Therapeutic inertia: how can we measure it? The AMD Annals experience

Inerzia terapeutica: come possiamo misurarla? L'esperienza degli Annali AMD

A. Nicolucci[1]
[1] CORESEARCH - Center for Outcomes Research and Clinical Epidemiology, Pescara.

I would like to give my heartfelt thanks to AMD for giving me the privilege of being here today and sharing with you some new data regarding the Annals, which has just been processed. The data allow me to show you a series of indicators of therapeutic inertia taken from the Annals initiative.

The AMD Annals initiative originated in 2004, and the first edition was published in 2006. This initiative now involves more than 300 diabetes centres throughout Italy and a database covering more than 15 years, with more than 450,000 people with type 2 diabetes each year. This is an enormous source of information that allows us to create a picture of how the quality of the care provided to people with diabetes, both type 1 and type 2, is evolving in our country.

For a long time, we have been using a series of indicators that, albeit indirectly, allow us to see the extent of the problem of 'therapeutic inertia' in caring for the people with diabetes. For example, we estimate how many patients are not treated with insulin although they have glycated haemoglobin of 9% or more; how many patients treated with insulin still have glycated haemoglobin of 9% or more despite the insulin treatment; how many patients are not treated with statins while having LDL cholesterol of 130 mg/dL or more; how many of those treated with statins continue to have elevated cholesterol levels; how many are not treated with anti-hypertensive medications despite blood pressure levels above 140/90 mmHg, and how many of those who are treated do not achieve the desired targets. These are, therefore, indicators of the inertia related to the start of therapy, as well as indicators of the inertia in intensifying treatment after its initiation.

Comparing these indicators in 2011 and 2018 highlights how the share of subjects with glycated haemoglobin >9% not treated with insulin has fallen from 40.5% to 28.2%, while the share of subjects who continue to have glycated haemoglobin >9% despite insulin treatment has fallen from 25.7% to 16.1%. There was no significant change in the ratio of subjects not treated with statins despite elevated LDL cholesterol levels (from 57.5% to 52.4%). There was, however, a reduction to very low levels of patients who – while being treated with statins – continue to present LDL cholesterol values >130 mg/dl (from 18.1% to 10.2%). The data on blood pressure is less positive; indeed, a significant share of untreated subjects persists despite blood pressure values ≥140/90 mmHg (30.2% in 2011 and 26.2% in 2018); even among subjects treated with anti-hypertensive medications, almost one out of two continues to have blood pressure values ≥140/90 mmHg (56.8% in 2011 and 48.5% in 2018). Therefore, the AMD Annals show a variegated situation revealing a clear improvement for some indicators, and less sharp, while still significant, progress for other indicators.

To assess more in detail the problem of therapeutic inertia in the intensification of therapy in people with type 2 diabetes, HbA_{1c} values were evaluated at the time a second medication was added on metformin; upon the addition of a third medication in subjects previously treated with two oral medications; at the beginning of therapy with basal insulin; and upon the addition of rapid-acting insulin in patients already being treated with basal insulin. In addition to the HbA_{1c} value at the time of therapeutic intensification, we evaluated values up to three years before and three years after intensification.

The average HbA_{1c} values at the time of adding a second medication after failure of treatment with metformin alone are clearly elevated, being of 8.4% ; looking back over 3 years from the start of a second therapeutic line, , the average glycated haemoglobin values were around 7.5% 3 years before, with a gradual increase over the years. One year after the start of second-line therapy, glycated haemoglobin went down by 1%, from 8.4% to 7.4%, then it slowly started to rise again in the second (average HbA_{1c} of 7.5%) and third year (average HbA_{1c} of 7.6%) following therapeutic intensification.

This article is adapted from a presentation given by Antonio Nicolucci, on November 30, 2019 at the XXII Congresso Nazionale AMD.

Three years before intensification, about one quarter of patients had glycated haemoglobin >8%; these data clearly document the persistence of a substantial delay in therapeutic intensification. In the three years following therapeutic intensification, a significant number (around 25%) of subjects continued to have HbA_{1c} values >8%, indicating a delay in intensifying therapy once the second medication was added.

At the time a third medication was added to a previous dual oral therapy, the average glycated haemoglobin values were 8.1%. In this case as well, 20-25% of patients had glycated haemoglobin values >8% one, two and three years before therapeutic intensification. After therapeutic intensification, we found a significant drop in glycated haemoglobin values (HbA_1c of 7.3% after 12 months), with a tendency to creep upwards over the years; from one out of four to one out of five patients continued to have values >8% one, two and three years after therapeutic intensification.

Therapeutic inertia is even more evident at the start of treatment with basal insulin. In this case, the average glycated haemoglobin values were 9% at the introduction of insulin therapy; these patients had had glycated haemoglobin of 7.9% three years earlier. The benefits of therapeutic intensification are obvious: after 12 months, average HbA_{1c} values decreased to 7.8%, and those values were maintained after 24 and 36 months. Two to three years before the start of insulin therapy, 40% of patients had glycated haemoglobin >8%, documenting an even more marked delay than with the start of a 'dual-oral therapy' or a 'triple-oral therapy'. And in this case, too, at a distance of one, two and three years from the start of basal therapy, 40% of patients continued to have glycated haemoglobin >8%, showing not only a significant inertia in beginning insulin therapy but insufficient titration of insulin therapy as well.

When do we add rapid-acting insulin to basal insulin? Again, with a notable delay. Here the average glycated haemoglobin values are around 9% and were already higher than 8% three years before the start of multiple daily injections. The initiation of multiple-injection therapy is associated with a reduction in glycated haemoglobin, which reached an average of 7.8% at 12 months. We can imagine that many of these patients were elderly and fragile and had multiple complications, so we do not expect these patients to be taken back to a glycated haemoglobin level <7%. Nevertheless, more than one-third of patients three years before the start of multiple daily injection therapy had HbA_{1c} values >8.0% and would have needed therapeutic intensification.

What changed during these 15 years of data in the Annals? To answer this question, the entire observation period was split into three five-year periods (2005-2009, 2010-2014 and 2015-2019), and the average glycated haemoglobin levels were evaluated at the time of therapeutic intensification. Unfortunately, compared to 10-15 years ago, the average levels of glycated haemoglobin to which a new therapy was added remained practically unchanged, showing a persistent lack of proactive approaches to therapeutic intensification as the years went by. However, there are some positive findings: the values achieved at one year after therapeutic intensification were gradually reduced: for an add-on to metformin, HbA_{1c} values dropped from 7.6% in 2005-2009 to 7.2% in 2015-2019; for an add-on to the 'dual-oral', they went from 7.5% to 7.2%; not much changed with respect to the start of therapy with basal insulin (HbA_{1c} of 8.2% in the first five-year period as well as the last); but the glycated haemoglobin value one year following the start of multiple-injection therapy did in fact drop: from 8.1% to 7.7%. Thus, while difficulty in starting a new treatment persists, once the therapy is undertaken it probably has more of an impact; one year after the therapeutic intensification, we actually reach better values than we saw 5, 10 or 15 years ago.

In addition to the indicators of therapeutic inertia we have used so far, it is certainly possible to identify some new ones. The new classes of anti-hyperglycaemic medicines could, in fact, help reduce therapeutic inertia just because they overcome some of the most significant barriers, like fear of hypoglycaemia and weight gain. We therefore have tried to imagine what might be the new generation of indicators of therapeutic inertia/appropriateness in light of the most recent data available. First of all, based on the results of cardiovascular safety trials, we could ask: how many patients with a previous major cardiovascular event are now treated with an SGLT2 inhibitor or with a GLP1-Receptor Agonist (GLP1-RA)? Out of the total subjects with a previous major cardiovascular event in the Annals database (more than 64,000, or 14% of the total sample of patients seen in one year), 11% were in treatment with an SGLT2 inhibitor in 2018, and fewer than 5% were in treatment with a GLP1-RA: this means that about 84% of patients do not benefit from the treatments that are currently recommended by all national and international guidelines.

The most recent guidelines of the European Society of Cardiology (ESC) suggest using these two classes of medications in subjects at very high cardiovascular risk, defined as the presence of a previous major cardiovascular event, organ damage, or at least three of the cardiovascular risk factors (age, hypertension, high BMI, cigarette smoking and dyslipidaemia). In the Annals population, 93.1% of subjects fit the definition of 'very high cardiovascular risk'; in practice, based on the ESC guidelines, almost all patients seen in the normal clinical practice of Italian diabetes centers should be considered at very high cardiovascular risk. But how many of these subjects are currently in treatment with one of the two recommended classes of medications? A little less than 10% are getting SGLT2 inhibitors and a little less than 6% are getting GLP1-RAs; there is thus much to be done to get in line with the most recent scientific evidence.

Another emerging indication supported by solid evidence is that of using SLGT2 inhibitors in patients with heart failure. In the AMD Annals database, the number of subjects with heart failure is relatively low, probably due to little uniformity in reporting data related to heart failure in computerised medical records. In any case, of the patients whose records show the presence of heart failure, about 16% are in treatment with SLGT2 inhibitors. Here, too, there is a significant proportion of patients who could benefit from treatment and who currently have not yet been treated with these medications.

Equally relevant are the data supporting the protective effect of SGLT2 inhibitors in the progression of kidney damage; therefore, another indicator could be the percentage of subjects with albuminuria and with an estimated glomerular filtration rate that is not markedly reduced (≥60 ml/min) who use this class of medications. In this case as well, the percentage is around 13%.

Finally, and perhaps a little surprisingly, the class of patients that to date seems to use the new classes of medications the most are obese patients (BMI >30 kg/m^2) with poor metabolic control (HbA_{1c} >8.0%). In this case, about one-third of patients is in treatment with SGLT2 inhibitors (20.4%) or a GLP1-RA (10.6%). It is likely that these patients more often present a previous cardiovascular event or other risk factors that lead to the prescription of new medications.

Another way to look at therapeutic inertia involves patients with a new diagnosis of type 2 diabetes at their first visit to diabetes centers. In particular, we assessed how much time is needed for patients who had glycated haemoglobin >7% on their first visit to be brought back to target (HbA_{1c} <7%). The median time to achieve a target <7% is 6 months; this is quite a positive data finding, as it indicates that 50% of newly diagnosed patients reach the target of <7% at 6 months from their first visit at a diabetes center (of those who did not already have glycated haemoglobin <7% at the first visit). Nevertheless, within 12 months, 63% of patients reached the target, and that percentage rose to 74% in 24 months. This means that one out of four patients has not reached the target after two years. Dr Eckel emphasized the problem of therapeutic inertia tied to the concept of metabolic legacy; we know how important a particularly proactive approach is, especially during the early stages of the disease, in avoiding or delaying the onset of long-term complications. These data tell us that, in essence, there is a non-negligible proportion of patients who have not yet reached the therapeutic target after two years. Probably not all these patients have clinical characteristics that make a <7% target recommendable; it is equally true, however, that being newly diagnosed patients, most of them are not especially complex or compromised.

Obviously, this is a preliminary analysis of new data: we will do everything to attain a better understanding of the characteristics of patients who, two years after diagnosis and the first meeting with a diabetes facility, have not reached the recommended target yet.

Finally, there is another aspect of therapeutic inertia that we have not mentioned yet. Inertia does not consist only of a failure to intensify therapy when indicated, but can also be seen in a failure to de-intensify therapy if necessary. Take the case of patients aged ≥75 years with HbA_{1c} <7%, treated with secretagogues or insulin; in these patients, de-intensifying therapy is probably indicated to reduce the risk of hypoglycaemia. The AMD Annals show how 16.4% of patients with these characteristics could benefit from shifting from a sulphonylurea to a DPP4-inhibitor or, perhaps, if they are patients on insulin therapy, a reduction of dosages should be taken into consideration. It must be remembered that many patients, especially the elderly, use emergency services or are admitted to hospital due to episodes of severe hypoglycaemia at a significant cost, both from a clinical perspective and from a financial and human perspective. Thus, de-prescription should also become an important indicator of therapeutic inertia for all purposes.

In conclusion, measurement is the first step in making improvements. There is a constantly

increasing need to measure therapeutic inertia. In agreement with the American Diabetes Association and other scientific societies, it is important for us to establish a shared set of indicators of therapeutic inertia that can then be measured in a constant and reproducible way over the years. We have seen how the Annals database offers infinite ways to assess therapeutic inertia, by using the old indicators as well as considering an entire series of possible new indicators. Dr Di Bartolo strongly emphasized the importance of educating not just patients but healthcare professionals as well; certainly, all this information on therapeutic inertia could become part of specific education tools aimed at the recognition and overcoming of therapeutic inertia. As a researcher, I am hoping for the possibility of taking specific educational measures at certain centres compared to others to evaluate whether these educational measures are actually able to change clinical practice, using as a measurement of efficacy the selected inertia indicators. Furthermore, in order to improve the quality of our care, some of these indicators could be added to the medical records and made visible in real time to allow the physician to have an immediate idea for which patients it is important to intensify - or de-intensify – therapy, based on their characteristics.

I sincerely hope that this is only the beginning of a process that could truly lead to a reduction of the inertia documented in the Annals. The first signals of improvement provide significant hope, but there is still a long way to go. A scientific association like AMD can play an essential role and must invest a lot seeking to reduce such an important and widespread phenomenon.