New European guidelines for management of hypertension: what is relevant for the nephrologist

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It is well established among nephrologists that advanced renal failure is associated with an increased prevalence of cardiovascular (CV) disease including myocardial infarction, stroke and heart failure [1]. Recently, a great amount of information has become available, which demonstrates that the finding of minor abnormalities of renal function also predicts more CV risk in the general population, as well as in hypertensive patients [2].

Recently, the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) have published their guidelines for the management of arterial hypertension [3]. This came only a short time after the JNC 7 report had been published [4]. Some of the relevant changes refer to the introduction of new risk factors that have come to complete the list of major CV risk factors. In this sense, both guidelines recognize the relevance of minor abnormalities of renal function, easily detectable by practicing physicians, for the stratification of patients with arterial hypertension. The Seventh Report of the Joint National Committee [4] considers the findings of microalbuminuria or diminished estimated level of glomerular filtration rate (eGFR) (<60 ml/min) as major CV risk factors. These also include hypertension, cigarette smoking, obesity, physical inactivity, dyslipidaemia, diabetes mellitus, age >55 years in men and 65 years in women, and a family history of premature CV disease. Similarly the ESH/ESC guidelines [3] contemplate among the factors influencing prognosis in hypertensive patients the finding of a slight elevation in serum creatinine (>1.3 mg/dl in men and 1.2 mg/dl in women) and/or microalbuminuria. The presence of chronic kidney disease, defined in ESH/ESC guidelines as serum creatinine values >1.5 mg/dl in men and 1.4 mg/dl in women or by the presence of proteinuria (>300 mg/day), is also considered as a CV risk factor. The ESH/ESC guidelines also recommend to estimate either the creatinine clearance (using the Cockroft–Gault formula) or the glomerular filtration rate [eGFR—using the modified Modification of Diet in Renal Disease (MDRD) formula] [3].

**Detection and prevalence of minor abnormalities of renal function in clinical practice**

The finding of subtle changes in renal function, by non-nephrologists, is usually based on the determination of serum creatinine, creatinine clearance and/or urinary albumin excretion. The Hypertension Detection and Follow-up Program trial [5] showed for the first time that the presence of elevated serum creatinine values (>1.7 mg/dl) at baseline was a very potent predictor for 5- and 8-year all-cause mortality. The data were later confirmed and extended by the Hypertension Optimal Treatment (HOT) trial [6], and many other trials performed in hypertensive patients. Serum creatinine was an excellent predictor, as good as or better than any of the well established major CV risk factors such as diabetes or a history of myocardial infarction [7]. Importantly, in hypertensive subjects, creatinine concentrations that are still within the normal range may already predict outcome [8].

In hypertensive patients the prevalence of an elevated serum creatinine has been shown to be progressively
higher in parallel with progressively higher CV risk. An elevated concentration of serum creatinine was found in only 2.5% of the participants of the HOT study [6], which represents the general population of hypertensive patients. It was found in 10.5% of the participants of the HOPE study [9] that included patients with elevated blood pressure and very high global CV risk and in 12.1% of patients followed in hospital-based hypertension units [10].

The National Health And Nutrition Examination Survey (NHANES) III data in US revealed that 3% of the population presented with elevated levels of serum creatinine values [11]. This high prevalence is not explained by the simultaneous presence of diabetes. Rather it is related to inadequate treatment of high blood pressure [11].

The measurement of creatinine clearance using timed urine collection has been substituted by the estimated creatinine clearance using the Cockcroft–Gault formula [12] or more precisely by eGFR, using a formula developed and validated in the MDRD study [13]. The presence of an estimated creatinine clearance of GFR < 60 ml/min/1.73 m² at baseline was associated with a significant increase in CV risk in the hypertensive population included in the HOT study [6]. Similar results have also been shown in the analysis of data of eGFR from population-based studies such as the Atherosclerotic Cardiovascular Outcomes in the Community study [14] and the HOORN study [15].

Microalbuminuria and proteinuria as predictors of CV risk in hypertensive patients

Epidemiological data have shown that microalbuminuria is associated with an increased incidence of CV events and death, as well as with a higher all-cause mortality. The initial observations concerned high-risk patients, in particular diabetic patients. They were later confirmed by the data of the HOPE study [16]. This study also showed that as a predictor, microalbuminuria was equipotent in diabetic and non-diabetic patients. The predictive value of this parameter has been confirmed in non-diabetic hypertensive patients [17,18] and also in the general population [19]. Interestingly, some of these studies [16,19] found that the relationship between urinary albumin and CV risk is a continuum that starts below the cut-off point of 30 mg/day (or 30 mg/g of creatinine) of albumin that classifies a patient as having microalbuminuria. This fact raised the question whether the current threshold of defining the normal range of albuminuria is adequate [20]. Interestingly, the finding of an elevated excretion of albumin in the urine below the range defined as overt proteinuria is often made before any change in serum creatinine has occurred and in the presence of a preserved or even elevated (hyperfiltration) eGFR value [19,21]. This finding predicts the eventual development of renal failure in non-diabetic patients as well as in diabetic patients [19,21].

Microalbuminuria can be detected in up to 40% of the population with established hypertension, particularly in those patients not controlled satisfactorily by anti-hypertensive therapy [22]. Even blood pressure levels between 130 and 139/80 and 89 mmHg are significantly associated with microalbuminuria [23]. An elevated urinary excretion of albumin < 300 mg/day also predicts a progressive deterioration of renal function, as occurs in both type 1 and type 2 diabetes mellitus [21,24]. In fact, the presence of microalbuminuria predicts the development of overt proteinuria (> 300 mg albumin/day) in non-diabetic and in diabetic patients as shown by the data of the HOPE study [25]. Thus, a progressive and parallel rise in both the renal and the CV risk can be expected in patients in whom microalbuminuria is detected.

The presence of proteinuria in patients with treated essential hypertension varies between 4 and 16% in different series of treated hypertensive patients [26]. The INSIGHT study [27] assessed the role of proteinuria as a CV risk factor in hypertensive patients treated with a long-acting dihydropiridine and a diuretic. Analysis of the different risk factors revealed that small amounts of proteinuria (usually < 1 g/day) conferred a very powerful risk.

Mechanisms underlying the increase in CV risk

An accelerated progression of atherosclerosis and arterial stiffness seems to underlie the higher prevalence of myocardial infarction, stroke, heart failure, CV and all-cause mortality observed in association with abnormalities of renal function in hypertensive patients [1,28]. The association is seen in men and women and is independent of age [29–31]. Some data indicate that nephrosclerosis, often found in hypertensive patients, is associated with atherosclerosis of large arteries [32,33].

A very recent publication from Leoncini et al. [34] examined the presence of subclinical CV damage, localized in the heart and in the carotid artery, in hypertensive patients with either microalbuminuria and a creatinine clearance < 60 ml/min/m². After adjusting for duration of hypertension, mean blood pressure, smoking habits and age, the risk of left ventricular hypertrophy and/or carotid atherosclerosis was increased by 43% with each SD reduction in creatinine clearance and by 89% with each SD increase in microalbuminuria. Mildly increased serum creatinine has been shown to be associated with angiographic coronary artery disease in women [35]. An increased left ventricular mass has been amply demonstrated in patients with microalbuminuria [36]. These and other recently reviewed [22] data indicate that microalbuminuria can be considered as an integrated marker of subclinical organ damage starting with the early stages of arterial hypertension. Microalbuminuria is then a useful tool for risk profiling.

Detection of a slightly diminished value of creatinine clearance at baseline is accompanied by higher initial
levels of blood pressure, more frequently male gender, higher initial levels of uric acid and triglycerides and lower levels of high-density lipoprotein cholesterol [24]. Mild degrees of renal failure and or the presence of microalbuminuria have been shown to be associated to a series of risk factors or markers that are summarized in Table 1.

Gender differences have been shown to exist with respect to the association between CV risk factors and albuminuria. At higher age, higher body mass index and higher plasma glucose concentrations men are more likely to have elevated urinary albumin excretion compared with women [37].

Available data point to the association between alterations of renal function in hypertensives and presence of components of the metabolic syndrome. Very recent data from our unit have shown that among treated hypertensive patients with metabolic syndrome and normal renal function, those presenting with a fasting plasma glucose > 99 mg/dl exhibit a three times increased risk of developing clinical nephrosclerosis during 13 years of average follow-up [38].

Are minor renal abnormalities preventable and/or correctable?

Chronic kidney disease has emerged as a public health problem. The prevalence in the US adult population is estimated to be 11% (19.2 million) according to NHANES III data [39]. The data justify the need for an adequate prevention and treatment of renal damage in the population. Furthermore, any activity in this sense must contemplate the simultaneous protection of the renal and the CV systems both in diabetic and in non-diabetic patients. Recently, it has been proposed that screening for microalbuminuria in the general population could be a tool to detect subjects at risk for progressive renal failure based on the fact that glomerular hyperfiltration and microalbuminuria are early signs of a later development of progressive renal failure in diabetic and in non-diabetic patients [40]. The cost of albumin determination in the general population probably makes this possibility unfeasible. However, the estimation of GFR followed by albumin/creatinine ratio in those presenting with hyperfiltration could be further more cost-effective.

The existence of a defective renal function can be at the origin of arterial hypertension [41]. A defective number of nephrons [42], the presence of sustained renal vasoconstriction [43,44], and a defective tubular capacity for sodium handling [45] are among the possible renal mechanisms leading to the development of high blood pressure. Some of these renal defects, in particular a diminished number of nephrons at birth and/or the existence of persistence vasoconstriction in the kidney, could facilitate a more rapid fall in GFR with aging, as well as, the possible appearance of microalbuminuria.

Later on, it is well established that renal damage can be the consequence of uncontrolled blood pressure elevation. However, available data show that a very strict (<130/80 mmHg) blood pressure control does not ensure a better outcome of GFR when compared with values in the high normal range [46–48], albeit this control could offer other benefits in particular for the CV system.

Table 2 summarizes the therapeutic approaches that must be considered in the presence of renal damage. They are aimed at simultaneous CV and renal protection. The first goal is to obtain life-style changes, with particular emphasis on diminishing salt intake, avoiding obesity and refraining from smoking. Strict blood pressure control (probably <125/75 mmHg) is required, and the administration of a combination of anti-hypertensive drugs will be required in almost every patient [3,4]. The presence of an angiotensin-converting enzyme inhibitor in this combination has demonstrated to improve the long-term renal outcome of patients with nephrosclerosis [46,49]. Recently, the dual blockade of renin–angiotensin system combining and angiotensin-converting enzyme inhibitor and an angiotensin receptor blocker have demonstrated its efficacy in lowering blood pressure and proteinuria in chronic kidney disease [50].

Strict control of the other CV risk factors present is also required and has to be aimed at similarly as if CV protection were the only aim. CV and renal protection aims for different goals by means of therapies with potential synergistic or additive actions, many of which remain unexplored.

Conflict of interest statement. None declared.

**Table 1.** CV risk factors associated to minor abnormalities of renal function

<table>
<thead>
<tr>
<th>Central obesity</th>
<th>Insulin resistance</th>
<th>Low HDL cholesterol levels</th>
<th>High triglyceride levels</th>
<th>Systolic hypertension</th>
<th>Absent nocturnal drop in blood pressure</th>
<th>Salt sensitivity</th>
</tr>
</thead>
</table>

**Table 2.** Therapeutic approaches in patients with chronic kidney disease and hypertension

<table>
<thead>
<tr>
<th>Life-style changes</th>
<th>Salt intake, body weight and smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strict blood pressure control</td>
<td>( &lt;130/80 mmHg). Combination therapy required in most cases</td>
</tr>
<tr>
<td>Blockade of angiotensin II effects is required</td>
<td></td>
</tr>
<tr>
<td>Control of associated risk factors</td>
<td></td>
</tr>
<tr>
<td>Lipids: statins, fibrates</td>
<td></td>
</tr>
<tr>
<td>Insulin resistance: insulin sensitizers (metformin, glitazones?)</td>
<td></td>
</tr>
<tr>
<td>Platelet aggregation: aspirin, others?</td>
<td></td>
</tr>
</tbody>
</table>

[Salt intake, body weight and smoking]
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Statins to prevent cardiovascular events in hypertensive patients. The ASCOT-LLA study

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Introduction

The recently published Lipid-Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes Study Trial (ASCOT-LLA) [1] provides interesting evidence for the use of statins in hypertensive patients with average cholesterol levels and other cardiovascular risk factors. In this study, 19,342 hypertensive patients with at least three other cardiovascular risk factors were randomized to two antihypertensive regimes (amlodipine and/or perindopril vs atenolol and/or clorthalidone) and were planned to be followed for 5 years.

The LLA was comprised of those patients with baseline total cholesterol levels ≤6.5 mmol/l (~260 mg/dl), who were also randomized to receive daily atorvastatin 10 mg vs placebo. A total of 10,305 patients entered in the LLA, which was stopped prematurely by the safety committee after a mean follow-up of only 3.3 years due to a significantly lower incidence of the primary objective (non-fatal acute myocardial infarction and fatal coronary artery disease) in the atorvastatin group. The results showed that 100 patients in the atorvastatin arm and 154 in the placebo arm met criteria for the primary end-point (relative risk reduction 36%, P = 0.0005). The analysis

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