

nergic blocker indefinitely, unless, of course, they cannot tolerate it or there is a contraindication to its use. As the results of the study by Hochman et al. show, nowadays only a relatively small minority of such patients (10 to 15%) cannot be treated with beta-adrenergic blockers. This small minority may benefit from the mechanical restoration of antegrade flow in the occluded infarct-related artery days, weeks, or even several months after myocardial infarction.

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## Thiazolidinediones for Initial Treatment of Type 2 Diabetes?

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The twin epidemics of obesity and type 2 diabetes mellitus have spawned a public health crisis. In the United States, an estimated 1.5 million new cases of diabetes occur every year,<sup>1</sup> and the projected microvascular and cardiovascular complications<sup>2</sup> — already the greatest cause of blindness, kidney failure, and amputations in the Western world, and a substantial contributing factor in heart disease — are likely to become the major cause of preventable disease and premature death in this millennium.

The gravity of this epidemic is reflected by evidence-based efforts to stem it.<sup>3,4</sup> Moreover, in the United States, approval of five new classes of antidiabetes drugs in the past decade — three in the past year — has been stimulated by the need to keep glycemia in the near-normal range to prevent and delay the long-term complications of diabetes.<sup>5,6</sup> The underlying insulin resistance

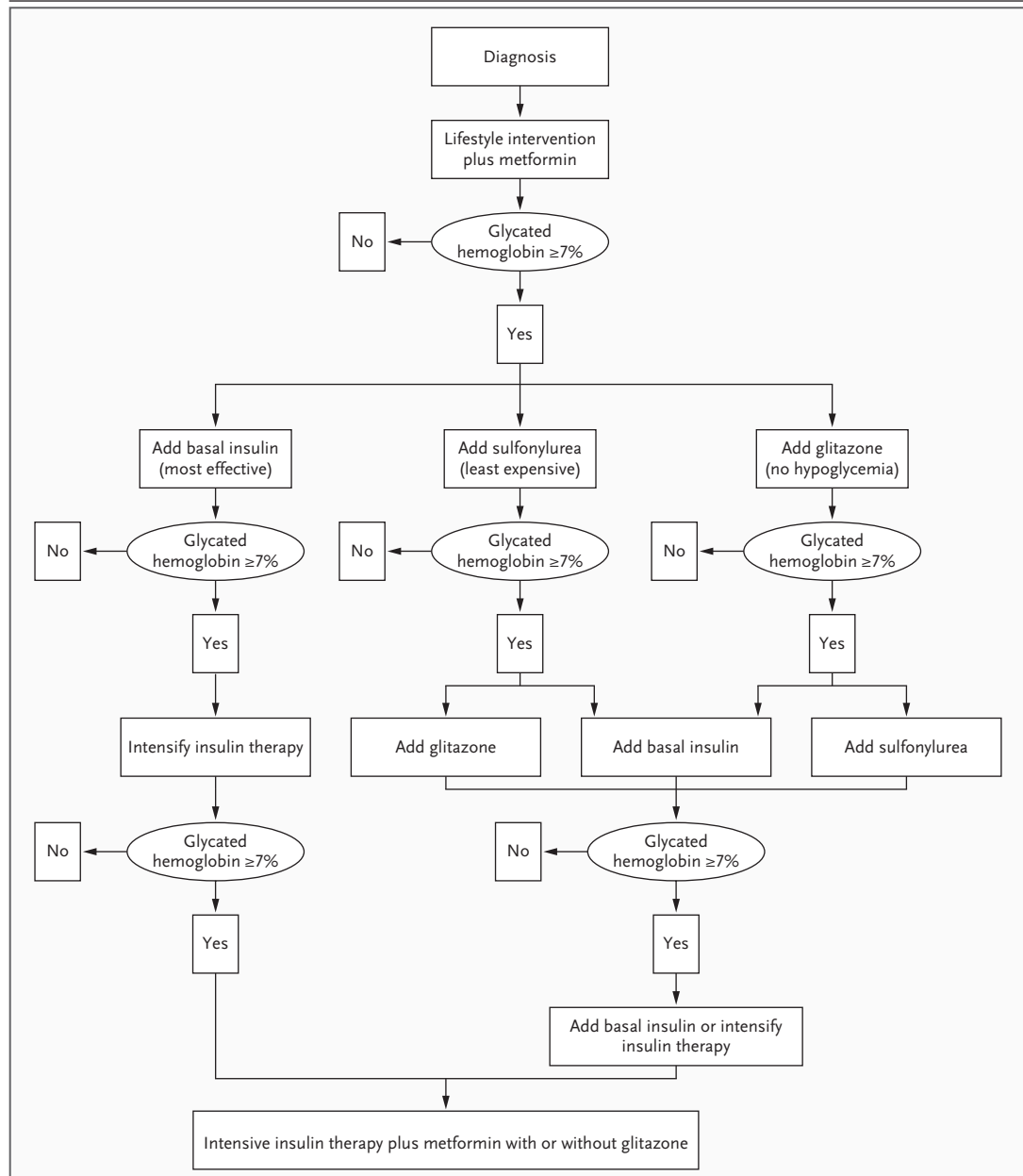
and impaired insulin secretion in patients with type 2 diabetes worsen over time, necessitating the use of increasingly powerful drugs, often in combination, to control glycemic levels.

The increasing number of available medications has left clinicians unsure of which to use first or how to change or combine medications when the metabolic disorder worsens over time. Consensus recommendations for the treatment of type 2 diabetes have recently been published.<sup>7</sup> These guidelines emphasize the long-term maintenance of glycemic control, as estimated by levels of glycosylated hemoglobin, as close to the nondiabetic range as is safely possible. They also emphasize the initiation of treatment with metformin in patients who have newly diagnosed disease (concurrent with lifestyle interventions) and the changing of medications no less frequently than every 3 months if glycosylated hemoglobin lev-

els are 7% or more (Fig. 1). The algorithm provided in the guidelines includes early, aggressive use of insulin, the most powerful antidiabetes drug, when metabolic goals are not achieved. Of note, thiazolidinediones, sulfonylureas, and insulin were

included as possible second-step medications to be combined with metformin and lifestyle interventions if metabolic goals are not achieved or maintained.

Thiazolidinediones, which are agonists of



**Figure 1. Metabolic Management of Type 2 Diabetes.**

Practitioners should reinforce lifestyle interventions with patients at every visit. Glycated hemoglobin levels should be checked every 3 months until the level is under 7%; after that, levels should be checked at least every 6 months. Although three oral drugs can be used, initiation and intensification of insulin therapy are preferred on the basis of effectiveness and expense. The algorithm is adapted from Nathan et al.<sup>7</sup> No indicates that no change in pharmacologic intervention is indicated.

the peroxisome-proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), are one of the new classes of antidiabetes drugs. Early studies suggested that thiazolidinediones were no more effective in lowering glycemia than were older oral medications.<sup>8</sup> The results of such studies, together with the side effects of the thiazolidinediones (which include weight gain, fluid retention, and the risk of congestive heart failure), contributed to the decision not to include them in the first-line treatment of diabetes.<sup>7</sup> In addition, the cost of brand-name thiazolidinediones is higher than that of generic metformin.

This issue of the *Journal* includes a report on the multicenter study by Kahn et al.,<sup>9</sup> called A Diabetes Outcome Progression Trial (ADOPT), which was sponsored and analyzed by GlaxoSmithKline, the manufacturer of rosiglitazone. The study was designed to test the efficacy of rosiglitazone as first-line monotherapy in patients with recently diagnosed type 2 diabetes. Rosiglitazone was tested against two much older and mechanistically different drugs — glyburide, a long-duration sulfonylurea with a relatively high risk of hypoglycemia, as compared with other sulfonylureas,<sup>10</sup> and the biguanide metformin. The choice of time to failure based on a confirmed fasting glucose level of more than 180 mg per deciliter as the primary outcome, rather than one based on glycated hemoglobin levels, seems anachronistic. Glycated hemoglobin is the measure of glycemia that correlates best with the risk of complications and has been used as the metabolic target for therapy for more than a decade, as cited in the design protocol for ADOPT.<sup>11</sup> Nevertheless, as compared with metformin and glyburide, rosiglitazone extended the period before treatment failure occurred. At 5 years, when only 20% of the original cohort was being followed, the reported cumulative incidence of treatment failure was 15% in the rosiglitazone group, 21% in the metformin group, and 34% in the glyburide group. The reductions in relative risk among patients receiving rosiglitazone, as compared with metformin (32%) and glyburide (63%), were highly significant.

Despite the reduction in time to failure, according to the primary outcome, the glycated hemoglobin results suggest a clinically less impressive effect. The mean glycated hemoglobin level at 4 years was 0.13 less in the rosiglitazone group than in the metformin group and 0.42 less than

in the glyburide group. Similarly, the fraction of the study cohort that was still receiving its assigned treatment and had a glycated hemoglobin level of less than 7% was only 4% higher in the rosiglitazone group than in the metformin group (40% vs. 36%) and 14% higher than in the glyburide group. Although these differences are statistically significant, the relatively small difference in glycated hemoglobin levels achieved over 4 years in the rosiglitazone group as compared with the metformin group is of questionable clinical significance. The benefits of rosiglitazone over glyburide, which is often not recommended for older patients because of its increased risk of hypoglycemia, are more convincing.

The durability of glycemic control in the rosiglitazone group was robust in comparison with that in the glyburide group; however, it was modest in comparison with the durability in the metformin group. Such findings must be tempered by the surprisingly high proportion of patients who withdrew from the study; only about 60% of the cohort completed the study. The loss of so many patients, which required an expansion in the number of patients evaluated and the duration of follow-up, weakens the results, since the outcomes in the entire randomized population cannot be ascertained. The high rate of withdrawal, which was multifactorial and not explained solely on the basis of side effects of the medications, may have been related to the small number of patients who were followed at many of the almost 500 clinical sites.

The choice among antidiabetes medications with similar glycemic-lowering effectiveness is often based on side effects and “value-added” characteristics. ADOPT brings some of the extraglycemic effects of the medications into focus. Weight gain at year 4 was significantly higher with rosiglitazone (2.5 kg) than with glyburide and was much higher (6.9 kg) than with metformin. Some of the weight gain with rosiglitazone was probably a result of fluid retention, even though patients with any degree of heart failure were excluded from participation. The rosiglitazone group had increased use of loop diuretics and statins. Side effects of glyburide, such as weight gain and hypoglycemia, and the gastrointestinal side effects of metformin were also documented.

The hope that thiazolidinediones may affect

the underlying pathophysiology of type 2 diabetes by protecting  $\beta$ -cell function and may alter the course of the disease is only weakly supported by ADOPT. The initial improvement in insulin secretion at 1 year was not sustained, and the difference in insulin secretion between rosiglitazone and metformin over time, albeit significant, was small. Improved insulin sensitivity appears to be the most durable effect of rosiglitazone. Finally, a decreased risk of cardiovascular events purportedly shown in another thiazolidinedione study, the controversial Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE),<sup>12</sup> was not supported by the ADOPT study. In the latter trial, glyburide was associated with fewer serious cardiovascular events.

The authors conclude that the “relative costs of these medications, their profiles of adverse events, and their potential risks and benefits” should be considered in choosing among them. Given the modest glycemic benefit of rosiglitazone (with the risk of fluid retention and weight gain) and higher cost (including the need for more statins and diuretics), metformin remains the logical choice when initiating pharmacotherapy for type 2 diabetes.

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