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Global approach to cardiovascular risk in chronic kidney disease: Reality and opportunities for intervention

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The current implementation into nephrology clinical practice of guidelines on treatment of cardiovascular (CV) risk factors in chronic kidney disease (CKD) is unknown. We designed a cross-sectional analysis to evaluate the prevalence and treatment of eight modifiable CV risk factors in 1058 predialysis CKD patients (stage 3: $n = 486$; stage 4: $n = 430$, stage 5: $n = 142$) followed for at least 1 year in 26 Italian renal clinics. The median nephrology follow-up was 37 months (range: 12–391 months). From stages 3 to 5, hypertension was the main complication (89, 87, and 87%), whereas smoking, high calcium-phosphate product and malnutrition were uncommon. The prevalence of proteinuria (25, 38, and 58%), anemia (16, 32, and 51%) and left ventricular hypertrophy (51, 55, and 64%) significantly increased, while hypercholesterolemia was less frequent in stage 5 (49%) than in stages 4 and 3 (59%). The vast majority of patients received multidrug antihypertensive therapy including inhibitors of renin–angiotensin system; conversely, diuretic treatment was consistently inadequate for both frequency and dose despite scarce implementation of low salt diet (19%). Statins were not prescribed in most hypercholesterolemics (78%), and epoietin treatment was largely overlooked in anemics (78%). The adjusted risk for having a higher number of uncontrolled risk factors rose in the presence of diabetes (odds ratio 1.29, 95% confidence interval 1.00–1.66), history of CV disease (odds ratio 1.48, 95% confidence interval 1.15–1.90) and CKD stages 4 and 5 (odds ratio 1.75, 95% confidence interval 1.37–2.22 and odds ratio 2.85, 95% confidence interval 2.01–4.04, respectively). In the tertiary care of CKD, treatment of hypertension is largely inadequate, whereas therapy of anemia and dyslipidemia is frequently omitted. The risk of not achieving therapeutic targets is higher in patients with diabetes, CV disease and more advanced CKD.

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Prevention of cardiovascular (CV) disease is now recognized as the main goal of conservative treatment of chronic kidney disease (CKD).[1] In CKD patients, CV risk rises proportionally to the decline of renal function and becomes remarkable when glomerular filtration rate (GFR) is below 60 ml/min/1.73 m^2.[2,3] The impact of CV complications is so important that the risk for fatal and nonfatal CV events overcomes that for renal disease progression; the mortality rate, in fact, has been found up to eightfold greater than that of renal replacement therapy.[2,3] These data are consistent with the observation that in CKD, at variance with general population, the age-adjusted death rates have not declined in the last two decades.[4]

Several modifiable determinants of CV risk have been identified in these patients, the main being hypertension, hypercholesterolemia, left ventricular hypertrophy (LVH), smoking, anemia, abnormal calcium-phosphate (Ca-P) metabolism, proteinuria and malnutrition.[1] Furthermore, the International Guidelines on prevention of CV disease have repeatedly recommended intensive treatment of the main CV risk factors in CKD population since 1997–1998.[5–10] These recommendations have been reiterated in 1999 also by the Italian Society of Nephrology, which issued guidelines on this topic that circulated amply and in various formats among the Italian nephrology community.[11]

To efficaciously prevent CV disease in CKD patients, the preliminary knowledge of the prevalence and management of CV risk factors is required.[4] Indeed, observational studies are now considered as essential tools to verify whether efficacy of specific interventions, proven in the experimental setting of randomized trials and diffused by means of guidelines, translates into effective treatment in routine practice.[12] To date, however, the degree of implementation into clinical practice of the recommendations on treatment of CV risk factors in CKD is still unknown. The information provided by the few observational studies on the care of these patients, in fact, is largely inadequate because of small sample size, limited assessment of risk factors and outdated data collection, that is, performed when therapeutic targets were less restrictive.[13–17] Furthermore, in the previous studies, patient population was heterogeneous for type of care provider and the examined patients were generally incident. On the contrary, to the best analysis of management and, consequently, to identify the main areas of intervention, it is essential to evaluate the global approach to CV risk in patients followed for an adequate period in the nephrology setting, that is, the reference of care for CKD patients.

This multicentric cross-sectional study was aimed at evaluating treatment and prevalence of the main modifiable determinants of CV risk in patients with CKD stages 3–5 followed for at least 1 year in Italian nephrology clinics.

RESULTS

Overall, 1353 consecutive patients with CKD stages 3–5, followed for at least 1 year in the 26 participating renal clinics, were screened. We did not enrol 295 patients on the basis of exclusion criteria or lack of information at the time of study visit; therefore, 1058 patients were included in the final analysis and divided in the three GFR categories (stage 3: $n = 486$, 46%; stage 4: $n = 430$, 41%; stage 5: $n = 142$, 13%). The median follow-up in the nephrology referral centers was 37 months (range: 12–391 months) with no difference in the three stages.

Table 1 depicts the main clinical characteristics of the study subjects. More advanced disease was coupled with greater prevalence of female and diabetic patients, although no relevant difference was detected in age, body mass index, blood pressure (BP) values and prevalence of CV disease. The causes of CKD were equally distributed in the three stages with the exception of diabetic nephropathy that was less prevalent in patients with mild CKD. Of note, the prevalence of patients with CKD secondary to diabetes was largely inferior to that of diabetic patients.

The laboratory data collected at study visit are reported in Table 2. Creatinine clearance overestimated GFR. This finding was confirmed by regression analysis and Bland–Altman plot (Figure 1), with a difference between the two methods (3.6 ml/min/1.73 m^2 on average) that increased with the increment of GFR. As depicted in Table 2, more severe disease was associated with decreasing levels of serum cholesterol, hemoglobin and Ca, whereas proteinuria, serum P and Ca-P product progressively increased from stage 3 to 5.

Table 2 | Laboratory characteristics of patients in the three stages of CKD

	Stage 3 (n=486)	Stage 4 (n=430)	Stage 5 (n=142)	P-value
Total cholesterol (mg/dl)	200±40	201±44	188±45	0.004
Hemoglobin (g/dl)	13.1±1.8	12.1±1.7	11.4±1.5	<0.0001
Serum creatinine (mg/dl)	1.6±0.3	2.8±0.6	5.1±1.3	<0.0001
eGFR (ml/min/1.73 m^2)	42.1±8.1	22.2±4.2	11.2±2.5	<0.0001
CrCl (ml/min/1.73 m^2)	45.2±12.5	26.4±8.4	13.9±4.5	<0.0001
Serum P (mg/dl)	3.6±0.8	4.0±0.8	4.5±1.0	<0.0001
Serum Ca (mg/dl)	9.4±0.7	9.2±0.7	9.1±0.8	<0.0001
Ca-P product (mg^2/dl^2)	34±8	37±8	40±9	<0.0001
Albumin (g/dl)	3.9±0.5	3.9±0.5	3.9±0.5	0.600
Proteinuria (g/24 h)	0.83±1.33	1.12±1.39	1.76±1.99	<0.0001
$U_{Na}V$ (mmol/24 h)	154±56	149±58	148±54	0.357
UUN (g/24 h)	7.4±3.3	6.5±3.1	5.6±2.8	<0.0001

Ca-P=calcium-phosphate; CKD=chronic kidney disease; CrCl=creatinine clearance measured from 24-h urine collection; eGFR=GFR value estimated by MDRD equation; $U_{Na}V$=urinary sodium excretion; UUN=urinary urea nitrogen.

Table 1 | Clinical characteristics of patients in the three stages of CKD

	Stage 3 (n=486)	Stage 4 (n=430)	Stage 5 (n=142)	P-value
Age (years)	66±14	67±14	65±14	0.248
Male sex (%)	313 (64.4)	218 (50.7)	64 (45.1)	<0.0001
Body mass index (kg/m^2)	27.0±4.1	27.2±4.7	26.8±4.7	0.673
Diabetes (%)	113 (23.2)	121 (28.1)	47 (33.1)	0.011
Systolic BP (mmHg)	138±17	141±19	140±19	0.292
Diastolic BP (mmHg)	81±10	81±11	80±9	0.991
CVD (%)	139 (28.6)	133 (30.9)	42 (29.6)	0.665
Renal disease (%)				
Diabetes	39 (8.0)	65 (15.1)	22 (15.4)	
Hypertension	123 (25.3)	90 (20.9)	29 (20.4)	
GN/IN/PKD	145 (29.8)	122 (28.4)	48 (33.8)	
Other	179 (36.8)	153 (35.6)	43 (30.3)	

BP=blood pressure; CKD=chronic kidney disease; CVD=cardiovascular disease defined as history of coronary, cerebrovascular or peripheral vascular disease or congestive heart failure; GN=glomerulonephritis; IN=interstitial nephritis; PKD=polycystic kidney disease.
Quantitative variables are reported as mean and standard deviation, categorical variables as absolute numbers and percentages (%).

Analysis of 24-h urine collection revealed that only 19% of patients had, on average, a sodium intake $\leqslant 100$ mmol/24 h, with no difference in the three stages (16, 22, and 16%, $P = 0.40$). Protein intake (g/kg body wt/day) decreased with GFR decline, being 0.85 ± 0.31 in stage 3, 0.78 ± 0.27 in stage 4 and 0.69 ± 0.26 in stage 5 ($P < 0.0001$).

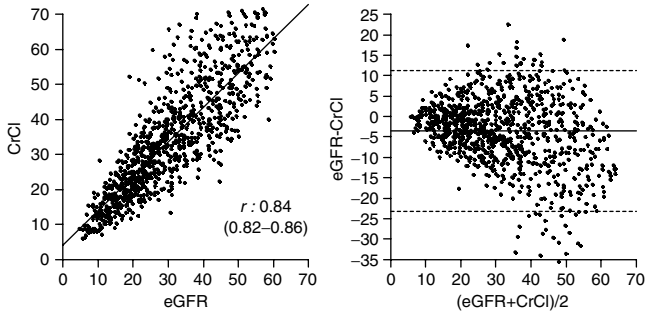

Figure 1 | Comparison between CrCl measured from 24-h urine collection (CrCl, ml/min/1.73 m^2) and GFR estimated by Modification of Diet in Renal Disease equation (eGFR, ml/min/1.73 m^2). The graph on the left represents the regression statistics: CrCl is indicated on the *Y*-axis and eGFR on the *X*-axis; line represents the linear regression and *r* indicates the linear correlation coefficient with the values of the 95% interval of confidence in parenthesis. The graph on the right is the Bland–Altman plot: mean and difference of the two measures are the *X*- and *Y*-axis, respectively; the solid line represents the mean of the differences between the two values for each individual, whereas the upper and lower dotted lines indicate the 95% distribution of the difference.

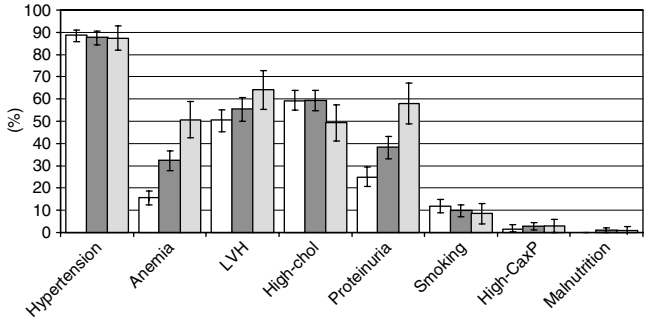

Figure 2 | Prevalence of uncontrolled cardiovascular risk factors in CKD stages 3 (white bars), 4 (dotted bars) and 5 (gray bars), and 95% confidence interval. See Materials and Methods for definition of risk factors. χ^2 for trend: $P = 0.56$ for hypertension, $P < 0.0001$ for anemia, $P = 0.01$ for LVH, $P < 0.0001$ for proteinuria, $P = 0.10$ for high-chol, $P = 0.20$ for smoking, $P = 0.13$ for CaxP and $P = 0.11$ for malnutrition.

Figure 2 depicts the distribution of uncontrolled CV risk factors in the three CKD stages examined. The prevalence of anemia, LVH and proteinuria progressively rose from stages 3 to 5, whereas hypercholesterolemia was less frequent in stage 5. In particular, 58% of the whole group of patients had cholesterol levels >190 mg/dl, with a distribution in the three stages that was similar to that of low-density lipoprotein >100 mg/dl (analysis available in 612/1058 subjects). Poor hypertension control represented the main complication, with only 12.0% (95% confidence interval 10.0–14.0) of patients showing BP values $<130/80$ mmHg; in particular, 21.6% (95% confidence interval 19.1–24.0) of patients reached the target for systolic BP, whereas isolated diastolic BP target was detected in 28.8% (95% confidence interval 26.1–31.6) of subjects. Of note, the majority of patients (61%) did not even reach the less restrictive goal of 140/90 mmHg indicated for patients with essential hypertension and normal renal function. The weight of this CV risk factor is also evidenced by the prolonged exposition of patients to this complication; median duration of hypertension, in fact, was 76 months (range: 3–511 months), with no difference in the three stages. Conversely, a negligible prevalence was found for the other examined CV risk factors, such as smoking and abnormal Ca-P metabolism. Also, malnutrition, defined by the concomitant presence of serum albumin <3.5 g/dl and body mass index <20 kg/m^2, was rare; on the contrary, isolated hypoalbuminemia was detected in 14.8% of patients. On average, the number of uncontrolled modifiable CV risk factors per patient significantly increased from stages 3 to 5 (2.4 ± 1.0, 2.7 ± 1.0, 3.0 ± 1.2, $P < 0.0001$), although it was not influenced by the type of referral center ($P = 0.481$).

As depicted in Table 3, the number of uncontrolled risk factors became larger in the presence of diabetes, history of CV disease and with worsening of renal function, although it was not affected by age, gender and duration of renal disease. This association was confirmed by multivariate analysis shown in Table 4. Specifically, the risk of having an increased number of uncontrolled CV risk factors was significantly

Table 3 | Characteristics of CKD patients grouped by number of uncontrolled cardiovascular risk factors

	0–1 (*n*=148)	2 (*n*=375)	3 (*n*=347)	$\geqslant$4 (*n*=188)
Age (years)	65 ± 15	66 ± 14	67 ± 14	65 ± 15
Male sex (%)	86 (58.1)	206 (54.9)	192 (55.3)	111 (59.0)
Body mass index (kg/m^2)	27.5 ± 4.8	26.7 ± 4.2	27.4 ± 4.4	26.7 ± 4.5
Diabetes (%)*	35 (23.8)	87 (23.2)	93 (26.8)	66 (35.1)
Serum creatinine (mg/dl)*	2.2 ± 1.1	2.4 ± 1.1	2.6 ± 1.2	3.2 ± 1.6
eGFR (ml/min/1.73m^2)*	35 ± 13	32 ± 14	29 ± 13	24 ± 12
Duration of renal disease (months)	73 ± 73	67 ± 59	65 ± 53	69 ± 61
CVD (%)*	41 (27.7)	82 (21.9)	128 (36.9)	64 (34.0)

CKD=chronic kidney disease; CVD=cardiovascular disease defined as history of coronary, cerebrovascular or peripheral vascular disease or congestive heart failure; eGFR=GFR value estimated by MDRD equation.
Quantitative variables are reported as mean and standard deviation, and categorical variables as absolute numbers and percentages (%).
*$P < 0.01$.

Table 4 | Adjusted odds ratios relating to the number of uncontrolled modifiable cardiovascular risk factors to age, gender, diabetes, cardiovascular disease and CKD stage

Variable	Odds ratio	95% CI	*P*-value
Age (10 years)	0.96	0.88–1.04	0.293
Gender (male *vs* female)	1.13	0.90–1.41	0.305
Diabetes (yes *vs* no)	1.29	1.00–1.66	0.049
CVD (yes *vs* no)	1.48	1.15–1.90	0.002
CKD stage			<0.0001
4 *vs* 3	1.75	1.37–2.22	
5 *vs* 3	2.85	2.01–4.04	

CKD=chronic kidney disease; CVD=cardiovascular disease defined as history of coronary, cerebrovascular or peripheral vascular disease or congestive heart failure.

higher in diabetic patients, in patients with established CV disease and in patients with more advanced CKD. Test of the proportional odds assumption was not significant, indicating that the proportional odds model was appropriate for these data and separate binary logistic regression analyses yielded to odds ratios comparable to those reported in Table 4 (data not shown). The modified Pearson's χ^2 test revealed good fit of the model with values of 139.7 (df = 136, $P = 0.40$). As the first-order interactions were not statistically significant, they were not entered into the final model. The lack of significant interaction supports the multiplicative effect of the odds ratios estimated by the model. Therefore, we could estimate the global risk by multiplying the respective odds ratios, meaning that the risk resulted more than three- and fivefold greater in patients with diabetes, CV disease and CKD stages 4 and 5, respectively, than with patients with CKD stage 3 and neither diabetes nor CV disease.

The therapeutic approach to the main modifiable CV risk factors by CKD stage is depicted in Table 5. The vast majority of patients showed BP levels above target despite treatment, whereas only 3.7% of patients with uncontrolled BP was left untreated. Treatment modality changed when considering the other two main CV risk factors. Indeed, most anemic and hypercholesterolemic patients did not receive any treatment. Specifically, epoietin treatment was omitted in the majority of anemic patients (stages 3–5: 89, 77, and 67%), and statin therapy was not prescribed in most hypercholesterolemic patients (stages 3–5: 77, 78, and 81%).

Other cardioprotective medications, such as anti-aggregant agents, nitroderivates and digitalis-like drugs, were overall similarly prescribed from stages 3 to 5 (17, 19, and 21%, $P = 0.19$).

As hypertension was the main modifiable CV risk factor in the population studied, a detailed analysis of antihypertensive therapy was performed (Table 6). From stages 3 to 5, the number of prescribed drugs per patient only increased slightly (2.0 ± 1.0, 2.2 ± 1.1, and 2.1 ± 1.1%, $P = 0.016$). The majority of hypertensive patients received at least two drugs (stages 3–5: 68, 74, and 74%, $P = 0.043$). Most patients were treated with inhibitors of activity of renin–angiotensin system; the prescriptions of converting enzyme inhibitors overcame those of angiotensin II receptor blockers. The prescription of renin–angiotensin system inhibitors significantly decreased from stages 3 to 5, whereas that of calcium channel blockers and β-blockers slightly increased. Furosemide, that is the loop diuretic almost exclusively used, was the third drug after renin–angiotensin system inhibitors and calcium channel blockers. This drug was given to a minority of hypertensive patients, and in more than 50% of these cases, the prescribed dose resulted inappropriately low for the degree of GFR impairment.

Table 5 | Treatment and control rates of the main modifiable cardiovascular risk factors in CKD stage 3 (*n*=486), stage 4 (*n*=430), and stage 5 (*n*=142)

	Target reached		Target not reached	
	Treated	Untreated	Treated	Untreated
Hypertension				
Stage 3	46 (9.5)	9 (1.9)	415 (85.4)	16 (3.3)
Stage 4	52 (12.0)	2 (0.5)	364 (84.7)	12 (2.8)
Stage 5	16 (11.3)	2 (1.4)	113 (79.6)	11 (7.7)
Overall	114 (10.8)	13 (1.2)	892 (84.3)	39 (3.7)
Anemia				
Stage 3	3 (0.6)	407 (83.7)	8 (1.6)	68 (14.0)
Stage 4	31 (7.2)	260 (60.5)	32 (7.4)	107 (24.9)
Stage 5	25 (17.6)	45 (31.7)	24 (16.9)	48 (33.8)
Overall	59 (5.6)	712 (67.3)	64 (6.0)	223 (21.1)
Hypercholesterolemia				
Stage 3	40 (8.2)	158 (32.5)	65 (13.4)	223 (45.9)
Stage 4	38 (8.8)	137 (31.9)	56 (13.0)	199 (46.3)
Stage 5	10 (7.0)	62 (43.7)	13 (9.2)	57 (40.1)
Overall	88 (8.3)	357 (33.7)	134 (12.7)	479 (45.3)

CKD=chronic kidney disease.
Data are expressed as the number and % of patients. Target values are defined as following: blood pressure <130/80 mmHg, hemoglobin ⩾11 g/dl (female) and 12 g/dl (male) and serum total cholesterol ⩽190 mg/dl.

Table 6 | Classes of antihypertensive drugs in the three stages of CKD

	Stage 3 (*n*=486)	Stage 4 (*n*=430)	Stage 5 (*n*=142)
CEI	58	56	40
ARB	21	24	18
CEI+ARB	5	4	4
CCB	46	46	50
Furosemide	27	42	51
Dosage (mg/day)[a]	41 ± 50	55 ± 50	85 ± 83[b]
Dosage ⩽25 mg/day	69	46	31[b]
Thiazides	9	7	1
BB	16	17	22
Other	22	29	31

ARB=angiotensin receptor blocker; BB=beta-blockers; CCB=calcium channel blockers; CEI=converting enzyme inhibitors; CKD=chronic kidney disease.
Data are expressed as % of treated patients.
[a]Mean ± standard deviation.
[b]$P < 0.0001$ for trend.

DISCUSSION

The novel finding of this study is that despite the wide diffusion of guidelines, recognized CV risk factors are poorly

controlled in most CKD patients regularly followed by nephrologist. Furthermore, this study identifies, for the first time, the predictors of control of the main modifiable determinants of CV risk and the major areas of improvement as well. An additional strength of the study is the stratification of patients by CKD stage. In this regard, it is important to note that we provide evidence from Italian patients of the tendency of 24-h creatinine clearance to overestimate kidney function, as previously shown in the US patients,[18] especially for higher GFRs (Figure 1).

The population examined in this study was characterized by a high prevalence of advanced age and diabetes, and one patient out of three, moreover, had at least one CV event in his clinical history. In the presence of this unmodifiable CV risk, most of the main modifiable factors resulted insufficiently controlled (Figure 2). Only 12% of patients had their BP controlled to less than 130/80 mmHg. A recent analysis of the Fourth National Health and Nutrition Survey has shown a BP control rate of 37% in a sample of CKD patients living in the US;[19] that survey, however, is not comparable with the current study as definition of BP target was less restrictive, entity of renal dysfunction was minor and the methodology used to measure BP was different.

We also detected hypercholesterolemia in 50–60% of patients throughout the three stages; the prevalence of anemia, proteinuria and LVH rose proportionally to GFR decline reaching a value greater than 50% in stage 5. The prevalence of smoking habit and elevated Ca-P product was irrelevant. Also malnourished patients were rare. In contrast, patients with hypoalbuminemia and normal body mass index represented about 15% of the population examined. Previous studies have suggested an independent association between hypoalbuminemia and inflammation/comorbidities in this subgroup of patients.[20,21]

This study likely underestimates the true dimension of the 'undertreatment' problem in CKD patients; we in fact studied patients with prolonged follow-up in nephrology centers, whereas control of complications is certainly worse in unreferred patients.[22,23] Indeed, there is large consensus that early referral of CKD patients to nephrologist is highly desirable.[8] These considerations should therefore induce nephrologists at optimizing the conservative care of CKD.

The majority of patients received multidrug antihypertensive therapy including renin–angiotensin system inhibitors. This is the most important point of adherence to the current guidelines on CKD care and, at the same time, it represents a main difference with previous studies that showed BP levels generally greater than 140/90 mmHg in the presence of a minor use of these agents.[13,15] While it is not possible to exclude that further increases in the number of antihypertensive agents may be useful, the present analysis evidences an inadequate therapeutic approach to the extracellular volume expansion, which is a key determinant of CKD-related hypertension.[24–26] More than 80% of patients showed excessive salt intake. This critical information is original as no survey on hypertension control in CKD has evaluated salt intake by measuring 24-h urinary sodium excretion. Furthermore, a loop diuretic was given to only a limited number of patients, and frequently at a dose inappropriately low for the degree of renal dysfunction. In this regard, it is remarkable that the dose of furosemide was still $\leqslant 25$ mg/day in one-third of patients with eGFR (GFR estimated by Modification of Diet in Renal Disease equation) < 15 ml/min. Conversely, in a small previous intervention trial by our group, effective salt restriction decreased *per se* mean arterial pressure of as much as 10 mmHg in patients with moderate to advanced CKD.[27] Similarly, therapy with loop diuretics at high dose has been found efficacious in reaching and maintaining low BP levels.[24,25] Indeed, uptitration of loop diuretic dosage is required in CKD because of the reduced number of functioning nephrons, lower renal blood flow, accumulation of organic acids and proteinuria.[26] These data, therefore, identify the treatment of volume expansion as a major area of improvement in the conservative care of CKD patients. It is important to note, however, that renin–angiotensin system inhibition was only apparently optimal; in fact, we found an extremely low rate of prescriptions of combination therapy with converting enzyme inhibitors and angiotensin II receptor blockers despite the large evidence of the major renoprotective efficacy, in the absence of significant side effects, of this intervention.[28]

At variance with hypertension, the other two main modifiable CV risk factors, such as anemia and hypercholesterolemia, resulted inadequately controlled mainly because of omitted rather than insufficient therapy. Within the anemic subgroup of the population examined, in fact, 64% did not receive epoietin, whereas only 18% resulted undertreated. Conversely, about 50% of treated patients reached the hemoglobin target. Therefore, these data suggest that, at odds with therapy of hypertension whose target was reached in 12% of treated patients, hemoglobin goal can be more easily achieved when therapy is started. Furthermore, omission of therapy involved a relatively higher fraction of anemic patients with mild to moderate CKD probably because of greater underestimation of the problem in the initial phases of disease. This point is not trivial; recent studies, in fact, have revealed beneficial effects of epoietin on both CV disease and progression of renal disease when treatment is established early.[29–31] Nevertheless, we noted only a slight improvement in epoietin prescription with respect to previous surveys.[13,14,31,32] These early studies, in fact, showed a maximal treatment rate of 16–27% in advanced CKD, whereas in our stage 5 patients, epoietin was prescribed in 35% of cases. The increasing omission of intervention on anemia from stages 3 to 5 likely accounted, together with the poor BP control, for the parallel increment detected in the prevalence of LVH. In this regard, it is important to underline that a recent pooled analysis has demonstrated that LVH is an independent risk factor for CV disease from the earlier stages of CKD, and that patients who have both LVH and anemia are at particularly increased risk.[33] Similarly to anemia, we observed a pervasive lack of

intervention on hypercholesterolemia. Indeed, despite statin prescription in our cohort was double than that reported in the past,[14,15] the vast majority of hypercholesterolemic patients was still left untreated. Again, this observation becomes crucial when considering the positive CV and renal effects of statins in CKD.[34,35]

At variance with pharmacological interventions, a particular attention was dedicated to the nutritional care of patients. Dietary protein intake was on average adherent to the levels recommended by the guidelines,[8,11] and, consequently, hyperphosphatemia was absent in virtually all patients. As in the case of 24-h urinary sodium excretion, this finding is original as no survey in CKD has evaluated the current recommendations on protein intake by measuring 24-h urinary excretion of urea.

This study, which was meant to represent clinical practice, has the limitation of evaluating prescription rather than adherence to therapy. However, this potential bias becomes irrelevant when considering that the prescribed therapy was *per se* inadequate. Therefore, this study discloses a 'clinical inertia' in this high-risk population. In particular, the adjusted risk of a worse management of CV risk factors was 75 and 185% greater in stages 4 and 5 than in stage 3, and the presence of diabetes or CVD increased the risk by 29 and 48%, whereas the simultaneous presence of diabetes, CVD and more advanced CKD maximized the risk of being undertreated. These data indicate that nephrologists do not properly intensify therapy when the CV burden increases in parallel with worsening of disease. Similar data have also been collected in settings other than nephrology. In particular, coronary heart disease has been found insufficiently treated in CKD patients;[36–39] such an erroneous attitude is not justifiable anymore as ischemic CV disease results 'normally' responsive to treatment throughout the entire spectrum of CKD.[37–39]

An additional finding of this survey is the gross disparity between the prevalence of diabetes and diabetic nephropathy. The relatively lower number of patients with diabetic nephropathy was likely owing to the strict criteria adopted here to identify them and, consequently, to limit diabetic nephropathy misclassification, which is a critical problem raised in the US as in European countries.[40]

In conclusion, this systematic analysis evidences that in patients with CKD stages 3–5 regularly followed in the nephrology care setting: (a) treatment of the main modifiable CV risk factors is far to be optimal, (b) while hypertension is undertreated possibly because of inadequate approach to extracellular volume expansion, therapy of anemia and hypercholesterolemia is frequently omitted and (c) patients with a combination of diabetes, established CVD and advanced renal disease carry the greatest risk for not achieving the therapeutic targets. These findings call for action; the pervasive lack of intervention on these risk factors may, in fact, greatly contribute to the high CV risk. This hypothesis is substantiated by recent studies showing that in CKD, the main modifiable CV risk factors have larger association with CV mortality than novel risk factors.[41–43]

MATERIALS AND METHODS

This is a multicentric cross-sectional study of nondialyzed and nontransplanted adult CKD patients followed on regular basis in tertiary care. Twenty-six Italian nephrology referral centers took part in the research program; 10 centers were in academic institutions, 15 in public hospitals and one was a clinical research unit of the Italian National Research Council. Inclusion criteria of the centers were: presence of outpatient clinic dedicated to the conservative care of CKD, with attending patient population seen at least twice per year; presence of clinical and laboratory protocols for the care of these patients, including double measurement by physician of BP 5 min apart in sitting position after 10 min of rest, with Korotkoff phases I and V defining systolic BP and diastolic BP values; measurement of creatinine in plasma and urine by means of the modified kinetic Jaffé reaction; and complete blood and urine analysis profile performed at least two times per year. The protocol was approved by the Ethical Committee of the Second University of Naples.

Patients

We considered eligible all the consecutive patients consulting the centers during a 6-month period of 2003 that had diagnosis of CKD and estimated GFR < 60 ml/min/1.73 m^2. We excluded patients with changes of GFR greater than 30% in the previous 6 months. As the aim of the current study was to study patients steadily followed by nephrologist, we excluded patients whose first visit at the renal clinic dated back less than 1 year.

Data collection and definitions

For each patient, information covered demographic and medical history data, including diagnosis of diabetes mellitus, history of CV event, defined as the presence in the patient's history of any event among coronary artery disease, congestive heart failure, cerebrovascular and peripheral vascular disease. Diagnosis of underlying nephropathy was also requested; in diabetic patients, diabetic nephropathy was considered as the cause of CKD when, after exclusion of known nondiabetic kidney disease, both albuminuria and diabetic retinopathy were reported in the clinical history. Clinical data, including therapy with the indication of prescribed dose, and laboratory data were collected at the time of study visit, which was planned in 2003. Laboratory analysis included measurement of serum Na, K, and creatinine, serum total cholesterol, low-density lipoprotein cholesterol, hemoglobin, serum albumin, serum phosphate (P) and calcium (Ca), 24-h measured creatinine clearance (CrCl), 24-h proteinuria, 24-h urinary sodium excretion and 24-h urinary urea nitrogen.

The case report forms were filled in at each center, keeping anonymous the patients' identity, and sent to the coordinating center at the Second University of Naples for analysis.

Twenty-four urine collection was considered inaccurate and discarded if the value of measured creatinine excretion rate was outside the 60–140% range of the value calculated according to Dwyer and Kenler.[44] Daily salt intake (g/day) was calculated dividing 24-h urinary sodium excretion by 17 and daily protein intake was calculated by measuring urinary urea nitrogen.[27]

CKD stage was defined by the category of estimated GFR (stage 3: GFR 30–59; stage 4: GFR 15–29; stage 5: GFR <15).[8] GFR was estimated using a formula derived by the Modification of Diet in Renal Disease study group: estimated GFR $= 186.3 \times$ (serum creatinine)$^{-1.154} \times$ age$^{-0.203} \times (0.742$ if women$) \times (1.21$, if black).[18]

At the time of study visit, we assessed the prevalence of eight modifiable CV risk factors. These factors were defined as uncontrolled according to thresholds indicated by expert panels:[1,5–11] hypertension (BP $\geqslant$130/80 mmHg), anemia (hemoglobin $<$11 g/dl in women and $<$12 g/dl in men), LVH (detected at either electrocardiography or echocardiography), clinically significant proteinuria (protein excretion $>$1.0 g/24 h), high cholesterol levels (serum total cholesterol $>$190 mg/dl), smoking habit (smoking in the last 6 months), frank malnutrition (serum albumin $<$3.5 g/dl and body mass index $<$20 kg/m^2) and abnormal Ca-P metabolism (Ca-P product $>$55 mg^2/dl^2).

Statistical analysis

Data were analyzed using SAS version 8.1 (SAS Inc., Cary, NC, USA). We report quantitative variables as mean and standard deviation, and categorical variables as absolute numbers and percentages (%). Differences in clinical and laboratory characteristics of patients in the three CKD stage were tested by means of one-way ANOVA and χ^2 methods for quantitative and qualitative variables, respectively. Agreement between estimated GFR and 24-h measured clearance creatinine was studied first by linear regression and correlation coefficient, and second by Bland–Altman method.[45] Multivariate analyses were performed, using ordinal logistic regression under a proportional odds model,[46] to evaluate the predictors of number of the uncontrolled CV risk factors examined (NRF: hypertension, anemia, LVH, high cholesterol levels, proteinuria, malnutrition, smoking, high Ca-P product). NRF was grouped into four ordered categories (0–1, 2, 3, and $\geqslant$4) owing to the low prevalence of subject with none or more than four NRF. This approach simultaneously models three cumulative logits that corresponds to using binary cut points at 2, 3, and 4, written as $\log\{\Pr(\mathrm{NRF}\geqslant 2)/\Pr(\mathrm{NRF}<2)\}$, $\log\{\Pr(\mathrm{NRF}\geqslant 3)/\Pr(\mathrm{NRF}<3)\}$ and $\log\{\Pr(\mathrm{NRF})\geqslant 4/\Pr(\mathrm{NRF}<4)\}$, respectively. Under this proportional odds model, one coefficient is estimated for each predictor in the model. The coefficient represents the effect of a one-unit increase in the predictor variable on the logit (log odds), which is assumed to be the same for all three logits. A score test was used to verify the proportional odds assumption in the final model.[47] To further verify the proportional odds model, we fit binary logistic regressions using NRF cutoffs of at least 2, 3, and 4, and compared the results with those of the ordinal regressions. The first-order interactions of the main effects of the model were tested one by one by means of likelihood ratio test. Goodness of fit was assessed using a method recently proposed by Pulkestenis and Robinson based on the modified version of the Pearson χ^2 test that is appropriate for assessing goodness of fit in ordinal response models when both categorical and continuous covariates are present.[48]

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Appendix A1. The TArget Blood Pressure LEvels in Chronic Kidney Disease Study Group

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