

Glycemic Control in Type 2 Diabetes: Time for an Evidence-Based About-Face?

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Some diabetes guidelines set low glycemic control goals for patients with type 2 diabetes mellitus (such as a hemoglobin A_{1c} level as low as 6.5% to 7.0%) to avoid or delay complications. Our review and critique of recent large randomized trials in patients with type 2 diabetes suggest that tight glycemic control burdens patients with complex treatment programs, hypoglycemia, weight gain, and costs and offers uncertain benefits in return. We believe clinicians should prioritize supporting well-being and healthy lifestyles, preventive care, and cardiovascular risk reduction in these patients. Glycemic

control efforts should individualize hemoglobin A_{1c} targets so that those targets and the actions necessary to achieve them reflect patients' personal and clinical context and their informed values and preferences.

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When the facts change, I change my mind. What do you do, sir?

—John Maynard Keynes

Routine treatment for type 2 diabetes has targeted tight glycemic control to reduce diabetes complications. A low hemoglobin A_{1c} (HbA_{1c}) value has been the objective of clinical care and a measure of its quality. In this article, we summarize trials that evaluated tight glycemic control in patients with type 2 diabetes and offer practical evidence-based suggestions for managing these patients.

RECENT EVIDENCE

We focus on large trials that compared clinical outcomes among patients with type 2 diabetes who were randomly assigned to tight versus less tight glycemic targets (1–5). We do not discuss trials that did not test contemporary treatment approaches (6, 7), trials of multifactorial risk reduction interventions (8, 9), or trials designed either to compare a single antihyperglycemic agent against placebo (10) or to assess glycemic durability (11).

The **Table** shows that trials that compared different glycemic targets involved different patient populations and had heterogeneous interventions, targets, and follow-up protocols. The UKPDS (United Kingdom Prospective Diabetes Study) trials (3, 4) are the oldest trials, involved patients with newly diagnosed diabetes, achieved less tight glycemic control, and had longer follow-up than the more recent trials. The results of all of the trials, except for the UKPDS metformin trial (3), suggest that tight glycemic control may not reduce the risk for all-cause or cardiovascular mortality, stroke, amputations, or even microvascular complications (**Figure**). These findings are inconclusive, however, because estimates of effects were imprecise as few patients developed complications and effects varied importantly across trials. Reported results of all trials did suggest that intensive glycemic control might reduce the risk for nonfatal myocardial infarction by about 16%. A clear ad-

verse consequence of tight glycemic control was a 2- to 3-fold increased risk for severe hypoglycemia: Trials with the lowest HbA_{1c} targets had the highest incidence of hypoglycemia. Intensive glycemic control also led to a 2% weight gain in all but the metformin versus conventional comparison in the UKPDS trial (3).

VARIABILITY IN OUTCOMES ACROSS THE TRIALS

Results for some outcomes, such as all-cause and cardiovascular mortality, varied across trials (**Figure**). For instance, the UKPDS metformin trial (3) reported that tight glycemic control reduced mortality risks, whereas the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial (5) reported that tight control increased these risks. The favorable effect of metformin observed in the UKPDS is not evident in the latest comparative effectiveness systematic review (12) or in ADOPT (A Diabetes Outcome Progression Trial) (11), and the mechanism of this finding remains unknown. Possible explanations for the increased mortality risk with tight control in the ACCORD trial include adverse effects from hypoglycemia or rosiglitazone and chance. The data monitoring committee and National Institutes of Health stopped the trial early because of mortality risks, and early stopping can lead to overestimates of the effect of interventions on the monitored outcome (13).

The choice of participants and follow-up duration could explain differences across trial results. The most recent trials enrolled patients with long-standing diabetes who had cardiovascular disease and had relatively brief

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Table. Study Characteristics

Variable	ADVANCE, 2008 (1)	ACCORD, 2008 (5)	VADT, 2009 (2)	UKPDS(a), 1998 (4)*	UKPDS(b) and UKPDS(c), 1998 (3)*
Study characteristics					
Patients, <i>n</i>	11 140	10 251	1791	3867	1704
Follow-up, <i>y</i>	5	3.5	5.6†	10†	10.7†
Lost to follow-up, %	14	9	4	4	3
Eligibility criteria	Age >55 <i>y</i> and history of 1 macro- (32%) or microvascular (10%) complication or 1 additional CV risk factor; demonstrated adherence to the protocol in a run-in period	Age 40–79 <i>y</i> with HbA _{1c} ≥7.5% and CAD or age 55–79 and CV risk factors, BMI <45 kg/m ² , and no history of severe hypoglycemia or kidney impairment	Age >45 <i>y</i> with HbA _{1c} ≥7.5%; BMI <40 kg/m ² ; and no history of CV events in the previous 6 mo, advanced CHF, severe angina, or hepatic or kidney impairment	Recent diagnosis; age 25–65 <i>y</i> with basal glycemia of 6.1–15.0 mmol/L (110–270 mg/dL) after a run-in period of diet and exercise; no history of ketonuria, vascular disease, or retinopathy requiring laser treatment or ongoing coronary disease	Recent diagnosis; age 25–65 <i>y</i> with basal glycemia of 6.1–15.0 mmol/L (110–270 mg/dL) after a run-in period of diet and exercise; no history of ketonuria, vascular disease, or retinopathy requiring laser treatment or ongoing coronary disease
Patient characteristics					
Age, <i>y</i>	66	62	60	53†	53†
Duration of diabetes, <i>y</i>	8	10†	11.5	Recent diagnosis	Recent diagnosis, overweight (>120% ideal body weight)
Mean HbA _{1c} level, %	7.5	8.3	9.4	7.1	7.2
CVD, %	32	35	40	0	0
Intervention					
Target	HbA _{1c} ≤6.5%	HbA _{1c} <6%	HbA _{1c} <6%	FPG <6.0 mmol/L (<108 mg/dL)	FPG <6.0 mmol/L (<108 mg/dL)
HbA _{1c} level achieved, %	6.5	6.4	6.9†	7.0‡	7.0‡
Agents used	Gliclazide (90%) plus protocol: dose increase in gliclazide and addition of metformin (74%), glitazone (17%), acarbose (19%), or insulin (40%)	All available agents allowed: metformin (95%), secretagogue (87%), glitazone (91%), acarbose (23%), exenatide (12%), or insulin (77%)	Maximal doses of 2 oral agents (glimepiride + rosiglitazone if BMI <27 kg/m ² and metformin + rosiglitazone if BMI >27 kg/m ² ; if HbA _{1c} >6%, then insulin therapy was started; subsequent changes determined according to guidelines	Patients were randomly assigned to SU (chlorpropamide [20%] or glibenclamide [20%]) or insulin (30%); at end of trial: diet alone (12%), SU (54%), metformin (10%), or insulin (38%); subsequent changes only if marked hyperglycemia developed in order to achieve maximal exposure to each agent	Patients were randomly assigned to metformin (20%), chlorpropamide (24%), glibenclamide (15%), or insulin (16%); subsequent changes only if marked hyperglycemia developed in order to achieve maximal exposure to each agent
Typical follow-up visits	Every 3 mo	Every 2 mo, with monthly interim telephone calls	Every 6 wk	Every 3–4 mo	Every 3–4 mo
Control					
Target	HbA _{1c} per local guidelines	HbA _{1c} 7.0%–7.9%	HbA _{1c} 8%–9%	Best achievable FPG	Best achievable FPG
HbA _{1c} level achieved, %	7.3	7.5	8.4†	7.4‡	8.0‡
Agents used	Switched from gliclazide to another SU; SU (59%), metformin (67%), glitazone (11%), acarbose (13%), insulin (24%), or none (6%)	Any agents allowed: metformin (87%), secretagogue (74%), glitazone (58%), acarbose (5%), exenatide (4%), or insulin (55%)	Half-maximal doses of 2 oral agents (glimepiride + rosiglitazone if BMI <27 kg/m ² and metformin + rosiglitazone if BMI >27 kg/m ² ; if HbA _{1c} >9%, then insulin started; subsequent changes determined according to guidelines	Diet alone; drugs added only if FPG >15 mmol/L (>270 mg/dL). At end of trial: diet alone (58%), SU (25%), metformin (10%), or insulin (16%)	Diet alone; drugs added only if FPG >15 mmol/L. At end of trial: 44% required medication (metformin 20%, chlorpropamide 16%, glibenclamide 16%, insulin 24%)
Typical follow-up visits	Every 6 mo	Every 4 mo	Every 6 wk	Every 3–4 mo	Every 3–4 mo
Other CV risk factors					
Management of other CV risk factors	BP factorial trial	BP and lipid factorial trials	Other CV risk factors managed	BP trial embedded	BP trial embedded
End-of-study systolic BP: intervention vs. control, <i>mm Hg</i> (<i>P</i> value)	136 vs. 138 (<0.001)	126 vs. 127 (0.002)	127 vs. 125 (0.27)	NR	NR

ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CV = cardiovascular; CVD = cardiovascular disease; FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}; NR = not reported; SU = sulfonylurea; UKPDS = United Kingdom Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.

* UKPDS(a) refers to the main UKPDS trial, which included 2729 patients in the intervention group and 1138 patients in the conventional group. We subdivided the main UKPDS trial in overweight patients with diabetes into 2 comparisons: UKPDS(b), which included 342 overweight patients in the intervention group with metformin and 411 in the conventional group, and UKPDS(c), which included all 1293 overweight patients in the intervention group (metformin, glibenclamide, and insulin) and 411 in the conventional group.

† Median.

‡ Median HbA_{1c} value throughout follow-up.

follow-up. A hypothesis-generating subgroup analysis from the ACCORD trial suggested that patients without a previous cardiovascular event may have had a lower risk for cardiovascular events with tight glycemic control than patients with a previous event (5). This subgroup analysis and the UKPDS metformin trial findings suggest that patients with earlier and milder disease could benefit from aggressive treatment. This is somewhat contradicted by the comparable outcomes of tight glycemic control reported in the main UKPDS trial in patients with newly diagnosed diabetes (4) and in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial in patients with longstanding diabetes (1). Thus, this possibility should be evaluated in long-term clinical trials, because premature assumption of its truth exposes a very large population to a resource-intensive intervention with still-uncertain benefits and certain harms.

Perhaps differences in medications used to achieve glycemic control could explain the observed differences across the trials. Some research, for example, has linked rosiglitazone to adverse cardiovascular outcomes (14) and metformin to cardiovascular benefits (12). The tight glycemic control trials, however, were not designed to link outcomes to the medications used. Thus, perhaps glycemic control is effective, but not with the treatment strategies tested, or we may have failed to fully understand the mechanisms by which diabetes causes complications and may have chosen incorrect therapeutic targets and goals.

The nature of the outcomes measured, reported, and emphasized in the trials may confuse or mislead interpretation of results and cause “apparent” inconsistency of findings. In the ADVANCE trial, focus on the composite end point suggests that tight control was associated with “prevention of all diabetes related complications by 10%” (1), whereas this effect is driven mainly by a reduction in the incidence of albuminuria. In UKPDS, decreases in the number of patients requiring photocoagulation made up most of the effect of tight glycemic control captured by the composite end point “any [of 14] diabetes complications” (4). To aid interpretation and avoid being misled by composite end points, we presented (Figure) and recommend focus on the effect of treatment on the components of composite end points that matter to patients.

Focus on a surrogate end point, such as HbA_{1c}, could also mislead if it did not capture all of the effect of the intervention on the outcomes that matter. The appropriateness and adequacy of the surrogate end point may be specific to patients, interventions, and outcomes. For instance, HbA_{1c} seems to appropriately capture the effect of intensive insulin therapy on microvascular complications in patients with type 1 diabetes (15). Yet, the trials we reviewed in type 2 diabetes show that reductions in HbA_{1c} level achieved with contemporary therapies do not uniformly predict major benefits for either micro- or macrovascular outcomes in patients with type 2 diabetes. Fur-

thermore, analyses of UKPDS data showed that intensive therapy with metformin was associated with improved macrovascular outcomes compared with intensive therapy with other agents despite both groups achieving similar HbA_{1c} levels (3).

CONCLUSION AND RECOMMENDATIONS

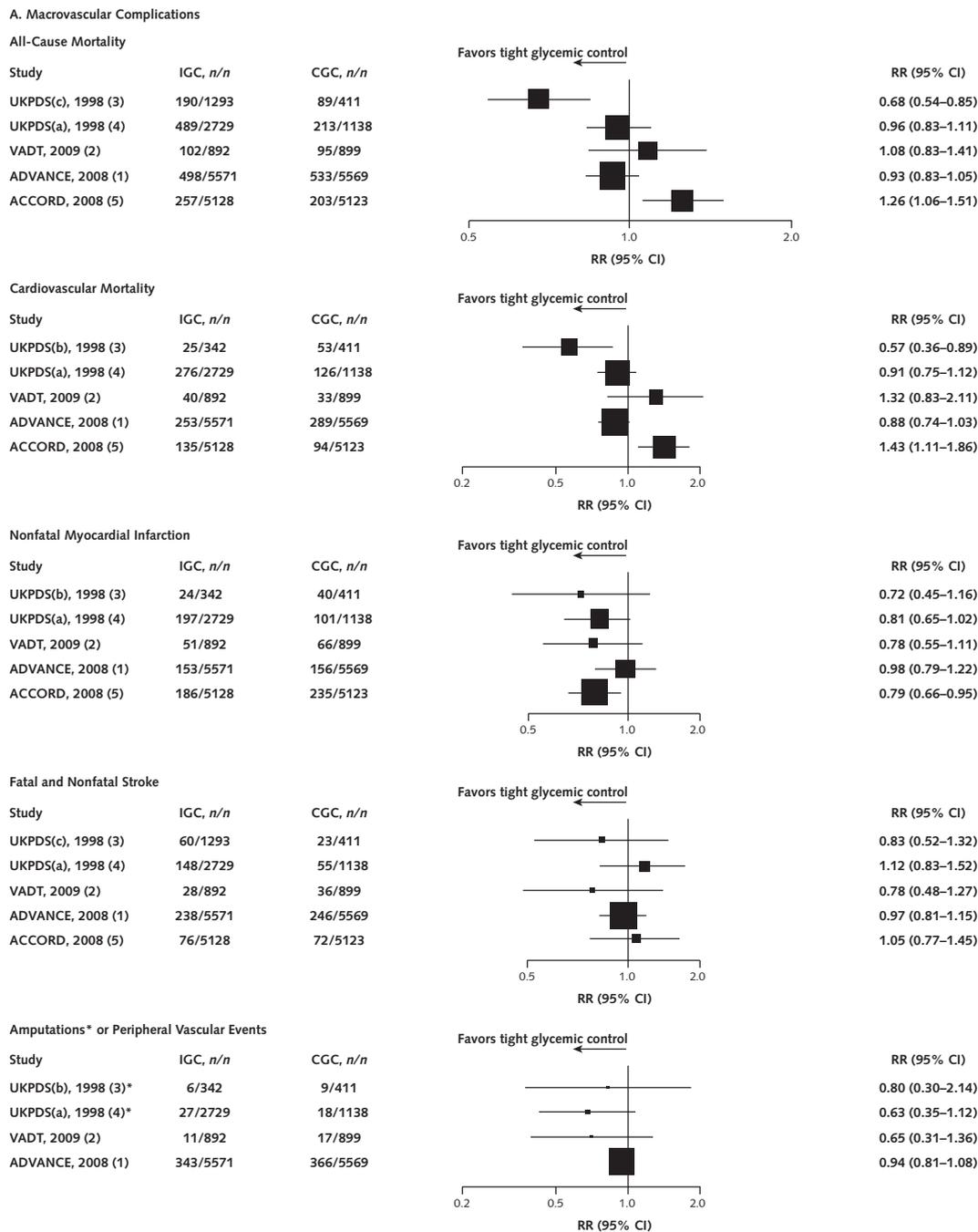
Current best evidence requires a change in emphasis in our care for patients with type 2 diabetes. Clinicians should prioritize supporting well-being and healthy lifestyles, preventive care, and cardiovascular risk reduction for these patients. The randomized trial evidence that we reviewed does not strongly support tight glycemic control as more beneficial than harmful in reducing the risk for diabetes complications. Although we should not dismiss potentially effective approaches (for example, early tight glycemic control for patients with newly diagnosed diabetes), we require additional research to confirm or refute such approaches before we impose them on patients, particularly given the unequivocal patient burden, cost, and harm of serious hypoglycemia associated with tight control.

Given that patients with diabetes often have comorbid conditions, clinicians should avoid glycemic control interventions that overwhelm the patients’ capacity to cope clinically, psychologically, and financially. Tight disease-centered goals that require highly complex and burdensome treatment programs may promote frustration, non-adherence, and financial stress in some patients. For instance, many patients will not benefit from and could reduce or eliminate glucose self-monitoring (16–18).

Patients may opt to control their glycemia to a level that best balances the burden of medication, including the risk for hypoglycemia, with the benefit in reducing symptoms, which may appear with glycemia greater than 10 mmol/L (>180 mg/dL). Keeping the HbA_{1c} level between 7% and 7.5% (estimated average glucose level, 8.5 to 9.5 mmol/L [150 to 160 mg/dL]) seems reasonable and feasible for many patients. For others—particularly those with severe insulin deficiency—achieving this range requires substantial effort, including physiologic insulin dosing (that is, basal-bolus regimens) and intense monitoring.

Glycemic targets can be adjusted up or down according to the burden of treatment; side effects; and the patient’s context, values, and preferences. Given the possibility that tighter control may be beneficial, some patients who are less concerned about downsides, and are ready to do whatever may possibly help, may choose tighter control. The need to set individual glycemic targets suggests that HbA_{1c} targets for clinical use cannot be the same when used to measure quality of care. Policymakers who want to use HbA_{1c} as a performance measure should use an upper limit, such as an HbA_{1c} level greater than 9%, to indicate possibly inadequate care, rather than one that would invite clinicians to ignore patient burden, context, and goals (for example, HbA_{1c} level <7%).

Figure. Forest plots of trials measuring the effect of intensive glycemic control on macrovascular complications (A), microvascular complications (B), and weight gain and severe hypoglycemia (C).



For all plots, no difference between intensive and less intensive glycemic control is denoted by the vertical continuous line. UKPDS(a) refers to the main UKPDS trial, which included 2729 patients in the intervention group and 1138 patients in the conventional group. We subdivided the main UKPDS trial in overweight patients with diabetes into 2 comparisons: UKPDS(b), which included 342 overweight patients in the intervention group with metformin and 411 in the conventional group, and UKPDS(c), which included all 1293 overweight patients in the intervention group (metformin, glibenclamide, and insulin) and 411 in the conventional group. When possible, we presented the results using data from UKPDS(c). We calculated the number of cardiovascular deaths in UKPDS(a) by subtracting all noncardiovascular deaths from all reported deaths. When trials used different outcome definitions, the asterisk and dagger identify which trial reported which outcome definition or combination of outcomes (when both symbols accompany the trial name). ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease; Preterax and Diamicon Modified Release Controlled Evaluation; CGC = conventional glycemic control; IGC = intensive glycemic control; RR = relative risk; UKPDS = United Kingdom Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.

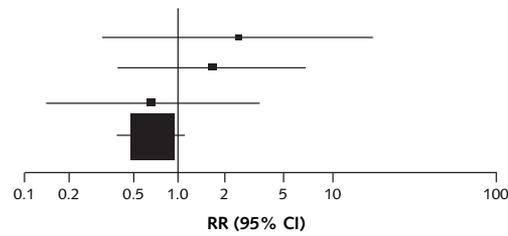
Figure—Continued

B. Microvascular Complications

Death due to Renal Causes*/Need for Renal Replacement†

Study	IGC, n/n	CGC, n/n
UKPDS(b), 1998 (3)*†	2/342	1/411
UKPDS(a), 1998 (4)*†	8/2729	2/1138
VADT, 2009 (2)*	2/892	3/899
ADVANCE, 2008 (1)†	22/5571	33/5569

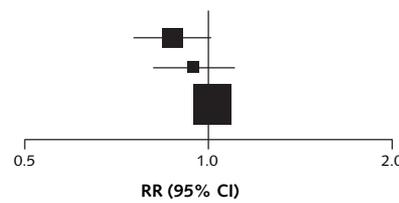
Favors tight glycemic control ←



Neuropathy (Any*, New or Worsening†, or Vibration Threshold >25 V)

Study	IGC, n/n	CGC, n/n
UKPDS(a), 1998 (4)	398/2729	190/1138
VADT, 2009 (2)*	202/892	218/899
ADVANCE, 2008 (1)†	2353/5571	2311/5569

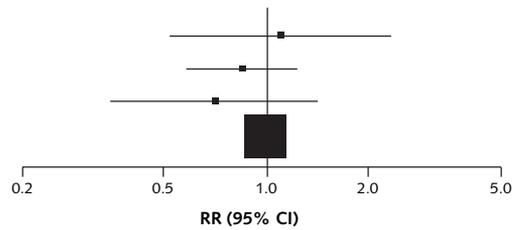
Favors tight glycemic control ←



Progression to Macular Edema, Visual Deterioration*, or Blindness†

Study	IGC, n/n	CGC, n/n
UKPDS(b), 1998 (3)†	12/342	13/411
UKPDS(a), 1998 (4)†	78/2729	38/1138
VADT, 2009 (2)	12/892	17/899
ADVANCE, 2008 (1)*	3033/5571	3015/5569

Favors tight glycemic control ←

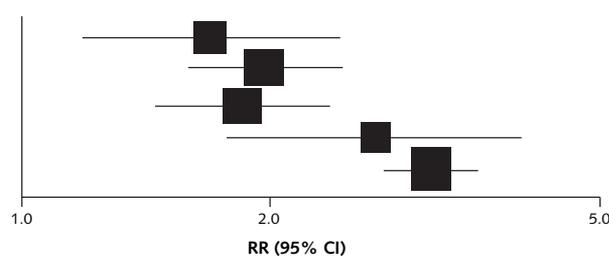


C. Other Complications

Severe Hypoglycemia

Study	IGC, n/n	CGC, n/n
UKPDS(c), 1998 (3)	166/1293	31/411
UKPDS(a), 1998 (4)	382/2729	80/1138
VADT, 2009 (2)	150/892	81/899
ADVANCE, 2008 (1)	76/5571	28/5569
ACCORD, 2008 (5)	830/5128	261/5123

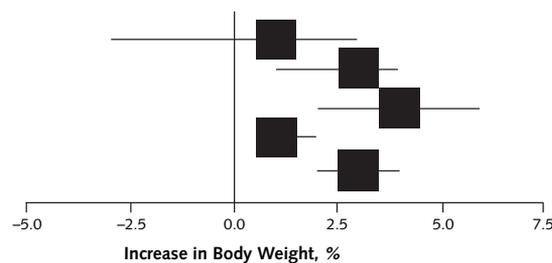
Favors tight glycemic control ←



Weight Gain

Study
UKPDS(b), 1998 (3)
UKPDS(a), 1998 (4)
VADT, 2009 (2)
ADVANCE, 2008 (1)
ACCORD, 2008 (5)

Favors tight glycemic control ←



Once clinicians and patients have set an HbA_{1c} target, which is often an iterative process, they need to decide how to achieve the target. Because we cannot confidently distinguish the relative effectiveness of different diabetes medications in reducing complications (12, 19), we recommend basing their selection on such factors as burden of administration and side effects. We have developed and are studying tools to promote patient involvement in choosing diabetes medications (20). We hope that tools and tactics that encourage patient involvement in treatment decisions prove to be effective and lead to treatment programs that are both evidence-based and consistent with patients' context, values, and preferences.

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