11th Pan-Hellenic Congress on
Arterial Hypertension

Treatment of Hypertension in Type 2 Diabetes - an update 2009

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ESC/EASD guidelines for diabetes and CV disease

Rydén, Standl et al: Europ Heart J and Diabetologia 2007

Variable		Target	
Lifestyle modification		Structured education	
Smoking cessation		Obligatory	
BP		<130 / 80 mm Hg	
HbA1c (DCCT standard)		≤ 6.5%	
		mmol/l	mg/dl
Venous plasma glucose		<6.0	108
Cholesterol		<4.5	175
LDL		<1.8	70
HDL	male >1.0; female >1.2		40; 76
Triglycerides		<1.7	150

Multifactorial intervention in patients with type-2 diabetes : the Steno-2 randomized study

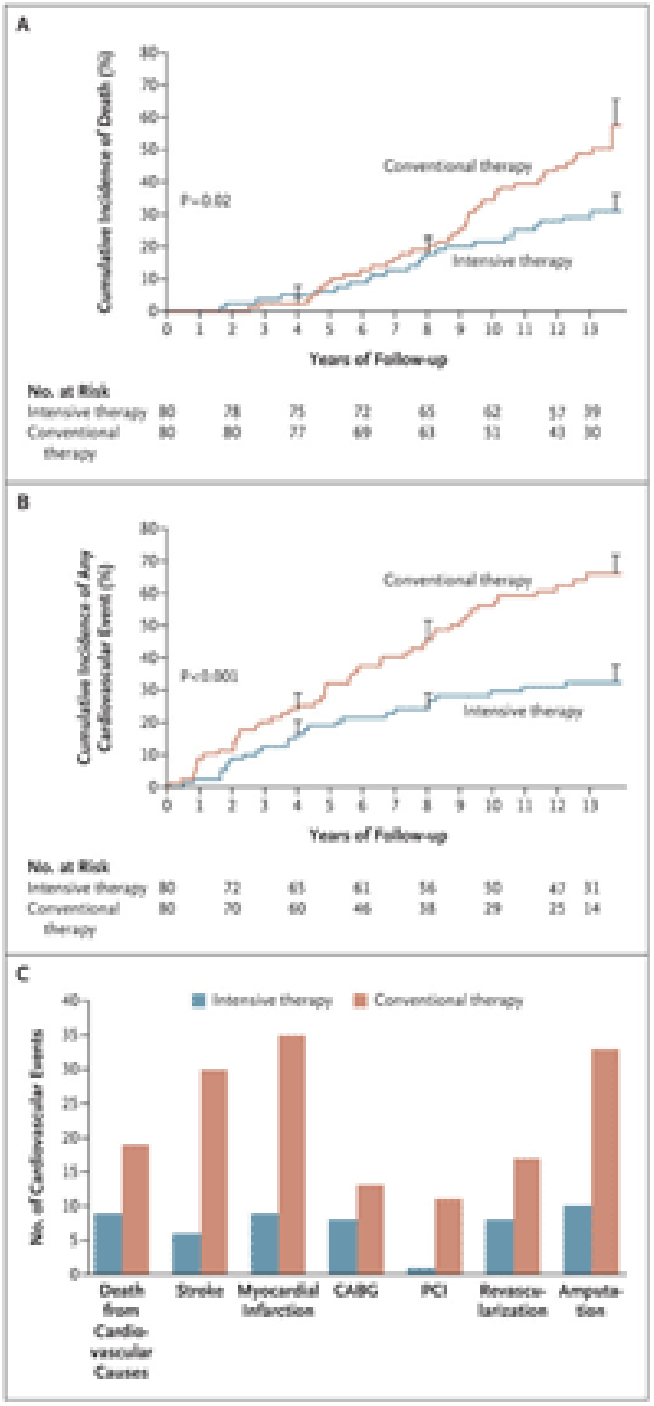
- 160 type-2 diabetics, mean age 55 years with microalbuminuria were randomised to standard treatment or intensive multi-factorial intervention
- Open study with parallel groups
- Mean follow-up 7.8 years - 130 pat
- Focusing on development of macroalbuminuria
- Significant reduction also of macrovascular end-points
- Cost-effective treatment (abstract, EASD 2006)

Gaede P, *NEJM,* 2003, 2008

Steno-2 trial

Long-term follow-up 13.8 years:

Benefits on mortality risk and primary endpoints



Gaede P, *et al*

N Engl J Med 2008;358:580-91

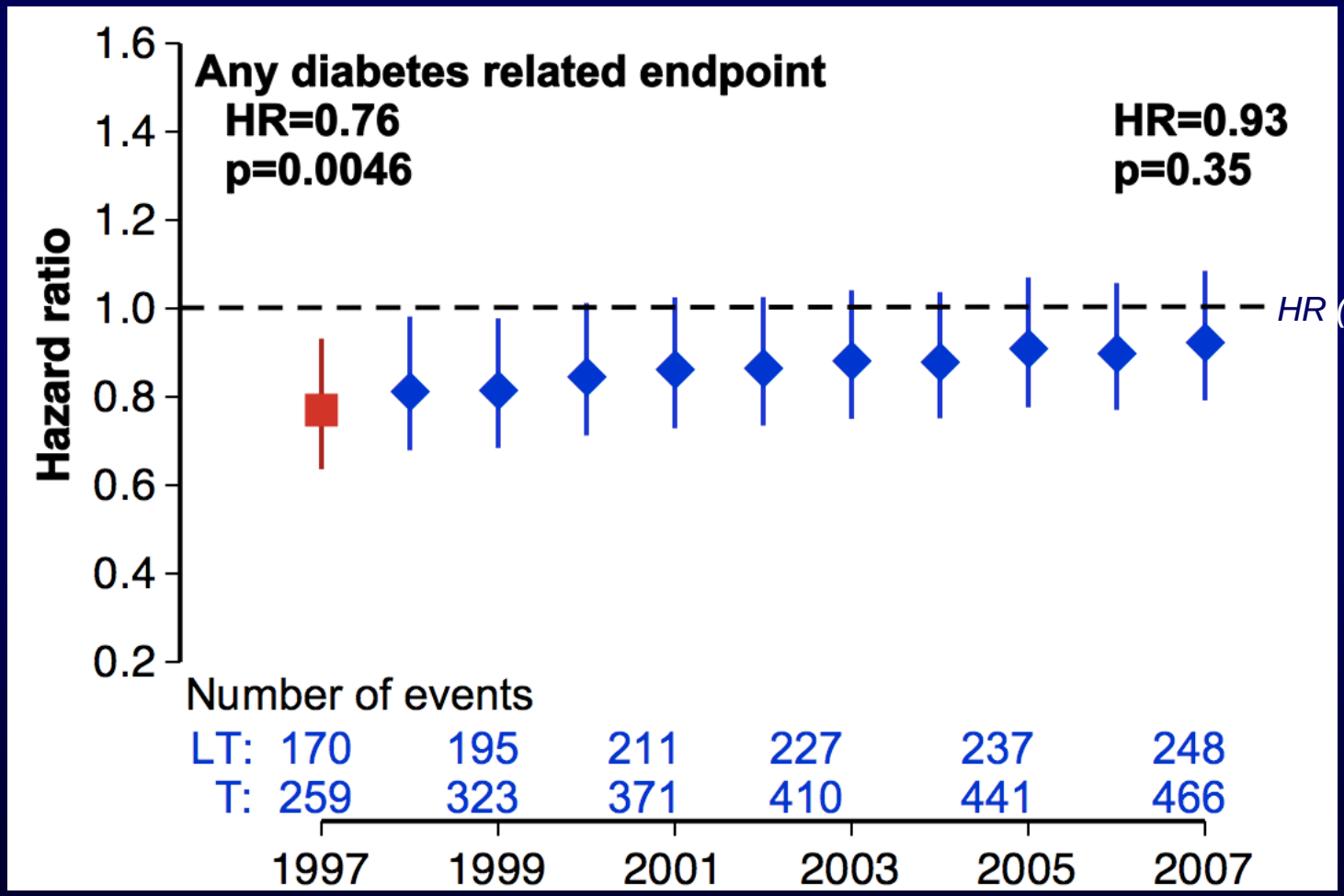
Rury Holman

ukpds

N Engl J Med 2008

UKPDS 10: Less-tight *vs.* Tight blood pressure control

Any Diabetes Related Endpoint (Hazard Ratio)



Holman R, et al. N Engl J Med 2008

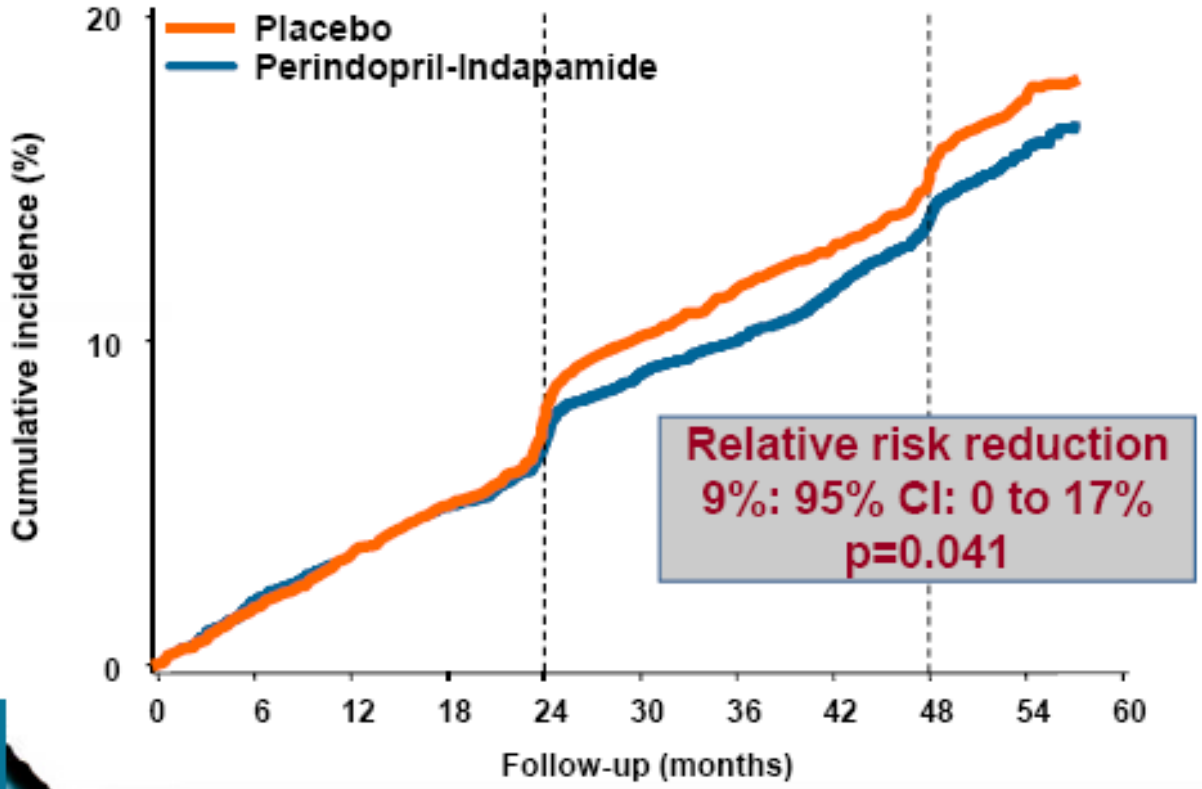
Useful AHT drug combinations

- ACE-I/ARB + low-dose TD
- ACE-I/ARB + CaA
- BB + CaA
- ACE-I + ARB (unfavourable for renal function in ONTARGET – no added benefit! *Lancet 2008*)

ADVANCE

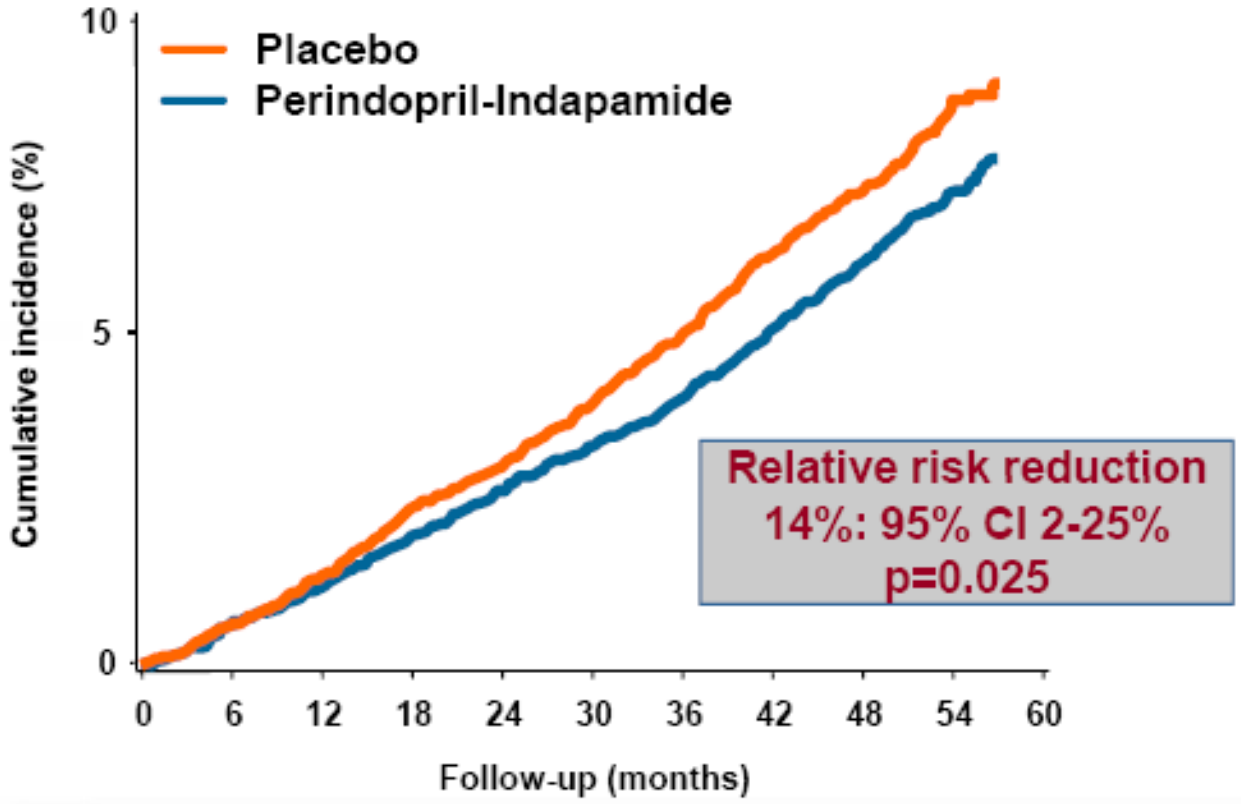
Combined primary outcomes

Major macro or microvascular event

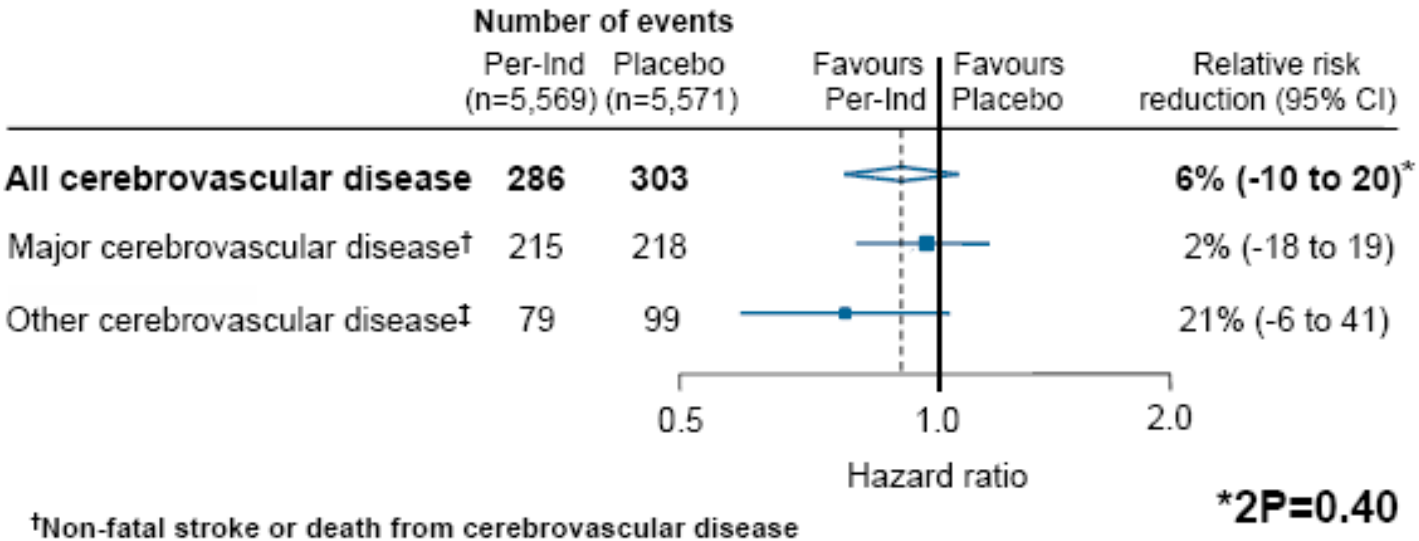


The George Institute for International Health

All-cause mortality



Cerebrovascular events



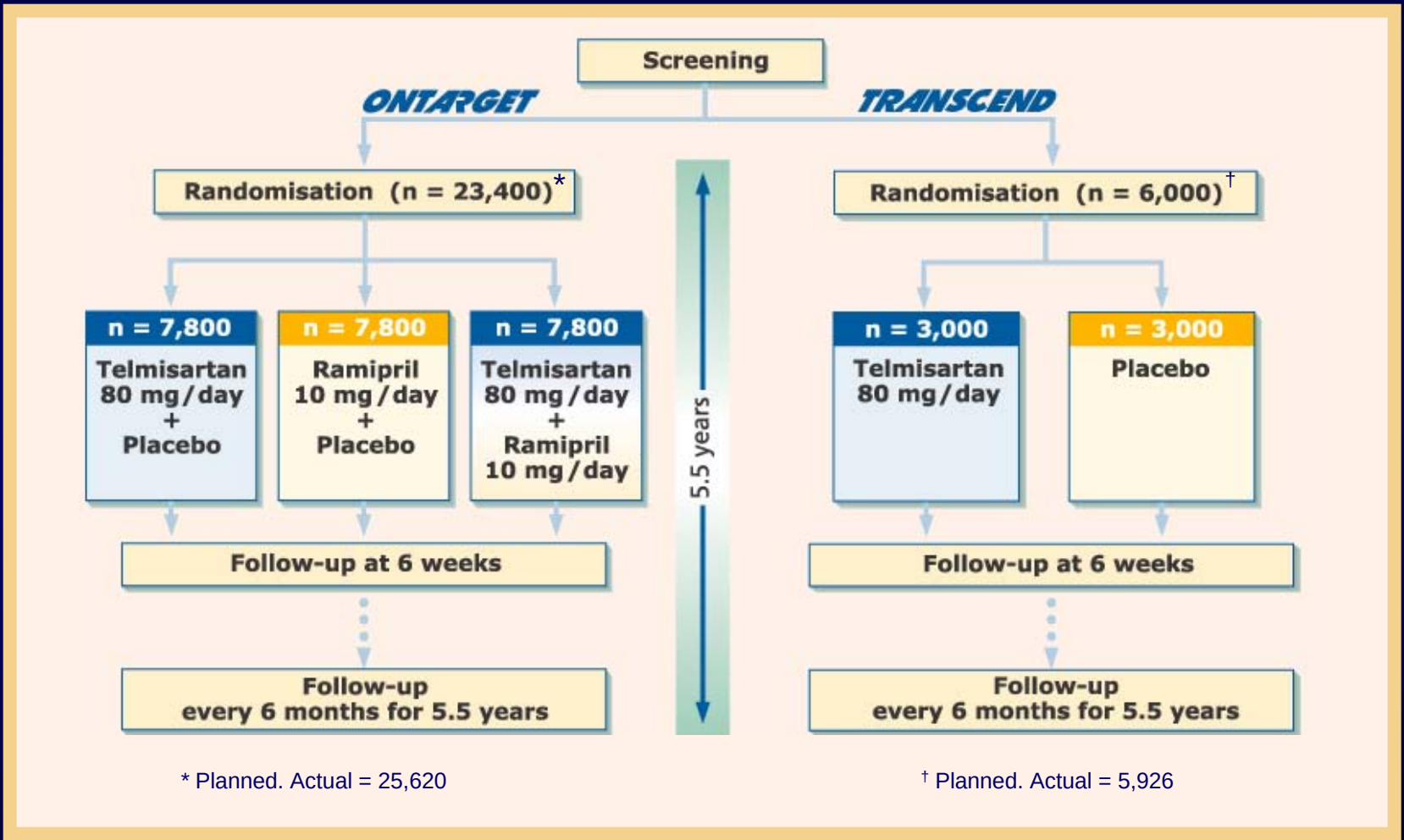
*2P=0.40

†Non-fatal stroke or death from cerebrovascular disease

‡Transient ischaemic attack or subarachnoid haemorrhage

The ONTARGET Trial Programme

Study Design

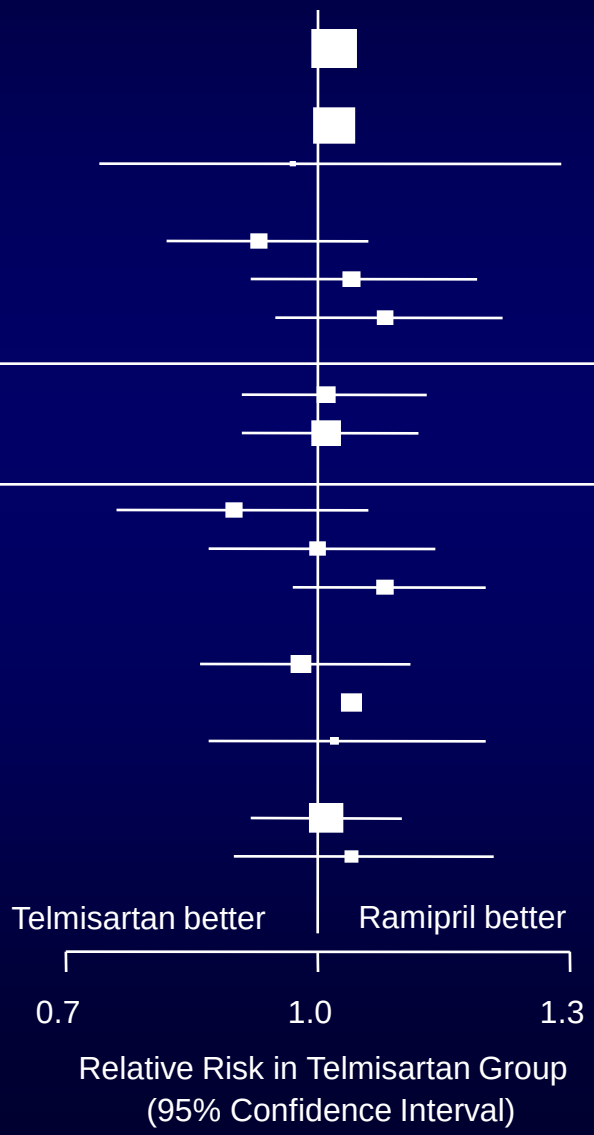


The ONTARGET/TRANSCEND Investigators. Am Heart J 2004;148:52–61
N Engl J Med 2008

T v R: Pre-specified Subgroup Analysis

ONTARGET

	No. of Patients	Incidence of Primary Outcome in Ramipril Group
Primary Composite	17118	16.4
Hx of CVD	15627	16.7
No Hx of CVD	1486	13.1
SBP < 134	5704	16.2
134 - 150	6042	14.9
> 150	5352	18.3
Diabetes	6390	20.6
No Diabetes	10723	14.0
HOPE Risk Score Low	5709	10.4
Medium	5664	15.0
High	5745	23.8
Age < 65	7319	13.0
65 - 75	7310	17.2
> 75	2489	24.1
Male	12537	16.7
Female	4581	15.7



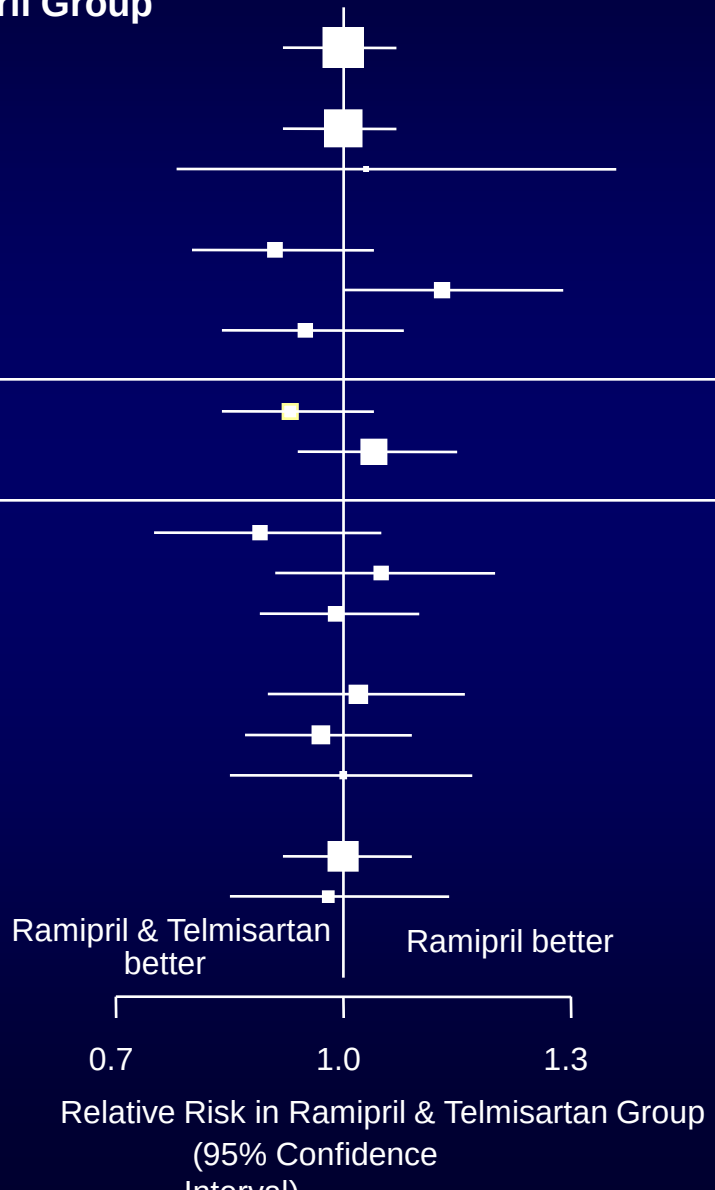
38% DM of all patients

N Engl J Med 2008

Tel + Ram versus Ram: Pre-specified Subgroups

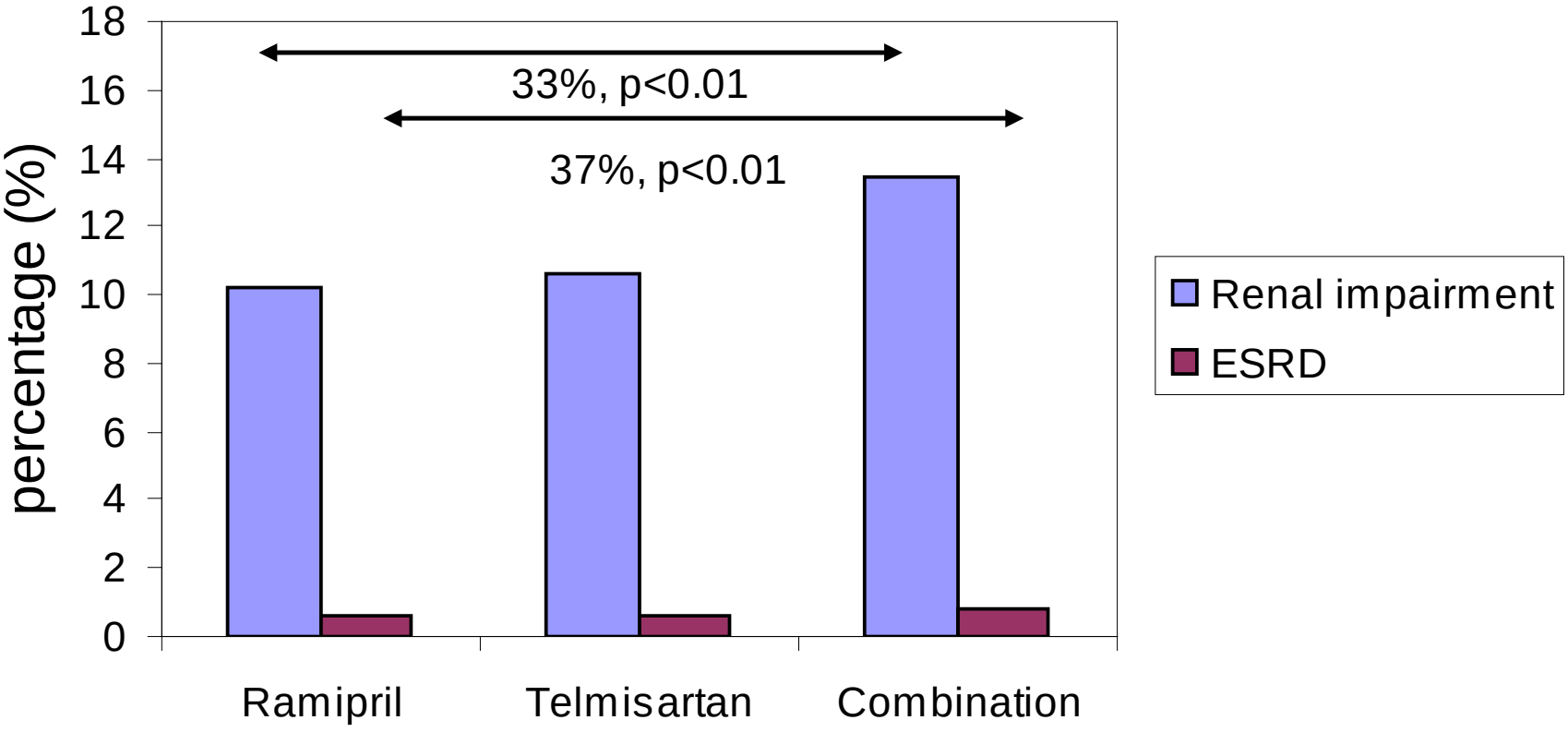
ONTARGET

	No. of Patients	Incidence of Primary Outcome in Ramipril Group
Primary Composite	17078	16.4
Hx of CVD	15589	16.7
No Hx of CVD	1484	13.1
SBP <= 134	5714	16.2
134 < SBP <= 150	6019	14.9
SBP > 150	5329	18.3
Diabetes	6364	20.6
No Diabetes	10709	14.0
HOPE Low Risk Score	5637	10.4
HOPE Medium Risk Score	5596	15.0
HOPE High Risk Score	5845	23.8
Age < 65	7362	13.0
65 <= Age < 75	7177	17.2
Age >= 75	2539	24.1
Male	12497	16.7
Female	4581	15.7



N Engl J Med 2008

Ontarget Trial: Renal Outcomes



Yusuf S *et al.*, N Engl J Med 2008;358:1547-59

RESULTS
ACC March 2008

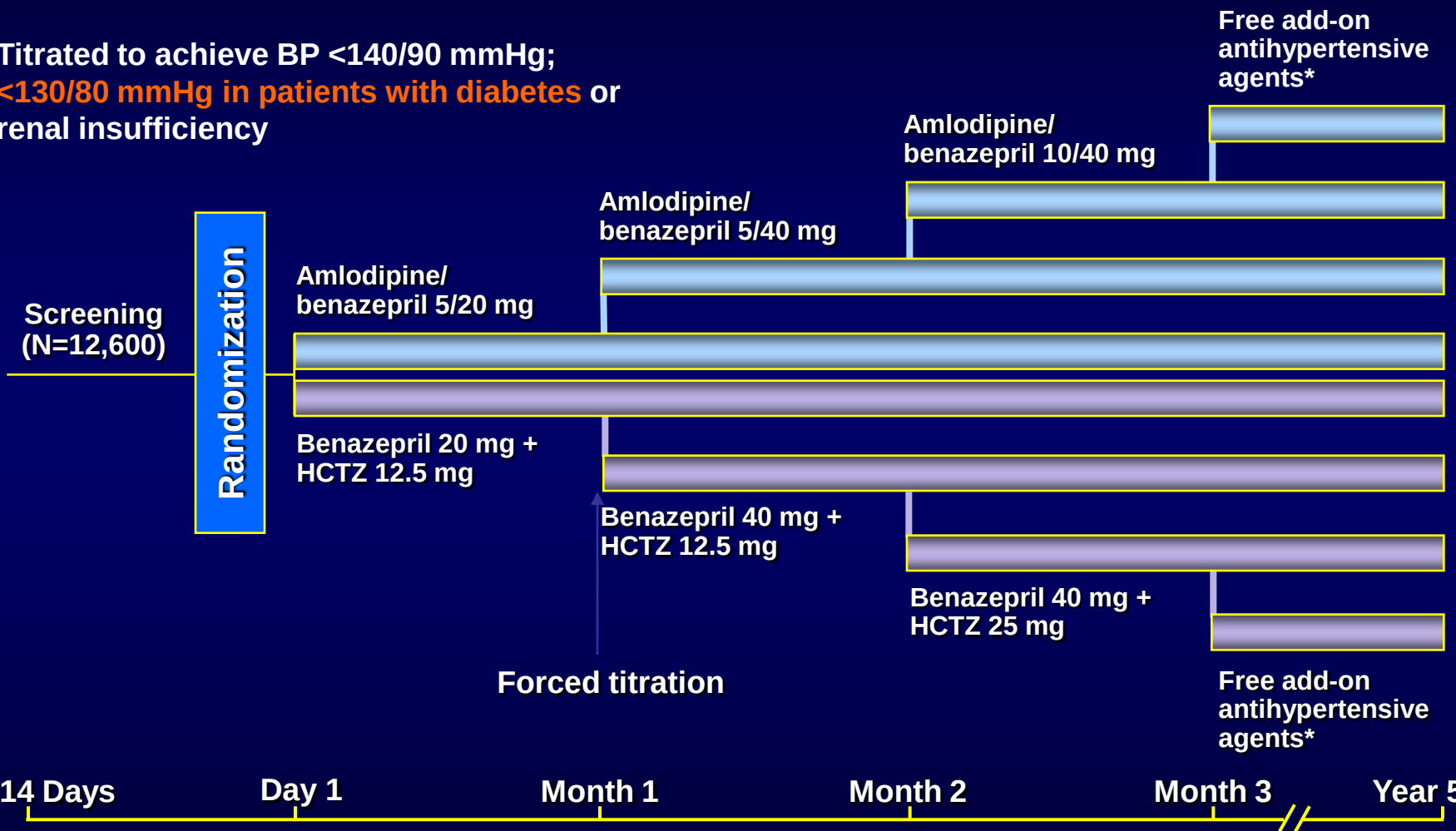
Jamerson K, *et al,* N Engl J Med 2009

Baseline Traits of the ACCOMPLISH Cohort (n= 11,400)

- 50% of patients were obese
- 60% of patients had Diabetes Mellitus
- 97% of patients were treated previously for hypertension
- 74% of patients were treated with ≥ 2 antihypertensive agents

- Only 37.5% of patients were controlled to <140/90 mmHg

Design



*Beta blockers; alpha blockers; clonidine; loop diuretics. Patients were seen at 6 months after the start of study and thereafter at 6-month intervals until the end of the 5 year trial.

Jamerson KA et al. *Am J Hypertens*. 2004;17:793–801.

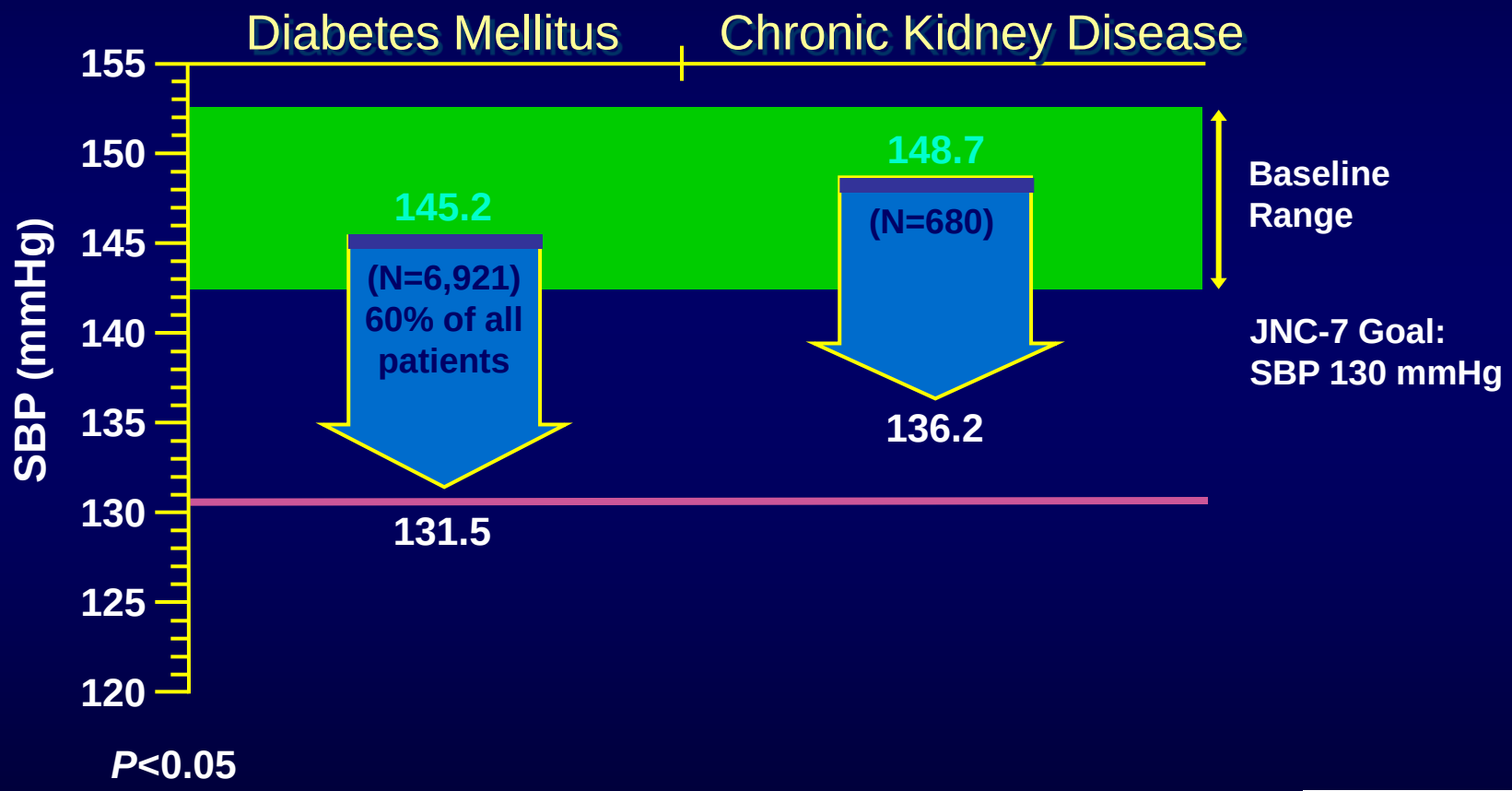
ACCOMPLISH: Reduction in systolic blood pressure in different populations

Patient population	Baseline systolic blood pressure (mm Hg)	Systolic blood pressure at 18 mo (mm Hg)	p
All (n=11 400)	145.4	131.8	<0.05
•Nordic (n=3333)	152.6	136.8	<0.05
•American (n=8067)	142.4	129.4	<0.05
•African American (n=1361)	145.1	133.6	<0.05
•Diabetes mellitus* (n=6921)	145.2	131.5	<0.05
•Chronic kidney disease* (n=680)	148.7	136.2	<0.05

*Did not achieve systolic blood pressure goal of 130 mm Hg as recommended by the JNC-7 for these populations

Jamerson KA et al. American Society of Hypertension 2007 Scientific Sessions; May 21, 2007; Chicago, IL.

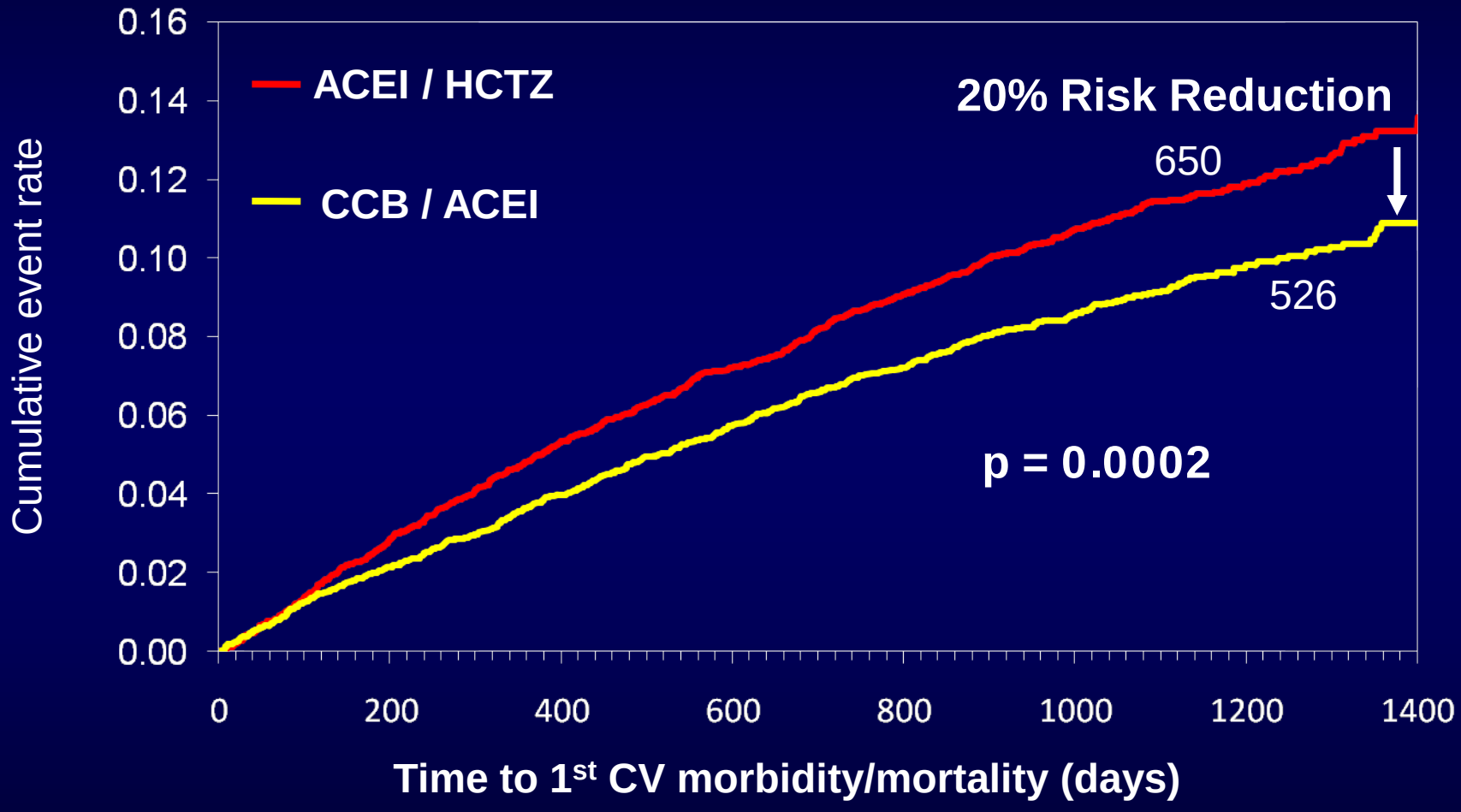
ACCOMPLISH: Significant Decrease in SBP Levels in Difficult-to-Treat Patient Subgroups



Jamerson ASH 2007

ACCOMPLISH

Kaplan Meier for Primary Endpoint



HR (95% CI): 0.80 (0.72, 0.90)

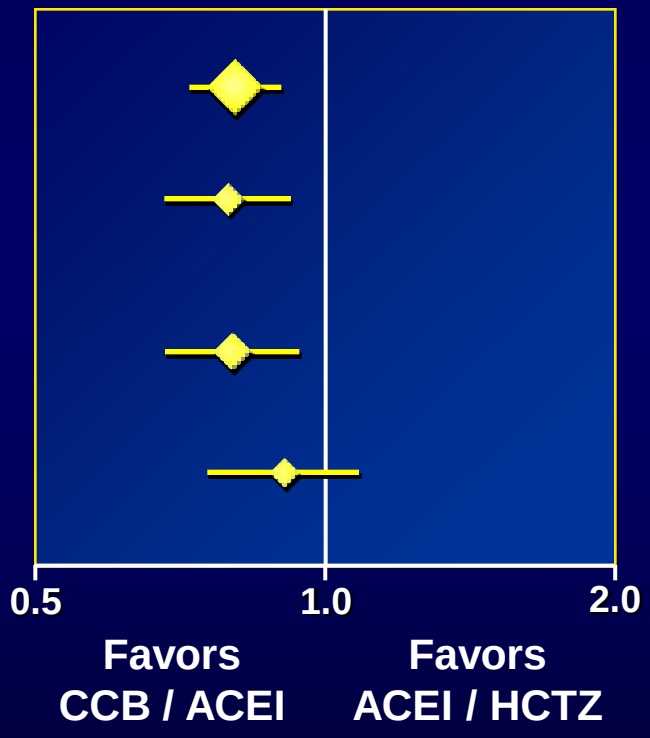
INTERIM RESULTS March 2008, *N Engl J Med 2009*

ACCOMPLISH

Primary and Other Endpoints

Incidence of adjudicated primary endpoints, based upon cut-off analysis date 3/24/2008

(Intent-to-treat population)



	Risk Ratio (95%)
Composite CV mortality/morbidity	0.80 (0.72–0.90)
Primary w/o revascularization	0.79 (0.68–0.92)
Hard CV endpoint (CV death, non-fatal MI, non-fatal stroke)	0.80 (0.68–0.94)
All cause mortality	0.90 (0.75–1.08)

INTERIM RESULTS March 2008

ACCOMPLISH

Action to Control Cardiovascular Risk in Diabetes
ACCORD

Blood Pressure Hypothesis

In middle-aged or older people with type 2 diabetes who are at high risk for a CVD event:

In the context of good glycaemic control, does a therapeutic strategy that targets systolic blood pressure (SBP) of

< 120 mm Hg reduce the rate of CVD events more than a strategy that targets SBP < 140 mm Hg?

Results are expected during late 2009 or in early 2010

Action to Control Cardiovascular Risk in Diabetes
ACCORD

Blood Pressure Trial
(42% of ACCORD participants)

4,200

Age-eligible, high risk people with type 2 diabetes

Intensive Group

Standard Group

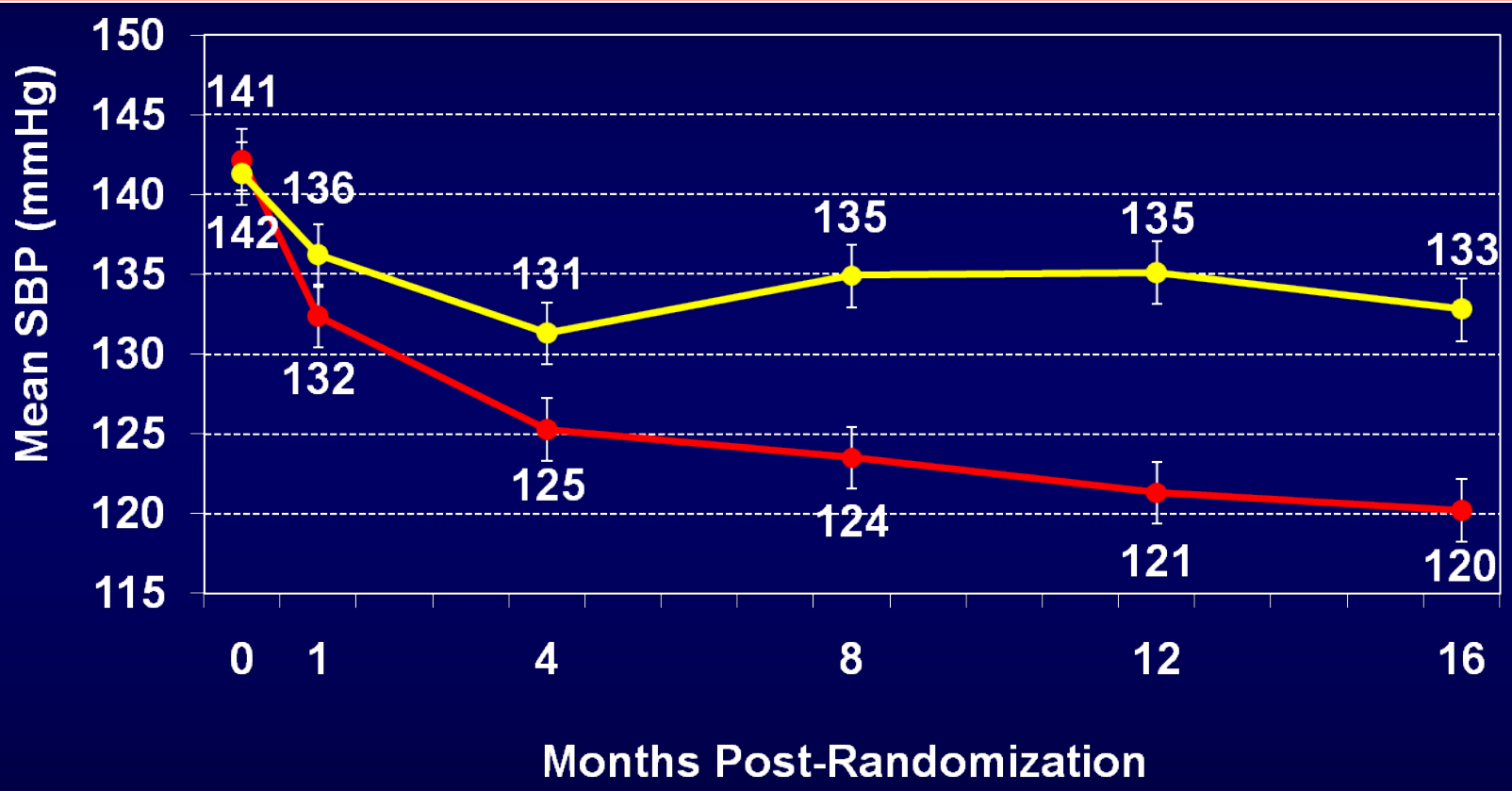
Treated and followed
for > 4 years (mean 5.5 yrs)

MAJOR CVD EVENTS

ACCORD: Achieved Systolic Pressures

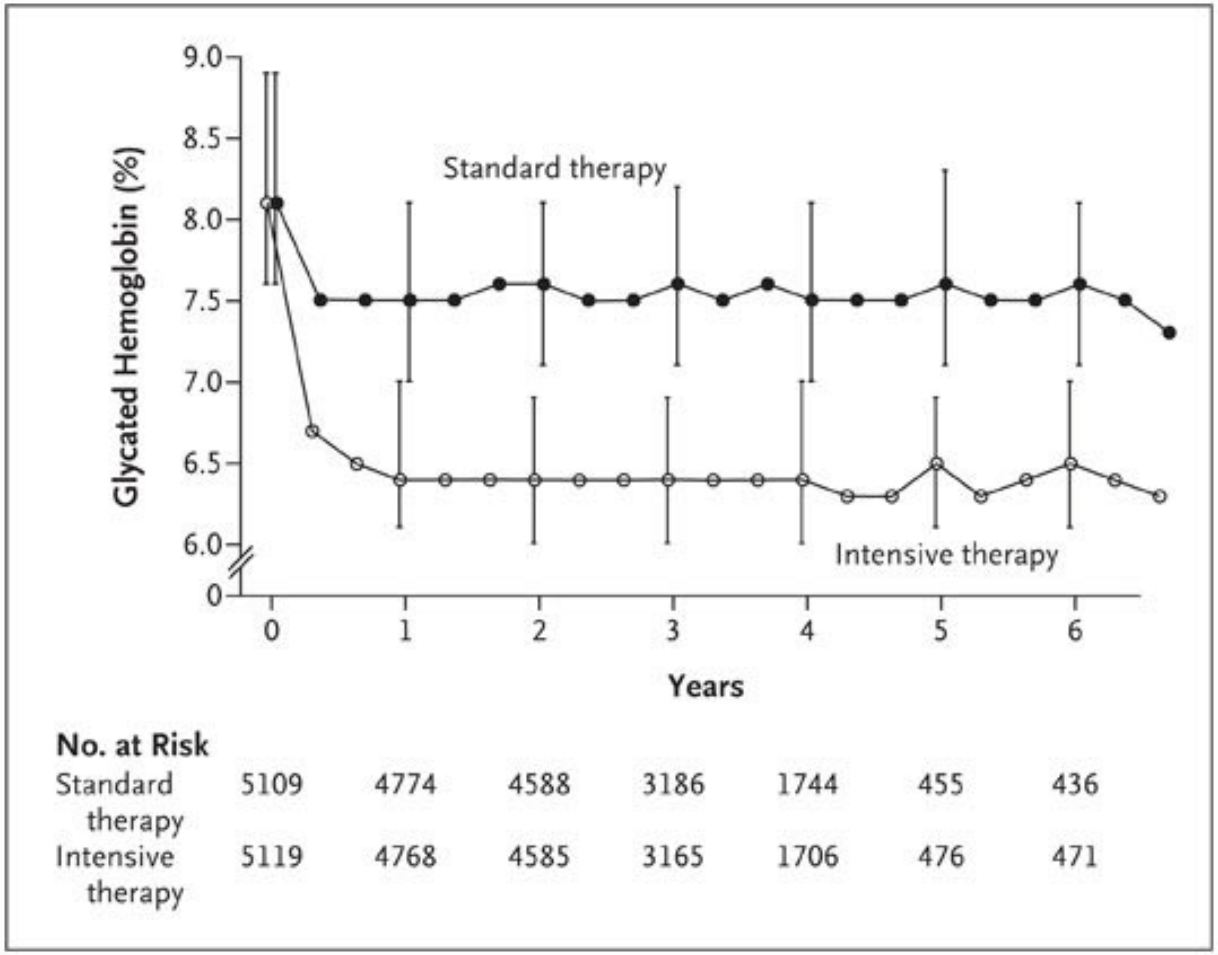
Means +/- 95% Confidence Intervals

Mean # Meds:	1.5	1.7	1.8	1.9	**1.8**
Mean # Meds:	1.9	2.4	2.8	3.0	**3.1**



Cushman WC *et al*. ASH 2008

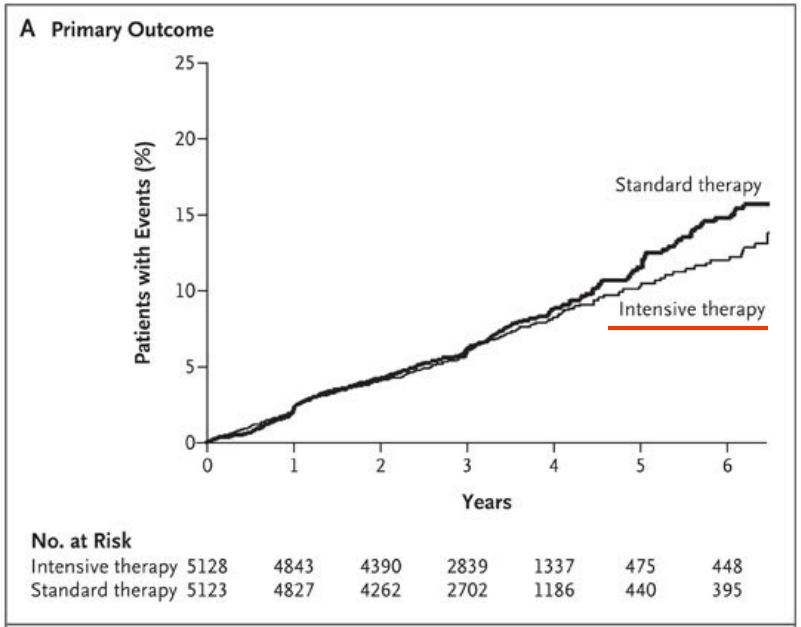
Median Glycated Hemoglobin Levels at Each Study Visit in the ACCORD trial



The Action to Control Cardiovascular Risk in Diabetes Study Group.
N Engl J Med 2008;10.1056/NEJMoa0802743

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan-Meier Curves for the Primary Outcome and Death from Any Cause in ACCORD

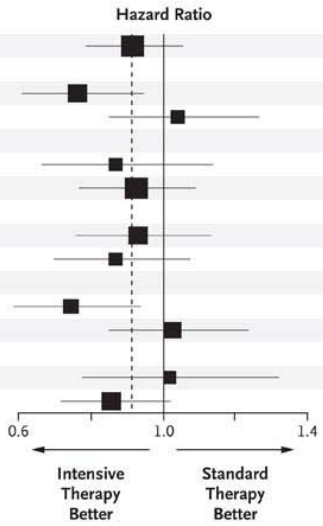


The NEW ENGLAND JOURNAL of MEDICINE

Hazard Ratios for the Primary Outcome and Death from Any Cause in Prespecified Subgroups

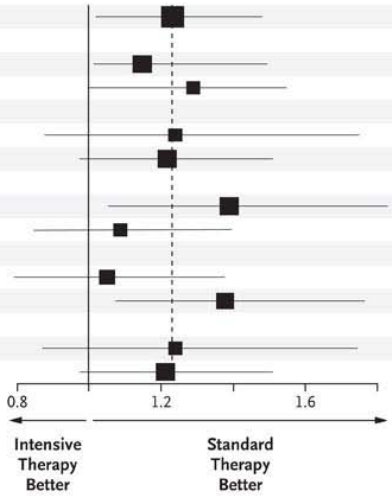
A Primary Outcome

Subgroup	No. of Patients	No. of Events	P Value
Total	10,251	723	
Previous cardiovascular event			0.04
No	6,643	330	
Yes	3,608	393	
Sex			0.74
Female	3,952	212	
Male	6,299	511	
Age at baseline			0.65
<65 yr	6,779	383	
≥65 yr	3,472	340	
Glycated hemoglobin at baseline			0.03
≤8.0%	4,868	284	
>8.0%	5,360	438	
Race			0.29
Nonwhite	3,647	222	
White	6,604	501	



B Death from Any Cause

Subgroup	No. of Patients	No. of Events	P Value
Total	10,251	460	
Previous cardiovascular event			0.53
No	6,643	220	
Yes	3,608	240	
Sex			0.92
Female	3,952	132	
Male	6,299	328	
Age at baseline			0.19
<65 yr	6,779	212	
≥65 yr	3,472	248	
Glycated hemoglobin at baseline			0.15
≤8.0%	4,868	204	
>8.0%	5,360	256	
Race			0.93
Nonwhite	3,647	131	
White	6,604	329	



Possible explanations?

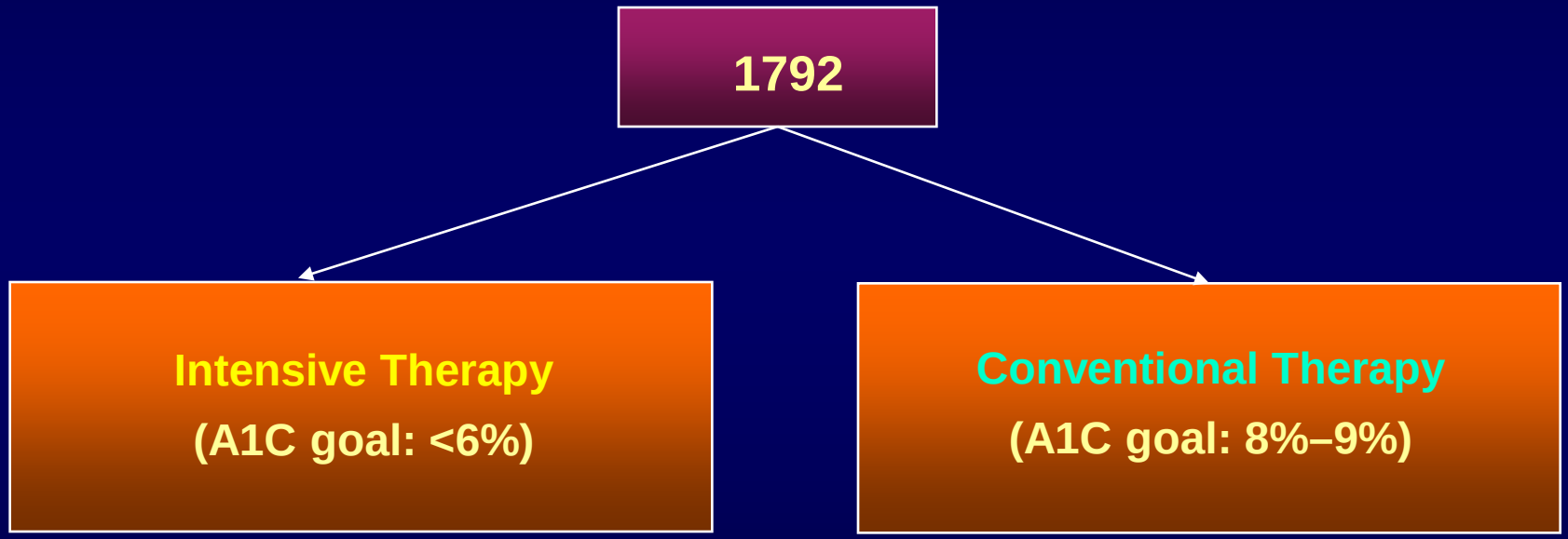
- Increased mortality influenced by hypoglycaemia
- Susceptible patients due to co-morbidities or other heterogeneity of study population
- No firm evidence of any causative drug (even if 90% were on glitazone therapy in the intensive control arm)
- Could more ACE-I therapy in the intensive BP arm lead to increased insulin sensitivity and thereby increase the risk of hypoglycaemia in the intensive glucose control arm? A sub-analysis should be carried out when all data becomes available in ACCORD

The VADT Trial
Study Design

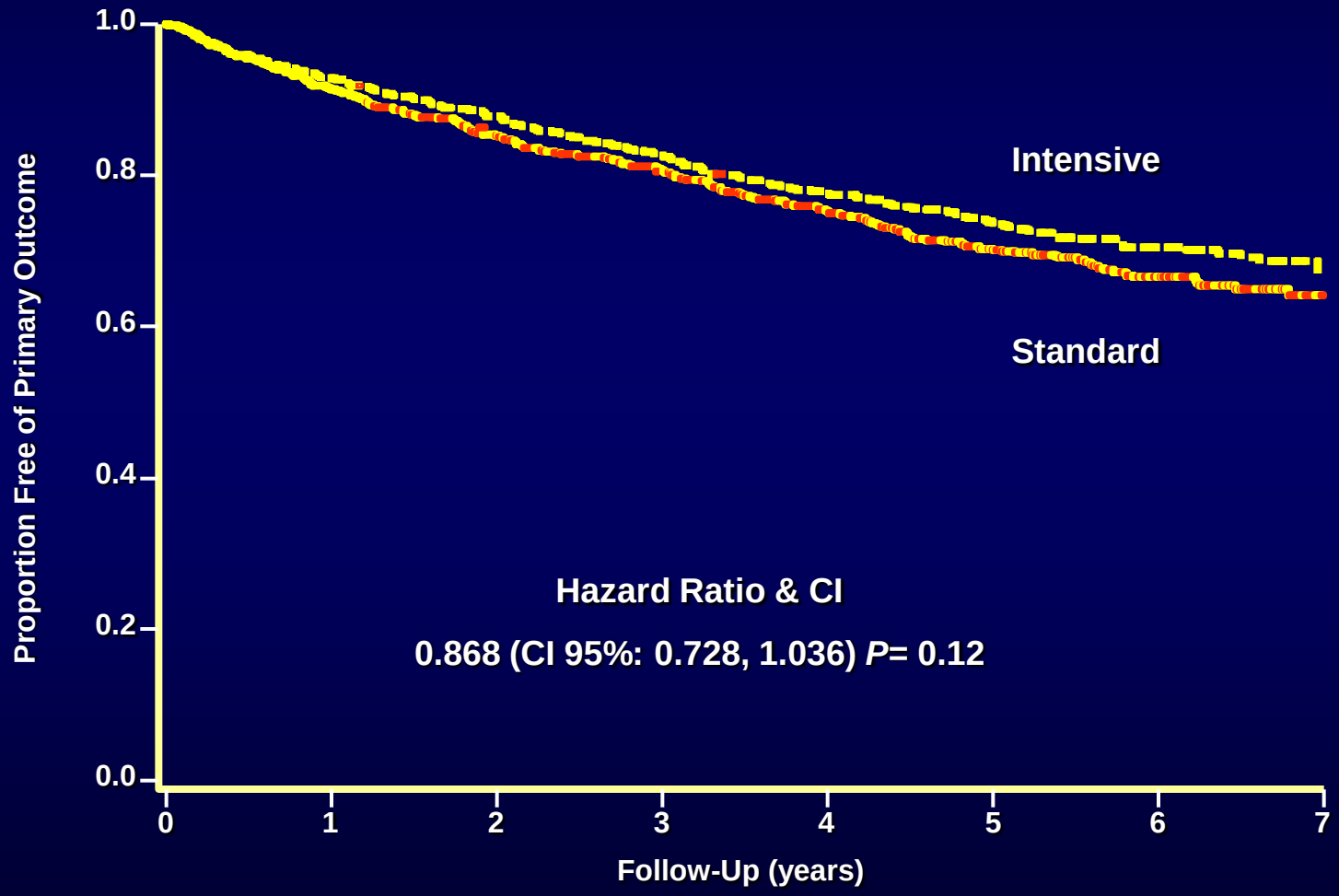
VADT is a 5- to 7-year, randomized, multicenter trial following 1792 older patients with T2DM in the VA System

N Engl J Med 2008

The VADT Trial
Study Randomization

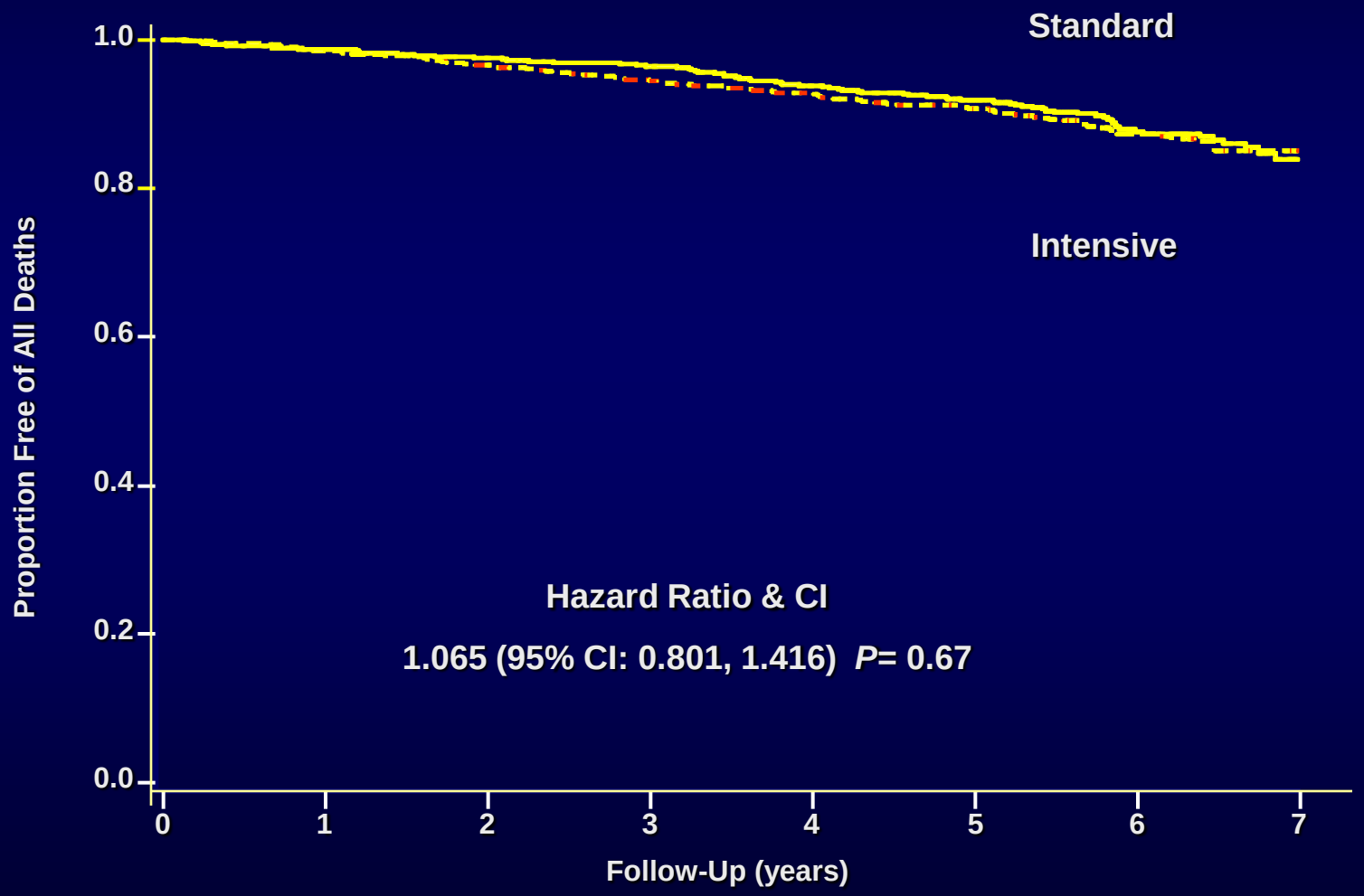


VA Diabetes Trial: Primary Outcome



Duckworth WC. ADA 68th Scientific Sessions; June 8, 2008; San Francisco, CA.

VA Diabetes Trial: Total Mortality



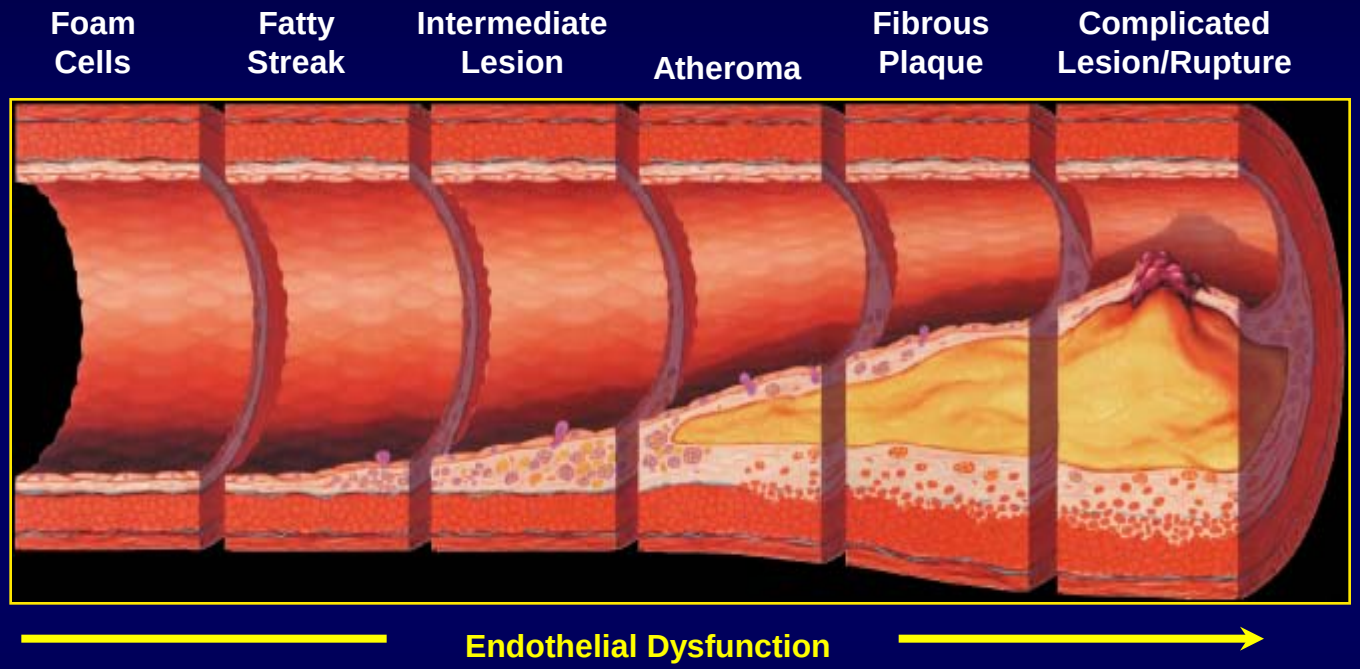
Duckworth WC. ADA 68th Scientific Sessions; June 8, 2008; San Francisco, CA.

The Human Genome 2002
Genetics of Hypertension 2009

- Natriuretic peptides (*Nature Genetics*, March 2009)
- Global BP-gene project (*Nature Genetics*, May 2009)

ejt 0201–202

Early Vascular Ageing (EVA):
Atherosclerosis and arterial stiffening



Nilsson PM, Lurbe E, Laurent S, J Hypertens 2008

Summary

- Hypertension in diabetes is an important risk factor, and should be treated according to guidelines
  - ESH Newsletter 2005, ESC/EASD guidelines 2007, ESH/ESC guidelines 2007, EASD/ADA 2008, 2009

- Trial data support that clinical benefits can be achieved by treating blood pressure and insulin resistance. HbA_{1c} normalization is controversial
  - ASCOT, PRO-Active, ADVANCE, ACCORD, VADT

- ONTARGET trial provides controversial findings
  - No benefit by combining ramipril and telmisartan for CVD prevention or improved renal function

PN 2009