DIABETES LANDMARK OUTCOME TRIALS: Glycemic Control & Prevention Summary

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Type 1 (T1DM)

Trials Mean follow-up	Population Risk, hx, age	Intervention	A1C: baseline⇨final	Results
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 CVD, ↑BP, ↑TC, 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 3AM 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° / △ 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%
DCCT / EDIC [2] ~17yrs; n=1,394 for CV	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)

Trials Mean follow-up	Population Risk, hx, age	Intervention	A1C: baseline⇨final	Results
UKPDS-33 [3] ✦ ~10yrs; n=3,867	New T2DM; Age 54; with FPG 6.1-15 on diet alone	Intensive SU or insulin vs diet. Target FBG <6mmol/L vs <15mmol/L	median 7%⇨ 7% over 10yr vs 7.9%	◆↓microvascular endpoints NNT=42/10yr; mostly retinal ◆↔CV events✦ ◆↑ hypoglycemia esp insulin
UKPDS-34 [9] ✦ ~10.7yrs; n=1,704	Obese T2DM; Age 53 Wt=87kg; BMI=31	Metformin 1700mg am, 850mg pm vs conventional (diet mostly)	7%⇨7.4% median/10yr vs 8%	◆↓diabetes endpoint NNT=10/10yr (RRR=32%) ✦ ◆↓ all-cause death NNT=14/10yr; ↓stroke NNT=48/10yr
Kumamoto [10] 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 [11] ~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 [12] ~3.5yrs; n=10,251; ↑death @5yr & ↑CV death @9yr f/u	High CV risk; ~10yr hx T2DM; Age 62; 93kg; North American	Intensive A1C target <6% {most on 3 OAHAs + 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 [13] Follow-up ADVANCE-ON~10yr ~5yrs; n=11,140 No macrovasc benefit @>5yr follow-up	Hx of CVD; 8yr hx T2DM; age 66; 78kg; Austral-Asian/European	Intensive A1C target 6.5% {most on SU (gliclazide MR) + MF} vs standard A1C target ~ 7%	7.5%⇨6.5% vs 7.3%	◆↓ microvascular events/5yrs, NNT=67/5yr; post-hoc analysis ↓ ESRD NNT=410 /5yr overall. ↑severe hypoglycemia NNH=83/5yr; minimal wt change

STENO-2 [14]: 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 f/u;⇨ ↓ death, NNT=5 / 13.3yr p=0.02, ↓ macro & microvascular events. (Only 1 pt achieved all 5 targets at 13yrs). 21yr f/u⇨ 7.9yrs gained

ADDITION-Europe [32]: n=3057 new T2DM, age ave ~60; 5.3yrs; multifactorial intensive (A1C, BP, ACEI, TC, lifestyle) ⇨slightly improved 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) & microvasc complications.

UGDP [15]: (1971) n=1027; ~8yrs; T2DM. Tolbutamide ↑ CV mortality 2.9x; 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 (2008) [16]: n=1791, ~5.6yr, Age~60yr, ♂ mostly, T2DM x 11.5yr; 40% CAD Hx veterans). Intensive vs standard A1C Achieved: 6.9 vs 8.4%. NS effect: CV event, death 102 vs 95 or microvascular complications; but ↑SAE 17.6 vs 24.1% eg. hypoglycemia. ↑CVD risk if DBP<70. 10yr follow-up: some ↓CV events, not mortality. 2015

ORIGIN: n=12,537, 6.2yr, Age~63yr, ♂ ~63%, early x ~5.5yr T2DM^80%, or *pre-diabetes*; 59% CAD Hx. Early basal insulin *glargine* vs standard *non-glargine*; A1C 6.4→ 6.5 vs 6.2%. NS effect: CV death & non-fatal MI/stroke; ↓/delay new DM NNT=13 / 6.2yrs; ↑ hypoglycemia, ↑wt~2kg; ↔ ca. [2x2 factorial n-3 fatty acids NS]

SAVOR-TIMI 53 [33]: n=16,492, 2.1yr, Age ~65, T2DM hx ~10yr + CVD/risk, A1c 8→7.7%; saxagliptin 5mg po daily vs Pl; CV neutral. Harms:↑ hospitalization for HF NNH=143.

EXAMINE [34]: n=5,380, ~1.5yr, Age ~61, T2DM hx ~7yr + recent ACS event, A1c 8→7.7%; alogliptin 25mg po daily vs Pl.; CV neutral. Harms: none. SAE ↔.

TECOS [35]: n=14,671, ~3yr, Age ~65, T2DM hx ~12yr + CVD, A1c 7.2→6.9%; sitagliptin 100mg po daily vs Pl.; CV neutral. Harms: none. SAE ↔.

ELIXA [36]: n=6068, ~2.1yr, Age ~60, T2DM hx ~9.3yr + recent ACS event, A1c 7.7→7.4%; lixisenatide 10-20mcg SC daily; CV neutral; ↓wt 0.7kg; ↑AE leading to DC NNH=24; SAE↔

SUSTAIN-6 [37]: n=3297, ~2.1yr, Age ~65, T2DM hx ~14yr +CVD/risk, CKD, A1c 8.7→7.3-7.6%; semaglutide 0.5-1mg SC/wk; ↓CV events NNT=43; ↓wt 3-4kg; ↑retinopathy NNH=83.

LEADER [38]: n=9340, 3.8yr, Age ~64, T2DM hx ~13yr + CVD/risk, CKD, A1c 8.7→7.6% vs 8%; liraglutide 0.6-1.8mg SC daily vs Pl; Benefits /3.8yr: ↓ CV or death NNT=53, ↓ all-death NNT=72 , ↓ wt 2.3kg, ↓ nephropathy NNT=67, ↓ severe hypoglycaemia NNT=111; Harms: ↑ gallbladder dx NNH=84, ↑ AE leading to DC (mostly GI) NNH=46. SAE ↔

EMPA-REG [39]: n=7020, ~3.1yr, Age ~63; T2DM hx 57% >10yr; + CVD; A1c 8% →7.5% at 12wk & 7.8% overtime; empaglifozin 10mg or 25mg po daily; Benefits /3.1yr: ↓ CV event NNT=63, ↓ all-death NNT=39, ↓ wt ~1-2kg, ↓ AE leading to DC NNT=48, ↓ SAE NNT=24; Harms: genital infection ♀ NNH=14, ♂ NNH=29. Benefit similar with 10mg dose as 25mg. Of note: benefit seen at relatively high A1c levels (7.5-7.8%); BP was slightly lower in empaglifozin group (3-4 / 1-2).

T2DM Prevention

FDPS [17]: 4yr, n=522, Age ~55; Intensive lifestyle vs control. (Detailed, individualized counseling with nutritionist; individualized exercise circuit. Goal setting. 1°: incident diabetes (4yrs): 11% vs 23%, RRR= 58%, HR = 0.4 (0.3-0.7) NNT/4yrs =8; 10yr follow-up saw no effect on CV or total mortality

DPP (Diabetes Prevention Project) [18]: 2.8yr, n=3,234; Age ~51. Arms: 1) Intensive lifestyle: ↓ wt by 7% (diet, exercise, education/behaviour modification); 2) Lifestyle + MF 850mg po BID; 3) Lifestyle + placebo; 4) Troglitazone (stopped early due to liver toxicity). Intensive lifestyle best, followed by MF. Outcomes vs lifestyle +placebo: 1) Intensive lifestyle: NNT= 7 / 2.8yrs for intensive lifestyle (RRR: 58%; 71% age 60+); 2) MF: NNT= 14 / 2.8yrs for MF (RRR: 31%) Other outcomes of interest: Weight ↓: 5.6kg Lifestyle, 2.1kg MF, 0.1kg (p<0.001) ; 10yr follow-up: delays diabetes⇒lifestyle by 4yr, MF by 2yr

IDPP [19]: India 2.5yr, n=531. Lifestyle vs MF 250mg po BID vs control; 1°: incident diabetes (2.5yrs): lifestyle 39.3%, NNT=6; MF 40.5%, NNT=7; 55% control.

Stop-NIDDM [20]: 3.3yr, n=1,429. Acarbose 100mg TID vs placebo {also encouraged exercise; met with dietitian}; Benefits: ↓ T2DM & ↓ CV events; 1°: incident diabetes (3.3yrs): 32.4% vs 41.5%; NNT=11 / 3.3 yrs {↓CV events 2.5%; NNT=40}[21] . Harms: GI AEs 83% vs 60% & stopped Tx: 31% vs 19%

XENDOS [22] Orlistat 120mg TID vs placebo, weight loss study; also ↓calorie diet & ↑ physical activity; high drop-out rate, ↑GI AE's. incident diabetes NNT=36/4yrs

DREAM-Rosi [23]: 3yr, n=5,269; Rosiglitazone 8mg po daily vs pl; {RCT stopped 5months early due to ↓ diabetes NNT=7 /3yr; but trend ↑ CV events, HR=1.37; CI 0.97-1.94}

DREAM-Rami [24]: 3yr, n=5,269; Ramipril 15mg po daily (start 5mg/d x2 months, then ↑10mg/d till 1 yr) vs pl. 1°: incident diabetes or death: 18.1% vs 19.5% NS

NAVIGATOR [25]: Nateglinide: no ↓ in progression to diabetes or ↓CV event. Valsartan ↓ diabetes RR 14% but no CV benefit (5 yr)

Summary of RCT Outcome Evidence

Type 1 Diabetes (T1DM)

{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 △ 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 level.)
- ↑severe hypoglycemia including coma/ seizures NNH=9 /100pt-yr & hospitalizations 54 vs 36
- ↓ in macro- & micro-vascular GFR complications in long-term follow up ~17yrs; ↓mortaliy ~27yrs NNT=37; but limitations such as unmasking & intermediate endpoints bias results.

Type 2 Diabetes (T2DM)

- intensive glucose control may ↑ or ↓ risk depending on type of patient & treatment {e.g. in ACCORD, intensive A1C lowering associated with ↑ death; no benefit in VADT; ADVANCE, not quite as intensive tx ok; ✦ UKPDS 33,34 show variability between tx choice, extent of ↓A1C & outcomes.}
- BG control⇨ microvascular benefit ADVANCE, ADVANCE-ON & UKPDS; not ACCORD
- metformin - in new, obese T2DM: ↓CV events & all-cause death without ↑ weight or hypoglycemia UKPDS-34, 80; - ↓CV events vs glipizide SPREAD-DIMCAD ✦
- empaglifozin – in those with established CV disease: ↓CV events & all-cause death EMPA-REG (only SGLT-2 inhibitor drug studied; positive outcomes)
- liraglutide – in established CV disease or high risk: ↓CV events & all-cause death LEADER; Scale (Semeglutide also ↓CV events, but lixisenatide neutral.)
- gliptins (DDP-4i): neutral on CV outcomes; however some variability re harms: saxagliptin & CV events "↔", but ↑ admission for HF SAVOR-TIMI 53;
- pioglitazone ↓CV events (2° outcome, statistical concerns)[6], but ↑ HF, wt, fracture. SR-Liao {rosiglitazone: ↑HF, wt, fractures; uncertain CV outcomes (neutral in RECORD, but limitations: see online)} 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 {ramipril 10mg/d MICROHOPE}. Lifestyle alone ineffective/10yr Look AHEAD

Type 2 Diabetes (T2DM) - PREVENTION (see Online Extras)

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, **150 minutes/wk** or 30 minutes/day
     - iv. Diet: healthy, low calorie, low fat (<30% of total kcal & <10% saturated fat), ↑ fibre (>15g/1000kcal).

   [Chinese 6yr study & 23yr follow-up: ↓ death NNT=10 Da Qing DPS]

2) **Pharmacological Options** (+ some lifestyle measures)
   - a. Effective but less so than intensive lifestyle*
     - i. **Metformin (MF)** 250-850mg po BID (Meta-analysis[4])
       - 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 <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 delay, not prevent after D/C; concerns {↑wt, edema, ↑HF, ↑fracture, (& ?CV Rosi)}[5,6]
     - ii. Glitazones (Rosi- & Pio-glitazone ACT NOW n=602; 2.4yrs; IRIS): effective
     - iii. Nateglinide: ↑ risk of hypoglycemia without any benefits

*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.[7]}

Of note: early intensive insulin Tx (x2 wks) may induce remission in some new T2DM.[8]

✦ **UKPDS 80**: 10 year observational follow-up to UKPDS 33 & 34 (Sep/08): 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 33.1⇨25.9 per 1000 patient-yrs.} [26]

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 NS=non-sig PPBG=post-prandial blood glucose SAE=serious adverse events SU=sulfonylurea Tx=treatment wt=weight yr=year

Links: CDA Professional: http://guidelines.diabetes.ca/fullguidelines ADA Type 2 diabetes: http://care.diabetesjournals.org/content/37/Supplement_1.toc . AACE Prediabetes link[27] NICE T2DM: http://www.nice.org.uk/guidance/CG87 COMPUS: link [28] Ann Int Med: link [29]

EXTRAS Page for Diabetes Landmark Outcome Trials: Glycemic Control & Prevention Summary

T2DM "Prevention" Trials *Pre-diabetes*		Intervention	Results {Note: *delay* may be better term than *prevent*}	Summary {Note: "prevention of DM" is a non-clinical outcome.}
Effective Options	**FDPS** 4yr, n=522 (Finnish Diabetes Prevention Study)	Age 40-65 (mean 55); 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: ↓ wt >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 7.4cases/100 person-yrs 10yr follow-up: no effect on CV or total mortality
	DPP 2.8yr, n=3,234 (Diabetes Prevention Project) [Troglitazone arm stopped early due to liver toxicity[35]]	Age >25 (mean 51); 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+ MF 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 MF; 11 case/100 person yr placebo, ◆NNT= 7 / 2.8yrs for lifestyle (RRR: 58%; 71% age 60+) ◆NNT= 14 / 2.8yrs for 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 (India) 2.5yr, n=531	Mean age 46; BMI 26 IGT – in Asian Indians	Lifestyle vs MF 250mg po BID vs control	1°: incident diabetes (2.5yrs): lifestyle 39.3%, NNT=6; MF 40.5%, NNT=7; 55% control
	Stop-NIDDM 3.3yr, n=1,429	Age 40-70 (mean 54); 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}[36] {GI AEs 83% vs 60% & stopped Tx: 31% vs 19%}
	XENDOS 4yr, n=3,305	Age 30-60;(mean 43); BMI≥30; no CVD; 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°: ↓wt 5.8kg vs 3kg; ↑ GI AE's: 91% vs 65%/1yr}
	DREAM-Rosi 3yr, n=5,269 {CANOE Rosi 2mg+MF500mg bid n=207 3.9yr, NNT=4}	Age ≥30 (~55); IGT +/- IFG or IFG Mean FBG=5.8mmol/l No DM or CVD (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 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 {↔CV event rate 2.6% vs 2.4%}
	NAVIGATOR 5yr	IGT & ↑CV risk/disease	Nateglinide: no ↓ in progression to diabetes or ↓CV event. Valsartan ↓diabetes RR 14% but no CV benefit.	

Summary

3) **Intensive Lifestyle Interventions** ✓
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   - **b.** How intensive was *intensive lifestyle*?
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     - i. **Metformin (MF)** 250-850mg po BID (Meta-analysis[30])
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Links: CDA Professional: http://guidelines.diabetes.ca/fullguidelines ADA Type 2 diabetes.· http://care.diabetesjournals.org/content/37/Supplement_1.toc . AACE Prediabetes link[37] NICE T2DM: http://www.nice.org.uk/guidance/CG87 COMPUS: link[38] Ann Int Med: link[39]

Other Trials of Interest

- EXAMINE: alogliptin after ACS in T2DM – aloglyptin not inferior to placebo for major CV in high-CV risk patients. White WB, Cannon CP, Heller SR, Nissen SE, et al; the EXAMINE Investigators. Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes. N Engl J Med. 2013 Sep 2.

- 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

- RECORD [31]: 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);

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; 40 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 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=1.11;0.86-1.43); non-fatal MI: ↓ (RR=0.85, 0.74-0.96);
  Severe hypoglycaemia: ↑↑ (RR=2.33, 1.62-3.36) 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); photocoagulation (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 disconcordence 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 idolatry of the surrogate. BMJ. 2011 Dec 28;343:d7995. http://www.bmj.com/content/343/bmj.d7995

Multfactorial 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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