Nephropathy in Type 1 Diabetes: Can One Identity the Patients at Risk ?

Pierre Lefèbvre

University of Liège , Belgium

Cuba, November 2007

Nephropathy in Type 1 Diabetes

- It has been known for years that the risk of nephropathy is not the same for all patients with Type 1 diabetes
- Are they favouring or protective factors ?
- Our Group has addressed this question in three studies that will be briefly reviewed.

Nephropathy in Type 1 Diabetes

- *Factors predictive of nephropathy in DCCT Type 1 diabetic patients with good or poor metabolic control* (Zhang *et al :Diabet.Med.2003,20:580-585*)
- *Different patterns of insulin resistance in relatives of Type 1 diabetic patients with retinopathy or nephropathy* (Hadjaj et al : *Diabetes Care, 2004,27: 27:2661-2668*)*
- *Diabetic nephropathy development is conditioned by the Glu298Asp polymorphism of endothelial nitric oxide synthase gene(NOS3): additive effects with angiotensin-converting enzyme gene(ACE) I/D polymorphism* (Weekers et al: 2007, submitted)*

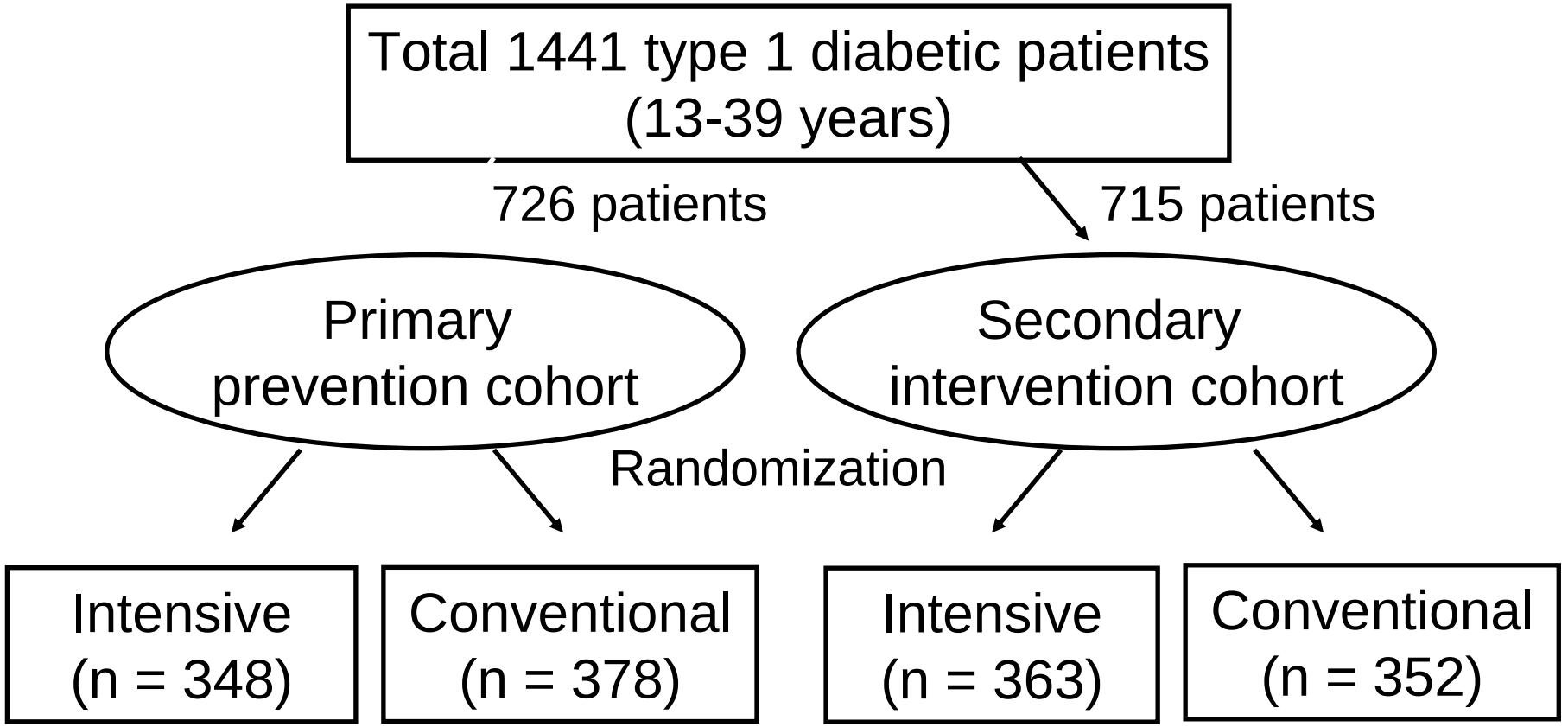
*Collaboration with the Group of M.Marre in Paris

Factors predictive of nephropathy in DCCT Type 1 patients

Zhang, Krzentowski,Albert and Lefèbvre,Diabetic Medicine 2003

The DCCT Study

- Design in the full-scale clinical trial:

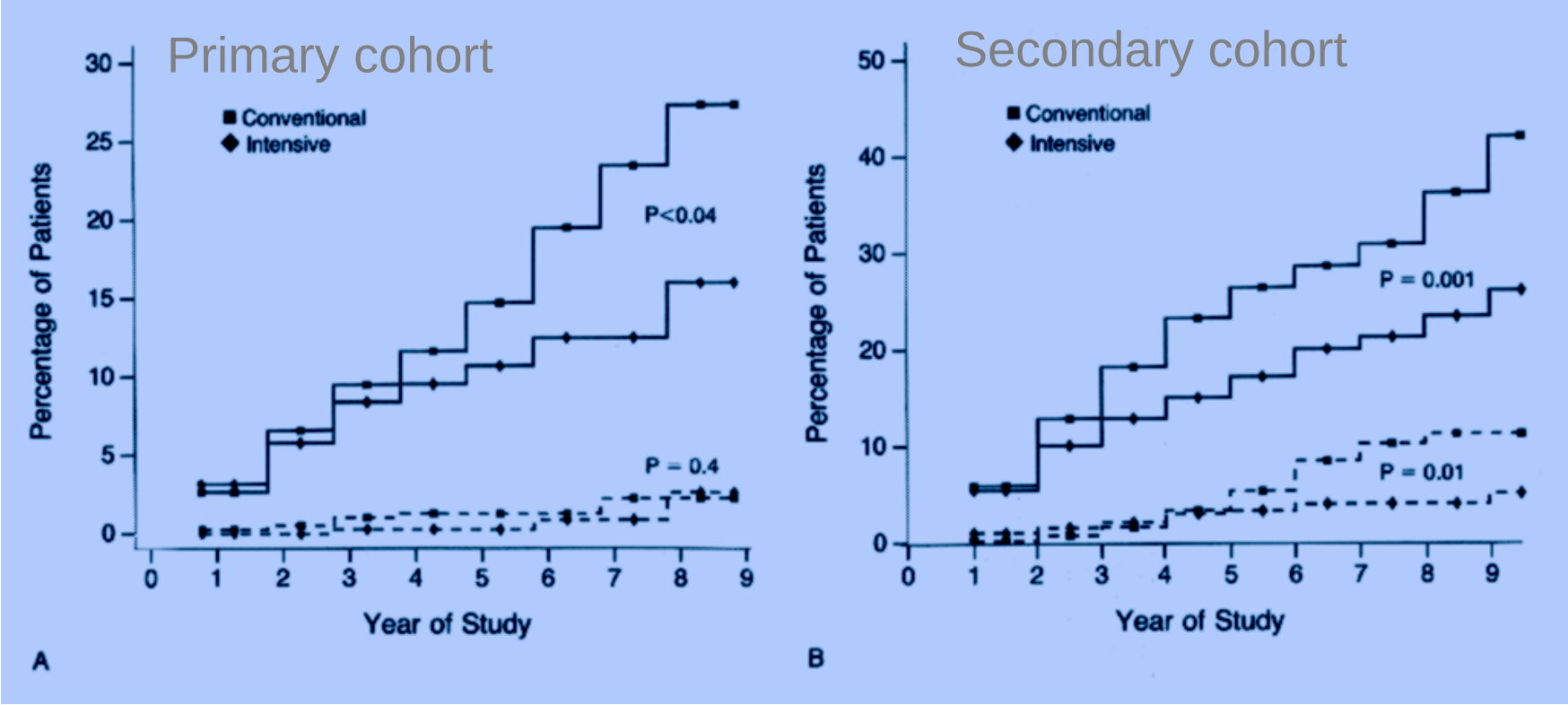


Intensive: CSII (continuous subcutaneous insulin infusion) or multiple daily injections of insulin

Conventional: up to 2 daily injections of insulin.

Metabolic Control and Complications

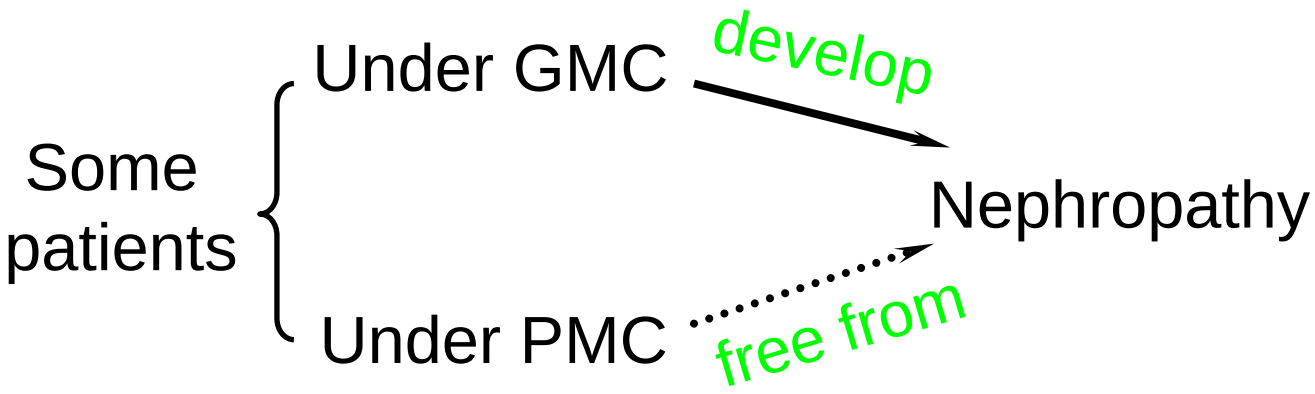
- Diabetes Control and Complications Trial (DCCT, 1983-1989)



Microalbuminuria (solid lines) and albuminuria (dotted lines)

Aims of the Work

- Questions:



- Aims:

  To assess the risk of a given patient developing diabetic nephropathy despite good metabolic control (GMC) or the chance of escaping nephropathy despite poor metabolic control (PMC)

A great example of Democracy in Science

DCCT Database made available by
the US National Technical Information
Service of the Dpt. of Commerce

The DCCT Study

- Risk covariates at baseline:
  - Quantitative variables

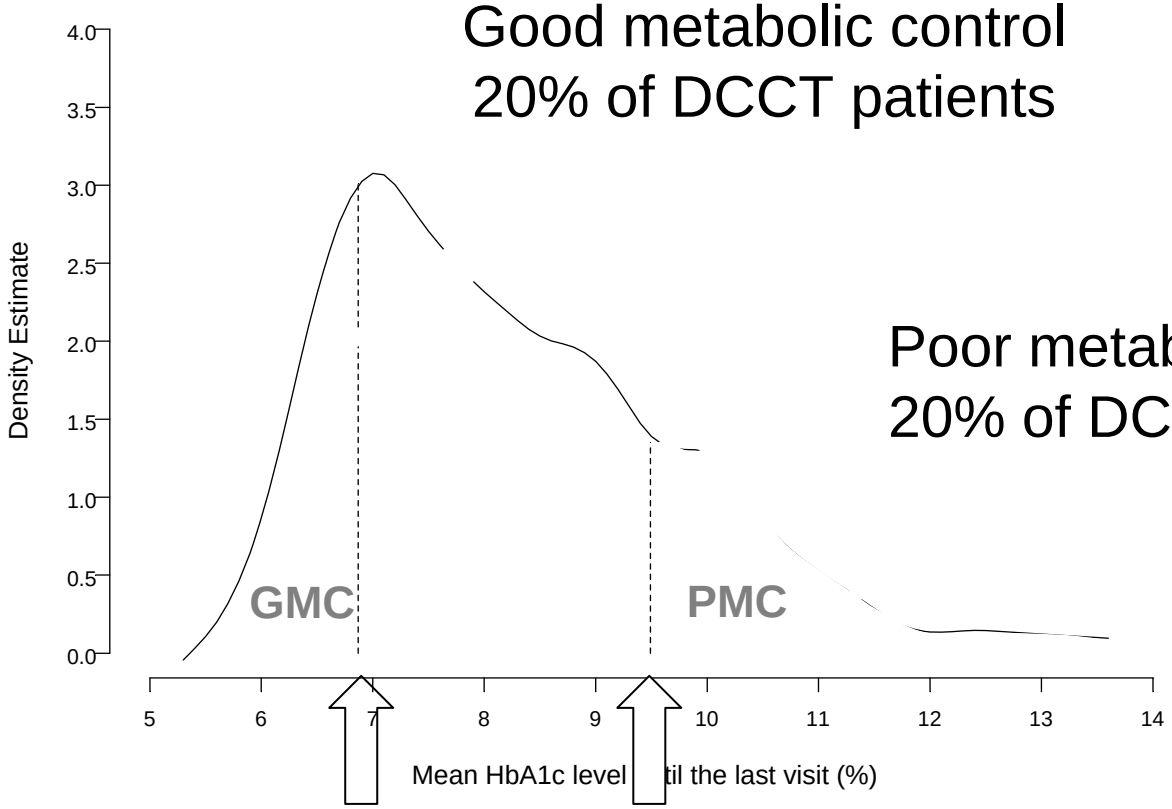
    Age at entry (year)
    BMI (kg/m^2)
    Duration of diabetes (months)
    HbA_{1c} at baseline (%)
    AER (mg/24h)
    Stimulated C-peptide (pmol/ml)
    Mean blood glucose (mg/dl)
    Arterial blood pressure (mmHg)
    …….
  - Categorical variables

    Gender
    Adulthood
    Family history
    Marital status
    Smoking status
    …….
- Time-related variables (HbA1c, AER, …..)

Definition of GMC or PMC

All DCCT patients irrespective of treatment

Good metabolic control
20% of DCCT patients



Poor metabolic control
20% of DCCT patients

HbA1c level: 6.9% 9.5%

Diabetic Nephropathy

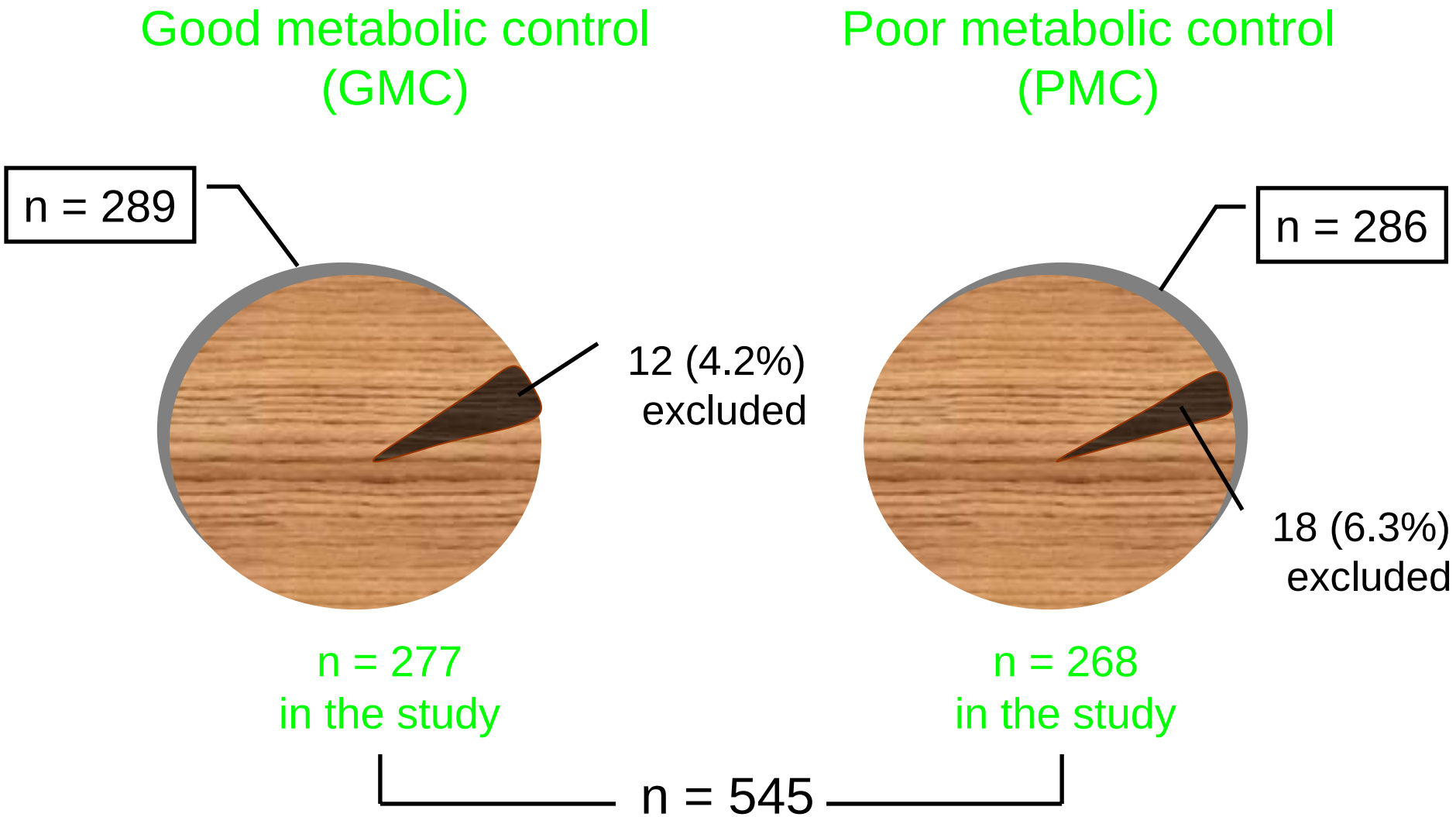
- Aims: To assess the risk of developing nephropathy in patients maintained for several years under GMC or PMC

- Patients: DCCT primary and secondary cohort under GMC or PMC but without nephropathy at baseline (n = 545)

- Definition: An observed urinary albumin excretion rate (AER) $\geq$ 40 mg/24h (measured annually)

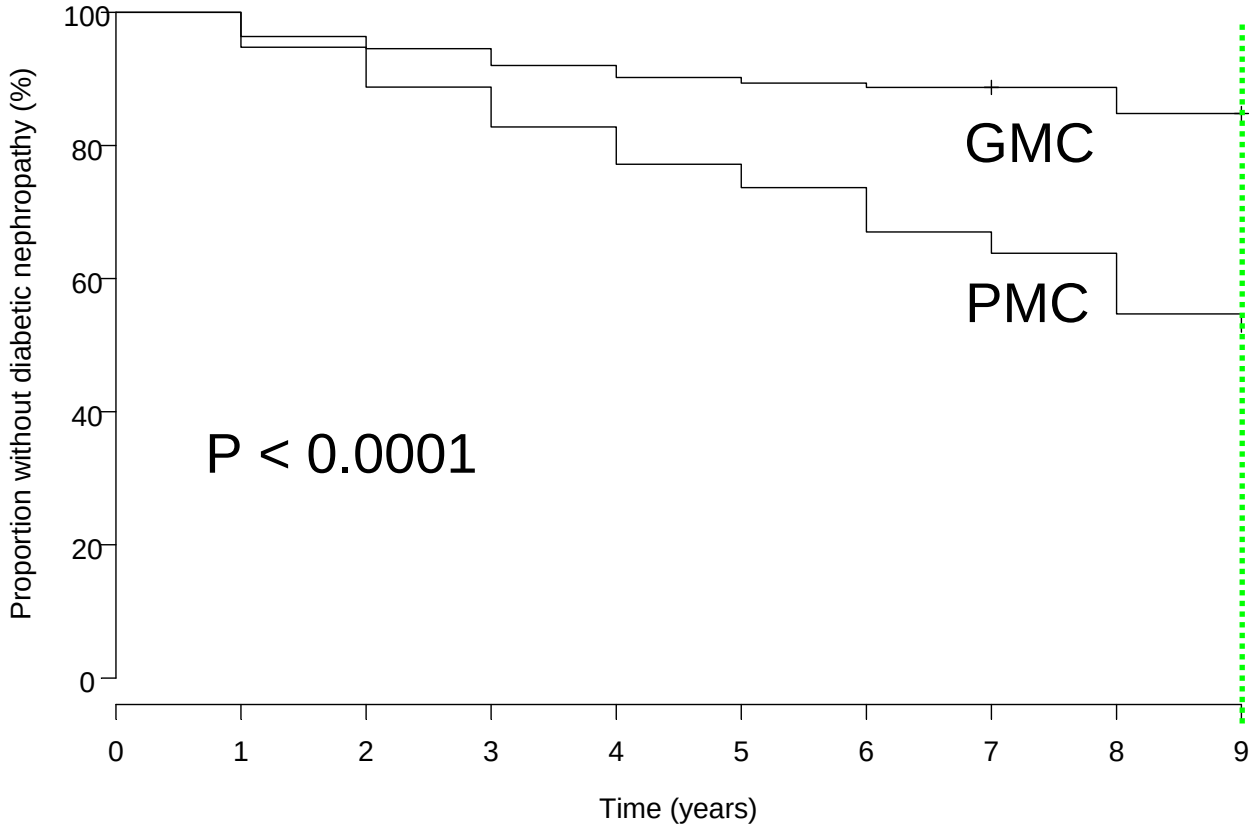
Diabetic Nephropathy

- The database



Diabetic Nephropathy

- The effect of MC confirmed by Kaplan-Meier curve:



After 9 years: 15% developed nephropathy in GMC

52% did not develop nephropathy in PMC

Diabetic Nephropathy

- Factors predictive of nephropathy in backward stepwise Cox PH regression when adjusted for MC:

Variable	Coef (± SE)	P	Risk ratio (95% CI)
Single effects			
Age (years)	–0.094 (± 0.016)	< 0.0001	0.91 (0.88-0.94)
AER (mg/24h) ↑	0.54 (± 0.15)	0.0004	1.72 (1.27-2.31)
Duration of diabetes (months) ↑	0.41 (± 0.12)	0.0011	1.50 (1.18-1.91)
BMI (kg/m^2) ↓	–0.10 (± 0.034)	0.0025	0.90 (0.84-0.96)
Gender (0 = male; 1 = female)	0.73 (± 0.35)	0.0389	2.07 (1.04-4.11)
Interaction effects			
Age × MC ←	0.064 (± 0.013)	< 0.0001	1.07 (1.04-1.09)
Gender × MC ←	–1.05 (± 0.40)	0.0091	0.35 (0.16-0.77)

The interaction terms: the major role of MC
the differential effects of age and gender.

Diabetic Nephropathy

- A risk ratio $\lambda = \exp(R)$:

$$R = 0.54 \times \log(AER) + 0.405 \times \log(\text{Disease duration}) - 0.103 \times BMI - 0.0943 \times Age + 0.0635 \times Age \times MC + 0.725 \times Gender - 1.05 \times Gender \times MC$$

GMC (MC = 0)

$$R = 0.54 \times \log(AER) + 0.405 \times \log(\text{Disease duration}) - 0.103 \times BMI - 0.0943 \times Age + 0.725 \times Gender^{*}$$

Under GMC

The risk of developing nephropathy is higher in women (risk ratio = 2.1) and decreases with age (risk ratio = 0.91).

1= female; 0= male *

Diabetic Nephropathy

- A risk ratio $\lambda = \exp(R)$:

$$R = 0.54 \times \log(AER) + 0.405 \times \log(\text{Disease duration}) - 0.103 \times BMI - 0.0943 \times Age + 0.0635 \times Age \times MC + 0.725 \times Gender - 1.05 \times Gender \times MC$$

PMC (MC = 1)

$$R = 0.54 \times \log(AER) + 0.405 \times \log(\text{disease duration}) - 0.103 \times BMI - 0.0308 \times Age - 0.325 \times Gender^{*}$$

* 1 = female; 0= male. Risk ratio: 0.97 for age and 0.72 for gender

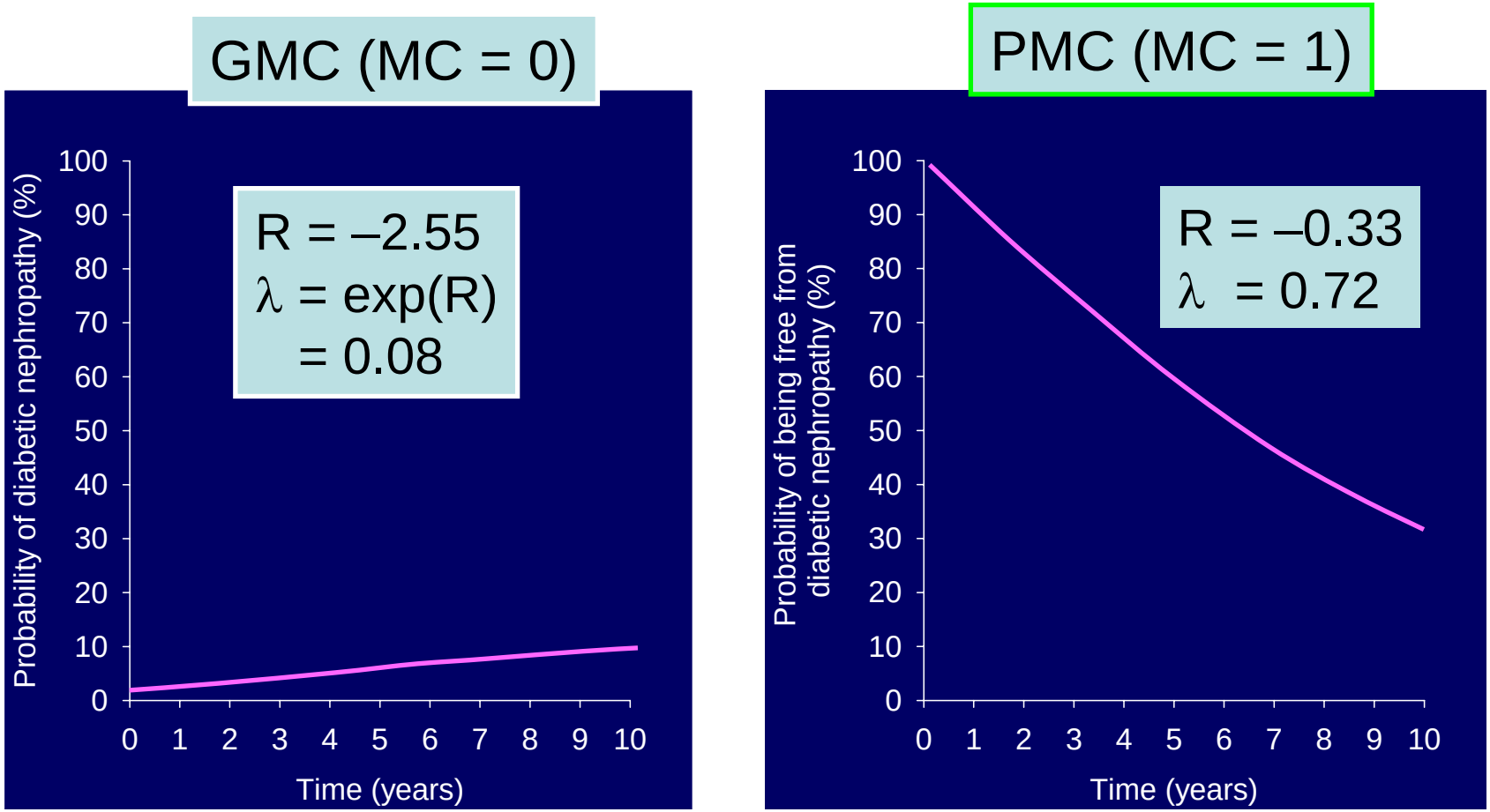
<u>Under PMC</u>

Male patients are more at risk of developing nephropathy than female patients.

Diabetic Nephropathy

- Example:

  Man 1, 35 years old, disease duration: 60 months
  BMI: 23 kg/m^2, AER: 15 mg/24h.



Conclusions (1)

- In patients with good metabolic control (HbA1c<or = 6.5% for 9 years), diabetic nephropathy occured in 15% of the patients
- Despite poor metabolic control (HbA1c= or > 9.5% for 9 years) , diabetic nephropathy did not develop in 52% of the patients

Conclusions (2)

- Regardless of metabolic control, the risk of diabetic nephropathy is increased with:

  -higher AER (within the «normal range»)at baseline

  -longer duration of diabetes

  -lower BMI

Conclusions (3)

- Under good metabolic control, the risk of diabetic nephropathy seems higher in women than in men and decreases with age
- Under poor metabolic control, the effect of age vanishes and the risk of diabetic nephropathy seems higher in men …

Take-home message 1

- It is confirmed that Type 1 diabetic patients with good MC may develop diabetic nephropathy and that those with poor MC may escape the condition
- Higher AER , within the « normal range » already indicate early DR
- Risk of DN is higher at younger age and lower BMI
- The effect of gender is ambiguous

Different patterns of insulin resistance in relatives of Type 1 diabetic patients with retinopathy or nephropathy

Hadjaj, Péan, Gallois, Passa, Aubert, Weekers, Rigalleau, Bauduceau, Bekherraz, Roussel, Dussol, Rodier, Maréchaud, Lefèbvre, and Marre for the GENESIS France-Belgium Study

Diabetes Care 2004

Genesis Franc-Belgium Family Study

- 853 subjects recruitefd
- 578 relatives
- 275 probands: -130 with
  -145 without diabetic nephropathy

Nephropathy stages

- Absent: repeated microalbuminuria < 30mg/24 h
- Incipient: microalbuminuria 30-300mg/24h
- Established: AER > 300mg/24h with creatinine <150µmol/l
- Advanced: increased AER,Creatinine> 150µmol/l or renal replacement

« Insulin resistance score » in first degree relatives

- Composite score taking into consideration:

-History of hypertension

dyslipidemia

Type 2 diabetes

-Body weight*

*Diabetes Care , 2004

Results

- Nephropathy in the probands correlated with:
- Insulin resistance score in first degree relatives ($p<0.04$), particularly in mothers ($p=0.02$)
- Personal history of Type 2 diabetes ($p<0.0001$), obesity ($p<0.0001$) and lipid disorders ($p<0.007$) , but not hypertension, in first degree relatives

Clustering of risk factors in parents of patients with nephropathy and Type 1 diabetes

- Earl et al , 1992: CVD
- De Cosmo et al ,1997: risk factors for CVD
- Tarnow et al , 2000: CVD
- Verhage et al , 1999: Syndrome X
- Lindsey et al, 1999: stroke
- Fagerudd et al , 1999: Type 2 DM
- Thorn et al, 2007: Hypertension , CVD and Type 2 DM

Take-home message 2

The risk of diabetic nephropathy in patients with Type 1 diabetes seems to be increased if one or both parents have experienced:

- Cardiovascular disease
- Type 2 diabetes
- Metabolic Syndrome/Insulin resistance
- Hypertension (?)

Diabetic nephropathy development is conditioned by the Glu298Asp polymorphism of endothelial nitric oxide synthase gene (NOS3): Additive effect with angiotensin-converting enzyme gene (ACE) I/D polymorphism

Weekers, Hadjaj, Guilloteau,Gallois, Pean, Roussel, Antkoche, Tichet, Lefèbvre and Marre on behalf of GENEDIAB and DESIR Study Groups

, 2007 : submitted

A candidate gene study among many others

- Endothelial nitric oxide synthase (eNOS) is a key regulator of renal hemodynamics. Is there an association with DN and two polymorphisms of the eNOS gene (NOS3)?
- Angiotensin-converting enzyme (ACE) insertion/deletion polymorphism is a risk factor for DN, the ACEII genotype conferring the lowest risk .
- Is there a combined effect of these 2 polymorphisms ?

Diabetologia (2005) 48: 1008–1016
DOI 10.1007/s00125-005-1726-2

ARTICLE

D. P. K. Ng · B. C. Tai · D. Koh · K. W. Tan · K. S. Chia

Angiotensin-I converting enzyme insertion/deletion polymorphism and its association with diabetic nephropathy: a meta-analysis of studies reported between 1994 and 2004 and comprising 14,727 subjects

Review of the results of 47 studies in 14,727 subjects
Risk of DN is 22% lower in subjects with II Genotype than Carriers of the D-allele.
The association is more marked (-35%) in diabetic Asians (Chinese, Japanese, Koreans)

Prospective study

- 297 Type 1 diabetic patients followed at the Angers (France) diabetes clinic for 7 years
- Primary outcome : diabetic nephropathy (see Study 2)

Results

- eNOS: exon 7 polymorphism (Asp/Asp patients versus Glu allele carriers) was associated with a lower risk of DN progression :HR 0.32, 95% CI 0.11-0.96
- ACE: II genotype was also associated with a lower risk of DN progression: HR 0.27, 95% CI 0.08-0.86
- The lowest risk was associated with the combination of ACE II and NOS3 Asp/Asp genotypes

43rd EASD Annual Meeting
Amsterdam
17-21 September 2007

OP 11 Nephropathy: mechanisms

0061

EURAGEDIC study: identification of new candidate genes for diabetic nephropathy

N. Hager-Vionnet[1,2], D. A. Trégouët[1,2], L. Tarnow[3], H.-H. Parving[3], P.-H. Groop[4,5], C. Forsblom[4,5], S. Hadjadj[6,7], M. Marre[8,9], I. Gut[10], R. Cox[11], D. Gauguier[12], G. Kazeem[12], M. Farrall[12], F. Cambien[1,2], M. Lathrop[10];

[1]UMR S 525, INSERM, Paris, France, [2]Umr s 525, Université Pierre et Marie Curie-Paris6, France, [3]Steno Diabetes Centre, Copenhagen, Denmark, [4]Department of Medicine, Helsinki University Central Hospital, Finland, [5]Biomedicum, Folkhälsan Institute of Genetics, Helsinki, Finland, [6]Diabetology department, Poitiers Hospital, France, [7]Erm 324, INSERM, Poitiers, France, [8]Department of Diabetology, Bichat Hospital, Paris, France, [9]U695, INSERM, Paris, France, [10]CNG, CNRG, Evry, France, [11]MRC Mammalian Unit, Mammalian Research Council, Didcot, United Kingdom, [12]Wellcome Trust Centre for Human Genetics, University of Oxford, United Kingdom.

New candidates: PARP1 (glucose-induced apoptosis)
SLC12A3 and EDN1(renal Na excretion and systemic blood pressure)

Original Article

Genome-Wide Scans for Diabetic Nephropathy and Albuminuria in Multiethnic Populations

The Family Investigation of Nephropathy and Diabetes (FIND)

Sudha K. Iyengar,[1] Hanna E. Abboud,[2] Katrina A.B. Goddard,[1] Mohammed F. Saad,[3] Sharon G. Adler,[4] Nedal H. Arar,[2] Donald W. Bowden,[5] Ravi Duggirala,[2] Robert C. Elston,[1] Robert L. Hanson,[6] Eli Ipp,[4] W.H. Linda Kao,[7] Paul L. Kimmel,[8] Michael J. Klag,[7] William C. Knowler,[6] Lucy A. Meoni,[7] Robert G. Nelson,[6] Susanne B. Nicholas,[3] Madeleine V. Pahl,[3] Rulan S. Parekh,[7] Shannon R.E. Quade,[1] Stephen S. Rich,[5] Jerome I. Rotter,[3] Marina Scavini,[9] Jeffrey R. Schelling,[10] John R. Sedor,[10] Ashwini R. Sehgal,[10] Vallabh O. Shah,[9] Michael W. Smith,[11] Kent D. Taylor,[3] Cheryl A. Winkler,[11] Philip G. Zager,[9] Barry I. Freedman,[5] on behalf of the Family Investigation of Nephropathy and Diabetes Research Group*

Diabetes , 2007, 56 : 1577-1585

Take-home message 3

- Potential candidate genes underlying susceptibility to, or protection from, diabetic nephropathy have been indentified
- Large genome scan investigations are in progress to map genes involved in multiethnic populations

Diabetic Nephropathy

- Conclusions:
  - Under GMC, nephropathy develop in patients with specific baseline pattern. By contrast, patients with PMC can remain free from the complication for a long time period.
  - Major role of MC on time to nephropathy
  - Baseline risk factors: AER, age, gender, BMI and duration of diabetes.Diabetic nephropathy may already be present at AER < 40mg/24 hours

- The effect of age: younger patients are associated with nephropathy.

  - The effect of gender: under GMC, women tend to develop nephropathy more often but appear to be better protected under PMC.