# 1st International Congress of Chinese Nephrologists (ICCN 2015) – Importance of Hypertension and Proteinuria Management in Type 2 Diabetes

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*A recent lunch symposium held during the 1st International Congress of Chinese Nephrologists focused on the intimate relationship between proteinuria and hypertension, and their management in diabetic patients. This report highlights key points from the symposium, featuring renowned nephrologist Professor Enyu Imai.*

Blood pressure (BP) and proteinuria control may have positive effects on cardiovascular and renal outcomes in diabetic patients with hypertension and chronic kidney disease (CKD).[1] Both hypertension and CKD are frequently comorbid in patients with type 2 diabetes mellitus (T2DM).[2] Diabetic nephropathy, characterized by hypertension, progressive albuminuria, glomerulosclerosis, and decline in glomerular filtration rate (GFR) (**Table**), is the leading cause of end-stage renal disease (ESRD) worldwide.[2-4] Landmark studies have confirmed that treatment of hypertension with angiotensin II receptor blockers (ARBs) in patients with comorbid T2DM also reduces proteinuria, thus slowing the rate of renal function decline.[4]

## Reduction of proteinuria and impact on renal outcomes

Proteinuria is strongly linked to the progression of CKD. A post hoc analysis of the Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial (ORIENT) – ORIENT-proteinuria – which involved Asian T2DM patients with overt nephropathy, determined that either >30% reduction of urine protein/creatinine ratio (UPCR) or remission of nephropathy, defined as UPCR <1.0 g/gCr, predicted significant renoprotection, while patients with residual UPCR ≥1.0 g/gCr were at a higher risk of renal outcomes. These results suggest that UPCR is an independent predictor of CKD risk, and may be used as a therapeutic target in the prevention of further nephropathy in T2DM patients with microalbuminuria.[4] A meta-regression analysis of 21 clinical trials revealed that, for every 30% reduction in albuminuria, the risk of ESRD decreased by 23.7% (p=0.001) (**Figure 1**).[5] Another meta-analysis of nine randomized clinical trials also showed that, in 98% of patients, short-term reductions in proteinuria strongly correlated with long-term improvements in renal outcomes.[6]

## Target BP in diabetic patients with CKD

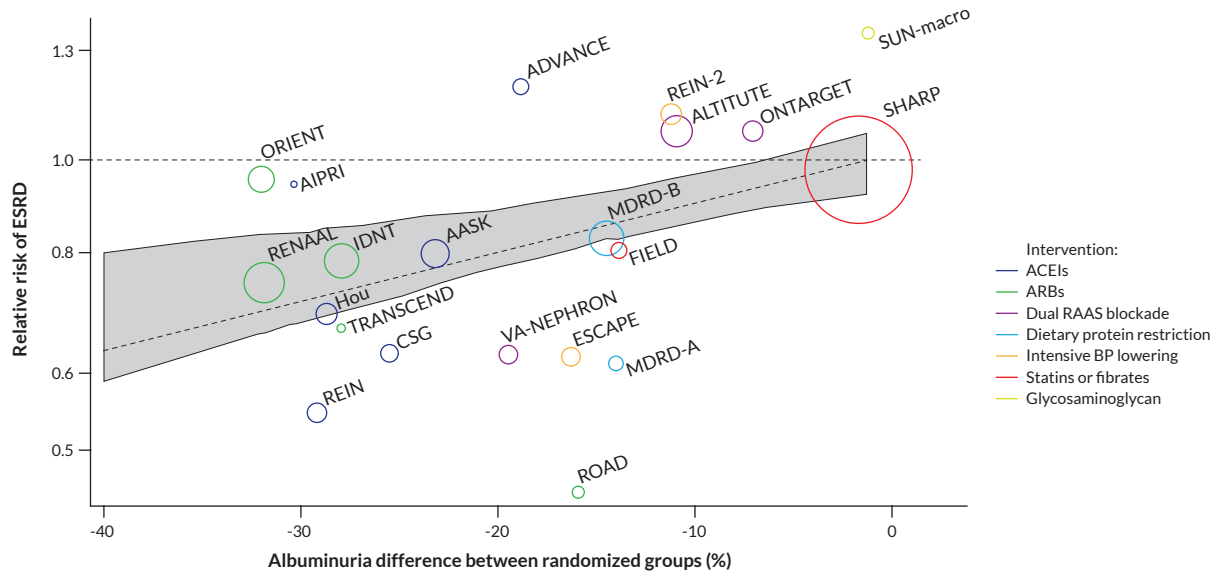
Although high BP has been associated with increased rates of premature mortality, cardiovascular diseases and progressive loss of kidney function in patients with T2DM and CKD, the target BP for these patients remains controversial; published recommendations are also largely based on data from white and black populations and might not be applicable to Asian patients. In a post hoc analysis of ORIENT, conducted to explore the optimal systolic BP (SBP) level for prevention of renal and cardiovascular outcomes in 566 T2DM patients from Japan and Hong Kong with

**Table. Diabetic nephropathy stages: Cutoff values of urine albumin for diagnosis and main clinical characteristics[3]**

| | Albuminuria cutoff values | Clinical characteristics | | Albuminuria cutoff values | Clinical characteristics |
|---|---|---|---|---|---|
| Microalbuminuria | 20-199 µg/min<br>30-299 mg/24 h<br>30-299 mg/g* | Abnormal nocturnal decrease of BP and increased BP levels<br>Increased triglycerides, total and LDL-cholesterol, and saturated fatty acids<br>Increased frequency of metabolic syndrome components<br>Endothelial dysfunction<br>Association with diabetic retinopathy, amputation, and cardiovascular disease<br>Increased cardiovascular mortality<br>Stable GFR | Proteinuria | ≥200 µg/min<br>≥300 mg/24 h<br>>300 mg/g* | Hypertension<br>Increased triglycerides and total and LDL-cholesterol<br>Asymptomatic myocardial ischemia<br>Progress GFR decline |

*Spot urine sample
BP, blood pressure; GFR, glomerular filtration rate; LDL, low-density lipoprotein

**Figure 1. Treatment effects on albuminuria significantly correlated with the treatment effects on ESRD[5]**




Different colors indicate different types of interventions. The size of each circle is inversely proportional to the standard error of mean of the treatment effect on ESRD.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; ESRD, end-stage renal disease; RAAS, renin-angiotensin-aldosterone system

overt nephropathy (ORIENT-blood pressure), follow-up SBP was found to be linearly associated with increased risk of renal events and renal function decline; reduction of SBP to ≤130 mmHg reduced renal risk, especially in patients with proteinuria ≥1 g/gCr (**Figure 2**), while SBP of ≥140 mmHg was associated with an increased incidence of cardiovascular disease in patients without any prior history. Physicians may, therefore, consider reducing SBP to 130 mmHg or lower to achieve renoprotection in patients with T2DM.[1]

The presence of proteinuria is an important factor for determining the BP goal. For example, in high-risk patients with proteinuria, intensive SBP control may be beneficial and a target BP of <130/80 mmHg is recommended; in patients without proteinuria, however, target BP can be less aggressively set at <140/90 mmHg.[1,7] Interestingly, the Hisayama study, which looked at autopsy samples that did not receive hypertension treatment before death, showed that not only hypertension, but also *prehypertension*, was significantly associated with renal arteriosclerosis, regardless of the presence or absence of target organ damage.[8]

> ***"First-line treatment of hypertension in patients with T2DM and macroalbuminuria should include ARBs, which are effective in reducing proteinuria."***

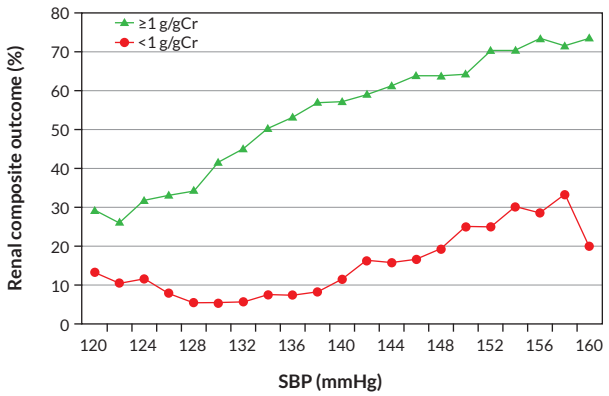
## Role of ARBs in the management of hypertension and nephropathy in T2DM patients

Landmark trials have established that first-line treatment of hypertension in patients with T2DM and macroalbuminuria should include ARBs, which are effective in reducing proteinuria.[4] In ORIENT, an ARB effectively managed BP level, proteinuria and the rate of change of reciprocal serum creatinine, with these beneficial effects being especially prominent in patients who achieved SBP of ≤130 mmHg.[1,9] In other trials, ARBs were able to demonstrate superiority to calcium channel blockers in protecting against nephropathy progression due to T2DM, independent of the reduction in BP, as well as confer significant renal benefits in patients with T2DM beyond that attributed to BP control.[10-12]

## Summary

Proteinuria and BP control are strongly linked to the progression of kidney function loss in diabetic patients with CKD and hypertension. In such patients, reductions in these parameters, which can be effectively achieved with the use of ARBs, can have positive effects on renal outcomes, ultimately lowering the risk of ESRD. In particular, Asian patients with diabetic nephropathy should look into treatment with ARBs that can effectively enable them to achieve BP and UPCR goals.

**Figure 2. SBP was linearly associated with increased risk of renal events and renal function decline[1]**




SBP, systolic blood pressure

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