Paris, le 25 novembre 2008

11e Rencontres des Amicales des Médecins de Paris

Antihypertenseurs et Rétinopathie Diabétique

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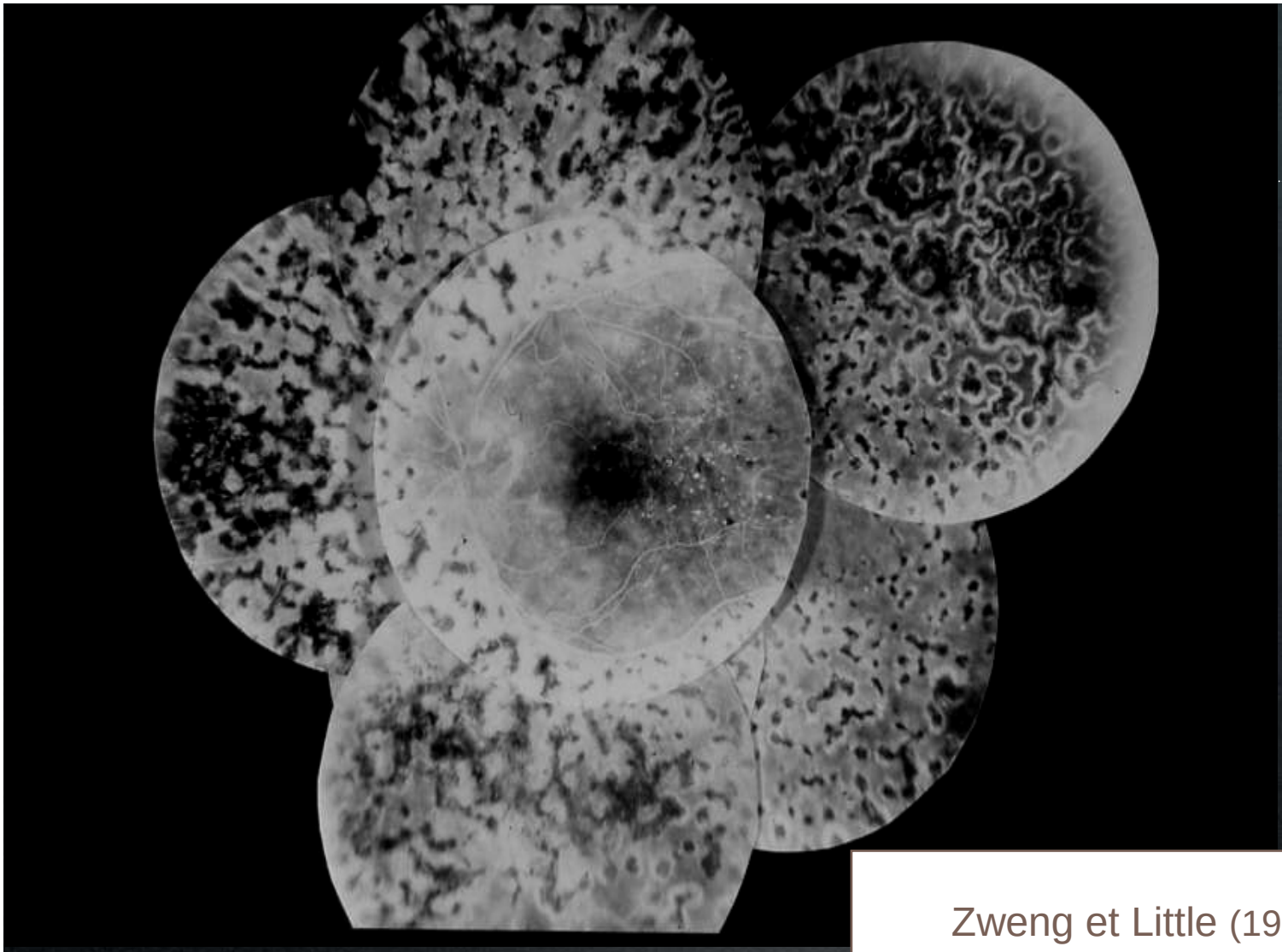
Epidémiologie et FDR de la RD

- La rétinopathie diabétique (RD) est une affection fréquente et potentiellement grave
  - Prévalence : 30 à 40% des diabétiques (800 000 personnes)
  - Responsable de 500 à 1000 nouveaux cas de cécité par an
  - Première cause de cécité et de malvoyance dans la population active (avant 60 ans)

- Les 3 FDR les plus importants de la RD, dans l'ordre :
  - Ancienneté du diabète
  - Control glycémique
  - Pression artérielle

1. *Klein R, et al. Ophthalmology 1998; **105**: 1801–1815.*
2. *Manaviat MR, et al. BMC Ophthalmology 2004; **4**: 9.*
3. *Varma R, et al. Ophthalmology 2007;114:1332-40.*



Zweng et Little (1965):

la destruction de la rétine périphérique ischémique doit faire disparaître les néovaisseaux prérétiniens

= photocoagulation panrétinienne (PPR)

L'Etude DIRECT – Rétinopathie

Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials

Nish Chaturvedi, Massimo Porta, Ronald Klein, Trevor Orchard, John Fuller, Hans Henrik Parving, Rudy Bilous, Anne Katrin Sjølie, for the DIRECT Programme Study Group*

Summary

Background Results of previous studies suggest that renin-angiotensin system blockers might reduce the burden of diabetic retinopathy. We therefore designed the DIabetic REtinopathy Candesartan Trials (DIRECT) Programme to assess whether candesartan could reduce the incidence and progression of retinopathy in type 1 diabetes.

Methods Two randomised, double-blind, parallel-design, placebo-controlled trials were done in 309 centres worldwide. Participants with normotensive, normoalbuminuric type 1 diabetes without retinopathy were recruited to the DIRECT-Prevent 1 trial and those with existing retinopathy were recruited to DIRECT-Protect 1, and were assigned to candesartan 16 mg once a day or matching placebo. After 1 month, the dose was doubled to 32 mg. Investigators and participants were unaware of the treatment allocation status. The primary endpoints were incidence and progression of retinopathy and were defined as at least a two-step and at least a three-step increase on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, respectively. These trials are registered with ClinicalTrials.gov, numbers NCT00252733 for DIRECT-Prevent 1 and NCT00252720 for DIRECT-Protect 1.

Findings 1421 participants (aged 18–50 years) were randomly assigned to candesartan (n=711) or to placebo (n=710) in DIRECT-Prevent 1, and 1905 (aged 18–55 years) to candesartan (n=951) or to placebo (n=954) in DIRECT-Protect 1. Incidence of retinopathy was seen in 178 (25%) participants in the candesartan group versus 217 (31%) in the placebo group. Progression of retinopathy occurred in 127 (13%) participants in the candesartan group versus 124 (13%) in the placebo group. Hazard ratio (HR for candesartan *vs* placebo) was 0·82 (95% CI 0·67–1·00, p=0·0508) for incidence of retinopathy and 1·02 (0·80–1·31, p=0·85) for progression of retinopathy. The post-hoc outcome of at least a three-step increase for incidence yielded an HR of 0·65 (0·48–0·87, p=0·0034), which was attenuated but still significant after adjustment for baseline characteristics (0·71, 0·53–0·95, p=0·046). Final ETDRS level was more likely to have improved with candesartan treatment in both DIRECT-Prevent 1 (odds 1·16, 95% CI 1·05–1·30, p=0·0048) and DIRECT-Protect 1 (1·12, 95% CI 1·01–1·25, p=0·0264). Adverse events did not differ between the treatment groups.

Interpretation Although candesartan reduces the incidence of retinopathy, we did not see a beneficial effect on retinopathy progression.

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Introduction

Loss of vision due to retinopathy remains one of the most feared complications in people with diabetes.[1] Intense glycaemic control is the only proven intervention to reduce both incidence and progression of retinopathy in diabetes.[2] However, optimised glycaemic control is not easy to achieve[3,4] and, even when it is achieved, cannot completely abolish risks of retinopathy.[4,5]

The findings of the EUrodiab Controlled trial of Lisinopril in Insulin-dependent Diabetes (EUCLID)[6] suggested that blockade of the renin-angiotensin system, with the angiotensin-converting enzyme inhibitor lisinopril, could reduce both incidence and progression of retinopathy in type 1 diabetes. However, since EUCLID[6] was not primarily designed to study retinopathy, we sought to confirm and extend these findings definitively in a new series of clinical trials in the DIabetic REtinopathy Candesartan Trials (DIRECT) Programme.

In this programme, consisting of three separate randomised, double-blind, placebo-controlled clinical trials, we assessed whether the angiotensin-receptor antagonist candesartan could reduce incidence of retinopathy in type 1 diabetes (DIRECT-Prevent 1); progression of retinopathy in type 1 diabetes (DIRECT-Protect 1); and progression of retinopathy in type 2 diabetes (DIRECT-Protect 2).

In this paper, we report the findings of the first two trials (DIRECT-Prevent 1 and DIRECT-Protect 1).

Methods

Participants

Detailed methods and baseline data have already been published.[7,8] We enrolled men and women with type 1 diabetes (age at diagnosis <36 years, with continuous insulin use within 1 year of diagnosis) who were both normoalbuminuric (at least one of two overnight urinary

Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial

Anne Katrin Sjølie, Ronald Klein, Massimo Porta, Trevor Orchard, John Fuller, Hans Henrik Parving, Rudy Bilous, Nish Chaturvedi, for the DIRECT Programme Study Group*

Summary

Background Diabetic retinopathy remains a leading cause of visual loss in people of working age. We examined whether candesartan treatment could slow the progression and, secondly, induce regression of retinopathy in people with type 2 diabetes.

Methods We did a randomised, double-blind, parallel-group, placebo-controlled trial in 309 centres worldwide. We recruited normoalbuminuric, normotensive, or treated hypertensive people with type 2 diabetes with mild to moderately severe retinopathy and assigned them to candesartan 16 mg once a day or placebo. After a month, the dose was doubled to 32 mg once per day. Investigators and patients were unaware of the treatment allocation status. Progression of retinopathy was the primary endpoint, and regression was a secondary endpoint. Analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00252694.

Findings 1905 participants (aged 37–75 years) were randomised to candesartan (n=951) or placebo (n=954). 161 (17%) patients in the candesartan group and 182 (19%) in the placebo group had progression of retinopathy by three steps or more on the Early Treatment Diabetic Retinopathy Study scale. The risk of progression of retinopathy was non-significantly reduced by 13% in patients on candesartan compared with those on placebo (hazard ratio [HR] 0·87, 95% CI 0·70–1·08, p=0·20). Regression on active treatment was increased by 34% (1·34, 1·08–1·68, p=0·009). HRs were not attenuated by adjustment for baseline risk factors or changes in blood pressure during the trial. An overall change towards less severe retinopathy by the end of the trial was observed in the candesartan group (odds 1·17, 95% CI 1·05–1·30, p=0·003). Adverse events did not differ between the treatment groups.

Interpretation Treatment with candesartan in type 2 diabetic patients with mild to moderate retinopathy might induce improvement of retinopathy.

Funding AstraZeneca and Takeda.

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Introduction

Diabetic eye disease, including retinopathy with macular oedema, remains the leading cause of blindness in people of working age.[1,2] At diagnosis, nearly 40% of people with type 2 diabetes already have some degree of retinopathy; another 22% will develop it over 6 years.[3]

Strict glycaemic control and control of blood pressure in those with hypertension substantially reduce the progression of diabetic eye disease.[4–6] Lowering blood pressure, can also be of benefit, even in normotensive patients,[6] although retinopathy has not been tested as a primary outcome. Optimal control of blood glucose and blood pressure, however, is not achievable in all patients with type 2 diabetes[7,8] and, even when obtained, is not always effective.[9] Laser photocoagulation can reduce the risk of blindness from proliferative retinopathy,[10] but is less effective for treatment of diffuse macular oedema,[11] and has side-effects.[12]

The specific role of blockade of the renin–angiotensin system has not been studied in retinopathy in type 2 diabetes, whereas it has been shown to reduce risks for nephropathy and cardiovascular disease.[13–15] Angiotensin receptor blockers are now recommended for people with type 2 diabetes with microalbuminuria or macroalbuminuria,[16] and might prevent development of microalbuminuria in hypertensive patients with type 2 diabetes.[17] We designed three separate randomised, double-blind, placebo-controlled clinical trials to assess whether the angiotensin receptor blocker candesartan could reduce the incidence of retinopathy in type 1 diabetes (DIabetic REtinopathy Candesartan Trials [DIRECT]-Prevent 1); progression of retinopathy in type 1 diabetes (DIRECT-Protect 1); and progression of retinopathy in type 2 diabetes (DIRECT-Protect 2). In this paper, we report the findings of the third trial.

Methods

Participants

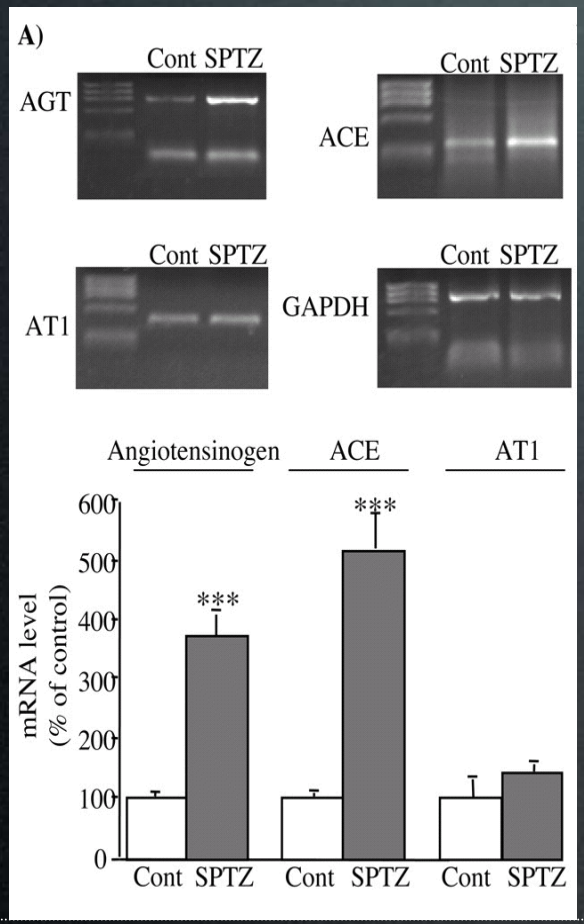
The study design and baseline data have previously been described in detail.[18,19] We screened men and women who were aged 37–75 years and had known type 2 diabetes for between 1 and 20 years in 309 centres worldwide. Inclusion criteria were age at onset of 36 years or older, and no need for continuous insulin treatment within a

Système Rénine Angiotensine et Rétinopathie Diabétique

SRA et rétinopathie diabétique

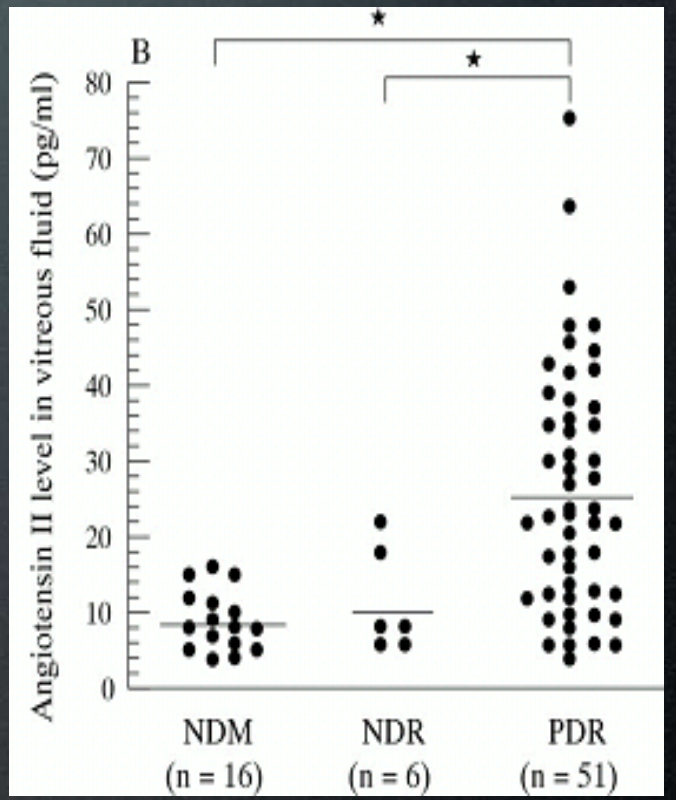
- Tous les éléments du SRA sont présents dans la rétine (rat) [1]
- Le SRA rétinien est activé au cours du diabète :

Mice



Ebrahimian TG, et al. Arterioscler Thromb Vasc Biol 2005; 25: 65-70

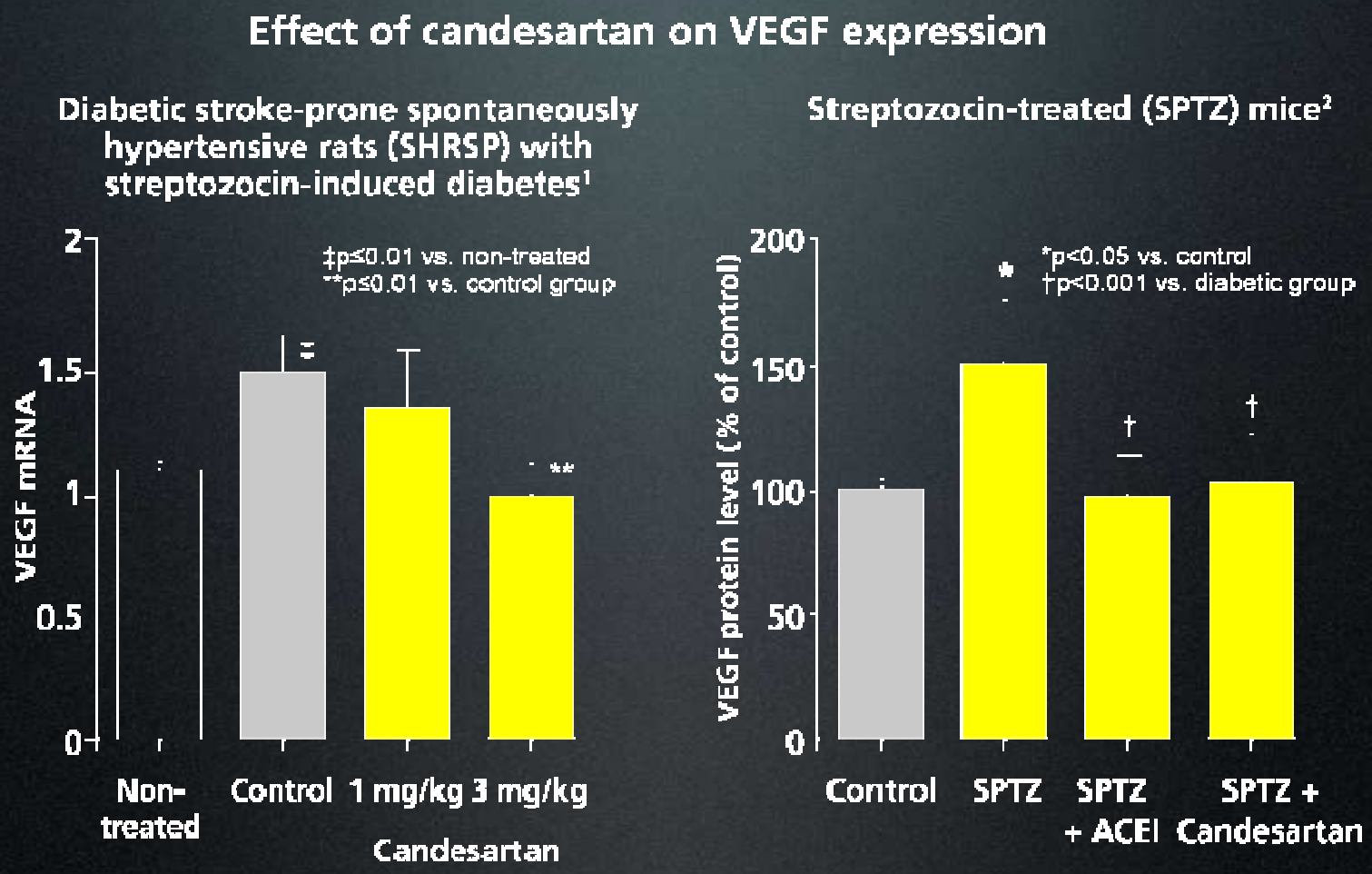
Human



Funatsu et al. Brit J Ophthalmol 2002; 86, 311–315

*1.Sarlos S, et al. Inv Ophth Vis Sci 2005; **46**:1069–1077.*

Effets du blocage du SRA



1. Nagisa Y, et al. Diabetologia 2001; **43**: 883–888.
2. Ebrahimian TG, et al. Arterioscler Thromb Vasc Biol 2005; **25**: 65–70.

L'Etude EUCLID

- Patients ayant un diabète de type 1, considérés comme normotendus (<155-90 mmHg), sans albuminurie ou microalbuminurie
- Lisinopril (10mg) *vs* placebo durant 2 ans

- Lisinopril a réduit
  - Le risque de progression de la RD de 50 % (p=0,02)
  - La progression vers une RD proliférante de 20 % (p=0,03)

- Mais chiffres pressionnels plus faibles dans le groupe traité par lisinopril…
- La rétinopathie était un critère d'évaluation secondaire

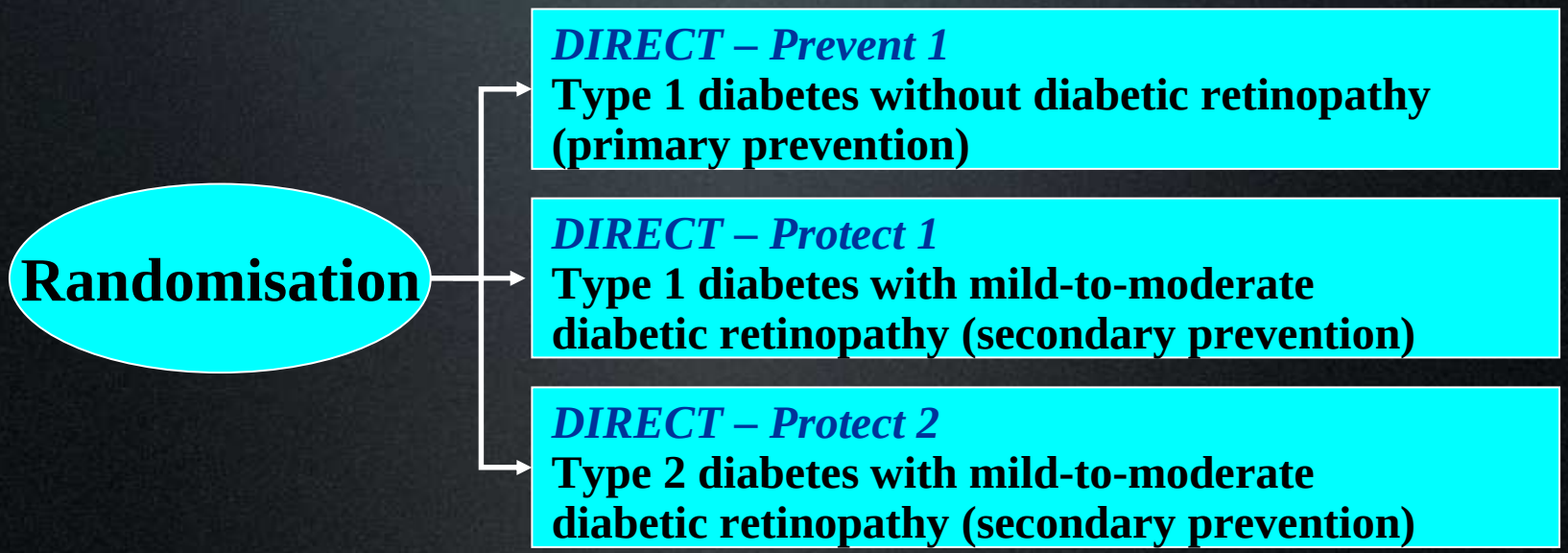
Chatuverdi N et al. Lancet 1998, 351: 28-31

L'Etude DIRECT

DIRECT

- DIabetic REtinopathy Candesartan Trial

5231 patients diabétiques de type 1 or type 2 inclus dans 309 centres dans le monde et suivis durant 4 ans.

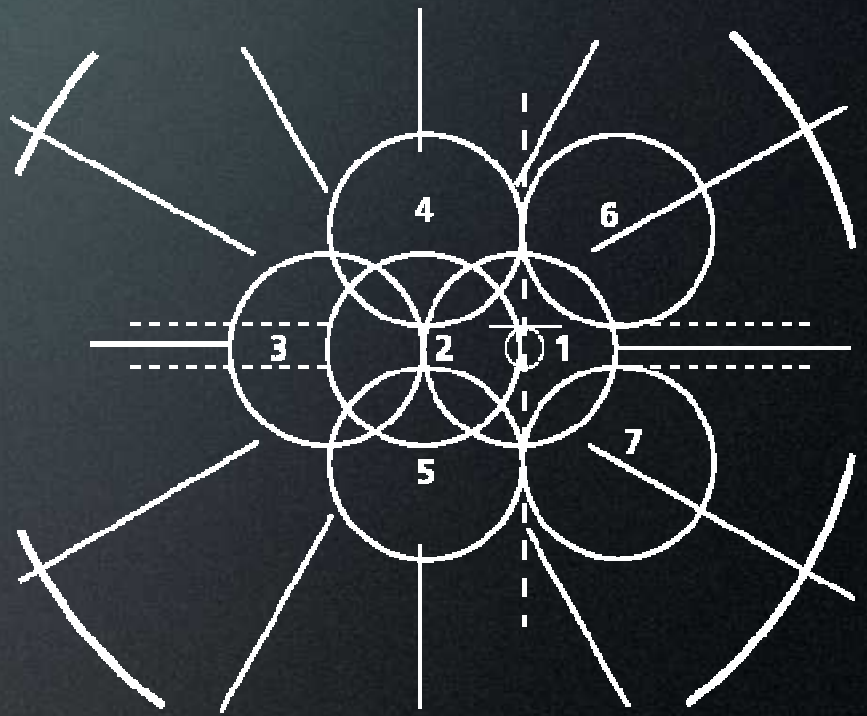


Co financement par les Laboratoires Takeda et AstraZeneca

DIRECT Programme Study Group. *J Renin Angiotensin Aldosterone Syst* 2002; **3**: 255–261.

The ETDRS scale

- Based on Airlie House classification of diabetic retinopathy[1]
- Extended for use in the Early Treatment Diabetic Retinopathy Study (ETDRS)[2]
- Uses fundus photographs of seven overlapping standard fields[2,3]
- Features graded in the photographic fields (excluding the macula)



1. Wilkinson CP, *et al*. *Ophthalmology* 2003; **110**(9): 1677–1682.
2. ETDRS Research Group. *Ophthalmology* 1991; **98**: 786–806.
3. Royal College of Ophthalmology, 2005.

The ETDRS scale

The overall grading score for all of the features is matched with severity of retinopathy using the table below:

ETDRS score	Severity of retinopathy
10	None
20	Microaneurysms only
35	Mild NPDR
43	Moderate NPDR
47	Moderately severe NPDR
53A–D	Severe NPDR
53E	Very severe NPDR
61 65	Mild PDR Moderate PDR
71, 75 81, 85	High-risk PDR Advanced PDR

NPDR: non-proliferative diabetic retinopathy
PDR: proliferative diabetic retinopathy

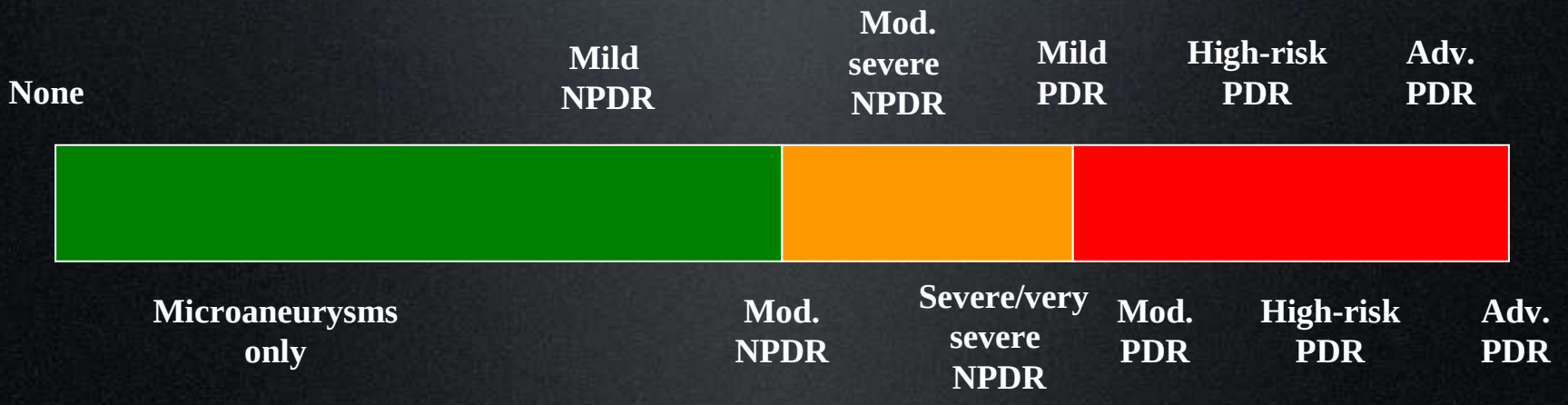
Royal College of Ophthalmology, 2005.

Clinically meaningful measures of disease progression

Reanalyses of the epidemiological data from the WESDR :

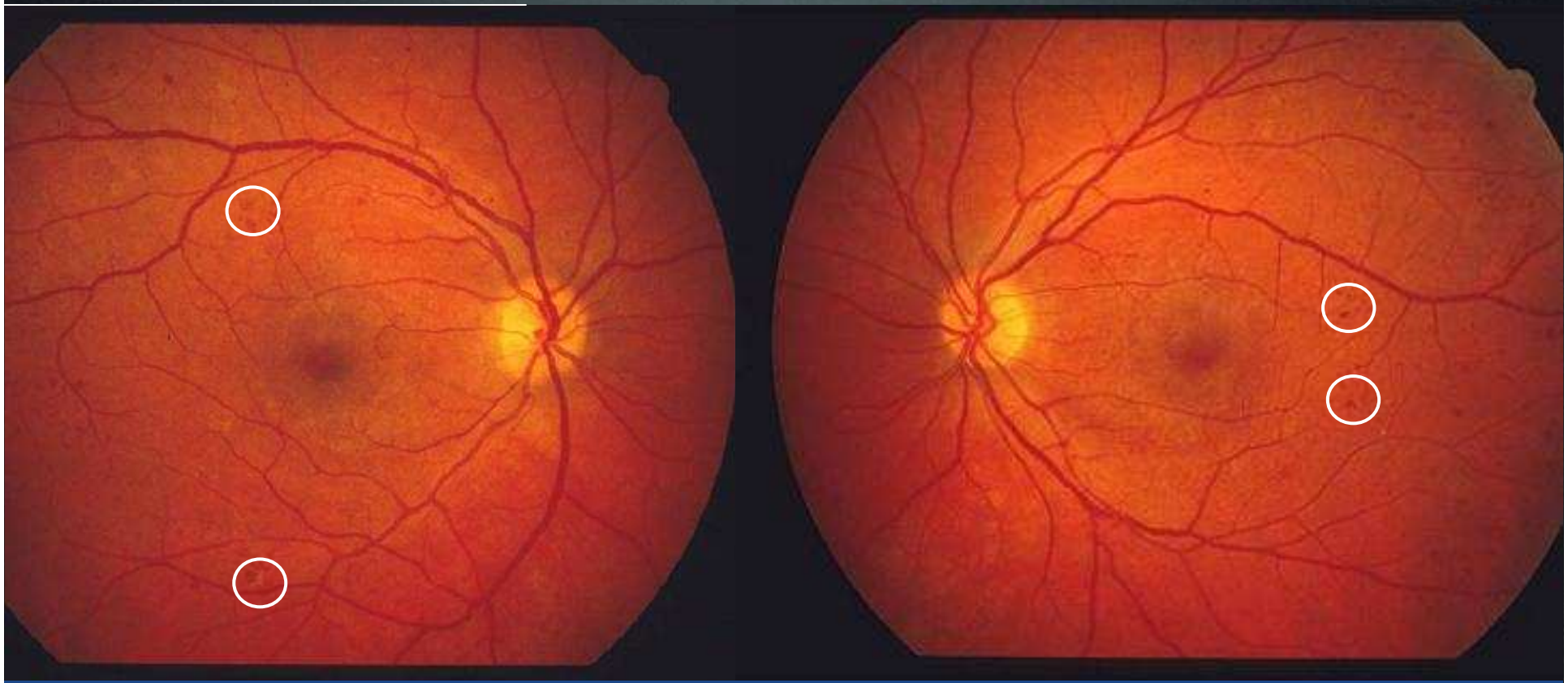
- A 2-step change in diabetic retinopathy severity is predictive of the development of proliferative diabetic retinopathy or clinically significant macular oedema over a 10-year period[1]
- A 2-step change has equivalent predictive power to a three-step change[2]

"Regulatory authorities consider a two- or three-step change in the ETDRS scale as an acceptable surrogate endpoint for blindness" [3]



1. Klein R, *et al*. *Arch Ophthalmol* 2001; **119**(4): 547–553.
2. DIRECT Programme Study Group. *J Renin Angiotensin Aldosterone Syst* 2002; **3**: 255–261.
3. DIRECT Programme Study Group. *J Renin Angiotensin Aldosterone Syst* 2005; **6**: 26–32.

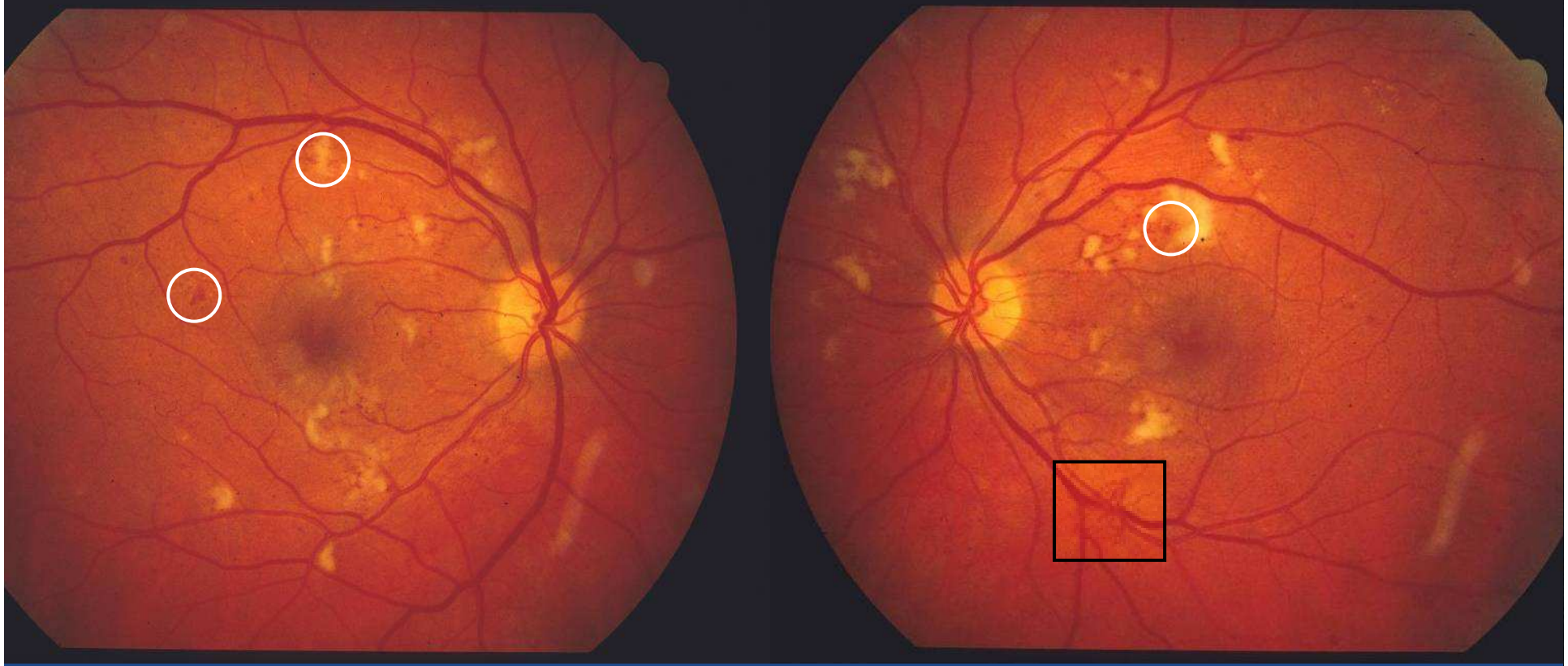
Level 20 / 20 - microaneurysms only



Right eye **Left eye**

3-step change

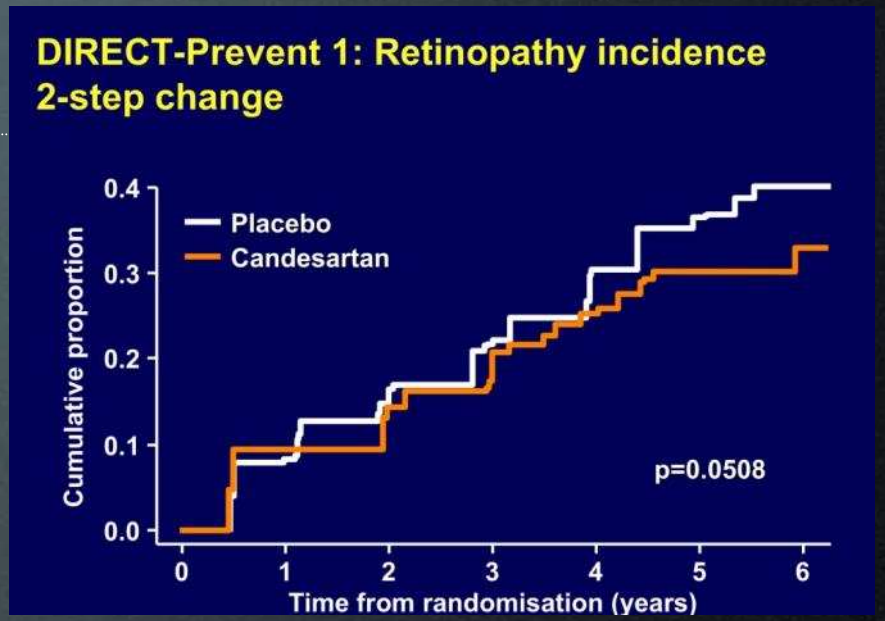
Level 35 **Level 43**

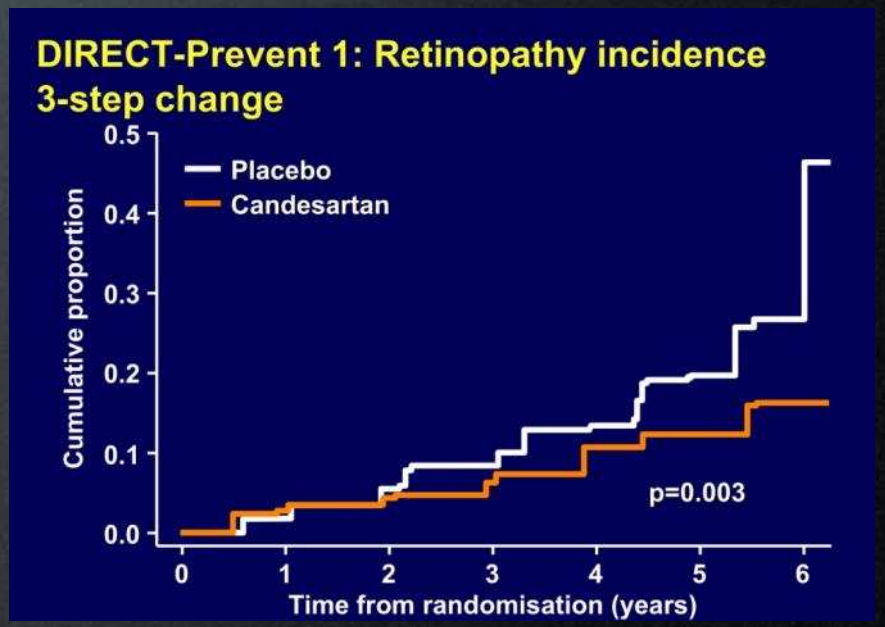


Right eye **Left eye**

DIRECT-PREVENT 1 :

- **Réduction de l'incidence de la rétinopathie :**
  - HR : 0.82 (0.67-1.00), P=0.0508 (changement de 2 stades)
  - HR : 0.65 (0.48-0.87), P=0.003 (changement de 3 stades, analyse post-hoc)
  - Les résultats restent qualitativement inchangés après ajustement





HR: Hazard Ratio

Progression de la RD (changement de 3 stades)

- Pas d'effet significatif sur la progression de la rétinopathie

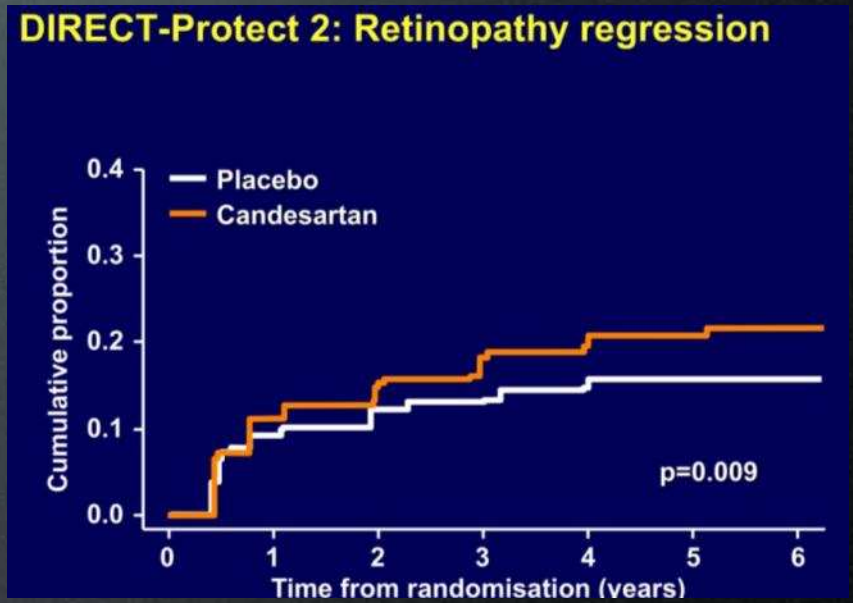
  - DIRECT-PROTECT 1 : HR = 0.94 (0.74-1.21) après ajustement*
  - DIRECT-PROTECT 2 : HR = 0.86 (0.69-1.06) après ajustement*

- Tolérance excellente à la fois dans PREVENT-1, PROTECT-1 et 2

*: après ajustement sur stade initial de la rétinopathie, durée du diabète, HbA1c et PA systolique

DIRECT-PROTECT 2 :

- **Significativement plus de patients ont une régression de leur rétinopathie**
  - HR : 1.34 (1.08-1.68) avant ajustement
  - HR : 1.38 (1.11-1.73) après ajustement*



*: après ajustement sur stade initial de la rétinopathie, durée du diabète, HbA1c, excrétion urinaire d'albumine, PA systolique et traitement antihypertenseur

DIRECT : une étude positive pour la rétinopathie diabétique

- Sur le plan fondamental :
  - Candesartan a réduit l'incidence de la rétinopathie chez les sujets diabétiques de type 1 normoalbuminuriques normotendus (-18% à -35%)
  - Pas d'effet significatif sur la progression de la rétinopathie au cours du diabète de type 1 et 2, mais régression plus fréquente (+34%) de la rétinopathie au cours du diabète de type 2
  - Le score ETDRS final moyen du groupe sous Candesartan était significativement mieux que celui du groupe témoin
  - La tolérance du traitement : très bonne

- Sur le plan pratique :
  - Quels liens de causalité?
  - Quelles significations et valeurs cliniques?
  - Quelles implications pour la pratique?

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vs placebo

CONCLUSION

- Le dépistage précoce de la RD est primordial :
  - FO / rétinophotographie, au minimum annuel
  - Prévention de la cécité
  - RD est un FDR des complications micro mais aussi macrovasculaires.

- Le traitement de la RD :
  - Des traitements ophtalmologique dont surtout le laser
  - L'équilibration de la glycémie et de la pression artérielle

- Arguments biologiques et aujourd'hui cliniques (Etude DIRECT /Candesartan) pour l'intérêt de l'inhibition du SRA

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