Therapeutic inertia in type 2 diabetes: insights from the PANORAMA study in France

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Abstract

“Therapeutic inertia” is usually defined as the failure to change or uptitrate treatment strategy when a disease is uncontrolled. In patients with type 2 diabetes (T2D) this may occur with antidiabetes treatments and/or treatment for various cardiovascular risk factors. The PANORAMA study (NCT00916513) compared individual HbA1c targets and actual HbA1c levels in 5817 patients with T2D in nine European countries, and investigated the reasons why therapeutic choices made by physicians sometimes differ from expert guidelines for this disease. Thus it provides an insight into therapeutic inertia, a fashionable paradigm which can be challenged. This article reports data specifically from the French cohort of patients (n=759). We will try to demonstrate that criticising physicians for not strictly applying the expert T2D guidelines would not be beneficial as the clinical background for this apparent therapeutic inertia is complex. It appears that it may be more clinically relevant and useful to understand the reasons why the therapeutic choice made by the physician-patient partnership can sometimes differ from guidelines. This pragmatic approach would not detract from the need to develop and implement expert guidelines as it is essential to have benchmarks to assess temporal trends of quality of healthcare delivered to patients with T2D at the national level. However, these treatment targets must be put into perspective for clinical practice. Following the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, it appears mandatory to individualize glycaemic targets to enable physicians to identify the most appropriate antidiabetes treatment for each patient.

Keywords: Epidemiology; Type 2 diabetes; Antidiabetes treatment

Résumé

Inertie thérapeutique et diabète de type 2. Données françaises de l’Étude Panorama

L’« inertie thérapeutique » est généralement définie comme le retard à modifier ou intensifier le traitement en cas de contrôle insuffisant de la maladie. Chez les patients diabétiques de type 2 (DT2) cela peut s’appliquer aussi bien au traitement antidiabétique qu’aux traitements des différents facteurs de risque cardiovasculaire. L’étude PANORAMA (NCT00916513) a comparé les taux d’HbA1c réels aux valeurs cibles individuelles de 5817 patients atteints de diabète de type 2 dans neuf pays européens, et a cherché les raisons pour lesquelles les choix thérapeutiques effectués par les médecins différaient parfois des recommandations officielles des experts. Cette approche doit permettre d’éclairer l’inertie thérapeutique, paradigme à la mode qui mérite d’être discuté et mis en question. Cet article rapporte les données spécifiques à la cohorte française (n = 759). Nous tenterons de démontrer qu’il n’est pas utile de stigmatiser les médecins prescripteurs considérés comme de « mauvais élèves » s’ils n’appliquent pas strictement les recommandations des experts concernant le DT2, car l’explication clinique de cette inertie thérapeutique est complexe. Il apparaît beaucoup plus pertinent et profitable de comprendre les raisons qui ont pu aboutir à ce que l’option thérapeutique prise par le couple médecin-patient s’écarte parfois des recommandations. Cette vision ne condamne pas l’élaboration de recommandations d’experts car il est essentiel de disposer de repères pour suivre au fil des années l’évolution de la qualité de la prise en charge des patients DT2 à l’échelle du pays, mais elle relativise leur importance pour la pratique clinique. Depuis les résultats de l’étude ACCORD, la nécessité d’individualiser les objectifs glycémiques afin de choisir le traitement antidiabétique le mieux adapté à chaque patient apparaît en effet impérative.

Keywords: Épidémiologie ; Diabète de type 2 ; Traitement antidiabétique

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1. Introduction

“Therapeutic inertia” can be defined as a less than optimal intensification of therapy or delay in the prescription of treatment recommended by the official, evidence-based guidelines concerning the disease for which the patient is being treated. The word “inertia” generally has a negative connotation, implying that the physician is entirely culpable for not using treatments appropriately or as intensively as they should be, to ensure patients reach expert-recommended targets. In type 2 diabetes (T2D), therapeutic inertia concerns as well antidiabetic treatment as other treatments aiming at reducing cardiovascular risk (antihypertensive drugs, normolipemic agents, antiplatelet therapies). In T2D, therapeutic inertia is often used when a patient is maintained under oral antidiabetic agents while guidelines indicate insulin treatment should have been initiated [1-3].

It is estimated that 4.4% of the population in France have T2D and in recent years, small improvements in glycaemic control and patient follow-up have been observed [4]. This article reports data from the French cohort of patients with T2D, evaluated in the European-wide PANORAMA study. These findings help to understand the basis for apparent therapeutic inertia in France based on examination of physician-imposed glycaemic targets, actual levels of glycaemic control, physicians’ opinions on why patients do not achieve target and the reasons why physicians are reluctant to intensify treatment and the therapeutic actions that are taken.

2. Methods

2.1. Study design and patient recruitment

PANORAMA was an observational, multicentre, cross-sectional study primarily designed to evaluate diabetes-related quality of life (QoL) and treatment satisfaction in patients with T2D (NCT00916513) [5]. Secondarily, it has also provided interesting data on therapeutic goals set by physicians to achieve the individual glycaemic targets defined for each patient. Overall, 5817 patients were enrolled from nine European countries: Belgium; France; Germany; Greece; Italy; the Netherlands; Spain; Turkey; and the United Kingdom. This report focuses on the French cohort of patients (n=759).

It was intended that patient recruitment (May 2009 – February 2010), would be adapted in each country to obtain a representative sample of their T2D patients. Thus, patients were selected either through primary care physicians or specialists, depending on the national policy of care delivery to such patients. However, in France, this paradigm was not applied as robustly as it might have been as only primary care physicians (n=71) recruited patients into the study whereas in the French healthcare system, patients with T2D are also regularly treated by specialists. In each participating centre, all consecutive patients with T2D attending consultations who were aged ≥40 years and diagnosed at least 1 year prior to study entry, with at least 1 year of medical records available and no change in treatment within the last 3 months, were included if they fulfilled the additional study inclusion criteria, had no exclusion criteria and had given their informed consent [5].

To take part in this study, T2D patients could have been treated with diet and exercise advice, and could also have been treated with OADs and/or injectables (insulin and/or glucagon-like peptide-1 analogues). Insulin-treated patients were considered to have T2D if insulin treatment had been initiated at least 2 years after diagnosis. Patients with type 1 diabetes and/or a history of diabetic ketoacidosis or secondary diabetes, pregnant women and patients unable to complete the study questionnaires were not included in this study.

2.2. Study procedures and data management

At the study visit, information was collected from participating patients and their medical records for the previous 2 years. Data collected included patients’ sociodemographic details, biological measures (including a standardized measurement of HbA1c), patient-reported outcomes of health status and QoL, disease-related variables, health-economic variables and their physicians’ sociodemographic details. HbA1c levels were measured for each patient by the physician, using an identical point-of-care device (A1c Now®, Bayer HealthCare, Tarrytown, NY, USA) certified by the US National Glycohemoglobin Standardization Program.

In this study, each physician was asked to define an HbA1c target for each patient and, if this target was not achieved, to provide explanations for this, selecting from a pre-specified list. These reasons included therapeutic failure of current antihyperglycaemic drug regimen, poor adherence to lifestyle recommendations (diet and/or physical exercise), poor adherence to self-monitoring of blood glucose (SMBG) recommendations, poor adherence to medication (including insulin), resistance/reluctance of the patient to intensify the medication regimen and/or reluctance of the physician to intensify the regimen. Physicians were asked to select all the reasons from this list considered applicable to the particular patient. Treatment intensification was defined as either the prescription of a new class of antidiabetic drug or an increase in dose of an already prescribed drug. Physicians were also asked to select their reasons for their reluctance to initiate treatment intensification, again from a pre-specified list. This list comprised: fear of hypoglycaemia, fear of causing additional weight gain, fear of causing unwanted side effects such as gastrointestinal symptoms and peripheral oedema, fear of potential interactions with other medications or cost of treatment. In addition, if the patient had not reached glycaemic target, the physician was asked to indicate the key action(s) taken to improve glycaemic control (educational approach, increased dosage of current antidiabetes drug, addition of a new OAD, initiation of insulin therapy, referral of patient to specialist or no specific action).

Before the study commenced, all questionnaires and case record forms were translated from English into the preferred national language, and then translated back into English, to
check the quality of the translation. An electronic case-report form was provided (a paper version was also available) for the collection, monitoring and processing of the data. Due to the nature of the study, it should be noted that data were not collected for all respondents for each variable. All study procedures were carried out in accordance with the guidelines for Good Clinical Practice [6].

2.3. Statistical methods

All statistical analyses were conducted using the usual statistical methods: t tests for comparisons of quantitative variables and χ² tests for categorical variables. The sample size per country was determined to obtain the desired precision for the 95% confidence intervals (CI) for each of the country-specific estimated means, taking into consideration the expected standard deviation (SD) in the proposed study population. It was estimated that a sample size of 753 patients per country would provide sufficient precision for the proposed primary and secondary outcomes.

3. Results

Baseline characteristics and demographics of patients with T2D from France were as follows: mean (SD) age 65.7 (11.0) years; 63.0% male; mean (SD) weight 85.3 (17.6) kg; body mass index (BMI) normal (<25.0 kg/m²) 15.2%; BMI overweight (25.0–30.0 kg/m²) 36.5%; BMI obese (>30.0 kg/m²) 48.3%; and mean (SD) duration of T2D 9.7 (7.6) years.

The mean of the individual HbA₁c targets set by French physicians for their patients was 6.6%. Overall, patients had a mean (SD) HbA₁c level of 7.0% (1.1). The results also indicate that in the PANORAMA French cohort, 42.3% of patients with T2D remained uncontrolled (HbA₁c ≥7.0%); this increased to 66.0% when a 6.5% HbA₁c threshold was used. Over half (58.0%) of French physicians felt that poor patient adherence to lifestyle measures such as diet and exercise was the main reason for not meeting the appropriate HbA₁c target (Table 1). Of the physicians who were reluctant to intensify their patients’ antidiabetes treatment, the main reason given was patient reluctance to have their treatment intensified (16.4%) (Table 2). When glycaemic target was not reached, physicians indicated the action(s) they took. Reinforcement of therapeutic education was proposed for over half (52.9%) of patients enrolled in the study with physicians stating that they would increase the dosages of current treatment or add a new OAD in only 22.6% and 10.0% of patients respectively. Only 7.0% of physicians reported that no action was taken (Table 2).

Physicians reported that 60.3% of their patients with T2D in France had been struggling with weight gain since diabetes medication was initiated (Fig. 1). Patient adherence to lifestyle recommendations as reported by physicians was considered “moderate” in 45.2% of patients and “good” in 23.9%. Patient adherence to medication, as reported by physicians was considered “good” in over three-quarters (76.4%) of patients, moderate in 18.9% and poor in 4.7% of patients (Fig. 1).

4. Discussion

In this large French cohort of over 750 patients with T2D from the PANORAMA study, the mean of the individual patient HbA₁c targets set by physicians was 6.6%, indicating a good awareness of the guidelines for diabetes care in France. However, this study also identified that over two thirds of patients had a mean HbA₁c of ≥6.5% (over 40% for ≥7.0%) suggesting that there is a disconnect between target levels and actual levels of glycaemic control in patients with T2D. The overall mean HbA₁c level identified (7.0%) in patients enrolled in PANORAMA is similar to the mean value of 7.1% recorded in the 2007 French ENTRED (Echantillon National Témoin Représentatif des Personnes Diabétiques; national representative sample of diabetic patients) study [7], and this may also suggest a lack of improvement in glycaemic control in France in the last 3 years. However, in contrast to these results, a recent article reported improvements in glycaemic control in patients with T2D in France, although this review was conducted in a patient population with T2D and renal

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<tr>
<th>Table 1</th>
<th>Reasons for not reaching HbA₁c target from physician’s perspective (%)*.</th>
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<tr>
<td>Therapeutic failure of current treatment</td>
<td>26.9</td>
</tr>
<tr>
<td>Poor adherence to lifestyle recommendations (diet and physical exercise)</td>
<td>58.0</td>
</tr>
<tr>
<td>Poor adherence to medication</td>
<td>13.6</td>
</tr>
<tr>
<td>Poor adherence to self-monitoring blood glucose</td>
<td>11.5</td>
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</tbody>
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*Sum of percentages is >100% as physicians were allowed to enter more than one response for each patient

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Treatment intensification: reasons for physician reluctance to intensify treatment and actions taken.</th>
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<tr>
<td>Reasons for reluctance of physician to intensify regimen (%)</td>
<td>Patient reluctance to intensify treatment 16.4</td>
</tr>
<tr>
<td>Fear of hypoglycaemic attacks</td>
<td>3.7</td>
</tr>
<tr>
<td>Fear of side effects such as gastrointestinal effects and oedema</td>
<td>2.8</td>
</tr>
<tr>
<td>Fear of potential interactions between medications</td>
<td>1.2</td>
</tr>
<tr>
<td>Fear of weight gain</td>
<td>1.6</td>
</tr>
<tr>
<td>Cost</td>
<td>0.1</td>
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Actions taken (%)*

| Patient education | 52.9 |
| Increasing dose of current antidiabetes treatment | 22.6 |
| Add oral antidiabetes agent | 10.0 |
| Referral to a diabetologist | 9.2 |
| None | 7.0 |
| Initiate treatment with insulin | 2.6 |

*Sum of percentages is >100% as physicians were allowed to enter more than one response for each patient.
impairment [4] – a higher risk patient population that may be more likely to be treated intensively.

In PANORAMA, when HbA1c target was not reached, physicians reported that in over half of their patients they considered this to be due to the patient’s poor adherence to lifestyle recommendations. The second most common reason, identified for a quarter of patients, was therapeutic failure of current treatment. Poor adherence to medication or SMBG was only reported as the cause of glycaemic target failure for a small proportion of patients in this study. Concerning SMBG, this is not surprising as very little benefit, if any, has been demonstrated for glycaemic control and quality of life in T2D patients not treated by insulin, who use it [8].

When physicians were asked to identify any treatment-related issues they believed their patients to be experiencing, adherence to medication was again not considered to be a problem for a high proportion of patients with over three quarters of patients considered by their physicians to have good adherence to medication. Physicians considered the main issue for their patients with T2D to be unwanted weight gain, which is a well-documented concern [9]. Whether this is a specific concern of patients in France, perhaps related
to French sociocultural attitudes will be discussed in other publications.

In cases where HbA1c was not on target, physicians only proposed adding an oral anti-diabetes medication or initiating insulin treatment in very low proportion of patients. This finding may infer that French physicians could be partly responsible for therapeutic inertia in this patient population. However, physician reluctance to intensify treatment was primarily attributed to their patients’ reluctance to have their antidiabetes treatment intensified, therefore forcing the physician into therapeutic inertia. From a clinical perspective, as this study was performed in France more than 1 year after publication of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, it may be related to the significantly increased mortality rates observed in the intensively treated group in this study [10], potentially linked to hypoglycaemic episodes in frail patients at high cardiovascular risk [11]. Indeed, in 2007 the ENTRED Study yet showed a rather low proportion of diabetic patients treated by insulin in France (19%), although it had increased of 2% compared to the 2001 ENTRED Study [7]. Thus, probably it just means that insulin use is not very popular in France. This cannot lead, in my opinion, to consider that French physicians are guilty of therapeutic inertia. Indeed, two recent meta-analyses of large, long-term, randomized clinical trials of 34,533 and 28,614 patients with T2D showed that intensive glycemic control did not reduce all-cause mortality and cardiovascular mortality, which were even slightly, non significantly, increased in both publications, while at best it had a modest effect on microvascular complications, but induced a more than twofold increase of severe hypoglycaemia [12,13].

Overall, a more likely explanation for physicians’ reluctance to intensify treatment when therapeutic goals are not achieved is that more complex anti-hyperglycemic therapies (mainly injectables) are less utilised therapeutic options in France. Certainly the 2007 ENTRED study supports this observation as it reported that only a minority of patients with T2D are treated with insulin in France (19%). In addition, when therapeutic failure occurs, improving the patient’s self-management education, rather than treatment intensification, was the most popular action taken. This is an encouraging finding as it appears that the diabetes education programmes initiated for type 1 diabetes in the 1970s [14] have been successfully applied to T2D, following the positive evaluations reported a decade ago [15].

The strengths of the PANORAMA study are that it is the first observational study to have used the same methodology across several European countries, with the same questionnaires translated from English to each national language then back-translated to English to check the quality of translation. Secondly, HbA1c measurement, the key-stone of this article, was recorded by a standardised method, using the same device for all the patients. In addition particular care was taken to obtain a representative sample of patients with T2D in each country. For this French cohort, this correlated well with the general profile of the T2D population as age and diabetes duration for PANORAMA were closely similar to those observed in the representative sample obtained for the ENTRED Study in 2007 [7]. The main difference between these two study populations in France is the gender ratio, with more men recruited in the PANORAMA than in ENTRED (63% vs 54% respectively). There is no clear explanation for this although the recruitment methods did differ between the two studies. In PANORAMA French patients with T2D were recruited through primary care physicians whereas in the ENTRED Study, patients were selected from the health insurance system (CNAMTS) database, 14% of whom had been cared for by a diabetologist [16]. Although diabetologists did not participate in the French cohort of PANORAMA, this is not likely to be a major limitation since primary care physicians were able to switch treatment regimens and initiate additional oral antidiabetes medications or insulin, so it is not thought that lack of specialist recruitment would be a contributing factor to the therapeutic inertia observed.

In conclusion, the PANORAMA Study shows that diabetes treatment could be improved in France. Probably repeated assessment of diabetes care delivery as performed in our country by the ENTRED Studies is very useful to be able to assess temporal trends of the quality of care delivered to T2D patients. For that purpose, expert guidelines are needed to have benchmarks for this evaluation at a national level, then to be able to fill the gap if it exists. Indeed, at the individual level, if a gap is found between the HbA1c target and the HbA1c level measured in a patient, it is most important not to stigmatize the physician and/or the patient but rather to try to understand the reasons why the physician-patient stays outside the guidelines, as it has been done in the PANORAMA Study. In addition, the two recent meta-analyses discussed above [12,13] must lead to take carefully into consideration risks and benefits of intensifying glucose lowering treatment, as this balance will vary substantially between patients [17]. In particular, current guidelines for antidiabetic treatment are not relevant for most of the elderly people, and should not distract from multifactorial intervention on the other cardiovascular risk factors (hypertension and dyslipidemia), easier to control than hyperglycaemia, with less side-effects and a great efficacy on cardiovascular complications and all-cause death in at-risk T2D patients [18,19]. Thus, besides diabetes education programmes aiming at lifestyle improvement, it is mandatory to move on from the simplistic “one size fits all” to a nuanced individual adaptation to decide how, when and why aggressive glucose lowering should be implemented in a T2D patient [20].

Acknowledgements

The author acknowledges medical writing support from Jennie Frain, PhD, at QXV Communications, Macclesfield, UK, funded by AstraZeneca. The author would also like to acknowledge the PANORAMA steering committee: Clare Bradley, Eveline Eschwège, Linda Gönder-Frederick, Pedro de Pablos-Velasco, Klaus G Parhofer.
This study was funded by Bristol-Myers Squibb and AstraZeneca.

Disclosure of interest

D. Simon has participated in Expert Committees or been an invited speaker at meetings organized by AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Sanofi-Aventis and Servier and has participated as an investigator in clinical studies conducted by Lilly-France and Novartis.

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