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Review article

Glucoregulation in type 2 diabetes: The lower the better? Glycosylated HbA1c of 6.5% seems to be the limit

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1. Introduction

Patients with type 2 diabetes mellitus (DM2) are at increased risk for micro- and macrovascular complications. Indeed, the risk for cardiovascular death is 2–4 times increased compared to non-diabetic persons [1,2]. This excess risk can only partially be explained by traditional cardiovascular risk factors such as obesity, hypertension and dyslipidemia. Hence, hyperglycemia is thought to be responsible via disturbances in intracellular pathways and deleterious effects of glycosylated end products and reactive oxygen species [3].

Several studies showed a graded relationship between the height of the HbA1c-value and the occurrence of microvascular complications in type 1 (DM1) and type 2 diabetic patients [4,5]. In addition, 2 large randomized-controlled trials demonstrated that improved glucoregulation with reduced HbA1c-levels led to a decrease in microvascular complications in DM1 and 2 [6,7]. The risk at macrovascular disease also seems to increase with rising HbA1c-levels [8]. After correction for other risk factors every 1% increase in HbA1c is associated with an 18% increase in risk for cardiovascular disease [8] and a 12% increase in the risk of death [9]. However, the efficacy of tighter glucose control on the prevention of macrovascular disease has not been proven yet. In the United Kingdom Prospective Diabetes Study (UKPDS) a 0.9% difference in HbA1c between intensively and standard-treated DM2 over 10 years, only led to a lower cardiovascular risk in a small subgroup of patients also treated with metformin [10]. In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCTT/EDIC) study in DM1, a favorable effect of intensive glucose control on cardiovascular complications became apparent only many years later [6].

Nevertheless, the American Diabetes Association, in accordance with the adagium “the lower the better” applicable to cholesterol [11], recommended an HbA1c <7% in general and as close to normal as possible individually (<6%) [12]. Recently 2 studies have been published that evaluated the effect of lowering glucose to near-normal levels on cardiovascular risk in DM2 [13,14].

2. Action to Control Cardiovascular Risk in Diabetes (ACCORD) study

The ACCORD study [13] was conducted in the United States and Canada and included 10.251 patients with DM2 (Table 1). Inclusion criteria were HbA1c ≥7.5%, either age 40–79 years with cardiovascular disease or age 55–79 years with anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least 2 additional risk factors for cardiovascular disease. Main exclusion criteria included frequent or serious hypoglycemic events, unwillingness to do home blood glucose monitoring or inject insulin, BMI>45 kg/m^2, serum creatinin>133 μmol/l or other serious illness.

Patients were randomly assigned to receive intensive glucose-lowering therapy targeting an HbA1c level of <6% or standard therapy targeting an HbA1c level of 7.0–7.9%. Every glucose-lowering agent, including insulin, could be used to achieve target values.

The primary outcome was first occurrence of non-fatal myocardial infarction or non-fatal stroke or death from cardiovascular causes. Secondary outcomes included death from any cause, microvascular disease, hypoglycemia, cognition and quality of life.

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Table 1
Patient characteristics at study entry.

Characteristics	ACCORD study	ADVANCE study
Patients		
Number	10.251	11.140
% women	38	42
Age (years)	62.2±6.8	66±6
Duration DM2 (years)[a]	10	8 (±6)
HbA1c (%)	8.3±1.1	7.5±1.5
Fasting plasma glucose (mmol/L)	9.7±3.1	8.5±2.8
% patients with macrovascular disease	35	32
BMI (kg/m^2)	32.2±5.5	28±5
Blood pressure (systolic/diastolic, mmHg)	136±17/75±10	145±21/80±11
Medication		
% patients on insulin therapy	35	1.5
% patients with statin	62	28
% patients with aspirin	54	44
% patients with antihypertensives	85	75

Values are expressed as mean±standard deviation unless stated otherwise.
[a] Duration of DM2 expressed as median in the ACCORD and as mean in the ADVANCE.

2.1. Results

Within 4 months after randomization the median HbA1c value declined from 8.1% to 6.7% in the intensive-therapy group and 7.5% in the standard-therapy group. After 1 year, stable median HbA1c-values of 6.4 and 7.5% respectively, were achieved and maintained throughout the study. Patients in the intensive-treatment group had more frequent visits and medication adjustments (4.4 versus 2.0 times a year) and used more glucose-lowering medication (Table 2) than the standard group. The latter was at the expense of higher rates of hypoglycemia, weight gain (mean 3.1 kg; 27.8% more than 10 kg versus 14.1% in the standard group) and fluid retention.

The study had to be discontinuated early (median follow-up 3.5 years) because of a higher mortality in the intensive-treatment group. This included total mortality (5.0 vs. 4.0%, hazards ratio 1.22; CI 1.01–1.46, $p=0.04$) as well as death from cardiovascular causes (2.6 vs. 1.8%, hazards ratio 1.35, CI 1.01–1.76, $p=0.02$). The occurrence of the composite primary outcome was lower in the intensive-treatment group with a trend towards separation between treatment groups in favor of intensive treatment after 3 years. This trend was not significant however. The amount of non-fatal myocardial infarctions was significantly lower in the intensive-therapy group though. In addition, there was a suggestion of a greater benefit of intensive therapy on the primary outcome in patients with lower HbA1c-values (<8%) or without cardiovascular disease at inclusion.

3. Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)

The ADVANCE study [14] was conducted in 20 countries from Asia, Australasia, Europe and North America. Included were 11,140 patients with DM2, age ≥30 years at diagnosis DM2 and age ≥55 years at study entry, and a history of major micro- or macrovascular disease or at least one other risk factor for vascular disease. Exclusion criteria included a definite indication for, or contra-indication to, any of the study medications or a definite indication for long-term insulin therapy at study entry.

Patients were randomly assigned to intensive glucose-lowering therapy (target HbA1c ≤6.5%) or standard therapy (target HbA1c as locally established). Basal therapy in the intensive-treatment group consisted of gliclazide modified release, 30–120 mg daily. Other sulfonylureas (SU) had to be discontinued. When target HbA1c was not reached with maximal doses of gliclazide other blood glucose-lowering medication could be used: the protocol suggested sequential addition and increase in dose of metformin, thiazolidinediones, acarbose or insulin. No gliclazide use was allowed in the standard-treatment group.

The primary outcomes were a composite of macrovascular events (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke) and a composite of microvascular events (new or worsening nephropathy of retinopathy), considered both jointly and separately. Secondary outcomes included death from any cause, death from cardiovascular causes, major coronary events, total coronary events, major cerebrovascular events, total cerebrovascular events, heart failure, peripheral vascular events, new or worsening nephropathy, retinopathy or neuropathy, decline in cognition and dementia.

Table 2
Differences between the ACCORD and ADVANCE studies.

	ACCORD study	ADVANCE study
Intervention		
Target HbA1c-value (%)	<6	≤6.5
Median duration of follow-up (years)	3.4	5.0
Medication at end of study (%), intensive-therapy vs standard-therapy group		
Insulin	77 vs 55	41 vs 24
Metformin	95 vs 87	74 vs 67
Insuline-secretagogue	87 vs 74	94 vs 62
Thiazolidinedione derivative	92 vs 58	17 vs 11
Incretin	18 vs 5	Not mentioned
Statin	88 vs 88	46 vs 48
Aspirin	76 vs 76	57 vs 55
Antihypertensives	91 vs 92	Not mentioned
Outcome		
Median HbA1c-value (%)	6.4 vs 7.5[a]	6.4 vs 7.0
Death (%)		
All cause	5.0 vs 4.0[a]	8.9 vs 9.6
Cardiovascular	2.6 vs 1.8[a]	4.5 vs 5.2
Non-fatal myocardial infarction (%)	3.6 vs 4.6[a]	2.7 vs 2.8
Non-fatal cerebrovascular accident (%)	1.3 vs 1.2	3.8 vs 3.8
Hypoglycemia/year needing medical assistance (ACCORD) or severe hypoglycemia/100 patients/year (ADVANCE) (%)	3.1 vs 1.0[a]	0.7 vs 0.4
Weight gain (kg)	3.5 vs 0.4	0.0 vs −1.0[a]

Values are expressed as mean±standard deviation unless stated otherwise.
[a] The comparison between intensive-therapy and standard-therapy groups was significant.