ally have a lower risk of cardiovascular disease, a major cause of death in dialysis patients, compared with type 2 diabetic patients, and approximately one-third of their subjects had type 1 diabetes. Furthermore, one-third of their subjects underwent peritoneal dialysis. In general, peritoneal dialysis patients have considerably different metabolic disorders and risk factors for cardiovascular diseases compared with hemodialysis patients. The use of dialysate with high-glucose solution and continuous ultrafiltration induces different states of glycemic control, dyslipidemia, nutrition, and cardiac function. Furthermore, their patients with poor glycemic control and complications were prescribed higher doses of dialysis, which may result in a better prognosis. Second, as Snit et al. also pointed out, age and creatinine level of their subjects differed considerably from our subjects and among their three groups. Third, the existence of cardiac diseases and medications among their groups were not clearly described. In our study, these factors also strongly affected our findings.

Many confounding factors contribute to the prognosis of life in diabetic patients on dialysis. Thus, more careful analyses and interpretations will be needed in such an observational study. We hope that clinical implications of glycemic control in dialysis patients will be reexamined by many investigators for the sake of a better life for dialysis patients.

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DOI: 10.2337/dc06-2096
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Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A Consensus Statement From the American Diabetes Association and the European Association for the Study of Diabetes

Response to Nathan et al.

The consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes published in both Diabetes Care (1) and Diabetes Care (2) included the following statement concerning the incidence of hypoglycemia in insulin-treated type 2 diabetes: “In clinical trials aimed at normoglycemia and achieving a mean A1C of ~7%, severe hypoglycemic episodes (defined as requiring help from another person to treat) occurred at a rate of between 1 and 3 per 100 patient-years.” This is not a balanced description of the published literature.

The authors cited five publications to support the statement quoted (3–7). However, two of those do not include event rates for severe hypoglycemia as defined in the statement (5,6), and one was a review with no original data (7). Notably, however, the latter review cited studies reporting severe hypoglycemia event rates of 28 and 35 per 100 patient-years in insulin-treated type 2 diabetes (7), event rates well in excess of “between 1 and 3 per 100 patient-years” (1,2). Thus, only two (3,4) of the five publications cited, involving 127 patients with insulin-treated type 2 diabetes, support the authors’ statement (Table 1).

The authors did not cite original publications reporting severe hypoglycemia event rates of 10 (8), 28 (9), 35 (10), 44 (11), and 73 (12) per 100 patient-years, involving 907 patients with insulin-treated type 2 diabetes (Table 1). (Admittedly, one [11] was published at about the same time as the consensus statement.) These five reports included a prospective study of a population-based random sample of patients with insulin-treated type 2 diabetes that found a severe hypoglycemia event rate of 35 per 100 patient-years (10). These severe hypoglycemia event rates, which ranged from 10 to 73 per 100 patient-years in insulin-treated type 2 diabetes (8–12), approach those ranging from 62 to 170 per 100 patient-years in type 1 diabetes (10,12–14) (Table 1).

Furthermore, the authors did not cite additional population-based data in which the event rates for severe hypoglycemia requiring emergency medical treatment in insulin-treated type 2 diabetes ranged from 40 (15) to 100% (16) of those in type 1 diabetes.

The barrier of hypoglycemia precludes maintenance of euglycemia over a lifetime of diabetes and thus full realization of the now well-established vascular benefits of glycemic control (17). In contrast to type 1 diabetes, hypoglycemia is relatively infrequent early in the course of type 2 diabetes when glucose counterregulatory defenses against falling plasma glucose concentrations are intact (17,18). However, as discussed here and summarized in Table 1, there is a body of evidence, including prospective, population-based data, that indicates that hypoglycemia becomes progressively more frequent, approaching its incidence in type 1 diabetes, as patients approach the insulin-deficient end of the spectrum of type 2 diabetes, when physiological and behavioral defenses against falling glucose levels become compromised (17,18).

I agree with the authors of the consensus statement that “[i]nsulin is the most effective of diabetes medications in lowering glycemia” (1,2). In my opinion, insulin should be introduced earlier, rather than later, in inadequately controlled type 2 diabetes. However, our associations should provide a balanced view of the downside of that effective therapy: hypoglycemia.

PHILIP E. CRYER, MD
Type 2 diabetes

| Author (ref.) | n   | AIC (%) | Event rate (per 100 patient-years) | Comment |
|--------------|-----|---------|-----------------------------------|---------|
| Ohkubo et al. (3) | 52  | 7.1 ± 1.1 | 0                                 | Clinical trial, intensive insulin group |
| Abraira et al. (4) | 75  | <7.3     | 3                                 | Clinical trial, intensive insulin group |
| Saudek et al. (8) | 62  | 7.5 ± 0.8 | 10                               | Clinical trial, multiple insulin injection group |
| Henderson et al. (9) | 215 | 8.6 ± 1.5 | 28                               | Retrospective clinic survey |
| Donnelly et al. (10) | 173 | 8.9 ± 1.4 | 35                               | Prospective study of a population-based random sample |
| Akram et al. (11) | 401 | 8.3      | 44                               | Retrospective clinic survey |
| MacLeod et al. (12) | 56  | NA       | 73                               | Retrospective clinic survey |

Type 1 diabetes

| Author (ref.) | n   | AIC (%) | Event rate (per 100 patient-years) | Comment |
|--------------|-----|---------|-----------------------------------|---------|
| DCCT Research Group (13) | 711 | ∼7.1   | 62                               | Clinical trial, intensive insulin group |
| Reichard and Pihl (14) | 48  | 7.1 ± 0.7 | 110                              | Clinical trial, intensive insulin group |
| Donnelly et al. (10) | 94  | 8.5 ± 1.6 | 115                              | Prospective study of a population-based random sample |
| MacLeod et al. (12) | 544 | NA       | 170                              | Retrospective clinic survey |

Data are means ± SD unless otherwise indicated. DCCT, Diabetes Control and Complications Trial. NA, not available.

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DOI: 10.2337/dc06-1670

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Acknowledgments—This work was supported, in part, by U.S. National Institutes of Health Grants R37 DK27085, M01 RR00036, P60 DK02579, and T32 DK07120 and a fellowship award from the American Diabetes Association.

Janet Dedeke assisted in the preparation of this manuscript.

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Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A Consensus Statement From the American Diabetes Association and the European Association for the Study of Diabetes

Response to Nathan et al.

We applaud the efforts of those who developed the American Diabetes Association/European Association for the Study of Diabetes algorithm for managing type 2 diabetes (1). Although the algorithm provides a comprehensive assessment of the clinical utility of various medications, the authors’ strong focus on A1C as a measure of glycemic control may lead to inadequate management of glycemia because it fails to consider important issues relevant to diabetes pathophysiology and outcomes.

First, the algorithm assumes that patients have only recently developed type 2 diabetes and that the A1C is only slightly elevated. The majority of type 2 diabetes is diagnosed 9–12 years after it develops (2). Further, the algorithm suggests that individuals should first be started on lifestyle modification and metformin and then evaluated at 3 months regardless of current A1C. This initial therapy is inappropriate for patients with an A1C >10% because the average lowering capacity of metformin at a 2,000-mg dose is ~2%. In addition, not all patients are responders or candidates for that specific therapy (as with most medications). Early and aggressive intervention improves outcomes; however, the algorithm neither promotes nor supports early, aggressive management.

Second, although the authors focus on an A1C <7% as the goal, the contribution of postprandial glucose (PPG) to A1C is ignored. Monnier et al. (3) showed that PPG is the primary contributor to glycemia when A1C levels are <7.3% and very similar to fasting at levels of 8.4%. Earlier studies (4,5) showed fasting plasma glucose to be an inexact measure of glycemic control relative to A1C. Why, then, should we recommend that clinicians and patients rely on fasting plasma glucose measures to guide daily diabetes management?

Third, there is a strong link between postchallenge/PPG excursions and macrovascular disease independent of A1C levels (6,7). Monnier et al. (8) showed that glucose fluctuations during postprandial periods exhibited a more specific triggering effect on oxidative stress than chronic sustained hyperglycemia. Further, reducing glycemic excursions is causally associated with carotid intima-media thickness, a validated surrogate cardiovascular end point (7).

Assessing the benefit of a given therapy cannot be based solely on cost and efficacy in lowering glucose. The STOP-NIDDM (9) study showed a clear association between treatment with acarbose and a significant reduction in cardiovascular disease and hypertension. Use of rapid insulin reduces hypoglycemia (10). Newer medications, such as pramlintide and exenatide, have demonstrated improved PPG control and significant weight loss (11,12).

The mission of the American Diabetes Association is “to prevent and cure diabetes and to improve the lives of all people affected by diabetes” (13). Is it prudent to ignore or diminish the value and clinical utility of these medications simply because they do not meet subjective criteria regarding cost versus A1C-lowering effects? Exenatide, in combination with metformin, could be used earlier to get more patients to target and avoid costly long-term complications. We must remember that the highest cost in diabetes is not the medications; rather, it is the complications that result from not achieving good diabetes control.

The algorithm is substantially incomplete in communicating the necessity for early, aggressive management using treatment modalities that address all glycemic abnormalities. We strongly urge the authors to reevaluate their focus on A1C and expand the algorithm to include strategies to manage postprandial hyperglycemia, which is clearly required to achieve normal metabolic control.

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C.G.P. has received consulting fees from Abbott Diabetes Care, Bayer Diagnostics, Eli Lilly, EMD Pharmaceuticals, Roche Diagnostics, and Sanofi-Aventis Pharmaceuticals.

DOI: 10.2337/dc06-1858 © 2007 by the American Diabetes Association.

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