L’ipertensione oggi e la migliore aderenza alla terapia con le associazioni precostituite

Dott. Enrico Strocchi
Poor BP control in the HTN population: reasons

- “Inappropriate” use of drugs
- Use of “inadequate” doses of drugs
- Activation of mechanism of counter-regulation (es. NaCl)
- Poor adherence/persistence on treatment
- Insufficient use of (rationale) drug combinations
Cardiac output
Peripheral resistance
Genes
ACE/angiotensinogen polymorphisms
Sodium sensitivity
Ion channels isoforms
Environment
Stress
Diet
Lifestyle choices
Insulin
CNS
Vasoconstriction
Vascular remodelling
Blood volume
Kidneys
GFR
Sodium retention
BP
Combination therapy vs monotherapy in reducing BP: meta-analysis on 11000 participants from 42 trials

Combination versus doubling dose: $P<0.05$ for all comparisons

Low-Dose Quadruple Antihypertensive Combination more efficacious than individual agents

BP measured 3 hrs after dosing!  
(Mahmud & Feeley, Hypertension 2007)
Quarter-dose quadruple combination therapy for initial treatment of hypertension: placebo-controlled, crossover, randomised trial and systematic review

<table>
<thead>
<tr>
<th></th>
<th>Quadpill treatment period</th>
<th>Placebo treatment period</th>
<th>Difference* (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (week 0 or week 6)</td>
<td>End of treatment (week 4 or week 10)</td>
<td>Baseline (week 0 or week 6)</td>
<td>End of treatment (week 4 or week 10)</td>
</tr>
<tr>
<td>24-h systolic blood pressure</td>
<td>138.4 (7.3)</td>
<td>119.6 (7.6)</td>
<td>137.1 (10.4)</td>
<td>138.2 (10.0)</td>
</tr>
<tr>
<td>24-h diastolic blood pressure</td>
<td>86.7 (10.6)</td>
<td>73.3 (8.7)</td>
<td>85.1 (9.4)</td>
<td>87.6 (11.9)</td>
</tr>
<tr>
<td>Daytime ambulatory systolic blood pressure</td>
<td>141.7 (7.7)</td>
<td>121.4 (7.9)</td>
<td>140.3 (11.6)</td>
<td>143.7 (10.5)</td>
</tr>
<tr>
<td>Daytime ambulatory diastolic blood pressure</td>
<td>89.9 (11.0)</td>
<td>75.7 (9.2)</td>
<td>87.9 (9.5)</td>
<td>91.1 (12.5)</td>
</tr>
<tr>
<td>Night-time ambulatory systolic blood pressure</td>
<td>128.8 (13.4)</td>
<td>114.4 (9.0)</td>
<td>126.2 (9.2)</td>
<td>125.4 (13.4)</td>
</tr>
<tr>
<td>Night-time ambulatory diastolic blood pressure</td>
<td>77.7 (12.9)</td>
<td>66.8 (8.9)</td>
<td>77.8 (10.0)</td>
<td>79.4 (13.1)</td>
</tr>
<tr>
<td>Office systolic blood pressure</td>
<td>149.9 (16.7)</td>
<td>122.1 (8.8)</td>
<td>145.8 (10.2)</td>
<td>144.6 (12.2)</td>
</tr>
<tr>
<td>Office diastolic blood pressure</td>
<td>87.4 (10.0)</td>
<td>71.8 (8.9)</td>
<td>86.1 (11.3)</td>
<td>84.8 (12.1)</td>
</tr>
</tbody>
</table>

Data are mean (SD), unless otherwise stated. *Difference in change between quadpill and placebo period.

(Irbesartan 37.5 mg + Amlodipine 1.25 mg + HCTZ 6.25 mg + Atenolol 12.5 mg)  
(Chow et Al, Lancet 2017)
On the whole the suggestion, given in the 2007 ESH/ESC Guidelines (2) of considering initiation with a drug combination in patients at high risk or with markedly high baseline BP can be reconfirmed.
Box 10 Position statement: Monotherapy versus combination therapy

- In most, if not all, hypertensive patients, treatment should be started with a single agent in order to facilitate achievement of target pressure values achieved with a single agent, and simplify patient management.
- To reach target blood pressure, a large proportion of patients require combination therapy with multiple agents.
- According to the balance of clinical benefits, presence or absence of adverse events and patient preference, it may be reasonable to initiate treatment with a single agent or combination therapy from the outset.
- There are advantages and disadvantages for each approach.

Box 12 Position statement: Monotherapy versus combination therapy

- Regardless of the drug employed, monotherapy allows to achieve BP target in only a limited number of hypertensive patients.
- Use of more than one agent is necessary to achieve target BP in the majority of patients. A vast array of effective and well tolerated combinations is available.
- Initial treatment can make use of monotherapy or combination of two drugs at low doses with a subsequent increase in drug doses or number, if needed (Figures 3 and 4).
- Monotherapy could be the initial treatment for a mild BP elevation with a low or moderate total cardiovascular risk. A combination may be preferred in the group where risk is high or very high.
- Fixed combination therapy is useful, particularly in several drug classes or in patients already requiring multiple drugs, and may allow simpler treatment.
- In uncomplicated hypertension, gradual pressure reduction is recommended. Intensive treatment of very high pressure stages favours initial treatment with a combination of drugs.

5.2.2 Monotherapy and combination therapy

5.2.2.1 Pros and cons of the two approaches

The 2007 ESH/ESC Guidelines underlined that, no matter which drug is employed, monotherapy can effectively reduce BP in only a limited number of hypertensive patients and that most patients require the combination of at least two drugs to achieve BP control. Therefore, the issue is not whether combination therapy is useful, but whether it should always be preceded by an attempt to use monotherapy, or whether—and when—combination therapy may be the initial approach.
Combination therapy vs monotherapy in reducing cardiovascular events in the clinical practice

Corrao et al. Hypertension 2011
Initial monotherapy and combination therapy and hypertension control the first year

106621 Pts.
SPC = Single Pill Combinations

(Egan et Al, Hypertension 2012)
Gli «ingredienti» per una associazione fissa di successo:

- Farmaci efficaci e con meccanismi d’azione diversi e possibilmente complementari;
- Durata d’azione dei singoli farmaci sufficiente a coprire le 24 ore;
- Buona tollerabilità dei singoli componenti;
- Riduzione degli effetti indesiderati di ciascun componente per effetto dell’associazione.
Compliance, Safety and Effectiveness of Fixed-Dose Combinations of Antihypertensive Agents. A Meta-analysis

(Gupta et al, Hypertension 2010)
Single-Pill vs Free-Equivalent Combination Therapies for Hypertension: a Meta-Analysis of Health Care Costs and Adherence

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Single Pill</th>
<th>Free Equivalent</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.3.1 Naive patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brixner 2008</td>
<td>64.2</td>
<td>57.6</td>
<td>6.60 [2.81, 10.39]</td>
</tr>
<tr>
<td>Jackson 2008</td>
<td>73.1</td>
<td>60.5</td>
<td>12.60 [3.55, 21.65]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2247</td>
<td>626</td>
<td>8.13 [3.00, 13.26]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 5.47; Chi^2 = 1.44, df = 1 (P = 0.23); I^2 = 30%
Test for overall effect: Z = 3.11 (P = 0.002)

<table>
<thead>
<tr>
<th><strong>3.3.2 Experienced patients</strong></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dickson 2008</td>
<td>58.6</td>
<td>48.1</td>
<td>10.50 [7.64, 13.36]</td>
</tr>
<tr>
<td>Dickson-elderly 2008</td>
<td>63.4</td>
<td>49</td>
<td>14.40 [12.97, 15.83]</td>
</tr>
<tr>
<td>Gerbino 2007</td>
<td>87.9</td>
<td>69.2</td>
<td>18.70 [16.93, 20.47]</td>
</tr>
<tr>
<td>Hess 2008</td>
<td>76.9</td>
<td>54.4</td>
<td>22.50 [21.34, 23.66]</td>
</tr>
<tr>
<td>Taylor 2003</td>
<td>80.8</td>
<td>73.6</td>
<td>7.00 [5.16, 8.84]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>18516</td>
<td>17651</td>
<td>14.66 [8.97, 20.36]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 41.31; Chi^2 = 236.93, df = 4 (P < 0.00001); I^2 = 98%
Test for overall effect: Z = 5.05 (P < 0.00001)

| Total (95% CI)                | 20763       | 18277           | 13.31 [8.26, 18.35]               |

Heterogeneity: Tau^2 = 42.94; Chi^2 = 264.57, df = 6 (P < 0.00001); I^2 = 98%
Test for overall effect: Z = 5.17 (P < 0.00001)
Test for subgroup differences: Chi^2 = 26.20, df = 1 (P < 0.00001), I^2 = 96.2%

(Sherrill et Al, J clin Hypertens 2011)
Treatment adherence, clinical outcomes and economics of triple-drug therapy in hypertensive patients

<table>
<thead>
<tr>
<th>Measure</th>
<th>ARB</th>
<th>ACEi</th>
<th>BB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 Pill</td>
<td>2 Pill</td>
<td>3 Pill</td>
</tr>
<tr>
<td>n</td>
<td>1335</td>
<td>4005</td>
<td>3041</td>
</tr>
<tr>
<td>Follow-up in days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1053 (539)</td>
<td>1040 (545)</td>
<td>1012 (540)</td>
</tr>
<tr>
<td>PDC Mean (SD)</td>
<td>0.41 (0.29)</td>
<td>0.53 (0.30)</td>
<td>0.43 (0.30)</td>
</tr>
<tr>
<td>Median</td>
<td>0.37</td>
<td>0.57</td>
<td>0.40</td>
</tr>
<tr>
<td>PDC &lt;0.50 (%)</td>
<td>60.9</td>
<td>45.0</td>
<td>58.4</td>
</tr>
<tr>
<td>0.50&lt;PDC&lt;0.80 (%)</td>
<td>25.3</td>
<td>39.2</td>
<td>25.6</td>
</tr>
<tr>
<td>PDC ≥0.80 (%)</td>
<td>13.8</td>
<td>25.8</td>
<td>16.0</td>
</tr>
<tr>
<td>Odds (95% CI) of PDC ≥0.80 (reference = 3 pill)</td>
<td>2.061 (1.79–2.39)</td>
<td>1.63 (1.47–1.81)</td>
<td>2.63 (2.13–3.25)</td>
</tr>
<tr>
<td>Significant therapy gaps (≥1 pill) (%)</td>
<td>0</td>
<td>10.2</td>
<td>17.5</td>
</tr>
<tr>
<td></td>
<td>≥1</td>
<td>89.8</td>
<td>82.5</td>
</tr>
<tr>
<td>Odds (95% CI) of therapy gaps ≥1 (reference = 3 pill)</td>
<td>0.56 (0.49–0.64)</td>
<td>0.76 (0.69–0.83)</td>
<td>0.46 (0.37–0.57)</td>
</tr>
</tbody>
</table>

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; PDC, proportion of days with 3 components; SD, standard deviation.

*P < .05, †P < .01, ‡P ≤ .001 vs corresponding 3-pill combination, based on t-test.

§ Maximum number of gaps across ARB/ACEi/BB cohorts and 3-pill/2-pill dose type was 28.

(Panjabi et al, J Am Soc Hyperten 2013)
Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

(Williams et Al, Lancet 21 sept. 2015)
How many options are there for a hypertensive patient requiring 3 medications?

Permutations & Combinations:

If one starts with the assumption that the initial decision is related to the selection of 3 out of 5 classes of drugs to combine, and that the order of initiation of drug therapy is not important, the appropriate formula is:

\[
\frac{n!}{r!(n-r)!}
\]

where \(n=5\) classes, and \(r=3\) choices, and the solution to this formula yields 10 choices.

If combinations of ACEi with ARB are excluded, 7 choices remain, such that the number of independent options to be considered by the hypertension practitioner can be calculated as:

\[
\text{Therapeutic options } = (\text{ACEi x diuretic x CCB}) + (\text{ACEi x diuretic x BB}) + (\text{ACEi x CCB x BB}) + (\text{ARB x diuretic x CCB}) + (\text{ARB x diuretic x BB}) + (\text{ARB x CCB x BB}) + (\text{diuretic x CCB x BB})
\]

**Scenario A:** where only one dose per drug is used and order of initiation is not important
Therapeutic options = 2985

**Scenario B:** where lowest and median treatment doses are considered for all available drugs and order of initiation is not important
Therapeutic options = 37 164

**Scenario C:** where lowest and median doses are considered for all available drugs and where the order of initiation IS important
Therapeutic options = 222 984

(note that formula changes to \(\frac{n!}{(n-r)!}\))

(Dresser & Feldman, Current Opinion in Cardiology 2010)
Conclusioni

• Una terapia di associazione è spesso necessaria per raggiungere un sufficiente controllo della PA;
• Per una maggiore efficacia la scelta dei farmaci da associare deve rispettare alcune regole;
• L’impiego di associazioni fisse può contribuire a migliorare la compliance dei pazienti, ma le cause del problema sono molteplici e la semplificazione della terapia le risolve solo in minima parte;