Controversies for Glucose Control Targets in Type 2 Diabetes: Exposing the Common Ground

Philip Home

Diabetes Care 2019;42:1615–1623 | https://doi.org/10.2337/dci19-0002

Glycated hemoglobin targets have been given in guidelines for the last three decades, mostly without change at around 6.5–7.0% (47–53 mmol/mol). Personalization of such targets has also long been advocated, but often with little and inappropriate guidance. More recently some have suggested higher targets might be indicated, and more specifically lower targets avoided, even in those in whom they are easily attained without seeming burden or risk. Prospective data from randomized and observational studies, in people with type 2 diabetes and indeed those without diabetes, find cardiovascular and mortality risk are uniformly lowest at lower levels including into the normal range. In some studies with large populations, a high proportion of people are found to attain such levels, and the UK Prospective Diabetes Study (UKPDS) and more recent studies appear to confirm the importance of starting low and continuing long. Studies of cardiovascular events and mortality in people with diabetes will already factor in any effect of hypoglycemia, which therefore should not be double-counted in setting targets. Nevertheless, some factors should lead to modification of target levels, and these will include experience of hypoglycemia where therapy change and glucose monitoring cannot ameliorate it and sometimes prospectively in those at social or occupational risk. The fact that clinical experience will modify targets emphasizes that targets will not be stable over time but will change, for example, with occurrence of adverse events or perceptions of increase/decreased burden of therapy. The evidence suggests that glucose control takes 5 years or more to have any impact on vascular outcomes or mortality, so targets may also be higher in those with shorter life expectancy or higher health burden or simply reflect individual preferences. This article discusses the evidence behind these conclusions.

Targeting of glucose control has been an intrinsic part of diabetes clinical practice for as long as clinicians were able to help people with diabetes ameliorate hyperglycemia. Evidently, earlier in clinical history such a target would be amelioration of symptoms related to glycosuria and weight loss, but with the advent of semi-quantitative testing for urinary glucose and the demonstration of association of the degree of glycosuria with microvascular complications (1), targets based on glucose measurements appeared. Insulin therapy added to the symptomatic targeting through the desire to avoid hypoglycemia, notably prior to the availability of blood glucose measurements that might enable prediction of it.

The advent of self-measurement of blood (later calibrated as plasma) glucose and assay of glycated hemoglobin (HbA_{1c}) enabled people with diabetes and their advisors to develop individual targets of glucose control, notably with the rise of new insulin and insulin delivery methods in the early 1980s. These assessment and therapy tools

Newcastle University, Newcastle upon Tyne, U.K.

Corresponding author: Philip Home, philip.home@newcastle.ac.uk

Received 20 March 2019 and accepted 22 April 2019

also led to the major clinical trials conceived around that time, and while those randomized more optimal therapeutic approaches against traditional approaches, the effect cannot be distinguished from better versus more neglected blood glucose control. In both the Diabetes Control and Complications Trial (DCCT) (and Epidemiology of Diabetes Interventions and Complications [EDIC] follow-up) and UK Prospective Diabetes Study (UKPDS), the glucose control characteristics of the randomized cohorts and relationship with vascular complications were largely described in terms of HbA_{1c}, even though in both studies therapy adjustments were driven by plasma glucose estimation (2,3). Accordingly, it is HbA_{1c} that has become the principle modality for targeting both in clinical practice and for regulatory purposes, with a very recent challenge appearing from continuous glucose monitoring (4).

While the studies confirm benefit from more physiological glucose control (discussed further below), there are caveats to that, notably in how quickly such benefits are realized. Indeed, the feasibility study for the DCCT, the Kroc study, alerted researchers to the paradoxical effect of improved glucose control on retinopathy progression in the short term, which was confirmed in the main study where advantage only began to emerge after 3 years—perhaps to a clinically useful extent after 5 years (2,5). In type 2 diabetes (T2D) the situation is similar, with Kaplan-Meier curves suggesting advantage certainly after 5 years and for some outcomes (e.g., death reduction with metformin) after 8 years (3,6). Meanwhile, concern over hypoglycemia as an acute tolerability problem came to be joined by concern over the possibility of precipitation of vascular events. While less voiced, but perhaps with a larger effect on targeting, concern came from people with diabetes being evidently burdened by the self-management of their condition and its associated medical problems.

A consequence of the continuous relationships between control and complications, most evident for macrovascular disease where there is no threshold level (7) and the poorly and uncertainly defined risk from hypoglycemia, has been huge variations in clinical practice. Further, it has been difficult to understand the extent to which therapeutic inertia in attaining glucose control nearer to physiological levels has been due to these uncertainties, the way diabetes care is practiced, or the perceived burden of management. Guidelines for diabetes have suggested HbA_{1c} should be targeted to close to the upper end of the normal range since about 1990 (8), but the reality since that time has been and remains very different, despite demonstrations in the current century that even with those needing insulin therapy such approaches are realistic.

Most guidance on targets for HbA_{1c} is on common ground, with 7.0% (53 mmol/mol) with some modification upward appearing commonly (Table 1). Indeed, the current discrepancies between standards are small compared with what is being achieved in clinical practice and mostly relate to whether marginally lower levels (6.5% [48 mmol/mol]) should be strived for, or even lower levels accepted if tolerated without documented risk. Nevertheless, the epidemiological data from the studies (discussed below) do suggest the differences are meaningful, and it therefore behooves the diabetes community to understand what the quantitative evidence tells us and then consider how to put that into practice in the face of clinical reality.

PERSONALIZATION: AGREED NEED, BUT VARYING APPROACHES

Individualization of targets for HbA_{1c} has been recognized as desirable or needed in guidance published over the last 30 years (Table 1), although often as a simple list of reasons to assess target appropriateness rather than advice on how to proceed. Secular changes in emphasis on individualization can however be recognized with, for example, "the elderly" and the discrimination that implies, being moderated into "frailty" and the presence of comorbidities. Currently life expectancy in the U.K. (50% chance) is 8–9 years at age 80 years dependent on sex and thus long enough to benefit from HbA_{1c} reduction, with a 1 in 4 chance of living to 93–94 years (20). If you attain age 90 years, the average life expectancy does drop to 4–5 years, which is perhaps not long enough to gain vascular benefit of tighter glucose control (see below). But these are average figures that include the frail, the diseased, and the unfit and take no account of family history of longevity. While having diabetes will on average reduce these figures, the loss of life expectancy at later age is lower than in middle age (21), so a fit person with diabetes will perhaps be similar to the average of the general population.

While age is an obvious association with frailty and a higher burden of comorbidities, many older adults are indeed relatively fit these days, emphasizing that it is individual assessment of risk, life expectancy, and disease/therapy burden that is required rather than labeling by age (Table 2). Presently, guidelines on HbA_{1c} targeting are very disparate on personalization, but this is mostly due to neglect or superficial coverage of the issue, with the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) Position Statement of 2012/2015 being the obvious exception (16,17). Duration of diabetes from diagnosis is included as a criterion in that but is also problematic; it certainly associates with disease burden and difficulty of achieving good glucose control, but these things can be individually or iteratively assessed rather than using the label of long duration. Again, clinical practice tells us that many people of very long diabetes duration can still manage glucose control close to physiological levels and without troublesome tolerability issues or other risk.

The concept of iterative setting of targets is rarely promulgated in published guidance but is usual in clinical practice and central to the setting of individual targets. Clinically, people with diabetes are seen recurrently, and this means that such things as experience of adverse events (or otherwise, such as absence of symptomatic or biochemical hypoglycemia) can and should modify a personal glucose control target with time. Similarly, evolving burden of disease, notably from therapy changes themselves, can best be assessed over a series of consultations, while personal preferences may evolve. Fairly obviously, other factors may and will also change over time, such as clinical events affecting life expectancy and development of frailty or social isolation.

These factors also associate with personal preferences, which make a fairly late entry into the criteria for target

Table 1—A history of some approaches to targeting of HbA_{1c} for people with T2D

Source	Group	Year	HbA_{1c} target		Caveats/notes
			%	mmol/mol	
IDF Europe	European NIDDM Policy Group (8)	1989	Good <6.8*	<51	Individualized for each patient; including the elderly
			Poor >7.5*	>58	
St. Vincent Initiative†	European NIDDM Policy Group (9)	1993	Good <6.5	<48	Individualized for each patient; including the elderly
			Poor >7.5	>58	
IDF Europe	European Diabetes Policy Group (10)	1999	Low risk ≤6.5	≤48	Level for intervention with oral agents; ≤7.5% for insulin
ADA	Standards of Care (11)	2000‡	<7.0	<53	Lower if easily achieved; higher if comorbidities or unfeasible
IDF Global	Clinical Guidelines Task Force (12)	2005	<6.5	<48	If feasible and easily attained; raise if hypoglycemia risk
ADA/EASD	Consensus Group (13)	2009	<7.0	<53	Follows ADA Standards of Care 2008
IDF Global	Clinical Guidelines Task Force (14)	2012	<7.0	<53	Lower if easily achieved; higher if comorbidities or unfeasible
AACE	Consensus Statement (15)	2013§	<6.5	<48	Unless unsafe or inappropriate
ADA/EASD	Position Statement (16,17)	2012/2015	<7.0	<53	More and less stringent individualization emphasized
ADA/EASD	Consensus Report (18)	2018	<7.0	<53	Personalized on preferences, risk of adverse events, frailty, comorbidity
ACP	Guidance Statement (19)	2018	7.0–8.0	53–64	Personalized; concern if <6.5% (48 mmol/mol)

AACE, American Association of Clinical Endocrinologists; ACP, American College of Physicians; IDF, International Diabetes Federation; NIDDM, non-insulin-dependent diabetes mellitus; WHO, World Health Organization. *Given as HbA1 and converted here to HbA_{1c} by the current author. †An initiative of WHO Europe and IDF Europe. ‡Published and updated yearly, but with no change in this standard. §Subsequent revisions in conjunction with American College of Endocrinologists—unchanged target.

setting. Personal preferences differ from "attitude and expected treatment efforts" of the ADA/EASD 2012/2015 document (16,17), a criterion again better assessed iteratively by trials of therapy rather that predefined prejudice. Personal preferences also differ from resource and adherence issues but may be related to them. All these things do require informed discussion, and this would again be around burden of disease and benefit-risk from more attentive management.

Hypoglycemia is for the most part an issue of disease burden (tolerability)—the issue of cardiovascular (CV) risk from hypoglycemia is discussed below. Most guidelines that do mention it (surprisingly few) refer to "risk" rather than burden of hypoglycemia. In practice, the risk even with sulfonylureas and basal insulin is low and is perhaps best assessed by an informed trial of therapy (3,22). Evidently, there are individuals for whom the risk from hypoglycemia is higher. In these circumstances, it is perhaps choice of a glucose-lowering agent rather than an HbA_{1c} target that needs to be addressed; however, where insulin therapy is inevitable, that target may have to be modified, although this can subsequently be guided by experience of hypoglycemia and variability in the results of day-to-day glucose monitoring.

None of the guidance documents properly address the extent to which HbA_{1c} targets may be changed by individualization. A *Diabetes Care* Editors' Expert Forum did attempt this and suggested levels up to 7.5–8.5% (58–69 mmol/mol) from a usual <7.0% (53 mmol/mol) level, informed by social and psychological management issues as well as personal preferences and comorbidities (23). But there is little evidence to inform these higher levels. We do know that poor glucose control is associated with lethargy, acute changes in thrombogenicity, infection risk, symptomatic glycosuria, and urinary incontinence (Table 3), but the potential health burdens from these are for the most part difficult to assess in the individual, and quantitative data on association with HbA_{1c} are unavailable. Some of these issues, in particular those associated with glycosuria, sarcopenia, and tiredness, are a particular burden in the frail older adult, and as such at least partially offset any impetus to higher glucose control targets in such people.

GLUCOSE TARGETS TO AMELIORATE VASCULAR RISK

The evidence base for the relationship between glucose control as a continuous variable, as needed to set targets, and vascular outcomes or death is necessarily observational, although such data may best be obtained within the context of glucose control or therapy trials. Randomized trials of control levels such as Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) may achieve differential control, but the better controlled group will have a mean at just one level, although some indication may be obtained from subanalysis by control level, as in ADVANCE (24). Randomized trials of specific therapy approaches such as the UKPDS have generated HbA_{1c} trajectories that

Table 2—Comments on some of the criteria given in guidelines on individualization of targeting HbA_{1c}

Criterion	Sources	Current author's comment
The elderly/age	Many, beginning with European NIDDM Policy Group 1989 (8)	Discriminatory and unacceptable. The factors associated with higher acute risk or poor life expectancy can be clinically ascertained.
Good control easily achieved	ADA Standards of Care 2000 (11); IDF Global 2005 (12)	Logically correct, and observational studies confirm association with good outcomes well into the normal range of HbA_{1c}. Clinical practice would suggest that for people on insulin, assessments of diurnal glucose to detect periods of hypoglycemia are sensible.
Duration of diabetes	ADA/EASD Position Statement 2012/2015 (16,17)	As with age, discriminatory, and better to assess burden of disease and burden of therapy; vascular complications can develop after many decades, so while some people are seemingly immune, good control should not be abandoned.
Life expectancy	ADA/EASD Position Statement 2012/2015 (16,17)	Use average life expectancy tables for age, but then modify according to the presence of comorbidities. Logical, as glucose control takes years to affect vascular outcomes.
Presence of comorbidities	ADA Standards of Care 2000 and others since (11)	A determinant of life expectancy, of ease of attaining good HbA_{1c}, and of risk of hypoglycemia including severe hypoglycemia; thus, useful if assessed carefully.
Presence of CV complications	ADA/EASD Position Statement 2012/2015 (16,17)	No evidence that this differs from "presence of comorbidities"; hypoglycemia may or may not be causative for CV events, but can be a problem at any level of HbA_{1c}.
Risk of hypoglycemia	IDF Global 2005 (12); ADA/EASD Position Statement 2012/2015 (16,17)	Problematic, as associates with problems of attaining good HbA_{1c}, comorbidities, and therapy burden; otherwise better managed by iterative management of therapy and targets as it occurs. Exceptions would be frail people living alone and the like; occupational/recreational risk better managed by glucose monitoring rather than prospective HbA_{1c} target change.
Attitude and expected treatment efforts	ADA/EASD Position Statement 2012/2015 (16,17)	Patronizing and unacceptable. Patient involvement is best assessed iteratively with trials of agreed therapy. Burden of therapy and preferences may then become reasons for accepting higher targets.
Personal preferences	EASD/ADA Consensus Group 2018 (18)	Certainly needs informed discussion; long a part of acceptable diabetes practice.
Insulin therapy vs. oral agents	IDF Global 2005 (12)	Overlaps with what is achievable and burden of therapy; in practice best approached iteratively to find what is achievable.
Resources and support system	ADA/EASD Position Statement 2012/2015 (16,17)	Sadly, occasionally realistic. Intrinsic to the IDF Global 2005 "Minimal care" approach. Practically not a predetermined criterion to adjust targets, but may be a driver toward accepting higher levels.

deteriorate with time (3), so the average control in the intervention and control groups has little meaning except in calculating a difference between them (the difference being largely stable over 12 years). Accordingly, within-study observational analysis can be useful in understanding how CV risk and mortality relate to updated (study average) HbA_{1c} levels (7). A small number of other studies provide prospective data on this relationship (Table 4), which is useful because these include diverse scenarios such as insulin-treated people (insulin starters), very large population studies including those of the newly diagnosed, and a study of a population mainly of people who do not have diabetes (Table 4).

Retrospective observational studies are not useful for this purpose. As with the old cholesterol and blood pressure studies, and indeed studies of body weight, J-shaped curves abound. The cause of this is easily understood for all these measures as well as HbA_{1c}, because ill people with, for example, heart failure, malignancy, incapacitating CV disease, and serious psychological disease (among many others) tend to be anorexic, lose weight, and drop blood glucose levels, serum cholesterol, and blood pressure. Such studies are then confounded at lower levels of the independent variable. Examples are a U.K. study and a recent study from Hong Kong

Table 3—Adverse events and symptoms affected in the short-term by poorer blood glucose control

Event or symptom
Urinary frequency
Urinary incontinence
Urinary and genitourinary tract infection
Systemic infection (septicemia, skin, fascitis, foot, other)
Infection-associated ketoacidosis and hyperosmolarity
Weight loss and sarcopenia
Tiredness and lethargy
Painful neuropathy
Thrombogenicity (CV events)

(30,31). Confounding of a different kind may be a limitation of the prospective studies in Table 4. HbA_{1c} will associate with other CV and mortality risk factors, again notably blood pressure and serum cholesterol, and although some studies statistically adjusted for these, there may be other hidden confounders, such as attitude toward self-care or access to optimal medical care. For example, some of the finds of the Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk) study may be so affected (28).

The message from the studies listed in Table 4 is universally consistent in saying there is no lower level of HbA_{1c} that is not associated with better CV (or mortality) outcomes, that is, the lower the better well into the normal range. In the analysis by Stratton et al. (7) from the UKPDS, myocardial infarction has a linear positive relationship with HbA_{1c} extending from the lowest cohort at 5.0–6.0% (all assays in these articles appear to be NGSP standardized, or in this case normalized). Log-linear relationships are presented for hazard, again increasing from the lowest cohort, with diabetes-related death and all-cause mortality increases of 21 and 14% per 1.0% (11 mmol/mol) increase in HbA_{1c}. In ACCORD, the data are presented by Riddle et al. for mortality; the data in the intensively managed group are clearly log-linear from HbA_{1c} 6.0% upward with tightest CI in the 6.0–7.0% region, with more equivocal findings in the standard control group (25). ADVANCE data are only available for subgroup analysis for people with HbA_{1c} $<$7.2% but whom had dramatically lower CV event rates by some 37% compared with those with HbA_{1c} $\geq$7.2% (24). This was equally true for both the more intensive and more conventionally managed groups, providing a useful sensitivity analysis. The Cardiovascular Risk Evaluation in people with Type 2 Diabetes on Insulin Therapy (CREDIT) study was of insulin starters on diverse investigator-chosen insulin regimens, and the post hoc (but planned) multiple regression analysis showed independent effect of HbA_{1c} on CV events of 25% reduction per 1.0% (11 mmol/mol) HbA_{1c} over a range with a lowest interquartile of 6.7% (50 mmol/mol), implying 25% of patients below that level (26).

Population studies include the large North Island New Zealand study of people with T2D, aged 50–70 years (interquartile range [IQR]) (27). The HbA_{1c}:CV risk relationship is log-linear upward beginning with the cohort with HbA_{1c} 5.0–6.0% (31–42 mmol/mol). With 25% of the population below an HbA_{1c} of 6.4% (46 mmol/mol) at first annual review and half below 7.1% (54 mmol/mol), the study is powerful in the lower range. Data from the recently published Diabetes & Aging Study generates some methodological concern because of the conditional inclusion of 10-year survivors but is useful because newly diagnosed people are also a criterion for inclusion, and some effect of duration of tighter control from diagnosis can be seen graphically (29). Thus, both for microvascular and major vessel disease, the cohort with HbA_{1c} $<$6.5% (47 mmol/mol) for the first year, or any period of years from diagnosis up to 7 years, did better than the cohorts with higher HbA_{1c}, with risk being incremental and worsening with the duration of higher HbA_{1c}. Lastly, the EPIC-Norfolk study was in men (mostly without diabetes) and thus with cohorts mainly within the normal range for HbA_{1c} (28). Lowest rates (age-adjusted) of CV and all-cause death were in the group with HbA_{1c} $<$5.0% (31 mmol/mol), increasing across the four cohorts with highest rates then in those with HbA_{1c} $\geq$7.0% (53 mmol/mol)

Table 4—Larger studies reporting prospective observational data on the relationship of HbA_{1c} to mortality and vascular outcomes

Study	Population	Follow-up (years)	*n*	Findings (CV events and mortality)
UKPDS	Recently diagnosed T2D (7)	10	3,642	Myocardial infarction lower with lower HbA_{1c} down to within the normal range (cohort of 5.0–6.0%)
ACCORD	T2D (8 years) (25)	3.4	10,251	Mortality lowest with lower HbA_{1c} down to 6.0% (intensive therapy group)
ADVANCE	T2D (8 years; global population) (24)	5	11,140	37% less vascular events at HbA_{1c} $<$7.2% vs. higher levels
CREDIT	T2D insulin starters (26)	4	2,999	25% increased risk of CV events per 1.0% HbA_{1c} (updated HbA_{1c} IQR 6.7–8.4%)
Elley et al.	New Zealand T2D (27)	1–5	48,444	Steady exponential rise in CV event risk from lowest HbA_{1c} cohort (5.0–6.0%) upward
EPIC-Norfolk	Men, aged $>$45 years (population-based) (28)	2–5	4,662	Mortality and CV events lower with lower HbA_{1c} over range of $<$5.0 to $>$7.0%
Diabetes & Aging Study	Newly diagnosed T2D, 10-year survivors (29)	13	34,737	HbA_{1c} $<$6.5% from diagnosis (1–7 years) less CV events with progression of risk at any higher level

HbA_{1c} units (%, mmol/mol): 5.0, 31: 6.0, 42; 6.5, 47; 6.7, 49; 7.0, 53; 8.4, 68; 1.0% change, 11 mmol/mol.

but with no effect on non-CV death. The authors performed multiple regression analysis adjusting for conventional CV risk factors, showing a 29 and 38% increase per 1.0% (11 mmol/mol) increase in HbA_{1c}.

While it is clear that better blood glucose control is associated with better outcomes (for hypoglycemia, see below) at any level, including those recommended by the lowest guideline targets, some uncertainly does remain over the size of the effect. Perhaps more reliable estimates are obtained from the meta-analyses published after the first articles from the ACCORD, ADVANCE, and Veterans Affairs Diabetes Trial (VADT) studies (32–34). The findings of these are consistent within a small range; perhaps the most robust is that of Turnbull et al. (33) using patient-level data from these studies and UKPDS. There was no interaction for major CV events between HbA_{1c} groups (lowest <7.5%), although numerically better in the lower groups, suggesting no adverse effect. Effect size for myocardial infarction was a 15% reduction for an HbA_{1c} improvement of 0.85% (9 mmol/mol). That is notably consistent with the UKPDS itself, the only primary prevention study, which showed a 15% protection for myocardial infarction at the end of the extension study (35).

For microvascular disease, less extensive analyses have been performed. A threshold of some kind must exist as people without diabetes do not develop diabetic retinopathy (lesions similar to early retinopathy may develop in association with some other clinical conditions but do not show the same progression). Data from UKPDS suggest a 37% reduction per 1.0% (11 mmol/mol) lower HbA_{1c}, log-linearly including between the cohorts of 5.0–6.0 and 6.0–7.0% (31–42 and 42–53 mmol/mol) (7). A difficulty here is inclusion of microalbuminuria together with retinopathy, as microalbuminuria seems more a measure of vascular inflammation in T2D than of microvascular disease. Further diagnosis is delayed in T2D by 5–10 years on average, so there may be a legacy effect driving retinopathy in the early years after diagnosis even if blood glucose control is to target (36,37).

In type 1 diabetes (T1D), the data on HbA_{1c} and vascular disease relationships are less extensive and indeed largely confined to analyses of the DCCT and follow-up cohorts (EDIC) (2,38). Reanalysis of the relationships between the randomization groups by Lachin et al. (39) shows that independently of randomization, group retinopathy progression was least, and indeed virtually absent, in the 6.5–7.49% HbA_{1c} group, but no analysis is available for CV events. The EDIC studies do however show that the legacy effect of the DCCT is a delay in the rise of CV event incidence with time and thus age of around 6 years, which corresponds to the duration of the original study when HbA_{1c} was controlled to a mean of 7.2% (SD 0.9%) (55 [10] mmol/mol) (2). Together, these observations would seem to justify a target HbA_{1c} of 7.0% (53 mmol/mol) in this population.

WHAT IS ATTAINABLE?

Targets are only rational if attainable. As noted above, an individual HbA_{1c} close to or within the normal range may be reached iteratively over a number of clinical visits if desired and if safety is assured, partly through use of self-measurement and in particular continuous glucose monitoring. Other people, as in the ACCORD study, can seemingly get "stuck" at levels over 8.0% (64 mmol/mol) with problems of hypoglycemia and higher risk of death (25).

Prospectively, a target is perhaps reasonable if a significant proportion of the population under care can attain it. In the New Zealand study, this was 25% below an HbA_{1c} of 6.4% (46 mmol/mol) at first annual review, and half below 7.1% (54 mmol/mol) (27). In the UKPDS, starting at HbA_{1c} of 9.0% at diagnosis and only selecting those that did not meet a fasting glucose target of remission, the mean HbA_{1c} at 1 year after monotherapy was 6.2% (44 mmol/mol) and mean on monotherapy did not exceed 7.0% (53 mmol/mol) until after 5 years from randomization (3).

A number of treat-to-target studies for insulin starters report that mean levels of HbA_{1c} of around or lower than 7.0% (53 mmol/mol) can be achieved within 6 months, even though in nearly all of these, the baseline HbA_{1c} is higher than recommended for starting insulin therapy, that is the insulin is started late (40,41). In the CREDIT prospective observational study (Europe, Canada, Japan), HbA_{1c} was steady over 4 years in all insulin groups, with the basal insulin group maintaining 7.3% (SD 1.1%) (56 [12] mmol/mol) at 4 years despite a preinsulin level of 9.2% (1.8%) (77 [20] mmol/mol) (22). In the less-resourced world (Africa, Asia, South America), starting levels were again too high (9.5% (1.8%) [80 (20) mmol/mol]), but at 6 months nevertheless achieved 7.4% (1.1%) (57 [12] mmol/mol) (42). In a recent presentation, studying people with T2D previously using a basal and prandial insulin, Rosenstock et al. (43) found an HbA_{1c} of 6.7% (0.8%) (50 [9] mmol/mol) after discontinuation of the prandial insulin and substitution of a relatively low efficacy GLP-1 receptor agonist.

The conclusion would appear to be that a very high proportion of those diagnosed with T2D can or already achieve HbA_{1c} below 6.5% (47 mmol/mol) in the early years after diagnosis, and that this is important given the Diabetes & Aging Study results discussed above (29). For insulin therapy with modern approaches, and perhaps in particular if beginning insulin is not delayed, achieving <7.0% (<53 mmol/mol) or even lower is safely attainable in a majority.

In some studies, observationally or as a result of dietary intervention in primary care, HbA_{1c} is normalized off therapy (44,45). If such people do not find themselves burdened by the effort of their achievement, it would seem their personal target should remain an HbA_{1c} in the normal range.

TIME EFFECTS OF GLUCOSE EXPOSURE

The discussion above that life expectancy should be taken into account when agreeing glucose targets presupposes understanding of the secular effects of improved blood glucose control. Put another way, if an agent provides early reduction in risk (within 1 year), as for example do statins, GLP-1 receptor agonists in the presence of CV disease, and SGLT2 blockers for those at heart failure risk, then these agents are immediately indicated. For glucose control however the evidence is that it takes time (years) to gain the advantage, just as it takes years to incur the damage. The likely pathophysiological basis of this will not be discussed here.

In the DCCT, despite, or perhaps because of, large differences in HbA_{1c} between cohorts, no effect was seen for primary prevention of 3-step retinopathy progression until 3 years from randomization, while in the secondary prevention group initially the good control

cohort did worse than the conventional with the Kaplan-Meier curves crossing at between 2–3 years (2). Occurrence of new macroalbuminuria was similarly delayed. However since most people with T1D have life expectancy well beyond this time scale, these findings will only affect targeting of HbA_{1c} in the unfortunate few with life-threatening comorbidities. No useful data are available for CV risk within 8 years as the number of events in this relatively young cohort results in erratic time to event curves (38).

For T2D, the combined patient-level analysis discussed above had a mean exposure of 4.4 years in attaining a modest effect size, but the Kaplan-Meier curves of the underlying studies suggest this is a minimum time to see effects (24,46,47). More comprehensive data are given for the UKPDS glucose study and for its metformin substudy (3,6). Metformin had no effect on microvascular end points in that study, so the relevant curves are for myocardial infarction and diabetes-related mortality. Numbers, particularly in the metformin-treated group, are small, so there is considerable uncertainty; however, diabetes-related death separates from the lifestyle and sulfonylurea/insulin groups only after 8 years, while myocardial infarction separation may be as early as 3 years from lifestyle alone and again 8 years from the sulfonylurea/insulin group (6). In the main glucose study, microvascular advantage is again seen for sulfonylureas/insulin from 8 years, while for myocardial infarction, although there is separation between 3 and 6 years, the events rates are similar from 6 to 12 years.

Taken together, in people with T2D, glucose control improvements of the order of 1% HbA_{1c} appear to take at least 5 years and possibly as long as 8 years to have any measureable impact, likely reflecting the legacy effect of metabolic abnormalities before and after diagnosis.

PUTTING HYPOGLYCEMIA INTO THE EQUATION

If CV or mortality risk exist as a result of hypoglycemia, then it should be noted that it will already be factored in to outcome data given above for the general T2D population at any HbA_{1c} level. It is therefore important in general target setting not to double-count potential hypoglycemia risk when the individual risk of that is unknown (before treatment). The data above suggest that for the average individual, the target to be set should be the best likely to be attainable but then modified for individual preferences, disease burden, and life expectancy. This includes use of insulin and sulfonylureas.

Hypoglycemia will first modify targets according to acute personal risk, including social issues around living alone, for example, and perhaps occupational issues. However, a better approach will be not to modify the target HbA_{1c} but to select alternative therapies. Given that alternatives now exist, for example, to prandial insulin in T2D, or choice of basal insulin, or to sulfonylureas, or between sulfonylureas, optimal medical practice should be to select those alternatives, generally prospectively. Hypoglycemia may however modify HbA_{1c} targets iteratively once optimal therapy is given a trial of therapy simply because it may limit the level of glucose control attainable, despite best efforts. One issue here is that highlighted by the ACCORD study, namely, that hypoglycemia occurring at HbA_{1c} levels well above usual target levels is a marker for mortality risk (25), but that will perhaps be obvious clinically from the presence other comorbidities and raised health burden. As the increased mortality experience of the intensive group nearly entirely related to that in the third year (46), the possibility also speculatively exists that particular types of therapy (for example, prandial insulin) titrated over the course of the study to maintain the improved glucose control level might, in those stuck at higher levels due to hypoglycemia, have influenced risk.

While hypoglycemia was more common in the poorly controlled (rather than better) population of the intensive group in ACCORD (25), the obverse has been found in other studies (48,49). Hypoglycemia could not be found to be a cause of adverse outcomes in ACCORD, despite intense post hoc epidemiological analysis (50,51), and was not an independent associate with CV risk in the insulin-starter CREDIT study (26). Reducing the rate of severe hypoglycemia with a modern basal insulin analog does not reduce experience of CV events in T2D (52).

Clinical experience, however, is that normal or near-normal glucose concentrations in people with T1D are a warning of events of serious hypoglycemia requiring medical assistance. However, the approach to this is now made much easier by the advent of reliable systems of continuous glucose monitoring, and that should perhaps be used first to temper insulin regimens rather than preemptively changing HbA_{1c} targets.

CONCLUSIONS

Current HbA_{1c} targets do not vary widely between guidelines, generally being 6.5–7.0% (47–53 mmol/mol) with allowance for higher levels in appropriate circumstances. If easily attained, there is however no reason to raise target levels for individuals who are at the normal range or close to it, particularly if this is through appropriate lifestyle measures. Where this occurs on insulin therapy, use of continuous glucose monitoring is advised to provide reassurance over possible periods of exceptional undetected hypoglycemia. Age should only be used to modify glucose targets as data to determine baseline life expectancy for an individual, whence disease burden and comorbidities may modify choice usually through discussion of personal preferences. Social risks from frailty, sometimes in association with loss of mental capacity, may also dictate caution over acute hypoglycemia risks, whence alterative therapy choices are an alternative approach. However, significantly higher HbA_{1c} levels are associated with a range of acute medical issues (Table 3) and should be avoided.

Acknowledgments. The author is grateful for extended discussions with local, national, and international colleagues who have thus helped form his opinions as expressed in this article.

Duality of Interest. P.H. or institutions with which he is associated have received direct or indirect financial support from AntriaBio, Boehringer Ingelheim, GlaxoSmithKline, Hanmi, Janssen, Merck, Novo Nordisk, and Sanofi for his advisory, research, or speaking activities. No other potential conflicts of interest relevant to this article were reported.

Prior Presentation. Parts of this study were presented at the 79th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 7–11 June 2019.

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