Estimated arterial stiffness and cardiovascular risk in chronic kidney disease – a study protocol

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Abstract:

Introduction The prevalence of chronic kidney disease (CKD) in the general population is 9.1%. Current guidelines recommend a cut-off GFR value of 60 mL/min/1.73 m^2 for diagnosis of CKD, without considering the physiological decline of GFR with aging, or the association with cardiovascular (CV), cerebrovascular or renal outcomes. There is also an increase in arterial stiffness with aging, which is estimated by pulse wave velocity (PWV). **Aim** The aim of this study is to show how the ePWV predicts CV incidents independently of SCORE chart and traditional risk factors. **Materials and Methods** This prospective observational study will include 2058 subjects from the Endemic nephropathy in Croatia – epidemiology, diagnosis and etiopathogenesis scientific research project. **Conclusion** This will be the first study that could show how the estimated arterial stiffness, independently of CKD contributes to overall CV, cerebrovascular and renal risk. We could also, based on the results, propose an age-independent definition of CKD based on the association with CV disease and mortality.

Keywords: chronic kidney disease, ePWV, cardiovascular risk, arterial stiffness

Sažetak:

Procijenjena arterijska krutost i kardiovaskularni rizik u kroničnoj bubrežnoj bolesti – protokol studije

Uvod Učestalost kronične bubrežne bolesti (KBB) u općoj populaciji iznosi 9,1%. Današnje smjernice za dijagnozu preporučuju graničnu vrijednost glomerularne filtracije (GFR) od 60 mL/min/1,73m^2, ne uzimajući u obzir fiziološki pad GFR sa starenjem niti povezanost s kardiovaskularnim (KV), cerebrovaskularnim (CV) ili renalnim ishodima. Sa starenjem dolazi i do porasta krutosti velikih krvnih žila, koja se procjenjuje brzinom pulsnoga vala (ePWV). **Cilj rada** Cilj ovoga rada je pokazati kako ePWV predviđa KV incidente neovisno o procjeni KV rizika uporabom tablica SCORE i tradicionalnih čimbenika rizika. **Materijali i metode** Ovo prospektivno opservacijsko istraživanje uključit će 2058 ispitanika znanstveno-istraživačkoga projekta Endemska nefropatija u Hrvatskoj – epidemiologija, dijagnostika i etiopatogeneza. **Zaključak** Ovo će biti prva studija koja bi mogla pokazati kako procijenjena krutost velikih krvnih žila neovisno o KBB doprinosi ukupnom KV, CV i renalnom riziku. Također bismo na temelju rezultata mogli predložiti o dobi neovisnu definiciju KBB na temelju povezanosti s KV pobolom i smrtnosti.

Ključne riječi: kronična bubrežna bolest, ePWV, kardiovaskularni rizik, krutost velikih krvnih žila

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Determination of chronic kidney disease and cardiovascular risk

According to the results of the epidemiological studies, the prevalence of chronic kidney disease (CKD) in 2017 in the general population is 9.1% with an observed increase trend of 29.3% in the period from year 1990 to 2017 (1). High mortality from CKD was recorded in 2017 when the total number of deaths was more than 1 million, while CKD as the leading cause of death in the period from year 1990 to 2017 went from 12th to 17th place (1, 2). The most important factors that lead to an increase in prevalence of CKD are diabetes, arterial hypertension, and obesity (3,4,5). CKD is associated not only with the risk of end-stage renal disease and the need for replacement therapy, but already in the early stages it is an independent factor of cardiovascular (CV) risk. Research have shown that only one in five patients with CKD experience the need for replacement therapy, while the rest die most often due to CV or cerebrovascular causes (4,5,6). The presence of CKD, whether manifested as proteinuria, i.e. albuminuria or a decrease in glomerular filtration rate (GFR), is an independent risk factor for fatal and non-fatal CV outcomes (7,8). CV risk in CKD increases with decreasing estimated GFR (eGFR) value, from a 43% higher CV risk with eGFR values of 45 to 59 mL/min/1.73 m^2 to a 343% increase in CV risk with an eGFR value of less than 15 mL/min/1.73 m^2 (6). According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for the assessment and treatment of chronic kidney disease from 2012, the diagnosis of CKD is defined as a proven impairment of kidney function lasting longer than 3 months with a decrease in eGFR <60 mL/min/1.73 m^2 or without it and/or with the presence of albuminuria defined as the ratio of albumin to creatinine in the urine (English albumin creatinine ratio, ACR) >30 mg/g (7). The KDIGO 2012 guidelines recommend the use of the 2009 CKD Epi equation for determining eGFR in the adult population and alternative equations if they show greater precision compared to the CKD Epi equation (7,9). And according to the KDIGO guidelines for the treatment of glomerular diseases from 2021, the determination of creatinine clearance and the determination of glomerular filtration with cystatin and the use of the MDRD equation are recommended in the case when the value of glomerular filtration is less than 60 mL/min (10). The disadvantages of the CKD Epi equation are: 1. it is adjusted according to the unique value of the average body surface area (BSA), which is 1.73 m^2, which is significantly different from today's actual BSA value; 2. study in which the equation was derived included a small percentage of subjects over 70 years of age (9). There are debates about the proper definition of CKD and the threshold value of GFR for establishing the diagnosis of CKD (11-16). Today's guidelines recommend the use of an eGFR cut-off value of 60 mL/min/1.73 m^2, considering neither the physiological decline of GFR with aging nor the association with CV, cerebrovascular or renal outcomes (16). Today, an age-adjusted definition of CKD has been proposed, where eGFR threshold values are different for those younger than 40 and older than 65 and are determined according to CV risk (16). This way of determining eGFR could distinguish physiological changes in GFR with age from those associated with actual CKD.

Estimated arterial stiffness and cardiovascular risk

In addition to the fact that with aging there is a decrease in GFR, there is also an increase in the arterial stiffness. The increase in arterial stiffness with aging is a consequence of several pathophysiological mechanisms that lead to damage of the function of the vascular system. With aging, there are structural changes in the arteries, i.e. the degeneration of elastin fibres and their replacement by collagen that is much less elastic, and an increase in the production of vasoconstrictors with a decrease in the bioavailability of endothelial relaxation factors such as nitric oxide (NO) (17). In patients with CKD and end-stage kidney disease (ESKD), hyperphosphatemia, hypercalcemia and the development of secondary hyperparathyroidism also contribute to the increase in arterial stiffness (18). The increased concentration of serum phosphates plays a significant role in the formation of calcifications i.e., it leads to reduced arterial elasticity, and consequently increased arterial stiffness and higher CV mortality (19,20). Arterial stiffness, which is assessed by pulse wave velocity (PWV), is a strong predictor of CV incidents and mortality in the general population, in patients with arterial hypertension and especially in patients with CKD (21-23). According to the guidelines of the European Society of Cardiology from 2018, a PWV value >10 m/s is considered a pathological value that has a predictive value for CV incidents in hypertensive patients (24-27). Today, PWV can be reliably measured by different methods, such as tonometric, sonographic, oscillometric, piezoelectric methods or by implementation in existing devices for 24-hour continuous measurement of arterial pressure (28). The gold standard for determining PWV is the measurement of PWV from carotid to femoral artery (cfPWV). However, direct measurements of cfPWV have proven to be impractical in daily clinical work and in epidemiological studies. Recently, it has been shown that estimated PWV (ePWV) calculated by a validated equation that includes age and mean arterial pressure correlates well with cfPWV and has a predictive role in hypertensive patients with different degrees of CV risk (29). ePWV predicts CV events independently of CV risk assessment using SCORE tables and traditional risk factors defined according to the Framingham study (30-33). Studies have shown that ePWV should be used in daily clinical practice due to its simplicity of execution and high predictive value in CV risk assessment (27,32,33).

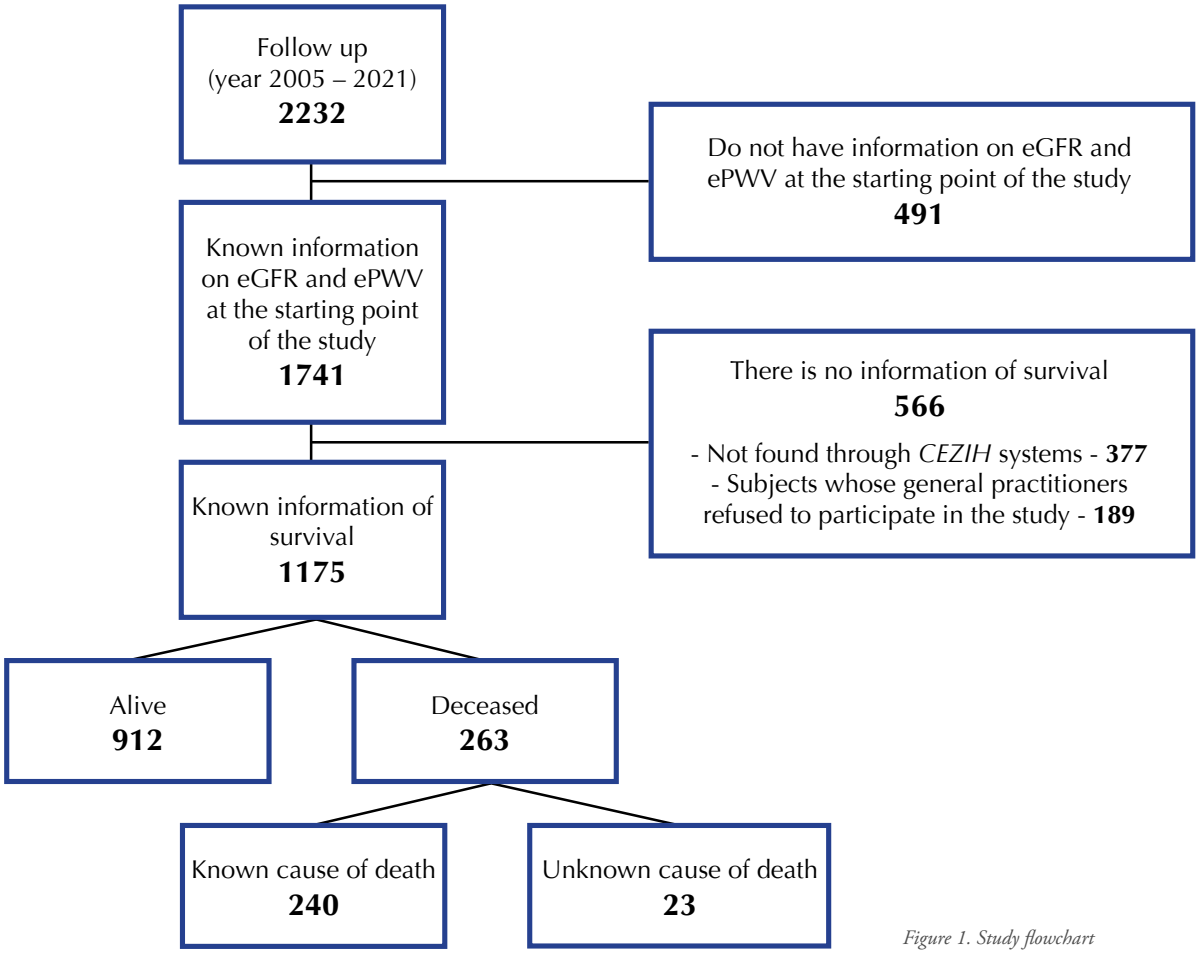

Figure 1. Study flowchart

Although it is known that CKD is an independent factor of CV risk, it is an open question how much does ePWV contributes to CV, cerebrovascular and renal risk in CKD that is defined with an age-adjusted definition.

Study aims

The aim of this study is to determine whether the predictivity of estimated arterial stiffness (ePWV) for fatal and nonfatal CV, cerebrovascular, and renal outcomes is independent of guideline-defined chronic kidney disease (CKD) that is defined as eGFR <60 mL/min/1.73 m^2 or age-adjusted definition of CKD. Also, this study will analyse risk factors for ePWV depending on the stage of CKD determined according to the guidelines and using an age-adjusted definition of CKD. We will show predictability of all traditional CV risk factors and ePWV for total and CV mortality, and for certain fatal and non-fatal outcomes and analyse causes of death and frequency of morbidity depending on ePWV in subjects classified as persons with CKD defined in both ways, and in persons without CKD.

Study design and subjects

This will be a prospective, observational study that will include 2,058 adults, subjects of the scientific research project Endemic nephropathy in Croatia - epidemiology, diagnostics and etiopathogenesis (Ministry of Science, Education and Sports 108-0000000329). Subjects will be monitored for an average of 12 years (2005-2021). At the initial follow-up point, all subjects signed a written informed consent and filled out an extensive questionnaire containing information on personal and family history and were clinically examined, and blood and first urine sample was taken. In final follow-up point we will obtain the data on fatal and non-fatal CV, cerebrovascular and renal outcomes from the archives of general practitioners and from the register of deaths of the Croatian Institute of Public Health. Causes of fatal and non-fatal outcomes will be classified using International Classification of Diseases (ICD 10) codes. We will calculate ePWV values using the validated equation: ePWV = 9.587 – 0.402 × age + 4.560 × 10–3 × age2 – 2.621 × 10–5 × age2 × mean arterial pressure (MBP) + 3.176 × 10–3 × age × MBP – 1.832 × 10–2 × MBP (29). The total risk will be calculated using accepted risk sums (Heart Score and Framingham risk score).

Scientific contribution

The expected scientific contribution of this study is that, based on the obtained results, the contribution of the ePWV, independent of CKD, to the total CV, cerebrovascular and renal risk could be confirmed, which was not done in previous studies. Secondly, our results would contribute to the introduction of an age-adjusted definition of CKD in clinical practice.

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