Nephrol Dial Transplant (2015) 30: 1526–1533
doi: 10.1093/ndt/gfv101
Advance Access publication 16 April 2015

Achievement of therapeutic targets in patients with diabetes and chronic kidney disease: insights from the Associazione Medici Diabetologi Annals initiative

Salvatore De Cosmo[1], Francesca Viazzi[2], Antonio Pacilli[1], Carlo Giorda[3], Antonio Ceriello[4], Sandro Gentile[5], Giuseppina Russo[6], Maria Chiara Rossi[7], Antonio Nicolucci[7], Pietro Guida[8], Paolo Di Bartolo[9], Roberto Pontremoli[2] and the AMD-Annals Study Group

[1]Department of Medical Sciences, IRCCS Casa Sollievo Della Sofferenza, S. Giovanni Rotondo, FG, Italy, [2]Università Degli Studi and IRCCS Azienda Ospedaliera Universitaria San Martino-IST, Genova, Italy, [3]Diabetes and Metabolism Unit, ASL Turin 5, Chieri, TO, Italy, [4]Institut d'Investigacions Biomèdiques August Pii Sunyer (IDIBAPS) and Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Barcelona, Spain, [5]Department of Clinical and Experimental Medicine, 2nd University of Naples, Naples, Italy, [6]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, [7]Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, S. Maria Imbaro, CH, Italy, [8]Associazione Medici Diabetologi, Roma, Italy and [9]Diabetes Unit, ASL Della Romagna, Ravenna, Italy

Correspondence and offprint requests to: Salvatore De Cosmo; E-mail: sdecosm@tin.it

ORIGINAL ARTICLE

ABSTRACT

Background. Chronic kidney disease (CKD) entails a worse cardiovascular outcome. The aim of our work was to study the relationship between CKD and the achievement of recommended targets for glycated haemoglobin (HbA1c), low-density lipoprotein cholesterol (LDL-c) and blood pressure (BP) in a real-life sample of patients with type 2 diabetes mellitus (T2DM).
Methods. We analysed a sample of 116 777 outpatients from the Network of the Italian Association of Clinical Diabetologists; all patients had T2DM and at least one measurement of HbA1c, LDL-c, BP, serum creatinine and albuminuria in the year 2010. The outcome was the achievement of HbA1c, LDL-c and BP values as recommended by International Guidelines.
Results. In the entire sample, the mean value of HbA1c was 7.2 ± 1.2%, of LDL-c was 102 ± 33 mg/dL and of BP was 138/78 ± 19/9 mmHg. CKD and its components were associated with poor glycaemic and BP control, notwithstanding greater use of glucose and BP-lowering drugs, while no association was found with LDL-c values. Factors independently related to unsatisfactory glycaemic control included female gender, body mass index, duration of disease and high albuminuria. Men, older people and those taking statins were more likely to reach LDL-c target levels. Male gender, age and high albuminuria strongly affected the achievement of BP targets.
Conclusions. CKD or its components, mainly high albuminuria, are associated with failure to reach therapeutic targets, especially for HbA1c and BP, despite a greater use of drugs in patients with T2DM.

Keywords: antihypertensive treatment, arterial hypertension, cardiovascular risk factors, diabetic nephropathy, hypercholesterolaemia

INTRODUCTION

The worldwide prevalence of diabetes is expected to reach 552 million subjects by 2030 [1]. Up to 40% of patients with type 2 diabetes mellitus (T2DM) develop some degree of renal impairment over the course of their lifetime [2–4]. The presence of albuminuria and/or the reduction in glomerular filtration rate exert a severely unfavourable impact on patient outcome and contribute significantly to increasing the cost of health care for many national health systems worldwide [5]. Besides being the most prevalent cause of end-stage renal disease in Western countries, chronic kidney disease (CKD) is a well-known risk multiplier and entails a dramatic increase in macrovascular complications [6, 7].

In the past several years it has consistently been shown that glycaemic control as well as a reduction of cholesterol and blood pressure (BP) [8–17] are associated with decreased micro- and

macrovascular complications. As the current therapeutic approach to cardiovascular risk correction is graded and proportional to each patient's individual burden of risk, guidelines for diabetes care recommend reaching specific treatment targets in the presence of renal impairment [18–22].

Large-scale clinical studies however indicate that due to a number of different possible reasons [23, 24], control of risk factors is unsatisfactory in up to 50% of diabetic patients [25–28] and therefore residual risk remains unacceptably elevated. Investigating the residual gaps in quality of care and their relationship with factors which may influence these gaps may prove useful for devising more effective strategies to prevent diabetic complications.

We therefore attempted to investigate the association of CKD and its components with the achievement of recommended therapeutic targets in a large cohort of patients with T2DM attending outpatient diabetes clinics in Italy.

MATERIALS AND METHODS

The Italian health care system

All Italian citizens, regardless of social class or income, are cared for by a general practitioner as part of the National Health System. It is estimated that over three million citizens have been diagnosed with diabetes in Italy. Care for people with diabetes is mainly provided by a public network of about 700 diabetes clinics that provide diagnostic confirmation, therapy, prevention and early diagnosis of complications through close patient follow-up by a team of specialists and schedule regular check-ups. Most patients are referred to these centres by their general practitioner and care is free of charge [29–32].

Patients

In the present report we describe the results of an analysis of a large sample of patients diagnosed with T2DM who were followed-up at 294 diabetes centres in Italy. The analysis was performed using the data set of electronic medical records that were collected between 1 January 2010 and 31 December 2010. The centres involved in this study include about one-third of all the Italian centres for diabetes, homogeneously distributed throughout the country and therefore representative of the Italian population suffering from T2DM.

Starting from a population of 510 247 patients with T2DM, we identified a sample of 116 777 outpatients aged 18 years or older with complete data for albuminuria, serum creatinine, low-density lipoprotein cholesterol (LDL-c), HbA1c and BP. In cases of multiple records collected during the year for the same patient, the last available visit was included. Information on the presence of diabetic retinopathy was also available. Demographic and clinical characteristics of patients included and excluded were similar, in particular with regard to the prevalence of subjects reaching therapeutic targets for HbA1c, LDL-c and BP (50 versus 51%, 50 versus 47% and 45 versus 45%, respectively).

Data collection

As already reported [28–31], the analysis of the database is an attempt by the Italian Association of Clinical Diabetologists (Associazione Medici Diabetologi, AMD; see Supplementary Data) to identify a set of indicators that can be used in the context of continuous quality improvement. Participating centres adopted the same software systems for the everyday management of outpatients, while a specially developed software package allowed us to extract the information we intended to analyse from all the clinical databases (AMD Data File). Moreover, data from all participating centres were collected and centrally analysed anonymously [29–32].

This initiative includes measuring and monitoring HbA1c, BP, lipid profile (LDL-c or total and high-density lipoprotein cholesterol and triglycerides). The use of specific classes of drugs (insulin, statins and two or more antihypertensive agents) was also evaluated. In the case of multiple entries during the year, the most recent values were considered for the analyses. Because normal ranges for HbA1c varied among centres, the percentage change with respect to the upper normal value (measured value/upper normal limit) was estimated and multiplied by 6.0 in order to allow comparisons among the centres. Kidney function was assessed by serum creatinine and urinary albumin excretion measurements. Glomerular filtration rate was estimated for each patient using a standardized serum creatinine assay and the Chronic Kidney Disease Epidemiology Collaboration formula [33]. Increased urinary albumin excretion was diagnosed and defined as high albuminuria if the urinary albumin concentration was >30 mg/L or urinary albumin excretion rate was >20 μg/min or urinary albumin-to-creatinine ratio was >2.5 mg/mmol in men and 3.5 mg/mmol in women. CKD was defined as diabetes with high albuminuria or low glomerular filtration rate (<60 mL/min/1.73 m^2) or both.

For the purpose of the analysis, the target thresholds we considered in this study were <7% (53 mmol/mol) for HbA1c, and <100 mg/dL for LDL-c according to the American Diabetes Association's (ADA) guidelines [19] and the Standard Italiani per La Cura del Diabete Mellito 2014 [20]. Target BP threshold was defined according to four clinical guidelines: the Clinical Recommendations of the American Diabetes Association and Standard Italiani per la Cura del Diabete Mellito 2014 (<140/80 mmHg) [19, 20], the European Society of Hypertension and the European Society of Cardiology (ESH-ESC) (<140/85 mmHg) [21] and, finally, the KDIGO guidelines (<140/90 or 130/80 mmHg in people with albuminuria) [22].

Statistical analysis

Continuous variables are expressed as mean ± standard deviation; discrete variables are described as frequencies and percentages. Between-group comparisons were not performed due to the large sample size that allowed us to detect statistical significance even for negligible differences. Data were analysed using a mixed model with diabetes clinics fitted as random, so that possible differences in data across centres could be considered. A multivariate mixed logistic regression model was fitted to evaluate determinants of failure to reach recommended therapeutic targets (three separate models for HbA1c ≥7%,

LDL-c ≥100 mg/dL or systolic BP ≥140 mmHg). Odds ratios (OR) were reported with their 95% confidence interval (95% CI). A missing indicator variable was used for patients with missing smoker status. The analyses were made using STATA software, Version 12 (StataCorp, College Station, Texas). P values of <0.05 were considered statistically significant.

RESULTS

The main clinical features of the analysed population are summarized in Table 1. Overall, the mean age was 67 ± 11 years, 56.7% were males and the mean duration of diabetes was 11 ± 9 years. Twenty-one per cent of patients had CKD stage ≥3, while high albuminuria was present in 26.9% of the population. Taken as a whole, the population we studied had a mean HbA1c level of 7.2 ± 1.2%, with 50.0% of the patients having HbA1c levels below the target value. The mean level of LDL-c was 102 ± 33 mg/dL and 50.6% of the patients had LDL-c below the target value. Regarding BP control, the distribution of the population was as follows: the ADA BP target (systolic/diastolic BP <140/80 mmHg) was achieved by 25.7% of the patients while the ESH-ESC BP target (systolic/diastolic BP <140/85 mmHg) was reached by 45.0% of the patients. Based on KDIGO guidelines, we analysed patients with normoalbuminuria or with high albuminuria separately: in the former group the proportion of patients who reached BP target (<140/90 mmHg) was 49.8%, while in the latter group BP target (<130/80 mmHg) was reached by 13.3% of patients.

Considering the whole population, the proportion of patients who did not meet any of the recommended targets was 13.4%. Thirty-seven percent of patients met only one of the recommended therapeutic targets, 36.4% met two, and 13.4% met all three.

The clinical characteristics of patients according to achievement of HbA1c, LDL-c and BP target values are reported in Table 2. A higher percentage of patients with low estimated glomerular filtration rate and high albuminuria was present among those whose HbA1c was above the recommended value: 22.7 versus 19.3% and 30.5 versus 23.2%, low estimated glomerular filtration rate and high albuminuria, respectively. Patients who did not meet HbA1c target values were more often females and had a longer duration of disease; in addition, they were on more intensive antihyperglycaemic treatment. Regarding LDL-c, kidney dysfunction does not seem to impact on the achievement of LDL-c target and, as expected, the proportion of patients taking statins was greater among those with LDL-c levels below the recommended values. As far as BP is concerned, similarly to HbA1c, there clearly was a higher proportion of patients with kidney dysfunction (especially those with high albuminuria) among those who did not meet their recommended targets. A greater number of patients taking antihypertensive drugs, particularly angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, was also evident among these latter patients.

To get a more in-depth understanding of the relationship between kidney dysfunction and the achievement of HbA1c, LDL-c and BP target values, we stratified the whole population according to the presence/absence of low estimated glomerular filtration rate or high albuminuria (Table 3). It would appear that high albuminuria, even more than low estimated glomerular filtration rate, affects the chance of reaching HbA1c and BP target values, while it bears no relationship with recorded LDL-c levels. It is noteworthy that the lowest proportion of patients reaching HbA1c (42%) and BP target levels (22.4%) was observed among patients with the simultaneous presence of high albuminuria and low estimated glomerular filtration rate even though the highest proportion of patients taking more intensive antihyperglycaemic or antihypertensive therapy (91.1%) was also found in the same group. It is also evident that the presence of high albuminuria entails the greatest difficulty in reaching BP target.

Table 1. Clinical features of 116 777 patients with T2DM

Male gender *n* (%)	66 260 (56.7)
Age (years)	67 ± 11
BMI (kg/m^2)	30 ± 5
Serum creatinine (mg/dL)	0.97 ± 0.52
eGFR (mL/min/1.73 m^2)	77 ± 21
eGFR < 60 mL/min/1.73 m^2, *n* (%)	24 514 (21.0)
High albuminuria, *n* (%)	31 354 (26.9)
Known duration of diabetes (years)	11 ± 9
HbA1c (%)	7.2 ± 1.2
HbA1c < 7% (53 mmol/mol), *n* (%)	58 389 (50.0)
Total cholesterol (mg/dL)	178 ± 38
Triglycerides (mg/dL)	133 ± 76
HDL-c (mg/dL)	50 ± 14
LDL-c (mg/dL)	102 ± 33
LDL-c <100 mg/dL *n* (%)	59 037 (50.6)
SBP (mmHg)	138 ± 19
DBP (mmHg)	78 ± 9
SBP/DBP <140/80 mmHg	30 022 (25.7)
SBP/DBP <140/85 mmHg	52 562 (45.0)
Patients with normoalbuminuria (*n* = 85 423)	
SBP/DBP <140/90 mmHg, *n* (%)	42 550 (49.8)
Patients with high albuminuria (*n* = 31 354)	
SBP/DBP <130/80 mmHg *n* (%)	4177 (13.3)
Pulse pressure (mmHg)	60 ± 17
Retinopathy, *n* (%)	18 084 (15.5)
Smokers, *n* (%)[a]	11 887 (17.2)
Lipid-lowering treatment, *n* (%)	70 523 (60.4)
Treatment with statins, *n* (%)	65 114 (55.8)
Treatment with fibrates, *n* (%)	3 515 (3.0)
Antihypertensive treatment, *n* (%)	86 673 (74.2)
Treatment with ACE-Is/ARBs, *n* (%)	74 317 (63.6)
Aspirin, *n* (%)	39 436 (33.8)
Antidiabetic Rx	
Diet *n* (%)	6099 (5.2)
OAD *n* (%)	74 112 (63.5)
OAD + insulin, *n* (%)	19 766 (16.9)
Insulin, *n* (%)	16 800 (14.4)
Patients with none of the variables below the target value, *n* (%)	15 753 (13.4)
Patients with only one variable below the target value, *n* (%)	42 943 (36.8)
Patients with two variables below the target value, *n* (%)	42 465 (36.4)
Patients with all three variables below the target value, *n* (%)	15 616 (13.4)

eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; OAD, oral antidiabetic drugs.

[a]Smoke habit was available for 69 231 patients.

Table 2. Clinical features of patients with T2DM divided according to the achievement of glycated haemoglobin, LDL-c and blood pressure target levels

	HbA1c < 7% (53 mmol/mol)		LDL-c < 100 mg/dL		SBP/DBP < 140/85 mmHg	
	No *n* = 58 388	Yes *n* = 58 389	No *n* = 57 740	Yes *n* = 59 037	No *n* = 64 215	Yes *n* = 52 562
Male gender (%)	53.9	59.5	53.4	60.0	56.5	57.1
Age (years)	68 ± 11	67 ± 11	67 ± 11	68 ± 10	68 ± 10	66 ± 11
BMI (kg/m^2)	30 ± 5	29 ± 5	30 ± 5	30 ± 5	30 ± 5	29 ± 5
Serum creatinine (mg/dL)	0.98 ± 0.52	0.97 ± 0.52	0.95 ± 0.51	0.99 ± 0.53	0.98 ± 0.53	0.96 ± 0.51
eGFR (mL/min/1.73 m^2)	76 ± 21	78 ± 20	78 ± 21	76 ± 21	76 ± 20	78 ± 21
eGFR <60 mL/min/1.73 m^2 (%)	22.7	19.3	19.6	22.3	22.0	19.7
High albuminuria (%)	30.5	23.2	25.5	28.2	30.3	22.7
Known duration of diabetes (years)	13 ± 9	9 ± 8	10 ± 9	12 ± 9	11 ± 9	11 ± 9
HbA1c (%)	8.1 ± 1.1	6.3 ± .5	7.2 ± 1.3	7.1 ± 1.2	7.2 ± 1.2	7.1 ± 1.2
Total cholesterol (mg/dL)	179 ± 39	177 ± 37	205 ± 30	152 ± 24	180 ± 38	176 ± 38
Triglycerides (mg/dL)	140 ± 85	125 ± 64	137 ± 69	129 ± 81	134 ± 73	131 ± 79
HDL-c (mg/dL)	50 ± 14	51 ± 14	51 ± 13	49 ± 15	51 ± 14	50 ± 14
LDL-c (mg/dL)	102 ± 33	102 ± 32	128 ± 24	77 ± 16	103 ± 33	101 ± 32
SBP (mmHg)	139 ± 19	137 ± 18	139 ± 19	137 ± 18	150 ± 15	123 ± 9
DBP (mmHg)	78 ± 10	78 ± 9	79 ± 10	77 ± 9	82 ± 9	73 ± 7
Pulse pressure (mmHg)	61 ± 17	59 ± 16	60 ± 17	60 ± 16	68 ± 16	49 ± 9
Retinopathy (%)	20.1	10.9	13.7	17.2	16.9	13.8
Smokers (%)	17.5	16.9	17.7	16.6	15.3	19.4
Lipid-lowering treatment (%)	61.9	58.9	50.3	70.2	60.6	60.1
Treatment with statins (%)	57.1	54.4	45.2	66.1	56.0	55.4
Treatment with fibrates (%)	3.1	2.9	3.4	2.6	3.1	2.9
Antihypertensive treatment (%)	75.0	73.4	69.2	79.1	78.8	68.6
Treatment with ACE-Is/ARBs (%)	64.6	62.7	58.9	68.3	69.0	57.1
Aspirin (%)	35.7	31.8	28.9	38.5	35.6	31.6
Antidiabetic Rx						
Diet (%)	1.1	9.4	6.6	3.9	4.8	5.8
OAD (%)	54.3	72.6	64.5	62.5	63.3	63.7
OAD + insulin (%)	25.5	8.3	15.2	18.6	18.1	15.5
Insulin (%)	19.1	9.7	13.8	15.0	13.9	15.0

HbA1c, glycated haemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; OAD, oral antidiabetic drugs.

Table 3. Proportion of patients with T2DM stratified according to the achievement of therapeutic targets and their current treatment on the basis of the presence/absence of high albuminuria or low estimated glomerular filtration rate

n (%)	Alb−/eGFR− 70 779 (60.6)	Alb−/eGFR+ 14 644 (12.5)	Alb+/eGFR− 21 484 (18.4)	Alb+/eGFR+ 9 870 (8.5)
HbA1c <7% (%)	53.4	48.4	43.6	42.0
LDL-c <100 mg/dL (%)	49.0	52.7	52.0	55.4
SBP/DBP <140/80 mmHg (%)	27.1	28.8	20.7	22.4
SBP/DBP <140/85 mmHg (%)	48.0	45.5	38.2	37.5
Patients with normoalbuminuria				
SBP/DBP <140/90 mmHg (%)	50.4	47.0		
Patients with high albuminuria				
SBP/DBP <130/80 mmHg (%)			13.2	13.6
Lipid-lowering treatment (%)	58.0	64.1	63.0	66.6
Treatment with statins (%)	53.7	58.0	58.8	60.5
Treatment with fibrates (%)	2.7	4.3	2.7	3.9
Antihypertensive treatment (%)	67.7	87.5	78.9	91.1
Treatment with ACE-Is/ARBs (%)	57.5	74.4	70.3	77.5
Aspirin (%)	30.0	41.7	35.5	45.0
AntidiabeticRx				
Diet (%)	6.2	4.9	3.3	2.6
OAD (%)	68.7	54.2	62.3	42.1
OAD + insulin (%)	14.8	17.3	22.0	20.5
Insulin (%)	10.2	23.5	12.4	34.9

Alb−, normoalbuminuria; Alb+, high albuminuria; eGFR−, estimated glomerular filtration rate ≥60 mL/min/1.73 m^2; eGFR+, estimated glomerular filtration rate <60 mL/min/1.73 m^2; HbA1c, glycated haemoglobin; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; OAD, oral antidiabetic drugs.

Finally, by means of multivariate analysis, we explored the independent correlates of the achievement of recommended therapeutic targets (Table 4). Younger subjects, females with higher body mass index, longer duration of disease and high albuminuria were less likely to achieve HbA1c target values. Males, the elderly and those taking statins were more likely to reach LDL-c target levels. Male gender, age and high albuminuria, regardless of low estimated glomerular filtration rate, strongly affected the achievement of BP targets.

We further analysed the association of CKD with various BP target values (Table 5) according to the above reported guidelines [19–22]. Overall, results confirm an association between male gender, age, body mass index, HbA1c, LDL-c and the presence of microvascular complications, including retinopathy and high albuminuria with failure to achieve recommended BP control.

DISCUSSION

In a large sample of adults with diabetes attending a network of National Health System outpatient clinics and representative of real-life care in Italy, we found that only ∼13% of patients achieved recommended treatment goals for all three parameters we examined, while ∼36–37% had either one or two out of three indicators within target levels, and 13% were found to be outside the recommended targets for all parameters. It is surprising that 87% of patients did not meet all three target levels simultaneously. The proportion of patients reaching recommended targets was disappointingly low in the presence of CKD, especially high albuminuria. Conversely renal abnormalities were not associated with the failure in the achievement of LDL-c targets.

Therapeutic strategies aimed at correcting multiple risk factors, namely hyperglycaemia, increased cholesterol levels and hypertension in patients with T2DM have proven to significantly reduce the risk of micro- and macrovascular complications associated with diabetes [8–17]. Accordingly, current guidelines recommend specific, often tighter therapeutic goals based on the risk burden of each individual patient [19–22]. However, previous studies in the USA and elsewhere [25–30] have reported that a relatively low number of patients with T2DM reach recommended therapeutic levels for traditional, modifiable risk factors. Thus, our findings seem to confirm and extend what has very recently been reported by the NHANES study, i.e. that although there have been improvements over the last decade, almost half of American adults with diabetes do not meet the recommended goals for diabetes care [28].

Recommended target levels of HbA1c were reached by only half of the patients and by an even lower number (42%) in the presence of low estimated glomerular filtration rate and/or high albuminuria, indicating that the proportion of diabetic patients meeting the recommended HbA1c target is still far from satisfactory. Although the need for caution has recently been emphasized [19, 20], results from the main clinical trials and surveys [8–11] confirm the benefits of glycaemic control in reducing the risk of the onset and progression of micro- and macrovascular complications. This has translated into more stringent recommended HbA1c targets for the majority of patients [19, 20]. Shurraw *et al.* have recently shown that higher

Table 4. Determinants of failure to reach recommended therapeutic targets

	HbA1c ≥ 7% (53 mmol/mol)		LDL-c ≥ 100 mg/dL		SBP ≥ 140 mmHg	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Male gender	0.802 (0.779–0.825)	<0.001	0.727 (0.709–0.746)	<0.001	1.024 (0.998–1.052)	0.075
Age (by 5 years)	0.984 (0.976–0.991)	<0.001	0.972 (0.965–0.979)	<0.001	1.162 (1.154–1.171)	<0.001
BMI (by 1 kg/m^2)	1.025 (1.023–1.028)	<0.001	0.999 (0.996–1.001)	0.256	1.032 (1.030–1.035)	<0.001
Known duration of diabetes (by 1 year)	1.032 (1.030–1.034)	<0.001	0.991 (0.989–0.992)	<0.001	1.005 (1.003–1.007)	<0.001
HbA1c (by 1%)			1.079 (1.066–1.091)	<0.001	1.044 (1.031–1.056)	<0.001
LDL-c (by 10 mg/dL)	1.024 (1.019–1.028)	<0.001			1.032 (1.028–1.036)	<0.001
SBP (by 10 mmHg)	1.036 (1.028–1.045)	<0.001	1.066 (1.058–1.073)	<0.001		
Retinopathy	1.159 (1.113–1.207)	<0.001	0.905 (0.872–0.939)	<0.001	1.225 (1.180–1.272)	<0.001
Smokers	1.087 (1.038–1.138)	<0.001	1.056 (1.011–1.102)	0.014	0.847 (0.811–0.884)	<0.001
Lipid-lowering treatment	1.127 (1.094–1.161)	<0.001	0.502 (0.489–0.516)	<0.001	0.962 (0.935–0.989)	0.006
Antihypertensive treatment	0.827 (0.785–0.871)	<0.001	0.752 (0.717–0.789)	<0.001	1.094 (1.043–1.149)	<0.001
Treatment with ACE-Is/ARBs	1.010 (0.965–1.057)	0.664	0.985 (0.945–1.027)	0.469	1.436 (1.377–1.497)	<0.001
Aspirin	1.033 (1.002–1.066)	0.038	0.833 (0.810–0.857)	<0.001	1.016 (0.987–1.046)	0.271
Antidiabetic Rx						
Diet	0.144 (0.132–0.157)	<0.001	1.538 (1.450–1.631)	<0.001	0.926 (0.873–0.982)	0.010
OAD	Reference		Reference		Reference	
OAD + insulin	3.975 (3.811–4.146)	<0.001	0.811 (0.781–0.842)	<0.001	1.003 (0.965–1.042)	0.877
Insulin	2.415 (2.314–2.520)	<0.001	0.901 (0.865–0.938)	<0.001	0.845 (0.811–0.880)	<0.001
High albuminuria and low eGFR						
Alb−/eGFR−	Reference		Reference		Reference	
Alb−/eGFR+	0.963 (0.921–1.008)	0.104	1.004 (0.963–1.046)	0.851	0.789 (0.756–0.822)	<0.001
Alb+/eGFR−	1.336 (1.285–1.388)	<0.001	1.001 (0.966–1.038)	0.942	1.415 (1.364–1.467)	<0.001
Alb+/eGFR+	1.072 (1.016–1.132)	0.011	0.991 (0.943–1.041)	0.713	1.130 (1.075–1.188)	<0.001

HbA1c, glycated haemoglobin; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; OAD, oral antidiabetic drugs; Alb−, normoalbuminuria; Alb+, high albuminuria; eGFR, estimated glomerular filtration rate; eGFR−, eGFR ≥60 mL/min/1.73 m^2; eGFR+, eGFR<60 mL/min/1.73 m^2.

Table 5. Determinants of failure to reach different recommended blood pressure targets

	SBP ≥ 140/80 mmHg		SBP ≥ 140/85 mmHg	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Male gender	1.057 (1.026–1.089)	<0.001	1.057 (1.029–1.085)	<0.001
Age (by 5 years)	1.042 (1.034–1.050)	<0.001	1.111 (1.103–1.119)	<0.001
BMI (by 1 kg/m^2)	1.047 (1.044–1.050)	<0.001	1.038 (1.036–1.041)	<0.001
Known duration of diabetes (by 1 year)	0.998 (0.996–0.999)	0.011	1.002 (1.001–1.004)	0.004
HbA1c (by 1%)	1.055 (1.040–1.069)	<0.001	1.051 (1.038–1.063)	<0.001
LDL-c (by 10 mg/dL)	1.036 (1.031–1.041)	<0.001	1.035 (1.031–1.039)	<0.001
Retinopathy	1.132 (1.084–1.181)	<0.001	1.192 (1.148–1.238)	<0.001
Smokers	0.806 (0.769–0.845)	<0.001	0.846 (0.810–0.883)	<0.001
Lipid-lowering treatment	0.943 (0.913–0.973)	<0.001	0.946 (0.920–0.973)	<0.001
Antihypertensive treatment	1.076 (1.021–1.135)	0.006	1.095 (1.043–1.148)	<0.001
Treatment with ACE-Is/ARBs	1.363 (1.301–1.428)	<0.001	1.418 (1.360–1.478)	<0.001
Aspirin	0.970 (0.938–1.003)	0.070	0.997 (0.968–1.026)	0.824
Antidiabetic Rx				
Diet	0.957 (0.897–1.021)	0.180	0.930 (0.877–0.985)	0.014
OAD	Reference		Reference	
OAD + insulin	0.928 (0.888–0.970)	0.001	0.980 (0.943–1.019)	0.309
Insulin	0.752 (0.719–0.786)	<0.001	0.816 (0.783–0.850)	<0.001
High albuminuria and low eGFR				
Alb−/eGFR−	Reference		Reference	
Alb−/eGFR+	0.777 (0.742–0.814)	<0.001	0.802 (0.769–0.836)	<0.001
Alb+/eGFR−	1.336 (1.279–1.394)	<0.001	1.399 (1.349–1.451)	<0.001
Alb+/eGFR+	1.124 (1.060–1.191)	<0.001	1.150 (1.093–1.210)	<0.001

HbA1c, glycated haemoglobin; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; ACE-Is, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor antagonists; OAD, oral antidiabetic drugs; Alb−, normoalbuminuria; Alb+, high albuminuria; eGFR, estimated glomerular filtration rate; eGFR−, eGFR ≥60 mL/min/1.73 m^2; eGFR+, eGFR < 60 mL/min/1.73 m^2.

HbA1c levels were strongly and independently associated with excess risk of renal and cardiovascular outcomes in a large population with T2DM and CKD. Furthermore, they found that the relationship between glycometabolic control and mortality was U-shaped, with a significantly greater risk for HbA1c values both below 6.5% (48 mmol/mol) and above 8.0% (64 mmol/mol) [18].

A number of other factors, such as gender, age, duration of disease and household income, have been evoked to explain the observed failure to reach HbA1c target levels. To the best of our knowledge this is the first study investigating the potential role of kidney dysfunction in this regard. Noteworthy, CKD and its components, mainly high albuminuria, were more frequent among patients with HbA1c ≥7% (53 mmol/mol), despite a greater use of glucose-lowering agents. Moreover, when a multivariate analysis model was performed, kidney dysfunction turned out to be strongly and independently associated with a lower probability of meeting recommended HbA1c targets.

As there is some heterogeneity among various guidelines regarding the recommended target values for BP, we explored different thresholds for optimal BP control. Only about one out of two patients resulted on target when either ADA (<140/80 mmHg) [19] or ESH-ESC (<140/85 mmHg) [21] recommendations were considered, a percentage that dropped dramatically when a more stringent value (<130/80 mmHg) was considered in the subgroup of patients with high albuminuria. These results are even more noteworthy when one considers that patients with CKD or one of its components received, on average, more antihypertensive drugs including agents that block the rennin–angiotensin–aldosterone system as compared with those with normal renal function, thus reducing the likelihood that therapeutic inertia may play a role. Accordingly, in the multivariate analysis kidney dysfunction, high albuminuria mainly emerges as a significant and independent predictor of failure to achieve therapeutic target levels.

As for cholesterol levels, data from the AMD network database indicate that the use of statins is associated with lower LDL-c levels. However, even when assuming a target LDL-c level <100 mg/dL regardless of each patient's specific clinical status or risk profile [19, 20], the number of patients reaching recommended values does not exceed 50%. These data suggest that although the use of statins in diabetic patients has risen over the last decade [34], considerable gaps remain to be filled before reaching a satisfactory standard of care in the real-life clinical setting. Interestingly, at variance with what we observed for BP and glycaemic control, our data seem to convey a somewhat different picture with respect to lipid levels in the presence of CKD. In fact, LDL-c levels and prevalence of patients reaching their recommended cholesterol target are almost superimposable in patients with and without CKD. The percentage of diabetic patients receiving a statin was even greater in the presence of renal complications (high albuminuria and/or estimated glomerular filtration rate reduction), suggesting that the presence of CKD is perceived as a condition of increased cardiovascular risk by diabetologists. The significant association we found between insulin or angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers treatment and not achieving HbA1c or BP target values, respectively, is likely due to an indication bias since the presence of CKD greatly limits pharmacological options for antidiabetic treatment and is widely taken as a mandatory indication for the use of renin–angiotensin–aldosterone system inhibitors.

Taken together, the data presented here indicate a large area of potential therapeutic improvement that could optimize cardiovascular risk profile and therefore prevent further micro- and macrovascular complications. Several implications of our results deserve to be commented upon. The persisting gaps in care depicted in our study might, in principle, be due to the interaction of different factors involving patients (lack of motivation), care providers (therapeutic inertia) or, lastly and more generally, health systems (logistical or financial barriers for patient access to care). In this study we specifically wanted to investigate whether the presence of CKD may be a factor associated with failure to achieve treatment goals, and we believe that the results presented herein clearly indicate that this is the case, at least for glycaemic control and BP. While the cross-sectional nature of this study does not allow us to draw any definitive pathophysiological conclusions, we feel our data suggest that impairment of renal function may hamper the effectiveness of antihypertensive treatment and impose limits on the choice of hypoglycaemic drugs in clinical practice while altering the risk–benefit ratio. Although a detailed analysis of the reasons for this disappointing situation is clearly beyond the scope of this study, our data showing a slightly but significantly greater percentage of statin treatment in the subgroup of patients with CKD suggest that therapeutic inertia towards a high-risk situation cannot be claimed as the major or sole cause in the therapeutic failure that we observed. This is further supported by the observation that, likely thanks to a greater awareness of the well-known high-risk status and possibly stronger therapeutic effort associated with this condition, the prevalence of patients receiving a statin was higher in the presence of CKD or even only of one of its components. On the other hand, we cannot exclude that the worse glycaemic and BP control we observed is itself causative of kidney damage. Thus, an alternate hypothesis to explain our results is that patients under suboptimal glycaemic and BP control are in a higher proportion to those with renal impairment. In this regard, the relatively low use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers in our sample is alarming, especially in patients with documented high albuminuria.

From the standpoint of public health and economics, our results seem to indicate the need to reiterate widespread diffusion and implementation of therapeutic guidelines and recommendations to further reduce the residual risk of diabetic patients, especially those with CKD. This would certainly lead to a further reduction in morbidity and mortality and consequently a containment of costs for the National Health System. Furthermore, specific studies aimed at improving treatment strategies for patients with CKD are clearly needed to help close the gap in diabetes care.

Some limitations of our study should be acknowledged. First of all, laboratory parameters were not measured in a single centralized laboratory and this may have led to considerable variability, especially in the evaluation of serum creatinine (and therefore glomerular filtration rate estimation). Although creatinine determination cannot always be referred to IDMS procedures, most laboratories around the country currently use the Jaffè method, which has been shown to have good reproducibility. In addition, we have information on high albuminuria only as a categorical trait.

On the other hand, our study has several strengths since the large size of the database and the homogeneous geographical distribution of participating centres allow us to provide a realistic snapshot of risk-factor control and preventive practices in a real life situation representative of the Italian health care system.

In conclusion, our findings provide evidence that the presence of CKD and its individual components, especially high albuminuria, are associated with a greater likelihood of failure to achieve recommended therapeutic targets for BP and glycaemic control in diabetic patients. Further longitudinal specifically designed studies will better clarify our observations and should aim at breaking down barriers which decrease the chance to achieve guideline recommendations.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. IDF Diabetes Atlas Update 2013. Available at: http://www.idf.org/diabetesatlas/6e/update2013
2. Whiting DR, Guariguata L, Weil C *et al.* IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011; 94: 311–321
3. Williams ME. Diabetic CKD/ESRD 2010: a progress report? Semin Dial 2010; 23: 129–133
4. US Renal Data System. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: US Renal Data System, 2013
5. Fox CS, Matsushita K, Wooward M *et al.* Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 2012; 380: 1662–1673
6. Ninomiya T, Perkovic V, de Galan BE *et al.* Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol 2009; 20: 1813–1821
7. Afkarian M, Sachs MC, Kestenbaum B *et al.* Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol 2009; 24: 302–308
8. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood–glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 1998; 352: 837–853
9. Ray KK, Seshasai SR, Wijesuriya S *et al.* Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet 2009; 373: 1765–1772
10. Turnbull FM, Abraira C, Anderson RJ *et al.* Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009; 52: 2288–2298
11. Kelly TN, Bazzano LA, Fonseca VA *et al.* Systematic review: glucose control and cardiovascular disease in type 2 diabetes. Ann Intern Med 2009; 151: 394–403
12. Cholesterol Treatment Trialists' (CTT) CollaboratorsKearney PM, Blackwell L, Collins R *et al.* Efficacy of cholesterol-lowering therapy in 18,686

people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008; 371: 117–125
13. Baigent C, Landray MJ, Reith C *et al.* The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011; 377: 2181–2192
14. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998; 317: 703–713
15. Adler AI, Stratton IM, Neil HA *et al.* Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000; 321: 412–419
16. Rönnback M, Isomaa B, Fagerudd J *et al.* Complex relationship between blood pressure and mortality in type 2 diabetic patients. Follow-up of the Botnia Study. Hypertension 2006; 47: 168–173
17. Gæde P, Lund-Andersen H, Parving HH *et al.* Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008; 358: 580–591
18. Shurraw S, Hemmelgarn B, Lin M *et al.* Association between glycemic control and adverse outcomes in people with diabetes mellitus and chronic kidney disease: a population-based cohort study. Arch Intern Med 2011; 171: 1920–1927
19. American Diabetes Association. Standards of Medical Care in Diabetes 2014. Diabetes Care 2014; 37(Suppl 1): S14–S80
20. Associazione Medici Diabetologi and Società Italiana di Diabetologia. Standard Italiani Per La Cura del Diabete Mellito, 2014. http://www.standarditaliani.it/skin/www.standarditaliani.it/pdf/STANDARD_2014_May28.pdf
21. Mancia G, Fagard R, Narkiewicz K *et al.* ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013; 31: 1281–1357
22. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in chronic kidney disease. Kidney Int 2012; 2 (Suppl): 337–414
23. Ko KD, Kim BH, Park SM *et al.* What are patient factors associated with the quality of diabetes care? Results from the Korean National Health and Nutrition Examination Survey. BMC Public Health 2012; 12: 689
24. Fraser SDS, Roderick PJ, Mcintyre NJ *et al.* Suboptimal blood pressure control in chronic kidney disease stage 3: baseline data from a cohort study in primary care. BMC Family Practice 2013; 14: 88
25. Cadwell B, Gregg EW, Engelgau MM *et al.* Improvements in diabetes processes of care and intermediate outcomes: United States, 1988–2002. Ann Intern Med 2006; 144: 465–474
26. Casagrande SS, Fradkin JE, Saydah SH *et al.* The prevalence of meeting A1c, Blood pressure, and LDL goals among people with diabetes, 1988–2010. Diabetes Care 2013; 36: 2271–2279
27. Cheung BMY, Ong KL, Cherny SS *et al.* Diabetes prevalence and therapeutic target achievement in the United State, 1999 to 2006. Am J Med 2009; 122: 443–453
28. Ali MK, Bullard KM, Saaddine JB *et al.* Achievement of goals in U.S. diabetes care, 1999–2010. N Engl J Med 2013; 368: 1613–1624
29. Nicolucci A, Rossi MC, Arcangeli A *et al.* Four-year impact of a continuous quality improvement effort implemented by a network of diabetes outpatient clinics: the AMD-Annals initiative. Diabet Med 2010; 27: 1041–1048
30. Rossi MC, Lucisano G, Comaschi M *et al.* Quality of diabetes care predicts the development of cardiovascular events: results of the AMD-QUASAR. Diabetes Care 2011; 34: 347–352
31. Rossi MC, Cristofaro MR, Gentile S *et al.* Sex disparities in the quality of diabetes care: biological and cultural factors may play a different role for different outcomes: a cross-sectional observational study from the AMD Annals initiative. Diabetes Care 2013; 36: 3162–3168
32. De Cosmo S, Rossi MC, Pellegrini F *et al.* Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes. Nephrol Dial Transplant 2014; 29: 657–662
33. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604–612
34. Kuznik A, Mardekian J. Trends in utilization of lipid- and blood pressure-lowering agents and goal attainment among the U.S. diabetic population, 1999–2008. Cardiovasc Diabetol 2011; 10: 31

Received for publication: 20.1.2015; Accepted in revised form: 24.3.2015

ORIGINAL ARTICLE