ONLY ACEI’s Save Lives

Hany RAGY, MD
Consultant Cardiologist
Head of Cardiology Departments
NHI, Egypt

In EGYPT ...

✓ 33.6% are hypertensives.

✓ Only 8% are controlled.

MOH, Central Epidemiology & Disease Surveillance, NCD Units - 2006
In EGYPT ...

✓ 23% are smokers
✓ 70% have low physical activity*, 79% with poor dietary habits**
✓ 22% of males, and 39% of females are obese

* <10 minutes exercise/day, ** <5 servings of fruits or vegetables/day
MOH, Central Epidemiology & Disease Surveillance, NCD Units - 2006

In Egypt..... CVD is the leading cause of death

WHO 2014
Hypertension is the leading cause for global mortality and morbidity

“Biggest single contributor to the global burden of disease and to global mortality, leading to 9.4 million deaths each year.”

Special attention to coronary heart disease!

<table>
<thead>
<tr>
<th>Leading causes of death in Egypt</th>
<th>Deaths rate Per 100,000 population</th>
<th>%</th>
<th>World Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Coronary Heart Disease</td>
<td>186.36</td>
<td>18.6</td>
<td>23</td>
</tr>
<tr>
<td>2 Stroke</td>
<td>122.58</td>
<td>12.2</td>
<td>51</td>
</tr>
<tr>
<td>3 Liver Disease</td>
<td>67.54</td>
<td>6.7</td>
<td>2</td>
</tr>
<tr>
<td>4 Hypertension</td>
<td>37.54</td>
<td>3.7</td>
<td>13</td>
</tr>
</tbody>
</table>
Do we really address the real goals of hypertension management?

*The primary goal of treatment of the hypertensive patient is to achieve the maximum reduction in the long-term total risk of CV morbidity and mortality.*


- A powerful antihypertensive that achieves BP control
- An antihypertensive that achieves the goal of treatment (i.e. evidence to reduce MI and mortality)
Do we really think that ACEI & ARBs are the same?
Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin–angiotensin–aldosterone system inhibitors involving 158,998 patients

Laura C. van Vark1, Michel Bertrand2, K. Martijn Akkerhuis3, Jasper J. Brugts1, Kim Fox3, Jean-Jacques Mourad4, and Eric Boersma1

1Department of Cardiology, Thoraxcenter, Erasmus MC, 3015 GE Rotterdam, The Netherlands; 2Life Heart Institute, Lillic, France; 3Royal Brompton and National Heart Hospital, London, UK; and 4Avicenne University Hospital, Bobigny and Paris 13 University, Paris, France

Only ACEis reduce all-cause mortality!
Difference between ACE inhibitors and ARBs on mortality reductions in recent meta-analyses


ACEIs Mode of Action

Bradykinin: Further Therapeutic Perspectives

The bradykinin ("slow-moving" in greek) might mediate a "fast and furious" antihypertensive efficacy

High dose is important to promote the preservation of bradykinin

Taddei and Bortolotto Am J Cardiovasc Drugs 2016
ACE-I in high risk patients: HOPE

- 9,297 Pts.
- CAD or DM+1 RF
- No CHF or LV dysfunction

CV death, AMI or stroke
RRR 28% (14-30)

OR: 0.78
(95%CI: 0.78 - 0.86)

EUROPA (Post-MI, preserved EF)
Fatal & Non Fatal MI

ASCOT-BPLA: Reduction in mortality
Amlodipine ± Perindopril vs. Atenolol ± HCZ


Perindopril + Indapamide reduce All-cause Mortality in Diabetes, ADVANCE

Lancet 2007
Indapamide is more potent than HCTZ at reducing systolic blood pressure

Roush meta-analysis (2015)

Indapamide is significantly more potent than HCTZ at reducing systolic blood pressure, which is not the case with chlorthalidone.

Systematic review and meta-analysis; head-to-head RCTs comparing HCTZ vs indapamide (10 RCTS, n=813) and HCTZ vs chlorthalidone (3 RCTS, n=70).

Indapamide SR preserves lipid and glucose metabolism in the short and long term

Unlike all other diuretics, Indapamide is metabolically neutral

Indapamide reduces left ventricular hypertrophy

Indapamide SR significantly reduces left ventricular hypertrophy


Thiazide-like diuretics are better than thiazide-type diuretics in reducing stroke

Stroke reduction with thiazide diuretics is mainly driven by thiazide-like diuretics and not thiazide-type diuretics

**Indapamide provides effective protection on mortality, stroke and heart failure**

Protection against stroke with indapamide

Indapamide reduces the risk of heart failure

Indapamide–based treatment reduces the risk of death from cardiovascular causes

**HYVET study (2008)**


**Indapamide based therapy reduces CV outcomes**


Indapamide significantly reduces microalbuminuria in Diabetics

**Albumine-creatinine urinary ratio (mg/mmol)**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Indapamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>-35%*</td>
</tr>
</tbody>
</table>

n=283 type 2 diabetic hypertensive patients with microalbuminuria

*P<0.05
Duration=1 year

Meta-analysis of ACE inhibitor trials in CAD patients *without* HF or LV dysfunction

<table>
<thead>
<tr>
<th>Event</th>
<th>RRR vs placebo (%)</th>
<th>* or **</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>-14% P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>-19% P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>-18% P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Stroke*</td>
<td>-23% P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>-42% P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Myocardial revascularisation</td>
<td>-8% P=0.008</td>
<td></td>
</tr>
<tr>
<td>Heart failure hospitalisation</td>
<td>-24% P&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

* End point not reported in QUIET
** End point not reported in PEACE and CAMELOT

ARBs are only similar in Stroke and New-Onset of Diabetes


**ARBs Mode of Action**

**Australia**

**ACE inhibitors, and not ARBs, are first-line treatment**

**Management of hypertension**
- Unless there are good reasons for an alternative choice, we recommend **ACE inhibitors as first-line antihypertensives** in patients with pre-existing CVD, including CHD, stroke, and peripheral vascular disease, or in patients with diabetes and hypertension.

- In patients with diabetes and proteinuria, start treatment with either an ACE inhibitor or angiotensin II receptor antagonist (ARA) if ACE inhibitor–intolerant.

**ACE inhibitors/ARAs**
- We recommend prescribing **ACE inhibitors for everyone** with CHD, especially in patients at high risk of recurrent events, unless contraindicated. Start therapy early post-MI.

- Consider prescribing ARAs for patients who develop unacceptable side effects while taking ACE inhibitors. Monitor renal function among patients taking these agents.

Heart Foundation and Cardiac Society of Australia and New Zealand. Updated 2012.
FRANCE

Medical Authorities take position

ANSM (French regulatory body in charge of medical safety) press release. 13/03/2013

USA

2013 ACC/AHA/CDC Effective Approach For Controlling Hypertension in Adults

No longer any room for doubt

Comprehensive affinity of ACE inhibitors for bradykinin vs angiotensin I binding sites of ACE

<table>
<thead>
<tr>
<th></th>
<th>BK/Ang I selectivity ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perindoprilat</td>
<td>1.44</td>
</tr>
<tr>
<td>Ramiprilat</td>
<td>1.16</td>
</tr>
<tr>
<td>Quinaprilat</td>
<td>1.09</td>
</tr>
<tr>
<td>Trandolaprilat</td>
<td>1.08</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* BK: bradykinin; Ang I: angiotensin I

Comparative affinity of ACE inhibitors for bradykinin vs angiotensin I binding sites of ACE.

Even though it is notoriously difficult to link experimental to clinical data, it is relevant to underline that the largest reductions in mortality in the hypertension trials were observed with trials that involved one member of the ACE inhibitor class (i.e. full-dose perindopril) [2] (Fig. 1). Interestingly, other studies have demonstrated that this is also the member of the class with the strongest affinity for the bradykinin binding sites resulting in powerful reductions of bradykinin breakdown and endothelial apoptosis [18,19].
Differential Affinity for tissue ACE

![Graph showing tissue potency for different ACE inhibitors]

Tissue potency ($DD_{50} \times 10^{-11}$)

- Perindopril
- Quinalapril
- Ramipril
- Enalapril
- Fosinopril
- Captopril


ACEIs and apoptosis: a variable class effect

![Graph showing rate of apoptosis]

24-hour Antihypertensive Efficacy of RAASIs

![Graph showing 24-hour Antihypertensive Efficacy of RAASIs]


ESH / ESC Guidelines 2013:
Possible combinations of classes of antihypertensive drugs

![Diagram showing possible combinations of classes of antihypertensive drugs]


ISH/ASH, 2014

“OPTIMAL” 2-DRUG RX: GENERAL HTN POPULATION

\[ \text{ASD, 2014} \]

- Effectively ↓ BP, ↓ CVD events, ↓ side effects
- ACE-I (ARB) ⊕ Thiazide
  - ↓ BP additively, many studies
  - ↓ CVD in RCTs: HYVET, PROGRESS, ADVANCE
  - ↓ hypokalemia
- ACE-I (ARB) ⊕ CCB (amlodipine)
  - ↓ BP additively, many studies
  - ↓ CVD in RCTs: ASCOT, ACCOMPLISH
  - ↓ CCB-induced edema
A favorable effect of Perindopril/indapamide combination for hypertensive diabetic patients

Perindopril/Indapamide combination offers primary & secondary prevention of nephropathy

<table>
<thead>
<tr>
<th>Event</th>
<th>Favor Current Therapy + Per/Ind (n=5569)</th>
<th>Favor Current Therapy + Placebo (n=5571)</th>
<th>Relative Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point (Combined macro- + microvascular events)</td>
<td>▼ 9% P=0.041</td>
<td>▼ 8% P=0.020</td>
<td></td>
</tr>
<tr>
<td>Total coronary events</td>
<td>▼ 14% P=0.020</td>
<td>▼ 14% P=0.02</td>
<td></td>
</tr>
<tr>
<td>Total renal events</td>
<td>▼ 21% P=0.0001</td>
<td>▼ 19% P=0.0001</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>▼ 18% P=0.027</td>
<td>▼ 15% P=0.025</td>
<td></td>
</tr>
<tr>
<td>Total mortality</td>
<td>▼ 14% P=0.025</td>
<td>▼ 12% P=0.025</td>
<td></td>
</tr>
</tbody>
</table>

Primary prevention

- Progression of nephropathy
  - Risk reduction with Perindopril/Indapamide
    - New onset microalbuminuria: -21% (P<0.0001)
    - New onset macroalbuminuria: -31% (P<0.003)

Secondary prevention

- Regression of nephropathy
  - Risk improvement with Perindopril/Indapamide
    - Restoration to normoalbuminuria: +15% (P<0.007)
A review of renal, cardiovascular and mortality endpoints in antihypertensive trials in diabetic patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Mean followup (years)</th>
<th>ΔBP mmHg active vs control</th>
<th>(Micro)albuminuria</th>
<th>Renal events vs control (RRR)</th>
<th>Mortality (RRR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDNT n=1715</td>
<td>Irbesartan vs placebo</td>
<td>2.6</td>
<td>-3.3</td>
<td>-</td>
<td>-13% P=0.003</td>
<td>-8% NS</td>
</tr>
<tr>
<td>RENAAL n=1513</td>
<td>Losartan vs placebo</td>
<td>3.4</td>
<td>-2</td>
<td>-35% P=0.01</td>
<td>-25% P=0.006</td>
<td>+2% NS</td>
</tr>
<tr>
<td>ROADMAP n=4447</td>
<td>Olmesartan vs placebo</td>
<td>3.2</td>
<td>-3</td>
<td>23% P=0.01</td>
<td>-</td>
<td>+70% (NS)</td>
</tr>
<tr>
<td>ADVANCE n=11140</td>
<td>Perindopril vs placebo</td>
<td>4.3</td>
<td>-5.6</td>
<td>-21% P=0.001</td>
<td>-22% P=0.001</td>
<td>-14% P=0.025</td>
</tr>
<tr>
<td>ONGTARGET n=25620</td>
<td>Telmisartan vs Ramipril 4.7</td>
<td>-2.4</td>
<td>-6% NS</td>
<td>-17% NS</td>
<td>+7% NS</td>
<td>-2% NS</td>
</tr>
<tr>
<td>TRANSCEND n=5927</td>
<td>Telmisartan vs placebo 4.7</td>
<td>-4</td>
<td>-</td>
<td>-42% P=0.018</td>
<td>+29% NS</td>
<td>+5% NS</td>
</tr>
<tr>
<td>DIRECT n=5231</td>
<td>Candesartan vs placebo</td>
<td>4.7</td>
<td>-3.3</td>
<td>-5% P=0.024</td>
<td>-5.5% P=0.024</td>
<td>+3% NS</td>
</tr>
</tbody>
</table>

The only treatment providing primary and secondary prevention of renal events together with significant benefits in terms of all-cause and cardiovascular mortality, is the perindopril indapamide combination in the ADVANCE study.

Perindopril10mg/Indapamide2.5mg: Effective in reducing BP in hypertensive diabetic patients

Perindopril10mg/Indapamide2.5mg:
Confirmed efficacy in reducing BP in hypertensive diabetics

>3,000 patients


Perindopril10mg/Indapamide2.5mg:
Effective in reducing BP over 24hr

T/P ratio
Ramipril = 50-63%
Enalapril = 40-64%
HCTZ = 32%

T/P ratio
Losartan = 66-76%
Valsartan = 58-78%
Olmesartan = 60-80%
HCTZ = 32%

T/P ratio
Perindopril = 100%
Indapamide = 100%
A favorable effect of Perindopril/amlodipine combination on all outcomes

Perindopril / Amlodipine:
Effective in Controlling hypertensive patients

Uncontrolled on Monotherapy

Uncontrolled on Combination

Perindopril / Amlodipine:
Effective in Controlling hypertensive patients

Uncontrolled on Combination


Perindopril 10mg/amlopidine 10mg:
The record reduction of BP in hypertensive patients

Perindopril Evidence Across The Cardiovascular Continuum


Perindopril Evidence Across The Cardiovascular Continuum

**Perindopril 10mg**
- Coronary artery disease (n=1216)
  - CV death/MI/Death: 20%

**Indapamide ± Perindopril 5mg**
- Elderly hypertensives (n=3463)
  - Fatal from fatal strokes: 15%

**Perindopril 5mg ± Indapamide**
- Type 2 Diabetes (n=150)
  - CV mortality: 16%
  - Total mortality: 11%

**Amlodipine ± Perindopril 5/10mg**
- Perindopril 5mg
  - CAD
  - Myocardial ischemia
  - Myocardial infarction

**CV Continuum**
- Coronary heart disease
- Stroke
- Myocardial infarction
- Ventricular dilation
- Remodeling
- Heart failure

**Post-stroke**
- Elderly post-MI (n=150)
  - Death/HF/Coronary remodeling: 12%

**Diastolic HF**
- (n=80)
  - HF Hospitalisation: 37%
  - CV Mortality/HF: 30%

**Hypertension Canada guidelines 2017**
- “Compared to placebo, Only thiazide-like diuretics (e.g. chlorthalidone and Indapamide) reduced the risk of coronary events and all-cause mortality”

**Diabetes Care Standards of Medical Care in Diabetes – 2018**
- “Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as Chlorthalidone and Indapamide, are preferred.”
South African hypertension practice guideline 2014

“In black hypertensive patients a diuretic and/or a CCB is recommended. […] Compared to whites, blacks respond poorly to ACEI and β-blockers as monotherapy.

![Diagram showing the combination of ACEI or ARB, CCB, Thiazide or thiazide-like as treatment options.]

The PIANIST Study: antihypertensive effect of the triple combination Perindopril/Indapamide/Amlodipine

![Graph showing ABPM results over 24-hour, daytime, and nighttime periods.]

### PIANIST Study: side effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle edema</td>
<td>0.2%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0.1%</td>
</tr>
<tr>
<td>Cough</td>
<td>0.08%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.08%</td>
</tr>
</tbody>
</table>


### Take Home Message

- There is high prevalence of HTN and poor control of BP in Egypt.
- HTN and its complications are the leading cause of death, mainly through CHD.
- The Recipe for success to achieve the ultimate goal of treatment of HTN is to give an antihypertensive that reduces both; BP and outcomes.
- ACEIs reduce MI and Mortality, unlike ARBs.
- Perindopril-based solutions have the largest evidence to reduce outcomes.
- Perindopril/Indapamide has the evidence to effectively control and protect hypertensive diabetics.
- Perindopril/Amlodipine is the strongest to control uncontrolled patients and save their lives.
ONTARGET: Equivalence or Non-Inferiority?

<table>
<thead>
<tr>
<th>Clinic SBP and DBP</th>
<th>Telmisartan</th>
<th>Ramipril</th>
<th>Combination</th>
<th>Overall P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>275</td>
<td>284</td>
<td>271</td>
<td></td>
</tr>
<tr>
<td>Clinic SBP, mm Hg</td>
<td>135.5 (16.0)</td>
<td>136.3</td>
<td>131.9 (16.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Clinic DBP, mm Hg</td>
<td>77.1 (9.9)</td>
<td>78.4 (10.1)</td>
<td>76.6 (10.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>124.0 (14.8)</td>
<td>127.1</td>
<td>122.7 (16.1)</td>
<td>0.162</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>70.8 (6.2)</td>
<td>71.9 (6.9)</td>
<td>70.6 (6.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Daytime SBP, mm Hg</td>
<td>126.0 (15.4)</td>
<td>128.5</td>
<td>123.7 (16.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Daytime DBP, mm Hg</td>
<td>72.9 (8.7)</td>
<td>74.0 (9.2)</td>
<td>72.4 (9.8)</td>
<td>0.009</td>
</tr>
<tr>
<td>Nighttime SBP, mm Hg</td>
<td>117.5 (16.4)</td>
<td>121.7</td>
<td>117.9 (18.3)</td>
<td>0.011</td>
</tr>
<tr>
<td>Nighttime DBP, mm Hg</td>
<td>65.3 (8.7)</td>
<td>66.6 (10.3)</td>
<td>55.6 (10.4)</td>
<td>0.267</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.
*P<0.05 vs telmisartan.
†P<0.01 vs telmisartan.
‡P<0.05 vs combination.
§P<0.01 vs combination.

ONTARGET: Equivalence or Non-Inferiority?

Table 3. Incidence of the Primary Outcome, Its Components, and Death from Any Cause.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ramipril (N=8576)</th>
<th>Telmisartan (N=8542)</th>
<th>Combination Therapy (N=8502)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure*</td>
<td>1412 (16.5)</td>
<td>1423 (16.7)</td>
<td>1396 (16.3)</td>
<td>1.01 (0.94-1.09)</td>
</tr>
<tr>
<td>Death from cardiovascular causes, myocardial infarction, or stroke†</td>
<td>1210 (14.1)</td>
<td>1190 (13.9)</td>
<td>1200 (14.3)</td>
<td>0.99 (0.93-1.07)</td>
</tr>
<tr>
<td>Myocardial infarction‡</td>
<td>413 (4.8)</td>
<td>440 (5.2)</td>
<td>438 (5.2)</td>
<td>1.07 (0.94-1.22)</td>
</tr>
<tr>
<td>Stroke‡</td>
<td>405 (4.7)</td>
<td>369 (4.3)</td>
<td>373 (4.4)</td>
<td>0.92 (0.78-1.06)</td>
</tr>
<tr>
<td>Hospitalization for heart failure‡</td>
<td>554 (6.4)</td>
<td>594 (6.6)</td>
<td>532 (6.3)</td>
<td>1.12 (0.97-1.29)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>603 (7.0)</td>
<td>598 (7.0)</td>
<td>620 (7.3)</td>
<td>1.00 (0.89-1.12)</td>
</tr>
<tr>
<td>Death from noncardiovascular causes</td>
<td>411 (4.8)</td>
<td>391 (4.6)</td>
<td>445 (5.2)</td>
<td>0.96 (0.83-1.10)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>1014 (11.8)</td>
<td>989 (11.4)</td>
<td>1065 (12.5)</td>
<td>0.98 (0.90-1.07)</td>
</tr>
</tbody>
</table>

* Patients could have multiple events in this category. The numbers of events were 2058 (24.0%) in the ramipril group, 2042 (23.9%) in the telmisartan group, and 2006 (23.5%) in the combination-therapy group. The differences were not significant (P=0.83 for telmisartan vs. ramipril, and P=0.38 for combination therapy vs. ramipril).
† This composite was the primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) trial.
‡ Patients could have multiple events in this category. The category includes both fatal and nonfatal events.