

# The Effect of Probucol on Diabetic Nephropathy

This treatment may suppress diabetic nephropathy and lengthen time to hemodialysis therapy.

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**D**iabetic nephropathy is a major complication of diabetes. In the early stage, microalbuminuria is observed and followed by massive proteinuria. In the advanced stage, renal function decreases and uremia occurs. If nephropathy progresses, hemodialysis has to be initiated. Accordingly, suppressing the progression of diabetic nephropathy is important and urgent for the patient's quality of life.

Blood sugar control, blood pressure control and low protein intake are generally recommended as the stan-

dard of care for diabetic nephropathy. These treatments are effective in the early stage of diabetic nephropathy; they are hardly effective, however, in the advanced stage when increased serum creatinine occurs. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists have been reported to reduce the progression of diabetic nephropathy to some extent.

Oxidative stress is a mechanism by which complications develops in diabetes. Probucol (Lorelco; not commercially available in the United States), developed as a cholesterol-lowering agent, has antioxidant effects. We hypothesized that probucol suppresses the progression of diabetic nephropathy through its antioxidant as well as its cholesterol-lowering effects. In this trial, we examined the effect of probucol on the progression of diabetic nephropathy.<sup>1</sup>

## SUBJECT, METHODS

The randomized open study was performed at Sakura Hospital, Fukuoka, Japan. A total of 102 patients with type 2 diabetes (according to World Health Organization criteria) with clinical albuminuria (urinary albumin excretion >300 mg/g Cr) were enrolled in the study. Patients were randomly assigned to

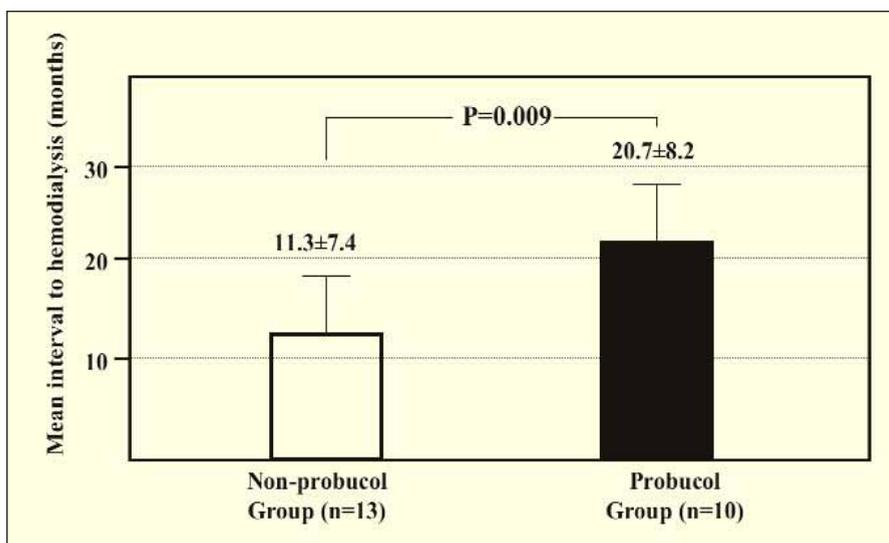


Figure 1. Mean interval to initiation of hemodialysis in advanced patients with serum creatinine >2 mg/dL. Open bar denotes non-probucol group (n=13, 11.3 ± 7.4 months) and closed bar denotes probucol group (n=10, 20.7 ± 8.2 months). Data are expressed as mean ± SD.

either the probucol group (probucol 500 mg/day, n=51) or non-probucol group (n=51). Patients from either group with serum creatinine  $\geq 2.0$  mg/dL were defined as advanced cases (n=40). Patients were followed for a maximum 3 years; they underwent monthly checkups and twice-yearly blood pressure and laboratory measurements. The primary endpoint of the study was initiation of hemodialysis therapy. If patients reached the endpoint or stopped clinical visits, measurements up to this point were recorded and used in analyses. No death occurred during the study.

The probucol and non-probucol groups had similar demographic, blood pressure and blood biochemical characteristics at baseline. Probucol significantly decreased total and HDL cholesterol compared with the non-probucol group. It also significantly suppressed increased urinary protein and serum creatinine in patients, including those in the advanced group.

### INITIATION OF HEMODIALYSIS

Patients in both the probucol and non-probucol groups who received an ACE inhibitor had an increase in serum creatinine. Changes were not statistically significant between these groups. Increase of urinary protein was significantly higher in the non-probucol group ( $+0.042 \pm 0.051$  g/day/month) versus the probucol

Probucol significantly suppressed increased urinary protein and serum creatinine.

group ( $-0.005 \pm 0.039$  g/day/month).

During the study, 23 advanced-case patients (13 non-probucol and 10 probucol) initiated hemodialysis. The mean interval to initiation of hemodialysis was  $11.3 \pm 7.4$  months in the non-probucol group and  $20.7 \pm 8.2$  months in probucol group. This was significantly longer ( $P=.009$ ) in the probucol group (Figure 1).

### EARLY, OVERT AND ADVANCED STAGES

Hemodialysis-free survival in patients with advanced diabetic nephropathy was also analyzed. The cumulative hemodialysis-free rate was significantly higher ( $P=0.02$ ) in the probucol group than in the non-probucol group (Figure 2). From this data, we determined that probucol may delay hemodialysis initiation.

Increased urinary protein was significantly suppressed and increased serum creatinine was noted in the probucol group compared with the non-probucol group. In advanced-case patients, increases of both serum creatinine and urinary protein were significantly suppressed in the probucol group compared with the non-probucol group. These results suggest that probucol may prevent the progression of not only early-stage but also overt nephropathy and advanced-stage diabetic nephropathy.

Proteinuria and increased serum creatinine only indicate a part of renal function. The mean interval to initiation of hemodialysis was longer in the probucol group than in non-probucol group (Figure 1), and the cumulative hemodialysis-free rate was also higher in the probucol group (Figure 2). Results indicated that probucol prevented the progression of

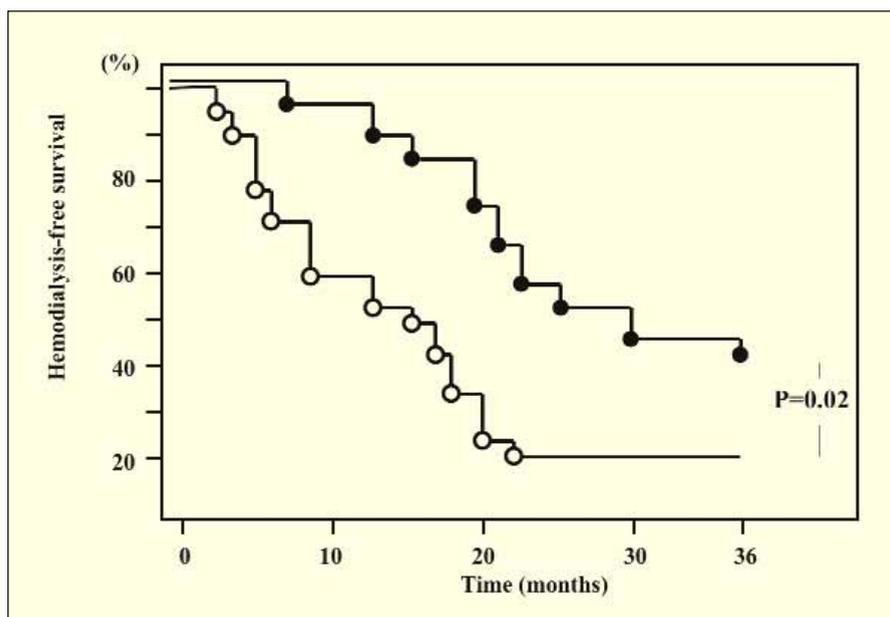


Figure 2 Hemodialysis-free survival in advanced patients with serum creatinine  $>2$  mg/dL. Open circle denotes non-probucol group (n=19) and closed circle denotes probucol group (n=21). Hemodialysis-free rate is significantly higher ( $P=.02$ ) in probucol than in non-probucol group.

diabetic nephropathy in these patients.

Although the mechanism by which probucol suppresses progression of diabetic nephropathy is unclear, we speculate that probucol's antioxidant effect may be involved. Oxidative stress has been associated with diabetic complications; oxidative products such as oxysterols may produce cell injury in the basal membrane of kidney. Probucol possesses antioxidant as well as cholesterol-lowering effects. Thus, the antioxidant effect of probucol might be involved in this renoprotection.

### STRONGER ANTIOXIDANT EFFECTS

Vitamin E is also known to have an antioxidant effect, although it is weaker than the effect seen with probucol and has not been reported to prevent the progression of diabetic nephropathy. The strong renoprotective effect of probucol demonstrated in this study may be caused by the stronger antioxidant effect.

### STATIN INHIBITS DIABETIC NEPHROPATHY

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) were also reported to have a beneficial effect on diabetic nephropathy. Usui et al<sup>2</sup> reported that in streptozotocin-induced rats, statin inhibited the progression of diabetic nephropathy, depending on antiinflammation and antioxidation. The difference of renoprotective mechanisms between probucol and statins is unclear.

Progression of diabetic nephropathy may be affected by not only oxidative stress but also by abnormality of lipid metabolism. We speculate that the antioxidative effect of probucol may be stronger than in statins, although the potential of normalization of lipid metabolism is more powerful in the latter. In the present study, probucol extended the interval to initiation of hemodialysis therapy. However, no report has shown that patients administered statins were followed until initiation of hemodialysis therapy. If the renoprotective potential of statins is equal to that of probucol, the same effect could be expected in statins. We consider that combination therapy (probucol plus statin) could provide an additional renoprotective effect. Further investigations are required regarding the renoprotective effect of this combination therapy.

### OTHER RENOPROTECTIVE TREATMENTS

ACE inhibitors and ARBs are also known to prevent the progression of diabetic nephropathy, with renoprotective mechanisms that include restricting renal angiotensin activity, lowering intraglomerular pressure and reducing oxidative stress. In our study, the number of patients administered ACE inhibitors was the same across probu-

col and non-probucol patients. Furthermore, patients in the non-probucol group who received an ACE inhibitor had an increased urinary protein that was significantly higher than those who received an ACE inhibitor in the probucol group. This indicated that ACE inhibitors were not a bias on the present data, and probucol might have an additional renoprotective effect. We considered that the same effect may be expected in the case of combination therapy of probucol plus ARBs.

Reverse cholesterol transport by probucol might help prevent progression of atherosclerosis in the kidney.

In this study, probucol reduced HDL cholesterol levels. As a mechanism of this effect, probucol is known to activate cholesterol ester transfer protein. Generally, low HDL levels aggravate atherosclerosis. However, probucol is known to increase reverse cholesterol transport. Furthermore, antiatherogenic effects of probucol have been reported. These data suggest that despite the HDL cholesterol lowering action, probucol has antiatherogenic effects. We speculate that reverse cholesterol transport by probucol might also help prevent progression of atherosclerosis in the kidney and suppresses diabetic nephropathy.

Our results support the hypothesis that probucol prevents the progression of diabetic nephropathy, and extends the interval to initiation of hemodialysis therapy. Administering probucol and ACE inhibitors, ARBs or statins in combination is expected to have additive or synergistic effect to prevent diabetic nephropathy. Further investigation is required. ■

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2. Usui H, Shikata K, Matsuda M, et al. HMG-CoA reductase inhibitor ameliorates diabetic nephropathy by its pleiotropic effects in rats. *Nephrol Dial Transplant*. 2003;18(2):265-272.