DIABETES AND THE KIDNEY – AT THE LIMITS

Blood pressure control and SGLT-2 inhibitors

KEY MESSAGES
• In a patient with diabetes and chronic kidney disease (CKD), evidence points to an optimal target blood pressure of 140/80 mmHg and lower, to 130/80 mmHg, when albuminuria is present
• All blood pressure-lowering agents can be used to lower blood pressure in patients with diabetes and CKD
• Clinicians should include an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB) in the antihypertensive regimen
• Dual or triple renin angiotensin aldosterone system (RAAS) blockade is a high-risk strategy and is not recommended for routine practice
• New SGLT-2 inhibitor agents may enhance reno-protection over and above that offered by ACE-I/ARB therapy.

Introduction

The most recent CKD classification published by ‘The Kidney Disease Improving Global Outcome Initiative’ (KDIGO) is based on a two-dimensional risk model, which uses the parameters of glomerular filtration rates (eGFRs) and albuminuria, based on the urinary albumin:creatinine ratio. This categorisation provides clinical guidance for the evaluation and management of CKD1 (Table 1).

Table 1: CKD classification by eGFR and albuminuria

<table>
<thead>
<tr>
<th>eGFR ml/min/1.73 m²</th>
<th>Albuminuria categories (Based on urinary albumin:creatinine ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A 1 &lt;3 mg/mmol</td>
</tr>
<tr>
<td>G1 ≥90</td>
<td>No CKD</td>
</tr>
<tr>
<td>G2 60–89</td>
<td>No CKD</td>
</tr>
<tr>
<td>G3a 45–59</td>
<td>G3a A1</td>
</tr>
<tr>
<td>G3b 30–44</td>
<td>G3b A1</td>
</tr>
<tr>
<td>G5 &lt;15</td>
<td>G5 A1</td>
</tr>
</tbody>
</table>

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The colour from a ‘safe’ green to a ‘red alert’ defines the degree of risk that a patient is exposed to for developing end-stage kidney disease (ESKD), acute kidney injury and mortality or morbidity related to cardiovascular risk. The presence of albuminuria at any eGFR increases the level of overall risk.

Professor David Wheeler, University College London, addressed the evidence for blood pressure-lowering targets in CKD and diabetes, while proposing new approaches using new agents ‘at the limits’ of current care.

**Blood pressure control in patients with diabetes and CKD**

The focus in determining target blood pressure in an individual patient is an exercise of weighing up risks and benefits; in the elderly, patients with coronary artery disease or those with wide pulse pressure, there is a greater risk of an adverse event when blood pressure is pushed lower than 140/90 mmHg.

Most patients with CKD die from cardiovascular disease before reaching ESKD. Yet, unlike hypertensive patients without kidney disease, patients with CKD have not consistently shown a positive association between blood pressure and cardiovascular risk. This may be due to the longstanding CKD-related hypertension’s causing changes in cardiac structure and function, which lower blood pressure while increasing overall cardiovascular risk.

The association between systolic blood pressure and risk of vascular events in CKD was recently investigated in the SHARP study using data from 8 666 participating patients (23% had diabetes mellitus). Patients with a history of vascular disease (or a Troponin-I concentration >0.01 ng/ml) and those with no CVD (and a low Troponin-I concentration <0.01 ng/ml) were separated into two groups and the association between systolic blood pressure and vascular events was examined.

This clearly showed that the U-shaped relationship between blood pressure and vascular risk was confined to CKD patients with CVD or at high probability of having subclinical cardiovascular disease (Figure 1). This supports the view that there is a need for clinical trials of more intensive blood pressure-lowering among patients with moderate-to-advanced CKD without cardiovascular disease, including patients on haemodialysis and peritoneal dialysis.

![Figure 1. Association between usual blood pressure and risk of cardiovascular events in SHARP](image-url)
These SHARP data support the view that blood pressure targets in patients with CKD without cardiovascular disease, but with type 2 diabetes, should be at levels of 130/80 mmHg.

**Informative trials of intensive blood pressure-lowering in type 2 diabetes**

In the ACCORD trial\(^3\) in type 2 diabetes, mainly without CKD, intensive blood pressure-lowering did not provide additional cardiovascular protection. There was concern also about kidney events, but numbers were small – five patients with ‘renal failure’ in the intensive arm as compared to one in the standard blood pressure-lowering arm. This was a disappointing outcome, Professor Wheeler noted.

The STENO trial, an older and smaller trial\(^4\) of 160 patients with type 2 diabetes and microalbuminuria, used ACE-Is or ARBs to achieve blood pressure lower than 130/80 mmHg in the intensive arm and standard therapy to achieve blood pressure ≥135/85 mmHg. This trial favoured intensive therapy to reduce progress to nephropathy and other microvascular complications (retinopathy and autonomic neuropathy).

In 2012, using these and other studies, the KDIGO Work Group recommended blood pressure targets for stage 1-5 CKD in patients with diabetes (Table 2).

<table>
<thead>
<tr>
<th>Albumin:creatinine ratio (mg/mmol)</th>
<th>Blood pressure target CKD with diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 (A1, normo)</td>
<td>≤140/90 (1B)</td>
</tr>
<tr>
<td>3-30 (A2, micro)</td>
<td>≤130/80 (2D)</td>
</tr>
<tr>
<td>&gt;30 (A3, macro)</td>
<td>≤130/80 (2D)</td>
</tr>
</tbody>
</table>

A subsequent meta-analysis of 45 randomised trials published in 2015,\(^5\) of which 13 included only type 2 diabetes patients, concurred that achieving a systolic blood pressure of <130 mmHg compared to <140 mmHg further reduced the risk of stroke and reduced albuminuria beyond the blood pressure-lowering to <140 mmHg, which reduced mortality, stroke and CVD.

Nonetheless, a caution is to individualise blood pressure targets, be sensible and not push targets too low in, for example, the elderly, Professor Wheeler commented.

Studies such as the Irbesartan type 2 Diabetic Nephropathy (IDNT) study\(^6\) support the approach of using an ARB, as these agents lower intraglomerular pressure by vasodilatation of the efferent arteriole of the glomerulus. The use of an ACE-I and an ARB in a dual RAAS blockade approach slows kidney disease, but is associated with increased risk of acute kidney injury and hyperkalaemia.\(^7\)

Combinations of ACE-I/ARB should therefore only be used in specialised units where additional monitoring for hyperkalaemia and acute kidney injury can be introduced.

**SGLT-2 inhibitors are antihypertensive**

The SGLT-2 inhibitors clearly have antihypertensive effects as shown in a recent meta-analysis by the Baker IDI Heart and Diabetes Institute\(^7\) (Figure 2). This blood pressure-lowering effect is seen across all of the current SGLT-2 inhibitors relative to placebo and other oral agents.

A recent secondary analysis of the CANATA-SU study\(^8\) has also shown that canagliflozin slows the progression of renal function decline, independently of its glycaemic effects.\(^9\)
What is exciting for a nephrologist is that therapy with SGLT-2 inhibitors, after the initial acute reduction in kidney function, produces an overall stabilisation of kidney function which lasts in the longer term.

The antihypertensive effect of the SGLT-2 inhibitors may result from their constrictive action on the afferent arteriole, whereas as mentioned earlier, ACE-Is or ARBs dilate the efferent arteriole – both actions are potentially synergistic, resulting in lower intraglomerular pressure and lower albuminuria.

Other possible mechanisms for the reno-protective effects of SGLT-2 inhibitors include increased sodium excretion, which leads to reduced plasma volume. Reduced cardiac workload may protect the heart in the longer term. Also, tubuloglomerular feedback is increased.10

Nephrologists are interested in evaluating the use of SGLT-2 inhibitors in patients with kidney disease and proteinuria without diabetes.

References


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