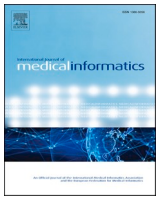
International Journal of Medical Informatics 190 (2024) 105550

Contents lists available at ScienceDirect

International Journal of Medical Informatics

journal homepage: www.elsevier.com/locate/ijmedinf



A transparent machine learning algorithm uncovers HbA1c patterns associated with therapeutic inertia in patients with type 2 diabetes and failure of metformin monotherapy

Nicoletta Musacchio [a], Rita Zilich [b,*], Davide Masi [c,*], Fabio Baccetti [d], Besmir Nreu [e], Carlo Bruno Giorda [f], Giacomo Guaita [g], Lelio Morviducci [h], Marco Muselli [i], Alessandro Ozzello [j], Federico Pisani [b], Paola Ponzani [k], Antonio Rossi [l,p], Pierluigi Santin [m], Damiano Verda [i], Graziano Di Cianni [n], Riccardo Candido [o]

[a] AMD-AI National Group Coordinator, UOS Integrating Primary and Specialist Care, ASST Nord Milano, Via Filippo Carcano 17, 20149 Milan, Italy
[b] Mix-x Partner, Via Circonvallazione 5, Ivrea (TO), Italy
[c] Department of Experimental Medicine, Section of Medical Pathophysiology, Food Science and Endocrinology, Sapienza University of Rome, 00161 Rome, Italy
[d] ASL Nordovest Toscana. ASL Nordovest, Massa Carrara (MS), Italy
[e] Diabetology Unit, Careggi Hospital, Largo G.A. Brambilla, 3, 50134 Florence (FI), Italy
[f] Diabetes and Endocrinology Unit, ASL TO5, Chieri, Turin (TO), Italy
[g] Diabetes and Endocrinology UNIT ASL SULCIS, Carbonia-Iglesias, Italy
[h] UOC Diabetologia e Dietologia, Ospedale S. Spirito - ASL Roma 1, Borgo Santo Spirito, Roma (RM), Italy
[i] Rulex Innovation Labs, Rulex Inc, Via Felice Romani 9/2, 16122 Genoa (GE), Italy
[j] AMD regional past President, Gruppo nazionale AI AMD, Bruino, Torino (TO), Italy
[k] Diabetes and Metabolic Disease Unit ASL 4 Liguria, Chiavari (GE), Italy
[l] IRCCS Ospedale Galeazzi-Sant'Ambrogio, 20149 Milan, Italy
[m] Data Scientist Deimos, Udine (UD), Italy
[n] AMD Past President, Diabetes and Metabolic Diseases Unit, Health Local Unit Nord-West Tuscany, Livorno Hospital, Pad. 4 Viale Alfieri 36, Livorno (LI), Italy
[o] AMD New President, Azienda Sanitaria Universitaria Giuliano Isontina, 34128 Trieste, Italy
[p] Department of Biomedical and Clinical Sciences, Università di Milano, Milan, Italy

ARTICLE INFO

Keywords:
Type 2 diabetes
Machine learning
Artificial intelligence
Therapeutic inertia
Metformin monotherapy
Metformin failure
HbA1c

ABSTRACT

Aims: This study aimed to identify and categorize the determinants influencing the intensification of therapy in Type 2 Diabetes (T2D) patients with suboptimal blood glucose control despite metformin monotherapy.
Methods: Employing the Logic Learning Machine (LLM), an advanced artificial intelligence system, we scrutinized electronic health records of 1.5 million patients treated in 271 diabetes clinics affiliated with the Italian Association of Medical Diabetologists from 2005 to 2019. Inclusion criteria comprised patients on metformin monotherapy with two consecutive mean HbA1c levels exceeding 7.0%. The cohort was divided into "inertia-NO" (20,067 patients with prompt intensification) and "inertia-YES" (13,029 patients without timely intensification).
Results: The LLM model demonstrated robust discriminatory ability among the two groups (ROC-AUC = 0.81, accuracy = 0.71, precision = 0.80, recall = 0.71, F1 score = 0.75). The main novelty of our results is indeed the identification of two main distinct subtypes of therapeutic inertia. The first exhibited a gradual but steady HbA1c increase, while the second featured a moderate, non-uniform rise with substantial fluctuations.
Conclusions: Our analysis sheds light on the significant impact of HbA1c levels over time on therapeutic inertia in patients with T2D, emphasizing the importance of early intervention in the presence of specific HbA1c patterns.

* Corresponding authors.
E-mail addresses: rita.zilich@mix-x.com (R. Zilich), davide.masi@uniroma1.it (D. Masi), fabio.baccetti@uslnordovest.toscana.it (F. Baccetti), nreub@aou-careggi.toscana.it (B. Nreu), giacomo.guaita@aslsulscis.it (G. Guaita), leliomorviducci@aslroma1.it (L. Morviducci), marco.muselli@ieiit.cnr.it (M. Muselli), paola.ponzani@asl4.liguria.it (P. Ponzani), antonio.rossi1@unimi.it (A. Rossi), p.santin@e-deimos.it (P. Santin), damiano.verda@rulex.ai (D. Verda), graziano.dicianni@uslnordovest.toscana.it (G. Di Cianni), riccardo.candido@asugi.sanita.fvg.it (R. Candido).

https://doi.org/10.1016/j.ijmedinf.2024.105550
Received 17 March 2024; Received in revised form 7 July 2024; Accepted 12 July 2024
Available online 15 July 2024

1. Introduction

"Therapeutic inertia" (TI) occurs when a physician delays the initiation or intensification of a medication in patients with uncontrolled risk factors [1,2]. Over the past decade, TI has emerged as a prevailing issue among patients with T2D [3]. Notably, it is not limited to insulin therapy but can also affect the start or intensification of first- or second-line therapies [4], negatively impacting glycemic control, quality of life, healthcare costs and the development of both macrovascular and microvascular complications [5]. The latter, in particular, are especially linked to the degree of glycemic control and the duration of T2D [6]; therefore, current guidelines recommend achieving glucose targets early to mitigate long-term risks [7].

Conversely, timely and effective significantly reduces cardiovascular and all-cause mortality rates [7], prevents vision loss and delays the progression of diabetes-related retinopathy [8].

Metformin and dietary changes are generally regarded as first-line treatments for T2D however; lack of glycemic control [i.e., HbA1c levels over 7.0 % (53 mmol/mol)] during metformin treatment should prompt intensification with second-line therapy [9]. Nevertheless, on average, patients on metformin monotherapy with suboptimal control receive intensification with a second-line therapy after 2.9 years [10] and only 40 % of patients with T2D meet their individualized HbA1c goals [11], leading to a significant increase in cardiovascular events [12]. TI results from multiple factors including, among others, physician hesitation, patient fear, poor adherence to treatment, and inadequate monitoring of glucose levels. Traditional statistical approaches showed that patients with higher HbA1c values are less likely to experience TI, but HbA1c thresholds and the time frame for assessing TI varied widely across published studies, making it challenging to draw solid conclusions [13]. To date, only a few studies have employed artificial intelligence (AI) and machine learning (ML) techniques to identify possible causative factors [14]. ML algorithms analyze big data by uncovering hidden patterns and relationships [15,16,17,18] and revolutionizing data analysis in diabetes research for prediction, diagnosis and management [19]. Previous studies have applied ML to investigate glycemic target attainment [15] and treatment intensification in patients with T2D [20]. Berlowitz et al. employed classification and regression trees, a form of ML based on decision trees, to predict antidiabetic drug intensification, but did not focus on TI [20]. Recently, McDaniel and collaborators developed and validated a ML model to predict TI, incorporating area-level social determinants of health [14]; however, the ML methods employed in this study are often categorized as "black-box" algorithms due to their non-transparent nature, making it challenging to extract explicit knowledge or interpret the decision-making process from the generated models. To address this limitation, our study employed the Logic Learning Machine (LLM), a "clear box-explainable" AI algorithm [21] to uncover the determinants of TI in patients with T2D.

In summary, our study involves 4 stages: (1) Data Collection and Preprocessing; (2) Application of the Rulex AI Algorithm, to identify and categorize the determinants influencing therapy intensification; (3) Analysis and Interpretation of Results; and (4) Discussion and Implications, where we contextualize findings in personalized interventions for patients with T2D and acknowledge the limitations of the study.

2. Material and methods

2.1. Study design and population

This is a longitudinal, retrospective, and cross-sectional study. Data were collected from electronic records of 1.5 million patients seen at 271 diabetes clinics that are part of the Association of Medical Diabetologists (AMD) network, covering the period from 2005 to 2019. Patients' data were fully anonymized ensuring compliance with ethical and regulatory standards and, as any previous research conducted with data from the same database, named AMD-Annals [22,23] the study was approved by the local institutional review board. All patients consented to participate. This study was conducted on individuals on metformin monotherapy with HbA1c levels above 7.0 % in two consecutive measurements. Patients with HbA1c levels below 4.5 % (<26 mmol/mol) or above 14 % (>30 mmol/mol) and those aged 75 or older were excluded, due to likely personalized therapeutic strategies. The final cohort was divided into two groups: the inertia-NO group of 20.067 patients who received therapeutic intensification within 2 years of two consecutive visits, the latter termed T-Index, with a mean HbA1c of > 7.0 %, and the inertia-YES group of 78.967 patients who did not receive therapy intensification within the same timeframe, as detailed in Fig. 1. In particular, this group consisted of those who either underwent treatment intensification after two years or remained without it. Among them, 3,834 out of 13,029 (29.4 %) did not receive intensification, while the rest experienced delayed intensification. Further, this group was limited to patients who still had an HbA1c level above the threshold at two years (+0–3 months) after the T-Index, with a total of 13,029 patients.

A change in therapy was considered as any alteration in previous oral medication. The analysis was based on real-life data and do not include either information on dosage or treatment adherence/changes in lifestyle. The two-year interval was chosen to include patients who had been seen at least twice, reflecting normal clinical practice in diabetes clinics in Italy, where the average time between patient visits is typically 6–8 months with the possibility of some clinics having a patient load that requires longer intervals between visits [24].

A flowchart illustrating the research methodology is presented in Fig. 2.

2.2. Data preparation

The steps adopted for data preparation are given below:

- Data filtering: Only measurements within a reasonable range for each variable were retained; outliers were discarded.
- Time intervals: HbA1c measurements were considered only if there was an interval of at least 2 months between them; shorter intervals were discarded.
- Clinical factors: For each HbA1c measurement, we noted the value of clinical factors (e.g., systolic blood pressure) closest in time, within a maximum interval of 4 months before and after the date of the HbA1c measurement.
- Permanent factors: Permanent factors (such as acute myocardial infarction) were tracked up to the date of their first detection.
- Medication tracking: For each HbA1c measurement, medications related to the previous measurement were tracked, on the assumption that the achievement of specific goals depends on the treatments followed in the period before the HbA1c measurement.

2.3. Logic learning machine

As opposed to "black-box" AI algorithms, Rulex® (Innovation Lab, Rulex Analytics) LLM is a type of transparent ML that utilizes the Switching Neural Network technique for supervised data mining [21,25,26]. When utilized for prediction, it is able to explain patient response to an initial premise via the creation of models, following the selection of the most relevant variables, without prior knowledge, demonstrating accuracy comparable to, or even surpassing, the best ML algorithms [27]. The technical workflow of Rulex has been previously described in detail [26,28].

To summarize the Rulex® data analysis process:

1) Training phase: model creation using 70 % of the available data and all known variables.

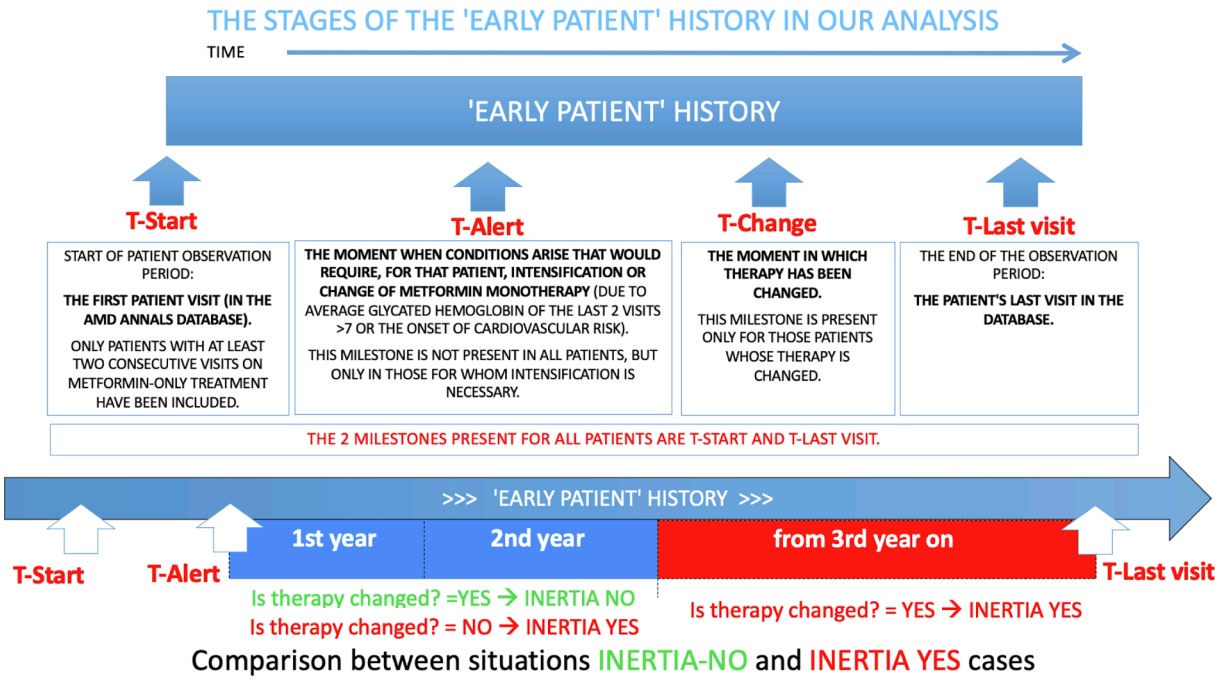


Fig. 1. Diagram illustrating the various time points examined in the study, highlighting the selection of cohorts.

2) Test phase: the newly created model is tested on the remaining 30 % of the data to evaluate its performance, including sensitivity, specificity, precision, accuracy, and the calculation of ROC-AUC.
3) Creation of the feature ranking: elicitation of a list, in order of importance, of the relevant variables that explain the starting premise.
4) Identification of threshold values: presentation of the threshold values, if any, for the most relevant variables.
5) Prediction: when employed for prediction, the model explicitly explains the reason for its response, considering the variables of a new patient.

In this analysis, a predictive model using LLM identified true TI in patients on metformin monotherapy, based on whether therapy intensification occurred within two years. The analysis assumed therapy intensification within two years if needed at T0 (YES/NO). The model was developed using data from two patient groups, termed "inertia-YES" and "inertia-NO", as explained above. The mean time to delayed intensification was calculated specifically for the former subgroup. For both groups, the mean, standard deviation (SD), and median were computed for various variables at T-Index. To compare the groups, these statistics were also calculated at the time of treatment intensification (T-Intensify) for the inertia-NO group and approximately two years after T-Index (T-Index + 2 years) for the inertia-YES group. The model utilized descriptive variables (demographic, clinical, organizational) available at specific visits and dynamically derived variables, which change over time, referring to the period after T-Index. (Table 1).

3. Results

3.1. Characteristics of subjects

The total number of patients included in the study was 33.096 of which 13.462 (41 %) were females and 19.634 (59 %) were males. The percentage of patients with high/very high cardiovascular risk (CVD risk) as defined by the ESC guidelines for diabetes [29] was 71 % in both groups, with 14.273 out of 20.067 in the inertia-NO group and 9.261 out of 13.029 in the inertia-YES group. At T-Intensify, 17.352 out of 20.067 patients in the inertia-NO group (86 %) had high/very high CVD risk, while 11.462 out of 13.029 patients in the inertia-YES group (88 %) had high/very high CVD risk at T-Index + 2 years. Table 2 shows the characteristics for both patient groups at T-Index and at T-Intensify for the inertia-NO group and T-Index + 2 years for the inertia-YES group. The student's *t*-test uncovered important differences between the two groups of patients: those with inertia-NO and those with inertia-YES regarding certain clinical variables. Specifically, it showed that patients with observable TI generally have slightly lower average values of key metabolic syndrome parameters at the T-index, such as HDL cholesterol, triglycerides, HbA1c, BMI, and systemic blood pressure. This suggests that these patients, on average, appear to be less complicated. However, it's worth considering that these differences might be influenced by the large sample size. To address this, we conducted a ML analysis, which helped us identify which of these clinical variables truly played a significant role in predicting TI.

3.2. LLM models and performance evaluation

The LLM analysis yielded two models: one using descriptive variables only and another combining descriptive and dynamic variables that reflect patients' progress after the T-Index. The first model had a modest performance yielding a ROC-AUC of 0.66, an accuracy of 0.62, a precision of 0.66, and a recall of 0.63. The addition of the dynamic variables improved the model's performance, resulting in an increase of the ROC-AUC to 0.81 with a 95 % confidence interval of 0.793–0.820 (Fig. 3), accuracy to 0.71, precision to 0.80, and recall to 0.71.

The F1 Score, the harmonic mean between precision and recall, effectively addresses both false positives and false negatives and is a suitable measure for evaluating our unbalanced dataset [30]. The F1 Score ranges from 0 (indicating a complete lack of classification ability) to 1 (perfect classification of all variables). Our model, incorporating both descriptive and dynamic variables, achieved an F1 Score of 0.75, demonstrating its good performance (Table 3) in identifying features correlated with the defined outcomes of the analysis (inertia yes/no).

Table 4 displays the Feature Ranking (FR) generated by the ML algorithm, which identifies parameters with a relevance > 0.1 and ranks them based on their significance relative to a threshold value.

The table highlights the prominent role of HbA1c in determining TI, both as a single visit measure and as regards its trend pattern after T-

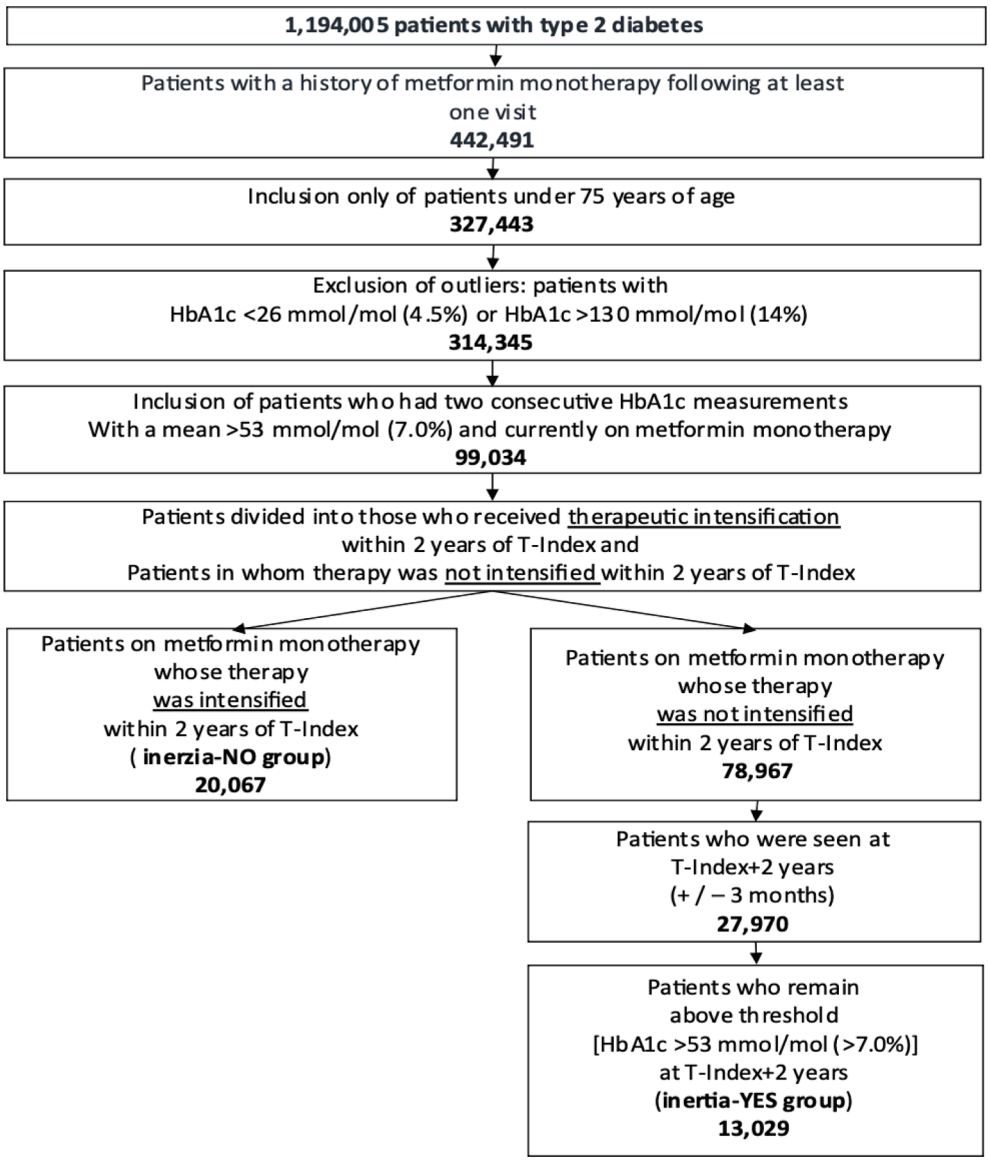


Fig. 2. Study Flowchart.

Index. For the inertia-NO group, the threshold HbA1c at a current visit was > 7.6 % (>60 mmol/mol), while the HbA1c yearly trend after T-Index was > +0.12, the mean HbA1c after T-Index was > 7.7 % (61 mmol/mol) and there was no threshold value for the HbA1c standard deviation (SD) after T-Index. For the inertia-YES group, the threshold value HbA1c at a current visit was < 7.6 % (<60 mmol/mol), the mean HbA1c after T-Index was < 7.7 % (<61 mmol/mol), the HbA1c yearly trend after T-Index was <+0.12, and HbA1c SD after T-Index was < +0.10 OR > +0.57. These findings suggest that a slight increase in HbA1c, with significant fluctuations (HbA1c SD > +0.57), is more likely to result in TI compared to a situation with greater HbA1c increases and lower fluctuations. In addition, one other case of inertia also exists. In this situation, there is a trend toward a slight increase and very low fluctuation (HbA1c SD < +0.10).

Interestingly, the frequency of patient visits, or mean interval between visits, was ranked third in importance. If the frequency was less than 4 months it was correlated with inertia-NO, but if it was greater than 6 months, it was associated with inertia-YES.

In our study, we also found that fasting glucose had a significant impact on the prediction of inertia-NO or inertia-YES. A fasting glucose value greater than 190 was associated with inertia-NO, while a value less than 160 was associated with inertia-YES. Age was also identified as a significant factor. Individuals under the age of 55 or over 67 were more likely to have inertia-NO, while those between 60 and 67 years old were more likely to have inertia-YES. The feature ranking continues with several other variables used in the machine learning model, which means that they contribute to the accuracy of the forecast, but their relevance is < 0.1 and therefore they have not been included in Table 4.

Given these results which showed a dominant role of HbA1c from various perspectives, we sought to determine whether the HbA1c at the current visit, the mean HbA1c after T-Index, the HbA1c yearly trend, and the HbA1c SD were individually dominant variables or whether their integrated effect, which describes a patient's glycemic trend dynamics, was more significant, as suggested by the LLM model. To investigate this, we calculated the ROC-AUC for each variable independently, and the results (0.59, 0.65, 0.54, and 0.59, respectively) show only a slight predictive performance. In contrast, when we utilized only these four variables, in the machine learning model, the resulting ROC-AUC was 0.76. These findings confirm that the variation of HbA1c, represented by the 4 variables that trace its fluctuation over time, can correctly predict the "inertia-NO" or "inertia-YES" condition with 76 % accuracy.

Table 1
Summary of the variables included in the LLM analysis.

Antropometric parameters	Organizational parameters
Age;	Q-score;
Sex;	Years of clinical observation (considered a proxy of duration of diabetes);
Weight;	**Treatments**
Height;	Drug therapy for diabetes (type and associations);
Body mass index (BMI);	Drug therapy for dyslipidemia (type and associations);
Systolic blood pressure (BP), diastolic BP;	Drug therapy for hypertension (present or not);
and derived variables or index.	Additional drugs.
Biochemical parameters	**Diabetes complications and comorbidities***
HbA1c at current visit; HbA1c at previous visit, HbA1c drop speed, HbA1c gap between visits	Presence of nephropathy;
Fasting glucose;	Presence of atrial fibrillation;
Triglycerides;	History of heart failure;
Total cholesterol;	History of stroke;
High-density lipoproteins (HDL);	History of cardiac complications;
Low-density lipoproteins (LDL);	Presence of vasculopathy;
Creatinine;	Presence of lower limb complications;
Estimated glomerular filtration rate (eGFR);	Presence of neuropathy;
Micro–macro/albuminuria;	Presence of foot complications;
Serum uric acid;	Presence of eye complications;
Serum glutamic oxaloacetic transaminase (GOT);	Presence of hepatopathy.
Serum glutamic pyruvic transaminase (GPT);	
Mean, SD and trend for each variable and same variables for follow-up visits.	

* Further details on the classification of complications can be found in the supplementary material of our previously published work [15].

4. Discussion

TI is a widespread issue in T2D patients, with a reported prevalence of up to 50 % [31]. Even in our study involving patients on metformin monotherapy, 39 % (13,029 out of 33,096) experienced TI despite the availability of multiple therapeutic options. Over the years, several efforts have been made to define TI yet major improvements are lacking [24].

Here, we sought to pinpoint factors indicating higher inertia risk. The main strength and novelty of our approach was the use of a transparent ML technique to generate the model, as opposed to the traditional statistical approaches. We incorporated for the first time standard patient visit data [32,33] and dynamically-derived variables such as mean, trend, and SD in patients with T2D, to capture the dynamics associated with each patient's progress.

Our study confirms a delay in therapeutic action both in terms of the size of the phenomenon and in the HbA1c level, 8.0 % (64 mmol/mol), which on average is accepted without intervention [34]. Moreover, our findings indicate that there are two different types of TI, potentially reflecting different approaches taken by the physician. The first is characterized by a slight but constant increase in HbA1c, with values that do not fluctuate significantly. In this case, the physician may miss the fact that though the increase in HbA1c is slight, the patient nevertheless remains in a state of poor glycemic control, which in turn could lead to poor health outcomes. The second type involves a slight increase in HbA1c, but with significant fluctuations in values. In this situation, as the HbA1c is increasing slightly, but the fluctuations in its values are significant, the physician may assume that the HbA1c will eventually normalize under the existing therapeutic conditions, especially when its levels are not significantly elevated [i.e., below 7.6 % (60 mmol/mol)]. This delay is considered "tolerable," but it can result in the patient's HbA1c remaining at or exceeding the optimal target level, leading to diabetes-related complications and even increased CVD risk [35].

The results of our study also demonstrate the critical importance of incorporating transparent LLM analysis alongside traditional statistical methods to gain a more comprehensive and nuanced understanding of complex medical data. Specifically, when examining HbA1c as a static, isolated variable, there was no significant difference between the two study groups, a finding that is confirmed by LLM. This suggests that HbA1c value at a single visit, alone, is not strongly correlated with meaningful outcomes. However, when combined with other variables that describe the dynamics of the T2D patient's glycemic trend, HbA1c becomes an important predictor of outcomes. Similarly, our results suggest that TI may stem from a limited long-term perspective on how variables interrelate with poor glycemic outcomes. Although traditional statistical analysis found no significant age difference across the two groups, our LLM analysis uncovered that age plays a key role in determining glycemic outcomes, further emphasizing the value of incorporating AI techniques such as LLM to better identify patients subgroups bearing specific combination of variables which, taken together, might affect the clinical outcome.

Our study provides valuable insights into the factors contributing to therapy intensification delays in T2D patients. However, it is crucial to acknowledge the limitations of our research, which may impact the interpretation of our findings. First, as a retrospective real-life study, not all variables had consistent data available for each patient, leading to some missing data as detailed in Table 2, and while efforts were made to mitigate this limitation, it could potentially affect the overall robustness of the analysis. However, it is important to note that the Rulex AI algorithm employed in our study can manage missing values effectively, as it does not include them in the specific rules generated. This capability helps to minimize the impact of missing data on the overall analysis and findings.

Moreover, our analysis is based on real-world data collected from 271 distinct diabetes centres in Italy; consequently, the inherent diversity of data sources introduces the possibility of a "Batch effect" caused by fluctuations in measurements and analytical techniques. While we acknowledge this potential source of bias, its complete exclusion is challenging in real-world data analyses. While our study utilized a large and robust dataset, a notable limitation is the lack of detailed information on medication dosage, treatment adherence, and changes in lifestyle. These factors could have provided a more comprehensive understanding of the determinants influencing TI. Future studies should consider incorporating these variables to gain deeper insights into the multifaceted nature of TI in T2D management. Furthermore our study lacks of comparison with other machine learning algorithms, which may have resulted in suboptimal performance. Additionally, the internal validation of results, without external validation using independent datasets, limits the generalizability of the findings. Future studies should consider validating our model using external datasets to enhance the robustness of our conclusions. Finally, this study uses data gathered over a large timeframe (2005–2019), which poses challenges in identifying those physicians who may have changed their approach over time including their willingness to intensify therapy or make other adjustments. Over this period, there were updates to diabetes management guidelines and the introduction of new antidiabetic drugs into the market. These changes might have influenced the treatment approaches adopted by physicians, potentially biasing our analysis towards identifying primarily the "common" drivers over the entire period. Consequently, specific drivers associated with distinct sub-periods may not have been fully captured. To overcome this limitation, future studies may benefit from using more recent data that provide a more up-to-date and nuanced view of physicians' attitudes and practices regarding therapy intensification in T2D patients.

Despite these limitations, we strongly believe that the findings of this study could encourage the physician to gain greater awareness about the dynamic aspects of the course of T2D and adopt mechanisms that allow them to self-correct, remain updated on the latest developments in

Table 2
Characteristics of patients who experienced treatment inertia and those who did not, measured across two consecutive visits (T-Index), after treatment intensification (T-intensify), and at least two years after the initial T-Index.

	TOTAL	NO INERTIA (intervention < 2 years)		YES INERTIA (no intervention for > 2 years or no intervention at all)		P values T-index NO vs YES INERTIA	P values T-intensify/ Tindex+2years NO vs YES INERTIA
CHARACTERISTICS:		**T-Index**	**T-intensify**	**T-Index**	**T-Index+2 years**	**(alpha 0.05)**	**(alpha 0.05)**
Number of patients [n]	33096	20067	20067	13029	13029		
Number of patients with high/very high cardiovascular risk (CVR)[n]	23534	14273	17352	9261	11462		
% Patients with high/very high CVR	71%	71%	86%	71%	88%		
Females [n]	13462 (41%)	8103		5359			
Males [n]	19634 (59%)	11964		7670			
Mean time to intensification of treatment relative to T-Index [years]	2.36	1.23		4.1		<0.0001	<0.0001
SD time to intensification of treatment relative to T-Index [years]	1.97	0.45		2.14			
Median time to intensification of treatment relative to T-Index [years]	1.73	1.22		3.39			
N° of samples Time to TIndex	33096	20067	20067	13029	19029		
% Missing Data Time to TIndex	0%	0%	0%	0%	0%		

(*continued on next page*)

Table 2 (*continued*)

Interquartile Range Time to TIndex	1.09-2.87	0.88-1.61	0.88-1.61	2.5-5.06	2.5-5.06		
Mean Quality of care summary score (Q-SCORE)	24.89	24.96	25.06	24.78	25.03	<0.0001	0.415
SD Q-SCORE	2.59	2.60	2.54	2.58	2.53		
Median Q-SCORE	24.91	24.94	24.98	24.84	25.09		
N° of samples Q-SCORE	29572	18151	18803	11421	12722		
% missing Data Q-SCORE	10.65%	9.55%	6.3%	12.34%	2.36%		
Interquantile Range Q-SCORE	23.18-26.60	23.26-26.65	23.36-26.77	23.02-26.48	23.34-26.76		
Mean Serum Glutamic Pyruvic Transaminase (GPT) [mg/dL]	35.35	35.31	33.74	35.42	32.74	0.782	0.017
SD GPT	25.23	24.02	26.33	27.11	26.01		
Median GPT[mg/dL]	29.0	29.0	27.0	29.0	26.0		
N° of samples GPT	18443	11458	10640	6985	6347		
% missing data GPT	44%	42,90%	46,98%	46.39%	51,29%		
Interquantile range GPT	22.00-42.00	20.00-43.00	19.00-40.00	21.00-42.00	19.00-38.00		
Mean Serum Glutamic Oxaloacetic Transaminase (GOT) [mg/dL]	26.21	26.20	25.796	26.24	25.03	0.877	0.009
SD GOT	15.78	15.84	18.23	15.68	16.96		
Median GOT [mg/dL]	22.0	22.0	21.0	22.0	21.0		
N° Samples GOT	17578	10927	9958	6651	5906		
% missing data GOT	46.89%	45.55%	50.53%	48-95%	54.67%		
Interquantile range GOT	17.00-29.00	17-29	17-28	18-29	17-27		
Mean Estimated Glomerular Filtration Rate (eGFR) [ml/min/1.73m^2]	88.03	88.15	86.71	87.85	86.73	0.188	0.949
SD eGFR	16.65	17.07	18.46	15.92	16.51		
Median eGFR[ml/min/1.73m^2]	90.51	90.78	90.14	90.06	89.88		
N° samples GFR	23335	14487	14259	8848	8760		
% missing data GFR	29.49%	27.81%	28.94%	32.09%	32.77%		
Interquantile range GFR	77.54-99.24	77.37-99.93	75.92-99.28	77.86-99.36	76.91-97.62		
Mean Triglycerides [mg/dL]	178.39	182.69	165.43	171.49	155.81	<0.0001	<0.0001
SD Triglycerides	151.0	152.67	123.68	148.02	98.99		
Median Triglycerides [mg/dL]	144.0	147.0	137.0	140.0	131.0		
N° sampls Triglycerides	25305	15603	15139	9702	9402		
% missing data Triglycerides	23,54%	22.25%	24.56%	25.54%	27.84%		
Interquantile range Triglycerides	103.00-207.00	104-212	99-195	100-200	95-187		
Mean High-Density Lipoprotein (HDL) [mg/dL]	47.82	47.48	47.74	48.37	48.69	<0.0001	<0.0001
SD HDL	13.27	13.18	13.24	13.39	13.0		
Median HDL[mg/dL]	46.0	46.0	46.0	47.0	47.0		
N° samples HDL	24687	15210	14842	9477	9267		
% missing data HDL	25.41%	24.20%	26.04%	27.26%	28.87%		
Interquantile Range HDL	39.00-55-00	39-54	39-55	40-55	40-55		
Mean Low-Density Lipoprotein (LDL)[mg/dL]	119.56	118.45	105.04	121.38	104.34	<0.0001	0.151

(*continued on next page*)

Table 2 (*continued*)

SD LDL	38.06	38.10	34.85	37.93	34.65		
Median LDL[mg/dL]	118.0	117.0	102.0	120.0	102.0		
N° samples LDL	21342	13235	13177	8107	8087		
% missing data LDL	33.51%	34.05%	34.33%	37.78%	37.93%		
INterquartile range LDL	93.00-143.40	92-142	80.40-126.80	95-145	80.2-125.0		
Mean Body mass index (BMI) [kg/m^2]	30.94	31.05	30.86	30.77	30.54	<0.0001	<0.0001
SD BMI	5.49	5.59	5.69	5.33	5.33		
Median BMI [kg/m^2]	30.1	30.25	30.10	29.94	29.76		
N° samples BMI	25269	15257	19533	10012	12724		
% missing data BMI	23.65	23.97%	2.66%	23.16%	2.34%		
Interquartile range BMI	23.14-33.86	27.14-34-09	26.92-33.95	27.12-33.56	26.89-33.31		
Mean Hemoglobin A1c (HbA1c) [%]	8.36	8.46	7.99	8.2	7.71	<0.0001	<0.0001
SD HbA1c	1.33	1.38	1.17	1.24	0.82		
Median HbA1c [%]	7.90	8.00	7.80	7.80	7.50		
N° samples HBA1c	33096	20067	20067	13029	13029		
% Missing data HBA1c	0%	0%	0%	0%	0%		
Interquartile HBA1c	7.4-8.8	7.5-9	7.3-8.5	7.4-8.6	7.2-8.0		
Mean Age [years]	59.08	59.0	60.22	59.21	61.22	0.031	<0.0001
SD Age	8.79	9.18	9.18	8.17	8.17		
Median Age [years]	60.00	60.00	61.00	60.00	62.00		
N° samples Age	33096	20067	20067	13029	13029		
% Missing Data Age	0%	0%	0%	0%	0%		
Interquartile Age	53-66	52-66	54-68	54-66	26-68		
Mean fasting glucose [mg/dL]	171.94	175.44	164.43	166.58	153.03	<0.0001	<0.0001
SD fasting glucose	49.18	50.95	46.28	45.82	33.95		
Median fasting glucose[mg/dL]	160.00	164.00	156.00	156.00	147.00		
N° samples fasting glucose	28445	17218	17010	11227	(DBP)		
% missing Data fasting Glucose	14.05%	14.2%	15.23%	13.83%	14.89%		
Interquartile Range Fasting Glucose	140-190	142-196	135-183.88	138-182	132-167		
Mean Systolic blood pressure (SBP) [mmHg]	136.79	136.68	136.12	136.95	135.78	0.240	0.133
SD SBP	18.41	18.57	18,02	18.14	17.34		
Median SBP [mmHg]	135.00	135.00	135.00	135.00	135.00		
N° samples SBP	27538	16822	16559	10716	9548		
% missing Data SBP	16.79%	15.17%	17.48%	17.75%	26.72%		
Interquartile range SBP	120-150	120-150	120-146	123-150	120-145		
Mean Diastolic blood pressure (DBP) [mmHg]	81.32	81.31	80.30	81.33	79.90	0.863	0.001
SD DBP	10.18	10.35	9.67	9.90	9.38		
Median DBP [mmHg]	80.00	80.00	80.00	80.00	80.00		
Number of Samples DBP	27520	16810	16554	10710	9543		
% Missing Data DBP	16.85%	16.23%	17.51%	17.8%	26.76%		
Interquartile Range DBP	75-90	75-90	75-85	75-90	74-85		

diabetes care, and consequently avoid TI. Furthermore, we propose incorporating the model described in this study into a patient's electronic record to automatically alert the physician to the need for immediate action, eliminating any potential for TI. By leveraging technology in this manner, we could help to improve the quality of care provided to T2D patients.

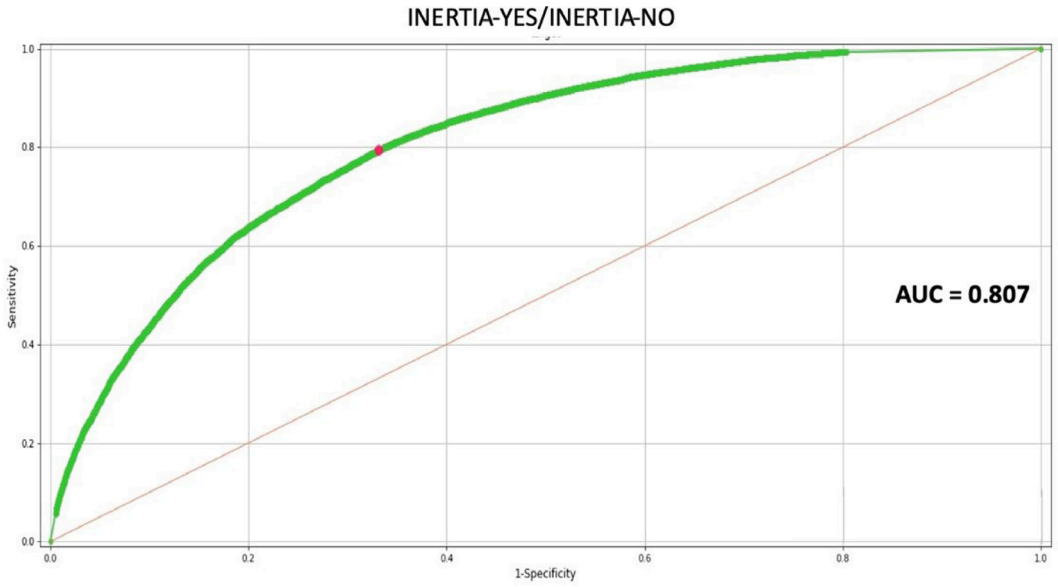


Fig. 3. ROC-AUC for the combination of descriptive and dynamic variables.

Table 3
Performance of the LLM analysis.

Parameters	Values
ROC-Area under the curve (AUC)	0.81
Confidence interval (95 %)	0.793–0.820
Accuracy	0.71
Precision	0.80
Recall	0.71
F1 score	0.75

Table 4
Ranking of most relevant factors for Inertia-YES and Inertia-NO situations.

Relevant factors	Threshold Inertia-NO	Threshold Inertia-YES	Relevance (0–1)
Hemoglobin A1c (HbA1c) at current visit	> 60 mmol/mol (>7.6 %)	< 60 mmol/mol (<7.6 %)	0.671
Mean HbA1c after T-Index	> 61 mmol/mol (>7.7 %)	< 61 mmol/mol (<7.7 %)	0.388
Mean Interval between two consecutive visits T-Index	< 4 months	> 4 months	0.186
HbA1c trend after T-Index (yearly trend)	> +0.12	< +0.12	0.179
Fasting glucose	> 190	< 160	0.174
Age at current visit	> 67 OR < 55	> 60 AND < 67	0.172
HbA1c standard deviation (SD) after T-Index		< +0.10 OR > +0.57	0.111

5. Conclusion

Modern physicians are confronted with a vast array of variables when making medical decisions, making it challenging to evaluate all the data simultaneously. Luckily, the emergence of "augmented intelligence" techniques offers crucial support to clinicians, helping prevent treatment delays, reduce negative patient outcomes, and lower healthcare costs.

Our findings bring attention to the time-based risk of specific HbA1c patterns, in which HbA1c levels, although not stably very high, remain decompensated for prolonged periods, thereby increasing the risk of complications. The results highlight the significance of the time duration during which HbA1c remains decompensated, rather than solely focusing on its levels. This study, alongside others utilizing cutting-edge technologies to enhance medical decision-making, emphasizes the importance of exploring areas such as TI. Through our real-world analysis of a substantial patient cohort, we have discovered novel parameters that, when identified and addressed, can effectively mitigate TI. This valuable insight opens the door to developing personalized treatment strategies for patients with T2D.

6. Fundings

Funding for this research was provided by Novo Nordisk S.p.A., the Italian subsidiary of Novo Nordisk A/S, Novo Allé, 2880 Bagsvaerd, Denmark.

CRediT authorship contribution statement

Nicoletta Musacchio: Validation, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Rita Zilich:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Formal analysis, Conceptualization. **Davide Masi:** Writing – review & editing, Writing – original draft, Methodology. **Fabio Baccetti:** Validation. **Besmir Nreu:** Supervision. **Carlo Bruno Giorda:** Validation, Supervision, Resources, Conceptualization. **Giacomo Guaita:** Validation, Supervision, Investigation. **Lelio Morviducci:** Supervision, Investigation, Formal analysis. **Marco Muselli:** Supervision, Software, Resources. **Alessandro Ozzello:** Supervision, Methodology, Investigation, Conceptualization. **Federico Pisani:** Software, Resources. **Paola Ponzani:** Validation, Supervision, Resources, Investigation, Funding acquisition. **Antonio Rossi:** Supervision. **Pierluigi Santin:** Supervision, Software, Formal analysis, Data curation. **Damiano Verda:** Validation, Supervision, Software. **Graziano Di Cianni:** Validation, Supervision. **Riccardo Candido:** Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

References

[1] M.M. Safford, R. Shewchuk, H. Qu, J.H. Williams, C.A. Estrada, F. Ovalle, et al., Reasons for not intensifying medications: differentiating "Clinical Inertia" from appropriate care, J. Gen. Intern. Med. 22 (2007) 1648–1655, https://doi.org/10.1007/s11606-007-0433-8.

[2] S.L. Karam, J. Dendy, S. Polu, L. Blonde, Overview of therapeutic inertia in diabetes: prevalence, causes, and consequences, Diabetes Spectrum 33 (2020) 8–15, https://doi.org/10.2337/ds19-0029.

[3] B.R. Shah, J.E. Hux, A. Laupacis, B. Zinman, C. Van Walraven, Clinical Inertia in Response to Inadequate Glycemic Control, Diabetes Care 28 (2005) 600–606, https://doi.org/10.2337/diacare.28.3.600.

[4] K. Khunti, Overcoming therapeutic inertia: ADA perspective, JAMD 25 (2022) 31. https://doi.org/10.36171/jamd22.25.1.5.

[5] S. Khunti, K. Khunti, S. Seidu, Therapeutic inertia in type 2 diabetes: prevalence, causes, consequences and methods to overcome inertia, Therapeutic Adv. Endocrinol. 10 (2019) 204201881984469, https://doi.org/10.1177/2042018819844694.

[6] B.B. Kidanie, G. Alem, H. Zeleke, M. Gedfew, A. Edemealem, A. Andualem, Determinants of diabetic complication among adult diabetic patients in debre markos referral hospital, northwest ethiopia, 2018: unmatched case control study, DMSO 13 (2020) 237–245, https://doi.org/10.2147/DMSO.S237250.

[7] R.R. Holman, S.K. Paul, M.A. Bethel, D.R. Matthews, H.A.W. Neil, 10-year follow-up of intensive glucose control in type 2 diabetes, N. Engl. J. Med. 359 (2008) 1577–1589, https://doi.org/10.1056/NEJMoa0806470.

[8] M. Al-Shabrawey, W. Zhang, D. McDonald, Diabetic retinopathy: mechanism, diagnosis, prevention, and treatment, Biomed Res. Int. 2015 (2015) 1–2, https://doi.org/10.1155/2015/854593.

[9] U. Kartoun, K. Iglay, R.R. Shankar, A. Beam, L. Radican, A. Chatterjee, et al., Factors associated with clinical inertia in type 2 diabetes mellitus patients treated with metformin monotherapy, Curr. Med. Res. Opin. 35 (2019) 2063–2070, https://doi.org/10.1080/03007995.2019.1648116.

[10] K. Khunti, M.L. Wolden, B.L. Thorsted, M. Andersen, M.J. Davies, Clinical inertia in people with type 2 diabetes, Diabetes Care 36 (2013) 3411–3417, https://doi.org/10.2337/dc13-0331.

[11] D. Lautsch, R. Boggs, T. Wang, C. Gonzalez, G. Milligan, S. Rajpathak, et al., Individualized HbA1c goals, and patient awareness and attainment of goals in type 2 diabetes mellitus: a real-world multinational survey, Adv. Ther. 39 (2022) 1016–1032, https://doi.org/10.1007/s12325-021-01985-3.

[12] S.K. Paul, K. Klein, B.L. Thorsted, M.L. Wolden, K. Khunti, Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes, Cardiovasc. Diabetol. 14 (2015) 100, https://doi.org/10.1186/s12933-015-0260-x.

[13] K. Khunti, M.B. Gomes, S. Pocock, M.V. Shestakova, S. Pintat, P. Fenici, et al., Therapeutic inertia in the treatment of hyperglycaemia in patients with type 2 diabetes: A systematic review, Diabetes Obes. Metab. 20 (2018) 427–437, https://doi.org/10.1111/dom.13088.

[14] C.C. McDaniel, W.-H. Lo-Ciganic, J. Huang, C. Chou, A machine learning model to predict therapeutic inertia in type 2 diabetes using electronic health record data, J. Endocrinol. Invest. 47 (2023) 1419–1433, https://doi.org/10.1007/s40618-023-02259-1.

[15] C.B. Giorda, F. Pisani, A. De Micheli, P. Ponzani, G. Russo, G. Guaita, et al., Determinants of good metabolic control without weight gain in type 2 diabetes management: a machine learning analysis, BMJ Open Diab Res Care 8 (2020) e001362.

[16] S. Han, H. Mao, W.J. Dally, Deep compression: compressing deep neural networks with pruning, Trained Quantization and Huffman Coding (2015). https://doi.org/10.48550/ARXIV.1510.00149.

[17] A. Dagliati, S. Marini, L. Sacchi, G. Cogni, M. Teliti, V. Tibollo, et al., Machine learning methods to predict diabetes complications, J. Diabetes Sci. Technol. 12 (2018) 295–302, https://doi.org/10.1177/1932296817706375.

[18] S.B. Nagaraj, G. Sidorenkov, J.F.M. Boven, P. Denig, Predicting short- and long-term glycated haemoglobin response after insulin initiation in patients with type 2 diabetes mellitus using machine-learning algorithms, Diabetes Obes. Metab. 21 (2019) 2704–2711, https://doi.org/10.1111/dom.13860.

[19] I. Kavakiotis, O. Tsave, A. Salifoglou, N. Maglaveras, I. Vlahavas, I. Chouvarda, Machine learning and data mining methods in diabetes research, Comput. Struct. Biotechnol. J. 15 (2017) 104–116, https://doi.org/10.1016/j.csbj.2016.12.005.

[20] D.R. Berlowitz, A.S. Ash, M. Glickman, R.H. Friedman, L.M. Pogach, A.L. Nelson, et al., Developing a quality measure for clinical inertia in diabetes care, Health Serv. Res. 40 (2005) 1836–1853, https://doi.org/10.1111/j.1475-6773.2005.00436.x.

[21] M. Muselli, Extracting knowledge from biomedical data through Logic Learning Machines and Rulex, Embnet j 18 (2012) 56. https://doi.org/10.14806/ej.18.B.549.

[22] M.C.E. Rossi, A. Nicolucci, A. Arcangeli, A. Cimino, G. De Bigontina, C. Giorda, et al., Baseline quality-of-care data from a quality-improvement program implemented by a network of diabetes outpatient clinics, Diabetes Care 31 (2008) 2166–2168, https://doi.org/10.2337/dc08-0469.

[23] A. Nicolucci, M.C. Rossi, A. Arcangeli, A. Cimino, G. De Bigontina, D. Fava, et al., Four-year impact of a continuous quality improvement effort implemented by a network of diabetes outpatient clinics: the AMD-Annals initiative: Quality initiative in diabetes care, Diabet. Med. 27 (2010) 1041–1048, https://doi.org/10.1111/j.1464-5491.2010.03055.x.

[24] M.C. Rossi, R. Candido, A. Ceriello, A. Cimino, P. Di Bartolo, C. Giorda, et al., Trends over 8 years in quality of diabetes care: results of the AMD Annals continuous quality improvement initiative, Acta Diabetol. 52 (2015) 557–571, https://doi.org/10.1007/s00592-014-0688-6.

[25] Muselli M. Switching Neural Networks: A New Connectionist Model for Classification. In: Apolloni B, Marinaro M, Nicosia G, Tagliaferri R, editors. Neural Nets, vol. 3931, Berlin, Heidelberg: Springer Berlin Heidelberg; 2006, p. 23–30. https://doi.org/10.1007/11731177_4.

[26] D. Masi, R. Risi, F. Biagi, D. Vasquez Barahona, M. Watanabe, R. Zilich, et al., Application of a machine learning technology in the definition of metabolically healthy and unhealthy status: a retrospective study of 2567 subjects suffering from obesity with or without metabolic syndrome, Nutrients 14 (2022) 373, https://doi.org/10.3390/nu14020373.

[27] D. Verda, S. Parodi, E. Ferrari, M. Muselli, Analyzing gene expression data for pediatric and adult cancer diagnosis using logic learning machine and standard supervised methods, BMC Bioinf. 20 (2019) 390, https://doi.org/10.1186/s12859-019-2953-8.

[28] D. Masi, R. Zilich, R. Candido, A. Giancaterini, G. Guaita, M. Muselli, et al., Uncovering predictors of lipid goal attainment in type 2 diabetes outpatients using Logic Learning Machine: insights from the AMD Annals and AMD Artificial Intelligence Study Group, JCM 12 (2023) 4095, https://doi.org/10.3390/jcm12124095.

[29] F. Cosentino, P.J. Grant, V. Aboyans, C.J. Bailey, A. Ceriello, V. Delgado, et al., 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD, Eur. Heart J. 41 (2020) 255–323, https://doi.org/10.1093/eurheartj/ehz486.

[30] S.A. Hicks, I. Strümke, V. Thambawita, M. Hammou, M.A. Riegler, P. Halvorsen, et al., On evaluation metrics for medical applications of artificial intelligence, Sci. Rep. 12 (2022) 5979, https://doi.org/10.1038/s41598-022-09954-8.

[31] F. Andreozzi, R. Candido, S. Corrao, R. Fornengo, A. Giancaterini, P. Ponzani, et al., Clinical inertia is the enemy of therapeutic success in the management of diabetes and its complications: a narrative literature review, Diabetol. Metab. Syndr. 12 (2020) 52, https://doi.org/10.1186/s13098-020-00559-7.

[32] S.N. Rajpathak, S. Rajgopalan, S.S. Engel, Impact of time to treatment intensification on glycemic goal attainment among patients with type 2 diabetes failing metformin monotherapy, J. Diabetes Complications 28 (2014) 831–835, https://doi.org/10.1016/j.jdiacomp.2014.06.004.

[33] N. Musacchio, A. Giancaterini, G. Guaita, A. Ozzello, M.A. Pellegrini, P. Ponzani, et al., Artificial Intelligence and Big Data in Diabetes Care: A Position Statement of the Italian Association of Medical Diabetologists, J. Med. Internet Res. 22 (2020) e16922.

[34] R. Mahabaleshwarkar, F. Gohs, H. Mulder, N. Wilkins, A. DeSantis, W.E. Anderson, et al., Patient and provider factors affecting clinical inertia in patients with type 2 diabetes on metformin monotherapy, Clin. Ther. 39 (2017) 1658–1670.e6, https://doi.org/10.1016/j.clinthera.2017.06.011.

[35] A. Ceriello, M.C. Rossi, S. De Cosmo, G. Lucisano, R. Pontremoli, P. Fioretto, et al., Overall quality of care predicts the variability of key risk factors for complications in type 2 diabetes: an observational, longitudinal retrospective study, Diabetes Care 42 (2019) 514–519, https://doi.org/10.2337/dc18-1471.