Feasibility and Effectiveness in Clinical Practice of a Multifactorial Intervention for the Reduction of Cardiovascular Risk in Patients With Type 2 Diabetes

The 2-year interim analysis of the MIND.IT study: a cluster randomized trial

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OBJECTIVE—To evaluate the feasibility and effectiveness of an intensive, multifactorial cardiovascular risk reduction intervention in a clinic-based setting.

RESEARCH DESIGN AND METHODS—The study was a pragmatic, cluster randomized trial, with the diabetes clinic as the unit of randomization. Clinics were randomly assigned to either continue their usual care ($n = 5$) or to apply an intensive intervention aimed at the optimal control of cardiovascular disease (CVD) risk factors and hyperglycemia ($n = 4$). To account for clustering, mixed model regression techniques were used to compare differences in CVD risk factors and HbA_{1c}. Analyses were performed both by intent to treat and as treated per protocol.

RESULTS—Nine clinics completed the study; 1,461 patients with type 2 diabetes and no previous cardiovascular events were enrolled. After 2 years, participants in the interventional group had significantly lower BMI, HbA_{1c}, LDL cholesterol, and triglyceride levels and significantly higher HDL cholesterol level than did the usual care group. The proportion of patients reaching the treatment goals was systematically higher in the interventional clinics (35% vs. 24% for LDL cholesterol, $P = 0.1299$; 93% vs. 82% for HDL cholesterol, $P = 0.0005$; 80% vs. 64% for triglycerides, $P = 0.0002$; 39% vs. 22% for HbA_{1c}, $P = 0.0259$; 13% vs. 5% for blood pressure, $P = 0.1638$). The analysis as treated per protocol confirmed these findings, showing larger and always significant differences between the study arms for all targets.

CONCLUSIONS—A multifactorial intensive intervention in type 2 diabetes is feasible and effective in clinical practice and it is associated with significant and durable improvement in HbA_{1c} and CVD risk profile.

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Cardiovascular disease (CVD) is the leading cause of death, hospital admission, and disability among people with type 2 diabetes, and the overall burden is expected to increase further as the result of a worldwide diabetes epidemic (1). The incidence of CVD in people with diabetes is more than twice that observed in nondiabetic people, and the case fatality rate after a first myocardial infarction in people with diabetes is much higher than that in nondiabetic people (2,3). This makes primary prevention of CVD particularly important in people with diabetes. Compelling evidence has accumulated on the effectiveness of optimal blood pressure (BP) management and cholesterol lowering in the reduction of CVD incidence in people with diabetes (4–8). A targeted multifactorial intervention involving glucose control and the correction of multiple CVD risk factors substantially reduces CVD and all-cause mortality in people with type 2 diabetes (9,10). On the basis of this evidence, the disease management approach currently endorsed by international guidelines recommends the correction of all major CVD risk factors to target levels that closely approach values of low-risk populations (11–13). Notwithstanding the efforts to develop and propagate CVD prevention guidelines, the recommended target values for BP and lipids are achieved only in a small proportion of diabetic patients in clinical practice (14–16); in addition glucose control is often less than optimal, and there is evidence that HbA_{1c} may increase with time irrespective of treatment (17,18). It remains debatable whether the evidence resulting from clinical trials can be translated into actual clinical practice, particularly when an intervention strategy targeting multiple risk factors is

involved. Such intervention is, in fact, much more demanding for both the patient and the physician than treating a single factor, and it is therefore particularly difficult to implement. The most commonly mentioned factors in poor implementation of guidelines include organizational factors, inadequate perception of the patient's global risk, a clinical inertia resulting in inadequate up titration of therapy when the target is not reached, and poor patient adherence to chronic treatments related to polypharmacy (19–21).

The Multiple INtervention in type 2 Diabetes.ITaly (MIND.IT) study is a pragmatic, cluster randomized trial (clinical trials.gov identifier NCT01240070) that compares the usual clinical practice with a protocol-driven treatment strategy aimed at the optimal correction of hyperglycemia and major CVD risk factors in patients with type 2 diabetes and no previous cardiovascular events. The study aim is to evaluate in a clinical, practice-based setting the feasibility and the efficacy of a multifactorial intervention designed according to guidelines for primary CVD prevention in people with type 2 diabetes. In this article, we present data on the effects of a 2-years intervention on major CVD risk factors and HbA_{1c}.

RESEARCH DESIGN AND METHODS

The study was a pragmatic, cluster-randomized, open, two-armed intervention trial with the diabetes clinic as the unit of randomization. This study design was used to allow control for contamination of interventions associated with patient randomization when the intervention requires practice changes and the intended effect is at the institutional level.

The study was conducted in 10 large outpatient diabetes clinics that volunteered to participate. Each center was asked to recruit 250 consecutive patients (men and women) with type 2 diabetes of at least 2 years' duration. Additional inclusion criteria were as follows: age 50 to 70 years, no previous cardiovascular events, serum creatinine <1.5 mg/dL. The study consisted of two phases. Phase 1 was designed as a cross-sectional clinical audit study to evaluate the degree of implementation in clinical practice of the guidelines for the primary prevention of CVD in patients with type 2 diabetes; these results have been published (22). After phase 1, one center withdrew participation before randomization; the remaining 9 centers were randomly allocated to carry on the usual care (UC, n = 5) or to implement a target-driven interventional protocol of intensive care (IC, n = 4) aimed at the optimal control of hyperglycemia, lipids, and BP (phase 2). A few weeks after the start of the trial, one of the centers randomized to IC (Carrara) declared to be unable to comply with the requirements of the study protocol because of staff shortage continued the study according to the UC protocol. In each center, all the patients with a high CVD risk seen in phase 1 were enrolled in the interventional study. High CVD risk was defined as the coexistence of two or more conditions among the following: LDL cholesterol >130 mg/dL, triglycerides >200 mg/dL, HDL cholesterol <35 (males) or <45 (females) mg/dL, and systolic BP >140 or diastolic BP >90 mmHg, regardless of treatment. In the IC centers, the investigators were provided with a multifactorial stepwise protocol to support the application of a treat-to-target approach. This protocol, briefly described in Table 1, included a lifestyle intervention in addition to pharmacological treatment. The investigators were free in prescribing and titrating the pharmacological interventions but were required to follow stepwise incremental protocols for the optimal correction of blood glucose, BP, and lipids with the following targets: HbA_{1c} <7% (<53 mmol/mol), LDL cholesterol <100 mg/dL, triglycerides <150 mg/dL, HDL cholesterol >40 mg/dL in men and > 45 mg/dL in women, and BP <130/80 mmHg. In addition, weight loss of >5% (if overweight) and the implementation of antiplatelet therapy were to be pursued. Consultation was provided every 3 months. In the UC group, the investigators followed the usual clinical practice. In both study arms, annual visits were scheduled to assess biochemistry, anthropometry, BP, electrocardiogram, and treatment target achievement. This report gives the results of the prespecified analyses performed after all patients had completed 2 years of follow-up.

The investigation methods have been described in detail elsewhere (22). At baseline and at each follow-up visit, anthropometry and sitting BP were measured according to a standard protocol; serum total cholesterol, HDL cholesterol, and triglycerides were measured by standard methods; HbA_{1c} was measured by high-performance liquid chromatography; and LDL cholesterol was calculated according to the Friedewald equation for participants with fasting triglycerides <400 mg/dL. Biochemical testing was performed at each center in a single laboratory. Before enrollment, each participating laboratory underwent an external quality control assessment to verify the reliability and comparability of analytical methods and to reach a standard of quality and traceability among the participating centers. Quality control was monitored thereafter during the whole study period. The external quality control assessment was provided by the San Raffaele Hospital (Milan, Italy), which takes part in an international network for the standardization of laboratory methods.

The study protocol was approved by the local ethics committees. Informed consent was obtained from all participants.

Statistical methods

Data are given as mean ± SE or as % (SE). Calculation of intracluster correlation coefficients (ICCs) and between groups comparisons of baseline characteristics were performed as suggested by Donner and Klar (23). The study outcomes were analyzed by mixed-model regression techniques to account for clustering in a group-randomized trial according to procedures described by Murray et al. (24). The SAS procedures MIXED (for continuous variables) and GLIMMIX (for binary variables) with the REML (restricted maximum likelihood) estimation were used with adjustment for baseline and including a time by treatment interaction term. The analysis was conducted according to the intent to treat (ITT) principle. Because of an obvious protocol violation by one center (Carrara), a sensitivity analysis was also performed excluding protocol violations (i.e., as treated per protocol).

The main outcome was the change from baseline in major CVD risk factors and HbA_{1c}. The study had 90% power for detecting minimum differences between the two study arms of 3 mmHg for systolic or diastolic BP and 8 mg/dL for LDL cholesterol and for detecting a 0.5% reduction in HbA_{1c}, with $\alpha = 0.05$ two-sided and assuming an ICC between 0.02 and 0.05 (25). All statistical analyses were performed with the SAS statistical software package (version 9.3; SAS Institute, Cary, NC).

RESULTS

—Nine clinics were randomized to the two intervention strategies.

Table 1—*Brief description of the treatment algorithm to be applied in the interventional group*

	Target	Lifestyle intervention	If above target	If still above target	If still above target	Additional treatments
Weight	BMI <25 or 5% reduction of body weight	Diet and exercise	Reinforce diet and exercise	Reinforce diet and exercise	Reinforce diet and exercise	
Blood glucose	HbA_{1c} <7% (<53 mmol/mol)	Diet and exercise	Add metformin (500–2500 mg) if obese or overweight; add sulphonylureas or like drugs at increasing dose if normal weight	Add sulphonylureas or like drugs if obese; add acarbose or bedtime insulin if normal weight	Add bedtime insulin if obese; add preprandial insulin if normal weight	Thiazolidinedione, insulin multiple injections
BP (mmHg)	<130/80	Diet and exercise	Add ACE inhibitors or angiotensin II receptor antagonists	Add long-acting calcium-channel blockers, β-blockers, or low-dose diuretics as appropriate	Add a third drug	
Lipids (mg/dL)	LDL cholesterol <100; TG <150	Diet and exercise	If LDL >130, add statins; if LDL <100 and TG >200, add fibrates	Increase dose of statins or fibrates	Increase dose of statins or fibrates	

TG, triglycerides.

A total of 1,461 patients (i.e., 60% of those seen in phase 1) qualified for the intervention study and were enrolled. During the 2 years of follow-up, the clinics lost contact with 11.6% of the patients, thus leaving in the study 1,292 patients (771 in the UC clinics and 521 in the IC clinics by ITT analysis). Only participants with complete 2 years of follow-up were included in the analyses. No significant differences were observed in the baseline clinical characteristics and CVD risk factors profile between patients seen at follow-up and those not seen.

The demographic, clinical, biochemical, and treatment data of the study participants at baseline are given in Table 2 according to treatment arm. There were no significant differences between participants enrolled by IC or UC clinics in both ITT and as treated per protocol analyses. At follow-up (Table 3), participants in the IC clinics had significantly lower BMI, HbA_{1c}, LDL cholesterol, and triglycerides and significantly higher HDL cholesterol than did the participants enrolled in the UC clinics (ITT analysis). These results were confirmed in the as treated per protocol population, which in addition showed a significantly lower systolic BP and a lower diastolic BP in the IC clinics. Notably, the improvement in glucose control was not accompanied by weight gain in the IC arm; on the contrary, a slight but statistically significant reduction in BMI was observed.

The proportion of patients achieving the treatment goals after 2 years was systematically higher in the IC clinics than in the UC clinics for all targets (Fig. 1). In the ITT analysis, the proportions of patients reaching the treatment goals were 35% vs. 24% for LDL cholesterol ($P = 0.1299$), 93% vs. 82% for HDL cholesterol ($P = 0.0005$), 80% vs. 64% for triglycerides ($P = 0.0002$), 39% vs. 22% for HbA_{1c} ($P = 0.0259$), and 13% vs. 6% for BP ($P = 0.1638$) in the IC and UC clinics, respectively. Findings in the as treated per protocol analysis were qualitatively consistent; however, the magnitude of the differences between UC and IC clinics were larger and always formally significant (43% vs. 24% for LDL cholesterol, 95% vs. 82% for HDL cholesterol, 82% vs. 64% for triglycerides, 54% vs. 22% for HbA_{1c}, 23% vs. 6% for BP in UC and IC clinics, respectively) (Fig. 1). It is relevant, however, that even in the IC clinics the treatment remained suboptimal. Even in the best case scenario, only 55% of the participants reached the goal

Table 2—*Baseline characteristics of the study population by randomized intervention strategy (ITT and as treated analyses)*

	ITT analysis set				As treated analysis set			
	UC (*n* = 771)	IC (*n* = 521)	*P* value*	ICC	UC (*n* = 771)	IC (*n* = 411)	*P* value*	ICC
Age (years)	61.3 ± 0.5	60.3 ± 0.6	0.2616	0.0394	61.3 ± 0.5	60 ± 0.6	0.1587	0.0361
Male (%)	54.7 (1.8)	48.5 (2.2)	0.3403	0.0298	54.7 (1.8)	53.5 (2.4)	0.8055	0.0110
BMI (kg/m^2)	29.2 ± 0.5	29.9 ± 0.5	0.3055	0.0392	29.2 ± 0.5	30.3 ± 0.6	0.1386	0.0300
HbA_{1c} (%)	7.4 ± 0.2	7.8 ± 0.2	0.1416	0.0661	7.4 ± 0.2	7.6 ± 0.2	0.3102	0.0388
HbA_{1c} (mmol/mol)	57.9 ± 1.7	62.3 ± 1.7			57.9 ± 1.7	60.4 ± 1.7		
LDL cholesterol (mg/dL)	140.7 ± 2.2	146.5 ± 2.5	0.1238	0.0158	140.7 ± 2.2	144.5 ± 2.5	0.2690	0.0108
HDL cholesterol (mg/dL)	49.0 ± 1.6	45.8 ± 1.7	0.2200	0.0744	49.0 ± 1.6	45 ± 2.1	0.1768	0.0763
Triglycerides (mg/dL)	175.9 ± 8.7	178.9 ± 9.8	0.8218	0.0312	175.9 ± 8.7	176.7 ± 11.8	0.9548	0.0386
Systolic BP (mmHg)	145.9 ± 2.4	146.3 ± 2.7	0.9308	0.043	145.9 ± 2.4	143.8 ± 2.5	0.5162	0.0460
Diastolic BP (mmHg)	86.8 ± 1.3	86 ± 1.5	0.6899	0.1233	86.8 ± 1.3	85.4 ± 1.7	0.5447	0.0920
Glucose-lowering treatment (%)								
Diet only	11.8 (1.1)	18.0 (1.6)	0.3845	0.0830	11.8 (1.1)	22.6 (2.0)	0.1467	0.0703
Oral agents only	74.4 (1.5)	68.9 (2.1)	0.4829	0.0608	74.4 (1.5)	66.9 (2.3)	0.4017	0.0668
Insulin alone or in combination with oral agents	13.7 (1.2)	13.1 (1.5)	0.8519	0.0158	13.7 (1.2)	10.4 (1.5)	0.3165	0.0107
Antihypertensive treatment (%)								
Any one	60.5 (1.8)	67.5 (2.1)	0.1969	0.0207	60.5 (1.8)	70.0 (2.2)	0.1178	0.0227
Two or more	44.5 (2.3)	50.0 (2.7)	0.5317	0.0547	44.5 (2.3)	52.7 (2.9)	0.3935	0.0578
Statins (%)	31.7 (1.7)	28.9 (2.0)	0.6952	0.0455	31.7 (1.7)	28.9 (2.2)	0.7295	0.0511
Antiplatelet treatment (%)	20.3 (1.4)	27.6 (1.9)	0.4463	0.1052	20.3 (1.4)	30.1 (2.1)	0.3669	0.114

Values are mean ± SE or % (SE). **P* values are adjusted for the effect of clustering. UC, usual care; IC, intensive care; ICC, intraclass correlation coefficient.

for HbA_{1c}, 43% reached the goal for LDL cholesterol, and 23% reached the goal for BP.

Table 4 shows the proportions of patients on different medication regimens in the IC and UC clinics at 24 months. A significantly higher proportion of participants in the IC clinics were receiving statins and antiplatelet therapy in the ITT analysis. These findings were confirmed in the as treated analysis, which in addition showed significantly more frequent use of antihypertensive treatment in the IC clinics. The pattern of antihypertensive medication use was similar in the two study arms, with the ACE inhibitors or angiotensin II receptor blockers being the most frequently prescribed antihypertensive agents, followed by calcium-channel blockers.

CONCLUSIONS—The study shows that in clinical practice an intervention to promote a target-driven management of diabetes and CVD risk factors in patients with type 2 diabetes and high CVD risk is feasible and is associated with significant intensification of treatment and improvement in glucose control and CVD risk factors. At variance with other studies, the improvement in glucose control was not accompanied by weight gain, probably as a result of the inclusion of weight control in the IC management targets. Several studies have documented the gap between the management of diabetes recommended by guidelines and the actual care delivered in the clinical setting (14–16,22). Our results demonstrate that a target-driven management protocol for diabetes and CVD risk factors can be implemented in clinical practice, and in a 2-year period can improve the overall quality of care and the CVD risk factors profile beyond results achieved in the usual practice. This suggests a great potential for the primary prevention of CVD in diabetes. The differences achieved between the study arms at the end of 2 years of follow-up for most end points were statistically and clinically

Table 3—*HbA_{1c} and major CVD risk factors at 2 years' follow-up in the two study arms*

	ITT analysis set				As treated analysis set			
	UC (*n* = 771)	IC (*n* = 521)	Mean difference	*P* value	UC (*n* = 771)	IC (*n* = 411)	Mean difference	*P* value
BMI (kg/m^2)	29.4 ± 0.51	29.0 ± 0.51	−0.38 ± 0.12	0.0097	29.4 ± 0.51	28.9 ± 0.11	−0.50 ± 0.13	0.0046
HbA_{1c} (%)	7.73 ± 0.11	7.19 ± 0.12	−0.53 ± 0.16	0.0119	7.73 ± 0.11	6.92 ± 0.10	−0.81 ± 0.12	0.0003
HbA_{1c} (mmol/mol)	61.0 ± 1.1	55.2 ± 1.1	−5.8 ± 1.7		61.0 ± 1.1	52.2 ± 1.0	−8.8 ± 1.1	
LDL cholesterol (mg/dL)	123.2 ± 3.53	112.8 ± 3.11	−10.4 ± 4.15	0.0370	123.2 ± 3.53	106.2 ± 2.33	−17.0 ± 4.15	0.0005
HDL cholesterol (mg/dL)	48.2 ± 0.74	51.2 ± 0.84	3.06 ± 1.12	0.0253	48.2 ± 0.74	52.6 ± 0.87	4.40 ± 1.12	0.0043
Triglycerides (mg/dL)	156.9 ± 2.97	143.9 ± 3.47	−12.9 ± 4.57	0.0125	156.9 ± 2.97	140.2 ± 3.58	−16.7 ± 4.51	0.0029
Systolic BP (mmHg)	141.8 ± 1.68	137.4 ± 1.88	−4.33 ± 2.52	0.1180	141.8 ± 1.68	133.1 ± 1.41	−8.70 ± 2.52	0.0011
Diastolic BP (mmHg)	80.5 ± 0.54	80.8 ± 0.61	0.36 ± 0.81	0.6661	80.5 ± 0.54	79.4 ± 0.41	−1.10 ± 0.52	0.0780

Reported values are least squares means ± SE and their respective differences at the end of 2 years of follow-up adjusted for baseline values and cluster design. The time by treatment interaction term was significant for HbA_{1c} ($P < 0.0001$), LDL cholesterol ($P < 0.0001$), HDL cholesterol ($P = 0.0003$), and systolic BP ($P = 0.0001$).

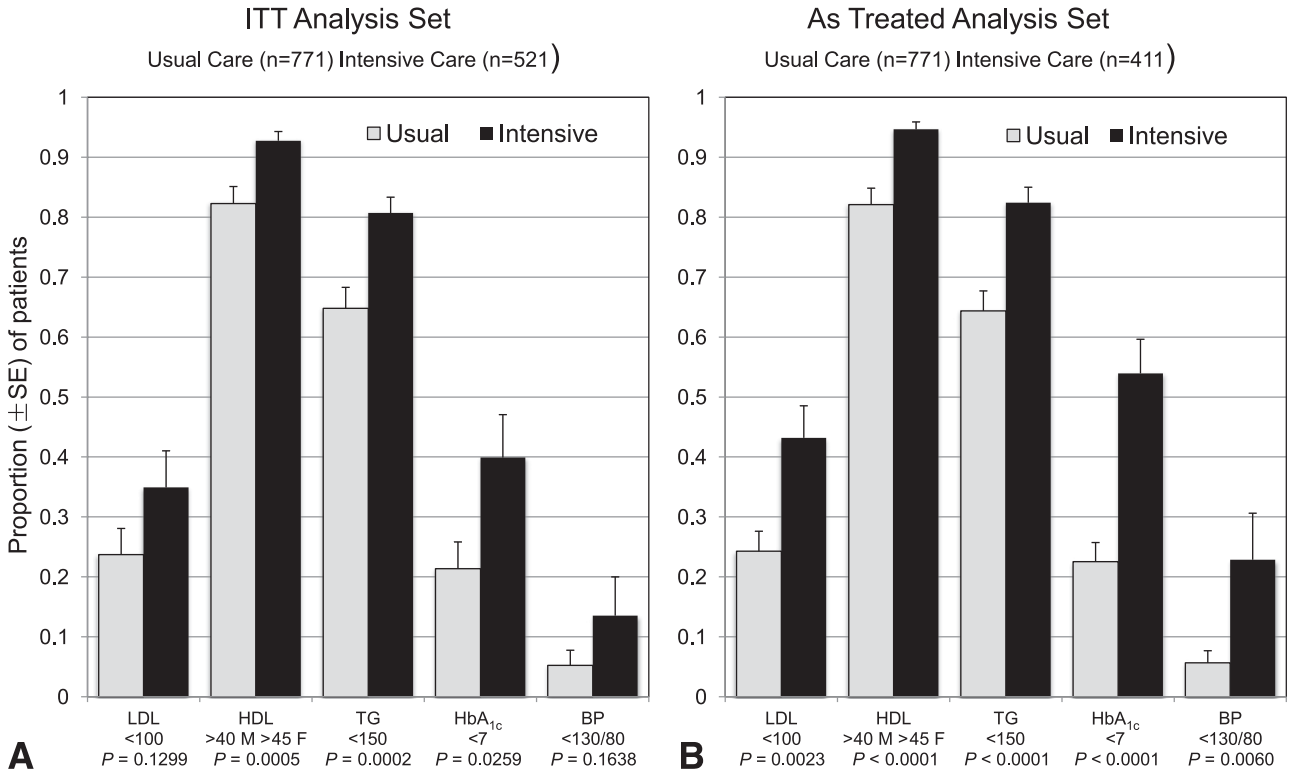

Figure 1—*Proportions (±SE) of patients with CVD risk factor values meeting the treatment intervention targets at follow-up in ITT* (A) *and as treated* (B) *analyses. Estimates are adjusted for cluster design and baseline values. TG, triglycerides.*

significant, and all favored the IC group. It is also relevant that the trial was undertaken against a background of general improvements in the delivery of diabetes care associated with the spreading of evidence-based guidelines and the introduction of national standards of care endorsed by the Italian Diabetes Society (13,26,27), which may have somewhat narrowed the achievable differences between the treatments groups.

The quality of care in the IC clinics remained, however, suboptimal. Nearly half of the patients did not achieve the goals for HbA_{1c}, only one in three reached optimal BP or LDL cholesterol values, and a very small proportion met all three goals. These results are in keeping with previous findings (14–16,28,29) and underline the difficulty in reaching the desired therapeutic targets in patients with type 2 diabetes in clinical practice. The reasons for the repeatedly documented gap between the ideal and the actual care delivered to diabetic patients are complex. Factors affecting care delivery may be more important than guidelines themselves or the strategies used to spread them; physicians' beliefs and patient compliance are also crucial issues (19–21). Guidelines on their own are not beneficial; effective implementation strategies should accompany their development. Pay for performance programs have been introduced in several countries to improve the quality of care, and there is evidence that the introduction of explicit financial incentives is associated with improvements in the quality indicators for diabetes care (30). It is difficult, however, to disentangle the impact of these measures from other concomitant quality initiatives, because few studies have adjusted for underlying trends in quality of care. Furthermore, relevant aspects of diabetes management, such as the patient's empowerment and continuity of care, are not captured by the quality and outcomes framework. In addition, concerns that pay for performance programs might erode equity in the provision of health care have been raised (30,31). In our study, quarterly counseling was recommended in the IC clinics; this may ensure sufficient continuity of care and at the same time be compatible with routine clinical practice in most settings. The implementation of this recommendation and the provision of a stepwise protocol to support the application of a treat-to-target approach may have been key factors in the overall improvement of quality of care in the IC group. The improvement of quality of care is similar to what has been reported in clinical practice–based programs in the U.K. and in the U.S. (31,32) and was obtained without allocation of extra resources or financial incentives, but rather through a physician-led effort made possible by the commitment of the personnel involved.

The potential study limitations need to be discussed. Because the intervention was delivered within the setting of routine clinical practice, we randomized the clinics rather than the individual participants to avoid contamination. The study included a limited number of clinics, and those enrolled were selected on the basis of their willingness to participate in the project. This may somewhat limit the generalizability of our findings. The randomized design, however, and the large number of patients recruited in each clinic may partially offset these problems. In addition, we covered a large geographical area, and the participating centers were fairly representative for key characteristics of the diabetes clinics all over Italy (26). The study was designed in 2001, and therefore the treatment algorithms, particularly those for the correction of hyperglycemia, are not fully consistent with current recommendations (27,33). Finally, in this analysis we only assessed intermediate

Table 4—*Medication use at 2-year follow-up in the two study arms.*

	ITT analysis set			As treated analysis set		
	UC (*n* = 771)	IC (*n* = 521)	*P* value for difference between proportions	UC (*n* = 771)	IC (*n* = 411)	*P* value for difference between proportions
Glucose-lowering treatment (%)						
Diet only	5 (2)	6 (3)	0.6856	5 (2)	11 (3)	0.0778
Oral agents only	74 (3)	73 (4)	0.7279	74 (3)	74 (4)	0.9975
Insulin alone or combined with oral agents	21 (2)	21 (3)	0.8074	21 (2)	15 (3)	0.1448
Antihypertensive treatment (%)						
Any one	87 (3)	92 (2)	0.1072	87 (3)	96 (1)	<0.0001
Two or more	45 (5)	54 (6)	0.2268	45 (5)	66 (3)	<0.0001
ACE inhibitor	68 (3)	76 (3)	0.0467	68 (3)	80 (3)	0.0019
Angiotensin II receptor blocker	34 (3)	26 (3)	0.0527	34 (3)	27 (3)	0.0789
β-Blocker	17 (4)	12 (3)	0.3098	17 (4)	10 (3)	0.1845
Calcium-channel blocker	34 (5)	46 (6)	0.1172	34 (5)	51 (6)	0.0439
Diuretic	40 (7)	54 (6)	0.1449	40 (7)	59 (7)	0.0609
α-Blocker	8 (2)	6 (2)	0.2566	8 (2)	4 (1)	0.0436
Statins (%)	24 (6)	64 (8)	0.0003	24 (6)	76 (5)	<0.0001
Antiplatelet treatment (%)	19 (5)	73 (7)	<0.0001	19 (5)	84 (3)	<0.0001

Data are proportions of patients (SE), as estimated with adjustment for baseline values and cluster design. The time by treatment interaction term was significant for antihypertensive treatment ($P = 0.0113$), statin use ($P < 0.0001$), and antiplatelet treatment ($P < 0.0001$).

outcome measures, and no information was collected on the frequency and severity of hypoglycemic events. Whether such intervention would effectively reduce the occurrence of cardiovascular events can only be inferred from changes in the CVD risk factor profile (8,9). A similar study conducted to investigate the effect of early multifactorial treatment after diabetes diagnosis by screening showed a small, nonsignificant, difference in the incidence of cardiovascular events (28). The changes in the CVD risk factor profile observed in that study were, however, considerably smaller than those achieved in our study.

In conclusion, a multifactorial, target-driven intervention for the management of type 2 diabetes is feasible and effective in clinical practice. An intensive intervention strategy delivered at the clinic level is associated with a significant and durable improvement in major CVD risk factors and HbA_{1c}, well beyond that achieved with the usual practices.

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O.V. contributed to study design and analysis and wrote the manuscript. L.F. analyzed data and contributed to writing the manuscript. R.M., F.C., M.B., P.D.F., A.A.R., and M.T. contributed to study design and analysis and reviewed the manuscript. D.A. contributed to data analysis, researched funds, and reviewed the manuscript. G.R. analyzed data and reviewed the manuscript. I.Z. contributed to study design, researched funds, and reviewed the manuscript. O.V. is the guarantor of this work and, as such, had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

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