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DIABETES PREVENTION IN PATIENTS AT RISK FOR T2DB – EVIDENCE REVIEW

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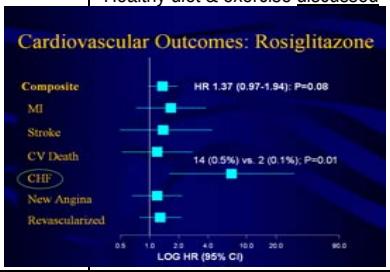
Study	Intervention	Patient Population	Trial Length	Results	Comments
XENDOS Torgerson[1] et al.	3305 pts randomized to **orlistat 120 mg TID** $155/30d n = 1650 or **placebo** n = 1655. Both groups on calorie reduced diet & encouraged to ↑ physical activity	Pts were 30-60 yrs of age (mean age ~ **43 yrs**) BMI≥ 30 kg/m^2. Pts could not have DM or active cardiovascular dx. 21% of pts had IGT †	**4 yrs**	**1° endpoint:** Diabetes incidence: 6.2% with orlistat & 9.0% with placebo RRR = 37%. NNT/4 yrs = 36 Subgroup analysis was performed; orlistat's diabetes preventative effects were seen in pts with IGT, not in pts with normal glucose tolerance (NGT) {18.8%vs 28.8% in IGT; 2.6% vs 2.7% in NGT} **1° endpoint:** Weight reduction was 5.8 kg with orlistat & 3 kg with placebo at 4 yrs.	◆ GI adverse effects: 91% of orlistat pts vs. 65% of placebo pts. in 1st year ◆Completed the trial: 52% of orlistat pts vs. 34% of placebo pts. ◆ results given based on single +'ve test; *repeat +'ve test* results are quite different **Effective in overweight IGT patients if able to tolerate**
DREAM (Rosiglitazone) Gertsein [2] et al	5269 pts randomized to **rosiglitazone 8 mg OD** n = 2635 $102/30d or **placebo** n = 2634. Healthy diet & exercise discussed  	Pts were > 30 yrs (median age = 55 yrs) ~ 60% females Pts had IGT and/or IFG or isolated IFG‡. Mean FBG = 5.8 mmol/L No pts with DM or known CV dx. ~ 44% with hypertension {original eligibility criteria expanded during trial}	Median = **3 yrs** (2.5-4.7 yr)	**1° endpoint:** incident diabetes or death: 11.6% with rosiglitazone 26.0 % with placebo NNT = 7 (p<0.0001) {driven by diabetes rates, not death (1.1 vs 1.3% NS)} **Diabetes incidence**: 10.6% with rosiglitazone & 25 % with placebo, NNT/3 yrs =7 **Heart failure** was significantly ↑ with rosiglitazone (0.5%) vs. placebo (0.1%) p = 0.03 NNH/3 yrs= 250. **Other CV events:** 2.9% vs. 2.1% HR=1.37 (CI: 0.97-1.94) {All CV outcome events on side of harm.} **Weight gain:** +2.2 kg with rosiglitazone p<0.0001, ↑ in waist circumference +1.8 cm therefore, a ↓ in the hip:waist ratio p<0.0001 **Effective but concerns about CV outcomes.**	◆ The trial was **stopped 5 months early** due to large difference in the 1° endpoint when rosiglitazone & placebo were compared. ◆ **CV Concerns** - ↑ risk of HF; ?↑MI & ?↑CV events. - Recent rosiglitazone CV meta-analysis suggests harm Nissen NEJM May07 (↑MI: OR 1.43 CI 1.03-1.98; ↑CV death: OR 1.64 CI 0.98-2.74) - **PROactive** [7] trial with pioglitazone ACTOS studied CV event rates in DM pts with evidence of CV dx. NS for 1° endpoint; some reductions in 2° CV events, but ↑ HF with pioglitazone 10.8% vs. pl 7.5%; NNH=34/3yr.
DREAM (Ramipril) Bosch [3] et al	5269 pts randomized to **ramipril 15 mg OD** $50/30d (start 5 mg OD x 2 months then ↑ to 10 mg OD, then ↑ 15 mg OD at 1yr, n = 2623) or **placebo** n = 2646. Healthy diet & exercise were discussed	Pts were > 30 yrs of age (mean age = 54.7 yrs) IGT and/or IFG or isolated IFG‡. No pts with DM or known CV dx. ~ 44% with hypertension	Median = **3 yrs**	**1° endpoint**: incident diabetes or death 18.1% with ramipril & 19.5% with placebo. (p=0.15) **NS** **Regression to normoglycemia** FBG <6.1mmol/L, 2hBG <7.8mmol/L 42.5% pts with ramipril 38.2% pts with placebo. HR = 1.16 (1.07-1.27) p=0.001 NNT/3 yrs = 23 No significant difference in rate of CV events. 2.6 vs 2.4% HR = 1.08 (0.76-1.52) **Not effective and lack of CV benefit.**	◆ The trial was stopped early as explained above. ◆ **Cough**: 9.7% of pts d/c ramipril & 1.8% of pts d/c placebo.
STOP-NIDDM Chiasson[4] et al	1429 pts randomized to **acarbose 100 mg TID** $42/30d (n = 714, 32 excluded from analysis), or **placebo** (n = 715, 29 excluded from analysis) Pts were encouraged to exercise & met with a dietitian	Pts were aged 40-70 yrs (mean age = 54 yrs) IGT (2hBG ≥ 7.8 & <11.1 mmol/L, with a FBG of 5.6-7.7 mmol/L). Mean FBG = 6.2 mmol/L	Mean = **3.3 yrs**	**1° endpoint**: incidence of diabetes based on single +'ve test. 32.4% pts with acarbose 41.5% pts with placebo. HR = 0.75 (0.63-0.9) NNT/3.3 yrs = 11 **Regression to NGT** 2hBG <7.8 mmol/L. 35% in the acarbose group 31% in the placebo group. (p<0.001) **Effective but high drop-out rate**	◆ GI related adverse: 83% of acarbose pts vs 60% with placebo pts. ◆ D/c treatment early: 31% of acarbose pts & 19% of placebo pts
Diabetes Prevention Program (DPP) Knowler[5] et al.	3234 pts were randomized into 3 groups: **Lifestyle + + metformin 850 mg BID** $14/30d n=1073, **Lifestyle + + placebo** n=1082, or **Intensive lifestyle +** n=1079 {See footnote for how intensive this was!}	Patients were aged >25 yr (mean = **51 yrs**) BMI >24kg/m^2 {mean =34} FBG of 5.3-6.9 mmol/L, & a 2hBG of 7.8-11 mmol/L. 68% female participation. ~ 45% of participants were from racial/ethnic minority	Mean = **2.8 yrs** (1.8-4.6 yr)	**1° endpoint**:incident diabetes: 4.8 cases/100 person yrs for **intensive lifestyle** 7.8 cases/100 person yrs for **metformin**, 11 cases/100 person yrs for **placebo**, ◆NNT/2.8 yrs = **7** for **lifestyle** ◆NNT/2.8 yrs = **14** for **metformin**. **Average weight loss**: 5.6 kg with intensive lifestyle, 2.1 kg with metformin 0.1 kg with placebo (p<0.001) **Intensive lifestyle most effective; metformin also effective.**	◆ The trial was **stopped one year early** on the basis that the author's efficacy measure had been met. ◆ Troglitazone∂ was initially included in the study, but was withdrawn from the trial due to potential **liver toxicity** caused by the drug[8]. When studied [8], troglitazone significantly ↓ diabetes for a short time (0.9 yrs). ◆ **Intensive lifestyle intervention** was more cost-effective vs. metformin [10].

Indian Diabetes Prevention Program (IDPP): 531 pts; Lifestyle vs metformin (MF) 250mg po BID vs control.
Results: Cumulative incidence of diabetes/2.5yrs: Lifestyle 39.3% NNT=6; MF 40.5% NNT=7, Control 55% (NNTs vs Control).
Metformin Meta-analysis: 6 trials, 3119 pts without diabetes, but with abdominal obesity, IGT, family hx T2DM. Results: MF 1000-1500mg/day ↓ onset of diabetes over ≤3 yrs; NNT=12.5 CI: 9.1-20. Salpeter 2008

Study	Intervention	Patient Population	Trial Length	Results	Comments
Finish Diabetes Prevention Study (FDPS) Tuomilehto [6] et al.	522 pts randomized to an **intensive lifestyle intervention group**‡ n = 265, or **control group**‡ n = 257. {see footnote}	Pts were aged 40 – 65 yrs (mean = **55 yrs**) BMI ≥ 25 kg/m^2 (mean=31.1) IGT = 2hBG >7.8 but <11.0 mmol/L, & a FBG < 7.8 mmol/L	Median = **4 yrs**	**1° endpoint:** incident diabetes**:** 11% with intensive lifestyle intervention 23% for control RRR= 58% HR = 0.4 (0.3-0.7) NNT/4 yrs = 8 **Change in Body weight:** -4.2 kg (-4.8 to –3.6) with the intervention -0.8 kg (-1.3 to –0.3) with the control	**Post-hoc 3 yr follow-up analysis:** [9] **(total of 7 yr follow-up)** **1° endpoint** of incident diabetes: 4.3 cases/100 person yrs with intervention (75 cases, 28.3%) 7.4 cases/100 person yrs with control (110 cases, 42.8%) RRR = 43% HR = 0.57 (0.43-0.76) NNT/7 yrs = 7 **Body weight** remained significantly diffierent in both groups[84.3 kg vs 85.6 kg.]

† IGT = 2h PG <10 mmol/L, FBG <6.7 mmol/L

‡ IGT = 2h PG >7.8 mmol/L & <11.1 mmol/L, FBG <7 mmol/L. IFG = 2h BG <11.1 mmol/L, FBG >6.1 mmol/L & <7 mmol/L. Isolated IFG = 2h BG <7.8 mmol/L, FBG >6.1 mmol/L & <7 mmol/L

‡**DPP**: Standard lifestyle intervention: included written information & individual sessions on healthy lifestyle. The goal of the **Intensive Lifestyle Modification** was to reduce weight by 7% through a healthy diet and physical exercise (≥ 150 minutes/week), and 16 individualized lessons, covering diet, exercise and behavior modification.

‡**FDPS: Intensive Lifestyle Intervention**: detailed and individualized counseling, sessions with a nutritionist, & free use of a individualized circuit for exercise. The goals of the intervention were to reduce weight by ≥5%, fat <30% of all energy, fibre ≥ 15g/1000 kcal, & moderate exercise for ≥ 30 minutes/day. **Control**: general verbal and written information on a healthy diet & exercise.

∂ **Troglitazone** was studied by Knowler[8] et al. At 0.9 years, there were 3 diabetes cases/100 patient years with troglitazone, 5.1 cases/100 person years for intensive lifestyle intervention, 6.7 cases/100 person years for metformin, and 12/100 person years for placebo. A significant reduction in incident diabetes was seen when troglitazone was compared to metformin (p=0.02), and placebo (p<0.001), but not when compared with intensive lifestyle intervention (p=0.18).

ARR=Absolute Risk Reduction **DREAM**=Diabetes REduction Assessment with ramipril & rosiglitazone Medication **CV**=Cardiovascular **DM**=Diabetes Mellitus **Dx**=Disease **FBG**=Fasting Blood Glucose **HR**=Hazard Ratio **IFG**=Impaired Fasting Glucose **IGT**=Impaired Glucose Tolerance **NGT**=Normal Glucose Tolerance **NNH**=Number Needed to Harm **NNT**=Number Needed to Treat **NS**=Non-Significant **Pt**=Patient **PROactive**=PROspective pioglitAzone Clinical Trial in macroVascular Events **STOP-NIDDM**=Study TO Prevent Non-Insulin Dependent Diabetes Mellitus **RRR**=Relative Risk Reduction **T2DM=** type 2 diabetes melitis **XENDOS**=XENical in the Prevention of Diabetes in Obese Subjects **2hBG**=Blood glucose measure 2 hours after a 75g oral glucose load

The Bottom Line: Counsel & encourage weight loss, physical activity, monitor for the development of diabetes every 1-2yrs & treat CVD risk factors [eg. tobacco use, hypertension & dyslipidemia] ADA 2007

- **Lifestyle Intervention**[5,6]: Is the **most effective** intervention for preventing diabetes when patients are motivated to be compliant. Individualized counseling/education is very important. Exercise: from 150 minutes/week, to 30 minutes/day of moderate intensity activity. Diet: healthy, low calorie, low fat diet[<30% kcal fat, <10% kcal saturated fat] and >15g fibre/1000 kcal consumed. **A small weight loss of only 5kg from these trials has shown enormous benefits.**
- **Metformin**[5]: is effective in preventing diabetes [250mg - 850 mg BID] when compared to placebo. {Benefits including ↓mortality, have been found in obese patients with diabetes [UKPDS-34 [12]]}.
- **Orlistat**[1] and **Acarbose**[4]: some evidence in their efficacy in preventing diabetes in IGT, but the tolerability (eg. ↑ GI side effects) of these medications limit their use
- **Rosiglitazone**[2]: is effective in preventing diabetes [8mg OD] compared to placebo. However, concern over weight gain, edema, CV events & the risk of ↑ heart failure [0.5% rosi, vs. 0.1% NNH=250.]
- **Ramipril**[3]: despite promising preliminary evidence[13,14,15], ramipril was not effective in preventing diabetes [15mg OD DREAM] when compared to placebo

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Upcoming Trials in Diabetes/CV Risk Prevention:

◆ **NAVIGATOR** (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research); ◆ **TRANSCEND** (Telmisartan Randomized Assessment Study in aCE iNtolerant subjects with cardiovascular Disease); ◆ **ONTARGET** (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial); ◆ **ACCORD**: Action to Control Cardiovascular Risk in Diabetes (standard therapy vs. intensive therapy of type 2 diabetes). ; **RAPSODI** (rimonabant in diabetes prevention)

See *updated* HTN, Lipid & Diabetes Glucose Trials charts at:
ftp://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-HTN-trial-summary.pdf ;
http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-lipid%20agents-major%20trials.pdf
http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf

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Salpeter SR, Buckley NS, Kahn JA, Salpeter EE. Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. Am J Med. 2008 Feb;121(2):149-157.e2. Using metformin to treat patients at risk for diabetes decreases their likelihood of developing diabetes over a 3-year period. Longer studies are needed to determine whether the likelihood of diabetes is truly decreased or simply delayed. We have no research to tell us whether, in the long run, patients live longer or live better if they are treated at this stage of (pre)diabetes. (LOE = 1a)