Case Study

“Hypertensive Patient with Coronary Artery Disease”

NIKOLAOS KOUREMENOS MD

Cardiology Dept, Asklepeion General Hospital, Athens Greece
A 72 years-old women is referred for CV evaluation in our Hypertension clinic for a routine examination for her blood pressure.

She rarely complaints for palpitations.

From the previous medical history, MI 5 years ago, diabetes mellitus treated orally and mild COPD.

Recent stress echo negative for ischemia
ESH/ESC Guidelines and Search for Subclinical Organ Damage

2003 GLs

↑ SCr (> 1.4-1.5 mg/dl)
   EKG †

LVH (Echo)
CA thickening / plaques
MA

2007 GLs

↑ SCr (> 1.4-1.5 mg/dl)
↓ eCrCl / GFR
MA
EKG †

LVH (Echo)
Concentric LVH
LA enlargement
CA thickening / plaques
Ankle/Brachial ratio
Arterial stiffening (PWV)*

Search for multiorgan OD
OD assessed before and during T

* Depending on availability / also shown by high SBP / low DBP
† LVH / MI-ischemia / Arrhythmias
## ESH/ESC Guidelines
### Stratification of CV Risk in Four Categories

<table>
<thead>
<tr>
<th>Other Risk Factors, OD or Disease</th>
<th>Normal SBP 120-129 or DBP 80-84</th>
<th>High Normal SBP 130-139 or DBP 85-89</th>
<th>Grade 1 HT SBP 140-159 or DBP 90-99</th>
<th>Grade 2 HT SBP 160-179 or DBP 100-109</th>
<th>Grade 3 HT SBP ≥ 180 or DBP ≥ 110</th>
</tr>
</thead>
<tbody>
<tr>
<td>No other risk factors</td>
<td>Average risk</td>
<td>Average risk</td>
<td>Low added risk</td>
<td>Moderate added risk</td>
<td>High added risk</td>
</tr>
<tr>
<td>1-2 risk factors</td>
<td>Low added risk</td>
<td>Low added risk</td>
<td>Moderate added risk</td>
<td>Moderate added risk</td>
<td>Very high added risk</td>
</tr>
<tr>
<td>3 or more Risk Factors, MS, OD or Diabetes</td>
<td>Moderate added risk</td>
<td>High added risk</td>
<td>High added risk</td>
<td>High added risk</td>
<td>Very high added risk</td>
</tr>
<tr>
<td>Established CV or renal disease</td>
<td>Very high added risk</td>
<td>Very high added risk</td>
<td>Very high added risk</td>
<td>Very high added risk</td>
<td>Very high added risk</td>
</tr>
</tbody>
</table>

Cardiovascular event rate in 10 years
Risk for cardiovascular death in 10 years (SCORE)

<table>
<thead>
<tr>
<th>&lt;10%</th>
<th>10-15%</th>
<th>15-20%</th>
<th>20-30%</th>
<th>&gt;30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4%</td>
<td>4-5%</td>
<td>5-8%</td>
<td>&gt;8%</td>
<td></td>
</tr>
</tbody>
</table>
Case Presentation

BP: 144/84mm HG

Blood test: Blood sugar: 100 mg/dL, HbA1C: 6.5
LDL-C: 100 mg/dL
Normal renal function

ECG: Q waves in inferior leads, with HR: 78 b/min

ECHO: IVS: 12 mm
PW: 11 mm
LVDD: 49 mm
LA: 47 mm
EF: 45%

Under treatment: Perindopril 5mg
Amlodipine 5 mg
Aspirin 80 mg
Atorvastatin 40 mg
Antidiabetic drug therapy
Question 1

Was the above the appropriate treatment?

- Perindopril 5 mg
- Amlodipine 5 mg
- Aspirin 80 mg
- Atorvastatin 40 mg
- Antidiabetic drug therapy

- Yes
- No
2007 ESH/ESC Guidelines
Combinations between Some Classes of Antihypertensive Drugs

- Thiazide diuretics
- ACE inhibitors
- Calcium antagonists
- AT1-receptor antagonists
- ß-blockers
- α-blockers

ACCOMPLISH
ADVANCE
HYVET
ASCOT
ONTARGET

- Pronounced antihypertensive effect
- CV protection
- Optimal tolerability
# 2007 ESH/ESC Guidelines

## Preferred Drugs

### Condition
- **ISH (elderly)**
  - [→] D / CA
- **MS (or risk of incident DM)**
  - [→] ACEI / ARB (+CA / low dose D)
- **DM**
  - [→] ACEI / ARB
- **Pregnancy**
  - [→] CA / MD / BB
- **Blacks**
  - [→] D / CA

### Subclinical OD
- **LVH**
  - [→] ACEI / CA / ARB
- **Asympt. atherosclerosis**
  - [→] CA / ACEI
- **MA**
  - [→] ACEI / ARB
- **Renal dysfunction**
  - [→] ACEI / ARB

### Clinical Event
- **Previous stroke**
  - [→] any BP lowering agent
- **Previous MI**
  - [→] BB / ACEI / ARB
- **Angina pectoris**
  - [→] BB / CA
- **CHF**
  - [→] D / BB / ACEI / ARB / ALD ant
- **AF (recurrent)**
  - [→] BB / nonDHCA
- **AF (permanent)**
  - [→] ACEI / ARB / loop D
- **ESRF/proteinuria**
  - [→] CA
- **PAD**
  - [→] CA
BP: 144/84 mm Hg

Under treatment: Perindopril 5mg
Amlodipine 5 mg
Atorvastatin 40 mg
Aspirin 80 mg

Antidiabetic drug therapy

β- blocker?
Question 2
Can we use β-blockers in COPD, and if yes, which one?

BP: 144/84 mm Hg

Under treatment: Perindopril 5 mg
Amlodipine 5 mg
Aspirin 80 mg
Antidiabetic drug therapy
Atorvastatin 40 mg

β- blocker?
COPD (even moderate or severe) is not a contraindication to beta-blockers.

Low dose initiation and gradual up-titration is recommended.

Cardioselectivity is paramount, metoprolol, bisoprolol and nebivolol are candidates.
Cardioselectivity of Different beta-blockers

<table>
<thead>
<tr>
<th>Beta-blocker</th>
<th>Cardioselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bucindolol</td>
<td>0.4</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>0.7</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>4.2</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>15.6</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>40.7</td>
</tr>
</tbody>
</table>
Question 3: Which is our Blood Pressure Target?

BP: 140/80 mm Hg

Under treatment:
- Perindopril 5 mg
- Amlodipine 5 mg
- Aspirin 80 mg
- *Antidiabetic drug therapy*
- Atorvastatin 40 mg
- Nebivolol 5 mg
**Question 4: Which is our Blood Pressure Target?**

**2007 ESH/ESC Guidelines**

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Target</th>
<th>General HT population</th>
<th>High risk patients (CAD/Cerebrovasc. disease/ Diabetes/Renal dysfunction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 140/90</td>
<td>&lt; 140/90</td>
<td>≥ 130/85</td>
<td>&lt; 130/80</td>
</tr>
</tbody>
</table>

Concept of flexible threshold/target for treatment in relation to total CV risk
Recently, there has been some withdrawal from a perhaps excessive enthusiasm for aggressive lowering of BP, based on the data of some trials as well as post hoc analyses of the results of other trials on high-risk patients.

*These data have raised the doubt that in patients at high cardiovascular risk, antihypertensive treatment regimens that reduce SBP to values close or below 120–125mmHg and DBP below 70–75mmHg may be accompanied by an increase (rather than a further reduction) in the incidence of coronary events, that is, by a J-curve phenomenon.*
INVEST
(CAD pts)

ONTARGET
(high risk pts, mainly with CAD)

VALUE
(High risk pts)

TNT
(CAD pts)
BP and CV Events in ACCORD

SBP

Years since randomization

Mean no. of medications prescribed

Intensive

Standard

No. of patients

Intensive

Standard

SBP: 70 vs 62 mm Hg

Primary outcome

Proportion with events

Years

P = 0.20

The ACCORD Study Group, NEJM 2010; March 14
Relative Risk of Stroke / MI in ACCORD

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR</th>
<th>RR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI</td>
<td>0.5</td>
<td>0.87</td>
<td>0.25</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.0</td>
<td>0.59</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Intensive: SBP 119.3 mmHg
Standard: SBP 133.5 mmHg

The ACCORD Study Group, NEJM 2010
Question 5

Perindopril or any ACE-inhibitor?

BP: 140/84 mm Hg

Under treatment:
Perindopril 5 mg
Amlodipine 5 mg
Aspirin 80 mg
Antidiabetic drug therapy
Atorvastatin 40 mg

β-blocker?
PEACE vs EUROPA

Primary CV end point

PEACE

EUROPA

![Graph showing incidence of primary end point over years after randomization for Placebo and Trandolapril for PEACE.](image)

![Graph showing incidence of primary end point over time for Placebo and Perindopril for EUROPA.](image)

Logrank $p=0.0003$

«The possibility that not all ACE inhibitors are equally effective for all indications should also be considered…

I will continue to use ACE inhibitors that have been shown to be effective for this indication in several groups of patients»
SMILE 4: Primary endpoint: one Year CV Mortality and one Year Hospitalisation for CV

Log Rank test, $p<0.05$

RR (95% CI) = 0.70
(0.52-0.96)
Adjusted $p=0.028$
Question 6
Doubling the dose of antihypertensive drug or adding another drug?

BP: 140/80 mm Hg

Under treatment: Perindopril 5 mg
Amlodipine 5 mg
Aspirin 80 mg
Antidiabetic drug therapy
Atorvastatin 40 mg
Nebivolol 5 mg
Ratio of observed to expected incremental blood pressure-lowering effects* of adding a drug or doubling the dose according to the class of drug

* The expected incremental effect is the incremental blood pressure reduction of the added (or doubled drug), assuming an additive effect and allowing for the smaller reduction from 1 drug (or dose of 1 drug) given the lower pretreatment blood pressure because of the other

Wald DS et al., Am J Med 2009; 122: 290
% of patients on target dose

EUROPA

Perindopril: 93%

HOPE

Ramipril: 70.9%

PEACE

Trandolapril: 57.8%

Efficacy results of the target dose 10 mg
Case Presentation: Treatment

BP: 130/80 mm Hg

Under treatment:  Perindopril  10mg
                  Amlodipine  5 mg
                  Atorvastatin  40 mg
                  Aspirin  80 mg
                  Antidiabetic drug therapy
                  Nebivolol  5 mg
Question 7
Doubling the dose of Atorvastatin or adding another hypolipidemic drug?

BP: 130/84 mm Hg  LDL-C: 100 mg/dL

Under treatment:
Perindopril 5 mg
Amlodipine 5 mg
Aspirin 80 mg
**Antidiabetic drug therapy**
Atorvastatin 40 mg
Question 8

Which is the next step in diagnostic approach?

- Exercise stress test
- Th 201 Scintigraphy
- Holter monitoring
72 years old

Women

Hypertension

LVH

LA: 47 mm

Diabetes Mellitus
Risk Factor for the Development of AF
38-year follow-up of the Framingham study

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Age-adjusted odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarettes</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.2</td>
</tr>
<tr>
<td>ECG LVH</td>
<td>3.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.6</td>
</tr>
<tr>
<td>BMI</td>
<td>1.0</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Holter Monitoring: Asymptomatic AF
Question 9
Is there need for anticoagulation treatment?

- Yes
- No
### CHADS$_2$–VaSc Score and Annual Risk of Stroke

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Recent congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A Age $\geq$ 75 y</td>
<td>2</td>
</tr>
<tr>
<td>D Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S History of stroke or transient ischemic attack</td>
<td>2</td>
</tr>
<tr>
<td>V Vascular disease (prior MI, PAD, or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>A Age 65-74</td>
<td>1</td>
</tr>
<tr>
<td>S Sex category (female sex)</td>
<td>1</td>
</tr>
</tbody>
</table>

#### Stroke Rate%

<table>
<thead>
<tr>
<th>CHADS$_2$ Score</th>
<th>Stroke Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>4</td>
<td>8.5</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>18.2</td>
</tr>
</tbody>
</table>

**CHADS$_2$–VaSc Score: 6**
ΕΥΧΑΡΙΣΤΩ
# Warfarin vs New Antithrombotics

<table>
<thead>
<tr>
<th>Trial</th>
<th>RELY</th>
<th>ROCKET-AF</th>
<th>AVERROES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug used</td>
<td>Dabigatran Vs Warfarin</td>
<td>Rivaroxaban vs Warfarin</td>
<td>Apixaban vs Aspirin</td>
</tr>
<tr>
<td>Dose</td>
<td>150 or 110 mg BID vs Warfarin (INR 2-3)</td>
<td>20 or 15mg QD vs Warfarin (INR 2-3)</td>
<td>5mg BID</td>
</tr>
<tr>
<td>No. of Patients</td>
<td>18.113</td>
<td>14.000</td>
<td>5.600</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>71.5</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td>Percentage of Hypertension</td>
<td>80%</td>
<td>90%</td>
<td>86%</td>
</tr>
<tr>
<td>Mean CHADS² Score</td>
<td>2.1</td>
<td>2.1</td>
<td>3.5</td>
</tr>
</tbody>
</table>

**Conclusions:**
- 
  - **Dabigatran 110mg** non-inferior to warfarin, with 20% less major bleedings
  - **Dabigatran 150 mg superior to warfarin with similar rate of major bleedings**
  - **Rivaroxaban non-inferior to warfarin on intention to treat analysis but superior in on treatment analysis**
  - **Similar rate of major bleedings**
- **Apixaban superior to aspirin, with same rate of major bleedings**

**Approval**
- FDA
- FDA approved 9/11
  - Doses of 150 mg and 75mg (if Cl Cr 15-30 mL/min)
  - EMA: under consideration
  - EMA: positive opinion