Therapeutic Inertia: Still a Long Way to Go That Cannot Be Postponed

Manel Mata-Cases,[1,2,3]* Josep Franch-Nadal,[1,2,4]* Mònica Gratacòs,[1] and Dídac Mauricio[1,2,5]

[1]DAP-Cat Group, Unitat de Suport a la Recerca Barcelona, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain; [2]CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain; [3]Primary Health Care Center La Mina, Gerència d'Àmbit d'Atenció Primària Barcelona Ciutat, Institut Català de la Salut, Sant Adrià de Besòs, Spain; [4]Primary Health Care Center Raval Sud, Gerència d'Atenció Primaria, Institut Català de la Salut, Barcelona, Spain; [5]Department of Endocrinology and Nutrition, Hospital Universitari de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Barcelona, Spain

In the context of type 2 diabetes, the definition of therapeutic inertia should include the failure not only to intensify therapy, but also to deintensify treatment when appropriate and should be distinguished from appropriate inaction in cases justified by particular circumstances. Therapy should be intensified when glycemic control deteriorates to prevent long periods of hyperglycemia, which increase the risk of complications. Strategic plans to overcome therapeutic inertia must include actions focused on patients, prescribers, health systems, and payers. Therapeutic inertia affects the management of glycemia, hypertension, and lipid disorders, all of which increase the risk for cardiovascular diseases. Thus, multifactorial interventions that act on additional therapeutic goals beyond glycemia are needed.

Clinical or Therapeutic Inertia? When Semantics Matter

Questions remain as to whether the lack of or delay in treatment intensification for patients not reaching therapeutic targets represents true inappropriate care or whether it is an acceptable decision to prevent the risks of overtreatment. The latter has been termed "appropriate inaction"—in opposition to "inappropriate inertia"—and is considered to be a factor contributing to the low treatment intensification rates observed in clinical practice (1,2). In type 2 diabetes, where clinical guidelines advocate a patient-centered approach (3–5), appropriate inaction could be exemplified by providers' decisions regarding complex patients (e.g., the elderly or individuals with impaired awareness of hypoglycemia) who are either near their goal or for whom the "best" blood glucose level has already been achieved at a particular intensification step (e.g., the elderly, those for whom polypharmacy is an issue, and individuals with comorbidities). Despite being widely accepted as a source of confusion when quantifying inertia, appropriate inaction is an aspect rarely assessed in clinical studies (6). Additionally, some authors postulate that therapeutic inertia should also include the failure to withhold or reduce therapy when further prescription is not needed or not supported by evidence, a circumstance termed "therapeutic momentum," or "reverse clinical inertia" (7–9).

Within this broader definition of therapeutic inertia, the failure to advance treatment results in failure to achieve a goal and may have both short- and long-term consequences (e.g., missed opportunities to prevent complications at early stages or increased risk of end-stage micro- and macrovascular complications) (10). Conversely, the failure to deintensify therapy, albeit largely neglected in therapeutic guidelines (11,12), raises safety concerns and may contribute to overtreatment and in turn to avoidable direct and indirect health care costs. For example, overmedication to achieve tight glycemic levels could be detrimental in older patients, particularly those with complications and serious comorbidities, because of their high likelihood of severe hypoglycemia. Such episodes in the elderly have implications for both short-term (e.g., risk of falls, accidents, hospitalizations, and death) and long-term (e.g., lower quality of life, decreased cognitive function, and increased risk of cardiovascular [CV] mortality) negative outcomes (13,14).

Outcomes of Sustained Glycemic Targets and Why Intensification Is Important

Persistent elevated glycemic levels remain a major public health problem, with about 40–60% of patients worldwide not at A1C goal (15,16). In the United States, recent data

Corresponding author: Dídac Mauricio, didacmauricio@gmail.com

*M.M.-C. and J.F.-N. contributed equally to this work.

https://doi.org/10.2337/ds19-0018

showed that 36% of patients with diabetes are not able to achieve individualized targets, and up to 16% have an A1C >9% (17).

Several long-term studies have shown that intensifying therapy at the first sign of deteriorating glycemic levels may be crucially important. In people with newly diagnosed type 2 diabetes, the U.K. Prospective Diabetes Study showed that early intensive glycemic management (i.e., mean A1C ≤7%) had long-lasting benefits; when A1C values converged between subjects on conventional therapy and subjects on intensive therapy 10 years after the completion of the trial, those who received intensive therapy still showed persisting reductions in microvascular events, CV events, and mortality (18,19). This phenomenon was called the "legacy effect" (18,19) and had been previously observed in patients with type 1 diabetes on intensive therapy after 6.5 years of follow-up in the Diabetes Control and Complications Trial and was termed "metabolic memory" (20–22). Of note, the legacy effect has also been reported in a recent real-world study in people with newly diagnosed type 2 diabetes (23).

However, in high-risk patients (i.e., those with either established CV disease [CVD] or additional CV risk factors) with a long duration of type 2 diabetes, two large independent trials (ACCORD [Action to Control Cardiovascular Risk in Diabetes] and ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation]) reported that the risk of CV events was similar between those on 5 years of intensive therapy and those on conventional therapy, although intensive therapy prevented microvascular complications (24,25). Of note, the intensive blood glucose–lowering treatment arm of the ACCORD trial was terminated early because of increased CV mortality among participants in this group compared with those in the standard treatment arm after an average of 4 years of treatment, although the reasons for this higher risk remain unclear (26). Finally, a meta-analysis corroborated that this beneficial effect was not detectable regarding CVD rates in patients with a long duration of diabetes (27).

Therapeutic inertia is a barrier to effective treatment intensification and a common and widespread problem; it typically affects the care of 30–50% of people with uncontrolled type 2 diabetes worldwide (15) and even up to 30% of individuals with personalized A1C goals (28). The lack of or delay in intensification results in the accumulation of several years of hyperglycemia before treatment is intensified (i.e., "avoidable glycemic burden"), which has been documented at every stage in the natural history of type 2 diabetes (29–31). For example, as shown in Figure 1, if we sum up delays from all treatment steps, patients may spend up to 10 years with an A1C >7% and about 10 years with an A1C >8% from diagnosis until starting insulin (29–31). Moreover, in the 12 months after the A1C level rises above a target threshold, the proportion of patients receiving intensification is in most cases <50% (29). As a result, the median time patients spend above their target A1C level is unnecessarily long, in many cases over several years, increasing in parallel with the number of oral antidiabetic drugs (OADs) added and decreasing as the A1C level increases. In summary, failure to intensify treatment

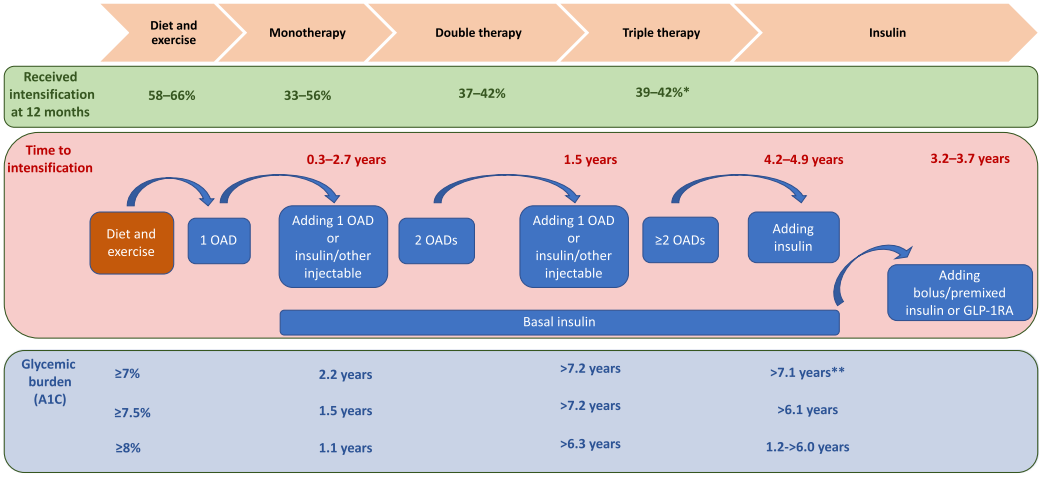

FIGURE 1 Schematic of therapeutic inertia showing the proportion of patients above target receiving intensification within 12 months (in green); the median time to intensification from the time at which the A1C level is above the threshold (in red); and the glycemic burden (i.e., the length of time with A1C level above target [≥7, 7.5, or 8%]) during a given period of time (in blue) (29). *Estimated in patients with two OADs and three OADs after 14 months. **Estimated in patients with three OADs. GLP-1RA, glucagon-like peptide 1 receptor agonist.

leads to avoidable delays, which in turn result in increased "bad" metabolic memory or dysglycemic legacy from excessively long periods of hyperglycemia, eventually increasing the risk of micro- and macrovascular diabetes-related complications (32,33).

The Need for Multifaceted Implementation Strategies to Overcome Therapeutic Inertia

There is a growing interest in implementing active measures to promote the timely escalation of treatment for patients with type 2 diabetes (34–36). Primary Care Diabetes Europe in 2018 issued a call to action against inertia (37). Similarly, the American Diabetes Association recently launched a new initiative focused on overcoming therapeutic inertia (38).

What is indisputable is that strategic plans to overcome therapeutic inertia must be comprehensive and fully multifaceted, including actions focused on patients, prescribers, health systems, and payers (39–42). Approaches at these different levels and available evidence of their implementation in diabetes are summarized in Table 1.

Briefly, providers require education to achieve sound knowledge on all aspects of the disease (e.g., modifiable risk factors, natural history, and proper management through clinical guidelines) and also need to continue medical education throughout their professional life. Moreover, they may benefit from the use of telemedicine, electronic medical records, and computerized reminders (e.g., providing patient-specific recommendations or information on target attainment). The use of protocols and titration algorithms to overcome decision uncertainty is also helpful to facilitate the choice of the simplest or most tolerable available treatment. In addition, providers may increase their motivation through feedback from other health care professionals (e.g., regular visit reviews with an endocrinologist to analyze decisions if in primary care, collaboration with pharmacists, and assistance from nurses). Finally, providers must consider clinical factors together with patient preferences to mutually agree with patients on the most adequate treatment (i.e., shared treatment decision-making).

From their side, patients need to be educated in self-care behaviors through educational programs, and their emotional status and psychosocial issues (e.g., diabetes-related distress) have to be taken into consideration to improve their quality of life.

From the health authority perspective, therapeutic inertia can be tackled through initiatives to motivate providers to improve their practice (e.g., financial incentives) and through the implementation of coordinated health care plans and disease management programs aligned with policy initiatives to increase the patient-centered management of diabetes.

Last but not least, there is a need to tackle out-of-pocket costs and financial barriers to decreasing drug costs and providing covered treatment for all patients. This aspect is particularly important in countries or regions in which there is partial medication coverage or reimbursement (e.g., copayment or coinsurance) or where administrative restrictions to specific glucose-lowering drugs apply (e.g., negative economic incentives for physicians when prescribing the newest and more expensive drugs).

The Need to Move Beyond a Glycemic-Centered View of Therapeutic Inertia in Diabetes

Therapeutic inertia is not only a barrier to the appropriate management of glycemia, but is also present in the treatment of other conditions involved in the risk for CVD. Indeed, therapeutic inertia in the management of hypertension and LDL cholesterol in patients with diabetes has been estimated to occur in 68 and 80% of clinical practice consultations, respectively (43). As a result, it has been estimated that therapeutic inertia related to the management of diabetes, hypertension, and lipid disorders may contribute to up to 80% of heart attacks and strokes (44). This situation is worrisome if we take into account the corresponding legacy effect through the reported persistent benefits of early and intensive blood pressure and lipid-lowering therapies in lowering all-cause mortality and death due to CVD (45–50).

As recently reviewed (51), there is evidence of the long-term benefit of lowering multiple risk factors. The Danish Steno-2 trial randomized patients with type 2 diabetes and albuminuria to intensified multifactorial intervention targeting known modifiable risk factors with individualized lifestyle interventions and tailored polypharmacy (i.e., strict glycemic, lipid, and blood pressure targets and the use of ACE inhibitors and aspirin). Compared with subjects with targets based on the Danish national standards of care, those on intensified multifactorial interventions had a reduction in the risk of microvascular complications of ~50% after 4 years of intervention (52), a 53% reduction in CV end points after 8 years of intervention (53), a 46% reduction in total mortality at 13 years of follow-up (54), and a reduction in overall and CV mortality and a reduced risk of hospitalization for heart failure by 70% 21 years after trial initiation (55). Moreover, the benefits of multitargeted intervention have also been reported recently in Chinese primary care patients with type 2 diabetes (56). Of note, achieving a greater number of targets (i.e., glycemia, blood pressure, and LDL cholesterol) incrementally reduced the risk of CV outcomes, and the benefit seemed to be greatest

TABLE 1 Potentially Useful Approaches to Overcome Therapeutic Inertia in Type 2 Diabetes

Approach	What to Do	Evidence/Examples
Provider education	Enhance providers' medical knowledge on diabetes and its treatment, including: • The natural history of the disease, from correcting modifiable risk factors to drug treatment and further need for titration • The evidence coming from guidelines • How to use clinical guidelines • The reasons behind therapeutic decisions and appropriate selection of medications • The appropriateness of guidelines for each particular patient • The phenomenon of lack of patient engagement and therapeutic inertia	Redesign professional health education to adapt professional competencies to specific contexts (58) (e.g., teaching about ethics and social science as part of the undergraduate/graduate medical curriculum to convince providers of the benefit of applying rules of best practice and of their importance as health care providers (41).
	Promote continuing medical education throughout professional life.	Educational meetings and interactive workshops improve professional practice and health care outcomes for patients (59,60). Simulated case-management interventions have also been shown to improve the diabetes management skills, knowledge, and confidence of primary care residents (61).
	Use reminders (e.g., in the form of an electronic spreadsheet) and feedback systems (e.g., regarding patients' treatment target attainment).	Reminders and feedback have been shown to improve physicians' use of clinical practice guidelines and ability to overcome therapeutic inertia in diabetes and hypertension (62).
Facilitation	Simplify treatments and/or use medications with fewer side effects.	Complex treatments lower patient engagement (63), and fear of side effects can lead to less medication taken and to providers' therapeutic inertia. The use of medications with fewer side effects or using combined forms of medications may reduce therapeutic inertia and improve treatment success (64,65). The use of improved insulin delivery devices helps to reduce patient nonadherence (66).
	Use protocols and algorithms to reduce decision uncertainty.	Giving simple algorithms of titration to providers has a positive effect on treatment intensification and improves glucose and blood pressure levels (67). The use of computer-assisted decision support in primary care is effective in improving the management of type 2 diabetes (68).
	Use electronic medical records.	The use of electronic medical records and implementation of electronic reminders help in monitoring patients and have a positive effect on quality of diabetes care (69–73).
	Implement disease management programs.	Disease management programs or structured treatment plans help patients better manage their disease and maintain and improve quality of life (e.g., including medication and other treatments, training courses, and regular checkups). Implementation of disease management programs in diabetes has shown improvements in glycemic levels, screening rates, and engagement (74–76).
	Establish coordinated health care plans aligned with policy initiatives to increase the accountability and patient-centeredness of disease management.	Disease management at the population level has significant potential for improving diabetes care and outcomes, but published evaluations of specific diabetes population care approaches are scarce (77,78).

CONTINUED ON P. 54 ›

‹ CONTINUED FROM P. 53

TABLE 1 Potentially Useful Approaches to Overcome Therapeutic Inertia in Type 2 Diabetes

Approach	What to Do	Evidence/Examples
	Overcome providers' lack of time through health information technologies (telemedicine).	Compared with standard care, the addition of health information technologies, and in particular mobile phone–based approaches and systems that allow medication adjustments, is an effective tool for glycemic management among people with type 2 diabetes (79,80).
	Increase sharing of patient data among health care professionals.	Improved access to patient data among health care professionals, combined with data-sharing agreements, may facilitate timely intensification by primary care providers and therefore improved glycemic levels in type 2 diabetes (81).
Reinforcement of health professionals	Provide incentives from health authorities (i.e., pay-for-performance models) to motivate providers to improve their practices.	There is evidence of improvement in achieving A1C targets using financial incentives to primary care physicians in the United Kingdom, although the evidence is limited in other countries and the effect is variable (82,83). In the United States, financial incentives improved glucose monitoring during the incentive period but did not significantly improve glycemic levels among adolescents and young adults with type 1 diabetes (84).
	Provide incentives from peers.	Communication and collaboration between diabetologists and primary care providers is important to overcome therapeutic inertia (85). Concurrent visit reviews with peers have been shown to increase intensification rates (86).
	Provide incentives by other health care professionals (e.g., pharmacists and nurses)	A study in the Netherlands showed that therapeutic inertia was less frequent when physicians were assisted by a nurse (87). Collaboration between physicians and pharmacists has been shown to decrease clinical inertia scores for blood pressure treatment (88).
Reinforcement of patients	Develop shared treatment decision-making between providers and patients in a patient-centered approach.	Shared decision-making in type 2 diabetes has been reported to improve engagement with health care recommendations and glycemic levels (89,90).
	Encourage patients through structured self-management education (e.g., on side effects, managing injections, and insulin dose adjustments).	Providing patients with the ability and skills necessary for proper diabetes management determines treatment satisfaction and is effective at improving aspects of diabetes care (91,92). Remote type 2 diabetes care (nurse-led online management program) can facilitate glycemic control compared with usual care (93).
	Remove financial barriers and reduce patients' out-of-pocket costs.	High out-of-pocket costs are a barrier to self-management and result in increased likelihood of elevated glycemic levels and intermediate outcomes and lower engagement with regard to diabetes medications (94).
	Address psychosocial issues.	Increasing patients' perceptions about their own abilities and self-efficacy is an important factor related to improved diabetes self-management and treatment outcomes (94). Psychological barriers such as inadequate family or social support, misinformation or inaccurate beliefs about illness and treatment, emotional distress or depression symptoms, or deficits in problem-solving or coping skills are associated with lower adherence to diabetes medications (95). Intensive psychosocial interventions are associated with significant reductions in both diabetes distress and A1C in patients with elevated glucose levels and at least one risk factor for poor outcomes (96).

among subjects at early disease stages (56,57). Given these results, it seems clear that, while overcoming therapeutic inertia with regard to managing glycemic levels is essential, there is also a true need to act on additional therapeutic goals to prevent long-term complications of diabetes.

Conclusion

The concept of therapeutic inertia should be reviewed and further studied through the distinction of the appropriateness of the therapeutic decision, namely appropriate inaction versus inappropriate inertia, the latter including both the failure to advance and to deintensify therapy. This approach would allow the accurate assessment of overtreatment in patients for whom harm is likely to outweigh benefit (e.g., vulnerable and frail populations).

Moreover, there is a need to raise awareness that therapeutic inertia regarding glycemic management and other risk factors (e.g., hypertension and dyslipidemia) has a deleterious effect in long-term CV outcomes and that these risk factors have to be tackled early in the course of the disease. In a patient-centered approach to diabetes management, it is key that providers, in particular those in general practice, pay attention to therapeutic inertia from a global perspective and provide integrated multifactorial treatment. This approach entails actions not only focused on physicians' attitudes and actions, but also necessarily includes involving other health professionals (e.g., nurses, psychologists, and pharmacists); promoting patient education, self-management, and well-being; and calling on health systems to implement effective policies that have a direct impact on the unmet needs of patients with diabetes.

ACKNOWLEDGMENTS

CIBER of Diabetes and Associated Metabolic Diseases (CIBERDEM) is an initiative from the Instituto de Salud Carlos III in Madrid, Spain. The authors acknowledge Amanda Prowse for providing support in the manuscript editing.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

All of the authors researched data, wrote the manuscript, contributed to discussion, and reviewed and edited the manuscript. D.M. is the guarantor of this work and, as such, had full access to the content and takes responsibility for the accuracy of the data.

REFERENCES

1. Safford MM, Shewchuk R, Qu H, et al. Reasons for not intensifying medications: differentiating "clinical inertia" from appropriate care. J Gen Intern Med 2007;22:1648–1655
2. Lebeau JP, Biogeau J, Carré M, et al. Consensus study to define appropriate inaction and inappropriate inertia in the management of patients with hypertension in primary care. BMJ Open 2018;8: e020599
3. American Diabetes Association. Introduction: *Standards of Medical Care in Diabetes—2019*. Diabetes Care 2019;42(Suppl. 1):S1–S2
4. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2018 executive summary. Endocr Pract 2018;24:91–120
5. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–149
6. Seidu S, Than T, Kar D, et al. Therapeutic inertia amongst general practitioners with interest in diabetes. Prim Care Diabetes 2018; 12:87–91
7. Rodrigo C, Amarasuriya M, Wickramasinghe S, Constantine GR. Therapeutic momentum: a concept opposite to therapeutic inertia. Int J Clin Pract 2013;67:97–98
8. Giugliano D, Esposito K. Clinical inertia as a clinical safeguard. JAMA 2011;305:1591–1592
9. Khunti K, Davies MJ. Clinical inertia: time to reappraise the terminology? Prim Care Diabetes 2017;11:105–106
10. Mohan V. Expanding the concept of clinical inertia in diabetes. Journal of Diabetology 2019;10:1–3
11. Khunti K, Davies MJ. Clinical inertia versus overtreatment in glycaemic management. Lancet Diabetes Endocrinol 2018;6:266–268
12. Giugliano D, Maiorino MI, Bellastella G, Esposito K. Clinical inertia, reverse clinical inertia, and medication non-adherence in type 2 diabetes. J Endocrinol Invest 2019;42:495–503
13. Müller N, Khunti K, Kuss O, et al. Is there evidence of potential overtreatment of glycaemia in elderly people with type 2 diabetes? Data from the GUIDANCE study. Acta Diabetol 2017;54:209–214
14. Seidu S, Kunutsor SK, Topsever P, Hambling CE, Cos FX, Khunti K. Deintensification in older patients with type 2 diabetes: a systematic review of approaches, rates and outcomes. Diabetes Obes Metab 2019;21:1668–1679
15. Blonde L, Meneghini L, Peng XV, et al. Probability of achieving glycemic control with basal insulin in patients with type 2 diabetes in real-world practice in the USA. Diabetes Ther 2018;9:1347–1358
16. Stone MA, Charpentier G, Doggen K, et al.; GUIDANCE Study Group. Quality of care of people with type 2 diabetes in eight European countries: findings from the Guideline Adherence to Enhance Care (GUIDANCE) study. Diabetes Care 2013;36:2628–2638
17. Carls G, Huynh J, Tuttle E, Yee J, Edelman SV. Achievement of glycated hemoglobin goals in the US remains unchanged through 2014. Diabetes Ther 2017;8:863–873
18. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
19. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med 2008;359:1565–1576
20. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. JAMA 2003;290: 2159–2167
21. Nathan DM, Cleary PA, Backlund JY, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–2653

22. White NH, Sun W, Cleary PA, et al. Prolonged effect of intensive therapy on the risk of retinopathy complications in patients with type 1 diabetes mellitus: 10 years after the Diabetes Control and Complications Trial. Arch Ophthalmol 2008;126:1707–1715
23. Laiteerapong N, Ham SA, Gao Y, et al. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (the Diabetes & Aging Study). Diabetes Care 2019;42:416–426
24. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
25. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
26. Genuth S, Ismail-Beigi F. Clinical implications of the ACCORD trial. J Clin Endocrinol Metab 2012;97:41–48
27. Zhang X, Liu Y, Zhang F, Li J, Tong N. Legacy effect of intensive blood glucose control on cardiovascular outcomes in patients with type 2 diabetes and very high risk or secondary prevention of cardiovascular disease: a meta-analysis of randomized controlled trials. Clin Ther 2018;40:776–788.e3
28. Lin J, Zhou S, Wei W, Pan C, Lingohr-Smith M, Levin P. Does clinical inertia vary by personalized A1c goal? A study of predictors and prevalence of clinical inertia in a U.S. managed-care setting. Endocr Pract 2016;22:151–161
29. Khunti K, Gomes MB, Pocock S, et al. Therapeutic inertia in the treatment of hyperglycaemia in patients with type 2 diabetes: a systematic review. Diabetes Obes Metab 2018;20:427–437
30. Reach G, Pechtner V, Gentilella R, Corcos A, Ceriello A. Clinical inertia and its impact on treatment intensification in people with type 2 diabetes mellitus. Diabetes Metab 2017;43:501–511
31. Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. Diabetes Care 2004;27:1535–1540
32. Paul SK, Klein K, Thorsted BL, Wolden ML, Khunti K. Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes. Cardiovasc Diabetol 2015;14:100
33. Osataphan S, Chalermchai T, Ngaosuwan K. Clinical inertia causing new or progression of diabetic retinopathy in type 2 diabetes: a retrospective cohort study. J Diabetes 2017;9:267–274
34. Phillips LS, Branch WT, Cook CB, et al. Clinical inertia. Ann Intern Med 2001;135:825–834
35. Strain WD, Cos X, Hirst M, et al. Time to do more: addressing clinical inertia in the management of type 2 diabetes mellitus. Diabetes Res Clin Pract 2014;105:302–312
36. Okemah J, Peng J, Quiñones M. Addressing clinical inertia in type 2 diabetes mellitus: a review. Adv Ther 2018;35:1735–1745
37. Primary Care Diabetes Europe. Primary Care Diabetes Europe issues call to action against clinical inertia in the treatment of type-2 diabetes. Available from www.pcdeurope.org/3703-2. Accessed 26 September 2019
38. American Diabetes Association. Overcoming therapeutic inertia. Available from professional.diabetes.org/meeting/other/overcoming-therapeutic-inertia. Accessed 26 September 2019
39. Zafar A, Stone MA, Davies MJ, Khunti K. Acknowledging and allocating responsibility for clinical inertia in the management of type 2 diabetes in primary care: a qualitative study. Diabet Med 2015;32:407–413
40. Russell-Jones D, Pouwer F, Khunti K. Identification of barriers to insulin therapy and approaches to overcoming them. Diabetes Obes Metab 2018;20:488–496
41. Reach G. Overcoming true clinical inertia. In *Clinical Inertia: A Critique of Medical Reason*. Reach G, Ed. Switzerland, Springer International Publishing, 2013, p. 97–119
42. Zafar A, Davies M, Azhar A, Khunti K. Clinical inertia in management of T2DM. Prim Care Diabetes 2010;4:203–207
43. Whitford DL, Al-Anjawi HA, Al-Baharna MM. Impact of clinical inertia on cardiovascular risk factors in patients with diabetes. Prim Care Diabetes 2014;8:133–138
44. Byrnes PD. Why haven't I changed that? Therapeutic inertia in general practice. Aust Fam Physician 2011;40:24–28
45. Volpe M, Cosentino F, Tocci G, Palano F, Paneni F. Antihypertensive therapy in diabetes: the legacy effect and RAAS blockade. Curr Hypertens Rep 2011;13:318–324
46. Kostis WJ, Thijs L, Richart T, Kostis JB, Staessen JA. Persistence of mortality reduction after the end of randomized therapy in clinical trials of blood pressure-lowering medications. Hypertension 2010;56:1060–1068
47. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392–1406
48. Kostis WJ, Moreyra AE, Cheng JQ, Dobrzynski JM, Kostis JB. Continuation of mortality reduction after the end of randomized therapy in clinical trials of lipid-lowering therapy. J Clin Lipidol 2011;5:97–104
49. Sever PS, Chang CL, Gupta AK, Whitehouse A, Poulter NR; ASCOT Investigators. The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow-up of the lipid-lowering arm in the U.K. Eur Heart J 2011;32:2525–2532
50. Ford I, Murray H, McCowan C, Packard CJ. Long-term safety and efficacy of lowering low-density lipoprotein cholesterol with statin therapy: 20-year follow-up of West of Scotland Coronary Prevention Study. Circulation 2016;133:1073–1080
51. Khunti K, Kosiborod M, Ray KK. Legacy benefits of blood glucose, blood pressure and lipid control in individuals with diabetes and cardiovascular disease: time to overcome multifactorial therapeutic inertia? Diabetes Obes Metab 2018;20:1337–1341
52. Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. Lancet 1999;353:617–622
53. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383–393
54. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580–591
55. Oellgaard J, Gæde P, Rossing P, et al. Reduced risk of heart failure with intensified multifactorial intervention in individuals with type 2 diabetes and microalbuminuria: 21 years of follow-up in the randomised Steno-2 study. Diabetologia 2018;61:1724–1733
56. Wan EYF, Fung CSC, Yu EYT, et al. Effect of multifactorial treatment targets and relative importance of hemoglobin A1c, blood pressure, and low-density lipoprotein-cholesterol on cardiovascular diseases in Chinese primary care patients with type 2 diabetes mellitus: a population-based retrospective cohort study. J Am Heart Assoc 2017;6:e006400
57. Wong ND, Zhao Y, Patel R, et al. Cardiovascular risk factor targets and cardiovascular disease event risk in diabetes: a pooling project of the Atherosclerosis Risk in Communities Study, Multi-Ethnic Study of Atherosclerosis, and Jackson Heart Study. Diabetes Care 2016;39:668–676
58. Frenk J, Chen L, Bhutta ZA, et al. Health professionals for a new century: transforming education to strengthen health systems in an interdependent world. Lancet 2010;376:1923–1958
59. Forsetlund L, Bjørndal A, Rashidian A, et al. Continuing education meetings and workshops: effects on professional practice and

health care outcomes. Cochrane Database Syst Rev 2009: CD003030

60. Davis D, Galbraith R; American College of Chest Physicians Health and Science Policy Committee. Continuing medical education effect on practice performance: effectiveness of continuing medical education: American College of Chest Physicians Evidence-Based Educational Guidelines. Chest 2009;135(Suppl.):42S–48S
61. Sperl-Hillen J, O'Connor PJ, Ekstrom HL, et al. Educating resident physicians using virtual case-based simulation improves diabetes management: a randomized controlled trial. Acad Med 2014;89: 1664–1673
62. Lüders S, Schrader J, Schmieder RE, Smolka W, Wegscheider K, Bestehorn K. Improvement of hypertension management by structured physician education and feedback system: cluster randomized trial. Eur J Cardiovasc Prev Rehabil 2010;17:271–279
63. Bailey CJ, Kodack M. Patient adherence to medication requirements for therapy of type 2 diabetes. Int J Clin Pract 2011;65:314–322
64. Nicolucci A, Rossi MC. Incretin-based therapies: a new potential treatment approach to overcome clinical inertia in type 2 diabetes. Acta Biomed 2008;79:184–191
65. Triplitt C. Improving treatment success rates for type 2 diabetes: recommendations for a changing environment. Am J Manag Care 2010;16(Suppl.):S195–S200
66. Davies MJ, Gagliardino JJ, Gray LJ, Khunti K, Mohan V, Hughes R. Real-world factors affecting adherence to insulin therapy in patients with type 1 or type 2 diabetes mellitus: a systematic review. Diabet Med 2013;30:512–524
67. Hyman DJ, Pavlik VN, Greisinger AJ, et al. Effect of a physician uncertainty reduction intervention on blood pressure in uncontrolled hypertensives—a cluster randomized trial. J Gen Intern Med 2012;27:413–419
68. Cleveringa FG, Gorter KJ, van den Donk M, van Gijsel J, Rutten GE. Computerized decision support systems in primary care for type 2 diabetes patients only improve patients' outcomes when combined with feedback on performance and case management: a systematic review. Diabetes Technol Ther 2013;15:180–192
69. Varroud-Vial M. Improving diabetes management with electronic medical records. Diabetes Metab 2011;37(Suppl. 4):S48–S52
70. Benhamou PY. Improving diabetes management with electronic health records and patients' health records. Diabetes Metab 2011;37(Suppl. 4):S53–S56
71. Cebul RD, Love TE, Jain AK, Hebert CJ. Electronic health records and quality of diabetes care. N Engl J Med 2011;365:825–833
72. Koppel R, Majumdar SR, Soumerai SB. Electronic health records and quality of diabetes care [Letter]. N Engl J Med 2011;365: 2338–2339; author reply 2339
73. Graetz I, Huang J, Brand R, et al. The impact of electronic health records and teamwork on diabetes care quality. Am J Manag Care 2015;21:878–884
74. Benson G. The role of disease management in diabetes care. Diabetes Spectr 2010;23:116–118
75. Fuchs S, Henschke C, Blümel M, Busse R. Disease management programs for type 2 diabetes in Germany: a systematic literature review evaluating effectiveness. Dtsch Arztebl Int 2014;111:453–463
76. Kostev K, Rockel T, Jacob L. Impact of disease management programs on HbA1c values in type 2 diabetes patients in Germany. J Diabetes Sci Technol 2017;11:117–122
77. Mitri J, Gabbay R. Understanding population health through diabetes population management. Endocrinol Metab Clin North Am 2016;45:933–942
78. Schmittdiel JA, Gopalan A, Lin MW, Banerjee S, Chau CV, Adams AS. Population health management for diabetes: health care system-level approaches for improving quality and addressing disparities. Curr Diab Rep 2017;17:31
79. Faruque LI, Wiebe N, Ehteshami-Afshar A, et al.; Alberta Kidney Disease Network. Effect of telemedicine on glycated hemoglobin in diabetes: a systematic review and meta-analysis of randomized trials. CMAJ 2017;189:E341–E364
80. Yoshida Y, Boren SA, Soares J, Popescu M, Nielson SD, Simoes EJ. Effect of health information technologies on glycemic control among patients with type 2 diabetes. Curr Diab Rep 2018;18:130
81. Demiris G, Kneale L. Informatics systems and tools to facilitate patient-centered care coordination. Yearb Med Inform 2015;10:15–21
82. Huang J, Yin S, Lin Y, Jiang Q, He Y, Du L. Impact of pay-for-performance on management of diabetes: a systematic review. J Evid Based Med 2013;6:173–184
83. Latham LP, Marshall EG. Performance-based financial incentives for diabetes care: an effective strategy? Can J Diabetes 2015;39:83–87
84. Wong CA, Miller VA, Murphy K, et al. Effect of financial incentives on glucose monitoring adherence and glycemic control among adolescents and young adults with type 1 diabetes: a randomized clinical trial. JAMA Pediatr 2017;171:1176–1183
85. Avignon A, Attali C, Sultan A, Ferrat E, Le Breton J. Clinical inertia: viewpoints of general practitioners and diabetologists. Diabetes Metab 2012;38(Suppl. 3):S53–S58
86. Fiscella K, Volpe E, Winters P, Brown M, Idris A, Harren T. A novel approach to quality improvement in a safety-net practice: concurrent peer review visits. J Natl Med Assoc 2010;102:1231–1236
87. van Bruggen R, Gorter K, Stolk R, Klungel O, Rutten G. Clinical inertia in general practice: widespread and related to the outcome of diabetes care. Fam Pract 2009;26:428–436
88. Carter BL, Bergus GR, Dawson JD, et al. A cluster randomized trial to evaluate physician/pharmacist collaboration to improve blood pressure control. J Clin Hypertens (Greenwich) 2008;10:260–271
89. Saheb Kashaf M, McGill ET, Berger ZD. Shared decision-making and outcomes in type 2 diabetes: a systematic review and meta-analysis. Patient Educ Couns 2017;100:2159–2171
90. Branning G, Worthy SL, Vater M. Emphasize shared decision-making between physicians and patients to improve diabetes outcomes. Am Health Drug Benefits 2017;10:242–245
91. Krebs JD, Parry-Strong A, Gamble E, et al. A structured, group-based diabetes self-management education (DSME) programme for people, families and whanau with type 2 diabetes (T2DM) in New Zealand: an observational study. Prim Care Diabetes 2013;7:151–158
92. Boels AM, Vos RC, Hermans TGT, et al.; GUIDANCE study group. What determines treatment satisfaction of patients with type 2 diabetes on insulin therapy? An observational study in eight European countries. BMJ Open 2017;7:e016180
93. Tang PC, Overhage JM, Chan AS, et al. Online disease management of diabetes: engaging and motivating patients online with enhanced resources-diabetes (EMPOWER-D), a randomized controlled trial. J Am Med Inform Assoc 2013;20:526–534
94. TRIAD Study Group. Health systems, patients factors, and quality of care for diabetes: a synthesis of findings from the TRIAD study. Diabetes Care 2010;33:940–947
95. Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial care for people with diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016;39:2126–2140
96. Mathiesen AS, Egerod I, Jensen T, Kaldan G, Langberg H, Thomsen T. Psychosocial interventions for reducing diabetes distress in vulnerable people with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Metab Syndr Obes 2018;12: 19–33