A cardiovascular insight to treatment of patients with diabetes based on recent large trials (NAVIGATOR and ACCORD)

Diabetes is a condition of increasing prevalence related to poor diet, lack of physical activity and obesity. One in five or six patients attended by a clinical cardiologist has type II diabetes, a situation that demands the adoption of therapeutic strategies with many open questions: Up to what level should we try to lower glycemia (or should it be better to refer the patient to a diabetologist)? Is it better to lower cholesterol levels with statins or triglyceride levels with fibrates? Should we adopt tighter monitoring on blood pressure with these patients than with non-diabetic patients? In the antihypertensive therapy, should we give priority to angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB)? Final outcomes from several trials were presented at the recent Congress of the American College of Cardiology; these outcomes may imply a change in the replies to the questions posed, and result in a change of our clinical behaviors. Moreover, these findings invite reflection on the fundamentals of our daily health care decisions and the strength of the evidences.

CONTROL OF GLYCEMIA

General Approach

The approach to type 2 diabetes has been conducted by specialists who have historically focused on restoring the lost balance, ie, regulating glucose levels to reach circadian levels similar to the physiological ones. The model of glycemic control in insulin-dependent diabetes –with its obsessive need for control and measurements– has also been used for type 2 diabetes. Do we have evidence that tight glycemic control is beneficial to prevent cardiovascular problems?

Studies with oral hypoglycemic agents in large populations were planned in 1960s. The most important of them all, UGDP, was stopped because of an increase of cardiovascular mortality, (1) a decision that deserved harsh methodological criticism and might be considered premature or wrong today. However, for one reason or another, the research organized by the pharmacy industry did not follow the model of large trials to assess hypoglycemic agents. It preferred to introduce drugs to the market according to their metabolic effects, ie, their capacity to control altered glycemic levels, glycosylated hemoglobin, or postprandial glycemia. This gap was initially filled by large independent community studies like the UKPDS (2) almost a decade ago, ant the recent ones, ACCORD (3) and VADT. (4)

In a very schematic way, we have learned that 'microvascular' problems (retinopathy and nephropathy) are related to glycemia and are prospectively reduced with better control of their levels. The link between macrovascular problems (atherosclerotic vascular disease in different territories: coronary artery disease, stroke and pheripheral vascular disease) and glucose levels and their control has been much more elusive, with inconsistent outcomes.

In 2008, the outcomes of the intensive glycemic control arm from the ACCORD trial showed a significant warning sign. (3) The trial included 10,251 patients with a mean glycosylated hemoglobin Hb A(1c) of 8.1%, and compared two blood sugar control regimes: an intensive control regime aiming at achieving Hb A(1c) $< 6\%$, and a less tight regime aiming at maintaining a level between 7% and 7.9%. The 35% of the patients had a history of cardiovascular events. The trial was stopped because of a 22% increase of cardiovascular mortality in the intensive control group. The incidence of hypoglycemia that required treatment was higher in the intensive control group, and so was the incidence of weight gain > 10 kg.

In 2009, a meta-analysis (5) of the five clinical trials was published; they included patients with diabetes, and assessed the long-term outcomes of a glucose-lowering therapy with higher or lower levels of intensity: UKPDS, (2) Proactive, (6) ADVANCE, (7) VADT (4) and ACCORD. They included a total of 33,040 patients. Mortality rate was similar for both treatment groups, without confirming the negative outcomes of ACCORD, although there was heterogenity in the trials. Tight glycemic control had no preventive effects on the incidence of stroke, but significantly reduced the incidence of non-fatal infarction (RRR 17%) and appearance of coronary artery disease (RRR 15%); as a result of these events, the effect of the trials was homogeneous. Clearly, there are no strong reasons to sustain the advantages of tight glycemic control in a general way, particularly in patients with cardiovascular disease.

The current recommendation from the 2010 guideline of the American Diabetes Association is to maintain Hb A(1c) levels below 7%. (8)

From a pathophysiological point of view, outcomes leave open a complex issue: lowering glycemic levels reduces the development of atherosclerotic disease (coronary artery disease), but this is not reflected in benefits regarding mortality, probably due to side effects of hypoglycemia or others.

How can these findings be explained?

It is difficult to consolidate a pathophysiological vision of the relationship between glycemic levels and the risk

for cardiovascular disease, on the basis of epidemiological knowledge and treatment outcomes. In the first place, it is important to bear in mind that the current definition of diabetes has lowered the threshold for diagnosis based on fasting glucose from 140 mg/dl to 126 mg/dl, which has led to a 50% increase in the number of people diagnosed with diabetes. There are several reasons to sustain that the higher the glucose level –or, as it has been recently published, the higher the Hb A(1c) level–, the greater the risk of developing macrovascular and microvascular disease. The risk for cardiovascular disease is not dichotomous (diabetes – no diabetes): the higher the glycemic levels are, the greater the risk is. This can be estimated quantitatively, as in the series of 11,092 individuals who did not have a history of diabetes or cardiovascular disease, and with a follow-up of more than 15 years, which is summarized in Table 1. (9) An increased percentage of the risk of coronary heart disease, stroke, and death was observed, compared with the increase of glucose levels and Hb A(1c), even adjusted for multiple fisk factors: mortality increases 12% for every 1% increase of Hb A(1c), and 2.1% for every 10 mg/dl of glycemia.

Can we revert that tendency by lowering glucose levels? Clearly, we can reduce retinopathy and nephropathy without impacting on mortality rate. Its link to cardiovascular disease is more difficult to prove: decreasing the incidence of coronary heart disease and infarction suggests that glycemic control does change the progression of atherosclerosis. But then there is an increase of hypoglycemia that can be devastating for vascular patients, and maybe some other adverse effect that we do not fully understand, and limitates the potential benefit of this strategy. One of those problems are the drugs used for its control.

The problem with oral hypoglycemic agents

Results of the NAVIGATOR study and the problem of "new diabetes" as an event

An additional problem about the risk-benefit equation of the tighter control of glycemia is the association of rosiglitazone with an increased risk of heart failure and 'macrovascular' complications, which has motivated an interesting and passionate debate, with meta-analysis and inconsistent results. A recent article from the Mayo Clinic showed that findings about rosiglitazone are strongly influenced by the affiliation and financing of the authors. (10) The increased mortality observed in the ACCORD trial was not attributed to this drug, and the tendency was similar for different hypoglycemic agents.

On the basis of the unexpected cardiovascular risk in the debate on glitazones, the FDA, in order to grant patents on new drugs for diabetes, has decided to require the companies studies of sufficient size, with cardiovascular endpoints, in patients with or without known pathology. (11, 12)

Another research area is the assessment of short-acting drugs that have an impact on postprandial glycemia.

Results of the NAVIGATOR study were presented in the ACC Congress, (13) which assessed valsartan versus placebo in a factorial design, and nateglinide versus placebo at a metabolic branch point. A total of 9,306 patients with impaired glucose tolerance and high cardiovascular risk factors were included, and endpoints for nateglinide were considered for the development of new diabetes and cardiovascular events. Nateglinide is a hypoglycemic agent that concentrates its major effect on reducing postprandial glycemia.

Table 1. Effects of blood glucose levels on the risk*

	Glycosylated hemoglobin Hb A(1c) For every 1% increase (reference 5% = risk 1)		Fasting glycemia For every 10 mg/dl increase (reference 100 mg/dl = risk 1)	
	Adjusted by age and sex	Adjusted by other factors	Adjusted by age and sex	Adjusted by other factors
Death	1.21 (1.13-1.28)	1.12 (1.05-1.21)	1.035 (1.012 -1.058)	1.021 (0.99-1.045)
Coronary heart disease	1.34 (1.27-1.42)	1.19 (1.11-1.27)	1.058 (1.034-1.082)	1.013 (0.986-1.041)
Ischemic stroke	1.41 (1.30-1.54)	1.34 (1.22-1.48)	1.089 (1.057-1.121)	1.068 (1.034-1.104)

* Late follow up (more than 15 years) of the ARIC epidemiological study in 11,092 individuals without known diabetes or history of cardiovascular disease. (9) Values are expressed in hazard ratio, and their confidence intervals, 95%. Hazard ratio is a synonym of relative risk in follow-up studies. In each case, the second column adds other factors to the adjustment by age and sex: LDL and HDL cholesterol levels, triglycerides, body mass index, dichotomous hypertension, physical exercise, education, and smoking. To interpret the result: The adjusted HR of coronary heart disease was 1.013 every 10mg/dl increase for glycemia compared with 100mg/dl, which means that the risk increases by 1.3% every 10 mg/dl mean fasting glycemia. Also, adjusted HR of coronary heart disease for each 1% increase in the value of Hb A(1c) is 1.019, which means that risk increases 19% every 1% increase in Hb A(1c). It should be noted that in the model for glycemia between 100 abd 126 mg/dl, the increased risk of events is not statistically significant, and increases more steeply afteRwards. Summary table of tables 2 and 3 from quote 9.

The study had a negative result: The drug did not modifiy the incidence of cardiovascular events. What was surprising was that the nateglinide did not reduce but increased the incidence of new diabetes: RR 1.07 (CI 95% 1 to 1.15), p = 0.05. Since new diabetes was defined by a fasting glucose level > 126 mg/dl or > 200 mg/dl at two hours of sugar overload, it is surprising that a documented hypoglycemic agent such as the nateglinide may have had a paradoxical effect. To make it simple, failing to reduce new diabetes might be related to the lack of impact on the prevention of cardiovascular events. Further analysis on the effect of nateglinide on glycemia is recommended.

The new diabetes

The impact on the definition of new diabetes was surprising: nateglinide is a hypoglycemic agent, and mean fasting glucose fell 0.47 mg/dl. If the fasting glucose level had been the only criterion for the new diabetes, the drug would have been effective: it reduced the level significantly (13%). However, for purposes of the tolerance curve, the result was reversed: the number of patients with > 200 mg/dl at two hours increased 24%. Patients did not have to take their medication that morning, and since it was a short-acting drug, the curve was performed without pharmacological effect. Surprisingly, the level of glycosylated hemoglobin with nateglinide in the new diabetic patients was 6.1%, lower than that of the control group: 6.3%; both p < 0.001. We thus see that the two criteria for defining new diabetes are opposed and dependent on the drug half-life; on the other hand, we do not know if the so-called new diabetes is clinically relevant.

We have discussed that in a recent epidemiological meta-analysis that assessed the impact of glucose levels on the clinical outcome, it was observed –taking into consideration the other risk factors– that every 10 mg/dl of glucose, risk of death increased 2.1%, risk of stroke 6.8%, and risk of coronary heart disease 1.3%. Through this simple association, it is clear that only major differences in glycemic levels may have cardiovascular impact. It is possible that the small variations in glycemic levels –which lead to cross the limit of 126 mg/dl and thus get a chemical diagnosis of new diabetes– have little clinical relevance, thus confirming the need for trials with clinical and non-pathophysiological endpoints. In this regard, outcomes of the DREAM trial have been heavily discussed, (14) which reported that rosiglitazone reduced 60% the incidence of new diabetes in 3 years of follow up, from 26% in the placebo group to 11.6% in the treated group. Expressed as absolute risk reduction, it was prevented that 14 every 100 individuals were diagnosed as new diabetes with the preventive glucose-lowering therapy. Since this effect was not associated with clinical benefits, it was (15) argued that the study contribution is that if 100 individuals are continuously treated with rosiglitazone, it is possible that 14 individuals do not need it as a result of spontaneous increase of glucose after 2 years, with no other benefit. It is a real nonsense. It is preferable to wait the necessary amount of time, and treat only those individuals who need it.

CONTROL OF BLOOD PRESSURE

Contributions of the ACCORD and NAVIGATOR trials

The epidemiological series have shown a consistent relationship between levels of systolic blood pressure from 110 mm Hg and cardiovascular risk. Thus, the definition of "hypertension" has become operational, dependent on the risk model and on the availability of safe drugs that lower blood pressure. Different trials have shown that this relationship is even more evident in patients with diabetes, and it has been suggested to try and reach mean values > 120/80 mmHg. There is also a preference to start treatment with ACE inhibitors or ARB. The reason is that, from the metabolical perspective, both betablockers and thiazides are associated with increased development of new diabetes in hypertensive patients, while, in several studies, the use of ACE inhibitors or ARB is associated with a reduction or at least a neutral effect, and is beneficial for diverse pathophysiological aspects.

I will briefly summarize the studies and their implications about two questions.

What is the goal to be achieved in the blood pressure figures?

ACCORD – Antihypertensive Arm (16)

A prospective assessment of the eventual reduction of cardiovascular events in 4,733 patients, associated with bringing blood pressure down to 120 mmHg with respect to the target of 140 mmHg. By the end of the first year of treatment, patients in the intensive therapy group had a mean blood pressure of 119.3 mm Hg, and 133 mm Hg in the standard therapy group. At 4.7 year follow up, there was no reduction in mortality (7% higher in the intensive therapy group, ns). There was a non-significant reduction of 12% in major events (cardiovascular death, myocardial infarction or stroke), and a significant reduction in the rate of stroke, impressive in percentages (RRR 41%, CI 11-61%), but low in absolute terms: from 0.5 to 0.3 yearly, ie, a reduction of two events every a thousand treated patients. This occurred at the expense of an increase in serious adverse effects of antihypertensive medication: 3.3% in the intensive therapy group, versus 1.3% in the standard therapy group, ie, an increase of two events every a hundred patients treated for a period of five years. The authors' conclusion is that more intensive control of blood pressure –which was properly managed, but at the expense of a higher risk of hypotension– was not associated with reduced cardiovascular events.

These results may be questioned by a number of limitations of the study. The rate of events was lower than expected, and may not have been able to detect minor differences. In my opinion, at least with our current resources, patients with diabetes do not require

a different approach to achieving the values in the control of blood pressure.

Do ARBs reduce the incidence of events in patients with diabetes?

NAVIGATOR – Valsartan Arm (17)

The study revealed the role of valsartan at a daily dose of 160 mg versus placebo in 9,306 patients with impaired glucose tolerance (glycemia between 95-126 mg/dl, mean 110 mg/dl), and abnormal tolerance curve (2-hour glycemia levels between 140-200 mg/dl). Patients had to have established cardiovascular disease or high risk factors to develop it in evolution. The study had a factorial design, and nateglinide was the other assessed medication. The goal of the study was to evaluate whether valsartan would reduce the incidence of new diabetes and would prevent cardiovascular events. At follow-up, with a median of 5 years, it was observed a 36.8% incidence reduction of new diabetes in the placebo group to 33.1% in the valsartan group, RRR 14% (8-20%). The absolute impact on mean fasting glucose was very low –only 0.5 mg/dl–, and on 2-hour glucose tolerance curve it was only 3 mg/dl.

Based on a mean of 140 mm Hg, blood pressure dropped in both groups, but more pronounced during the first year in the valsartan group: On average, systolic blood pressure was 2.8 mm Hg lower, and dyastolic blood pressure was 1.4 mm Hg lower; both were statistically significant. This blood pressure reduction was not associated with individual or group benefits in cardiovascular events (non-fatal infarction, cardiovascular death, general mortality, stroke).

How can those results be interpreted?

A way to read this work in favor of valsartan would indicate that the drug lowers blood pressure and prevents diabetes, becoming metabolically preferred over other antihypertensive drugs such as diuretics, for example. However, diuretics have been associated with reduced mortality in the treatment of high blood pressure, even in diabetic patients, despite their known effect of slight increase of glucose. If, instead of interpreting the findings on the basis of dichotomous definitions (diabetes – no diabetes) established by conventional criteria, the real impact is observed: the change of the glycemia obtained versus the placebo was so low that it is unlikely that it could have the clinical impact that the medical belief would relate to a new diabetes reduction of 14%. Tables show that patients in the placebo group received significantly more betablockers and thiazide diuretics, which is associated with increased glucose. In the VALUE trial (18), a reduction of new diabetes with valsartan compared to amlodipine had already been observed, but with a tendency to increased cardiovascular risk and no clinical benefit. Another fact in favor of not continuing to use new diabetes as endpoint in clinical trials. (19)

What is most surprising about this trial is that valsartan, even lowering blood pressure, was not superior to placebo in preventing cardiovascular events.

Summary of findings in trials of hypertension in diabetes, and implications for the clinical practice

These trials obtained very dissenting outcomes compared with what was expected, and according to our conceptual thinking about the relationship between blood pressure and cardiovascular risk in diabetes. The first one –prospectively exploring the goal currently recommended by the guidelines based on epidemiological data and subgroup analysis– failed to show that reduced blood pressure, a mean of 14 mm Hg, be linked to cardiovascular benefits. The second one –assessing the effects of valsartan– reduced blood pressure based on a mean of 140 mm Hg; the difference between groups was less pronounced and was not associated with improved cardiovascular risk.

THE PROBLEM OF TRIGLYCERIDES IN PATIENTS TREATED WITH STATINS

ACCORD – Fibrate Arm (20)

A total of 5,518 patients with type 2 diabetes were assigned, who were being administered 40 mg of simvastatin and were also treated with fenofibrate versus placebo. Its goal was to assess the modification of a combined endpoint of cardiovascular death, infarction or stroke. The mean baseline cholesterol level was 170 mg/dl, LDL level was 100 mg/dl, HDL was 38 mg/dl, and the median triglyceride level was 162 mg/dl.

Median triglycerides fell from 189.0 to 147.0 mg/dl in the fenofibrate group, and from 186.2 to 170.0 mg/dl in the placebo group. The difference between both groups was 23 mg/dl in the triglyceride levels (147 versus 170 mg/dl). There was no beneficial impact on clinical outcomes. The annual rate of combined event was 2.2% in the fenofibrate group and 2.4% in the control group. Mortality rate did not change either: 1.5% versus 1.5%, respectively.

As favorable outcome, the incidence of muscle disorders was not increased. The reference of myalgias unrelated to exertion was 41.5% in both treatment groups. In the following analysis, the authors found that in patients with HDL < 40 mg/dl and TGC level > 200 mg/dl, event reduction was statistically significant, which coincides with the analysis of subgroups from previous studies [BIP, (21) FIELD, (22) and HHS, (23)] (Table 2).

This observation should be taken just as a hypothesis, because it is an analysis of a subgroup that comprises only 20% of patients. As stated by the authors, the real conclusion of the study is that adding fenofibrate to statins in patients with diabetes does not alter prognosis –despite reducing triglyceride levels–, and leaves open the question of the eventual benefit

Trial (drug)	Hypertriglyceridemic Subgroup		
	Effect on the combined cardiovascular event	Definition of the subgroup	Effect on the combined cardiovascular event
HHS (gemfibrozil) TG	-34% (p < 0.02)	TGC > 200 mg/dl C-LDL/C-HDL > 5.0	-71% (p = 0.005)
BIP (bezafibrate)	-7.3% (ns)	TG > 200 mg/dl	–39.5% (p = 0.02)
FIELD (fenofibrate)	–11% (ns)	TG > 200 mg/dl C-HDL < 42 mg/dl	–27% (p = 0.005)
ACCORD (fenofibrate)	–8% (ns)	TG > 204 mg/dl C-HDL < 34 mg/dl	–31% (p = 0.05)

There was no significant reduction of cardiovascular events in the general population –except in the HHS trial–, and there was a significant reduction effect in all trials, considering patients with triglyceride levels > 200 mg/dl, and in three trials associated with reduced HDL. These are post hoc subgroup analyses, so they should be considered as hypotheses for further research. Taken from the Appendix I of the ACCORD Study. (24)

Table 2. Effects of the fibrates in the four large placebo-controlled trials that were published.

of concentrating, restricting or limiting the treatment in patients with higher triglyceride levels.

READING OF THE TRIALS: BY WAY OF CONCLUSION

Regarding the metabolic management of diabetes, studies carried out in the last couple of years provide valuable elements:

1. There is no evidence that tight glycemic control aiming at achieving Hb A(1c) < 6% provides benefits in terms of prevention of cardiovascular events, compared to a less tight control, tolerating glycosylated Hb of 7-7.5%. As mentioned, the American Diabetes Association sets a target of Hb A(1c) level below 7% as current goal.
2. The definition of new diabetes in the pharmacological clinical trials does not imply a clinical event as registered in medical belief. Prevention through changes in lifestyle, exercise and diet reduces 58% the development of new diabetes, and this benefit persists for a decade. New diabetes defined by glycemia evaluating drugs that change it metabolically is not an event in the sense of risk involved, but only a pathophysiological effect. As shown in the study with nateglinide, incidence of new diabetes lowers 13% or rises 24%, depending on how it is defined and what time the drug is administered. To consider diabetes as a dichotomous problem (above or below 126 mg/dl) even has a limited epidemiological value and no relevance in pharmacological studies with hypoglycemic agents. It becomes much more relevant in the assessment of non-pharmacological interventions in populations.
3. Fibrates are not drugs of obligatory use in patients with diabetes and high cardiovascular risk. Their systematic use, or their use in patients with low HDL but no high triglycerides, is not beneficial when patients are under statin therapy. The trials leave open the possibility of a benefit for patients with high triglyceride levels (> 200 mg/dl) and low HDL levels, but, in this regard, the evidence is weak. The lack of muscular complications when combining a high dose of simvastatin with fibrates is a reassuring fact. Recommendations from the American Diabetes Association are summarized in Table 3. Little value is given to fibrates in this consensus statement, except in the case of patients with hypertriglyceridemia; therefore, its absence in the table is natural, even without knowing the results of the ACCORD trial confirming that position. There is no consensus on the triglyceride level above which fibrates should be indicated for patients with diabetes, but there is likely to be agreement on more than 200 to 250 mg/dl, not controlled with diet and exercise.

Table 3. Recommendations from the 2010 consensus of the American Diabetes Association. Control of glycemia, blood pressure, and lipids in adults with diabetes

Objectives	
Glycosylated Hb	7%
Blood pressure	130/80 mm Hg
LDL Cholesterol	
Primary prevention	100 mg/dl (2.6 mmol/L)
Secondary prevention	70 mg/dl (1.8 mmol/L)

Regarding blood pressure management and the drug to recommend:

1. The studies presented do not consolidate the doctrine that the lower the blood pressure, the better the clinical outcome, even in high cardiovascular risk groups such as patients with diabetes. The target of 140 mm Hg for systolic pressure seems logical on the basis of the ACCORD trial findings. ***The American Diabetes Association proposes 130/80 in its new systematic review, which is similar to the target in nondiabetic patients.***
2. Preference of angiotensin-converting enzyme and ARB to other agents in patients with diabetes. The outcome of the NAVIGATOR trial is in sharp contrast to this consideration. Despite having been compared to placebo, achieving a greater reduction of blood pressure and its effect of lowering glucose levels had no significant clinical impact. ***The American Diabetes Association, in its***

new systematic review, still considers ACE inhibitors and ARB as first-line agents for the treatment of hypertension in patients with diabetes. Would it be recommended to indicate the most effective and best tolerated antihypertensive agent?

A GENERAL CONCLUSION

Studies independent from the industry, such as ACCORD, which have posed clinically relevant hypotheses oriented to patients with diabetes (up to what value it is recommended to lower glucose and blood pressure, or if lowering triglyceride levels is or is not beneficial), have produced outcomes that the studies oriented to potential benefits from specific drugs cannot provide. The puzzle of the pharmacological management of patients with glycemia or high Hb A(1c) levels is still arranging pieces, and on the basis of this new information we can approach to control blood pressure, cholesterol and glucose levels with goals that are easier to achieve, and with less interference in the patient's quality of life.

In the coming months, we will see renewed discussions about the outcomes of these trials, which will change our clinical practice.

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