Longer Term All-Cause and Cardiovascular Mortality With Intensive Blood Pressure Control

A Secondary Analysis of a Randomized Clinical Trial

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Disclosures

I have nothing to disclose.

TL;DR

- After SPRINT, from 2016-2020, the mean systolic blood pressure levels of participants returned to about 140 mm Hg, and the benefit of intensive blood pressure control attenuated.
- Additional follow-up from 2020-2023 provides an opportunity to think carefully about interventions that had a beneficial effect.
- Slides are available at https://www.byronjaeger.com/talk/ (google byron jaeger biostats talks)

Overview

- Background: SPRINT
- Why is longer term follow-up relevant?
- How did SPRINT do longer term follow-up on *all-cause and CVD mortality*?
- Results
- Conclusion

SPRINT

Two treatments with different systolic blood pressure (SBP) targets:

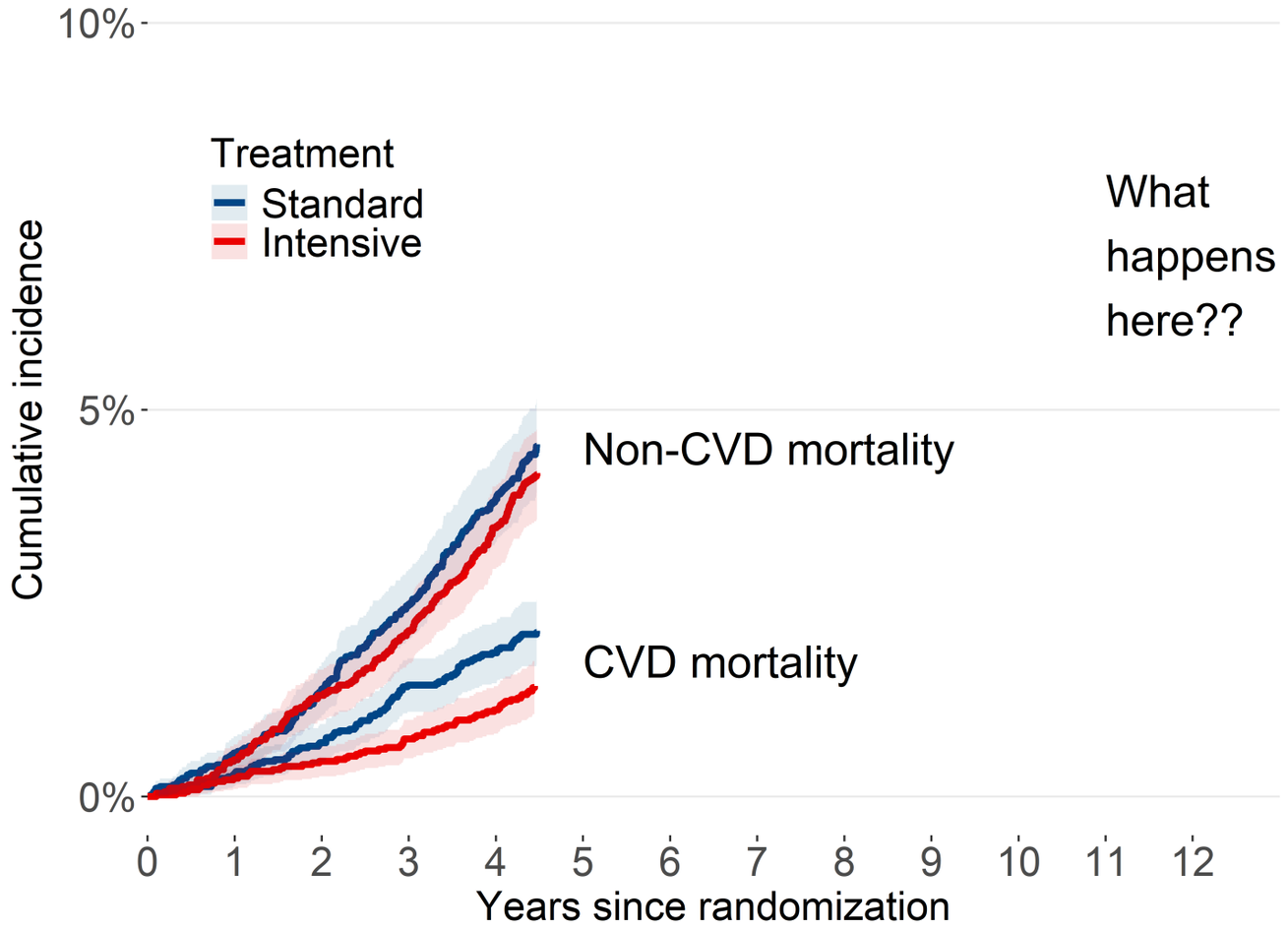
- *Standard*: SBP target of < 140 mm Hg
- *Intensive*: SBP target of < 120 mm Hg

Participants:

- aged 50 years or older
- with hypertension and increased cardiovascular risk
- without diabetes or history of stroke

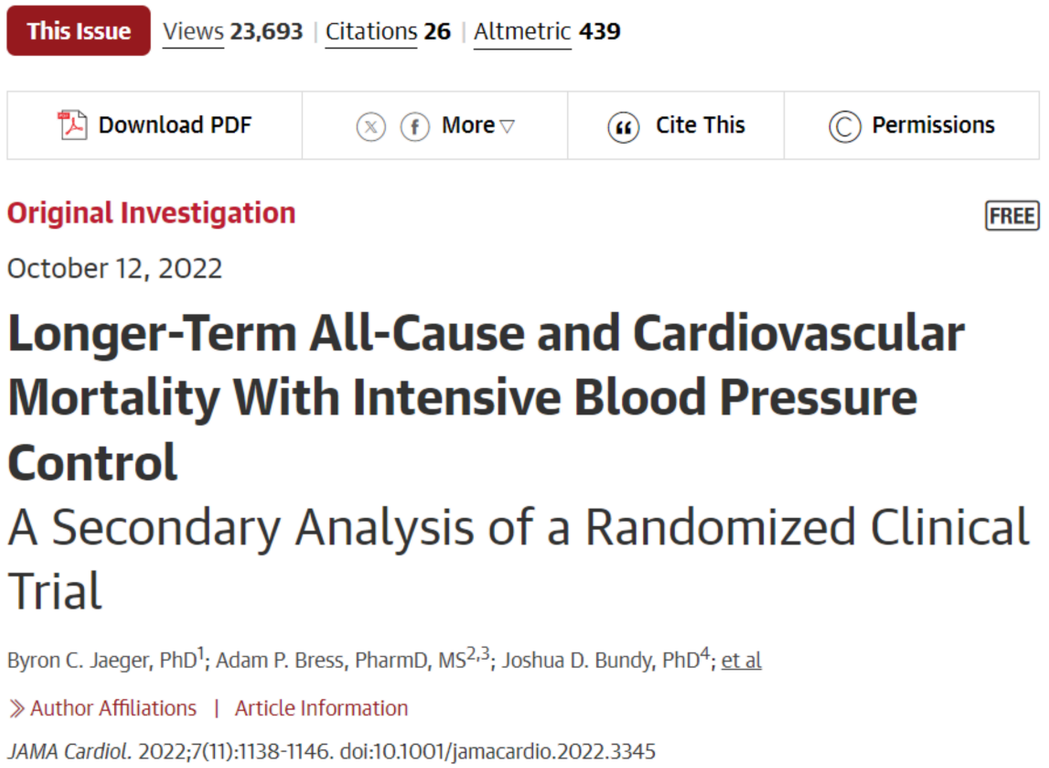
Why do longer term follow-up?

- Investigate the legacy effect of intensive treatment
- Does targeting SBP < 120 mm Hg have long term benefits or harms compared to targeting SBP < 140 mm Hg?



Longer term all-cause/CVD mortality

- We assessed all-cause[1] and cardiovascular disease[2] (CVD) mortality post-trial via the US National Death Index (NDI) from 2016-2020 (Jaeger et al. 2022).
- Among 2944 trial participants,[3] post-trial SBP levels were analyzed (Drawz et al. 2020).



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Results

Number of events

2016-2020

- 1644 all-cause mortality events
- 521 CVD mortality events

2016-2023

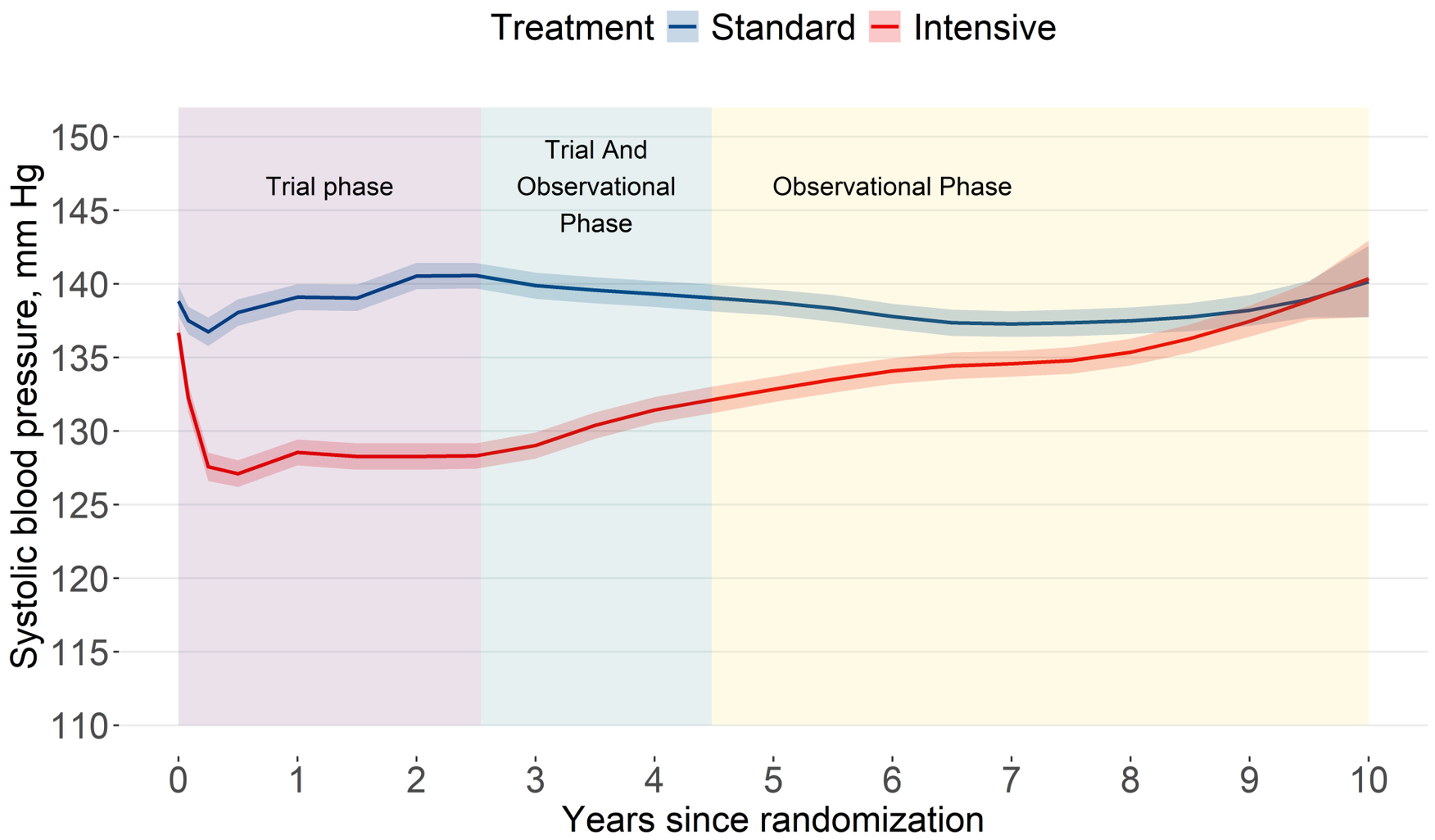
- 2597 all-cause mortality events
- 907 CVD mortality events

Difference:

- 953 additional all-cause mortality events
- 386 additional CVD mortality events
- No additional analyses on BP

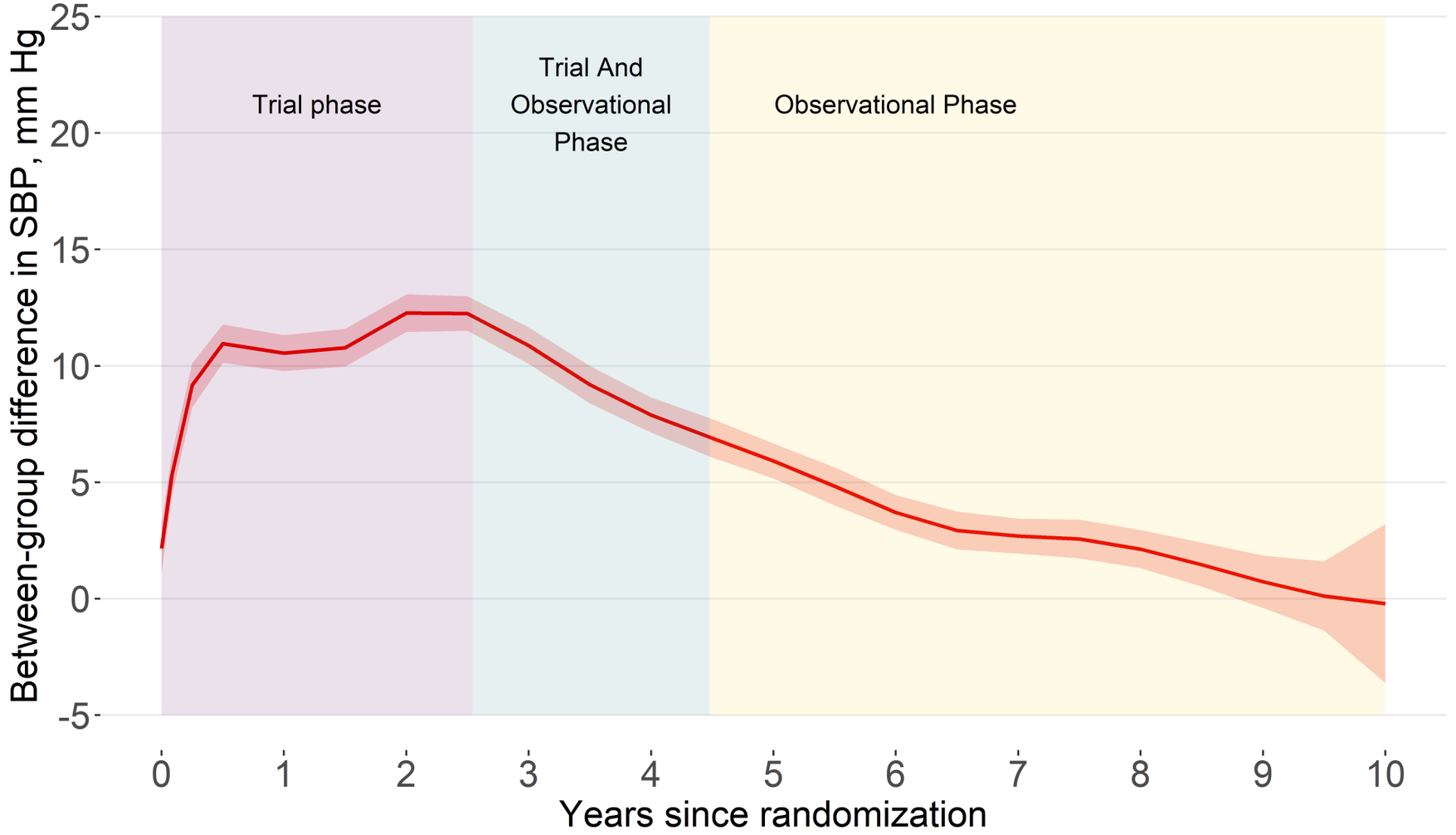
Systolic BP levels

SBP levels among the intensive group increased after the trial.



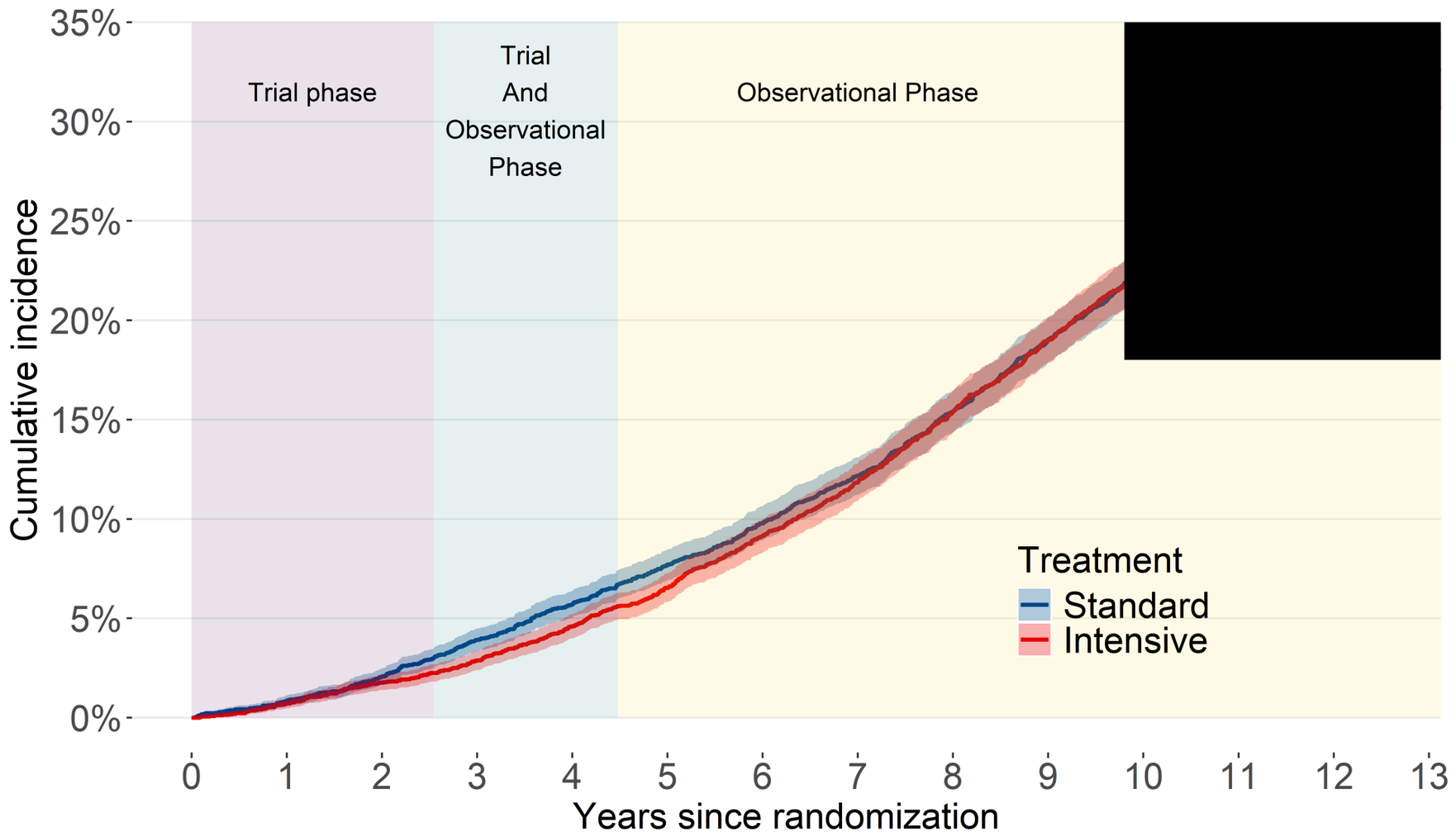
Systolic BP difference

By year 10, the estimated difference was about 0



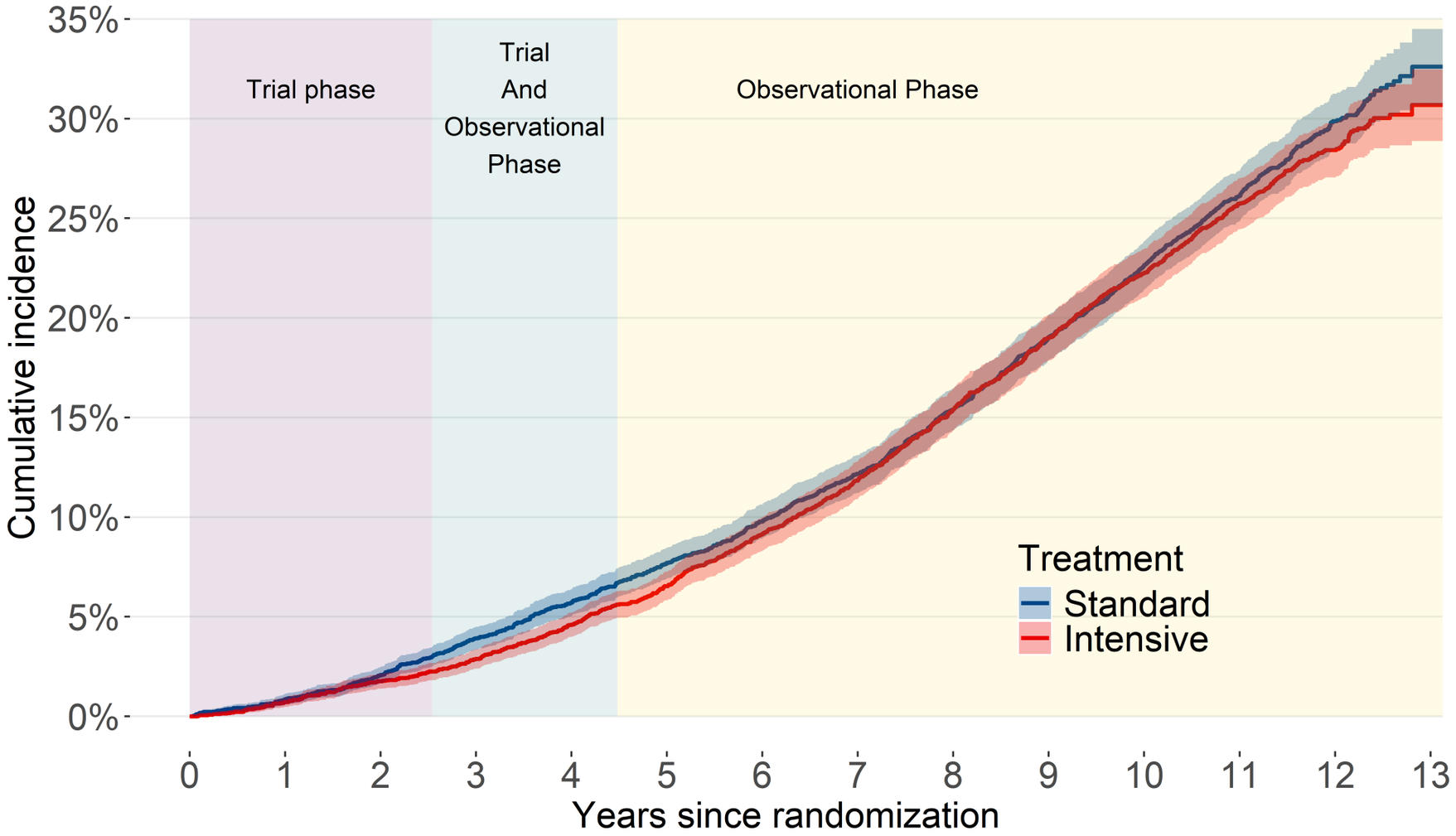
All-cause mortality (2016-2020)

Our original analysis showed the benefit for all-cause mortality attenuated quickly



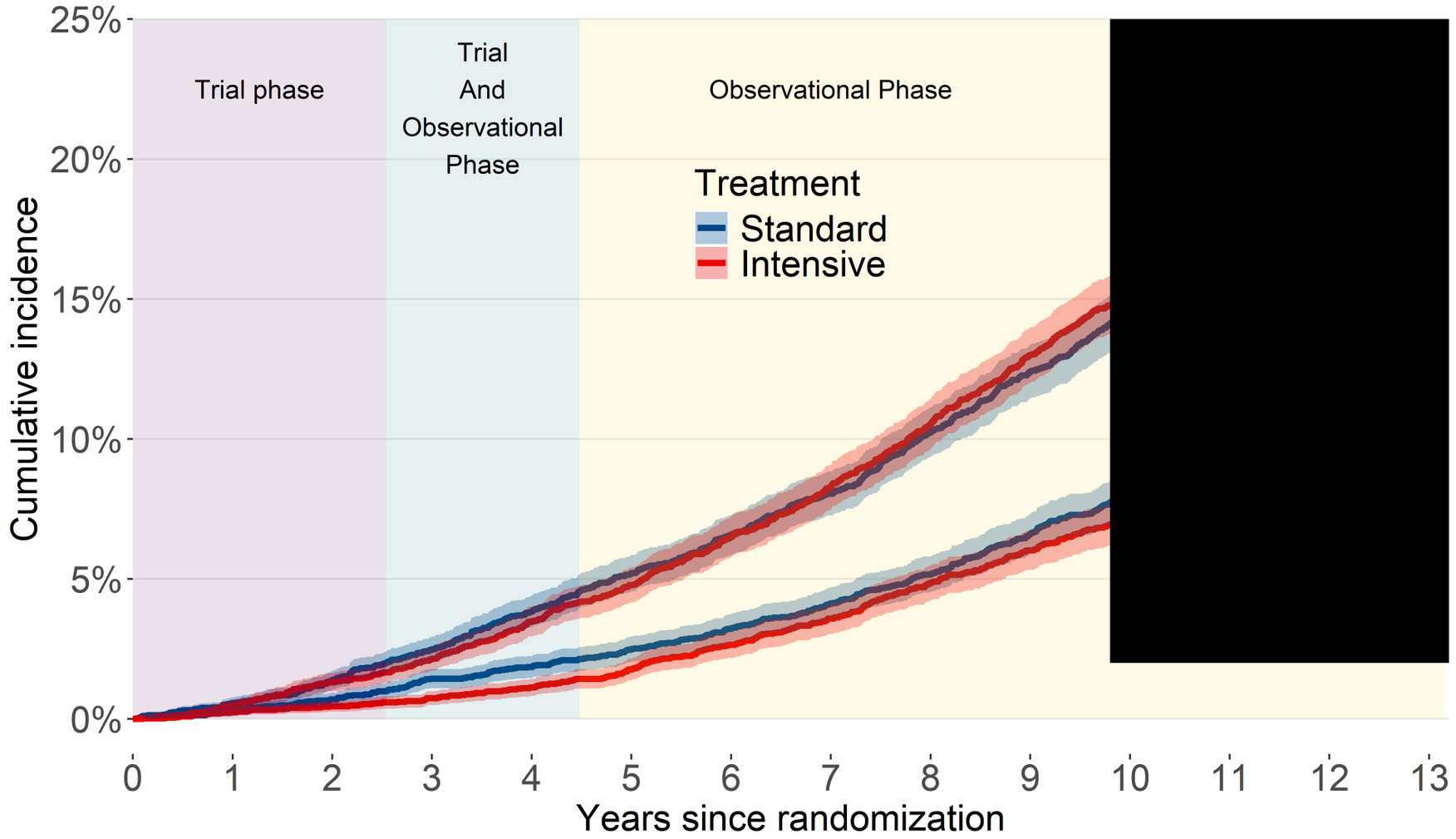
All-cause mortality (2016-2023)

This update shows an unexpected separation after several years of overlap



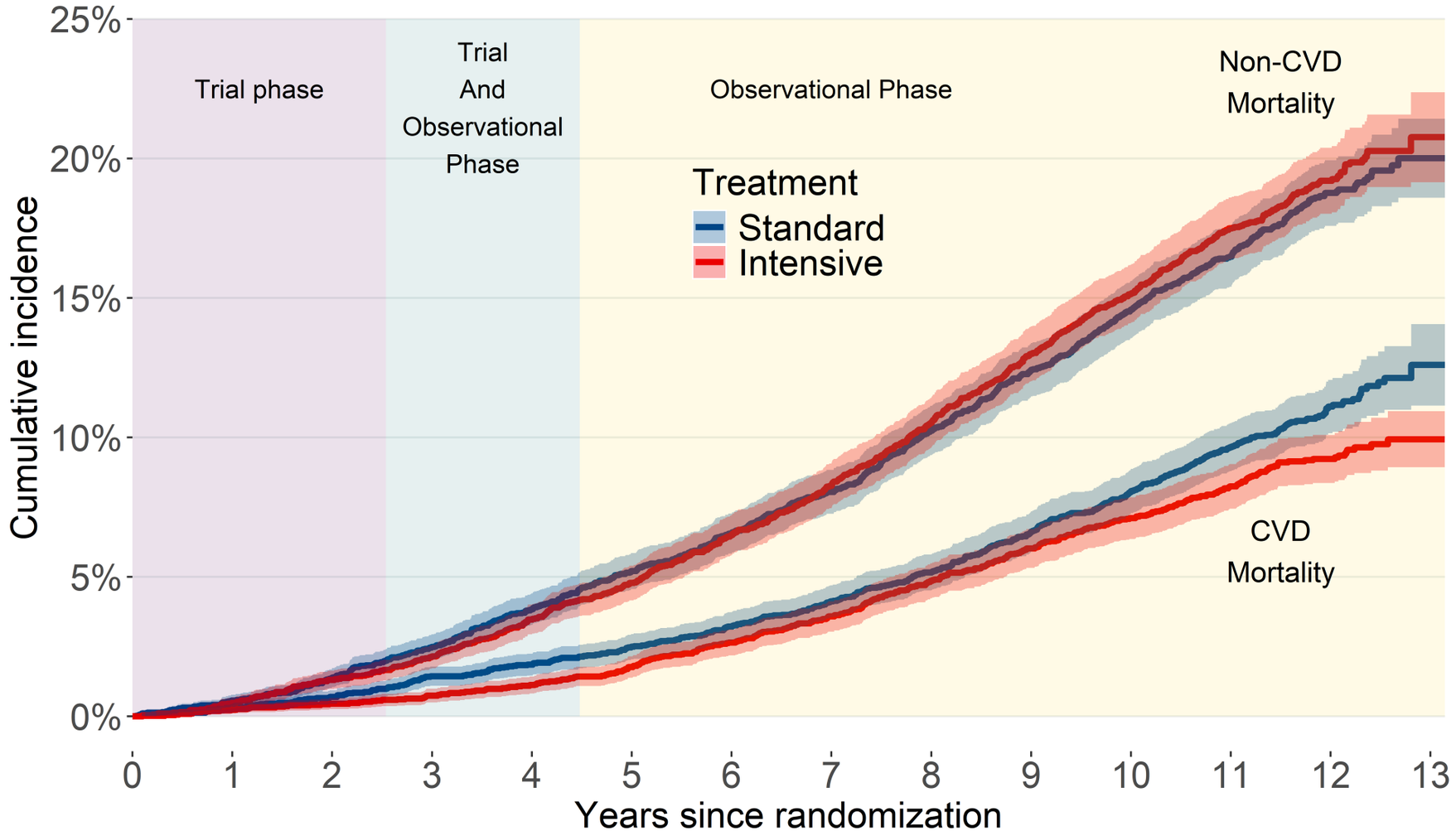
CVD mortality (2016-2020)

Our original analysis showed benefit for CVD mortality attenuated.



CVD mortality (2016-2023)

A bit of a head-scratcher.



Conclusion

- After SPRINT, from 2016-2020, SBP returned to about 140 mm Hg, and the benefit of intensive blood pressure control attenuated.
- The latest update shows what appears to be a resurfaced benefit in terms of CVD mortality. This could be attributed to:
  - participants in the intensive blood pressure control group who maintained control after the trial
  - intensive blood pressure control has higher estimated benefit for younger adults.

References

Drawz, Paul E., Anil Agarwal, Jamie P. Dwyer, Edward Horwitz, James Lash, Kristin Lenoir, Andrew McWilliams, et al. 2020. “Concordance Between Blood Pressure in the Systolic Blood Pressure Intervention Trial and in Routine Clinical Practice.” *JAMA Internal Medicine* 180 (12): 1655–63. https://doi.org/10.1001/jamainternmed.2020.5028.

Jaeger, Byron C, Adam P Bress, Joshua D Bundy, Alfred K Cheung, William C Cushman, Paul E Drawz, Karen C Johnson, et al. 2022. “Longer-Term All-Cause and Cardiovascular Mortality with Intensive Blood Pressure Control: A Secondary Analysis of a Randomized Clinical Trial.” *JAMA Cardiology* 7 (11): 1138–46.

BONUS ROUND

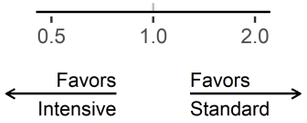
How did we analyze longer term follow-up?

- assumed treatment group differences would not be constant over time.
- split each participant's follow-up time into non-overlapping trial and observational phases
- estimated regression coefficients for intensive treatment separately during each phase.

All-cause mortalty (time-split analysis)

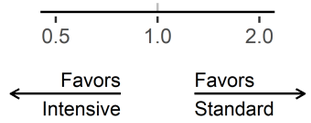
Trial phase

Characteristic	Intensive	Standard	Hazard ratio (95% CI)	P value
	no. of all-cause deaths / no. at risk (%)			
Overall	241/4,678 (5.15)	290/4,682 (6.19)	0.83 (0.68, 1.01)	
Age group				0.88
<75 years	115/3,361 (3.42)	137/3,364 (4.07)	0.84 (0.63, 1.11)	
≥75 years	126/1,317 (9.57)	153/1,318 (11.6)	0.82 (0.62, 1.07)	
Sex				0.60
Male	170/2,994 (5.68)	212/3,035 (6.99)	0.80 (0.64, 1.01)	
Female	71/1,684 (4.22)	78/1,647 (4.74)	0.89 (0.61, 1.28)	
Race				0.69
Non-Black	173/3,224 (5.37)	209/3,189 (6.55)	0.80 (0.64, 1.01)	
Black	68/1,454 (4.68)	81/1,493 (5.43)	0.85 (0.59, 1.24)	
Chronic Kidney Disease				0.47
No	126/3,485 (3.62)	163/3,491 (4.67)	0.77 (0.59, 1.01)	
Yes	112/1,170 (9.57)	125/1,160 (10.8)	0.89 (0.66, 1.19)	
Cognitive Function				0.02
>10th percentile	152/3,389 (4.49)	212/3,396 (6.24)	0.70 (0.55, 0.89)	
≤10th percentile	83/1,257 (6.60)	77/1,253 (6.15)	1.13 (0.79, 1.62)	
Frailty Status				0.64
Fit	18/751 (2.40)	21/728 (2.88)	0.90 (0.43, 1.87)	
Pre-frail	93/2,359 (3.94)	107/2,406 (4.45)	0.90 (0.66, 1.24)	
Frail	127/1,538 (8.26)	161/1,523 (10.6)	0.75 (0.57, 0.98)	



Observational phase

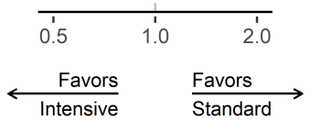
Characteristic	Intensive	Standard	Hazard ratio (95% CI)	P value
	no. of all-cause deaths / no. at risk (%)			
Overall	1,029/4,274 (24.1)	1,036/4,259 (24.3)	1.00 (0.90, 1.10)	
Age group				0.01
<75 years	472/3,123 (15.1)	521/3,129 (16.7)	0.90 (0.78, 1.04)	
≥75 years	557/1,151 (48.4)	515/1,130 (45.6)	1.13 (0.98, 1.30)	
Sex				0.37
Male	711/2,745 (25.9)	706/2,743 (25.7)	1.02 (0.91, 1.15)	
Female	318/1,529 (20.8)	330/1,516 (21.8)	0.94 (0.78, 1.12)	
Race				0.60
Non-Black	770/2,953 (26.1)	759/2,896 (26.2)	1.01 (0.90, 1.13)	
Black	259/1,321 (19.6)	277/1,363 (20.3)	0.95 (0.78, 1.15)	
Chronic Kidney Disease				0.89
No	644/3,250 (19.8)	641/3,232 (19.8)	0.98 (0.87, 1.11)	
Yes	381/1,012 (37.6)	392/1,006 (39.0)	0.97 (0.82, 1.15)	
Cognitive Function				0.11
>10th percentile	740/3,125 (23.7)	707/3,100 (22.8)	1.05 (0.93, 1.18)	
≤10th percentile	283/1,131 (25.0)	324/1,135 (28.5)	0.89 (0.74, 1.08)	
Frailty Status				0.46
Fit	82/715 (11.5)	92/684 (13.5)	0.86 (0.61, 1.22)	
Pre-frail	477/2,193 (21.8)	501/2,244 (22.3)	0.99 (0.86, 1.14)	
Frail	469/1,349 (34.8)	439/1,317 (33.3)	1.03 (0.89, 1.20)	



CVD mortalty (time-split analysis)

Trial phase

Characteristic	Intensive	Standard	Hazard ratio (95% CI)	P value
	no. of CVD deaths / no. at risk (%)			
Overall	65/4,678 (1.39)	92/4,682 (1.96)	0.65 (0.48, 0.88)	
Age group				0.37
<75 years	27/3,361 (0.80)	45/3,364 (1.34)	0.53 (0.36, 0.79)	
≥75 years	38/1,317 (2.89)	47/1,318 (3.57)	0.78 (0.49, 1.26)	
Sex				0.44
Male	47/2,994 (1.57)	68/3,035 (2.24)	0.61 (0.42, 0.90)	
Female	18/1,684 (1.07)	24/1,647 (1.46)	0.75 (0.45, 1.26)	
Race				0.23
Non-Black	44/3,224 (1.36)	67/3,189 (2.10)	0.58 (0.42, 0.81)	
Black	21/1,454 (1.44)	25/1,493 (1.67)	0.82 (0.46, 1.45)	
Chronic Kidney Disease				0.29
No	29/3,485 (0.83)	50/3,491 (1.43)	0.55 (0.36, 0.83)	
Yes	36/1,170 (3.08)	41/1,160 (3.53)	0.81 (0.50, 1.31)	
Cognitive Function				0.50
>10th percentile	40/3,389 (1.18)	62/3,396 (1.83)	0.56 (0.36, 0.88)	
≤10th percentile	23/1,257 (1.83)	29/1,253 (2.31)	0.76 (0.41, 1.43)	
Frailty Status				0.33
Fit	1/751 (0.13)	7/728 (0.96)	0.14 (0.02, 1.12)	
Pre-frail	23/2,359 (0.97)	34/2,406 (1.41)	0.59 (0.34, 1.03)	
Frail	41/1,538 (2.67)	51/1,523 (3.35)	0.77 (0.53, 1.13)	



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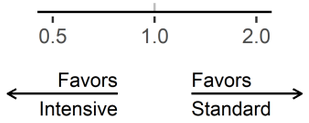
Characteristic	Intensive	Standard	Hazard ratio (95% CI)	P value
	no. of CVD deaths / no. at risk (%)			
Overall	349/4,274 (8.17)	401/4,259 (9.42)	0.92 (0.81, 1.05)	
Age group				0.29
<75 years	145/3,123 (4.64)	198/3,129 (6.33)	0.83 (0.67, 1.02)	
≥75 years	204/1,151 (17.7)	203/1,130 (18.0)	1.00 (0.81, 1.22)	
Sex				0.62
Male	247/2,745 (9.00)	286/2,743 (10.4)	0.95 (0.81, 1.11)	
Female	102/1,529 (6.67)	115/1,516 (7.59)	0.87 (0.66, 1.15)	
Race				0.37
Non-Black	266/2,953 (9.01)	290/2,896 (10.0)	0.96 (0.82, 1.13)	
Black	83/1,321 (6.28)	111/1,363 (8.14)	0.82 (0.60, 1.11)	
Chronic Kidney Disease				0.25
No	212/3,250 (6.52)	229/3,232 (7.09)	0.98 (0.81, 1.20)	
Yes	136/1,012 (13.4)	170/1,006 (16.9)	0.84 (0.69, 1.02)	
Cognitive Function				0.96
>10th percentile	252/3,125 (8.06)	282/3,100 (9.10)	0.92 (0.79, 1.07)	
≤10th percentile	94/1,131 (8.31)	117/1,135 (10.3)	0.92 (0.72, 1.17)	
Frailty Status				0.32
Fit	20/715 (2.80)	31/684 (4.53)	0.61 (0.35, 1.05)	
Pre-frail	159/2,193 (7.25)	185/2,244 (8.24)	0.96 (0.75, 1.22)	
Frail	170/1,349 (12.6)	183/1,317 (13.9)	0.94 (0.77, 1.15)	



Footnotes

1.

Deaths were treated as confirmed if they were a Class 1 match, or a Class 2, 3, or 4 match with a probabilistic score above cutoffs recommended by the NDI.

2.

Cardiovascular mortality for NDI-based follow-up used the NDI Plus System, which automatically identifies underlying causes of death from death certificates, including conversion to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes. We defined CVD mortality as any death containing the ICD-10 codes of I00 to I99

3.

We identified 3074 participants with 3 or more electronic health record reports of outpatient blood pressure measurements during the trial. After excluding 130 participants without electronic health record data following July 2016 (ie, conclusion of the trial), a total of 2944 patients were included for the ancillary blood pressure analysis.