

# Strict Glycemic Control is a Main Goal in the Treatment of Patients with Type 2 Diabetes Mellitus

## Agonist

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At present, there is clear evidence that glycemic control significantly delays the beginning of microvascular complications in patients with type 1 and type 2 diabetes mellitus. (1, 2) In addition, diabetics are more likely to present cardiovascular events; (3, 4) even more, hyperglycemia correlates with greater cardiovascular risk and mortality. (5, 6) Based on these data, different research studies were carried out to prove the “glycemic hypothesis”. The current controversy focuses on this issue and presents different angles that should be analyzed to answer the fundamental question whether glycemic control is a central goal in the treatment of diabetic patients.

We should consider three aspects of the problem: firstly, the meaning of “strict” glycemic control; secondly, whether target HbA1c levels should be the same for all diabetics; and thirdly, how to achieve optimal levels of glycemia or HbA1c.

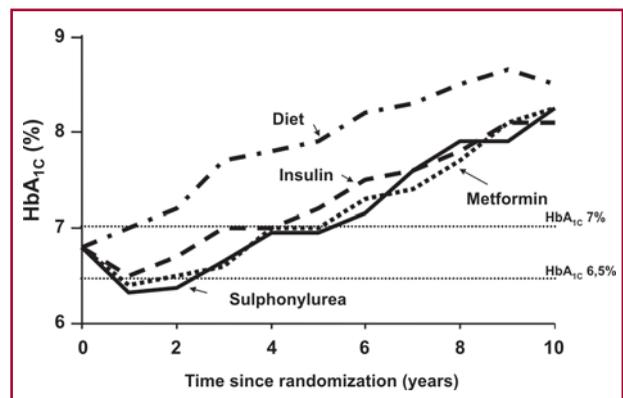
In order to place the problem in its perspective, all physicians treating diabetic patients should restrict the discussion of the optimal value of HbA1c 6.5%, 7% or 7.5% to the environment of research, medical publications and/or scientific meetings. In the real world of medical practice, satisfactory glycemic control is achieved in only 38.8% of diabetics and in 15.2% of insulin-dependent diabetic patients according to data of the NHANES IV. (7)

In the UKPDS, one of the most frequently quoted trials in diabetes, HbA1c levels < 7% were achieved by all treatment arms at 1 year of follow-up, and after 5 years HbA1c levels were about 8.5% (Figure 1). It is clear that control of glycemia and HbA1c levels should be stricter in diabetic patients.

The second aspect is specifically focused on the optimal level of HbA1c. As HbA1c is considered a parameter for chronic control of glycemia, we should define its optimal level. Outcomes at 17 years of follow-up of the UKPDS trial provide interesting data; the first 5 years correspond to interventional follow-up and the remaining 9 years to post-trial monitoring. Patients in the intensive therapy group had a reduction of 0.8% in HbA1c levels, and at 10 years the risk reductions were 9% for any diabetes-related end point (p = 0.04) and 24% for microvascular disease (p = 0.001). In addition, post-trial risk reductions were

statistically significant for diabetes-related death (17%), myocardial infarction (15%), and death from any cause (17%). (8) Recently, three randomized trials have assessed the effect of intensive therapy versus conventional therapy. In this sense, the results have provided controversial information regarding the cut-off points for glycated hemoglobin levels. The ADVANCE study recruited 11,140 patients with a history of diabetes treated for 8 years. After 5 years of follow-up, the mean glycated hemoglobin values were 6.5% in the intensive-control group versus 7.3% in the standard-control group. On average, the rate of severe hypoglycemic events was 0.7 events per 100 patients per year in the intensive-control group versus 0.4 events per 100 patients per year in the standard-control group. A reduction of 10% in the incidence of combined primary outcome of major macrovascular or microvascular events was observed, and the main contributor was a reduction in the risk of nephropathy. (9)

The VADT trial included 1,792 patients with a history of diabetes diagnosed 12 years before and levels of HbA1c of 6.9% versus 8.4%. Patients were followed-up for 6.25 years. This study demonstrated a significant reduction in cardiovascular events. (10)



**Fig. 1.** HbA1c levels in the UKPDS according to treatment. Adapted from the UKPDS 34 trial. *Lancet* 1998;352:854-65.

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Finally, The ACCORD trial, (11) included 10,251 patients with a history of diabetes diagnosed 10 years before and levels of HbA1c of 6.4% versus 7.5%. The mean duration of follow-up at the time the trial was stopped was 3.5 years, due to increase by 22% in general mortality and by 35% in cardiovascular deaths in the intensive therapy group. The rate of hypoglycemic episodes was 3.1% in the intensive-therapy group versus 1.0% in the standard-therapy group, and weight gain of more than 10 kg was more frequent in the group with HbA1c of 6.4% (28% versus 14%). These differences might partially explain the findings of this study.

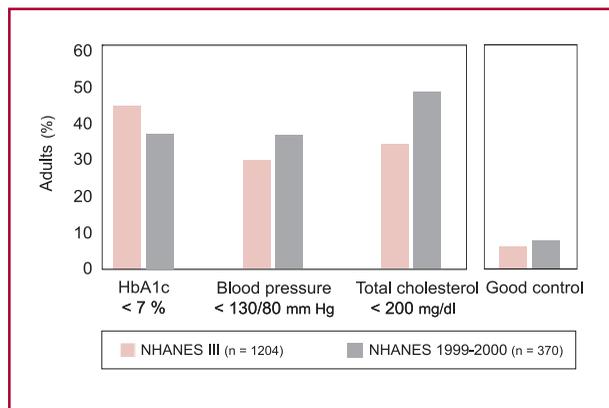
Compared to the ADVANCE trial, control of other risk factors was lower, and the incidence of hypoglycemic episodes was greater in the ACCORD trial. This information is extremely important as it is well known that low blood sugar levels are associated with seizures, myocardial ischemia, dysautonomia and greater cardiovascular morbidity and mortality, especially in the elder. (12) In addition, the percentage of patients treated with thiazolidinediones was low in the ADVANCE trial (17% in the intensive therapy group), while 92% of patients in the ACCORD trial were receiving these drugs (especially rosiglitazone, 90%) which may increase the risk of myocardial infarction and cardiovascular mortality. (13)

These data should be taken into account for the analysis of the results, as the increase in mortality might be due to these particular findings of the ACCORD trial rather than to tight glycaemic control.

Based on what has been previously discussed, we might consider that strict glycaemic control should be applied to all patients. However, hypoglycemia should be avoided; it is important to use safe hypoglycemic or normoglycemic agents and to bear in mind that therapies should be adapted to suit the individual needs of each patient.

In this context, different clinical scenarios might be built.

1. Young patients with type 2 diabetes mellitus with absence of vascular disease. In these patients, strict glycaemic control may reduce the progression of atherosclerosis and prevent cardiovascular disease (CVD) and microvascular complications (especially neuropathy according to data from the ADVANCE trial).
2. Middle-aged patients and > 70 years with risk factors or history of cardiovascular disease, with absence of microvascular disease.
  - a) Subjects with risk factors and absence of CVD. In this subgroup of patients, strict glycaemic control seems to be beneficial to prevent CVD. The drugs prescribed should be safe to avoid hypoglycemia or cardiovascular adverse events.
  - b) Patients treated for diabetes for more than 10 years and multiple risk factors or CVD. In these patients,



**Fig. 2.** Risk factors control in diabetic patients. Modified from Saydah SH, Fradkin J, Cowwie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA* 2004;291:335-42.

HbA1c level of 7% associated with intensified interventions aimed at the other risk factors is a reasonable goal. We should speak of “strict control of risk factors” in accordance with the title of this controversy. This strategy was found to be the most effective and it was used in the STENO II trial. (14)

- c) Patients with diabetes and evidence of active or progressive CVD. There is still lack of evidence regarding optimal levels of HbA1c in this special group of patients; the results of the BARI 2 D trial will provide the answer to this issue. (15)

Finally, I consider that strict glycaemic control is essential to reduce the incidence of macrovascular and microvascular events among diabetics. However, this strategy alone is not enough if other risk factors are not controlled. Figure 2 illustrates the lack of strict multifactorial control in diabetic patients during daily medical practice.

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### Competing interests

Dr. Rey reports to be lecturer for Astra Zeneca, Bayer, MSD Argentina, and researcher of Pfizer, Astra Zeneca, Takeda

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### BACKGROUND

Diabetes is a highly prevalent metabolic disorder. In 2007 the prevalence of diabetes was 23.6 million people in the United States, and 23.1 percent of diabetics were > 60 years old. A total of 1.6 million new cases of diabetes were diagnosed in people in the same year. (1) Data from surveys of the Centers for Disease Control and Prevention show that the crude prevalence of diagnosed diabetes increased 132% from 1980 through 2006. (2)

People with diabetes have a two-fold higher risk of mortality adjusted for age and gender than people without diabetes. (3) Cardiovascular diseases are the most frequent causes of morbidity and mortality among diabetics. (3, 4) Although heart disease-related mortality has declined in non diabetics, this trend was smaller in diabetic subjects, particularly women. These temporary trends - increase in the prevalence of diabetes, along with the observation that the relative risk of mortality has not declined - might probably explain the increase in cardiovascular risk attributed to diabetes that was reported in the Framingham study. (6)

There is a positive correlation between glycemia, glycated hemoglobin (HbA1c) and the incidence of macrovascular events, and this relationship is continu-

ous and extends below the diabetic threshold in several observational studies. (7, 8) The meta-analysis by Selvin et al. reported that the risk of cardiovascular events increased by 18% for every 1-percentage point increase in HbA1c. (8)

These data emphasize the necessity of effective therapies to prevent cardiovascular diseases in subjects with diabetes, and suggest that reductions in glycemia and HbA1c levels to those of non diabetics might prevent premature deaths and reduce the incidence of major cardiovascular complications. This hypothesis was evaluated in randomized clinical trials (RCT) designed to compare intensive with conventional diabetes therapy with regard to their effects on preventing the development of symptomatic hyperglycemia.

### STUDIES ASSESSING THE EFFECTS OF STRICT GLYCEMIC CONTROL ON CARDIOVASCULAR EVENTS

Six RCT compared the efficacy of different intensive therapy regimes (with oral hypoglycemic drugs and multiple daily doses of insulin) with conventional therapy for glucose control (Table 1).

The UGDP trial included 823 patients with type 2 diabetes mellitus that were assigned to 4 treatment

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**Table 1.** Characteristics of the studies comparing intensive therapy with conventional therapy for glucose control

Trial	Year	n	Inclusion criteria	Intervention	Intensive group target	Age, years	HbA1c (%)	Hypertension (%)	Current smoking (%)	Coronary artery disease (%)	Stroke (%)	Follow-up, years	HbA1c at the end of the study
UGDP*	1978	823	Type 2 diabetes mellitus diagnosed < 12 months before	Insulin/tolbutamide	Glycemia < 110 mg/dl	60	NA	NA	NA	NA	NA	13	NA
VA CSDM†	1997	153	Type 2 insulin-requiring diabetes mellitus, 40 to 69 years	Insulin/glipizide	HbA1c ≤ 6.1%		9.8	53	15	19	6.5	2.9	7.0% vs. 9.5%
Kumamoto	1995	110	Type 2 diabetes mellitus, absence of retinopathy and neuropathy, albuminuria < 300 mg/24 hrs, age < 70 years, creatinine levels < 1.5 mg/dl, absence of hypertension or dyslipemia	Insulin	HbA1c ≤ 7.0%	51	9.1	0	NA	0	0	6	7.1% vs. 9.4%
UKPDS‡	1998	3,867	Patients aged 25 to 65 years with newly diagnosed diabetes. Patients with renal failure, ketonuria > 3 mmol/L, recent myocardial infarction, angina or heart failure or more than one previous vascular event	Chlorpropamide / glyburide/ insulin	Glycemia < 110 mg/dl	53.3	7.08	NA	66	NA	NA	11.1	7.0% vs. 7.9%
ACCORD§	2008	10,251	Patients with type 2 diabetes mellitus, between the ages of 40 and 79 years, HbA1c eH 7.5%, and with cardiovascular disease or between the ages of 55 and 79 years and risk factors for cardiovascular disease - Patients with creatinine >1,5 mg/dl were excluded	Oral hypoglycemic drugs/ Insulin	HbA1C < 6%	62.2	8.1	NA	14	35.2	NA	3.5	6.4% vs. 7.5%
ADVANCE*	2008	11,140	Type 2 diabetes mellitus, age ≥ 55 years, history of major macrovascular or microvascular disease or other risk factor for vascular disease.	Glicazide/ Other oral hypoglycemic drugs/ Insulin	HbA1c ≤ 6.5%	66	7.5	75.1	13.9	12	9.1	5	6.5% vs. 7.3%

NA: Non available.

\* University Group Diabetes Program.

† Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes.

‡ United Kingdom Prospective Diabetes Study.

arms: intensive control with insulin, low-dose insulin, tolbutamide and placebo. (9) Initially, the study had a phenformin arm that was prematurely stopped due to development of lactic acidosis. The tolbutamide arm was also discontinued due to an increase in cardiovascular mortality. After 13 years of follow-up, there were no significant differences between intensive therapy, low-dose insulin and placebo groups with respect to cardiovascular events.

In Japan, the Kumamoto trial, 110 patients with type 2 diabetes were randomly assigned to intensive insulin therapy or to conventional insulin therapy. (10) The aim of the study was to examine the effects of the intensive therapy on the incidence or progression of microvascular complications (retinopathy or nephropathy). During the 8-year follow-up period, intensive insulin therapy reduced the risk of severe proliferative retinopathy and that of treatment of photocoagulation by 50% and the risk of albuminuria > 30

mg/day by 60%. During the same period, 4 patients in the intensive therapy group and 7 in the conventional therapy group presented cardiovascular events (cardiovascular death, myocardial infarction, stroke, angina or intermittent claudication).

In preparation for a long-term RCT, the VA CSDM trial was a feasibility study of 153 patients that compared standard versus intensive insulin therapy to assess the rate of development of new cardiovascular events. (11) After 27 months of follow-up, the incidence of events was 32% in the intensive treatment arm and 20% in the standard treatment arm (p = 0.10).

The UKPDS trial randomized 3,867 patients with newly diagnosed type 2 diabetes to different therapeutic strategies. (12) Patients with overweight were assigned to intensive therapy with insulin or sulphonylureas or metformin or conventional therapy with diet; patients without overweight were rando-

mized to intensive therapy with insulin or sulphonylureas, or only diet. Median follow-up was 10 years. Intensive therapy was associated with a reduction of 25% in the risk of microvascular events ( $p = 0.01$ ); however, no significant differences were reported in the incidence of major cardiovascular events.

The ACCORD trial included 10,251 patients with type 2 diabetes mellitus and a glycosylated hemoglobin level of 7.5% or more and who either were between the ages of 40 and 79 years and had cardiovascular disease or were between the ages of 55 and 79 years and had anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, current status as a smoker, or obesity). Patients were randomly assigned to receive intensive therapy targeting glycosylated hemoglobin level of less than 6.0% or to receive standard therapy targeting a level of 7.0 to 7.9%. The finding of higher mortality in the intensive-therapy group led to a discontinuation of intensive therapy after a mean follow-up of 3.5 years (5% versus 4%; HR 1.22; 95% CI 1.01 to 1.46;  $p = 0.04$ ). The rate of myocardial infarction was lower in the intensive therapy group (HR, 0.76; 95% CI, 0.62 to 0.92;  $p = 0.004$ ) but there was no significant difference in the rate of stroke (HR, 1.06; 95% CI, 0.75 to 1.50;  $p = 0.74$ ) (13). The result was independent of the dosage schedule used for glycemic control.

Finally, the ADVANCE trial (14) included 11,140 patients with type 2 diabetes, an age of at least 55 years, and a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease. Patients were randomly assigned to undergo either standard glucose control or intensive glucose control, defined as the use of gliclazide plus other drugs as required to achieve a glycosylated hemoglobin value of 6.5% or less. Median follow-up was 5 years. The primary outcome, a composite of macrovascular and microvascular events, was significantly lower in the intensive therapy group (HR 0.90; 95% CI 0.82 to 0.98%;  $p = 0.01$ ) due to reduction in the incidence of microvascular events (HR, 0.86; 95% CI, 0.77 to 0.97;  $p = 0.01$ ); however, there were no differences in mortality, (HR 0.93, 95% CI, 0.83 to 1.06,  $p = 0.28$ ), myocardial infarction 2.7% versus 2.8%, respectively) or stroke (3.8% in both groups).

Data from RCT were combined and analyzed using a random effects meta-analysis. (15)

#### EFFECTS OF INTENSIVE CONTROL ON MORTALITY

Meta-analysis of the six RCT demonstrates that there are no significant differences in terms of mortality between intensive therapy and standard therapy for glycemic control (RR 1.03; 95% CI 0.90 to 1.17) (Figure 1).

#### EFFECTS OF INTENSIVE CONTROL ON MAJOR ADVERSE CARDIOVASCULAR EVENTS

Figure 2 shows the effects of intensive control on major cardiovascular events. Again, there are no differences between intensive therapy and standard therapy in the incidence of cardiovascular mortality (RR 1.12; 95% CI 0.87 to 1.45) and stroke (RR 1.05; 95% CI 0.90 to 1.21). As opposed to the negative trends observed with other end points, strict glycemic control produced a modest reduction of 14% in the incidence of myocardial infarction (RR 0.86; 95% CI 0.76 to 0.96).

#### NEPHROPATHY AND ADVERSE EVENTS

Figure 2 illustrates the effects of intensive therapy on the development of nephropathy as indicator of microvascular complications. The results show that although intensive therapy significantly reduces the development of proteinuria or its progression (RR 0.70; 95% CI 0.56 to 0.88), the incidence of renal failure or the need of renal replacement therapy was not significantly different (RR 0.74; 95% CI 0.48 to 1.14).

The incidence of episodes of severe hypoglycemia requiring treatment was greater in patients assigned to strict glycemic control (RR 2.22; 95% CI 1.60 to 3.09) as expected due to intensive glucose control therapy.

#### QUALITY OF LIFE

Several studies have demonstrated that diabetes and its microvascular and macrovascular complications have a significant impact on patients' quality of life. Nevertheless, indicators of quality of life did not improve in spite of intensive therapy or strict glycemic control. Although intensive therapy did not reduce the health-related quality of life, it is important to consider that episodes of hypoglycemia were not contemplated in the analyses. (16-18)

#### CONCLUSIONS

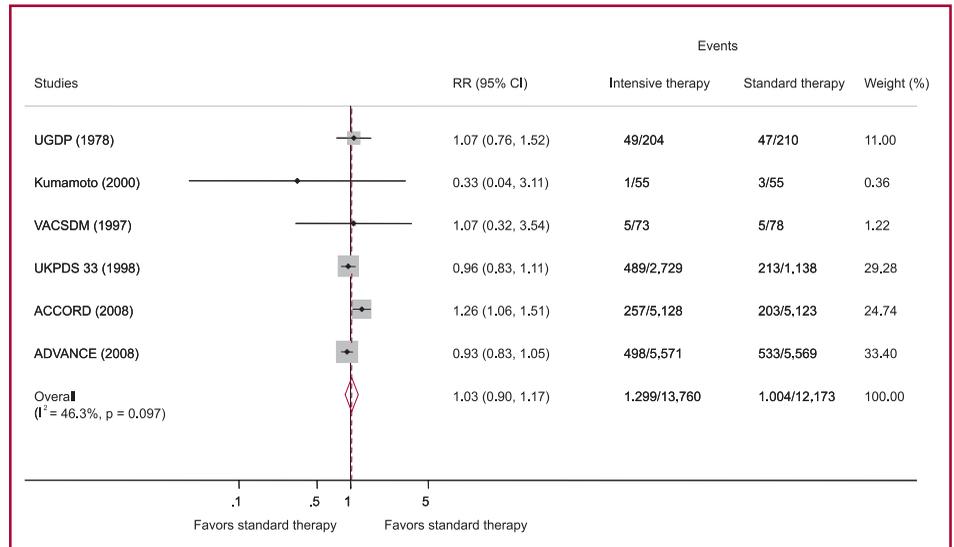
*Is strict glycemic control a main goal in the treatment of patients with type 2 diabetes mellitus? No, it isn't.*

The results of the meta-analysis demonstrate that intensive therapy does not reduce all-cause mortality or cardiovascular mortality. Strict glycemic control has a modest impact on the incidence of myocardial infarction, with no effects on the incidence of stroke.

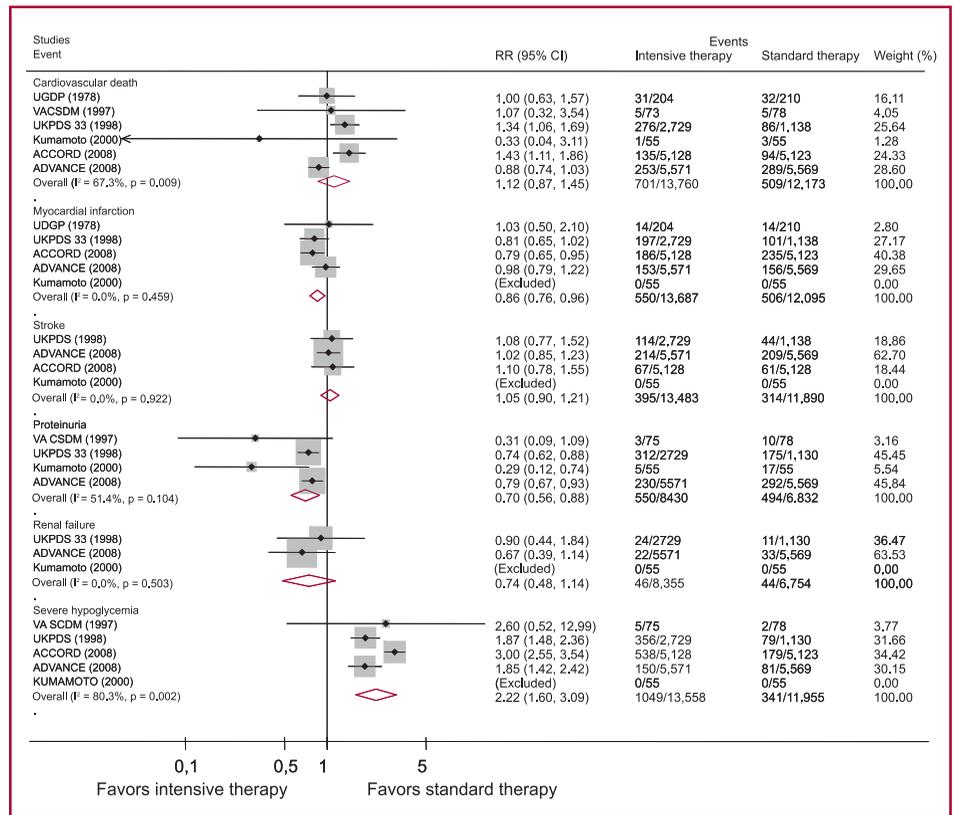
*Should intensive therapy for glucose control be systematically indicated, based only on the reduction of the incidence in myocardial infarction? No, it shouldn't.*

Although the meta-analysis revealed a discrete reduction in the incidence of infarction, two aspects

**Fig. 1.** Effects of intensive glyce-mic control on mortality



**Fig. 2.** Effects of intensive glyce-mic control on macrovas-cular and microvascular events and on the incidence of severe hypoglycemia.



should be taken into account. Firstly, the upper limit of the confidence interval is close to 1, meaning that the real effect might be lower or even absent. Secondly, as the absolute risk reduction is small, it would be necessary to treat 171 patients during 5.4 years to prevent a nonfatal myocardial infarction (5.9 infarctions prevented per 1000 patients treated; 95% CI 1.7 to 10). To conclude, this result should be con-

sidered as a hypothesis generator rather than a therapeutic option at the moment of decision-making.

*Does the reduction in microvascular events justify the indication of intensive therapy in all patients? No, it doesn't.*

The meta-analysis showed a significant effect on the development or worsening of proteinuria; however, strict glyce-mic control did not reduce the inci-

dence of renal failure or the requirement of renal replacement therapy.

*Do patients included in the intensive therapy arm of randomized trials represent the population of type 2 diabetics in the community?* This is partially true.

A recent epidemiological study demonstrated that patients with newly diagnosed type 2 diabetes are older than patients included in most RCT. (19) The prevalence of hypertension, coronary artery disease and renal compromise is also higher in the community at the moment of diagnosis.

In this context, a decision analysis demonstrated that among older diabetic patients, the presence of multiple comorbidities and functional impairments diminished the expected benefits of intensive therapy. (20) In this way, randomized trials included patients that were more likely to benefit from intensive glycemic control; yet, the general outcomes in terms of macrovascular events were neutral.

*Is intensive glycemic control safe?* No, it isn't.

The incidence of severe hypoglycemia in RCT was 2.2 times greater in patients under intensive therapy, which means one episode every 28.7 patients or 34.8 episodes per 1000 treated patients (95% CI 17.1 to 59.6).

The incidence of hypoglycemia in observational studies is greater than in RCT and it is directly related to the use of insulin and inversely related to HbA1c levels. (21, 22)

According to available data, it is not possible to consider that strict glycemic control is a main goal in the treatment of patients with type 2 diabetes mellitus.

Cardiovascular complications are very frequent among diabetics and constitute the main causes of morbidity and mortality; thus, therapeutic efforts should be focused on appropriate blood pressure control, low cholesterol levels and use of aspirin in this population, as all these interventions that reduce the development of complications are still underused in diabetic patients. (19, 23-25)

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**Competing interests**

None declared

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**ANSWER FROM THE AGONIST**

Recent publications have reported that glycemic control has not demonstrated a significant reduction in the incidence of cardiovascular events. The ACCORD trial and the ADVANCE trial have been the most relevant studies with follow-up periods of 3.5 and 5 years, respectively. However, when studies with longer follow-up periods, such as the UKPDS and the DCCT-EDIC are analyzed the incidence of cardiovascular events is less frequent in patients undergoing initial strict glycemic control. These data show the complexity of this matter and the necessity to keep on with the follow-up of patients included in the ACCORD and ADVANCE trials. As it has been previously mentioned, glycemic control is important for management of the diabetic patient, trying to prevent the development of hypoglycemic episodes and using safe hypoglycemic or normoglycemic agents. As clinical cardiologists we should understand that diabetes is a complex disease, frequently associated with hypertension and dyslipemia. Consequently, glycemic control together with adequate management of major risk factors, are therapeutic strategies aimed at inhibiting atherosclerosis development.

**Dr. Ricardo Rey**

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**ANSWER FROM THE ANTAGONIST**

I would like to propose an alternative point of view to Dr. Rey's statement:

1. The discussion regarding target therapeutic levels of HbA<sub>1c</sub> and those practically achieved is not a minor issue; although a few patients achieve target levels in daily practice, this failure implies changes in drug schemes.
2. The results of the last three trials are not discrepant. Data from the VADT trial recently presented does not demonstrate the superiority of intensive treatment over conventional treatment: CV death 2.1% versus 1.7%, myocardial infarction 6.1% versus 6.3%, heart failure 5.3% versus 5.6%, amputation 0.4% versus 0.8%, photocoagulation 8.8% versus 7.0%, renal failure 0.8% versus 1.2%, for intensive therapy and standard therapy, respectively. All differences were not statistically significant. Interestingly, the results of the UDGP study published in 1978 are also consistent with those reported by recent trials.
3. Intensive therapy prevents only those microvascular events of relative relevance due to treatment-associated risks. There are no differences in the incidence of blindness, kidney failure or renal-related death.

Finally, I would like to think about an additional aspect. According to current knowledge, it is necessary to redefine the real role of hyperglycemia on the cardiovascular risk of patients with type 2 diabetes. Glucose might not be a pathogenic "effector" but a marker of other conditions responsible of the increased risk. Alternatively, glycemia might exert direct damage, playing a minor role compared to other cardiovascular risk factors. Yet, its deleterious effects might be similar to those of the other risk factors, but the negative effects of hypoglycemic drugs (due to episodes of hypoglycemia or to other recognized adverse events) might overshadow any potential benefit derived from intensive hypoglycemic therapy.

**Dr. Javier A. Mariani**



