

	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-mod 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 1° or 2° 1° Retinopathy: Δ Rate/100 pt yr NNT=100per pt yr RRR 63% 2° Microalb.: 1° ↓3.5 NNT=29 2° ↓4.1 NNT=24 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% Hypoglyc SEVERE ↑43 NNH=2.3; ↑Hosp 7.6% vs 4.9%	Type 1 Diabetes (ENDIT, nicotinamide & 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=9/1000-yr & 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.} ♦ glucose control offers predominantly microvascular benefit ♦ 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 ⁶ , 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%	♦ ↓ 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 >1° 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=30/2.9yr & edema.		
	ACCORD 7 ~3.5yrs; n=10,251	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%	♦ ↑ 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)						
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 11 : n=1791, ~5.6yr, Age ~60yr, ♂ mostly, T2DM x 11.5yrs; 40% CAD Hx (Veterans Affairs). Intensive vs standard A1C Achieved: 6.9% vs 8.4%. No significant effect on CV events, deaths 102 vs 95 or microvascular complications; but ↑ serious adverse events 17.6 vs 24.1% mostly hypoglycemia.							
* UKPDS 80: 10 year observational follow-up to UKPDS 33 & 34 (Sep08); glyemic 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 33.1 → 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 ΔBody 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 case/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	2) Pharmacological Options (+ some lifestyle measures) a. Effective but less so than intensive lifestyle* i. Metformin 250-850mg po BID (Meta-analysis ¹⁴) ♦ 6 trials, n=3119, abd. obesity, IGT, family hx: ↓ time to diabetes onset ≤ 3yrs; NNT=12.5 CI: 9.1-20 {better if age <60yr} ii. Orlistat 120mg po TID ♦ Effective if able to tolerate GI side effects; high cost >\$150/mo iii. Acarbose 100mg po TID (CV benefit did not persist) ♦ Effective if able to tolerate GI side effects; high cost >\$120/mo b. Not Effective or Harm/Outcome Concerns* i. Ramipril: not effective; valsartan ↓ diabetes RR 14%, not CV ii. Glitazones (Rosiglitazone & Pioglitazone): effective but concerns {↑wt, ↑ HF, ↑ fracture, & ?CV Rosi ^{15,16} } iii. Nateglinide: ↑ risk of hypoglycemia without any benefits
	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 dietician}	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	Age ≥ 30yrs (~55yrs); IGT +/- IFG or IFG Mean FBG=5.8mmol/l	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	No DM or CV disease (eligibility expanded during trial)	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.		

2hBG=2hr blood glucose BMI=body mass index CV=cardiovascular FBG=fasting blood glucose HC=hypercholesterolemia HF=heart failure hx=history IGT=impaired glucose tolerance MF=metformin PPBG=post-prandial blood glucose SU=sulfonylurea Tx=treatment wt=weight yr=year
Links: CDA Professional: <http://www.diabetes.ca/for-professionals/resources/2008-cpgp> ADA Prevention/delay of type 2 diabetes: http://care.diabetesjournals.org/cgi/content/full/30/3suppl_1/S4#SEC14. AACE Prediabetes link²⁸ NICE T2DM: <http://www.nice.org.uk/guidance/index.jsp?action=byD&id=11963> COMPUS: link²⁹ Ann Int Med: link³⁰ 30

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 observation that "with every one percent 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). Current evidence call this assumption into question.

- 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 that 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... (See also; <http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Targets-ACCORD-A1C.pdf>).
- 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,^{b860} 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!

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

¹ DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993 Sep 30;329(14):977-86.

² Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005 Dec 22;353(25):2643-53.

de Boer IH, Kestenbaum B, Rue TC, et al. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Insulin therapy, hyperglycemia, and hypertension in type 1 diabetes mellitus. Arch Intern Med. 2008 Sep 22;168(17):1867-73. Hyperglycemia is a risk factor for incident hypertension in type 1 diabetes, and intensive insulin therapy reduces the long-term risk of developing hypertension.

{Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-Day Clinical Course of Type 1 Diabetes Mellitus After 30 Years' Duration: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications Experience (1983-2005). Arch Intern Med. 2009;169(14):1307-1316.}

White NH, Sun W, Cleary PA, et al. Effect of Prior Intensive Therapy in Type 1 Diabetes Mellitus on 10-year Progression of Retinopathy in the DCCT/EDIC: Comparison of Adults and Adolescents. Diabetes. 2010 Feb 11.

Albers JW, Herman WH, Pop-Busui R, et al. for the DCCT/EDIC Research Group. Effect Of Prior Intensive Insulin Treatment During The Diabetes Control And Complications Trial (DCCT) On Peripheral Neuropathy In Type 1 Diabetes During The Epidemiology Of Diabetes Interventions, And Complications (EDIC) Study. Diabetes Care. 2010 Feb 11.

³ Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):837-53.

⁴ Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):854-65. Erratum.

- 5 Ohkubo Y, Kishikawa H, Araki E, Miyata T, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract.* 1995 May;28(2):103-17. (Kumamoto study)
- 6 Dormandy JA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study. (PROspective pioglitAzone Clinical Trial in macroVascular Events): a RCT. *Lancet.* 2005; 366: 1279-1289. [InfoPOEMs Aug 2008: Pioglitazone (Actos), unlike its chemical cousin rosiglitazone (Avandia), does not seem to increase the likelihood of cardiovascular events (N Engl J Med. 2007;356:2457-2471). The researchers conducting this study stretched -- and broke -- the scientific method when claiming benefit, but any claims of benefit are specious. (LOE = 1a-)]
- 7 Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008 Jun 12;358(24):2545-59. {RxFiles Trial Summary: [ACCORD](#)} Miller ME, Bonds DE, Gerstein HC, et al. [ACCORD](#) Investigators. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ.* 2010 Jan 8;340:b5444. doi: 10.1136/bmj.b5444.
- 8 Patel A; ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, Woodward M, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet.* 2007 Sep 8;370(9590):829-40. {RxFiles Trial Summary: [ADVANCE](#) <http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-ADVANCE-trial.pdf>} Zoungas S, de Galan BE, Ninomiya T, et al. on behalf of 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.
- 9 Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. (STENO-2) *N Engl J Med.* 2008 Feb 7;358(6):580-91.
- 10 UGDP.
- 11 Duckworth W, Abraira C, Moritz T, et al. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. *N Engl J Med.* 2008 Dec 17. (VADT study) Intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications. [InfoPOEMs Mar09: Like the ACCORD and ADVANCE studies, this trial provides additional evidence that intensive glucose control does not improve outcomes in patients with type 2 diabetes mellitus. It is important to note that these patients had well-controlled hypertension (mean blood pressure = 126/68) and well-controlled hyperlipidemia (mean low-density lipoprotein = 80 mg/dL.)]
- 12 Holman R, Sanjoo 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 RR=0.85 \(CI: 0.74-0.97\); ↓ Death 30.3⇒26.8 per 1000 patient-yrs RR=0.87 \(CI: 0.79-0.96\); \(MF vs control: ↓ MI, 21.1⇒14.8 per 1000 patient-yrs RR=0.67 \(CI: 0.51-0.89\); ↓ Death 33.1⇒25.9 per 1000 patient-yrs RR=0.73 \(CI: 0.59-0.89\)\)}](#) {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 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)"}]
- 13 Lindstrom J, Ilanne-Parikka P, et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *The Lancet.* 2006; 368:1673-1679.
- 14 Uusitupa M, Peltonen M, Lindström J, et al. 2009 Ten-Year Mortality and Cardiovascular Morbidity in the Finnish Diabetes Prevention Study—Secondary Analysis of the Randomized Trial. *PLoS ONE* 4(5): e5656. doi:10.1371/journal.pone.0005656.
- 15 Salpeter SR, Buckley NS, Kahn JA, Salpeter 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)]
- 16 Nissen SE, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. *N Engl J Med.* 2007 May 21; [Epub ahead of print] <http://content.nejm.org/cgi/content/full/NEJMoa072761>
- 17 ACT-NOW: preliminary report positive results with pioglitazone in IGT; ↓progression to T2DM but ↑weight & edema.
- 18 Montori VM, Isley WL, Guyatt GH. Waking up from the DREAM of preventing diabetes with drugs. *BMJ* 2007;28:334(7599):882-4. Accessed online: <http://www.bmj.com/cgi/content/extract/334/7599/882>
- 19 Weng J et al. Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: A multicentre randomised parallel-group trial. *Lancet* 2008 May 24; 371:1753.
- 20 Knowler WC, Barret-Connor E, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. (DPP trial) *N Engl J Med.* 2002; 346: 393-403.
- 21 Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet.* 2009 Nov 14;374(9702):1677-86.
- 22 Knowler WC, Hamman RF, Edelstein SL, et al. Prevention of type 2 diabetes with troglitazone in the diabetes prevention program. *Diabetes.* 2005; 54: 1150-1156.
- 23 Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V; Indian Diabetes Prevention Programme (IDPP). *Diabetologia.* 2006 Feb;49(2):289-97. Epub 2006 Jan 4. n=531 over 2.5yrs
- 24 Ramachandran A, Snehalatha C, Mary S, Selvam S, Kumar CK, Seeli AC, Shetty AS. Pioglitazone does not enhance the effectiveness of lifestyle modification in preventing conversion of impaired glucose tolerance to diabetes in Asian Indians: results of the Indian Diabetes Prevention Programme-2 (IDPP-2). *Diabetologia.* 2009 Mar 10. [Epub ahead of print]
- 25 Chiasson JL, Josse RG, et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomized trial. *The Lancet.* 2002; 359: 2072-2077.
- 26 Chiasson JL, Josse RG, Gomis R, et al. Acarbose Treatment and the Risk of Cardiovascular Disease and Hypertension in Patients with Impaired Glucose Tolerance: The STOP-NIDDM Trial. *JAMA* 2003; 290(4): 486-494.
- 27 Torgerson JS, Boldrin MN, et al. XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study. *Diabetes Care.* 2004; 27: 155-161.
- 28 DREAM (Diabetes REDUction Assessment with ramipril and rosiglitazone Medication) Trial Investigators; Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet.* 2006 Sep 23;368(9541):1096-105. Erratum in: *Lancet* 2006;18;368:1770.
- 29 DREAM Trial Investigators; Bosch J, Yusuf S, Gerstein HC, et al. Effect of ramipril on the incidence of diabetes. *N Engl J Med.* 2006 Oct 12;355(15):1551-62. Epub 2006 Sep 15.
- 30 NAVIGATOR Study Group. Effect of Nateglinide on the Incidence of Diabetes and Cardiovascular Events. *N Engl J Med* 2010 0: NEJMoa1001122. NAVIGATOR Study Group, Effect of Valsartan on the Incidence of Diabetes and Cardiovascular Events. *N Engl J Med* 2010 0: NEJMoa1001121.
- 31 AACE: THE DIAGNOSIS AND MANAGEMENT OF PRE-DIABETES IN THE CONTINUUM OF HYPERGLYCEMIA. July 2008. Accessed online at: <http://www.aace.com/meetings/consensus/hyperglycemia/hyperglycemia.pdf>
- 32 Canadian Optimal Medication Prescribing & Utilization Service (COMPUS), Current Topics, Diabetes: <http://cadth.ca/index.php/en/compus/current-topics-dm1> (www.cadth.ca)
- 33 Montori V, Fernandez-Balsells M. Glycemic Control in Type 2 Diabetes: Time for an Evidence-Based About Face? *Ann Int Med* 2009; 150(11). Available at: <http://www.annals.org/cgi/content/full/0000605-200906020-00118v1> on 2009 Apr 21.
- 34 Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA.* 2008 Aug 27;300(8):933-44. In critically ill adult patients, tight glucose control is not associated with significantly reduced hospital mortality but is associated with an increased risk of hypoglycemia.
- 35 Arabi YM, Dabbagh OC, Tamim HM, et al. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. *Crit Care Med.* 2008 Dec;36(12):3190-7.
- 36 NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* 2009 Mar 26;360(13):1283-97. Epub 2009 Mar 24. In this large, international, randomized trial, we found that intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter.
- 37 Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ; RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet.* 2009 Jun 20;373(9681):2125-35. {Commentary & limitations: <http://www.medscape.com/viewarticle/704038>}
- 38 Komajda M, McMurray JJ, Beck-Nielsen H, et al. Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial. *Eur Heart J* 2010; DOI: 10.1093/eurheartj/ehp604.
- 39 Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009;373:2125-2135.

Additional References

[ADA-American Diabetes Association Guidelines- Standards of Medical Care in Diabetes—2010](#) http://care.diabetesjournals.org/content/33/Supplement_1/S11.full.pdf+html

[ADA, ACC & AHA Position Statement](#) - Intensive Glycemic Control & the prevention of CV Events - Jan/2009 Implications of ACCORD, ADVANCE & VA Diabetes Trials (ePublished - accessed Dec 30, 2008)

<http://care.diabetesjournals.org/misc/finaldc9026.pdf>

- BMJ 2009;338:b800. Mar 2009. Editorials: **Tight control** of blood glucose in long standing type 2 diabetes. Accessed at http://www.bmj.com/cgi/content/full/338/mar05_2/b800?ct
- Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. *Diabet Med.* 2009;26:142-8. {InfoPOEMs Apr09: This meta-analysis found no evidence to support the contention that diabetes alone is a coronary heart disease (CHD) risk equivalent to a history of prior myocardial infarction (MI). The blanket use of aspirin and statins for patients with type 2 diabetes, regardless of their lipid levels, is not supported by the evidence. (LOE = 2a)}
- DeFronzo RA, Banerji M, Bray GA, et al. Actos Now for the prevention of diabetes (**ACT NOW**) study. *BMC Endocr Disord.* 2009 Jul 29;9:17. (pioglitazone)
- Franks, Paul W., Hanson, Robert L., Knowler, William C., et al. **Childhood Obesity, Other Cardiovascular Risk Factors, and Premature Death.** *N Engl J Med* 2010 362: 485-493.
- Haynes RB, Haynes GA. What does it take to put an ugly fact through the heart of a beautiful hypothesis? *Evid Based Med.* 2009 Jun;14(3):68-9. <http://ebm.bmj.com/cgi/content/full/14/3/68?linkType=FULL&journalCode=ebmed&resid=14/3/68>
- Hippisley-Cox J, Coupland C, Robson J, Sheikh A, Brindle P. Predicting risk of type 2 diabetes in England and Wales: prospective derivation and validation of QDScore. *BMJ.* 2009 Mar 17;338:b880. doi: 10.1136/bmj.b880.
- Holman, Rury R., Farmer, Andrew J., Davies, Melanie J., et al. the 4-T Study Group. **Three-Year Efficacy of Complex Insulin Regimens in Type 2 Diabetes.** *N Engl J Med* 2009 0: NEJMoa0905479.
- Kahn HS, Cheng YJ, Thompson TJ, Imperatore G, Gregg EW. Two risk-scoring systems for predicting incident diabetes mellitus in U.S. adults age 45 to 64 years. *Ann Intern Med.* 2009 Jun 2;150(11):741-51. Basic information identified adults at high risk for diabetes. Additional data from fasting blood tests better identified those at extreme risk.
- Kawamori R, Tajima N, et al. Voglibose Ph-3 Study Group. Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. *Lancet.* 2009 May 9;373(9675):1607-14.
- 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.
- Montori V, Fernandez-Balsells M. Glycemic Control in Type 2 Diabetes: Time for an Evidence-Based About Face? *Ann Int Med* 2009; 150(11). Available at: <http://www.annals.org/cgi/content/full/0000605-200906020-00118v1> on 2009 Apr 21.
- Mozaffarian D, Kamineni A, Carnethon M, et al. Lifestyle risk factors and new-onset diabetes mellitus in older adults. *Arch Intern Med* 2009; 169:798-807.
- Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomized controlled trials. *Lancet* 2009; 373: 1765-72.
- Rosenstock J, Klaff LJ, Schwartz S, et al. Effects of Exenatide and Lifestyle Modification on Body Weight and Glucose Tolerance in Obese Subjects With and Without Prediabetes. *Diabetes Care.* 2010 Mar 23. n=152 over 24weeks.
- Saitz R. How Much Evidence Do We Need to Change Practices in Which We Firmly Believe? Enough already! Randomized trials show that tight glucose control in patients with long-standing type 2 diabetes isn't beneficial. <http://general-medicine.jwatch.org/cgi/content/full/2009/730/1#R9>
- Zinman B, Harris SB, Gerstein HC, Young TK, Raboud JM, Neuman J, Hanley AJ. Preventing type 2 diabetes using combination therapy: design and methods of the CANadian Normoglycaemia Outcomes Evaluation (CANOE) trial. *Diabetes Obes Metab.* 2006 Sep;8(5):531-7.