### Diabetes Prevention in Patients at Risk for T2DB – Evidence Review

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| **XENDOS**  
Torgerson et al. | 3305 pts randomized to orlistat 120 mg TID $115/30d 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/m². Pts could not have DM or active cardiovascular dx. 21% of pts had IGT  
4 yrs | 1° endpoint: Diabetes incidence: 6.2% with orlistat & 8.0% with placebo RRR = 37%. NNT/4 yrs = 36  
Subgroup analysis was performed: orlistat's diabetes preventive 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. 85% of placebo pts.  
• Completed the trial: 52% of orlistat pts vs. 34% of placebo pts  
• Results generated based on single +ve test; repeat +ve test results are quite different  
| **DREAM**  
(Rosiglitazone) Gertsein et al. | 5269 pts randomized to rosiglitazone 8 mg OD n = 2634 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 IGF²  
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.  
Heart failure was significantly ↑ with rosiglitazone (0.5%) vs. placebo (0.1%)  
HR = 0.75 (0.63-0.9) NNT/3 yrs =7  
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 & in waist circumference↑*8%* therefore, a ↓ in the hip:waist ratio p<0.001  
| • 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  
  - PROactive trial with pioglitazone ACTOS studied CV event rates in DM pts with evidence of CV dx. NS for 1° endpoint, but 1 HF with pioglitazone 10.8% vs. pl 7.5% NNH=34/3yr.  
| **DREAM**  
(Ramipril) Bosch 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 = 2632) or placebo n = 2634  
Healthy diet & exercise discussed | Pts were > 30 yrs of age (mean age = 54.7 yrs) IGT and/or IFG or isolated IGF²  
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 normoglycemia³ BG ≤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; 1.8% vs 2.4%  
HR = 1.08 (0.76-1.52)  
| • 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 et al. | 1429 pts randomized to acarbose 100 mg TID $55/30d (n = 714, 32 excluded from analysis), or placebo (n = 715, 29 excluded from analysis) | 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)  
| • GI related adverse: 83% of acarbose pts vs 60% with placebo pts.  
• D/c treatment early: 31% of acarbose pts & 19% of placebo pts  
Effective but high drop-out rate  
| **Diabetes Prevention Program (DPP)**  
Knoller et al. | 3234 pts were randomized into 3 groups:  
Lifestyle + metformin 850 mg Bid $74/30d n=1073  
Lifestyle + placebo  
Intensive lifestyle (See footnote for how intensive this was!) | Patients were aged >25 yr (mean age = 51 yrs) BMI >24kg/m² (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:  
48 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)  
| • 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.  
• When studied ‡, troglitazone significantly ↓ diabetes for a short time (0.9 yrs).  
• Intensive lifestyle intervention was more cost-effective vs. metformin †.  

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**Indian Diabetes Prevention Program (DPP):** 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=5; Control 55% (NNTs vs Control).  
Metformin Meta-analysis: 6 trials, 319 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: 9.1-20. Salpeter 2008  

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**RxFiles Diabetes Select Charts**
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| Finish Diabetes Prevention Study (FDPS) Tuomilehto et al. | 522 pts randomized to an intensive lifestyle intervention group or control group | Pts were aged 40 – 65 yrs (mean = 55 yrs) BMI > 25 kg/m² (mean = 31.1) IGT = 2hBG > 7.8 but <11.0 mmol/L, & a FBG < 7.8 mmol/L | Median = 4 yrs | 1st endpoint: incident diabetes: 11% with intensive lifestyle intervention 23% for control 
RRR= 58% HR = 0.4 (0.3-0.7) NNT/4 yrs = 8 | Post-hoc 3 yr follow-up analysis: 
(total of 7 yr follow-up) 
1st 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 different in both groups |

1. IGT = 2h BG < 10 mmol/L, FBG < 6.7 mmol/L
2. IGT = 2h BG > 7.8 mmol/L & < 11.1 mmol/L, FBG < 6.1 mmol/L, IFG = 2h BG < 11.1 mmol/L, FBG > 6.1 mmol/L & < 7 mmol/L, Isolated IFG = 2h < 7.8 mmol/L, FBG > 6.1 mmol/L & < 7 mmol/L

**FDPS**: Intensive Lifestyle Intervention: detailed information & individual sessions on healthy lifestyle.

The goal of the **Intensive Lifestyle Modification** was to reduce weight by >25%, fat <30% of all energy, BMI >25 kg/m², & moderate exercise for >30 minutes/day.

Control: general verbal and written information on a healthy diet & exercise.

2. T2Dm= type 2 diabetes melitis

**The Bottom Line**: Counsel & encourage weight loss, physical activity, monitor for the development of diabetes every 1-2 yrs & treat CVD risk factors.

**Lifestyle Intervention**: 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

A small weight loss of only 5kg from these trials has shown enormous benefits.

Metformin**: is effective in preventing diabetes 2500mg - 800 mg BD when compared to placebo. (Benefits including ↓ mortality, have been found in obese patients with diabetes UKPDS 34 ).

Orilistat** and Acarbose**: some evidence in their efficacy in preventing diabetes in IGT, but the tolerability (eg. GI side effects) of these medications limit their use

Rosiglitazone**: is effective in preventing diabetes compared to placebo. However, concern over weight gain, edema, CV events & the risk of ↑ heart failure

Ramipril**: despite promising preliminary evidence, was not effective in preventing diabetes when compared to placebo.

References:


Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V; Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin 250mg bid prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 2006 Feb;49(2):289-97. Epub 2006 Jan 4. n=531 over 2.5yrs

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)