Type 2 Diabetes (T2DM) Prevention (see Online Extras)

Type 2 Diabetes (T2DM) - 2019

1) Intensive Lifestyle Interventions

a. Most effective intervention for patients with IGT

b. How intensive was intensive lifestyle?

2) Pharmacological Options

a. Effective but less so than intensive lifestyle*
**TDM “Prevention” Trials**  

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| FDPS | 4yr, n=522 (Finnish Diabetes Prevention Study) | Age 40-65 (mean 55); BMI ≥25 (mean 31); IGT (a FBG >7.8mmol/L; 2h-BG ≤7.8 but ≤11 mmol/L) | Intensive lifestyle vs control (Lifestyle: detailed, individualized counseling with nutritionist; individualized exercise circuit. Goals: ↓ insulin, 5-%, ↓ fat <30% of all energy, fibre >15g/100kcal, & moderate exercise > 30 minutes/day) | 1° incident diabetes (4yrs); 11% vs 23%; RR= 58% HR = 0.4 (0.3-0.7) NNT/4yrs= 8 | 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% Td up to 10%  
iii. Exercise: moderate, 150 minutes/week or 30 minutes/day  
d. Diet: healthy, low calorie, low fat (<30% of total kcal & <10% saturated fat), fibre (>15g/100kcal), [Chinese 5yrs study & 23yrs follow-up + death NNT= 10 Da Qing DSP] |
| DPP | 2.8yr, n=3,234 (Diabetes Prevention Project) | Age >25 (mean 51); BMI ≥25 (mean 34); IGT (FBG 5.3-6.9 mmol/L; 2h-BG 7.9-11.1 mmol/L) 68 % ≥45 ethnic (Troglitazone arm stopped early due to liver toxicity) | Lifestyle* (not 1079)  
Lifestyle + placebo (not 1082, or)  
*Lifestyle: ↓ weight by 7% (healthy diet & exercise > 150 minutes/week), & 16 individualized lessons, covering diet, exercise & behaviour modification. | 1° incident diabetes (2yrs): 4.8 cases/100 person yrs for intensive lifestyle  
7.8 cases/100 person yr for intensive lifestyle  
NNT=7.2/8 years for lifestyle (RR: 58%, 77% age 60y)  
NNT= 14/2.5yrs for mef (28%)  
Weight ↓ 5.6kg, 2.1yrs, 0.1kg (p<0.001)  
10yr follow-up: delays onset of lifestyle by 4yrs, MF by 2yr | 3) 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% Td up to 10%  
iii. Exercise: moderate, 150 minutes/week or 30 minutes/day  
d. Diet: healthy, low calorie, low fat (<30% of total kcal & <10% saturated fat), fibre (>15g/100kcal), [Chinese 5yrs study & 23yrs follow-up + death NNT= 10 Da Qing DSP]  
4) Pharmacological Options  
a. Effective, but less than intensive lifestyle*  
  i. Metformin (MF) 250-850mg po BID (Meta-analysis30)  
  - 6 trials, n=3119, abd obesity, IGT, family hx: ↓ time to diabetes onset ≤3yrs; NNT=12.5 CI: 9.1-20 (Most effect if age <60y)  
  ii. Orlistat 120mg po TID  
  - Effective if able to tolerate GI side effects; high cost (P=105mo)  
  iii. Acarbose 100mg po TID (CV benefit did not persist)  
  - Effective if able to tolerate GI side effects; high cost (P=313mo)  
  b. Not Effective or Harm/Outcome Concerns  
  i. Ramlipril: not effective; valseartan diabetes (not CV, not effective)  
  ii. Glitazone (Pioglitazone & Rosiglitazone, CV risk [43%; CV death]), effective after 3.9yrs; concerns with T2DM, edema, HF, fracture, & CV Risks31,32  
  iii. Nateglinide: ↑ risk of hypoglycemia without any benefits |

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**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)

- **RECORD**: n=4,447, ~ 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.

**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): RAPSODI (rimonabant in diabetes prevention); CANOE (rosiglitazone 2mg bid & metformin 500mg bid in diabetes prevention);

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**Pre-diabetes**

- 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 most recommended, but A1c screen also advocated by some.


**Tight glucose control in critically ill hospitalized pts may ↑ mortality & ↑ risk of hypoglycemia** [JAMA 08, 40; Nice-Sugar NNH=3860day]
Q&A: Limitations & Unanswered Questions Regarding A1C Control and Clinical Outcome - Benefits or Risks

There are some important qualifications 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.**


- 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 RCT/categorisations 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, 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 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 VADE, a 1.5% reduction (6.9% intensive 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, 0.86-1.43); non-fatal MI: ↓ (RR=0.85, 0.74-0.98); Severe hypoglycaemia: ↑↑ (RR=2.33, 1.62-3.38) 1.9-6.8% 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 0.7%-3.1%; 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 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.)

See also: Yudkin JS, Lipska KJ, Montori VM. The idolatry of the surrogate. BMJ. 2011 Dec 28;343:d7995. [http://www.bmj.com/content/343/bmj.d7995](http://www.bmj.com/content/343/bmj.d7995)

**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. (InfoPOEMS: 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))


6. DeFronzo Ralph A., Tripathy D, Schwenke DC, Banerji M, et al. Diabetes Incidence and Glucose Tolerance after Termination of Intensive Diabetes Therapy in Persons at Risk for Diabetes Mellitus. Am J Med 2008;121:149–157.e2. {InfoPOEMS: 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)}


Zoungas S, de Galan BE, Ninomiya T, et al. The ADVANCE Collaborative Group. The combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes; new results from ADVANCE. Diabetes Care. 2009 Aug 3. [Epub ahead of print] The effects of routine blood pressure lowering and intensive glucose control were independent of one another and when combined produced additional reductions in clinically relevant outcomes.

Zoungas S et al. Severe hypoglycaemia and risks of vascular events and death (Advance). N Engl J Med 2010 Oct 7; 363:1410. During a median follow-up period of 5 years, 231 patients (2.1%) had at least one severe hypoglycaemic episode; 150 had been assigned to intensive glucose control (2.7% of the 5571 patients in that group), and 81 had been assigned to standard glucose control (1.5% of the 5569 patients in that group).


15 UGDP.


Holtman R, Sanjey P, Bethel MA, Matthews D, Neil A. 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. (UKPDS-80). N Engl J Med 2008;359:1-13. ([SU]Insulin vs control, ↓ Mi 19.6%±16.8 per 1000 patient-yrs (OR 0.85; CI: 0.74-0.95)).

↓ Death: 30.3%±29.8 per 1000 patient-yrs (OR 0.97; CI: 0.74-1.28), [MF vs control, ↓ Mi, 21.1%±14.8 per 1000 patient-yrs (OR 0.87; CI: 0.71-1.08), ↓ Death: 33.1%±25.9 per 1000 patient-yrs (OR 0.73; CI: 0.54-0.99)). (Daily POES: The advantages of tight blood sugar control seen in the United Kingdom Prospective Diabetes Study (UKPDS) trial were maintained and to some extent extended during a 10-year nonrandomized follow-up period, even though all patients quickly had similar glycohemoglobin levels. The benefit was most pronounced with metformin. Note that patients in the "intensive therapy" group had a mean glycohemoglobin of approximately 8% at the end of the randomized portion of the study, and the recent ACCORD study found that more aggressive control offered no benefit and may be harmful (N Engl J Med 2008;358:2545-59, POEM #100825). (LOE = 2b)


Zinman B, Inzucchi SE, Lachin JM, et al. Avenell A, Cook JA, MacLennan GS, McPherson GC; Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a randomised trial. N Engl J Med 2008;360:1283-92. (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 reason to tell our patients whether, in the long run, patients live longer or live better if they are treated at this stage of (pre)diabetes. (LOE = 1a))


Griffin SJ, Borch-Johnsen K, Davies MJ, et al. Eff ec of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe) a cluster-randomised trial. Lancet 2011; published online June 25. (In 2014, another publication showed that the 5 year microvascular event rates were also not significantly reduced. (Sandbaek, et al. Diabetes Care. 2014 Jul;37(7):2015-23.))

Recent Trials, Post-2015


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.


Orozco LJ, Buclintheer AM, Gimenez G, Roqué 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 exercise only interventions and studies exploring the effect of exercise and diet on quality of life, morbidity and mortality, with special focus on cardiovascular outcomes.


