Concerns About Meta-analysis of Glucose Control and Cardiovascular Disease in Type 2 Diabetes

TO THE EDITOR: The proposition that glucose lowering affects cardiovascular risk in patients with type 2 diabetes is very important. Although we recognize the value of the article by Kelly and colleagues (1), we would like to draw attention to errors in their meta-analysis that we believe affect the conclusions reached.

First, Kelly and colleagues combined data from 3 recent studies (2–4) with 2 substudies of the UKPDS (United Kingdom Prospective Diabetes Study) (5, 6) to suggest that many outcomes differed between the “early” and “late” studies. In so doing, they did not notice that the 411 participants and their associated events in the conventional treatment (diet) group of the metformin substudy, UKPDS 34 (6), were also included in the conventional treatment group in the main study, UKPDS 33 (5). By using the same studies and methodology as Kelly and colleagues, but without double-counting, we analyzed UKPDS 33 and 34 as 1 study, including the additional data from the intensive treatment group of the patients treated with metformin in UKPDS 34. Thus, the relative risk for cardiovascular death is 1.05 (95% CI, 0.82 to 1.33) instead of 0.97 (CI, 0.76 to 1.24), the relative risk for all-cause mortality is 1.03 (CI, 0.89 to 1.19) instead of 0.98 (CI, 0.84 to 1.15), and the reduction in risk for cardiovascular events is 8 percentage points (CI, 1 to 14 percentage points) instead of 10 percentage points (CI, 2 to 17 percentage points). The recalculation reduces the difference between the early and late trials, with the only end points now showing substantial heterogeneity in overall pooled effect estimates being cardiovascular death (F = 75%), all-cause mortality (F = 67%), and severe hypoglycemia (F = 79%). Second, one might debate whether it was appropriate to include UKPDS 34 in the meta-analysis; trialists involved in the original studies performed a similar meta-analysis without including it (7). Finally, use of different definitions of end points (such as including or not including sudden death as a cardiovascular disease) is a problem that can be solved only with meta-analysis of individual patient data.

Therefore, we conclude that little evidence exists of differences in outcomes between early and late trials of glucose control for type 2 diabetes. We think that current epidemiologic and trial evidence suggests that intensive glycemic control will reduce coronary heart disease by about two thirds and will not statistically significantly affect stroke, cardiovascular mortality, or total mortality. Moreover, we believe that data suggest that treating 100 persons with intensive glycemic control for 10 years would prevent about 3 cardiovascular events at the expense of inducing 8 serious hypoglycemic events.

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References

IN RESPONSE: We thank Drs. Yudkin and Richter for their interest in our meta-analysis. The decision to analyze the subgroups of early and more recent trials was an a priori determination based on important differences in patient populations, targeted hemoglobin A1c levels, and treatment regimens. Specifically, the early UKPDS trials included only patients with newly diagnosed diabetes, whereas the more recent ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease), and VADT (Veterans Affairs Diabetes Trial) studies included patients with prevalent diabetes. The intensive glucose control target in the UKPDS was similar to the conventional glucose control target in the more recent trials. Finally, the UKPDS used diet as the primary method of conventional treatment, whereas the more recent trials used hypoglycemic agents. We included UKPDS 34 in our meta-analysis because the 342 patients assigned to metformin for intensive treatment were completely independent of the 2729 patients assigned to sulfonylureas or insulin for intensive treatment in UKPDS 33 (1). Results from different treatment groups of clinical trials that share a common control group are sometimes combined, although ideally our estimates should have accounted for underlying correlation between the effect size, which they did not (2, 3). The UKPDS 34 control group comprises a relatively small proportion of the UKPDS 33 control group (approximately 36%), and no meta-analytic methods exist to account for correlations in binary end points of trials that use partially shared control groups. We believe that the UKPDS 34 provides important information on the effects of intensive glucose control on cardiovascular disease, and any correlation it may have with the UKPDS 33 due to a partially shared control group does not warrant its exclusion from the meta-analysis.

Drs. Yudkin and Richter raised an issue about different definitions of outcomes among individual trials. However, all-cause mor-

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tality and cardiovascular disease mortality are “hard clinical outcomes,” which should be similar among trials. Our meta-analysis indicated that heterogeneity was significant in these outcomes between individual trials, which supported our decision to do subgroup analyses. We appreciate the concerns of Drs. Yudkin and Richter but stand by our methods and conclusions.

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References

Pulse Versus Daily Oral Cyclophosphamide in ANCA-Associated Vasculitis

TO THE EDITOR: de Groot and colleagues (1) reemphasize the advantages of pulse cyclophosphamide over daily oral cyclophosphamide in antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides, which is the mainstay of therapy for induction of remission. However, in developing countries, such as India, tuberculosis is common. In fact, it is sometimes hard to differentiate between active tuberculosis and ANCA-associated vasculitis (mainly Wegener granulomatosis) either clinically or histopathologically. In many cases, latent tuberculosis may coexist with ANCA-associated vasculitis. Oral daily cyclophosphamide therapy is easier to withdraw in the event that the patient has tuberculosis. Giving pulse cyclophosphamide may aggravate underlying tuberculosis, which can be fatal; therefore, treatment should be individualized in developing countries. When tuberculosis is adequately ruled out, pulse cyclophosphamide remains the first choice.

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Potential Conflicts of Interest: None disclosed.

Reference

TO THE EDITOR: de Groot and colleagues (1) provide a balanced discussion of the strengths and weaknesses of their randomized trial. Unfortunately, that balance was lost in the abstract’s Conclusion section, which, if taken verbatim, clearly favors pulse (intravenous) cyclophosphamide over daily oral cyclophosphamide. The back story, however, is far more complex and provides substantial support for the daily oral regimen.

First, recovery of kidney function may have been better with daily oral therapy. The graph showing trends in estimated glomerular filtration rate (eGFR) censored the eGFR values after onset of end-stage renal disease (ESRD). This inflated the eGFR in the pulse group, because it had 5 ESRD events versus only 1 ESRD event in the daily oral group. We suggest the eGFR analysis be repeated after assigning an eGFR of 5 mL/min per 1.73 m² to each patient with ESRD.

Second, by 6 months, the pulse group had 4 patients with ESRD and the daily oral group had none. This is consistent with the notion that administering cyclophosphamide “up front,” when it is probably most needed, is better achieved with the daily oral regimen than with the pulse regimen.

Third, measures of quantitative proteinuria are not provided. This is a key concern because proteinuria magnitude is the strongest single predictor of GFR decrease (2), and proteinuria during follow-up was probably higher in the pulse group because it had more frequent flares. If proteinuria data are provided, they should be presented as the protein–creatinine ratio of the intended 24-hour urine collections rather than the face value of the protein content of the intended 24-hour collections, because the protein–creatinine ratio is a more reliable measure of the magnitude of proteinuria (3).

Finally, de Groot and colleagues describe pulse cyclophosphamide as “simpler.” However, in the United States, pulse cyclophosphamide requires a visit to an infusion center at a cost in excess of $1000 per visit, along with loss of a day’s work and other inconveniences. The pulse regimen is ideal for nonadherent patients; however, to subject every patient to intravenous cyclophosphamide when only a few will benefit does not seem justified.

In summary, de Groot and colleagues’ work is very important; however, it does not show that the pulse regimen is better than the daily oral regimen. Indeed, if the data on proteinuria and true eGFR trends are made available, the conclusion may be that the daily oral regimen is superior to the pulse regimen.

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Potential Conflicts of Interest: None disclosed.

References
TO THE EDITOR: The study by de Groot and colleagues (1) shows that the higher cumulative dosing of traditional (2 mg/kg) daily oral cyclophosphamide regimens offers no advantage over lower-dose regimens delivered by intravenous pulse for the induction of remission in patients with ANCA-associated vasculitis. However, the authors did not evaluate whether lower-dose (1.0 to 1.25 mg/kg) daily oral regimens, with their lower risks for bone marrow and bladder toxicities, would be similarly efficacious in achieving remission. Before intravenous pulse cyclophosphamide for induction of remission in this patient population is broadly recommended, comparison studies with less toxic oral regimens are needed.

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Potential Conflicts of Interest: None disclosed.

Reference

IN RESPONSE: We appreciate our colleagues’ comments and are glad that our analysis has stimulated further thought among clinicians. We agree with Dr. Padhan that Wegener granulomatosis may be difficult to differentiate from tuberculosis infection. However, studies suggest that the presence of both positive cytoplasmic ANCA by immunofluorescence and proteinase 3 enzyme-linked immunosorbent assay has a low prevalence in tuberculosis (1). Even in those rare patients in whom the diagnosis of Wegener granulomatosis is doubted and the balance of evidence favors ANCA-associated vasculitis, we believe that patients should be treated with pulse cyclophosphamide rather than with daily oral cyclophosphamide. The cumulative dose of cyclophosphamide when administered in a pulse dose is half that of the oral regimen. For example, a person who weighs 70 kg receives a 1-g pulse of cyclophosphamide over 2 weeks compared with 2 g of the oral regimen. In persons with suspected latent tuberculosis or a history of tuberculosis, cyclophosphamide should be administered together with isoniazid prophylaxis, regardless of the cyclophosphamide regimen.

Drs. Hebert and Rovin suggests that evidence may exist to support use of the daily oral regimen. Five patients in the pulse group had ESRD compared with one patient in the oral group; this was not statistically significant. We performed the analysis comparing change in eGFR, imputing eGFR for patients who developed ESRD at 5 mL/min and found no difference in recovery of renal function between the 2 groups (P = 0.28). We disagree with the assertion that more ESRD in the pulse group correlates with less rapid improvement in inflammation.

The rate of normalization of C-reactive protein levels or Birbeck assay has a low prevalence in tuberculosis (1). Even in those rare patients in whom the diagnosis of Wegener granulomatosis is doubted and the balance of evidence favors ANCA-associated vasculitis, we believe that patients should be treated with pulse cyclophosphamide rather than with daily oral cyclophosphamide. The cumulative dose of cyclophosphamide when administered in a pulse dose is half that of the oral regimen. For example, a person who weighs 70 kg receives a 1-g pulse of cyclophosphamide over 2 weeks compared with 2 g of the oral regimen. In persons with suspected latent tuberculosis or a history of tuberculosis, cyclophosphamide should be administered together with isoniazid prophylaxis, regardless of the cyclophosphamide regimen.

TO THE EDITOR: We would like to clarify one aspect of Comi’s (1) commentary on glucose control in the intensive care unit and amplify another. First, although the NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) (2) control group was stated to have a target glucose level less than 10.0 mmol/L (<180 mg/dL), it was actually much less than that, because insulin infusions were continued until the blood glucose level reached 8.0 mmol/L (144 mg/dL). Indeed, the time-weighted mean blood glucose level in the control group was 8.0 mmol/L (144 mg/dL). Data on the mean glucose levels in patients who received insulin therapy were not provided. Thus, the standard for glucose control seems to be closer to 8.0 mmol/L (144 mg/dL) rather than below 10.0 mmol/L (180 mg/dL) as suggested by Comi.

In addition, we believe the relationship between hypoglycemia and adverse outcomes deserves increased scrutiny. Data from our own medical intensive care unit (target glucose level <8.0 mmol/L [<140 mg/dL]) show that for every episode of blood glucose level less than 2.2 mmol/L (<40 mg/dL), there are 12 episodes of blood venously; further pulses could be administered orally at the investigator’s discretion, which is a cost-effective measure and routine practice in our centers. As suggested, the regimen is likely to improve adherence. It was also associated with less leukopenia, which in the longer term is likely to translate to better patient safety and less use of granulocyte colony-stimulating factor. We believe that our study supports use of the pulse regimen. Of course, differences in long-term disease control, toxicity, and treatment-related damage may come to light only after longer follow-up; these data have been collected and are being analyzed.

As Dr. Levine rightly comments, no trials have compared lower-dose daily cyclophosphamide administered as a pulse dose or the historical standard dose of 2 mg/kg cyclophosphamide per day. There would of course be differences in the kinetics between administering intravenous cyclophosphamide as a total dose at day 1 and a slower accumulation over 14 days of an equivalent total dose given as 1 mg/kg per day. These differences might have implications for response to treatment and rate of disease control. Our trial supports use of a lower cumulative dose of cyclophosphamide administered in a pulsed manner and should now form the standard for future clinical trials testing different experimental regimens.

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Reference
glucose level between 2.2 and 2.9 mmol/L (40 and 70 mg/dL). Evaluation of short-term hypoglycemia (mean nadir for 5 minutes, 2.9 mmol/L [52 mg/dL]) in healthy volunteers was associated with statistically significant blunting of neuroendocrine, autonomic nervous system, and metabolic counterregulatory responses with subsequent episodes of hypoglycemia (3). Also, hypoglycemic hyperinsulinemic clamp studies in healthy volunteers showed significant increases in interleukin-6, adrenocorticotropic hormone, and cortisol at mean blood glucose levels of 2.8 mmol/L (50 mg/dL) (4). Thus, deleterious effects of hypoglycemia probably begin at glucose levels greater than 2.22 mmol/L (>40 mg/dL).

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References

CLINICAL OBSERVATION

Spoons Systematically Bias Dosing of Liquid Medicine

Background: Spoon dosing has been identified as a major cause of dosing errors and pediatric poisonings (1). Although the U.S. Food and Drug Administration recommends against using kitchen utensils to dose liquid medicine (2), most persons still use spoons when pouring medicine for themselves and their families (3). Although dosing errors remain modest when using kitchen teaspoons, they may increase when using various sizes of larger spoons (4). If the size of a spoon leads a teaspoonful of liquid medicine to seem like markedly more or less than 5 mL (5), a person may compensate by under- or overdosing (Figure).

Objective: To examine whether the dose of liquid medicine varies depending on the size of the spoon onto which it is poured.

Methods: During the cold and flu season, we asked 195 university students (109 men; mean age, 20.1 years [SD, 1.7]) to pour 5 mL of cold medicine into a teaspoon (5 mL, 2.7 × 4 cm), a medium-sized tablespoon (15 mL, 4 × 6 cm), and a larger spoon (45 mL, 6 × 9 cm). We told them that they were participating in a study about cold medicine and asked them to suppose they were at home with a cold, taking liquid medicine with a recommended dose of 1 teaspoon. So participants would better understand the volume of a teaspoon, we first gave them a full bottle of cold medicine and a teaspoon and asked them to pour exactly 1 teaspoon (5 mL). Next, we asked participants to pour the same 5-mL dose into each of the remaining 2 spoons in a randomized order. After each of these 2 pours, we asked participants to indicate how confident they felt that they had poured 5 mL (1 = not very confident; 9 = very confident) and how effective they believed their poured dose would be (1 = not very effective; 9 = very effective). After they left the room, we measured the volume of cold medicine they had poured into each of the 2 spoons.

Results: The amount of cold medicine that participants poured varied directly with the size of the spoon (4.58 vs. 5.58 mL; t = 2.30; P = 0.022) and overdosed when using the larger spoon (5.58 vs. 5 mL; t = 2.39; P = 0.017). Although the capacity of the spoons was never a constraint, participants dosed 8.4% less than prescribed into the medium-sized spoon and 11.6% more into the larger spoon. Notwithstanding this aggregate bias of 20%, participants had above-average confidence that their pouring was accurate and believed that the doses they poured into both spoons would be equally effective.

Discussion: The amount of liquid medicine a person doses may vary with the size of the spoon used. Participants underdosed by

![Figure. Attempts to pour 5 mL of medicine into larger-sized spoons.](image-url)
8.4% when using medium-sized spoons and overdosed by 11.6% when using larger spoons. Although these educated participants had poured in a well-lit room after a practice pour, they were unaware of these biases and were confident that they had poured the correct doses in both spoons. Whereas the clinical implications of an 8% to 12% dosing error in a 1-tsp serving of medicine may be minimal, the dosing error is likely to accumulate among fatigued patients who are medicating themselves every 4 to 8 hours for several days.

Although one would expect more experienced pourers, such as nurses or practiced parents, to be less biased, this may not be so. Even confident veteran bartenders poured 28% more liquor into short, wide glasses than into tall, slender glasses of the same volume (6). If a medicine’s efficacy is tied to its dose, it is more effective to strongly encourage a patient to use a measuring cap, dosing spoon, measuring dropper, or dosing syringe than to assume that they can rely on their pouring experience and estimation abilities with kitchen spoons.

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Potential Conflicts of Interest: None disclosed.

References

Correction
Correction: Glucose Control and Cardiovascular Disease in Type 2 Diabetes

In the recent meta-analysis by Kelly and colleagues (1), tables and figures presented data from 2 UKPDS (United Kingdom Prospective Diabetes Study) trials that compared intensive glucose-lowering therapy with diet: UKPDS 33 and 34. The UKPDS 34 was actually a substudy of UKPDS 33, limited to overweight patients who had been randomly assigned to metformin or diet in the parent study. However, in UKPDS 33, overweight patients randomly assigned to diet in the UKPDS 34 substudy (n = 411) were included in a combined diet-comparison group (n = 1138). Thus, the comparison group of 411 overweight patients in the UKPDS 34 study had already been included in the analysis of UKPDS 33. The meta-analysis by Kelly and colleagues considered the 2 studies as separate trials and, as such, double-counted those 411 patients. Authors of a letter to the Editor pointed out the double counting and provided effect estimates that avoided the problem by merging the 2 studies into 1 (2). For interested readers, several other approaches that minimize the bias introduced when comparisons use a common control group are available (3–5).

References