

# Response to Intensive Therapy Steps and to Glipizide Dose in Combination With Insulin in Type 2 Diabetes

VA feasibility study on glycemic control and complications (VA CSDM)

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**OBJECTIVE** — The feasibility study for the VA Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes (VA CSDM) prospectively studied 153 insulin-requiring type 2 diabetes patients, randomized between an intensively treated arm and a standard treatment arm during a mean follow-up of 27 months. The glycemic response to each of the progressive, sequential phases of insulin treatment was assessed, along with the incidence of hypoglycemic reactions and the relative efficacy of different doses of glipizide in combination with fixed doses of insulin.

**RESEARCH DESIGN AND METHODS** — Five medical centers participated; half of the patients were assigned to the intensive treatment arm aiming for normal HbA<sub>1c</sub> levels. Age of patients was 60 ± 6 years, duration of diabetes 8 ± 3 years, and BMI 30.7 ± 4 kg/m<sup>2</sup>. A four-step management technique was used, with patients moving to the next step if the operational goals were not met: Phase I, evening intermediate or long-acting insulin; phase II, added daytime glipizide; phase III, two injections of insulin alone; and phase IV, multiple daily insulin injections. Home glucose monitoring measurements were done twice daily and at 3:00 A.M. once a week. Hypoglycemic reactions and home glucose monitoring results were recorded and counted in each of the treatment phases.

**RESULTS** — Baseline HbA<sub>1c</sub> was 9.3 ± 1.8%, and fasting plus serum glucose was 11.4 ± 3.3 mmol/l. Fasting serum glucose fell to near normal in phase I, and remained so in the other treatment phases. An HbA<sub>1c</sub> separation of 2.1% between the arms was maintained during the course of the study, while the intensive arm kept HbA<sub>1c</sub> levels below 7.3% ( $P = 0.001$ ). Most of the decrease in HbA<sub>1c</sub> occurred with one injection of insulin alone (phase I, -1.4%) or adding daytime glipizide (phase II, -1.9% compared with baseline). HbA<sub>1c</sub> did not decrease further after substituting two injections of insulin alone, with twice the insulin dose. Multiple daily injections resulted in an additional HbA<sub>1c</sub> fall (-2.4% compared with baseline). However, two-thirds of the patients were still on one or two injections a day at the end of the study. Changes in home glucose monitoring levels paralleled those of the HbA<sub>1c</sub>, as did the increments in number of reported hypoglycemic reactions, virtually all either "mild" or "moderate" in character. For the combination of glipizide and insulin (phase II), the only significant effect was obtained with daily doses up to 10 mg a day; there were no significant additional benefits with up to fourfold higher daily doses, and HbA<sub>1c</sub> levels had an upward trend with doses >20 mg/day.

**CONCLUSIONS** — A simple regime of a single injection of insulin, alone or with glipizide,

seemed sufficient to obtain clinically acceptable levels of HbA<sub>1c</sub> for most obese, insulin-requiring type 2 diabetes patients. Further decrease of HbA<sub>1c</sub> demanded multiple daily injections at the expense of doubling the insulin dose and the rate of hypoglycemic events. In combination therapy, doses of glipizide >20 mg/day offered no additional benefit.

The feasibility trial for the VA Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes (VA CSDM) evaluated whether near-normal glycohemoglobin (HbA<sub>1c</sub>) levels could be maintained for a 2-year period with intensive therapy in patients with type 2 diabetes previously uncontrolled on maximum oral agents or conventional insulin treatment, keeping a significant separation from an arm receiving standard insulin treatment. Other endpoints were adherence to protocol, measurement of endpoints for a long-term trial, and evaluation of side effects (1). All these objectives have been met (2–4). In the intensive therapy arm, a step therapy regime was used. The protocol called for regular collection of home blood glucose monitoring data and incidence of hypoglycemia and the prospective assessment of the responses to the sequential phases of treatment, which, as in common clinical practice, were progressively complex.

The second phase of the step therapy design provided that in addition to a constant dose of an evening injection of insulin, a daytime glipizide be given in increments up to maximum dose. Several European reports pointed out that the maximum recommended doses of sulfonylureas in the U.S. are larger than those used, or even recommended, in Europe (5,6). Some of these studies showed maximal effect of glipizide at 10–15 mg per day and that higher doses had a negative effect (6,7). Combination of insulin with sulfonylureas is now a recommended modality in the current standards of treatment for type 2 diabetes (8). Assessment of the relative efficacy of different dose ranges of glipizide in combination with fixed insulin doses is relevant to the effective use of combination therapy.

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Received for publication 7 October 1997 and accepted in revised form 17 December 1997.

A comprehensive list of the VA CSDM Study Group is published in Ref. 1 and complemented in Refs. 2–4.

**Abbreviations:** VA CSDM, VA Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes.

## RESEARCH DESIGN AND METHODS

The entry and exclusion criteria and the randomization process have been described (1). Briefly, 153 adult men with type 2 diabetes were entered, age 40–69 years, who were either treated with insulin or clinically judged to require insulin because of failure of oral therapies. Admission blood HbA<sub>1c</sub> was more than three standard deviations above the mean normal (>6.55%). Diabetes >15 years' duration, serious illness, clinical proteinuria, or incapacitating cardiovascular disease were cause for exclusion. Standard therapy patients were treated with one injection of insulin a day to avoid symptomatic hyperglycemia; however, HbA<sub>1c</sub> could not exceed more than two standard deviations above mean levels in the outpatient clinics of participating centers (12.9%, "alert value"). In the intensively treated arm, the aim was to reduce HbA<sub>1c</sub> to as close to normal (5.1 ± 1%) as possible. A stepped regimen began with a bedtime intermediate or long-acting insulin (phase I); if goals were not met, therapy was intensified by adding daytime glipizide (phase II), or later, two injections of insulin alone (phase III), or multiple daily injections of insulin (phase IV). Home blood glucose monitoring was mandatory in this treatment arm only (twice each day and once weekly at 3:00 A.M.). During each treatment phase (phases I–III), the investigators were instructed to consider transition to the next phase if, while aiming at normal fasting blood glucose levels and other preprandial glucose determinations, target HbA<sub>1c</sub> could not be obtained or recurrent hypoglycemia appeared that could not be corrected except by reducing the dose of the insulin injection(s) scheduled in the treatment phase. Patients in both arms were seen every 3 months for comprehensive assessment, care, and data collection. In addition, there were monthly visits and weekly telephone calls in the intensive arm, solely for the purpose of adjusting the treatment of hyperglycemia on the basis of home blood glucose monitoring data. Dietary treatment was identical in both arms, with modest caloric restriction prescribed when indicated, but avoiding rapid weight loss. Management of dyslipidemia and hypertension was identical in both treatment arms. Home blood glucose monitoring was standardized by using either Acucheck (Boehringer Mannheim Diagnostics, Indianapolis, IN) or Exact Tech glucose meters (Medisense, Cambridge, MA). Nurse coordinators rechecked calibration and measurement skills and retrained the

patients monthly, at which time the total number of measurements of the last month was recorded, and the full record of the previous week was transcribed.

During evening insulin and daytime glipizide treatment (phase II), the physicians were expected to increase the glipizide dose from an initial dose of 2.5 or 5 mg/day up to 40 mg per day, in suggested increments of 2.5 to 5 mg, until meeting HbA<sub>1c</sub> goals or maximum dose. To compare the effects of the different dosage ranges, fasting plasma glucose, HbA<sub>1c</sub>, and insulin doses were determined first, at the most recent monthly determination for all patients within each dose range interval, whether or not they progressed to higher dosages or shifted to two injections of insulin alone (phase III). Data were missing when patients were no longer in the study (death or discontinuance) or when patients progressed through each dose interval faster than 1 month. As there were more patients with data in the lower doses, paired analyses of the data on patients who reached the highest dose range and for whom data were also available at each lower dose interval were separately performed.

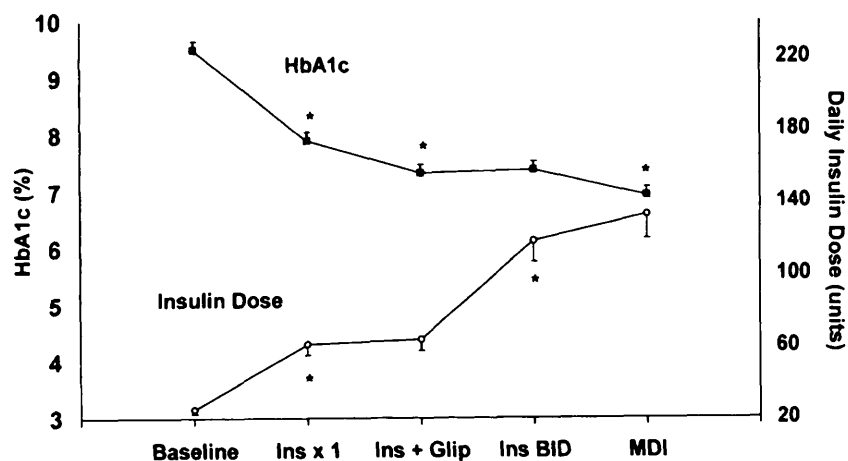
### Measurements and statistical analysis

Glycohemoglobin (HbA<sub>1c</sub>) was measured in a central laboratory (University of Minnesota) using high-pressure liquid chromatography. Blood chemistry profiles were determined at each center. Quality control of HbA<sub>1c</sub> was performed in the central laboratory, and reports were periodically sent for review by an independent data monitoring board. Ten percent of the specimens drawn from study patients were split samples, and were sent blinded to the central laboratory for assessment of performance. The Pearson product moment correlation coefficient between the first and second samples was >0.90 for all assessments. Examination of the pairs for percent deviation from the mean revealed that >90% of the pairs deviated <10%.

Hypoglycemia was defined by measured blood glucose <2.7 mmol/l by home monitoring, with or without symptoms. In the absence of glucose measurement, hypoglycemia was defined by symptoms that were relieved by treatments expected to raise the level of blood glucose. Severe hypoglycemia was defined as impaired consciousness requiring help by another person; mild hypoglycemia by either no symptoms or symptoms self-corrected without interfer-

ence in activities or alertness; and moderate hypoglycemia by intermediate symptoms not classifiable as mild or severe. Statistical comparisons between independent groups of patients were done using the two-sample *t* test. Statistical comparisons within patients (e.g., from one phase to another, or at different times of the day within phases) were done using the paired *t* test. All tests were two-sided, and a *P* value of ≤0.05 was considered to be statistically significant.

**RESULTS** — As reported before, 153 patients were randomized into both treatment arms (2). Seventy-five were assigned to the intensive treatment arm. Their mean age was 60 ± 6 years; their BMI was 30.7 ± 4 and their duration of diabetes was 8 ± 3 years. These characteristics were similar to those of the standard treatment arm (2). Both groups had a high prevalence of hypertension (68% of patients were on antihypertensive treatment at the end of the feasibility study), dyslipidemia (20% were on hypolipidemic therapy at end of study), and obesity (80% had BMI >27 kg/m<sup>2</sup>). There were no differences in lipid levels, blood pressure, or weight between arms throughout (2). The mean follow-up time was 27 months (range 18–35 months). Patients kept 98% of their scheduled quarterly visits. Four patients were terminated from the study for causes unrelated to diabetic treatment, and 10 patients died during the course of the trial (2). In the intensive group, mean fasting serum glucose was reduced from 11.4 ± 3.3 mmol/l at baseline to close to the normal range from the 3rd month onward and remained at a mean of 6.5 mmol/l throughout, whereas the standard arm retained mean quarterly fasting glucose levels between 11.2 and 12.8 mmol/l (difference from intensive arm *P* = 0.0001). Intensive treatment resulted in a fall of mean HbA<sub>1c</sub> from 9.3 ± 1.8% at baseline to steady levels below 7.3% after the second quarterly visit, whereas the standard arm mean quarterly levels were between 9.6 and 9.0% (difference from intensive arm *P* = 0.001) (2). At the end of year 1, 85% of patients were receiving one evening injection of insulin only, either alone or with glipizide (phases I or II), and only 15% were on two or multiple daily injections of insulin (phase III or phase IV). The mean ± SD daily insulin dose at 12 months was 67 ± 49 U (vs. 56 ± 38 in the standard treatment arm). However, at the end of the study, 64% of patients were receiving two or more injections of insulin a day (half of these subjects were in phase III,



**Figure 1**—Maximal effects of each treatment phase. Data represent means  $\pm$  SE glycohemoglobin and insulin daily dose, as the last values recorded at each step-treatment phase, including patients who remained in the phase at the end of the study and those who progressed to higher treatment phases. The asterisks denote significant difference from the values reported in the preceding phase. Ins  $\times$  1, evening insulin injection; Ins + Glip, evening injection and daytime glipizide; Ins BID, two daily injections of insulin; MDI, multiple daily injections of insulin.

two injections, and half were in phase IV, multiple daily injections). The mean  $\pm$  SD insulin dose at 24 months for the full cohort was  $96 \pm 69$  U; that was also the highest mean quarterly dose, as the mean dose of the 30 patients followed at 30 months was  $78 \pm 42$  U/day (the standard arm doses were  $62 \pm 39$  U at 24 months and  $61 \pm 31$  at 30 months). There was no trend or correlation between the final treatment phase reached and baseline HbA<sub>1c</sub>, duration of diabetes, or modality of treatment prior to entry (oral agents or insulin). The mean duration of treatment in each of the four phases was  $8 \pm 7$ ,  $10 \pm 7$ ,  $7 \pm 5$ , and  $5 \pm 3$  months, respectively. Most of the decrease in HbA<sub>1c</sub> occurred with a single dose of insulin at bedtime, with a final dose of  $61 \pm 38$  U (phase I,  $P < 0.05$ ; Fig. 1). Added daytime glipizide in 66 patients (phase II) resulted in further lowering of final HbA<sub>1c</sub>, without changing the insulin dose ( $P < 0.03$ ). Forty-eight patients were advanced to two injections of insulin alone daily (phase III), and although within this phase HbA<sub>1c</sub> levels fell by 0.3%, the final HbA<sub>1c</sub> was identical to that of phase II, notwithstanding an insulin dose double that of phase II. ( $116 \pm 68$  U/day,  $P < 0.05$ ). There was a small, nonsignificant increment of insulin dose in the 25 patients advanced to multiple daily injections (phase IV), but a further decrease in final HbA<sub>1c</sub> levels ( $P < 0.05$  vs. phase II; Fig. 1). The mean HbA<sub>1c</sub> levels of each group of patients entering a new phase paralleled the final HbA<sub>1c</sub> levels of the somewhat larger cohort in each pre-

ceding phase: phase II,  $7.8 \pm 1.3\%$ ; phase III,  $7.7 \pm 0.8$ ; phase IV,  $7.2 \pm 0.7$ .

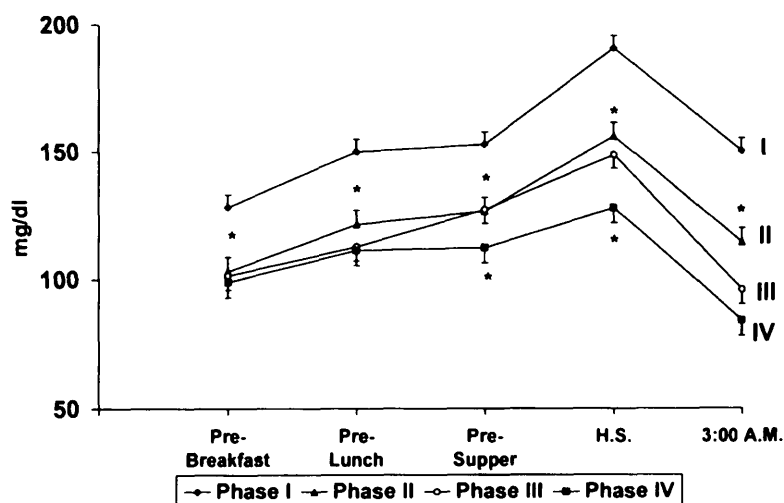
#### Home glucose monitoring

The frequency of home glucose readings in the intensive therapy group was similar in each of the treatment phases:  $63 \pm 25$ ,  $60 \pm 21$ ,  $64 \pm 26$ , and  $74 \pm 26$  readings in the last month of phases I–IV, respectively. The overall trends in home glucose monitoring were consistent with the HbA<sub>1c</sub> results. Thus, mean daily blood glucose levels were significantly lower in phase II than in phase I at all

reported times ( $P < 0.001$ ; Fig. 2). There were no changes in values between phases II and III, except at 3:00 A.M., when there was a trend toward slightly lower levels ( $P = 0.09$ ). In phase IV, predinner ( $P = 0.04$ ) and bedtime ( $P = 0.03$ ) values were significantly lower than in phase III, but 3:00 A.M. values were not significantly lower. In all phases, the highest daily determination was obtained at bedtime ( $P < 0.001$ ). In phases with a single evening insulin injection (I and II), the lowest determination occurred before breakfast ( $P < 0.05$ ) (Fig. 2). When daytime insulin injections were also given (phases III, morning intermediate insulin added, and IV, multiple premeal daily injections added), the lowest mean determination was at 3:00 A.M. ( $P < 0.005$ ).

#### Hypoglycemic reactions

Severe hypoglycemic reactions were extremely rare and not significantly different from those occurring in the standard therapy group (0.02 reactions per patient per year in the full cohort). Of the reported hypoglycemic reactions, 84% were mild and 16% were moderate in severity. The incidence of mild and moderate hypoglycemia was higher with intensive therapy (intensive arm, 16.5 per patient per year; standard, 1.5 per patient per year,  $P < 0.0001$ ). Overall, the frequency of hypoglycemic reactions increased along with the improved glycemic control of each successive treatment phase (Table 1). After the initial mean HbA<sub>1c</sub> fell in phase I to 7.8% with relatively few hypoglycemic events, each additional 0.5% fall of



**Figure 2**—Daily patterns of mean  $\pm$  SE home glucose monitoring results at the end of each treatment phase. The asterisks denote significant difference from the values reported in the preceding treatment phase. H.S., bedtime.

**Table 1—Mean number of nonsevere hypoglycemic reactions in 3 months, per patient, at end of each treatment phase**

Phase	Patients (n)	Mean $\pm$ SD
I (evening insulin dose)	75	2.8 $\pm$ 5
II (evening insulin and glipizide)	66	7.9 $\pm$ 10*
III (two daily insulin injections)	48	7.4 $\pm$ 9*
IV (multiple daily injections)	25	12.4 $\pm$ 13†

\*P = 0.001 compared with phase I; †P = 0.063 compared with phase III.

HbA<sub>1c</sub> caused a doubling of the reported number of reactions (Table 1).

### Efficacy of glipizide dose in combination therapy

Sixty-six patients in the intensive arm were eventually treated with phase II, glipizide insulin combination therapy. The last data collected at low glipizide dose (up to 10 mg/day; mean 8  $\pm$  2), intermediate dose (up to 20 mg/day; mean 18  $\pm$  3), and high dose (up to 40 mg/day; mean 38  $\pm$  4) intervals are presented in Table 2. Fasting plasma glucose and daily insulin doses were virtually identical throughout. Mean HbA<sub>1c</sub> showed a significant fall after insulin plus the low dose of glipizide, as compared with insulin alone. No further significant changes were seen with up to fourfold increments in glipizide dose. Of the patients who reached the high dose of glipizide, paired data at each lower dose interval were available in 49 patients. In virtually identical results to those of the full cohort, the comparison of the HbA<sub>1c</sub> between baseline (insulin alone) and the low-dose range (insulin plus glipizide up to 10 mg/day) showed a highly significant drop in glycohemoglobin, from 7.9  $\pm$  1 to 7.4  $\pm$  1% (P < 0.008). There were non-significant changes with additional glipizide increments (intermediate dose, 7.3  $\pm$  0.9%; high dose, 7.4  $\pm$  0.6%).

**CONCLUSIONS** — In a recent update on the current treatment of type 2 diabetes, it was stated that we do not yet know whether insulin treatment is beneficial, adverse, or neutral in the prevention of macrovascular complications (9). Glycemic control as close to normal as possible has recently been recommended by several authorities, with the safeguard that goals be moderated in the presence of obesity, severe cardiovascular disease, or advanced age (8,10). Because the majority of patients with type 2 diabetes in the developed countries are over 55 years of age, obese, and have a

high prevalence of cardiovascular disease, there is no clear goal universally accepted for such patients (1,2,4). The VA CSDM Feasibility Trial is, to our knowledge, the only relatively prolonged, prospective study in patients who had failed to attain control with diet and oral agents at maximal dose and had high prevalence of obesity and cardiovascular risk factors (1,2). The separation in glycemic control between treatment arms was comparable to that of the Diabetes Control and Complications Trial in type 1 diabetes (2,11). The experience in the efficacy of the different progressive treatment steps used in the VA CSDM trial might serve as a guidance to attain different glycemic goals with simple pharmacological steps.

If a glycemic goal of HbA<sub>1c</sub> of about 8% is accepted as a compromise until long-term data confirm the safety of insulin treatment intensification aiming at normal HbA<sub>1c</sub> levels (5.1  $\pm$  1%) in type 2 diabetes (4), a single evening injection of insulin is apparently sufficient (phase I; Fig. 1). Addition of oral agents after maximal benefits of a single injection of insulin alone (phase II) might prolong the effectiveness of a single insulin injection for this moderate degree of control. In this VA CSDM feasibility study, addition of glipizide to insulin actually attained a HbA<sub>1c</sub> of 0.5% lower than one injection of insulin alone and similar to the reported overall added efficacy of the combination of insulin and sulfonylureas (12). The majority of patients in the feasibility trial were even-

tually advanced to two injections of insulin alone per day (phase III) in an attempt to attain normal HbA<sub>1c</sub> level as the protocol required. However, the success of phase III was no better than a single injection (alone or with daytime glipizide), even though using two injections of insulin alone virtually doubled the insulin dose for similar end results (Fig. 1). The only treatment modality that attained mean HbA<sub>1c</sub> levels <7% was multiple daily injections (phase IV). The efficacy of multiple daily injections has already been demonstrated in shorter trials (13) and for several years in the U.K. study (14). On the other hand, the majority of patients in the VA CSDM feasibility trial remained in phases I to III (one or two injections/day), at the end of the study.

The protocol stipulated that phase advancement was to be exerted in search of HbA<sub>1c</sub> levels as normal as possible, if the participating investigator determined that maximum effect short of that goal was obtained with the earlier phase treatment modality (1). There was no significant difference among the cohorts of the different treatment phases in duration of diabetes, type of therapy, or prevalent HbA<sub>1c</sub> levels prior to entry into the study. Likewise, the mean initial HbA<sub>1c</sub> levels of the patients entering each of the phases were very close to the final mean HbA<sub>1c</sub> levels of the patients at the preceding phase, which included patients who did not shift phases. It would appear that there was no segregation of more poorly controlled or "treatment-resistant" subjects in the higher phases. Rather, phase advancement was effected with the intention of attaining even lower HbA<sub>1c</sub> levels.

Home blood glucose monitoring levels paralleled the effectiveness of the different treatment phases in lowering HbA<sub>1c</sub> (Fig. 2). The highest daily level in all treatment phases was the bedtime home blood glucose determination. When single evening insulin injections were used (phases I and II), the lowest mean daily level of blood

**Table 2—Daily glipizide doses in combination with insulin (phase III): all subjects**

	Glipizide dose (mg/day)			
	Baseline (insulin alone)	Low (2.5–10)	Intermediate (12.5–20)	High (25–40)
n	66	64	54	52
Fasting plasma glucose (mmol/l)	6.7 $\pm$ 3	6.5 $\pm$ 2.3	6.5 $\pm$ 2.3	6.2 $\pm$ 1.8
HbA <sub>1c</sub> (%)	7.80 $\pm$ 1.3	7.39 $\pm$ 1.0*	7.27 $\pm$ 0.8*	7.48 $\pm$ 0.6†
Daily insulin dose (U)	64 $\pm$ 39	61 $\pm$ 36	61 $\pm$ 36	66 $\pm$ 44

\*P = 0.01 compared with insulin alone; †P = 0.09 compared with HbA<sub>1c</sub> at intermediate dose.

glucose occurred before breakfast. When daytime injections were added (phase III and IV), the mid-sleep blood glucose levels were slightly lower than the prebreakfast levels. These observations are in keeping with an earlier report that single evening intermediate insulin injection as a primary strategy to normalize fasting glycemia is not associated with lower mid-sleep low glucose levels than is the administration of morning intermediate insulin injections (15). Furthermore, it would seem that with predinner regular insulin (phase IV), suboptimal bedtime glycemic levels might have to be allowed to prevent too low mid-sleep levels, which would increase the risk of undetected hypoglycemia. New, rapid-acting insulins might obviate this problem (16). There is not yet unequivocal evidence of this potential advantage (17).

The overall incidence of mild and moderate hypoglycemic reactions about doubled with each therapy step after phase I, if lower final glycohemoglobin levels resulted. Phases II (evening insulin with daytime glipizide) and III (twice-daily insulin injections) had similar incidences of hypoglycemic events and of final HbA<sub>1c</sub>, although insulin dose was twice as high in phase III.

In combination therapy (phase II), the lowest mean HbA<sub>1c</sub> was obtained with a glipizide dose of 20 mg/day, although the mean level of HbA<sub>1c</sub> was not significantly different from the level obtained with 10 mg/day. The majority of patients in combination therapy reached maximum doses of glipizide, and their response to lower doses was no different than that of the full cohort. The results of the combination of glipizide with insulin confirm the earlier observations with glipizide alone, that the maximum effective dose is ~10–15 mg/day, whereas doses >20 mg/day have a tendency to impair response (5–7). Saturation of  $\beta$ -cell sulfonylurea receptors at the glipizide blood levels attained with low doses might be the main mechanism responsible for this effect (5). In practical terms, combination therapy of evening insulin with glipizide was effective and convenient in extending the action of a single insulin injection, but daily doses of glipizide >20 mg/day were not advantageous. The current U.S. formulation of the slow-release glipizide recommends a maximum dose of 20 mg/day.

In the present feasibility trial, there were no significant weight changes in the intensive arm different from those in the standard arm, probably because of the gradual incor-

poration of progressive treatment steps and the relatively low daily insulin doses in phases I ( $61 \pm 38$  U) and II ( $64 \pm 41$  U) (2). When multiple daily injections were used in other studies as initial treatment in type 2 diabetes, aside from the added inconvenience, there was substantial weight gain (13,18). This did not occur in the recently reported Kumamoto Trial (19). However, that cohort had unusually low insulin requirements (20–25 units/day, and mean BMI of only 20 kg/m<sup>2</sup>). In the VA CSDM, the reduction of mean HbA<sub>1c</sub> levels from the near-normal levels obtained with a single injection of insulin and glipizide (phase II) to only a 0.5% lower level with multiple injections (phase IV) demanded twice the daily insulin dose and a much greater incidence of mild and moderate hypoglycemic reactions. It should also be taken into account that within the limited power and duration of the VA CSDM feasibility trial, there was an increased incidence of nonfatal new cardiovascular events with lower attained HbA<sub>1c</sub> levels, regardless of treatment phase (4). The VA CSDM group has stated the opinion that a long-term prospective clinical trial is needed to assess the risk-benefit ratio of intensive insulin therapy for type 2 diabetes in patients who require it (4).

**Acknowledgments**— Supported by the Cooperative Studies Program of the Department of Veteran Affairs Medical Research Service, Washington, DC, and by a grant-in-aid from Roerig/Pfizer Pharmaceuticals, New York, NY. The following organizations gave generous support in pharmaceutical and reagents: Boehringer Mannheim Diagnostics, Indianapolis, IN; Eli Lilly, Indianapolis; Medisense, Cambridge, MA; Miles Diagnostics, Elkhart, IN; Progene, Overland Park, KS; and Squibb-Novo, Princeton, NJ.

Special thanks to K. Tir for statistical work; D. Kernan, RN, and B. Christine for the preparation of graphs; and E. Comejo and A. Doup for typing.

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