

Benefits and harms of treating blood pressure in adults over age 60

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Disclosure

This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the Portland VA Medical Center, Portland, OR funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative (QUERI). The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

Evidence-based Synthesis Program (ESP) Overview

- Sponsored by VA Office of R&D and Quality Enhancement Research Initiative (QUERI).
- Established to provide timely and accurate syntheses/reviews of healthcare topics identified by VA clinicians, managers and policy-makers, as they work to improve the health and healthcare of Veterans.
- Builds on staff and expertise already in place at the Evidence-based Practice Centers (EPC) designated by AHRQ. Four of these EPCs are also ESP Centers:
 - Durham VA Medical Center; VA Greater Los Angeles Health Care System; Portland VA Medical Center; and Minneapolis VA Medical Center.

ESP Overview

- Provides evidence syntheses on important clinical practice topics relevant to Veterans, and these reports help:
 - develop clinical policies informed by evidence,
 - the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
 - guide the direction for future research to address gaps in clinical knowledge.
- Broad topic nomination process – e.g. VACO, VISNs, field – facilitated by ESP Coordinating Center (Portland) through online process:

<http://www.hsrd.research.va.gov/publications/esp/TopicNomination.cfm>

ESP Overview

- Steering Committee representing research and operations (PCS, OQP, ONS, and VISN) provides oversight and guides program direction.
- Technical Expert Panel (TEP)
 - Recruited for each topic to provide content expertise.
 - Guides topic development; refines the key questions.
 - Reviews data/draft report.
- External Peer Reviewers & Policy Partners
 - Reviews and comments on draft report
- Final reports posted on VA HSR&D website and disseminated widely through the VA.

<http://www.hsrd.research.va.gov/publications/esp/reports.cfm>

Blood pressure targets: shifting sands

JNC 7

2003

< 140/90

JNC 8

2014

Age \geq 60:
< 150/90



2015

?



More benefit, more harm?

- Balance of benefits and harms among older adults is uncertain
 - hypertension is a common modifiable risk factor for cardio- and cerebrovascular disease and death
 - older adults may be more susceptible to harms from blood pressure lowering

Uncertainty in stroke

- JNC8 had no specific recommendation about blood pressure treatment targets in patients with prior stroke

Key questions

- Systematically review the evidence of benefits and harms of lowering BP in adults over age 60
 - 1) What are the health outcome effects of differing blood pressure targets?
 - 1b. In patients who have suffered TIA or stroke, what are the effects of lower blood pressure treatment targets?
 - 2) What are the harms of BP lowering in older adults?

Key questions

- 3) How does age modify the benefits and harms of BP lowering?
- 4) How does patient burden of comorbidities modify the benefits and harms of BP lowering?

Also:

- CV risk
- Diabetes

Methods

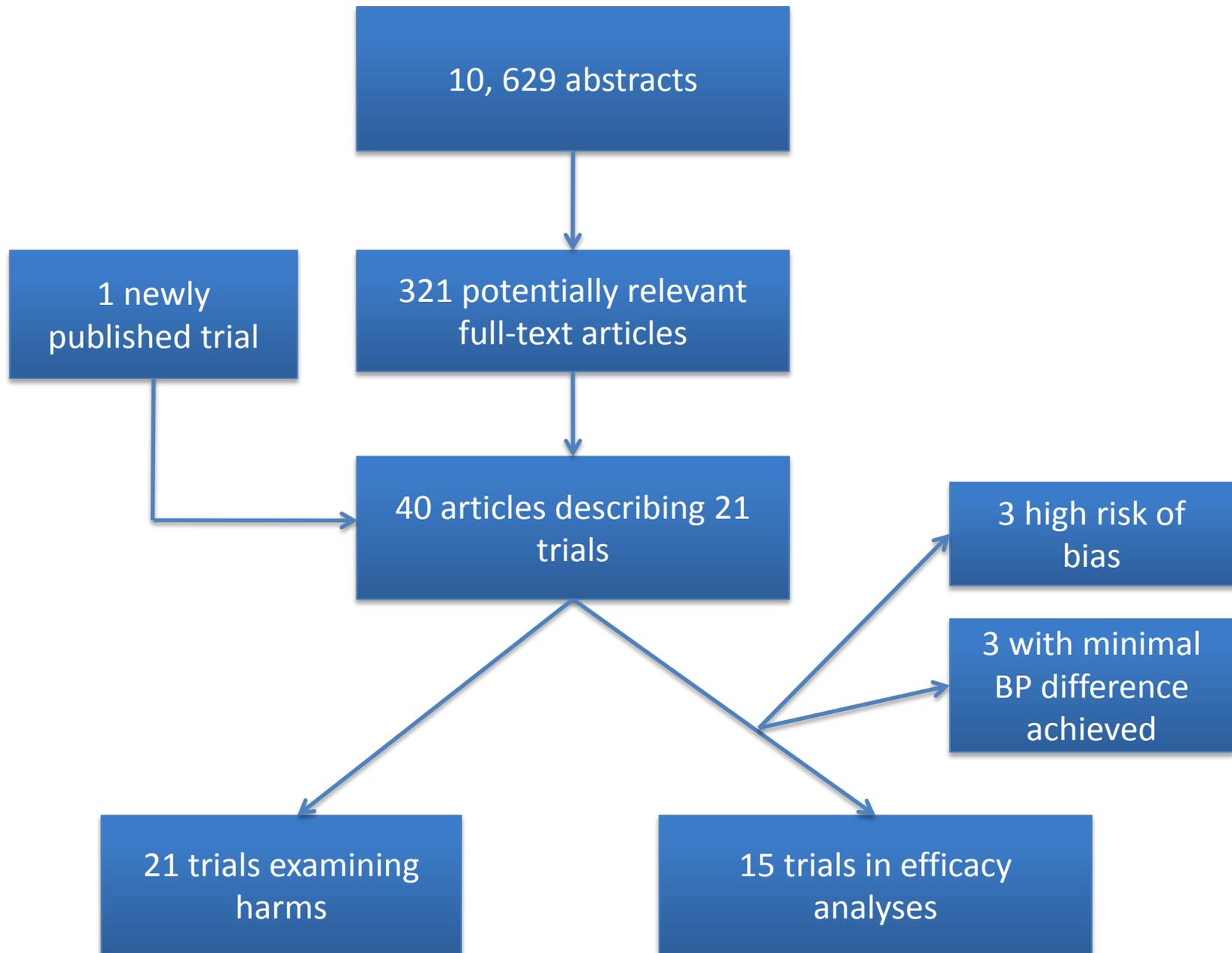
- Study inclusion
 - Population: mean age ≥ 60 ; hypertensive
 - Compared BP treatment targets, or compared the addition of blood pressure medication to placebo
- Exclusion
 - Comparative effectiveness studies
- Search
 - Medline, EMBASE, OVID EBM reviews to Jan 2015
 - ClinicalTrials.gov
 - Included any in-progress trials completed by Dec 2015

Data synthesis

- Quality assessment: Cochrane Risk of Bias
- Strength of evidence (SOE): Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group tool

Data synthesis

- Outcomes
 - All-cause mortality,
 - Cardiac events (fatal/nonfatal MI, sudden cardiac death),
 - Stroke (fatal/nonfatal)
 - Adverse events, syncope, cognition, falls, fracture, QOL, renal outcomes, functional status
- Meta-analysis
 - Profile-likelihood random-effects model



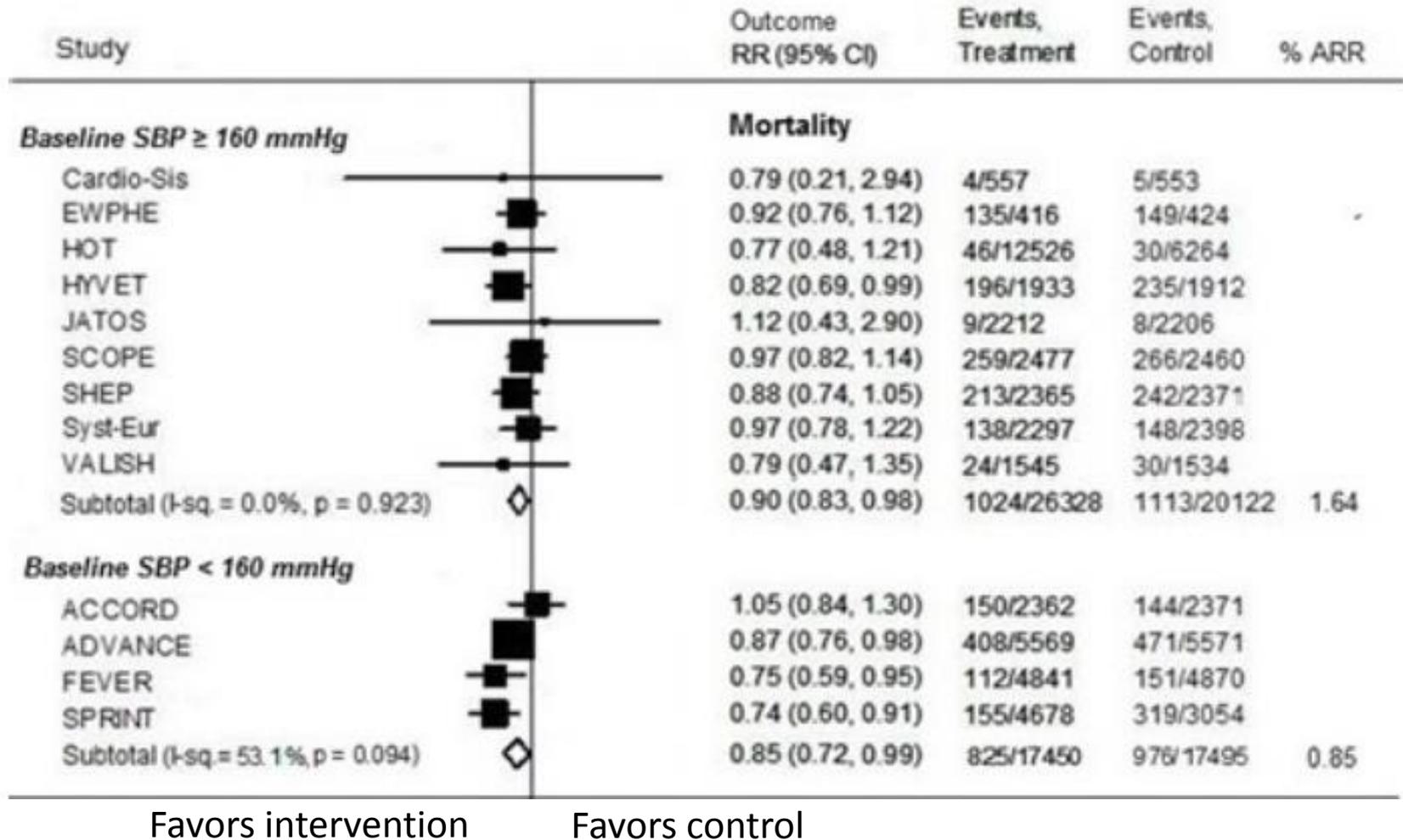
1) What are the health outcome effects of differing blood pressure targets?

- Effects in patients with moderate-severe hypertension
- Effects in patients with mild hypertension
- Incremental effects of strict control as compared to more moderate control

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- Effects in patients with moderate-severe hypertension
- Effects in patients with mild hypertension

All-cause mortality



All trials achieved BP < 150/90 mmHg

Health outcome effects – current guideline targets

Treatment target	N trials (N participants)	Outcome	Findings	SOE	Rationale for SOE
<150/90	9 (46,450)	Mortality	RR 0.90 (0.83-0.98); ARR 1.64	High	Precise, consistent, large N, low ROB
		Stroke	RR 0.72 (0.64-0.81); ARR 1.13	High	
		CV events	RR 0.77 (0.69-0.86); ARR 1.25	High	

By comparison: 4 trials with baseline SBP < 160 mmHg

Mortality: RR 0.85 (0.72-0.99), ARR 0.85

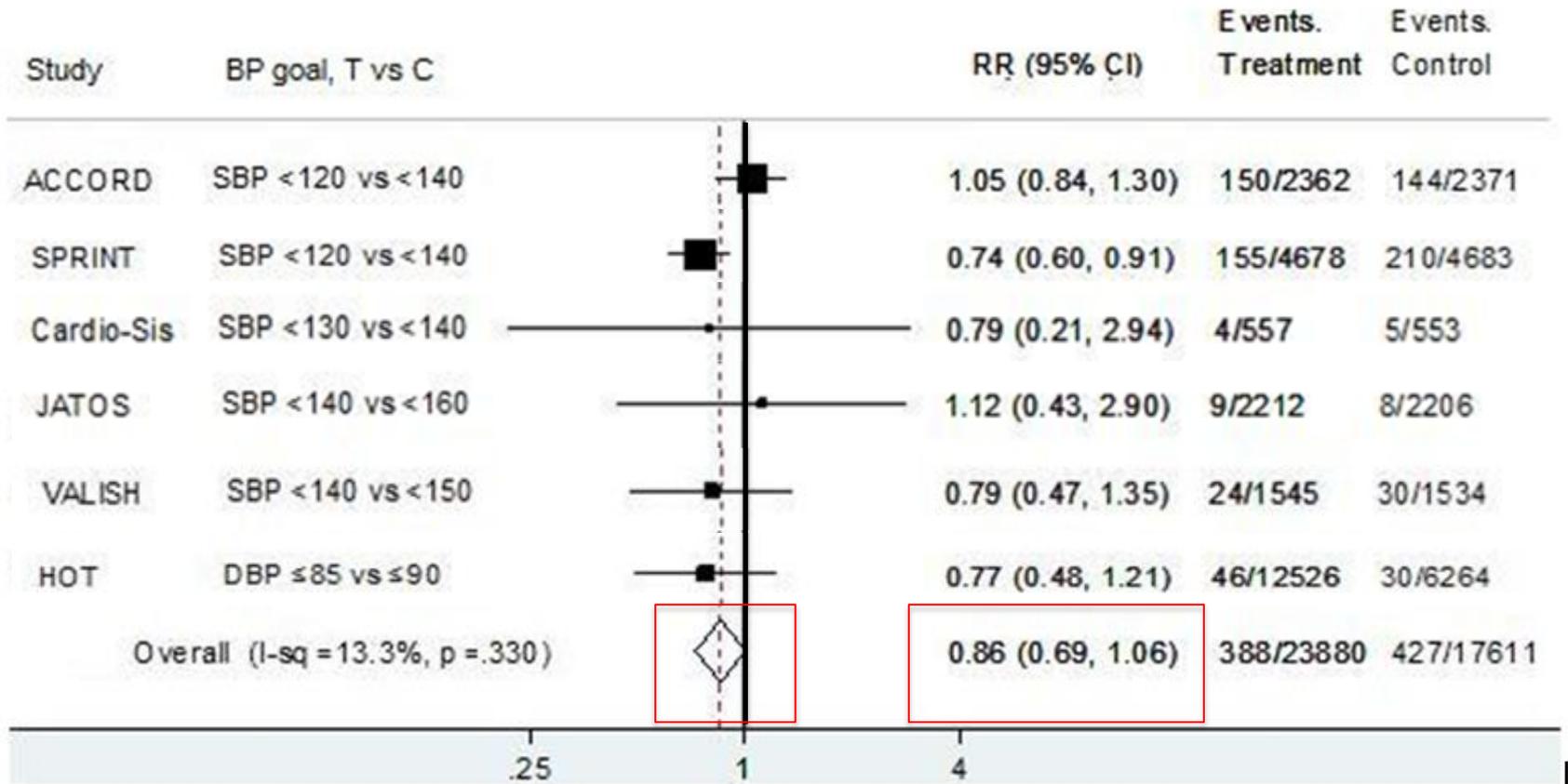
Stroke: RR 0.80 (0.62-1.01), ARR 0.63 (but I²=67%)

Cardiac events: (RR 0.86, 95% CI 0.72-0.96), ARR 0.68

1) What are the health outcome effects of differing blood pressure targets?

- Effects in patients with moderate-severe hypertension
- Effects in patients with mild hypertension
- Incremental effects of strict control as compared to more moderate control

Mortality effects of lower BP targets



Favors intervention

Favors control

Health outcome effects – targets below current guidelines

Treatment target	N trials (N participants)	Outcome	Findings	SOE	Rationale for SOE
<140/85	6 (41,491)	Mortality	RR 0.86 (0.69-1.06)	Low	Inconsistent, imprecise
		Stroke	RR 0.79 (0.59-0.99); ARR 0.49	Mod	Imprecise, more consistent results
		CV events	RR 0.82 (0.64-1.00); ARR 0.94	Low	Inconsistent, imprecise
<150/90	9 (46,450)	Mortality	RR 0.90 (0.83-0.98); ARR 1.64	High	Precise, consistent, low ROB
		Stroke	RR 0.72 (0.64-0.81); ARR 1.13	High	
		CV events	RR 0.77 (0.69-0.86); ARR 1.25	High	

Treat to target trials: ACCORD and SPRINT

	ACCORD	SPRINT
Target SBP	< 120	< 120
Baseline SBP	139	140
High CV risk population	Yes	Yes
Outcomes	Reduced stroke; not death or CV events	Reduced death and CV events; not stroke
Mean age	62	68
Diabetics	Included	Excluded
Years follow-up	4.7	3.3 (stopped early for benefit)

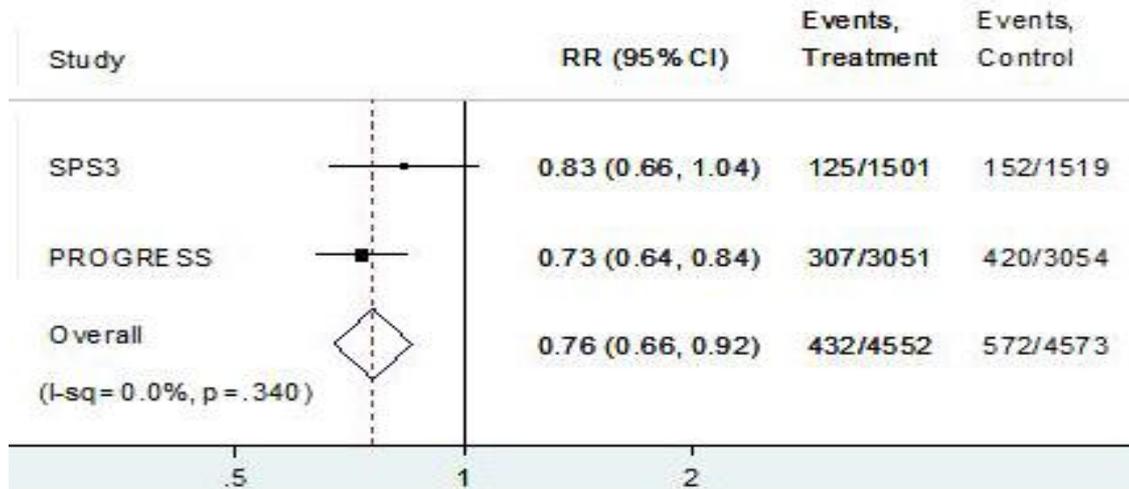
The middle ground: SBP 140-150mmHg

- Very little data to address this question
 - ADVANCE trial the only one with a baseline SBP between 140-150
 - Achieved SBP < 140
 - Improved mortality, no effect on stroke, trend toward reduction in cardiac events

In patients who have suffered TIA or stroke, what are the effects of lower blood pressure treatment targets?

Finding	N (n pts)	Summary effect	SOE	Notes
Targeting SBP < 140 mmHg improved outcomes	2 (9125)	Stroke: 0.76 (0.67-0.85) Cardiac events: 0.78 (0.63-0.96) Mortality: 0.96 (0.86-1.12)	Moderate	Only 2 trials, but precise estimate with generally consistent results

Secondary stroke prevention



- SPS3 – lacunar strokes
 - Target < 130 mmHg vs 130-149
 - Achieved 127 vs 138
- Progress – hemorrhagic or ischemic strokes, TIA
 - CCB +/- thiazide vs placebo in patients with baseline SBP 147 (achieved 138 vs 147)

3) What are the harms of BP lowering in older adults?

21 trials comparing more vs less aggressive BP treatment, or different BP treatment targets

Harms of more vs less aggressive blood pressure treatment

Outcome	N trials (N participants)	Finding	SOE	Comment
Adverse events	19 (98,964)	Study withdrawal: ↑ in 4 of 10 trials	---	Heterogeneity in outcome definition and reporting
Syncope	3	RR 1.52, 95% CI 1.22-2.07, NNH 110	Low	Small increase in 2 studies, none in a third
Cognitive decline, incident dementia	7 (25,901)	No effect; Incident dementia [4 trials: OR 0.89 (0.74-1.07)]	Mod	Similar results in trials achieving SBP 140-150 and < 120 mmHg
Fracture	3 (11,680)	No effect	Mod	Similar results in trials achieving SBP 140-150 and < 120 mmHg

Harms

Outcome	N trials (N participants)	Finding	SOE	Comment
Falls	3 (17,196)	No effect	Low	No difference in 2 studies, small increase in third
QOL	4 (7,154)	No effect	Mod	Achieved SBP 140-150 mmHg
Functional status	1 (4736)	No effect	Low	Only one study
Renal outcomes	12 (63,997)	No effect	Low	Varied outcome definitions; low event rates for clinically impt endpoints

Medication burden

- Method of reporting varied considerably, making a summary estimate impossible
- Medication burden generally higher in the more aggressive BP treatment group

How does age modify treatment effects?

- Similar results in our analyses comparing trials with mean age ≥ 70 and < 70
- 12 trials conducted age subgroup analyses of benefits
 - Most found no significant differences according to (dichotomized) age groups
 - But results varied, even among outcomes within same study
 - Insufficient evidence

Age and harms

- 3 trials – no evidence of differences across age (all compared ≥ 75 to < 75), but limited
 - SPRINT just published more comprehensive age subgroup data – no significant differences
 - SPS3 found similar results
 - JATOS – just reported renal failure by age – no differences

To what age groups does the evidence apply?

- Most studies mean age 60-80
- However, two studies showing benefit purposefully enrolled pts > age 80
 - HYVET (entire study), goal < 150/80, mean age 83
 - SPRINT (subgroup), goal < 120
 - Mean age in > 75 subgroup 79 years
 - Similar results in older and younger age groups

How does comorbidity burden modify treatment effects?

- No studies (most studies did not measure comorbidity burden)
- SPRINT just published outcomes according to measures of frailty, but post-hoc and no other studies
- Most studies excluded patients with multiple significant comorbidities...

Comorbidities and applicability

Condition	Excluded some or all (N=21)	Included	Not reported or unclear
Dementia/frailty	15	0	6
Chronic kidney disease	15	2	4
Congestive heart failure	17	0	4
Diabetes mellitus	9	4	8

Cardiovascular risk and treatment effects

- Low strength evidence that absolute treatment effects are probably greater in those at high CV risk
 - ADVANCE and SHEP
 - NNT CV event ranged from 200 to 37 according to risk group
 - HOT trial
 - Reduction in MI only significant in high CV risk group
 - Significant mortality, CV effects in DM subgroup only (higher event rates in this group)

Diabetes and BP control

- Diabetes specific recommendations are, in some sense, an artifact of choices by prior guideline groups
 - Also, HOT study – DM subgroup benefits – achieved blood pressure interpreted as treatment target
- SPRINT has been interpreted as a lower target for non-diabetics, but it is not clear that diabetes was major difference driving results

Diabetes subgroup analyses

- All studies have found that diabetics benefit as much, and often more, than non-diabetics
- Event rates in diabetics are typically higher, suggesting perhaps it is overall CV risk rather than DM status accounting for varied treatment effects
- Our own analyses – only 4 studies with only diabetics – clinically heterogeneous

Limitations

- Study-level data
- Clinical heterogeneity of studies
- Scope, inclusion criteria different than other recent high-profile reviews
 - Age
 - Studies of normotensive pts (eg – HOPE)

Conclusions

- Lowering blood pressure improves outcomes in adults over 60
 - The largest body of evidence and largest effects are in patients with systolic ≥ 160 mmHg achieving moderate blood pressure control ($<150/90$ mmHg)
 - Lower treatment targets ($<140/85$ mmHg) are likely to be beneficial for some patients
 - Important inconsistencies in the evidence
 - Perhaps smaller absolute effects overall
 - Lower treatment targets are likely beneficial for patients with prior stroke
 - Large treatment effect for secondary stroke prevention

Conclusions

- Choice of lower treatment target
 - Patients with prior stroke
 - Patients at high CV risk
 - Little direct data to guide choice of target within the 120-140 range
 - Must be balanced against risk of hypotension/syncope in susceptible individuals, and added medication burden

Conclusions

- Potential for increased adverse events, but low to moderate strength evidence that most serious harms are not increased
- Little evidence to assess risks and benefits in the frail elderly or those with multiple comorbidities

Our team: thank you

- Michele Freeman
- Allie Low
- Amy Kerfoot
- Makalapua Motu'apuaka
- Rochelle Fu
- Robin Paynter
- Karli Kondo

Panel and case discussion

- Stroke: confusion and inertia on the front lines
- Choosing a lower target in the real-world
 - Balancing benefits and harms
 - BP measurement
 - Should we literally aim for < 120 mmHg?
- Geriatrics and BP control

Case 1

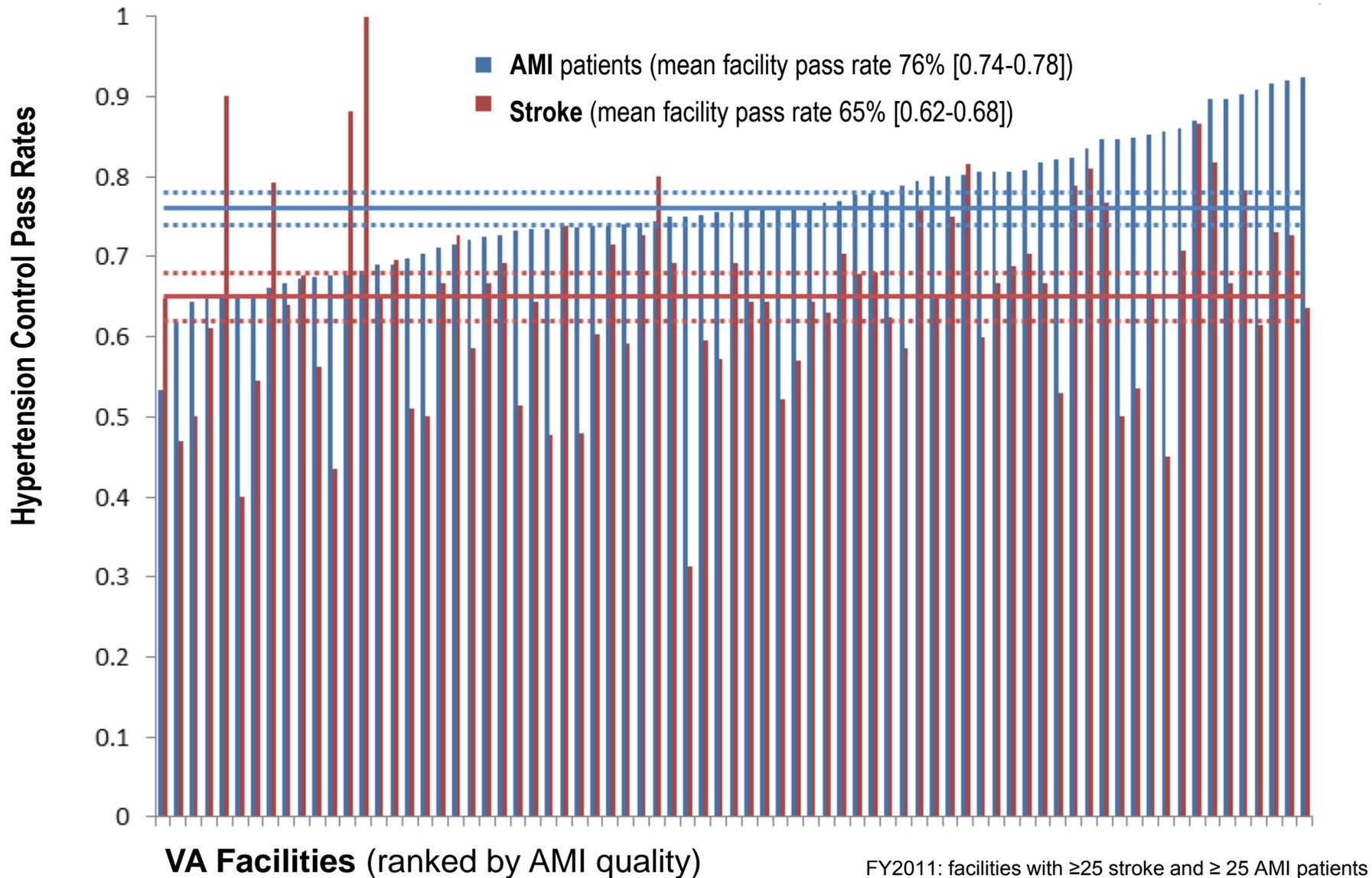
A 65 yo female comes to see you in primary care clinic. She had been hospitalized with a left MCA ischemic stroke 4 weeks ago and has steadily recovered strength since. On hospital discharge she had a BP 148/78 and was continued on lisinopril 5 mg. On recheck two weeks later and again today it is 146/82. She is unsure if she is seeing neurology again and wonders if she needs more blood pressure medication.

Hypertension Control The Stroke Perspective

- Hypertension management is a cornerstone of stroke prevention
- Globally: improved hypertension control has been temporally associated with improved stroke incidence
- Within the stroke community, there was concern that a recommendation to raise the target blood pressure would eliminate the progress that has been made in stroke risk reduction

VA Facility Rates for Hypertension Control One-Year after Ischemic Stroke vs AMI

Stroke patients had worse BP control than AMI patients at 87% of VAMCs



Hypertension Issues for Veterans with Stroke

Standard in-patient practice	Hold antihypertensives on admission, then resume outpatient regimen at discharge: discharge SBP, 37% >140, 11% >160 However, 48% did not achieve BP <140/90 pre-stroke suggesting need for timely outpatient follow-up focused on BP control
Adherence	Stroke patients have similar adherence rates as other Veteran populations: half adhere to antihypertensives
Discoordination between services	Neurology: "Hypertension is the responsibility of primary care...I won't change their anti-hypertensives"
	Primary Care: <i>"I don't know the evidence on this but it's probably is worthwhile to have them auto-regulate off of medication."</i>
Outpatient visits	Stroke: ~6 outpatient visits/y (0.8 neurology visits/y) AMI: ~8 visits (2.5 cardiology visits/y)
Clinical inertia	Stroke patients have ~2 intensification opportunities/y Medication intensification occurs in ~60% opportunities
Ongoing movement in primary care to avoid overtreatment	

Case 2

- 70 year old male with hypertension, hyperlipidemia, prior smoker has had blood pressures ranging 135-153/70-90 over the last 6 months. He is very fit and hikes regularly with no trouble. He takes HCTZ 12.5 mg and amlodipine 5 mg. The resident asks whether we should increase his blood pressure medications.

BP Measurement in SPRINT

- Visit BP: average of 3 seated office BP measurements obtained using an automated measurement device: Omron 907XL.
- Appropriate cuff size was determined by arm circumference.
- Participant was seated with back supported and arm bared and supported at heart level.
- Device was set to delay 5 minutes and then take/average 3 BP measurements, during which time participant refrained from talking.

BP Readings Taken Manually in Routine Clinical Practice by the Patient's Own Physician, Readings Taken as Part of a Research Study Using a Hg Sphygmomanometer or Automated Office Device (BpTRU) and the Mean Awake ABPM

Study, First Author	N	Type of Blood Pressure Measurement (mm Hg)			
		Routine Clinical Practice	Research Quality Office	Automated Office	Mean Awake Ambulatory
Myers ⁷	147	146/87	140/83	...	132/78
Brown ⁸	611	161/95	152/85	...	139/82
Myers ⁹	309	152/87	140/80	132/75	134/77
Graves ¹⁰	104	152/84	138/74	136/79	...
Gustavsen ¹¹	420	165/104	156/100	...	147/96
Beckett ¹²	481	151/83	...	140/80	142/80
Dawes ¹³	5918	164/96	149/90

Myers, et al. Hypertension 2010. 55;185-200

Implications of SPRINT for Guidelines and Performance Measures

- Achieved systolic BP goals in SPRINT intensive group:
 - SBP <120 mmHg: 50-60%
 - SBP <130 mm Hg: 75-80%
- I believe guidelines should recommend goal treatment SBP <120 mm Hg in many patients at high CVD risk
- However:
 - This assumes proper/careful BP measurement
 - For a performance measure: perhaps SBP <130 mm Hg in 70-80%
 - Uncertainty in some groups: DM, prior stroke, in nursing home, severe CKD (eGFR <20), age <50 years

Case 3

- An 82 yo woman comes to see you for follow up of her hypertension after discharge from SNF. She has history of HTN, CKD IV (baseline eGFR 26-29), mild dementia, and recent hip fracture (her reason for SNF stay). Her blood pressure in clinic is 159/66 (HR 66) on arrival and 156/64 (HR 59) on recheck at the end of the appointment. Readings at home range from 145-165 systolic. She takes metoprolol 25 mg bid, nifedipine ER 60 mg qhs, and hydralazine 25 mg tid. After her recent stay she feels very strongly about NOT returning to SNF care and hopes to prioritize quality of life and independence.

ACCORD,
ADVANCE,
RENAAL,
TRANSCEND

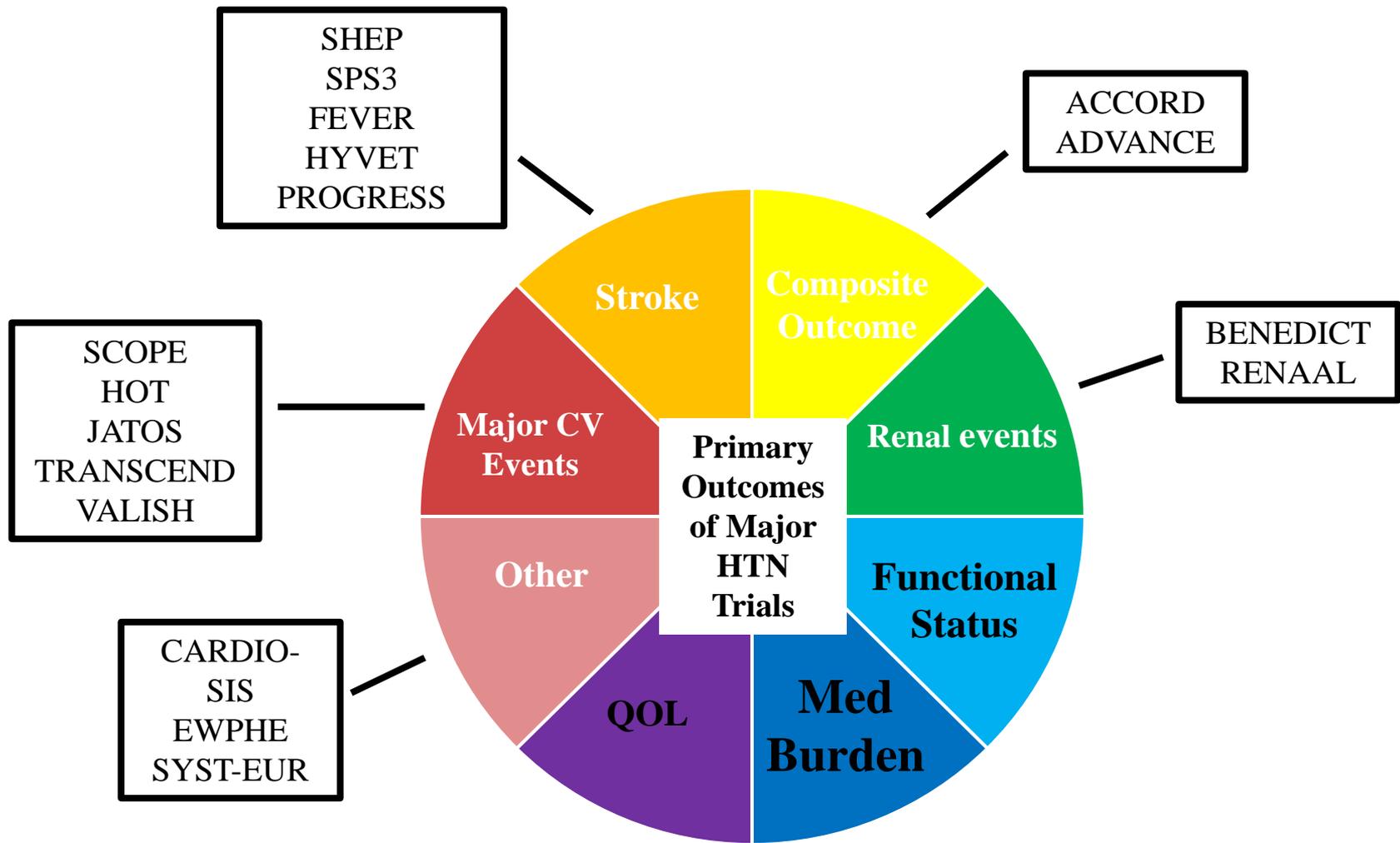
ACCORD
BENEDICT
EWPHE
HOT
JATOS
RENAAL
SCOPE
SPRINT
STONE
TRANSCEND
VALISH



CARDIO-SIS,
EWPHE, HOT,
JATOS, SHEP,
SPRINT, STONE

ACCORD, HYVET,
SPRINT

HYVET, SCOPE,
SHEP, SPRINT,
SYST-EUR



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