ADA AMD JOINT SYMPOSIUM ON CLINICAL INERTIA

Therapeutic inertia and its impact on treatment and diabetes outcomes: the ADA approach

Inerzia terapeutica e suo impatto sugli esiti del trattamento e del diabete: l'approccio ADA

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It's really my pleasure to represent the American Diabetes Association here at your biennial AMD meeting. I met so many of you and it seems like a great crowd all supporting the improvement of the lives of people with diabetes which is really the American Diabetes Association's mission. So, I am here representing the organisation as its president-elect. I will become president on January 1, 2020, and I will take over for professor Lou Philipson from the University of Chicago who is the outgoing president. My topic this morning is "Therapeutic inertia and its impact on treatment and diabetes outcomes: the American Diabetes Association approach."

In the United States (U.S.), 1 in 11 Americans have diabetes and 84 million people (using the current criteria to define prediabetes) have pre-diabetes, with only 10% of those with pre-diabetes aware that they are at risk for developing diabetes. There is currently substantial controversy related to using HbA1c 5.7% to 6.5% to define prediabetes. We will certainly know that those individuals whose HbA1c is between 6.2% and 6.5% are at far greater risk than individuals who have HbA1c of 5.7% to 5.9%.

The economic cost of diabetes in the U.S. is huge, with 327 billion dollars spent in 2017 on diagnosed diabetes. This includes 237 billion dollars spent on direct medical costs and 90 billion dollars lost to reduced productivity. Direct medical costs represent a 26% increase, adjusted for inflation, since 2012. This change is due to both the increased prevalence of diabetes and the increased cost per person affected by diabetes. Complications that contribute to increasing cost of care include neurological issues, peripheral vascular disease, cardiovascular disease, nephrotic syndrome, progressive renal insufficiency, issues related to ophthalmology, and foot care, among others. Unfortunately, many people with diabetes suffer from multiple comorbidities and complications. Indirect costs related to diabetes include more than 300 million workdays per year lost in the U.S. and 277,000 premature deaths attributed to diabetes. Many of these deaths are listed with cardiovascular disease as the primary cause, but we know well that diabetes and cardiovascular disease are increasingly overlapping entities with a strong association between diabetes and increased risk for stroke, heart attack and death from cardiovascular disease.

Medications account for a substantial part of cost of taking care of patients with diabetes. Of the 31 billion dollars spent each year in the U.S., half of that is for insulin. The cost of insulin in the U.S. has skyrocketed over the last 5 to 10 years, and it is difficult to explain why our country, more so than the rest of the world, is paying so much for insulin. Care for people with diagnosed diabetes accounts for 1 in 4 health care dollars in the U.S., and 1 in every 7 health care dollars in the U.S., or about 14% of U.S. health care costs, can be attributed directly to the care of diabetes.

We've seen a lot of therapeutic advances over the past 20 years, but lifestyle remains critically important. By lifestyle we mean adequate nutrition, adequate physical activity, and cessation from tobacco use to try to modify the natural history of diabetes and its related comorbidities. The discovery of insulin in 1921 was perhaps one of the greatest medical advances in human health. Sulphonylureas were then introduced in the 1960s followed by metformin which was approved in Europe far before receiving approval by the U.S. Food and Drug Administration. Since the approval of metformin we have seen a

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cascade of new treatment options including alpha-glucosidase inhibitors, rapid-acting insulins, basal insulins, thiazolidinediones, the glinides which are rarely used now in the U.S., the GLP-1 receptor agonists, pramlintide (which has minimum use currently), the DPP-4 inhibitors, and bromocriptine. Most recently we have seen the SGLT-2 inhibitors with increasing evidence of their benefit, not only to treat the glycaemic burden we associate with diabetes, but also their benefit in reducing cardiovascular disease risk and progression of diabetic nephropathy.

Despite the increasing number of new diabetes medications and related technologies such as pumps and sensors, the achievement of individualized HbA1c targets has declined from nearly 70% in the early 2000s to less than 64% in the years 2011 to 2014. Over that same interval, particularly from 2007 to 2014, the proportion of patients with HbA1c >9.0% increased from 12.6% to 15.5%. Despite the advances in technology, in medications, we are seeing this overall decline.

So, what's wrong with this picture? First, there is a decline in patients achieving an arbitrary HbA1c of less than 7%. At best, only 50% of patients are at individualized goals for the treatment of diabetes. Second, there is an increase in percent of patients with very poor control. Third, there is an unacceptable level of morbidity and mortality that relates to diabetes leading to tremendous costs to society, not only in terms of the cost medical care and prescriptions, but in terms of lost work time.

At the root of the problem is the concept of therapeutic inertia – the failure to establish appropriate targets and to subsequently escalate treatment to achieve those goals. It is responsible for substantial, preventable complications of diabetes, with the associated excess in both direct and indirect heath care costs.

Data by Fu and his colleagues (Fu AZ et al. DOM 2011) show that the medium time for intensification of patients who were on metformin only and had an HbA1c ≥7.0% was 14 months. In this study mean index HbA1c was 8.0% overall, with 66%, 19% and 15% of patients having an index HbA1c of 7% to <8%, 8% to <9% and ≥9%, respectively. Median time to treatment intensification was 19, 8.7 and 4.5 months for patients with index HbA1c of 7% to <8%, 8% to <9% and ≥9%, respectively. Furthermore, those patients that were at higher doses of metformin (≥1500 mg/day) and presumably failed in reaching the target had an average intensification time of nearly 9 months, while for those with a lower metformin dose it took almost 2 years to intensify their treatment regimen. Of course, we can also argue whether an HbA1C of 7% is an appropriate goal for all patients. The truth is that many of the patients I take care have an HbA1c goal of 8% or even higher because the comorbidities are substantial and ultimately their life expectancy is limited.

At the American Diabetes Association, we think that, although therapeutic inertia impacts all populations, targeting individuals with type 2 diabetes is our obvious first priority. The causes of clinical inertia can be debated but they are clearly multifactorial, with contributory elements from five stakeholders groups, including: 1) people with diabetes themselves; 2) clinicians and other healthcare professionals who are inadequately informed or are not proactive; 3) the healthcare systems which may be less of an issue in Italy, but is clearly an issue in the U.S; 4) payers that are in contractual relationships with the healthcare system to assure the provision of adequate and updated care to patients with diabetes; 5) industry that sets the cost of medications and devices. In the U.S. another contributor to the problem is PBMs (pharmacy benefit managers). These organisations act as middlemen between the pharmaceutical industry and pharmacies and are responsible for maintaining the formulary, contracting with pharmacies, negotiating discounts and rebates with drug manufacturers, and processing and paying prescription drug claims.

The promoters of therapeutic inertia often cited include clinician-related issues, patient-related issues, and healthcare system/practice-related issues. For the clinician all the issues relate to challenge of taking care of patients including insufficient time, failure to set appropriate goals, and failure to initiate or advance treatment in a timely manner when indicated. Factors related to the patient include the denial of diabetes as a disease, an inadequate health history that is provided to the clinician, being already on many medications, refusing advances in therapy, and lack of trust in the physician. Lifestyle factors also clearly play a role. It's hard to convince a patient to increase medication when the HbA1c elevation doesn't hurt, when they can't feel their blood pressure elevation and when their cholesterol is high, yet they don't experience any symptoms. Healthcare system factors include the lack of adequate clinical guidelines, difficulties in planning visits or lack of active outreach to patients, lack of team approach to care, and poor communication between physician and staff.

Clinical inertia plays an important role in delaying intensification. A 2013 study showed that going from a single oral agent to multiple agents, including injectable therapy such as GLP-1 receptor agonists, can take up to 7 or 8 years, based on a UK database (Khunti et al. Diabetes Care 2013). It is important to note that this study did not include more recent drugs such as SGLT2 inhibitors. More updated data by the same group from the UK show the glycaemic burden defined as the length of time with an HbA1c level above an individualized target during a given period (Khunti et al. DOM 2018). These data show that the delay in intensification based on a target level of HbA1c is anywhere from about 4 to 5 months up to 7.2 years or even longer.

The analysis of electronic medical records relative to 37,053 patients who initiated basal insulin showed that 40.7%, 15.3%, 16.0%, and 28.0%, respectively, had uncontrolled HbA1c for <6, 6 to <12, 12 to <18 and 18 to 24 months before insulin initiation (index date) (Raccah D et al. 2019). Mean follow-up HbA1c values were higher with longer preindex-date duration of uncontrolled HbA1c (8.0% ± 1.7%, 8.2% ± 1.6%, 8.5% ± 1.7%, and 8.6% ± 1.7% for <6, 6 to <12, 12 to <18, and 18 to 24 months). Attainment of HbA1c <7.0% worsened with increasing preindex-date duration of HbA1c ≥7.0% (29.6%, 20.0%, 14.6%, and 11.5% for <6, 6 to <12, 12 to <18, and 18 to 24 months).

Ultimately this can have significant impact on complications. Different studies have looked at patients whose HbA1c remained elevated in the absence of intensification, and those in fact who had more rapid intensification. The delay in intensification produces a dysglycaemic legacy effect. Taking longer to intensify treatment and achieve a HbA1c closer to the target levels is associated with a greater risk of myocardial infarction, stroke, heart failure and a composite cardiovascular diseases outcome (Khunti K. Primary Care Diabetes 2016).

Now, what's in a name? - Compliance, adherence, concordance, persistence. These are all adjectives to describe therapeutic inertia and its impact on our dated existences as healthcare professionals. Is this due in fact to lack of individualized target setting for HbA1c, or is it reluctance of patients and physicians towards prescribing more medications, including injectable therapies, and/or costs? It is unclear, but I think it's all the above. So, the elements of a multifaceted approached to improve medication adherence include positive relationships and quality of the clinical environment we all exist within. In addition, the ongoing reinforcement, motivation, and support provided at every step along the path of the health care system that deals with patients with diabetes is critical. We are talking about not only the physician, but we are also talking about the diabetes educator, the nurse practitioner, the physician assistant, the pharmacy doctors, and everyone who may have contact with our patients with diabetes.

Simplifying dosage regimens also plays an important role in helping reduce inertia. Prescribing combination oral therapies or combination therapies for injectables like GLP-1 receptor agonist and insulin when appropriate is important. However, the cost as we well know, can drive many of these decisions we make in a clinic.

Involving the patient in the decision-making process and setting goals that are later reviewed with the patient is certainly relevant to treating patients to targeted and individualized goals. Education about the medication, its side-effects, the duration of therapy, and what a patient can expect is fundamental. Furthermore, we need to consider the importance of follow-up care. Think about statin guidelines in 2013 which I was part of. People tended never to measure the cholesterol again after an initial goal was achieved, but that's wrong. So, I think ultimately adherence and follow-up is critical. It is therefore important to have both the patient and the provider understand what an appropriate follow-up interval might be. Social support, including family members, is also important.

While our conversation relates mostly to type 2 diabetes, between 5 to 7% of people with diabetes have type 1 diabetes. The therapeutic decision-making process is somewhat different there, but increasingly does include the use of drugs like GLP-1 receptor agonists, and more so, SGLT2-inhibitors in patients with type 1 diabetes.

Finally let's talk about self-management. Patients themselves need to have ownership for diabetes as a life, not a disease. Thinking about it as a life, there are day-to-day operations that must be consider. This is an important message to transmit to our patients and important to help modify therapeutic inertia in the right direction to achieve better control. So, what else is important to know about this concept of therapeutic inertia? The legacy effect of early aggressive management has clearly been demonstrated for both type 1 and type 2 diabetes. Early tight control leads to longer term maintenance of glycaemic control. The science behind this may be βell function to a large extent in type 2 diabetes.

Improving the ability of β-cells to respond to glucose stimuli is an important legacy effect we need to learn more about. Therapeutic inertia also leads to a reduced likelihood of achieving target goals later and impacts the trajectory of β-cell failure in type 2 diabetes. So therapeutic inertia, modified to a more proactive approach, can relieve that burden. Early intensification of treatment, particularly in select patients, is associated with a shorter time to subsequent glycemic control. I've showed you some data that represents the delay and have had mild effect not only on glycemic control, but also on complications of diabetes. Finally, therapeutic inertia has been associated with reduced quality of life for the patient, along with increased risks of morbidity and mortality. Intensifying therapy earlier on has benefits not only for HbA1c and reaching targeted goals but also for giving the patient an improved quality of life and ultimately a reducing comorbidities and mortality related to diabetes.

Drivers and enablers of therapeutic inertia: is there a hierarchy?

Driver e fattori abilitanti dell'inerzia terapeutica: esiste una gerarchia?

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During my presentation, I will seek to answer two questions:

1. Is there a single driver of therapeutic inertia?
2. If there are multiple causes, is it possible to establish a hierarchy among the different possible drivers of therapeutic inertia?

An answer to the first question is partially answered by reading Bob Eckel, who provides a good definition of therapeutic inertia as the failure to begin treatment or failure to intensify treatment faced with HbA_{1c} values far beyond the established therapeutic target. This dimension of therapeutic inertia, which Dr Eckel showed us in the context of the United States, can be measured effectively in Italy using data from the AMD Annals. The data tell us that 47% of our patients with type 2 diabetes do not have glycated haemoglobin < 7%, and that 16% of patients have HbA_{1c} values > 8%. If we turn to a composite endpoint, shown by the proportion of patients who simultaneously have glycated haemoglobin values < 7%, LDL cholesterol < 100 mg/dL and blood pressure < 140/90 mmHg, only 20% of the population treated in our country's Diabetology Services meet these criteria.

The published data clearly demonstrate the consequences of therapeutic inertia, which is responsible for an increased risk of developing the chronic complications of diabetes. How aware are we, though, of the possible consequences of therapeutic inertia? To answer this question, we used a web survey, which was taken by a fair number of clinical diabetologists (153) who participate in the activities in our AMD assistance network. Each question could be answered on a scale from 0 (no impact) to 10 (maximum impact).

The first question was, 'In your opinion, what is the impact of therapeutic inertia?'

The survey documented substantial agreement among the participants on the impact of inertia on the risk of having cardiovascular events, of not bringing blood glucose control to target, of developing complications associated with diabetes and, finally, the risk of all causes mortality. For each of these items, the score was very high (7.8-7.9), indicating an awareness among physicians of the significance of therapeutic inertia.

At this point, we could already attempt to answer the first question: is there a single cause of therapeutic inertia? The answer is no. We can frame therapeutic inertia as a very complex, multi-factorial element; this phenomenon is becoming increasingly relevant, and obviously does not only involve diabetes but other chronic conditions as well. Considering therapeutic inertia as a multi-factorial condition,

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we must recognize that some of these factors must be ascribed to the patients, and some are due to us, the healthcare professionals (HCPs), but also partially due to the healthcare system we are working in every day.

A review of the previous studies published more than one year ago effectively summarised the portrait of the factors contributing to therapeutic inertia (fig. 1) (Okemah J et al. Diabetes Ther 2018). Therapeutic inertia, which is today's subject, is at the centre, and it is supported by three tiers of factors: related to the patient, related to the HCP and related to the healthcare system. The barriers correlated to the patient include: a denial of the disease, a lack of awareness of the progressive nature of diabetes, a lack of awareness of the implications of suboptimal blood glucose control, the fear of side effects, the anxiety of not being able to handle complicated treatment regimens during everyday life; too many medications, the cost of treatment (which, fortunately, is not significant for the patient in Italy), a lack of communication with clinicians, or the team; a lack of support; and a lack of trust in the clinician.

In the web survey cited above, we attempted to raise questions about this issue with Diabetologists, to find out what they think: 'In your opinion, how much impact do these factors related to the patient have on therapeutic inertia?'

Infirmity, lack of compliance, advanced age, a patient living in poor social conditions, a patient without good cognitive abilities, and others including fear of hypoglycaemia and poor school education were all considered relevant aspects, with high average scores (around 7).

Going back to the review of the published studies mentioned above, an interesting consideration should be made: when we enrol our patients in a randomised clinical study, the problem of therapeutic inertia does not exist or is very much contained. The most important element making the difference between a patient involved in a randomised clinical study and normal clinical practice is that we clinicians and the team supporting us in a trial provide the patient with continued, constant educational inputs that buffer many of the elements listed above that are the cause and reason for therapeutic inertia on the patient's part.

Therefore, the lesson we can learn from the 'artificial' setting of randomised controlled trials is that good education and continuing support can be – and must be – one of the solutions to therapeutic inertia when we see it in our patients.

From this perspective, it is important to understand our patients' perceptions: fear of beginning or intensifying a treatment is indeed often associated with a feeling of failure in the patient's mind, or them seeing the intensification as a sort of threat: 'After all, I can do something. This suggestion of intensification is just a threat, but I can get along in some other way'.

Patient education plays an essential role in confronting and resolving these perceptions, a role clearly demonstrated by scientific evidence. A systematic review of 118 studies of therapeutic education in self-management of people with type 2 diabetes documented a significant reduction in HbA_{1c} levels to 0.57% compared to the usual care (Chrvala CA et al. Patient Education and Counseling 2015). The same systematic review found that the greatest benefits are obtained if the educational measures last 10 hours or more and if they include a combination of individual and group sessions.

As part of AMD's initiatives, a special initiative was promoted aimed at understanding which of the activities a Diabetologist performs in his/her normal daily clinical practice brings about the best results for people with diabetes. In this initiative, called Diabetes Intelligence, we sought to measure the impact on outcomes of all activities performed during our clinical interactions with patients. We asked an especially sophisticated algorithm, driven by Artificial Intelligence (AI), to produce a score; the results show that the highest points in this score can be attributed to educational aspects in our daily interactions with people with diabetes. This gave rise to an experiment aimed at describing what the core curriculum should be for those striving effectively to manage people with diabetes. Consequently we developed an accreditation process for certain clinical skills, most notably one that views the diabetologist as an expert in Diabetes Self-Management Education and that makes a large impact on the resolution of therapeutic inertia.

Turning to another dimension of therapeutic inertia: although patients are part of the system, there are other components that come into play: we as HCPs, and all those elements, not just the organisational ones, that characterise the environment in which we work.

Then there are what we consider to be factors to be attributed to us clinicians that support ther-

apeutic inertia, once again referring to our web survey. Among the causes of therapeutic inertia, we see the practice of defensive medicine, difficulties in managing especially complex therapeutic regimens, the lack of a sufficient and adequate knowledge/understanding of what the new clinical recommendations are, a fear of the side effects of medications we have little familiarity with, or a fear of hypoglycaemia or weight gain. We assigned scores between 5 and 6.5 to these elements.

Regarding clinicians' opinions on the factors to be attributed to the healthcare system, the organisational facility and the world we find ourselves working in, among the elements responsible for therapeutic inertia we find the lack of a team, the lack of time, the need for complex authorisation procedures for prescribing certain drugs, local expenditure ceilings, lack of possibility for General Practitioners (GP) to prescribe certain medications and the financial barriers to their prescription (scores from 6 to 7.5).

When we compare the average scores of the responsibilities we tend to attribute to patients and those attributable to the healthcare system with those we attribute to clinicians, it appears that, while we are aware of having a certain responsibility for part of the problem, we clearly tend to attribute the causes of therapeutic inertia to external factors unassociated with our work.

Now, if we ask the clinician about what can help us resolve this aspect, we find the need for more human resources, for decision-making support to be integrated into our electronic medical records, for more pressure from scientific societies on policy makers to improve treatment plans and prescription limitations, a need for educational campaigns, reducing the cost of treatment, local campaigns to measure therapeutic inertia, regularly performed audits, removing spending ceilings in budgeting discussions, annual, national campaigns to measure therapeutic inertia, with additional educational efforts on this aspect and – why not? – we need the support of new technologies: telemedicine and eHealth.

Something has been done about this: since an experiment started in Italy, in AMD, in the late 1990s, more than 90% of the Italian Diabetes Units now use the same computerised medical records. The record issues an alert when the patient has a fasting blood sugar level and a glycated haemoglobin level that are over the target, with therapy featuring basal insulin, and advises to titre the insulin upwards; or, in another case when the patient has target fasting blood glucose and glycated haemoglobin over the target and only basal insulin as therapy, an approach to postprandial blood glucose control should be introduced, and the system suggests some alternatives. The new version of the software also has a dashboard that proposes treatment goals to the Diabetologist when values are outside the target. We think this would be helpful, but we are already living in the future. A recent systematic review suggests that Artificial Intelligence could change the approach to diabetes treatment (Dankwan-Mullan I et al. Population Health Management 2019). There are many articles emphasizing the possibility of having decision-making support and predictive risk stratification for the patient.

If the future is now, AMD is not simply standing by; we tried proposing a 'white box' AI platform using the Rulex system, a large mass of data to allow evaluation of descriptive and predictive elements with the greatest chances of achieving the therapeutic target, such as with glycated haemoglobin without weight increase.

Diabetologists asked for help in our web survey with regularly measuring therapeutic inertia and implementing educational procedures, and that is what we did. The data from the AMD Annals tell us, when gauging as an indicator the number of people with HbA1c <7%, which we progressively changed from 43% in 2011 to 51% in 2016 and to 53% in 2018. For the proportion of people with HbA1c >8%, we progressively moved from 27% to 18%; those with HbA1c >9% not receiving insulin therapy went from 40% to 28%; then, if we consider the proportion of people with HbA1c >9% although currently using insulin therapy, we dropped from 26% to 16%.

All this did not take place spontaneously: we think that AMD has made a great contribution. For example, our association held many events on therapeutic inertia in 2018 and 2019, and more than 550 diabetologists attended more than 40 meetings. We believe that this initiative, along with others of the same type, if supported by educational campaigns, can make a clear contribution to resolving and improving aspects correlated with therapeutic inertia.

When we shifted the focus from the clinician to the policy-maker or the healthcare system and ask Diabetlogists which parts of the national

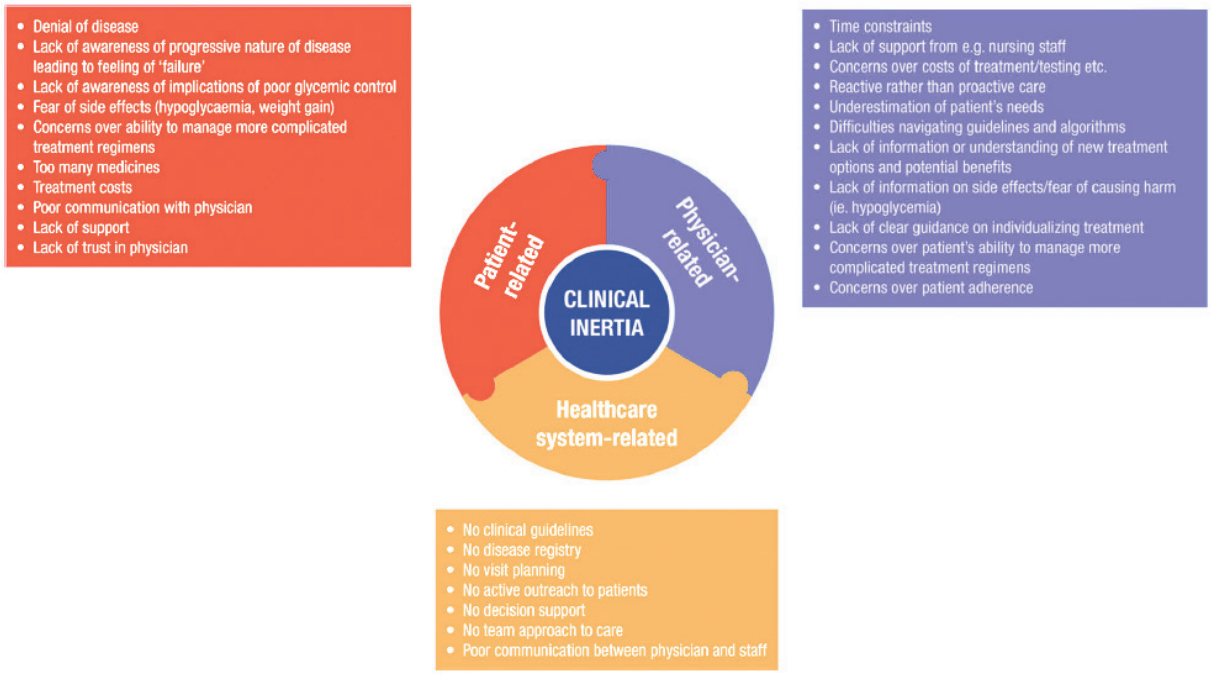

Figura 1 | Factors contributing to therapeutic inertia.

health system contribute to therapeutic inertia, we identified four aspects: the need to get authorisations for some drugs, spending ceilings for local prescriptions, obstacles preventing General Practitioners from writing prescriptions and financial barriers to prescriptions. All these aspects are fundamental to the problems related to costs.

We asked how to resolve these issues. Certainly we need to move away from the mindset of budgeting silos; we must be able to persuade the policy-maker that the level of budget monitoring must shift from simply considering the pharmaceutical therapy as a cost to assess the outcomes, leaving us the freedom (if we truly show that we can be responsible) to allocate resources to what we really think is the right way to invest money to provide positive outcomes for the patient. We think the way to do this is through the development of a virtuous alliance with our General Managers. That is why we designed and created an alliance with the Federazione Italiana Aziende Sanitarie e Ospedaliere [the Italian Federation of Healthcare Organizations] (FIASO), because with them we must describe the educational pathway that allows us clinicians to master the language needed to become credible to the decision-makers; and, most of all, a language allowing us to let the General Managers see that we are now facing solutions that can change the history of diabetes and the history of our patients.

We therefore need a global vision that does not view a single aspect of the problem and allows us to take all the actions we can (and should) do to face and resolve the problem of therapeutic inertia.

In my personal list of the drivers behind therapeutic inertia from the perspective of patients, clinicians and policy-makers, the top item is always the same: a lack of education. Similarly, education is the essential element in helping solve the problem, buffering it and minimising it, for the patients as well as clinicians and decision-makers.

In conclusion, my answer is 'yes' to the question whether there is a hierarchy among the causes of therapeutic inertia. A lack of education for patients, HCPs and decision-makers is at the top of the list of factors fostering therapeutic inertia. I firmly believe that the ADA and AMD have an opportunity to establish a virtuous alliance leading to the sharing of tools and indicators and to the promotion of specific educational projects to help all the stakeholders to overcome their own barriers.

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

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

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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.

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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.

Therapeutic inertia in type 2 diabetes: getting from where we are to where we want to be

Inerzia terapeutica nel diabete di tipo 2: arrivare da dove siamo a dove vogliamo essere

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It's impressive what AMD is doing in the area of therapeutic inertia to modify the assessment and care of patients with diabetes. I'm going to update you on what the American Diabetes Association is doing in this field.

The topic for ending this session is: "Therapeutic Inertia in Type 2 Diabetes: Getting from where we are to where we want to be," and again, I think AMD is doing a great job moving in that direction. I'm here representing the position of the American Diabetes Association (ADA) and will discuss their multi-pronged strategy and approach to address therapeutic inertia. The ADA's campaign "Connecting for life: Therapeutic inertia - Treating the Whole Patient" has four pillars of activity. The first is reframing the conversation; the second is precision medicine going forward; the third is removing the hurdles or barriers that exist; and finally, we will focus on disease state campaigns.

Let's review each of these pillars sequentially. The first is: "Reframing the Conversation." For millions of affected people, diabetes is a silent disease, a disease that is asymptomatic and not apparent. But once the disease progresses and comorbidities arise it becomes more evident. Therefore, education is incredibly important in terms of informing the patient. Another element that I don't think is being adequately addressed is changing human behaviour. We can educate patients infinitely in what diabetes is and how to manage their disorder but changing the patient's behaviour remains a challenge for all of us in the clinical space. Patients need to be heard, whether that is a child with type 1 diabetes or her mother, other family member or caretaker. Finally, we need to acknowledge that we don't have to brave this alone. Treating diabetes successfully needs a team approach and diabetologists in Italy appear to be implementing this on a daily basis.

So, let's move to the second pillar: "Precision Medicine" which is transforming practice. Over the last 15 years much progress has been made and precision medicine

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will likely be the standard of care in another decade or two. Right now, we need to continue to understand the disease, the natural history of the disease, and who is at risk. We need to develop a better framework of biomarkers that can be used to assess risk for diabetes and risk of complications. We then need to develop algorithms related to these biomarkers that can be used to predict risk, complications and what medications will work best for a given patient. Those predictions could be genetically based or environmentally influenced. They may also be based on so called "epigenetic phenomena", where DNA sequences don't change but gene expression is modified individually. We also need to consider regulatory engagement and how regulations within Italy, the United States or globally can be modified to adopt this personalized approach to patient care. We also need to think about precision approaches related to health and environmental assessment. Ultimately, we need to translate ongoing investigations into clinical care so we can modify prescriptions for each individual patient, and then and inform the patient what we're trying to accomplish.

The third pillar of this therapeutic inertia is "Removing the Hurdles or Barriers." Here we are looking at practice optimization, improving patient access, doing research on what works best to modify therapeutic inertia, and looking at policy and partnerships to support our efforts. Practice optimization implies addressing the full range of barriers affecting therapy and decision-making related to it. Improving patient access requires focusing on identifying solutions to address barriers for access to medicines and devices and non-medical therapies like diabetes education. It also involves understanding addressing social and emotional barriers to patient adherence to therapies. Research implies developing a deeper understanding of what works and refining metrics and milestones to assess progress and success. And finally, it will be important to identify and establish collaborations with partnerships with relevant organizations like AMD.

The fourth pillar is "Disease Specific Campaigns." I've been very much a part of a program called "Know Diabetes by Heart", which was instituted a in November of 2018. This is a joint-venture between the American Diabetes Association and the American Heart Association, with the goal of increasing the knowledge of heart disease risk in patients with diabetes and ultimately implementing effective evidence-based strategies to modify that risk. This is a $40 million initiative that is supported by pharmaceutical industry partners who have drugs and devices in diabetes space. The next disease specific campaigns will include eye health, or the ophthalmological complications of diabetes, followed by renal disease and obesity, all important issues for this patient population. Changing the obesity epidemic in the U.S., much less globally, is a tremendous challenge. However, even a 5 to 10% weight loss can provide significant benefit to patients. Modifying this identifiable biomarker related to cardiovascular disease and diabetes really is an important next step. As for renal disease, it is clear we now have new therapeutic agents that modify the natural history of the decline in eGFR that occurs in patients at risk for progressive nephropathy. In the fourth quarter of 2020, the emphasis is going to be on non-alcoholic fatty liver disease. All of these components related to type 2 diabetes can be modified to benefit our patients downstream.

Dr. William Cefalu, the former Chief Science and Medical Officer for the American Diabetes Association said, "despite the availability of 40 new branded medications developed in the past 20 years, as well as a wealth of education and information resources for people who have diabetes, the hard truth we must face is that the average A1c in the United States (and by the way in Italy), has not substantially changed". So, what's wrong with this picture? We need to do better.

Will Cefalu made an interesting observation – he evaluated time-related change in HbA1c in participants with type 2 diabetes who received conventional therapy (i.e. metformin) with add-on therapy going forward versus those who were treated initially with triple drugs therapy (Khan A, Cefalu WT. Diabetes Care 2016; S2:S137-45). You can think of any triple drug therapy that might be appropriate for your own implementation, but ultimately if you follow these people for the first six months, there's a greater fall in A1C when triple therapy is prescribed at baseline. At 24 months, A1C was 0.55% lower, on average, with triple therapy.

So, what's the solution to this problem? Well, we think a big part of overcoming this inertia is removing the hurdles to optimal diabetes care. There are three pillars to this approach. First is to work to cure diabetes. I think this is an inappropriate goal and that in another decade or two we will, in fact, be able to cure diabetes. Second is preventing diabetes in patients with pre-diabetes, which is an important part of the mission of the American Diabetes Association, as I'm sure it is for AMD. Third is to directly reduce of prevent therapeutic inertia by promoting adoption of evidence-based practices, strategies, programs and tools that address key determinants of therapeutic inertia in diabetes care, leading to improved, timely treatment modification and improved overall glycaemic control in diabetes patients.

So here are the objectives of the solution to reducing therapeutic inertia that the ADA is facing, and you are facing here: 1) Improve baseline understanding of therapeutic inertia and what it stands for; 2) Identify and promote activities, skills, and methodologies that are closely aligned with improved glycemic control; 3) Provide skill-based education, tools and other resources to improve adherence to the ADA guidelines (or the AMD guidelines); 4) Develop user-friendly solutions to support point of care clinical decision-making; 5) Identify the most critical policy barriers contributing to therapeutic inertia, and develop a long-term strategy to promote changes through coalition building and active advocacy support; 6) identify and support ongoing initiatives led by other coalitions, associations and governmental organizations that are determined to have a direct impact on therapeutic inertia.

So why the ADA? The American Diabetes Association's Standards of Medical Care is internationally recognized and trusted as the authority in diabetes care. These Standards of Medical Care that come out in January of each year are intended to be the Bible, if you will, for the next year related to diabetes assessment and care. In addition, the Standards of Medical Care are now updated on a rolling basis when the evidence changes, further supporting our ability to assess and treat diabetes using the best available evidence. Here are some facts about the ADA and the Standards of Medical Care:

- Sixty-four thousand primary care providers in the US are using and turning to the Standards of Medical Care for Diabetes;
- 1.2 million website visitors per month over more than half a million are active subscribers;
- 400,000+ volunteers nationwide including Healthcare Professionals are active in ADA related activities;
- 35,000 ADA Journal subscribers to "Diabetes", "Diabetes Care", and "Clinical Diabetes";
- 874,000 social media followers;
- 6 million readers of Diabetes Forecast, that reaches all our patients who are on the mailing list for the journal, a very informative lay-level publication of the ADA;
- Nearly 50,000 Health Care Professionals who are certified to use the ADA in-person and online programming;
- We have over 15,000 professional members and all of you are welcome to join in any time. Yes, there is a fee, but nevertheless there are a lot of benefits to occur being a member of the ADA.

The ADA's essential role in addressing therapeutic inertia is ultimately: 1) convening and aligning stakeholders related to diabetes and modifying therapeutic inertia through that mechanism; 2) collecting and assessing what works (and what doesn't work) going forward; and 3) disseminating and evaluating the impact of this transition from therapeutic inertia at rest and therapeutic inertia that is more proactive. Part of the solution also includes building patient engagement and trust, optimizing and personalizing care and leveraging tools and technology that relate to better care.

What's the timeline? The first step is a modification of our understanding based on an extensive literature review, landscape scan and meta-analysis. The second is the development of a market research survey to understand how clinicians currently think about clinical inertia. This will be followed by a robust awareness campaign aimed at increasing urgency of addressing therapeutic inertia now. We will then move into a best practice collection pathway and continue to track progress, monitoring and evaluating the data gathered. Finally, we will report our outcomes of modifying therapeutic inertia and share what works. This is the plan for the next one year as we work to change therapeutic inertia as we currently understand it.

Here is an overview of current therapeutic inertia projects conducted by the ADA. In November of 2018 the ADA convened an "Overcoming the Therapeutic Inertia Summit" that brought together all stakeholders in the diabetes environment to examine this problem from many angles. Then, in October 2019, ADA began a series of regional clinical workshop pilot programs aimed at helping clinicians optimize office workflow and improve patient communication to reduce therapeutic inertia. Planning is underway to create an awareness campaign that promotes the urgency of this issue and engages critical alliance partners. I see no reason why AMD can't join as a partner, ultimately to globalise the importance of addressing therapeutic inertia. The ADA also plans to publish a white paper detailing its entire plan to address therapeutic inertia in detail. In addition, they will be taking the findings form the systematic literature review I mentioned earlier and turning this into a journal article to discuss what seems most effective in addressing therapeutic inertia in clinical practice. So, this is the current list of projects the ADA has in the therapeutic inertia space and we hope to see favourable outcomes to follow.

Finally, I would like to discuss an approach clinical decision-making by healthcare professionals that I believe helps improve patient engagement

and outcomes. First, it is critical to address patient characteristics, assessing where they are right now, how much knowledge they have, understanding what the next step may be, and modifying our approach to address their needs. Second, we must consider specific factors that impact the choices of treatment. Remember, lifestyle remains important, including nutrition, physical activity, and the absence of tobacco and other illicit drug use. Third we need to create a personalized diabetes management plan for each patient that considers the current state of their diabetes, as well as their personal challenges, strengths and values. Fourth, we need to use shared decision making to agree on the management plan with the patient him/herself. Finally, we need to implement the plan, provide ongoing monitoring and support, and ultimately reassess regularly as time goes on to assure that the patient continues progress toward goal.

So, in summary, ADA priorities in the area of therapeutic inertia include: 1) looking at research including systematic review and possible pragmatic trial addressing issues in the therapeutic inertia space; 2) Practice optimization; 3) Patient access and engagement, and 4) the Standards of Medical Care and patient-centered research and care. This is ADA's effort to continue to modify therapeutic inertia in a favourable way so that the outcomes for a patient to follow are ultimately favourable.