Αντιυπερτασικά 2ης γραμμής
β-αποκλειστές, ανταγωνιστές αλδοστερόνης, κεντρικώς δρώντα, κλπ
Πότε και σε ποιους;

Μιχάλης Δούμας
Παθολόγος
Β’ Π Π Κλινική ΑΠΘ
Hypertension poorly controlled worldwide

Percentage of patients with controlled BP (<140/90 mm Hg)

- Belgium: 25%
- Canada: 16%
- China: 3%
- England: 6%
- France: 33%
- Italy: 9%
- Poland: 4%
- Russia: 6%
- Spain: 16%
- USA: 24%

Erdine. European Society of Hypertension Scientific Newsletter 2000
Framingham Offspring Study: Men aged 18–74

- 81% of hypertension (HTN) occurs in the absence of other risk factors.
- 19% with at least one additional cardiovascular (CV) risk factor.

β-αποκλειστές
Choosing drugs for patients newly diagnosed with hypertension

**Abbreviations:**
- A = ACE inhibitor (consider angiotensin-II receptor antagonist if ACE intolerant)
- C = calcium-channel blocker
- D = thiazide-type diuretic

Black patients are those of African or Caribbean descent, and not mixed-race, Asian or Chinese patients.

**Step 1:**
- Younger than 55 years
- 55 years or older or black patients of any age

**Step 2:**
- A
- C or D

**Step 3:**
- A + C or A + D
- A + C + D

**Step 4:**
- Add
  - further diuretic therapy
  - alpha-blocker
  - beta-blocker
- Consider seeking specialist advice
Right driving
God save the queen
Blood Pressure >140/90 in Adults Aged >18 years
(For age >80 years, pressure >150/90 or >140/90 if high risk [diabetes, kidney disease])

Start Lifestyle Changes
(Lose weight, reduce dietary salt and alcohol, stop smoking)

Drug Therapy
(Consider a delay in uncomplicated Stage 1 patients)*

Stage 1
140-159/90-99

Black Patients
CCB or Thiazide
If Needed, Add ...
ACE-i or ARB OR combine CCB+Thiazide
If Needed ...

non-Black Patients
Age <60 Years
ACE-i or ARB
If Needed, Add ...
CCB or Thiazide
If Needed ...

Age ≥60 Years
CCB or Thiazide
If Needed, Add ...
ACE-i or ARB
If Needed ...

Stage 2
>160/100

Start Drug Therapy (in all patients)

Special Cases

All Patients
Start With 2 Drugs
CCB or Thiazide + ACE-i or ARB

Stage 2
>160/100

* In stage 1 patients without other cardiovascular risk factors or abnormal findings, some months of regularly monitored lifestyle management without drugs can be considered.

If Needed, add other drugs e.g. spironolactone; centrally acting α-receptors; β-blockers

If Needed, Refer to a Hypertension Specialist

J Hypertens 2014
Adult aged ≥18 years with hypertension

Implement lifestyle interventions (continue throughout management).

Set blood pressure goal and initiate blood pressure lowering medication based on age, diabetes, and chronic kidney disease (CKD).

General population (no diabetes or CKD)  Diabetes or CKD present

Age ≥60 years

Age <60 years

All ages Diabetes present
No CKD

All ages
CKD present with or without diabetes

Blood pressure goal
SBP <150 mm Hg
DBP <90 mm Hg

Blood pressure goal
SBP <140 mm Hg
DBP <90 mm Hg

Blood pressure goal
SBP <140 mm Hg
DBP <90 mm Hg

Blood pressure goal
SBP <140 mm Hg
DBP <90 mm Hg

Nonblack
Black

Initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination.

Initiate thiazide-type diuretic or CCB, alone or in combination.

Initiate ACEI or ARB, alone or in combination with other drug class.

Select a drug treatment titration strategy
A. Maximize first medication before adding second or
B. Add second medication before reaching maximum dose of first medication or
C. Start with 2 medication classes separately or as fixed-dose combination.

JAMA 2014
2013 ESH/ESC guidelines
Risk Reduction With β-Blockers in Post-MI Patients

15 Trials (n = 18,995)

Overall mortality: -22%
Sudden cardiac death: -33%
Non-sudden death: -20%
Nonfatal MI: -20%

# Survival studies of β-blockade in HF

<table>
<thead>
<tr>
<th>Study</th>
<th>Favor β-blocker</th>
<th>Patients (N)</th>
<th>Total mortality</th>
<th>NYHA class</th>
<th>EF mean</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS-II Bisoprolol</td>
<td>Green</td>
<td>2647</td>
<td>228/156</td>
<td>III/IV</td>
<td>28%</td>
<td>0.0001</td>
</tr>
<tr>
<td>MERIT-HF Metoprolol succinate CR/XL</td>
<td>Red</td>
<td>3991</td>
<td>217/145</td>
<td>II-IV</td>
<td>28%</td>
<td>0.00009</td>
</tr>
<tr>
<td>COPERNICUS Carvedilol</td>
<td>Red</td>
<td>2289</td>
<td>190/130</td>
<td>III/IV*</td>
<td>20%</td>
<td>0.00013</td>
</tr>
<tr>
<td>All pooled</td>
<td>Blue</td>
<td>8927</td>
<td>635/431</td>
<td></td>
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</tr>
</tbody>
</table>

Relative risk and 95% CI

*not recorded in COPERNICUS, but placebo mortality indicates III/IV

### Clinical end point |
| Any diabetes related end point | 1.10 (0.86 to 1.41) |
| Deaths related to diabetes | 1.27 (0.82 to 1.97) |
| All cause mortality | 1.14 (0.81 to 1.61) |
| Myocardial infarction | 1.20 (0.82 to 1.76) |
| Stroke | 1.12 (0.59 to 2.12) |
| Peripheral vascular disease | 1.48 (0.35 to 6.19) |
| Microvascular disease | 1.29 (0.80 to 2.10) |

#### Relative risk for captopril (95% CI)
β-αποκλειστές στην υπέρταση
Kaplan Meier curves for primary composite endpoint

Dahlof-LIFE, Lancet, 2002
ASCOT-BPLA
n=19257, ys 5.5
secondary endpoints

Figure 5: Kaplan-Meier curves of cumulative incidence of fatal and non-fatal stroke (A), total cardiovascular events and procedures (D), cardiovascular mortality (C), and all-cause mortality (D)
INVEST
ατενολόλη έναντι βεραπαμίλης

Pepine, JAMA 2003
Μετα-ανάλυση β-αποκλειστές ΑΕΕ

<table>
<thead>
<tr>
<th>Stroke</th>
<th>β blocker n/N</th>
<th>Other drug n/N</th>
<th>RR 95% CI</th>
<th>RR 95% CI</th>
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<tbody>
<tr>
<td>ASCOT-BPLA</td>
<td>422/9618</td>
<td>327/9639</td>
<td>1.29 (1.12–1.49)</td>
<td>1.29 (1.12–1.49)</td>
</tr>
<tr>
<td>CONVINCE</td>
<td>118/8297</td>
<td>133/8179</td>
<td>0.87 (0.68–1.12)</td>
<td>1.58 (0.69–3.64)</td>
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<tr>
<td>ELSA</td>
<td>14/1157</td>
<td>9/1177</td>
<td>0.77 (0.49–1.23)</td>
<td>1.14 (0.93–1.39)</td>
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<tr>
<td>HAPPY</td>
<td>32/3297</td>
<td>41/3272</td>
<td>1.34 (1.13–1.58)</td>
<td>1.34 (1.13–1.58)</td>
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<tr>
<td>INVEST</td>
<td>201/11309</td>
<td>176/11267</td>
<td>1.22 (0.98–1.53)</td>
<td>1.22 (0.98–1.53)</td>
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<tr>
<td>LIFE</td>
<td>309/4588</td>
<td>232/4605</td>
<td>1.12 (0.96–1.30)</td>
<td>1.12 (0.96–1.30)</td>
</tr>
<tr>
<td>MRC Old</td>
<td>56/1102</td>
<td>45/1081</td>
<td>0.90 (0.48–1.69)</td>
<td>0.56 (0.21–1.48)</td>
</tr>
<tr>
<td>NORDIL</td>
<td>196/5471</td>
<td>159/5410</td>
<td>2.28 (1.31–3.95)</td>
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<tr>
<td>STOP-2</td>
<td>237/2213</td>
<td>422/4401</td>
<td>1.16 (1.04–1.30)</td>
<td>1.16 (1.04–1.30)</td>
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<tr>
<td>UKPDS</td>
<td>17/358</td>
<td>21/400</td>
<td>1.03 (0.72–1.48)</td>
<td>1.03 (0.72–1.48)</td>
</tr>
<tr>
<td>Yurenev</td>
<td>6/150</td>
<td>11/154</td>
<td>1.12 (0.96–1.30)</td>
<td>1.12 (0.96–1.30)</td>
</tr>
<tr>
<td>MRC</td>
<td>42/4403</td>
<td>18/4297</td>
<td>1.03 (0.72–1.48)</td>
<td>1.03 (0.72–1.48)</td>
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<tr>
<td>Total events</td>
<td>1650/51963</td>
<td>1594/53882</td>
<td>1.16 (1.04–1.30)</td>
<td>1.16 (1.04–1.30)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2=22.39$ (p=0.02)
Beta-blockers

CHD Prevention
- Superior to other drugs in CHD patients
- Similar to other drugs in patients with no CHD

Stroke Prevention
- Inferior to CA
- Similar to other drugs

CHF Prevention
- Superior to CA
- Similar to other drugs

Law et al., BMJ 2009; 338: b1665
<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic organ damage</td>
<td>ACE inhibitor, calcium antagonist, ARB</td>
</tr>
<tr>
<td>LVH</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Asymptomatic atherosclerosis</td>
<td>Calcium antagonist, ACE inhibitor</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Clinical CV event</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>Any agent effectively lowering BP</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>BB, ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>BB, calcium antagonist</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonists</td>
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<tr>
<td>Aortic aneurysm</td>
<td>BB</td>
</tr>
<tr>
<td>Atrial fibrillation, prevention</td>
<td>Consider ARB, ACE inhibitor, BB or mineralocorticoid receptor antagonist</td>
</tr>
<tr>
<td>Atrial fibrillation, ventricular rate control</td>
<td>BB, non-dihydropyridine calcium antagonist</td>
</tr>
<tr>
<td>ESRD/proteinuria</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>ACE inhibitor, calcium antagonist</td>
</tr>
<tr>
<td>Other</td>
<td></td>
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<tr>
<td>ISH (elderly)</td>
<td>Diuretic, calcium antagonist</td>
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<tr>
<td>Metabolic syndrome</td>
<td>ACE inhibitor, ARB, calcium antagonist</td>
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<tr>
<td>Diabetes mellitus</td>
<td>ACE inhibitor, ARB</td>
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<tr>
<td>Pregnancy</td>
<td>Methyldopa, BB, calcium antagonist</td>
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<tr>
<td>Blacks</td>
<td>Diuretic, calcium antagonist</td>
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</table>
Είναι όλοι οι β-αποκλειστές ίδιοι ;;;
Μετα-ανάλυση
Ατενολόλη

<table>
<thead>
<tr>
<th>Stroke</th>
<th>β blocker</th>
<th>Other drug</th>
<th>RR</th>
<th>95% CI</th>
<th>RR</th>
<th>95% CI</th>
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<tr>
<td>ASCOT-BPLA</td>
<td>422/9618</td>
<td>327/9639</td>
<td>1.29</td>
<td>(1.12–1.49)</td>
<td>1.34</td>
<td>(1.13–1.58)</td>
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<tr>
<td>ELSA</td>
<td>14/1157</td>
<td>9/1177</td>
<td>1.58</td>
<td>(0.69–3.64)</td>
<td>1.22</td>
<td>(0.83–1.79)</td>
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<tr>
<td>INVEST</td>
<td>201/11309</td>
<td>176/11267</td>
<td>1.14</td>
<td>(0.93–1.39)</td>
<td>0.90</td>
<td>(0.48–1.69)</td>
</tr>
<tr>
<td>LIFE</td>
<td>309/4588</td>
<td>232/4605</td>
<td>1.34</td>
<td>(1.13–1.58)</td>
<td>1.26</td>
<td>(1.15–1.38)</td>
</tr>
<tr>
<td>MRC Old</td>
<td>56/1102</td>
<td>45/1081</td>
<td>1.22</td>
<td>(0.83–1.79)</td>
<td>0.90</td>
<td>(0.48–1.69)</td>
</tr>
<tr>
<td>UKPDS</td>
<td>17/358</td>
<td>21/400</td>
<td>1.26</td>
<td>(1.15–1.38)</td>
<td>1.26</td>
<td>(1.15–1.38)</td>
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<tr>
<td>Total events</td>
<td>1019/28132</td>
<td>810/28169</td>
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Test for heterogeneity: $\chi^2 = 3.01$ (p=0.70)

<table>
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<tr>
<th>Myocardial infarction</th>
<th>β blocker</th>
<th>Other drug</th>
<th>RR</th>
<th>95% CI</th>
<th>RR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>ASCOT-BPLA</td>
<td>444/9618</td>
<td>390/9639</td>
<td>1.14</td>
<td>(1.00–1.30)</td>
<td>0.96</td>
<td>(0.50–1.85)</td>
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<tr>
<td>ELSA</td>
<td>17/1157</td>
<td>18/1177</td>
<td>0.97</td>
<td>(0.85–1.11)</td>
<td>1.63</td>
<td>(1.15–2.32)</td>
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<tr>
<td>INVEST</td>
<td>441/11309</td>
<td>452/11267</td>
<td>0.95</td>
<td>(0.78–1.16)</td>
<td>0.84</td>
<td>(0.59–1.20)</td>
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<tr>
<td>LIFE</td>
<td>188/4588</td>
<td>198/4605</td>
<td>1.63</td>
<td>(1.15–2.32)</td>
<td>1.05</td>
<td>(0.91–1.21)</td>
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<tr>
<td>MRC Old</td>
<td>80/1102</td>
<td>48/1081</td>
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<tr>
<td>UKPDS</td>
<td>46/358</td>
<td>61/400</td>
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<tr>
<td>Total events</td>
<td>1216/28132</td>
<td>1167/28169</td>
<td></td>
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Test for heterogeneity: $\chi^2 = 11.58$ (p=0.04)

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<tr>
<th>Mortality of all causes</th>
<th>β blocker</th>
<th>Other drug</th>
<th>RR</th>
<th>95% CI</th>
<th>RR</th>
<th>95% CI</th>
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<tr>
<td>ASCOT-BPLA</td>
<td>820/9618</td>
<td>738/9639</td>
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<td>(1.01–1.22)</td>
<td>1.33</td>
<td>(0.65–2.73)</td>
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<tr>
<td>ELSA</td>
<td>17/1157</td>
<td>13/1177</td>
<td>1.02</td>
<td>(0.93–1.11)</td>
<td>1.13</td>
<td>(0.99–1.29)</td>
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<td>INVEST</td>
<td>893/11309</td>
<td>873/11267</td>
<td>1.13</td>
<td>(0.99–1.29)</td>
<td>1.22</td>
<td>(0.99–1.51)</td>
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<tr>
<td>LIFE</td>
<td>431/4588</td>
<td>383/4605</td>
<td>1.22</td>
<td>(0.99–1.51)</td>
<td>0.88</td>
<td>(0.64–1.20)</td>
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<tr>
<td>MRC Old</td>
<td>167/1102</td>
<td>134/1081</td>
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<td></td>
<td>1.08</td>
<td>(1.02–1.14)</td>
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<tr>
<td>UKPDS</td>
<td>59/358</td>
<td>75/400</td>
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<tr>
<td>Total events</td>
<td>2387/28132</td>
<td>2216/28169</td>
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<td></td>
<td></td>
<td></td>
</tr>
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</table>

Test for heterogeneity: $\chi^2 = 5.80$ (p=0.33)

Lindholm, Lancet 2005
Μετα-ανάλυση
β-αποκλειστές εκτός ατενολόλης

<table>
<thead>
<tr>
<th></th>
<th>β blocker n/N</th>
<th>Other drug n/N</th>
<th>RR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yurenev</td>
<td>6/150</td>
<td>11/154</td>
<td>0.56 (0.21–1.48)</td>
</tr>
<tr>
<td>MRC</td>
<td>43/4403</td>
<td>18/4297</td>
<td>2.28 (1.31–3.95)</td>
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<tr>
<td>Total events</td>
<td>48/4553</td>
<td>29/4451</td>
<td>1.20 (0.30–4.71)</td>
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<tr>
<td><strong>Myocardial infarction</strong></td>
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<tr>
<td>Yurenev</td>
<td>7/150</td>
<td>6/154</td>
<td>1.20 (0.41–3.48)</td>
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<tr>
<td>MRC</td>
<td>103/4403</td>
<td>119/4797</td>
<td>0.84 (0.65–1.10)</td>
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<td>Total events</td>
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<td>0.86 (0.67–1.11)</td>
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<td><strong>Mortality of all causes</strong></td>
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<td>Berglund</td>
<td>5/53</td>
<td>4/53</td>
<td>1.25 (0.36–4.40)</td>
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<td>1/150</td>
<td>7/154</td>
<td>0.15 (0.02–1.18)</td>
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<tr>
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<td>126/4606</td>
<td>139/4504</td>
<td>0.89 (0.70–1.12)</td>
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Test for heterogeneity: χ² = 6.09 (p = 0.01)

Test for heterogeneity: χ² = 0.39 (p = 0.53)

Test for heterogeneity: χ² = 3.21 (p = 0.20)

*Lindholm, Lancet 2005*
Ανταγωνιστές αλδοστερόνης
Primary aldosteronism

Douma, Lancet 2008
Resistant hypertension
Small clinical studies

\[ \text{Nishizaka, Am J Hypertens 2003} \]
Spironolactone
ASPIRANT study

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Spironolactone (n=55)</th>
<th>Placebo (n=56)</th>
<th>Between-Group Difference*</th>
<th>P†</th>
</tr>
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<tbody>
<tr>
<td><strong>Systolic BP</strong></td>
<td></td>
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<tr>
<td>ABPM daytime systolic BP, mm Hg</td>
<td>$-9.3 (\pm 12.6)$</td>
<td>$-3.9 (\pm 12.1)$</td>
<td>$-5.4 (\pm 10.0; -0.8)$</td>
<td>0.024</td>
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<tr>
<td>ABPM nighttime systolic BP, mm Hg</td>
<td>$-11.2 (\pm 17.6)$</td>
<td>$-2.6 (\pm 17.7)$</td>
<td>$-8.6 (\pm 15.2; -2.0)$</td>
<td>0.011</td>
</tr>
<tr>
<td>24-h ABPM systolic BP, mm Hg</td>
<td>$-13.8 (\pm 11.8)$</td>
<td>$-4.0 (\pm 12.7)$</td>
<td>$-9.8 (\pm 14.4; -5.2)$</td>
<td>0.004</td>
</tr>
<tr>
<td>Office systolic BP, mm Hg‡</td>
<td>$-14.6 (\pm 15.6)$</td>
<td>$-8.1 (\pm 14.8)$</td>
<td>$-6.5 (\pm 12.2; -0.8)$</td>
<td>0.011</td>
</tr>
<tr>
<td><strong>Diastolic BP</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ABPM daytime diastolic BP, mm Hg</td>
<td>$-4.2 (\pm 8.0)$</td>
<td>$-3.2 (\pm 8.2)$</td>
<td>$-1.0 (\pm 4.0; 2.0)$</td>
<td>0.358</td>
</tr>
<tr>
<td>ABPM nighttime diastolic BP, mm Hg</td>
<td>$-5.6 (\pm 10.5)$</td>
<td>$-2.6 (\pm 11.0)$</td>
<td>$-3.0 (\pm 7.0; 1.0)$</td>
<td>0.079</td>
</tr>
<tr>
<td>24-h ABPM diastolic BP, mm Hg</td>
<td>$-4.2 (\pm 7.0)$</td>
<td>$-3.2 (\pm 7.7)$</td>
<td>$-1.0 (\pm 3.7; 1.7)$</td>
<td>0.405</td>
</tr>
<tr>
<td>Office diastolic BP, mm Hg‡</td>
<td>$-6.6 (\pm 9.6)$</td>
<td>$-4.1 (\pm 8.6)$</td>
<td>$-2.5 (\pm 5.9; 0.9)$</td>
<td>0.079</td>
</tr>
</tbody>
</table>

Office bp reduction: **6.5 / 2.5 mmHg**

ABPM daytime reduction: **5.4 / 1.0 mmHg**
Congestive heart failure - Spironolactone

Pitt, NEJM 1999
Congestive heart failure – Eplerenone - EMPHASIS
Total mortality

Hazard ratio, 0.76 (95% CI, 0.62–0.93)
P=0.008

No. at Risk
Placebo  1373  947  587  242
Eplerenone 1364  972  625  269

Zannad, NEJM 2011
Post MI – EPHESUS
Total mortality

P = 0.008
RR = 0.85 (95% CI, 0.75–0.96)

Cumulative Incidence (%)

No. at Risk
Placebo 3313 3064 2983 2830 2418 1801 1213 709 323 99 2 0 0 0
Eplerenone 3319 3125 3044 2896 2463 1857 1260 728 336 110 0 0 0

Months since Randomization
• Primary aldosteronism
• Resistant hypertension
• Congestive heart failure
• Post MI
• Secondary aldosteronism
• Hypokalemia
Adverse effects - Hyperkalemia

Juurlink, NEJM 2004
Adverse effects - Gynecomastia

- ASCOT  6%
- EPHESUS  1%
- Lower blockade of androgen and progesteron receptors
- Cost ???
### Adherence to therapy

#### Frequency of prescribed drugs (whole medication)

<table>
<thead>
<tr>
<th></th>
<th>163 out-patients</th>
<th>176 in-patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blockers</td>
<td>139 (85.3%)</td>
<td>168 (95.5%***</td>
</tr>
<tr>
<td>β-blockers</td>
<td>116 (71.2%***</td>
<td>30 (17.1%)</td>
</tr>
<tr>
<td>Centrally acting drugs</td>
<td>122 (74.9%***</td>
<td>20 (11.4%)</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>138 (84.7%***</td>
<td>27 (15.3%)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>115 (70.6%***</td>
<td>23 (13.1%)</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>86 (52.8%***</td>
<td>15 (8.5%)</td>
</tr>
</tbody>
</table>

#### Compliance (calculated only from analyzed medication)

<table>
<thead>
<tr>
<th></th>
<th>163 out-patients</th>
<th>176 in-patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blockers</td>
<td>61/97 (62.9%)</td>
<td>140/157 (89.2%***</td>
</tr>
<tr>
<td>β-blockers</td>
<td>60/87 (69.0%)</td>
<td>13/21 (61.9%)</td>
</tr>
<tr>
<td>Centrally acting drugs</td>
<td>27/40 (67.5%)</td>
<td>6/8 (75.0%)</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>81/122 (66.4%)</td>
<td>12/23 (52.2%)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>60/82 (73.2%)</td>
<td>16/19 (84.2%)</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>47/69 (68.1%)</td>
<td>6/15 (40.0%)</td>
</tr>
<tr>
<td>α-blockers</td>
<td>18/45 (40.0%)</td>
<td>124/145 (85.5%***</td>
</tr>
<tr>
<td>Furosemide</td>
<td>7/7 (40.0%)</td>
<td>1/3 (33.3%)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>14/43 (33.6%)</td>
<td>7/7 (100%***</td>
</tr>
<tr>
<td>Direct renin inhibitor (aliskiren)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Averaged compliance</td>
<td>65.4 ± 42.0%</td>
<td>86.2 ± 30.9%***</td>
</tr>
</tbody>
</table>

*Strauch, J Hypertens 2013*
a-blockers
Table 4. Changes in Biochemical Parameters During Doxazosin Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Participants Included in Analyses</th>
<th>Before Doxazosin</th>
<th>After Doxazosin</th>
<th>Mean Within-Individual Difference (SD)</th>
<th>Paired t Test P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>2945*</td>
<td>5.91 (1.04)</td>
<td>5.64 (1.02)</td>
<td>-0.28 (0.73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>2853*</td>
<td>3.82 (0.93)</td>
<td>3.61 (0.91)</td>
<td>-0.21 (0.66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>2934*</td>
<td>1.28 (0.36)</td>
<td>1.28 (0.37)</td>
<td>0.00 (0.22)</td>
<td>0.97</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2936*</td>
<td>1.86 (1.07)</td>
<td>1.69 (0.92)</td>
<td>-0.17 (0.88)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>3409†</td>
<td>5.48 (0.68)</td>
<td>5.59 (0.82)</td>
<td>0.11 (0.80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>7790</td>
<td>140.3 (2.8)</td>
<td>140.2 (2.9)</td>
<td>-0.1 (2.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>7739</td>
<td>4.25 (0.48)</td>
<td>4.22 (0.48)</td>
<td>-0.03 (0.52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>7816</td>
<td>98.3 (18.3)</td>
<td>98.9 (19.9)</td>
<td>0.6 (11.6)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Subjects who received no lipid-lowering agent or received lipid-lowering therapy after starting doxazosin.
†Those without diabetes at baseline.
Heart Failure

Rel Risk  95% CI
2.04  1.79-2.32

\[ z = 10.95, \; p < 0.0001 \]

Cumulative Event Rate

Years of Follow-up

C: 15,268
D: 9,067

Σε ποιους ασθενείς;;;

- Phaeochromocytoma
- BPH
- Resistant hypertension
- Hypertensive emergencies
- Reynaud's syndrome
- Sexual dysfunction?
• Co-administration with PDE-5 inh?

• Orthostatic hypotension

• Urinary incontinence, especially in females, due to bladder outlet relaxation

• Ophthalmic adverse events
Sympatholytics
Centrally acting drugs
• 2\textsuperscript{nd} most prescribed drug in the ’60s and ’70s after diuretics

• Pregnancy
Tips to remember

• LVH
• Liver toxicity
• Haemolytic anaemia
• Phaeochromocytoma diagnosis
• Resistant hypertension
• Hypertensive urgencies
• Stroke
• Sedation
• Dry mouth
• Sodium and water retention
• Rebound hypertension
• Severe hypotension
Κλονιδίνη
Άλλες καταστάσεις

• Opiate – alcohol withdrawal
• Alcoholic cirrhosis
• Menopausal hot flashes
• Diarrhea in diabetic neuropathy
• Restless legs
• Perioperative use???
Effects of moxonidine (0.4mg/day for 8 weeks) in hypertensive patients with reduced insulin sensitivity in a double-blind, placebo-controlled, randomised, parallel group study.

Insulin sensitivity evaluated by hyperinsulinaemic euglycaemic clamp test. Insulin sensitivity index = glucose infusion rate/mean insulin concentration at steady-state.
Moxonidine – Heart Failure
MOXCON study

Cohn J, Eur J Heart Fail 2003
Peripheral acting drugs
• Indian snake Rauwolfia serpentina
• Very effective
• Severe sodium retention – Always with diuretic
• Hygroton-reserpine (0.25-50mg)

• Sedation, depression
• Diarrhea, cramps
Direct vasodilators
• Restricted use nowadays
• Pregnancy?
• Blacks – Heart failure
• Resistant hypertension

• Oral form not available in Greece (IFET)
• Headache, flush, tachycardia
• Nausea, vomiting, diarrhoea
• Paresthesia, tremor, muscle cramps
• Lupus like syndrome, Fever, Arthritis

• Not in CAD, dissecting aortic aneurysm, recent ICH
• Very potent
• Very useful in CKD
• Always use with b-blockers - 90% ST-T change within 2 weeks, later resolve
• Fluid retention - Diuretics in high doses
• 2.5-20mg once daily
• Hirsutism
• Pericarditis
Chateau Lafite
World’s most expensive wine
Take home message
Nitrates for ISH

Long-Term Effectiveness of Extended-Release Nitrate for the Treatment of Systolic Hypertension

Gordon S. Stokes, Alexandra J Bune, Natasha Huon, Edward S. Barin

Abstract—Isosorbide mononitrate (ISMN) is effective in the short-term for decreasing systolic blood pressure, pulse pressure, and pulse wave reflection in patients with systolic hypertension. To determine whether tolerance negates the efficacy of this nitrate in the long-term, a placebo-controlled study was performed in which ISMN was withdrawn briefly in a group of patients (n=16) who had received extended-release ISMN 60 to 120 mg once daily for 16 to 109 months. Blood pressure and wave reflection were determined by 24-hour ambulatory recorder and tonometer, respectively. During a 4-hour delay of the regular morning dose of ISMN, mean systolic blood pressure was higher than with the regular ISMN dosing schedule (P<0.0001). The maximum placebo-active difference was 16±4 mm Hg. The corresponding difference in augmentation index (a measure of pulse wave reflection) corrected for heart rate was 25±4% (P<0.001). The difference in pulse pressure was 13±3 mm Hg (P<0.001). There was no significant difference in diastolic blood pressure. For a subgroup (n=12) in which the effects of a single ISMN dose had been determined at the initiation of regular ISMN therapy, the mean change in augmentation index was of similar magnitude to that observed in their initial study. Thus, tolerance does not seriously diminish the antihypertensive efficacy of ISMN used as adjunct therapy in the chronic treatment of systolic hypertension. This agent lowers systolic blood pressure sufficiently to achieve therapeutic goal in some patients refractory to conventional treatment regimens. (Hypertension. 2005;45:380-384.)
a-methyldopa – LVH Prevention
Peripheral sympatholytics
Ganglion blockers
Veratrum alkaloids

Evolution of antihypertensive therapy

Effectiveness
Tolerability


Doumas, Loutraki 2011
But ...
Evolution of Antihypertensive Therapies

Effectiveness

Tolerability


020

Direct vasodilators

Peripheral sympatholytics

Ganglion blockers

Veratrum alkaloids

Thiazides diuretics

Central α2 agonists

Calcium antagonists non DHPs

β blockers

Spironolactone

Calcium antagonists DHPs

ACE inhibitors

ARBs

VPIs

Others
Sharon Stone
The devil is in the details
## LIFE STUDY

<table>
<thead>
<tr>
<th>Drug doses</th>
<th>Losartan</th>
<th>Atenolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg only</td>
<td>434 (9%)</td>
<td>436 (10%)</td>
</tr>
<tr>
<td>50 mg plus additional drugs*</td>
<td>844 (18%)</td>
<td>930 (20%)</td>
</tr>
<tr>
<td>100 mg with or without additional drugs*</td>
<td>2284 (50%)</td>
<td>1979 (43%)</td>
</tr>
<tr>
<td>Alone</td>
<td>95 (2%)</td>
<td>78 (2%)</td>
</tr>
<tr>
<td>With HCTZ only</td>
<td>829 (18%)</td>
<td>713 (16%)</td>
</tr>
<tr>
<td>With other drugs only</td>
<td>162 (4%)</td>
<td>172 (4%)</td>
</tr>
<tr>
<td>With HCTZ and other drugs</td>
<td>1198 (26%)</td>
<td>1016 (22%)</td>
</tr>
<tr>
<td>Off study drugs</td>
<td>1043 (23%)</td>
<td>1243 (27%)</td>
</tr>
</tbody>
</table>

*Including hydrochlorothiazide (HCTZ).

Number of participants on study drug at endpoint or end of follow-up

_Dahlof-LIFE, Lancet, 2002_
ASCOT-BPLA
n=19257, ys 5.5

Primary endpoints (Non-fatal MI and fatal CHD)

Lancet, 2005
### ASCOT: BP over time by treatment group

78% combination treatment

<table>
<thead>
<tr>
<th>Time point</th>
<th>Atenolol/Diur</th>
<th>Amlodipine/Perind</th>
<th>Δ (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>163.6/95.1</td>
<td>163.4/94.8</td>
<td></td>
</tr>
<tr>
<td>3 month</td>
<td></td>
<td></td>
<td>5.9/2.4</td>
</tr>
<tr>
<td>Mean ΔBP</td>
<td></td>
<td></td>
<td>2.7/1.9</td>
</tr>
<tr>
<td>Final</td>
<td>137.7/79.2</td>
<td>136.1/77.4</td>
<td>1.6/1.8</td>
</tr>
</tbody>
</table>

*Dahlof, Lancet, 2005*
β-Blockers in Hypertension—The Emperor Has No Clothes: An Open Letter to Present and Prospective Drafters of New Guidelines for the Treatment of Hypertension

Franz H. Messerli, D. Gareth Beevers, Stanley S. Franklin, and Thomas G. Pickering

Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis

Lars Hjalmar Lindholm, Bo Carlberg, Ola Samuelsson

EDITORIAL COMMENT

Beta-Blockers in Hypertension

Adding Insult to Injury*

Norman M. Kaplan, MD

Dallas, Texas
Συνεπώς...

Οι β-αποκλειστές έχουν ένδειξη τουλάχιστον για κάποιες ομάδες ασθενών
### Relative Risk of CHD Events in Single Drug BP Difference Trials according to Drug (β-blocker or Other), Presence of CHD, and for β-blockers according to Acute MI on Entry

<table>
<thead>
<tr>
<th></th>
<th>No. of trials</th>
<th>No. of events</th>
<th>Relative Risk (95% CI)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trials of β-blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>People with history of CHD</td>
<td>37</td>
<td>2524</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>Entry after acute MI</td>
<td>27</td>
<td>255</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Entry after long term CHD</td>
<td>11</td>
<td>369</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>People with no history of CHD</td>
<td>6</td>
<td>851</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td><strong>Trials of drugs other than β-blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>People with history of CHD</td>
<td>37</td>
<td>5834</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>People with no history of CHD</td>
<td>24</td>
<td>3217</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>All trials except ones of β-blockers in people with history of CHD</td>
<td>64</td>
<td>9417</td>
<td>0.85</td>
<td></td>
</tr>
</tbody>
</table>

*Law et al., BMJ 2009; 338: b 1665*
Συμπεράσματα
Καθημερινή κλινική πράξη
2013 ESH/ESC guidelines
Resistant hypertension
Low PRA

Doumas, Loutraki 2011
Aldosterone antagonists

Reduce the number of sacks on the wagon
Aldosterone effects on the kidney and heart

Dluhy, NEJM 2004
Post MI – EPHESUS
Sudden Cardiac Death

Pitt, NEJM 2003
Post MI – EPHESUS
Total mortality – HTN history

**A**

Prior History of HTN

- Cumulative Hazard Rate
- EPL
- PBO

- P < 0.0001
- HR = 0.71 (95% CI, 0.59–0.85)

**B**

No Prior History of HTN

- Cumulative Hazard Rate
- EPL
- PBO

- P = 0.435
- HR = 0.91 (95% CI, 0.72–1.15)

No. of patients at risk

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>EPL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1838</td>
<td>1838</td>
</tr>
<tr>
<td>6</td>
<td>1644</td>
<td>1692</td>
</tr>
<tr>
<td>12</td>
<td>1312</td>
<td>1377</td>
</tr>
<tr>
<td>18</td>
<td>673</td>
<td>742</td>
</tr>
<tr>
<td>24</td>
<td>175</td>
<td>204</td>
</tr>
</tbody>
</table>

Pitt, Hypertension 2008

29%
Tips to remember

• How to use – When to stop
• Proteinuria
• Left ventricular hypertrophy
Hyperkalemia - EPHESUS

![Bar chart showing patients' percentage in different serum potassium concentration levels for Eplerenone and Placebo groups.](image-url)
Hyperkalemia - EPHESUS

![Graph showing days to maximum serum potassium level for eplerenone-treated patients.](image)
Case report

• Vasilis H.
• 42 years old, Reporter
• Albuminuria: 3.8 gr/day, SCr: 1.6 mg/dl
• Unsuccessful renal biopsy – Denied retry

• Candesartan 32mg
• Albuminuria: 2.9 gr/day
• Spironolactone: 50mg
• Urinary albumin: 250 mg/day
Spironolactone - Albuminuria

Mehdi, JASN 2009
Eplerenone - Albuminuria

Case report

- Hristos K.
- 58 years old, Doctor
- On triple therapy for 3y
- Severe LVH: 192 gr
- BP: 156/96 mmHg
- Spironolactone: 50 → 25mg for 1y
- LVMI: 154 gr
Left ventricular hypertrophy

Pitt, Circulation 2003
Alpha blockers
Some $\alpha$-receptor blocking agents

- **Phentolamine**
- **Tolazoline**

Block both $\alpha_1$ and $\alpha_2$

- **Prazosine**

Blocks $\alpha_1$ selectively
The preferred combinations in the general hypertensive population are represented as thick lines. The frames indicate classes of agents proven to be beneficial in controlled intervention trials.
Decision to Drop an ALLHAT Arm

- January 24, 2000 – NHLBI Director accepts the recommendation of an independent review group to terminate doxazosin arm
  - Futility of finding a significant difference for primary outcome
  - Statistically significant 25 percent higher rate of major secondary endpoint, combined CVD outcomes
Doxazosin is not recommended as first-line therapy in hypertension.

ALLHAT does not allow an assessment of the effect of doxazosin compared with placebo on the incidence of CVD.

The use of doxazosin as a step-up drug for treating hypertension was not tested in this trial.

These findings are likely to apply to all alpha-blockers.
Case report

- Maria K.
- 68 years old, HTN-DM
- Resistant hypertension

- Hytrin 5mgX2
- First dose: 1mg
- Severe orthostatic hypotension
Case report

• Kostas V.
• 74 years old, HTN-BPH
• Cataract surgery

• Retinal detachment
• Tamsulozin
Case report

- Vasiliki A.
- 64 years old, HTN
- ACE-inh- diuretic fixed combo
- Hytrin 3 months

- Urinary incontinence
- Gynecological – Urological exams: Within normal
α2-Adrenergic Agonists Reduce Blood Pressure by Reducing Sympathetic Output from the Brain

Decreased sympathetic tone
- Decr. HR
- Decr. Contractility
- Decr. Renin release
- Decr. Vasoconstriction
α-Methyldopamine acts as a ‘false transmitter’ in the central nervous system
Case report

• Hristos K.
• 58 years old, Doctor
• On triple therapy for 3y
• Severe LVH: 192 gr
• BP: 156/96 mmHg

• Spironolactone: 50 → 25mg for 1y
• LVMI: 154 gr

Aldomet 500mgX2
BP: 134/82 mmHg
LVMI: 121 gr
Case report

- Andriani A.
- 72 years old, HTN
- Aldomet 500mg X3

- SGOT: 76, SGPT: 94, Bil: 3.8, Albumin: 2.8, INR: 1.4
- Alcohol: no – Viral: negative
- Biopsy
Liver biopsy

Steroids
Partial improvement
Case report

- Niki D.
- 76 years old, HTN
- Aldomet 500mg X2
- Anemia, Splenomegaly, Ht: 28, LDH:1200, Ret:6%
- Hemolytic anemia
Clonidine
Mode of action

Directly stimulates pre-synaptic brain α-2 receptors & ↓ sympathetic activity
Clonidine - Perioperative

![Graph showing survival rates over days after surgery between Clonidine and Placebo groups.](Wallace, Anesthesiology 2004)
Reserpine inhibits the vesicular accumulation of catecholamines and of serotonin

- Blocks reuptake of catecholamines at sympathetic nerve endings
- Depletes store & release of noradrenaline, dopamine & 5-HT in peripheral & central neurons
Combination of isosorbide and hydralazine in blacks with HF

- V-HeFT I suggests that black patients more likely to benefit
- 1050 blacks randomized to fixed dose iso/hydra or placebo + standard therapy
- NYHA III & IV
- Improved survival and QOL

Taylor. NEJM 2004;351:2049-2057
Minoxidil-Associated Pericarditis and Fatal Cardiac Tamponade

JOHN M. KREHLIK, MD
Juneau, Alaska
DAVID A HINDSON, MD
JOSEPH J. CROWLEY, Jr, MD
LAWRENCE L. KNIGHT, MD
Boise, Idaho

The use of minoxidil is associated with pericarditis. There have been no reports in the literature of hemorrhagic pericarditis caused by minoxidil. We report this case of hemorrhagic pericardial tamponade in a patient receiving minoxidil and heparin to underscore this potential complication.
Adverse effects

• Hyperkalemia
• Renal function deterioration
• Gynecomastia
Cardiovascular Disease

Rel Risk    95% CI
1.25  1.17-1.33

z = 6.77,  p < 0.0001

C: 15,268
D:  9,067

a-blockers prescription patterns
Adverse effects

- First dose effect
- Orthostatic hypotension

Graham, BMJ 1976
**Female urinary incontinence**

**Urinary incontinence caused by prazosin**

The antihypertensive effect of prazosin is thought to result primarily from arteriolar smooth muscle relaxation and consequent peripheral vasodilatation. Soon after its introduction reports appeared of collapse due to postural hypotension (“first dose phenomenon”), suggesting an effect on the sympathetic nervous system. Recent experimental data favour the hypothesis that prazosin interferes with α-adrenoceptor function at the postsynaptic level. Our patient furnishes a new clinical argument for this hypothesis.

**Table 3. Bivariable Logistic Regression Analysis of Urinary Incontinence and Current* and Past† Medication Use in Older Women (N = 959)**

<table>
<thead>
<tr>
<th>Type or Class of Current Drug Use</th>
<th>N</th>
<th>Crude Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha blocker</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>22</td>
<td>4.04 (1.72–9.46)</td>
</tr>
<tr>
<td>Thiazide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>233</td>
<td>1.09 (0.76–1.58)</td>
</tr>
</tbody>
</table>
How to?

- Start: 250mg X2
- Maximum 1500mg X2
- CKD: Half dose
- Maximum efficacy: 4h
a-methyldopa – LVH Therapy

Sen, Circ Res 1974
Methyldopa Liver Damage

P. J. TOGHILL, P. G. SMITH, PATRICIA BENTON, R. C. BROWN, H. L. MATTHEWS

*Methyldopa* withdrawal

Full recovery

Summary

Twenty patients are described in whom liver damage appeared to be directly related to the use of methyldopa. Sixteen had hepatic symptoms and they recovered on stopping methyldopa; four of these patients had recurrences of jaundice after a second course of the drug. Features suggestive of active chronic hepatitis were found in two patients. There were two deaths attributed to methyldopa, one of these being in a patient with pre-existing undiagnosed macronodular cirrhosis.

Various three years (cases 6, 14, 15, 17, 18, 19) cases were originally reported to the Committee. We have followed these patients and obtained permission from the referring physicians to report further details. There were 14 women and six men with a range of 35 to 84 years. None admitted to a history of hepatitis and none of 11 patients tested positive for hepatitis A antigens or antibodies. Two patients were taking another potentially hepatotoxic drug (chlorozapexol) at the onset of jaundice. In one of these patients, chlorozapexol was stopped after her episode of liver damage without ill effects.

Drugs taken by other patients in addition to methyldopa included bendrofluazide, hydrochlorothiazide, frusemide, and chlorothiazide; amylorbidite and nitrazepam; and nalidixic acid and thyroxine. So far as could be determined none of the patients were alcoholics or drug addicts.

Tohill, Br Med J 1974
Autoimmune haemolytic anaemia complicating methyldopa therapy

Ivor S. Capper, B.M., B.Ch.
Senior House Officer

Dorothy S. McInnes, B.M., F.R.C.P.
Consultant Physician

E. Parry
M.R.C.P., F.C.Path.
Consultant Pathologist

Autoimmune haemolytic anaemia and alpha methyldopa
A case report and comment
B. W. McGuinness, M.D.
Bridgnorth
How to?

• Start: 0.075mg X2 (1/2 X2)
• Maximum: 0.6mg X2 (4 X2)

• Action: 30min
• Maximum efficacy: 2-4h
• Duration: 8-12h
Centrally acting drugs

- Methyldopa
  - $\alpha_2$-adrenergic receptors
  - $\alpha_2$-adrenergic receptors
  - Refractory nuclei
  - Parasympathetic withdrawal
  - Reduction of arterial pressure

- Clonidine
  - Mixed-acting
  - Endogenous adrenal cortical
  - Sympathetic withdrawal
  - Noradrenaline release suppression
  - Reduction of heart rate
  - Reduction of arterial pressure

- Moxonidine
  - Mixed-acting
  - $H_1$-imidazoline receptors
  - Endogenous adrenal cortical
  - Sympathetic withdrawal
  - Noradrenaline release suppression
  - Reduction of heart rate
  - Reduction of arterial pressure

NTS = terminal nucleus of the pneumogastric and glossopharyngeal nerve
RVLM = Rhyechosidic nucleus of the pneumogastric nucleus and the reticular nucleus of the medulla

The VA Cooperative Study, 1967

<table>
<thead>
<tr>
<th>Cohort</th>
<th>143 men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>51 years</td>
</tr>
<tr>
<td>Eligibility</td>
<td>Diastolic BP 115-129 mmHg</td>
</tr>
<tr>
<td>Design</td>
<td>Double blind; placebo control</td>
</tr>
<tr>
<td>Therapy</td>
<td>HCTZ, reserpine, hydralazine</td>
</tr>
<tr>
<td>Duration</td>
<td>1.5 years</td>
</tr>
<tr>
<td>BP change</td>
<td>-43/30 mmHg</td>
</tr>
</tbody>
</table>

HCTZ=hydrochlorothiazide
Aldosterone - Discovery

Simpson and Tait 1951
Aldosterone-Mediated Vascular Injury

Joffe, Heart Fail Rev 2005
Hyperkalemia – Renal function

- Check serum potassium at 3d, 1w, 3w, 3 to 6m according to potassium levels
- Check serum creatinine at the same timepoints

- Extreme caution when GFR < 30 or Creatinine > 2.5 mg/dl or potassium > 4.8
- Stop if creatinine > 4 or potassium > 6 mg/dl
Phaeochromocytoma – Pre-op use

Doumas, Loutraki 2011
### Table 3. Changes in SBP and DBP During Doxazosin Treatment in Subgroups

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic BP, mm Hg</th>
<th>Diastolic BP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Doxazosin</td>
<td>After Doxazosin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n=10 069)</td>
<td>158.7 (18.3)</td>
<td>147.0 (20.4)</td>
</tr>
<tr>
<td>Age ≤60 y (n=3678)</td>
<td>154.9 (16.4)</td>
<td>145.4 (18.9)</td>
</tr>
<tr>
<td>Age &gt;60 y (n=6391)</td>
<td>160.8 (19.1)</td>
<td>147.9 (21.2)</td>
</tr>
<tr>
<td>Male (n=8024)</td>
<td>157.9 (17.8)</td>
<td>146.7 (19.8)</td>
</tr>
<tr>
<td>Female (n=2045)</td>
<td>161.6 (20.2)</td>
<td>148.1 (22.6)</td>
</tr>
<tr>
<td>Atenolol (n=5787)</td>
<td>162.0 (20.0)</td>
<td>148.6 (21.8)</td>
</tr>
<tr>
<td>Amlodipine (n=4282)</td>
<td>154.2 (14.8)</td>
<td>144.8 (18.2)</td>
</tr>
<tr>
<td>Without diabetes (n=6840)</td>
<td>159.1 (17.8)</td>
<td>146.7 (20.2)</td>
</tr>
<tr>
<td>With diabetes (n=3229)</td>
<td>157.8 (19.4)</td>
<td>147.5 (20.9)</td>
</tr>
<tr>
<td>Without metabolic syndrome (n=5487)</td>
<td>159.3 (18.3)</td>
<td>147.1 (20.6)</td>
</tr>
<tr>
<td>With metabolic syndrome (n=4582)</td>
<td>157.9 (18.4)</td>
<td>148.8 (20.2)</td>
</tr>
</tbody>
</table>

*Second listed compared with first listed; ANCOVA difference in postdoxazosin BP adjusted for pre-doxazosin BP.

**Chapman, Circulation 2008**
Cindy Crawford

Cindy's raciest photo shoot ever

Still sexy at 43

Doumas, 2014
Υπάρχει θέση για τα αντιυπερτασικά 2ης γραμμής???
Resistant hypertension
ASCOT trial

\[ \Delta SBP = 21.9 \]
\[ (95\% CI 20.8, 23.0) \]

\[ \Delta DBP = 9.5 \]
\[ (95\% CI 9.0, 10.1) \]