Multidrug Treatment of Type 2 Diabetes

A challenge for compliance

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Type 2 diabetes is a chronic and progressive condition associated with the risk of invalidating micro- and macrovascular complications. Hyperglycemia is the hallmark of the condition and, despite much discussion, glycemic control remains a main goal of treatment in the attempt to prevent chronic complications.

A beneficial effect of glycemic control was initially supported by the UK Diabetes Prospective Study showing that intensive treatment, compared with conventional therapy, resulted in an average HbA_{1c} level of 7% and was associated with a 24% relative risk reduction of any diabetes-related end point and a 37% reduction in the risk of microvascular disease. Moreover, a nonsignificant 16% reduction ($P = 0.052$) in the risk of acute myocardial infarction was reported (1). Similar results were confirmed in the Kumamoto study (2), whereas the results of more recent intervention trials remain questionable. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study (3), a lower mean HbA_{1c} level was achieved in the intensive-control group than in the standard-control group (6.6 vs. 7.3%). Intensive control reduced the incidence of combined major macro- and microvascular events (hazard ratio [HR] 0.90; 95% CI 0.82–0.98; $P = 0.01$), as well as that of major microvascular events (HR 0.86; 0.77–0.97; $P = 0.01$). However, there was no significant effect of glucose control on major macrovascular events, death from cardiovascular causes, or death from any cause. In the Veteran Administration Diabetes Trial (VADT) (4), median HbA_{1c} levels were 8.4% in the standard therapy group and 6.9% in the intensive therapy group. There was no significant difference between the two groups in the rate of cardiovascular events or in the rate of death from any cause (HR 1.07; 0.81–1.42; $P = 0.62$). No differences between the two groups were observed for microvascular complications as well. Finally, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (5) was prematurely interrupted because of excess mortality in the intensively treated group. A more recent report concluded that intensive therapy did not reduce the risk of advanced measures of microvascular outcomes but delayed the onset of albuminuria and some measures of eye complications and neuropathy (6).

The results of these "megatrials" have generated much discussion, and several points of concern have been raised (7). It was noted that these trials have dealt with patients with long duration of diabetes and with a prior history of poor glycemic control. On the other hand, patients enrolled in the UK Diabetes Prospective Study were newly diagnosed patients with low cardiovascular risk (1). Ten years after the end of the active trial, patients originally randomized to intensive treatment continued to have low rates of diabetes-related end points and microvascular complications, along with a significant reduction in the risk of myocardial infarction (relative risk reduction 15%, $P = 0.0014$) and all-cause mortality (13%, $P = 0.007$) (8).

Altogether, these results suggest that, at least within the timeframe of the intensive treatment of the trials, there is less opportunity to influence the development and/or progression of complications in individuals with longstanding diabetes. Only when the results of all intervention trials were pooled (9–11), it was possible to conclude that intensive control significantly reduces coronary events without an increased risk of death. By meta-regression analysis, Mannucci et al. (11) concluded that the efficacy of intensive treatment is maximal when implemented early in the course of the disease; the benefits become less apparent when they are initiated later and may even put patients at risk if this treatment intensification is initiated too late in the natural history of the disease.

Therefore, the true shift in the paradigm for the treatment of type 2 diabetes will require the implementation of appropriate treatment at the time of the diagnosis (12), if not earlier. Such a treatment should focus on strict glycemic control while dealing with all concomitant cardiovascular risk factors.

Yet this may be easier said than done, since achieving strict glycemic control may not be a simple task, as suggested by ACCORD (5), ADVANCE (3), and VADT (4). In the three studies, intensive treatment ensured HbA_{1c} levels $<7.0\%$ at the expense of multiple complex treatments. In ACCORD, >60% of the intensively treated patients required more than three drugs, with 10% of them requiring four or five different medications to achieve target HbA_{1c} (5). A large number of medications as well as more frequent visits and regimen modifications were also needed to ensure stringent glycemic control in ADVANCE (3) and VADT (4).

The patients included in these trials were, by and large, individuals with high cardiovascular risk. As such, they required careful control of blood pressure and lipid profile and common use of antiplatelet therapy. The Steno-2 study clearly provided evidence that multifactorial

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treatment is necessary to reduce the risk of both micro- and macrovascular disease (13). Such a treatment may require 3–10 tablets a day, i.e., 21–70 tablets a week, 84–280 tablets a month, or 1,008–3,360 tablets a year—a very overwhelming task for the diabetic patient.

The complexity of the treatment may contribute to the limited capacity of implementation of multifactorial intervention in the diabetic population. Data from the National Health and Nutrition Examination Survey (NHANES) show that in the U.S., from 1999 to 2006, the age-adjusted percentage of people with diabetes achieving glycemic, LDL cholesterol, and blood pressure targets increased from 43.1 to 57.1% ($P = 0.001$), from 36.1 to 46.5% ($P = 0.03$), and from 39.2 to 45.5% ($P = 0.12$), respectively. Yet, the age-adjusted percentage of patients achieving all three targets increased insignificantly from 7.0 to 12.2% ($P = 0.06$) (14). Therefore, improving these figures requires identification of hurdles in multidrug treatment in type 2 diabetes.

PATIENT ADHERENCE TO MEDICATIONS

—Adherence to oral diabetes medications (ODMs) in type 2 diabetic patients was retrospectively analyzed using the medical and pharmacy claims from a managed care plan in Oregon (15). Among 2,741 type 2 diabetic patients who newly initiated ODM therapy, overall adherence was 81%, and 65% of subjects had good adherence (>80%). Interestingly, there was an inverse relationship between ODM adherence and HbA_{1c}; controlling for baseline HbA_{1c} and therapy regimen, each 10% increase in ODM adherence was associated with a 0.1% HbA_{1c} decrease ($P = 0.0004$), suggesting that adherent patients were more likely to achieve glycemic control than the nonadherent ones.

Lack of adherence to chronic cardiovascular treatments is an even greater matter of concern. Adherence to treatment was calculated in a retrospective cohort study of 11,532 diabetic patients to ascertain the impact on the control of cardiovascular risk factors, all-cause hospitalization, and all-cause mortality (16). During the follow-up, nonadherent patients had higher HbA_{1c}, systolic and diastolic blood pressure, and LDL cholesterol levels. In multivariable analyses, nonadherence to medication remained significantly associated with increased risks for all-cause hospitalization (odds ratio 1.58; 95% CI 1.38–1.81; $P < 0.001$) and for all-cause mortality (odds ratio 1.81; 1.46–2.23; $P < 0.001$) (Fig. 1). It is readily apparent how lack of treatment adherence may jeopardize the beneficial effects of available medications.

Several factors may contribute to loss of treatment adherence. In the study by Poluzzi et al. (17), both persistence and coverage for oral hypoglycemic, antihypertensive, and lipid-lowering agents and nitrates progressively declined after the first year of analysis, with <50% receiving an amount of drugs consistent with daily treatment at the end of a 3-year observation period.

This progressive loss of adherence may well reflect lack of confidence in immediate or future benefits of treatment. Moreover, side effects can favor treatment withdrawal. In a relatively small study including 128 type 2 diabetic patients (18), the total number of medicines prescribed was not correlated with medication adherence. Rather, adherence was significantly lower for medicines not felt to improve current or future health (6.1 vs. 6.9 days out of 7, $P < 0.001$). Among patients on three or more medications, 71% (15 of 21 patients) with suboptimal adherence were adherent to all but one medicine. Side effects were the most commonly reported problem with medication use, suggesting that careful assessment of the risk-to-benefit ratio may help in improving adherence for patients on multiple pharmacologic treatments. In a survey carried out in 2,507 adults, a medication was not taken in 45% of participants because of concerns about side effects (19).

Obviously, other factors should be considered, many of them directly involving the patient's perception about the nature and severity of his or her illness; the assumption that once symptoms have improved, medications can be discontinued; and personal fears with respect to disease worsening, hypoglycemia, needles, and weight gain as well as worries about social stigma associated with taking medicine. Therapies that may reduce the burden related to these factors can translate into greater treatment adherence. From this point of view, great expectation has been generated by new forms of treatment such as the incretin-based therapies because of very low risk of hypoglycemia and favorable effects on body weight (20).

TREATMENT COMPLEXITY (POLYPHARMACY)

—Evidence-based medicine represents the foundation of medical care. In the past years, numerous clinical trials provided stronger evidence for appropriate reduction of the risk of cardiovascular disease and mortality in type 2 diabetic patients, leading to practice guidelines that emphasize the need for concomitant treatment of multiple risk factors (21). As a result of these approaches, treatment of type 2 diabetes has become more complex over time.

Using U.S. sampled survey data, Grant et al. (22) found a marked increase in the complexity of ambulatory medical management of diabetes from 1991 to 2000. In particular, they reported that the increased use of multiple ODM and increased treatment of hypertension and

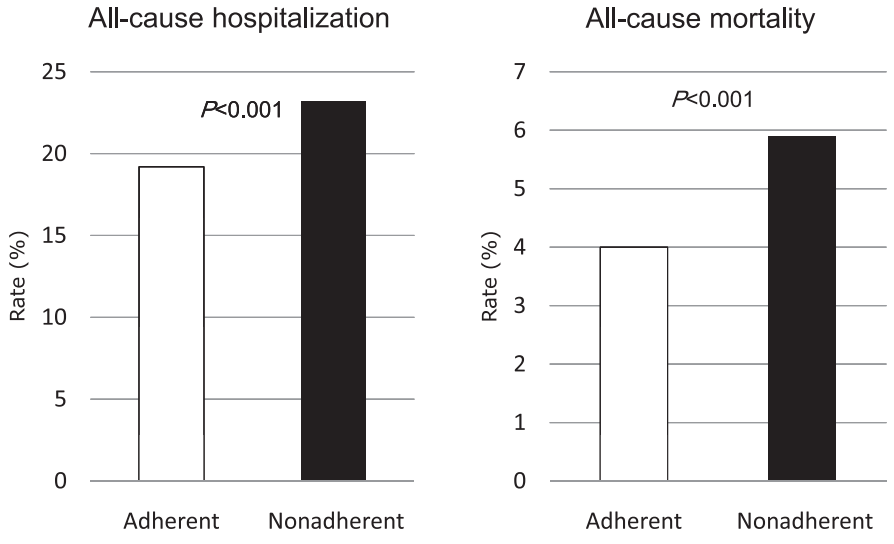

Figure 1—*Unadjusted association between medication nonadherence (proportion of days covered <80%) and outcomes in 11,532 patients with diabetes. Adapted from Ho et al. (16).*

hyperlipidemia were the main contributors to the expansion of medical regimen complexity. During such a period, the number of visits listing at least five prescriptions increased from 18.2 to 29.9% ($P < 0.01$). In the ARNO Italian survey, 75% of type 2 diabetic patients on ODM also received cardiovascular medications, 34% lipid-lowering agents, 40% aspirin, 12% antithrombotic agents, 40% anti-inflammatory medications, and 35% anti-ulcer treatment (23). In such a scenario, the large number of medications prescribed at the time of medical visits without sufficient time to explain the reason for prescribing and without patients appreciating advantages and potential side effects of prescribed medications can easily result in patient's refusal and resistance to comply with regular use of medications.

The Diabetes Audit and Research in Tayside Scotland (DARTS) group studied 2,849 type 2 diabetic patients to identify their level of adherence to prescribed medication (24). These patients were prescribed oral hypoglycemic drugs for a period of over 12 months. The study showed adequate adherence (>90%) in 31 and 34% of patients prescribed sulfonylureas and metformin as monotherapy, respectively. However, only 13% of patients receiving a combination of both of these drug classes showed adequate adherence, with an average of only 266 days of treatment a year.

Reducing the number of tablets may help. Combining more than one drug in one pill may provide some advantage. Analyses have been retrospectively performed in a database including 16,490 subjects with one or more prescription fills for rosiglitazone, a sulfonylurea, or rosiglitazone/glimepiride fixed-dose combination therapy. Both adherence (medication possession ratio) and HbA_{1c} levels significantly improved when switching to fixed-dose combination therapy, in comparison with switching to dual therapy (25). Based on these observations, a range of fixed-dose combination of oral hypoglycemic agents in several different dosage strengths have been made available, and the strategies for optimal implementation of these options continue to evolve. This line of reasoning has lead to the consideration of developing a polypill. The idea is that combining in one pill drugs that have been proven, in controlled trials, to reduce cardiovascular events and mortality (aspirin, β-blockers, ACE inhibitors, and statins) may reduce the risk of recurrent vascular events. The idea was initially introduced by Wald and Law (26). They proposed to administer the polypill to all individuals >55 years old, irrespective of previous cardiovascular events. More recently, efficacy and safety of the Polycap (a polypill including 12.5 mg thiazide, 50 mg atenolol, 5 mg ramipril, 20 mg simvastatin, and 100 mg aspirin) were evaluated in a double-blind trial in 2,053 individuals without cardiovascular disease (27). The results of the study indicated that the Polycap could be conveniently used with good tolerability. By simple multiplication of risk ratios estimated for the individual effect of each component of the Polycap, it was calculated that treatment could potentially reduce cardiovascular disease by 62% and stroke by 48%. Clinical trials, however, particularly in diabetic individuals, are needed to demonstrate not only better adherence, but also safety and efficacy.

CLINICAL INERTIA—Adherence to therapy is not just a problem of the patients, but it involves the physician as well. Too often, physicians are slow in making changes of suboptimal medical regimens in diabetic patients not at target. Shah et al. (28) analyzed data from 591 patients with specialist care and 1,911 with exclusively primary care (Fig. 2). In the matched cohorts, only 45.1% of patients with specialist care versus 37.4% with primary care had drug intensification ($P = 0.009$) in response to inadequate glycemic control (HbA_{1c} <8%). Most of the differences between specialists and primary care physicians could be attributed to specialists' more frequent initiation of insulin in response to elevated HbA_{1c}, whereas clinical inertia with respect to other therapeutic measure were similar in the two groups of patients.

The physician attitude toward correction of cardiovascular risk factors has been recently evaluated by assessing use of lipid-lowering and antihypertensive medications according to the LDL cholesterol and blood pressure levels attained in 2,465 type 2 diabetic patients free of cardiovascular events (29). The proportion of patients on lipid lowering agents did not increase with increasing LDL cholesterol. Even worse, 71% of patients with LDL cholesterol >160 mg/dL were not treated at all. A better figure was obtained when hypertension was considered: the proportion of subjects being treated paralleled the increase in blood pressure, although up to 27% of patients with systolic blood pressure >160 mmHg were not treated at all. When the population was analyzed on the basis of their 10-year absolute CHD risk, there was no change in the use of lipid-lowering medications with increasing risk, whereas a slight increase was apparent for antihypertensive and antiplatelet agents, even though the proportion of treated patients remained much lower than desired.

Such a lack of therapeutic appropriateness is unlikely to be explained solely by poor patients' adherence. Moreover, the definition and estimation of treatment adherence is not a simple task. Previous studies have shown that physicians'

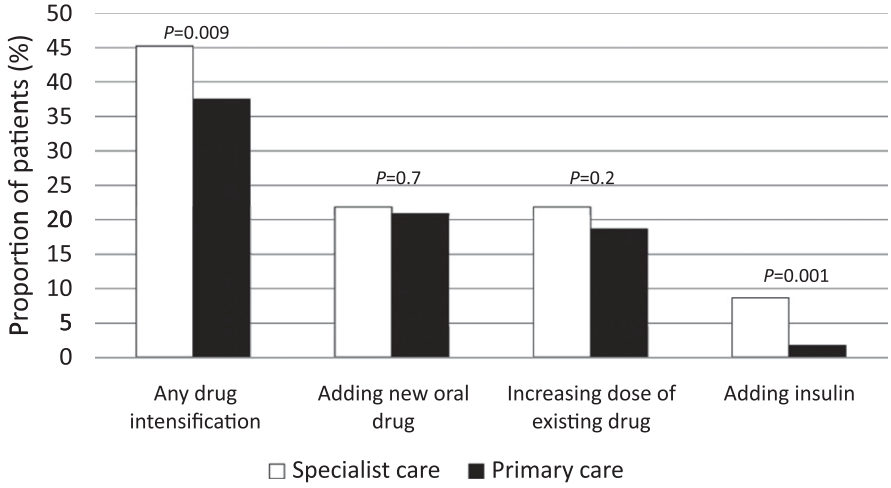

Figure 2—*Proportion of patients in specialist care and in exclusively primary care with drug regimen intensification in response to poor glycemic control (HbA_{1c} >8%). Adapted from Shah et al. (28).*

estimate of patient's adherence is far from being realistic (30). To make the picture even more complex, poor patient adherence is often associated with physician's clinical inertia, i.e., lack of therapeutic adjustment in patients not attaining therapeutic goals (31). Multiple factors contribute to therapy procrastination, including reluctance to embark in complex therapeutic regimens, overconfidence with prescribed treatment, lack of effective result tracking, and insufficient time at clinical visit (32).

Therefore, overcoming clinical inertia is essential to achieve and maintain therapeutic targets. Clinical results support this conclusion. In the Multifactorial Intervention in type 2 Diabetes Italy (MIND-IT) study, a simply reiterating treatment goal allowed a 13–15% increase in the percentage of patients at target for HbA_{1c}, blood pressure, and LDL cholesterol (33).

CONCLUSIONS—Type 2 diabetes is a complex and progressive disease, requiring increasingly more complex treatments over time. Multifactorial intervention, in addition to glycemic control, may provide cardiovascular protection, but the complexity of the therapeutic strategy may become a challenge for both the patient and physician. Achieving treatment goals requires continuous effort by both. The patient must appreciate the short- and long-term benefit of treatment; the physician should be able to recognize the patient's needs and concerns. The result of this process should personalize treatment where goals and medication options are based on individual factors such as age, duration of the disease, presence or absence of diabetes complications, underlying pathophysiology, and risk/benefit of each medication and their combination. With this goal in mind, we have recently proposed an HbA_{1c} and ABCD algorithm for the treatment of diabetes (34). The algorithm helps in identifying individualized HbA_{1c} targets as well as personalized therapy based on Age (A), Body weight (B), Complications (C), and Duration of diabetes (D). Treatment personalization may improve adherence to multitherapy; reduction of clinical inertia may provide a more sustained metabolic control. Obviously, this is not an easy task, but new opportunities may be available. The use of metformin, glucagon-like peptide-1 receptor agonists, and dipeptidyl-peptidase inhibitors are all associated with very low risk of hypoglycemia and neutral, if not favorable, effects on body weight (20), two common concerns for both the patient and the physician. A series of fixed combination of oral antidiabetes agents as well as the use of rational combinations of oral and injectable drug treatments may reduce the number of tablets taken per day and provide a better opportunity for sustained glycemic control. The basis of a successful therapy relies on being aware of the complexity of the pathogenesis of the disease and on the need for careful assessment of risk-to-benefit ratio of each form of treatment.

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