

ACCORD TRIAL- BLOOD PRESSURE

(effect of Intensive Blood Pressure Control in
Type 2 Diabetes)

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Two Previous Studies Measuring Outcome and Blood Pressure

SHEP

NAVIGATOR

UKPDS

HOT

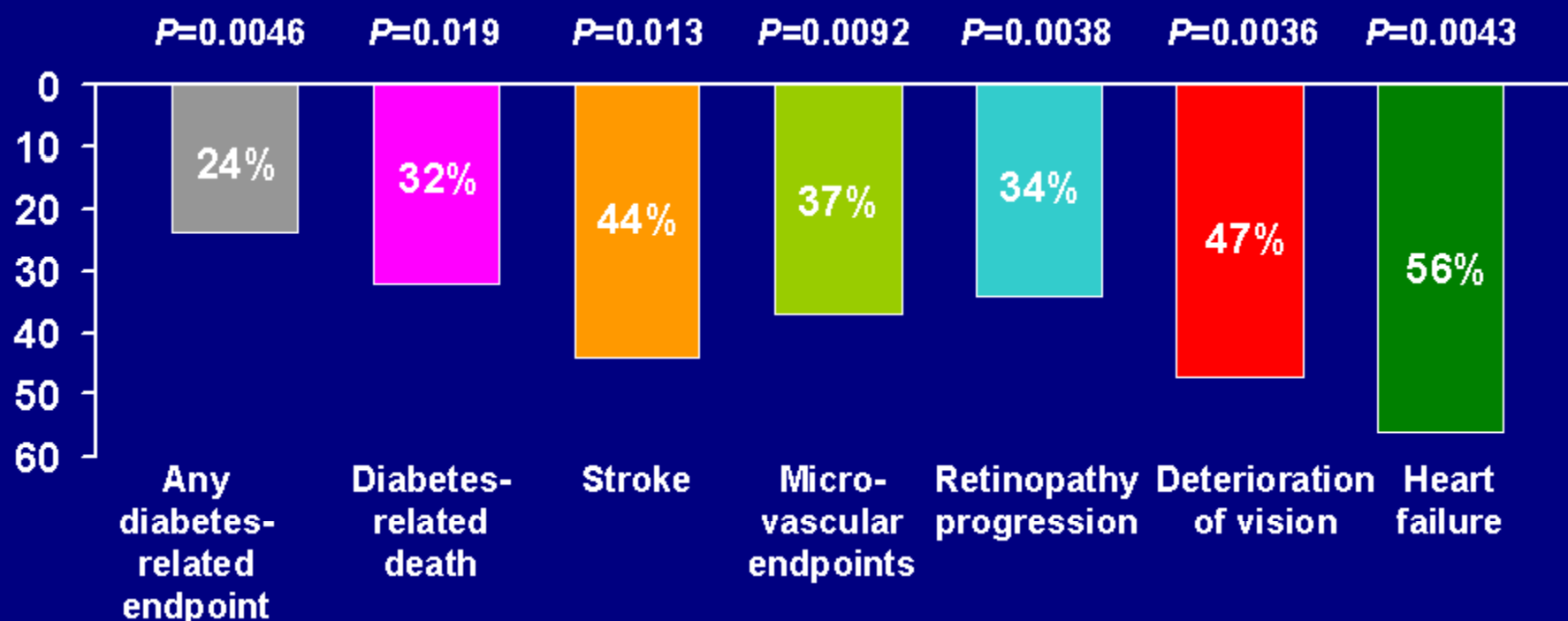
Why was ACCORD Blood Pressure Trial performed ?

- Lack of evidence to support Blood pressure less than 135-140 for prevention CVD in T2DM



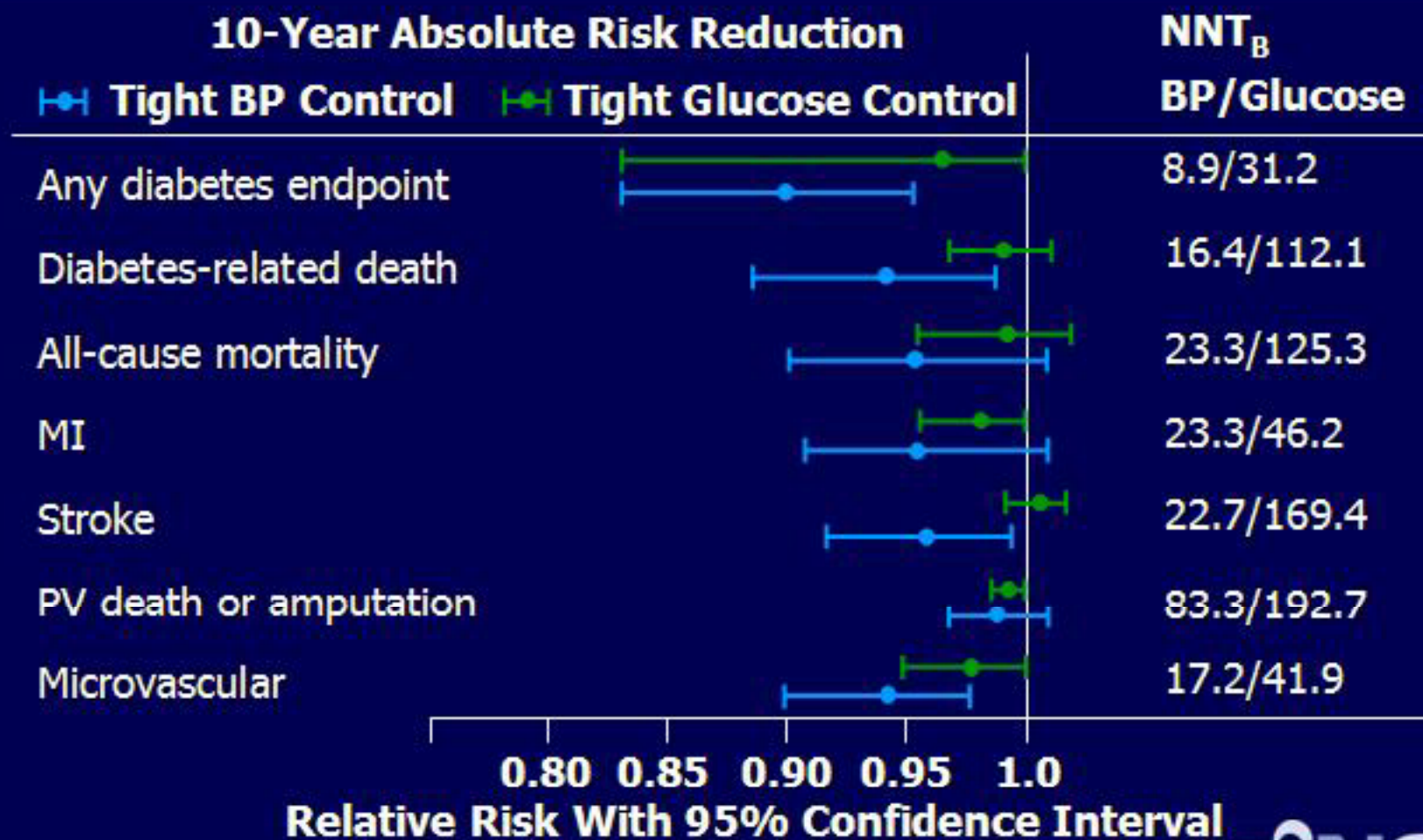
UKPDS Results: Tight BP Control

Risk Reduction*



*Compared with less tight control. Captopril and atenolol were equally effective in reducing risk and were equally safe in patients with diabetes.

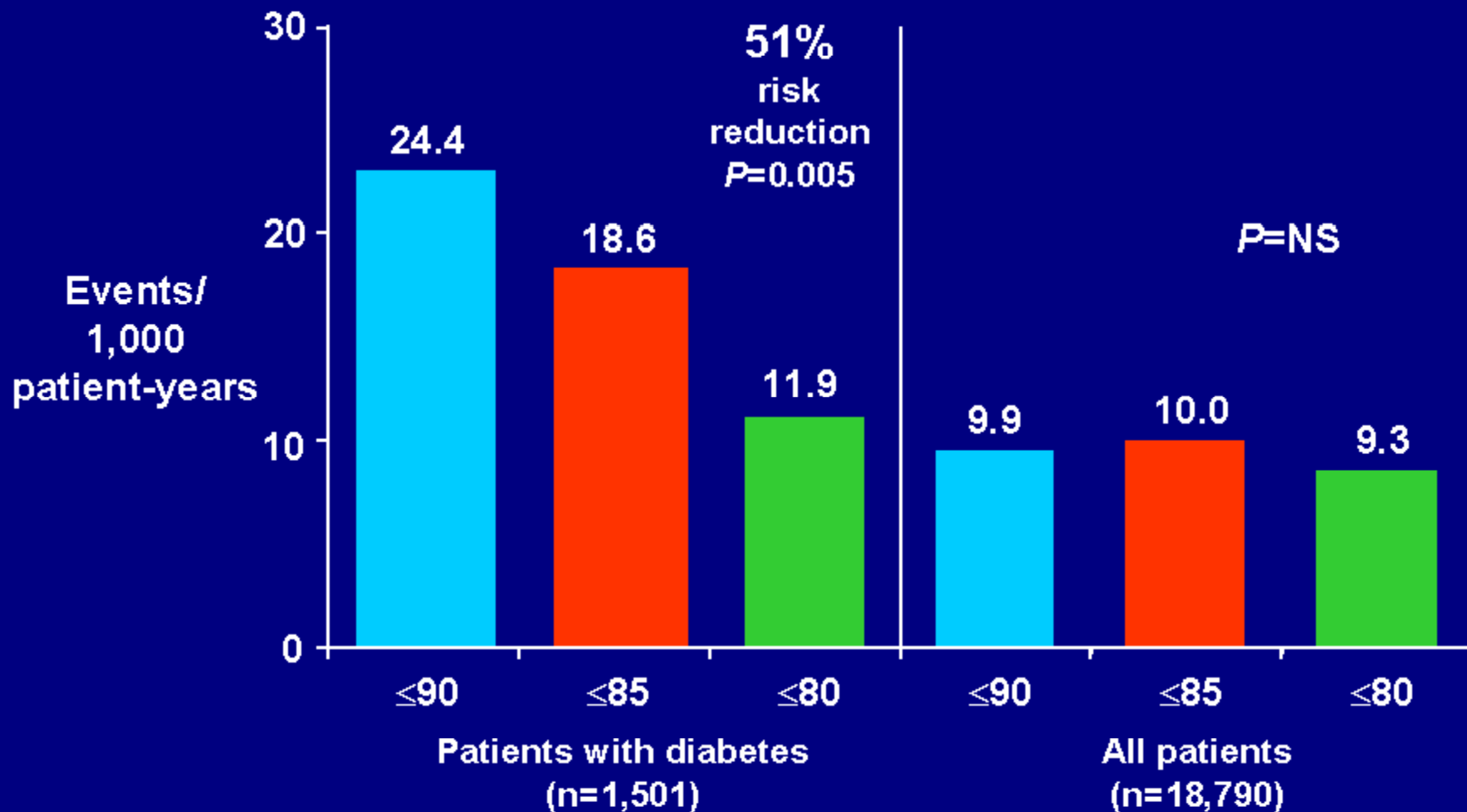
CVD Risk Reduction From Tight Control of BP and Glucose in Type 2 Diabetes



PV = peripheral vascular; NNT_B = number-needed-to-treat for benefit
 Vijan S et al. *Ann Intern Med.* 2003;138:593-602.



HOT Trial: Effect of Targeted DBP on Cardiovascular Events Over 4 Years



Hansson L et al. *Lancet*. 1998; 351:1755-1762.



ADA: Goals for Glycemic, Blood Pressure, and Lipid Control

A1C	<7.0% ^a
Blood pressure	<130/<80 mm Hg
Lipids	LDL-C: <100 mg/dL <70 mg/dL for those with diabetes and CVD For maximally tolerated, drug-treated patients who do not reach target, reduction in LDL-C 30%–40% from baseline is alternative

^aReferenced to a nondiabetic range of 4.0%–6.0% using a Diabetes Control and Complications Trial-based assay.

CVD=cardiovascular disease.

ADA. *Diabetes Care*. 2010;33(suppl 1):S31.

Inclusion criteria

- Type 2 Diabetes
- Hgb A1C \geq or equal to 7.5%
- 40 years of age or older with CVD or 55 years of age or older with anatomical evidence of risk
- Individuals with systolic blood pressure 130-180 mm Hg taking three or fewer antihypertensive medications and a 24 protein of less than 1 gm

Exclusion Criteria

- BMI more than 45
- Serum creatinine more than 1.5 mg/dl
- Other serious illness

ACCORD Double 2 x 2 Factorial Design

	Lipid		BP		
	Placebo	Fibrate	Intensive	Standard	
Intensive Glycemic Control	1383	1374	1178	1193	5128
Standard Glycemic Control	1370	1391	1184	1178	5123
	2753	2765	2362	2371	10,251
	5518		4733*		

* 94% power for 20% reduction in event rate, assuming standard group rate of 4% / yr and 5.6 yrs follow-up

ACCORD- Blood Pressure (Design)

- Randomized nonblinded trial at 77 clinical sites in United States and Canada
- Entire ACCORD trial 10,251 high-risk participants with stable type 2 diabetes mellitus (**glucose control was the driver**)
- Randomly assigned to targeted therapy of 120 mm Hg (intensive treatment) or 140 mm Hg (standard therapy)
- Treatment strategy study to achieve blood pressure goal rather than evaluating efficacy of a specific therapy

Primary Endpoint

- Composite of Nonfatal MI, nonfatal stroke, and CVD death
- Intensive less than 120mm Hg
- Standard less than 140mm Hg

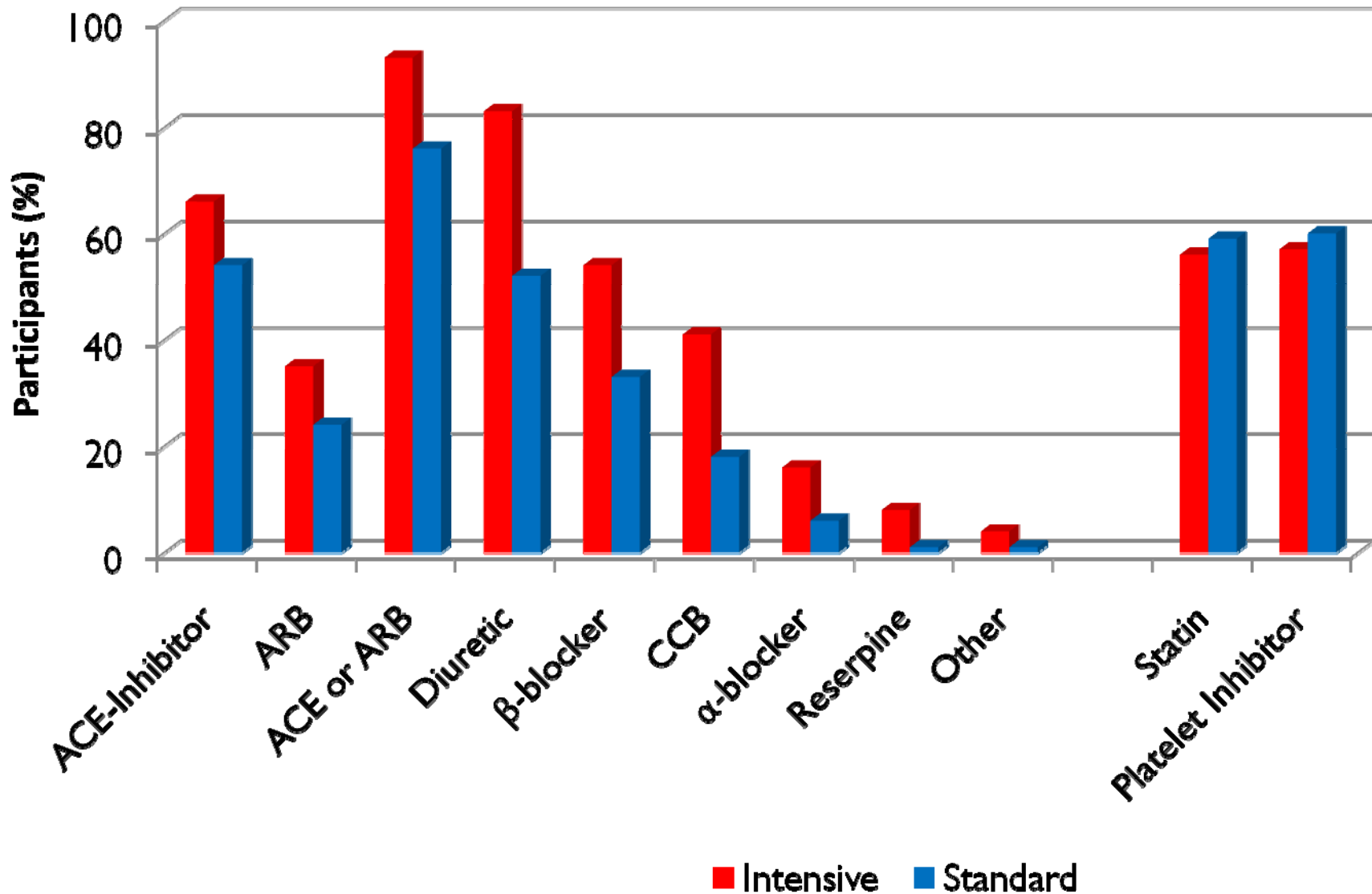
ACCORD BP Trial Eligibility

- **Stable Type 2 Diabetes >3 months**
- HbA1c 7.5% to 11% (or <9% if on more meds)
- High CVD risk = clinical or subclinical disease or ≥ 2 risk factors
- **Age (limited to <80 years)**
 - ≥ 40 yrs with history of clinical CVD (secondary prevention)
 - ≥ 55 yrs otherwise
- **Systolic blood pressure**
 - 130 to 160 mm Hg (if on 0-3 meds)
 - 161 to 170 mm Hg (if on 0-2 meds)
 - 171 to 180 mm Hg (if on 0-1 meds)
- Urine protein <1.0 gm/24 hours or equivalent
- Serum Creatinine ≤ 1.5 mg/dl

Drug Titration

- Many drugs/combinations provided to achieve goal BP according to randomized assignment.
- Intensive Intervention:
 - 2-drug therapy initiated: thiazide-type diuretic + ACEI, ARB, or β -blocker.
 - Drugs added and/or titrated at each visit to achieve SBP <120 mm Hg.
 - At periodic "milepost" visits: addition of another drug "required" if not at goal.
- Standard Intervention:
 - Intensify therapy if SBP \geq 160 mm Hg @ 1 visit or \geq 140 mm Hg @ 2 consecutive visits
 - Down-titration if SBP <130 mm Hg @ 1 visit or <135 mm Hg @ 2 consecutive visits

Medications Prescribed (12 Month Visit)



- Evaluated effects of intensive BP control (<120 mm Hg SBP) on CVD events among high-risk subjects with type 2 diabetes
- Subjects (N=4,733)
 - SBP between 130-180 mm Hg
 - taking ≤3 antihypertensives
 - <1.0 g 24-hour protein exchange rate
 - randomized to intensive (SBP <120 mm Hg) or standard (SBP <140 mm Hg) therapy
 - BP assessment was conducted once/month for 4 months and every 2 months thereafter for intensive therapy, and at months 1 and 4 and every 4 months thereafter for standard therapy
- Primary outcome: first occurrence of major CV event, including nonfatal MI, nonfatal stroke, or death from CV causes

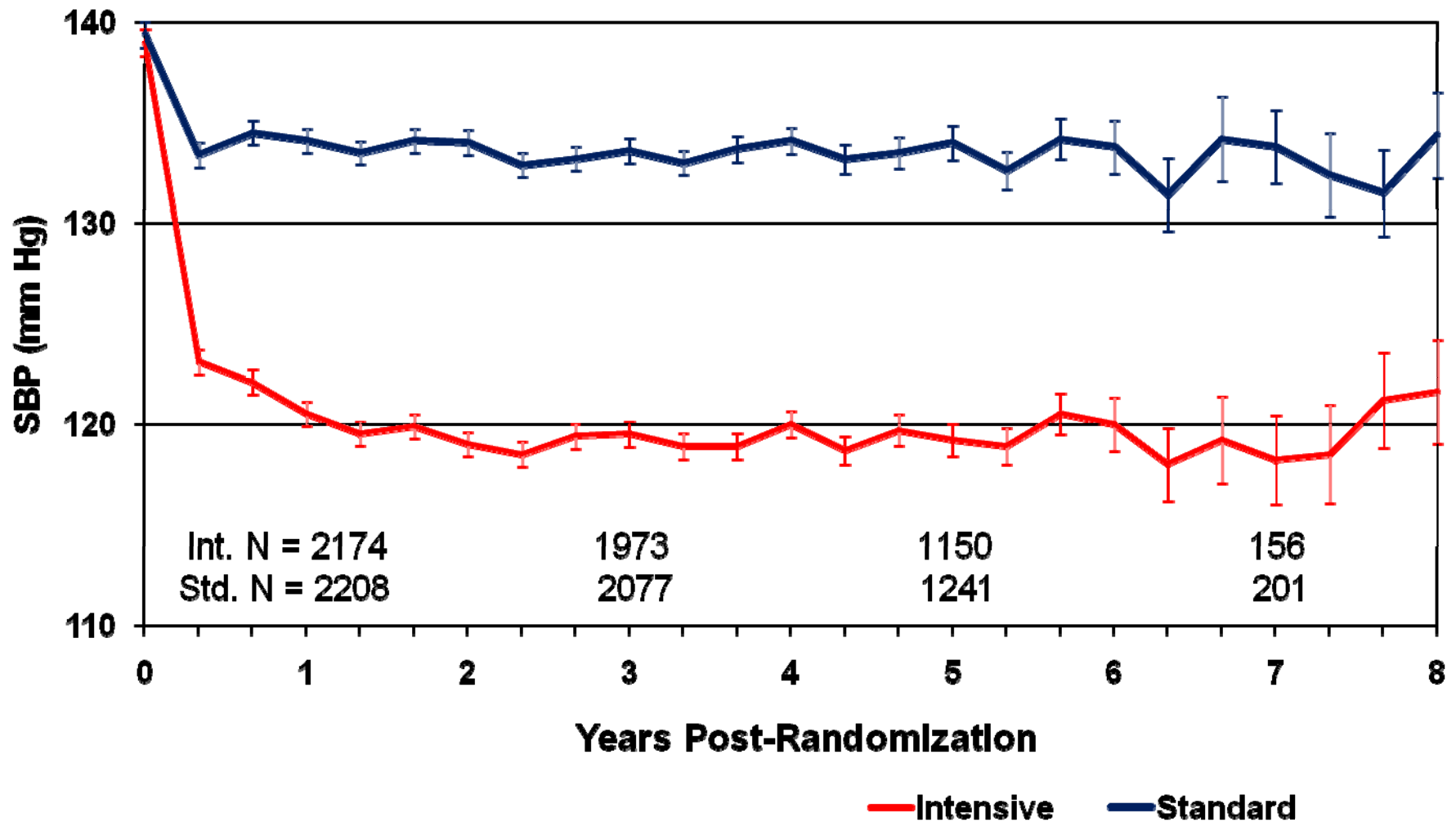
ACCORD=Action to Control Cardiovascular Risk in Diabetes

BP=blood pressure; CVD=cardiovascular disease; MI=myocardial infarction; SBP=systolic blood pressure

Visit schedule

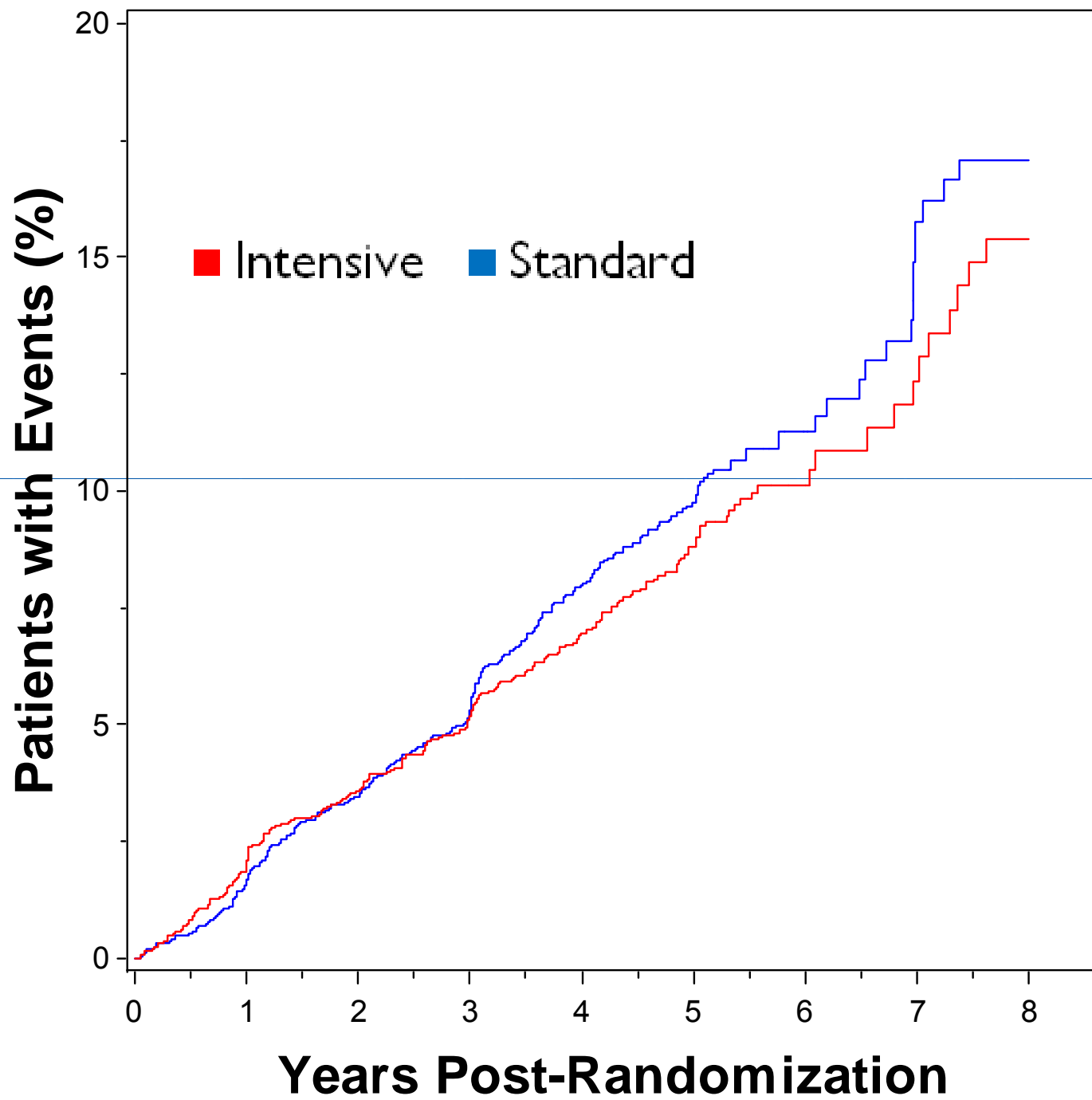
- Intensive arm once monthly for 4 months
- Every 2 months thereafter
- Standard arm months 1 and 4 then 4 months thereafter
- Additional visits were scheduled on an as needed basis
- 4 month visits study outcome and adverse events were ascertained –some of which were self reported

Systolic Pressures (mean \pm 95% CI)

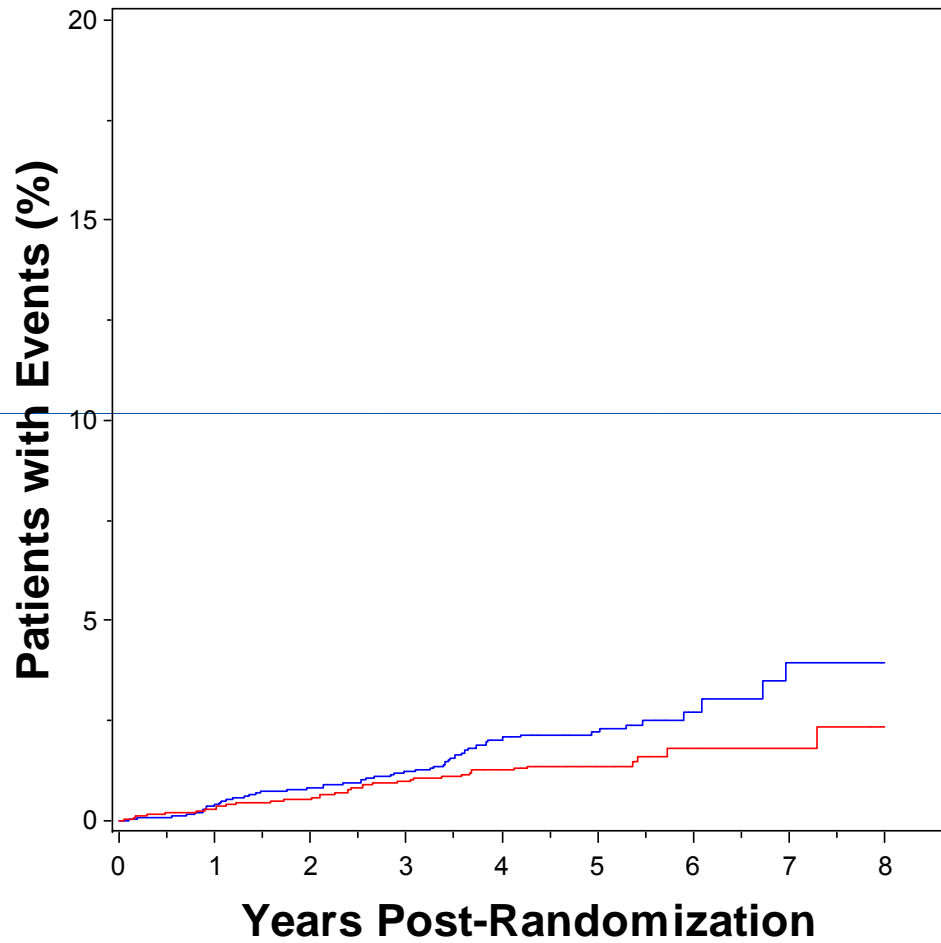


What do you observe?

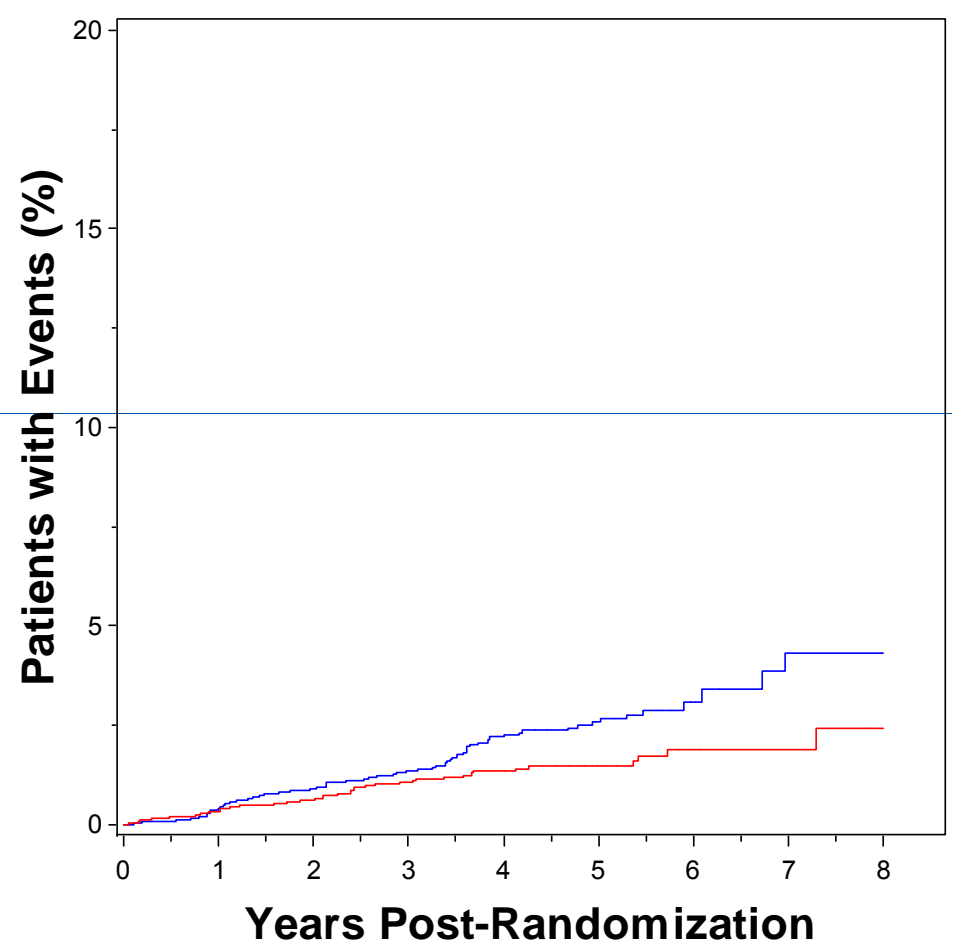
- Within 4 months BP reduced to 119 mm Hg in the intensive arm versus 134 mm Hg in the standard arm
(15 mm difference)



Nonfatal Stroke



Total Stroke



■ Intensive ■ Standard

Primary & Secondary Outcomes

	Intensive Events (%/yr)	Standard Events (%/yr)	HR (95% CI)	P
Primary	208 (1.87)	237 (2.09)	0.88 (0.73-1.06)	0.20
Total Mortality	150 (1.28)	144 (1.19)	1.07 (0.85-1.35)	0.55
Cardiovascular Deaths	60 (0.52)	58 (0.49)	1.06 (0.74-1.52)	0.74
Nonfatal MI	126 (1.13)	146 (1.28)	0.87 (0.68-1.10)	0.25
Nonfatal Stroke	34 (0.30)	55 (0.47)	0.63 (0.41-0.96)	0.03
Total Stroke	36 (0.32)	62 (0.53)	0.59 (0.39-0.89)	0.01

Adverse Events

	Intensive N (%)	Standard N (%)	P
Serious AE	77 (3.3)	30 (1.3)	<0.0001
Hypotension	17 (0.7)	1 (0.04)	<0.0001
Syncope	12 (0.5)	5 (0.2)	0.10
Bradycardia or Arrhythmia	12 (0.5)	3 (0.1)	0.02
Hyperkalemia	9 (0.4)	1 (0.04)	0.01
Renal Failure	5 (0.2)	1 (0.04)	0.12
GFR ever <30 mL/min/1.73m ²	99 (4.2)	52 (2.2)	<0.001
Dizziness on Standing [†]	217 (44)	188 (40)	0.36

Conclusions

- The ACCORD BP trial evaluated the effect of targeting a SBP goal of 120 mm Hg, compared to a goal of 140 mm Hg, in patients with type 2 diabetes at increased cardiovascular risk.
- The results provide no conclusive evidence that the intensive BP control strategy reduces the rate of a composite of major CVD events in such patients.

Summary

- ACEI/ARB were the most commonly used medications
- There was **no difference** in the primary outcome composite of nonfatal MI, nonfatal stroke or CVD death
- Secondary outcome of **nonfatal and fatal stroke** was significantly improved in the intensively treated verses standard groups (numbers of events were small 32 Int verses 62 Std)
- Side effects of syncope and **hypotension** was **greatest** in the intensively treated group (2.6 fold)
- **Hypokalemia** more individuals in the intensively treated group
- **Same number** in both groups progressed to **ESRD** (systolic BP to 140 mm Hgb may be sufficient to progress to ESRD)
- End of study **intensively** treated group had **lower GFR** than standard group

- Small number of stroke events and under powdered

94% power for 20% reduction in event rate, assuming standard group rate of 4% / yr and 5.6 yrs follow-up

Stroke Results

- Assuming that this finding was real, the number needed to treat to the lower SBP level to prevent one stroke over 5 years was 89.

Clinical Parameters assessed at last clinic visit

	<u>Intensive</u>	<u>Standard</u>	<u>P</u>
Potassium (mean mg/dl)	4.3	4.4	0.17
Serum Creatinine (mean mg/dl)	1.1	1.0	<0.0001
Estimated GFR (mean mL/min/1.73m ²)	74.8	80.6	<0.0001
Urinary Alb/Cr (median mg/g)	12.6	14.9	<0.0001
Macroalbuminuria (%)	6.6	8.7	0.009