The Clinical Risk Associated With Randomizing Participants to a Control Arm in Hypertension Device Trials

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THERE IS GLOBAL CONSENSUS ON ACHIEVING HEALTHY BLOOD PRESSURE LEVELS

IN SUBJECTS WITH HIGH RISK HYPERTENSION THERE IS GLOBAL CONSENSUS FOR A BP TARGET <130/80

Recent Evidence Based Recommendations for Blood Pressure Targets in Older Adults

Organization	JNC 8 (committee report 2014)	HT Canada (2017)	ACP/AAFP (2017)	AHA/ACC (2017)	ESH (2018)
BP Goal (mmHg)	**<150/90**	**<140/90 <120/80 (Age>50, SBP> 130 and high risk)**	**<150/90 strong <140/90 (additional benefit)**	**<130/80 and CVD risk > 10%**	**<140/90 <130/80 or <120/80, for high risk**
Approach to analysis	**RCT's, age >60** (SHEP,SYST-EUR, HYVET,CARDIO-SIS, JATOS, VALISH)	**RCT's, cohorts, and published BP guidelines**	**RCT's age >60 with 2 BP goals (placebo) JNC 8, BP-Trialists**	**RCT's standard vs more intensive BP targets (no placebo)**	**RCT's meta analyses, and systematic reviews.**

Changes in BP Categories from JNC7 to the New Guideline

SBP		DBP	JNC7	2017 ACC/AHA
<120	and	<80	Normal BP	Normal BP
120–129	and	<80	Prehypertension	Elevated BP
130–139	or	80–89	Prehypertension	Stage 1 hypertension
140–159	or	90-99	Stage 1 hypertension	Stage 2 hypertension
≥160	or	≥100	Stage 2 hypertension	Stage 2 hypertension

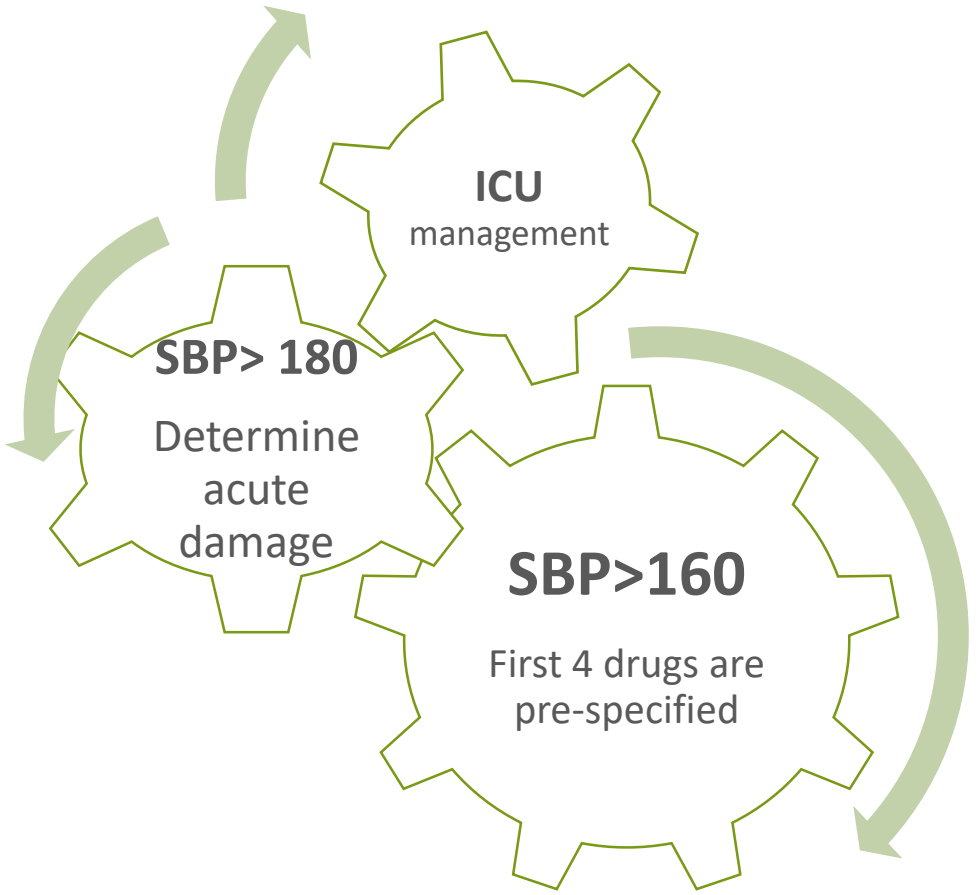
The 2017 ACC/AHA guideline definition of hypertension:

SBP ≥ 130 mm Hg or

DBP ≥ 80 mm Hg

STANDARD OF CARE OPTIONS FOR MANAGEMENT OF RESISTANT HYPERTENSION

- **Individuals with treatment resistant hypertension is a high risk group**
  - **RR for CVA,MI, and total mortality: 1.69 5 year risk, CI 1.27-2.24**
- **Short term risk is unclear:**
  - **Cautionary tale from VALUE**
- **Withholding treatment in study participants with SBP 150-180 mmHg requires suspension of current standard of care recommendations**

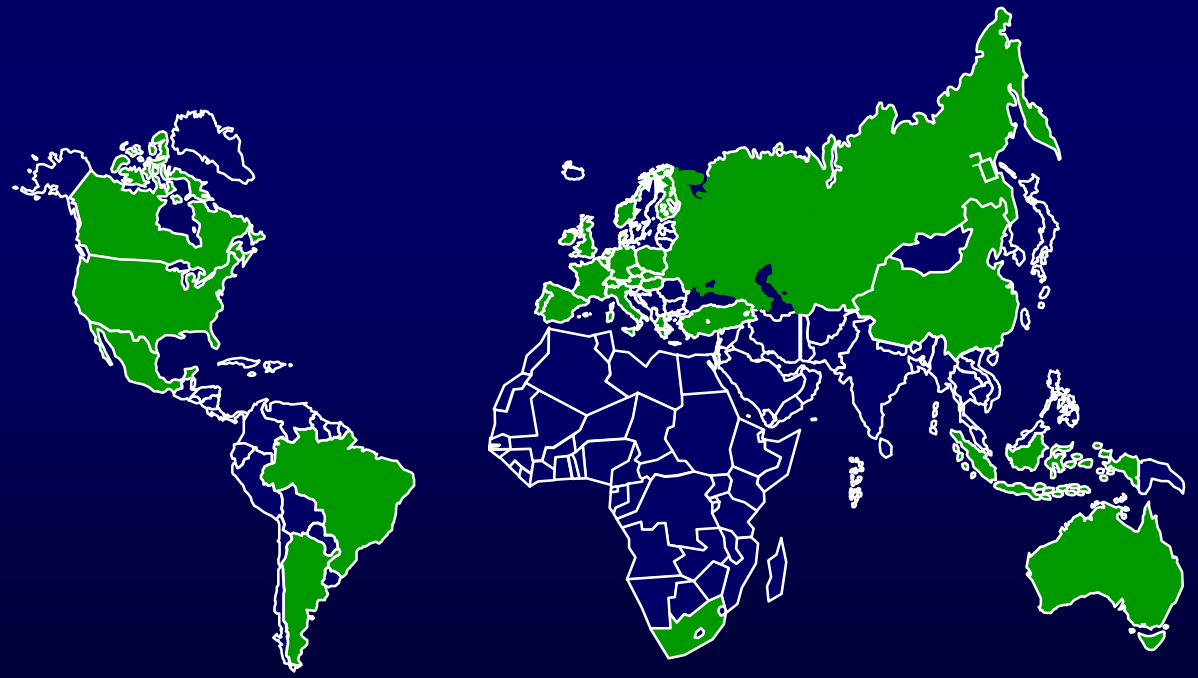


Irwin J Am Soc Hypertens June 2014 8(6) 405-413

VALUE

Valsartan Antihypertensive Long-Term Use Evaluation

15,313 randomised at 942 sites in 31 countries
Average follow up 4.2 years



Julius S et al. *Lancet*. June 2004;363.

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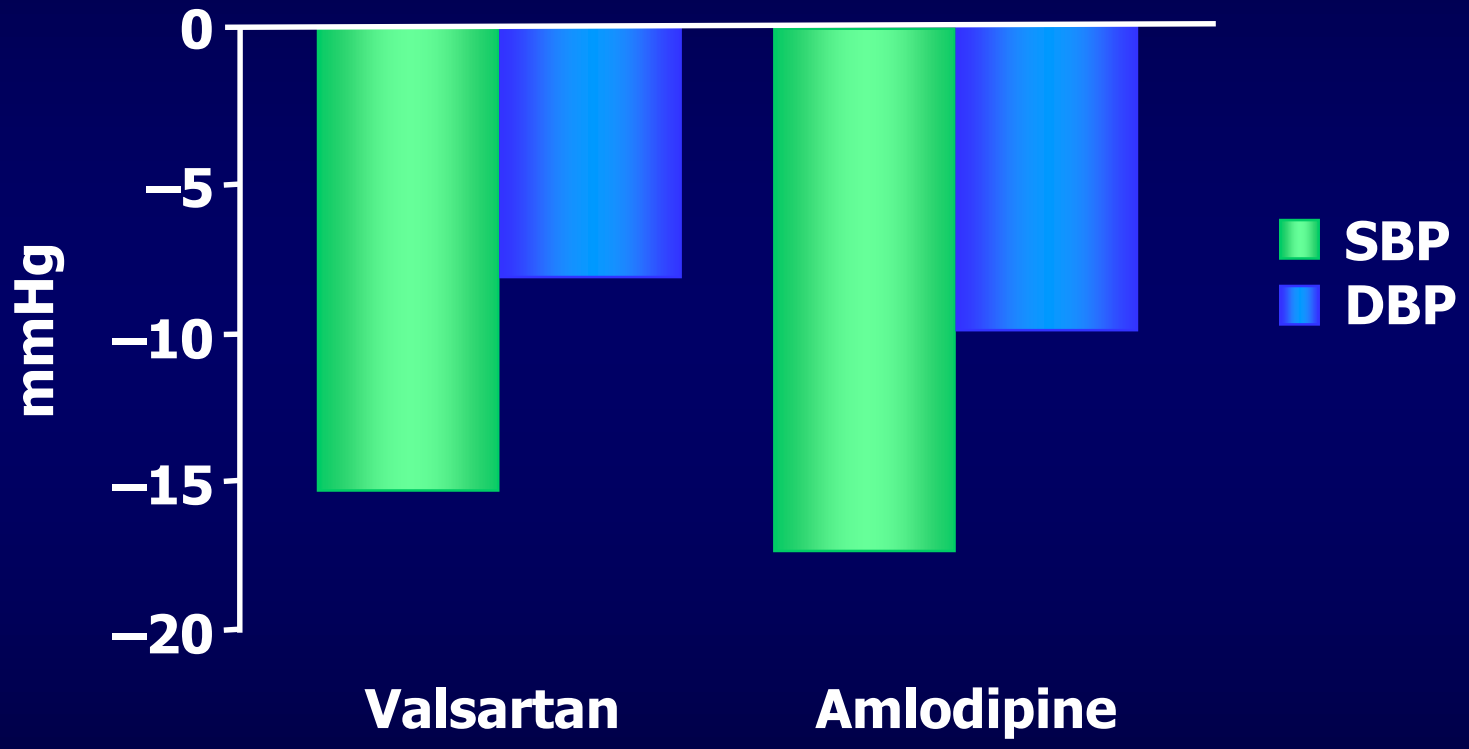
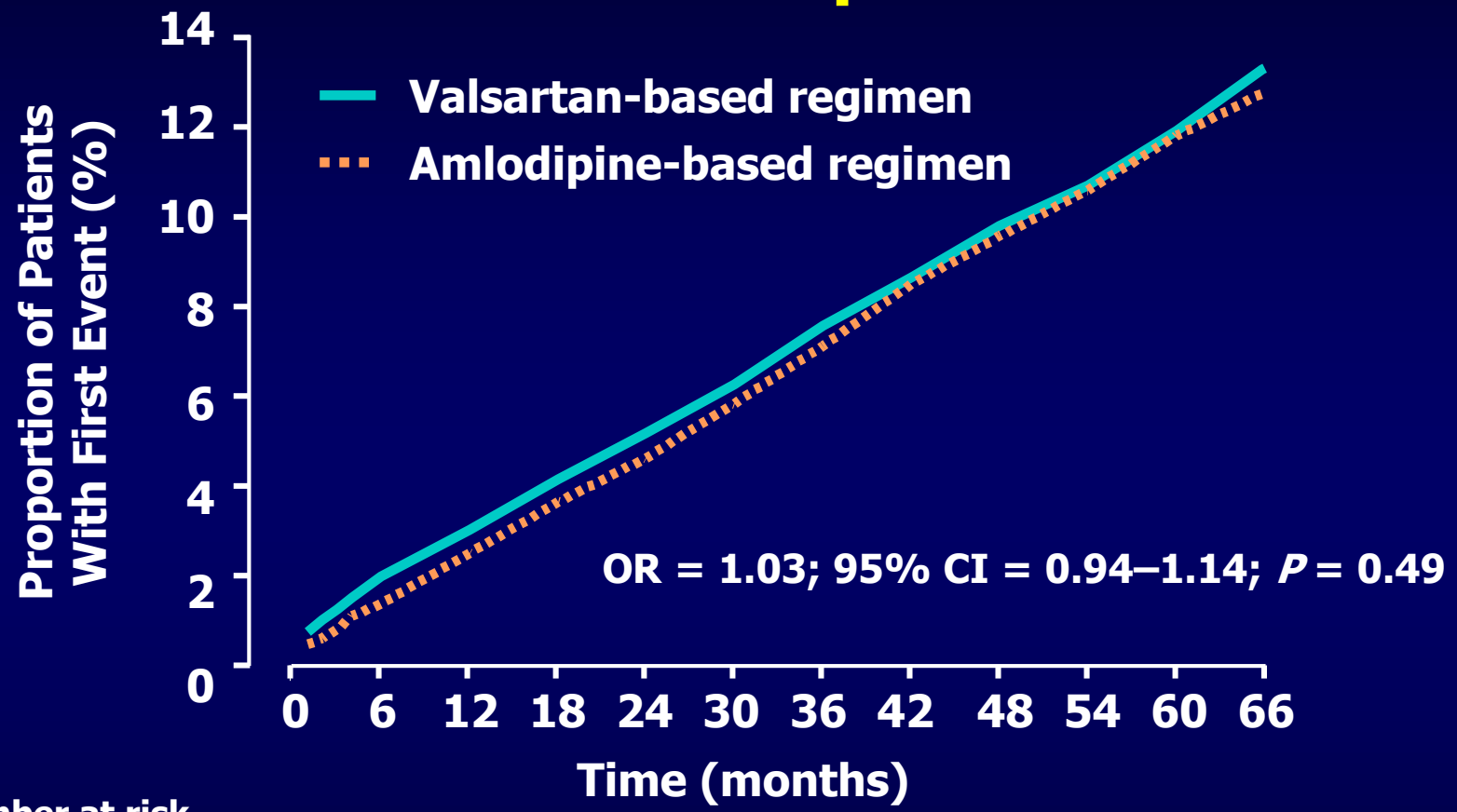
VALUE: Blood Pressure Changes From Baseline to the End of the Study



Julius S et al. *Lancet*. June 2004;363.

VALUE: Primary Composite Cardiac Endpoint



Number at risk												
Valsartan	7649	7459	7407	7250	7085	6906	6732	6536	6349	5911	3765	1474
Amlodipine	7596	7469	7424	7267	7117	6955	6772	6576	6391	5959	3725	1474

Julius S et al. *Lancet*. June 2004;363.

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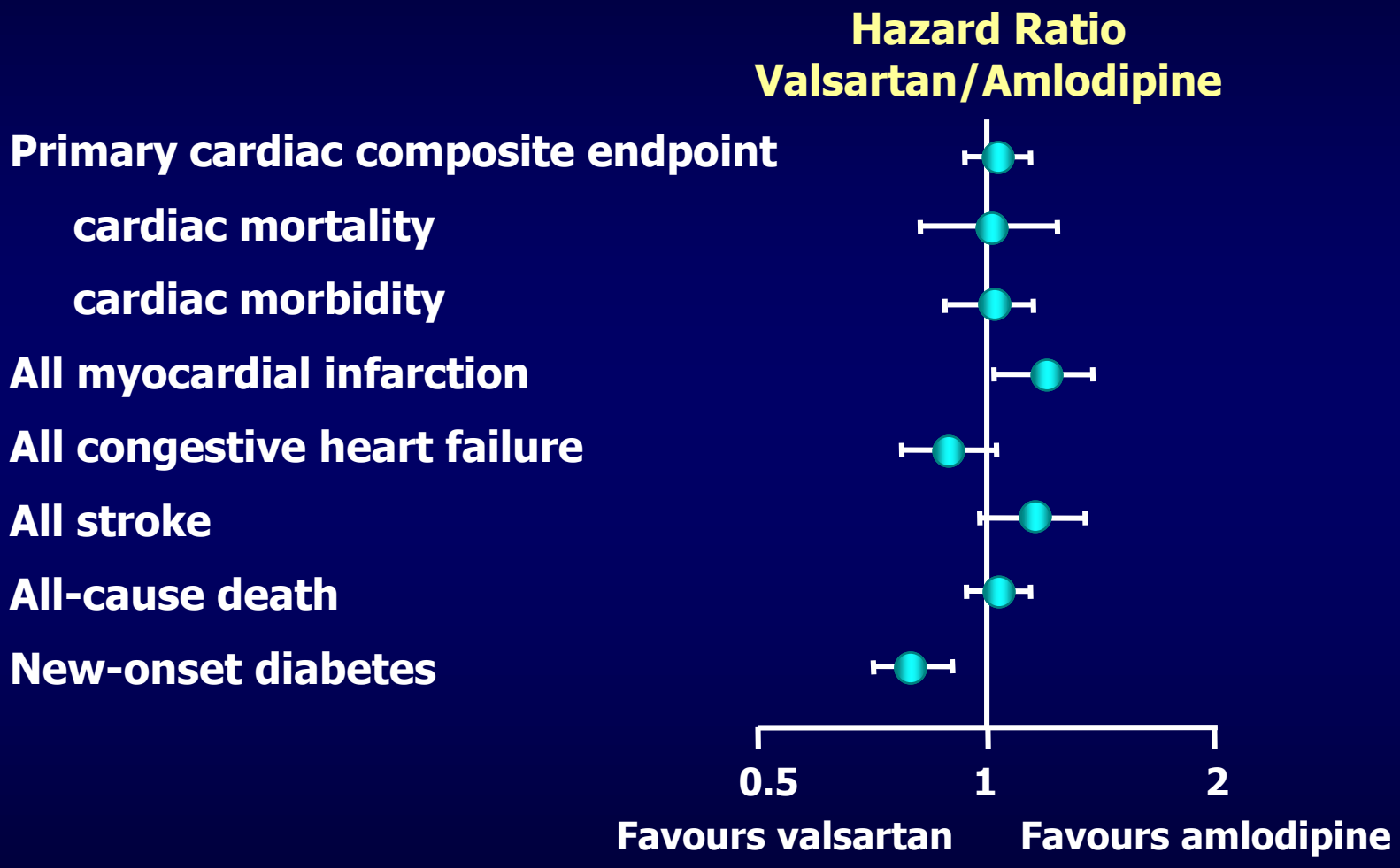
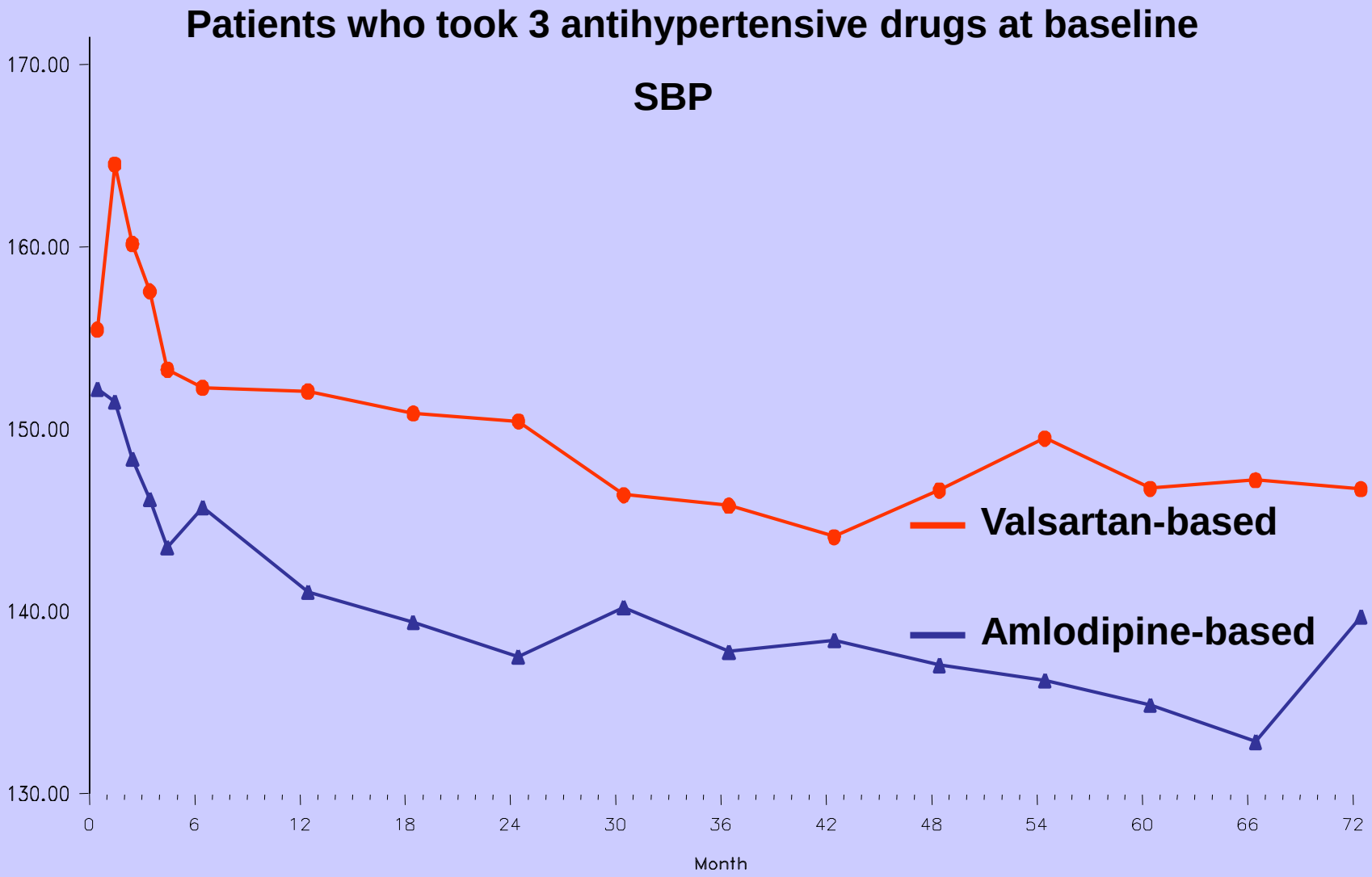
VALUE: Hazard Ratios for Pre-specified Analyses



Julius S et al. *Lancet*. June 2004;363.


Patients who took 3 antihypertensive drugs at baseline
SBP
170.00
160.00
150.00
140.00
130.00
0
6
12
18
24
30
36
42
48
54
60
66
72
Month
Valsartan-based
Amlodipine-based

CAUTIONARY LESSONS FROM THE VALUE TRIAL

- There was an early unintended difference in BP in the treatment groups.
- Withdrawal of antihypertensive medication (in subjects on 3 drugs at baseline) resulted in escape from control with residual effects over the course of the trial.
- The washout, run-in, and titration period of 3 months was associated with excess CV events.

SUMMARY COMMENTS

- **Individuals with resistant hypertension are high risk group for CVD**
- **Assignment to a control group in a device trials that allows SBP remain in the range of 150-180 mmHg confers excess risk of CVD (5 year risk of CVD event >60%). The excess risk during 3-6 months is clear but exact magnitude has not been determined.**
- **There is uniform consensus that a BP target of <140/90 mmHg is recommended for individuals with high risk hypertension (global consensus of hypertension experts recommend a target of <130/80 mmHg).**
- **Prompt control of BP utilizing hygienic, pharmacologic, and devices may improve CV outcomes.**

CONCLUDING COMMENTS

- **A global consensus for more aggressive BP control has emerged over the past year, it has implications for the design of device trials that preceded these recommendations.**
- **When considering the equipoise of allowing higher untreated blood pressure in device trials, individual manufacturer should asses the profile and BP signal of their device to minimize the degree and duration of uncontrolled blood pressure**