Glucose Control and Vascular Outcomes in Type 2 Diabetes: Is the Picture Clear?

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The overall impact of glucose lowering on vascular complications and major clinical outcomes, including mortality, in type 2 diabetes is still an open issue. While intensive glucose control has undoubted benefit for microvascular end points, the relationship between glucose-lowering approaches and reduced incidence and/or progression of macrovascular complications is less clear. This review article will discuss the effect of glucose lowering per se as well as the effects of specific glucose-lowering therapies on vascular outcomes in type 2 diabetes. The role of lifestyle changes on cardiovascular outcomes will be also addressed. Recent analyses from large cardiovascular outcome studies (ACCORD, ADVANCE, and VADT) provide new information on factors that modulate the impact of intensive glucose lowering on outcomes, helping to identify the specific clinical characteristics of the patients receiving the intervention that would show a better response. While several studies on cardiovascular outcomes with diabetes drugs are available, they do not clearly highlight a benefit from using a specific medication or will require additional evidence, as for the sodium–glucose cotransporter 2 blockers.

Vascular complications and cardiovascular disease (CVD) are major causes of morbidity and mortality in people with type 2 diabetes (T2D) (1). The overall impact of glucose lowering on vascular complications in T2D is still debated. The UK Prospective Diabetes Study (UKPDS) was the first trial showing that control of hyperglycemia provides benefit; however, until publication of the extension study the benefit was largely for microvascular end points (2,3). The more recent studies of intensification, Action in Diabetes and Vascular Disease: PreterAx and Diamicron MR Controlled Evaluation (ADVANCE) (4), Action to Control Cardiovascular Risk in Diabetes (ACCORD) (5), and the Veterans Affairs Diabetes Trial (VADT) (6), also showed a decrease in the risk of microvascular end points but not in the primary cardiovascular end point. In ADVANCE, intensive glucose control was defined as use of gliclazide plus any other medication required to achieve an HbA_{1c} of $\leq$6.5% ($\leq$48 mmol/mol) (4) (Table 1). This resulted in a reduction of combined major macrovascular and microvascular events, primarily through reduction in nephropathy. In VADT, patients with suboptimally controlled T2D, 40% with established CVD, were randomized to either intensive glucose lowering, targeting an absolute reduction of 1.5% (16 mmol/mol) HbA_{1c}, or standard therapy (Table 1). After follow-up of 5.6 years, intensive glucose control prevented the increase in albuminuria but without significant difference in major cardiovascular events or all-cause mortality (6). ACCORD (5) (Table 1) randomized 10,251 participants with T2D to either intensive therapy targeting an HbA_{1c} level $<$6.0% (42 mmol/mol) or standard therapy targeting HbA_{1c} between 7.0 and 7.9% (53 and 63 mmol/mol). The primary outcome, a composite of nonfatal myocardial infarction (MI), nonfatal stroke, or death from

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Table 1—Characteristics and outcomes of the larger (n > 1,000) cardiovascular outcome studies of more intensive glucose lowering and the major meta-analyses thereof

Study/meta-analysis	N	Follow-up (years)	Age (years)	Diabetes duration (years)	CVD history (%)	HbA_{1c} (%) for intensive vs. standard	Primary end point[a]	Primary end point, HR (95% CI)	All-cause mortality, HR (95% CI)
ACCORD	10,251	3.5	62	10	35	6.4 vs. 7.5	MACEs	0.90 (0.78–1.04)	1.22 (1.01–1.46)
ACCORD extension	8,912	1.4				7.4 vs. 7.8	MACEs	0.91 (0.81–1.03)	1.19 (1.03–1.38)
ADVANCE	11,140	5.0	66	8	32	6.5 vs. 7.3	MACEs	0.94 (0.84–1.06)	0.93 (0.83–1.06)
ADVANCE extension	8,494	4.9	66	8	30		MACEs	1.00 (0.92–1.08)	1.00 (0.92–1.08)
VADT	1,791	5.6	60	12	40	6.9 vs. 8.4	MACEs + new or worsening HF, vascular surgery, ischemic amputation	0.88 (0.74–1.05)	1.07 (0.81–1.42)
VADT extension	1,655	9.8	60			7.5 vs. 8.5	Same as base study	0.83 (0.70–0.99)	1.05 (0.89–1.25)
UKPDS	3,867	10	54	0	2	7.0 vs. 7.9	MI	0.84 (0.71–1.00)	0.94 (0.80–1.10)
UKPDS extension	3,277	17					MI	0.85 (0.74–0.97)	0.87 (0.79–0.96)
Ray et al. (14)[b]	33,040	4.9				Difference 0.9	MI	0.83 (0.75–0.93)	1.02 (0.87–1.19)
Turnbull et al. (15)[c]	27,049	4.4				Difference 0.9	MACEs	0.91 (0.84–0.99)	1.04 (0.90–1.20)

Information from refs. 2–6,14,15,24,44,45. MACEs: cardiovascular death plus nonfatal MI or stroke. [a]For UKPDS, cardiovascular end points are given separately; here, MI is given. [b]Includes PROactive (see Table 3). [c]UKPDS data censored at 5 years.

cardiovascular causes (major adverse cardiovascular events [MACEs]), occurred similarly in the two arms, although the arm of intensive therapy showed lower rates of nonfatal MI and higher rates of all-cause and cardiovascular mortality when prematurely stopped after 3.5 years. In ACCORD, intensive therapy delayed the onset of albuminuria and some measures of eye complications and neuropathy (7,8).

Other key studies have explored the impact of specific drug therapy on cardiovascular end points rather than through controlling hyperglycemia per se. In these studies, some degree of glycemic equipoise occurs, intended or otherwise, owing to extra use of other glucose-lowering therapies in the placebo arm. The PROspective PioglitAzone Clinical Trial in macrovascular Events (PROactive) assessed pioglitazone in people with TD2 with evidence of macrovascular disease (9). The broad primary cardiovascular end point was not significantly different compared with standard care, but the "main" secondary end point of all-cause death, stroke, and MI was significantly decreased by 16%. Participants with previous MI showed greater reductions of fatal/nonfatal MI by 28% and acute coronary syndrome by 37% (10). In the Outcome Reduction With Initial Glargine Intervention (ORIGIN) study (11), using insulin glargine in a large cohort of individuals with T2D, impaired fasting glucose (IFG), or impaired glucose tolerance (IGT), all with multiple cardiovascular risk factors, there was no effect on MACEs or these events plus revascularization or hospitalization for heart failure (HF) over 6.2 years.

Both use of a combined pharmacological approach to aggressively correct hyperglycemia and trials of a specific medication are associated with hypoglycemia and weight gain, either of which might have countered any benefit from HbA_{1c} reduction. However, the Look AHEAD (Action for Health in Diabetes) study (12), exploring the effects of decreased caloric intake and increased physical activity in individuals with T2D, showed no benefit on cardiovascular outcome over >13 years.

Reducing HbA_{1c} to Target: How and With Which Risks and Benefits?

Adverse Effects of Intensive Glucose Lowering

Building on the individual outcome studies, meta-analyses have assessed the

potential benefit of intensive glucose lowering on mortality and cardiovascular events in T2D (13–17), generally showing limited benefit for mortality, an ~10% reduction in the risk of microalbuminuria, and a 15–20% reduction in the incidence of nonfatal MI—these for an average glucose lowering of ~1.0% (11 mmol/mol) HbA_{1c}. A 16–20% reduction in MI in the intensive compared with standard therapy group was recently reported in ACCORD (18). The relatively limited benefits of intensive glucose lowering on macrovascular outcomes and mortality can partly be explained by good glucose control in the standard arms, inclusion of people with long-standing T2D and advanced vascular damage, concomitant control of other cardiovascular risk factors, aggressive medication regimens associated with risk of hypoglycemia and weight gain, and drug-drug interactions (19). Indeed, established CVD may have dampened the benefits of intensive glycemic control in the high-risk cohorts of ACCORD, ADVANCE, and VADT, all with a long duration of T2D (10 years) compared with the newly diagnosed population in UKPDS.

The role of hypoglycemia as contributing to excess mortality is debated. Specifically, it is unclear whether hypoglycemia has a causal effect or simply identifies frail individuals. Rates of hypoglycemia were increased in the intensive therapy groups of ACCORD, ADVANCE, and VADT (10.5 vs. 3.5, 2.7 vs. 1.5, and 21.2 vs. 9.9%, respectively) (4–6). Unfortunately monitoring of hypoglycemia in these trials was relatively crude and did not include detailed data that could help with understanding the issues. Biological mechanisms have been proposed for any causative role for hypoglycemia in CVD outcomes, including catecholamine release increasing myocardial workload (20), electrocardiogram QT-interval lengthening predisposing to ventricular tachycardia (21), increased vascular inflammation (raised C-reactive protein, interleukin-6 and -8, tumor necrosis factor-α, and endothelin-1) potentiating endothelial dysfunction and thrombotic risk (20), and perhaps increased vessel wall stiffness (22). However, post hoc and follow-up analyses from ACCORD and ADVANCE have questioned hypoglycemia as a causative factor for mortality with intensive glucose lowering. In ACCORD, severe hypoglycemia was associated with a higher risk of death in the standard rather than intensive therapy arm (4.5 vs. 2.8%) (23). Moreover, the excess deaths in the intensive arm persisted after further follow-up of 1.3 years in spite of convergence of diabetes therapy and HbA_{1c} (24). Similar conclusions were drawn from ADVANCE (25). The ACCORD Memory in Diabetes (ACCORD-MIND) trial found on brain MRI that symptomatic severe hypoglycemia was not associated with brain atrophy or white matter abnormalities (26). In ACCORD, severe episodes of hypoglycemia occurred more frequently in individuals with poor cognitive function and were frequently preceded by change in food intake (27,28). A similar association between severe cognitive dysfunction and severe hypoglycemia emerges from ADVANCE (29). These results suggest that cognitive function assessment and education programs might be indicated to potentially prevent hypoglycemia in patients with T2D. Severe hypoglycemia was associated with insulin deficiency, anti-islet autoimmunity, and baseline insulin use, suggesting that C-peptide levels and islet autoantibodies may serve as biomarkers for risk of severe hypoglycemia (30).

Weight gain is also associated with intensive glucose control. The ACCORD intensive therapy group gained 3.5 kg compared with 0.4 kg in the standard group (5), while in VADT the gain was 8.2 vs. 4.1 kg (6). Significant weight gain in the insulin/sulfonylurea arm was observed in UKPDS (2). In ACCORD, reduction of HbA_{1c} from baseline was associated with weight gain only when baseline HbA_{1c} was high, and in both ACCORD and ADVANCE beginning a thiazolidinedione or insulin was particularly associated with weight gain (31,32). The clinical significance of such weight gain is unclear, as both peroxisome proliferator–activated receptor-γ agonists and insulin are associated with increased insulin sensitivity.

HbA_{1c} Targets in Specific Subgroups

It has been noted that the populations studied, particularly in ACCORD and VADT, do not necessarily represent the average person with T2D as seen in ambulatory care. The study participants had 10-year disease duration or more, elevated HbA_{1c} at baseline (i.e., 8.2–9.4% [66–79 mmol/mol]), and established CVD or multiple risk factors (5,6). This has led to the hypothesis that the benefits of intensive glycemic control on macrovascular outcomes can be observed only in newly diagnosed T2D and after a long duration of intervention, as indeed seen in UKPDS (2). In agreement, a substudy of 301 participants with T2D in VADT showed a better effect of intensive compared with standard therapy to reduce cardiovascular events in people without computed tomography–detectable coronary artery calcification, a benefit lost with higher calcification score (33). In contrast, intensive glycemic control significantly increases the risk of cardiovascular and all-cause mortality in T2D patients with mild/moderate chronic kidney disease (34).

Current recommendations suggest that more stringent goals (HbA_{1c} <6.0–6.5% [<42–48 mmol/mol]) might further reduce complications in people with long life expectancy without documented macrovascular disease and/or if drugs not causing hypoglycemia are used. Moreover, glycemic goals should be pursued with caution in people with severe or frequent hypoglycemia. Aiming for an HbA_{1c} of 7.0–8.5% (53–69 mmol/mol) may be reasonable in people with very long diabetes duration, a history of severe hypoglycemia, advanced atherosclerosis, significant comorbidities, frailty, and limited life expectancy (35–38). However, it is not clear with what priority these criteria should be implemented and how to plan conduct when multiple elements are present. Tight glucose control will need to be maintained for >3–5 years to yield benefit. In ACCORD, excess mortality was found in those who showed an increase in HbA_{1c} with intensive glucose control (39); thus, people with worsening glycemic control when exposed to intensive treatment should be set less stringent glucose targets. Additionally, intensive treatment was associated with improved primary outcomes in people with low and moderate hemoglobin glycation index (HGI) (HGI = observed HbA_{1c} − predicted HbA_{1c}) but not with high HGI at baseline, and higher total mortality in intensively treated patients was confined to the high-HGI subgroup (40). A high HGI was also associated with greater risk for hypoglycemia (40). Finally, a retrospective subgroup analysis of the ACCORD data set, assessing the impact and tolerability of intensive glucose management in older versus younger adults (≥65 vs. <65 years), showed a 71% increased risk of cardiovascular

mortality in the intensive arm for the younger subgroup (41). However, older participants in the ACCORD trial were people in community/ambulatory care and not frail/disabled or institutionalized. A list of factors that may help in individualizing HbA_{1c} targets is given in Table 2.

Table 2—Potential criteria for individualization of glucose targets in T2D

	HbA_{1c} <6.5–7.0%	HbA_{1c} 7.0–8.0%
Individual preference	High input/motivation	Higher short-term focus
Age (years)	<55	>55
Diabetes duration (years)	<10	>10
Life expectancy (years)	>5	<5
Possible to perform IGC for >5 years	Yes	No
Usual HbA_{1c} level (%)	<8.0	>8.0
CVD	No	Yes
Prone to hypoglycemia (cognitive dysfunction, insulin deficiency)	No	Yes
Reduction of HbA_{1c} level upon IGC	Yes	No
HGI	Low/moderate	High

Information from refs. 3–6, 25–30,40. IGC, intensive glucose control.

Long-term Effects of Reducing HbA_{1c}

In ADVANCE, but not ACCORD, intensive glucose lowering showed benefit for surrogate end points of renal damage (microalbuminuria and macroalbuminuria or progression/regression of albuminuria) but also for renal outcomes (end-stage renal disease) (7,42). In UKPDS, the effects of tighter blood glucose control on MI took years to become evident and statistically significant, including for metformin (3). Even all-cause mortality eventually reached statistical significance after 17 years, though caution is needed in interpreting that result.

As our perspective on glucose control should be long-term, consistency of HbA_{1c} and glucose targets over time becomes important, since variability of these measures is associated with higher risk of vascular events and mortality, as shown in ADVANCE (43). More recently, long-term results from ACCORD, ADVANCE, and VADT, describing results over the years after a previous period of intensive glucose lowering, have become available (24,44,45). In ADVANCE, after 5.4 years follow-up with no evident between-group differences in HbA_{1c}, no differences were observed in the risk of all-cause or cardiovascular death between study cohorts (44). However, in VADT, with follow-up of ~10 years, a 17% lower risk of the primary outcome in the prior intensive glucose-lowering arm was noted, but total mortality and cardiovascular mortality were unchanged (45). The 5-year outcomes of 3.7 years of intensive glucose lowering in ACCORD showed trends for excess mortality and reduced nonfatal MI similar to those during the active intervention period. Altogether, these findings suggest that aggressive glucose lowering does not reduce mortality in the medium term in cohorts of individuals with advanced T2D and CVD. The benefit of previous intensive glucose control to reduce macrovascular complications in follow-up was confirmed in ACCORD and emerged in VADT but was not apparent in ADVANCE. Variations in participant characteristics, in-trial differences in HbA_{1c} between arms, duration of follow-up, HbA_{1c} trends, and management of other cardiovascular risk factors may explain the diverse findings in these posttrial extensions.

What Is the Role of Lifestyle Intervention?

The results from T2D prevention studies have been very positive in terms of preventing or delaying the development of T2D (46). The question here is, rather, whether such lifestyle intervention also prevents CVD and related events. However, none of these studies were designed or powered for CVD outcome evaluation. Nevertheless, they have provided useful information about the prevention of CVD in the high-risk group with IGT. Three types of information have been published

1. CVD mortality was significantly decreased in the former intervention group compared with the former control group in the Chinese Da Qing Diabetes Prevention Study (47). This difference started to be visible after 10 years from randomization (4 years after the intervention program had been stopped) and became statistically significant by the 23-year follow-up.
2. The Swedish Malmö Feasibility Study in middle-aged men with IGT provided lifestyle intervention and compared CVD outcomes with data from men who did not take up the interventions offered (48). CVD mortality was lower in the participants in the intervention arm and, indeed, almost similar to that in normoglycemic men from the original screened population.
3. The Finnish Diabetes Prevention Study (DPS) (51) gave results similar to those of the Swedish study. Outcomes of participants to the DPS were compared with those from a population survey using similar methods (49,50). The results showed that people with IGT in the DPS had significantly lower CVD incidence and mortality than in people with IGT in the survey cohort. Indeed, total mortality was >50% lower in the DPS cohort than in normoglycemic people in the background population, although prevalence of the metabolic syndrome was almost identical at baseline (51).

In line with the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) data (52,53), there was no indication in the DPS that a single measurement of fasting plasma glucose is useful for prediction of CVD risk (54). There is no evidence that people with IFG will benefit from lifestyle intervention, the only study in those with isolated IFG being negative (55). Thus, measurement of fasting plasma glucose for the assessment of CVD risk is not justified, consistent with the recommendations provided in the current European guideline on diabetes, prediabetes, and CVD (56).

In addition to the lifestyle intervention trials, the Study to Prevent NIDDM (STOP-NIDDM) using acarbose as the intervention in individuals with IGT showed a statistically significant reduction in CVD rates (57) but with few CVD events. A further

study is ongoing in China (58). In the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study, involving 9,306 individuals with IGT, participants with CVD or one or more additional cardiovascular risk factors were randomized to receive nateglinide, valsartan, or placebo and followed for CVD events (cardiovascular mortality, nonfatal stroke, or MI [MACEs]) for 6 years (59). Pedometer-assessed baseline ambulatory activity and change in ambulatory activity at 12 months were inversely associated with CVD events (60). Results for change in ambulatory activity were unaffected after adjustment for changes in BMI and other potential confounding variables at 12 months.

In contrast, in people with T2D the effects of intensive lifestyle intervention using decreased calorie intake and increased physical activity showed no benefit on the primary outcome (MACEs or hospitalization for angina) over a follow-up of >13 years in spite of greater weight loss, lower HbA_{1c} levels, and early improvement in multiple cardiovascular risk factors (12).

Does Choice of Glucose-Lowering Therapy Matter?

The evidence on glucose-lowering therapy and cardiovascular outcomes, reviewed above, leaves open the question as to what medication might be chosen to improve outcomes or to avoid adverse events. Even after 50 years of use of three of the classes of glucose-lowering therapies, the answer is uncertain. Newer therapies in three drug classes have been tested recently, but study design will probably lead to some clinical confusion and debate for reasons like populations studied and comparator therapies.

Widespread use of glucose-lowering therapies should allow examination of their performance in routine clinical practice. However, observational studies lack suitability for this, except perhaps in a hypothesis setting (61). The major problem is that the circumstances of prescription (e.g., ambulatory care, referral to secondary care, hospital admission) and the prescriber (e.g., primary health care, diabetologist, tertiary care) should have very large effects on outcomes, dwarfing differences between drug classes, but are not generally ascertained. Because of the stepped algorithm for glucose-lowering therapy, with preference of order for some classes before others, and because of contraindications associated with vascular disease, biases related to comorbidities are likely to be large.

Understanding of pathogenetic mechanisms can be useful to explain a known issue, such as hypoglycemia with sulfonylureas. However, where an in vitro finding might suggest a speculative effect (e.g., sulfonylureas and cardiac ion channels, insulin and arterial cell wall proliferation), the prior probability of a clinically significant issue is little changed, despite our innate drive to use weak knowledge. Presently, understandings of mechanisms of efficacy are poor—that of metformin is still disputed, as is control of hepatic glucose output by insulin.

Thus, only evidence from randomized controlled trials (RCTs) is presently of value in determining clinical practice. However, the RCT evidence is of limited fit for purpose, mainly owing to difficulties regarding generalizability to typical populations with diabetes.

Metformin

Metformin is first line in therapy algorithms, combining effective glucose lowering with weight neutrality and no hypoglycemia (62). The RCT evidence for vascular protection comes from a substudy of UKPDS in which it was mostly used as monotherapy and not as per current practice (63). The overweight substudy numbers investigated were small (n = 753), and despite long duration of follow-up (10.7 years), so were events (MI, n = 112; 39 on metformin). The estimate of reduction of MI was good, but the CIs were large; the upper bound (0.89) overlaps the central estimate for sulfonylureas/insulin (Table 3). The follow-on study showed some loss of effect, suggestive of regression to the mean. The conclusion is that metformin gives vascular protection in monotherapy but that the extent of this is unknown and not different from sulfonylureas and insulin. Use of metformin in ADOPT (A Diabetes Outcome Progression Trial), and as a comparator to rosiglitazone use in RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes), is discussed below; these studies do not suggest that metformin differs from other medications in cardiovascular protection.

Sulfonylureas

Sulfonylureas were major components of the UKPDS (2). However, the primary result was analyzed together with basal insulin therapy, complicating interpretation of the results. For this combined group, the effect on MI became mired in uncertainty, but an upper bound of 1.00 of the 95% CI against conservative therapy suggests caution in deciding the probability of vascular protection (Table 3). However, in the extension phase, with larger numbers of events and no change in the central estimate of risk reduction (15%), the CIs shrink to 0.74–0.97, suggesting benefit and not harm. There was also a statistically significant reduction in all-cause mortality (3) (Table 3).

In ADOPT, with vascular outcomes a secondary safety outcome and relatively small numbers (e.g., 5% of 1,441 participants in the sulfonylurea cohort), glibenclamide outperformed both metformin and rosiglitazone with regard to MI (64,65). In RECORD, where half the participants were randomized to sulfonylureas versus rosiglitazone, vascular outcomes were identical and by extension similar to metformin (66) (Table 3). In ADVANCE, although not a study of specific therapies, the primary glucose-lowering intervention choice was gliclazide; as the central estimate of effect on vascular outcomes was <1.00 and the upper CI only 1.06, an adverse effect of the sulfonylurea is denied (4).

Acarbose

Post hoc meta-analysis of seven RCTs with acarbose in 2,180 people with T2D and ≥1 year follow-up (67) suggested decrease in MI and any CVD. A definitive RCT seems warranted (58).

Peroxisome Proliferator–Activated Receptor-γ Agonists

Vascular outcome studies after licensing were mandated by the European authorities because of HF concerns. For pioglitazone, the 3-year PROactive study had a composite vascular end point that was not statistically significant due to the inclusion of peripheral arterial interventions, which diverged from the usual cardiovascular study outcomes (9) (Table 3). A secondary analysis (prespecified shortly before study completion) of

Table 3—Characteristics and outcomes of the larger (n > 1,000) cardiovascular outcome studies of specific glucose-lowering therapies

Study	N	Follow-up (years)	Medication and comparator	CVD inclusion criteria	CVD history (%)	Primary end point[a]	Primary end point, HR (95% CI)	All-cause mortality, HR (95% CI)
UKPDS Glucose[a]	3,867	10	Sulfonylurea or insulin vs. none	Most excluded	2	MI	0.84 (0.71–1.00)	0.94 (0.80–1.10)
UKPDS Glucose extension[a]	3,277	17	Sulfonylurea or insulin vs. none	Most excluded	2	MI	0.85 (0.74–0.97)	0.87 (0.79–0.96)
UKPDS metformin[a]	753	11	Metformin vs. none	Most excluded	Not given	MI	0.61 (0.41–0.89)	0.64 (0.45–0.91)
PROactive	5,238	2.9	Pioglitazone vs. "placebo"[b]	CVD	100	Broad CV composite, MACEs[c]	0.90 (0.80–1.02), 0.84 (0.72–0.98)	0.96 (0.78–1.18)
RECORD	4,447	5.5	Rosiglitazone vs. sulfonylurea or metformin	No recent event	21	Any CV hospitalization, MACEs	0.99 (0.85–1.16), 0.93 (0.74–1.15)	0.86 (0.68–1.08)
SAVOR-TIMI	16,492	2.1	Saxagliptin vs. "placebo"[b]	CVD or high CV risk	78	MACEs	1.00 (0.89–1.12)	1.11 (0.96–1.27)
EXAMINE	5,380	1.5	Alogliptin vs. "placebo"[b]	Post-ACS	100	MACEs	0.96 (0.83–1.16)	0.88 (0.71–1.09)
TECOS	14,724	3.0	Sitagliptin vs. "placebo"[b]	CVD	100	MACEs	0.99 (0.89–1.11)	1.01 (0.90–1.14)
EMPA-REG OUTCOME	7,020	3.1	Empagliflozin vs. "placebo"[b]	CVD	100	MACEs	0.86 (0.74–0.99)	0.68 (0.57–0.82)

Information from refs. 2,9,66,68–71. MACEs: cardiovascular death plus nonfatal MI or stroke. ACS, acute coronary syndrome; CV, cardiovascular. EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction; TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin. [a]For UKPDS, cardiovascular end points are given separately; here, MI is given. [b]"Placebo" plus titration of other glucose-lowering therapies. [c]MACEs in PROactive included all-cause mortality—not cardiovascular mortality.

the classic MACEs, but using all-cause mortality, did provide evidence of vascular protection (95% CI 0.72–0.98). One difficulty, which also affects several current cardiovascular outcome trials, is that the comparator arm was investigator-discretion standard of care (described misleadingly as "placebo"), meaning that it is unclear what pioglitazone was being compared with. Indeed, pioglitazone has good glucose-lowering efficacy, but the HbA_{1c} difference at end point was 0.5% (5 mmol/mol), suggesting efficacy of other medications in the placebo group; if these were beneficial, then the pioglitazone effect is greater than described, and, if adverse, lesser.

Secondary data for rosiglitazone as monotherapy are available for myocardial ischemia from ADOPT, with results similar to those of metformin but worse than those of glibenclamide (64,65). In RECORD, over 5 years, rosiglitazone was compared with metformin and sulfonylureas, all as dual therapy (66). Cardiovascular outcomes were not worse than these, including all-cause mortality (RR 0.86 [95% CI 0.68–1.08]) and MACEs (0.93 [0.74–1.15]) and against the two comparators individually. The exception was HF, increased by ~1 in every 400 person-years, though including HF with MACEs still gave equivalence (0.99 [0.81–1.20]). Because a small and flawed meta-analysis of early rosiglitazone studies gave an adverse result, the RECORD study data were reanalyzed independently and not found wanting (68).

Incretin-Based Therapies and Sodium–Glucose Cotransporter 2 Blockers

No definite information is yet available as to whether dipeptidyl peptidase 4 inhibitors or GLP-1 receptor agonists (GLP-1RAs) offer cardiovascular advantage as glucose-lowering agents, except by extension from glucose-lowering results with other agents in UKPDS and ACCORD (2,5) and the meta-analyses of such studies (13–17). Although cardiovascular outcome studies have been reported, they have been performed in high-risk populations for short periods of time as safety studies and suffer the same problem of pseudo-placebo comparators as discussed for pioglitazone (69–71) (Table 3). In some studies, glycemic equipoise was an aim (equal glucose control in the two arms to test

medication differences only) but not achieved (71).

For sodium–glucose cotransporter 2 (SGLT-2) blockers, a similar situation pertains, in that the only reported study (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients [EMPA-REG OUTCOME]) is in people with prior CVD and had an unusually high initial event rate (72). The primary objective was a significant reduction of MACEs (hazard ratio [HR] 95% CI 0.74–0.99), but its components of cardiovascular death, MI, and stroke behaved very differently. While cardiovascular mortality was reduced significantly in the empagliflozin group (95% CI 0.49–0.77, $P < 0.001$), it was a secondary outcome when considered alone, and it is unclear that this is related to classic cardiac events or more specifically to improvement of HF (95% CI 0.50–0.85 for hospitalization). It is unlikely that the results were due to glucose lowering. Stroke incidence was not reduced (95% CI 0.89–1.56) despite significant fall in blood pressure with empagliflozin.

Both SGLT-2 blockers and GLP-1RAs might be expected to affect the fundamental defect of T2D in the liver by improving net substrate load (calorie balance) and, as a result, improving features of that defect (metabolic syndrome, fatty liver, inflammation) that are associated with CVD. Therapies that produce a negative calorie balance may well show advantage additional to that of glucose lowering in time. Such a comment has little relevance on probability of clinical cardiovascular advantage until further RCT results are available.

Insulin Therapy

The RCT evidence regarding insulin is not easy to interpret. In UKPDS, insulin was part of the major glucose-lowering interventions used as monotherapy (though discontinued by 30% of those randomized to it and not titrated intensively); the conclusions above from that study for sulfonylureas apply in part to insulin (2). In ACCORD, insulin was a major part of the group of therapies showing cardiovascular advantage for ischemic heart disease when the study was stopped prematurely but impossible to separate from them (5,18). A post hoc analysis of different therapies

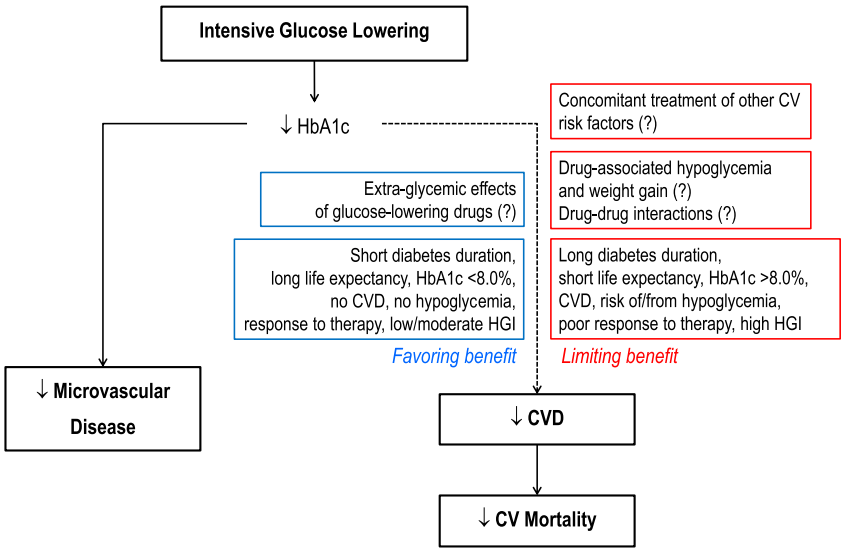

Figure 1—Relationship between intensive glucose control and vascular complications in T2D. CV, cardiovascular.

was shown in the initial ACCORD results' presentation but has never been published. The ORIGIN results are discussed in the first section of this review (11), but here again the comparators are a mix of other agents, with little separation in HbA_{1c} and at levels close to the diagnostic cutoff for diabetes.

Conclusions

The findings from UKPDS, ACCORD, ADVANCE, and VADT have provided important insights into the balance of benefits and risks associated with the use of glucose control in people with T2D. However, the relationship between control of hyperglycemia and cardiovascular risk remains relatively controversial, and evidence that intensive antihyperglycemic therapy will reduce mortality in T2D patients in the long-term is evident in some but not in all studies. Individualization of therapy then becomes important and should be implemented based on multiple factors, including diabetes duration, preexisting CVD, hypoglycemia risk, comorbidities, response to therapy, frailty, and other factors (Fig. 1). While lifestyle intervention may reduce CVD outcomes in individuals with IGT, such evidence in overt T2D is still lacking. Nevertheless, healthy diet and physical activity do not result in harmful effects and can be associated with other benefits besides CVD prevention.

The evidence for the cardiovascular benefit of any one class of glucose-lowering medications compared with any other is also weak at present. This may potentially change if the medications that improve calorie balance (i.e., SGLT-2 blockers and GLP-1RAs) turn out to change the metabolic milieu to a degree that will improve the underlying mechanisms of T2D and CVD. The recent results from the trial with empagliflozin are interesting and promising, but we need to wait for results from other ongoing trials with SGLT-2 blockers in order to understand whether they really reduce CVD risk in T2D patients or affect predominantly cardiovascular mortality and worsening HF. Choice of therapies to achieve optimal outcomes is still largely to be based not on comparative vascular outcomes but on other features such as tolerability (hypoglycemia, gastrointestinal side effects, body weight gain), safety, cost, and convenience.

Duality of Interest. F.G. has served on an advisory panel for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Roche Pharmaceuticals, Takeda Pharmaceutical Company, and Janssen Pharmaceuticals; has served as a consultant for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, LifeScan Animas, Merck Sharp & Dohme (MSD), Novo Nordisk, and Sanofi; and has received research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, LifeScan Animas, and Sanofi. P.D.H. has served on an advisory panel for AstraZeneca, Antriabio, GlaxoSmithKline, Janssen, MSD, Novo Nordisk, Roche Diagnostics, Sanofi, and Skyepharma; has received speaking honoraria for AstraZeneca, Biocon, Eli Lilly, MSD, Novo Nordisk, and Sanofi; and has

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