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Cost-effectiveness of the adherence with recommendations for clinical monitoring of patients with diabetes

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Periodic examinations;
Population-based cohort study;
Real-world

Abstract *Background and aims:* To validate a set of indicators for monitoring the quality of care of patients with diabetes in 'real-life' practice through its relationship with measurable clinical outcomes and healthcare costs.

Methods and results: A population-based cohort study was carried out by including the 20,635 patients, residents in the Lombardy Region (Italy), who in the year 2012 were newly taken-in-care for diabetes. Adherence with clinical recommendations (i.e., controls for glycated haemoglobin, lipid profile, urine albumin excretion and serum creatinine) was recorded during the first year after the patient was taken-in-care, and categorized according whether he/she complied with none or almost none (0 or 1), just some (2) or all or almost all (3 or 4) the recommendations, respectively denoted as poor, intermediate and high adherence. Short- and long-term complications of diabetes, and healthcare cost incurred by the National Health Service, were assessed during follow-up.

Compared with patients with poor adherence, those with intermediate and high adherence respectively showed (i) a delay in outcome occurrence of 13 days (95% CI, −2 to 27) and 23 days (9–38), and (ii) a lower healthcare cost of 54 € and 77 €. In average, a gain of 18 Euros and 15 Euros for each day free from diabetic complication by increasing adherence respectively from poor to intermediate and from poor to high were observed.

Conclusion: Close control of patients with diabetes through regular clinical examinations must be considered the cornerstone of national guidance, national audits, and quality improvement incentive schemes.

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Introduction

Type 2 diabetes, a major challenge for human health in the 21st century [1–3], requires continuous medical care and appropriate diagnostic and treatment strategies to reduce macro and microvascular complications [4]. Scientific societies, including the American, European and Italian Diabetes Associations, regularly report and adapt clinical guidelines to achieve these goals and reduce diabetes-related outcomes as effectively as indicated by trial-based outcome evidence [4–6].

Although the benefits of adherence with guidelines on diabetes have been widely investigated [7–9], current knowledge is scanty on at least three key issues. First, studies have mostly focused on adherence with drug therapy recommended by guidelines [10–15], while other recommendations, e.g. medical visits and clinical examinations, have been considered only by a few authors [16]. Second, attention has been mainly directed to intermediate outcomes, such as glycemic control [10,11], while just a few studies have investigated the impact of adherence on clinical outcomes (e.g., diabetic complications) [16] and health-care costs [17]. Finally, to avoid diabetes-related complications and reduce healthcare-related costs, guidelines always recommend risk stratification-based management of patients with diabetes [4,18,19]. However, to the best of our knowledge, evidence on how adherence to guidelines affects outcomes according to patients' clinical complexity is limited.

The influence of adherence with clinical evaluations recommended by guidelines (i.e., periodic controls of glycaemic and lipid profiles, kidney function and dilated eye examination) on hospitalization for complications of diabetes has been recently assessed by a panel denoted "Monitoring and assessing diagnostic-therapeutic paths (MAP)" that operates under the auspices of the Italian Ministry of Health [20]. The aim of the current study was to assess the cost-effectiveness of adherence with recommendations, based on the findings obtained from the largest Italian region (Lombardy), taking into account the uncertainty of the estimated effectiveness and costs. Cost-effectiveness according to the clinical profile of patients with diabetes was also investigated. A set of sensitivity analyses was performed in order to evaluate the robustness of the results.

Methods

Data source

All Italian citizens have equal access to health care services as part of the National Health Service (NHS). An automated system of healthcare utilization (HCU) databases allows each Italian region to locally manage NHS. HCU data include information on residents who receive NHS assistance (NHS beneficiaries), diagnosis at discharge from public or private hospitals, outpatient drug prescriptions, specialist visits and diagnostic examinations reimbursable by the NHS, and co-payment exception for diagnosed chronic disease, including diabetes. The cost of every single service supplied to a NHS beneficiary and reimbursed to health provider (i.e., direct healthcare cost for the Regional Health Authority) is also routinely recorded. As a unique identification code is systematically used for all databases within each region, their record linkage allows searching out the complete care pathway of NHS beneficiaries. In order to preserve privacy, identification codes are automatically converted into anonymous codes, and the inverse process being allowed only to the Regional Health Authority on request from judicial authorities.

Diagnostic, therapeutic and procedural codes used for the current study are given in Supplementary material (Table S1).

Study cohort

The data used for this study were retrieved from the HCU databases of Lombardy, a region of Italy that accounts for about 16% (almost ten millions) of its population. Residents in Lombardy who in 2012 (the index year) were aged 18 years or older constituted the target population. Subjects belonging to the target population were considered eligible for entering into the study cohort if in the index year they left specific 'footprints' on services provided by the NHS, i.e., if they 1) had at least two prescriptions of antidiabetic agents in two distinct dates 2) experienced at least one hospitalization with diabetes as primary or secondary diagnosis and/or 3) took advantage of exemption from co-payment for diabetes. Patients were excluded if in the previous three years they had already experienced at least one dispensation of an antidiabetic agent, at least one hospitalization reporting diabetes or diabetic complications as primary or secondary diagnosis, and/or exemption for diabetes. Patients recorded as NHS beneficiaries after 2008 (i.e., those who did not have three backward years for applying exclusion criteria) were also excluded from the cohort. The exclusion was extended to patients who did not reach at least one year of follow-up after the index year. The remaining patients were considered newly "taken-in-care", and were then included into the study cohort. The taken-in-care date was assumed to be that of the second antidiabetic drug prescription, the first hospitalization for diabetes, or the documentation of co-payment exemption, whichever came first.

Adherence with recommendations

Assessments of glycated haemoglobin, lipid profile (total and HDL cholesterol and triglycerides), urine albumin excretion and serum creatinine performed on cohort members during the first year after a patient was taken-in-care, were identified. With respect to the previous experience by our group [20], we did not include dilated eye examination in the current investigation. A reason for this was that only 12% of patients were adherent to this

recommendation, which may mean that a relevant portion of patients with diabetes received eye examination from private services thereby escaping our database. A patient was considered adherent to recommendations if he/she submitted to at least two glycated haemoglobin examinations and at least one of the other evaluations [20–22]. A score of increasing adherence was developed by categorizing each cohort member according to whether he/she complied with none or almost none (0 or 1), just some (2) or all or almost all (3 or 4) the recommendations. This identified three categories of increasing adherence to recommendations, respectively denoted as poor, intermediate and high adherence.

Additional measurements

Baseline characteristics of cohort members included gender, age, drug therapies and comorbidities recorded within three years prior to the date of taken-in-care. Drug therapies included antiplatelet agents, digitalis glycosides, nitrates, antiarrhythmics, blood pressure- and lipid-lowering agents, antidepressants, non-steroidal anti-inflammatory drugs, anti-gout agents and drugs for chronic obstructive pulmonary disease. Comorbidities were identified by hospitalization for cancer, heart failure, and ischaemic heart, cerebrovascular, respiratory and kidney diseases. The total number of services provided by the NHS (the clinical 'footprints' which patients with diabetes left when they had accessed to medical care during the three-year period before they were taken-in-care) was recorded. Finally, patients were categorized also according to the Multisource Comorbidity Score (MCS), a new index of patients' clinical status derived from inpatients diagnostic information and outpatient drug prescriptions provided by the regional Italian data and validated for outcome prediction [23]. To simplify comparisons, as well as for providing them with sufficient power, the original five categories of worsening clinical profile (0, 1, 2, 3 and 4) as defined by MCS were reduced to milder (MCS $=$ 0), middle ($1 \leq$ MCS$\leq$2) and more severe ($3 \leq$ MCS$\leq$4) categories.

Clinical outcomes

Cohort members accumulated person-years of follow-up starting from one year after the patient was "taken-in-care", until the occurrence of the study clinical outcome (see below), death, migration or end of follow-up, i.e., four years after starting, regardless of which of these events came first. Overall, the time-span accumulated during this period was denoted "health-related follow-up". A composite clinical outcome was developed to take into account potentially avoidable complications of diabetes. A cohort member was considered as having the outcome if he/she experienced at least one hospital admission during the health-related follow-up in which one or more of the following events was mentioned at discharge: (i) short-term diabetes complications (including diabetes with other coma), (ii) uncontrolled diabetes (including diabetes with ketoacidosis), (iii) long-term outcomes (including heart failure, arrhythmias and renal disease), and (iv) traumatic lower limb amputation of non-traumatic origin (see the Supplementary Table S1 for the complete list of the considered diagnoses). The date of the first hospitalization with one of these events was considered as the outcome occurrence.

Healthcare costs

Costs were calculated from the amount that the Regional Health Authority reimbursed to health providers and included hospitalizations for diabetic complications, or other causes, NHS dispensed antidiabetic agents, as well as other drugs free-of-charge, outpatients services specifically related to diabetes monitoring recommended by guidelines, and all other services provided free-of-charge by NHS such as specialist visits, laboratory examinations and instrumental examinations. Healthcare costs accumulated by each cohort member started from the date when that member was "taken-in-care" until death, migration, or end of follow-up, i.e., five years after the patient was "taken-in-care", regardless of which of these events came first. The time-span accumulated during this period was denoted "cost-related follow-up".

Matching design

For each cohort member classified into the category of high adherence, one cohort member on intermediate and another one on poor adherence were randomly selected to be matched for gender, age ($\pm$3 years), total number of services received by the NHS during three years prior to the date of taken-in-care ($\pm$5 services), and category of MCS. In this way a 1:1:1 matching design was realized by which three matched cohorts differing for adherence level, and expected to be balanced for several factors, were generated.

Statistical analyses

With the aim of verifying between-group balancing, the standardized difference was calculated for each measured covariate before and after matching.

To investigate the demographic and clinical predictors of adherence, a proportional odds logistic regression was fitted to estimate the odds ratio, and its 95% confidence interval (CI), of the three-level overall adherence in relation to the above-mentioned covariates.

Healthcare costs and health-related outcomes were separately considered for each matched cohort. Healthcare costs accumulated during the time horizon of five years were calculated by means the Bang & Tsiatis estimator [24], a method that takes into account censored cost data. With the aim of expressing cost as a rate, healthcare costs overall accumulated by a given matched cohort were divided for the amount of person-months accumulated from that cohort during the "cost-related follow-up". The corresponding measure was denoted average daily

healthcare cost (DHC) and expressed in Euros every person-day.

As far as health-related outcome is a concern, Kaplan–Meier curves depicting time-free-to-complications until the time horizon of four years, and corresponding 95% confidence profiles, were calculated. The restricted mean survival time (RMST), calculated through the area under the Kaplan–Meier curve [25], represents the time free from complications on average experienced by each cohort member [26,27]. In the current application, the corresponding measure was denoted days free from complications on average experienced by each cohort member (DCF).

The incremental cost-effectiveness ratio (ICER) was measured by dividing the differences in healthcare costs (DHC) and health-related outcomes (DCF) between two matched cohorts (say, between intermediate and poor adherence cohorts, as well as high and poor adherence ones). The ICER is the healthcare expenditure expected to be saved (or added, depending on the sign) for gaining one complication-free month because of enhancing adherence with recommendations at a certain level [28]. Non-parametric bootstrap method based on 1000 re-samples [29] was used to explore the uncertainty in the cost-effectiveness estimates [30]. The ICER was estimated for the whole cohorts, as well as according with strata of MCS.

Sensitivity analyses

Besides the primary analyses, a set of sensitivity analyses was performed to assess the robustness of the cost-effectiveness estimates. One, because of the arbitrary categorization of the adherence to recommendations, poor, intermediate and high adherence were established according whether 0, (1 or 2) and (3 or 4) recommendations were followed at variance from (0 or 1), 2 and (3 or 4) recommendations as in the main analysis. Two, because adherence to recommendations (as well as healthcare costs and health-related outcomes) are likely to change over time, an analysis was performed in the cohort enrolled in the year 2007, instead 2012 as in the main analysis. Finally, as in the primary analysis residual confounding could not be excluded, a high-dimensional propensity-score (HDPS) matching design was used to ensure that patients classified according to their adherence with recommendations had similar baseline characteristics [31], using a HDPS algorithm that empirically identified and prioritized covariates that were proxies for unmeasured confounders in large electronic healthcare databases [31]. The predicted probability of being classified in the high-adherence with respect to poor adherence category was estimated through a logistic regression model that included as covariates all possible causes of hospital discharge experienced, all drugs prescribed and all outpatient services provided to the study cohort members in the 3-year period prior to the index date, with two levels of adherence as the outcome of interest. The 200 most predictive covariates were selected. The matching procedures above described were modified by adding that cohort members must also be matched for HDPS through the nearest neighbour matching algorithm [32].

All analyses were performed using SAS 9.4 (Cary, NC). A 2-sided p-value of 0.05 or less was considered significant.

Ethical issues

The Ethical Committee of the University of Milano-Bicocca evaluated the protocol and established that the study (i) was exempt from informed consent (according to General Authorization for the Processing of Personal Data for Scientific Research Purposes Issued by the Italian Privacy Authority on December 15, 2016; http://www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/docweb/5805552) (ii) provides sufficient guarantees of individual records anonymity, and (iii) was designed according to quality standards of good practice of observational research based on secondary data.

Results

Patients

Among the NHS beneficiaries forming the whole target population, 36,098 subjects met the criteria for the definition of newly taken–in-care patients with diabetes in the year 2012, the standardised rate being 4.5 newly taken-in-care patients with diabetes every 1000 person-year. Among the 36,098 newly taken-in-care patients with diabetes, 20,635 reached at least one year of follow-up and were included into the study cohort. At baseline, their mean age was about 60 years and 51% of them were men.

Adherence with recommendations

During the first year of follow-up, adherence with recommendations was poor for 43% of cohort members, that is, more than two out of five patients did not adhere to any or to only one recommendation, while 21% had good adherence, that is, one out of five patients adhered to all or almost all recommendations. A better adherence profile was observed in men, with a milder clinical profile, who more frequently received services provided by the NHS, and more often received drug prescriptions of antihypertensive and statins (Table 1). Matched pairs cohort members, on the other hand, were better balanced for all considered covariates, being standardized differences systematically less than 10%.

Male sex, older age, the use of antihypertensive agents, lipid-lowering drugs, NSAIDs, the presence of ischemic heart disease, the use of antidiabetic drugs and the presence of the co-payment exception for diabetes were predictors for a higher adherence to recommendations (Supplementary Table S2). Conversely, a worse clinical profile, the use of antiplatelets, digitalis glycosides, organic

Table 1 Baseline characteristics of original (before matching) and 1:1:1 matched cohort members who were newly taken in care for diabetes by the regional NHS according to their adherence with recommendations.

	Original cohort[a]					Matched cohort[a]				
	Number of recommendations[b]					Number of recommendations[b]				
	0 or 1 N = 8880 (43%)	2 N = 7332 (36%)	3 or 4 N = 4423 (21%)	Standardized difference		0 or 1 N = 3298 (33%)	2 N = 3298 (33%)	3 or 4 N = 3298 (33%)	Standardized difference	
	(A)	(B)	(C)	A vs B	A vs C	(A)	(B)	(C)	A vs B	A vs C
Male gender	3981 (44.8%)	3866 (52.7%)	2626 (59.4%)	0.158	0.294	1759 (53.3%)	1759 (53.3%)	1759 (53.3%)	MV	MV
Age ≥ 65 years	3411 (38.4%)	3342 (45.6%)	1710 (38.7%)	0.146	0.005	1530 (46.4%)	1530 (46.4%)	1530 (46.4%)	MV	MV
Clinical profile (MCS) [c]									MV	MV
Milder	6959 (78.4%)	5691 (77.6%)	3658 (82.7%)	0.018	0.110	2707 (82.1%)	2707 (82.1%)	2707 (82.1%)		
Middle	1627 (18.3%)	1474 (20.1%)	704 (15.9%)	0.045	0.064	557 (16.9%)	557 (16.9%)	557 (16.9%)		
More severe	294 (3.3%)	167 (2.3%)	61 (1.4%)	0.063	0.128	34 (1.0%)	34 (1.0%)	34 (1.0%)		
Number of contacts (mean [SD]	94 [77]	111 [88]	103 [81]	0.206	0.114	105 [80]	105 [81]	108 [85]	MV	MV
Medications [c]										
Antiplatelet	1875 (21.1%)	1824 (24.9%)	989 (22.4%)	0.089	0.030	789 (23.9%)	773 (23.4%)	764 (23.2%)	0.011	0.018
Digitalis glycosides	128 (1.4%)	107 (1.5%)	41 (0.9%)	0.001	0.048	39 (1.2%)	46 (1.4%)	41 (1.2%)	0.019	0.006
Organic nitrates	234 (2.6%)	205 (2.8%)	92 (2.1%)	0.010	0.037	100 (3.0%)	82 (2.5%)	96 (2.9%)	0.033	0.007
Antiarrhythmics	123 (1.4%)	128 (1.8%)	57 (1.3%)	0.029	0.008	41 (1.2%)	46 (1.4%)	30 (0.9%)	0.013	0.032
Anti-hypertensive drugs	4161 (46.9%)	4145 (56.5%)	2371 (53.6%)	0.195	0.135	1923 (58.3%)	1928 (58.5%)	1916 (58.1%)	0.003	0.004
Lipid lowering agents	1541 (17.4%)	1898 (25.9%)	1031 (23.3%)	0.208	0.148	800 (24.3%)	859 (26.1%)	824 (25.0%)	0.041	0.017
Antidepressants	764 (8.6%)	726 (9.9%)	352 (8.0%)	0.045	0.023	325 (9.9%)	296 (9.0%)	295 (8.9%)	0.030	0.031
NSAIDs	1783 (20.1%)	1794 (24.5%)	1026 (23.2%)	0.106	0.076	842 (25.5%)	802 (24.3%)	815 (24.7%)	0.028	0.019
Anti-gout drugs	323 (3.6%)	340 (4.6%)	155 (3.5%)	0.050	0.007	138 (4.2%)	150 (4.6%)	115 (3.5%)	0.018	0.036
Drugs for COPD	882 (9.9%)	805 (11.0%)	416 (9.4%)	0.034	0.018	311 (9.4%)	318 (9.6%)	324 (9.8%)	0.007	0.013
Comorbidities [c]										
Cancer	376 (4.2%)	268 (3.7%)	125 (2.8%)	0.030	0.076	73 (2.2%)	65 ((2.0%)	70 (2.1%)	0.007	0.070
Ischemic heart disease	269 (3.0%)	283 (3.9%)	148 (3.4%)	0.046	0.018	101 (3.1%)	121 (3.7%)	100 (3.0%)	0.044	0.087
Cerebrovascular disease	272 (3.1%)	178 (2.4%)	81 (1.8%)	0.039	0.080	66 (2.0%)	62 (1.9%)	57 (1.7%)	0.012	0.054
Heart failure	172 (1.9%)	99 (1.4%)	44 (1.0%)	0.046	0.078	40 (1.2%)	26 (0.8%)	35 (1.1%)	0.015	0.043
Respiratory disease	458 (5.2%)	311 (4.2%)	126 (2.9%)	0.043	0.118	62 (1.9%)	72 (2.2%)	46 (1.4%)	0.031	0.037
Kidney disease	75 (0.8%)	36 (0.5%)	10 (0.2%)	0.043	0.085	14 (0.4%)	16 (0.5%)	8 (0.2%)	0.014	0.006

MV: matching variable; MCS: Multisource comorbidity score; NSAIDs: Non-steroidal anti-inflammatory drugs; COPD: chronic obstructive pulmonary disease.

[a] Original (unmatched) cohort members who met inclusion criteria (N = 20,635) and 1:1:1 matched cohort members (N = 3298*3 = 9894) were considered, the latter being investigated to take into account for differences in gender, age at baseline, and MCS and number of contacts with NHS services measured in the 3-year period before cohort entry.

[b] A score of increasing adherence with selected recommendations (controls for lipid profile, serum creatinine, glycated haemoglobin, urine albumin excretion) was developed by categorizing each cohort member according whether none or almost none (0 or 1), just some (2) or all or almost all (3 or 4) recommendations were followed within the first year of follow-up.

[c] According to drug dispensed or hospital admission occurred in the 3-year period before cohort entry.

nitrates, the presence of cancer and kidney disease were associated with poorer adherence.

Clinical outcomes

Matched cohort members accumulated 75,492 person-year (PY) of follow-up and experienced 61 hospital admissions for brief-term diabetes complications (incidence rate, 0.8 cases every 1000 PY), 398 uncontrolled diabetes (5.0 every 1000 PY), 2490 long-term outcomes (32.9 every 1000 PY), and 41 non-traumatic lower limb amputation (0.5 every 1000 PY). The first hospital admission for one of these reasons (i.e., the composite outcome of interest) involved 2679 cohort members with an incidence rate of 35.5 cases every 1000 PY.

Adherence → clinical outcome association

During a period of four years, 86%, 87% and 88% of matched-cohort members belonging to the poor, intermediate and high adherence category had not yet experienced the outcome of interest, respectively (Fig. 1). The corresponding average time free from complications was 1349, 1362 and 1372 days. This means that, compared with patients with poor adherence, the delay in outcome occurrence was of 13 days (95% CI, −2 to 27 days), and 23 days (95% CI, 9−38 days) among those with intermediate and high adherence, respectively.

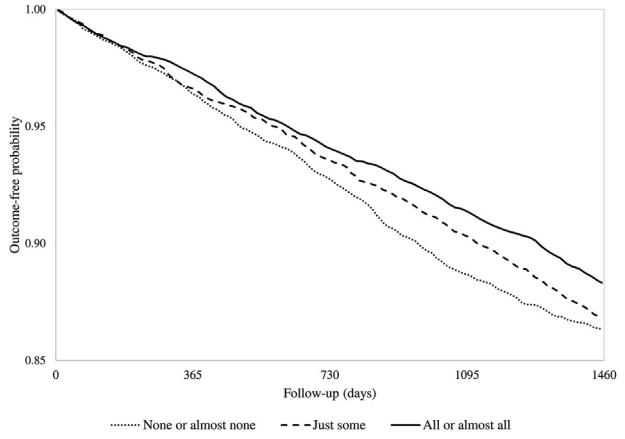

Figure 1 Time-free-to-complications among matched cohorts differentiated according to whether none or almost none, just some or all or almost all recommendations were followed. Footnote. A score of increasing adherence with selected recommendations (controls for lipid profile, serum creatinine, glycated haemoglobin, urine albumin excretion) was developed by categorizing each cohort member according whether none or almost none (0 or 1), just some (2) or all or almost all (3 or 4) recommendations were followed within the first year of follow-up. A cohort member was considered to experience the outcome whether during follow-up at least one hospital admission occurred with primary or secondary diagnosis, or correlated procedures, of brief-term diabetes complications, uncontrolled diabetes, long-term vascular outcomes, or no traumatic lower limb amputation. The date of first hospitalization with one of these diagnoses was considered as the date of outcome onset.

Adherence → costs association

During a period of five years, a progressive reduction of the healthcare costs with increasing levels of adherence with recommendations was observed, the costs for poor, intermediate and high adherence being 1551, 1497 and 1474 Euros respectively (Table 2). Costs for drug dispensed and outpatient services increased with increasing levels of adherence (respectively from 395 to 457 Euros, and from 367 to 400 Euros). However, these cost increases were compensated by a reduction of costs for inpatient services (from 789 to 617 Euros) making adherence economically convenient for NHS.

Cost-effectiveness profile

The ICER values indicated an average gain of 18 Euros and 15 Euros for each day free from diabetic complication by an increase in adherence respectively from poor to intermediate and from poor to high (Fig. 2). The ICER value was suggestive of both clinical effectiveness (delay in diabetic complications with increasing adherence) and negative costs (monetary gain with increasing adherence) respectively in 77% and 92% of the 1000 bootstrap replications.

The cost-effectiveness profile was strongly affected by the patient's clinical complexity (Fig. 3). Indeed, although the ICER values suggested that enhancing adherence from poor to high adherence always increased average clinical effectiveness and monetary gain, this occurred in 90%, 67% and 100% of the 1000 bootstrap replications among cohort members with milder, middle and more severe clinical profile respectively. In other terms, the worse was the clinical profile, the better was the cost-effectiveness of enhancing adherence.

Table 2 Average annual healthcare cost (Euros) per patient according to adherence with recommendations.

	Adherence with recommendations[a]		
	Poor	Intermediate	High
Hospitalizations for diabetic complications	273	245	214
Hospitalizations for other causes	516	476	403
Antidiabetic agents	52	65	85
Other drugs	343	348	372
Diabetes-related outpatients services	17	25	34
Other outpatients services	350	338	366
Total costs	1551	1497	1474

[a] score of increasing adherence with selected recommendations (controls for lipid profile, serum creatinine, glycated haemoglobin, urine albumin excretion) was developed by categorizing each cohort member according whether none or almost none (0 or 1), just some (2) or all or almost all (3 or 4) recommendations were followed within the first year of follow-up.

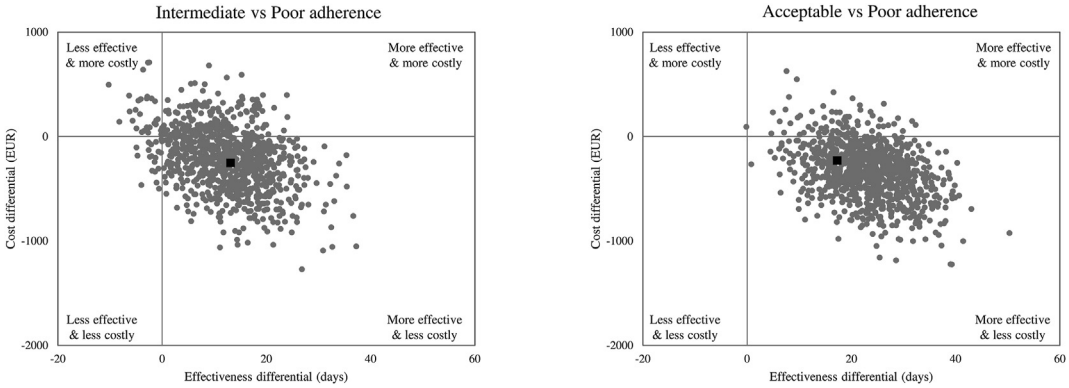

Figure 2 ICER scatterplot comparing patients with intermediate and high adherence with respect to those with poor adherence. Footnote. A score of increasing adherence with selected recommendations (controls for lipid profile, serum creatinine, glycated haemoglobin, urine albumin excretion) was developed by categorizing each cohort member according whether none or almost none (0 or 1), just some (2) or all or almost all (3 or 4) recommendations were followed within the first year of follow-up. Costs were calculated from the amount that the Regional Health Authority reimbursed to health providers. Time free from complications was calculated by means of the restricted mean survival time. The incremental cost-effectiveness ratio (ICER) was measured by dividing the differences in healthcare costs and health-related outcomes between two matched cohorts (i.e., between intermediate and poor adherence cohorts, as well as high and poor adherence ones). Non-parametric bootstrap method based on 1000 re-samples was used to explore the uncertainty in the estimates of cost-effectiveness.

Findings robustness

The cost-effectiveness profile varied in several sensitivity analyses but on average it remained in the quadrant with negative costs and positive effectiveness when adherence categorization was modified (21 days of hospital admission delay, 68 Euros of monetary gaining), by looking at the 2007 cohort (40 days of hospital admission delay, 405 Euros of monetary gaining) and by adopting a 1:1 HDPS matching design (15 days of hospital admission delay, 245 Euros of monetary gaining, supplementary Figure S1).

Discussion

The present study confirms previous observations that guidelines for the management of diabetes are not often followed in 'real-life' practice [33], and that this is definitively the case in the Italian setting [34]. It further provides, however, three new findings. First, compared to patients who did not receive any or almost any clinical evaluation recommended by guidelines at the time of diagnosis, those who adhered to all or almost all the guidelines recommendations exhibited on average almost one month delay in hospital admission for diabetes complications. Second, adherence with the clinical evaluations recommended by guidelines showed benefits not only for patients, but also for the health care system [35]. Indeed, based on our data, if all patients adhered to recommended clinical evaluations, from 233 to 338 Euros per patient could be saved over a period of five years. This result is in line with previous observations which show that the increase in costs for outpatient services is compensated by a reduction of costs for inpatient services [17]. Third, although the cost saving extended to patients with all degrees of clinical complexities, the economic benefit was much greater for

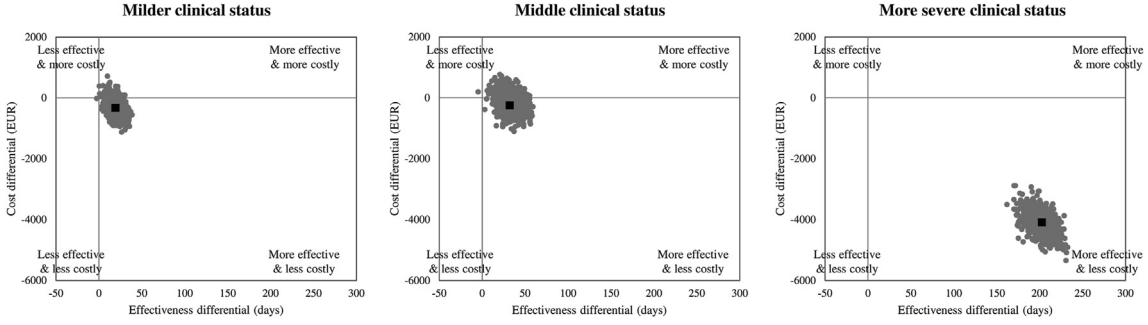

Figure 3 ICER scatterplot comparing patients with high adherence with respect to those with poor adherence according to clinical profile. Footnote. A score of increasing adherence with selected recommendations (controls for lipid profile, serum creatinine, glycated haemoglobin, urine albumin excretion) was developed by categorizing each cohort member according whether none or almost none (0 or 1), just some (2) or all or almost all (3 or 4) recommendations were followed within the first year of follow-up. Costs were calculated from the amount that the Regional Health Authority reimbursed to health providers. Time free from complications was calculated by means of the restricted mean survival time. The incremental cost-effectiveness ratio (ICER) was measured by dividing the differences in healthcare costs and health-related outcomes between two matched cohorts (i.e., between intermediate and poor adherence cohorts, as well as high and poor adherence ones). Non-parametric bootstrap method based on 1000 re-samples was used to explore the uncertainty in the estimates of cost-effectiveness. Patients' clinical status was assessed by the Multisource Comorbidity Score (MCS), a new index derived from inpatients diagnostic information and outpatient drug prescriptions. Three categories of clinical profile were defined: milder (MCS = 0), middle ($1 \leq MCS \leq 2$) and more severe ($3 \leq MCS \leq 4$).

patients with more severe than for those in the mild and intermediate clinical complexity categories, the saving associated with adherence with guidelines recommendations being 4115 Euros rather than the 330 euros calculated for less complicated patients. Thus, protection of patients with diabetes depends not only on adherence with treatment recommendations, but also on appropriate evaluation at initial visits which is essential for the design of a plan for continuing care that make adherence with the entire management strategies clinically important. Of considerable interest is also that a greater adherence with recommended medical examinations does not lead to increased healthcare costs, but on the contrary, it allows a cost saving by reducing hospitalizations, whose costs in patients with greater clinical complexities are considerable.

In patients with diabetes, routine evaluations of glycosylated haemoglobin, lipid profile, serum creatinine and urinary albumin are recommended by all guidelines [21,22]. Consistently with other reports [9,36], we found a wide gap between these guidelines-driven recommendations and their clinical implementation in real life. This is exemplified by the observation that in only 32% of the patients, glycosylated haemoglobin was controlled twice a year as recommended by guidelines, while just a bit more than one in five patients with diabetes adhered to all or almost all the recommended examinations. This finding is of particular concern because nearly one fifth of participants had a history of hospitalization for cardiovascular disease while three out of five patients had comorbidities associated to an increased risk of mortality.

Several factors affect adherence to the recommended examinations. Among those related to the patient, our study identified the demographic and clinical predictors of adherence. For example, male sex, older age, a good clinical profile, and some prescribed drugs (antihypertensive agents, lipid-lowering drugs and NSAIDs) are the main predictors of high adherence. However, previous studies found that also the healthcare system affects the monitoring of diabetes patients in several ways. First, patients who are closely followed by their primary care physician show higher adherence to the recommended examinations [37]. Second, the primary care physician is as highly involved in the carrying out of these examinations as the patient, and previous studies identified the physician's characteristics associated with the implementation of these measures (e.g., the number of patient encounters per unit time, the practice experience) [38]. Finally, the presence of a structured chronic care model has shown to improve the overall adherence to clinical guidelines [39]. Future studies should shed light on how these components affect the implementation of the recommended examinations and which interventions would increase compliance with guidelines.

Few and inconsistent reports are available on the relationship between adherence with individual recommendations and clinical outcomes [40–43]. The inconsistency is likely to originate from the difficulties inherent to the systematic uncertainty of observational evaluations such as the impact on the evaluations of adherence misclassification and the effect of unmeasured confounding. In fact, patients who had more severe diabetes (i.e., those more likely to experience an outcome) could be more carefully treated by the NHS service (thus generating a differential misclassification), but also to be more adherent to guidelines recommendations (thus generating an unmeasured confounding).

However, rather than each individual recommendation, the number of recommendations as a whole may offer a better marker of the quality of care for patients with diabetes in 'real-life' practice. We showed that the better was the adherence with recommendations, the higher were the costs for medications and outpatient services, with a concomitant reduction in the incidence and costs for inpatients services. This suggests that progression of diabetes might be mitigated by structured care, of which adherence to the timing and type of the recommended clinical examinations might serve as a proxy. However, the latter sentence is a speculation not directly investigated in our study. The effect of the continuity of care of chronic patients, including those with type 2 diabetes [44], is a topic of great interest that deserves to be extensively explored.

Our study has several strengths. First, the study was based on a very large unselected population, which was made possible because in Italy the healthcare system is free or almost free of cost for virtually all citizens. Second, both the hospital and outpatient data included in the database are accurate because all services claimed by the health providers to obtain reimbursement by the Regional Health Authority are checked, and incorrect reports may have legal consequences. Third, the adopted incident users design reduced the potential for selection bias [45]. Finally, the consistency of estimates provided by sensitivity analyses is in favour of the robustness of our findings.

There are also some limitations that need to be taken into account. One, epidemiological considerations as well as the age of our patients make our data representative of type 2 diabetes. Nevertheless, a limited number of patients with type 1 diabetes was presumably also included. Whether in this subgroup the relationship between adherence with recommended clinical evaluations and outcome was different from the overall diabetic population cannot be determined by our results.

Two, although our figure on the incidence of diabetes (4.5 cases of every 1000 PY) was within the range of the worldwide figures (from 2 to 7 cases every 1000 PY in Ireland and USA respectively [46,47]), the accuracy of detection of type 2 diabetes in Italy has been questioned by a recent survey [48]. In addition, because patients with undetected diabetes have been shown to be less adherent than those who were detected [48], overall adherence with clinical recommendations may be worse than the one found in our cohort.

Three, adherence misclassification may affect our findings in several ways. The above-mentioned Italian survey showed that administrative data and medical records had a good concordance in detecting patients who adhered to microalbuminuria, glycated haemoglobin, lipid profile and creatinine examinations [48]. However, adherence during the first year after the patient was taken-in-care was

considered as a proxy of the adherence during follow-up, which may not be invariably the case. For example, patients with diabetes who initially followed recommendations might be less carefully controlled afterwards. It has been however speculated that the initial period after diagnosis of type 2 diabetes may be critical not only for early but also for pronged glycaemic as well as for the chance of the application of lifestyle measures such as weight-loss interventions [49,50].

Four, outcome misclassification can also not be excluded. For example, incorrect diagnostic codes might be opportunistically used for receiving higher reimbursement from the Regional Health Authority. Yet, only complications of diabetes requiring hospital admission were captured by our study, so that our conclusions should be limited to severe adverse outcomes.

Five, adherence with pharmacological therapy (i.e. to antidiabetic agents) was not taken into account in our analysis. However, as high costs for drug therapy were observed for patients on better adherence, we could speculate that a portion of the benefits observed in these patients may be attributed to the unobserved better adherence with antidiabetic drugs, of which the considered clinical examinations should be considered a proxy.

Finally, because patients with more frequent examinations as recommended by guidelines are expected to have different clinical features than those with rarer examinations, our results could be affected by confounding by indication. That is, the reduction in diabetes-related hospitalization associated with better adherence might have been generated by uncontrolled factors, accompanying but different from adherence. To minimize the potential for residual confounding, we employed multiple approaches, including use of HDPS matching design. This does not entirely avoid the problem of confounding, one aspect of which is that because adherence may be a surrogate for overall health-seeking behaviour, more adherent patients might also have more regularly followed healthy lifestyle advices and treatment indications [51].

Conclusions

Because benefits for patients and health care system are expected from improving adherence with guidelines-driven recommendations, tight control of patients with diabetes through regular clinical examinations must be considered the cornerstone of national guidance, national audits, and quality improvement incentives schemes.

Contributors

GC contributed to the initial study idea, study concept and design, interpretation of the results, and drafting of the manuscript. FR was responsible for the preparation of the dataset for the analysis, data analysis and review of the manuscript. GM and GP contributed to the interpretation of results under their clinical perspective and to review the manuscript. LM was responsible for data integrity, contributed to abstracting data and authorized their use. NM and SC supervised the project, contributed to the interpretation of results and to review the manuscript. FC contributed to the initial study idea and review the manuscript. All authors read and approved the final manuscript.

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Patient consent for publication

Not required.

Data availability statement

The data that support the findings of this study are available from Lombardy Region, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the Lombardy Region upon reasonable request.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Declaration of competing interest

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Other authors declare that they have no conflict of interest to disclose.

Appendix

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2021.07.014.

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