Diabetes and Chronic Kidney Disease

The CKD Symposium

November 30, 2013

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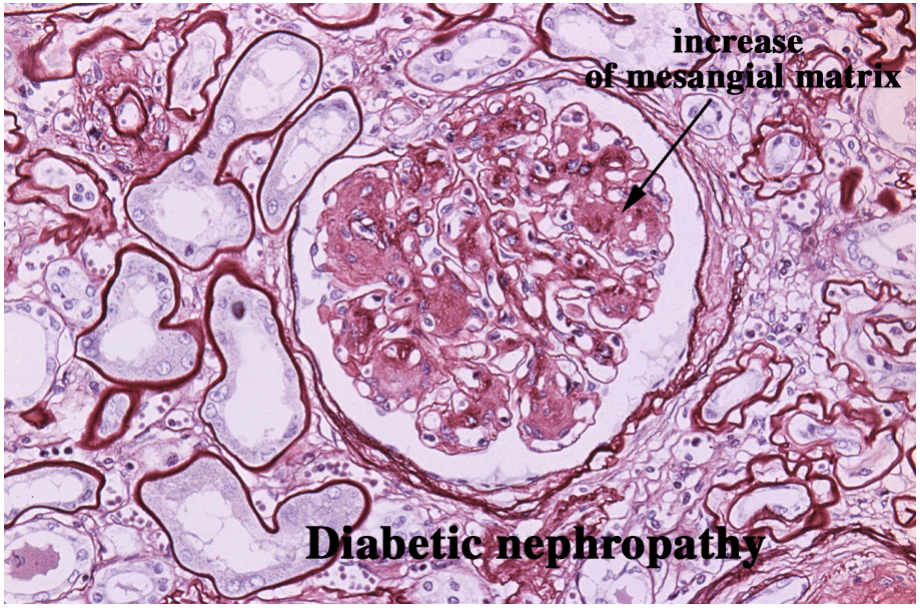


Outline

- Understand the link between diabetes and kidney disease

- Management of diabetic kidney disease
  - Primarily grades I-IV

Background

- Nearly 21 million people in the United States, or 7% of the population, have diabetes
  - 90-95% is type 2

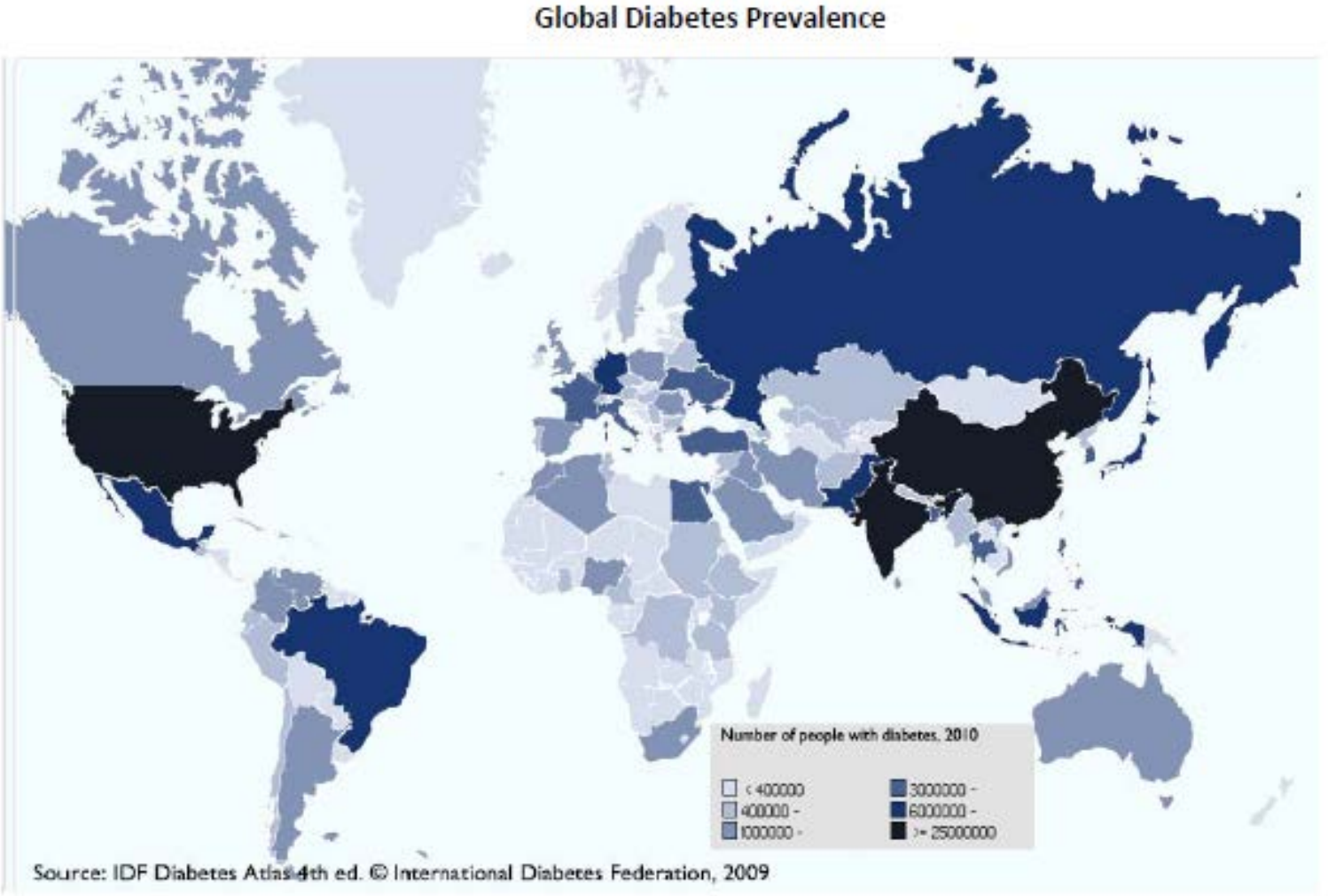
- Diabetes is the leading cause of CKD in developed countries
  - becoming the leading cause in developing countries due to global increase in type 2 diabetes and obesity

Background

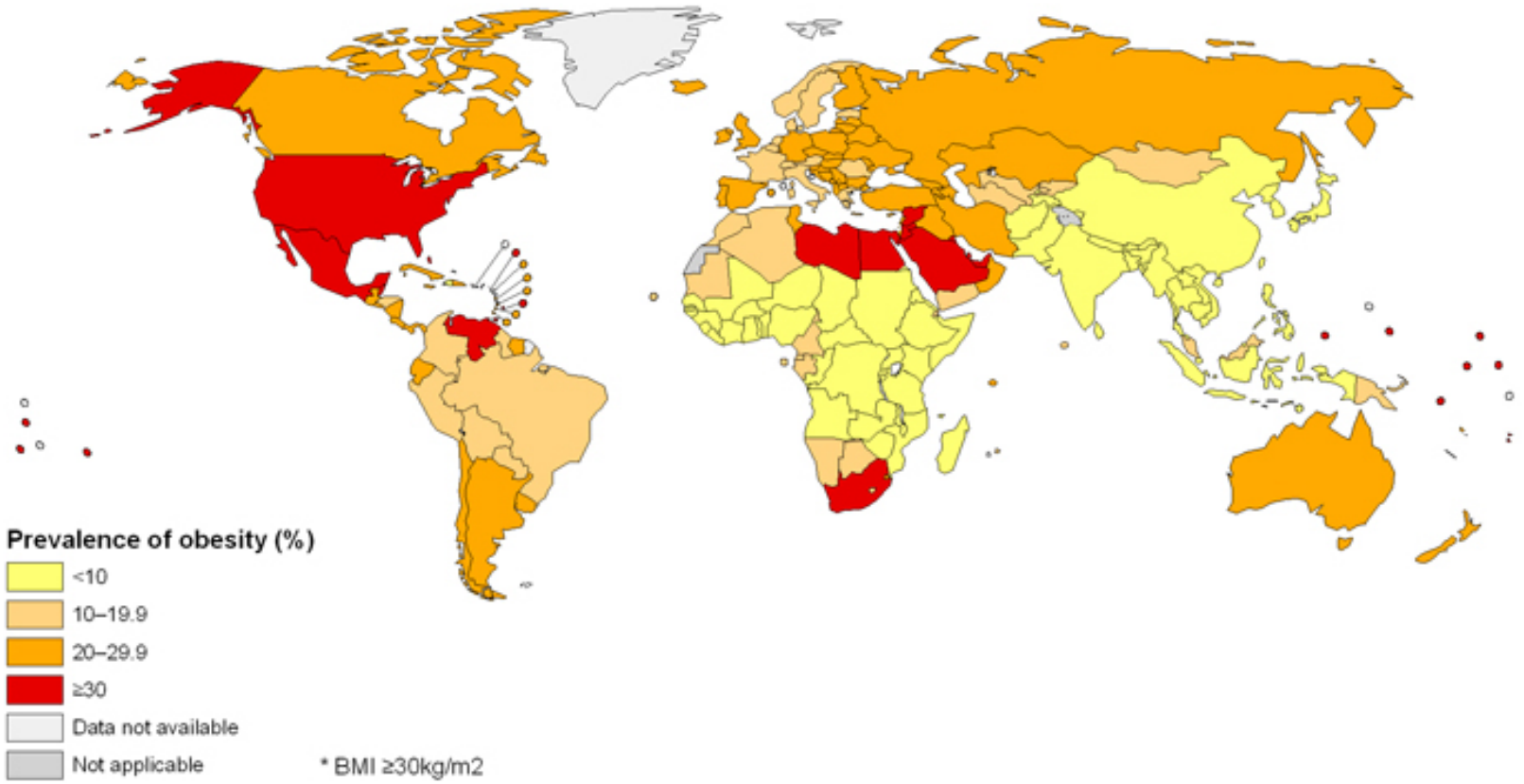
- Diabetes prevalence increasing most rapidly in developed countries and in developing countries undergoing transition from traditional to modern lifestyles

- The global burden of diabetes is expected to **double** between 2000 and 2030, with greatest increases in prevalence occurring in the Middle East, sub-Saharan Africa, and India

Prevalence of Diabetes



Prevalence of Obesity



Cardiovascular disease

- 25-40% of diabetics develop Chronic Kidney Disease
  - Greater risk CVD, morbidity, premature mortality
  - UKPDS showed once microalbuminuria develops, death rates outpace CKD progression by 2:1

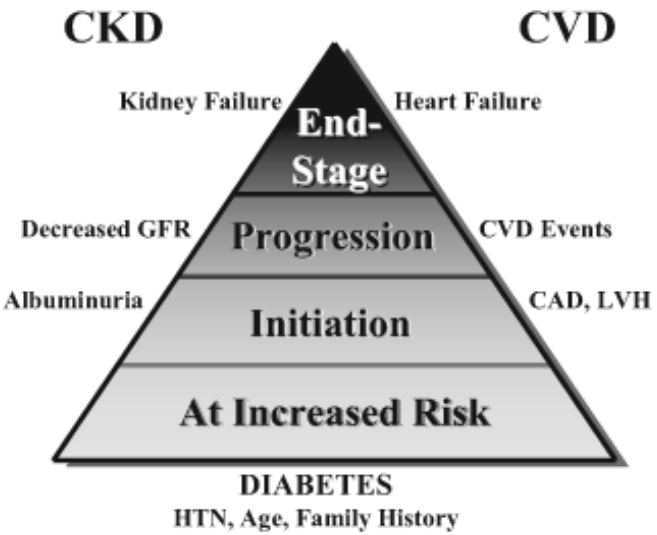


Figure 4. Diabetes Amplifies the CKD and CVD Paradigm.

Causes of Diabetic Kidney Disease (DKD)

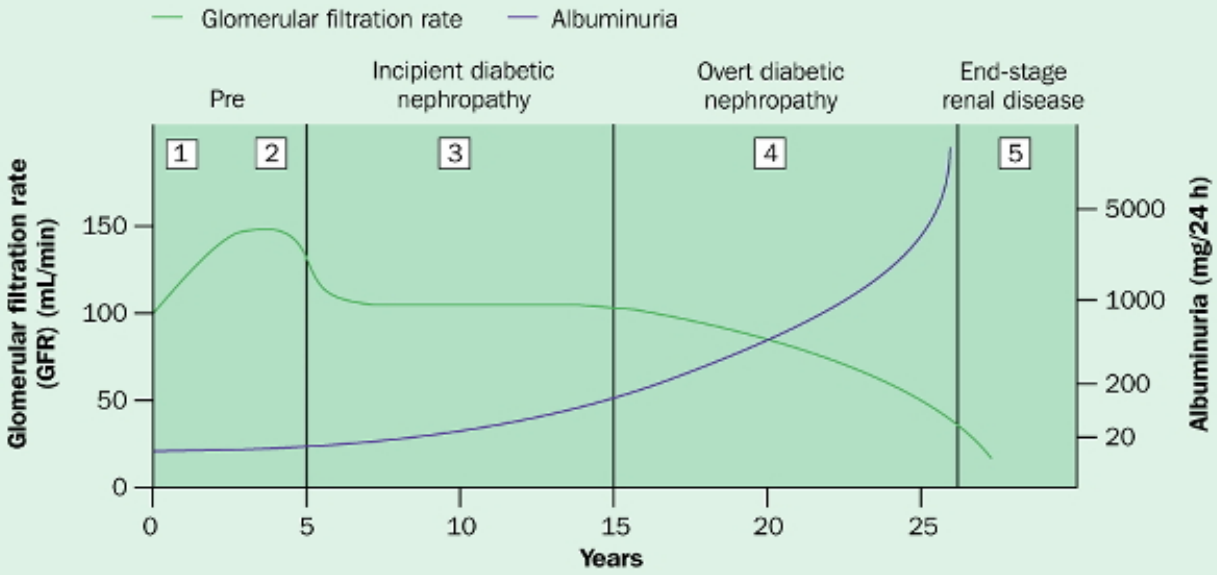
- Several pathways:
  - Microvascular disease affecting the glomeruli → diabetic nephropathy
  - Generalized diffuse atherosclerosis → atherosclerotic renal vascular disease and ischemic nephropathy
  - Ischemic nephropathy → papillary necrosis
  - Autonomic dysfunction → obstructive uropathy and recurrent UTIs
  - Increased risk of nephrotoxicity and AKIs (NSAIDs, contrast, aminoglycosides, etc.)

Presentation and natural history

- One of earliest changes is hyperfiltration and increase in GFR (mostly type 1)
- Next is generally microalbuminuria
  - 5-10 yrs after onset
- Then macroalbuminuria and overt diabetic nephropathy
  - 15 yrs after onset
  - Drop in GFR
  - Increase prevalence of hypertension (but may proceed)
- Then end stage renal disease

- Diabetic retinopathy is present in almost all type 1 DM with nephropathy and only 50-60% of type II DM with nephropathy

Natural history of type 1 diabetic nephropathy



Stage	Pre	Incipient	Overt
Functional	GFR ↑ (25–50%)	Microalbuminuria, hypertension	Proteinuria, nephrotic syndrome, GFR ↓
Structural	Renal hypertrophy	Mesangial expansion, glomerular basement membrane thickening, arteriolar hyalinosis	Mesangial nodules (Kimmelstiel–Wilson lesions) Tubulointerstitial fibrosis

Screening and diagnosis of DKD

- Diabetics should be screened annually with serum creatinine and eGFR and urine alb:creatinine (ACR)
  - Starting 5 yrs after diagnosis of type 1
  - Starting at the diagnosis of type II
- Elevated urine ACR confirmed 2 more times and not in setting of UTI
  - Microalbuminuria= ACR 3-30 mg/mmol
  - Macroalbuminuria= ACR >30 mg/mmol
- Consider other causes of CKD if:
  - active urine sediment
  - rapidly falling eGFR
  - rapidly rising proteinuria
  - absence of diabetic retinopathy
  - refractory hypertension
  - duration of type 1 DM <10 yrs

Management (CKD 1-IV and DM)

Risk Factor	Target
Glycemic control	HbA1C ≤ 7%
Blood pressure control	<140/90 if no proteinuria <130/80 if proteinuria
Proteinuria	<1g/d ACR < 100 mg/mmol Treat with ACE inh. Or ARB
Dyslipidemia	Treat all with statins
Smoking	Cessation
Dietary protein intake	0.8 g/kg/day
Obesity	BMI 18.5-25

Glycemic control

- Lowering HgA1C to <7% reduced the development of microalbuminuria in both type I and type II DM

HbA1C 8%
both groups

Intensive HgA1C 7.2%
Conventional HgA1C
9.1% in DCCT

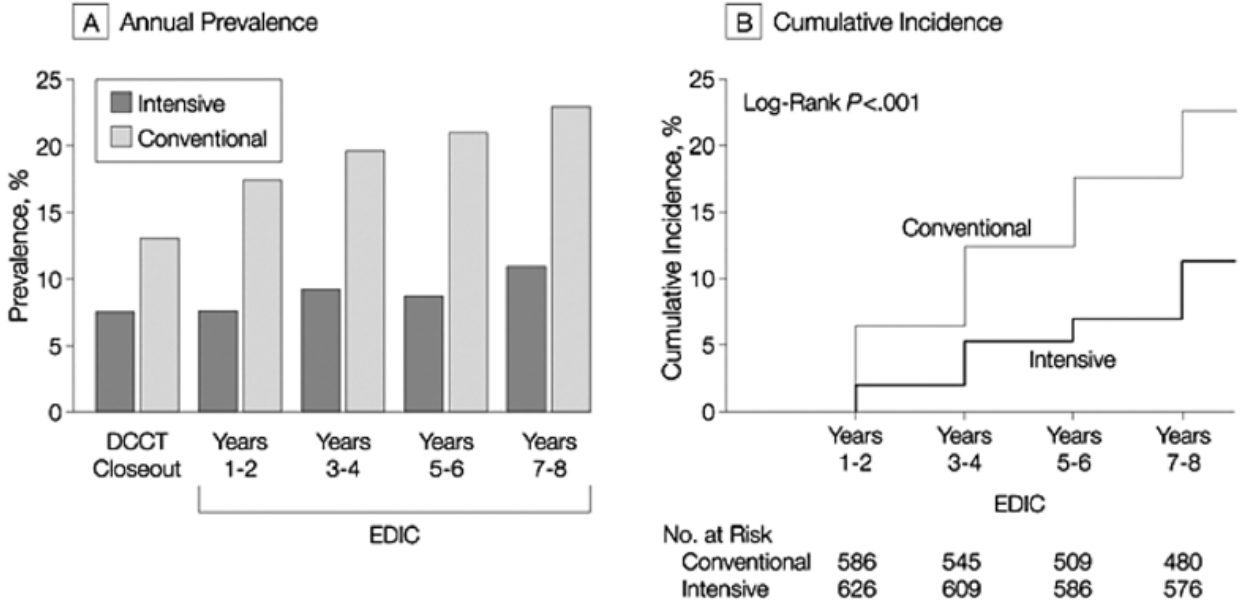


Figure 9. Prevalence and Cumulative Incidence of Microalbuminuria.

Glycemic control

- Lowering HbA1C to <7% decreases development of macroalbuminuria in both type I and type II DM
  - Numbers in studies small, therefore not statistically significant

- Lowering HbA1C to <7% reduces the rate of decrease in eGFR (?)
  - Most RCTs have such small numbers reaching outcome of decrease in GFR but eGFR drop is less in type I and type II

- HgA1C target should not be <7% in those at risk for hypoglycemia
  - Including advanced CKD, multiple comorbidities, limited life expectancy

- ADVANCE, ACCORD, VADT achieved HgA1C 6.5%, 6.4%, 6.9% respectively
  - Reduction in micro and macro albuminuria
  - No Benefit to eGFR or CVD end points
  - Substantial increase in hypoglycemia
  - Increase in all-cause mortality in ACCORD

Medication choices (KDOQI guidelines)

Table 22. Dosing Adjustments by CKD Stage for Drugs Used to Treat Hyperglycemia

Class	Drug	Dosing Recommendation CKD Stages 3, 4, or Kidney Transplant	Dosing Recommendation Dialysis
First-generation sulfonylureas	Acetohexamide	Avoid	Avoid
	Chlorpropamide	Reduce dose by 50% when GFR <70 and ≥50 mL/min/1.73 m^2 Avoid when GFR <50 mL/min/1.73 m^2	Avoid
	Tolazamide	Avoid	Avoid
	Tolbutamide	Avoid	Avoid
Second-generation sulfonylureas	Glipizide	Preferred sulfonylurea No dose adjustment necessary	Preferred sulfonylurea No dose adjustment necessary
	Gliclazide	Preferred sulfonylurea No dose adjustment necessary Not available in US	Preferred sulfonylurea No dose adjustment necessary Not available in US
	Glyburide	Avoid	Avoid
	Glimepiride	Initiate at low dose, 1 mg daily	Avoid
Alpha-glucosidase inhibitors	Acarbose	Not recommended in patients with SCr >2 mg/dL	Avoid
	Miglitol	Not recommended in patients with SCr >2 mg/dL	Avoid
Biguanides	Metformin	Contraindicated with kidney dysfunction defined as SCr ≥1.5 mg/dL in men or ≥1.4 mg/dL in women	Avoid
Meglitinides	Repaglinide	No dose adjustment necessary	No dose adjustment necessary
	Nateglinide	Initiate at low dose, 60 mg before each meal	Avoid
Thiazolidinediones	Pioglitazone	No dose adjustment necessary	No dose adjustment necessary
	Rosiglitazone	No dose adjustment necessary	No dose adjustment necessary
Incretin mimetic	Exenatide	No dose adjustment necessary	No dose adjustment necessary
Amylin analog	Pramlintide	No dose adjustment necessary for GFR 20-50 mL/min/1.73 m^2	No data available
DPP-4 inhibitor	Sitagliptin	Reduce dose by 50% (50mg/day) when GFR < 50 and ≥ 30 mL/min/1.73 m^2 and by 75% (25 mg/day) when GFR < 30 mL/min/1.73 m^2	Reduce dose by 75% (25 mg/day)

Blood pressure control

- Target in DM and CKD without proteinuria= ≤ 140/90
  - these patients may be more likely to be elderly, prone to falls, marked systolic hypertension, severe autonomic neuropathy
  - Evidence for lower targets weaker but can be considered on an individual basis

- Target in DM and CKD with proteinuria (>30mg/d) = ≤130/80

- ACEi/ARB preferred antihypertensives if proteinuria > 30mg/d

Lipid control

- KDIGO 2013 guidelines: all diabetics with CKD should be treated with a statin or statin/ezetimibe combination
  - Independent of cholesterol levels
- Statins should not be initiated if on dialysis
  - May be continued if on prior to dialysis

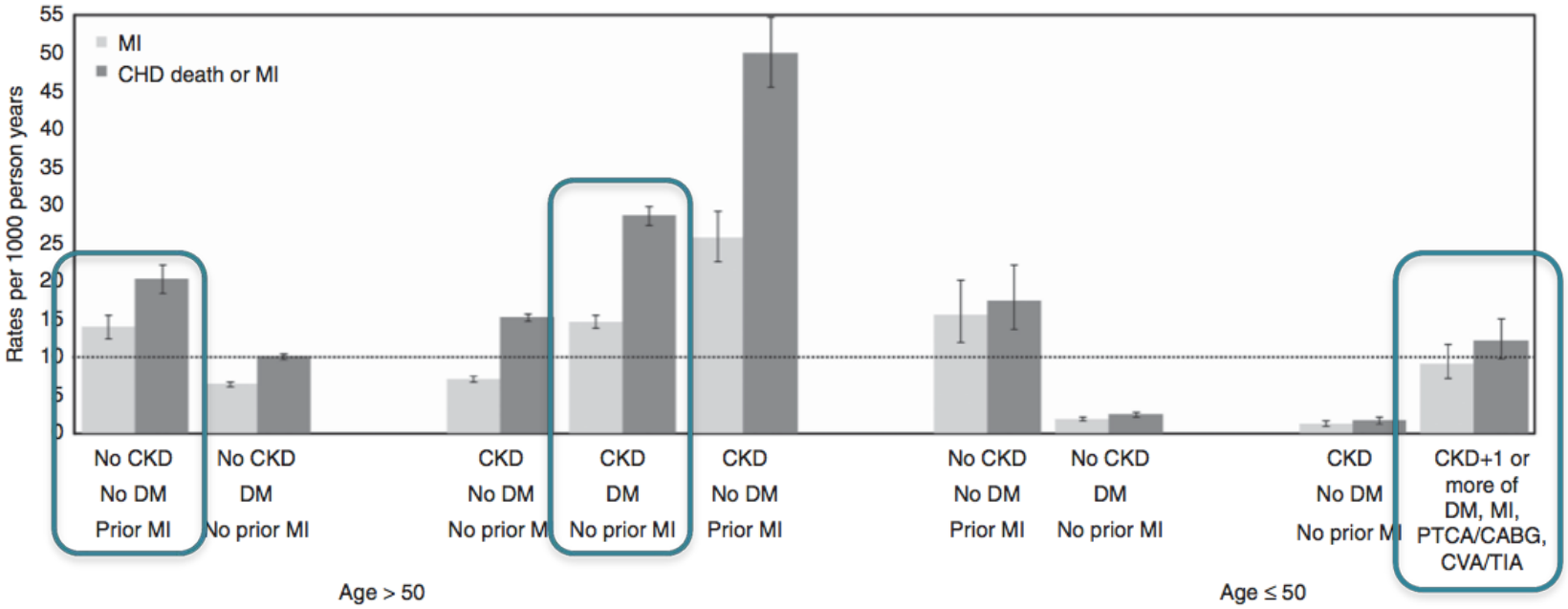


Figure 2 | Future 10-year coronary risk based on various patient characteristics. Data are unadjusted rates from 1,268,029 participants

Nutrition management

- Dietary restrictions can be very challenging considering simple carbohydrate restriction, Na restriction, K and Phos restriction, fluid restriction, etc.
  - Specialty trained registered dietician involvement recommended
- Omega-3 and monounsaturated fats may be beneficial in CKD
- Na should be restricted to <2g/d
- Dietary protein intake (CKD I-IV) should be 0.8 g/kg/d
  - Lowering protein reduces loss of kidney function and reduces proteinuria
  - However, overly strict protein restriction can lead to malnutrition

Nutritional recommendations

Nutrient	Stage of CKD		
	1-2	1-4	3-4
Sodium (g/d)		<2.3	
Total fat* (% of calories)		<30	
Saturated fat (% of calories)		<10	
Cholesterol (mg/d)		<200	
Carbohydrate (% of calories)		50-60	
Protein (g/kg/d, % of calories)			
No diabetes	1.4 (~18)		0.6-0.8 (~8-10)
Diabetes	0.8 (~10)		0.6-0.8 (~8-10)
Phosphorus (g/d)	1.7		0.8-1.0
Potassium (g/d)	>4		2.4

Note: Adapted from the DASH diet and NKF-KDOQI™ CPGs for Hypertension and Antihypertensive Agents in CKD, modified for diabetes and stages of CKD.[5,199]

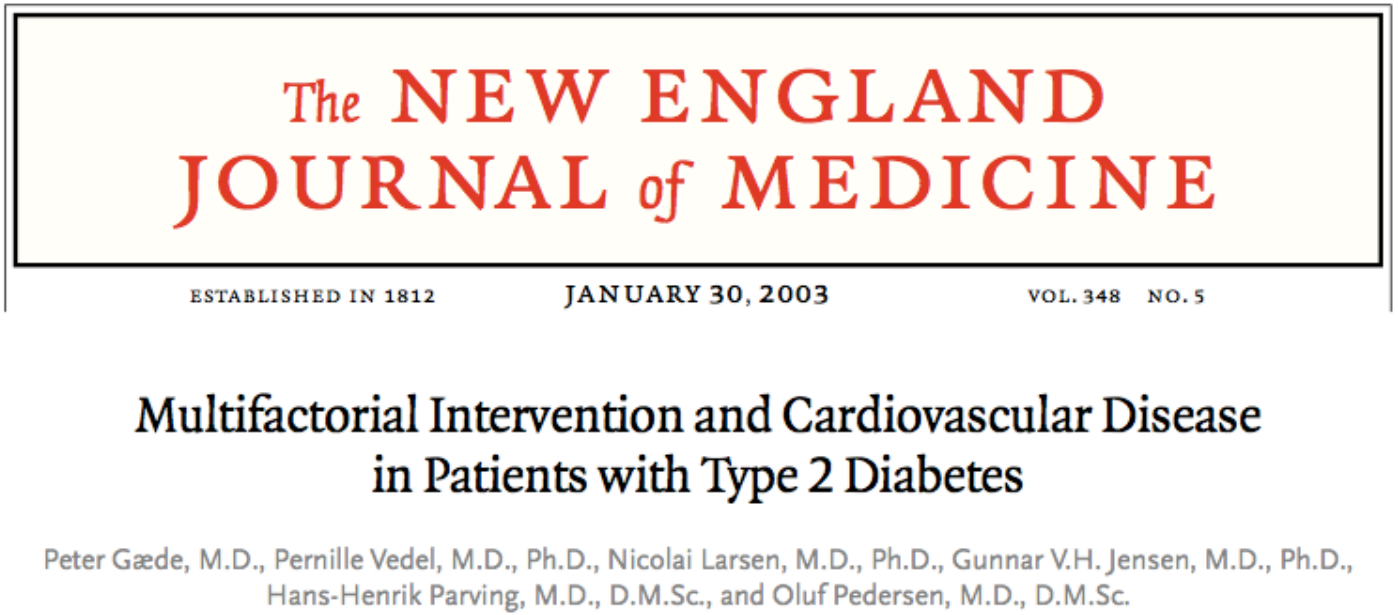
*Adjust so total calories from protein, fat, and carbohydrate are 100%. Emphasize such whole-food sources as fresh vegetables, whole grains, nuts, legumes, low-fat or nonfat dairy products, canola oil, olive oil, cold-water fish, and poultry.

Proteinuria

- RAS inhibition does not prevent the development of microalbuminuria and therefore ACEi/ARBs not recommended for primary prevention of DKD
- RAS inhibition effectively reduces albuminuria progression and improves clinical outcomes in hypertensive patients with DKD
- However diabetics, macroalbuminuria, and normal blood pressure were rarely included in available studies
  - relatively weak evidence for prognosis of kidney disease
- Lowering proteinuria decreases cardiovascular risk
- Overall, normotensive diabetics with proteinuria should be treated with ACEi/ARB

Multifaceted approach

- The Steno Study- randomized trial investigated a multifaceted treatment approach versus usual care in type 2 diabetes and microalbuminuria



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Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes

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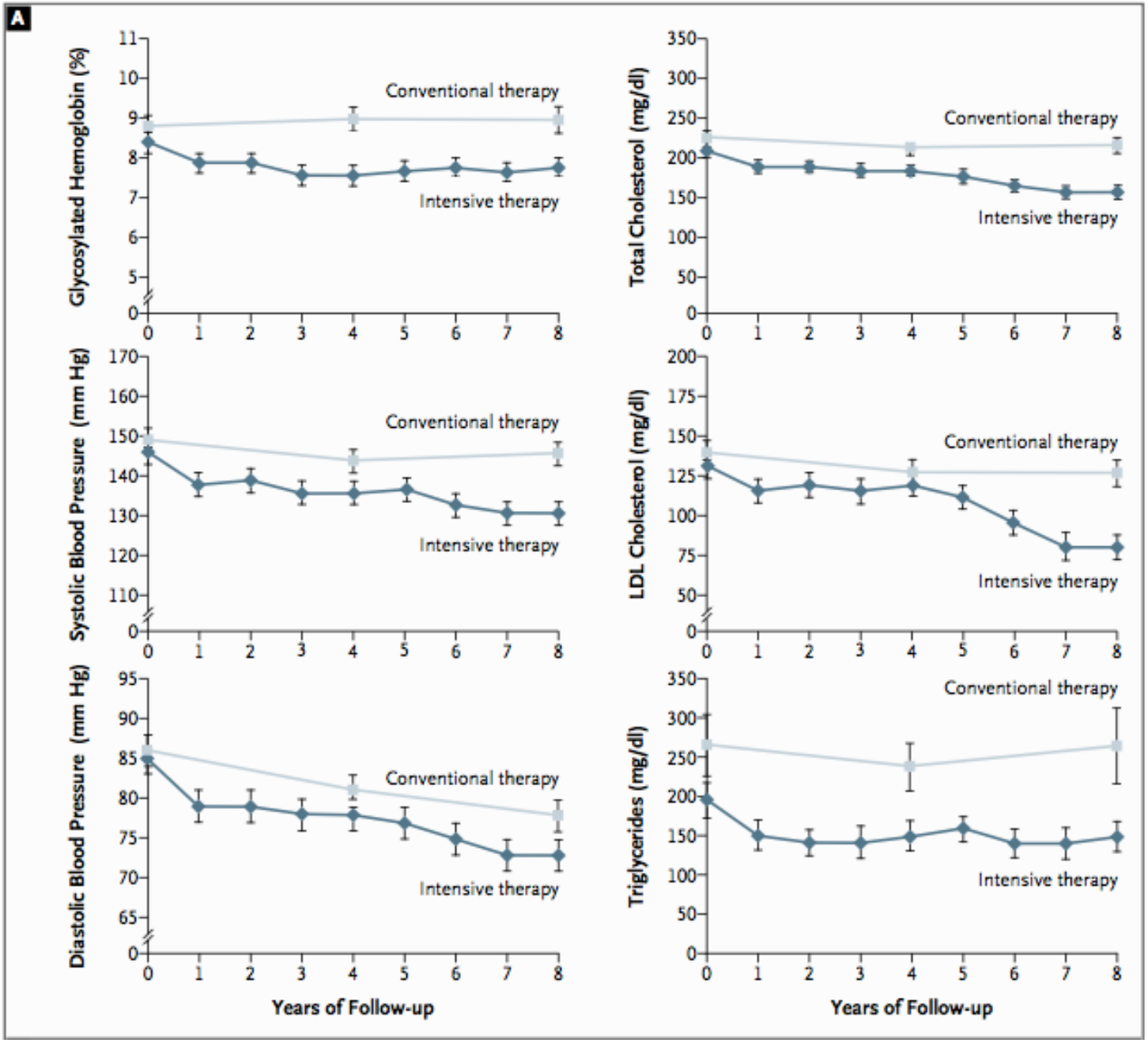
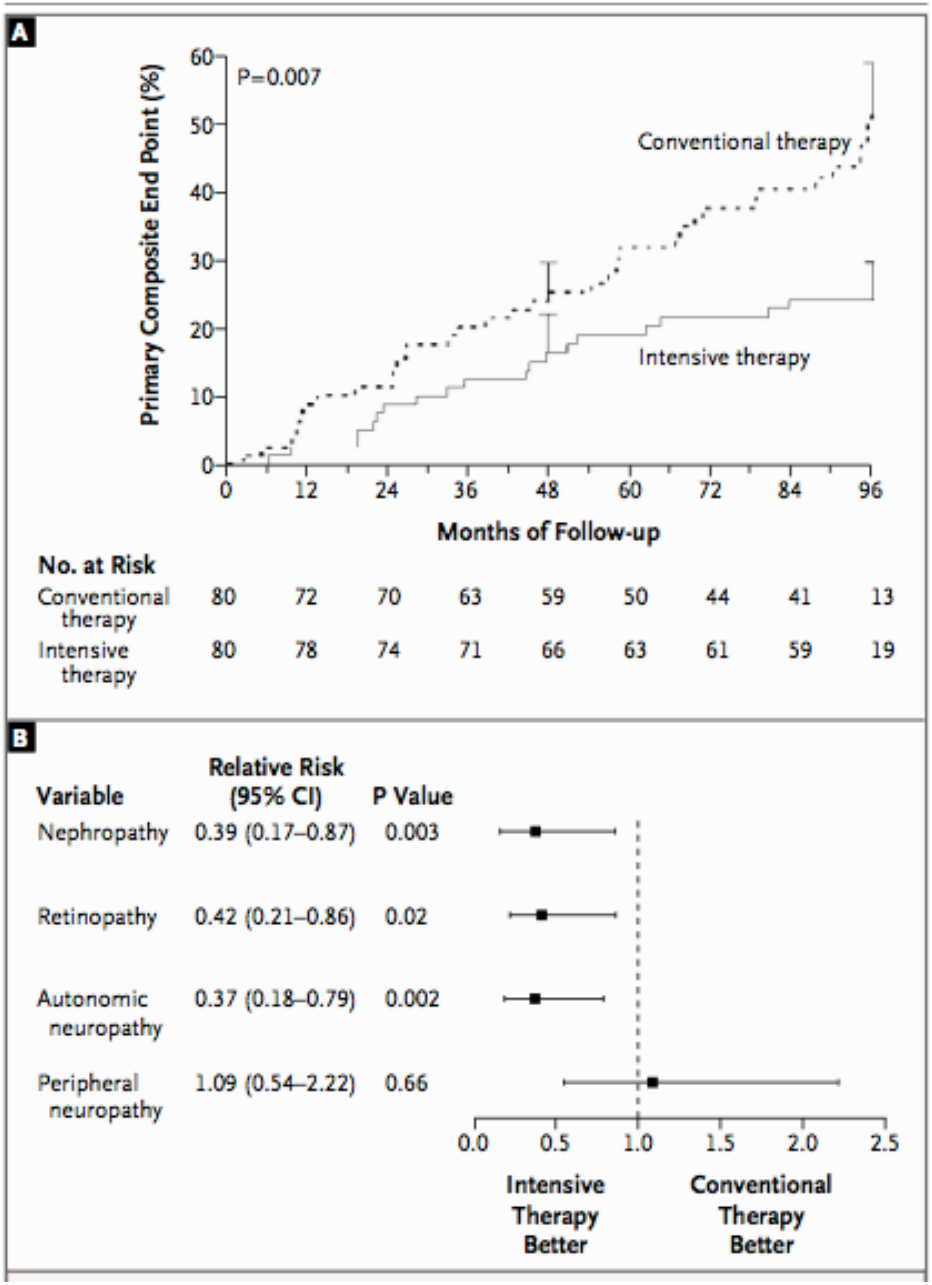
Table 1. Treatment Goals for the Conventional-Therapy Group and the Intensive-Therapy Group.*

Variable	Conventional Therapy		Intensive Therapy	
	1993–1999	2000–2001	1993–1999	2000–2001
Systolic blood pressure (mm Hg)	<160	<135	<140	<130
Diastolic blood pressure (mm Hg)	<95	<85	<85	<80
Glycosylated hemoglobin (%)	<7.5	<6.5	<6.5	<6.5
Fasting serum total cholesterol (mg/dl)	<250	<190	<190	<175
Fasting serum triglycerides (mg/dl)	<195	<180	<150	<150
Treatment with ACE inhibitor irrespective of blood pressure	No	Yes	Yes	Yes
Aspirin therapy				
For patients with known ischemia	Yes	Yes	Yes	Yes
For patients with peripheral vascular disease	No	No	Yes	Yes
For patients without coronary heart disease or peripheral vascular disease	No	No	No	Yes


A
Glycosylated Hemoglobin (%)
Conventional therapy
Intensive therapy
Total Cholesterol (mg/dl)
Conventional therapy
Intensive therapy
Systolic Blood Pressure (mm Hg)
Conventional therapy
Intensive therapy
LDL Cholesterol (mg/dl)
Conventional therapy
Intensive therapy
Diastolic Blood Pressure (mm Hg)
Conventional therapy
Intensive therapy
Triglycerides (mg/dl)
Conventional therapy
Intensive therapy
Years of Follow-up
Years of Follow-up


A
Primary Composite End Point (%)
P=0.007
Conventional therapy
Intensive therapy
Months of Follow-up
No. at Risk
Conventional therapy 80 72 70 63 59 50 44 41 13
Intensive therapy 80 78 74 71 66 63 61 59 19
B
Variable
Relative Risk (95% CI)
P Value
Nephropathy 0.39 (0.17–0.87) 0.003
Retinopathy 0.42 (0.21–0.86) 0.02
Autonomic neuropathy 0.37 (0.18–0.79) 0.002
Peripheral neuropathy 1.09 (0.54–2.22) 0.66
Intensive Therapy Better
Conventional Therapy Better

Summary

- Diabetes is very common and increasing rapidly in prevalence
- Diabetes is leading cause of CKD
- High proportion of diabetics develop CKD
- CKD and DM combination= very high cardiovascular risk
- Aggressive risk factor management