ADVANCE Trial [1,2,3]: Is intensive glucose control with a gliclazide based regimen better than standard glucose control with a non-gliclazide based regimen in high risk, but not too hard to control T2DM?

Trial Methodology

- **Who was in the trial?** n=11,140; ~8yr hx of T2DM; age 66yr; 42%♀; mean A1C: 7.5%; FBG=8.5mmol/L; weight=78kg [BMI=28] only 4% North American; 32% had hx of CV disease; all survived a 6wk pre-trial run-in period (13.5% withdrew after run-in)
  - Inclusion: age 55+ yrs; T2DM onset at age ≥30; a history of macrovascular or microvascular disease or 1+ additional risk factors
  - Exclusion: definite indication for, or contraindication to, any study treatments or a definite indication for long-term insulin at time of study entry (also, of 12,877 registered for a 6 week run in period; 13.5% withdrew & 11,140 went on to study randomization)
- **A1C Target:** Intensive group: ≤6.5%; Standard group: ~7% depending on local guidelines; randomized controlled; not blinded.
- **Intervention drugs:** Gliclazide modified release [90%vs <2%] {DIAMICRON MR 30 to 120mg [70.4% @ 120mg dose ($170/month)]} + other drugs {other sulfonylureas [2% vs 57%]; sequential addition of metformin [74% vs 67%], glitazones [17% vs 11%], acarbose [19% vs 13%], insulin [40% vs 24%] basal +/- short acting insulin}
  - Intensive patients also had 31 study visits compared to 11 for standard group (3x more contact with health providers)
  - 2x2 factorial design (other arm of trial, perindopril + indapamide vs placebo previously published [Patel, Lancet 2007 4])
- **Primary (1°) Endpoints:** Composites of major macrovascular (CV death, non-fatal MI/stroke) & major microvascular events (new/worsening nephropathy or retinopathy). {1° endpoints reviewed by independent End Point Adjudication Committee; blinded.}
- **Sponsored by:** Servier but investigators independent. **Conducted in:** Asia [37%], Australasia [13%], Europe [45%], North America [4%].

Results – after 5 years follow-up

Outcome (1°, 2°, other) {color denotes risk or benefit}	**Intensive A1C Tx** n=5571	**Standard A1C Tx** n=5569	**ARR / ARI** over ~5yrs	**NNT/NNH** over ~5yrs	**HR, (95% CI); p-value** (taken from trial)
A1C Achieved	6.5%	7.3%	-	-	-
Macro or Microvascular Event (1°)	1009 (18.1%)	1116 (20.0%)	↓ 1.9%	53 CI: 30-226	0.90, (0.82-0.98) p=0.01
Major MACROvascular Events (1°) {CV death, nonfatal MI, nonfatal stroke}	557 (10%)	590 (10.6%)	↓ 0.6%	ns	0.94, (0.84-1.06) p=0.32
Major MICROvascular Events (1°) {nephropathy, retinopathy}	526 (9.4%)	605 (10.9%)	↓ 1.5%	67 CI: 38-264	0.86, (0.77-0.97) p=0.01
Death – all cause	498 (8.9%)	533 (9.6%)	↓ 0.7%	ns	0.93, (0.83-1.06) p=0.28
Death – CV associated	253 (4.5%)	289 (5.2%)	↓ 0.7%	ns	-
Nephropathy: new/ worsening (UA:Cr or ↑SCr) *	230 (4.1%)	292 (5.2%)	↓ 1.1%	91 CI: 53-314	0.79, (0.66-0.93) p=0.02
MACROalbuminuria: new/worsening	(2.9%)	(4.1%)	↓1.2%	83 CI: 53-193	0.70, (0.57-0.85) p<0.001
MICROalbuminuria: new onset	1318 (23.7%)	1434 (25.7%)	↓ 2%	50 CI: 28-251	0.91, (0.85-0.98) p=0.02
Retinopathy	332 (6%)	349 (6.3%)	↓0.3%	ns	-
Hospitalization – any cause	2501 (44.9%)	2381 (42.8%)	↑ 2.1%	42 CI: 25-388	1.07, (1.01-1.13); p=0.03
Hypoglycemia – Severe Severe; events per 100 patient yr Minor; events per 100 patient yr	150 (2.7%) 0.7 (or 3.5 / 5yr) 120 (or 600 / 5yr)	81 (1.5%) 0.4 (or 2 / 5 yr) 90 (or 450 / 5yr)	↑ 1.2%	83 CI: 58-150	1.86, (1.42-2.40) p<0.001 [↑ hospitalizations due to severe hypoglycemia: 1.1% vs 0.7% p=0.04]
Weight loss (mean)	Loss of ~ 0.1kg	Loss of ~ 1kg	-	-	{↑ 0.7kg vs standard Tx}

only surrogate renal endpoints stat signif. A1C=glycosylated hemoglobin CI 95%= confidence interval CV=cardiovascular FBG=fasting blood glucose HR=Hazard ratio NNT= number needed to treat to benefit one NNH= number needed to treat to harm one (both values calculated from raw event rates) ns=non-significant [Of interest, intensive group had 2mmHg lower systolic BP (perhaps due to more provider contact?]

Considerations

- **Limitations**: treatment group had about 3x as much contact with health care providers; population 96% non-North American
- **Compared to ACCORD**: ADVANCE patients were **less obese** [baseline weight: 78kg vs 93.5 kg], had **less weight gain** [0.7 vs 3.5kg], had shorter hx of T2DM [8yr vs 10yr,] had a **lower baseline A1C** [7.5% vs 8.3%], & were **less likely to end up on insulin** [40% vs 77%], aspirin [57% vs 76%], statins [46% vs 88%] or **glitazones** [17% vs 91%]. Overall aggressiveness of drug regimens/dosages was less in ADVANCE. {in ACCORD, the aggressive A1C target group (target ≤6%; achieved 6.4%) was halted due to ↑ all cause death (NNH=95). See RxFiles ACCORD Trial Summary}
- **What we knew**: - glucose control & ↓ A1C levels do not always reduce heart, stroke & death endpoints. [UKPDS-33, ACCORD, VADT, etc.]
  - glucose control does ↓ microvascular endpoints somewhat [UKPDS-33 (retinal)] with an ↑ risk of hypoglycemia
- **What we still don't know**: - Does gliclazide offer outcome advantages or disadvantages compared to other sulfonylureas?
  - What are the prime factors that predict likelihood of ↑ risk [e.g. ACCORD] vs benefit with aggressive hypoglycemic regimens?
  - Would we see benefits or risks on CV or death endpoints if we were able do a study over a longer time frame?
- **Want more "bang for the buck" & less adverse events?**: Consider BP meds [Micro-HOPE], statin [CARDS/HPS], ASA & lifestyle.

What this study adds - *Bottom Line*

- **In ADVANCE type patients, pursuing an A1C of ≤ 6.5% over 5 yrs** (with most patients on gliclazide + metformin) **is associated with:**
  - **a reduction in major microvascular events, particularly nephropathy, in 1 out of 67 patients**
  - **an ↑ risk of severe hypoglycemia** in 1 out of 83 patients **& an ↑ rate of hospitalization** in 1 out of 42 patients
  - **no benefit or risk on macrovascular outcomes (MI, CV death, non-fatal stroke) or all-cause death**
- Taking into consideration both the ACCORD and ADVANCE trials, any discussion of proposed A1C targets will need to consider the patient, the risks of the disease and the adverse effects of the treatment intervention. Lowering A1C by 1% may be associated with benefit or risk (automatic benefit often quoted based on epidemiologic data can not be assumed).

Individualize therapy. Let the target serve the patient, not the patient the target!

2016, Dec - Update: ADVANCE-ON Follow-up Trial

- 8,494 ADVANCE participants followed for median of 5.4 additional years
- In-trial A1C differences disappeared by first post trial visit
- Reduction in ESKD persisted after 9.9 years; 29 vs 53 events; HR 0.54, p <0.01
  - Effect greater in earlier stange CKD, and at lower baseline SBP.
- No macrovascular benefit seen (e.g. death, CV death, major CV event)

Related RxFiles Links:

- Diabetes Hypoglycemics Drug Comparison Chart (from book): http://www.rxfiles.ca/acrobat/cht-diabetes.pdf
- Avandia & CV Controversies Q&A: http://www.rxfiles.ca/acrobat/Diabetes-Avandia-CV-Meta-Comments.pdf
- For more, see www.RxFiles.ca

References continued from Page 1.

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[4] Patel A; ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, Poulter N, Marre M, Cooper M, Glasziou P, Grobbee DE, Hamet P, Heller S, Liu LS, Mancia G, Mogensen CE, Pan CY, Rodgers A, Williams B. 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. 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.