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FACING THE CHALLENGE OF CLINICAL INERTIA IN 2021

What could it be the importance of a multi-scientific alliance in defeating therapeutical inertia?

Agostino Consoli[1]
[1]DMSI & CAST Università G. d'Annunzio, Chieti – Pescara.

Corresponding author: **consoli@unich.it**

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Therapeutical inertia means failing in intensely pursue therapeutic goals. As far as diabetes in concerned these should be:

1) achieve HbA1c targets;
2) achieve a composite target (target HbA1c, no hypoglycemia and no weight gain);
3) prevent or delay macro- and microvascular complications.

This is why at present time clinical inertia should be declined in two different ways. One is lack of treatment intensification and failure to achieve an optimal HbA1c target, the other is the inappropriate delay in adopting treatment strategies with a proven impact on cardio-vascular-renal risk. Unfortunately, we are facing both types of inertia.

As far as inertia in achieving ambitious HbA1c is concerned, one has to carefully consider that "blood glucose levels matter"! Plenty of evidence has accumulated demonstrating that achieving target HbA1c level does decrese occurrence and progression of diabetes complications, both micro- and macro-vascular. Furthermore, achieving target HbA1c levels also allows costs saving.

A recent analysis by Stephen Bain et al evaluated a population of type 2 diabetes patients in the UK, looking at the economic burden associated with diabetes-related complications due to clinical inertia [(1)]. For patients with an HbA1c level of 8.2%, 7 years in poor glucose control sensibly increased the mean costs associated with diabetes-related complications and with lost workplace productivity compared with subjects achieving good glycemic control (HbA1c 7.0%) over a 7-year and a 10-year time horizon. The total cost savings associates with timely enforcement of good glycemic control would be, according to the model of Stephen Bain et al, of about 2,600 million GBP.

This study should constantly be reminded to payers and decision makers in support of the notion that investing in better glucose control will actually decrease and not increase the budget burden associated with diabetes.

Furthermore, although some have interpreted the results of major cardiovascular outcome trials (CVOT) as proof that glucose control is not really important for reducing the risk of diabetes cardiovascular complications, Francesco Giorgino et al have shown the existence of a significant linear

correlation between the risk of major adverse cardiac events (MACE) and the difference in HbA1c levels between baseline and end of the follow-up in several of the CVOTs conducted with glucagon-like peptide-1 receptor agonists (GLP1-RAs)[2]. Furthermore, a meta-regression analysis performed by Giugliano et al on SGLT2i and GLP-1 Ras CVOTs results demonstrated a correlation between HbA1c reduction and risk of MACE[3].

If achieving optimal glucose control is important, using the appropriate drugs is important as well. A recent network meta-analysis published by a large group of investigators summarized the absolute effect on all-cause mortality for GLP1-RAs and SGLT2-is. Both classes of drugs lowered all-cause mortality, cardiovascular mortality, as well as non-fatal myocardial infarction and kidney failure[4].

As far as patients in the "high" to "very high" risk are considered, the meta-analysis shows that, relative to the endpoint "All Cause Mortality" 17 to 24 fewer events per 1000 persons over five years were reported in subjects treated with GLP-1 RAs as compared to placebo. Considering that about 30% of subjects with diabetes do fall within these category of high/very high risk, this, in Italy, corresponds to about 30,000 deaths saved in 5 years. Similar results are obtained by repeating the calculation with SGLT2-is: in this case the data are even more impressive, since one could calculate that about 56,000 deaths will be saved over 5 years[4].

Nevertheless, use of these drugs is still not as widespread as it should be, according to both national and international data[5].

It appears, then, that we still face an important "inertia problem" both in timely implementation of tight glucose control and in the use of innovative treatments with proven positive effects on the risk of complications. We have to realize that inertia in type 2 diabetes should not be "ascribed" to patients, but it mostly rests instead within physicians. A study conducted in the US showed that physician-based interventions perform worse than nurse, certified diabetes educator (CDE), or pharmacist interventions[6].

Schernthaner et al published a paper in Cardiovascular Diabetology addressing the problem of clinical inertia, listing the most likely causes for it, such as: preference for agents physicians have more extensive clinical experience of; insufficient opportunities for treatment re-evaluation; lack of interdisciplinary care and exchange between specialists; and maybe, even limited knowledge about CVOTs results[7]. The authors of this paper propose a "manifesto" for defeating clinical inertia in diabetes, calling for 7 actions labeled by the first seven letters of the alphabet, in the following order:

A. Advocate for post-CVOT treatment pathways that separate HbA1c targets from cardiorenal protection;
B. Be a voice for local guidelines that are ambitious for patients and regularly updated *(AMD and SID have recently published their joint guidelines for the treatment of type 2 diabetes, which are supported and published online by the Istituto Superiore di Sanità)*;
C. Collaborate on local education initiatives;
D. Deliver interdisciplinary care;
E. Educate reimbursement authorities;
F. Facilitate patient empowerment while helping patients understand the goals of cardiorenal protection;
G. Gauge individual physician performance to provide feedback and incentivize change;

Inertia is one of the greatest forces in the universe, as Isaac Newton stated five hundred years ago: «The vis insita, or innate force of matter, is a power of resisting by which every body, as much as in it lies, endeavours to preserve its present state». This means that we are "genetically" resistant to change. However, another great physicist (Albert Einstein), five hundred years after Newton, said: «Nothing happens until something moves». So, let's make the move! Let's foster access to most powerful therapies for a much larger number of patients! Let's defeat inertia and achieve a better treatment!

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