Interarm systolic blood pressure as a predictor of cardiovascular events in patients with chronic kidney disease

Borja Quiroga, Isabel Galán, Soledad García de Vinuesa, Marian Goicoechea, Úrsula Verdalles and José Luño

Nephrology Unit, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Correspondence and offprint requests to: Borja Quiroga; E-mail: borjaqg@gmail.com

ABSTRACT

Background. Increased interarm systolic blood pressure difference (IASBPD) is associated with mortality and cardiovascular (CV) events both in the general population and in patients at high CV risk. The aim of the present study was to assess the value of IASBPD ≥10 mmHg for predicting CV events in patients with chronic kidney disease (CKD).

Methods. The study sample comprised 652 patients with CKD (age 67 ± 15 years, 58.1% men). Follow-up was 19 ± 5 months. We recorded increased IASBPD and related factors and assessed the predictive value of this variable for CV events.

Results. We recorded diabetes mellitus in 136 patients (20.8%), history of CV disease in 213 (32.6%) and dyslipidaemia in 327 (50.1%). The mean glomerular filtration rate was 45.9 ± 18.9 mL/min/1.73 m², and the median albumin/creatinine ratio was 26(0–151) mg/g. IASBPD was ≥10 mmHg in 184 patients (28.1%). The factors associated with IASBPD ≥10 mmHg were age, systolic blood pressure levels, history of congestive heart failure, lower levels of high-density lipid cholesterol and higher use of hypertensive drugs. Fifty-eight patients (8.5%) developed a CV event during the follow-up. IASBPD ≥10 mmHg [HR, 1.802, 95%CI (1.054–3.079); P = 0.031] was an independent predictor of CV events.

Conclusions. Increased IASBPD is an independent predictor of CV events in CKD patients.

Keywords: blood pressure, cardiovascular events, cardiovascular risk, chronic kidney disease, increased interarm systolic blood pressure difference

INTRODUCTION

Patients with chronic kidney disease (CKD) are highly likely to develop cardiovascular (CV) events [1–3] caused by traditional (e.g. hypertension, diabetes mellitus and dyslipidaemia) and non-traditional factors (e.g. inflammation, uraemia, anaemia or mineral metabolism abnormalities) [4]. Community-based studies have shown that the severity of CV risk factors correlates with the decrease in glomerular filtration rate, although subclinical abnormalities can be detected even at early stages of CKD [5, 6].

An interarm systolic blood pressure difference (IASBPD) of ≥10 mmHg has been correlated with CV risk factors in the general population and in patients with specific conditions such as diabetes mellitus and vascular disease [7–10]. Consequently, in those patients with comorbidities, prognosis is poor, and an IASBPD of ≥10 mmHg can predict CV events and mortality [7, 8]. Despite the finding of an association with all-cause mortality in CKD and non-CKD patients [11], the literature provides little data on IASBPD and CV disease in patients with kidney impairment. Agarwal et al. evaluated the IASBPD in a cohort of 421 veteran patients, including 218 with CKD. Overall mortality was increased in those patients having an IASBPD of ≥10 mmHg even after adjusting for the presence of CKD. However, in this study, CKD patients are not deeply analysed separately (only mortality is assessed in survival curves) and CV events are not evaluated [11]. In addition, Okada et al. showed that IASBPD was related to the progression of diabetic kidney disease, as the development of albuminuria was independently associated to systolic blood pressure differences in type 2 diabetes patients. No data regarding CV prognosis are shown in this study [12].

The objective of the present study was to assess the prevalence and prognostic value of IASBPD in a cohort of CKD patients and to establish related factors.

SUBJECTS AND METHODS

This is a prospective observation study performed to evaluate the predictable value of IASBPD in patients with CKD. The eligible study population comprised 652 consecutive patients with...
hypertension and CKD. The inclusion criteria were age ≥18 years, CKD Stages 1–3 (not on dialysis) defined according to KDQI guidelines [13] and the presence of hypertension diagnosed using the definitions of the Seventh Report of the Joint National Committee and/or therapy with antihypertensive drugs [14]. The exclusion criteria were recent hospitalization (within the previous 4 months), the presence of an arteriovenous fistula and refusal to participate in the study.

The data recorded at baseline were as follows: age and sex, aetiology of CKD (identified by clinical features and confirmed mainly by biopsy), previous CV disease [congestive heart failure (CHF) determined by echocardiography within the previous 3 months, myocardial infarction, peripheral vascular disease (PVD) and cerebrovascular disease], classic CV risk factors such as dyslipidaemia (defined using the ATP III guidelines or according to whether the patient was receiving statins [15]), diabetes mellitus and concomitant antihypertensive medication. Renal function was assessed at baseline (glomerular filtration rate was estimated using the four-variable Modification of Diet in Renal Disease equation and urinary albumin/creatinine ratio). The nutritional and inflammatory values recorded were low-density lipid (LDL) cholesterol, high-density lipid (HDL) cholesterol, total cholesterol and high-sensitivity C-reactive protein (CRP). Routine clinical and biochemical variables were measured using standardized methods on autoanalysers. Plasma CRP level was measured using a latex-based turbidimetric immunoassay on a Hitachi analyser (Sigma Chemical Co., St. Louis, Missouri, USA). Urinary albumin excretion was measured using an immunonephelometric method.

Brachial systolic blood pressure was measured simultaneously in both arms three times with the patient seated and relaxed for at least 10 min using two sphygmomanometers. The average of the last two measurements was recorded in each arm, and the absolute difference was considered in- 

Results

Interarm systolic blood pressure difference

IASBPD was ≥10 mmHg in 184 patients (28.2%). The median IASBPD was 5 (2–10) mmHg. Patients with IASBPD ≥ 10 mmHg were older; received more antihypertensive drugs; and had higher rates of CHF, higher levels of systolic blood pressure and lower levels of HDL (Table 2). CKD was Stage 1 or 2 in 13% of patients, Stage 3a in 40.1% and Stage 3b in 46.9%. No differences in IASBPD were found between the stages of CKD (P = 0.52). Similar findings were obtained when IASBPD was taken as a continuous variable (Table 3).

Cardiovascular events during follow-up

During follow-up (19 ± 5 months), 56 patients (8.5%) experienced a CV event: 24 of 184 patients with IASBPD ≥ 10 mmHg (13%) and 32 of 468 patients with IASBPD < 10 mmHg (6.8%) (P = 0.008). CV events were distributed as follows: CHF; 53.6%; myocardial infarction, 26.8%; peripheral vascular event, 8.9% and cerebrovascular accident, 0.8%.

Increased CV risk was associated with age, male sex, diabetes mellitus, dyslipidaemia, previous CV events, lower diastolic blood pressure, worse renal function (estimated by MDRD-4), lower levels of HDL, the use of more antihypertensive drugs and IASBPD (≥10 mmHg, and per 10 mmHg increase) (Table 4). Kaplan–Meier survival plots (Figure 1) showed worse CV survival in patients with IASBPD ≥ 10 mmHg (log-rank, 7.23; P = 0.007).
The results of the Cox regression model adjusted for age, sex, diabetes mellitus, renal function (MDRD-4), dyslipidaemia and therapy with antihypertensive drugs showed that IASBPD ≥ 10 mmHg, diastolic blood pressure and previous CV disease predicted CV events in CKD patients (Table 5).

Finally, an age- and sex-adjusted interaction was found between IASBPD and history of PVD, myocardial infarction, CHF, dyslipidaemia and diabetes (P for interaction <0.0001 for all the factors) (Figure 2).

**Discussion**

In this prospective cohort study of patients with CKD, IASBPD ≥ 10 mmHg was found to be an independent predictor of CV events after a follow-up period of 19 ± 5 months.

The prevalence of IASBPD ≥ 10 mmHg in our population was 28.2%, which is consistent with the findings of studies based on patients with PVD, although it is higher than that reported for primary care patients, patients with diabetes and elderly patients [7, 10, 16, 17]. CKD plays a major role in atherosclerosis and vascular disease, and several reports have suggested CKD to be as important as other CV risk factors in this regard [4]. Our results agree in part with this hypothesis, as higher prevalence of comorbidities was found in our cohort.
events and IASBPD

and considering normal a difference lower than 10 mmHg [18]. No specific analyses have been developed to detect target organ damage in patients with renal impairment was associated with a higher prevalence of IASBPD, and also eGFR was not an independent predictor of CV events (it was only associated in univariate analysis). In the only study published including CKD patients, renal impairment was associated with a higher prevalence of IASBPD when compared with non-CKD patients, although no data were provided about the different stages [11]. In our study, we did not include patients without CKD, so this hypothesis could not be confirmed, despite its biological plausibility.

Current guidelines recommend measuring blood pressure in both arms, and, if a difference is detected, decisions on therapy should be based on the higher of the two readings [18, 19]. Only National Institute for Health and Clinical Excellence guidelines refer to IASBPD suggesting that a difference of 20 mmHg could be associated to vascular disease, and considering normal a difference lower than 10 mmHg [18]. No specific analyses have been developed to detect target organ damage in patients with IASBPD. However, some authors have demonstrated excellent correlations between IASBPD and increased CV risk [9]. In our study, we found an association between age, lower levels of HDL, history of CHF, higher systolic blood pressure and IASBPD greater than 10 mmHg. Data reported recently by Sun et al. are consistent with our findings, namely, that the increase in IASBPD was more pronounced in patients with higher systolic blood pressure levels [20]. Other reported associations support a causal link between IASBPD and CV risk factors [10, 21, 22].

The most important finding of our study is that increased IASBPD is predictive of CV events in CKD patients, even after adjustment for classic risk factors, such as history of CV disease. These results confirm our initial hypothesis that in patients with CKD, IASBPD higher than 10 mmHg is an interesting marker for stratifying their CV profile. This predictive capacity is explained by the fact that a difference in blood pressure between arms could be caused by aortic aneurism, coarctation of the aorta, vasculitis, fibromuscular dysplasia, connective tissue disorders and thoracic compression; however, in most cases, the difference is due to subclinical atherosclerosis [10]. The association between differences in systolic blood pressure and atherosclerosis has not been clearly demonstrated. This association was previously reported in the general population, primary care patients and other risk groups, such as patients with diabetes mellitus, patients who have had acute ischaemic stroke and patients with PVD [7, 8, 16, 17, 23]. Although the majority of reports have found a greater prevalence of CV morbidities in those patients with higher rates of IASBPD, the lack of imaging evidence still remains. In a recent study, Su et al. demonstrated that IASBPD was associated with pulse-wave velocity and left ventricular hypertrophy, both indirect markers of atherosclerosis [24].

Regarding CKD patients, a study conducted by Agarwal et al. showed a worse prognosis in terms of global mortality in those patients who had higher IASBPD (mortality increased 28% per each 10 mmHg increase in the difference between arms) [11]. In our study, an association between CV events and IASBPD was found as well [RR 1.34, 95%CI (1.08–1.67), P = 0.008], and probably the importance of this data in this population (CKD) lies in its high-risk CV profile.

Our findings led us to hypothesize that patients with CKD can stratify their CV risk with regular monitoring of blood pressure. In addition, patients with increased IASBPD should be considered at high risk of CV events, and probably intensive control and early treatment could improve their prognosis.

### Table 4. Univariate Cox regression analysis for CV events

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.04 (1.02–1.06)</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1.63 (0.91–2.92)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.80 (1.65–4.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>3.76 (1.97–7.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of CHF</td>
<td>5.93 (3.50–10.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>5.81 (3.43–9.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of PVD</td>
<td>4.76 (2.73–8.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of cerebrovascular disease</td>
<td>3.03 (1.43–6.41)</td>
<td>0.004</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.03 (0.99–1.02)</td>
<td>0.58</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>0.95 (0.92–0.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive drugs (n)</td>
<td>1.64 (1.36–1.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (MDRD-4) (ml/min/1.73 m²)</td>
<td>0.96 (0.95–0.98)</td>
<td>0.001</td>
</tr>
<tr>
<td>Urinary albumin/creatinine ratio (per 1 mg/g)</td>
<td>1.00 (1.00–1.00)</td>
<td>0.37</td>
</tr>
<tr>
<td>Total cholesterol (per 1 mg/dl)</td>
<td>0.98 (0.98–0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol (per 1 mg/dl)</td>
<td>0.98 (0.98–0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol (per 1 mg/dl)</td>
<td>0.96 (0.94–0.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (per 1 mg/dl)</td>
<td>0.99 (0.87–1.14)</td>
<td>0.90</td>
</tr>
<tr>
<td>Interarm systolic blood pressure difference ≥10 mmHg</td>
<td>2.03 (1.19–3.46)</td>
<td>0.009</td>
</tr>
<tr>
<td>Interarm systolic blood pressure difference (per each 10 mmHg increase)</td>
<td>1.34 (1.08–1.67)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Table 5. Multivariate Cox regression model for CV events

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.004 (0.980–1.030)</td>
<td>0.73</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.843 (0.466–1.525)</td>
<td>0.57</td>
</tr>
<tr>
<td>History of CV disease</td>
<td>6.013 (2.845–12.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive drugs (n)</td>
<td>1.194 (0.963–1.481)</td>
<td>0.107</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>0.971 (0.948–0.994)</td>
<td>0.014</td>
</tr>
<tr>
<td>Interarm systolic blood pressure difference ≥10 mmHg</td>
<td>1.802 (1.054–3.079)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Diabetes mellitus and dyslipidaemia were excluded from the final model after assessing confusion.

![Figure 1](image1.png)

**FIGURE 1**: Kaplan–Meier plot illustrating association between CV events and IASBPD ≥ 10 mmHg (chi-square test, 7.23; P = 0.007).
However, intervention studies must be performed to confirm this statement.

Interestingly, in our study, the interaction between history of CV disease (PVD, CHF and myocardial infarction) and CV risk factors (dyslipidaemia and diabetes) increased the risk of CV events, thus illustrating the pronounced effect of atherosclerosis and other well-known predictors of CV disease.

Our study is subject to three limitations. First, we used simultaneous measurements. Other authors have assessed IASBPD using sequential measurements, with the same oscillometric devices and avoiding calibration bias [7]. However, in our opinion, simultaneous measurement better reflects real blood pressure and enables comparison between arms. In addition, we used the same device to avoid bias. Second, given that our data are from a single centre, the results should be confirmed in community-based studies including CKD patients. Finally, the prevalence of CV comorbidities is high, so extrapolation of these results must be applied cautiously.

In conclusion, increased IASBPD is an independent predictor of CV events in patients with CKD.

ACKNOWLEDGEMENT

The authors want to thank Thomas O’Boyle for proofreading the manuscript.

TRANSPARENCY DECLARATIONS

None declared.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part, except in abstract format.

(See related article by Clark and Aboyans. Interarm blood pressure difference: more than an epiphenomenon. Nephrol Dial Transplant 2015; 30: 695–697.)

REFERENCES


Luca De Nicola1,2, Chiara Donfrancesco3, Roberto Minutolo1,2, Cinzia Lo Noce3, Luigi Palmieri3, Amalia De Curtis4, Licia Iacoviello4, Carmine Zoccali1,5, Loreto Gesualdo1,6, Giuseppe Conte1,2, Diego Vanuzzo7,8 and Simona Giampaoli3 on behalf of the ANMCO-SIN Research Group*

1Italian Society of Nephrology, Italy, 2Division of Nephrology, Second University of Naples, Naples, Italy, 3Cardiovascular Epidemiology Observatory, National Institute of Health, Roma, Italy, 4Laboratory of Molecular and Nutritional Epidemiology, Department of Epidemiology and Prevention, IRCCS Mediterranean Neurologic Institute Neuromed, Pozzilli, IS, Italy, 5Nephrology Division, Center of National Research, Institute of Biomedicine and Molecular Immunology Hospital, Reggio Calabria, Italy, 6Division of Nephrology, University of Bari, Bari, Italy, 7National Association of Hospital Cardiologists, ANMCO (Associazione Nazionale Medici Cardiologi Ospedalieri) and Heart Care Foundation (Fondazione per il Tuo Cuore) Onlus, Firenze, Italy and 8Center for Cardiovascular Prevention, ASS 4 'Medio Friuli', Udine, Italy

Correspondence and offprint requests to: Luca De Nicola; E-mail: luca.denicola@unina2.it

*See Supplementary data for the complete list of participants.

ABSTRACT

Background. National surveys in countries outside Europe have reported a high prevalence (11–13%) of chronic kidney disease (CKD). Studies in Europe have provided a variable prevalence likely due to differences in study design, including age and extent of geographic areas, equation used to evaluate estimated glomerular filtration rate (eGFR) and CKD stages examined.

Methods. The 2008–12 National Health Examination Survey in Italy randomly extracted samples from the general population aged 35–79 years, stratified by age and gender, from the resident list of each Italian region (440 persons/1.5 million of residents). We estimated the prevalence of CKD by means of urinary albumin : creatinine ratio and eGFR (CKD-EPI equation–enzymatic assay of serum creatinine). Cardiovascular (CV) risk profile was also evaluated.

Results. Three thousand eight hundred and forty-eight men and 3704 women were examined. In the whole population, mean age was 57 ± 12 and 56 ± 12 years in men and women, respectively; hypertension was prevalent in men and women, respectively (56 and 43%) and the same held true for...