Adherence to and persistence with antidiabetic medications and associations with clinical and economic outcomes in people with type 2 diabetes mellitus: A systematic literature review

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Abstract
We designed a systematic literature review to identify available evidence on adherence to and persistence with antidiabetic medication in people with type 2 diabetes (T2D). Electronic screening and congress searches identified real-world noninterventional studies (published between 2010 and October 2020) reporting estimates of adherence to and persistence with antidiabetic medication in adults with T2D, and associations with glycaemic control, microvascular and/or macrovascular complications, hospitalizations and healthcare costs. Ninety-two relevant studies were identified, the majority of which were retrospective and reported US data. The proportions of patients considered adherent (median [range] 51.2% [9.4%-84.3%]) or persistent (median [range] 47.7% [16.9%-94.0%]) varied widely across studies. Multiple studies reported an association between greater adherence/persistence and greater reductions in glycated haemoglobin levels. Better adherence/persistence was associated with fewer microvascular and/or macrovascular outcomes, although there was little consistency across studies in terms of which outcomes were improved. More adherent and more persistent patients were typically less likely to be hospitalized or to have emergency department visits/admissions and spent fewer days in hospital annually than less adherent/persistent patients. Greater adherence and persistence were generally associated with lower hospitalization costs, higher pharmacy costs and lower or budget-neutral total healthcare costs compared with lower adherence/persistence. In conclusion, better adherence and persistence in people with T2D is associated with lower rates of microvascular and/or macrovascular outcomes and inpatient hospitalization, and lower or budget-neutral total healthcare expenditure. Education and treatment...
1 | INTRODUCTION

Type 2 diabetes (T2D) is a chronic, progressive disease that has a substantial clinical impact on patients as well as imposing an economic burden on healthcare systems. T2D is associated with cardiovascular, renal, retinal and neurological complications, and it has been estimated that 50% of people with T2D have early signs of these conditions at diagnosis. Complications account for a considerable proportion of the lifetime costs of treating diabetes, and are also linked to reduced health-related quality of life and increased indirect costs from lost workplace productivity. The risk of T2D complications is higher in patients with poor glycaemic control and are also linked to reduced health-related quality of life and increased indirect costs from lost workplace productivity. The risk of T2D complications is higher in patients with poor glycaemic control and are also linked to reduced health-related quality of life and increased indirect costs from lost workplace productivity.

Patients are closely monitored in clinical trials, therefore adherence and persistence during these trials is not representative of medication-taking behaviour in real-world settings. Observational studies must thus be used to estimate adherence and persistence rates and to evaluate the link between medication-taking behaviour and clinical or economic outcomes. As there is a considerable volume of real-world evidence in T2D, a systematic review of the literature is a robust way to identify such studies and collate their results. An earlier systematic literature review (SLR) of articles published from 2007 to 2014 found that higher rates of adherence to antidiabetic medication were associated with not only better glycaemic control and fewer hospitalizations but also lower healthcare costs. During the past few years, however, the use of newer drug classes such as dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors has increased. Consequently, a new review of the literature is warranted to examine medication-taking behaviour and its link to outcomes across the current spectrum of available antidiabetic medications.

The present SLR was designed to identify relevant evidence on the patterns of adherence to and persistence with antidiabetic medication in people with T2D, as well as clinical and economic outcomes linked to adherence and persistence, over the period of 2010 to 2020.

2 | MATERIALS AND METHODS

2.1 | Systematic literature review

Electronic searches were designed to identify real-world non-interventional studies reporting estimates of adherence to and persistence with antidiabetic medications in people with T2D and associations with clinical and economic outcomes. Journal publications from January 2010 to October 2020 were included in electronic searches, and relevant congress publications from January 2018 to October 2020 were also identified. Systematic searches were conducted in October 2020 in the Medical Literature Analysis and Retrieval System Online (MEDLINE), Embase, Evidence-Based Medicine Reviews and EconLit. Any databases that were not up to date were also searched via the University of York Centres for Reviews and Dissemination website. The search strategy for MEDLINE is shown in Table S1. The congresses searched are listed in Table S2.

Titles and abstracts were screened in a double-blind manner by two independent reviewers to determine whether they met the eligibility criteria for inclusion (Table 1). Any disagreements between reviewers were referred to a third reviewer and resolved by consensus. The reference lists of included studies and relevant reviews/editorials were reviewed to identify any further eligible publications that had not been detected in the database searches. All publications meeting the criteria were obtained as full articles and reassessed, and relevant data from publications included after full-text review were entered into a data extraction table. Quality assessment was carried out on the studies using the critical appraisal tools from the Joanna Briggs Institute.

2.2 | Outcomes

Relevant outcomes in the SLR were estimates of adherence to and persistence with antidiabetic medications and their associations with glycaemic control, microvascular and macrovascular outcomes, hospitalizations and healthcare costs. We defined adherence as the extent to which a person's antidiabetic medication-taking behaviour corresponds with recommendations from their healthcare provider. In the studies identified, it was most often measured as proportion of days covered (PDC) by medication, or medication possession ratio (MPR) as detailed below. Persistence, the duration of antidiabetic medication use by a patient, was usually measured as the proportion of patients who remained on treatment for a specified period or as the mean number of days to treatment discontinuation within the observation period.
3 | RESULTS

3.1 | Search results

In total, 3227 references were included for screening, of which 508 were determined to be relevant for full-text review (see Figure S1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] diagram). In total, 255 publications met the inclusion criteria at full-text review, and an additional eight publications were identified by hand searches.

Only full publications reporting data on the associations between adherence/persistence and the clinical/economic outcomes of interest were prioritized for data extraction and are the focus of this manuscript (n = 92). The remaining 171 publications (conference abstracts [n = 47] and full publications reporting estimates of adherence/persistence but not associations with clinical/economic outcomes [n = 124]) were excluded.

3.2 | Study characteristics

Of the 92 full publications included, 39 studies were published from 2010 to 2015 and 53 from 2016 to 2020. Most of the studies were retrospective observational cohort studies or database analyses; only 13 of the 92 studies (14%) were prospective. Sixty of the 92 studies (65%) were from the United States. The remaining studies were from Europe (German), Italy, Spain, Sweden and Switzerland (7% of studies in total), Asia (China, India, Iran, Israel, Pakistan and Taiwan; 9% of studies in total), Canada (2%) and Australia (1%). Three studies were multinational...
Estimates of persistence were reported in 31 studies (Table S3). In most studies, persistence was estimated based on the fill time between prescriptions or medication insurance claims. A gap in medication of ≥90 days was used to define discontinuation of medication (non-persistence) in nine studies, whereas thresholds of ≥30, ≥51, ≥89, 45, ≥79, ≥80, 60, ≥90, ≥107, or ≥120 days were used in other studies. Thirteen studies used other definitions for treatment gaps indicating discontinuation, such as a gap exceeding the 90th percentile of the mean duration of prescription fills.

Estimates of adherence were reported in 71 studies (Table S3). There was variation in how adherence was defined: 30 studies used PDC, and 26 studies used the MPR. Estimates of persistence were reported in 31 studies (Table S3). In over 25% of studies, persistence was estimated based on the fill time between prescriptions or medication insurance claims. A gap in treatment fills exceeding the 90th percentile of the mean duration of prescription fills.

All 31 studies were retrospective. Study duration ranged from 6 months to 3 years, and was 12 months in 17 studies. However, six studies examined persistence with OADs, GLP-1RAs, and injectable GLP-1RAs, and four studies with combination therapies.

As was the case for adherence, persistence estimates varied widely among studies. The proportion of persistent patients ranged from 16.9% to 94.0% (median: 47.7%) in the studies reporting persistence with the most frequently studied classes of antidiabetic medication.

3.5 | Associations between adherence/persistence and clinical and economic outcomes

3.5.1 | Glycaemic control

The specific glycaemic outcomes assessed in the studies examining adherence and persistence were overall change in glycated haemoglobin (HbA1c) level, expressed as a percentage, the proportion of patients achieving a target HbA1c or the incidence of hypoglycaemia.

An association between medication adherence and glycaemic control was reported in 42 studies (Table S3), of which investigated OADs or multiple classes of antidiabetic medications. Better adherence to antidiabetic medication was generally associated with improved glycaemic control. A significantly greater decrease in HbA1c, or a lower HbA1c at follow-up, in more adherent versus less adherent patients was reported by most studies investigating this outcome. The studies also consistently reported a significantly higher likelihood of more adherent patients achieving specific HbA1c targets, such as a ≥1.0% reduction or reduction to <7%, than less adherent patients.

Four studies investigated the association between adherence to antidiabetic medication and risk of hypoglycaemia. Two of these studies investigated OADs (including sulphonylureas) and found no significant association, and two studies investigating multiple antidiabetic medication classes found significantly lower rates of acute complications, including hypoglycaemia, in more versus less adherent patients.
or a trend for better outcomes in persistent than in nonpersistent patients. However, the results were more heterogeneous in the studies investigating combination therapies, with only two studies clearly demonstrating superior glycaemic control in persistent compared with nonpersistent patients. Lin et al. in a study of patients receiving GLP-1RAs and basal insulin, also reported that medication persistence was linked to lower rates of hypoglycaemia. Figure 1 summarizes the findings from studies investigating the association between adherence or persistence and change in HbA1c.

**FIGURE 1** Change in HbA1c level from baseline by A, adherence to and B, persistence with antidiabetic medication in studies reporting this outcome. Bars with an asterisk indicate statistically significant results for adherent/persistent versus nonadherent/nonpersistent patients (P < 0.05). Min et al. and Reynolds et al. did not report P values for adherent versus nonadherent patients. Eliasson et al. and Melzer-Cohen et al. did not report P values for persistent versus nonpersistent patients. For adherence, studies were included if they reported change in HbA1c (follow-up times varied, as indicated for each study); for persistence, studies were included if they reported change in HbA1c over 6, 12 or 24 months. *Data shown are means, except for Min et al. which are median. HbA1c, glycated haemoglobin.
| Study                      | Country, design         | Treatment                                                                 | Number of patients | Follow-up | Statistically significant associations | No significant associations found |
|----------------------------|-------------------------|---------------------------------------------------------------------------|--------------------|-----------|----------------------------------------|----------------------------------|
| **Adherence**              |                         |                                                                          |                    |           |                                        |                                   |
| An and Nichol             | United States, retrospective | OADs (biguanides, SUs, TZDs and/or insulin-sensitizing agents) and hypertension medication | 2334               | 33 months | Any microvascular outcome (from renal failure and diabetic retinopathy) | Any macrovascular outcome (from MI and stroke) |
| Fukuda and Mizobe        | Japan, retrospective     | NR                                                                       | 11 331             | 96 months | Retinopathy                             | IHD Cerebrovascular disease Chronic arterial occlusion |
| Gatwood et al            | United States, retrospective | OADs (not specified)                                                     | 159 032            | 5 years   | Retinopathy Stroke                      | Neuropathy TIA Angina |
| Gibson et al             | United States, retrospective | SU, meglitinides, biguanides, TZDs or AGIs                             | 55 356             | 18 months | Amputations/ulcers Renal events Neuruphagy Retinopathy | MI PVD Cerebrovascular disease |
| Kim et al                | Korea, retrospective     | Biguanide, SUs and others                                                | 65 067             | 10 years  | Retinopathy                             | Cerebrovascular disease NR MI |
| Samu et al               | India, prospective      | NR                                                                       | 86                 | 3 months  | Neuropathy (diabetic foot)              | NR MI |
| Sattler et al            | United States, prospective | OADs (not specified)                                                     | 243                | 12 months | Rate of “no (microvascular or macrovascular) complication” was higher in adherent than nonadherent patients | PVD Nephropathy Neuruphagy Cerebrovascular complications Cardiovascular complications |
| Simpson et al            | United States, retrospective | OADs (not specified)                                                     | 54 505             | 2.3 years (mean) | Any macrovascular outcome (from MI, stroke, heart failure, angina, CABG and angioplasty) | Any microvascular outcome (nephropathy, neuruphagy, PVD or retinopathy) |
| Yu et al                 | United States, retrospective | Insulin and/or OADs                                                      | 4708               | 12-90 months | Any microvascular outcome (from diabetic foot, neuropathy, retinopathy and nephropathy) | NR NR NR |
3.5.2 | Microvascular and macrovascular outcomes

Nine studies investigated the associations between adherence to antidiabetic medications and microvascular and/or macrovascular outcomes.\textsuperscript{22,46,48,50,63,97-99} Five of these examined OADs\textsuperscript{48,50,63,98,99} medication class was mixed or not specified in the remaining studies.\textsuperscript{22,46,97,108} Most studies were retrospective, and four of these studies had >54 000 participants.\textsuperscript{48,50,63,99} The two prospective studies were small, with <250 patients each.\textsuperscript{97,98} Follow-up ranged from 3 months\textsuperscript{97} to 10 years,\textsuperscript{63} and was ≥ 5 years in four studies.\textsuperscript{46,48,63,108}

The microvascular outcomes examined included peripheral vascular disease, retinopathy, nephropathy, renal events, neuropathy and amputations/ulcers. The macrovascular outcomes included cerebrovascular disease, stroke, transient ischaemic attack, ischaemic heart disease, myocardial infarction and angina (Table 2). Six studies examined both microvascular and macrovascular outcomes.\textsuperscript{22,46,48,50,98,99}

In general, adherence to antidiabetic medication was associated with lower rates of both microvascular and macrovascular complications compared with nonadherence, but there was substantial heterogeneity across the study results (Table 2). For example, the four largest studies, all of which assessed adherence to OADs, found that adherent patients have significantly lower rates of some outcomes but not others, with no consensus on which outcome category (microvascular or macrovascular) was significantly linked to adherence.\textsuperscript{48,50,63,99} The medications that patients received were not fully reported in each study, and therefore no inferences between outcomes and medication class can be made using these data.

Two large US studies that examined the association between persistence and microvascular and macrovascular outcomes were identified (Table 2). Iglay et al\textsuperscript{58} included 104 082 patients followed up for 1 year and found lower rates in persistent versus nonpersistent patients for all cardiovascular, cerebrovascular and peripheral vascular outcomes examined. Kalirai et al\textsuperscript{61} studied 23 645 patients and reported significantly lower rates of nephropathy and neuropathy after insulin initiation in persistent versus nonpersistent patients, but no significant difference in the rates of retinopathy, cardiovascular disease (CVD) or cerebrovascular disease.\textsuperscript{61}

3.5.3 | Hospitalizations

The association between medication adherence and rates of hospitalization was reported in 18 studies, for patients receiving insulin,\textsuperscript{26,88} OADs\textsuperscript{33,48,54,55,71,73} injectable GLP-1RAs\textsuperscript{63} or multiple treatment classes,\textsuperscript{28,34,36,47,50,101} or with treatment not specified.\textsuperscript{93,100} The specific outcomes investigated included hospital inpatient admissions, emergency department (ED) visits and admissions, and outpatient visits. Follow-up duration ranged from 6 months to 7 years, with a median of 3 years. Most studies included >5000 patients; six studies had >90 000 patients (Table S4).\textsuperscript{28,34,48,50,100,101}

Patients who were more adherent to antidiabetic medications were generally less likely to be hospitalized (and/or were less likely to
have ED visits or admissions, or spent fewer days in hospital annually) than less adherent patients in the majority of studies across all treatment classes (Table S4). The association between adherence and outpatient visits was more complex. Some studies found no significant association between adherence and outpatient visits, whereas others found that adherence...
was linked to having more outpatient visits (Table S4). Among the latter studies, two were designed to investigate whether the rate of outpatient visits influenced adherence, and concluded that more frequent outpatient visits led to better adherence to antidiabetic medication; however, these studies did not report rates of hospitalization or other interactions with the healthcare system. The third study reported that greater adherence was linked to more outpatient visits, but fewer ED visits and hospitalizations.

Eleven studies reported data on the association between persistence and the rate of hospitalization (including ED visits and/or ED admissions) in patients receiving insulin, injectable GLP-1RAs, OADs or combination therapy. Follow-up duration ranged from 6 months to 3 years, and sample sizes ranged from 534 to 23,645 patients (Table S5). Interruption or discontinuation of therapy was associated with an increased rate of hospitalization and longer hospital stays in most studies, but not in all studies. However, four of the five studies that reported data on outpatient visits found no significant association with persistence (Table S5).

3.5.4 Healthcare costs

Associations between adherence and healthcare costs in people with T2D were reported in 20 studies that investigated OADs, insulin, injectable GLP-1RAs or multiple treatment classes, or that did not specify the treatment. Thirteen studies were from the United States, with the remaining studies from Canada, Italy, Japan, Korea and Taiwan. Seven studies had a follow-up duration of ≤1 year and nine studies had ≥3 years’ follow-up. Sample size varied widely, from 301 to 7,982 million patients, with a median of 17,982 patients.

Despite substantial heterogeneity across studies, greater adherence was generally associated with lower inpatient admission costs but higher pharmacy costs. Most studies found that total healthcare expenditure in adherent patients was lower than or similar to that in non-adherent patients (Figure 2), but in two studies adherence was associated with higher total costs than nonadherence.

In total, 11 studies reported data on healthcare costs associated with persistence on insulin, injectable GLP-1RAs and/or combination therapies. The study duration was relatively short for studying persistence: 6 months or 12 months in most studies and 24 months in two studies. Persistence was typically associated with higher pharmacy costs but lower healthcare costs, including acute care costs, inpatient and outpatient visits and ED visits. Overall, total healthcare expenditure for persistent patients across studies was typically lower than or similar to that for nonpersistent patients (Figure 2).

4 DISCUSSION

Observational studies are recognized by payers and other stakeholders as an important means of obtaining data on medication-taking behaviour, which cannot be assessed in clinical trials. We reviewed the available evidence from observational studies on adherence to and persistence with antidiabetic medication in people with T2D, and how these relate to clinical and economic outcomes. Despite heterogeneity across studies in terms of antidiabetic medications used, length of follow-up, geography, patients’ clinical and demographic characteristics and the specific outcomes examined, some findings were consistent. Overall rates of adherence and persistence in people with T2D are suboptimal, as previously reported, but better adherence and persistence are associated with clinical benefits, including improved glycaemic control, fewer hospitalizations and ED visits, and lower incidences of microvascular and macrovascular complications. Adherence and persistence were linked to lower rates of some microvascular and/or macrovascular outcomes but not others, which may be attributable in part to disparities in medications used, study setting and design. Overall, several outcomes that predict disability and absenteeism in people with T2D, including myocardial infarction, stroke, peripheral neuropathy, retinopathy and diabetic foot, were associated with worse adherence and/or persistence in at least some of the studies identified in this review, highlighting the relevance of these outcomes in treatment decision-making.

As a chronic condition affecting multiple organ systems, T2D is associated with substantial and rising healthcare costs. The International Diabetes Federation estimates that the worldwide health expenditure due to diabetes in adults has increased threefold in the past 15 years, from $232 billion in 2007 to $760 billion in 2019, of which 50% is attributable to managing diabetes complications; therefore, the influence of adherence and persistence on healthcare costs in T2D is a pertinent area for study. In the present SLR, we found an association between better adherence and persistence and either lower or similar total healthcare costs, compared with worse adherence and persistence. Cost estimates varied widely across the studies identified, which was likely to be owing to disparities in study variables and location. Generally, both adherence and persistence were associated with higher pharmacy costs that were offset by lower hospitalization costs, resulting in lower or budget-neutral total healthcare expenditure for adherent/persistent patients. An association between adherence and reduced total health expenditure has been reported for several other chronic conditions. Notably, more than two-thirds of the studies reporting cost data were from North America, and most of the remainder were from Asia, with only one study from a European country (Italy). Further evidence is therefore needed, in particular from Europe, on the associations between adherence and persistence and healthcare costs.

This was a large SLR, including studies from all geographical regions and examining a broad range of outcomes. Although the outcomes examined are not independent from each other—for example, reduced rates of complications result in lower healthcare costs—this is
nonetheless a comprehensive overview of the impact of adherence and persistence. Further SLRs could be used to capture additional outcomes linked to suboptimal adherence and persistence; previous studies have reported increased absenteeism, more days of short-term disability and greater mortality. Although most studies reported the antidiabetic medication class used, discrepancies across studies in patient characteristics, study methodology and duration did not enable direct comparisons to be made between medication classes for any of the outcomes. Approximately half of the studies identified in the SLR were published between 2010 and 2015, meaning that more recently approved antidiabetic medications were not included in most of these studies. Further good-quality observational studies are needed to systematically compare adherence and persistence across different drug classes and drugs with different modes and frequency of administration and different treatment benefits for complications such as CVD.

Several limitations of the studies identified in this review should be noted, particularly the fact that many were retrospective analyses using healthcare and claims databases. Such studies are inherently vulnerable to the effects of confounding, whereby certain factors, such as education, lifestyle and other sociodemographic variables, could influence both adherence to medication and health outcomes. Inertia in treatment decision-making may also confound the relationship between medication-taking behaviour and outcomes: adherence to or persistence with antidiabetic medication that has not been optimized is unlikely to be reflected in clinical benefit. Furthermore, PDC and MPR are useful proxies for adherence, but may not always accurately reflect actual medication-taking behaviour. Finally, although comparing different antidiabetic medication classes is of great clinical interest, the substantial inter-study heterogeneity in patient characteristics and methods used to estimate adherence/persistence in this SLR did not enable meaningful comparisons across drug classes.

The present SLR highlights the benefits that can be achieved by using therapeutic approaches that improve adherence and persistence as well as clinical outcomes. Across various diseases, higher compliance, a close correlate of adherence, has been reported for dosing regimens that require less frequent administration. To illustrate, a study included in this SLR examining two populations receiving GLP-1RAs in Germany and the United Kingdom found that twice-daily exenatide was associated with a 30% to 40% greater likelihood of treatment discontinuation than once-daily liraglutide. Furthermore, a recent meta-analysis of seven studies investigating 75 159 people with T2D reported an 11% lower risk of nonadherence with once-weekly versus once-daily injectable GLP-1RAs. Persistence is also favourably influenced by less frequent dosing regimens: in a real-world, United States-based study, the use of once-weekly injectable GLP-1RAs was associated with better persistence and adherence than daily regimens in propensity score-matched cohorts. Evidence from populations with other chronic diseases such as osteoporosis and CVD also indicates that lower dosing frequency predicts better adherence and/or persistence. The use of medications early in the treatment pathway that are linked to symptomatic benefit in addition to adherence and persistence may provide an ongoing positive effect on health outcomes; however, to achieve sustained improvements, the use of treatment regimens that enhance adherence and persistence should also be considered as part of wider, holistic treatment strategies for people with T2D. As indicated by the studies identified in this review, many of which were carried out in primary care databases, routine management of patients with T2D is increasingly delivered in a primary care setting. Consequently, it is vital that primary care physicians receive education in strategies to maximize adherence and persistence, in communicating the benefits of this to patients, and in understanding and addressing reasons for poor adherence or persistence. Other approaches to maximizing the likelihood of adherence and persistence that may be applicable in primary care include the use of personalized digital technologies.

In this SLR of studies published between 2010 and 2020, greater adherence to and persistence with antidiabetic medication in adults with T2D was typically associated with better clinical and economic outcomes. These findings suggest that the clinical benefits of adherence and persistence for patients are likely to be reflected in positive impacts for payers, healthcare systems and society. Further investigation of the factors that determine medication-taking behaviour should be used to identify barriers to optimal adherence and persistence in people with T2D.

ACKNOWLEDGMENTS
The development of this SLR was carried out by Mtech Access, Bicester, UK, funded by Novo Nordisk A/S. The authors acknowledge the medical writing support of Oxford PharmaGenesis, Oxford, UK, funded by Novo Nordisk A/S.

CONFLICT OF INTEREST
M.E. has received honoraria from AstraZeneca, Boehringer Ingelheim and Novo Nordisk. S.E. and M.F. are employees of Novo Nordisk A/S. J.F. was an employee of Novo Nordisk A/S at the time of the review, and is now an employee of Ferring Pharmaceuticals A/S. P.H. is an employee of Mtech Access, funded by Novo Nordisk A/S to carry out the SLR. W.P. has served as a consultant for Eli Lilly, Novo Nordisk and Sanofi.

AUTHOR CONTRIBUTIONS
Mads Faarby, João Diogo Da Rocha Fernandes and Pollyanna Hudson: designed the SLR. All authors contributed to the interpretation of data and critical review of the manuscript and approved the final version for submission.

PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14603.

DATA AVAILABILITY STATEMENT
‘All data analyzed during this systematic literature review are published elsewhere, and relevant collated data are included in this article.
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