Glucose Lowering Agents In Prevention Of Cardiovascular Complications In Type 2 Diabetes

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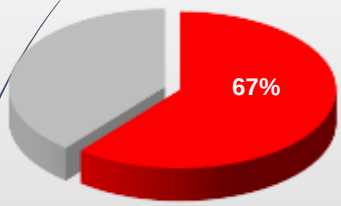
The Problem

2/3 of People With Diabetes Die of CVD

Among people with diabetes, macro-vascular complications are the leading causes of morbidity and mortality.



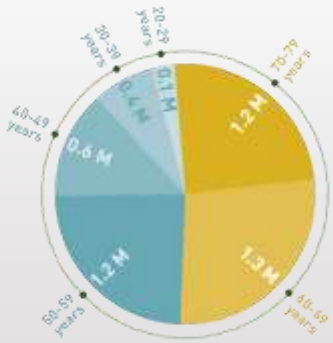
Causes of mortality in diabetics

- **CHD, stroke & peripheral vascular disease.**
- **Other.**

Alexander CM, Antonello S Pract Diabet 2002;21:21-28.

Half of people who die from diabetes are under the age of 60.

DEATHS ATTRIBUTABLE TO DIABETES BY AGE (20-79 YEARS)



The Problem

- After many decades of treating patients with type 2 diabetes with non insulin agents, our knowledge of the impact of these medications on CV events was until fairly recently limited.
- Metformin has a CV benefit. Beyond that, the data are conflicting.
- There is some concern about the CV safety of the sulfonylureas,
- Data about thiazolidinediones are conflicting
- The newer categories of antidiabetic medications, such as the incretin-based therapies and SGLT2 inhibitors, are still being studied.

Important data have recently appeared

Metformin

In 1980, Scambato *et al.* reported that, in a 3-year observational study of 310 patients with ischaemic cardiomyopathy, patients treated with metformin had reduced rates of re-infarction, occurrence of angina pectoris, acute coronary events other than acute myocardial infarction, and death.

Sgambato S, Varricchio M, Tesauro P, Passariello N, Carbone L: Use of metformin in ischemic cardiopathy.Clin Ther 1980, 94:77-85.

Metformin

- Metformin provided statistically significant reductions in the risk of all-cause mortality, diabetes-related mortality (p = 0.017), and any end-point related to diabetes (p = 0.002), but not in myocardial infarction (p = 0.052)

Prospective Diabetes Study (UKPDS) Group: Lancet 1998, 352(9131):854-865

- The UKPDS post-trial reported significant and persistent risk reductions for any diabetes-related end point (21%, p = 0.01), myocardial infarction (33%, p = 0.005), and death from any cause (27%, p = 0.002).

Holman RR, et al: 10-year follow up of intensive glucose control in type 2 diabetes.N Engl J Med 2008, 359:1577-1589.

Metformin subsequent studies showed similar effects

- *Johnson JA, Majumdar SR, Simpson SH: Decreased mortality associated with the use of metformin compared with sulfonylurea Monotherapy in type 2 diabetes. Diabetes Care 2002, 25:2244-2248.*
- *Kao J, Tobis J, Mc Clelland RL: Relation of metformin treatment to clinical events in diabetic patients undergoing percutaneous intervention. Am J Cardiol 2004, 93:1347-1350.*
- *Kooy A, de Jager J, Lehert P: Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med 2009, 169:616-625.*
- *Jadhav S, Ferrell W, Greer IA, Petrie JR, Cobbe SM, Sattar N: Effects of metformin on microvascular function and exercise tolerance in women with angina and normal coronary arteries. J Am Coll Cardiol 2006, 48:956-963.*
- *Boussageon R, Supper I, Bejan-Angoulvant T: Reappraisal of metformin efficacy in the treatment of type 2 diabetes: a meta-analysis of randomised controlled trials. PLoS Med 2012, 9(4):e1001204*

Sulphonylureas

- In the UKPDS no adverse effect of sulfonylureas on cardiovascular outcomes was noted.
- However, the lack of a beneficial effect of sulfonylureas on macrovascular outcomes, despite improved glycaemic control and a reduced risk of microvascular outcomes, could be inferred as further evidence of direct cardiovascular toxicity.
- The complicated analysis strategy in the UKPDS makes interpretations difficult

Sulphonylureas

- In contrast, another study found no increased risk of mortality among patients who were prescribed sulfonylureas and metformin in combination, compared with those prescribed either drug as monotherapy

Gulliford M, Latinovic R (2004) Mortality in type 2 diabetic subjects prescribed metformin and sulphonylurea drugs in combination: cohort study. Diabetes Metab Res Rev 20:239–245

Sulphonylureas

- In a cohort study of patients newly treated with oral hypoglycaemic agents, those treated with sulfonylureas only, or combinations of sulfonylureas and metformin, were at higher risk of adverse cardiovascular outcomes than those treated with metformin alone.

Evans et al, Diabetologia (2006) 49: 930–936

Sulphonylureas

- 2013, meta-analysis of 115 trials.
- Sulfonylureas are associated with increased mortality with MACE unaffected.
- DPP4 inhibitors are superior on Sus in CV risk reduction
- Limitations in trial quality of data.
- Long-term cardiovascular outcome trials.
- Class versus individual effect.

Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2013;15:938-953.

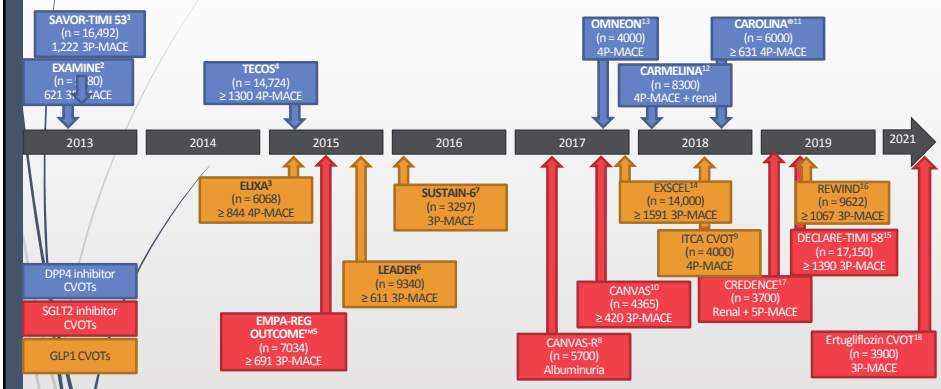
Thiazolidindiones

- Rosiglitazone
- Pioglitazone

Rosiglitazone

- May 2007 meta-analysis.
- RECORD study 2010
- Practically stopped (Risk Evaluation and Mitigation Strategy REMS) 2010.
- Results of RECORD readjudication 2013.
- However, it has not been back.

CV safety trials are being conducted for each compound within the newer classes

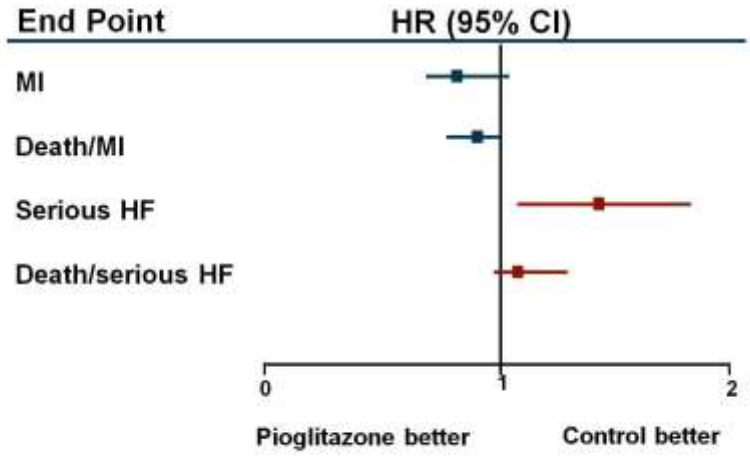


Timings represent estimated completion dates as per ClinicalTrials.gov

Adapted from Johansen. World J Diabetes 2015; in press (references 1–18 expanded in slide notes)

Pioglitazone Meta-analysis

Heart Failure & MI



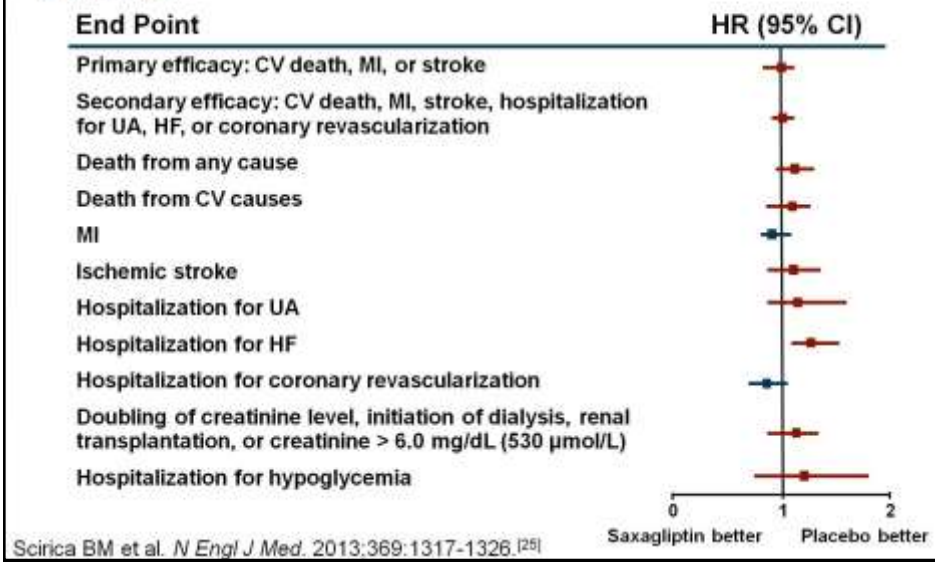
Lincoff AM, et al. *JAMA*. 2007;298:1180-1188.[7]

DPP4 inhibitors

- SAVOR
- EXAMINE
- TECOS

SAVOR-TIMI 53

Clinical End Points: Saxagliptin (DPP4 Inhibitor) vs Placebo



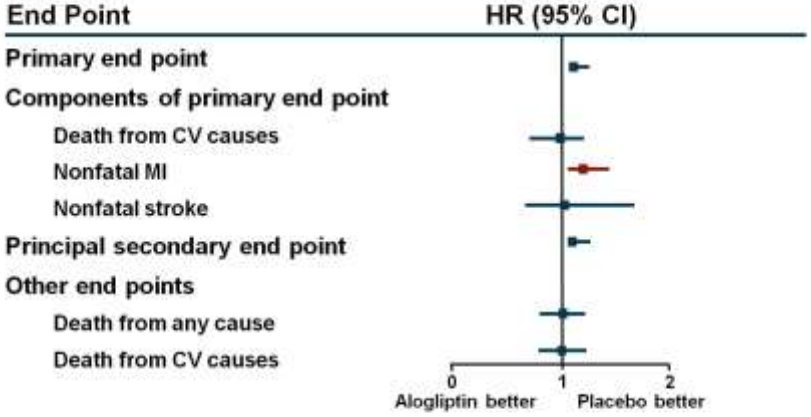
Scirica BM et al. *N Engl J Med*. 2013;369:1317-1326.[25]

SAVOR-TIMI 53
Safety Endpoints

End Point	Saxagliptin N = 8280, %	Placebo N = 8212, %	*P* Value
Bone fracture	2.9	2.9	1.00
Cancer	3.9	4.4	.15
Any pancreatitis	0.3	0.3	.77
Any liver abnormality	0.7	0.8	.28
Any hypoglycemia	15.3	13.4	< .001
Major	2.1	1.7	.047
Minor	14.2	12.5	.002

Scirica BM et al. *N Engl J Med*. 2013;369:1317-26.[25]

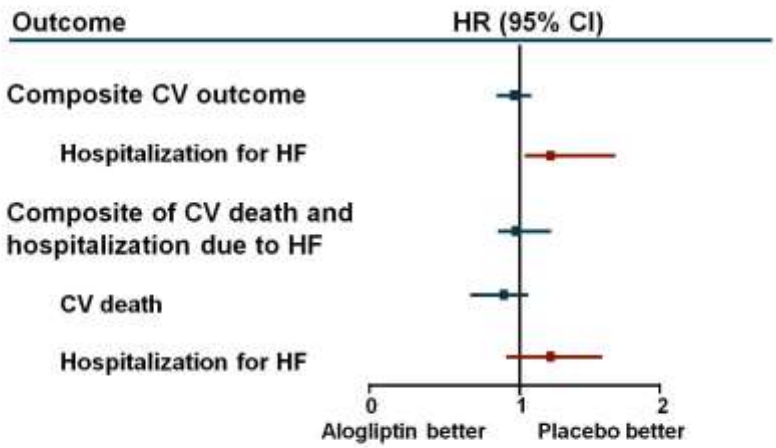
EXAMINE
Safety End Points: Alogliptin (DPP4 Inhibitor) vs Placebo



- Primary end point: death from CV causes, nonfatal MI, or nonfatal stroke
- Secondary end point: death from CV causes, nonfatal MI, nonfatal stroke, or urgent revascularization due to unstable angina within 24 hours after hospital admission

White WB, et al. *N Engl J Med*. 2013;369:1327-1335.[27]

EXAMINE
Heart Failure Outcomes



- Composite CV outcome: first occurrence of all-cause mortality, nonfatal MI and stroke, urgent revascularization due to unstable angina, and hospitalization for HF

Zannad F, et al. *J Am Coll Cardiol*. 2014;63(12_S):A117.[28]

TECOS Study

* Results of Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) were announced in April 2015. The trial achieved its primary endpoint of non-inferiority for the composite cardiovascular (CV) endpoint.

*Among secondary endpoints, there was no increase in hospitalization for heart failure in the sitagliptin group versus placebo.

*The complete results of TECOS was presented on June 8, 2015 at the 75th Scientific Sessions of the American Diabetes Association

Why No Benefit??

- Many of the studies under way are relatively too short to be able to show a CV benefit.
- Because of the slow nature of the atherosclerotic process, we may need a longer duration of exposure before we know whether any of these compounds have an intrinsic, beneficial effect on CV events.

Clinical Trial Design Considerations

- Current trial designs
  - Follow-up not long enough to show CV risk reduction
  - Focus on CV safety and not CV benefit
    - Enrollment of high-risk patients to show occurrence of events quickly to demonstrate noninferiority
- Future trial considerations to show CV benefit
  - Larger trials
  - Longer follow-up
  - Population not at high ischemic risk
    - No recent ACS
    - No previous MI
    - No previous stroke
  - Population with early atherosclerotic disease

Concluding Remarks

- Aggressive lipid management with
  - Statins
  - Newer agents: PCSK9 inhibitors and CEPT inhibitors
- Other CV risk factor management
  - Obesity
  - Hypertension
  - Inflammation
- Lifestyle modification

SGLT2 inhibitors

- Empareg for Empagliflozine Sept. 2015

EMPA-REG OUTCOME® Trial Design

- Study medication was given in addition to standard of care
  - Key inclusion criteria:
    - Adults with type 2 diabetes and established CVD
    - BMI ≤ 45 kg/m^2; HbA_{1c} 7%–10%; eGFR ≥ 30 mL/min/1.73m^2 (MDRD)
  - Prespecified analysis: Pooled empagliflozin vs placebo
  - Primary outcome: 3-point MACE (CV death, MI, stroke)

BMI, body mass index; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

Zinman B, et al. *N Engl J Med*. 2015 [Epub ahead of print].

Primary Outcome

- CV outcomes: Empagliflozin is the first glucose-lowering drug to show reduction in risk for CV death

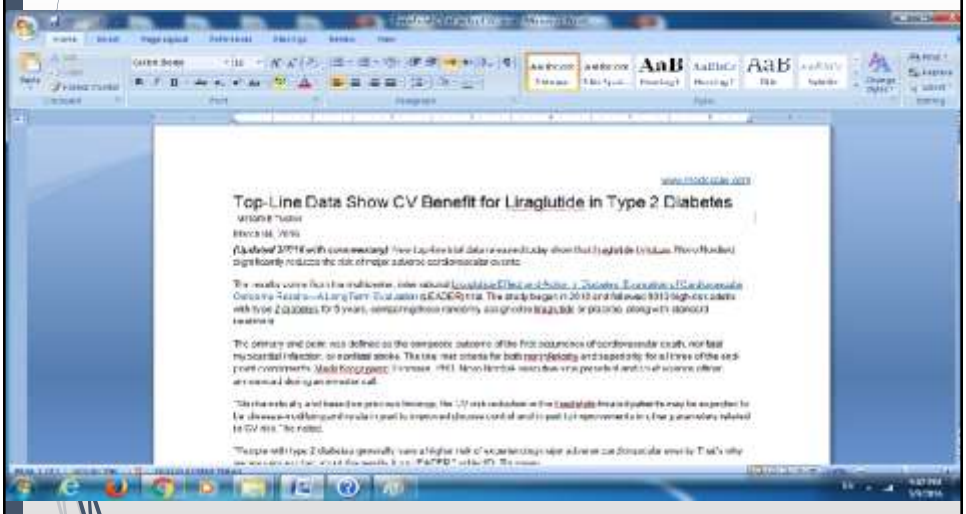
Primary Outcome		HR	(95% CI)	*P* Value
3-point MACE	(14% RRR)	0.86	(0.74-0.99)	.0382
CV death	(38% RRR)	0.62	(0.49-0.77)	< .0001
Nonfatal MI		0.87	(0.70-1.09)	.2189
Nonfatal stroke		1.24	(0.92-1.67)	.1638

Zinman B et al. *N Engl J Med*. 2015 [Epub ahead of print].

EMPA-REG OUTCOME Trial
Implications for Clinical Practice

- Unknown if this is a class effect; studies on additional SGLT-2 inhibitors are in progress
- Possible mechanism behind CV benefit: osmotic diuresis?
  - HF hospitalization: HR 0.65 (0.50-0.85) *P* = .0017 (35% RRR)
  - All-cause death: HR 0.68 (0.57-0.82) *P* < .0001 (32% RRR)
- Implications for practice: consider empagliflozin in patients with overt cardiovascular disease
- Few adverse events, mainly genitourinary infections
- Limitations: duration, no baseline data on ventricular function

LEADER March 7th 2016



Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results - A Long Term Evaluation (LEADER®)

- The study began in 2010 and followed 9340 high-risk adults with type 2 diabetes for 5 years, comparing those randomly assigned to liraglutide or placebo, along with standard treatment.
- The primary end point was defined as the composite outcome of the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

LEADER

- The trial met criteria for both noninferiority and superiority for all three of the end-point components.
- The full data set from LEADER was presented in June at the American Diabetes Association's Annual Scientific Sessions.
- Liraglutide is now the first of the glucagonlike peptide-1 (GLP-1) class to show cardiovascular benefit . Another GLP-1 agonist, lixisenatide did not show CV benefit in the ELIXA trial reported at the ADA meeting last year.

SUSTAIN for Simaglutide

Some Light At The End Of The Tunnel


THANK YOU