Decreased glomerular filtration rate as calculated by the Cockckroft-Gault and MDRD formulas does not always predict cardiovascular morbidity and mortality in hypertensive patients treated in primary care

F.J. Tovillas-Morán[1,2], M. Vilaplana-Cosculluela[2,3], A. Dalfó-Pibernat[4], E. Zabaleta-del-Olmo[2], J.M. Galcerán[5], A. Coca[6], A. Dalfó-Baqué[2,3]

[1] Martí i Julià Primary Care Team (PCT). Cornellá, Barcelona, Spain. [2] Gòtic PCT. Barcelona. Spain. [3] Vallcarca PCT. Barcelona, Spain. [4] Instituto de Investigación en Atención Primaria (Primary Care Research Institute) (IDIAP) Jordi Gol. Barcelona, Spain. [5] ALTHAIA Foundation. Manresa Barcelona, Spain. [6] Hypertension Unit. Institute of Medicine and Dermatology. Teaching Hospital. University of Barcelona. Barcelona, Spain.

Nefrologia 2010;30(6):653-60

doi:10.3265/Nefrologia.pre2010.Jun.10297

ABSTRACT

Background: A decrease in renal function is associated with cardiovascular morbidity and mortality. The aim of this study was to analyse the association of cardiovascular morbidity and mortality with baseline glomerular filtration rate (GFR), calculated according to the Cockcroft-Gault and MDRD formulas, with the incidence of major adverse cardiovascular events (MACEs) in a cohort of hypertensive individuals followed for 12 years. **Method:** We performed a prospective study of a random sample of 223 hypertensive patients free of MACEs, who were followed in an urban Primary Care Centre. GFR was estimated using both formulas. MACEs were considered as the onset of ischaemic heart disease, heart failure, heart attacks, peripheral vascular disease or cardiovascular death. Data were analysed using the life-table method and Cox regression modeling. **Results:** The median follow-up was 10.7 (interquartile range, 6.5-12.1) years. Follow-up was completed in 191 participants (85.7%). The cumulative survival was 64.7% (95% Confidence Interval [CI], 57.9-71.6). The incidence of MACEs during the follow-up period was 3.6 (95% CI, 2.7-4.4) per 100 subject-years. The final multivariable model showed that the most predictive variables of MACEs in the study population were the presence of diabetes mellitus and the estimation of GFR >60ml/min/1.73 m^2 by the MDRD equation. **Conclusions:** There was a relationship between the occurrence of MACEs and an estimated GFR by MDRD above 60 ml/min/1.73 m^2 at study entry, inversely to what was expected. GFR estimated by the C-G formula was not associated with cardiovascular risk.

Key words: Hypertension. Cardiovascular disease. Primary Health Care. Survival Analysis. Glomerular Filtration Rate. Renal Insufficiency.

El filtrado glomerular reducido según las fórmulas de Cockcroft-Gault y MDRD no siempre predice la morbimortalidad cardiovascular en los pacientes hipertensos atendidos en atención primaria

RESUMEN

Antecedentes: *El deterioro de la función renal se ha asociado con un incremento de la morbimortalidad cardiovascular. El objetivo del estudio fue analizar la asociación del filtrado glomerular (FG) basal, según las fórmulas de Cockcroft-Gault y MDRD, con la incidencia de eventos cardiovasculares (ECV) en una cohorte de personas hipertensas seguida durante 12 años.* ***Métodos:*** *Estudio prospectivo de una muestra aleatoria de 223 hipertensos libres de ECV atendidos en un centro de atención primaria urbano. Se estimó el FG mediante ambas fórmulas. Se consideró ECV la aparición de cardiopatía isquémica, insuficiencia cardíaca, accidente cerebrovascular, vasculopatía periférica o muerte por ECV. Se analizaron los datos mediante el método actuarial y modelos de regresión de Cox.* ***Resultados:*** *La mediana de tiempo de seguimiento fue de 10,7 años (rango intercuartílico, 6,5-12,1). El seguimiento fue completo en 191 participantes (85,7%). La supervivencia acumulada fue del 64,7% (inter-*

Correspondence: Francisco Javier Tovillas-Morán
Equipo de Atención Primaria (EAP) Martí i Julià.
Avenida Baix Llobregat, 17. 08940 Cornellà. Barcelona. Spain.
javiertovillas@yahoo.es
ezabaleta@idiapjgol.org

valo de confianza [IC] del 95%: 57,9-71,6%). La tasa media de incidencia de ECV durante todo el período de seguimiento fue de 3,6 (IC del 95%, 2,7-4,4%) por 100 personas hipertensas/año. El modelo multivariable final mostró que las variables con mayor poder predictivo de ECV en la población de estudio fueron la diabetes y la estimación del FG ≥60 ml/min/1,73 m² mediante fórmula MDRD. ***Conclusiones:*** *Se observó una relación entre la aparición de ECV y los valores de FG estimados por la fórmula MDRD al inicio del seguimiento superiores a 60 ml/min/1,73 m², inversa a la esperada. La estimación del FG mediante fórmula de Cockcroft-Gault no se asoció con el riesgo cardiovascular.*

Palabras clave: *Hipertensión. Enfermedad cardiovascular. Atención Primaria de salud. Análisis de supervivencia. Filtrado glomerular. Insuficiencia Renal.*

INTRODUCTION

Arterial hypertension (AHT) is a major health problem since it is a known risk factor for developing cardiovascular disease.[1] One of the organ disorders derived from AHT is chronic kidney disease (CKD), defined initially by the presence of kidney damage and in later stages, as a decrease in glomerular filtration rate (GFR).

Various publications have shown that CKD is responsible for increased cardiovascular morbidity and mortality, which is proportional to kidney function deterioration.[2-4] For this reason, various professional associations and organisations[5-8] include reduced GFR as one of the consequences to consider in hypertensive patients. They also state that it is useful in therapeutic decision tables. Current recommendations[9,10] are aimed more towards minimising the progression of kidney deterioration and treating the complications inherent in kidney failure, thus reducing the cardiovascular risk associated with CKD.

CKD is a condition that can be diagnosed in primary care (PC) in its early stages by estimating GFR through various formulas (hidden CKD) since serum creatinine is not usually altered until more advanced stages. The most widely used and validated are the Cockcroft-Gault[11] and MDRD[12] formulas, which have various advantages and limitations. They are recommended depending on the stage of renal function alteration in the literature.[13-15] In addition, their association with the appearance of cardiovascular events (CVE) has been discovered.

There have been few studies carried out in Spain which have analysed the evolution of long-term cardiovascular morbidity and mortality in cohorts of hypertensive patients monitored in PC, according to renal function. Since AHT is detected and controlled mainly in PC, it stands to reason that the general hypertensive population is better represented by the population cared for in PC.

In 1993, a prospective study was conducted in which the prevalence of left ventricular hypertrophy was determined in a general hypertensive population that was free of cardiovascular disease and that was being treated in a primary care centre.[16] The cohort of patients was monitored from that year onwards.[17]

The aim of this study was to analyse the association between cardiovascular morbidity/mortality and initial renal function, according to the Cockcroft-Gault and MDRD formulas, in a cohort of hypertensive individuals followed during 12 years.

MATERIAL AND METHOD

The «Gòtic» prospective study of a cohort of hypertensive patients treated at a health centre in Barcelona (Spain) was the source of data for this study. Monitoring began in 1993 and lasted 12 years. The selection criteria of the population and the variables analysed have been previously published.[17] For this study, we also excluded patients with extremes of body weight (body mass index [BMI] less than 19 kg/m² or greater than 35 kg/m²), significant alterations in muscle mass, acute renal failure, pregnancy, severe liver disease, generalised oedema or ascites, and those who continued treatment with drugs that blocked secretion of creatinine. Finally, the study cohort included a total of 223 hypertensive individuals.

GFR was calculated according to the Cockcroft-Gault (GFR=[140-age]*weight(kg)/[serum creatinine*72]*0.85, if female)[11] and MDRD (GFR=186*serum creatinine$^{-1.154}$*age$^{-0.203}$*1.212, if black*0.742, if female)[12] formulas and was classified according to the CKD stage.[9]

A CVE was considered to be the appearance of the following episodes during the follow-up period: heart failure; ischaemic cardiopathy (angina, acute myocardial infarction); stroke (permanent or temporary); peripheral vasculopathy (symptoms of intermittent claudication or confirmation through eco-Doppler); death due to cardiovascular event and sudden death. Sudden death was defined as death occurring within one hour after onset of symptoms or individuals dying without any witnesses who had no prior diagnosis of coronary heart disease or other presumably deadly diseases. The recording of the onset of CVE was done during AHT follow-up visits. All CVEs recorded were confirmed with the patients' doctor and with the information and registration systems in hospitals and PC centres.

Strategies were developed to minimise losses during the follow-up period and to recover information related to mortality.[17]

The CVEs and the causes of death were evaluated by an external committee of doctors who were unaware of the patients' situations regarding their kidney function.

The study was approved by the Ethics Committee for Clinical Research of IDIAP Jordi Gol of the Catalan Institute of Health.

Survival time was measured from the date when the subject was included in the study until the occurrence of a CVE, if such an event occurred. The censoring variable was the presence or absence of a CVE from the inclusion of subjects in the study (1993) to the end date of the follow-up (2005). Only the initial event was taken into account if there were various episodes of the same event in the same patient. Survival and incidence rates were estimated using the actuarial method. For the bivariate analysis, we used the Student's t-test or its corresponding nonparametric test in the case of continuous variables, and the Chi-squared test in the case of categorical variables. We used the kappa index to evaluate the correlation between the estimates of GFR carried out with both formulas.[18] The prognostic value of GFR calculated with each of the two formulas was evaluated using Cox proportional hazards regression models, as well as the prognostic value of the adjustment factors. One model was evaluated for each of the formulas used.

The covariate adjustments for the initial models were: age (years), sex (male/female), time of AHT diagnosis (months), mean systolic and diastolic blood pressure of the last two visits, obesity at the start of the study (BMI>30 kg/m^2), diabetes mellitus (DM), dyslipidaemia and tobacco consumption. The variables included in the final model were selected by combining statistical and substantive criteria.[19,20] We evaluated the confounding and interaction effects between the model's variables. Furthermore, we checked the proportional hazards assumption for the various covariates and for the group of those included in the final model, as well as the presence of multicollinearity. Quantitative data were described by estimating the mean and standard deviation when they followed a normal distribution. Otherwise, the median was used along with the interquartile range (IQR). The estimates related directly with the objective of the study are accompanied by their respective 95% confidence intervals (CI). The accepted level of statistical significance was P<.05. The data analysis was performed using the SPSS 15.0 statistical software for Windows.

RESULTS

Of the 265 individuals in the cohort at baseline, GFR could only be measured in 223 (84.2%). The relationship and reasons for exclusion were: 25 (9.4%) had a BMI>35 kg/m^2 and 17 (6.4%) for other reasons, such as consumption of drugs that blocked creatinine secretion, presence of severe liver disease, and creatinine readings were not available.

Table 1 shows the characteristics of the participants at the start of monitoring, as well as the mean analytical values, the frequency of different cardiovascular risk factors (CRF), the distribution of GFR estimates according to the Cockcroft-Gault and MDRD formulas, and the proportion of patients treated with antihypertensive drugs.

The median follow-up time was 10.7 (IQR 6.5 to 12.1) years. Follow-up was complete in 191 participants (85.7%) and incomplete in a total of 32 (14.3%). The latter group differed from the first group in mean age (68.5 years versus 64.2 years) and mean time to diagnosis of hypertension (149 months versus 82 months). The distribution of the remaining study variables was similar in both groups.

The cumulative survival, or the proportion of participants who remained free of cardiovascular events by the end of the study, was 64.7% (95% CI, 57.9-71.6). The mean incidence of CVE during the entire follow-up period was 3.6 (95% CI, 2.7-4.4) per 100 hypertensive individuals/year.

The distribution of estimated GFR with both formulas at the start of the study is shown in Table 2. The agreement between the two estimates was moderate (kappa=0.501; 95% CI, 0.399-0.604). Most patients were classified in stages 2 and 3 by both formulas. Within stage 3, stage 3a was more frequent: 86.8% for calculations performed using the Cockcroft-Gault formula and 76.1% when using the MDRD formula.

Table 3 shows the results obtained in the bivariate analysis, which compared participants according to whether or not they suffered a CVE during follow-up. Only the presence of DM was related with a higher probability of presenting at least one CVE during follow-up. Conversely, female sex and a GFR<60 ml/min/1.73 m^2 according to the MDRD formula were associated with a lower risk of CVE. However, there was no association between the occurrence of CVE and a GFR as estimated by the Cockcroft-Gault formula.

In the final multivariable model (Table 4), only a GFR ≥60 ml/min/1.73 m^2 estimated using the MDRD formula and the presence of DM at the start of the study were associated with an increased cardiovascular risk.

DISCUSSION

In this study, a moderately reduced GFR was not associated with increased cardiovascular risk. Even patients with a GFR ≥60 ml/min/1.73 m^2 according to the MDRD formula had a higher incidence of events. This was the opposite to what has

Table 1. Characteristics of the study cohort at the start of follow-up (n=223)

Variables[a]	Total (n = 223)	95% CI[b]
Age	64.8 (10.1)	63.5-66.1
Sex, % female	63.7	57.1-70.2
Time from diagnosis of hypertension; months	91.5 (96.7)	78.6-104.4
Mean systolic BP in the last two visits; mm Hg	159.2 (18.0)	156.9-161.6
Mean diastolic BP in the last two visits; mm Hg	89.6 (10.2)	88.3-91.0
Body mass index; kg/m^2	28.3 (3.4)	27.9-28.8
Obesity; %	33.2	26.8-39.6
Diabetes mellitus; %	14.8	9.9-19.7
Dyslipidaemia; %	42.6	35.9-49.3
Total cholesterol; mg/dl	229.7 (44.6)	223.8-235.6
HDL cholesterol; mg/dl	47.6 (12.4)	45.9-49.3
LDL cholesterol; mg/dl	158.1 (41.2)	152.0-164.2
Smokers; %	14.3	9.5-19.2
Additional cardiovascular risk factors;%		
- None	30.0	23.8-36.3
- One	40.0	33.3-46.6
- Two or more	30.0	23.8-36.3
Left ventricular hypertrophy (LV): %	64.1	57.6-70.6
Creatinine; mg/dl	1.1 (0.2)	1.09-1.15
Glomerular filtration rate according to MDRD; ml/min/1.73m^2	60.1 (11.1)	58.6-61.6
Glomerular filtration rate according to MDRD <60 ml/min/1.73 m^2; %	51.6	44.8-58.4
Glomerular filtration rate according to Cockcroft-Gault formula; ml/min	61.1 (15.6)	59.0-63.1
Glomerular filtration rate according to Cockcroft-Gault formula <60 ml/min/1.73 m^2; %	49.8	42.9-56.6
Antihypertension drug treatment; %	74.4	68.5-80.4

[a] The quantitative variables are expressed as mean and standard deviation (SD).

[b] Confidence Interval (CI).

been described in the literature.[2,21] These results are not confirmed by the measurement of GFR according to the Cockcroft-Gault formula.

The MDRD formulas is useful to estimate GFR below 60 ml/min/1.73 m^2 and has a tendency to underestimate higher values.[14,15,22] Its author has recently explained[12] the new equation CKD-EPI that has a greater precision than MDRD for GFR ≥60 ml/min/1.73 m2.[12] The Cockcroft-Gault formula, which is also appropriate for these values of GFR, underestimates renal function less for values above 60 ml/min/1.73 m^2.

Other studies have produced conflicting results regarding the performance of the MDRD formula depending on the stages of kidney failure.

In a study performed in Spain with a retrospective cohort of the general population between 35 and 75 years of age and with stage 3 renal function (GFR between 30 and 60 ml/min/1.73 m^2), Buitrago et al[14] reported that the Cockcroft-Gault formula detected more hidden CKD in men, with higher cardiovascular risk and greater age. MDRD, on the other hand, did this more in women with higher obesity, higher diastolic blood pressure and higher triglyceride readings. The MDRD equation could therefore avert significantly important cases from the point of view of cardiovascular event prevention. These authors found only moderate consistency between the estimates performed with both formulas, which was similar to the results in our study. As with our study, they also did not find any evidence of a relationship between hidden CKD detected by one or the other formula and cardiovascular morbidity and mortality.[23] Similar observations have been reported in other studies with larger sample sizes, such as the NHANES-I[24] study in the general U.S. population.

Table 2. Distribution of the study population according to glomerular filtration rates (GFR) at the start of the study, estimated using the MDRD and Cockcroft-Gault formulas

	GFR (ml/min/1.73 m²) according to Cockcroft-Gault					
GFR (ml/min/1.73 m²) according to MDRD	**GFR≥90**	**GFR 60-89**	**GFR 30-59**	**GFR 15-29**	**GFR<15**	**Total**
GFR≥90	**1**	1	0	0	0	2
GFR 60-89	8	**74**	24	0	0	106
GFR 30-59	1	27	**85**	1	0	114
GFR 15-29	0	0	0	**1**	0	1
GFR<15	0	0	0	0	**0**	0
Total	10	102	109	2	0	223

This questions the importance of GFR as a predictive tool for cardiovascular risk by itself, or at least the usefulness of considering Stage 3 as a single group.[25] Indeed, various studies found that the risk increased significantly with GFR below 45 ml/min/1.73 m² (stage 3b), with the risk of patients with higher GFR (stage 3a) comparable to those with normal

Table 3. Characteristics at the start of the study of patients who completed the follow-up (n=191) according to the presence or absence of cardiovascular events (CVE) during that period

Variables[a]	**Total (n = 191)**	**CVE**		**p**
		No (n = 125)	**Yes (n = 66)**	
Age	64.2 (10.3)	63.2 (11.0)	66.0 (8.8)	0.125
Sex, % female	63.4	68.8	53.0	0.031
Time from diagnosis of hypertension; months	82.0 (85.8)	85.1 (92.9)	76.7 (68.3)	0.968
Mean systolic BP in the last two visits; mm Hg	158.7 (18.1)	159.7 (19.1)	156.8 (15.9)	0.287
Mean diastolic BP in the last two visits; mm Hg	89.7 (9.9)	90.7 (9.2)	87.7 (10.8)	0.099
Body mass index; kg/m²	28.2 (3.3)	28.4 (3.2)	27.9 (3.6)	0,327
Obesity; %	31.9	30.4	34.8	0.531
Diabetes mellitus; %	13.6	8.8	22.7	0.008
Dyslipidaemia; %	42.4	45,6	36,4	0.219
Total cholesterol; mg/dl	229.5 (45.7)	227.6 (45.5)	233.1 (46.3)	0.427
HDL cholesterol; mg/dl	48.2 (12.8)	49.3 (13.4)	45.9 (9.7)	0.070
LDL cholesterol; mg/dl	158.3 (42.7)	158.1 (44.7)	158.9 (38.8)	0.911
Smokers; %	14.1	12.8	16.7	0.466
Additional cardiovascular risk factors; %	69.1	68.0	71.2	0.648
- None	30.9	32.0	28.8	0.785
- One	40.3	40.8	39.4	
- Two or more	28.8	27.2	31.8	
Left ventricular hypertrophy (LV): %	62,3	60.8	65.2	0.555
Creatinine; mg/dl	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	0.264
Glomerular filtration rate according to MDRD; ml/min/1.73 m²	60.5 (10.6)	59.1 (11.0)	63.3 (9.3)	0.009
Glomerular filtration rate according to MDRD <60ml/min/1.73 m²; %	49.7	57.6	34.8	0.003
Glomerular filtration rate according to Cockcroft-Gault formula; ml/min/1.73 m²	61.6 (15.0)	61.6 (16.2)	61.6 (12.4)	0.992
Glomerular filtration rate according to Cockcroft-Gault formula <60 ml/min/1.73 m²; %	48.7	52.0	42.4	0.208
Antihypertensive drug treatment; %	72.8	72.0	74.2	0.741

[a] The quantitative variables are expressed as mean and standard deviation (SD).

Table 4. Final Cox regression model to determine the predictive power of cardiovascular events on the study variables at 12 years follow-up of the cohort of hypertensive individuals (n=223)

Variables	Comparison	Beta coefficient	Standard error	Hazard Ratio (95% CI)	P
Age >65 years	versus <65 years	0.492	0.260	1.6 (0.98-2.72)	0.058
GFR according to MDRD					
>60 ml/min/1.73 m^2	*versus* GFR <60 ml/min/1.73 m^2	0.832	0.281	2.3 (1.33-4.00)	0.003
Female	Versus male	-0.450	0.264	0.6 (0.38-1.07)	0.637
Diabetes	Yes versus no	0.637	0.301	1.9 (1.05-3.41)	0.035

renal function.[2,26] In our study, most patients in stage 3 corresponded to stage 3a, both by the Cockcroft-Gault and the MDRD formulas.

The controversy between formulas persists even in more advanced stages of kidney failure (4 and 5) for which some authors advocate the superiority of the Cockcroft-Gault formula over the MDRD.[27]

Furthermore, ageing reduces the relationship between estimated GFR and morbidity and mortality as shown in some studies.[28] Other authors[29] did not report any increase in mortality in elderly patients with GFR between 45 and 59 ml/min/1.73 m^2. Other factors, such as sex, may also affect the prognostic value of GFR. A lower correlation has been reported in women[25,30] and it is females that make up the majority of our sample.

As with other studies[2-4] that did find a relationship between reduced GFR and cardiovascular morbidity and mortality, a first group corresponded to the general population. The mean age in our study was higher than those of patients in the Go et al. and Hallan et al. studies. This may contribute to a different cardiovascular risk and may change the importance of the renal function prognosis. The Keith et al. study, with a mean sample age similar to ours, found that the prognostic differences between stage 2 and 3 were less than 5%, with statistical significance in large samples but not in smaller ones such as ours. Furthermore, the Go et al. study reported that the greatest prognostic differences occurred when GFR<45 ml/min/1.73 m^2 (stages 3b to 5), especially between 60 and 80 years of age, and with an GFR<30 ml/min/1.73 m^2 in those over 80 years of age, which was a lot less among stages with better renal function.

In studies of hypertensive patients, Ruilope et al.[31] found that GFR had a predictive value, but in patients with high cardiovascular risk.

Our study has various limitations. One of them lies in the greater likelihood of losses due to the long duration of the follow-up (longer than in other studies). This could increase the possibility of a selection bias that would affect internal validity. However, a number of strategies used[17] meant that in the end the percentage of losses was 14.3%.

Another drawback was the lack of monitoring of certain parameters such as the evolution of GFR over time. This could be of great importance since it has been recently reported that the rate of decline in renal function for individuals over 65 years old is higher in relation to cardiovascular risk than baseline creatinine.[32]

Also, albuminuria and proteinuria were not recorded systematically at the start of the study. In 1993, their measurement was not included in the assessment protocols for hypertensive patients. Several studies have emphasised the importance of this parameter, which has a greater prognostic value than GFR estimated by MDRD. Hemmelgarn et al.[26] found an increased cardiovascular risk and progression of renal deterioration in patients in stages 1-2 with proteinuria compared to patients in stage 3a without proteinuria. Furthermore, the PREVEND study[33] showed that individuals with GFR<60 ml/min/1.73 m^2 with no proteinuria did not have a higher cardiovascular risk than those with higher GFR. Combining reduced GFR with proteinuria may improve risk prediction.[25,26,34]

Other markers, such as cystatin C, have recently been shown to be predictors of cardiovascular risk and renal disorders in elderly patients with GFR ≥60 ml/min/1.73 m^2 to a greater extent than GFR according to MDRD[25,35] as occurs with the aforementioned CKD-EPI.[15] However, there is little access to both of these methods in PC.

Lastly, the expected influences of antihypertensive treatment were not evaluated during the follow-up, nor were other treatments such as hypolipidaemic or antiplatelet therapy.

In conclusion, this study does not demonstrate an increased cardiovascular risk in hypertensive patients with moderately reduced GFR.

The formula estimates of GFR on its own, currently recommended by clinical practice guidelines, may be less useful for predicting CVE in hypertension as they do not reflect the real risk of some important populations. It may be advisable to consider redefining the values of risk factors of renal function (stages 3 or 3b) and assess the possible benefit of incorporating gender and the value of albuminuria to improve the predictive value of estimated GFR.

Hypertensive patients in stages 2-3a are the most prevalent in PC and are therefore the ones who need the best strategies to prevent cardiovascular events.

Acknowledgements

This study was made possible thanks to the collaboration of the entire "Gothic" PCT of Barcelona who contributed to the optimal monitoring of the patients. Furthermore, the study was supported by the IDIAP Jordi Gol, as well as assistance (FIS Exp. PI040356) from the Carlos III Health Institute of the Ministry for Science and Innovation. The authors of this study declare that there are no conflicts of interest.

REFERENCES

1. Kaplan NM. Clinical Hypertension (9.th ed.) Philadelphia: Lippincott Williams & Wilkins, 2006.
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-305.
3. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 2004;164:659-63.
4. Hallan SI, Dahl K, Oien CM, Grootendorst DC, Aasberg A, Holmen J, et al. Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey. BMJ 2006;333:1047.
5. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560-72.
6. Brosius FC, III, Hostetter TH, Kelepouris E, Mitsnefes MM, Moe SM, Moore MA, et al. Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease: a science advisory from the American Heart Association Kidney And Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: developed in collaboration with the National Kidney Foundation. Circulation 2006;114:1083-7.
7. Mancia G, De BG, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105-87.
8. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens 2009;27:2121-58.
9. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1-266.
10. Alcázar R, Egocheaga MI, Orte L, Lobos JM, González PE, Álvarez GF, et al. Documento de consenso SEN-SEMFYC sobre la enfermedad renal crónica. Nefrologia 2008;28:273-82.
11. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
12. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70.
13. Gracia S, Montanes R, Bover J, Cases A, Deulofeu R, Martín de Francisco AL, et al. Documento de consenso: Recomendaciones sobre la utilización de ecuaciones para la estimación del filtrado glomerular en adultos. Nefrologia 2006;26:658-65.
14. Buitrago F, Calvo JI, Gómez-Jiménez C, Canon L, Robles NR, Angulo E. Comparación y concordancia de las ecuaciones de estimación de filtrado glomerular de Cockcroft-Gault y MDRD en el diagnóstico de enfermedad renal crónica oculta. Nefrologia 2008;28:301-10.
15. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, III, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
16. Dalfo A, Bayo J, Gil M, Campillo M, Botey A, Vila MA, et al. Hipertrofia ventricular izquierda en una población hipertensa general de Barcelona. Med Clin (Barc) 1995;105:361-6.
17. Tovillas-Morán FJ, Zabaleta-del-Olmo E, Fo-Baque A, Vilaplana-Cosculluela M, Galceran JM, Coca A. Cardiovascular morbidity and mortality and left ventricular geometric patterns in hypertensive patients treated in primary care. Rev Esp Cardiol 2009;62:246-54.
18. Abraira V. El índice Kappa. SEMERGEN 2000;27:247-9.
19. Kleinbaum DG, Klein M. Survival Analysis. A Self-Learning Text (2.th ed.). New York: Springer Science Business Media, 2005.
20. Katz MH. A multivariable Analysis. A Practical Guide for Clinicians (2.th ed.). New York: Cambridge University Press, 2006.
21. Redon J, Cea-Calvo L, Lozano JV, Fernández-Pérez C, Navarro J, Bonet A, et al. Kidney function and cardiovascular disease in the hypertensive population: the ERIC-HTA study. J Hypertens 2006;24:663-9.
22. Stevens LA, Coresh J, Feldman HI, et al. Evaluation of the modification of diet in renal disease study equation in a large diverse population. J Am Soc Nephrol 2007;18:2749-57.
23. Calvo Hueros JI, Gómez JC, Canon BL, Martín Hidalgo-Barquero MV, Robles Pérez de Monteoliva NR, Buitrago RF. Episodios cardiovasculares en pacientes con insuficiencia renal oculta detectada mediante fórmulas de filtrado glomerular. Aten Primaria 2008;40:623-30.
24. Garg AX, Clark WF, Haynes RB, House AA. Moderate renal insufficiency and the risk of cardiovascular mortality: results from the NHANES I. Kidney Int 2002;61:1486-94.
25. Lou Arnal L, Campos B, Gracia O, López I, Turón A. Fórmulas de cálculo de la función renal: fortalezas y debilidades. Nefrologia 2009;29(Sup. Ext. 5):94-100.
26. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, et al. Relation between kidney function, proteinuria, and adverse outcomes. JAMA 2010;303:423-9.

27. Teruel JL, Sabater J, Galeano C, Rivera M, Merino JL, Fernández LM, et al. La ecuación de Cockcroft-Gault es preferible a la ecuación MDRD para medir el filtrado glomerular en la insuficiencia renal crónica avanzada. Nefrologia 2007;27:313-9.
28. O'Hare AM, Bertenthal D, Covinsky KE, Landefeld CS, Sen S, Mehta K, et al. Mortality risk stratification in chronic kidney disease: one size for all ages? J Am Soc Nephrol 2006;17:846-53.
29. Manjunath G, Tighiouart H, Coresh J, Macleod B, Salem DN, Griffith JL, et al. Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. Kidney Int 2003;63:1121-9.
30. Derose S, Crooks P, Rutkowski M, Levin N. Age, GFR and the risk of ESRD or death. En: Renal Week Abstracts Archive. Washington: American Society Nephrology;2007:46A.
31. Ruilope LM, Zanchetti A, Julius S, McInnes GT, Segura J, Stolt P, et al. Prediction of cardiovascular outcome by estimated glomerular filtration rate and estimated creatinine clearance in the high-risk hypertension population of the VALUE trial. J Hypertens 2007;25:1473-9.
32. Shlipak MG, Katz R, Kestenbaum B, Siscovick D, Fried L, Newman A, et al. Rapid decline of kidney function increases cardiovascular risk in the elderly. J Am Soc Nephrol 2009;20:2625-30.
33. Brantsma AH, Bakker SJ, Hillege HL, De ZD, De Jong PE, Gansevoort RT. Cardiovascular and renal outcome in subjects with K/DOQI stage 1-3 chronic kidney disease: the importance of urinary albumin excretion. Nephrol Dial Transplant 2008;23:3851-8.
34. Cirillo M, Lanti MP, Menotti A, Laurenzi M, Mancini M, Zanchetti A, et al. Definition of kidney dysfunction as a cardiovascular risk factor: use of urinary albumin excretion and estimated glomerular filtration rate. Arch Intern Med 2008;168:617-24.
35. Shlipak MG, Katz R, Sarnak MJ, Fried LF, Newman AB, Stehman-Breen C, et al. Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. Ann Intern Med 2006;145:237-46.

Sent for Review 7 Jun. 2010 | Accepted: 23 Jun. 2010