Efficacy of intensive multitherapy for patients with type 2 diabetes mellitus: a randomized controlled trial

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∞ See related article page 1467

Abstract

Background: National guidelines for managing diabetes set standards for care. We sought to determine whether a 1-year intensive multitherapy program resulted in greater goal attainment than usual care among patients with poorly controlled type 2 diabetes mellitus.

Methods: We identified patients with poorly controlled type 2 diabetes receiving outpatient care in the community or at our hospital. Patients 30–70 years of age with a hemoglobin A_{1c} concentration of 8% or greater were randomly assigned to receive intensive multitherapy ($n = 36$) or usual care ($n = 36$).

Results: The average hemoglobin A_{1c} concentration at entry was 9.1% (standard deviation [SD] 1%) in the intensive therapy group and 9.3% (SD 1%) in the usual therapy group. By 12 months, a higher proportion of patients in the intensive therapy group than in the control group had achieved Canadian Diabetes Association (CDA) goals for hemoglobin A_{1c} concentrations (goal ≤ 7.0%: 35% v. 8%), diastolic blood pressure (goal < 80 mm Hg: 64% v. 37%), low-density lipoprotein cholesterol (LDL-C) levels (goal < 2.5 mmol/L: 53% v. 20%) and triglyceride levels (goal < 1.5 mmol/L: 44% v. 14%). There were no significant differences between the 2 groups in attaining the targets for fasting plasma glucose levels, systolic blood pressure or total cholesterol:high-density lipoprotein cholesterol ratio. None of the patients reached all CDA treatment goals. By 18 months, differences in goal attainment were no longer evident between the 2 groups, except for LDL-C levels. Quality of life, as measured by a questionnaire, increased in both groups, with a greater increase in the intensive therapy group (13% [SD 10%] v. 6% [SD 13%], $p < 0.003$).

Interpretation: Intensive multitherapy for patients with poorly controlled type 2 diabetes is successful in helping patients meet most of the goals set by a national diabetes association. However, 6 months after intensive therapy stopped and patients returned to usual care, the benefits had vanished.

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Reducing plasma glucose levels,[1,2] blood pressure[3–5] or lipoprotein levels[6–8] delays the development or progression of complications in patients with type 2 diabetes mellitus. This has prompted calls for intensive multitherapy treatment.[9,10] To date, only 4 studies of multitherapy management have been published, all of which showed major beneficial effects on long-term outcome.[11–14] The Canadian Diabetes Association (CDA)[15] and the American Diabetes Association (ADA)[16] both publish guidelines on a regular basis and recommend that people with type 2 diabetes receive tailored, stepwise and proactive therapy including lifestyle intervention and pharmacologic treatment from a multidisciplinary team. However, neither set of guidelines has been evaluated by a prospective study.

We hypothesized that a 12-month, intensive multitherapy program provided by a multidisciplinary team would reduce fasting plasma glucose levels, hemoglobin A_{1c} concentrations, blood pressure and lipoprotein levels to the CDA-recommended goals, that these benefits would be maintained beyond the intervention period (i.e., at least 6 months later), and that the intervention would improve patient quality of life. To assess the effects and feasibility of intensive multitherapy in the vast population of patients who are commonly seen by family practitioners and endocrinologists, we chose subjects in whom the disease was poorly controlled and who, although at very high risk of micro- and macrovascular events,[2,4,6] were without significant complications.

Methods

A full description of the methods is available in the unabridged version of this article (www.cmaj.ca/cgi/content/full/173/12/1457).

In brief, we recruited patients from the Diabetes Daycare Centres of our hospital, through endocrinologists and primary care physicians in the Sherbrooke area and through newspaper advertisements. Eligible participants were 30–70 years of age and had type 2 diabetes mellitus and hemoglobin A_{1c} concentrations of 8% or greater. We excluded patients with hypoglycemia unawareness, severe cardiovascular disease, or major complications of diabetes, and patients who were unable to perform the exercise program.

Box 1: Summary of the components of intensive multitherapy for patients with type 2 diabetes mellitus*

- Monthly visits for follow-up and individual education
- Patients monitor blood glucose twice daily
- Patients receive 2 or more phone calls per month for therapy adjustment and motivation

Diet

- Patients encouraged to follow a diet in which carbohydrates contribute 50%–55% to total daily energy intake, total fats < 30% and saturated fats < 10%

Exercise

- Patients provided with an exercise bicycle and elastic exercise bands for use at home
- Weekly exercise at least 3 times per week for 45 minutes and progressively increased

Drug therapy

- Oral agents or insulin gradually increased to achieve CDA targets
- Antihypertensive agents gradually increased to achieve BP control
- Lipid-lowering agents used to achieve CDA targets
- ASA 80 mg daily

Note: CDA = Canadian Diabetes Association, BP = blood pressure.
*A full description of the multitherapy program is available in the unabridged version at www.cmaj.ca/cgi/content/full/173/12/1457.

Patients were randomly assigned to receive intensive multitherapy (see Box 1) or usual care. At the end of the 12-month intervention period, patients who had received intensive multitherapy resumed usual care. A final assessment was performed at 18 months. Primary study endpoints were the proportions of patients who achieved the CDA-recommended goals.

The study was approved by the ethics committee of the Centre Hospitalier Universitaire de Sherbrooke, and participants signed a written informed consent in accordance with the Helsinki declaration.

Results

Baseline

Of 418 patients initially recruited, 36 patients were randomly assigned into each treatment arm (Fig. 1). There was no significant difference between the 2 groups in age, sex, duration of diabetes, smoking or antihypoglycemic medications (Table 1). The number of complications was similar in both groups. A total of 24 patients in the intervention group and 31 in the control group, or 76% of all study subjects, had participated in a 4-day diabetes education program in the 12 months before entry in the study, and 70% ($n = 25$ in each group) were under the care of endocrinologists in addition to their general practitioner. Glycemic indices showed poor control in all subjects (Table 1). A total of 7 study participants (5 in the intervention group v. 2 in the control group) were normotensive, 13 (8 v. 5) were at target for systolic blood pressure, and 19 (11 v. 8) were at target for diastolic blood pressure; 23 in the intervention group and 21 in the control group were taking antihypertensive medications. No patient had a normal lipid profile, but 17 (8 in the intervention group v. 9 in the control group) were at treatment target for low-density lipoprotein cholesterol levels, 5 (1 v. 4) for total cholesterol:high-density lipoprotein cholesterol ratio and 12 (10 v. 2) for triglyceride levels; one-third (12 v. 15) were taking lipid-lowering agents. Quality-of-life scores were identical in the 2 groups (Table 2 of the unabridged version of this article [available at www.cmaj.ca/cgi/content/full/173/12/1457]).

At 12 months

At 12 months, a higher proportion of patients in the intervention group than in the control group had achieved CDA goals for hemoglobin A_{1c} concentrations, diastolic blood pressure, and low-density lipoprotein cholesterol and triglyceride levels (Fig. 2) (Table 3 of the unabridged version of this article [available at www.cmaj.ca/cgi/content/full/173/12/1457]). There were no significant differences between the groups in goal attainment for fasting plasma glucose levels, systolic blood pressure or total cholesterol:high-density lipoprotein cholesterol ratio. Results remained similar (data not shown) when we performed an analysis that included the 3 subjects who withdrew during the first 12 months (2 in the intervention group and 1 in the control group).

Although no patients achieved all of the targets, improvements were significantly greater in the intervention group compared with the control group with respect to fasting plasma glucose levels, hemoglobin A_{1c} concentrations, systolic blood pressure and triglyceride levels (Fig. 2) (Table 4 in the unabridged version of this article [www.cmaj.ca/cgi/content/full/173/12/1457]). Significant differences were already observed at 6 months (data not shown). There was no significant increase in weight in either study group.

Energy and fat intake (total fat, saturated fatty acids and cholesterol) decreased significantly between baseline and 12 months in the intervention group (Table 2 of the unabridged version). In both groups, the proportion of subjects who met the recommendations for carbohydrate, total fat and saturated fatty acid intake was identical: 56%, 28% and 37%, respectively.

Exercise volume improved between baseline and 12 months in the intervention group, and the mean time during the tolerance test increased to over 6 minutes in this group (Table 2 of the unabridged version). Twenty subjects had 3 or more exercise sessions per week, and those who exercised less often than 3 sessions per week were compliant with the prescribed duration and intensity of sessions (91.2% and 100%, respectively). Exercise volume did not change in the control group.

At the end of 12 months, 68% of patients in the intervention group were taking insulin compared with 40% in the control group ($p < 0.05$) (Table 4 of the unabridged version), and the dosage of insulin was increased (0.32 μ/kg per day); consequently, the dosage of glyburide was decreased by 41% in those taking insulin in the intervention group (Table 5 of the unabridged version of this article [available at www.cmaj.ca/cgi/content/full/173/12/1457]). Among patients in the intervention group taking oral antihyperglycemic agents only, dosages increased (by 34% for glyburide and by 22% for metformin), but

the number of pills remained stable (Table 4 of the unabridged version). The number of patients receiving intensive multitherapy who required 3 or more antihypertensive agents tripled over time, and dosages increased by 30%. Of 9 patients in the intervention group who were not taking antihypertensive medication at 12 months, 5 were at the target blood pressure at baseline and had remained there, and the other 4 had borderline blood pressure values (systolic blood pressure 134 (SD 3) mm Hg, diastolic blood pressure 77 (SD 9) mm Hg) and were reluctant to start treatment. Lipid-lowering medication was prescribed for 29 patients in the intervention group, and dosage increased by 50%. Of 5 patients in the intervention group with hypolipidemia, 4 reached low-density lipoprotein cholesterol and triglyceride targets with lifestyle changes only, and one patient, who refused hypolipidemic agents, did not achieve the targets.

No change was observed in the number or dosages of antihyperglycemic, antihypertensive or antihyperlipidemic prescriptions in the control group.

Overall, 42% of participants experienced at least one minor hypoglycemic episode per month. The mean number of episodes per month was similar in both groups (1.7 in the intervention group v. 1.9 in the control group). In the intervention group, 3 severe hypoglycemic episodes (one concomitant with acute alcohol intoxication) were reported. Two nonlethal cardiac events were reported in each group.

Quality-of-life scores improved significantly in both groups (Table 2 of the unabridged version). However, this improvement was significantly greater in the intervention group than in the control group (13% [SD 10%] v. 6% [SD 13%]) over the 12 months ($p = 0.003$).

At 18 months

At 18 months, or 6 months after the intervention stopped, hemoglobin A_{1c} concentrations, systolic blood pressure and body weight had increased significantly in the intervention

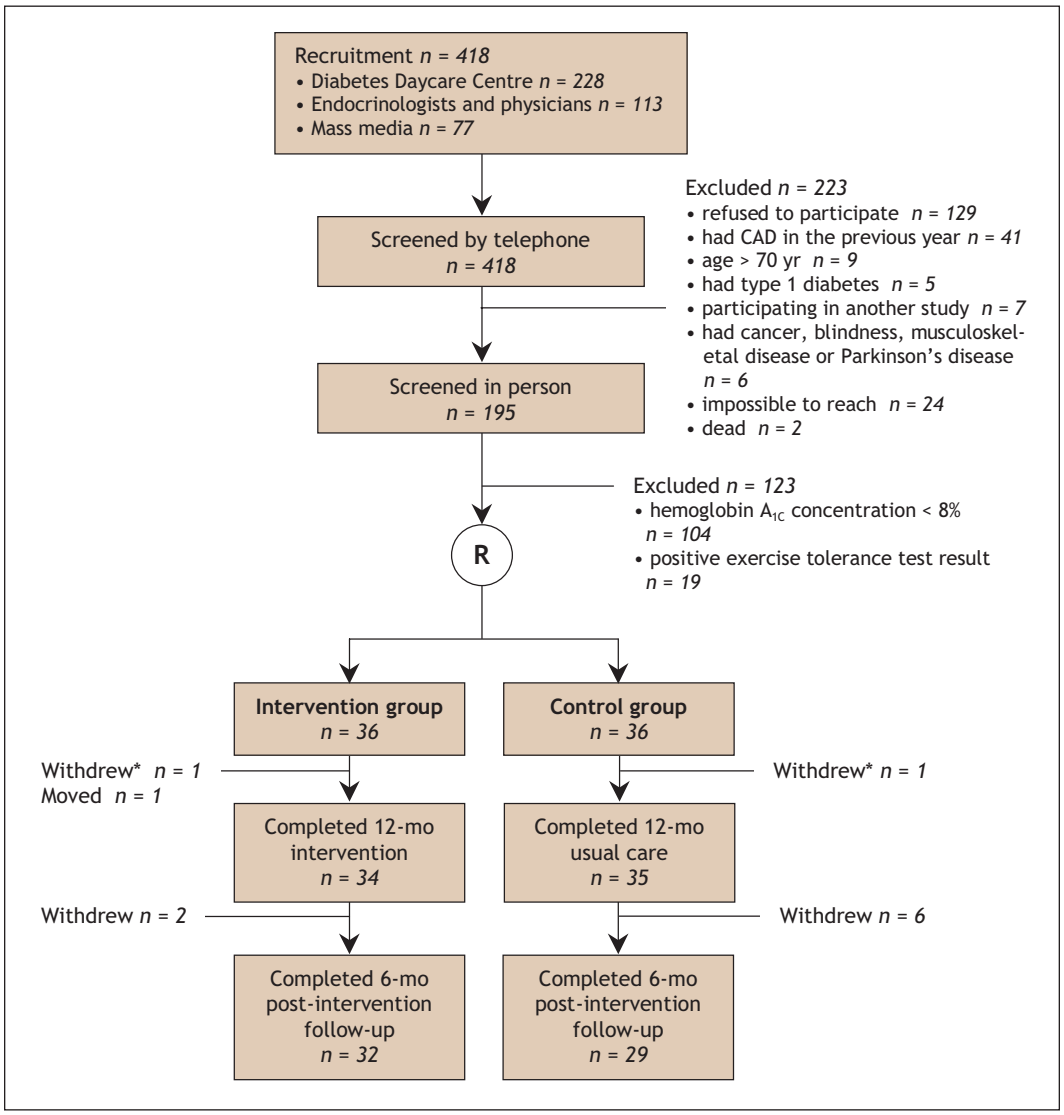

Fig. 1: Flow of participants through the study. CAD = coronary artery disease. *Did not attend the 12-month visit but attended all other visits.

group. Exercise volume had decreased in the intervention group (–10.62 [SD 13.32] METs, $p < 0.001$) and in the control group (–4.19 [SD 10.24] METs, $p = 0.015$), with no difference between the groups when decreases in exercise were expressed as percentages of 12-month values. In the intervention group, time devoted to exercise had negative correlations with weight ($r = 0.363$, $p = 0.041$) and with systolic blood pressure ($r = 0.430$, $p = 0.016$). However, all outcome variables remained significantly improved when compared with baseline ($p < 0.03$), with the exception of systolic blood pressure ($p = 0.085$).

Medication at 18 months was maintained from that at 12 months except for the dosage of statins in the intervention group, which had increased by 12%, and sulfonylureas in the control group, which had increased by 25%.

Table 1: Baseline characteristics of patients with poorly controlled type 2 diabetes mellitus receiving intensive multitherapy (intervention group) and usual care (control group)

Characteristic	Intervention group *n = 36*	Control group *n = 36*
Age, mean (SD), yr	53.7 (7.5)	55.9 (8.6)
Sex, men/women	27/9	22/14
Duration of diabetes, mean (SD), yr	10.6 (6.7)	10.0 (7.7)
Smoker, no.	5	6
Biochemical variables, mean (SD)		
Weight, kg	93.5 (20.1)	88.5 (18.3)
BMI, kg/m^2	32.9 (5.5)	32.6 (5.7)
Systolic BP, mm Hg	144 (20)	143 (17)
Diastolic BP, mm Hg	85 (11)	86 (10)
FPG, mmol/L	10.8 (3.5)	10.8 (3.0)
HbA_{1c}, %	9.1 (1.0)	9.3 (1.0)
LDL-C, mmol/L	3.26 (1.03)	2.98 (1.18)
C:HDL-C ratio	6.38 (2.14)	6.03 (1.96)
Triglycerides, mmol/L	3.08 (3.09)	3.68 (2.48)
Medications, no.		
Antihyperglycemic medications		
None	1	0
OHA	22	24
Insulin	1	4
OHA + insulin	12	8
Antihypertensive medications	23	21
Lipid-lowering medications	12	15
Complications, no.		
Nonproliferative retinopathy	6	3
Microalbuminuria*	9	5
Erectile dysfunction	4	2
Neuropathy†	6	5
Myocardial infarction‡	2	6
Stroke	1	1
Total no. of complications	28	22

Note: SD = standard deviation, BMI = body mass index, BP = blood pressure, FPG = fasting plasma glucose, HbA_{1c} = hemoglobin A_{1c}, LDL-C = low-density lipoprotein cholesterol, C:HDL-C = total cholesterol:high-density lipoprotein cholesterol, OHA = oral antihyperglycemic agents.
*30–299 mg/L.
†Decreased sensation using a 10-g monofilament.
‡More than 1 year ago.

Interpretation

Using intensive and demanding therapy for type 2 diabetes over a 12-month period is feasible, and in our study it resulted in the attainment of most of the CDA-recommended goals. A higher proportion of intervention patients than control patients achieved goals for control of hemoglobin A_{1c} concentrations, diastolic blood pressure, and low-density lipoprotein cholesterol and triglyceride levels. Intensive therapy is acceptable for patients with poorly controlled type 2 diabetes: no patient in the intervention group withdrew because of the therapy, and the quality-of-life scores were significantly improved at 12 months in that group compared with those of patients receiving usual care. However, 6 months after the intervention ended, there were no statistically significant differences in goal attainment between the study groups other than for low-density lipoprotein cholesterol levels.

Our study has some limitations. For ethical reasons, patients in the control group had protocol-driven laboratory tests, and they and their physicians received information about diabetes and its management as well as the results of these tests. Thus, control group patients may have received more aggressive treatment and attention than they normally would have. Similarly, patients receiving the intensive multitherapy may have been susceptible to the Hawthorne effect (people who know that performance is being measured perform with more care than they would normally). This may also have played a role in the improvements observed in the intervention group.[17]

Attainment of the CDA clinical practice goals was only partly achieved in the intervention group, and this effect did not continue after the end of intensive care. Our results are in accordance with those of the Steno-2 study,[18] which showed limited achievement of the goals of the Danish Medical Association. In day-to-day clinical practice, achieving the recommended goals may be even more difficult. Several reasons may explain these relatively disappointing results. First, in this study, the next target to reach was discussed at each visit, along with acceptance of a new medication and dosage by patients. This approach may explain why some medications were not prescribed and dosages not increased. Second, as well as patients' resistance to intensifying treatment, it is well-known that many physicians have concerns about treatment that is too aggressive. The fear of hypoglycemia for this patient population, the belief that even low or average levels of metabolic control can exert a positive effect and the idea that patients are unable to achieve recommended goals[19,20] are strong components of practitioner behaviour. Although it is paradoxical in this experimental setting, we think that this behaviour, as well as the desire to retain patients in the trial,

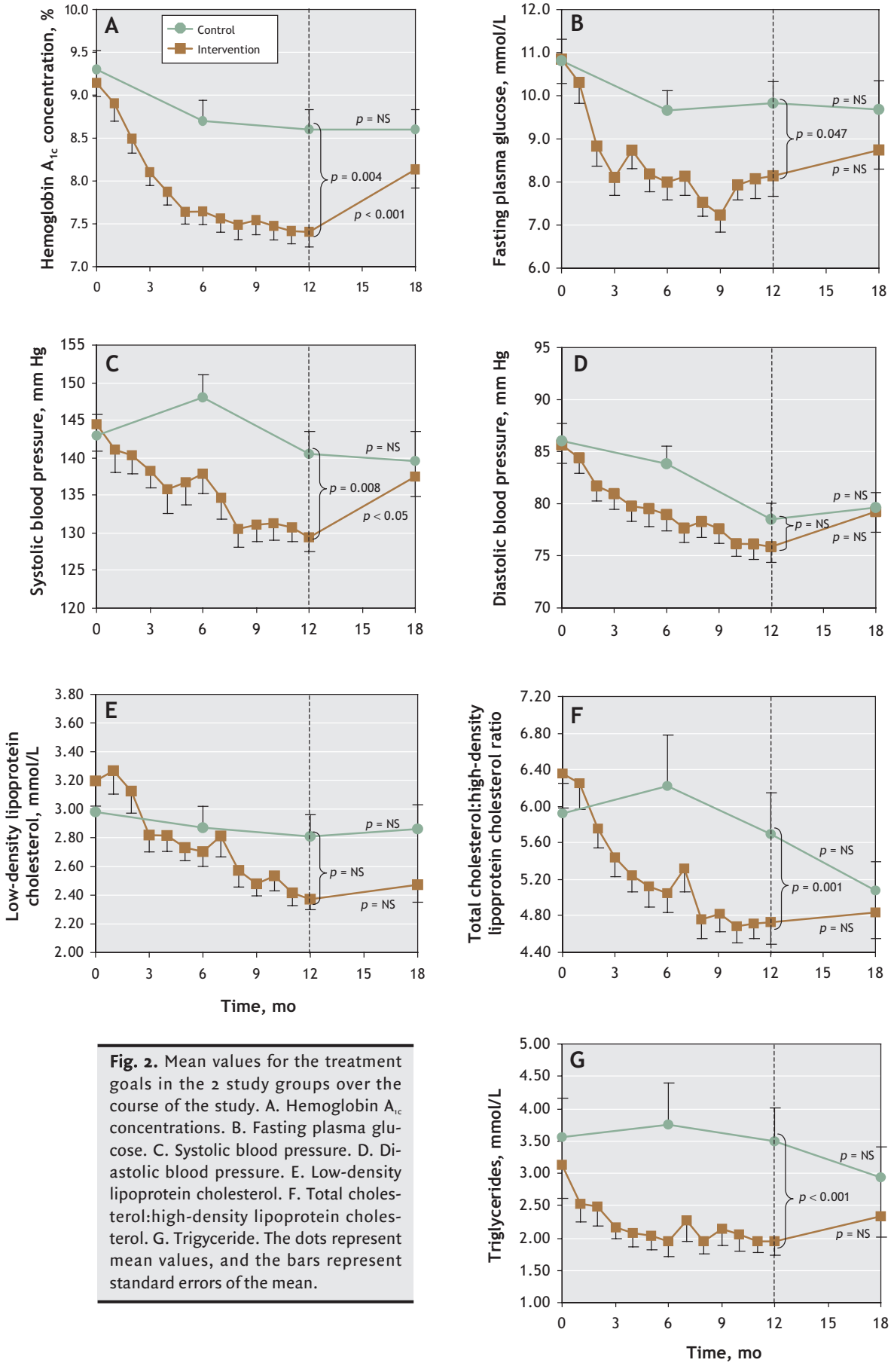

Fig. 2. Mean values for the treatment goals in the 2 study groups over the course of the study. A. Hemoglobin A_{1c} concentrations. B. Fasting plasma glucose. C. Systolic blood pressure. D. Diastolic blood pressure. E. Low-density lipoprotein cholesterol. F. Total cholesterol:high-density lipoprotein cholesterol. G. Trigyceride. The dots represent mean values, and the bars represent standard errors of the mean.

was present in the participating practitioners. However, the therapy given to the patients in our intensive multitherapy group was aggressive when compared with that described in a recent Canadian survey:[21] among those with high blood pressure or dyslipidemia, 76% (v. 20% in the survey) were taking statins (plus 10% who were taking fibrates) and 89% (v. 41%) were prescribed angiotensin-converting enzyme inhibitors. It is important to point out that the intervention group and control group patients were taking the same number of pills; patients in the intervention group may have experienced better outcomes because dosages were more appropriate in this group.

Hypoglycemia and weight gain are major concerns in intensive treatment. In this study, the number of hypoglycemic episodes in the intervention group was comparable to those seen in studies in which comparable fasting plasma glucose levels and hemoglobin A_{1c} concentrations were achieved.[1,11] However, as in the Steno-2 study,[11] we did not find a difference in the number of episodes between the 2 groups. More hypoglycemic episodes would have been recorded if lower hemoglobin A_{1c} concentrations had been reached.[19] Body weight was stable over the intervention period, as was also observed in 2 earlier studies,[1,11] even though many patients started or increased insulin therapy, which is usually associated with weight increase.[22]

At 6 months post-intervention, body weight, hemoglobin A_{1c} concentrations and systolic blood pressure had increased significantly. This deterioration contrasts with the sustained quality-of-life scores achieved during the demanding multitherapy program. Thus it can be concluded that multitherapy is not detrimental to quality of life. The success of permanent lifestyle changes is dependent on patients' degree of motivation, psychosocial condition, risk profile and compliance: patient nonadherence to the lifestyle regimen is the most common barrier to care.[23,24] Further studies are required to determine the best process for inducing long-lasting change in behaviour in type 2 diabetic patients. The Diabetes Control and Complications Trial, which studied intensive management of type 1 diabetes, also reported post-intervention worsening, but this occurred 4 years after the intervention.[25] The rapid deterioration seen in our study seems to be related to a decrease in physical activity (–50%) and probably in diet compliance, as suggested by the statistically significant increase in weight at 18 months and the negative correlations of exercise with weight and systolic blood pressure. These results underline the importance of close follow-up organized around a multidisciplinary team that provides comprehensive and shared care.[24,26,27] We may conclude that patients adhered to the program as long as they were being "coached."

Our intention was not to evaluate the contribution of each component of the intensive multitherapy management separately. Many other trials have focused on one or 2 interventions.[28–31] We targeted lifestyle intervention through education and intense team-based follow-up, as is recommended in national association guidelines.[15,16] In the absence of precise recommendations, we arbitrarily chose monthly follow-up, but the intensity and frequency of the monitoring should be evaluated in future studies.

Although intensive multitherapy is feasible and effective if maintained for 12 months, the benefits vanish rapidly when the patients resume usual care. The CDA treatment goals are very difficult to reach for patients with poorly controlled type 2 diabetes.

Editor's take

- The Canadian Diabetes Association, along with other national associations, recommends specific targets for the metabolic control of diabetes. But are these guidelines and outcomes realistic?
- In this randomized controlled trial, frequent counselling regarding diet and weight loss; exercise, including provision of home exercise equipment; and aggressive management of diabetes, hypertension and hyperlipidemia over 12 months resulted in the attainment of at least some of the goals by between 20% and 64% of patients. Far fewer of the usual-care patients attained the CDA goals. Yet, 6 months after the study ended and multitherapy was discontinued, goal attainment in the intervention group had returned to levels similar to those of the control group.

Implications for practice: Physicians should expect few of their patients to attain the CDA goals and even fewer to maintain the goals over extended periods.

This article has been peer reviewed.

From the Diabetes and Metabolism Research Group (Ménard, Baillargeon, Maheux, Tessier, Ardilouze) and the Cardiology Unit, Clinical Research Centre (Lepage), Centre Hospitalier Universitaire de Sherbrooke, and the Research Centre on Aging (Payette, Tessier), Sherbrooke Geriatric University Institute, Sherbrooke, Qué.

Competing interests: None declared.

Contributors: Julie Ménard and Jean-Luc Ardilouze both contributed to the study concept, design and supervision; data acquisition, analysis and interpretation; and drafting of the manuscript; Julie Ménard also provided statistical expertise. Hélène Payette contributed to the study concept, design and supervision; data analysis and interpretation; and drafting of the manuscript, and provided statistical expertise. Jean-Patrice Baillargeon contributed to the study supervision and data acquisition, analysis and interpretation. Pierre Maheux contributed to the data acquisition, analysis and interpretation and provided statistical expertise. Serge Lepage contributed to data acquisition. Daniel Tessier contributed to data analysis and interpretation. All of the authors critically revised the manuscript for important intellectual content and gave final approval of the article to be published.

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