DCCT:
- 6.8 yrs; n=1,441; Concluded between 1983-1993.
- 1st & 2nd endpoints, as well as 1st & 2nd cohorts.
- Intensive insulin (3-4x/day or pump) with target A1C of 6.0% vs 7.6% (mostly strict, >60% protocol compliance).
- Pre-prandial mean BG 3.9-4.7 mmol/L, PPBG >10 mmol/L, weekly AM BG 3.3-6.2 mmol/L vs Standard insulin (1-2x/day).
- Intensive vs Std.: 8.8% vs 9.1%.
- Endpoint: Rate per 100 pt yrs: 9.1 vs 11.4.
- Type 1 DM.

DCCT / EDIC:
- 17 yrs; n=3,867.
- 93% of DCCT in follow up till Feb 05; age 40-60; 24x hrs.
- As above, but 94% of standard group changed to intensive insulin.
- Intensive: 7.4% vs 9.7%.
- Rate per 100 pt yrs: 6.8 vs 7.9%.
- Endpoint: 7.4 vs 9.1%.

UKPDS-33:
- 10 yrs; n=3,867.
- New T2DM; Age 54; with FPG 6.1 mmol/L in diet alone.
- Intensive: Target FBG <6.2 mmol/L; 2.5 mmol/L fasting drop with 40% of DCCT.
- Intensive vs Std.: 8.7% vs 9.7%.
- Rate per 100 pt yrs: 7.4 vs 8.5%.
- Endpoint: Rate per 100 pt yrs: 6.0 vs 7.0%.

UKPDS-34:
- 11 yrs; n=1,704.
- Obese T2DM; Age 53; 37.7 kg/m².
- Metformin 1700mg am, 850mg pm vs conventional diet (diet alone).
- Intensive vs Std.: 7.7% vs 7.4%.
- Rate per 100 pt yrs: 6.5 vs 5.7%.
- Endpoint: Rate per 100 pt yrs: 5.3 vs 6.9%.

Kumamoto:
- 13 yrs; n=237.
- Japanese with 60+ vs 40-49 yrs, placebo vs placebo.
- Multiple insulin injection tx (MTI) vs conventional diet (CT). 8.2% vs 8.9%.
- Intensive vs Std.: 8.2% vs 8.9%.

PROACTIVE:
- 2yrs; n=5,238.
- High CV risk: Age 61; BMI: 30; A1c: 6.1.
- Placebo vs 10% higher rate of insulin use.
- Intensive vs Std.: 7.8% vs 7.7%.

ACCORD:
- 3.5yrs; n=10,251; with CV event; Age 50-79 yrs.
- Intensive A1C target <6% (most on SU, glitazide MR + MF) vs Standard target A1C >7%.
- Intensive vs Std.: 6.8% vs 7.2%.
- Rate per 100 pt yrs: 6.5% vs 6.9%.
- Endpoint: Rate per 100 pt yrs: 6.8 vs 6.9%.

ADVANCE:
- 5.5yrs; n=14,671.
- Nondiabetic, high CV risk, Type 2 DM.
- Early basal insulin glargine vs standard on placebo.
- Intensive vs Std.: 7.3% vs 7.0%.
- Rate per 100 pt yrs: 7.3% vs 7.6%.
- Endpoint: Rate per 100 pt yrs: 7.3 vs 7.7%.

STENO-2:
- 5yrs; n=16,702; T2DM & microalbuminuria.
- Multifactorial intensive (A1C; BP; CE; TC; lifestyle) vs slightly improved surrogates (A1C; LDL; BP).
- Intensive vs Std.: 56% vs 46%.
- Rate per 100 pt yrs: 45% vs 56%.

SAVOR-TIMM:
- 16; n=19,292; T2DM.
- Intensive vs standard A1C achieved: 6.0% vs 7.4%.
- NS effect: CV event, death; 5.0% vs 5.6%.
- Intensive vs Std.: 6.0% vs 6.8%.

EXAMINE:
- 5,380; 1.5yrs; Age 56-70 yrs; with T2DM, atorvastatin 10mg/d.
- Intensive vs Std.: 2.7% vs 3.1%.

TECOS:
- 14,671yrs; n=14,671.
- Diabetes 70-80 yrs.
- Intensive vs Std.: 7.0% vs 7.3%.

ELIXA:
- 6,068; 2.1yrs; Age 60-70 yrs; with T2DM.
- Intensive vs Std.: 7.7% vs 7.4%.

SUSTAIN-6:
- 2,527; n=2,527.
- Diabetes 65+ yrs; atorvastatin 10mg/d.
- Intensive vs Std.: 6.0% vs 6.5%.

LEADER:
- 5,930; 3yrs; Age 64-87 yrs; with T2DM.
- Intensive vs Std.: 6.0% vs 5.9%.

EMPA-REG:
- 2,063; n=2,063.
- Diabetes 60-79 yrs.
- Intensive vs Std.: 3.3% vs 1.3%.

FDA:
- 17yrs; n=522.
- Intensive lifestyle vs control.
- Detailed, individualized counseling with nutritionist; individualized exercise circuit.
- Goal setting: 
  1. incidence of diabetes (4yrs): 11% vs 36%, 
  2. HR of diabetes death (7yrs): 0.4x vs 1.0x, 
  10y follow-up: saw no effect on CV or total mortality.

DPP:
- Diabetes Prevention Program (DPP): 2.8yrs; n=3,234; Age ~51. 
- Arms: 1) Intensive lifestyle: with 7y vs 7% (diet, exercise, education/behaviour modification).
  2) Lifestyle + MF 850mg po BID; 3) Lifestyle + placebo; 4) Troglitazone (stopped due to liver toxicity).
- Intensive vs placebo: baseline. Intensive vs Std.: 0.7% vs 2.4%.
- Rate per 100 pt yrs: 1.2 vs 2.6%.

TPDM:
- 10yrs; n=2,531.
- Diabetes 55-65 yrs; with troglitazone.
- Intensive vs Std.: 4.2% vs 5.7%.
- Rate per 100 pt yrs: 2.0 vs 2.7%.

FDPS:
- 17yrs; n=522.
- Intensive lifestyle vs control.
- Detailed, individualized counseling with nutritionist; individualized exercise circuit.
- Goal setting: 
  1. incidence of diabetes (4yrs): 11% vs 36%, 
  2. HR of diabetes death (7yrs): 0.4x vs 1.0x, 
  10y follow-up: saw no effect on CV or total mortality.
# T2DM “Prevention” Trials Pre-diabetes

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<th>T2DM “Prevention” Trials</th>
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| **FDPS 4yr, n=522** (Finnish Diabetes Prevention Study)** | Intensive lifestyle vs control (**Lifestyle: detailed, individualized counseling with nutritionist; individualized exercise circuit. Goals: ↓ wt 5%, fat <30% of all energy, fib >15g/100g/cal, & moderate exercise > 30 minutes/day.)** | **1%** | **Note:** delay may be better term than prevent)
| **ΔRRR= 58% HR = 0.4 (0.3-0.7) NNT/4yrs = 8 **ΔΔBody wt. ↓ 4.2kg (1-6.3) ↓ ΔΔΔBlood glucose ↓ 8.6 (7.2-10) ↓ ΔΔΔΔBMI ↓ 1.35 (1.03-0.73); contd.** | **7 yr follow-up: effect persists 4.3 vs 7 % decrease/100 person yrs** |
| **10yr follow-up: no effect on CV or total mortality** | **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% Tbd 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), < > fiber (>15g/100g kcal), [Chinese 6yr study & 23 yr follow-up (+) death NNT=10 Da Qing DSP]** |
| **c. 3.0yr, n=5,234 (Diabetes Prevention Project)** | Lifestyle + placebo n=10703 | **1%** | **Note:** prevent diabetes of 7.8% cases/100 person yrs for intensive lifestyle 7.8% cases/100 person yr of Mf; 11 cases/100 person yr placebo, **NNT = 7.2/8yrs for lifestyle** (RRR: 58%, 7%, 80% & 90%)
| **2.8yr, n=3,234** | Lifestyle + placebo n=10702, or | **4.8 cases/100 person yrs for intensive lifestyle** 7.8% cases/100 person yr of Mf, 11 cases/100 person yr placebo, **NNT = 14.2/8yrs for lifestyle** (RRR: 58%, 7%, 80% & 90%)
| **3.0yr, n=522** (NIDDM Prevention Project) | Lifestyle vs Mf 850mg po BID n=1072 | **1%** | Repeat for 1yr to 3yr
| **DPP (Diabetes Prevention Project)** | Lifetstyle vs short-acting insulin (BID) n=1072 | **1%** | Repeat for 1yr to 3yr
| **IDPP (India)** | Intensive lifestyle* n=21 | **1%** |
| **Stop-NIDDM 3.3yr, n=1,429** | Acarbose 100mg TID vs placebo (also encouraged exercise; met with dietitian) | **1%** | Repeat for 1yr to 3yr
| **DREAM-Rosi 3yr, n=5,269** (Canberra Randomized Intervention Study) | Rosiglitazone 8mg po daily vs placebo (also encouraged exercise; met with dietitian) | **2%** | Repeat for 1yr to 3yr
| **DREAM-Rami 3yr, n=5,269** (Canberra Randomized Intervention Study) | Ramipril 15mg po daily (start 5mg/d x2 months, then 7.5mg/d till 1 yr) vs placebo | **1%** | Repeat for 1yr to 3yr
| **NAVIGATOR 5yr** | Nateglinide no + in progression to diabetes or CV event. Valsartan + diuretics. **RRR= 58% HR = 0.4 (0.3-0.7) NNT/4yrs = 8 **ΔΔΔΔBody wt. ↓ 4.2kg (1-6.3) ↓ ΔΔΔΔBlood glucose ↓ 8.6 (7.2-10) ↓ ΔΔΔΔΔBMI ↓ 1.35 (1.03-0.73); contd.** | **7 yr follow-up: effect persists 4.3 vs 7 % decrease/100 person yrs** |
| **10yr follow-up: no effect on CV or total mortality** | **Intensive Lifestyle Interventions ✓** |
| **a. Most effective but less than intensive lifestyle** |
| **i. Metformin (Mf) 250-850mg po BID (Meta-analysis)** |
| **• 6 trials, n=3119, abd obesity, IGT, family hx; + time to diabetes onset ≤ 3 yrs; NNT=12.5 CI: 9.1-20** |
| **• 30% risk ↓** |
| **ii. Acarbose 100mg po TID (CV benefit did not persist)** |
| **• Effective if able to tolerate GI side effects; high cost** |
| **• Effective if able to tolerate GI side effects; high cost** |
| **b. Not Effective or Harm/Outcome Concerns** |
| **i. Ramlipril: not effective; valsartan +diabetes, **RRR= 58% HR = 0.4 (0.3-0.7) NNT/4yrs = 8 **ΔΔΔΔBody wt. ↓ 4.2kg (1-6.3) ↓ ΔΔΔΔBlood glucose ↓ 8.6 (7.2-10) ↓ ΔΔΔΔΔBMI ↓ 1.35 (1.03-0.73); contd.** | **7 yr follow-up: effect persists 4.3 vs 7 % decrease/100 person yrs** |
| **ii. Gliptazones (Post-Prandial Glucose Reduction Study)** |
| **• Effective; lifestyle delay, not prevent after 4yr; concerns (Wt, edema, \( \text{HF} \), Fracture, & \( \text{CV} \) Risk) **
| **iii. Nateglinide: ↑ risk of hypoglycemia without any benefits** |

**PREVENTION OF DM IS NOT PREVENTION OF DM**

**Prevention strategies utilizing drugs have potential to harm otherwise healthy people; knowledge of long-term efficacy, safety & impact on healthcare resources need to be established.**

**Note:** all outcomes positive

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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 >13.6 kg, 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=4447, ~ 5.5yr; T2DM (A1C mean ~ 7.9% to 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 (rabinomat 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 Test 1h screen, but A1c screen also advocated by some.


**Tight glucose control in critically ill hospitalized pts may ↑ mortality & ↑ risk of hypoglycemia:** [JAMA 2008; 30: None-Sugar NNH=3860day](http://m.jama.ama-assn.org)
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.

- 5 year ACCORD™ follow-up results published Mar 2011. 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, 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 obese T2DM).

- 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.

- 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 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 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=1.11,95%CI 0.91-1.34); non-fatal MI, ↓ (RR=0.85, 95%CI 0.74-0.96);

  Severe hypoglycaemia: ↑↑ (RR=2.33, 95%CI 1.62-3.36) 1.9-6.6% of patients required tx for severe hypoglycaemia over 5 yrs. 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 (0.31, 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); AFR 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!


15 Zoungas S, de Galan BE, Nimmori Y, 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.

16 Zoungas S et al. Severe hypoglycaemia and risks of major cardiovascular 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 5517 patients in that group); and 81 had been assigned to standard glucose control (1.5% of the 5569 patients in that group). Persson V, Heesink HL, Chalmers J, et al. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. (Advance) Kidney Int. 2013 Jan 9.


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Additional References

Recent Trials, Post-2015


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Orizzo Lj, Buchleitner AM, Gimenez LF, et al. Exercise or exercise and diet for preventing type 2 diabetes mellitus in high risk groups (people with impaired glucose tolerance or the metabolic syndrome). 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.


