Lower Baseline Glycemia Reduces Apparent Oral Agent Glucose-Lowering Efficacy

A meta-regression analysis

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Perusal of advertisements for oral hypoglycemic agents in this and many other medical journals shows an emphasis on the absolute reduction in HbA_{1c} (A1C). Evidence linking reduction in A1C in diabetic patients to prevention of macrovascular events is weak. However, epidemiological evidence suggests that the risk for cardiovascular disease in this group may actually begin at A1C concentrations well within the normal range (1). This association has led a number of professional organizations to recommend that A1C levels be brought to levels <6.5% (2). An important question to be asked is whether the reduction in A1C differs at lower versus higher baseline levels of A1C. Expectations for the degree of reduction to be attained with a given agent may be excessively optimistic when a person's initial A1C is already <7.5–8.0%.

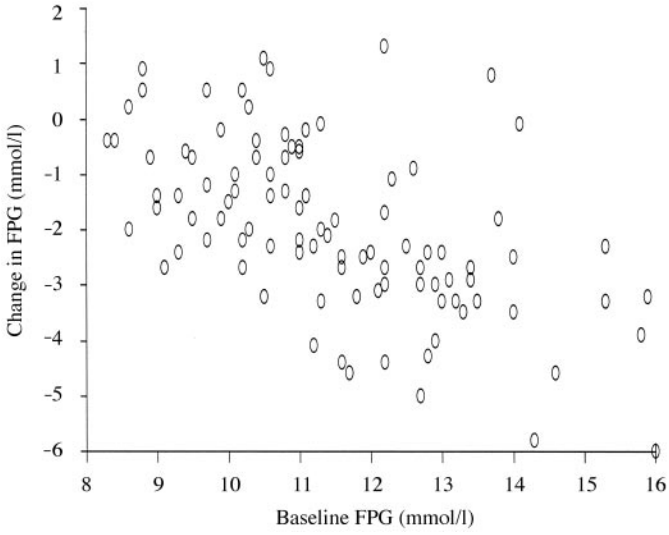

Figure 1—*Relationship between baseline FPG and change in FPG with active treatment.* $R^2 = 0.34$, $P < 0.0001$.

Some of the deliberations of policy advisory groups are available. The European Agency for the Evaluation of Medicinal Products has published guidelines for diabetes product evaluation suggesting that the change in A1C be utilized as "primary analysis" of drug efficacy, although allowing the baseline A1C to be included as a covariate (3). A meeting of the Center for Drug Evaluation and Research Endocrinologic and Metabolic Drugs Advisory Committee of the U.S. Food and Drug Administration concluded that A1C should be the primary outcome variable for diabetes drugs and suggested an absolute decrease of 0.7% as the minimal acceptable level for approval (4). This may prevent acceptance of agents that are as effective as existing treatments at A1C levels <7.5–8.0%, yet still above current therapeutic goals. A potential consequence is that the pharmaceutical industry may become reluctant to develop agents effective for glycemic treatment of individuals with early diabetes, based on a perception that studying agents under those circumstances may give the appearance of inadequate efficacy. As an example, a recently presented obesity study showed a 0.6% fall in A1C from a baseline of 7.3 to 6.7% in a subset of 1,045 obese type 2 diabetic individuals treated for 1 year with 20 mg rimonabant daily (5). Currently, drugs of the dipeptidyl peptidase IV class are being studied in phase 3 clinical trials. In a 12-week study of 107 individuals receiving metformin, with baseline A1C 7.7%, fasting glucose decreased 10 mg/dl and A1C decreased 0.6% with vildagliptin, while showing no change with placebo (6), and similar A1C lowering has been reported with sitagliptin (7), suggesting that the effectiveness of these agents on A1C appears to be near the absolute threshold of −0.7%. Again, however, most of these

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Abbreviations: FPG, fasting plasma glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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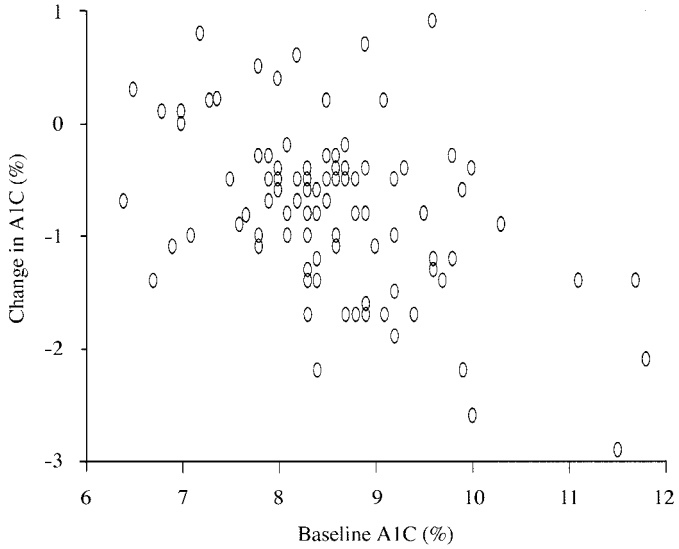

Figure 2—*Relationship between baseline A1C and change in A1C with active treatment.* R^2 = *0.18,* P < *0.0001.*

trials have involved groups of patients with much lower A1C levels than previously studied in registration trials involving other agents. In addition, many institutional review boards will no longer allow a "washout" period during clinical trials of antihyperglycemic agents. Accordingly, patients recruited into diabetes clinical trials in recent years have lower baseline A1C than in previous years. It may therefore be difficult to compare the relative efficacies of glucose-lowering drug therapies reported in the medical literature. Our analysis did not take into account trial duration, although most lasted 3–6 months; A1C typically plateaus after 3 months.

To further investigate the relationship between baseline glycemia and reduction in A1C, we performed a meta-regression analysis of published oral agent trials of glucose lowering in individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Using previously described criteria (8), a total of 61 studies (some including more than one active therapy group) were identified involving the five major oral agent classes (sulfonylureas, meglitinides, metformin, thiazolidinediones, α-glucosidase inhibitors), published before 2004. Fifteen of these studies included oral agent combinations. Routinely in pharmacologic studies, a period far less than the required 3 months to ensure stability of the patient's initial A1C will have elapsed between withdrawal of prior treatment and trial initiation. We therefore felt that use of A1C at the beginning of the therapy period underestimated the extent to which it would be anticipated to increase, were the patient allowed to equilibrate in an untreated state. To address this, we analyzed the decreases from baseline in fasting plasma glucose (FPG) as well as in A1C. The number of subjects in each study was used for a weighted regression analysis with SAS statistical software (SAS Institut, Cary, NC).

RESULTS

— Overall, mean (±SD) baseline FPG was 11.2 ± 1.8 mmol/l and baseline A1C 8.6 ± 1.0%. There were no statistical differences between groups when sorted by therapeutic class. A significant correlation was observed between mean baseline FPG and mean decrease in FPG ($R^2 = 0.34$, $F = 50.19$, $P < 0.0001$; Fig. 1) and between mean baseline A1C and mean decrease in A1C ($R^2 = 0.18$, $F = 21.20$, $P < 0.0001$; Fig. 2). Notably, the correlation between the change in FPG and baseline FPG is stronger than that between change in A1C and baseline A1C. This likely reflects the more immediate change in FPG during washout and the variable washout periods used in these studies. That is, the "baseline" A1C during a short washout phase may not reliably reflect the baseline glycemic status of the patient.

When active therapy groups were stratified by baseline FPG quartile, the mean decrease in FPG was −0.3 mmol/l for groups with initial glucose <10.2 mmol/l, −1.1 mmol/l for groups with initial glucose 10.2–11.2 mmol/l, −2.4 mmol/l for initial glucose 11.2–12.7 mmol/l, and −2.5 mmol/l for initial glucose >12.7 mmol/l (P for linear trend = 0.04). Additionally, groups with subjects in the lowest quartile of mean baseline FPG were nearly 10 times less likely to show a change in A1C of at least −1.0% compared with groups in the highest quartile (8 vs. 73%, $P = 0.002$). Significantly greater reductions in FPG and A1C were observed in those groups with higher baseline A1C (Table 1). Indeed, when the baseline A1C was <8.0%, the reduction from active therapy is only 0.1–0.2% greater than in the control group.

CONCLUSIONS

— Irrespective of drug class, the baseline glycemic status of patients who have been recruited into clinical trials strongly influences the FPG and A1C reduction following pharmacologic intervention. Our therapeutic assumptions as to the intensiveness of treatment required to attain near-normal glycemic levels may be flawed by undue extrapolation from the effects of these agents on individuals with markedly higher glucose levels. These findings should be taken into account by clinical investigators and study sponsors as the effectiveness of newer antihyperglycemic agents are tested, especially since the mean baseline A1C of clinical trial participants has fallen significantly over the past decade. Moreover, these findings should

Table 1—*The relationship between baseline A1C group and observed reduction from baseline in A1C and in FPG*

Baseline A1C (%)	*n* enrolled in clinical trials	Change in A1C (%)	Change in FPG (mmol/l)
6.0–6.9	410	−0.2	−0.5
7.0–7.9	1,620	−0.1	−0.8
8.0–8.9	5,269	−0.6	−1.6
9.0–0.9.9	1,228	−1.0	−2.3
10.0–11.8	266	−1.2	−3.4

also be considered by approval agencies in proposing expectations for efficacy of new antihyperglycemic agents being tested in individuals with modest but still important degrees of hyperglycemia.

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