DIABETOCARDIOLOGY: A New Specialty

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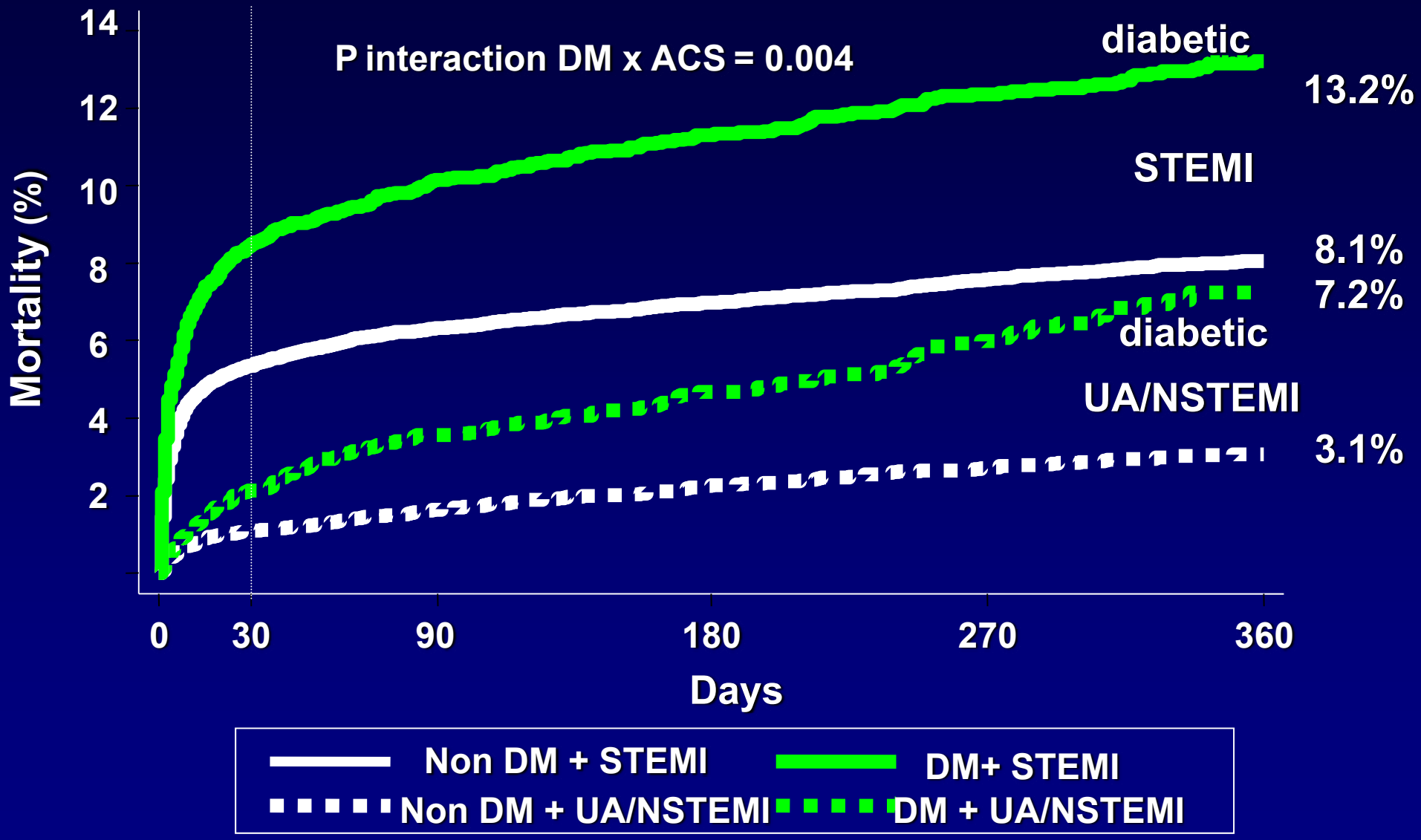
Israel Heart Society
Jerusalem
April 22, 2013

Disclosures

Research Support for Clinical Trials

Squibb	SAVE, CARE
Bristol Myers Squibb	PROVE IT (TIMI 22) SAVOR (TIMI 53)
Astra Zeneca	SAVOR (TIMI 53)
Lilly/Daiichi Sankyo	TRITON (TIMI 38) ENGAGE (TIMI 48)
Johnson & Johnson	ATLAS 2 (TIMI 51)
GSK	SOLID (TIMI 52)
Merck	TRA-2P (TIMI 50) REVEAL (TIMI 55)

1 YEAR MORTALITY AFTER ACS



Donahoe SM et al. JAMA 2007;298:765

The NEW ENGLAND JOURNAL of MEDICINE

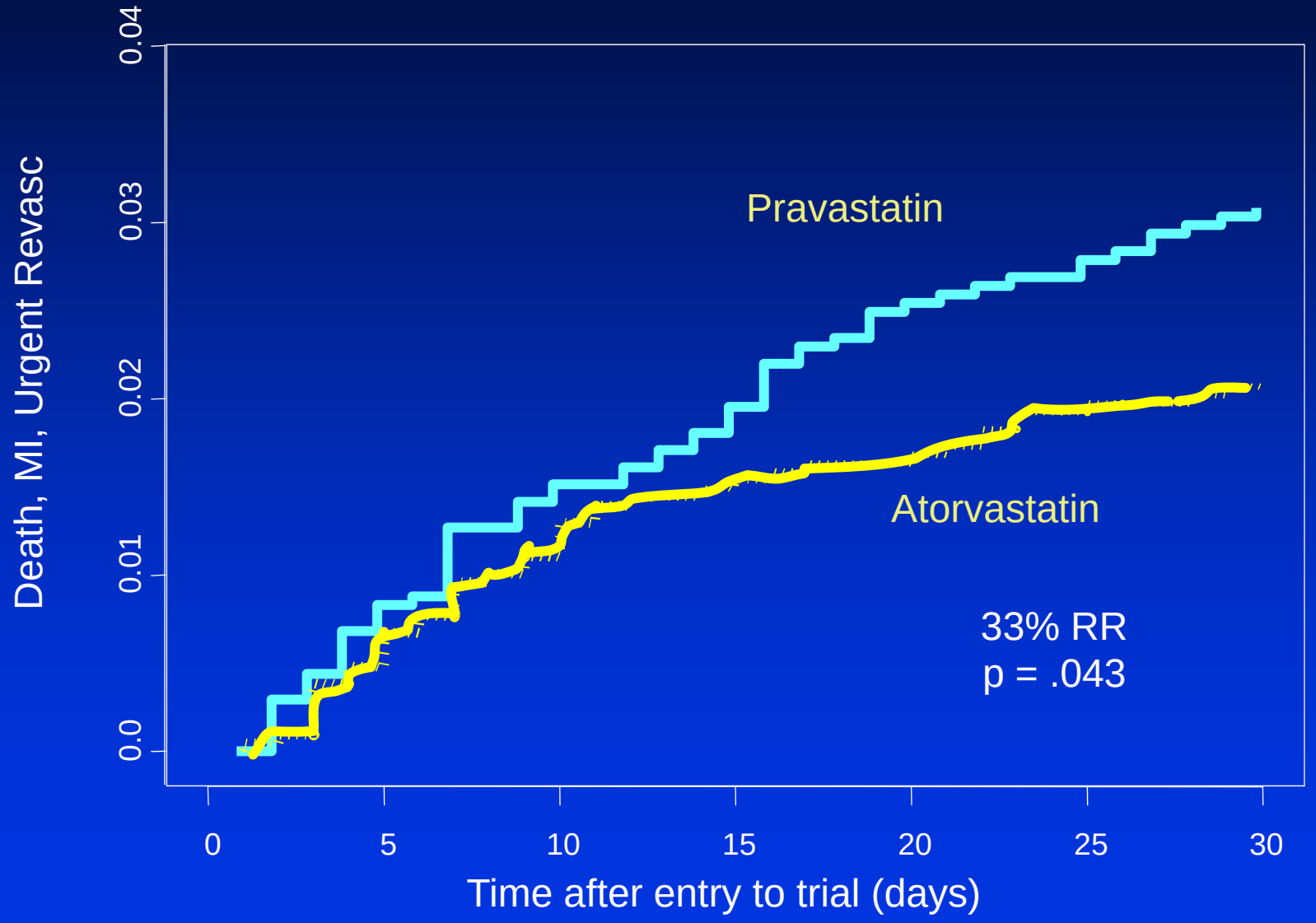
ESTABLISHED IN 1812 APRIL 8, 2004 VOL. 350 NO. 15

Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Daniel J. Rader, M.D., Jean L. Rouleau, M.D., Rene Belder, M.D., Steven V. Joyal, M.D., Karen A. Hill, B.A., Marc A. Pfeffer, M.D., Ph.D., and Allan M. Skene, Ph.D., for the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators*

2004;350:1495

ALL-CAUSE DEATH, NON-FATAL MI, OR URGENT REVASCULARIZATION



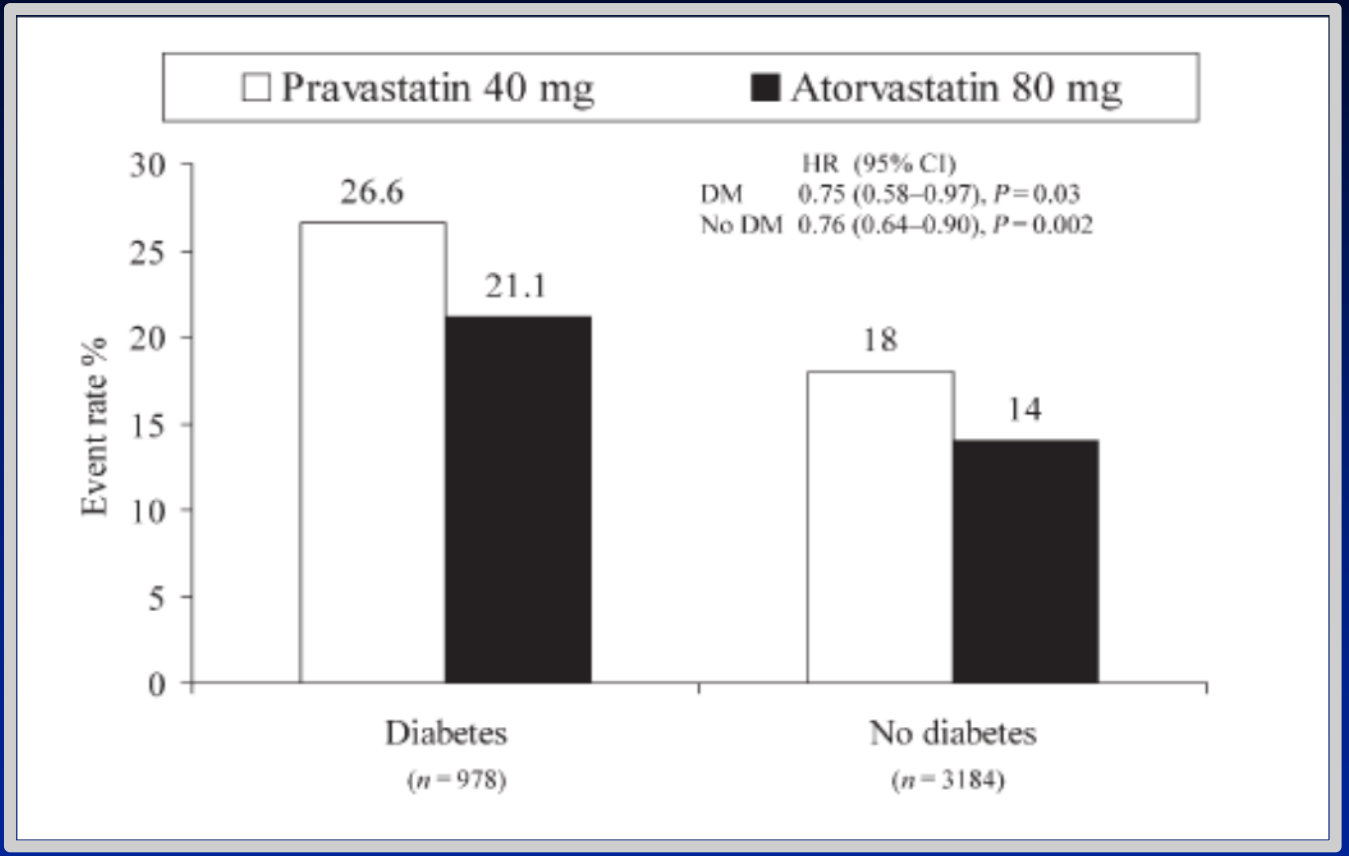
Ray KK, Cannon CP, Braunwald E et al. JACC 2005;46:1405

Acute coronary syndromes and diabetes: is intensive lipid lowering beneficial? Results of the PROVE IT-TIMI 22 trial

Shaheeda Ahmed, Christopher P. Cannon*, Sabina A. Murphy, and Eugene Braunwald

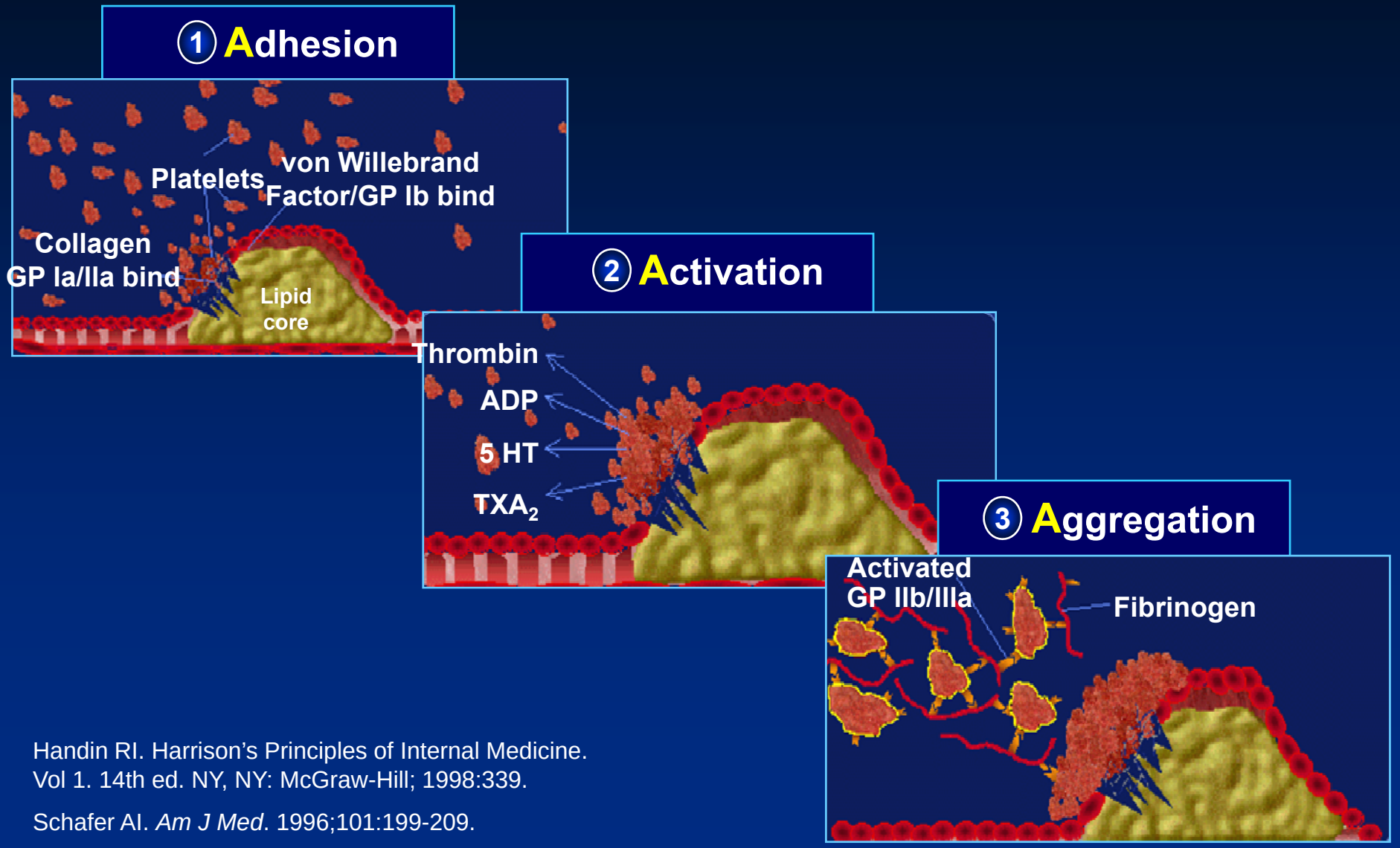
The TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, 350 Longwood Avenue, First Floor, Boston, MA 02115, USA

Eur Heart J 2006;27:2323



Ahmed S et al.
Eur Heart J 2006;27:2323

PLATELET CASCADE IN THROMBUS FORMATION



Handin RI. Harrison's Principles of Internal Medicine. Vol 1. 14th ed. NY, NY: McGraw-Hill; 1998:339.

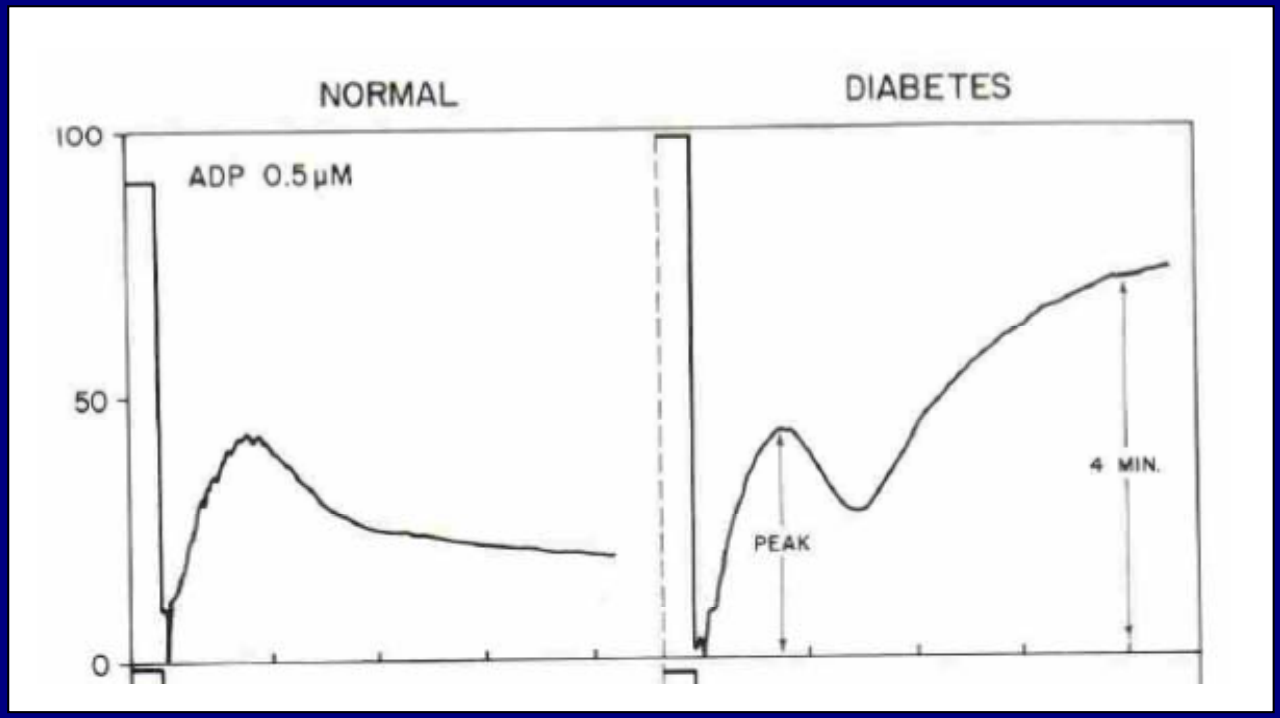
Schafer AI. *Am J Med*. 1996;101:199-209.

Increased Platelet Aggregation in Early Diabetus Mellitus

JULIUS SAGEL, M.B., Ch.B., JOHN A. COLWELL, M.D., Ph.D., LYNN CROOK, Ph.D., and MARTA LAIMINS, Johannesburg, South Africa, and Charleston, South Carolina

Ann Intern Med 1975;82:733

RESPONSE OF NORMAL AND DIABETIC PLATELET-RICH PLASMA TO ADENOSINE

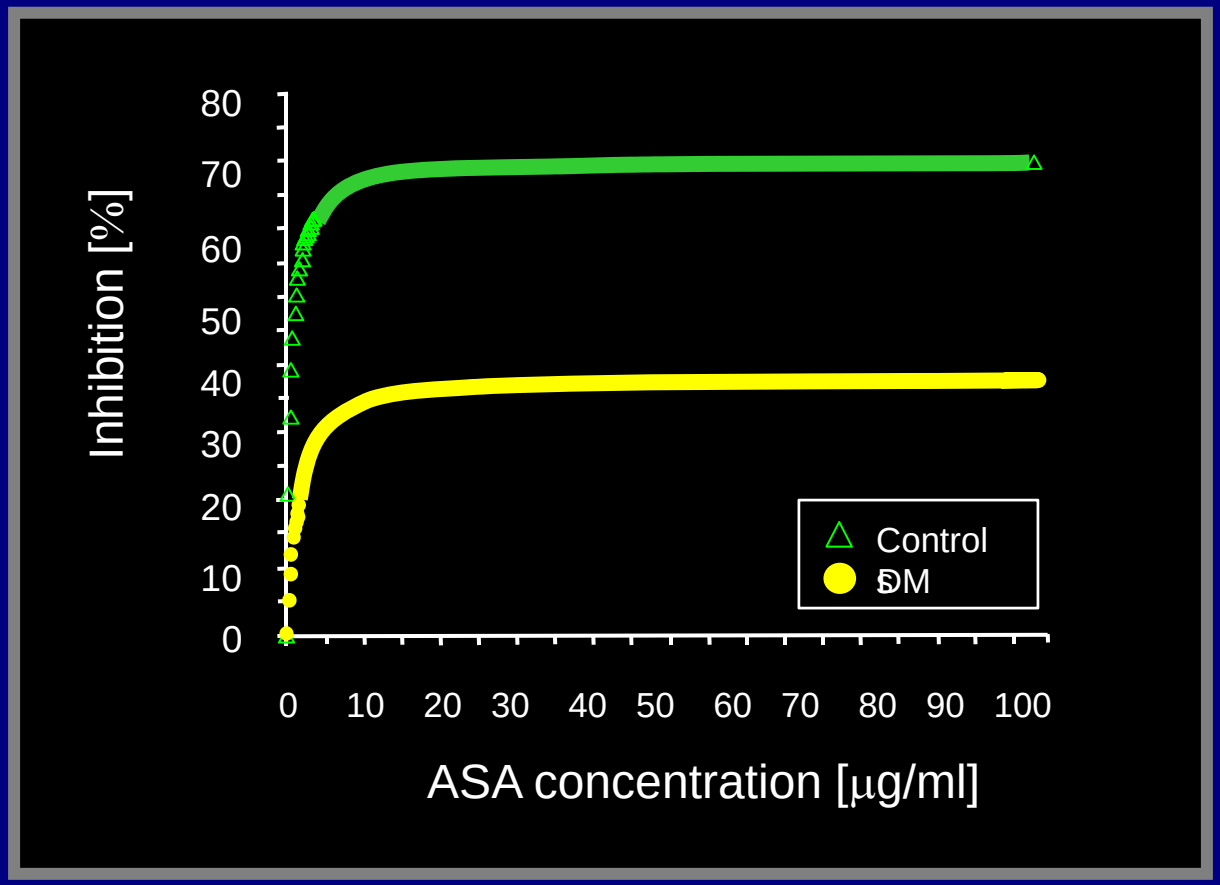


% Aggregation

Minutes

Sagel J et al.
Ann Int Med 1975;82:733

ASA INHIBITION OF ARACHIDONIC ACID-INDUCED PLATELET AGGREGATION



Watala C et al
Thrombosis Res 2004;113:101

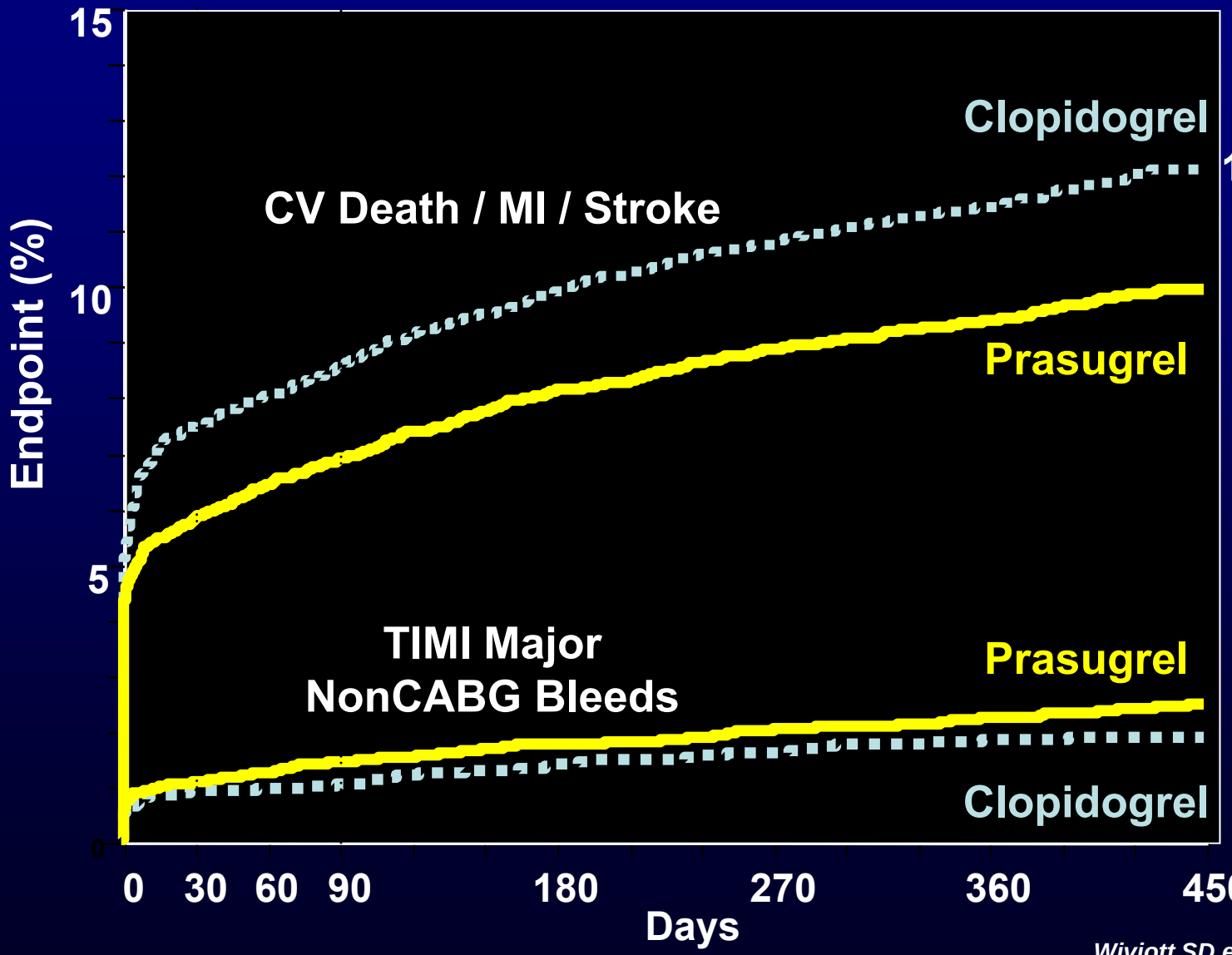
Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

Stephen D. Wiviott, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D., Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D., Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesmeyer, M.D., Govinda Weerakkody, Ph.D., C. Michael Gibson, M.D., and Elliott M. Antman, M.D., for the TRITON–TIMI 38 Investigators*

N Engl J Med 2007;357:2001

TRITON TIMI-38

Balance of Efficacy and Safety



↓ 138 events

HR 0.81
(0.73-0.90)
P=0.0004

NNT = 46

↑ 35 events

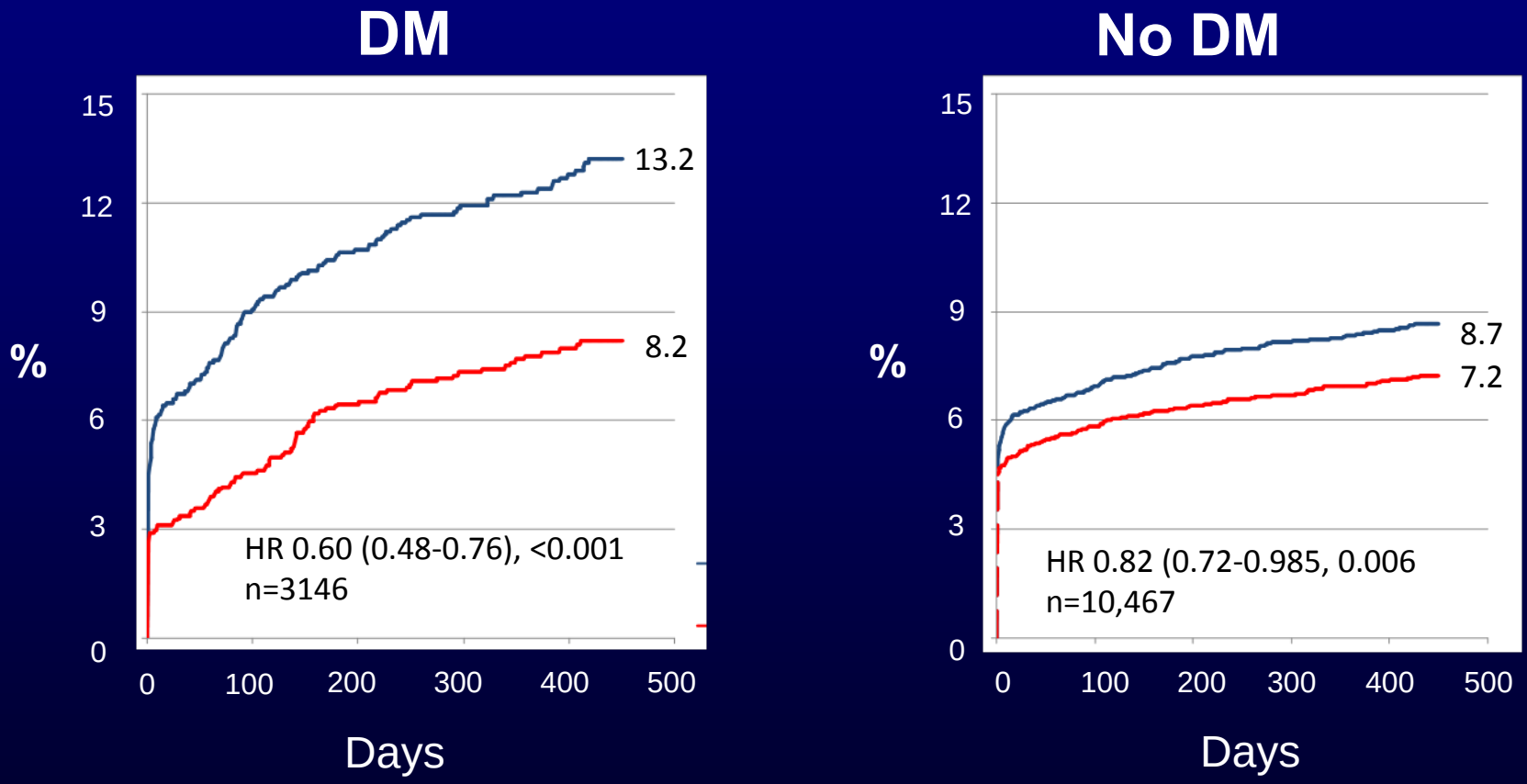
HR 1.32
(1.03-1.68)
P=0.03

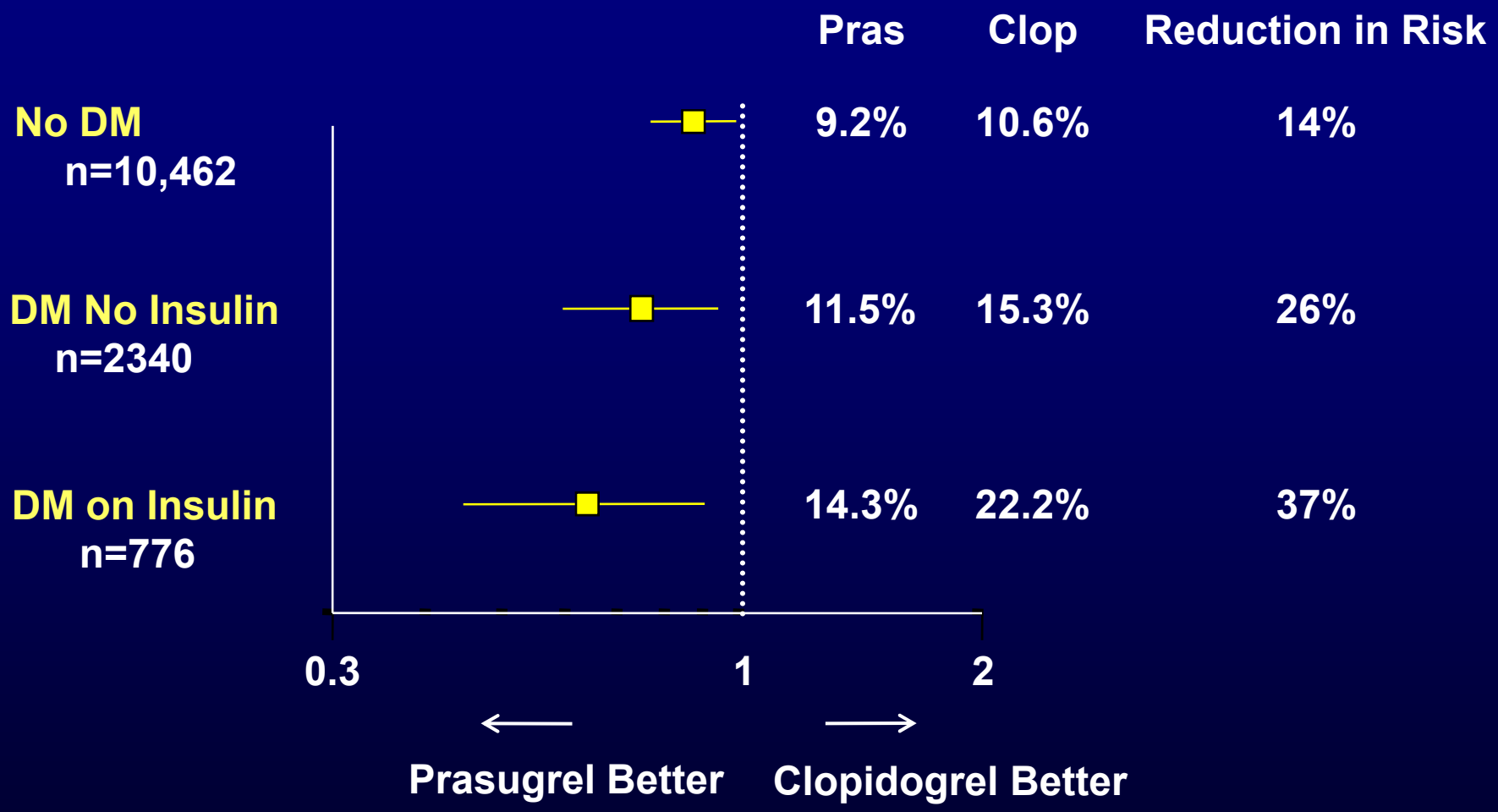
NNH = 167

Wiviott SD et al. NEJM 2007;357: 2001

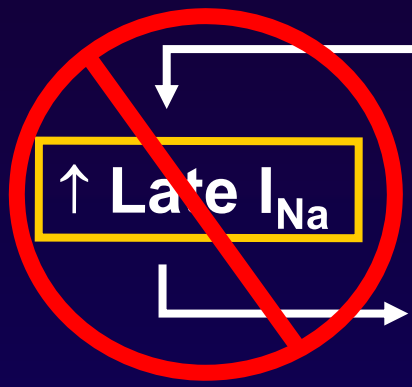
TRÎTON TIMI·38

Myocardial Infarction




Pras
Clop
Reduction in Risk
No DM
n=10,462
9.2%
10.6%
14%
DM No Insulin
n=2340
11.5%
15.3%
26%
DM on Insulin
n=776
14.3%
22.2%
37%
0.3
1
2
Prasugrel Better
Clopidogrel Better

IONIC DISTURBANCES IN ISCHEMIA AND HEART FAILURE AND THEIR CONSEQUENCES



Ranolazine

Ischemia
Heart Failure

Na^+ Overload

Reverse $Na^+/Ca^{2+}X$

Ca^{2+} Overload

Late I_{Na} is increased by (in)
- Hypoxia
- Ischemic metabolites
- O_2 reactive species
- Heart failure
- Post-MI remodelled myocytes

Dysfunction

1. Electrical
Arrhythmias

2. Mechanical
Abn. Contractility
↑ diastolic tension
(-) force-freq. relation

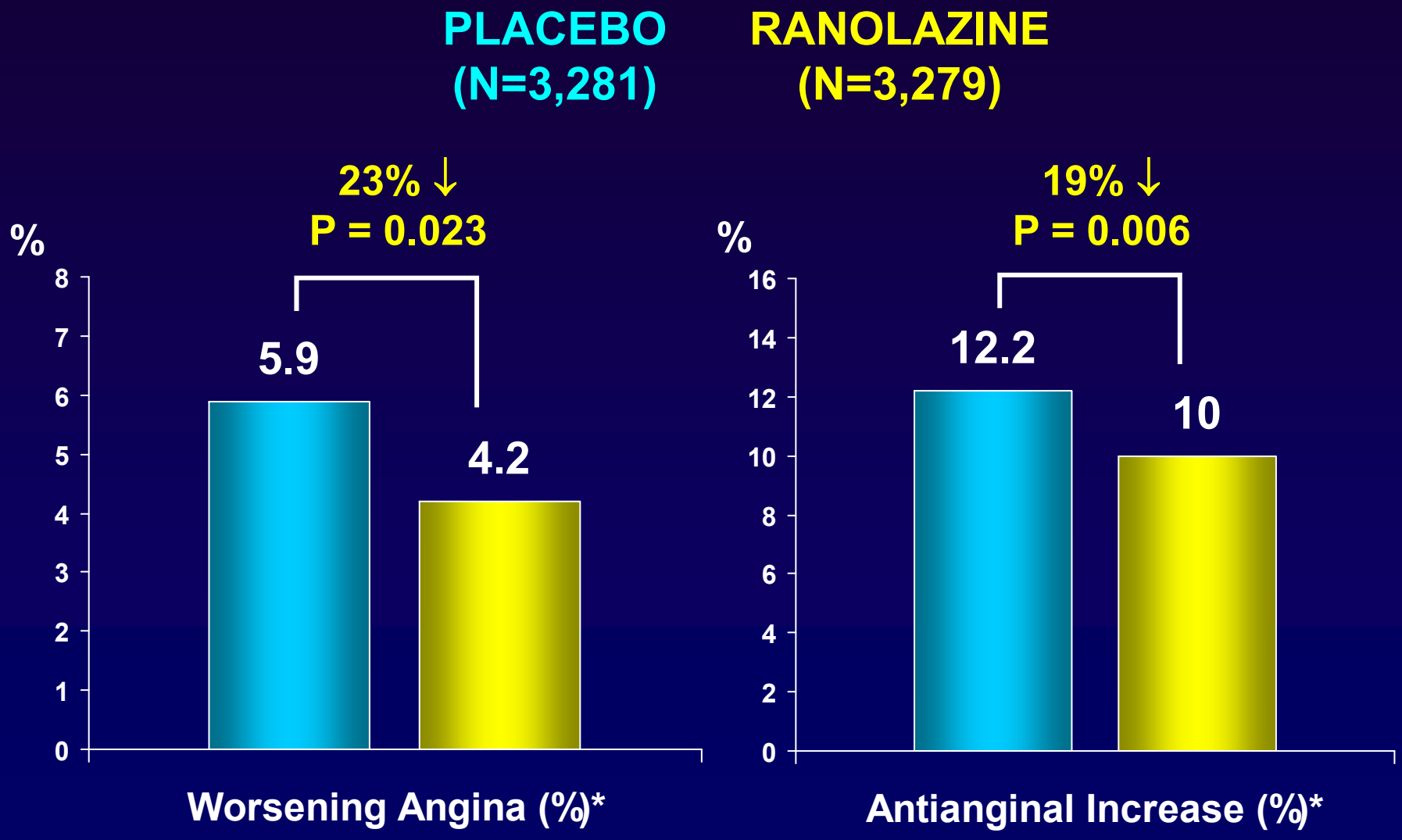
↑ATP Hydrolysis

↑Cell Injury

Assessment of Anti-anginal Effects

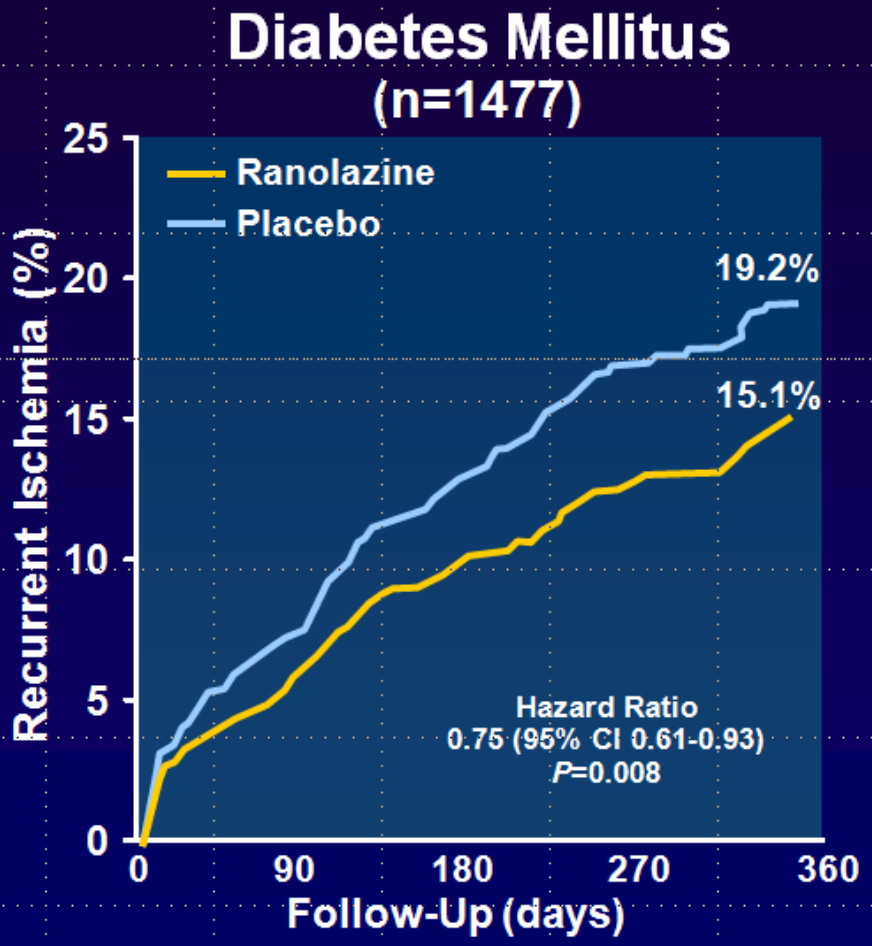
MERLIN TIMI 36

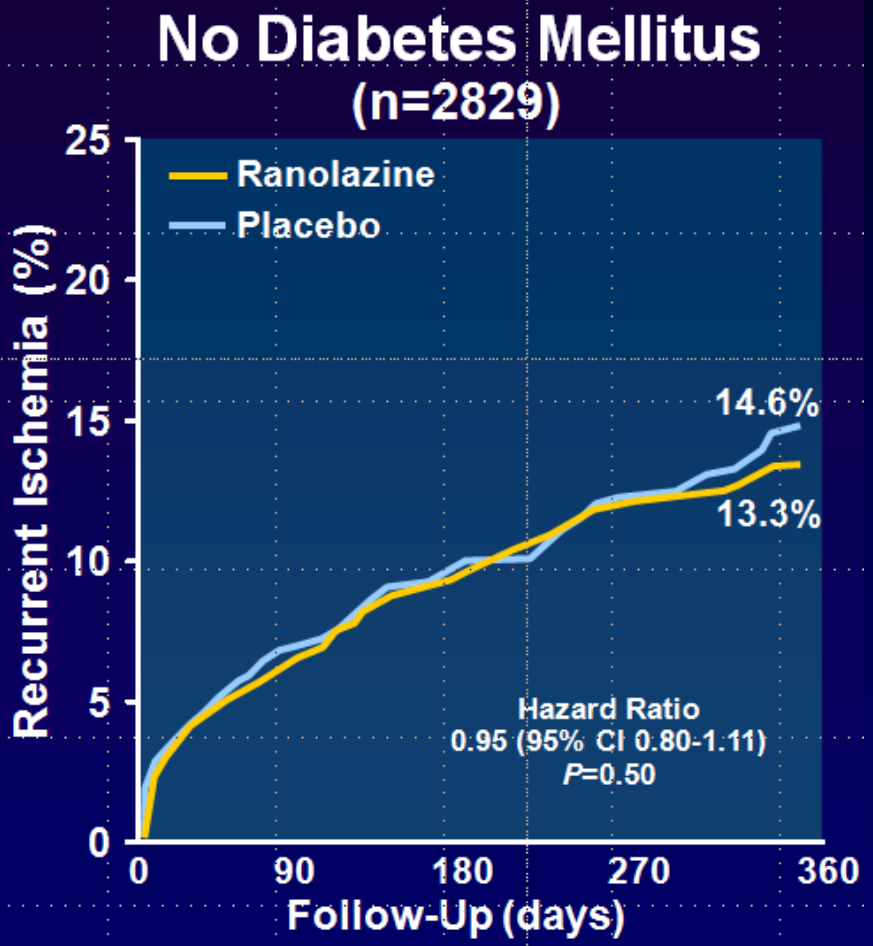
Results



*KM Cumulative Incidence at 12 months

MERLIN-TIMI 36 DIABETES SUBANALYSIS FOR RECURRENT ISCHEMIA





Morrow DA, et al. *Circulation.* 2009;119:2032-2039.

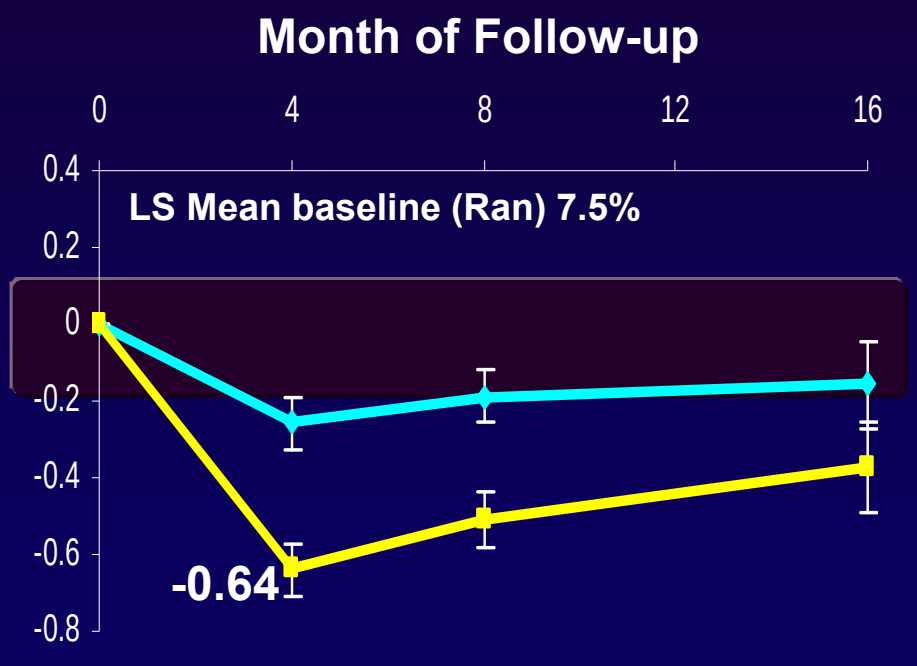
Evaluation of the Glycometabolic Effects of Ranolazine in Patients With and Without Diabetes Mellitus in the MERLIN-TIMI 36 Randomized Controlled Trial

David A. Morrow, MD, MPH; Benjamin M. Scirica, MD, MPH; Bernard R. Chaitman, MD; Darren K. McGuire, MD; Sabina A. Murphy, MPH; Ewa Karwatowska-Prokopczuk, MD, PhD; Carolyn H. McCabe, BS; Eugene Braunwald, MD; for the MERLIN-TIMI 36 Investigators

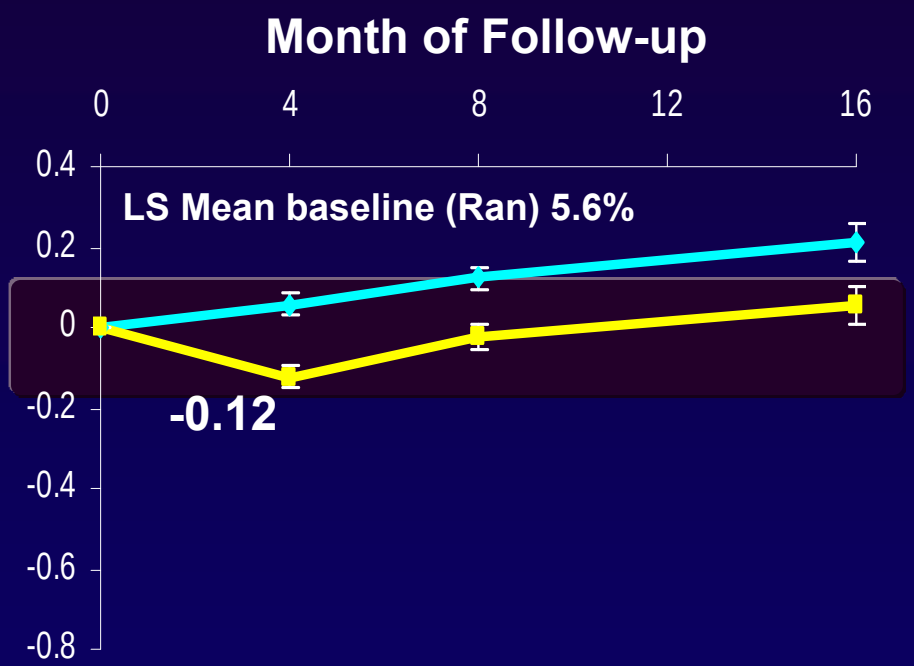
Circulation 2009;119:2032

MERLIN-TIMI 36: CHANGE IN HbA1c (%) STRATIFIED BY DIABETES STATUS

Patients with Diabetes Mellitus



No Diabetes Mellitus



	M4	*M8*	*M16*	*M4*	*M8*	*M16*
Placebo	N = 770	N = 598	N = 122	N = 1428	N = 1113	N = 260
Ranolazine	N = 707	N = 535	N = 112	N = 1401	N = 1113	N = 266
P-value	<0.001	<0.001	= 0.16	<0.001	= 0.002	= 0.03

Morrow DA et al. Circulation. 2009;119:2032-39.

Persistent Dilemmas in Diabetes Therapy

- Many studies have demonstrated that improved glucose control reduces *microvascular* (eg, retinal, renal, neuropathic) complications.
- However, no glucose lowering regimen, let alone a particular agent, has definitively been shown to reduce *macrovascular* complications (eg, MI, stroke, angina)
- In fact, several agents are suspected to worsen CV outcomes (e.g., sulfonylureas, rosiglitazone, insulin)

TRIALS OF INTENSIVE GLYCEMIC CONTROL AND CV DISEASE

	MACE	MORTALITY
ACCORD n = 10,251 HbA1c 7.5/6.4	0.90	1.22*
ADVANCE n = 11,140 HbA1c 7.3/6.5	0.94	0.93
VADT n = 1791 HbA1c 8.4/6.9	0.88	1.07

n = 23,182

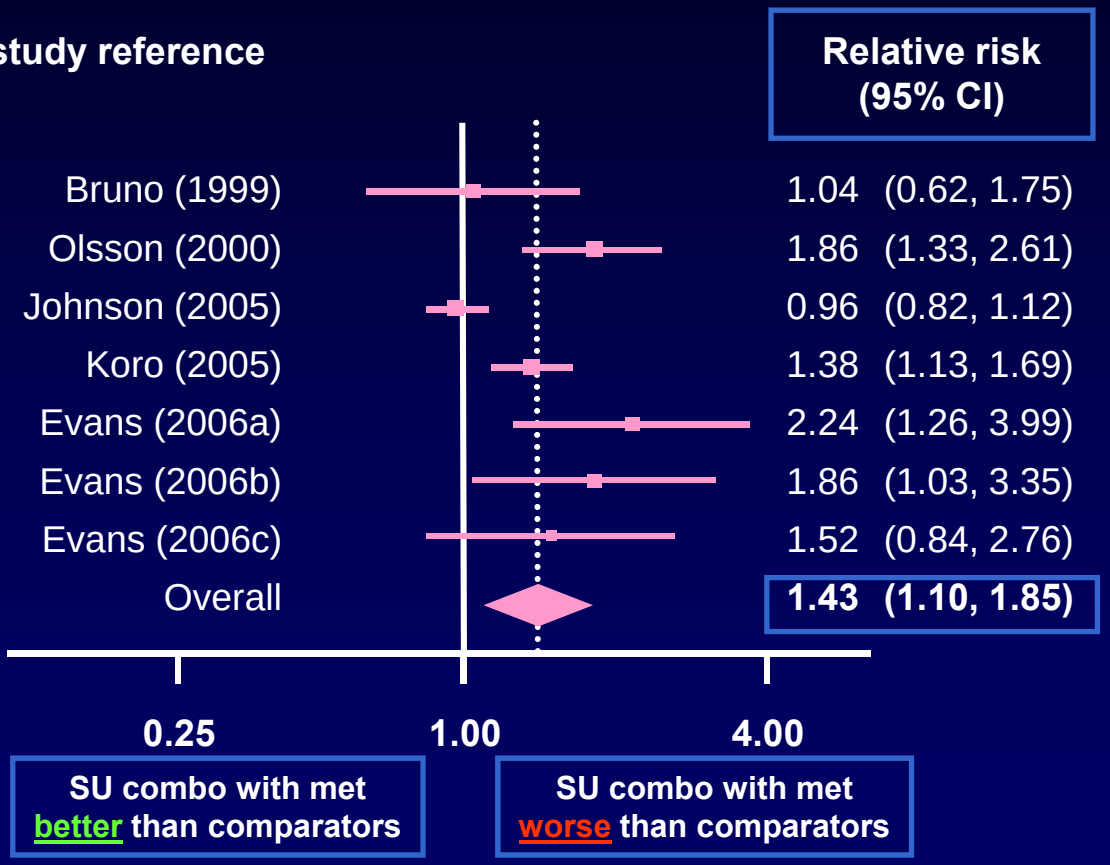
Monami M et al.
Diabetes Obes Metab 2013;15:112

Diabetes Therapy and CV Risk

Combination of SUs and Metformin may be Linked to Higher Risk for CVD and All-cause Mortality*

Meta-analysis data from 9 clinical studies

Risk ratios for composite end point of CVD hospitalizations or CVD mortality*

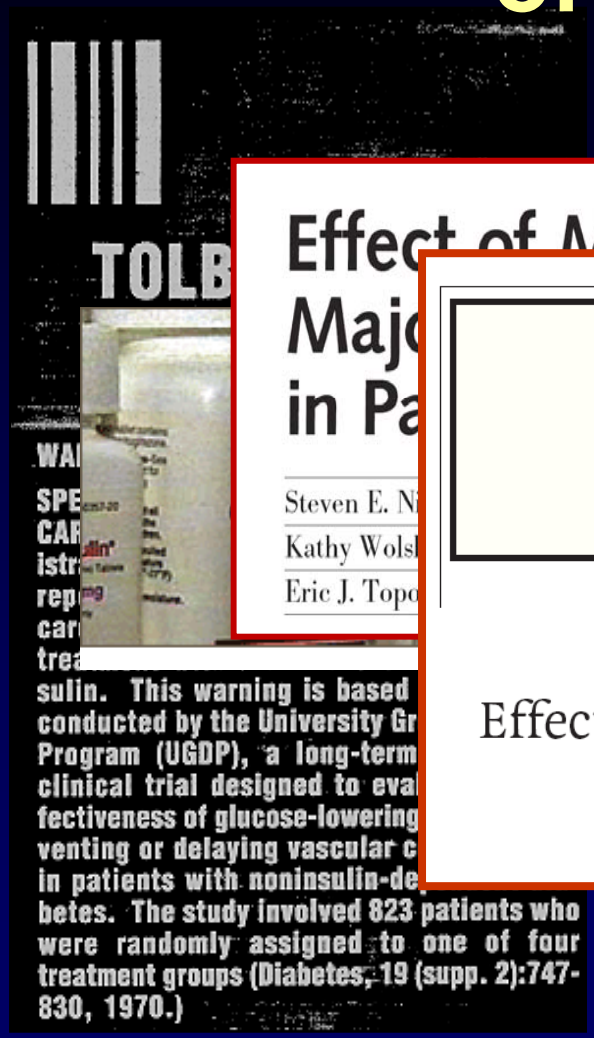


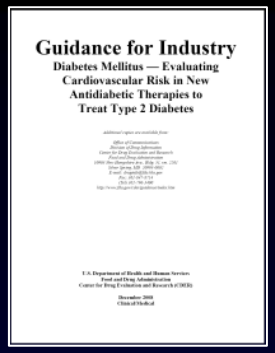
CI=confidence interval; CVD=cardiovascular disease; met=metformin; NS=not specified; SU=sulfonylureas

*Composite end point of CVD hospitalizations or CVD mortality – only statistically significantly increased end point.

Rao A, et al. *Diabetes Care*. 2008; 31: 1672–1678.

Concerns About the Safety of Diabetic Therapy




Guidance for Industry
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

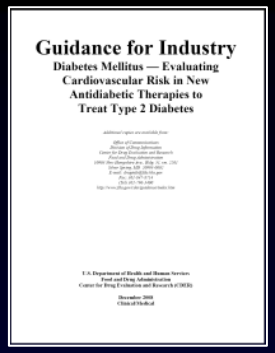
Regulatory Obligations for All New Diabetes Medications – 2008
A Two Step Process

Step 1 - Initial Approval

- **Show effective HbA1c reduction**
- ***Exclude excess risk in Phase II/III***
  - *More patients in Phase II/III*
  - *Higher risk population (CVD, CKD)*
  - *Longer follow-up (minimum 2-years)*
  - *Pre-defined CV endpoints with independent blind adjudication*
  - *Statistical plan to perform meta-analysis of CV events in Phase II/III program*

An upper-bound of 95%CI <1.8 "supports approval"

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf


Guidance for Industry
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

Regulatory Obligations for all New Diabetes Medications - 2008

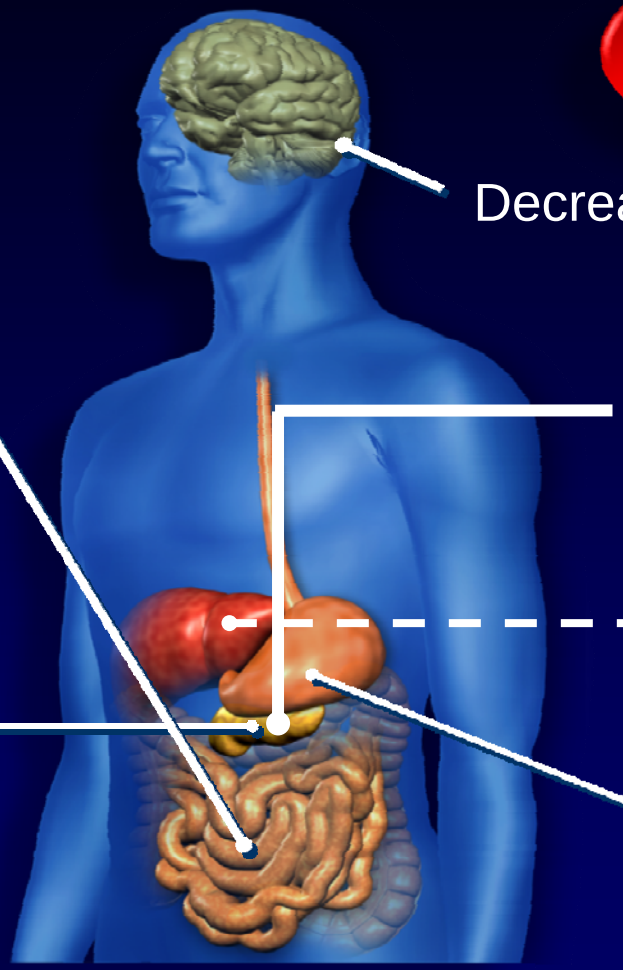
Step 2 - Post-marketing Obligation

"…a post-marketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent CI for the estimated risk ratio is less than 1.3.

This can be achieved by conducting a single trial that is adequately powered or by combining the results from a premarketing safety trial with a similarly designed post-marketing safety trial. This clinical trial will be a required post-marketing safety trial."

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

GLP-1 Effects in Humans



GLP-1/ GIP secreted upon the ingestion of food

↓ Beta-cell workload

Decreases appetite

Reduces glucagon secretion

↑ Beta-cell response

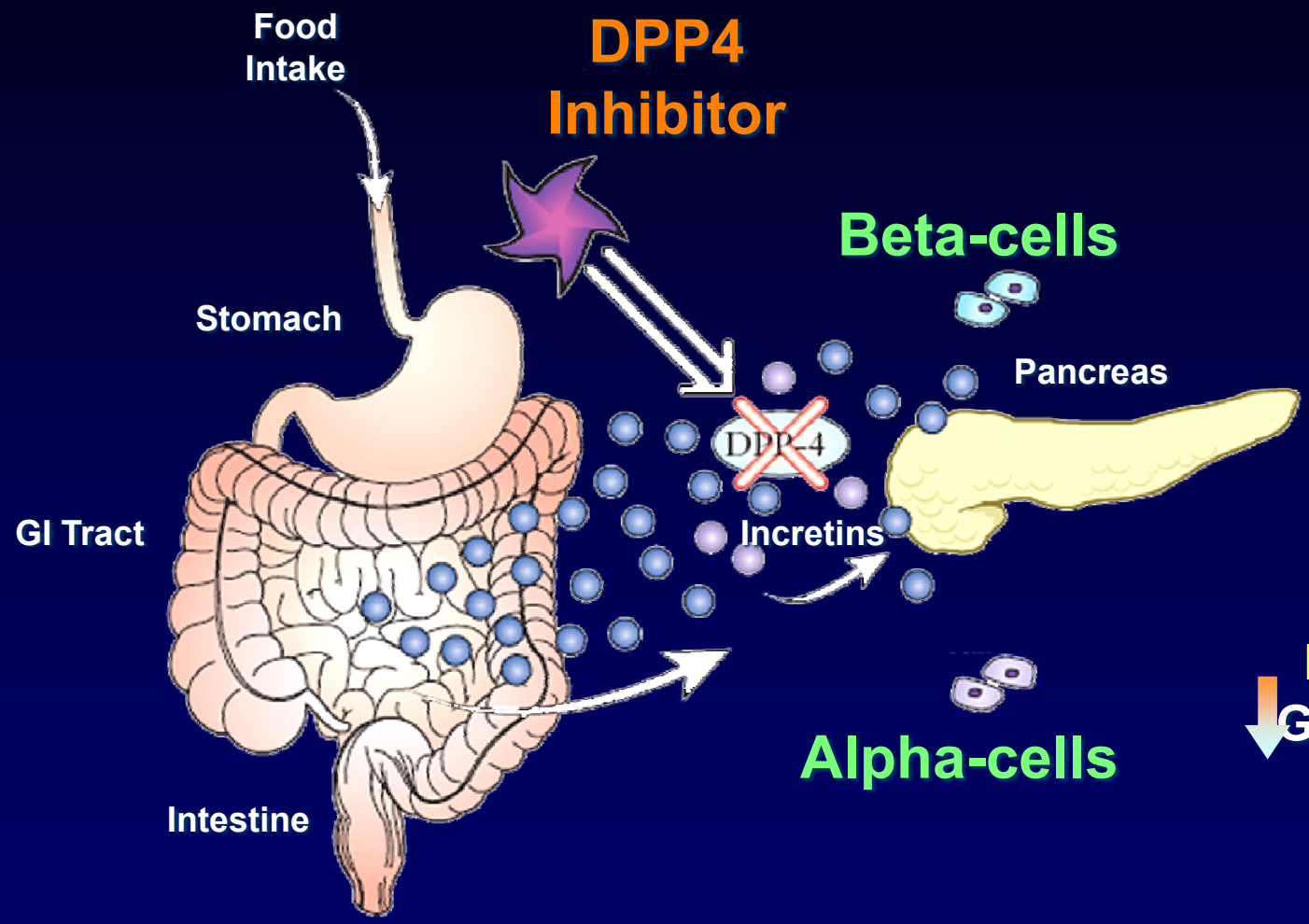
Reduced hepatic glucose production

Increased insulin secretion

Delayed gastric emptying

Adapted from Flint A, et al. *J Clin Invest*. 1998;101:515-520
Adapted from Larsson H, et al. *Acta Physiol Scand*. 1997;160:413-422
Adapted from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553
Adapted from Drucker DJ. *Diabetes*. 1998;47:159-169

How DPP4 Inhibitors Work



↑GLP-1 / GIP
Effects on β-cells:
↑ Insulin Release

Net Effect:
↓ Blood Glucose

↑ GLP-1
Effect on α-cells:
↓ Glucagon secretion

Adapted from Drucker and Nauck, 2006; Idris and Donnelly, 2007; Barnett, 2006

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-TIMI 53

savor TIMI 53
TIMI STUDY GROUP / HADASSAH MEDICAL ORG

Start Date
- May 2010

Estimated Study Completion Date
- June 2014

Documented Type 2 Diabetes

N =16,500

Established CV Disease or Multiple Risk Factors

RANDOMIZE 1:1 DOUBLE BLIND

Dosing based on eGFR

All other DM Rx per treating MD

SAXAGLIPTIN 2.5 or 5 mg/d

PLACEBO

Follow-up
Estimated time ~ 3 yr

Duration
Event driven (n=1040)
Estimated time ~ 5 yr

Follow up visits Q6 months

Final Visit

Primary EP
CV Death, MI, Ischemic Stroke

Major Secondary EP: CV death, MI, stroke, or hospitalization for heart failure, unstable angina pectoris, or coronary revascularization

ClinicalTrials.gov Identifier: NCT01107886

Scirica BM et al., Am Heart J. 2011;162(5):818-825

Trial Evaluating Cardiovascular Outcomes With Sitagliptin

Start Date
- Dec 2008

Estimated Study Completion Date
- Dec 2014

Documented Type 2 Diabetes

N ~14,000

Stable, Established CV dDsease; HbA1c 6.5-8.0%

SITAGLIPTIN

Rx with metformin, pioglitazone, SU, sulfonylurea, Insulin

PLACEBO

Final Visit

Primary EP

CV death, MI, ischemic stroke, UA requiring revascularization

Secondary EPs: CV death, MI, stroke; all cause mortality; heart failure; change in renal function

ClinicalTrials.gov Identifier: NCT00790205

Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials

M. Monami[1], B. Ahrén[2], I. Dicembrini[3] & E. Mannucci[4]

Diabetes Obes Metab 2013;15:112

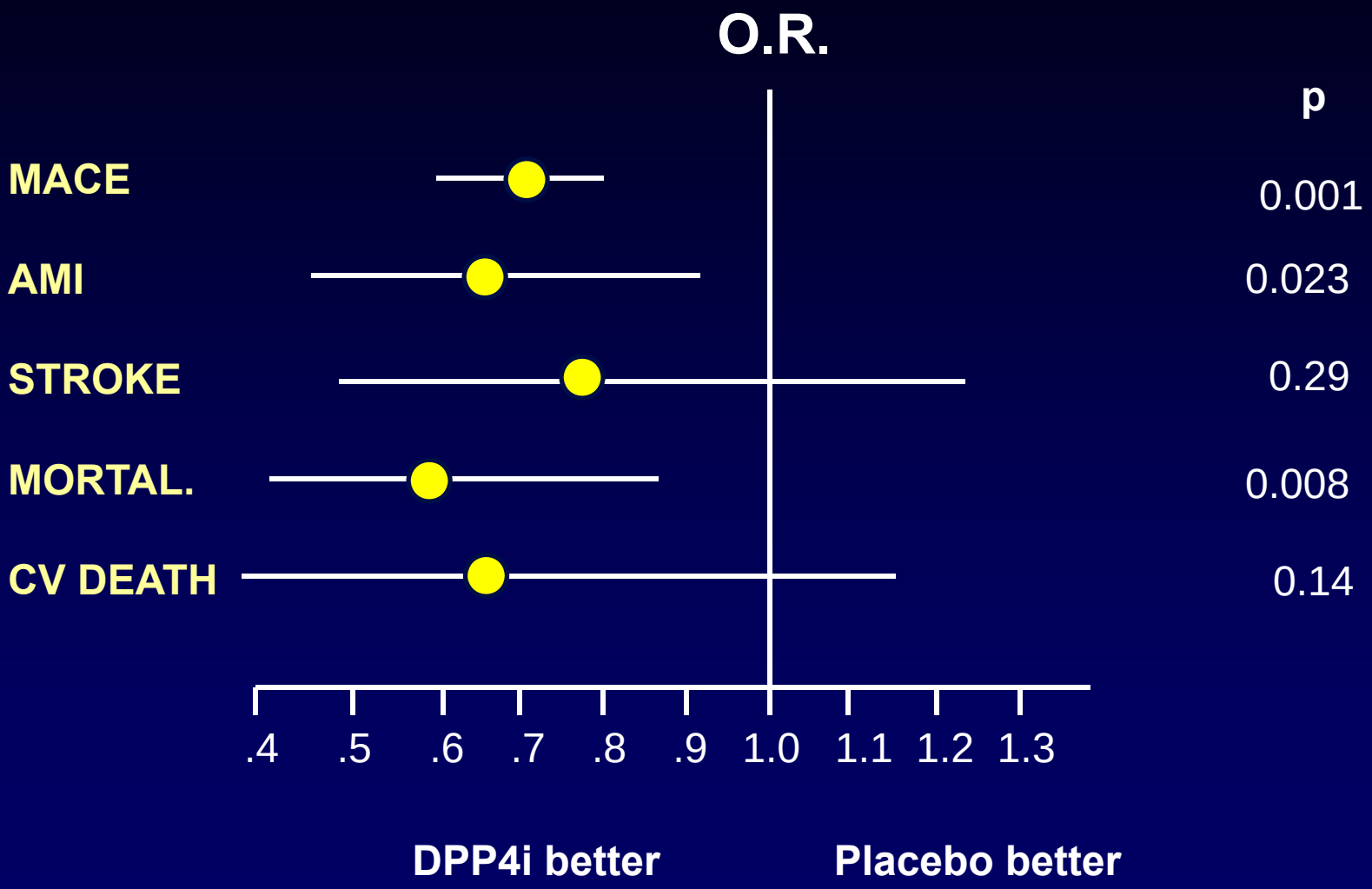
DDP4 INHIBITOR META-ANALYSIS

- 70 trials
- 41,959 patients
- 41,307 patient years

MACE = CV death, non-fatal MI, stroke, ACS

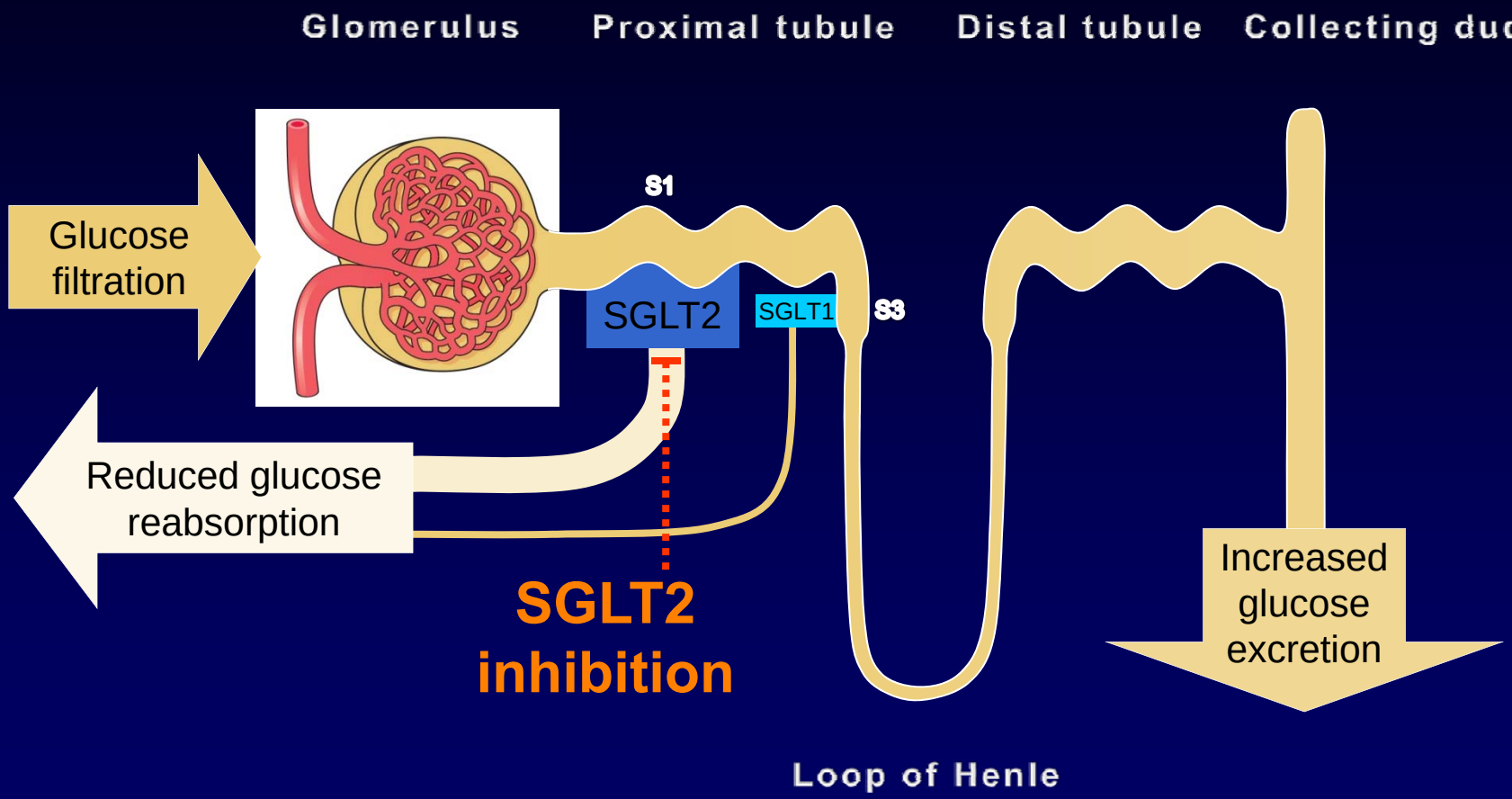
Monami M et al.
Diabetes Obes Metab 2013;15:112

DDP4i META-ANALYSIS



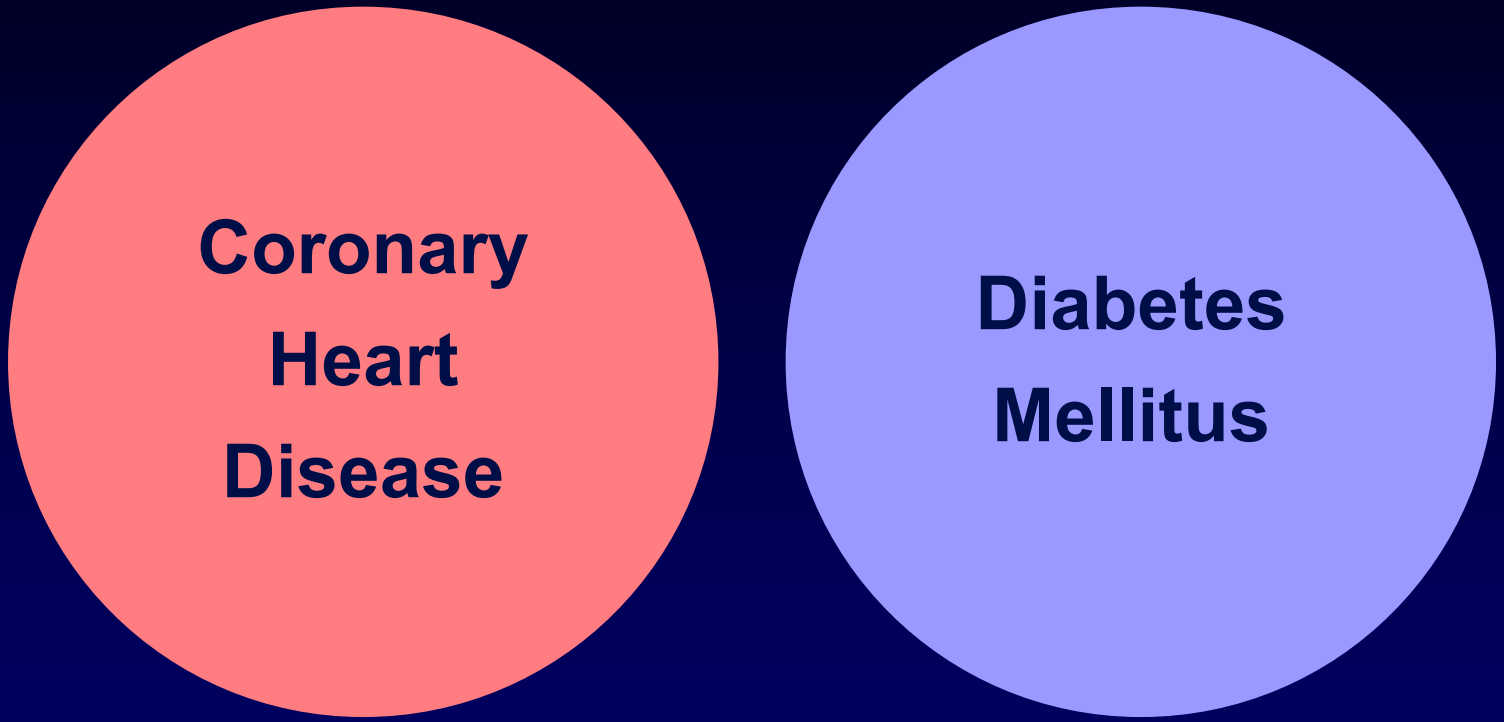
Monami M et al.
Diabetes Obes Metab 2013;15:112

SGLT2 Inhibition



Wright, EM. *Am J Physiol Renal Physiol.* 2001;280:F10–8; Lee ,YJ et al. *Kidney Int Suppl.* 2007;106:S27–35, Han S. Diabetes 2008;57:1723–1729.

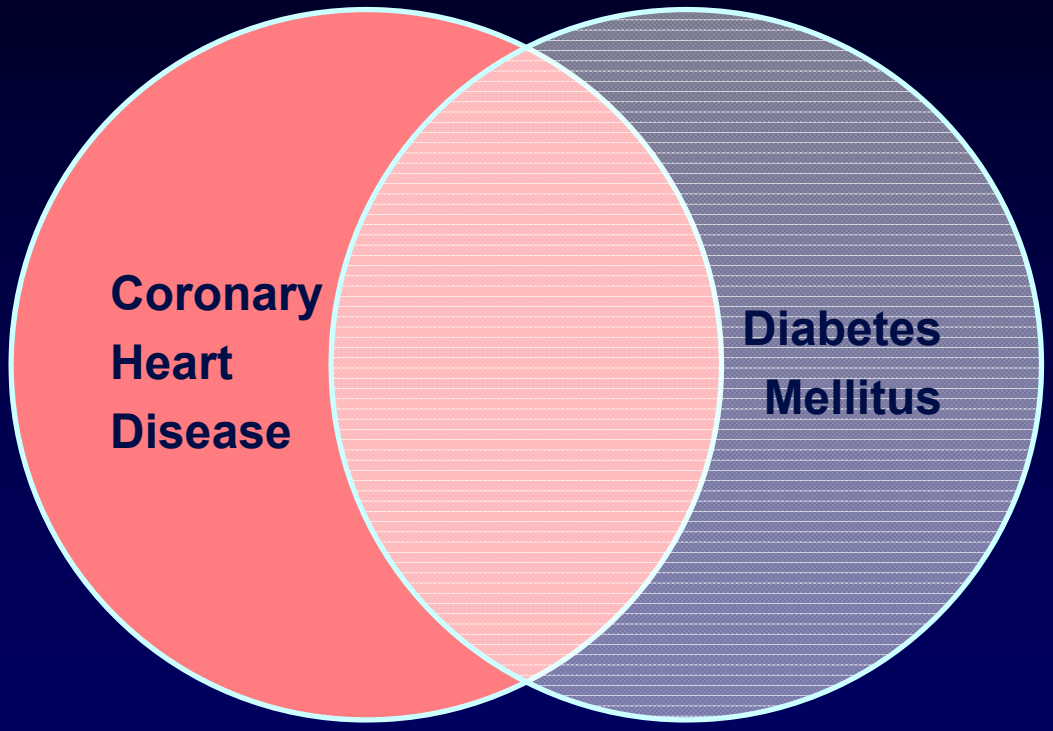
20th CENTURY MODEL



Cardiologist

Diabetologist

21st CENTURY MODEL



Diabetocardiologist