DCCCT (1993-1999); n=1,441 (type 1 diabetes, age 21 yrs, mean HbA1C 7.4%)
Exclusion: if ever had CVD, T2P, T2C, complications.
1st & 2nd: different trials; 1st: 2-18yrs; HbA1C 7.4% vs 7.9%, P=0.001.
Asymptomatic microvascular events: 8.9% vs 11.0% (P=0.005) & early microvascular complications (retinopathy, neuropathy, nephropathy).
2nd: 17yrs; n=1,441
4.3% NNT=29
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**T2DM “Prevention” Trials**

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<th>Pre-diabetes</th>
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<th>Results</th>
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| FDPS 4y, n=522  | Intensive lifestyle vs control (Lifestyle: detailed, individualized counseling with nutritionist; individualized exercise program. Goals: ↓ wt >5%, fat <10% of all energy, fibre >15g/1000 kcal, moderate exercise > 30 minutes/day) | 1°: incident diabetes (4yrs): 11% vs 23%  
RRR= 58%  
Body wt: ↓4.2kg (4.8 to –3.6) vs –0.8kg (1.3 to –0.3)  
NNT= 8  
7 yr follow-up: effect persists 4yr, n=522 | Intensive lifestyle interventions: **best term than prevention of DM** is a non-clinical outcome. |
| DPP 2.8y, n=3,234  | Intensive lifestyle+ MF 850mg po BID  
**note:** Lifestyle: weight loss >7% (healthy diet & exercise >150 minutes/week), & 16 individualized lessons, covering diet, exercise & behaviour modification.  
Low-cal diet: ↓450 kcal/day; e.g. 1500 kcal/d for 80-95 kg | 1°: incident diabetes (2.8yrs): 4.8% cases/100 person-yrs for intensive lifestyle  
7 yr follow-up: delays diabetes  
RRR= 58%  
Body wt: ↓4.2kg (4.8 to –3.6) vs –0.8kg (1.3 to –0.3)  
NNT= 7/2.8yrs  
7 yr follow-up: delays diabetes | Effective but less so than intensive lifestyle* |
| IDDP (Indian Diabetes Prevention Program)  | Mean age 46; BMI 26  
Intensive lifestyle vs MF 250mg po BID  
**note:** also encouraged exercise; met with dietitian | 1°: incident diabetes (2.5yrs): lifestyle 39.3%, 55% control  
2°: delayed diabetes  
RRR= 68%  
Body wt: ↓7% (BMI 26 vs >15g/1000 kcal, & moderate exercise >30 minutes/day.} |
| Stop-NIDDM 3.3y, n=1,429  | Acarbose 100mg TID vs placebo (also encouraged exercise; meet with dietitian) | 1°: incident diabetes (3.3yrs): 32.4% vs 41.5%;  
55% control  
3°: delayed diabetes  
RRR= 55%  
Body wt: ↓7% (BMI 26 vs >15g/1000 kcal, & moderate exercise >30 minutes/day.} |
| XENODOS 4y, n=3,305  | Orlistat 120mg TID vs placebo (weight loss study) | 1°: incident diabetes: 6.2% vs 9%  
NNT= 36/4yr  
2°: delayed and diabetes RR 14% but no CV benefit.  
CV event rate approaching statistical significance.} |
| DREAM-Rosi 3yr, n=5,269  | Rosiglitazone 8mg po daily vs placebo (Trial stopped 5months early due to diabetes, but CV event rate approaching statistical significance.) | 1°: incident diabetes or death: 11.6% vs 26%;  
NNT=71/3.3 yrs  
2°: delayed diabetes  
RRR= 55%  
Body wt: ↓7% (BMI 26 vs >15g/1000 kcal, & moderate exercise >30 minutes/day.} |
| DREAM-Rami 3yr, n=5,269  | Ramipril 15mg po daily (start 5mg x 2 months, then 10mg/d till 1 yr) vs placebo | 1°: incident diabetes: 11.6% vs 26%;  
NNT=71/3.3 yrs  
2°: delayed diabetes  
RRR= 55%  
Body wt: ↓7% (BMI 26 vs >15g/1000 kcal, & moderate exercise >30 minutes/day.} |
| NAVIGATOR 5yr  | Nateglinide: no improvement in CV risk or diabetes event.  
Valsartan + MF* but no CV benefit  
*(Note: early intensive insulin Tx (x2 wks) may induce remission in some new T2DM) |

**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** 31: n=4447, ~ 5.5yr; T2DM (A1C mean ~ 7.9% vs 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);  

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

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**Tight glucose control in critically ill hospitalized pts may ↑mortality & ↑risk of hypoglycemia**  
[Arora A, 48 Nune-Sugar NNN=38960day]
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 vascular 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 Mar 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% \(\text{NNH}=100/5yr\);
  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 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% **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; 99%CI 0.91-1.19); CV death, no difference (RR=1.10; 0.86-1.43); non-fatal MI ↓ (RR=0.85; 0.74-0.96);

  Severe hypoglycaemia: \(\uparrow\) (RR=2.33,1.62-3.38) 1.9-6.6% 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); photoangiopathy (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.)**


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


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


Ugdp.


ACT-NOW J Long-term progression to T2DM (annual incidence of diabetes was 2.1 vs 7.6%/yr; NNT=19/yr) but weight (3.9kg vs 0.7kg) & adipen (12.9 vs 6.4%).  


Recent Trials, Post-2015


Additional References

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