Appendix 3: Methods [posted as supplied by author]

Estimating differences in incremental effects on systolic blood pressure across baseline drug use and patient subgroups. For standard multivariable adjusted models, we implemented interaction models to formally test whether incremental effects of antihypertensive drugs varied systematically across baseline number of drug classes. Specifically, we included an interaction between the baseline number and final number of antihypertensive drug classes. We did not estimate similar interaction models for instrumental variable models because interacting the instrument (randomization status) with a potential confounder (the number of drug classes at baseline) would render the instrumental variable analysis invalid.

For instrumental variable models, we instead tested for trends in the incremental effects by testing for differences in the incremental effects of adding a: (a) first versus second drug class; (b) second versus third drug class; (c) fourth versus third class; and (d) fourth or more versus a first drug class. To do this, we estimated separate models stratified by baseline number of drug classes and tested for differences in effect estimates across baseline strata in the following four steps: (1) estimated the two-stage least-squares regression for patients in the first stratum (e.g., using zero drug classes at baseline) “by hand”, i.e., estimating the effect of the predicted number of antihypertensive drug classes from the first stage as a function of randomization status and covariates; (2) estimated the two-stage least-squares regression for patients in the second stratum (e.g., using one drug class at baseline), again by hand; (3) combined the parameter estimates and associated (co)variance from the two models (using Stata’s “suest” command); (4) evaluated whether the incremental effects

differed between the strata by testing whether linear combinations of the two parameter estimates differed from zero).

In these analyses (reported in online appendix table 9), differences in the incremental effects across baseline strata can be interpreted in the following manner: $\Delta < 0$ mm Hg suggests a synergistic benefit (i.e., relatively greater reductions in blood pressure); $\Delta > 0$ mm Hg suggests a diminishing benefit; and $\Delta = 0$ mm Hg suggests an additive benefit. In online appendix table 9, all models failed to reject the null hypothesis that incremental effects varied across baseline strata, suggesting that incremental effects on systolic blood pressure are approximately additive (vs. diminishing or synergistic), i.e., similar with each added drug. This is in accordance with Figure 1, which demonstrates a relatively stable effect of estimate of approximately 14-15 mm Hg drop in SBP with each added drug. For example, where Figure 1 displays the incremental effect of adding the 1st drug (-13.9 mm Hg) and the effect of adding the 2nd drug (-14.2 mm Hg), table H in appendix 4 shows that the difference between adding the 2nd drug and 1st drug is -14.2 - (-13.9) = -0.3 (95% -2.2, 1.5) mm Hg. Furthermore, because estimating instrumental variable estimates by hand does not account for the combined statistical uncertainty of both the first- and second-stages, this procedure results in overly precise parameter estimates and is thus more likely to falsely reject the null hypothesis that incremental effects do not differ across baseline strata (Type I error). Thus, our failure to reject the null hypothesis further confirms our conclusion that the effects of antihypertensive drugs are additive (i.e., do not diminish) with each added drug.

We followed a similar procedure for standard multivariable adjusted models, now estimating blood pressure changes as a function of observed rather than predicted antihypertensive drug use. We also

repeated this procedure to test for differences in the incremental effects of antihypertensive drugs across patient subgroups, e.g., difference in the incremental effect of adding the 1st drug between men and women (reported in table I in appendix 4).

Estimating incremental effects on major cardiovascular events and serious adverse events. We estimated a recently validated two-stage additive hazards model to examine the incremental effect of antihypertensive drugs on major cardiovascular events and serious adverse events.[30] In the first stage, we estimated the predicted number of antihypertensive drug classes as a linear function of randomization status and covariates. In the second stage, we estimated cardiovascular or adverse risk as a function of the predicted number of antihypertensive drug classes (from the first stage) and covariates. We estimated Aalen additive hazards models in the second stage to account for the right-censored nature of survival outcomes. To account for the combined statistical uncertainty of the two stages, we implemented a bootstrap estimator and based statistical inference on 95% confidence intervals derived from 2000 nonparametric bootstraps.

We specifically used additive hazards models rather than proportional hazards models (e.g., Cox proportional hazards) because prior work has demonstrated that estimating a two-stage proportional hazards model is valid only when the outcome is “rare” (i.e., with survival approaching unity),[30] an assumption that is not met in the present study. We estimated fully non-parametric additive hazards models and based parameter estimates on the weighted linear regression of the cumulative estimates plot. We did so to provide a useful measure of the overall size of the effect.

We performed three sensitivity tests to evaluate the assumptions of the additive hazards models, namely that the effects of antihypertensive drugs and other factors are additive and constant over time (i.e., time-invariant.). First, we plotted observed cumulative estimates over time of the effects of antihypertensive drugs and other covariates on composite major cardiovascular events. Second, we formally tested whether effects were additive and constant using the Kolmogorov-Smirnov test, which is a nonparametric goodness-of-fit test that assesses the degree to which the observed cumulative distribution function (CDF) fits a hypothetical CDF based on the assumption of time-invariant additive effects. Finally, we compared estimates from semi-parametric time-invariant additive hazards models to pooled estimates from non-parametric time-varying additive hazards models. The results of these sensitivity analyses are given in table G and figure G in appendix 4.