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Preserving kidney health during intensive blood pressure control

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Abstract

Intensive lowering of blood pressure can decrease the risk of death and cardiovascular events in individuals with hypertension. A reanalysis of data from the SPRINT and ACCORD trials suggests that intensive blood pressure lowering increases the risk of chronic kidney disease (CKD).

Hypertension is linked to serious, life-threatening events, including stroke, heart failure and renal disease. Consequently, both the American College of Cardiology and the American Heart Association have developed guidelines recommending stricter blood pressure (BP) control¹. The findings of the SPRINT and ACCORD trials indicate that intensive lowering of systolic BP below 120 mmHg versus standard lowering below 140 mmHg reduced the risk of death and of adverse cardiovascular events^{2,3}. Results from SPRINT also suggested that intensive BP lowering might increase the risk (by 3.5-fold) of incident chronic kidney disease (CKD), defined as a 30% decrease in estimated glomerular filtration rate (eGFR).

To assess whether intense control of systolic BP might affect renal function, Beddhu and collaborators carried out a secondary analysis of data from the SPRINT and ACCORD trials, focusing on participants who did not have evidence of CKD at baseline⁴. In the ACCORD trial, after 3 years the cumulative incidence of CKD was 10% for the intensive treatment versus 4.1% for the standard treatment, whereas in SPRINT, the incidence of CKD for the intensive treatment was 3.5% versus 1.0% for the standard treatment. The researchers rightly concluded that intensive BP lowering increased the risk of renal disease in individuals with or without diabetes and cautioned that close monitoring of renal function was needed⁴. These studies elicit some considerations. Identifying an ‘optimal’ systolic BP level (perhaps somewhere between 120–130 mmHg) that provides cardiovascular protection while preserving kidney function might be an understandable initial reaction. Although additional studies to identify this optimum BP seem warranted, the presence of many variables in every single patient will make it somewhat challenging to arrive at definitive conclusions. Furthermore, it seems that appropriate BP values might need to be related to (and in the case of patient management, personalized to) the structural and functional status of the kidneys

Competing interests

The authors declare no competing interests.

Refers to Beddhu, S. et al. Intensive systolic blood pressure control and incident chronic kidney disease in people with and without diabetes mellitus: secondary analyses of two randomised controlled trials. *Lancet Diabetes Endocrinol.*, doi:10.1016/S2213-8587(18)30099-8 (2018).

before and during treatment. Here, we discuss experimental data that might explain the renal outcomes described above (for further discussion of these and other trials, see Refs ⁵⁻⁷).

Whether the kidneys are adversely affected by the intensity of BP-lowering treatment will depend, at a minimum, on the general health of an individual, the medication that is being used to control BP, how quickly BP is brought under control, the total nephron count (which ranges from 400, 000 to 2.4 million) and the presence of undetected structural damage to the kidneys. However, aside from an assessment of an individual's general health and their cardiovascular haemodynamic status, most clinicians do not have this crucial information about the kidneys when treating hypertension. Thus, BP intervention trials should perhaps incorporate an assessment of these parameters or meaningful surrogates.

For years, the conventional wisdom was that healthy kidneys could regulate blood flow over a wide range of BPs that is usually compatible with the BP targets mentioned above. However, some medications used to treat hypertension, although extremely effective in BP control, might impair renal regulation of blood flow.

Results from animal studies might be illuminating. For example, the haemodynamic and renal consequences of inhibiting the renin-angiotensin system (RAS) were examined in rats with severe hypertension⁸. Animals were treated for 14 days with the angiotensin II receptor antagonist valsartan, the direct renin inhibitor aliskiren or both inhibitors. Although all treatments markedly improved BP, cardiac hypertrophy and proteinuria, blind histological examination of the kidneys detected tubular dilatation and tubular cell proliferation, interstitial and periglomerular fibrosis and focal vascular thickening of arterioles for all treatments, contrary to all expectations. Remarkably, these alterations were more pronounced in the dual treatment group. A significant finding of this study is that proteinuria, which is commonly used to indicate renal injury, was improved in the treated rats, giving the false initial impression that no renal damage existed. In light of these results, a clear need exists to identify markers that accurately reflect the structural integrity of the kidneys. Several factors might account for the observed kidney damage. Although not formally studied, the researchers postulated that the ability of the kidneys to regulate blood flow was impaired in their study conditions⁸. Interestingly, dual blockade of the RAS resulted in a marked increase in the number of renin-producing cells along the renal arterioles. It is well-known that smooth muscle cells of the renal arterioles adopt an endocrine phenotype that diminishes their contractility when the RAS is inhibited, which perhaps explains the failure of these arterioles to regulate blood flow. Under these conditions, a substantial drop in BP could lead to renal ischaemia, followed by the structural damage observed in the study. Furthermore, experimental or spontaneous mutations in the RAS genes (in rodents and humans) or prolonged pharmacological inhibition of the RAS in early life result in concentric vascular hypertrophy of the renal arterioles⁹. Studies in renin-null mice showed that the vascular hypertrophy was due to the presence of concentric, disorganized layers of renin-lineage cells and smooth muscle cells, which thickened the vessel walls and narrowed their lumens¹⁰. The researchers suggested that cells attempting to make renin might also secrete factors that stimulated the growth of adjacent smooth muscle cells; these factors might be useful biomarkers of early renal damage that precedes the development of functional deterioration. Of note, permanent loss of kidney function is

usually preceded by a substantial dropout of structurally damaged nephrons. As histological assessment during the evaluation of patients with hypertension or in the design of clinical trials is usually not indicated, developing biochemical markers and improved imaging technologies that better reflect renal structural integrity before and during treatment is imperative. This data is necessary not only to assess the safety of treatments but also to improve the interpretation of clinical trial results. Clinicians should not have to choose between cardiovascular and renal protection. Although many well-designed trials have been carried out, crucial information about renal integrity is still missing. Given the unprecedented technology at our disposal, it seems timely to return to the bench and design experiments in animal models to improve understanding of the pathogenesis of renal disease ensuing from or concomitant with the treatment of hypertension. This knowledge should enable the design of trials to not only identify a meaningful, biologically relevant BP value but also to improve current treatment strategies with the goal of maintaining both cardiovascular and renal health. The rush to ‘translate’ basic research into clinical outcomes should be based on and tempered by solid data from experimentation. The old adage ‘primum non nocere’ (first, do no harm) still stands.

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FIGURE 1.
Potential factors leading to renal damage when lowering BP.