TURIN, 20TH—21ST NOVEMBER 2008

GREAT INNOVATIONS IN CARDIOLOGY

4TH JOINT MEETING WITH MAYO CLINIC

4TH TURIN CARDIOVASCULAR NURSING CONVENTION

SESSION III: **HOT SESSION**
NEW THERAPIES AND NEW TREATMENTS

P. Cavallo Perin (Torino)

Part I Selective rear block in the cardio metabolic protection: new evidence from DIRECT study

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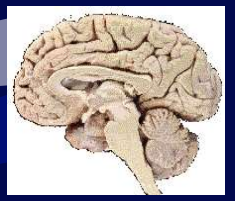
Selective rear block in the cardiometabolic protection: new evidence from DIRECT study.

Torino, 20 novembre 2008

Diabetes: A Systemic Disease

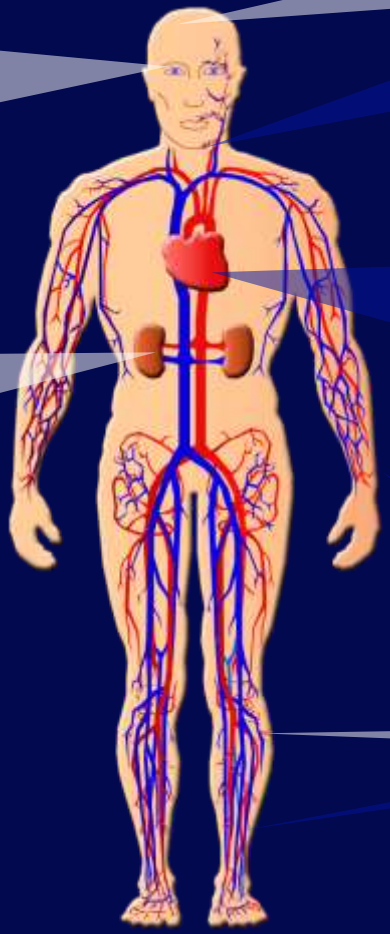
Leading cause of blindness in working age adults

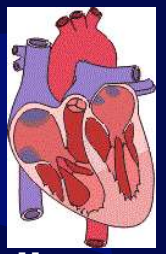
Diabetic Retinopathy



Stroke

2- to 4- fold increase in cardiovascular mortality and stroke

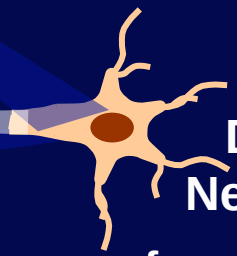




Cardiovascular Disease

Diabetic Nephropathy

Leading cause of end-stage renal disease



Diabetic Neuropathy

Leading cause of non-traumatic lower extremity amputations

National Diabetes Information Clearinghouse. Diabetes Statistics–Complications of Diabetes. (website) http://www.niddk.nih.gov/health/diabetes/pubs/dmstats/dmstats.htm#comp.

DIRECT: background and rationale

Microvascular complications of diabetes mellitus remain important causes of morbidity in all patients:

- Visual loss is the most feared complication
- Improved glycaemic control can reduce but not abolish the risk of retinopathy and nephropathy (DCCT, UKPDS)
- BP lowering can also reduce the risk (UKPDS)

DIRECT Studies

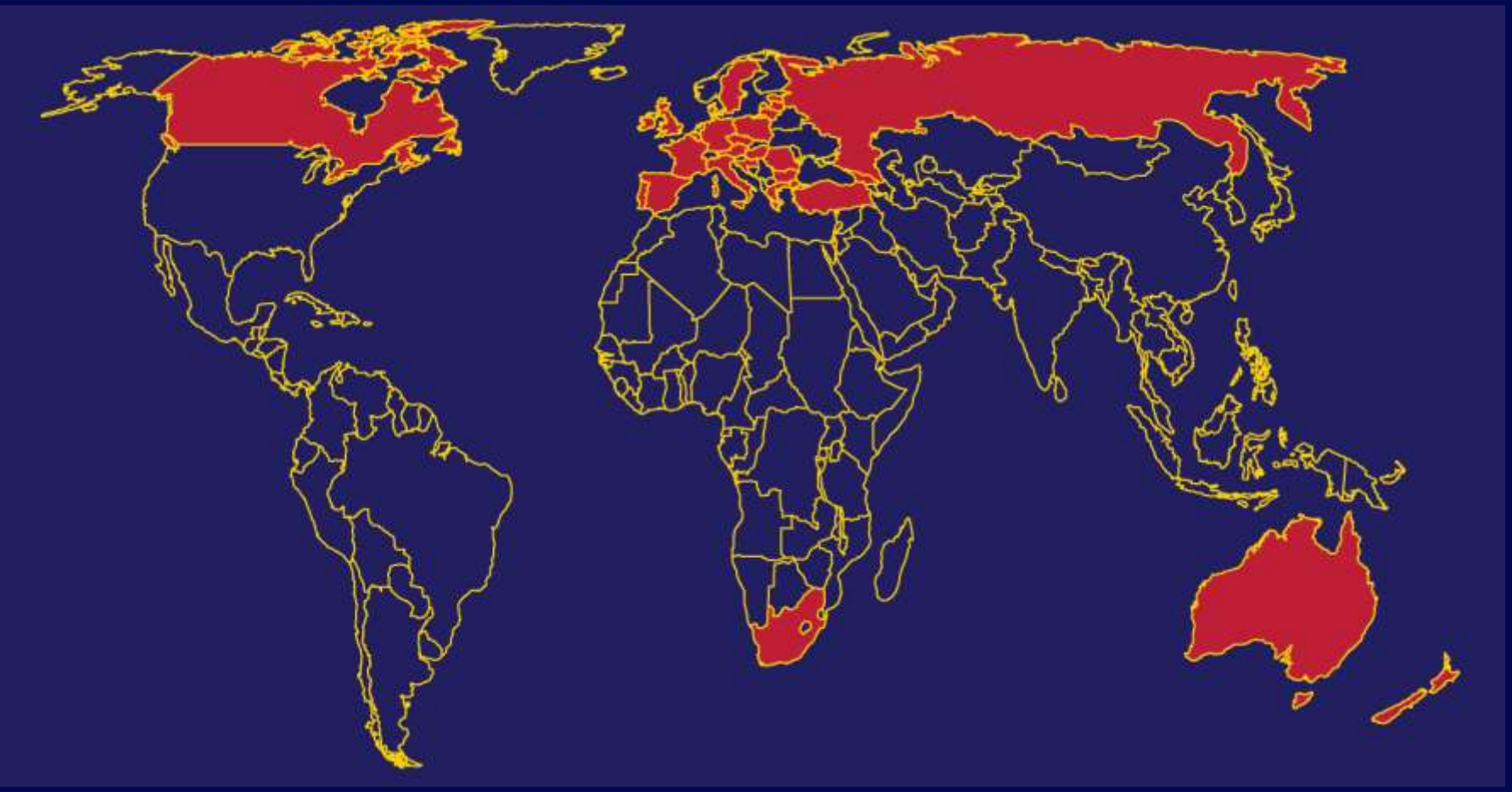
Three RPCT on the effects of the ARB candesartan on incidence and progression of diabetic retinopathy:

- **DIRECT-Prevent 1** *Lancet 2008;372:1394-1402*
- **DIRECT-Protect 1** *Lancet 2008;372:1394-1402*
- **DIRECT-Protect 2** *Lancet 2008;372:1385-1393*

DIRECT Programme: Inclusion criteria

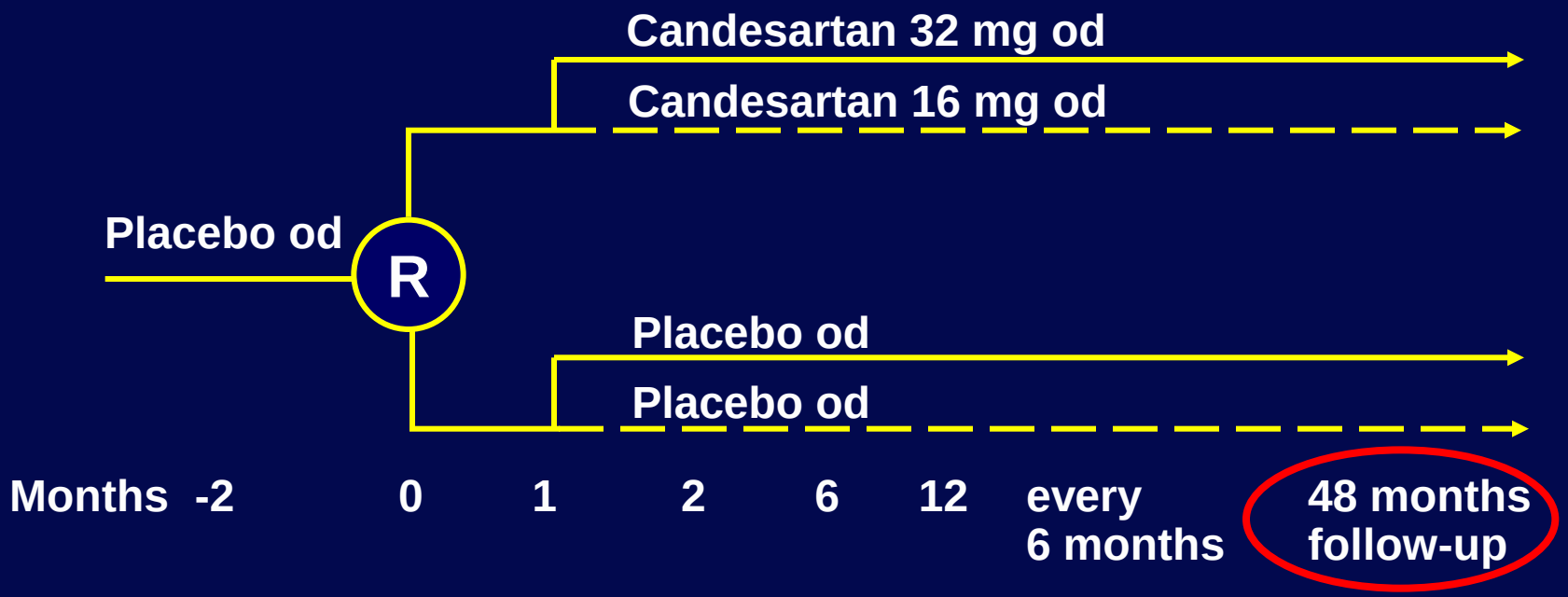
	DIRECT-Prevent 1	DIRECT-Protect 1	DIRECT-Protect 2
Number of patients	1421	1905	1905
Age (years)	18-50	18-55	37-75
Diabetes duration (years)	1-15	1-20	1-20
Microalbuminuria	No	No	No
Blood pressure (mmHg)	SBP ≤130 DBP ≤85	SBP ≤130 DBP ≤85	No HTN treatment SBP ≤130 DBP ≤85 HTN treatment SBP ≤160 DBP ≤90
Retinal grading level (ETDRS scale)	10/10	≥20/10 up to ≤47/47	≥20/10 up to ≤47/47

DIRECT Programme



309 centres in 30 countries

DIRECT: Individual study designs



Investigations:

Retinal photographs	annually
Urinary albumin excretion rate	annually
Blood pressure	six monthly
Adverse events	six monthly

ETDRS retinopathy scale (based on 7-field stereo photographs)

Early Treatment of Diabetic Retinopathy Study

Level	Severity
10	DR absent
20	MA only
35	Mild NPDR
43	Moderate NPDR
47	Moderately severe NPDR
53	Severe NPDR
61, 65, 71, 75, 81	Proliferative DR

DR Diabetic retinopathy
MA Microaneurysms
NPDR Non-proliferative diabetic retinopathy

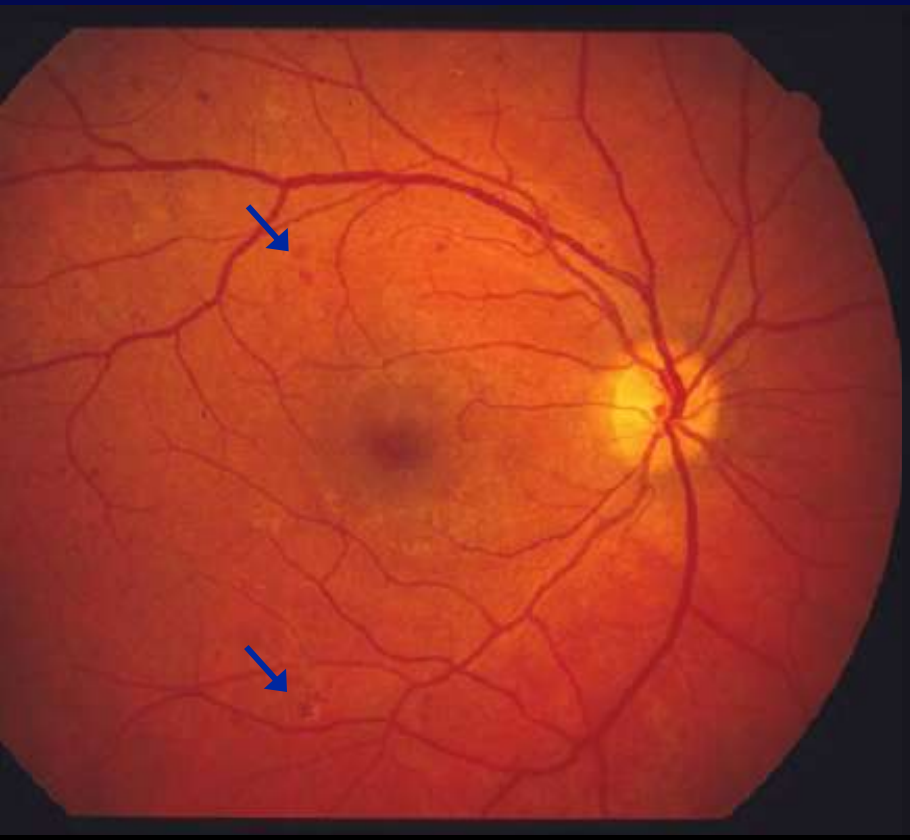
DIRECT Programme: Outcome measures

- The primary endpoint is
  - 2-step change in ETDRS level for incidence
  - 3-step change in ETDRS level for progression
- Secondary endpoints include
  - regression of retinopathy
    (3-step or 2-step sustained)
- Change in overall retinopathy severity

Diabetic retinopathy: Microaneurysms only

Level 20

Level 20



Right eye

Left eye

DIRECT-Prevent 1

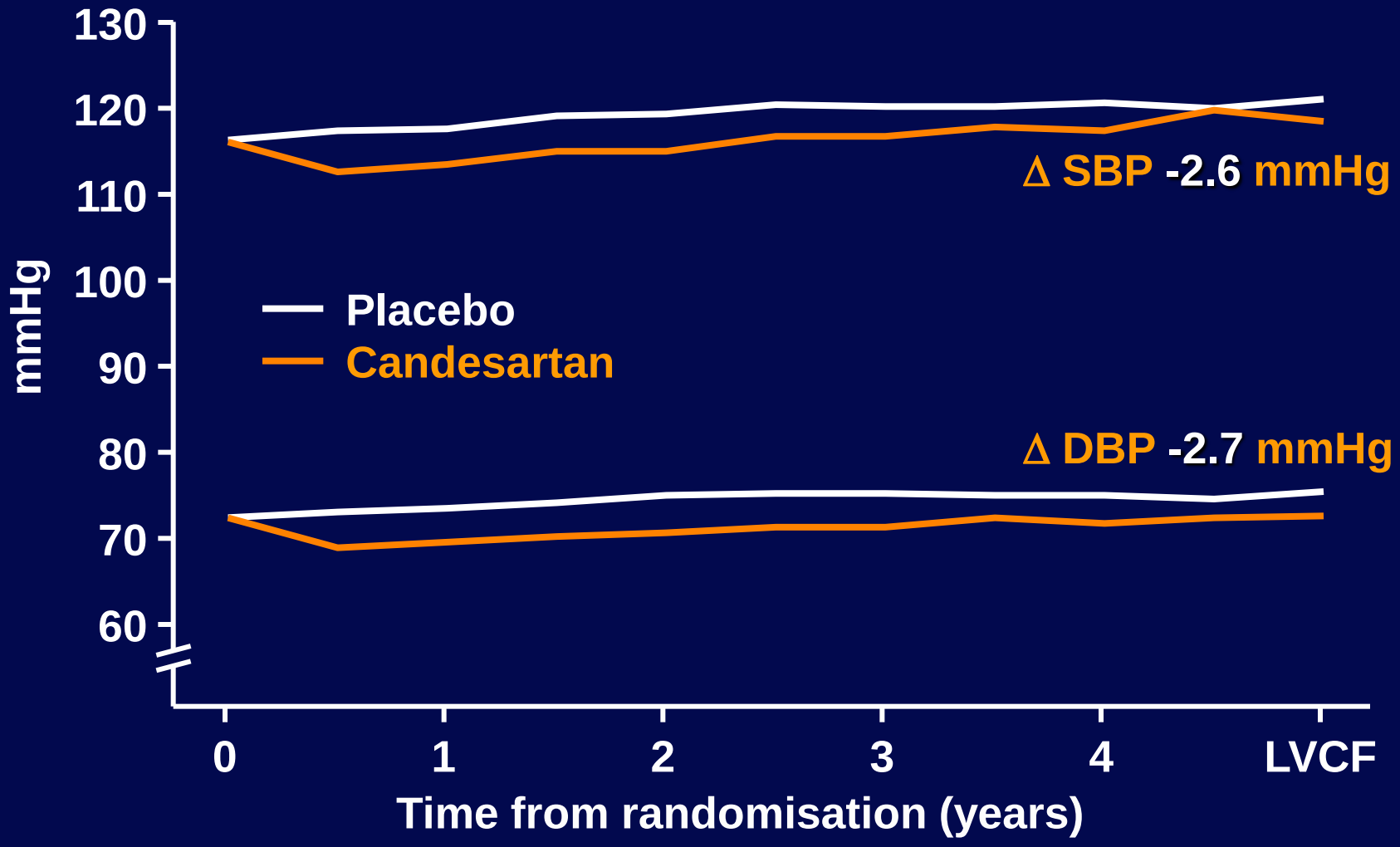
Effect of candesartan on incidence of retinopathy in type 1 diabetic patients

DIRECT Prevent-1: Baseline characteristics

	Candesartan n=711	Placebo n=710
Male	413 (58%)	392 (55%)
Age (years)	29.6 ± 8.0	29.9 ± 8.1
Diabetes duration (years)	6.6 ± 3.9	6.8 ± 3.9
HbA_{1c} (%)	8.0 ± 1.7	8.2 ± 1.7
SBP (mmHg)	116 ± 9.5	116 ± 9.6
DBP (mmHg)	72 ± 6.9	72 ± 7.3

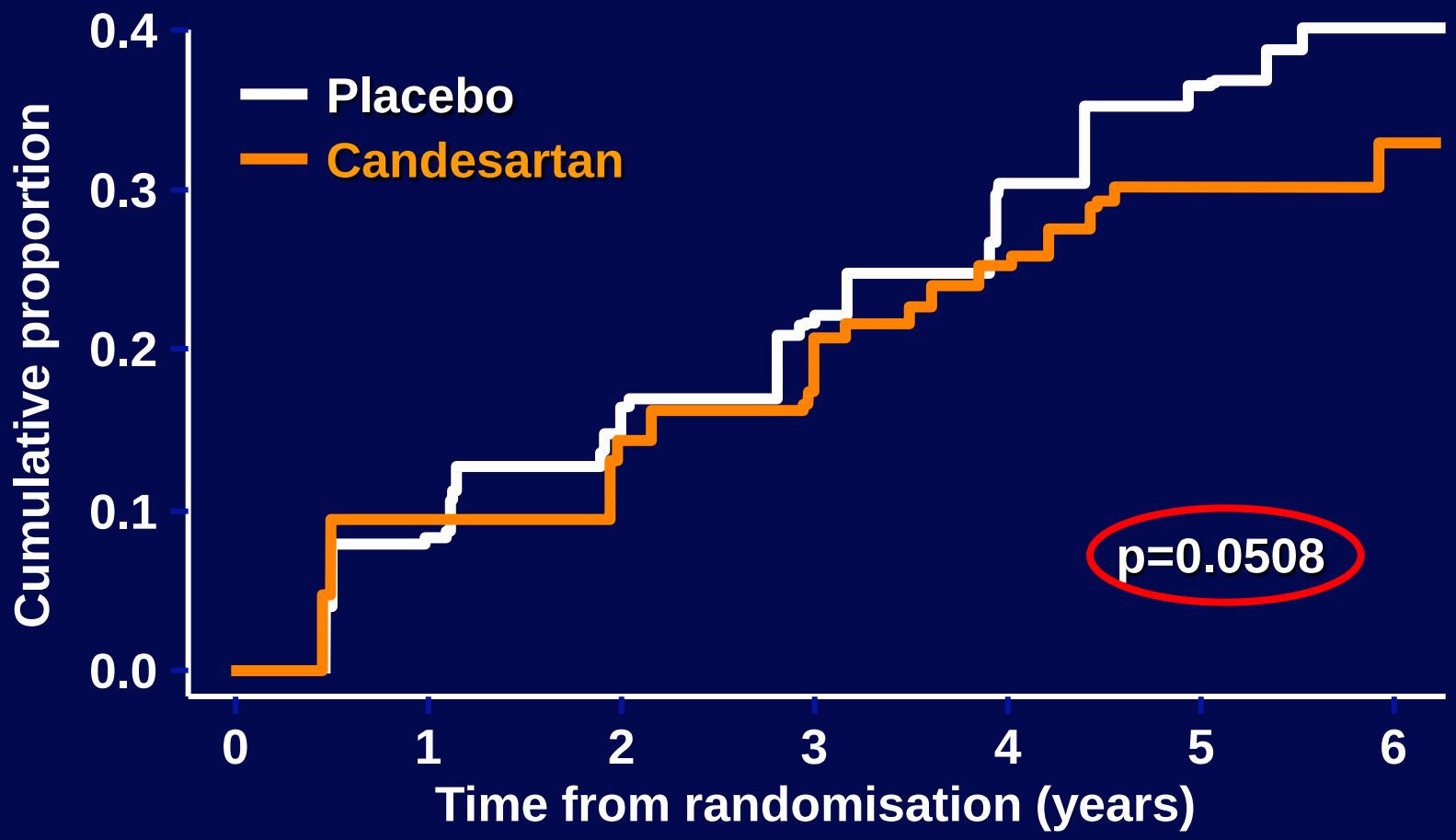
mean ± SD

DIRECT-Prevent 1: Systolic and diastolic BP



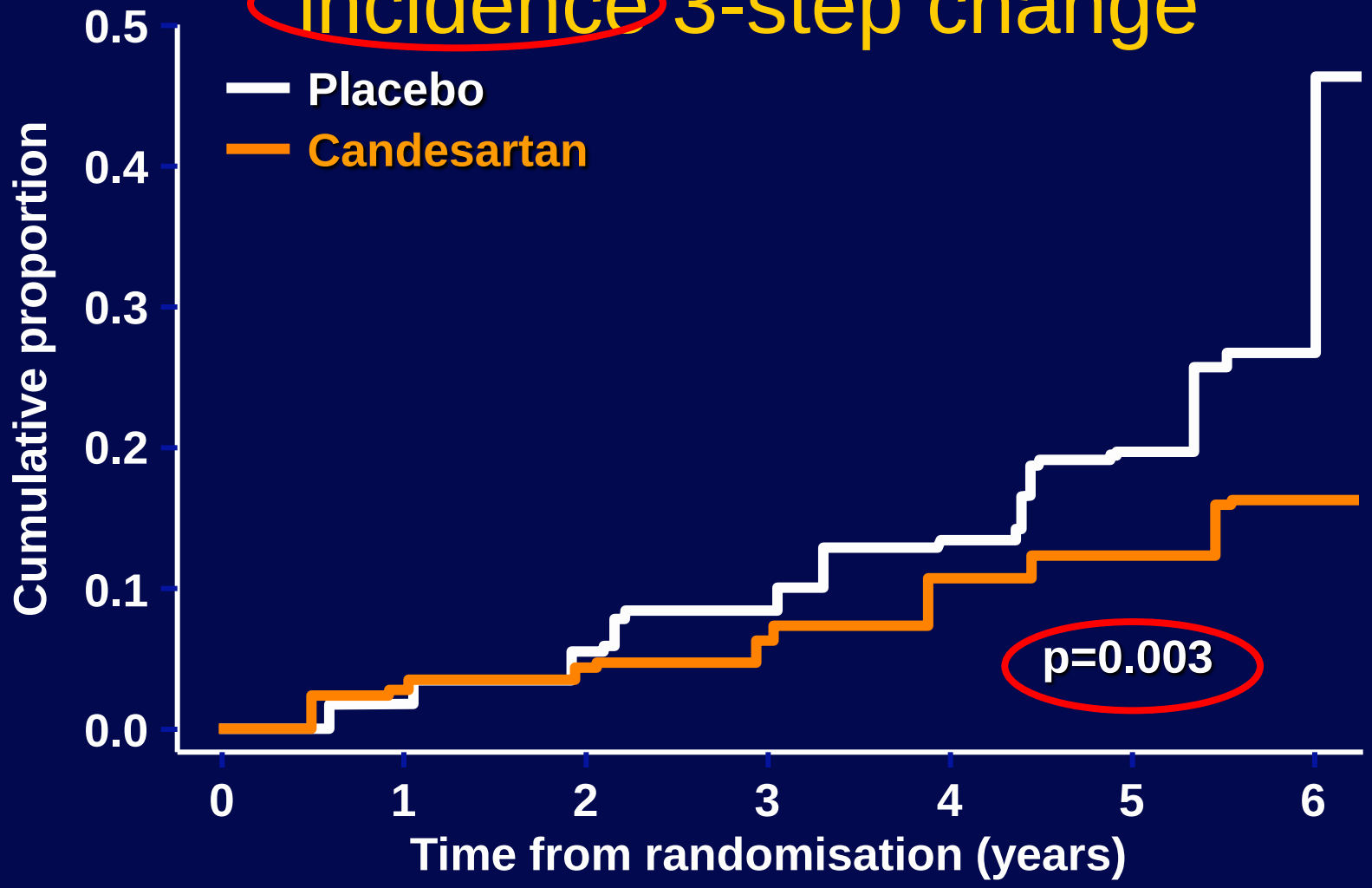
LVCF = Last Value Carried Forward

DIRECT-Prevent 1: Retinopathy incidence 2-step change



No at risk							
Placebo	710	644	585	518	347	87	0
Candesartan	711	633	573	524	356	92	1

DIRECT-Prevent 1: Retinopathy incidence 3-step change



No at risk							
Placebo	710	663	630	587	419	109	1
Candesartan	711	651	615	587	422	108	1

DIRECT-Protect 1

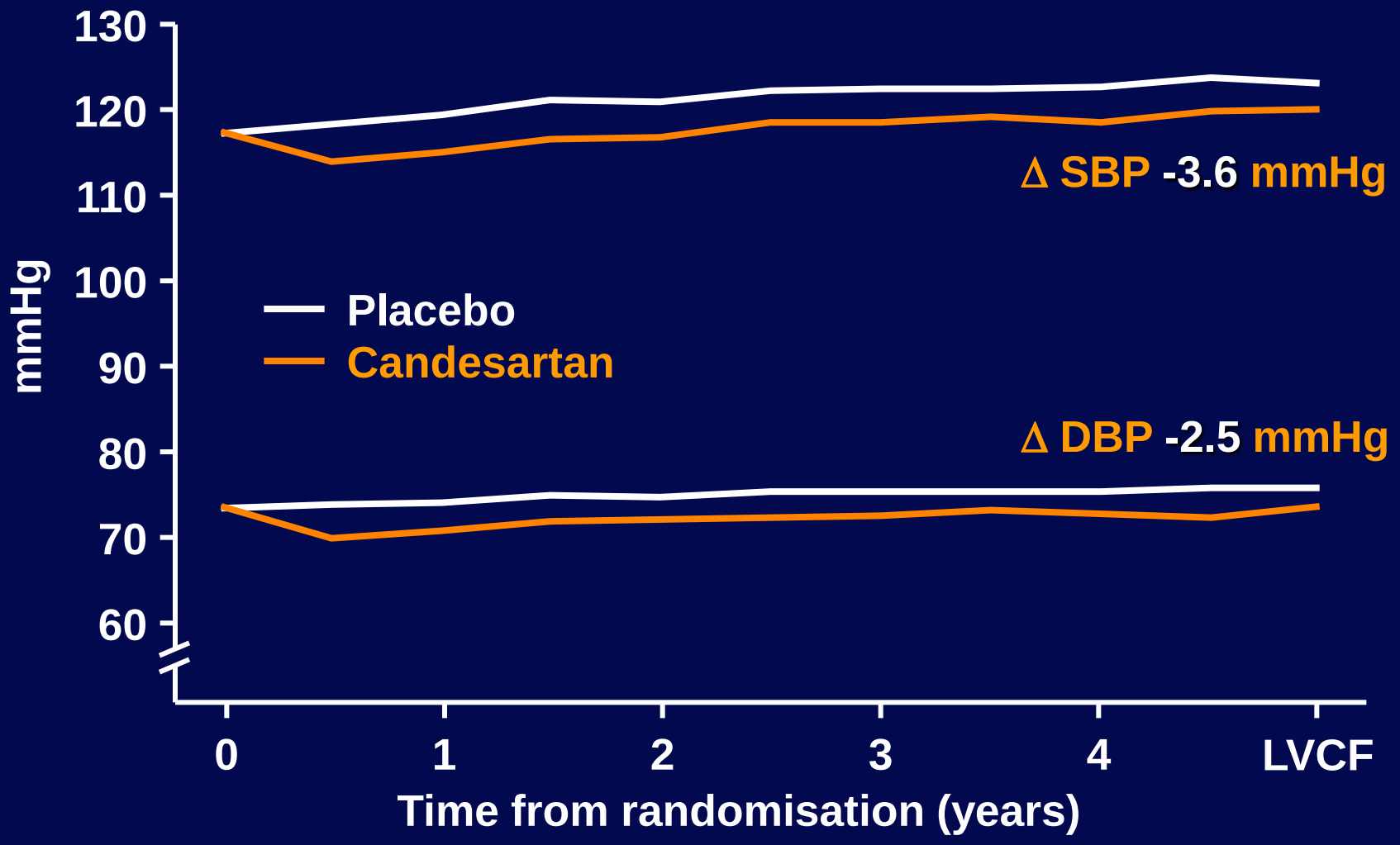
Effect of candesartan on progression of retinopathy in type 1 diabetic patients

DIRECT-Protect 1: Baseline characteristics

	Candesartan n=951	Placebo n=954
Male	538 (57%)	553 (58%)
Age (years)	31.5 ± 8.5	31.9 ± 8.5
Diabetes duration (years)	10.9 ± 4.3	11.0 ± 4.3
HbA_{1c} (%)	8.5 ± 1.6	8.5 ± 1.6
SBP (mmHg)	117 ± 9.6	117 ± 9.8
DBP (mmHg)	74 ± 6.5	73 ± 6.9

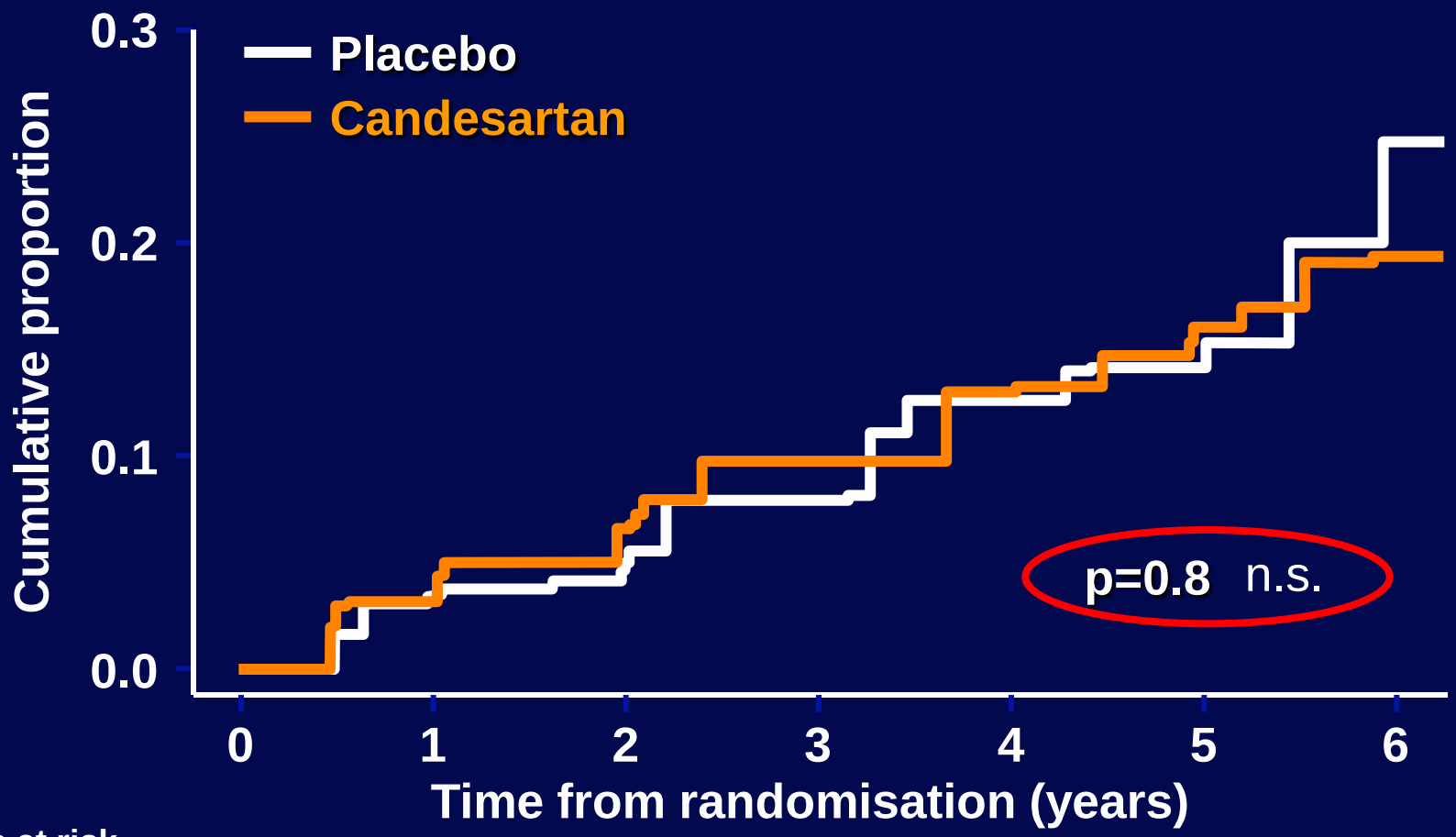
mean ± SD

DIRECT-Protect 1: Systolic and diastolic BP



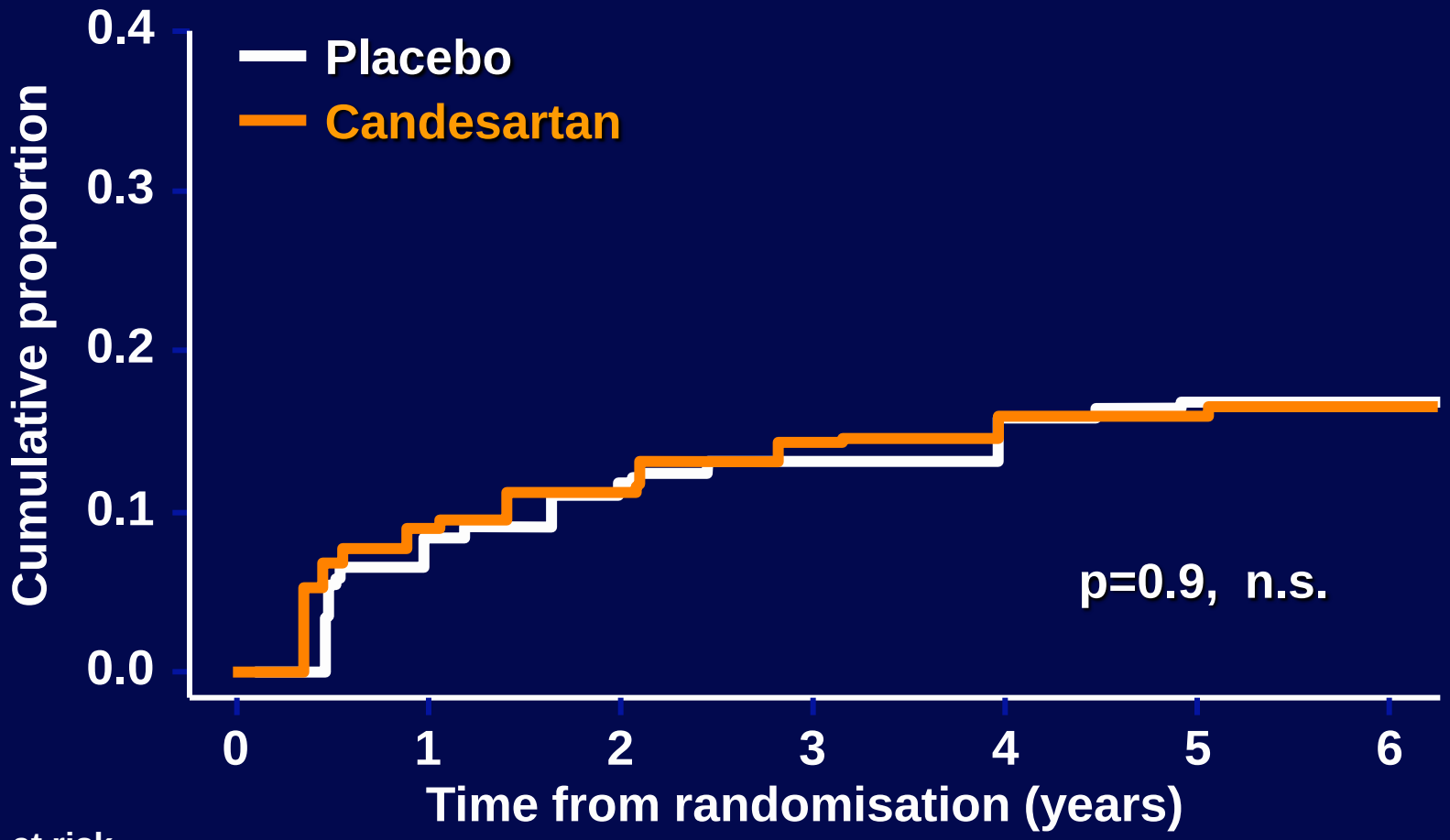
LVCF = Last Value Carried Forward

DIRECT-Protect 1: Retinopathy progression 3-step change



No at risk							
Placebo	954	875	820	770	612	188	4
Candesartan	951	863	814	767	626	195	5

DIRECT-Protect 1: Retinopathy regression



No at risk							
Placebo	954	840	772	713	559	167	5
Candesartan	951	820	773	728	591	187	5

DIRECT-Prevent 1 and DIRECT-Protect 1:
Adverse events for the safety population, n (%)

	DIRECT-Prevent 1		DIRECT-Protect 1	
	Candesartan	Placebo	Candesartan	Placebo
Safety population	710	710	951	951
All adverse events during treatment *	505 (71.1)	517 (72.8)	738 (77.6)	721 (75.8)
Discontinued study medication due to adverse event	22 (3.1)	18 (2.5)	17 (1.8)	16 (1.7)
Deaths	7 (1.0)	5 (0.7)	7 (0.7)	8 (0.8)

* Most common were nasopharyngitis, hypoglycaemia, hypotension, headache

DIRECT-Protect 2

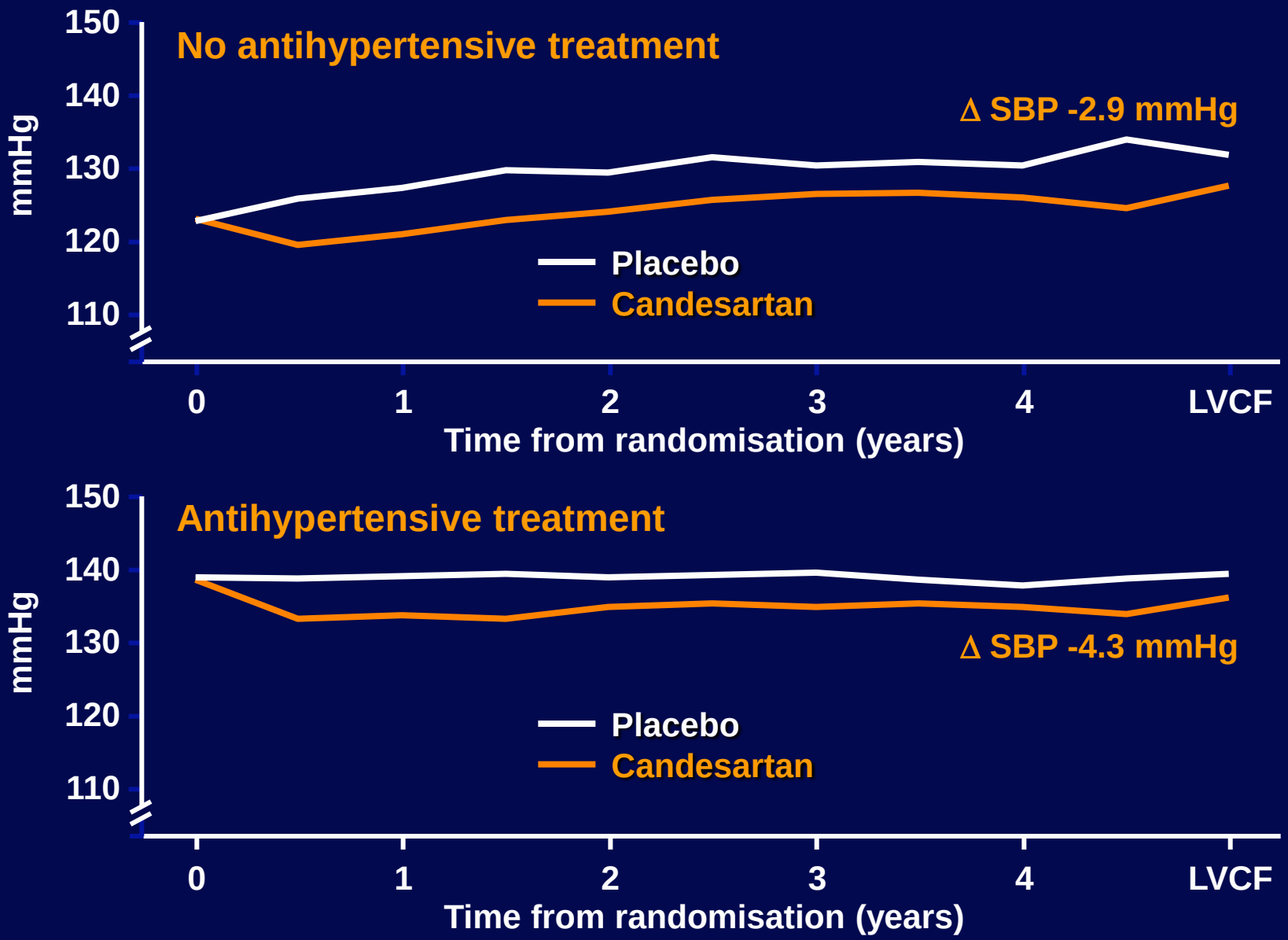
Effect of candesartan on progression of retinopathy in type 2 diabetic patients

DIRECT-Protect 2: Baseline characteristics

	Candesartan n=951	Placebo n=954
Male	466 (49%)	482 (51%)
Age (years)	56.9 ± 7.6	56.8 ± 7.9
Diabetes duration (years)	8.8 ± 4.9	8.7 ± 4.8
HbA_{1c} (%)	8.2 ± 1.6	8.2 ± 1.6
No antihypertensive treatment SBP/DBP (mmHg)	123/75	123/76
Antihypertensive treatment (62%) SBP/DBP (mmHg)	139/79	139/80

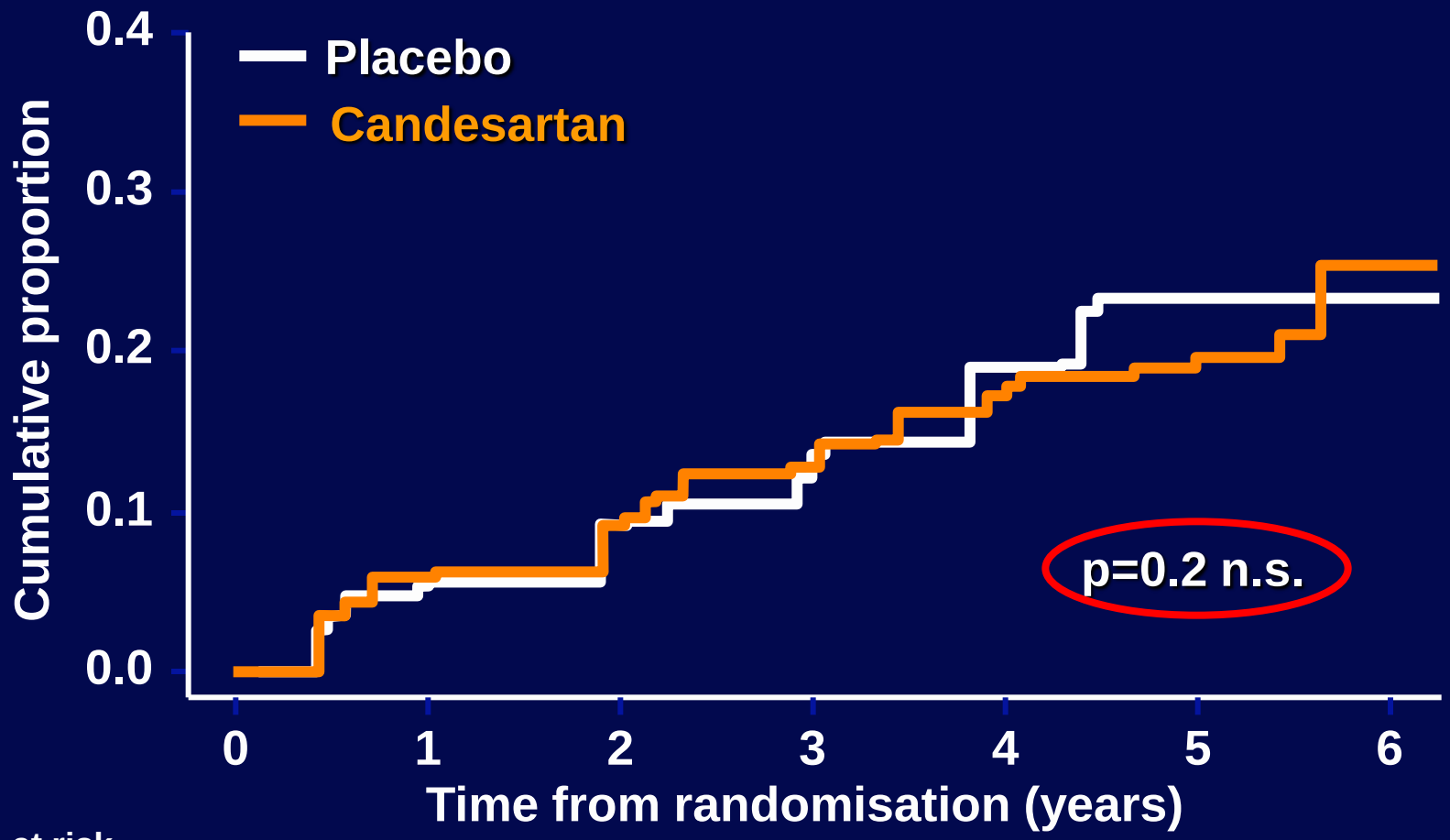
mean ± SD

DIRECT-Protect 2: Systolic BP



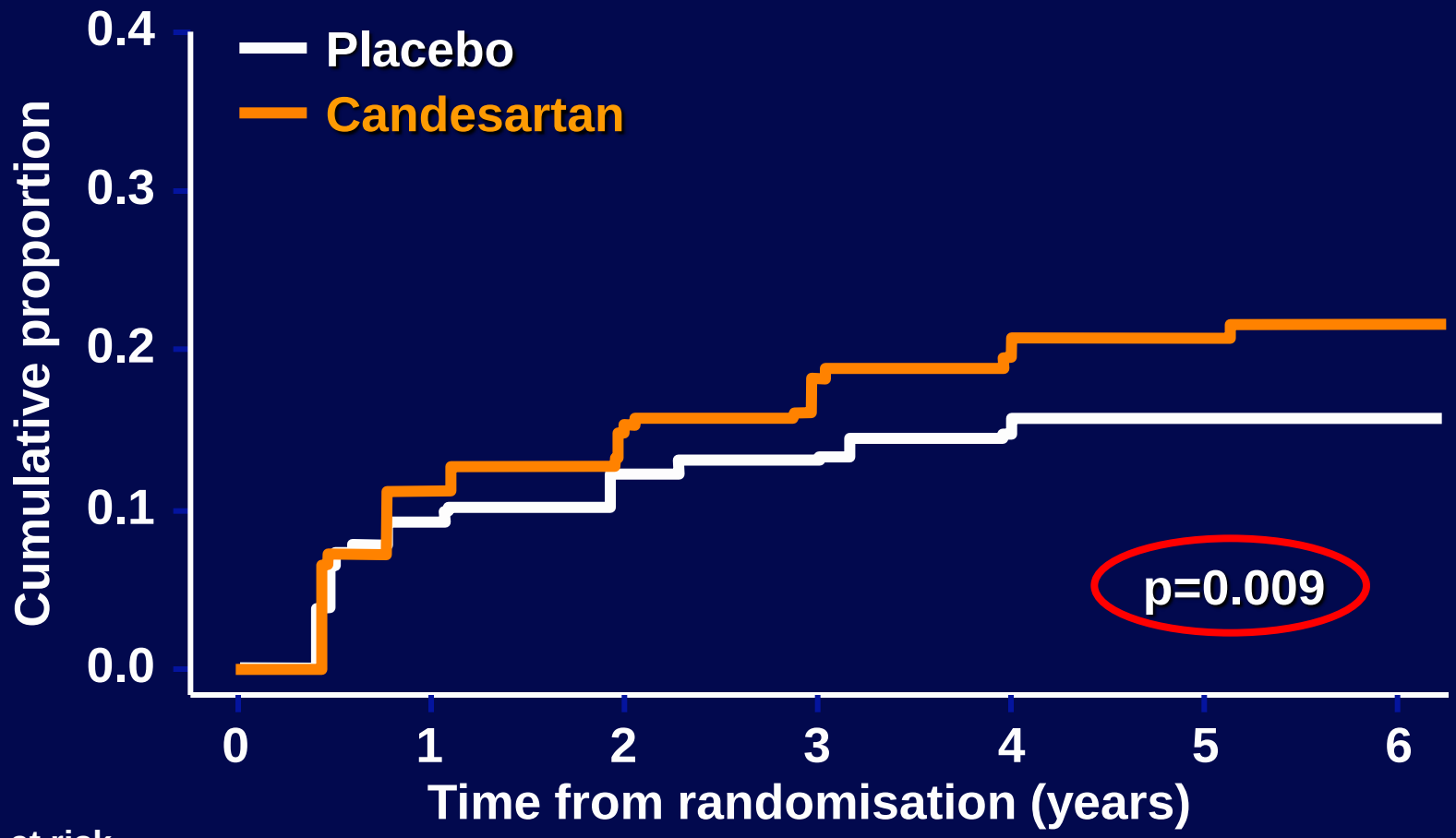
LVCF = Last Value Carried Forward

DIRECT-Protect 2
Retinopathy progression 3-step change



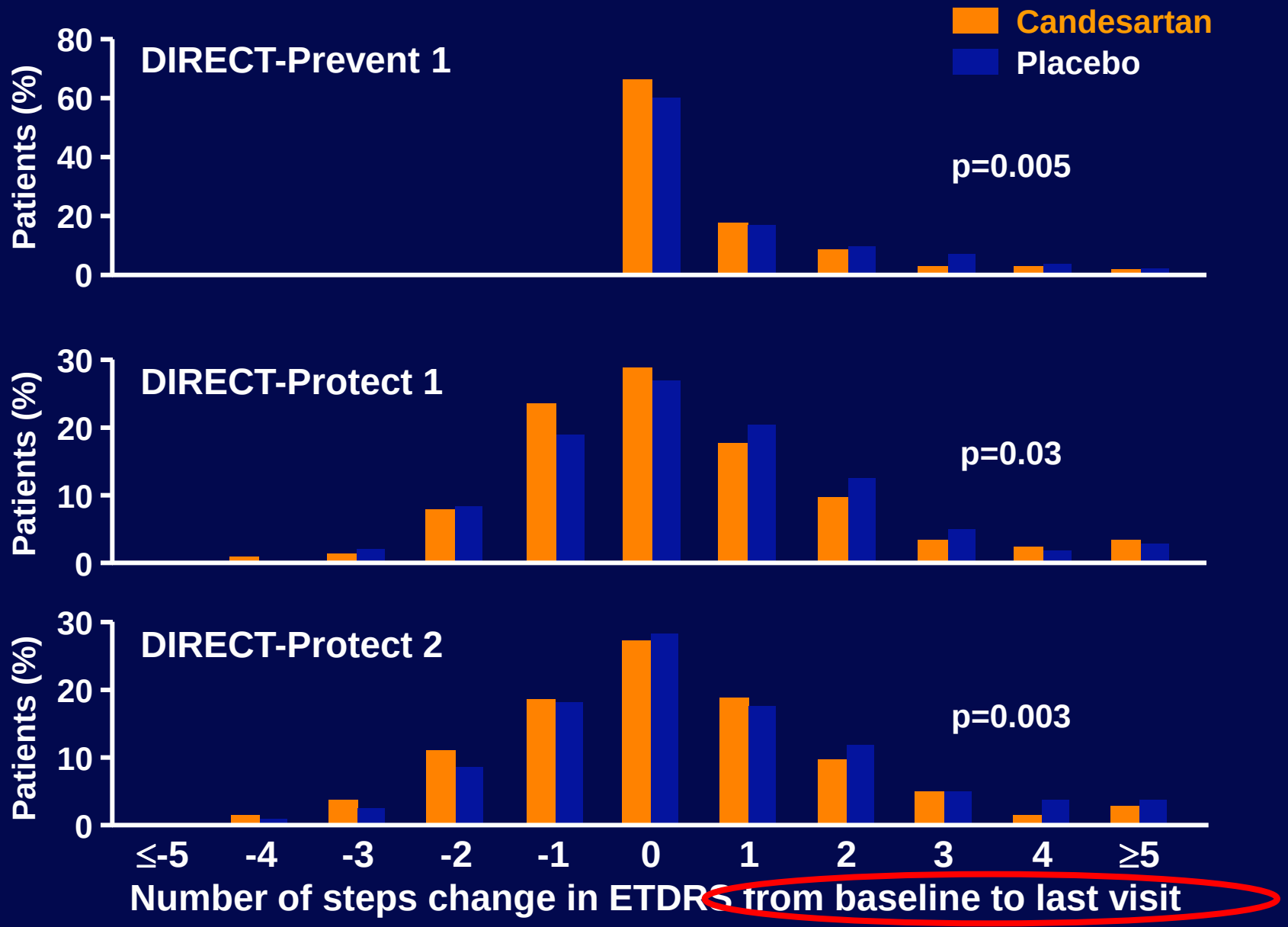
No at risk							
Placebo	954	845	794	737	513	112	3
Candesartan	951	848	807	737	540	123	0

DIRECT-Protect 2: Retinopathy regression



No at risk							
Placebo	954	812	760	713	510	93	1
Candesartan	951	811	755	692	492	100	0

DIRECT Programme: Change in ETDRS level



Summary

- Candesartan reduced incidence of retinopathy in normoalb-normotens type 1 diabetes by 18% (p=0.0508) 2-step change, primary endpoint 35% (p=0.003) 3-step change, post hoc analysis
- No effect on progression of retinopathy in type 1 diabetes, but there was a non-significant 13% reduction in type 2 patients (p=0.2)
- Candesartan enhanced regression of retinopathy by 34% (p=0.009) in type 2 diabetes
- Level of retinopathy was more favourably affected on Candesartan at the end of all three studies compared to placebo

The DIRECT Programme Steering Committee

Anne Katrin Sjølie	Denmark	Anders Svensson	Sweden
Rudy Bilous	UK	James Hainer	USA
Nish Chaturvedi	UK	Ronald Klein	USA
Ywonne Fox	Sweden	Trevor Orchard	USA
John Fuller	UK	Hans-Henrik Parving	Denmark
Michael George	UK	Massimo Porta	Italy
		Ingrid Warnold	Sweden

Would like to extend their thanks to:

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All the patients

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Please visit www.direct-results.org for more information

Studio Steno-2

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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.

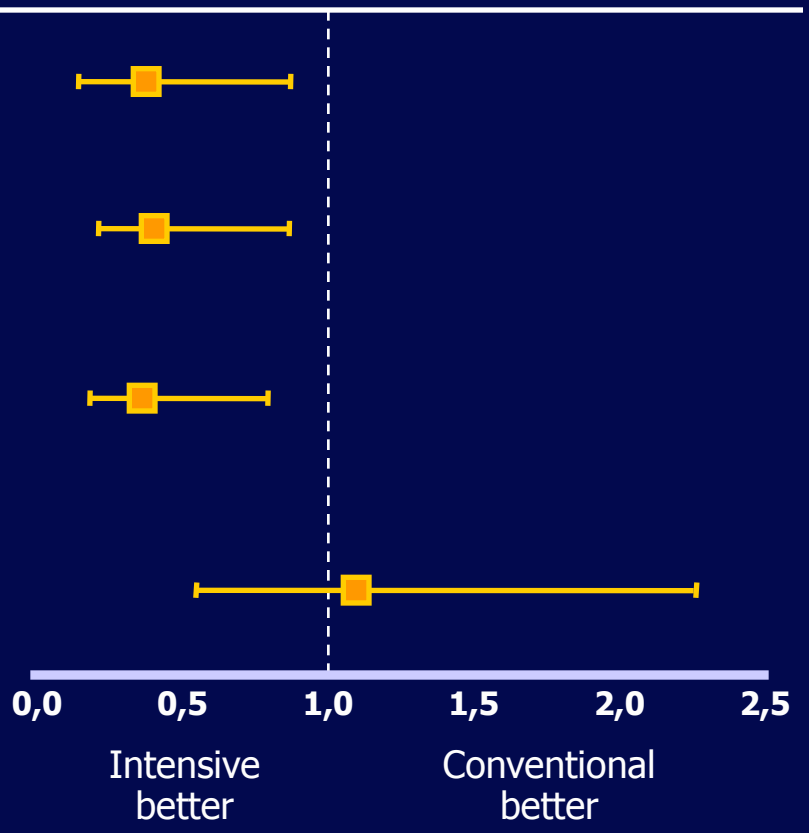
Peter Gæde MD et al., N Engl J Med 2003;348:383-93

Steno-2 Study

Onset/progression of microangiopathy in DM-2

intensive vs conventional

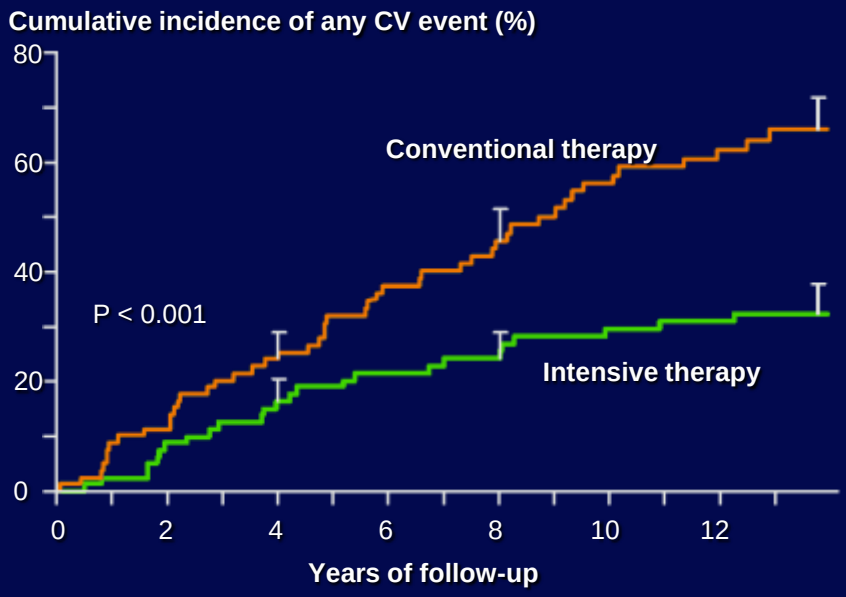
Variable	Relative Risk (95% IC)	p value
Nephropaty	**0,39** (0,17-0,87)	**0,003**
Retinopathy	**0,42** (0,21-0,86)	**0,02**
Autonomic Neuropathy	**0,37** (0,18-0,79)	**0,002**
Peripheral Neuropathy	**0,09** (0,54-2,22)	**0,66**



Peter Gæde MD et al., N Engl J Med 2003;348:383-93

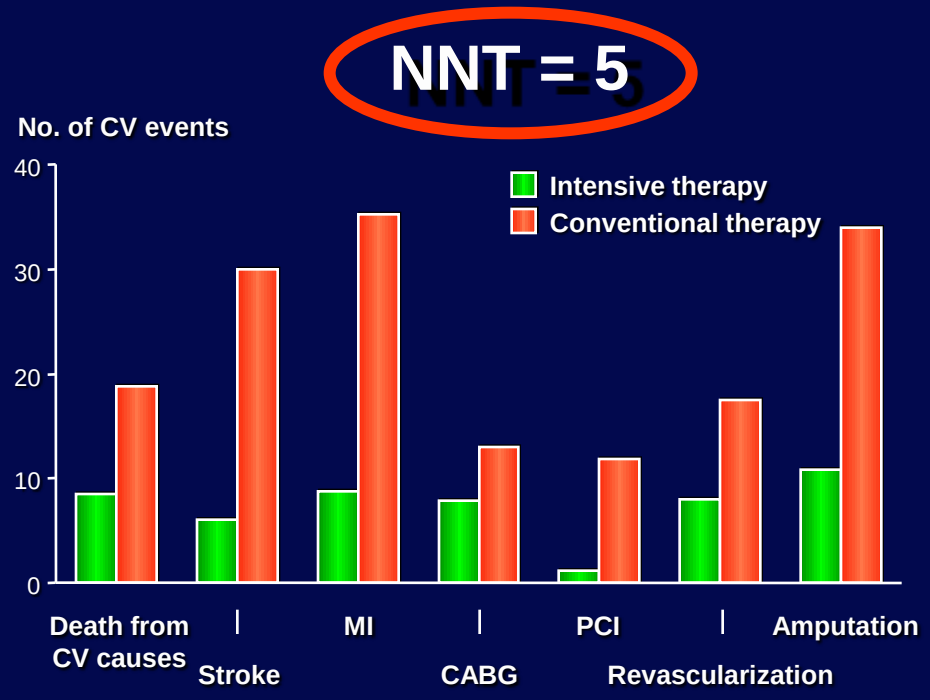
Steno-2 Study

Reduction of macroangiopathy in DM-2 intensive vs conventional



No. at risk

80	72	65	61	56	50	47	31	Intensive therapy
80	70	60	46	38	29	25	14	Conventional therapy



CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention

Gaede P et al, N Engl J Med 2008; 358: 580-591