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

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>BP Goal (mmHg)</td>
<td>&lt;150/90</td>
<td>&lt;140/90</td>
<td>&lt;150/90 strong</td>
<td>&lt;130/80 and CVD risk &gt; 10%</td>
<td>&lt;140/90</td>
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<tr>
<td></td>
<td>&lt;120/80 (Age&gt;50, SBP&gt;130 and high risk)</td>
<td>&lt;140/90 (additional benefit)</td>
<td>&lt;140/90</td>
<td>&lt;130/80 or &lt;120/80, for high risk</td>
<td></td>
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<tr>
<td>Approach to analysis</td>
<td>RCT’s, age &gt;60 (SHEP, SYST-EUR, HYVET, CARDIOSIS, JATOS, VALISH)</td>
<td>RCT’s, cohorts, and published BP guidelines</td>
<td>RCT’s age &gt;60 with 2 BP goals (placebo) JNC 8, BP-Trialists</td>
<td>RCT’s standard vs more intensive BP targets (no placebo)</td>
<td>RCT’s meta analyses, and systematic reviews.</td>
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## Changes in BP Categories from JNC7 to the New Guideline

<table>
<thead>
<tr>
<th>SBP</th>
<th>DBP</th>
<th>JNC7</th>
<th>2017 ACC/AHA</th>
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<tbody>
<tr>
<td>&lt;120</td>
<td>&lt;80</td>
<td>Normal BP</td>
<td>Normal BP</td>
</tr>
<tr>
<td>120–129</td>
<td>&lt;80</td>
<td>Prehypertension</td>
<td>Elevated BP</td>
</tr>
<tr>
<td>130–139</td>
<td>80–89</td>
<td>Prehypertension</td>
<td>Stage 1 hypertension</td>
</tr>
<tr>
<td>140–159</td>
<td>90–99</td>
<td>Stage 1 hypertension</td>
<td>Stage 2 hypertension</td>
</tr>
<tr>
<td>≥160</td>
<td>≥100</td>
<td>Stage 2 hypertension</td>
<td>Stage 2 hypertension</td>
</tr>
</tbody>
</table>

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
Valsartan Antihypertensive Long-Term Use Evaluation

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

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

**VALUE: Primary Composite Cardiac Endpoint**

![Graph showing the proportion of patients with first event over time for Valsartan and Amlodipine-based regimens.](image)

- **OR = 1.03; 95% CI = 0.94–1.14; P = 0.49**

**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

VALUE: Hazard Ratios for Pre-specified Analyses

Hazard Ratio
Valsartan/Amlodipine

- Primary cardiac composite endpoint
- Cardiac mortality
- Cardiac morbidity
- All myocardial infarction
- All congestive heart failure
- All stroke
- All-cause death
- New-onset diabetes

Patients who took 3 antihypertensive drugs at baseline

SBP

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 assess the profile and BP signal of their device to minimize the degree and duration of uncontrolled blood pressure.