LES GRANDES ETUDES DANS LE DIABETE DE TYPE 2

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Les données épidémiologiques

Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study

Irene M Stratton, Amanda I Adler, H Andrew W Neil, David R Matthews, Susan E Manley, Carole A Cull, David Hadden, Robert C Turner, Rury R Holman on behalf of the UK Prospective Diabetes Study Group

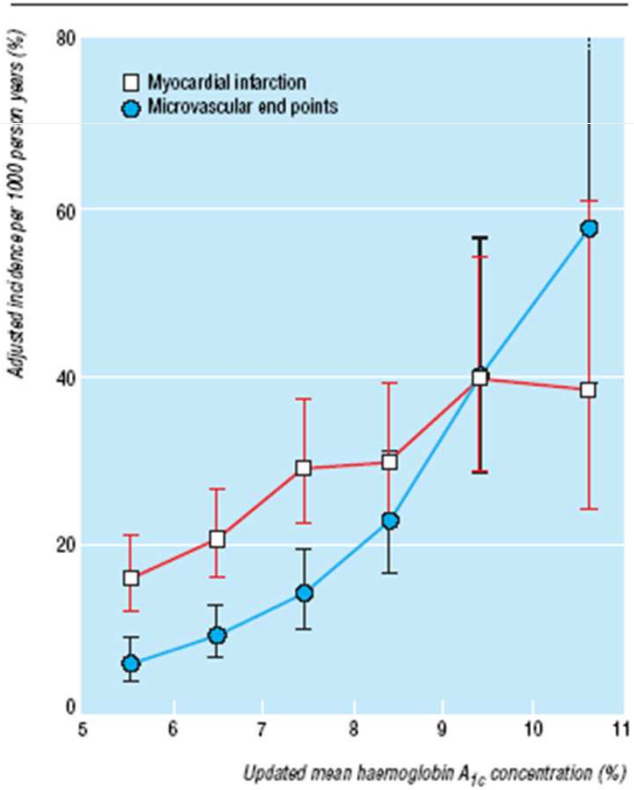

Fig 2 Incidence rates and 95% confidence intervals for myocardial infarction and microvascular complications by category of updated mean haemoglobin A_{1c} concentration, adjusted for age, sex, and ethnic group, expressed for white men aged 50-54 years at diagnosis and with mean duration of diabetes of 10 years

1/Relation + HbA1c / IDM

2/ Bénéfice max HbA1c 6%

Stratton IM, Adler AI, Neil HAW et al .BMJ 2000;321:405–412.

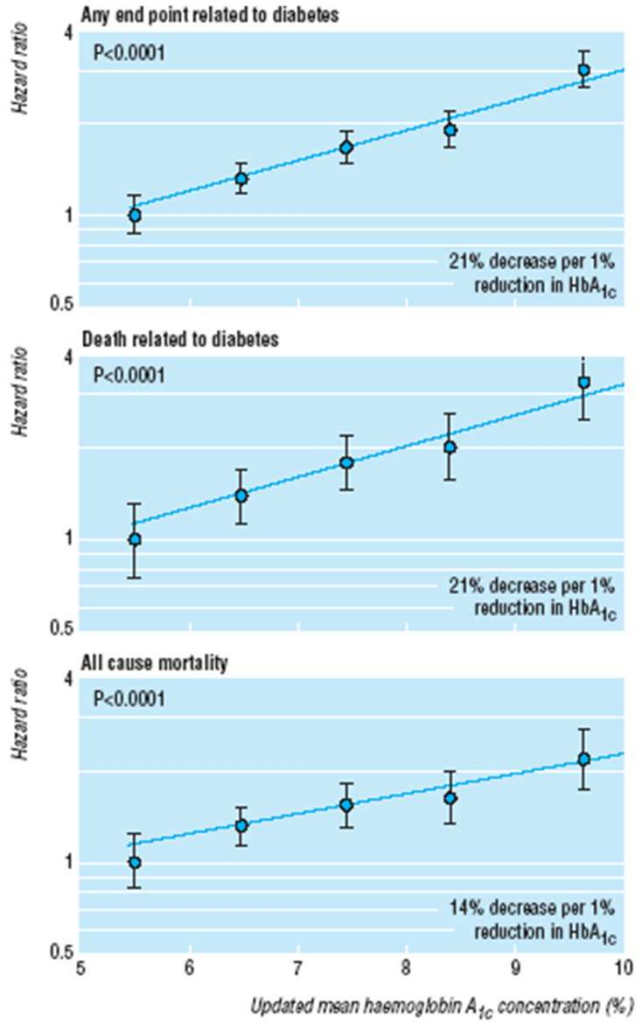

Fig 3 Hazard ratios, with 95% confidence intervals as floating absolute risks, as estimate of association between category of updated mean haemoglobin A_{1c} concentration and any end point or deaths related to diabetes and all cause mortality. Reference category (hazard ratio 1.0) is haemoglobin A_{1c} <6% with log linear scales. P value reflects contribution of glycaemia to multivariate model. Data adjusted for age at diagnosis of diabetes, sex, ethnic group, smoking, presence of albuminuria, systolic blood pressure, high and low density lipoprotein cholesterol, and triglycerides

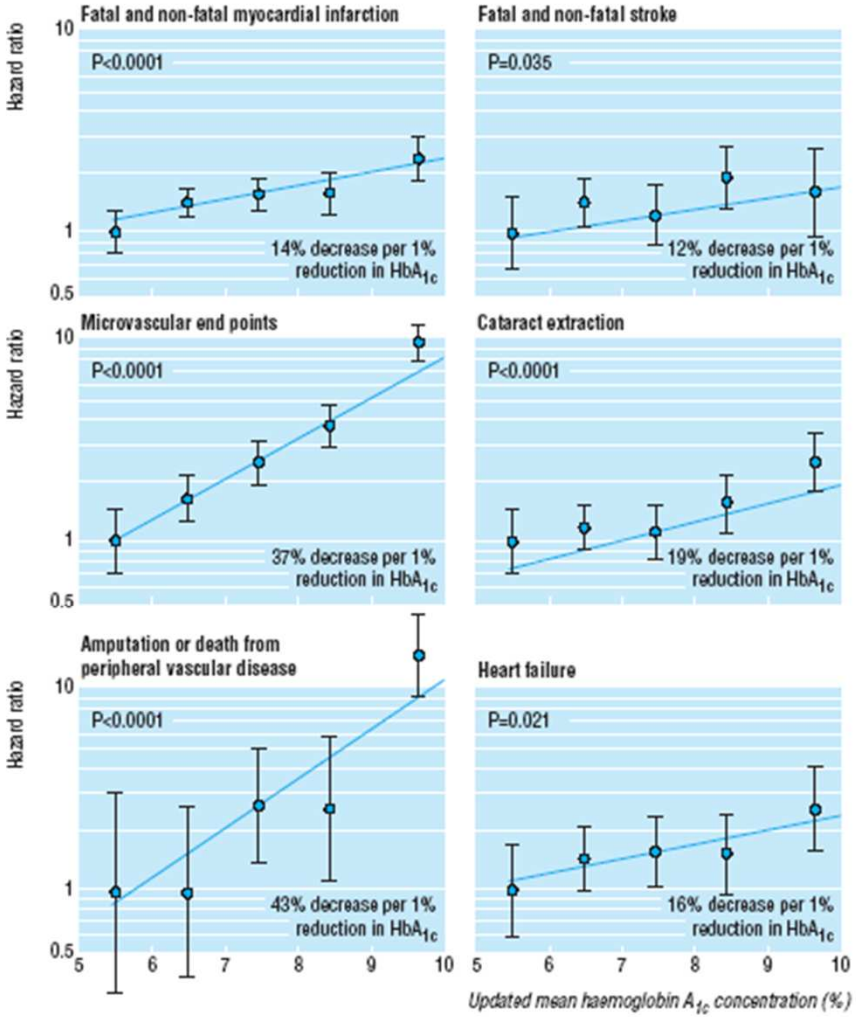

Fig 4 Hazard ratios, with 95% confidence intervals as floating absolute risks, as estimate of association between category of updated mean haemoglobin A_{1c} concentration and myocardial infarction, stroke, microvascular end points, cataract extraction, lower extremity amputation or fatal peripheral vascular disease, and heart failure. Reference category (hazard ratio 1.0) is haemoglobin A_{1c} <6% with log linear scales. P value reflects contribution of glycaemia to multivariate model. Data adjusted for age at diagnosis of diabetes, sex, ethnic group, smoking, presence of albuminuria, systolic blood pressure, high and low density lipoprotein cholesterol, and triglycerides

What is already known on this topic

The risk of developing complications of diabetes increases with increasing concentrations of hyperglycaemia

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Reduction of hyperglycaemia in these individuals reduces the risk of complications

What this study adds

There is a direct relation between the risk of complications of diabetes and glycaemia over time

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No threshold of glycaemia was observed for a substantive change in risk for any of the clinical outcomes examined

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The lower the glycaemia the lower the risk of complications

The rate of increase of risk for microvascular disease with hyperglycaemia is greater than that for macrovascular disease

Les études d'intervention…

L'Etude d'intervention dans le diabète de type 2: l'UKPDS...

UKPDS: UK Prospective Diabetes Study

- Etude randomisée, multicentrique UK
- Evaluer les effets du contrôle glycémique optimisé sur complications micro et macrovasculaires
- Traitement optimal *vs* conventionnel du D2
- 4209 D2 récent, age moyen 54 ans

OS1

- Ttt conventionnel : objectif glycémique GAJ <15 mmol/l
- Ttt intensif: objectif glycémique GAJ < 6 mmol/l
- Insuline /Différents Sulfamides en l'absence de surpoids
- Metformine + Insuline /Sulfamides si surpoids
- Suivi moyen 10 ans
- End-points: (i) évts liés au diabète (mort subite, IDM fatal ou non, angor, insuff. Rénale, amputation...)
  (ii) décès liés au diabète
  (iii) Mortalité toute cause

Diapositive 8

UKPDS: UK Prospective Diabetes Study

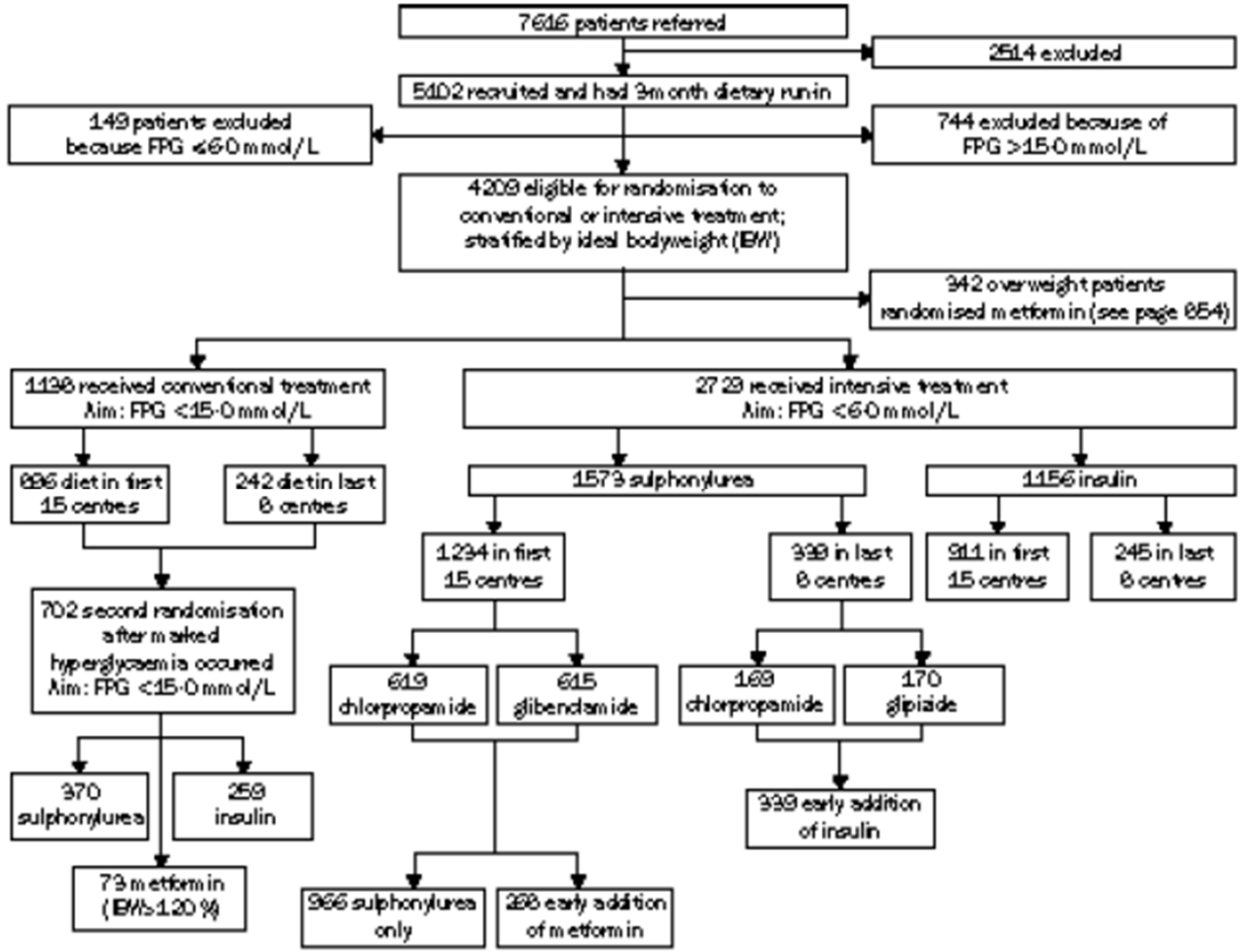


Figure 1: **Trial profile**

UKPDS: UK Prospective Diabetes Study

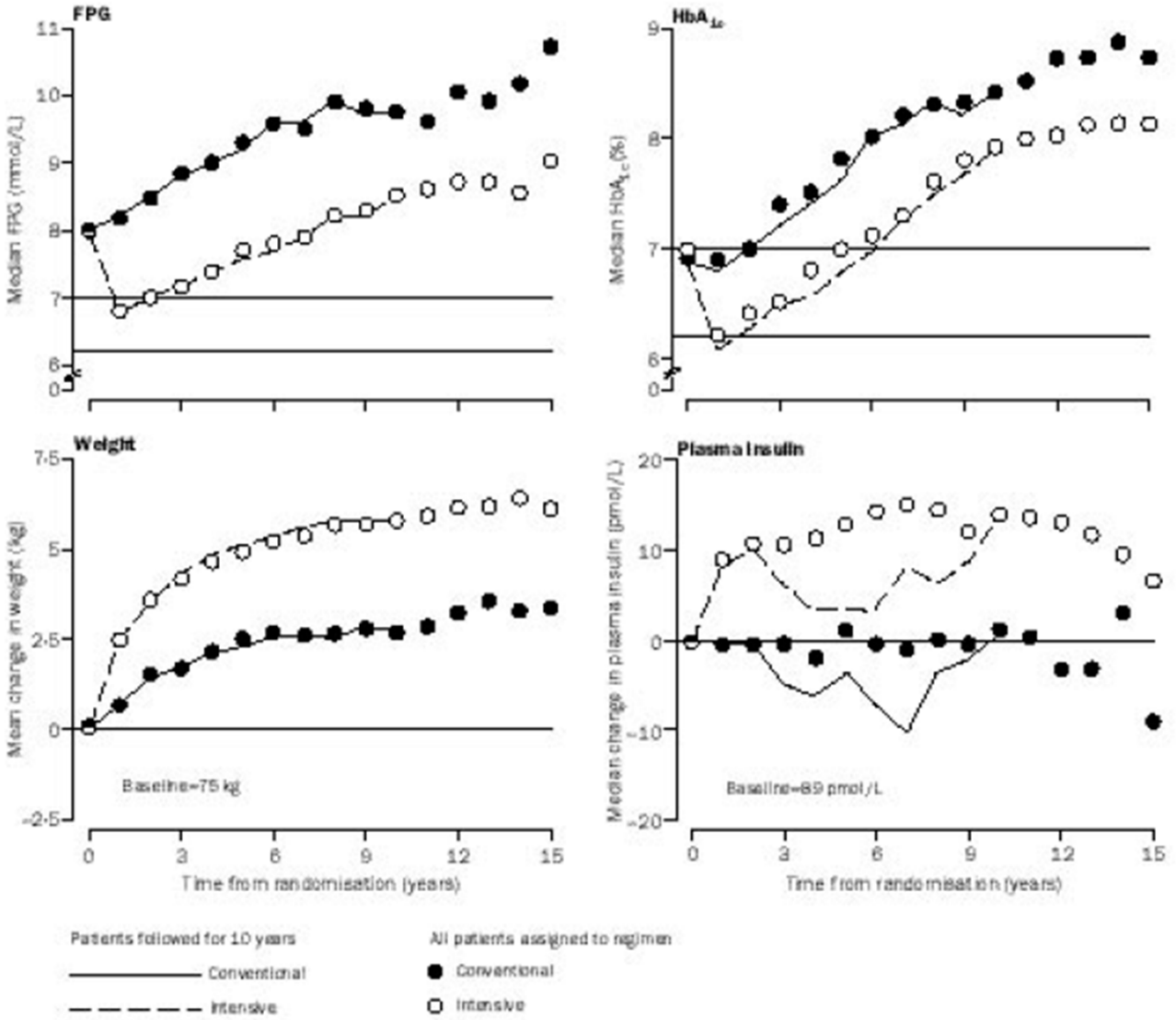
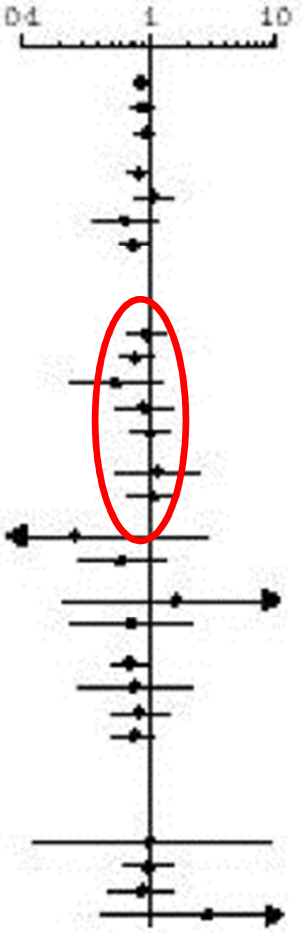


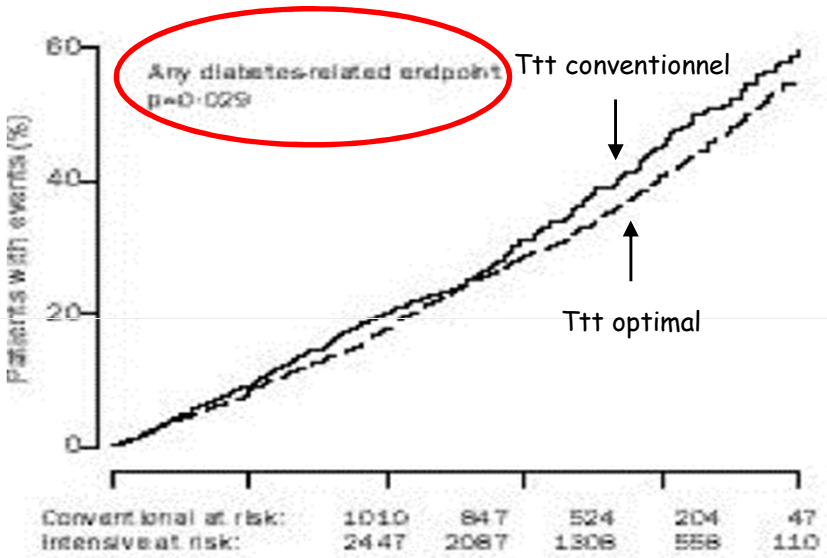
Figure 2: **Cross-sectional and 10-year cohort data for FPG, HbA_{1c}, weight, and fasting plasma insulin in patients on intensive or conventional treatment**

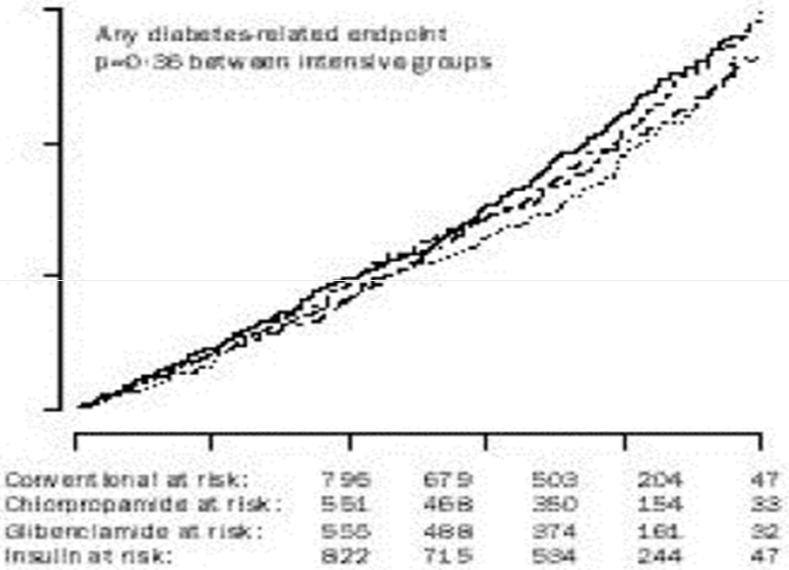
UKPDS: UK Prospective Diabetes Study

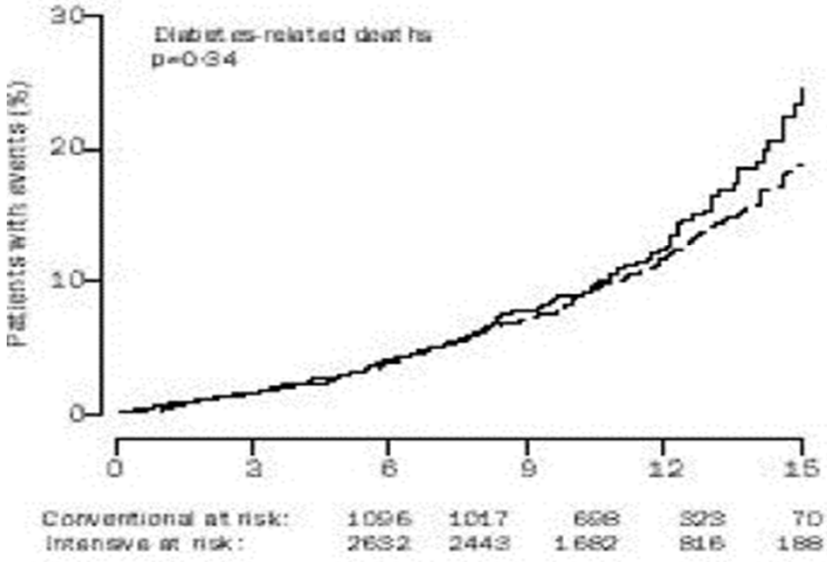
	Patients with clinical endpoints		Absolute risk events per 1000 patient-years		Log-rank p	RR for intensive policy (CI)
AGGREGATE ENDPOINT	Intensive (n=2729)	Conventional (n=1138)	Intensive	Conventional		
Any diabetes-related endpoint	963	438	40·9	46·0	0·029	0·88 (0·79–0·99)
Diabetes-related deaths	285	129	10·4	11·5	0·34	0·90 (0·73–1·11)
All-cause mortality	469	213	17·9	18·9	0·44	0·94 (0·80–1·10)
Myocardial infarction	387	186	14·7	17·4	0·052	0·84 (0·71–1·00)
Stroke	148	55	5·6	5·0	0·52	1·11 (0·81–1·51)
Amputation or death from PVD	29	18	1·1	1·6	0·15	0·68 (0·38–1·19)
Microvascular	225	121	8·6	11·4	0·0099	0·75 (0·60–0·93)
SINGLE ENDPOINTS						
Fatal myocardial infarction	207	90	7·6	8·0	0·63	0·94 (0·68–1·30)
Non-fatal myocardial infarction	197	101	7·5	9·5	0·057	0·79 (0·58–1·09)
Fatal: sudden death	24	18	0·9	1·6	0·047	0·54 (0·24–1·21)
Heart failure	80	36	3·0	3·3	0·63	0·91 (0·54–1·52)
Angina	177	72	6·8	6·7	0·91	1·02 (0·71–1·46)
Fatal stroke	43	15	1·6	1·3	0·60	1·17 (0·54–2·54)
Non-fatal stroke	114	44	4·3	4·0	0·72	1·07 (0·68–1·69)
Death from peripheral vascular disease	2	3	0·1	0·3	0·12	0·26 (0·03–2·77)
Amputation	27	18	1·0	1·6	0·099	0·61 (0·28–1·33)
Death from renal disease	8	2	0·3	0·2	0·53	1·63 (0·21–12·45)
Renal failure	16	9	0·6	0·8	0·45	0·73 (0·25–2·14)
Retinal photocoagulation	207	117	7·9	11·0	0·0081	0·71 (0·53–0·96)
Vitreous haemorrhage	19	10	0·7	0·9	0·51	0·77 (0·28–2·11)
Blind in one eye	76	38	2·9	3·5	0·39	0·84 (0·51–1·40)
Cataract extraction	149	80	5·6	7·4	0·046	0·76 (0·53–1·06)
Death from hyperglycaemia	0	1	0	0·1		
Death from hypoglycaemia	1	0	0	0		
Fatal accident	5	2	0·2	0·2	0·99	1·01 (0·12–8·70)
Death from cancer	120	50	4·4	4·4	0·92	0·96 (0·64–1·52)
Death from any other specific cause	65	30	2·4	2·7	0·57	0·88 (0·50–1·56)
Death from unknown cause	14	2	0·5	0·2	0·14	2·88 (0·41–20·19)

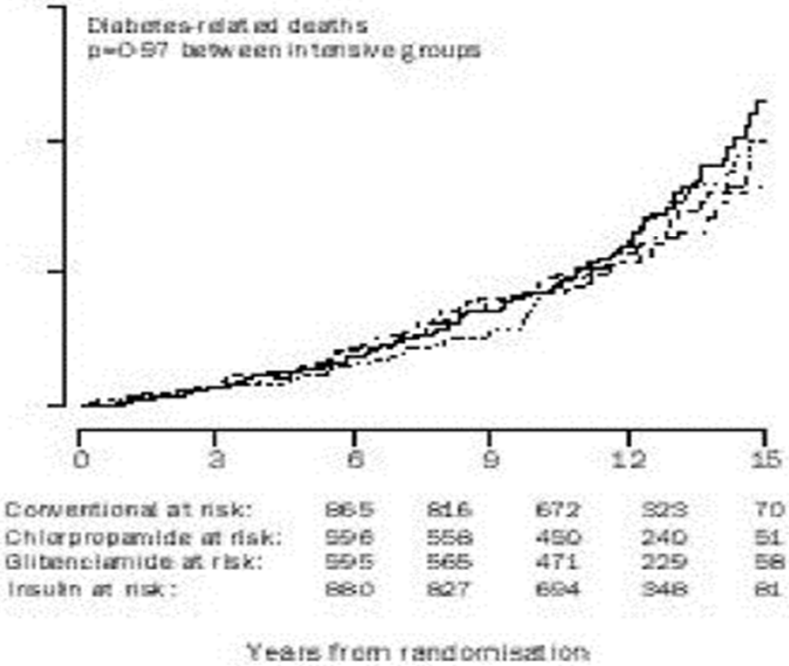


RR=relative risk. 95% CI for aggregate and 99% CI for single endpoints. PVD=peripheral vascular disease.



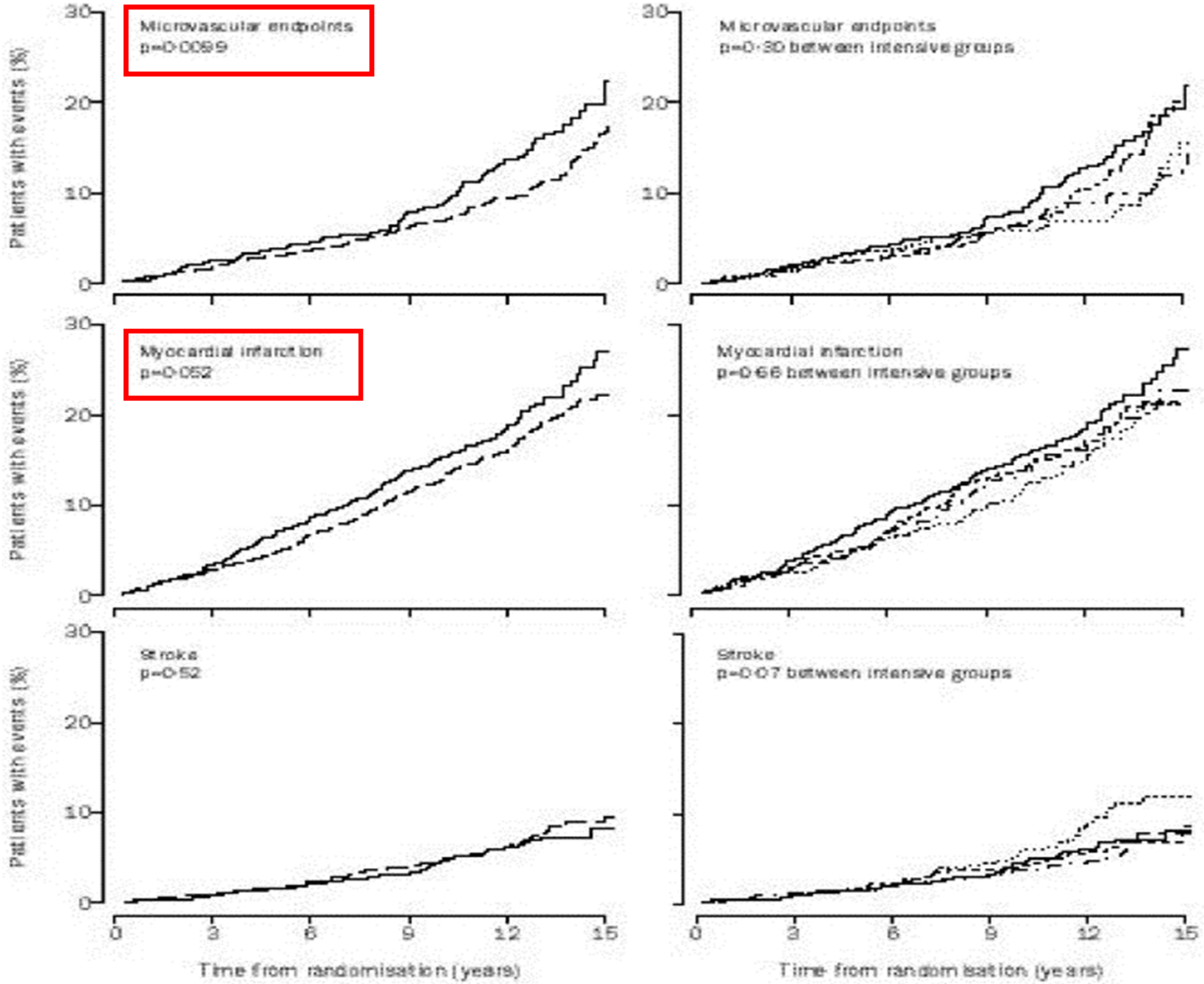






UKPDS Group (1998) Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352:837–853

UKPDS: UK Prospective Diabetes Study


Microvascular endpoints
p=0·0059
Microvascular endpoints
p=0·30 between intensive groups
Myocardial infarction
p=0·052
Myocardial infarction
p=0·66 between intensive groups
Stroke
p=0·52
Stroke
p=0·07 between intensive groups
Patients with events (%)
0
10
20
30
0
3
6
9
12
15
Time from randomisation (years)

UKPDS: UK Prospective Diabetes Study

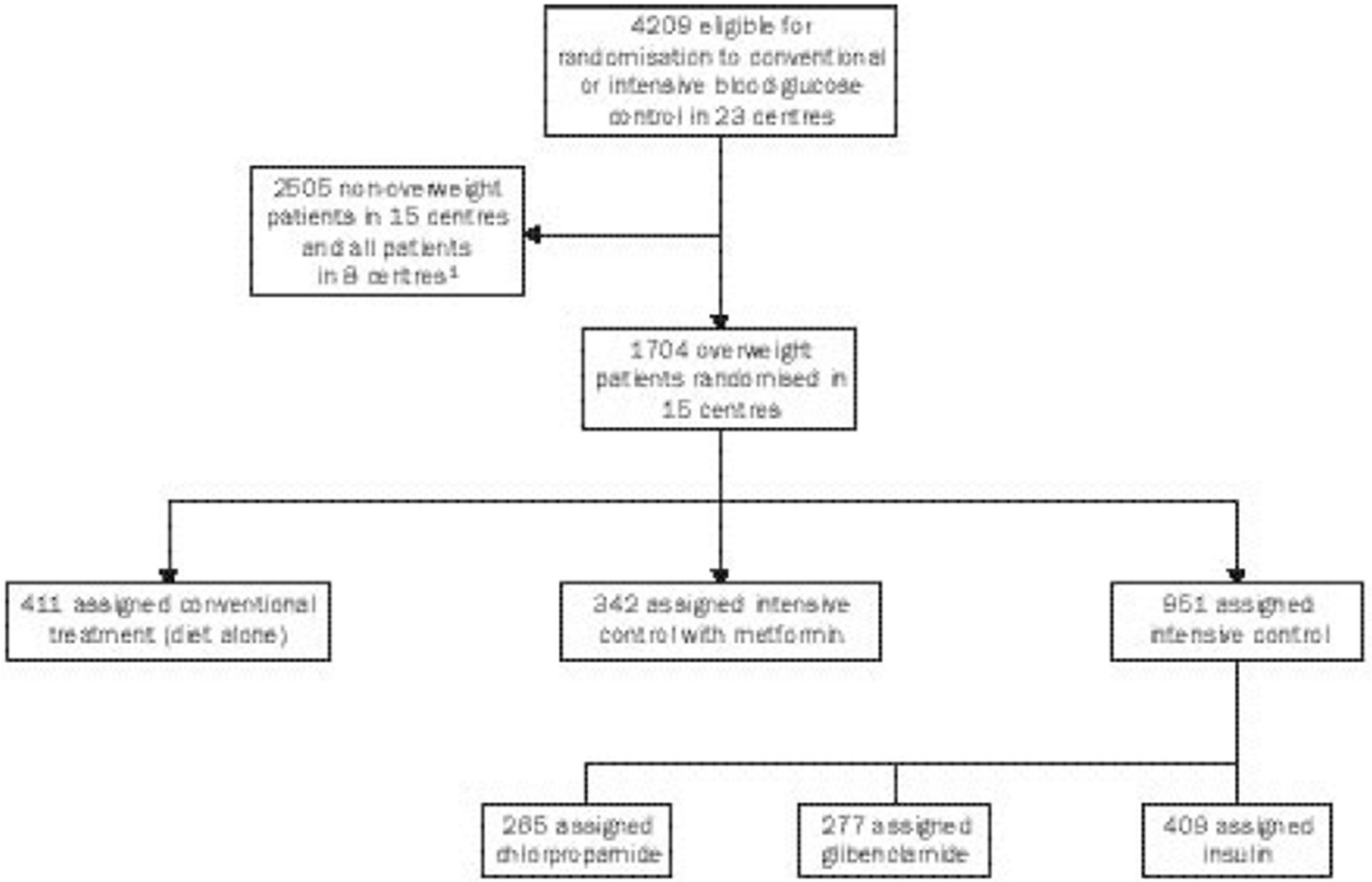
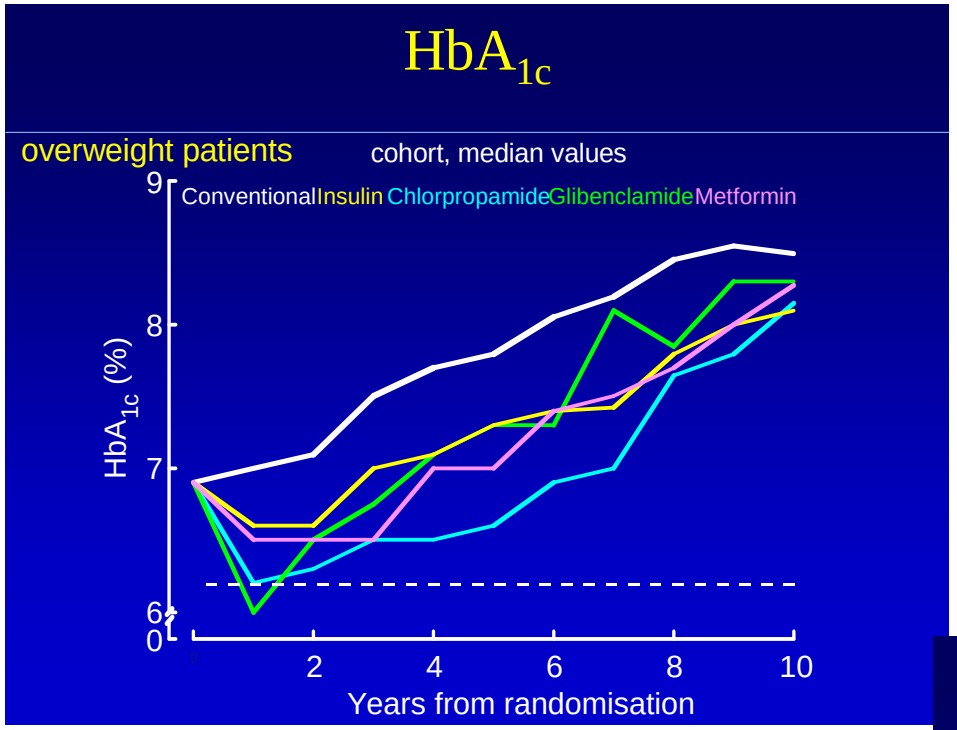
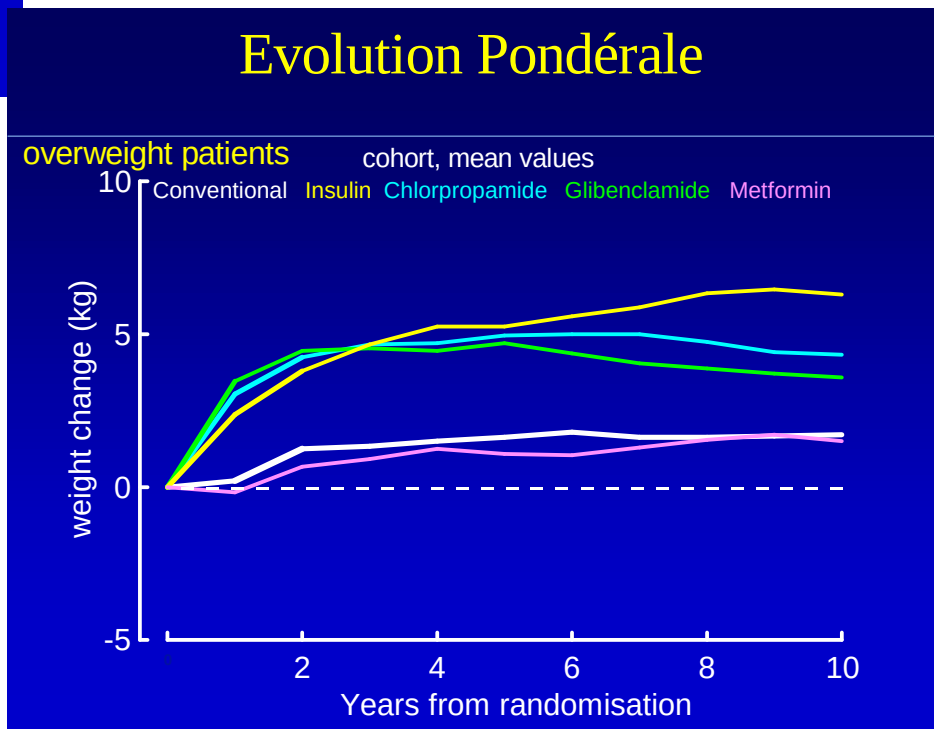


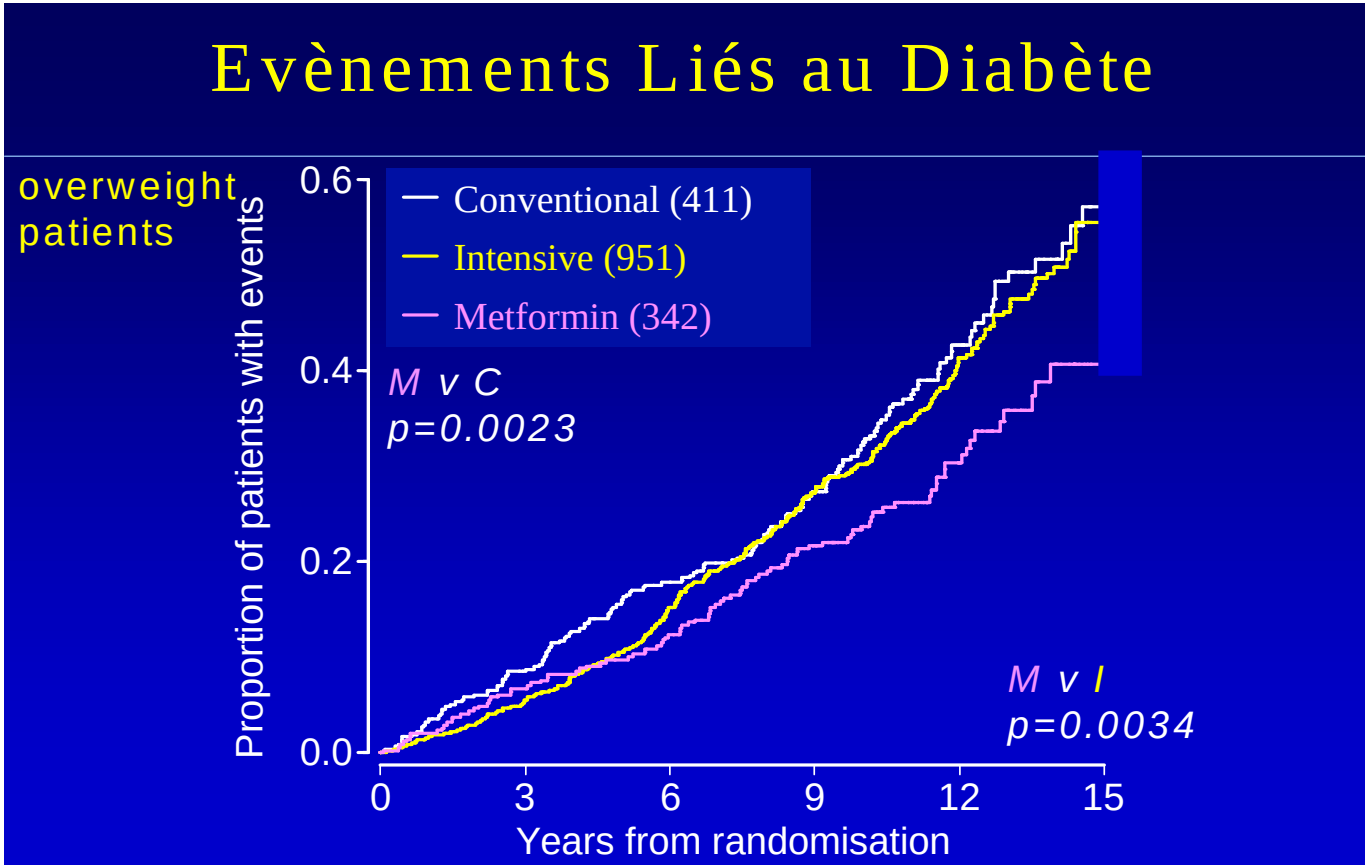
Figure 1: **Trial profile for diet/metformin study in overweight diet-treated patients**



UKPDS: UK Prospective Diabetes Study



UKPDS: UK Prospective Diabetes Study



Bénéfice Metformine ++++

Etude Glucose : Sommaire

Traitement intensif de la glycémie : HbA_{1c} 7,0 vs 7,9 %
Réduction du risque

12%	pour l'ensemble des évènements	p=0.029
25%	pour les évènements microvasculaires	p=0.0099
16%	pour IDM	p=0.052
24%	pour cataracte	p=0.046
21%	pour rétinopathie à 12 ans	p=0.015
33%	pour albuminurie à 12 ans	p=0.000054

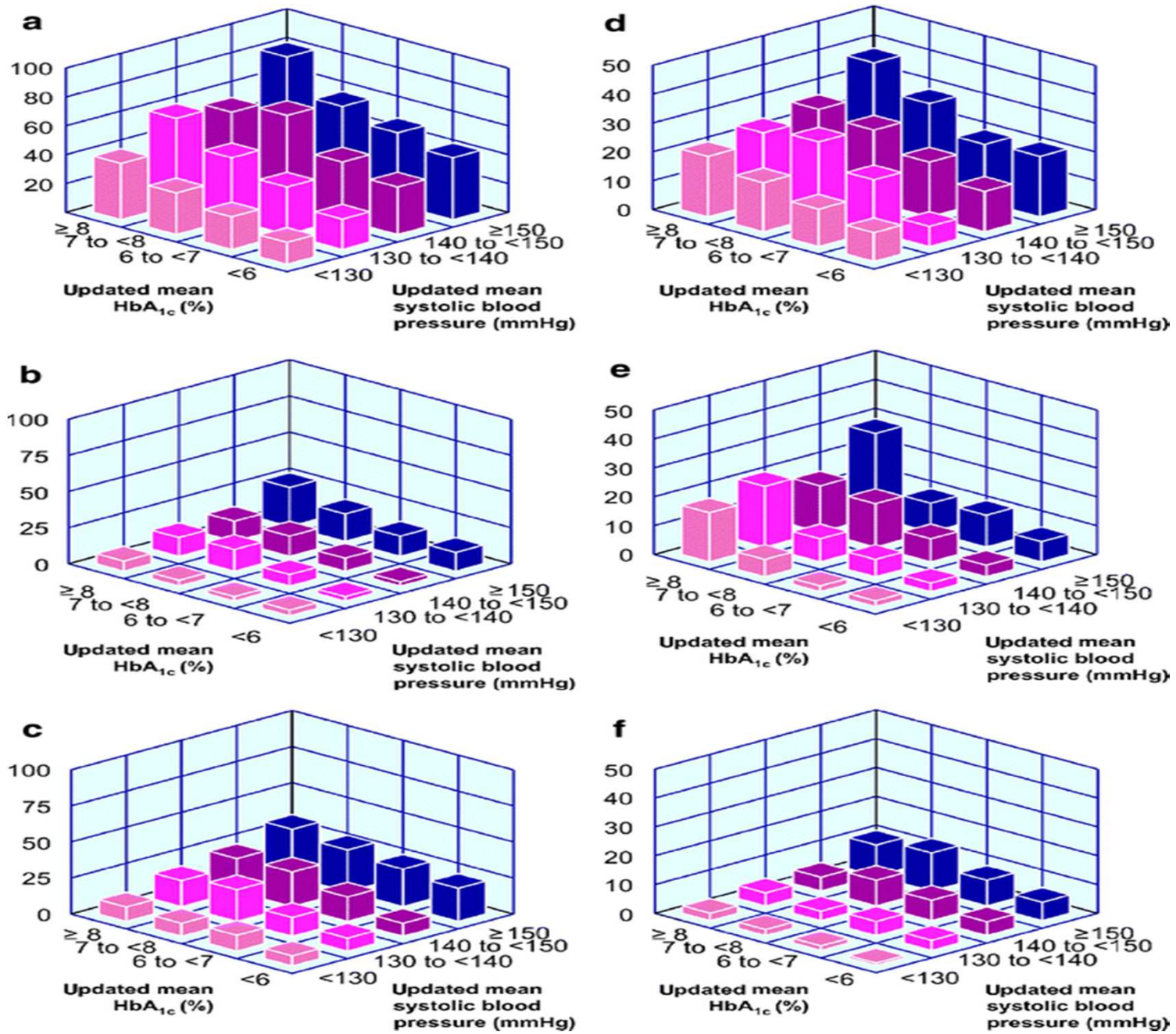
UKPDS: UK Prospective Diabetes Study

Diabetologia (2006) 49: 1761–1769
DOI 10.1007/s00125-006-0297-1

ARTICLE

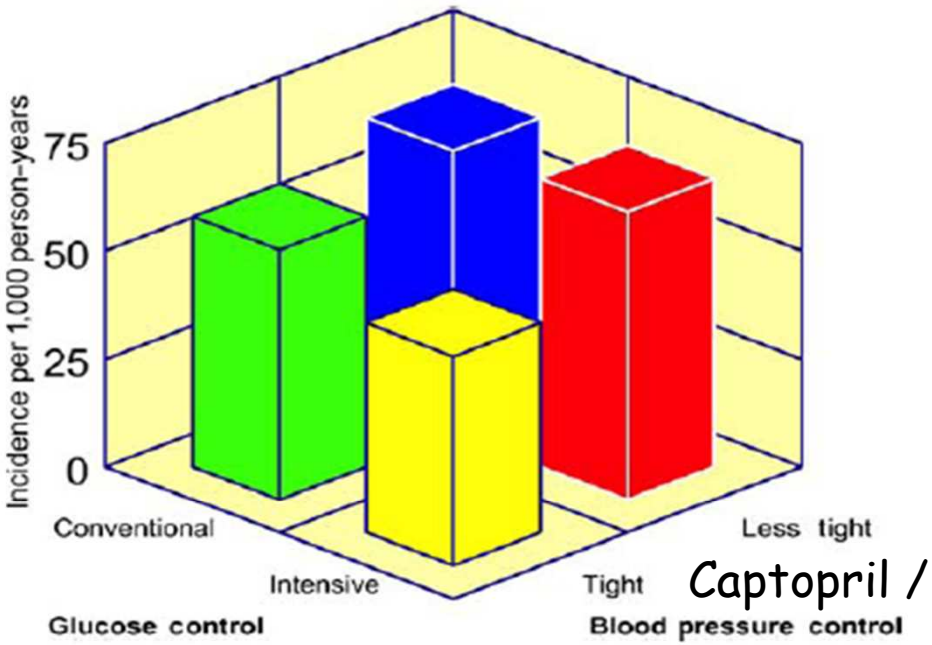
I. M. Stratton · C. A. Cull · A. I. Adler ·
D. R. Matthews · H. A. W. Neil · R. R. Holman

Additive effects of glycaemia and blood pressure exposure on risk of complications in type 2 diabetes: a prospective observational study (UKPDS 75)



Incidence of UKPDS composite endpoints in 4,320 patients, as rate per 1,000 person-years. **a** Any diabetes-related endpoint, **b** diabetes-related deaths, **c** all-cause mortality, **d** myocardial infarction, **e** microvascular disease, **f** stroke.

UKPDS: UK Prospective Diabetes Study



Captopril / Atenolol

Fig. 2 Incidence of the UKPDS primary composite 'any diabetes-related endpoint' by intention-to-treat, as rate per 1,000 person-years, in the 887 patients randomised in a factorial design between the four different interventions: a conventional or intensive glucose control policy and a less tight or tight BP control policy. Only endpoints that occurred following each patient's randomisation into the BP control study are included. Those allocated to both the intensive glucose and the tight BP control policies had fewer events than those allocated to either policy alone or to neither (p for trend 0.024)

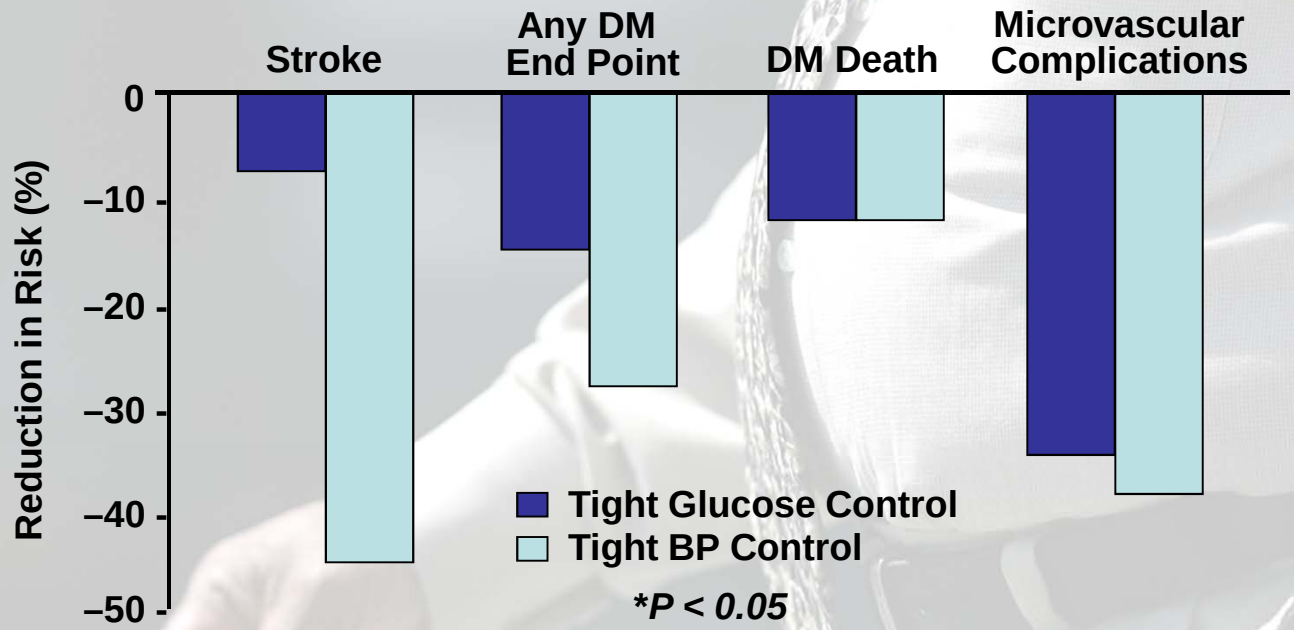
UKPDS: UK Prospective Diabetes Study

Table 3 Risk reductions in 3,418 UKPDS patients

	Number of endpoints	Risk decrease per 1% decrement in updated mean HbA_{1c} (95% CI)	*p*	Risk decrease per 10 mmHg decrement in updated mean SBP (95% CI)	*p*	*p* for interaction
Primary composite endpoints						
Any diabetes-related endpoint	1,172	21% (17–24)	<0.0001	11% (9–13)	<0.0001	0.028
Diabetes-related death	325	22% (16–28)	<0.0001	16% (12–20)	<0.0001	0.11
All-cause mortality	556	14% (11–19)	<0.0001	12% (9–16)	<0.0001	0.74
Secondary composite endpoints						
Myocardial infarction	461	14% (8–19)	<0.0001	11% (7–15)	<0.0001	0.68
Stroke	153	11% (0–21)	0.045	18% (13–23)	<0.0001	0.075
Microvascular disease	298	37% (33–41)	<0.0001	10% (7–14)	<0.0001	<0.0001

Risks reductions were calculated for a 1% decrement in updated mean HbA_{1c} and a 10-mmHg decrement in updated mean SBP using a proportional hazards model adjusted for sex, age at diagnosis, ethnicity, smoking, HDL-cholesterol, LDL-cholesterol, triglycerides and albuminuria. A product term for HbA_{1c} and SBP was included in the model to test for possible interactions with a 1% level of significance chosen to avoid potential Type 1 errors. Non-statistically significant product terms are indicative of additive effects

Pression artérielle : UKPDS



UKPDS Group. *BMJ.* 1998:317;703–713.

En résumé..l'UKPDS..

Importante étude dans le D2

Réduction non significative des complications CV sous ttt optimisé glycémie

Mais durée du suivi???

Bénéfice +++ prise en charge optimisée de l'HTA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes

Rury R. Holman, F.R.C.P., Sanjoy K. Paul, Ph.D., M. Angelyn Bethel, M.D., David R. Matthews, F.R.C.P., and H. Andrew W. Neil, F.R.C.P.

N Engl J Med 2008;359:1577-89.

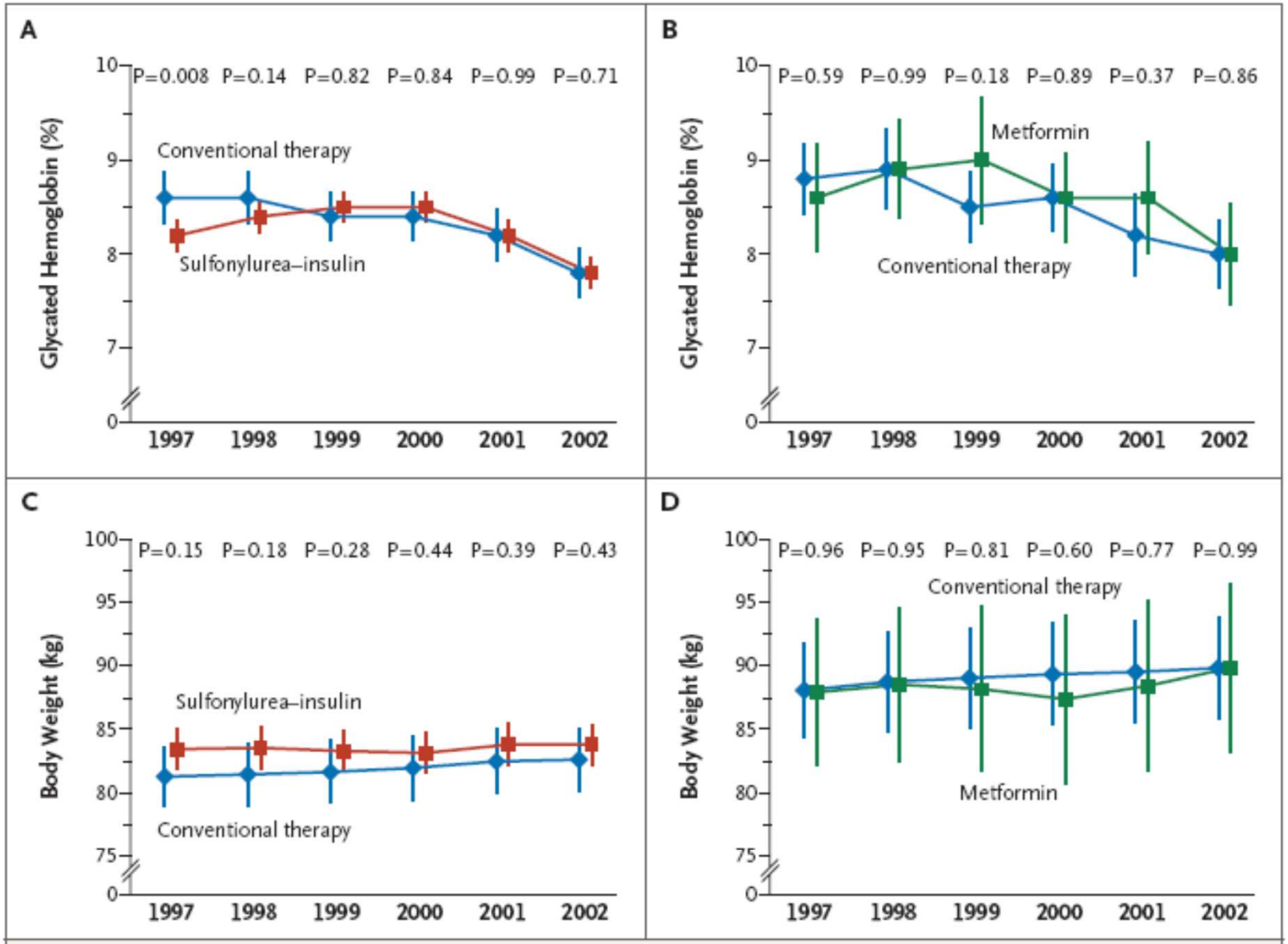


Figure 2. Mean Glycated Hemoglobin Levels and Body Weight.

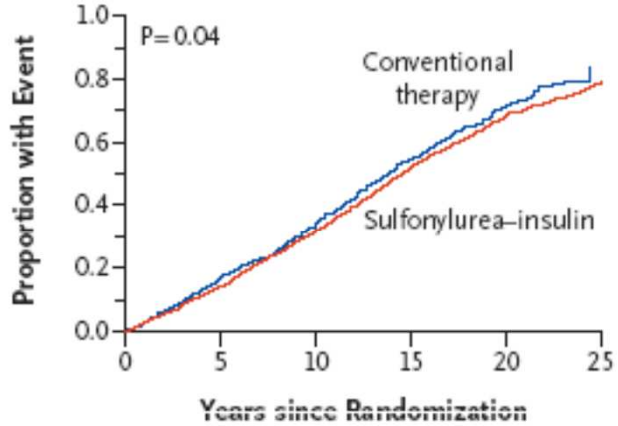
Glycated hemoglobin levels for patients who were originally assigned to receive either sulfonylurea–insulin or conventional therapy (Panel A) or metformin or conventional therapy (Panel B) are shown. Panels C and D show the corresponding mean body weights in the two groups. Clinical data were not available in years 6 through 10, when questionnaires were used. The vertical bars represent 95% confidence intervals.

Table 2. Aggregate Outcomes for Patients during Follow-up.*

Aggregate Outcome	Patients with Clinical Outcome		Absolute Risk†		P Value‡	Risk Ratio for Intensive-Therapy Regimen (95% CI)
	Intensive Therapy	Conventional Therapy	Intensive Therapy	Conventional Therapy		
	no. of patients					
Sulfonyurea–insulin group	2729	1138				
Any diabetes-related end point	1571	686	48.1	52.2	0.04	0.91 (0.83–0.99)
Diabetes-related death	618	297	14.5	17.0	0.01	0.83 (0.73–0.96)
Death from any cause	1162	537	26.8	30.3	0.007	0.87 (0.79–0.96)
Myocardial infarction	678	319	16.8	19.6	0.01	0.85 (0.74–0.97)
Stroke	260	116	6.3	6.9	0.39	0.91 (0.73–1.13)
Peripheral vascular disease	83	40	2.0	2.4	0.29	0.82 (0.56–1.19)
Microvascular disease	429	222	11.0	14.2	0.001	0.76 (0.64–0.89)
Metformin group	342	411				
Any diabetes-related end point	209	262	45.7	53.9	0.01	0.79 (0.66–0.95)
Diabetes-related death	81	120	14.0	18.7	0.01	0.70 (0.53–0.92)
Death from any cause	152	217	25.9	33.1	0.002	0.73 (0.59–0.89)
Myocardial infarction	81	126	14.8	21.1	0.005	0.67 (0.51–0.89)
Stroke	34	42	6.0	6.8	0.35	0.80 (0.50–1.27)
Peripheral vascular disease	13	21	2.3	3.4	0.19	0.63 (0.32–1.27)
Microvascular disease	66	78	12.4	13.4	0.31	0.84 (0.60–1.17)

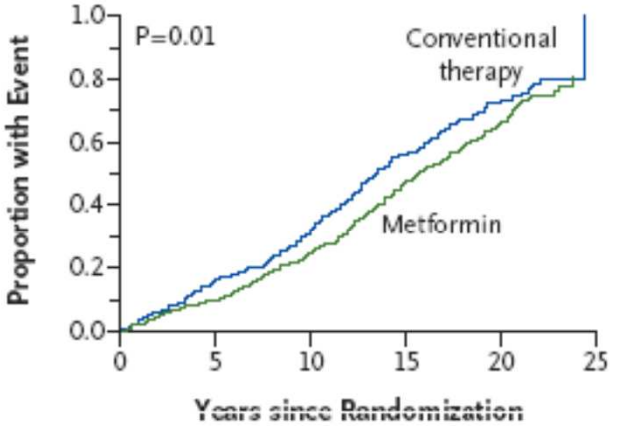
* Shown are the numbers of patients who were followed for up to 30 years, including up to 10 years of post-trial monitoring, with aggregate clinical outcomes after assignment in the interventional phase of the United Kingdom Prospective Diabetes Study to the sulfonylurea–insulin group or the metformin group or to the corresponding conventional-therapy group.
† The absolute risk is the number of events per 1000 patient-years.
‡ P values were calculated with the use of the log-rank test.

A Any Diabetes-Related End Point



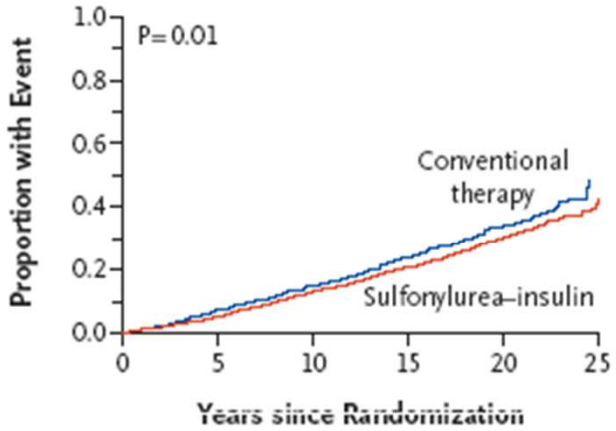
No. at Risk						
Conventional therapy	1138	913	679	370	104	5
Sulfonylurea–insulin	2729	2270	1692	933	277	32

B Any Diabetes-Related End Point



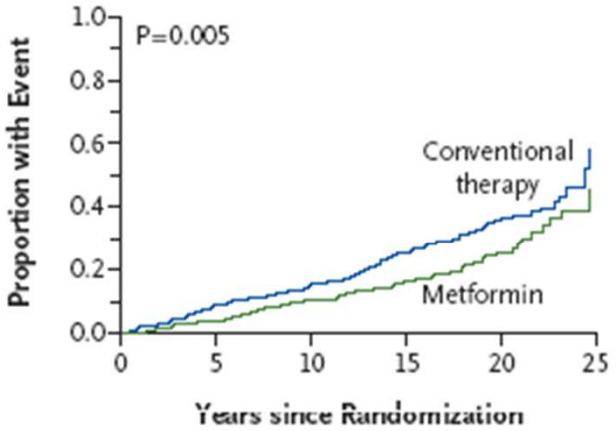
No. at Risk						
Conventional therapy	411	333	255	132	45	2
Metformin	342	300	236	144	62	7

C Myocardial Infarction



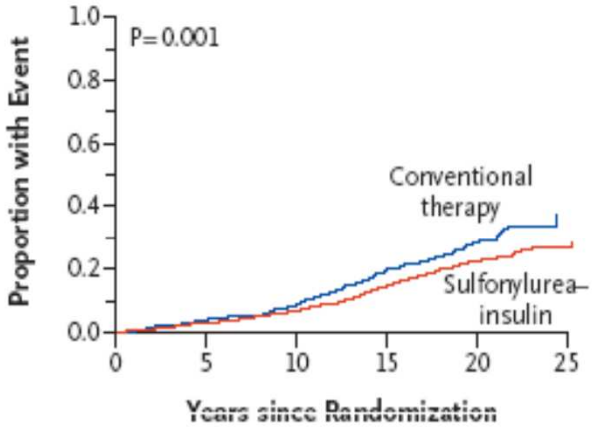
No. at Risk						
Conventional therapy	1138	1013	857	578	221	20
Sulfonylurea–insulin	2729	2488	2097	1459	577	66

D Myocardial Infarction



No. at Risk						
Conventional therapy	411	360	311	213	95	4
Metformin	342	317	274	214	106	16

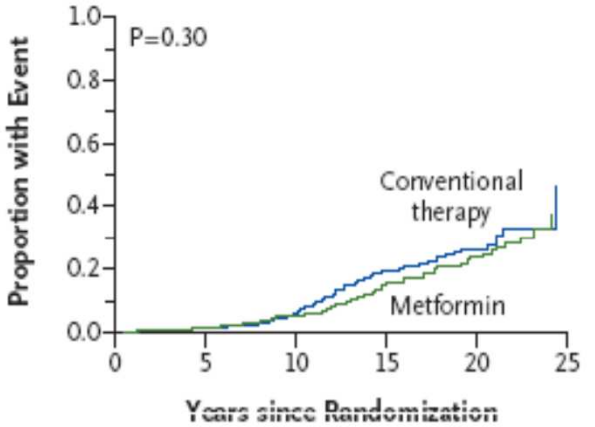
E Microvascular Disease



No. at Risk

Conventional therapy	1138	1018	844	508	172	13
Sulfonylurea–insulin	2729	2465	2076	1368	488	53

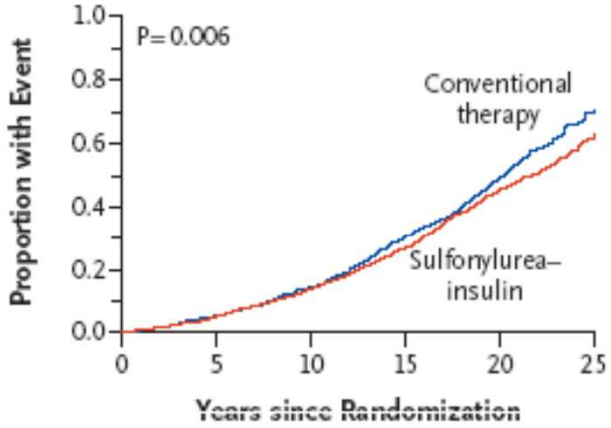
F Microvascular Disease



No. at Risk

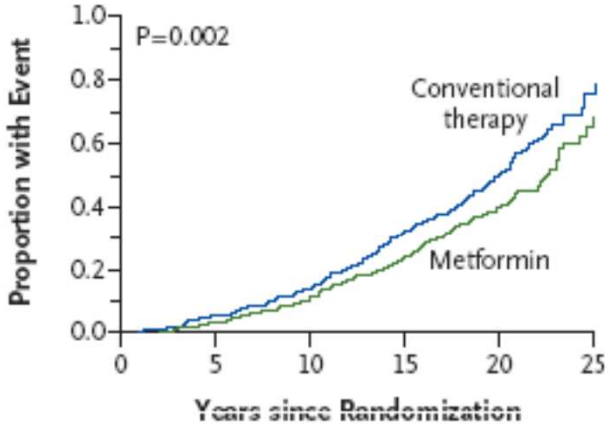
Conventional therapy	411	377	316	186	72	2
Metformin	342	319	278	197	92	16

G Death from Any Cause



No. at Risk						
Conventional therapy	1138	1066	939	665	270	28
Sulfonylurea–insulin	2729	2573	2276	1675	680	83

H Death from Any Cause



No. at Risk						
Conventional therapy	411	387	345	246	116	7
Metformin	342	328	296	239	124	11

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes

Rury R. Holman, F.R.C.P., Sanjoy K. Paul, Ph.D., M. Angelyn Bethel, M.D.,
David R. Matthews, F.R.C.P., and H. Andrew W. Neil, F.R.C.P.

Notion de mémoire glycémique

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group*

Critères d'inclusion:

- D2
- HbA1c> 7.5%
- age entre 40 -79 ans et atcd CV
- age 55-79 ans et athérome clinique, microalb, HVG ou 2 FDR CV

Randomisation:

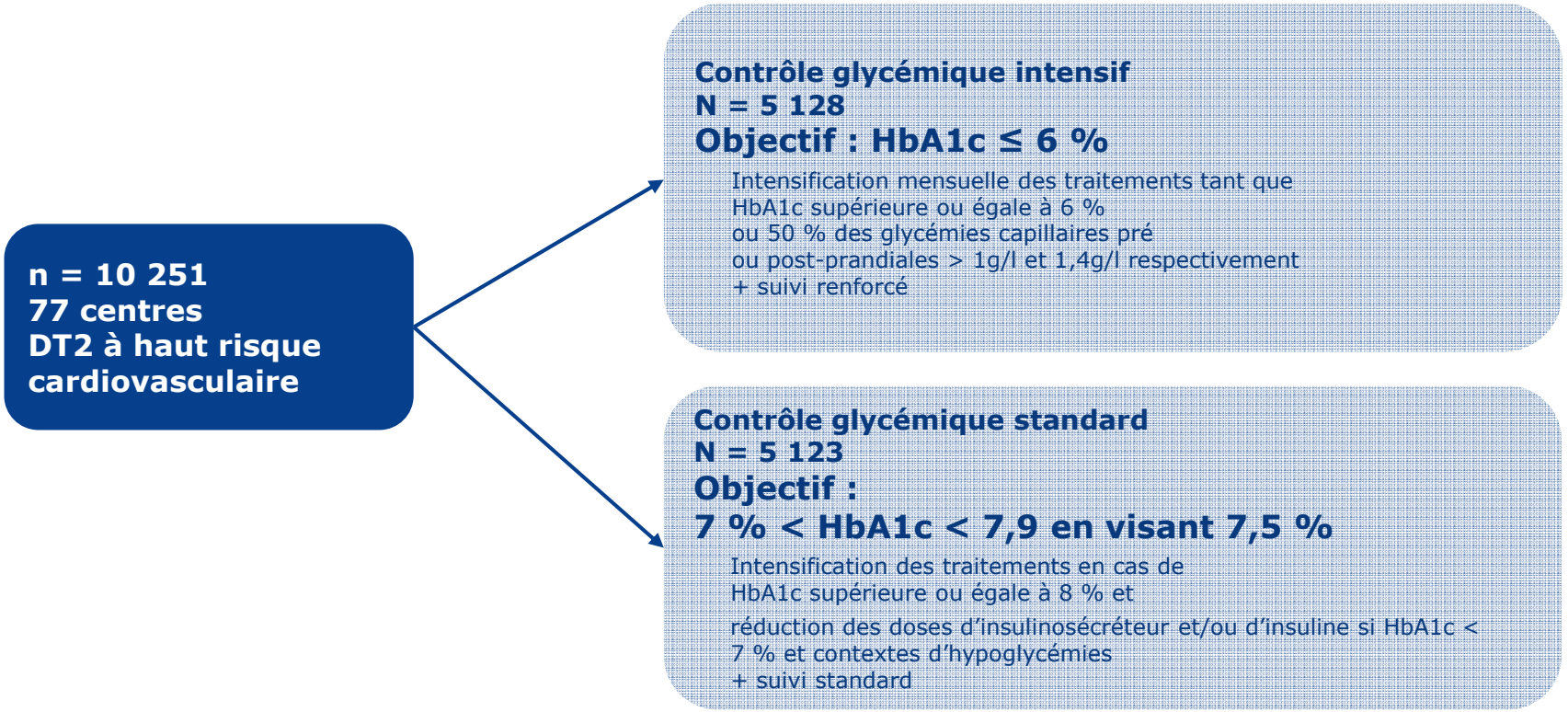
ttt intensif HbA1c < 6.0%

ttt standard HbA1c entre 7.0 - 7.9%.

Critère principal: 1er IDM non fatal ou 1er AVC non fatal ou DC cause CV

Méthodologie de l'étude

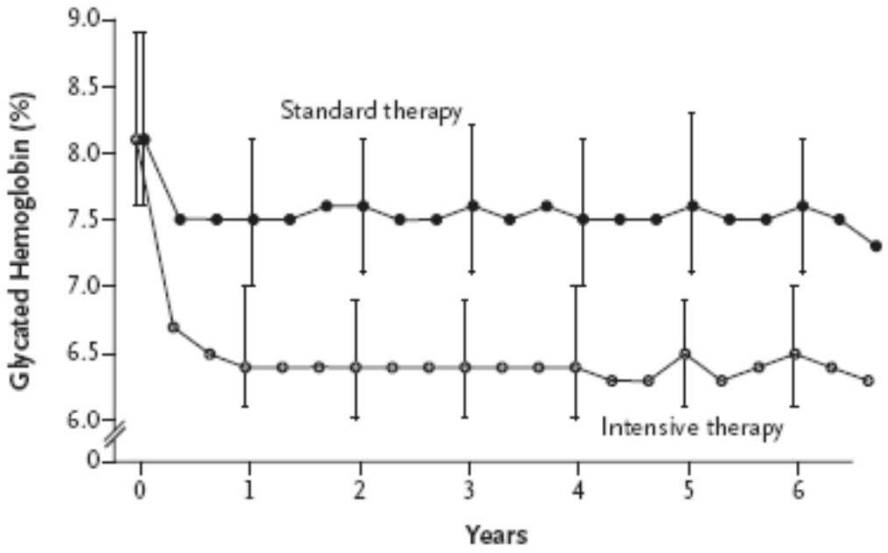
ACCORD



The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose in type 2 diabetes; June 12, 2008: N Engl J Med. 358; 2545-59.

Table 1. Characteristics of the Patients at Baseline.*

Variable	Intensive Therapy (N=5128)	Standard Therapy (N=5123)
Age (yr)	62.2±6.8	62.2±6.8
Female sex (%)	38.7	38.4
Median duration of diabetes (yr)	10	10
Previous cardiovascular event (%)	35.6	34.8
Previous congestive heart failure (%)	4.9	4.8
Cigarette-smoking status (%)		
Current	14.3	13.7
Former	44.4	44.0
Never	41.3	42.3
Weight (kg)	93.5±18.7	93.6±18.7
Body-mass index	32.2±5.5	32.2±5.5
Waist circumference (cm)	106.8±14.3	106.8±13.8
Blood pressure (mm Hg)		
Systolic	136.2±17.0	136.5±17.2
Diastolic	74.8±10.6	75.0±10.7
Medications (%)		
Insulin	34.1	35.7
Metformin	59.7	60.0
Any sulfonylurea	50.8	49.4
Any thiazolidinedione	19.5	19.2
Any antihypertensive agent	84.9	86.0
Angiotensin-converting–enzyme inhibitor	53.0	53.0
Aspirin	54.8	54.1
Beta-blocker	28.7	29.9
Any thiazide diuretic	26.5	26.4
Statin	61.7	62.4
Glycated hemoglobin (%)		
Mean	8.3±1.1	8.3±1.1



No. at Risk							
Standard therapy	5109	4774	4588	3186	1744	455	436
Intensive therapy	5119	4768	4585	3165	1706	476	471

Figure 1. Median Glycated Hemoglobin Levels at Each Study Visit.

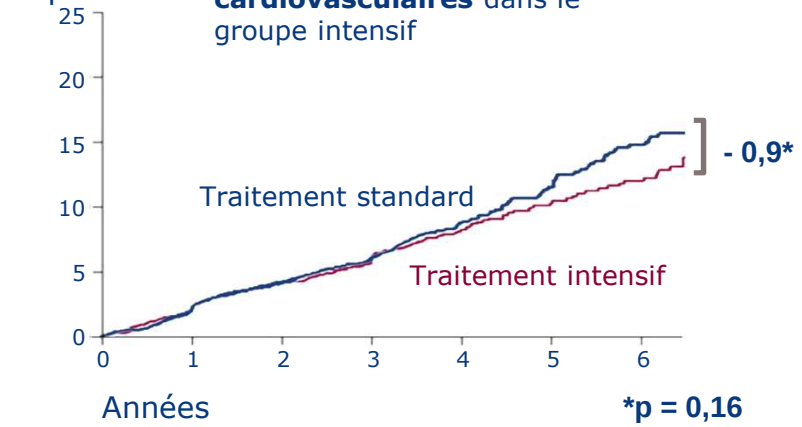
I bars denote interquartile ranges.

Résultat du traitement intensif : augmentation significative de la mortalité globale

ACCORD

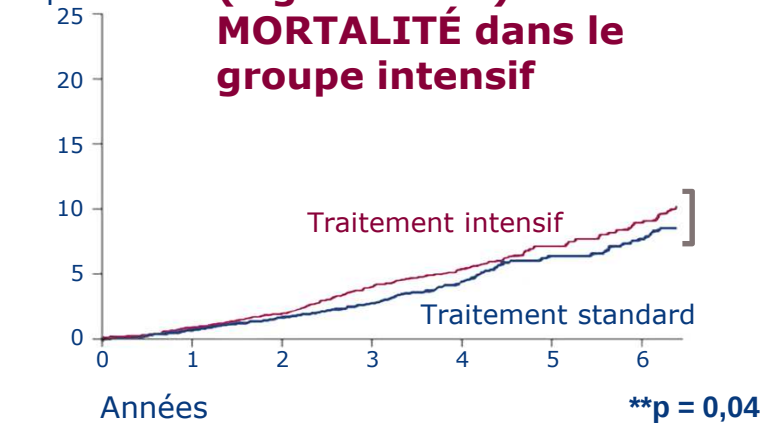
- **Critère principal : tout événement CV**

Réduction (non significative) du nombre global d'**événements cardiovasculaires** dans le groupe intensif



- **Mortalité globale**

Augmentation (significative) de la MORTALITÉ dans le groupe intensif



Arrêt du bras intensif en février 2008 (3,5 ans)

Surmortalité **non observée** dans VADT et ADVANCE

- hypothèses: hypoglycémies majeures et prise de poids importante

The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose in type 2 diabetes; June 12, 2008: N Engl J Med. 358; 2545-59.

Table 3. Adverse Events, Clinical Measures, Tobacco Use, and Use of Nonglycemic Medication after Randomization.*

Variable	Intensive Therapy (N=5128)	Standard Therapy (N=5123)	P Value†
Adverse events			
Hypoglycemia — no. (%)			
Requiring medical assistance	538 (10.5)	179 (3.5)	<0.001
Requiring any assistance	830 (16.2)	261 (5.1)	<0.001
Fatal or nonfatal heart failure — no. (%)	152 (3.0)	124 (2.4)	0.10
Motor vehicle accident in which patient was driver — no./total no. (%)	9/5033 (0.2)	14/5036 (0.3)	0.40
Any nonhypoglycemic serious adverse event — no. (%)	113 (2.2)	82 (1.6)	0.03
Fluid retention — no./total no. (%)‡	3541/5053 (70.1)	3378/5054 (66.8)	<0.001
Clinical measures			
Weight gain >10 kg since baseline — no./total no. (%)	1399/5036 (27.8)	713/5042 (14.1)	<0.001
Alanine aminotransferase >3 times ULN — no./total no. (%)§	51/5065 (1.0)	77/5061 (1.5)	0.02
Low-density lipoprotein cholesterol — mg/dl¶	90.8±33.5	90.6±34.0	0.74
Blood pressure — mm Hg¶			
Systolic	126.4±16.7	127.4±17.2	0.002
Diastolic	66.9±10.5	67.7±10.6	<0.001
Cigarette-smoking status — no. (%)‖			0.54

Hypoglycémies et Mortalité

ACCORD

	Standard Glycemia (n=175 with events)	Intensive Glycemia (n=528 with events)	HR (95% CI)
No severe hypoglycemia	1.0 % / year 180 deaths 17,516 person years	1.3 % / year 220 deaths 17, 031 person years	**1.24 (1.02-1.52)**
At least one severe hypoglycemia event	4.9 % / year 17 deaths 345 person years	2.8 % / year 34 deaths 1,208 person years	**0.55 (0.31-0.99)**
HR (95% CI)	2.87 (1.73-4.76)	1.28 (0.88-1.85)	

Etude ACCORD interrompu après 3,5 ans devant augmentation nb de DC dans le groupe intensif

CONCLUSIONS

As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes. (ClinicalTrials.gov number, NCT00000620.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*

Critères d'inclusion:

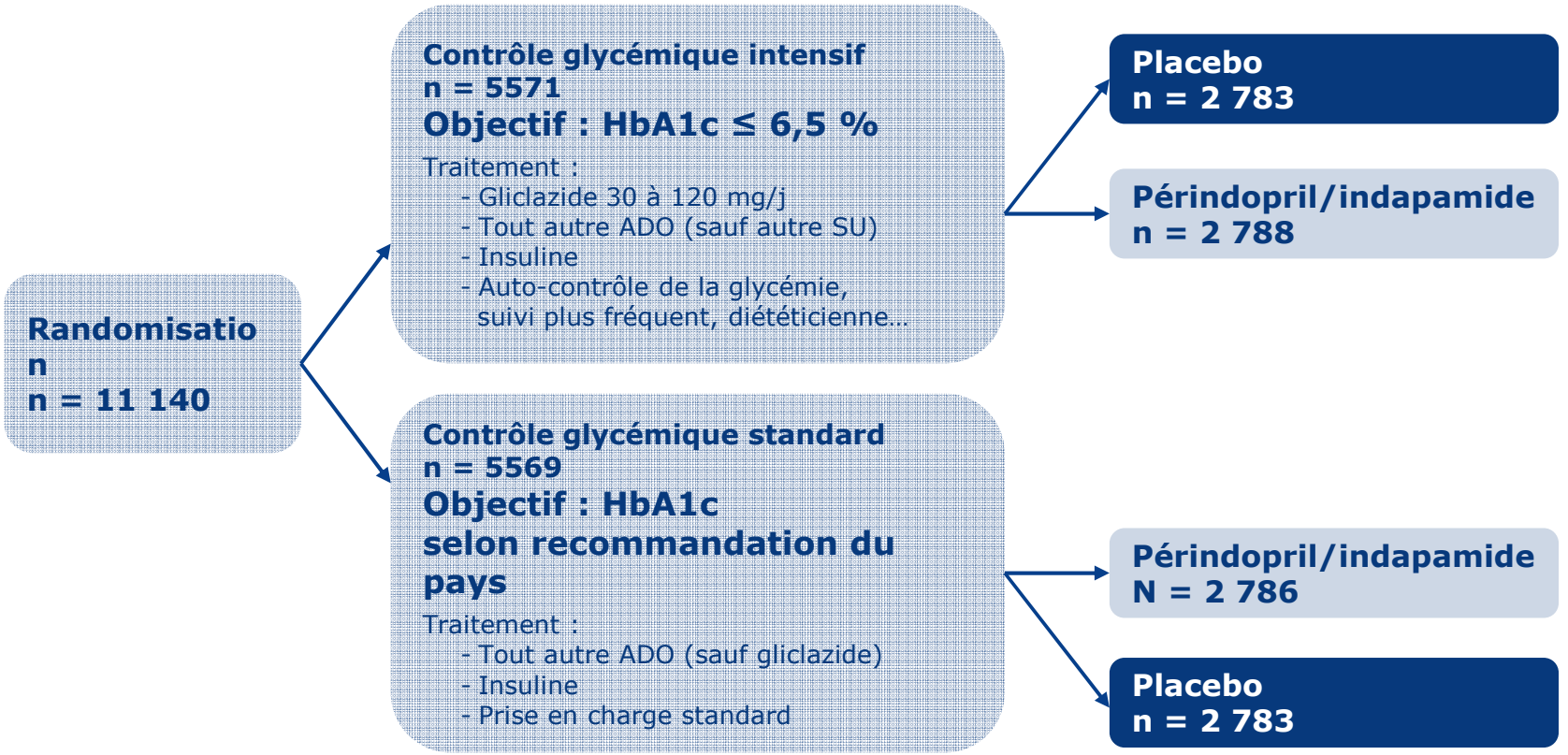
Diabète de type 2 âgé d'au moins 55 ans
avec atcd de complication micro et macrovasculaire
Ou au moins 1 FDR CV associé

Pas de critère d'inclusion sur l'HbA1c à l'entrée

Randomisation ttt intensif HbA1c, ≤6.5% avec Gliclazide 30- 120 mg /j
Ou ttt standardisé :objectif HbA1c adapté aux normes locales

Critère principal:
Evts Composite: évts macrovasc + évts microvasc

Méthodologie de l'étude ADVANCE



Rationale and design of the ADVANCE study. J Hypertens. 2001;19(suppl 4):S21-S28.
ADVANCE-baseline characteristics. Diabet Med. 2005;22:1-7.

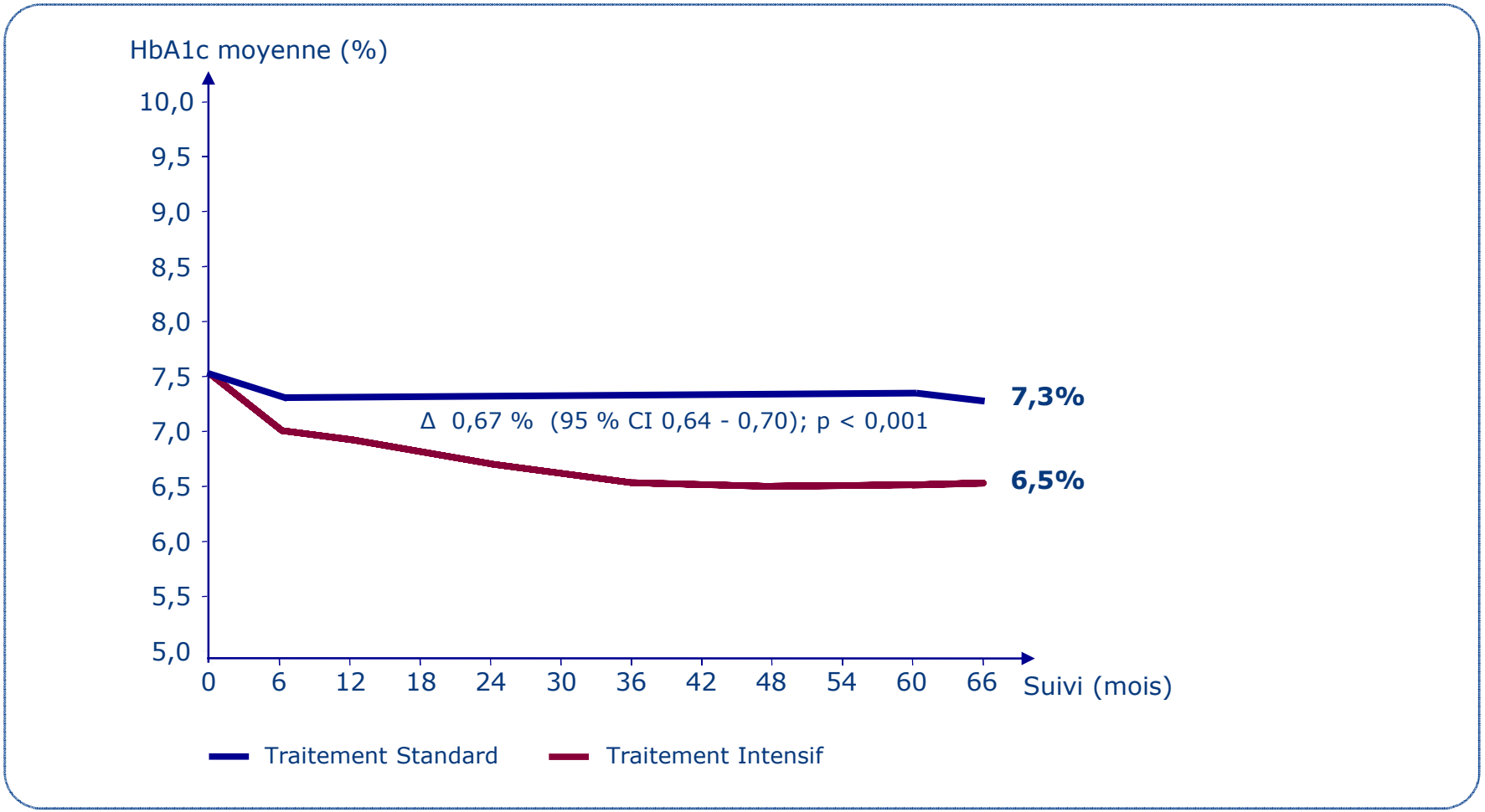
Table 1. Characteristics of Participants at Baseline and at the End of the Follow-up Period.*

Characteristic	Baseline		End of Follow-up	
	Intensive Control (N=5571)	Standard Control (N=5569)	Intensive Control (N=4828)	Standard Control (N=4741)
Age — yr	66±6	66±6		
Female sex — no. (%)	2376 (42.6)	2357 (42.3)		
Age when diabetes first diagnosed — yr	58±9	58±9		
Duration of diabetes — yr	7.9±6.3	8.0±6.4		
Region — no. (%)				
Australia and New Zealand	744 (13.4)	741 (13.3)		
Asia	2069 (37.1)	2067 (37.1)		
Europe	2538 (45.6)	2545 (45.7)		
North America	220 (4.0)	216 (3.9)		
Previous vascular disease				
History of major macrovascular disease — no. (%)	1794 (32.2)	1796 (32.3)		
Myocardial infarction	668 (12.0)	666 (12.0)		
Stroke	515 (9.2)	508 (9.1)		
Other	683 (12.3)	678 (12.2)		
History of major microvascular disease — no. (%)	571 (10.3)	584 (10.5)		
Macroalbuminuria†	189 (3.4)	215 (3.9)		
Microvascular eye disease‡	403 (7.2)	392 (7.0)		
History of microalbuminuria — no. (%)	1434 (27.0)	1423 (26.7)		
Glycated hemoglobin, standardized level — %				
Mean ±SD	7.48±1.65	7.48±1.63	6.49±0.99	7.24±1.38

Other major risk factors				
Blood pressure — mm Hg				
Systolic	145.0±21.7	145.0±21.4	135.5±17.6	137.9±18.4
Diastolic	80.8±11.0	80.5±10.8	73.5±9.8	74.3±9.9
Serum cholesterol — mmol/liter				
Low-density lipoprotein	3.12±1.04	3.11±1.02	2.64±0.97	2.65±1.06
High-density lipoprotein	1.26±0.35	1.25±0.35	1.24±0.35	1.25±0.35
Serum triglycerides — mmol/liter				
Median	1.60	1.64	1.45	1.59
Interquartile range	1.20–2.30	1.20–2.30	1.03–2.03	1.10–2.20
Serum triglycerides — μmol/liter	1.95±1.29	1.96±1.29	1.70±1.06	1.82±1.15
Serum creatinine — μmol/liter	86±24	87±27	94±37	93±41
Weight — kg	78.2±16.8	78.0±16.8	78.1±17.5	77.0±16.7
Body-mass index§	28±5	28±5	28±5	28±5
Waist circumference — cm	99±13	98±13	99±14	98±13
Current smoking — no. (%)	793 (14.2)	757 (13.6)	385 (8.3)	350 (7.8)

Intensification progressive du traitement pour atteindre les objectifs d'HBA1c

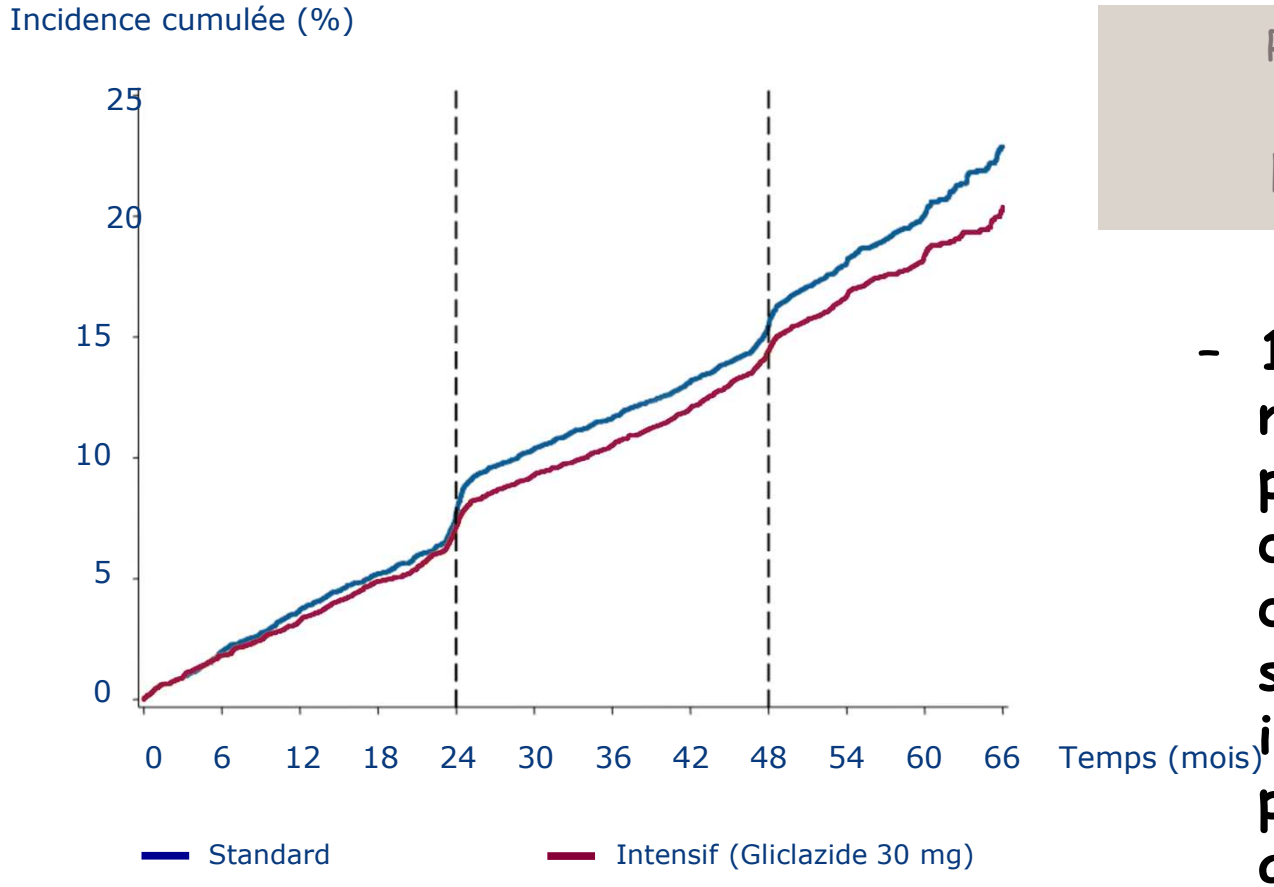
ADVANCE



ADVANCE collaborative group. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes NEJM. 2008; vol 358:2560-72.

Traitement intensif : réduction de 10 % de l'incidence d'événements macro et microvasculaires majeurs

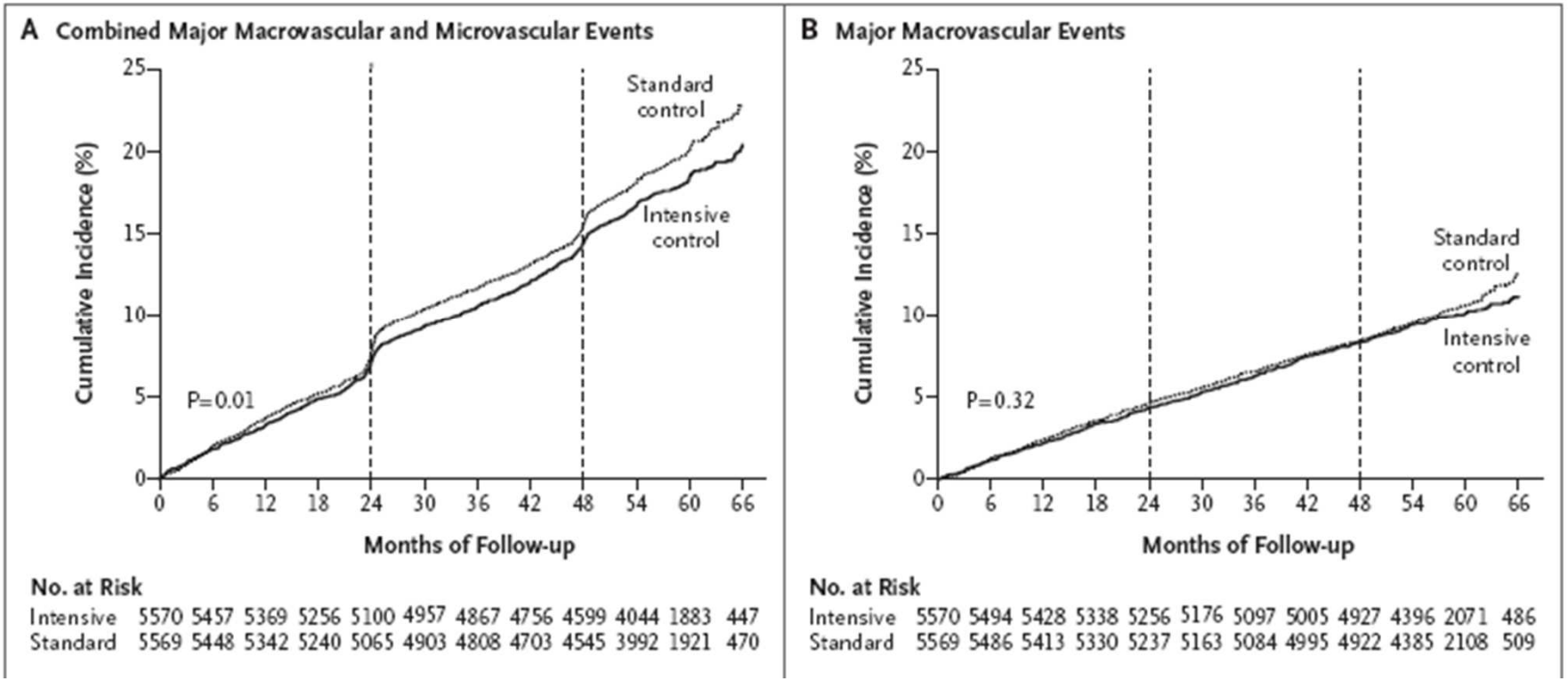
ADVANCE



Réduction du risque relatif 10 %
[95 % CI : 2 à 18 %]
p = 0,01

- **1 événement majeur évité pour 52 diabétiques de type 2 sous contrôle intensif pendant 5 ans**

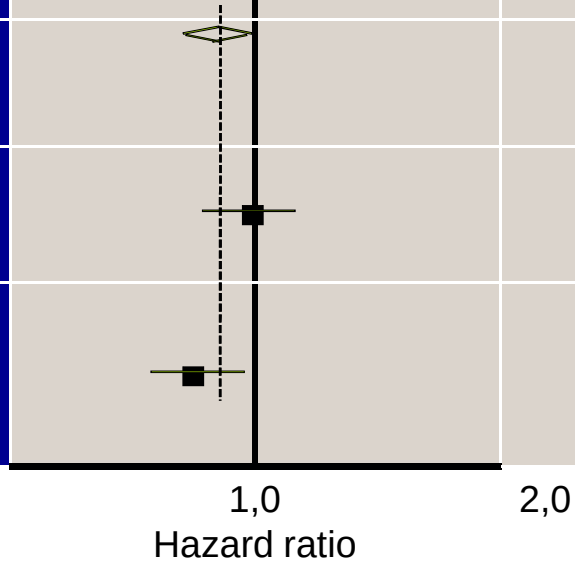
ADVANCE collaborative group. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes NEJM. 2008; vol 358:2560-72.


A Combined Major Macrovascular and Microvascular Events
Cumulative Incidence (%)
25
20
15
10
5
0
Standard control
Intensive control
P=0.01
0 6 12 18 24 30 36 42 48 54 60 66
Months of Follow-up
No. at Risk
Intensive 5570 5457 5369 5256 5100 4957 4867 4756 4599 4044 1883 447
Standard 5569 5448 5342 5240 5065 4903 4808 4703 4545 3992 1921 470
B Major Macrovascular Events
Cumulative Incidence (%)
25
20
15
10
5
0
Standard control
Intensive control
P=0.32
0 6 12 18 24 30 36 42 48 54 60 66
Months of Follow-up
No. at Risk
Intensive 5570 5494 5428 5338 5256 5176 5097 5005 4927 4396 2071 486
Standard 5569 5486 5413 5330 5237 5163 5084 4995 4922 4385 2108 509

Traitement intensif : réduction significative de 14 % de l'incidence des événements microvasculaires majeurs

ADVANCE

	% de patients présentant un événement majeur				
	Tt intensif (n = 5 571)	Tt standard (n = 5 569)	En faveur Tt intensif	En faveur Tt standard	Réduction du risque relatif (IC 95 %)
Combiné micro et macrovasculaires	**1 009 (18,1)**	**1 116 (20,0)**			**10 %** ***p = 0,013***
Macrovasculaires	557 (10,0)	590 (10,6)			6 % **NS**
Microvasculaires	**526 (9,4)**	**605 (10,9)**			**14 %** ***p = 0,015***

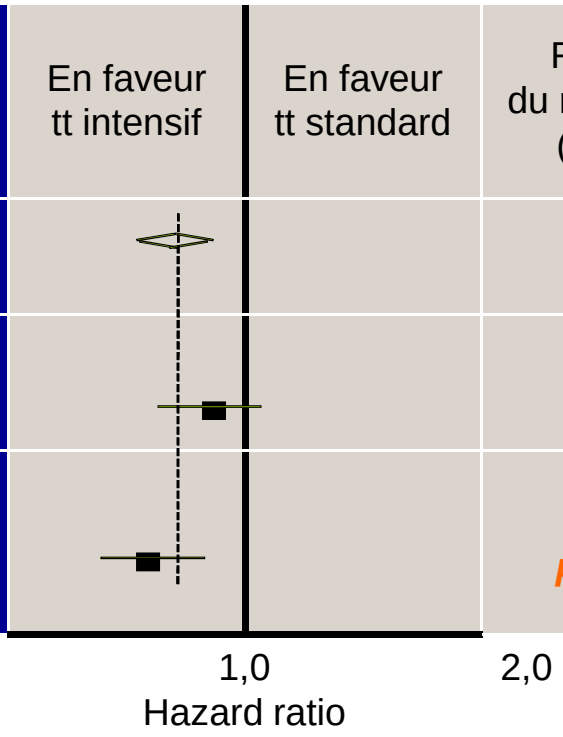


ADVANCE collaborative group. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes NEJM. 2008; vol 358:2560-72.

Traitement intensif : effet significatif sur les néphropathies (-21 %)

ADVANCE

	% de patients présentant un événement majeur		
	Tt intensif (n = 5 571)	Tt standard (n = 5 569)	Réduction du risque relatif (IC 95 %)
Microvasculaires	**526 (9,4)**	**605 (10,6)**	**14 %** ***p = 0,01***
Rétinopathie (apparition, aggravation)	332 (6,0)	349 (6,3)	5 %
Néphropathie (apparition ou aggravation)	**230 (4,1)**	**292 (5,2)**	**21 %** ***p = 0,006***

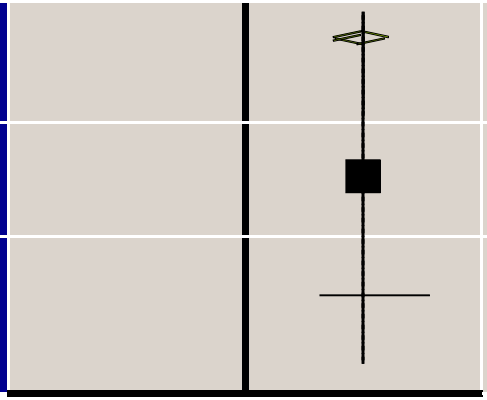


ADVANCE collaborative group. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes NEJM. 2008; vol 358:2560-72.

Traitement intensif : incidence des hypoglycémies sévères plus fréquentes

ADVANCE

	% de patients présentant un événement majeur				
	Tt intensif (n = 5 571)	Tt standard (n = 5 569)	En faveur tt intensif	En faveur tt standard	Augmentation du risque relatif (IC 95 %)
Toutes hypoglycémies	**2654**	**1870**			**42 %***
Mineures	2598	1834			42 %*
Sévères	**150 (2,7)**	**81 (1,5)**			**85 %***



***p < 0,001 vs tt standard**

ADVANCE collaborative group. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes NEJM. 2008; vol 358:2560-72.

Conclusions sur la prise en charge intensive de 11 140 patients DT2

ADVANCE

- Pas de réduction significative de l'incidence des événements macrovasculaires majeurs (AVC/ IDM non fatals & morts d'origine cardiovasculaire)
- Réduction significative de l'incidence de néphropathie sans effet significatif sur la rétinopathie
- Majoration de l'incidence des hypoglycémies sévères
- Faible variation de poids en moyenne

ADVANCE collaborative group. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes NEJM. 2008; vol 358:2560-72.

ORIGINAL ARTICLE

Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes

William Duckworth, M.D., Carlos Abraira, M.D., Thomas Moritz, M.S., Domenic Reda, Ph.D., Nicholas Emanuele, M.D., Peter D. Reaven, M.D., Franklin J. Zieve, M.D., Ph.D., Jennifer Marks, M.D., Stephen N. Davis, M.D., Rodney Hayward, M.D., Stuart R. Warren, J.D., Pharm.D., Steven Goldman, M.D., Madeline McCarren, Ph.D., M.P.H., Mary Ellen Vitek, William G. Henderson, Ph.D., and Grant D. Huang, M.P.H., Ph.D., for the VADT Investigators*

Critères d'inclusion:

Échec ttt ADO ou insuline

Critères d'exclusion:

HbA1c < 7.5%,

Survenue d'un évt CV dans les 6 mois précédents

BMI sup 40

Insuff rénale ou perturbation BH

Patients avec BMI sup 27 kg/m2: bittt metformine + rosiglitazone

Patients avec BMI inf BMI à 27 : glimepiride+ rosiglitazone.

Patients gpe intensif : dose max ADO

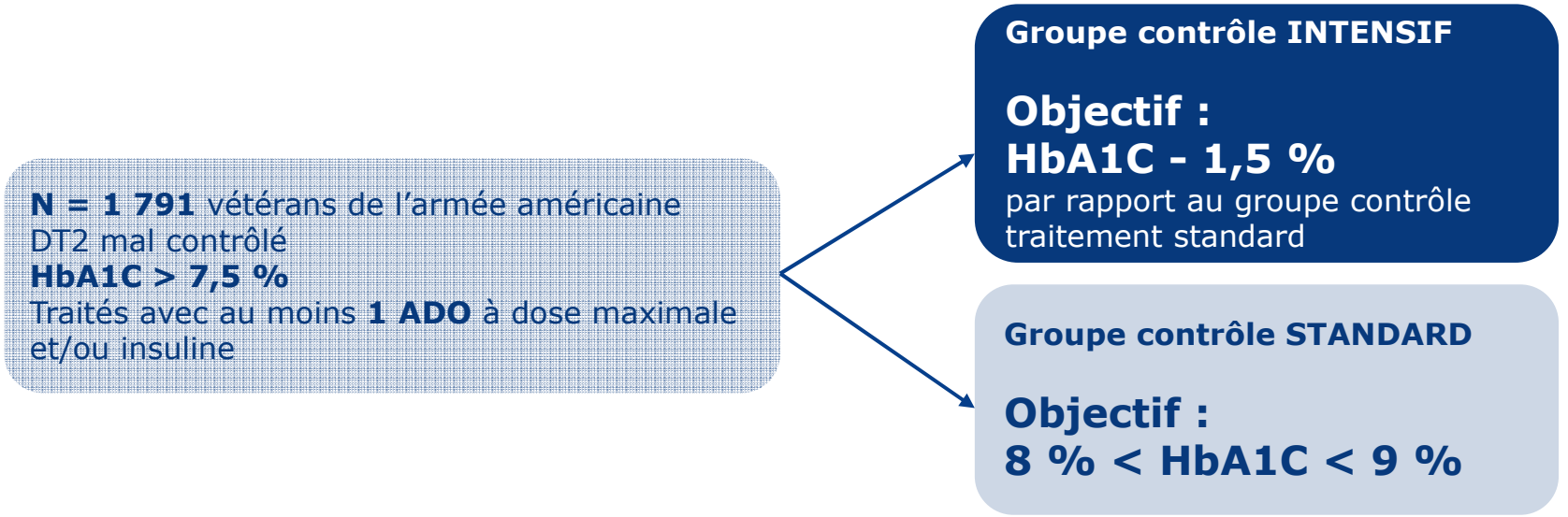
Patient gpe standard: demi-dose ADO in the intensive-therapy

Critère principal: survenue évts CV

Méthodologie de l'étude

VADT

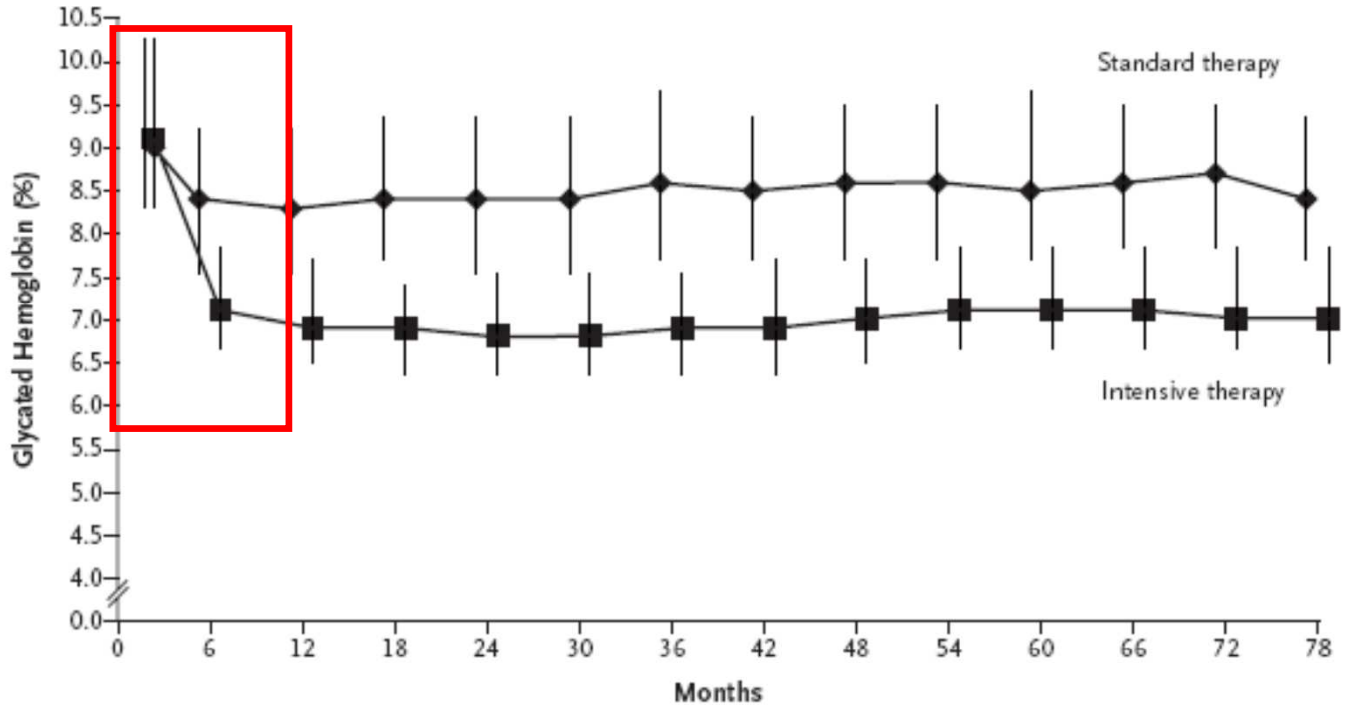
- Étude prospective, randomisée, multicentrique
  - 1791 patients
  - 20 centres aux Etats-Unis



Duckworth W. et al. Glucose control and vascular complications in veterans with type 2 diabetes. N. Engl. J. Med. 2009; 360.

Table 1. Characteristics of the Patients at Baseline and Follow-up.*

Variable	Baseline		
	Standard Therapy (N = 899)	Intensive Therapy (N = 892)	P Value
Age (yr)	60.3±9.0	60.5±9.0	0.64
Sex (no.)			0.98
Male	873	866	
Female	26	26	
Time since diagnosis of diabetes (yr)	11.5±7.0	11.5±8.0	0.96
Patients with previous cardiovascular event (no.)	368	355	0.62
Patients with hypertension (no.)†	650	642	0.83
Race or ethnic group (no.)‡			0.51
Non-Hispanic white	572	539	
Hispanic white	136	155	
Black	147	152	
Other	44	46	
Glycated hemoglobin level (%)§	9.4±2.0	9.4±2.0	0.91
Weight (lb)	214±36	214±36	0.97
Body-mass index	31.2±4.0	31.3±3.0	0.61



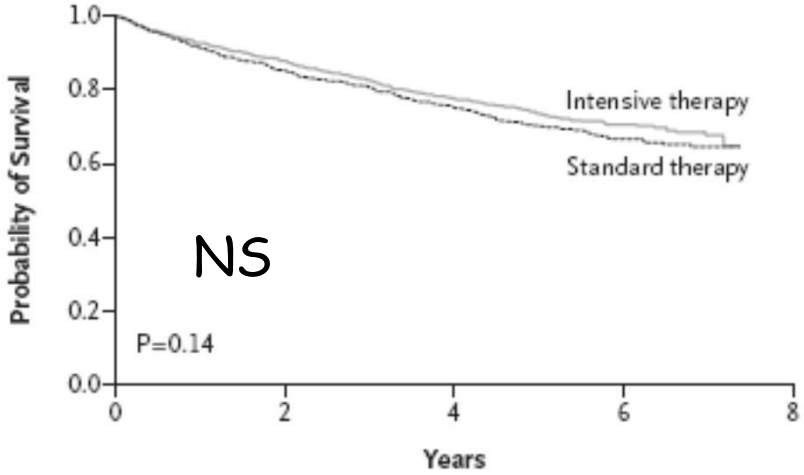
No. at Risk

Standard therapy	899	811	812	759	760	727	727	707	688	667	644	472	329	225
Intensive therapy	892	801	805	763	754	729	706	692	668	661	639	489	340	223

Figure 2. Changes in Median Glycated Hemoglobin Levels from Baseline through 78 Months.

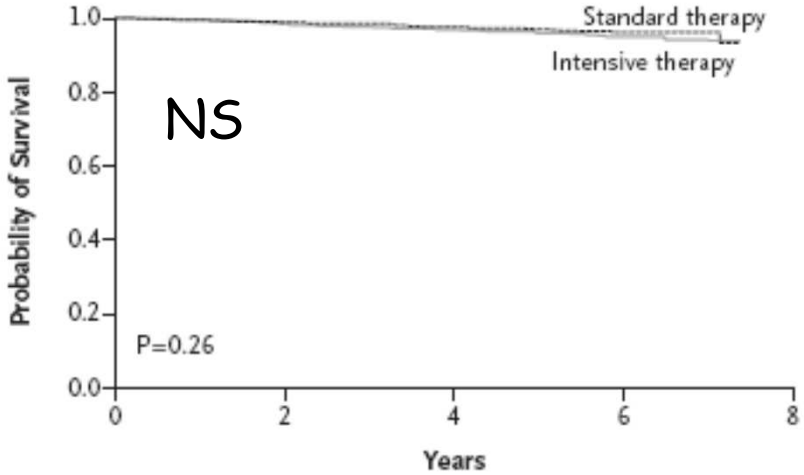
The vertical bars represent interquartile ranges.

A Primary Outcome

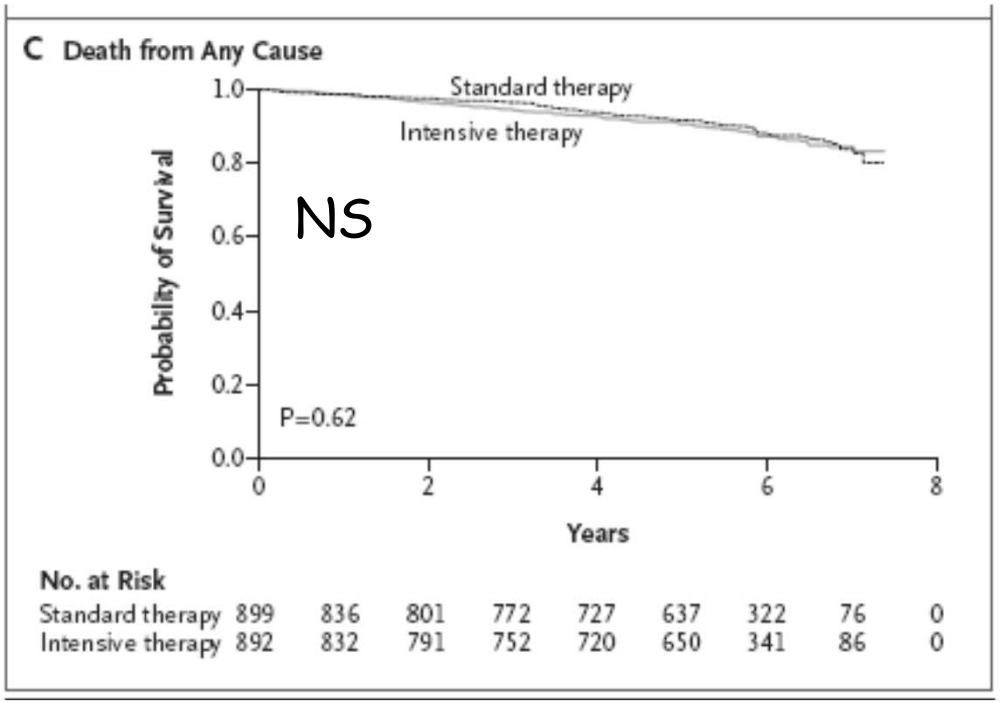


No. at Risk									
Standard therapy	899	770	693	637	570	471	240	55	0
Intensive therapy	892	774	707	639	582	510	252	62	0

B Death from Cardiovascular Causes



No. at Risk									
Standard therapy	899	833	797	767	724	635	320	75	0
Intensive therapy	892	828	786	746	713	646	337	85	0


C Death from Any Cause
Standard therapy
Intensive therapy
NS
P=0.62
Probability of Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
Years
No. at Risk
Standard therapy 899 836 801 772 727 637 322 76 0
Intensive therapy 892 832 791 752 720 650 341 86 0

Résultats

VADT

TTT	Insulino thérapie	Hypoglycémies	Événements CV majeurs n	Décès de causes CV n	Décès toutes causes n
Standard **N= 899**	74 %	17,6 %	264	33	95
Intensif **N= 892**	90 %	24,1 %	235	40	100
HR **(IC95)** **p**	-	-	0,88 **(0,74-1,05)** **p = 0,14**	**NS**	1,07 **(0,81-1,42)** **p = 0,62**

Duckworth W. et al. Glucose control and vascular complications in veterans with type 2 diabetes. N. Engl. J. Med. 2009; 360.
Weiss I.A. et al. Impact of glycemic treatment choices on cardiovascular complications in type 2 diabetes. Cardiology in review. 2009; 17 : 165-75.

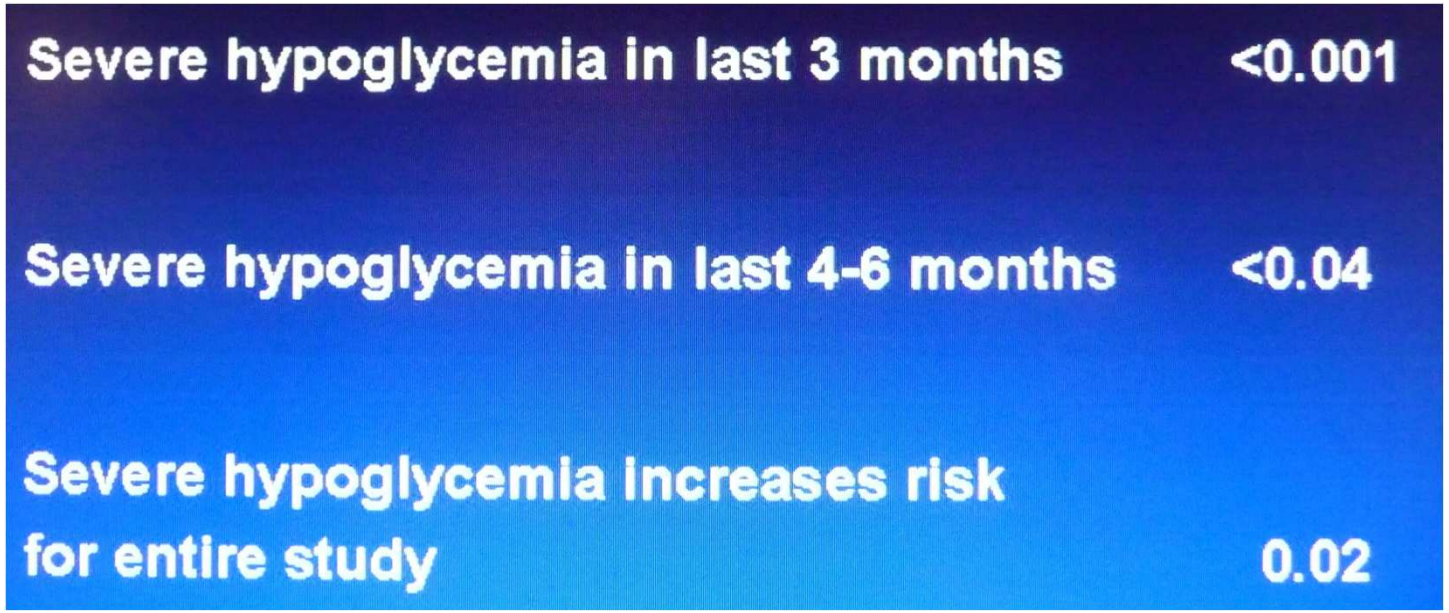
Facteurs Prédictifs de Mortalité CV

VADT

Age	2.1	<0.0001
Prior Cardiovascular Event	3.1	0.0001
HbA1c at Baseline	1.2	<0.04
HDL	0.2	0.01
Creatinine	1.8	<0.0001
Recent Severe Hypoglycemia	3.7	0.01

Hypoglycémies sévères et Mortalité Totale

VADT



CONCLUSIONS

Intensive glucose control in patients with poorly controlled type 2 diabetes had no significant effect on the rates of major cardiovascular events, death, or microvascular complications. (ClinicalTrials.gov number, NCT00032487.)

Prise en charge multifactorielle dans le diabète de type 2: L'étude Sténo 2..

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 30, 2003 VOL. 348 NO. 5

Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes

Peter Gæde, M.D., Pernille Vedel, M.D., Ph.D., Nicolai Larsen, M.D., Ph.D., Gunnar V.H. Jensen, M.D., Ph.D., Hans-Henrik Parving, M.D., D.M.Sc., and Oluf Pedersen, M.D., D.M.Sc.

Prise en charge multifactorielle dans le diabète de type 2: L'étude Sténo 2..

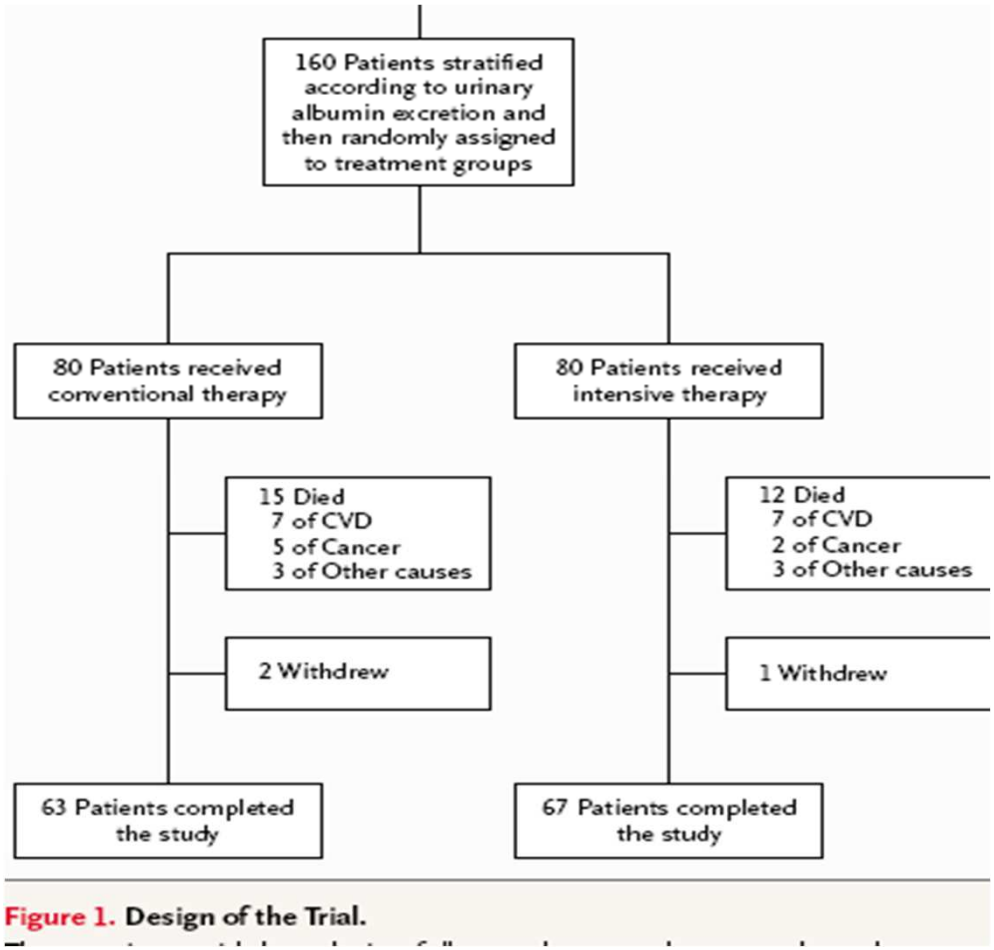


Figure 1. Design of the Trial.

- Etude randomisée
- D2 avec microalbuminurie (55 ans)
- Ttt intensif FDR vs ttt conventionnel
- Suivi 7,8 ans
- I end-point:DC CV, IDM, AVC, amputation
- II end-point: microangiopathie

Gaede P, Vedel P, Larsen N, Jensen G, Parving H-H, Pedersen O (2003) Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 348:383–393

Prise en charge multifactorielle dans le diabète de type 2: L'étude Sténo 2..

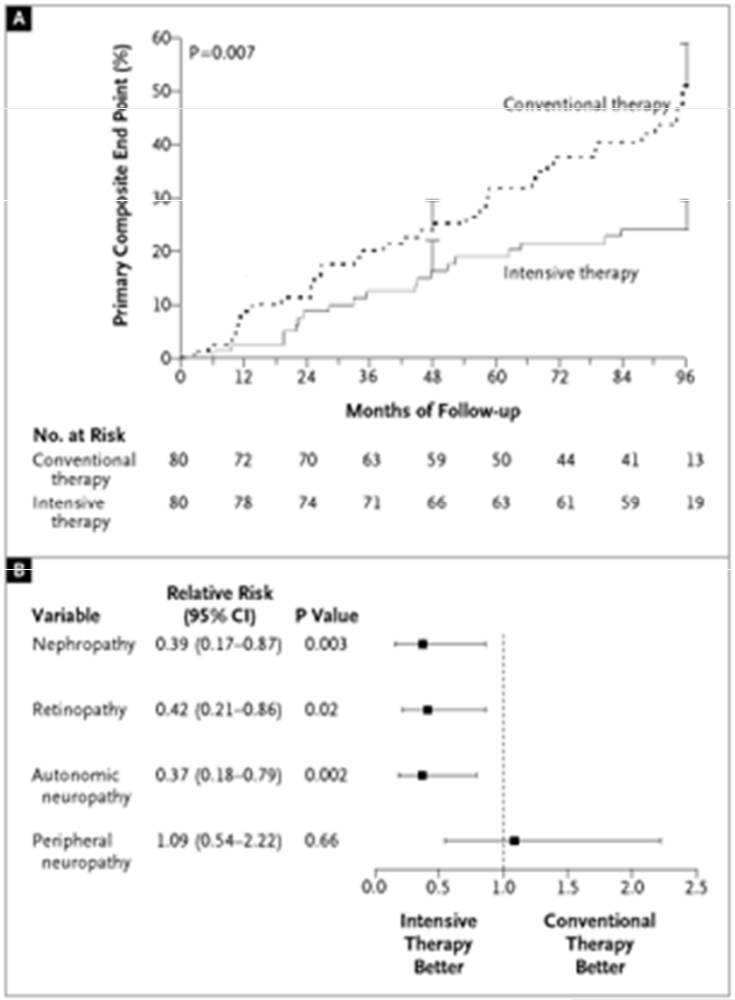
Table 1. Treatment Goals for the Conventional-Therapy Group and the Intensive-Therapy Group.*

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

* To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. ACE denotes angiotensin-converting enzyme.

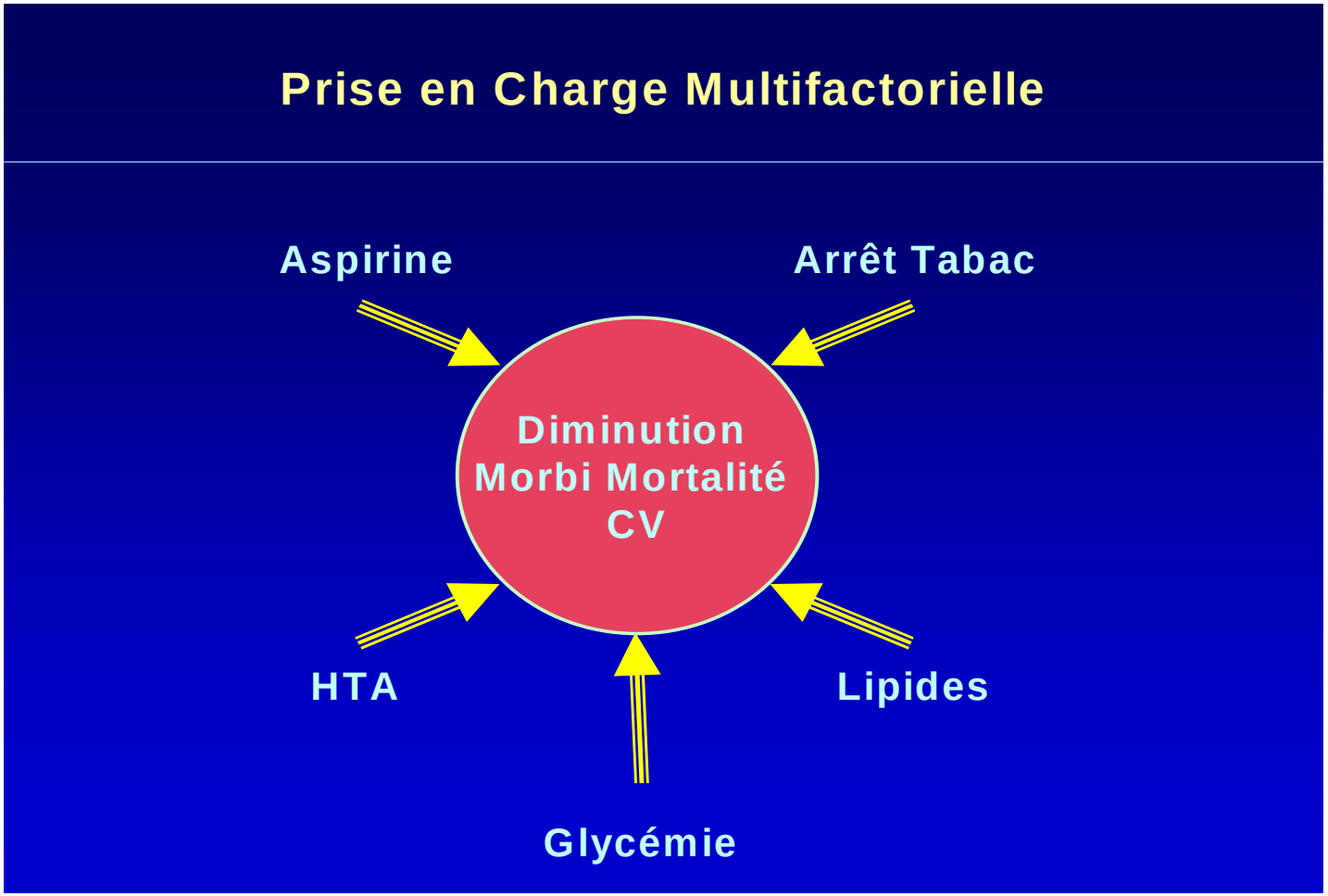
Gaede P, Vedel P, Larsen N, Jensen G, Parving H-H, Pedersen O (2003) Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 348:383–393

Prise en charge multifactorielle dans le diabète de type 2: L'étude Sténo 2..



Gaede P, Vedel P, Larsen N, Jensen G, Parving H-H, Pedersen O (2003) Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 348:383–393

Prise en Charge Multifactorielle



En conclusion les données récentes dans le D2

- Optimisation de l'équilibre glycémique +++ en début de prise en charge!
- Optimisation de l'équilibre "moins bénéfique" en cas de diabète ancien

- Attention aux hypoglycémies chez les patients avec atcd CV

- Prise en charge multifactorielle essentielle

Etude d'intervention en prévention secondaire..: PROactive

PROspective pioglitazone Clinical Trial in Macrovascular Events

Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial

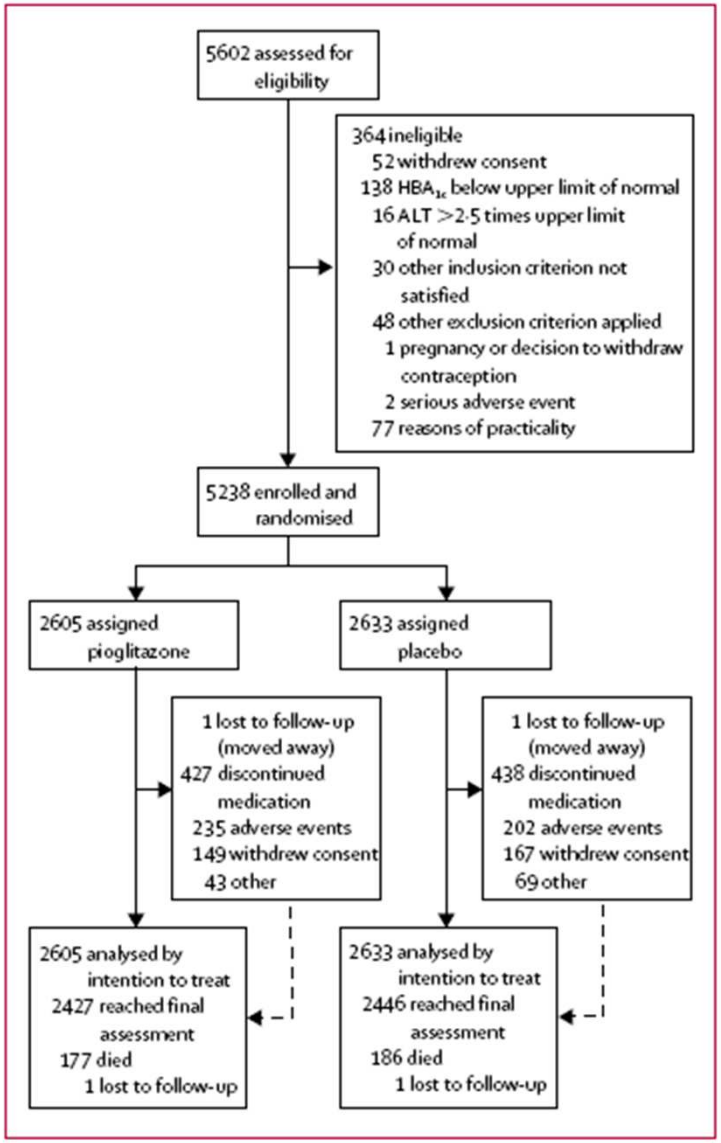
John A Dormandy, Bernard Charbonnel, David J A Eckland, Erland Erdmann, Massimo Massi-Benedetti, Ian K Moules, Allan M Skene, Meng H Tan, Pierre J Lefèbvre, Gordon D Murray, Eberhard Standl, Robert G Wilcox, Lars Wilhelmsen, John Betteridge, Kåre Birkeland, Alain Golay, Robert J Heine, László Korányi, Markku Laakso, Marián Mokáň, Antanas Norkus, Valdis Pirags, Toomas Podar, André Scheen, Werner Scherbaum, Guntram Schernthaner, Ole Schmitz, Jan Škrha, Ulf Smith, Jan Taton, on behalf of the PROactive investigators*

Lancet 2005; 366: 1279–89

PROspective pioglitazone Clinical Trial in Macrovascular Events

- Etude randomisée multicentrique
- D2 entre 35-75 ans, HbA1c > 6,5%
- + complication cardiovasculaire connue
- Randomisation Pioglitazone 45 mg vs pcb, + ttt habituel
- Suivi moyen 34 mois
- I End-points: délai avant évt cardiovasc majeur
- II End-point: délai avant IDM, AVC

PROspective pioglitazone Clinical Trial in Macrovascular Events



PROspective pioglitazone Clinical Trial in Macrovascular Events

	Pioglitazone	Placebo	p
HBA_{1c} (% absolute change)	−0·8 (−1·6 to −0·1)	−0·3 (−1·1 to 0·4)	<0·0001
Triglycerides (% change)	−11·4 (−34·4 to 18·3)	1·8 (−23·7 to 33·9)	<0·0001
LDL cholesterol (% change)	7·2 (−11·2 to 27·6)	4·9 (−13·9 to 23·8)	0·003
HDL cholesterol (% change)	19·0 (6·6 to 33·3)	10·1 (−1·7 to 21·4)	<0·0001
LDL/HDL (% change)	−9·5 (−27·3 to 10·1)	−4·2 (−21·7 to 15·8)	<0·0001
Micral test results (baseline to final visit)			
Improved (number, %)	492 of 2218 (22%)	451 of 2225 (20%)	0·286
Worsened (number, %)	555 of 2218 (25%)	563 of 2225 (25%)	

Data are median (IQR) unless otherwise stated.

Table 7: **Change in laboratory data from baseline to final visit**

PROspective pioglitazone Clinical Trial in Macrovascular Events

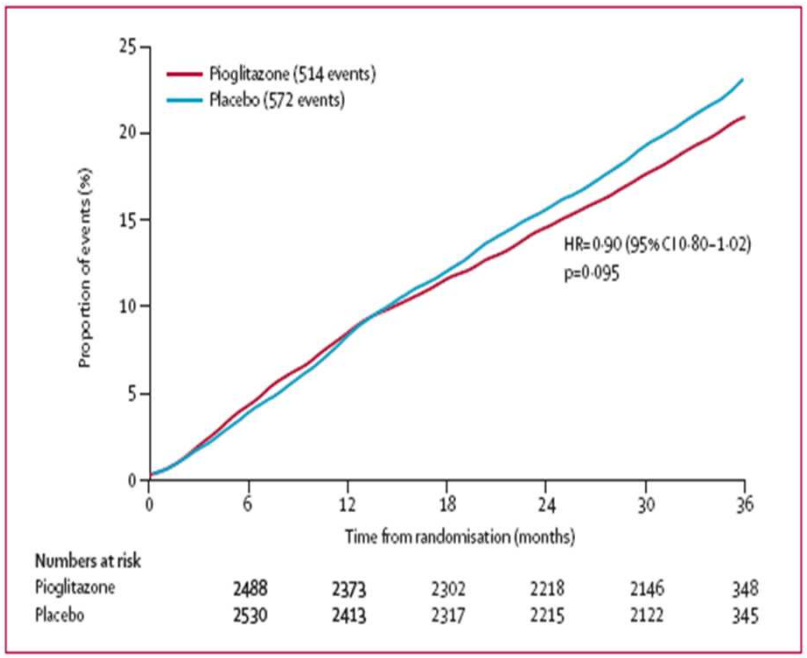


Figure 2: Kaplan-Meier curve of time to primary endpoint*
*Death from any cause, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, leg amputation, coronary revascularisation, or revascularisation of the leg.

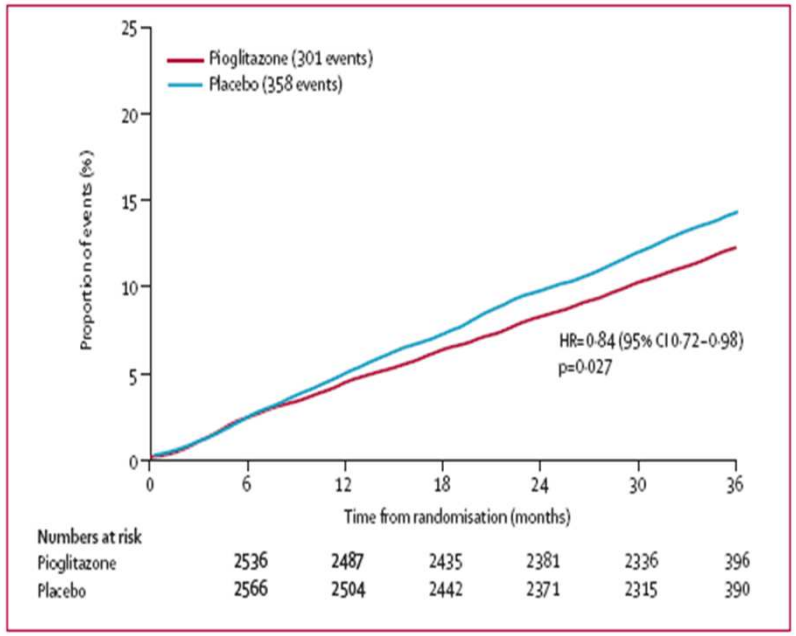


Figure 3: Kaplan-Meier curve of time to main secondary endpoint*
*Death from any cause, non-fatal myocardial infarction (excluding silent myocardial infarction), or stroke.

En résumé, PROactive...

Pas de réduction tx d'évts cardiovasculaires majeurs sous Pioglitazone dans une population à haut risque en prévention secondaire

Bénéfice significatif en terme d'objectif IIaire, mais réduction modeste...RR 16%

Pas d'argument pour une utilisation des TZD en prévention cardiovasculaire