Continuous Subcutaneous Insulin Infusion Versus Multiple Daily Injections

The impact of baseline A1c

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OBJECTIVE — Rapid-acting insulin analogs (insulin lispro and insulin aspart) have emerged as the meal insulin of choice in both multiple daily insulin injection (MDII) therapy and continuous subcutaneous insulin infusion (CSII) for type 1 diabetes. Thus, a comparison of efficacy between CSII and MDII should be undertaken only in studies that used rapid-acting analogs for both intensive regimens.

RESEARCH DESIGN AND METHODS — We performed a pooled analysis of the randomized controlled trials that compared CSII and optimized MDII therapy using rapid-acting analogs in adults with type 1 diabetes.

RESULTS — The three studies that met inclusion criteria provided data on 139 patients, representing 596 patient-months for CSII and 529 patient-months for MDII. Mean age was 38.5 years, with duration of diabetes of 18.0 years. The studies differed significantly in mean baseline A1c (7.95, 8.20, and 9.27%). The pooled estimate of treatment effect comparing the percentage reduction in A1c by CSII with that by MDII (CSII − MDII) was 0.35% (95% CI −0.10 to 0.80, $P = 0.08$) using a random effect to account for heterogeneity between studies. Importantly, the interaction between baseline A1c and treatment modality emerged as an independent predictor of treatment effect (CSII − MDII) ($P = 0.002$). The relative benefit of CSII over MDII was found to increase with higher baseline A1c. A model derived from these data predicts that in a patient with a baseline A1c of 10%, CSII would reduce the A1c by an additional 0.65% compared with MDII. Conversely, there would be no A1c benefit of CSII compared with MDII if baseline A1c were 6.5%. There was no significant difference between CSII and MDII in the rate of hypoglycemic events.

CONCLUSIONS — When using rapid-acting insulin analogs in CSII and MDII regimens in adult patients with type 1 diabetes, insulin pump therapy is associated with better glycemic control, particularly in those individuals with higher baseline A1c. Thus, CSII emerges as an important modality for implementing intensive therapy and may be uniquely advantageous in patients with poor glycemic control.

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Abbreviations: CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; MDII, multiple daily insulin injection.

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

The Diabetes Control and Complications Trial (DCCT) confirmed the central importance of intensive management in reducing the risk of microvascular complications in patients with type 1 diabetes (1). Intensive therapy can be implemented using either continuous subcutaneous insulin infusion (CSII) or multiple daily insulin injection (MDII) regimens. Although the goal of near-normal glycemic control using intensive management has been widely accepted, debate has emerged regarding the optimal delivery of such therapy.

A recent meta-analysis of studies comparing CSII and MDII demonstrated a small improvement in glycemic control (0.51% greater reduction in A1c) using CSII compared with MDII therapy (2). However, several caveats must be considered in the interpretation of this result. Most of the studies included in this meta-analysis were from the 1980s and used older, more problematic insulin pump systems. Secondly, some of the studies used nonoptimized regimens involving fewer than three daily injections of premeal bolus insulin. Finally, it is particularly important to recognize that all but 1 of the 12 studies included in this meta-analysis used regular insulin for premeal boluses, rather than newer, more appropriate meal insulin analogs.

Rapid-acting insulin analogs (insulin lispro and insulin aspart) exhibit important pharmacokinetic and pharmacodynamic advantages over regular insulin, including significantly faster absorption, earlier onset, and shorter duration of action (3–5). In MDII regimens, the use of rapid-acting analogs, rather than regular insulin, for preprandial bolus therapy is associated with improvements in both postprandial glycemia and A1c concentration (6–9). Similarly, in CSII regimens, the use of rapid-acting analogs results in a significant decrease in postprandial glycemia, A1c concentration, and rates of hypoglycemia when compared with CSII using human regular insulin (10–13). Thus, when comparing the efficacy of

CSII and MDII regimens, the optimal comparison is provided by studies in which both regimens use rapid-acting analogs. As such, we performed a pooled analysis of the published randomized controlled trials that have compared CSII and optimized MDII therapy using rapid-acting insulin analogs in adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Identification and selection of studies

We conducted a search of the medical literature using MEDLINE (1982–2002), Premedline, CDSR, ACP Journal Club, DARE, CCTR, and reference lists of selected randomized controlled trials and meta-analyses. Search terms included the following: CSII; insulin infusion systems; pump therapy; insulin/aa (analogs & derivatives); diabetes, insulin-dependent; hemoglobin A, glycosylated; and randomized controlled trials. Articles describing randomized controlled trials comparing optimized MDII to CSII regimens using rapid-acting insulin analogs in adult patients with type 1 diabetes were selected for inclusion in the analysis. Optimized MDII therapy required at least three premeal injections of rapid-acting insulin per day. We excluded studies of short duration (2 weeks on either therapy) or those involving either patients with newly diagnosed type 1 diabetes or pregnant patients. Three studies were identified for inclusion in the analysis: DeVries et al. (14), Tsui et al. (15), and Hanaire-Broutin et al. (16).

Study participants

Inclusion criteria in the DeVries study included a diagnosis of type 1 diabetes, age between 18 and 70 years, and persistent poor glycemic control with three or more insulin injections per day (defined as mean A1c ≥8.5% in the 6 months preceding the trial). Before randomization, 89 potential participants underwent a 14-week qualification phase. Eight patients discontinued participation during the qualification phase. One patient was excluded from randomization because of infrequent self-monitoring of blood glucose during qualification. One other patient was excluded before randomization because of improved A1c below the predefined limit of 7.5% during the qualification phase.

In the Tsui study, adult patients between the ages of 18 and 60 years with type 1 diabetes were considered for inclusion if onset of diabetes was at or before the age of 40, duration of disease was >2 years, and the patient was capable of complying with the treatment protocol. Inclusion criteria in the Hanaire-Broutin study included A1c <10%, negative C-peptide, and experience with intensive insulin therapy.

Meta-analysis

The treatment effects on A1c and insulin dose from the three studies were pooled using the standard fixed effects model based on the inverse variance method and the DerSimonian and Laird (17) random effects model. Heterogeneity was assessed by the Q statistic. The CIs for treatment effect on A1c and insulin dose in the study by Hanaire-Broutin et al. (16) (Figs. 1 and 3, respectively) were based on the *P* values (<0.001 and <0.0001, respectively) reported in the original article describing this study. The laboratory reference range for A1c was 4.3–6.1 in the DeVries study, 4.1–6.5 in the Tsui study, and 4.0–6.0 in the Hanaire-Broutin study.

Pooled analysis

Investigators from each of the three studies agreed to pool their respective raw trial data to facilitate a pooled analysis. For assessment of within-patient variation of treatment effect on A1c and rate of hypoglycemia, data were drawn from the cross-over phase in each study. Cross-over data were available for 105 patients (54 from DeVries et al., 40 from Hanaire-Broutin et al., and 11 from Tsui et al.). Also included in the pooled dataset were data from an additional 34 patients (18 from DeVries et al. and 16 from Tsui et al.) who only participated in a single treatment phase. Note that, by design, the CSII group in the study by Tsui et al. was not crossed over to MDII.

The treatment effect on A1c was analyzed using a mixed linear modeling approach (using the MIXED procedure in SAS 8.2), with an isotropic exponential spatial covariance structure used to model the intrasubject correlation of the repeated measurements and random effects used to model both patient and patient treatment effects. All fixed and random effects were initially allowed to differ between studies, with the Akaike Information Criterion approach used to reduce model complexity. Fixed effects in the final model included the following: *1*) baseline A1c, *2*) a separate intercept for each study, *3*) a linear trend for month by study, *4*) treatment modality, and *5*) the interaction between baseline A1c and treatment effect. The interaction between study and treatment effect was not a significant predictor. Two data points were excluded from the pooled analysis because of extreme influence on the results: the patient in question from the study by DeVries et al. had A1c values of 5.7 and 5.0% after being crossed over to CSII compared with 13.0% at baseline (and 12.6 and 11.7% on MDII). Inclusion of these omitted observations would further strengthen the overall conclusions of this study. As such, the current statistical analysis of treatment effect on A1c reported in this study should be interpreted as conservative.

Pooled analysis of the incidence of hypoglycemia was performed using the number of hypoglycemic events during the last 3 weeks of each treatment period in the DeVries study, the last 2 weeks of both treatment periods in the Hanaire-Broutin study, and months 3–9 of the first treatment phase in the study by Tsui et al. In the DeVries study, mild hypoglycemia was defined as a value ≤3.9 mmol/l on self-monitoring of blood glucose. In the Hanaire-Broutin study, hypoglycemia was defined by capillary blood glucose <3.3 mmol/l. In the Tsui study, hypoglycemia was defined as hypoglycemic symptoms relieved by the ingestion of glucose and/or capillary blood glucose <3 mmol/l. The pooled data were analyzed in a generalized linear model using the negative binomial error distribution with a log link function and an offset for the logarithm of the number of weeks model. (This model is similar to the standard model for Poisson regression, with the negative binomial scale parameter to account for overdispersion.) A generalized estimating equations approach was used to account for the within-subject correlation in the data, and CIs were derived using the robust empirical standard error estimates. The statistical model included fixed effects for study (thus accommodating the different thresholds for hypoglycemia used in each study) and treatment. Supplementary models included terms for treatment by study interaction (to test the homogeneity of

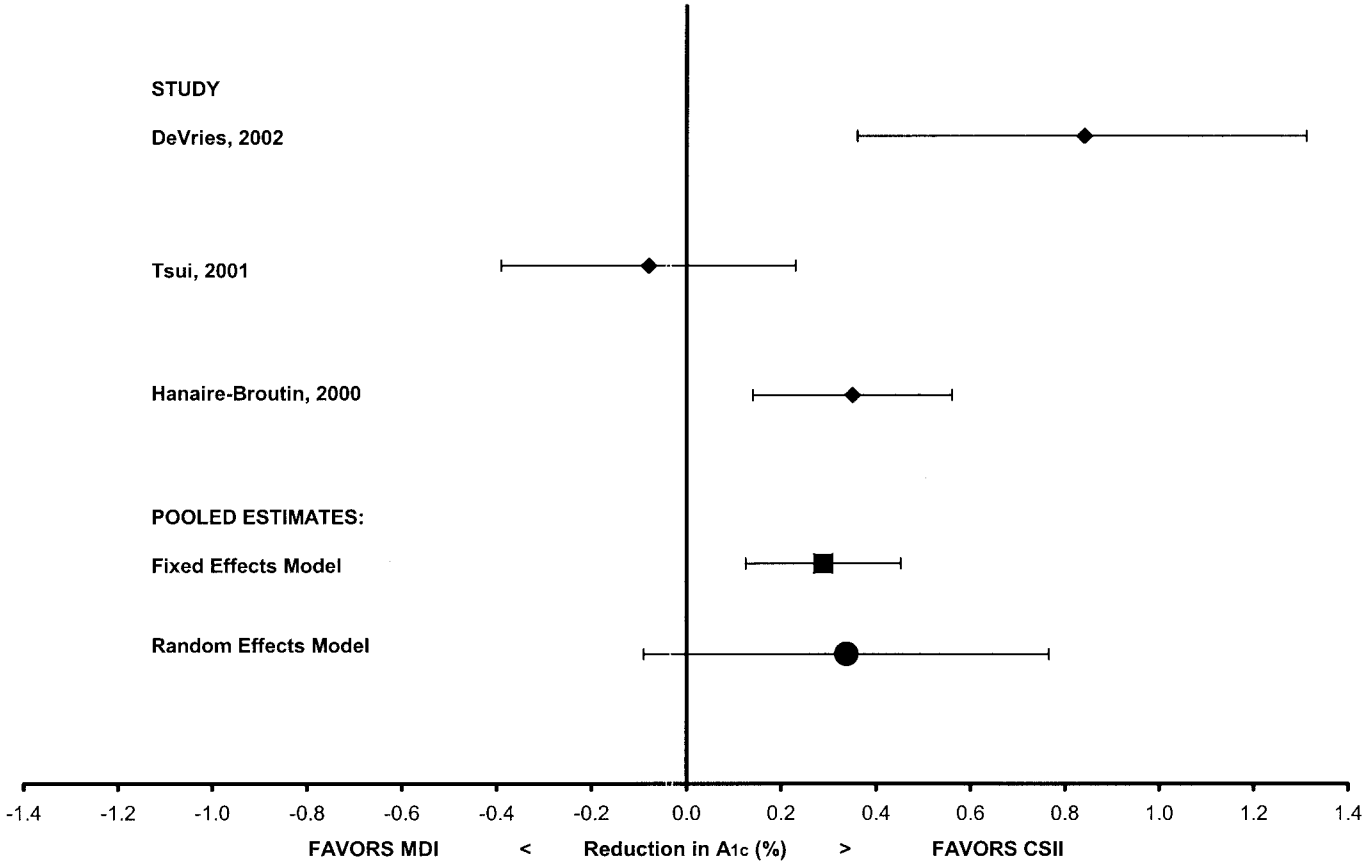

Figure 1—*Treatment effect on A1c, by study, with 95% CI.*

treatment effect between studies) and baseline A1c (to assess the impact of adjusting for baseline risk).

RESULTS — We identified three randomized controlled trials that compared glycemic control with CSII and MDII using rapid-acting insulin analogs in adults with type 1 diabetes (14–16). Table 1 shows the characteristics of these studies. The study by Hanaire-Broutin et al. used a cross-over design. The study by DeVries et al. also used a cross-over design, although this trial had previously been analyzed as a parallel study because of significant patient drop out at cross-over. The three studies provided data on 139 patients, representing 596 patient-months for CSII treatment and 529 patient-months for MDII therapy. Mean age was 38.5 years, with a mean duration of diabetes of 18.0 years. Baseline A1c was significantly different between the three studies, with highest initial glycemia in the trial by DeVries et al. (9.27%), followed by the studies by Hanaire-Broutin et al. (8.20%) and Tsui et al. (7.95%) (14–16).

Figure 1 shows the overall treatment effect comparing the reduction in A1c by CSII with that by MDII (expressed as CSII − MDII) in each of the studies. The estimate of treatment effect favoring CSII by the fixed effects model was 0.29% (95% CI 0.13–0.45). The estimate by the random effects model was similar at 0.34% but exhibited a substantial widening of the 95% CI (−0.09 to 0.77). This finding reflected the heterogeneity of the estimates from these studies and suggested that there was no significant overall difference in the reduction in A1c by CSII compared with MDII.

To further evaluate the treatment effect on A1c, a pooled analysis was performed by combining the raw patient data from the three studies. The pooled estimate of treatment effect comparing the percentage reduction in A1c by CSII with that by MDII (CSII − MDII) was 0.35% (95% CI −0.10 to 0.80, $P = 0.08$) using a random effect to account for heterogeneity between studies. Importantly, the interaction between baseline A1c and treatment modality emerged as an independent predictor of treatment effect ($P = 0.002$). When the change in A1c is plotted against baseline A1c by treatment modality in those patients for whom cross-over data are available, it is apparent that the relative benefit of CSII over MDII increases with higher baseline A1c (Fig. 2). Using these data, a model was derived wherein the treatment effect (CSII − MDII) can be predicted as follows: treatment effect = 1.2158 − 0.1861 × baseline A1c. This model predicts that in a patient with a baseline A1c of 10%, CSII would reduce the A1c by an additional 0.65% compared with MDII. Conversely, there would be no A1c benefit of CSII compared with MDII if baseline A1c were 6.5%.

Overall, there were 2.2 hypoglycemic events per week with CSII and 2.0 events per week with MDII. The pooled estimate of the percentage difference in hypoglycemic risk comparing the rate of hypoglyce-

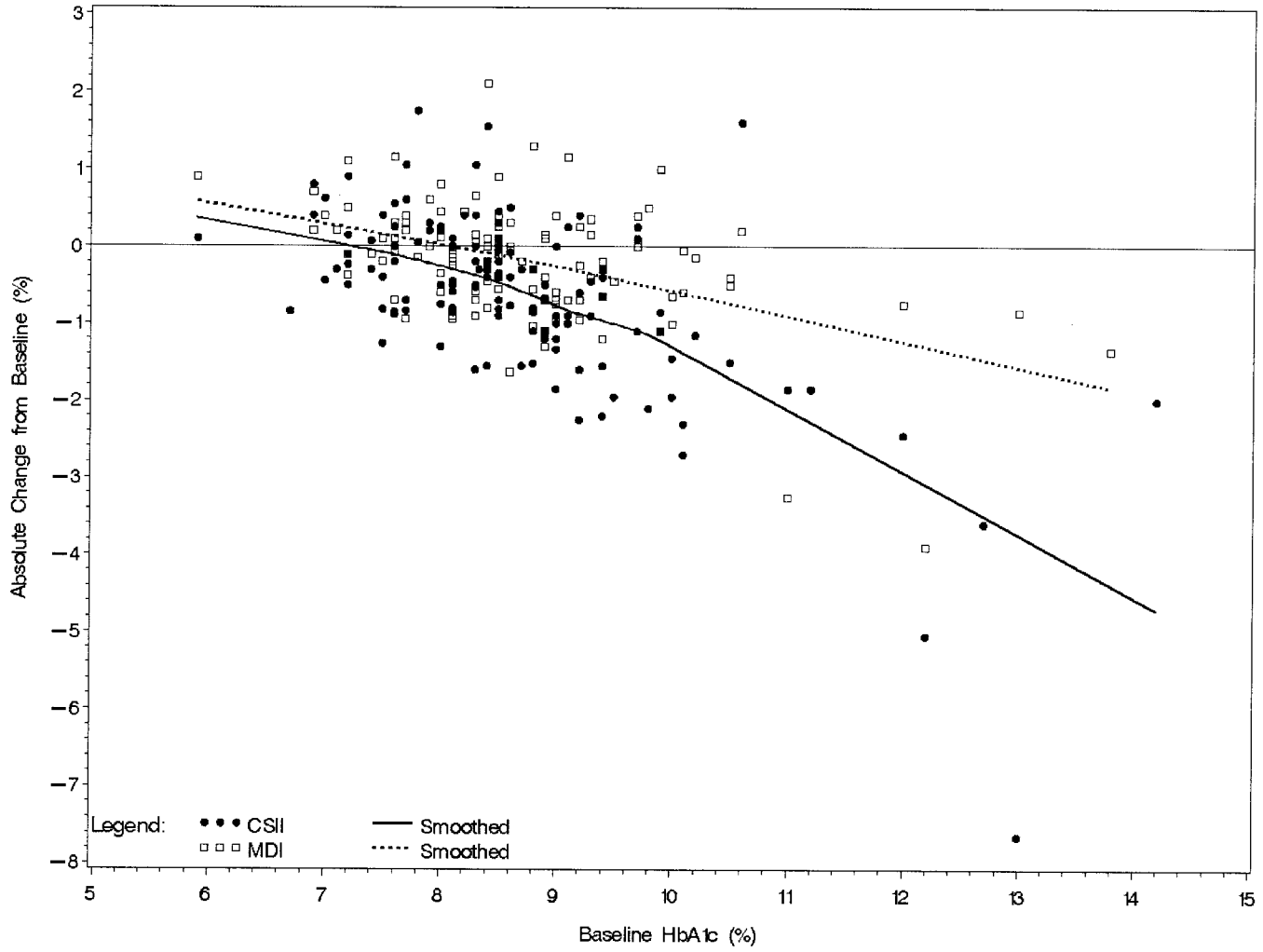

Figure 2—*Plot of mean change in A1c from baseline versus baseline A1c by treatment modality.*

mic episodes with CSII with that with MDII (CSII − MDII) was 9.7% (95% CI −11.3 to 35.8, $P = 0.39$), suggesting no significant difference in hypoglycemic risk between the two treatment modalities. Moreover, although hypoglycemic risk is negatively correlated with A1c, inclusion of baseline A1c as a covariate in a supplementary model did not significantly change this overall pooled estimate (estimate = 8.8% [95% CI −12.6 to 35.4]).

Figure 3 shows the reduction in total daily insulin dose comparing CSII with MDII (CSII − MDII) in each of the studies. The estimate for reduction in total daily insulin was 12.2 units/day (95% CI 6.4–18.0) using a random effects model. The estimate from the fixed effects model was similar at 11.3 units/day (7.8–14.8). Overall, there was one episode of ketoacidosis in each of the two treatment groups.

Table 1—*Characteristics of studies included in meta-analysis*

Study (ref. no.)	Design	Study arm	*n**	Age (years)	Duration of diabetes (years)	Baseline A1c (%)	Type of insulin	Treatment duration (months)
DeVries et al. (14)	Parallel†	CSII	39	36.2 ± 10.3	17.6 ± 9.8	9.27 ± 1.4	Aspart	4
		MDII	40	37.3 ± 10.6	18.0 ± 9.4	9.25 ± 1.4	Aspart, NPH	4
Tsui et al. (15)	Parallel‡	CSII	13	36 ± 12	17 ± 10	7.7 ± 0.6	Lispro	9
		MDII	14	36 ± 10	15 ± 9	8.2 ± 0.7	Lispro, NPH	9
Hanaire-Broutin et al. (16)	Cross-over	CSII/MDII	41	43.5 ± 10.3	20 ± 11.3	8.39 ± 0.87	Lispro/lispro, NPH	4/4

Data are means ± SD. *Seven patients withdrew from the study by DeVries et al. before reaching an evaluation visit, and 1 patient withdrew from the study by Hanaire-Broutin et al., yielding a total of 139 patients for the current analysis. †Originally designed as a cross-over study but ultimately analyzed as a parallel study. ‡Cross-over data were collected for 11 participants after the completion of the parallel study.

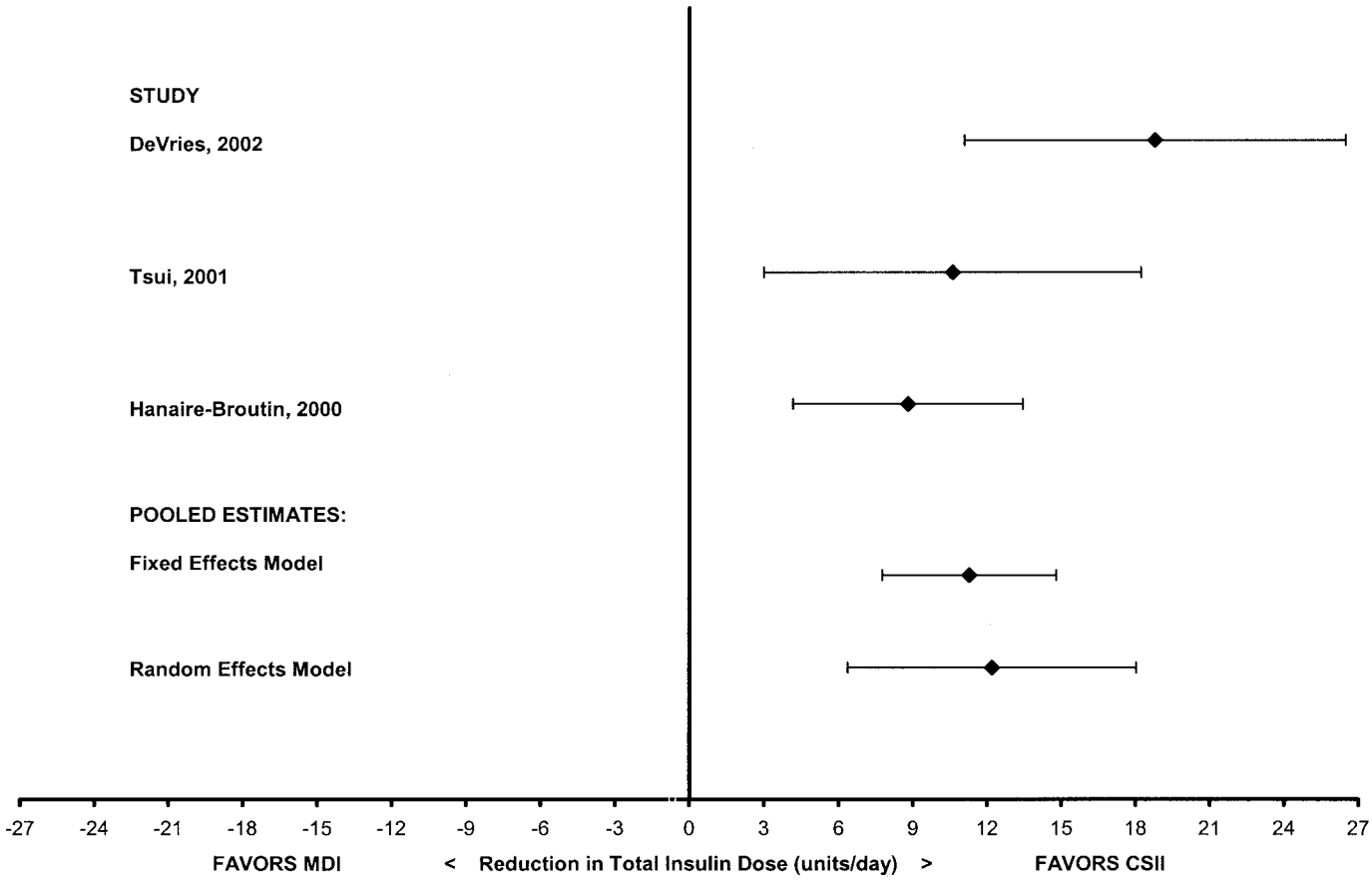

Figure 3—*Reduction in daily insulin dose, by study, with 95% CI.*

CONCLUSIONS — In this analysis, we demonstrated that the use of rapid-acting insulin analogs in CSII and MDII regimens in adult patients with type 1 diabetes is associated with better glycemic control with insulin pump therapy. Importantly, the glycemic advantage of CSII over MDII was found to increase with worsening baseline A1c, such that patients with the poorest initial glycemic control obtained the greatest benefit with insulin pump therapy. These results suggest that, when intensive insulin therapy is implemented, baseline A1c may be another element to consider when choosing between CSII and MDII.

The observation of a modest, although nonsignificant, trend toward better glycemic control with CSII in this analysis is broadly consistent with previous investigations. The largest previous experience was provided by the DCCT, in which 124 participants used CSII for ≥90% of the time for a mean 6.5-year study duration (18). Mean A1c in this group of patients was 0.2% lower than that in the cohort of intensively treated patients receiving MDII therapy. Although the incidence of severe hypoglycemic events was similar between the two groups, the frequency of episodes resulting in coma or seizure was higher in the CSII cohort than in the MDII group. However, because patients who were randomly assigned to receive intensive treatment in the DCCT could choose between CSII and MDII (i.e., were not randomly allocated to the type of intensive therapy), the results from this study may provide a biased estimate of the comparative merits of these therapies. In a recent meta-analysis of trials comparing CSII and MDII regimens, Pickup, Mattock, and Kerry (2) reported a difference in A1c of 0.51%, favoring CSII therapy. This modest improvement with CSII compared with MDII was achieved with an average reduction in total daily insulin dose of 7.6 units/day. Given the introduction of insulin analogs with superior pharmacodynamics, advances in pump technology, and greater experience with intensified regimens, it was not clear whether these earlier studies would reflect current clinical practice. Nevertheless, despite all of these changes, the relative effects of CSII compared with those of MDII on glycemic control and total daily insulin dose in the current analysis remain similar to earlier findings.

The current study demonstrates a relationship between baseline A1c and the magnitude of benefit from CSII compared with MDII therapy. The pooled analysis suggests that the relative benefit of CSII over MDII in regard to glycemic control is directly proportional to baseline A1c. The model describing this relationship holds significant clinical implications. First, CSII emerges as a particularly important therapeutic consideration in patients with poor glycemic control. Second, the model provides an estimate of the magnitude of benefit associated with CSII compared with MDII. Finally, baseline A1c becomes another factor to consider when choosing between CSII and MDII regimens for intensive insulin therapy.

Careful patient selection is widely recognized as an important element in the judicious use of CSII therapy. The most recent American Diabetes Association position statement on insulin pump therapy suggests that motivated individuals with a willingness to assume substantial responsibility for their own care may be considered candidates for CSII (19). Flexibility of lifestyle and pregnancy are also noted by the American Diabetes Association as patient factors that may affect the decision to use pump therapy. Pickup and colleagues (2,20) have further suggested the consideration of CSII in patients with either unpredictable hypoglycemia or a marked increase in blood glucose concentration at dawn, despite best efforts with an optimized MDII regimen. The current study suggests that long-standing poor glycemic control should be another factor to consider in patient selection for insulin pump therapy.

The findings of this study must be interpreted within the context of certain limitations. One limitation is that there have only been three published randomized controlled trials comparing CSII and optimized MDII using rapid-acting analogs in adults with type 1 diabetes. To offset this limitation, however, the current analysis was performed by pooling the study data from all three of these trials. This approach also allowed for assessment of response to therapy across a wide continuum of baseline A1c values, reflective of clinical practice. A second consideration is that any benefit in glycemic control with CSII compared with MDII when using rapid-acting analogs is probably caused by superior titration of basal insulin replacement with pump therapy. As such, with the recent development of long-acting insulin analogs (such as insulin glargine) with more neutral basal pharmacokinetics than NPH or ultralente insulin, a question of clear interest is the comparison between CSII and MDII regimens that use long-acting insulin analogs. In this regard, a recent chart audit of 103 patients reported similar glycemic control with both CSII and MDII using rapid- and long-acting insulin analogs (21). Comparison of these treatment regimens by randomized controlled trial is needed.

In summary, when rapid-acting insulin analogs are used in CSII and MDII regimens in adult patients with type 1 diabetes, insulin pump therapy is associated with better glycemic control, particularly in those individuals with higher baseline A1c. Thus, CSII emerges as an important modality for implementing intensive therapy and may be uniquely advantageous in the high-risk population of patients with poor glycemic control.

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References

1. The Diabetes Control and Complications Trial (DCCT) Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
2. Pickup J, Mattock M, Kerry S: Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomized controlled trials. *BMJ* 324:1–6, 2002
3. Dimarchi RD, Chance RE, Long HB, Shields JE, Slieker LJ: Preparation of an insulin with improved pharmacokinetics relative to human insulin through consideration of structural homology with insulin-like growth factor 1. *Horm Res* 41 (Suppl 2):93–96, 1994
4. Howey DC, Bowsher RR, Brunelle RL, Rowe HM, Santa PF, Downing-Shelton J, Woodworth JR: [Lys(B28), Pro(B29)]-human insulin: a rapidly absorbed analogue of human insulin. *Diabetes* 43:396–402, 1994
5. Jacobs MA, Keulen ET, Kanc K, Casteleijn S, Scheffer P, Deville W, Heine RJ: Metabolic efficacy of preprandial administration of Lys(B28), Pro(B29) human insulin analog in IDDM patients: a comparison with human regular insulin during a three-meal test period. *Diabetes Care* 20: 1279–1286, 1997
6. Ciofetta M, Lalli C, Del Sindaco P, Torlone E, Pampanelli S, Mauro L, Chiara DL, Brunetti P, Bolli GB: Contribution of postprandial versus interprandial blood glucose to HbA_{1c} in type 1 diabetes on physiologic intensive therapy with lispro insulin at mealtime. *Diabetes Care* 22:795–800, 1999
7. Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L: Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. *Diabetes Care* 23: 583–588, 2000
8. Home PD, Lindholm A, Riis A: Insulin aspart vs human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial: European Insulin Aspart Study Group. *Diabet Med* 17:762–770, 2000
9. Lalli C, Ciofetta M, Del Sindaco P, Torlone E, Pampanelli S, Compagnucci P, Cartechini MG, Bartocci L, Brunetti P, Bolli GB: Long-term intensive treatment of type 1 diabetes with the short-acting insulin analog lispro in variable combination with NPH insulin at mealtime. *Diabetes Care* 22:468–477, 1999
10. Zinman B, Tildesley H, Chiasson JL, Tsui E, Strack T: Insulin lispro in CSII: results of a double-blind crossover study. *Diabetes* 46:440–443, 1997
11. Melki V, Renard E, Lassmann-Vague V, Boivin S, Guerci B, Hanaire-Broutin H, Bringer J, Belicar P, Jeandidier N, Meyer L, Blin P, Augendre-Ferrante B, Tauber JP: Improvement of HbA_{1c} and blood glucose stability in IDDM patients treated with lispro insulin analog in external pumps. *Diabetes Care* 21:977–982, 1998
12. Renner R, Pfutzner A, Trautmann M, Harzer O, Sauter K, Landgraf R, the German Humalog-CSII Study Group: Use of insulin lispro in continuous subcutaneous insulin infusion treatment: results of a multicenter trial. *Diabetes Care* 22:784–788, 1999
13. Zinman B: Insulin pump therapy and rapid acting insulin: what have we learned? *Int J Clin Pract* 123:47–50, 2001
14. DeVries JH, Snoek FJ, Kostense PJ, Masurel N, Heine RJ: A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with long-standing poor glycemic control. *Diabetes Care* 25:2074–2080, 2002
15. Tsui E, Barnie A, Ross S, Parkes R, Zinman B: Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. *Diabetes Care* 24:1722–1727, 2001
16. Hanaire-Broutin H, Melki V, Bessieres-Lacombe S, Tauber JP: Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using insulin lispro in type 1 diabetic patients on intensified treatment: a ran-

domized study. *Diabetes Care* 23:1232–1235, 2000
17. DerSimonian R, Laird N: Meta-analysis in clinical trials. *Control Clin Trials* 7:177–188, 1986
18. The Diabetes Control and Complications Trial (DCCT) Research Group: Implementation of treatment protocols in the Diabetes Control and Complications Trial. *Diabetes Care* 18:361–376, 1995
19. American Diabetes Association: Continuous subcutaneous insulin infusion. *Diabetes Care* 27 (Suppl. 1):S110, 2004
20. Pickup J, Keen H: Continuous subcutaneous insulin infusion at 25 years: evidence base for the expanding use of insulin pump therapy in type 1 diabetes. *Diabetes Care* 25:593–598, 2002
21. Harmel AP, Mathur R: Similar A1c outcomes in type 1 diabetic patients undergoing intensive diabetes management with preprandial rapid-acting insulin and either CSII or glargine. *Diabetes Care* 27: 272–273, 2004