Medications Affecting the Biochemical Conversion to Type 2 Diabetes: A Systematic Review and Meta-Analysis

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Context: The extent to which some pharmacological interventions reduce or increase the risk of biochemical conversion to type 2 diabetes mellitus (T2DM) in at-risk individuals is unclear.

Methods: We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and Scopus through 24 August 2017 for randomized controlled trials evaluating the effect of drugs suspected to modify the risk of biochemical conversion to T2DM.

Results: We included 43 trials with 192,156 subjects (mean age, 60 years; 56% men; mean body mass index, 30.4 kg/m^2). α-Glucosidase inhibitors, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, metformin, orlistat, phentermine/topiramate, and pioglitazone significantly reduced the risk of biochemical conversion to T2DM, whereas statins and nateglinide increased the risk. There was insufficient direct evidence regarding the effects of sulfonylureas, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium-glucose cotransporter-2 inhibitors. Most trials were brief and evaluated this outcome during treatment without a withdrawal or washout period.

Conclusions: Several drugs modify the risk of biochemical conversation to T2DM, although whether this effect is persistent and clinically relevant is unclear. Future studies need to focus on cardiovascular disease prevention, mortality, and patient-important outcomes instead of biochemical conversion to T2DM. (***J Clin Endocrinol Metab*** **104: 3986–3995, 2019)**

Owing to the increasing incidence of type 2 diabetes mellitus (T2DM), its prevention has become a high priority for clinicians and policymakers. Although interventions to promote healthier physical activity and dietary patterns are difficult to translate into sustained lifestyle changes without concomitant social and environmental changes (1), they are widely recommended. The relative ineffectiveness of these interventions has drawn attention to potential pharmacological interventions. Some medications tested for T2DM prevention

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Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AGI, α-glucosidase inhibitor; ARB, angiotensin II receptor blocker; BcT2DM, biological conversion to T2DM; DPP-4, dipeptidyl peptidase-4; ER, extended release; GLP-1 agonist, glucagon-like peptide-1 receptor agonist; NNH, number needed to harm; NNT, number needed to treat; RCT, randomized controlled trial; RR, relative risk; SGLT-2, sodium-glucose cotransporter-2; T2DM, type 2 diabetes mellitus.

reduce blood glucose; accordingly, these agents may only delay or mask the biochemical conversion to T2DM (BcT2DM). The extent to which the use of these drugs averts the undesirable consequences of T2DM, such as microvascular complications, days of life without illness, or treatment burden (suffering or functional impairment) due to T2DM or its treatment, is unclear. Appraising and synthesizing the available evidence is central to the formulation of primary prevention guidelines and clinical decision making.

The Endocrine Society convened a task force to develop clinical practice guidelines for the primary prevention of atherosclerotic cardiovascular disease and T2DM in at-risk individuals. To support the development of this guideline, we conducted this systematic review to evaluate the effect of pharmacological interventions on BcT2DM.

Methods

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (2). Search and analysis methods, eligibility criteria, and the outcomes of interest were specified in advance in a protocol developed by the study investigators with input from the Endocrine Society's clinical practice guideline writing committee. Supplemental material to this manuscript is publicly shared in an online repository (3).

Eligibility criteria

We included randomized controlled trials (RCTs) in any language evaluating pharmacological interventions and reporting the incidence of BcT2DM in adult patients at risk for developing T2DM. The task force chose *a priori* the following pharmacological interventions: α-glucosidase inhibitors (AGIs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), meglitinides, metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 agonists), sulfonylureas, orlistat, phentermine/topiramate, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and statins.

Data sources and searches

We searched MEDLINE Epub Ahead of Print, MEDLINE In-Process and Other Non-Indexed Citations, MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and Scopus. The search was designed and executed by a medical reference librarian with input from study investigators from each database's earliest inclusive dates to 24 August 2017. The search was restricted to humans and adults but had no language restrictions. Controlled vocabulary supplemented with key words was used to search for drug therapy for diabetes prevention. Searches were conducted separately for RCTs and for systematic reviews. Details of both of these strategies are available in an online repository (3).

Data collection

Titles and abstracts were uploaded into an online reference management system (DistillerSR). Two reviewers independently screened each abstract for eligibility. Abstracts deemed eligible by at least one reviewer were included for further review. Full texts of eligible abstracts were retrieved, and each was independently reviewed by two reviewers. Disagreements at this level were resolved by discussion and consensus. Using a standardized piloted Web-based form, reviewers extracted descriptive, methodologic, and outcome data from all eligible studies. Extracted data were collated by a third independent reviewer (J.P.D.), and inconsistencies were resolved by referring to the full-text article.

Methodological quality assessment and certainty in the evidence

Two reviewers independently assessed the methodological quality of the included studies. We used the Cochrane risk of bias assessment tool (4) to evaluate the domains of randomization, blinding, allocation concealment, baseline imbalances, loss to follow-up, and other potential biases.

The overall certainty in the evidence was assessed following the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) approach (5). Certainty in evidence generated from RCTs starts as high but can be lowered due to methodological limitations, imprecision, indirectness, inconsistency, and the likelihood of reporting and publication biases (5).

Data synthesis and analysis

BcT2DM was assessed as a dichotomous variable based on criteria determined by each trial. We estimated pooled relative risks (RRs) and 95% CIs using the random-effects model described by DerSimonian and Laird (6). Heterogeneity was evaluated using the I^2 index in general, with an I^2 value $>50\%$ suggesting substantial heterogeneity (7).

To help patients and providers make informed decisions we report the numbers needed to treat and to harm (NNT and NNH) for the medications that showed a significant effect. To generate NNT and NNH, we modeled three arbitrary baseline risks (8). The medium risk category was based on observational data showing that the incidence of DM in patients with impaired fasting glucose or impaired fasting tolerance was 25% for 3 to 5 years (9). Two other categories (10% higher and 10% lower than the 25%) were also used.

Results

Included studies

The literature search yielded 822 relevant citations; additionally, six RCTs (10–15) were identified from four published systematic reviews (16–19). Ultimately, we included 43 RCTs; of these RCTs, 37 (20–56) provided quantitative data sufficient for meta-analysis (Fig. 1). The trials enrolled 192,156 subjects (mean age, 60 years; 56% men; mean body mass index, 30.4 kg/m^2; mostly whites, but included smaller proportions of Asians, Native Americans, and Hispanic enrollees). Only three RCTs (25, 28, 31) were funded by not-for-profit organizations; the remaining RCTs were either partially or completely funded by for-profit entities. The baseline characteristics of the included trials are summarized in an online repository (3).

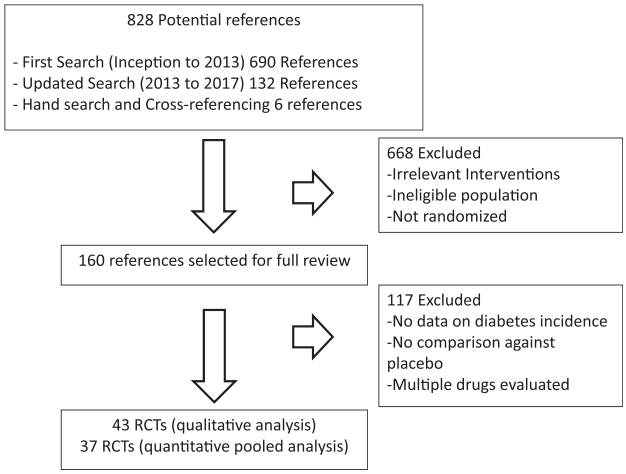

Figure 1. The process of study selection.

Risk of bias

Most RCTs evaluated BcT2DM while subjects were still receiving the assigned pharmacological intervention, whereas only two RCTs (12, 20) allowed for a washout period before outcome evaluation. The incidence of T2DM was a predefined outcome in 28 of 43 (65%) trials and a *post hoc* outcome in the remaining trials (primarily *post hoc* in statin and ACE inhibitor trials). Other risk of bias indicators are summarized in an online repository (3).

Pharmacological interventions associated with a lower incidence of BcT2DM

We identified five RCTs of AGIs (acarbose and voglibose) (23, 24, 32, 50, 54). During the active intervention period [mean (SD), 3.26 (1.7) years; range, 0.3 to 5.0 years], the risk of BcT2DM was reduced by an RR (95% CI) of 0.68 (0.52, 0.88), with an I^2 of 56%. Estimated NNT (95% CI) was 21 (14, 56) for low-risk patients, 13 (8, 33) for average-risk patients, and 9 (6, 24) for high-risk patients.

We identified six RCTs of ACEIs (enalapril, perindopril, quinapril, ramipril, and trandolapril) (20, 27–29, 33, 34). During the active intervention period [mean (SD), 4.03 (0.8) years; range, 2.9 to 5.0 years), the risk of BcT2DM was reduced by an RR (95% CI) of 0.81 (0.68, 0.96), with an I^2 of 74%. Estimated NNT (95% CI) was 35 (21, 167) for low-risk patients, 21 (13, 100) for average-risk patients, and 15 (9, 71) for high-risk patients.

We identified six RCTs of ARBs (candesartan, telmisartan, and valsartan) (21, 22, 26, 31, 35, 49). One of the six trials (the Kyoto Heart Study) was withdrawn and therefore excluded from meta-analysis (31). During the active intervention period [mean (SD), 3.87 (0.8) years; range, 2.0 to 5.0 years], the risk of BcT2DM was reduced by an RR (95% CI) of 0.90 (0.86, 0.94), with an I^2 of 0%. Estimated NNT (95% CI) was 56 (37, 133) for low-risk patients, 33 (22, 80) for average-risk patients, and 24 (16, 57) for high-risk patients.

We identified four RCTs of metformin (25, 30, 37, 53). During the active intervention period [mean (SD), 1.93 (0.95) years; range, 1.0 to 3.2 years], the risk of BcT2DM was reduced by an RR (95% CI) of 0.71 (0.63, 0.80), with an I^2 of 0%. Estimated NNT (95% CI) was 23 (18, 33) for low-risk patients, 14 (11, 20) for average-risk patients, and 10 (8, 14) for high-risk patients.

We identified one RCT of pioglitazone (51). During the active intervention period of 2.4 years, the risk of BcT2DM was reduced by an RR (95% CI) of 0.30 (0.17, 0.52). Estimated NNT (95% CI) was 10 (8, 14) for low-risk patients, 6 (5, 8) for average-risk patients, and 4 (3, 6) for high-risk patients.

We identified one RCT for orlistat (14) and one RCT for phentermine/topiramate (52). During the active intervention period of 4 years, orlistat reduced the risk of BcT2DM by an RR (95% CI) of 0.34 (0.19, 0.62), yielding an estimated NNT (95% CI) of 11 (9, 18) for low-risk patients, 6 (5, 11) for average-risk patients, and 4 (3, 8) for high-risk patients. During the active intervention period of 108 weeks, phentermine/topiramate extended release (ER) (15 mg/92 mg) reduced the risk of BcT2DM by an RR (95% CI) of 0.11 (0.01, 0.91), yielding an estimated NNT (95% CI) of 7 (6, 74) for low-risk patients, 4 (5, 44) for average-risk patients, and 3 (2, 32) for high-risk patients.

A summary of estimated relative risk reductions is available in Table 1. Estimated numbers needed to treat are presented in Table 2.

Pharmacological interventions associated with a higher incidence of BcT2DM

We identified one RCT of nateglinide (55). During the active intervention period of 5 years, the risk of BcT2DM increased by an RR (95% CI) of 1.06 (1.01, 1.12), yielding an estimated NNH (95% CI) of 111 (667, 56) for low-risk patients, 67 (400, 33) for average-risk patients, and 48 (286, 24) for high-risk patients.

We identified 13 RCTs on statins (atorvastatin, pravastatin, rosuvastatin, and simvastatin) (36, 38–48, 56) evaluating 15 comparisons against placebo. During the active intervention period [mean (SD), 4.71 (1.42) years; range, 2.0 to 7.8 years), the risk of BcT2DM increased by an RR (95% CI) of 1.1 (1.03, 1.18), with an I^2 of 29%. Estimated NNH (95% CI) was 67 (222, 37) for low-risk patients, 40 (133, 22) for average-risk patients, and 29 (95, 16) for high-risk patients.

A summary of relative risk estimates is available in Table 1. Estimated numbers needed to harm are presented in Table 2.

Pharmacological interventions not associated with significant change in BcT2DM

For DPP-4 inhibitors, we included one RCT (11) of vildagliptin. After 12 weeks, there was no significant

Table 1. Summary of Findings

Drug	Length of Follow-Up	No. of Included RCTs	RR 95% CI	I^2
Drugs associated with lower biochemical conversion to T2DM				
AGI (23, 24, 32, 50, 54)	0.3–5.0 y	5	0.68 0.52, 0.88	56%
ACEIs (20, 27–29, 33, 34)	2.9–5.0 y	6	0.81 0.68, 0.96	74%
ARBs (21, 22, 26, 31, 35, 49)	2.5–5.0 y	5	0.90 0.86, 0.94	0%
Metformin (25, 30, 37, 53)	1.0–3.2 y	4	0.71 0.63, 0.80	0%
Orlistat (14)	4 y	1	0.34 0.19, 0.62	n/a
Phentermine/topiramate ER (15 mg/92 mg) (52)	108 wk	1	0.11 0.01, 0.91	n/a
Pioglitazone (51)	2.4 y	1	0.30 0.17, 0.52	n/a
Drugs associated with higher biochemical conversion to T2DM				
Nateglinide (55)	5 y	1	1.06 1.01, 1.12	n/a
Statins (36, 38–48, 56)	2–7.8 y	13[a]	1.10 1.03, 1.18	29%
Drugs associated with no differences on biochemical conversion to T2DM				
SGLT-2 inhibitors (16)	n/a	0	n/a	
DDP-4 inhibitors (11)	12 wk	1	2.97 0.31, 7.98	n/a
GLP-1 agonists	24 wk (10)	2[b]	1.62 0.28, 9.44	n/a
	56 wk (15)		0.28 0.18, 0.45	n/a
Sulfonylureas (12, 13)	1.0–3.7 y	2	0.75 0.54, 1.04	0%
Phentermine/topiramate ER (7.5 mg/46 mg) (52)	108 wk	1	0.71 0.21, 2.34	n/a

Abbreviation: n/a, not applicable.

[a]Fifteen different comparisons coming from 13 different RCTs.

[b]Unable to perform a meta-analysis owing to very high heterogeneity.

difference in BcT2DM (RR, 2.97; 95% CI, 0.31, 7.98). For the GLP-1 agonist, two RCTs with conflicting results were identified. One trial (15) showed a significant reduction in BcT2DM after 56 weeks of liraglutide (RR. 0.28; 95% CI, 0.18, 0.45), and the other RCT (10) using exenatide for 24 weeks showed no significant differences (RR, 1.62; 95% CI, 0.28, 9.44).

Two RCTs (12, 13) evaluated sulfonylureas (glipizide and glimepiride). During the active intervention period [mean (SD), 2.35 (1.35) years; range, 1.0 to 3.7 years), meta-analysis of the two trials showed no significant differences in BcT2DM (RR, 0.75; 95% CI, 0.54, 1.04; I^2 of 0) (18). However, one trial was of low-dose glimepiride (1 mg), which may explain the lack of effectiveness. The glipizide trial showed a statistically significant reduction in diabetes prevalence 12 months after discontinuing active treatment but the trial was very small (33 subjects).

Phentermine/topiramate ER (7.5 mg/46 mg) failed to achieve a significant reduction in BcT2DM (52). Our search strategies and a Cochrane review (16) were unable to identify RCTs for SGLT-2 inhibitors.

Certainty in the body of evidence

Evidence of moderate certainty supports the effect of AGIs, ACEIs, ARBs, metformin, and statins, with the degree of certainty affected by methodological limitations of the included trials. Some heterogeneity among trials was observed for some medications, but overall this was not concerning, as the point estimates did not substantially vary across relevant studies, and their 95% CIs frequently overlapped.

Certainty was low for orlistat, pioglitazone, phentermine/topiramate, nateglinide, DPP-4 inhibitors, GLP-1 agonists, and sulfonylureas due to imprecision, brief follow-up periods, and significant inconsistency in the case of GLP-1 agonists.

Discussion

Summary of findings

This systematic review supports the notion that AGIs, ACEIs, ARBs, metformin, orlistat, phentermine/topiramate, and pioglitazone significantly reduce the risk

Table 2. Estimated Numbers Needed to Treat and Harm

Drug	Population Risk	NNT (95% CI)
Drugs associated with lower biochemical conversion to T2DM		
AGIs (23, 24, 32, 50, 54)	Low risk[a]	21 (14, 56)
	Average risk[b]	13 (8, 33)
	High risk[c]	9 (6, 24)
ACEIs (20, 27–29, 33, 34)	Low risk	35 (21, 167)
	Average risk	21 (13, 100)
	High risk	15 (9, 71)
ARBs (21, 22, 26, 31, 35, 49)	Low risk	56 (37, 133)
	Average risk	33 (22, 80)
	High risk	24 (16, 57)
Metformin (25, 30, 37, 53)	Low risk	23 (18, 33)
	Average risk	14 (11, 20)
	High risk	10 (8, 14)
Orlistat (14)	Low risk	11(9, 18)
	Average risk	6 (5, 11)
	High risk	4 (3, 8)
Pioglitazone (51)	Low risk	10 (8, 14)
	Average risk	6 (5, 8)
	High risk	4 (3, 6)
Phentermine/topiramate ER (15 mg/92 mg) (52)	Low risk	7 (6, 74)
	Average risk	4 (5, 44)
	High risk	3 (2, 32)
Drugs associated with higher biochemical conversion to T2DM		
Statins (36, 38–48, 56)	Low risk	67 (222, 37)
	Average risk	40 (133, 22)
	High risk	29 (95, 16)
Nateglinide (55)	Low risk	111 (667, 56)
	Average risk	67 (400, 33)
	High risk	48 (286, 24)

Abbreviation: n/a, not applicable.

[a]Low risk: 15%, lower risk than an average patient with impaired fasting glucose or impaired glucose tolerance.

[b]Average risk: 25%, average risk of an average patient with impaired fasting glucose or impaired glucose tolerance.

[c]High risk: 35%, higher risk than an average patient with impaired fasting glucose or impaired glucose tolerance.

of BcT2DM. Statins and nateglinide may increase this risk. There was insufficient evidence supporting an effect of sulfonylureas, GLP-1 agonists, DPP-4 inhibitors, and SGLT-2 inhibitors on BcT2DM.

Limitations and strengths

Most included trials were funded by industry, which has an association with favorable results for sponsored products more often than in independent trials (57–60). The issue of addressing a surrogate outcome also warrants caution. Although asymptomatic elevations of blood glucose concentrations can function as a surrogate for patient-important outcomes (*e.g.*, risk for microvascular complications such as diabetic retinopathy), the patient-important benefits of preventing BcT2DM using medications remain unclear. The lack of a washout period before outcome assessment increases the risk of biased results favoring a beneficial effect. That is, because T2DM is defined by blood glucose levels, medications that lower blood glucose may simply mask a diagnosis rather than truly prevent it. Moreover, the trials were published during a period of time (1996 to 2017) in which several definitions for T2DM and impaired glucose tolerance were used.

The strengths of this review relate to the comprehensive literature search, the use of two independent reviewers for study selection and appraisal, and the collaboration of methodologists with content experts from the Endocrine Society. The findings are consistent with other evidence synthesis attempts (61–65) and expand the body of evidence by including additional medications in the conversation about BcT2DM.

Clinical implications

There is no implicit value in preventing the BcT2DM if the approach pursued does not prevent disease complications, decrease disease burden, or lessen the burden of treatment. Regular medication use is a major source of treatment burden in patients with T2DM. We suggest that taking diabetes medications to prevent BcT2DM could be reasonable only if their use could fundamentally alter the clinical course, for example, by averting severe

forms of T2DM. The available evidence may only respond to the question of the extent to which medications lower glycemia in a manner that could mask or delay the BcT2DM, meaning that no recommendation could be made in relation to the goal of truly preventing T2DM. Delaying the diagnosis without modifying the course of the disease or reducing its treatment burden seems to be a hard sell for well-informed patients and their clinicians. Given this reality and the challenges of implementing and sustaining individual lifestyle interventions, we suggest that resources should be more intentionally directed toward fundamental changes in the social ecology that is fueling the T2DM epidemic, rather than promoting prevention strategies that involve drugs used to treat established T2DM.

Alternatively, knowing the glycemic effects of drugs not used for diabetes can help clinicians interpret the results of glycemic parameters when these drugs are started or stopped for their primary indications. For example, glycemic parameters may appear reassuring when these drugs are in use, and substantial changes may follow after they are discontinued. These changes in biochemistry may not otherwise affect the safety or efficacy of these drugs. A similar argument applies to medications that contribute to BcT2DM. For example, to the best of our knowledge, the expected benefits of statins on cardiovascular risk are not mitigated in individuals who biochemically convert to T2DM.

In terms of choosing a medication to prevent or delay BcT2DM, metformin seems to be a clear first choice for most patients because of its known effect on reducing cardiovascular mortality in patients with established T2DM (66, 67). Of note, the washout study of the Diabetes Prevention Program demonstrated that a 25% relative risk reduction remained after a 1- to 2-week washout period, suggesting that a substantial protective effect may remain after drug discontinuation (68). Other medications may be considered based on comorbidities and clinical context. Acarbose has a possible beneficial effect on cardiovascular morbidity and is associated with a reduction in body mass index (69). ACEIs and ARBs are first-line therapies for essential hypertension; thus, they can be beneficial in patients dealing with hypertension and impaired glucose tolerance or impaired fasting glucose. Orlistat and phentermine/topiramate may reduce BcT2DM, although data suggest that improvement in glucose tolerance depends on changes in body weight (61). Whether these medications lead to better glucose control beyond the effect of weight loss remains unknown. Pioglitazone may be a less suitable option to prevent BcT2DM due to concerns about the safety of thiazolidinediones as a class [bladder cancer (70), heart failure (71), and weight gain (72, 73)]. In a washout study of rosiglitazone, an agent not studied in this meta-analysis, it delayed a diabetes diagnosis during treatment, but BcT2DM reverted to the placebo rate when the drug was stopped (74).

Data were limited for GLP-1 agonists, DPP-4 agonists, and SGLT-2 inhibitors. Considering the uncertainty regarding their effectiveness, long-term safety, and their current cost, they are unlikely to be reasonable options at this time.

This review has shown that nateglinide and statins confer a higher incidence of BcT2DM. The estimate of nateglinide was imprecise; therefore, it would not be surprising if future studies show a more neutral effect on BcT2DM, but it should not be used for T2DM prevention.

In the case of statins, the increased risk of T2DM should be considered when using statins for primary prevention in low-risk patients (75). This adverse effect in secondary prevention is likely outweighed by the well-established benefits of statins when used in adults with established cardiovascular disease (76). Overall, the magnitude of the association of statins with BcT2DM is small, highlighted by the large NNH presented in this review and estimated at a 0.12% increase in HgA1c in prior studies (77). A recent observational study in Japan (78) suggested that the association between new-onset T2DM and statins was dose and potency related. Therefore, we suggest that physicians could opt for lower potency statins unless a moderate or high potency statin therapy is clearly indicated (79, 80).

To date, lifestyle interventions remain the most reasonable first approach to prevent progression to diabetes in patients with prediabetes or metabolic syndrome (81–84). From a public health standpoint, a diagnosis of diabetes is associated with increased health care utilization. However, whether drug use to reduce BcT2DM would reduce long-term health care expenditures or lead to a significant benefit in patient-important outcomes (85) has yet to be determined.

Conclusions

Lifestyle changes remain the cornerstone for the prevention of T2DM. Metformin is a possible additional beneficial intervention. Several other pharmacological interventions reduce or increase the risk of a diagnosis of diabetes. Future studies need to focus on prevention of microvascular complications, cardiovascular disease, mortality, and patient-important outcomes instead of BcT2DM.

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Additional Information

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Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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