What's New and Improved in Type 2 Diabetes

Dr. Jihad Haddad
Consultant Endocrinologist
M.D, Ph.D.

“Diabetes is a remarkable affliction, not very frequent among men… The course is the common one, namely, the kidneys and the bladder; for the patients never stop making water, but the flow is incessant, as if from the opening of aqueducts.

“Moreover, life is disgusting and painful; thirst, unquenchable; excessive drinking, which, however, is disproportionate to the large quantity of urine, for more urine is passed; and one cannot stop them either from drinking or making water.”

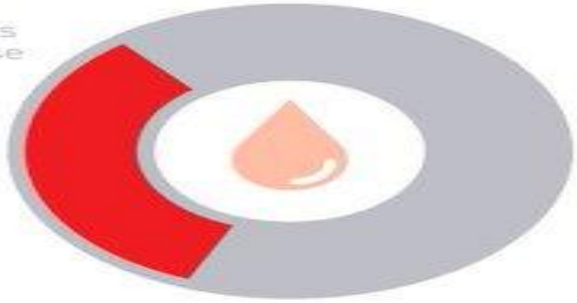
DIABETES

DIABETES IS ON THE RISE

422 MILLION
adults have diabetes

3.7 MILLION
deaths due to diabetes and high blood glucose

1.5 MILLION
deaths caused by diabetes



THAT'S 1 PERSON IN 11

Main types of diabetes

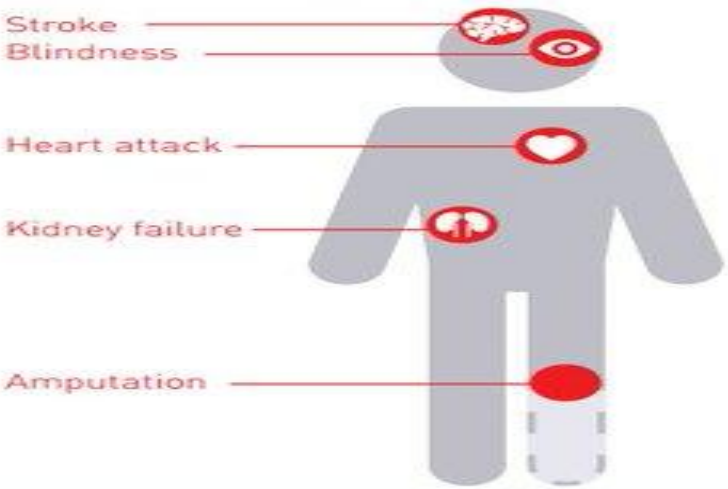
TYPE 1 DIABETES
Body does not produce enough insulin

TYPE 2 DIABETES
Body produces insulin but can't use it well

GESTATIONAL DIABETES
A temporary condition in pregnancy

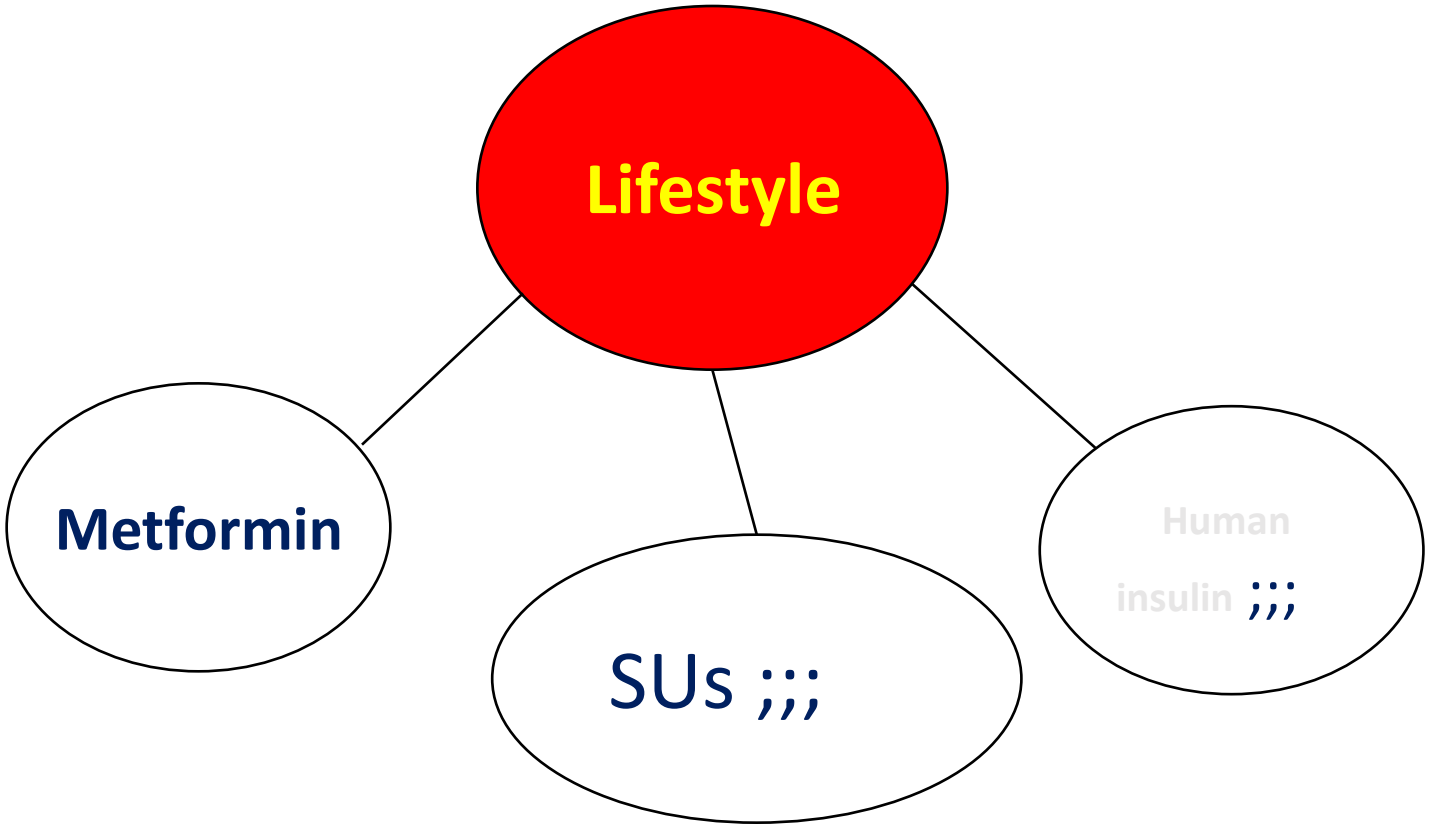
Consequences

Diabetes can lead to complications in many parts of the body and increase the risk of dying prematurely.



IN THE PAST

Core Therapies



Drug Availability for Diabetes 1950 to Present

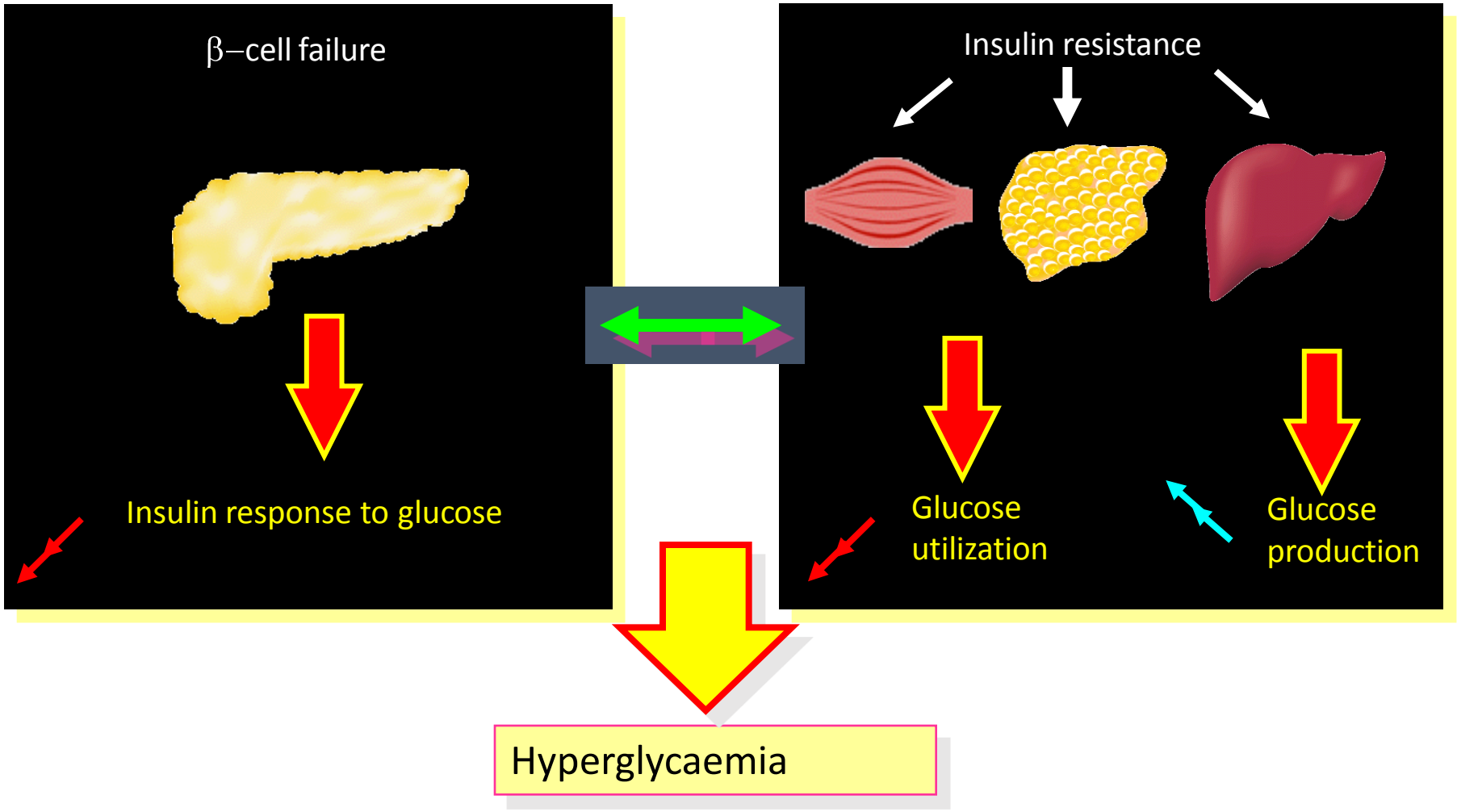
Before 1995: insulin, SFUs,

1995: metformin

The Diabetes Epidemic

Now: many formulations

PATHOPHYSIOLOGY OF TYPE 2 DIABETES
A SCHEMATIC REPRESENTATION

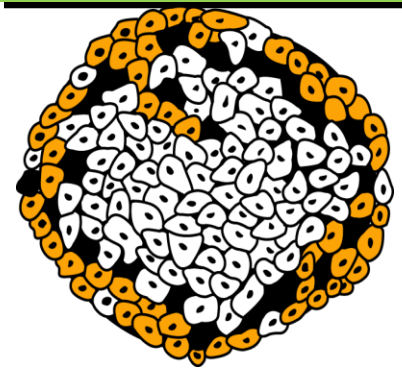


Decreased Insulin Secretion

Decreased Incretin Effect

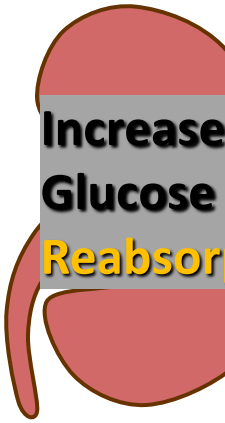
Increased Lipolysis

Islet–α cell



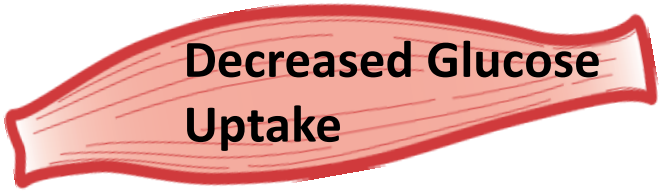
HYPERGLYCEMIA

Increased Glucose Reabsorption

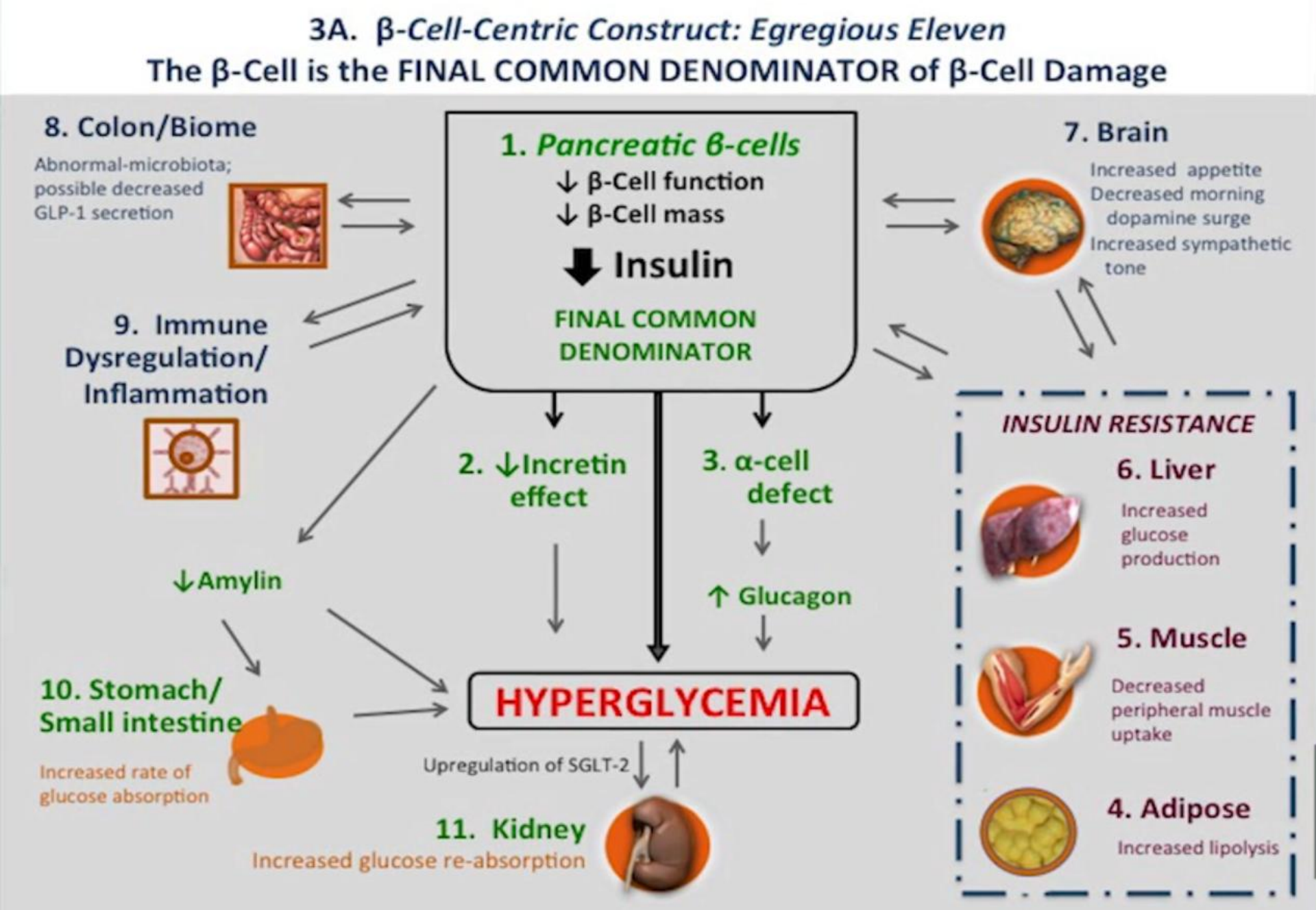


Increased Glucagon Secretion

Neurotransmitter Dysfunction



EGREGIOUS ELEVEN



GLYCEMIC CONTROL AND COMPLICATION OUTCOME IN T2DM: WHERE HAVE WE BEEN;;;;

Effect Of Rosiglitazone on the risk Of Myocardial Infraction and Death From Cardiovascular Causes

Nissens meta analysis of 42 Rosiglitazone Studies:

OR of 1.43 for Acute MI risk
and 1.64 for the risk of cardiac death

The US FDA revised their approval process for newer Antidiabetic agents recommending that apart from lowering HbA1c, sponsors should Demonstrate that the therapy does not increase CV risk to an unacceptable extent

Mortality Risk with Sulfonylurea

- **Meta-analysis in Diabetes Care (May 08) suggests CV risk increased by 43% compared to active control**
- **Most likely mediated through hypos and weight gain**

Diabetes Care (May 08)

Mortality Risk with Sulfonylurea Monotherapy

Diabetes Care Publish Ahead of Print, published online March 9, 2010

The Risk of Overall Mortality in Patients with Type 2 Diabetes Receiving Glipizide, Glyburide, or Glimepiride Monotherapy: A Retrospective Analysis

Short Running Title: Mortality Risk with Sulfonylurea Monotherapy

Kevin M. Pantalone DO[1], Michael W. Kattan PhD[2], Changhong Yu MS[2], Brian J. Wells MD, MS[2], Susana Arrigain MA[2], Anil Jain MD[3], Ashish Atreja MD, MPH[4], Robert S. Zimmerman MD, FACE[1]

1 Endocrinology and Metabolism Institute, Cleveland Clinic, Cleveland, OH
2 Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH
3 Medicine Institute, Cleveland Clinic, Cleveland, OH
4 Digestive Disease Institute, Cleveland Clinic, Cleveland, OH

Corresponding Author:
Kevin M. Pantalone
E-mail: [redacted]

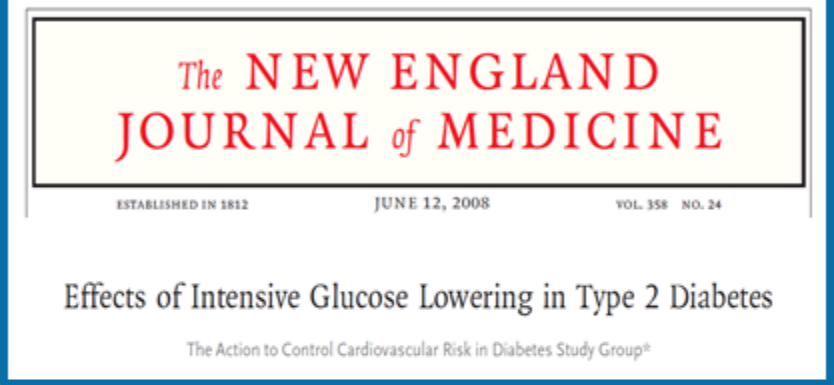
Submitted 5 January 2010 and accepted 1 March 2010.

Results did not identify an increased mortality risk among the individual sulfonylureas.

Pantalone KM. et al Diabetes Care 2010 ; 33:1224-29

Glycemic Control and Macrovascular Disease

ACCORD

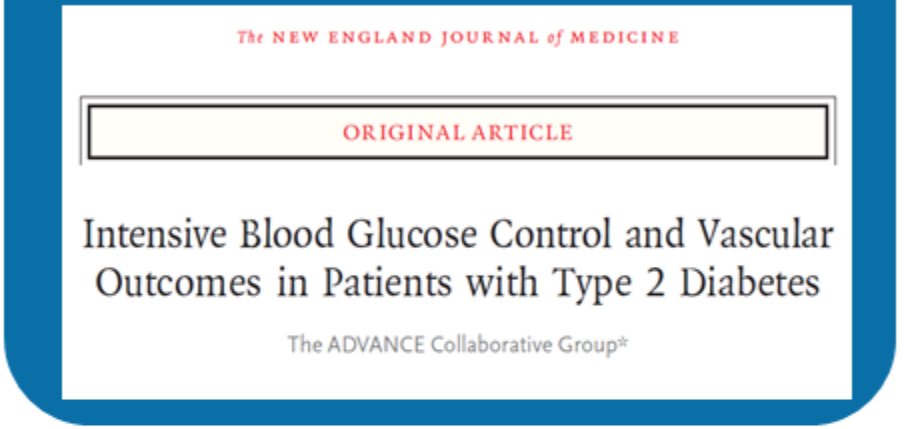

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group*

ADVANCE

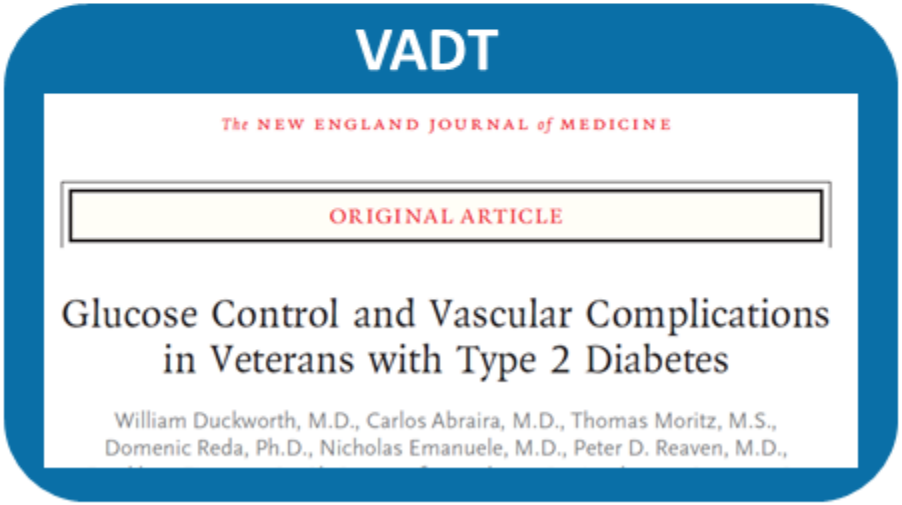

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*

VADT


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes

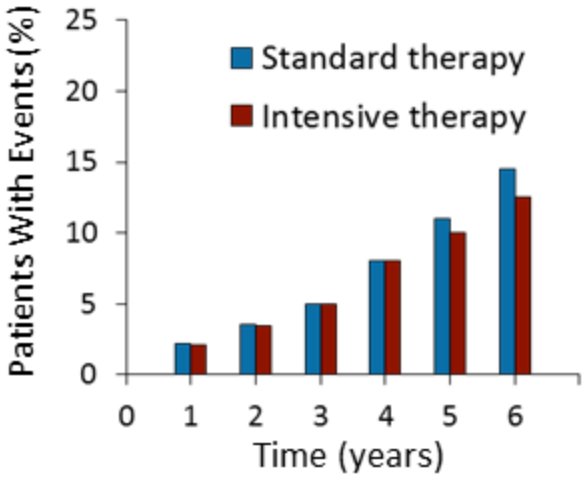
William Duckworth, M.D., Carlos Abraira, M.D., Thomas Moritz, M.S., Domenic Reda, Ph.D., Nicholas Emanuele, M.D., Peter D. Reaven, M.D.,

ACCORD Study Group. *N Engl J Med*. 2008;358:2545-2559.
The ADVANCE Collaborative Group. *N Engl J Med*. 2008;358:2560-2572.
Duckworth W, et al. *N Engl J Med*. 2009;360:129-139.

Intensive Glycemic Control Increased All-cause Mortality (ACCORD)[a]

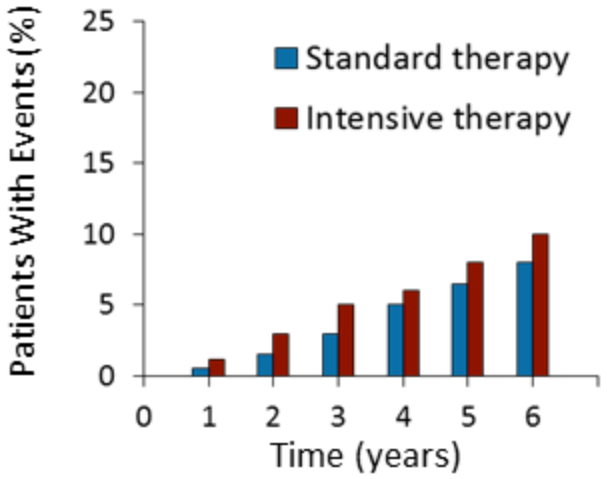
Primary outcome*

Nonsignificant reduction in CV events in intensive group (HR = 0.90, *P* = .16)



Death from any cause

Increased mortality in intensive group (HR = 1.22, *P* = .04)



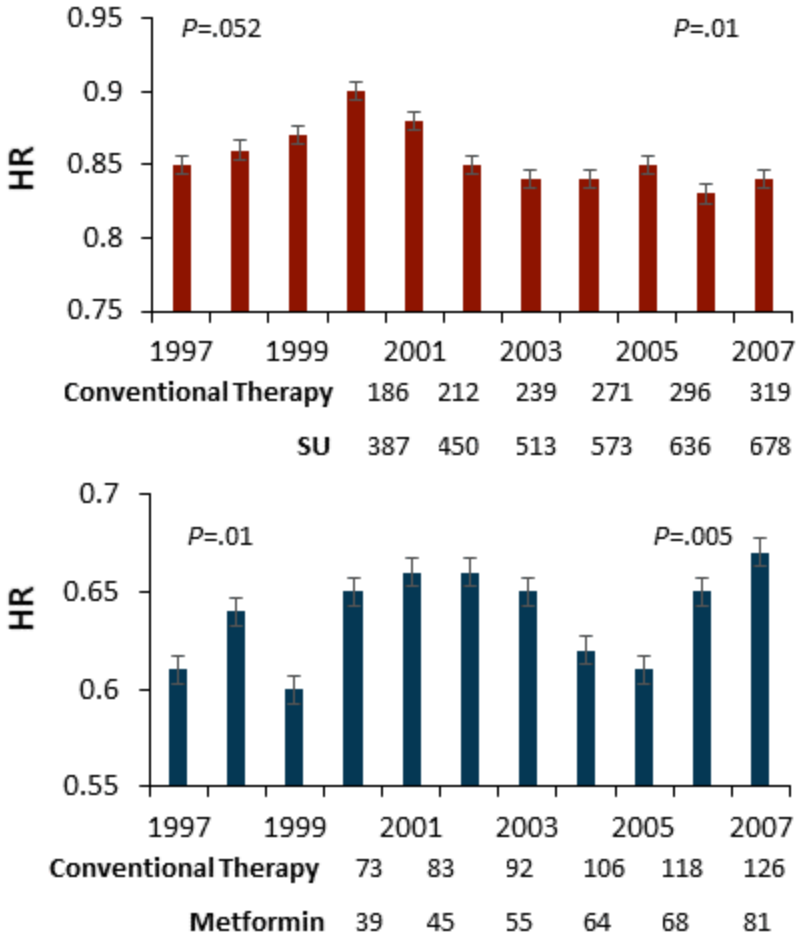
Mortality did not increase in other outcome trials (eg, VADT and ADVANCE)[b,c]

*MACE: nonfatal MI, nonfatal stroke, or CV death

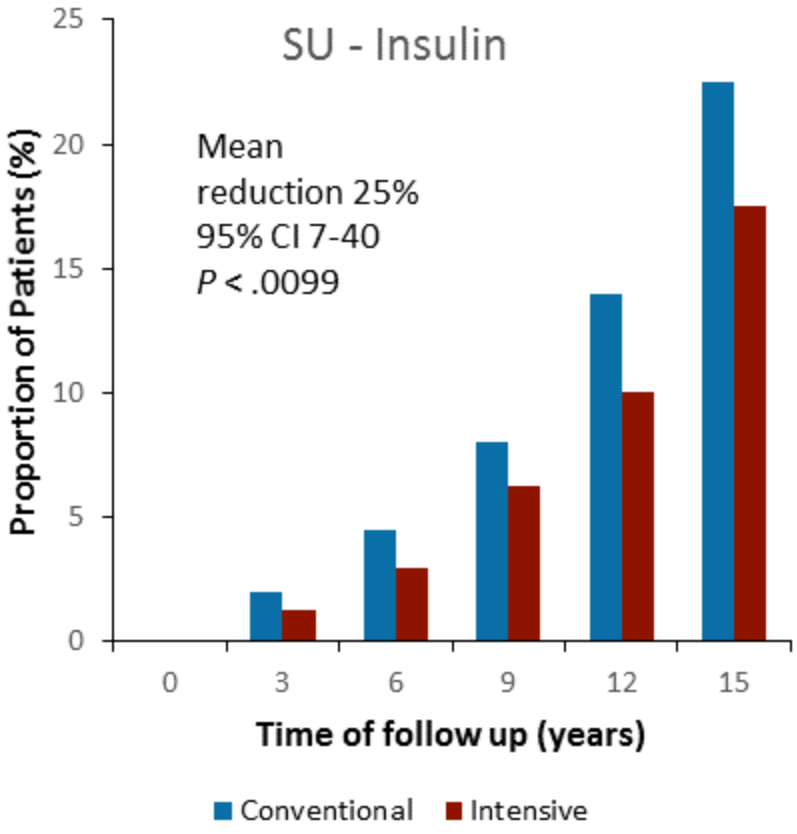
a. ACCORD Study Group. *N Engl J Med.* 2008;358:2545-2559.
b. Duckworth W, et al. *N Engl J Med.* 2009;360:129-139.
c. The ADVANCE Collaborative Group. *N Engl J Med.* 2008;358:2560-2572.

Glucose-lowering Drugs in T2DM: Effect on CV Endpoints (cont)

Decrease in MI by HbA1c -0.9% in T2DM[a]



Decrease in microvascular complications by HbA1c -0.9% in T2DM[b]



a. Holman RR, et al. *N Engl J Med*. 2008;359:1577-1589.
b. UKPDS study group. *Lancet*. 1998;352:837-853.

The Need for CV Outcomes Studies

- In 2008, the US FDA recommended that manufacturers developing new drugs and biologics for T2D provide evidence that the therapy will not increase the risk of CV events
- Applies to all T2D drugs currently under development

Glucose control by itself has not been definitively shown to reduce CV events

FDA website

December 2008 FDA Guidance on Evaluating CV Risk in New Antidiabetic Therapies for T2DM

Guidance for Industry

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

III. RECOMMENDATIONS

To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. To ensure that a new therapy does not increase cardiovascular risk to an unacceptable extent, the development program for a new type 2 antidiabetic therapy should include the following.

For new clinical studies in the planning stage:

- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.

- Sponsors should ensure that phase 2 and phase 3 clinical trials are appropriately designed and conducted so that a meta-analysis can be performed at the time of completion of these studies that appropriately accounts for important study design features and patient or study level covariates. To obtain sufficient endpoints to allow a meaningful estimate of risk, the phase 2 and phase 3 programs should include patients at higher risk of cardiovascular events, such as patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment. Because these types of patients are likely to be treated with the antidiabetic agent, if approved, this population is more appropriate than a younger and healthier population for assessment of other aspects of the test drug's safety.

- Sponsors also should provide a protocol describing the statistical methods for the proposed meta-analysis, including the endpoints that will be assessed. At this time, we believe it would be reasonable to include in a meta-analysis all placebo-controlled trials, add-on trials (i.e., drug versus placebo, each added to standard therapy), and active-

FDA.org

Traditional vs. diabetes cardiovascular outcomes trials

Traditional CVOTs

Aim: Demonstrate CV benefit

Initiation of treatment vs. active comparator

No treatment adjustment

Difference (e.g. HbA_{1c}) observed between treatment arms

Significant reduction in CV outcomes vs. active comparator

Lower CV risk vs. comparator

Diabetes CVOTs

Aim: Demonstrate CV safety

Initiation of blinded treatment/placebo

Maintain similar HbA_{1c} levels in treatment arms

Treatment adjustment

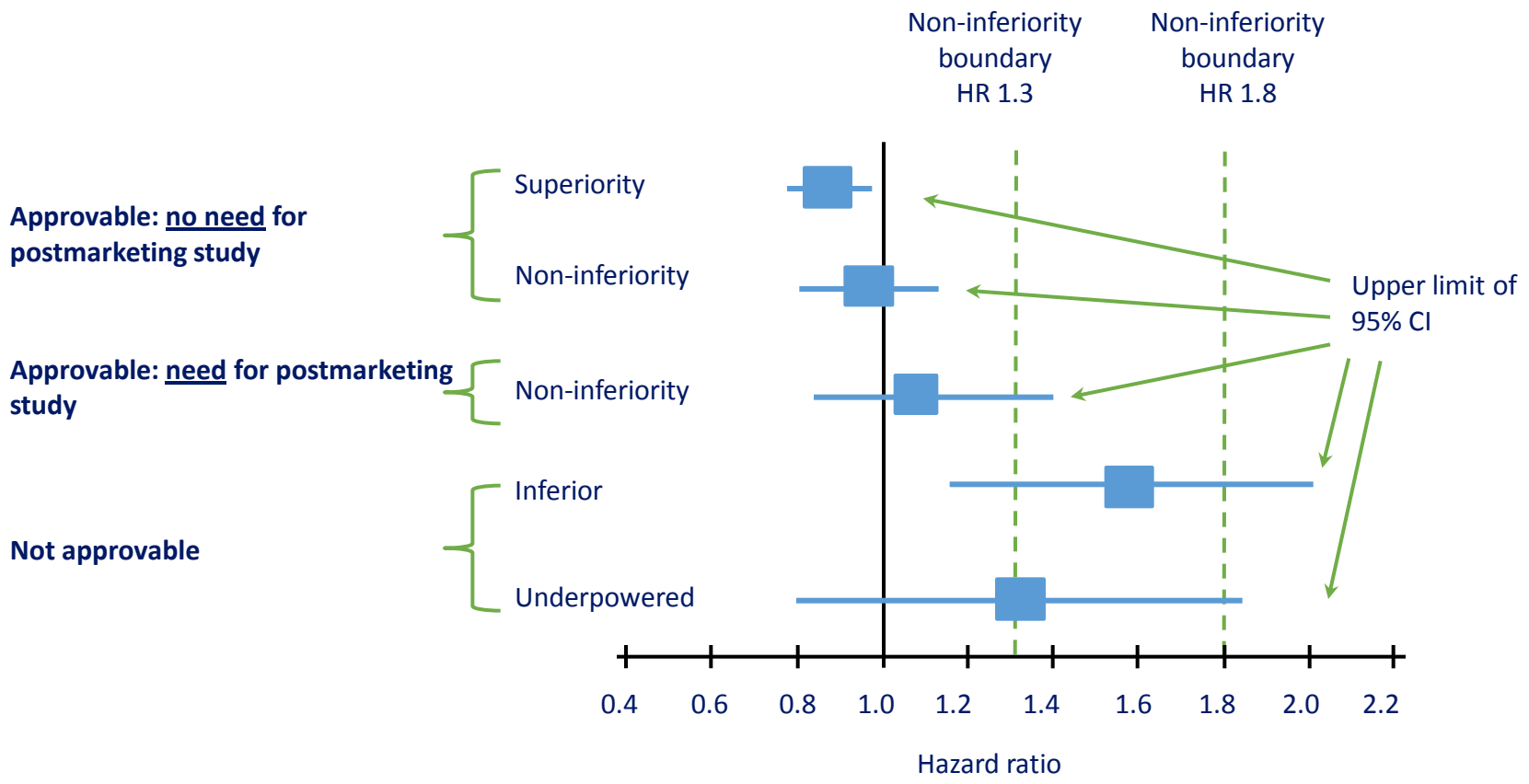
Small/no difference (e.g. HbA_{1c}) observed between treatment arms

Noninferiority vs. placebo

No unacceptable increase in CV risk vs. placebo as part of standard care

CV, cardiovascular; CVOTs, cardiovascular outcomes trials

FDA criteria for requirement of a postmarketing CV outcomes trial

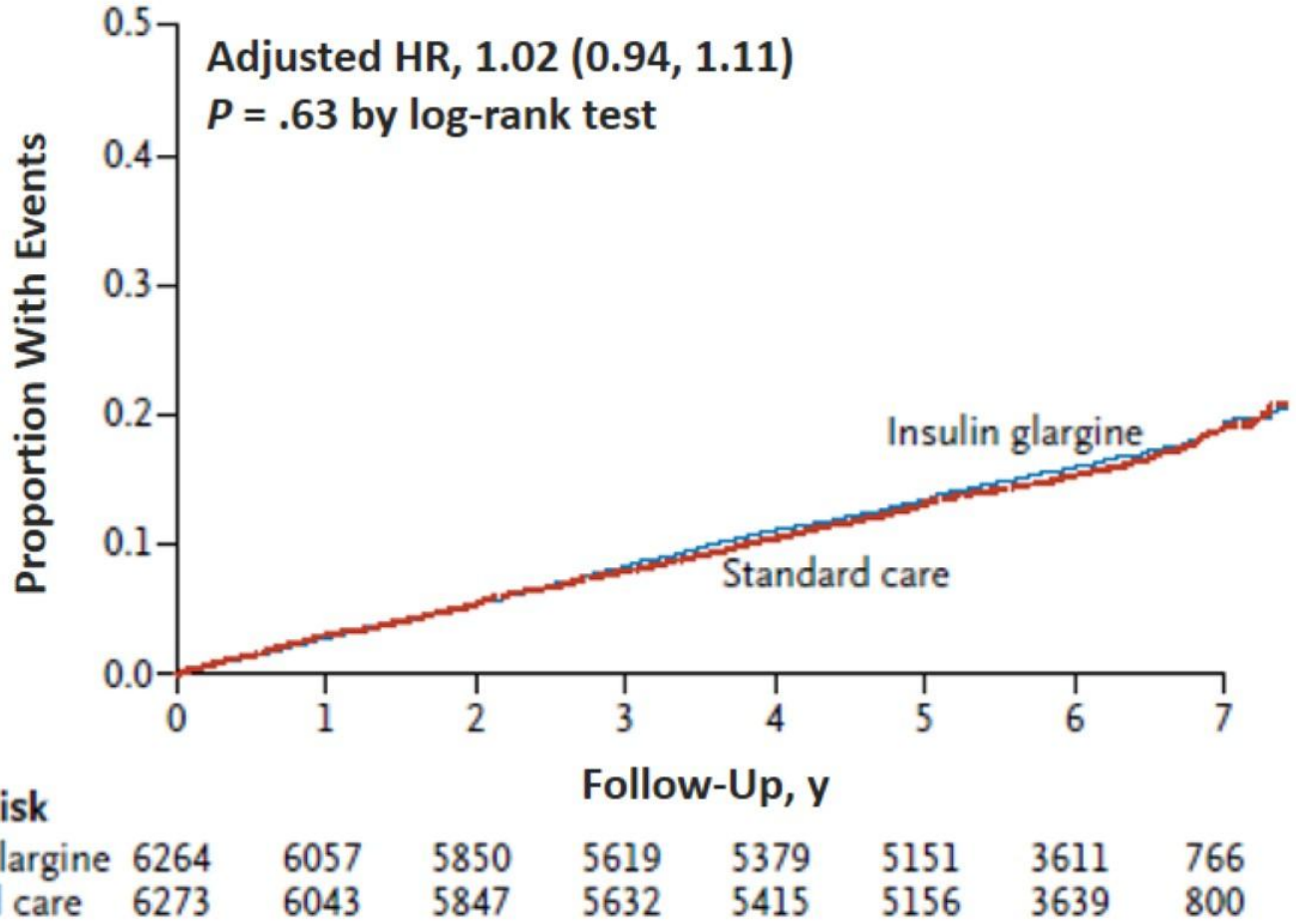


CV, cardiovascular; FDA, Food and Drug Administration; HR, hazard ratio

Hirshberg, Raz. *Diabetes Obes Metab* 2011;34(Suppl. 2):S101–6

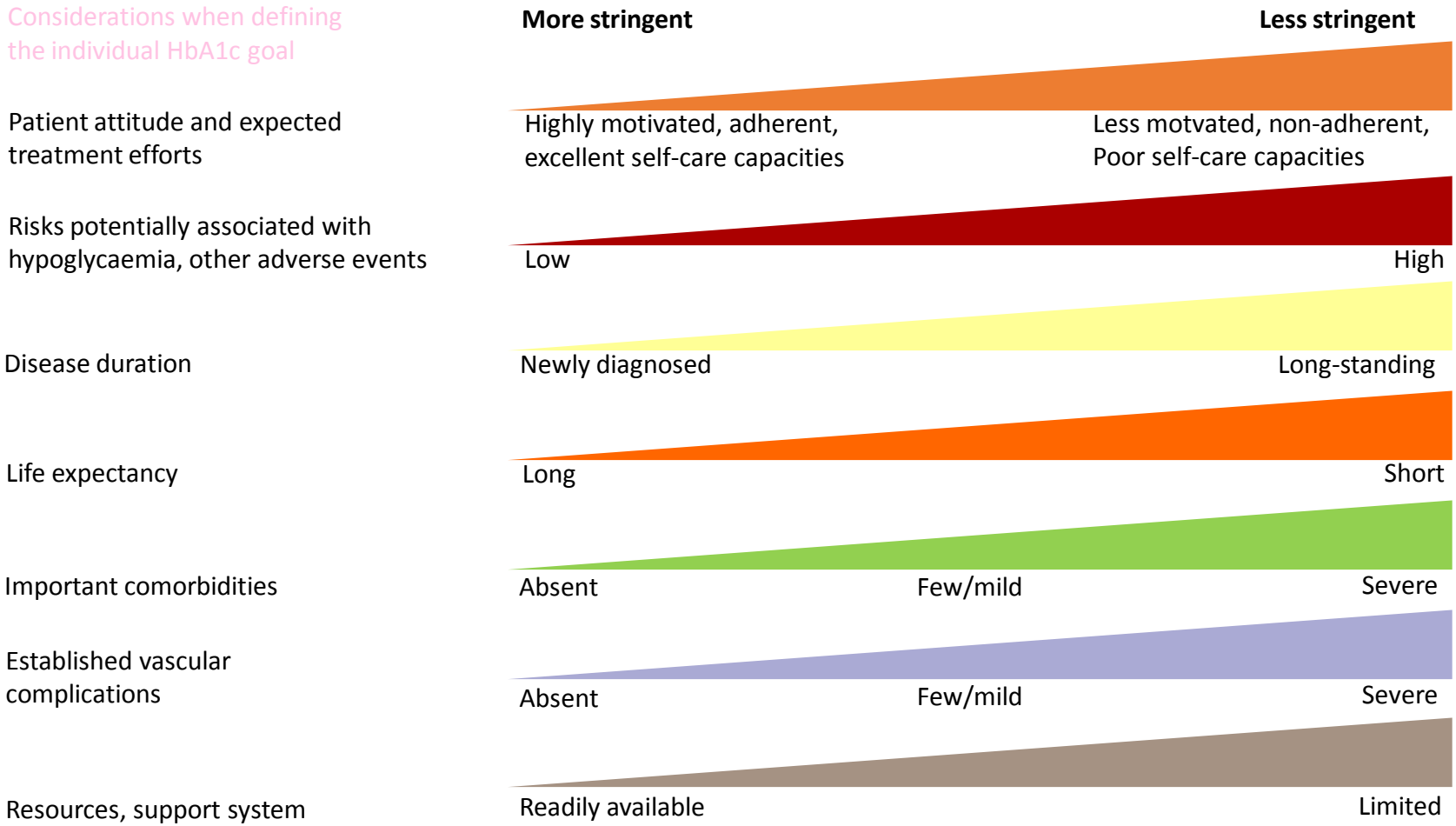
ORIGIN

MI, Stroke, or Death From CV Causes

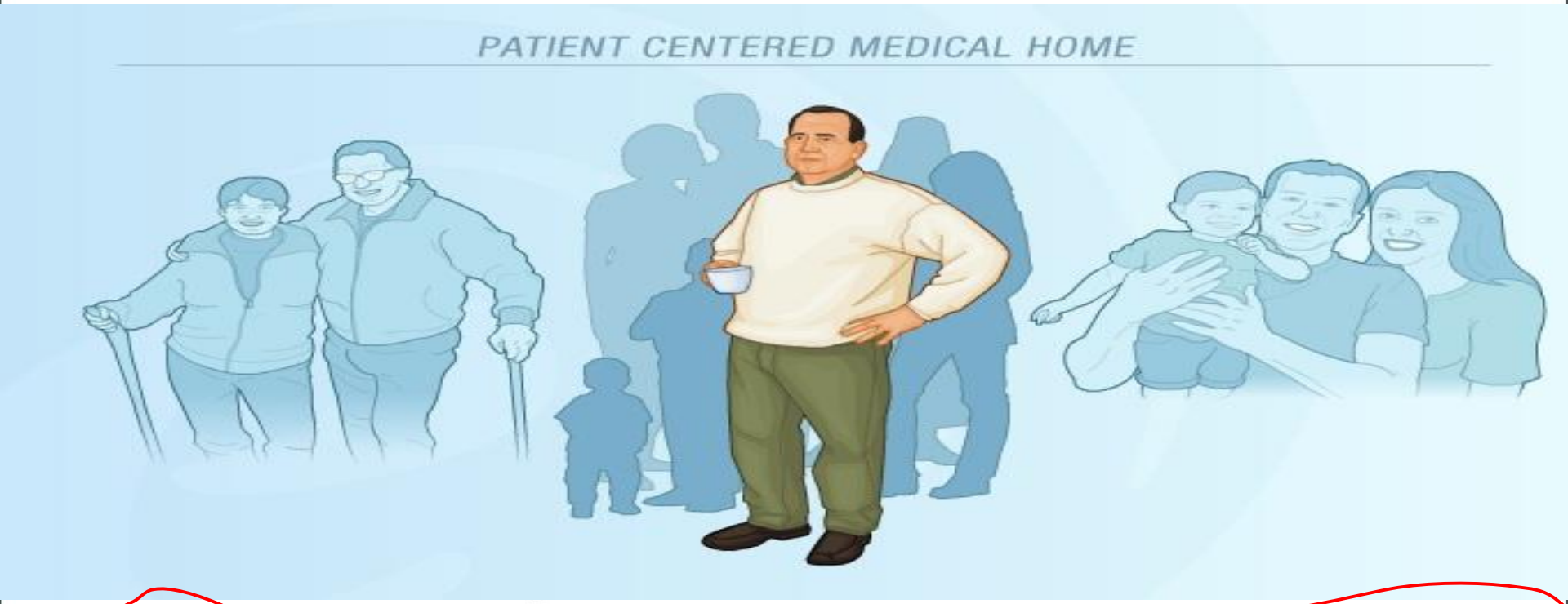


ORIGIN Trial Investigators. *N Engl J Med.* 2012;367:319-328.

ADA/EASD position statement: A patient-centered approach but a potential inducer of clinical inertia?



Adapted from ADA/EASD position statement; Inzucchi et al. Diabetologia /Diab. Care (2012)



- "Not every drug is for every patient, not every patient is for every drug"

Hippocrates

It's far more important to know what person the disease has than what disease the person has.

Modern Antihyperglycemic Agents

Drug Class	Clinical Actions	Effect on Weight	Risk of Hypoglycemia
GLP-1 receptor agonists	↓ Glucagon ↑ Insulin release	Loss	Low
DPP-4 inhibitors	↓ Glucagon ↑ Insulin release	Neutral	Low
SGLT2 inhibitors	↑ Urinary glucose excretion	Loss	Low

Complementary mechanisms of action; agents may be combined together

Inzucchi SE, et al. *Diabetes Care*. 2015;38:140-149.

DPP4 INHIBITORS
Drugs belonging to this class are:

Gemigliptin (approved in Korea in 2012, marketed by LG Life Sciences) Marketed as Zemiglo

Anagliptin (approved in Japan in 2012, marketed by Sanwa Kagaku Kenkyusho Co., Ltd. and Kowa Company, Ltd.)

Teneligliptin (approved in Japan in 2012)

Alogliptin (FDA approved 2013, marketed Takeda Pharmaceutical Company

Trelagliptin (approved for use in Japan in 2015)

Omarigliptin (MK-3102) (approved in Japan in 2015,developed by Merck & Co.; research showed that omarigliptin can be used as once-weekly treatment and generally well-tolerated throughout the base and extension studies

Evogliptin (approved for use in South Korea)

Dutogliptin (being developed by Phenomix Corporation

- **retagliptin**

SAVOR-TIMI 53: Primary Endpoint: CV Death, Nonfatal MI or Nonfatal Ischemic Stroke

No. at risk						
Placebo	8212	7983	7761	7267	4855	851
Saxagliptin	8280	8071	7836	7313	4920	847

Scirica BM et al. *N Engl J Med.* 2013;369:1317–1326.

savor TIMI 53
TIMI STUDY GROUP / HADASSAH MEDICAL ORG

Individual Endpoints

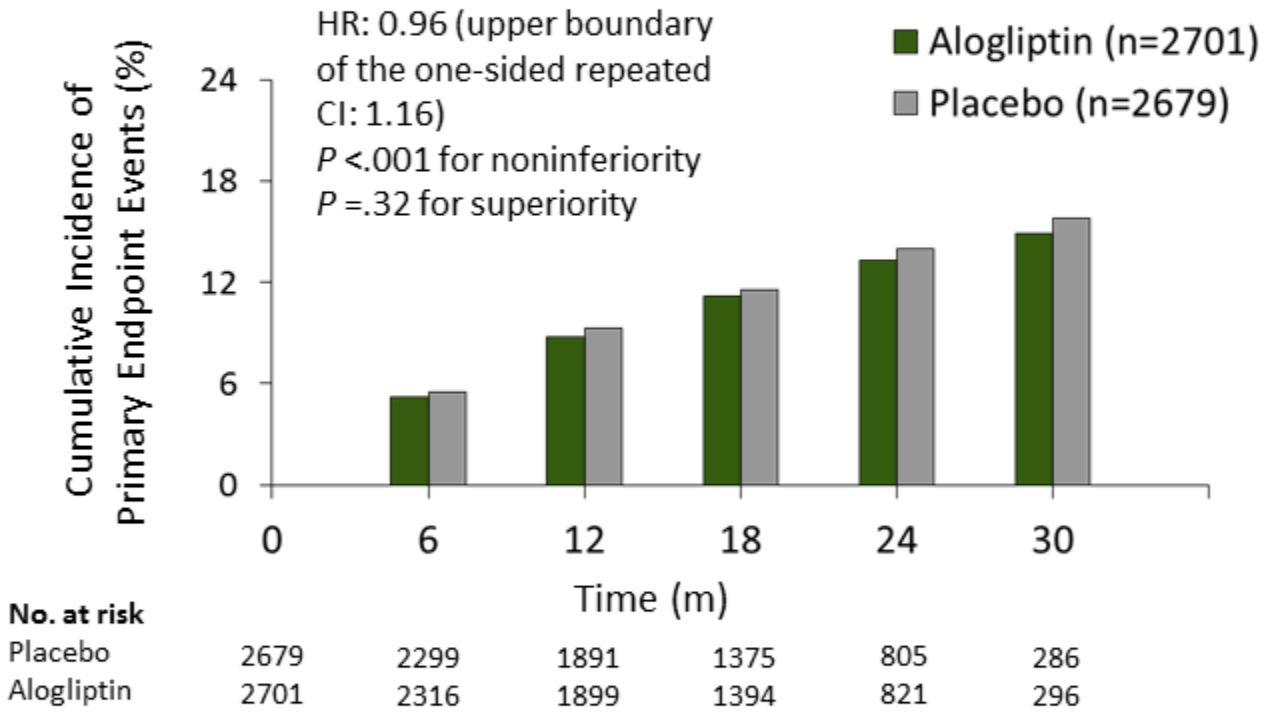
ITT Population

	2-year KM rate (%)			
	Placebo (N=8,212)	Saxagliptin (N=8,280)	HR	*p value for superiority*
CV Death	2.9	3.2	1.03 (0.87-1.22)	0.72
MI	3.4	3.2	0.95 (0.80-1.12)	0.52
Ischemic Stroke	1.7	1.9	1.11 (0.88-1.39)	0.38
Hosp for Cor. Revasc	5.6	5.2	0.91 (0.80-1.04)	0.18
Hosp for UA	1.0	1.2	1.19 (0.89-1.60)	0.24
Hosp for Heart Failure	2.8	3.5	1.27 (1.07-1.51)	0.007
All-Cause Mortality	4.2	4.9	1.11 (0.96-1.27)	0.15

Scirica BM, Bhatt DL, Braunwald E, et al…. Raz I. *NEJM* 2013 at www.NEJM.org.

TIMI

EXAMINE: Time to First Occurrence of Primary Endpoint



After a median exposure of 18 months, the rates of primary composite endpoints were similar in the alogliptin and placebo groups (11.3% and 11.8%, respectively)

Primary endpoint: composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke.

White WB, et al. *N Engl J Med* 2013; 369: 1327-1335.

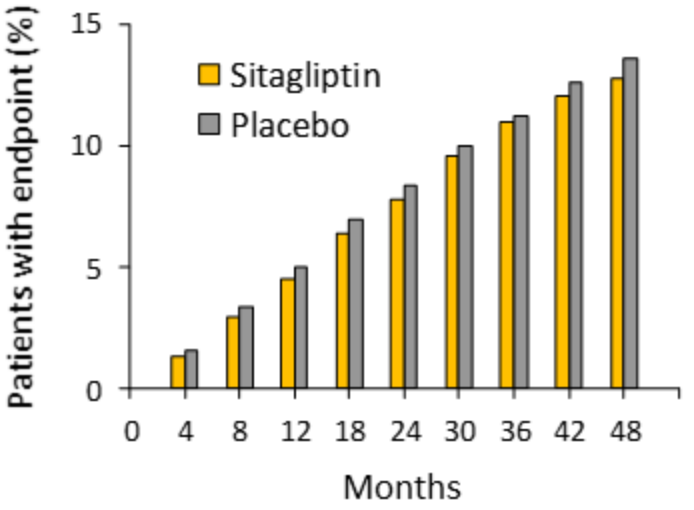
TECOS: Sitagliptin CV Outcomes

MACE analysis[a]

	Sitagliptin-exposed N=5429	Non-exposed (placebo or active comparator; N=4817)
MACE incidence rate/100 P-Y	0.65	0.74
Exposure-adjusted rate ratio (95% CI)	0.83 (0.53; 1.30)	

TECOS[b]

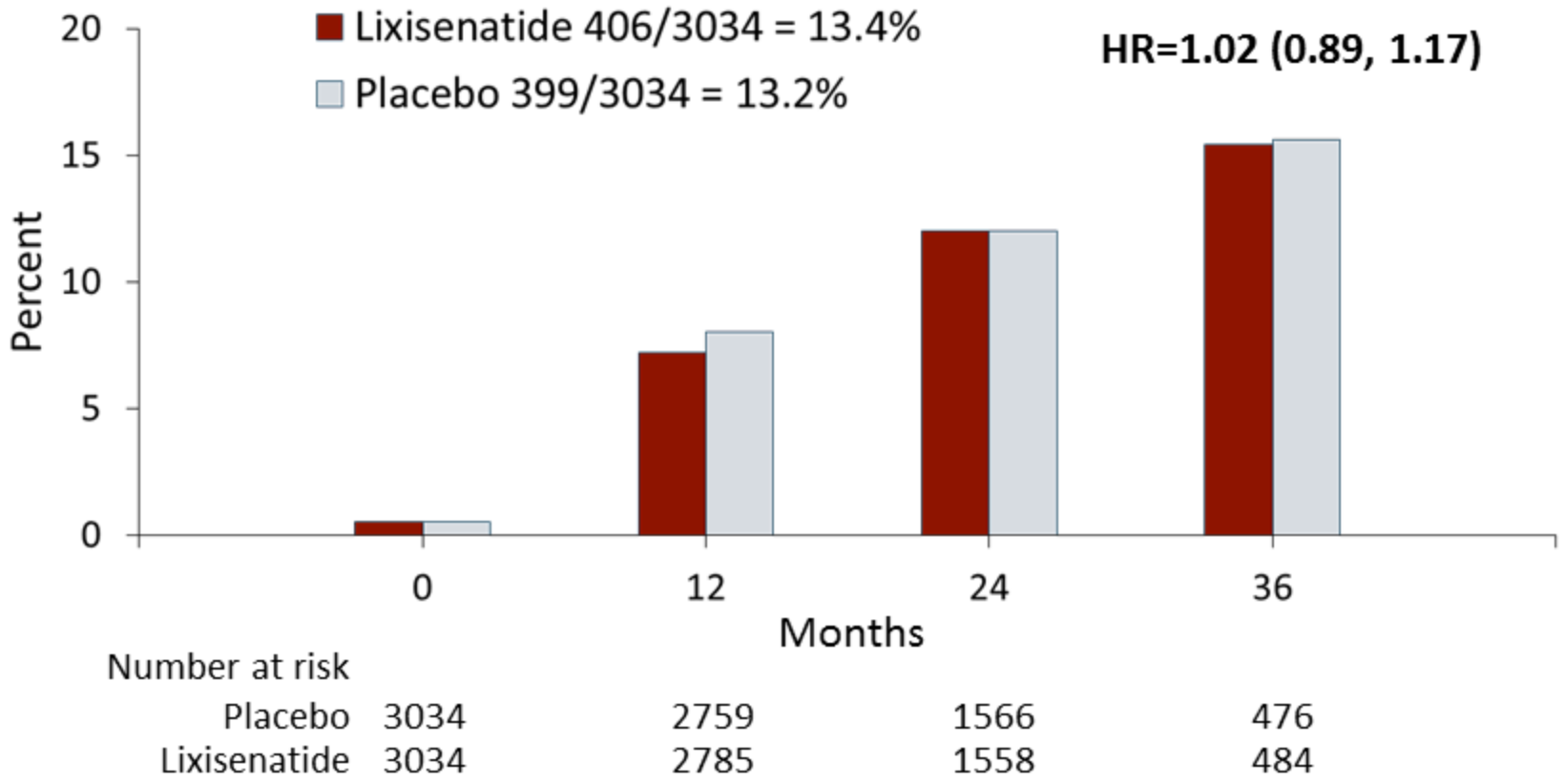
CV-related death, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalization



Hazard ratio (95% CI) 0.98; (0.88, 1.09)
P < .001 for noninferiority

a. Engel SS, et al. *Cardiovasc Diabetol.* 2013;12:1-11.
b. Green JB et al. *N Engl J Med.* 2015; 373: 232-242.

ELIXA: Primary Outcome: CV Death, Nonfatal MI, Nonfatal Stroke, or Hospitalization for Unstable Angina



- Subgroup interactions were analysed, but none were significant

Pfeffer MA, et al. *N Engl J Med*. 2015;33:2247-2257.

Trials of glucose lowering drugs in T2DM

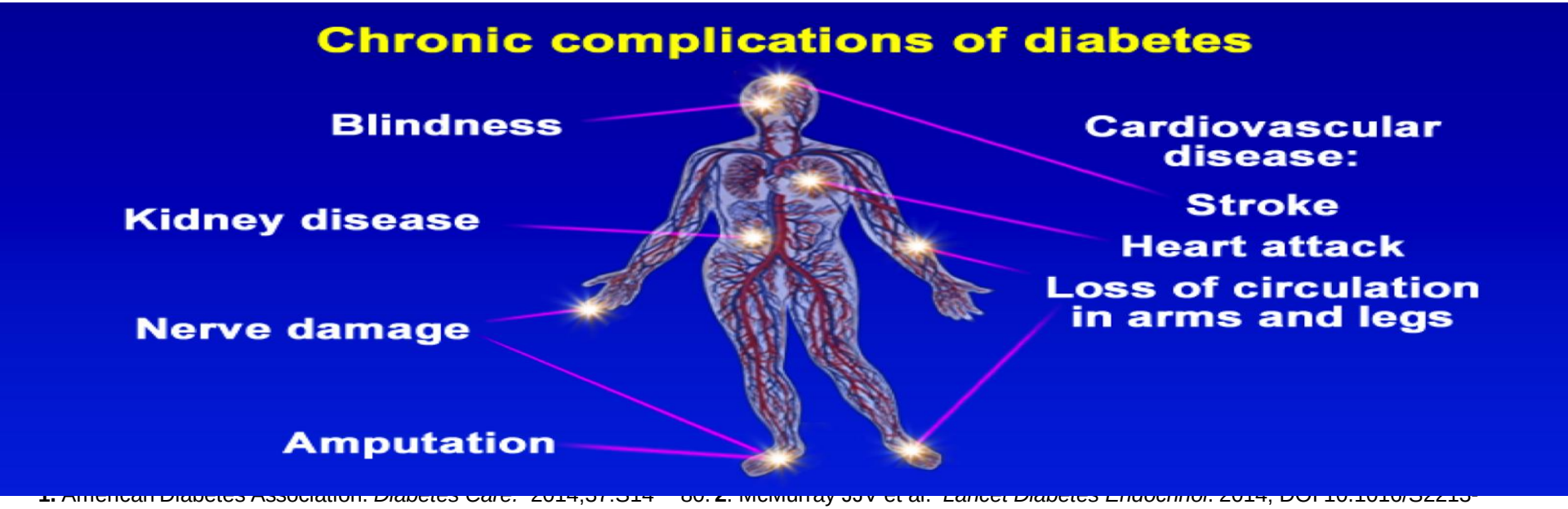
Neutral outcome

Trial	Drug	Patients	FU (yrs)	Endpoint	Results
SAVOR TIMI 53	Saxa-gliptin	T2DM + CVD ACS or High risk for CVD	2.1	Cardvasc death or Non-fatal myocardial infarction or stroke	No diffe-rence
EXAMINE	Alo-gliptin		1.5		
TECOS	Sita-gliptin		3.0		
ELIXA	Lixise-natide		2.1		

Rydén et al. Clin Therap 2016; 38: 1279

Impact of Intensive vs Conventional Glycemic-Lowering Strategies on Risk of CV Outcomes Is Unclear

- Lowering of HbA_{1c} has been shown to reduce microvascular disease[1,2]
  - Reduction of macrovascular risk has not been consistently observed[3–5]



1. American Diabetes Association. *Diabetes Care*. 2014;37:S14–80. **2.** McMurray JJV et al. *Lancet Diabetes Endocrinol*. 2014; DOI:10.1016/S2213-8587(14)70031-2. **3.** ADVANCE Collaborative Group et al. *N Engl J Med*. 2008;358:2560–2572. **4.** Gerstein HC et al. *N Engl J Med*. 2008;358:2545–2559. **5**. Duckworth W et al. *N Engl J Med*. 2009;360:129–139.