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## Review

# Clinical inertia to insulin initiation and intensification in the UK: A focused literature review

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## ABSTRACT

Achieving tight glycaemic control early following the diagnosis of type 2 diabetes is key to optimising clinical outcomes, yet many patients and clinicians are reluctant to initiate and intensify insulin therapy. Reasons for this arise primarily from a lack of time, clinical expertise and patient understanding. However, meaningful progress can be achieved with self-management educational programmes soon after diagnosis. Clinician education and training, along with easy-to-use and well-tolerated therapies (for example, those carrying a low risk of hypoglycaemia and/or avoiding weight gain), may also increase the likelihood of patient adherence.

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E-mail addresses: [kk22@leicester.ac.uk](mailto:kk22@leicester.ac.uk), [rkg4@le.ac.uk](mailto:rkg4@le.ac.uk) (K. Khunti).<http://dx.doi.org/10.1016/j.pcd.2016.09.003>1751-9918/© 2016 The Authors. Published by Elsevier Ltd on behalf of Primary Care Diabetes Europe. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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## 1. Introduction

Currently, 387 million people worldwide are living with diabetes, of whom 3.9 million are in the UK [1]. The majority remain in poor glycaemic control and at risk of vascular complications, which may already be developing at the time of diagnosis [2,3].

The UK Prospective Diabetes Study (UKPDS) revealed that intensive diabetes management from diagnosis was associated with a reduced risk of microvascular complications by the end of the 10-year trial period [4], and a reduced risk of myocardial infarction and all-cause death reported in the decade following [5]. Subsequent shorter-term landmark trials that recruited patients at high risk of cardiovascular disease (CVD) with a long duration of diabetes, and that involved stringent glycaemic targets and more complex treatment regimens in the intensive arm, did not show such clear-cut benefits in terms of macrovascular complications and mortality [6]. All the trials demonstrated a reduced risk of microvascular complications (some more substantial than others) but only UKPDS demonstrated a reduced risk of macrovascular disease and mortality at the end-of-trial (reaching significance in the 10-year follow-up) [5]. Follow-up of the Veterans Affairs Diabetes Trial (VADT) for almost 10 years revealed a reduced risk of cardiovascular event but not all-cause mortality in participants from the intensive treatment arm [7]. Results from these trials demonstrate the importance of individualising treatment targets (according to established vascular complications and comorbidities [2]) and suggest that delayed treatment intensification can allow irreversible diabetes-related complications to develop. The latest results from a retrospective cohort study confirm this, since a 1-year delay in treatment intensification in uncontrolled patients significantly increased the risk of myocardial infarction, heart failure, stroke and a composite endpoint of cardiovascular events (Fig. 1) [8].

The current guidelines recommend stepwise intensification [2,3], and while resistance to intensification is evident at every step, it appears to be more pronounced when considering initiating insulin [9], despite this being the most effective agent for lowering blood glucose when used appropriately [2]. Furthermore, few patients intensify their insulin regimen appropriately [10,11]. The failure to close the gap between best practice and the patient's usual level of care is termed 'clinical inertia' [12].

The majority of clinical inertia studies are focused on the US, the UK and Canada. In the present study, we review the evidence for clinical inertia in the UK, where healthcare is free for all, and also the barriers and potential solutions.

## 2. Methods

A focused literature search for studies on clinical inertia relating to insulin initiation and intensification in patients with

type 2 diabetes in the UK was conducted using PubMed, Scopus and Google Scholar. Search terms included 'type 2 diabetes', 'insulin intensification', 'delay', 'time', 'inertia', 'insulin avoidance', 'escalation' and 'reluctance'. Only studies conducted in the UK were included. Table 1 illustrates some of the key studies [9,10,13-18].

## 3. What evidence is there of clinical inertia?

Studies show that insulin initiation is delayed until after multiple oral antidiabetic drug (OAD) failures and deterioration of glycaemic control well beyond recommended guidelines [19]. Clinical inertia is not restricted to the UK, as demonstrated by results of the Study of Once Daily Levemir (SOLVE™; Table 1) [11,13]. Reasons why blood glucose levels were higher in the UK at the time of insulin initiation were not reported.

Relatively few studies examine clinical inertia with insulin intensification, but results show similar delays (Table 1). A retrospective analysis of data from insulin-treated patients with type 2 diabetes within The Health Improvement Network (THIN) UK primary care database demonstrated that intensification was associated with high HbA<sub>1c</sub> (mean 77 mmol/mol [9.2%] before change) and longer duration of diabetes, whereas lack of intensification was associated with an increased risk of co-morbidities. The proportion of patients who intensified basal insulin or switched to prandial/premixed insulin had a mean HbA<sub>1c</sub> of 71 mmol/mol (8.6%) and 69 mmol/mol (8.5%) following change in therapy, respectively. This is in contrast to the mean HbA<sub>1c</sub> values that were achieved by participants of phase 3 clinical trials investigating these prandial or premix insulin analogues [10].

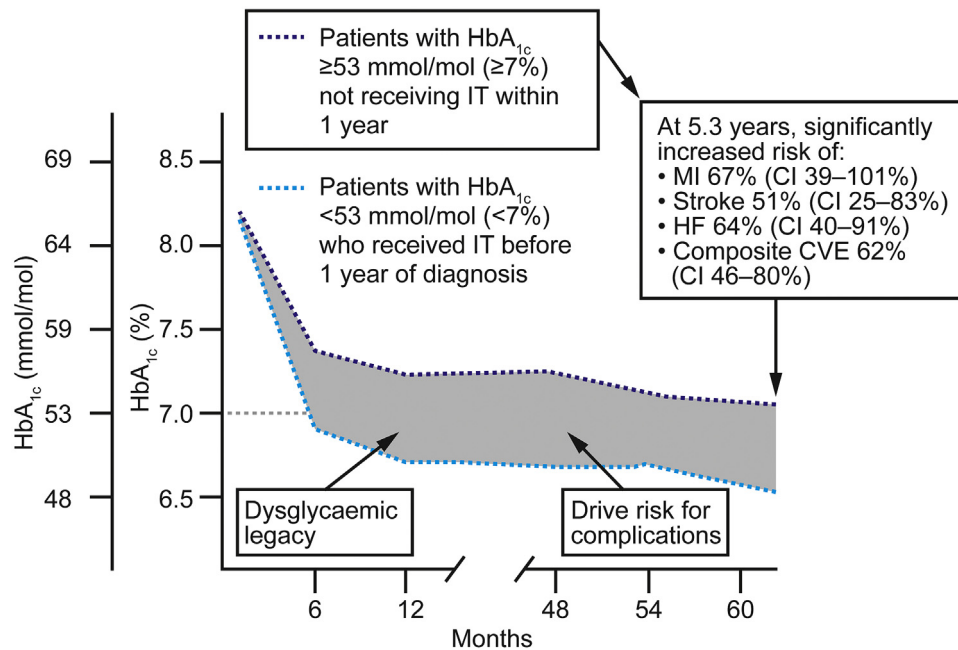
A retrospective cohort study of 11,696 insulin-treated UK patients revealed that 31% of patients who were clinically eligible for intensification (HbA<sub>1c</sub> of 58 mmol/mol [ $\geq 7.5\%$ ]) were treated accordingly (Table 1) [18]. Older age, longer duration of diabetes and higher Charlson comorbidity index were all associated with a longer time to intensification, which might be expected given that less stringent HbA<sub>1c</sub> targets are recommended for these populations [2,3]. However, only a small reduction in time to intensification was observed when applying a less stringent HbA<sub>1c</sub> cut-off of  $\geq 64$  mmol/mol (8.0%) to the same entire study population. Use of OADs also had a significant association with time to intensification, correlating with a longer delay; yet receiving  $\geq 2$  OADs was associated with a reduced delay versus receiving one OAD [18].

Results from a multinational survey, 'Management Of Diabetes In Future Years' (MODIFY), revealed that 30% of primary care physicians overall never/rarely personally intensified insulin (compared with 4% of specialists), despite 92% of physicians agreeing with the statement "insulin intensification is an essential element of diabetes management". However, it is not known whether any of these primary care physicians were lacking the necessary resources for insulin

**Table 1 – Studies reporting clinical inertia for insulin therapy in the UK.**

Study	Number of patients	Key findings
Khunti et al. [13]	UK cohort of SOLVE (n = 761)	At the time of insulin initiation, the UK cohort had a higher baseline HbA <sub>1c</sub> compared with the global population of SOLVE (84 mmol/mol [9.8%] vs. 74 mmol/mol [8.9%], respectively), despite a shorter duration of disease
Mata-Cases et al. [14]	2783	Of 997 not achieving glycaemic targets, only 66.8% intensified, with an even smaller proportion of them initiating insulin treatment (3.7%). Mean HbA <sub>1c</sub> values in patients for whom treatment intensified vs non-intensified were 68 mmol/mol (8.4%) vs. 66 mmol/mol (8.2%), <i>p</i> < 0.05.
Khunti et al. [9]	81,573	Retrospective cohort study on patients with type 2 diabetes in Clinical Practice Research Datalink looked at time to treatment intensification in those receiving one, two or three OADs. Mean HbA <sub>1c</sub> at intensification with an OAD or insulin for people taking one, two or three OADs was 72 mmol/mol (8.7%), 76 mmol/mol (9.1%) and 83 mmol/mol (9.7%). Median time to intensification with insulin was >7.1, >6.1 or 6.0 years, respectively.
Evans et al. [15]	128,568	Retrospective cohort-based study revealed that mean HbA <sub>1c</sub> at insulin initiation was 80 mmol/mol (9.5%) (one OAD), 81 mmol/mol (9.6%) (two), 83 mmol/mol (9.7%) (three) and 87 mmol/mol (10.1%) (four), with insulin initiated only after there had been an average increase in HbA <sub>1c</sub> of 8 mmol/mol (0.7%).
Calvert et al. [16]	14,824 people on DIN-LINK database included	Study examined the extent of monitoring and glycaemic control in patients with type 2 diabetes prescribed oral agents and/or insulin, and investigated transition to insulin. Only 34% had HbA <sub>1c</sub> assessments 6 months before and after initiation of their last oral therapy. Of the patients with HbA <sub>1c</sub> assessments, 62% had evidence of poor glycaemic control following therapy. Median time to insulin for patients prescribed multiple oral agents was 7.7 years.
Zografou et al. [17]	509	Retrospective study examining patients who initiated insulin therapy between 2002 and 2011 from the Scottish Care Information-Diabetes Collaboration (SCI-DC) database (Scotland). Patients spent a median period of 49 (0–325) months with HbA <sub>1c</sub> > 53 mmol/mol (>7%), 25 (0–163) months with HbA <sub>1c</sub> >64 mmol/mol (>8%) and 10 (0–135) months with HbA <sub>1c</sub> >75 mmol/mol (>9%), and concluded that healthcare professionals delay the initiation of insulin in patients with type 2 diabetes until their HbA <sub>1c</sub> exceeds 86 mmol/mol (10%). As a result, patients are exposed to a significant glycaemic burden.
Blak et al. [10]	4045	Retrospective cohort study on patients in The Health Improvement Network (THIN) database who initiated insulin for the first time between 2004 and 2006. Of 3815 patients followed up, the initial insulin regimen remained unchanged for 75.1%, while 13.7% discontinued, 7% switched and only 4.7% intensified, despite only 17.3% of patients achieving glycaemic target <53 mmol/mol (7%).
Khunti et al. [18]	11,696	31% of patients in the UK Clinical Practice Research Datalink database receiving basal insulin therapy between 2004 and 2011 who were clinically eligible for treatment intensification were treated accordingly. Of the 37% of patients who did have treatment regimens intensified, 50%, 43% and 7% were intensified with bolus insulin, premix insulin or GLP-1RAs, respectively. The median time to intensification was 4.3 years [4.1; 4.6] <sub>95%CI</sub> from basal insulin initiation in all patients and 3.7 years [3.4; 4.0] <sub>95%CI</sub> from the time HbA <sub>1c</sub> ≥ 7.5% was recorded.

CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA<sub>1c</sub>, glycated haemoglobin; OAD, oral antidiabetic drug.



**Fig. 1 – Consequences of delayed intervention in patients without previous CVD.**

The risk of CVD is shown for patients with HbA<sub>1c</sub> consistently above 53 mmol/mol (7%) in the 2 years following diagnosis for whom treatment intensification is delayed by at least 1 year versus that of patients with HbA<sub>1c</sub> consistently below 53 mmol/mol (7%) in the same period [8].

CI, confidence interval; CVD, cardiovascular disease; CVE, cardiovascular event; HbA<sub>1c</sub>, glycated haemoglobin; HF, heart failure; IT, intensification of treatment; MI, myocardial infarction.

Illustration based on data from Paul et al. [8]. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>).

intensification and so referred patients to a specialist [20]. A total of 95% of physicians cited “excessive levels of HbA<sub>1c</sub>” as a key indicator to consider intensification, but it was not reported to what extent the time their patients spent uncontrolled contributed to their decision [21].

To summarise, these studies demonstrate that current guidelines are largely not being adhered to.

#### 4. Do the current guidelines help?

The proportion of people with diabetes uncontrolled on their current therapy seems at odds with the wide range of effective antidiabetic therapies now available. However, the challenge is to consolidate the plethora of clinical trial and real-world data into a clear set of guidelines on how to manage diabetes both effectively and economically.

The key points of the joint American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) statement [2] and the National Institute for Health and Care Excellence (NICE) guidelines [3] regarding timely achievement of glycaemic control in type 2 diabetes are summarised in Table 2.

The NICE guidelines [3] advise treatment escalation when HbA<sub>1c</sub> rises to >58 mmol/mol (>7.5%) until control is achieved, implying that clinicians should be content with HbA<sub>1c</sub> of between 48 and 58 mmol/mol (6.5–7.5%) even in patients for whom 48 mmol/mol (6.5%) would be a suitable target. Little

information is offered regarding the time a patient should spend at hyperglycaemia before treatment intensification. This propagates a reactive approach wherein clinicians wait for the worsening of hyperglycaemia or complications to arise before intensifying treatment, and patients will likely reach glycaemic targets for only short periods, if at all (Fig. 2) [22].

The joint statement update issued from ADA/EASD [2], however, does provide clear timelines of up to 3 months for escalation.

The detrimental effect that variation between the ADA/EASD and NICE guidelines could have on clinician adherence to guidelines has been discussed elsewhere [23]. Between 2000 and 2007, the mean HbA<sub>1c</sub> of insulin users with type 2 diabetes in the UK reduced by only 1 mmol/mol (0.1%) from 69 mmol/mol (8.5%) to 68 mmol/mol (8.4%), despite – and in contrast to – the NICE and ADA/EASD guidelines introduced during this period [24].

The guidelines also have a number of drawbacks in common, an unavoidable one being that they quickly become out of date because of the constantly changing landscape of diabetes treatment. In addition, both guidelines recommend stepwise addition of therapy according to HbA<sub>1c</sub> levels. This approach often fails to correct the underlying pathophysiological defects of type 2 diabetes [25]. While the therapeutic benefit of a medication must be balanced against its financial cost, the focus on cost-effectiveness by NICE has been criticised as short-sighted in view of the risk of diabetic com-

**Table 2 – A comparison of the current guidelines for type 2 diabetes [2,3].**

	EASD/ADA	NICE
Targets	Recommends lowering HbA <sub>1c</sub> to <53 mmol/mol (<7%) in most patients to reduce the incidence of microvascular disease. More stringent HbA <sub>1c</sub> targets (e.g. 42–48 mmol/mol [6–6.5%]) might be considered in selected patients (short disease duration, long life expectancy, no significant CVD) if this can be achieved without significant hypoglycaemia or other adverse events. Conversely, less stringent HbA <sub>1c</sub> goals (e.g. 58–64+ mmol/mol [7.5–8%+]) are appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced complications, extensive comorbid conditions and those in whom the target is difficult to obtain despite “best efforts according to guidelines”	Set a target HbA <sub>1c</sub> level of 48 mmol/mol (6.5%) for most adults with type 2 diabetes that is managed either by lifestyle and diet, or by lifestyle and diet in combination with a single drug that is not associated with hypoglycaemia. For adults receiving a drug associated with hypoglycaemia, aim to achieve HbA <sub>1c</sub> of 53 mmol/mol (7.0%). If HbA <sub>1c</sub> levels are not adequately controlled by a single drug and rise to ≥58 mmol/mol (7.5%), intensify drug treatment, set a target HbA <sub>1c</sub> of 53 mmol/mol (7.0%) and reinforce advice about diet, lifestyle and adherence to drug treatment. Consider less stringent HbA <sub>1c</sub> targets (~53–58 mmol/mol [7.0–7.5%]) in appropriate cases, similar to those outlined in ADA/EASD statement [2].
Treatment	While encouraging therapeutic lifestyle change is important at diagnosis, periodic counselling should also be integrated into the treatment programme. Insulin is a possible first intensification step of metformin in the two-drug combination tier depending on patient- and disease-specific factors present. Addition of a third drug, namely TZD, DPP-4i, SGLT2i or GLP-1RA, is then recommended if the patient remains uncontrolled. Similarly, addition of insulin to those uncontrolled on metformin + GLP-1RA is another recommendation. More complex insulin strategies are ultimately recommended if the combinations above fail	Sensible recommendations regarding lifestyle, patient education, monitoring and targets. Insulin recommended as the second intensification of drug treatment only. GLP-1RAs are only recommended in patients if triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, and who either would benefit from weight loss or for whom insulin therapy would have a significant occupational impact. Lacking clear information regarding intensification of insulin, particularly with OADs. A limited number of insulin intensification strategies are included in the NICE algorithm: switching to pre-mix insulins; or intensification with a GLP-1RA (with specialist support) or an SGLT2i.
Timelines	If HbA <sub>1c</sub> target not achieved after ~3 months of therapy, add additional therapy	Lacking explicit guidelines, with the exception of stopping rules for GLP-1RA and pioglitazone. Recommends testing HbA <sub>1c</sub> levels every 3–6 months until stable on unchanged therapy, and every 6 months thereafter.

CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA<sub>1c</sub>, glycated haemoglobin; SGLT2i, sodium-glucose co-transporter-2 inhibitor; TZD, thiazolidinedione.

plications later in life [26]. Therefore, the task of tackling clinical inertia should be kept in mind when updating the guidelines.

While there is certainly room for improvement in the guidelines, particularly those from NICE, the evidence suggests that clinical inertia in the UK is also caused by a lack of adherence to any of the available guidelines.

## 5. Why is there clinical inertia?

### 5.1. Clinician-level barriers

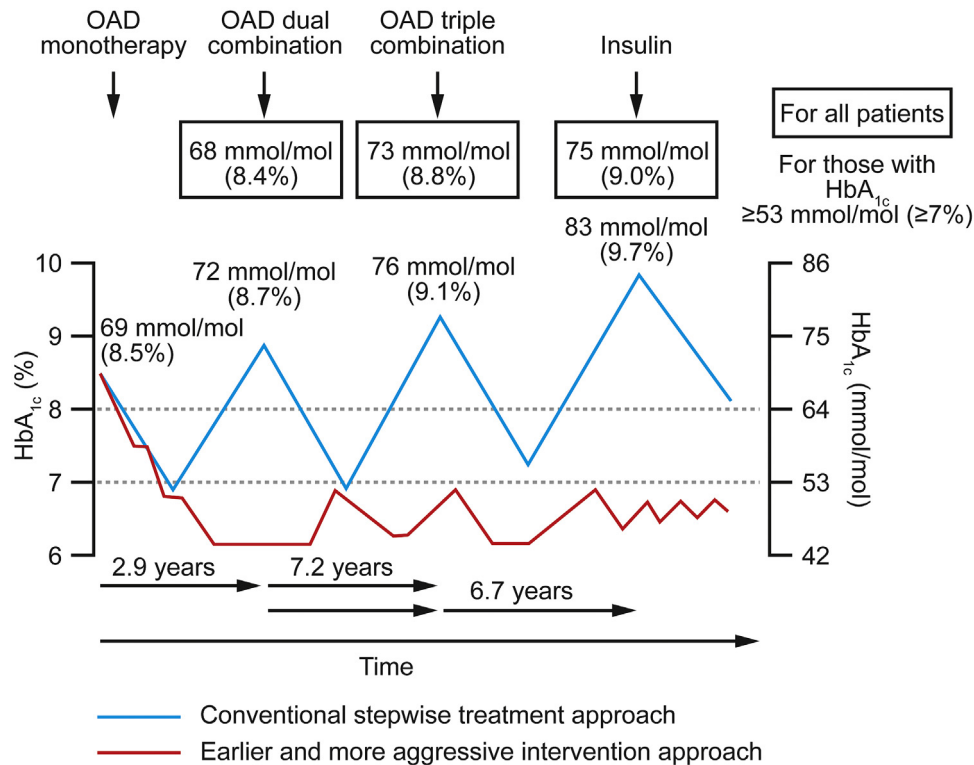
Barriers to treatment intensification can be divided into those at the patient, clinician or system level, and the majority of these barriers were discussed in a set of interviews conducted for a UK-based qualitative study [27].

A major clinician-level hurdle is a limited awareness of clinical inertia, resulting in overestimation by clinicians of their quality of care and adherence to guidelines [12,19]. This issue may be exacerbated as the management of chronic diseases increasingly becomes a primary care responsibility

because insulin therapy requires specialist training and more patient-contact time than OAD therapy.

Development of vascular complications increases the patient's risk of mortality and it is therefore important to address increases in HbA<sub>1c</sub> and risk factors for CVD, as demonstrated by the Steno-2 study [28]. However, GPs may not be familiar with the current opinion that aggressive control early on following diagnosis leads to significant benefit in appropriate patients [27]. As a result, the precious time GPs do have is often focused on their patients' current HbA<sub>1c</sub> and cholesterol levels, as well as their blood pressure and meeting Quality Outcomes Framework targets, rather than the glycaemic burden caused by the duration of poor glucose control [17].

Patients with multimorbidity are common and pose a major challenge [29], with respect to balancing the benefit of lowering blood glucose against the risk of adverse side effects in these patients. Following results from VADT, ADVANCE and ACCORD, and as documented in a key study by Currie et al. [30], the fear of adverse side effects impacts the decisions made by patients and clinicians. In a global survey of 1250 physicians, including 150 from the UK, 75.5% reported that they would intensify treatment more readily if it were not for concerns about hypoglycaemia [31].



**Fig. 2 – Median time to intensification and mean HbA<sub>1c</sub> at intensification in patients with type 2 diabetes currently treated with one or two OADs with intensification to two OADs or insulin, respectively.**

OAD, oral antidiabetic drug.

Republished with permission of Medinews (Cardiology) News Ltd, from Campbell IW, *Br J Cardiol* 2000;7:625–31; permission conveyed through Copyright Clearance Center, Inc. Adapted with permission from Del Prato et al. [22], with data from Khunti et al. [9].

Other clinician-level barriers stem from their concerns over patient adherence, perceiving their patients as unable or unwilling to adapt to the increasingly complex regimen. Results from a questionnaire revealed that fear of injection pain was a low-ranking factor for patients considering insulin therapy, whereas family physicians perceived this to be a major patient concern [32]. The belief that patients will refuse to initiate/intensify insulin therapy is a major cause of psychological insulin resistance [33], and the results from this questionnaire suggest it might be untrue.

These barriers are exacerbated by the lack of time available to GPs to adequately tackle concerns.

## 5.2. Patient-level barriers

There are several misperceptions about insulin therapy (reviewed in Polonsky et al. [34]) that are more frequently contributory factors for insulin-naïve versus insulin-experienced patients [35], suggesting that further education on these issues would resolve them [27]. Problematic patient beliefs include the belief that insulin therapy is not efficacious [36], that their quality of life will drop considerably [35,36], and that they will not be able to adhere to increasingly complex regimens [36]. Patient fear of unwanted side effects such as weight gain and hypoglycaemia [31,34,35], and of injection pain [37], can also delay intensification. Insulin-experienced patients,

unsurprisingly, do not view insulin regimens to be as highly burdensome as do insulin-naïve patients, until multiple injections are involved [37].

In a systematic review of factors affecting adherence to insulin therapy [38], positive predictors of insulin adherence included diabetic nurse specialist support; switching to a pen device; hypoglycaemia awareness; experience of liaison psychiatry or cognitive behavioural therapy; and lower perceived consequences of diabetes/higher perception of personal control. Negative predictors included a large number of injections, female gender and lower HbA<sub>1c</sub>. However, few of these predictors were consistently reported across studies included in the systematic review.

Self-reported rates of adherence also varied across these studies from 43–86% [38]. Another study revealed that one-third of patients reported insulin omission on at least one day in the last month, while three-quarters of physicians reported that their patients did not take insulin as prescribed [31]. These discrepancies highlight the problem with objective assessment of adherence (i.e. it is difficult to define and is perceived differently according to the questions posed and background knowledge).

A more objective, although arguably less informative, output is the proportion of patients who discontinue insulin therapy. Among 6072 insulin-treated patients in the UK Clinical Practice Research Datalink database, 32.1% stopped basal

insulin therapy. Reasons for stopping were unknown [18]. Pscherer et al. [39] compared persistence after 2 years with treatment regimens involving insulin glargine, insulin detemir or neutral protamine Hagedorn insulin in combination with either a prandial insulin or an OAD. In basal-oral therapy regimens, 2-year persistence varied from 53% to 65%, whereas in intensified conventional therapy, persistence was around 85%. Reasons for discontinuation are unknown, but predictors for discontinuation included type of insulin, diabetic co-medication and patient characteristics (diagnosed heart failure). In a small US study (N=1563 patients uncontrolled on insulin), 97 patients discontinued insulin therapy and 157 did not initiate therapy [40]. The most common reason for discontinuation was injection-related concerns (74%), with 47.1% of 'discontinuers' and 86.1% of 'non-initiators' doing so on a healthcare professional's (HCP's) advice. Further details regarding the HCPs' reasons were not available but this highlights how patient and clinician barriers overlap [40].

## 6. What can we do to overcome clinical inertia?

### 6.1. Tackling clinician barriers

The shift of responsibility from secondary care to primary care in the UK necessitates extra resources for GPs. This may be in the form of formal education, assistance from nurses and informed feedback. In the US, non-insulin-treated patients with hypertension and type 2 diabetes (N=157) benefited from a significant improvement in mean HbA<sub>1c</sub> (−8 mmol/mol [−0.7%],  $p=0.02$ ) and high-density lipoprotein cholesterol (+2.6 mg/dL,  $p=0.02$ ) when a new disease management programme was implemented by a nurse practitioner and physician duo, versus usual care by a physician [41]. These findings are supported by several other studies that describe more timely treatment intensification when GPs are assisted by nurses [19].

Perhaps a simpler avenue proposed for tackling clinician barriers is setting up channels of computer-based direction and/or specialist feedback to assist GPs [42]. For example, significantly more clinicians who were supported with an automated decision support tool and/or an educational DVD in a randomised controlled trial (RCT) correctly identified a glycaemic anomaly and proceeded with the appropriate treatment regimen [43].

Other methods to support GPs have included case management with a practice nurse or pharmacist directing treatment decisions according to an approved, detailed treatment algorithm under the supervision of a physician, and automated appointment reminders for patients [42].

### 6.2. Tackling patient-level barriers

Rectifying the issue of inadequate patient education and impaired communication between the patient and HCP involves a great deal of time [19]. Therefore, time-saving educational strategies such as self-management programmes that empower and equip the patient to manage their blood glucose have been investigated. Promising results were reported

in a systematic review with meta-analyses that evaluated the effect of group-based diabetes self-management education (DSME) [44]. This systematic review revealed that DSME was associated with a significant reduction in HbA<sub>1c</sub> at 6 months (0.44% points;  $p=0.0006$ , 13 studies, 1883 participants), and this reduction was maintained at 2 years (0.87% points;  $p<0.00001$ , 3 studies, 397 participants) according to RCTs conducted up to January 2008 [44].

Clinical trials have demonstrated significantly greater reductions in HbA<sub>1c</sub> versus that of usual care when a Diabetes Education and Self-Management for Ongoing and Newly Diagnosed (DESMOND) model of education was coupled with an intensive treatment regimen in patients referred from UK general practices and specialist clinics [45]. In patients with type 2 diabetes and microalbuminuria, randomisation to intensive intervention with a structured DESMOND model of patient education yielded significant improvements in HbA<sub>1c</sub>, blood pressure and cholesterol versus that of usual care. Importantly, this tight control was achieved with a lower incidence of moderate and severe hypoglycaemia. It therefore appears that the DESMOND model had equipped patients to optimise their self-management with an intensive treatment regimen, thus providing evidence that effective education is important in helping to overcome clinical inertia. NICE has stated that a structured educational programme is recommended, with regular updates to reinforce this learning [3], but the cost-effectiveness of this approach has yet to be determined.

More basic patient education should begin as early in the disease trajectory as possible to dispel the idea that insulin represents 'the end of the road' [33]. Explaining, at diagnosis, that the progressive nature of type 2 diabetes means that the majority of patients will eventually require insulin could tackle the perception that insulin therapy represents a failure in diabetes management [33]. Indeed, the joint ADA/EASD statement does not consider insulin therapy to be the last resort, and does not denote any preference in the order of treatments after lifestyle changes and metformin [2].

### 6.3. Tackling therapeutic barriers

Another way in which clinical inertia is continually addressed is by the development of new therapeutic options that have minimal effect on the patient's quality of life. In pursuit of this goal, longer-acting insulins with a lower risk of hypoglycaemia have been developed [46].

Additionally, combining insulin analogues with the newer classes of drugs has widened the options for intensification. Inhibitors of the sodium-glucose-linked transporter-2 protein (SGLT2i), which is responsible for the majority of renal glucose absorption, are the newest class of OADs to become available. They achieve a reduction in both HbA<sub>1c</sub> and body weight, and are associated with a low risk of hypoglycaemia [2,47]. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and inhibitors of the protease dipeptidyl peptidase-4 (DPP-4) are also both associated with a low risk of hypoglycaemia because of their glucose-dependent effects. Both would also be of interest to patients with concerns regarding body weight as DPP-4 inhibitors are weight-neutral and GLP-1RAs promote weight loss [2].

Insulin analogues can be intensified with GLP-1RAs and vice versa to combine the clinical advantages of, and mitigate the side effects associated with, the individual components [2]. Fixed-ratio products, such as insulin degludec/liraglutide (IDegLira) and lixisenatide/insulin glargine (LixiLan), enable such a combination to be given with a single daily injection, simplifying the regimen for patients [48–50].

To summarise, multiple therapy options have recently become available, enabling individualisation of type 2 diabetes treatment. However, older medications that may be less effective, such as sulphonylureas [2,3], remain in widespread use [51,52] and are promoted by the guidelines, often because of their lower costs. Physicians may resist prescribing newer, more appropriate therapies because of a lack of knowledge, experience and confidence in prescribing these medications. Therefore, it is important for post-marketing studies to focus on real-world evidence, training programmes and cost-effectiveness, and for the guidelines to be updated regularly so that they reflect the full range of therapeutic options available, to facilitate appropriate use in clinical practice.

## 7. Conclusion

Clinical inertia with insulin intensification in diabetes is a chronic problem globally, although more so in the UK, despite the availability of a wide range of new therapies as outlined in the ADA/EASD and NICE guidelines. There is insufficient focus, particularly in the new NICE guidelines, on how long a patient should remain uncontrolled before intensification of treatment. Overcoming clinical inertia also requires education of patients as to the long-term benefits of lowering their blood glucose and how best to achieve this. This will likely necessitate further education of HCPs in the form of formal training as well as professional feedback, together with increased nursing support. Finding the time, funding and human resources (particularly of nursing staff) to overcome these barriers will be the greatest challenge, particularly in the current economic and political climate, so research should continue to evaluate the most cost-effective means of tackling clinical inertia. This will encourage patients and HCPs to use the best available therapy option appropriately.

## Conflict of interest

KK has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Janssen, Astra Zeneca and Boehringer Ingelheim. He has received grants in support of investigator and investigator-initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim, Merck Sharp & Dohme, Janssen and Roche. He has also received funds for research, honoraria for speaking at meetings and has served on advisory boards for Lilly, Sanofi-Aventis, Merck Sharp & Dohme and Novo Nordisk, Boehringer Ingelheim, Janssen and Astra Zeneca.

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