ing to define which test and which cutoff points of the latter would qualify as low or undetectable seems no more an abnegation of responsibility than the unwillingness of this committee to propose "rudimentary assessments" of insulin resistance by clamp studies or frequently sampled intravenous glucose tolerance test (FSIVGTT). The tasks of establishing appropriate physiologic thresholds and of highlighting the known basis for these cutpoints are quite different from recommending standards and technical procedures that are useful in defining the nature and severity of the pathophysiologic defect(s) that drive the marker of interest. While it is certainly a worthwhile and even necessary undertaking, a task such as the one proposed by Dr. Service belongs to a technical review panel empowered by some clinical laboratory oversight rather than in a classification work group. Such considerations might explain why the Joint National Commission on Detection, Evaluation, and Treatment of Hypertension listed pheochromocytoma as an important cause of secondary hypertension, becuase of the underlying increased adrenergic tone, but did not provide recommendations for assessment of plasma catecholamines.

While it is regrettable that Dr. Service feels that the committee engaged in a "complete intellectual retreat," it seems clear that his expectations of the prerogatives of a panel of this type are somewhat different from the ones that have typically defined the constraints on classification work groups, including the National Diabetes Data Group. As evidence continues to accrue, procedures continue to be refined, and mechanisms become more completely understood, perhaps it will become more likely that further improvements will be made on our imperfect attempts to classify heterogeneous diseases like diabetes.

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## Risk of Severe Hypoglycemia in Diabetic Patients Taking ACE Inhibitors

The recent article by Morris et al. (1) once again raises the important issue of whether the use of ACE inhibitors is associated with an increased risk of severe hypoglycemia (2). The interpretation of some of the results presented in the paper can, however, be queried. The number of patients admitted to the hospital who experienced an episode of severe hypoglycemia while taking an ACE inhibitor was very small (7 of 64 patients were admitted with severe hypoglycemia). As a result, the adjusted and unadjusted 95% CIs for the odds ratios (ORs) associating the use of ACE inhibitors with severe hypoglycemia were very broad, making it difficult to determine reliably the overall effect size. Also, the data for several of the most important confounding factors were strikingly incomplete. For example, <50% of the patients' serum creatinine values were available, which suggests that for some parameters only a proportion of subjects were included in the logistic regression analysis. In addition, the regression analysis showed that after adjustment for serum creatinine concentration, the OR linking ACE inhibitor use with risk of severe hypoglycemia was not statistically significant. We would accept that this latter OR could become significant in a larger study, but we feel that overall, the authors have provided interesting, but not convincing, evidence linking the use of ACE inhibitors with severe hypoglycemia.

It is important to emphasize, as do the authors of the article, that any potential increase in the risk of severe hypoglycemia that may be associated with the use of an ACE inhibitor is greatly outweighed by the other benefits of ACE inhibition in the treatment of heart failure and diabetic nephropathy, and by the fact that there are many other, more important risk factors for severe hypoglycemia, such as impaired hypoglycemia awareness (3). In addition, the authors are correct in asserting that their findings cannot be applied directly to the overwhelming majority of cases of severe hypoglycemia managed in the community or in hospital emergency departments. Further studies are required to provide a definitive answer to this important question.

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## ACE Inhibitors and Risk of Hypoglycemia in People With Diabetes

Morris et al. (1) find that the use of ACE inhibitors in people with diabetes is associated with a three- to fourfold increase in the risk of hypoglycemia. They rightly criticize previous studies (2) for employing a case-control approach, which is notoriously prone to bias, but they employ the same study design themselves. We assume, although it is not stated, that a matched analysis, using conditional logistic regression, was employed, because calculated unmatched odds ratios are very different from those presented in the paper. The authors find that people who had experienced a hypoglycemic event were about five times more likely to be receiving hospital care; adjust-

ment for this variable substantially reduced the risk of hypoglycemic events associated with ACE inhibitors. Hospital care can act as a proxy for several important factors, such as disease severity, and there must therefore be a degree of residual confounding. We could hypothesize that those patients under hospital care had a previous history of poor glycemic control; attempts to improve control under the aegis of hospital care may at the time of the study have had the desired effect of normalizing glycated hemoglobin, but at the cost of increased hypoglycemic events. This situation would have little to do with ACE inhibitor therapy. Furthermore, data on key confounders, such as glycemic control and diabetes duration, were missing for 25–50% of patients.

The only way to address the issue of ACE inhibitors and hypoglycemic risk satisfactorily is to use data from clinical trials in people with diabetes. We have recently published findings from the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes (EUCLID) study (3), a placebo-controlled randomized trial of the effects of the ACE inhibitor lisinopril on albumin excretion rate in 530 patients with IDDM (265 patients randomized to each group). This is the largest trial of an ACE inhibitor conducted in people with diabetes. We clearly show that there was no difference in glycemic control between the treatment and placebo groups at any time during the study. A hypoglycemic event was defined as that requiring the assistance of another person. There were 10 reports of these events in 8 people administered placebo, and 12 such reports in 12 people administered lisinopril. These findings do not require statistical testing to confirm that there are no group differences in hypoglycemic event rates.

We conclude that evidence indicating a role for ACE inhibitors in the causation of hypoglycemic events is weak and based on studies with biased methodology. We clearly show in a properly designed randomized controlled trial that ACE inhibitors do not cause hypoglycemic events in people with diabetes.

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## Response to Strachan and Frier and to Chaturvedi and Fuller

We welcome Drs. Strachan's and Frier's interest in our article on the association between ACE inhibitor use and hospitalization for severe hypoglycemia (1). In their letter, they suggest that our study was too small to reliably measure the size of the association between ACE inhibitors and hospitalization for severe hypoglycemia (2). They point out that the CIs for the unadjusted odds ratio (OR) of 3.2 are wide (i.e., 1.2–8.3). Although it is true that our results are based essentially on seven exposed cases, it should be remembered that our study included 504 subjects of a population of 6,649. This number represents a high sampling fraction of 8%, which means that the OR of 3.2 is probably more reliable than the CIs may suggest. A better question than "How reliable is our estimate?" would be "How typical is Tayside of other populations?" The fact that our findings are comparable to those of Herings et al. (3) suggests that our results may well be typical.

Strachan and Frier claim that "the data for several of the most important confounding factors were strikingly incomplete," and they particularly emphasize that only 49% of serum creatinine values were available. In fact, serum creatinine was not a confounding factor. In order for it to be a confounder, the OR for exposure must change after adjustment. In our study, serum creatinine was not even associated with hypoglycemia. Thus, given that serum creatinine was not a confounding variable, it is not surprising that the OR remained at 3.2 after adjustment. A possible weakness of our study, however, was that one of the true confounding variables was only 74% complete, namely, duration of diabetes. Reassuringly, this variable was one that actually increased the OR from 3.2 to 3.6. Strachan and Frier also point out that the association between ACE inhibitors and hypoglycemia was not statistically significant after adjustment for serum creatinine. We do not consider this point to be relevant because the point estimate remained unchanged. The concept of confounding is important but is difficult to understand at times. We therefore described the phenomenon carefully in our article.

Chaturvedi and Fuller (4) also make several valid comments about our work. To answer their specific comments, our study was an electronic nested case-control study. It was not subject to the recall bias often seen in case-control studies. The biases may be similar to an electronic observational cohort study. We stated clearly in the METHODS section that conditional logistic regression analysis was used, which explains why the ORs presented in our article differ from calculated unmatched ORs.

We note with interest Chaturvedi and Fuller's comment that the only way to address the question of ACE inhibitor–associated hypoglycemia is from clinical trials in people with diabetes. They are quite right to state that since publication of our work, reassuring data have emerged from the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes (EUCLID) study (5). In this randomized placebo-controlled study of lisinopril in 530 patients (median age, 33 years) with type 1 diabetes, there was no treatment difference in hypoglycemic events or glycemic control throughout the study. We would argue, however, that clinical trials, which often enroll selected "low-risk" patients, are not always good at examining the unintended effects of drugs. The OR of 1.5 for the risk of severe hypoglycemia associated with ACE inhibitors in the EUCLID study is certainly an interesting