Outcomes and Perspectives of Single-Pill Combination Therapy for the modern management of hypertension

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Systolic BP levels in Patients included in Hypertension Surveys performed in Italy between 2001-2012

BP goals in hypertensive patients

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>A SBP goal &lt;140 mmHg:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) is recommended in patients at low–moderate CV risk;</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>b) is recommended in patients with diabetes;</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>c) should be considered in patients with previous stroke or TIA;</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>d) should be considered in patients with CHD;</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>e) should be considered in patients with diabetic or non-diabetic CKD.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>In elderly hypertensive patients less than 80 years old with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In fit elderly patients less than 80 years old SBP values &lt;140 mmHg may be considered, whereas in the fragile elderly population SBP goals should be adapted to individual tolerability.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>In individuals older than 80 years and with initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg provided they are in good physical and mental conditions.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>A DBP target of &lt;90 mmHg is always recommended, except in patients with diabetes, in whom values &lt;85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated.</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

### Treatment strategies and choice of drugs

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<tr>
<td>Diuretics (thiazides, chlorthalidone and indapamide), beta-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor blockers are all suitable and recommended for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations with each other.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of OD.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline BP or at high CV risk.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>The combination of two antagonists of the RAS is not recommended and should be discouraged.</td>
<td>III</td>
<td>A</td>
</tr>
<tr>
<td>Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favoured, because reducing the number of daily pills improves adherence, which is low in patients with hypertension.</td>
<td>IIb</td>
<td>B</td>
</tr>
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However, there are substantial differences among various classes of antihypertensive drugs.
Cumulative incidence of modification of initial monotherapy: discontinuation from any antihypertensive agent, combination with another class of antihypertensive agents, and switching to another class of antihypertensive agents.

In 445,356 newly hypertensive patients in whom the initial prescription consisted of a single antihypertensive drug treatment (monotherapy), discontinuation amounted to 33% of the patients after 6 months, 41% after 1 year and 50% after 5 years.

Effect of the class of drugs used for initial antihypertensive therapy on the cumulative incidence of discontinuation, combination with another drug after 1 year and switching

N=445,356

<table>
<thead>
<tr>
<th>Initial antihypertensive drug class</th>
<th>Discontinuation</th>
<th>Combination</th>
<th>Switching</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>ARBs</td>
<td>0.92 (0.90-0.94)</td>
<td>0.64 (0.63-0.66)</td>
<td>1.54 (1.50-1.58)</td>
</tr>
<tr>
<td>CCBs</td>
<td>1.08 (1.06-1.09)</td>
<td>0.72 (0.70-0.73)</td>
<td>1.34 (1.31-1.36)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>1.83 (1.81-1.85)</td>
<td>0.31 (0.31-0.32)</td>
<td>1.05 (1.03-1.07)</td>
</tr>
<tr>
<td>α-Blockers</td>
<td>1.23 (1.20-1.27)</td>
<td>0.63 (0.60-0.65)</td>
<td>1.42 (1.36-1.47)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>1.64 (1.62-1.67)</td>
<td>0.50 (0.49-0.51)</td>
<td>0.77 (0.75-0.79)</td>
</tr>
</tbody>
</table>

*a Estimates are obtained by fitting the Fine and Gray subdistribution proportional hazards model. Estimates are adjusted for age at entry (continuous), sex, and for concomitant use of digitalis glycosides, organic nitrates, lipid-lowering agents, other cardiovascular drugs, and antidiabetic drugs. b ACE inhibitors, angiotensin-converting enzyme; ARBs, angiotensin II type 1 receptor blocking agents; CCBs, calcium channel blockers. CI, confidence interval.

ACE inhibitors, ARBs and CCBs are the most tolerated antihypertensive drug classes

Meta-analysis of RCT directly comparing ACE Inhibitors with ARBs for stroke, coronary heart disease and heart failure

No significant differences between ACE inhibitors and ARBs on protection from major CV events (MI, stroke, heart failure)
Kaplan–Meier Curves for the Primary Composite Outcome in the Three Study Groups

No significant differences between ACE inhibitors and ARBs on protection from major CV events (MI, stroke, heart failure)

Possible combinations of classes of antihypertensive drugs

Green continuous lines: preferred combinations; green dashed line: useful combination (with some limitations); black dashed lines: possible but less well-tested combinations; red continuous line: not recommended combination.
The use of combination therapy is able to provide effective 24-hour BP control

- Agents dosed once-daily need to control BP over the whole 24-hour dosing period, particularly during the early morning.

- Drugs that are dosed once-daily are recommended because they favour compliance.¹,²

- Guideline recommendations include combining an angiotensin receptor blocker (ARB) with a calcium channel blocker (CCB) or a diuretic¹,²

- “…a large body of evidence exists that combining an ARB with a calcium antagonist or a diuretic provides effective reduction of BP and a high rate of BP control in a variety of hypertension categories…”²

Rationale for combination therapy in hypertension treatment (3/3): better CV outcomes and improved event-free survival

• The vast majority of hypertensive patients at different CV risk profile included in large, randomized clinical trials have been treated with combination therapies (not monotherapies).

• Combination therapies were started early during each trial and maintained throughout the follow-up, to ensure effective and sustained BP control.

• Combination therapies predominantly included CCB-based strategy combined with either ACE inhibitors or ARBs.
BP reductions and Kaplan-Meier curves for a component of the Primary Endpoint (Fatal and non-fatal Stroke)

About 30% of patients allocated in all treatment arms was on combination therapy at 6 months after the beginning of the study with more than 65% at the end of the study; Proportions of treated controlled hypertensive patients raised from 30% to 60%, accordingly.

1. The ALLHAT Study Group. JAMA 2002;288:2981-2997
BP reductions and Kaplan-Meier curves for the Time to First Primary Composite Endpoint (Fatal and non-fatal Stroke)

At 2 years, 25.8%, 23.9%, and 49.5% of patients in the active-treatment group were receiving indapamide alone, indapamide and perindopril 2 mg, and indapamide and perindopril 4 mg, respectively; 14.2%, 13.4%, and 71.8% of patients in the placebo group, respectively, were receiving the corresponding placebos.

ASCOT-BPLA Trial

BP reductions and Kaplan-Meier curves for a component of the Primary Endpoint (Fatal and non-fatal Stroke)

By the end of the trial, most patients (78%) were taking at least two antihypertensive agents, and only 15% and 9% were taking amlodipine and atenolol monotherapy, respectively.
BP reductions and Kaplan-Meier curves for the incidence of new-onset diabetes mellitus

ASCOT-BPLA Trial

BP reductions and Kaplan-Meier curves for the Primary Composite Endpoint (Stroke, CHD, CV mortality)

100% of patients received (fixed) combination therapies from the beginning of the study

Hazard Ratios for the Primary Composite Outcome and the Individual Components of the Primary Endpoint

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of death from cardiovascular causes and cardiovascular events</td>
<td>0.80 (0.72–0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>0.80 (0.62–1.03)</td>
<td>0.08</td>
</tr>
<tr>
<td>Myocardial infarction (fatal or nonfatal)</td>
<td>0.78 (0.62–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Stroke (fatal or nonfatal)</td>
<td>0.84 (0.65–1.08)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>0.75 (0.50–1.10)</td>
<td>0.14</td>
</tr>
<tr>
<td>Coronary revascularization procedure</td>
<td>0.86 (0.74–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Resuscitation after sudden cardiac arrest</td>
<td>1.75 (0.73–4.17)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

0.5  1.0  2.0
Benazepril plus Amlodipine Better
Benazepril plus Hydrochlorothiazide Better

Monotherapy vs. drug combination strategies to achieve target BP
Monotherapy vs. drug combination strategies to achieve target BP

Mild BP elevation
Low/Moderate CV risk

Single Agent

Switch to different Agent

Previous Agent at full dose


Marked BP elevation
High/Very High CV risk

Choose between

Two Drug Combination

Previous Combination at full dose

Add a third Drug

Choose between

Three Drug Combination at full dose

Full Dose Monotherapy

Two Drug Combination at full dose

Switch to different Two-Drug Combination

Previous Agent at full dose

How to improve BP control in daily clinical practice of hypertension?

Strategie per migliorare il controllo della pressione arteriosa in Italia: dalla stratificazione del rischio cardiovascolare globale alla terapia di combinazione

Documento di Indirizzo 2012 della Società Italiana dell’Ipertensione Arteriosa (SIIA)

Massimo Volpe¹, Ettore Ambrosioni², Claudio Borghi², Santina Cottone³, Cesare Cuspidi⁴, Nicola De Luca⁵, Francesco Fallo⁶, Claudio Ferri⁷, Alberto Morganti⁸, Maria Lorenza Muiesan⁹, Riccardo Sarzani¹⁰, Leonardo Sechi¹¹, Agostino Virdis¹², Giuliano Tocci¹, Enrico Agabiti-Rosei¹³, Bruno Trimarco⁶, Alessandro Filippi¹⁴, Giuseppe Mancia⁴

Dual Combination Therapy

• Approximately 70–80% of patients with hypertension require a combination therapy based on at least two classes of drugs (dual combination therapy) in order to achieve the recommended BP goals.

• Clinical studies have demonstrated that this type of strategy allows significant improvement of both systolic and diastolic BP control in about 70–80% of treated hypertensive patients.

• Possible combination therapies that may be used for hypertension treatment and control are listed: 1) ACE inhibitors plus thiazide diuretics (HCTZ or indapamide); 2) ACE inhibitors plus CCBs; 3) ACE inhibitors plus beta-blockers; 4) ARBs plus diuretics (HCTZ); 5) ARBs plus CCBs; 6) ARBs plus beta-blockers.

Concept 1: A treatment algorithm can achieve effective BP control in the general population

STITCH algorithm

Initial low-dose ACEI/diuretic or ARB/diuretic combination

IS BLOOD PRESSURE CONTROLLED?

Yes
- Continue with current therapy

No
- Up-titrates successively to highest dose
- Add CCB and up-titrates
- Add an α-blocker, β-blocker or spironolactone
- Continue with current therapy

Patients with controlled BP (%)

Usual care* 52.7
STITCH algorithm 64.7

*Based on Canadian Hypertension Education Program (CHEP) guidelines

Adapted from Feldman et al. Hypertens 2009;53:646–53
Triple Combination Therapy

• In 20–30 % of patients who do not achieve satisfactory BP control under a combination therapy based on the use of two classes of antihypertensive drugs (**dual combination therapy**), it should be useful to use a combination strategy based on the use of three or more classes of antihypertensive drugs (**triple combination therapy**).

• It is possible to use combination therapy based on three classes of drugs, including **ACE inhibitors, CCBs and thiazide diuretics** (triple combination therapy).

• Today in Italy, the only single-pill 3-drug combination therapy available for the clinical management of hypertension is based on Perindopril-Indapamide-Amlodipine at different dosages (2.5-10/0,625-2,5/5-10 mg).

Advanced Combination Therapy

• If the recommended BP targets are not achieved under triple combination therapy, **a fourth antihypertensive drug class should be added.**

• The addition of any antihypertensive class, different from the previous three classes (beta-blockers, alpha-blockers, aldosterone agents, direct renin inhibitors, centrally acting agents) has demonstrated to be able to provide additional BP reductions and to achieve effective BP control in a number of patients with moderate-to-severe hypertension, and in hypertensive patients who are difficult to treat.

• At present, **the optimal choice of the 4th and 5th line antihypertensive agents has not been addressed** by proper randomized trials.

**ACE inhibitor-based personalized antihypertensive drug treatment: Lessons learned from ALLHAT and ASCOT trials in medium CV risk patients (1/2)**

<table>
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<tr>
<th>Other risk factors, asymptomatic organ damage or disease</th>
<th>Blood Pressure (mmHg)</th>
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<tbody>
<tr>
<td>High-normal SBP 130–139 or DBP 85–89</td>
<td>Grade 1 HT SBP 140–159 or DBP 90–99</td>
</tr>
<tr>
<td>Grade 2 HT SBP 160–179 or DBP 100–109</td>
<td>Grade 3 HT SBP ≥180 or DBP ≥110</td>
</tr>
</tbody>
</table>

1. **No other RF**
   - **Grade 1 HT**: BP uncontrolled after 6 weeks, add BP drugs targeting <140/90
   - **Grade 2 HT**: Life-style changes for several months, then add BP drugs targeting <140/90
   - **Grade 3 HT**: Immediate BP drugs targeting <140/90

2. **1-2 RF**
   - **No BP intervention**: Add BP drugs targeting <140/90
   - **Grade 1 HT**: BP uncontrolled after 6 weeks, add CCB at medium/full dose
   - **Grade 2 HT**: Life-style changes for several months, then add BP drugs targeting <140/90
   - **Grade 3 HT**: Immediate BP drugs targeting <140/90

3. **≥3 RF**
   - **No BP intervention**: Add BP drugs targeting <140/90
   - **Grade 1 HT**: BP uncontrolled after 6 weeks, add CCB at medium/full dose
   - **Grade 2 HT**: Life-style changes for several months, then add BP drugs targeting <140/90
   - **Grade 3 HT**: Immediate BP drugs targeting <140/90

4. **OD, CKD stage 3 or Diabetes**
   - **No BP intervention**: Add BP drugs targeting <140/90
   - **Grade 1 HT**: BP uncontrolled after 6 weeks, add CCB at medium/full dose
   - **Grade 2 HT**: Life-style changes for several months, then add BP drugs targeting <140/90
   - **Grade 3 HT**: Immediate BP drugs targeting <140/90

5. **Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs**
   - **No BP intervention**: Add BP drugs targeting <140/90
   - **Grade 1 HT**: BP uncontrolled after 6 weeks, add CCB at medium/full dose
   - **Grade 2 HT**: Life-style changes for several months, then add BP drugs targeting <140/90
   - **Grade 3 HT**: Immediate BP drugs targeting <140/90
2013 ESH/ESC Hypertension Guidelines

ACE inhibitor-based personalized antihypertensive drug treatment: Lessons learned from ALLHAT and ASCOT trials in high CV risk patients (2/2)

<table>
<thead>
<tr>
<th>Blood Pressure (mmHg)</th>
<th>Other risk factors, asymptomatic organ damage or disease</th>
<th>No other RF</th>
<th>1-2 RF</th>
<th>≥3 RF</th>
<th>OD, CKD stage 3 or Diabetes</th>
<th>Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-normal</td>
<td>Use ACEi + CCB at full dose</td>
<td></td>
<td></td>
<td></td>
<td>• Life-style changes</td>
<td>• Life-style changes</td>
</tr>
<tr>
<td>Grade 1 HT</td>
<td>• Life-style changes for several months</td>
<td>• Life-style changes</td>
<td>• Life-style changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP 130–139 or DBP 85–89</td>
<td>• Then add BP drugs targeting &lt;140/90</td>
<td>• Then add BP drugs targeting &lt;140/90</td>
<td>• Life-style changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2 HT</td>
<td>• Life-style changes for several months</td>
<td>• Then add BP drugs targeting &lt;140/90</td>
<td>• Immediate BP drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP 140–159 or DBP 90–99</td>
<td>• Then add BP drugs targeting &lt;140/90</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Grade 3 HT</td>
<td>• Life-style changes for several months</td>
<td>• Then add BP drugs targeting &lt;140/90</td>
<td>• Immediate BP drugs</td>
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<tr>
<td>SBP ≥180 or DBP ≥110</td>
<td>• Then add BP drugs targeting &lt;140/90</td>
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ACE inhibitor-based personalized antihypertensive drug treatment: Lessons learned from ACCORD and ADVANCE trials in diabetic high CV risk patients

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<td></td>
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<td>≥3 RF</td>
<td>• Life-style changes • No BP intervention</td>
<td>• Life-style changes • BP drugs targeting &lt;140/90</td>
<td>• Life-style changes • BP drugs targeting &lt;140/90</td>
<td>• Life-style changes • Immediate BP drugs targeting &lt;140/90</td>
<td></td>
</tr>
</tbody>
</table>

| 1-2 RF                | • Life-style changes for several months • Then add BP drugs targeting <140/90 | If BP uncontrolled after 6 weeks, Titrate ACEi to medium/full dose | If BP uncontrolled after 6 weeks, Add CCB at medium/full dose | If BP uncontrolled after 6 weeks, Add D at medium/full dose |

| OD, CKD stage 3 or Diabetes | • Life-style changes • No BP intervention | • Life-style changes • BP drugs targeting <140/90 | • Life-style changes • BP drugs targeting <140/90 | • Life-style changes • Immediate BP drugs targeting <140/90 |

Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs

Start ACEi at low dose

ACE inhibitor-based personalized antihypertensive drug treatment: Lessons learned from HOPE, PEACE, PROGRESS, EUROPA trials in very high CV risk

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</tr>
<tr>
<td>Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs</td>
<td>Life-style changes, No BP intervention</td>
</tr>
</tbody>
</table>

Final Considerations

- BP control and outcomes have been unsuccessfully achieved worldwide for many years.

- The focus on simplification therapy and implemented adherence is progressively influencing a dramatic improvement in BP control.

- The cornerstone of this modern strategy of hypertension therapy is based on a personalized single-pill approach based on a platform algorithm, which we currently propose for an effective management of high BP levels in various groups of hypertensive patients.