PERSONALIZING THE INTENSITY OF BLOOD PRESSURE CONTROL: Modeling the Heterogeneity of Risks and Benefits from the SPRINT Trial

Saint Luke's MID AMERICA HEART INSTITUTE

Krishna K. Patel, MD[1,2]; Suzanne V. Arnold, MD, MHA[1,2]; Paul S. Chan, MD, MSc[1,2]; Yuanyuan Tang, PhD[1]; Yashashwi Pokharel, MD, MSCR[1,2]; Philip G. Jones, MS[1]; John A. Spertus, MD, MPH[1,2]

[1]Saint Luke's Mid America Heart Institute, [2]University of Missouri–Kansas City, Kansas City, MO

UMKC School of Medicine

BACKGROUND

- In SPRINT (Systolic blood PRessure INtervention Trial), patients with hypertension and high cardiovascular risk treated with intensive blood pressure (BP) control (< 120mmHg) had fewer major adverse cardiovascular events (MACE) and deaths, but higher rates of treatment-related serious adverse events (SAE), than patients randomized to standard BP control (<140mmHg).
- However, the degree of benefit or harm for an individual patient likely varies due to heterogeneity in treatment effect.

METHODS

- Using patient-level data from 9361 randomized patients in SPRINT, with median follow-up of 3.3 years, we developed models to predict risk for
  - MACE or death (MI, non-MI ACS, stroke, ADHF, all-cause death)
  - Treatment-related SAE (hypotension, syncope, injurious falls, AKI, electrolyte abnormalities, others)
- Models developed using logistic regression
  - Candidate variables selected a priori
  - Interaction terms between treatment and all candidate variables were added to assess heterogeneity
  - Model reduction with Harrell's backward selection strategy
- Distribution of predicted absolute risks of both outcomes between the 2 treatment strategies (difference in predicted absolute risks of MACE or death and treatment-related SAE, respectively, for each SPRINT patient if treated with intensive and standard BP control) were plotted with histograms.
- Validation
  - Internal with Bootstrap resampling
  - External in ACCORD trial (4741 Diabetics with hypertension- mean follow-up of 4.7 years)

RESULTS

- 755 (8.1%) patients had a MACE or death event.
- 338 (3.6%) had a treatment-related SAE.
- The MACE/death model included treatment interactions with age, baseline SBP and DBP and the SAE model included treatment interaction with baseline number of BP medications.

RESULTS

Table 1: Patient Characteristics

	MACE/Death			Rx Related SAE		
	Yes N = 755 (8.1%)	No N= 8606	p-value	Yes N=338 (3.6%)	No N=9023	p-value
Age	71.9 ± 10.0	67.6 ± 9.3	< 0.001	71.5 ± 9.6	67.8 ± 9.4	< 0.001
Male gender	70.5%	63.9%	< 0.001	62.4%	64.5%	0.438
Black race	26.6%	31.9%	0.002	32.0%	31.5%	0.849
Systolic BP	141.3 ± 16.4	139.5 ± 15.5	0.002	141.1 ± 16.2	139.6 ± 15.6	0.078
Diastolic BP	75.9 ± 12.9	78.3 ± 11.8	< 0.001	76.0 ± 12.2	78.2 ± 11.9	< 0.001
Current smoker	17.6%	12.9%	< 0.001	15.7%	13.2%	0.185
S. Creatinine	1.2 ± 0.5	1.1 ± 0.3	< 0.001	1.2 ± 0.4	1.1 ± 0.3	< 0.001
Clinical CVD	32.3%	15.3%	< 0.001	22.8%	16.5%	0.002
Subclinical CVD	7.3%	5.1%	0.009	7.7%	5.2%	0.041
T. Cholesterol	185.6 ± 43.0	190.5 ± 41.0	0.001	187.0 ± 43.5	190.2 ± 41.1	0.151
HDL-Cholesterol	51.5 ± 14.7	53.0 ± 14.4	0.006	55.5 ± 16.0	52.8 ± 14.4	< 0.001
No. of HTN agents	2.0 ± 1.1	1.8 ± 1.0	< 0.001	2.2 ± 1.0	1.8 ± 1.0	< 0.001

Figure 1: MACE or Death Model

c-statistic= 0.72; Optimism corrected c-statistic= 0.72

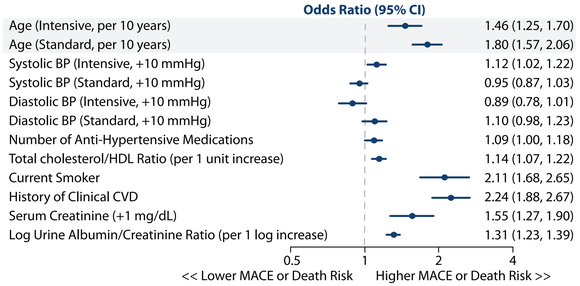
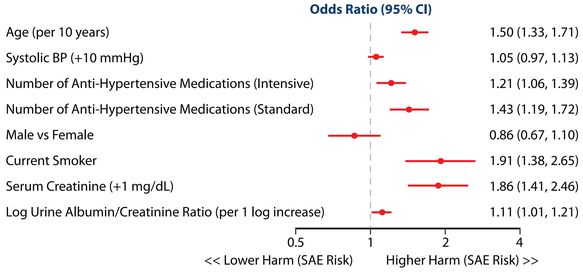


Figure 2: Treatment-related SAE Model

c-statistic= 0.70; Optimism corrected c-statistic= 0.70



RESULTS

Figure 3: Validation in ACCORD

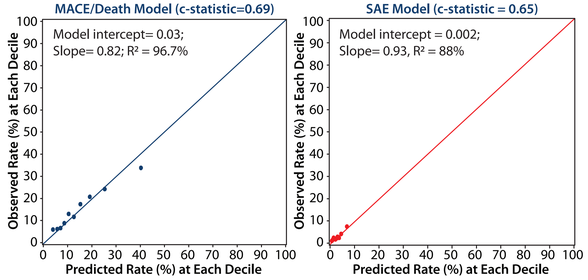


Figure 4: Distribution of Predicted Absolute Risk Difference between Treatment with Intensive & Standard BP Control in SPRINT Trial

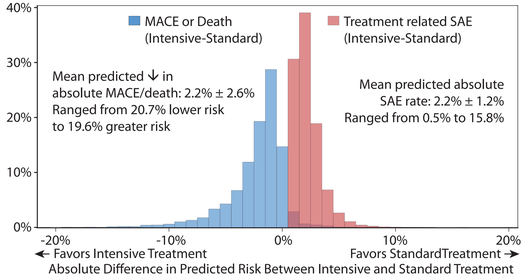
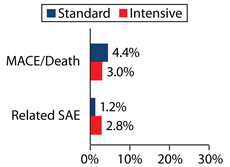


Figure 5: Potential Model Output at Point of Care Using these Risk Prediction Models

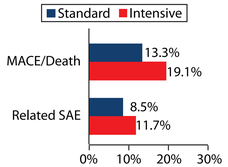
Case 1

- 68 YO M; 150/90 mmHg
- Amlodipine
- Non-smoker, No CVD,
- TC: 180 mg/dL, HDL-C: 50mg/dL,
- Cr: 1.0 mg/dL; urine Alb/Cr: 5 mg/g



Case 2

- 50 YO F; 170/85 mmHg
- Amlodipine, metoprolol, HCTZ, lisinopril
- Current smoker
- TC: 200 mg/dL, HDL-C: 35 mg/dL
- Cr: 1.8 mg/dL; urine Alb/Cr: 100 mg/g



LIMITATIONS

- Inability to consider potentially related but unmeasured/unavailable factors.
- Patients enrolled in clinical trials are generally healthier, more compliant with treatments, and better monitored for safety than patients in the real world.
- While we did find evidence of some treatment interactions suggesting heterogeneity in treatment effect, there might be other interactions which we did not have the power to detect.

CONCLUSION

- These models enable the results of a landmark clinical trial to be used in routine patient care to tailor the treatment approach.
- Comparable performance of our models in a cohort of patients with vastly different baseline characteristics strongly supports their external generalizability.
- Further studies are needed to understand the clinical impact of using these models in care and to define performance in other populations including low-risk, younger patients with HTN.

CITATION

- Patel KK, Arnold SV, Chan PS, Tang Y, Pokharel Y, Jones PG, Spertus JA. Personalizing the Intensity of Blood Pressure Control: Modeling the Heterogeneity of Risks and Benefits From SPRINT (Systolic Blood Pressure Intervention Trial). Circ Cardiovasc Qual Outcomes. 2017 Apr;10(4). pii: e003624. doi: 10.1161/ CIRCOUTCOMES. 117.003624. PMID: 28373269

DISCLOSURES

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- The other authors report no conflicts.