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Editorial
DIABETOLOGY & CARDIOLOGY: THE FUTURE IS NOW!

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In July 2019 the American Board of Internal Medicine published a position statement in which a new sub-specialty alongside a new training curriculum was proposed: cardiometabolic medicine [1].

This new sub-specialty is a natural advance in the collaboration between two twinned medical specialties: diabetology and cardiology. The links between the two specialties are more evident as a continuous body of evidence is building regarding a long set of inter-connections. For a long time the links between the two specialties were considered merely based on the macro-vascular complications arising in patient with Type 2 Diabetes Mellitus (T2DM); in the early era of diabetes knowledge it was hypothesized that the macro-vascular complications arisen mainly due to an improper glycemic control associated to the presence of T2DM.

Nowadays, the paradigm is progressively changing, and the arising evidences are pointing to common pathogenic pathways between T2DM, atherosclerotic cardiovascular diseases or heart failure. More, therapeutic interventions developed for treating T2DM were demonstrated to be associated with a significant impact on cardiovascular risk, some of the molecules from recently developed classes (i.e. GLP-1 receptor agonists or SGLT2-inhibitors) decreasing the risk of cardiovascular events while older classes having molecules associated with demonstrated (i.e. rosiglitazone) or hypothesized (i.e. less SUR1 selective derivates of sulphonylurea) increases of the cardiovascular risk [2-4].

The connections between diabetology and cardiology are emphasized by a long series of facts [5]:

- people with T2DM are 4-5 times more likely to die due to cardiovascular causes and not due to diabetes-related causes;
- more than 50% of the excess of mortality which causes the decrease of life expectancy associated with the occurrence of T2DM is attributable to cardiovascular diseases;
- most patients, at the moment of T2DM are already having established atherosclerotic cardiovascular diseases or heart failure. The relationship is also valid vice-versa: an overwhelming proportion of patients with acute coronary syndrome or newly diagnosed heart failure if screened for, a diagnosis of T2DM or pre-diabetes is found - this is why both diabetes and cardiology guidelines are

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recommending the cross-screening of these pathologies if one is found.

- the glycemic imbalance is not the sole factor causing the excess of the cardiovascular risk in diabetes; more, the Accord study, pointed that aggressive interventions regarding glycemic control, with consequently aggressive HbA1c targets are increasing the cardiovascular mortality and overall cardiovascular risk. Surprisingly, at the post-hoc analysis of the Accord study, it was observed that the excess of mortality which was observed in the aggressively-intensive sub-group was not necessarily associated with episodes of hypoglycemias [6]. This was the moment in which the treatment paradigm of diabetes started to change again - the hypothesis that regarding the patient's cardiovascular risk it counts more how you decrease glycemia but not at the same extent how much you decrease glycemia.

Despite the fact that from a historical point of view the diabetes guidelines were somehow neutral regarding the choice of one or another anti-diabetic pharmacological class of drugs (when reaching the secondary therapeutic failure it was recommended to add another agent - from another class - according to a stepwise algorithm, but the class of choice was not ranked - there were just presented the advantages and disadvantages of choosing representatives from that class) the approach begun to change in the autumn of 2018 when the ADA/EASD Consensus was published. The joint position of the two most-important scientific societies involved in diabetes-care was to define clusters of patients, based on their particularities, inside which the choice of anti-diabetic classes was ranked in a hierarchical manner. First defined cluster of patients included patients with cardiovascular diseases (both atherosclerotic as well as heart failure) and chronic kidney disease): in this cluster of patients, the guideline stated that a drug with demonstrated superiority (either a GLP-1 receptor agonist in case of atherosclerotic cardiovascular disease predominance or a SGLT2 inhibitor in case of heart failure or chronic kidney disease predominance) in regard to cardiovascular risk **should be the treatment of choice** after metformin. More, regarding the treatment if initiation of an injectable therapy is needed, the same guideline clearly states that in most cases the addition of a GLP1-RA is preferable versus the addition of basal insulin and this is due to the long series of pleiotropic effects of GLP1-RA in patients with T2DM and thus not only to the global cardiovascular risk reductions observed or better glycemic control without the risk of hypoglycemias but also due to long set of desirable effects on several biomarkers like weight, blood pressure or lipid profile [7].

Evolution or revolution?

In Paris, September 2019 the European Society of Cardiology presents a new, radically improved guideline addressing the overall management of patient with cardiovascular diseases and T2DM. (8) This guideline comes in a short timeframe after the previous position statement proposed by the same society regarding this issue, which was released in 2013. As recognized in the beginning of the guideline, new recommendations were needed since *"it has been a period in which we have seen an unprecedented increase in the evidence base available for practicing healthcare professionals to refer to in their daily consultations. This has been characterized by the presentation and publication of a number of CV safety trials for type T2DM treatments, the results of which, to the casual observer, must seem both exciting and bewildering*" [8].

The most important changes that appeared in this edition of the guideline are addressing the pharmacotherapy of the patient with T2DM. This is the first guideline from the modern era of diabetes care which states that in patient with T2DM and atherosclerotic cardiovascular disease or high/very-high cardiovascular risk, the classes of drugs which demonstrated superiority regarding the cardiovascular risk **(SGLT2i or GLP1-RA) should be used in monotherapy before metformin** and should be regarded as the **first pharmacological intervention**. Only if the glycemic control is not reaching the desired thresholds, metformin should be added as the second pharmacological option for the dual anti-hyperglycemic intervention. If the HbA1c is not reaching the desired value neither in dual-therapy, one representative from the other class (than the first option) with demonstrated cardiovascular superiority (SGLT2i or GLP1-RA). In the same time, the guideline states that the **sulphonylureas should be used only as the last resort**, when all other therapeutic options (including here also insulin) failed or are contraindicated, regardless the patient's cardiovascular risk profile (thus sulphonylureas should be avoided both in patients with high/very high cardiovascular risk as well as in patients at low or moderate risk).

In the spectrum of the increasing body of evidence, the guideline agrees and makes class I level A (the highest level of evidence) recommendations that in respect to glucose-lowering drugs:

- "**Empagliflozin, canagliflozin, or dapagliflozin** are recommended in patients with T2DM and cardiovascular disease, or at very high/high cardiovascular risk, **to reduce cardiovascular events"**
- "**Empagliflozin** is recommended in patients with T2DM and CVD to **reduce the risk of death"**
- SGLT2 inhibitors (**empagliflozin, canagliflozin, or dapagliflozin**) are recommended to **lower the risk of heart failure** hospitalization
- **SGLT2 inhibitors** are recommended to **reduce progression of diabetic kidney disease**
- "**Liraglutide, semaglutide, or dulaglutide** are recommended in patients with T2DM and cardiovascular disease, or at very high/high cardiovascular risk, to **reduce CV events**"
- "**Liraglutide** is recommended in patients with T2DM and cardiovascular disease, or at very high/high cardiovascular risk, to **reduce the risk of death**"

Another significant novelty, with immediate impact on the current clinical practice is that the ESC/EASD 2019 guideline recommends a downgrade of metformin's position in the pharmacological interventions ranking: now metformin should be regarded the first option only in case of overweight patients with T2DM without cardiovascular diseases and low cardiovascular risk (class IIa, level of evidence C).

Besides glucose-lowering therapies recommendations

Even if not as spectacular as the changes related to diabetes pharmacotherapy, several important new or modified recommendations are to be observed in the new edition of the ESC/EASD 2019 guideline:

It is now recommended that in patients with T2DM or pre-diabetes an individualized blood-pressure target should be adopted. Instead the former 140/85 mmHg threshold, the current guideline recommends a systolic blood pressure of 130 mmHg and, if tolerated, even lower than 130 mmHg but not lower than 120 mmHg. The exception from this rule addresses elderly

patients (>65 years old), in which a systolic blood pressure between 130-139 mmHg respectively a diastolic blood pressure between 70-80 mmHg are recommended.

In the field of lipids, the novelty addresses the cluster of patients with very high cardiovascular risk, patients in which a LDLc lower than 55 mg/dL (or a higher than 50% reduction vs. baseline) is recommended instead of the former lower than 70 mg/dL recommendation.

The combination of sacubitril and valsartan is recommended instead ACEIs in patients with T2DM and heart failure with reduced ejection fraction which are still symptomatic despite the treatment with ACEIs, beta-blockers and MRAs [8].

Instead of conclusions

We are assisting now to a veritable live revolution regarding the management of the patient with T2DM. The overwhelming and unprecedented evidences that have arisen in the latter years are radically changing our perspective on T2DM treatment in an extremely short timeframe: if in the late years of the previous decade we hoped to find efficient glucose-lowering drugs neutral on the cardiovascular disease, recent evidences demonstrated that novel therapies from modern classes of treatment (i.e. SGLT2 inhibitors and GLP1-RA) are not only having a desirable impact on the glycemic control but also a major impact in reducing cardiovascular risk, improving the overall patient's prognosis or even in increasing the patient's life expectancy - aims at which we didn't dare to hope ten years ago. Thus, the paradigm of T2DM is radically changing, irreversibly switching from a glucose-centerd to a patient-centered approach. Basically, if all T2DM drugs have demonstrated efficacy regarding glycemic control to a certain extent and thus regardless our choice we will be efficient in treating numbers (i.e. glycemias), if we want to treat our patient and not only his glycemia, if we want to prolong his life and to protect him from the most prevalent and worrisome complications and comorbidities, the wisely choice of a therapy with multiple demonstrated benefits, that goes far beyond glycemia is most probably the sole solution.

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