Effect of clinical inertia and trial participation in younger and older adults with diabetes having comorbidities and progressive complications

Strain, William David

2020-08

http://hdl.handle.net/10138/332452
https://doi.org/10.1016/j.diabres.2020.108310

cc_by_nc_nd
acceptedVersion

Downloaded from Helda, University of Helsinki institutional repository.
This is an electronic reprint of the original article.
This reprint may differ from the original in pagination and typographic detail.
Please cite the original version.
Title: Effect of clinical inertia and trial participation in younger and older adults with type-2 diabetes having comorbidities and progressive complications

Short title: Effect of clinical inertia and trial participation in patients with chronic conditions

William David Strain$^{1,2}$, Päivi Maria Paldánius$^{3,4}$

$^1$University of Exeter Medical School, Exeter, United Kingdom; 
$^2$Academic Department of Healthcare for the Elderly, Royal Devon & Exeter NHS Foundation Trust, Exeter, United Kingdom

$^3$Children’s Hospital, Helsinki University and Helsinki University Hospital, Helsinki, Finland; 
$^4$Program for Clinical and Molecular Metabolism, Helsinki University, Helsinki, Finland.

Corresponding author

David Strain

Diabetes and Vascular Medicine Research Centre, Institute of Biomedical and Clinical Science and NIHR Exeter Clinical Research Facility, University of Exeter Medical School, Barrack Rd, Exeter, EX2 5AX, UK.

Tel: +44 1392 403058

Fax: +44 1392 403027

E-mail: d.strain@exeter.ac.uk.

ORCID-ID 0000-0002-6826-418X
ABSTRACT

Aim: Clinical inertia is a multifactorial phenomenon, with contributing factors from people with diabetes and their healthcare team. It is widely cited that clinical inertia is minimised by participation in clinical trials. We assessed whether trial participation *per se* improves metabolic parameters in patients with diabetes, or a specific focus on glycaemia is required.

Methods: We compared improvement in glycaemic control in a pooled set of patients assigned to the “placebo” arm from 25 glycaemia-focused trials with a pooled group of people with diabetes allocated to sham or non-pharmacological intervention for the treatment of diabetic retinal disease. Mean change in HbA1c% (ANCOVA) was evaluated.

Results: The overall placebo effect in studies focused on glucose control (N=3081) was comparable between strata groups with and without complications. Adjusted least square mean change in HbA1c% at 24 weeks was between −0.23% (−2.50 mmol/mol) and −0.32% (−3.50 mmol/mol). In studies focused on retinal disease (N=288), the change from baseline in HbA1c% was +0.10% (1.10 mmol/mol) and fasting plasma glucose was +0.50 mmol/L showing no improvement in metabolic parameters at 12 months.

Conclusions: Clinical trial participation alone does not seem to improve metabolic parameters in patients living with diabetes. The benefits observed in glycaemia-focused studies were independent of age and comorbidities.

Keywords: chronic kidney disease; clinical inertia; placebo effect; randomised controlled trials; type 2 diabetes mellitus
**Highlights**

- The present analysis pooled placebo or sham treated individuals with diabetes from randomised clinical development trials and grouped on basis of age and chronic kidney disease (CKD) status to explore the effect of non-pharmacological clinical inertia across the population.

- Clinical trials exhibit a characteristic placebo effect, which reduces the impact of clinical inertia when compared to routine clinical practice due to the correction of non-pharmacological component of clinical inertia.

- Our results reveal no significant difference in the response of younger or older adults and those with or without CKD, to placebo in randomised clinical trial settings focusing on management of glycaemia; suggesting that the correction of non-pharmacological component of clinical inertia is independent of age and comorbidities while highly dependent on focused management strategies for optimised diabetes care.
INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex and progressive disease that has reached epidemic proportions globally [1]. Due to its asymptomatic nature at early stages, diagnosis and timely intensification of treatment is often delayed. This results in micro- and macrovascular complications that not only impact the well-being of a person, but also poses a vast economic burden on the healthcare systems [1]. Despite compelling cumulative evidence of the benefit of early good glycaemic control [2,3] and guideline recommendations [4], more than half of the people living with T2DM remain inadequately controlled [5]. Further intensification of therapy as their disease progresses occurs late at all disease stages [6,7].

A significant contributing factor for poor glycaemic control is clinical inertia [7–9]. Clinical inertia in diabetes can be defined or displayed as “a failure to initiate or intensify treatment in a timely manner in people with diabetes whose health is likely to improve with this intensification” or “a failure to establish appropriate targets and escalate treatment to achieve treatment goals” [10]. Although, clinical inertia is a complex, multifactorial phenomenon with pronounced effect on the morbidity and mortality of people with uncontrolled T2DM, it is believed that a significant proportion is avoidable with improved interactions between people with diabetes, physicians and the systems in which they operate [10–12].

Multiple sources cite that clinical trials are unaffected by clinical inertia due, in part, to the protocol-driven consultations, tackling the pharmacological aspects, and the increased time spent engaging between people with diabetes and their health care professionals, addressing some of the behavioural aspects of clinical inertia. The “placebo” or Hawthorne effect of trials is well documented [13,14], and is thought to represent the gap between ideal implementation of standard of care and real-world practice. It is uncertain, however, how much the increased
engagement, *per se*, is of benefit, or whether focused consultations are required to improve outcomes.

We aimed to explore whether the placebo effect of participation in clinical trials including participants with diabetes as a surrogate for clinical inertia did indeed differ by the nature of increased engagement time. The determination of this placebo or Hawthorne effect was used as a proxy for the clinical inertia prior to enrolment in the study. Differing effects between clinical trials focused on glycaemic control with protocol driven consultations and those evaluating retinal interventions, which increased time exposure between investigators and participants thereby addressing the non-pharmacological aspects of clinical inertia. Further, we wished to determine whether complexity of diabetes or age predicted the placebo effect achieved.

**METHODS**

**Study population and design**

We used the pooled data from participants in two different Novartis clinical development trial programs as the comparators. In order to explore the impact of the placebo effect in a “glycaemia orientated” drug study, we used data from the dipeptidyl peptidase-4 (DPP-4) inhibitor, vildagliptin, development program from individuals randomly allocated to receive placebo. This comprised of 25 phase II-III studies with at least 24 weeks of duration, to be included in the current analysis. The patients participants who received oral matching placebo tablets matching the appearance of those containing vildagliptin represented all stages of disease management; from treatment naïve individuals to those with long-standing T2DM, receiving
their first treatment or and already were on multiple anti-diabetes medications after several sequential treatment intensifications.

These data were compared with the glycaemic parameters of participants in the “inertia group”, i.e. individuals allocated to receive in either sham or non-pharmacological intervention (retinal laser photocoagulation) in five studies in of the Novartis clinical development programme for the intra-vitreal anti-VEGF treatment, ranibizumab, which focused on progression of diabetic macular oedema (DME) and retinopathy in patients people with type 2 diabetes and microvascular disease.

Data were stratified in a factorial design by age (young: <70 or older: ≥70 years) and the presence of CKD (impaired renal function defined as estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m²).

**Study assessments and statistical analysis**

For the vildagliptin clinical development trial programme, the least squares (LS) mean change in HbA1c were assessed at 24 weeks using an analysis of variance (ANCOVA) model and predictors of any differences in response were explored from the available baseline characteristics. The LS mean change in HbA1c by comorbidities was adjusted for baseline HbA1c values. These trials used “standard of care” in addition to lifestyle and dietary intervention protocols with the exclusion of other DPP-4 inhibitors in the placebo arm as the guidance for investigators.

In the ranubizumab development programme, investigators were advised to “optimise glycaemic control according to local guidelines”. The original, intensive follow-up protocol for retinal
specialists targeted changes in visual acuity and central retinal thickness for the DME clinical development programme at quarterly visits. As glycaemia was not the primary focus of these studies, metabolic parameters such as HbA1c and fasting plasma glucose (FPG) were only incorporated in databases at 12 months. Our analysis included LS mean change using ANCOVA model that was adjusted for baseline HbA1c values. Demographic parameters including age, gender, body mass index (BMI), HbA1c, eGFR, T2DM-diabetes and DME disease duration, if applicable, were collected.

All datasets included in the analysis were based on intention-to-treat approach, i.e. initial treatment assignment within respective studies for both placebo and sham interventions.

RESULTS

Baseline demographics

Among the 3081 placebo-treated patients with T2DM included from the vildagliptin trial programme in the current analysis, 80% were aged <70 years and 45% of all patients were women. At baseline, the BMI (mean±SD) was similar in both the young (<70 years) and the older (≥70 years) age groups, although it was slightly higher in the older patients with CKD. As expected, the duration of T2DM was longer in patients with CKD, in both younger (12.15±9.28 vs. 6.46±6.07 years) and older (13.66±10.08 vs. 10.19±8.15 years) groups of patients as compared to the non-CKD patients in both the age groups.

At baseline, there was a tendency for younger patients without CKD to have a higher baseline HbA1c [(8.16±1.19% (66.0±13.0 mmol/mol) vs. 7.95±1.04% (63.0±11.40 mmol/mol) in older patients)] although this the difference was not statistically significantly
different (Table 1). There was no age difference in those with and without CKD. Renal function in both CKD groups corresponded to stage 3B CKD (eGFR 30–44 mL/min/1.73m²) [15].

In the clinical development programme in patients with DME and retinopathy (N=288), 46% were women, the mean age (mean±SD) was 62.90±9.20 years, and diabetes and DME durations were 12.60±9.0 and 1.50±2.20 years, respectively. The mean baseline HbA1c was similar in older adults (7.60±1.02%; 60.0±11.10 mmol/mol) to that in the glycaemia focused studies, although was marginally (non-significantly) better in the younger participants (7.40±1.10%; 57.0±1.02 mmol/mol) with multiple oral and injectable regimens. The mean baseline eGFR was 84.10±25.10 mL/min/1.73m² and generally, most patients were treated close to a normotensive target (mean blood pressure of 137/78 mmHg). The demographic and clinical characteristics were comparable among both the young and old age groups (Table 1).

**Placebo effect in glycaemia focused studies compared to retinal focused studies**

In trials of glycaemic control, baseline-adjusted HbA1c was improved by between 0.23±0.03% (-2.50±0.30 mmol/mol) to 0.32±0.07% (-3.50±0.80 mmol/mol). There was a trend that with increasing complexity, the improvement was greater, such as: younger with normal renal function getting the least improvement, then younger with CKD, then older with normal function and finally the older participants with CKD getting the most benefit, although none of these individual comparisons reached statistical significance. In the studies of retinal treatments, however, there was no change in glycaemia over 48 weeks (Figure 1).

**DISCUSSION**
Our study has shown for the first time that the placebo effect in the treatment of T2DM is independent of age and presence of the complications of the underlying disease. There was no significant difference in the response of younger or older participants, those with or without CKD, to placebo in randomised clinical trial setting. However, our results also suggest that clinical trial participation per se does not automatically improve metabolic parameters of people living with diabetes.

Evidence suggests that in real-world clinical practice, clinical inertia can have a profound impact on the older adults, people with comorbidities, people on multiple pills, and those with limited access to healthcare resources [16,17]. However, results of the current exploratory and rather conceptual analysis with an artificial decoy of pharmacological treatment, placebo, demonstrated that the placebo effect is similar across the age groups (<70 or ≥70 years) and is independent of the CKD status, suggesting the presence of non-pharmacological factors that play a role in clinical inertia. These findings are echoed in the INTERVAL study where the elderly patients with T2DM demonstrated a 0.3% reduction in HbA1c levels after 24 weeks of placebo treatment on top of their standard of care [18].

In an effort to understand the non-pharmacological aspects of clinical inertia, a unique online survey, ‘Time2DoMore in diabetes’ was conducted across six countries; Brazil, India, Japan, Spain, UK and USA and included 652 people with diabetes and 337 physicians [10]. The findings from the survey suggested that physicians believed older people with diabetes and its related late-stage complications such as CKD are more susceptible to clinical inertia than younger people with uncomplicated diabetes [10].
This substantial placebo effect, seen in many randomised controlled trials (RCTs), is believed to be a result from the extended and frequent patient visits, timely and tailored treatment regimens along with emphasis on physician accountability, which combats therapeutic inertia [194].

Inclusion of the DME cohort where the retinal specialists were allowed, but probably preferred not or seldom, to introduce initiate changes in glycaemic control to avoid masking the effect of the tested intra-vitreal drug on diabetic retinopathy, introduced a new conceptual opportunity to precipitate the effect of study participation in this genuine “inertia group”. The more motivated nature of clinical trial participants over the general population, that has been previously described, suggests the issue is a matter of availability of support rather than a desire to engage.

Lifestyle and dietary changes play an important role in successful management of diabetes at any stage and of any severity [20]. Placebo-controlled clinical study protocols (re)introduce systematic dietary and lifestyle programmes at the time of enrolment as fundamental diabetes care on top of which the genuine effect of the tested drug is to be defined. In real-world setting continuous implementation of individualised advice and access to tailored programmes are, however, some the most challenging aspect of care for both patients and healthcare practitioners. Even if the effect of repeated lifestyle advice on glycaemic outcomes attenuates over time, even among those receiving placebo or even active therapeutic regimens in clinical trials [21], the lack of change in HbA1c in our “inertia group” could be only partially explained by the fact that they most likely received no additional lifestyle advice from the retinal specialists whilst being a part of a study cohort. Yet, our results support the general notion that under real world conditions as well as within trials, we should introduce and take time to focus on patient education and the importance of lifestyle changes as one component of glycaemic control.
Nevertheless, the results from the present analysis demonstrated that there is no improvement in any metabolic parameter, where the trial focus is not on change in metabolic control. This implies that simply providing more time for engagement with the person living with diabetes at every available opportunity will not improve metabolic control. It is unlikely that this lack of benefit is due to misperception or lack of disease severity, as we have previously shown that retinopathy is the most feared complication of diabetes [10]. We therefore propose that improving diabetes control requires a focused approach during consultations between people with diabetes and their healthcare providers on glycaemia, with separate appointments for discussing the complications of diabetes or co-morbidities.

Thus, consideration of including non-pharmacological aspects of management, as observed in clinical trials, should be equally emphasised in treatment guidelines in order to minimise clinical inertia in the management of chronic yet asymptomatic diseases such as T2DM. A remarkable feature of clinical trials that can be adapted in routine clinical practice is the clear documentation of clinical record forms and monitoring adherence to treatment. Similarly, it has been proposed that analysis and documentation of factors leading to clinical inertia should be a mandate for assurance of treatment quality for physicians treating T2DM, where they can review their performance against guideline recommendations with an effort to implement changes for better treatment outcomes for patients/people with T2DM [229]. It is noteworthy that a wider healthcare team comprising of community-based health promoters, nurses and pharmacists can be instrumental in supporting diabetologists and healthcare systems to overcome clinical inertia in the management of T2DM [234]. The increasingly patient-centric guidelines have laid emphasis on the impact of diabetes self-management and personal accountability on better health
outcomes of the patients and provides insights on the role of patient education to prevent and manage T2DM [24, 25]. A recent multinational study has also emphasised the need for continuous medical education programmes for physicians, which may have an impact on minimising the widespread delay of treatment intensification in people with T2DM [26].

Additionally, setting individualised treatment targets are strongly encouraged by all international and local guidelines [4, 25] while these at times seemingly rather arbitrary numbers, if not well documented in advance of treatment decisions, often become a source of inertia, providing an opportunity for retrospective, false reporting of success especially in elderly patients [26]. Setting individualised treatment targets are strongly encouraged by all international and local guidelines [4, 25] while these at times seemingly rather arbitrary numbers, if not well documented in advance of treatment decisions, often become a source of inertia, providing an opportunity for retrospective, false reporting of success especially in elderly patients [26].

Likewise, a lack of re-evaluating therapy can result in the failure to identify treatment success, resulting in a missed opportunity for timely reduction or change in therapy when no longer needed or indicated. This ‘reverse clinical inertia to appropriate de-escalation can lead to hypoglycaemia and other adverse events especially in vulnerable patients such as the elderly [27]. Acknowledging the permanent state of flux reflecting the complex progressive nature of diabetes and adjusting the targets, attitudes and actions accordingly, are essential first steps on the path of combatting clinical inertia. Therefore, the gap between the routine clinical practice and RCTs should be bridged by improving access to appropriate healthcare resources wherein for example nurse education and empowering people with T2DM to take responsibility over their own disease outcomes within the limits of their own feasible action are crucial in optimising the management of T2DM.

The exploratory analysis demonstrated similar degrees of clinical inertia, as demonstrated by a consistent placebo effect, across both the age groups (<70 or ≥70 years) regardless of the presence or absence of CKD. This suggests that the non-pharmacological component of clinical inertia in people with diabetes may be independent of age and comorbidities, thus not dependent
on physician perceptions but on systematic issues within the healthcare provision. However, where the trial focus is not on metabolic control such as that in patients the clinical trials with DME and retinopathy, trial participation per se does not improve metabolic parameters of people with diabetes. Hence, there is a need for more focused consultations between patients people living with diabetes and healthcare providers, and equal emphasis on the non-pharmacological components of diabetes management, including lifestyle changes, is required to minimise clinical inertia.
Acknowledgements

Sponsorship and article processing charges for this study were funded by Novartis. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval to the version to be published. The authors thank Giovanni Bader, MD, PhD for providing his valuable statistical inputs for the manuscript. The authors also acknowledge Ishita Guha Thakurta, PhD, CMPP and Lakshmi Deepa G, PhD, of Novartis Healthcare Private Limited, India for medical writing support, which was funded by Novartis Pharma AG, Basel, Switzerland, in accordance with good publication practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Conflict of Interest

The study was funded by Novartis. WDS holds research grants from Novo Nordisk and Takeda. WDS would like to acknowledge the support of the NIHR Exeter Clinical Research Facility and the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) for the South West Peninsula. WDS would like to add that the views expressed in this publication are those of the authors and not necessarily those of the NIHR Exeter Clinical Research Facility, the NHS, the NIHR or the Department of Health in England. PMP was employed by Novartis at the time of the initial analyses.
References


Figure 1. Mean HbA1c in Vildagliptin and DME and retinopathy studies

Values are expressed as mean.

DME, diabetic macular oedema; HbA1c, glycated haemoglobin
Table 1. Patient and clinical characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Vildagliptin studies</th>
<th>DME and retinopathy studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Young,*</td>
<td>Young,*</td>
</tr>
<tr>
<td></td>
<td>non-CKD (n=2176)</td>
<td>non-CKD (n=229)</td>
</tr>
<tr>
<td></td>
<td>Young, with CKD</td>
<td>Young, with CKD</td>
</tr>
<tr>
<td></td>
<td>(n=304)</td>
<td>(n=263)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.41±9.22</td>
<td>59.70±7.18</td>
</tr>
<tr>
<td></td>
<td>60.60±6.81</td>
<td>75.80±3.14</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>29.61±5.78</td>
<td>27.30±5.17</td>
</tr>
<tr>
<td></td>
<td>29.94±5.12</td>
<td>27.80±5.20</td>
</tr>
<tr>
<td>*Duration of conditions (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2DM duration</td>
<td>6.46±6.07</td>
<td>-</td>
</tr>
<tr>
<td>Diabetes duration (T1/T2DM)</td>
<td>-</td>
<td>11.60±8.4</td>
</tr>
<tr>
<td>DME duration</td>
<td>-</td>
<td>16.40±10.88</td>
</tr>
<tr>
<td>Baseline eGFR, MDRD (mL/min)</td>
<td>92.21±21.37</td>
<td>88.30±23.89</td>
</tr>
<tr>
<td></td>
<td>42.31±14.48</td>
<td>67.30±22.95</td>
</tr>
<tr>
<td>Baseline HbA1c(%)</td>
<td>8.16±1.19</td>
<td>7.40±1.11</td>
</tr>
<tr>
<td>(mmol/mol)</td>
<td>66.0±13.0</td>
<td>7.60±1.02</td>
</tr>
<tr>
<td>Glycaemic outcomes</td>
<td>Week 24</td>
<td>Week 48</td>
</tr>
<tr>
<td>HbA1c change(%)</td>
<td>-0.27±1.09</td>
<td>0.10±0.96</td>
</tr>
<tr>
<td>(mmol/mol)</td>
<td>-3.0±11.90</td>
<td>0.0±0.79</td>
</tr>
<tr>
<td>After adjustment for baseline HbA1c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS mean HbA1c change(%±SEM)</td>
<td>-0.23±0.03</td>
<td>0.10±0.06</td>
</tr>
<tr>
<td></td>
<td>-0.27±0.07</td>
<td>0.10±0.13</td>
</tr>
<tr>
<td>(mmol/mol±SEM)</td>
<td>−2.50±0.30</td>
<td>−3.00±0.80</td>
</tr>
<tr>
<td>----------------</td>
<td>------------</td>
<td>------------</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or SEM (for adjusted HbA1c change). Patients with CKD defined as <60 mL/min/1.73m² and without CKD as eGFR ≥60 mL/min/1.73m². *Young: <70 years; **Old: ≥70 years.

CKD, chronic kidney disease; DME, diabetic macular oedema; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; LS, least squares; MDRD, modification of diet in renal disease; SEM, standard error mean; SD, standard deviation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.
Title: Effect of clinical inertia and trial participation in younger and older adults with diabetes having comorbidities and progressive complications

Short title: Effect of clinical inertia and trial participation in people with chronic conditions

William David Strain¹,², Päivi Maria Paldánius³,⁴

¹University of Exeter Medical School, Exeter, United Kingdom;
²Academic Department of Healthcare for the Elderly, Royal Devon & Exeter NHS Foundation Trust, Exeter, United Kingdom
³Children’s Hospital, Helsinki University Hospital, Helsinki, Finland;
⁴Program for Clinical and Molecular Metabolism, Helsinki University, Helsinki, Finland.

Corresponding author

David Strain

Diabetes and Vascular Medicine Research Centre,
Institute of Biomedical and Clinical Science and NIHR Exeter Clinical Research Facility,
University of Exeter Medical School,
Barrack Rd, Exeter, EX2 5AX, UK.
Tel: +44 1392 403058
Fax: +44 1392 403027
E-mail: d.strain@exeter.ac.uk.
ORCID-ID 0000-0002-6826-418X
**ABSTRACT**

**Aim:** Clinical inertia is a multifactorial phenomenon, with contributing factors from people with diabetes and their healthcare team. It is widely cited that clinical inertia is minimised by participation in clinical trials. We assessed whether trial participation *per se* improves metabolic parameters in people with diabetes, or a specific focus on glycaemia is required.

**Methods:** We compared improvement in glycaemic control in a pooled set of people assigned to the “placebo” arm from 25 glycaemia-focused trials with a pooled group of people with diabetes allocated to sham or non-pharmacological intervention for the treatment of diabetic retinal disease. Mean change in HbA1c (ANCOVA) was evaluated.

**Results:** The overall placebo effect in studies focused on glucose control (N=3081) was comparable between strata groups with and without complications. Adjusted least square mean change in HbA1c at 24 weeks was between −0.23% (−2.50 mmol/mol) and −0.32% (−3.50 mmol/mol). In studies focused on retinal disease (N=288), the change from baseline in HbA1c was +0.10% (1.10 mmol/mol) and fasting plasma glucose was +0.50 mmol/L showing no improvement in metabolic parameters at 12 months.

**Conclusions:** Clinical trial participation alone does not seem to improve metabolic parameters in people living with diabetes. The benefits observed in glycaemia-focused studies were independent of age and comorbidities.

**Keywords:** chronic kidney disease; clinical inertia; placebo effect; randomised controlled trials; type 2 diabetes mellitus
**Highlights**

- The present analysis pooled placebo or sham treated individuals with diabetes from randomised clinical development trials and grouped on basis of age and chronic kidney disease (CKD) status to explore the effect of non-pharmacological clinical inertia across the population.

- Clinical trials exhibit a characteristic placebo effect, which reduces the impact of clinical inertia when compared to routine clinical practice due to the correction of non-pharmacological component of clinical inertia.

- Our results reveal no significant difference in the response of younger or older adults and those with or without CKD, to placebo in randomised clinical trial settings focusing on management of glycaemia; suggesting that the correction of non-pharmacological component of clinical inertia is independent of age and comorbidities while highly dependent on focused management strategies for optimised diabetes care.
INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex and progressive disease that has reached epidemic proportions globally [1]. Due to its asymptomatic nature at early stages, diagnosis and timely intensification of treatment is often delayed. This results in micro- and macrovascular complications that not only impact the well-being of a person, but also poses a vast economic burden on the healthcare systems [1]. Despite compelling cumulative evidence of the benefit of early good glycaemic control [2,3] and guideline recommendations [4], more than half of the people living with T2DM remain inadequately controlled [5]. Further intensification of therapy as their disease progresses occurs late at all disease stages [6,7].

A significant contributing factor for poor glycaemic control is clinical inertia [7–9]. Clinical inertia in diabetes can be defined or displayed as “a failure to initiate or intensify treatment in a timely manner in people with diabetes whose health is likely to improve with this intensification” or “a failure to establish appropriate targets and escalate treatment to achieve treatment goals” [10]. Although, clinical inertia is a complex, multifactorial phenomenon with pronounced effect on the morbidity and mortality of people with uncontrolled T2DM, it is believed that a significant proportion is avoidable with improved interactions between people with diabetes, physicians and the systems in which they operate [10–12].

Multiple sources cite that clinical trials are unaffected by clinical inertia due, in part, to the protocol-driven consultations, tackling the pharmacological aspects, and the increased time spent engaging between people with diabetes and their health care professionals, addressing some of the behavioural aspects of clinical inertia. The “placebo” or Hawthorne effect of trials is well documented [13,14] and is thought to represent the gap between ideal implementation of standard of care and real-world practice. It is uncertain, however, how much the increased
engagement, *per se*, is of benefit, or whether focused consultations are required to improve outcomes.

We aimed to explore whether the placebo effect of participation in clinical trials including participants with diabetes did indeed differ by the nature of increased engagement time. The determination of this placebo or Hawthorne effect was used as a proxy for the clinical inertia prior to enrolment in the study. Differing effects between clinical trials focused on glycaemic control with protocol driven consultations and those evaluating retinal interventions, which increased time exposure between investigators and participants thereby addressing the non-pharmacological aspects of clinical inertia. Further, we wished to determine whether complexity of diabetes or age predicted the placebo effect achieved.

**METHODS**

**Study population and design**

We used the pooled data from participants in two different Novartis clinical development trial programmes as the comparators. In order to explore the impact of the placebo effect in a “glycaemia orientated” drug study, we used data from the dipeptidyl peptidase-4 (DPP-4) inhibitor, vildagliptin, development programme from individuals randomly allocated to receive placebo. This comprised of 25 phase II-III studies with at least 24 weeks of duration, to be included in the current analysis. The participants who received oral placebo tablets matching the appearance of those containing vildagliptin represented all stages of disease management; from treatment naïve individuals to those with long-standing T2DM, receiving their first treatment or already on multiple anti-diabetes medications after several sequential treatment intensifications.
These data were compared with the glycaemic parameters of participants in the “inertia group”, i.e. individuals allocated to receive either sham or non-pharmacological intervention (retinal laser photocoagulation) in five studies of the Novartis clinical development programme for the intra-vitreal anti-VEGF treatment, ranibizumab, focused on progression of diabetic macular oedema (DME) and retinopathy in people with diabetes and microvascular disease.

Data were stratified in a factorial design by age (young: <70 or older: ≥70 years) and the presence of CKD (impaired renal function defined as estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m²).

**Study assessments and statistical analysis**

For the vildagliptin clinical development trial programme, the least squares (LS) mean change in HbA1c were assessed at 24 weeks using an analysis of variance (ANCOVA) model and predictors of any differences in response were explored from the available baseline characteristics. The LS mean change in HbA1c by comorbidities was adjusted for baseline HbA1c values. These trials used “standard of care” in addition to lifestyle and dietary intervention protocols with the exclusion of other DPP-4 inhibitors in the placebo arm as the guidance for investigators.

In the ranubizumab development programme, investigators were advised to “optimise glycaemic control according to local guidelines”. The original, intensive follow-up protocol for retinal specialists targeted changes in visual acuity and central retinal thickness for the DME clinical development programme at quarterly visits. As glycaemia was not the primary focus of these studies, metabolic parameters such as HbA1c and fasting plasma glucose were only incorporated
in databases at 12 months. Our analysis included LS mean change using ANCOVA model that was adjusted for baseline HbA1c values. Demographic parameters including age, gender, body mass index (BMI), HbA1c, eGFR, diabetes and DME disease duration, if available, were collected.

All datasets included in the analysis were based on intention-to-treat approach, i.e. initial treatment assignment within respective studies for both placebo and sham interventions.

RESULTS

Baseline demographics

Among the 3081 placebo-treated participants with T2DM included from the vildagliptin trial programme in the current analysis, 80% were aged <70 years and 45% of all participants were women. At baseline, the BMI (mean±SD) was similar in both the young (<70 years) and the older (≥70 years) age groups, although it was slightly higher in the older people with CKD. As expected, the duration of T2DM was longer in people with CKD, in both younger (12.15±9.28 vs. 6.46±6.07 years) and older (13.66±10.08 vs. 10.19±8.15 years) groups of people as compared to the non-CKD participants in both the age groups.

At baseline, there was a tendency for younger participants without CKD to have a higher baseline HbA1c [8.16±1.19% (66.0±13.0 mmol/mol) vs. 7.95±1.04% (63.0±11.40 mmol/mol) in older participants] although the difference was not statistically significant (Table 1). There was no age difference in those with and without CKD. Renal function in both CKD groups corresponded to stage 3B CKD (eGFR 30–44 mL/min/1.73m²) [15].

In the clinical development programme in participants with DME and retinopathy (N=288), 46% were women, the age (mean±SD) was 62.90±9.20 years, and diabetes and DME durations were
12.60±9.0 and 1.50±2.20 years, respectively. The mean baseline HbA1c was similar in older adults (7.60±1.02%; 60.0±11.10 mmol/mol) to that in the glycaemia focused studies, although was marginally (non-significantly) better in the younger participants (7.40±1.10%; 57.0±1.02 mmol/mol) with multiple oral and injectable regimens. The mean baseline eGFR was 84.10±25.10 mL/min/1.73m² and generally, most people were treated close to a normotensive target (mean blood pressure of 137/78 mmHg). The demographic and clinical characteristics were comparable among both the young and old age groups (Table 1).

**Placebo effect in glycaemia focused studies compared to retinal focused studies**

In trials of glycaemic control, baseline-adjusted HbA1c was improved by between 0.23±0.03% (2.50±0.30 mmol/mol) to 0.32±0.07% (3.50±0.80 mmol/mol). There was a trend that with increasing complexity, the improvement was greater, such as: younger with normal renal function getting the least improvement, then younger with CKD, then older with normal function and finally the older participants with CKD getting the most benefit, although none of these individual comparisons reached statistical significance. In the studies of retinal treatments, however, there was no change in glycaemia over 48 weeks (Figure 1).

**DISCUSSION**

Our study has shown for the first time that the placebo effect in the treatment of T2DM is independent of age and presence of the complications of the underlying disease. There was no significant difference in the response of younger or older participants, those with or without CKD, to placebo in randomised clinical trial setting. However, our results also suggest that
clinical trial participation *per se* does not automatically improve metabolic parameters of people living with diabetes.

Evidence suggests that in real-world clinical practice, clinical inertia can have a profound impact on the older adults, people with comorbidities, people on multiple pills, and those with limited access to healthcare resources [16,17]. However, results of the current exploratory and rather conceptual analysis with an artificial decoy of pharmacological treatment, placebo, demonstrated that the placebo effect is similar across the age groups (<70 or ≥70 years) and is independent of the CKD status, suggesting the presence of non-pharmacological factors that play a role in clinical inertia. These findings are echoed in the INTERVAL study where the older adults with T2DM demonstrated a 0.3% reduction in HbA1c levels after 24 weeks of placebo treatment on top of their standard of care [18].

In an effort to understand the non-pharmacological aspects of clinical inertia, a unique online survey, ‘Time2DoMore in diabetes’ was conducted across six countries; Brazil, India, Japan, Spain, UK and USA and included 652 people with diabetes and 337 physicians [10]. The findings from the survey suggested that physicians believed older people with diabetes and its related late-stage complications such as CKD are more susceptible to clinical inertia than younger people with uncomplicated diabetes [10].

This substantial placebo effect, seen in many randomised controlled trials (RCTs), is believed to be a result from the extended and frequent patient visits, timely and tailored treatment regimens along with emphasis on physician accountability, which combats therapeutic inertia [19].

Inclusion of the DME cohort where the retinal specialists were allowed, but probably preferred
not or seldom, to initiate changes in glycaemic control to avoid masking the effect of the tested intra-vitreal drug on diabetic retinopathy, introduced a new conceptual opportunity to precipitate the effect of study participation in this genuine “inertia group”. The more motivated nature of clinical trial participants over the general population, that has been previously described, suggests the issue is a matter of availability of support rather than a desire to engage.

Lifestyle and dietary changes play an important role in successful management of diabetes at any stage and of any severity [20]. Placebo-controlled clinical study protocols (re)introduce systematic dietary and lifestyle programmes at the time of enrolment as fundamental diabetes care on top of which the genuine effect of the tested drug is to be defined. In real-world setting continuous implementation of individualised advice and access to tailored programmes are, however, some the most challenging aspect of care for both patients and healthcare practitioners. Even if the effect of repeated lifestyle advice on glycaemic outcomes attenuates over time, among those receiving placebo or even active therapeutic regimens in clinical trials [21], the lack of change in HbA1c in our “inertia group” could be only partially explained by the fact that they most likely received no additional lifestyle advice from the retinal specialists whilst being a part of a study cohort. Yet, our results support the general notion that under real world conditions as well as within trials, we should introduce and take time to focus on patient education and the importance of lifestyle changes as one component of glycaemic control. Nevertheless, the results from the present analysis demonstrated that there is no improvement in any metabolic parameter, where the trial focus is not on change in metabolic control. This implies that simply providing more time for engagement with the person living with diabetes at every available opportunity will not improve metabolic control. It is unlikely that this lack of
benefit is due to misperception or lack of disease severity, as we have previously shown that retinopathy is the most feared complication of diabetes [10]. We therefore propose that improving diabetes control requires a focused approach during consultations between people with diabetes and their healthcare providers on glycaemia, with separate appointments for discussing the complications of diabetes or co-morbidities.

Thus, consideration of including non-pharmacological aspects of management, as observed in clinical trials, should be equally emphasised in treatment guidelines in order to minimise clinical inertia in the management of chronic yet asymptomatic diseases such as T2DM. A remarkable feature of clinical trials that can be adapted in routine clinical practice is the clear documentation of clinical record forms and monitoring adherence to treatment. Similarly, it has been proposed that analysis and documentation of factors leading to clinical inertia should be a mandate for assurance of treatment quality for physicians treating T2DM, where they can review their performance against guideline recommendations with an effort to implement changes for better treatment outcomes for people with T2DM [22]. It is noteworthy that a wider healthcare team comprising of community-based health promoters, nurses and pharmacists can be instrumental in supporting diabetologists and healthcare systems to overcome clinical inertia in the management of T2DM [23]. The increasingly patient-centric guidelines have laid emphasis on the impact of diabetes self-management and personal accountability on better health outcomes of the patients and provides insights on the role of patient education to prevent and manage T2DM [24,25]. A recent multinational study has also emphasised the need for continuous medical education programmes for physicians, which may have an impact on minimising the widespread delay of treatment intensification in people with T2DM [26]. Additionally, setting individualised
treatment targets are strongly encouraged by all international and local guidelines [4, 25] while these at times seemingly rather arbitrary numbers, if not well documented in advance of treatment decisions, often become a source of inertia, providing an opportunity for retrospective, false reporting of success especially in older adults with less stringent targets. Likewise, a lack of re-evaluating therapy can result in the failure to identify treatment success, resulting in a missed opportunity for timely reduction or change in therapy when no longer needed or indicated. This inertia to appropriate de-escalation can lead to hypoglycaemia and other adverse events especially in vulnerable adults such as the elderly [27]. Acknowledging the permanent state of flux reflecting the complex progressive nature of diabetes and adjusting the targets, attitudes and actions accordingly, are essential first steps on the path of combatting clinical inertia. Therefore, the gap between the routine clinical practice and RCTs should be bridged by improving access to appropriate healthcare resources wherein for example nurse education and empowering people with T2DM to take responsibility over their own disease outcomes within the limits of their own feasible action are crucial in optimising the management of T2DM.

The exploratory analysis demonstrated similar degrees of clinical inertia, as demonstrated by a consistent placebo effect, across both the age groups (<70 or ≥70 years) regardless of the presence or absence of CKD. This suggests that the non-pharmacological component of clinical inertia in people with diabetes may be independent of age and comorbidities, thus not dependent on physician perceptions but on systematic issues within the healthcare provision. However, where the trial focus is not on metabolic control such as that in the clinical trials with DME and retinopathy, trial participation per se does not improve metabolic parameters of people with diabetes. Hence, there is a need for more focused consultations between people living with
diabetes and healthcare providers, and equal emphasis on the non-pharmacological components of diabetes management, including lifestyle changes, is required to minimise clinical inertia.
Acknowledgements

Sponsorship and article processing charges for this study were funded by Novartis. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval to the version to be published. The authors thank Giovanni Bader, MD, PhD for providing his valuable statistical inputs for the manuscript. The authors also acknowledge Ishita Guha Thakurta, PhD, CMPP and Lakshmi Deepa G, PhD, of Novartis Healthcare Private Limited, India for medical writing support, which was funded by Novartis Pharma AG, Basel, Switzerland, in accordance with good publication practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Conflict of Interest

The study was funded by Novartis. WDS holds research grants from Novo Nordisk and Takeda. WDS would like to acknowledge the support of the NIHR Exeter Clinical Research Facility and the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) for the South West Peninsula. WDS would like to add that the views expressed in this publication are those of the authors and not necessarily those of the NIHR Exeter Clinical Research Facility, the NHS, the NIHR or the Department of Health in England. PMP was employed by Novartis at the time of the initial analyses.
References


Figure 1. Mean HbA1c in Vildagliptin and DME and retinopathy studies

DME, diabetic macular oedema; HbA1c, glycated haemoglobin
### Table 1. Patient and clinical characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Vildagliptin studies</th>
<th>DME and retinopathy studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Young,* non-CKD</td>
<td>Young,* non-CKD</td>
</tr>
<tr>
<td></td>
<td>(n=2176)</td>
<td>(n=229)</td>
</tr>
<tr>
<td></td>
<td>Young, with CKD</td>
<td>Older, with CKD</td>
</tr>
<tr>
<td></td>
<td>(n=304)</td>
<td>(n=263)</td>
</tr>
<tr>
<td></td>
<td>Older, non-CKD</td>
<td>Older, with CKD</td>
</tr>
<tr>
<td></td>
<td>(n=338)</td>
<td>(n=263)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.41±9.22</td>
<td>59.70±7.18</td>
</tr>
<tr>
<td></td>
<td>60.60±6.81</td>
<td>75.80±3.14</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.61±5.78</td>
<td>27.30±5.17</td>
</tr>
<tr>
<td></td>
<td>29.94±5.12</td>
<td>27.80±5.20</td>
</tr>
<tr>
<td>Duration of conditions (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2DM duration</td>
<td>6.46±6.07</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>12.15±9.28</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>10.19±8.15</td>
<td>11.60±8.4</td>
</tr>
<tr>
<td></td>
<td>13.66±10.08</td>
<td>16.40±10.88</td>
</tr>
<tr>
<td>Diabetes duration (T1/T2DM)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>16.40±10.88</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>15.0±2.27</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>15.0±1.94</td>
</tr>
<tr>
<td>DME duration</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>1.50±2.27</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>1.50±1.94</td>
</tr>
<tr>
<td>Baseline eGFR, MDRD (mL/min)</td>
<td>92.21±21.37</td>
<td>88.30±23.89</td>
</tr>
<tr>
<td></td>
<td>42.31±14.48</td>
<td>67.30±22.95</td>
</tr>
<tr>
<td></td>
<td>81.57±16.71</td>
<td></td>
</tr>
<tr>
<td></td>
<td>44.44±11.16</td>
<td></td>
</tr>
<tr>
<td>Baseline HbA1c (%)</td>
<td>8.16±1.19</td>
<td>7.40±1.11</td>
</tr>
<tr>
<td>(mmol/mol)</td>
<td>66.0±13.0</td>
<td>6.60±1.02</td>
</tr>
<tr>
<td></td>
<td>62.0±11.80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>63.0±11.40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>62.0±10.40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>57.0±12.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60.0±11.10</td>
<td></td>
</tr>
<tr>
<td>Glycaemic outcomes</td>
<td>Week 24</td>
<td>Week 48</td>
</tr>
<tr>
<td>HbA1c change (%)</td>
<td>-0.27±1.09</td>
<td>-0.21±0.97</td>
</tr>
<tr>
<td>(mmol/mol)</td>
<td>-3.0±11.90</td>
<td>-2.30±10.60</td>
</tr>
<tr>
<td>After adjustment for baseline HbA1c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS mean HbA1c change (%)±SEM</td>
<td>-0.23±0.03</td>
<td>0.10±0.06</td>
</tr>
<tr>
<td></td>
<td>-0.27±0.07</td>
<td>0.10±0.13</td>
</tr>
<tr>
<td></td>
<td>-0.29±0.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.32±0.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.10±0.06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.10±0.13</td>
<td></td>
</tr>
<tr>
<td>Values</td>
<td>Young</td>
<td>Old</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>-----</td>
</tr>
<tr>
<td>(mmol/mol±SEM)</td>
<td>-2.50±0.30</td>
<td>-3.00±0.80</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or SEM (for adjusted HbA1c change). Patients with CKD defined as <60 mL/min/1.73m² and without CKD as eGFR ≥60 mL/min/1.73m². *Young: <70 years; **Old: ≥70 years.

CKD, chronic kidney disease; DME, diabetic macular oedema; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; LS, least squares; MDRD, modification of diet in renal disease; SEM, standard error mean; SD, standard deviation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus
Declaration of interests

☐ 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.

☒ The authors declare the following financial interests/personal relationships, which may be considered as potential competing interests:

The study was funded by Novartis. WDS holds research grants from Novo Nordisk and Takeda. WDS would like to acknowledge the support of the NIHR Exeter Clinical Research Facility and the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) for the South West Peninsula. WDS would like to add that the views expressed in this publication are those of the authors and not necessarily those of the NIHR Exeter Clinical Research Facility, the NHS, the NIHR or the Department of Health in England. PMP was employed by Novartis at the time of analyses.