Novel Diabetes Treatments:

Update 2015

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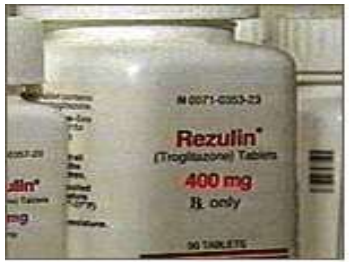
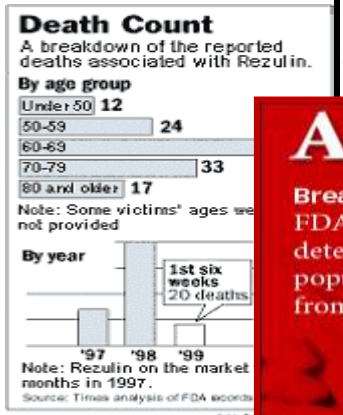
Disclosure of Statement of Financial Interests

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
Grant/Research Support/Clinical trials	Novo Nordisk, Terumo, The Medicines Company, AstraZeneca, Bristol-Myers Squibb
Consulting Fees/Honoraria	Novo Nordisk, St. Jude Medical
Major Stock Shareholder/Equity	None
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

Off-target Safety Signals of DM Drugs





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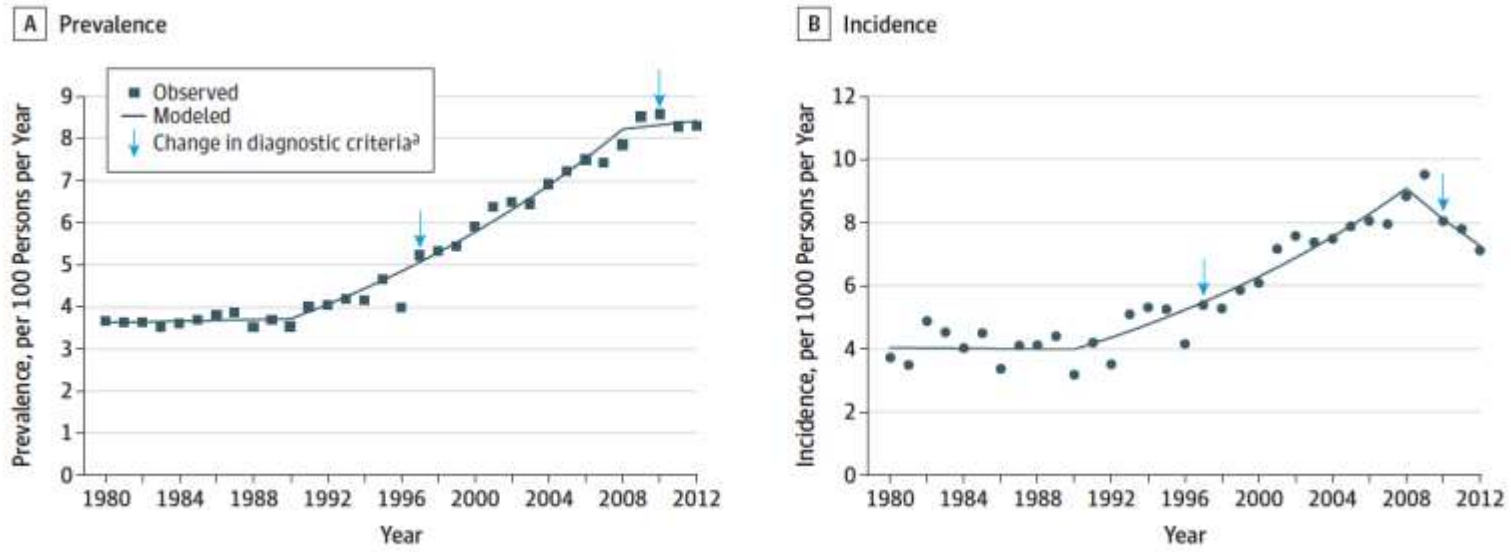
Converging Pressures for Regulatory Change for DM Drugs: Beyond HbA1c

- Diabetes common and increasing
  - >10% of US adult population and >350 million worldwide
- Increasing awareness of the cardiovascular consequences of DM
- Proliferation of glucose-lowering therapeutic alternatives
  - Before 1995: insulin, sulfonylureas
  - 1995: acarbose; metformin
  - Now: >40 formulations representing 12 classes
- Lessons learned from failed/withdrawn medications
- HbA1c as target for CVD risk reduction
    - Failure of hypothesis?
    - On target adverse effects?
    - Off target adverse effects?
    - Too little, too late?

Trends in Age-Adjusted Diagnosed Diabetes



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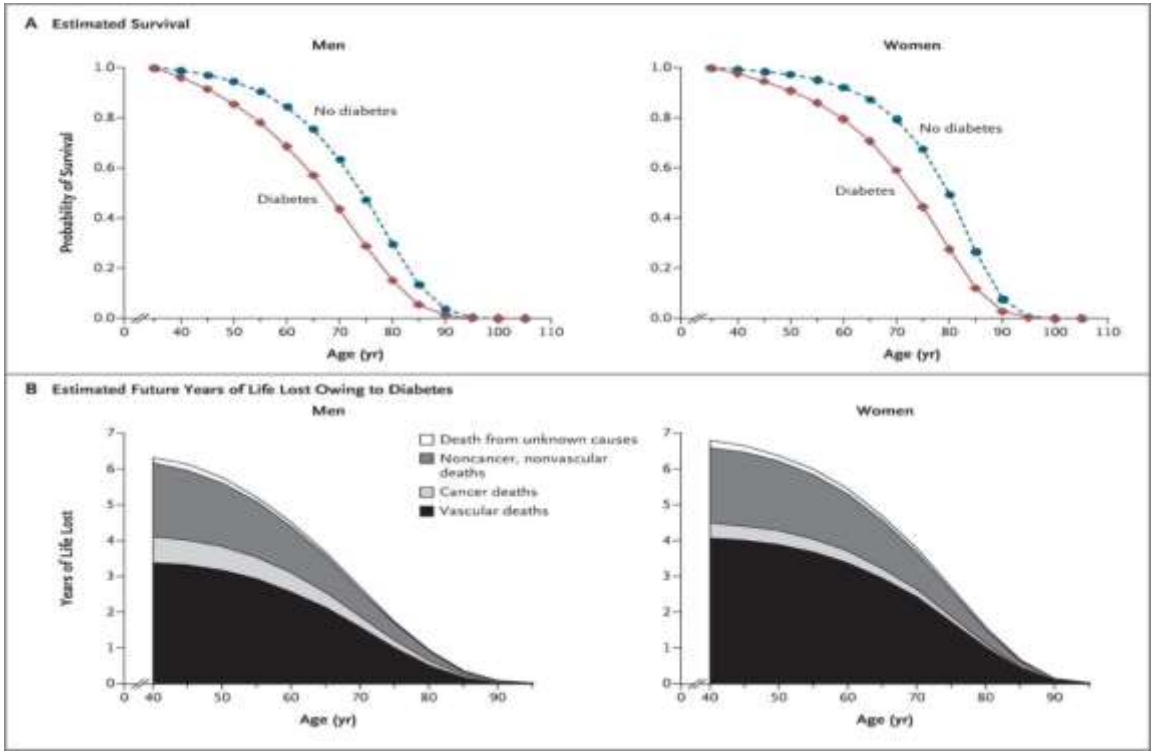
Geiss et al JAMA.2014:312: 1218-1226

Diabetes and Survival, According to Sex and Diabetes Status.



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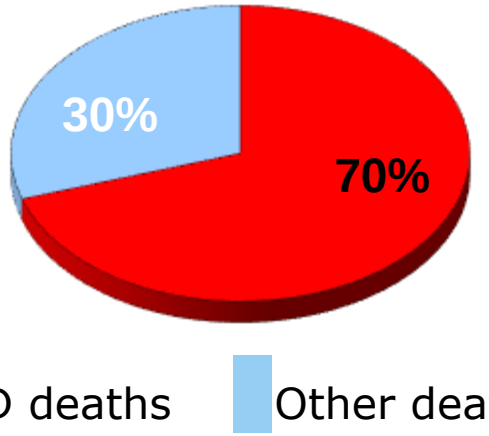
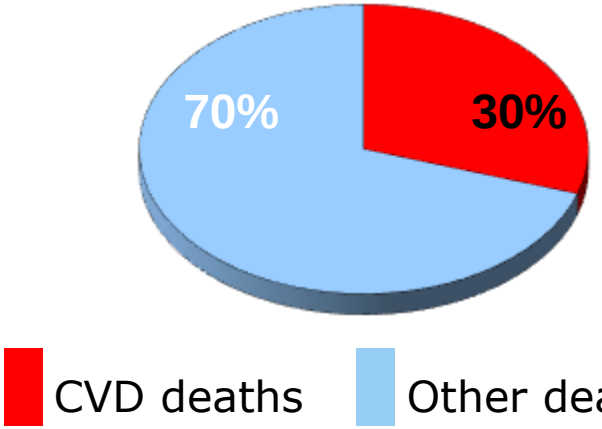
The Emerging Risk Factors Collaboration. N Engl J Med 2011;364:829-841

T2DM Increases CVD Mortality

Patients with Type 2 Diabetes[1]

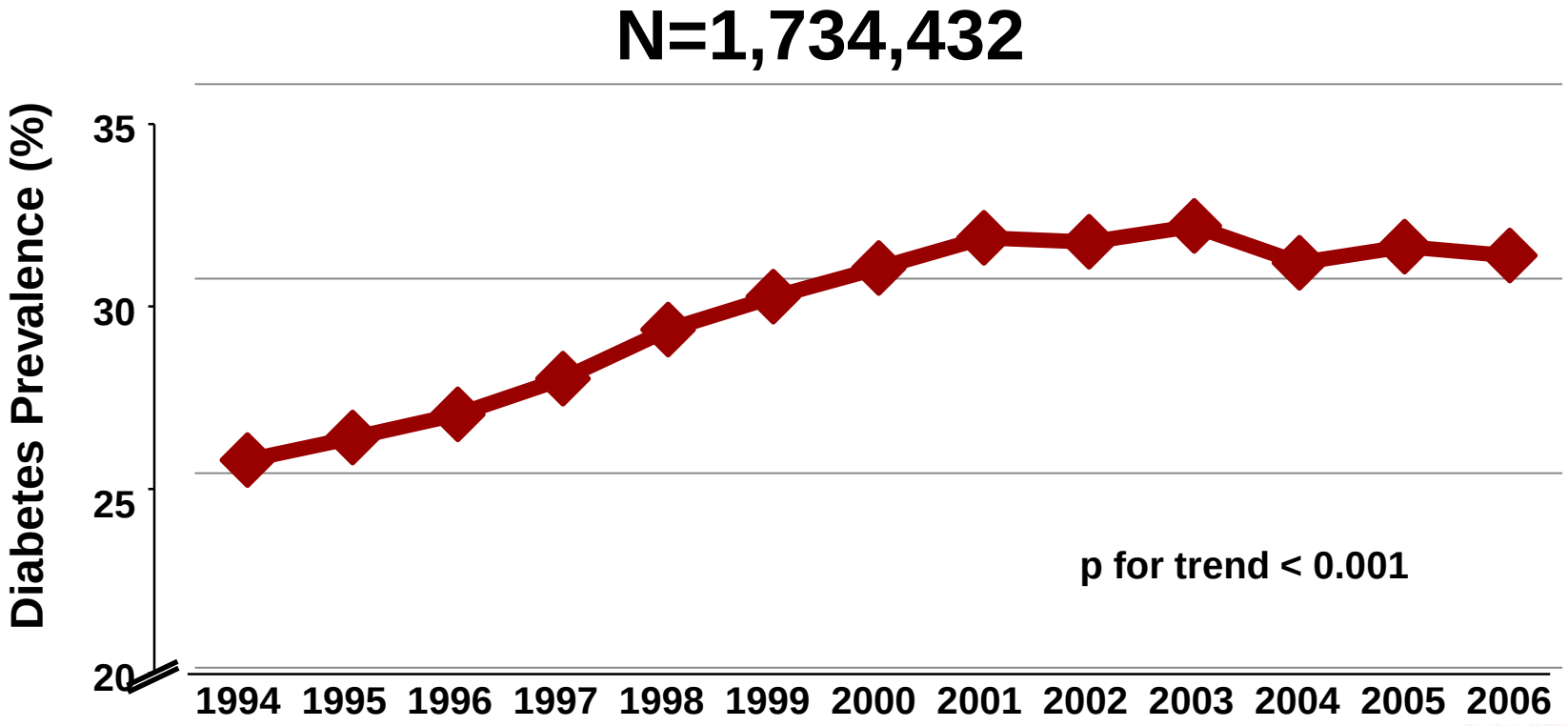


General Population[2]



1. CDC. National diabetes fact sheet, 2007
2. WHO. http://www.who.int/mediacentre/factsheets/fs317/en/print.html

Diabetes Prevalence Among AMI Patients: Observations from NRMI



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Gore MO, et al. Circ QCO 5:791; 2012

While it is true that modern health care has favorably altered CV survival for patients with and without diabetes, **there remains an unyielding "incremental CV risk" for patients with T2DM.**

- 2-4 fold Increased Risk
- Death, MI, Stroke
- Unmet need

Is tight glycemic control associated with improved CV outcomes in patients with T2DM?

UKPDS

- **An intensive glucose control policy HbA_{1c} 7.0% vs. 7.9% reduces risk of**
  - **Any diabetes-related endpoints** **12%** **P = 0.030**
  - **Microvascular endpoints** **25%** **P = 0.010**
  - **Myocardial infarction** **16%** **P = 0.052**

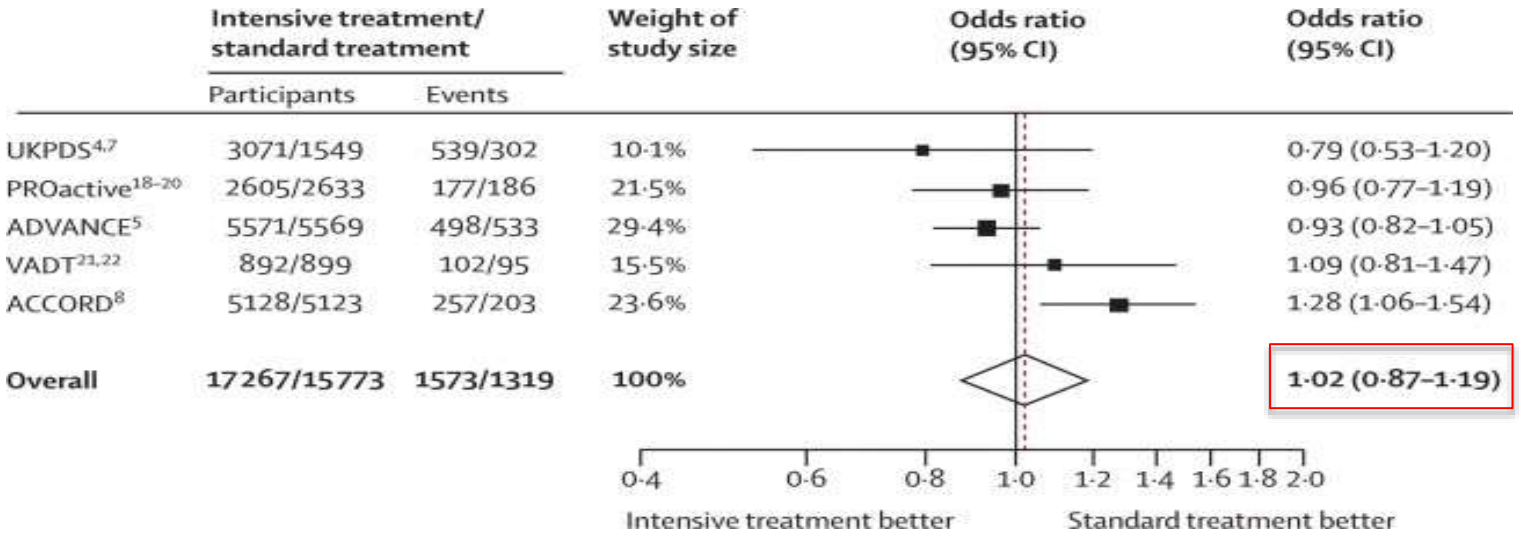
Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials

Kausik K Ray, Sreenivasa Rao Kondapally Seshasai, Shanelle Wijesuriya*, Rupa Sivakumaran*, Sarah Nethercott*, David Preiss, Sebhat Erqou, Naveed Sattar*

- **5 prospective randomized controlled trials (UKPDS, PROactive, ADVANCE, VADT, ACCORD)**
- **33,040 patients**
- **MACE**
  - **All cause mortality(2892)**
  - **Non-fatal MI(1497)**
  - **Stroke (1127)**
  - **CHD (fatal and non-fatal MI, stroke, 2318)**

Ray et al. Lancet 2009;373:1765-1772

All Cause Mortality Analysis Intensive vs Standard Glucose Lowering



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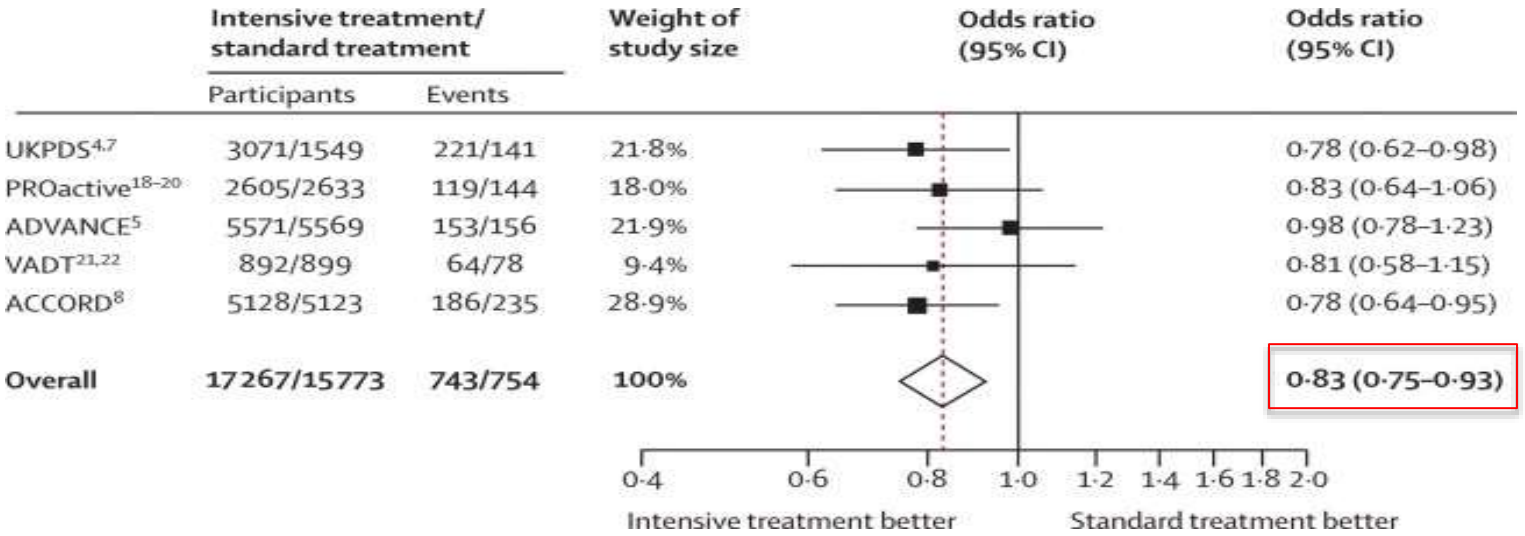
Ray et al. Lancet 2009;373:1765-1772

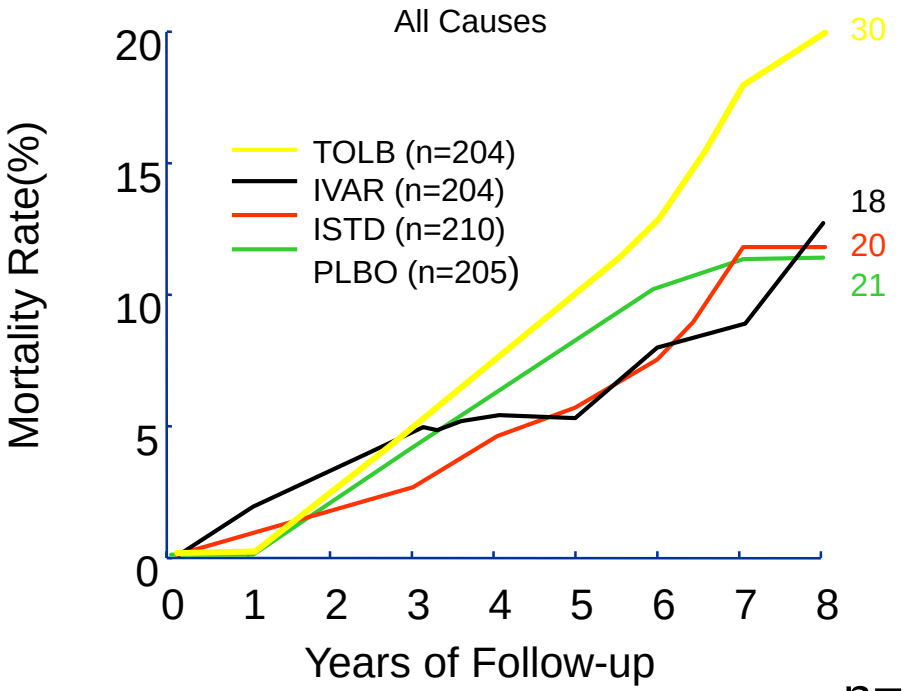
Nonfatal MI Analysis Intensive vs Standard Glucose Lowering



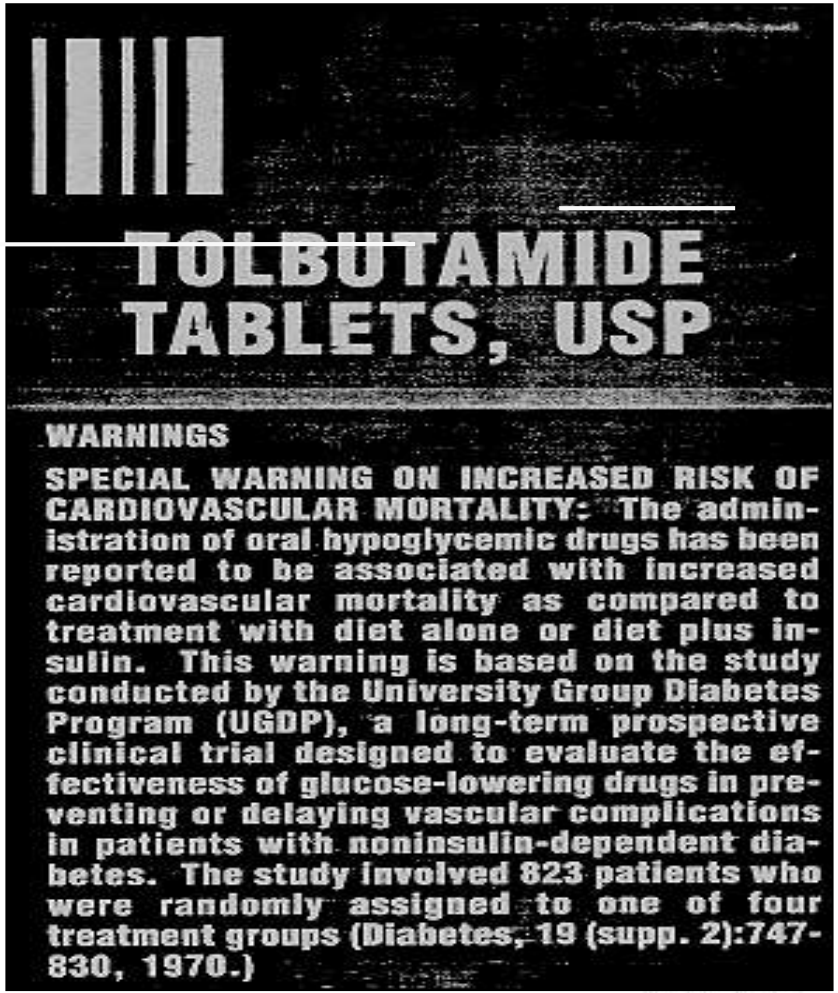
Ray et al. Lancet 2009;373:1765-1772

Are drugs to manage hyperglycemia safe?

Mortality Impact of Glycemic Control:
University Group Diabetes Program

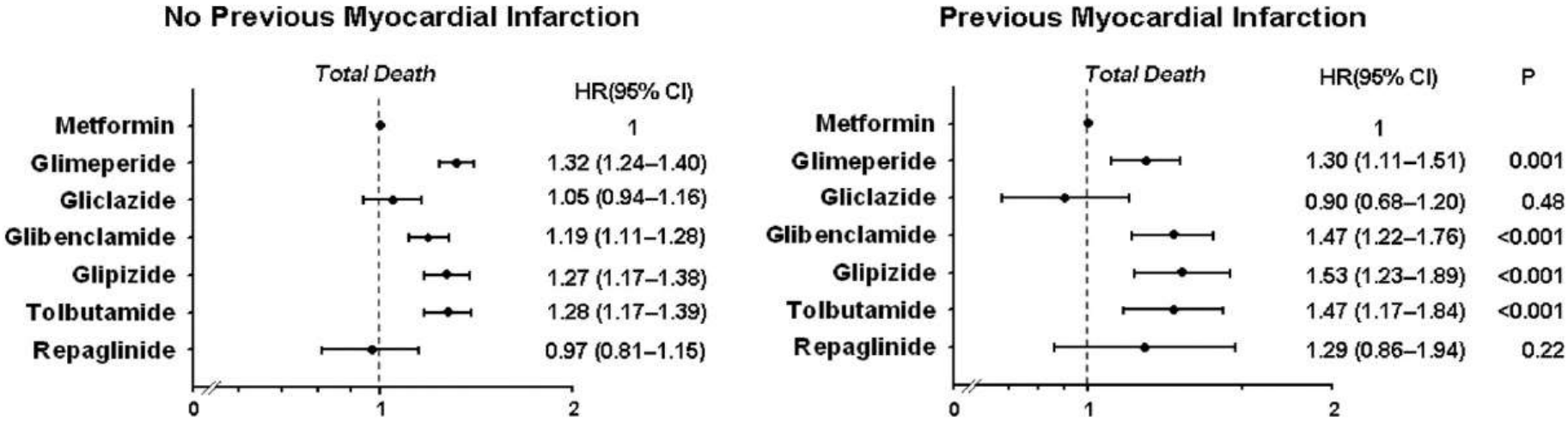


n=823



Associations between Insulin Secretagogues and Mortality

N=107,806 Danish Adults Initiating Glucose-lowering Therapy
F/U up to 9 yrs (mean 3.3 yrs)
9505 Deaths for Analysis



Schramm et al EHJ 2011;32:1900-08

Rosiglitazone Meta-Analysis

- **42 Trials:**
  - **Treatment for 24 weeks to 52 weeks**
  - **Randomized design with active group receiving rosiglitazone**
  - **Death or MI outcome**
  - **116 studies, 42 trials used**
  - **158 nonfatal myocardial infarctions**
  - **Fixed effects model**
  - **56 years, HbA1c 8.2%**

Nissen et al. N Engl J Med; 2007;356:2457-2471

Rates of MI and Death from Cardiovascular Causes

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P-Value
	No. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,280 (0.43)	22/6105 (0.36)	1.45 (0.88-2.39)	0.15
DREAM	15/2635 (0.57)	9/2634 (0.34)	1.65 (0.74-3.68)	0.22
ADOPT	27/1456 (1.85)	41/2895 (1.44)	1.33 (0.80-2.21)	0.27
Overall	**86**	**72**	1.43 (1.03-1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6557 (0.38)	7/3700 (0.19)	2.40 (1.17-4.91)	0.02
DREAM	12/2365 (0.51)	10/2634 (0.38)	1.20 (0.52-2.78)	0.67
ADOPT	2/1456 (0.14)	5/2854 (0.18)	0.80 (0.17-3.86)	0.78
Overall			1.64 (0.98-2.74)	0.06

Nissen et al. N Engl J Med; 2007;356:2457-2471

TZDs and CV Risk

- **Studies have suggested that the use of rosiglitazone may be associated with an increased risk of serious cardiovascular events compared with other treatments for type 2 diabetes.**

- **In mid-2007, a meta-analysis of 42 randomized controlled trials involving rosiglitazone reported a 1.4-fold increase in risk of acute myocardial infarction (AMI) compared with non-thiazolidinedione therapies.** (Nissen et al. *N Engl J Med* 2007;356:2457-2471)

- **Subsequently, a meta-analysis of 19 randomized controlled trials with pioglitazone found a statistically significant reduction in the composite outcome of nonfatal AMI, stroke, and all-cause mortality and a nearly statistically significant reduction in nonfatal AMI alone,[2] thereby suggesting a potential difference in cardiovascular risk between the 2 thiazolidinediones.**

Lincoff et al. *J Am Med Asoc* 2007:298:1180-88

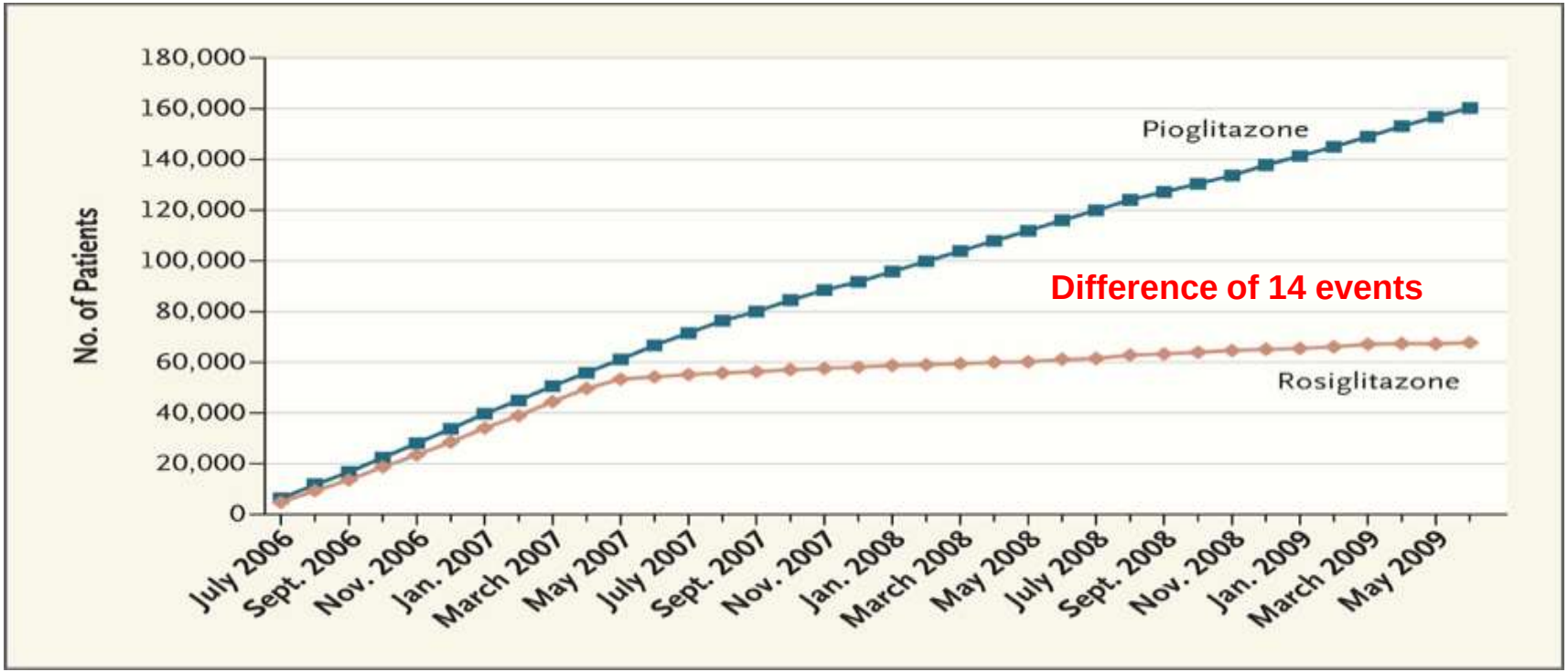
CMS Beneficiary Analysis: Rosiglitazone vs Pioglitazone

1999-2009
2.84 M years of rosi use

	Events, No.		Incidence Rate per 100 Person-Years		Attributable Risk (85% CI) per 100 person-years	No. Needed to Harm (95% CI), Person-Years	HR (95% CI)	
End Point	Rosi	Pio	Rosi	Pio			Unadjusted	Adjusted[a]
AMI	523	1223	1.83	1.68	0.15 (-0.03 to 0.33)	NA[b]	1.07 (0.97-1.19)	1.06 (0.96-1.18)
Stroke	363	689	1.27	0.95	0.32 (0.71-0.47)	313 (213-588)	1.31 (1.15-1.49)	1.27 (1.12-1.45)
Heart failure	1125	2182	3.94	3.00	0.94 (0.68-1.20)	106 (83-147)	1.27 (1.18-1.37)	1.25 (1.16-1.34)
All-cause mortality	814	1748	2.85	2.40	0.45 (0.22-0.67)	222 (149-455)	1.17 (1.07-1.27)	1.14 (1.05-1.24)[c]
AMI, stroke, heart failure or all-cause mortality	2593	5386	9.10	7.42	1.68 (1.27-2.08)	60 (48-79)	1.20 (1.14-1.26)	1.18 (1.12-1.23)[c]

[a] Cox proportional hazards model stratified by history of cardiovascular end point.
[b] Attributable risk was not statistically significant.
[c] Test of proportional hazards assumption not met.

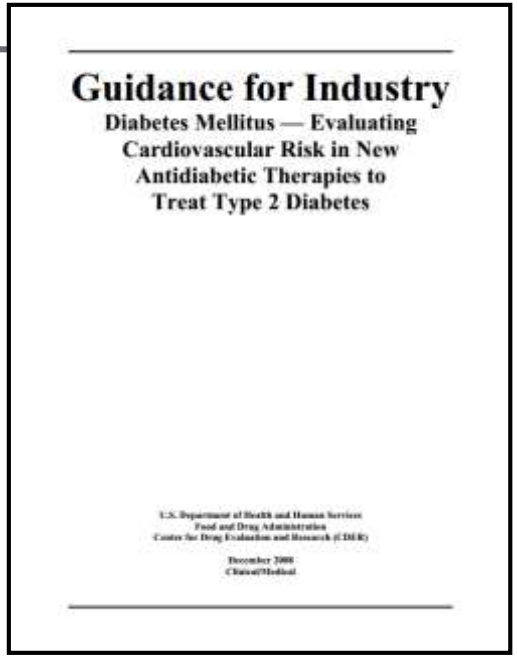
Graham et al. JAMA 2010;304:411-418



Rose n CJ. N Engl J Med 2010;363:803-806

FDA guidance for industry

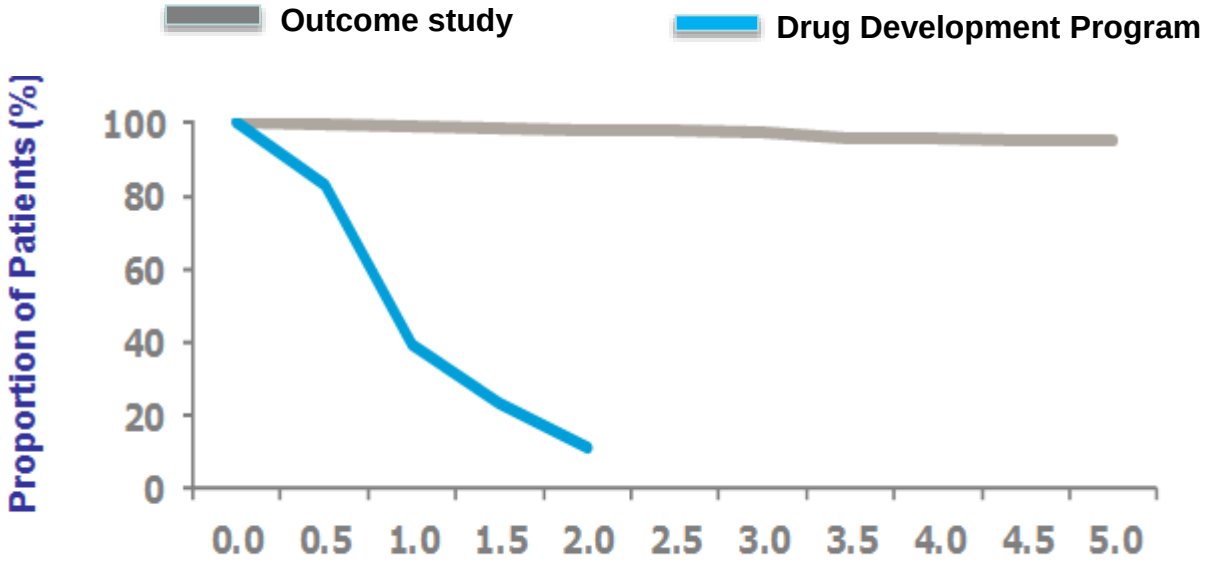
- **In December 2008, the US FDA issued guidance to industry for evaluating CV safety in diabetes drugs**
- **Industry should demonstrate new therapy will not results in an unacceptable increase in CV risk**
  - **The upper bound of the two-sided 95% CI of the risk ratio should be <1.8**


Guidance for Industry

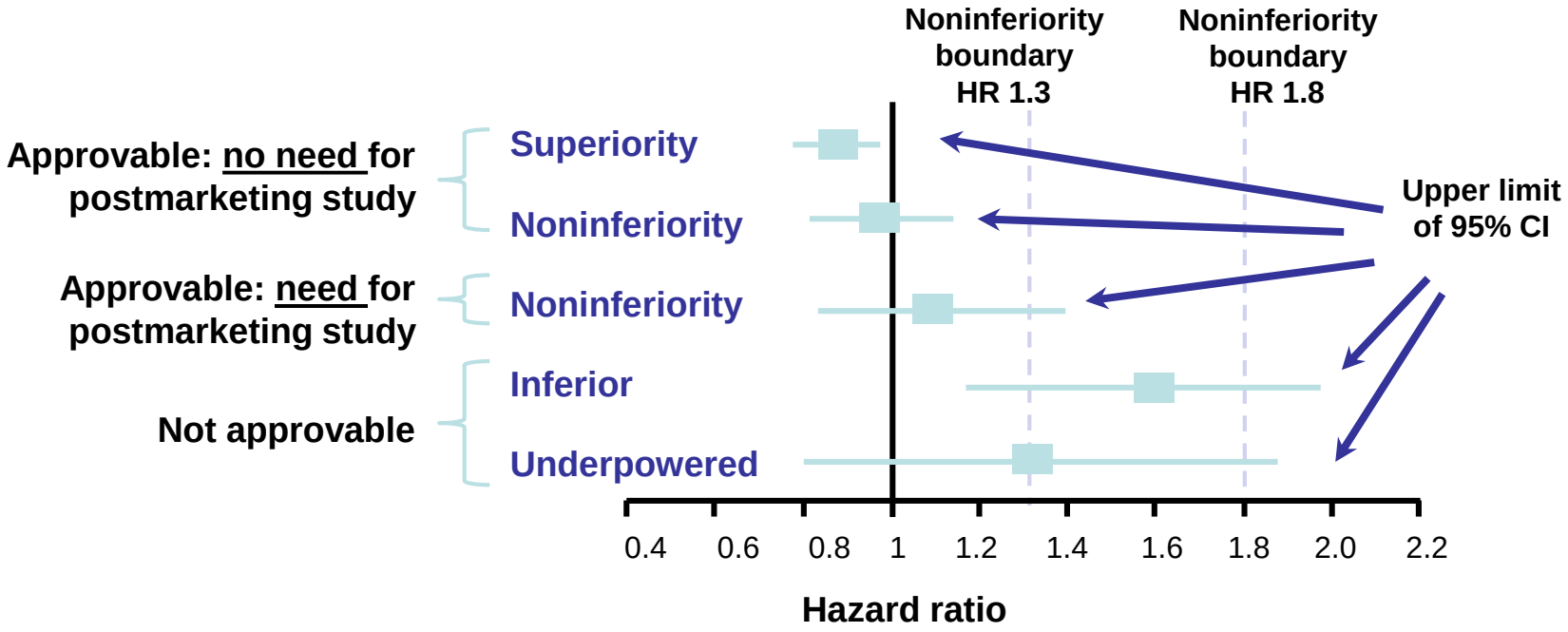
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

•FDA. Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. 2008. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

Duration of follow up

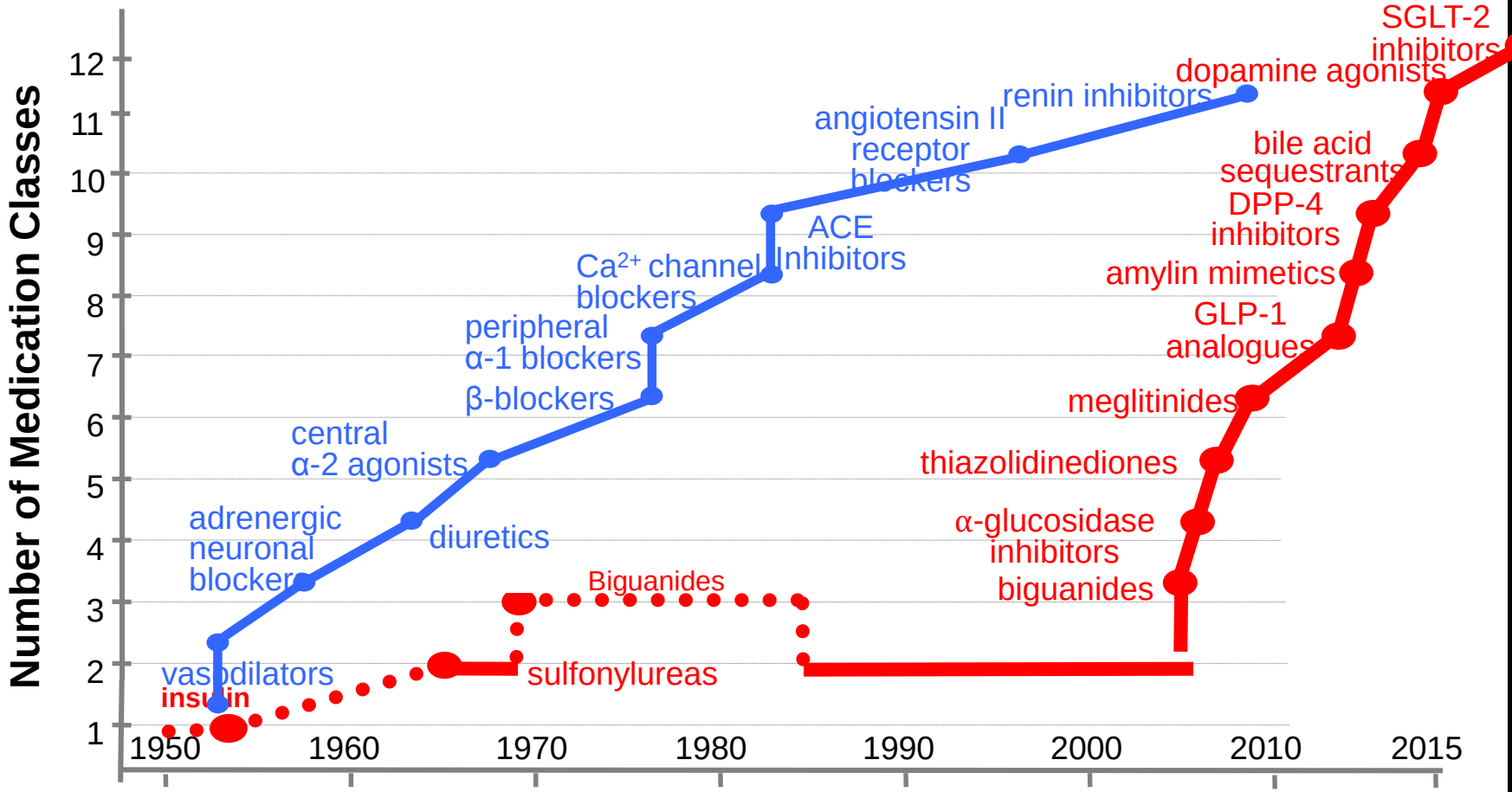


FDA Criteria – Postmarketing CV Outcomes Trial



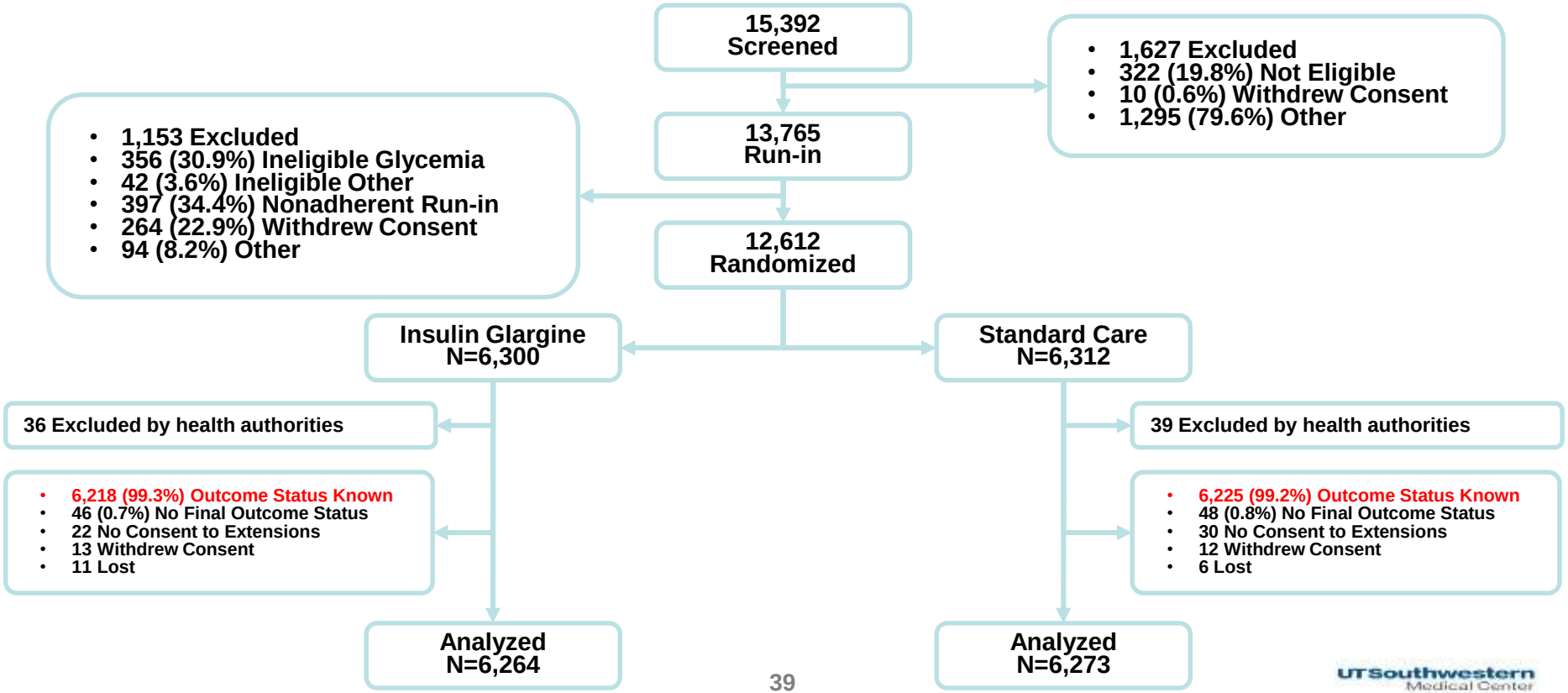
Hirshberg & Raz. *Diabetes Care* 2011;34(Suppl. 2):S101–6

Half-Century of HTN & T2DM Medications in U.S.



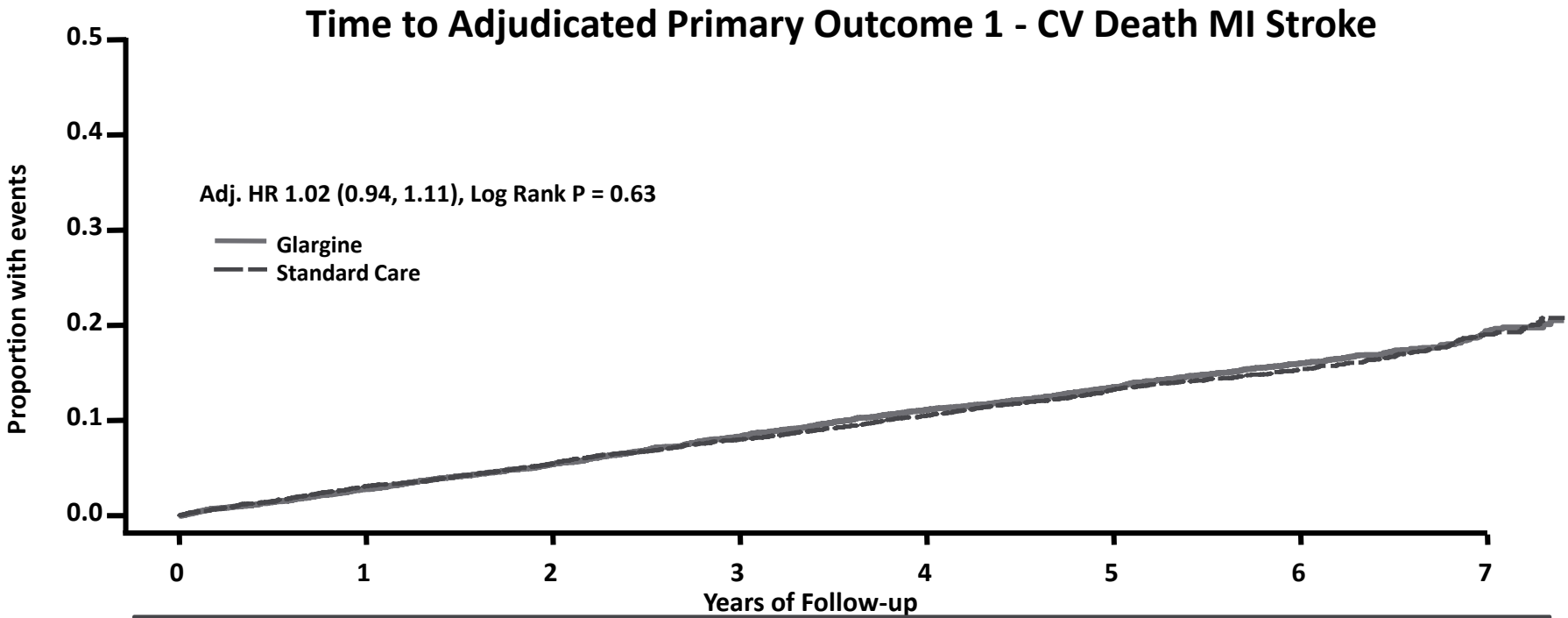
Courtesy of Silvio Inzucchi, MD, Yale University

ORIGIN: Design



Gerstein et al. *N Engl J Med* 2012;367:319-328

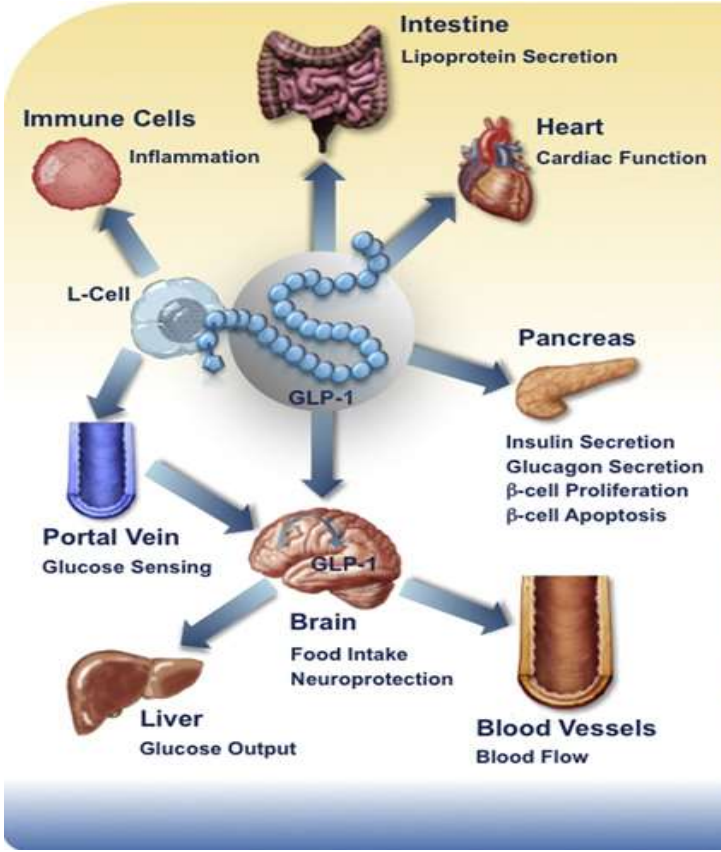
ORIGIN: 1st co-primary: MI, stroke, or CV death



# at Risk		1	2	3	4	5	6	7
G	6264	6057	5850	5619	5379	5151	3611	766
SC	6273	6043	5847	5632	5415	5156	3639	800

Gerstein et al. *N Engl J Med* 2012;367:319-328

Incretion Hormones Biology



Physiological Actions of GLP-1

Physiology	Impairment of GLP-1 action
Fasting Glucose	Increased
Glucose-Dependent Insulin Secretion	Decreased
Glucagon Secretion	Increased
β-cell Signal Transduction	Abnormal
β-cell Apoptosis	Increased
β-cell Proliferation	Decreased
Islet Size	Decreased
Food Intake	Increased
Energy Expenditure	Increased
Locomotion	Increased
Body Weight	Increased
Portal Glucose Sensing	Decreased
Postprandial Lipid Metabolism	Decreased
CNS Control of Blood Flow	Decreased
Cardiovascular Function	Decreased
CNS Stress Response	Increased
Susceptibility to Neural Injury	Increased
Immune System	Decreased
Gastric Emptying	Normal
Susceptibility to Pancreatitis	Normal

Campbell & Drucker Cell metabolism 2013

Table 1-2. Comparison of Incretin-Based Therapies

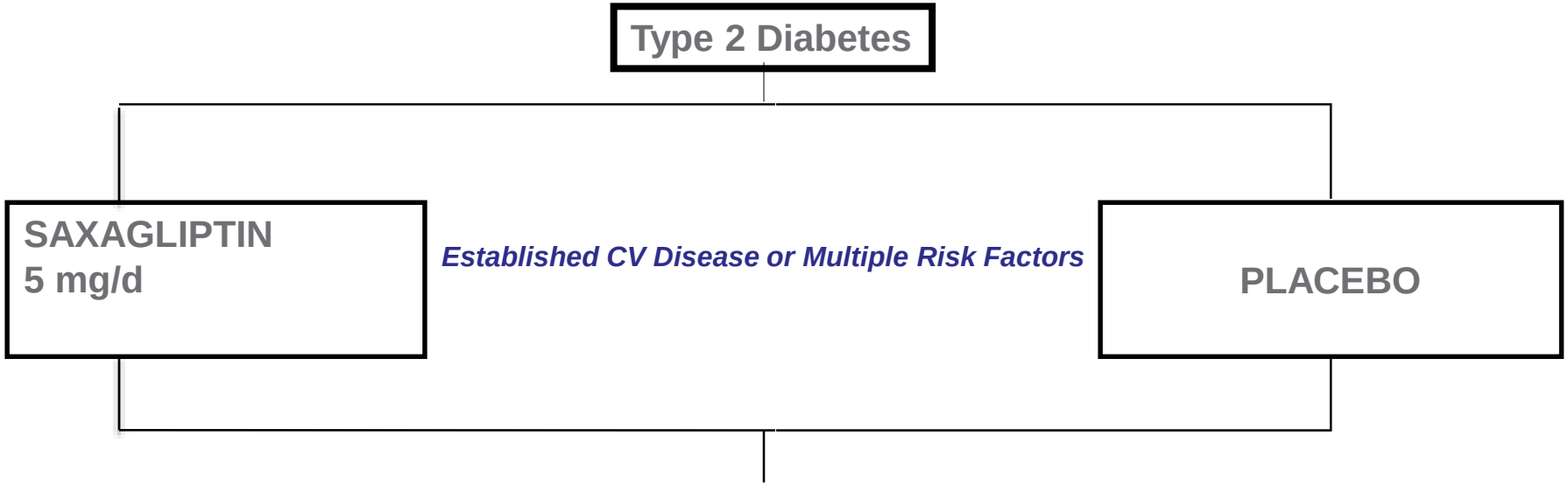
	Sitagliptin	Saxagliptin	Linagliptin	Twice-Daily Exenatide	Liraglutide	Once-Weekly Exenatide
Dosage	100 mg/day	2.5–5 mg/day	5 mg/day	5 mcg bid for 1 month; then 10 mcg bid if tolerated	0.6 mg/day; increase weekly as tolerated up to 1.8 mg/day	2 mg once weekly
Dosage adjustment with kidney impairment	CrCl ≥ 30–49: 50 mg/day CrCl < 30: 25 mg/day	CrCl ≤ 50: 2.5 mg/day	Adjustment not needed	Adjustment not needed, but use caution if CrCl is 30–50, and avoid if < 30	Adjustment not needed Use with caution in patients with kidney impairment	Same as for twice-daily formulation
Primary glycemic focus	Postprandial	Postprandial	Postprandial	Postprandial	Postprandial	Fasting and Postprandial
Adverse effect profile	Upper respiratory tract infection, urinary tract infection, headache, hypoglycemia (when taken with sulfonylurea), angioedema (rare), case reports of acute kidney failure and pancreatitis			Nausea, vomiting, constipation, diarrhea, hypoglycemia, case reports of acute kidney failure and pancreatitis		Injection site pruritus, nausea, vomiting, diarrhea
Comparative efficacy[a]						
Monotherapy vs. placebo	–0.79%	–0.63 to 0.65%	–0.69%	–0.7% to 0.9%	–1.65%	NS
Monotherapy vs. metformin	0.145%–0.51%	0.24%–0.30%	NS	NS	NS	–0.05%
Monotherapy vs. pioglitazone	0.48%	NS	NS	NS	NS	0.10%
Monotherapy vs. GLP-1 agonist	0.38%	NS	NS	NA	NA	NA
Monotherapy vs. DPP-4 inhibitor	NA	NA	NA	NS	NS	–0.38%
Monotherapy vs. sulfonylurea	NS	NS	NS	NS	–0.81%	NS
+ Metformin vs. placebo	–0.65%	–0.82%	–0.64% to 0.73%	–0.60% to 0.86%	–1.1%	NS
+ Metformin vs. sulfonylurea	0.035%–0.07%	0.06%	NS	NS	0.0%	NS
+ Metformin vs. thiazolidinedione	0.06%	NS	NS	NS	NS	–0.3%
+ Metformin vs. DPP-4 inhibitor	NA	NA	NA	NS	–0.9%	–0.6%
+ Metformin vs. GLP-1 agonist	0.9%	NS	NS	NA	NA	NA

[a]Efficacy denoted as between group difference in A1C change from baseline (positive difference suggests the comparator medication more effective).
bid = twice daily; CrCl = creatinine clearance (mL/minute); DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide 1; NA = not applicable; NS = not studied.

Recently completed CV outcome trials

Trial	Drug	Start-end	Duration	Patients	MACE Endpoint
EXAMINE	Alogliptin	2009 – 13	up to 4.75 yrs	5400	CV death, MI, Stroke
SAVOR-TIMI 53	Saxagliptin	2010 –13	4 yrs	16,500	CV death, MI, Stroke

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with DM (SAVOR) - TIMI 53



1º Endpoint:
CV Death, MI, Ischemic Stroke

Event-driven: 1040 endpoints
(or median f/u>2 years)

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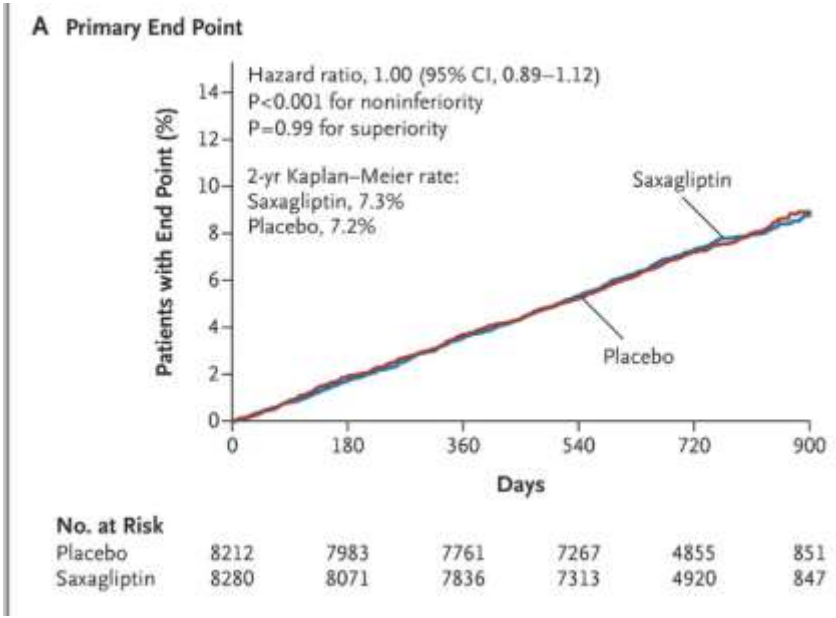
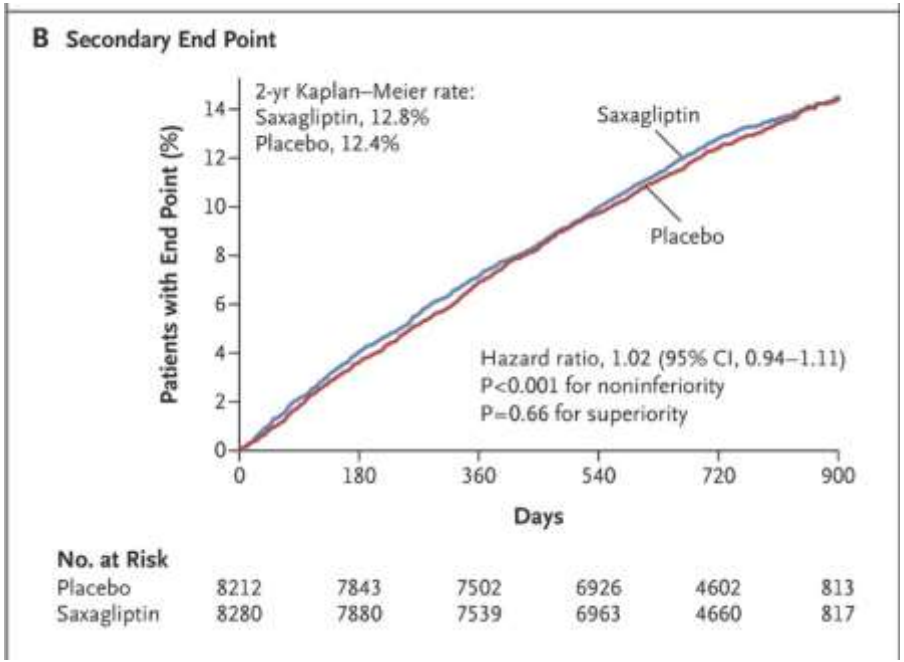
N Engl J Med 2013; 369:1317-1326

Savor TIMI 53





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N Engl J Med 2013; 369:1317-1326

SAVOR TIMI 53

Table 2. Prespecified Clinical End Points.*

End Point	Saxagliptin (N=8280)	Placebo (N=8212)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94–1.11)	0.66
Death from any cause	420 (4.9)	378 (4.2)	1.11 (0.96–1.27)	0.15
Death from cardiovascular causes	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
Myocardial infarction	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemic stroke	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
Hospitalization for unstable angina	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dl (530 μmol/liter)	194 (2.2)	178 (2.0)	1.08 (0.88–1.32)	0.46
Hospitalization for hypoglycemia	53 (0.6)	43 (0.5)	1.22 (0.82–1.83)	0.33

N Engl J Med 2013; 369:1317-1326

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

William B. White, M.D., Christopher P. Cannon, M.D., Simon R. Heller, M.D., Steven E. Nissen, M.D., Richard M. Bergenstal, M.D., George L. Bakris, M.D., Alfonso T. Perez, M.D., Penny R. Fleck, M.B.A., Cyrus R. Mehta, Ph.D., Stuart Kupfer, M.D., Craig Wilson, Ph.D., William C. Cushman, M.D., and Faiez Zannad, M.D., Ph.D., for the EXAMINE Investigators*

- **Primary objective: To demonstrate that major CV event rates are not higher with alogliptin than with placebo in type 2 diabetes patients with recent ACS who are receiving standard of care for diabetes and secondary CV prevention**
  - **Primary end point: composite of first occurrence of CV death, nonfatal MI, and nonfatal stroke**

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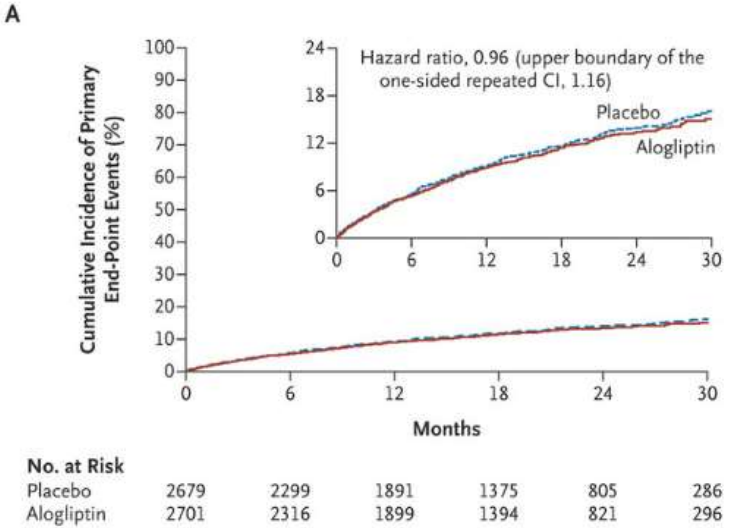
White et al. NEJM 2013

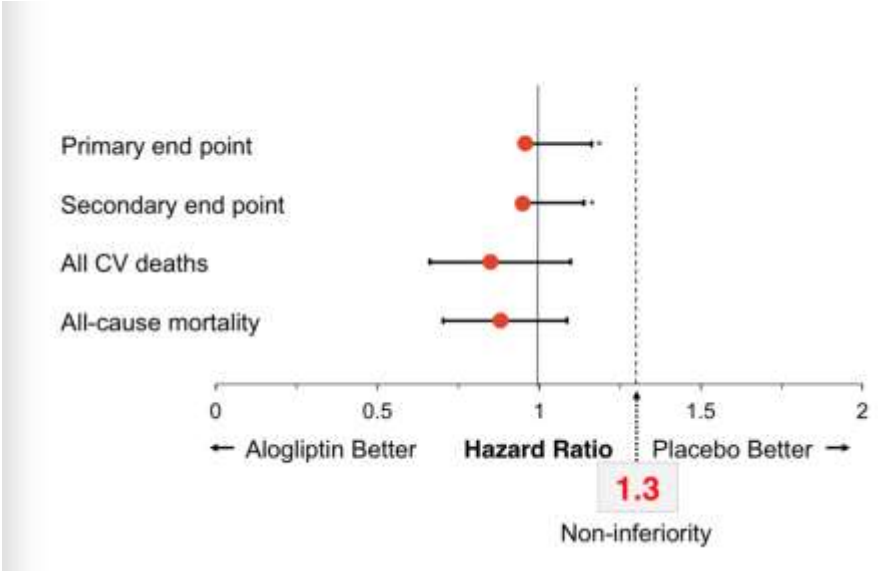
EXAMINE: Population

- **T2DM receiving antihyperglycemic therapy**
  - **DPP-4i and GLP-1 agonists excluded**
- **ACS within 15-90 days**
- **Unstable CV symptoms were excluded**

White et al. NEJM 2013

Examine: Results





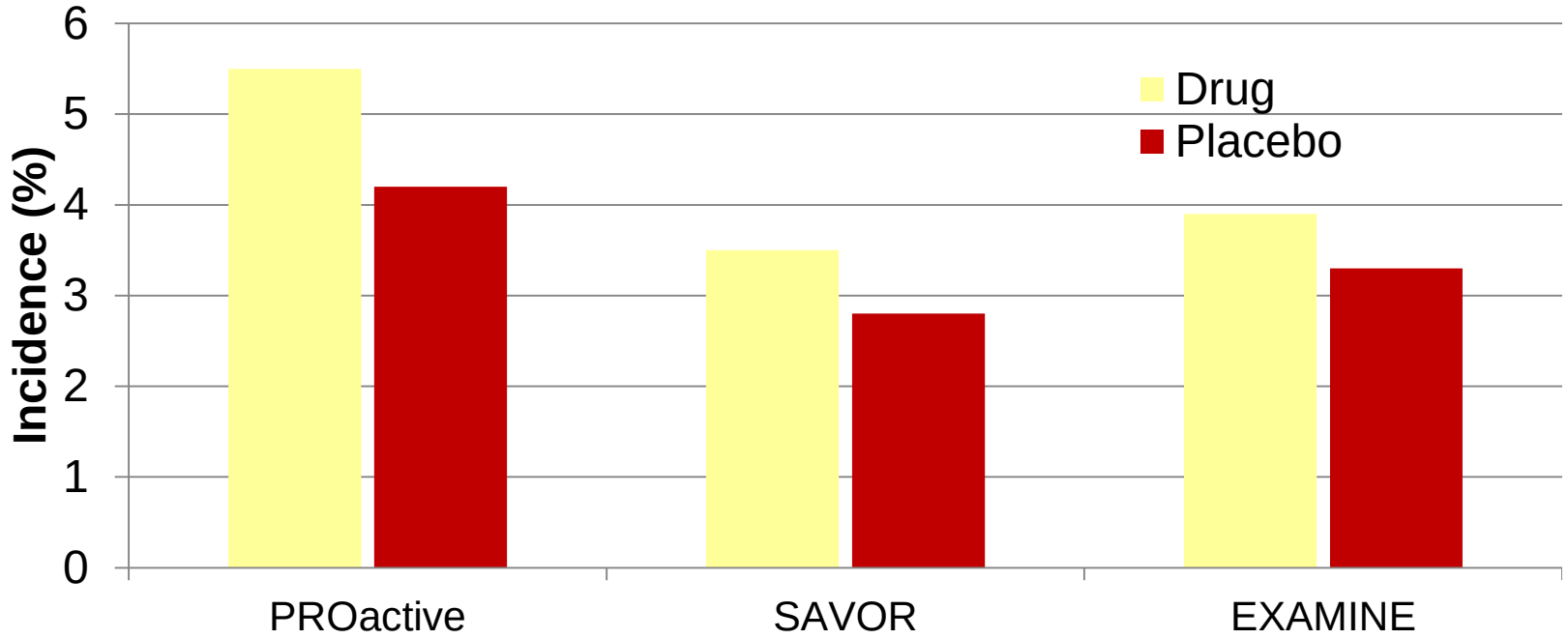
White et al. NEJM 2013

Examine: Summary

- **MACE was similar in alogliptin compared with placebo in T2DM pts with recent ACS**
- **HbA_{1c} reduced 0.36% with alogliptin**
- **11% event rate over 18 months**
- **No difference in hypo, malignancies, pancreatitis**

White et al. NEJM 2013

Hospitalized Heart Failure in PROactive, SAVOR and EXAMINE



	PROactive	SAVOR	EXAMINE
Annualized Absolute Risk Increment	0.45%	0.33%	(0.40%)

Dormandy JA, et al. *Lancet*. 2005;366:1279-1289
Scirica BM, et al. N Engl J Med 369: 1317-1326.
White WB et al. EASD Barcelona 10/2013

CV Outcomes Trials in Type 2 DM

>200,000 patients

Trial	Drug	Sample Size	Stage
ORIGIN	Insulin glargine	12,500	Completed
TOSCA IT	Pio vs. SU	3371	Started 9/2008
TECOS	Sitagliptin	14,000	Started 12/2008
ACE	Acarbose	7500	Started 2/2009
TIDE	Rosi/Pio	16,000	Halted
EXAMINE	Alogliptin	5,400	Completed
CANVAS	Canagliflozin	4500	Completed
T-emerge 8	Taspoglutide	2,000	Halted
AleCardio	Aleglitazar	7,000	Halted
SAVOR TIMI-53	Saxagliptin	16,500	Completed
ELIXA	Lixisenatide	6000	Started 6/2010
EXSCEL	Exenatide LAR	12,000	Started 6/2010
EMPA-REG Outcome	Empagliflozin	7000	Started 7/2010
CAROLINA	Linagliptin	6000	Started 10/2010
LEADER	Liraglutide	8723	Started 8/2010
GRAND 306	Tak 875	5000	Halted
AlePrevent	Aleglitazar	19,000	Halted
REWIND	Dulaglutide	9622	Started 7/2011
SUSTAIN 6	Semaglutide	3260	Started 2/2013
DECLARE TIMI 58	Dapaglifozin	17,000	Started 4/2013
CARMELINA	Linagliptin	8300	Started 7/2013
DEVOTE	Insulin Degludec	7500	Started 10/2013
MK-8835-004	Ertugliflozin	3900	Started 11/2013
CANVAS-R	Canagliflozin	5700	Started 12/2013
CREDENCE	Canagliflozin	3700	Started 2/2014

Conclusions

- CV outcomes trials are necessary to ensure new therapies do not result in unacceptable CV risk
- When designing a CV outcomes study, it is necessary to ensure:
  - Adequate event accrual to rule out unacceptable CV risk
  - Patients remain in the study to avoid incomplete data
- FDA guidance has been developed to guide the industry in the CV risk assessment of developed or in-development products
  - This has resulted in a large number of CV outcome trials being initiated in recent years
- Studies completed to date are “negative”.
  - No Harm
  - No Benefit
- Many, many more to come.