Diabetes Landmark Outcome Trials: Glycemic Control & Prevention Summary

**Type 1 (T1DM)**

<table>
<thead>
<tr>
<th>Trials</th>
<th>Mean follow-up</th>
<th>Population (sex, age)</th>
<th>Intervention</th>
<th>A1C baseline</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT</td>
<td>~6 yrs; n=1,441</td>
<td>Age 13-39 yrs (10%)</td>
<td>Intensive insulin (3x-4x daily or pump) with target A1C of &lt;6.0% without hypoglycemia</td>
<td>7.9±0.2%</td>
<td>Rate reduction in microvascular complications in T1DM prevention.</td>
</tr>
<tr>
<td>ADDENDA</td>
<td>~7 yrs; n=1,074</td>
<td>Age 13-17 yrs</td>
<td>Intensive insulin (3x-4x daily or pump) with target A1C of &lt;6.5%</td>
<td>8.0±0.4%</td>
<td>No macrovascular benefit.</td>
</tr>
</tbody>
</table>

**Type 2 (T2DM)**

<table>
<thead>
<tr>
<th>Trials</th>
<th>Mean follow-up</th>
<th>Population (sex, age)</th>
<th>Intervention</th>
<th>A1C baseline</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS-34</td>
<td>7 yrs; n=2,250</td>
<td>Age 44-64 yrs (56%)</td>
<td>Intensive insulin (3x-4x daily or pump) with target A1C of &lt;6.5%</td>
<td>8.4±0.3%</td>
<td>Reduction of risk of microvascular complications.</td>
</tr>
<tr>
<td>UKPDS-38</td>
<td>10 yrs; n=1,704</td>
<td>Age 24-70 yrs (40%)</td>
<td>Intensive insulin (3x-4x daily or pump) with target A1C of &lt;6.5%</td>
<td>8.0±0.3%</td>
<td>No benefit.</td>
</tr>
</tbody>
</table>

**Diabetes Control and Outcomes**

- **Intensive glycemic control may increase** or decrease risk depending on type of patient & treatment (e.g. in ACCORD, intensive A1C lowering associated with death; in VADT, ADVANCE, not quite as intensive as DCCT; in UKPDS-33/34, not intensive enough to achieve outcomes).
- **BG control** = microvascular benefit.
- **metformin** = in new, obese T2DM; CV events & all-cause death without weight or hypoglycemia (UKPDS-34, TRILOGY; also CV events vs glipizide SPREAD-O-MATIC).
- **Empagliotin** = in those with established CV disease; CV events & all-cause death EMPA-REG (SGLT-2 inhibitor drug studied; positive outcomes).
- **liraglutide** = in established CV disease or high risk: CV events & all-cause death LEADER (Semaglutide also CV events, but bismetoline neutral.)
- **glinipins** (GDP-146) = neutral on CV outcomes; however some variability re harms: saxagliptin & CV events ‘++’, but ↑ admission for HF SAVOR-TIMI 55.
- **pioglitazone CV events (2 events, statistical concern), but ↑ HF, wt, fracture.**  
  (rosiglitazone = not shown, not neutral outcomes; see RECORD & ACCORD results).
- **macrovacular benefits seen** with multifactorial approach to Tx: lifestyle, −smoking, diet, exercise, BP, ACEI, statin, AS, A1C, E2, STENO2.
- **statin therapy** (simvastatin 40mg/PP, atorvastatin 10mg/gINS) → ↓ CV & microvascular complications.
- **ACEI & LBP (ramipril 10mg/doses)**; no evidence of benefit on 10yr Look Ahead

**Type 2 Diabetes (T2DM) - Prevention**

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*
     - i. Metformin (MF) 250-850mg po BID (Meta-analysis)**
     - ii. GLP-1R agonists
     - iii. SGLT-2 inhibitors
     - iv. Other medications

3. **Non-steroidal inflammatory agents**
   - b. ACEI or ARB treatment.

4. **Nutritional supplements**
   - a. Protein or amino acid supplementation in high-risk groups.

5. **Other interventions**
   - a. Exercise
   - b. Weight loss
   - c. Hypertension

6. **Other considerations**
   - a. Lifestyle modifications
   - b. Medications

7. **Additional considerations**
   - a. Cost-effectiveness
   - b. Side effects

8. **Conclusion**
   - a. 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.
   - b. Note: many of these studies are not randomized control trials.

**Branding/Marketing/Outcomes**

- Prediabetes 5-year risk
- Type 2 Diabetes (T2DM) prevalence

**Type 1 Diabetes (1T1D)**

- In microvascular complications in type 1 diabetes (mostly retinal on fundus photo and neuropathy).
- 10% relative reduction in A1C (regardless of what the initial A1C value was) resulted in a 43% relative risk ↓ in progression of retinopathy & a 25% relative risk ↓ in microvascular complications. (Substantially less at lower A1C level.)

**Type 2 Diabetes**

- Glucose control may increase or decrease risk depending on type of patient & treatment (e.g. in ACCORD, intensive A1C lowering associated with death; in VADT, ADVANCE, not quite as intensive as DCCT; in UKPDS-33/34, not intensive enough to achieve outcomes).
- Intensive glycemic control may increase or decrease risk depending on type of patient & treatment (e.g. in ACCORD, intensive A1C lowering associated with death; in VADT, ADVANCE, not quite as intensive as DCCT; in UKPDS-33/34, not intensive enough to achieve outcomes).
- BG control = microvascular benefit.
- metformin = in new, obese T2DM; CV events & all-cause death without weight or hypoglycemia (UKPDS-34, TRILOGY; also CV events vs glipizide SPREAD-O-MATIC).
- Empagliotin = in those with established CV disease; CV events & all-cause death EMPA-REG (SGLT-2 inhibitor drug studied; positive outcomes).
- liraglutide = in established CV disease or high risk: CV events & all-cause death LEADER (Semaglutide also CV events, but bismetoline neutral.)
- glinipins (GDP-146) = neutral on CV outcomes; however some variability re harms: saxagliptin & CV events ‘++’, but ↑ admission for HF SAVOR-TIMI 55.
- pioglitazone CV events (2 events, statistical concern), but ↑ HF, wt, fracture. (rosiglitazone = not shown, not neutral outcomes; see RECORD & ACCORD results).
- statin therapy (simvastatin 40mg/PP, atorvastatin 10mg/gINS) → ↓ CV & microvascular complications.
- ACEI & LBP (ramipril 10mg/doses); no evidence of benefit on 10yr Look Ahead
## T2DM “Prevention” Trials

<table>
<thead>
<tr>
<th>** FDPS 4yr, n=522</th>
<th>**DPP 2.8yr, n=3,234</th>
<th>**IDPP (India) n=5,531</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 40-65 (mean 55); BMI ≥25 (mean 31); IGT (a FBG ≥7.8mmol/L, 2hBG ≥7.8 but &lt; 11mmol/L)</td>
<td>Age &gt;25 (mean 51); BMI≥24 (mean 34); IGT (FBG of 5.3-8.9 mmol/L, 2hBG of 7.8-11.1 mmol/L) 88%; ø: -45% ethnic</td>
<td>Mean age 46; BMI 26 IGT – in Asian Indians</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td><strong>Intensive lifestyle</strong>*</td>
<td><strong>Lifestyle vs MF 850mg po BID</strong></td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>1°: incident diabetes (2.8ys): RR=58% HR= 0.4 (0.3, 0.7) NNT/4yrs= 8</td>
<td>1°: incident diabetes (2.8ys): 4.8 cases/100person yrs for intensive lifestyle 7.8 cases/100person yr MF; 11 cases/100person yr placebo,</td>
</tr>
<tr>
<td></td>
<td>7yr follow-up: effect persists 3.4 vs 5.4 [4.3 vs 7.4] cases/100person yrs</td>
<td><strong>NNT=7.2/8yrs for lifestyle</strong> (RR: 58%; 7% age 60%)</td>
</tr>
<tr>
<td></td>
<td>10yr follow-up: no effect on CV or total mortality</td>
<td><strong>NNT=2/8yrs for MF</strong> (mean yrs)</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td>(Note: treatment delays CV event. Valsartan 1°: beneficial vs control but no CV benefit.</td>
<td><strong>NNT=14</strong></td>
</tr>
<tr>
<td></td>
<td>NNT=1:4yrs; n=1079</td>
<td>1°: intensive lifestyle (2.5yrs): lifestyle 39.3%, NNT=6; MF 40.5%, NNT=7; placebo 55%</td>
</tr>
<tr>
<td></td>
<td>2°: ACARBOSE 100mg TID placebo (also encouraged exercise; met with dietitian) 1°: intensive lifestyle (3.3yrs): 32.4% vs 41.5%</td>
<td>1°: incident diabetes (3.3yrs): 11.8% vs 26%; NNT=7/3yrs (drivers; diabetes; no difference in CV events; CV events: 2.9% vs 2.1% [p&lt;0.001])</td>
</tr>
<tr>
<td></td>
<td>2°: Rosiglitazone 8mg po daily vs placebo</td>
<td>1°: incident diabetes or death: 18% vs 19.5% n=1079) &amp; CV event rate: 2.6% vs 2.4% (p=0.001)</td>
</tr>
</tbody>
</table>

### Effective Options

**Prevention Options**

- **treatment** = 2hr blood glucose

**Options** = Individualized counseling/education important  
- **Weight loss**: goal of at least 5-7% Td up to 10%  
- **Exercise**: moderate, 150 minutes/wk or 30 minutes/day  
- **Diets**: healthy, low calorie, low fat (<30% of total kcal & <10% saturated fat), fibre (>15g per 100g kcal),  

---

### Pharmacological Options

- **Metformin** (MF 250-850mg po BID) 
  - Meta-analysis: 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 <40yrs)  
- **Orlistat 120mg po TID**  
  - Effective if able to tolerate GI side effects; high cost  
- **Acarbose 100mg po TID** (CV benefit did not persist)  
- **Nateglinide**: risk of hypoglycemia without any benefits

### 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 about 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

- **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.

### 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)
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 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%  

> 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 34 vs 33)

- 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 (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 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 0.96-1.24); non-fatal MI: ↓ (RR=0.85, 97%CI 0.74-0.98);

  **Severe hypoglycaemia**: ↑↑ (RR=2.33, 95%CI 1.62-3.38) 1.9-6.8% 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**: ↓ (0.30, 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 idiocy 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)


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 hypoglycemia and risks of major vascular events and death (Advance). N Engl J Med 2010 Oct 7; 363:1410. During a median follow-up of 5 years, 231 patients (2.1%) had at least one severe hypoglycemic 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). Perkovic V, Heerspink HL, Chalmers J, et al. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. (Advance) Kidney Int. 2013 Jan 9.


21 Death: 30.3±28.8 per 1000 patient-yrs NNT=4.08 (CI: 1.74-4.5). [MF vs control]; DI 21.1±14.8 per 1000 patient-yrs NNT=4.08 (CI: 1.74-4.5). Death: 33.1±25.9 per 1000 patient-yrs NNT=4.08 (CI: 1.74-4.5). (Daily POEM: 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 non-randomized follow-up period, even though all patients quickly had similar glycemia levels. The benefit was most pronounced with metformin. Note that patients in the "intensive therapy" group had a mean glycemia 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 = B/7)


23 Avenell A, Cook JA, MacLennan GS, McPherson GC; Home PD, Pocock SJ, Beck Griffin SJ, Borch Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a bl...

24 Knowler WC, Hamman RF, Edelstein SL, et al. Diabetes Prevention: Results from the diabetes control and prevention (DCP) study. N Engl J Med. 1987 Dec 3;317(24):1497-508. ([SU]Metformin vs placebo]; DI 0.79 per 1000 patient-yrs NNT=1724 (CI: 1.16-2.0). [MF vs control]; DI 0.79 per 1000 patient-yrs NNT=1724 (CI: 1.16-2.0). (Daily POEM: The Diabetes Control and Prevention (DCP) study showed a 12% reduction in the incidence of diabetes among patients treated with metformin compared to those receiving placebo. This study also demonstrated that the benefit of metformin was most pronounced in younger, non-obese patients. (LOE = B/1)


27 Griffin SJ, Borch Wiener RS, Wiener DC, Larson RJ. Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. Ann Intern Med. 2008;148:394-401. ([SU]Metformin vs placebo]; DI 0.31 per 1000 patient-yrs NNT=3088 (CI: 1.11-7.9). [MF vs control]; DI 0.31 per 1000 patient-yrs NNT=3088 (CI: 1.11-7.9). (Daily POEM: Metformin significantly reduced the risk 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 us whether, in the long run, patients live longer or live better if they are treated at this stage of (pre)diabetes. (LOE = A1a)


30 AACE -) progression to T2DM (annual incidence of diabetes was 2.1 vs 7.6%/yr; NNT=19/yr) but "weight (3.3kg vs 0.77kg) & edema (12.9 vs 6.4%).

31 Loke Yoon Kong, Kwok Chun Shing, Singh Senal. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. BMJ 342:d10136.bmj.com


39 NICE -43.1% reduction in the incidence of diabetes among adults in the ICU: a bl...

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. Lind M, Bounias I, Olsson M, Gubbiørmadsøtt S, et al. Glycaemic control and incidence of heart failure in 20,985 patients with type 1 diabetes: an observational study. Lancet 2011; published online June 25.


