Cardiovascular Outcome Trials of Anti-diabetic Drugs

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Agenda

❖ Concepts of Cardiovascular Outcome Trials (CVOTs).
❖ Landmark trials for each anti-diabetic drug.
❖ Conclusion.
Before 2008 cardiovascular adverse effects of antidiabetic drugs were made out from the events that occur during the course of the trial.

These cardiovascular events were not pre-specified.

Since the subjects included in these trials were younger, of low CV risk, shorter duration of both disease and the trial, the number of CV events occurred during the trial were low.

The low event rates lead to poor estimates of CV safety of these agents.
In 2007, a meta-analysis that caused some controversy was published. The analysis included 42 rosiglitazone trials involving 27843 patients and reported an increased risk of MI (RR: 1.43, 95% CI: 1.03–1.98, P =0.03) with the use of rosiglitazone.


That made FDA to issue a guidance in 2008 recommended that a new anti-diabetic drug should not increase cardiovascular risk to an unacceptable extent.

Requirements

1. An upper bound of the 95% CI for the hazard ratio of important CV events should be less than 1.3.
2. Study patients must include individuals with advanced disease, elderly patients, and patients with degree of renal impairment.
3. A minimum of 2 years’ CV safety data must be provided.
4. All studies should include a prospective independent CV events. Events should include CV mortality, MI, and stroke and can include hospitalization for ACS, urgent revascularization procedures, and possibly other end points.
5. The analysis of CV events may include a meta-analysis of all placebo controlled trials, add-on trials (i.e., drug vs. placebo, each added to standard therapy)
Landmark Trials for each Anti-diabetic Drug

1. 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).


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).


Metformin subsequent studies showed similar effects

2. Sulfonylureas
Sulfonylureas; The CV Safety of is not established

Conflicting results

SU studies

Most SU studies have not been designed to examine CV safety, and differences in data reporting makes comparisons difficult.

Meta-analysis of 115 SU studies

Treatment with SUs was associated with increased mortality and a higher risk of stroke, but no effect on the overall incidence of MACE was observed.

Long-term SU studies

Analysis of 15 RCTs of SU versus an active comparator for ≥72 weeks duration there was a non-significant reduction in the composite CV endpoint UKPDS showed a reduction in microvascular risk in SU-insulin users.

One on-going study (CAROLINA) is powered to demonstrate differences in CV events between a sulfonylurea (glimepiride) and a DPP-4 inhibitor (linagliptin).

3. Thiazolidindiones (Glitazones)
Rosiglitazone

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolz, M.P.H.

CONCLUSIONS
Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance.

Record trial

- **Finding:** Heart failure hospitalization or CV death occurred in 61 people in the rosiglitazone group and 29 in the control group (HR 2·10, 1·35–3·27)

- **Interpretation:** Addition of rosiglitazone to glucose-lowering therapy in people with type 2 diabetes is confirmed to increase the risk of heart failure.
Pioglitazone

Meta-analysis 2007


Meta-analysis 2017

Pioglitazone was associated with reduced risk of MACE in people with DM. However, the risks of heart failure, bone fracture, oedema and weight gain were increased.

4. DPP4 inhibitors

- Saxagliptin
- Alogliptin
- Sitagliptin
**Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with DM - TIMI 53**

**Documented Type 2 Diabetes**

- N = 16,492
  - Established CV Disease or Multiple Risk Factors

**RANDOMIZED 1:1 DOUBLE BLIND**

**SAXAGLIPTIN 5 mg/d**

- All other DM Rx per treating MD
  - 2.5 mg/d if eGFR ≤ 50 ml/min

**PLACEBO**

**Duration**

- Event driven (n=1040)
  - Median duration 2.1y
  - LTFU 0.2%
  - W/C 2.4%

**Follow up Visits**

- Q6 months

**Primary EP**

- CV Death, MI, Ischemic Stroke

**Major Secondary EP**

- CV death, MI, ischemic stroke, or hosp. for heart failure, unstable angina, or coronary revascularization


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**Primary Endpoint**

**HR 1.00**

- 95% CI 0.89-1.12
  - p<0.001 (non-inferiority)
  - p=0.99 (superiority)

2y KM

- Saxagliptin 7.3%
- Placebo 7.2%

Secondary Endpoint

HR 1.02
95% CI 0.94-1.11
p<0.001 (non-inferiority)
p=0.66 (superiority)

Baseline NT-pro BNP and Hospitalization for Heart Failure

Preliminary data (N=12,397 patients; 387 HF events)

HR 1.27 95% CI (1.04-1.55) p=0.02
(overall HR for Saxagliptin versus Placebo in those with baseline NT-proBNP data)
Conclusions

- When added to standard of care in patients with T2DM at high CV risk, saxagliptin neither reduced nor increased the risk of the primary composite endpoint of CV death, MI, or ischemic stroke.


Conclusions (Heart Failure)

- The higher incidence of hospitalization for heart failure was unexpected, but it was a pre-defined, adjudicated endpoint.
- It merits further evaluation given the history of other diabetic agents and heart failure.
They assigned 5380 patients with type 2 diabetes and either an acute myocardial infarction or unstable angina requiring hospitalization within the previous 15 to 90 days to receive alogliptin or placebo.

Primary and secondary end points were nearly the same as SAVOR TIMI trial.
❖ Conclusion of EXAMINE:
❖ The rates of major adverse cardiovascular events were not increased with the DPP-4 inhibitor Alogliptin as compared with placebo.
❖ There was slight increase in HF hospitalization events compared to placebo (but not statistically significant).
Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes


14,735 Patients underwent randomization

- 64 Were excluded from all analyses
  - 11 Did not provide consent
  - 53 Had GCP deviations (at 1 site)

14,671 Were included in the intention-to-treat population

7332 Were assigned to receive sitagliptin
- 66 Did not receive sitagliptin

7339 Were assigned to receive placebo
- 65 Did not receive placebo
Conclusion of TECOS

Sitagliptin did not appear to increase the risk of MACE, hospitalization for heart failure, or other adverse events.

This provides reassurance that even if the increased HF signal seen with Saxagliptin in SAVOR trial is true, it is not a ‘class effect’ associated with all DPP4 drugs – especially TECOS had a larger sample size and longer follow up.
ALL DPP4 INHIBITORS SEEMED TO BE SAFE BUT WHY NOT CARDIOVASCULAR PROTECTIVE???

- Many of these studies 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.

5. GLP1 Receptor Agonist
Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular outcome Results
LEADER®

- S.P. Hanlo, G.H. Daniels, K.B. Frandsen,
- The LEADER Steering Committee on behalf of the LEADER Trial Investigators

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes
Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

June 13, 2016, at NEJM.org. DOI: 10.1056/NEJMoa1603827
LEADER: Study design

9340 patients
- Double blinded
- 2-week placebo run-in
- Placebo run-in
- Liraglutide 0.6–1.8 mg OD + standard of care
- Safety follow-up
- Placebo + standard of care
- Randomisation (1:1)
- Duration 3.5–5 years
- End of treatment
- 30 days
- 2 weeks

Key inclusion criteria
- T2DM, HbA1c ≥7.0%
- Antidiabetic drug naive; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure
- Age ≥60 years and risk factors for CV disease

Key exclusion criteria
- T1DM
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

CV, cardiovascular; HbA1c, glycosylated haemoglobin; OAD, oral antidiabetic drug; OD, once daily; T2DM, type 2 diabetes mellitus.


Primary and key secondary outcomes

**Primary outcome**

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<thead>
<tr>
<th>Time to first MACE composed of</th>
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<tbody>
<tr>
<td>• CV death</td>
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<tr>
<td>• Non-fatal MI</td>
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<td>• Non-fatal stroke</td>
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**Key secondary outcomes**

<table>
<thead>
<tr>
<th>Time to first occurrence of</th>
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<tr>
<td>• Expanded composite CV outcome</td>
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<tr>
<td>• All-cause death</td>
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<tr>
<td>• Each individual component of expanded composite CV outcome</td>
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CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.

❖ The trial met criteria for both noninferiority and superiority for all three of the end-point components.
❖ Liraglutide not only safe but also shows CVS protection.
❖ Mechanism is not clearly understood....

6. SGLT2 INHIBITORS
**EMPA-REG OUTCOME® Trial design**

- Study medication was given in addition to standard of care.
- Key inclusion criteria:
  - Adults with type 2 diabetes and CV disease (heart attack, stroke, etc.)
  - HbA1c 7–10%; eGFR ≥30 mL/min/1.73m2 (MDRD)
- 1ª outcome = ‘3-point MACE’ (CV death, non-fatal MI, non-fatal stroke)
EMPA-REG OUTCOME: CV death

EMPA-REG OUTCOME: HF Hospitalizations
EMPA-REG OUTCOME: All cause death

- Robust CVS benefit, especially mortality and HF
- CVS benefits occurred within first few weeks (early divergence of the curves).
- Exact mechanisms not fully understood and could not be explained by glycemic control only.
- Possible mechanisms: BP control, decrease arterial stiffness and weight reduction....
- Seems to be class effect after supporting evidence of Canagliflozin in CANVAS trial in 2017
In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, empagliflozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms

Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.
Conclusion

❖ Clinical research in the field of type-2 diabetes is facing many challenging issues.

❖ Several areas of uncertainty remain. These include time of follow-up for future trials; contribution of adverse effects such as hypoglycaemia or weight gain to observed clinical outcomes.
❖ It is entirely reasonable to take a "first, do no harm." approach in approving new therapies. Patients take these drugs lifelong!!!
❖ Modern CVOTs are designed to demonstrate safety!!!