

## Peripheral Artery Disease and Kidney Function in Hypertensive Patients

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### Abstract

**Background:** Patients with peripheral arterial disease (PAD) have a high risk of developing cardiovascular events. There is a high prevalence of PAD in individuals with kidney disease and both are important risk factors for cardiovascular events.

**Objective:** The aim of this study was to investigate the association between PAD and renal function in hypertensive patients.

**Methods:** The sample consisted of 909 individuals with arterial hypertension. The presence of PAD was evaluated using the ankle-brachial index (ABI) method and renal function was assessed based on the estimated glomerular filtration rate (eGFR). The subjects were divided into groups, according to abnormal (ABI  $\leq$  0.9) and normal ABI (ABI 0.9-1.4).

**Results:** The percentage of subjects with abnormal ABI was 8%. In the group of individuals with abnormal ABI, prevalence of CKD was 23.4%, compared to a prevalence of 11.2% in patients with normal ABI. Multivariable logistic regression analysis, after adjusting the model to the conventional cardiovascular risk factors, identified a statistically significant and independent effect of eGFR on the likelihood of developing PAD, with an OR of 0.987 (CI: 0.97-1.00).

**Conclusion:** An independent association between PAD and chronic kidney disease was observed in the present study. Therefore, the combination of an accurate diagnosis of kidney disease and routine ABI evaluation could constitute a more efficient means to identify subclinical PAD, allowing individuals to benefit from early interventions, aiming at reducing cardiovascular risk. (Arq Bras Cardiol. 2013;100(4):362-367)

**Keywords:** Peripheral Arterial Disease; Hypertension; Kidney Diseases / complications.

### Introduction

Chronic kidney disease (CKD) has received particular attention in the last 10 years, being recognized as a public health problem due to the growing number of people it affects. Its prevalence is about 10-11% of the adult population in the U.S. and around 8% of the adult population in Europe. This part of the population has increased 4-5% a year and the disease is expected to affect approximately 24,000 people by 2025<sup>1,2</sup>.

As CKD shares many risk factors with peripheral arterial disease (PAD), it is not surprising that the prevalence of PAD is high in patients with CKD<sup>3-5</sup>. It is known that individuals with different degrees of CKD have a high burden of morbidity and mortality from atherosclerotic cardiovascular disease. Moreover, individuals with PAD more frequently have kidney failure than individuals without the disease<sup>1</sup>. CKD patients have a high tendency toward the development of accelerated atherosclerosis, even in the absence of certain cardiovascular risk factors such as hypertension, diabetes mellitus and dyslipidemia, which contribute to the development of endothelial dysfunction and atherosclerosis progression.

These patients often have not only the traditional risk factors, but also elevated inflammatory mediators and activation of the renin-angiotensin system that promote oxidative stress and enhances and accelerates the atherosclerotic process<sup>3,5-7</sup>.

Arterial calcification is also an important factor in the intima occurring in association with atherosclerosis, thus contributing to plaque formation and in the media, causing a loss of arterial distensibility due to alterations in promoter and inhibitor factors of calcification and mainly due to differentiation of smooth muscle cells to osteoblast cells<sup>5,8,9</sup>.

It is known that there is a high prevalence of PAD in patients with kidney disease, both of which are important risk factors for the occurrence of cardiovascular events. Therefore, the objective of this study was to verify whether there was an independent association between PAD and kidney function and also to assess whether the decrease in kidney function was associated with an increased risk of cardiovascular events.

### Methods

#### Sample

The study sample consisted of individuals with hypertension followed in basic family health units, who were being medicated for systemic arterial hypertension (SAH). The study sample comprised 909 subjects, of which 466 were

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Manuscript received June 21, 2012; revised manuscript July 04, 2012; accepted October 24, 2012.

DOI: 10.5935/abc.20130052

women and 443 men, with ages between 20 and 98 years, with a mean age of 64 years. These were divided into groups according to abnormal ( $\leq 0.9$ ) ankle-brachial index (ABI) and normal ( $0.9$  to  $1.4$ )<sup>1</sup>.

The study was approved by the ethics committee of the institutions involved in the study, in accordance with the Declaration of Helsinki.

### Ankle-brachial index (ABI) assessment

To assess the ABI, cuffs were placed on the lower (ankle) and upper limbs (arm) and blood pressure measurements were performed bilaterally using an adapted mercury sphygmomanometer. The procedure was performed with the subject in the supine position after a 10-minute resting period. Three measurements were performed in each limb and then the mean blood pressure was calculated for each limb. To calculate the left and right ABI, the ratio between the ankle systolic pressure (left and right) and the highest brachial systolic pressure was estimated. The ABI value selected for the study was the one that showed the lowest index.

### Covariables

The information obtained consisted in a survey, containing information related each individual's family and personal history, medical tests, medication, concomitant diseases and previous cardiovascular events.

Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg on at least two different occasions, or current antihypertensive treatment. Hypercholesterolemia was defined as documented amount of total cholesterol  $\geq 200$  mg/dL or current antihypercholesterolemic treatment. Diabetes mellitus was defined by current treatment with insulin or oral antidiabetic drugs, or abnormal levels of fasting blood glucose. The smoking status classification was divided as smokers or ex-smokers and nonsmokers. The body mass index was calculated based on anthropometric measurements ( $\text{kg}/\text{m}^2$ ).

### Kidney function assessment

Kidney function assessment was based on the calculation of the estimated glomerular filtration rate (eGFR) using the formula developed in the "Modification of Diet in Renal Disease" (MDRD) study, in which the  $\text{eGFR} = 186.3 \times (\text{Serum Creatinine}^{-1.154}) \times (\text{Age}^{-0.203}) \times (0.72 \text{ if female}) \times 1.210 \text{ if Black}^3$ .

Based on eGFR, chronic kidney disease was defined as normal kidney function ( $\text{GFR} \geq 60 \text{ mL}/\text{min}/1.73 \text{ m}^2$ ); slight impairment of kidney function ( $\text{GFR} = 45$  to  $59.9 \text{ mL}/\text{min}/1.73 \text{ m}^2$ ); moderate impairment of kidney function ( $\text{GFR} = 30$  to  $44.9 \text{ mL}/\text{min}/1.73 \text{ m}^2$ ); severe impairment of kidney function ( $\text{GFR} = 15$  to  $29.9 \text{ mL}/\text{min}/1.73 \text{ m}^2$ ); end-stage kidney disease ( $\text{GFR} < 15 \text{ mL}/\text{min}/1.73 \text{ m}^2$ )<sup>3</sup>.

### Statistical Analysis

The data related to individuals in the sample were computerized and processed using the Statistical Package for the Social Sciences (SPSS) for Windows, release 19.0.

Variable distribution was tested for normality using the Kolmogorov-Smirnov test and for variance homogeneity, Levene's test. Simple descriptive statistics was used for the general characterization of the sample and the distribution of qualitative and quantitative variables. The values of quantitative variables are shown as mean  $\pm$  standard deviation and range. The values of qualitative variables are shown as absolute values and percentage. Comparisons between groups for parametric variables were performed using Student's *t* test for independent samples (comparisons between two groups) or ANOVA with post hoc Tukey's test (comparisons between 3 or more groups). The Chi-square test was used to compare categorical variables.

Logistic regression was also used for the statistical analysis and PAD was defined as the dichotomous dependent variable. Regression models assessed in the study included classic cardiovascular risk variables, namely gender, age, history of cardiovascular disease, hypercholesterolemia, hypertension, diabetes mellitus, smoking status, systolic (SBP) and diastolic (DBP) blood pressure, smoking habits and BMI. Statistical significance was set at  $p \leq 0.05$  for a confidence interval of 95%.

## Results

The general characteristics of the study sample are described in Table 1. Of the 909 subjects in this study, the mean age was 64 years, with a similar percentage of men and women (49% and 51%, respectively). Regarding cardiovascular risk factors in the sample, 34% of the subjects had diabetes, only 11% were smokers, 56% were sedentary and 60% had dyslipidemia.

Individuals were divided into two groups according to the ABI (group with normal ABI *versus* group with reduced ABI). The percentage of individuals with an abnormal and a normal ABI was 8% and 92%, respectively. When compared with individuals with a normal ABI, individuals with an  $\text{ABI} \leq 0.9$  were older, had higher prevalence of diabetes and dyslipidemia, as well as higher values of SBP and triglycerides.

There were no significant differences between the groups in relation to physical inactivity, smoking habits, BMI and total cholesterol. Regarding kidney function, individuals with an  $\text{ABI} \leq 0.9$  showed higher creatinine levels and lower eGFR. In the group of patients with abnormal ABI, the prevalence of CKD was 23.4% (of these, 86.8% had mild kidney function impairment and 13.2% had moderate kidney function impairment), compared with a prevalence of 11.2% (of these, 79.5% had mild kidney function impairment, 19.6% had moderate kidney function impairment and 0.9% had severe kidney function impairment) in the group with normal ABI.

The univariate logistic regression analysis (see Table 2) showed an association of PAD with age (odds ratio [OR] = 1.079, 95% confidence interval [95%CI] :1.052 - 1.106), diabetes (OR = 1.883; 95%CI: 1.149-3.086), dyslipidemia (OR = 2.546, 95%CI: 1.414 - 4.586), SBP (OR = 1.033, 95%CI: 1.022 - 1.044), eGFR (OR = 0.976, 95%CI: 0.963-0.989) and creatinine (OR = 4.517, 95%CI: 1.045-3.638).

**Table 1 - Characteristics of the study sample based on the ABI classification**

	Total n = 909	Abnormal ABI ≤ 0.9 n = 69	Normal ABI > 0.9 n = 840	p
Age (years)	64.23 ± 12.3	73.06 ± 9.886	63.60 ± 12.205	p < 0.001
Sex: M : F*	49:51	49:50	48:51	1.000
Diabetes Yes : No*	34:66	48:52	33:67	0.012
Smoker Yes : No*	11:89	13:87	11:89	0.690
Sedentary lifestyle Yes : No*	56:44	58:42	56:44	0.801
Dyslipidemias Yes : No*	60:40	78:22	59:41	0.001
BMI (kg/m <sup>2</sup> )	28.79 ± 11.85	28.11 ± 5.40	28.85 ± 12.28	0.630
SBP (mmHg)	150.14 ± 20.69	164.981 ± 24.17	149.120 ± 19.92	p < 0.001
DBP (mmHg)	86.28 ± 10.91	84.71 ± 13.23	86.45 ± 10.70	0.204
Total Col. (mg/dl)	196.61 ± 41.15	194.18 ± 44.27	197.02 ± 41.06	0.583
LDL Col. (mg/dl)	116.31 ± 37.62	114.95 ± 40.09	116.63 ± 37.60	0.722
HDL Col (mg/dl)	54.46 ± 21.47	52.69 ± 21.44	54.577±21.44	0.495
Triglycerides (mg/dl)	134.84 ± 67.88	150.39 ± 77.85	133.81 ± 66.99	0.051
Creatinine	0.88 ± 0.22	0.97 ± 0.25	0.88 ± 0.22	0.002
eGFR (mL/min/1.73m <sup>2</sup> )	84.73 ± 23.28	74.66 ± 19.91	85.64 ± 23.41	p < 0.001
Cerebrovascular Event Yes : No*	7:93	13:87	6:94	0.047
LL Ischemia * Yes : No	7:93	15:85	7:93	0.026

Values: Mean ± SD; \* Values in percentage; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; eGFR: estimated Glomerular Filtration Rate; LL: lower-limb.

**Table 2 - Univariate analysis**

	Odds Ratio	CI (95%)	p
Age	1.079	1.052-1.106	p < 0.001
Sex	1.024	0.627-1.673	0.926
BMI	0.988	0.947-1.031	0.588
Diabetes	1.883	1.149-3.086	0.012
Smoking	1.220	0.586-2.539	0.596
Dyslipidemias	2.546	1.414-4.586	0.002
Sedentary lifestyle	1.096	0.667-1.802	0.717
SBP	1.033	1.022-1.044	p < 0.001
DBP	0.985	0.962-1.008	0.204
eGFR	0.976	0.963-0.989	p < 0.001
Creatinine	4.517	1.705-11.971	0.002
Cerebrovascular event	1.950	1.045-3.638	0.036

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; eGFR: estimated Glomerular Filtration Rate.

Performing the multivariable logistic regression analysis (see Figure 1), including in the analysis model the classic risk factors for cardiovascular disease that showed greater association with PAD in the univariate logistic regression model (criterion: p < 0.1), we identified a statistically significant

and independent effect of eGFR on the likelihood of PAD development, with an OR of 0.987 (95%CI: 0.97-1.00). That is, for each decrease of 10 mL/min/1.73 m<sup>2</sup> in the eGFR, the probability of PAD increases by approximately 10%. A statistically significant and independent association was also

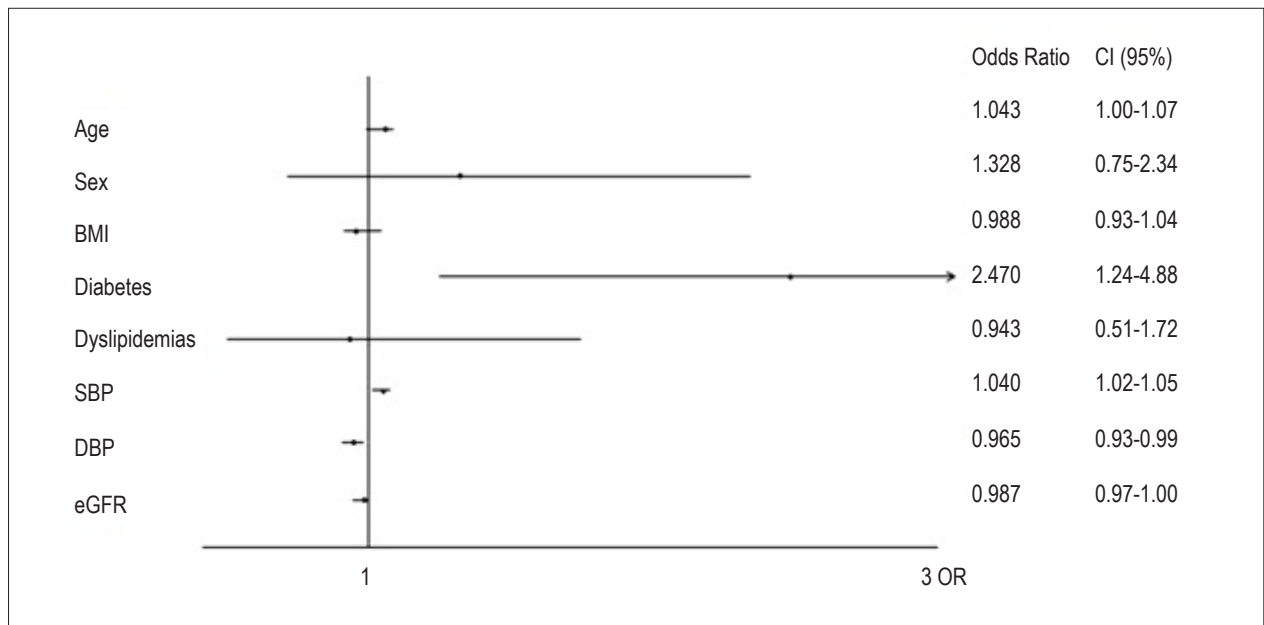


Figure 1 – Multivariate logistic regression for the PAD event.

observed with age, diabetes and SBP. It is noteworthy the importance of diabetes as an independent risk factor for PAD, with an OR of 2.470 (95%CI: 1.24-4.88), indicating a strong association between this risk factor and atherosclerotic disease in the lower limbs.

When remaking the multivariable logistic regression analysis including in the analysis of a dichotomized version of eGFR (normal vs. abnormal), it was observed that individuals with impaired kidney function have a 2.28-fold higher probability of having PAD (OR = 2.28; 95%CI: 1.207-4.307), which is in accordance with the previous analysis. We also observed a significant and independent effect of eGFR decrease with the occurrence of previous cerebrovascular accidents (OR 2.247, 95%CI: 1.166 to 4.339).

Given the evidence of a significant and independent association between PAD and eGFR, we sought to identify its profile and thus, the study sample was divided by eGFR tertiles, showing a curvilinear association of risk for PAD with eGFR (1<sup>st</sup> tertile, OR = 1; 2<sup>nd</sup> tertile, OR = 1.354, 95%CI: 0.628-2.916; 3<sup>rd</sup> tertile, OR = 2.984, 95%CI: 1.057-5.907), thus demonstrating an increasing risk of PAD, with an exponential growth for progressively smaller values of eGFR (see Figure 2).

## Discussion

Although the prevalence of CKD is high in patients with PAD, only a few studies have assessed this association<sup>1,2,5,7,9-12</sup>. On the other hand, CKD also has been evaluated as a potential risk factor for the development of PAD. In this study, carried out in a sample of hypertensive individuals, we observed the existence of an independent and statistically significant association between PAD and CKD. In the study sample, the prevalence of PAD was 8%.

Individuals with abnormal ABI values showed higher creatinine levels, as well as lower eGFR and the prevalence of CKD in this group was higher (23.4% compared to 11.2% in the group with normal ABI). However, when compared with individuals with normal ABI, individuals with an ABI  $\leq 0.9$  were older, had a higher prevalence of diabetes and dyslipidemia, as well as higher levels of SBP and triglycerides.

The possible mechanisms through which an abnormal ABI may be associated with increased likelihood of CKD occurrence are based on the fact that atherosclerosis is a multisystem process, whereby the presence of atherosclerotic manifestations in the lower limbs is definitely associated with atherosclerosis elsewhere in the circulatory system and also involving small and medium-sized renal arteries. A narrowing of the renal arteries can, in turn, lead to functional and ischemic failure through a series of intermediate steps<sup>1</sup>.

In this study, it was observed that the eGFR may also be a predictor of PAD occurrence regardless of other cardiovascular risk factors. It was verified that individuals with impaired kidney function were 2.28-fold more likely to have PAD, as well as the existence of an increasing risk of PAD with decreasing eGFR values. This association between CKD and PAD may partly result from the association of CKD with other risk factors such as hypertension, diabetes and dyslipidemia, thereby accelerating the atherosclerotic process and progression of PAD.

However, there may be other unknown mechanisms involved in both diseases, which may lead to an accelerated progression of one or another disease over time. These two diseases may share not only traditional cardiovascular risk factors, but also non-traditional risk factors, such as increased inflammatory markers, oxidative stress and endothelial dysfunction, which may contribute to accelerated atherosclerosis<sup>9,13</sup>.

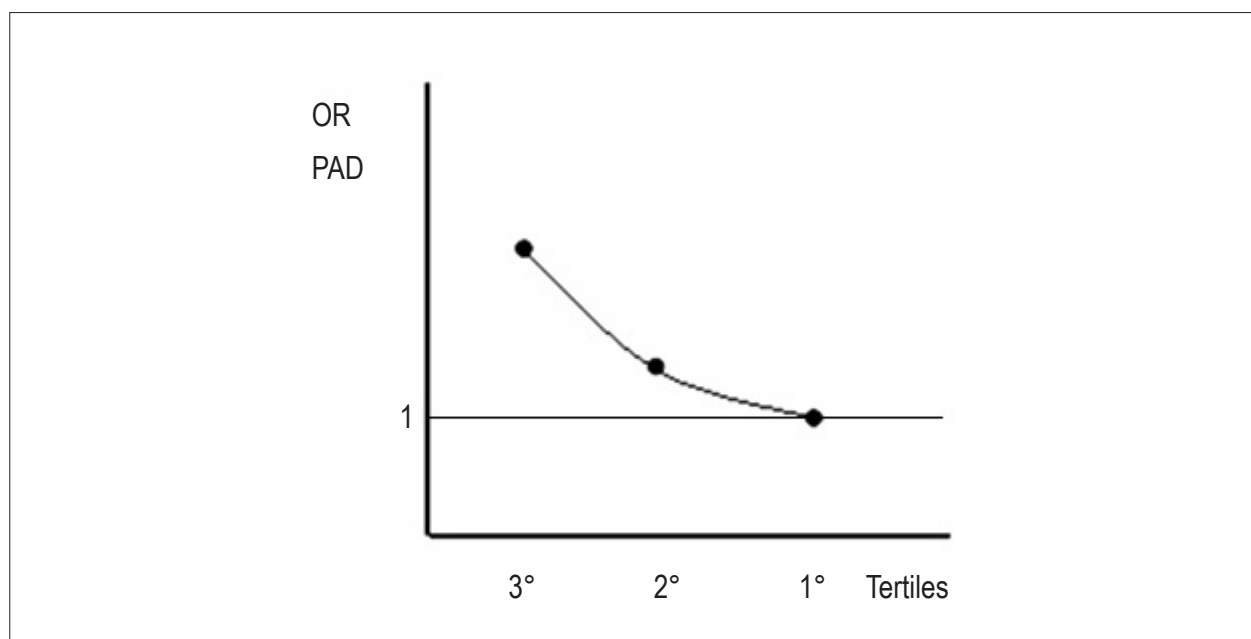


Figure 2 - Risk of PAD according to eGFR tertiles.

On the other hand, we also observed a greater likelihood of previous cerebrovascular events in patients with impaired kidney function. It is known that morbidity and mortality in CKD patients is extremely high and the presence of CKD worsens the effects of cardiovascular disease. At each stage of CKD, cardiovascular mortality risk is several times greater than the risk of progression to end-stage kidney disease; however, the responsible mechanisms are still unknown<sup>4</sup>. CKD and PAD are important predictors of cardiovascular disease and all-cause mortality.

PAD patients have a high prevalence of cardiovascular events such as myocardial infarction, stroke and heart failure, also being associated with high mortality – three-fold that of the general population, even in patients without CKD<sup>10,13</sup>. According to some studies, the mortality rate is significantly higher in patients with CKD combined with PAD both for cardiovascular and all-cause mortality<sup>4,8,9</sup>.

Although an association between chronic kidney disease and peripheral arterial disease was observed, both providing important predictors of cardiovascular disease and all-cause mortality, especially in patients with hypertension, it is important that additional studies be carried out in order to understand and quantify this association, as well as identify new potentially reversible risk factors.

On the other hand, the study's retrospective and cross-sectional design constitutes a major limitation, making it important to carry out prospective studies to attain full clarification of the association implied herein. The inability to establish beyond any doubt a temporal association between the onset of CKD and PAD is also a limitation attributable to the study design, limiting the establishment of causal associations and reinforcing the need for prospective studies to better understand the observed association.

## Conclusion

An independent association between PAD and chronic kidney disease was verified, indicating the existence of a pathophysiological association between kidney impairment and atherosclerotic processes in the lower limbs. Thus, the combination of an accurate diagnosis of kidney disease and the routine measurement of the ABI can be an efficient means of identifying subclinical PAD, allowing individuals to benefit from early interventions aimed at reducing cardiovascular risk.

## Author contributions

Conception and design of the research: Sarmiento C, Pereira T, Maldonado J, Conde J; Acquisition of data, Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Sarmiento C, Pereira T, Maldonado J; Critical revision of the manuscript for intellectual content: Pereira T, Maldonado J, Conde J.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

## Sources of Funding

There were no external funding sources for this study.

## Study Association

This study is not associated with any post-graduation program.

## References

1. Kshirsagar AV, Coresh J, Brancati F, Colindres RE. Ankle brachial index independently predicts early kidney disease. *Ren Fail.* 2004;26(4):433-43.
2. Ix JH, Katz R, De Boer IH, Kestenbaum BR, Allison MA, Siscovick DS, et al. Association of chronic kidney disease with the spectrum of ankle brachial index: the CHS (Cardiovascular Health Study). *J Am Coll Cardiol.* 2009;54(13):1176-84.
3. Traynor J, Mactier R, Geddes CC, Fox JG. How to measure renal function in clinical practice. *BMJ.* 2006;333(7571):733-7.
4. Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, et al. Cardiovascular disease risk status in elderly persons with renal insufficiency. *Kidney Int.* 2002;62(3):997-1004.
5. O'Hare AM, Glidden DV, Fox CS, Hsu CY. High prevalence of peripheral arterial disease in persons with renal insufficiency: results from the National Health and Nutrition Examination Survey 1999-2000. *Circulation.* 2004;109(3):320-3.
6. Resnick HE, Lindsay RS, McDermott MM, Devereux RB, Jones KL, Fabsitz RR, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. *Circulation.* 2004;109(6):733-9.
7. de Vinuesa SC, Ortega M, Martinez P, Goicoechea M, Campdera FG, Luño J. Subclinical peripheral arterial disease in patients with chronic kidney disease: prevalence and related risk factors. *Kidney Int Suppl.* 2005;93:S44-7.
8. Henry RM, Kostense PJ, Bos G, Dekker JM, Nijpels G, Heine RJ, et al. Mild renal insufficiency is associated with increased cardiovascular mortality: the Hoorn Study. *Kidney Int.* 2002;62(4):1402-7.
9. Liu H, Shi H, Yu J, Chen F, Jiang Q, Hu D. Is chronic kidney disease associated with a high ankle brachial index in adults at high cardiovascular risk? *J Atheroscler Thromb.* 2011;18(3):224-30.
10. Luo Y, Li X, Li J, Wang X, Xu Y, Qiao Y, et al. Peripheral arterial disease, chronic kidney disease, and mortality: the Chinese Ankle Brachial Index Cohort Study. *Vasc Med.* 2010;15(2):107-12.
11. Liew YP, Bartholomew JR, Demirjian S, Michaels J, Schreiber MJ Jr. Combined effect of chronic kidney disease and peripheral arterial disease on all-cause mortality in a high-risk population. *Clin J Am Soc Nephrol.* 2008;3(4):1084-9.
12. Vinhas J, Gardete-Correia L, Boavida JM, Raposo JF, Mesquita A, Fona MC, et al. Prevalence of chronic kidney disease and associated risk factors, and risk of end-stage renal disease: data from the PREVADIAB study. *Nephron Clin Pract.* 2011;119(1):c35-40.
13. Black C, Sharma P, Scotland G, McCullough K, McGurn D, Robertson L, et al. Early referral strategies for management of people with markers of renal disease: a systematic review of the evidence of clinical effectiveness, cost-effectiveness and economic analysis. *Health Technol Assess.* 2010;14(21):1-184.