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REVIEW ARTICLE

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Challenges to hemoglobin A1c as a therapeutic target for type 2 diabetes mellitus

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Abstract

Glycated hemoglobin (HbA1c) is widely accepted as the most reliable measure of long-term glycemia. However, there is disagreement among professional medical societies on a proper glycemic target for long-term benefits in type 2 diabetes (T2D). The use of some glucose-lowering drugs was associated with heart failure despite substantial lowering of HbA1c. The failure of intensive glycemic control to reduce cardiovascular risk in some trials again brought into question the usefulness of HbA1c as a therapeutic target in T2D. In large cardiovascular outcome trials, some newer glucose-lowering drugs were associated with higher risks of heart failure or amputation despite comparable glycemic control between the test and placebo groups. Here, we provide evidence that variation in hemoglobin glycation between individuals is responsible for these inconsistencies. We suggest that further research be conducted in this area and that the findings be applied to clinical trials and practice.

KEYWORDS
cardiovascular diseases, clinical trials, glycated hemoglobin, hypoglycemic agents, outcome assessment, type 2 diabetes mellitus

1 | INTRODUCTION

In 2017, the numbers of adults with diabetes mellitus were estimated to be 425 million worldwide and over 7.2 million in Japan.[1] Of the two principal types, approximately 95% of all diabetes cases were classified as type 2 (T2D).[2] Adults with T2D have a higher risk of cardiovascular (CV) mortality than those without T2D.[3] Many observational studies have reported an association between an increase in glycated hemoglobin (HbA1c) and CV risk in patients with T2D,[4,5] which is why professional society guidelines have historically recommended strict control of blood glucose, assessed using HbA1c, in patients with T2D. In addition, regulatory authorities have approved medicines for the treatment of T2D on the basis of the use of HbA1c as the primacy therapeutic endpoint.[6] However, data from large randomized trials[7,8] have questioned the value of intensive glycemic control. As a result, recent revisions to such guidelines have moved away from the use of uniform intensive glycemic control as a target and toward individualized HbA1c goals, but the ideal target, which optimally balances benefits and risks, requires further clarification. Some of the published guidelines[9–12] recommend standard glycemic control, with HbA1c targets of 7% or 8%, whereas those from the American Association of Clinical Endocrinologists (AACE),[13] the American Diabetes Association (ADA),[14] and the Japan Diabetes Society[15] recommend intensive glycemic control, with HbA1c targets of below 7% or 6.5%.

The American College of Physicians (ACP) have reviewed these guidelines and five large randomized controlled trials[16–20] comparing standard and intensive glycemic control. In their guidance statement issued in March 2018,[21] the ACP recommended that clinicians should aim to achieve standard control, with an HbA1c between 7% and 8%, instead of intensive control in most adult patients with T2D. However, the ADA, AACE, the American Association of Diabetes

Educators (AADE), and the Endocrine Society immediately issued a joint statement that strongly repudiated the ACP guidance,[22] causing confusion among healthcare professionals.[23,24]

This controversial conclusion not only questioned the efficacy of intensive glycemic control, but rekindled the long-standing debate[25] about the usefulness of HbA1c targets in the treatment of T2D. Three problems can be identified. First, hypoglycemia and low HbA1c concentrations are associated with higher CV risk.[26] Second, the use of either conventional[27,28] or newer antidiabetic agents[29,30] is associated with a higher risk of heart failure. Third, recent CV outcome trials (CVOTs) have shown that drugs that lower HbA1c to similar concentrations are associated with differing CV outcomes.[31,32] As a result, a recent survey showed that stakeholders in drug development considered HbA1c as an imperfect target.[25] In this review, we aim to assess the usefulness of HbA1c as a therapeutic target and to discuss measures that could be implemented to improve the performance of HbA1c as a therapeutic target in T2D.

2 | THE RELEVANCE OF HBA1C AS A TARGET FOR T2D THERAPY

2.1 | Biological factors affecting HbA1c concentration

Glycated hemoglobin, a minor fraction of adult hemoglobin, is formed slowly and continuously by the nonenzymatic chemical modification of hemoglobin molecules. The glycation reaction is essentially irreversible,[33] and the rate of formation of HbA1c is directly proportional to the ambient glucose concentration. The concentration of HbA1c therefore reflects glycemic history, that is, the time-weighted mean glucose over the preceding 8-12 weeks, which is determined primarily by red blood cell (RBC) lifespan.[34] HbA1c has been proven to provide a superior estimate of mean glycemia than routine determinations of blood glucose concentration.[35,36] Therefore, the use of HbA1c is endorsed for screening and the diagnosis of diabetes, because its concentration increases well in advance of the clinical development of diabetes.[37] The International Expert Committee recommended the use of an HbA1c ≥6.5% for the diagnosis of diabetes in 2009,[38] and this recommendation was subsequently adopted by the ADA,[39] the World Health Organization,[40] and other professional groups.[41]

Glycated hemoglobin concentration can be affected by a variety of genetic, hematologic, and disease-related factors,[42,43] but the specific effects depend on the specific hemoglobin variant or derivative and the HbA1c assay used. This is because structural variants of hemoglobin in patients with hemoglobinopathies, such as thalassemia or sickle-cell disease, interfere with some HbA1c assays.[44] Even when the effect of carbamylated hemoglobin is excluded, high HbA1c values in nondiabetic patients are still associated with chronic kidney diseases.[45,46]

Glucose-independent racial differences in HbA1c concentrations have been observed in people both with[47] and without diabetes.[48,49] Black people have been reported to have 0.4% (95% CI, 0.2-0.6) higher HbA1c than white people at comparable mean glucose concentrations.[49] However, the implications of this ethnic difference in HbA1c for both the diagnosis and treatment of T2D have been debated,[50,51] and it does not appear to affect CV outcomes in people without diabetes.[52]

Apart from genetic variation, the major determinants of HbA1c are conditions influencing RBC lifespan (Table 1).[42,53] HbA1c values are inappropriately low if RBC lifespan is short (eg, in hemolysis) or if RBC age is low (eg, in acute blood loss), and are inappropriately high in iron deficiency anemia, although this can be corrected by iron supplementation.[54]

2.2 | Discordance between HbA1c and mean circulating glucose concentration

The degree of glycation of hemoglobin is generally believed to depend exclusively on the concentration of glucose, because the A1c-Derived Average Glucose (ADAG) study[55] showed a strong linear correlation ($R = 0.84$, $p < 0.0001$) between HbA1c and mean glucose, permitting the calculation of an estimated mean glucose concentration from an HbA1c value. However, there is substantial unexplained variability in the relationship between mean glucose and HbA1c.[56–58] The ADAG study showed that mean glucose has a 95% CI of 123-185 mg/dL at an HbA1c of 7.0% and the 95% CI is 100-152 mg/dL at an HbA1c of 6.0%. Thus, patients with identical measured HbA1c values may have had quite different mean glucose

TABLE 1 Conditions influencing HbA1c *via* an effect on erythrocyte lifespan

HbA1c	Change in erythrocyte lifespan	Condition/Disease
Lower	Relative reduction in lifespan	
	Loss of erythrocytes	Acute blood loss
		Hemolysis
		Hypersplenism
		Liver cirrhosis
		Megaloblastic anemia
		Myelodysplastic syndrome
	Higher rate of erythropoiesis	Transfusion
		Administration of
		Iron
		Vitamin B12
		Erythropoietin
Higher	Relative increase in lifespan	
	Slower loss of erythrocytes	Splenectomy
	Lower rate of erythropoiesis	Iron deficiency
		Vitamin B12 deficiency
Variable		Hemoglobinopathies

concentrations. Random measurement error or fluctuations in blood glucose cannot explain this discordance, because it is repeatable within individuals.[59] This suggests that factors other than glucose concentration affect the glycation of hemoglobin.

The use of a standard HbA1c value as a target for glycemic control in all individuals has been questioned, in particular because of the discordance between HbA1c and mean glucose,[60] because this could lead to over- or undertreatment, resulting in hypoglycemia or an increase in the risk of diabetic complications, respectively. In the ACCORD trial, efforts to identify a cause for the greater mortality in the intensive treatment arm[61,62] led to the demonstration that the degree of glycation of hemoglobin for a given mean glucose concentration varied among individuals.[63] This variability occurred in the absence of a known cause, such as a hemoglobinopathy. This discordance between HbA1c and mean glucose among individuals, which is referred to as the "glycation gap,"[64] is consistent with the "high glycator-low glycator" hypothesis.[65] Hempe et al.[66] showed that intensive glycemic control was disproportionately associated with hypoglycemia in "high glycators," the subgroup of ACCORD participants with a high hemoglobin glycation index (observed HbA1c—predicted HbA1c). This finding suggests that it is unwise to use an HbA1c value alone as a therapeutic goal in the absence of information regarding the relationship between HbA1c and mean glucose in each individual.

2.3 | Estimated HbA1c as an individualized therapeutic target

Most of the conditions influencing HbA1c concentration affect RBC lifespan (Table 1), which can be quite variable. The mean age of circulating RBCs has been shown to range from 39 to 56 days in diabetic subjects and 38 to 60 days in nondiabetic controls,[34] and this variation is large enough to cause clinically significant differences in HbA1c for a given mean glucose concentration. Using large sets of continuous glucose monitoring (CGM) data from individual patients, Malka et al[67] derived a mathematical model to estimate the patient-specific nonglycemic determinants of HbA1c, including RBC lifespan. This model enabled them to determine that interpatient variation in RBC lifespan can explain all the glucose-independent variation in HbA1c and to estimate a patient-specific mean blood glucose from their HbA1c concentration.

Whether or not it recommends the use of intensive glycemic control, every guideline advocates individualized treatment for patients with T2D. The use of mean glucose estimated from HbA1c alone, implying the application of a population mean to an individual, can be misleading.[68] CGM, using a protocol approved by the FDA in June 2018,[69] can be used to compute a mean glucose that can be compared with the patient's HbA1c.[68] The estimated HbA1c derived from CGM can be compared with the measured HbA1c to obtain an individualized hemoglobin glycation index. If this index is taken into account when management decisions are made, irrespective of the guideline used,[21,22] superior individualized therapy for T2D can be provided.

3 | CONFLICTING FINDINGS WITH REGARD TO THE USE OF HBA1C AS A THERAPEUTIC TARGET

A major controversy in clinical T2D research is the conflicting data regarding the effects of glucose-lowering agents on CV complications. The use of HbA1c as a surrogate for macrovascular risk in patients with T2D has faced repeated challenges.

3.1 | Observational studies: the association between HbA1c and CV risk

Many observational studies have reported an association between increases in HbA1c and CV risk in patients with T2D. The United Kingdom Prospective Diabetes Study (UKPDS) 35[70] was a prospective observational study of 3642 patients with newly diagnosed T2D that were recruited between 1977 and 1991. It showed a log-linear relationship between mean HbA1c and the incidence of CV events, without a threshold. In UKPDS 35, each 1% reduction in HbA1c was associated with 14%, 12%, and 16% reductions in the relative risk (RR) of myocardial infarction, stroke, and heart failure, respectively. The EPIC-Norfolk study[71] was another prospective population study that enrolled 4662 men and 5570 women. Their HbA1c and CV disease risk factors were assessed between 1995 and 1997, with CV disease events and mortality being followed until 2003. In this study, the CV risk and all-cause mortality of the participants had continuous associations with HbA1c concentration across its full distribution. A 1% increase in HbA1c was associated with an RR of death from any cause of 1.24 (95% confidence interval [CI], 1.14-1.34) in men and 1.28 (95% CI, 1.06-1.32) in women. These RRs were independent of age, body mass index, waist-to-hip ratio, systolic blood pressure, serum cholesterol concentration, cigarette smoking, and any history of CV diseases. A meta-analysis of observational studies of associations between HbA1c and CV events in patients with T2D[5] yielded a pooled RR estimate for coronary heart disease or stroke of 1.18 (95% CI: 1.10-1.26) for each 1% increase in HbA1c.

In contrast to the above, other observational studies have shown J- or U-shaped, rather than linear, relationships between HbA1c and mortality, which may reflect the higher mortality in patients undertaking intensive glycemic control.[7] In a retrospective cohort study of 47 970 patients with T2D who had been on intensive treatment, the adjusted hazard ratio (HR) for all-cause mortality in the lowest HbA1c decile (median HbA1c 6.4%) was 1.52, and 1.79 in the highest decile (median HbA1c 10.5%), whereas the HbA1c decile with the lowest hazard had a median HbA1c of 7.5%.[72] A J-shaped curve was also identified by analyses of two US cohort studies,[52,73] which showed an association between low HbA1c and high all-cause mortality. A meta-analysis of seven observational studies, including 147 424 participants,[74] also revealed a significant J-shaped relationship between HbA1c and all-cause mortality, implying higher risks of mortality at both high and low HbA1c concentrations.

TABLE 2 Characteristics of five major trials of intensive vs standard glycemic control in patients with type 2 diabetes

Trial	UKPDS 33[16]	UKPDS 34[17]	ACCORD[18]	ADVANCE[19]	VADT[20]
Year	1998	1998	2008	2008	2009
No. of participants	3867	753	10 251	11 140	1791
Baseline					
Age, y	53	53	62	66	60
Men, %	61	46	61	58	3
Body mass index, kg/m^2	28	32	32	28	31
Duration of diabetes, y	Newly diagnosed	Newly diagnosed	10	8	11.5
HbA1c at baseline, %	7.1	7.2	8.3	7.5	9.4
Treatment protocol					
Intervention	Sulfonylurea or insulin	Metformin	Not specified	Gliclazide	Not specified
Follow-up, y	11.1	10.7	3.5	5	5.6
HbA1c achieved, %, I vs C[a]	7.0 vs 7.9	7.4 vs 8.0	6.4 vs 7.5	6.5 vs 7.3	6.9 vs 8.4
Outcomes					
Primary outcome	Any diabetes-related endpoint	Any diabetes-related endpoint	Combined incidence of major macrovascular events	Combined incidence of major macrovascular or microvascular events	Combined incidence of macrovascular or heart failure events
HR or RR for primary outcome (95% CI)	RR, 0.88 (0.79-0.99)	RR, 0.68 (0.53-0.87)	HR, 0.9 (0.78-1.04)	HR, 0.9 (0.82-0.98) Macrovascular events only: 0.94 (0.84-1.06)	HR, 0.88 (0.74-1.05)
HR or RR for all-cause mortality (95% CI)	HR, 0.94 (0.80-1.10)	RR, 0.64 (0.45-0.91)	HR, 1.22 (1.01-1.46)	HR, 0.93 (0.83-1.06)	HR, 1.07 (0.81-1.42)
HR or RR for microvascular outcome (95% CI)	RR, 0.75 (0.60-0.93)	RR, 0.71 (0.42-1.19)	No difference	HR, 0.86 (0.77-0.97)	No difference

BMI, body mass index; CI, confidence interval; HbA1c, glycated hemoglobin A1c; HR, hazard ratio; RR, relative risk.
[a]I vs C, intensive vs control arm.

3.2 | Intervention trials: benefits and risks of intensive glycemic control

To investigate the benefits and risks of intensive glycemic control, the ACP reviewed five large, long-term, randomized, open-label trials (Table 2): UKPDS 33[16] and 34[17]; Action to Control Cardiovascular Risk in Diabetes (ACCORD)[18]; Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)[19]; and the Veterans Affairs Diabetes Trial (VADT).[20] These trials compared the use of intensive (HbA1c target of 6.3%-7.4%) and standard (HbA1c target of 7.3%-8.4%) therapeutic targets in adults with T2D. Four of the trials (not including UKPDS 34) failed to show that intensive therapy consistently reduces the incidences of macrovascular events and death. Furthermore, the patients undergoing intensive therapy required more glucose-lowering agents at higher doses, which led to more frequent adverse events, including hypoglycemia, than those undergoing standard therapy. Another trial comparing Japanese patients with T2D in the standard therapy group and those in the intensive therapy group, the Japan Diabetes Optimal Integrated Treatment study for three major risk factors of cardiovascular diseases (J-DOIT3),[75] also failed to show a reduction in macrovascular events by intensive therapy.

The UKPDS involved two separate trials, UKPDS 33 and 34, which compared intensive glycemic control and conventional treatment. In the larger UKPDS 33 (n = 3867, 36% of whom had baseline retinopathy), intensive glycemic control using sulfonylureas (chlorpropamide or glibenclamide) or insulin had no significant effect on the incidences of diabetes-related death, all-cause mortality, myocardial infarction, stroke, or amputation. The reduction in risk of the primary outcome (RR: 0.88, 95% CI: 0.79-0.99) was largely due to a reduction in the incidence of microvascular endpoints, which included photocoagulation for asymptomatic retinopathy that had been detected on screening. The smaller UKPDS 34 compared intensive glycemic control using metformin and conventional treatment (mostly with diet alone) in overweight adults (n = 753). Compared with the patients allocated to the conventional treatment, those allocated to metformin (n = 342) had relative risk reductions of 32% for any diabetes-related endpoint, 42% for diabetes-related death, and

TABLE 3 Characteristics of twelve trials that evaluated cardiovascular safety in patients with type 2 diabetes

Trial	Drug (Class)	No. of subjects	Age, y	Men %	BMI	Baseline HbA1c, %	Median follow-up period, y	Primary endpoint	Primary endpoint[a]	HbA1c achieved, %	Adverse events[b]
EXAMINE[83,84]	Alogliptin (DPP-4)	5380	61.0	68.0	28.7	8.0	1.5	3 MACE	0.96 (≤1.16)	<7	Heart failure
CARMELINA[85]	Linagliptin (DPP-4)	6979	66.1	61.5	31.4	8.0	2.2	3 MACE	1.02 (0.89-1.17)	<7.4	
SAVOR-TIMI[86]	Saxagliptin (DPP-4)	16 492	65.1	66.6	31.1	8.0	2.1	3 MACE	1.00 (0.98-1.12)	<7.5	Heart failure
TECOS[87]	Sitagliptin (DPP-4)	14 671	65.4	70.9	30.2	7.2	3.0	4 MACE	0.98 (0.89-1.08)	<6.8	
HARMONY[88]	Albiglutide (GLP-1)	9463	64.1	70.0	32.3	8.7	1.6	3 MACE	0.78 (0.68-0.90)	<7.7	
EXSCEL[89]	Exenatide (GLP-1)	14 752	62.0	62.0	31.8	8.0	3.2	3 MACE	0.91 (0.83-1.00)	<7.2	
LEADER[90]	Liraglutide (GLP-1)	9340	64.2	64.5	32.5	8.7	3.8	3 MACE	0.87 (0.78-0.97)	<7	
ELIXA[91]	Lixisenatide (GLP-1)	6068	59.9	69.6	30.1	7.7	2.1	4 MACE	1.02 (0.89-1.17)	<7	
SUSTAIN-6[92]	Semaglutide (GLP-1)	3297	64.7	61.5	32.8	8.7	2.1	3 MACE	0.74 (0.58-0.95)	<6.8	
CANVAS[93]	Canagliflozin (SGLT2)	10 142	63.2	64.9	31.9	8.2	3.6	3 MACE	0.86 (0.75-0.97)	<7.5	Amputation
DECLARE-TIMI[94]	Dapagliflozin (SGLT2)	17 160	63.9	63.1	32.1	8.3	4.2	3 MACE	0.93 (0.84-1.03)	<7.6	
EMPA-REG OUTCOME[95,96]	Empagliflozin (SGLT2)	7028	63.1	71.2	30.6	8.1	3.1	3 MACE	0.86 (0.74-0.99)	<7.3	

BMI, body mass index; CANVAS, Canagliflozin Cardiovascular Assessment Study; CARMELINA, Cardiovascular and Renal Microvascular Outcome Study With Linagliptin; CI, confidence interval; DECLARE-TIMI, Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction; DPP-4, dipeptidyl peptidase-4 inhibitor; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG OUTCOME, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin vs Standard of Care; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; GLP-1, glucagon-like peptide 1 receptor agonist; HARMONY, Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease; HbA1c, glycated hemoglobin A1c; HR, hazard ratio; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; 3 MACE, three-component major adverse cardiovascular event (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke); 4 MACE, four-component major adverse cardiovascular event (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina); P, placebo; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction; SGLT2, sodium glucose cotransporter 2 inhibitor; SUSTAIN 6, Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin.

[a]Data are presented as the hazard ratio (95% confidence interval).

[b]Adverse events were significantly more frequent in the test drug group.

36% for all-cause mortality, over a median follow-up of 10.7 years, despite a modest difference in HbA1c (7.4% in the metformin group vs 8.0% in the conventional group).

The results of UKPDS 33 and 34 imply that not all glucose-lowering agents are equivalent in terms of CV risk reduction. Intensive glycemic control with metformin, but not with insulin or sulfonylureas, reduced diabetes-related CV risk. However, when the UKPDS results are compared with those of other trials, it must be remembered that this was an open trial that enrolled only newly diagnosed adults, of whom one-third had retinopathy at baseline, and commenced in 1977, well before aspirin, statins, and angiotensin-converting enzyme inhibitors were commonly administered.

The three more recent trials, ACCORD, ADVANCE, and VADT (Table 2), showed that intensive glycemic control does not reduce the incidence of macrovascular events, further questioning the usefulness of HbA1c as a surrogate for CV risk reduction. The ACCORD trial was stopped prematurely (mean follow-up, 3.5 years) because of high all-cause mortality (HR: 1.22, 95% CI: 1.01-1.46) and CV-related death (HR: 1.35, 95% CI: 1.04-1.76) in the intensive therapy arm, but even after patients in this arm were switched to the standard therapy, the higher mortality persisted (HR: 1.19, 95% CI: 1.03-1.38) during the additional 5-year follow-up period.[76] Two post hoc analyses[61,62] were performed to identify any differences in the incidence or severity of hypoglycemia between the two groups,

but these failed to identify causes for the higher mortality in the intensive therapy arm. However, the interindividual differences in HbA1c[66] that were observed may be able to explain the higher mortality in the intensive therapy arm of the trial, as discussed below.

The ADVANCE trial was conducted over a median of 5 years, and compared intensive treatment with standard treatment, but showed no differences in the incidences of major macrovascular events, all-cause mortality, or CV-related death. However, more severe hypoglycemic events were observed in the intensive than in the standard therapy arm (2.7% vs 1.5%; HR: 1.86, 95% CI: 1.42-2.40). In the 6-year posttrial follow-up period (ADVANCE-ON),[77] investigators found no differences in the risks of death from any cause (HR: 1.00, 95% CI: 0.92-1.08) or major macrovascular events (HR: 1.00, 95% CI: 0.92-1.08) between the study arms. These results are in clear contrast to those of UKPDS 80,[78] in which the subjects who undertook intensive glucose control showed persistent reductions in the risks of CV events and all-cause mortality, despite the elimination of the difference in HbA1c concentration between the intensive and standard therapy groups 10 years after the termination of UKPDS. One possible explanation for the difference between ADVANCE-ON and UKPDS 80 is the characteristics of the patients enrolled. Younger patients with newly diagnosed T2D, like those enrolled in UKPDS, may benefit more from early, intensive glycemic control than older patients with a longer duration of T2D and higher CV risk, like those enrolled in ADVANCE.[79]

In the VADT trial, 1791 military veterans with poorly controlled T2D were randomly assigned to receive either intensive or standard glucose control. There was no significant difference between the two groups with regard to the primary outcome (HR in the intensive therapy group: 0.88, 95% CI: 0.74-1.05), any of its components, or the incidence of death from any cause. In addition, no differences were observed between the two groups with regard to microvascular complications. After nearly 10 years of follow-up,[80] patients assigned to intensive therapy had suffered from 8.6 fewer major CV events per 1000 person-years than those assigned to standard therapy, but no differences were identified in the incidences of CV death or overall survival. Nevertheless, it remains to be determined whether the response to intensive glycemic control in patients with long-standing T2D is different to that in those with newly diagnosed T2D.

J-DOIT3[75] was conducted over a median of 8.5 years. In this open-label trial, 2542 T2D Japanese patients aged 45-69 years with an HbA1c of 6.9% or higher were randomly assigned (1271 in each group) to receive either conventional therapy for glucose, blood pressure, and lipid control (targets: HbA1c <6.9%, blood pressure <130/80 mm Hg, and LDL cholesterol <120 mg/dL [or 100 mg/dL in patients with a history of coronary artery disease]) or intensive therapy (HbA1c <6.2%, blood pressure <120/75 mm Hg, and LDL cholesterol <80 mg/dL [or 70 mg/dL in patients with a history of coronary artery disease]). The primary outcome was occurrence of any of a composite of myocardial infarction, stroke, revascularization, and all-cause mortality. The trial showed no significant difference in the incidence of the composite endpoint (HR: 0.81, 95% CI: 0.63-1.04). Nonsevere hypoglycemia (521 [41%] vs 283 [22%], $P < 0.0001$) and edema (193 [15%] vs 129 [10%], $P = 0.0001$) were more frequent in the intensive therapy group.

4 | HBA1C TARGETS AND CV RISK REDUCTION ASSOCIATED WITH NEWER GLUCOSE-LOWERING AGENTS

The use of conventional glucose-lowering agents, such as insulin[81] and sulfonylureas,[28,82] has been reported to be associated with higher CV risk. Rosiglitazone, which had been expected to exert cardioprotective effects, actually caused an increase in the frequency of CV events.[29,30] This finding raised concerns about newer glucose-lowering agents and led to the issue of FDA guidance requiring post-approval CVOTs.[6]

Twelve CVOTs (listed in Table 3),[83–96] all of which were performed in accordance with the FDA guidance[6], had been published by November 30, 2018. The basic design was common to all 12 trials: They were randomized, double-blind, placebo-controlled, noninferiority trials. The primary endpoint was a four-component measure of major adverse CV events (MACE; CV death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina) in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)[87] and the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA),[91] whereas in the other ten trials, the primary endpoint was a three-component MACE (CV death, nonfatal myocardial infarction, and nonfatal stroke). During each study, the use of open-label, glucose-lowering agents as required was encouraged, to achieve individually appropriate HbA1c targets, because patients in the test drug group would be expected to have lower HbA1c than those in the placebo group. The aim of this approach was to assess test drug-specific effects by minimizing the potentially confounding effects of differential glucose control.

All the test drugs showed their noninferiority to placebo with regard to their primary endpoint. In five of the twelve CVOTs, the Albiglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Cardiovascular Disease (HARMONY),[88] the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER),[90] the Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6),[92] the Canagliflozin Cardiovascular Assessment Study (CANVAS),[93] and the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME),[95,96] the primary CV endpoint was significantly lower in the test drug than the placebo group. The CV efficacy shown in the five CVOTs was achieved alongside moderate glycemic control, with HbA1c values not less than 6.8% (Table 3), as recommended by the ACP guidance.[21]

With regard to the safety of the test substances, CV adverse events were more frequent in the test drug group in three of the twelve trials of newer glucose-lowering agents. Two dipeptidyl peptidase-4 (DPP-4) inhibitors increased the incidence of heart failure. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53),[86]

more patients in the saxagliptin group were hospitalized for heart failure than in the placebo group. In the Examination of Cardiovascular Outcomes with Alogliptin vs Standard of Care (EXAMINE),[84] among those participants without a history of heart failure at baseline, the risk of hospital admission for heart failure was significantly higher in the alogliptin group than in the placebo group. In response to these findings, the FDA added a heart failure warning, not only to alogliptin and saxagliptin labels in April 2016,[97] but also to sitagliptin and linagliptin labels in August 2017. The supplementary approval letters for these two gliptins[98,99] state that heart failure is believed to be a class effect common to DPP-4 inhibitors. The action taken by the FDA regarding the latter two DPP-4 inhibitors was unexpected, because the TECOS[87] and the Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA)[85] trials did not show higher incidences of heart failure in the sitagliptin[87] or linagliptin[85] groups. In fact, it remains to be established definitively whether the use of DPP-4 inhibitors is associated with a higher incidence of heart failure as a class effect.[100–103] CANVAS showed that canagliflozin doubles the risk of lower-limb amputation, representing a vascular adverse event other than heart failure. In response, the FDA added a new warning to the canagliflozin label.

The other seven drugs, five glucagon-like peptide 1 (GLP-1) agonists and two sodium glucose cotransporters (SGLT2) inhibitors, carry no warning of potential CV adverse events on their labels. Nevertheless, in the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) study, which aimed to determine whether a GLP-1 agonist would improve the clinical stability of patients with advanced heart failure,[104] liraglutide was shown to increase the incidence of the composite endpoint of death and heart failure in participants with T2D at baseline (HR: 1.54, 95% CI: 0.97-2.46) compared with those without (HR: 1.02, 95% CI: 0.60-1.72). In another study,[105] which aimed to determine the effect of liraglutide on left ventricular function in chronic heart failure patients with and without T2D, treatment with liraglutide was associated with a higher heart rate and more serious cardiac adverse events.

5 | CONCLUSION

The results of recent clinical trials call into question the validity of HbA1c as a therapeutic target for T2D. UKPDS showed that metformin, but not other conventional glucose-lowering agents, reduces CV risk despite similar levels of glycemic control. Rosiglitazone, which had been approved on the basis of its effect to reduce HbA1c, was found to be associated with heart failure, even when glycemic control was good. In the ACCORD, ADVANCE, VADT, and J-DOIT3 trials, the failure of intensive glycemic control to reduce CV risk again brought into question the usefulness of HbA1c as a therapeutic target in T2D. The recent CVOTs, in which glycemic control was found to be comparable between the test drug and placebo groups, showed that the use of three newer glucose-lowering agents is associated with greater risks of heart failure or amputation, whereas others are associated with lower CV risk. These findings have offered an opportunity to reevaluate the use of HbA1c as a surrogate for mean blood glucose concentration in T2D treatment. To determine the effect of interindividual variation in hemoglobin glycation on its use as a therapeutic target in T2D, the use of individual HbA1c estimated using mean glucose values determined by CGM should be validated and applied to the outcome of clinical trials and in practice.

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CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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