

## Both glucocentric and cardiocentric approaches are necessary for a resilient disease such as diabetes

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### SUMMARY

Diabetes mellitus (DM) is a complex disease that compromises almost all systems in the human organism. Independently of the intrinsic mechanisms, the source of all consequences of DM is hyperglycemia, a condition associated to intense metabolic changes that will lead to increased morbidity and mortality in the long term. Several different therapeutic hypoglycemic oral agents were developed and significantly facilitated the treatment of hyperglycemia acting at different sites, since patients could take more than one agent. This glucocentric approach was somehow criticized as those hypoglycemic drugs have shown weaker than expected benefits in terms of cardiovascular outcomes and there was a sub use of statins and antihypertensive agents in this population. On the other hand, the catastrophic cardiovascular consequences of hypoglycemia in older adults submitted to tight glycemic control and the results of recent clinical trials that showed impressive reduction in cardiovascular outcomes with less potent antidiabetic agents seem to pave the way to a cardiocentric approach including a lax treatment of DM. Interestingly, the results obtained in recent studies with SGLT2 inhibitors are being mostly attributed to mechanisms other than its hypoglycemic effect in spite of including patients at high cardiovascular risk already taking hypoglycemic agents. Considering the worldwide growing number of patients with diabetes, caregivers must follow a dialectical thinking and choose a synthesis approach where glycemic control is the first and foremost target to be achieved, followed by control of cardiovascular risk factors.

**Keywords:** Atherosclerosis. Diabetes Mellitus. Risk Factors. Coronary Artery Disease.

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Diabetes mellitus (DM) is a complex disease that compromises almost all systems in the organism. Regardless of the intrinsic mechanisms, the cornerstone of all consequences of DM is hyperglycemia, a condition associated to intense metabolic changes leading to increased long-term morbidity and mortality. The introduction of hypoglycemic treatment, mainly insulin and the first oral antidiabetic agents in the first part of the 20<sup>th</sup> century has changed this scenario, promoting an epidemiologic transition. Indeed, in the second half of the last century, the life expectancy of patients with diabetes increased and cardiovascular-renal diseases became the leading causes of death. As a natural consequence, cardiovascular endpoints became the holy grail in clinical trials with patients with diabetes. The UKPDS trial demonstrated that metformin significantly decreased myocardial infarction rate

in patients with diabetes and body weight > 120% of their ideal mass.<sup>1</sup> It is important to notice, however, that, in the UKPDS trial, the average LDL-cholesterol level was 141 mg/dL at baseline and remained above the recommended target for this high-risk cardiovascular group after the long-term follow-up suggesting suboptimal cardiovascular risk factors control.<sup>1,2</sup>

Several different therapeutic hypoglycemic oral agents were developed for the treatment of hyperglycemia acting at different sites. In 2009, a pathophysiological approach was proposed as a new paradigm to achieve durable glycemic control in patients with DM. The new paradigm is based on a creative scheme called *the ominous octet* that has hyperglycemia in its core.<sup>3</sup> According to this algorithm, a triple combination of hypoglycemic drugs should be added to lifestyle intervention targeting HbA1c < 6.0%.

The ACCORD trial, however, put a damper on the glucocentric approach and was stopped earlier than anticipated due to higher mortality in patients enrolled in the intensive glycemic control group, without benefit in major cardiovascular events during 3.5 years of follow-up.<sup>4</sup> In addition, concerns rose for the consequences of severe hypoglycemia seen in the UKPDS trial that revealed a two-fold increase in the occurrence of major hypoglycemic events with the use of glibenclamide, a first generation sulphonylurea.<sup>5</sup> The development of second generation sulphonylureas has significantly decreased the occurrence of severe hypoglycemic events. The incidence of severe hypoglycemia in the intensive treatment arm in the ADVANCE trial that included the second generation modified release sulphonylurea gliclazide was 2.7%.<sup>6</sup> Interestingly, in the second 5-year-phase of this study (ADVANCE-ON), the use of oral antidiabetic drugs was at discretion of the attending physician, and the results showed that the mean between-group difference in glycated hemoglobin levels (lower in the intensive arm in the first phase) was no longer evident. Moreover, in spite of the increased glycated hemoglobin levels in both arms in the ADVANCE-ON, the occurrence of severe hypoglycemia was higher, 8.4% on average, suggesting that both safer drugs and closer follow-up care are necessary for DM patients.<sup>7</sup> Unfortunately, optimal glycemic control remains far below desirable rates in recent studies, indicating careless glycemic control, especially for the treatment of older DM patients.<sup>8</sup>

In conjunction with the concerns related to severe hypoglycemia and increased focus on cardiovascular prevention for DM patients, the results of recent clinical trials showing impressive reduction in cardiovascular outcomes with less potent antidiabetic agents seemed to pave the way to a cardiocentric approach.<sup>9</sup> Actually, the results obtained in recent studies with SGLT2 inhibitors are being mostly attributed to mechanisms beyond the hypoglycemic effect and directed only to patients with diabetes presenting high cardiovascular risk and that were already under an “essential” therapy that includes, most of the time, insulin and sulphonylureas.

In conclusion, we recognize that severe hypoglycemia is a condition to be absolutely avoided but not at the expense of a lax glycemic control.<sup>10</sup> Both the glucocentric and cardiocentric approaches are necessary for a disease as resilient as diabetes mellitus. In addition, the adequate care of patients with DM must involve early diagnosis of hypoglycemia, the control of cardiovascular risk factors (dyslipidemia and hypertension), as well as the identification of patients with established or high risk for heart failure, a major complication. Considering the worldwide growing number of patients with diabetes, caregivers must follow a dialectical thinking and choose a synthesis approach where glycemic control is as important as control of cardiovascular risk factors and should remain a target to be achieved.

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