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# Facteurs de risques cardiovasculaires et grandes études

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Cours DES 9 février 2013

Anne-Cécile Paepegaey

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# Plan

- I. Certitudes sur l'intérêt du contrôle strict de la glycémie
    - Chez type 2
    - Chez type 1
  - II. Facteurs de risques cardiovasculaires et études d'intervention non glycémique
  - III. Jusqu'où aller trop loin
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# Certitudes sur l'intérêt du contrôle strict de la glycémie

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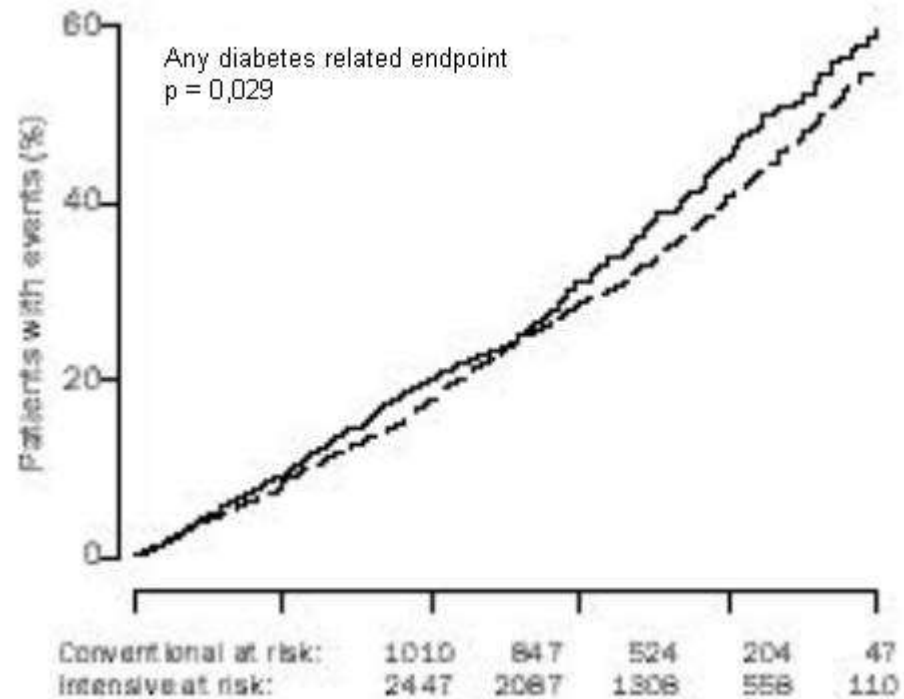
# Intensive blood-glucose control with sulphonylurea or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. UKPDS 33. Lancet 1998

HbA1C :

- intensif : 7,0%
- conventionnel : 7,9%

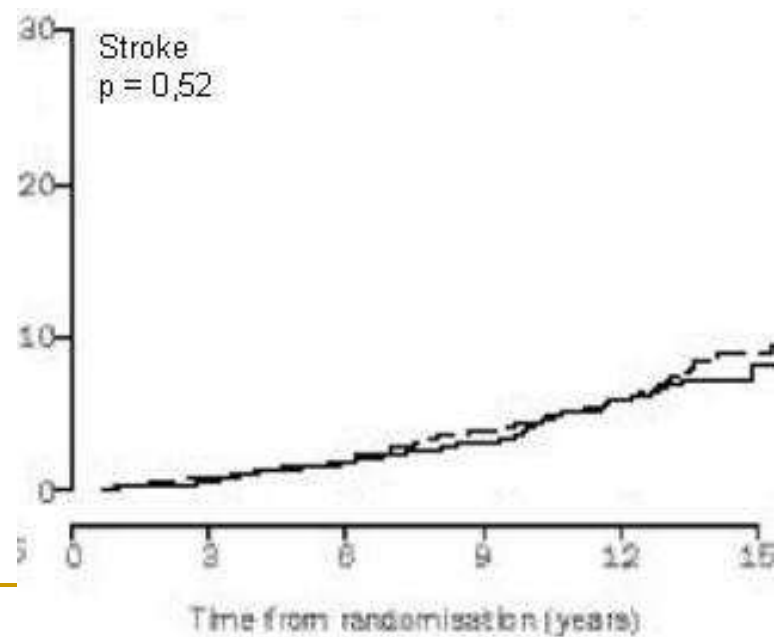
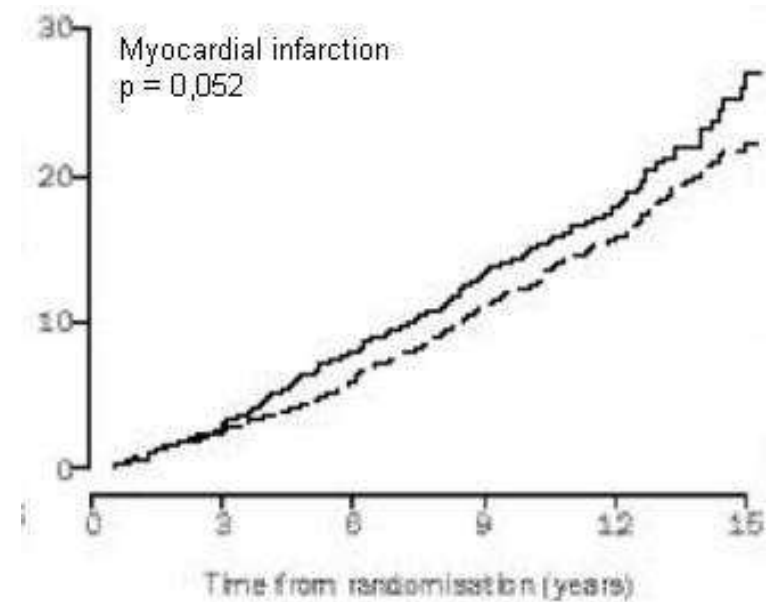
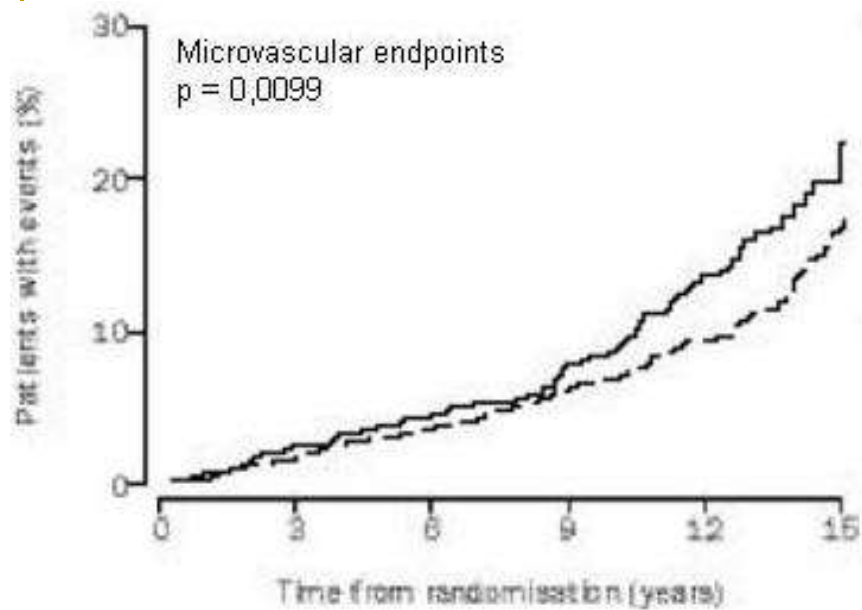
Diabetes related endpoint :

- mort subite
- mort hypo/hyperglycémie
- IDM/angor/ACR
- AVC
- Irénale, amputation, hémorragie IV, RD avec photocoagulation, cécité, cataracte

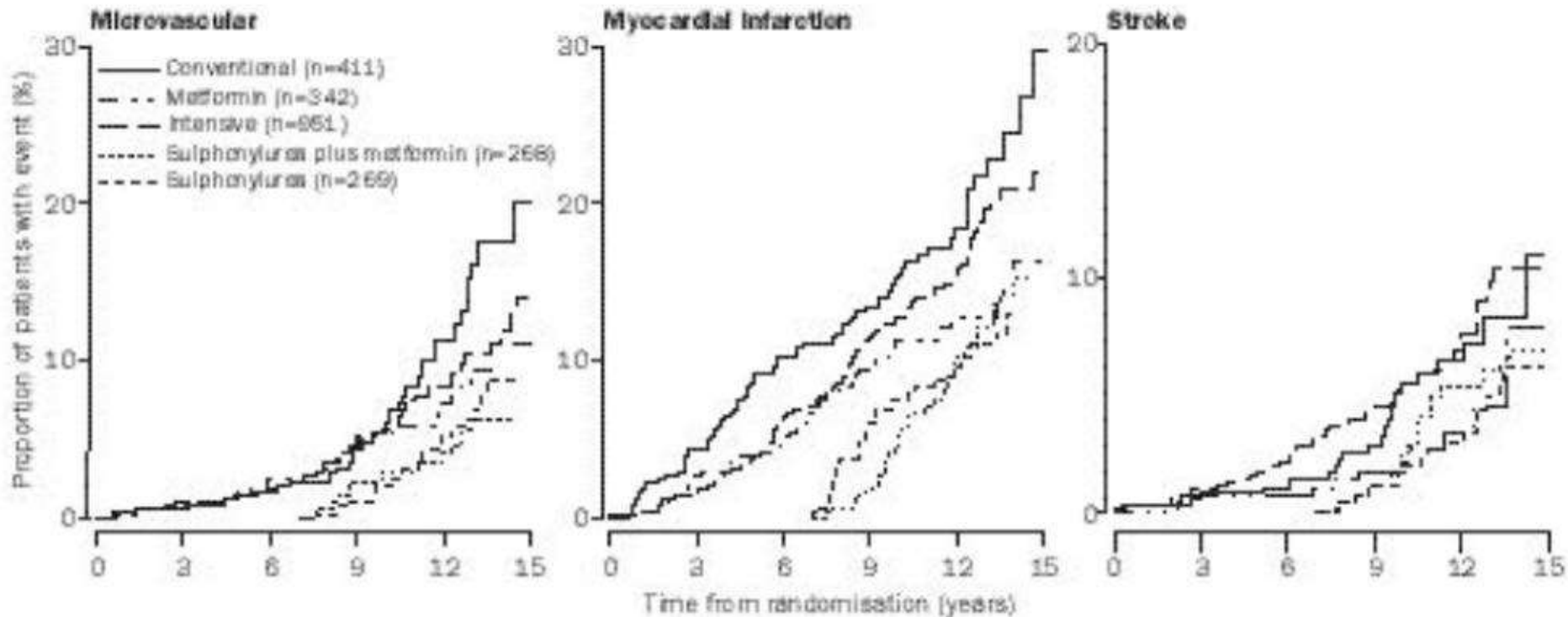


— traitement intensif

- - - : traitement conventionnel

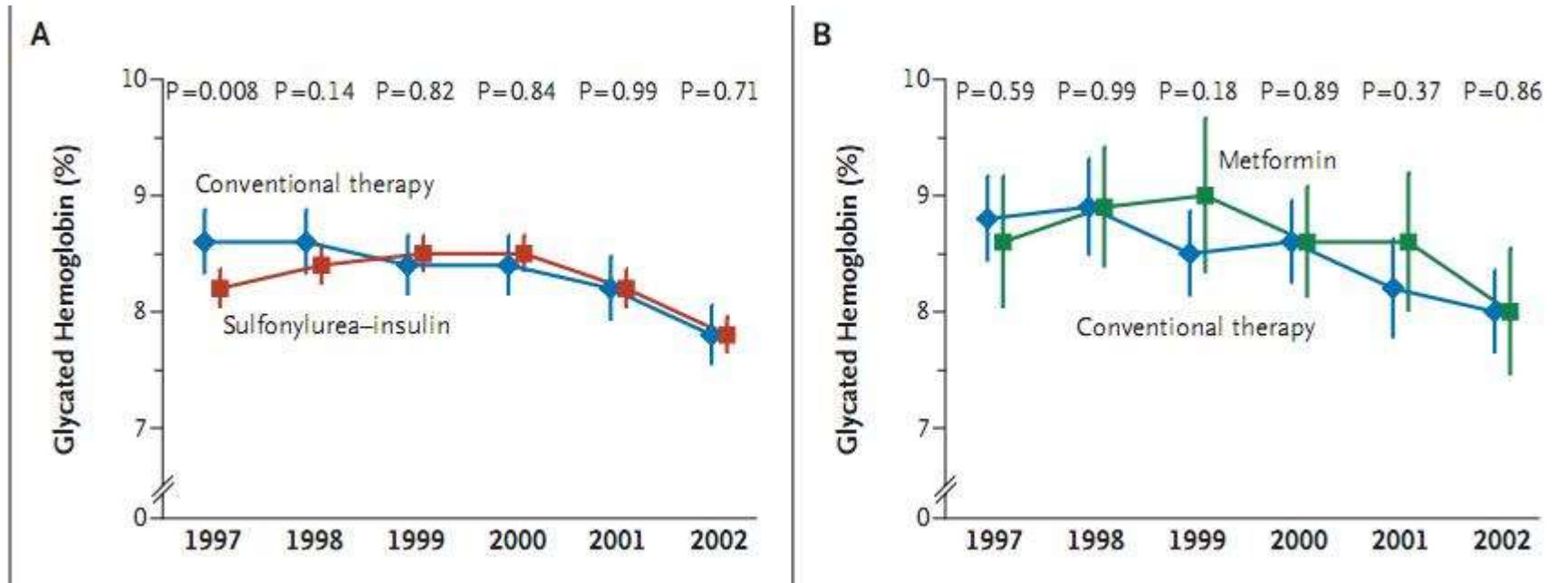


# Effet of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes. UKPDS 34. Lancet 1998.

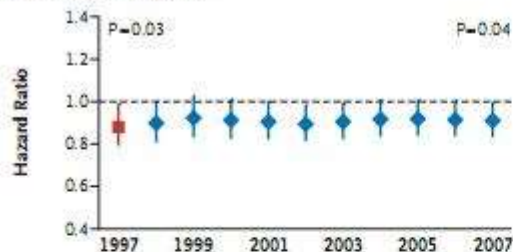


→ Metformine doit être utilisé en 1ere intention

# 10-year follow up of intensive glucose control in type 2 diabetes. NEJM 2008

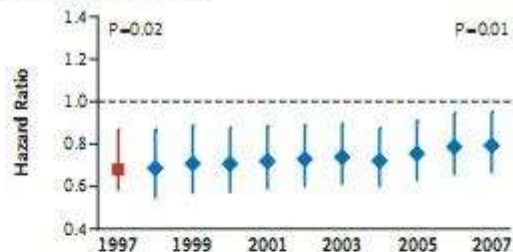


### A Any Diabetes-Related End Point



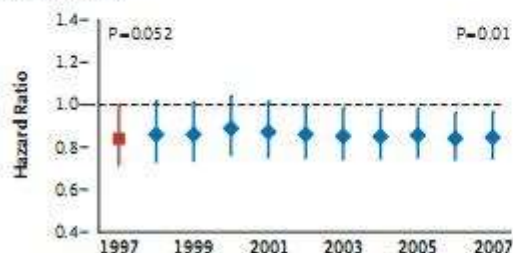
No. of Events	1997	1999	2001	2003	2005	2007
Conventional therapy	438	498	571	620	651	686
Sulfonylurea-insulin	963	1151	1292	1409	1505	1571

### B Any Diabetes-Related End Point



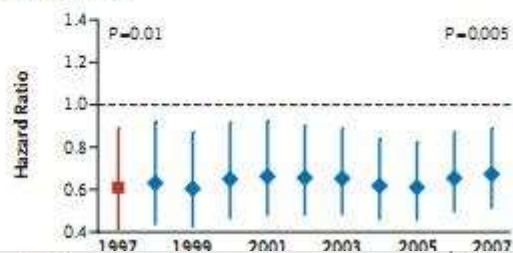
No. of Events	1997	1999	2001	2003	2005	2007
Conventional therapy	160	190	220	240	252	262
Metformin	98	126	152	175	189	209

### C Myocardial Infarction

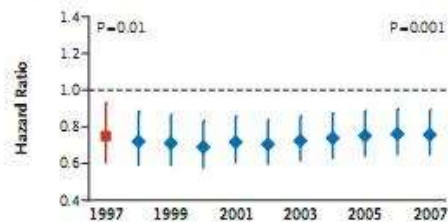


No. of Events	1997	1999	2001	2003	2005	2007
Conventional therapy	186	212	239	271	296	319
Sulfonylurea-insulin	387	450	513	573	636	678

### D Myocardial Infarction

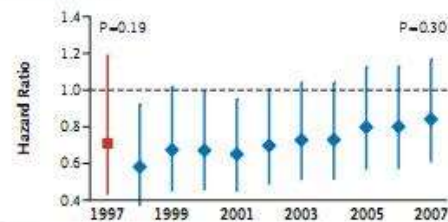


### E Microvascular Disease



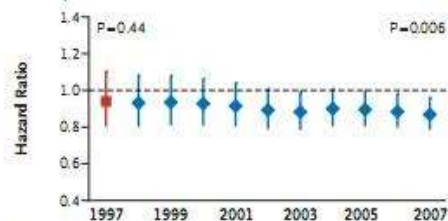
No. of Events	1997	1999	2001	2003	2005	2007
Conventional therapy	121	155	187	205	212	222
Sulfonylurea-insulin	225	277	338	378	406	429

### F Microvascular Disease



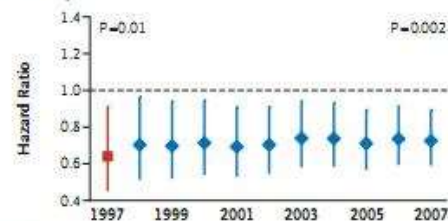
No. of Events	1997	1999	2001	2003	2005	2007
Conventional therapy	38	58	70	73	74	78
Metformin	24	37	44	52	58	66

### G Death from Any Cause



No. of Events	1997	1999	2001	2003	2005	2007
Conventional therapy	213	267	330	400	460	537
Sulfonylurea-insulin	489	610	737	868	1028	1163

### H Death from Any Cause



No. of Events	1997	1999	2001	2003	2005	2007
Conventional therapy	89	113	136	160	183	217
Metformin	50	70	86	110	123	152



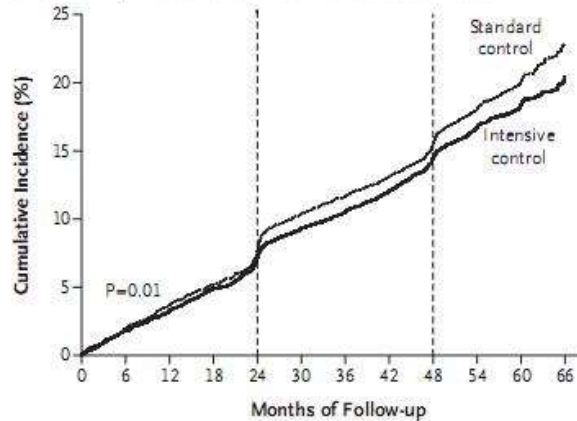
# Intensive blood-glucose control and vascular outcomes in patients with type 2 diabetes. ADVANCE. NEJM2008

HbA1C

-Conventionnel 7,3%

- Intensif 6,5

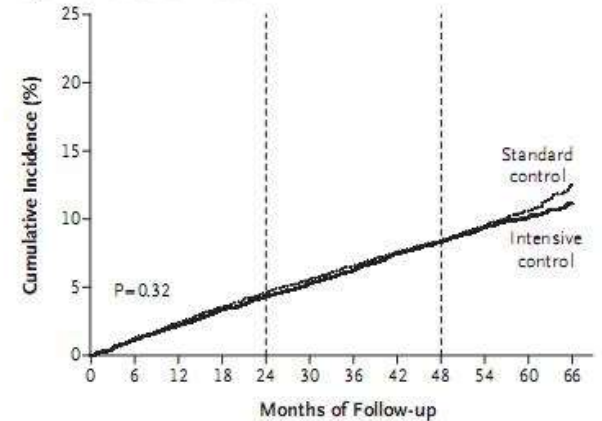
**A Combined Major Macrovascular and Microvascular Events**



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

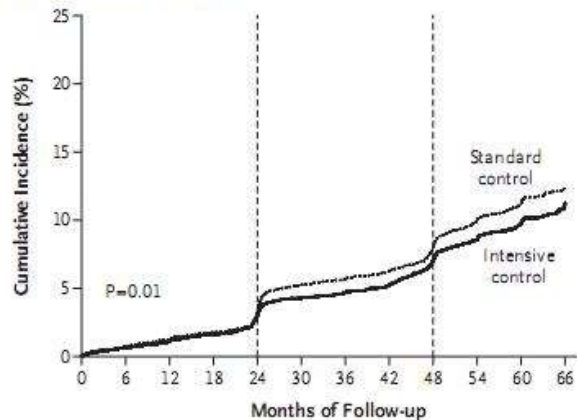
**B Major Macrovascular Events**



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

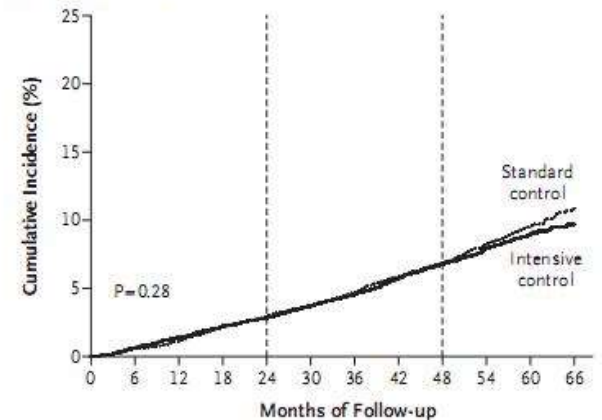
**C Major Microvascular Events**



No. at Risk

Intensive	5571	5495	5430	5358	5233	5120	5055	4968	4824	4258	1992	473
Standard	5569	5498	5431	5353	5207	5069	4995	4911	4764	4204	2024	494

**D Death from Any Cause**



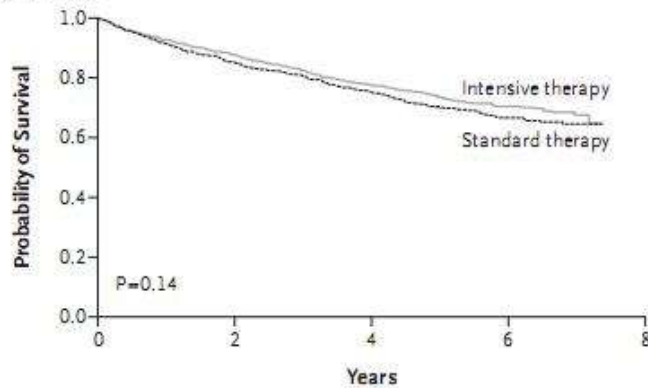
No. at Risk

Intensive	5571	5533	5490	5444	5411	5361	5312	5246	5189	4653	2211	523
Standard	5569	5537	5503	5445	5399	5354	5301	5237	5178	4643	2240	544

Figure 3. Cumulative Incidences of Events, According to Glucose-Control Strategy.

# Glucose control and vascular complications in veterans with type 2 diabetes. VADT. NEJM 2009

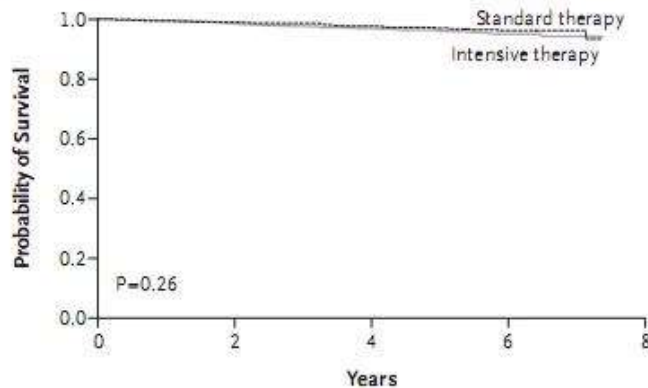
**A Primary Outcome**



**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

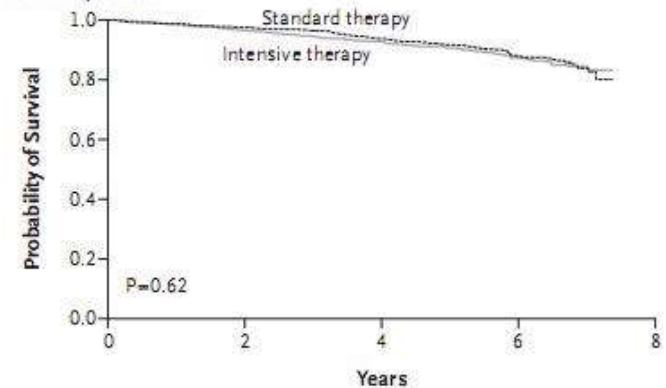
**B Death from Cardiovascular Causes**



**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

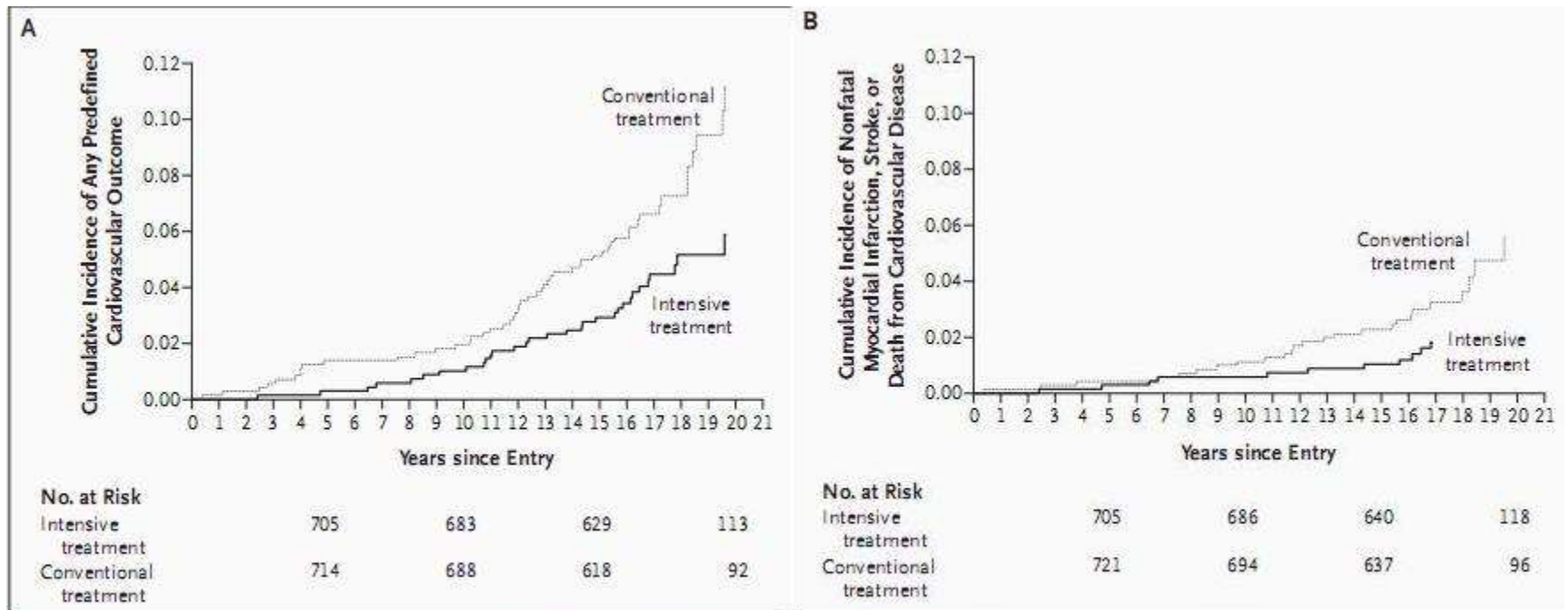
**C Death from Any Cause**



**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

# Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. DCCT/EDIC. NEJM 2005



**Figure 1.** Cumulative Incidence of the First of Any of the Predefined Cardiovascular Disease Outcomes (Panel A) and of the First Occurrence of Nonfatal Myocardial Infarction, Stroke, or Death from Cardiovascular Disease

Diminution de

-42% maladie CV (IC95% à 9-63)  $p = 0,02$

- 57% décès CV (IC95% à 12-79)  $p = 0,02$

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# Facteurs de risques cardiovasculaires et études d'intervention non glycémique

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# Diabetes other risk factors and 12-year cardiovascular mortality for men screened in the multiple risk factor intervention trial. Stamler. 1993

Table 2—Number of deaths by cause and age-adjusted death rate for men with (n = 5163) and without (n = 342,815) diabetes at initial screening for the MRFIT

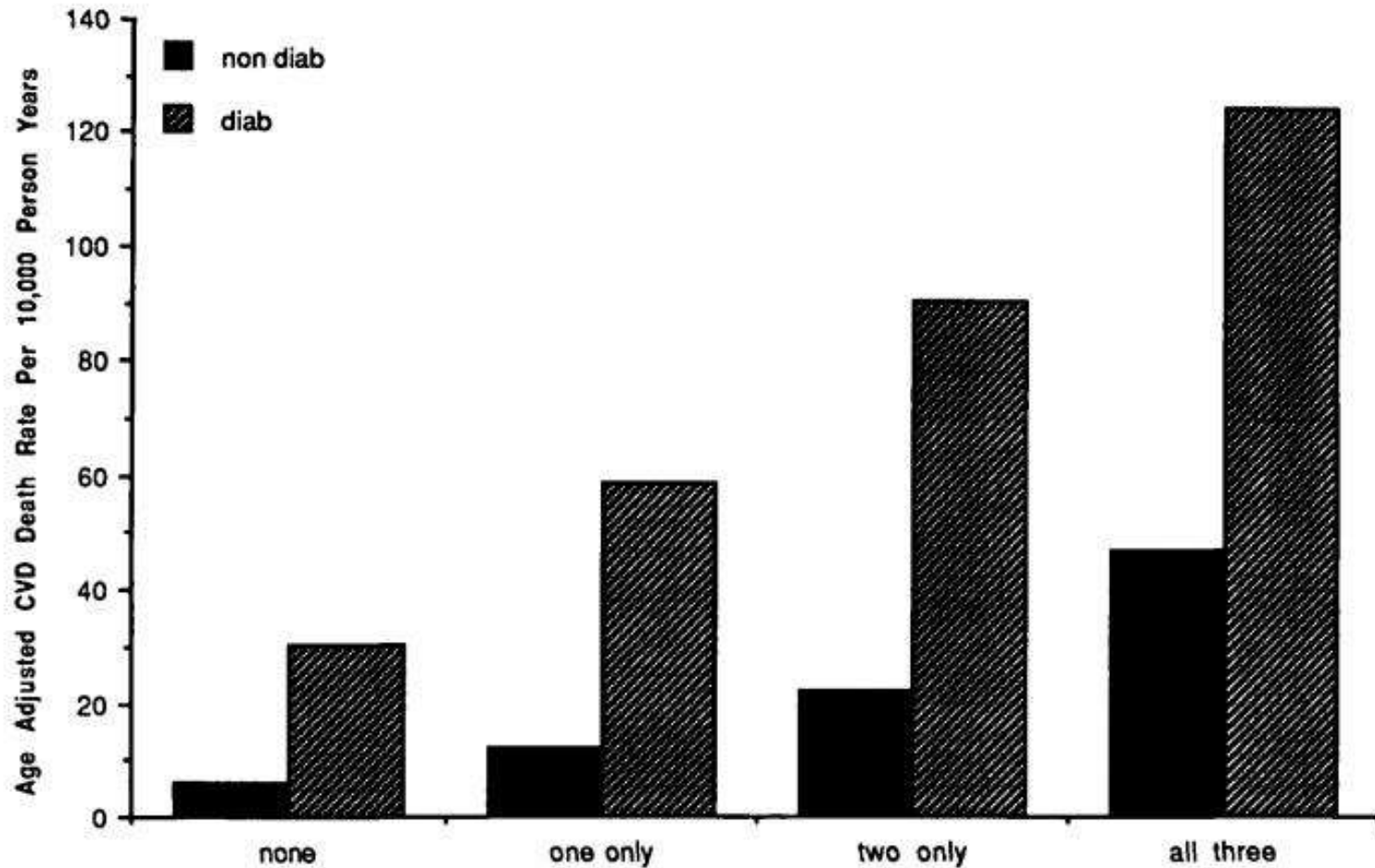
CAUSE OF DEATH (ICD-9 CODE)	MEN WITH DIABETES		MEN WITHOUT DIABETES		ADJUSTED RR FOR DIABETIC/NONDIABETIC* (95% CI)
	DEATHS (N)	RATE (PER 10,000 PERSON-YR)	DEATHS (N)	RATE (PER 10,000 PERSON-YR)	
CVD (390–459)	603	85.13	8965	22.88	3.0 (2.8–3.3)
CHD (410–414, 429.2)	469	65.91	6681	17.05	3.2 (2.9–3.5)
STROKE (430–438)	48	6.72	685	1.75	2.8 (2.0–3.7)
OTHER CVD	86	12.49	1599	4.08	2.3 (1.8–2.9)
ALL DEATHS	1092	160.13	20,867	53.20	2.5 (2.4–2.7)

\*Adjusted for age, race, income, serum cholesterol level, sBP, and number of cigarettes/day.

But : - déterminer les FDR de mortalité CV

- étudier l'effet indépendant du diabète sur le risque CV

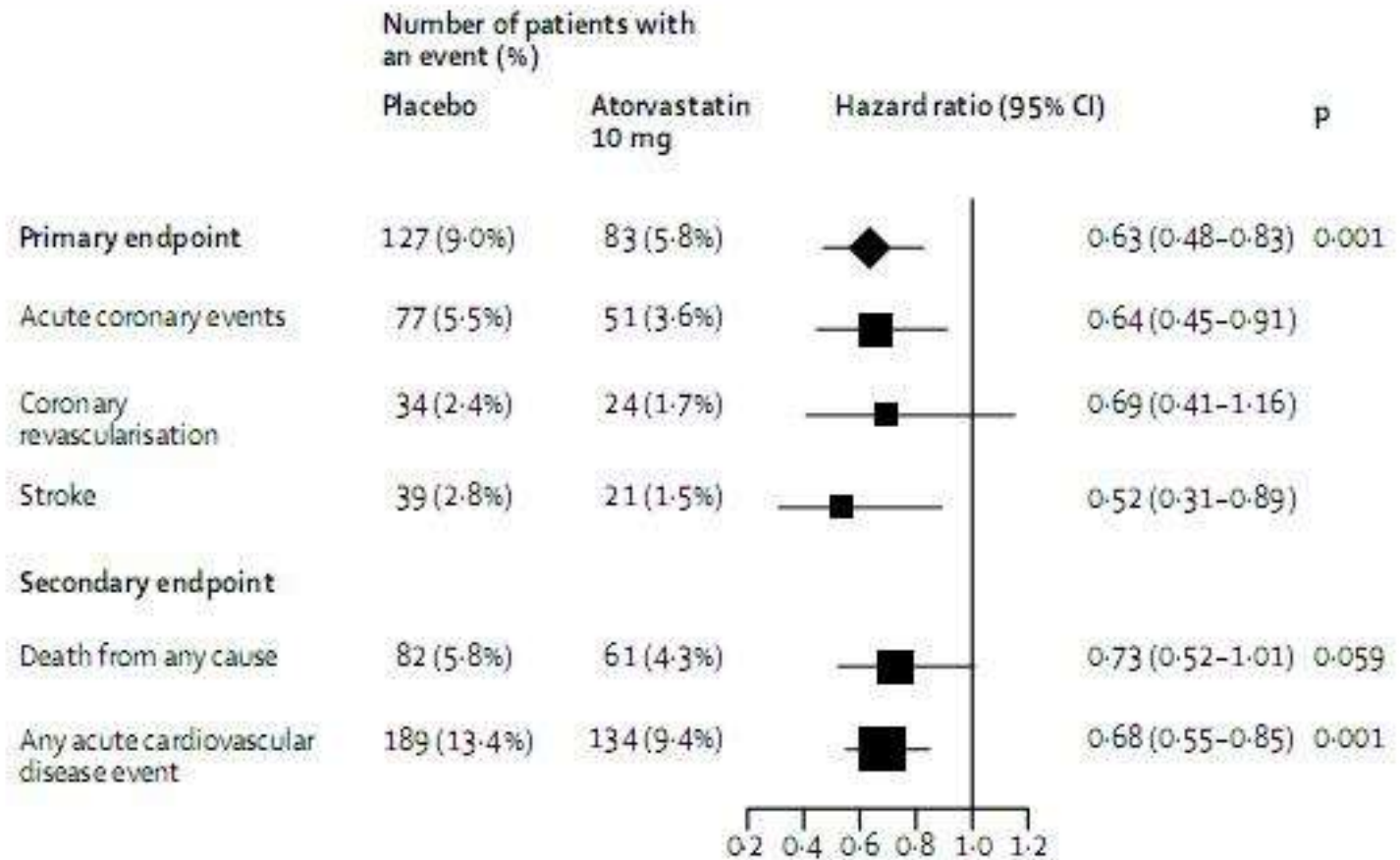
Risque CV ; diabète, taux de cholestérol, PAs, tabac



**Figure 2**—Age-adjusted CVD death rates by presence of number of risk factors for men screened for MRFIT, with and without diabetes at baseline.



# Primary prevention of cardiovascular disease with atorvastatine in type 2 diabetes in CARDS. Lancet 2004



Essai interrompu 2 ans à l'avance au vu des résultats du groupe statine

Figure 3: Effect of treatment on primary and secondary endpoints

# Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes : UKPDS 38. BMJ 1999

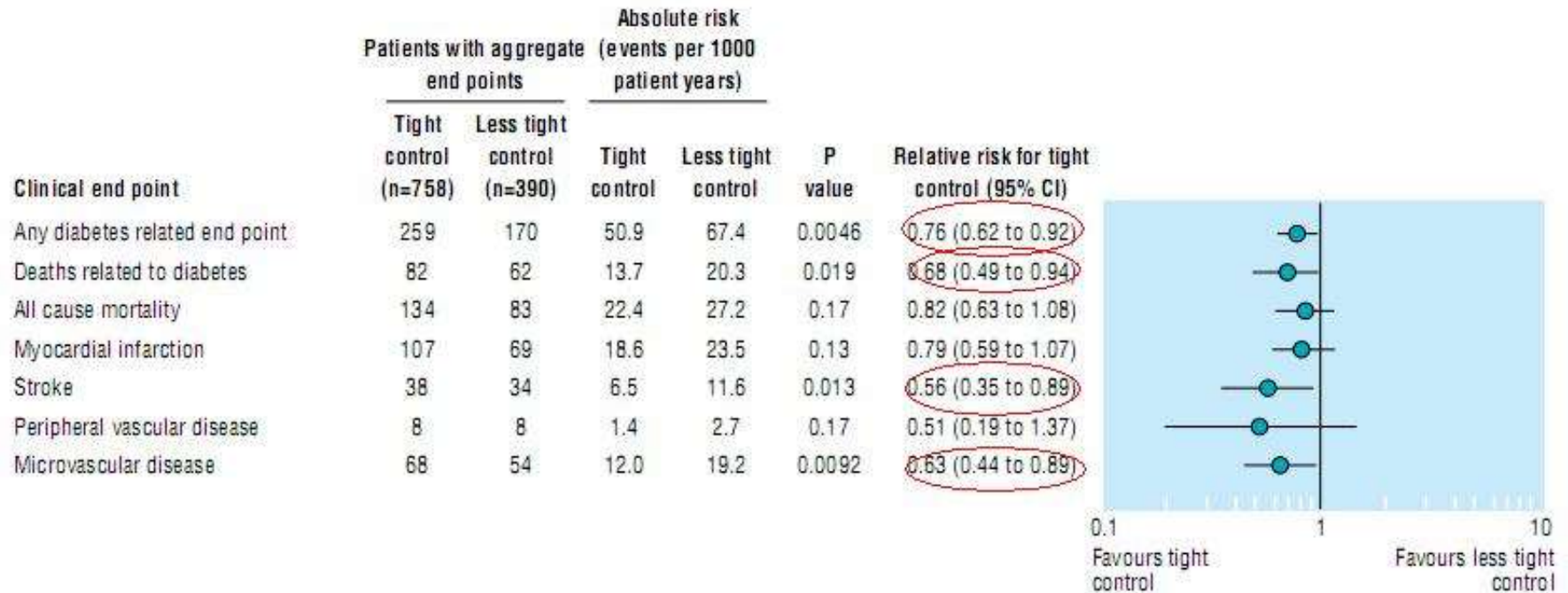


Fig 4 Numbers of patients who attained one or more clinical end points in aggregates representing specific types of clinical complications, with relative risks comparing tight control of blood pressure with less tight control

« Tight control » : PA : 144/82

« Less tight » : PA 154/87

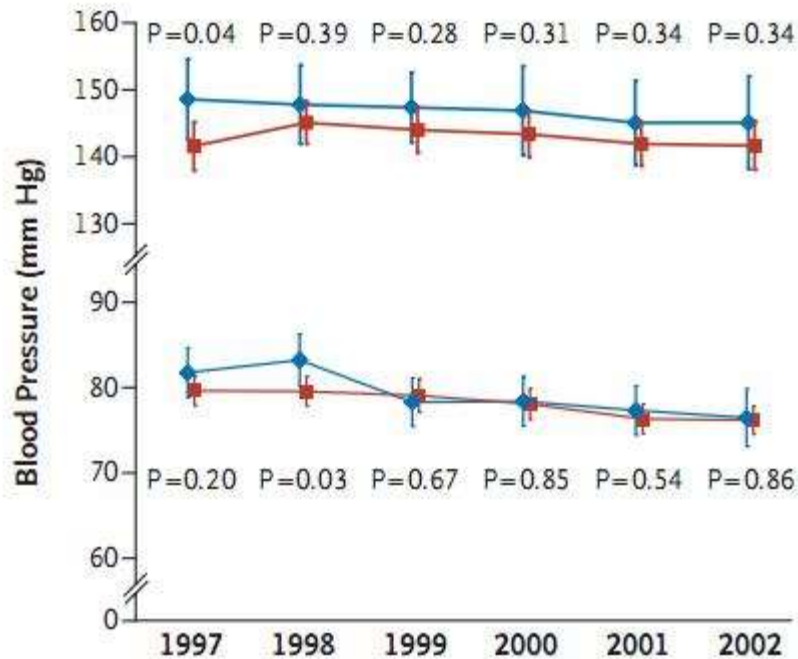
p<0 0001



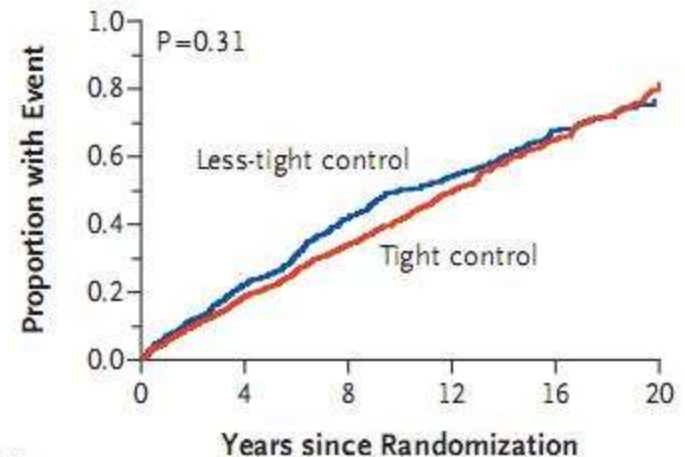
# Long term follow up after tight control of blood pressure in type 2 diabetes. Rury R. Holman. NEJM 2008

◆ Less-tight control  
 ■ Tight control

A



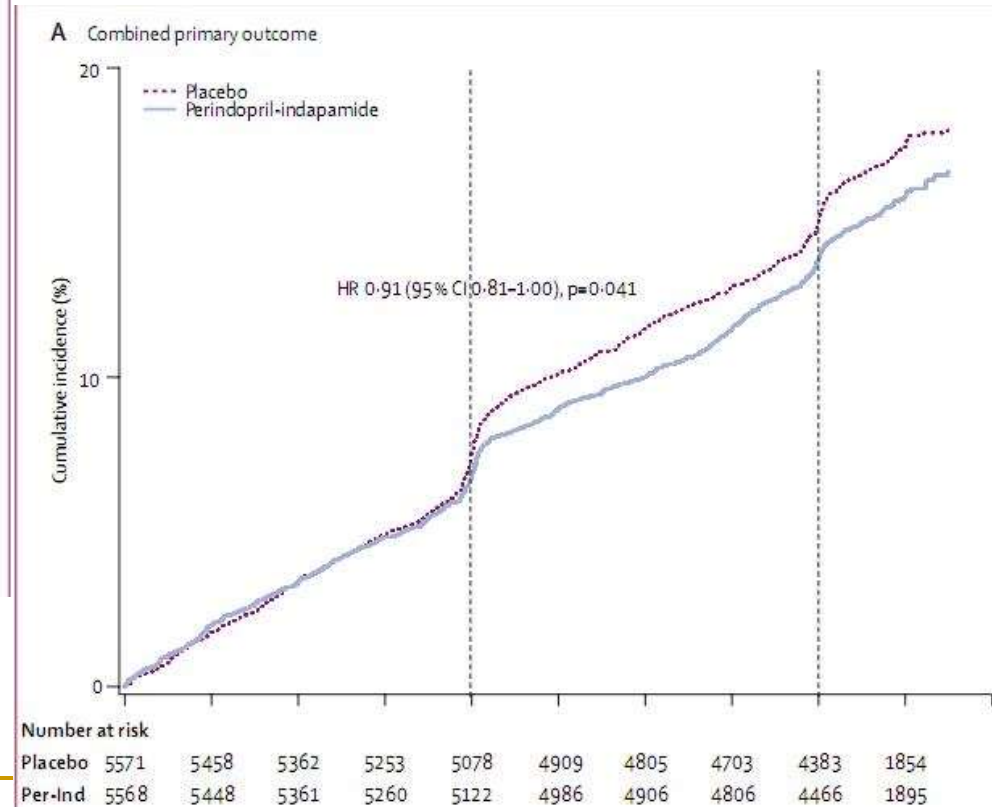
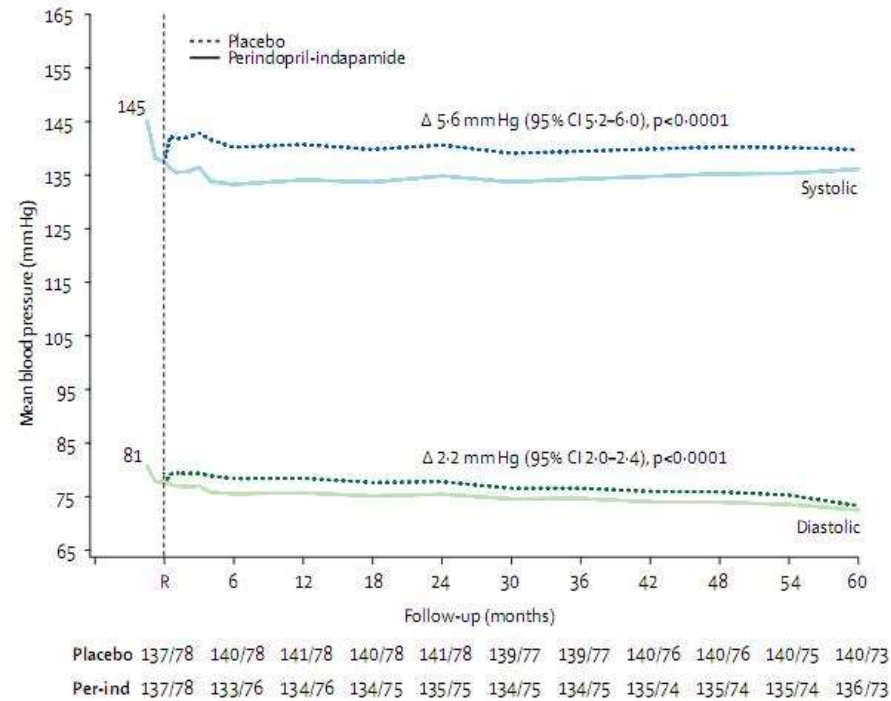
A Any Diabetes-Related End Point



No. at Risk

Less-tight control	390	296	214	138	68	11
Tight control	758	601	458	296	133	19

# Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in diabetes type 2. ADVANCE. Lancet 2007



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Jusqu'où aller trop loin ?

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# Cardiorenal end points in a trial of aliskiren for type 2 diabetes. ALTITUDE Investigators. NEJM dec2012.

**Table 2.** Prespecified Primary and Secondary Composite Outcomes and Deaths.\*

Outcome	Aliskiren (N = 4274)	Placebo (N = 4287)	Hazard Ratio (95% CI)	P Value†
	<i>no. of patients (%)</i>			
Primary composite outcome	783 (18.3)	732 (17.1)	1.08 (0.98–1.20)	0.12
Death from cardiovascular causes	246 (5.8)	215 (5.0)	1.16 (0.96–1.39)	0.12
Cardiac arrest with resuscitation	19 (0.4)	8 (0.2)	2.40 (1.05–5.48)	0.04
Myocardial infarction (fatal or nonfatal)	147 (3.4)	142 (3.3)	1.04 (0.83–1.31)	0.72
Stroke (fatal or nonfatal)	147 (3.4)	122 (2.8)	1.22 (0.96–1.55)	0.11
Unplanned hospitalization for heart failure	205 (4.8)	219 (5.1)	0.95 (0.78–1.14)	0.56
ESRD, death attributable to kidney failure, or loss of kidney function‡	121 (2.8)	113 (2.6)	1.08 (0.84–1.40)	0.56
Doubling of baseline serum creatinine	210 (4.9)	217 (5.1)	0.97 (0.80–1.17)	0.75
Cardiovascular composite outcome	590 (13.8)	539 (12.6)	1.11 (0.99–1.25)	0.09
Renal composite outcome	257 (6.0)	251 (5.9)	1.03 (0.87–1.23)	0.74
Death from any cause	376 (8.8)	358 (8.4)	1.06 (0.92–1.23)	0.42

Arret prématuré de l'essai. Majoration du CJP sous Rasilez



**Table 3. Most Commonly Reported Adverse Events and Study-Drug Discontinuation.\***

Event	Any Event Reported		P Value	Event Leading to Permanent Study-Drug Discontinuation		P Value
	Aliskiren (N = 4272)	Placebo (N = 4285)		Aliskiren (N = 4272)	Placebo (N = 4285)	
	<i>no. of patients (%)</i>			<i>no. of patients (%)</i>		
Hyperkalemia	1670 (39.1)	1244 (29.0)	<0.001	205 (4.8)	111 (2.6)	<0.001
Peripheral edema	686 (16.1)	706 (16.5)	0.60	11 (0.3)	7 (0.2)	0.34
Hypotension	519 (12.1)	357 (8.3)	<0.001	28 (0.7)	13 (0.3)	0.02
Diarrhea	417 (9.8)	312 (7.3)	<0.001	11 (0.3)	7 (0.2)	0.34
Hypertension	429 (10.0)	469 (10.9)	0.17	3 (0.1)	9 (0.2)	0.15
Renal impairment	418 (9.8)	371 (8.7)	0.07	65 (1.5)	54 (1.3)	0.30
Nasopharyngitis	405 (9.5)	383 (8.9)	0.39	1 (<0.1)	0	NA
Hypoglycemia	393 (9.2)	341 (8.0)	0.04	1 (<0.1)	3 (0.1)	NA
Back pain	363 (8.5)	353 (8.2)	0.67	1 (<0.1)	2 (<0.1)	NA
Dizziness	327 (7.7)	314 (7.3)	0.57	4 (0.1)	4 (0.1)	NA
Urinary tract infection	326 (7.6)	288 (6.7)	0.10	4 (0.1)	2 (<0.1)	NA
Anemia	316 (7.4)	307 (7.2)	0.68	0	0	—
Pain in extremity	302 (7.1)	317 (7.4)	0.56	1 (<0.1)	2 (<0.1)	NA
Arthralgia	302 (7.1)	313 (7.3)	0.67	0	1 (<0.1)	NA
Cough	265 (6.2)	283 (6.6)	0.45	1 (<0.1)	1 (<0.1)	NA
Bronchitis	242 (5.7)	239 (5.6)	0.86	0	0	—
Dyspnea	223 (5.2)	213 (5.0)	0.60	6 (0.1)	5 (0.1)	0.76
Upper respiratory tract infection	223 (5.2)	229 (5.3)	0.80	1 (<0.1)	0	NA
Cataract	229 (5.4)	223 (5.2)	0.75	0	0	—
Constipation	203 (4.8)	241 (5.6)	0.07	0	1 (<0.1)	NA
Headache	200 (4.7)	220 (5.1)	0.33	2 (<0.1)	4 (0.1)	NA

# Strategy for multivessel revascularisation in patients with diabetes. Farkouh ME. NEJM dec2012.

**Table 2.** Kaplan–Meier Estimates of Key Outcomes at 2 Years and 5 Years after Randomization.

Outcome	2 Years after Randomization		5 Years after Randomization		Patients with Event		P Value*
	PCI	CABG	PCI	CABG	PCI	CABG	
	<i>number (percent)</i>				<i>number</i>		
Primary composite†	121 (13.0)	108 (11.9)	200 (26.6)	146 (18.7)	205	147	0.005‡
Death from any cause	62 (6.7)	57 (6.3)	114 (16.3)	83 (10.9)	118	86	0.049
Myocardial infarction	62 (6.7)	42 (4.7)	98 (13.9)	48 (6.0)	99	48	<0.001
Stroke	14 (1.5)	24 (2.7)	20 (2.4)	37 (5.2)	22	37	0.03§
Cardiovascular death	9 (0.9)	12 (1.3)	73 (10.9)	52 (6.8)	75	55	0.12

## Revascularisation des patients pluritronculaires

- diminution du CJP par diminution des décès et des IDM si pontage vs angioplastie

- mais augmentation des AVC