Review

Outline of Cardiovascular effects of antidiabetic agents from clinical trials and comparative study data

Ruvan A I Ekanayaka[1],
1 Norris Clinic/ Nawaloka Hospitals PLC
Corresponding author: Ruvan A. I. Ekanayaka
Email: ruvan_nishali.ekanayaka@yahoo.com

One of the major objectives of treating diabetes mellitus would be to prevent life threatening or disabling coronary, cerebral or peripheral vascular disease. Unfortunately the currently available antidiabetic drugs, in the large measure, have sparse evidence of benefit in this regard. The data is poor and conflicting so that clinicians tend to rely on a satisfactory HbA1c as a surrogate for clinical benefit. The new trials do not justify this basis of treatment. Until the publication of the meta-analysis of rosiglitazone trials by Nissen *et al* in 2007 it was generally held that tight control of glycaemia could directly lead to a beneficial effect on cardiovascular outcomes. However the rosiglitazone trials proved this to be an incorrect supposition. Consequent to this finding the FDA mandated cardiovascular safety to be demonstrated for at least two years with regard to new antidiabetic drugs. A brief compendium of trial and comparative study data regarding the cardiac outcomes with various antidiabetic drugs will be presented in this review.

Studies regarding atherosclerotic coronary disease

Margolis *et al* published a study on the prevalence of arteriosclerotic coronary disease in all diabetics (N-63579) who were on various antidiabetic therapies[1].

Drug	Fully adjusted hazard rates for known diabetics	Hazard ratios for de-novo diabetics
Insulin	1.2 (1.1,1.3)	2.4 (2.0,2.9)
Sulfonylureas	1.03 (.97,1.09)	1.4 (1.2,1.7)
Biguanides	0.8 (.7, .8)	0.5 (0.4,0.5)
Meglitinides	1.2 (.99,1.5)	0.9 (0.4,2.1)
Rosiglitazone	0.6 (0.5,0.6)	0.8 (0.6,1.0)
Pioglitazone	0.5 (0.4,0.7)	0.9 (0.6, 1.0)

The authors conclude that, overall, insulin was associated with increased risk of myocardial infarction. It's risk also increased with longer use. Risk emerged with long term use of sulfonylureas and biguanides, as well.

Conversely, a protective effect emerged with longer use of rosiglitazone or pioglitazone.This is a contradictory finding to that of Nissen's meta analysis for which several explanations have been offered; One being that the benefits were seen with > 6 months therapy. The study demonstrated that antidiabetic agents influence the atherogenic process as well but it gives no indication of the mechanism responsible for the varying influence.

Metformin

The United Kingdom Prospective Diabetes Study (UKPDS) found that early initiation of metformin resulted in a 32% reduction in microvascular and macrovascular complications in type II obese diabetics. The risk reduction with metformin appear to be significantly better than with sulphonyl ureas or insulin. Metformin seemed to perform better than insulin or sulphonylureas as a 39% risk reduction in acute myocardial infarction and 50% risk reduction in coronary deaths was seen with it's use.

Sulphonylureas

The University Group Diabetes Program (UGDP) suggested that tolbutamide increases cardiac deaths. However the UKDPS did not confirm this adverse finding. The evidence available favors second generation sulphonylureas over tolbutamide. Some data suggests that amongst the sulphonylureas, gliclazide has benefit in preventing cardiodiabetic complications.

The ADVANCE study used gliclazide which did not result in adverse cardiac effects but had no definite cardiac benefits either.

The DIGAMI trial in acute myocardial infarction found sulphonylureas to be inferior compared to glucose insulin infusions.

Insulin secretagogues/ metformin

Tina Ken Schramm at al published an important study done in Denmark in 2011, wherein the cardiovascular risk associated with insulin

secretagogues or metformin was comparatively studied[2].

The data was analyzed for the 107806 subjects included in the study of which 9607 had a previous MI.

Most insulin secretagogues appeared to be associated with increased mortality and cardiovascular risk compared to metformin. The least risk was associated with gliclazide and repaglinide. Based on this study, no generalized distinction could be made between first or second generation sulphonylureas.

However lipid studies for all study subjects were not accessible to the investigators and hence we cannot correlate the cardiovascular outcomes to any lipid parameter.

Insulin secretagogues

Schramm et al studied the cardiovascular outcomes associated with insulin secretagogues. All sulphonylureas were associated with increased cardiac risk compared to metformin[2].

PPAR- γ agonists (thiazolidinediones)

Concerns have been raised regarding the adverse cardiac effects of peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists. Gerrtis et al made a study of 29911 patients utilizing data from a health care insurer. The patients selected were on either pioglitazone or rosiglitazone[3].

The unadjusted hazard ratio (HR) for acute myocardial infarction was .82 (CI:67-1:01). The adjusted HR for baseline covariates was .78 (CI:63-.98).

The authors concluded that this study showed a 22% relative risk reduction of hospitalization for AMI in patient with T2DM who were treated with pioglitazone compared to rosiglitazone.

Rosiglitazone was associated with a 34%-41% higher risk for all-cause mortality, compared to pioglitazone. Pioglitazone had a significant 31%-39% lower risk for all-cause mortality compared to metformin.

Thus even within a given class of antidiabetic agents individual molecules may lead to diverse outcomes.

The 2010 science advisory form AHA and ACCF regarding the cardiovascular risk of thiazolidinediones concluded that an association between rosiglitazone and ischemic cardiac outcomes is not firmly established [4]. With regard to pioglitazone, the same science advisory says that the majority of published studies do not suggest an increased risk for IHD.

There is no consensus as to when thiazolidinediones should be used in diabetic therapy.

DPP-4 inhibitors (Gliptins)

Three large double blind studies are now published regarding the cardiovascular effects of gliptins.

SAVOR- TIMI 53

(Saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus).

This was a double blind study in patients with either established coronary disease or multiple risk factors, comparing saxagliptin to standard therapy. Although the reduction of the HbA1c was significantly better in the saxagliptin arm the composite endpoint of cardiovascular mortality, non-fatal myocardial infarction or ischaemic stroke was the same in both treatment groups. Cardiovascular mortality was more when the baseline HbA1c was higher. This fact however had no bearing on saxagliptin outcomes.

In SAVOR- TIMI 53, saxagliptin resulted in a greater incidence of hospitalization for heart failure. Elevated levels of serum creatinine or BNP and preexisting heart failure were the associated risk factors for adverse outcomes in this trial.

EXAMINE

(Examination of cardiovascular outcomes with alogliptin versus standard care).

This study recruited patients with an acute coronary event. Alogliptin was compared with standard therapy. At 18 months the major cardiac and cerebral ischemic events were comparable, although the alogliptin arm had lower HbA1c levels. There was no significant increase in heart failure.

TECOS

(Trial evaluating cardiovascular outcomes and sitagliptin).

The study population consisted of patients with vascular disease entities ie. Coronary, cerebral and peripheral vascular disease.
At 3 years sitagliptin was non inferior to placebo with regard to major cardiovascular outcomes although sitagliptin reduced the HbA1c greater than standard care. Hospitalization for heart failure was not increased.

A meta-analysis of eight phase III trials regarding the cardiovascular safety of linagliptin was conducted by Erik Johansen et al[5]. The primary end points were a composite of cardiovascular death, CVA, myocardial infarction and unstable angina. The primary endpoint occurred in 11 (0.3%) patients on linagliptin and in 23 (1.2%) of those on comparator treatment. The hazard rate for the primary endpoints showed a significantly lower risk for linagliptin (HR 0.34, CI 1.6-0.70). Thus the results raise the possibility that linagliptin may have some cardiovascular benefits in patients with T2DM.

Glucogon like peptide 1 analogues

Two drugs in this class have been studied in well conducted clinical trials for cardiovascular outcomes.

LEADER

(Liraglutide and cardiovascular outcomes in typeII diabetics)

This was a double blind study comparing liraglutide with placebo in a cohort of patients with high cardiovascular risk. In a time to event analysis the liraglutide treated group had a significant reduction in the primary end point composite of first occurrence of death from cardiovascular causes, non-fatal MI and non-fatal stroke. The NNT to prevent one event in three years was 66 for the primary outcome and 98 for death from any cause.

SUSTAIN- 6

This was very similar to the LEADER trial studying the drug semaglutide. The results were encouraging regarding cardiovascular outcomes and basically followed the LEADER results.

Note: Not all glutides have shown cardiovascular benefit.

Sodium glucose cotransporter inhibitor (Gliflozins)

Two important double blind trials regarding glifozins have been published.

EMPA-REG OUTCOME

(Empagliflozin cardiovascular event trial).

This is one of the two trials using a SGLT- 2 inhibitor which has been completed. All patients had established coronary disease.

Patients were randomized to receive empagliflozin or placebo. At 3.1 years of follow up the relative risk of major cardiac and cerebral outcomes was significantly reduced by over 30% with the test drug.

The major benefit was from the reduction of deaths from cardiovascular causes but not by non-fatal myocardial infarctions. With regard to strokes however empagliflozin seem to raise an adverse signal. There was a significant reduction in the hospitalization for heart failure.

The SGLT-2 inhibitors available are empaglifloxin, canagliflozin and dapagliflozin. These drugs have a diversity of actions which include diuresis, reducing blood pressure and mitigating albuminuria. It is currently unclear as to which action is responsible for reduction in cardiovascular outcomes with SGLT-2 inhibitors.

CANVAS

(Canaglifozin and cardiovascular renal events in type 2 diabetes).

The patients included were at a high risk for cardiovascular disease. The study recruits were randomized to canagliflozin or placebo arm. Follow up was for a mean of 188.2 weeks. The major coronary and cerebral arterial events were significantly reduced by canagliflozin.

The CANVAS trial also produced evidence for renal protection with canagliflozin. However there was an increased risk of distal amputation of the toe or metatarsal.

Lavalle gonzalez et al published a study in 2013 evaluating the efficacy and safety of canagliflozin vs placebo and sitagliptin, in T2DM patients on background metformin. One of the pre specified secondary endpoints of this study was HDL-C[6].

Canagliflozin (both 100mg and 300mg dosages) significantly increased HDL-C at 26 weeks. However LDL levels too increased. This was seen also with empagliflozin. No significant change occurred in the triglycerides. In the sitagliptin arm, all three lipid particles – TG,HDL,LDL, nonHDL-C were elevated.

Thus the lipid effects of anti-diabetic agents are not always beneficial.

Insulin

Insulin can have diverse effects on cardiovascular disease causation and progression[7,8].

T2Dm patients have 3 main glycemic conditions :-

(i) chronic hyperglycemia
(ii) glycaemic variability and
(iii) iatrogenic hypoglycemia.

They also have elevated levels of chronic inflammation and oxidative stress in addition to lipid disorders and endothelial dysfunction.

Insulin has beneficial effects, which are anti-inflammatory, anti-thrombotic and anti-oxidative.

However, large insulin doses seem to be associated with increased cardiovascular risk. It is probably correct to say that small doses of insulin early in the disease is better than large doses later in the disease. However there is no good evidence that small insulin doses prevent the necessity for larger doses later on.

Sulphonylureas / thiazolidinediones

Tzoulaki et al performed a retrospective cohort study of T2DM patients attending an UK general practice in order to assess the cardiovascular risk and all-cause mortality with respect to oral antidiabetic therapies[9].

91521 Patients were enrolled. The endpoint studies were myocardial infarction, congestive cardiac failure (CCF) and all-cause mortality.

Sulphonylureas

Monotherapy with first and second generation Sulphonylureas was associated with a 24%-61% excess risk for all-cause mortality, compared to metformin.

The second generation Sulphonylureas were associated with 18%-30% excess risk for CCF.

Rosiglitazone/metformin / sulphonylureas

Mc Afree et al published a study of propensity matched cohorts regarding the coronary heart disease outcomes in patients receiving various anti diabetics agents, namely rosiglitazone, metformin or sulphonylurea[10].

26931 patients were on monotherapy: 4080 on dual therapy and 2346 had addition of insulin.

The results suggested that the cardiovascular outcomes of rosiglitazone may lie in between the CV risk for sulphonylureas (ie. higher incidence) and metformin (ie. lower incidence)

Thiazolidinediones/metformin/ sulphonylureas

A retrospective study of myocardial infarction (MI) and coronary revascularization (CR) in diabetes treated with thiazolidinediones, metformin or sulphonylurea was published in 2007[11].

The investigators found that in the absence of insulin, metformin had the lowest rates of MI+CR, whereas sulphonylureas had the highest with thiazolidinediones having an incidence of MI+CR in-between metformin and sulphonylureas. There seemed to be no difference between rosiglitazone and pioglitazone regarding risk of MI and CR.

Saroglitazar

This is a dual PPAR -α /γ agonist. It's main advantage is the significant improvement in the diabetic dyslipidemia - ie. triglycerides, VLDL, apo lipoprotein B and non HDL-C are all reduced, whereas HDL-C levels are elevated.

At present data is not available regarding macrovascular protection afforded by saroglitazar.

Hypoglycemia

Although hyperglycemia is well established as a causative factor of atherosclerosis, the role played by hypoglycemia is less clear. The lack of benefit from strict glycemic control regimens which invariably lead to increased incidence of hypoglycemic episodes support the view that even asymptomatic hypoglycemia has atherogenic potential.

Insulin treated T1DM and T2DM patients appear to have increased risk of cardiovascular disease related to the occurrence of hypoglycemia.

In 2017, Mita et al demonstrated that frequent episodes of hypoglycemia are associated with the carotid atherosclerotic process in T1DM patients.[12]

Studies regarding heart failure

Skrtic et al reported in 2016 that in a cohort of 94332 patients with T2DM, hyperglycemia could be a risk factor for heart failure (HF). The authors calculate that for 1% increase in HbAIC, the risk of HF rose by 6-15%.[13]

In the editorial review of this paper, risk factors other than hyperglycemia are highlighted as possible contributors for HF, namely insulin resistance, hyperinsulinemia, endothelial dysfunction, dyslipidemia, pro-inflammation, hypercoagulability and vascular calcification.

Eurich at al made a systematic review of the literature (upto 2017) in order to detect the benefits and harms of various antidiabetic agents with reference to heart failure and mortality[14].

Eight studies were included in the review.

Insulin – Three of the 4 studies found that all-cause mortality increased with usage of insulin.

Metformin – Two studies found a significantly reduced mortality. A third study showed a similar trend. There was no worsening of HF.

Thiazolidinediones – Four studies found a reduction in all-cause mortality. However worsening heart failure was seen. (The RECORD study which is a randomized controlled trial confirms this finding).

Sulfonylureas – The results were conflicting in the two studies included.

The authors conclude that metformin was the sole antidiabetic therapeutic agent not associated with harm in heart failure patients.

DPP- 4 inhibitors – Certain trials have raised safety issues regarding DPP-4 inhibitors with reference to heart failure[15].

The prevalence of heart failure in T2DM is estimated to be 20-30%, whereas it is 4-6% in non diabetics. An analysis of a large cohort of 196986 patients with T2DM and heart failure, using Taiwan's National health insurance research database, studied the effects of DPP-4 inhibitors on several parameters which included myocardial infarction and stroke and hospitalization for heart failure.

The results showed that the (i) risk of mortality, (ii) combines of myocardial infarction + ischemic stroke and (iii) aggravation of heart failure were not adversely effected by DPP-4 inhibitors.

The data supplied by the investigators do not allow for any statement regarding the lipid status of the cohorts studied. 60:3% of the DPP-4 inhibitor users were on statin therapy. Even allowing for this fact, the DPP-4 inhibitor users had reduced myocardial infarction and ischemic strokes.

The SAVOR- T1M1 -53 trial reported a 27% increase in the risk of hospitalization for heart failure, in the saxagliptin treated group.

The VIVIDD trial and the EXAMINE trial showed no clinically significant increase in heart failure with vildagliptin and alogliptin respectively.

The TECOS trial studied sitagliptin and found no increase in heart failure.

Heart failure seems to be reduced by empagliflozin. It is postulated that the diuretic action of empagliflozin may contribute towards this reduction. In the EMPA-REG trial the HbAIC was reduced only by .5%. From this trial it is calculated that 1% reduction of HbAIC leads to a relative reduction of risk for heart failure by 7-10%. Metformin and the thiazolidinediones are thought to be deleterious in patients with T2DM in heart failure.

An observational study was conducted by Masoudi et al in 2005 involving 16417 subjects out of which 2226 patients were on a thiazolidinedione and 1861 on metformin. 12069 patients received neither of these treatments.[16]

The crude 1 year mortality rate was lower in the group treated with thiazolidinedione or metformin compared to the 12060 patients receiving neither drug.

In multivariate models, the risk of death too was significantly lower in the metformin or thiazolidinedione treated T2DM patients.

Note: In 2007 the FDA removed heart failure as a contraindication for metformin therapy.

The meglitinides and alpha glucocidase inhibitors have no satisfactory clinical trial data to suggest cardiovascular benefit.

Ongoing clinical trials

Several clinical trials are in progress, which when completed would give better answers regarding cardiovascular protection afforded by anti-diabetic drugs.

Some important trials are CARDINA (linagliptin), DECLARE (dapagliflozin), TOSCA (pioglitazone) and VERTIS (ertugliflozin).

Summary

Based on the clinical trial data provided above regarding the comparative benefits of antidiabetic drugs, the following hierarchical listing may be proposed (albeit with insufficient good quality data in most cases). i.e - metformin, gliflozins, liraglutide, pioglitazone, gliclazide, repaglinide, gliptins. Placement of insulin in this list has not been attempted due to paucity of comparative data.

Listing of these drugs may be controversial as numerous studies using small series could well be suggesting benefit or harm from anti diabetic drugs which are not confirmed by larger studies. Clinicians are well advised to keep abreast of current large scale double blind studies specifically designed to test for cardiovascular outcomes.

References

1. Margolis, D.J., O. Hoffstad, and B.L. Strom, *Association between serious ischemic cardiac outcomes and medications used to treat diabetes.* Pharmacoepidemiol Drug Saf, 2008. **17**(8): p. 753-9.
2. Schramm, T.K., et al., *Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study.* Eur Heart J, 2011. **32**(15): p. 1900-8.
3. Gerrits, C.M., et al., *A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes.* Pharmacoepidemiol Drug Saf, 2007. **16**(10): p. 1065-71.
4. Kaul, S., et al., *Thiazolidinedione drugs and cardiovascular risks: a science advisory from the American Heart Association and American College of Cardiology Foundation.* Circulation, 2010. **121**(16): p. 1868-77.
5. Johansen, O.E., et al., *Cardiovascular safety with linagliptin in patients with type 2 diabetes mellitus: a pre-specified, prospective, and adjudicated meta-analysis of a phase 3 programme.* Cardiovasc Diabetol, 2012. **11**: p. 3.
6. Lavalle-Gonzalez, F.J., et al., *Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial.* Diabetologia, 2013. **56**(12): p. 2582-92.
7. Monnier, L., et al., *Insulin and atherosclerosis: how are they related?* Diabetes Metab, 2013. **39**(2): p. 111-7.
8. Dong, Y., et al., *Role of endoplasmic reticulum stress signalling in diabetic endothelial dysfunction and atherosclerosis.* Diab Vasc Dis Res, 2017. **14**(1): p. 14-23.
9. Tzoulaki, I., et al., *Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database.* Bmj, 2009. **339**: p. b4731.
10. McAfee, A.T., et al., *Coronary heart disease outcomes in patients receiving antidiabetic agents.* Pharmacoepidemiol Drug Saf, 2007. **16**(7): p. 711-25.
11. Walker, A.M., C.E. Koro, and J. Landon, *Coronary heart disease outcomes in patients receiving antidiabetic agents in the PharMetrics database 2000-2007.* Pharmacoepidemiol Drug Saf, 2008. **17**(8): p. 760-8.
12. Mita, T., et al., *Relationship between frequency of hypoglycemic episodes and changes in carotid atherosclerosis in insulin-treated patients with type 2 diabetes mellitus.* Scientific Reports, 2017. **7**: p. 39965.
13. Skrtic, S., et al., *Contemporary risk estimates of three HbA1c variables in relation to heart failure following diagnosis of type 2 diabetes.* Heart, 2017. **103**(5): p. 353-358.
14. Eurich, D.T., et al., *Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review.* BMJ, 2007. **335**(7618): p. 497.
15. Ou, S.M., et al., *Dipeptidyl peptidase-4 inhibitors and cardiovascular risks in patients with pre-existing heart failure.* Heart, 2017. **103**(6): p. 414-420.
16. Masoudi, F.A., et al., *Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study.* Circulation, 2005. **111**(5): p. 583-90.