SPREAD-DIMCAD[1] – Cardiovascular (CV) Outcomes Trial Summary

Effect of Metformin Versus Glipizide Glucotrol on Cardiovascular Outcomes in Patients with Type 2 Diabetes (T2DM) & Coronary Artery Disease (CAD)

Trial Background: n=304 patients with T2DM with hx of CAD

- Metformin 500mg TID vs glipizide 10mg TID (after titration from half target dose). Higher doses could be tried as necessary & insulin could be added after 3 months if glucose control not achieved A1C <7%, FBG <7mmol/L, PPBG <10mmol/L.
- Randomized, concealed allocation probable, double-blind, multicenter 15 centres in **China**
- Primary outcome: composite of recurrent CV events: non-fatal MI, nonfatal stroke, arterial revascularization by percutaneous transluminal coronary angioplasty or coronary artery bypass graft, CV death, or all-cause death
- INCLUSION: T2DM (WHO 1999 criteria), CAD (hx of actue MI or stenosis >50% of lumen diameter in at least 1 major epicardial coronary artery) , ♂ & ♀ <80 yrs
- EXCLUSION: severe liver dysfx, NYHA >class III, psychiatric disease, severe infection, severe anemia, or neutropenia, other severe organic heart diseases, insulin-dependent T2DM, pregnant or lactating, recent drug or alcohol abuse
- Baseline Characteristics: ♂ ~78%; ethnicity Chinese; age: 63 mean; weight mean ~69 kg ~64% > 80 kg; BMI 25.2kg/m^2 mean, duration of diabetes 5.6 yrs; duration of CAD 3 years mean; A1c 7.6% mean; SCr mean 83.8-86.7+/-18.9 umol/L; hypertension 67-71%, prior MI 53-63%, prior stroke 13-18%, prior arterial revascularization 62-64%, no significant baseline differences between CV & T2DM medications

Table 1: Results: 1° & 2° Endpoints - study period for 3 years; median follow-up of 1° endpoint was 5 years {ITT analysis}

Clinical Endpoints {see trial for additional 2° endpoint data}	Glipizide n=148	Metformin n=156	Comments MF=metformin
1° Composite CV events, CV death, nonfatal MI (5 vs 6), non-fatal stroke (10 vs 15), arterial revascularization (21 vs 25), all-cause death (7 vs 14)	at 5 yrs **35%** {n=52}	at 5 yrs **25%** {n=39}	**Primary (1°) composite endpoint @5yr: Metformin ↓ risk HR=0.54** 95% CI 0.3-0.9 **; RRR** 0.1/0.35 **= 29%; NNT$_{ITT}$: 10 / over 5 years** **At end of follow up:** Glipizide n=97; Metformin n=111 **A1C** achieved was very similar: (7.6% → 7.1% glipizide, 7.0% metformin) **BMI & waist circumference**: lower in MF group @5yrs, 25.7 vs 24.7 p=0.026 **Hypoglycemia**: was not significantly different between groups. **Statin use**: lower in the MF vs glipizide 60% vs 74%; but LDL similar. **Overall: In high risk patients with a hx of CAD and T2DM, metformin ↓ CV events more than glipizide at 5 yrs, although the A1C lowering between both groups appeared similar.**
2° Cardiovascular endpoints (glipizide vs metformin): ◆ No significant differences in individual endpoints (at 3 yrs) {New or worsening angina 48% vs 49%, new or worsening heart failure 6.8% vs 5.8%, new critical cardiac arrhythmia 18.2% vs 19.2%, & new peripheral vascular events 0.6% vs 4.1% (p=0.059)}			

Strengths, Limitations & Uncertainties

Strengths	◆ first double-blind randomized, RCT to compare different effects of glipizide and metformin in major CV events among pts with CAD and T2DM; use of CV meds were well controlled for in this study ◆extends the generalizability of UKPDS-34 to high-risk patients with existing diabetes (5yrs)
Limitations	◆ trial used glipizide to represent SU but various SUs may differ in their effects on glucose control & CV risk in T2DM patients ◆the trial did not have a wash-out period ◆relatively small trial some variation in baseline characteristics

Comments:

◆The authors postulate that metformin's benefits may be due antiatherogenic effects beyond its antihyperglycemic action. Research has postulated that metformin may work by altering hepatic lipogenesis, increasing the sensitivity of insulin.[2]

◆Uncertainties: Are outcomes similar with all sulfonylureas? What is the association between A1C & macrovascular events?

The Bottom Line

⇨**When considering the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction/stroke, arterial revascularization and all-cause death, metformin was associated with a greater reduction in cardiovascular events compared to glipizide in patients with T2DM and CAD despite achieving similar A1C levels.**

⇨This is the first RCT to directly compare the effect of a sulfonylurea (glipizide not available in Canada) and metformin on the recurrence of major cardiovascaular events in high risk "CAD" patients with existing diabetes. It is **consistent with the findings of the UKPDS-34** where a reduction in macrovascular events, all-cause death NNT=14/10yr was also seen with metformin in obese T2DM patients despite less A1C lowering than that of the sulfonylurea & insulin group (UKPDS-33).

See also: Diabetes Agents - Outcomes Summary Table: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Agents-Outcomes-Comparison-Summary-Table.pdf

References:
1.) Hong J, Zhang Y, Lai S, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care. 2013 May;36(5):1304-11.
2.) Fullerton MD, Galic S, Marcinko K, et al. Single phosphorylation sites in Acc1 and Acc2 regulate lipid homeostasis and the insulin-sensitizing effects of metformin. Nat Med. 2013 Nov 3.
3.) UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (**UKPDS 34**). Lancet. 1998 Sep 12;352(9131):854-65.