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The uraemic hypertensive patient: a therapeutic challenge—right you are (if you think so)

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High blood pressure (BP) is a leading cause of chronic kidney disease (CKD) and at the same time represents its most frequent complication. High BP is an independent risk factor for advanced CKD; on the other hand, at least 40% of patients with normal glomerular filtration rate (GFR) and virtually all patients with GFR <30 mL/min are hypertensive. CKD and microalbuminuria are powerful risk factors for cardiovascular morbidity and mortality. Consequently, in uraemic hypertension, it is of utmost importance to carefully manage both high BP and microalbuminuria, in order to slow down the progression of kidney damage and to reduce the incidence of cardiovascular events. The first purpose of the medical treatment in hypertensive patients is to normalize BP, regardless of the drug used. Nevertheless, some drugs have an 'additional' nephroprotective effect at the same BP target achieved. In this regard, first-line drugs are definitely renin–angiotensin–aldosterone inhibitors, mainly for their proved efficacy in reducing hypertension-related kidney damage and proteinuria. Anyway, a combined approach (two or more drugs) is usually needed to achieve the optimal BP target and reduce the worsening of CKD.

General considerations

High blood pressure (BP) is still a leading cause of chronic kidney disease (CKD) and at the same time represents its most frequent complication.

The perception that arterial hypertension and chronic renal failure were intimately connected dates back to Richard Bright's pioneering insights,[1] although the scientific evidence supporting the causal link between these two diseases is relatively recent. The Multiple Risk Factor Intervention Trial (MR-FIT),[2] conducted in the mid-1990s on a cohort composed exclusively of men, was the first study to show that even moderately high BP values represent an independent risk factor for end-stage renal disease (ESRD). Several years later a large Japanese study demonstrated that the risk of ESRD linearly increases with the rise of systolic and diastolic BP values.[3] Although a relatively small percentage of hypertensive patients will develop ESRD in the course of their life (roughly 6%), systemic hypertension represents a major global health concern because it currently affects about a quarter of the worldwide population and its prevalence is expected to increase in the near future as a consequence of the ageing population. When arterial hypertension and renal failure coexist, they become part of a vicious circle that exacerbate the target organs damage. In particular, long-standing arterial hypertension may lead to the development of nephron-angiosclerosis, an important cause of ESRD, meanwhile, CKD may aggravate arterial hypertension due to different pathogenetic mechanisms such as volume overload, renin–angiotensin system (RAS) activation, sympathetic hyperactivity, and endothelial dysfunction (*Figure 1*). Renal dysfunction is a well-established risk factor for cardiovascular morbidity and mortality,[4] meanwhile micro-albuminuria (MA), defined as a urinary albumin excretion between 30 and 300 mg/day or an albumin/creatinine ratio on spot urine between 30 and 300 mg/g, has been only recently recognized as a cardiovascular risk factor. In fact, MA is not only a marker of kidney damage with a strong prognostic role in diabetic

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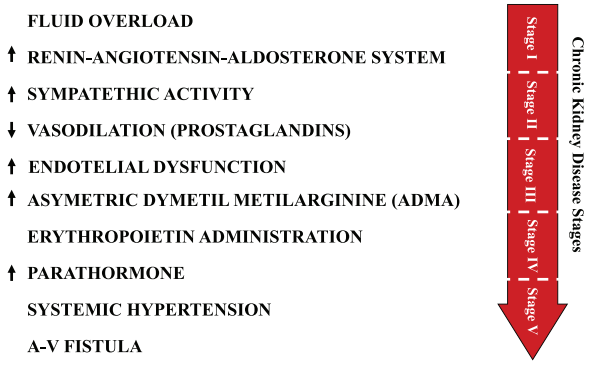

Figure 1 Pathogenetic contributors to the onset of arterial hypertension in different stages of chronic kidney disease.

nephropathy, but it has been also recently proved to portend an adverse cardiovascular prognosis, regardless of BP value and renal dysfunction.[5] The reduction of MA, together with the slowing down of renal damage progression, was demonstrated to reduce cardiovascular events.[6] Accordingly, since 2007 ESH (European Society of Hypertension)/ESC (European Society of Cardiology) guidelines have established that both renal function and MA must be assessed for the correct stratification of the overall cardiovascular risk in hypertensive patients.[7]

Therapeutic targets

In uraemic hypertension is essential to carefully manage BP and proteinuria, in order to reduce the progression of kidney damage and the incidence of cardiovascular events. Accordingly, the ESC guidelines recommend to achieve a BP $\leq$130/80 mmHg in patients with CKD, although they clearly declare that these cut-offs are to some extent arbitrary as they are not supported by strong evidences.[8] Anyway, the debate on the optimal pressure cut-off to pursue in hypertensive patients with CKD in clinical practice often becomes merely speculative, since it is very difficult to achieve BP targets, especially systolic. Over the past few years, in the absence of definite indications, physicians medically managed hypertensive patients with CKD very heterogeneously, remembering the Pirandello drama 'Right You Are (if you think so)', where each protagonist, after a vain search for evidence, finally speaks his 'truth'.

Choice of the antihypertensive drug

The first studies that demonstrated the nephron-protective effect of BP control were conducted when the therapeutic armamentarium basically included only diuretics, sympatholytics and vasodilators. Even though the first purpose of the antihypertensive treatment is to reduce BP, regardless of the drug with which it is obtained, some specific class of drugs have 'additional' nephron-protective effects and therefore should be preferred as a first choice. However, it should be noted that BP control in uraemic hypertension almost always requires a combination therapy with two or more drugs, making difficult to create precise therapeutic indications. A further aspect to consider is the adoption of optimal dosages. In fact, because some drugs exert a nephroprotective action irrespective of the BP values, the reduction of proteinuria and the antihypertensive effect may occur at different doses (i.e. sartans exert a growing anti-proteinuric effect at higher doses than those usually administered for BP management, without a higher incidence of side effects). Lifestyle interventions, such as physical activity, body weight control, and smoking cessation, have shown to be important in treating hypertension and remain valid also in hypertensive patients with CKD, where the indication to reduce alcohol, saturated, and total fat and obviously protein intake become crucial, especially in subjects with lower glomerular filtration rate (GFR) values.

Antagonists of the renin-angiotensin system

Several animal and human studies have shown that RAS is involved in the progression of kidney damage through different mechanisms. Among these, the most important is the vasoconstrictive action of angiotensin II (AII) on the efferent arteriole of the glomerulus, with a consequent increase of intra-glomerular pressure and in turn of transmembrane proteins filtration. In addition, AII exerts pro-inflammatory and pro-thrombotic effects, stimulates growth factors and ultimately favours glomerular and tubulo-interstitial fibrosis. On the basis of these pathophysiological assumptions, for many years we have looked at RAS antagonists as first choice drugs in the treatment of patients with arterial hypertension and CKD, particularly when associated with proteinuria.

Angiotensin-converting enzyme inhibitors

The first class of RAS antagonist made available for clinical use was angiotensin-converting enzyme (ACE) inhibitors (ACEi). Their nephroprotective effect was first demonstrated in mid 90 s in the AIPRI (Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency) trial.[9] Interestingly, in this study, patients treated with the RAS antagonist benazepril showed a greater reduction of GFR compared to placebo at the follow-up. This trend in GFR reduction, that is a constant in the treatment with RAS antagonists and often induces clinicians to discontinue therapy, is instead the mirror of RAS blockade on intra-glomerular pressure and is followed, over time, by a less severe GFR reduction than with other antihypertensive drugs. After AIPRI trial, several other large randomized clinical trials confirmed the valuable nephroprotective action of ACEi.[10] Accordingly, ACEi should be considered first-choice drugs in uraemic hypertension.

Angiotensin receptor antagonists

ACEi block the formation of AII from angiotensin I (AI) acting on ACE. Several studies demonstrated that long-term treatments with ACEi is often associated with so-called 'angiotensin escape', characterized by the return of plasma AII concentration to pre-treatment levels through the action of the serine proteases such as cathepsin G and chymase. Angiotensin receptor blockers (ARBs) or sartans are a class of drugs that directly act on AII receptor, and

therefore they work independently from AII levels. Moreover, because ARBs do not inhibit ACE, they do not cause an increase in bradykinin, which contributes to the vasodilation and also causes some of the side effects of ACEi (i.e. cough and angioedema). The Irbesartan Diabetic Nephropathy Trial (IDNT),[11] was designed to assess whether irbesartan or amlodipine slow the progression of nephropathy in type 2 diabetes patients with proteinuria and mild renal insufficiency (mean serum creatinine 1.67 mg/dL), independent of effects on systemic BP lowering. During an average follow-up of 2.6 years, the risk to achieve the primary endpoint, defined as a composite of doubling of serum creatinine, onset of ESRD or death from any cause, was 20% lower in the irbesartan group compared to placebo (32.6% vs. 39.0%, $P = 0.02$) and was 23% lower than in the amlodipine group (32.6% vs. 41.1%, $P = 0.006$) irrespective of BP values. In addition, irbesartan slowed the rate of doubling of serum creatinine compared to amlodipine (by 21%, $P = 0.02$) and placebo (by 24%, $P = 0.008$). The groundbreaking Diabetics Exposed to Telmisartan And enalaprIL (DETAIL) trial[12] was designed to address the absence of comparative data on the long-term effects of ARBs vs. ACEi on renoprotection and survival in 250 patients with hypertension and early type 2 diabetic nephropathy. DETAIL has shown that telmisartan is comparable to enalapril in reducing GFR decline and that it provides renoprotection in type 2 diabetic nephropathy. In clinical practice, ACEi and sartans can be considered equivalent in the treatment of hypertensive patient with CKD and, for both of them, the use of the higher possible dosage is recommended in order to maximize the AII blockade. It should be emphasized that a low pre-treatment GFR value does not constitute an absolute contraindication to the use of ACEi and ARBs, unless the serum creatinine levels rise more than 50% from baseline value after the first few weeks of therapy. In these cases, it could be appropriate to exclude the possibility of renal artery stenosis, where AII plays a critical role in the maintenance of GFR.

Direct renin inhibitors

Aliskiren is a direct renin inhibitor with a powerful antihypertensive and nephroprotective effect. In the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study[13] aliskiren in combination with losartan demonstrated a greater reduction in proteinuria than losartan alone, achieving the renoprotective effects independent of its blood-pressure-lowering effect. Accordingly, aliskiren may represents an interesting therapeutic option in patients with hypertension, type 2 diabetes, and nephropathy who are receiving the recommended renoprotective treatment.

Diuretics

Diuretics play a major role in BP management in patients with CKD, considering the specific nature of arterial hypertension in these cohort characterized by high sodium and volume retention. It should be noted that sodium retention not only plays a major role in the pathogenesis of uraemic hypertension but also precludes the achievement of an optimal BP control by several antihypertensive drugs (mainly vasodilators) (*Figure 2*). The antihypertensive effects of a low-sodium diet has been extensively documented in patients with CKD and should be strongly recommended.[15] In consideration of the above-mentioned volume retention, with a consequent increase in extracellular fluid, both loop and thiazide diuretics should be considered essential drugs in the treatment of hypertensive patients with CKD. In this context, the choice of the most appropriate drug should be made on the basis of the severity of renal dysfunction (*Figure 3*). In fact, with the notable exception of high-dose metolazone (10–20 mg daily) and loop diuretics, the large majority of diuretics lose their efficacy when GFR declines below 40 mL/min. Furosemide is a powerful loop diuretic that induces intense diuresis and natriuresis, but due to its pharmacokinetic properties, this effect is limited to 6 h after intake and followed by a long phase (roughly 18 h) of reactive sodium retention. Consequently, to obtain a persistent and effective natriuretic and diuretic action, the total daily dose of furosemide should be fractioned over the 24-h period.

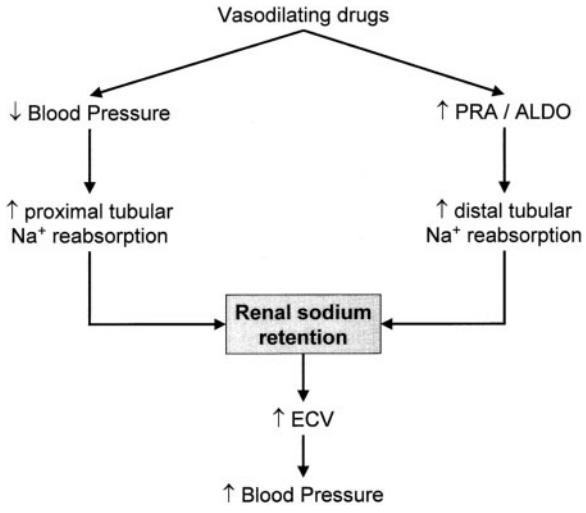

Figure 2 Effects of vasodilating drugs on pathophysiology of hypertension in chronic kidney disease. ALDO, aldosterone; ECV, extra cellular volume; PRA, plasma renin activity. Modified from De Nicola *et al.*[14]

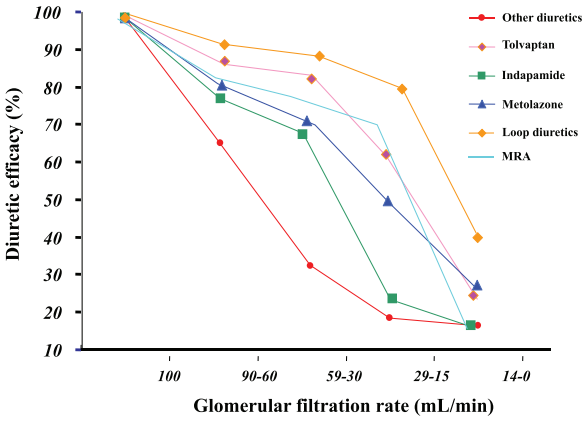

Figure 3 Diuretics efficacy according to different degrees of renal dysfunction. MRA, mineralocorticoid antagonists.

The different site and duration of action of diuretics and their additive effect when used together represent the pathophysiological basis for the combined use of different diuretics, a therapeutic approach known as 'sequential nephron blockade'.

Potassium-sparing diuretics have generally weak diuretic action and work by interfering with the sodium-potassium exchange in the distal convoluted tubule of the kidneys or as antagonists at the aldosterone receptor. Among them, spironolactone has been shown to have a powerful anti-proteinuric effect when associated to ACEi or ARBs mediated by the reduction of aldosterone-induced vasoconstriction on the efferent arteriole.[16] Hyperkalaemia is the most common side effect of potassium-sparing diuretics, with an increased risk in presence of double RAS blockade or severely reduced GFR ($<$30 mL/min).

Calcium channel blockers

Dihydropyridine calcium channel blockers (CCBs) are powerful antihypertensive drugs with a good safety profile in uraemic patients due to the almost complete hepatic excretion. Nevertheless, their use in monotherapy is not recommended since they cause preferential dilatation of the pre-glomerular afferent arteriole that in turn determines an increase in glomerular capillary pressure with consequent hyperfiltration and proteinuria. Accordingly, as demonstrated in the African American Study of Kidney Disease and Hypertension Study (AASK trial)[17] and in the IDNT trial,[11] the anti-proteinuric effect of dihydropyridine CCBs, and to a lesser extent of non-dihydropyridine CCBs,[18] is lower than that of RAS antagonists at the same achieved BP. Anyway, it should be noted that in both AASK trial and IDNT trial more than 80% of the patients took CCBs, underlining the importance of these drugs in achieving optimal BP targets.

Betablockers

Chronic renal failure is associated with a broad activation of the sympathetic nervous system,[19] which leads to renin secretion through the stimulation of beta-adrenoceptors of the juxtaglomerular apparatus and contributes to the worsening of kidney disease itself. In this context, beta-blockers may play an important role in controlling BP values and slowing down renal damage, as well as in reducing mortality.[20] Nonetheless, in clinical practice betablockers are rarely used in hypertensive patients with CKD, mainly because of their negative effects on metabolism. Third generation betablockers such as nebivolol, carvedilol, and bisoprolol, have been demonstrated to be safe and tolerable (because of their mainly hepatic excretion) in patients with hypertension and CKD, with favourable effects on renal haemodynamics.[21].

Association therapy

As already mentioned, in order to achieve adequate BP control in hypertensive patients with CKD it is often needed to combine different antihypertensive drugs, mainly in diabetic nephropathy. Therefore, if the first choice relates almost constantly to the RAS antagonists, the association with a diuretic is usually a valid option as add-on therapy because this combination shows a synergistic antihypertensive action and is effective in limiting the side effects of both drugs. In particular, diuretics induce sodium and volume depletion, with the consequent RAS activation, that is modulated by ACEi/ARBs action. Moreover, diuretics and RAS antagonists counteract each other the risk of electrolyte imbalance due to their mechanism of action (while diuretics can cause hypokalaemia, RAS antagonist can cause hyperkalaemia).

Calcium channel blockers, that are metabolically neutral and highly effective in their antihypertensive action, can also be safely associated with RAS antagonists. Notably, in this combination the unfavourable effect on glomerular haemodynamics of CCBs described above is counterbalanced by the action of RAS inhibitors on AII (opposite effects on glomerular capillary pressure).

The double blockade of RAS

The rationale for combining ACEi and ARBs in the treatment of hypertensive patients lies on the fact that neither of these two classes of drugs completely inhibits RAS activity. It is well known that long-term treatment with ACEi is often associated with so-called 'angiotensin escape', characterized by the return of plasma AII concentration to pre-treatment levels.[22] This event occurs mainly due to the enhanced activity of alternative metabolic pathways that bypass the ACE blockade, such as the serine proteases cathepsin G and chymase, whose synthesis is stimulated by ACE inhibition. Moreover, the reactive increase in renin secretion induced by the interruption of the negative feedback exerted by the AII on the renin itself may contribute to the increase of AII plasma concentration during treatment with ACEi. This last mechanism also applies to ARBs, since the increase of circulating AII can compete with the drug for tissue receptor. For all these reasons, the combination of ACEi and ARBs has been considered beneficial in the treatment of hypertension, although the additive effect on BP lowering is modest. Notably, current evidences show that the ACEi/ARBs combination has a beneficial effect on the reduction of proteinuria in hypertensive nephropathic patients, higher than that of the individual classes alone, although it has never been demonstrated any improvement in renal endpoints.[23] Accordingly, on the basis of the available data, double RAS blockade should be mainly used in kidney diseases with a prevalent proteinuric expression.

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