REVIEW ARTICLE

Time to benefit for stroke reduction after blood pressure treatment in older adults: A meta-analysis

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Abstract

Background: Hypertension treatment in older adults can decrease mortality, cardiovascular events, including heart failure, cognitive impairment, and stroke risk, but may also lead to harms such as syncope and falls. Guidelines recommend targeting preventive interventions with immediate harms and delayed benefits to patients whose life expectancy exceeds the intervention's time to benefit (TTB). Our objective was to estimate a meta-analyzed TTB for stroke prevention after initiation of more intensive hypertension treatment in adults aged ≥65 years.

Methods: Studies were identified from two Cochrane systematic reviews and a search of MEDLINE and Google Scholar for subsequent publications until August 31, 2021. We abstracted data from randomized controlled trials comparing standard (untreated, placebo, or less intensive treatment) to more intensive treatment groups in older adults (mean age ≥ 65 years). We fit Weibull survival curves and used a random-effects model to estimate the pooled annual absolute risk reduction (ARR) between control and intervention groups. We applied Markov chain Monte Carlo methods to determine the time to ARR thresholds (0.002, 0.005, and 0.01) for a first stroke.

Results: Nine trials ($n = 38,779$) were identified. The mean age ranged from 66 to 84 years and study follow-up times ranged from 2.0 to 5.8 years. We determined that 1.7 (95%CI: 1.0–2.9) years were required to prevent 1 stroke for 200 persons (ARR = 0.005) receiving more intensive hypertensive treatment. Heterogeneity was found across studies, with those focusing on tighter systolic blood pressure control (SBP < 150 mmHg) showing longer TTB. For example, in the SPRINT study (baseline SBP = 140 mmHg, achieved SBP = 121 mmHg), the TTB to avoid 1 stroke for 200 patients treated was 5.9 years (95%CI: 2.2–13.0).

See related Editorial by Mark A. Supiano in this issue.

An oral presentation based in part on the study findings was given at Plenary Paper Session at the American Geriatrics Society Annual Scientific meeting on June 24, 2020.

Conclusions: More intensive hypertension treatment in 200 older adults prevents 1 stroke after 1.7 years. Given the heterogeneity across studies, the TTB estimates from individual studies may be more relevant for clinical decision-making than our summary estimate.

KEYWORDS

hypertension, stroke, time to benefit

INTRODUCTION

Hypertension is a strong and common modifiable risk factor for stroke. In the United States, hypertension affects 47% adults (245 million) and 76% of older adults ≥65 years of age (48.0 million).[1,2] The prevalence of stroke is strongly age-dependent, and hypertension dramatically increases the risk of stroke in older adults.[3,4] Data from Framingham Study suggests that hypertension doubles the risk of stroke in older adults age 65–94, with a relative risk (RR) of 1.9 in men and 2.3 in women.[5] While hypertension treatment has been shown to reduce stroke risk,[6] it is less clear when stroke reduction occurs. In contrast, the harms of hypertension treatment, which include orthostatic hypotension, syncope, falls, and electrolyte abnormalities, appear to occur soon after treatment initiation.[7–9] For example, the risk of falls and fractures was found to be increased in the first 7–45 days after the initiation of antihypertensive medications.[10–14] Thus, while hypertension treatment decreases stroke risk over time, it can also lead to an increased risk for adverse effects.

For interventions with short-term potential harms and long-term potential benefits, we previously proposed a framework for individualizing prevention decisions that focuses on a patient's life expectancy and an intervention's time to benefit (TTB).[15] Older adults with a limited life expectancy should avoid preventive interventions with an extended TTB, since these older adults would be exposed to the up-front harms of the intervention with little chance they would survive to experience the benefits. Although many indexes to predict life expectancy for older adults have been validated and are available through websites such as ePrognosis (ePrognosis.ucsf.edu), the TTB for hypertension treatment to prevent strokes is unclear.

To help clinicians identify, which patients are most likely to benefit from hypertension treatment (and which patients are more likely to be harmed), our objective was to determine the TTB of hypertension treatment for the primary prevention of stroke. We conducted a survival meta-analysis of major randomized clinical trials to determine the TTB for various stroke absolute risk reduction

Key points

- More intensive hypertension treatment in 200 older adults prevents 1 stroke after 1.7 years.
- For older adults with baseline systolic blood pressures (SBP) below 150 mmHg, the time to benefit (TTB) of more intensive hypertension treatment appears to be substantially longer than 1.7 years; for older adults with baseline SBP above 190 mmHg, the TTB appears to be shorter than 1.7 years.

Why does this paper matter?

- Since the overwhelming majority of older adults have a life expectancy >1.7 years, our results suggest that almost all older adults with hypertension would benefit from treatment.

(ARR) thresholds. Specifically, we sought to quantify how many years of hypertension treatment was necessary before 1 stroke was prevented for 500 older adults treated (TBB to reach an ARR of 0.002). Similarly, we sought to quantify the TTB for ARR of 0.005 (1 stroke prevented for 200 treated) and TBB for ARR of 0.01 (1 stroke prevented for 100 treated).

METHODS

Literature search

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement guidelines were followed (Table S1). One reviewer (VSH) identified randomized control trials from two systematic reviews (2017 Cochrane review entitled, "Blood pressure targets for hypertension in older adults"[16] and 2019 Cochrane review entitled, "Pharmacotherapy for hypertension in adults 60 years
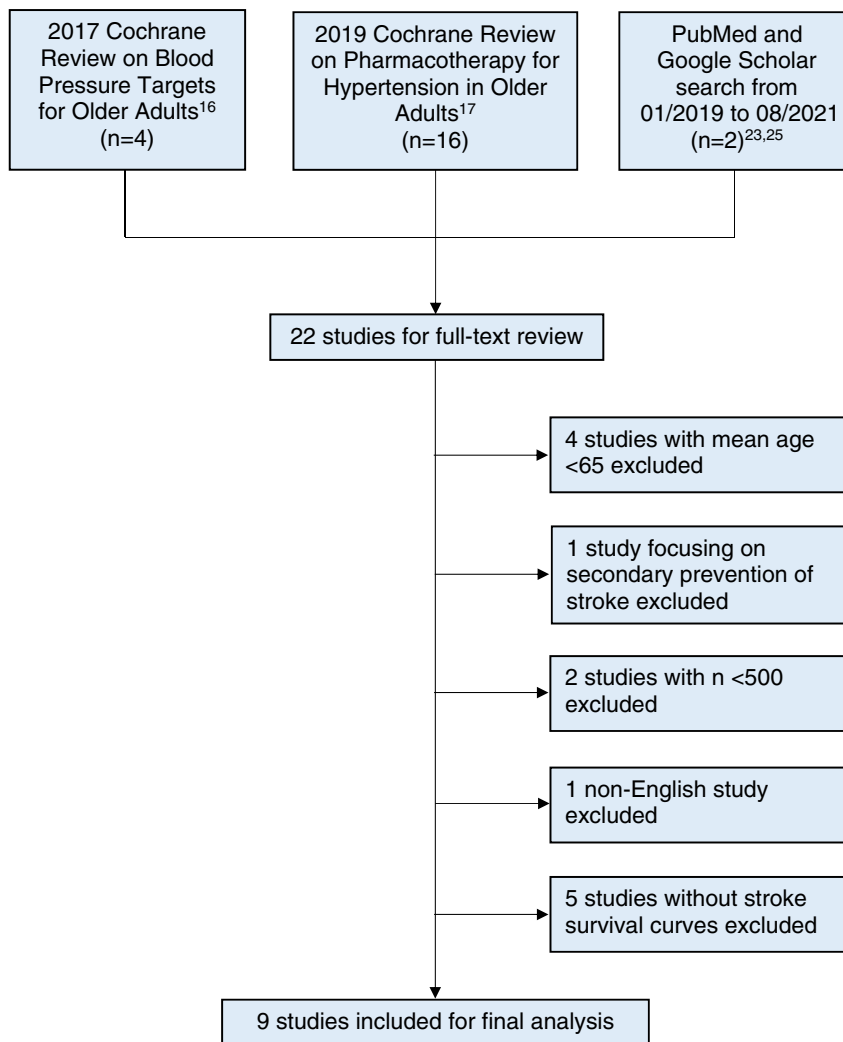
or older"[17]). We also searched MEDLINE–PubMed and Google Scholar for subsequently published relevant studies up until August 31, 2021 using the search terms *blood pressure, hypertension, antihypertensive, older, elderly*, and *stroke.* The trial names, authors, and references of included trials and published systematic reviews were screened for other potential trials. The search strategy is detailed in Figure 1. Since this project relied on previously published data, the Committee on Human Research at the University of California, San Francisco determined that this did not meet the definition of human subjects research and thus did not require review.

Eligibility criteria

This study focused on the primary prevention of stroke in older adults. Thus, we excluded trials with a mean age <65 years, trials focusing on secondary stroke prevention, smaller studies with $n < 500$ and non-English studies. Since our outcome was the time to stroke

prevention, we required studies to present time to stroke data and excluded studies without stroke survival curves.

Data extraction

We utilized previously validated methods to quantify data from published survival curves. Specifically, we scanned the published survival curves and used the program DigitizeIt to reconstruct the data underlying the survival curves.[18] As a sensitivity analysis, we manually quantified the scanned survival curves from two studies and compared the manual quantification with the DigitizeIt program results.

Outcomes of interest

Our primary outcome was time to stroke reduction after initiation of more intensive blood pressure treatment.

TABLE 1 Characteristics of excluded studies

Cochrane review	Study[a]	Reason(s) for exclusion				
		Mean age <65 years	Secondary prevention of stroke	Sample size (n < 500)	Non-English study	No stroke survival curve
Garrison[16] 2017	JATOS[26] 2008					x
	VALISH[27] 2010					x
	Steurer[28] 2016				x	
Musini[17] 2019	Carter[29] 1970		x			
	VA-II[30] 1970	x		X		x
	HSCSG[31] 1974	x	x			
	ATTMH[32] 1981	x				
	Kuramoto[33] 1981			x		
	Sprackling[34] 1981			X		
	EWPHBPE[35] 1989					x
	SHEP-P[36] 1989					x
	MRC-TMH[37] 1992	x				
	HYVET P[38] 2003					x

Abbreviations: ATTMH, Australian therapeutic trial in mild hypertension; EWPHBPE, European working party on high blood pressure in the elderly; HSCSG, hypertension-stroke cooperative study group; HYVET P, hypertension in the very elderly trial pilot; JATOS, Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients; MRC-TMH, medical research council trial of treatment of mild hypertension; n, number of participants; SHEP-P, systolic hypertension in the elderly program pilot; VA-II, Veterans administration cooperative study group on antihypertensive agents; VALISH, Valsartan in elderly isolated systolic hypertension.
[a]Studies are listed chronologically.

Statistical methodology

Our statistic of interest was the "time to benefit," which is not routinely reported by individual studies. In order to calculate the TTB for each study, we fit random-effects Weibull survival curves using the annual event data for the control and intervention groups, allowing both the scale and shape Weibull parameters to vary for each arm of the study. We then used 100,000 Markov Chain Monte Carlo (MCMC) simulations to acquire point estimates, standard errors, and confidence intervals for mortality rates in control and intervention arms of each study. From this model, we obtained estimates of time to specific ARR thresholds (ARR = 0.002, 0.005 and 0.01) for each study. Similar ARR thresholds have been used in previously published time to benefit analyses and risk prediction tools for shared decision-making.[19,20]

Next, we pooled the estimates from each study using a random-effects meta-analysis model. We employed the χ^2 test of homogeneity and I^2 statistics (with $p < 0.05$ and $I^2 > 50\%$, respectively, indicating significant heterogeneity) to determine variability in the intervention effects across studies due to statistical heterogeneity. MCMC computations were conducted in SAS 9.4, estimates for individual studies were obtained using R 3.4.0 and a random-effects meta-analysis was conducted in STATA 14.2. We utilized similar methods to estimate TTB for cancer screening in previously published studies.[21,22]

RESULTS

We examined the meta-analyses conducted by the Cochrane Collaboration in 2017[16] and 2019[17] and identified 22 studies (Figure 1). A search of Google scholar and Medline for subsequently published studies revealed two studies, which met our inclusion criteria: 1) a post hoc analysis[23] of the SPRINT study[24] and 2) the STEP trial.[25] Of the 22 studies that underwent full-text review, 13 studies[26–38] were excluded. Four studies were excluded because the mean age of participants was <65 years. One study focusing on secondary prevention of stroke was excluded. Two studies with $n < 500$ were excluded and one non-English study was excluded. Finally, five studies did not present survival curves or time to stroke data and were also excluded. Two excluded studies met more than one exclusion criterion (Table 1).

We identified nine randomized controlled trials[24,25,39–45] that met our inclusion criteria (total

$n = 38{,}779$). The trials ranged in size from 724 to 9361 participants. The mean age in the included trials ranged from 66 to 84 years. Five of the studies were placebo-controlled studies, one study compared observation only (no treatment) to active hypertension treatment, and three studies focused on standard hypertension treatment compared to more intensive hypertension treatment. Older trials focused on patients with a higher baseline systolic blood pressure (SBP), resulting in a higher stroke risk. For example, our earliest included study (Coope 1986[39]) had a baseline SBP of 196 mmHg with a 9.5% stroke risk in the standard treatment group. On the other hand, our most recent included study (STEP 2021[25]) had a baseline SBP of 146 mmHg with a 1.7% stroke risk in the standard treatment group. Across the studies, the mean follow-up ranged from 2.0 to 5.8 years. The RR of stroke reported by each individual study ranged from 0.55 to 0.89. The stroke risk in the standard treatment group varied widely across studies, ranging from 1.5% to 10.0%. Characteristics of included studies are summarized in Table 2.

Our survival meta-analysis suggested that the benefit of more intensive hypertension treatment increased steadily with longer follow-up. (Figure 2). For example, at 1 year, 0.3 strokes were prevented for 100 persons treated with more intensive hypertension treatment. At 3 and 5 years after treatment initiation, 1.0 and 1.8

strokes were prevented for 100 persons treated with more intensive hypertension treatment, respectively.

We determined that it took 3.0 years (95%CI: 1.8–4.9) for more intensive hypertension treatment to prevent 1 stroke in 100 older patients treated (ARR = 0.01;
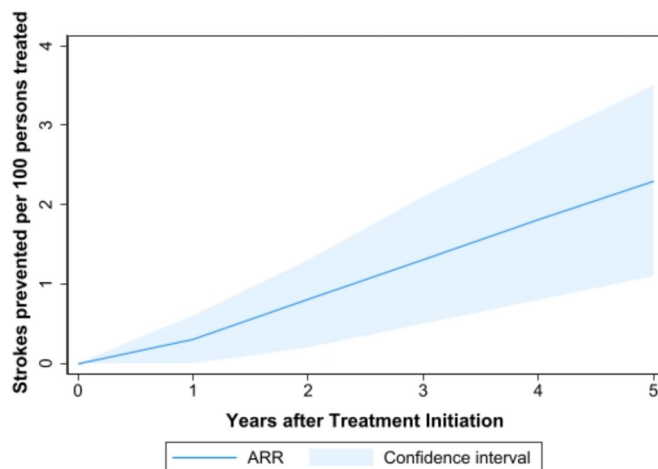

FIGURE 2 Meta-analyzed absolute risk reduction over time with more intensive blood pressure treatment. The dark blue line signifies the difference in number of stroke events between standard and more intensive blood pressure treatment groups. The light blue areas above and below the line indicate the upper and lower 95% confidence limits of the ARR, respectively

TABLE 2 Characteristics of Included Studies

Study[a]	n	Mean Age (Range), y	Intervention Groups Std Tx	Int Tx	Mean SBP[b] (Std Tx/Int Tx), mmHg Baseline	Achieved	Mean FU, y	ΔSBP achieved, mmHg	Stroke Risk in Std Tx, %	Stroke RR (95% CI)
Coope[39] 1986	884	69 (60–79)	Obs only	A	196.4/196.7	180.4/162.3	4.4	−18.1	9.5	0.58(0.36–0.94)
SHEP[40] 1991	4736	72 (>60)	P	A	170.1/170.5	155.1/144.0	4.5	−11.1	6.3	0.65(0.50–0.83)
STOP[41] 1991	1627	76 (70–84)	P	A	195.0/195.0	186.0/167.0	2.1	−19.0	6.5	0.55(0.35–0.85)
MRC-O[42] 1992	4396	70 (65–74)	P	A	184.7/184.7	165.0/151.6	5.8	−13.5	6.1	0.76(0.58–0.97)
Syst-Eur[43] 1997	4695	70 (>60)	P	A	173.9/173.8	160.9/150.8	2.0[c]	−10.1	3.4	0.58(0.41–0.84)
HYVET[44] 2008	3845	84 (80–105)	P	A	173.0/173.0	158.3/143.5	2.1	−14.8	3.5	0.74(0.52–1.05)
Wei[45] 2013	724	77 (>70)	Std Tx	Int Tx	160.3/158.8	149.7/135.7	4.0	−14.0	10.0	0.58(0.35–0.97)[d]
SPRINT[24] 2015	9361	68 (>50)	Std Tx	Int Tx	139.7/139.7	134.6/121.4	3.3[c]	−13.1	1.5	0.89(0.63–1.25)
STEP[25] 2021	8511	66 (60–80)	Std Tx	Int Tx	146.0/146.1	135.9/126.7	3.3[c]	−9.3	1.7	0.67(0.47–0.97)

Abbreviations: ΔSBP, difference in SBP Achieved = (Intensive SBP achieved − Standard SBP achieved); A, active treatment; CI, confidence interval; FU, follow-up; HYVET, hypertension in the very elderly trial; Int Tx, intensive treatment; MRC-O, medical research council trial of treatment of hypertension in older adults; n, number of participants; Obs, observation; P, placebo; RR, relative risk; SBP, systolic blood pressure; SHEP, systolic hypertension in the elderly program; SPRINT, systolic blood pressure intervention trial; Std Tx, standard treatment; STEP, strategy of blood pressure intervention in elderly hypertensive patients; STOP, Swedish trial in old patients with hypertension; Syst-Eur, systolic hypertension in Europe; y, years.
[a]Studies are listed chronologically.
[b]Sitting or supine SBP.
[c]Reported as median (mean follow-up years was not provided by the study).
[d]Calculated by the authors of this article (CI was not provided by the study).

FIGURE 3 Forest plots for time to benefit to achieve ARR thresholds.
(A) Forest plot for ARR = 0.002.
(B) Forest plot for ARR = 0.005.
(C) Forest plot for ARR = 0.01

(A)

Study	TTB (95% CI)	Weight (%)
Coope 1986	2.6 (0.5,8.4)	10.9
SHEP 1991	0.9 (0.2,2.5)	12.7
STOP 1991	0.4 (0.1,1.4)	9.7
MRC-O 1992	3.0 (0.9,7.7)	13.8
Syst-Eur 1997	0.4 (0.1,0.9)	15.5
HYVET 2008	1.0 (0.2,3.3)	10.5
Wei 2013	0.5 (0.0,1.6)	7.9
SPRINT 2015	4.0 (0.8,12.0)	11.3
STEP 2021	1.1 (0.1,3.9)	7.7
Random Effects Overall	**0.9 (0.5,1.7)**	100.0

Heterogeneity
χ²=16.67 (p=0.033),
I²=52.02%

Time to benefit in years

(B)

Study	TTB (95% CI)	Weight (%)
Coope 1986	3.0 (0.9,7.6)	11.1
SHEP 1991	1.5 (0.6,3.1)	13.6
STOP 1991	0.7 (0.2,1.8)	10.1
MRC-O 1992	3.9 (1.7,7.9)	14.0
Syst-Eur 1997	0.9 (0.4,1.8)	13.6
HYVET 2008	1.6 (0.4,4.1)	10.9
Wei 2013	0.8 (0.1,2.7)	7.1
SPRINT 2015	5.9 (2.2,13.0)	12.9
STEP 2021	4.5 (0.6,17.1)	6.8
Random Effects Overall	**1.7 (1.0,2.9)**	100.0

Heterogeneity
χ²=20.07 (p=0.010),
I²=60.14%

Time to benefit in years

(C)

Study	TTB (95% CI)	Weight (%)
Coope 1986	3.5 (1.4,7.6)	11.0
SHEP 1991	2.4 (1.2,4.1)	13.1
STOP 1991	1.0 (0.3,2.4)	10.2
MRC-O 1992	5.3 (2.8,9.2)	13.2
Syst-Eur 1997	2.0 (0.7,4.3)	10.4
HYVET 2008	2.5 (0.9,5.6)	10.3
Wei 2013	1.5 (0.2,4.6)	6.6
SPRINT 2015	7.8 (4.3,13.3)	13.4
STEP 2021	8.4 (3.8,16.5)	12.0
Random Effects Overall	**3.0 (1.8,4.9)**	100.0

Heterogeneity
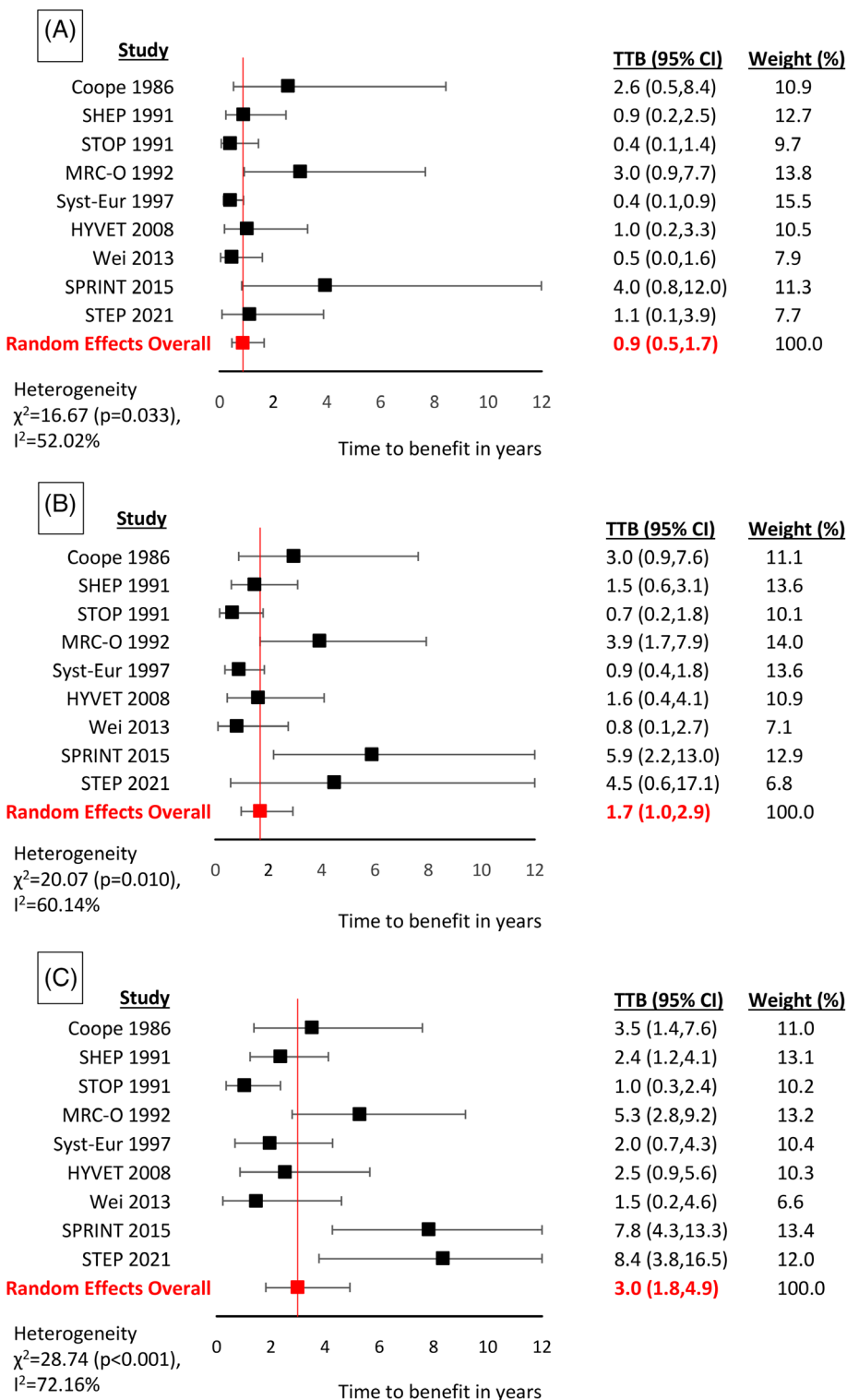χ²=28.74 (p<0.001),
I²=72.16%

Time to benefit in years

Figure 3C and Table S2). Similarly, 200 older adults would need to receive more intensive blood pressure treatment (ARR = 0.005; Figure 3B and Table S2) for 1.7 years (95%CI: 1.0–2.9) to prevent 1 stroke and 500 older adults would need more intensive blood pressure treatment (ARR = 0.002; Figure 3A and Table S2) for 0.9 years (95%CI: 0.5–1.7) to avoid 1 stroke.

We found evidence of substantial heterogeneity in TTB across studies (Figure 3 and Table S2). For example, while the pooled time to prevent 1 stroke per 200 persons treated (ARR = 0.005) was 1.7 years (95%CI: 1.0–2.9), the equivalent TTB for individual trials ranged from 0.7 years (95%CI: 0.2–1.8) in the STOP study to 5.9 years (95%CI: 2.2–13.0) in the SPRINT study. For all ARR thresholds, statistical tests

for heterogeneity indicated that the variability between individual studies was larger than would be expected by chance ($p = 0.02$ at ARR = 0.002; $p = 0.01$ at ARR = 0.005; $p < 0.001$ at ARR = 0.01). Furthermore, I^2 values ranged from 52% at ARR = 0.002 to 72.2% at ARR = 0.01, suggesting substantial statistical heterogeneity.[46]

Earlier trials with higher baseline blood pressures and higher stroke risk appeared to have shorter times to benefit than more recent trials with lower baseline blood pressures and lower stroke risk. For example, the time to prevent 1 stroke per 200 persons treated was 0.7 years (95%CI: 0.2–1.8) in the STOP study (published in 1991, baseline SBP of 195 mmHg and stroke risk of 6.5%). In contrast, the time to prevent 1 stroke per 200 persons treated was 5.9 years (95%CI: 2.2–13.0) in the SPRINT study (published in 2015, baseline SBP of 140 mmHg and stroke risk of 1.5%).

DISCUSSION

In this survival meta-analysis of 9 randomized trials of hypertension treatment in older adults, the TTB to prevent 1 stroke per 200 older adults treated with more intensive hypertension therapy was 1.7 years. Since the overwhelming majority of older adults have a life expectancy >1.7 years, our results suggest that almost all older adults with hypertension would benefit from treatment.

We found evidence of heterogeneity in TTB across studies, with most earlier trials focusing on older adults with higher baseline blood pressures and higher stroke risk showing a TTB <1.7 years (for ARR threshold of 0.005) and more recent studies focusing on older adults with lower baseline blood pressures and lower stroke risk showing TTB >1.7 years (for ARR threshold of 0.005). Given the clinical and statistical heterogeneity across studies, individual patients may be best served by focusing on TTB results from an individual study rather than focusing on our pooled TTB results. For example, for patients whose hypertension is already relatively well-controlled with SBP near 140 mmHg and are being considered for treatment intensification to a target SBP of 120 mmHg, the SPRINT TTB results are likely to be most relevant. For these patients, the TTB to avoid a stroke is more likely to range from 4.0 years (ARR of 0.002) to 7.8 years (ARR of 0.01) rather than our pooled TTB estimates (0.9 years for ARR = 0.002 to 3.0 years for ARR = 0.01). On the other hand, for patients whose hypertension is poorly controlled with an SBP over 190 mmHg, the STOP TTB results are likely to be more relevant, with TTB to avoid stroke ranging from 0.4 years (ARR of 0.002) to 1 year (ARR of 0.01). Thus, although our summary TTB results provide a global estimate for the primary prevention of stroke with antihypertensive treatment, individual patients will likely be better served by focusing on TTB results from individual studies with participants that most closely resemble the patient.

Potential harms of antihypertensive medications

The preponderance of evidence from observational studies, meta-analyses, and randomized trials suggests that more intensive hypertension treatment increases the risk for adverse events such as hypotension, syncope, and falls.[47] Leipzig and colleagues showed in a systematic review and meta-analysis published in 1999 that while diuretics were associated with an increased risk of falls, the association between falls and the use of other classes of antihypertensive medications did not reach statistical significance.[48] In a meta-analysis published in 2009, Woolcott and colleagues updated the Leipzig study and found that antihypertensive medications increased the risk of falls.[49] A recent meta-analysis of randomized trial data showed that while the more intensive blood pressure treatment did not increase the risk of falls, but did increase the risk of hypotension and syncope.[50] Taken together, these results suggest that more intensive blood pressure treatment can lead to hypotension, syncope, and falls.

Recent studies have suggested that the risk of falls and fractures is transiently increased shortly after initiation and intensification of blood pressure treatment. Butt and colleagues demonstrated that within 45 days of new initiation of antihypertensive medications, the risk of injurious falls requiring hospital care increased 69% and the risk of hip fracture increased 43%.[11,12] Shimbo and colleagues found that antihypertensive medication initiation and intensification was associated with an increased risk of serious fall injury for 15 days, with attenuated nonsignificant associations beyond 15 days.[13] Berry and colleagues showed that the risk of hip fracture increased two-fold in the first 14 days after initiation of diuretic antihypertensives.[14] These and other studies were summarized in a recent meta-analysis, which concluded that the risk of falls is highest immediately after antihypertensive medication intensification, with chronic use of antihypertensive medications not being associated with falls.[10] Thus, emerging evidence suggests that antihypertensive medication initiation and intensification may result in a short-term but transiently elevated risk of falls and fractures.

The findings from these observational studies are supported by the SPRINT study,[24] which found a borderline increase in the number of injurious falls (defined as life threatening or requiring an emergency room visit) in

the intensive versus standard treatment groups (HR = 2.22, p = 0.05). The study also showed that intensive treatment also led to increased hypotension (HR = 2.24, p < 0.001) and syncope (HR = 2.13, p = 0.005) compared to standard treatment. While SPRINT focused on older hypertensive patients without common diseases such as diabetes, stroke, and congestive heart failure, the rates of adverse effects are expected to be much higher in the relatively less healthy patient population that was excluded from the study. Consequently, these results highlight the importance of postural blood pressure measurements and the close monitoring of orthostatic symptoms during initiation or intensification of antihypertensive medications.

While hip fracture and injurious falls are clinically important harms, falls without injury can also lead to long-term harms. Falls and dizziness are potent risk factors for fear of falling,[51,52] which has been shown to be associated with restriction or avoidance of daily activities, loss of independence, reduction in social activity, depression, and a reduction in quality of life.[53,54] Thus, while noninjurious falls are clearly less immediately harmful than injurious falls or fractures, they are not benign and can lead to long-term adverse effects for older adults.

Individualizing hypertension treatment decisions

Our results can help inform and individualize hypertension treatment discussions. There is overwhelming evidence that improved blood pressure control can significantly reduce cardiovascular disease morbidity and mortality. For most older adults, the benefit of avoiding stroke and subsequent permanent disability is of paramount importance. Since these older adults place great value in avoiding stroke, they may focus on a relatively small ARR (i.e., ARR = 0.002) as clinically significant and choose to initiate or continue hypertension treatment as long as their life expectancy is >0.9 years. In contrast, other older adults with a preexisting fear of falling may feel that the risks of hypotension and falls are substantial. They may focus on larger ARRs for stroke (i.e., ARR = 0.01) instead, and choose to initiate or continue hypertension treatment as long as their life expectancy is >3.0 years. By presenting a spectrum of times to benefit across a range of ARRs, our study can inform treatment discussions for older adults prioritizing avoiding stroke as well as for older adults prioritizing avoiding hypotension and falls.

Hypertension treatment decisions need to be informed by benefits and harms beyond stroke prevention and falls. Hypertension treatment benefits beyond stroke include decreased all-cause mortality and decreased major adverse cardiovascular outcomes, including heart failure and myocardial infarction, and decreased incidence of cognitive impairment.[16,17,49,55] Hypertension treatment harms beyond hypotension, syncope, and falls include hyperkalemia and acute kidney injury,[49] which are usually reversible.[17] For older adults with substantial frailty or comorbidities, contextual factors such as polypharmacy may also be important considerations. Thus, individualized hypertension treatment decisions should account for the benefits beyond stroke prevention as well as for the risks beyond falls and fractures.

Heterogeneity

Heterogeneity was observed to increase with larger ARR thresholds and longer times to benefit. Specifically, at ARR of 0.002, I^2 = 52.0% (p = 0.034). The I^2 value increases to I^2 = 60.1% (p = 0.01) and I^2 = 72.2% (p < 0.001) at ARRs of 0.005 and 0.01, respectively. The I^2 statistic estimates the proportion of the variation in individual study results that are due to heterogeneity rather than chance[46] and an I^2 value of 50% to 90% is generally considered to suggest "moderate" to "substantial" heterogeneity.[56]

The observed statistical heterogeneity in our study results is likely due to important clinical differences between included studies (Table 2). For example, the SPRINT study[24] showed the longest times to benefit (Figure 3 and Table S2). These findings are likely due to its relatively modest efficacy (RR = 0.89) and low baseline risk of stroke (1.5%). SPRINT's modest RR and low baseline risk of stroke, and the subsequently long TTB, can be attributed to its focus on well-controlled hypertension (mean baseline SBP of 139.7 mmHg; target SBP <140 mmHg in standard treatment group versus <120 mmHg in intensive treatment group) and the active treatment of both intervention groups. The STEP study[25] also showed long times to benefit, most likely due to lower baseline SBP (146 mmHg) and lower baseline risk of stroke (1.7%). In general, more recent trials (such as the SPRINT and STEP trials) focused on older adults with lower baseline blood pressures and lower stroke risk, resulting in longer estimates for TTB thresholds.

In contrast to SPRINT and STEP, earlier trials focused on older adults with higher blood pressures and higher stroke risk, resulting in shorter estimates of TTB. For example, the STOP study[41] showed the shortest TTB. This result is most likely due to a combination of relatively high efficacy (RR = 0.55) and higher risk of stroke (6.5%) in participants with poorly controlled hypertension (mean baseline SBP of 195 mmHg). In general, earlier studies (such as STOP) focused on older adults with

higher blood pressures and higher stroke risk, resulting in shorter estimates of TTB.

Strength and limitations

A major strength of our study is that, to our knowledge, this is the first study to use quantitative methods to determine the TTB for the primary prevention of stroke with more intensive hypertension treatment in adults with a mean age ≥ 65 years. Thus, our study fills a critical gap, informing discussions between clinicians and patients about when the benefits of more intensive antihypertensive therapy are most likely.

One limitation is that, because SBP treatment targets have evolved over time, there is a substantial range in blood pressures in both the standard and intensive treatment arms across the included studies. Thus, there is clinical and methodologic heterogeneity that likely contributed to the observed statistical heterogeneity.[56] We utilized random-effects meta-analysis methods, which incorporate an assumption of underlying heterogeneity to more flexibly account for variable treatment effects across studies.[57] When we discovered evidence of heterogeneity, we followed recommended best practices to explore the potential causes of heterogeneity and found that baseline blood pressure and baseline stroke risk to be likely contributing factors to the observed heterogeneity. While heterogeneity is moderate to substantial, we believe the fundamental similarities in our included studies (comparison of stroke rates among patients randomized to standard versus intensive blood pressure treatment) allow for a meaningful pooled summary measure. However, as noted previously, evidence of heterogeneity suggests that for a given patient, TTB estimates from an individual study may be more relevant than our pooled TTB estimates.

A second potential limitation of our study is that only the SPRINT study provided age-stratified results, precluding the presentation of age-stratified meta-analyses. Thus, our study included participants as young as 50 years in SPRINT and as young as 60 years in 4 other included studies (Table 2). Since stroke risk increases almost exponentially with age, it is possible that our TTB to stroke reduction is an underestimate for the oldest patients. Since mean ages in our included studies ranged from 64 to 84 years, our TTB estimates are likely most relevant for older adults in this age range.

Finally, because all of our included studies focused on primary stroke prevention after the initiation or intensification of antihypertensive medications, it is unclear whether our results can be extrapolated to inform deprescribing decisions.

CONCLUSIONS

In this meta-analysis, we found that 200 adults aged ≥65 years would need to be treated for 1.7 years to avoid 1 stroke. Since the overwhelming majority of older adults have a life expectancy >1.7 years, these results suggest that almost all older adults with hypertension would benefit from treatment. We found substantial heterogeneity across studies suggesting that for older adults with poorly controlled hypertension (i.e., SBP >190 mmHg), the TTB to prevent 1 stroke for 200 persons treated is likely substantially shorter than 1.7 years. Conversely, for older adults with relatively well-controlled hypertension (i.e., SBP <150 mmHg), the TTB to prevent 1 stroke for 200 persons treated is likely substantially longer than 1.7 years.

CONFLICT OF INTEREST
The author declares that there is no conflict of interest.

AUTHOR CONTRIBUTIONS
All authors have read and approved the submission of this manuscript. Vanessa S. Ho and Sei J. Lee conceived the study and designed the protocol. Vanessa S. Ho performed the literature search, selected the studies, and extracted the survival data, which was reviewed by Sei J. Lee. Vanessa S. Ho, Irena S. Cenzer, Brian T. Nguyen, and Sei J. Lee synthesized the data. Vanessa S. Ho wrote the first draft of the article. All authors critically revised successive drafts of the article and approved the final version. Sei J. Lee obtained funding. Vanessa S. Ho and Sei J. Lee are the study co-guarantors. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Table S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Checklist and PRISMA 2020 for Abstracts Checklist.

Table S2. Time to Benefit for the Primary Prevention of Stroke for Older Adults Treated with More Intensive Hypertension Treatment.