Appendix 1: Study plan (12/7/16) [posted as supplied by author]

Background. Millions of Americans take multiple antihypertensive drugs to control their blood pressure and reduce risk. Although the addition of a new drug is done routinely in clinical practice, its incremental benefits and risks are unknown. It has been presumed that the addition of a new drug typically leads to less improvements in blood pressure but increase the risks of side effects due to potential drug-drug interactions. There is limited empirical evidence to support these ideas.
The SPRINT trial presents a unique opportunity to study this question. The purpose of the trial was to compare intensive therapy for blood pressure with conservative therapy. Although the overall trial showed a benefit in regards to lower adverse cardiac events and mortality, concerns were raised given a higher risk of side effects. For a clinical provider it would be very useful to know how these benefits and risks varied as the number of antihypertensive drugs increased in use.
Accordingly, we will use the design of the SPRINT trial to answer the important question of how the marginal benefits and risks varied when adding a second, third, or fourth or more drug onto a patient's regimen. We will evaluate changes in cardiovascular events, adverse events, and blood pressure. We will leverage the study design of the SPRINT trial to create an instrument by which randomization to intensive therapy would increase the likelihood the addition of a new drug and then measured its marginal effects.

Objective. To assess the incremental effects of adding antihypertensive drugs while accounting for confounding.

Data. We will perform a secondary data analysis of data collected from the Systolic Blood Pressure Intervention Trial (SPRINT; n=9361)

Study population. SPRINT inclusion/exclusion criteria:

- Age ≥ 50
- Systolic blood pressure between 130 mm Hg and 180 mm Hg
- No history of diabetes or stroke
- 1+ cardiovascular risk factor: cardiovascular disease (other than stroke or chronic kidney disease); FRS ≥ 15%; age ≥ 75.

Participants. 9,092 SPRINT participants with hypertension and increased cardiovascular risk but no history of diabetes or stroke.

Outcomes. Our main study outcomes are composite major cardiovascular events and composite serious adverse events. Our secondary outcome is systolic blood pressure. Major cardiovascular events are defined in SPRINT as any occurrence of the following: myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or death from cardiovascular causes. Serious adverse events are defined in SPRINT as any occurrence of the following: emergency department evaluations for hypotension, syncope,

bradycardia, electrolyte imbalance, injurious fall, or hospitalizations for acute kidney injury or acute renal failure. Blood pressure is defined as the final measurement of SPRINT.

Exposure. Our exposure is patients' average number of antihypertensive medications over the study period.

Statistical analysis. To account for confounding by indication, we will perform an instrumental variable analysis to assess the incremental ("marginal") effect of adding an additional antihypertensive medication on cardiovascular events and adverse events. Specifically, we will instrument for patients' mean exposure to antihypertensive medications over the study period by whether they were randomized to the intensive or standard group. We will then stratify by the number of antihypertensive medications at baseline to assess whether the marginal effect of antihypertensive medications varies by whether it was the first, second, third, or fourth or more medication added to a patient's regimen.

We will estimate effects on cardiovascular and adverse events using Aalen additive hazard models to account for the right-censored nature of clinical events. We will estimate effects on blood pressure using two-stage least squares models. We will compare results from instrumental variable analyses to results from multivariable regression models that do not account for endogeneity.

We will perform several sensitivity analyses to assess whether the three conditions for instrument validity are met.

> Condition #1: Random assignment. We will assess covariate balance across the intensive (target < 120 mm Hg) versus standard (target < 140 mm Hg) groups.
>
> Condition #2: Instrument strength. We will assess the correlation between the instrument (randomization status) and the endogenous treatment (mean number of drugs over the study period).
>
> Condition #3: Exclusion restriction. We will assess whether randomization to the intensive vs. standard group affects patient outcomes through mechanisms other than antihypertensive regimen changes. These include nonpharmacologic interventions (more behavioral counseling to intensive patients, resulting in greater changes in exercise, diet, alcohol consumption, smoking, etc.) and pharmacologic interventions (increased adherence, increases dosages, substitution for more powerful classes/agents, etc.). We will examine test for differences in the following outcomes across intensive vs. standard groups: (A) differential nonpharmacologic interventions: decreasing smoking status; altered lipid profile; decreased weight; and (B) differential pharmacologic interventions: increased dosages; altered classes, improved adherence (described by the Adherence Scale).

Results.

Table A. Baseline characteristics of the SPRINT study participants

		By number of antihypertensive drugs at baseline				
Characteristics	Total	0	1	2	3	4+
n						
Age > 75						
Female						
Black						
BMI > 35						
Smoking status						
Framingham 10-yr cardiovascular disease risk score						
Previous cardiovascular disease						
Previous CKD						
Blood pressure						

Figure A. Incremental effect on major cardiovascular events

Forest plot consisting of the following:

- Models not adjusted for confounding
  - Overall effect
  - 0 drugs at baseline
  - 1 drug at baseline
  - 2 drugs at baseline
  - 3 drugs at baseline
  - 4+ drugs at baseline
- Instrumental variable models
  - Overall effect
  - 0 drugs at baseline
  - 1 drug at baseline
  - 2 drugs at baseline
  - 3 drugs at baseline
  - 4+ drugs at baseline

Figure B. Incremental effect on serious adverse events: (same as Figure A)

Figure C. Incremental effect on systolic blood pressure: (same as Figure A)

Table B. Subgroup analysis of incremental effects on major cardiovascular events, serious adverse events, and systolic blood pressure

Subgroup	Major cardiovascular events	Serious adverse events	Systolic blood pressure
Models not adjusted for confounding			
Age			
< 75 yr			
≥ 75 yr			
Sex			
Female			
Male			
Race			
Black			
Nonblack			
BMI			
BMI < 35			
BMI ≥ 35			
Framingham risk score			
FRS < ?			
FRS ≥ ?			
Previous CVD			
Yes			
No			
Previous CKD			
Yes			
No			
Instrumental variable analysis			
(Repeat as above)			

Major revisions to the original study plan

Exposure.

Due to data limitations, we evaluated changes in the number of antihypertensive drug classes instead of number of antihypertensive drug agents. Although the SPRINT team did collect data on number of antihypertensive drug agents, drug class, and drug dosage, these data were not available to outside researchers at the time of our analysis. As a result, we used number of drug classes both as our main exposure and when stratifying by number of drug (classes) at baseline. When stratifying by number of drug classes at baseline, we pooled patients who used four (rather than five) or more drug classes at baseline to improve the precision of our estimates. Additionally, for our main exposure we selected the number of drug classes at the study's end, rather than the mean number of drug classes over the study period.

Primary outcomes.

We included systolic blood pressure as a primary outcome in addition to major cardiovascular events and major serious adverse events. Additionally, we shifted toward using blood pressure instead of clinical events for our subgroup and sensitivity analyses. When creating our research plan, we were uncertain about the number of clinical events that occurred in SPRINT. Upon receiving the data we became aware that these events were sporadic enough that we were not powered to stratify simultaneously by number of drugs at baseline and other covariates (e.g., gender, race). As a result, we performed the majority of our secondary analyses using systolic blood pressure, an important surrogate outcome.

Sensitivity analyses.

We were unable to perform several of our planned sensitivity analyses due to data limitations. Specifically, we were unable to verify whether randomization status was associated with changes to smoking status, weight, lipid profiles (i.e., nonpharmacologic interventions) or changes to antihypertensive drug adherence, dosage, or specific classes (i.e., pharmacologic interventions other than number of antihypertensive drug classes). In light of these data limitations, we assessed for differential exposure to nonpharmacologic interventions by assessing whether incremental effects in our main analysis were similar to those assessed: (1) at times we considered too early to be driven by behavioral changes (i.e., 3-month visit); (2) among patients we considered unlikely to be targeted for nonpharmacologic interventions (i.e., patients who were not obese at baseline, patients who did not smoke at baseline).