Strategies for overcoming therapeutic inertia in type 2 diabetes: A systematic review and meta-analysis

Rhea E. Powell MD1 | Francesco Zaccardi PhD2 | Christine Beebe MS3 | Xin Mei Chen4 | Alyssa Crawford MSPH1 | John Cuddeback MD5 | Robert A. Gabbay MD4,6 | Lauren Kissela BS4 | Michelle L. Litchman PhD7 | Rajesh Mehta RPh8 | Luigi Meneghini MD9 | Kevin M. Pantalone DO10 | Swapnil Rajpathak MBBS11 | Paul Scribner4 | Jessica W. Skelley PharmD12 | Kamlesh Khunti FMedSci2

Abstract

Aims: To systematically investigate the effect of interventions to overcome therapeutic inertia on glycaemic control in individuals with type 2 diabetes.

Materials and Methods: We electronically searched for randomized controlled trials or quasi-experimental studies published between January 1, 2004 and December 31, 2019 evaluating the effect of interventions on glycated haemoglobin (HbA1c) control. Characteristics of included studies and HbA1c difference between intervention and control arms (main outcome) were extracted. Interventions were grouped as: care management and patient education; nurse or certified diabetes educator (CDE); pharmacist; or physician-based.

Results: Thirty-six studies including 22,243 individuals were combined in nonlinear random-effects meta-regressions; the median (range) duration of intervention was 1 year (0.9 to 36 months). Compared to the control arm, HbA1c reduction ranged from: −17.7 mmol/mol (−1.62%) to −4.4 mmol/mol (−0.40%) for nurse- or CDE-based interventions; −13.1 mmol/mol (−1.20%) to 3.3 mmol/mol (0.30%) for care management and patient education interventions; −9.8 mmol/mol (−0.90%) to −6.6 mmol/mol (−0.60%) for pharmacist-based interventions; and −4.4 mmol/mol (−0.40%) to 2.8 mmol/mol (0.26%) for physician-based interventions. Across the included studies, a reduction in HbA1c was observed only during the first year (6 months: −4.2 mmol/mol, 95% confidence interval [CI] −6.2, −2.2 [−0.38%, 95% CI −0.56, −0.20]; 1 year: −1.6 mmol/mol, 95% CI −3.3, 0.1 [−0.15%, 95% CI −0.30, 0.01]) and in individuals with preintervention HbA1c >75 mmol/mol (9%).

Conclusions: The most effective approaches to mitigating therapeutic inertia and improving HbA1c were those that empower nonphysician providers such as nurses and diabetes educators.
pharmacists, nurses and diabetes educators to initiate and intensify treatment independently, supported by appropriate guidelines.

**KEYWORDS**
glycaemic control, systematic review, type 2 diabetes

1 | INTRODUCTION

Diabetes mellitus is a pressing global health issue, affecting over 30 million adults in the United States and 463 million people worldwide, and it is projected to rise in the coming decades. A leading cause of death, diabetes is associated with excess mortality, adverse outcomes and increased use of healthcare resources.

The adverse outcomes associated with diabetes, and the resulting costs of care, can be reduced with effective treatments, preventive strategies, and diabetes self-management education and support, as outlined in standards of care available to providers from the American Diabetes Association (ADA) and others. These standards of care, and the evidence base that underlies the standards of care, provide recommendations for actions to improve diabetes prevention and management. There is strong evidence to recommend an individualized approach that targets a glycated haemoglobin (HbA1c) of less than 7.0% (53 mmol/mol) for most nonpregnant adults. Achieving glycaemic targets early in the course of the disease may establish a “legacy” effect, by which lower HbA1c levels are maintained for longer and associated with a lower risk of vascular complications. These benefits can persist even if the targets achieved early are not sustained.

Despite the availability of effective treatment options and well-established management guidelines, corresponding improvement in reaching glycaemic targets has lagged. Therapeutic inertia—the failure of healthcare providers to initiate or intensify treatment when indicated, or to deescalate therapy when appropriate—is a contributing factor to the gap between population health goals for diabetes and current outcomes.

Therapeutic inertia is multifactorial, resulting from patient-level factors, provider-level factors and system-level factors. Patient-level factors include misperceptions about medication use and fear of unwanted side effects, as well as the impact of social determinants of health. System-level factors include costs of new medications, formulary limitations and non-medical switching of therapeutics due to insurance formulary changes. Provider-level factors include competing priorities and lack of time, overconfidence in the quality of care and adherence to guidelines, lack of awareness of therapeutic inertia, delay in adopting new guidelines, discomfort or lack of familiarity with prescribing new medications, and perceptions that patients will not be amenable or adherent to medication changes.

Understanding which interventions have been tested and are effective at mitigating therapeutic inertia is a critical step toward improving evidence-based management of type 2 diabetes. Although several studies have tested individual interventions, no systematic review and meta-analysis has yet been reported that summarizes the literature to date on interventions for overcoming therapeutic inertia.

This systematic review and meta-analysis investigates interventions to overcome therapeutic inertia in the management of type 2 diabetes, in order to evaluate the quality of the evidence and the effect of these interventions on glycaemic control.

2 | MATERIALS AND METHODS

2.1 | Data sources and searches

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (checklist in the Supplemental Material). The search of relevant publications was conducted in five databases—Ovid MEDLINE, EBSCOhost CINHAL with Full Text, Epistemonikos, Elsevier Scopus, and the Cochrane Database of Systematic Reviews. The detailed search methodology, including criteria for inclusion and exclusion and search terms with Boolean operators, is reported in the Supplemental Material and was organized to reflect five concepts: (a) the theory of therapeutic inertia; (b) patients with type 2 diabetes; (c) relevant clinical outcomes; (d) types of patient-, provider- and system-level interventions; and (e) rigorous study designs. The keywords within each concept were selected to be broad and inclusive and were separated with “OR” statements, whereas concepts were separated by “AND” statements to capture studies with a reasonable likelihood of meeting the inclusion criteria. Search result records were uploaded into Rayyan (http://rayyan.qcri.org/), a free web application that supports screening for systematic reviews.

2.2 | Study selection

We focused on therapeutic inertia, defined as the failure to initiate or intensify therapy when appropriate to do so. Inclusion criteria required publication in English in a peer-reviewed journal between January 1, 2004 and December 31, 2019. Studies were selected that tested the effect of interventions in healthcare settings, with providers commonly involved in the therapeutic management of diabetes, including primary care physicians, endocrinologists, nurse practitioners, physician assistants, clinical pharmacists, diabetes educators, and nurses. We identified interventions designed to catalyse the appropriate initiation or intensification of medications, and excluded...
studies that focused only on de-escalation of medications. We did not target studies that focused primarily on improving medication adherence, a related, but distinct concept from therapeutic inertia (therapeutic inertia refers to the failure of healthcare providers to initiate or intensify treatment when indicated, while medication adherence refers to the failure of patients to adhere to a given treatment regimen). We did not exclude studies that may have impacted both inertia and adherence, but we excluded those studies which focused only on patient-focused interventions to improve medication adherence. Studies that included patients with diabetes as well as patients with other chronic conditions (such as hypertension) were included, providing that the authors presented results by condition and results related to the population with diabetes could be isolated in the review. Included studies were randomized controlled trials (RCTs) or rigorous quasi-experimental studies with a comparison group to represent the counterfactual. The primary outcome of interest was between-arm difference in HbA1c. Thus, included studies must also have had reported assessment of changes in HbA1c associated with the study.

Research team members screened abstract records for all non-duplicate records. Among those that met criteria based on abstract review, the research team members read full-text articles to determine which studies met the established inclusion and exclusion criteria. This systematic review and meta-analysis was registered with PROSPERO International Prospective Register of Systematic Reviews in April 2020 (#180577).

2.3 Data extraction and quality assessment

Among studies that met the criteria for the systematic review, we extracted data on study population, intervention type and duration, mean between-arm difference in HbA1c (intervention – control arm) and its measure of uncertainty. Studies were categorized based on the primary type of intervention into one of four broad groups: (a) care management and patient education, which included care management interventions, patient education programmes, virtual coaching (including patients’ use of mobile applications), telemonitoring, point-of-care testing, and use of alerts, shared-decision-making tools, or embedded practice advisories in the electronic health record; (b) physician-based interventions, which included programmes delivered to physicians and designed to influence physician behaviour, such as physician education, physician feedback or reminders, or other practice quality improvement programmes delivered to physicians; (c) nurse- or certified diabetes educator (CDE)-based interventions that focused on medication management; and (d) pharmacist-based interventions. Interventions involving nurses and nurse diabetes educators were categorized based on the primary role of the nurse in the intervention. If an intervention was targeted specifically at patient education and coordinating care, then that intervention was categorized with care management and patient education; nurses making medication decisions was grouped in nurse-and diabetes educator-based interventions. For programmes or interventions that used more than one approach, the study authors may have signalled that one approach was primary (by flagging it as such in the article text or title); in that case, we designated that approach as the primary intervention type for the purposes of summarizing the information, and noted secondary types. If the article did not explicitly make clear which of multiple approaches the authors considered primary, the research team categorized the primary intervention type after reviewing the article. Example activities for each of the four intervention types are shown in Table 1.

We assessed the risk of bias in individual studies using the approach described by Higgins et al to assess random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete data reporting, and selective reporting. We also used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to rate the quality of evidence in systematic reviews.10

2.4 Data synthesis and analysis

The primary outcome of interest for the quantitative analyses was the mean difference in HbA1c change between the intervention group(s) and control group(s). Because studies report findings from interventions differently, we took steps to construct the data elements needed, where possible. If the standard error was not reported in a publication, we followed procedures in the Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (July 2019) for our estimations.11 In studies with more than two arms, a pooled estimate was obtained with a fixed-effect meta-analysis. In studies that did not report the difference in mean HbA1c between intervention and control groups but reported the HbA1c change within each group (ie, pre-post), the between-group differences were calculated assuming independence between the two estimates. For one study reporting HbA1c values before and after intervention, the standard error of within-arm difference was estimated assuming a correlation of $\rho = 0.5$. When differences were reported as median and interquartile range, they were transformed into mean and standard deviation using the R package “estmeansd”. A DerSimonian and Laird non-linear random-effect meta-regression with the Hartung-Knapp modification was conducted to explore the reduction of HbA1c in relation to the duration of the intervention; non-linearity was modelled using restricted cubic splines. Reduction of HbA1c was also investigated across study-level mean baseline (ie, pre-intervention) HbA1c using the same approach. For supplementary analyses performed to adjust for the initiation or intensification of insulin as a treatment approach, we categorized the types of medication management approaches that occurred for the study population (no insulin use, insulin and oral medications or noninsulin injectable medications, or only insulin initiation and intensification). Publication bias was visually inspected using a contour-enhanced funnel plot and small-study effects were formally assessed using Egger’s test accounting for the two moderators (duration of intervention and baseline HbA1c). Studies were excluded from the meta-regression if data were not available on HbA1c reduction (ie, the treatment
effect and its standard error could not be calculated from the data reported) or on the duration of intervention. All analyses were conducted in Stata v.16.0\textsuperscript{12} and results are reported with 95% confidence interval (CI).

3 | RESULTS

3.1 | Study selection and characteristics

The systematic review search identified 1440 records, of which 1338 nonduplicate abstracts were screened and 102 articles were reviewed in full text. Among those, 36 met the criteria for inclusion in the systematic review and meta-analysis.\textsuperscript{13-48} A flow diagram reflecting details on search records identified at each stage is shown in Figure 1.

Among articles screened by abstract, the most common reason for exclusion was not meeting study design criteria (465 studies; eg, guideline papers, editorials and commentaries, as well as retrospective or observational studies investigating the prevalence of therapeutic inertia without an intervention designed to overcome it). Articles were also excluded based on study design criteria if they tested an intervention in a single cohort without a comparison group. The second most frequent reason for exclusion among abstracts screened was the investigation of outcomes not relevant to this systematic review (n = 428). Similarly, among articles excluded after full-text review, the most common reasons for exclusion were not meeting criteria related to study design (n = 30) or outcome (n = 11).

The characteristics for each of the 36 publications meeting the inclusion criteria are presented in Table 2 and their quality assessment is reported in Table S1. More than two-thirds of the studies were conducted in the United States and most interventions were tested in primary care practices or groups of practices. Among the studies included, 28 were RCTs and eight used a quasi-experimental design with a comparison group (ie, prospective nonrandomized groups, such as a comparison practice within the same health system, as well as retrospective matched comparison groups). A high or unclear risk of bias ranged from 42% for “incomplete outcome data” to 94% for “blinding of participants and personnel”.

In addition to assessing HbA1c, a wide range of other outcomes were also evaluated, including: diabetes treatment intensification; global cardiovascular risk and specific cardiovascular risk factors (ie, blood pressure, cholesterol, and tobacco use); quality of life; and process outcomes, such as frequency of HbA1c testing. In addition, a few studies reported on utilization of emergency department visits and hospitalizations. Medication management was guided by use of an algorithm or protocol in some studies,\textsuperscript{23,29-31,48} while in others medication changes were made based on clinical judgement, supported by collaborative practice agreements\textsuperscript{37,38} or expanded scope of practice policies.\textsuperscript{13} Three studies provided nurse, CDE or pharmacist autonomy to manage insulin only,\textsuperscript{23,27,31} while medication management in other interventions involved initiating or intensifying both oral medications and insulin.

3.2 | HbA1c reduction

Of the 36 studies that met the inclusion criteria, 20 were categorized as care management and education interventions, seven as physician-based interventions, five as nurse- and CDE-based interventions, and four as pharmacist-based interventions: HbA1c reductions, alongside heterogeneity across studies, are summarized in Figure 2.

Outcomes associated with care management and patient education interventions were mixed: a few studies were associated with statistically and clinically significant greater reductions in HbA1c,\textsuperscript{19,26,32,39,46} while most others were not. Only one of seven physician-based interventions was associated with a significantly greater reduction in mean HbA1c compared to usual care.\textsuperscript{35} Of the four categories of intervention, all of the nurse and CDE-based and pharmacist-based interventions were effective at reducing HbA1c. Nurse- and CDE-based interventions were associated with greater reductions in HbA1c compared to controls, with a mean HbA1c difference ranging from \(-17.7\) mmol/mol (\(-1.62\%\)) to \(-4.4\) mmol/mol (\(-0.40\%\)), while for pharmacist-based interventions reductions ranged from \(-9.8\) mmol/mol (\(-0.90\%\)) to \(-6.6\) mmol/mol (\(-0.60\%\)). Corresponding estimates for care management and patient education interventions and for physician-based interventions were
−13.1 mmol/mol (−1.20%) to 3.3 mmol/mol (0.30%) and −4.4 mmol/mol (−0.40%) to 2.8 mmol/mol (0.26%), respectively.

When accounting for the different durations of intervention across the included studies (median 1 year [range 0.9 to 36 months]), a reduction of HbA1c was only observed during the first year (Figure 3). At 6 months, the pooled HbA1c reduction was −4.2 mmol/mol (95% CI −6.2, −2.2; −0.38% [95% CI −0.56, −0.20]); the corresponding value at 1 year was −1.6 mmol/mol (95% CI −3.3, 0.1; −0.15% [95% CI −0.30, 0.01]). However, HbA1c reduction was different in relation to the type of intervention ($P < 0.0001$). Similarly, interventions lowered HbA1c only in individuals with preintervention HbA1c >75 mmol/mol (9%; Figure 3).

There was significant heterogeneity across studies in the analysis accounting for duration of intervention ($I^2 = 88\%$) and baseline HbA1c ($I^2 = 67\%$). The visual inspection of the contour-enhanced funnel plot suggests the presence of a small-study effect related to publication bias (Figure S1); accounting for study duration and baseline HbA1c, Egger’s $P$ values for small-study effect were 0.008 and 0.0423, respectively.

We used the GRADE scale to rate the certainty of the evidence in each of the four intervention types. The studies that described pharmacist-based interventions and nurse- or CDE-based interventions were of high-quality study design, as they were primarily RCTs, and had consistent effect on outcomes; however, there was a risk of publication bias (Figure S1), which downgraded the body of evidence for these groups to moderate quality. The funnel plots for the care management and patient education intervention group and the physician-based intervention group did not reveal similar publication bias, however, there was inconsistency in effect on outcomes in both groups, and five of the 20 studies in the care management were of quasi-experimental design, also introducing risk of bias. For this reason, the body of evidence for these intervention groups was also determined to be of moderate quality.

In a sensitivity analysis, after the exclusion of studies with a duration of intervention lower than 3 or 6 months, there was a smaller effect of interventions for higher baseline HbA1c levels and a more constant effect over time (Figure S2).

A summary of the medication changes that were implemented in the intervention are included in Table S2. Accounting for these changes, there were overlapping mean HbA1c reductions at 6 and 12 months, with a possible greater effect (although of small magnitude) for treatment strategies in the intervention group with insulin only; or insulin and oral or non-insulin injectable treatments (Figure S3).
| First author, year published, reference number | Country | Study design | Clinical setting | Number of participants | Primary type of intervention | Study duration, months | Outcomes assessed | Summary of results |
|-----------------------------------------------|---------|--------------|------------------|------------------------|----------------------------|----------------------|------------------|-------------------|
| **Pharmacist-based interventions**             |         |              |                  |                        |                            |                      |                  |                   |
| Al Hamarneh, 2017                             | Canada  | RCT          | Pharmacy         | 573                    | Pharmacist medication management | 3                    | HbA1c, medication changes, cardiovascular risk, cholesterol, blood pressure, tobacco cessation, exercise, diet | Medication therapy management consultations with pharmacists were associated with reductions in HbA1c, cholesterol, tobacco use, and cardiovascular risk scores, compared to controls |
| Jameson, 2010                                 | United States | RCT          | Primary care     | 104                    | Pharmacist medication management | 12                   | HbA1c, number of patients who reduced HbA1c by 1% | Pharmacists performing diabetes education, adherence assessment, medication review, and making guideline-based medication changes to adjust insulin doses as needed was associated with improvements in HbA1c. |
| Tilton, 2019                                  | United States | Quasi-experimental | Primary care | 316                    | Pharmacist medication management | 12                   | HbA1c, blood pressure, emergency department visits, hospitalizations | A pharmacist-run medication therapy management clinic was associated with statistically significant and consistent decreases in HbA1c at 12 months, but not emergency department visits or hospitalizations |
| Prudencio, 2018                               | United States | RCT          | Primary care     | 811                    | Pharmacist medication management | 13                   | HbA1c, achievement of goal glycaemic targets, blood pressure, and cholesterol | Pharmacists had 40-minute, in-person visits and follow-up phone visits during which they performed comprehensive medication management. Pharmacists had a collaborative practice agreement that enabled them to optimize medication management. Patients in the intervention group also had significantly higher improvements in systolic blood pressure and statin goal attainment |
| **Care management and patient education interventions** |         |              |                  |                        |                            |                      |                  |                   |
| Hsu, 2016                                     | United States | RCT          | Primary care     | 40                     | Virtual patient coaching | 12                   | HbA1c, time with provider, treatment satisfaction | Care through virtual visits, text messaging, shared-decision-making tools, and patient self-tracking tools to facilitate communication about glycaemic control and insulin doses was associated with improvements in HbA1c and improved communication |
| First author, year published, reference number | Country       | Study design          | Clinical setting | Number of participants | Primary type of intervention | Study duration, months | Outcomes assessed                                                                 | Summary of results                                                                                                                                                                                                 |
|-----------------------------------------------|---------------|-----------------------|------------------|------------------------|----------------------------|------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Egede, 2017                                  | United States | RCT                   | Primary care     | 113                    | Care management           | 6                      | HbA1c, rate of decrease of HbA1c                                                  | Nurse-led technology-assisted case management via a telehealth glucose monitor with medication titration was associated with improved glycaemic control in rural adults with poorly controlled diabetes. |
| Quinn, 2011                                   | United States | RCT                   | Primary care     | 213                    | Virtual patient coaching  | 12                     | HbA1c, blood pressure, cholesterol, patient-related outcomes: depressive symptoms, distress scale, symptom inventory | This study compared a patient coaching app only to a patient coach with a web portal or patient-provider secure messaging; and patient coaching, web portal, and management decision support for providers. The authors found greater decreases in mean HbA1c in the maximal treatment group compared to usual care, but no differences in diabetes distress, depression, blood pressure, or lipid levels. |
| Cowart, 2019                                 | United States | Quasi-experimental    | Primary care     | 483                    | Care management           | 3                      | HbA1c, treatment intensification, number of patients with HbA1c reduction 0.5%, number of patients who achieved HbA1c goal, time to HbA1c goal | Patients exposed to pharmacist care management in addition to usual physician care had lower time to treatment intensification, but no significant difference in HbA1c. |
| Mash, 2016                                   | South Africa  | Quasi-experimental    | Primary care     | 300                    | Point-of-care testing     | 12                     | HbA1c, insulin initiation, testing frequency                                      | Point-of-care testing for HbA1c at community health centres did not improve test coverage, treatment intensification, counselling, or glycaemic control. |
| Frias, 2017                                  | United States | RCT                   | Primary care     | 120                    | Telemonitoring            | 4                      | HbA1c, blood pressure, fasting glucose, proportion of participants reaching blood pressure goal, patient activation, medication changes | Use of a wearable sensor patch, and a mobile device that transmitted data to the healthcare team who could titrate medications and provide patient education was associated with increased patient activation but no changes in HbA1c. |

(Continues)
| First author, year published, reference number | Country | Study design | Clinical setting | Number of participants | Primary type of intervention | Study duration, months | Outcomes assessed                                                                                                                                                                                                 | Summary of results                                                                                                                                                                                                 |
|-----------------------------------------------|---------|--------------|------------------|------------------------|-----------------------------|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| McFarland, 201223                           | United States | Quasi-experimental | Primary care | 103                     | Telemonitoring              | 6                      | HbA1c, insulin intensification, % of patients with HbA1c <7% [53 mmol/mol], number of patient contacts, the time spent with patient, number of medication changes                                                   | Use of a care coordination home telehealth programme by pharmacy specialists that enabled communication among patients, providers, and clinical pharmacist specialists in the interval between face-to-face visits was associated with improvements in HbA1c at 3 months, but not at 6 months |
| Bellido, 201914                             | Spain   | Quasi-experimental | Outpatient    | 228                     | Virtual patient coaching  | 6                      | HbA1c, optimal insulin dose within 6 months, glucose, body mass index after 6 months                                                                                                                                    | A telephone support tool for diabetes patients who were initiating or intensifying insulin was associated with reaching optimal insulin doses and reductions in HbA1c within 6 months |
| von Storch, 201996                          | Germany | RCT           | Primary care   | 115                     | Telemonitoring              | 12                     | HbA1c, self-reported diabetes self-management behaviours, weight loss, and physical activity                                                                                                                            | A telemedicine-assisted self-management programme for diabetes patients was associated with greater declines in HbA1c in the intervention |
| Tang, 201343                                | United States | RCT           | Primary care   | 415                     | Telemonitoring              | 12                     | Medication initiation, LDL cholesterol, blood pressure, weight, Framingham risk, knowledge about glucose testing, diabetes understanding, treatment satisfaction                                                                 | The intervention, which included a wireless glucometer upload system, a diabetes summary dashboard including a patient’s action plan, nutrition and exercise logs, insulin record, online messaging with the health team, a nurse care manager and dietician providing medication management, and a patient-specific text and video educational content was evaluated but was not associated with significant difference in HbA1c |
| Young, 201747                               | United States | RCT           | Primary care   | 450                     | Telemonitoring              | 12                     | HbA1c, health-related quality of life                                                                                                                                                                                  | This study compared three approaches to self-monitoring of blood glucose on HbA1c levels and quality of life among patients with non-insulin-treated diabetes and found that self-monitored blood glucose with tailored feedback was not associated with significant differences in HbA1c levels or quality of life scores |
| First author, year published, reference number | Country | Study design | Clinical setting | Number of participants | Primary type of intervention | Study duration, months | Outcomes assessed                                                                 | Summary of results                                                                                                                                 |
|---------------------------------------------|---------|--------------|-----------------|------------------------|-----------------------------|------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Greenwood, 2015<sup>25</sup>                | United States | RCT | Health system | 90 | Telemonitoring | 6 | Change in medication, satisfaction with care, blood pressure, glucose, foot care | Telehealth remote monitoring with asynchronous virtual visits with a CDE who communicates with primary care providers was associated with improvements in HbA1c |
| Curtis, 2009<sup>18</sup>                    | United States | Quasi-experimental | Primary care | 2345 | Care management | 19 | HbA1c, hypoglycaemic episodes, visit for hypoglycaemia | Retrospective study comparing diabetes education from nurse care managers with or without medication adjustment to usual care. Care management plus medication adjustment was superior to usual primary care in improving HbA1c |
| Sharp, 2018<sup>80</sup>                     | United States | RCT | Primary care | 244 | Care management | 24 | Changes in systolic and diastolic blood pressure, cholesterol, body mass index, quality of life, and perceived social support | In this crossover study patients received community health worker support in either the first or the second year of the study. Both groups received clinical pharmacist support for both years of the study. There were no significant HbA1c differences between the intervention and control groups; declines in both groups were similar |
| Stone, 2012<sup>42</sup>                     | United States | RCT | Primary care | 101 | Telemonitoring | 6 | HbA1c, transmission of glucose data | This study re-randomized patients who previously participated in a study comparing care management and telemonitoring to care coordination. Patients initially receiving active care management were randomized to care coordination with or without continued telemonitoring; patients initially receiving care coordination were re-randomized to continued care coordination or usual care. Improvements in HbA1c were sustained for 6 months after re-randomization in both home telemonitoring and care coordination groups |
| Smith, 2008<sup>41</sup>                     | United States | RCT | Primary care | 639 | Virtual coaching | 12 | HbA1c, metabolic and vascular risk factor control, cardiovascular disease risk, cost of care | The telemedicine intervention comprised a virtual consultation with an endocrinologist before each visit with a patient with diabetes. The intervention was not associated with greater improvements in HbA1c or cardiovascular risk factors |

(Continues)
| First author, year published, reference number | Country          | Study design | Clinical setting | Number of participants | Primary type of intervention | Study duration, months | Outcomes assessed                                                                 | Summary of results                                                                                                                                 |
|----------------------------------------------|-----------------|--------------|------------------|------------------------|----------------------------|------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| Gabbay, 201336                              | United States   | RCT          | Primary care     | 545                    | Care management            | 24                     | HbA1c, blood pressure, cholesterol, diabetes distress, quality of life, diabetes treatment satisfaction, depression symptoms | Participants with exposure to nurse care managers trained in motivational interviewing and providing medication titration had improvements in blood pressure but not HbA1c |
| Fairhall, 201630                             | South Africa    | RCT          | Primary care     | 4393                   | Patient education          | 14                     | HbA1c, treatment intensification, cardiovascular disease risk, blood pressure, smoking, quality of life, mortality, healthcare utilization | Expanded nurses’ role through educational outreach sessions and use of a clinical management tool with prescribing guidelines was associated with treatment intensification but no significant difference in HbA1c |
| Fiscella, 201021                             | United States   | RCT          | Health system    | 727                    | Care management            | 12                     | HbA1c, treatment intensification, blood pressure, cholesterol                     | Patients who received a visit from a “peer clinician” (a peer of their primary care provider who focused only on diabetes management) were significantly more likely to have their treatment intensified but did not show any difference in HbA1c at 12 months |
| Platt, 201035                               | United States   | RCT          | Primary care     | 119                    | Patient education          | 36                     | HbA1c, cholesterol, and blood pressure, self-monitoring of blood glucose, quality of well-being | An intervention with certified diabetes educator, patient and provider education, and decision support was compared to patient education alone and usual care. They report that improvements observed at 1-year follow-up in glycaemic control and blood pressure control were sustained in the chronic care model group at 3 years |

**Physician-based interventions**

| Phillips, 200535                            | United States   | RCT          | Primary care     | 4138                    | Physician feedback/reminders | 15                     | HbA1c, treatment intensification, attainment of ADA goals for HbA1c, cholesterol, blood pressure | Providers received either hard-copy computerized reminders with patient-specific recommendations, or individual face-to-face feedback on performance for 5 minutes every 2 weeks, or both. Blood pressure improved significantly in intervention group patients, but not HbA1c |
| First author, year published, reference number | Country | Study design | Clinical setting | Number of participants | Primary type of intervention | Study duration, months | Outcomes assessed                                                                 | Summary of results                                                                 |
|-----------------------------------------------|---------|--------------|------------------|------------------------|----------------------------|------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| van Bruggen, 2009[45]                         | Netherlands | Quasi-experimental | Primary care | 1283 | Physician education | 6-12 | Treatment intensification, blood pressure, cholesterol, HbA1c | A nurse specialist trained providers in the use of the 1999 guidelines for type 2 diabetes management from the Dutch College of General Practitioners, analysed barriers to change in the practice. The nurse specialist intervention was associated with a significant difference in the percentage of patients who received appropriate treatment intensification for blood pressure among individuals with diabetes, but not diabetes changes |
| Bieszk, 2016[56]                              | United States | RCT | Outpatient | 6234 | Physician education | 12 | HbA1c, frequency of testing, medication intensification, insulin initiation, medication discontinuation, hypoglycaemic events | Clinician and patient educational materials mailed to participating providers and patients were not associated with improvements in HbA1c. |
| O'Connor, 2009[34]                            | United States | RCT | Primary care | 3703 | Physician quality improvement | 12 | HbA1c, treatment intensification, HbA1c testing rate, LDL cholesterol testing rate, LDL cholesterol values | Providers were given a list of diabetic patients every 4 months with feedback (e.g., ranking physician compared to colleagues) and a decision support feedback for diabetes management, reminders and notification of inappropriate therapy. There were no significant differences in HbA1c, LDL, or medication titration |
| Reutens, 2012[23]                             | United Kingdom | RCT | Primary care | 386 | Physician education | 12 | Percentage who achieved HbA1c <6.5% [48 mmol/mol], hypoglycaemic events, percentage who achieved target blood pressure or cholesterol, healthcare utilization, number of HbA1c measurements | Physician education was provided related to regional diabetes management guidelines. Most patients did not receive intensification of therapy according to guidelines in both arms, with no significant differences between the intervention and control groups |
| Kulzer, 2018[23]                              | Germany | RCT | Primary care specialty - outpatient | 907 | Physician education | 12 | HbA1c, percentage achieving an HbA1c reduction >5.5 mmol/mol [0.5%], diabetes therapy adjustments, changes in glucose testing frequency | An integrated personalized diabetes management intervention arm in which physicians received structural assessment and education, and patient participants were advised on glucose self-monitoring. The intervention was associated with increased frequency of changes in medication |
TABLE 2  (Continued)

| First author, year published, reference number | Country          | Study design | Clinical setting | Number of participants | Primary type of intervention | Study duration, months | Outcomes assessed                                                                 | Summary of results                                                                                                                                 |
|-----------------------------------------------|------------------|--------------|------------------|------------------------|----------------------------|------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bieszk, 2017<sup>15</sup>                    | United States    | RCT          | Outpatient       | 2792                   | Physician education        | 12                     | HbA1c, insulin initiation rates, all-cause medical and pharmacy costs, diabetes medical and pharmacy costs | Physician educational materials provided via mail and in video conference were not associated with improvements in HbA1c                                                                 |
| Nurse- or certified diabetes educator-based interventions | Magee, 2019<sup>29</sup> | United States | Quasi-experimental | Health system 732    | CDE medication management  | 36                     | HbA1c, 30-day and 90-day emergency department visits, hospitalizations          | A team-based “diabetes boot camp” programme incorporating technology-enabled medication management by CDEs following an algorithm-based guideline was associated with improvements in HbA1c |
|                                                | Magee, 2015<sup>30</sup> | United States | RCT              | Emergency department 101 | CDE medication management | 1                      | HbA1c, fasting glucose, hypoglycaemia, medication adherence                     | An intervention delivered by CDEs in the emergency department was associated with improvements in HbA1c at 4 weeks                                                                 |
|                                                | Zgibor, 2018<sup>48</sup> | United States | RCT              | Primary care 240     | CDE medication management | 12                     | HbA1c, medication initiation, blood pressure, cholesterol medication intensification | Primary care practices implemented use of evidence-based diabetes management protocols by CDEs. This change was associated with improvements in HbA1c, medication changes, and increased likelihood of being at goal |
|                                                | Furler, 2017<sup>23</sup> | Australia    | RCT              | Primary care 266     | Nurse medication management | 12                     | HbA1c, insulin initiation, depressive symptoms, diabetes distress, quality of life, weight | An enhanced role for primary care practice nurses in diabetes care, including treatment intensification and titration, was associated with improvements in HbA1c and quality of life |
|                                                | Manski-Nankervis, 2017<sup>31</sup> | Australia | RCT              | Primary care 266     | Nurse medication management | 24                     | HbA1c, insulin initiation or intensification                                      | 24-month follow-up of a study testing an enhanced role for nurses providing treatment intensification and titration was associated with sustained improvements in HbA1c and timely treatment intensification |

Abbreviations: ADA, American Diabetes Association; CDE, certified diabetes educator; HbA1c, glycated haemoglobin; RCT, randomized controlled trial.
Study-specific glycated haemoglobin (HbA1c) reduction. HbA1c reductions are shown for the 36 studies with available information, grouped by intervention. Squares and bars indicate, respectively, study-specific mean HbA1c reduction compared to the control arm and 95% confidence interval. I² refers to the heterogeneity across studies. US, United States.

## Types of intervention, First author (Ref) Year Follow up (months) Country

### Pharmacist-based intervention [I, 0%]

| Study | Year | Follow up (months) | Country |
|-------|------|-------------------|---------|
| Al Hamarneh (13) | 2017 | 3 | Canada |
| Jameson (27) | 2010 | 12 | US |
| Tilton (41) | 2019 | 12 | US |
| Prudencio (37) | 2018 | 13 | US |

### Care management and patient education [I, 73%]

| Study | Year | Follow up (months) | Country |
|-------|------|-------------------|---------|
| Hsu (26) | 2016 | 12 | US |
| Egide (19) | 2017 | 6 | US |
| Quinn (38) | 2011 | 12 | US |
| Cowart (17) | 2019 | 3 | US |
| Mashi (32) | 2016 | 12 | South Africa |
| Frias (22) | 2017 | 2.8 | US |
| McFarland (33) | 2012 | 6 | US |
| Bellido (14) | 2019 | 6 | Spain |
| Von Storch (46) | 2019 | 12 | Germany |
| Tang (43) | 2013 | 12 | US |
| Young (47) | 2017 | 12 | US |
| Greenwood (25) | 2015 | 6 | US |
| Curtis (18) | 2009 | 1 | US |
| Sharp (40) | 2018 | 24 | US |
| Stone (42) | 2012 | 6 | US |
| Smith (41) | 2008 | 12 | US |
| Gabay (24) | 2013 | 24 | US |
| Fairhall (20) | 2016 | 14 | South Africa |
| Fiscella (21) | 2010 | 12 | US |
| Piatt (36) | 2010 | 36 | US |

### Physician-based intervention [I, 69%]

| Study | Year | Follow up (months) | Country |
|-------|------|-------------------|---------|
| Phillips (35) | 2005 | 15 | US |
| van Bruggen (45) | 2009 | 12 | Netherlands |
| Bieszk (16) | 2016 | 12 | US |
| O'Connor (34) | 2009 | 12 | US |
| Reutens (39) | 2012 | 12 | United Kingdom |
| Kulzer (28) | 2018 | 12 | Germany |
| Bieszk (15) | 2017 | 12 | US |

### Nurse- or CDE-based interventions [I, 88%]

| Study | Year | Follow up (months) | Country |
|-------|------|-------------------|---------|
| Magee (29) | 2019 | 3 | US |
| Magee (30) | 2015 | 0.9 | US |
| Zgibor (48) | 2018 | 12 | US |
| Furler (33) | 2017 | 12 | Australia |
| Manski-Nankervis (31) | 2017 | 24 | Australia |

**FIGURE 2** Study-specific glycated haemoglobin (HbA1c) reduction. HbA1c reductions are shown for the 36 studies with available information, grouped by intervention. Squares and bars indicate, respectively, study-specific mean HbA1c reduction compared to the control arm and 95% confidence interval. I² refers to the heterogeneity across studies. US, United States.

## DISCUSSION

The findings from this systematic review and meta-analysis provide a view of the numerous approaches that have been implemented and evaluated to mitigate therapeutic inertia in type 2 diabetes management and give important insight into patients’ characteristics and types and duration of interventions which may improve our ability to overcome therapeutic inertia.

The most effective approaches to mitigating therapeutic inertia and improving HbA1c identified in our study were those interventions where nonphysician providers such as pharmacists, nurses and CDEs had autonomy to address therapeutic inertia in partnership with primary care providers. A common characteristic of the nurse-, CDE- and pharmacist-led medication management interventions identified was that nonphysician providers could independently initiate and intensify treatment, supported by appropriate guidelines, protocols and collaborative agreements. For example, in an RCT by Al Hamarneh et al, patients were randomized either to an intervention arm which received medication therapy management consultations with pharmacists, or to usual care by primary care physicians and pharmacists. The usual care arm in this study included pharmacists who did not make medication changes, suggesting that the inclusion of pharmacists or other nonphysician team members in diabetes care teams is not sufficient to improve diabetes outcomes; those team members must also be empowered to implement guideline-based medication changes.

The effectiveness of interventions may depend on the delivery methods and frequency of intervention to patients rather than the type of provider who delivered the intervention. While studies included in this review did not consistently report frequency of patient communication between study arms, among those that were effective, several reported that the interventions involved regular in-
Meta-regression of glycated haemoglobin (HbA1c) reduction. The size of the circle is proportional to random-effects weights for intervention and control groups; grey area is the 95% confidence interval. $P < 0.0001$ for differences among the four types of intervention for duration of intervention and $P = 0.0023$ for HbA1c. Stratified analysis by type of intervention was not possible as few studies were available in some types of intervention. CDE, certified diabetes educator

Among the studies assessed in this systematic review, findings from interventions focused on changing clinician behaviour through education, feedback or quality improvement activities were least likely to be associated with greater improvements in HbA1c compared to usual care. Variation in the effectiveness of physician-based interventions may be driven in large part by intervention intensity. Interventions that involved frequent or intense education were more likely to be associated with improvements in HbA1c than one-time or light-touch education interventions. The one effective clinician education intervention identified through the review involved one-on-one guidance provided by endocrinologists to internal medicine residents practising in a primary care practice, suggesting that education tools can be effective strategies to mitigate therapeutic inertia but probably require investments in time and personnel to achieve programme goals. Furthermore, an approach that requires time-intensive specialist feedback to providers may be challenging to implement in settings where specialty care is less available. Other factors that may contribute to the fact that physician-based interventions were less effective than others could include that management of other comorbid conditions during physician visits may result in significant competing priorities, while nonphysician providers’ clinical activities may be focused specifically on diabetes, resulting in fewer competing priorities and greater time focused on diabetes management.

Regardless of type of intervention, the present study found that the reduction of HbA1c was observed during the first year and primarily in patients with baseline HbA1c levels >9% [75 mmol/mol], possibly because the degree of modifiable risk may influence success of strategies, and it may be that those individuals with higher HbA1c or those where intervention occurs earlier in their treatment course may also be those with the greatest room for improvement.
Notably, strategies to overcome therapeutic inertia may have increasing importance as patients and healthcare systems respond to and recover from the dramatic shifts in healthcare use related to the COVID-19 pandemic. Early evidence suggests that healthcare for chronic disease management has been delayed or foregone due to COVID-19-related changes, potentially exacerbating therapeutic inertia. Healthcare providers, practices and systems seeking to mitigate impacts of delayed care may benefit from targeting resources toward strategies that have demonstrated effectiveness in overcoming therapeutic inertia.

This study has several limitations, and, as such, the results should be interpreted and translated into clinical practice with caution. An important challenge in drawing conclusions about effective interventions is that many interventions use a complex approach with several combined strategies, and therefore we cannot determine the relative contribution of different components of interventions from the published reports, which is further confirmed analytically by the presence of statistical heterogeneity across studies. Evaluation of complex interventions presents unique challenges, as outlined by the Medical Research Council framework for complex interventions. We grouped interventions based on the main intervention component but recognize that successful implementation of programmes to improve care requires incorporating several components of effective interventions and taking into account context and cost. A limitation is that detailed reporting of the interventions varied and in some cases was lacking, making interpretation of key components of different programmes difficult.

Another important consideration is that the intervention types varied in terms of to whom the intervention was directed. Physician education interventions, for example, were directed at physicians as the target of the intervention, and could only have indirect impact on patients, while other intervention types directly involved patients, which may have contributed to their relative efficacy.

Another limitation is that the populations included in the studies differed and the interventions used a range of medication management approaches in addressing therapeutic inertia. For example, some studies focused on patients who were initiating or intensifying insulin, in particular, while other studies involved a wider range of medication changes including initiation or intensification of oral medications, insulin and noninsulin-injectable medications. These medication changes may have varying impacts on HbA1c, and a study where therapeutic inertia is mitigated primarily by initiation of insulin may be more likely to show positive effects than an intervention where therapeutic inertia is mitigated primarily by intensification of oral medications. However, when accounting for these different intensification strategies, we observe consistent effects at least at 6 and 12 months of intervention, with a possible greater effect of small magnitude when insulin was used alone or in combination with other medications. Nevertheless, our approach to adjusting for medication intervention types for these analyses (which used the categories of either no insulin use, insulin and other medications, or only insulin) may not fully capture additional differences in efficacy within different medication groups.

Another challenge to interpreting these results is that the frequency of communication between patient and clinicians was not consistently reported across all studies. As such, we cannot definitively say to what degree frequent contact or total time spent with patients contributed to the observed improvements in HbA1c, rather than the provider type. Notably, no single provider type was uniquely associated with improvements in diabetes care, suggesting that systems or practices looking to implement a medication management programme may consider different clinician types depending on what is most appropriate for the setting, and who can support frequent communication with patients.

Furthermore, while nearly all studies reported HbA1c among outcomes, it is possible that studies included in the meta-analysis focused on other outcomes beyond HbA1c as a primary outcome of the interventions tested, which may complicate use of HbA1c as a measure by which to compare the relative effectiveness of the studies included.

Although our findings provide valuable information on interventions that may overcome therapeutic inertia in the management of type 2 diabetes, there remain some gaps regarding implementation across a broad range of healthcare settings. Of the RCTs and quasi-experimental studies, the majority were tested in academic healthcare settings, which may benefit from infrastructure associated with their affiliated university or larger health systems, or may benefit directly from the infrastructure offered by a research study such as research coordinators and formal follow-up processes, regardless of whether the study is in a larger academic setting. Given that outcomes were most improved in interventions that involved nonphysicians, it is possible that well-resourced clinical settings are better positioned to have staff time and resources to support therapeutic changes, potentially confounding results.

Relatively few studies included in this systematic review reported assessments of resources required to implement programmes, cost, or cost-effectiveness. Costs associated with long-term impacts of treatment delay and shifts toward value-based care may incentivize investments in the resources needed to implement programmes that overcome therapeutic inertia. Better understanding of the resources and costs associated with interventions to overcome therapeutic inertia are needed to support their implementation.

Additionally, this study focuses on interventions which can overcome therapeutic inertia, defined as failure to initiate or intensify treatment appropriately, but does not focus on interventions that may facilitate appropriate de-escalation of therapy, or those interventions that address failure to adhere to guidelines related to diabetes management beyond just pharmacological treatment intensification. As such, these interventions should be considered part of a suite of important strategies for mitigating clinical inertia broadly.

Likewise, this study does not include studies that explicitly focus on medication adherence, however, it is possible that some interventions—particularly those that included care management or self-management and education—may have also had effects on adherence which could act synergistically with impacts on therapeutic
inertia. Future research could explore how factors such as adherence are impacted by efforts to overcome therapeutic inertia. Future research may also consider how to integrate strategies to overcome therapeutic inertia with population health approaches to identify those at risk for therapeutic inertia.

While there is limited evidence of the effectiveness of programmes to overcome therapeutic inertia from studies longer than 1 year, our results suggest that the HbA1c reduction diminishes over time and is larger in individuals with higher preintervention HbA1c, as previously demonstrated for glucose-lowering therapies\(^5\); this would indicate that the beneficial effects are greater in some subgroups of individuals with type 2 diabetes. Of note, we observed a smaller effect of interventions for higher baseline HbA1c levels and a more constant effect over time after the exclusion of studies of shorter duration, possibly because the excluded studies (with shorter duration) had also a higher baseline HbA1c and greater reduction. These estimates, moreover, are based on aggregate-level data and may be susceptible to ecological bias\(^5\); investigations using individual-level data are therefore required to confirm these results.

The risk of bias across the included studies was deemed moderate to high. Given the approaches tested, neither the providers who participated nor the researchers could be blinded to participant group assignment. Additionally, quasi-experimental studies included were, by definition, not randomized. Moreover, some were retrospective, which may introduce bias. Lastly, formal statistical tests indicated the presence of small-study effects, likely to be related to a publication bias as suggested by the visual inspection of the contour-enhanced funnel plot. In considering potential small-study effects and publication bias, we acknowledge that the more powerful a study was, the less likely it was to show an effect of any kind, which is a limitation to interpreting these results. Future efforts to further evaluate strategies to overcome therapeutic inertia should be designed to include large sample sizes. Finally, while this study did not limit country of origin to studies performed in the United States, the study did limit included findings to those that were available in the English language, and most studies identified and included were from the United States. As such, findings may not be generalizable worldwide.

Findings from this systematic review and meta-analysis suggest that therapeutic inertia can be mitigated by empowering pharmacists, nurses and diabetes educators with the ability to initiate and intensify treatment, supported by appropriate guidelines, protocols and collaborative agreements. Approaches that leverage technology to facilitate frequent communication between patients and healthcare teams and those focused on educating and changing clinician practices, while necessary, may not be sufficient to address therapeutic inertia in diabetes management.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

R.E.P. contributed to study planning, performed the systematic review search and wrote the manuscript. F.Z. performed meta-analysis, reviewed and edited the manuscript. C.B. contributed to study planning and reviewed and edited the manuscript. J.C., R.A.G., M.L.L., R.M., L.M., K.M.P., S.R., J.W.S. contributed to study planning and reviewed/edited the manuscript. A.C. contributed to study planning, wrote methods, and reviewed/edited the manuscript. X.M.C. and L.K. contributed to planning and implementation of supplemental analyses and reviewed/edited the manuscript. P.S. and K.K. contributed to study conception and planning and reviewed/edited the manuscript. K.K. is the study guarantor.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the article and reference list. These data were derived from the systematic searches.

ORCID

Kevin M. Pantalone https://orcid.org/0000-0002-3897-4551
Kamlesh Khunti https://orcid.org/0000-0003-2343-7099

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