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The number of nephroprotection targets attained is associated with cardiorenal outcomes and mortality in patients with diabetic kidney disease. The CKD-REIN cohort study

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Abstract

Aim: The risk of cardiorenal events remains high among patients with diabetes and chronic kidney disease (CKD), despite the prescription of recommended treatments. We aimed to determine whether the attainment of a combination of nephroprotection targets at baseline (glycated haemoglobin <7.0%, urinary albumin-creatinine ratio <300 mg/g, blood pressure <130/80 mmHg, renin-angiotensin system inhibition) was associated with better cardiorenal outcomes and lower mortality.

Materials and Methods: From the prospective French CKD-REIN cohort, we studied 1260 patients with diabetes and CKD stages 3-4 (estimated glomerular filtration rate: 15-60 ml/min/1.73 m^2); 69% were men, and at inclusion, mean ± SD age: 70 ± 10 years; estimated glomerular filtration rate: 33 ± 11 ml/min/1.73 m^2. The median follow-up was 4.9 years.

Results: In adjusted Cox regression models, the attainment of two nephroprotection targets was consistently associated with a lower risk of cardiorenal events [hazard

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ratio 0.70 (95% confidence interval 0.57-0.85)], incident kidney failure with replacement therapy [0.58 (0.43-0.77)], four major adverse cardiovascular events (cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure) [0.75 (0.57-0.99)] and all-cause mortality [0.59 (0.42-0.82)] when compared with the attainment of zero or one target. For patients with a urinary albumin-creatinine ratio ≥300 mg/g, those who attained at least two targets had lower hazard ratios for cardiorenal events [0.61 (0.39-0.96)], four major adverse cardiovascular events [0.53 (0.28-0.98)] and all-cause mortality [0.35 (0.17-0.70)] compared with those who failed to attain any targets.

Conclusions: These findings suggest that the attainment of a combination of nephroprotection targets is associated with better cardiorenal outcomes and a lower mortality rate in people with diabetic kidney disease.

KEYWORDS

cardiovascular disease, diabetic nephropathy, pharmaco-epidemiology, type 2 diabetes

1 | INTRODUCTION

The number of people with diabetic kidney disease has been increasing worldwide.[1] Diabetes is the major leading cause of kidney failure in the world.[1,2] People with diabetes and chronic kidney disease (CKD) are known to be at high risk of both cardiovascular events and kidney failure. Even in people included in the recent studies and under recommended treatments, a residual risk persists, as reported in the placebo group in trials testing sodium-glucose cotransporter 2 (SGLT2) inhibitors or finerenone, highlighting the importance of further improving prevention in this population.[3–5] One of the main strategies to reduce the risks of kidney disease progression and cardiovascular events in people with diabetic kidney disease is to provide comprehensive care targeting multifaceted criteria such as blood pressure, albuminuria, glycaemia, and renin-angiotensin system (RAS) blockade, as recommended by international guidelines.[5–8] The results of the Steno type 2 randomized study published in 1999 showed that an intensified multifactorial intervention (mean follow-up of 3.8 years) targeting blood pressure, glycaemia, cholesterol and RAS blockade in people with type 2 diabetes and microalbuminuria was associated with a significant reduction in the risk of progression to overt nephropathy.[9] More recently, a multicentre randomized study showed in Chinese patients with type 2 diabetes with CKD [mean estimated glomerular filtration rate (eGFR): 31 ml/min/1.73 m^2] that structured care for 2 years was associated with more frequent attainment of multiple treatment targets and with a reduced risk of death and/or kidney failure, as compared with the usual care group.[10]

The NID-2 interventional trial showed that in patients with type 2 diabetes with albuminuria, intensive multifactorial therapy was associated with a lower incidence of cardiovascular events and all-cause death compared with standard care.[11]

Recent real-life assessments in various countries have shown that adherence to guideline implementation remains poor among patients with diabetic kidney disease.[12] Hence, there is a need for real-world studies (studies in populations that are more heterogeneous than those included in randomized trials) that validate the therapeutic targets indicated by guidelines.

In the present study of a large cohort of patients with diabetic kidney disease, we sought to determine whether the attainment of a combination of nephroprotection targets at baseline [urinary albumin-creatinine ratio (UACR) <300 mg/g, glycated haemoglobin (HbA1c) <7.0%, blood pressure <130/80 mmHg, prescription of RAS inhibitors (RASI)] was associated with better cardiorenal outcomes and survival. Given that albuminuria is a strong predictor of cardiorenal events and can influence the treatment strategy, we further stratified patients by their UACR level at baseline (<300 vs. ≥300 mg/g). This enabled us to determine whether the association between the attainment of nephroprotection targets (other than a lower UACR) and the study outcomes was observed in patients with severely increased albuminuria.

We chose to focus on nephroprotection targets rather than lifestyle intervention or cardiovascular treatments, such as the use of statin therapy. It has not been clearly shown that lipid-lowering drugs reduce the risk of kidney disease progression or all-cause mortality in patients with diabetic kidney disease.[13]

2 | MATERIALS AND METHODS

2.1 | Study population

CKD-REIN is a 5-year prospective French cohort study of 3033 adult patients with all-cause CKD but no maintenance dialysis or kidney transplantation.[14] Between July 2013 and April 2016, patients were recruited at 40 nationally representative nephrology outpatient clinics. The CKD-REIN study first screened all eligible adult (≥18 years) patients with moderate or severe CKD (stage G3 or G4, based on two eGFR measurements ≥15 and <60 ml/min/1.73 m^2 more than

1 month apart). During a routine nephrology consultation, patients who were able to give informed consent and who did not intend to change their outpatient clinic were then invited to participate in the CKD-REIN study. To limit selection bias, we included patients who had moved to stage G2 or G5 CKD (eGFR 60-90 or <15 ml/min/1.73 m^2, respectively, but were not on dialysis and had not received a kidney transplant) between the screening and inclusion phases.

The study protocol was approved by the institutional review board at the French Institute of Health and Medical Research (INSERM, Paris, France; reference: IRB00003888) and has been published on ClinicalTrials.gov (NCT03381950). All patients gave their written informed consent.

In all, 1307 patients were considered to have diabetes because they met at least one of the following criteria: physician-diagnosed diabetes reported in the medical records, the use of glucose-lowering medications, HbA1c ≥6.5%, fasting glucose ≥7.0 mmol/L or a random glucose measurement ≥11.0 mmol/L. The present analysis focused on 1260 patients with diabetes and a baseline eGFR between 15 and 60 ml/min/1.73 m^2, including 1086 patients with type 2 diabetes and 174 patients with another or unknown type of diabetes, as shown in a flow chart (Figure S1).

2.2 | Measures at baseline

Data from patient interviews, self-administered questionnaires and medical records (consulted by trained clinical research associates) were available for sex, age, duration of diabetes, educational level (years of formal education), smoking habit, physical activity, body mass index (BMI), medications and blood pressure. Patients were classified as having hypertension if it was reported in their medical records or if they used antihypertensive medication. Adherence to medication was determined using a validated score based on six questions about the patient's behaviour and actual use of the prescribed treatment.[15] A score of 6 indicates good adherence to prescribed medication, a score of 4-5 poor adherence and a score ≤3 non-adherence.[15]

The data on routinely measured biochemical variables (including HbA1c, fasting blood glucose, creatinine, lipids, and urine albumin and creatinine) came from local medical laboratories. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation,[16] and CKD stages were defined according to the 2012 Kidney Disease Improving Global Outcomes report.[17]

2.3 | Outcomes

The principal outcome studied is a composite cardiorenal event defined as (a) kidney failure, eGFR <15 ml/min/1.73 m^2, (b) kidney failure with replacement therapy (KFRT), and/or (c) major cardiovascular events 4 (MACE4: cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure). These three individual outcomes are also studied, along with all-cause mortality. Outcomes were documented annually by clinical research assistants. To ensure the complete collection of deaths and KFRT, records were linked to both the French national vital status registry and the French Renal Epidemiology and Information Network registry of dialysis and transplantation.

2.4 | Statistical analyses

The studied variables are presented as the mean ± SD, the median (interquartile range), or the frequency (percentage), stratified according to the number of nephroprotection targets attained at baseline, and compared in an analysis of variance or a chi-squared test.

The cardiorenal outcomes' respective incidence rates were calculated per 100 person-years for each of the four targets attained at baseline. We used Cox proportional hazards models to estimate cause-specific hazard ratios (HRs) and their 95% confidence intervals for each outcome associated with the four attained nephroprotection targets, after adjustment for the other targets. HRs were adjusted for age, sex, educational level >12 years, current smoking, eGFR, low-density lipoprotein (LDL)-cholesterol, BMI, and the prescription of aspirin or another platelet anti-aggregant, statin, or a glucagon-like peptide-1 receptor agonist. The proportional hazards assumption was checked by examining the Schoenfeld residuals. Time-dependent effects were estimated for covariates with non-proportional hazards.

Sensitivity analyses were also performed for each attained nephroprotection target alone and for their combination in the population with type 2 diabetes.

A secondary analysis was stratified on UACR <300 mg/g and ≥300 mg/g to determine whether the relationship between the number of targets attained and the outcomes was modified by the severity of the UACR.

We used multiple imputations by chained equations (MICE) to manage missing data (44 datasets were generated). Analyses were run on each data set, and results from the 44 Cox models were pooled with Rubin's rule.

To evaluate the time course of nephroprotection targets attained, Sankey plots describe the evolution of targets achieved over the first 2 years of follow-up in those for whom data were available, who were alive, and not under dialysis or transplantation.

All analyses used the R software (version 4.0.3).

3 | RESULTS

3.1 | Patient characteristics and attainment of nephroprotection targets at baseline

We studied 1260 people (69% men) with diabetic kidney disease, 61% of whom had a baseline UACR <300 mg/g (Table 1). Patients who attained at least three nephroprotection targets at baseline had a shorter time since diabetes onset, lower BMI and slightly higher GFR

TABLE 1 Baseline characteristics of the patients with diabetic kidney disease, as a function of the number of nephroprotection targets attained.

		Number of nephroprotection targets attained			
	Total	0 or 1	2	≥3	
Characteristics	n = 1260	n = 330	n = 528	n = 402	*p*-Value
Men	867 (69)	228 (69)	371 (70)	268 (67)	.498
Age, years	70 ± 10	69 ± 11	70 ± 9	70 ± 9	.181
Diabetes duration, years	18 ± 12	20 ± 12	18 ± 12	16 ± 12	<.001
Educational level >12 years	360 (29)	89 (27)	159 (30)	112 (28)	.568
Current smoking	133 (11)	34 (10)	66 (12)	33 (8)	.106
Physical activity[a]					.604
Intense	233 (23)	56 (22)	100 (23)	77 (24)	
Moderate	243 (24)	59 (23)	97 (23)	87 (27)	
Low	540 (53)	143 (55)	234 (54)	163 (50)	
BMI, kg/m^2	31.2 ± 6	32.1 ± 6.2	31.3 ± 5.9	30.4 ± 5.7	<.001
Laboratory data					
eGFR, ml/min/1.73 m^2	33.3 ± 11.5	30.3 ± 10.6	33.7 ± 11.5	35.4 ± 11.8	<.001
Albumin-creatinine ratio, mg/g	143 (25-590)	603 (380-1269)	135 (25-576)	37 (11-117)	<.001
HbA1c, %	7.15 ± 1.16	7.82 ± 1.13	7.2 ± 1.12	6.52 ± 0.88	<.001
Triglycerides, mmol/L	2.11 ± 1.29	2.17 ± 1.21	2.18 ± 1.37	1.98 ± 1.23	.045
LDL-cholesterol, mmol/L	2.37 ± 1.01	2.42 ± 1	2.38 ± 1	2.31 ± 1.04	.302
Diabetes treatments					
Not treated with medications	215 (17)	40 (12)	85 (16)	90 (22)	<.001
Insulin	618 (49)	217 (66)	262 (50)	139 (35)	<.001
Glucagon-like peptide receptor agonists	45 (4)	15 (5)	15 (3)	15 (4)	.415
Oral glucose lowering drugs	690 (55)	165 (50)	296 (56)	229 (57)	.124
Other treatments					
Statin	881 (70)	232 (70)	380 (72)	269 (67)	.246
Aspirin or another platelet anti-aggregant	688 (55)	184 (56)	306 (58)	198 (49)	.027
Total number of prescription medications[b]	10 (8-12)	10 (8-13)	10 (8-12)	9 (7-12)	.002
Adherent to medications (adhesion score = 6)[c]	413 (33)	96 (29)	170 (32)	147 (37)	.107
Nephroprotection targets					
Albumin-creatinine ratio <300 mg/g	770 (61)	54 (16)	340 (64)	376 (94)	<.001
HbA1c <7%	616 (49)	40 (12)	235 (45)	341 (85)	<.001
Blood pressure <130/80 mmHg	211 (17)	6 (2)	50 (9)	155 (39)	<.001
Renin-angiotensin system inhibitor	1004 (80)	188 (57)	431 (82)	385 (96)	<.001

Note: *p*-Values from an analysis of variance or a chi-squared test. Data shown as n (%), mean ± SD or median (quartiles). Based on the first imputed dataset for variables used in the survival analysis.
[a]244 missing.
[b]2 missing.
[c]5 missing.

compared with those who attained fewer targets (Table 1). There were no statistically significant differences in age, educational level, physical activity and statin treatment as a function of the number of targets attained. Use of aspirin or another antiplatelet agent was less prevalent in patients who attained at least three targets at baseline, compared with those who attained two or fewer targets (Table 1). There were no statistically significant differences in adherence to medication between the three groups. (Table 1).

Although only 4.0% of the population achieved all four nephroprotection targets at baseline, 74% attained two or more targets. While 80% of the patients were prescribed a RASI, only 17% achieved the nephroprotection targets for blood pressure. Of the patients

achieving only one target, 65% were prescribed a RASI (Figure S2). For those achieving three targets, the combination of the UACR, RASI and HbA1c targets was the most frequent (70%).

3.2 | Outcomes according to attainment of nephroprotection targets at baseline

During a median follow-up period of 4.9 years, 535 patients had at least one of the four studied cardiorenal events (Table 2): 261 kidney failure events; 240 KFRTs; 298 MACE4; and 234 deaths.

The crude frequency of the cardiorenal outcome decreased with an increasing number of targets attained at baseline: 35, 18, 12 and 8.7 per 100 person years for 0, 1, 2 and ≥3 targets attained, respectively ($p < .001$). The p-value for trend was statistically significant (<.001) for the adjusted HRs (Figure 1).

After adjustment for potential confounders and other nephroprotection targets, patients with normal or moderately increased albuminuria values (UACR <300 mg/g) had a much lower risk of cardiorenal events (Table 2). Use of RASIs was associated with a lower risk of MACE4 (albeit not statistically significantly), HR (95% confidence interval): 0.78 (0.59-1.03) and a statistically significant lower risk of all-cause mortality: 0.67 (0.50-0.91) (Table 2). Blood pressure values <130/80 mmHg were associated with a lower risk of incident kidney failure with HR 0.67 (0.45-1.00) and 0.60 (0.40-0.91) with or without replacement therapy, respectively. HbA1c <7.0% was not associated with a statistically significantly lower risk of cardiorenal outcome or mortality (Table 2).

Similar results were obtained when each nephroprotection target was considered separately, without adjustment for the others (Table S1).

The attainment of at least two nephroprotection targets was consistently associated with a lower risk of cardiorenal events, kidney failure, KFRT, MACE4 and all-cause mortality compared with the attainment of zero or one target (Figure 1); there were statistically significant trends for the number of targets attained.

A sensitivity analysis restricted to the 1086 patients with a reported diagnosis of type 2 diabetes showed that the risk was lower for those having attained at least two targets than for those having attained zero targets or one target attained (except for MACE4) (Supplementary Figure S2).

3.3 | Stratification by urinary albumin-creatinine ratio

Stratification by the UACR at baseline (<300 mg/g and ≥300 mg/g) showed that for patients with diabetic kidney disease and UACR <300 mg/g, attaining one or more of the other targets was not associated with a lower risk for any of the outcomes studied (Table 3). For those with a UACR ≥300 mg/g, attainment of least two of the three nephroprotection targets (excluding albuminuria <300 mg/g, by definition) was associated with a lower risk of cardiorenal events with HRs 0.61 (0.39-0.96), for MACE4 0.53 (0.28-0.98) and a marked statistically significant reduction in total mortality of 0.35 (0.17-0.70) as compared with those with none of the three targets (Table 3).

3.4 | Attainment of nephroprotective targets over 2 years of follow-up

The percentage of patients attaining a given number of targets changed little over the 2 years of follow-up, relative to baseline (Figure 2). The percentage of patients attaining four targets increased slightly over time (from 3% to 6%). Similarly, the percentage of patients attaining each individual target was fairly constant over time (Figures S3A-D).

4 | DISCUSSION

The main finding of the present study of patients with diabetic kidney disease is that the attainment of at least two nephroprotection targets is associated with better cardiorenal outcomes and lower all-cause mortality over a 5-year follow-up. Furthermore, in patients with severely increased albuminuria (≥300 mg/g), achievement of at least two of three targets (blood pressure <130/80 mmHg, HbA1c <7.0%, and RASI use) was associated with a lower risk of cardiorenal events and (in particular) all-cause mortality. These observations suggest that targeting blood pressure, glucose levels and RAS blockade is of particular interest in patients with elevated albuminuria.

In our cohort of patients with diabetic kidney disease, individuals with severely increased albuminuria (≥300 mg/g) had a high risk of subsequent cardiorenal events, even after adjusting for the eGFR. This finding is in line with a number of literature reports in which an elevated UACR is predictive of kidney failure and MACE4 in people with or without diabetes.[18] Furthermore, recent data from intervention trials have confirmed that residual albuminuria in treated patients (e.g. with a combination of a RASI and an SGLT2 inhibitor) is also linked to cardiorenal prognosis.[19] Our findings extend these trial results and suggest that attaining treatment targets other than reducing albuminuria will improve cardiorenal prognosis in treated patients with diabetic kidney disease and elevated albuminuria. Our results emphasize the importance of combining blood pressure control, glycaemic control and RASI use, notably in those with severe albuminuria. In contrast, we found that for patients with an UACR <300 mg/g, the attainment of at least two of the other nephroprotection targets was not associated with a lower risk for any of the outcomes studied. We may speculate that a longer follow-up would have been necessary to observe cardiorenal benefits in this group at lower risk. The benefits of a combined approach may also depend on the length of the follow-up.

In real-world settings, adherence to the international guidelines appears to be suboptimal in patients with CKD; adherence is therefore a key issue in routine clinical practice.[20]

TABLE 2 Incidence rates and HRs in patients with diabetic kidney disease, for the composite and individual cardiorenal outcomes, and all-cause mortality, as a function of the nephroprotection targets attained (each adjusted for the others)

Number of patients	n	Number of events	Rate per 100 person years	HR (95% CI)	*p*-Value
Composite cardiorenal outcome		535			
UACR					<.001
≥300 mg/g	490	287	20.9	1	
<300 mg/g	770	248	8.6	0.48 (0.40-0.59)	
HbA1c					.620
≥53 mmol/mol (7.0%)	644	274	12.7	1	
<53 mmol/mol (7.0%)	616	261	12.4	0.96 (0.80-1.14)	
Blood pressure					.520
≥130/80 mmHg	1049	453	12.8	1	
<130/80 mmHg	211	82	11.1	0.92 (0.72-1.18)	
Renin-angiotensin system inhibitor					.130
Not treated	256	121	15.9	1	
Treated	1004	414	11.8	0.85 (0.69-1.05)	
Kidney failure		261			
UACR					<.001
≥300 mg/g	490	177	11.9	1	
<300 mg/g	770	84	2.7	0.30 (0.22-0.42)	
HbA1c					.550
≥53 mmol/mol (7.0%)	644	121	5.1	1	
<53 mmol/mol (7.0%)	616	140	6.2	1.09 (0.83-1.42)	
Blood pressure					.020
≥130/80 mmHg	1049	235	6.1	1	
<130/80 mmHg	211	26	3.3	0.60 (0.40-0.91)	
Renin-angiotensin system inhibitor					.590
Not treated	256	55	6.6	1	
Treated	1004	206	5.4	1.09 (0.80-1.49)	
Kidney failure with replacement therapy		240			
UACR					<.001
≥300 mg/g	490	169	10.3	1	
<300 mg/g	770	71	2.2	0.27 (0.20-0.38)	
HbA1c					.840
≥53 mmol/mol (7.0%)	644	118	4.8	1	
<53 mmol/mol (7.0%)	616	122	5.2	1.03 (0.78-1.35)	
Blood pressure					.054
≥130/80 mmHg	1049	211	5.2	1	
<130/80 mmHg	211	29	3.6	0.67 (0.45-1.00)	
Renin-angiotensin system inhibitor					.308
Not treated	256	60	6.7	1	
Treated	1004	180	4.5	0.85 (0.63-1.16)	
MACE4		298			
UACR					.004
≥300 mg/g	490	124	8.3	1	
<300 mg/g	770	174	5.9	0.68 (0.53-0.88)	
HbA1c					.273
≥53 mmol/mol (7.0%)	644	165	7.3	1	
<53 mmol/mol (7.0%)	616	133	6	0.88 (0.69-1.11)	

(Continues)

TABLE 2 (Continued)

Number of patients	n	Number of events	Rate per 100 person years	HR (95% CI)	*p*-Value
Blood pressure					.130
≥130/80 mmHg	1049	244	6.6	1	
<130/80 mmHg	211	54	7.1	1.27 (0.93-1.72)	
Renin-angiotensin system inhibitor					.079
Not treated	256	70	8.6	1	
Treated	1004	228	6.2	0.78 (0.59-1.03)	
All-cause mortality		234			
UACR					.002
≥300 mg/g	490	97	5.9	1	
<300 mg/g	770	137	4.3	0.61 (0.45-0.82)	
HbA1c					.198
≥53 mmol/mol (7.0%)	644	126	5.1	1	
<53 mmol/mol (7.0%)	616	108	4.6	0.84 (0.64-1.10)	
Blood pressure					.187
≥130/80 mmHg	1049	191	4.7	1	
<130/80 mmHg	211	43	5.3	1.26 (0.90-1.77)	
Renin-angiotensin system inhibitor					.010
Not treated	256	64	7.2	1	
Treated	1004	170	4.3	0.67 (0.50-0.91)	

Note: The models were adjusted for age, sex, education level > 12 years, current smoking, estimated glomerular filtration rate, low-density lipoprotein cholesterol, body mass index, prescription of aspirin or another platelet anti-aggregant, statin, glucagon-like peptide-1 receptor agonist. Kidney failure was defined as an estimated glomerular filtration rate <15 ml/min/1.73 m^2.
Abbreviation: HbA1c, glycated haemoglobin; HR, hazard ratio; MACE4, four major cardiovascular events (i.e. cardiovascular death, myocardial infarction, stroke, hospital admission for heart failure); UACR, urinary albumin-creatinine ratio.

Our results suggest that (a) failure to achieve treatment targets in patients with diabetic kidney disease is associated with a poor cardiorenal prognosis, and (b) there is a need to tackle therapeutic inertia in this setting.

The ideal level of glycaemic control for patients with diabetic kidney disease is subject to debate.[21] The international guidelines favour individualized HbA1c targets, ranging from <6.5% to <8.0%.[6] For patients in whom the prevention of complications is the main goal, a lower HbA1c target (<7.0%) has been proposed.[6] A Cochrane review found that an HbA1c <7.0% target was associated with a lower incidence of non-fatal myocardial infarction and with the onset and progression of moderately elevated albuminuria.[22] However, the quality of the evidence was considered poor, and there was no observed effect on mortality.

In the present study, achievement of an HbA1c level <7.0% at baseline was not associated with a lower risk of adverse clinical outcomes after taking account of the other nephroprotection criteria and confounding factors. The few intervention trials to have specifically addressed the question of intensified glucose control in type 2 diabetes did not observe a clear association with all-cause mortality or even with cardiovascular events.[22] In the ADVANCE trial, however, a significantly lower incidence of nephropathy was observed in the group with intensive glycaemic control and an HbA1c target of ≤6.5%.[23] Furthermore, the risk of hypoglycaemic events in patients with diabetic kidney disease may hamper the intensification of glucose control.[24] In the future, real-life studies of larger populations might help to identify an optimal glycaemic target associated with slower progression of kidney disease and/or fewer cardiovascular events.

The clinical benefit conferred by the attainment of multifactorial targets in people with diabetic kidney disease was first suggested by the investigators of the Steno type 2 randomized trial in 1999, which included a relatively small number of patients with type 2 diabetes with albuminuria (n = 160).[9] Furthermore, the results of a trial in patients with type 2 diabetes and CKD in China showed that, compared with standard care, structured care was associated with the attainment of more treatment targets and a lower mortality/KFRT rate.[10]

The NID-2 interventional trial in 14 Italian diabetology clinics showed that in patients with type 2 diabetes with albuminuria in a primary prevention setting, intensive multifactorial therapy targeting the main cardiovascular risk factors (blood pressure <130/80 mmHg, HbA1c <7%; LDL-cholesterol <2.6 mmol/L, HDL-cholesterol <1.0/1.3 mmol/L in men/women, total-cholesterol <4.5 mmol/L) was

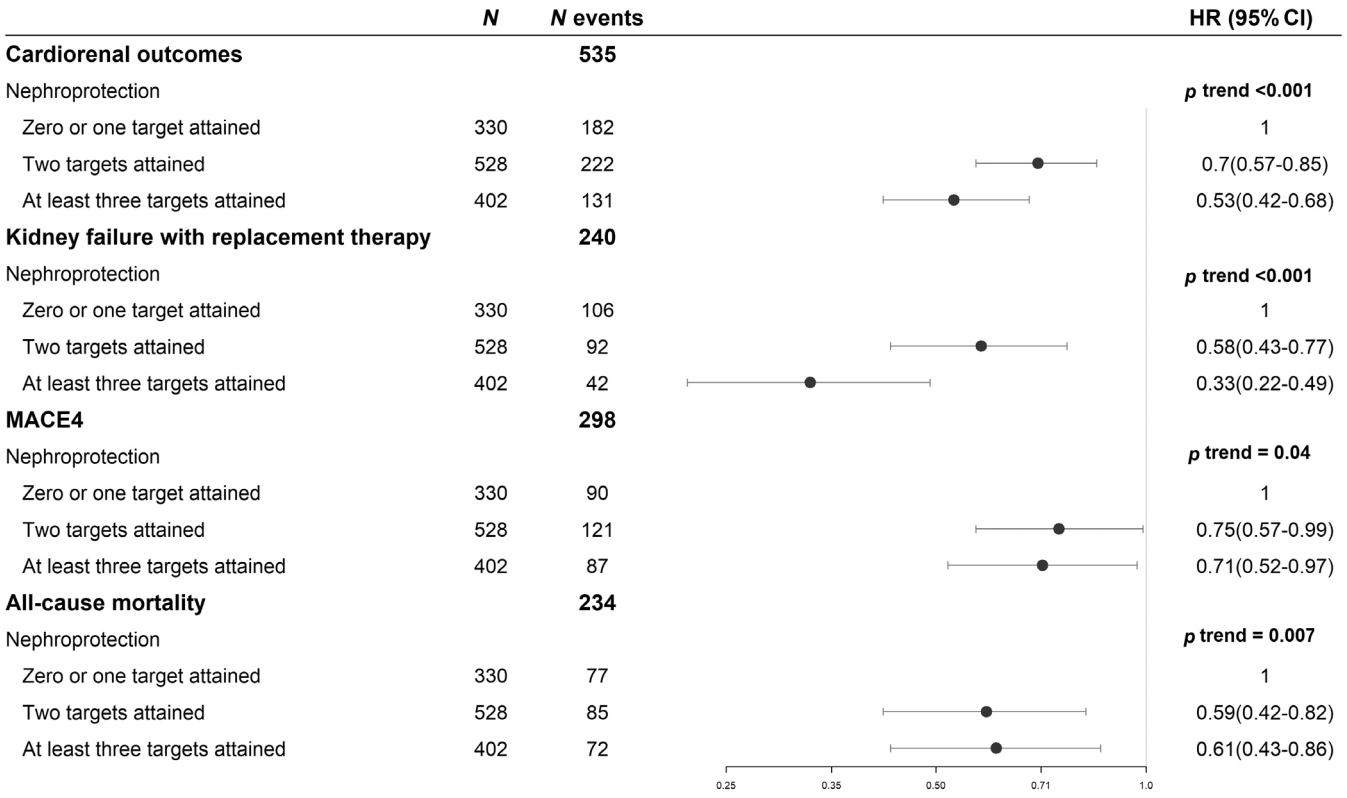

FIGURE 1 Forest plot of the adjusted hazard ratios (HRs) for the composite and individual cardiorenal outcomes, and all-cause mortality as a function of the number of nephroprotection targets attained in 1206 patients with diabetic kidney disease. HRs adjusted for age, sex, educational level >12 years, current smoking, estimated glomerular filtration rate, low-density lipoprotein-cholesterol, body mass index, prescription of aspirin or another platelet anti-aggregant, statin and glucagon-like peptide-1 receptor agonists.

associated with a lower incidence of cardiovascular events and all-cause death, compared with standard care.[11] In a post-hoc analysis of the NID-2 results, the number of risk factors on target correlated with better cardiovascular-free survival in this diabetic population with a high cardiovascular risk.[25] Our population had greater impairments in kidney function (a lower eGFR and greater albuminuria), and so our results extend previous findings to patients with moderate-to-severe CKD. Furthermore, we assessed the risk of kidney failure and not solely cardiovascular outcomes.

In a retrospective study of four cohorts in the United States, patients with diabetes who attained three treatment targets (HbA1c <7.0%, blood pressure <130/80 mmHg and LDL-cholesterol <3.1 mmol/L) had lower risks of micro- and macrovascular complications and all-cause mortality than patients who attained one or two targets.[26] However, KFRT was not evaluated separately from microvascular complications.[26] In a study of Japanese patients with type 2 diabetes who had preserved kidney function at baseline, attainment of a combination of the same targets as in the US cohorts was associated with a lower UACR in a cross-sectional analysis and with a smaller decline in eGFR and a smaller increase in UACR in a prospective analysis.[27]

The present study's observational design means that we cannot address the impact of a multifaceted intervention. However, our results are in line with those of intervention studies. Nowadays, it would be difficult to set up an interventional, prospective trial to test the benefits of applying versus not applying the recommended appropriate care. Observational studies of cohorts such as ours can help to determine which targets and which combinations of targets are most beneficial.

Our study had a number of limitations and strengths. Because of the late introduction of SGLT2 inhibitors to the French market (2020), none of our patients received these drugs; our study cannot address any specific, additional protection conferred by this therapeutic class. Attainment of nephroprotection targets was assessed at baseline and then 1 and 2 years thereafter; during the follow-up period, there were few changes in the percentages of patients attaining the various targets. The cohort included patients with different types of underlying kidney disease, and some patients probably had several. Few patients had a kidney biopsy. However, the patients' characteristics are probably similar to those seen in clinical practice with patients with diabetes and kidney disease. The study's strengths include patient recruitment from a representative sample of French nephrology outpatient clinics, a low proportion of missing data, in-depth phenotypic data and the documentation of a large number of well-characterized cardiorenal events over a median follow-up period of 5 years. Lastly, we systematically adjusted our

TABLE 3 Adjusted HRs for the composite and individual cardiorenal events and all-cause mortality as a function of the number of nephroprotection targets attained by albuminuria strata, in patients with diabetic kidney disease.

		Urinary albumin-to-creatinine ratio			
		<300 mg/g		≥300 mg/g	
		n = 770		n = 490	
Number of patients	n	HR (95% CI)	*p* for trend	HR (95% CI)	*p* for trend
Cardiorenal outcome					
Number of events		248		287	
Nephroprotection targets attained			.859		.070
None of the three targets	96	1		1	
One of the three targets	574	0.97 (0.55-1.70)		0.68 (0.44-1.05)	
At least two of the three targets	590	0.95 (0.55-1.66)		0.61 (0.39-0.96)	
Kidney failure					
Number of events		84		177	
Nephroprotection targets attained			.790		.400
None of the three targets	96	1		1	
One of the three targets	574	0.92 (0.35-2.43)		0.92 (0.48-1.76)	
At least two of the three targets	590	0.89 (0.35-2.26)		0.81 (0.42-1.56)	
Kidney failure with replacement therapy					
Number of events		71		169	
Nephroprotection targets attained			.820		.070
None of the three targets	96	1		1	
One of the three targets	574	1.81 (0.47-7.02)		0.82 (0.46-1.47)	
At least two of the three targets	590	1.63 (0.43-6.22)		0.63 (0.35-1.13)	
MACE4					
Number of events		174		124	
Nephroprotection targets attained			.992		.097
None of the three targets	96	1		1	
One of the three targets	574	0.91 (0.46-1.78)		0.59 (0.32-1.09)	
At least two of the three targets	590	0.94 (0.48-1.83)		0.53 (0.28-0.98)	
All-cause mortality					
Number of events		137		97	
Nephroprotection targets attained			.740		.010
None of the three targets	96	1		1	
One of the three targets	574	0.57 (0.29-1.10)		0.46 (0.23-0.90)	
At least two of the three targets	590	0.78 (0.42-1.46)		0.35 (0.17-0.70)	

Note: Models are adjusted for age, sex, education level >12 years, current smoking, estimated glomerular filtration rate, low-density lipoprotein cholesterol, body mass index, prescription of aspirin or another platelet anti-aggregant, statin and a glucagon-like peptide-1 receptor agonist. Kidney failure was defined as estimated glomerular filtration rate <15 ml/min/1.73 m^2. MACE4, four major cardiovascular events (i.e. cardiovascular death, myocardial infarction, stroke, hospital admission for heart failure).
Abbreviations: HR, hazard ratio.

multivariable models for eGFR at inclusion and several covariates that may influence the risks of cardiovascular events and kidney disease progression.[28]

In conclusion, our present results show that the attainment of at least two treatment targets was consistently associated with a lower risk of cardiorenal events, KFRT, MACE4 and all-cause mortality compared with the attainment of zero or one target only. Among patients with severely increased albuminuria, achievement of the other nephroprotection targets was associated with a better prognosis. Our findings suggest that the attainment of multiple treatment targets is important for the cardiorenal prognosis of inpatients with diabetic kidney disease.

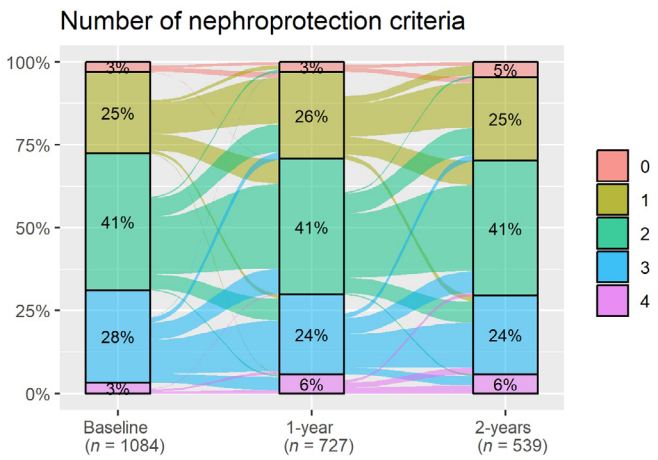

FIGURE 2 Sankey plots showing the change from baseline over 2 years in the number of nephroprotection targets attained by patients with diabetic kidney disease.

AUTHOR CONTRIBUTIONS

FB, BB, BS and DF contributed to the analysis and writing manuscript. YD and OL carried out the statistical analyses. BS contributed to the design of the cohort. CC, LF, ML, SL, ZM, MM, BS, and NAP conducted the study and data collection. All authors have reviewed the manuscript for important intellectual content. All authors approved the final version of the manuscript. NAP is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

FB has been a paid as consultant for AstraZeneca, Bayer, Boehringer, and NovoNordisk. BS has received research grants to support the cohort from AstraZeneca, Boeringher Ingelheim, Fresenius Medical Care, GSK, Vifor Fresenius. DF received travel support from Astellas, Theradial, lecture fees from Astellas, GSK, Lilly and participated to advisory board for Astellas, AstraZeneca, Dr Schar, GSK, and Vifor. Other authors have no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15507.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon reasonable request by contacting the CKD-REIN study coordination staff at ckdrein@inserm.fr.

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REFERENCES

1. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2020;395(10225):709-733.
2. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. *Lancet*. 2017;389(10075):1238-1252.
3. Neuen BL, Ohkuma T, Neal B, et al. Effect of Canagliflozin on renal and cardiovascular outcomes across different levels of albuminuria: data from the CANVAS program. *J Am Soc Nephrol*. 2019;30(11):2229-2242.
4. Bakris GL, Agarwal R, Anker SD, et al. Effect of Finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med*. 2020;383(23):2219-2229.
5. Rossing P, Caramori ML, Chan JCN, et al. Executive summary of the KDIGO 2022 clinical practice guideline for diabetes Management in Chronic Kidney Disease: an update based on rapidly emerging new evidence. *Kidney Int*. 2022;102(5):990-999.
6. Kidney Disease. Improving global outcomes diabetes work G. KDIGO 2020 clinical practice guideline for diabetes Management in Chronic Kidney Disease. *Kidney Int*. 2020;98(4S):S1-S115.
7. Eckardt KU, Delgado C, Heerspink HJL, et al. Trends and perspectives for improving quality of chronic kidney disease care: conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference. *Kidney Int*. 2023;104:888-903.
8. Navaneethan SD, Zoungas S, Caramori ML, et al. Diabetes Management in Chronic Kidney Disease: synopsis of the KDIGO 2022 clinical practice guideline update. *Ann Intern Med*. 2023;176(3):381-387.
9. Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the steno type 2 randomised study. *Lancet*. 1999;353(9153):617-622.
10. Chan JC, So WY, Yeung CY, et al. Effects of structured versus usual care on renal endpoint in type 2 diabetes: the SURE study: a randomized multicenter translational study. *Diabetes Care*. 2009;32(6):977-982.

11. Sasso FC, Pafundi PC, Simeon V, et al. Efficacy and durability of multifactorial intervention on mortality and MACEs: a randomized clinical trial in type-2 diabetic kidney disease. *Cardiovasc Diabetol*. 2021;20(1):145.
12. Stengel B, Muenz D, Tu C, et al. Adherence to the kidney disease: improving global outcomes CKD guideline in nephrology practice across countries. *Kidney Int Rep*. 2021;6(2):437-448.
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(9784):2181-2192.
14. Stengel B, Combe C, Jacquelinet C, et al. The French chronic kidney disease-renal epidemiology and information network (CKD-REIN) cohort study. *Nephrol Dial Transplant*. 2014;29(8):1500-1507.
15. Girerd X, Radauceanu A, Achard JM, et al. Evaluation of patient compliance among hypertensive patients treated by specialists. *Arch mal Coeur Vaiss*. 2001;94(8):839-842.
16. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.
17. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from kidney disease: improving global outcomes (KDIGO). *Kidney Int*. 2005;67(6):2089-2100.
18. Fox CS, Matsushita K, Woodward 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(9854):1662-1673.
19. Oshima M, Neuen BL, Li J, et al. Early change in albuminuria with canagliflozin predicts kidney and cardiovascular outcomes: a post hoc analysis from the CREDENCE trial. *J Am Soc Nephrol*. 2020;31(12):2925-2936.
20. Alencar de Pinho N, Levin A, Fukagawa M, et al. Considerable international variation exists in blood pressure control and antihypertensive prescription patterns in chronic kidney disease. *Kidney Int*. 2019;96(4):983-994.
21. Coca SG, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis intensive glucose control in type 2 diabetes. *Arch Intern Med*. 2012;172(10):761-769.
22. Ruospo M, Saglimbene VM, Palmer SC, et al. Glucose targets for preventing diabetic kidney disease and its progression. *Cochrane Database Syst Rev*. 2017;6(6):CD010137.
23. ADVANCE Collaborative Group, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24):2560-2572.
24. Balkau B, Metzger M, Andreelli F, et al. Impact of sex and glucose-lowering treatments on hypoglycaemic symptoms in people with type 2 diabetes and chronic kidney disease. The French chronic kidney disease - renal epidemiology and information network (CKD-REIN) study. *Diabetes Metab*. 2019;45(2):175-183.
25. Sasso FC, Simeon V, Galiero R, et al. The number of risk factors not at target is associated with cardiovascular risk in a type 2 diabetic population with albuminuria in primary cardiovascular prevention. Post-hoc analysis of the NID-2 trial. *Cardiovasc Diabetol*. 2022;21(1):235.
26. Shi Q, Liu S, Krousel-Wood M, Shao H, Fonseca V, Shi L. Long-term outcomes associated with triple-goal achievement in patients with type 2 diabetes mellitus (T2DM). *Diabetes Res Clin Pract*. 2018;140:45-54.
27. Minato S, Takenouchi A, Kitaoka K, et al. Associations of ABC (hemoglobin A1c, blood pressure and low-density lipoprotein cholesterol) goal achievement with chronic kidney disease in type 2 diabetic patients with preserved kidney function. *J Clin Med Res*. 2019;11(12):818-824.
28. Matsushita K, Coresh J, Sang Y, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol*. 2015;3(7):514-525.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX

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