Diabetic Kidney Disease

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Background

- Diabetic kidney disease (DKD) is a glomerulopathy specific to diabetes with characteristic structural and functional changes.
- The predominant structural changes –
  - mesangial expansion
  - glomerular basement membrane thickening
  - glomerular sclerosis.

Background

- The functional changes -
  - gradually increasing leakage of albumin in the urine
  - Progressive decline in glomerular filtration rate (GFR)
  - increase in systemic blood pressure

Ultimately leading - End Stage Renal Disease (ESRD)

Incidence of New ESRD in Diabetics

- DKD - LEADING CAUSE OF ESRD (2009)
  - 60% - Malaysia
  - 58% - Mexico
  - 45% - Japan
  - 44% - USA
  - 30% - Australia

USRDS 2011, Annual Data Report,.
UK Renal registry and International comparison - The Eleventh Annual report

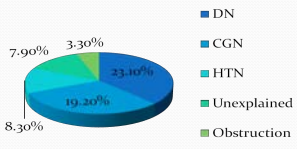
SECOND COMMON CAUSE OF ESRD

- Pakistan[1]: 33.28%
- Bangladesh[2]: 31%
- India[3] : 30.3%
- Nepal[4] : 16.8%

[1]Naqvi SAJ. NDT 2000; 15: 769-771.
[2] Rashid HU. Saudi J kidney Dis Transpl 2004; 15: 185-9.
[3] Mani MK. Nephrology 1998; 4: S4-S7.
[4] Khakurel S et al. JNMA 2009;48(174):126-3 .

Incidence of New DKD ESRD on RRT in Nepal (2000- 2009) – BIR, NKC, ARMY, BCH

- Total patients - 3769
- **Analysis** of etiology of 2460 (65.2%) patients revealed:
  - DN – 869 (23.1%)
  - CGN – 724 (19.2%)
  - HTN – 314 (8.3%)
  - Obstruction – 124 (3.3%)
  - Unexplained – 297 (7.9%)

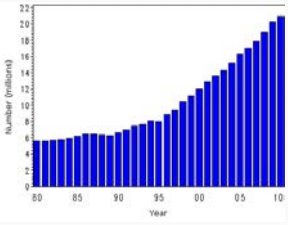


Incidence of diabetes

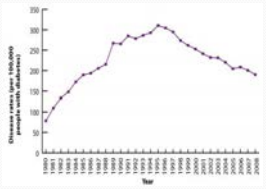
- Increasing rapidly due to growing and aging population, urbanization, and rising prevalence of obesity.
- Number of T2DM - 366 million in 2011
  - 552 million by 2030.
- The incidence of DN/ESRD is predicted to rise much higher.

Incidence of diabetes & ESRD in USA

- Number (in Millions) of Civilian, Non-institutionalized Persons with Diagnosed Diabetes, United States,



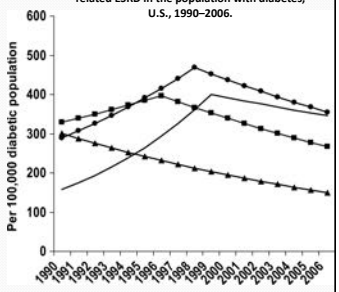
Incidence of Diabetes-Related End-Stage Renal Disease, United States, 1980–2008




Epidemiology/Health Services Research

Incidence of Treatment for End-Stage Renal Disease Among Individuals With Diabetes in the U.S. Continues to Decline

Modeled age-specific incidence of diabetes-related ESRD in the population with diabetes, U.S., 1990–2006.



Burrows N R et al. Dia Care 2010;33:73-77

American Diabetes Association.

Decline in rate of Diabetes related ESRD

➢ Better understanding of

- Pathogenesis
- Risk factors
- Natural history of diabetic kidney disease

➢ Early screening for DKD

Declined Trend of diabetic ESRD in USA

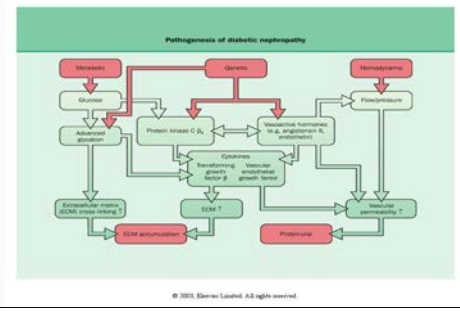
➢ Successful preventive and therapeutic measure

- Adequate control of sugar
- Adequate control of blood pressure - ACEI or ARB
- Use of lipid lowering agents

➢ Revised diabetic criteria by ADA in 1997
with FBG level decreased from 140 to 126 mg%.

Burrows N R et al. Dia Care 2010;33:73-77

Pathogenesis



Risk factors for development of DKD

1. Genetic susceptibility
2. Poor HbA_1C level
3. Long duration of diabetes
4. High systolic blood pressure
5. High diastolic blood pressure
6. Hyperlipidemia
7. Smoking

Natural History of DKD

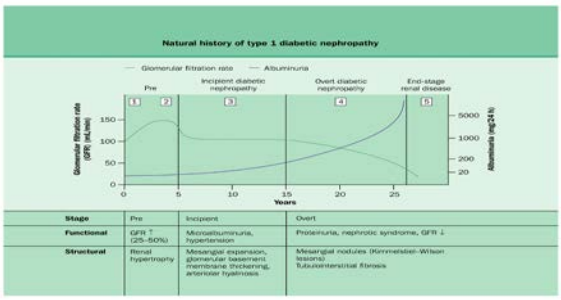


Table 1—*Diabetic nephropathy stages: cutoff values of urine albumin for diagnosis and main clinical characteristics*

Stages	Albuminuria cutoff values (ref. 14)	Clinical characteristics (ref. no.)
Microalbuminuria	20–199 μg/min	Abnormal nocturnal decrease of blood pressure and increased blood pressure levels (163)
	30–299 mg/24 h	Increased triglycerides, total and LDL cholesterol, and saturated fatty acids (164, 165)
	30–299 mg/g*	Increased frequency of metabolic syndrome components (166) Endothelial dysfunction (167) Association with diabetic retinopathy, amputation, and cardiovascular disease (168) Increased cardiovascular mortality (2, 169) Stable GFR (82)
Macroalbuminuria†	≥200 μg/min ≥300 mg/24 h	Hypertension (99) Increased triglycerides and total and LDL cholesterol (170)
	>300 mg/g*	Asymptomatic myocardial ischemia (171, 172) Progressive GFR decline (83, 84)

*Spot urine sample. †Measurement of total proteinuria (≥500 mg/24 h or ≥430 mg/l in a spot urine sample) can also be used to define this stage.

DIABETES CARE, VOLUME 28, NUMBER 1, JANUARY 2005

Incidence and prevalence of micro/ macroalbuminuria in Diabetes

- Type 1 DM –
  - Cumulative incidence of MA - 12.6% in 7.3 years and 33% in 17 years
  - Prevalence of Macroalbuminuria - 15 to 20%
- Type 2 DM –
  - Incidence of MA – 2% per year with 25% in 10 years
  - Prevalence of Macroalbuminuria – 5-20%

Incidence of albuminuria in diabetics in Nepal

Table 1. Prevalence of albuminuria

Ethnicity (n)	Microal buminuria (n)%	Macroal buminuria (n)%	Total Albu minuria (n)%
Jyapu (53)	(19) 35.89	(11) 20.75	(30) 56.64
Brahamin (53)	(20) 37.73	(2) 3.77	(22) 41.50
Total (106)	(39) 36.79	(13) 12.26	(52) 49.05

Maharjan BR et al. J Nepal Health Res Counc 2010 Oct;8(17):110-15

Incidence of albuminuria in diabetics in Nepal

Table 2. Grades of Proteinuria in different age groups

Age group (in yrs)	Without proteinuria (< 30mg/d)	Mircro-albuminuria (30-300mg/d)	Overt proteinuria (>300mg/d)	Total
30-45	24 (44.44%)	26 (48.15%)	4 (7.41%)	54
45-60	37 (48.05%)	30 (38.96%)	10 (12.99%)	77
60-75	9 (24.32%)	20 (54.05%)	8 (21.62%)	37
>75	2 (22.22%)	3 (33.33%)	4 (44.44%)	9
Total	72 (40.68%)	79 (44.63%)	26 ((14.69)	177

Jha P. J Nepal Med Assoc 2010;49(178):143-6.

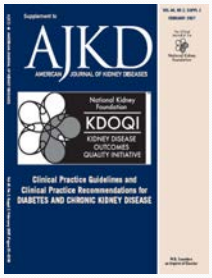
Macroalbuminuria- CKD

Stage	Description	eGFR (mL/min/1.73 m2)
1	Kidney damage with normal or ↑ eGFR plus persistent albuminuria	≥ 90
2	Kidney damage with mild ↓ eGFR plus persistent albuminuria	60-89
3	Moderate ↓ eGFR	30-59
4	Severe ↓ eGFR	15-29
5	Kidney failure	< 15 (or dialysis)

eGFR = estimated glomerular filtration rate

National Kidney Foundation (NKF). KDOQI Clinical Practice Guidelines for Chronic Kidney Disease, 2002.

Screening and treatment of DKD



- Guideline 1: Screening and Diagnosis of Diabetic Kidney Disease
- Guideline 2: Management of Hyperglycemia and General Diabetes Care in Chronic Kidney Disease
- Guideline 3: Management of Hypertension in Diabetes and Chronic Kidney Disease
- Guideline 4: Management of Dyslipidemia in Diabetes and Chronic Kidney Disease

National Kidney Foundation
KDOQI

KDOQI CLINICAL PRACTICE GUIDELINE FOR DIABETES AND CKD: 2012 UPDATE

- Guideline 2: Management of Hyperglycemia and General Diabetes Care in CKD
- Guideline 4: Management of Dyslipidemia in Diabetes and CKD
- Guideline 6: Management of Albuminuria in Normotensive Patients with Diabetes

Am J Kidney Dis. 2012;60(5):850-886

KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease

KDOQI - Guideline 3: Management of Hypertension in Diabetes and Chronic Kidney Disease

VOL 2 | ISSUE 5 | DECEMBER 2012

Table 1. Grade for Strength of Recommendation in the Diabetes and CKD Guideline

Grade*	Implications		
	Patients	Clinicians	Policy
Level 1 "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

*The additional category "Not Graded" is used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

Am J Kidney Dis. 2012;60(5):850-886 859

AJKD KDOQI Diabetes Guideline: 2012 Update

Table 2. Grade for Quality of Evidence in the Diabetes and CKD Guideline

Grade	Quality of Evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

GUIDELINE 1: SCREENING AND DIAGNOSIS OF DIABETIC KIDNEY DISEASE

- CKD in patients with diabetes may or may not represent DKD.
- In the absence of an established diagnosis, the evaluation of patients with diabetes and kidney disease should include investigation into the underlying cause(s).

SCREENING AND DIAGNOSIS OF DIABETIC KIDNEY DISEASE

1.1 Initial screening should commence:

- 5 years after the diagnosis of type 1 diabetes; (A)
- From diagnosis of type 2 diabetes. (B)

Then annually

1.1.1 Screening should include:

- Measurements of urinary ACR in a spot urine sample; (B)
- Measurement of serum creatinine and estimation of GFR. (B)

SCREENING AND DIAGNOSIS OF DIABETIC KIDNEY DISEASE

1.2 An elevated ACR should be confirmed in the absence of urinary tract infection with 2 additional first-void specimens collected during the next 3 to 6 months (B)

- Microalbuminuria is defined as an ACR between 30-300 mg/g.
- Macroalbuminuria is defined as an ACR > 300 mg/g.
- 2 of 3 samples should fall within the microalbuminuric or macroalbuminuric range to confirm classification.

SCREENING AND DIAGNOSIS OF DIABETIC KIDNEY DISEASE

1.3 In most patients with diabetes, CKD should be attributable to diabetes if:

- Macroalbuminuria is present; (B) or
- Microalbuminuria is present
  - in the presence of diabetic retinopathy. (B)
  - in type 1 diabetes of at least 10 years' duration. (A)

SCREENING AND DIAGNOSIS OF DIABETIC KIDNEY DISEASE

1.4 Other cause(s) of CKD should be considered in the presence of any of the following circumstances: (B)

- Absence of diabetic retinopathy;
- Low or rapidly decreasing GFR;
- Rapidly increasing proteinuria or nephrotic syndrome;
- Refractory hypertension;

SCREENING AND DIAGNOSIS OF DIABETIC KIDNEY DISEASE

- Presence of active urinary sediment
- Signs or symptoms of other systemic disease; or
- >30% reduction in GFR within 2-3 months after initiation of an ACE inhibitor or ARB

SCREENING AND DIAGNOSIS OF DIABETIC KIDNEY DISEASE

- What should we do when we first diagnose type 2 DM
- What should we do when we see first time a type 2 diabetic patient with no previous kidney evaluation

The answer is – evaluate for DKD and other causes of CKD now itself - Urine RME , RFT, USG abdomen

If no macroalbuminuria – evaluate for MA then annually

If macroalbuminuria – quantify – DO NOT evaluate for MA and treat as CKD according to eGFR

GUIDELINE: 2

Management of hyperglycemia and general diabetes care in CKD –

- Hyperglycemia - a fundamental cause of DKD.
- Intensive glycemic control prevents elevated albuminuria or delays its progression with increased risk of severe hypoglycemia.
- Evidence that intensive treatment has an effect on loss of glomerular filtration rate (GFR) is sparse.

GUIDELINE: 2.1

Target HbA1c in all diabetes - 7%

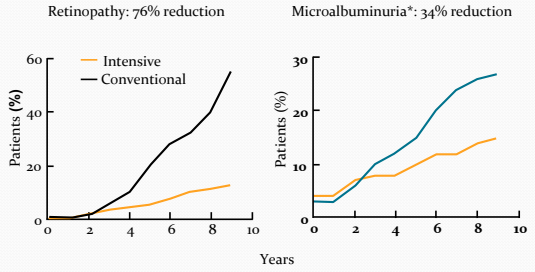
to prevent or delay progression of microvascular complication including DKD (1A).

Diabetes Control and Complications Trial (DCCT)

- Total number of type 1 DM – 1441
- Conventional treatment – 730 (HbA1C – 9%)
- Intensive insulin group – 711 (HbA1C – 7.1%)
- Primary prevention – no retinopathy
- Secondary prevention – mild retinopathy

N Eng J Med. 1993;329:977- 86.

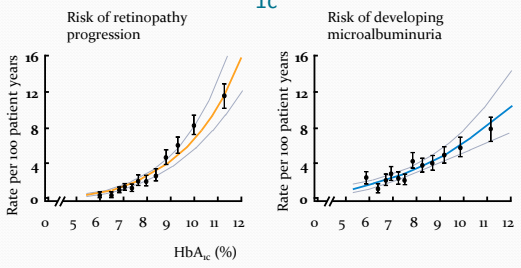
DCCT: intensive therapy reduces microvascular complications



Adapted from: N Engl J Med 1993;329:977–86

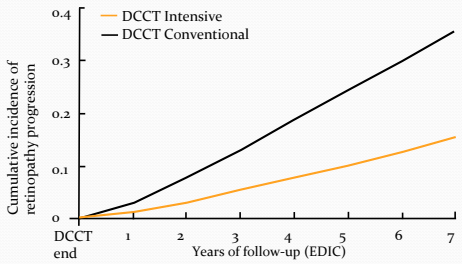
*urinary albumin excretion ≥40 mg per 24 hours

DCCT: microvascular complications increase as HbA_{1c} increases



DCCT: N Engl J Med 1993;329:977–86

Retinopathy 7 years after the DCCT



Adapted from: JAMA 2002: 287:2563–9

Epidemiology of Diabetes Interventions and Complications (EDIC) – follow up of DCCT

- Averaged mean HbA1c during the DCCT
  - 7.3% - intensive group
  - 9.1% - conventional group
- Averaged mean HbA1c during the EDIC
  - similar between those with the different treatment histories.
- Early intensive therapy - 50% risk reduction of renal impairment in 20 yrs

de Boer IH et al. N Eng J Med 2011;365(25)2306-2376.

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)

- Intensive insulin group – HbA1c (7% vs 7.9%)
- Duration - 10 years -
- Intensive insulin group had reduced risk of
  a. Diabetes related endpoint – 12%
  b. Diabetes related death – 10%
  c. All cause mortality - 6%
  d. Microvascular endpoints – 25%
- After 9 years – 67% reduction of doubling of creatinine.

UKPDS group. Lancet 1998; 352: 837–53

Action in Diabetes and Vascular Disease:Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)

- Total number – 11, 140 Type 2 DM
- Total duration of follow up – 5 years
- Intensive control (HbA1c 6.5% vs 7.3%)

- 10% relative reduction combined outcome of major macrovascular and microvascular events,

- 21% relative reduction in nephropathy

Patel A et al. N Engl J Med 2008;358:2560-72.

Action to Control Cardiovascular Risk in Diabetes (ACCORD)

- Total number of patients – 10250 Type 2 DM
- Intensive insulin therapy (HbA1c – 6.4% vs 7.6%)

- 32% reduction in macro albuminuria
- 21% reduction of micro albuminuria

Ismail-Beigi F et al. Lancet. 2010;376(9739): 419-430.

Veterans Affairs Diabetes Trial

- Total number of patients – 1791 Type 2DM
- Intensive treatment group – HbA1c (6.5% vs 8.4%)

Reduction of
Macroalbuminuria – 37%
Microalbuminuria – 32%

Duckworth W et al. N Eng J Med. 2009;360(2): 129-139.

GUIDELINE:2.2

Not to target HbA1c < 7% in diabetics at risk of hypoglycemia (1B)

EVIDENCES

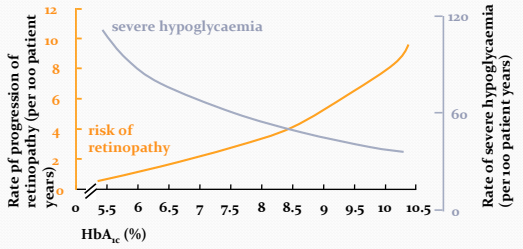
- Episodes of hypoglycemia: Intensive vs conventional

  ADVANCE – 2.7% vs 1.5%

  ACCORD – 26.7% vs 8.6%

  VADT – 24.1% vs 17.6%

DCCT: the price of improved diabetic control – hypoglycaemia



Adapted from: N Engl J Med 1993;329:977–86

GUIDELINE:2.3

Target HbA1c above 7% in diabetics with co-morbidities or limited life expectancy and risk of hypoglycemia (2C)

- Intensive glycemic control – shows benefits after long duration.
- Elderly diabetics with CKD – high comorbid condition with less life expectancy.
- HbA1c <7% - increased fall in diabetics with 70-79 years

So intensive control should not be implemented and target HbA1c >7%

Schwartz AV et al. Diabetes-related complications, glycemic control, and falls in older adults .Diabetes Care . Mar 2008;31(3):391–396

Special issue

- No RCT on CKD with stage 3-5 on glycemic control
- HbA1c level 7-9% - better outcome with survival/ hospitalization / CVD on haemodialysis patients
- Renal impairment results in accumulation of drugs with increased incidence of hypoglycemia

Anti diabetic drugs

- Insulin - Decreased clearance of insulin
  - Impaired renal gluconeogenesis by kidney
  - Reduced insulin degradation by kidney
- Insulin should be started in low dose and monitor- No need of dose modification – Detemir/ Glargin /NPH/ regular / Aspartate/ lispro
- Oral hypoglycemics that is excreted by kidney – accumulated - should not be used or dose modifications

Anti diabetic agents in CKD with diabetes

- Avoid first generation sulphonylurea
- Avoid metformin if scr > 1.5mg% or Ccr < 30 ml/min
- Avoid acarabose if Ccr is < 30 ml/min
- Repaglinide – start with 0.5 mg with meal if Ccr < 30ml/min
- Glimeperide – Start with 1 mg /day if Ccr < 30 ml/min
- Glipizide/glicazide/pioglitazone – Normal Dose

Anti diabetic drugs

- Dipeptidyl peptidase (DPP-4) inhibitor –

Sitagliptin – 100mg > 50 ml/min
- 50 mg 30 – 50 ml/min
- 25 mg < 30 ml/min

Saxa gliptin – 5 mg > 50 ml/min
2.5 mg < 50 ml/ min

Linagliptin – no dose modification

Vidagliptin – 50 mg Bd > 50 ml/ min
50 mg OD < 50 ml/min

Clinical Care/Education/Nutrition/Psychosocial Research

ORIGINAL ARTICLE

Efficacy and Safety of Sitagliptin Versus Glipizide in Patients With Type 2 Diabetes and Moderate-to-Severe Chronic Renal Insufficiency

OBJECTIVE—Patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease have an increased risk of micro- and macrovascular disease, but limited options for antihyperglycemic therapy. We compared the efficacy and safety of sitagliptin with glipizide in patients with T2DM and moderate-to-severe chronic renal insufficiency and inadequate glycemic control.

RESEARCH DESIGN AND METHODS—Patients (n = 426) were randomized 1:1 to sitagliptin (50 mg every day [q.d.] for moderate renal insufficiency and 25 mg q.d. for severe renal insufficiency) or glipizide (2.5 mg q.d., adjusted based on glycemic control to a 10-mg twice a day maximum dose). Randomization was stratified by: 1) renal status (moderate or severe renal insufficiency); 2) history of cardiovascular disease; and 3) history of heart failure.

RESULTS—At week 54, treatment with sitagliptin was noninferior to treatment with glipizide in A1C change from baseline (−0.8 vs. −0.6%; between-group difference −0.11%; 95% CI −0.29 to 0.06) because the upper bound of the 95% CI was less than the prespecified noninferiority margin of 0.4%. There was a lower incidence of symptomatic hypoglycemia adverse events (AEs) with sitagliptin versus glipizide (6.2 and 17.0%, respectively; $P = 0.001$) and a decrease in body weight with sitagliptin (−0.6 kg) versus an increase (1.2 kg) with glipizide (difference, −1.8 kg; $P < 0.001$). The incidence of gastrointestinal AEs was low with both treatments.

CONCLUSIONS—In patients with T2DM and chronic renal insufficiency, sitagliptin and glipizide provided similar A1C-lowering efficacy. Sitagliptin was generally well-tolerated, with a lower risk of hypoglycemia and weight loss versus weight gain, relative to glipizide.

Diabetes Care Publish Ahead of Print, published online December 17, 2012

GUIDELINE: 3

Management of Hypertension in Diabetes and CKD

- Most patients with DKD have hypertension. (Strong)
- Higher levels of blood pressure are associated with more rapid progression of DKD. (Strong)

Table 29. Prevalence of Hypertension in DKD

Clinical Features	Prevalence (%)
Type 1 diabetes, microalbuminuria	30-50
Type 1 diabetes, macroalbuminuria	65-88
Type 2 diabetes, microalbuminuria	40-83
Type 2 diabetes, macroalbuminuria	78-96

The prevalence in type 2 diabetes varies among ethnic populations and thus has a wider range.[149-153]

3.1 Hypertensive people with diabetes and CKD stages 1-4 with or without albuminuria should be treated with an ACE inhibitor or an ARB, usually in combination with a diuretic. (A)

3.2 Target blood pressure in diabetes and CKD stages 1-4 should be < 130/80 mm Hg. (B)

KDIGO guide line has advocated <140/90 mm Hg in normoalbuminuric and <130/80 mm Hg in albuminuric diabetes with CKD ND.

GUIDELINE:4

Management of Dyslipidemia in diabetes and CKD

- Dyslipidemia is common in people with diabetes and CKD.
- Cardiovascular events are a frequent cause of morbidity and mortality in this population.
- Lowering LDL-C with statin-based therapies reduces risk of major atherosclerotic events, but not all-cause mortality, in patients with CKD including those with diabetes

GUIDELINE:4.1

Use statin or Statin with ezetimibe in all diabetics with CKD including transplant recipients – to reduce risk of major atherosclerotic event (1B)

The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial

- Total number – 9270 patients of > 40 years age
  33% on MHD and 23% Diabetes
- Duration – 5 years
- Simvastatin 20mg + Ezetimibe 10 mg VS Placebo
- 17% relative reduction in major atherosclerotic events
- No reduction in all cause mortality in dialysis patients
- No reduction in renal *outcome in Non dialysis patients like doubling of creatinine/ progression* to ESRD

Lancet 2011; 377: 2181–92

GUIDELINE:4.2

Do not initiate Statin in diabetes who are in dialysis (1B)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atorvastatin in Patients with Type 2 Diabetes Mellitus Undergoing Hemodialysis

Christoph Wanner, M.D., Vera Krane, M.D., Winfried März, M.D., Manfred Olschewski, M.Sc., Johannes F.E. Mann, M.D., Günther Ruf, M.D., and Eberhard Ritz, M.D., for the German Diabetes and Dialysis Study Investigators*

METHODS

We conducted a multicenter, randomized, double-blind, prospective study of 1255 subjects with type 2 diabetes mellitus receiving maintenance hemodialysis who were randomly assigned to receive 20 mg of atorvastatin per day or matching placebo. The primary end point was a composite of death from cardiac causes, nonfatal myocardial infarction, and stroke. Secondary end points included death from all causes and all cardiac and cerebrovascular events combined.

CONCLUSIONS

Atorvastatin had no statistically significant effect on the composite primary end point of cardiovascular death, nonfatal myocardial infarction, and stroke in patients with diabetes receiving hemodialysis.

4D - Die Deutsche Diabetes Dialyse Studies.
N Engl J Med. 2005;353(3):238-48.

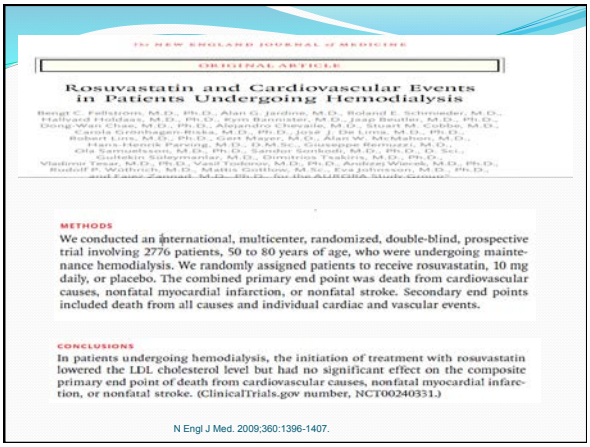
original article

Effect of atorvastatin on inflammation and outcome in patients with type 2 diabetes mellitus on hemodialysis

Vera Krane[1], Karl Winkler[2], Christiane Drechsler[1], Jürgen Lilienthal[3], Winfried März[4] and Christoph Wanner[1] for the German Diabetes and Dialysis Study Investigators

protein measurements was associated with significant increases in the risk of sudden death, stroke, all-cause mortality and composite vascular endpoint. Our results show that C-reactive protein was highly predictive of outcome, but atorvastatin treatment was not associated with reduced relative risks in the composite vascular endpoint or mortality in patients on hemodialysis with or without inflammation.

Kidney International (2008) **74,** 1461–1467; doi:10.1038/ki.2008.484; published online 24 September 2008



THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis

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METHODS

We conducted an international, multicenter, randomized, double-blind, prospective trial involving 2776 patients, 50 to 80 years of age, who were undergoing maintenance hemodialysis. We randomly assigned patients to receive rosuvastatin, 10 mg daily, or placebo. The combined primary end point was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Secondary end points included death from all causes and individual cardiac and vascular events.

CONCLUSIONS

In patients undergoing hemodialysis, the initiation of treatment with rosuvastatin lowered the LDL cholesterol level but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. (ClinicalTrials.gov number, NCT00240331.)

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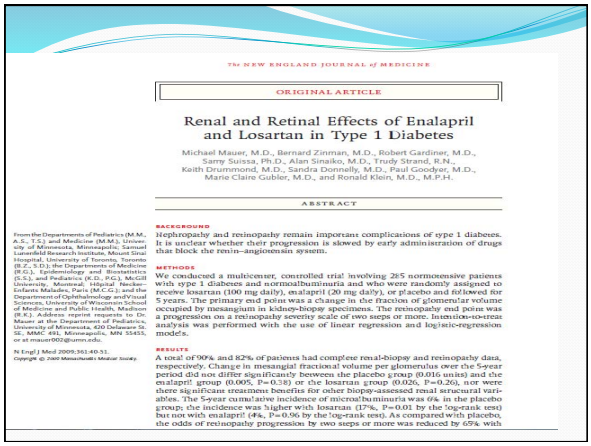
GUIDELINE:6

Management of albuminuria in normotensive patients with diabetes

- Treatments that produce a lasting decrease in urinary albumin excretion may slow the progression of DKD even in the absence of hypertension.
- However, most people with diabetes and albuminuria have hypertension.

GUIDELINE:6.1

Normotensive normoalbuminuric diabetics - Do not use ACI / ARB for primary prevention (1A)



THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Renal and Retinal Effects of Enalapril and Losartan in Type 1 Diabetes

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ABSTRACT

BACKGROUND

Nephropathy and retinopathy remain important complications of type 1 diabetes. It is unclear whether their progression is slowed by early administration of drugs that block the renin–angiotensin system.

METHODS

We conducted a multicenter, controlled trial involving 285 normotensive patients with type 1 diabetes and normoalbuminuria and who were randomly assigned to receive losartan (100 mg daily), enalapril (20 mg daily), or placebo and followed for 5 years. The primary end point was a change in the fraction of glomerular volume occupied by mesangium in kidney-biopsy specimens. The retinopathy end point was a progression on a retinopathy severity scale of two steps or more. Intention-to-treat analysis was performed with the use of linear regression and logistic-regression models.

RESULTS

A total of 90% and 82% of patients had complete renal-biopsy and retinopathy data, respectively. Change in mesangial fractional volume per glomerulus over the 5-year period did not differ significantly between the placebo group (0.016 units) and the enalapril group (0.005, P=0.38) or the losartan group (0.026, P=0.26), nor were there significant treatment benefits for other biopsy-assessed renal structural variables. The 5-year cumulative incidence of microalbuminuria was 6% in the placebo group; the incidence was higher with losartan (17%, P=0.01 by the log-rank test) but not with enalapril (4%, P=0.56 by the log-rank test). As compared with placebo, the odds of retinopathy progression by two steps or more was reduced by 65% with

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GUIDELINE:6.2

Normotensive with albuminuria > 30 mg/g – Use ACEI/ ARB for secondary prevention who are at high risk of DKD or its progression. (2C)

ACEI VS ARB in DKD

- ACEI in Type 1 DM and ARB in type 2 DM with CKD and macroalbuminuria -

  - beneficial in terms of loss of GFR (both rates of decline in eGFR and doubling of baseline (sCr) and ESRD.
- No long-term studies that examine the reno-protective efficacy of ACEI in type 2 or ARBs in type 1 diabetes.

Dosages of ACEI and ARBs

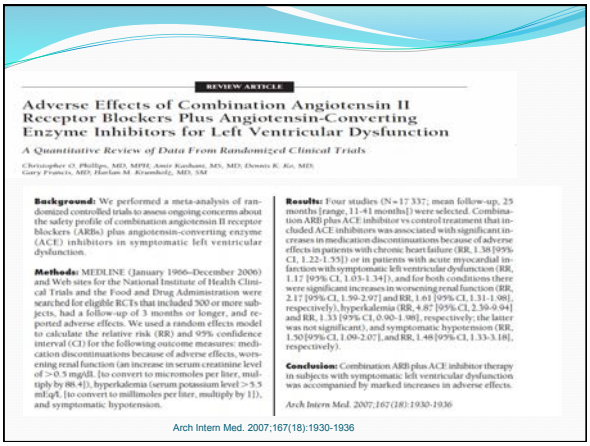
- In normotensive diabetics and albuminuria - the target dose of ACEI or ARBs is unknown.
- In hypertensive diabetics – titrate the dose up to maximum in the absence of side effects or adverse events (e.g., hyperkalemia or acute kidney injury).
- A reversible reduction in GFR of up to 30% (accordingly a 30% increase in SCr concentration) has been regarded as reasonably attributable to this physiological mechanism.
- Greater reductions may indicate underlying renal artery stenosis.

Adverse events of ACEI/ARB

- If hyperkalemia occurs in CKD patients taking a renal excreted ACEI –
  low potassium diet / reduce the dose
  switch to fosinopril or trandolapril / add a potassium-losing diuretic.
- All ARBs - excreted by the liver
  40% - candesartan / >95% - irbesartan and telmisartan
- The dose in ARBs is usually adjusted according to clinical effect rather than kidney function

Combination of ACEI and ARB

- Increased adverse events - particularly impaired kidney function, hyperkalemia and hypotesion compared to either agent alone, despite a reduction in albuminuria using combination therapy.
- Not recommended



REVIEW ARTICLE

Adverse Effects of Combination Angiotensin II Receptor Blockers Plus Angiotensin-Converting Enzyme Inhibitors for Left Ventricular Dysfunction

A Quantitative Review of Data From Randomized Clinical Trials

Christopher O. Phillips, MD, MPH; Amir Kashani, MS, MD; Dennis K. Ko, MD; Gary Francis, MD; Harlan M. Krumholz, MD, SM

Background: We performed a meta-analysis of randomized controlled trials to assess ongoing concerns about the safety profile of combination angiotensin II receptor blockers (ARBs) plus angiotensin-converting enzyme (ACE) inhibitors in symptomatic left ventricular dysfunction.

Methods: MEDLINE (January 1966–December 2006) and Web sites for the National Institute of Health Clinical Trials and the Food and Drug Administration were searched for eligible RCTs that included 500 or more subjects, had a follow-up of 3 months or longer, and reported adverse effects. We used a random effects model to calculate the relative risk (RR) and 95% confidence interval (CI) for the following outcome measures: medication discontinuations because of adverse effects, worsening renal function (an increase in serum creatinine level of >0.5 mg/dl, [to convert to micromoles per liter, multiply by 88.4]), hyperkalemia (serum potassium level >5.5 mEq/l, [to convert to millimoles per liter, multiply by 1]), and symptomatic hypotension.

Results: Four studies (N=17 337; mean follow-up, 25 months [range, 11-41 months]) were selected. Combination ARB plus ACE inhibitor vs control treatment that included ACE inhibitors was associated with significant increases in medication discontinuations because of adverse effects in patients with chronic heart failure (RR, 1.38 [95% CI, 1.22-1.55]) or in patients with acute myocardial infarction with symptomatic left ventricular dysfunction (RR, 1.17 [95% CI, 1.03-1.34]), and for both conditions there were significant increases in worsening renal function (RR, 2.17 [95% CI, 1.59-2.97] and RR, 1.61 [95% CI, 1.31-1.98], respectively), hyperkalemia (RR, 4.87 [95% CI, 2.39-9.94] and RR, 1.33 [95% CI, 0.90-1.98], respectively; the latter was not significant), and symptomatic hypotension (RR, 1.50 [95% CI, 1.09-2.07], and RR, 1.48 [95% CI, 1.33-3.18], respectively).

Conclusion: Combination ARB plus ACE inhibitor therapy in subjects with symptomatic left ventricular dysfunction was accompanied by marked increases in adverse effects.

Arch Intern Med. 2007;167(18):1930-1936

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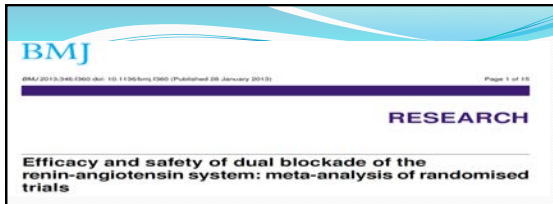

BMJ

RESEARCH

Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials

- 33 RCT – 68 405 patients (mean age 61 years, 71% men) and mean duration of 52 weeks.
- Dual blockade of the renin-angiotensin system vs monotherapy
- No significant benefit for all cause mortality and cardiovascular mortality.
- 18% reduction in admissions due to hospital for heart failure.

Adverse events of dual RAS Blockage

- 55% increase in the risk of hyperkalaemia
- 66% increase in the risk of hypotension
- 41% increase in the risk of renal failure
- 27% increase in the risk of withdrawal due to adverse events

Direct renin inhibitor - Aliskiren

- valuation of Proteinuria in Diabetes (AVOID) trial with Aliskerin and Losartan – type 2 DM with MA showed benefit.
- Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) –

  -was stopped early due to increased risk of stroke and adverse events including hyperkalemia, hypotension, and ESRD or death due to kidney disease.

So, Aliskerin should not be used.

Conclusion

- All patients with Type 2 DM should be screened for albuminuria at presentation and then annually.
- Strict control of sugar with HbA1c of 7% should be the target except with at risk of hypoglycemia.
- Elderly diabetics with advanced CKD should not be targeted for strict control of sugar.
- Anti diabetics with renal excretion should be avoided or prescribed with dose reduction in CKD patients.
- ACEI/ ARB should not be prescribed for normoalbuminuric and normotensive diabetics.

Conclusion

- ACEI / ARB be the choice of therapy for diabetics with albuminuria with or without hypertension and diabetics with hypertension with or without albuminuria with target BP of <130/80 mm Hg.
- Combination of ACEI and ARB to be avoided in CKD.
- Lipid lowering agent to be prescribed to all diabetics.
- Diabetics on dialysis should not be started Lipid lowering agent.