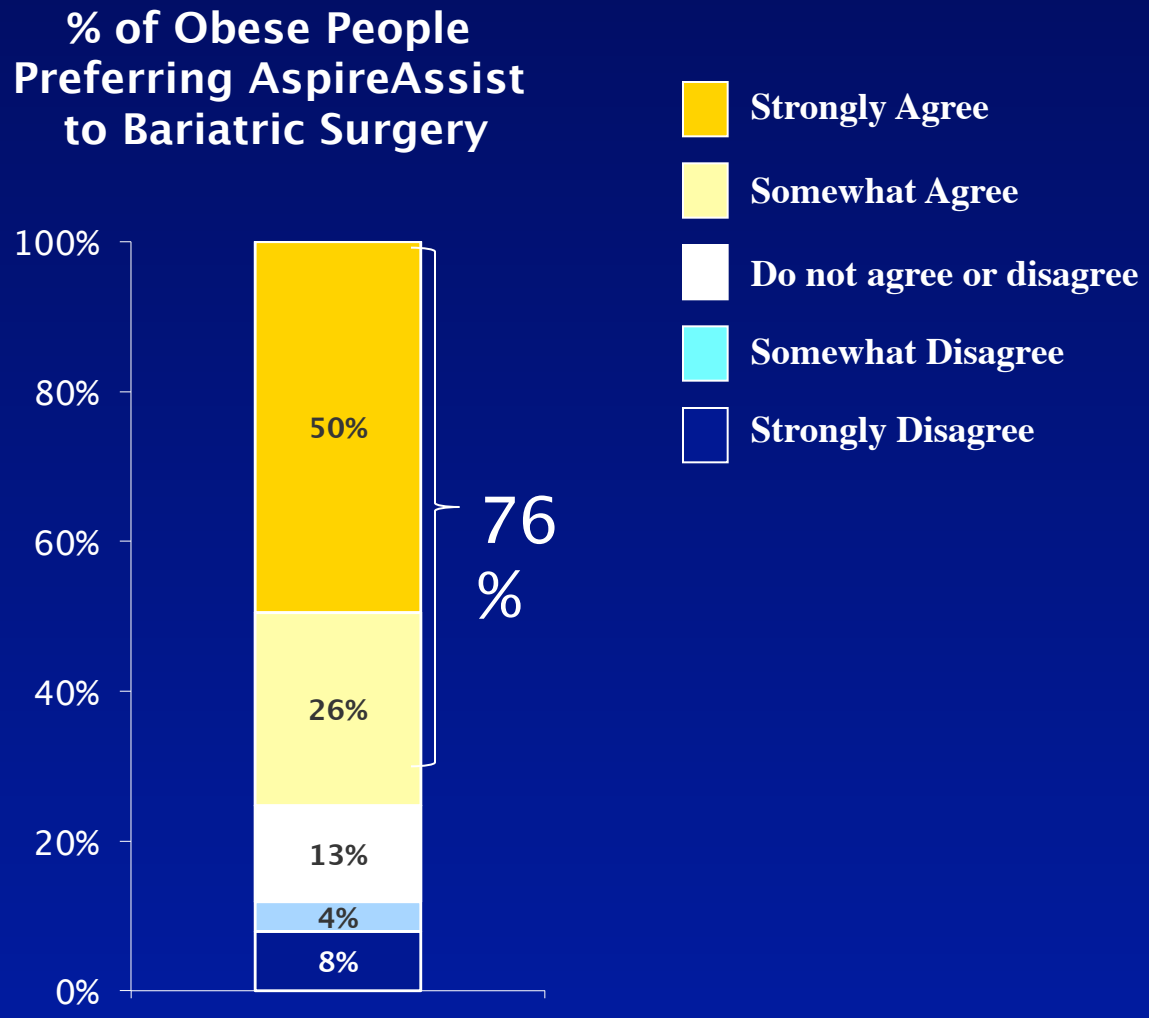
Believe AT will help achieve weight loss



Want to participate in clinical trial

Anonymous survey obtained after Information session in obese people (N=78) interested in weight loss studies

AspireAssist™ vs. Bariatric Surgery



Anonymous survey obtained after Information session in obese people (N=78) interested in weight loss studies


Thank You!

Late-Breaking Clinical Trials & FDA Update

Diabetes Update

Jay S. Skyler, MD, MACP
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University of Miami Miller School of Medicine
Deputy Director for Clinical & Academic Programs
Diabetes Research Institute
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FDA Diabetes Approvals 2014

Once Weekly GLP-1s

- Albiglutide
- Dulaglutide

SGLT2s

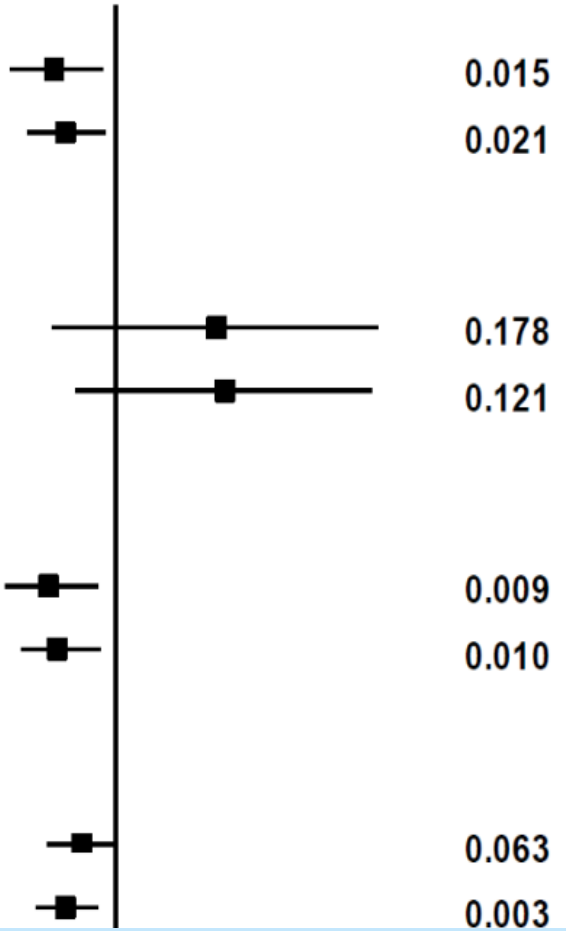
- Dapagliflozin
- Empagliflozin

Insulin

- Human Insulin Inhalation Powder

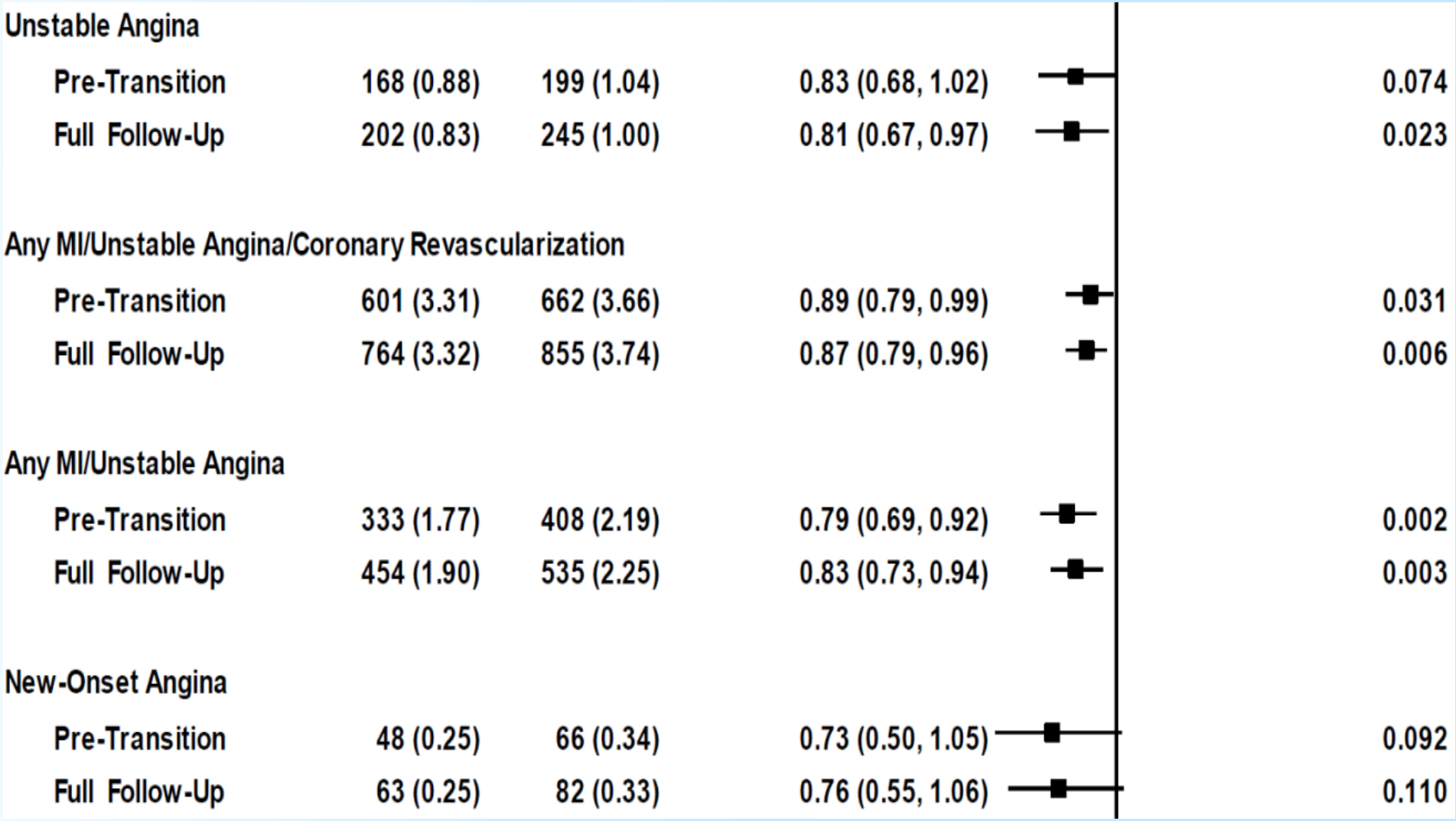
ACCORD: Glycemia and Ischemic Heart Disease

Outcome	# Events (% Annual Incidence) Intensive	Standard	Intensive to Standard Hazard Ratio (95% CI)	P Value
Fatal or Nonfatal MI				
Pre-Transition	220 (1.15)	267 (1.41)	0.80 (0.67, 0.96)	0.015
Full Follow-Up	304 (1.25)	355 (1.46)	0.84 (0.72, 0.97)	0.021
Fatal MI				
Pre-Transition	20 (0.10)	12 (0.06)	1.63 (0.80, 3.32)	0.178
Full Follow-Up	24 (0.09)	14 (0.05)	1.68 (0.87, 3.24)	0.121
Nonfatal MI				
Pre-Transition	207 (1.08)	257 (1.35)	0.78 (0.65, 0.94)	0.009
Full Follow-Up	287 (1.18)	344 (1.42)	0.81 (0.70, 0.95)	0.010
Coronary Revascularization				
Pre-Transition	469 (2.54)	517 (2.81)	0.89 (0.78, 1.01)	0.063
Full Follow-Up	565 (2.41)	658 (2.81)	0.84 (0.75, 0.94)	0.003



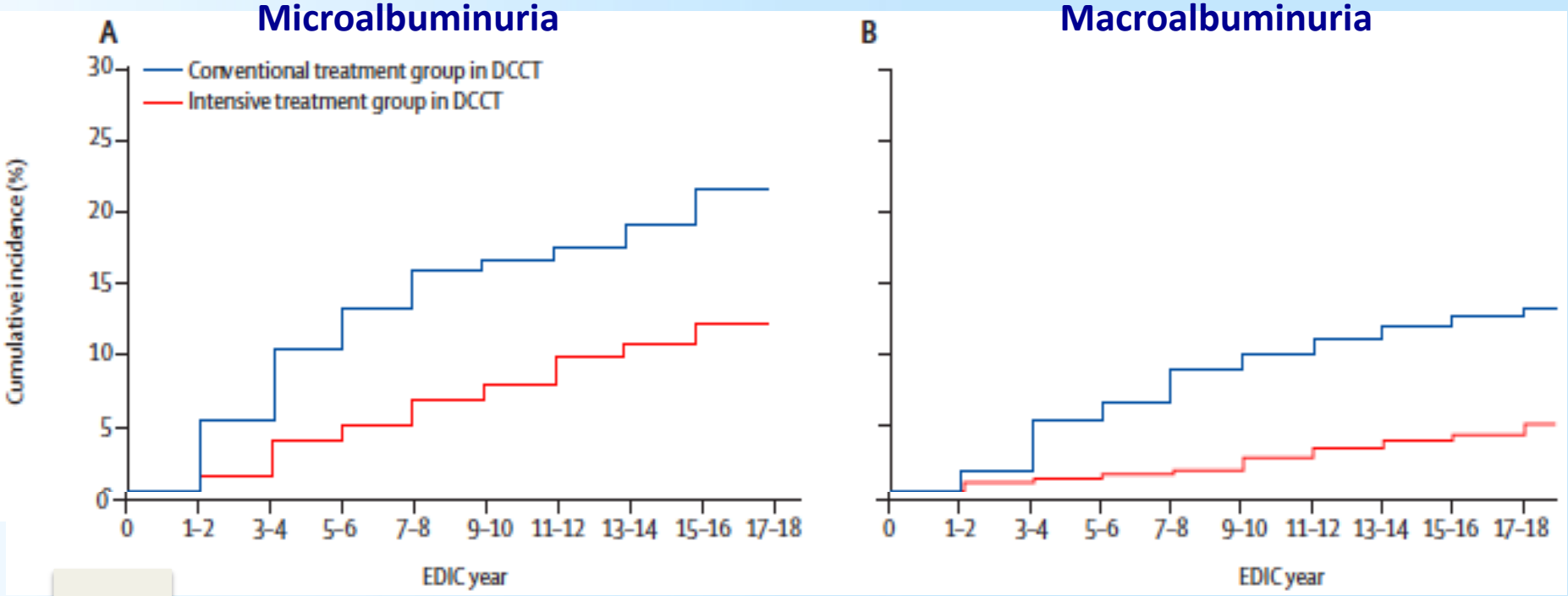
Gerstein et al. Lancet 2014 Jul 31. doi: 10.1016/S0140-6736(14)60611-5.

ACCORD: Glycemia and Ischemic Heart Disease



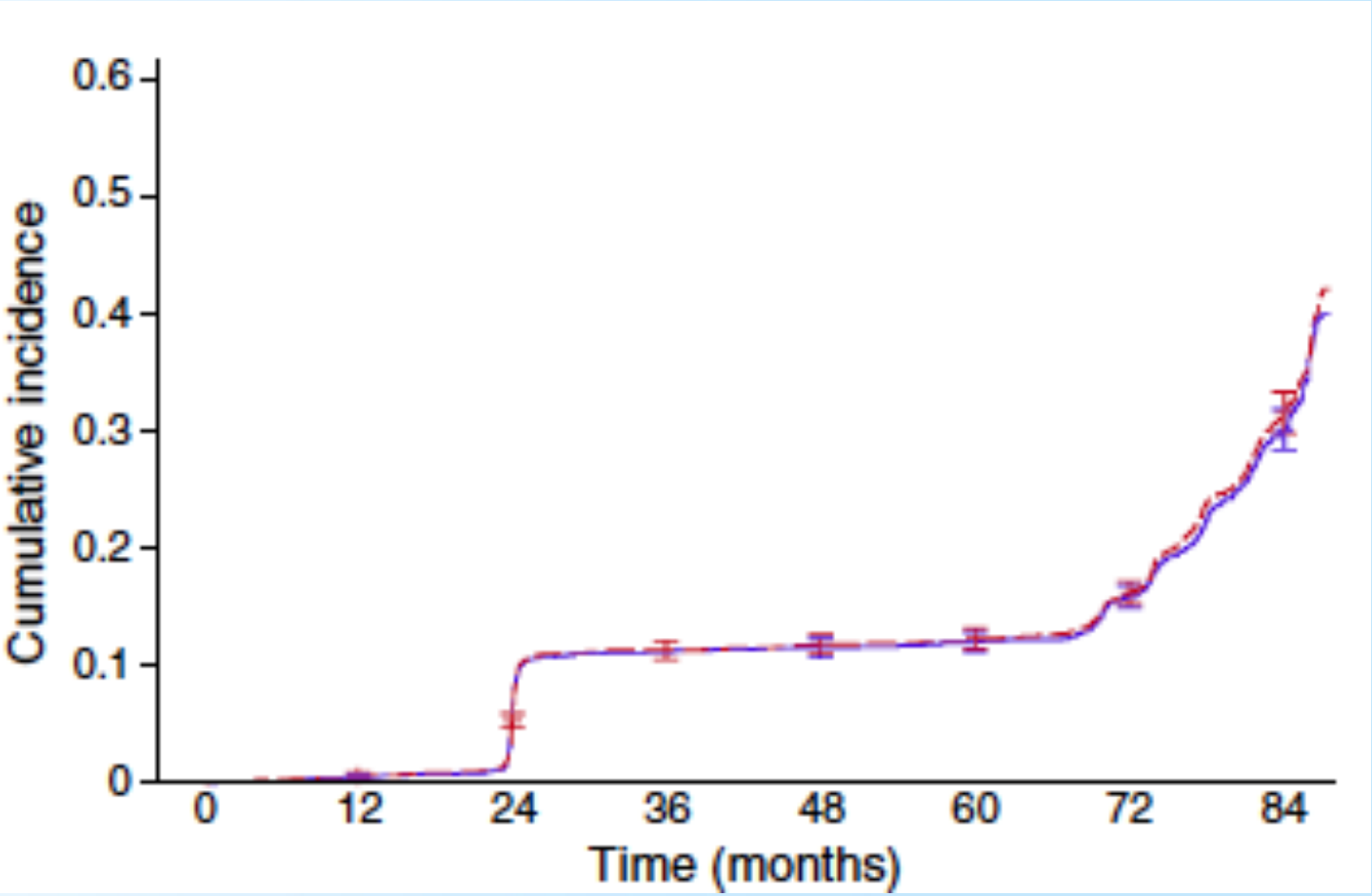
Gerstein et al. Lancet 2014 Jul 31. doi: 10.1016/S0140-6736(14)60611-5.

DCCT/EDIC – Long-Term Effects on Albuminuria



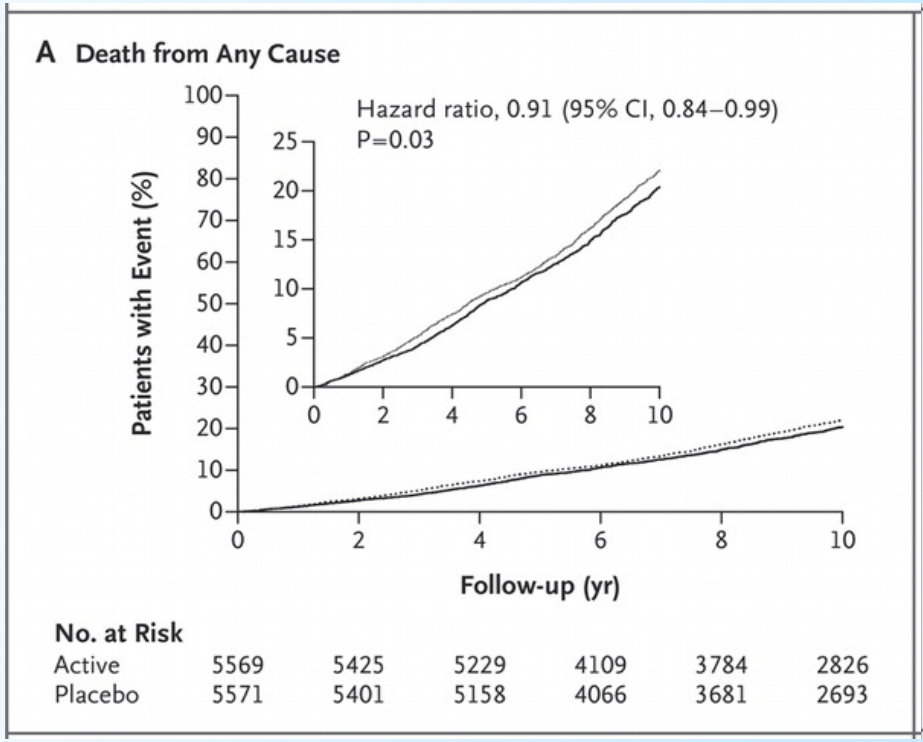
de Boer et al. Lancet Diabetes Endocrinol 2014. doi: 10.1016/S2213-8587(14)70155-X.

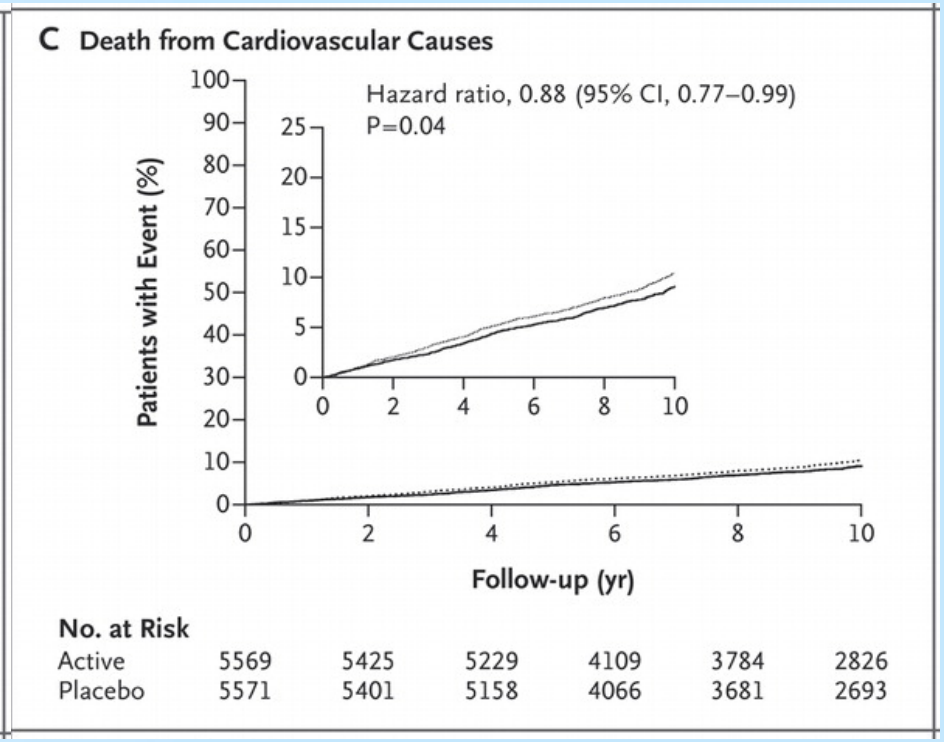
ORIGIN – Microvascular Outcomes



Gilbert et al. Diabetologia 2014; 57: 1325-31.

ADVANCE: Long-Term Effects of Blood Pressure

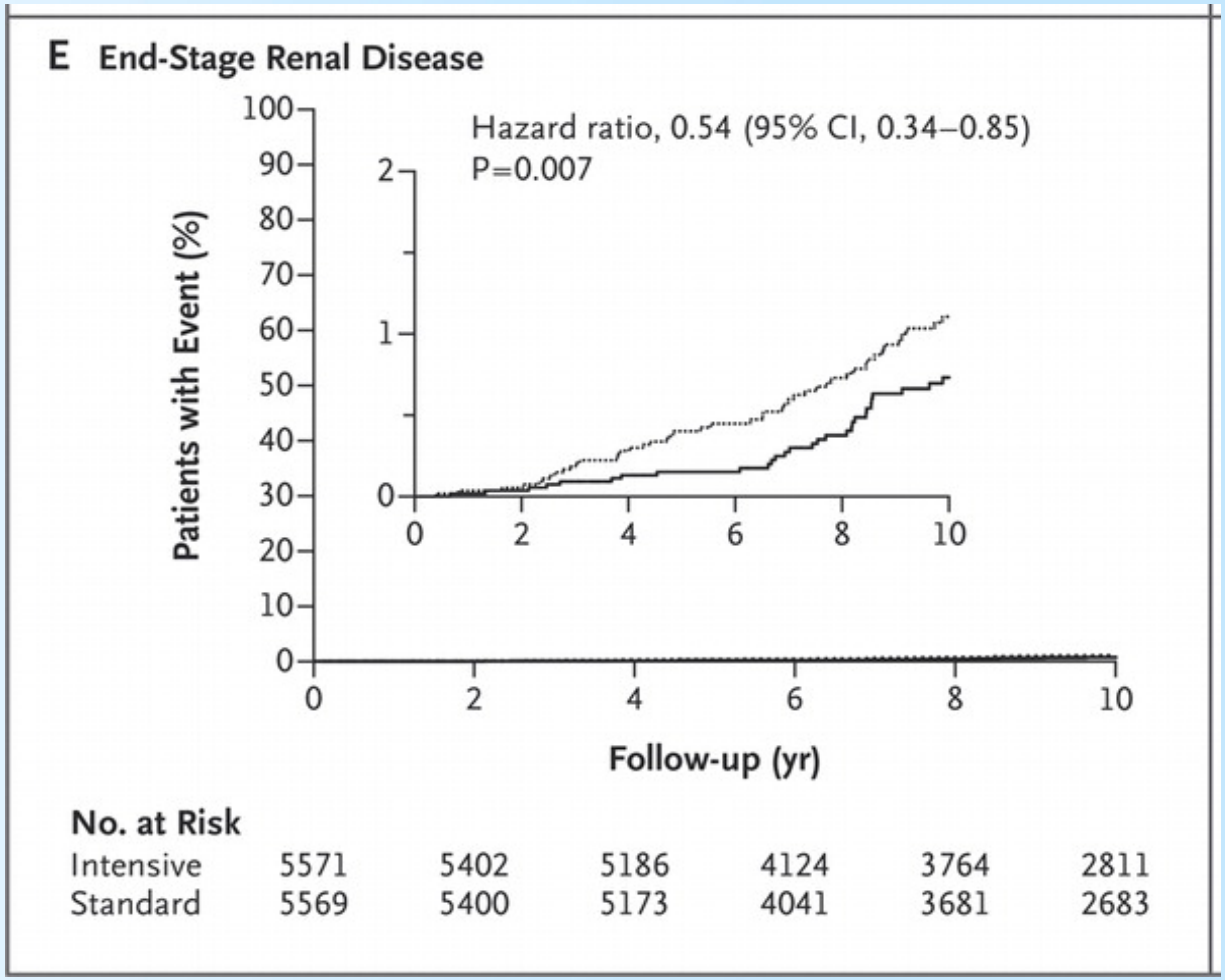




Cumulative Incidence of Events, According to Blood-Pressure–Lowering Study Group

Zoungas et al N Engl J Med 2014; Sep 19. [Epub ahead of print]

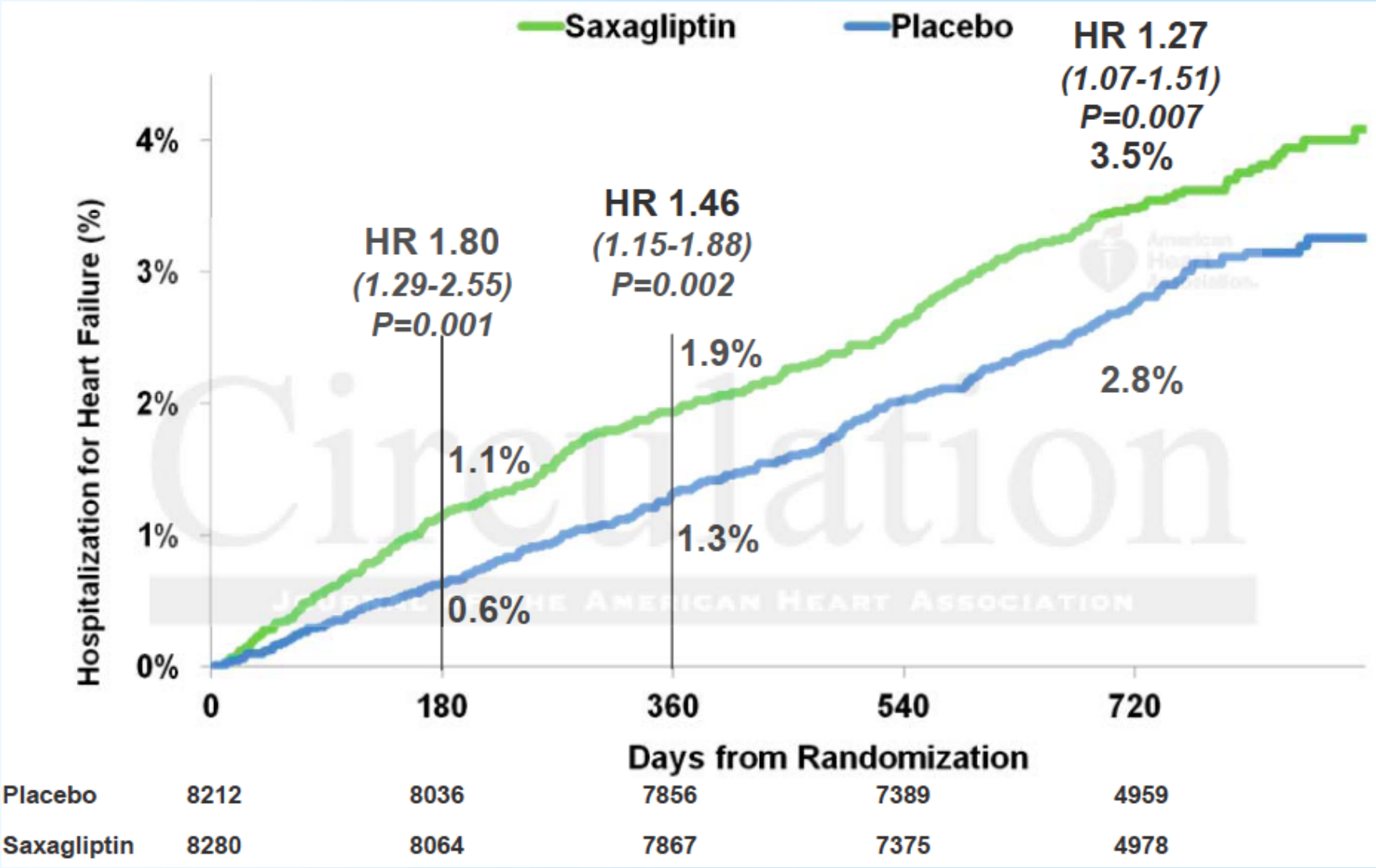
ADVANCE: Long-Term Effects of Glycemia



Cumulative Incidence of Events, According to Glucose-Control Study Group.

Zoungas et al N Engl J Med 2014; Sep 19. [Epub ahead of print]

SAVOR – Hospitalization for Heart Failure



Scirica et al. Circulation 2014; Sep 4. pii: CIRCULATIONAHA.114.010389. [Epub ahead of print]

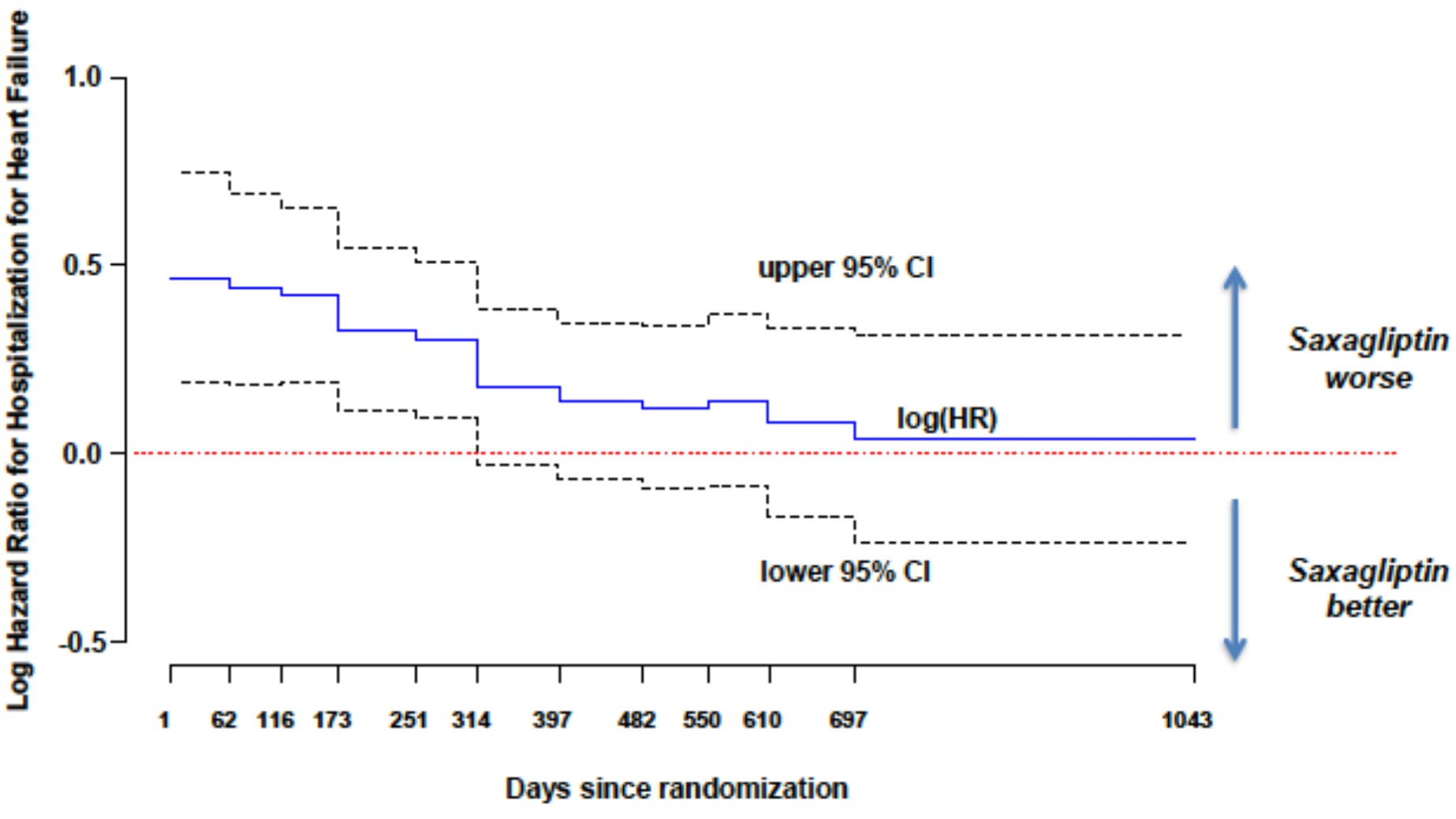
SAVOR – Hospitalization for Heart Failure

Increased risk highest among those with:

- **elevated levels of natriuretic peptide**
- **prior heart failure**
- **chronic kidney disease**

Scirica et al. Circulation 2014; Sep 4. pii: CIRCULATIONAHA.114.010389. [Epub ahead of print]

SAVOR – Hospitalization for Heart Failure



Scirica et al. Circulation 2014; Sep 4. pii: CIRCULATIONAHA.114.010389. [Epub ahead of print]

EXAMINE –Heart Failure

	Alogliptin	Placebo	HR	95% CI
Composite including HHF			0.98	0.86-1.12
HHF within composite	3.1%	2.9%	1.07	0.79-1.46
Post hoc CV death + HHF			0.98	0.82-1.21
CV death	3.5%	4.2%	0.84	0.64-1.10
HHF	3.9%	3.3%	1.19	0.90-1.58

Zannad et al. ACC 2014; Abstract 249

HHF=hospitalized heart failure

Late-Breaking Clinical Trials & FDA Update

Hypertension

Keith C. Ferdinand, MD
Professor of Clinical Medicine
Tulane University School of Medicine
New Orleans, Louisiana

FDA Review of CV Risks for Diabetics Taking HTN Drug Olmesartan: 6/24/14

FDA Drug Safety Communication: FDA review of cardiovascular risks for diabetics taking hypertension drug olmesartan not conclusive; label updates required

This information is in follow-up to the FDA Drug Safety Communication: Safety Review Update of Benicar (olmesartan) and cardiovascular events **[LINK TO http://www.fda.gov/Drugs/DrugSafety/ucm251268.htm]**

Safety Announcement

[6-24-2014] The U.S. Food and Drug Administration (FDA) has completed its safety review and has found no clear evidence of increased cardiovascular risks associated with use of the blood pressure medication olmesartan in diabetic patients. As a result, our recommendations for use of olmesartan (Benicar, Benicar HCT, Azor, Tribenzor, and generics) will remain the same, but we will require information about some of the studies to be included in the drug labels. Patients should discuss any questions they have with their health care professionals.

FDA Review CV Risks: Diabetics Taking Olmesartan (OLM)

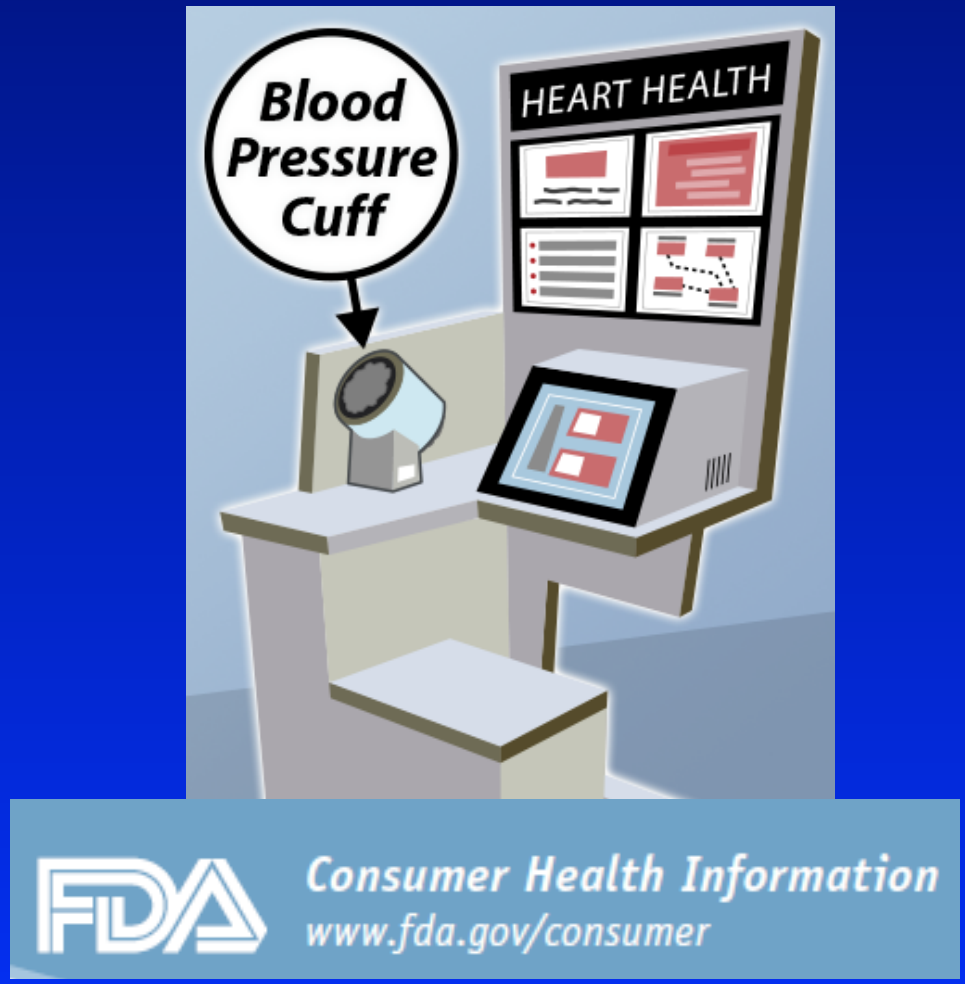
- ROADMAP (**R**andomized **O**lmesartan and **D**iabetes **M**icroalbuminuria **P**reventio n) unexpected finding of ↑risk of CV death. However, risk of non-fatal MI lower with OLM
- Also a large epidemiologic Medicare study suggested that high-dose OLM may ↑CV risk
- Data from all trials and studies not conclusive

http://www.fda.gov/downloads/Drugs/DrugSafety/UCM402339.pdf

FDA Review CV Risks: Diabetics Taking Olmesartan

- No clear evidence of ↑ CV risks associated with use of the BP medication OLM in diabetic patients
- FDA does not support changing recommendations for OLM use -- and
- Does not support recommending that its use be avoided in patients with diabetes.

FDA: Blood Pressure Monitoring Kiosks Aren't for Everyone



http://www.fda.gov/forconsumers/consumerupdates/ucm402287.htm

FDA Warns BP Kiosks May Not Show Correct Results

- BP kiosks available in public places such as pharmacies and grocery stores may not show accurate results
- Cuff is too small or too large.
- "They are easily accessible and easy to use. But it's misleading to think that the devices are appropriate for everybody. They are not one-size-fits-all."

Original Investigation

Hypertension, Antihypertensive Medication Use, and Risk of Psoriasis

JAMA Dermatol. July 2,2014

Shaowei Wu, MD, PhD; Jiali Han, PhD; Wen-Qing Li, MD, PhD; Abrar A. Qureshi, MD, MPH

IMPORTANCE Individuals with psoriasis have an elevated risk of hypertension, and antihypertensive medications, especially β-blockers, have been linked to psoriasis development. However, the association of prior existing hypertension and antihypertensive medications with risk of incident psoriasis has not been assessed using prospective data.

OBJECTIVE To evaluate the association of hypertension and antihypertensive medications with risk of psoriasis.

DESIGN, SETTING, AND PARTICIPANTS We performed a prospective cohort study (June 1, 1996, to June 1, 2008) of 77 728 US women from the Nurses' Health Study who provided biennially updated data on hypertension and antihypertensive medications.

MAIN OUTCOMES AND MEASURES Physician-diagnosed psoriasis.

RESULTS A total of 843 incident psoriasis cases were documented during 1 066 339 person-years of follow-up. Compared with normotensive women, women with a hypertension duration of 6 years or more were at a higher risk of developing psoriasis (hazard ratio [HR], 1.27; 95% CI, 1.03-1.57). In stratified analysis, the risk of psoriasis was higher among hypertensive women without medication use (HR, 1.49; 95% CI, 1.15-1.92) and among hypertensive women with current medication use (HR, 1.31; 95% CI, 1.10-1.55) when compared with normotensive participants without medication use. Compared with women who never used β-blockers, the multivariate HRs for psoriasis for women who regularly used β-blockers were 1.11 (95% CI, 0.82-1.51) for 1 to 2 years of use, 1.06 (95% CI, 0.79-1.40) for 3 to 5 years of use, and 1.39 (95% CI, 1.11-1.73) for 6 years or more of use (*P* for trend = .009). No association was found between use of other individual antihypertensive drugs and risk of psoriasis.

CONCLUSIONS AND RELEVANCE Long-term hypertensive status is associated with an increased risk of psoriasis. Long-term regular use of β-blockers may also increase the risk of psoriasis.

JAMA Dermatol. doi:10.1001/jamadermatol.2013.9957
Published online July 2, 2014.

Invited Commentary

Supplemental content at jamadermatology.com

CME Quiz at jamanetworkcme.com and CME Questions

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Corresponding Author: Abrar A. Qureshi, MD, MPH, Department of Dermatology, Warren Alpert Medical School, Brown University, Providence, RI 02909 (abrar_qureshi@brown.edu).

Original Investigation

Hypertension, Antihypertensive Medication Use, and Risk of Psoriasis

JAMA Dermatol. July 2,2014

Shaowei Wu, MD, PhD; Jiali Han, PhD; Wen-Qing Li, MD, PhD; Abrar A. Qureshi, MD, MPH

RESULTS A total of 843 incident psoriasis cases were documented during 1 066 339 person-years of follow-up. Compared with normotensive women, women with a hypertension duration of 6 years or more were at a higher risk of developing psoriasis (hazard ratio [HR], 1.27; 95% CI, 1.03-1.57). In stratified analysis, the risk of psoriasis was higher among hypertensive women without medication use (HR, 1.49; 95% CI, 1.15-1.92) and among hypertensive women with current medication use (HR, 1.31; 95% CI, 1.10-1.55) when compared with normotensive participants without medication use. Compared with women who never used β-blockers, the multivariate HRs for psoriasis for women who regularly used β-blockers were 1.11 (95% CI, 0.82-1.51) for 1 to 2 years of use, 1.06 (95% CI, 0.79-1.40) for 3 to 5 years of use, and 1.39 (95% CI, 1.11-1.73) for 6 years or more of use (*P* for trend = .009). No association was found between use of other individual antihypertensive drugs and risk of psoriasis.

risk of psoriasis. Long-term regular use of β-blockers may also increase the risk of psoriasis.

JAMA Dermatol. doi:10.1001/jamadermatol.2013.9957
Published online July 2, 2014.

Corresponding Author: Abrar A. Qureshi, MD, MPH, Department of Dermatology, Warren Alpert Medical School, Brown University, Providence, RI 02909 (abrar_qureshi@brown.edu).

Kaiser Permanente Southern California Treated Hypertension Study Cohort

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http://dx.doi.org/10.1016/j.jacc.2014.04.065

Impact of Achieved Blood Pressures on Mortality Risk and End-Stage Renal Disease Among a Large, Diverse Hypertension Population

John J. Sim, MD,* Jiaxiao Shi, PhD,† Csaba P. Kovesdy, MD,‡ Kamyar Kalantar-Zadeh, MD, PhD,§
Steven J. Jacobsen, MD, PhD†

JACC 2014;64(6):588–597

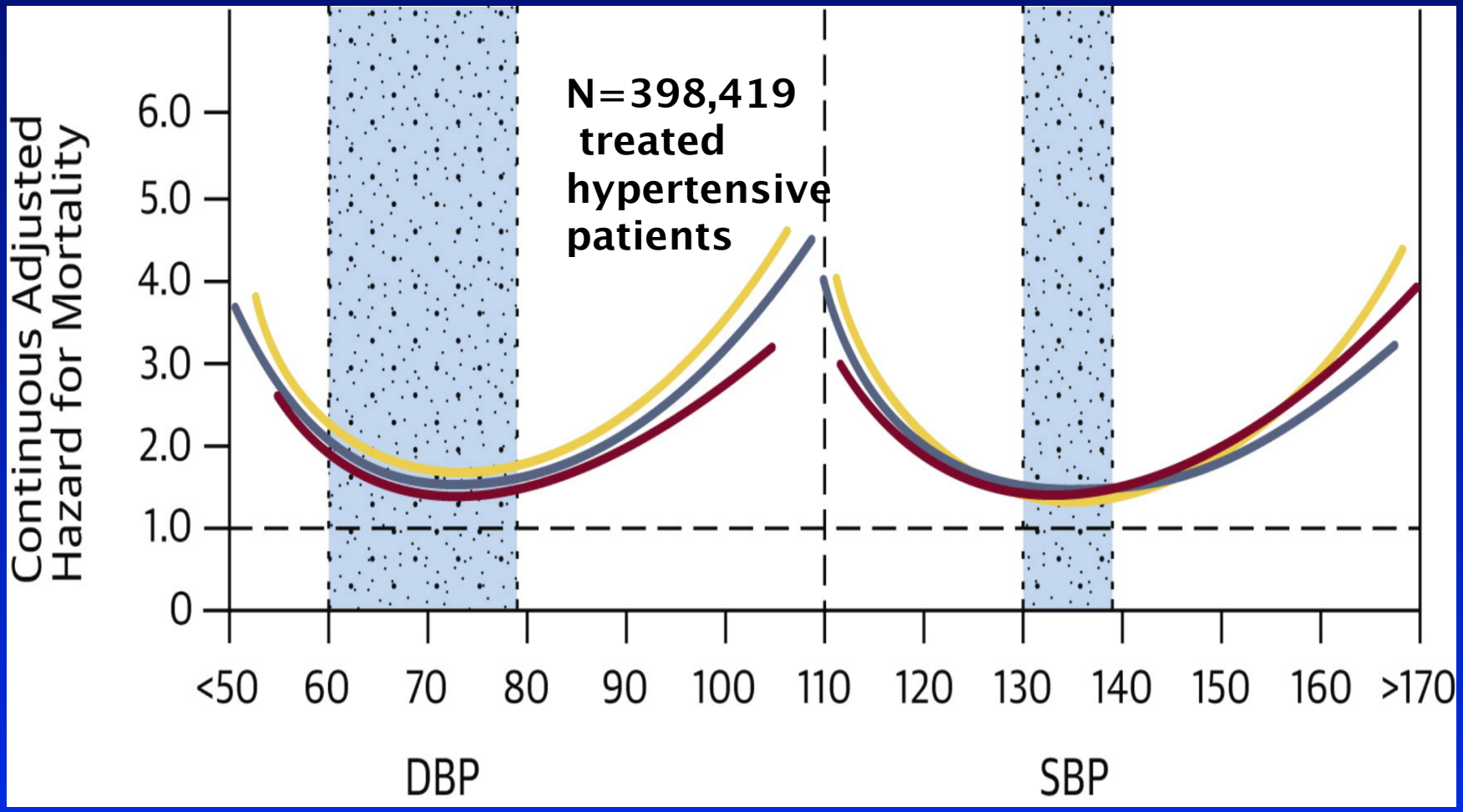
ABSTRACT

BACKGROUND Medical data or clinical guidelines have not adequately addressed the ideal blood pressure (BP) treatment targets for survival and renal outcome.

OBJECTIVES This study sought to evaluate ranges of treated BP in a large hypertension population and compare risk of mortality and end-stage renal disease (ESRD).

METHODS A retrospective cohort study within the Kaiser Permanente Southern California health system was performed from January 1, 2006, to December 31, 2010. Treated hypertensive subjects ≥18 years of age were studied. Cox proportional hazards regression models were used to evaluate the risks (hazard ratios) for mortality and/or ESRD among different BP categories with and without stratification for diabetes mellitus and older age.

Where Is Ideal BP in Treated



Mortality/ESRD HR across ranges of BP. Achieved SBP range 130 to 139 and DBP range 60 to 79 mm Hg associated with best outcomes.

Sim et al. J Am Coll Cardiol. 2014;64:588-97.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 14, 2014 VOL. 371 NO. 7

Mente A et al. N Engl J Med 2014;371:601–611.

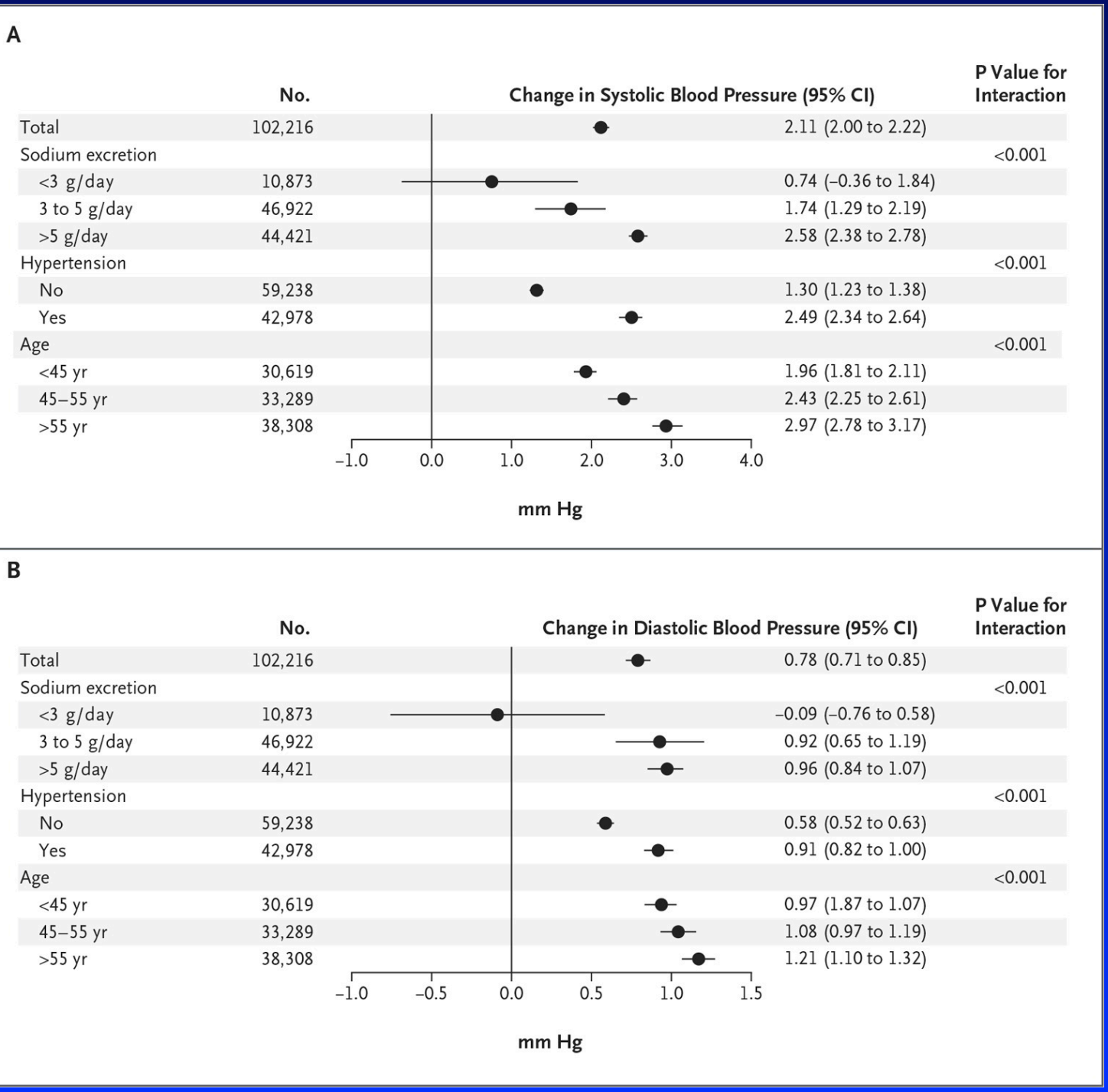
Association of Urinary Sodium and Potassium Excretion with Blood Pressure

Andrew Mente, Ph.D., Martin J. O'Donnell, M.B., Ph.D., Sumathy Rangarajan, M.Sc., Matthew J. McQueen, M.B., B.Ch., Paul Poirier, M.D., Ph.D., Andreas Wielgosz, M.D., Ph.D., Howard Morrison, Ph.D., Wei Li, Ph.D., Xingyu Wang, Ph.D., Chen Di, B.Sc., Prem Mony, M.D., Anitha Devanath, M.D., Annika Rosengren, M.D., Aytekin Oguz, M.D., Katarzyna Zatonska, M.D., Ph.D., Afzal Hussein Yusufali, M.D., Patricio Lopez-Jaramillo, M.D., Ph.D., Alvaro Avezum, M.D., Ph.D., Noorhassim Ismail, M.D., Ph.D., Fernando Lanas, M.D., Thandi Puoane, M.P.H., Ph.D., Rafael Diaz, M.D., Roya Kelishadi, M.D., Romaina Iqbal, Ph.D., Rita Yusuf, Ph.D., Jephat Chifamba, M.Phil., Rasha Khatib, M.H.S., Koon Teo, M.B., Ph.D., and Salim Yusuf, D.Phil., for the PURE Investigators*

Study Overview

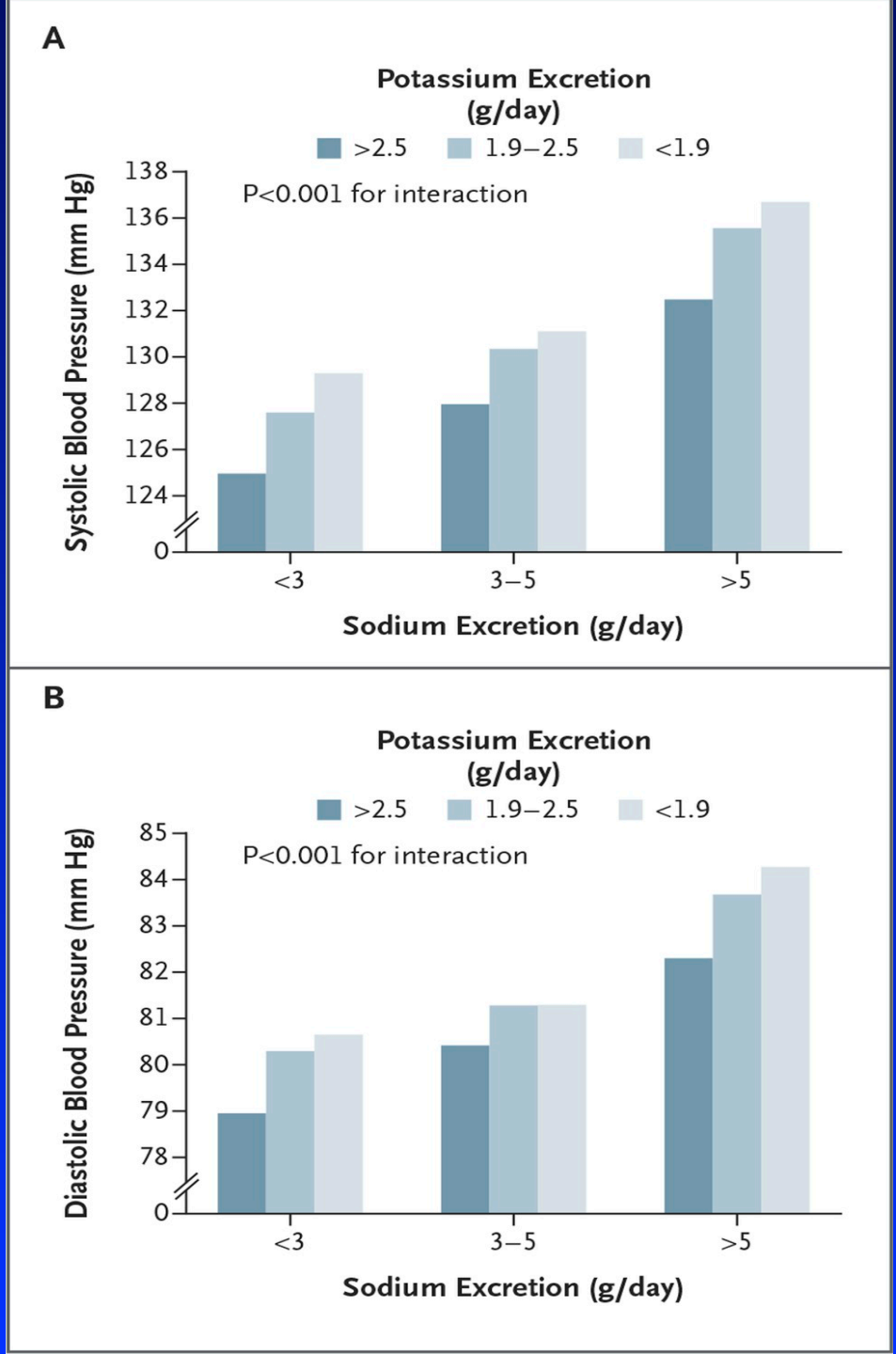
- In a large study in 18 countries, sodium and potassium intake were estimated from urine samples and correlated with BP.
- The correlations were nonlinear and were most pronounced among people with high sodium intake, those with hypertension, and older persons.

Changes in SBP and DBP for Every 1-g Increase in Sodium Excretion



Mente et al. N Engl J Med 2014;371:601-11

Mean SBP and DBP According to Sodium and Potassium Excretion



Mente et al. N Engl J Med 2014;371:601-11

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

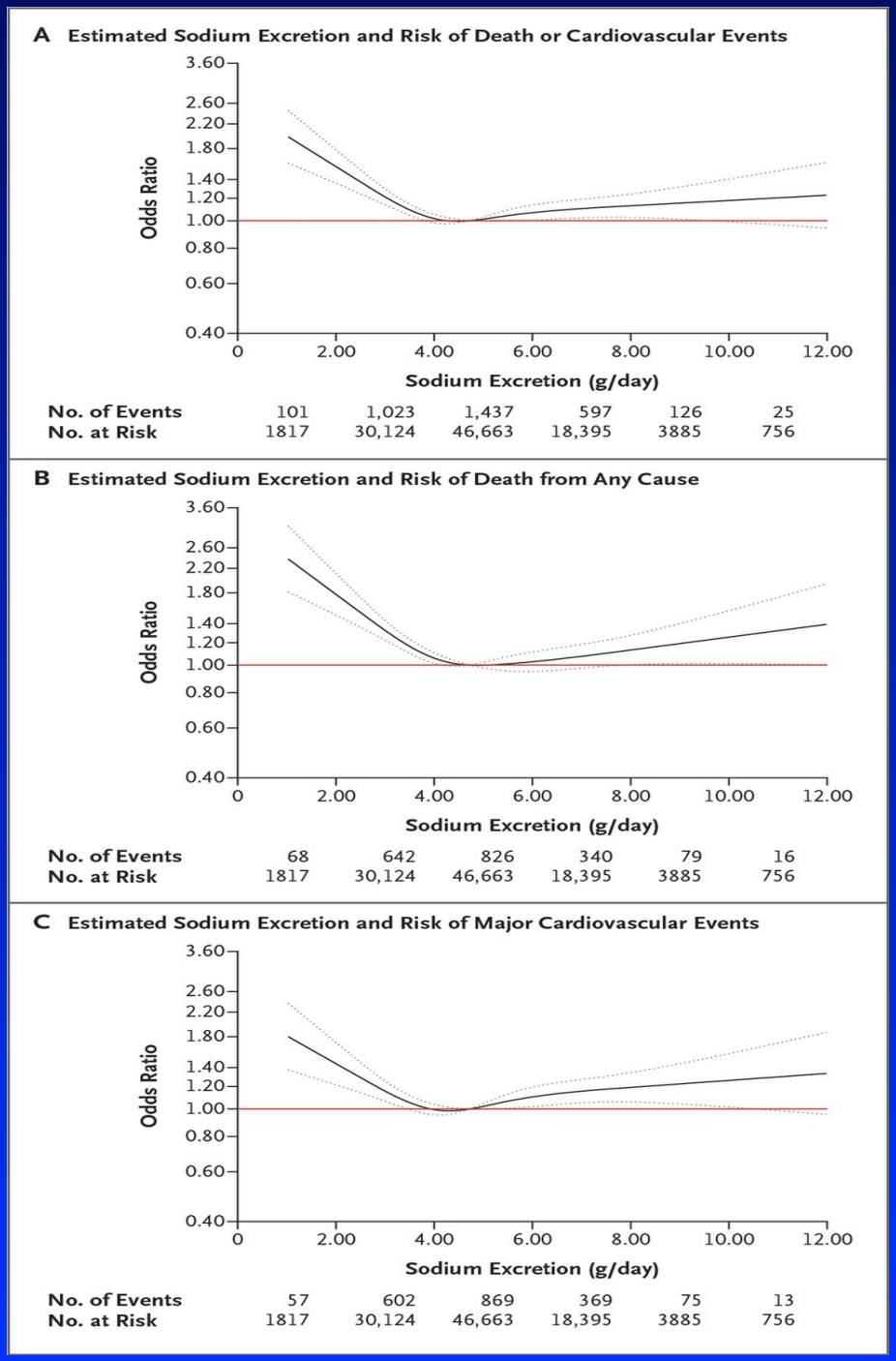
O'Donnell M et al. N Engl J Med 2014;371:612-623

Urinary Sodium and Potassium Excretion, Mortality, and Cardiovascular Events

Martin O'Donnell, M.B., Ph.D., Andrew Mente, Ph.D., Sumathy Rangarajan, M.Sc., Matthew J. McQueen, M.B., Ph.D., Xingyu Wang, Ph.D., Lisheng Liu, M.D., Hou Yan, Ph.D., Shun Fu Lee, Ph.D., Prem Mony, M.D., Anitha Devanath, M.D., Annika Rosengren, M.D., Patricio Lopez-Jaramillo, M.D., Ph.D., Rafael Diaz, M.D., Alvaro Avezum, M.D., Ph.D., Fernando Lanas, M.D., Khalid Yusoff, M.B., B.S., Romaina Iqbal, Ph.D., Rafal Ilow, Ph.D., Noushin Mohammadifard, M.Sc., Sadi Gulec, M.D., Afzal Hussein Yusufali, M.D., Lanthe Kruger, Ph.D., Rita Yusuf, Ph.D., Jephat Chifamba, M.Phil., Conrad Kabali, Ph.D., Gilles Dagenais, M.D., Scott A. Lear, Ph.D., Koon Teo, M.B., Ph.D., and Salim Yusuf, D.Phil., for the PURE Investigators*

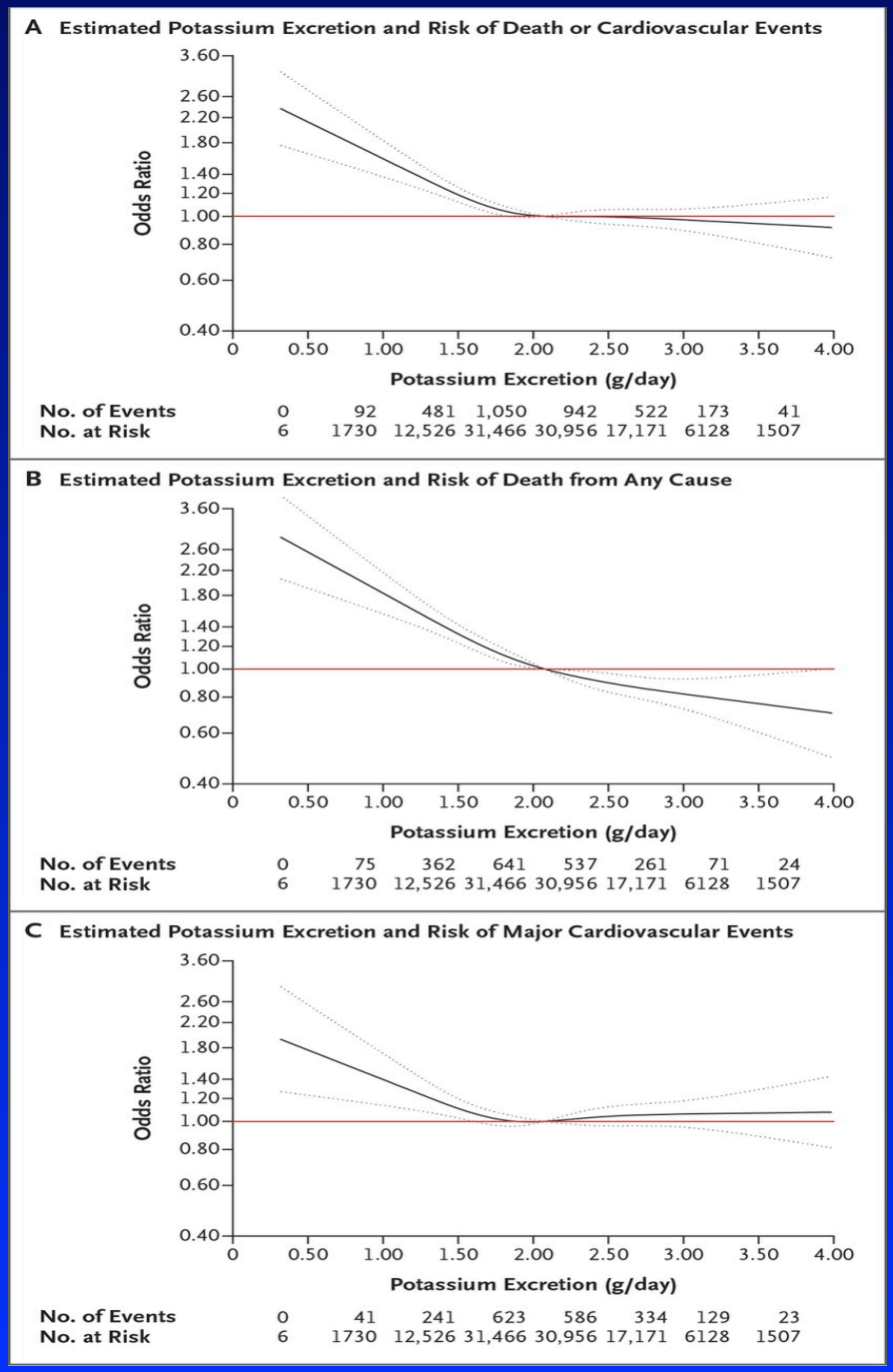
Study Overview

- In a large study in 17 countries, an estimated sodium intake either higher or lower than the average estimated sodium intake was associated with increased risk of CV events.
- A higher-than-average potassium intake was associated with reduced risk.



Estimated 24-Hr Urinary Sodium Excretion with Risk of Death and Major CV Events

O'Donnell et al. N Engl J Med 2014;371:612-23.



Estimated 24-Hr Urinary Potassium Excretion with Risk of Death and Major CV Events

O'Donnell et al. N Engl J Med 2014;371:612-23.

Conclusions

- Estimated sodium intake between 3 g per day and 6 g per day was associated with a lower risk of death and CV events than either a higher or lower estimated intake.
- As compared with estimated potassium excretion less than 1.50 g per day, higher potassium excretion was associated with a lower risk of death and CV events.

The NEW ENGLAND JOURNAL of MEDICINE

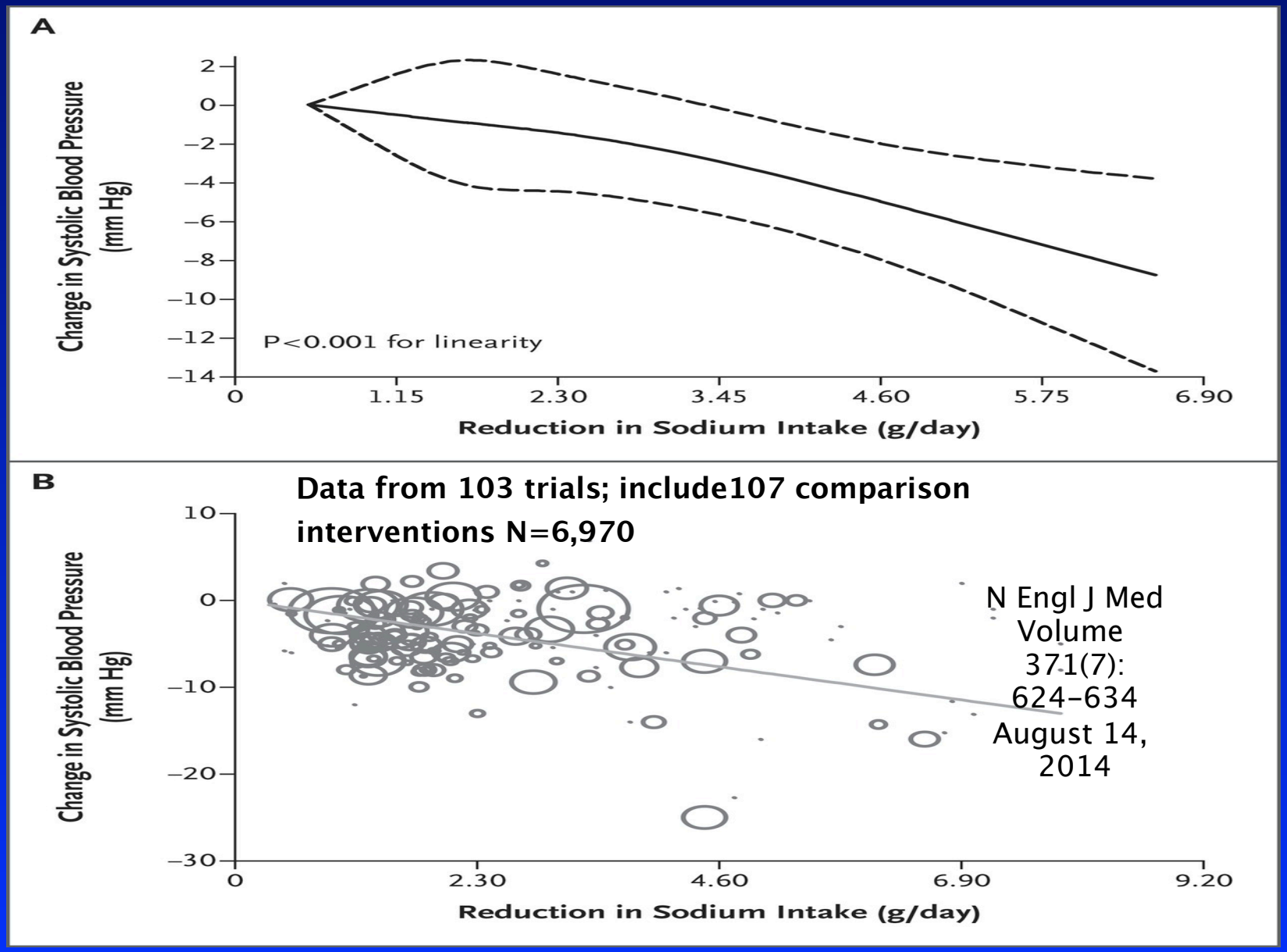
ORIGINAL ARTICLE

Mozaffarian,D. et al N Engl J Med 371(7):624-634 August 14, 2014

Global Sodium Consumption and Death from Cardiovascular Causes

Dariush Mozaffarian, M.D., Dr.P.H., Saman Fahimi, M.D., Gitanjali M. Singh, Ph.D., Renata Micha, R.D., Ph.D., Shahab Khatibzadeh, M.D., M.P.H., Rebecca E. Engell, B.A., Stephen Lim, Ph.D., Goodarz Danaei, Ph.D., Majid Ezzati, Ph.D., and John Powles, M.B., B.S., for the Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NUTRICODE)

Effects of Reduced Sodium Intake on SBP



N Engl J Med Volume 371(7): 624-634 August 14, 2014

Mozaffarian,et al N Engl J Med 371:624-34.

Conclusions

- In this modeling study, 1.65 million deaths from cardiovascular causes that occurred in 2010 were attributed to sodium consumption above a reference level of 2.0 g per day.

Original Article

Ferdinand,K. et al Hypertension. 2014

N=755

Effects of the Once-Weekly Glucagon-Like Peptide-1 Receptor Agonist Dulaglutide on Ambulatory Blood Pressure and Heart Rate in Patients With Type 2 Diabetes Mellitus

Keith C. Ferdinand, William B. White, David A. Calhoun, Eva M. Lonn, Philip T. Sager, Rocco Brunelle, Honghua H. Jiang, Rebecca J. Threlkeld, Kenneth E. Robertson, Mary Jane Geiger

Abstract—Glucagon-like peptide-1 receptor agonists, used to treat type 2 diabetes mellitus, are associated with small reductions in systolic blood pressure (SBP) and increases in heart rate. However, findings based on clinic measurements do not adequately assess a drug's 24-hour pharmacodynamic profile. The effects of dulaglutide, a once-weekly glucagon-like peptide-1 receptor agonist, on BP and heart rate were investigated using ambulatory BP monitoring. Patients (n=755; 56±10 years; 81% white; 48% women), with type 2 diabetes mellitus, taking ≥1 oral antihyperglycemic medication, with a clinic BP between 90/60 and 140/90 mm Hg were randomized to dulaglutide (1.5 or 0.75 mg) or placebo subcutaneously for 26 weeks. Ambulatory BP monitoring was performed at baseline and at 4, 16, and 26 weeks. The primary end point was change from baseline to week 16 in mean 24-hour SBP, a tree gatekeeping strategy compared the effects of dulaglutide to placebo. Both doses of dulaglutide were noninferior to placebo for changes in 24-hour SBP and diastolic blood pressure, and dulaglutide 1.5 mg significantly reduced SBP (least squares mean difference [95% confidence interval]), −2.8 mm Hg [−4.6, −1.0]; $P \leq 0.001$). Dulaglutide 0.75 mg was noninferior to placebo (1.6 bpm; [0.3, 2.9]; $P \leq 0.02$) for 24-hour heart rate (least squares mean difference [95% confidence interval]), but dulaglutide 1.5 mg was not (2.8 bpm [1.5, 4.2]). Dulaglutide 1.5 mg was associated with a reduction in 24-hour SBP and an increase in 24-hour heart rate. The mechanisms responsible for the observed effects remain to be clarified. (***Hypertension*****. 2014;64:00-00.)** • **Online Data Supplement**

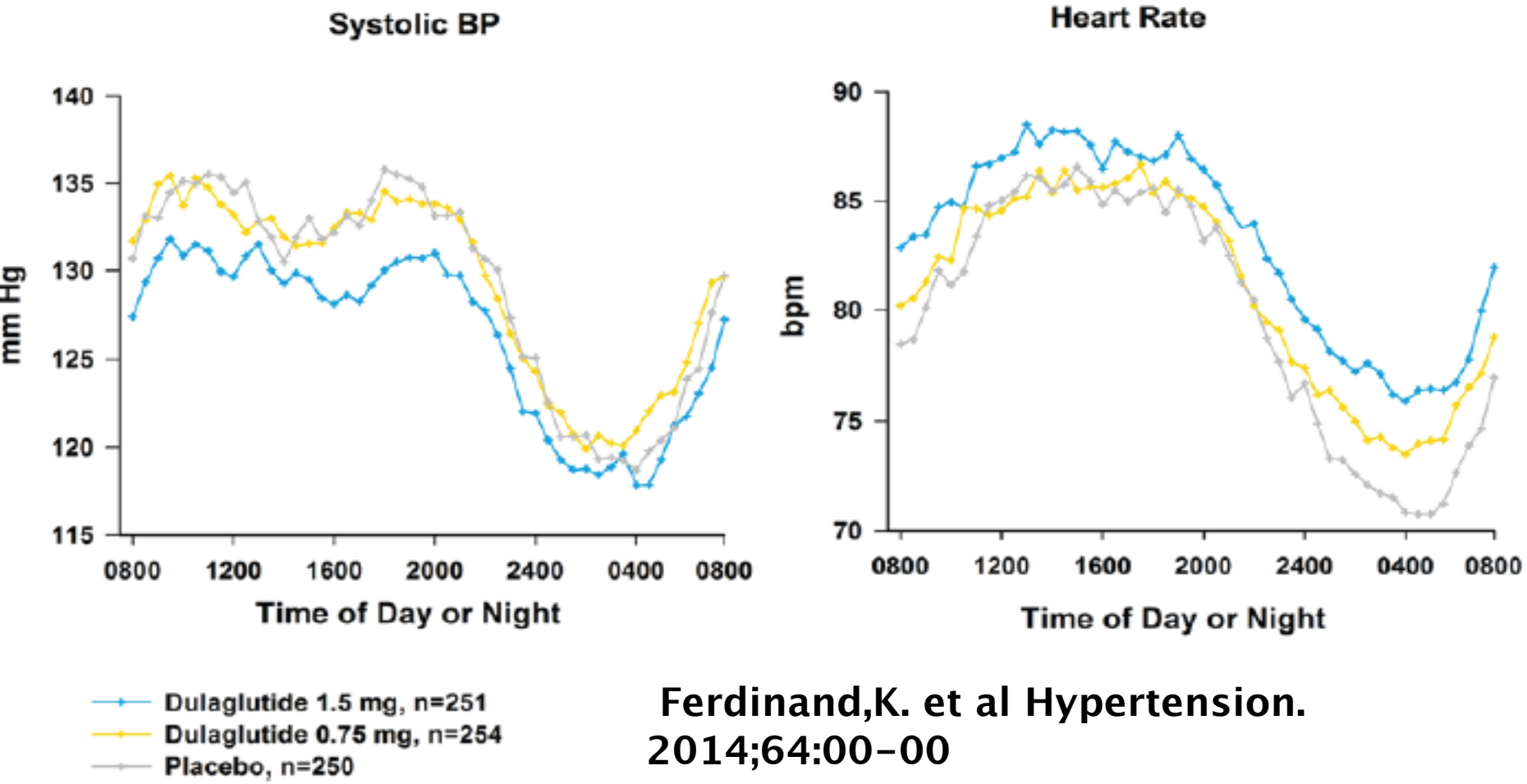
Key Words: blood pressure monitoring, ambulatory ■ blood pressure ■ dulaglutide ■ glucagon-like peptide-1 ■ heart rate ■ hypertension ■ type 2 diabetes mellitus

Effects of Dulaglutide on Ambulatory BP and HR

- What is New?
- This was a large, randomized placebo-controlled ABPM study designed to assess the effects of dulaglutide, a glucagon-like peptide-1 receptor(GLP-1) agonist, on BP and HR

Ferdinand et al. Hypertension. 2014 Jun 30. pii: HYPERTENSIONAHA.114.03062.

Figure 1. Effects of dulaglutide and placebo on ambulatory systolic blood pressure (BP) and heart rate during 24 hours. Least squares mean values are shown for systolic BP and heart rate.



Ferdinand,K. et al Hypertension. 2014;64:00-00

Effects of Dulaglutide on ABPM and HR

- What is Relevant?
- Both doses of dulaglutide were noninferior to placebo for changes in 24-hour SBP and DBP.
- Dulaglutide 1.5 mg significantly↓SBP ($P \leq 0.001$).
- The 0.75-mg dose was noninferior to placebo for 24-hour HR.
- Dulaglutide 1.5 mg was associated with a small ↑in 24-hour HR.

Ferdinand et al. Hypertension. 2014 Jun 30. pii: HYPERTENSIONAHA.114.03062.

Summary

Dulaglutide did not adversely affect blood pressure and may have some benefit. The relevance of a small increase in mean heart rate, while likely not detrimental, remains to be determined.

Ferdinand et al. Hypertension. 2014 Jun 30. pii: HYPERTENSIONAHA.114.03062.

ARTICLE IN PRESS

JACC: HEART FAILURE
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Sitagliptin Use in Patients With Diabetes and Heart Failure

A Population-Based Retrospective Cohort Study

Daniala L. Weir, BSc,*‡ Finlay A. McAlister, MD, MSc,† Ambikaipakan Senthilselvan, PhD,*
Jasjeet K. Minhas-Sandhu, MSc,‡ Dean T. Eurich, PhD*‡

ABSTRACT

OBJECTIVES The study objective was to evaluate the effects of sitagliptin in patients with type 2 diabetes (T2D) and heart failure (HF).

BACKGROUND There is uncertainty in the literature about whether dipeptidyl peptidase (DPP)-4 inhibitors cause harm in patients with HF and T2D.

Weir et al. JACC Heart Fail. doi: 10.1016/j.jchf.2014.04.005.

Sitagliptin Use with DM and HF Population-Based Retrospective Cohort Study

- OBJECTIVES: evaluate effects of sitagliptin in patients with T2D and HF
- Data from national commercially insured U.S. claims database
- Incident HF with metformin or sulfonylurea and sitagliptin
- N=7,620
- Subsequent sitagliptin compared with not using sitagliptin in the 90-day period

Weir et al. JACC Heart Fail. doi: 10.1016/j.jchf.2014.04.005.

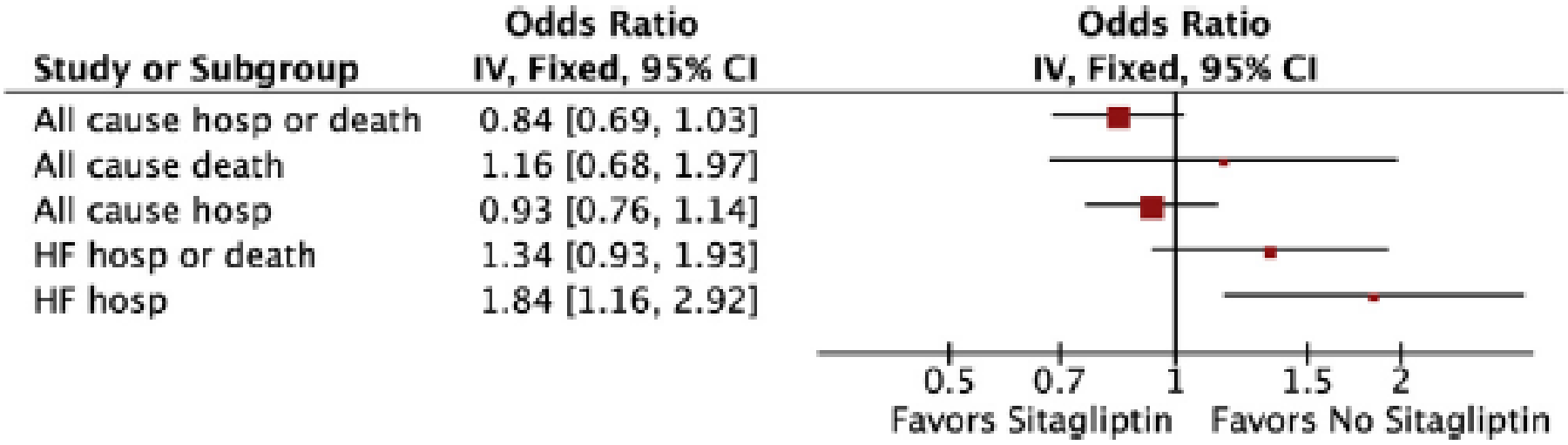


FIGURE 3 **Forest Plot of Primary and Secondary Endpoints According to Sitagliptin Use**

Primary and secondary endpoints after incident HF were evaluated according to sitagliptin use versus nonuse 90 days before each outcome. CI = confidence interval; HF = heart failure; hosp = hospitalization; IV = interval.

Weir et al. JACC Heart Fail. doi: 10.1016/j.jchf.2014.04.005.

Sitagliptin Use with DM and HF Population-Based Retrospective Cohort Study

- CONCLUSIONS: Sitagliptin use was not associated with an increased risk of all-cause hospitalizations or death, but was associated with an increased risk of HF-related hospitalizations among patients with T2D with pre-existing HF.

Bhatt et al. JACC Heart Fail doi: 10.1016/j.jchf.2014.05.005.

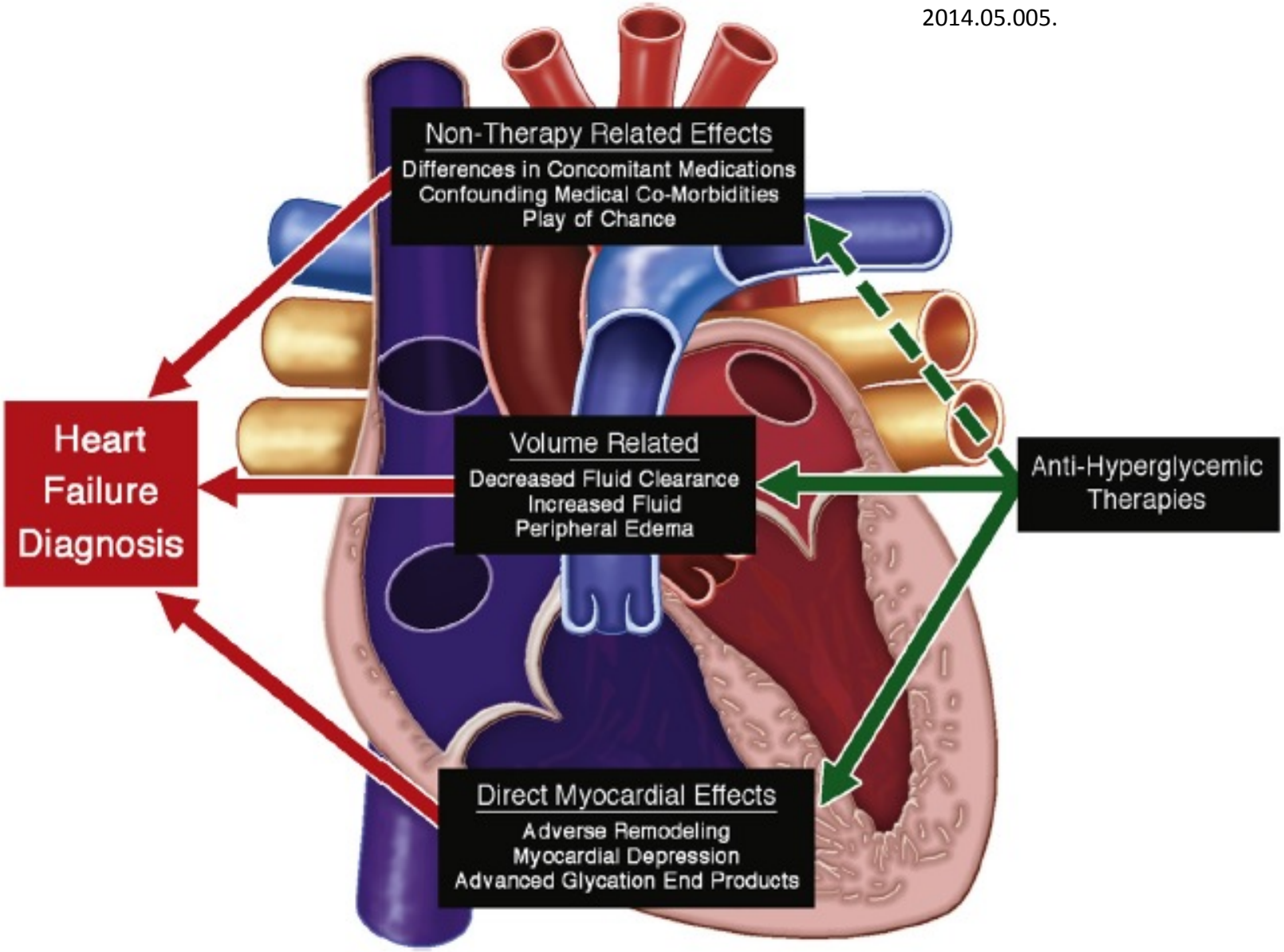


FIGURE 1 Antihyperglycemic Therapies and Heart Failure

Potential explanations for the association between antihyperglycemic therapies and heart failure seen in trial and registry analyses.

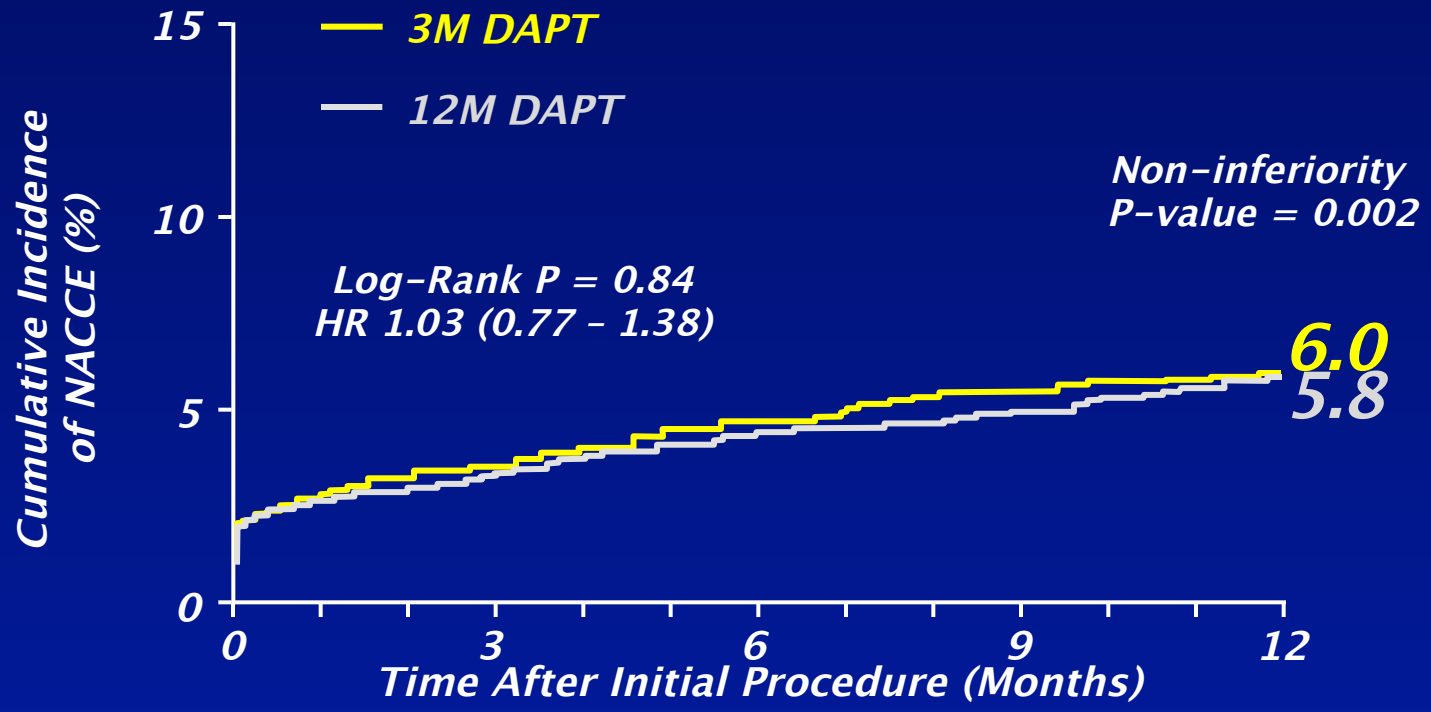
Thank You!

Late-Breaking Clinical Trials & FDA Update

Thrombosis

Deepak L. Bhatt, MD, MPH
Executive Director of Interventional Cardiovascular Program, BWH Heart and Vascular Center
Professor of Medicine, Harvard Medical School
Boston, Massachusetts

OPTIMIZE Trial: NACCE at 1 Year (All-Cause Death, MI, Stroke, Major Bleeding)

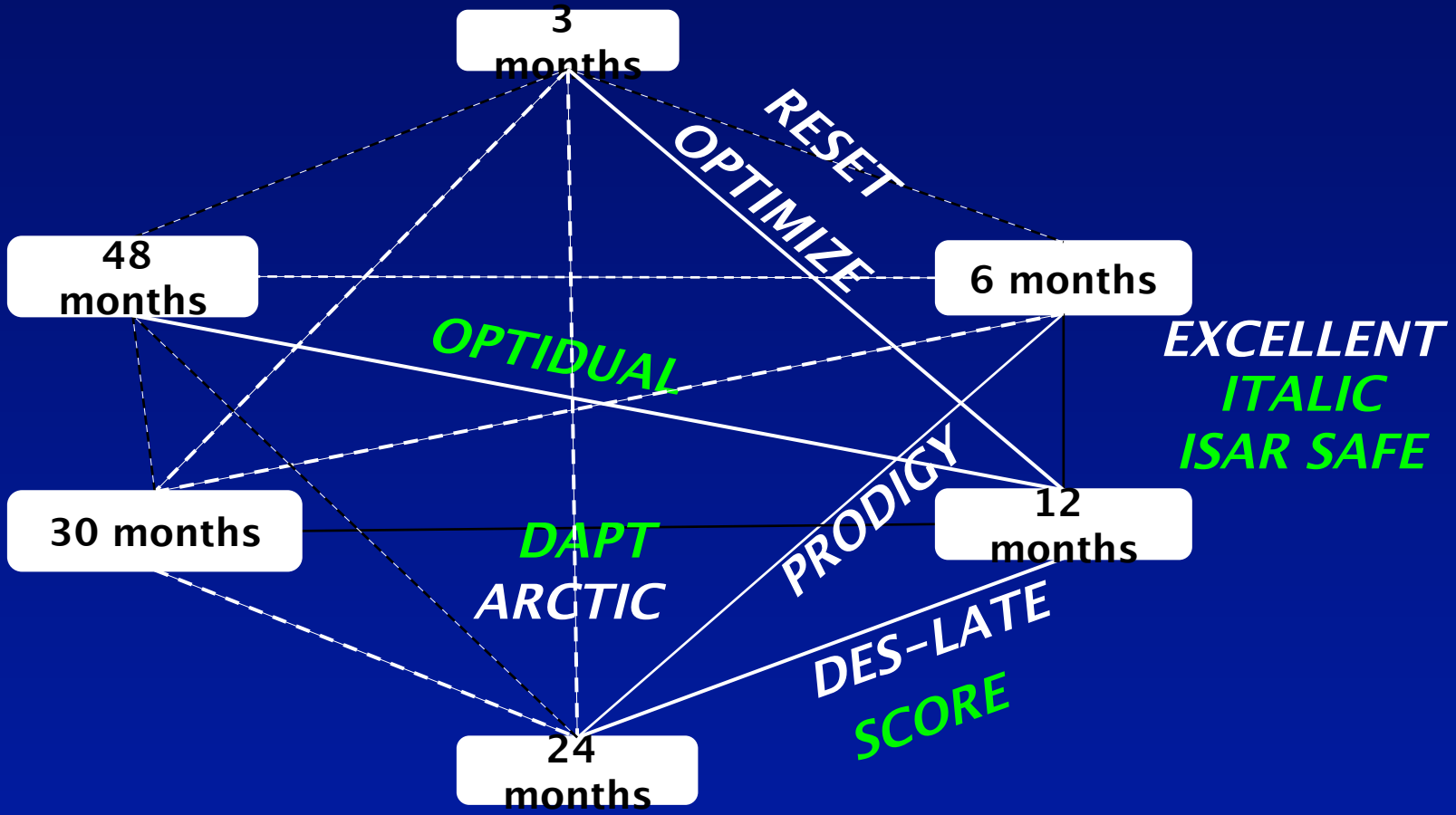


Month	0	1	3	6	12
No. at risk	1563	1520	1504	1468	1384
No. events	18	25	11	18	21
No. at risk	1556	1514	1497	1466	1381
No. events	16	25	11	16	22

DAPT=dual antiplatelet therapy

Feres et al. JAMA. 2013;310:2510-22.

Trials of DAPT: Duration



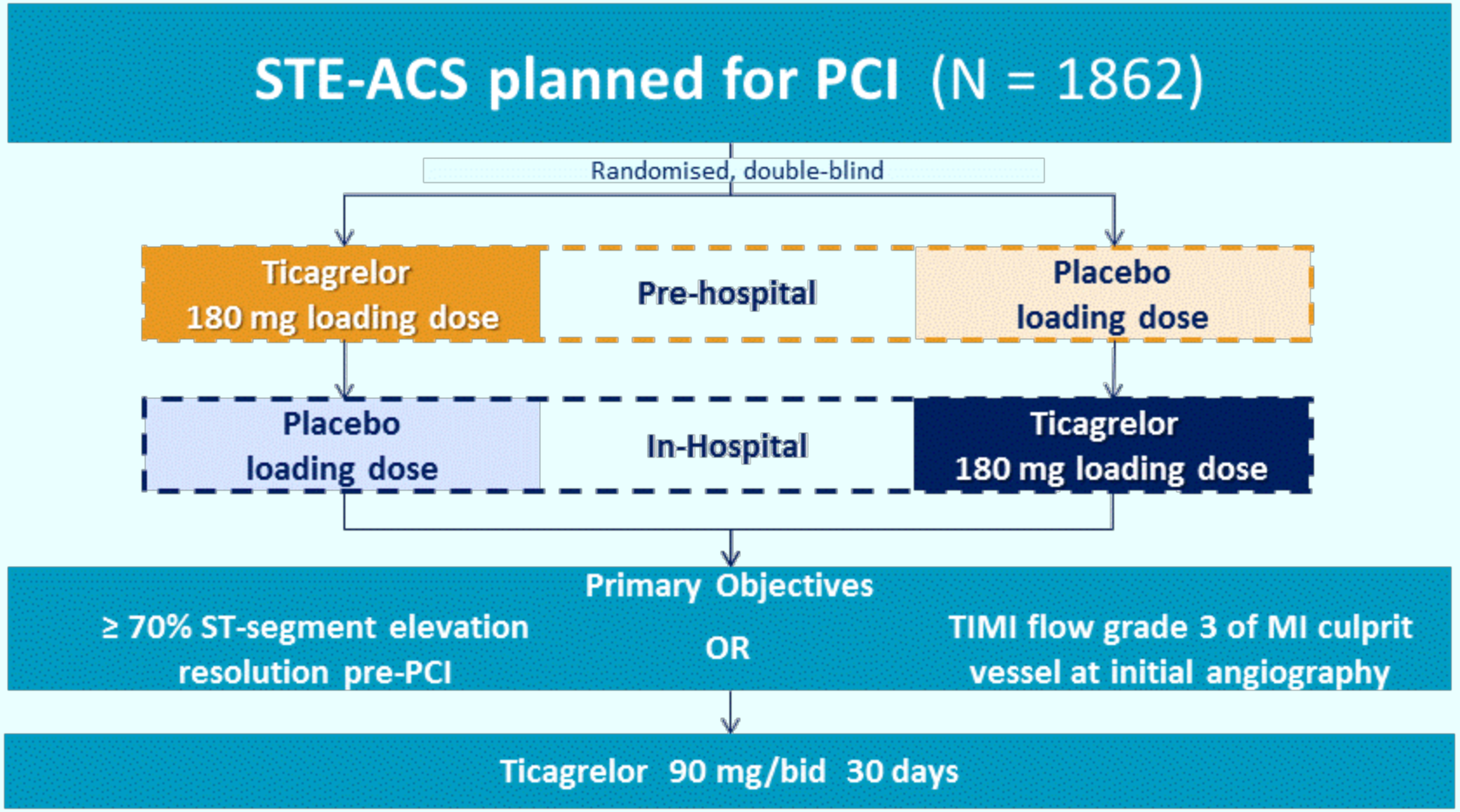
Ongoing trials in green

Capodanno, Angiolillo. Circulation. 2013;128:2785-98.

Study Population and Design

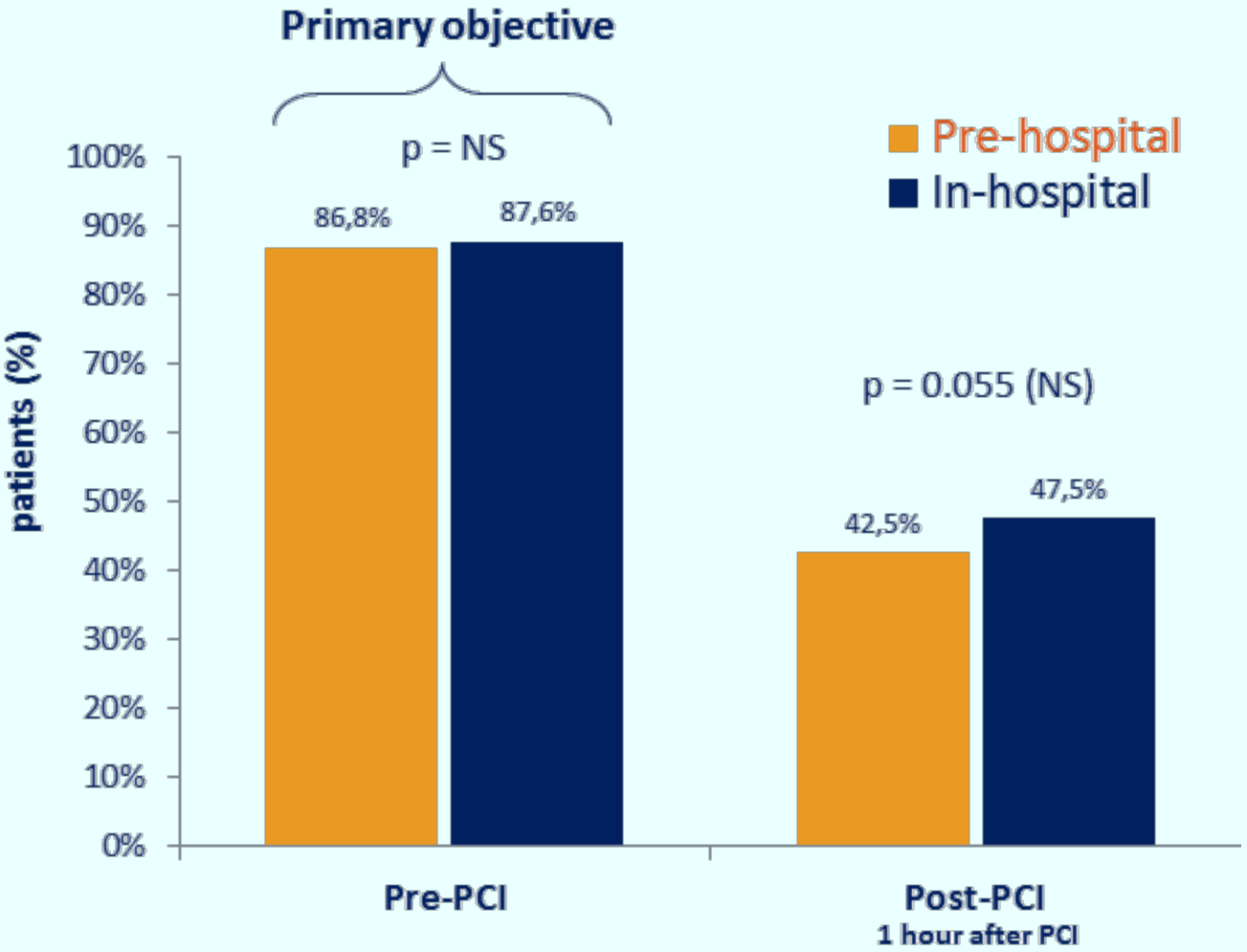
Atlantic Population

- Documented evidence of **STEMI**
- Planned for **angioplasty (PCI)**
- **onset of ischaemic symptoms within 6 h**
- **initially managed by ambulance physician/personnel**; also concerning patients not pre-treated for STEMI in **emergency rooms of non-PCI hospitals**



Montalescot G et al. *Am Heart J.* 2013;165:515–522.

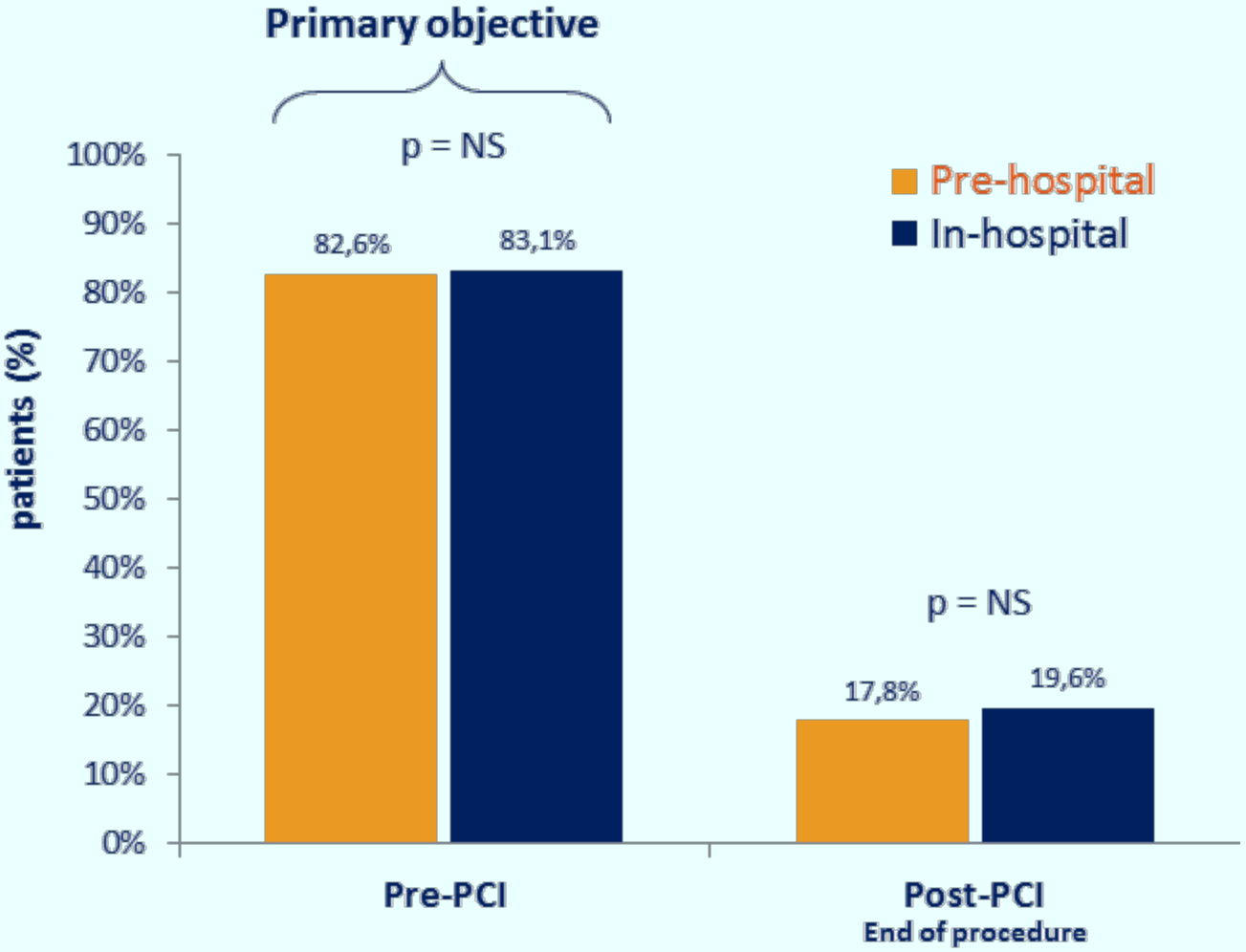
1st Co-Primary Endpoint
No ST-segment resolution (≥70%)



PCI=percutaneous coronary intervention

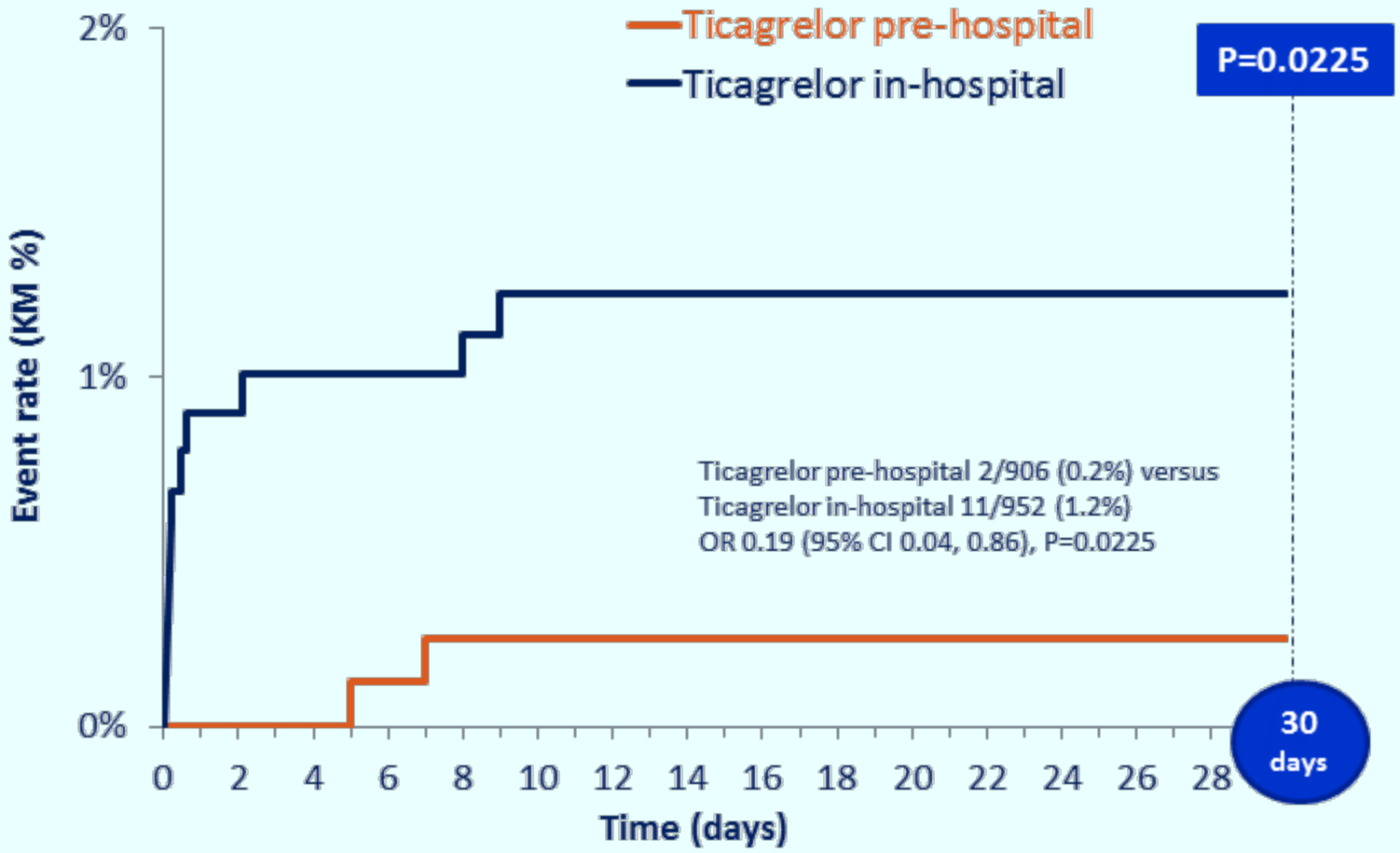
Montalescot G et al. NEJM 2014;371:1016-27.

2nd Co-Primary Endpoint
No TIMI 3 flow in infarct-related artery



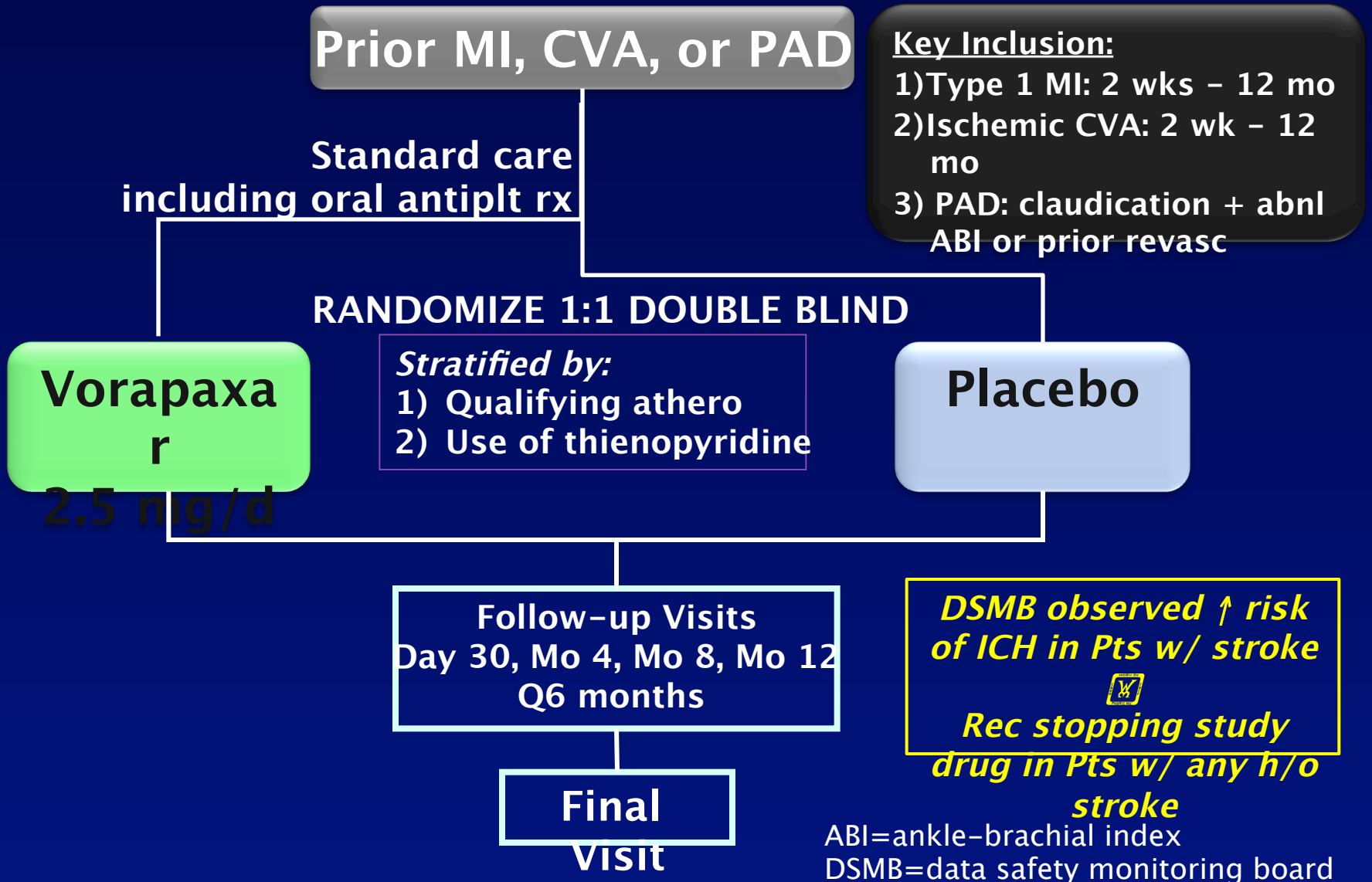
Montalescot G et al. NEJM 2014;371:1016-27.

Definite Stent Thrombosis Up to 30 Days



Montalescot G et al. NEJM 2014;371:1016-27.

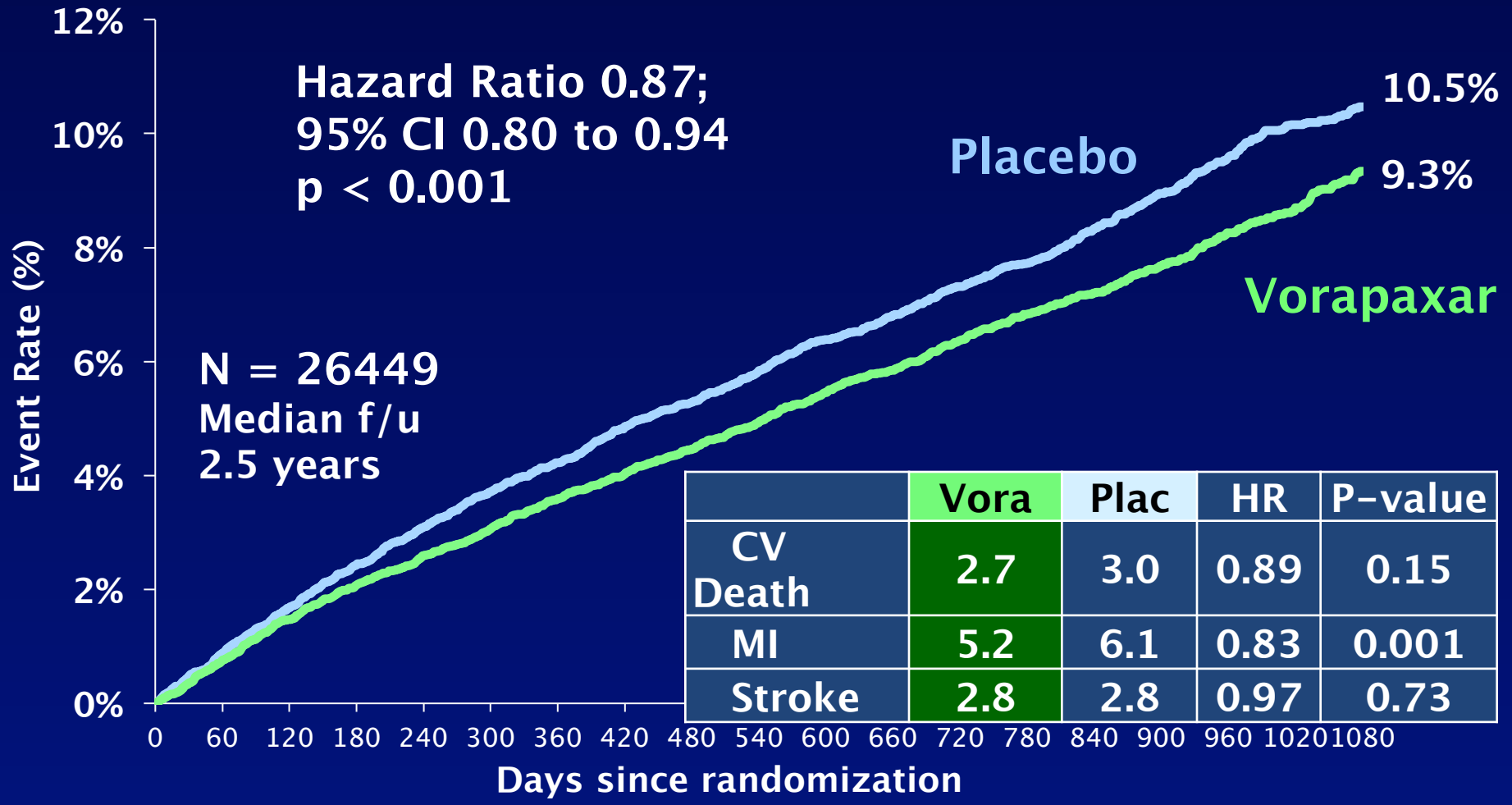
Trial Design



ABI=ankle-brachial index
DSMB=data safety monitoring board

Primary Efficacy Evaluation

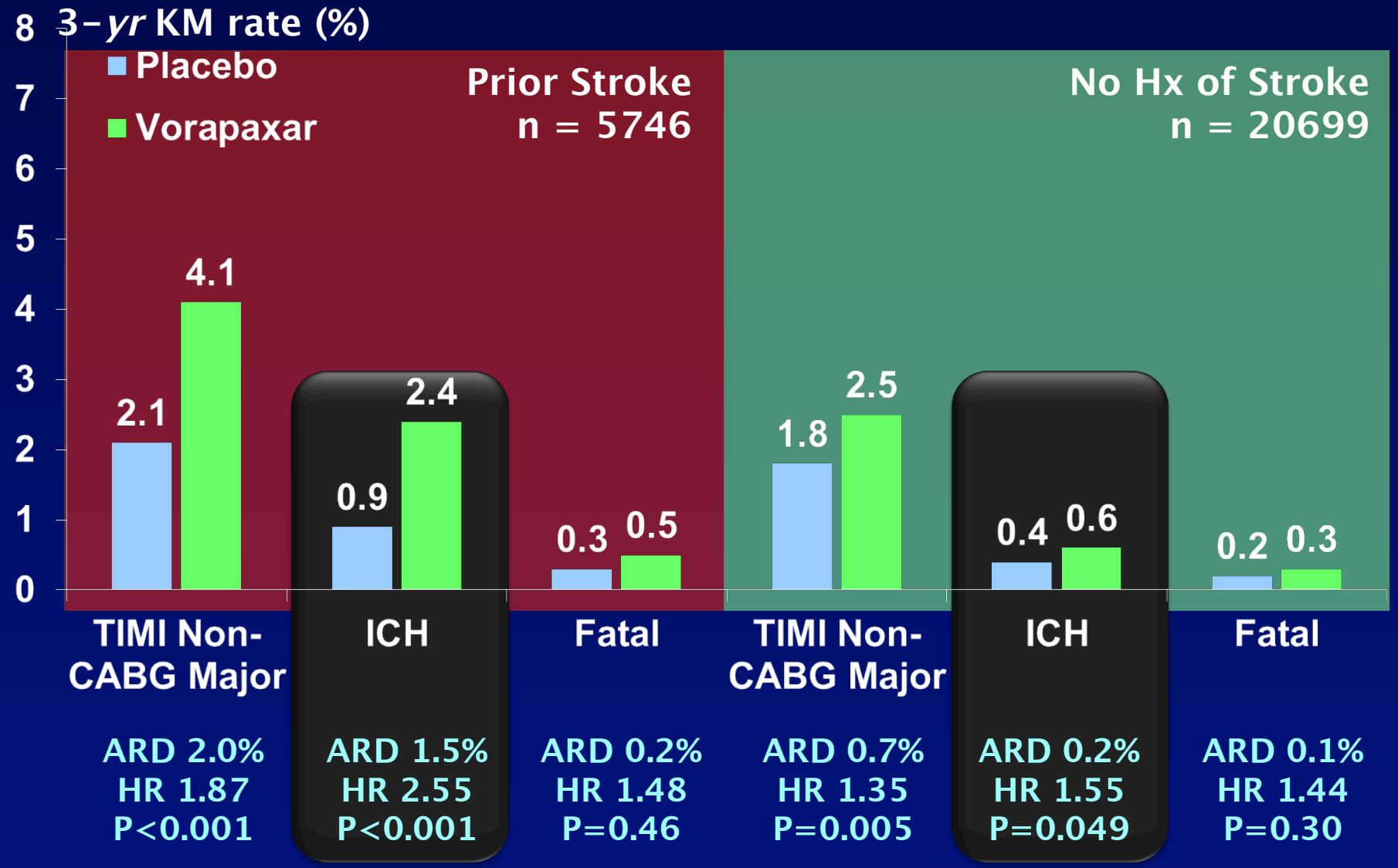
CV Death, MI, or Stroke



	Vora	Plac	HR	P-value
CV Death	2.7	3.0	0.89	0.15
MI	5.2	6.1	0.83	0.001
Stroke	2.8	2.8	0.97	0.73

Morrow et al. NEJM 2012;366:1404-13

Major Bleeding Endpoints



Morrow et al. NEJM 2012;366:1404-13

ICH=intracerebral hemorrhage; ARD=aortic root diameter

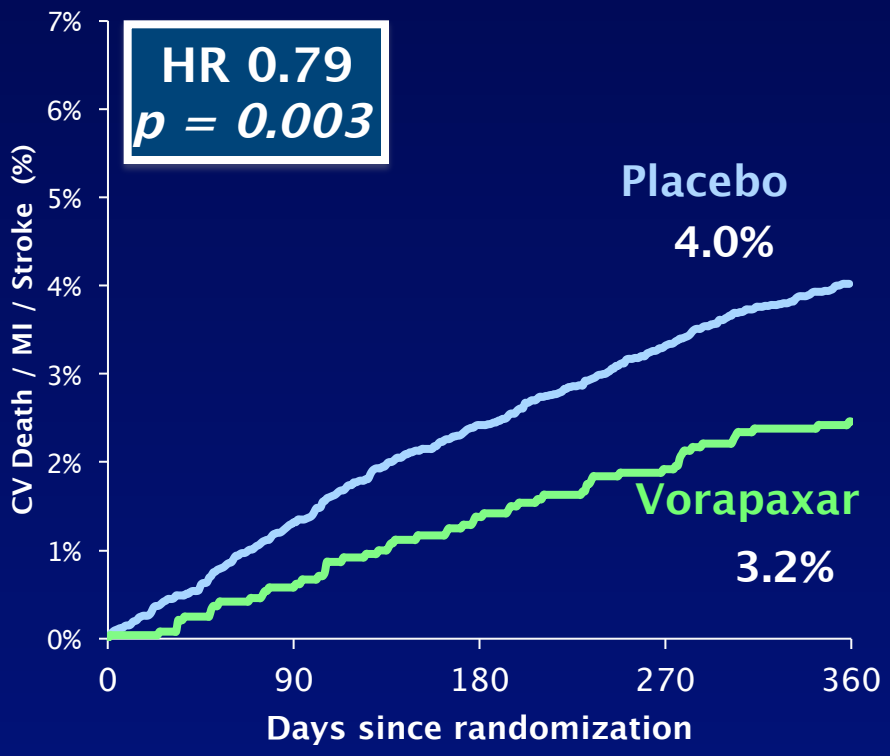
MI Cohort

TRA 2°P TIMI 50

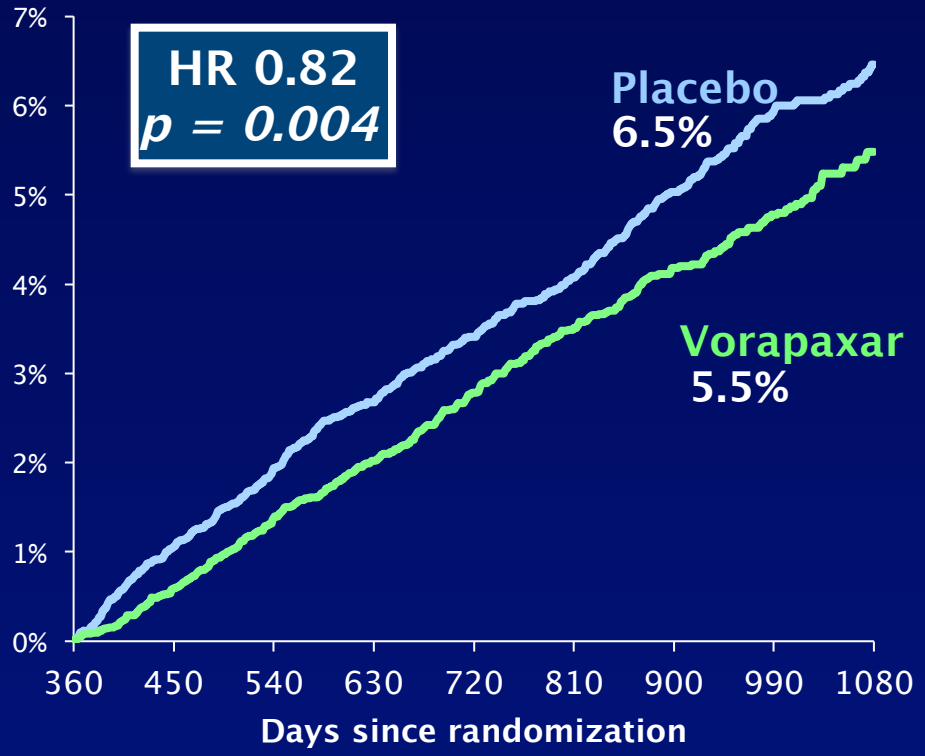
Efficacy, Early and Late

Prior MI Cohort

Days 0 to 360

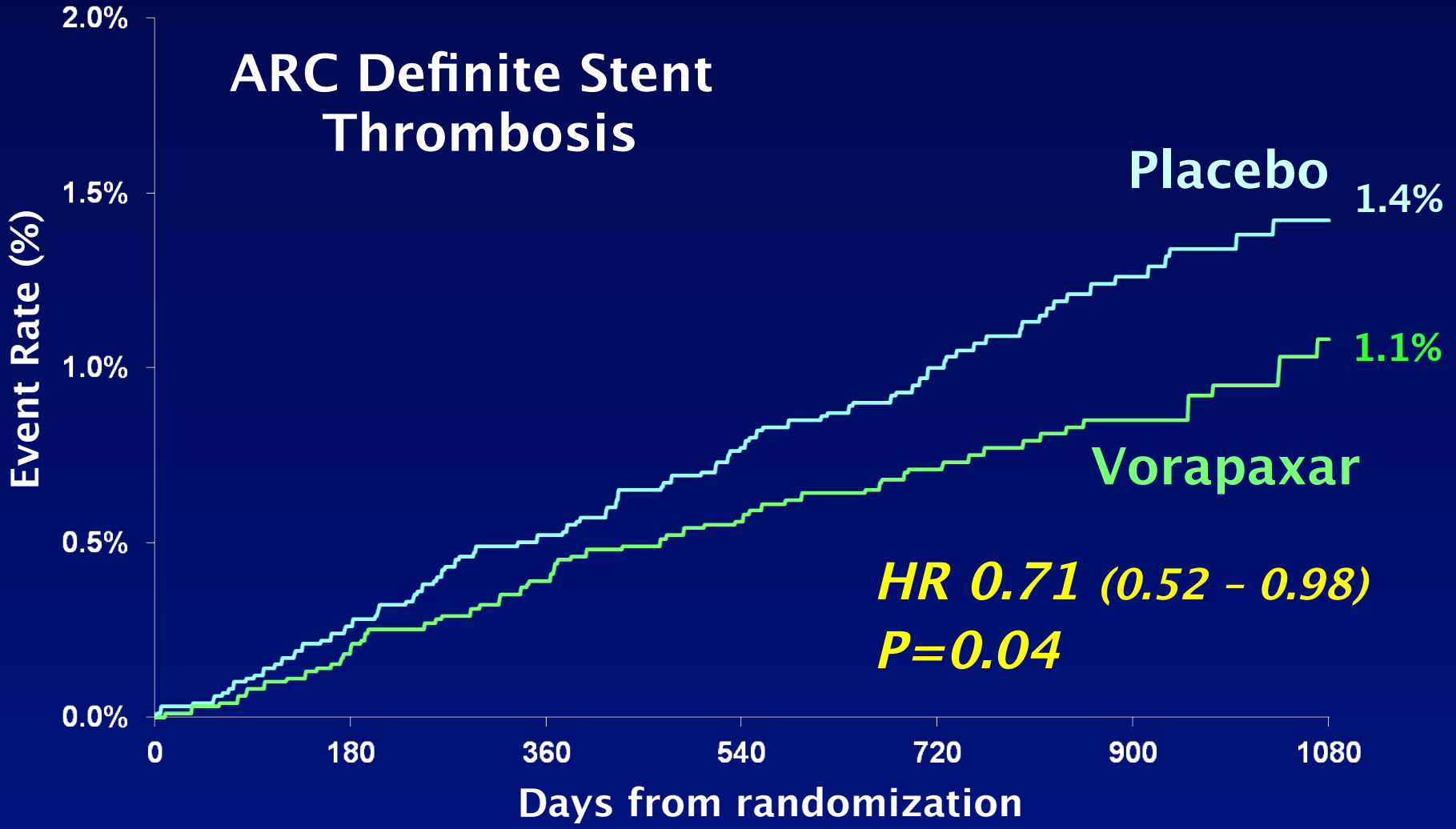


Days 360 to 1080



Scirica et al. Lancet 2012;380:1317-24

Stent Thrombosis by Randomized Treatment



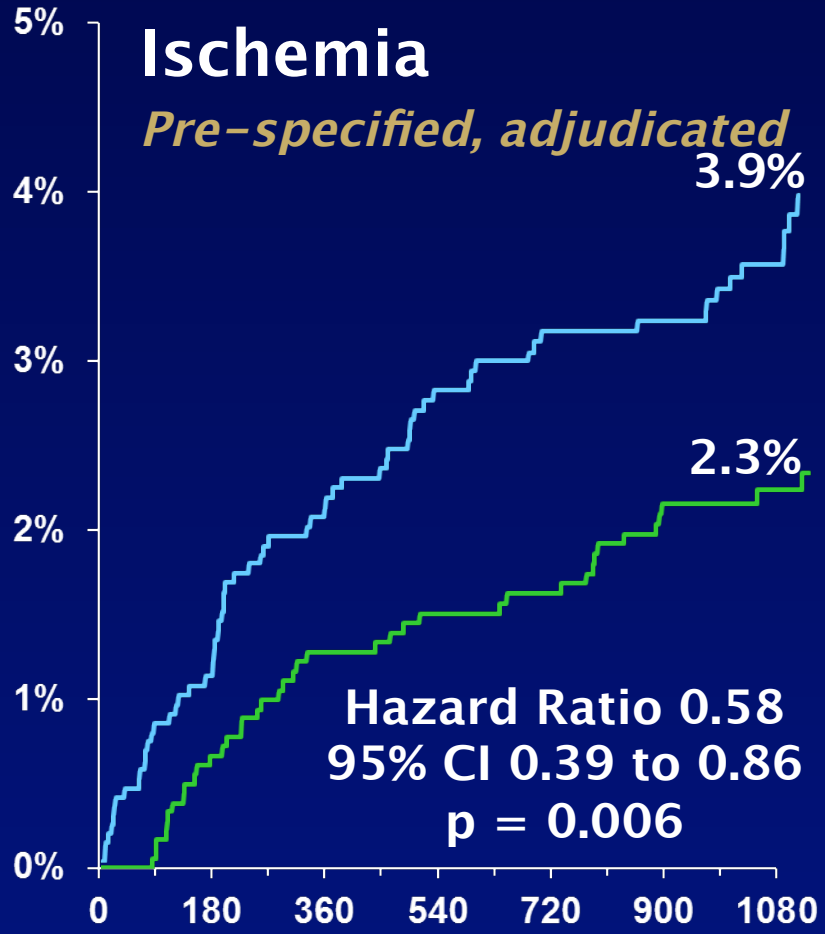
Bonaca et al. AHA 2013. Dallas, TX

Vorapaxar and Limb Vascular Efficacy

N = 3767

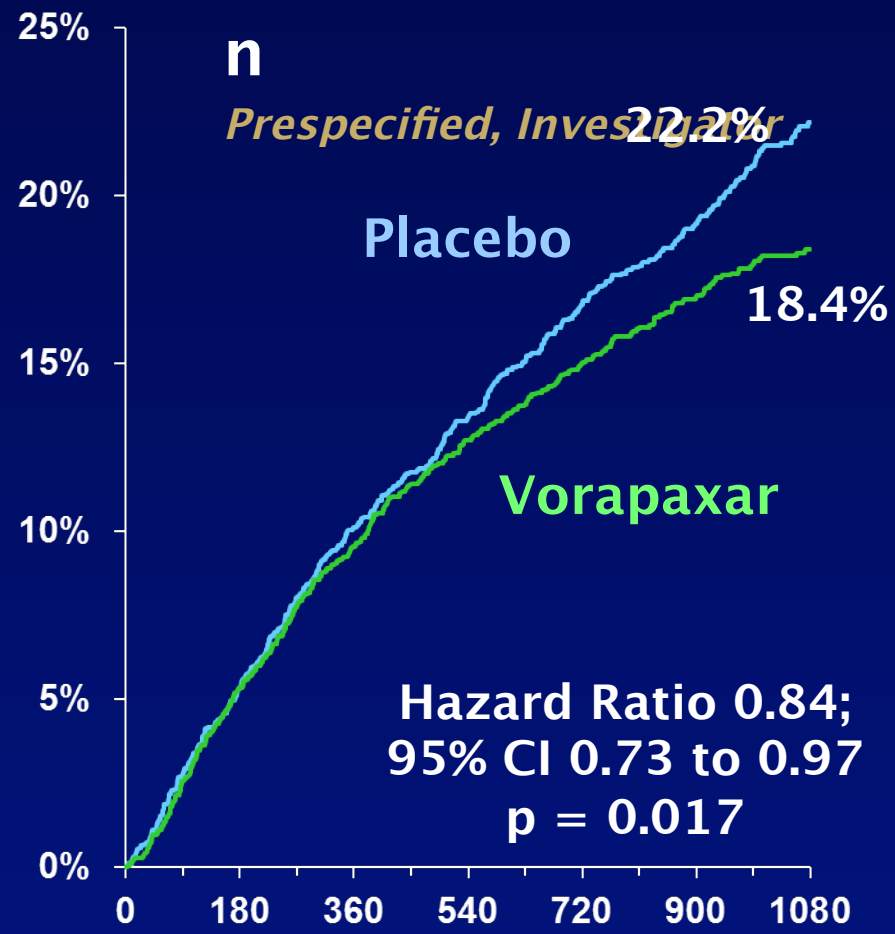
Hospitalization for Acute Limb Ischemia

Pre-specified, adjudicated



Peripheral Revascularization

Prespecified, Investigator

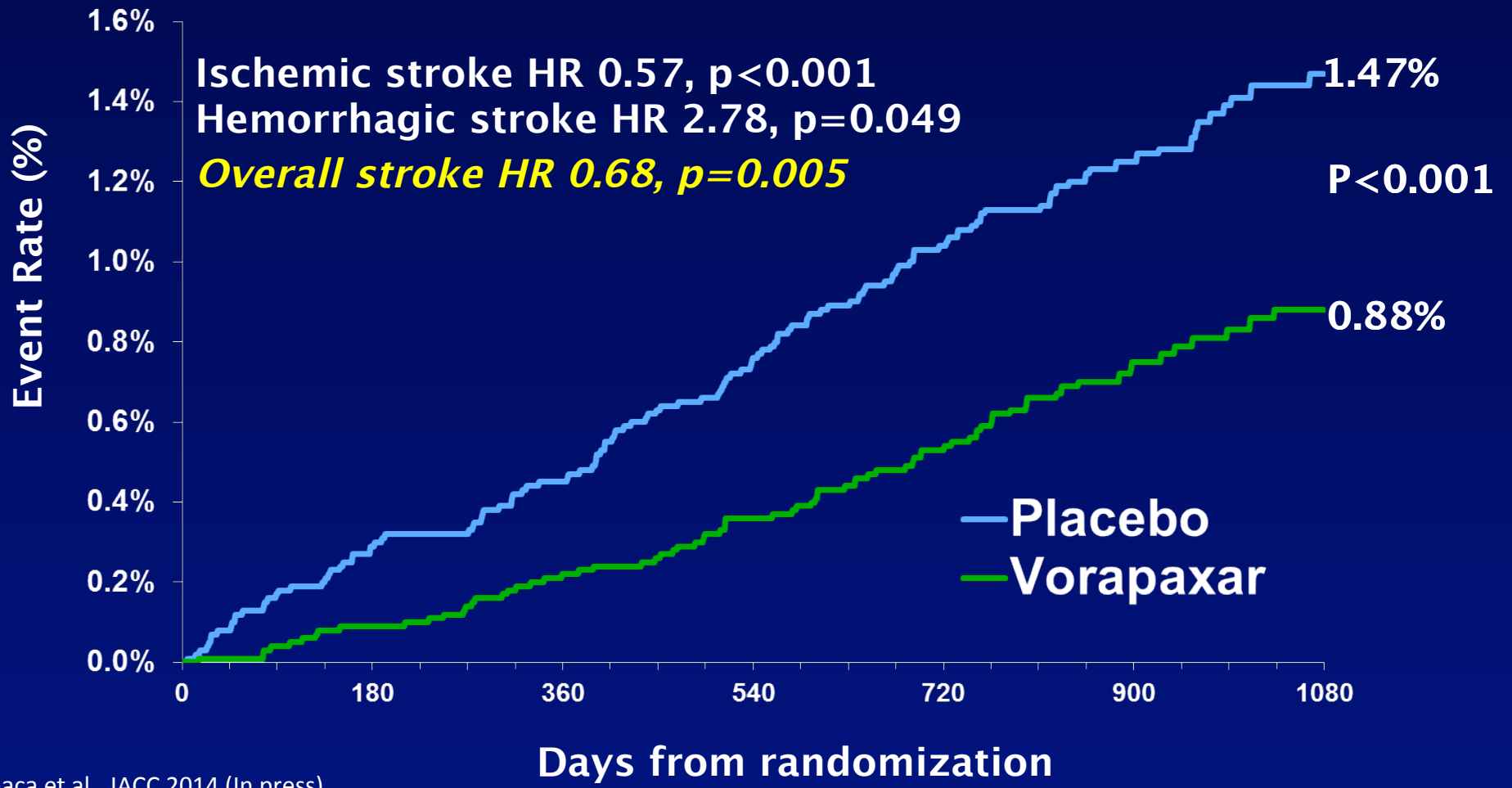


Days from randomization

Bonaca et al. Circulation 2013;127:1522-9

Incidence of New Ischemic Stroke

Patients without history of Stroke/TIA
N = 20,170

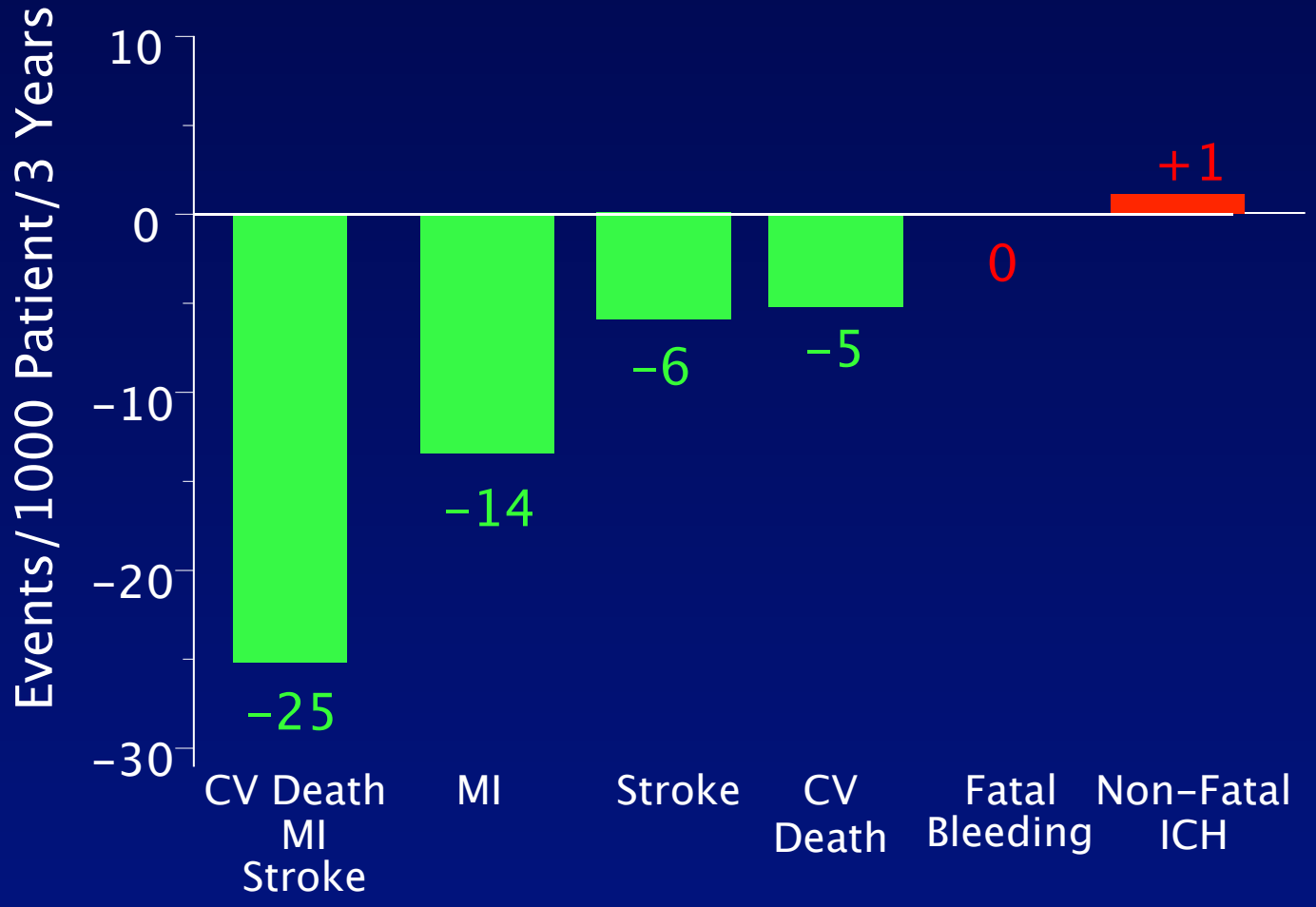


Bonaca et al. JACC 2014 (In press)

Patients with Prior MI and No Hx of Stroke or TIA

Risk Differences for 1000 Patients per 3 years- Vora vs. PBO

First Serious (Irreversible) Events



Braunwald E. Source: US FDA website - 20140115 CRDAC-S1-03

Study Design

21,105 PATIENTS
AF on electrical recording within last 12 months
Intended oral anticoagulant
$CHADS_2 \geq 2$

RANDOMIZATION
1:1:1 randomization is stratified by $CHADS_2$ score 2–3 versus 4–6 and need for edoxaban dose reduction*

Double-blind, Double-dummy

Low-dose Edoxaban 30* mg QD	High-dose Edoxaban 60* mg QD	Warfarin (INR 2.0–3.0)

*Dose reduced by 50%:
- CrCl 30–50 mL/min
- Weight ≤ 60 kg
- Strong P-gp inhibitor

1° Efficacy EP = Stroke or SEE
2° Efficacy EP = Stroke or SEE or CV mortality
1° Safety EP = Major Bleeding (ISTH criteria)

Non-inferiority
Upper 97.5% CI <1.38

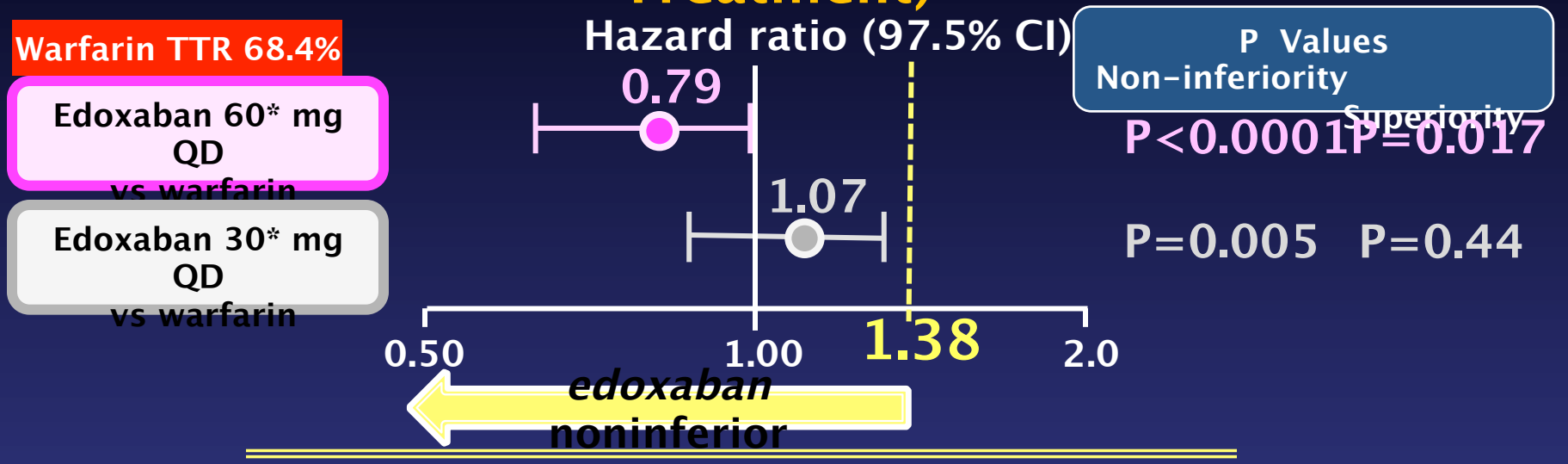
CI = confidence interval; CrCl = creatinine clearance;
ISTH=International Society on Thrombosis and Haemostasis;
P-gp = P-glycoprotein; SEE=systemic embolic event

Ruff et al. Am Heart J 2010; 160:635-41

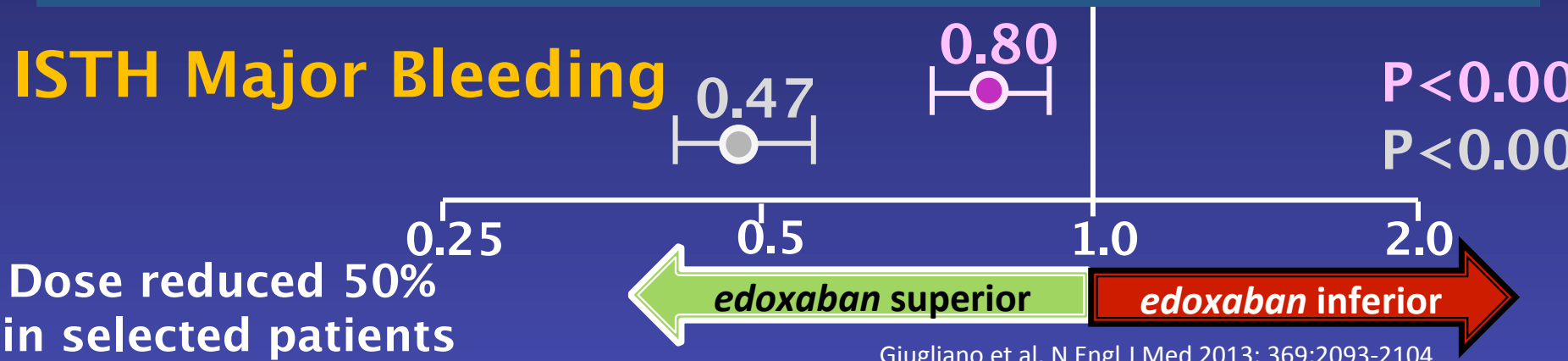
Primary Efficacy and Safety Results
(2.8 years median f/u)

Engage AF TIMI 48

Stroke/SEE: Noninferiority Analysis (mITT, On Treatment)



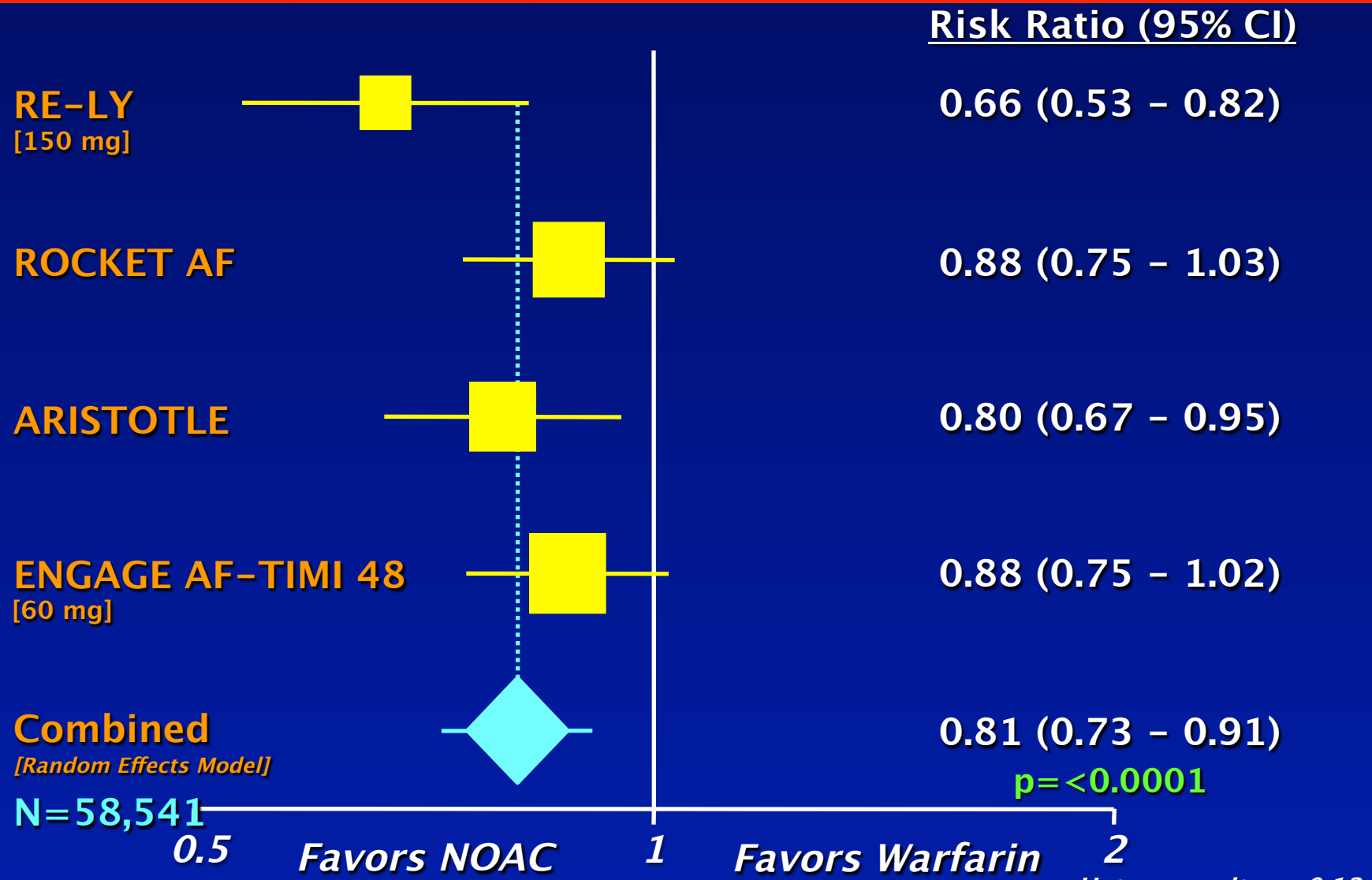
Major Bleeding: (Safety Cohort, On Treatment)



* Dose reduced 50% in selected patients

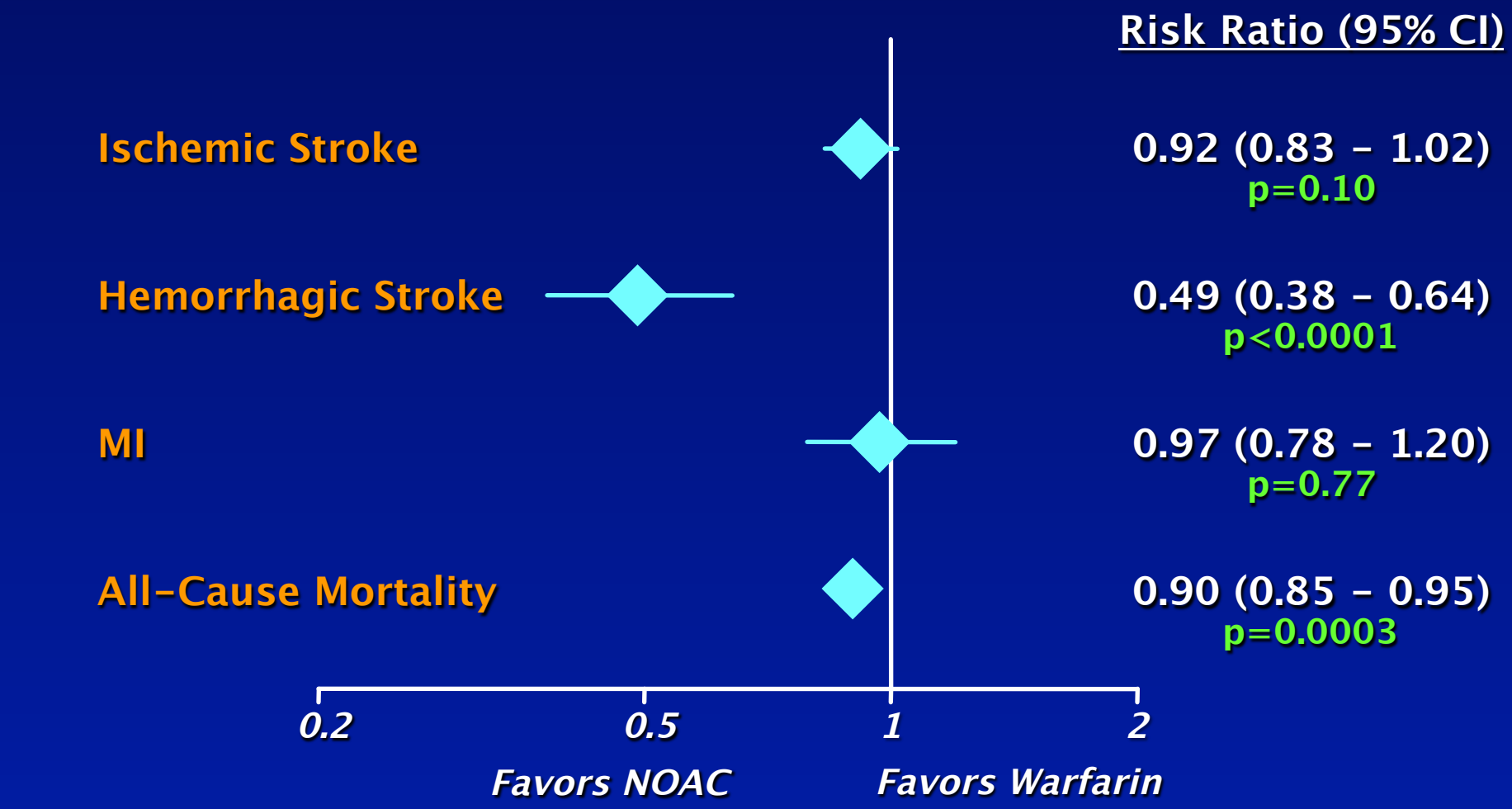
Giugliano et al. N Engl J Med 2013; 369:2093-2104

All Novel Oral Anticoagulants (NOAC): Stroke or SEE



Ruff et al. Lancet 2014;383:955-62

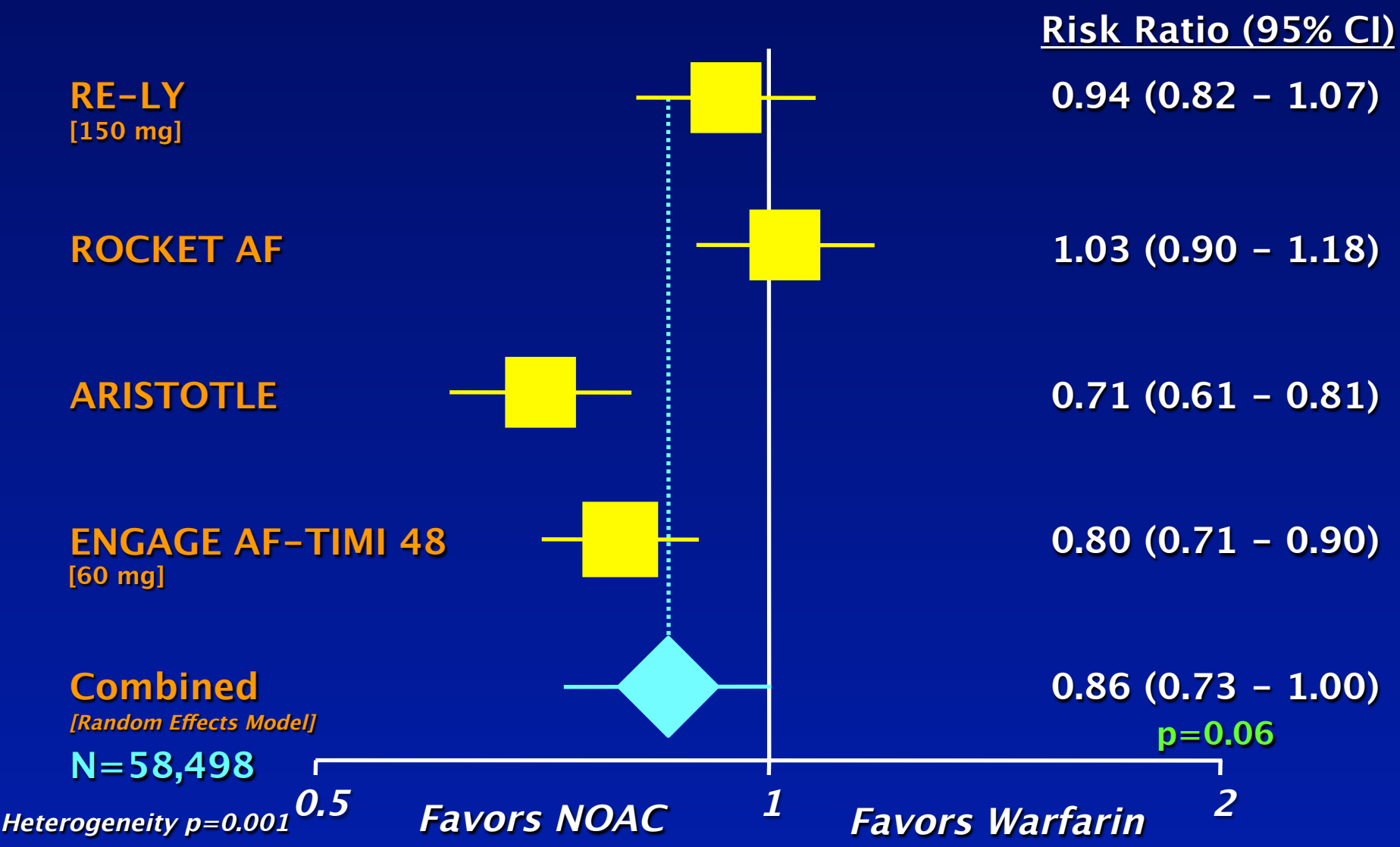
Secondary Efficacy Outcomes



Heterogeneity p=NS for all outcomes

Ruff et al. Lancet 2014;383:955-62

All NOACS: Major Bleeding



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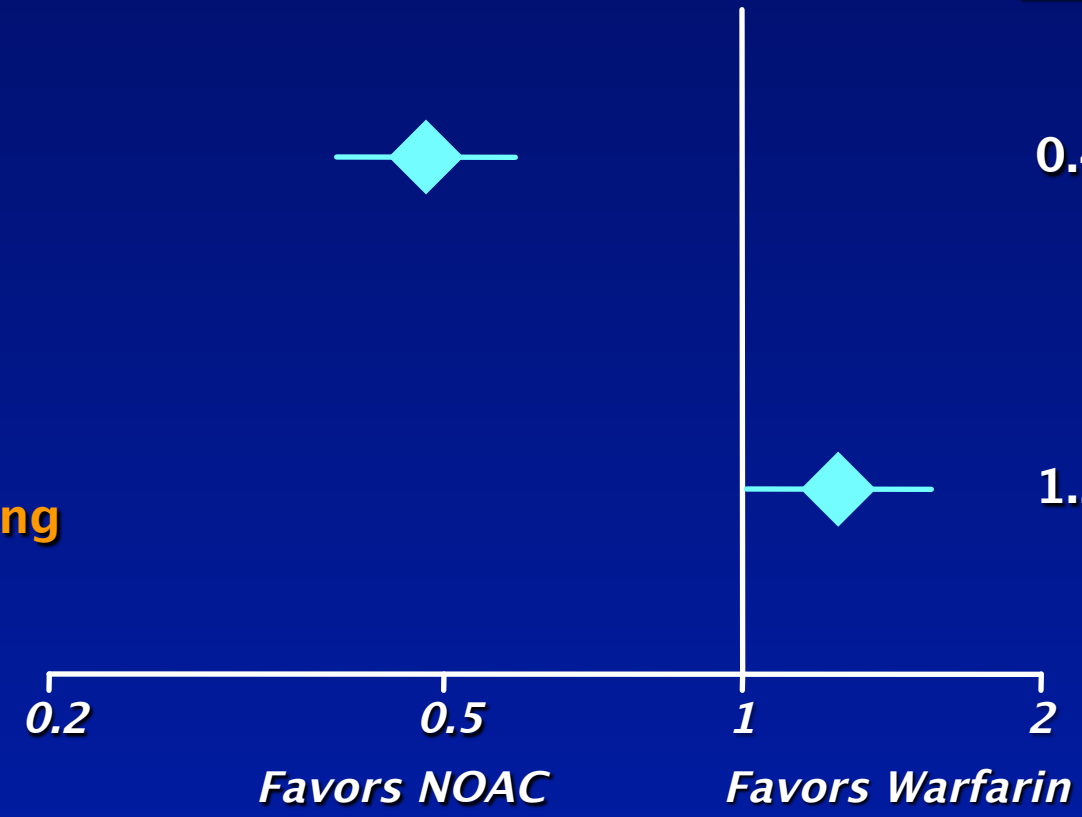
Secondary Safety Outcomes



Heterogeneity
ICH, p=0.22
GI Bleeding, p=0.009

Ruff et al. Lancet 2014;383:955-62

New Trial Data

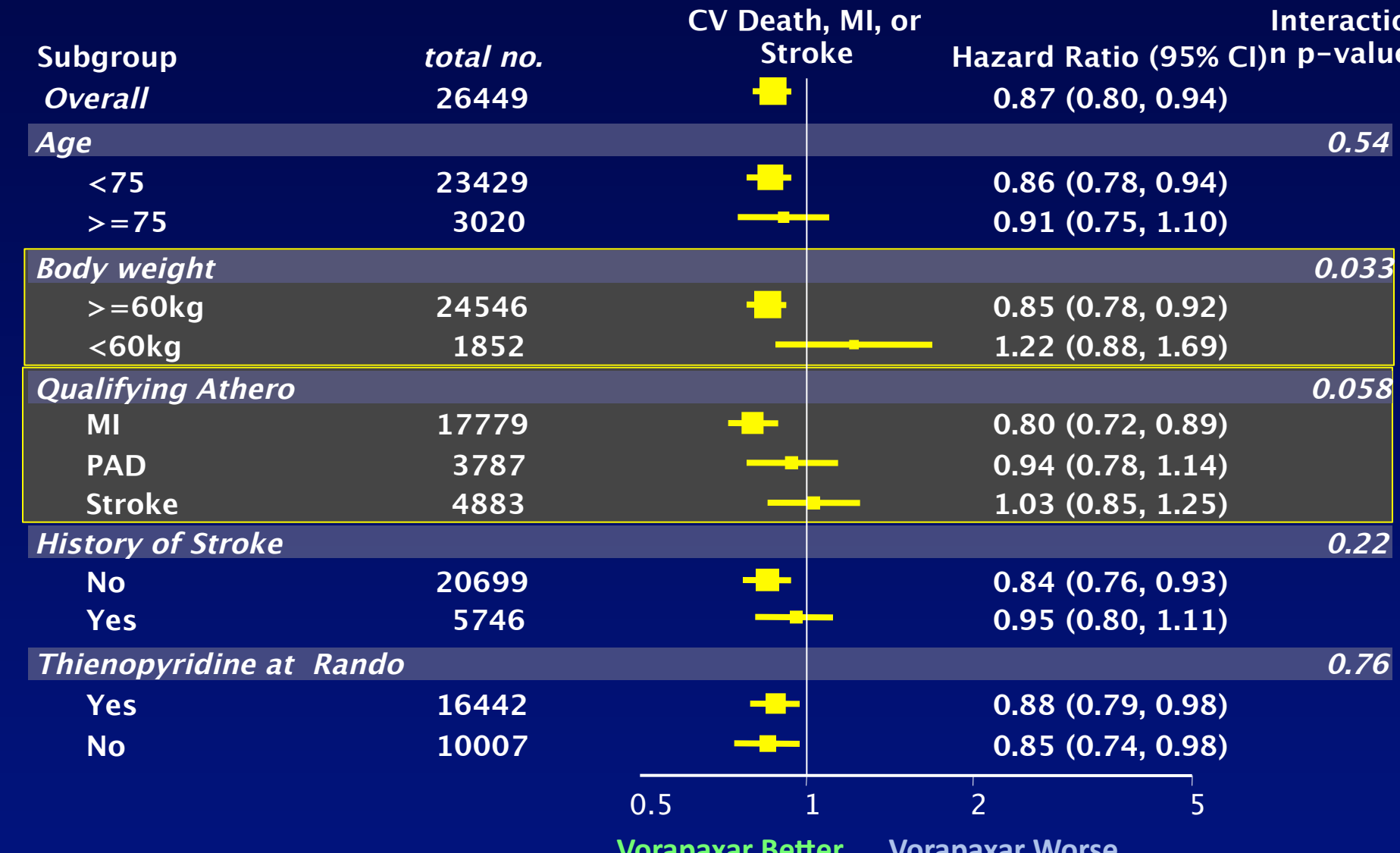
- OPTIMIZE – Shorter DAPT may be OK w/ low risk pts, 2nd gen drug-eluting stent (DES)
- ATLANTIC – Ticagrelor pretreatment may reduce stent thrombosis
- Vorapaxar – Now approved for post-MI patients, PAD patients
- ENGAGE AF TIMI 48 – Edoxaban appears very promising
- NOAC Meta-Analysis – NOACs superior to warfarin in afib

Background Therapy

		Placebo (N = 13224)	Vorapaxar (N = 13225)
Antiplatelet Therapy, %			
Qualifying MI	Aspirin	98	98
	Thienopyridine	78	78
PAD	Aspirin	88	88
	Thienopyridine	37	37
Stroke	Aspirin	81	81
	Thienopyridine	24	24
	Dipyridamole	19	20
Other Medications at Enrollment			
Lipid-lowering agent (%)		92	91
ACEI or ARB (%)		75	74
Beta-blocker (qualifying MI)		84	84

Morrow et al. NEJM 2012;366:1404-13

CV Death, MI, or Stroke in Major Subgroups



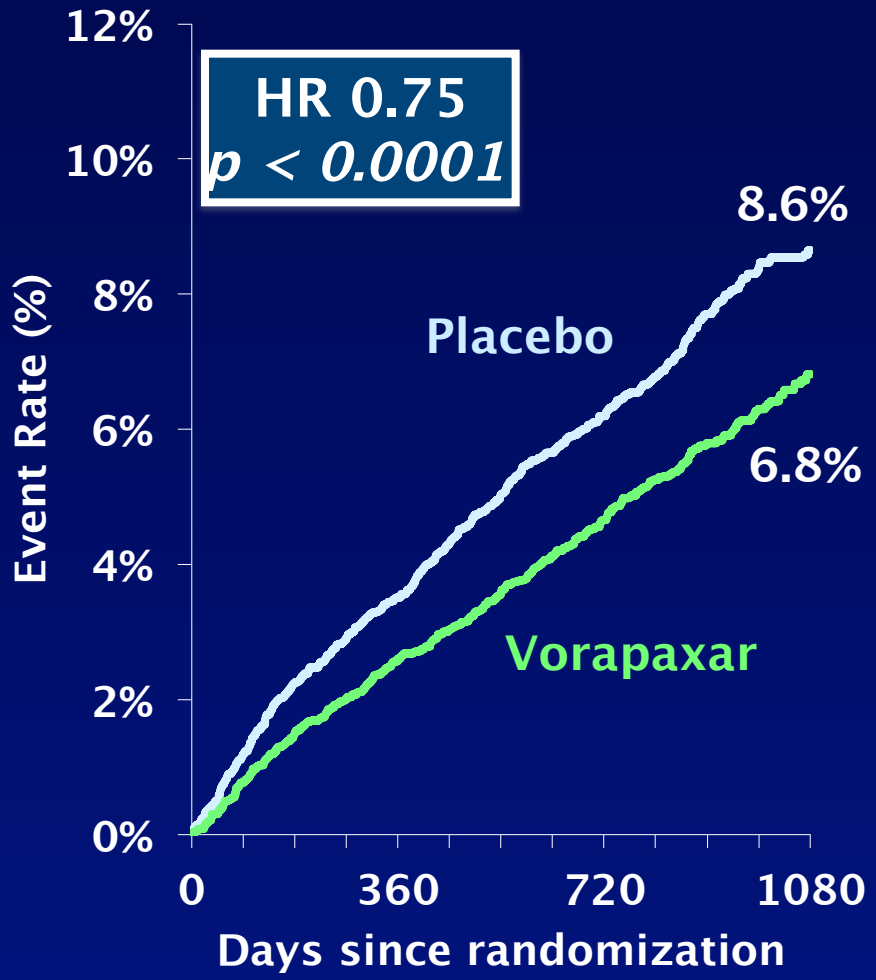
Morrow et al. NEJM 2012;366:1404-13

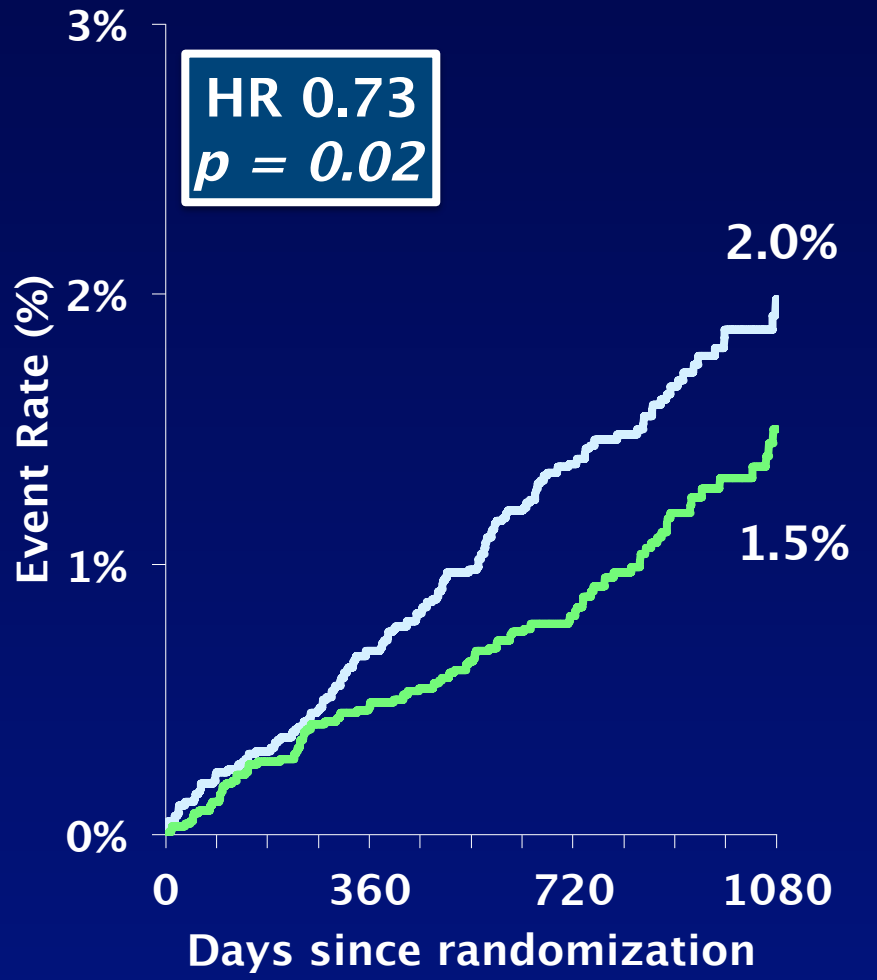
MI Cohort

TRA 2°P TIMI 50

Primary Efficacy Evaluation

Low Bleeding Risk Cohort (N= 14,909)*

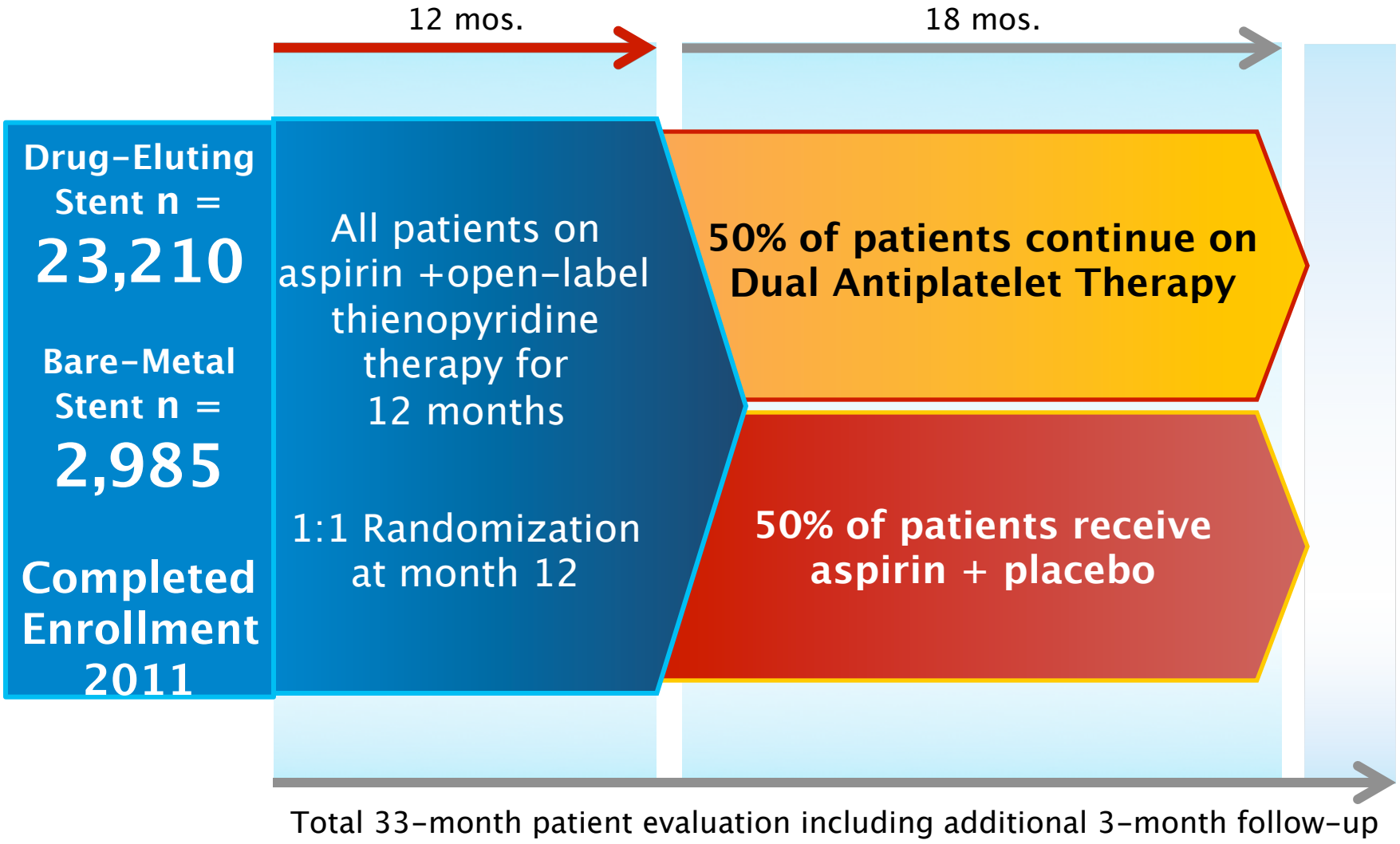




**Age <75 y, no h/o stroke/TIA, wt ≥60 kg*

Scirica et al. Lancet 2012;380:1317-24

DAPT: Design



Mauri et al. Am Heart J. 2010;160:1035-41.

www.daptstudy.org www.clinicaltrials.gov – NCT00977938

PEGASUS – TIMI 54

N ~ 21,000

Stable pts with history of MI 1–3 yrs prior + ≥1 additional atherothrombosis risk factor*

** Age ≥65 yrs, diabetes, 2nd prior MI, multivessel CAD, or chronic non-end stage renal dysfunction*

RANDOMIZE DOUBLE BLIND

Planned treatment with ASA 75 – 150 mg & Standard background care

- **Ticagrelor 90 mg bid**
- **Ticagrelor 60 mg bid**
- **Placebo**

Follow-up Visits Q4 mos for 1st yr, then Q6 mos

Min 12 mos and median 26 mos follow-up
Event-driven trial

Primary Efficacy Endpoint: CV Death, MI, or Stroke

Primary Safety Endpoint: TIMI Major Bleeding

Bonaca et al. Am Heart J. 2014;167:437-44.

THEMIS

Design and main eligibility criteria

Type 2 diabetes; men and women ≥ 50 years
≥ 6 months glucose-lowering drug treatment
*At high risk for CV events**
No previous MI or stroke
No planned use of ADP receptor antagonist or planned revascularisation

Low-dose ASA background therapy based on individual risk

** At high risk of CV events defined as history of PCI or CABG or angiographic evidence of ≥ 50% lumen stenosis of at least 1 coronary artery*

Ticagrelor | *Placebo*

Event driven study; 750 CV events required. 2 years mean follow-up. (n=17 000)

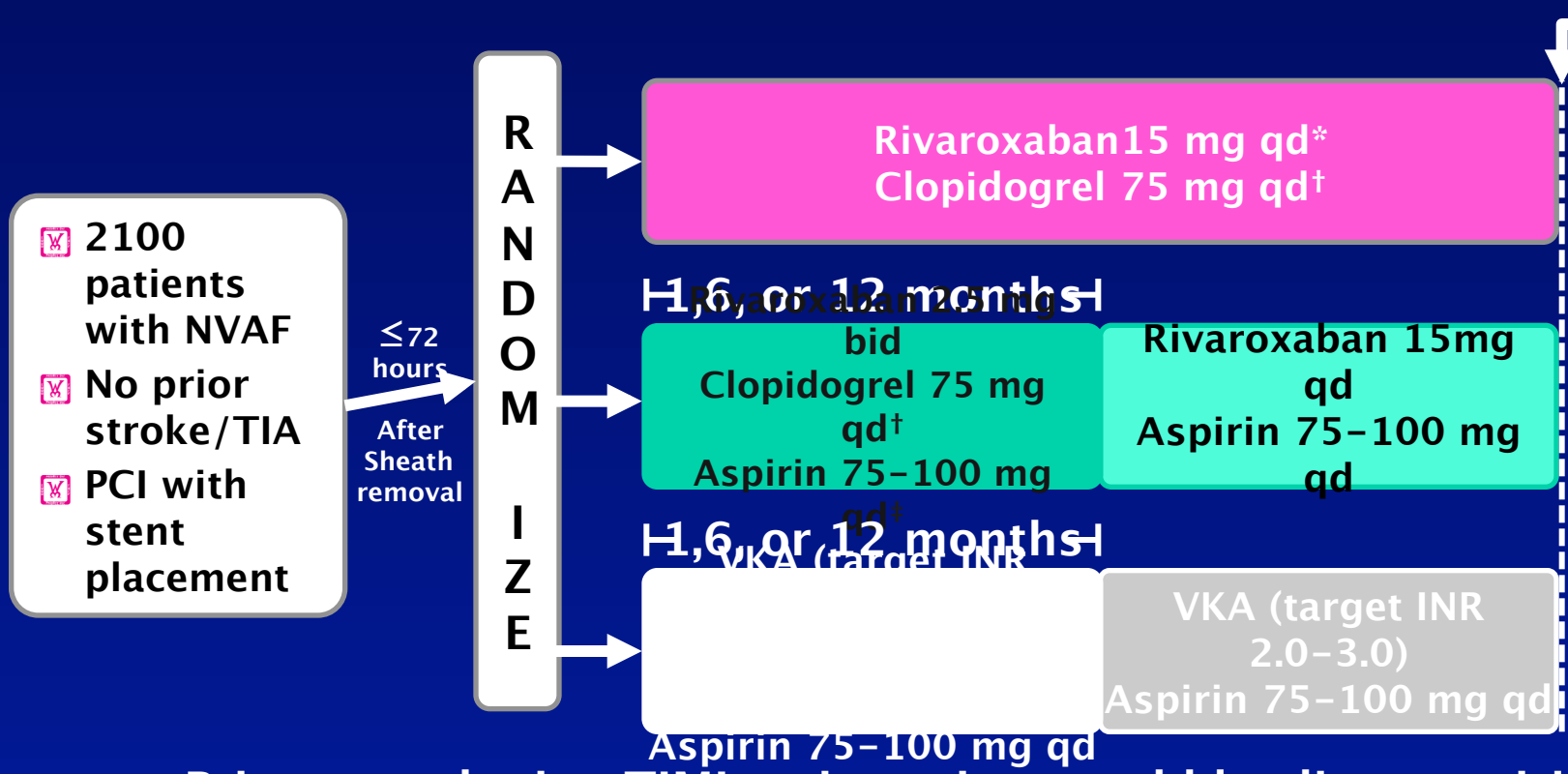
Primary endpoint : Composite of CV death, MI or stroke

Secondary endpoint: Composite of all-cause death, MI or stroke; CV death; All-cause death

Primary safety: TIMI Major bleeding

http://www.clinicaltrials.gov/show/NCT01991795 ADP=adenosine diphosphate

Rivaroxaban Use in Patients with AF Undergoing PCI: PIONEER AF-PCI



- Primary endpoint: TIMI major, minor, and bleeding requiring medical attention
- Secondary endpoint: CV death, MI, stroke, and stent thrombosis

*Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.

†Alternative $P2Y_{12}$ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.

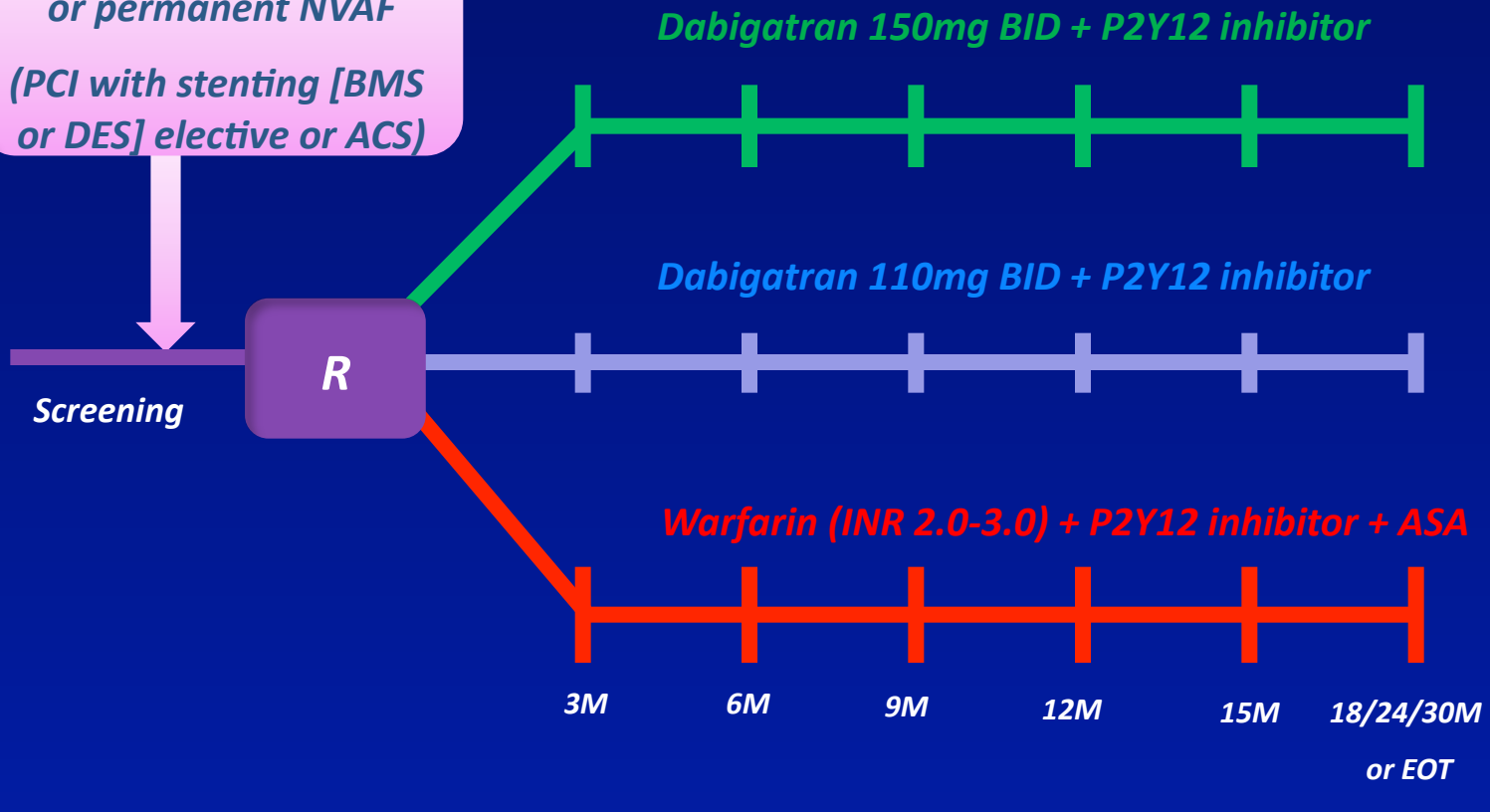
‡Low-dose aspirin (75-100 mg/d).

RE-DUAL PCI:
Study in NVAF Patients Undergoing PCI

Worldwide Event Driven Trial

Paroxysmal, persistent, or permanent NVAF

(PCI with stenting [BMS or DES] elective or ACS)



1° End Point

Thrombotic

Event Rate

(Death + MI + Stroke/SE)

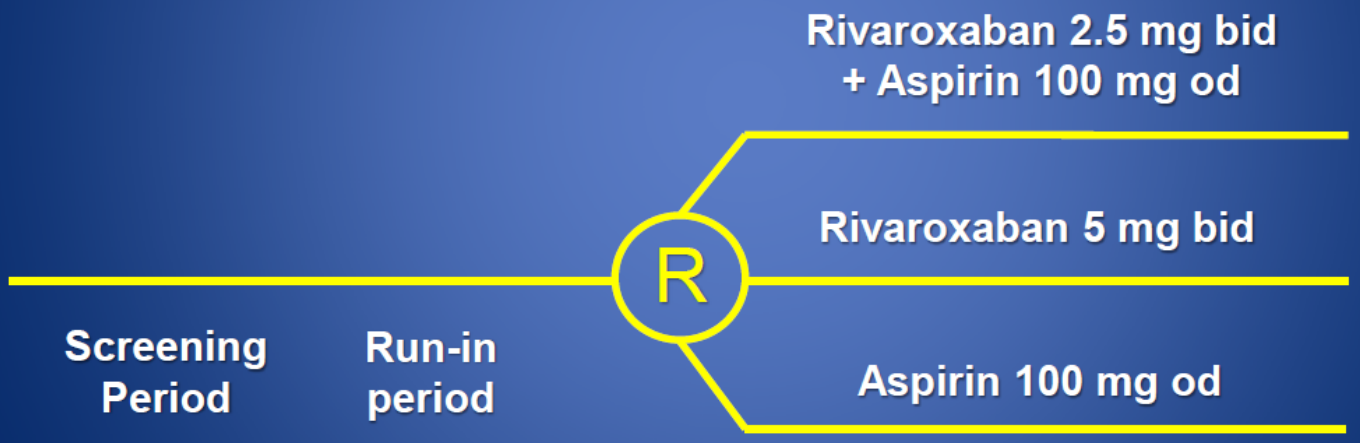
Plus

Clinically Relevant Bleeding Rate

(ISTH Major)

COMPASS

Rivaroxaban on top of aspirin and versus aspirin
in patients with coronary and/or peripheral artery disease



Primary outcome: MI, Stroke, CV death (n=2,200)
Mean follow up: 3-4 years

BRIGHAM AND WOMEN'S HOSPITAL

Heart & Vascular Center

Thank You!

Deepak L. Bhatt, MD, MPH
Executive Director of Interventional Cardiovascular Programs,
BWH Heart & Vascular Center
Professor of Medicine,
Harvard Medical School
1 (857) 307-1992
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Late-Breaking Clinical Trials & FDA Update

Lipids

Christie M. Ballantyne, MD
Center for Cardiovascular Disease Prevention
Methodist DeBakey Heart & Vascular Center
Baylor College of Medicine
Houston, Texas

FDA and Progress Update on:

1. Omega-3 FAs
2. PCSK9 inhibitors
3. CETP inhibitors
4. Lp-PLA_2 inhibitors
5. ETC 1002
6. Lp(a), apo C-III inhibitors

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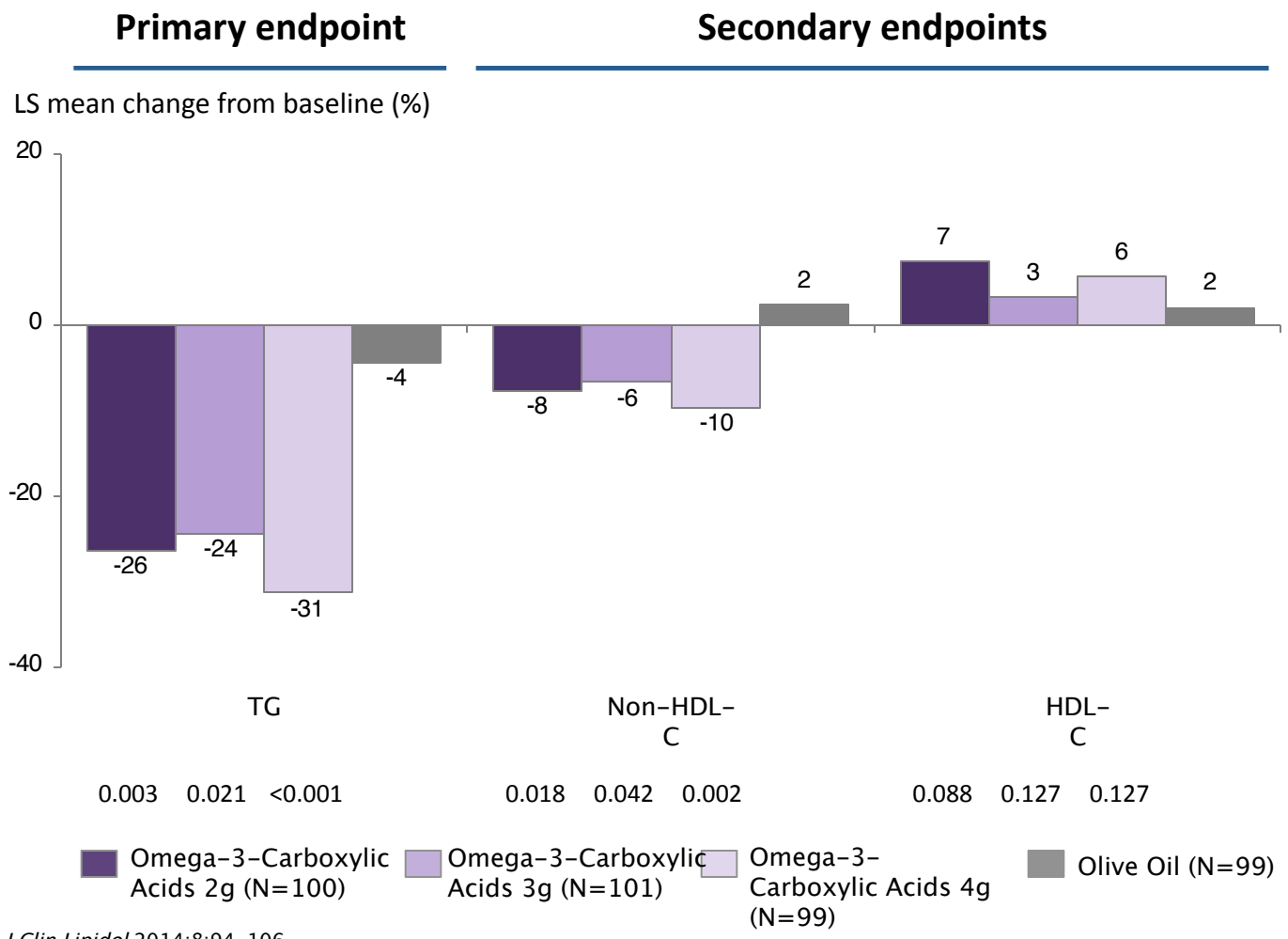

Kastelein JJ et al. *J Clin Lipidol* 2014;8:94-106

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PCSK9 Inhibitor Race to the Market

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By RON WINSLOW and JOSEPH WALKER CONNECT

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  - N = 18,000
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- FOURIER (evolucumab)
  - N = 22,500
  - Duration 5 years
- SPIRE-1 (bococizumab)
  - N = 12,000, LDL-C ≥70 and <100 mg/dL
- SPIRE-2 (bococizumab)
  - N = 6,300, LDL-C ≥100 mg/dL

http://clinicaltrials.gov/ct2/show/NCT01663402
http://clinicaltrials.gov/ct2/show/NCT01252953
http://clinicaltrials.gov/ct2/show/NCT01975376
http://clinicaltrials.gov/ct2/show/NCT01975389

PCSK9 Inhibitors in Development

Investigational Product	Company	Stage of Development
Monoclonal antibodies		
Alirocumab (SAR236553, REGN727)	Sanofi (Regeneron)	Phase III
Evolocumab (AMG 145)	Amgen	Phase III
Bococizumab (PF-0490615, RN316)	Pfizer (Rinat)	Phase III
MPSK 3169A (RG7652)	Genentech (Roche)	Phase II–terminated
LY3015014	Lilly	Phase I
PCSK9 synthesis inhibitor/siRNA		
Alnylam	ALN-PCS02	Phase I
Bristol-Myers Squibb/ Adnexus	BMS-962476 (Adnectin)	Phase I
Small molecule		
Serometrix	SX-PCK9	Preclinical

Adapted from Stein et al Curr Atheroscler Rep 2013; 15: 310

CETP Outcome Trials

- REVEAL (anacetrapib)
  - N = 30,000
  - Duration 4 years

- ACCELERATE (evacetrapib)
  - N = 12,000
  - Duration 4 years

http://clinicaltrials.gov/ct2/show/NCT01252953 http://clinicaltrials.gov/ct2/show/NCT01687998

$LpPLA_2$ Outcome Trials of Darapladib vs Placebo

- **STABILITY** [1]
  - 15,828 patients with stable CHD; median follow-up 3.7 years
  - No significant differences in primary endpoint (time to CV death, MI, or stroke; 9.7% vs 10.4%, HR 0.94, 95% CI 0.85-1.03, P=.20), individual components, or all-cause mortality
  - Additional secondary endpoints reduced with darapladib: major coronary events (9.3% vs. 10.3%; HR 0.90; 95% CI 0.82-1.00; P=0.045) and total coronary events (14.6% vs. 16.1%; HR 0.91; 95% CI 0.84-0.98; P = 0.02)
- **SOLID-TIMI 52** [2]
  - 13,026 patients post ACS; median follow-up 2.5 years
  - No differences in primary endpoint of major coronary events (CHD death, MI, or urgent coronary revascularization; 16.3% vs 15.6%, HR 1.00, 95%CI 0.91-1.09, P=.93) or secondary endpoints
- **Conclusion:** In CHD patients treated with guideline-recommended medical therapy, addition of darapladib did not reduce clinical events

1. STABILITY Investigators. *N Engl J Med* 2014;370:1702-11.
2. O'Donoghue ML et al, for the SOLID-TIMI 52 Investigators. *JAMA* 2014;312:1006-1

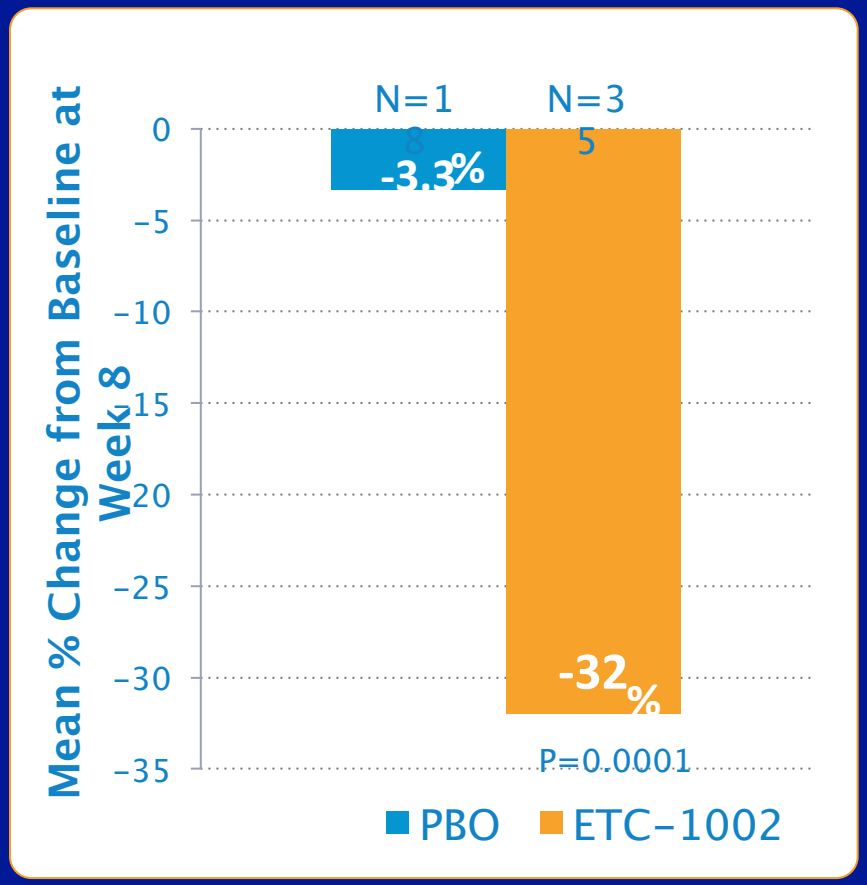
ETC-1002
Pharmacologic Properties

- Oral, once-daily small molecule
- Half-life: 15-24 hours
- Target organ: Liver
  - Minimal metabolism in preclinical and clinical studies
  - Primary biliary and minimal kidney excretion
- No competitive liver uptake with statins (e.g. OATP1B1)
- MOA: Inhibits ATP-citrate lyase (ACL) and activates AMP-activated protein kinase (AMPK)

Thompson P et al presented at ACC, 2014

ETC-1002-006 Efficacy in statin intolerant patients

LDL-C Mean Change From Baseline to Week 8



- Approximately 2/3 of patients reached their ATP-III NCEP LDL-C goal
- Baseline mean LDL-C =179 mg/dL

MITT analysis, Confidence Interval % change (-35.4, -22.1)

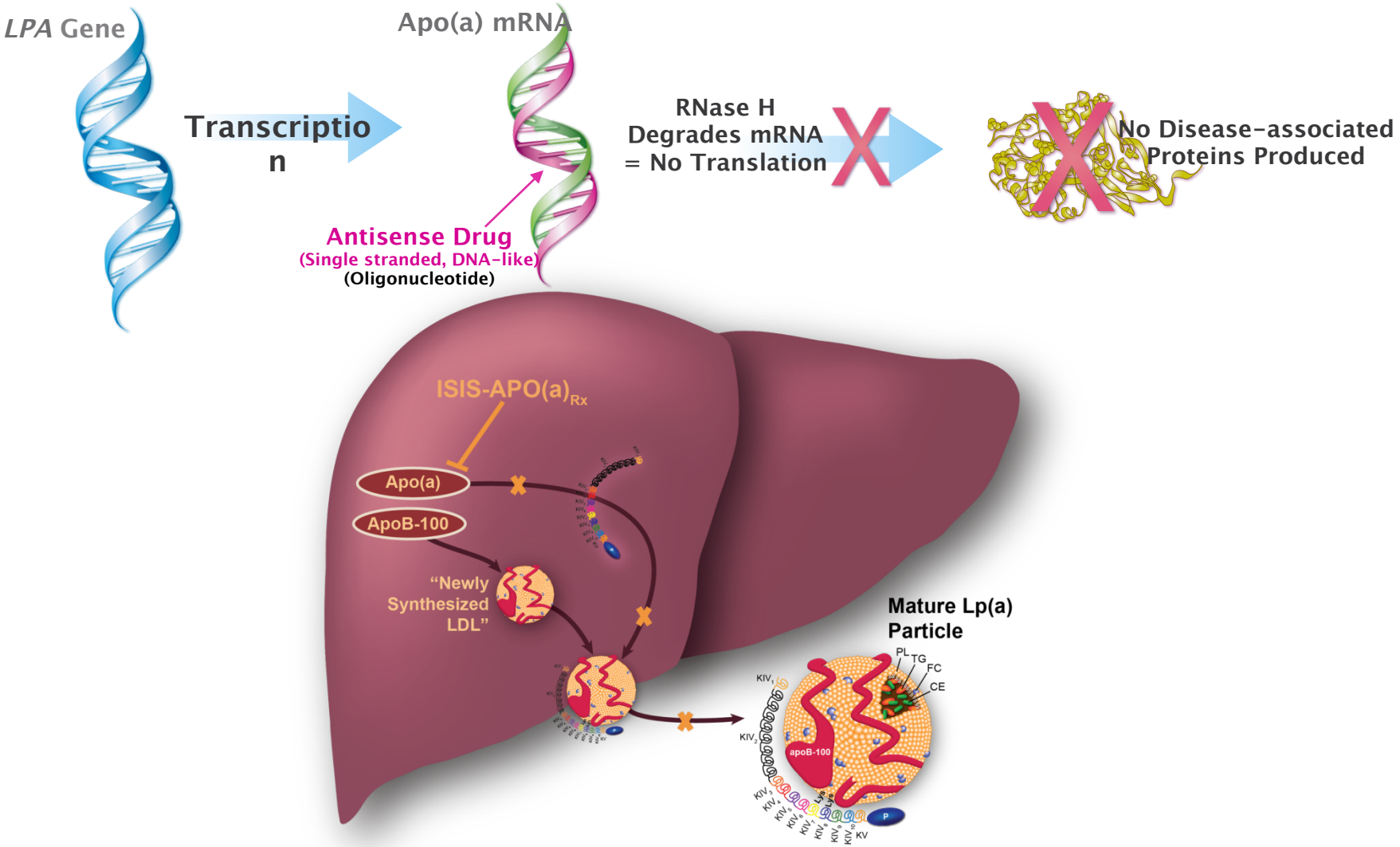
Thompson P et al presented at ACC, 2014

ETC-1002-006 Safety in Statin Intolerant Patients
Muscle-related Adverse Events

Treatment Emergent Occurrences	Number (%) of Patients	
	ETC-1002 N=37	PBO N=19
Any Muscle-Related AE(s)	10 (27%)	6 (32%)
Discontinuation Due to Muscle Related AE(s)	0 (0%)	3 (16%)

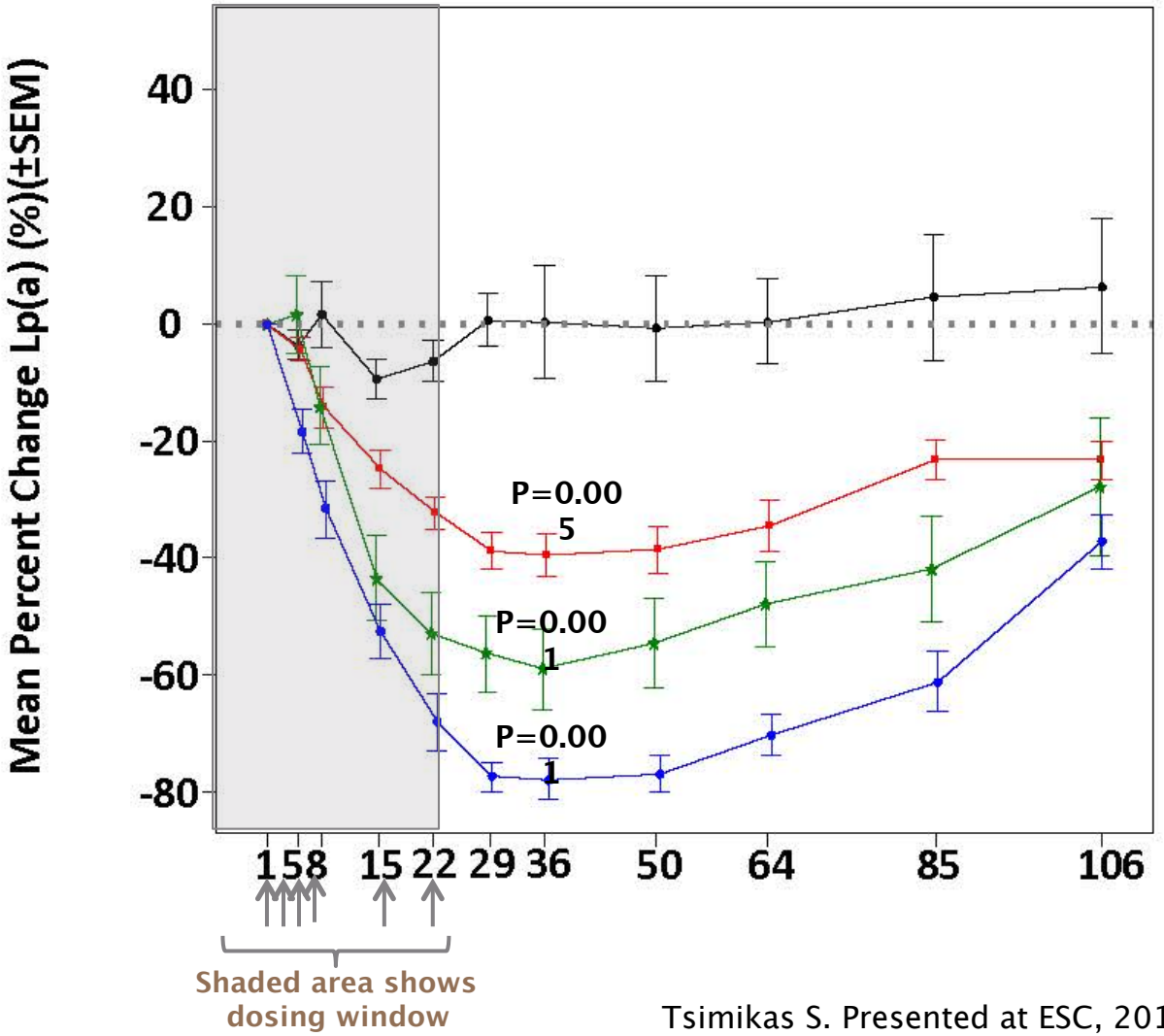
Thompson P et al presented at ACC, 2014

ISIS-APO(a)$_{Rx}$
Mechanism of Action in Reducing Plasma Lp(a)



Mean Percent Change Lp(a) Over Time by Treatment Groups

Multiple-Dose Cohorts (N=29)*

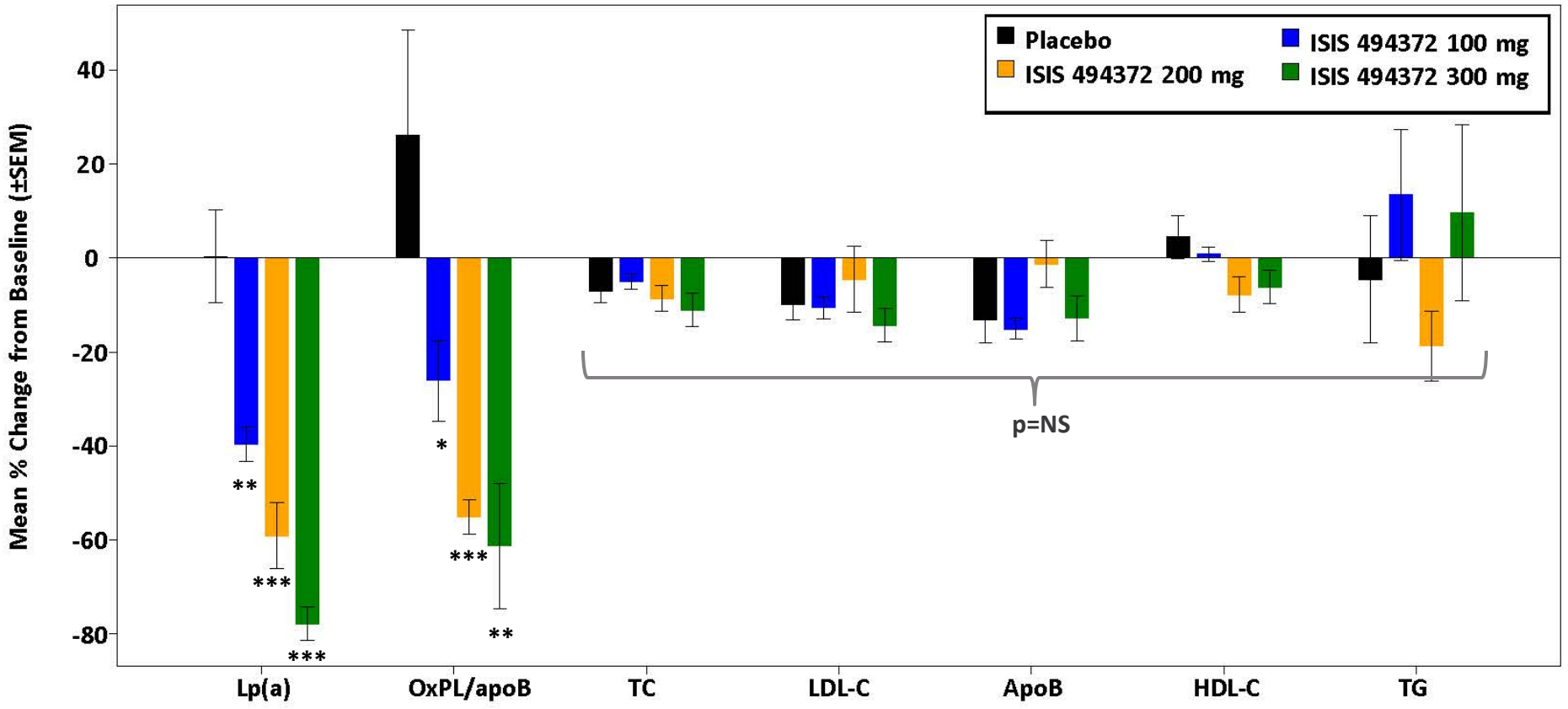


*Excludes 2 subjects who received < 3 doses of Study Drug

Wilcoxon Rank Sum Test p-value

Tsimikas S. Presented at ESC, 2014.

Mean Percent Change in Lp(a), OxPL/apoB, Lipid Profile and ApoB 2 Weeks After the Last Dose Phase 1 Multiple Dose Cohorts (Day 36)

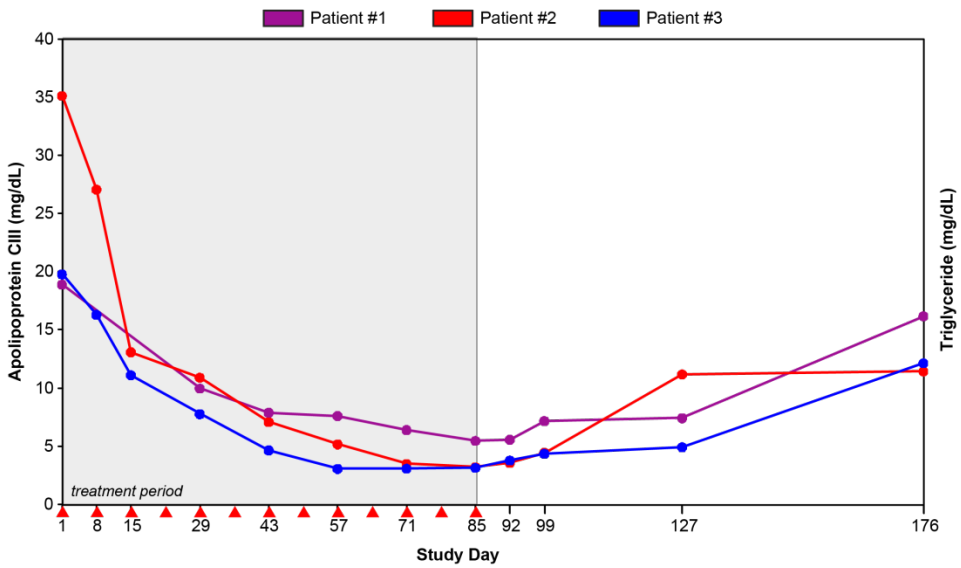


* p=0.02
** p≤0.008
*** p=0.001

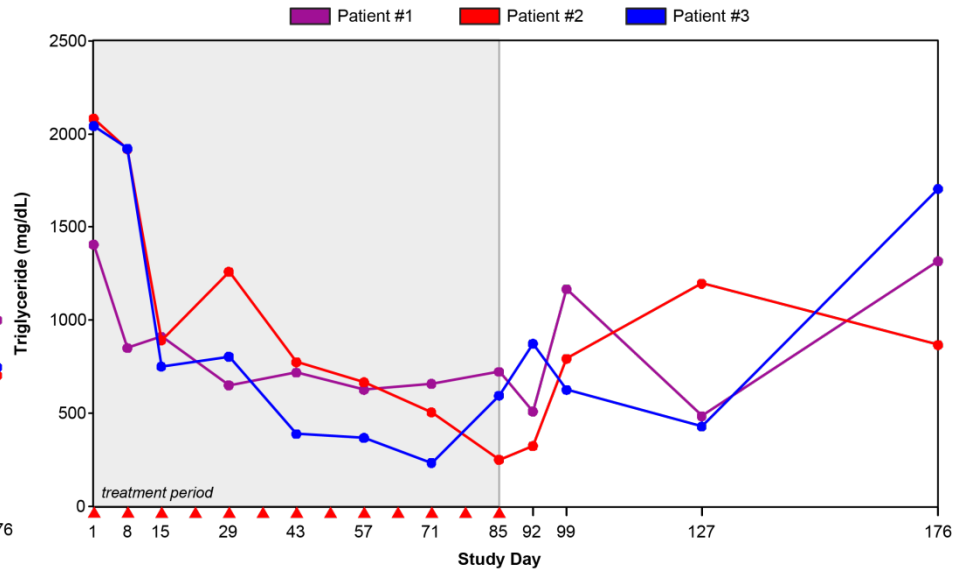
Tsimikas S. Presented at ESC, 2014.

ISIS-APOCIII$_{Rx}$ in FCS Patients
Reduced Fasting Plasma ApoC-III and TG Levels

Fasting ApoC-III Levels



Fasting Triglyceride Levels



Parameter (mg/dL)	Patient No.	Baseline*	Primary Endpoint†	Change from Baseline	% Change from Baseline
Triglyceride	1	1406	616.5	-789.5	-56.2
	2	2083	287.5	-1795.5	-86.2
	3	2043	734.5	-1308.5	-64.0
ApoC-III	1	18.9	5.5	-13.4	-70.9
	2	35.1	3.4	-31.7	-90.4
	3	19.8	3.5	-16.3	-82.5

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Lipids

Christie M. Ballantyne, MD
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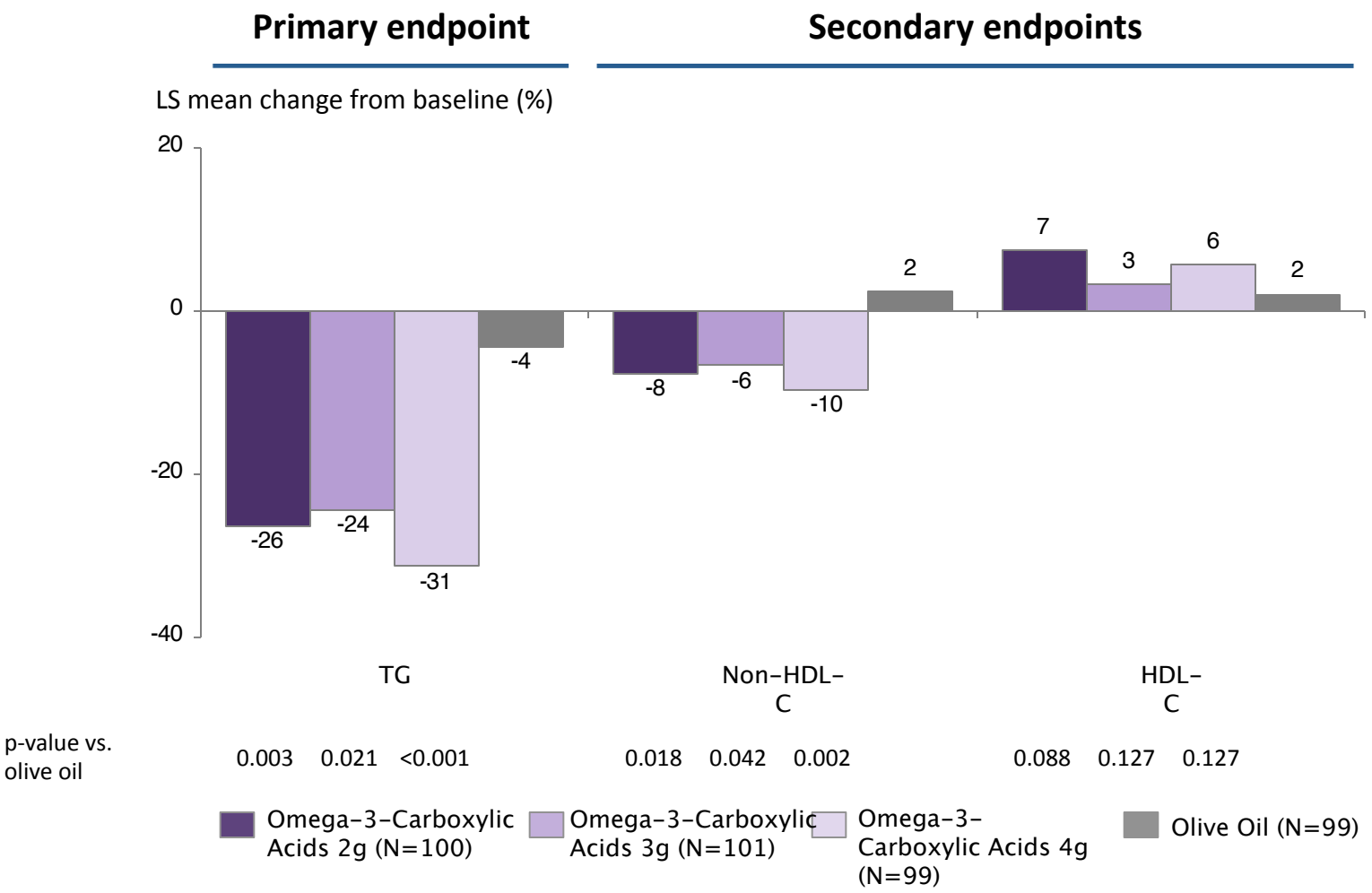

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http://clinicaltrials.gov/ct2/show/NCT01975389

PCSK9 Inhibitors in Development

Investigational Product	Company	Stage of Development
Monoclonal antibodies		
Alirocumab (SAR236553, REGN727)	Sanofi (Regeneron)	Phase III
Evolocumab (AMG 145)	Amgen	Phase III
Bococizumab (PF-0490615, RN316)	Pfizer (Rinat)	Phase III
MPSK 3169A (RG7652)	Genentech (Roche)	Phase II-terminated
LY3015014	Lilly	Phase I
PCSK9 synthesis inhibitor/siRNA		
Alnylam	ALN-PCS02	Phase I
Bristol-Myers Squibb/ Adnexus	BMS-962476 (Adnectin)	Phase I
Small molecule		
Serometrix	SX-PCK9	Preclinical

Adapted from Stein et al Curr Atheroscler Rep 2013; 15: 310

CETP Outcome Trials

- REVEAL (anacetrapib)
  - N = 30,000
  - Duration 4 years
- ACCELERATE (evacetrapib)
  - N = 12,000
  - Duration 4 years

http://clinicaltrials.gov/ct2/show/NCT01252953
http://clinicaltrials.gov/ct2/show/NCT01687998

$LpPLA_2$ Outcome Trials of Darapladib vs Placebo

- **STABILITY** [1]
  - 15,828 patients with stable CHD; median follow-up 3.7 years
  - No significant differences in primary endpoint (time to CV death, MI, or stroke; 9.7% vs 10.4%, HR 0.94, 95% CI 0.85-1.03, P=.20), individual components, or all-cause mortality
  - Additional secondary endpoints reduced with darapladib: major coronary events (9.3% vs. 10.3%; HR 0.90; 95% CI 0.82-1.00; P=0.045) and total coronary events (14.6% vs. 16.1%; HR 0.91; 95% CI 0.84-0.98; P = 0.02)
- **SOLID-TIMI 52** [2]
  - 13,026 patients post ACS; median follow-up 2.5 years
  - No differences in primary endpoint of major coronary events (CHD death, MI, or urgent coronary revascularization; 16.3% vs 15.6%, HR 1.00, 95%CI 0.91-1.09, P=.93) or secondary endpoints
- **Conclusion:** In CHD patients treated with guideline-recommended medical therapy, addition of darapladib did not reduce clinical events

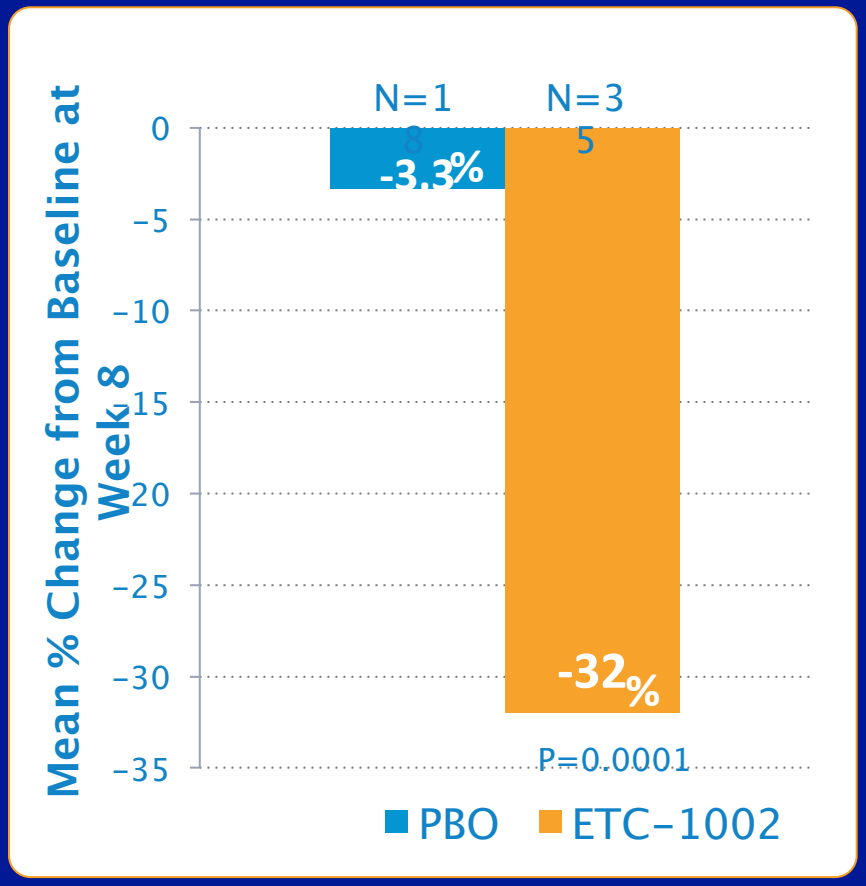
1. STABILITY Investigators. *N Engl J Med* 2014;370:1702-11.
2. O'Donoghue ML et al, for the SOLID-TIMI 52 Investigators. *JAMA* 2014;312:100

ETC-1002
Pharmacologic Properties

- Oral, once-daily small molecule
- Half-life: 15-24 hours
- Target organ: Liver
  - Minimal metabolism in preclinical and clinical studies
  - Primary biliary and minimal kidney excretion
- No competitive liver uptake with statins (e.g. OATP1B1)
- MOA: Inhibits ATP-citrate lyase (ACL) and activates AMP-activated protein kinase (AMPK)

Thompson P et al presented at ACC, 2014

ETC-1002-006 Efficacy in Statin Intolerant Patients
LDL-C Mean Change From Baseline to Week 8



- **Approximately 2/3 of patients reached their ATP-III NCEP LDL-C goal**
- **Baseline mean LDL-C =179 mg/dL**

MITT analysis, Confidence Interval % change (-35.4, -22.1)

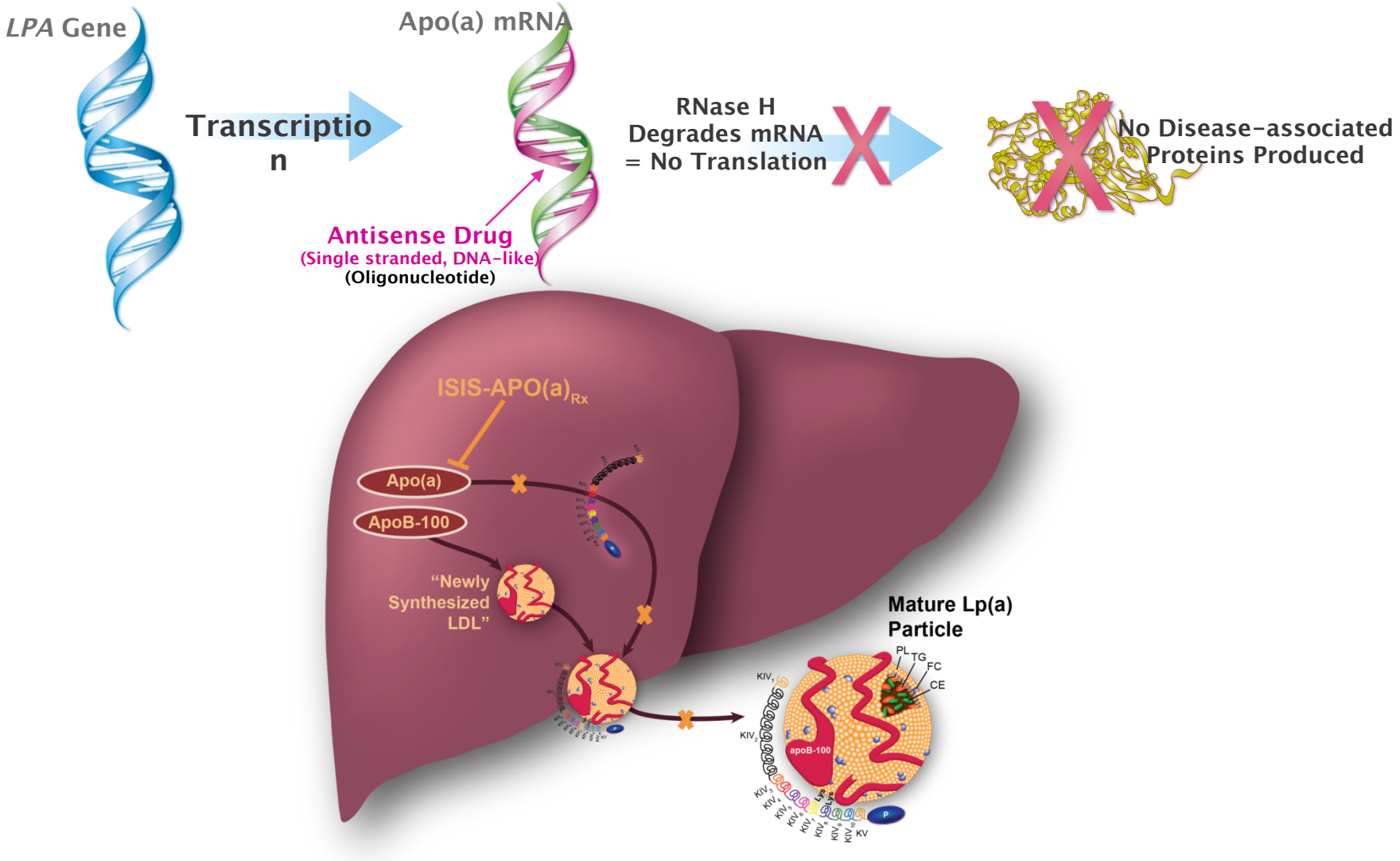
Thompson P et al presented at ACC, 2014

ETC-1002-006 Safety in Statin Intolerant Patients
Muscle-related Adverse Events

Treatment Emergent Occurrences	Number (%) of Patients	
	ETC-1002 N=37	PBO N=19
Any Muscle-Related AE(s)	10 (27%)	6 (32%)
Discontinuation Due to Muscle Related AE(s)	0 (0%)	3 (16%)

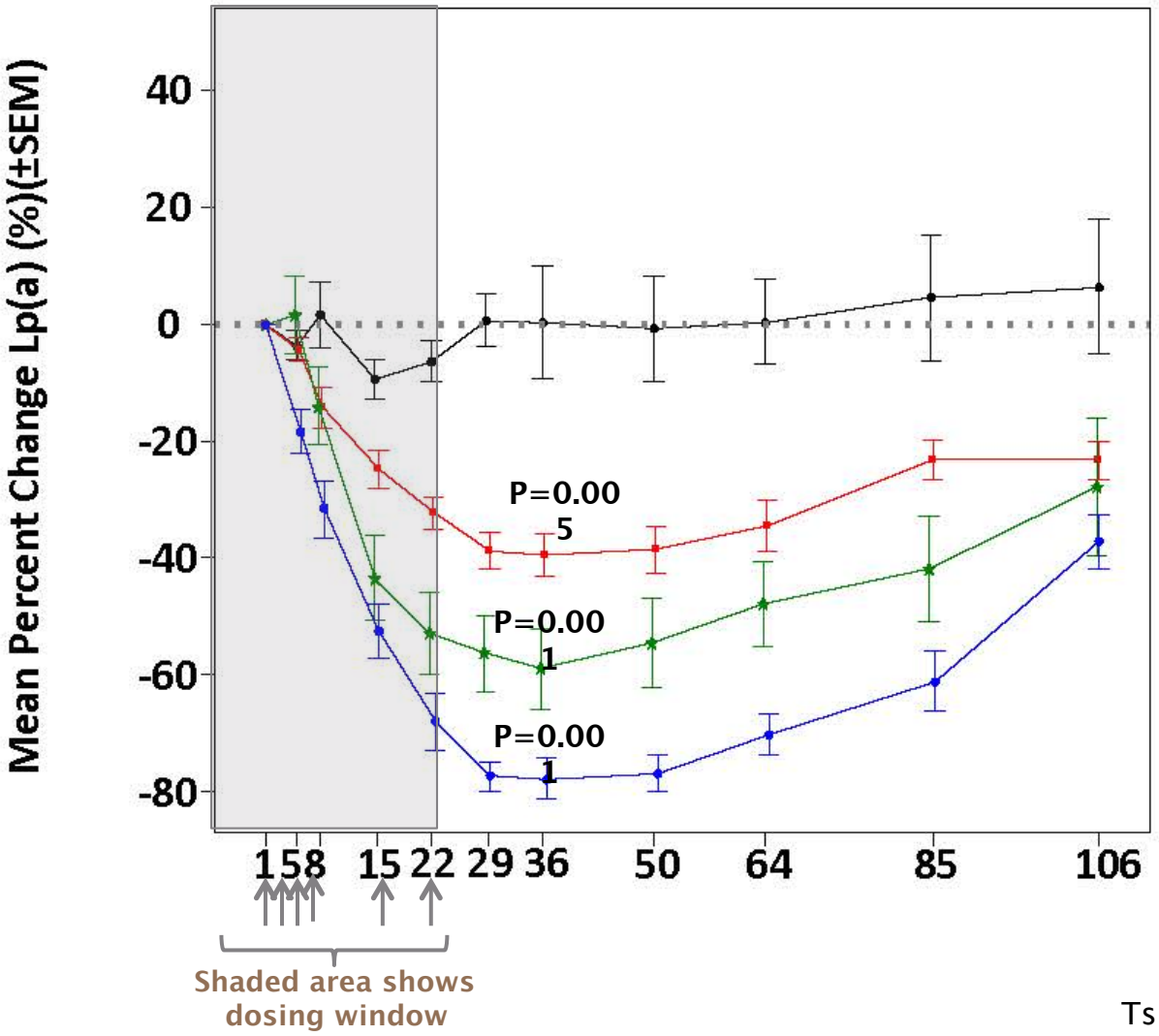
Thompson P et al presented at ACC, 2014

ISIS-APO(a)$_{Rx}$
Mechanism of Action in Reducing Plasma Lp(a)



Mean Percent Change Lp(a) Over Time by Treatment Groups

Multiple-Dose Cohorts (N=29)*



Placebo
100 mg
200 mg
300 mg

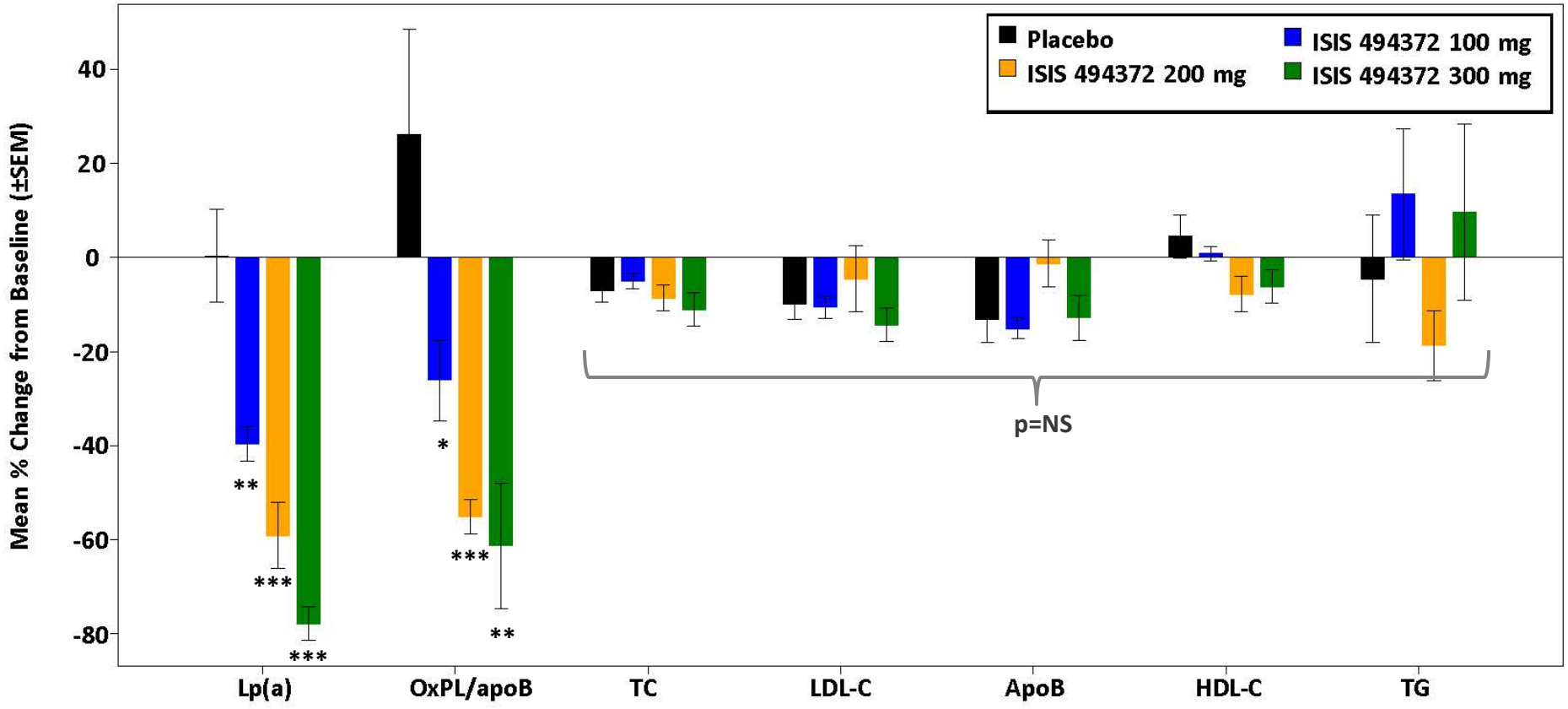
*Excludes 2 subjects who received < 3 doses of Study Drug

P=0.003
P=0.18
P=0.001

Wilcoxon Rank Sum Test p-value

Tsimikas S. Presented at ESC, 2014.

Mean Percent Change in Lp(a), OxPL/apoB, Lipid Profile and ApoB 2 Weeks After the Last Dose Phase 1 Multiple Dose Cohorts (Day 36)

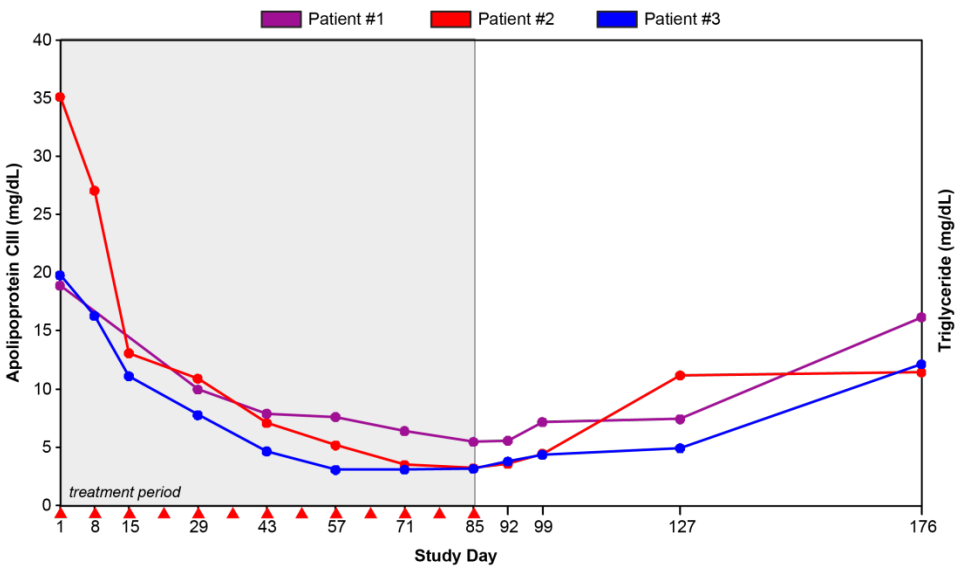


* p=0.02
** p≤0.008
*** p=0.001

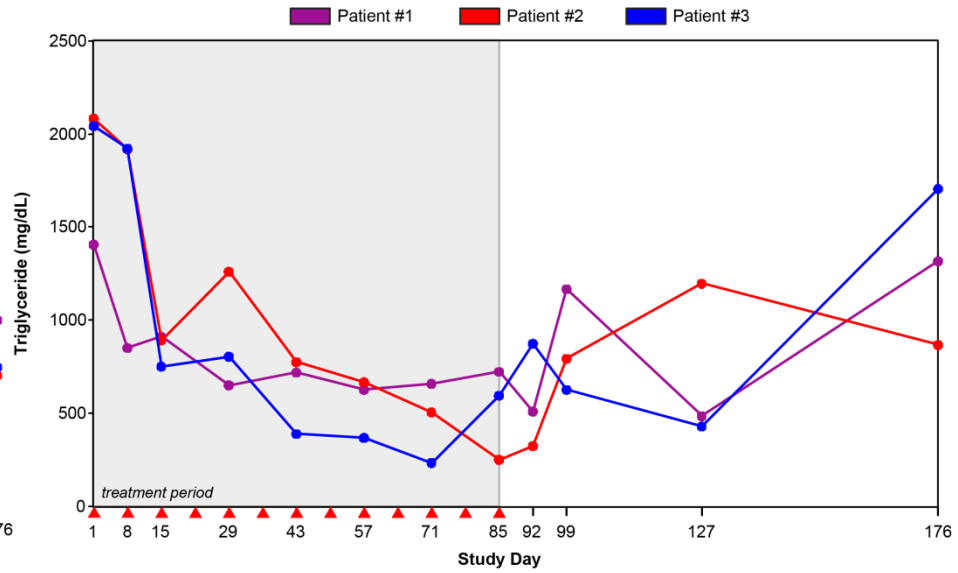
Tsimikas S. Presented at ESC, 2014.

ISIS-APOCIII$_{Rx}$ in FCS Patients
Reduced Fasting Plasma ApoC-III and TG Levels

Fasting ApoC-III Levels



Fasting Triglyceride Levels



Parameter (mg/dL)	Patient No.	Baseline*	Primary Endpoint†	Change from Baseline	% Change from Baseline
Triglyceride	1	1406	616.5	-789.5	-56.2
	2	2083	287.5	-1795.5	-86.2
	3	2043	734.5	-1308.5	-64.0
ApoC-III	1	18.9	5.5	-13.4	-70.9
	2	35.1	3.4	-31.7	-90.4
	3	19.8	3.5	-16.3	-82.5

Gaudet D. Presented at NLA Scientific Sessions, May 4,