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Supplementary information

Chronic kidney disease

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Box 1 | Evidence that arterial hypertension (HTN) is a consequence rather than a cause of chronic kidney disease (CKD)

1. HTN is strongly associated with CKD

Arguments against:

- Association does not imply causation. Indeed, numerous lines of evidence show that HTN is rather the first sign of (remnant) kidney overload.
- Monogenic forms of HTN (with genes or their targets not being expressed in the kidneys) do not cause CKD[1].
- Prospective interventional trials with antihypertensive drugs did not improve onset of CKD defined by impaired GFR or albuminuria[2-4].
- Prevalence of 'hypertensive nephropathy' did not decrease despite better antihypertensive therapy[5].
- Hypertensive nephropathy in patients with sub-Saharan ancestry was found to represent APOL1 nephropathy[6].
- In kidney donors, new onset of HTN is more prevalent [7,8]
- Adults with resolved paediatric glomerulonephritis develop HTN more often[9].
- In premature children with low nephron mass, hypertension is more prevalent[10].
- In children with a solitary kidney, hypertension is more prevalent[11].
- In paediatric AKI survivors or hereditary nephropathies, new onset HTN is the first sign of CKD[12,13].
- In clinical settings of kidney overload (obesity, diabetes mellitus or pregnancy), HTN precedes proteinuria or GFR loss[14].

2. HTN associates with poor kidney and cardiovascular outcomes in CKD

Argument against:

- As HTN is a sign of kidneys that can no longer maintain sodium and volume balance (functional overload), presence of HTN represents more severe CKD and implies worse kidney and cardiovascular outcomes compared to absence of HTN.

3. Rat models show that HTN precedes kidney injury

Arguments against:

- Of the various models of HTN in animals (such as Ang II-infused mice, spontaneous hypertensive rats, human renin overexpression), none show glomerulosclerosis, but spontaneous models are nephronopenic in the first place[15]
    - Goldblatt rats with two kidneys-one clipped show glomerulosclerosis, but only in the clipped kidney; that is, ischaemic glomerulosclerosis[15].

4. Hypertensive glomerulosclerosis is a common kidney biopsy finding

Argument against:

- Glomerulosclerosis is an unspecific lesion and the associated vascular signs of hypertension do not inform about causality. Such cases should be named 'CKD of unknown cause' and trigger further diagnostic steps to identify the factor(s) causing these lesions[16].

5. Primary hyperaldosteronism causes CKD

Argument against:

- Aldosterone excess activates mineralocorticoid receptor signalling, which triggers numerous cellular effects and extracellular matrix production unrelated to HTN. The effect of mineralocorticoid receptor antagonists on CKD is not explained by blood pressure control only [17]

6. If GFR and urine exams are normal, HTN cannot be CKD but is essential HTN

Argument against:

- Kidney Disease Improving Global Outcomes (KDIGO) defines CKD as "changes in kidney structure and function with health consequences" [18]. As HTN drives cardiovascular disease, HTN can define CKD also at a normal GFR and urine exams. Most cases with 'essential HTN' relate to the discrepancy between kidney capacity and respective sodium intake resulting in volume expansion that elevates blood pressure. In this setting, routine blood and urine exams will still be negative even if HTN is a clear sign of kidney dysfunction, that is, CKD.[1]

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