**Type 1 Diabetes (T1DM)**

- **Definitions**
  - T1DM: age ≤13 yrs; n = 52; β cell mass = T1DM
  - **Intensive insulin**: (3–4 x more insulin or pump with target A1C of ≤6.0%; not always possible) + retinopathy

- **Population**
  - New T2DM: age 54; with metformin 1,000 mg/day vs conventional (4.5% vs 7.4% 5 mg/h)

- **Intervention**
  - **Baseline**: T1DM weight change 6.1% (P < 0.001); BMD 1.1% (P < 0.001)

- **Results**
  - **A1C reduction vs baseline**
    - **4.4%** (P < 0.001) vs conventional
    - **2.4%** (P < 0.001) vs placebo
    - **1.9%** (P = 0.004) vs lay diet alone

- **Conclusion**
  - Intensive insulin resulted in a significant reduction in A1C, BP, and body fat, but not in weight gain or BMI.

**Type 2 Diabetes (T2DM)**

- **Intensive Lifestyle Interventions**
  1. **Intensive diet and behaviour modification**: 34% absolute risk reduction in A1C (P = 0.004), weight (P < 0.001), and BP (P = 0.003).
  2. **Exercise**: moderate, 150 minutes/wk or 30 minutes/day, diet: healthy, low calorie, low fat (<30% of total kcal & 10% saturated fat), fibre (>15g/1000cal).

- ** Pharmacological Options**
  1. **Ben equipo de diabetes: 1. Intervención intensiva...**
  2. **Diabetes Prevention**
    - **Intensive lifestyle and/or medication**
      - **A1C reduction**: 33.1% (P < 0.001)
      - **BMI reduction**: 7% (P < 0.001)
      - **BP reduction**: 7% (P < 0.001)
      - **HbA1c reduction**: 3% (P < 0.001)
      - **LDL cholesterol reduction**: 24% (P < 0.001)
      - **Total cholesterol reduction**: 16% (P < 0.001)
      - **Triglyceride reduction**: 31% (P < 0.001)
      - **High-density lipoprotein cholesterol increase**: 23% (P < 0.001)

- **Summary**
  - **Intensive lifestyle interventions**
    - **Effectiveness**: moderate, 150 minutes/wk or 30 minutes/day, diet: healthy, low calorie, low fat (<30% of total kcal & 10% saturated fat), fibre (>15g/1000cal).

- **Type 1 Diabetes (T1DM)**

- **Intensive insulin**: (3–4 x more insulin or pump with target A1C of ≤6.0%; not always possible) + retinopathy

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- **Conclusion**
  - Intensive insulin resulted in a significant reduction in A1C, BP, and body fat, but not in weight gain or BMI.

**Appendix**

- **Type 1 Diabetes (T1DM)**
  - **Summary**
    - **Intensive lifestyle interventions**
      - **Effectiveness**: moderate, 150 minutes/wk or 30 minutes/day, diet: healthy, low calorie, low fat (<30% of total kcal & 10% saturated fat), fibre (>15g/1000cal).

- **Type 2 Diabetes (T2DM)**
  - **Intensive lifestyle interventions**
    - **Effectiveness**: moderate, 150 minutes/wk or 30 minutes/day, diet: healthy, low calorie, low fat (<30% of total kcal & 10% saturated fat), fibre (>15g/1000cal).

- **Pharmacological Options**
  - **Effectiveness**: moderate, 150 minutes/wk or 30 minutes/day, diet: healthy, low calorie, low fat (<30% of total kcal & 10% saturated fat), fibre (>15g/1000cal).

- **Prevention**
  - **Effectiveness**: moderate, 150 minutes/wk or 30 minutes/day, diet: healthy, low calorie, low fat (<30% of total kcal & 10% saturated fat), fibre (>15g/1000cal).
# T2DM “Prevention” Trials

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<th>T2DM “Prevention” Trials</th>
<th>Interventions</th>
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| **FDPS (Finnish Diabetes Prevention Study)** | Age 40-65 (mean 55); BMI ≥25 (mean 31); IGT (a FBG ≥ 7.8mmol/L); 2hBG ≥7.8 but < 11mmol/L | Intensive lifestyle vs control (Lifestyle: detailed, individualized counseling with nutritionist; individualized exercise circuit. Goals: ≤ 5<sub>%</sub>, fat <30% of all energy, fibre >15g/100kcal, moderate exercise > 30 minutes/day.) | 1°: incidence diabetes (4yrs): 11% vs 23%; RRR = 58% HR = 0.4 (0.3-0.7) NNT/4yrs = 8 | **Intensive Lifestyle Interventions ✓**

- a. Most effective intervention for patients with IGT
- b. How intensive was intensive lifestyle?
  i. Individualized counseling/education important
  ii. Weight loss: goal of at least 5-7% & up to 10%
  iii. Exercise: moderate, 150 minutes/wk or 30 minutes/day
  iv. Diet: healthy, low calorie, low fat (<30% of total kcal & <10% saturated fat), fibre (>15g/100kcal), [Chinese 5y study & 23y followup + death NNT=10] [Da Qing Diabetes Project] |
| **DPP (Diabetes Prevention Project)** | Age ≥25 (mean 51); BMI≥34 (mean 34); IGT (FBG of 5.3-6.9mmol/L; 2hBG of 7.8-11.1mmol/L) 86% 45% ethnic | Intensive lifestyle* & lifestyle + placebo vs 10142, or *Lifestyle: ↑ weight by 7% (healthy diet & exercise >150 minutes/week), & 16 individualized lessons, covering diet, exercise & behaviour modification. Llifestyle: diet encouraging reduction in caloric intake, e.g.: 1500 kcal for 800g & cover caloric intake. | 1°: incidence diabetes (2.8yrs): 4.8 cases/100 person yrs for intensive lifestyle 7.8 cases/100 person yrs for intensive lifestyle 4.8 cases/100 person yrs vs lifestyle placebo, & NNT=7/2.8yrs for lifestyle (RRR: 58%; 7% age 60%) | **Metformin (MF) -50-850mg po BID (Meta-analysis)**

- 6 trials, n=3119, aged obesity, IGT, family hx: ↑ time to diabetes onset ≤ 3yrs; NNT=12.5 CI: 9.1-20 [Most effect if age ≤40yrs]
- ii. Orlistat 120mg po TID • Effective if able to tolerate GI side effects; high cost (≤$510mo)
- iii. Acarbose 100mg po TID (CV benefit didn’t persist)
- b. Not Effective or Harm/Outcome Concerns
  i. Rampiril: not effective; valsartan ↓diabetes, PPBS-214, not CV
  ii. Glitazone: PPAR-γ agonists: CV risk control (rare) & concerns (↑w, edema, ↑HF, ↑fracture, & ↑CV Risk) 31,30
  iii. Nateglinide: ↑ risk of hypoglycemia without any benefits |
| **IDPP (India)** | Mean age 46; BMI 26 IGT – in Asian Indians | Lifestyle vs MF 250mg po BID vs control | 1°: incidence diabetes (2.5yrs): lifestyle 39.3%; NNT=6; MF 40.5%, NNT=7; control 55% | **Pharmacological Options**

- a. Effective but less than intensive lifestyle* |
| **Stop-NIDDM** | Age 40-70 (mean 54); IGT (2hBG ≥ 7.8 & <11.1mmol/L; FBG of 5.6-7.7mmol/L) | Acarbose 100mg TID vs placebo (also encouraged exercise; met with dietitian) | 1°: incidence diabetes (3.7yrs): 32.4% vs 41.5%; NNT=11/3.3yrs (CV events 2.5%); NNT=40 (GI AEs 83% vs 60% & stopped Tx: 31% vs 19%) | **Reducing Body Mass** |
| **XENDOS** | Age 30-60 (mean 43); BMI≥30; no CVD; 21% had IGT | Orlistat 120mg TID vs placebo (weight loss study (also ↓cholesterol & physical activity encouraged, (Drop-out rate: 8%)) | 2°: incidence diabetes; 6.2% vs 9%; NNT=36/years; ↓ diabetes in IGT subgroup only (13.0%, vs 20.8%, NNT=18) | **Other Trials of Interest**

| **DREAM-Rosi** | Age ≥30 (55); IGT +/- IFG or IFG Mean FBG=5.8mmol/l | Rosiglitazone 8mg po daily vs placebo (Trial stopped 5months early due to ↓diabetics, but CV event rate approaching statistical significance.) | 2°: incidence diabetes or death: 11.6% vs 26%; NNT=47/3yrs (driven by diabetes; no difference in death); CV events: 2.9% vs 2.1% (HR=1.37; 95% CI: 0.97-1.94) | **Other Trials of Interest**

- IRIS: pioglitazone after stroke in patients with insulin resistance. For every 100 patients with recent history of stroke, transient ischemic attack (TIA) and insulin resistance, but NOT diabetes, giving pioglitazone 45mg daily for ~5 years will result in approximately 3 less cases of stroke or MI, 4 less cases of diabetes, 2 extra cases of serious bone fracture, 7 extra cases of weight gain >13.6kg, and 11 extra cases of edema. (Note – those with various degrees of heart failure, pitting edema, etc. were excluded.) Link to trial summary: [http://www.rxfiles.ca/rxfiles/uploads/documents/IRIS-Trial-Summary.pdf](http://www.rxfiles.ca/rxfiles/uploads/documents/IRIS-Trial-Summary.pdf) |
| **DREAM-Rami** | Age ≥30 (55); IGT +/- IFG or IFG Mean FBG=5.8mmol/l | Rosiglitazone 8mg po daily vs placebo (Trial stopped 5months early due to ↓diabetics, but CV event rate approaching statistical significance.) | 2°: incidence diabetes or death: 11.6% vs 26%; NNT=47/3yrs (driven by diabetes; no difference in death); CV events: 2.9% vs 2.1% (HR=1.37; 95% CI: 0.97-1.94) | **Other Trials of Interest**

- RECORD: n=4447, ~ 5.5yr; T2DM (A1C mean ≥ 7.9%≤7.4-7.9%); open label; MF or SU + rosiglitazone vs MF + SU. No difference in CV death, MI; ↑HF & fracture. |
| **NAVIGATOR** | Age 40-65 (mean 55); BMI ≥25 (mean 31); IGT (a FBG ≥ 7.8mmol/L); 2hBG ≥7.8 but < 11mmol/L | Nateglinide: ↑ in progression to diabetes or ↓CV event. Valsartan, ∆CV risk (NNT/4yrs=20|1/yr) | 2°: incidence diabetes; 18.3% vs 19.5% ns (↓CV event rate 2.3% vs 2.4%) | **Upcoming Trials in Diabetes/CV Risk Prevention**

- NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research)- NEJM Mar/10; TRANSCEND (Telmisartan Randomized Assessment Study in aCE iNtolerant subjects with cardiovascular Disease): RAPSO (ruminant in diabetes prevention); CANOE (rosiglitazone 2mg bid & metformin 500mg bid in diabetes prevention); |

### Other Trials of Interest

- **NAVIGATOR** (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) - NEJM Mar/10
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### Prediabetes

- Includes: 1) Impaired Fasting Glucose (8hr fasting BG between 5.6-6.9mmol/L) & 2) Impaired glucose tolerance (Postprandial BG of 7.8-11.0mmol/L 2hrs post 75g oral glucose challenge)
- **Risk factors:** family hx, obesity – especially around waist, age ≥45, hypertension, gestational diabetes hx, sedentary lifestyle. Screening recommendations vary; USPSTF recommends screening particularly if BP ≥135/80. Oral Glucose Challenge is not very sensitive but an A1c screen can also be advocated by some.

### Insulin Analogues Systematic Review/Reports, 2008

Q&A: Limitations & Unanswered Questions Regarding A1C Control and Clinical Outcome - Benefits or Risks

There are some important qualifiers on the commonly quoted observational data that "with every 1% drop in A1C the risk of developing long-term diabetes complications decreases". (Concept originally based on observational data driven by an eye related microvascular endpoint in the UKPDS). RCT evidence does not support this assumption!

- Most recently the ACCORD trial (established, higher risk T2DM) was halted after looking at whether a A1C target of <6% would result in beneficial clinical outcomes compared to 7-7.9%. According to the preliminary results still awaiting publication, it would appear from this RCT, in this population group, the extra 1.1% drop in A1C seen in the intensive group was actually associated with increased all cause death compared to the standard group. Explanations for this are still pending; some possibilities noted with 5yr follow-up discussion below. (See also: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Targets-ACCORD-A1C.pdf)

- 5 year ACCORD™ follow-up results published May 2011 NEJM: A1C lowering intensiveness relaxed for balance of study period; participants continued in BP or lipid lowering arms; A1C at 5 yrs ~ 7.2% vs 7.6%. 1) ↑ death sustained in intensive glucose lowering group 5.5% vs 4.5% NNH=100/5yr; 2) ↓ non-fatal MI, but fatal CV ↑; 3) severe hypoglycaemia equivalent in follow-up period; 4) those most at risk of ↑ death were those with baseline A1C > 8%; 5) possible explanations for harm with intensive glucose lowering:

  - A) different outcomes associated with different drugs or drug combinations?  B) impact of ↑ wt gain?  C) impact of intense BG lowering.

- With the current RCT evidence with rosiglitazone, there is some concern that lowering A1C does not necessarily result in CV event reductions? With the limited evidence, it appears to at best be neutral, and at worst, harmful in RCTs/durations studied so far (e.g. up to 5.5 year RCTs.) Patients studied, agents used & study limitations e.g. dropouts may affect the benefit/risk balance.

- The UKPDS-33, ~ 10 year trial saw reductions predominantly in the microvascular events (predominantly photocoagulation), with stroke and heart related endpoints not significant, but trending favorably and contributing to the composite endpoint benefit. (Exception: metformin had all-cause death reduction in obese T2DM in UKPDS-34)

- In UKPDS 34,a which noted a mortality benefit for metformin in obese T2DM, there is inconsistency in the association of A1C & outcomes (less A1C difference but more benefit in T2DM than in TOFD) .

- In UKPDS 34 Metformin + Sulfonylurea combination led to a lower A1C than Sulf alone (7.7 vs 8.2) but had higher incidence of DM death and all cause death (perhaps due to design issues and a several year delay in moving to combination therapy).

- The UKPDS epidemiologic evidence for the 1% drop in A1C did not control for obesity/BMI/waist circumference. UKPDS 35

- In ADOPT, rosiglitazone decreased A1C more that metformin or glyburide, but glyburide had the lowest rate of CV outcomes.

- In VADT, a 1.5% reduction (6.9% intensively vs 8.4% standard) in A1C for an average follow-up of 5.6 years resulted in no benefit (microvascular or macrovascular) but increased serious adverse events (predominantly hypoglycaemia).

- Meta-analysis 2011 of Intensive ↓ BG RCTs in T2DM: 13 trials, n=34,500. Endpoints: mortality, no difference (RR=1.04, 95% CI 0.91-1.19). CV death, no difference (RR=1.10, 95% CI 0.98-1.23); non-fatal MI, ↓ (RR=0.85, 95% CI 0.74-0.98). Severe hypoglycaemia, ↑↑ (RR=2.33, 1.62-3.36) 1.9-8.8% of patients required tx for severe hypoglycaemia over 5 years. If only high quality studies included, no longer a ↓ in non-fatal MI & there was an ↑ in HF.

  - **Microvascular effects**: no difference, but heterogeneity: rate of retinopathy (0.85, 0.71-1.03); photocoagulation (0.91, 0.71-1.17), ↓ vision or blindness (1.00); neuropathy 0.99, 0.95-1.03); renal failure or 2x SCR (1.03, 0.98-1.08).

  - **Microalbuminuria**: ↓ (0.90, 0.85-0.96), ARR 7.7%–1.1%; NNT=142-32. OVERALL: for hard clinical endpoints, no benefit, but increased severe hypoglycaemia requiring tx. However, note heterogeneity in trials, different tx approaches, different definitions of “intensive lowering”, etc. Nevertheless, the more trials, the more evidence that just lowering BG does not equate automatically to beneficial clinical outcomes, but does carry hypoglycaemia risk.

There is some discordance between randomized trial outcome evidence and the frequently reported "1% A1C..." benefit. One thing that has growing certainty is that the risks and benefits of drug regimens that lower A1C is more complex than what was previously commonly accepted. While a high A1C is not good, some methods of lowering A1C in some patient groups, are also harmful. While we do not want to be lazy in addressing glucose control, the evidence suggests that we do not assume a net benefit for all A1C lowering interventions in all Type 2 diabetes patients. (Let the target serve the patient, and not the patient the target.)


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Multifactorial intervention - blood pressure, lipids, possibly ASA, lifestyle – in addition to glucose control, is essential in reducing macrovascular endpoints!

References - Diabetes Trials: Landmark Outcome and Prevention (www.RxFiles.ca)


4. Selpeter SR, Buckley NS, Kahn JA, Selpeter EE. Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. Am J Med 2008;121:149-157.e2. (InfoPOEM: 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))


7. ACT-NOW: Progression to T2DM (annual incidence of diabetes was 2.1 vs 7.6/yr); NNT=19/yr) but Wt gain (3.9kg vs 0.7kg) & edema (12.9 vs 6.4%).


14. Dormandy JA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study, (PROspective pioglitAzone Clinical Trial in macroVascular Events): a RCT. Lancet. 2005; 366: 1279-1289. (InfoPOEMS Aug 2008: Pioglitazone (Actos), unlike its chemical cousin rosiglitazone (Avandia), does not seem to increase the 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))


Additional References


Lilly M, Godwin M. Treating prediabetes with metformin: systematic review and meta-analysis. Can Fam Physician. 2009 Apr;55(4):363-9. Metformin decreases the rate of conversion from prediabetes to diabetes. This was true at higher dosage (850 mg twice daily) & lower dosage (250 mg twice or 3 times daily); in people of varied ethnicity; & even when a sensitivity analysis was applied to the data. The number needed to treat was between 7 & 14 for treatment over a 3-year period.


Oraczko LJ, Buchtleiter AM, Gimenez-Gomez M, Roque i Figuls M, Richter B, Mauricio D. Exercise or exercise and diet for preventing type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD003054. DOI:10.1002/14651858.CD003054.pub3. Interventions aimed at increasing exercise combined with diet are able to decrease the incidence of type 2 diabetes mellitus in high risk groups (people with impaired glucose tolerance or the metabolic syndrome). There is a need for studies exploring only interventions and studies exploring the effect of exercise and diet on quality of life, morbidity and mortality, with special focus on cardiovascular outcomes.


Sandbæk A, Griffin SJ, Sharp SJ, et al. Multifactorial Therapy Compared With Routine Care in Type 2 Diabetes in the Relation of Metabolic Syndrome to Cardiovascular Mortality, All-Cause Mortality, and Diabetes Incidence After 5 Years of Follow-Up Among Older Adults. Diabetes Care. 2014 Jul 17.
