

Similarities and Differences in Response to Anti-hypertensive Agents in Adult and Pediatric Patients

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Outline



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- Pediatric vs. adult hypertension
- Case studies
 - Amlodipine
 - Valsartan
- Conclusions

Pediatric vs. Adult Hypertension



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- Etiology
 - Adult – overwhelmingly primary
 - Pediatric – varies by age

Pediatric vs. Adult Hypertension



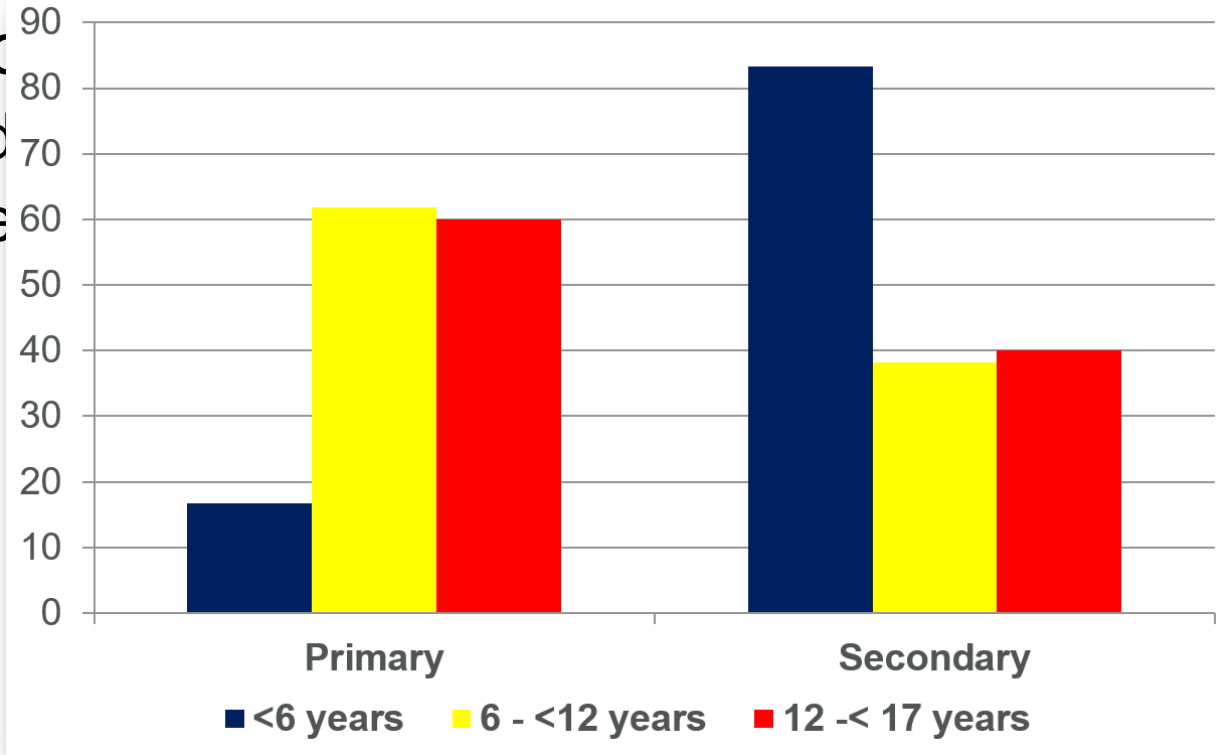
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- Etiology

- Acquired

- Primary



Pediatric vs. Adult Hypertension



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- Etiology
 - Adult – overwhelmingly primary
 - Pediatric – varies by age
- Diagnostic criteria
 - Adult – static thresholds based on hard end-points
 - Pediatric – percentile-based thresholds up to 13y

Pediatric vs. Adult Hypertension



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Etiology

TABLE 3 Updated Definitions of BP Categories and Stages

For Children Aged 1–<13 y	For Children Aged ≥ 13 y
Normal BP: <90th percentile	Normal BP: <120/<80 mm Hg
Elevated BP: ≥ 90 th percentile to <95th percentile or 120/80 mm Hg to <95th percentile (whichever is lower)	Elevated BP: 120/<80 to 129/<80 mm Hg
Stage 1 HTN: ≥ 95 th percentile to <95th percentile + 12 mmHg, or 130/80 to 139/89 mm Hg (whichever is lower)	Stage 1 HTN: 130/80 to 139/89 mm Hg
Stage 2 HTN: ≥ 95 th percentile + 12 mm Hg, or $\geq 140/90$ mm Hg (whichever is lower)	Stage 2 HTN: $\geq 140/90$ mm Hg

Pediatric vs. Adult Hypertension



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- Etiology
 - Adult – overwhelmingly primary
 - Pediatric – varies by age
- Diagnostic criteria
 - Adult – static thresholds based on hard end-points
 - Pediatric – percentile-based thresholds up to 13y
- Co-morbidities – common in adults, uncommon in children and adolescents

Pediatric vs. Adult Hypertension



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- Approach to treatment/prescribing
 - Adult
 - “one size fits all” dosing, escalation according to fixed tablet sizes
 - Emphasis on combination therapy
 - Pediatric
 - Weight- and age-based dosing → need for suspensions
 - Lack of data on combination therapy → stepped-care approach

Efficacy Assessment

- Absolute BP reduction (mmHg)
 - Typical clinical trial endpoint is SBP reduction compared to placebo
 - Usually based on office BP, some studies use ABPM
 - Maintenance of BP reduction over longer interval
- Achievement of target BP - percentage of patients whose BP reaches desired level
 - Change in S/DBP vs. specific threshold

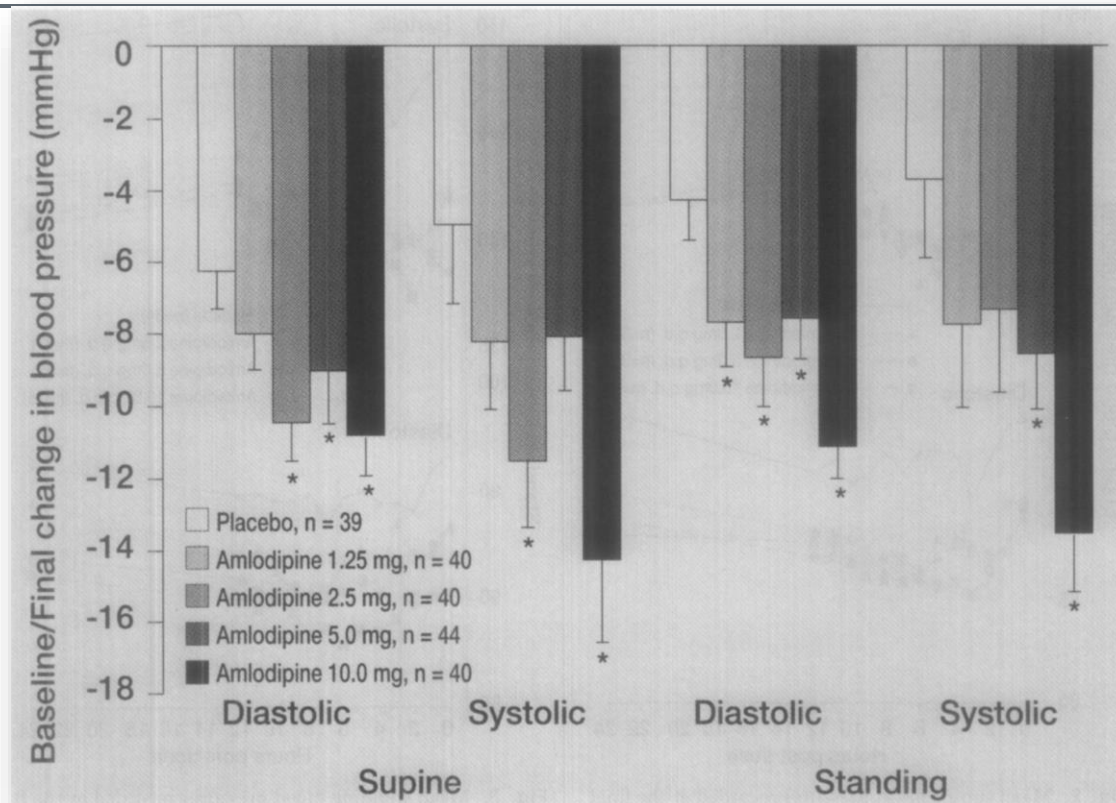
Case study: Amlodipine

- Long-acting DHP calcium channel blocker
 - Blocks Ca^{++} entry at L-type calcium channels in VSMC causing vasodilatation
- Approved for use in adults in 1987
- Off-label pediatric use reported since late 1990s
- Pediatric clinical trial conducted early 2000s under auspices of FDAMA incentives

Case study: Amlodipine

- Adult pivotal trials demonstrated
 - Avg placebo-corrected reductions of 13/7 mmHg in supine and 12/6 mmHg standing blood pressures
 - BP reduction maintained 24 hours post-dose
 - Patients with higher BP's had greater BP reductions compared to those with mild-moderate HTN
 - BP reduction generally dose-dependent at doses ranging from 2.5-10 mg daily

Case study: Amlodipine



Case study: Amlodipine

- Other early trials in adults compared amlodipine to HCTZ, atenolol, enalapril and losartan and showed comparable antihypertensive efficacy
 - Response rates 40% for amlodipine, 45% for HCTZ (defined as DBP <90 mmHg or ↓ DBP of ≥ 10 mmHg; *Rofman, J Cardiovasc Pharmacol 1988*)
- ALLHAT – no significant difference in BP reduction between amlodipine, lisinopril and chlorthalidone

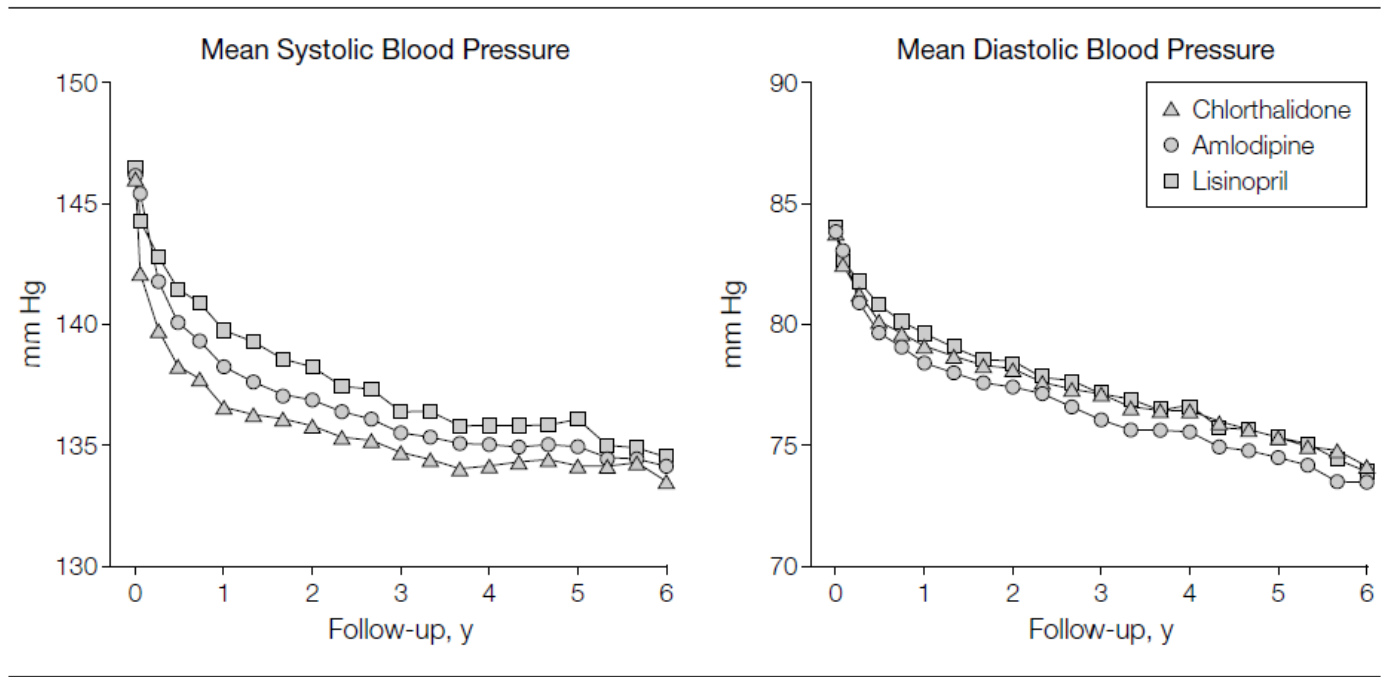
Case Study: Amlodipine



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Figure 2. Mean Systolic and Diastolic Blood Pressure by Year During Follow-up



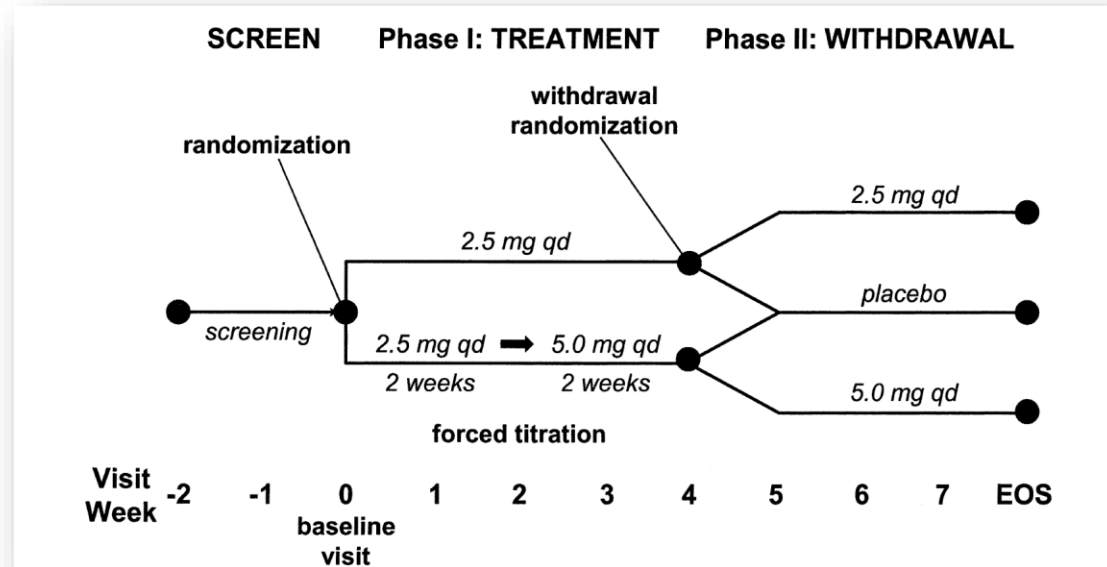
Case study: Amlodipine



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- Amlodipine pediatric trial
 - 268 children (12.1 ± 3.3 y/o) enrolled; 31% with primary HTN;
 - Eligible if BP $\geq 95^{\text{th}}$ percentile on 3 occasions
 - Study design:

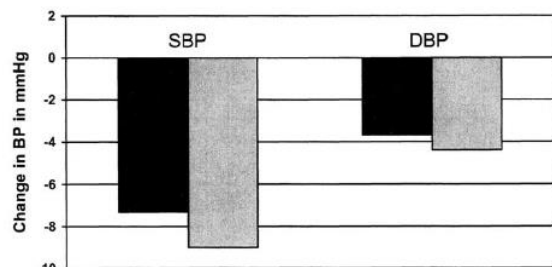


Case study: Amlodipine



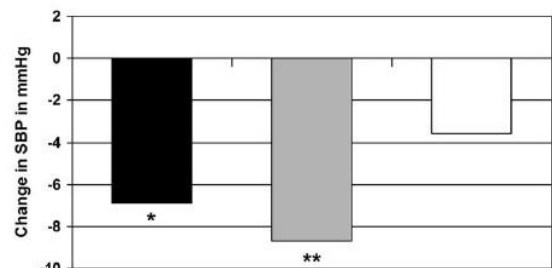
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A

■ 2.5 mg □ 5 mg



B

■ 2.5 mg □ 5 mg □ Placebo

Fig 2. A, Change in BP from baseline in phase 1. *SBP*, Systolic blood pressure; *DBP*, diastolic blood pressure. **B,** Change in SBP from baseline at end of phase 2. * $P = .045$ vs placebo; ** $P = .005$ vs placebo.

Table III. Percentage of subjects achieving blood pressure $\leq 95^{\text{th}}$ percentile at study end

	SBP $\leq 95^{\text{th}} \%^{*}$	DBP $\leq 95^{\text{th}} \%^{\dagger}$	SBP and DBP $\leq 95^{\text{th}} \%^{\ddagger}$
All patients	34.6	55.1	28.2
2.5-mg dose	39.7	41.7	\$
5-mg dose	34.8	75	\$
Placebo withdrawal	29.4	47.6	\$
Primary HTN	33.3	45	8.3
Secondary HTN	35.2	59.1	12.1

DBP, Diastolic blood pressure; *HTN*, hypertension; *SBP*, systolic blood pressure.

*Percentage of subjects with systolic hypertension at baseline whose end-of-study SBP was $\leq 95^{\text{th}}$ percentile.

$\dagger$ Percentage of subjects with diastolic hypertension at baseline whose end-of-study DBP was $\leq 95^{\text{th}}$ percentile.

$\ddagger$ Percentage of subjects with combined systolic and diastolic hypertension at baseline whose end-of-study SBP and DBP were $\leq 95^{\text{th}}$ percentile.

\$Numbers too small to calculate.

Case study: Amlodipine

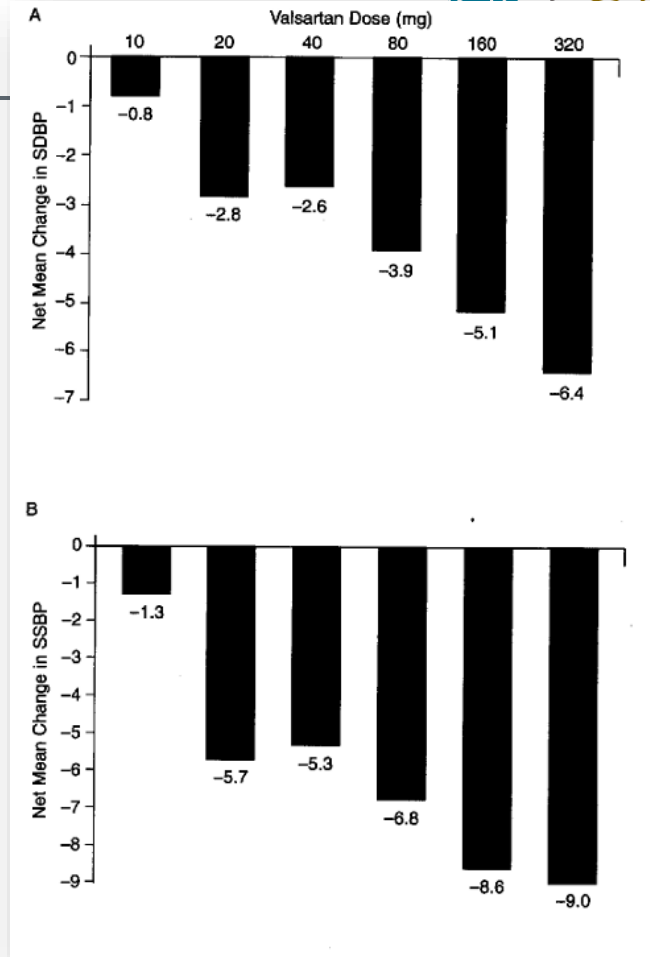
- While amlodipine reduced BP in pediatric patients, less of a dose-response was seen
 - Patients not stratified by weight/age/cause of HTN
 - Doses used relatively low, especially for adolescents
 - Consequently, FDA-approved label for amlodipine limited to 2.5 and 5.0 mg doses
- However, goal BP reached in a comparable proportion of pediatric patients as seen in adults

Case study: Valsartan

- Highly selective blocker of the AT₁ receptor, thereby inhibiting Ang-II induced vasoconstriction and aldosterone-secretion
- Approved for use in adults in 1996, initially for HTN, later for heart failure
- Two pediatric clinical trials conducted
 - 6-16 y/o (Wells et al 2011)
 - 1-5 y/o (Flynn et al 2008)

Case study: Valsartan

- Efficacy in adult hypertension established in clinical trials comparing valsartan to placebo, and to enalapril
- Produces dose-dependent decreases in systolic & diastolic BP →



Case study: Valsartan



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- Valsartan also produced effective BP control (DBP <90 mmHg or ↓DBP ≥ 10 mmHg) compared to placebo:

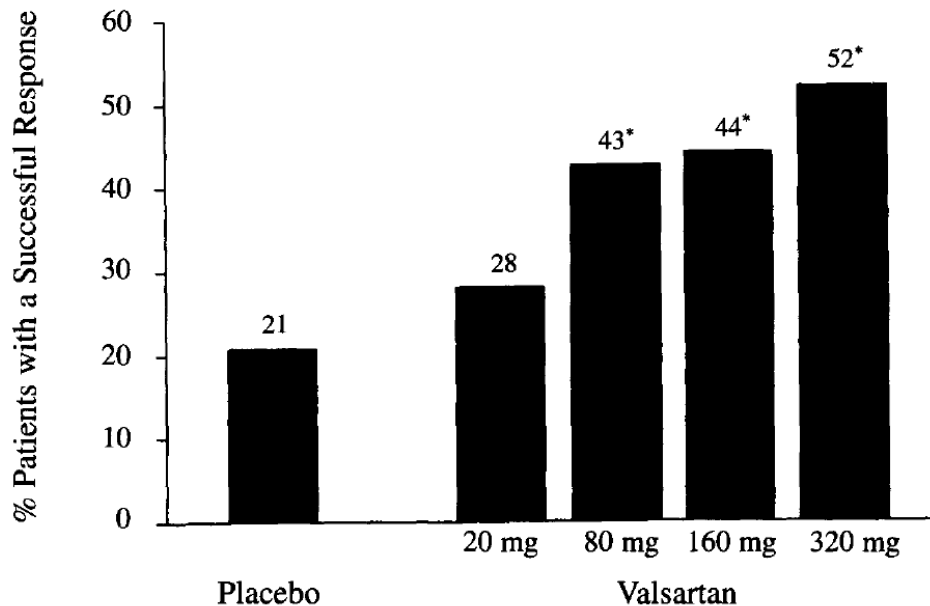


Figure. Proportion of patients with successful control of mean sitting diastolic blood pressure (MSDBP) at end point for placebo and valsartan 20, 80, 160, and 320 mg (intent-to-treat data set). Successful control was defined as MSDBP <90 mm Hg or a decrease of ≥10 mm Hg from baseline. * $P < 0.001$.

Case study: Valsartan

- The 2 pediatric trials both used adaptation of FDA trial design C
- Randomized to low, medium and high dose valsartan in phase 1, followed by randomization to placebo vs valsartan in phase 2
- Allows evaluation of dose-response and comparison to placebo with short exposure to placebo

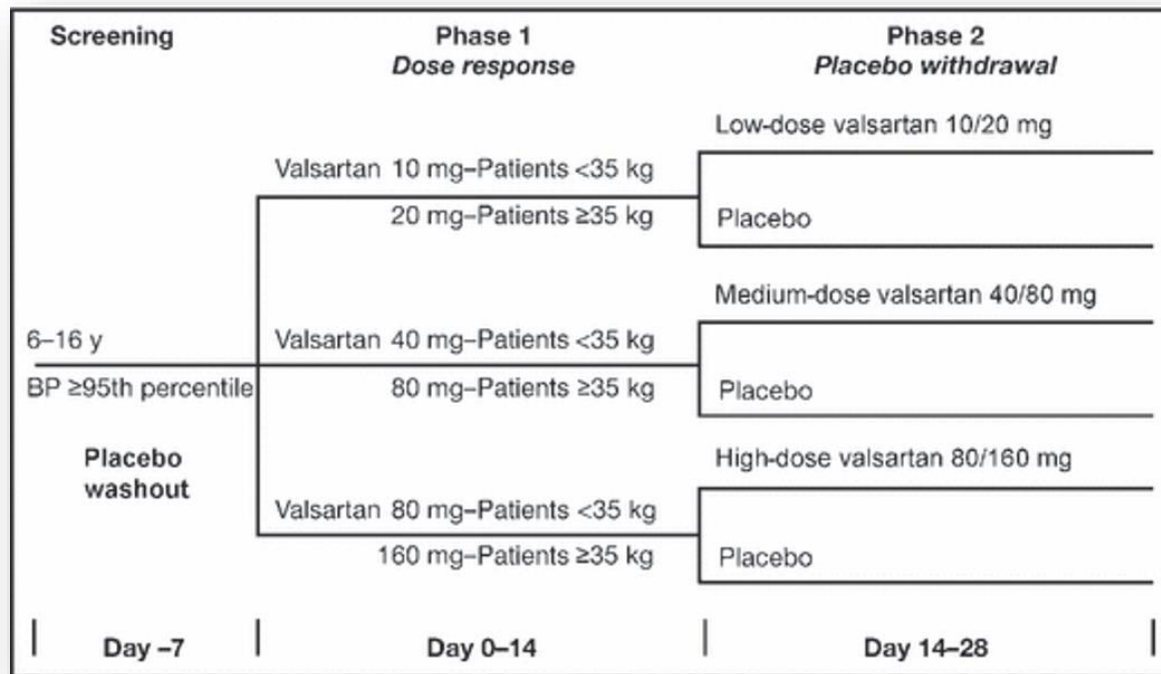
Case study: Valsartan



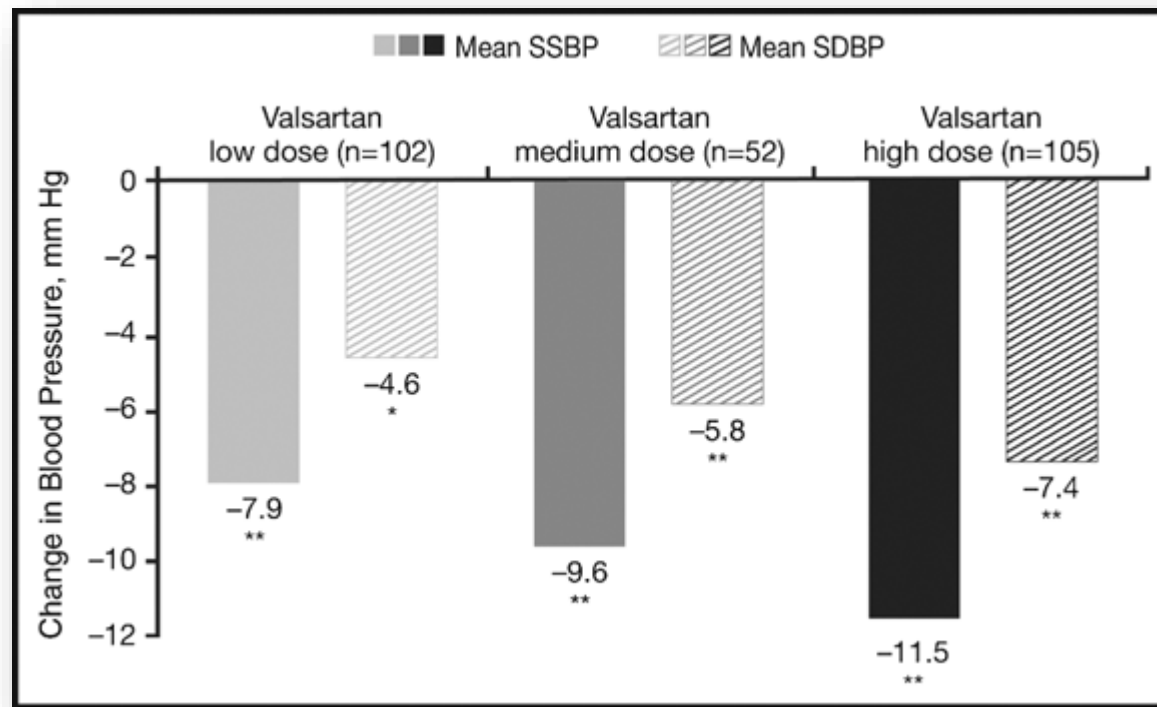
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- Valsartan doses in the trial of children 6-16 y/o ranged from 0.1 mg/kg - 4.6 mg/kg with stratification according to weight



Case study: Valsartan

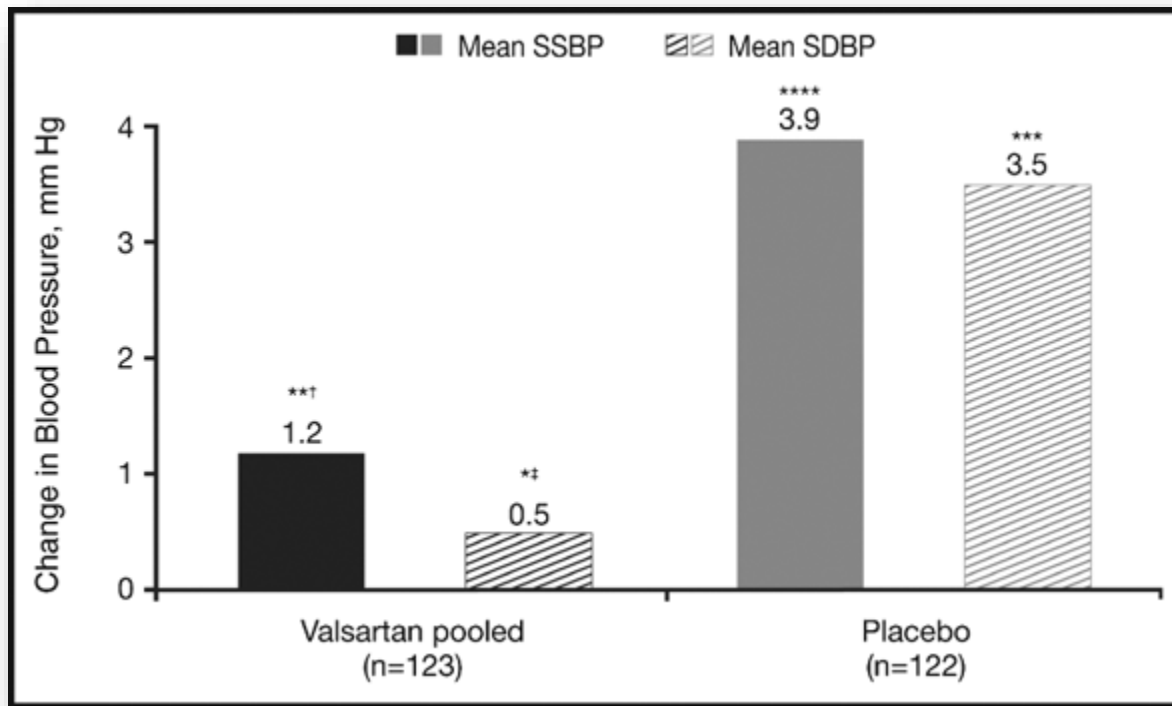


Case study: Valsartan



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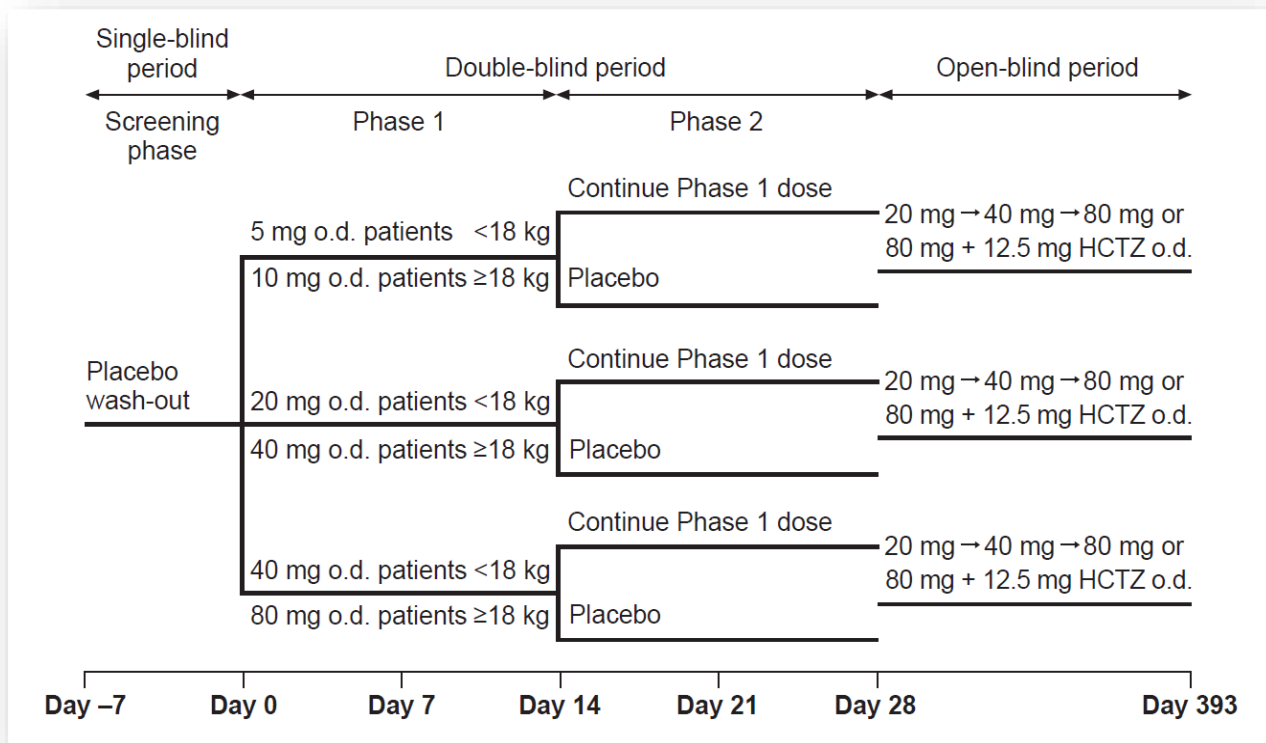


Case study: Valsartan



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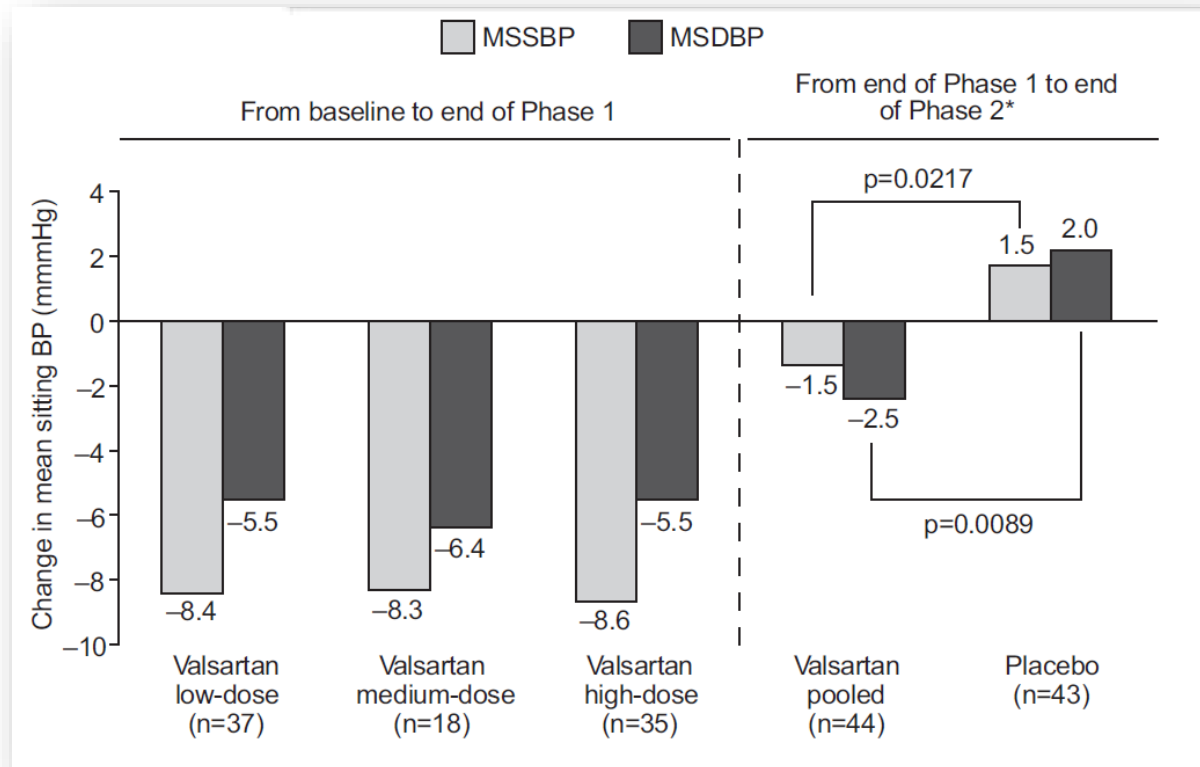
Case study: Valsartan



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- No dose-response seen in phase 1 but valsartan group had significantly lower BP at end of phase 1 compared to placebo



Case study: Valsartan

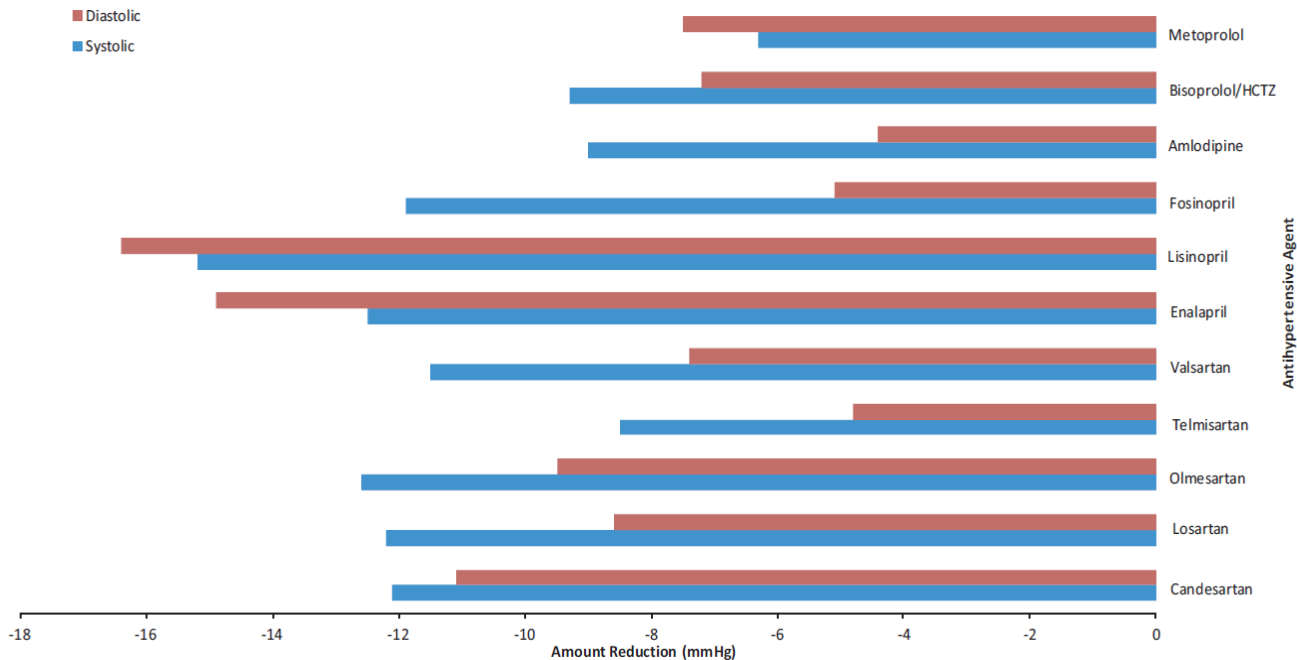
- Dose-response established for both adults and children aged 6-16 y/o
 - BP reductions similar in adults & children, with somewhat greater response to highest dose in children - ?more secondary HTN
- Failure to show dose-response in trial of 1-5 y/o likely due to issues of trial design (narrower dose range) and BP measurement

Conclusions/Questions

- Generally, antihypertensive medications lower BP across all age groups
- Pediatric efficacy seen in all classes studied



Absolute Reduction in Blood Pressure of Children Receiving Antihypertensive Agents



	Candesartan	Losartan	Olmesartan	Telmisartan	Valsartan	Enalapril	Lisinopril	Fosinopril	Amlodipine	Bisoprolol /HCTZ	Metoprolol	Allopurinol	Eplerenone
■ Diastolic	-11.1	-8.6	-9.5	-4.8	-7.4	-14.9	-16.4	-5.1	-4.4	-7.2	-7.5	-5.1	-3.1
■ Systolic	-12.1	-12.2	-12.6	-8.5	-11.5	-12.5	-15.2	-11.9	-9	-9.3	-6.3	-6.9	-8

Conclusions/Questions

- Generally, antihypertensive medications lower BP across all age groups
- Pediatric efficacy seen in all classes studied
 - Potentially greater response to RAAS blockers in younger children given prevalence of kidney disease
- Most agents still unstudied in those <6 y/o
- Pediatric data lacking for many older agents and some drug classes



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