

	Trials Mean follow-up	Population Risk, hx, age	Intervention	A1C: baseline → final	Results	Summary of RCT Outcome Evidence
Type 1 (T1DM)	DCCT 1 ~6.5yrs; n=1,441 {Conducted between 1983-1993. {note 1° & 2° endpoints, as well as 1° & 2° cohorts.}	T1DM; mean age 27 (13-39)yr; BMI=27 Excluded: if CV disease, ↑BP, HC, complications. 1° & 2° cohorts (2° if 1-15yr hx, existing mild-moderate retinopathy & microalbuminuria; 1°: 1-5yr hx)	Intensive insulin (3+ inj/day or pump) with target A1C of <6.05% (44% achieved once, but only 5% maintained), preprandial BG 3.9-6.7mmol/L, PPBG <10mmol/L, weekly 3A.M. BG >3.6mmol/L vs Standard insulin (1-2 inj/day)	Int. vs Std.: 8.8% → 7.4% vs 9.1% {Pre-prandial mean BG Int. vs Std. 8.6 vs 12.8mmol/L.} (↑ Wt 4.6kg/5yr)	Endpoint 1s or 2s: Δ Rate/100 pt yr NNT/H=100per pt yr RRR 1: Retinopathy 1° ↓3.5 NNT=29 2° ↓4.1 NNT=24 63% 2: Microalb. 1° ↓1.2 NNT=83 2° ↓2.1 NNT=48 39% 2: Macroalb. 1° ↓0.1 NS 2° ↓0.8 NNT=125 54% 2: Neuropathy@5yr ↓6.7 NNT=15 ↓9.1 NNT=11 60% Hypogly SEVERE ↑43 NNH=2.3; ↑Hosp 7.6% vs 4.9%	Type 1 Diabetes (ENDIT/acotinamide & DPT-1 low-dose insulin not effective in T1DM prevention) ♦ ↓ in microvascular complications in initial 6.5yrs (1° endpoint: retinal surrogates) (mostly ↓ retinal Δ on fundus photo 3 steps / 25 stage scale, microalbuminuria & neuropathy) ♦ a 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 microalbuminuria. (Substantially less at lower A1C levels.) ♦ ↑ severe hypoglycemia including coma/seizures NNH=9 /100ptyr & hospitalizations 54 vs 36 ♦ possible ↓ in macrovascular complications in long-term follow-up (~17yrs); however, limitations such as unmasking could bias results.
	DCCT / EDIC 2 ~17yrs; n=1,394	93% of DCCT in follow-up till Feb05. age 45; BMI=28; 24yr hx	As above, but 94% of standard group changed to intensive insulin.	7.4% → 7.9% 9.1% → 7.8%	♦ ↓ CV events (nonfatal MI, CV death, stroke, angina, revascularization) 5.8% vs 10.3% NNT=23/17yr CI=12-352. (RRR=42% ↓)	
Type 2 (T2DM)	UKPDS-33 3 † ~10yrs; n=3,867	New T2DM; age 54yrs; with FPG 6.1-15 on diet alone	Intensive SU or insulin vs diet. Target FBG <6mmol/L vs <15mmol/L	7% → 7% vs 7.9%	♦ ↓ microvascular endpoints NNT=42/10yr; mostly retinal ♦ no effect on CV events* † ↑ hypoglycemia esp insulin	Type 2 Diabetes ♦ intensive glucose control may ↑ or ↓ risk depending on type of patient & treatment {e.g. in ACCORD type patients, overly intensive pursuit of A1C target associated with ↑ death; no benefit in VADT; whereas in ADVANCE type patients, not quite as intensive tx had some benefit; UKPDS 33,34 reveal variability between extent of BG control & outcomes.} ♦ BG control ⇒ possible microvascular benefit ADVANCE & UKPDS; not ACCORD ♦ metformin in newly diagnosed obese T2DM: reduces macrovascular events & all-cause death without ↑ weight or hypoglycemia UKPDS-34, 80 ♦ pioglitazone may ↓ CV events (2° outcome & statistical concerns)†, but ↑ HF & wt (rosiglitazone: ↑ HF, wt, fractures; uncertain CV outcomes (neutral in RECORD, but limitations) 31 ♦ macrovascular benefits seen with multifactorial approach to Tx -lifestyle, ↓ smoking, diet, exercise, BP, ACEI, statin, ASA, A1C<6.5% STENO-2 -statin therapy { simvastatin 40mg/d HPS; atorvastatin 10mg/d CARDS } -ACEI, BP reduction {e.g. ramipril 10mg/d MICROHOPE}
	UKPDS-34 4 † ~10.7yrs; n=1,704	Obese T2DM; age 53yrs Wt=87kg; BMI=31	Metformin 1700mg am, 850mg pm vs conventional (diet mostly)	7% → 7.4% vs 8% vs 8%	♦ ↓ diabetes endpoint NNT=10/10yr (RRR=32%) † ♦ ↓ all-cause death NNT=14/10yr; ↓ stroke NNT=48/10yr	
	Kumamoto 5 6yrs; n=110	Japanese with 2- & without 1- retinopathy; UAE<300mg/24hr	Multiple insulin injection tx (MIT) vs conventional insulin tx (CIT)	9.2-9.4 → 7.1 vs 8.9 → 9.4	♦ ↓ early microvascular complications (retinopathy [2+ steps on 19 step scale]; nephropathy & neuropathy)	
	PROACTIVE 6 ~2.9yrs; n=5,238	High CV risk; Age 61; BMI=30; A1C ≥ 6.5	Pioglitazone 45mg po daily vs Placebo (>10% higher rate of insulin use)	7.8% → 7% vs 7.5%	♦ 1° composite-no effect; 2° ↓ CV events NNT=50/2.9yr ♦ ↑ wt 3.6kg/yr; ↑ HF NNH=31/2.9yr & edema.	
	ACCORD 7 ~3.5yrs; n=10,251; ↑ death maintained @5yr follow-up	High CV risk; ~10yr hx T2DM; age 62; 93kg; North American	Intensive A1C target <6% {most on 3 oral hypoglycemics + insulin} vs standard A1C target 7-7.9%	8.1% → 6.4% vs 7.5% 7.2% vs 7.6% @-5yrs	♦ ↑ all-cause death ↑ 22% in intensive group at 3.5yr resulted in halting trial (NNH=95/3.5yr); also severe hypoglycemia (NNH=9/3.5yr) & ↑ weight 3.5 vs 0.4kg	
	ADVANCE 8 ~5yrs; n=11,140	Hx of CV disease; 8yr hx T2DM; age 66; 78kg; Austral-Asian/European	Intensive A1C target 6.5% {most on SU (gliclazide) + metformin} vs standard A1C target ~ 7%	7.5% → 6.5% vs 7.3%	♦ ↓ microvascular events over 5yrs (NNT=67/5yr), mostly nephropathy indicators; also ↑ severe hypoglycemia (NNH=83/5yr) & minimal wt change	
	RECORD 31 : n=4447, ~ 5.5yr; T2DM (A1C mean ~ 7.9% → 7.4-7.9%); open label; metformin or SU + rosiglitazone vs metformin + SU. No difference in CV death, MI; ↑ HF & fracture.					
	STENO-2 9 : n=160, T2DM & microalbuminuria; multifactorial intensive (A1C <6.5% <20% achieved @13yrs 8.4 → 7.7%); BP, lipid, ACEI, ASA) vs conventional tx for 7.8yr+ 5.5yr follow-up; ⇒ ↓ death, NNT=5 / 13.3yrs p=0.02; ↓ macro & microvascular events. (Only 1 pt achieved all 5 targets at 13yrs)					
ADDITION-Europe 32 (Acute): n=3057 new T2DM, age avg ~60; 5.3yrs; multifactorial intensive (A1C, BP, ACEI, cholesterol & lifestyle) ⇒ slight improvement in surrogates (A1C, LDL, BP) but non-significant ↓ in CV events/death; 7.2% vs 8.5%; HR 0.83, 95% CI: 0.65-1.05						
UGDP 10 : (1971) n=1027; ~8yrs; T2DM. Tolbutamide ↑ CV mortality 2.9%; Phenformin ↑ CV 4x & all cause mortality. Insulin, even with adjustable dosing was no better than diet alone, but no harm. Results criticised e.g. ↑ death in more poorly controlled, etc. 13 yr follow-up.						
VADT (Debut) 11 : n=1791, ~5.6yr, Age~60yr, ♂ mostly, T2DM x 11.5yr; 40% CAD Hx (Veterans Affairs). Intensive vs standard A1C Achieved: 6.9 vs 8.4%. NS effect: CV event, death 102 vs 95 or microvascular complications; but ↑ serious adverse events 17.6 vs 24.1% mostly hypoglycemia. ↑ CVD risk if DBP < 70.						
† UKPDS 80: 10 year observational follow-up to UKPDS 33 & 34 (Sep08); glycemic difference lost in follow-up, however risk reduction emerged/sustained for endpoints (MI & Death), especially with MF. {SU/insulin vs control: ↓ Death 30.3 → 26.8 per 1000 patient-yrs; MF vs control: ↓ Death 31.3 → 25.9 per 1000 patient-yrs.} 12						

	T2DM "Prevention" Trials Pre-diabetes	Intervention	Results	Summary {Note: "prevention of DM" a non-clinical outcome.}	
Effective Options	FDPS 13 4yr, n=522 (Finnish Diabetes Prevention Study)	Age 40-65 (ave 55yrs); BMI ≥ 25 (mean 31); IGT (a FBG < 7.8mmol/L; 2hBG > 7.8 but < 11 mmol/L)	Intensive lifestyle vs control {Lifestyle: detailed, individualized counseling with nutritionist; individualized exercise circuit. Goals: ↓ weight > 5%, fat < 30% of all energy, fibre > 15g/1000kcal, & moderate exercise > 30 minutes/day.}	1°: incident diabetes (4yrs): 11% vs 23% RRR= 58% HR = 0.4 (0.3-0.7) NNT/4yrs = 8 Δ Body wt: -4.2kg (-4.8 to -3.6) vs -0.8kg (-1.3 to -0.3) control 7 yr follow-up: effect persists 4.3 vs 7.4 cases/100 person-yrs 10yr follow-up: no effect on CV or total mortality	1) 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 activity of 30 minutes/day or 150 minutes/week iv. Diet: healthy, low calorie, low fat (<30% of total kcal & <10% saturated fat), ↑ fibre (>15g/1000kcal).
	DPP 19 2.8yr, n=3,234 (Diabetes Prevention Project) {Troglitazone arm stopped early due to liver toxicity ²⁰ }	Age >25 (mean 51yrs); BMI ≥ 24 (mean=34); IGT (FBG of 5.3-6.9 mmol/L, 2hBG of 7.8-11 mmol/L.) 68% ♀; ~45% ethnic	Intensive lifestyle* n=1079 Lifestyle+ metformin 850mg po BID n=1073 Lifestyle + placebo n=1082, or *Lifestyle: ↓ weight by 7% (healthy diet & exercise ≥ 150 minutes/week), & 16 individualized lessons, covering diet, exercise & behaviour modification. {Low-cal diet: ↓450kcal/day ave; e.g. 1500kcal/d for 80-95kg ☺}	1°: incident diabetes (2.8yrs): 4.8 cases/100 person yrs for intensive lifestyle 7.8 cases/100 person yr metformin; 11 case/100 person yr placebo; ♦ NNT= 7 / 2.8yrs for lifestyle (RRR: 58%; 71% age 60+) ♦ NNT= 14 / 2.8yrs for metformin (MF) (RRR: 31%) Weight ↓: 5.6kg Lifestyle, 2.1kg MF, 0.1kg (p<0.001) 10yr follow-up: delays diabetes → lifestyle by 4yr, MF by 2yr	
	IDPP 21 (India) 2.5yr, n=531	Mean age 46yrs; BMI 26 IGT – in Asian Indians	Lifestyle vs metformin 250mg po BID vs control	1°: incident diabetes (2.5yrs): lifestyle 39.3%, NNT=6; metformin 40.5%, NNT=7; 55% control	
	Stop-NIDDM 22 3.3yr, n=1,429	Age 40-70 (mean 54yrs); IGT (2hBG ≥ 7.8 & <11.1mmol/L, FBG of 5.6-7.7 mmol/L).	Acarbose 100mg TID vs placebo {also encouraged exercise; met with dietitian}	1°: incident diabetes (3.3yrs): 32.4% vs 41.5%; NNT=11 / 3.3 yrs {↓ CV events 2.5%; NNT=40} 23 {GI SE's 83% vs 60%; Stop Tx: 31% vs 19%}	
	XENDOS 24 4yr, n=3,305	Age 30-60; (mean 43yrs); BMI ≥ 30; no CV disease; 21% had IGT	Orlistat 120mg TID vs placebo (weight loss study) {also ↓ calorie diet & physical activity encouraged.} {High drop-out rate.}	2°: incident diabetes: 6.2% vs 9% NNT=36/4yrs; ↓ diabetes in IGT subgroup only 18.8% vs 28.8% NNT=10 {1°: ↓ weight 5.8kg vs 3kg; ↑ GI SE's: 91% vs 65%/1yr}	
	DREAM-Rosi 25 3yr, n=5,269 {Canoe Rosi 2mg+MF500mg bid n=207 3.9yr, NNT=4}	Age ≥ 30yrs (~55yrs); IGT +/- IFG or IFG Mean FBG=5.8mmol/L No DM or CV disease (eligibility expanded during trial)	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=7/3yrs (driven by diabetes; no difference in death); CV events: 2.9% vs 2.1% HR=1.37; CI 0.97-1.94	
	DREAM-Rami 26 3yr, n=5,269		Ramipril 15mg po daily (start 5mg/d x2 months, then ↑ 10mg/d till 1 yr) vs placebo	1°: incident diabetes or death: 18.1% vs 19.5% NS {Also, no difference in CV event rate 2.6% vs 2.4%}	
NAVIGATOR 27 5yr	IGT & ↑ CV risk/disease	Nateglinide: no ↓ in progression to diabetes or ↓ CV event. Valsartan ↓ diabetes RR 14% but no CV benefit.			
*Prevention strategies that utilize drugs risk harming otherwise healthy people; knowledge of long term efficacy, safety & impact on healthcare resources need to be established. ¹⁷ † Note: early intensive insulin Tx (x2 wks) may induce remission in some new T2DM. ¹⁸					

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 ^{ADA}:

- 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.
- QDScore diabetes risk calculator: (UK Prediction Calculator for T2DM): <http://www.qdscore.org/>

Insulin Analogues Systematic Review/Reports, 2008: <http://www.cadth.ca/index.php/en/compus/insulin-analogs/reports>

Tight glucose control in critically ill hospitalized pts may ↑mortality & ↑↑risk of hypoglycemia. ^{JAMA'08; 31 Nice-Sugar NNH=38/90day}

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**^{7b} 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% ^{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,^{p860} 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 ^{UKPDS34 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. ^{UKPDS 35}
- In ADOPT, rosiglitazone decreased A1C more than 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).

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, may also be 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!

See also RxFiles Landmark Trials Chart: Summary of **Lipid, BP & ASA** diabetes related trials: <http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-DIABETES-Landmark-Trials-Non-Glucose.pdf>

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

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