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Supplementary information

The trials and tribulations of determining HbA_{1c} targets for diabetes mellitus

In the format provided by the authors and unedited

Study (year)	Diabetes type	Length of follow-up (years)	Intensive glycemic control target		Mean age at baseline (years)	Mean diabetes duration (years)	Baseline HbA1c (%)	Achieved HbA1c (%)	Microvascular outcomes	Macrovascular events	Mortality	Adverse events
DCCT (1993)[1]	T1D	median: 6.5	HbA1c <6.05%	primary intervention cohort (no retinopathy)	26 (standard) vs. 27 (intensive)	2.6	mean: 8.8	mean: 7.4 vs 9.1	Sustained retinopathy: RRR 76% (95% CI, 62-85) Microalbuminuria >40mg/24hr: RRR 34% (95% CI, 2-56) Neuropathy: RRR 69% (95% CI, 24-87)	No significant difference	No significant difference	Hypoglycemia: 62 per 100 patient years (intensive) vs 19 per 100 patient-years (conventional) Weight gain: 33% (intensive) vs 9.3% (conventional)
				secondary intervention cohort (baseline retinopathy)	27	8.6	Mean: 9	mean: 7.2 vs 9.1	Severe retinopathy: RRR 47% (95% CI, 15-67) Albuminuria >40mg/24hr: RRR 43% (95% CI, 21-58) Albuminuria >300mg/24hr: RRR 56% (95% CI, 18-76) Neuropathy: RRR 57% (95% CI, 29-73)			
UKPDS 33 (1998)[2] (SU, basal insulin)	T2D	median: 11.1	FPG <110 mg/dL vs FPG <270 mg/dL		54	newly diagnosed	mean: 7.08	median: 7.0 vs. 7.9	Combined microvascular: RRR 25% (95% CI, 7-40)	No significant difference	No significant difference	Weight gain: 3.1kg (95% CI, -0.9 to 7)
UKPDS 34 (1998)[3] (metformin)	T2D	Median: 10.7	FPG <110 mg/dL vs FPG <270 mg/dL		53	newly diagnosed	median: 7.2	median:7.4 vs. 8.0	Any diabetes related endpoint: RRR 32% (95% CI, 13-47) Retinopathy: Minimal slowing of progression, but not sustained	Myocardial infarction: RRR 39% (p=0.01) Composite macrovascular diseases: RRR 30% (95% CI, 5-48)	Any diabetes related death: RRR 42% (95% CI, 9-63) All cause mortality: RRR 36% (95% CI, 9-55)	96% increased risk for diabetes-related death, 60% increased risk of mortality with early addition of metformin to sulfonylurea therapy.
ACCORD (2008)[4]	T2D	mean: 3.5 (stopped early)	HbA1c <6.0%		62.2	10 (high risk for CVD)	median 8.1	median: 6.4 vs 7.5	No significant difference	MACE: HR 0.90 (95% CI, 0.78-1.04) Nonfatal MI: HR 0.76 (95% CI, 0.62-0.92) Death from CV causes: HR 1.35 (95% CI, 1.04-1.76)	All cause-mortality: HR 1.22 (95% CI, 1.01-1.46)	Increased risk of hypoglycemia requiring any assistance (16.2% vs. 51%) Weight gain: 3.5kg vs 0.4kg
ADVANCE (2008)[5]	T2D	median: 5	HbA1c <6.5%		66	7.9 (high risk for CVD)	mean: 7.5	mean: 6.5 vs 7.3	Major microvascular events: HR 0.86 (95% CI, 0.77-0.97) Renal events: HR 0.79 (95% CI, 0.66-0.93) no significant difference in neuropathy/retinopathy	No significant difference	No significant difference	Hypoglycemia: HR 1.86 (95% CI, 1.42-2.4), although hypoglycemia events were uncommon 2.7% (intensive) vs 1.5% (control)
VADT (2009)[6]	T2D	median: 5.6	Absolute HbA1c reduction of 1.5%		60.4	11.5 (high risk for CVD)	median: 9.4	median: 6.9 vs. 8.4	Any increase in albuminuria: 9.1% (intensive) vs. 13.8% (control) (p = 0.01)	No significant difference	No significant difference	Any serious AE: 24.1% (intensive) vs. 17.6% (control) (p = 0.05) Hypoglycemia was significantly increased in the intensive group. BMI 33.8 vs. 32.3 (p =0.01)

Table 1. Brief summary of the major findings in the guideline defining trials

ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: preterax and Diamicron Modified Release Controlled Evaluation; AE = adverse event; BMI = body mass index; CV = cardiovascular; CVD = cardiovascular disease; DCCT = Diabetes Control and Complications Trial; HbA1c = glycated hemoglobin; HR = hazard ratio; MACE = major adverse cardiac event (defined as time to first major CV event: nonfatal MI, nonfatal stroke, or death from CVD); MI = myocardial infarction; RR = relative risk; RRR = relative risk reduction; T1D = type 1 diabetes; T2D = type 2 diabetes; UKPDS = United Kingdom Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.

References

1 Nathan, D. M. *et al.* 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* **329**, 977-986 (1993).

2 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* **352**, 837-853 (1998).

3 UK Prospective Diabetes Study (UKPDS) Group. 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* **352**, 854-865 (1998).

4 Gerstein, H. C. *et al.* Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* **358**, 2545-2559 (2008).

5 Patel, A. *et al.* Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* **358**, 2560-2572 (2008).

6. Duckworth, W. *et al.* Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* **360**, 129-139 (2009).