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Clinical Research Article

Strong Negative Association of non-HDL Cholesterol Goal Achievement With Incident CKD Among Adults With Diabetes

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Abstract

Context: The relative importance of the control of different metabolic risk factors for the prevention of chronic kidney disease among patients with diabetes in real life conditions is insufficiently understood.

Objective: We evaluated the effect of the achievement of glycated hemoglobin A_{1c} (HbA_{1c}), systolic blood pressure (SBP), and low-density lipoprotein cholesterol (LDLc) or non–high-density lipoprotein cholesterol (non-HDLc) goals (ABC goals) on the development of incident chronic kidney disease (iCKD) among patients with diabetes.

Methods: In a nationwide registry of all individuals diagnosed with diabetes assisted by the health system in Colombia, we analyzed the association between baseline or sustained goal achievement and development of iCKD over a 4-year follow-up. iCKD was defined as a new occurrence of an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2, hemodialysis, peritoneal dialysis, or kidney transplant.

Results: The study included 998 790 adults with diabetes (56% female, mean age 59). There were 125 626 cases of iCKD. After adjustment for multiple confounders, a baseline SBP less than 130 mm Hg (odds ratio [OR] 0.79 [0.78-0.80]) and a baseline HbA_{1c} less than 7.0% (OR 0.86 [0.85-0.87]) were negatively associated with iCKD. Sustained achievement showed stronger negative associations with iCKD than just baseline achievement. Considering each goal separately, sustained non-HDLc less than 130 mg/dL had the strongest negative association with iCKD (OR 0.67 [0.65-0.69]). Patients who maintained the triple ABC goal over the entire follow-up had 32% (29-34) lower odds of developing CKD, 38% (34-42) if they additionally kept a normal body mass index (BMI). Sustained ABC control including a normal BMI was more strongly associated with a lower incidence of CKD in patients of Black race (OR 0.72 vs 0.89; *P* for interaction = .002).

Conclusion: At the country level, sustained achievement of ABC goals and most especially non-HDLc were associated with substantial reductions in iCKD.

Key Words: diabetes, chronic kidney disease, non-HDL cholesterol, metabolic control, diabetes complications, hypertension

Abbreviations: ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HbA_{1c}, glycated hemoglobin A_{1c}; iCKD, incident chronic kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; LDLc, low-density lipoprotein cholesterol; non-HDLc, non–high-density lipoprotein cholesterol; NRCKD, Colombian National Registry of Chronic Kidney Disease; OR, odds ratio; SBP, systolic blood pressure; UAER, urinary albumin excretion rate.

Chronic kidney disease (CKD) is a major health issue worldwide. Progressing CKD leads not only to end-stage renal disease (ESRD) but also to multiple adverse clinical outcomes, including cardiovascular disease, death, and disability [1]. In sharp contrast to other noncommunicable diseases, CKD prevalence seems to be increasing over time. Recent studies from the Global Burden of Disease Collaboration estimate the global prevalence of CKD at 9.1%, an increase of almost 30% over the last 30 years [2]. Low- or middle-income countries bear 80% of the disease burden from CKD [3].

Diabetes is currently the second leading cause of CKD and the top cause of ESRD [4]. In 2019, type 2 diabetes was estimated to have caused 2.5 million incident CKD (iCKD) cases and more than 400 000 deaths. The risk of developing diabetic nephropathy does not follow closely the degree of hyperglycemia, especially among patients with type 1 diabetes [5], indicating that other disturbances must act synergistically with hyperglycemia to promote the development of glomerular and tubular changes that characterize CKD. These alterations include excess plasma free fatty acids, oxidative stress, vascular shear stress induced by transmitted systemic hypertension,

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impaired autoregulation, hyperperfusion or hypoperfusion, and activation of the renin-angiotensin-aldosterone system [6].

This multifactorial pathogenesis suggests that successful and continued control of the main risk factors may substantially affect the appearance of new CKD in people with diabetes. The positive and long-lasting effect of early glycemic control on the development of CKD has been proven for patients with type 1 diabetes in the Diabetes Control and Complications Trial—Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC) study [7], and for patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS) [8]. However, the associations between tight blood pressure or blood lipids control and the risk of iCKD have not been equally robust. This may be due to a host of factors, but it is important to note that treatment goals, pharmacological agents, and guideline adoption have all changed notably since the publication of these milestone trials.

With this background, we aimed to evaluate the association between the achievement of glycated hemoglobin A_{1c} (HbA1c), systolic blood pressure (SBP), and low-density lipoprotein cholesterol (LDLc) or non–high-density lipoprotein cholesterol (non-HDLc) goals, the so-called ABC goals of diabetes, and the development of iCKD in a nationwide sample of nearly all patients with diabetes in the Colombian Health System. We also explored the differential effect of achieving these goals only at baseline vs sustaining them over time, and whether these associations differed in subgroups defined by race or body mass index (BMI).

Materials and Methods

We analyzed data from the Colombian National Registry of Chronic Kidney Disease (NRCKD), a nationwide database of people with diagnosed diabetes, hypertension, or CKD assisted by the Colombian Health System [9]. Data are mandatorily reported by all public and private insurers June 30 of every year, comprising information gathered since July 1 of the preceding year. Each data point registered in the database corresponds to the last measurement within the observation period, for that individual. Since more than 99% of the population is affiliated with the national health care system, the NRCKD has a national scope [9]. The NRCKD ensures data quality and completeness by taking the following steps: Initially an algorithm identifies mistakes in the reporting procedure. Then, an experienced team compares the reported information with clinical records by a well-established data-monitoring process in a representative sample of cases stratified by hypertension, diabetes, and CKD status [10]. If any inconsistency is identified, correct data are captured from clinical records.

Eligibility and Variables

We studied all individuals with diabetes reported to the NRCKD between July 1, 2015, and June 30, 2019. For each study year, people younger than 18 at the start of the year were excluded. We also excluded individuals whose estimated glomerular filtration rate (eGFR) calculated from the first plasma creatinine registered in the NRCKD was less than 60 mL/min, or who had received hemodialysis, peritoneal dialysis, or kidney transplant at the first observation period. The diagnosis of diabetes or hypertension was analyzed as reported to the NRCKD (yes/no [Y/N] as defined by the treating physician). Goals were defined according to the International Diabetes Federation, the American Diabetes Association, and the Latin American Diabetes Association—ALAD [11-13]. Treatment goals were HbA_{1c} less than 7% (< 53 mmol/mol), SBP less than 130 mm Hg, LDLc less than 100 mg/dL, and non-HDLc less than 130 mg/dL. The joint triple goal was HbA_{1c} less than 7% (< 53 mmol/mol), plus SBP less than 130 mm Hg, plus LDLc less than 100 mg/dL. For some analyses, we included BMI between 18.5 and 25.0 as an additional goal.

Data on age, sex, race or ethnic group, type of health insurance, weight, height, and clinical chemistry results were also taken from the NRCKD. BMI was classified as recommended by the World Health Organization [14]. For eGFR, we used the Modified Diet for Renal Disease (MDRD) equation, found to be more accurate than other equations among patients with diabetes [15]. Based on eGFR, CKD stages were defined as follows: stage 1: GFR greater than or equal to 90 mL/min; stage 2: GFR: 60 to less than 90 mL/min/1.73 m^2; stage 3a: GFR: 45 to less than 60 mL/min/1.73 m^2; stage 3b: GFR: 30 to less than 45 mL/min/1.73 m^2; stage 4: GFR 15 to less than 30 mL/min/1.73 m^2; and stage 5: GFR: less than 15 mL/min/1.73 m^2 [16]. Insurance was analyzed according to the 3 categories present in the Colombian Health System: third-party payer (run by private insurers), state insurance, and a special/exceptional health system for the security forces and some public universities [17].

We collapsed the NRCKD race categories "Raizal," "Palenquero," and "Black, Mulatto, Afro-Colombian, or Afro-descendant" into a single category called "Black" and analyzed self-reported race as Black vs all others. We made this decision because very few individuals (< 1% in any given year) identified themselves as belonging to one of the other race categories (indigenous or Roma).

Data Analysis

Quantitative variables are presented as means and SDs, categorical variables as absolute and relative frequencies. For all analyses, the main outcome was iCKD, defined as a new occurrence of any of the following: i, an eGFR less than 60 mL/min/1.73 m^2; ii, start of hemodialysis; iii, start of peritoneal dialysis; or iv, receiving a kidney transplant. All these variables are reliably captured and audited in the NRCKD.

The association between independent variables and incident CKD was evaluated using multivariable logistic regression models. There was a set of potentially confounding variables adjusted for in all models, including sex, age, race, insurance type, and BMI. Additionally, we adjusted for the variables representing goals other than the one being evaluated. Thus, in models to evaluate the association between HbA_{1c} goal and iCKD, we adjusted for the basic set of confounders, plus hypertension status and non-HDLc. When SBP was the main exposure, we adjusted for the basic confounders plus HbA_{1c} and non-HDLc. When one of the plasma lipids was the exposure, we adjusted for basic confounders plus hypertension status and HbA_{1c}. In models simultaneously evaluating all goals, we adjusted only for the basic confounders.

The first group of analyses considered the baseline achievement of each treatment goal as an independent variable. In contrast, a second group considered the sustained achievement of each treatment goal throughout the complete study period. The set of confounders being adjusted for was identical in both cases. We also performed stratified analyses to explore how goal achievement was related to iCKD in subgroups defined by race (Black vs other), and BMI category (normal,

overweight, or obesity). In a last set of analyses, we explored the association between baseline urinary albumin excretion rate (UAER) and the primary outcome. For this purpose, UAER was classified into 3 categories: i, less than 20 mg/L or less than 30 mg/g urinary creatinine; ii, 20 to 200 mg/L or 30 to 300 mg/g; and iii, greater than 200 mg/L or greater than 300 mg/g. The set of confounders adjusted for were the same as in prior analyses. Interactions were tested by the statistical significance of the regression coefficient associated with the multiplicative term between goal achievement status and the stratification variable. All associations are expressed as odds ratios (OR) with 95% CIs. All analyses were 2-sided and performed at a 5% significance level. Statistical analyses were carried out in Stata, version 17 (StataCorp LP).

Ethical Considerations

This research was based on anonymized secondary data sources and did not include any private information that could make any person identifiable. To protect privacy, data were anonymized through the use of a database-specific individual identification. This study has no risk for the participants and no informed consent or ethical approval was required. Colombian legislation (resolution 8430 of 1993 by the Colombian Ministry of Health) allows the use of deidentified clinical data reported by health insurers for analyses that may positively affect the follow-up and control of high-impact diseases. Confidentiality was guaranteed throughout the information processing (reporting, managing, and analysis).

Results

We studied 998 790 adults with diabetes, 56.6% of whom were female. Baseline mean age was 59.5 years, with only small differences in age distribution between sexes (Table 1). More than two-thirds of participants had third-party insurance. Patients of Black race accounted for 7.2% of the study sample, and nearly one-half of participants had a BMI in the obesity range. The prevalence of obesity was almost 5 percentage points higher among women than men. Mean HbA_{1c} was 7.52% (59 mmol/mol), and most patients were in CKD stage 1. Almost a quarter of participants had UAER above 30 mg/g of creatinine or 20 mg/L of urine. Follow-up was 1 year in 99 662 (10.0%), 2 years in 114 445 (11.5%), 3 years in 148 151 (14.8%), and 4 years in 636 532 participants (63.7%). At baseline, most participants (82.5%) attained the SBP goal, while the respective proportions were 52% for the HbA_{1c} goal, 40.7% for the non-HDLc goal, and 43.4% for the LDLc goal. There were 125 626 cases of incident CKD over the study follow-up. The incidence of CKD was 5.6% in 2017, 5.7% in 2018, and 7.0% in 2019, being always about 1.5% higher among women relative to men. The cumulative incidence of each of the renal outcome was as follows: eGFR less than 60 mL/min 12.1%, hemodialysis 0.47%, peritoneal dialysis 0.14%, and kidney transplant 0.01%.

Baseline Measures and Incident Chronic Kidney Disease

Among baseline control measures, an SBP less than 130 mm Hg showed the strongest negative association with iCKD (Table 2). An HbA_{1c} less than 7.0% was associated with reductions in iCKD only after multivariable adjustment (OR 0.86; 95% CI, 0.85-0.87). Plasma LDLc and non-HDLc within recommended thresholds were positively associated with iCKD. Joint achievement of the SBP, HbA_{1c}, and LDLc goal reduced the odds of incident CKD by 6% (95% CI, 5%-8%). Further, participants with good control of these 3 measures plus a normal BMI had 12% lower iCKD (95% CI, 9%-14%).

Analyses by Race

The negative association between baseline SBP goal and iCKD was similar among patients of Black race vs other races (Table 3). Conversely, a well-controlled HbA_{1c} at baseline was much more strongly associated with reduced odds of iCKD among participants of Black race (25% lower in Black race, 14% in other races; P for interaction < .001). This translated to a larger effect of achieving the triple goal at baseline for patients of Black race (P for interaction = .050) (see Table 3). The addition of a normal BMI to the triple goal also seemed to provide a larger benefit for patients of Black race (P for interaction = .002).

Analyses by Body Mass Index Category

The protective effect of reaching the SBP goal at baseline was similar in all BMI groups. Interestingly, achieving the HbA_{1c} goal at baseline lowered the odds of iCKD significantly more among patients with normal weight (P for interaction = .001). Consequently, the triple goal at baseline showed a statistically significant stronger negative association with iCKD among those with normal BMI (P for interaction = .001) (Table 4).

Effect of Sustained Risk Factor Control

Attainment of treatment goals at baseline reduced the odds of developing CKD, but the maintenance of such goals over time greatly potentiated this effect. Achieving and sustaining SBP and HbA_{1c} goals over the study follow-up decreased the odds of incident CKD by 28% and 22%, respectively (Fig. 1). Remarkably, a sustained non-HDLc less than 130 mg/dL showed the strongest negative association with incident CKD (OR 0.67; 95% CI, 0.65-0.69). Sustained achievement of the LDLc goal also had a negative association with outcome (OR 0.89; 95% CI, 0.87-0.91). Continued accomplishment of the triple goal reduced the odds of iCKD by 32%. This reduction increased to 38% when a normal BMI was also sustained. Despite the impressive consequences of reaching and keeping risk factors under control, only 5.5% of the study participants sustained the triple goal and only 1.2% of them were able to, in addition, maintain a normal BMI (see Fig. 1).

Baseline Albuminuria and Incident Chronic Kidney Disease

The presence of an abnormal UAER at baseline was substantially associated with iCKD. Relative to those with a UAER in the A1 Kidney Disease: Improving Global Outcomes (KDIGO) category (< 30 mg/g or < 20 mg/L), the multivariable-adjusted OR for the association between a UAER in the KDIGO A2 category (30-300 mg/g or 20-200 mg/L) and iCKD was 1.35 (95% CI, 1.32-1.37; n for model: 573 821). Among those with a baseline UAER in the A3 KDIGO category (> 300 mg/g or > 200 mg/L), the incidence of CKD over the follow-up more than doubled (OR 2.17; 95% CI, 2.10-2.25; n for model: 573 821). The effect of being in category A2 was significantly larger among patients of Black race (OR 1.67; 95% CI, 1.54-1.81 vs OR

Table 1. Baseline characteristics of study participants

	Men (n = 433 219)	Women (n = 565 571)	Total (n = 998 790)
Age, y	59.0 (13.1)	59.8 (13.3)	59.5 (13.2)
Age group, %			
< 40	7.4	6.9	7.1
40-49	15.1	13.4	14.1
50-59	27.9	28.8	28.4
60-69	28.0	27.6	27.8
70-79	16.0	16.6	16.3
≥ 80	5.6	6.8	6.3
Health insurance, %			
Third-party	73.2	63.2	67.5
State	23.3	35.9	31.3
Special/Exceptional	1.5	0.9	1.2
Race, %			
Black	6.6	7.6	7.2
Other	93.4	92.4	92.8
n for BMI	432 204	563 774	995 978
BMI	27.8 (4.8)	28.6 (5.6)	28.2 (5.3)
BMI category, %			
Normal weight	20.6	20.2	20.4
Overweight	32.3	28.1	29.9
Obesity	47.2	51.7	49.7
n for BP	428 210	560 189	988 399
SBP, mm Hg	123.5 (13.6)	123.9 (13.9)	123.7 (13.7)
DBP, mm Hg	76.8 (8.7)	76.6 (8.7)	76.7 (8.7)
n for HbA_{1c}	367 129	467 269	834 398
HbA_{1c}, %	7.59 (2.2)	7.46 (2.1)	7.52 (2.1)
HbA_{1c}, mmol/mol	59	58	59
n for blood lipids	369 658	496 385	866 043
Non-HDLc, mg/dL	140.0 (45.6)	146.3 (46.1)	143.6 (46.0)
LDLc, mg/dL	106.2 (38.0)	113.0 (39.5)	110.1 (39.0)
CKD stage, %			
1	65.7	60.8	63.0
2	34.3	39.2	37.0
Urinary albumin excretion, %			
< 30 mg/g or < 20 mg/L	72.24	78.72	75.85
30-299 mg/g or 20-199 mg/L	23.24	18.12	20.38
≥ 300 mg/g or ≥ 200 mg/L	4.52	3.16	3.76
Hypertension, %	60.9	68.0	64.9

Data are means (SD) unless indicated otherwise. CKD stages were defined according to the KDIGO classification.
Abbreviations: BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; HbA_{1c}, glycated hemoglobin A_{1c}; KDIGO, Kidney Disease: Improving Global Outcomes; LDLc, low-density lipoprotein cholesterol; non-HDLc, non–high-density lipoprotein cholesterol; SBP, systolic blood pressure.

1.33; 95% CI, 1.31-1.36 for other races; *P* for interaction < .001). For category A3, the association did not differ by race.

Having a normal weight was associated a greater relative influence of albuminuria on iCKD. The OR for UAER category A2 relative to A1 was 1.41 (95% CI, 1.36-1.46) for patients with normal BMI, 1.38 (95% CI, 1.34-1.42) for those with overweight, and 1.28 (95% CI, 1.24-1.32) for those with obesity (*P* for interaction <.001). Similarly, the OR for category A3 was 2.35 for patients of normal weight (95% CI, 2.19-2.53), 2.18 for those with overweight (95% CI, 2.06-2.31), and 2.06 for those with obesity (95% CI, 1.95-2.18; *P* for interaction <.001).

Discussion

In this prospective study of almost a million people representing the vast majority of patients with diagnosed diabetes in Colombia, we found that strict control of a few fundamental risk factors, and especially of non-HDLc, a frequently neglected target for CKD prevention, may notably affect the

Table 2. Association between measures of diabetes control at baseline and incident chronic kidney disease

Measure of interest	Unadjusted OR	Adjusted OR	n for adjusted model
SBP < 130 mm Hg at baseline[a]	0.74 (0.73-0.75)	0.79 (0.78-0.80)	755 844
HbA_{1c} < 7.0% at baseline[b]	1.00 (0.98-1.01)	0.86 (0.85-0.87)	758 088
Non-HDLc < 130 mg/dL[c]	1.18 (1.17-1.20)	1.05 (1.04-1.07)	758 285
LDLc < 100 mg/dL[c]	1.17 (1.15-1.18)	1.09 (1.07-1.10)	752 056
Joint SBP, HbA_{1c}, and LDLc goal[d]	1.03 (1.01-1.05)	0.94 (0.92-0.95)	719 010
Joint SBP, HbA_{1c}, LDLc, and BMI goal[e]	1.06 (1.03-1.09)	0.88 (0.86-0.91)	719 010

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin A_{1c}; LDLc, low-density lipoprotein cholesterol; non-HDLc, non–high-density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure.
[a]Adjusted for sex, age, race (Black vs other), insurance type, BMI, baseline HbA_{1c}, and baseline non-HDL cholesterol.
[b]Adjusted for sex, age, race (Black vs other), insurance type, BMI, baseline non-HDL cholesterol, and hypertension status.
[c]Adjusted for sex, age, race (Black vs other), insurance type, BMI, baseline HbA_{1c}, and hypertension status.
[d]Adjusted for sex, age, race (Black vs other), insurance type, and BMI.
[e]Adjusted for sex, age, race (Black vs other), and insurance type.

incidence of CKD. We observed a cumulative incidence of CKD of 12.4% over 4 years, corresponding to an average yearly incidence of 3.1%. Recent (2015-2020) data from an electronic health record–based registry in California showed a yearly incidence of CKD between 64 and 81 per 1000 person/years (6.4-8.1%/year) among adults with diabetes [18]. Thus, our results are plausible and comparable to those obtained in other populations.

When considering baseline values individually, SBP control had the strongest negative association with iCKD, but HbA_{1c} control was also a significant predictor. Good HbA_{1c} control seemed to have a significantly stronger association with favorable outcomes among patients of Black race, and among people with a normal BMI. Most important, the continued control of SBP, HbA_{1c}, and LDLc translated into approximately a third less iCKD. Sadly, however, only about 5% of patients achieved this, and only about 1% kept this triple goal plus a normal BMI over the study duration. We were surprised to find that sustained control of non-HDLc had the strongest negative association with iCKD. This result highlights the growing relevance of this metric, and the importance of addressing disturbances of lipoprotein metabolism as a measure to prevent CKD. As expected, the presence of an increased UAER at baseline translated into a higher incidence of CKD, so that it almost doubled when baseline UAER exceeded 300 mg/g or 200 mg/L.

The value of proactive management and simultaneous control of relevant metrics in patients with type 2 diabetes was proven in the Steno-2 study, in which goal-oriented intensive diabetes treatment for 8 years translated into a 61% lower risk of iCKD [19]. Likewise, a later cohort study with noncontemporaneous controls from the same center showed that implementation of goal-based treatment guidelines resulted in a lower incidence of CKD [20]. These impressive results, however, came from a trial of modest size in a very particular population from a single clinic, so their applicability to a broader context was uncertain. Our results confirm that even at the level of an entire country, achievement of the ABC goals may indeed considerably reduce the risk of iCKD. They also position non-HDLc as an important target for CKD prevention in diabetes. Our results seemed to suggest no additional benefit from achieving sustained goals over non-HDLc alone. In reality, variables reflected in treatment goals are correlated between them, so patients who achieve one of them are also more likely to achieve the others, so it is difficult to unequivocally attribute a portion of the overall benefit to a single goal. Also, it is possible that the time frame over which renal benefits are manifested is different for each treatment goal, so that the extra benefit of achieving each additional goal may require a follow-up longer than 4 years.

The importance of early glycemic control for the prevention of advanced CKD was demonstrated by a 5-year observational follow-up of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) study. In ADVANCE, differences in HbA_{1c} between the intensive and conventional treatment groups had already disappeared by the first posttrial visit. Still, after 9.9 years of total follow-up, intensive glucose control was associated with a 46% long-term reduction in ESRD [21]. In fact, a meta-analysis of more vs less strict glycemic control that included the landmark studies ACCORD, ADVANCE, UKPDS, and VADT found that more intensive glucose control reduced the incidence of total "kidney events" by 20% [22]. These results align with our findings of a 14% lower risk of iCKD for good baseline HbA_{1c} control, and a 22% lower risk for sustained control.

Considering BP control, solid evidence supports its importance in preventing CKD in diabetes. In the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study, every 10-mm Hg rise in baseline SBP increased the risk for ESRD or death by 6.7% [23]. Two large, prospective studies from Korea have found substantial increases in the risk of incident CKD with SBP elevations above 130 mm Hg [24, 25]. In our study, SBP control was clearly associated with reductions in CKD, with a larger effect size when this goal was maintained over time.

We were surprised to encounter a small but significant positive association between baseline achievement of lipid goals and iCKD. We believe that this was due to a reverse causation/confounding by indication problem, namely, that patients prescribed lipid-lowering drugs frequently received them because of a higher burden of cardiorenal risk factors or a history of cardiovascular events. Since such patients have lower LDLc and non-HDLc and a higher incidence of CKD, this would manifest itself as a spurious association between lower LDLc and iCKD. Despite this apparently paradoxical association between baseline plasma lipid goals and iCKD, we found a significant negative association between sustained lipid goal achievement and CKD, most notably for non-HDLc. This metric encompasses the cholesterol content of a variety of lipoproteins that contain apolipoprotein B and hence have atherogenic potential. Remarkably, participants who sustained a non-HDLc below 130 mg/dL had 33% less iCKD, the strongest negative association for any individual goal. Several observational studies have documented a lower incidence of CKD among people with reduced concentrations of triglycerides or triglyceride-rich lipoproteins, among them ARIC (Atherosclerosis Risk in Communities)

Table 3. Association between measures of diabetes control at baseline and incident chronic kidney disease, by race

Measure of interest	Race				*P* for interaction
	Black		Other		
Goal	Adjusted OR (95% CI)	n for model	Adjusted OR (95% CI)	n for model	
SBP < 130 mm Hg[a]	0.75 (0.70-0.81)	54 251	0.79 (0.78-0.81)	701 583	.15
HbA_{1c} < 7.0%[b]	0.75 (0.70-0.79)	54 291	0.86 (0.85-0.88)	703 786	< .001
Non-HDLc < 130 mg/dL[c]	1.18 (1.11-1.25)	54 291	1.04 (1.03-1.06)	703 983	< .001
LDLc < 100 mg/dL[c]	1.15 (1.08-1.21)	54 854	1.08 (1.07-1.10)	697 191	.022
Joint SBP, HbA_{1c}, and LDLc goal[d]	0.87 (0.81-0.94)	52 273	0.94 (0.92-0.96)	666 727	.050
Joint SBP, HbA_{1c}, LDLc, and BMI goal[e]	0.72 (0.64-0.82)	52 273	0.89 (0.87-0.92)	666 727	.002

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin A_{1c}; LDLc, low-density lipoprotein cholesterol; non-HDLc, non–high-density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure.
[a]Adjusted for sex, age, insurance type, BMI, baseline HbA_{1c}, and baseline non-HDL cholesterol.
[b]Adjusted for sex, age, insurance type, BMI, baseline non-HDL cholesterol, and hypertension status.
[c]Adjusted for sex, age, insurance type, BMI, baseline HbA_{1c}, and hypertension status.
[d]Adjusted for sex, age, insurance type, and BMI.
[e]Adjusted for sex, age, and insurance type.

Table 4. Association between measures of diabetes control at baseline and incident chronic kidney disease, by body mass index category

Goal	BMI category						*P* for interaction
	Normal weight		Overweight		Obesity		
	aOR (95% CI)	n for model	aOR (95% CI)	n for model	aOR (95% CI)	n for model	
SBP < 130 mm Hg[a]	0.80 (0.77-0.83)	155 901	0.82 (0.80-0.85)	246 096	0.76 (0.74-0.78)	353 847	.07
HbA_{1c} < 7.0%[b]	0.84 (0.82-0.86)	156 668	0.88 (0.86-0.90)	246 677	0.86 (0.84-0.88)	354 743	.001
Non-HDLc < 130 mg/dL[c]	1.02 (0.99-1.05)	156 729	1.04 (1.02-1.07)	246 727	1.08 (1.05-1.10)	354 829	< .001
LDLc < 100 mg/dL[d]	1.04 (1.02-1.07)	154 138	1.09 (1.07-1.12)	241 114	1.10 (1.08-1.13)	356 804	< .001
Joint SBP, HbA_{1c}, and LDLc goal[e]	0.89 (0.86-0.92)	146 829	0.97 (0.94-0.99)	231 054	0.94 (0.92-0.97)	341 127	.001

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; HbA_{1c}, glycated hemoglobin A_{1c}; LDLc, low-density lipoprotein cholesterol; non-HDLc, non–high-density lipoprotein cholesterol; SBP, systolic blood pressure.
[a]Adjusted for sex, age, race (Black vs other), insurance type, baseline HbA_{1c}, and baseline non-HDL cholesterol.
[b]Adjusted for sex, age, race (Black vs other), insurance type, baseline non-HDL cholesterol, and hypertension status.
[c]Adjusted for sex, age, race (Black vs other), insurance type, baseline HbA_{1c}, and hypertension status.
[d]Adjusted for sex, age, race (Black vs other) and insurance type.

[26], ETDRS (Early Treatment Diabetic Retinopathy Study) [27], and EURODIAB [28]. Furthermore, in the aforementioned ADVANCE trial, high HDLc (which is obviously inversely correlated with non-HDLc) was independently associated with a lower incidence of a composite CKD end point [29]. In post hoc analyses of 2 major diabetes trials, namely ACCORD-Lipid (Action to Control Cardiovascular Risk in Diabetes-Lipid) [30] and FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) [31], therapy with fenofibrate, an agent that strongly reduces non-HDLc, was associated with slower eGFR decline. Our results are in line with the accumulated evidence suggesting that non-HDLc control may provide renal benefits in diabetes, beyond its well-documented role in cardiovascular prevention. It is important to recognize that the information provided by non-HDLc goes beyond what is provided by HDL alone, and they may not always be inversely correlated [32].

We found that sustaining a normal BMI over the study period was associated with a modest additional benefit (~ 6% additional OR reduction) on iCKD, relative to achieving and sustaining just the triple HbA_{1c}/SBP/LDLc goal. Obesity is known to be associated with increased single-nephron GFR [33], which later results in loss of glomerular function. Overweight and obesity have been independently associated with iCKD [34] and ESRD [35], even in the absence of diabetes. Obesity seems to accelerate the age-induced deterioration of kidney function and consequent risk of CKD [36]. A longitudinal study of patients with diabetes in Korea found that both obesity and net weight gain were associated with iCKD over a 12-year follow-up [37]. Similar findings were reported in an observational subanalysis of patients from the ADVANCE trial. The 5-year risk of CKD increased by approximately 4% for each additional BMI point above 25 [38]. Of importance

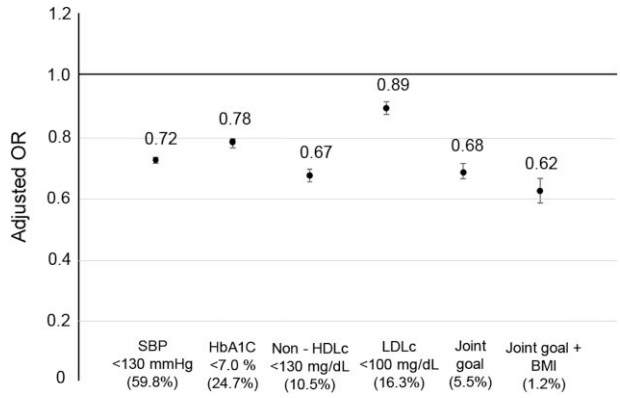

Figure 1. Association between sustained achievement of treatment goals and incident chronic kidney disease. Data are odds ratios (OR) compared to participants not reaching sustained achievement of each goal, adjusted for sex, age, race (Black vs other), insurance type, and baseline body mass index (BMI) (except for the model in which a normal BMI is part of the joint goal). Error bars represent 95% CI. Numbers in parentheses represent the percentage of study participants who sustained achievement of each goal over follow-up.

in the context of our study, overweight and obesity seem to be strong risk factors for CKD among Latino individuals: A retrospective study of Hispanic patients with type 2 diabetes found that excess BMI was more strongly associated with iCKD than even glycemic or BP control [39].

One of the central findings of our study was that, despite the large potential benefit of sustained risk factor control, an appallingly low proportion of patients achieve it in real practice. This is in accordance with findings from Colombia and other Latin American countries [40-42]. Therefore, a major effect on the prevention of CKD in diabetes can be expected from the implementation of strategies to measure, intervene, and closely monitor a few basic measures of treatment success. It is also important to consider that during our period of observation, the use of diabetes medications with specific renoprotective effects (ie, sodium glucose cotransporter 2 [SGLT-2] inhibitors, glucagon-like peptide 1 [GLP-1] agonists) had still not been broadly adopted. Thus, even greater benefits could be expected from the achievement of diabetes treatment goals through the use of newer, kidney-protecting medications.

Study Strengths and Limitations

Our study analyzed the association of treatment goal achievement with iCKD in the overwhelming majority of patients with diagnosed diabetes in an entire country of approximately 50 million inhabitants. Data come from a single, centrally administered registry. Being a database initially designed for the compulsory reporting of CKD and its precursor conditions, data related to kidney function and renal events are documented and audited with special attention. These characteristics endow the results both with large power and generalizability to other countries of a similar demographic and economic background.

Among the limitations, follow-up was only 4 years, which seems short in terms of the pathogenesis of CKD in diabetes. Nonetheless, even in this time span, very clear associations between measures of treatment success and iCKD were evident. The NRCKD does not capture diabetes type, so we do not know what proportion of participants had type 1 vs type 2 diabetes, although current epidemiological data from the region suggest that most patients with diabetes have type 2 diabetes [43]. Also, we did not have reliable data on current medications, so we did not include these important covariates, which could have helped us refine the estimation of the magnitude of the associations. The lack of such information may have introduced residual confounding, which is a possible limitation of our study. In any event, the effect of most of the key medications are reflected in glycemic levels, BP, or plasma lipids, variables that are closer to our end point of iCKD. We decided to analyze UAER as an exposure and not as a CKD end point because we considered eGFR and renal replacement therapies to be the true, unequivocal markers of the appearance of CKD, and thus a more reliable outcome. Finally, the nature of the data deposited in the NRCKD required us to define iCKD according to a single eGFR measurement being below the preestablished threshold.

In conclusion, we found that the successful control of non-HDLc, but also of HbA_{1c}, SBP, LDLc, and BMI, especially when sustained over time, were strongly associated with lower iCKD at a country level. These results have crucial clinical and health policy implications, and support the development of aggressive strategies to control non-HDLc and other essential treatment goals in the majority of patients with diabetes.

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Disclosures

The authors have nothing to disclose.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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