

## ORIGINAL ARTICLE

# Therapeutic inertia in the treatment of hyperglycaemia in patients with type 2 diabetes: A systematic review

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**Aims:** Therapeutic inertia, defined as the failure to initiate or intensify therapy in a timely manner according to evidence-based clinical guidelines, is a key reason for uncontrolled hyperglycaemia in patients with type 2 diabetes. The aims of this systematic review were to identify how therapeutic inertia in the management of hyperglycaemia was measured and to assess its extent over the past decade.

**Materials and Methods:** Systematic searches for articles published from January 1, 2004 to August 1, 2016 were conducted in MEDLINE and Embase. Two researchers independently screened all of the titles and abstracts, and the full texts of publications deemed relevant. Data were extracted by a single researcher using a standardized data extraction form.

**Results:** The final selection for the review included 53 articles. Measurements used to assess therapeutic inertia varied across studies, making comparisons difficult. Data from low- to middle-income countries were scarce. In most studies, the median time to treatment intensification after a glycated haemoglobin (HbA1c) measurement above target was more than 1 year (range 0.3 to >7.2 years). Therapeutic inertia increased as the number of antidiabetic drugs rose and decreased with increasing HbA1c levels. Data were mainly available from Western countries. Diversity of inertia measures precluded meta-analysis.

**Conclusions:** Therapeutic inertia in the management of hyperglycaemia in patients with type 2 diabetes is a major concern. This is well documented in Western countries, but corresponding data are urgently needed in low- and middle-income countries, in view of their high prevalence of type 2 diabetes.

## KEYWORDS

antidiabetic drug, glycaemic control, systematic review, type 2 diabetes

## 1 | INTRODUCTION

The importance of glycaemic control in patients with type 2 diabetes to reduce the risk of microvascular and macrovascular complications is well established<sup>1–5</sup> and widely recognized by current clinical guidelines.<sup>6–10</sup> For example, the joint position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) advocates a change of therapy if

glycated haemoglobin (HbA1c) targets are not achieved after 3 months.<sup>6</sup>

Despite the introduction of many glucose-lowering therapies that have proved to be efficacious in clinical trials, glycaemic control remains suboptimal in many patients globally. For example, in European countries with broad access to glucose-lowering therapies, the GUIDANCE (N = 7597) and PANORAMA (N = 5817) studies showed that only 53.6% and 62.6% of patients, respectively,

achieved the recommended HbA1c target of  $\leq 7\%$  (53 mmol/mol).<sup>11,12</sup>

Several studies have identified 2 main reasons for suboptimal glycaemic control in clinical practice: (1) patient non-adherence to prescribed treatment and (2) clinical or therapeutic inertia, defined as the failure to initiate or intensify therapy in a timely manner according to evidence-based clinical guidelines in individuals who are likely to benefit from such intensification.<sup>13,14</sup> The reasons for clinical or therapeutic inertia are multiple and complex, and include patient-, physician- and system-level barriers.<sup>15</sup>

The primary objective of this systematic review was to identify studies assessing the extent of therapeutic inertia in the treatment of hyperglycaemia in different populations of patients with type 2 diabetes. The secondary objective was to provide an overview of how therapeutic inertia was defined and assessed in different studies. Assessing the extent of therapeutic inertia is key to implementing interventions to reduce its occurrence, which will contribute to improving glycaemic control and ultimately patient outcomes.

## 2 | MATERIALS AND METHODS

This systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on April 13, 2016 (registration number CRD42016036483) and followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

### 2.1 | Data sources and searches

Systematic searches for articles published from January 1, 2004 to August 1, 2016 were conducted in MEDLINE and Embase using the OvidSP database search interface. A start date of January 1, 2004 was chosen, to include the seminal article on therapeutic inertia in the management of patients with type 2 diabetes by Brown et al. published in 2004.<sup>16</sup> This period also covers the publication of results from several outcome studies such as the Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) study,<sup>5</sup> the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study,<sup>17</sup> and the 10-year follow-up of the UK Prospective Diabetes Study (UKPDS),<sup>2</sup> which may have had an impact on the management of patients with type 2 diabetes in clinical practice.

Medical Subject Headings were used when available. A Medical Subject Heading for clinical or therapeutic inertia does not exist. Therefore, related terms were used instead (eg, "clinical competence," "health care delivery" and "guideline adherence"). Detailed search strings used for both MEDLINE and Embase, and the corresponding numbers of identified publications are shown in Tables S1 and S2, respectively.

### 2.2 | Study selection

Broad inclusion criteria were used to minimize the risk of excluding relevant studies. All publications involving studies of patients with type 2 diabetes that reported a quantitative measure of therapeutic

inertia were included. Conversely, articles covering studies with insufficient data (eg, those without a description of the intensification step and those not reporting the glycaemic level threshold used to determine whether treatment intensification was required) were excluded. No language restrictions were imposed, to increase the likelihood of finding data from as many countries as possible. Congress abstracts were excluded from this systematic review because they do not provide sufficient data for effective analysis. Non-original research articles (eg, editorials, letters, comments, guidelines and reviews) were also excluded. No other quality criteria were used to exclude studies from the systematic review.

Two researchers, S. Pi. and Andrew Mayhook (Oxford Pharma-Genesis, Oxford, UK), screened all titles and abstracts independently, in accordance with the inclusion and exclusion criteria described above. Full texts were retrieved for publications that met the inclusion criteria and for those that could not be adequately assessed for inclusion with the information provided in the abstract. The 2 researchers independently assessed the full texts for inclusion and discussed their decisions before reaching a consensus on the final list of articles to be included in the review.

### 2.3 | Data extraction

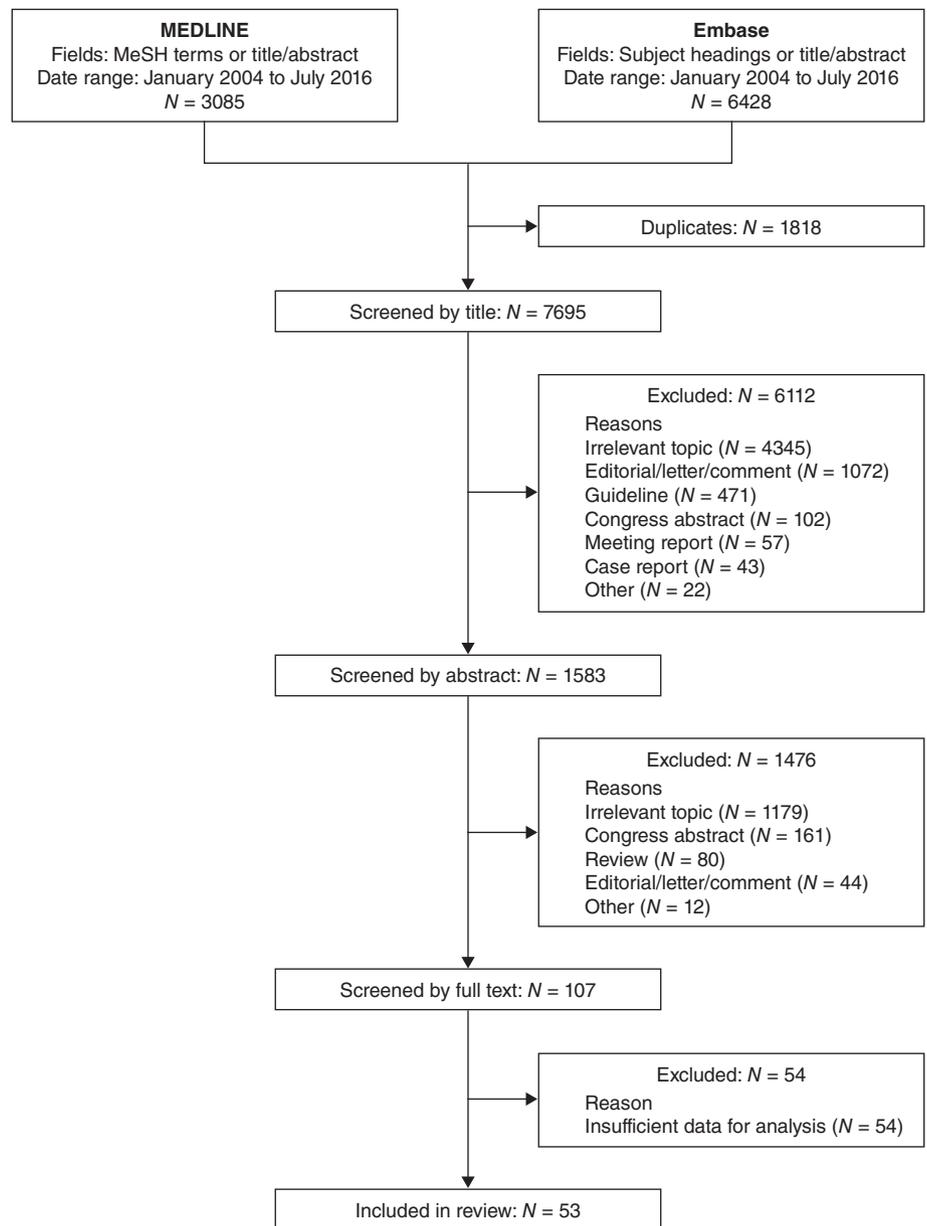
Data were extracted by a single researcher (S. Pi.). A standardized form was used to collect the following items when available: authors, year of publication, location, study design, period, sample size, patient and physician characteristics, definition of treatment intensification, glucose-lowering agents used before and after treatment intensification, and measure(s) of therapeutic inertia (including the HbA1c threshold used to identify patients who required treatment intensification).

## 3 | RESULTS

Out of 7698 combined search results, 53 articles were identified that reported at least 1 measure of therapeutic inertia in the management of hyperglycaemia in individuals with type 2 diabetes.<sup>16,18-69</sup> The main reasons for exclusion of publications other than duplicates and those covering irrelevant topics were that they reported non-original research (eg, editorials, letters, comments and guidelines) or they were congress abstracts (Figure 1). In addition, articles reporting the time to treatment intensification without reporting HbA1c results (eg, the time from type 2 diagnosis to insulin therapy initiation) were excluded.

### 3.1 | Study characteristics

Study characteristics are summarized in Table S3. The majority of studies were conducted in North America (29 studies) and Europe (20 studies). Three studies were carried out in Asia,<sup>35,47,53</sup> and a single study was conducted in Israel.<sup>62</sup> Articles mainly reported data from cohort studies, using data from medical records or chart reviews,<sup>20-22,26,28,30,32,44,46,47,51,52,57,60,62,64</sup> or from claims, clinical research or administrative databases.<sup>16,18,19,23-25,27,29,35-40,42,43,46,50,54-59,61,65,66,69</sup> Four articles reported results from cross-sectional studies, and the data were collected



**FIGURE 1** Flow diagram of study selection process. Titles, abstracts and full texts were screened independently by 2 researchers

using provider questionnaires or surveys.<sup>41,45,48,49</sup> A single publication reported results from a randomized clinical trial that evaluated the impact of physician education on the management of individuals with type 2 diabetes,<sup>53</sup> and another provided results from a post hoc analysis of a randomized controlled trial.<sup>63</sup>

Patients were managed by primary care providers in 21 studies,<sup>19,21,25,34,37–39,41,44,45,48,50,53,54,59–61,63–65,67</sup> by both primary care providers and secondary care specialists in 6 studies,<sup>23,30,35,47,58,68</sup> and by secondary care specialists alone in 1 study.<sup>69</sup> The healthcare providers responsible for patient care were not described in 25 studies.<sup>16,18,20,22,24,26–29,31–33,36,40,42,43,46,49,51,52,55–57,62,66</sup> Treatment characteristics varied across studies. Among articles that described therapy before treatment intensification, patients were managed exclusively with oral antidiabetic drugs (OADs) in most cases.<sup>16,18,19,23,28–31,35,39,43,47,50,51,54,58,62,65,66</sup> The study by Brown et al. also included a group of patients managed with non-pharmacological treatment (ie, diet and exercise exclusively).<sup>16</sup> Two studies included patients managed with OADs or diet and exercise

alone.<sup>22,46</sup> The study by Kristensen et al. included only patients managed with non-pharmacological treatment.<sup>40</sup> A single study considered 3 different treatment groups (OADs alone, insulin alone, and diet and exercise alone),<sup>68</sup> and 2 others investigated patients treated with OADs and/or injectable drugs.<sup>25,26</sup> Another group of studies included only patients who were not treated with insulin but did not describe their therapies in more detail (ie, glucagon-like peptide-1 [GLP-1] receptor agonists were not explicitly excluded).<sup>24,36,37,41,52,55,60,61,64,69</sup> By contrast, a study by Khunti et al. assessed treatment intensification in patients whose therapies included basal insulin.<sup>38</sup> Fifteen publications did not describe the treatments used before intensification.<sup>21,26,27,32,33,42,44,45,48,49,53,57,59,63,67</sup>

### 3.2 | Measures of therapeutic inertia

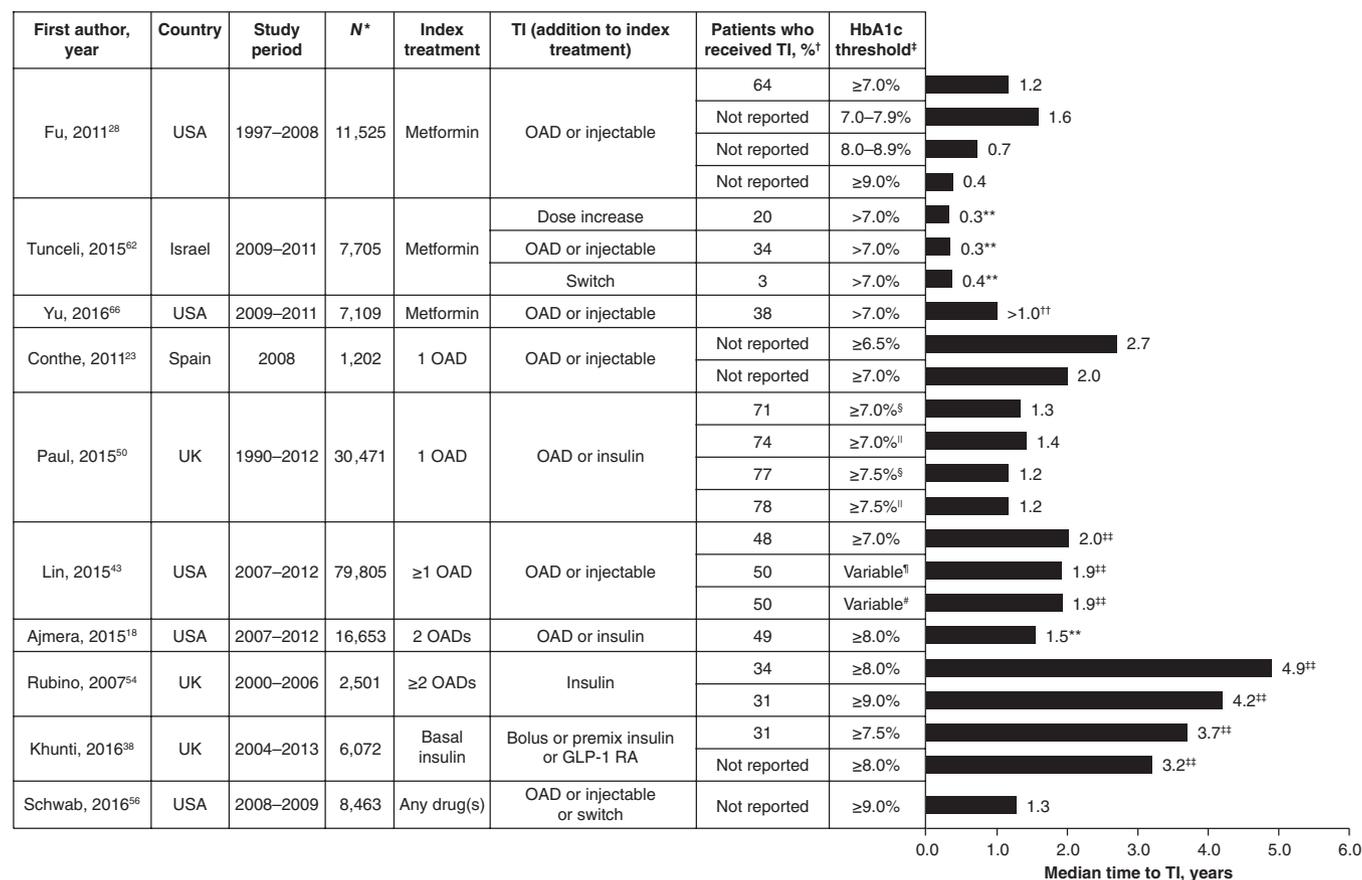
There is no accepted measure to describe clinical or therapeutic inertia. For the purpose of this systematic review, studies were classified into 4 categories based on the measurement(s) used to quantify

clinical/therapeutic inertia: (1) the mean or median length of time between at least one HbA1c measurement above a certain threshold and treatment intensification<sup>18,23,28,38,43,50,54,56,62,66</sup>; (2) the proportion of patients with at least 1 HbA1c measurement above a certain threshold who received treatment intensification within a given time frame<sup>18,19,21,22,24,25,27–29,31,32,35,37,40,42,43,46,47,50–53,55–66</sup>; (3) the glycaemic burden, defined as the length of time during which a patient had an HbA1c level above a certain threshold during a given period of time<sup>16,34,36,39,69</sup>; and (4) all other measurements.<sup>20,26,30,33,34,41,44,45,48,49,67,68</sup> HbA1c thresholds and the lengths of time to assess therapeutic inertia varied widely across the 53 studies, making comparisons difficult.

### 3.3 | Time to treatment intensification

Results from the 10 publications that reported the median time to treatment intensification are shown in Table S3 and Figure 2. For patients who received a single OAD,<sup>23,28,29,50,62,66</sup> the median time to treatment intensification with any drug (ie, by addition of 1 OAD or

insulin/other injectable drug) was 0.3 to 2.7 years after at least 1 HbA1c measurement above target. The time to treatment intensification was generally longer in studies that included patients treated with more than one OAD and ranged from 1.3 to 4.9 years.<sup>18,43,54,56</sup> In most of these studies, less than 50% of the patients received treatment intensification before the end of the follow-up period. The study by Rubino et al. specifically reported treatment intensification with insulin in patients using 2 or more OADs.<sup>54</sup> The time to treatment intensification estimated by Kaplan–Meier survival analysis was 4.9 and 4.2 years for patients with HbA1c levels of  $\geq 8.0\%$  and  $\geq 9.0\%$ , respectively. A single study assessed therapeutic inertia in patients using basal insulin.<sup>38</sup> The time to treatment intensification (addition of bolus insulin, premix insulin or a GLP-1 receptor agonist) was estimated by Kaplan–Meier survival analysis to be 3.7 and 3.2 years for patients with HbA1c levels of  $\geq 7.5\%$  and  $\geq 8.0\%$ , respectively. For each of the 5 studies that considered different HbA1c targets,<sup>23,28,38,50,54</sup> the median time to treatment intensification decreased with increasing HbA1c targets regardless of the index treatment.



**FIGURE 2** Median time to treatment intensification. Data are given as median times to treatment intensification from the time HbA1c level was above the threshold shown in the table, unless otherwise stated. \*Total number of patients for whom treatment intensification was required in each study. †Proportion of patients who received treatment intensification by the end of the study period. ‡HbA1c target used to define inadequate glycaemic control in patients who required treatment intensification. §Consistently above HbA1c target for 1 year post diagnosis. ‖Consistently above HbA1c target for 2 years post diagnosis. ¶Modified HbA1c target defined by Ismail-Beigi et al. that was based on patient age and the presence or absence of macrovascular and microvascular complications, resulting in an individualized HbA1c level between  $\leq 6.5\%$  and  $<8.0\%$ .<sup>70</sup> #Modified Healthcare Effectiveness Data and Information Set (HEDIS) target of HbA1c  $<7.0\%$  for patients aged  $<65$  years without evidence of significant morbidities and HbA1c  $<8.0\%$  for all other patients (set by the National Committee for Quality Assurance Healthcare in 2013). \*\*Median time to treatment intensification calculated only for patients who received treatment intensification during the study period. ††Fewer than 50% of patients had received treatment intensification by the end of the study period. †††Estimated by Kaplan–Meier analysis. GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; OAD, oral antidiabetic drug; TI, treatment intensification

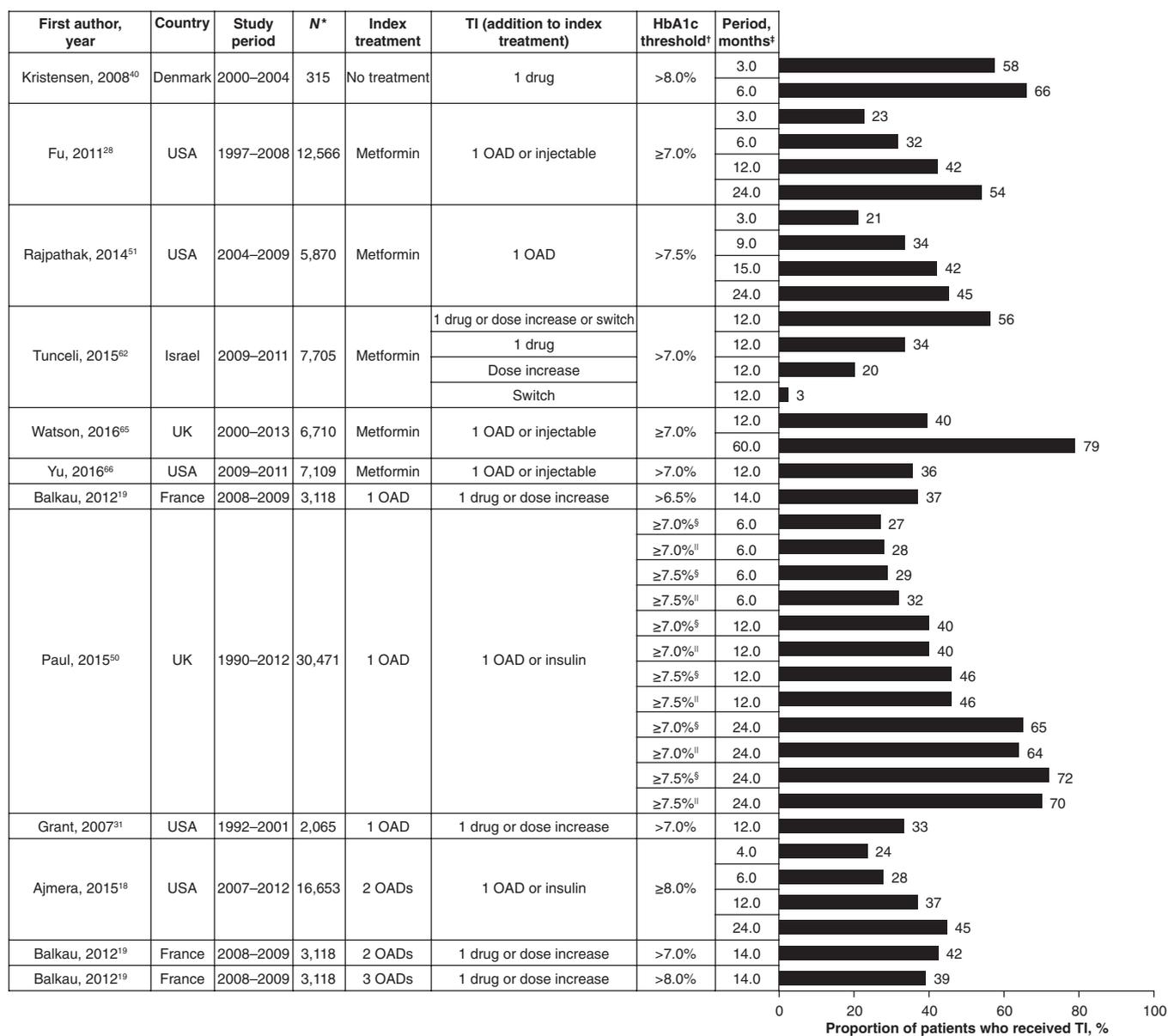
### 3.4 | Proportion of patients who received treatment intensification

A total of 34 studies reported the proportions of patients who received treatment intensification within a given a period of time (Table S3).<sup>18,19,21,22,24,25,27-29,31,32,35,37,40,42,43,46,47,50-53,55-66</sup> Results from studies that included a single treatment intensification step (eg, a specific number of OADs at baseline) and those combining several baseline treatments (eg, baseline treatment described as other than insulin) are summarized in Figures 3 and 4, respectively.

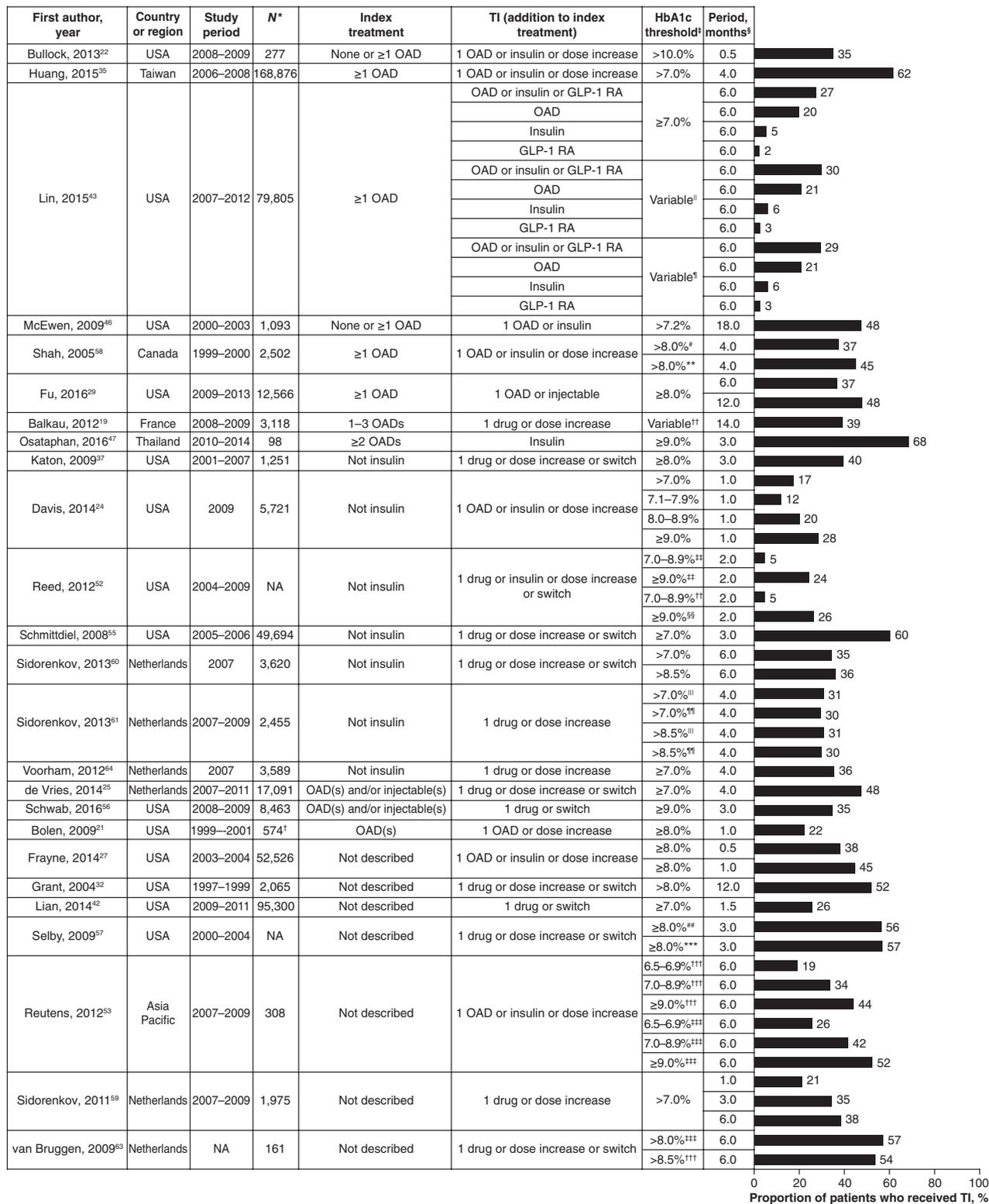
In most of these studies, less than 50% of patients received treatment intensification for follow-up periods of less than 12 months. Exceptions were observed for patients managed with diet and exercise only at baseline<sup>40</sup> and for patients with HbA1c levels  $\geq 9.0\%$ .<sup>47,53</sup> Four other studies found treatment intensification in

more than 50% of patients within 6 months or less of having an HbA1c level above target.<sup>35,55,57,63</sup> In 3 of these studies, patients were managed by physicians taking part in a pay-per-performance programme,<sup>35</sup> or they were members of a large, integrated managed care consortium (Kaiser Permanente Northern California).<sup>55,57</sup> The fourth study was a post hoc analysis of a randomized controlled trial concerning the implementation of locally adapted guidelines.<sup>63</sup>

Unsurprisingly, for studies that considered several follow-up periods, the proportion of patients who received treatment intensification rose with increasing lengths of follow-up. Nevertheless, even after periods longer than 12 months following an HbA1c measurement above target, the proportion of patients who had received treatment intensification was only 37% to 79%.<sup>18,19,28,51,65</sup> In 4 studies in which different HbA1c thresholds were analysed, the



**FIGURE 3** Proportion of patients who received treatment intensification after a given period of time (patients managed with a defined number of OADs). \*Total number of patients for whom treatment intensification was required. †HbA1c target used to define suboptimal glycaemic control in patients who required treatment intensification. ‡Length of time to assess treatment intensification after HbA1c level was above target. §Consistently above HbA1c target for 1 year post diagnosis. ||Consistently above HbA1c target for 2 years post diagnosis. HbA1c, glycated haemoglobin; OAD, oral antidiabetic drug; TI, treatment intensification



**FIGURE 4** Proportion of patients who received treatment intensification after a given period of time (number of drugs before treatment intensification not clearly defined). \*Total number of patients for whom treatment intensification was required. †Total number of clinical encounters that required treatment intensification. ‡HbA1c target used to define suboptimal glycaemic control in patients who required treatment intensification. §Length of time to assess treatment intensification after HbA1c level was above target. ¶Modified HbA1c target defined by Ismail-Beigi et al., which was based on patient age and the presence or absence of macrovascular and microvascular complications, resulting in individualized HbA1c levels between ≤6.5% and <8.0%.<sup>70</sup> ¶¶Modified Healthcare Effectiveness Data and Information Set (HEDIS) target of <7.0% for patients aged <65 years without evidence of significant morbidities and <8.0% for all other patients (set by the National Committee for Quality Assurance Healthcare in 2013). #Primary care. \*\*Specialist care. ††HbA1c level >6.5% for 1 OAD, >7.0% for 2 OADs and >8.0% for 3 OADs. †††Before implementation of electronic health record system. §§After implementation of electronic health record system. ¶¶¶One HbA1c measurement above target. ¶¶¶¶Two consecutive HbA1c measurements above target. ##In 2011. \*\*\*In 2013. ††††Control group. †††††Intervention group (healthcare professional training on clinical guidelines). Abbreviations: GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; NA, not available (not reported); OAD, oral antidiabetic drug; TI, treatment intensification

proportion of patients who received treatment intensification rose with increasing HbA1c values.<sup>24,50,52,53</sup> By contrast, in 2 studies by Sidorenkov et al.<sup>60,61</sup> the proportions of patients who received treatment intensification were similar for those with HbA1c >7.0% and those with HbA1c >8.5%.

In the single study that reported proportions of patients receiving treatment intensification within 6 months for different treatment regimens,<sup>43</sup> proportions were lower for insulin (5% to 6%) and GLP-1 receptor agonists (2% to 3%) than for addition of an OAD (20% to 21%).

### 3.5 | Glycaemic burden

Five publications reported glycaemic burden (ie, the length of time with HbA1c above target during a given period).<sup>16,34,36,39,69</sup> Results of these studies are summarized in Figure 5 and Table S3. The studies by Brown et al. and Khunti et al. identified patients who required treatment intensification, and they assessed the glycaemic burden until treatment intensification.<sup>16,39</sup> By contrast, 2 other studies identified a cohort of patients who initiated insulin and assessed glycaemic burden retrospectively.<sup>36,69</sup> In the study by Halimi et al.<sup>34</sup> patients with poor glycaemic control were identified during a routine visit, and the length of time their HbA1c level had been above target was calculated using medical records.

In the study by Brown et al.<sup>16</sup> the mean glycaemic burden ranged from 0.7 to 4.9 years, depending on therapy and HbA1c threshold. Glycaemic burden increased with the rising number of OADs used and was lower for patients with HbA1c levels >8.0% than for those with HbA1c levels >7.0%. The proportion of patients with HbA1c levels >8.0% who received treatment intensification by the end of the study decreased with the increasing number of OADs (19% to 67%). The study by Khunti et al. reported a median time to treatment intensification from 1.1 years to more than 7.2 years,<sup>39</sup> the median glycaemic burden rising with the increasing number of OADs and decreasing with increasing HbA1c values. The proportions of patients who received treatment intensification by the end of the study period were similar for patients with HbA1c levels  $\geq 7.0\%$ ,  $7.5\%$  and  $8.0\%$ , and decreased with the increasing number of OADs; these proportions were lower when treatment was intensified with insulin (7% to 22%) than when it was intensified with an OAD (30% to 67%). Halimi et al. identified patients who received OADs and whose HbA1c was inadequately controlled (2 consecutive HbA1c measurements  $\geq 6.5\%$ ,  $\geq 7.0\%$  and  $\geq 8.0\%$  for patients treated with 1, 2 and 3 OADs, respectively).<sup>34</sup> Although the HbA1c level had been over target for 0.9 to 1.2 years in these patients, few individuals (0% to 7%) received treatment intensification during the inclusion visit. In the study by Zografou et al.<sup>69</sup> glycaemic burden was assessed from diagnosis to insulin treatment initiation; the median time above target was 0.8 to 4.2 years and decreased with increasing HbA1c values. In the study by Hugie et al.,<sup>36</sup> glycaemic burden (HbA1c >8.0%) before insulin treatment initiation was 0.4 to 1.3 years and rose with the increasing number of OADs.

### 3.6 | Other measures of therapeutic inertia

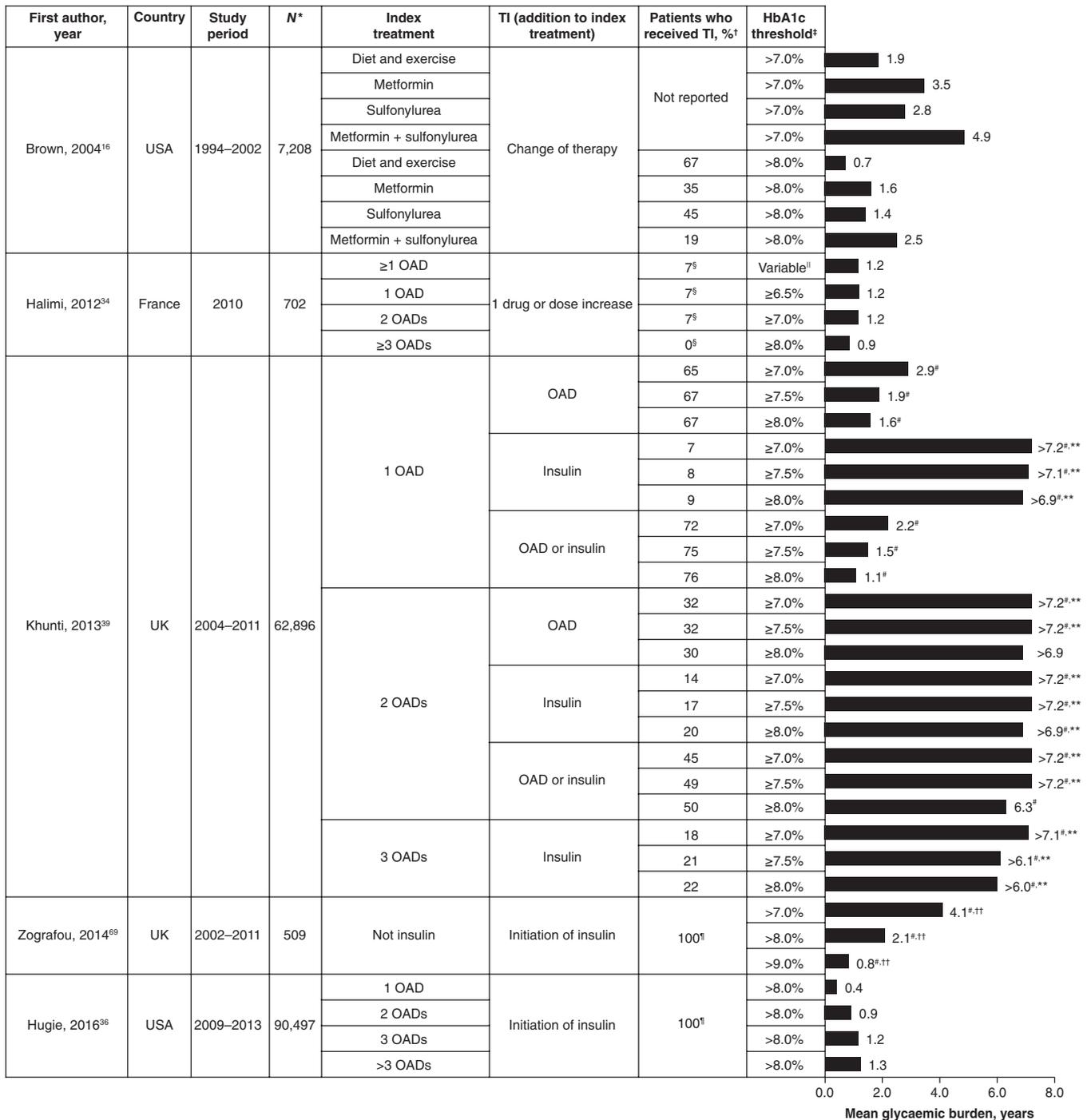
In addition to the studies above, 12 others determined the proportions of patients who received treatment intensification without

specifying a time frame<sup>30,33,34,44</sup> or measured therapeutic inertia by assessing the proportion of clinical encounters for which treatment intensification was recommended by guidelines and did not occur (Table S3).<sup>20,26,41,45,48,49,67,68</sup> In 4 of these studies, treatment intensification was assessed by questionnaires completed by physicians<sup>41,45,49</sup> or patients.<sup>48</sup> The different and insufficiently described methodologies precluded any comparisons among these studies. In the study by Ziemer et al.,<sup>68</sup> treatment intensification rates increased with rising plasma glucose levels and were higher in specialist care than in primary care settings. Similarly, in the studies by Parchman et al.<sup>48</sup> and Parnes et al.,<sup>49</sup> rates of treatment intensification increased with rising HbA1c values. An opposite trend was observed in the study by Lang et al.,<sup>41</sup> in which the proportions of patients who received treatment intensification decreased with increasing HbA1c values.

## 4 | DISCUSSION

To our knowledge, this is the first systematic review to analyse the global extent of therapeutic inertia in the management of hyperglycaemia in patients with type 2 diabetes within our search timeframe. The results clearly demonstrate that delays in treatment intensification are widespread in both primary and specialist care, and occur at all stages of the treatment pathway, from initiation of oral therapy after failure of non-pharmacological treatment (diet and exercise), through addition of OAD(s), to initiation and intensification of insulin therapy. In studies that considered several treatments, delay in intensification was found to increase with rising numbers of OADs. The longest delays were reported for initiation of insulin, which reflects reticence on the part of both patients and healthcare professionals to initiate and intensify insulin therapy, for reasons that include fear of injection pain, potential side effects (hypoglycaemia and weight gain) and reduced quality of life, alongside concerns about adherence to treatment.<sup>71-74</sup>

Although the ADA/EASD joint position statement recommends a change of therapy if HbA1c targets are not achieved after 3 months,<sup>6</sup> the reported times to treatment intensification were generally much higher than 3 months, and the proportion of patients who received treatment intensification after this period was low. In all studies that compared several HbA1c thresholds, higher HbA1c values were associated with shorter times to treatment intensification and/or a higher proportion of patients who underwent treatment change within a given follow-up period. Although the heterogeneity of the included studies precluded identification of secular trends in the evolution of therapeutic inertia, the results suggest that therapeutic inertia has been a persistent issue over the past decade. As mentioned previously, inertia does not have an associated Medical Subject Heading and may have diverse definitions, making the design of the search string difficult. Although we used a comprehensive search strategy and identified a large number of studies, some relevant publications may have been missed. The diversity of inertia measures, patient populations, treatments and HbA1c targets used to assess glycaemic control made comparisons among studies difficult and precluded any meta-analysis of the results. Indeed, the extent of therapeutic inertia depends on the definitions of treatment goals (based on different



**FIGURE 5** Glycaemic burden (defined as the length of time with HbA1c level above target during a given period of time). Data are shown as means unless otherwise stated. \*Total number of patients for whom treatment intensification was required. †Proportion of patients who received treatment intensification by the end of the study period. ‡HbA1c target used to define glycaemic burden. §Proportion of patients who received treatment intensification at the inclusion visit. ||HbA1c ≥6.5% for 1 OAD, HbA1c ≥7.0% for 2 OADs and HbA1c ≥8.0% for 3 OADs. ¶Only patients in whom insulin treatment was initiated were included in the study. #Median glycaemic burden. \*\*Fewer than 50% of patients had received treatment intensification by the end of the study period. ††Glycaemic burden was calculated from type 2 diabetes diagnosis to initiation of insulin therapy. HbA1c, glycated haemoglobin; OAD, oral antidiabetic drug; TI, treatment intensification

clinical guidelines), therapies and time windows selected to assess treatment intensification in individual studies. Despite these limitations, some useful inferences can be drawn from the data.

First, our systematic review highlighted a lack of data on treatment intensification outside North America and Western Europe. Although searches were not restricted to specific countries or regions

and languages, only 3 studies were conducted in Asia, only 1 in Eastern Europe (Croatia) and only 1 in Israel. Given the high prevalence of type 2 diabetes in many low- and medium-income countries,<sup>75</sup> studies to quantify and address therapeutic inertia in those countries may be a valuable opportunity to improve glycaemic control and patient outcomes.

Whether the delays in treatment intensification identified in this review represent true therapeutic inertia may be contentious. Most of the reviewed studies used generic targets (eg HbA1c level >7.0% for all patients as opposed to individualized targets) to assess glycaemic control and thus therapeutic inertia. Some studies may, therefore, overestimate the prevalence of therapeutic inertia because treatment intensification may not be warranted in certain patients (eg, in elderly individuals). It should be noted, however, that the study by Lin et al. found similar results for a generic HbA1c target of 7.0% and 2 alternative individualized HbA1c thresholds.<sup>43</sup>

Other methodological aspects of some of the studies should be carefully considered when interpreting the results and the degree to which they represent therapeutic inertia. Several studies quantified therapeutic inertia by calculating the number of visits during which treatment intensification was indicated by guidelines but did not occur.<sup>41,45,68</sup> This approach may not provide a representative picture of therapeutic inertia. At the level of a visit, competing demands may prevent treatment intensification, particularly in primary care. As visits are time-constrained, physicians and patients may prioritize more pressing issues (eg, symptomatic comorbidity or counselling for smoking-cessation) and thus delay treatment intensification to another visit.<sup>48</sup> Competing demands were one of the main reasons for inaction cited by healthcare providers in the study by Parnes et al.<sup>49</sup> In this context, there is an opportunity for pharmacists to play an important role in timely treatment intensification. However, none of the articles included in this review reported data on the management of patients by pharmacists. Some studies may also overestimate the prevalence of therapeutic inertia because they assess treatment intensification after a single HbA1c measurement above target. Some physicians may wait for confirmation of suboptimal glycaemic control (ie, a second consecutive HbA1c measurement above target) before intensifying treatment, particularly for patients who are close to their glycaemic target. In that case, assessing treatment intensification after 2 consecutive measurements above target or using glycaemic burden is likely to provide a more accurate estimate of true therapeutic inertia. Nevertheless, a study by Sidorenkov et al. found very similar proportions of patients receiving treatment intensification after a single HbA1c measurement or after 2 consecutive HbA1c measurements above target.<sup>60</sup> These variations in methodology across the included studies highlight the need for accepted definitions of therapeutic inertia for use in clinical research, to ensure that therapeutic inertia is accurately measured and reported.

Although delay in treatment intensification may be justified for some patients, it took longer than recommended by current clinical guidelines for significant proportions of patients to receive treatment intensification. Therapeutic inertia remains a significant barrier to adequate glycaemic control in North America and Europe. In other regions, data are scarce or non-existent, and studies are warranted to analyse the extent of therapeutic inertia, its causes, and its impact on glycaemic control and patient outcomes globally. Given the risk of microvascular and macrovascular complications associated with poor glycaemic control,<sup>4,76-79</sup> actions such as healthcare quality-improvement programmes are urgently required to increase adherence to guidelines and to identify patients who may benefit from closer glucose monitoring.

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## Conflict of interest

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## Author contributions

All authors contributed to the design of the search strategy. S. Pi. conducted the searches, screened the hits and extracted the data. K. K. and S. Pi. developed the figures and wrote the first draft of the manuscript. All authors contributed to the analysis and interpretation of the data, and critically reviewed all drafts. All authors approved the final draft for submission. The guarantor of this work is K. K.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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