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Article

Article

Effectiveness of adherence to recommended clinical examinations of diabetic patients in preventing diabetes-related hospitalizations

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Abstract

Objective: To validate a set of indicators for quality of diabetes care through their relationship with measurable clinical outcomes.
Design: A retrospective cohort study was carried out from 2010 to 2015.
Setting: Population-based study. Data were retrieved from healthcare utilization databases of three Italian regions (Lombardy, Emilia Romagna and Lazio) on the whole covering 20 million citizens.
Participants: The 77 285 individuals who were newly taken in care for diabetes during 2010 entered into the cohort.
Interventions: Exposure to selected clinical recommendations (i.e. periodic controls for glycated hemoglobin, lipid profile, urine albumin excretion, serum creatinine and dilated eye exams) was recorded.
Main outcomes measures: A composite outcome was employed taking into account hospitalizations for brief-term diabetes complications, uncontrolled diabetes, long-term vascular outcomes and no traumatic lower limb amputation. A multivariable proportional hazards model was fitted to estimate hazard ratio, and 95% confidence intervals (CI), for the exposure-outcome association.
Results: Among the newly taken in care patients with diabetes, those who adhered to almost none (0 or 1), just some (2 or 3) or almost all (4 or 5) recommendations during the first year after diagnosis were 44%, 36% and 20%, respectively. Compared patients who adhered to almost none recommendation, significant risk reductions of 16% (95% CI, 6–24%) and 20% (7–28%) were observed for those who adhered to just some and almost all recommendations, respectively.

Conclusions: Tight control of patients with diabetes through regular clinical examinations must to be considered the cornerstone of national guidance, national audits and quality improvement incentives schemes.

Key words: diabetes, healthcare utilization database, population-based cohort study, recommendations, periodic examinations, composite outcome

Introduction

Evidence exists that microvascular and cardiovascular complications may be appreciably reduced in patients with type 2 diabetes when multifactorial, intensive lifestyle modifications are implemented [1]. Accordingly, evidence-based clinical practice guidelines have been published [2–4], with specific recommendations for managing patients with type 2 diabetes. Nevertheless, studies investigating the success of guidelines on the management of diabetes have shown that treatment goals are often not met in 'real-life' practice, and implementation of strategies preventing the onset of complications in patients with type 2 diabetes remains suboptimal [5–7].

Several initiatives have been implemented for monitoring the quality of care for patients with diabetes in 'real-life' practice, while controlling costs [8–11]. The Diabetes Quality Improvement Project (DQIP), which was designed to influence the care of patients with diabetes from the USA [12], developed a set of indicators for monitoring care quality. Among these, the so-called accountability indicators consisting in verifying the percentage of diabetic patients who regularly receive clinical evaluations (e.g. glycaemic and lipid profiles, kidney functioning and dilated eye exams) are focused to compare health systems and plans or providers [9]. Although improvements in the process of diabetes care have been documented though these indicators, their effectiveness is largely untested [13–15], making evaluation essential.

According to the Italian Constitution, responsibility for guaranteeing citizens' health is shared by the Central Government and every of the 21 administrative units (19 regions and 2 autonomous provinces), so justifying the need of the first for comparing quality of care supplied by the latter. Accordingly, a system for assessing integrated care pathways across different levels for specific clinical conditions is on developing by a National expert working group of the Italian Health Ministry. In developing the system of indicators, particular attention was taken to what was actually measurable by, and comparable between, the Italian regions.

Taking inspiration by the above-mentioned DQIP accountability indicators, the working group developed a set of process indicators for quality of diabetes care. Because a better process profile, as measured by these indicators, not necessarily translate into better outcomes, a study for validating the set of indicators through their relationship with measurable clinical outcomes was designed. The current paper reports methods and main findings of the validation study, and discusses the implications of monitoring the process of diabetes care and, more in general, of the proposed approach.

Methods

Data sources

This study is based on computerized healthcare utilization databases from three Italian regions (Lombardy, Emilia Romagna and Lazio). Overall, these data covered almost 20 million beneficiaries of the Italian National Health Service (NHS), nearly one-third of the entire Italian population.

All Italian citizens have equal access to healthcare services as part of the NHS. Information systems of healthcare utilization databases exist within each of the 21 Italian administrative units to collect a variety of information, at least including: (1) an archive of residents who receive NHS assistance (the whole resident population), reporting demographic and administrative data, other than the dates in which the individual started (because he/she was born or immigrated) or stopped (because he/she died or emigrated) the condition of NHS beneficiary; (2) a database on hospital discharge records including information about primary diagnosis, co-existing conditions and performed procedures (coded according to the ICD-9 CM classification system); (3) a drug prescription database providing information on all community drugs reimbursed by the NHS (coded according to the Anatomical Therapeutic Chemical (ATC) classification system); (4) a database on outpatient visits, including visits in specialist ambulatories and diagnostic laboratories accredited from the NHS and (5) a database on co-payment exception for diagnosed chronic disease, including diabetes. As a unique identification code was used for all databases within each region, their record linkage allowed searching out the complete care pathway of beneficiaries of NHS. In order to preserve privacy, identification codes were automatically converted into anonymous codes, and the inverse process was prevented by deletion of the conversion table.

Harmonization and data processing

Although databases did not substantially differ across all regions for several aspects, a between regions data harmonization was performed, thus allowing data extraction processes to be targeted the same semantic concepts (e.g. information were uniformly encoded by using the same names, values and formats). Anonymized data were extracted and processed locally by using a common Statistical Analysis System program which was developed by one of ours (FR) according to protocol previously approved by the Italian Health Ministry working group.

Diagnostic and therapeutic codes used in the current study for drawing records and fields from databases are reported in Supplementary Table S1.

Capturing 'prevalent' and 'incident' diabetic patients

Beneficiaries of the NHS who in the index year (i.e. in 2014) had aged 18 years or older and were resident in three Italian regions (Lombardy, Emilia Romagna and Lazio) formed target population. With the aim of ensuring enough time back for capturing diabetic patients, subjects were excluded if they were recorded as beneficiaries of the regional NHS after the year 2011.

Subjects belonging to the target population were considered prevalent diabetic patients if they left 'footprints' of diabetes through supplied services from the NHS within a specified time-window. In particular, NHS beneficiaries who (i) from 2012 until 2014 had at least two prescriptions of antidiabetic agents in two distinct dates over 365 days, and/or (ii) in the same time-window experienced at least one hospital admission with primary or secondary diagnosis of diabetes, and/or (iii) in the year 2014 took advantage on co-payment exemption for diabetes, were considered to be affected by diabetes (i.e. prevalent cases). Among these latter, those who during the period 2011 until 2013 did not experience any specific drug prescription, hospital admission and co-payment exemption were considered newly taken in care for diabetes (i.e. incident cases).

Diabetes prevalence and incidence rates were separately calculated for each participant region and for the whole population of all the regions taken together. Rates were standardized (direct method) according to gender and 20-year intervals of age of the Italian population. Between-region differences in prevalence and incidence rates were evaluated by testing the null hypothesis of homogeneity.

Incident cohort features and follow-up

In order to have enough time to appreciate the effect of adherence to recommendations on the selected outcomes (see below), subjects who were detected as incident diabetic patients during 2010 were included in the study cohort: in other words, the clock was brought back 4 years with respect to the above reported time interval used for detecting incident diabetic patients.

Baseline characteristics of cohort members (i.e. those recorded at the date of cohort entry or during the previous 3 years) included gender, age, drug therapies and comorbidities. Drug therapies included antiplatelet, digitalis glycosides, organic 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 measured through previous hospitalizations for cancer, heart failure, and ischemic heart, cerebrovascular, respiratory and kidney disease. In addition, the so-called Multisource Comorbidity Score, a new comorbidity index obtained from both inpatients diagnostic information and outpatients drug prescriptions, and recently validated using data from the here considered Italian regions [16], was considered.

Cohort members accumulated person-years of follow-up starting from the date of cohort entry until the occurrence of one of the following events, whichever came first: the study outcome (hospital admission for selected diagnoses, see below), death, emigration, or end-point of follow-up, i.e. 31 December 2015.

Adherence to recommendations

Outpatient visits, including assessments of glycated hemoglobin, lipid profile (total and HDL cholesterol and triglycerides), urine albumin excretion, serum creatinine and dilated eye exams dispensed to cohort members during follow-up were identified. A patient was considered adherent to recommendations whether he/she every year was submitted to at least two glycated hemoglobin assays, and at least one of the other evaluations [17, 18].

Other than for each individual recommendation, the cumulative number of recommendations was calculated. A score of increasing adherence was developed by categorizing each cohort member according whether almost none (0 or 1), just some (2 or 3) or almost all (4 or 5) recommendations were followed in a given year.

Outcome

A composite outcome was developed to take into account complications of diabetes potentially avoidable. 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: (i) brief-term diabetes complications, (ii) uncontrolled diabetes, (iii) long-term vascular outcomes and (iv) no traumatic lower limb amputation (ICD-9 CM codes used for capturing outcomes are reported in Supplementary Table S1). The date of first hospitalization with one of these diagnoses was considered as the date of outcome onset.

Association between adherence and outcome

We used the following two-stage procedure for generating pooled meta-analytic estimates of adherence–outcome association.

In the first stage, a Cox proportional hazard regression model was fitted within each participant region for separately estimating the hazard ratio (HR) and its 95% confidence interval (CI), for the association between adherence to each recommendation taken individually, as well as to the total adherence score, and the risk of experiencing the outcome. Adjustments were made for above listed covariates (i.e. gender, age, drug therapies, comorbidities and Multisource Comorbidity Score). A time-dependent covariate was built by considering the adherence to recommendations experienced during the 1-year period before each risk set forms itself up, i.e. by the patient who experience the outcome at a given moment of the follow-up (case) and the cohort members who until then have not experienced it, having accumulated the same observation period of the case. In this way, the brief-term effect of adherence on the outcome onset (close adherence) was investigated. However, as more careful and frequent evaluations might be requested because of worsening clinical profile, we realized that a paradoxical positive adherence–outcome association might be observed by considering adherence so close to the outcome. To account for such a bias, which can be considered a form of protopathic bias [19], a time-dependent adherence delayed of 1 year with respect to the close adherence was also considered (delayed adherence).

In order of obtaining the summarized adherence–outcome relationship estimate, in the second stage a random effect meta-analysis [20] was performed for combining the HRs obtained from the considered regions. Between-region heterogeneity was tested by Cochran's *Q* test and measured with the I^2 statistics, that is the proportion of between-region variability due to heterogeneity [21].

For all hypotheses tested, two-tailed *P*-values <0.05 or, in an equivalent manner, 95% CI of HR that does not contain the value expected under the null hypothesis was considered significant.

Results

Prevalent and incidence diabetic patients

Table 1 shows that, among the nearly 16 million NHS beneficiaries forming the whole target population, 1 139 043 and 76 490 subjects, respectively, met our algorithm for capturing prevalent and incident diabetic patients in the year 2014, being the corresponding standardized rates 6.7 diabetic patients every 100 persons and 4.5 new diabetic patients every 1000 person-year. There was evidence that prevalence and incidence standardized rates significantly differed between regions, being higher rates observed for the population from Lazio.

Baseline characteristics of the cohort of 77 285 patients newly taken in care during 2010 are shown in Table 2. At baseline, more than one-half of cohort members were men, almost one-third of them were aged 70 years or older, most patients had signs of

Table 1 Diabetes prevalence (patients who in the index year and/or in the previous 2 years left 'footprints' of disease presence) and incidence (newly taken in care patients) among beneficiaries of the National Health Service (NHS) of three Italian regions

	Lombardy	Emilia Romagna	Lazio	Total
NHS beneficiaries aged 18 years or older[a]	8 277 623	3 734 707	4 902 165	16 914 495
All known diabetic patients (prevalent)[b]	516 547	256 670	365 826	1 139 043
Prevalence rate (every 100 persons)				
Crude	6.2	6.9	7.5	6.7
Standardized	6.2	6.6	7.7	6.7
Newly taken in care diabetic patents (incident)[c]	37 462	15 904	23 124	76 490
Incidence rate (every 1000 PY)				
Crude	4.5	4.3	4.7	4.5
Standardized	4.4	4.1	4.8	4.5

[a]Subjects who were NHS beneficiaries from <3 years were excluded.

[b]Subjects were considered prevalent cases of diabetes whether in the current year and/or in the previous 2 years had at least (i) two prescriptions of antidiabetic drugs in two distinct dates, and/or (ii) a hospital admission with primary or secondary diagnosis of diabetes; and/or those who in the current year (iii) took advantage on exemption to pay health service for diabetes.

[c]Subjects were considered incident cases of diabetes whether in the current year had at least (i) two prescriptions of antidiabetic drugs in two distinct dates, and/or (ii) a hospital admission with primary or secondary diagnosis of diabetes; and/or those who in the current year (iii) obtained for the first time the exemption to pay health service for diabetes; among these patients, those who in the 3 years before current had at least a prescription of antidiabetic drugs and/or a hospital admission with primary or secondary diagnosis of diabetes; and/or those who already had the exemption for diabetes, were excluded.

Table 2 Baseline characteristics of diabetic patients newly taken in care (incident cases) in three Italian regions

	Lombardy	Emilia Romagna	Lazio	Total
Male gender	18 987 (54.5%)	9225 (53.4%)	12 353 (49.1%)	40 565 (52.5%)
Age (years)				
18–30	547 (1.6%)	314 (1.8%)	760 (3.0%)	1621 (2.1%)
31–50	5472 (15.7%)	2778 (16.1%)	4313 (17.2%)	12 563 (16.3%)
51–70	17 759 (50.9%)	7654 (44.3%)	12 063 (48.0%)	37 476 (48.5%)
70–90	10 624 (30.5%)	6210 (36.0%)	7755 (30.8%)	24 589 (31.8%)
>90	460 (1.3%)	317 (1.8%)	259 (1.0%)	1036 (1.3%)
Medications[a]				
Antiplatelet	10 005 (28.7%)	4386 (25.4%)	8297 (33.0%)	22 688 (29.4%)
Digitalis glycosides	1265 (3.6%)	453 (2.6%)	1052 (4.2%)	2770 (3.6%)
Organic nitrates	2267 (6.5%)	653 (3.8%)	1641 (6.5%)	4561 (5.9%)
Antiarrhythmics	1099 (3.2%)	272 (1.6%)	856 (3.4%)	2227 (2.9%)
Blood-pressure lowering agents	20 651 (59.2%)	7837 (45.4%)	16 072 (63.9%)	44 560 (57.7%)
Lipid-lowering agents	7113 (20.4%)	3490 (20.2%)	7730 (30.7%)	18 333 (23.7%)
Antidepressants	3456 (9.9%)	1889 (10.9%)	3089 (12.3%)	8434 (10.9%)
NSAIDs	10 417 (29.9%)	4295 (24.9%)	12 870 (51.2%)	27 582 (35.7%)
Anti-gout drugs	2457 (7.1%)	1147 (6.6%)	1761 (7.0%)	5365 (6.9%)
Drugs for COPD	4254 (12.2%)	2057 (11.9%)	5310 (21.1%)	11 621 (15.0%)
Comorbidities[b]				
Cancer	3474 (10.0%)	1801 (10.4%)	2258 (9.0%)	7533 (9.7%)
Ischemic heart disease	2788 (8.0%)	1426 (8.3%)	1625 (6.5%)	5839 (7.6%)
Cerebrovascular disease	1984 (5.7%)	1138 (6.6%)	1313 (5.2%)	4435 (5.7%)
Heart failure	1551 (4.5%)	1063 (6.2%)	933 (3.7%)	3547 (4.6%)
Respiratory disease	3195 (9.2%)	1888 (10.9%)	1997 (7.9%)	7080 (9.2%)
Kidney disease	938 (2.7%)	601 (3.5%)	574 (2.3%)	2113 (2.7%)
Multisource comorbidity score				
0	21 859 (62.7%)	10 022 (58.0%)	12 783 (50.8%)	44 664 (57.8%)
1	5933 (17.0%)	3476 (20.1%)	6683 (26.6%)	16 092 (20.8%)
2	3630 (10.4%)	1926 (11.2%)	3176 (12.6%)	8732 (11.3%)
3	1367 (3.9%)	758 (4.4%)	1230 (4.9%)	3355 (4.3%)
4	2073 (6.0%)	1091 (6.3%)	1278 (5.1%)	4442 (5.8%)

NSAIDs, non-steroidal anti-inflammatory drugs; COPD, chronic obstructive pulmonary disease.

[a]According to drug dispensed in the three years before the current.

[b]According to hospital admission in the three years before the current.

cardiovascular disorders, mainly because they were in treatment with blood pressure- and lipid-lowering medicaments or previous ischemic heart or cerebrovascular disease or heart failure. Although beneficiaries from Lazio showed lower values of the Multisource Comorbidity Score, they had higher prevalence of drug users.

Adherence to recommendations

During the first year after diagnosis, newly taken in care patients (incident cases) had poor adherence to the considered recommendations, being only 16% of them submitted to dilated eye exam, little bit more than 30% to glycated hemoglobin and urine albumin excretion evaluations, and more than half to lipid profile and serum creatinine assays (Table 3). It is noteworthy that 20% and 44% of newly taken in care diabetic patients respectively adhered to almost all (4 or 5) or almost none (0 or 1) recommendations. Again, there was evidence that patients from Lazio were less adherent than those from Lombardy and Emilia Romagna ($P < 0.001$). Women, patients aged 70 years or older and those with more cotreatments and comorbidities were on average less adherent to recommendations (Table 4).

Table 3 Diabetic patients newly taken in care (incident cases) who during the first year after diagnosis adhered to selected recommendations in three Italian regions

	Lombardy	Emilia Romagna	Lazio	Total
Individual recommendations				
Glycated hemoglobin	13 881 (39.8%)	6349 (36.8%)	5997 (23.8%)	26 227 (33.9%)
Lipid profile	19 297 (55.4%)	9365 (54.2%)	11 575 (46.0%)	40 237 (52.1%)
Urine albumin excretion	11 976 (34.4%)	6565 (38.0%)	4841 (19.3%)	23 382 (30.3%)
Serum creatinine	21 176 (60.7%)	11 000 (63.7%)	14 314 (56.9%)	46 490 (60.2%)
Dilated eye exam	4204 (12.1%)	3888 (22.5%)	3936 (15.7%)	12 028 (15.6%)
Categories of cumulative number of recommendations				
0 or 1	14 015 (40.2%)	6702 (38.8%)	13 249 (52.7%)	33 966 (44.0%)
2 or 3	13 350 (38.3%)	6108 (35.4%)	8309 (33.0%)	27 767 (35.9%)
4 or 5	7497 (21.5%)	4463 (25.8%)	3592 (14.3%)	15 552 (20.1%)

Table 4 Baseline characteristics of diabetic patients according to cumulative number of recommendations

	Cumulative number of recommendations			*P*-trend[c]
	None or almost none (0 or 1) (n = 33 966)	Just some (2 or 3) (n = 27 767)	All or almost all (4 or 5) (n = 15 552)	
Male gender	17 313 (51.0%)	14 583 (52.5%)	8669 (55.7%)	<0.001
Age (years)				
≤70	21 650 (63.7%)	18 492 (66.6%)	11 518 (74.1%)	<0.001
>70	12 316 (36.3%)	9275 (33.7%)	2447 (25.9%)	
Medications[a]				
Antiplatelet	9973 (29.4%)	8553 (30.8%)	4162 (26.8%)	<0.001
Digitalis glycosides	1502 (4.4%)	904 (3.3%)	364 (2.3%)	<0.001
Organic nitrates	2253 (6.6%)	1636 (5.9%)	672 (4.3%)	<0.001
Antiarrhythmics	1085 (3.2%)	817 (2.9%)	325 (2.1%)	<0.001
Blood-pressure lowering agents	19 197 (56.5%)	16 671 (60.0%)	8692 (55.9%)	0.286
Lipid-lowering agents	6773 (19.9%)	7588 (27.3%)	3972 (25.5%)	<0.001
Antidepressants	3839 (11.3%)	3093 (11.1%)	1502 (9.7%)	<0.001
NSAIDs	11 851 (34.9%)	10 385 (37.4%)	5346 (34.4%)	0.512
Anti-gout drugs	2228 (6.6%)	2150 (7.7%)	987 (6.3%)	0.490
Drugs for COPD	5397 (15.9%)	4066 (14.6%)	2158 (13.9%)	<0.001
Comorbidities[b]				
Cancer	4136 (12.2%)	2372 (8.5%)	1025 (6.6%)	<0.001
Ischemic heart disease	2875 (8.5%)	2052 (7.4%)	912 (5.9%)	<0.001
Cerebrovascular disease	2526 (7.4%)	1401 (5.0%)	508 (3.3%)	<0.001
Heart failure	2222 (6.5%)	1011 (3.6%)	314 (2.0%)	<0.001
Respiratory disease	4152 (12.2%)	2065 (7.4%)	863 (5.5%)	<0.001
Kidney disease	1202 (3.5%)	697 (2.5%)	214 (1.4%)	<0.001
Multisource comorbidity score				
0	17 927 (52.8%)	16 248 (58.5%)	10 489 (67.4%)	<0.001
≥1	16 039 (47.2%)	11 519 (41.5%)	5063 (32.6%)	

NSAIDs, non-steroidal anti-inflammatory drugs; COPD, chronic obstructive pulmonary disease.
[a]According to drug dispensed in the three years before the current.
[b]According to hospital admission in the three years before the current.
[c]According to chi-square for the trend.

Outcome

During follow-up, cohort members accumulated 322 645 person-years and experienced 875 hospital admissions for brief-term diabetes complications (incidence rate, 2.4 cases every 1000 person-years (PY)), 4372 uncontrolled diabetes (12.0 every 1000 PY), 18 319 long-term vascular outcomes (55.7 every 1000 PY) and 262 no traumatic lower limb amputation (0.7 every 1 000 PY). The first occurring hospital admission for one of these causes (i.e. the composite outcome of interest) happened for 20 363 cohort members with incidence rate of 63.1 cases every 1000 PY. The first cause of hospitalization for the composite outcome was long-term vascular outcomes (87%), following by uncontrolled diabetes (12%) and brief-term diabetes complications (1%). No patient experience no traumatic lower limb amputation as the first occurring hospital admission among those considered for building the composite outcome. Baseline characteristics of the cohort members who experienced the composite outcome are shown in Supplementary Table S2.

Association between adherence and outcome

Forrest plots for the adherence–outcome relationship for each participant region, as well as for summarizing national data, are shown in Fig. 1. There was evidence than both close and delayed adherence to urine albumin excretion and lipid profile evaluations, exerted protective effect on the outcome occurrence. The protective action for glycated hemoglobin and serum creatinine was better highlighted by the delayed adherence than by the close one. For example, patients who adhered to serum creatinine during the 1-year period before the outcome occurs, had a paradoxical 50% higher risk than those who did not adhere to it during the same time-window. Conversely, adherence to serum creatinine (as well as to glycated hemoglobin) delayed of 1 year, was significantly associated with reduced outcome risk. Although usually significant (with the exception of dilated eye exam), adherence to each individual recommendation was weakly associated with the outcome, being summarized risks of adherent diabetic patients reduced of around 10% or less with respect to no adherent ones. It is noteworthy that there was never evidence of between regions heterogeneity of the estimated delayed adherence–outcome associations.

Figure 2 reports the trend in HRs according to increasing level of delayed adherence within each participant region, as well as for summarizing national data. A clear trend towards decreasing outcome risk as the total adherence score increases was observed for all regions, albeit with between-region differences. According to summarized estimates, compared to patients who adhered to none or almost none recommendation, significant risk reductions of 16% (95% CI, 6–24%) and 20% (7–28%) were observed for those who adhered to just some (2 or 3) and almost all (4 or 5) recommendations, respectively.

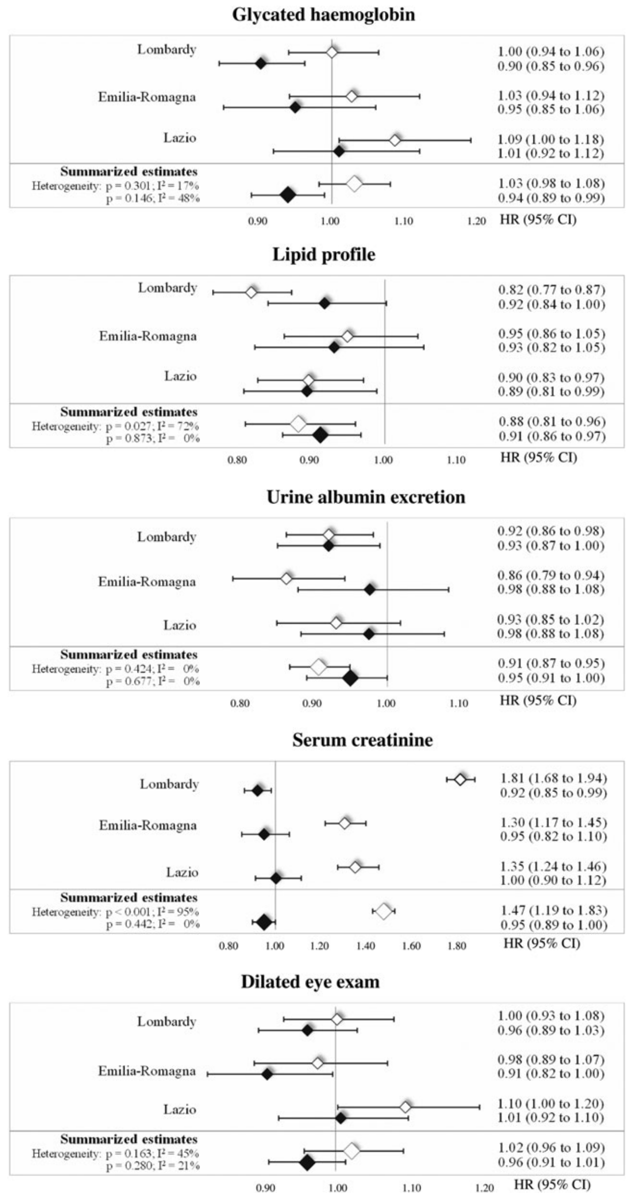

Figure 1 Forest plots of region-specific (smaller diamonds) and summarized (larger diamonds) hazard ratios (HR) for the association between time-dependent close (white diamonds) and delayed (black diamonds) adherence to selected recommendations, and the risk of hospital admission for selected causes, including brief-term diabetes complications, uncontrolled diabetes, long-term vascular outcome, and no traumatic lower limb amputation. Footnote. Adherence to recommendations experienced during the 1-year period before each risk set (close adherence) and delayed of 1 year with respect to the close adherence (delayed adherence) are considered. HR, and 95% confidence intervals (represented by horizontal lines), were estimated by fitting a Cox proportional hazard model. Estimates were adjusted for gender, age and selected medications and comorbidities (please see covariates listed in Table 2). Random effects model was used for summarized estimates. *P*-values and I^2 testing and measuring for heterogeneity between-region estimates are reported.

Discussion

The present study confirms previous observations that guidelines for the management of diabetes are often not met in the 'real-life' practice [9], even in the Italian setting [11]. In addition, evidence of regional variations in the management of diabetes within the same country [22, 23], was confirmed from our study. The new important finding, however, is that diabetic patients who regularly received all or almost all the recommended clinical evaluations had a 20% reduction of the risk of hospitalization for selected outcomes compared to patients who received none, or almost none evaluation. Assuming that these estimates are unbiased, the proportion of complication of diabetes attributable to suboptimal adherence to recommendations was of 9.8%, i.e. nearly 1990 of the 20 363 hospital admissions occurred among cohort members could have been avoided if all they had adhered to the considered recommendations [24]. This

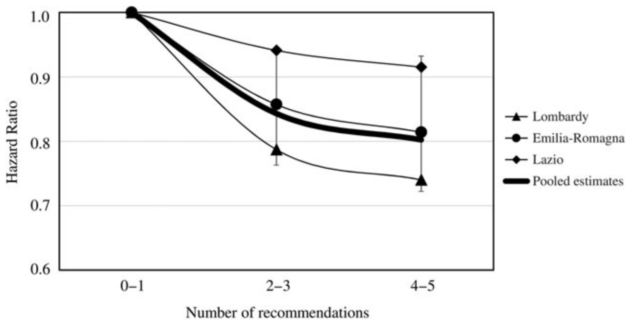

Figure 2 Trends in region-specific and summarized hazard ratios (HR) for the association between categories of total adherence to recommendations and the risk of hospital admission for selected causes, including brief-term diabetes complications, uncontrolled diabetes, long-term vascular outcomes and no traumatic lower limb amputation. Footnote. HR were estimated by fitting a Cox proportional hazard model. Estimates were adjusted for gender, age and selected medications and comorbidities (please see covariates listed in Table 2). Random effects model was used for summarized estimates. Vertical lines represent 95% confidence intervals of summarized HR.

finding is very important for reaching a consensus in how to measure and compare the quality of care of diabetic patients, to develop process improvements, and to reduce practice heterogeneity [11].

Our study was designed under the auspices of the Italian Health Ministry with the aim to obtain a simple tool for appreciating regional variations in the management of patients with diabetes. This implies the availability of good quality data useful for (i) capturing prevalent diabetic patients; (ii) identifying those who are newly taken in care; (iii) characterizing they as far as possible for their features; (iv) outlining their use of recommended clinical services and (v) identifying those who experience relevant clinical outcomes. This was made possible because in Italy, an automated system of databases providing information on essential healthcare, including those for diabetes care, was available in each of the 19 regions for the management of the public funded healthcare system virtually involving all citizens. Because of constraints limiting the free movement of electronic health data even within the same country [25], a two-stage procedure allowing for local data processing and subsequent pooling aggregate data, was adopted. Admitting comparability in data quality, guarantees of privacy respect and estimates accuracy are provided by the procedure [26].

Existing figures pertaining to general adult population showed prevalence rates ranging from 6% (UK) to 8% (USA) [27, 28], and incidence rates ranging from two cases every 1000 PY (Ireland) to seven cases every 1000 PY (USA) [27, 29]. We found prevalence and incidence rates, respectively, being 7% and five cases of every 1000 PY, therefore within the expected range according to the worldwide figures.

Routine laboratory tests of glycosylated hemoglobin, lipid profile, serum creatinine and urinary albumin are recommended for patients with diabetes [17, 18]. Consistently with other reports [30], some of which refer to the Italian setting [31], we found a wide gap between guidelines-driven recommendations and their clinical application. In fact, we observed that only 34% of the included incident diabetic patients controlled at least twice glycosylated hemoglobin, while only 20% of them adhered to all, or almost all, the recommended controls within the first year after they were taken in care. This finding is of particular concern given that (i) nearly one-fifth of participants had a history of major cardiovascular outcomes and three out five of them had comorbidities related to increasing mortality risk and (ii) patients on worse clinical profile, that is the older ones and those with more cotreatments and comorbidities, were less adherent to the recommendations.

Few and inconsistent evidence is available regarding the generally assumed relationship between adherence to recommendations and patient outcomes [32–34]. Inconsistency is likely due to serious difficulties inherent systematic uncertainty of observational evaluations. For example, in our application we found that adherence to recommendations in a given year, particularly to serum creatinine and glycosylated hemoglobin evaluations, was associated with increased risk of outcome. We suspect that protopathic bias might explain this paradoxical finding. In fact, the symptomatic onset of diabetic complications in the outpatient setting (unobserved true outcome) may have led to changing therapeutic regimen and then to increasing clinical evaluations for monitoring its effect. In these conditions, a paradoxical positive association between exposure and detected outcome (hospital admission) could be observed [19]. To address this possibility, a 1-year delayed lag-time period preceding the detected outcome was applied. As suspected, by this stratagem following the considered recommendations were found to exert a protective action on the outcome onset.

We found that rather than with each individual recommendation, the cumulative number of followed recommendations predicted the outcome onset, that is, the higher is its value, the better the protective action on diabetes-related hospitalizations. Among the possible explanations for this finding, the more reasonable is that the speed of diabetes progression might be reduced by structured care of which regular control might be a proxy.

Limitations of the study should be taken into account for correctly interpreting our results. One, as individuals aged less than 18 years were excluded from the considered target population, patients affected by, and taken in care for type 2 diabetes mellitus should have been mainly captured. Nevertheless, we cannot exclude that some patients with type 1 diabetes may have been included. This however, does not modify our main conclusion that diabetics, both type 1 and type 2, should benefit of more careful adherence to recommendations. Two, information about health service outpatient facilities supplied by private organizations are not available from our databases. Three, the length of follow-up might be insufficient to appreciate the effect of disease progression on clinical outcome. Four, adherence to pharmacological therapy (i.e. to antidiabetic agents) was not taken into account in our analysis. However, antidiabetic agents available in the Italian market at the time of our patients' follow-up have shown only modest beneficial effects on macrovascular complications [35–37], which are the main cause of hospital admission among those considered for building the composite outcome. In addition, not all diabetic patients need drug therapy since some of them achieve glycaemic control with diet and exercise alone. Finally, because patients with frequent controls are expected to have different clinical characteristics than those with less intensive examinations, our results could be affected by confounding by indication. That is, the reduction in diabetes-related hospitalization associated with better adherence to recommendations might have been generated by uncontrolled factors, accompanying but different from a better adherence. For example, less frequent controls might had been requested for patients who reached good glycaemic target. However, as the latter are at lower baseline risk of experiencing the outcome, the protective action of regular controls is expected to be higher than that observed in our study. Of course, this does not entirely eliminate the problem of confounding, one aspect of which is that because adherence may be a surrogate for overall health-seeking behavior, patients more adherent might also have more regularly followed healthy lifestyle advices, more effectively treated or dealt with diabetes more frequently as out- rather than in-hospital. Further evidence are thus urgently needed to confirm the protective role of adherence to recommendations among diabetic patients.

Conclusion

In the meantime, because benefits for patients and healthcare system are expected from improving adherence to guidelines-driven recommendations, tight control of diabetic patients through regular clinical examinations must to be considered the cornerstone of national guidance, national audits, and quality improvement incentives schemes.

Supplementary material

Supplementary material is available at *International Journal for Quality in Health Care* online.

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Conflict of interest

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