

Hypertension and Diabetes – *Should we be SPRINTING or Reaching an ACCORD?*

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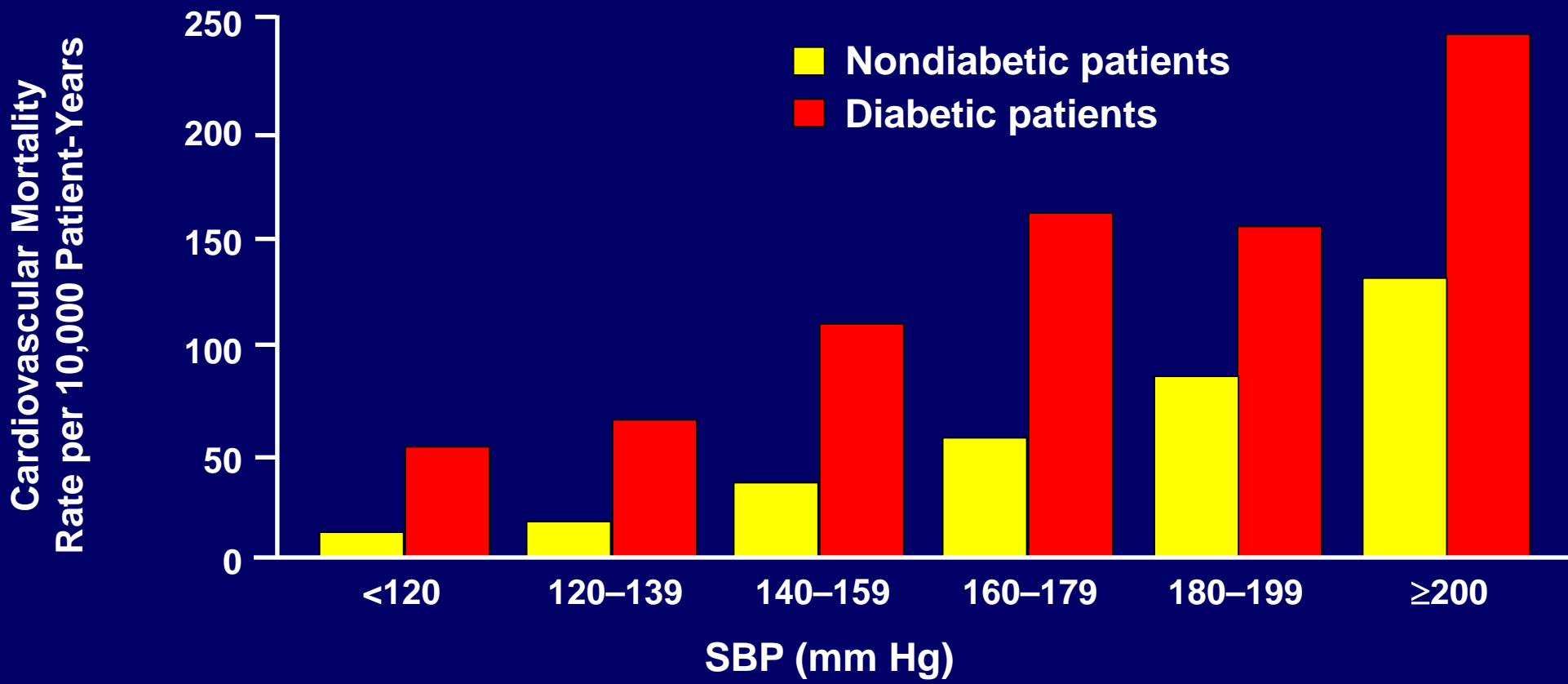
University of Rochester School of Medicine and Dentistry
University of Rochester Diabetes Conference: Diabetes *In and Out*

Rochester, New York
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Knowledge that will change your world

Elevated SBP in Type 2 Diabetes Increases Cardiovascular Risk

Elevated SBP increases risk of CV death almost twofold in diabetic vs nondiabetic patients



MRFIT

Special Communication

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults

Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; William C. Cushman, MD; Cheryl Dennison-Himmelfarb, RN, ANP, PhD; Joel Handler, MD; Daniel T. Lackland, DrPH; Michael L. LeFevre, MD, MSPH; Thomas D. MacKenzie, MD, MSPH; Olugbenga Ogedegbe, MD, MPH, MS; Sidney C. Smith Jr, MD; Laura P. Svetkey, MD, MHS; Sandra J. Taler, MD; Raymond R. Townsend, MD; Jackson T. Wright Jr, MD, PhD; Andrew S. Narva, MD; Eduardo Ortiz, MD, MPH

JAMA. 2014;311(5):507-520. doi:10.1001/jama.2013.284427. Published online December 18, 2013.

<http://jama.jamanetwork.com/article.aspx?articleid=1791497>

The Most Important Clinical Questions in Hypertension

- Does evidence from RCTs of antihypertensive treatment support (or refute) 140/90 mm Hg as a treatment threshold or goal?
- Should the threshold or goal be lower or higher in persons with diabetes or CKD, the elderly or those with other co-morbidities or special characteristics?
- Is there RCT evidence that BP lowering treatment with a particular drug or drug class improves outcomes compared to any other drug/drug class?

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RCTs Testing BP Goals In Hypertensive Diabetic Patients

Trial	n	Duration (years)	SBP goal, mmHg	DBP goal, mmHg	Mean BP, less intense, mmHg	Mean BP, more intense, mmHg	Outcome Risk Reduction	
SHEP	583	5	<148	none	155/72°	146/68°	Stroke	22% (ns)
							CVD	34%
							CHD	56%
Syst-Eur	492	2	<150	none	162/82	153/78	Stroke	69%
							CVD	62%
HOT	1,501	3	none	<80	148/85	144/81	CVD	51%
							MI	50%
							Stroke	30% (ns)
							CV death	67%
UKPDS	1,148	8.4	<150	<85	154/87	144/82	DM-related deaths	34%
							Stroke	32%
							Microvasc	44%
							Renal (1°)	37%
ABCD	470	5.3	none	<75	138/86	132/78	Microvasc	nc
							Death	nc
							CVD	49%
ACCORD	4,733	4.7	<120	none	134	119	CVD (1°)	12% (ns)
							Stroke	41%

Recommendation 5

- In the population ≥ 18 years of age with diabetes, initiate pharmacologic treatment to lower BP at SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg and treat to a goal SBP < 140 mm Hg and goal DBP < 90 mm Hg.

(Expert Opinion – Grade E)

The Most Important Clinical Questions in Hypertension

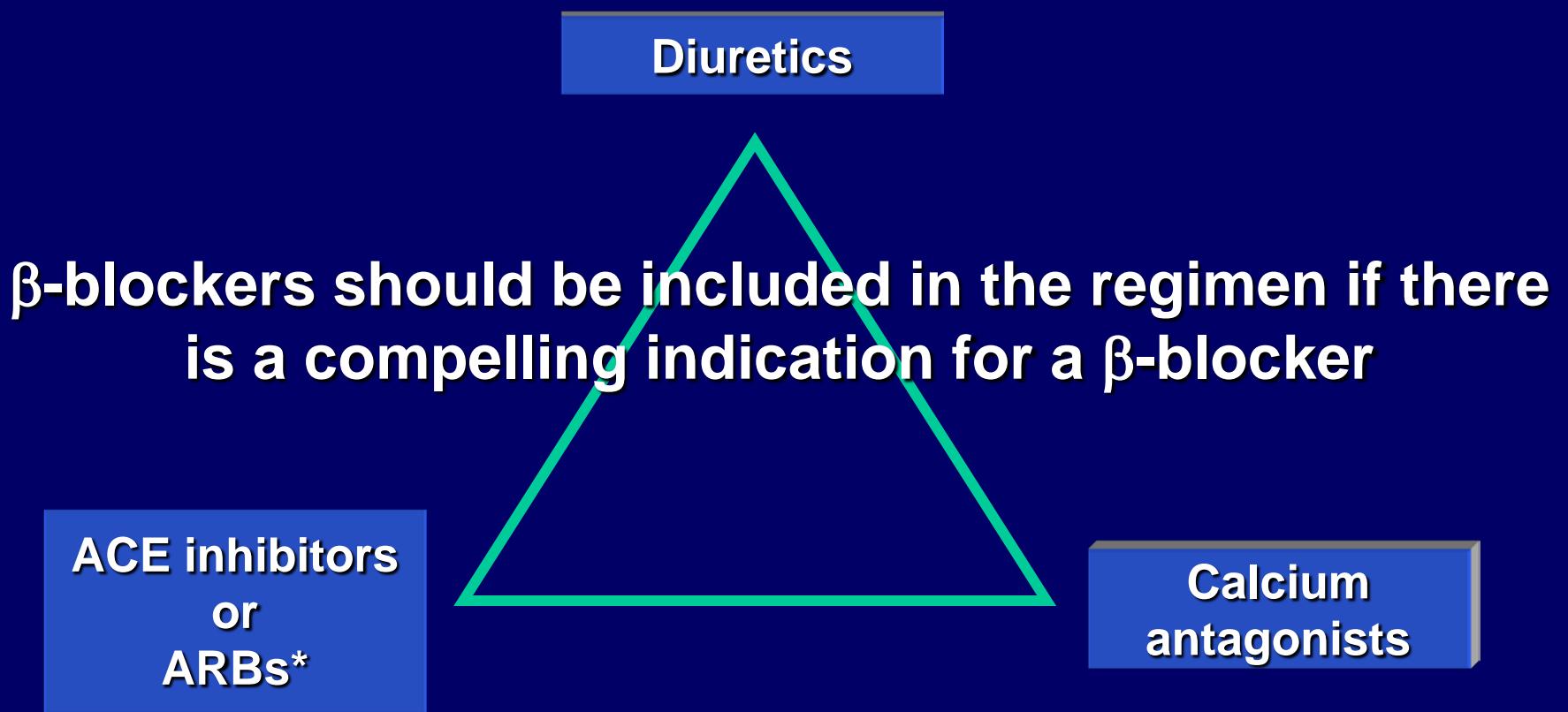
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- **Is there RCT evidence that BP lowering treatment with a particular drug or drug class improves outcomes compared to any other drug/drug class?**

Recommendation 6

- In the general non-Black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, CCB, ACEI or ARB.

Moderate Recommendation – Grade B

Initial Combinations of Medications



* Combining ACEI with ARB discouraged

Original Investigation

Blood Pressure Lowering in Type 2 Diabetes A Systematic Review and Meta-analysis

Connor A. Emdin, HBSc; Kazem Rahimi, DM, MSc; Bruce Neal, PhD; Thomas Callender, MBChB; Vlado Perkovic, PhD; Anushka Patel, PhD

IMPORTANCE Lowering blood pressure (BP) is widely used to reduce vascular risk in individuals with diabetes.

OBJECTIVE To determine the associations between BP-lowering treatment and vascular disease in type 2 diabetes.

DATA SOURCES AND STUDY SELECTION We searched MEDLINE for large-scale randomized controlled trials of BP-lowering treatment including patients with diabetes, published between January 1966 and October 2014.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted study characteristics and vascular outcome data. Estimates were stratified by baseline BP and achieved BP, and pooled using fixed-effects meta-analysis.

MAIN OUTCOMES AND MEASURES All-cause mortality, cardiovascular events, coronary heart disease events, stroke, heart failure, retinopathy, new or worsening albuminuria, and renal failure.

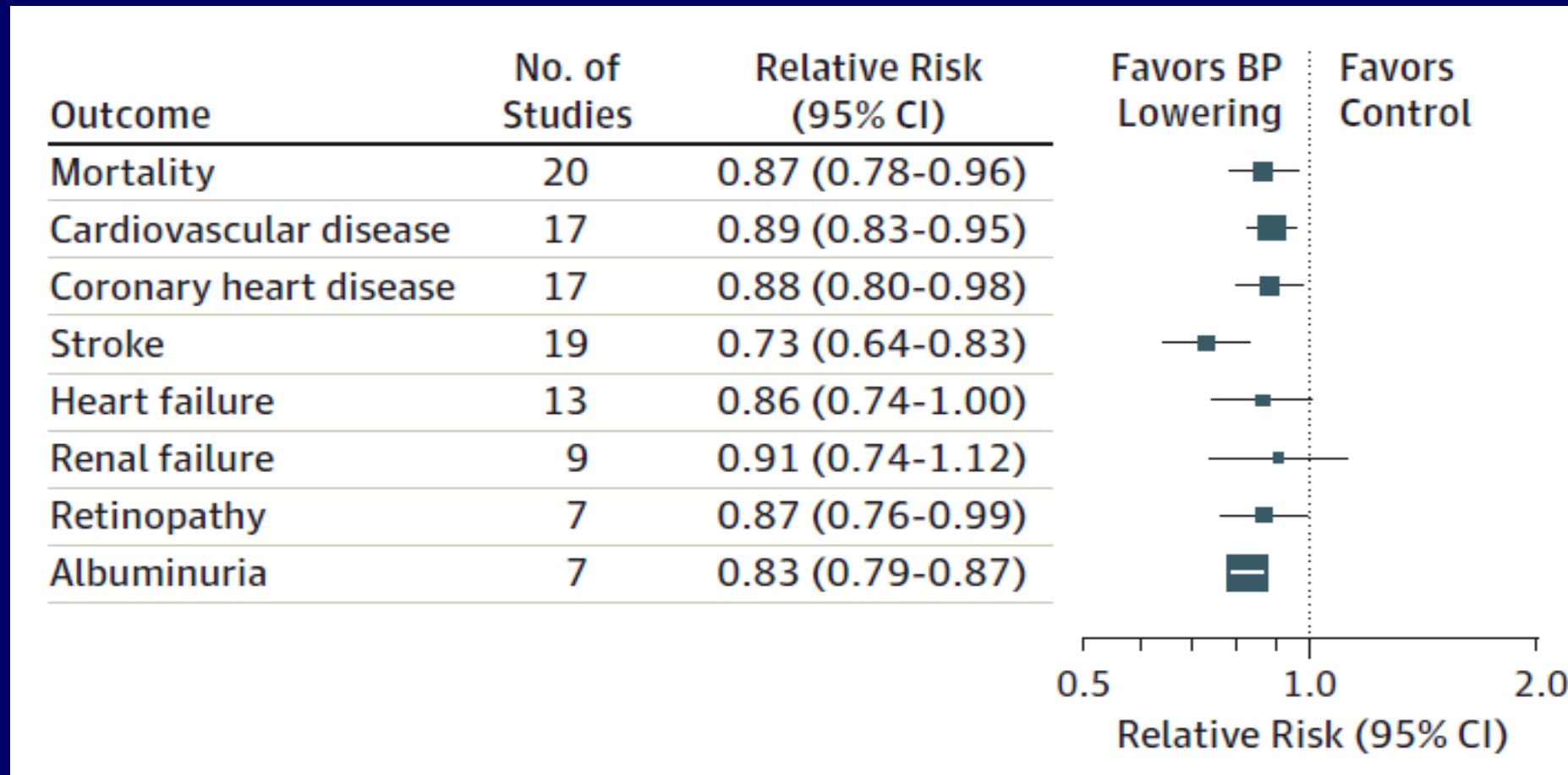
RESULTS Forty trials judged to be of low risk of bias (100 354 participants) were included. Each 10-mm Hg lower systolic BP was associated with a significantly lower risk of mortality (relative risk [RR], 0.87; 95% CI, 0.78-0.96); absolute risk reduction (ARR) in events per 1000 patient-years (3.16; 95% CI, 0.90-5.22), cardiovascular events (RR, 0.89 [95% CI, 0.83-0.95]; ARR, 3.90 [95% CI, 1.57-6.06]), coronary heart disease (RR, 0.88 [95% CI, 0.80-0.98]; ARR, 1.81 [95% CI, 0.35-3.11]), stroke (RR, 0.73 [95% CI, 0.64-0.83]; ARR, 4.06 [95% CI, 2.53-5.40]), albuminuria (RR, 0.83 [95% CI, 0.79-0.87]; ARR, 9.33 [95% CI, 7.13-11.37]), and retinopathy (RR, 0.87 [95% CI, 0.76-0.99]; ARR, 2.23 [95% CI, 0.15-4.04]). When trials were stratified by mean baseline systolic BP at greater than or less than 140 mm Hg, RRs for outcomes other than stroke, retinopathy, and renal failure were lower in studies with greater baseline systolic BP (P interaction <0.1). The associations between BP-lowering treatments and outcomes were not significantly different, irrespective of drug class, except for stroke and heart failure. Estimates were similar when all trials, regardless of risk of bias, were included.

CONCLUSIONS AND RELEVANCE Among patients with type 2 diabetes, BP lowering was associated with improved mortality and other clinical outcomes with lower RRs observed among those with baseline BP of 140 mm Hg and greater. These findings support the use of medications for BP lowering in these patients.

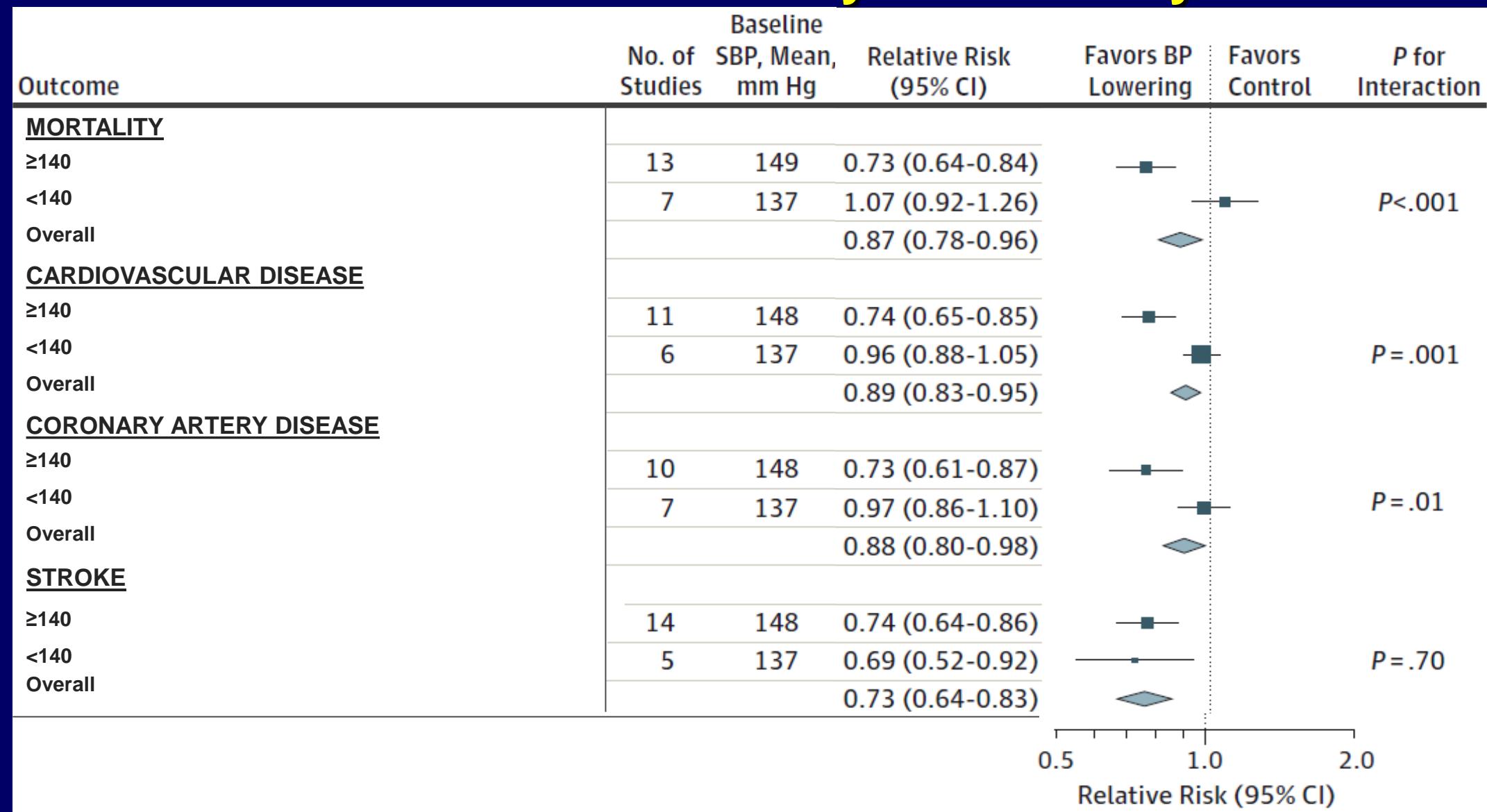
Comprehensive Overview of Effects of BP-lowering in Patients with Diabetes Regardless of the Presence or Absence of Defined Hypertension

- Who should be offered therapy ?
- What BP target(s) should be achieved ?
- 40 trials of high quality (low risk of bias)
- 100,354 participants
- All-cause mortality + 4 macrovascular and 3 microvascular outcomes

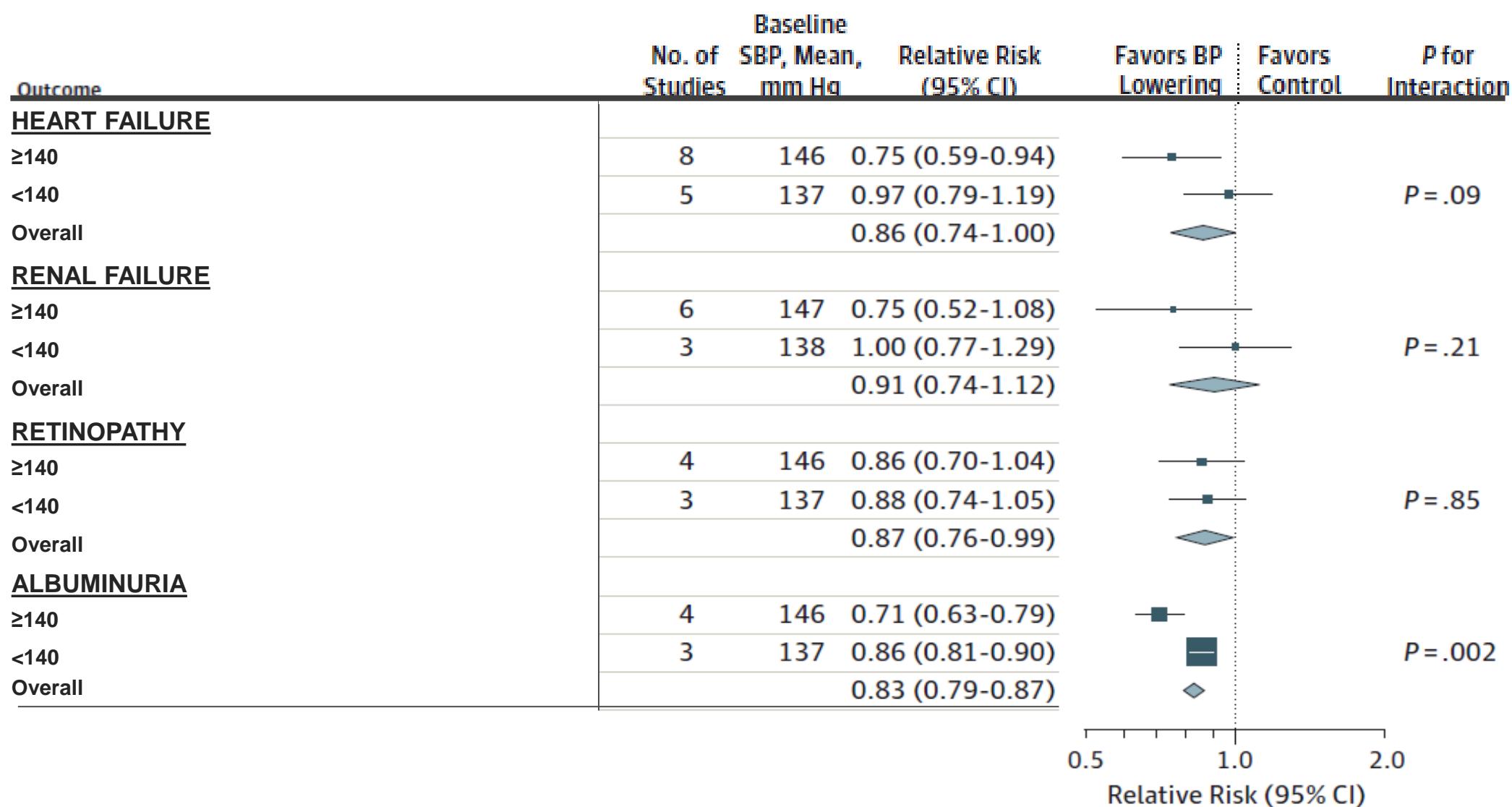
Associations Between 10 mmHg Lower SBP and Mortality, Macrovascular and Microvascular Outcomes in Diabetic Patients



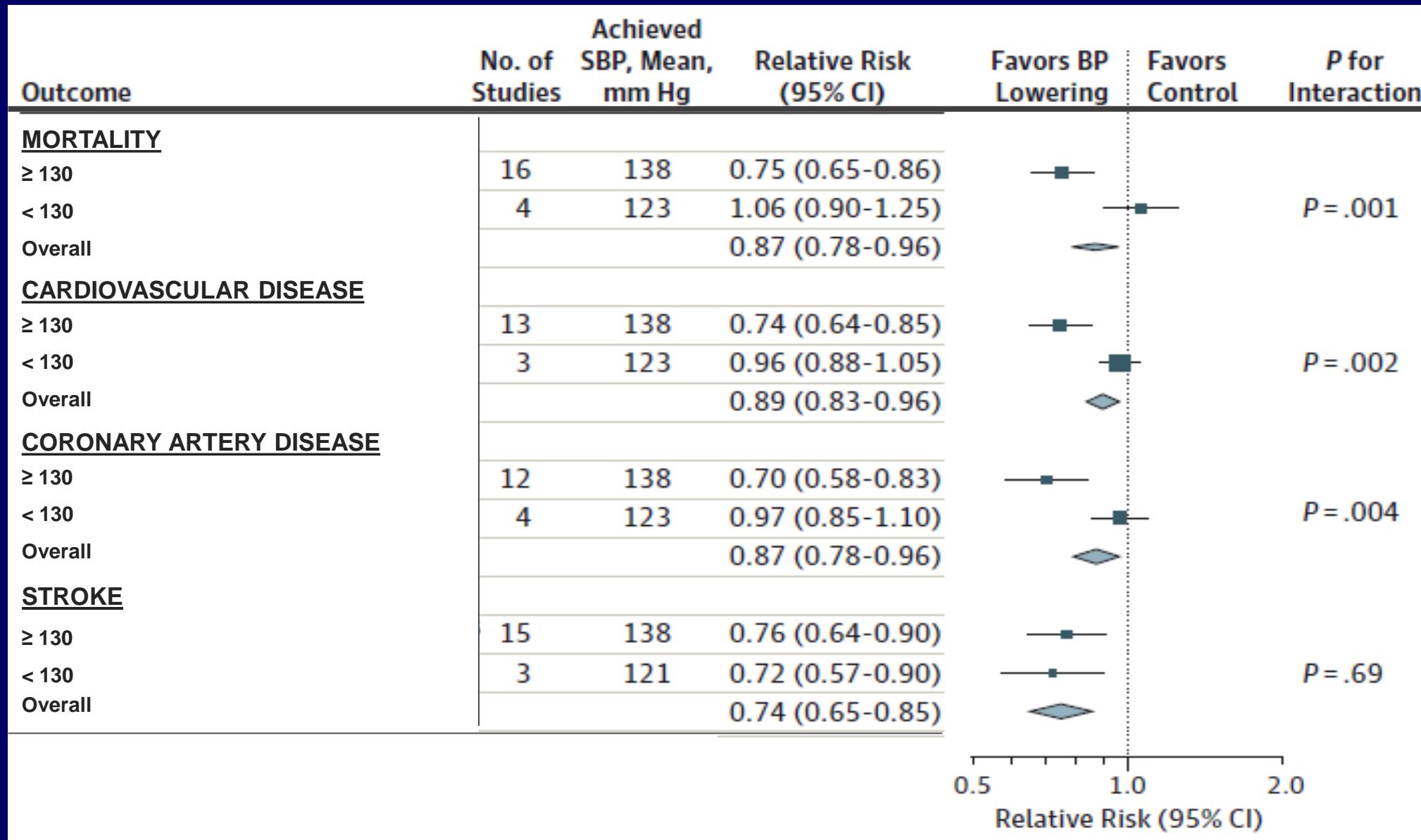
Associations Between 10 mmHg Lower SBP and CVD Outcomes Stratified by SBP at Entry



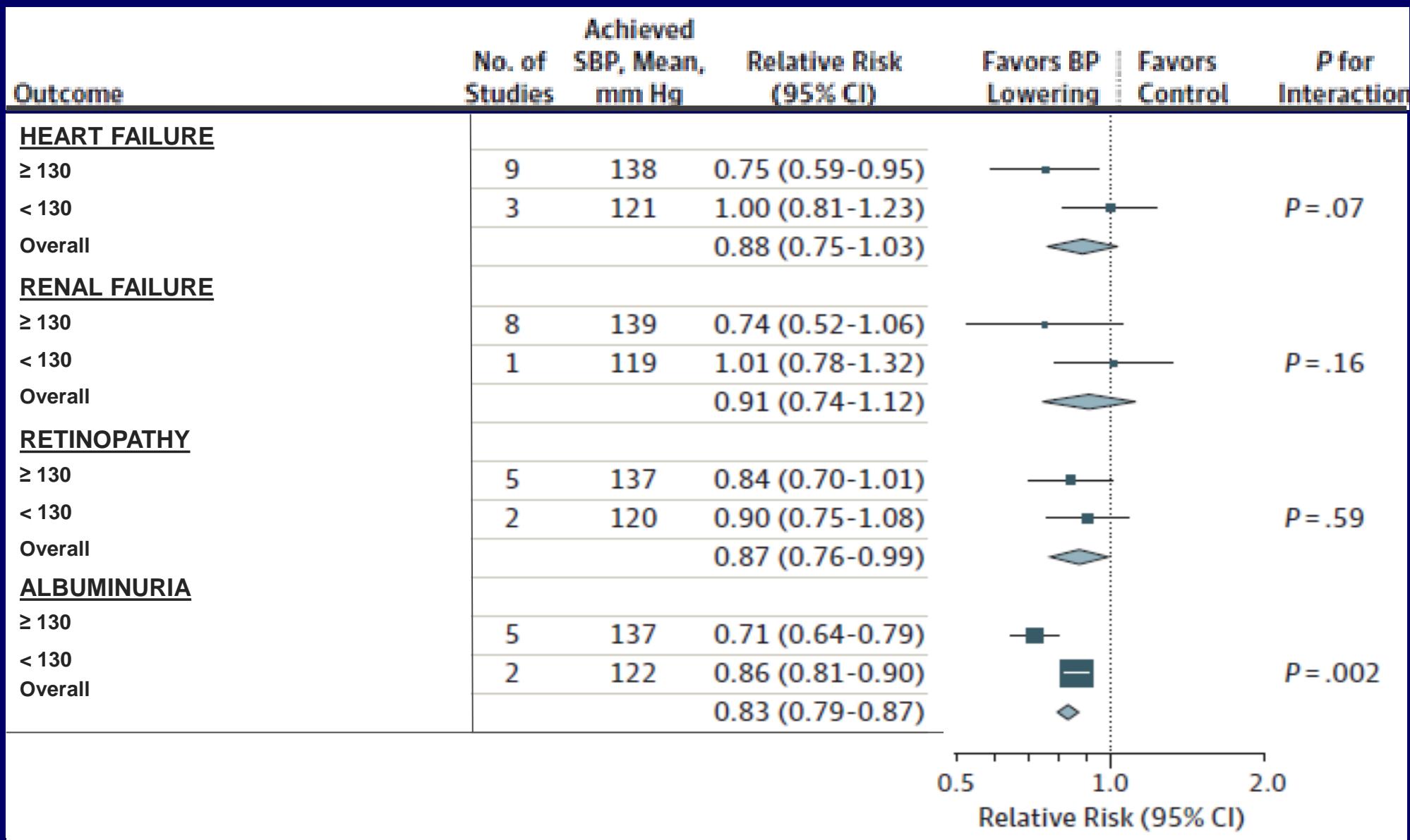
Associations Between 10 mmHg Lower SBP and CVD Outcomes Stratified by SBP at Entry



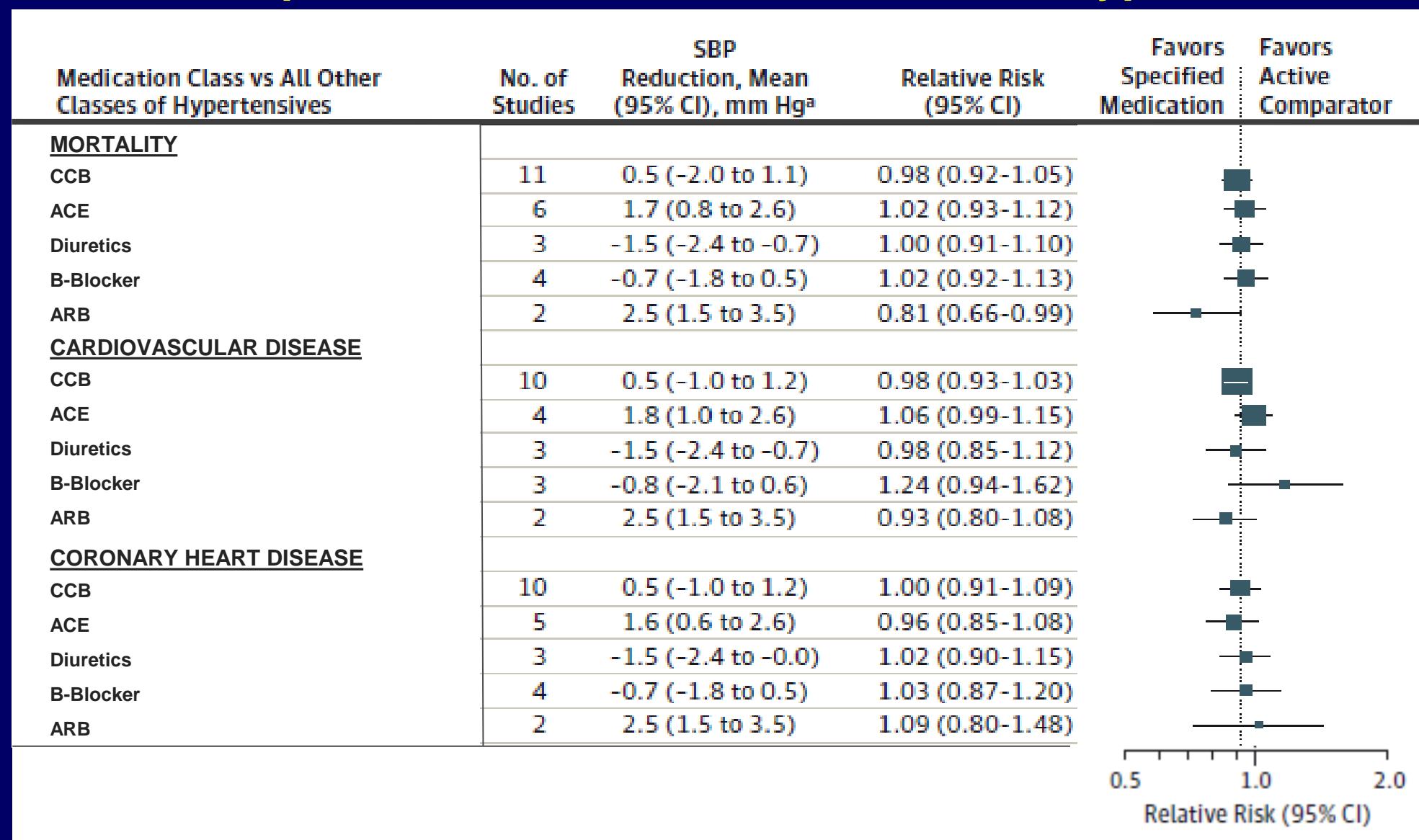
Associations Between 10 mm Hg Lower SBP and Outcomes Stratified by Achieved SBP



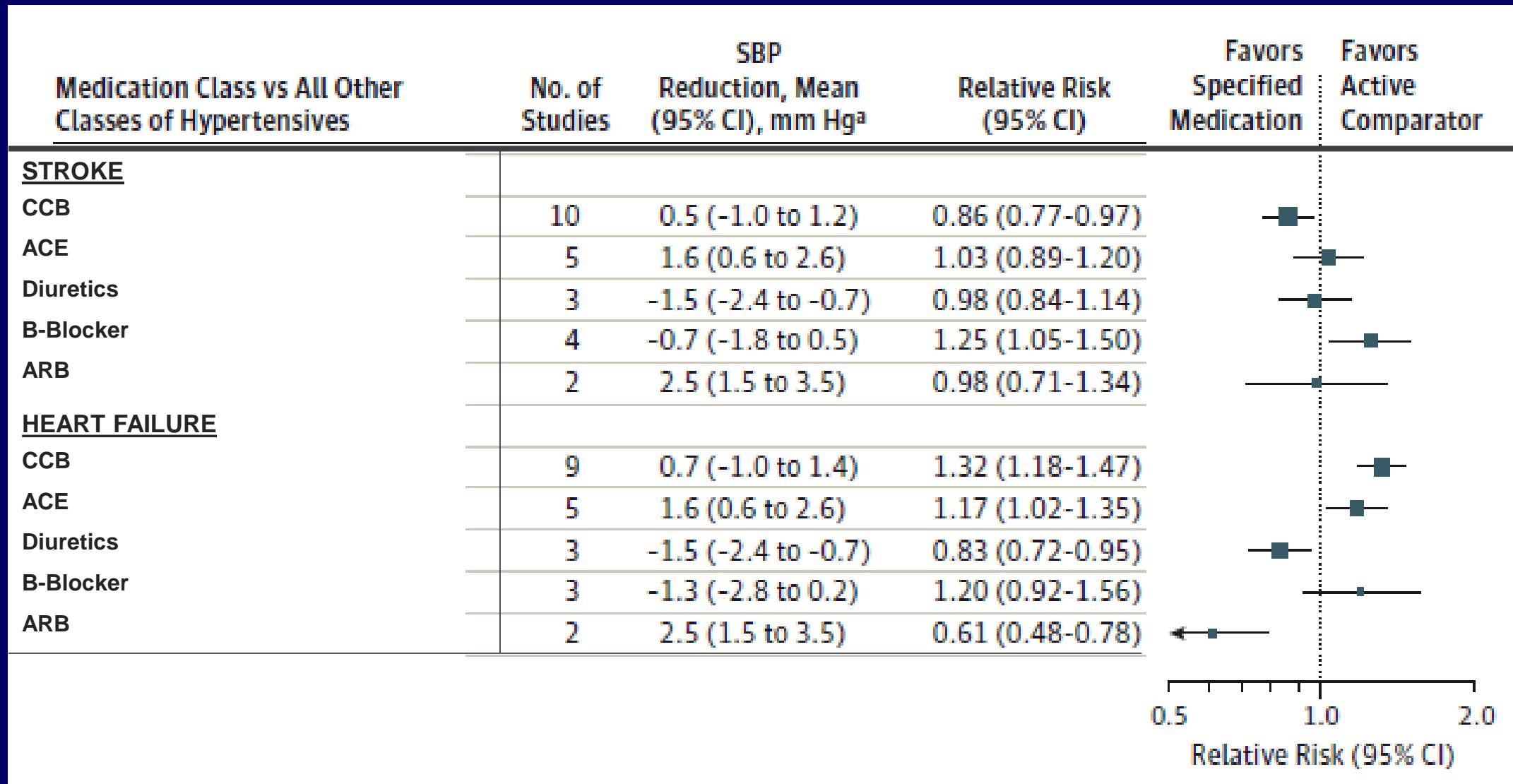
Associations Between 10 mm Hg Lower SBP and Outcomes Stratified by Achieved SBP



Associations of Each Class of Antihypertensive on Outcomes Compared With All Other Classes of Antihypertensives



Associations of Each Class of Antihypertensive on Outcomes Compared With All Other Classes of Antihypertensives



SUMMARY

- SBP reduction (10 mmHg) lowered risk of all-cause mortality, CVD and CHD events and stroke, as well as retinopathy and albuminuria, but not HF or renal failure in the diabetic population as a whole.
- SBP reduction lowered risk of mortality, CVD, CHD and HF only in those with baseline SBP ≥ 140 mm Hg.
- SBP reduction lowered risk of stroke and albuminuria in all participants, independent of baseline SBP.
- Reductions in mortality, CHD, CVD, HF and albuminuria were greater at achieved SBPs ≥ 130 mmHg than < 130 mmHg.

SUMMARY

- **Reductions in stroke and albuminuria were similar in both achieved BP strata.**
- **All classes of BP-lowering medications had similar effects except**
 - Diuretics and possibly ARBs were more effective in preventing HF.
 - CCBs were less effective in preventing HF and more effective in preventing stroke.
 - BBs were less effective in preventing stroke.
 - ARBs were more effective in preventing death (limited data).

RECOMMENDATIONS

- Among patients with type 2 diabetes, BP lowering was associated with reduction in mortality and other clinical outcomes in those with baseline BP ≥ 140 mmHg. These findings support the use of medications for BP lowering in these patients.
- For individuals at high risk of stroke, retinopathy, and progressive albuminuria (e.g., those with a history of cerebrovascular disease or mild nonproliferative diabetic retinopathy), beginning BP-lowering therapy at an initial SBP level below 140 mm Hg and treatment to a SBP level below 130 mm Hg should be considered.

RECOMMENDATIONS

- Individualized assessment of likely absolute benefits and risks is vital to shared decision-making between patients and clinicians.

Recent Recommendations for Antihypertensive Medications in Diabetes

Group	Preferred Medications*
ESH/ESC (2013)	All
ESC/EASD (2013)	All
AHA/ACC/CDC Science Advisory (US) – (2013)	ACEI or ARB, thiazide, BB, CCB
ADA (2013-14)	ACEI or ARB
ASH-ISH (2013)	ARB or ACEI
US JNC 8 Panel (2014)	thiazide-type diuretic, CCB, ACEI or ARB; Blacks: thiazide or CCB
US VA/DoD (2014)	Thiazide-type diuretic

* All guidelines recommend ACEI or ARB if proteinuria, some if any CKD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*

Cushman WC, Evans GW, Byington RP, et al, the Accord Study Group.
N Engl J Med 362(17):1575-1585, 2010.

ACCORD BP Study: Primary and Secondary Outcomes

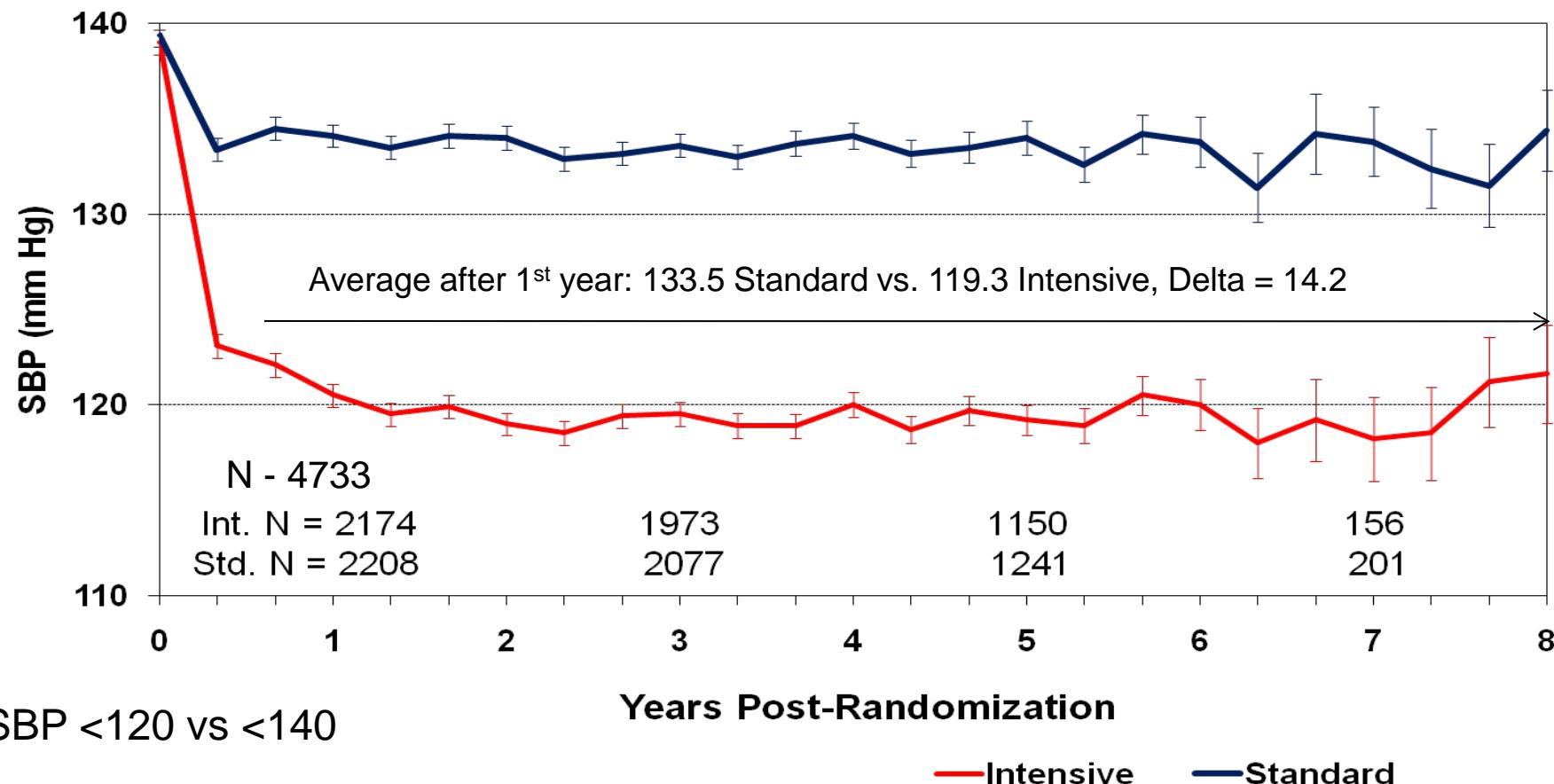
- Patients with T2D and hypertension (N = 4733)
- Random assignment
 - Intensive therapy: target SBP < 120 mm Hg
 - Standard therapy: target SBP < 140 mm Hg
- 1° outcome: nonfatal MI, nonfatal stroke, death from CV causes
- Mean follow-up = 4.7 y

Outcome	Intensive	Standard	HR	P-value
SBP after 1 year (mmHg)	119.3	133.5	NR	NR
1° outcome (annual rate)	1.87	2.09	0.88	.20
Death from any cause (annual rate)	1.28	1.19	1.07	.55
Stroke (annual rate)	0.32	0.53	0.59	.01
AEs (rate)	3.3	1.3	NR	<.001

ACCORD BP Trial: Systolic BP (mean \pm 95% CI)

Mean # Meds

Intensive:	3.2	3.4	3.5	3.4
Standard:	1.9	2.1	2.2	2.3



RZ: SBP <120 vs <140

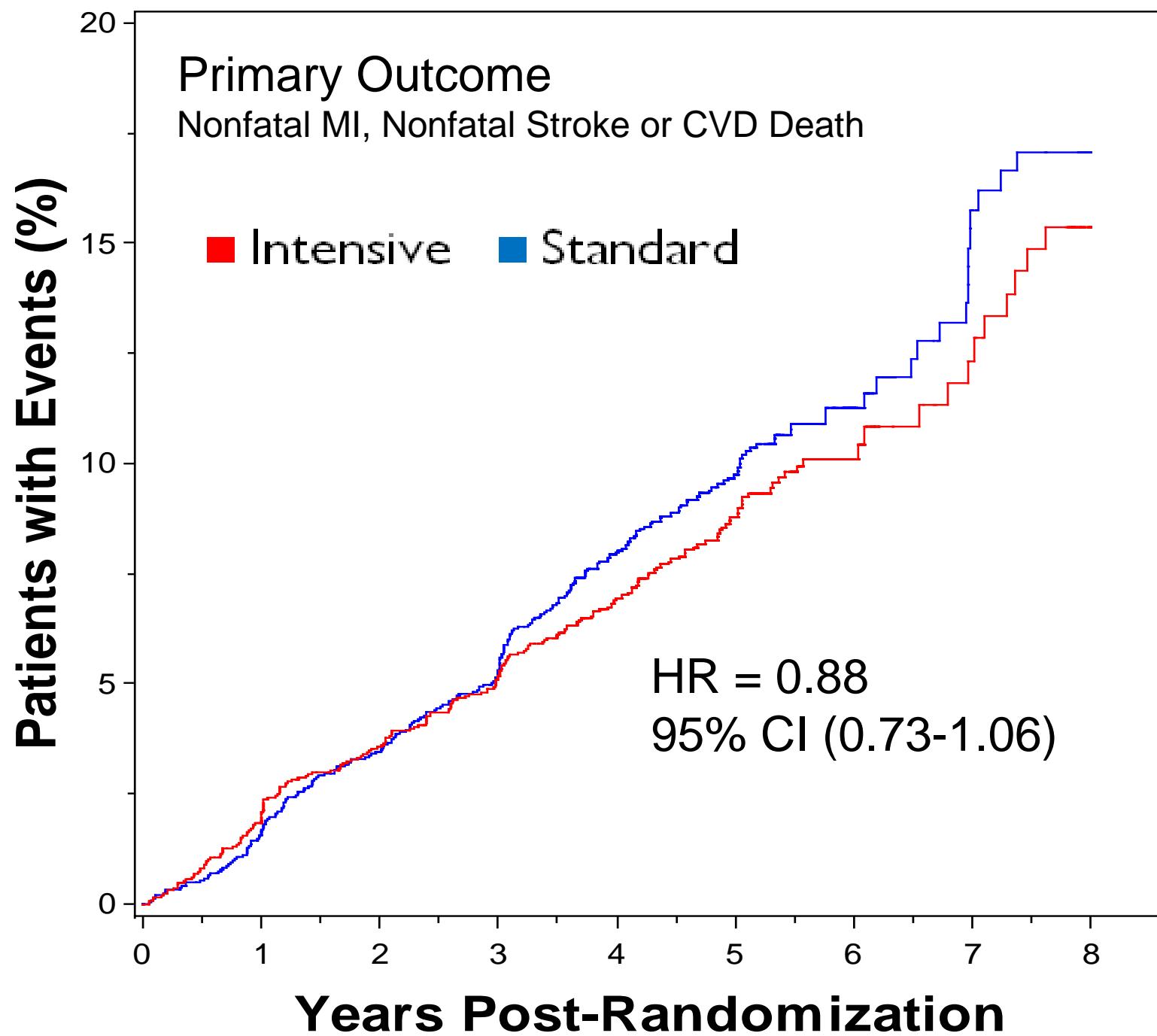
DBP for the same time interval averaged 70 & 64 mm Hg
(Delta = 6 mm Hg)

Cushman, et al. N Engl J Med. 2010;362:1575-85

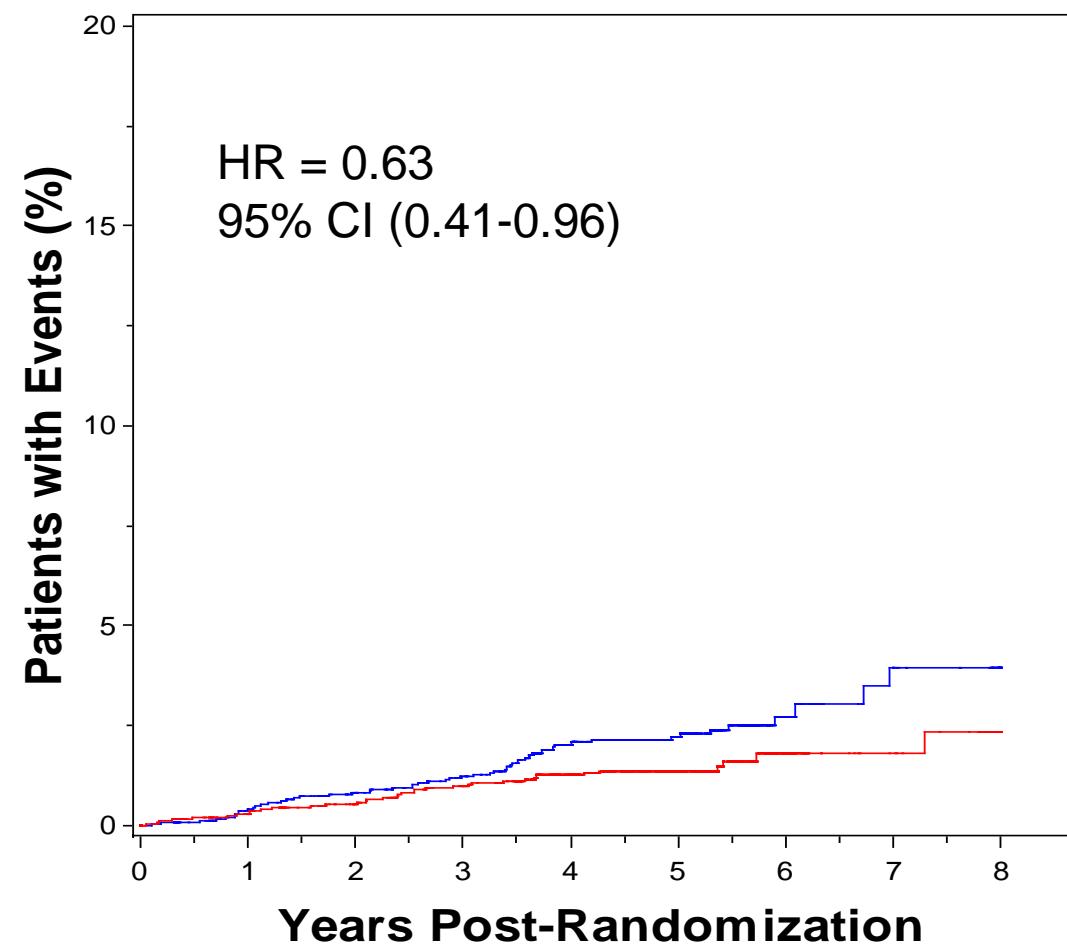
Primary & Secondary Outcomes

	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

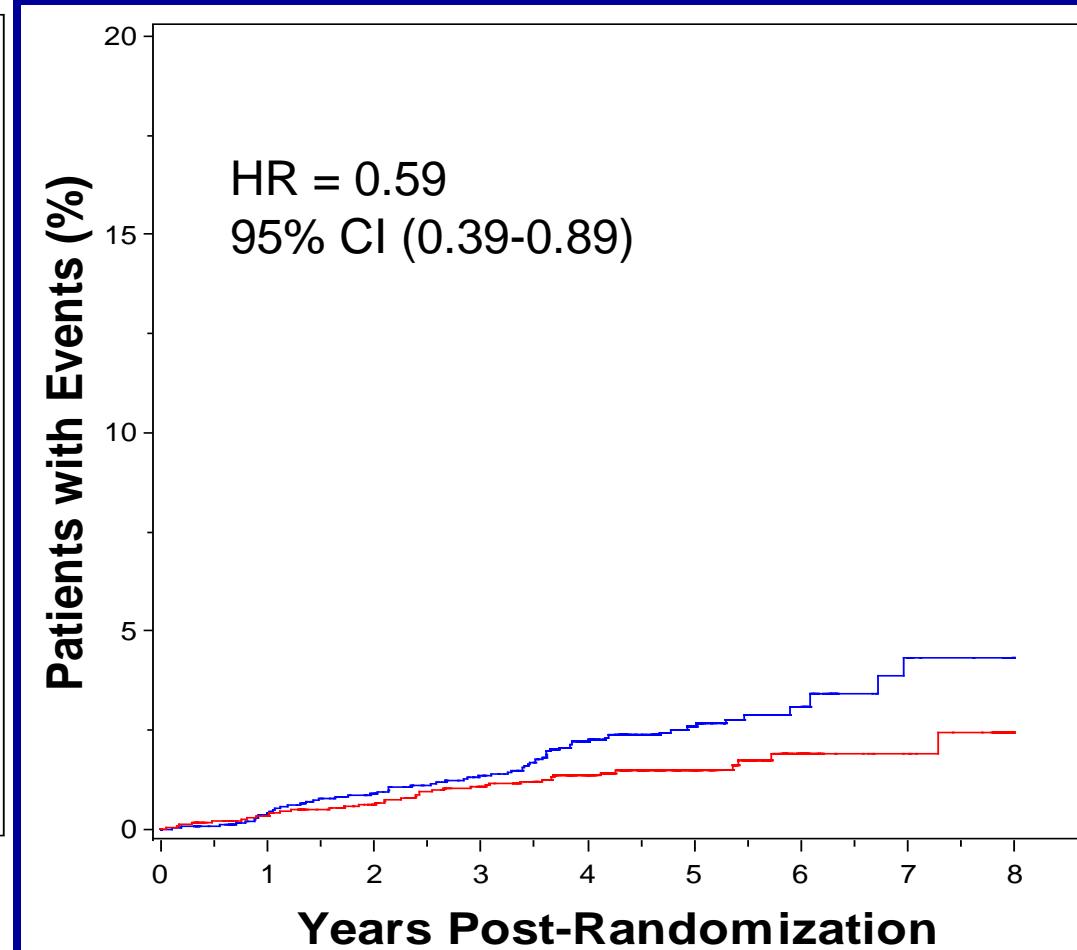
Also examined Fatal/Nonfatal HF (HR=0.94, p=0.67), a composite of fatal coronary events, nonfatal MI and unstable angina (HR=0.94, p=0.50) and a composite of the primary outcome, revascularization and unstable angina (HR=0.95, p=0.40)



Nonfatal Stroke



Total Stroke



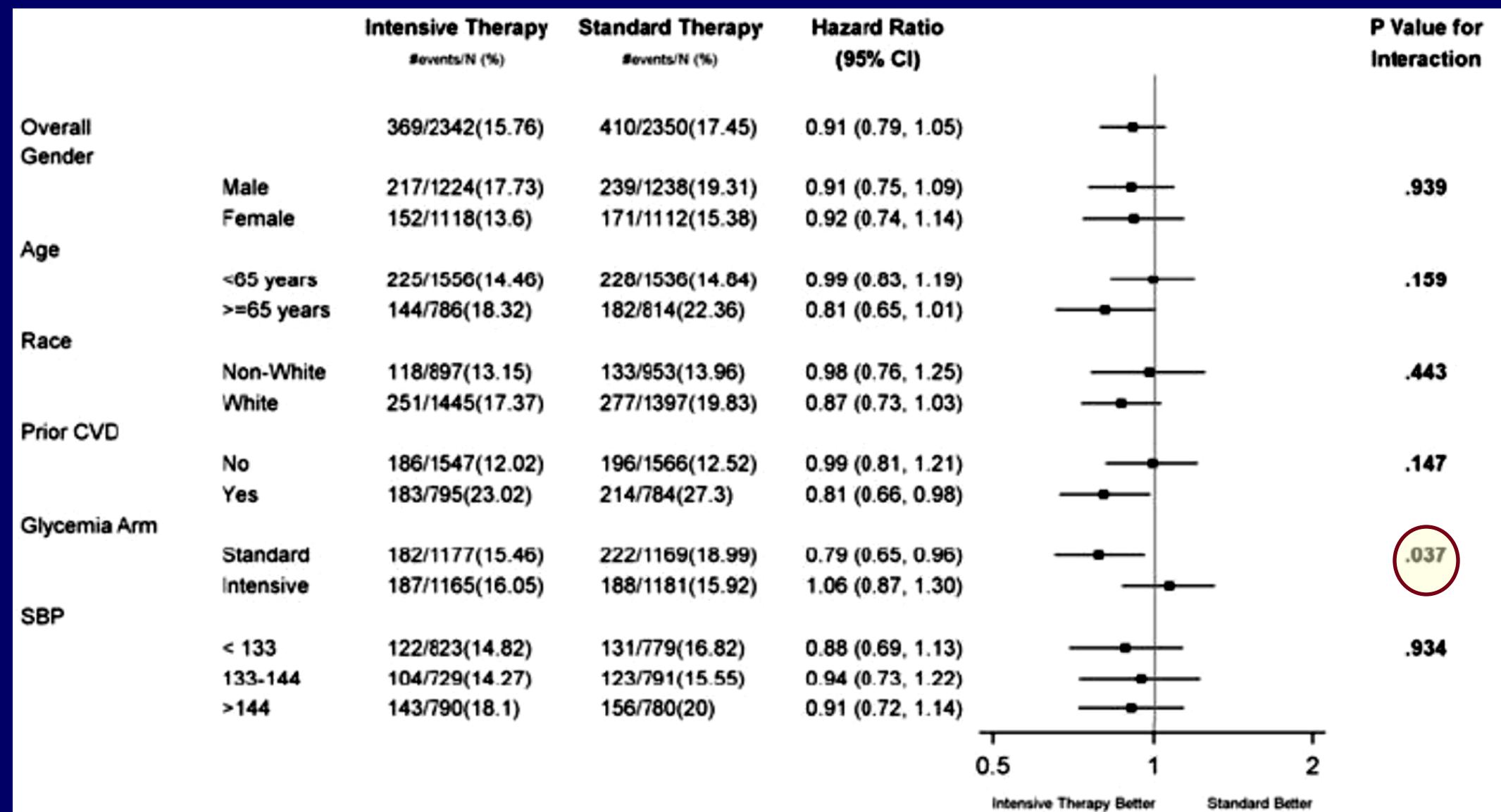
■ Intensive ■ Standard

Adverse Events

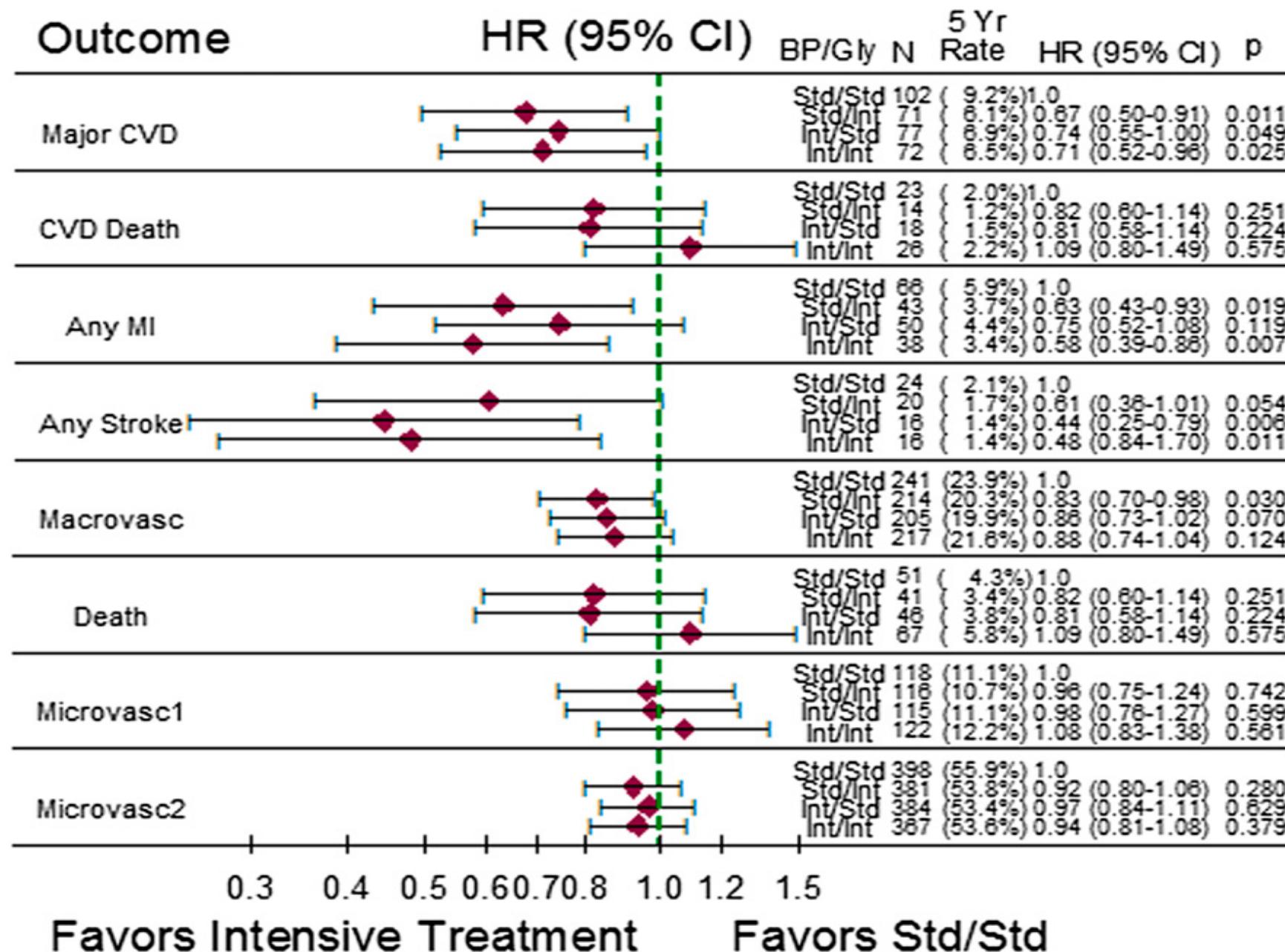
	Intensive N (%)	Standard N (%)	P
Serious AE	77 (3.3)	30 (1.3)	<0.0001
Hypotension	17 (0.7)	1 (0.04)	<0.0001
Syncope	12 (0.5)	5 (0.2)	0.10
Bradycardia or Arrhythmia	12 (0.5)	3 (0.1)	0.02
Hyperkalemia	9 (0.4)	1 (0.04)	0.01
Renal Failure	5 (0.2)	1 (0.04)	0.12
eGFR ever <30 mL/min/1.73m ²	99 (4.2)	52 (2.2)	<0.001
Any Dialysis or ESRD	59 (2.5)	58 (2.4)	0.93
Dizziness on Standing [†]	217 (44)	188 (40)	0.36

† Symptom experienced over past 30 days from HRQL sample of
N=969 participants assessed at 12, 36, and 48 months post-randomization

Primary Outcome by Pre-defined Sub-groups



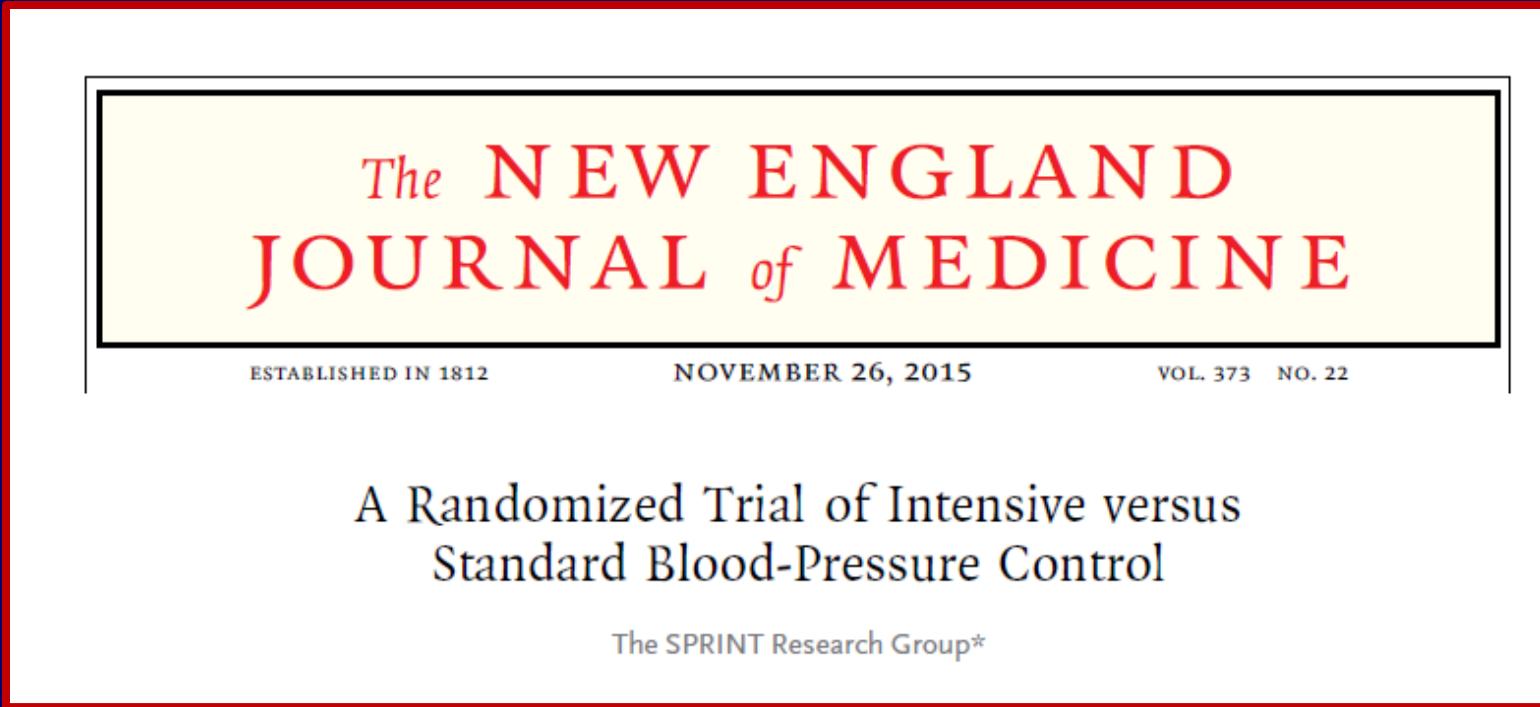
BP Trial



ACCORD BP Trial Conclusions

- ▶ The results provide no conclusive evidence that the intensive BP control strategy reduces combined CVD events in high risk patients with diabetes mellitus.
- ▶ However, the trial was unexpectedly underpowered (CI 0.73-1.06, rate 2%/yr).
- ▶ Therefore, ACCORD also does not conclusively prove that <120 mm Hg goal is not beneficial (equipoise).

Systolic Blood Pressure Intervention Trial (SPRINT)



SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC Jr, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. A Randomized Trial of Intensive versus Standard Blood-Pressure Control, 373(22):2103-2116, 2015.

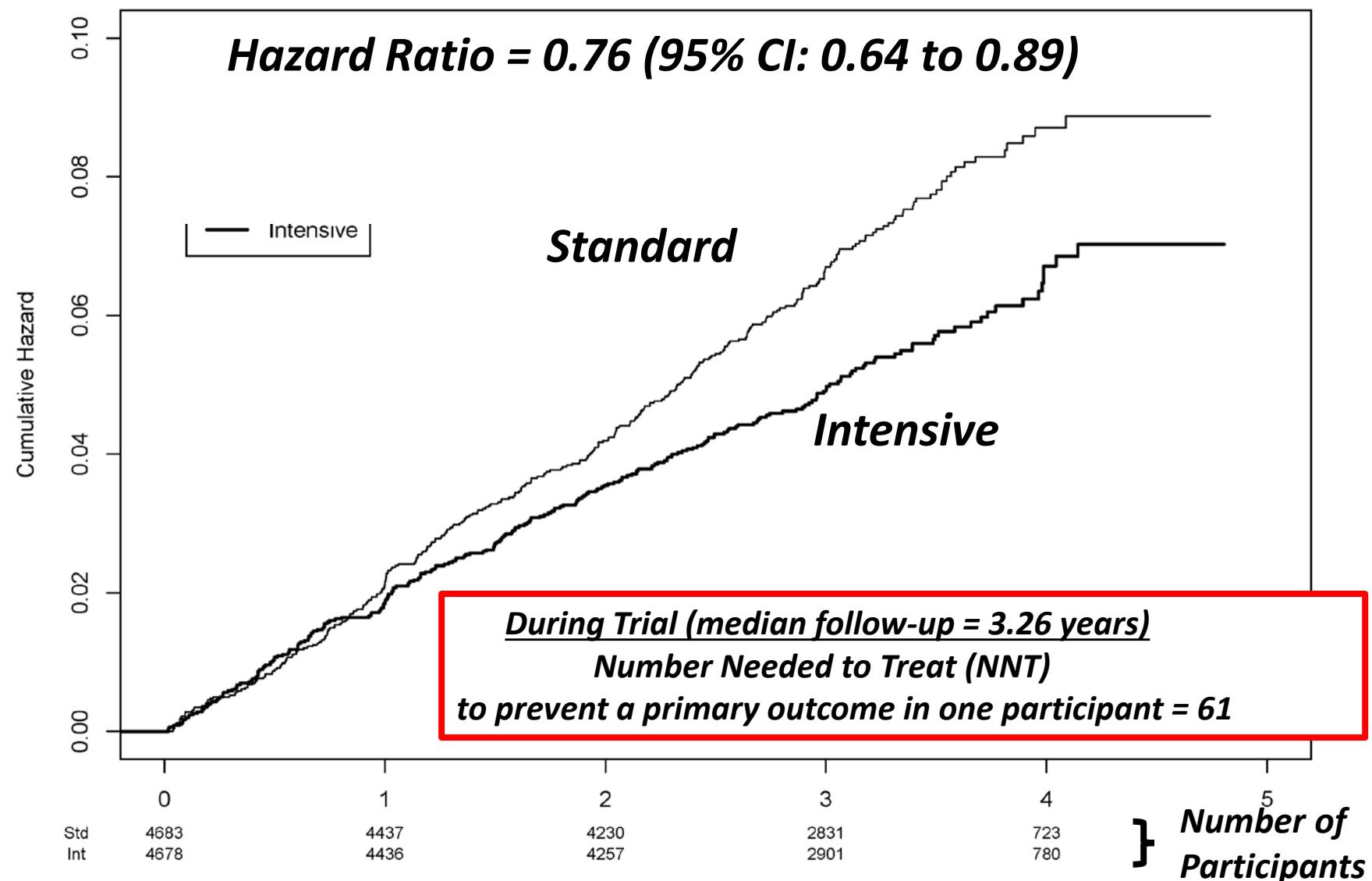
Major Exclusion Criteria

- Stroke
- Diabetes mellitus
- Polycystic kidney disease
- Congestive heart failure (symptoms or EF < 35%)
- Proteinuria >1g/d
- CKD with eGFR < 20 mL/min/1.73m² (MDRD)
- Adherence concerns

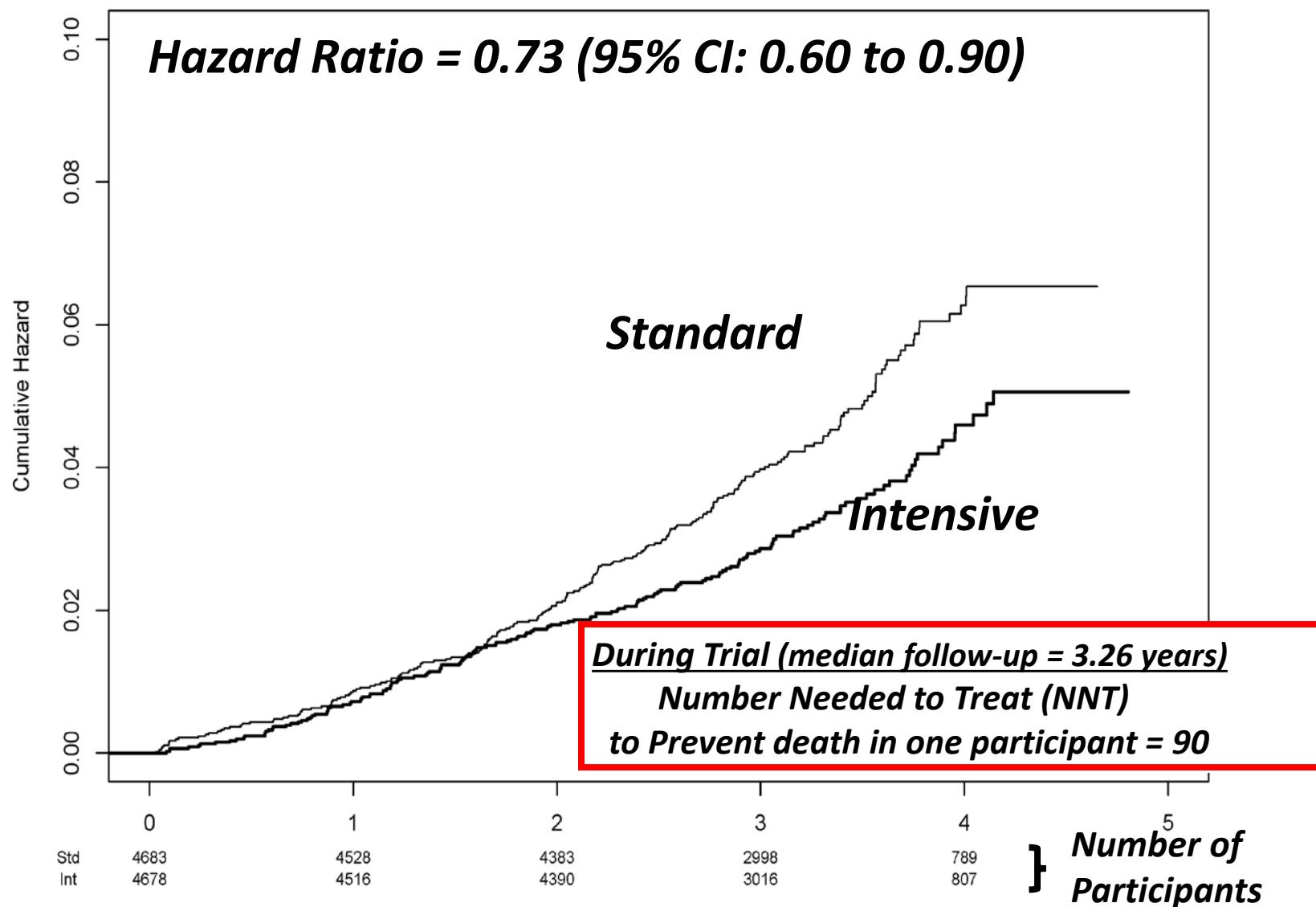
Decision to Stop BP Intervention

- On August 20th, 2015, NHLBI Director accepted DSMB recommendation to inform SPRINT investigators and participants of CVD results
- Concurrently, decision made to stop BP intervention
- This presentation based on adjudicated events that occurred through August 20th, 2015
 - Median follow-up = 3.26 years
- Data for some secondary non-CVD outcomes (e.g. dementia and cognitive impairment) being collected at close-out visit, and this process will be completed in Summer 2016

Cumulative Hazard for SPRINT Primary Outcome



Cumulative Hazard for All-cause Mortality



SPRINT Primary Outcome and Component Event Rates and Hazard Ratios

	Intensive		Standard			
	No. of Events	Rate, %/year	No. of Events	Rate, %/year	HR (95% CI)	P value
Primary Outcome	243	1.65	319	2.19	0.75 (0.64, 0.89)	<0.001
All MI	97	0.65	116	0.78	0.83 (0.64, 1.09)	0.19
Non-MI ACS	40	0.27	40	0.27	1.00 (0.64, 1.55)	0.99
All Stroke	62	0.41	70	0.47	0.89 (0.63, 1.25)	0.50
All HF	62	0.41	100	0.67	0.62 (0.45, 0.84)	0.002
CVD Death	37	0.25	65	0.43	0.57 (0.38, 0.85)	0.005

Serious Adverse Events* (SAE) During Follow-up

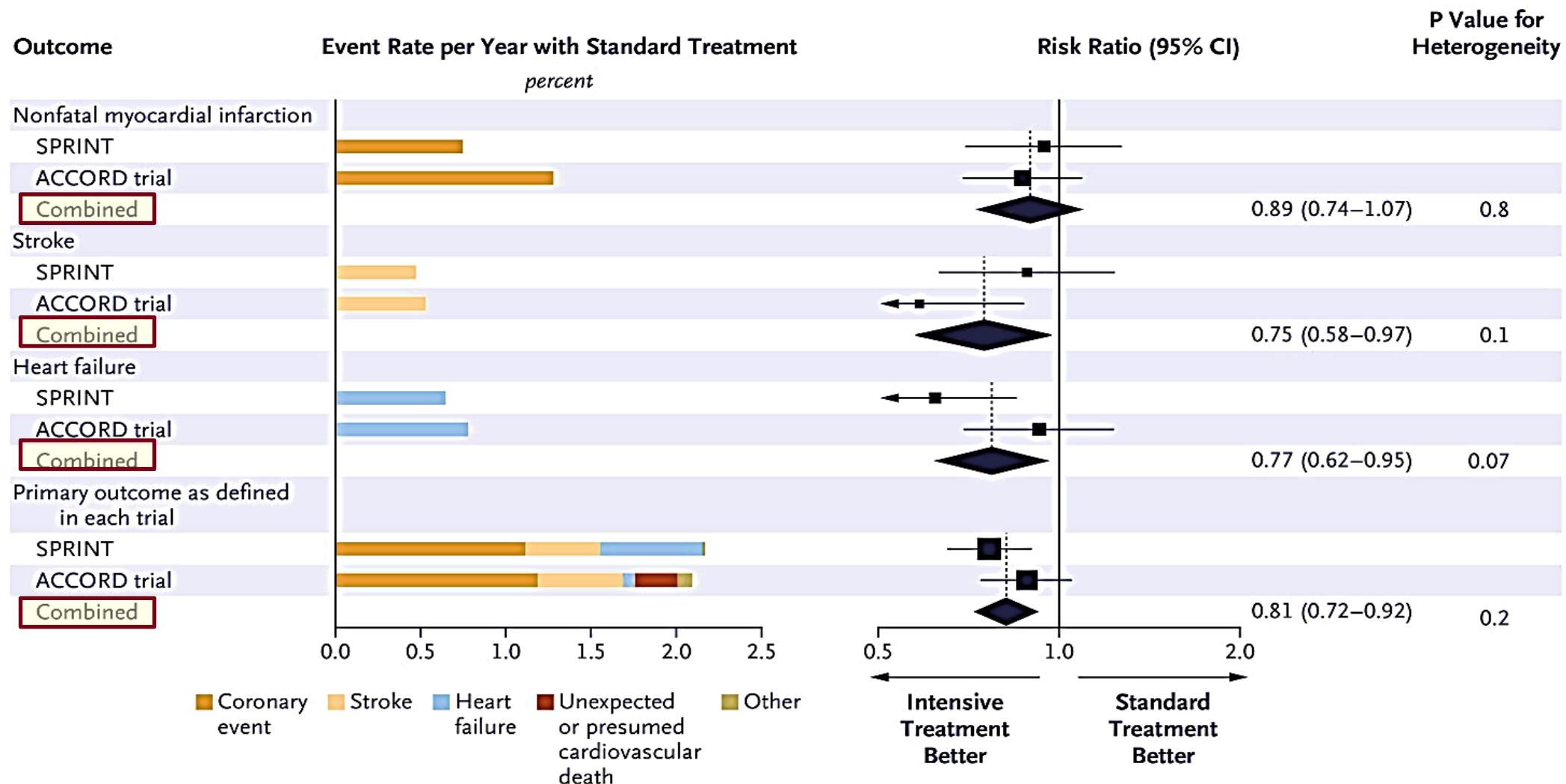
	<i>Number (%) of Participants</i>		
	Intensive	Standard	HR (P Value)
All SAE reports	1793 (38.3)	1736 (37.1)	1.04 (0.25)
SAEs associated with Specific Conditions of Interest			
Hypotension	110 (2.4)	66 (1.4)	1.67 (0.001)
Syncope	107 (2.3)	80 (1.7)	1.33 (0.05)
Injurious fall	105 (2.2)	110 (2.3)	0.95 (0.71)
Bradycardia	87 (1.9)	73 (1.6)	1.19 (0.28)
Electrolyte abnormality	144 (3.1)	107 (2.3)	1.35 (0.02)

FAQs ABOUT SPRINT

GENERALIZABILITY TO EXCLUDED POPULATIONS

- AGE < 50 years ?
- Diabetes ?
- Prior stroke ?
- Heart failure ?
- Secondary hypertension ?
- Severe CKD (eGFR < 20mL/min/1.73 m² or proteinuria) ?
- Frail elderly ?
- High CVD risk without hypertension ?
- Lower CVD risk with hypertension ?

Outcomes from SPRINT and ACCORD Trials and Combined Data from Both Trials.



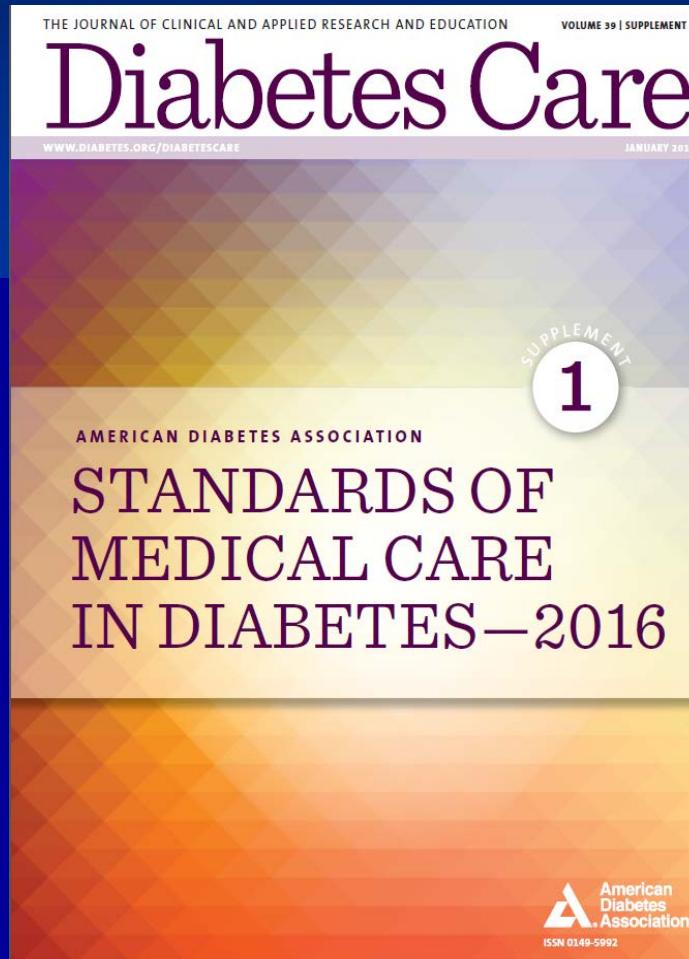
ACCORD vs SPRINT

1. SPRINT sample size was about twice that of ACCORD BP.
2. SPRINT participants were older (mean age 68 years) than ACCORD BP (mean age 62 years).
3. SPRINT included a cohort with CKD, but serum Cr >1.5 mg/dL was an exclusion in ACCORD BP.
4. The factorial design in ACCORD may have negatively affected the opportunity to test the effect of the BP intervention.

SBP Treatment Goals for Patients with Diabetes and Hypertension

- Strict interpretation of RCTs supports SBP goal of **<150 mm Hg**.
- Achieved SBP in ADVANCE and the standard group in ACCORD BP suggest **<140 mm Hg** may be a reasonable SBP goal (JNC 8 and most other current guidelines recommend this).
- A recent meta-analysis suggests **<130 mm Hg**.
- ACCORD benefit in the Standard Glycemia subgroup and SPRINT benefit in other high-risk groups support **<120 mm Hg**.

STANDARDS OF MEDICAL CARE IN DIABETES—2016



Diabetes Care 2016; 39(Suppl. 1):S1–S108 | DOI: 10.2337/dc16-S011.

ADA Evidence Grading System for Clinical Practice Recommendations

LEVEL OF EVIDENCE	DESCRIPTION
A	Clear or supportive evidence from adequately powered well-conducted, generalizable, randomized controlled trials; Compelling nonexperimental evidence
B	Supportive evidence from well-conducted cohort studies or case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies; Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

ADA RECOMMENDATIONS

Hypertension/BP Control

Goals

- People with diabetes and hypertension should be treated to a SBP goal of < 140 mmHg **A**
- Lower systolic targets, such as < 130 mmHg, may be appropriate for some, e.g., younger patients and higher-risk patients, if it can be achieved without undue treatment burden **C**
- Those with diabetes should be treated to a DBP < 90 mmHg **A**
- Lower diastolic targets, e.g., < 80 mmHg, may be appropriate for some, e.g., younger patients and higher-risk patients, if it can be achieved without undue treatment burden **B**

ADA RECOMMENDATIONS

Hypertension/BP Control

Treatment

- Patients with BP $>120/80$ mmHg should be advised on lifestyle changes to reduce BP **B**
- Patients with confirmed BP higher than 140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve BP goals **A**

ADA RECOMMENDATIONS

Hypertension/BP Control

*Treatment

- Pharmacological therapy for patients with diabetes and hypertension comprise a regimen that includes:
 - either an ACE inhibitor or angiotensin receptor blocker **B**; if one class is not tolerated, substitute the other **C**
- Multiple drug therapy (two or more agents at maximal doses) generally required to achieve BP targets **B**

*Inconsistent with JNC 8.

ADA RECOMMENDATIONS

Hypertension/BP Control

Treatment

- If ACE inhibitors, ARBs, or diuretics are used, serum creatinine/eGFR and potassium levels should be monitored **E**
- In pregnant patients with diabetes and chronic hypertension, BP target goals of 110–129/65–79 mmHg are suggested in interest of long-term maternal health and minimizing impaired fetal growth; ACE inhibitors, ARBs, contraindicated during pregnancy **E**

Management of Hypertension in Diabetes

- Hypertension is present in >2/3 of patients with type 2 diabetes.
- Hypertension and diabetes confer a much enhanced risk of cardiovascular disease than either one alone.
- Clinical trial evidence suggests that BP <140-150/85 mm Hg is a reasonable therapeutic goal in patients with type 2 diabetes mellitus. However, SPRINT + ACCORD suggest SBP <120 mm Hg may be considered.
- In patients with diabetes, a combination of a RAS-blocker and a thiazide-type diuretic might be the most reasonable initial antihypertensive regimen, although CCBs and CCB-ACEI combination are also effective.

BP Goals in People with Diabetes

- It is possible that there is an inherent difference in the CVD benefits of intensive SBP lowering in diabetic and non-diabetic adults.
- Because ACCORD BP was not definitive, it would be ethical to conduct another trial of intensive BP-lowering on major CVD outcomes in diabetics.
- Enrollment of a higher risk group (e.g., participants of older age and those with CKD) and enlarging the sample size would help to ensure adequate statistical power to answer this question.
- In the meantime, guideline committees and the medical community will have to decide whether the SPRINT results should be generalized to patients with hypertension and diabetes mellitus.



Thank You!

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