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Review Article and Clinical Experience: HYPERTENSION IN DIABETIC NEPHROPATHY The Five "Satan Circles", DHA-LiCOAR, the Roles of Valsartan

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ABSTRACT

On the basis of clinical experiences, 5 (five) "Satan Vicious Circles" in diabetic nephropathy (DN) are summarized. These vicious circles should be well recognized to understand the pathogenesis of DN, and to perform its rationale treatment. The 1st "Satan Circle": hypertension — proteinuria — glomerular injury — and then to hypertension again. The 2nd "Satan Circle": GLUT-1 — glucose — TGF-β — and then to GLUT-1 again. The 3rd "Satan Circle": AII — TGF-β — PAI-1 — and then to AII again. The 4th "Satan Circle": AII — PKC — AI — and then to AII again. The 5th "Satan Circle" or the "Deadly Satan Circle" (frequently happens in hemodyalized-patients). Dialysate, Membrane, and AOPP: these three components altogether stimulate the production of cytokines (VCAM1, MCP1, etc) — NADPH oxidase — increased ROS and RONS production — activated NFkB/API/MAPK — and then to cytokines (VCAM1, MCP1, etc) again. ROS and RONS also stimulate the production of MMP9. On the basis of clinical experiences in Surabaya, "DHA-LiCOAR" (Diabetes, Hypertension, Albuminuria – Lipid, Cigarette, Obesity, Antiplatelet, Renal replacement therapy) can be used as practical guideline for the treatment of patients with DN. MARVAL and VALUE are the two landmark studies of valsartan which favours microalbuminuria reduction of patients with DN and lower incidence of new-onset of diabetes, respectively. The results of MARVAL indicate a blood pressure-independent antiproteinuric effects of valsartan (blood pressure-independent effect). Compared with amlodipine, valsartan significantly lowered urinary albumin excretion rate of T2DM with microalbuminuria (-8% in amlodipine vs -44% in valsartan treated, $p < 0.001$). At 24-weeks, valsartan treated patients showed 29.9% reversion to normoalbuminuria compared with 14.5% in amlodipine treated patients ($p < 0.001$). In the VALUE study, valsartan showed 23% risk reduction of the new-onset diabetes ($p < 0.0001$). There was no significant difference in the outcomes in hypertensive patients at high cardiovascular risk treated with regiments based on valsartan or amlodipine. Valsartan (a highly selective ARB) improved "DHA" (the three essential components), and hence this ARB is in favour of the treatment of patients with diabetic nephropathy.

***Keywords**: DHA-LiCOAR, Valsartan, Five "Satan Circles", MARVAL, VALUE, diabetic nephropathy, hypertension, albuminuria*

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INTRODUCTION

In USA, diabetic nephropathy (DN) occurs in 20-40% of patients with DM and is the single leading cause of ESDR. Patients with microalbuminuria (30-299 mg/24h) who progress to macroalbuminuria (= 300 mg/24h) are likely to progress to ESRD. Over the past several years, a number of interventions have been demonstrated to reduce the risk and slow the progression of DN (Lewis et al 2001, Parving et al 2001). Persistent albuminuria has been shown to be the earliest stage of DN in T1DM and a marker for development of DN in T2DM; microalbuminuria is also a well – established marker of increased CVD risk (Garg et al 2002, Klausen et al 2004). Diagnosis criteria of DN in Surabaya is: diabetic patient with macroalbuminuria (in the absence of other causes), not microalbuminuria to be used (due to the laboratory cost) plus diabetic retinopathy. On the other hand, type 2 diabetic patients with microalbuminuria but no retinopathy may represent a group with characteristics of metabolic syndrome (Kim et al 2004). Strategies and goals for reno-and cardioprotection (RENCAR) in patients with DN recommended by ADA-2005 are also summarized (Table 1). Due to the limited facilities and laboratory cost, "DHA-LiCOAR" has been applied since 2004 in Surabaya as practical guideline to manage patients with DN (Tjokroprawiro 2004, 2005). The aim of this article is to deliver the recent knowledge of 5th "Satan Circle" (responsible for the pathogenesis of DN), Recommendations of ADA

2006 (selected), and clinical-practical guideline ("DHA-LiCOAR") for the treatment of DN to: GPs, residents (esp.-in the field of internal medicine), internists, and associated specialists. The roles of valsartan are also included.

PATHOGENESIS OF DIABETIC NEPHROPATHY (The Importance of the 5 "Satan Circles" in the Kidney)

On the basis of clinical experiences, 5 (five) "Satan Vicious Circles" are summarized. These vicious circles should be well recognized to understand the pathogenesis of diabetic nephropathy, and to perform its rationale treatment. The 1st "Satan Circle" (especially in glomerular and tubular cells): from hypertension — proteinuria — glomerular injury — then to hypertension again). This circle starts from hypertension which may worse proteinuria — glomerular injury — and back to hypertension again. Hence, hypertension and proteinuria are targets of treatment. Rationale treatment: ACE-1s, ARBs, Insulin and /or OAD. The 2nd "Satan Circle" (from GLUT-1 and then be back to GLUT-1 again). This circle occurs especially in the mesangial cells, and starts from GLUT-1 that permits glucose to enter the cell, and subsequently increases DAG production — increases activated PKC — and then increases TGF-β that inhibits NOS, and stimulates ECM production, and also activates GLUT-1. The increased production of ECM may promote the progression of diabetic nephropathy. Rationale treatment: excellent glycemic control, ACE-1s, and/or ARBs, TGF-β inhibitors.

The 3rd "Satan Circle" (in mesangial cells): from A-II and back to A-II. This "Satan Circle" starts from A-II (increased production is due to hyperglycemia) — stimulates TGF-β formation — stimulates PAI-1 — and then back to stimulate A-II formation. PAI-1 also decreases the activity of plasmin (which causes decreased matrix degradation, and diabetic nephropathy may pursue). Rationale treatment; excellent glycemic control, ARBs, TGF-β inhibitors, PAI-1 inhibitors. The 4th "Satan Circle" (in mesangial cells): from A-II — PKC — A-I and then back to A-II. This "Satan Circle" starts from A-II (due to hyperglycemia) which activates PKC — and this PKC may stimulate A-I and back to increase A-II production. Rationale treatment: excellent glycemic control, ACE-1s, ARBs, and PKC-antagonists.

The 5th "Satan Circle" (from cytokines: IL-1, IL-8, TNF-α, PAF, VCAM-1, and MCP-1 — increased ROS, and then back to these cytokines again). This "Deadly Satan Circle" most frequently occurs on hemodialyzed patients with diabetic nephropathy. The cytokines of this "Satan Circle" are generated by the 3 components (dialysate, membrane of the coil, and uremia or AOPP (Advanced Oxidation Protein Product) in which all of them are present in hemodialyzed patients. These cytokines — activate NADPH oxidase, p47, p67, p21, rec — stimulate ROS and RONS (reactive oxidative nitrogen species) and then to increase the production of MMP9 (which may cause acute thrombosis and vascular sudden death) and activated MAPK, NFkB/AP-1, and all of these may stimulate the production of the previous cytokines of this circle. Rationale treatment: excellent glycemic control, low protein diet to suppress the increased AOPP, and strong antioxidants, etc.

DIABETIC NEPHROPATHY: RECOMMENDATIONS OF ADA 2006

The recommendation of ADA 2006 are shortly described below to complete some information about DN which have been manifested in the summary.

General Recommendation

To reduce the risk and/or slow the progression of DN: reach excellent glycemic control and optimize blood pressure control (A)

Treatment of Diabetic Nephropathy

Either ACE-1s or ARBs should be used except during pregnancy (A). ACE-1s have been shown to delay the progression of DN for T1DM with hypertension and any degree of albuminuria (A). Patients with T2DM, hypertension, and microalbuminuria, ACE-1s and ARBs have been shown to delay the progression to macroalbuminuria (A). Patients with T2DM, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine > 1.5 mg/dl), ARBs have been shown to delay the progression of DN (A). If one class is not tolerated, the other should be substituted (E). The current adult – recommended dietary allowance for protein is to initiate protein restriction to ≤ 0.8 g/kg BW/day (~ 10% of daily calories). Further restriction may be useful in slowing the decline of GFR in selected patients (B). The use of DCCBs. As initial therapy is not more effective than placebo. Their use in DN should be restricted to additional therapy to further lower blood pressure in patients already treated with ACE-1s or ARBs (B). The use of non-DCCBs, ß-blockers, or diuretics are for the management of blood pressure. In the setting of albuminuria or nephropathy in patients unable to tolerate ACE-1s and/or ARBs, the use of non-DCCBs may reduce albuminuria in diabetic patients, including during pregnancy (E). Potassium level should be monitored if ACE-1s, ARBs, or diuretics are used

(B). Referral to a physician experienced in the care of diabetic renal disease should be made. The referral should be considered when the eGFR has fallen to < 60 ml/min/1.73 m2 or if difficulties occur in the management of hypertension or hyperkalemia (B).

STRATEGIES FOR RENO-AND CARDIOPROTECTION IN PATIENTS WITH DIABETIC NEPHROPATHY (POSITION STATEMENT – ADA 2005)

Position Statement of American Diabetes Association (ADA) on diabetic nephropathy released in 2005 can be summarized in Table 1.

SURABAYA CLASSIFICATION ON DIABETIC NEPHROPATHY

Surabaya classification of diabetic nephropathy established since 1986 has been revised in 2005 (Table 2). Physician may use the Levey modification of the Cockcroft and Gault equation (as built in the Table 2) to calculate estimated GFR (eGFR) from serum creatinine and to stage the patients with renal disease (Levey et al 1999). The ADA position statement (2004) on diabetic nephropathy published a complete discussion on the treatment of nephropathy. It is suggested that consultation with a nephrologists be obtained when the GFR is < 60 ml/min/1.73 m2 (B). Early referral of such patients have been found to reduce cost and improve quality of care and keep people off dialysis longer (Levinsky 2002).

TABLE – 1 Strategies and Goals for Reno- and Cardioprotection in Patients with Diabetic Nephropathy

(ADA Statement - 2005, Provided : Tjokroprawiro 2005, 2006)

Intervention by "DHA-LICOAR"	Goal for REN-CAR	
	Microalbuminuria	Macroalbuminuria
① • ACE-1 and/or ARB • Low Protein Diet 0.8 g/Kg/BW	Reduction or Reversion to Normalbuminuria	Proteinuria as low as possible or Less than 500 mg/day
② Target	GFR Stabilization	GFR Decline < 2ml/min/year
③ Blood Pressure	Less than 130/80 or 125/75 mmHg	
④ Strict Glycemic Control	A1C < 7%	
⑤ Statins	LDL-C < 100 mg/dl or LDL-C <70 mg in the Presence of CVD	
⑥ ASA	Thrombosis Prevention : 75-162 mg/day	
⑦ Smoking Cessation	Prevention of Atherosclerosis Progression	
	REN – CAR : Reno – Cardioprotection	

TABLE - 2 Surabaya Classification of Diabetic Nephropathy-2005

Div. Endocrinology-Metab. and Div. Nephrology-Hypertension 1986 (Revised: 2005)
(Tjokroprawiro, Yogiantoro et al 2005)

MNT	Stage	Micro / Macro Albuminuria	SC / eGFR	MNT – Diets OAD – INS	Life Expectancy (1986)
B2*)	1	Micro/Macro Alb.	N (eGFR ≥ 90)	B2, OAD, INS	- ? -
B2*)	2	Macro Alb.	< 2.5 (eGFR 60-89)	B2, OAD, INS	> 5 years
B2*)	3	Macro Alb.	2.5-4 (eGFR 30-59)	B2, OAD, INS	> 2 years
B3*)	4a	Macro Alb.	4-8 (eGFR 15-29)	B3, INS, Pre HD	4-18 Months
Be*)	4b		8-10 (eGFR 15-29)	Be, INS, HD	
Be*)	5 (ESDN)	Macro Alb.	> 10 (eGFR < 15)	Be, INS, HD Transpl.	2-5 Months

MNT: Medical Nutrition Therapy or Diets; **B2, B3, Be** (Types of MNT), **OAD** (Oral Agents for Diabetic), **INS** (Insulin)

B2 & B3-Diets (Pre-HD Phase):With Specific Composition plus low K^+ & Na^+, Protein 0.6-0.8 g/kg BW (↔10% of Daily Cal.). Be-Diet (HD Phase) : Low K^+ & Na^+ , Protein 1-1.2 g/kg BW/day, etc.

*) Diabetic Diets for DN are supplemented with Low Vit C, Folic Acid, Vit B6, Vit B12, Arginine, Glutamine

The Formula of Cockcroft – Gault

$$\text{eGFR (♂) (mL / min.)} = \frac{(140 - \text{Age}) \times \text{Body Weight (kg)}}{\text{Plasma Creatinine (mg/dl)} \times 72}$$

$$\text{eGFR (♀) (mL / min.)} = \frac{(140 - \text{Age}) \times \text{Body Weight (kg)}}{\text{Plasma Creatinine (mg/dl)} \times 72} \times 0.85$$

DHA-LiCOAR: THERAPEUTIC GUIDELINE FOR DIABETIC NEPHROPATHY

Based on Statements ADA 2003, ADA 2004, ADA 2005, ADA 2006, and PERKENI Consensus, and Clinical Experiences, "DHA-LiCOAR" can be used as practical guideline of the strategies for the management of diabetic nephropathy (Table 3)

THE ROLES OF VALSARTAN IN DIABETIC NEPHROPATHY

This topic will be briefly described. Inhibition of renin angiotensin system (RAS), either by ACE-1s or ARBs, prevents the development or reduces the level of proteinuria in the diabetic animal model, resulting in less renal structural damage. In patients with T2DM with microalbuminuria, ACE-1 treatment lowers album in excretion rate (UAER) and prevents the progression of renal disease as measured by serum creatinine. Selective blockage of the AT1 receptor by ARBs also lowers microalbuminuria in these patients to the extent as ACE-1 (Muirhead et al 2000).

THE MARVAL STUDY

The highly selective ARBs, valsartan, in MARVAL study (Viberti et al 2002) lowered UAER more effectively than amlodipine in patients with T2DM and microalbuminuria. The summary of the MicroAlbuminuria Reduction with VALsartan (MARVAL) study is shortly described. A number of 332 patients with T2DM and microalbuminuria, with or without hypertension, were randomly assigned to 80 mg/day valsartan or 5 mg/day amlodipine for 24 weeks.The UAER at 24 weeks was 56% (95% CI, 49.6 to 63.0) of base line with valsartan and 92% (95% CI, 81.7 to 103.7)of baseline with amlodipine, a highly significant between-group effects (– 44%, $p < 0.001$). More patients reversed to normoalbuminuria with valsartan (29.9% versus 14.5%, $p = 0.001$). In conclusion, valsartan significantly reduces microalbuminuria in patients with T2DM, an effect that appears to be in dependent of its blood pressure-lowering action.

TABLE – 3 "DHA-LiCOAR" : Therapeutic Guidelines for Diabetic Nephropathy

Clinical Experiences : Tjokroprawiro 2002, 2003, 2004, 2005, 2006
(Based on ADA 2003, 2004, 2005, 2006, ISE Consensus 2003)

D	Excellent Glycemic Control (A) : (A1C < 7%; A1C < 6% is Preferable) ① Salt Restriction (less than 3-6 g/day) ② Dietetic Regimens : - Pre-HD (Diet-B_2 : 0.6 g Diet-B_3 : 0.8 g Protein/kg BW) - HD (Diet-B_e : 1–1.2 g Protein/kg BW) - Protein Intake : ~ 10% of Daily Calories ③ Appropriate OADs and/or Insulin (for Anabolic and Anti Inflammatory Effect)
H	Optimize Blood Pressure mmHg (A) : < 130/80; < 125/75 if Proteinuria > 1 g/day For ISH : should be gradually lowered, up to 140/90
A	**Albuminuria (A) : ACE-1s and/or ARBs**
Li	Lipid Targets mg/dl : LDL <100, TG <150, HDL >40 (♂), >50 (♀), Tot-Chol <200
C	Cigarette : Stop Smoking
O	Obesity : Any Weight Loss if Obese — Light Regular Aerobic Exercise
A	Anti Platelet Agents : Aspirin, Dipyridamol, Etc.
R	Renal Replacement Therapies (RRTs) : HD, CAPD, Transplantation, TGF-β Blockers, Glycation (AGE) Inhibitors, PKC-β Inhibitors, GAG Sulodexide

ISE : Indonesian Society of Endocrinology; HD : Hemodialysis; ISH : Isolated Systolic Hypertension

THE VALUE TRIAL

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial (Julius et al 2004) offered a further opportunity to test the hypothesis that for the same blood pressure control, valsartan would reduce cardiac morbidity and mortality more than amlodipine in hypertensive patients at high cardiovascular risk.

Patients = 15.245, aged 50 years or older with treatment or untreated hypertension and high risk of cardiac events participated in randomized, double blind, parallel-group comparison of therapy based on valsartan or amlodipine. Patients from 31 countries were followed up for a mean of 4-2 years. In conclusion, Valsartan showed 23% RR of the new-onset T2DM, and the valsartan dose can be increased up to 320 mg/day.

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