Single pill combination therapy: Is there a foundation antihypertensive therapy upon which to base treatment?

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Key Questions

- How early should you start?
- How low should you go?
- What drugs and doses should you use?
- How many medications will you need?
Percent Chance of Cardiovascular Event in 5 Years: No Diabetes

**Men**

<table>
<thead>
<tr>
<th>BP (mm Hg)</th>
<th>Non- smokers Total Chol.: HDL-C</th>
<th>Smokers Total Chol.: HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>180/105</td>
<td></td>
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<tr>
<td>160/95</td>
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<td>140/85</td>
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<tr>
<td>120/75</td>
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</table>

**Women**

<table>
<thead>
<tr>
<th>BP (mm Hg)</th>
<th>Non- smokers Total Chol.: HDL-C</th>
<th>Smokers Total Chol.: HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>180/105</td>
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<tr>
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<tr>
<td>120/75</td>
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</tr>
</tbody>
</table>

Adapted with permission from Jackson R. *BMJ*. 2000;320:709-710.
Percent Chance of Cardiovascular Event in 5 Years: Diabetes

Adapted with permission from Jackson R. BMJ. 2000;320:709-710.
What is Your Definition of “Hypertension”?

- We must delete the word “hypertension”; it has no meaning.
- The blood pressure goal should be established for each patient.
LOWER IS BETTER: IHD RATES BY SBP, DBP AND AGE

Up to 8 out of 10 patients need multiple medications to help reach blood pressure treatment goals\textsuperscript{1,2}

\textsuperscript{1}Dahlof et al. Lancet 2005;366:895–906
\textsuperscript{2}Pepine et al. JAMA 2003;290:2805–16
Adding an Antihypertensive Agent is More Effective Than Titrating

‘The extra blood pressure reduction from combining drugs from 2 different classes is approximately 5 times greater than doubling the dose of 1 drug’

Conclusions from a meta-analysis comparing combination antihypertensive therapy with monotherapy in over 11,000 patients from 42 trials

Multiple-mechanism Therapy: Potential Efficacy Benefits

Components with a different mechanism of action interact on complementary pathways of BP control

Each component can potentially neutralize counter-regulatory mechanisms, e.g.

- Diuretics reduce plasma volume, which in turn stimulates the renin-angiotensin-aldosterone system (RAAS) and thus increases BP; addition of a RAAS blocker attenuates this effect

Multiple-mechanism therapy may result in BP reductions that are additive

BP = blood pressure

References:
1 Sica. Drugs 2002;62:443–62
Multiple-mechanism Therapy: Potential Tolerability Benefits

Components of multiple-mechanism therapy can be given at lower dosages to achieve blood pressure goal than those required as monotherapy therefore better tolerated

Compound-specific adverse events can be attenuated, e.g.,

- Renin-angiotensin-aldosterone system blockers may attenuate the oedema that is caused by calcium channel blockers

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1 Sica. Drugs 2002;62:443–62
Current Guidelines Recommend Initiating Combination Therapy Early in Patients with Stage 2 Hypertension or High Cardiovascular Risk

- **JNC 7 guidelines** recommend the consideration of initial therapy with two antihypertensive drugs when BP is more than 20/10 mmHg above goal\(^1\)

- **ESH/ESC guidelines** state\(^2\):
  
  ‘The combination of two antihypertensive drugs may offer advantages also for treatment initiation, particularly in patients at high cardiovascular risk in which early BP control may be desirable.’

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BP = blood pressure  
ESH = European Society of Hypertension  
ESC = European Society of Cardiology  
JNC = Joint National Committee

\(^1\)Chobanian et al. Hypertension 2003;42:1206–52  
Overview: single-pill combination (SPC) therapy

- Why?
- When?
- What combination?
Why?

- Most people need more than one drug to achieve appropriate BP targets
  - we start treatment too late
  - many patients have lower recommended SBP goals of less than 130 mmHg (heart disease, kidney disease, diabetes)
  - high dietary salt intake
  - obesity/sleep apnea

BP = blood pressure
SBP = systolic blood pressure
Why?

- Most medications, when appropriately dosed, offer about 10/5 mmHg BP reduction
- The rule of 10’s
Most guidelines recommend starting two medications, preferably as a SPC, if BP is more than 20/10 mmHg from goal\textsuperscript{1,2}

What combination?

- Many different combinations of medications are available
- One part of the SPC should include a RAAS blocker, as this is an important ‘foundation’ therapy

RAAS = renin-angiotensin-aldosterone system
Should RAAS blockade be considered the foundation of antihypertensive therapy?
Angiotensin II Dichotomy

Angiotensin II

Vasoconstriction
Modification of SNS
Renal Salt and Water Retention

Blood Pressure Homeostasis

? Modification of Disease
Progression

LVH
Atherogenesis
Glomerular Sclerosis
The hypertension damage model

Classic

HYPERTENSION

HEMODYNAMIC OVERLOAD

COMPLICATIONS

Proposed

HYPERTENSION

ENDOTHELIAL DYSFUNCTION

Angiotensin II
Bradykinin

ACE

NO

ENDOTHELIN

REMODELING

COMPLICATIONS

ACE = angiotensin converting enzyme

Alcocer L, Cardona EG. Hipertensiòn, SAM, 1998
What factors might be clinically important with RAAS blockers?

Is it simply better tolerability?
Vascular Benefits of RAAS Inhibition

- Endothelial Function
- Less Oxidative stress
- Diminished PAI-1
- Diminished TGF-beta
Emerging concept of the RAAS

P/R-R

Prorenin

Renin

Angiotensinogen

Ang I (1-10)

Ang II (1-8)

Ang-(1-7)

Mas-R

Vasodilation
Natriuresis
Anti-proliferation

AT_{1}-R

Vasoconstriction
Aldosterone
Sodium retention
Cell proliferation
Oxidative stress

AT_{2}-R

Vasoconstriction

AT_{3}-R

Unknown

AT_{4}-R

Modulation of endothelial function
(PAI-1 release, etc.)

AP-N

Ang III (2-8)

Ang IV (3-8)

? Prorenin/renin activation
? MAP kinases (ERK \( \frac{1}{2} \))

Bradykinin
Substance P

Inactive fragments

? Cathepsin G
? Tonin(s)
? Tissue Plasminogen Activator

? Chymase
? CAGE

AP-A

Inactive fragments


RAAS = renin-angiotensin-aldosterone system
Angiotensin II and the cardiovascular continuum

Risk factors
- Atherosclerosis
- Hypertrophy

Oxidative Stress/Endothelial Dysfunction

Pathological Remodeling
- Myocardial infarction
- Ventricular Enlargement

Target Organ Damage
- Heart Failure
- Death

ANGIOTENSIN II AND THE CARDIOVASCULAR CONTINUUM

normal vasoconstriction

Abnormal vasoconstriction

↑PAI-1/thrombosis

Platelet aggregation

Superoxide production

Vascular smooth muscle growth

Myocyte growth

↑Collagen

↑Endothelin

↑Vasopressin

↑Aldosterone

↑Contractility

Activate SNS

Oxidative Stress/Endothelial Dysfunction

Target Organ Damage

Risk factors
- Atherosclerosis
- Hypertrophy
Clinical trials with ACEIs

Risk factors:
- Diabetes
- Hypertension
- Hyperlipidemia
- Atherosclerosis
- Hypertrophy
- CAD
- Heart Failure
- Death
- Ventricular Enlargement
- HF SOLVD
- V-HeFT II
- SAVE, ATLAS
- MI CONSENSUS
- ISIS-4, GISSI-3
- SMILE, SAVE AIRE, TRACE
- CAPPP, ALLHAT
- DM ABCD, REIN, AASK

ACEIs = angiotensin-converting enzyme inhibitors
Clinical trials with ARBs

ARBs = angiotensin-receptor blockers
Mortality and Morbidity Endpoint Trials†‡¶ with Angiotensin Receptor Blockers

1. VALUE
2. VALIANT
3. NAVIGATOR
4. Val-HeFT
5. JIKEI HEART
6. KYOTO HEART*
7. VAT*
8. VALISH*
9. ONTARGET
10. ProFESS
11. TRANSCEND
12. HALT-PKD*
13. LIFE
14. OPTIMAAL
15. ELITE II
16. RENAAAL
17. NCT00090259*
18. VA NEPHRON-D*
19. CHARM
20. SCOPE
21. SCAST*
22. CASE-J
23. ACCOST
24. HIJ-CREATE
25. E-COST
26. I-PRESERVE


*Expected enrolment
†Ongoing and completed randomized controlled trials with death or hard CV events as or part of the primary endpoint
¶Valid as of January 2009
ONTARGET: time to primary outcome*

*Composite primary outcome of death from cardiovascular cause, MI, stroke, or hospitalization for HF

RAAS blockade with ARBs can be considered a foundation of antihypertensive therapy.
A RAAS blocker and …?

- Most patients need more than one drug
- Get to goal, and block the RAAS!
- Do you live longer if the RAAS blocker is paired with a thiazide diuretic or a CCB?
- Renin inhibitor? Two RAAS blockers?
A RAAS blocker
and
_________________?


ACCOMPLISH: Design

**Screening**
- Amlodipine 5 mg + benazepril 20 mg

**Randomization**
- Benazepril 20 mg + HCT 12.5 mg
- Amlodipine 5 mg + benazepril 40 mg

**Month 1**
- Benazepril 40 mg + HCT 12.5 mg

**Month 2**
- Benazepril 40 mg + HCT 25 mg

**Month 3**
- Amlodipine 10 mg + benazepril 40 mg

**Month 4**
- Free add-on antihypertensive agents*

**Month 5**
- Free add-on antihypertensive agents*

Titrated to achieve BP <140/90 mmHg; <130/80 mmHg in patients with diabetes or renal insufficiency

*Beta blockers; alpha blockers; clonidine; (loop diuretics)
HCT = hydrochlorothiazide

SBP over time

- **DBP: 72.8**
  - ACEI/HCT
  - n=5,733
- **DBP: 71.1**
  - CCB/ACEI
  - n=5,713

**Difference of 0.7 mmHg p<0.05**

<table>
<thead>
<tr>
<th>Month</th>
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<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
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<tbody>
<tr>
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<td>5,731</td>
<td>5,387</td>
<td>5,206</td>
<td>4,999</td>
<td>4,804</td>
<td>4,285</td>
<td>2,520</td>
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<td>5,709</td>
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<td>4,831</td>
<td>4,286</td>
<td>2,594</td>
<td>1,075</td>
</tr>
</tbody>
</table>

*Mean values are taken at 30 months follow-up visit

DBP = diastolic blood pressure

ACCOMPLISH: Impressive Blood Pressure (BP) Control*
Rates Achieved with Single-pill Combination-based Therapies

Only ~37% of patients had their BP controlled at baseline despite
~74% of patients receiving ≥2 antihypertensive agents as free
combination

*Control defined as BP <140/90 mmHg
‡Values calculated from mean BP after titration and mean BP control rate over the
duration of the study

ACCOMPLISH = Avoiding Cardiovascular events through COMbination therapy in
Patients Living with Systolic Hypertension; HCTZ = hydrochlorothiazide

Jamerson et al. Presented at ACC 2008
Kaplan-Meier for primary endpoint

INTERIM RESULTS Mar 08
CI = confidence interval; HR = hazard ratio

Change in Estimated GFR in Hypertensive Treated with B+A or B+H

Number of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Month</th>
<th>Patients</th>
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<tbody>
<tr>
<td>B+A Blacks</td>
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<td></td>
<td>3</td>
<td>655</td>
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<td>1654</td>
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<td>27</td>
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<td>B+H Blacks</td>
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<td>660</td>
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<tr>
<td></td>
<td>6</td>
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<td>Non-B+H Blacks</td>
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<td>21</td>
<td>1654</td>
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<td></td>
<td>24</td>
<td>1604</td>
</tr>
</tbody>
</table>

eGFR: estimated glomerular filtration rate; B+A: benazepril + amloidpine; B+H: benazepril + hydrochlorothiazide

Slope difference between B+A and B+H calculated from baseline: Blacks (p=0.017) Non-Blacks (p<0.0001)
HCT vs CCB as the add on to the RAAS blocker

- **Efficacy**

- **Tolerability**
  - men, CCB?
  - women, HCT?

- **Ability to prevent cardiovascular/renal events**
Combining agents with multiple, complementary mechanisms of action

Cardiac output \times \text{Total peripheral resistance} = \text{Arterial pressure} \times \text{Venous pressure} = \text{BP}

\text{Heart rate} \times \text{Stroke volume} = \text{Cardiac output}

\beta \text{-blockers} \quad \text{Diuretics} \quad \text{CCBs} \quad \text{ARBs} \quad \text{ACE-I}s

Different, but complementary mechanism of action

RAS blocker/CCB/diuretic combinations recognised in UK NICE guidelines for the treatment of hypertension

**Step 1**
- <55 years
  - ACE-I (or ARB*)
- ≥55 years or black patients at any age
  - CCB or thiazide-type diuretic

**Step 2**
- ACE-I (or ARB*) + CCB or ACE-I (or ARB*) + thiazide diuretic

**Step 3**
- ACE-I (or ARB*) + CCB + diuretic

**Step 4**
- Add further diuretic therapy, α-blocker, or β-blocker. Consider seeking specialist advice

*If ACE-I not tolerated*

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Hypertension: management of hypertension in adults in primary care (Quick Reference Guide)
Components supported by a wealth of evidence in CV outcomes trials

<table>
<thead>
<tr>
<th>Components supported by a wealth of evidence in CV outcomes trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
</tr>
<tr>
<td>PREVENT(^1)</td>
</tr>
<tr>
<td>CAMELOT(^2)</td>
</tr>
<tr>
<td>ASCOT(^3,4)</td>
</tr>
<tr>
<td>ALLHAT(^5)</td>
</tr>
<tr>
<td>ACCOMPLISH(^6)</td>
</tr>
</tbody>
</table>

**Amlodipine has a wealth of CV outcomes data**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Design</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREVENT</td>
<td>825 CAD patients (≥30%)</td>
<td>Multicentre, randomised, placebo controlled</td>
<td>No difference in mean 3 year coronary angiographic changes vs. placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>35% ↓ hospitalisation for heart failure + angina</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>43% ↓ revascularisation procedures</td>
</tr>
<tr>
<td>CAMELOT</td>
<td>1,991 CAD patients (&gt;20%)</td>
<td>Double-blind, randomised study vs. placebo and enalapril 20 mg</td>
<td>31% ↓ in CV events vs. placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>42% ↓ hospitalisation for angina</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27% ↓ coronary revascularisation</td>
</tr>
<tr>
<td>ASCOT-BPLA/CAFE</td>
<td>19,257 hypertension patients</td>
<td>Multicentre, randomised, prospective study vs. atenolol</td>
<td>10% ↓ in non-fatal MI &amp; fatal CHD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16% ↓ total CV events and procedures</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>30% ↓ new-onset diabetes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23% ↓ stroke</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11% ↓ all-cause mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ central aortic pressure by 4.3 mmHg</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>18,102 hypertension patients</td>
<td>Randomised, prospective study vs. lisinopril</td>
<td>No difference in composite of fatal CHD + non-fatal MI vs. lisinopril</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6% ↓ combined CVD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23% ↓ stroke</td>
</tr>
<tr>
<td>ACCOMPLISH</td>
<td>11,506 hypertension patients</td>
<td>Double-blind, randomised study vs. HCTZ (both in combination with benazepril)</td>
<td>20% ↓ in composite of death from CV causes, nonfatal MI/stroke, hospitalisation for angina, resuscitation after sudden cardiac arrest, and coronary revascularisation</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>21% ↓ death from CV causes + nonfatal MI/stroke</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>17% ↓ CV events</td>
</tr>
</tbody>
</table>

Valsartan has a wealth of CV outcomes data

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Primary Outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VALUE</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>15,245 high-risk hypertension patients: Double-blind, randomised study vs. amlodipine</td>
<td>No difference in composite of cardiac mortality and morbidity (primary) 23% ↓ new-onset diabetes</td>
</tr>
<tr>
<td><strong>VALIANT</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>14,703 MI patients: Double-blind, randomised study vs. captopril and vs. captopril + valsartan</td>
<td>No difference vs. captopril in all-cause mortality (primary) (valsartan is as effective as standard of care)</td>
</tr>
<tr>
<td><strong>Val-HeFT</strong>&lt;sup&gt;3–5&lt;/sup&gt;</td>
<td>5,010 heart failure II–IV patients: Double-blind, randomised study vs. placebo</td>
<td>13% ↓ morbidity and mortality (primary) ↓ left ventricular remodelling 37% ↓ AF occurrence ↓ heart failure signs/symptoms 28% ↓ heart failure hospitalisation</td>
</tr>
<tr>
<td><strong>JIKEI HEART</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
<td>3,081 Japanese patients on conventional treatment for hypertension, CHD, heart failure or combination of these: Multicentre, randomised, controlled trial comparing addition of valsartan vs. non-ARB to conventional treatment</td>
<td>39% ↓ composite CV mortality and morbidity 40% ↓ Stroke/TIA 47% ↓ Hospitalisation for heart failure 65% ↓ Hospitalisation for angina</td>
</tr>
<tr>
<td><strong>KYOTO HEART</strong>&lt;sup&gt;7&lt;/sup&gt;</td>
<td>3,031 Japanese patients on conventional treatment for hypertension and high CV risk; Multicentre PROBE trial comparing addition of valsartan vs. non-ARB to conventional treatment</td>
<td>45% ↓ Composite CV mortality and morbidity 45% ↓ Stroke/TIA 49% ↓ Angina pectoris 33% ↓ New-onset diabetes</td>
</tr>
</tbody>
</table>

HCTZ has been studied widely in hypertension

- Thiazide diuretics are the first-line recommendation in patients with uncomplicated hypertension,\(^1\) based on results of several large trials\(^2-4\)
- Diuretics are also widely used for enhancing hypertensive efficacy in multi-drug regimens, including in combination with ARBs and CCBs\(^1\)
- The ALLHAT study provided important evidence supporting the use of thiazide diuretics in patients with hypertension\(^4\)
- HCTZ has been shown to enhance antihypertensive efficacy when combined with Valsartan in numerous controlled clinical trials\(^5\)
  - More than 4,000 patients have been included in the Valsartan/HCTZ groups\(^5\)
  - HCTZ resulted in additive placebo-adjusted decreases in SBP and DBP when combined with Valsartan\(^5\)

EX-FAST study design

- **Primary endpoint:** proportion of patients reaching BP control after 16 weeks
  - msSBP <140 mmHg and msDBP <90 mmHg for patients with no diabetes
  - msSBP <130 mmHg and msDBP <80 mmHg for patients with diabetes
- **Mean baseline BP:** 150/91 mmHg

Screening Hypertension patients not controlled on monotherapy (no washout)

Randomization

1–2 weeks

8 weeks

4 weeks

4 weeks

Amlodipine/valsartan 5/160 mg (n=443)

Amlodipine/valsartan 10/160 mg (n=451)

+ HCT 12.5 mg (n=86)

+ HCT 25 mg (n=29)

+ HCT 12.5 mg (n=110)

+ HCT 25 mg (n=51)

msDBP = mean sitting DBP; msSBP = mean sitting SBP

Incremental BP drops after direct switch to amlodipine/valsartan in patients previously uncontrolled on monotherapy: Week 8

Overall b-blocker CCB ARB ACEI Diuretic

n= 440 449 76 55 53 70 175 175 92 105 41 39

Change in SBP (mmHg) from baseline to Week 8

Baseline BP: 150/91 mmHg

Week 8
msSBP, mmHg 131.9 129.8 130.1 128.8 132.9 131.7 132.8 130.8 131.4 127.1 131.1 130.0

**EX-EFFeCTS study design**

- **Primary endpoint:** change in SBP from baseline compared with amlodipine 10 mg alone, at Week 4 prior to HCT, in patients with stage 2 hypertension*

- **Baseline msSBP:** 171 mmHg

---

*Stage 2 hypertension defined as msSBP ≥160 mmHg*
Amlodipine/valsartan provides superior SBP reductions in stage 2 patients at Week 4 (endpoint)


*p<0.0001 vs amlodipine 10 mg
LSM = least squares mean
Amlodipine/valsartan SBP reductions in severe† patients at Week 4 (endpoint)

Mean baseline SBP 187.1 185.0

Δ −8.4* −31.7

*p=0.0018 vs amlodipine 10 mg
†Severe defined as SBP ≥180 mmHg;
Severe was a pre-specified sub-analysis

Amlodipine/valsartan/HCT triple combination therapy in hypertension

- **Study design:** 8-week, multicenter, randomized trial in patients with moderate-to-severe hypertension (msDBP ≥100 to <120 mmHg; msSBP ≥145 to <200 mmHg)

- **Primary objective:** to investigate whether triple combination therapy is superior to respective dual-combinations at lowering either msDBP or msSBP

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<table>
<thead>
<tr>
<th>Randomization</th>
<th>4 weeks</th>
<th>1 week</th>
<th>1 week</th>
<th>6 weeks</th>
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</thead>
<tbody>
<tr>
<td>Single-blind placebo run-in</td>
<td>Amlodipine/HCT 5/12.5 mg</td>
<td>Valsartan/HCT 160/12.5 mg</td>
<td>Amlodipine/valsartan 5/160 mg</td>
<td>Amlodipine/HCT 5/12.5 mg</td>
</tr>
<tr>
<td></td>
<td>Valsartan/HCT 160/12.5 mg</td>
<td>Amlodipine/valsartan/HCT 5/160/12.5 mg</td>
<td>Amlodipine/valsartan 10/320 mg</td>
<td>Amlodipine/valsartan/HCT 5/160/25 mg</td>
</tr>
<tr>
<td></td>
<td>Amlodipine/HCT 5/12.5 mg</td>
<td></td>
<td></td>
<td>Amlodipine/valsartan 10/320/25 mg</td>
</tr>
</tbody>
</table>

Rapid BP-lowering effect: 30 mmHg drop in msSBP after 2 weeks of therapy

Intent-to-treat population (n=2,271)

Clinical perspective

- Hypertension is a:
  - progressive
  - life-long
  - largely asymptomatic

  disease process
Clinical perspective

- Therapy needs to be:
  - simple
  - safe
  - effective
  - well-tolerated
SPCs have several advantages versus free combinations of two or more antihypertensive drugs

<table>
<thead>
<tr>
<th></th>
<th>SPC</th>
<th>Free</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplicity of treatment$^{1,2}$</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Adherence$^{1,2}$</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Efficacy$^2$</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tolerability$^2$</td>
<td>+*</td>
<td>−</td>
</tr>
<tr>
<td>Price$^2$</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Flexibility$^2$</td>
<td>+**</td>
<td>++</td>
</tr>
</tbody>
</table>

*Lower doses generally used in SPCs

**An increasing number of SPCs are becoming available with a range of doses

+ = potential advantage

Compliance Decreases as the Number of Medications Increases

Retrospective cohort study of MCO population. N=8,406 patients with hypertension who added antihypertensive therapy and LLT to existing prescription medications within a 90-day period. Compliance to concomitant therapy: sufficient antihypertensive and LL prescription medications to cover ≥80% of days per 91-day period

CI=confidence interval; LLT = lipid-lowering therapy

Compliant and Persistent Patients Achieve Superior BP Reductions Compared with Non-compliant/Non-persistent Patients

Compliant\(^1\) § (n=556) vs non-persistent; **p<0.0005 vs non-compliant

Persistent\(^2\) §§ (n=862) vs non-compliant or non-persistent patients, respectively

Systolic BP

Diastolic BP

\(^*\)p<0.05 vs non-persistent; **p<0.0005 vs non-compliant

§ Medication-possession ratio ≥80%; §§ Remaining on therapy for 12 months

\(^1\)Halpern et al. J Hypertens 2006;24(Suppl. 4):S154

\(^2\)Halpern et al. J Hypertens 2006;24(Suppl. 4):S182

N=982; BP = blood pressure
Compliance with Antihypertensive Therapy Results in More Patients Achieving Blood Pressure (BP) Goal (<140/90 mmHg)

Observational, cross-sectional study (n=1,000)

Patients achieving BP <140/90 mmHg (%)

Compliant: 80%

Non-compliant: 10%

p<0.005
Non-persistence with Antihypertensive Therapy is Associated with an Increased Risk of Myocardial Infarction and Stroke

Data based on 77,193 new users of antihypertensive treatment identified in the PHARMO record linkage system

Persistent patients (Reference)  
Adjusted* RR for non-persistent patients (95% CI)

Stroke  
1.28 (1.15, 1.45)

Acute myocardial infarction  
1.15 (1.00, 1.33)

*Adjusted for gender, age, type of prescriber, use of cardiovascular co-medication, initial antihypertensive therapy, number of different antihypertensive classes during the first 2 years of therapy
Better Compliance with Antihypertensive Drugs is Associated with a Lower Risk of Hospitalization

<table>
<thead>
<tr>
<th>Level of compliance (%)</th>
<th>All-cause hospitalization risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80–100</td>
<td>27</td>
</tr>
<tr>
<td>60–79</td>
<td>30*</td>
</tr>
<tr>
<td>40–59</td>
<td>36*</td>
</tr>
<tr>
<td>20–39</td>
<td>39*</td>
</tr>
<tr>
<td>1–19</td>
<td>44*</td>
</tr>
</tbody>
</table>

* p<0.05 vs 80–100% compliant group

Sokol et al. Med Care 2005;43:521–30
Better Compliance with Antihypertensive Therapy is Associated with a Decrease in Medical Costs

*Better Compliance with Antihypertensive Therapy is Associated with a Decrease in Medical Costs


*These differences are statistically significant (p<0.05 vs. 80–100% compliant group)
Patients Treated with Single-pill Combinations Use Less Resource

<table>
<thead>
<tr>
<th>Healthcare costs (US $)</th>
<th>Single-pill combination (n=2,336)</th>
<th>Component therapy (n=3,368)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>3,179</td>
<td>5,236</td>
</tr>
<tr>
<td>Ambulatory</td>
<td>1,120</td>
<td>1,646</td>
</tr>
<tr>
<td>Drug</td>
<td>1,322</td>
<td>1,952</td>
</tr>
<tr>
<td>Hospital</td>
<td>334</td>
<td>410</td>
</tr>
<tr>
<td>Other</td>
<td>402</td>
<td>1229</td>
</tr>
</tbody>
</table>

NS = not significant

Dickson, Plauschinat. Am J Cardiovasc Drugs 2008;8:45–50
Overview

- How early should you start?
- How low should you go?
- What drugs and doses should you use?
- How many medications will you need?
Answers

- Earlier the better

- Blood Pressure $<$130/80 mmHg, but likely less in higher risk patients.

- Multi-drug regimen including a full dose of a RAAS blocker

- Start early with effective well tolerated combinations of drugs preferably where you know the appropriate dose to provide both BP and CV risk reduction