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Editorial

SHIFTING THE PARADIGM IN TYPE 2 DIABETES TREATMENT. A PRAGMATIC APPROACH OF THE ADA/EASD 2018 CONSENSUS: THE DIABETES DECALOGUE

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On 5th of October 2018, at the 54th Annual Meeting of the European Association for the Study of Diabetes the two major professional associations from the field of Diabetes: the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) presented a consensus position paper regarding the new paradigm of Type 2 Diabetes Mellitus (T2DM) treatment [1]. This consensus paper was necessary because of the new scientific evidences built on the foundation of recent findings, mainly from cardiovascular outcome trials (CVOT) with innovative treatment classes, which provided new insights regarding safety and pleiotropic effects of diabetes pharmacotherapy. The importance of this new evidence is highlighted by the fact that ADA released its second position statement in one year regarding the management of hyperglycemia in T2DM, a rare occurrence in the history of the organization. Such an event would not have taken place if not for the paramount clinical importance of the new building evidence.

This consensus position paper is now being adapted to the changing paradigm of T2DM treatment, which currently is a patient-centered approach in contrast to the historical gluco-centric one. In contrast to the ADA/EASD consensus paper published in 2015 which has a neutral position regarding the treatment of choice in the second pharmaceutical step (just presenting the advantages vs. disadvantages of different medication classes and thus the decision of choice being transferred completely to the physician) the guidelines published in 2018 are radically switching the approach. Now, the 2018 ADA/EASD consensus defines clusters of patients, based on their clinical particularities, in which some classes of drugs **should be preferred** due to their proven benefit. Another key message of the recent guideline is that clinical inertia is a real phenomenon, which should be avoided irrespective of its costs: the patient **should be re-evaluated** every three months and if the individualized targets are not reached the treatment **should be intensified**.

Our aim is to propose a practical and feasible approach of the guideline's recommendations adapted to every real clinical scenario, which will be structured in 10 main tasks: **The 2018 Diabetes Decalogue**.

1. Emphasize on lifestyle optimization and diabetes self-management

Lifestyle optimization should be the **foundation stone** of each patient's diabetes management. This optimization includes

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individualized diet and physical exercise recommendations. At the same time, self-management of the disease may be a treatment burden in every chronic condition. Of course, in a life-long disease like T2DM its importance is emphasized: optimal results cannot be achieved in the absence of medical interventions unless the patient is adherent: to medication, to specific diet recommendations, to physical exercise, to glycemic monitoring or to self-decision making.

2. Use Metformin

Metformin should clearly be the drug of **initial choice** for the patients with T2DM. In addition, it should be added to therapies based on other drugs for as long as possible. Exceptions should only be made in cases in which metformin is or becomes contraindicated or not tolerated by the patient. If metformin is not tolerated at the desired daily dose, the clinician should attempt to decrease the dose to find the maximum tolerated dose and thus do everything that is possible to have even a minimum daily dose of metformin. In addition, possible scenarios to maximize metformin's tolerance include gradual increases of the dose from minimum (500 mg/day) to the recommended dose (2000 – 2500 mg/day) as well as switching between different commercial formulas available in case of intolerance.

3. Avoid clinical inertia

Clinical inertia is an acknowledged burden in the treatment of T2DM and it consists of delaying treatment intensification for longer than the recommended timeframe (3 months). The ADA/EASD 2018 consensus **emphasizes** that if the individualized glycemic targets are not reached, treatment **should be intensified in no longer than a 3 month interval**. This 3-month interval is perpetual during the T2DM treatment, irrespective to the background medication.

4. Find out if your patient belongs to one of the specified clusters

The consensus identifies the following clusters of patients in which some therapies should be clearly preferred:

- patients with atherosclerotic cardiovascular disease (ASCVD), Heart Failure (HF) or chronic kidney disease (CKD);
- patients in whom there is a compelling need to minimize weight gain or promote weight loss;
- patients in whom there is a compelling need to minimize the occurrence of hypoglycemia;
- patients in whom the cost of drugs represents a major issue.

For this, we should assess key patient characteristics: comorbidities, clinical characteristics, issues such as motivation and depression, and also cultural and socio-economic context. **Build your own checklist** to make sure that you're not under-detecting these scenarios!

5. If your patient has ASCVD, HF or CKD

In these patients, the consensus states that the second-line **drug of choice should clearly be** a Sodium-Glucose Co-Transporter 2 Inhibitor **(SGLT2i)** or a Glucagon-like Peptide 1 Receptor Agonist **(GLP-1 RA)** with proven cardiovascular (CVD) benefits. In this cluster of patients, a slight stratification may be implemented:

- **If heart failure (HF) or CKD is predominant**, a **SGLT2i with evidence of reducing HF and/or CKD progression is to be preferred**, if the estimated glomerular filtration rate is adequate. Otherwise, the second choice would be a GLP-1 RA with proven CVD benefits.

- **If ASCVD is predominant, the drug of choice will be a GLP-1 RA with CVD benefit or an SGLT2i**

If the glycemic targets are not achieved within 3 months, the cross-addition between these classes is recommended (GLP-1 RA over SGLT2i respectively SGLT2i over GLP-1 RA).

Highlight: *there is no evidence of benefit from this treatment in patients at lower CVD risk and the combination of an SGLT2 inhibitor and a GLP-1 RA has not been tested in CVOTs. There is also no evidence of additional benefit from a cardiovascular perspective with this combination.* ***NOT YET ?!?***

6. Avoid Thiazolidinediones (TZD) if your patient has heart failure

TZDs are effective in reducing insulin resistance, however are associated with significant side effects like fluid retention, congestive heart failure, weight gain, bone fracture and possibly bladder cancer. Thus, if the patient has any degree of heart failure, the use of TZDs is prohibited.

7. If there is a compelling need to minimize weight gain or to promote weight loss

For these patients, after metformin the choice should be either a GLP-1 RA with good efficacy for weight loss or a SGLT2i if eGFR is adequate. If the glycemic targets are not reached, a cross-addition between these classes is recommended (GLP-1 RA over SGLT2i respectively SGLT2i over GLP-1 RA). If possible, further addition of sulphonylureas, thiazolidindiones or insulin should be avoided.

8. If there is a compelling need to minimize the risk of hypoglycemia

In patients for which hypoglycemia represents an issue of a special interest the consensus recommends the addition after metformin an SGLTi, GLP-1 RA, a TZD, or a DPP-4 inhibitor, followed by re-intensification of lifestyle optimization and combination therapies if HbA1c is above target.

9. Start the injectable therapy with GLP-1 RA rather than basal insulin

If during the T2DM management the need for injectable therapy occurs, we should prefer to start with a GLP-1 RA rather than basal insulin. The exception will be cases in which GLP-1 RA therapy is counter indicated and those patients with extreme and symptomatic hyperglycemia. By prioritizing the addition of GLP-1 RA in the detriment of basal insulin, we may achieve a comparable effect on the HbA1c accompanied by a neutral effect on hypoglycemia risk, decreases in body weight and additional benefits regarding the cardiovascular and renal protection. If the addition of GLP-1 RA is not enough to reach the individualized glycemic targets, it is recommended to further add basal insulin; in patients having both basal insulin and GLP-1 RA in their treatment regimen, to increase treatment adherence and patient preference the use of fixed-ration combinations (insulin Degludec+Liraglutide or insulin Glargine+Lixisenatide) is recommended.

10. Metabolic surgery may be a solution

Metabolic surgery can be considered a very effective salvage therapy - consider it in patients with T2DM and a body mass index of 40 kg/m^2 or greater, regardless of the level of glycemic control, and in those with BMI of 35-39.9 when hyperglycemia is inadequately controlled despite lifestyle and optimal medical therapy. Evidences are pointing to frequent T2DM remissions after metabolic surgery that are sustainable for at least 5 years. Even if complete remission is not always achieved, most frequently the reduction in the number and dosage of glucose-lowering medications is observed.

The cardio-diabetes team

Based on the previously presented statements, it becomes clear that building cardio-diabetes and diabeto-cardiology teams will be the future core structures of diabetes care in most of our patients. Cardiologists have started therefore to learn a lot more about diabetes and diabetologists have become more involved in the follow-up of cardiac patients. Thus, cardio-diabetology alliance became a useful meeting point for two specialties with a common goal of delivering high quality comprehensive care to this high-risk population [2].

Instead of conclusions

In the view of recent evidences, the ADA/EASD 2018 Consensus Position Statement records a natural transition of the T2DM treatment paradigm which historically started with a glucose-centered "the lower the better" approach, continued with "as low as possible without hypoglycemias" and now bringing a patient-centered, multifactorial approach. The 2018 Consensus clearly states now that regarding the treatment of patients with T2DM the "one size fits all" approach is not anymore an accepted one. The drugs of choice after metformin are now being ranked regarding their desirability, the newer, innovative classes being preferred; and this preference is based on the fact that, mediated by their pleiotropic effects (i.e. cardiovascular or renal risk, hypoglycemias or body weight impact) are bringing quality life-years to our patients.

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REFERENCES

1. Davies MJ, D'Alessio DA, Fradkin J et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*, 2018.

2. Gale EAM. A meeting point for cardiologists and diabetologists. In: *Diabetic Cardiology*. Fisher M and McMurray JJ (Ed). John Wiley & Sons Ltd 373(9626): pp1741, 2008.